One-Pot Synthesis of *meta*-Substituted Phenols *via* Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling and Oxidation

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A thesis submitted to the Faculty of Graduate Studies of York University in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

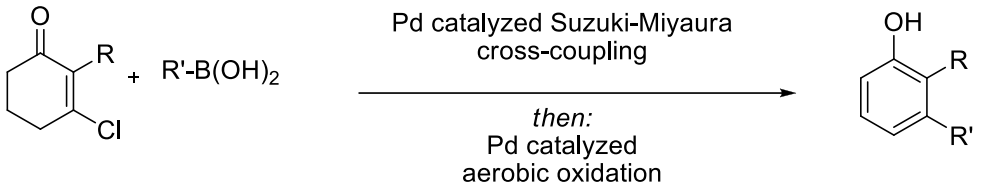
GRADUATE PROGRAM IN CHEMISTRY

York University, Toronto, Ontario

April 2017

Abstract

We have developed a two-step synthesis of *meta*-substituted phenols in one pot, in good to excellent yield. A Pd^{2+} source is the catalyst for both steps of the synthesis, which includes a cross-coupling reaction between β-chlorocyclohexenones with boronic acids, followed by aerobic oxidation of the resulting enone. This method is also suitable for the synthesis of *meta*- and *ortho*-disubstituted phenols, which have so far been especially difficult to access using existing synthetic methods.



The scope of the reaction was explored by combining different substituted β-chlorocyclohexenones with a wide range of different boronic acids and boronate esters using optimized reaction conditions, leading to the synthesis of *meta*-substituted phenols in moderate to good yields.

Acknowledgements

I would like to acknowledge my supervisor Dr. Arturo Orellana for his support and trust throughout this research. I would also like to acknowledge my committee members Dr. Michael Organ and Dr. Edward Lee-Ruff for their help in completing this work. A special thank you to my colleagues, Sadaf Samadi, Andrei Nikolaev, and Dr. Liam O'Donnell for their support and experienced advice, and finally to my fellow graduate students Minhao Zhang and Faizan Rasheed for their friendship.

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Ac……acetyl

DCM……..dichloromethane

DOM……..……directed *ortho*-metallation

DMA……dimethylacetamide

DMF…….dimethylformamide

DMSO…….dimethyl sulfoxide

dppf…… 1,1'-Bis(diphenylphosphino)ferrocene

equiv……...equivalents

EAS…….……electrophilic aromatic substitution

EtOH……..ethanol

IR……...infrared

L_n……ligands(s) (n = number of ligands)

LDA…….lithium diisopropyl amide

MeCN……..acetonitrile

m.p……..…melting point

MS…….mass spectrometry

NHC……N-heterocyclic carbene

N.R……No reaction

OAc…… acetate

OMe…….methoxy

Ph……Phenyl

PhMe……toluene

PPh_3……triphenylphosphine

r.t……..room temperature

TLC……..…thin layer chromatography

Chapter 1: Introduction

1.1 Transition Metals as Catalysts

In chemistry, a catalyst is a substance that increases the rate of reactions without being consumed in the process. Instead, the catalyst is regenerated after product formation. This allows a small amount of catalyst to facilitate the reaction of a much larger quantity of reactants, and in some cases allows reactions to proceed at lower temperatures.[1] This property of catalysts reduces costs of reactions, increases atom efficiency, and generally leads to a reduction of waste products. These advantages have made catalytic reactions more attractive from a sustainability point of view when compared to stoichiometric methods. In fact, catalysis is one of the 12 principles of green chemistry, defined by Anastas and Warner,[2] which outlines a set of guidelines to reduce or eliminate the use or generation of hazardous substances in the design, manufacture and applications of chemical products.

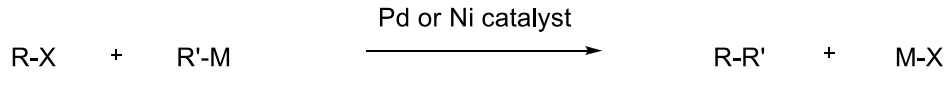
Transition metals are among the most popular catalysts in chemistry, largely owing to the number and configuration of electrons in their d orbitals, unique to each metal. They can exist at different oxidation states, and can form complexes with various organic and inorganic functional groups, facilitating reactions that are either otherwise impossible, or too slow and inefficient to be practical. During the 20th century, the catalytic properties of a wide range of transition metals, including titanium,[3] palladium,[4] zinc,[5] and many others have been extensively studied, facilitating a wide range of reactions in organic, inorganic, and materials chemistry. Of particular note in these studies was the development of transition metal catalyzed carbon-carbon bond forming reactions.

1.2 Transition Metal Catalyzed Carbon-Carbon Bond Formation

Although carbon is the backbone of all organic chemistry, carbon-carbon bonds are generally considered to be more difficult to construct than other common chemical bonds. In the late 20th century, however, a major breakthrough was under way: Cross-coupling

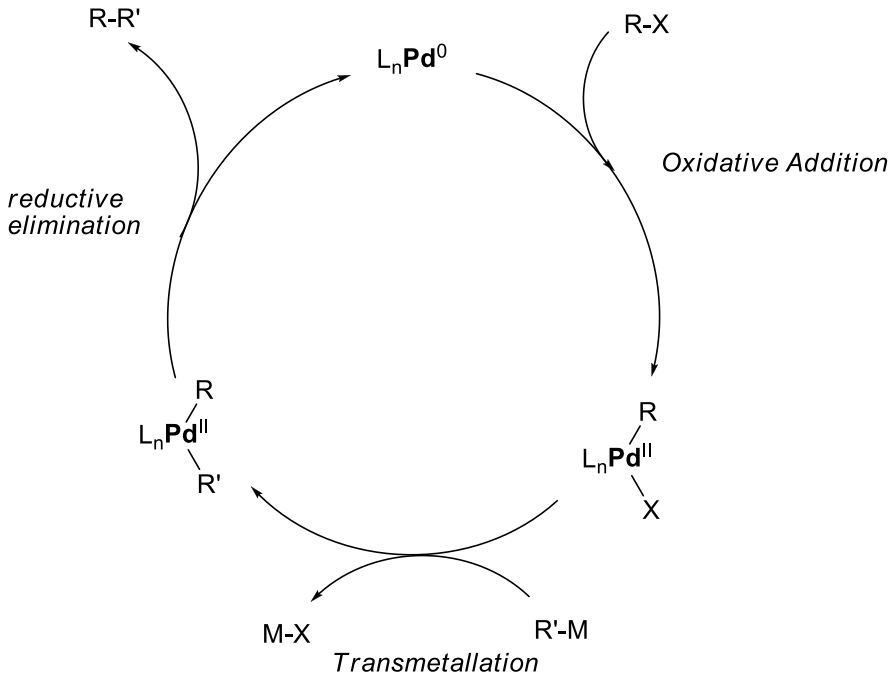
reactions, where two pre-functionalized hydrocarbon fragments are joined with the aid of a transition metal catalyst, most commonly palladium and to a lesser extent nickel. This opened up huge possibilities in organic synthesis by providing many new ways of linking carbon fragments, including the Stille coupling,[6] Negishi coupling,[7] Suzuki-Miyaura coupling,[8] Hiyama coupling,[9] and Kumada coupling reactions,[10] among others (Table 1). The mechanism for these reactions is generally understood to involve three distinct steps (Scheme 1): an aryl or alkenyl halide undergoes oxidative addition to a metal catalyst, most commonly Pd(0) or Ni(0), followed by transmetallation of a carbon-metal species to the oxidized Pd center, and finally reductive elimination, where the product containing a new carbon-carbon bond is formed and the reduced metal catalyst regenerated.

Table 1. General Scheme of cross-coupling reactions



X = Halogen
M = Electropositive metal

Name of Reaction	Metal (M)
Stille	SnR_3
Negishi	ZnX
Suzuki-Miyaura	$B(OR)_3$
Hiyama	SiR_3
Kumada	MgX



Scheme 1. General mechanism of cross-coupling reactions

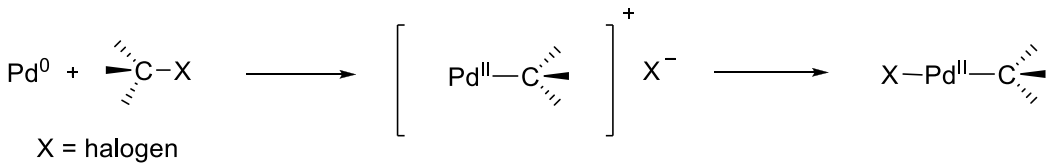
1.3 The Suzuki-Miyaura Cross-Coupling Reaction

Of particular note among the metal catalyzed coupling reactions is the Suzuki-Miyaura coupling reaction, which generates a new carbon-carbon bond by coupling an organoborane reagent with an organic halide using a Pd or Ni catalyst, at a loading level of as low as 0.001% to 5 mol%.[11] With the advantages of using shelf-stable, relatively non-toxic reagents, and easily removable inorganic by-products, the Suzuki-Miyaura coupling reaction has been a staple in academic and industrial chemistry research since the 1990s, although it was published by Dr. Akira Suzuki and Norio Miyaura in 1979.[8] For his work on cross-coupling chemistry, Suzuki received the Nobel Prize in Chemistry in 2010, along with fellow chemists Richard Heck and Ei-Ichi Negishi.

The reaction proceeds under basic conditions, and its mechanism generally follows the aforementioned three distinct steps of oxidative addition, transmetallation, and reductive elimination. However, this is only a simplified mechanism.

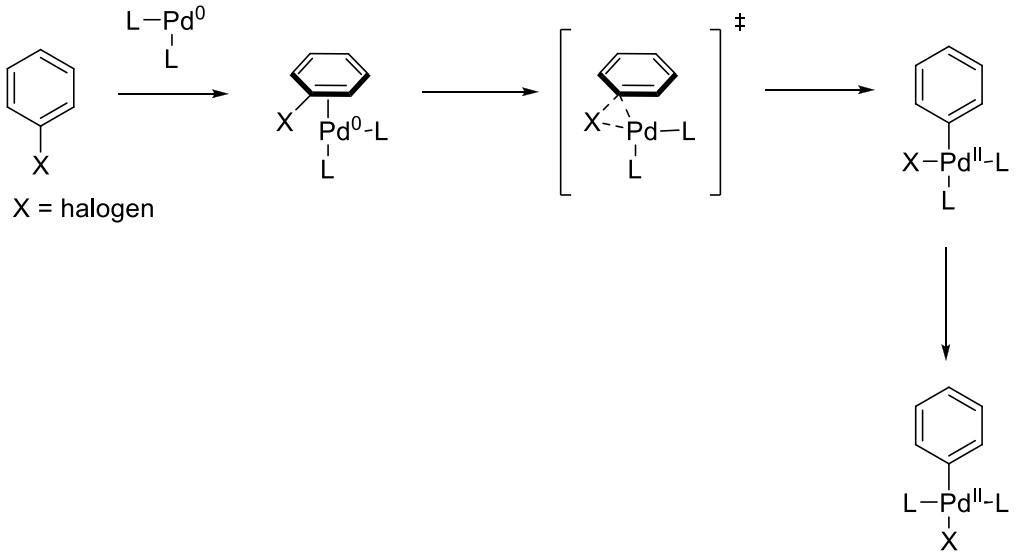
1.3.1 Oxidative Addition

In oxidative addition, both the electron count and the formal charge of the metal catalyst increase by two, typically from Pd(0) to Pd(II). Oxidative addition of alkyl halides can occur by an S_N2 mechanism in which the metal acts as a nucleophile, the electrophilic carbon undergoes inversion of configuration,[12,13] and the relative rates of alkyl halides are methyl > primary > secondary >> tertiary and I > Br > Cl >> F (Scheme 2).[14]



Scheme 2. Oxidative addition by S_n2 pathway

However, this mechanism cannot occur for oxidative addition of aryl and alkenyl halides. Moreover, most aryl halides lack the substituents that would render them sufficiently electrophilic to react by nucleophilic aromatic substitution pathways. Currently, the most widely accepted mechanism for the oxidative addition of an aryl halide to a d^{10} Pd(0) complex is a concerted pathway through a three-centered transition state,[15] and involves the coordination of the arene, then the insertion of the metal into the carbon-halogen bond, producing a *cis*-complex that quickly isomerizes into its more thermodynamically favorable *trans*-isomer (Scheme 3).[16]



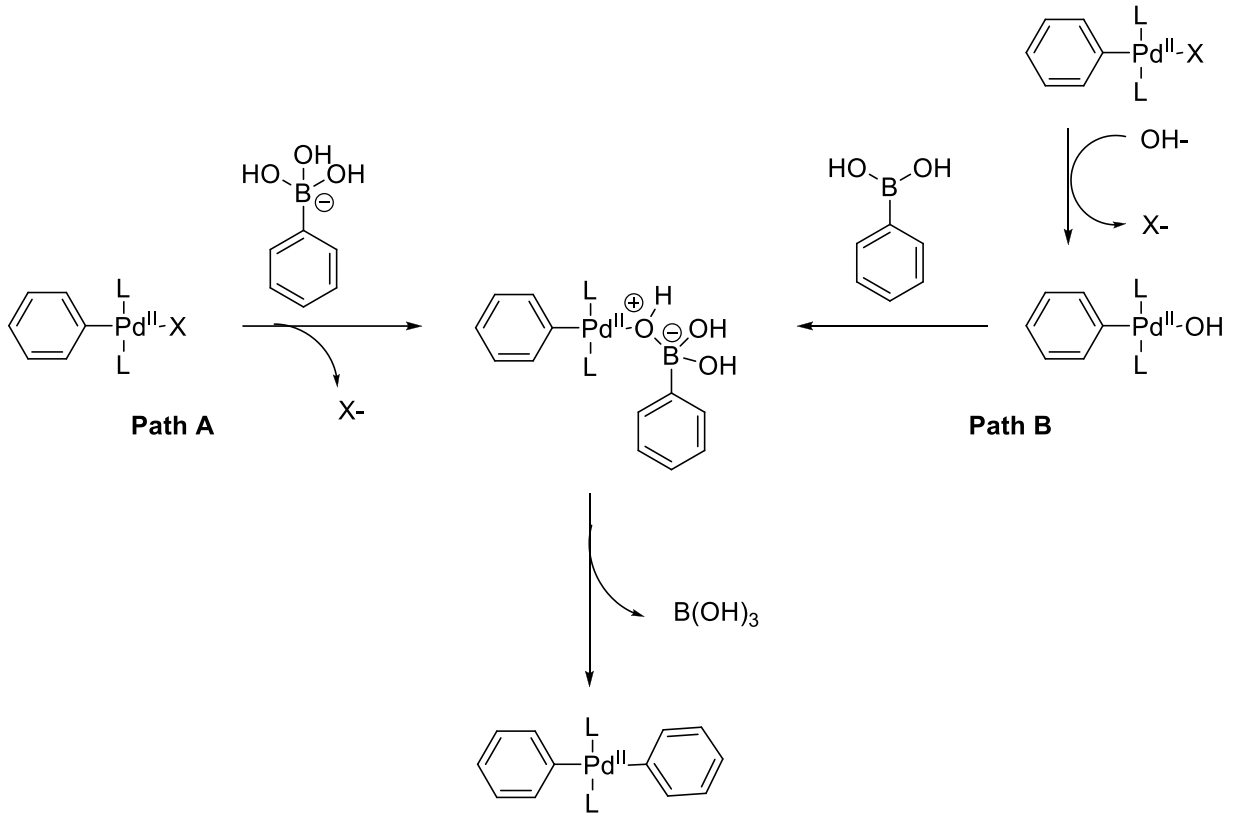
Scheme 3. Oxidative Addition of Aryl halides by concerted pathway

In general, the relative rates of oxidative addition of aryl halides, following their trend of reaction energies, is I > Br > Cl.[17,18] Oxidative addition favors electron-poor organic halides and electron-rich, coordinatively-unsaturated metal centers, as the incoming anionic ligands require vacant orbitals on the metal center to coordinate to.

1.3.2 Transmetallation

After oxidative addition, the transmetallation step of the Suzuki-Miyaura cross-coupling reaction involves the addition of a carbon-boron fragment to the Pd center to form the new carbon-carbon bond. A fundamental understanding of the mechanism behind this critical migratory event from boron to palladium, however, was lacking until recent years. A recurrent theme in the Suzuki-Miyaura cross-coupling reaction is the requirement of a base for transmetallation to proceed, and the exact role of the base has been unclear. For many years, chemists considered two possible pathways (Scheme 4): Path A, proceeding through the formation of a negatively charged four-coordinate boron species, which attacks the electrophilic Pd(II) center to displace the halide, and path B, proceeding through the neutral three-coordinate boron species, which accepts electron density from a palladium hydroxide complex.[19,20] Both pathways converge on an intermediate

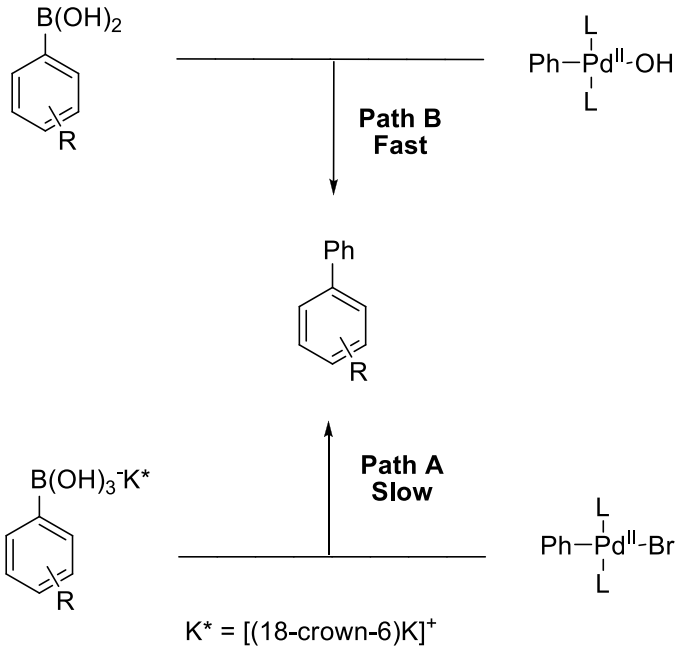
containing a Pd-O-B linkage,[21] ready to transfer an anionic species from boron to palladium.



Scheme 4. Two possible transmetallation pathways for the Suzuki-Miyaura Reaction

Due to the multistep nature of transmetallation, studying its mechanism using Hammett analysis is difficult. For example, electron-donating substituents on the boronic acid species $ArB(OH)_2$ would make the boron center less Lewis acidic, disfavoring interaction with –OH moieties, but would also favor the transfer of the organic fragment from boron to palladium due to increased nucleophilicity.[22] This would suggest that both pathways A and B can be fitted with positive, negative, and zero Hammett ρ values. However, the kinetics of transmetallation using stoichiometric reactions have been studied by Amatore and Jutland,[23] who found that the rate of transmetallation between boronic acid and palladium hydroxide complexes in DMF was very fast, while that between boronate species and palladium halides was significantly slower (Scheme 5). Independent studies by others produced the same result.[24] According to these studies, path B is kinetically

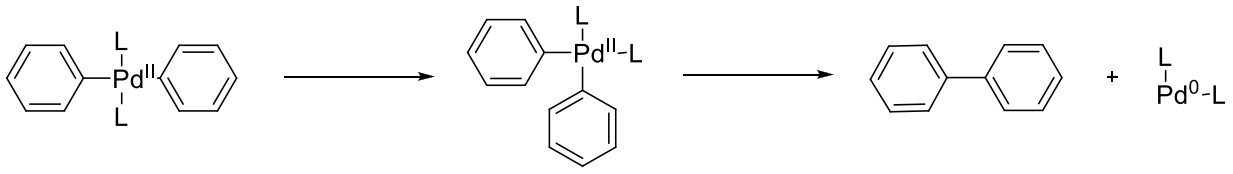
more favorable than path A by several orders of magnitude, at least for the systems they tested.



Scheme 5. Relative rates of transmetallation pathways

1.3.3 Reductive Elimination

Reductive Elimination is the opposite of oxidative addition, and favors electron-poor, sterically bulky metal complexes. The two carbon fragments must adopt a *cis*-configuration in order for reductive elimination to proceed (Scheme 6).[25]



Scheme 6. General mechanism of reductive elimination

1.3.4 Ligands in Suzuki-Miyaura Cross-Coupling Reactions

The ligands on palladium can have a significant impact on the outcome of the Suzuki-Miyaura cross-coupling reaction. The catalytic cycle of the Suzuki-Miyaura cross-coupling reaction begins with oxidative addition of Pd(0), but because Pd(0) catalysts are sensitive to air, Pd(II) salts such as $Pd(OAc)_2$ can be used instead, with the addition of phosphine ligands to reduce Pd(II) and generate Pd(0) species *in situ.*[26]

In addition to reducing Pd(II), phosphine ligands can also have a significant effect on the catalytic cycle itself. In general, the Suzuki-Miyaura cross-coupling reaction favors electron-poor aryl halides and electron-rich metal centers. Reactivity can be enhanced by selecting more electron-rich ligands in order to boost the nucleophilicity of Pd(0) and increase the rate of oxidative addition. Highly electron-donating ligands can also stabilize the zerovalent metal complex and prevent the precipitation of palladium black and the collapse of the catalytic cycle.[27] The electronic effect of various PR_3 ligands can be adjusted by changing the R group. The most well-known and accepted approach of characterising such ligand properties is the Tolman Electronic Parameter,[28] a measurement of the ν(CO) stretching frequencies in $Ni(CO)_3L$, where L = PR_3. More electron rich PR_3 ligands corresponds to a weaker CO bond, and is reflected in decreased ν(CO) stretching.

Bulky ligands, on the other hand, favor the formation of coordinatively-unsaturated metal centers that is required to initiate oxidative addition. In addition, sterically demanding environment around the Pd center favors reductive elimination, which can be critically important in increasing the overall rate of reaction and suppressing undesirable side reactions.[29,30] The steric profile of PR_3 ligands is classified using the Tolman cone angle θ, defined as the angle of a cylindrical cone where the metal is at the vertex and the outermost atoms of the ligand form the perimeter (Figure 1).[28]

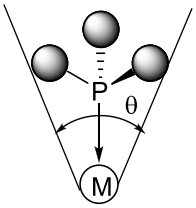


Figure 1. The Tolman cone angle

Phosphine-based ligands such as PPh_3 are common, but several novel and specifically designed ligands, such as SPhos and DPEPhos, can facilitate the Suzuki-Miyaura coupling reaction of aryl chlorides and highly hindered aryl bromides/iodides (Figure 2), which are otherwise notoriously unreactive.[31,32] Also popular are alkyl phosphine ligands, such as $P(t\text{-Bu})_3$,[33] which have high electron density and steric bulk, but suffer from lack of variability, as it is difficult to modify tertiary carbon atoms bonded to phosphorus.[34]

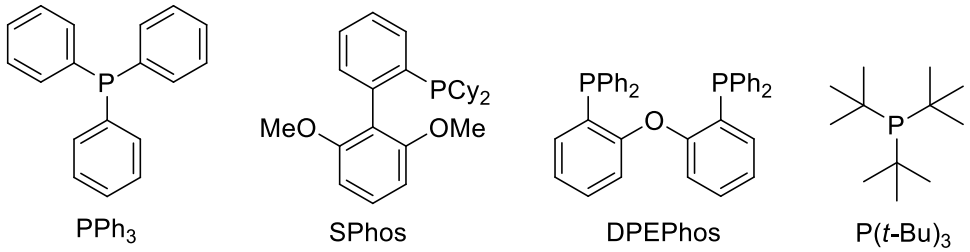


Figure 2. Structures of select phosphine ligands

Other than phosphine ligands, N-heterocyclic carbene (NHC) ligands have also gained importance in cross-coupling reactions. They boast several favorable attributes, including high thermal stability of the Pd-NHC bond, and the strong electron donating property of the carbene.[35] Pd-NHC catalyst systems have proven to be effective in a variety of Pd-catalyzed reactions, but their preparation, often involving free carbene, can require strict, anhydrous conditions.[36,37,38] An improvement was made by Organ who synthesized Pd-NHC pre-catalysts, featuring an extra pyridine-based ligand that is designed to dissociate in the catalytic cycle.[39] These pre-catalysts can be generated in open air, and became

known as Pd-PEPPSI (Pyridine-enhanced precatalyst preparation, stabilization, and initiation) pre-catalysts (Figure 3). Using these pre-catalysts, Organ successfully performed alkyl-alkyl cross-coupling reactions, as well as sterically congested cross coupling reactions, in moderate to high yield.[39]

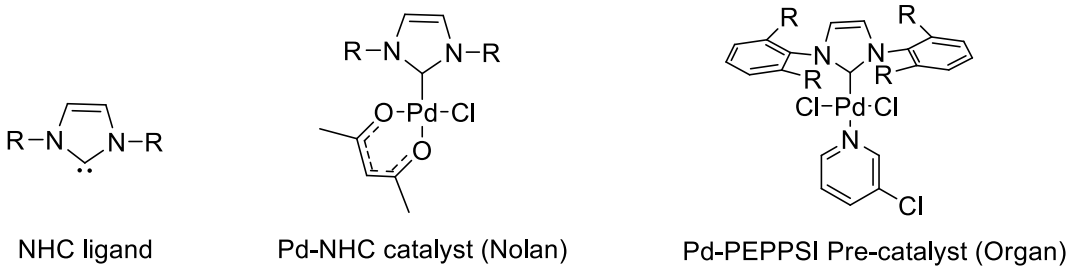
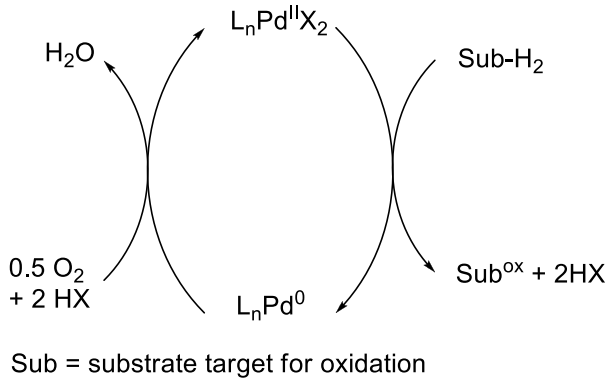


Figure 3. Pd-NHC catalyst systems

1.4 Palladium Catalyzed Aerobic Oxidation

Oxidation reactions are crucial for functional group transformations in chemistry, and increasing the usage of "green" oxidants has become a key issue in recent years. With its low cost, high atom efficiency, and lack of environmentally toxic byproducts, molecular oxygen (O_2) is an ideal oxidizing agent. As the use of transition metals in chemistry gained popularity in the 20th century, so did interest in transition metal catalyzed oxidations. Beginning with the discovery of the Wacker oxidation process in the 1950s,[40] Pd catalysis has been a staple of oxidative chemistry. In its simplest form, the mechanism of most Pd-catalyzed oxidations can be divided into two halves (Scheme 7): the oxidation of the substrate by Pd(II), and regeneration of Pd(II) by O_2.[41] These aerobic oxidations usually generate water or hydrogen peroxide, waste products that are easy to remove and environmentally friendly. For example, the aforementioned Pd-NHC catalyst can cleanly oxidize alcohols to their corresponding aldehydes or ketones in high to quantitative yield,[42] while producing far less toxic by-products than traditional chromium based oxidants.[43] Today, oxidative Pd catalysis is employed in the synthesis of a wide variety of chemicals, including diols,[44] furans,[45] arenes,[46] etc.



Scheme 7. General catalytic cycle of Pd-catalyzed aerobic oxidation

1.5 Phenols

Phenols are a class of organic compounds containing a hydroxyl group (-OH) directly bonded to a benzene ring. Although they share some similarities with alcohols, phenols (pka ~ 10) are significantly more acidic than alcohols (pka ~ 16). Phenols can have one or more substituents on the aromatic ring on the *ortho-, meta-,* or *para-* positions, giving rise to a wide variety of complex structures, many of which are of biological and pharmaceutical interest (Figure 4).[47,48,49] As a result, the motivation for developing and improving phenol synthesis methods is always present.

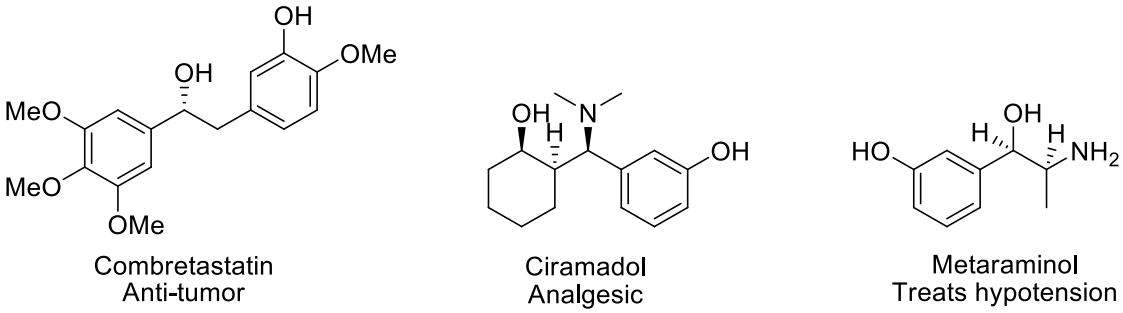
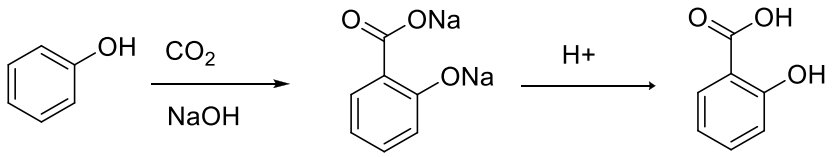


Figure 4. Natural and synthetic phenol compounds

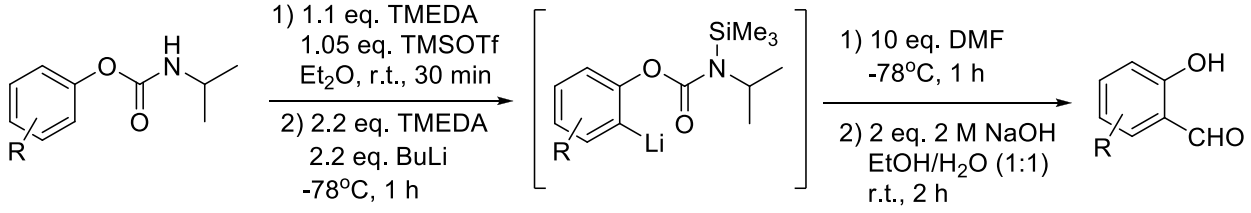
1.5.1 Existing Methods of Phenol Synthesis

One of the most well-established methods for synthesis of substituted phenols is electrophilic aromatic substitution (Scheme 8), using the activating property of phenol to direct substituents onto the nucleophilic *ortho*- and *para*- positions, giving *ortho*-substituted and *para*-substituted phenols respectively. This method has a long history,[50] but is unsuitable for synthesizing *meta*-substituted phenols, since the directing ability of the unshared pair of electrons on –OH does not extend to the *meta*- position.



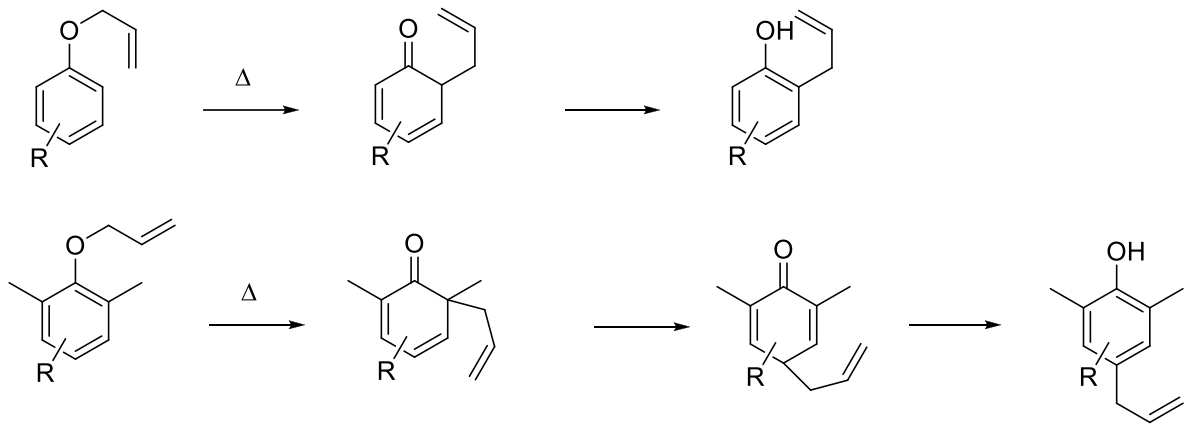
Scheme 8. Example of electrophilic aromatic substitution

Alternatively, directed *ortho*-metallation is a method that uses an O or N based directing group on phenol to direct substituents onto the ring, but requires extra steps for the installation and removal of the directing group, impacting its atom economy (Scheme 9).[51,52] It also has limited regioselectivity, since the *meta*- position is generally too distant from the phenol group to be affected by directing groups, although in some cases, *meta*-C-H functionalizations can be achieved with large, specifically designed templates.[53]

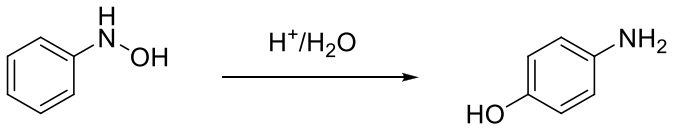


Scheme 9. Example of directed *ortho*-metallation

Metal-free phenol synthesis methods are also available. For example, the Claisen rearrangement of allyl phenyl ethers gives either *ortho*-substituted phenols, or *para*-substituted phenols if the *ortho*- positions are occupied (Scheme 10),[54] while the Bamberger rearrangement produces 4-animophenols from *N*-phenylhydroxylanimes under acidic conditions (Scheme 11).[55]



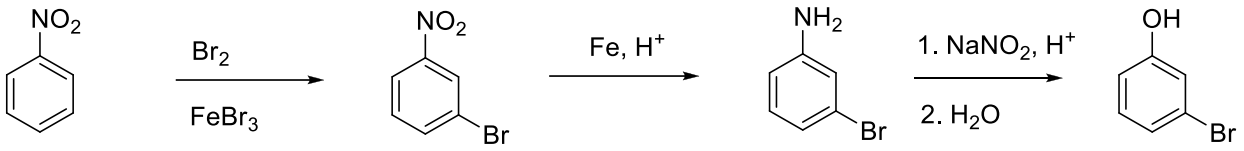
Scheme 10. Claisen rearrangement of allyl phenyl ethers



Scheme 11. Bamberger rearrangement of *N*-phenylhydroxylamines

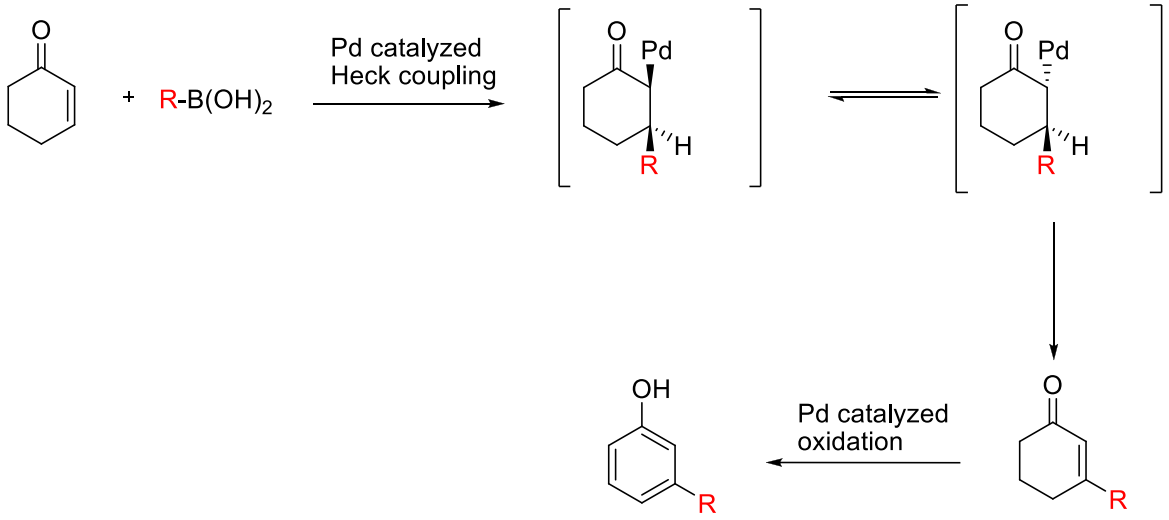
A pattern emerges when examining these methods of phenol synthesis: *meta*-substituted phenols are more difficult to synthesize than their *ortho*- and *para*- substituted analogues. One straightforward way to generate *meta*-substituted phenols is the Suzuki-Miyaura cross-coupling of a *meta*-substituted halophenol with a boronic acid, a mild one-step process.[56] However, this is only a partial solution, as although *meta*-substituted halophenols are commercially available and easily made from nitrobenzene (Scheme 12),[57] *meta*-substituted halophenols featuring a carbon substituent on the *ortho*-position between the hydroxyl group and the *meta*-substituent are much more rare and expensive,

restricting the production of *ortho-, meta*-disubstituted phenols. In fact, a recent Scifinder search yielded only a few examples relevant to Suzuki-Miyaura cross-coupling reactions of *ortho*-substituted, *meta*-halogenated phenols.



