Controlling Site-Selectivity in Palladium and Platinum-Catalyzed C–H Arylation Reactions

And

A Novel Method to Prepare Aryl Sulfides from Thioethers

by

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Table of Contents

List of Figures

List of Tables

List of Schemes

Abstract

In recent years, there has been an increased focus on developing transition-metal catalyzed reactions to directly functionalize carbon-hydrogen bonds. Specifically, efficient C-H arylation reactions to enable the rapid and green synthesis of biaryl molecules, which are useful as pharmaceuticals, materials, dyes, and agrochemicals, are highly sought after.

The majority of this dissertation focuses on site-selective C-H arylation reactions. First, an example of the substrate-controlled arylation of pyrroles with diaryliodonium salts is presented. The site-selectivity of this reaction was found to be dictated by the sterics of the pyrrole starting material. Next, the palladium-mediated oxidative cross-coupling of benzo[*h*]quinoline and 1,3-dimethoxybenzene was studied computationally and experimentally to determine why different anionic ligands provide complementary selectivity on the simple arene substrate. It was determined that a change in rate-determining step when acetate or carbonate was the anionic ligand led to the observed selectivities. A catalytic variant was also developed that shows the same selectivity-determining factors. Finally, the first intermolecular $Pt^{II/IV}$-catalyzed direct C-H arylation of simple arenes with diaryliodonium salts is presented. For this system, the substrate scope and selectivity are defined and mechanistic studies providing evidence that the rate- and selectivity-determining step for this platinum-

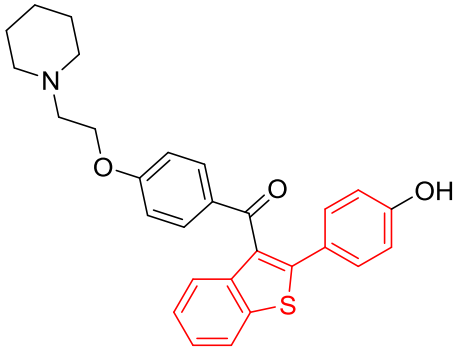
catalyzed reaction is reductive elimination are reported. This selectivity is complementary to the analogous palladium-catalyzed system in which oxidative addition is rate- and selectivity-determining and the opposite selectivity is observed upon reaction with naphthalene.

The last chapter of this dissertation discusses the metal-free coupling of diaryliodonium salts and thiols or alkyl thioethers, a reaction which was discovered during the optimization of the platinum-catalyzed C-H arylation reaction. This transformation provides complementary reaction conditions and substrate scope to known methods and allows for easy and green access to aryl sulfides, which are useful for pharmaceutical and materials applications.

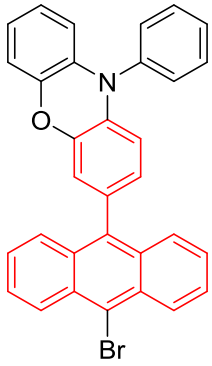
Chapter 1. Introduction

Aryl-aryl bonds constitute an important structural motif which is present in numerous pharmaceuticals, natural products, agrochemicals, dyes, materials, and supramolecular chemistry (Figure 1.1).[1] As such, efficient and selective ways to prepare these bonds are highly sought after.

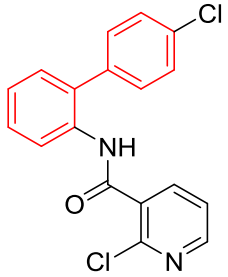
Figure 1.1. Examples of Molecules Containing the Biaryl Linkage



Evista (Eli Lilly)
estrogen modulator



Dow Advance Display Materials
Patent No. WO 2010114256
organic electroluminescence

