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Investigations on the Active Catalyst in Pd Catalyzed Organic Reactions

Riley McGraw

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Riley Jack McGraw

Department of Chemistry, Western Washington University, Bellingham WA

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Dr. Margaret Scheuermann

Abstract

Cross coupling and C-H functionalization reactions are valuable tools in the synthesis of pharmaceuticals, natural products, fine chemicals, and electronics. Molecular precatalysts are frequently used in both reactions but because the reactions use conditions like those employed in intentional preparation of nanoparticles, the presence of nanoparticles is highly likely for both systems. In the case of the cross-coupling reaction, nanoparticles have been shown to have catalytic relevance, but C-H functionalization reactions are widely thought to occur by means of a homogenous catalyst. To better understand the state of the active catalyst, a method of homogeneity analysis by centrifuge is proposed. For this centrifuge to isolate nanoparticle involvement as a variable, all other reaction components must be fully soluble. In this report, the cross-coupling system was first optimized for analysis by centrifuge as a validation of the proposed method. The C-H functionalization system, in which the identity of the active catalyst is more ambiguous was then similarly optimized.

Introduction

In the field of catalysis, research and development of new catalytically active molecules often focuses on mechanistic understanding of how alteration of specific ligands affects the effectiveness of the active catalyst. Studies on improving the reactivity and selectivity of the active catalyst often depend on the assumption that the homogenous precatalyst remains homogenous as the reaction progresses. In organometallic chemistry, these precatalysts are used to catalyze industrially relevant organic reactions significant to the formation of pharmaceuticals and natural products. The active species is assumed to remain homogenous in many literature reports, however these organic reactions bear similar conditions to those employed specifically to prepare nanoparticles.[1,2] This suggest that nanoparticles may be formed as organometallic reactions progress, challenging the assumption of a continuously homogenous active catalyst. In this report, two systems, a Suzuki-Miyaura cross-coupling and C-H functionalization will be studied to better understand the state of their respective active catalysts. For both systems, a method must

be used to assess the homogeneity of the active catalytic species. Interpreting whether the catalysis in each system is best explained by molecular or surface chemistry has implications for understanding the operation of catalytic systems, as well as in designing rational catalysts for synthetic chemistry.

Proposed Method: Homogeneity Analysis by Centrifuge

Assessing the role of in situ generated nanoparticles in catalysis has proven to be a difficult task. There are many existing methods in the literature for understanding the state of the active catalyst, each with their respective strengths and weaknesses.[3,4] A common problem with many of these methods, such as the Collman's test or mercury test, is that the test significantly alters the chemical environments of the studied reactions. This limits the ability to have single variable control in these studies.

Our strategy for assessing the role of in situ generated nanoparticles is to remove the nanoparticles as they form using a centrifuge and measure whether the catalyst performance changes. As nanoparticles precipitate during the reaction, gaining mass, the centrifugal forces supplied by the centrifuge will draw them to the bottom of the reaction tube where they will be trapped in a dense oil (Figure 1). Our proposed method minimally alters the chemical environment, allowing us to better understand the state of the active catalyst.

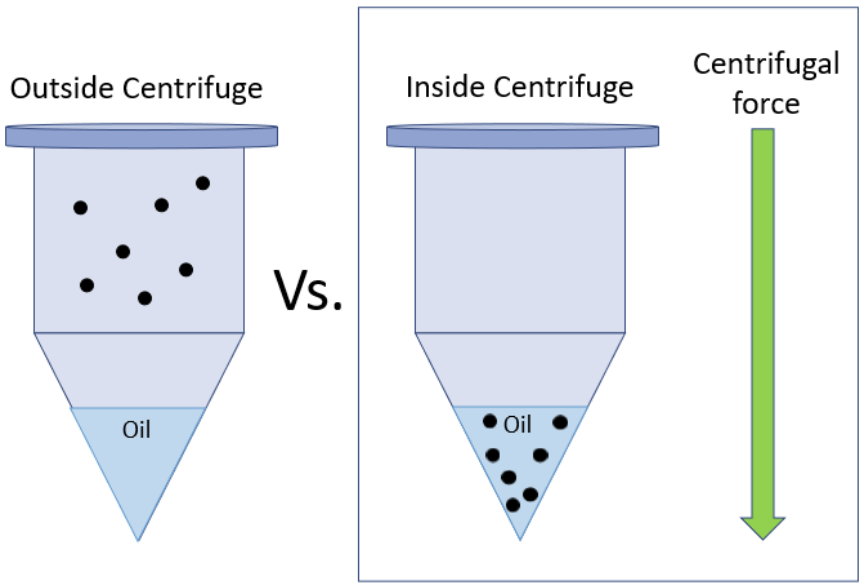


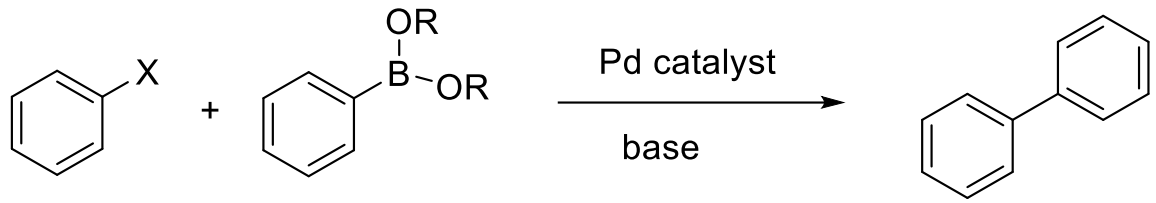
Figure 1. Proposed method of determining state of the active catalyst.

A crucial aspect of this method of analysis is the requirement for complete solubility of all other reagents within the reaction mixture. For both the cross-coupling and C-H functionalizing systems the reactions will be optimized for full solubility, and the nanoparticles will be removed using the centrifuge method, eliminating their ability to participate in the reaction should they have catalytic activity. The cross-coupling reaction, where the nanoparticles are widely thought to be catalytically relevant, will be first used to validate this method as a way of determining catalytic state. This method can then be applied to systems in which the role of nanoparticles is less clear, as in the C-H functionalization reaction.

Suzuki Miyaura Cross-Coupling System

The first system investigated in this report is a Suzuki Miyaura Pd catalyzed cross-coupling (Scheme 1). Pd catalyzed cross-couplings are recognized as a powerful tool in synthetic chemistry. These reactions allow for efficient and selective formation of carbon-carbon and carbon-heteroatom bonds, allowing chemists to access a wide range of valuable compounds with diverse applications in industrial and academic settings.[5,6] Considering its widespread applications, chemists continually strive to improve

catalytic efficiency for use in industrial processes- maximizing yield, increasing selectivity, and decreasing cost and energetic requirements.

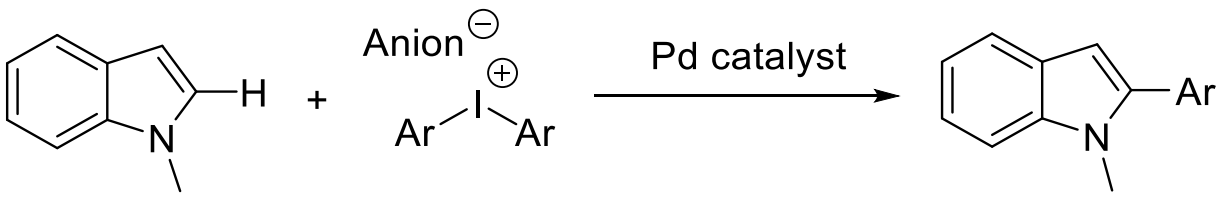


Scheme 1. Generic Suzuki Miyaura Cross-Coupling

In this type of organic reaction, there is strong evidence that Pd nanoparticles are involved in the catalytic mechanism. In this instance, understanding of the state of the active catalyst has shifted from molecular to surface chemistry for many types of cross-coupling reactions.[5,6,7] Considering the established evidence for nanoparticle involvement, the Suzuki Miyaura cross coupling reaction will be used as a form of method validation. The proposed method of assessing homogeneity by centrifuge will be applied first to this system, and then to one in which the role of nanoparticles is less clear.

Methyl Indole C-H Functionalization System

The second system investigated is a Pd catalyzed reaction that functionalizes a methyl indole starting material with an aryl ring (Scheme 2). C-H functionalization reactions hold great importance in organic synthesis as they allow for the direct transformation of carbon-hydrogen bonds into valuable functional groups. Indoles are a particularly useful substrate for C-H functionalization reactions due to their prevalence and importance in biologically active compounds, making them an attractive target for the development of new synthetic methodologies and the synthesis of complex molecules.[8,9]



Scheme 2. Generic C-H functionalization reaction of the arylation of N-methyl indole starting material using a Pd catalyst.

C-H functionalization reactions are commonly assumed to proceed by a homogenous catalytic cycle, however similar reactions such as the cross-coupling have been shown to involve heterogeneous catalytic species. Considering its potential for formed nanoparticles during the catalytic process of functionalizing these indole building blocks, the state of the active catalyst in this reaction has been recognized as requiring further investigation. In this report, work has been done toward understanding the state of the active catalytic species by use of the centrifuge method described above.

Results and Discussion

Palladium Catalyzed Cross Coupling Reaction

To examine the reaction in a centrifuge, this reaction was first evaluated for full solubility of all reaction components. The organohalide substrate was found to be soluble in organic solvents and insoluble in water (Figure 2). This was contrasted by the solubility of the base, which was insoluble in organics and completely soluble in water. This contradictory solubility pattern required modification of various components of the reaction.

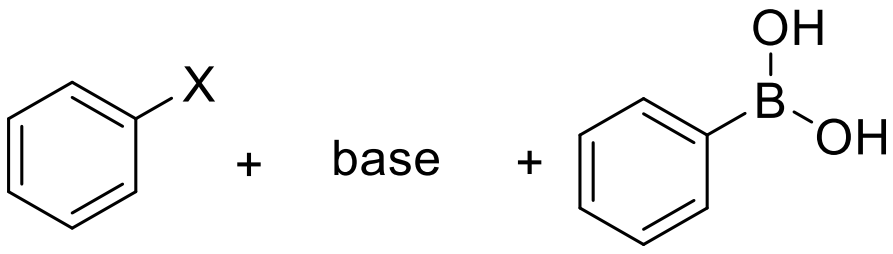


Figure 2. Cross coupling reaction components.

Toward this goal we opted for a phenol-substituted aryl halide, bromophenol. The phenol group's polarity and hydrogen-bonding site could marginally enhance its solubility in the types of polar reaction media in which the base would be most soluble.