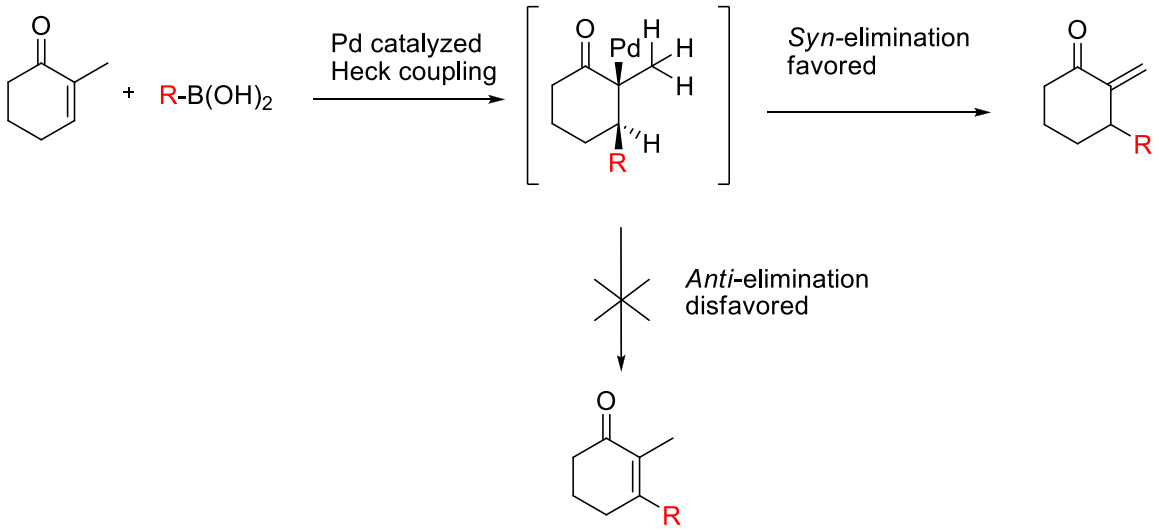
Scheme 12. Inexpensive production of *meta*-substituted halophenol

Recently, Stahl and coworkers developed the aerobic oxidative Heck coupling between cyclohexenone and boronic acid, followed by aerobic oxidation in the same pot, which allowed *meta*-substituted phenols to be synthesized from cyclohexenone in two steps, with DMSO as the solvent (Scheme 13a).[58] DMSO does not appear to participate in the redox chemistry of Pd-catalyzed oxidative transformations,[59] however, so its role appears to be associated with its Pd-coordination ability.



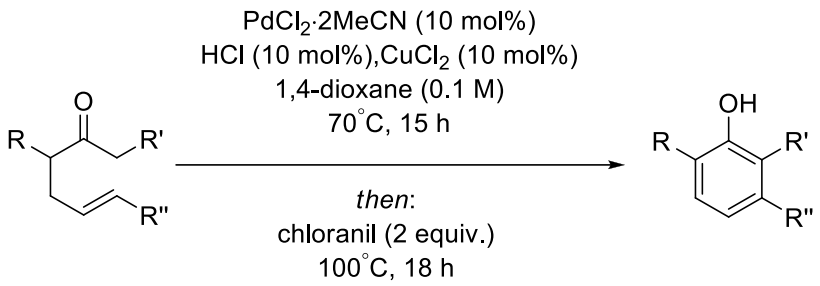
Scheme 13a. Generalized one-pot synthesis of *meta*-substituted phenols via oxidative Heck coupling and aerobic oxidation

The same problem persists, however, as this process still does not produce phenols substituted at both *ortho*- and *meta*- positions, most likely because introducing alkyl substituents on cyclohexenone would cause exocyclic *syn*-β-hydride elimination in the Heck coupling catalytic cycle to outcompete the endocyclic *anti*-β-hydride elimination that would likely need to isomerize first (Scheme 13b).



Scheme 13b. Oxidative Heck coupling with *ortho*-substituents

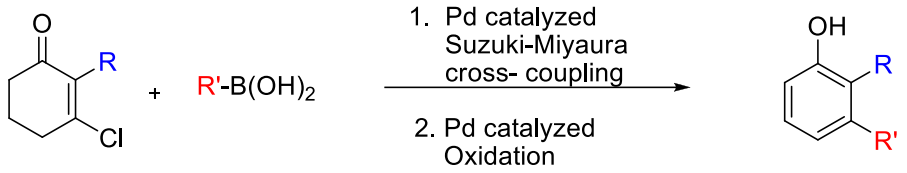
We have been interested in the problem of *meta*-substituted phenol synthesis before. Based on the idea of palladium catalyzing two reaction steps in one pot, we envisioned a scenario where γ, δ-unsaturated ketones are cyclized into cyclohexanones and then oxidized into phenol.[60] Under acidic conditions and with a Cu co-catalyst, we succeeded in producing substituted phenols after two steps (Scheme 14). The phenols with aryl groups at the *ortho*- position were produced in high yields, while the phenols with alkyl or hydrogen groups at the *ortho*- position were produced in significantly lower yields. We intend to address this synthetic gap and find a generalized, reliable pathway of synthesizing *meta*-substituted phenols, especially *ortho-, meta*-disubstituted phenols.



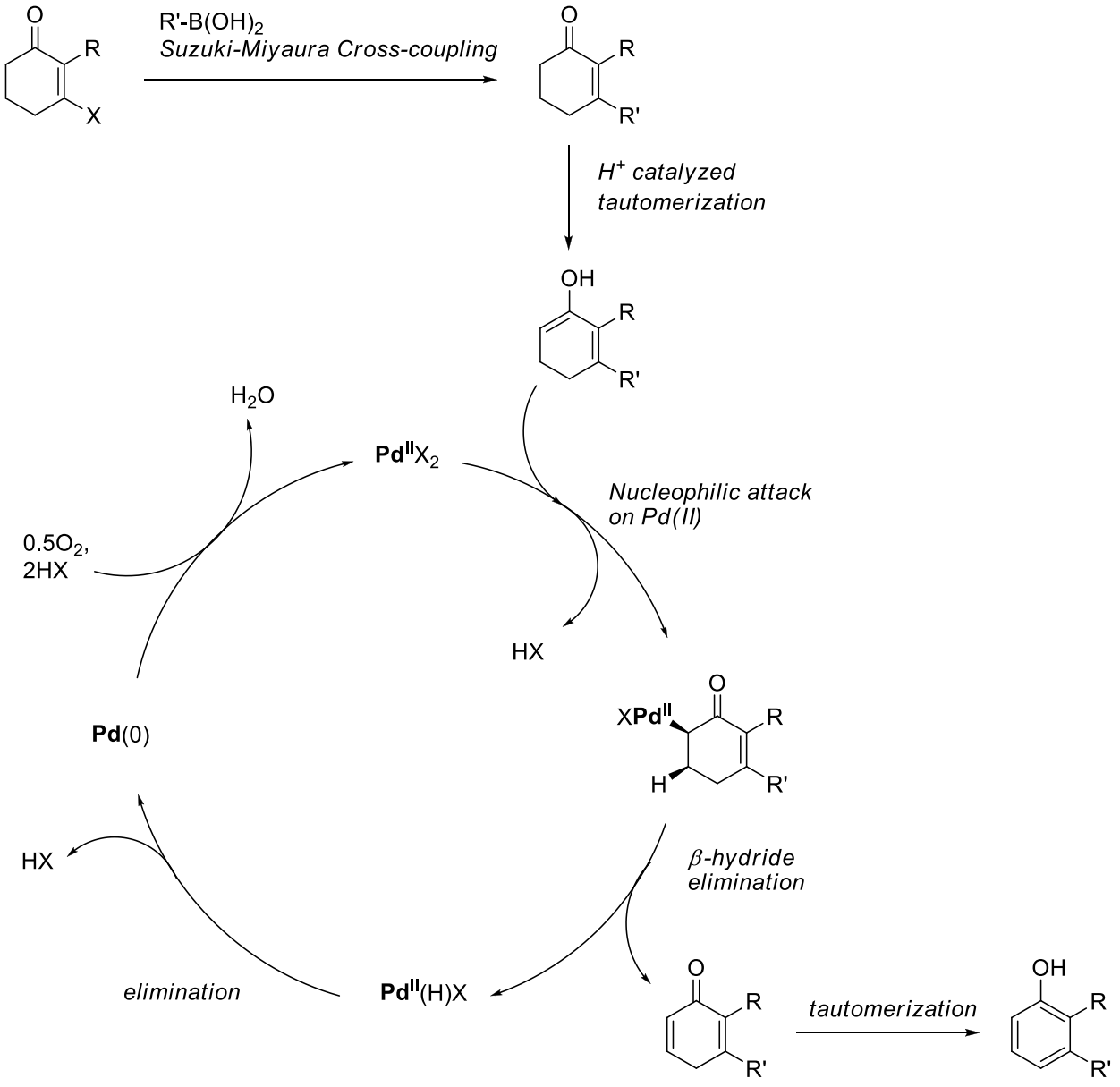
Scheme 14. Two-step synthesis of phenols from γ, δ-unsaturated ketones

1.6 Plan of Study

Our aim is to develop a general synthesis strategy for *meta*-substituted phenols, including *meta*- and *ortho*-disubstituted phenols, that can tolerate a variety of substituents. We will begin by subjecting β-chlorocyclohexenone to the Suzuki-Miyaura cross-coupling reaction to generate β-substituted cyclohexenones. The Suzuki-Miyaura cross-coupling reaction can accommodate alkyl substituents on the β-chlorocyclohexenone without causing β-hydride elimination side reactions, since any alkyl substituent would not interact with Pd during the catalytic cycle. Then, we will subject the β-substituted cyclohexenones to aerobic oxidation, leading to the corresponding phenol, with any existing substituents unaffected (Scheme 15a). Our strategy is to first identify the best conditions and reaction variables for the Suzuki-Miyaura cross coupling reaction, generate the substituted cyclohexenone intermediate, then oxidize the cyclohexenone in the same pot to arrive at *meta*-substituted phenols. A plausible mechanism for the aerobic oxidation of the cyclohexenone intermediate is given below (Scheme 15b).



Scheme 15a. One-Pot synthesis of *meta*-substituted phenols via Suzuki-Miyaura coupling and oerobic oxidation



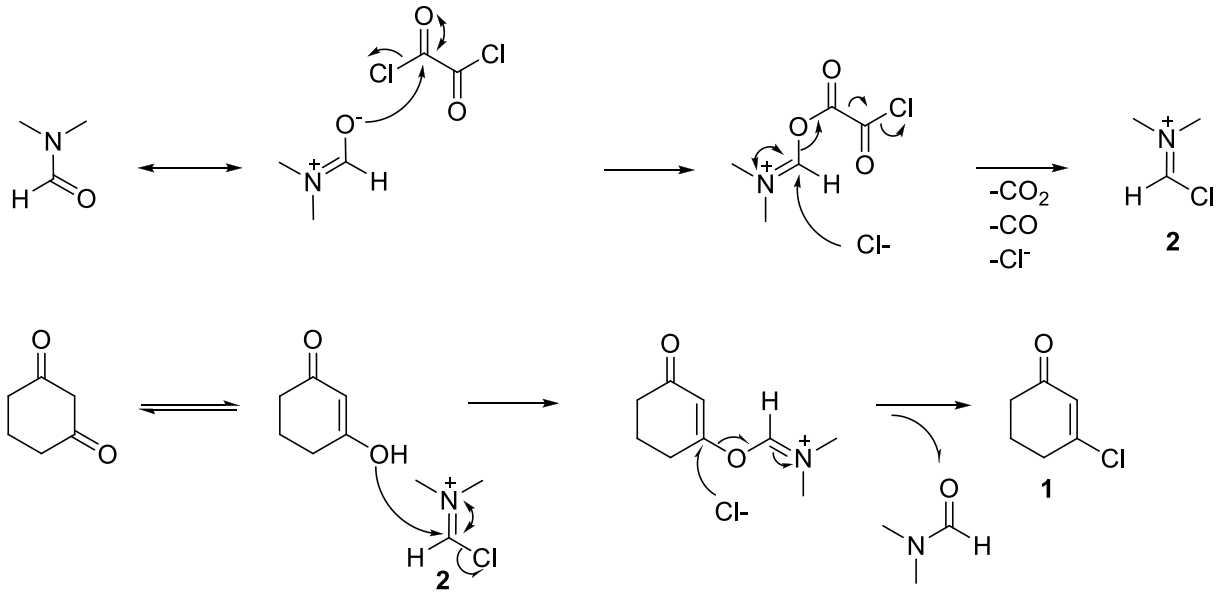
Scheme 15b. Proposed mechanism for the Pd-catalyzed aerobic oxidation

The large variety of commercially available boronic acids and boronate esters will be used to demonstrate the scope of this transformation. As well, the various β–chlorocyclohexenones that are readily prepared from low-cost materials will be used to synthesize the polysubstituted phenols.

Chapter 2: Results and Discussion

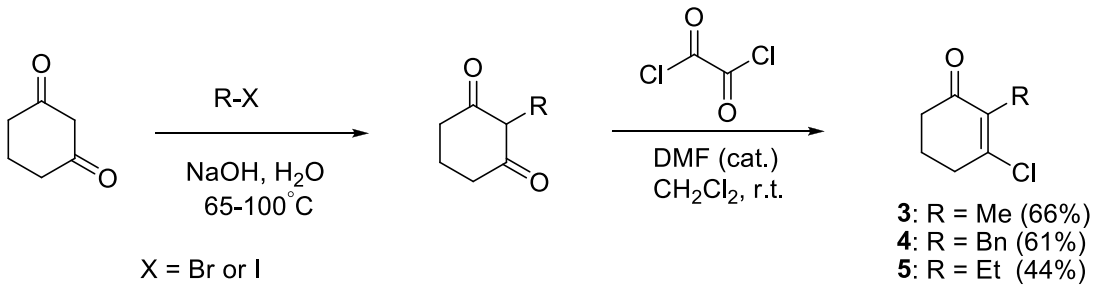
2.1 Substrate Preparation:

We chose our model substrate β-chlorocyclohexenone **1** for its ease of production from low-cost starting materials.[61] **1** was prepared from the commercially available 1,3-cyclohexanedione using oxalyl chloride and a catalytic amount of DMF (Scheme 16), involving the conversion of DMF to the imidoyl chloride derivative **2**.



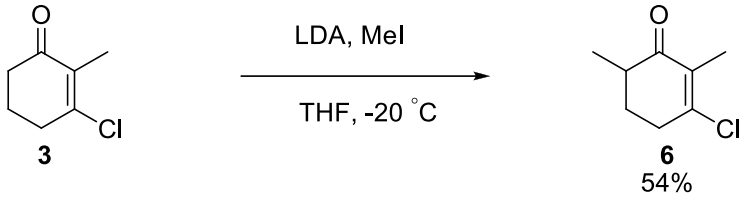
Scheme 16. Synthesis of β-chlorocyclohexenone **1**

Generating the mono-substituted β-chlorocyclohexenones **3-5** substrate requires an additional step of enolate alkylation of 1,3-cyclohexanedione using the appropriate alkyl or benzyl halide and sodium hydroxide (Scheme 17).[62]



Scheme 17. Synthesis of monosubstituted β-chlorocyclohexenones **3-5**

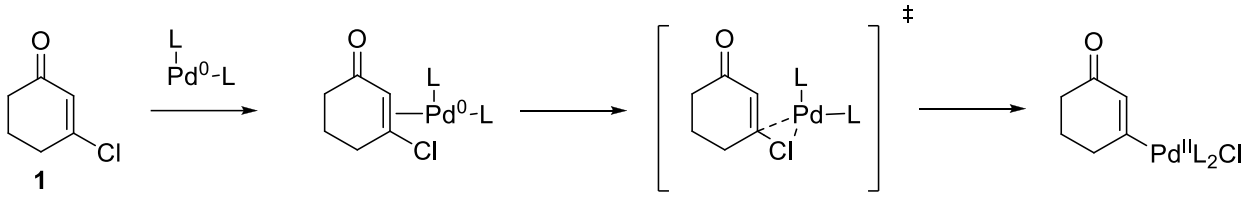
The preparation of the disubstituted β-chlorocyclohexenone **6** substrate required the enolate alkylation of **3** using lithium diisopropyl amide (LDA). (Scheme 18).



Scheme 18. Synthesis of disubstituted β-chlorocyclohexenone **6**

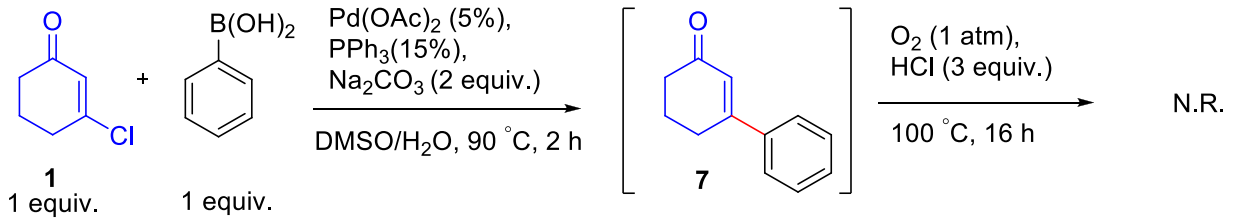
2.2 Proof of Principle Experiment

With our model substrates in hand, we turned our attention towards the Suzuki-Miyaura coupling reaction to generate the substituted α,β-unsaturated ketone intermediate. We reasoned that, although oxidative addition is more difficult with strong C-Cl bonds compared to weaker C-Br and C-I bonds, the vinyligous acid chloride **1** would be ideal for oxidative addition reactions since it contains an electron poor vinyl chloride (Scheme 19).



Scheme 19. Oxidative addition between Pd(0) and substrate **1**

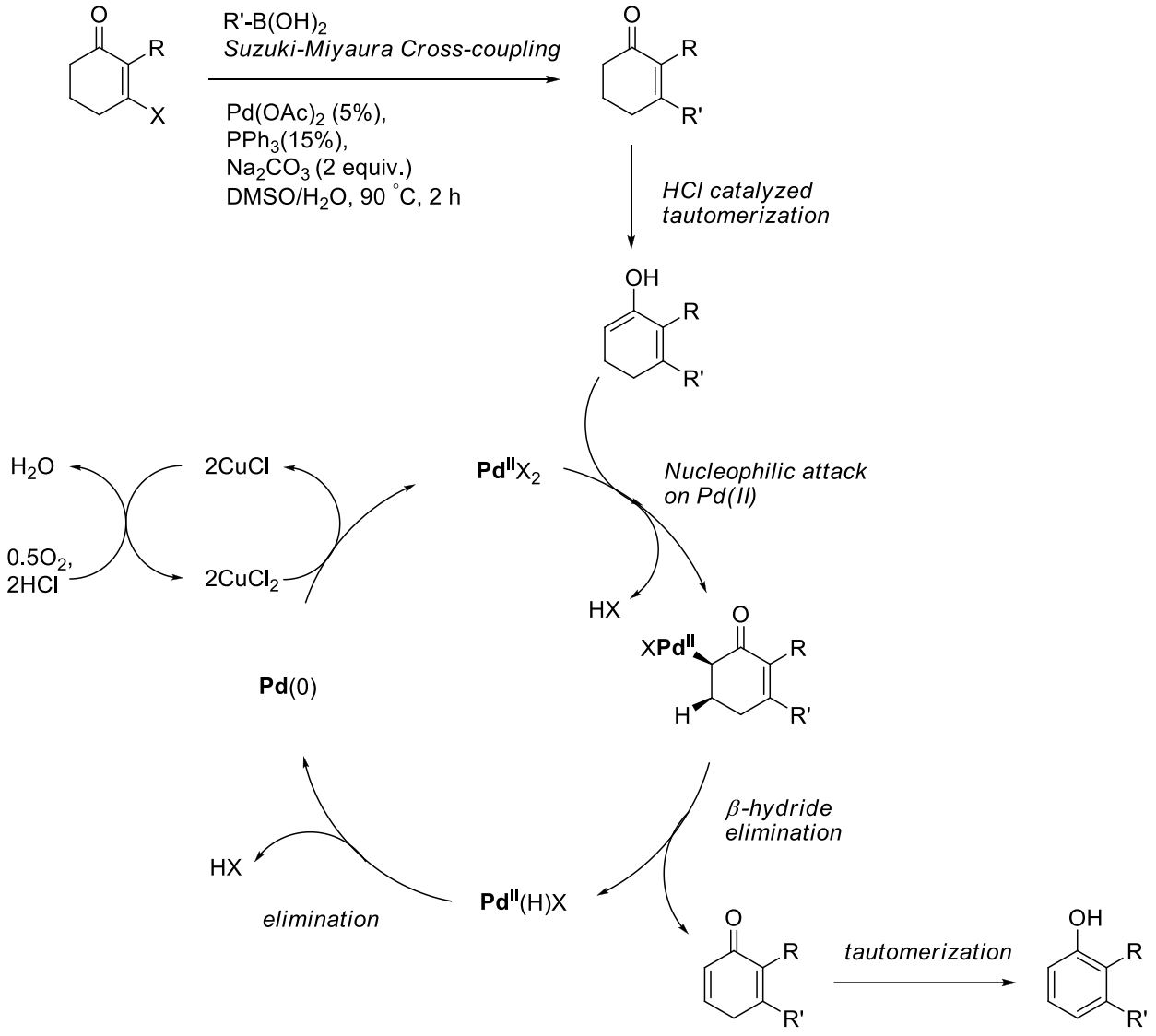
We conducted our initial experiment using an 1:1 ratio of β-chlorocyclohexenone and phenylboronic acid, and a catalytic system of $Pd(OAc)_2$ and PPh_3, and two equivalents of Na_2CO_3 as base. We chose to use O_2 or H_2O_2 as oxidizing reagents for their low cost and high atom efficiency. The Suzuki-Miyaura cross-coupling reaction proceeded smoothly in DMSO, so after confirming that all of the starting material **1** was converted into ketone **7**, we attempted aerobic oxidation using an oxygen balloon and a 4M solution of HCl in dioxane (Scheme 20), as the catalytic cycle of Pd-catalyzed aerobic oxidation generally requires H^+ to re-oxidize Pd, a process that leaves H_2O as a by-product.[58,60] However, after 16 hours of reaction, no phenol product was detected.



Scheme 20. Attempted synthesis of *meta*-phenylphenol from **1**

We then looked for ways to help facilitate the aerobic oxidation step of our reaction. We suspected that in our original proposed mechanism (Scheme 15b), Pd(0) was not being re-oxidized by O_2 and H^+. Recalling that Cu^{II} is an effective electron transfer agent between O_2 and Pd(0),[60] we decided to use $CuCl_2$ as an oxidation co-catalyst. With this

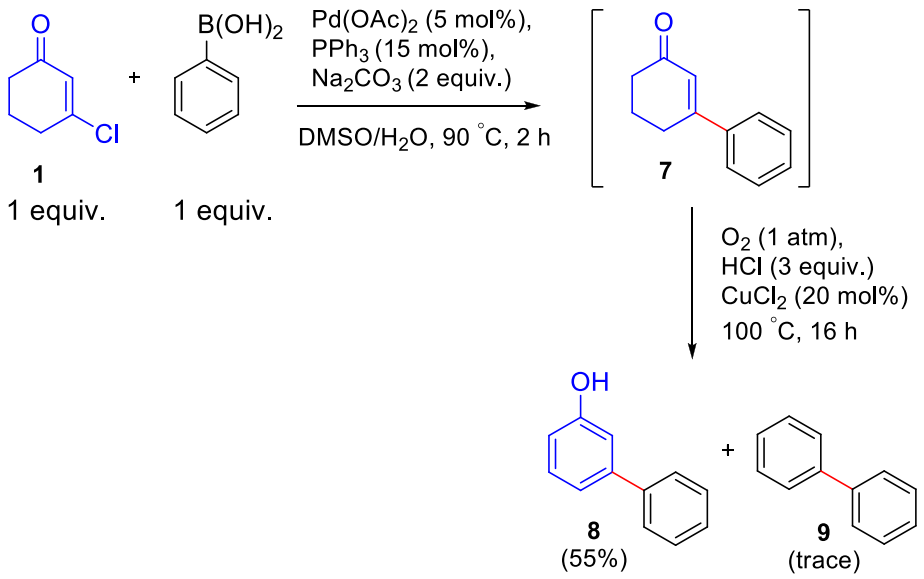
change, we propose a new, modified reaction mechanism for the aerobic oxidation step of our reaction as below (Scheme 21).



Scheme 21. Proposed mechanism for Pd-catalyzed aerobic oxidation, modified

When we added a catalytic amount of $CuCl_2$ and allowed the oxidation to progress overnight, we succeeded in producing 3-phenylphenol **8** in moderate yield, in addition to

trace (<5%) amounts of biphenyl **9** (Scheme 22). We chose to use this catalyst system for future work.

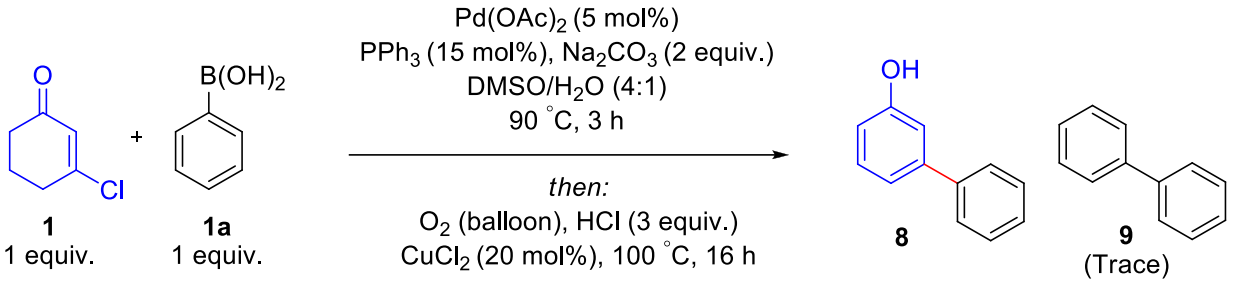


Scheme 22. Synthesis of *meta*-phenylphenol **8** from **1** using $CuCl_2$ co-catalyst

2.3 Optimization of Reaction Conditions

We then proceeded to optimize conditions for our process by employing a variety of common solvents, ligands, and bases for cross-coupling reactions (Table 2). We observed that although many different solvents are compatible with the Suzuki-Miyaura cross-coupling reaction, only DMSO was compatible with the subsequent aerobic oxidation. (Table 2, entries 1-4**)**. In a control reaction, we confirmed that acid was required for the oxidation reaction to occur (Table 2, entry 5). Pyridine-based ligands have often been used as ligands for aerobic oxidation,[63] but they proved ineffective here (Table 2, entry 6**)**, possibly due to their protonation in the acidic environment. Furthermore, H_2O_2 was ineffective as a terminal oxidant, performing significantly worse than O_2 (Table 2, entry 7**)**. In addition, replacing Na_2CO_3 with the more soluble Cs_2CO_3 resulted in an increase in yield (Table 2, entry 8**)**.[64]

Table 2. Optimization of *m*-phenylphenol synthesis in a one-pot Pd-catalyzed Suzuki-Miyaura cross-coupling and oxidation

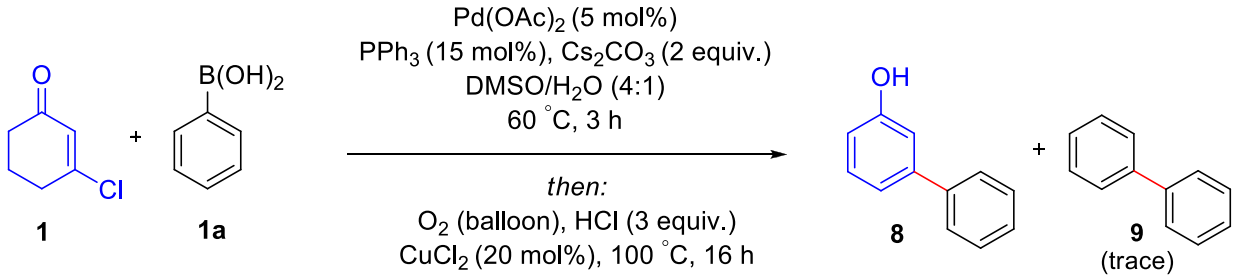


Entry	Variations from above conditions	Yield of 8
1	PhMe/EtOH/H_2O instead of DMSO/H_2O	0%
2	PhMe/DMSO/H_2O instead of DMSO/H_2O	20%
3	DMAc/DMSO/H_2O instead of DMSO/H_2O	26%
4	DMF/DMSO/H_2O instead of DMSO/H_2O	20%
5	no HCl	0%
6	20 mol% 2-OMe-pyridine	53%
7	500 mol% H_2O_2 instead of O_2	<10%
8	**Cs_2CO_3 instead of Na_2CO_3**	**64%**

During the course of our work, we noticed that β-chlorocyclohexenone slowly decomposed in storage at 0 °C, and it seemed reasonable that decomposition likely occurs faster at higher temperature. Therefore, we used it in slight excess, and observed a corresponding yield increase for **8** (table 3). The trace (<5%) amount of biphenyl side product **9** was likely the results of homocoupling of phenylboronic acid, which suggested that a slight excess of phenylboronic acid should be used. We tested these separate scenarios, and found consistently greater yield, relative to the appropriate limiting reagent, when β-chlorocyclohexenone was used in excess (Table 3, entries 2-5**)**, suggesting the effect of substrate decomposition was more pronounced. Out of concern about the decomposition of β-chlorocyclohexenone, we lowered the temperature of our cross-coupling reaction to 60 ˚C. Lower reactions temperatures than 60 ˚C caused incomplete conversion for cross-coupling. Finally, in a brief screening of Pd^{2+} sources, $Pd(MeCN)_4(BF_4)_2$ was found to produce the highest yield of product when compared to

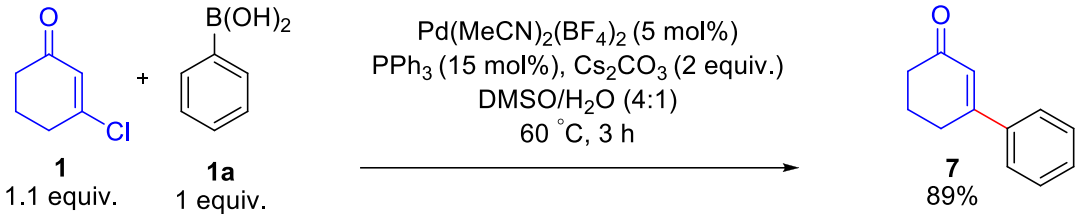
$Pd(OAc)_2$ and $PdCl_2$ (Table 3, entries 4-6**)**, but due to cost concerns, part of the study was conducted using $Pd(OAc)_2$. These measures resulted in a clean synthesis of *meta*-phenylphenol in an isolated yield of 88% (Table 3**,** entry 5**)**. We were concerned about the possibility of over-oxidation of the phenol to either quinones or hydroquinones, but these reactions require different conditions and oxidants,[65,66] and we report that no such over-oxidation was detected.

Table 3. Further optimization of *m*-phenol synthesis from one-pot Pd-catalyzed Suzuki-Miyaura coupling and oxidation



Entry	Variations from above conditions	Yield of 8
1	none	64%
2	10 mol% excess **1a**	75%
3	10 mol% excess **1**	83%
4	10 mol% excess **1a,** $Pd(MeCN)_4(BF_4)_2$ instead of $Pd(OAc)_2$	79%
5	**10 mol% excess 1, $Pd(MeCN)_4(BF_4)_2$ instead of $Pd(OAc)_2$**	**88%**
6	10 mol% excess **1a,** $PdCl_2$ instead of $Pd(OAc)_2$	73%

We then moved to find ways to optimize the aerobic oxidation step of our process. In order to assess the yield of Pd-catalyzed oxidation of α,β-unsaturated ketone **7** to phenol **8**, we conducted a separate parallel reaction to our most optimized process (Table 3, entry 5), that was stopped after the cross-coupling was complete, allowing us to collect the unsaturated ketone **7** in 89% yield (Scheme 23), suggesting that the overall yield of reaction is largely determined ·by the cross-coupling step, while the aerobic oxidation reaction was virtually quantitative, at least for this substrate.