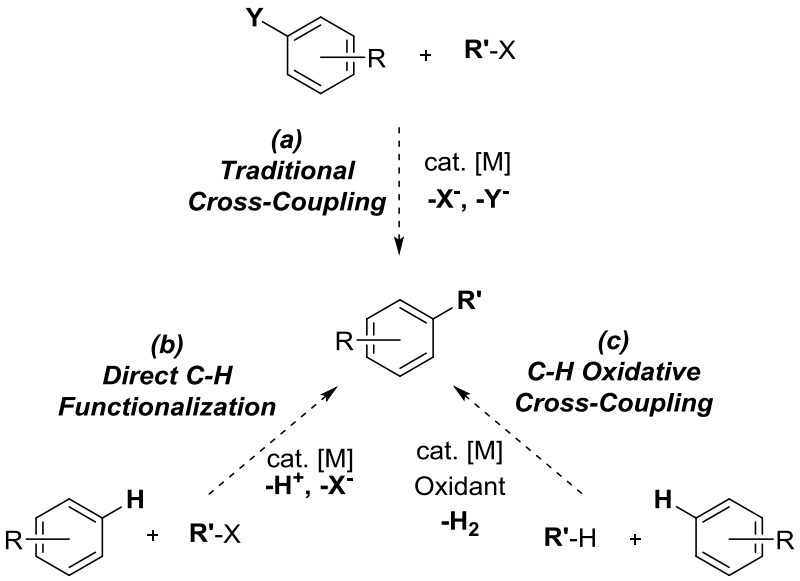


Boscalid
fungicide for food crops

Traditionally, this type of linkage has been prepared via the cross-coupling of two prefunctionalized starting materials using a transition metal catalyst (usually palladium, nickel, or copper, Scheme 1.1a).[2] While these cross-coupling reactions are extremely robust and widely used in preparing aryl-aryl and aryl-alkyl linkages; they do suffer from a number of drawbacks. These include the

necessity to prepare both starting materials independently and the production of stoichiometric amounts of toxic or undesirable byproducts, which diminish the "greenness" of this type of reaction. One way to negate the need for prefunctionalized starting materials is to take advantage of C–H bonds on one or both coupling partners, via direct C–H arylation (Scheme 1.1b) or oxidative cross-coupling (Scheme 1.1c), respectively.[3]

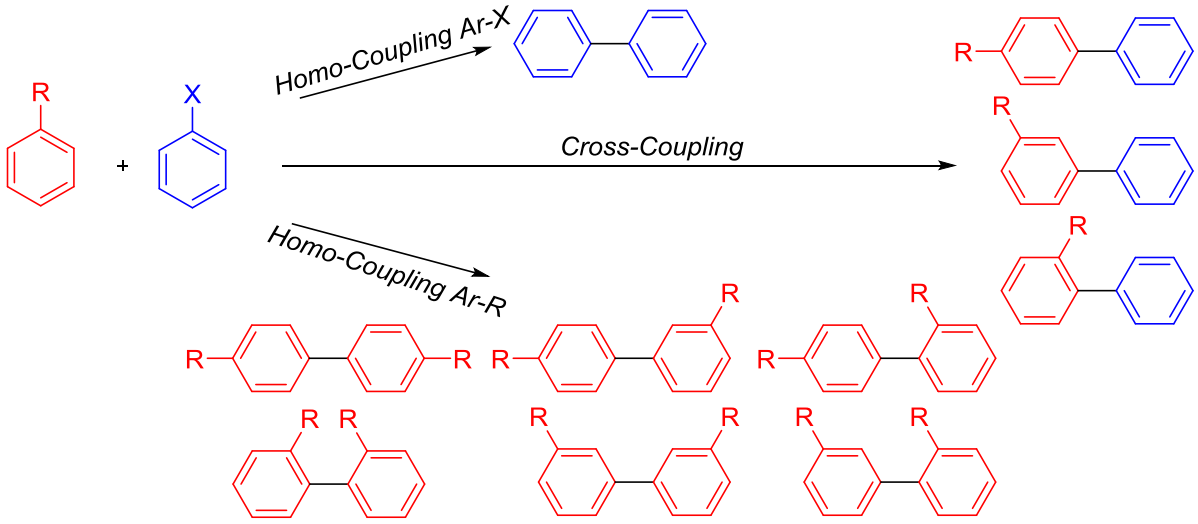
Scheme 1.1. Methods for Preparing the Biaryl Linkage



While these C–H activation methods represent a potentially simple, green way to produce biaryls;[4] the major issues with these strategies are chemoselectivity and the lack of selectivity between different C–H bonds. These difficulties are exemplified in the direct C–H arylation of a simple, mono-substituted arene and a coupling partner containing an activated C–X bond depicted in Scheme 1.2.