The next parameter that was investigated in order to attain full solubility of all reagents was the solvent. In the literature, ethanol (EtOH) and water were frequently employed as solvents, prompting the investigation of solubility for each reactant in different combinations of these two solvents. The 4-bromophenol solubility results are shown in Table 1. Solvent mixtures with 50% ethanol or greater gave acceptable levels of solubility.

Table 1. Solubility 4-bromophenol in various solvents[1]

Solvent	Observations
1:1 EtOH to H_2O	Mostly soluble, still particles in solution after 5 minutes
100 EtOH	Highly soluble, no particles in solution after 1-2 minutes
100 H_2O	Completely insoluble
75:25 EtOH to H_2O	Soluble, less particles in solution than 50:50 mixture
25:75 EtOH to H_2O	Partially soluble. Most of the solid stayed out of solution

[1]Solubility test performed with 0.5 g of bromophenol in 3 mL of solvent. Solubility tests conducted at higher concentration than the reaction conditions are responsible for the particle presence in the 1:1 EtOH to water solubility test.

Two different bases, cesium carbonate (Table 2) and potassium carbonate (Table 3) were then tested for their respective solubility in the same solvents. Cesium carbonate was observed to be soluble in 1:1 EtOH to H_2O at 0.083 g/mL (solubility was not tested above 0.083 g/mL). As seen in Table 2, there were no particles visible in the 1:1 EtOH to H_2O solubility test until monitored by a laser. Upon close observation, the potassium carbonate tests were seen to have small, almost invisible particles present in the solution. Cesium carbonate did not have any of these small particles after 2-3 minutes and appeared to be more soluble in the 1:1 EtOH to H_2O solvent system. The decision to use cesium carbonate over potassium carbonate as the primary base in this reaction was made using this series of observations.

Table 2. Solubility of cesium carbonate in various solvents[1]

Solvent	Observations
50:50 EtOH to H_2O	Completely transparent, small particles observed when monitored by laser
100 EtOH	Insoluble on first addition. 72 hours later white-gray crystals had precipitated out of solution
100 H_2O	Fully soluble, no particles in solution
75:25 EtOH to H_2O	Slightly soluble, but most of the base stayed in solid form. A white solid sludge formed after a few minutes.

[1]Solubility test performed with 0.5 g of cesium carbonate in 3 mL of solvent.

Table 3. Solubility of potassium carbonate in various solvents[1]

Solvent	Observations
50:50 EtOH to H_2O	95% soluble, still some small particles observable to the eye
100 EtOH	95% soluble, still some small particles observable to the eye
100 H_2O	Fully soluble
75:25 EtOH to H_2O	95% soluble, still some small particles observable to the eye
25:75 EtOH to H_2O	95% soluble, still some small particles observable to the eye

[1]Solubility test performed with 0.5 g of potassium carbonate in 3 mL of solvent.

A 1:1 EtOH to H_2O solvent system was chosen for this cross-coupling reaction after solubility testing for the 4-bromophenol substrate and both cesium carbonate and potassium carbonate bases. The 1:1 mixture gives sufficient solubility for 4-bromophenol and the chosen base, cesium carbonate. The boronic acid is also sufficiently soluble in this solvent system. Visible solids or small particles scattering laser light were not detected when solutions of the reaction components (Figure 3) were mixed in the absence of a catalyst.

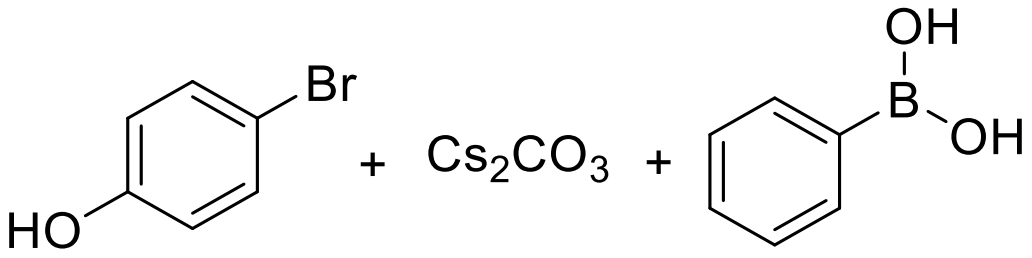


Figure 3. Reactants chosen for the cross-coupling system: 4-bromophenol (left), cesium carbonate (middle) and boronic acid (right).

Pre-Catalyst Solubility/ stability in solution

To accommodate a small reaction scale we opted to add the precatalyst as a stock solution. When selecting a Pd source and solvent for the stock solution the pre catalyst solution must be stable and not form solids before addition of the reaction mixture. Four Pd sources were explored based on these requirements, with the solubility results shown in Tables 4-7 below. $PdCl_2$ and $Pd(OAc)_2$ were first tested for solubility as seen in Tables 4 and 5.

Table 4. Solubility of and stability of $PdCl_2$ in various solvents[1]

Solvent	Observations
50:50 EtOH to H_2O	Low solubility, forms dark particles almost immediately on contact with the solvent
100 EtOH	Soluble. Dark particles form almost immediately
75:25 EtOH to H_2O	Higher solubility when more ethanol is introduced, has the same problem of forming particles very soon on addition

[1]Solubility test was performed with 50 mg of palladium chloride in 3 mL of solvent.

Table 5. Solubility of and stability of $Pd(OAc)_2$ in of various solvents[1]

Solvent	Observations
1:1 EtOH to H_2O	Low solubility, dark particles form 1-2 minutes on contact with the solvent
100 EtOH	Soluble. Dark particles form in similar time to the first solvent
75:25 EtOH to H_2O	Higher solubility when more ethanol is introduced, has the same problem of forming particles very soon on addition

[1]Solubility test was performed with 50 mg of palladium acetate in 3 mL of solvent.

It was found that when $Pd(OAc)_2$ or $PdCl_2$ was dissolved in the 1:1 EtOH to water solvent system dark particles formed even before the addition of the substrate. These suspected nanoparticles were formed prematurely. The Pd catalysts in Tables 6 and 7 were shown to have good stability in the 1:1 solvent mixture solvent mixture and were also suspected to slow the reaction due to their attached ligands.

Table 6. Solubility of and stability of $PdCl_2(SMe_2)_2$ in of various solvents[1]

Solvent	Observations
50:50 EtOH to H_2O	Color change observed, small particles still present in solution indicating limited solubility. Dark particles observed 5-7 minutes after addition.
100 EtOH	Fully soluble, particles do not form for an even longer time, around 11 minutes
75:25 EtOH to H_2O	The more ethanol is introduced (organic solvents in general), the higher the solubility. Particles do not form until about 9 minutes after contact

[1]Solubility test was performed with 50 mg of $PdCl_2(SMe_2)_2$ in 3 mL of solvent

Table 7. Solubility of and stability of $PdCl_2(PhCN)_2$ in of various solvents[1]

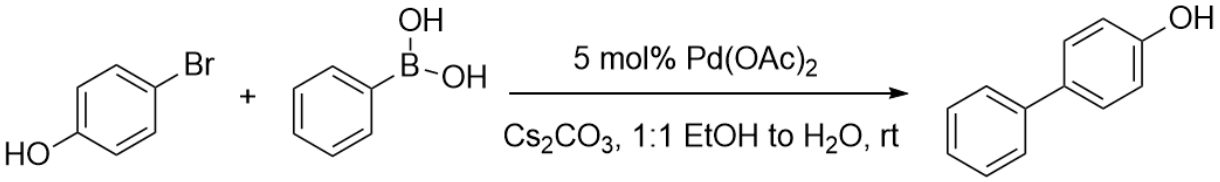
Solvent	Observations
50:50 EtOH to H_2O	Lower solubility but is still able to dissolve partially. Appears to be very stable and does not form particles instantly like palladium chloride or palladium acetate
100 EtOH	Completely soluble, does not form particles for 10-12 minutes
75:25 EtOH to H_2O	The more ethanol is introduced (organic solvents in general), the higher the solubility. Particles do not form until about 9 minutes after contact

[1]Solubility test was performed with 50 mg of $PdCl_2(PhCN)_2$ in 3 mL of solvent

Both $PdCl_2(SMe_2)$ and $PdCl_2(PhCN)_2$ were shown to have better stability in the 1:1 EtOH to H_2O solvent system, with suspected nanoparticles not forming during the first 5 minutes. However, when stock solutions of $PdCl_2(SMe_2)_2$ and $PdCl_2(PhCN)_2$ were used in a catalytic reaction the desired cross coupling product was not detected.

With all the precatayst stock solutions precipitating particles from ethanol or ethanol/water in less than 30 minutes, an alternative solvent for the stock solution was required. When stock solutions were prepared in THF there was no evidence of the formation of dark particles in any of these solubility tests. All tested catalysts were found to be soluble in THF when testing 50 mg per 3 mL, and it was also found that low amounts of THF did not affect the solubility of the reaction mixture. $Pd(OAc)_2$ was chosen as the primary catalyst for future reactions.

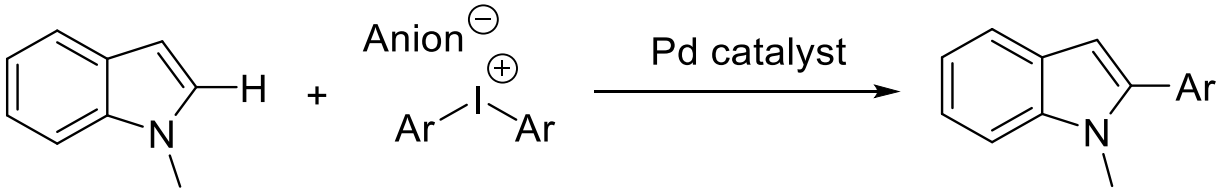
The fully optimized reaction for solubility included the following components (Scheme 3): 4-bromophenol, benzoboronic acid, $Pd(OAc)_2$ (in a stock solution of THF), Cs_2CO_3, and a 1:1 EtOH to DI water solvent system. Further investigations and centrifuge studies are being conducted by another lab member.



Scheme 3. Fully optimized system for centrifuge testing.

C-H Functionalization Reaction

The next system of interest was the C-H functionalization reaction seen in Scheme 4.[12] The proposed mechanism for this reaction proceeds by a $Pd^{II/IV}$ catalytic cycle. In this case, the active catalyst is proposed to maintain its homogeneity with the rest of the reaction mixture. However, as previously mentioned, the evidence of heterogeneity in similar Pd-catalyzed reactions provided a compelling reason to reexamine the active catalyst within this system.