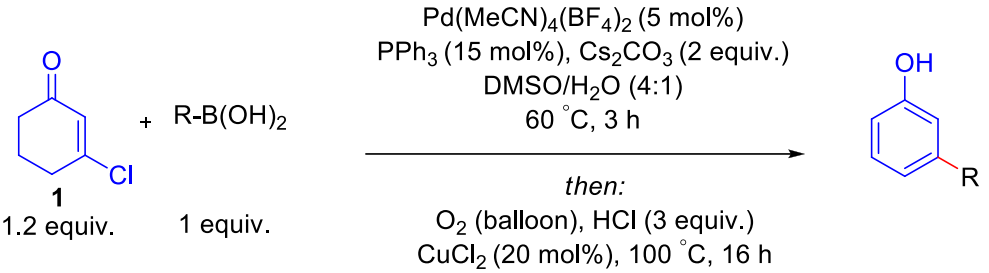


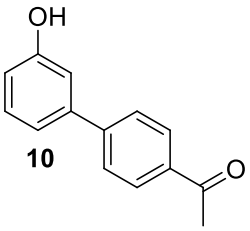
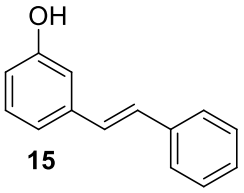
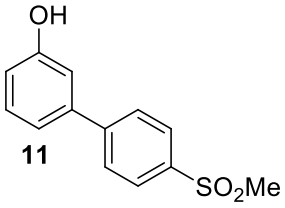
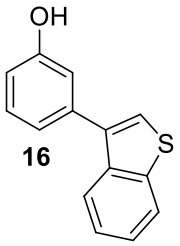
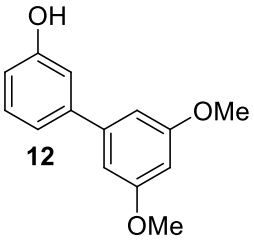
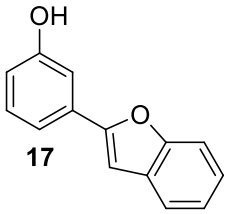
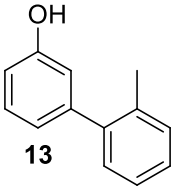
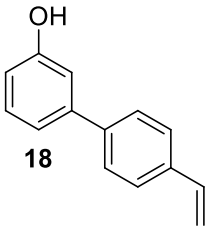
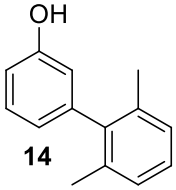
Scheme 23. Optimized Suzuki-Miyaura cross-coupling reaction

2.4 Substrate Scope

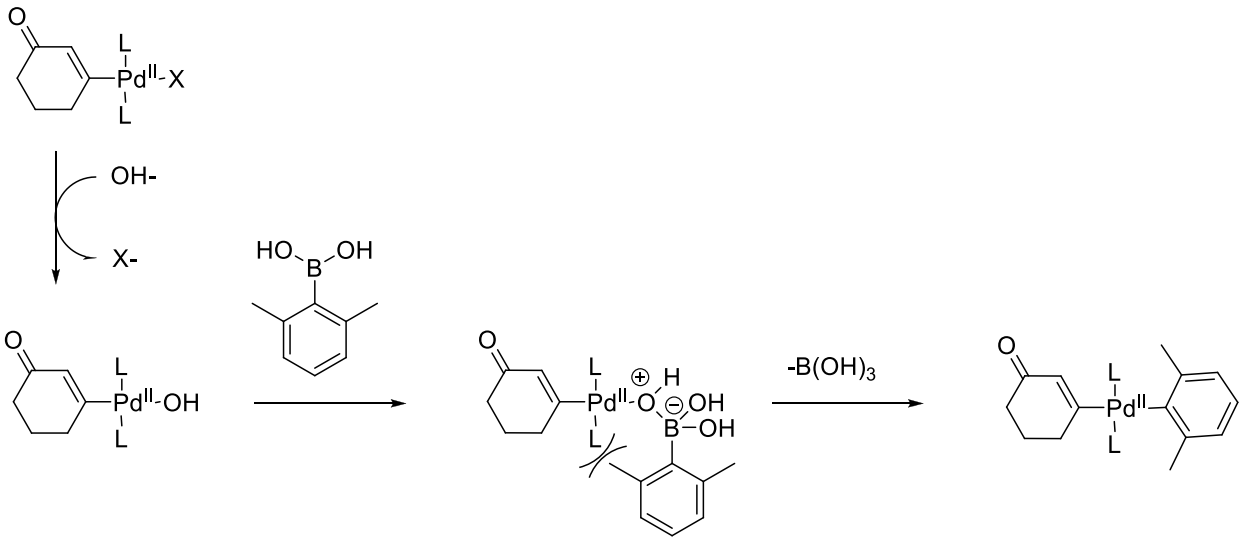
We then applied these optimized conditions to the Suzuki-Miyaura cross coupling reaction between β-chlorocyclohexenone and a sampling of boronic acids, and then their subsequent aerobic oxidation, in order to explore the scope of different substituted phenols (Table 4). Both electron-withdrawing and electron-donating substituents on the phenylboronic acid substrate produced high yields of phenols (Table 4, entries 1-3). Adding one *ortho*-substituent on the boronic acid did not significantly affect the yield (Table 4, entry 4). On the other hand, using phenylboronic acids hindered at both *ortho*-positions lowered the yield dramatically (Table 4, entries 5), suggesting high steric sensitivity of the reaction. A reasonable explanation for this effect lies in the transmetallation step of the Suzuki-Miyaura cross-coupling reaction (Scheme 24),[19-21] where there is significant steric clash between the *ortho*-substituents on the phenylboronic acid and the Pd metal center. A modest drop in product yield was also observed when *trans*-2-phenylvinylboronic acid (Table 4, entry 6) and heterocyclic boronic acids (Table 4, entries 7-8) were employed as substrates. One notable anomaly to the trend is the reaction using 4-vinylphenylboronic acid (Table 4, entry 9), which produced significantly poorer yield despite lack of steric hindrance, likely due to the vinyl functional group enabling various side reactions. In addition, we conducted several parallel Suzuki-Miyaura cross-coupling reactions to collect unsaturated ketones with yields similar to their oxidized counterparts (Table 4, in *italics*), providing further evidence that the Suzuki-Miyaura cross-coupling reaction was the factor that determined the final yield.

Table 4. Synthesis of various meta-substituted phenols from one-pot Pd-catalyzed Suzuki-Miyaura coupling and oxidation



Entry	Phenol	Yield of phenol (Yield *of ketone* in parallel reaction)	Entry	Phenol	Yield of phenol (Yield of *ketone* in parallel reaction)
1	 **10**	80% *(80%)*	6	 **15**	65% *(69%)*
2	 **11**	75% *(79%)*	7	 **16**	63% *(68%)*
3	 **12**	79% *(79%)*	8	 **17**	57%[a]
4	 **13**	81%	9	 **18**	40%[a]
5	 **14**	50%[a]			

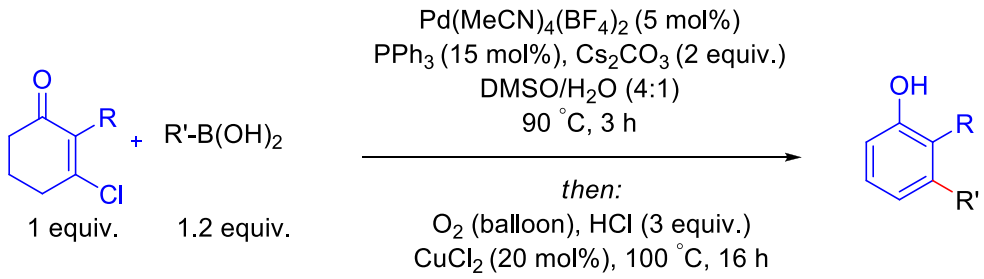
a) $Pd(OAc)_2$ used instead of $Pd(MeCN)_4(BF_4)_2$.

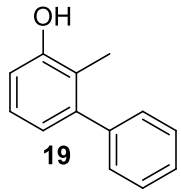
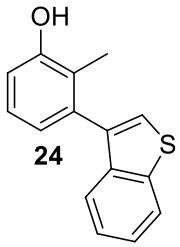
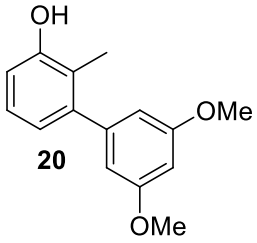
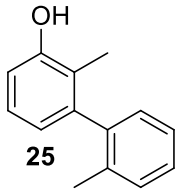
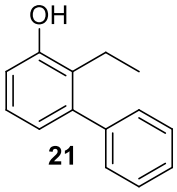
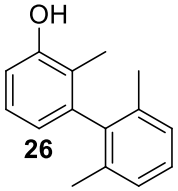
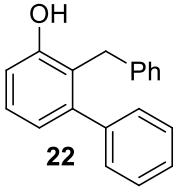
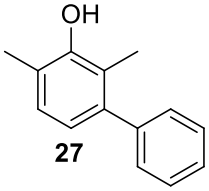
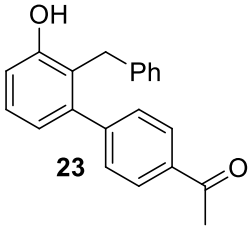


Scheme 24. The transmetallation step of the Suzuki-Miyaura cross-coupling reaction using hindered phenylboronic acids

We further explored the scope of our reaction with the more challenging synthesis of polysubstituted phenols, which required the enolate alkylation of β-chlorocyclohexenone (Schemes 17,18). These α-substituted β-chlorocyclohexenones did not decompose at high temperatures as their unsubstituted counterparts did, allowing us to use them as the limiting reagent. In each case, the phenols with *ortho*-substituents were produced in lower yields than those without (Table 5, 1-6). This is likely due to steric hindrance affecting the cross-coupling reaction during both the oxidative addition step, as well as the transmetallation step.[15,19-21] In cases where both coupling partners were hindered, no product was formed (Table 5, entries 7-8), reflecting on the strong steric sensitivity of these reactions. However, the yield of the di-*ortho*-substituted phenol **27** (Table 5, entry 9) was close to that of its mono-*ortho*-substituted analogue **19**, suggesting that the position of the second *ortho*-substituents generated little additional steric hindrance.

Table 5. Synthesis of various polysubstituted phenols from one-pot Pd-catalyzed Suzuki-Miyaura coupling and oxidation.

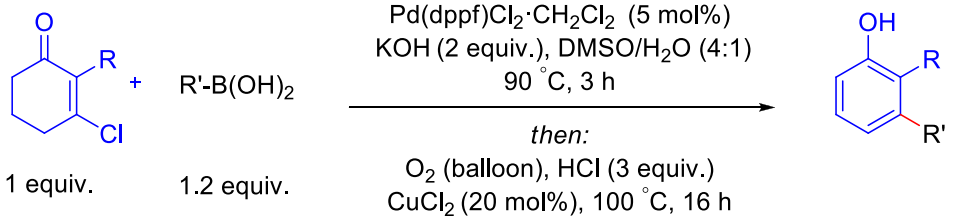


Entry	Phenol	Yield	Entry	Phenol	Yield
1	 **19**	70%	6	 **24**	39%[a]
2	 **20**	54%	7	 **25**	0%[a]
3	 **21**	48%[a]	8	 **26**	0%[a]
4	 **22**	66%[a]	9	 **27**	66%[a]
5	 **23**	62%[a]			

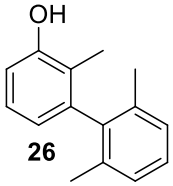
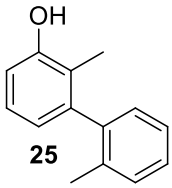
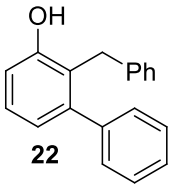
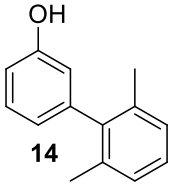
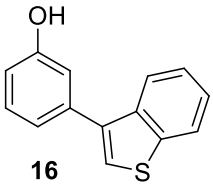
a) $Pd(OAc)_2$ used instead of $Pd(MeCN)_4(BF_4)_2$.

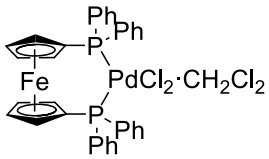
In order to synthesize the congested phenols **25** and **26**, we investigated the use of a select sample of ligands on Pd that have previously been shown to promote sterically hindered Suzuki-Miyaura cross coupling reactions.[31,32] Two of these ligands, SPhos and DPEPhos, did not satisfactorily facilitate coupling between α-substituted β-chlorocyclohexenone and hindered arylboronic acids (Table 6, entries 2-3), but the use of a 5% catalyst loading of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, along with KOH as base to replace Cs_2CO_3, proved successful and ultimately provided the hindered phenols in moderate yield after oxidation (Table 6, entries 4-5). This lead us to believe that we had found a better overall catalyst system, but the success of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ was not replicated in cross-coupling of other, less hindered substrates, where they performed worse than the standard Pd^{2+}/triphenylphosphine catalyst system (Table 6, entries 6-8).

Table 6. Modified reaction conditions for the synthesis of sterically hindered phenols



1 equiv. 1.2 equiv.

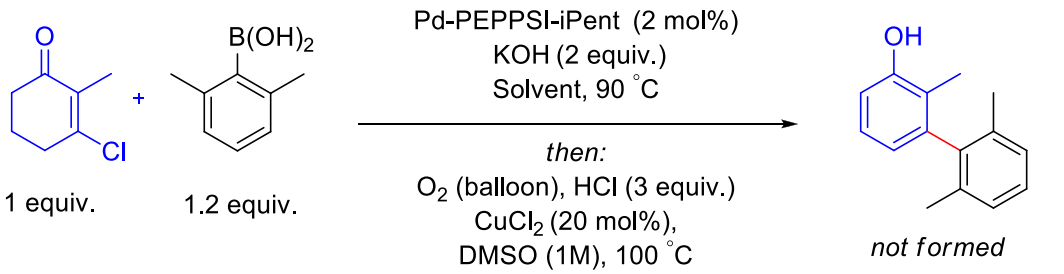
Entry	Variations from above conditions	Phenol	Yield
1	5% $Pd(OAc)_2$ and 15% PPh_3 instead of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$	 **26**	21%
2	5% $Pd(OAc)_2$ and 15% DPEPhos instead of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$	**26**	0%
3	5% $Pd(OAc)_2$ and 15% SPhos instead of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$	**26**	<10%
4	none	**26**	52%
5	none	 **25**	57%
6	none	 **22**	29%
7	none	 **14**	28%
8	none	 **16**	48%



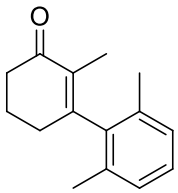
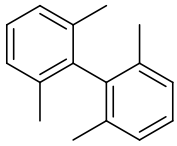
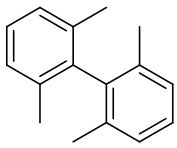
$Pd(dppf)Cl_2 \cdot CH_2Cl_2$

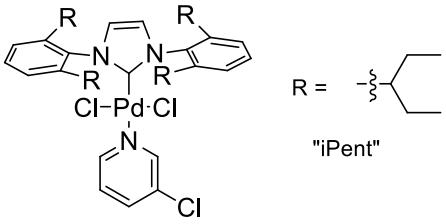
We were also interested in the potential of PEPPSI (Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation) catalysts, which have been shown to effectively catalyze a variety of cross-coupling reactions, especially between sterically hindered reagents.[39] Unfortunately, using a Pd-PEPPSI-iPent catalyst system, our cross-coupling reaction only proceeded under some circumstances, and no subsequent aerobic oxidation occurred (Table 7, entries 1-3). This departure from previous trials, where the aerobic oxidation step was trivial and near quantitative, was likely due to the $\sigma-$ donating effect of the NHC (N-heterocyclic carbene) ligand, decreasing the electrophilicity of the metal center and preventing β-hydride elimination.

Table 7. The use of PEPPSI catalysts in the Suzuki-Miyaura cross-coupling reaction and subsequent aerobic oxidation



1 equiv. 1.2 equiv. *not formed*

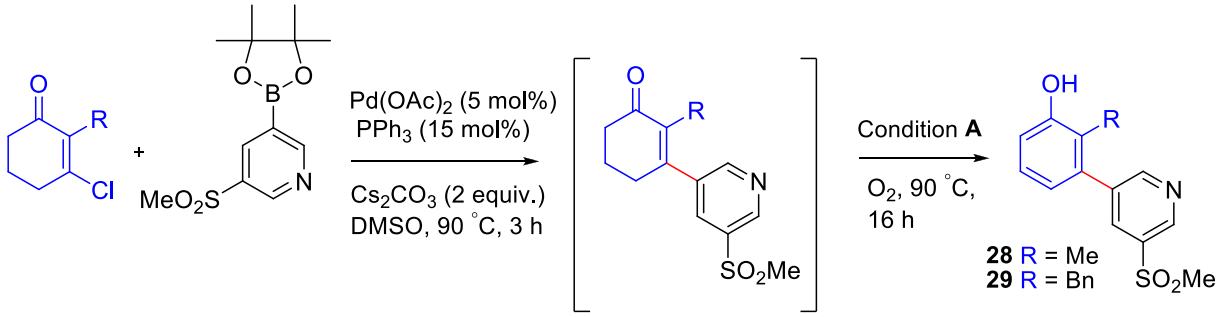
Entry	Solvent	Final product	Note
1	1,4-dioxane		Cross-coupling successful, but failed to oxidize
2	DMSO		Homo-coupling predominant, no cross-coupling
3	H_2O		Homo-coupling predominant, no cross-coupling



Finally, we turned our attention towards the synthesis of pyridine-substituted phenols. We opted to use pinacol boronic esters that were immediately available to us, instead of

boronic acids. Although the expected α,β-unsaturated ketone was generated from substrate **3** *via* Suzuki-Miyaura cross-coupling with little difficulty, the previously optimized aerobic oxidation conditions yielded no trace of the expected pyridine-substituted phenol **28**. (Table 8, entry 1). Replacing the Cu source or the acid source had no effect (Table 8, entries 2-4).

Table 8. The synthesis of pyridine-substituted phenols

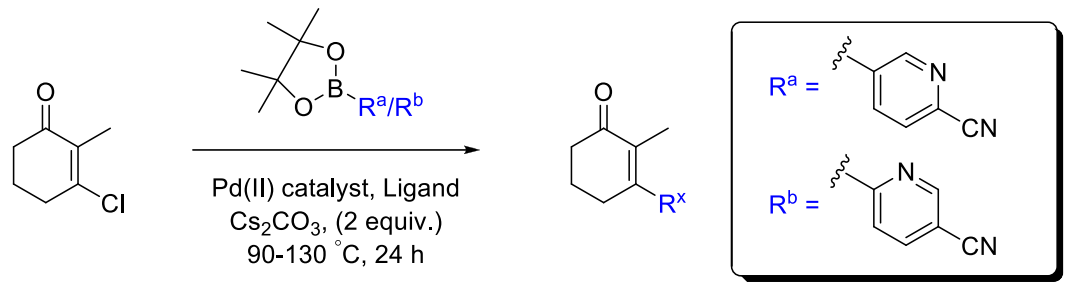


Entry	Condition A	Product	Yield of Phenol
1	HCl (3 equiv.) $CuCl_2$ (20 mol%)	**28**	0%
2	HCl (3 equiv.) $Cu(OAc)_2$ (20 mol%)	**28**	0%
3	CF_3COOH (3 equiv.) $CuCl_2$ (20 mol%)	**28**	0%
4	CF_3COOH (3 equiv.) $Cu(OAc)_2$ (20 mol%)	**28**	0%
5	HCl (4 equiv.) $CuCl_2$ (20 mol%)	**28**	0%
6	HCl (12 equiv.) $CuCl_2$ (20 mol%)	**28**	51%
7	HCl (12 equiv.) $CuCl_2$ (20 mol%)	**29**	52%

We reasoned that the aerobic oxidation conditions for the synthesis of benzothiophene-substituted and benzofuran-substituted phenols could not be directly replicated with pyridine-substituted phenols due to the low pKa of pyridinium (~5). If acid-catalyzed tautomerization of the ketone is required to begin oxidation, the acidic environment may not have been strong enough to protonate the ketone in the presence of the pyridine group. Increasing the amount of HCl from 3 to 4 mol equivalents (Table 8, entry 5) did not change the reaction outcome, but using 12 equivalents of HCl produced phenol **28** in moderate yield (Table 8, entry 6). Pyridine-substituted phenol **29** was produced in a similar manner (Table 8, entry 7).

Unfortunately, the scope of pyridine-substituted phenol synthesis is limited. The Suzuki-Miyaura cross-coupling reaction could not be completed with more electron-deficient pyridyl boronic esters (Tables 9, entries 1-8).

Table 9. Suzuki-Miyaura cross-coupling reaction using electron deficient pyridyl boronic esters



Entry	Pd(II) catalyst, Ligand	R^a/R^b	Solvent	Yield
1	$Pd(OAc)_2$ (5 mol%) PPh_3 (15 mol%)	R^a	DMSO	<20% Incomplete conversion
2	$Pd(OAc)_2$ (5 mol%) SPhos (15 mol%)	R^a	DMSO	0% No reaction
3	$Pd(OAc)_2$ (5 mol%) SPhos (15 mol%)	R^a	DMF	0% No reaction
4	$Pd(dppf)Cl_2.CH_2Cl_2$ (5 mol%) PPh_3 (15 mol%)	R^a	DMSO	0% No reaction
5	$Pd(OAc)_2$ (5 mol%) PPh_3 (15 mol%)	R^b	DMSO	<20% Incomplete conversion
6	$Pd(OAc)_2$ (5 mol%) SPhos (15 mol%)	R^b	DMSO	0% No reaction
7	$Pd(OAc)_2$ (5 mol%) PPh_3 (15 mol%)	R^b	DMF	0% No reaction
8	$Pd(dppf)Cl_2.CH_2Cl_2$ (5 mol%) PPh_3 (15 mol%)	R^b	DMSO	0% No reaction

2.5 Conclusion

We have developed a new method to synthesize *meta*-substituted phenols, especially *meta*- and *ortho*-disubstituted phenols in good to excellent yield from simple and

inexpensive reagents. The palladium source is the catalyst for both the cross-coupling and the oxidation processes, generating the target phenol in one-pot over two catalytic steps. This method solves many of the problems that have plagued previous methods of synthesizing *meta*-substituted phenols, especially *ortho*- and *meta*- disubstituted phenols.

Chapter 3: Experimental

3.1 General Experimental

Reactions were conducted in oven-dried glassware under an atmosphere of argon using freshly distilled solvents unless specified otherwise. Commercial reagents were used as received. Thin-layer chromatography was performed on Merck silica gel 60 F254 plates. Visualisation was carried out using UV light (254 nm) and $(NH_4)_2Ce(NO_3)_6$ solutions. Hexanes (ACS grade), ethyl acetate (ACS grade), and DMSO (ACS grade) were used as received. Flash column chromatography was carried out using Aldrich silica gel (230-400 mesh, 40-63 μ, 60 Å pore size). ^{1}H- and ^{13}C-NMR spectra were recorded on 400 AV, 300 AV, and DRX 600 NMR spectrometer in chloroform-d (99.8% deuterated), Acetone-d_6 (99.8% deuterated), and benzene-d_6 (99.8% deuterated) and using chloroform (7.26 ppm ^{1}H and 77.0 ppm ^{13}C), acetone (28.9 ppm and 206.5 ppm ^{13}C), DMSO (2.54 ppm), and benzene (127.7 ppm ^{13}C) as reference. Chemical shifts (δ) are reported in ppm and multiplicities are indicated by br (broad), s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet). Coupling constants *J* are reported in Hertz (Hz). Infrared (IR) spectra were recorded using Alpha-Platinum ATR Bruker, diamond crystal.

3.2 Experimental Procedures and data

3.2.1 Substrate Preparation.

General Procedure 1. Synthesis of 3-chlorocyclohexenone from 1,3-cycloehexanedione.

In a dry round bottom flask capped with a rubber septum and equipped with a magnetic stir bar was added 1,3-cyclohexanedione (1.0 equiv.) and placed under an argon atmosphere. Freshly distilled DCM was introduced into the flask *via* syringe to prepare a 0.4 M solution at room temperature. While stirring, oxalyl chloride (1.5 equiv.) was added dropwise, followed by catalytic DMF (5 drops). The reaction mixture was stirred overnight at room temperature. Upon completion, the reaction was diluted with brine. The organic layer was separated, and the aqueous layers were extracted with DCM. The combined organic phase was dried over Na_2SO_4, and concentrated *in vacuo* to afford the desired 3-chlorocyclohexenone.

General Procedure 2a. Synthesis of monosubstituted 3-chlorocyclohexenone from 1,3-cycloehexanedione.

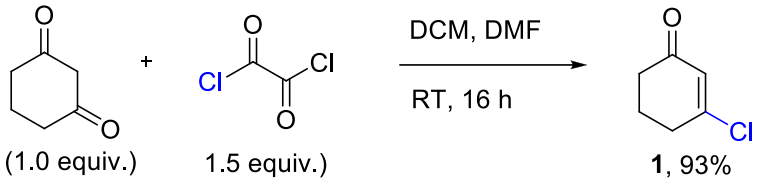
In a dry round bottom flask was dissolved 1,3-cyclohexanedione (1.0 equiv.) in a 5 M solution of NaOH (1.0 equiv.). The vessel was cooled using an ice bath, then charged with the appropriate alkyl/benzyl halide, stirred, and heated under reflux overnight. The precipitated solid was filtered and washed with cold hexane to give crude α–substituted-1,3-cyclohexanedione as a solid. The solid was dried and added to another dry round bottom equipped with a magnetic stir bar, and dissolved in dry DCM to prepare a 0.4 M solution, followed by dropwise addition of oxalyl chloride (1.5 equiv.) then catalytic DMF (5 drops) while stirring. The reaction mixture was stirred overnight at RT, then diluted with brine. The organic layer was separated, and the aqueous layers were extracted with DCM. The combined organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The

crude product was purified by flash column chromatography, eluting with the indicated solvent to afford the desired 3-chlorocyclohexenone.

General Procedure 2b. Synthesis of disubstituted 3-chlorocyclohexenone from monosubstituted 3-chlorocyclohexenone.

In a dry round bottom flask was charged with a 0.5 M solution of diisopropylamine (1.1 equiv.) in THF at -20°C, and then added with n-butyllithium (1.1 equiv.) dropwise. The vessel was cooled to -78°C, and charged with a 2.0 M solution of monosubstituted 3-chlorocyclohexenone acquired from *General Procedure 2* (1.0 equiv.) in THF. After stirring for 30 minutes, a 1.0 M solution of MeI (3.0 equiv.) was added over 5 min. The solution was stirred at -20°C with reaction progress monitored by ^{1}H-NMR analysis. After completion, the reaction was quenched with H_2O, and THF was evaporated. The aqueous phase was extracted twice with EtOAc, and the combined organic phase was dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with the indicated solvent to afford the desired disubstituted 3-chlorocyclohexenone.

Substrate 1: 3-chlorocyclohexenone



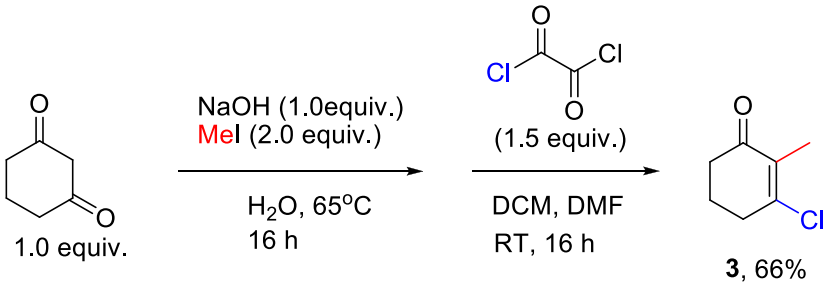
3-chlorocyclohexenone **1** was prepared following *General Procedure 1*, using 1,3-cyclohexanedione (2.0 g, 18 mmol, 1.0 equiv.) and oxalyl chloride (3.4 g, 2.3 mL, 27 mmol, 1.5 equiv.). 3-chlorocyclohexenone **1** (2.2 g, 93 % yield) was produced as an oil and used in the subsequent step without further purification. Data acquired on this material matches that previously reported.[67]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 2 H), 2.70 (t, *J* = 6.3 Hz, 2 H), 2.39 (t, *J* = 6.6 Hz, 2 H), 2.08 (tt, *J* = 6.6, 6.3 Hz, 2 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.9, 158.6, 128.5, 36.3, 33.9, 22.2

IR υ = 2954, 2890, 1675, 1605, 1340, 1289, 1230, 990, 880, 809, 745, 519 cm^{-1}

Substrate 3: 2-methyl-3-chlorocyclohexenone



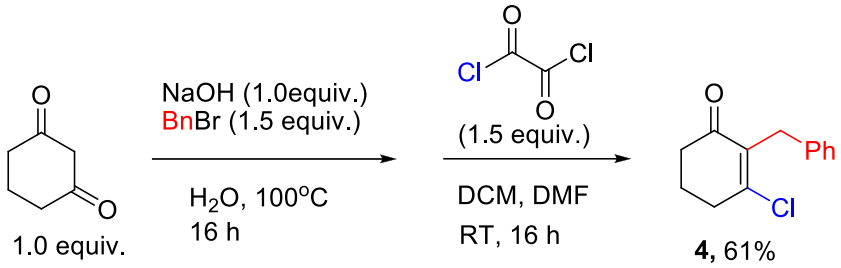
Substrate **3** was prepared following *General Procedure 2a*, using 1,3-cyclohexanedione (2.8 g, 25. mmol) in a 5 M solution of NaOH (5.0 mL), MeI (7.1 g, 3.1 mL, 50 mmol, 2.0 equiv.), and oxalyl chloride (4.9 g, 3.3 mL, 38 mmol, 1.0 equiv.) Purification with column chromatography (Hex 85:15 EtOAc, Rf = 0.4) produced substrate **3** (2.4 g, 66% yield) as an oil. Data acquired on this material matches that previously reported.[68]

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76-2.71 (m, 2 H), 2.45 (t, *J* = 6.6 Hz, 2 H), 2.03 (p, *J* = 6.6 Hz, 2 H), 1.90 (t, *J* = 1.5 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 153.2, 133.5, 36.9, 34.8, 21.8, 12.2

IR υ= 2951, 2871, 1673, 1625, 1338, 1325, 1247, 1039, 985, 902, 544cm^{-1}

Substrate 4: 2-benzyl-3-chlorocyclohexenone



Substrate **4** was prepared following *General Procedure 2a*, using 1,3-cyclohexanedione (2.8 g, 25.0 mmol, 1.0 equiv.) in a 5 M solution of NaOH (5.0 mL), benzyl bromide (6.4g, 4.5 mL, 38 mmol, 1.5 equiv.), and oxalyl chloride (4.9 g, 3.3 mL, 37.5 mmol, 1.0 equiv.) Purification with column chromatography (Hex 9:1 EtOAc, Rf = 0.4) produced substrate **4** (3.4 g, 61% yield) as an oil. Data reported on this material matches that previously reported.[69]

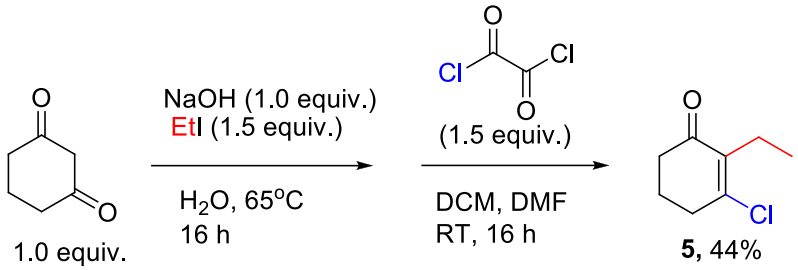
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27-7.15 (m, 5 H), 3.79 (s, 2 H), 2.79 (t, *J* = 6.4 Hz, 2 H), 2.47 (t, *J* = 6.4 Hz, 2 H), 2.04 (p, *J* = 6.4, 2 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.9, 154.4, 138.9, 136.8, 128.7, 128.2, 126.0, 37.1, 35.0, 32.1, 21.8

IR υ = 3028, 2935, 1672, 1617, 1342, 1286, 947, 900, 721, 697, 541 cm^{-1}

HRMS ESI Calculated for $(C_{13}H_{13}ClO)^+$ = 220.0655, found = 220.0651

Substrate 5: 2-ethyl-3-chlorocyclohexenone



Substrate **5** was prepared following *General Procedure 2a*, using 1,3-cyclohexanedione (1.4 g, 13 mmol) in a 5 M solution of NaOH (2.5 mL), ethyl iodide (2.9 g, 1.5 mL, 19 mmol, 1.5 equiv.), and oxalyl chloride (2.4 g, 1.6 mL, 19 mmol, 1.5 equiv.) Purification with column chromatography (Hex 9:1 EtOAc, Rf = 0.4) produced substrate **5** (0.88 g, 44% yield) as an oil.

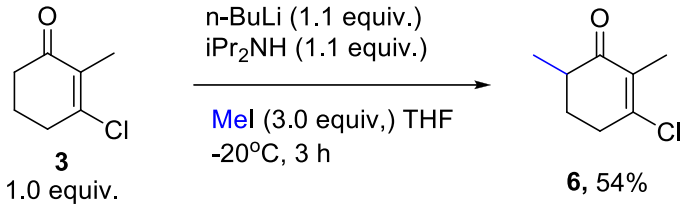
^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.73 (t, *J* = 6.4 Hz, 2 H), 2.46-2.41 (m, 4 H), 2.02 (p, *J* = 6.4 Hz, 2 H), 0.98 (t, *J* = 7.6 Hz, 3 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.0, 152.0, 139.0, 37.2, 34.9, 21.9, 20.0, 12.2

IR υ = 2967, 2936, 2874, 1673, 1619, 1342, 1330, 1254, 1057, 1005, 874, 814, 542 cm^{-1}

HRMS ESI Calculated for $(C_8H_{11}ClO)^+$ = 158.0498, found = 158.0492

Substrate 6: 2,6-dimethyl-3-chlorocyclohexenone



Substrate **6** was prepared following *General Procedure 2b*, using substrate **3** (0.58 g, 4.0 mmol), 1.6 M solution of n-butyllithium in hexane (0.28 g, 2.75 mL, 4.4 mmol), diisopropylamine (0.45 g, 0.62 mL, 4.4 mmol), and MeI (1.7 g, 0.75 mL, 12.0 mmol). Purification with column chromatography (Hex 9:1 EtOAc, Rf = 0.4) produced substrate **6** (0.34 g, 54% yield) as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.84-2.75 (m, 1 H), 2.71-2.65 (m, 1 H), 2.42-2.37 (m, 1 H), 2.10-2.03 (m, 1 H), 1.90 (s, 3 H), 1.82-1.71 (m, 1 H), 1.14 (d, *J* = 7.6 Hz, 3 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.9, 152.0, 132.7, 40.4, 34.0, 29.8, 15.8, 12.6

IR υ = 2977, 2944, 1674, 1619, 1341, 1334, 1034, 995, 876, 855, 540 cm^{-1}

3.2.2 One-pot Synthesis of meta-Substituted Phenols via Palladium-Catalyzed Suzuki-Miyaura Cross-coupling and Oxidation

Three reaction protocols were developed for the one-pot-synthesis of *meta*-substituted phenols from 3-chlorocyclohexenones. Procedure **3A** involved the use of Pd^{2+} salt and PPh_3 as the catalytic system. When this method failed for phenols that were too sterically hindered procedure **3B**, which involved the use of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, was used. A slightly modified reaction protocol **3C**, which also uses Pd^{2+} and PPh_3, was developed for the synthesis of pyridine-substituted phenols.

General Procedure 3A.

To a dry round bottom flask equipped with a magnetic stir bar were added, in order, the appropriate β-chlorocyclohexenone**,** anhydrous DMSO, and the appropriate boronic acid. The reaction mixture was purged with Ar for 30 minutes, prior to the addition of $Pd(MeCN)_4(BF_4)_2$ (0.05 equiv.), PPh_3 (0.15 equiv.), and a solution of Cs_2CO_3 (2.0 equiv.) in H_2O. The reaction mixture was stirred at 60 °C for 3 h, with reaction progress monitored by ^{1}H-NMR analysis. Upon completion, the mixture was charged with 4M HCl in dioxane (3 equiv.), and $CuCl_2$ (0.2 equiv.), and stirred at 100 °C overnight under an atmosphere of O_2 gas with a balloon. Upon reaction completion, the mixture was diluted with 1 M HCl and extracted with EtOAc (3x). The combined organic fractions were washed with saturated NaCl (3x), H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with the indicated solvent mixture to afford the desired phenol.