There are two major issues with this direct C–H arylation reaction. First, the simple arene has three types of C–H bonds that could be functionalized, *ortho*-, *meta*-, or *para*- to the R-substituent, which could lead to a difficult to separate mixture of three potential products. Second, homo-coupling between the simple arene or the activated arene is also possible, leading to an additional seven potential products. As a result the system must be finely tuned to determine the optimal catalyst, ratio of starting materials, temperature, and reaction time to maximize the amount of a single desired cross-coupling product. Thus, these reactions are often low yielding and only applicable to a very limited number of starting materials. There are numerous examples of unselective direct C–H arylation and oxidative cross-coupling reactions that illustrate these difficulties.[5]

Scheme 1.2. Coupling of Simple Arenes

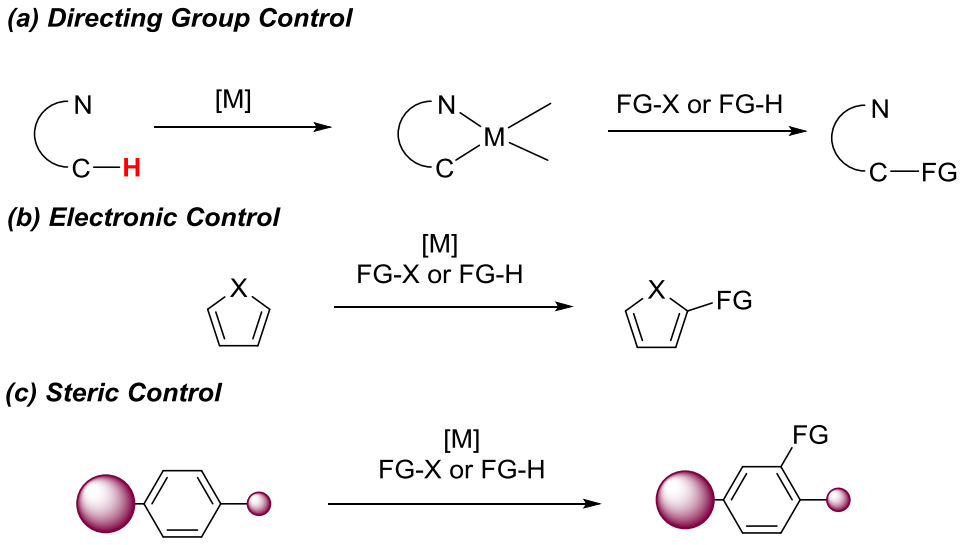


There are two ways to think about addressing these selectivity issues, substrate control and catalyst control. First, substrate control utilizes specific substrates to favor a certain cross-coupling product. Substrate control can be broken down into three distinct classes – electronic, steric, and directing-group control.

Scheme 1.3 demonstrates the way in which each class of substrate control provides selectivity. In directing group control, selectivity is achieved by using starting materials that contain Lewis-acidic "directing groups." These heteroatom directing groups bind to the transition metal as L-type ligands and hold the catalyst proximal to one C–H bond, allowing activation of that specific C–H bond (Scheme 1.3a).[6] In electronic control, substrates that are electronically biased to react at a specific position are employed (Scheme 1.3b).[7] Finally in steric control, starting materials that are sterically biased are used so reaction will only occur in one position, usually at the less hindered site (Scheme 1.3c).[8]

In chapter 2 of this dissertation, the direct C–H arylation of sterically differentiated 1,3- or 1,2,3-substituted pyrroles with diaryliodonium salts is discussed. Optimization for reactivity at the unactivated 3- and/or 4- position of pyrroles as well as the use of steric control to selectively generate, in most cases, a single biaryl product, is also presented. This chapter concludes with an example of the utility of this method; specifically, preparing difficult to obtain penta-substituted pyrrole derivatives.[8b]