Scheme 4. Generic C-H functionalization reaction.

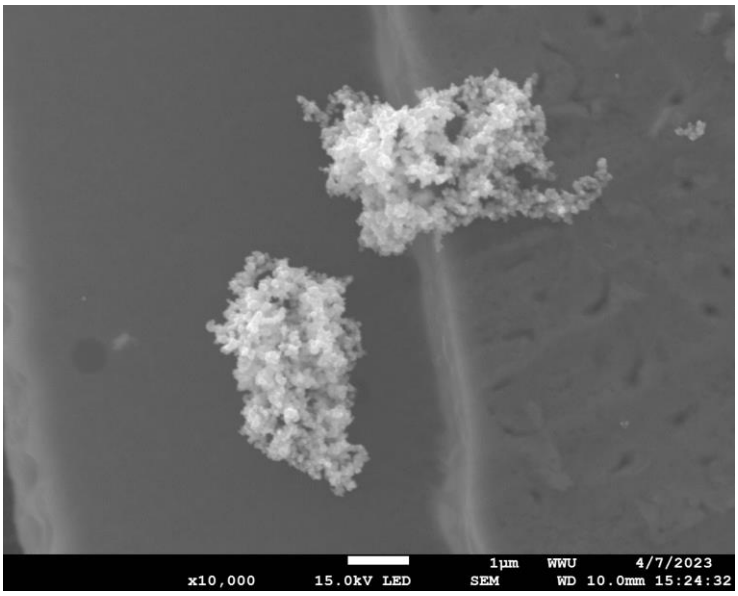
Determination of Particle Presence

Before optimization of this system for study in the centrifuge, it was essential to determine that Pd particles did form in reaction. This was accomplished in three ways. The first was by visibly observing the presence of a dark precipitate after the addition of Pd (Figure 4). On observation, there were clearly

particles forming as the reaction progressed. Particle presence was also confirmed from light scattering observed when the solution was exposed to a laser.

Figure 4. Particles visibly present in solution.

Next, these particles were isolated and imaged by use of SEM (Figure 5). SEM imaging confirmed on the nm scale the presence of these particles, with EDS analysis confirming that they were composed primarily of Pd. The individual particles were confirmed to be closer to 60-100 nm in diameter. In reaction, the Pd tended to aggregate significantly which was displayed by SEM.



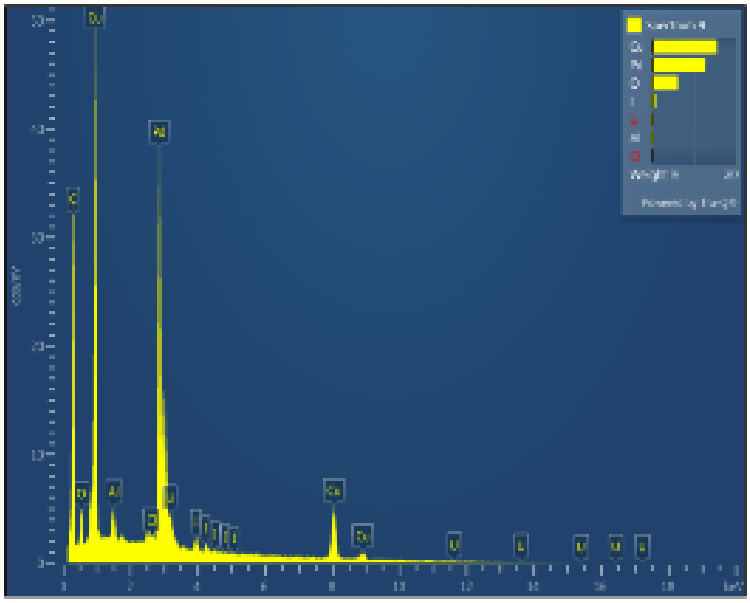


Figure 5. Secondary electron images of aggregated Pd nanoparticles. EDS analysis confirmed Pd as the primary elemental composition.

The last method of particle characterization was by DLS. A reaction was run in the DLS, in which scans were taken over a 5-minute span for 20 minutes as seen in Figure 6. The clusters were observed to grow over the span of 20 minutes, reaching 2.5 microns in size at their peak. This size of particle is in line with aggregate species observed by SEM.

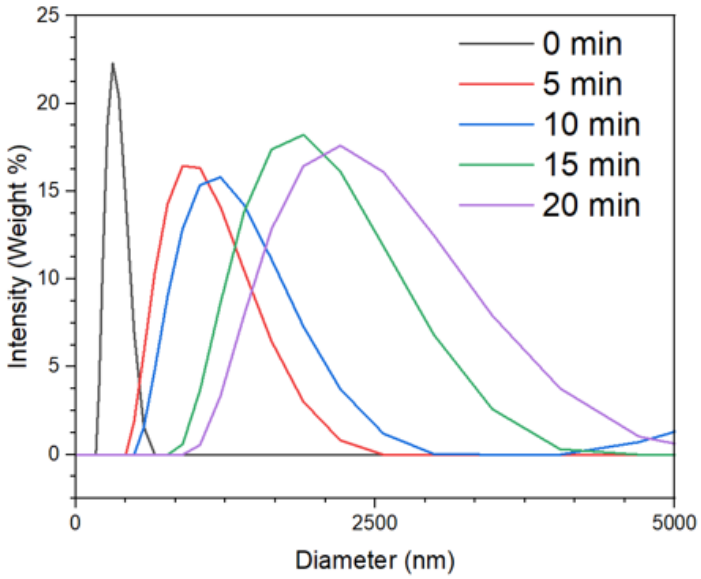
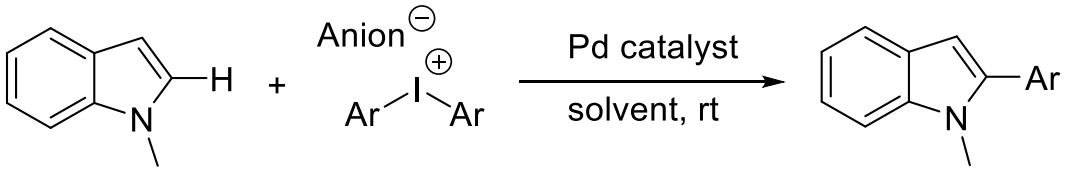


Figure 6. DLS scans in 5-minute intervals as the reaction progressed.

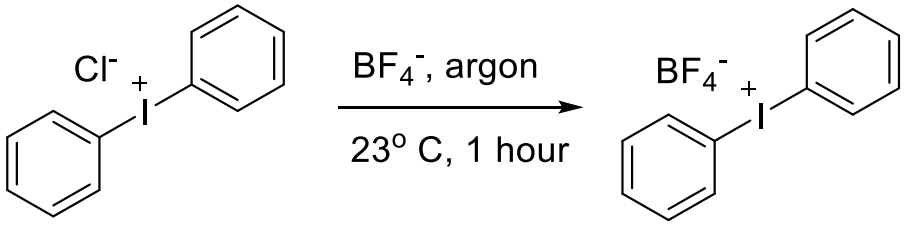
Solubility of the Reaction Components

As with the cross-coupling system, assessing the phase of the active catalyst using the centrifuge requires a homogenous solution of all starting materials for the C-H functionalization system (Scheme 5). N-methylindole, the starting material for this reaction, is fully soluble in organic solvents and completely insoluble in aqueous solvents. The diphenyliodonium salts used in initial experiments have the opposite problem, causing optimization of this reaction solubility to depend on factors such as solvent identity and quantity, iodonium salt anion and aryl group identity. These parameters were introduced into the system to test overall reaction solubility.



Scheme 5. Generalized C-H functionalization reaction.

The initial salt synthesized and proven to make product in a C-H functionalization reaction was diphenyliodonium tetrafluoroborate, compound ***2*** (Scheme 6).



Scheme 6. Synthesis of compound ***2***, diphenyliodonium tetrafluoroborate.

This salt, however, proved to be insoluble in the literature provided solvent of AcOH. Solubility testing was then conducted on compound ***2*** to potentially explore a new solvent system for the Pd

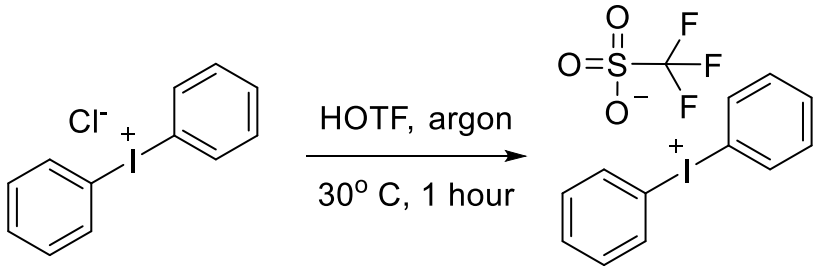
catalyzed indole reaction (Table 8). A 1:1 molar ratio of water and AcOH was tested but proved to not form product when tested in the C-H functionalization reaction.

Table 8. Solubility of compound ***2***, diphenyliodonoim tetrafluoroborate in AcOH and water[1]

Solvent Mixture of Acetic Acid: Water	Observations
100 DI	Within 5 minutes there were no visible particles floating in solution, indicating high solubility. Small particles present when monitored by a laser.
50:50 AcOH to DI	Mildly soluble on addition. Within 1 hour, still small particles visible in solution. After 1 day, visible particles had disappeared, but monitoring with a laser indicated small particles still in solution.
100 AcOH	Completely insoluble, no color change indicated at any time frame.

[1]Solubility tests performed with 10 mg of diphenyliodonium tetrafluoroborate and 3 mL total of solvent.

Due to the limited solubility of this salt in the reaction mixture, an alternative diphenyliodonium salt was investigated. As seen in figure 6, compound ***3*** was synthesized with a triflate anion to potentially increase its solubility in organic solvents such as AcOH.



Scheme 7. Synthesis of diphenyiodonium triflate, compound ***3***.

This salt proved to be partially, but not fully soluble in AcOH. DMSO was identified as a potentially useful solvent for the solubility requirements of the indole reaction, and solubility testing in AcOH and increasing amounts of DMSO was then performed on the diphenyliodonium triflate salt.