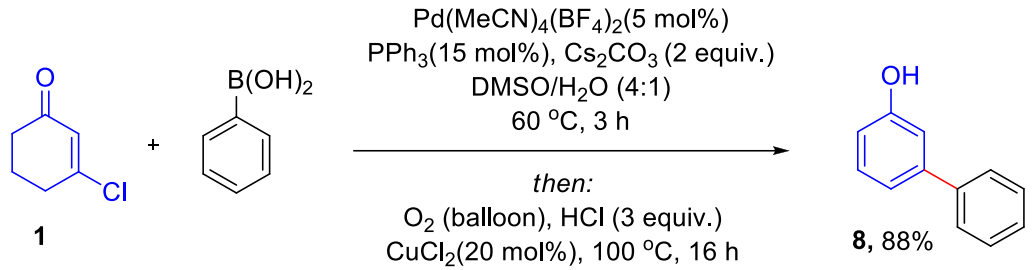
General Procedure 3B.

To a dry round bottom flask equipped with a magnetic stir bar were added, in order, the appropriate β-chlorocyclohexenone**,** anhydrous DMSO, and the appropriate boronic acid. The reaction mixture was purged with Ar for 30 minutes, prior to the addition of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.05 equiv.), PPh_3 (0.15 equiv.), and a solution of Cs_2CO_3 (2.0 equiv.) in H_2O. The reaction mixture was stirred at 90 °C for 3 h, with reaction progression monitored by ^{1}H-NMR analysis. Upon completion, the mixture was charged with 4 M HCl in dioxane (3 equiv.) then $CuCl_2$ (0.2 equiv.), and stirred at 100 °C overnight under an atmosphere of O_2 gas with a balloon. Upon reaction completion, the mixture was diluted with 1 M HCl and extracted with EtOAc (3x). The combined organic fractions were washed with saturated NaCl (3x), H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with the indicated solvent mixture to afford the desired phenol.

General Procedure 3C.

To a dry round bottom flask equipped with a magnetic stir bar were added, in order, the appropriate β-chlorocyclohexenone**,** anhydrous DMSO, and the appropriate boronic ester. The reaction mixture was purged with Ar for 30 minutes, prior to the addition of $Pd(OAc)_2$ (0.05 equiv.), PPh_3 (0.15 equiv.), and a solution of Cs_2CO_3 (2.0 equiv.) in H_2O. The reaction mixture was stirred at 90 °C for 3 h, with reaction progress monitored by ^{1}H-NMR analysis. Upon completion, the mixture was charged with 4M HCl in dioxane (12 equiv.), and $CuCl_2$ (0.2 equiv.), and stirred at 100 °C overnight under an atmosphere of O_2 gas with a balloon. Upon reaction completion, the mixture was diluted with a pH 8 buffer solution, made of 0.2 M NaOH (46.8 mL), 0.2 M KH_2PO_4 (50 mL), diluted to 200 mL. The aqueous phase was extracted with EtOAc (3x). The combined organic fractions were washed with saturated NaCl (3x), H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with the indicated solvent mixture to afford the desired phenol.

Phenol 8



Phenol **8** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **1** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), phenylboronic acid (0.19g, 1.5 mmol, 1.0 equiv.), $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 85:15 EtOAc, Rf = 0.25) yielded phenol **8** (0.23g, 88% yield) as a solid. NMR spectral data and melting point data acquired on this material matches that previously reported.[70,71]

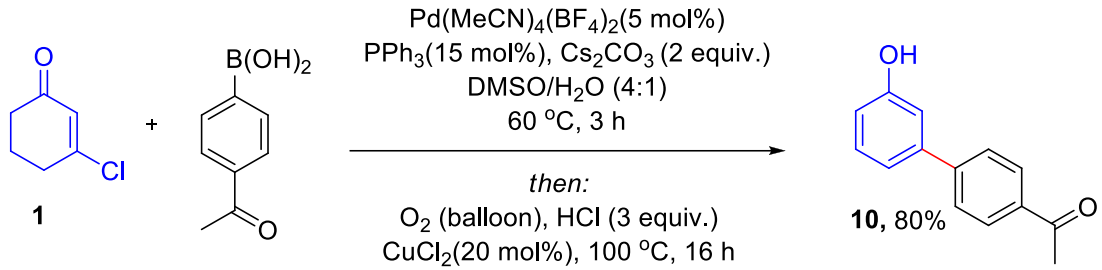
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5Hz, 2 H), 7.44 (t, *J* = 7.0 Hz, 2 H), 7.37-7.29 (m, 2 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 7.07 (s, *J* = 1 H), 6.82 (dd, *J* = 7.8, 2.1 Hz, 1 H), 4.76 (s, 1 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.7, 142.9, 140.6, 129.9, 128.6, 127.4, 127.0, 119.7, 114.0, 113.9

IR υ = 3255, 3032, 1588, 1459, 1296, 1183, 882, 752, 693 cm^{-1}

m.p. 72-75 °C

Phenol 10



Phenol **10** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **1** (0.24g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), 4-acetylphenylboronic acid (0.25g, 1.5 mmol, 1.0 equiv.), $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 85:15 EtOAc, Rf = 0.25) yielded phenol **10** (0.26g, 80%) as a solid. NMR spectral data and melting point data acquired on this material matches that previously reported.[72]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2 H), 7.67 (d, *J* = 8.0 Hz, 2 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 7.21 (d, *J* = 7.6 Hz, 1 H), 7.10 (m, 1 H), 6.87 (dd, *J* = 8.0, 2.4 Hz, 1 H), 4.85 (s, 1 H), 2.64 (s, 3 H)

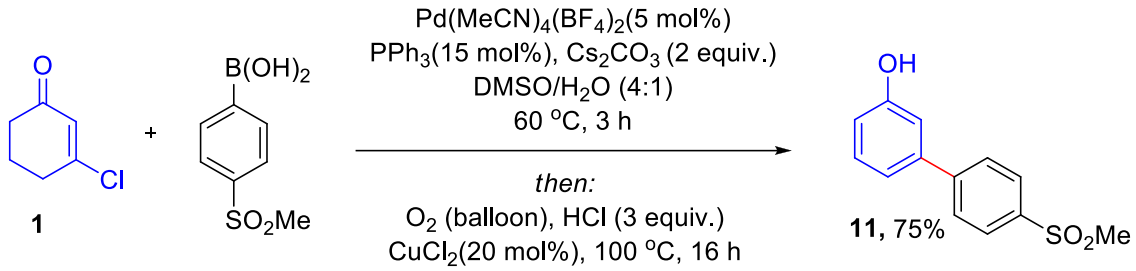
^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.7, 155.9, 145.2, 141.5, 135.9, 130.1, 128.8, 127.1, 119.8, 115.0, 114.1, 26.6

IR υ = 3176, 1656, 1583, 1478, 1404, 1308, 1271, 1202, 962, 827, 780, 693, 591 cm^{-1}

m.p. 165-169 °C

HRMS ESI Calculated for $(C_{14}H_{12}O_2)^+$ = 212.0837, found = 212.0833

Phenol 11



Phenol **11** was prepared following *general procedure 3a*, using β-chlorocyclohexenone **1** (0.24g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), 4-(methanesulfonyl)phenylboronic acid (0.31g, 1.5 mmol, 1.0 equiv.), $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 50:50 EtOAc, Rf = 0.30) yielded phenol **2b** (0.28g, 75% yield) as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 7.08 (s, 1 H), 6.90 (dd, *J* = 7.8, 1.8 Hz, 1 H), 4.94 (s, 1 H), 3.10 (s, 3 H)

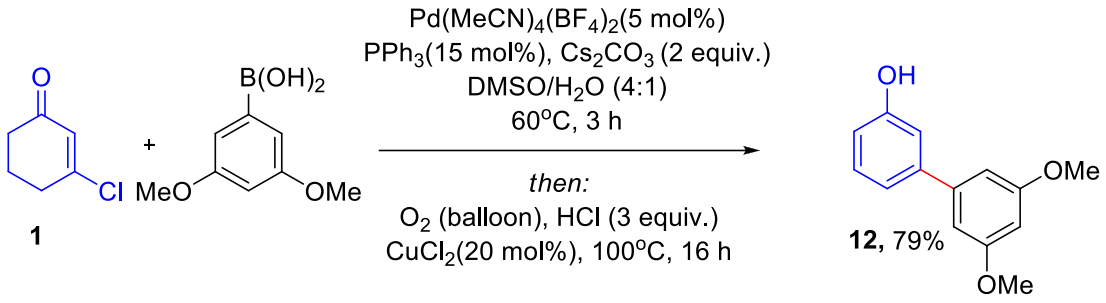
^{13}C-NMR (75 MHz, Acetone-d_6) δ 158.0, 145.9, 140.6, 140.1, 130.2, 127.8, 127.6, 118.5, 115.5, 114.0, 43.4

IR υ = 3425, 3006, 2925, 1595, 1451, 1297, 1210, 1148, 962, 773, 695, 542 cm^{-1}

m.p. 146-149 °C

HRMS ESI Calculated for $(C_{13}H_{12}O_3S)^+$ = 248.0507, found = 248.0502

Phenol 12



Phenol **12** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **1** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), 3,5-dimethoxyphenylboronic acid (0.28g, 1.5 mmol, 1.0 equiv.), $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 70:30 EtOAc, Rf = 0.20) yielded phenol **12** (0.28g, 79% yield) as an oil. NMR spectral data acquired on this material matches that previously reported.[73]

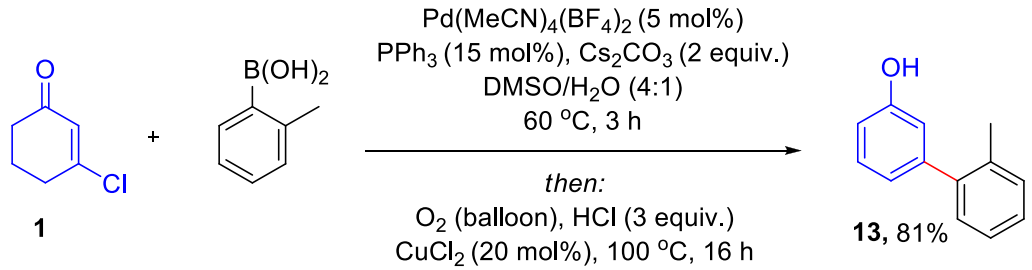
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 1 H), 7.15 (d, *J* = 7.6 Hz, 1 H), 7.05 (s, 1 H), 6.82 (dd, *J* = 8.0, 2.8 Hz, 1 H), 6.71 (d, *J* = 2.0 Hz, 2 H), 6.47 (t, *J* = 2.0 Hz, 1 H), 4.85 (s, 1 H), 3.84 (s, 6 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.9, 155.6, 142.9, 142.8, 129.8, 119.7, 114.3, 114.0, 105.2, 99.4, 55.3

IR υ = 3394, 2938, 2838, 1703, 1579, 1458, 1416, 1260, 1202, 1062, 1038, 834, 783, 691 cm^{-1}

HRMS ESI Calculated for $(C_{14}H_{14}O_3)^+$ = 230.0943, found = 230.0949

Phenol 13



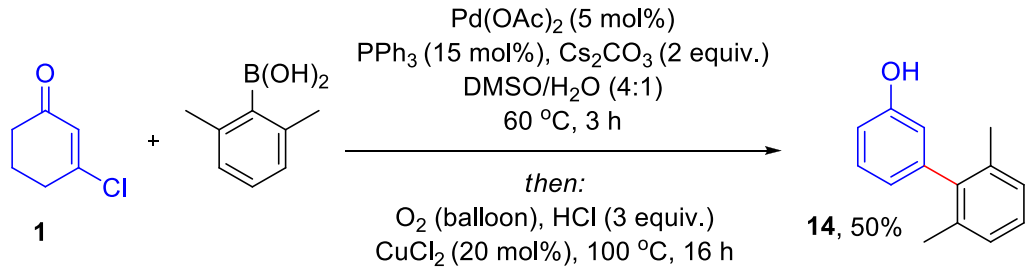
Phenol **13** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **1** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), *o*-tolylboronic acid (0.21g, 1.5 mmol, 1.0 equiv.), $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 80:20 EtOAc, Rf = 0.25) yielded phenol **13** (0.23g, 81% yield) as an oil. NMR spectral data acquired on this material matches that previously reported.[58]

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.21 (m, 5 H), 6.92 (d, *J* = 7.5 Hz, 1 H), 6.82 (m, 2 H), 4.80 (s, 1 H), 2.30 (s, 3 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.0, 143.6, 141.3, 135.2, 130.2, 129.5, 129.2, 127.2, 125.6, 121.8, 116.1, 113.6, 20.3

IR υ = 3342, 2981, 1703, 1583, 1476, 1442, 1302, 1273, 1204, 887, 757, 703 cm^{-1}

Phenol 14



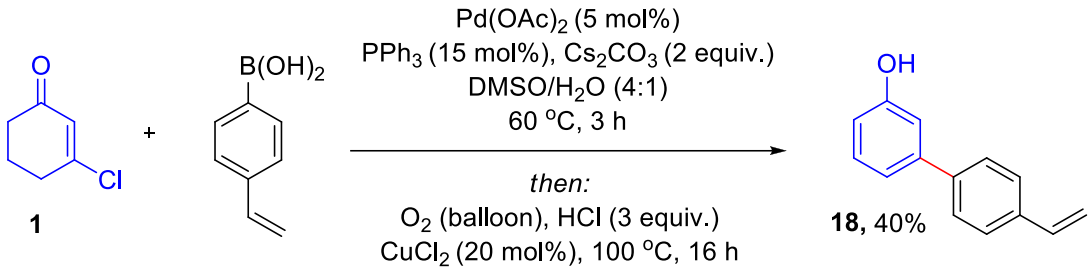
Phenol **14** was prepared following G*eneral Procedure 3a*, using β-chlorocyclohexenone **1** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), 2,6-dimethylphenylboronic acid (0.23 g, 1.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (17 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 85:15 EtOAc, Rf = 0.25) yielded phenol **14** (0.15g, 50% yield) as an oil. NMR spectral data acquired on this material matches that previously reported.[74]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.6 Hz, 1 H), 7.19-7.15 (m, 1 H), 7.12 (d, *J* = 7.1 Hz, 2 H), 6.82 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.64 (s, 1 H), 4.99 (s, 1 H), 2.06 (s, 6 H)

^{13}C-NMR (150 MHz, $CDCl_3$) δ 155.5, 142.8, 141.3, 135.9, 129.7, 127.2, 127.0, 121.6, 115.9, 113.5, 20.7

IR υ = 3343, 2951, 2919, 1580, 1462, 1441, 1288, 1187, 881, 769, 743, 705 cm^{-1}

Phenol 18



Phenol **18** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **1** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), 4-vinylphenylboronic acid (0.23 g, 1.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (17 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 70:30 EtOAc, Rf = 0.25) yielded phenol **18** (0.12g, 40% yield) as a solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.09 (s, 1 H), 6.83 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.78 (dd, *J* = 17.6, 11.2 Hz, 1 H), 5.81 (d, *J* = 17.6 Hz, 1 H), 5.30 (d, *J* = 11.2 Hz, 1 H), 4.82 (s, 1 H)

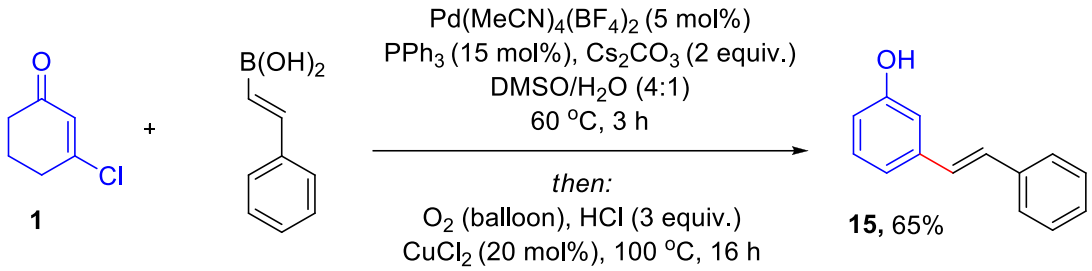
^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.7, 142.4, 139.9, 136.7, 136.2, 129.9, 127.1, 126.5, 119.5, 114.1, 113.9, 113.7

IR υ = 3268, 3085, 3032, 3002, 1587, 1483, 1452, 1300, 1184, 989, 902, 884, 835, 749, 688 cm^{-1}

m.p. 106-110 °C

HRMS ESI Calculated for $(C_{14}H_{12}O)^+$ = 196.0888, found = 196.0882

Phenol 15



Phenol **15** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **1** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), trans-2-phenylvinylboronic acid (0.23 g, 1.5 mmol, 1.0 equiv.) $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 80:20 EtOAc, Rf = 0.25) yielded phenol **15** (0.20g, 65% yield) as a solid. NMR spectral data and melting point data acquired on this material matches that previously reported.[75]

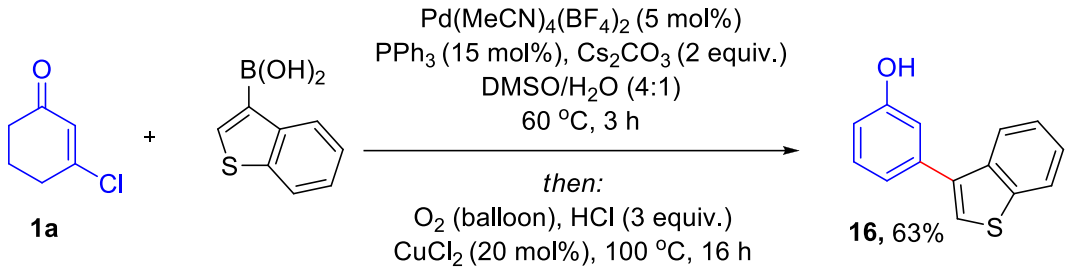
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 2 H), 7.36 (t, *J* = 7.2 Hz, 2 H), 7.29-7.21 (m, 2 H), 7.12-7.06 (m, 3 H), 7.00 (br, s, 1 H), 6.74 (dd, *J* = 8.0 , 2.4Hz, 1 H), 4.73 (s, 1 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.6, 139.0, 137.0, 129.8, 129.1, 128.6, 128.1, 127.6, 126.4, 119.3, 114.5, 112.8

IR υ = 3546, 3033, 1588, 1451, 1150, 964, 787, 751, 691cm^{-1}

m.p. 120-124 °C

Phenol 16



Phenol **16** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **1** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), thianaphthene-3-boronic acid (0.27g, 1.5 mmol, 1.0 equiv.), $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 80:20 EtOAc, Rf = 0.25) yielded phenol **16** (0.20 g, 63% yield) as an oil.

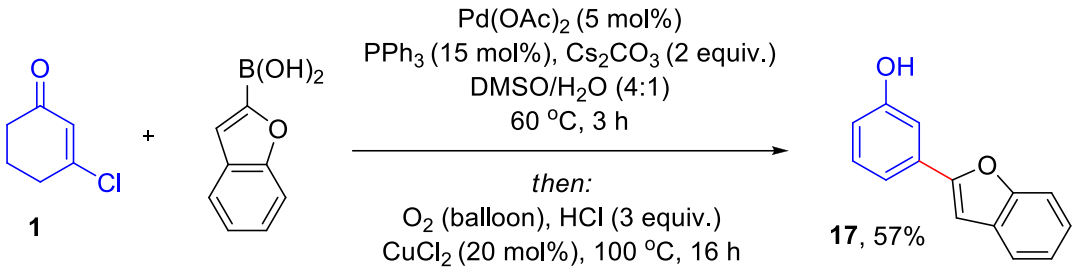
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95-7.90 (m, 2 H), 7.40-7.33 (m, 4 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 7.07 (br, s, 1 H), 6.88 (dd, *J* = 8.0, 2.1 Hz, 1 H), 4.91 (br, s, 1 H)

^{13}C-NMR (150 MHz, $CDCl_3$) δ 155.7, 140.6, 137.7, 137.58, 137.56, 129.9, 124.4, 124.3, 123.5, 122.91, 122.88, 121.3, 115.6, 114.5

IR υ = 3363, 2981, 1702, 1581, 1442, 1425, 1182, 815, 779, 760, 733, 695 cm^{-1}

HRMS ESI Calculated for $(C_{14}H_{10}OS)^+$ = 226.0542, found = 226.0458

Phenol 17



Phenol **17** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **1** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), 2-benzofuranylboronic acid (0.25 g, 1.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (17 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.08 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 80:20 EtOAc, Rf = 0.25) yielded phenol **17** (0.18 g, 57% yield) as a solid. . NMR spectral data and melting point data acquired on this material matches that previously reported.[76,77]

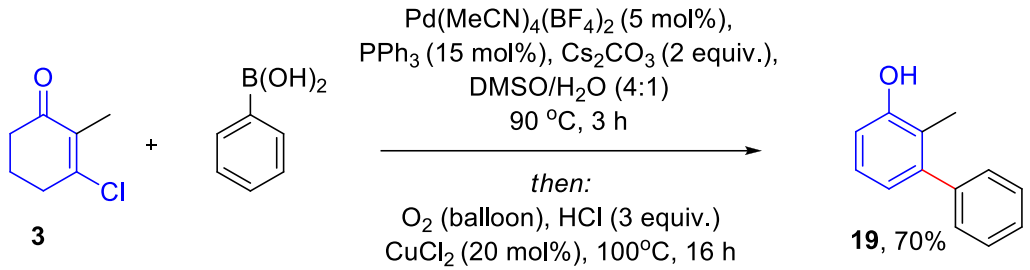
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0, 1 H), 7.35-7.23 (m, 4 H), 7.01 (s, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 4.89 (br, s, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 155.3, 154.7, 131.9, 130.0, 129.0, 124.3, 122.9, 120.9, 117.5, 115.5, 111.6, 111.1, 101.7

IR υ = 3497, 3194, 3058, 1568, 1454, 1441, 1257, 1222, 1191, 1042, 865, 782, 746 cm^{-1}

m.p. 114-117°C

Phenol 19



Phenol **19** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **3** (0.11 g, 0.75 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), phenylboronic acid (0.11 g, 0.9 mmol, 1.2 equiv.), $Pd(MeCN)_4(BF_4)_2$ (17 mg, 0.038 mmol, 0.05 equiv.), PPh_3 (28 mg, 0.11 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (0.49g, 1.5 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (0.58 mL, 2.3 mmol, 3 equiv.), and $CuCl_2$ (20 mg, 0.15 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 85:15 EtOAc, Rf = 0.35) yielded phenol **19** (88 mg, 70% yield) as an oil. NMR spectral data acquired on this material matches that previously reported.[78]

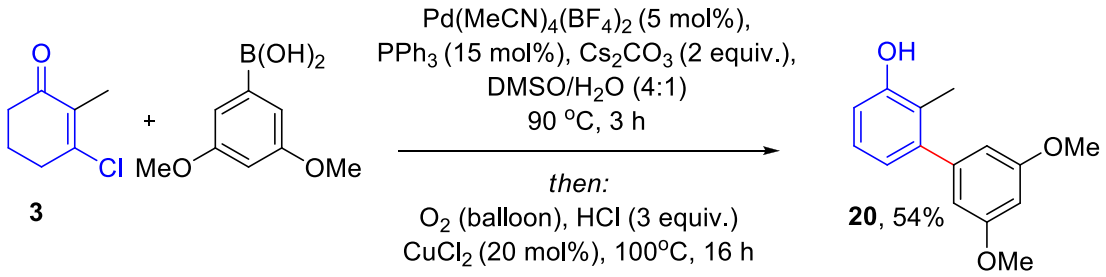
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.2 Hz, 2 H), 7.36-7.31 (m, 3 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 6.80 (d, *J* = 7.6 Hz, 1 H), 4.80 (s, 1 H), 2.16 (s, 3 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.9, 143.6, 141.5, 129.2, 127.9, 126.7, 126.1, 122.4, 121.4, 113.7, 12.9

IR υ = 3395, 2984, 2924, 1704, 1582, 1463, 1276, 1111, 1043, 760, 702cm^{-1}

HRMS ESI Calculated for $(C_{13}H_{12}O)^+$ = 184.0888, found = 184.0882

Phenol 20



Phenol **20** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **3** (0.24 g, 1.9 mmol, 1.2 equiv.), anhydrous DMSO (3 mL), 3,5-dimethylphenylboronic acid (0.28 g, 1.5 mmol, 1.0 equiv.), $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 80:20 EtOAc, Rf = 0.35) yielded phenol **20** (0.21 g, 54% yield) as a solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.45 (s, 3 H), 4.78 (s, 1 H), 3.81 (s, 6 H), 2.16 (s, 3 H)

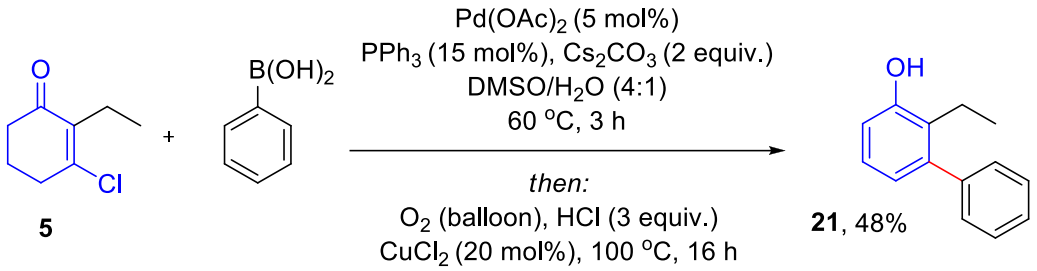
^{13}C-NMR (150 MHz, 87% $CDCl_3$ + 13% Benzene-d_6) δ 160.4, 154.0, 143.74, 143.72, 126.1, 122.1, 121.6, 113.8, 107.5, 99.1, 55.2, 12.9

IR υ = 3408, 2938, 2837, 1578, 1420, 1265, 1203, 1151, 1061, 828, 788 cm^{-1}

m.p. 79-83 °C

HRMS ESI Calculated for $(C_{15}H_{16}O_3)^+$ = 244.1099, found = 244.1092

Phenol 21



Phenol **21** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **5** (0.12 g, 0.75 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), phenylboronic acid (0.11 g, 0.90 mmol, 1.2 equiv.), $Pd(OAc)_2$ (9 mg, 0.038 mmol, 0.05 equiv.), PPh_3 (28 mg, 0.11 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (0.49 g, 1.5 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (0.58 mL, 2.3 mmol, 3 equiv.), and $CuCl_2$ (20 mg, 0.15 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 90:10 EtOAc, Rf = 0.25) yielded phenol **21** (71 mg, 48% yield) as a solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42-7.29 (m, 5 H), 7.10 (t, *J* = 8.0 Hz, 1 H), 6.80 (dd, *J* = 7.6, 7.6 Hz, 2 H), 4.76 (s, 1 H), 2.57 (q, *J* = 7.2 Hz, 2 H), 1.09 (t, *J* = 7.2 Hz, 3 H)

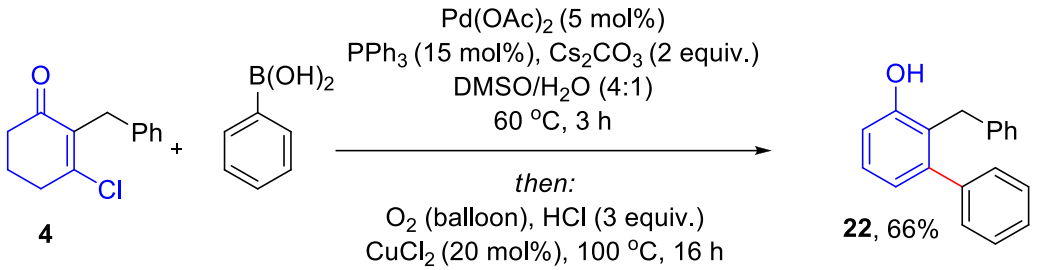
^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.6, 143.4, 141.7, 129.0, 128.0, 127.8, 126.7, 126.1, 122.6, 114.2, 20.2, 14.2

IR υ = 3369, 2967, 2933, 2872, 1574, 1458, 1320, 1117, 880, 763, 741, 701 cm^{-1}

m.p. 51-55 °C

HRMS ESI Calculated for $(C_{14}H_{14}O)^+$ = 198.1045, found = 198.1041

Phenol 22



Phenol **22** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **4** (0.22 g, 1.0 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), phenylboronic acid (0.15 g, 1.2 mmol, 1.2 equiv.), $Pd(OAc)_2$ (12 mg, 0.05 mmol, 0.05 equiv.), PPh_3 (37 mg, 0.15 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (0.65g, 2.0 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (0.75 mL, 3.0 mmol, 3 equiv.), and $CuCl_2$ (28 mg, 0.20 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 90:10 EtOAc, Rf = 0.25) yielded phenol **22** (0.17 g, 66% yield) as a solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 3 H), 7.26-7.18 (m, 6 H), 7.10 (d, *J* = 7.6 Hz, 2 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 4.73 (s, 1 H), 4.02 (s, 2 H)

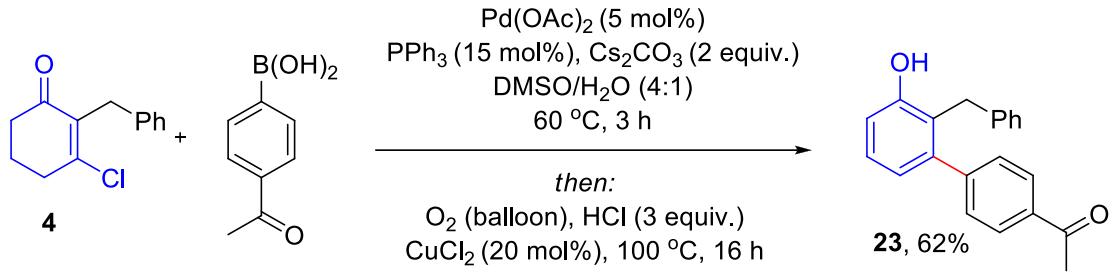
^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.3, 144.2, 141.3, 139.9, 129.0, 128.5, 128.0, 127.9, 127.3, 126.9, 126.1, 123.9, 122.8, 114.9, 32.9

IR υ = 3550, 3022, 2924, 1581, 1493, 1461, 1449, 1088, 947, 788, 762, 729, 700, 552 cm^{-1}

m.p. 83-86 °C

HRMS ESI Calculated for $(C_{19}H_{16}O)^+$ = 260.1201, found = 260.1208

Phenol 23



Phenol **23** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **4** (0.25 g, 1.1 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), 4-acetylphenylboronic acid (0.22 g, 1.4 mmol, 1.2 equiv.) $Pd(OAc)_2$ (14 mg, 0.057 mmol, 0.05 equiv.), PPh_3 (42 mg, 0.17 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (0.73g, 2.26 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (0.85 mL, 3.4 mmol, 3 equiv.), and $CuCl_2$ (32 mg, 0.23 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 80:20 EtOAc, Rf = 0.3) yielded phenol **23** (0.21 g, 62% yield) as a solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.26-7.19 (m, 4 H), 7.07 (d, *J* = 7.2 Hz, 2 H), 6.90 (dd, *J* = 7.4, 2.4 Hz, 2 H), 4.93 (s, 1 H), 3.98 (s, 2 H), 2.62 (s, 3 H)

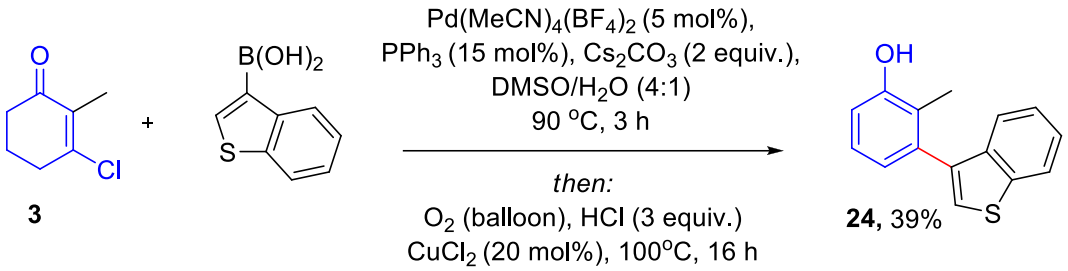
^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.8, 154.4, 146.3, 143.0, 139.6, 135.7, 129.3, 128.6, 128.1, 127.9, 127.5, 126.3, 123.8, 122.4, 115.5, 32.9, 26.6

IR υ = 3163, 2943, 1654, 1280, 826, 735, 699, 602 cm^{-1}

m.p. 133-135 °C

HRMS ESI Calculated for $(C_{21}H_{18}O_2)^+$ = 302.1307, found = 302.1303

Phenol 24



Phenol **24** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **3** (0.22 g, 1.5 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), thianaphthene-3-boronic acid (0.33 g, 1.9 mmol, 1.2 equiv.), $Pd(MeCN)_4(BF_4)_2$ (34 mg, 0.077 mmol, 0.05 equiv.), PPh_3 (57 mg, 0.22 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (1.0 g, 3.1 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.6 mmol, 3 equiv.), and $CuCl_2$ (42 mg, 0.31 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 85:15 EtOAc, Rf = 0.25) yielded phenol **24** (0.14 mg, 39% yield) as a solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz , 1 H), 7.45 (d, *J* = 7.3 Hz, 1 H), 7.39-7.32 (m, 2 H), 7.28 (s, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 6.87 (d, *J* = 7.6 Hz, 1 H), 4.82 (s, 1 H), 2.05 (s, 3 H)

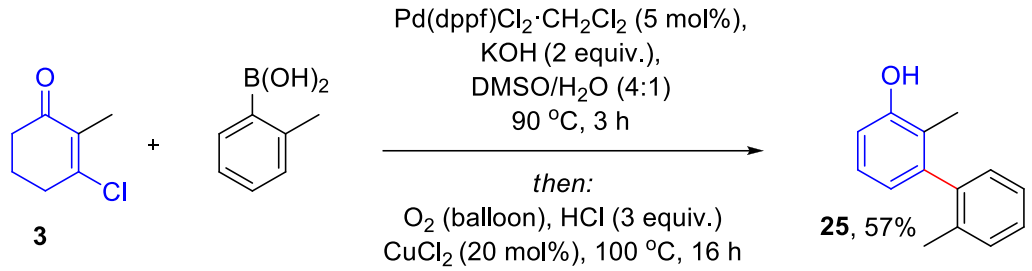
^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.0, 139.7, 138.9, 137.1, 136.9, 126.3, 124.2, 124.1, 123.7, 123.14, 123.06, 123.0, 122.6, 114.4, 12.9

IR υ = 3260, 1574, 1464, 1341, 1257, 1244, 1074, 1047, 790, 769, 758, 731, 719, 699 cm^{-1}

m.p. 103-107 °C

HRMS ESI Calculated for $(C_{15}H_{12}OS)^+$ = 240.0609, found = 240.0602

Phenol 25



Phenol **25** was prepared following *General Procedure 3b*, using β-chlorocyclohexenone **3** (0.11 g, 0.75 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), *o*-tolylboronic acid (0.12 g, 0.9 mmol, 1.2 equiv.), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (31 mg, 0.038 mmol, 0.05 equiv.), a solution of KOH (84 mg, 1.5 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (0.56 mL, 2.3 mmol, 3 equiv.), and $CuCl_2$ (20 mg, 0.15 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 90:10 EtOAc, Rf = 0.25) yielded phenol **25** (84 mg, 57% yield) as a solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (m, 3 H), 7.11 (t, *J* = 7.2, 2 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.73 (d, *J* = 7.6 Hz, 1 H), 4.76 (s, 1 H), 2.07 (s, 3 H), 1.96 (s, 3 H)

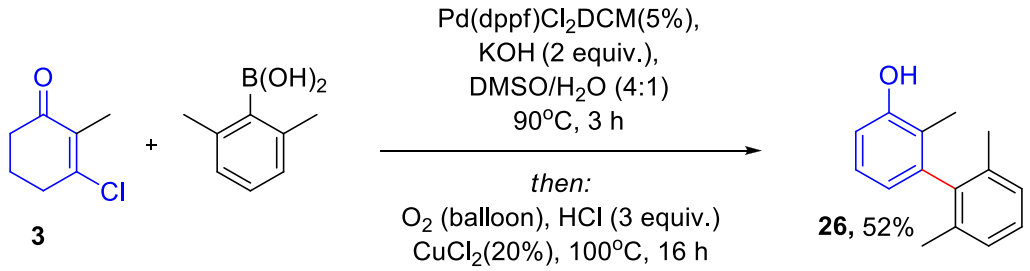
^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.7, 143.2, 141.2, 135.9, 129.7, 129.3, 127.2, 126.1, 125.5, 122.0,121.9,113.6, 19.8, 12.4

IR υ = 3283, 3012, 2951, 2921, 1578, 1462, 1263, 1125, 1095, 993, 871, 756, 723 cm^{-1}

m.p. 64-67 °C

HRMS ESI Calculated for $(C_{14}H_{14}O)^+$ = 198.1045, found = 198.1040

Phenol 26



Phenol **26** was prepared following *General Procedure 3b*, using β-chlorocyclohexenone **3** (0.14 g, 1.0 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), 2,6-dimethylphenylboronic acid (0.18 g, 1.2 mmol, 1.2 equiv.), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (41 mg, 0.05 mmol, 0.05 equiv.), a solution of KOH (0.11 g, 2.0 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (0.75 mL, 3.0 mmol, 3 equiv.), and $CuCl_2$ (28 mg, 0.2 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 90:10 EtOAc, Rf = 0.20) yielded phenol **26** (0.11, 52% yield) as a solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18-7.09 (m, 4 H), 6.80 (d, *J* = 8.4, Hz, 1 H), 6.66 (d, *J* = 7.6 Hz, 2 H), 4.77 (s, 3 H), 1.98 (s, 6 H), 1.90 (s, 3 H)

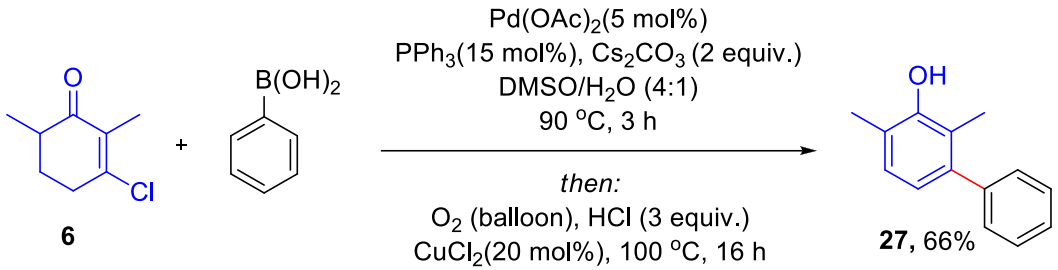
^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.9, 142.1, 140.6, 135.8, 127.0, 126.8, 126.6, 121.6, 121.4, 113.3, 20.2, 11.7

IR υ = 3254, 2919, 2858, 1580, 1459, 1275, 1164, 1122, 869, 786, 768, 734, 723 cm^{-1}

m.p. 86-90 °C

HRMS ESI Calculated for $(C_{15}H_{16}O)^+$ = 212.1201, found = 212.1205

Phenol 27



Phenol **27** was prepared following *General Procedure 3a*, using β-chlorocyclohexenone **6** (0.16 g, 1.0 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), phenylboronic acid (0.15g, 1.2 mmol, 1.2 equiv.), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.05 equiv.), PPh_3 (32 mg, 0.15 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (0.63g, 2.0 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (0.75 mL, 3.0 mmol, 3.0 equiv.), and $CuCl_2$ (27 mg, 0.20 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 9:1 EtOAc, Rf = 0.2) yielded phenol **27** (0.12 g, 66% yield) as a solid.