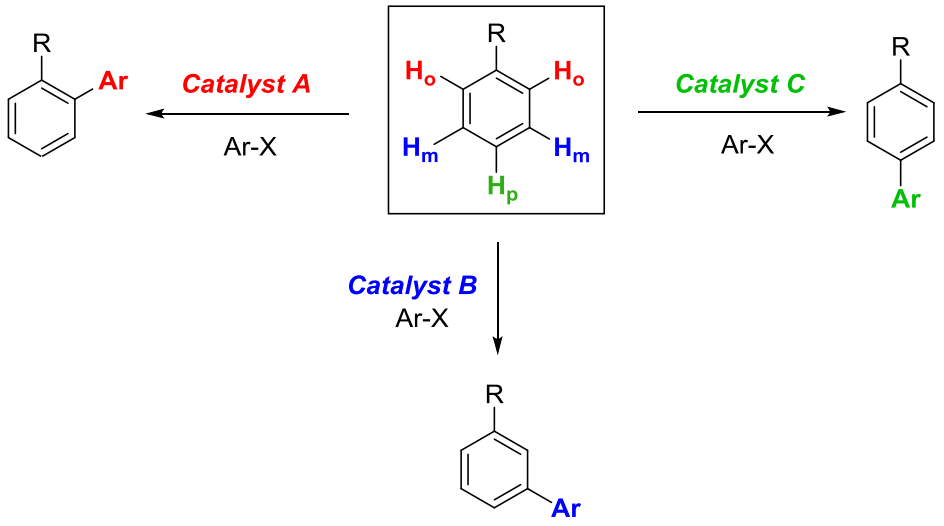
Scheme 1.3. Examples of Substrate Control in C–H Arylation Reactions



While substrate control has seen extensive use, the use of specific starting materials inherently restricts the widespread application of these techniques. Thus, it would be useful to have a more general and versatile way to address the selectivity challenge. The second way to address selectivity issues is through the use of catalyst control. Catalyst control represents an ideal way to control selectivity. Using this type of control, selectivity is conferred via the metallic catalyst, thus allowing widespread applicability to a broad range of substrates (Scheme 1.4). Currently there are a limited number of examples of catalyst control for preparing the biaryl linkage and those that are known are not very well understood.[9]

In chapters 3 and 4 of this dissertation, two selective, catalyst-controlled C–H arylation reactions are discussed. Chapter 3 outlines the computational and

Scheme 1.4. Selectivity via Catalyst Control

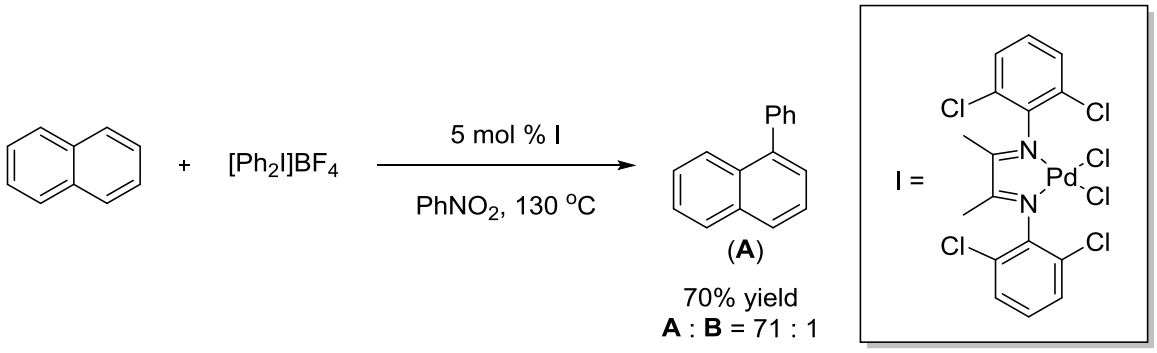


experimental details of the oxidative cross-coupling of 1,3-dimethoxybenzene and benzo[*h*]quinoline. While the selectivity in the benzo[*h*]quinoline coupling partner is dictated by directing group control, the selectivity for the simple arene is not well understood. In 2011, the Sanford group determined that changing the anionic ligand on palladium, from acetate to carbonate, led to a complete reversal in site-selectivity on the simple arene; from *meta/meta* with acetate to *ortho/para* with carbonate. This chapter discusses detailed computational experiments that provide an understanding of the overall mechanism of this reaction with the different anionic ligands.[10] Experiments that provide further evidence for the presented mechanism[10] as well as the development of a catalytic variant are also discussed.