Table 9. Solubility of diphenyiodonium triflate, ***3***, in AcOH and increasing amounts of DMSO[1]

Amount of DMSO Added (mL)	Observations
0	Partially soluble (approximately 20% dissolved)
0.5	Greatly increased solubility, only small particles present in solution
1	Highly soluble, no particles visible in solution. Small particles proved to refract light when monitored by laser

[1]Solubility tests performed with 20 mg of diphenyliodonium tetrafluoroborate in initially 5 mL of AcOH.

Results seen in table 11 indicated DMSO as a potentially useful solubility agent in solution. In reaction, 1 mL of DMSO did increase solubility of the reaction mixture to an acceptable level but reduced the product yield to < 5%.

Two other solvents were tested for their potential to increase overall reaction solubility with diphenyliodonium tetrafluoroborate as the salt: DMF and DMA. Both solvents were seen to have promising solubility results in a reaction mixture. DMF was the only solvent seen to form product at about a 50% yield qualitatively (Table 10).

Table 10. Reactions done with the same general procedure performed for compounds ***6-9.*** The iodonium salt used in both reactions was diphenyliodonium tetrafluoroborate, ***2***.[1]

Solvent	Solubility Results	Product Formed?
DMF	All components of the reaction mixture are highly soluble-solubility persists when components are combined.	Product formed at a 50% yield qualitatively
DMA	All components of the reaction mixture are highly soluble-solubility persists when components are combined.	Product not formed by NMR

[1]DMF was discarded as a potential solvent due to complications found in the aqueous workup.

DMF was discarded as a potential solvent for this system due to complications in product separation during the aqueous workup, causing a shift towards modifying the iodonium salt to increase reaction solubility. In future experiments, DMF should be considered as a potential option. All three salts seen in Figure 7 were tested for their effect on reaction solubility and yield. The left and middle salts correspond

to compounds ***4*** and ***5*** in the experimental. The rightmost salt is available commercially (CAS: 131717-99-2). All three salts were shown to have high solubility in AcOH under generalized C-H functionalization reaction conditions outlined in the general procedure for compounds ***6***-***8*** below. Salts ***4*** and ***5*** did not form product when tested in a C-H functionalization reaction. The rightmost salt formed product when tested in a C-H functionalization reaction and was fully soluble in AcOH. With the goal of solving the solubility problem in mind, the rightmost salt in Figure 7 has desirable solubility in AcOH as well as forming reasonable a qualitative yield of product.

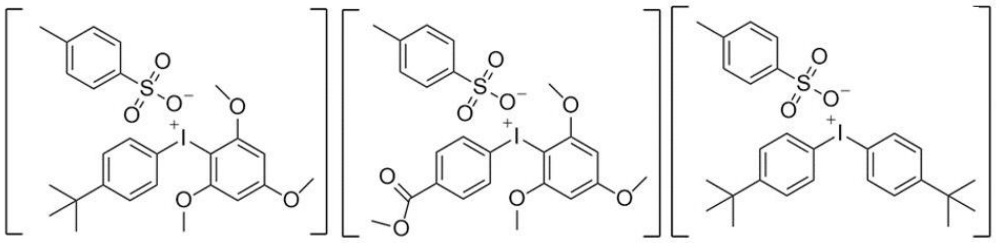
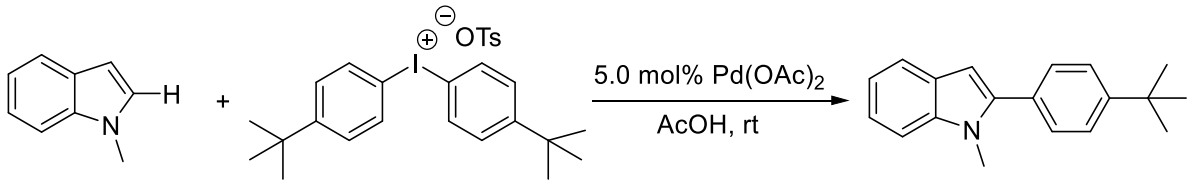


Figure 7. Different iodonium salts considered for use in reaction. Left (***4***): (4-(tert-butyl)phenyl)(2,4,6-trimethoxyphenyl)iodonium 4-methylbenzenesulfonate. Middle (***5***): (4-(methoxycarbonyl)phenyl)(2,4,6-trimethoxyphenyl)iodonium 4-methylbenzenesulfonate. Right: bis(4-(tert-butyl)phenyl)iodonium 4-methylbenzenesulfonate

The solubility-optimized reaction (Scheme 8) includes the following components: N-methylindole as the starting material, bis(tert-butylphenyl) iodonium 4-methylbenzenesulfonate, and $Pd(OAc)_2$ as the catalyst. Like the previously optimized cross-coupling reaction, the catalyst was dissolved in THF and added via micropipette.



Scheme 8. Final solubility optimized C-H functionalization reaction.

Isolating Product for Calibration Curve Reaction Monitoring

With all reaction components fully soluble and ready for centrifuge testing, a supply of pure product seen in Figure 8 was required to make calibration curves for quantification by GC-FID.

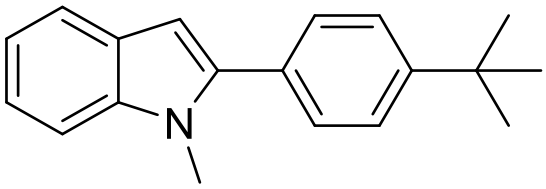


Figure 8. Desired product for the solubility optimized centrifuge reaction.

Purification by silica gel column chromatography was required to isolate this product. This proved to be a difficult task, as there was a high number of side and byproducts present in this reaction with similar R_f values to that of the desired product. Many iterations of this column were required to optimize the solvent system for this reaction (97:3 hexanes to EtOAc) to yield 21% product as compound ***8***. Calibration curves were then made for the starting material and ***8***.

To quantify by GC-FID, it was also necessary to choose an appropriate, non-reactive internal standard. The internal standard chosen was 1, 3, 5-trimethoxybenzene, and a calibration curve was also made for this compound. Reaction aliquots were subjected to an aqueous workup to neutralize the AcOH prior to GC-FID analysis.

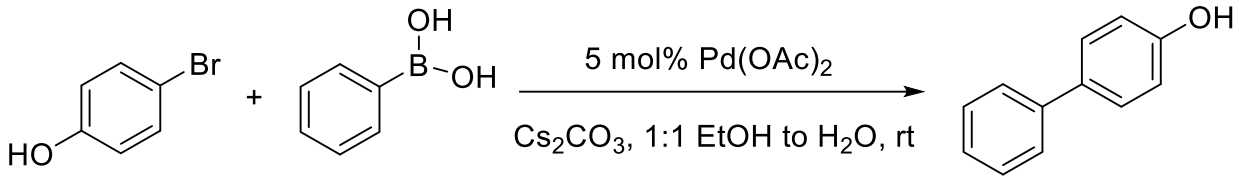
Conclusions and Future Work

The initial system, a Suzuki Miyaura cross coupling reaction was fully optimized for solubility by adjusting the substrate, base, and solvent mixture. Once optimized for solubility, the cross-coupling system was transferred to another lab member for further study, and the system of interest shifted to a C-H functionalization reaction in which the state of the active catalyst is less clearly established. Like the

cross-coupling system, the components of this reaction were modified for full solubility. GC-FID was chosen as the method of quantification for this system, and calibration curves were made for starting material, isolated product, and a non-reactive internal standard. With the C-H functionalization system prepared for testing using our chosen method, the next step is to move to the centrifuge. Many iterations of experiments in the centrifuge will potentially assist in understanding the state of the active catalyst in this reaction.

Experimental Section

Pd Catalyzed Cross Coupling Reaction



Synthesis of [1-1'-biphenyl]-4-ol (1)

Procedure adapted from (10). In a 20 mL vial, benzoboronic acid (121.93 mg, 0.0609 mmol, 0.5 eq.) and Cs_2CO_3 (325.82 mg, 0.57 mmol, 1.75 eq) were dissolved with 2 mL of 1:1 EtOH to DI water. 4-bromophenol (173.01 mg, 0.863 mmol, 0.5 eq.) was added to another 20 mL vial and dissolved with 1 mL of 1:1 EtOH to DI water. This was transferred to the vial containing the base and boronic acid along with a stir bar. 2 mL of 1:1 EtOH to H_2O was added to reaction vial containing the benzoboronic acid, Cs_2CO_3, and 4-bromophenol. $Pd(OAc)_2$ (13mg) was dissolved in 4 mL of THF. From this stock solution 57 microliters (5 mol%) was added to the reaction. The reaction was stirred and allowed to progress for 24 hours. The reaction mixture was then poured into brine (5 mL) and extracted with 4 x 10 mL of ether. The organic layer was dried using Mg_2SO_4 and solvent was removed under vacuo to yield 50.04 mg (84%) of isolated product. ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.22, 140.90, 134.19, 128.87, 128.54, 126.87, 115.78 ppm.

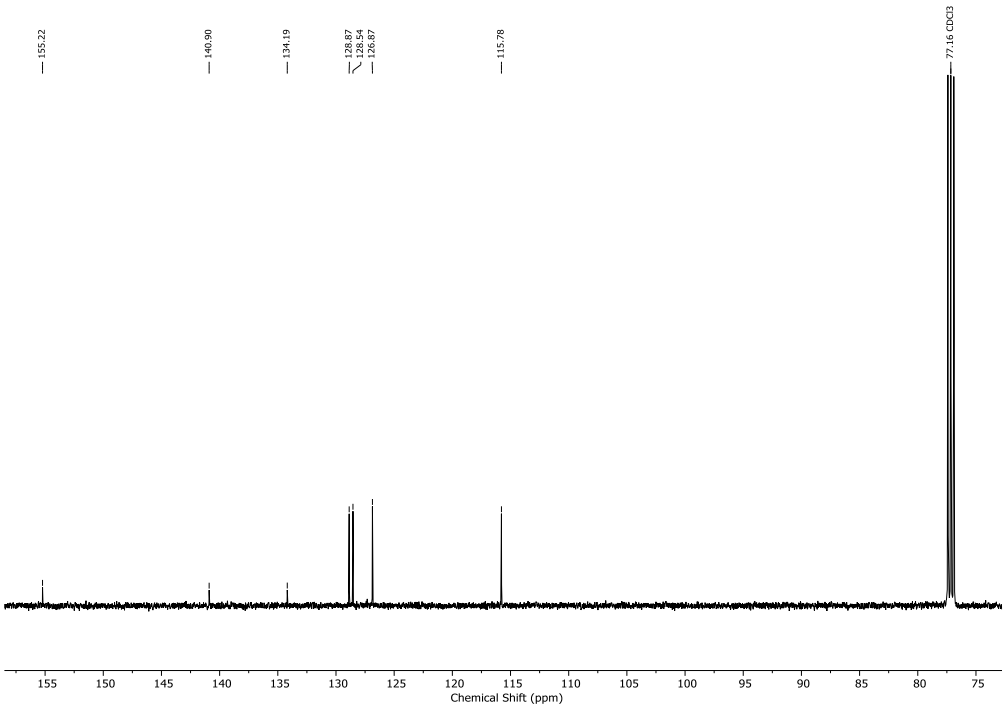
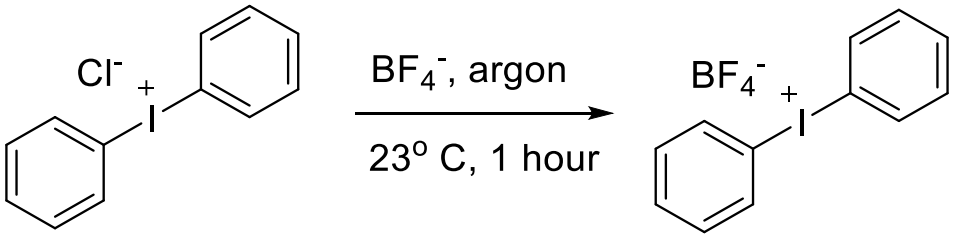