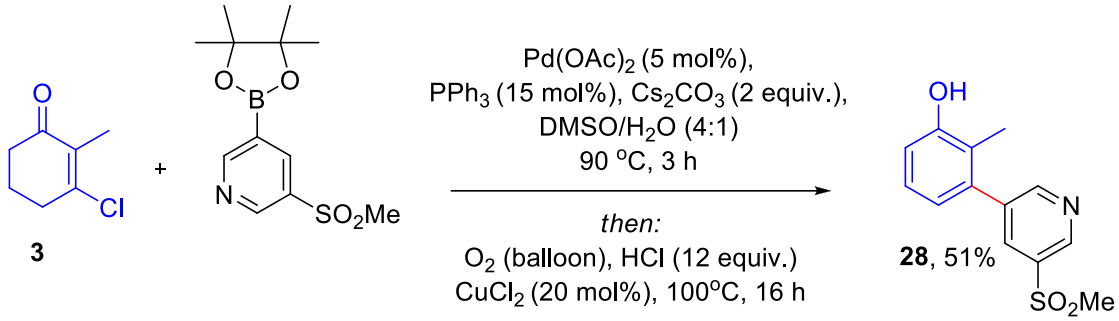
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.2, 7.2 Hz, 2 H), 7.36-7.30 (m, 3 H), 7.04 (d, *J* = 7.8 Hz, 1 H), 6.80 (d, *J* = 7.8 Hz, 1 H), 4.75 (s, 1 H), 2.32 (s, 3 H), 2.18 (s, 3 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.2, 141.7, 141.3, 129.3, 127.9, 127.6, 126.6, 121.7, 120.9, 120.6, 15.9, 13.1

IR υ = 3500, 2921, 2858, 1567, 1408, 1230, 1194, 1174, 1115, 988, 765, 703 cm^{-1}

m.p. 54-57 °C

Phenol 28



Phenol **28** was prepared following *General Procedure 3c*, using β-chlorocyclohexenone **3** (58 mg, 0.40 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), 3-(Methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.12 g, 0.44 mmol, 1.1 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 0.05 equiv.), PPh_3 (16 mg, 0.06 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (0.26 g, 0.8 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.8 mmol, 12.0 equiv.), and $CuCl_2$ (211 mg, 0.08 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 5:5 EtOAc, Rf = 0.2) yielded phenol **28** (53 mg, 51% yield) as a solid.

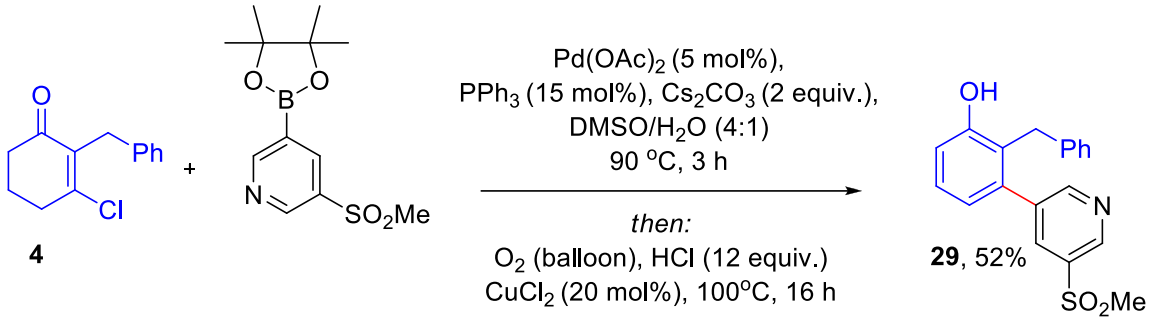
^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.14 (d, *J* = 2.0 Hz, 1 H), 8.86 (d, *J* = 1.6 Hz, 1 H), 8.18 (d, *J* = 2.0 Hz, 1 H), 7.19 (t, *J* = 8.0 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 4.92 (s, 1 H), 3.17 (s, 3 H), 2.16 (s, 3 H)

^{13}C-NMR (150 MHz, $CDCl_3$) δ 154.5, 154.4, 146.7, 137.9, 137.6, 136.6, 135.3, 127.0, 122.5, 122.1, 115.6, 44.9, 13.0

IR υ = 3416, 3009, 2926, 1583, 1434, 1291, 1281, 1134, 1100, 1009, 781, 537 cm^{-1}

m.p. 174-176 °C

Phenol 29



Phenol **29** was prepared following *General Procedure 3c*, using β-chlorocyclohexenone **4** (88 mg, 0.40 mmol, 1.0 equiv.), anhydrous DMSO (3 mL), 3-(Methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.12 g, 0.44 mmol, 1.1 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 0.05 equiv.), PPh_3 (16 mg, 0.06 mmol, 0.15 equiv.), a solution of Cs_2CO_3 (0.26 g, 0.8 mmol, 2.0 equiv.) in H_2O (0.7 mL), 4 M HCl in dioxane (1.2 mL, 4.8 mmol, 12.0 equiv.), and $CuCl_2$ (211 mg, 0.08 mmol, 0.2 equiv.) Purification using column chromatography (Hexane 5:5 EtOAc, Rf = 0.25) yielded phenol **29** (70 mg, 52% yield) as a solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1 H), 9.04 (d, *J* = 2.0 Hz, 1 H), 8.68 (d, *J* = 1.6 Hz, 1 H), 8.03 (s, 1 H), 7.27 (t, *J* = 7.8 Hz, 1 H), 7.19 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 6.87 (d, *J* = 7.6 Hz, 2 H), 6.82 (d, *J* = 7.6 Hz, 2 H), 3.92 (s, 2 H), 3.32 (s, 3 H)

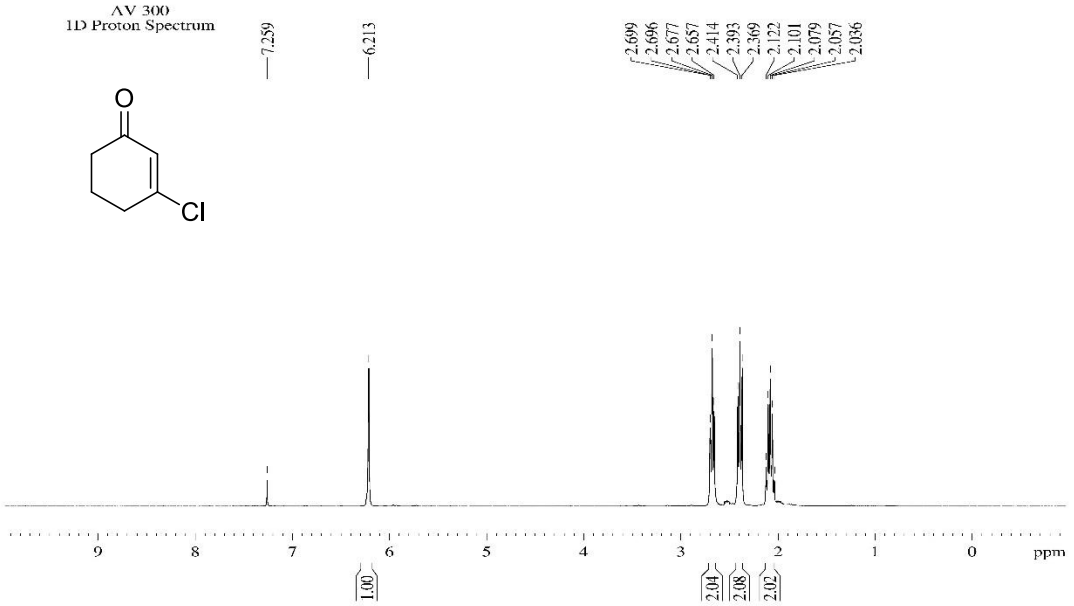
^{13}C-NMR (150 MHz, $CDCl_3$) δ 154.6, 154.0, 146.8, 139.3, 138.5, 137.6, 136.3, 135.2, 128.8, 128.1, 127.9, 126.5, 124.6, 122.9, 116.5, 44.0, 32.6

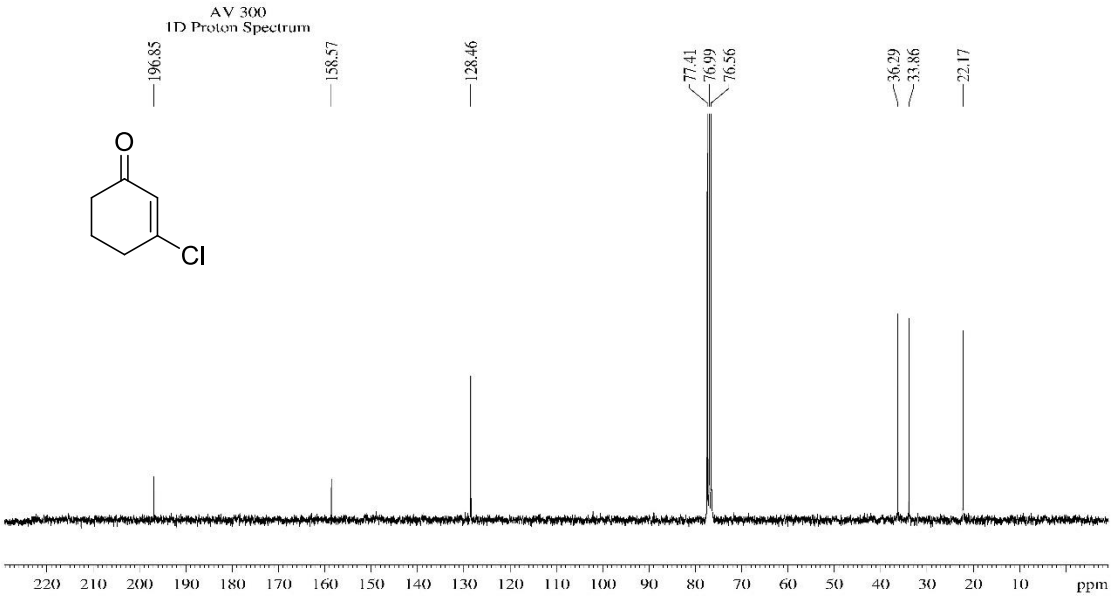
IR υ = 3416, 3002, 2923, 1581, 1433, 1146, 1097, 1074, 976, 796, 781, 754, 740, 532 cm^{-1}