The first example of intermolecular $Pt^{II/IV}$-catalyzed direct C–H arylation of simple arenes is presented in chapter 4. In 2011, the Sanford group determined that with palladium catalysts, the direct C–H arylation of naphthalene could be

performed in high yield, with good selectivity for 1-phenylnaphthalene **A** over 2-phenylnaphthalene **B** (Scheme 1.5).[11] However, this method was limited by a poor substrate scope (only naphthalene underwent high-yielding and site-selective C–H arylation) and only **A** could be obtained selectively. This chapter discusses the use of a platinum catalyst to address these issues. The ability to access 2-phenylnaphthalene selectively, the expanded substrate scope, and the detailed mechanistic studies which provide insight into the change in selectivity when either platinum or palladium are used as the catalyst are also presented.[12]

Scheme 1.5. Diimine-$PdCl_2$-Catalyzed Naphthalene Arylation



In the course of developing the site-selective platinum-catalyzed C–H arylation reaction in chapter 4, it was discovered that, in contrast to the other simple arenes, thioanisole underwent arylation of the sulfur atom with diaryliodonium salts. The final chapter of this dissertation, chapter 5, presents a synthetically useful, metal-free method to access aryl sulfides which was developed from this preliminary discovery.

Aryl sulfides have been found to have unique biological activity, are present in myriad pharmaceuticals,[13] and are the precursors to photoacid generators (PAGs) which are widely used in paints, anti-corrosives, microelectronics, and coatings.[14] However, many methods for their preparation require toxic transition metal catalysts, air-free conditions, a basic medium, and/or thiol starting materials.[15,16] The acid-mediated transformation presented in chapter 5 represents a complementary method to access this important motif. The scope and mechanism of this transformation are included.[17]

Overall, this dissertation will discuss the mechanisms and site-selectivities of a variety of arylation reactions.

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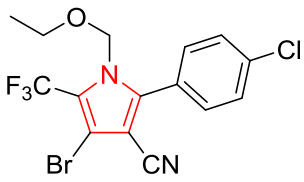
Chapter 2. Palladium-Catalyzed C–H Arylation of 2,5-Substituted Pyrroles[1]

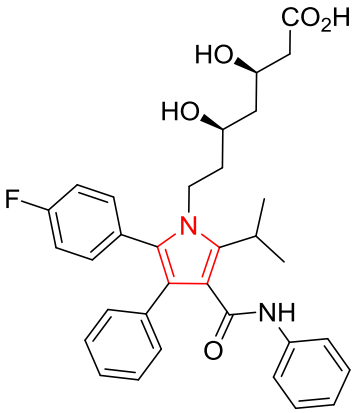
2.1 Introduction

Densely substituted pyrroles are an important class of heterocyclic compounds with useful biological and physical properties (Figure 2.1).[2] For example, tetra- and penta-substituted pyrroles feature prominently in natural products (*e.g.*, the lamellarin, lukianol, ningalin, polycitone, and storniamide classes of natural products),[3] pharmaceuticals (*e.g.,* Lipitor), agrochemicals (*e.g.,* chlorfenapyr), fluorescent dyes (*e.g.*, BODIPY derivatives),[4] and conducting polymers (*e.g.*, polypyrroles).[5]

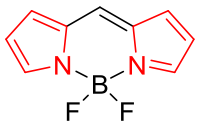
Figure 2.1 Examples of Substituted Pyrroles



Chlorfenapyr
pesticide



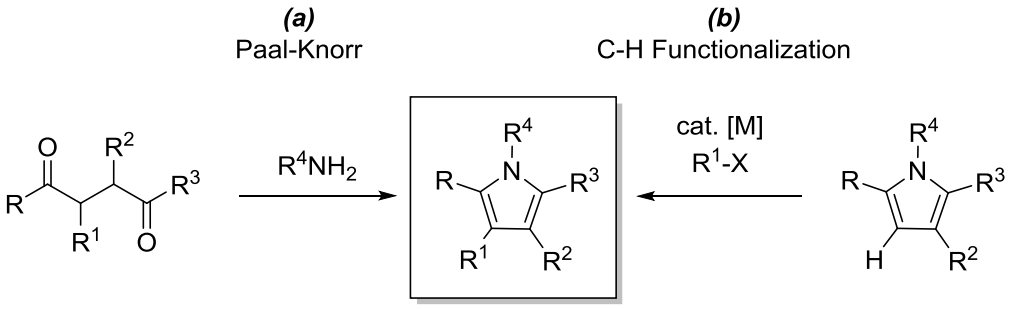
Lipitor
Lowers Cholesterol



BODIPY core
dye

The most common route to pyrrole derivatives involves cyclization reactions, such as the Knorr, Paal-Knorr, and Hantzsch reactions (for example, see Scheme 2.1a).[6] While these are all robust and versatile transformations, they require preassembly of appropriately substituted carbonyl precursors.[6] The direct C–H functionalization of pre-formed pyrrole derivatives (Scheme 2.1b) offers a highly complementary strategy for the synthesis and derivatization of these important heterocycles. In particular, this approach facilitates the late-stage diversification of the pyrrole core into a wide variety of functionalized structures.[7]