Figure 9. ^{13}C NMR of compound ***1***

C-H Functionalization Reaction



Synthesis of Diphenyliodonium Tetrafluoroborate (2)

Procedure adapted from (11). In a 50 mL RBF under nitrogen, diphenyliodonium chloride (3.085 g, 10 mmol , 1 eq) was added along with 25 mL of DCM and tetrafluoroboric acid (1.630 g, 10.0 mmol, 1 eq). A stir bar was added, and the RBF was capped to with a septum, where it was then transferred to a Schlenk line under argon. The RBF was heated to 23°C using a heating mantle and allowed to stir for 1

hour. The flask was then allowed to cool, and excess solvent was removed in vacuo again using the Schlenk line. Removing the septum and blanketing the RBF with argon, the RBF was quickly moved into the glove box under nitrogen. The product was washed with pentane (15 mL) and ether (15 mL) to yield 3.614g (84%) as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.0 Hz), 7.63 (t, *J* = 8.0 Hz), 7.50 (t, *J* = 8.0 Hz) ppm. ^{13}C NMR (126 MHz, DMSO): δ 135.10, 131.79, 131.68, 117.11 ppm. ^{19}F NMR (470 MHz, DMSO): δ -141.71.

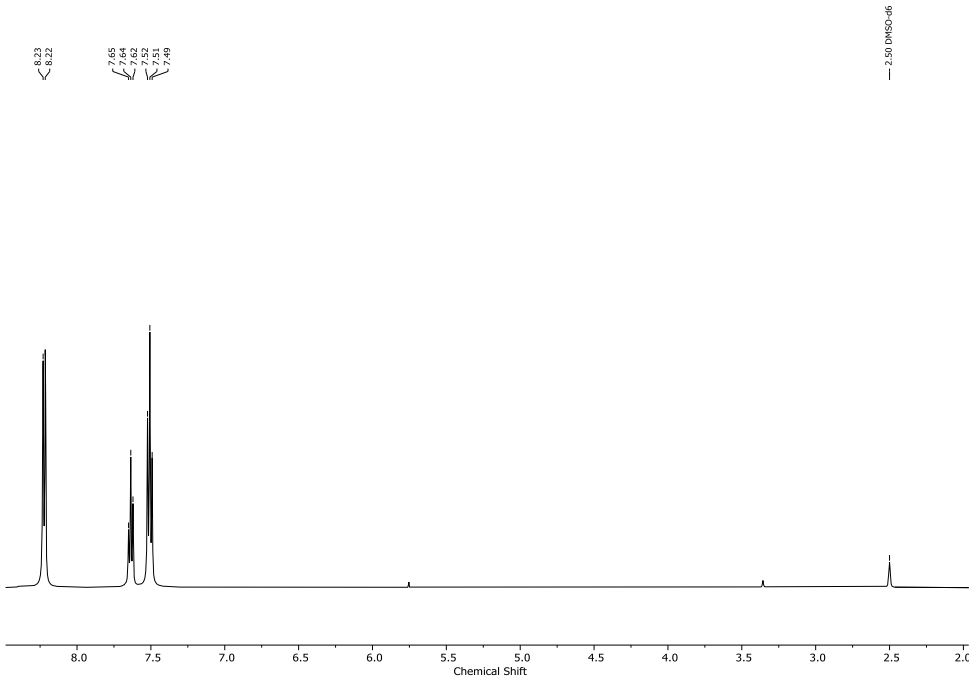


Figure 10. ^{1}H NMR of compound ***2***.

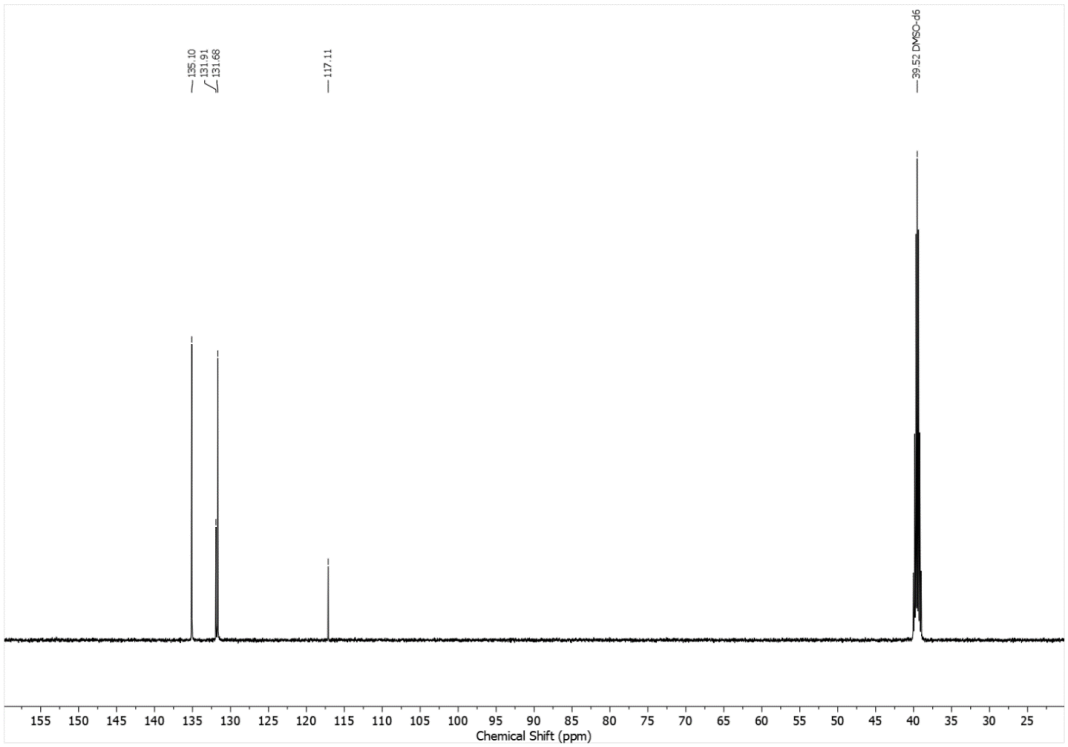


Figure 11. ^{13}C NMR of compound ***2***.

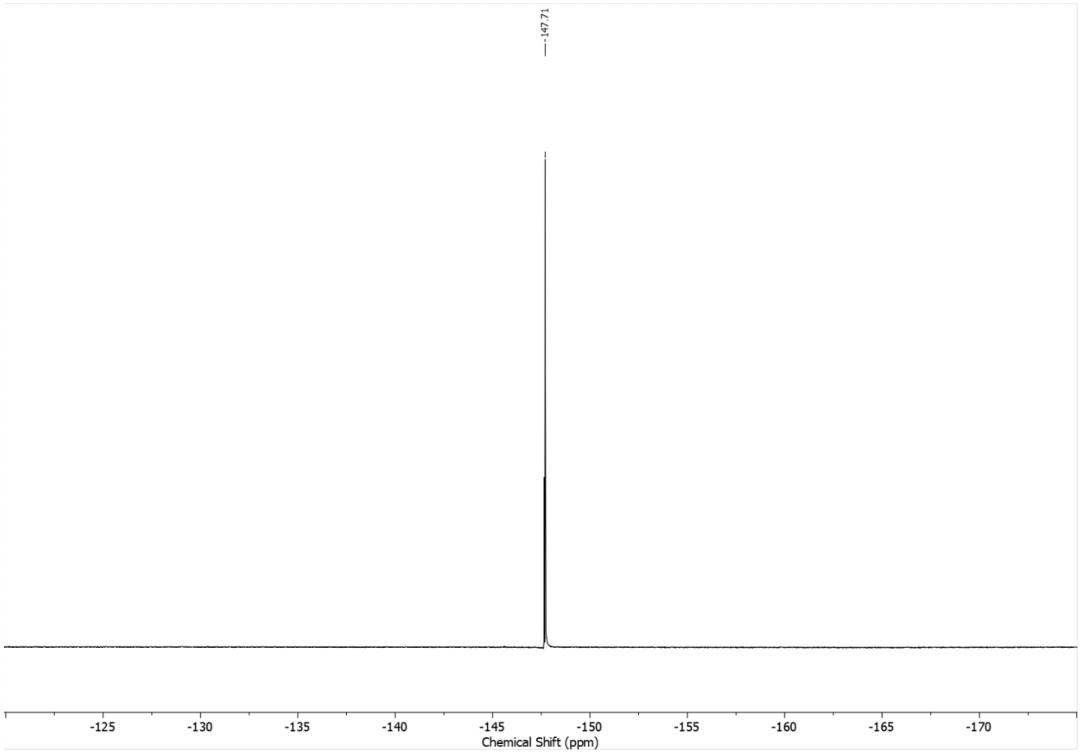
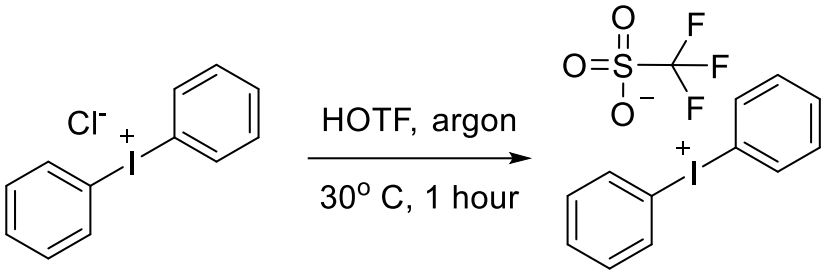


Figure 12. ^{19}F NMR of compound ***2.***



Synthesis of Diphenyliodonium Triflate (3)

Procedure adapted from (11). In a 20 mL vial in a nitrogen atmosphere, diphenyliodonium chloride (617 mg, 2 mmol, 1 eq) was added along with 5 mL of DCM and a stir bar. The solution was capped with a septum and transferred to a Schlenk line under argon. After 5 minutes, the vial was removed from the Schlenk line, and while blanketing the vial with argon, the septum was removed and triflic acid (300.16 mg, 0.18 mL, 2 mmol, 1 eq) was added via syringe. The vial was recapped and placed back onto the Schlenk line, where it was heated to 30° C and stirred. The vial was then removed from the Schlenk line, and the septum was replaced with a vial cap while blanketing with argon. Under a nitrogen atmosphere, solvent was evaporated, and the product was washed with 5 mL of both pentane and ether to yield 690 mg (80.2%) as a white crystalline solid. ^{13}C NMR (126 MHz, DMSO): 135.10, 131.91, 131.68, 117.11 ppm. ^{19}F NMR (470 MHz, DMSO): δ -77.72.