m.p. 250 °C

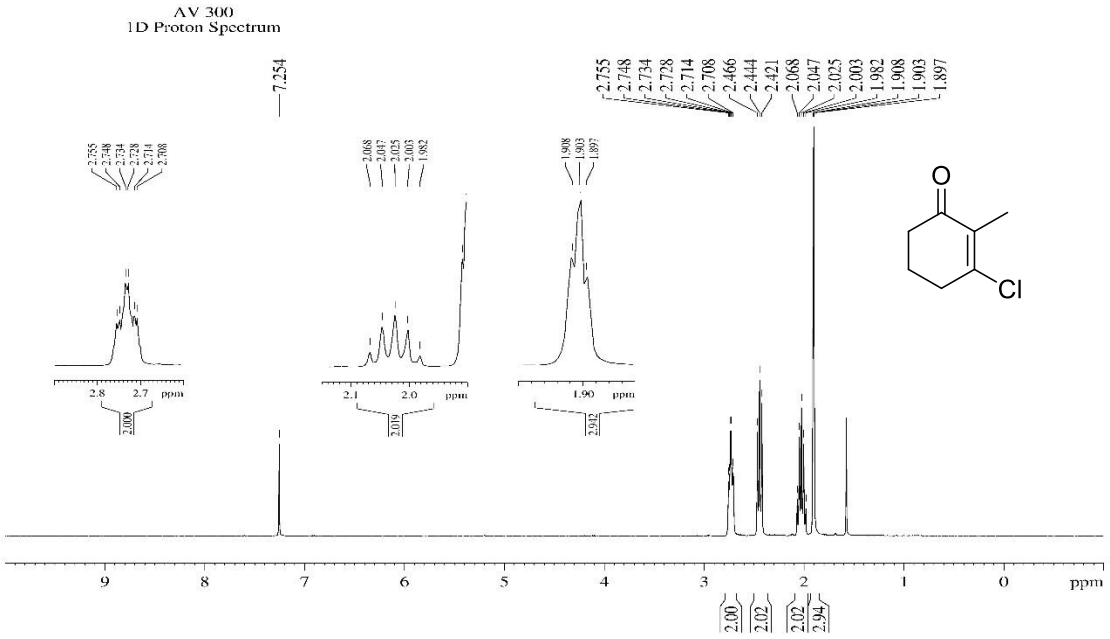
3.3 [1]H and [13]C-NMR spectra

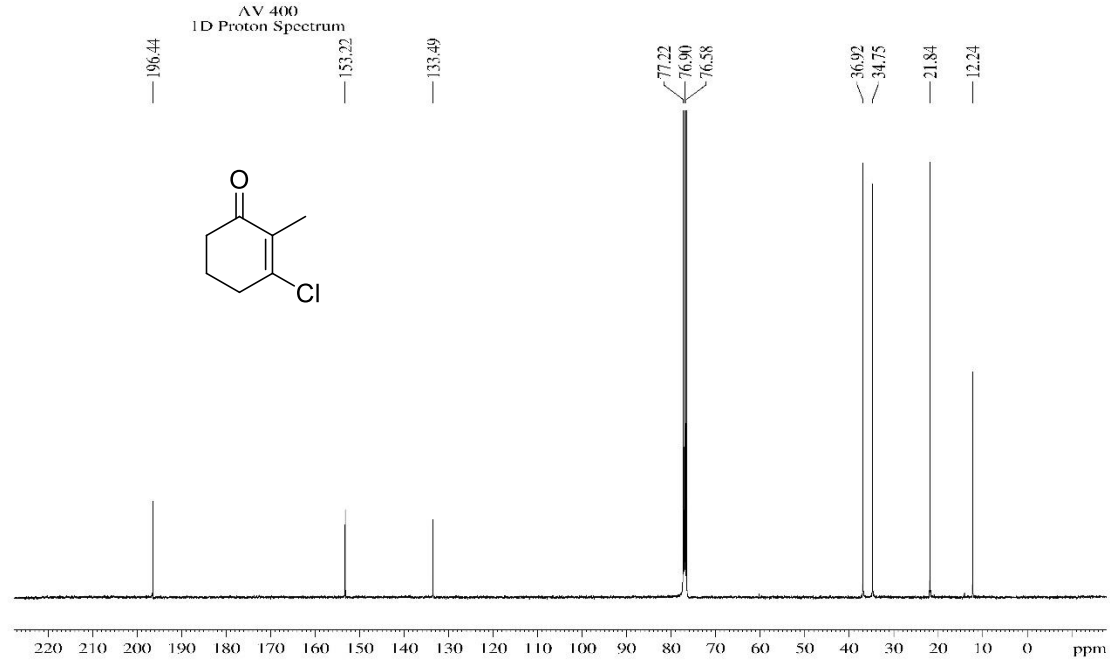
[1]H and [13]C spectra of Substrate 1



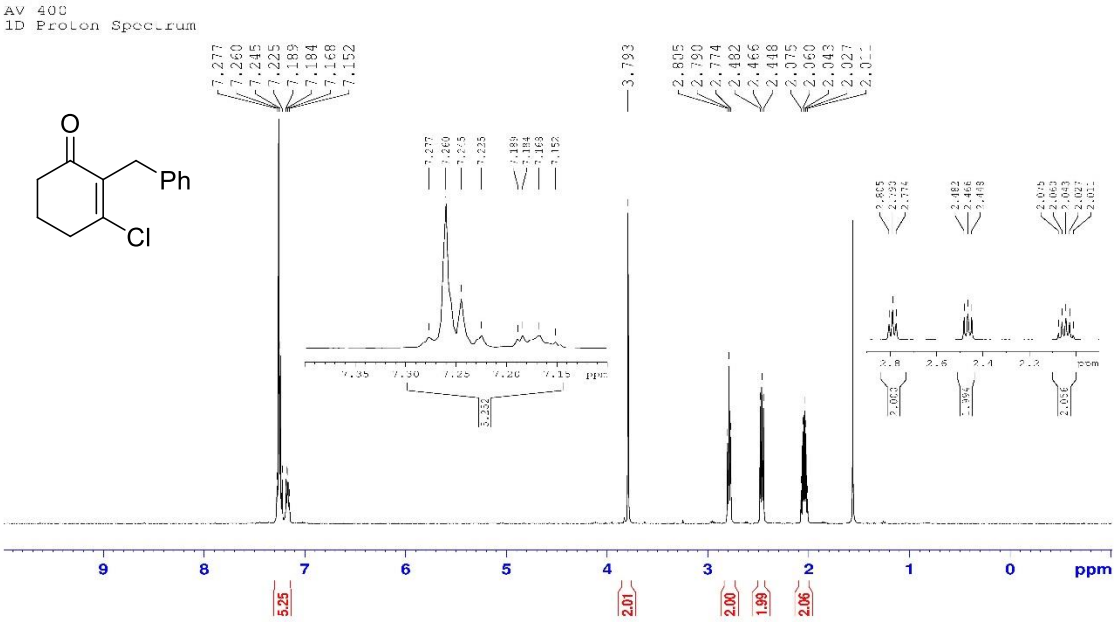


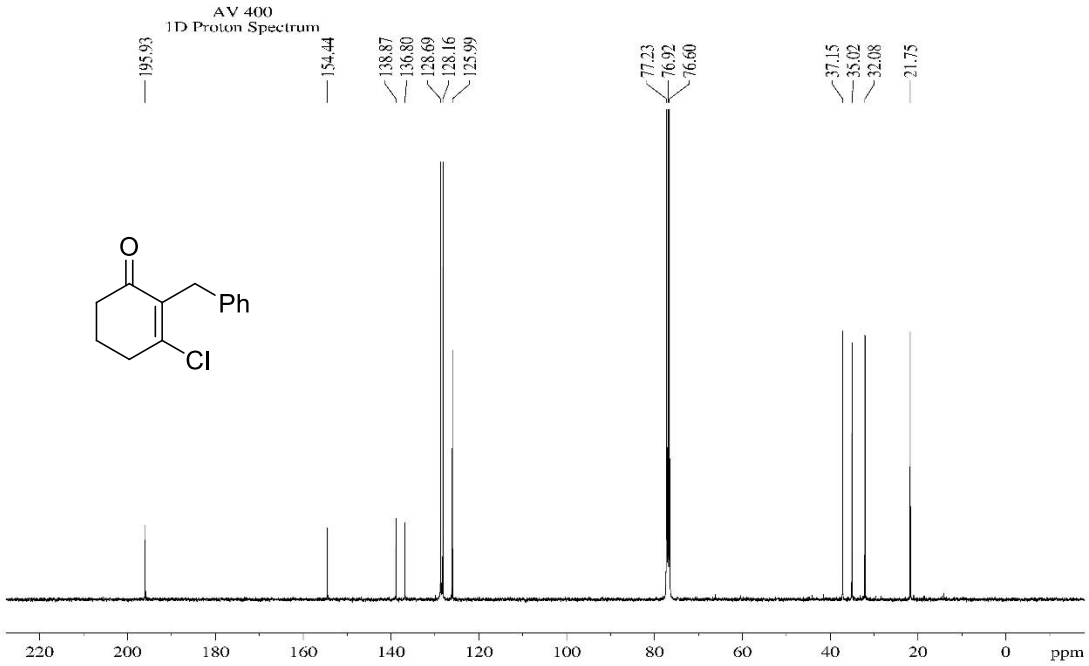
^{1}H and ^{13}C spectra of Substrate 3



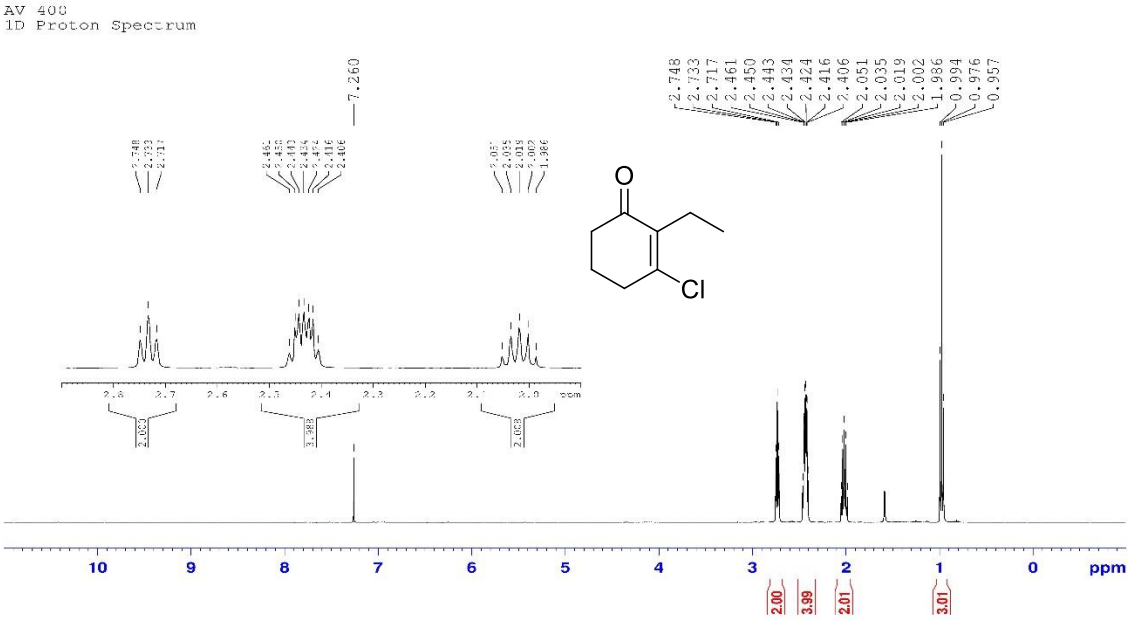


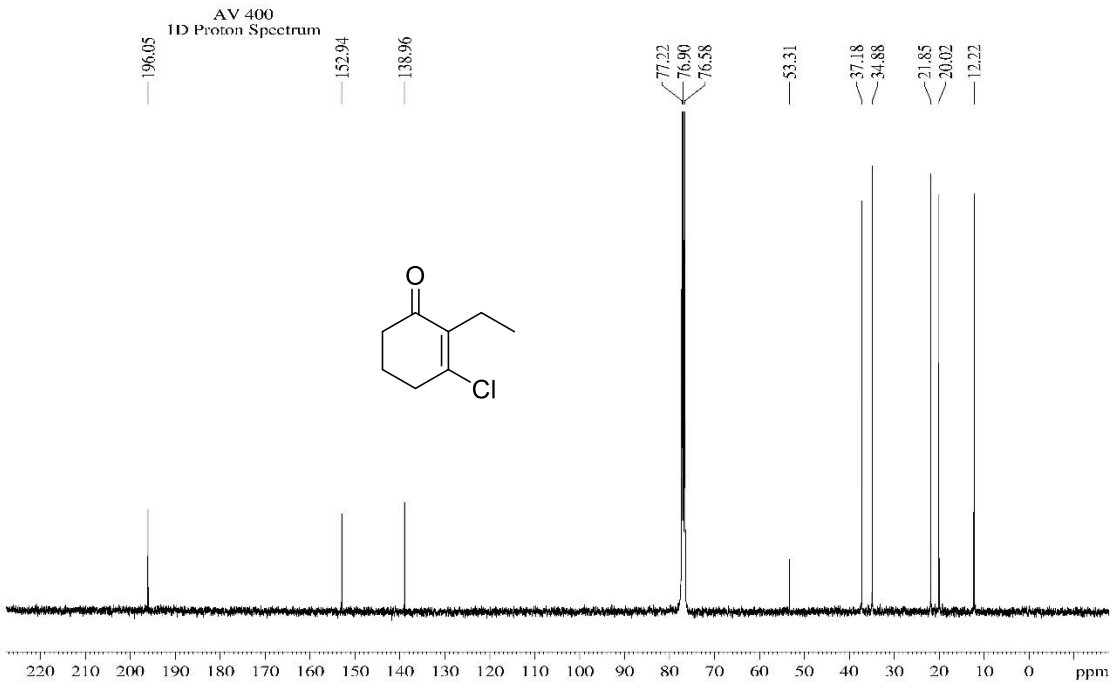
^{1}H and ^{13}C spectra of Substrate 4



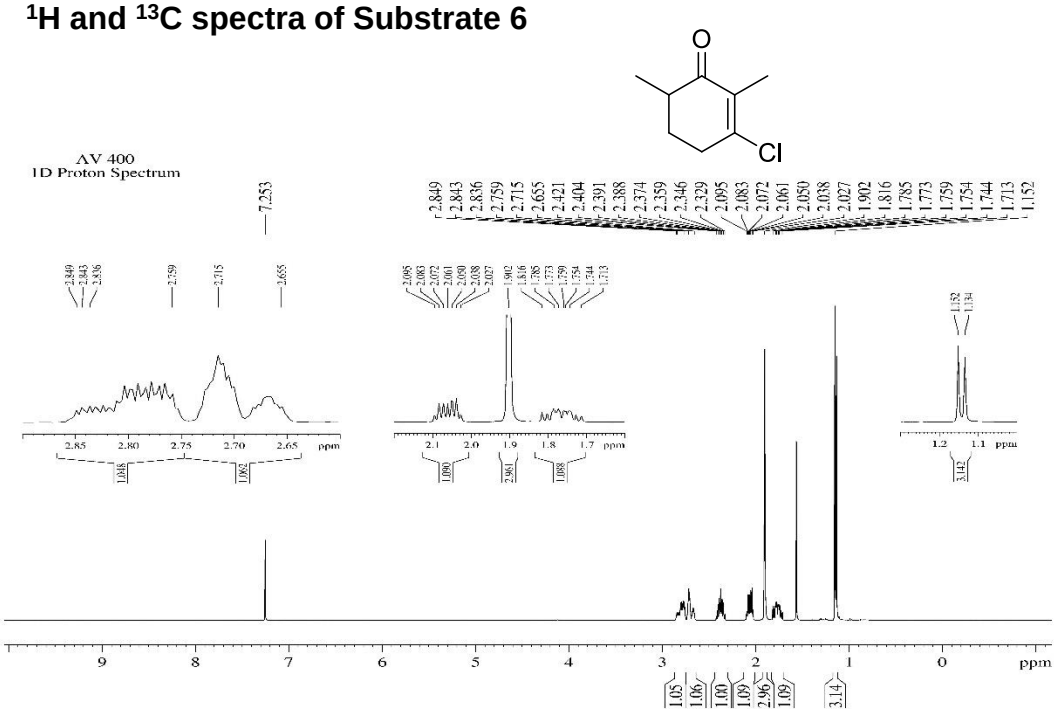


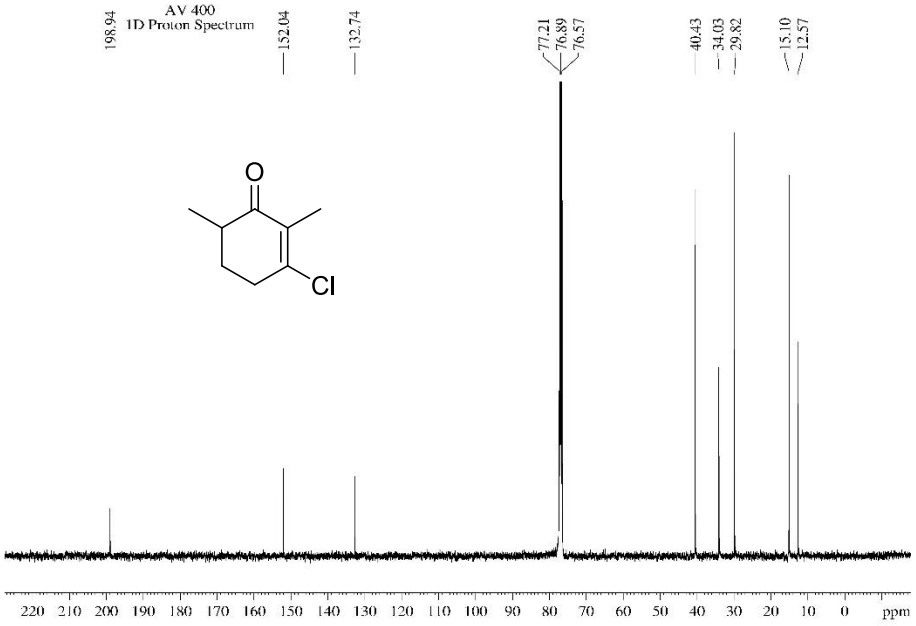
^{1}H and ^{13}C spectra of Substrate 5



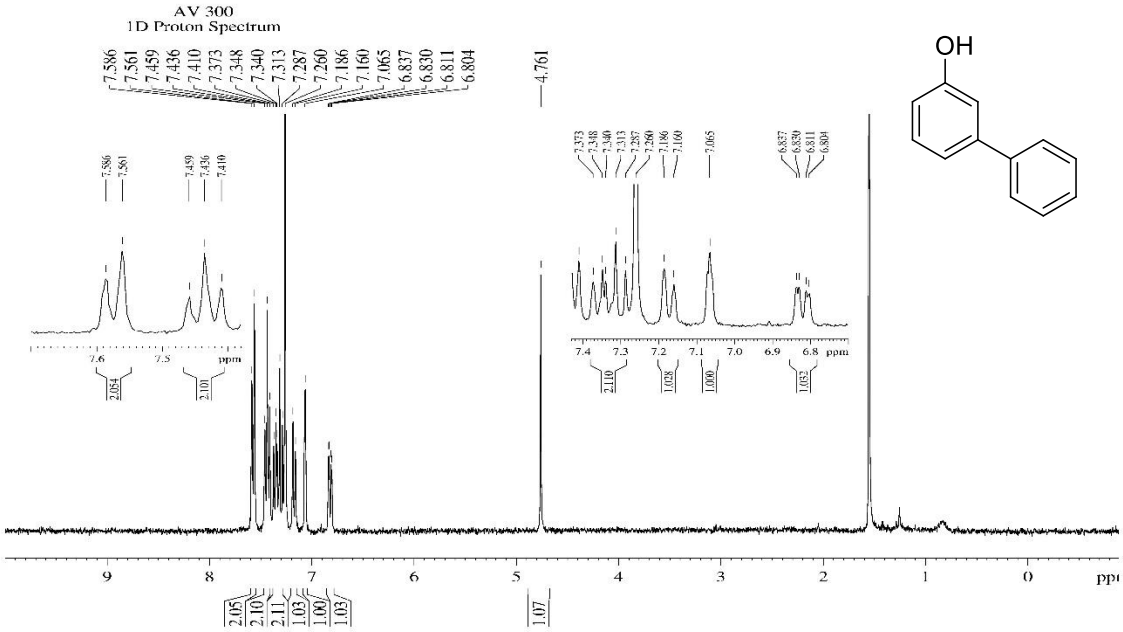


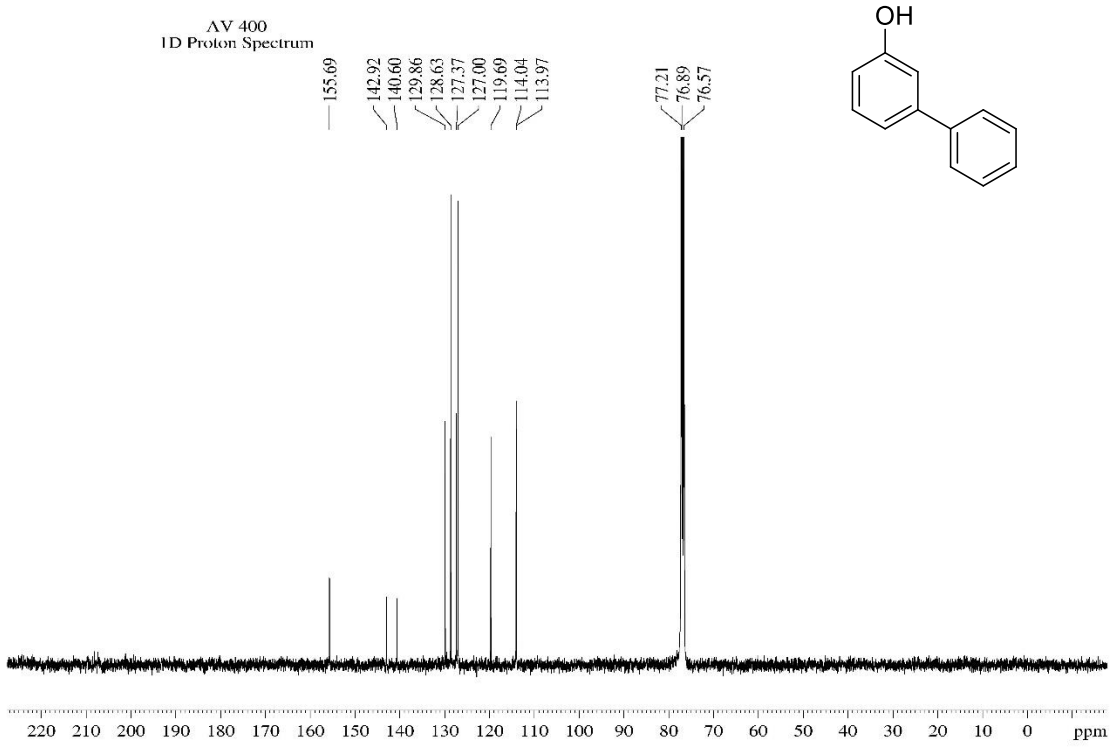
^{1}H and ^{13}C spectra of Substrate 6



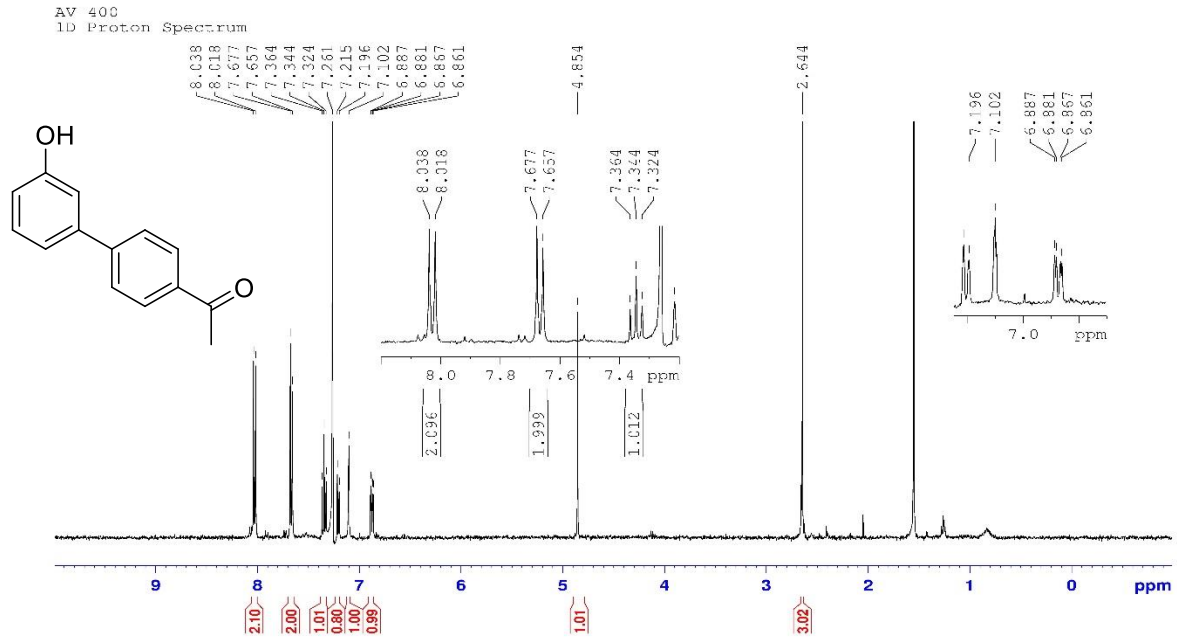


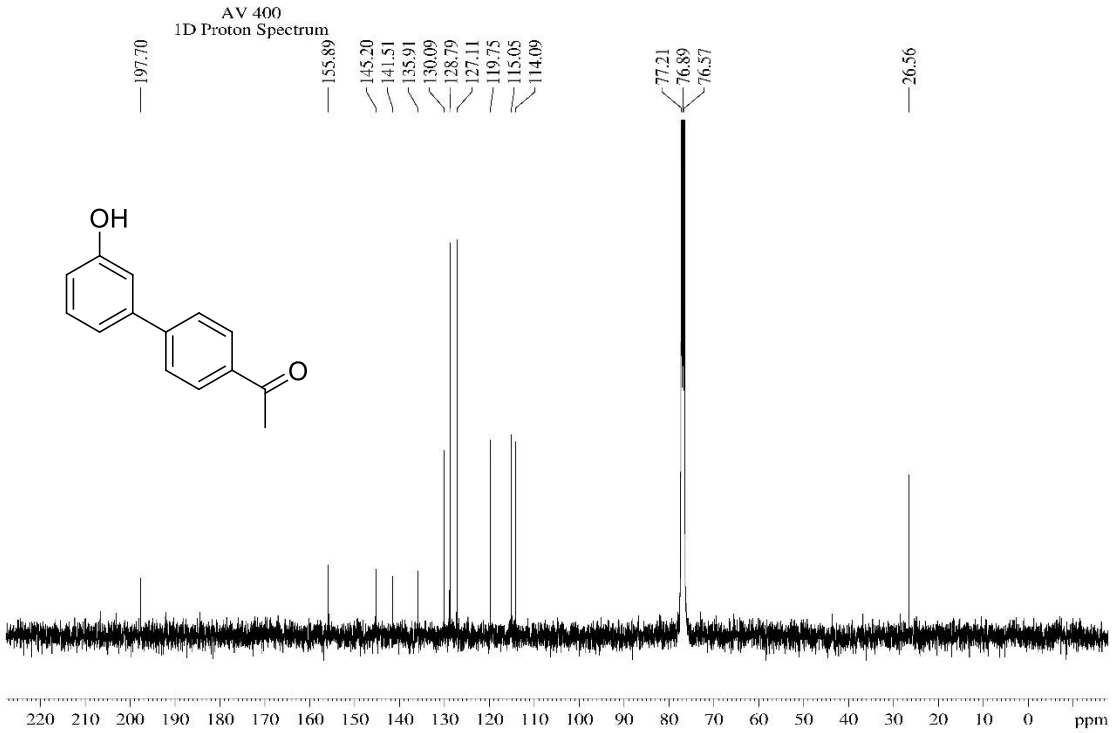
^{1}H and ^{13}C spectra of Phenol 8



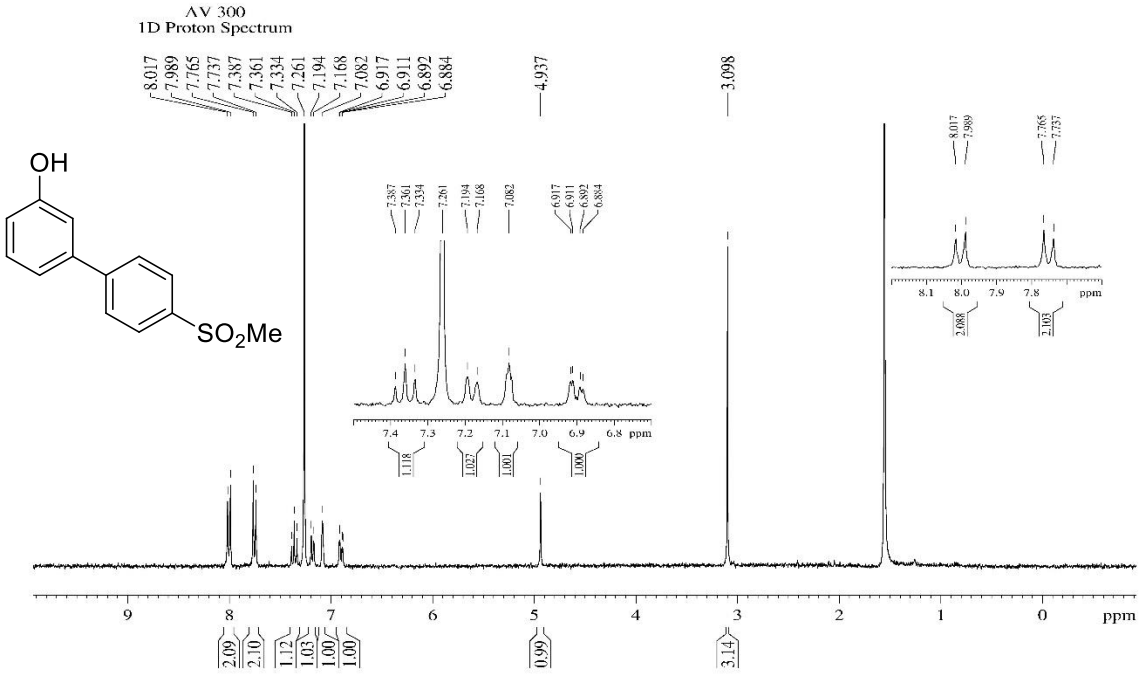


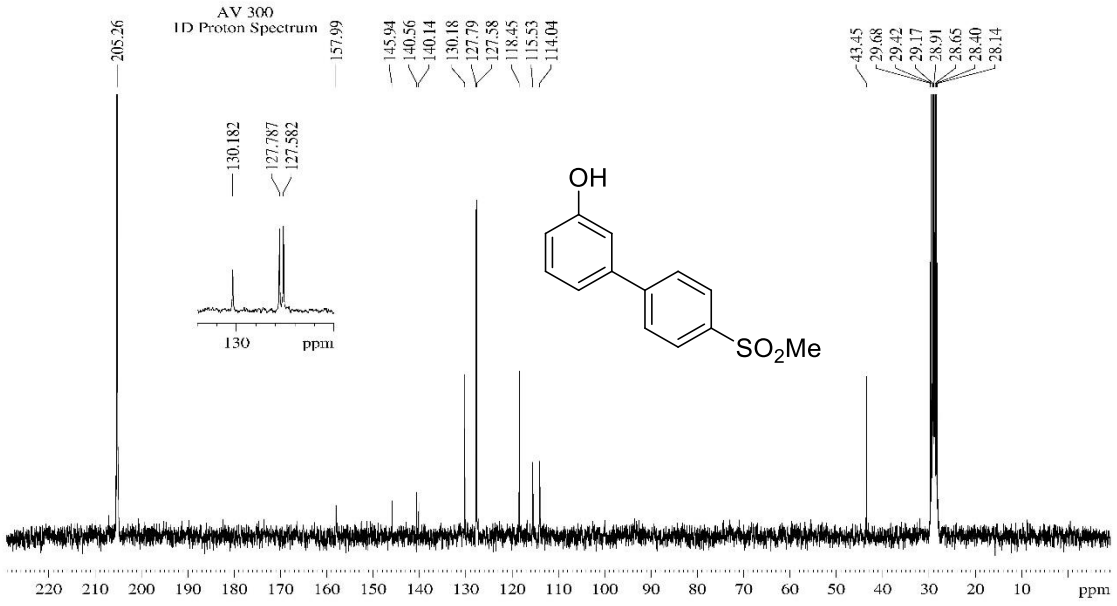
^{1}H and ^{13}C spectra of Phenol 10



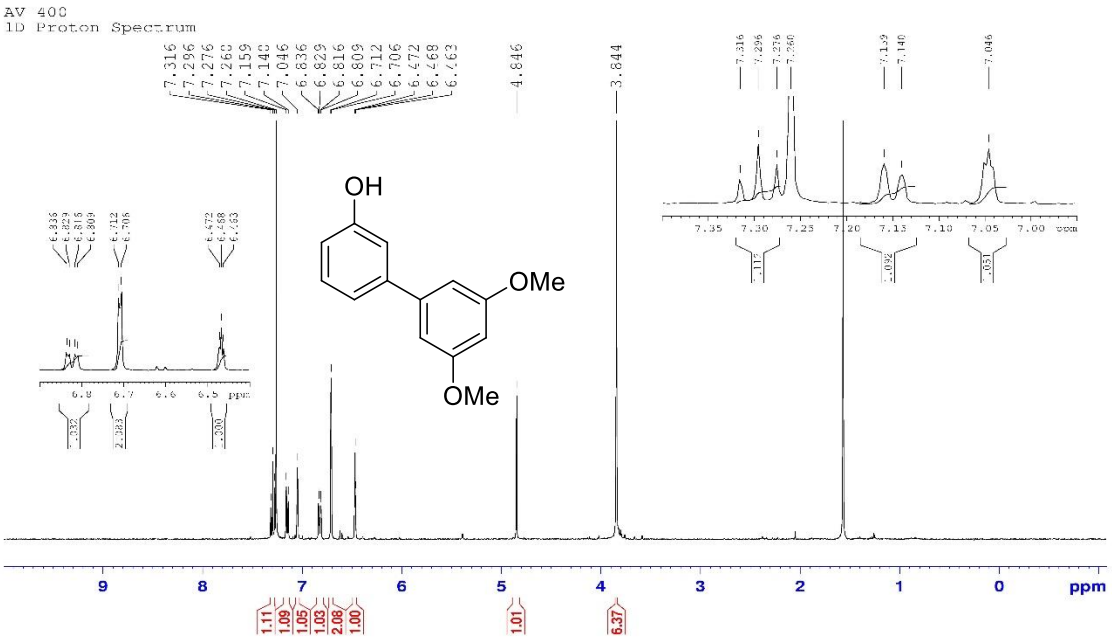


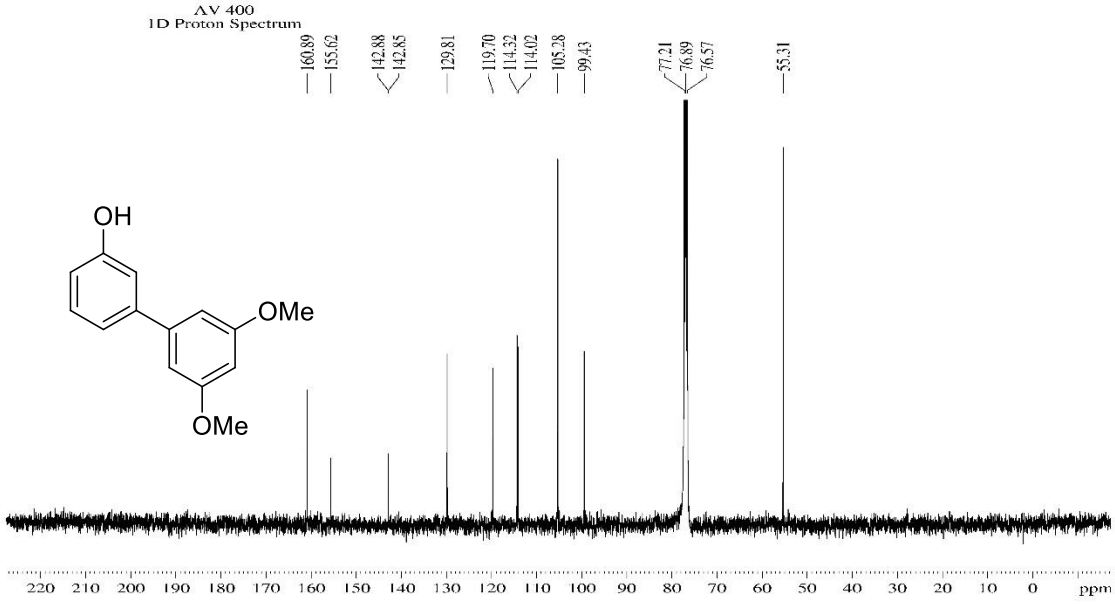
^{1}H and ^{13}C spectra of Phenol 11



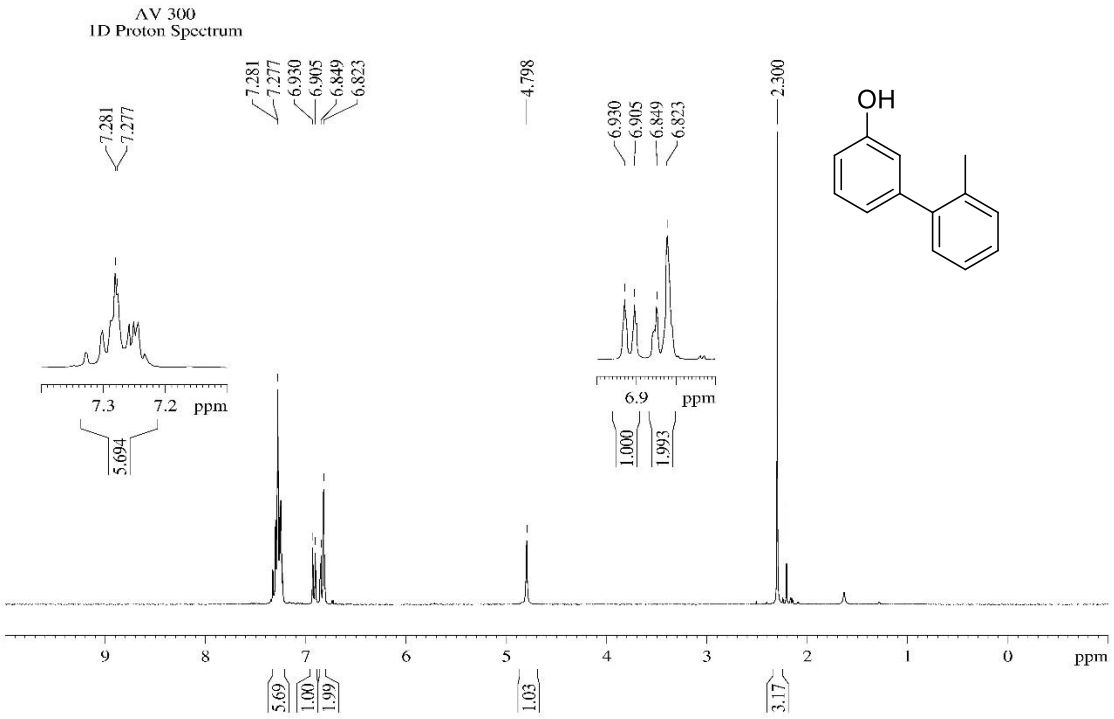


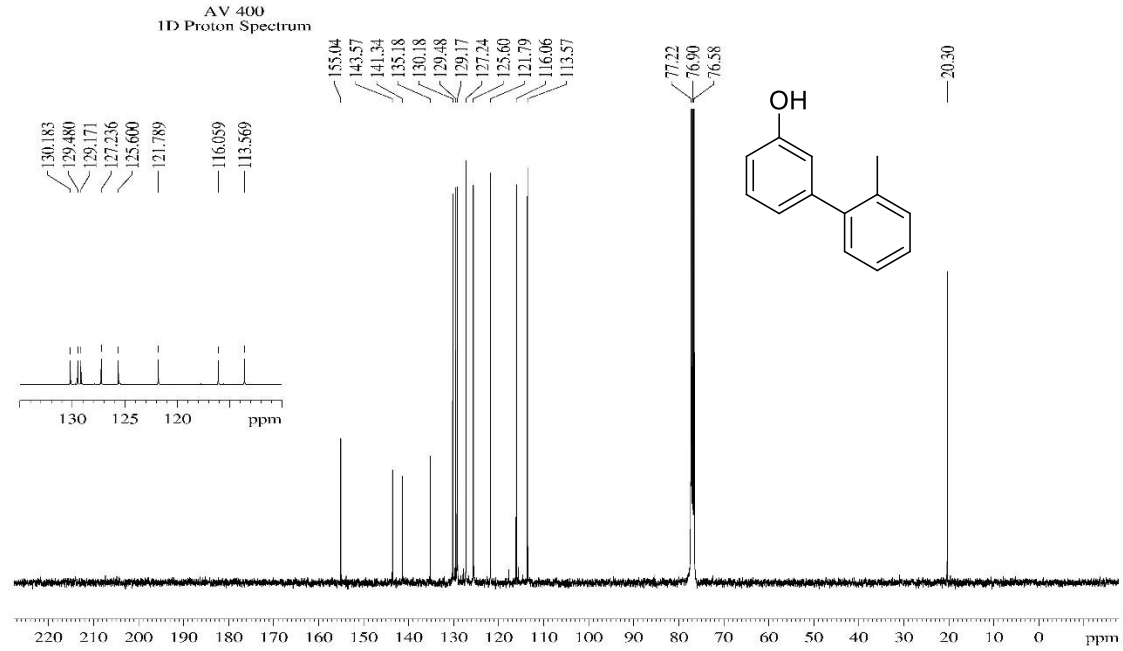
^{1}H and ^{13}C spectra of Phenol 12



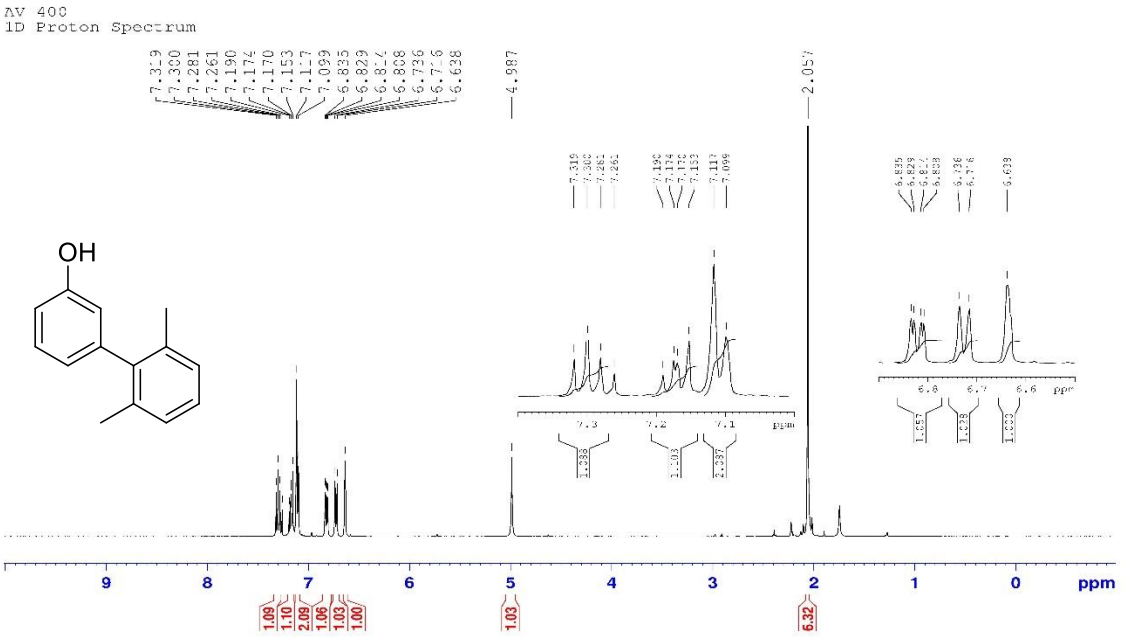


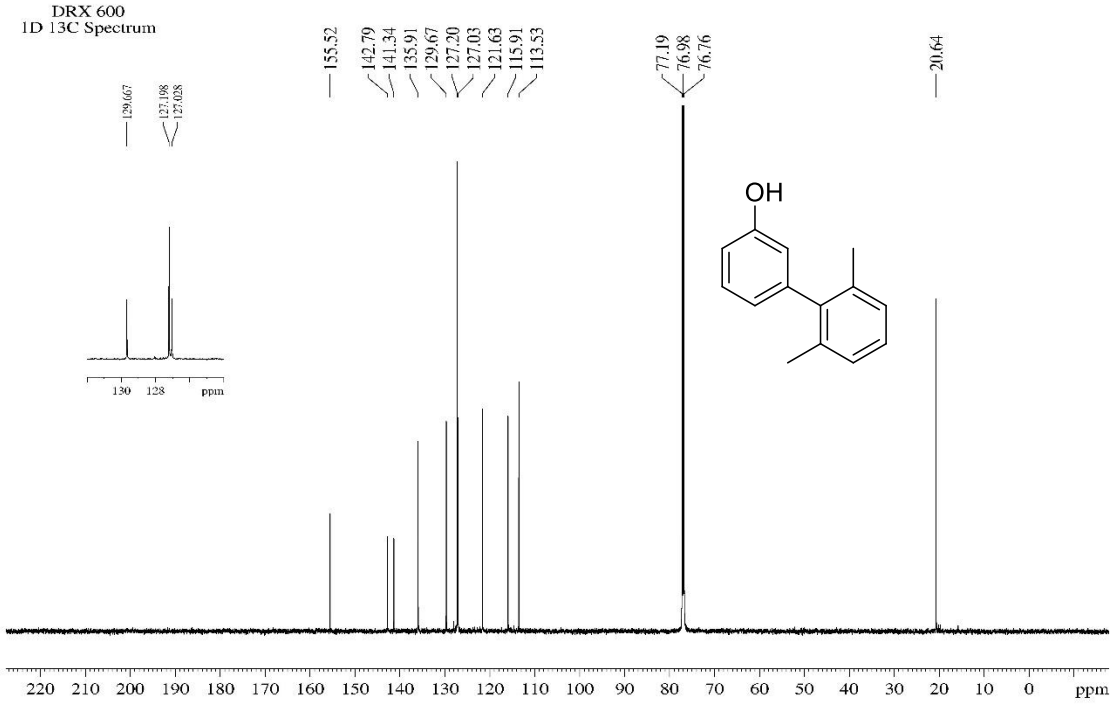
^{1}H and ^{13}C spectra of Phenol 13



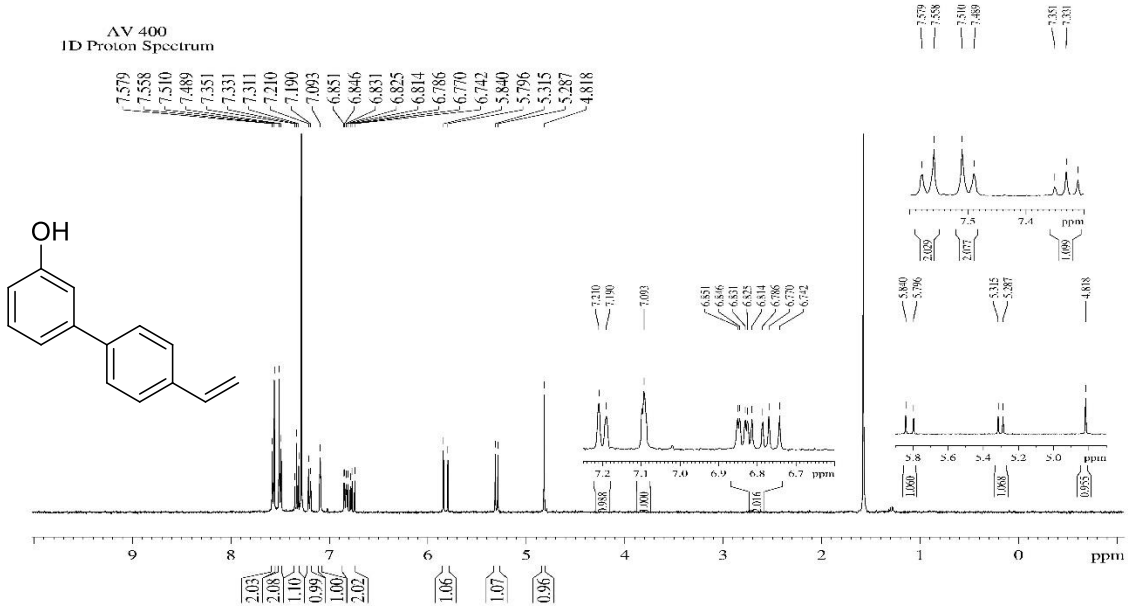


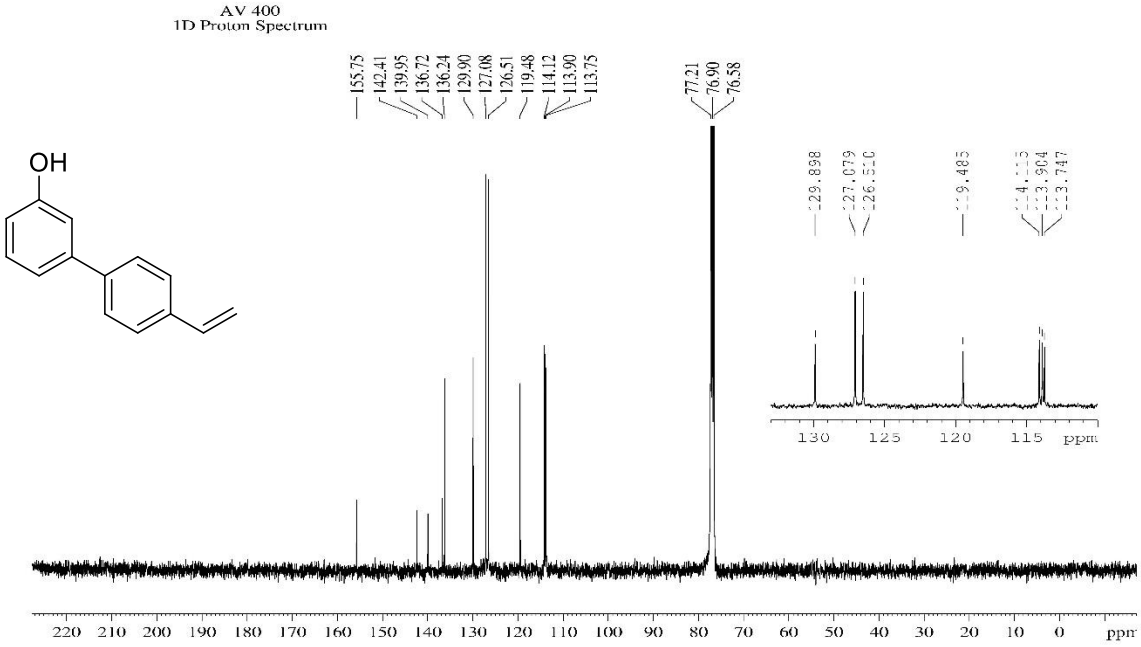
^{1}H and ^{13}C spectra of Phenol 14



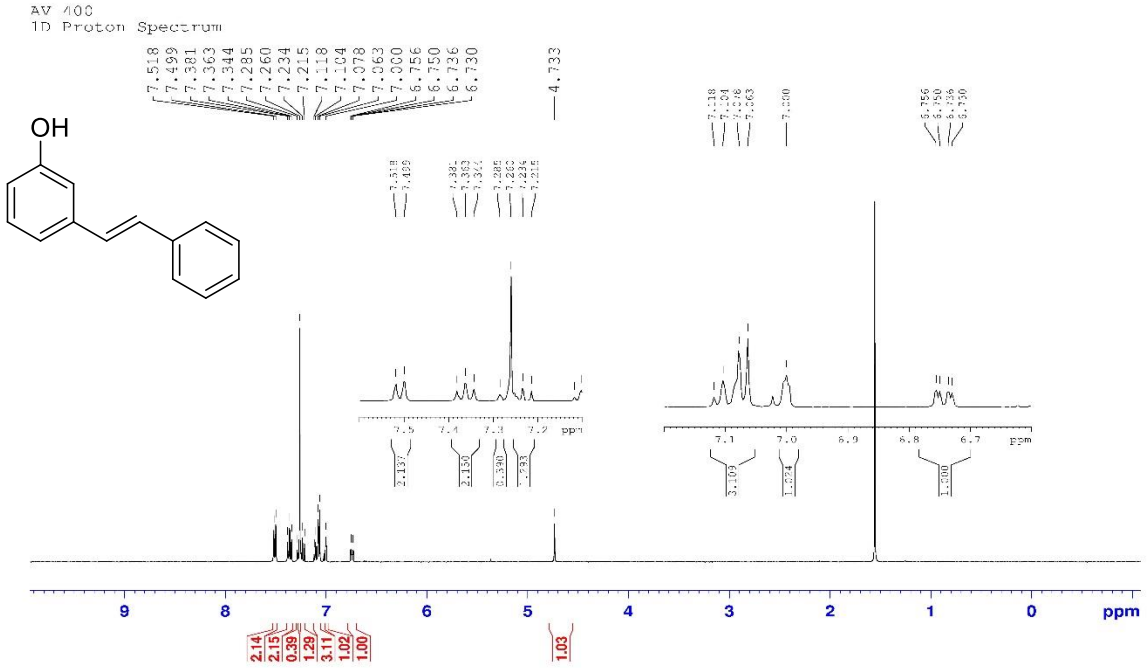


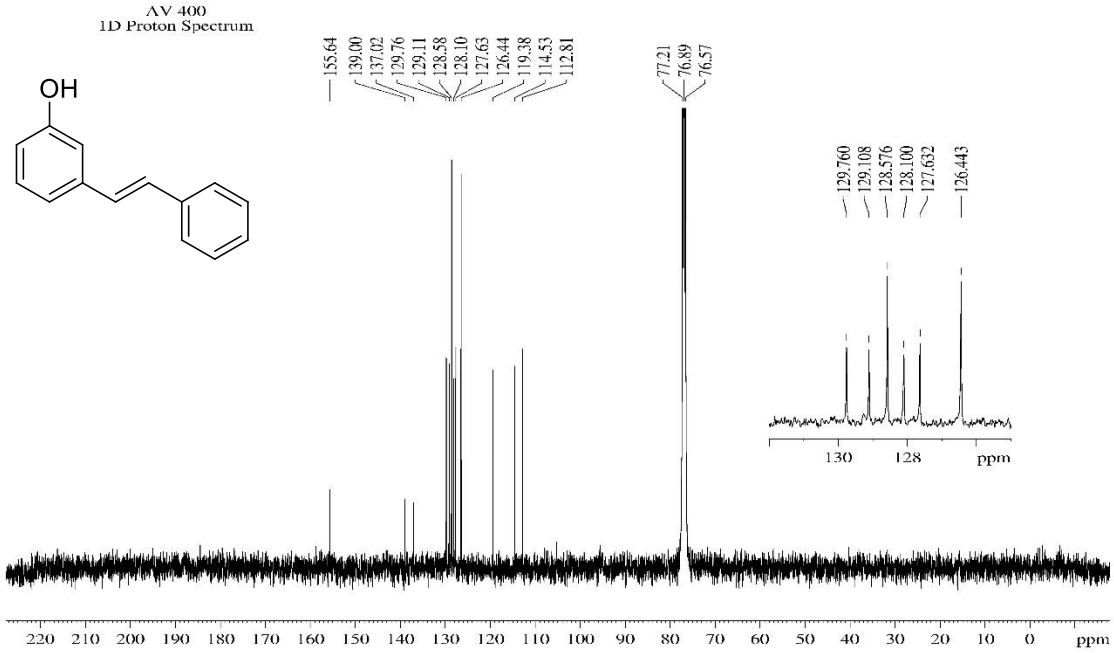
^{1}H and ^{13}C spectra of Phenol 18



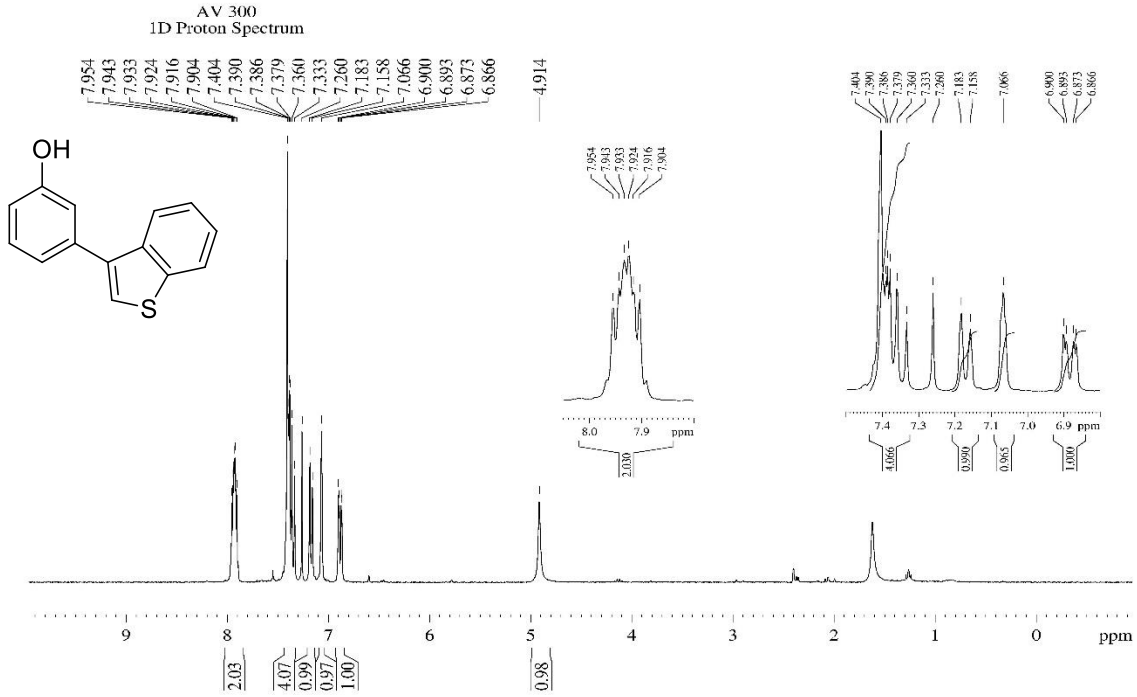


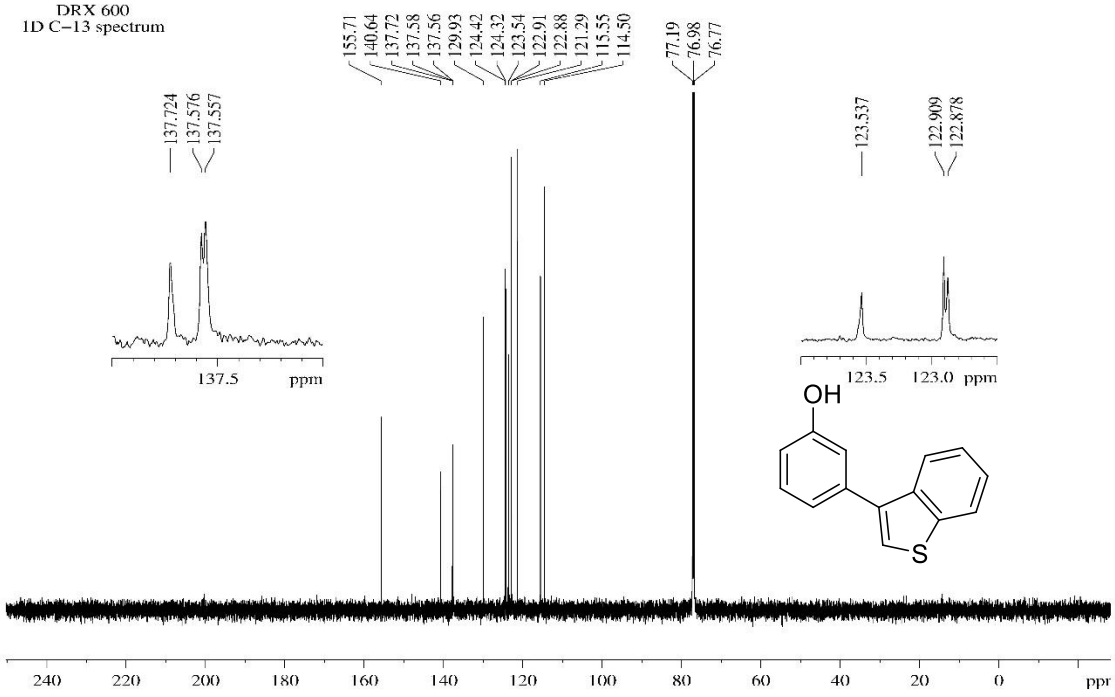
^{1}H and ^{13}C spectra of Phenol 15



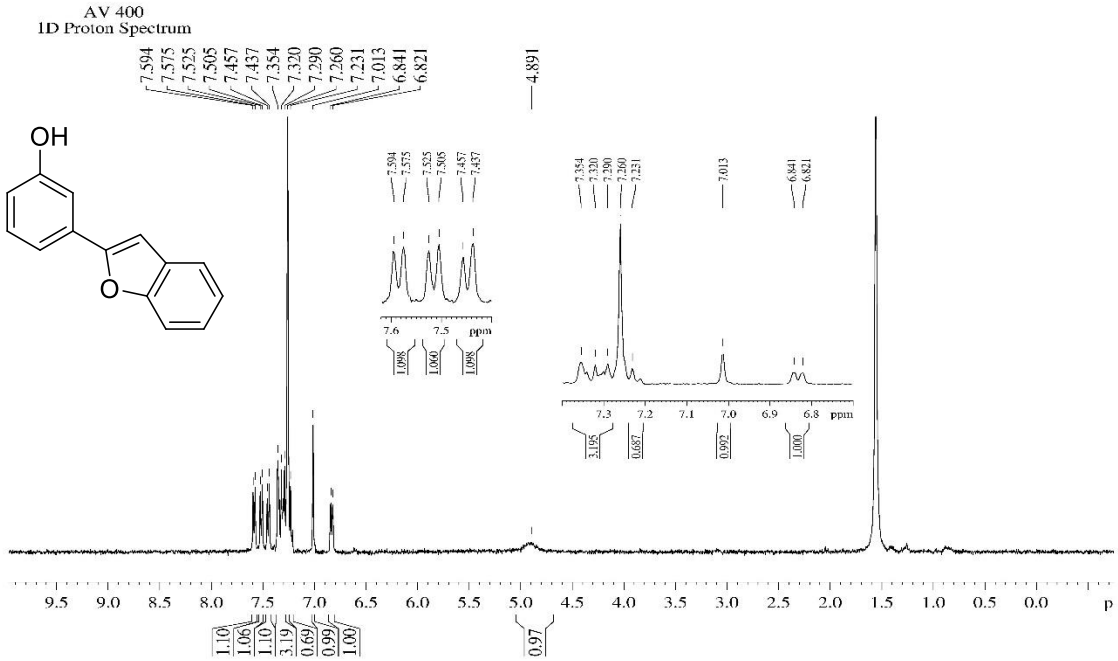


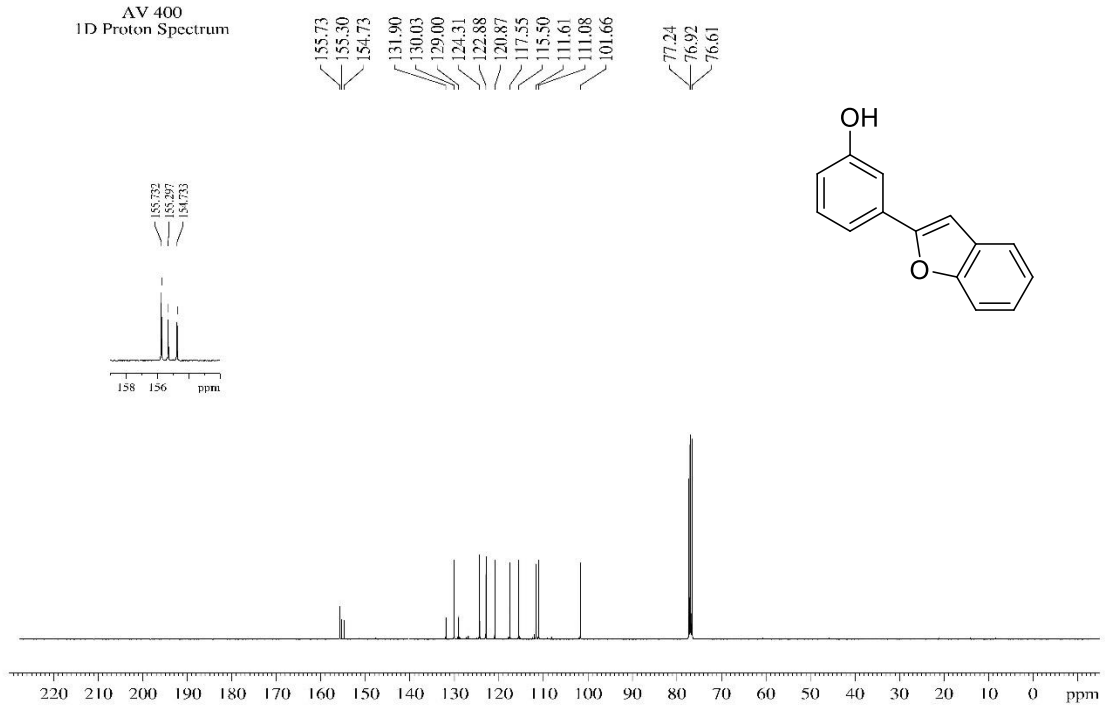
^{1}H and ^{13}C spectra of Phenol 16



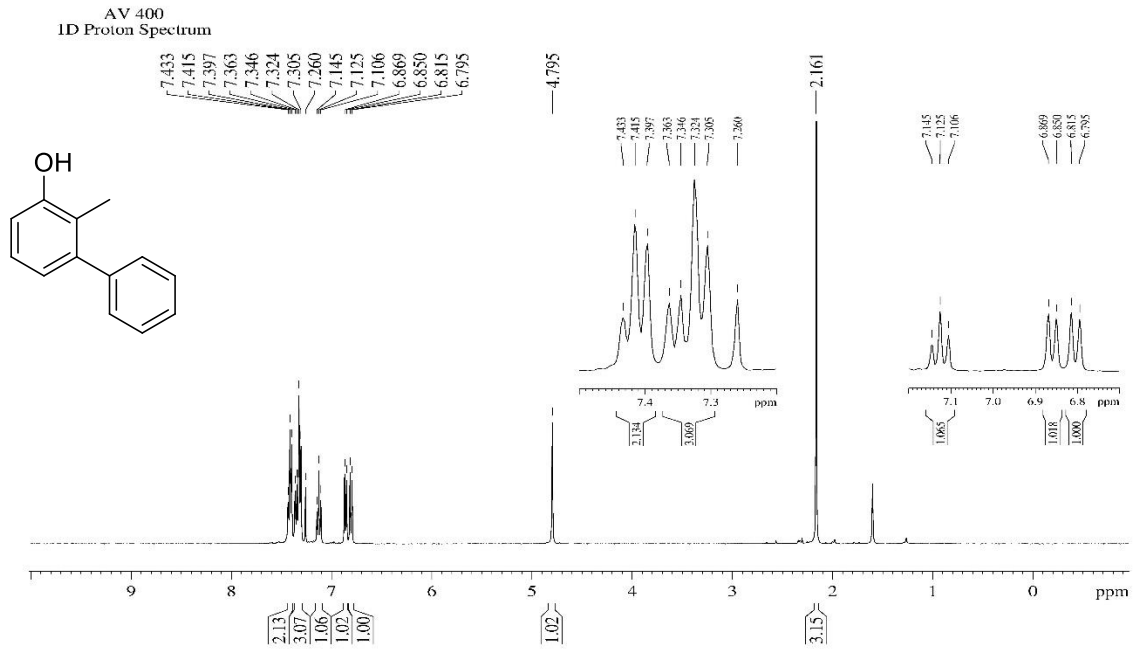


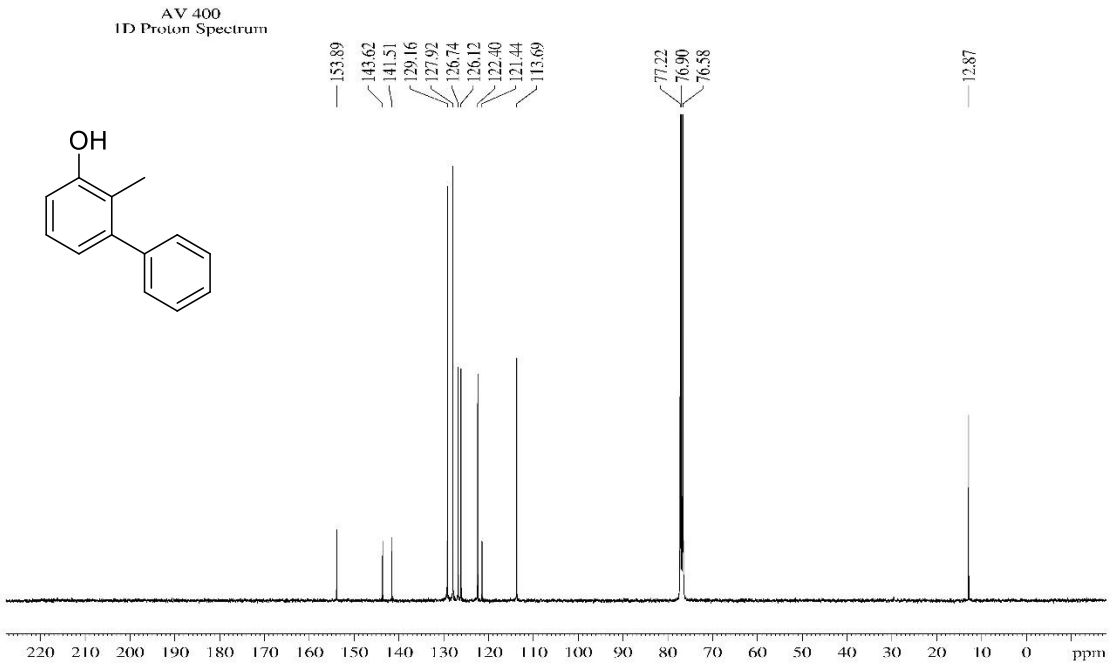
^{1}H and ^{13}C spectra of Phenol 17



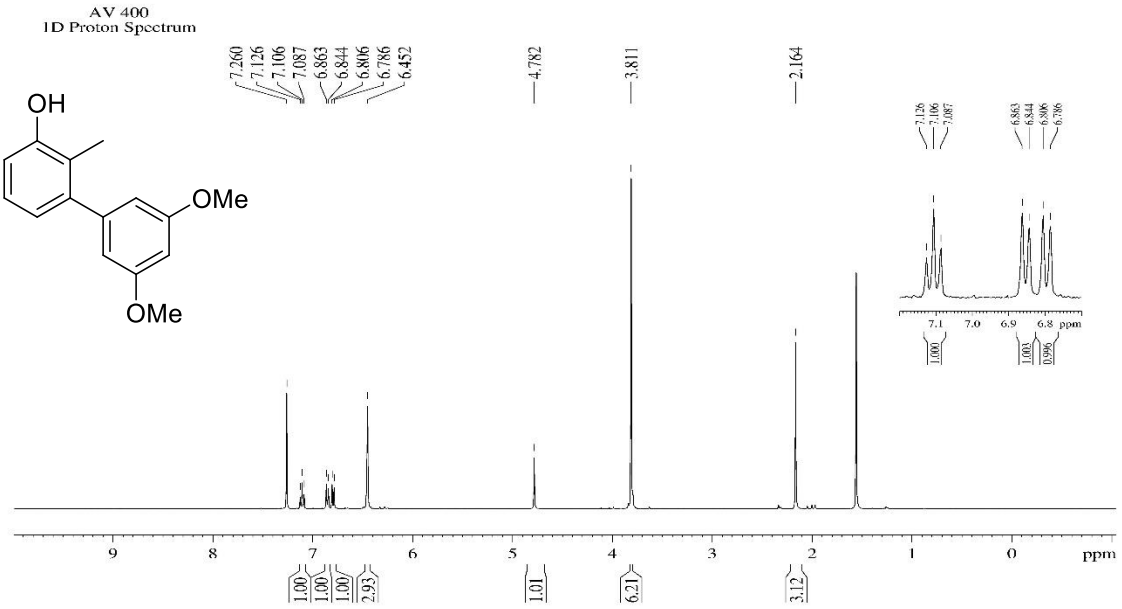


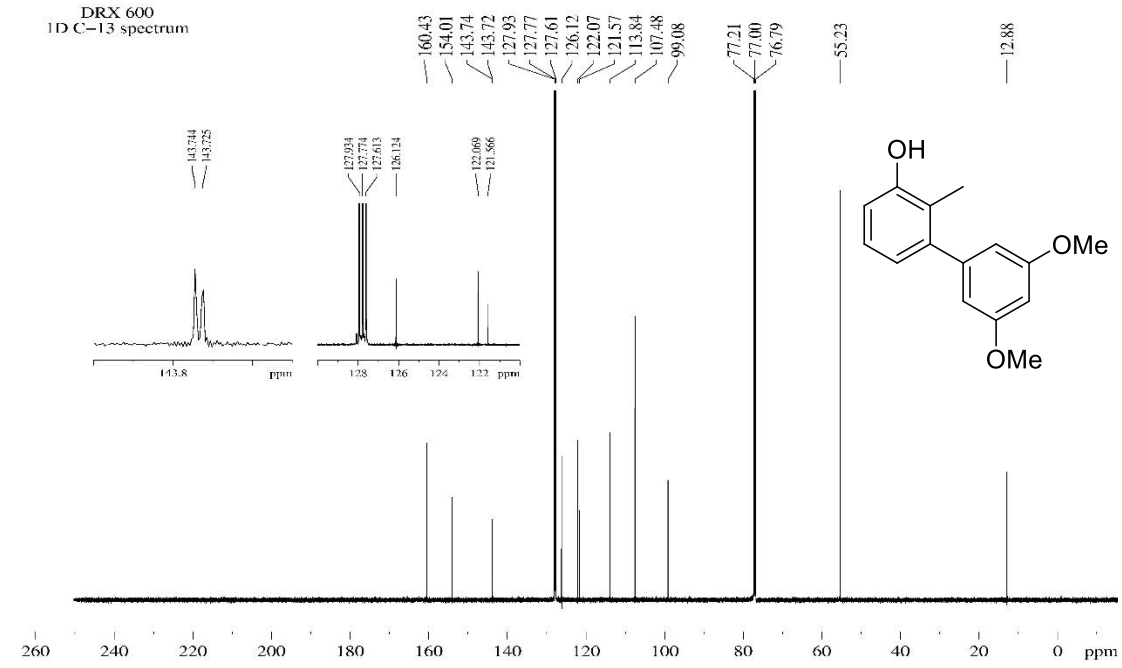
^{1}H and ^{13}C spectra of Phenol 19



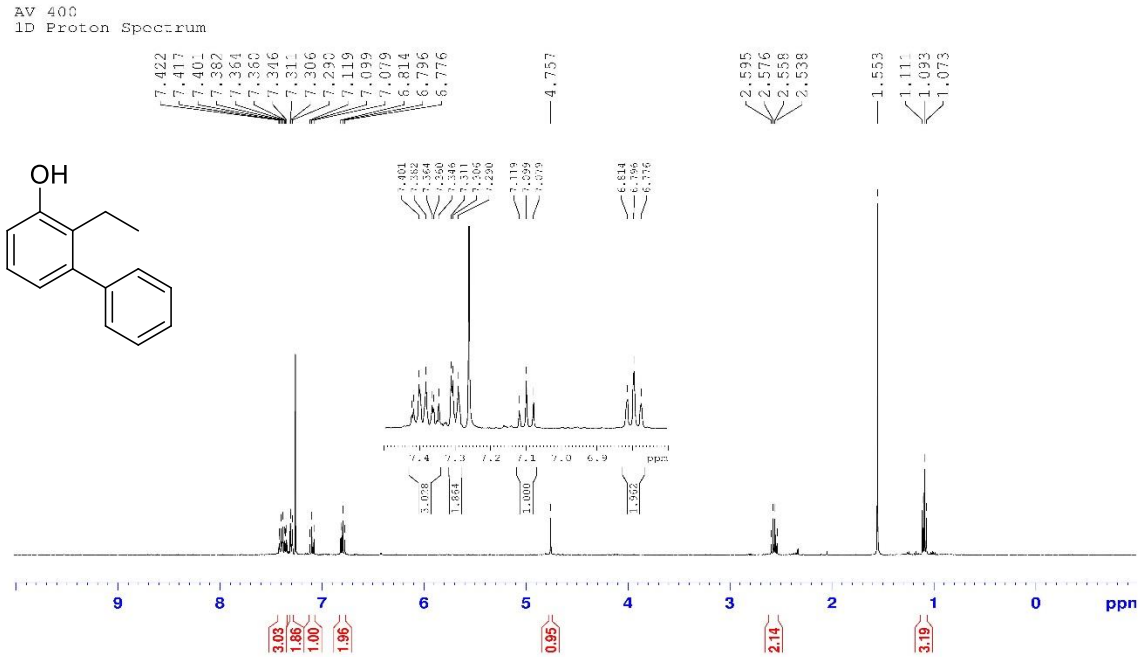


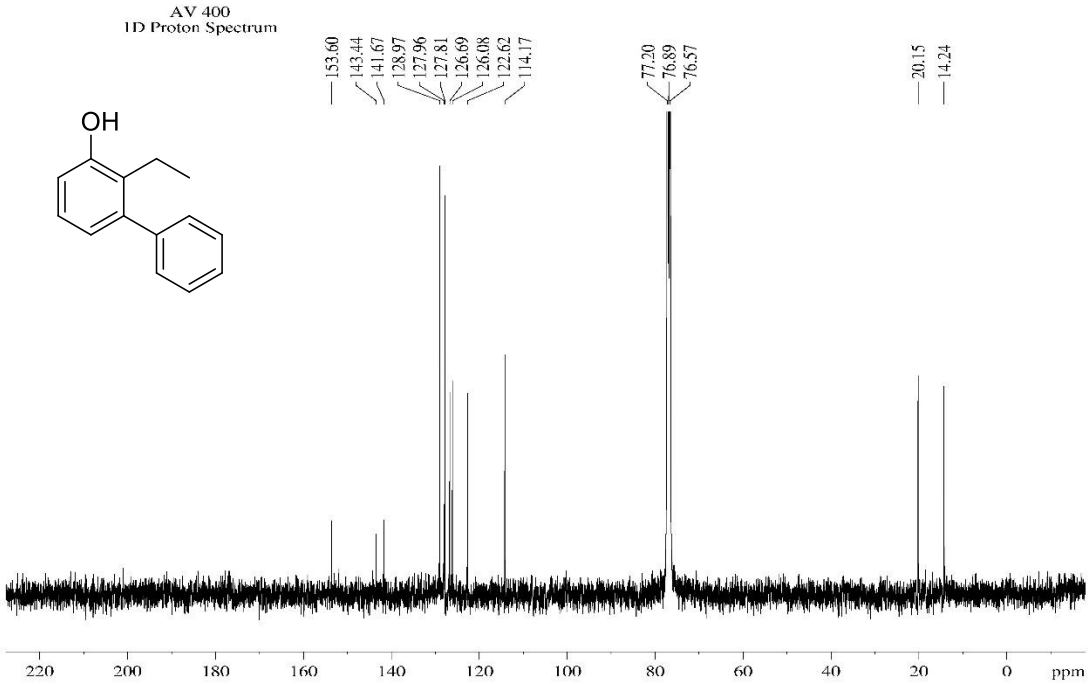
^{1}H and ^{13}C spectra of Phenol 20



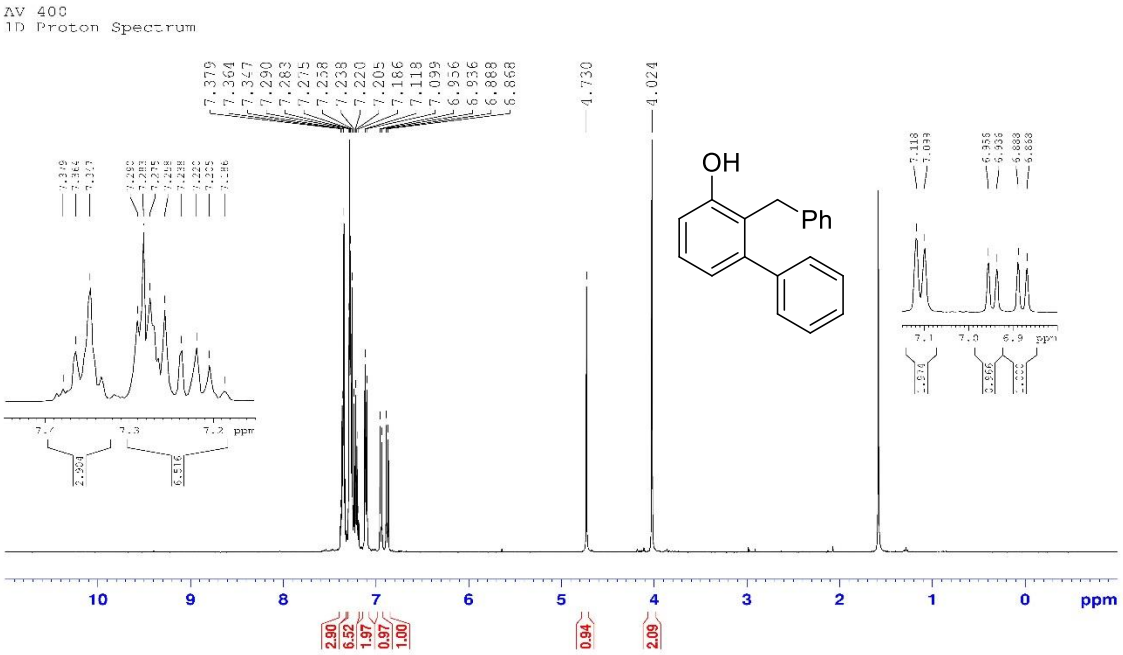


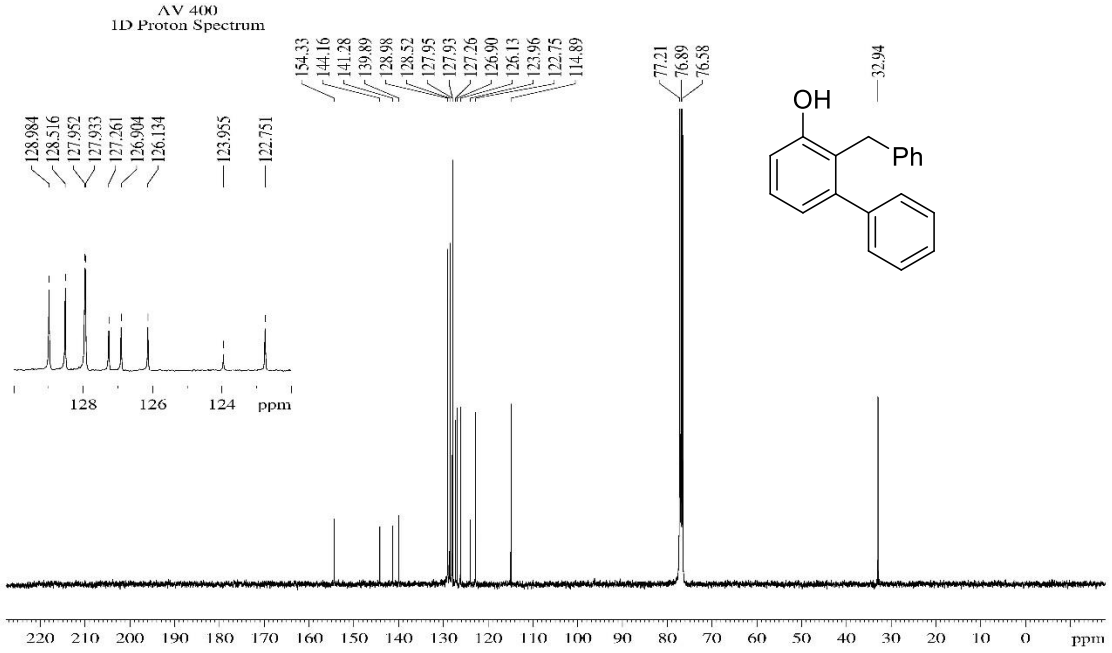
^{1}H and ^{13}C spectra of Phenol 21



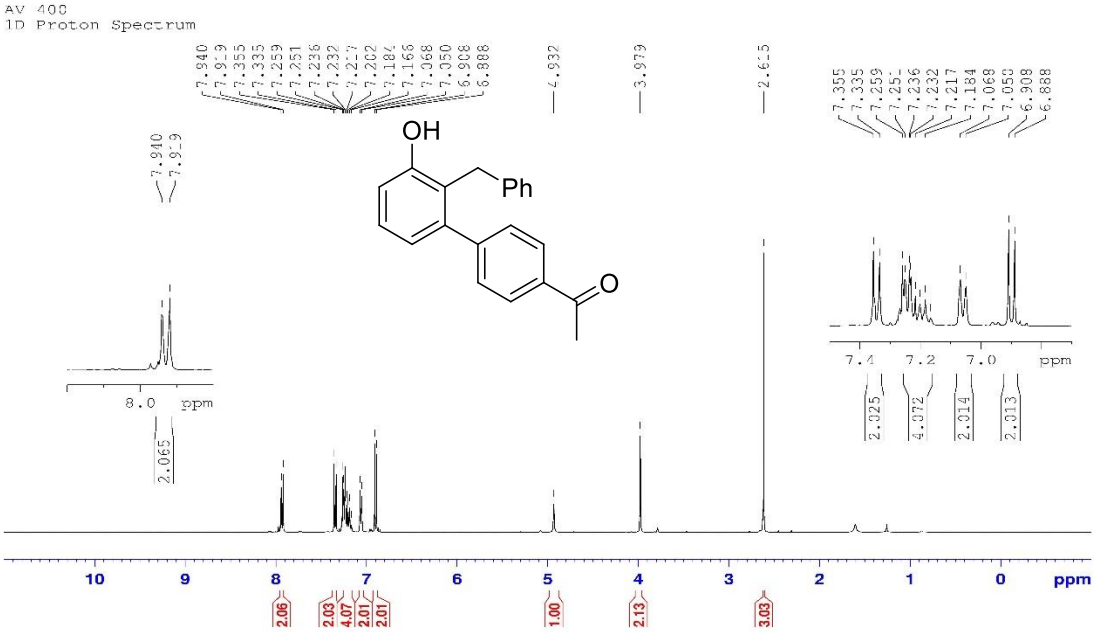


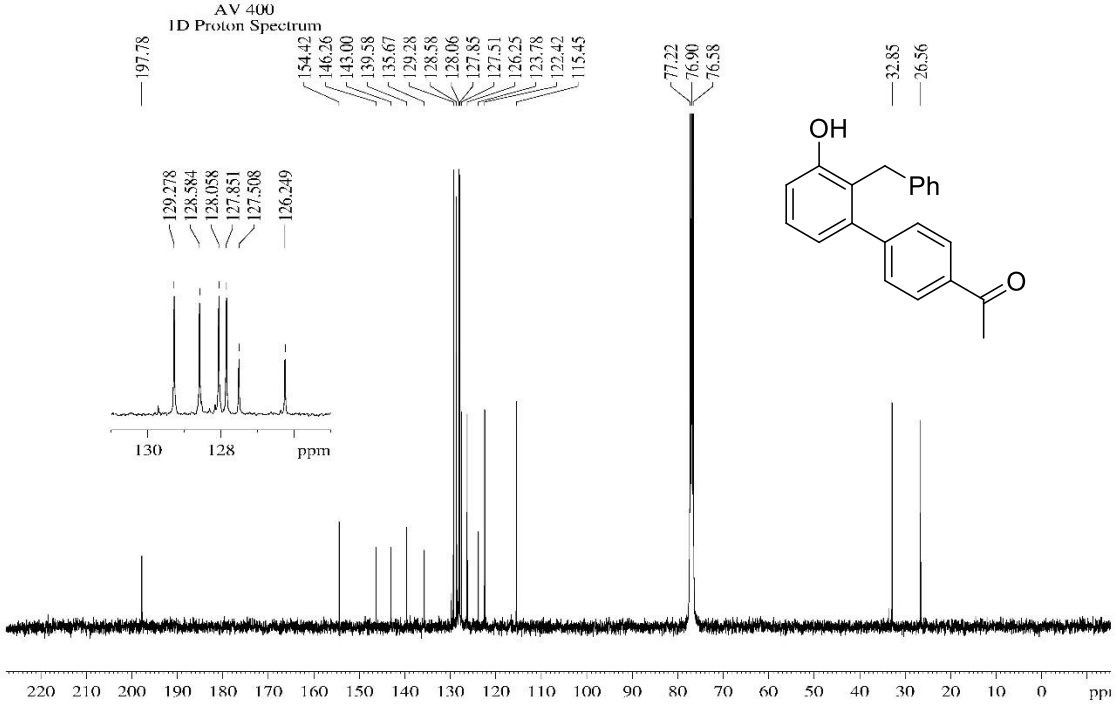
^{1}H and ^{13}C spectra of Phenol 22



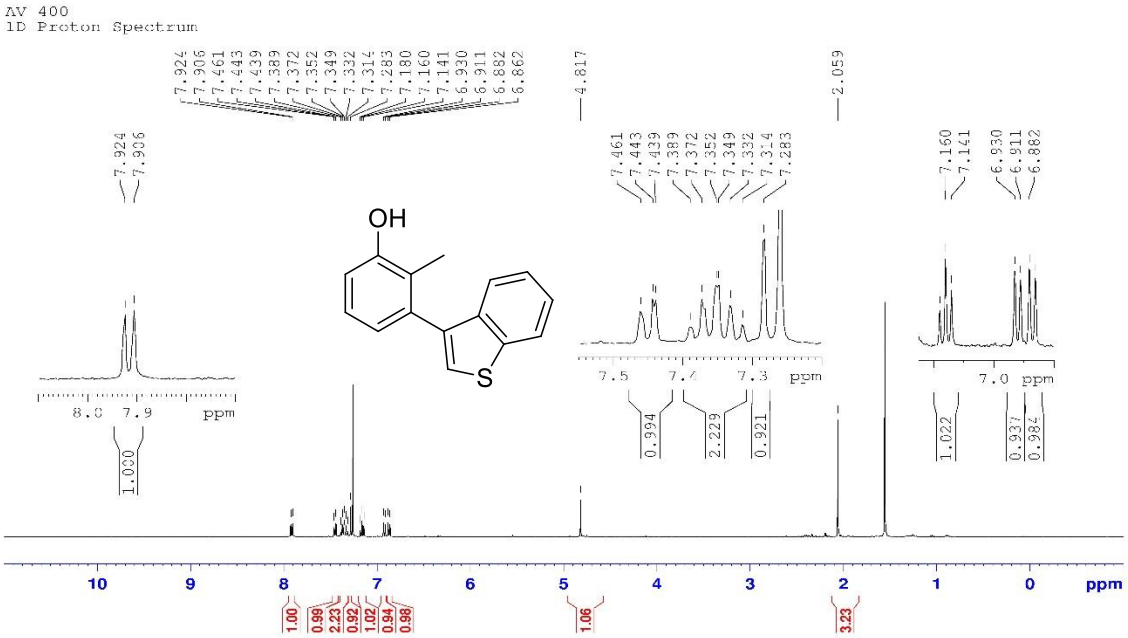


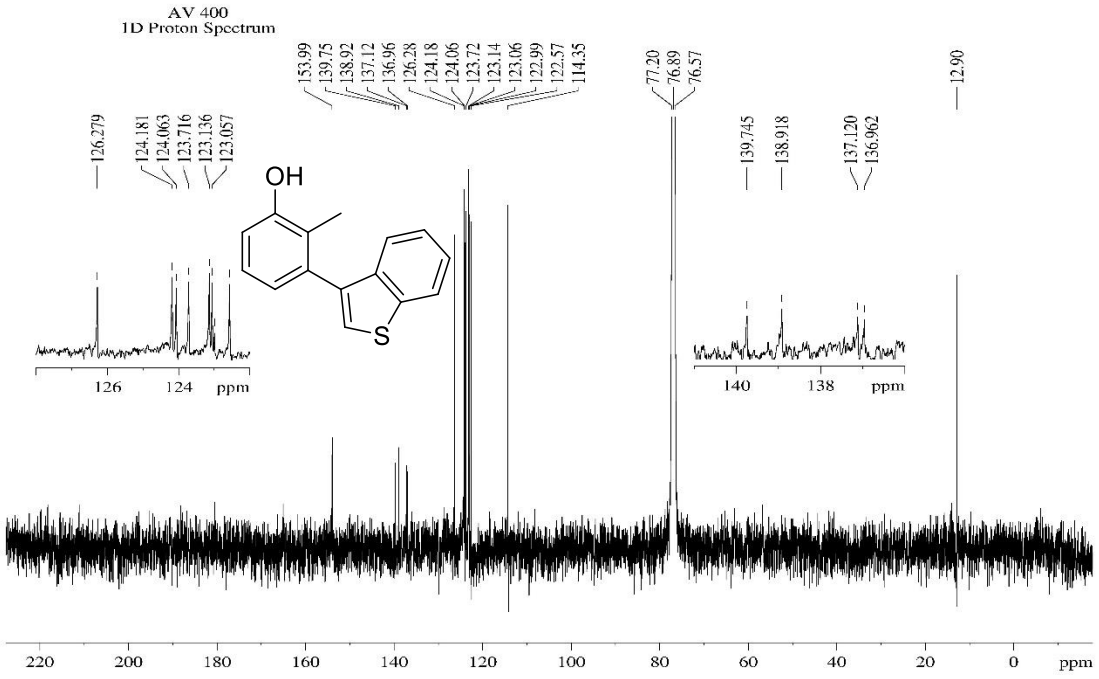
^{1}H and ^{13}C spectra of Phenol 23



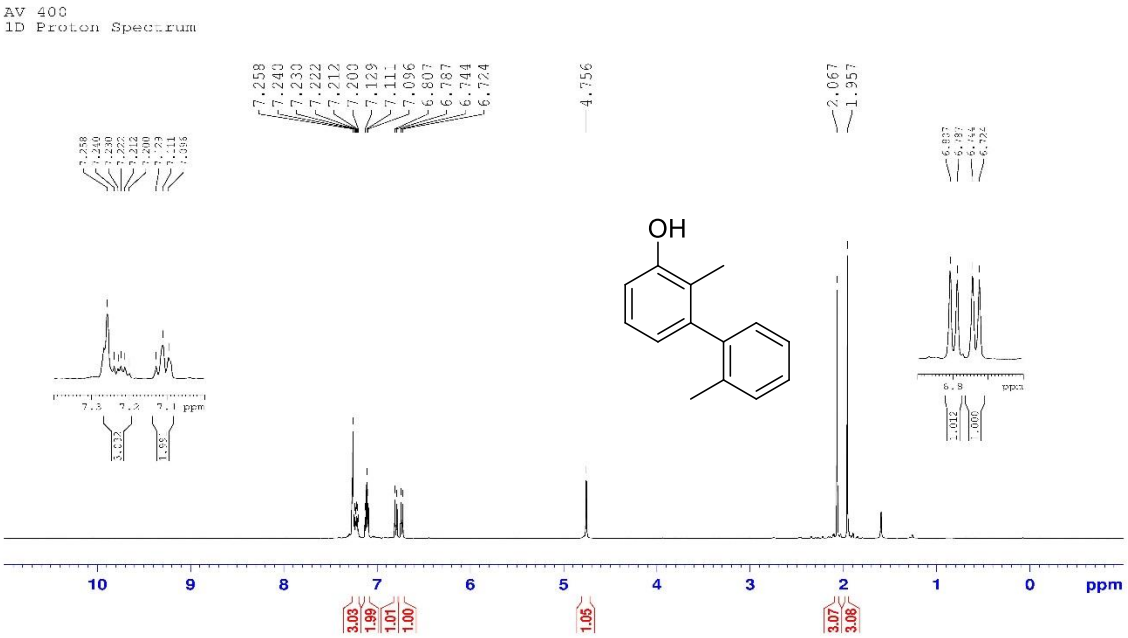


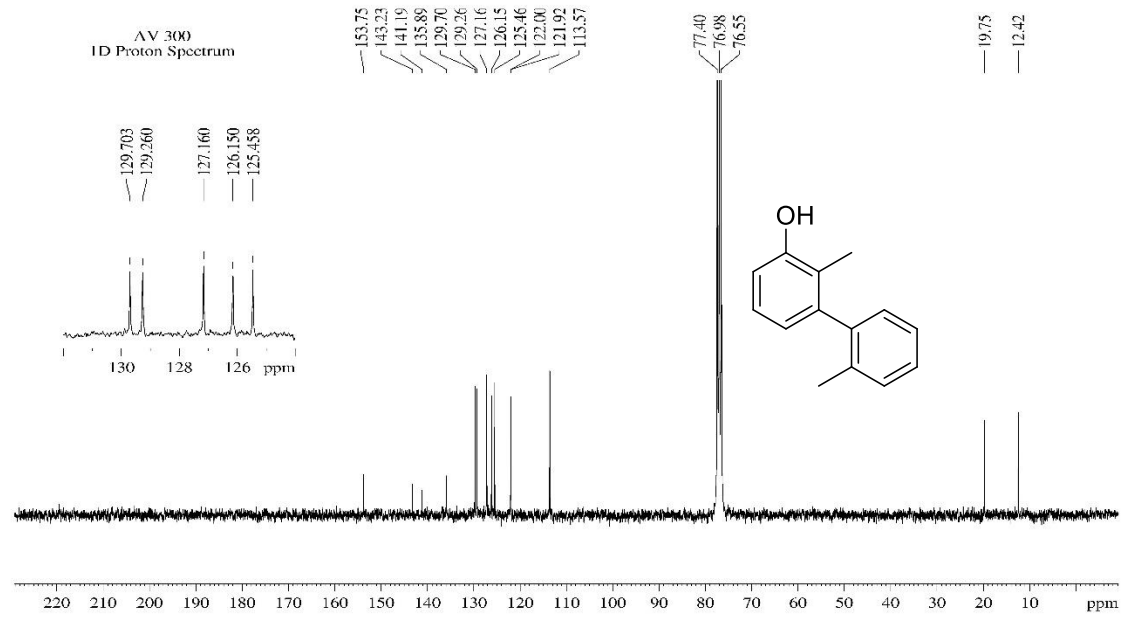
^{1}H and ^{13}C spectra of Phenol 24



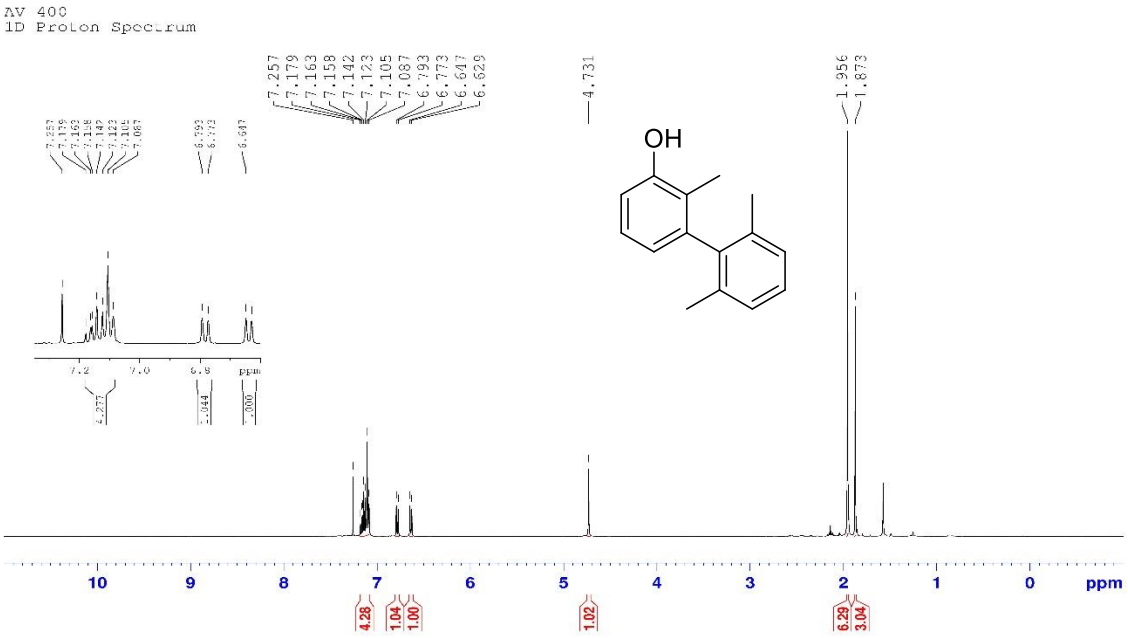


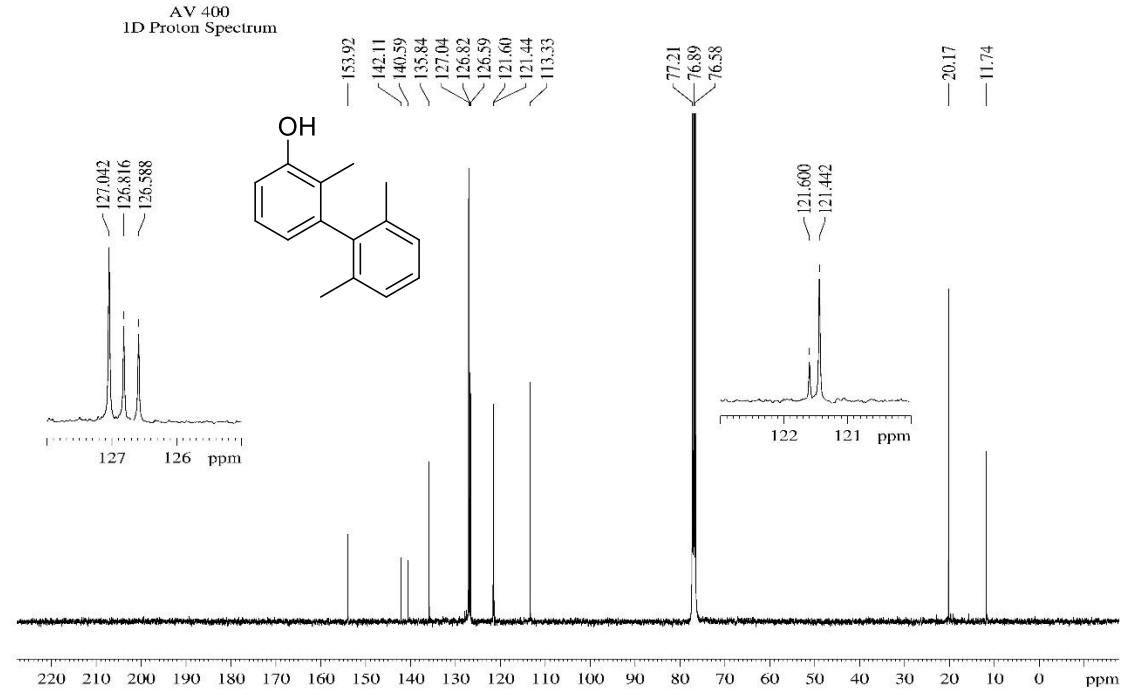
^{1}H and ^{13}C spectra of Phenol 25



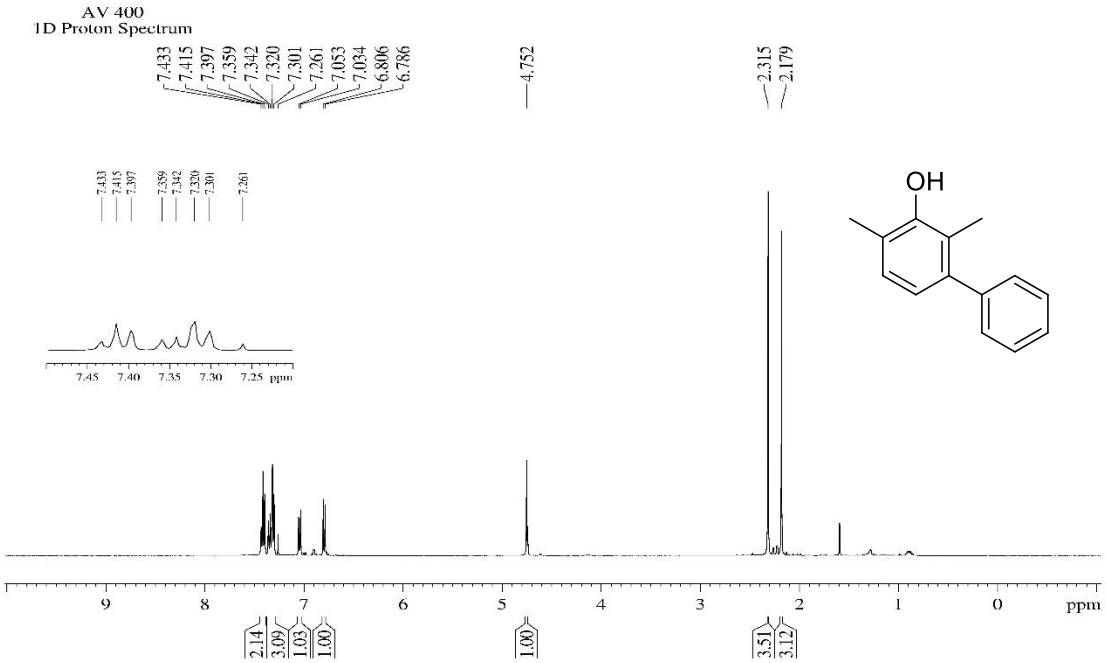


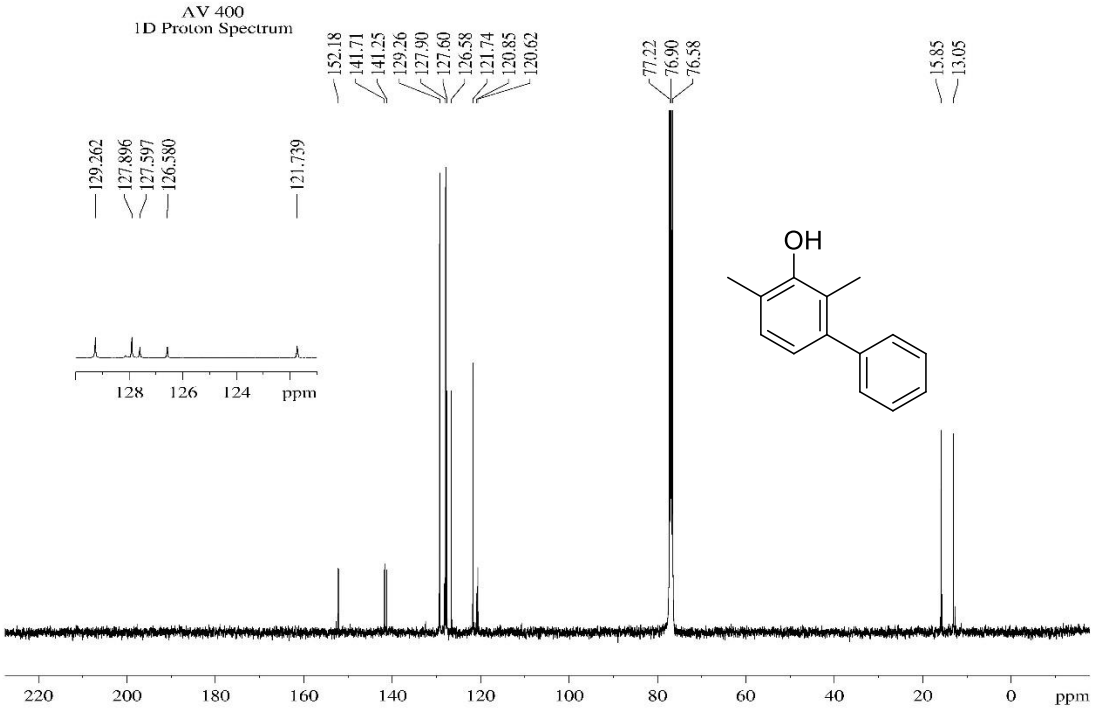
^{1}H and ^{13}C spectra of Phenol 26



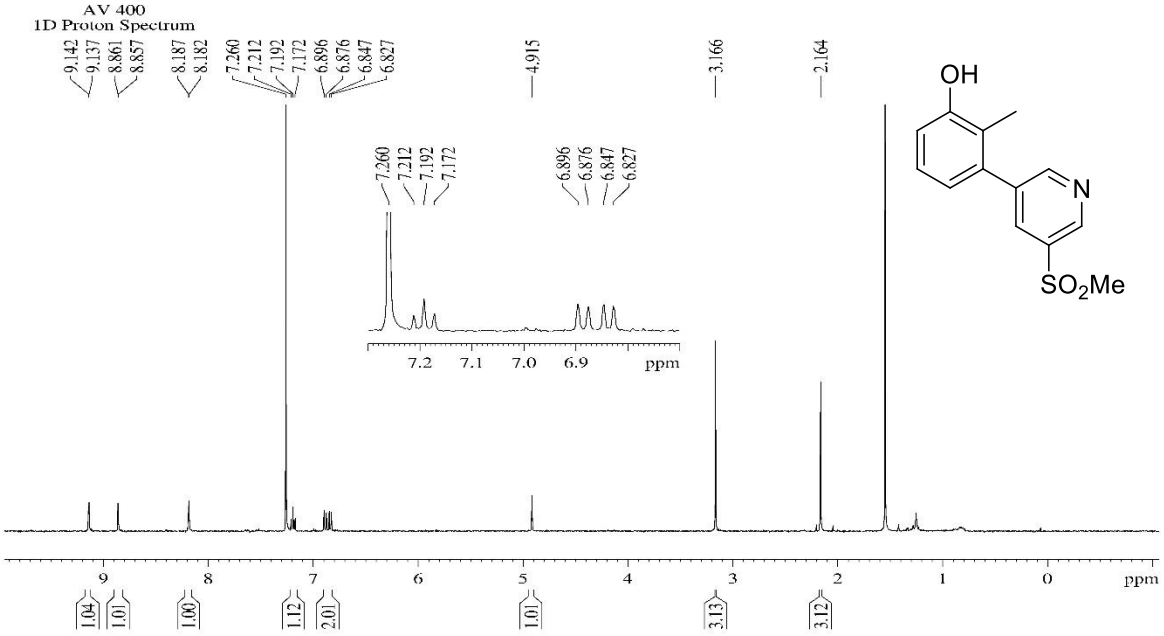


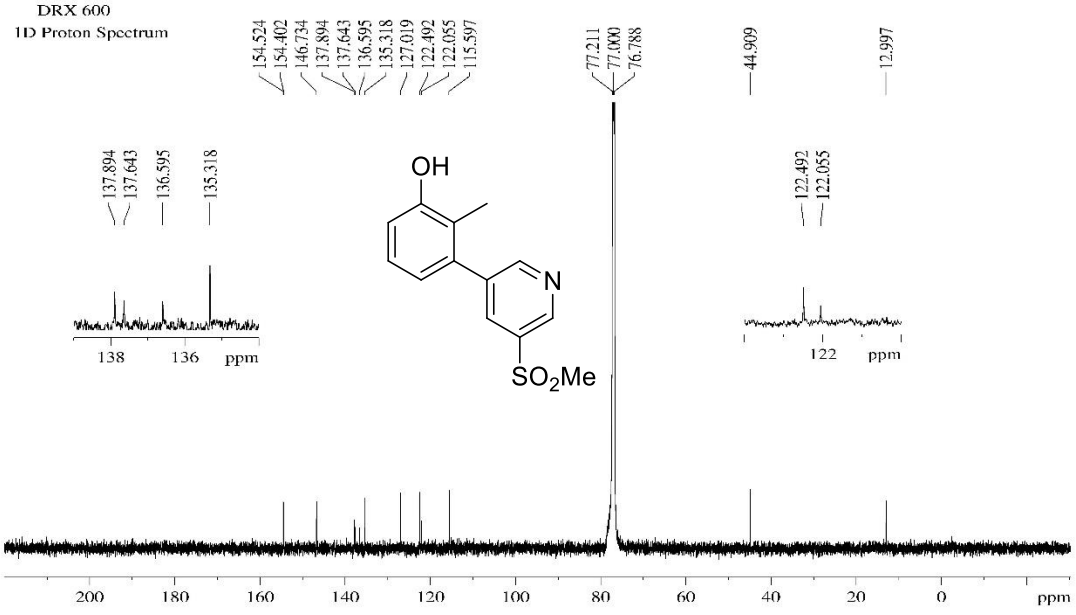
^{1}H and ^{13}C spectra of Phenol 27



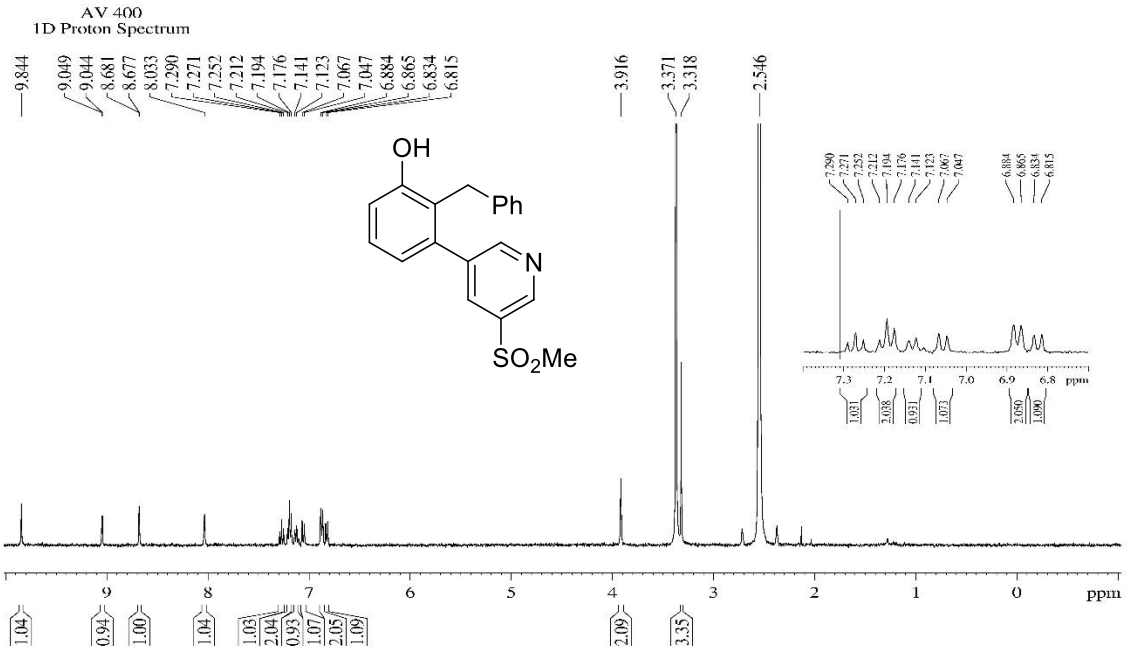


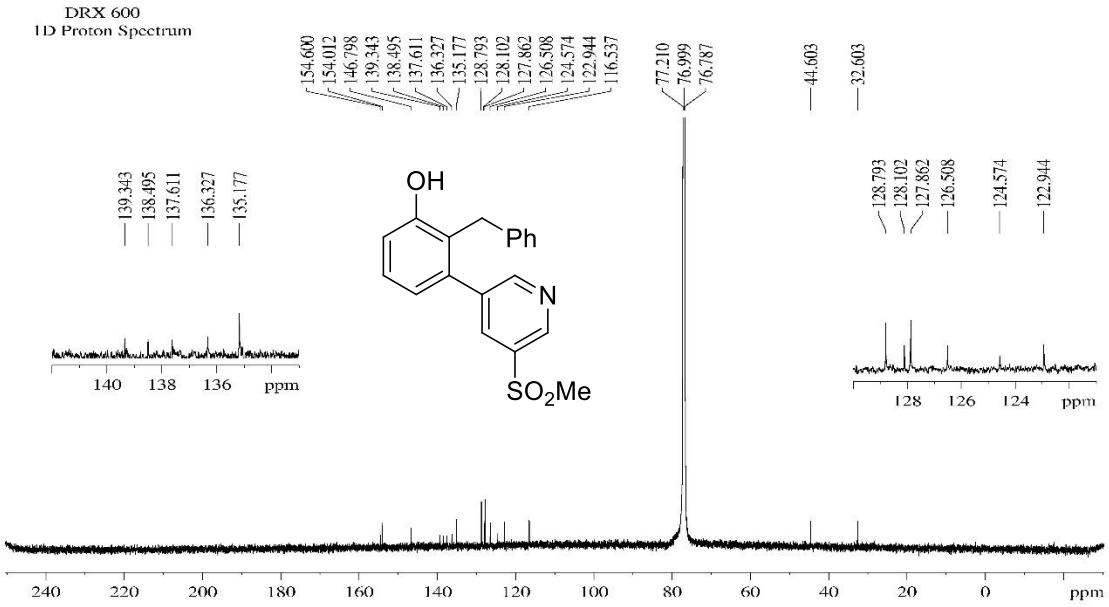
^{1}H and ^{13}C spectra of Phenol 28





^{1}H and ^{13}C spectra of Phenol 29





References

[1] Crabtree, R. H., *The Organometallic Chemistry of the Transition Metals;* Wiley: New York, 2009.