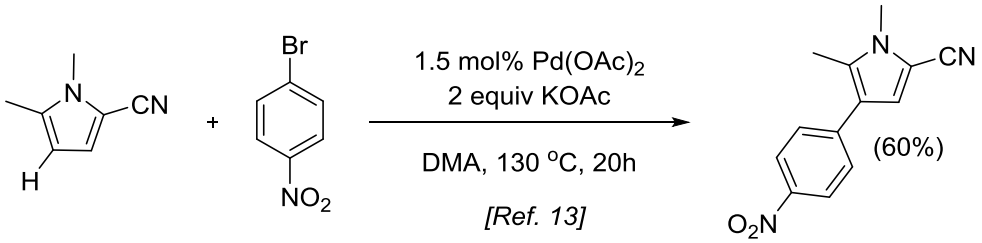
Scheme 2.1. Complementary Strategies for Pyrrole Synthesis



Over the past 5 years, a variety of elegant methods have been developed for the intermolecular C–H arylation,[7,8] olefination,[9] alkynylation,[10] and borylation[11] of pyrrole derivatives. The vast majority of these transformations involve functionalization at the 2- and/or 5-positions of pyrroles due to the inherent reactivity of these sites. In marked contrast, very little work has addressed the C–H functionalization of 2,5-disubstituted pyrroles.[9c,10b,12,13,14] Most relevant to the current studies, Doucet and Santelli have reported the

$Pd(OAc)_2$-catalyzed 3-arylation of several 1,2,5-trisubstituted pyrroles with aryl bromides (Scheme 2.2).[13] While this reactivity represents an important advance, the reaction suffers from several key limitations, including: (i) modest scope of pyrrole substrates, (ii) the requirement for electron deficient aryl bromides, (iii) high reaction temperatures (130 ºC), and (iv) moderate yields (typically <65%).

Scheme 2.2. Previous Examples of Pyrrole Arylation

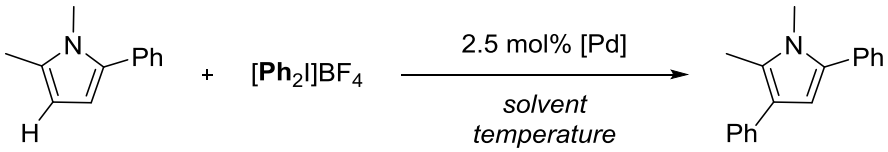


Previous studies from our group have shown that Pd^{II}- catalysts promote the 2-arylation of indoles and pyrroles with diaryliodonium salts.[15,16] These reactions proceed with high functional group tolerance and under extremely mild conditions (typically at room temperature). In contrast, most other Pd-catalyzed indole/pyrrole arylation methods require temperatures in excess of 100 ºC.[17] On the basis of our prior work, we hypothesized that combining a Pd^{II} catalyst and Ar_2IBF_4 might also promote the C–H arylation of 2,5-substituted pyrrole derivatives. We report herein that this strategy is effective for the synthesis of tri-, tetra-, and even penta-substituted pyrrole products.

2.2 Results and Discussion

Our initial investigations focused on the phenylation of 1,2-dimethyl-5-phenylpyrrole with Ph_2IBF_4 (Table 2.1). We first examined $Pd(OAc)_2$ as the

Table 2.1. Optimizing the Pd-Catalyzed C–H Phenylation of 1,2-Dimethyl-5-Phenylpyrrole with Ph_2IBF_4[a]



entry	[Pd]	solvent	temperature	yield (%)[b]
1	$Pd(OAc)_2$	AcOH	25 ºC[c]	3
2	$(MeCN)_2PdCl_2$	AcOH	25 ºC[c]	7
3	$(MeCN)_2PdCl_2$	DCE	25 ºC[c]	11
4	$(MeCN)_2PdCl_2$	DCE	40 ºC[c]	42
5	$(MeCN)_2PdCl_2$	DCE	60 ºC[d]	60
6	$(MeCN)_2PdCl_2$	DCE	80 ºC[e]	84