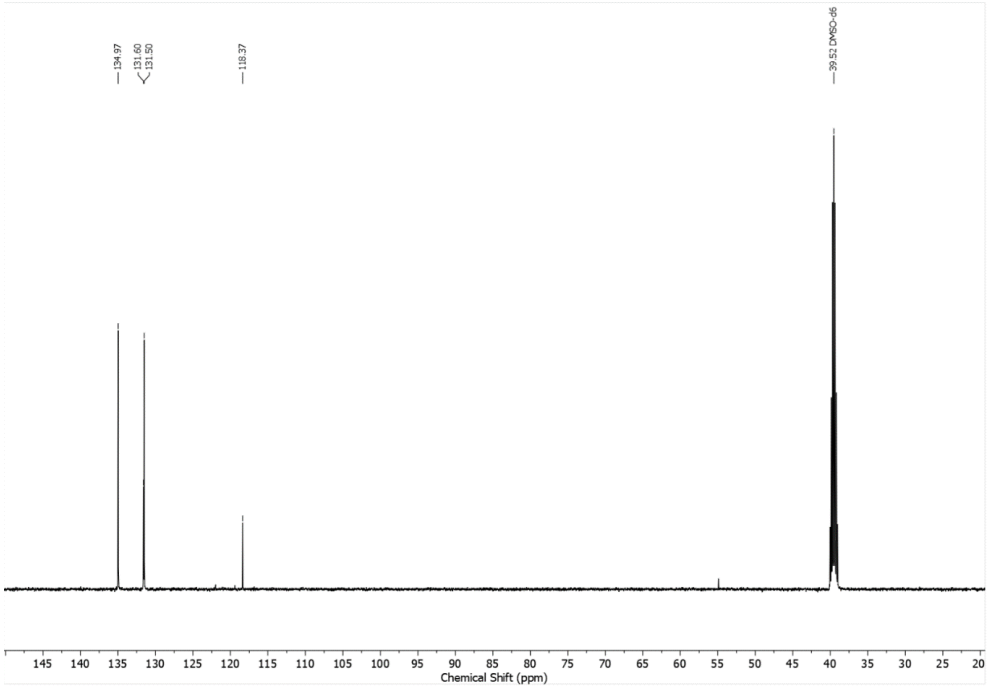


Figure 13. ^{13}C NMR of compound ***3***.

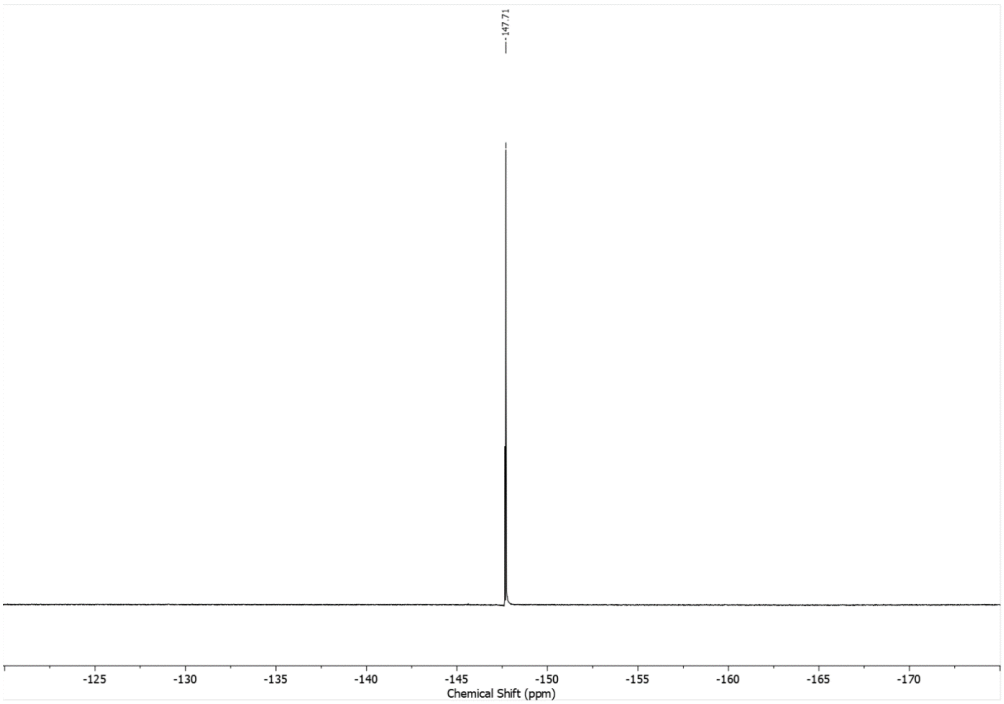
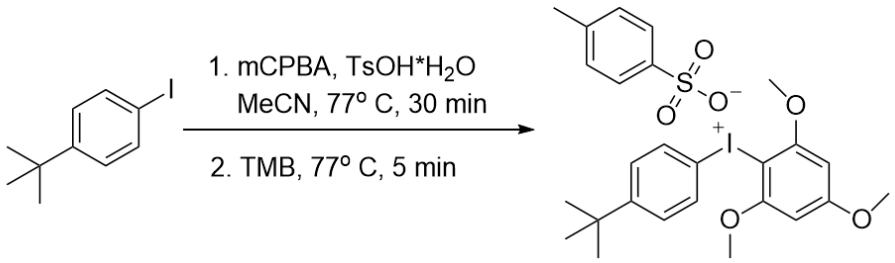


Figure 14. ^{19}F NMR of compound ***3.***



Synthesis of (4-(tert-butyl)phenyl)(2,4,6-trimethoxyphenyl)iodonium 4-methylbenzenesulfonate (4)

Procedure adapted from (11). To a 50 mL RBF, 1-tertbutyl-4-iodobenzene (130.1 mg, 0.5 mmol, 1eq) and 3 mL of MeCN were added. Toluene sulfonic acid (86.9 mg, 0.505 mmol, 1 eq) and mCPBA (87.15, 0.505 mmol, 1 eq) were dissolved in 1 mL of MeCN each and added to the RBF. A stir bar was added, and the mixture was heated using a water bath at 77° C for 30 minutes. The reflux condenser was removed, and 1, 3, 5-trimethoxybenzene (TMB, 84.94, 0.505 mmol, 1 eq) was then added to the mixture. The mixture was then allowed to reflux for 5 more minutes then removed from heat. Solvent was evaporated in vacuo, and 3 mL of ether was added to the resultant liquid to precipitate the product (note: for larger synthesis, the product can be added dropwise to a beaker of stirring ether. A small amount of MeCN may be left in the initial reaction flask to aid in transferring the product). The product was filtered under vacuum to yield 263.1 mg (94%) as a slightly pink crystalline solid. ^{13}C NMR (126 MHz, DMSO) δ 166.11, 159.37, 154.65, 159.37, 154.65, 145.80, 137.53, 134.15, 128.65, 128.01, 128.00, 125.48, 112.59, 92.04, 87.01, 57.34, 56.15, 34.80, 30.72, 20.76.

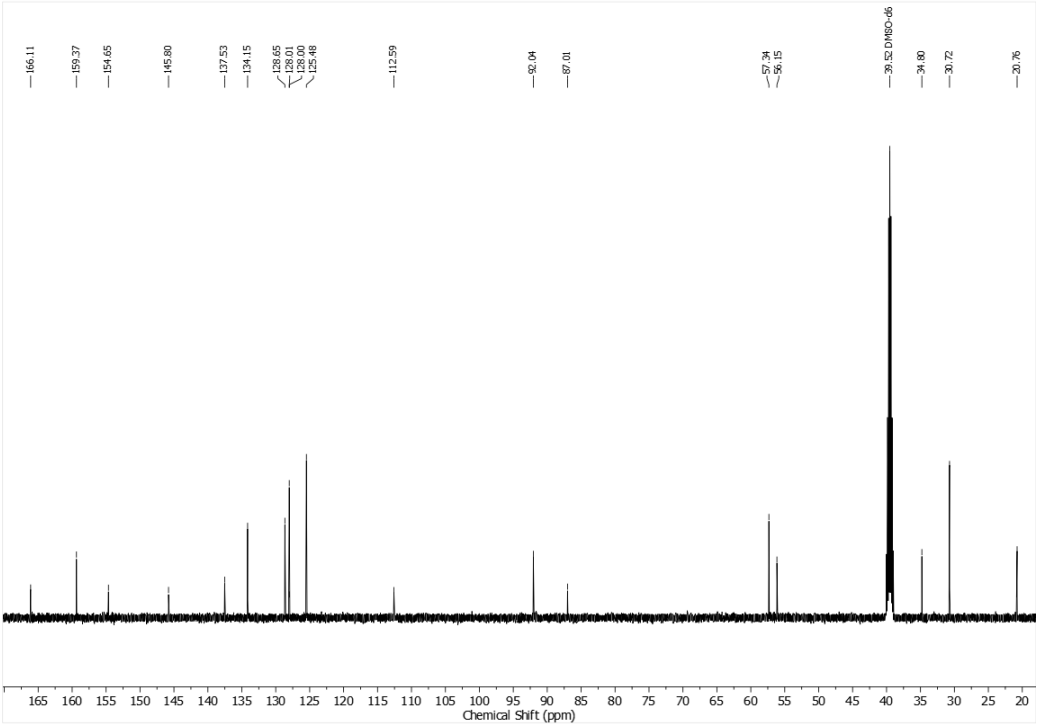
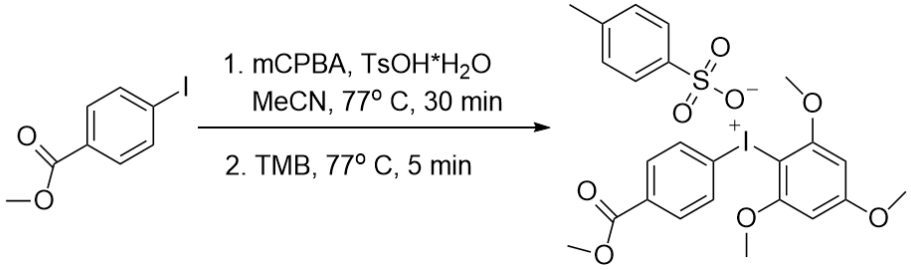