[2] Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice;* Oxford University Press: New York, 1998.

[3] Hartley, R. C.; Li, J.; Main, C. A.; McKiernan, G. J. *Tetrahedron,* **2007***, 63,* 4825-4864.

[4] Lindlar, H.; Dubuis, R. *Org. Synth.* **1966,** *5*, 880.

[5] Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81,* 4256.

[6] Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524.

[7] Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98,* 6729-6731.

[8] Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20,* 3437-3440.

[9] Hatanaka, Y.; Hiyama, T. *J. Org. Chem*. **1988,** *53,* 918-920.

[10] Tamao, K; Sumitani, K; Kumada, M. *J. Am. Chem. Soc.* **1972,** *94,* 4374-4376.

[11] Martin, R.; Buchwald, S. L., *Acc. Chem. Res*. **2008**, *41,* 1461-1473.

[12] Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98,* 5832.

[13] Bock, P. L.; Boschetto, D. J.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2814.

[14] Ellis, P. R.; Pearson, J. M.; Haynes, A.; Adams, H.; Bailey, N. A.; Maitlis, P. M. *Organometallics,* **1994**, 23, 3215.

[15] Senn, H. M.; Ziegler, T. *Organometallics,* **2004**, *23*, 2980.

[16] Casado, A.; Espinet, P. *Organometallics,* **1998,** *17,* 954-959.

[17] Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387-3388.

[18] Suzuki, A. *J. Organomet. Chem.* **1999**, *576,* 147-168.

[19] Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116-2119.

[20] Lennox, A.; Lloyd-Jones, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 7362-7370.

[21] Thomas, A.; Denmark, S. *Science*, **2016**, *352*, 329-332.

[22] Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149-151.

[23] Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011***, 17,* 2492-2503.

[24] Schmidt, A. F.; Kurokhtina, A. A.; Larina, E. V*. Russ. J. Gen. Chem.* **2011***, 81,* 1573-1574.

[25] Gillie, S. *J. Am. Chem. Soc.* **1980**, *102*, 4933.

[26] Amatore, C.; Carre, E.; Jutland, A.; M'Barke, M. A. *Organometalics,* **1995,** *14,* 1818.

[27] Wolfe, J. P., Buchwald, S. L. *Angew. Chem., Int. Ed.,* **1999**, *38,* 2413-2416.

[28] Tolman, C. A. *Chem. Rev.,* **1977**, *77*, 313-348.

[29] Culkin, D. A.; Hartwig, J, F. *Organometallics* **2004**, *23*, 3398-3416.

[30] Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J, F. *Organometallics,* **2003**, *22*, 2775-2789.

[31] Barder, T.; Walker, S.; Martinelli, J.; Buchwald, S. *J. Am. Chem. Soc*. **2005,** *127,* 4685-4696.

[32] Cowden, C. J.; Hammond, D. C.; Bishop, B. C.; Brands, K.; Davies, A. J.; Dolling, U.; Brewer, S. E. *Tetrahedron Lett.,* **2004**, *45*, 6125-6128.

[33] Fleckenstein, C. A.; Plenio, H. *Chem. Soc. Rev.,* **2010,** *39*, 694-711.

[34] Valentine, D. H., Hillhouse, J. H. *Synthesis,* **2003,** 2437-2460.

[35] Hermann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290-1329.

[36] Navarro, O.; Marion, N.; Scott, N. M.; Gonzalez, J.; Amaroso, D.; Bell, A.; Nolan, S. P. *Tetrahedron,* **2005**, *61,* 9716-9722.

[37] Viciu, M.S.; Stevens, E.D.; Peterson, J. L.; Nolan, S. P. *Organometallics*, **2004**, *23,* 3752-3755.

[38] Jensen, D. R., Schultz, M. J., Mueller, J. A., Sigman, M. S. *Angew. Chem. Int. Ed.* **2003,** *115,* 3940-3943.