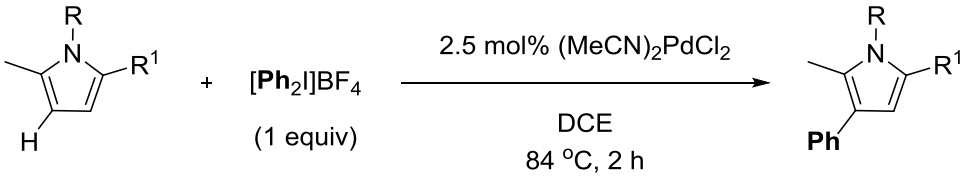
[a]1 equiv (0.5 mmol) of pyrrole, 1 equiv (0.5 mmol) of Ph_2IBF_4, 2.5 mL of solvent, 2.5 mol% of [Pd]. [b]Isolated yields (average of 2 or 3 runs). [c]15 h. [d]5 h. [e]2 h.

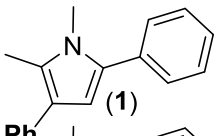
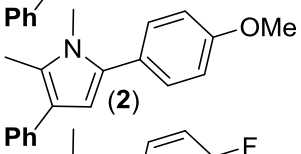
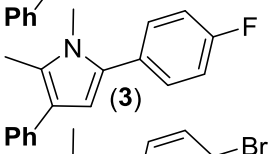
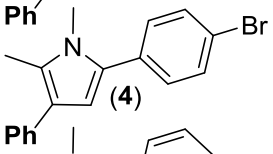
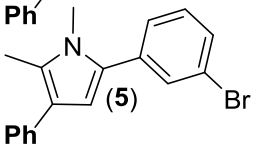
catalyst in AcOH at room temperature, since these were effective conditions for the C2-arylation of 1-methylpyrrole.[15] Gratifyingly, traces (3%) of the desired product **1** were obtained (entry 1). A screen of other Pd^{II} catalysts revealed that $(MeCN)_2PdCl_2$[18] provided significantly higher yield (7%, entry 2). Moving from AcOH to DCE as the solvent and increasing the reaction temperature from 25 ºC to 84 ºC further enhanced the yield to 84% (entry 6). Notably, the optimal conditions (2.5 mol % of [Pd], 84 ºC, 2 h in DCE) are mild compared to most

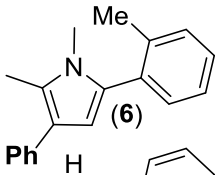
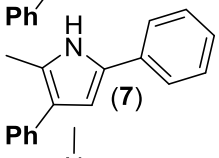
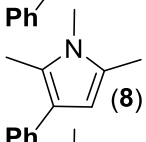
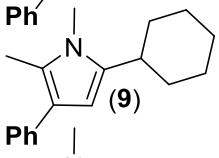
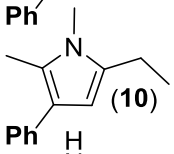
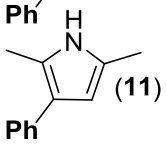
other Pd-catalyzed pyrrole arylation reactions reported in the literature.[7,8,13,14] In addition, this transformation was highly site selective, providing 1,2-dimethyl-3,5-diphenylpyrrole as the only regioisomer detected by GC and GCMS analysis.

As shown in Table 2.2, a variety of 1,2-dimethyl-5-aryl pyrrole derivatives were effective substrates for this transformation.[19] Electron withdrawing and electron donating substituents as well as *ortho*-substitution on the aryl ring were all well-tolerated (Table 2.2, entries 2-6).

Table 2.2. Scope of Pyrrole Substrates[a]



entry	R	R^1	product	yield (%)
1	CH_3	Ph	 (**1**)	84
2	CH_3	4-$MeOC_6H_4$	 (**2**)	54
3	CH_3	4-FC_6H_4	 (**3**)	75
4	CH_3	4-BrC_6H_4	 (**4**)	70
5	CH_3	3-BrC_6H_4	 (**5**)	59

entry	R	R^1	product	yield (%)
6	CH_3	2-MeC_6H_4	 (**6**)	83
7	H	Ph	 (**7**)	44
8	CH_3	Me	 (**8**)	54
9	CH_3	Cy	 (**9**)	82[b]
10	CH_3	Et	 (**10**)	53[c]
11	H	Me	 (**11**)	55

[a]1 equiv (1.0 mmol) of pyrrole, 1 equiv (1.0 mmol) of Ph_2IBF_4, 2.5 mol % $(MeCN)_2PdCl_2$ in 2.5 mL of DCE at 84 ºC for 2 h. [b]Isomer ratio = 29:1 as determined by ^{1}H NMR Spectroscopy. [c]Isomer ratio = 2.0:1 as determined by ^{1}H NMR. All results are an average of two runs. Moderate yields can be accounted for by competing oligimerization of pyrrole starting material. Excess hypervalent iodine reagent leads to decreased yields.