Figure 15. ^{13}C NMR of compound ***4.***



Synthesis of (4-(methoxycarbonyl)phenyl)(2,4,6-trimethoxyphenyl)iodonium 4-methylbenzene sulfonate (5)

Procedure adapted from (9). To a 50 mL RBF, methyl iodobenzoate (655.1 mg, 2.5 mmol, 1eq) and 15 mL of MeCN were added. Toluene sulfonic acid (434.5 mg, 2.75 mmol, 1 eq) and mCPBA (435.75, 2.75 mmol, 1 eq) were dissolved in 2.5 mL of MeCN each and added to the RBF. A stir bar was added, and the mixture was refluxed using a water bath heat source at 77° C for 30 minutes. The reflux condenser was removed, and 1, 3, 5-trimethoxybenzene (TMB, 467.17, 2.75 mmol, 1 eq) was then added to the mixture.

The mixture was then allowed to reflux for 5 more minutes before being removed from heat. Solvent was evaporated in vacuo until just a small amount of MeCN remained and was added dropwise to a stirring beaker of cold ether. This mixture was then filtered under vacuo to yield 1.17 g (84%) as a pink tinged white solid. ^{13}C NMR (126 MHz, DMSO): δ 166.37, 165.13, 159.41, 145.77, 137.55, 134.57, 132.14, 131.77, 128.02, 135.48, 120.91, 92.16, 86.90, 57.37, 56.20, 52.65, 20.76

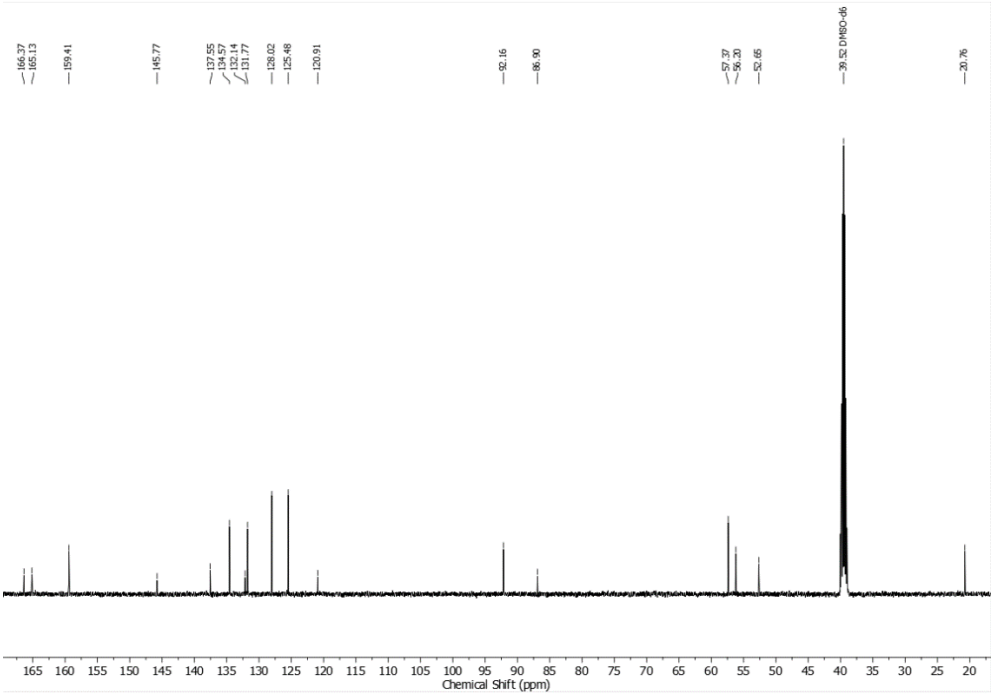
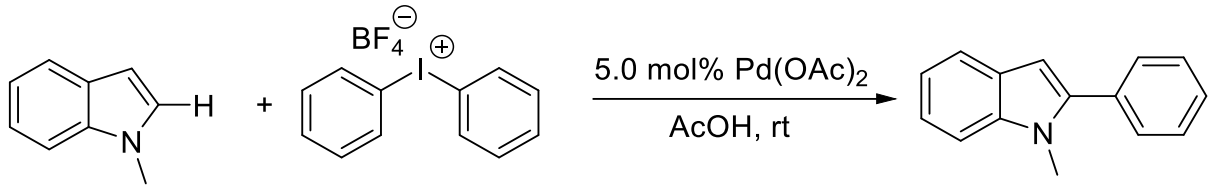


Figure 16. ^{13}C NMR of compound ***5.***

General Synthesis for compounds *6, 7, and 8.*

Procedure adapted from (10). To a 20 mL reaction vial, N-methylindole (49.85 mg, 0.38 mmol, 1 eq) and $Pd(OAc)_2$ (10.07 mg, 0.019 mmol, 0.05 eq) were dissolved in 1 mL of AcOH each and added. Iodonium salt (0.76 mmol, 2 eq) was then dissolved in 3 mL of AcOH and added. A stir bar was added, and the reaction was allowed to stir for 24 hours. The reaction mixture was filtered through a plug of celite, and solvent was evaporated under vacuum. The reaction mixture was then dissolved in 5 mL of DCM and washed twice with 5 mL of aqueous sodium bicarbonate. The mixture was dried using magnesium sulfate, filtered, and solvent was evaporated under vacuo.



Synthesis of 1-methyl-2-phenyl-1H-indole (6)

Consider the general synthesis above to form 78.2 mg (74.1%) isolated product as a white solid. Characterized using ^{13}C NMR. ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.38, 138.19, 132.67, 129.21, 128.36, 127.79, 127.71, 121.52, 120.32, 119.71, 109.47, 31.01 ppm.

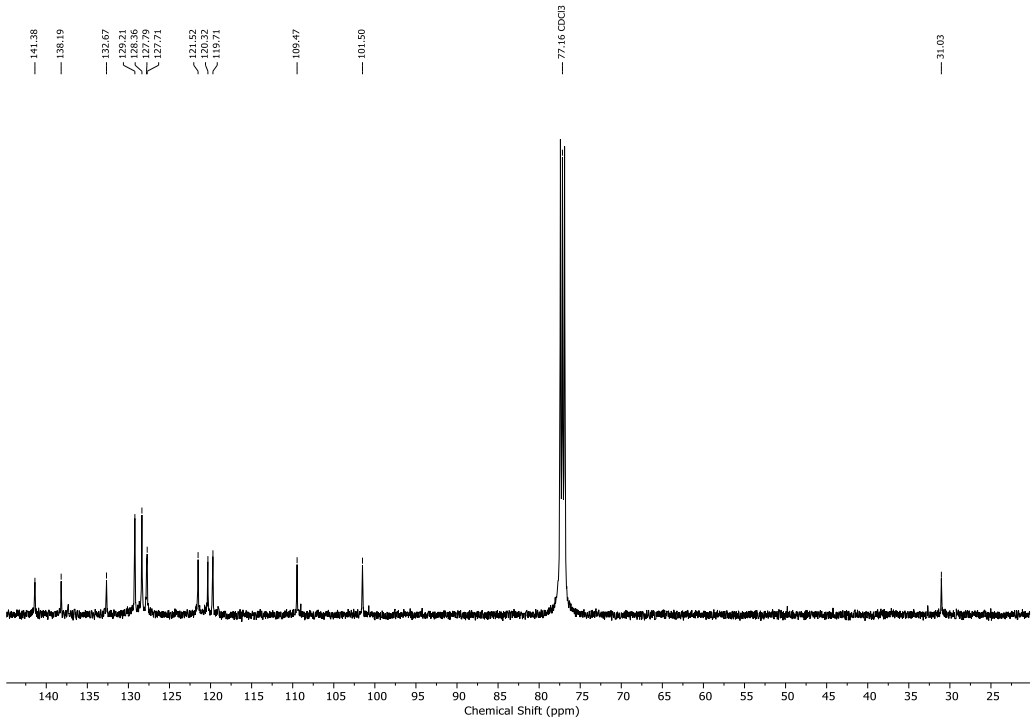
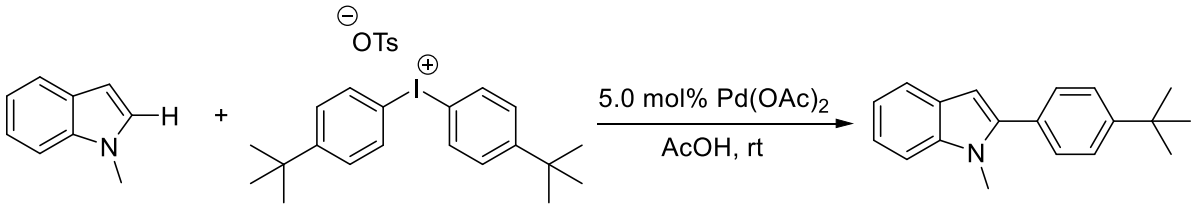


Figure 17. ^{13}C NMR of compound ***6***



Synthesis of 2-(4-(tert-butyl)phenyl)-1-methyl-1H-indole, using bis(4-(tert-butyl)phenyl)iodonium 4-methylbenzene sulfonate (8)

Consider the general synthesis above. The salt for this reaction was bought (CAS: 131717-99-2). After the full aqueous workup, the reaction mixture was purified using a silica gel column (Ethyl acetate and hexanes, 3:97) to yield 23.5 mg (21%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (dt, *J* = 5.0 Hz), 7.52-7.45 (qt, *J* = 2.0 Hz), 7.37 (d, *J* = 10.0 Hz), 7.24 (t, *J* = 1.0 Hz), 7.23 (d, *J* = 1.0 Hz), 7.15 (td, *J* = 1.0 Hz), 7.55 (d, *J* = 2 Hz), 3.77 (s), 1.55 (s), 1.39 (s), 1.27 (s) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.06, 141.79, 138.43, 130.05, 129.2, 128.16, 125.58, 121.62, 120.51, 119.91, 109.69, 101.50, 34.84, 31.49, 31.34.