[39] (a) O'Brien, C. J.; Kantchev, E.; Valente, C; Hadei, N; Chass, G. A.; Lough, A; Hopkinson, A. C.; and Organ, M. G.*, Chem. Eur. J.* **2006,** *12,* 4743-4748. (b) Valente, C., Calimsiz, S., Hoi, K. H., Mallik, D., Sayah, M., Organ, M. G., *Angew. Chem. Int. Ed.* **2012**, *51*, 3314-3332.

[40] Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. *Angew. Chem. Int. Ed.,* **1959**, *71*, 176-182.

[41] Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736-1748.

[42] Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2003**, *42,* 3810-3813.

[43] Tu, Y.; Frohn, M.; Wang, Z-X.; Shi, Y. *Org. Synth.* **2003,** *80*, 1.

[44] Wang, A.-Z.; Jiang, H.-F. *J. Org. Chem.* **2010**, *75*, 2321-2326.

[45] Huang, H.-W.; Jiang, H.-F.; Cao, H.; Zhao, J.-W.; Shi, D.-B. *Tetrahedron,* **2012**, *68*, 3135-3144.

[46] Jiang, H.-F.; Shen, Y.-X.; Wang, Z.-Y. *Tetrahedron,* **2008**, *64*, 508-514.

[47] Singh, R.; Kaur, H. *Synthesis,* **2009,** 2471-2491.

[48] Preston, K.; Bigelow, G.; Liebson, I. *J. Pharm. Exp. Ther*. **1987***, 240(3),* 900-910.

[49] Koga, S.; Shiraishi, K.; Saito, Y.*, J. Trauma Acute Care Surg.* **1990**, *30(12),* 1591-1593.

[50] Lindsey, A. S., Jeskey, H. *Chem. Rev.* **1957**, *57,* 583-620.

[51] Kauch, M.; Hoppe, D. *Synthesis,* **2006**, 1575-1577.

[52] Kauch, M.; Hoppe, D., *Can. J. Chem.* **2001,** *79(11),* 1736-1746.

[53] Dai, H.-X., Li, G., Zhang, X.-G., Stepan, A. F., Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135,* 7567-7571.

[54] Jocelyne, A., *J. Org. Chem.* **2003**, *68*, 5493-5499.

[55] Sone, T.; Hamamoto, K.; Seiji, Y.; Shinkai, S.; Manabe, O. *J. Chem. Soc., Perkin Trans. 2.* **1981**, *2*, 1596-1598.

[56] Ginam, P., *Green Chemistry*, **2013,** *15(12),* 3468-3473.

[57] Wothers, P.; Greeves, N.; Warren, S.; Clayden, J. *Organic Chemistry*; Oxford University Press: New York, 2001.

[58] Izawa, Y.; Stahl, S.; Zheng, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 3672-3675.

[59] Steinhoff, B. A.; Fix. S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124,* 766-767.

[60] Samedi, S.; Orellana, A. *ChemCatChem* **2016,** *8,* 2472-2475.

[61] Mewshaw, R. E. *Tetrahedron Lett.* **1989,** *30,* 3753-3756.

[62] Lertpibulpanya, D., Marsden, S. *Org. Biomol. Chem.* **2006**, *4*, 3498-3504.

[63] Izawa, Y.; Pun, D.; Stahl, S. *Science*. **2011**, 333, 209-213.

[64] Celia, J., Bacon, S. *J. Org. Chem.* **1984**, *49*, 1122-1125.

[65] Sethna, S. M. *Chem. Rev.* **1951**, *49 (1),* 91-101.

[66] Mackenzie, A. R., *Tetrahedron,* **1986**, *42,* 3259.

[67] Liang, X. R., *Org. Prep. Proc. Int.,* **2010**, *4*, 379-385.

[68] Constantino, M.G., *Magn. Reson. Chem*. **2005**, *4*, 346-347.

[69] Tamura, K. *Chem. Pharm. Bull.* **1974**, *22,* 1291-1296.

[70] Scheuermann, G. M., *J. Am. Chem. Soc*. **2009***, 23*, 8262-8270.

[71] Woods, G. F. *J. Am. Chem. Soc*. **1948**, *70*, 2174-2177.

[72] Xu, K.; Wetzel, M.; Hartmann, R.; Marcais-Oberwinkler, S; *Lett. Drug. Des. Discov.* **2011**, *8,* 406-421.

[73] Lebeuf, R.; Robert, F.; Landis, Y. *Org. Lett.* **2005**, *7,* 4557-4560.

[74] Barder, T. E., *J. Am. Chem. Soc.* **2005,** 13, 4685-4696.

[75] Lion, C., *J. Med. Chem.* **2005,** 4, 1292-1295.

[76] Takeda, N., *Eur. J. Org. Chem.* **2007**, 9, 1491-1509.

[77] Rizzo, S. *Eur. J. Org. Chem.* **2011**, *46(9)*, 4336-4343.

[78] Krysan, D.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114,* 1412-1418.