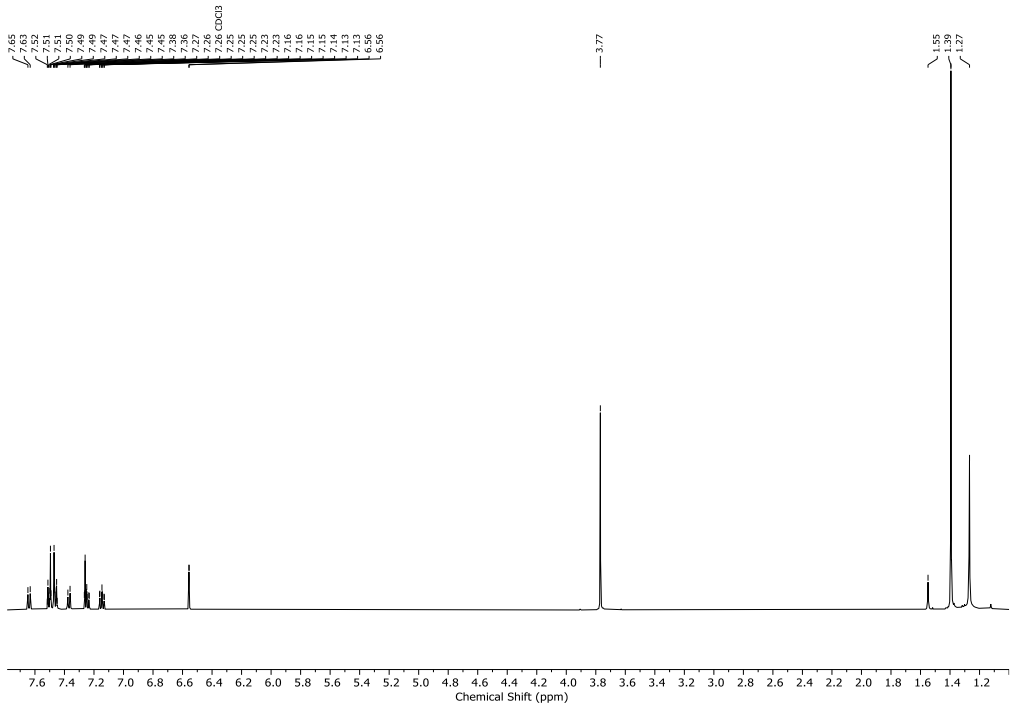


Figure 18. ^{1}H NMR of compound ***8*** after silica gel column

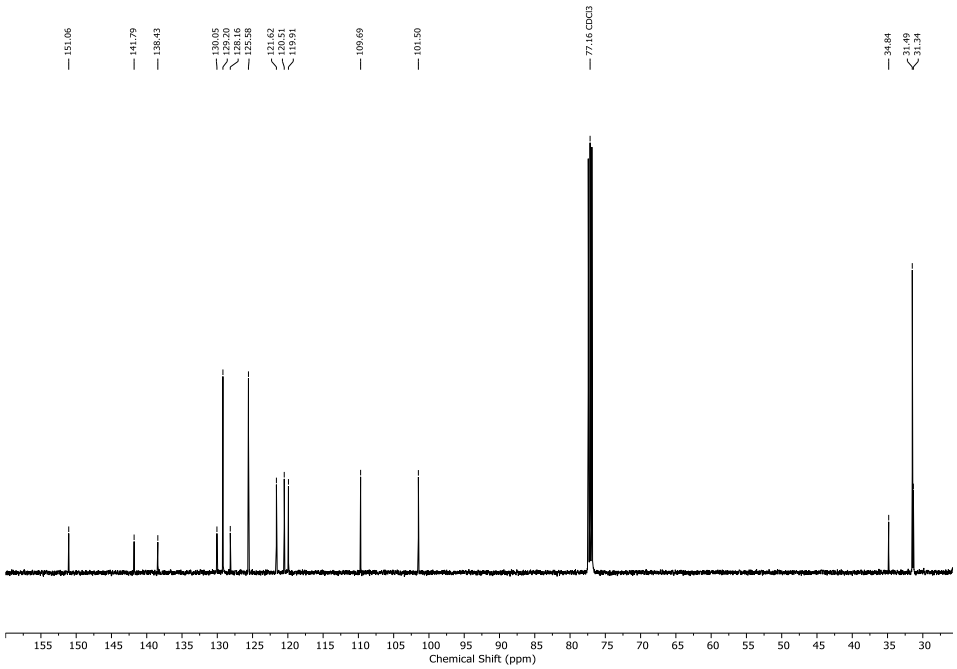


Figure 19. ^{13}C NMR of compound ***8*** after silica gel column.

Centrifuge Scale Procedure for C-H Functionalization Reactions

Procedure adapted from (13). To a 20 mL vial, N-methylindole (49.85 mg, 0.38 mmol, 1 eq), 1-3-5 trimethoxy benzene (38.2 mg, 0.22 mmol, 0.5 eq) and iodonium salt (0.76 mmol, 2 eq) were dissolved in 2 mL of AcOH each and added. 5-6 drops of fluorinated oil was placed at the bottom of four 1.5 mL centrifuge tubes. Using a 1 mL syringe with no needle, 1 mL of the fully dissolved reaction mixture was placed into each of the four centrifuge tubes containing fluorinated oil. A stock solution of $Pd(OAc)_2$ in THF was prepared. Using a micropipette, $Pd(OAc)_2$ (5 mol%) was quickly added to each of the centrifuge tubes. The centrifuge tubes were inverted once, and three of the four centrifuge tubes were centrifuged for 10 minutes at 13000 RPM. The fourth centrifuge tube served as a control. Four 20 mL vials were prepared with 200 μL of saturated $NaHCO_3$ and 3 mL of DCM. After the 10-minute period, 200 μL of the reaction mixture from each centrifuge tube was pipetted by micropipette into its corresponding vial containing $NaHCO_3$ and DCM to neutralize the AcOH. Each sample was then run through a pipette containing a Na_2SO_4 drying agent to remove aqueous layer. It can be noted that each

sample had a clean drying agent pipette prepared. The organic layer of the samples was then pipetted into GC vials for characterization by GC-FID. If there was any water left in a sample after the drying pipette, it was ensured that only the bottom organic layer was transferred to the GC vial.

References

1) Rodrigues, T. S.; Zhao, M.; Yang, T.; Gilroy, K. D.; Faustino, A.; Pedro; Xia, Y. Synthesis of Colloidal Metal Nanocrystals: A Comprehensive Review on the Reductants. *Chemistry: A European Journal* **2018**, *24* (64), 16944–16963. https://doi.org/10.1002/chem.201802194.

2) Littke, A. F.; Fu, G. C. A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Couplings of Aryl Chlorides and Arylboronic Acids. *Angewandte Chemie International Edition* **1998**, *37* (24), 3387–3388. https://doi.org/10.1002/(sici)1521-3773(19981231)37:24%3C3387::aid-anie3387%3E3.0.co;2-p.

3) Chernyshev, V. M.; Astakhov, A. V.; Chikunov, I. E.; Tyurin, R. V.; Eremin, D. B.; Ranny, G. S.; Khrustalev, V. N.; Ananikov, V. P. Pd and Pt Catalyst Poisoning in the Study of Reaction Mechanisms: What Does the Mercury Test Mean for Catalysis? **2019**, *9* (4), 2984–2995. https://doi.org/10.1021/acscatal.8b03683.

4) Hagen, C. M.; Widegren, J. A.; Maitlis, P. M.; Finke, R. G. Is It Homogeneous or Heterogeneous Catalysis? Compelling Evidence for Both Types of Catalysts Derived from [Rh(η5-C5Me5)Cl2]2as a Function of Temperature and Hydrogen Pressure. *Journal of the American Chemical Society* **2005**, *127* (12), 4423–4432. https://doi.org/10.1021/ja044154g.

5) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review. *Chemical Reviews* **2018**, *118* (4), 2249–2295. https://doi.org/10.1021/acs.chemrev.7b00443.

6) Pérez-Lorenzo, M. Palladium Nanoparticles as Efficient Catalysts for Suzuki Cross-Coupling Reactions. *The Journal of Physical Chemistry Letters* **2012**, *3* (2), 167–174. https://doi.org/10.1021/jz2013984.

7) Torborg, C.; Beller, M. Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries. *Advanced Synthesis & Catalysis* **2009**, *351* (18), 3027–3043. https://doi.org/10.1002/adsc.200900587.

8) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chemical Reviews* **2010**, *110* (2), 1147–1169. https://doi.org/10.1021/cr900184e.

9) Sharma, V.; Kumar, P.; Pathak, D. Biological Importance of the Indole Nucleus in Recent Years: A Comprehensive Review. *Journal of Heterocyclic Chemistry* **2010**, NA-NA. https://doi.org/10.1002/jhet.349.

10) Parr, Zachary S, et al. *Semiconducting Small Molecules as Active Materials for P-Type Accumulation Mode Organic Electrochemical Transistors*. Vol. 6, no. 6, 1 June 2020, pp. 2000215–2000215, https://doi.org/10.1002/aelm.202000215.

11) Seidl, T.; Sundalam, S. K.; McCullough, B.; Stuart, D. Unsymmetrical Aryl(2,4,6-Trimethoxyphenyl)Iodonium Salts: One-Pot Synthesis, Scope, Stability, and Synthetic Studies. **2016**, *81* (5), 1998–2009. https://doi.org/10.1021/acs.joc.5b02833.

12) Nicholas Ryan Deprez; Dipannita Kalyani; and Andrew Krause; Sanford, M. S. Room Temperature Palladium-Catalyzed 2-Arylation of Indoles. **2006**, *128* (15), 4972–4973. https://doi.org/10.1021/ja060809.