In all of these cases, excellent (>50:1) selectivity was observed for C–H functionalization adjacent to the CH_3 substituent. The only case in which another isomer was even detected was with the electron rich *p*-$MeOC_6H_4$-substituted pyrrole (entry 2). In this case, **2** was formed along with traces (~0.3%) of a minor isomer. Interestingly, 2-methyl-5-phenylpyrrole, which is unprotected at N, also showed modest reactivity to form **7** under these conditions (entry 7).

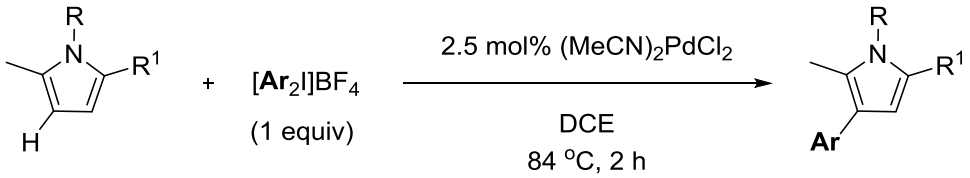
2,5-Methyl/alkyl substituted pyrroles also underwent efficient C–H arylation with diphenyliodonium tetrafluoroborate (Table 2.2, entries 8-11). In all cases examined, arylation adjacent to the CH_3 substituent was favored. The selectivity was modest (2.0:1) with R^1 = ethyl, but was very good (29:1) with R^1 = cyclohexyl (entries 9 and 10, respectively). These results suggest that steric factors are a major contributor to site-selectivity in this system.

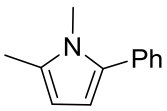
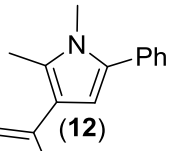
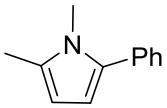
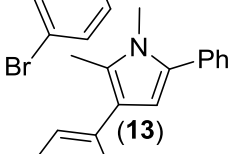
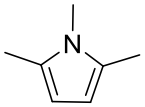
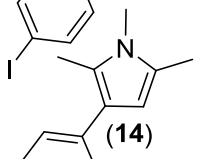
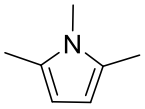
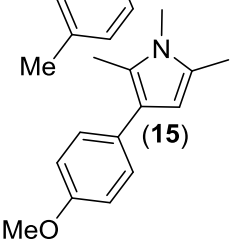
In contrast to the alkyl and aryl substituted derivatives in Table 2.2, pyrroles containing highly electron withdrawing substituents (*e.g.,* 1,5-dimethyl-2-pyrrolecarbonitrile, 1,2-dimethyl-5-pyrrolecarboxylic acid, and 1,5-dimethyl-2-pyrrolecarboxaldehyde) exhibited low reactivity. Under our standard reaction conditions, <5% yield of C–H arylation products were detected, and the mass balance was largely unreacted starting material. As such, the current method is highly complementary to the Doucet/Santelli chemistry (Scheme 2.2),[13] which works particularly well with 1,5-dimethyl-2-pyrrolecarbonitrile.[20]

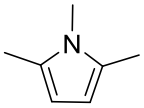
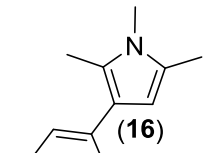
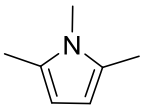
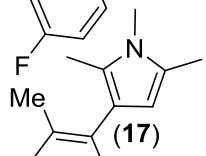
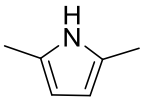
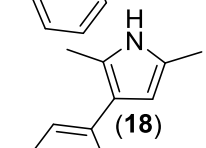
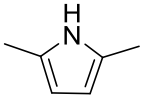
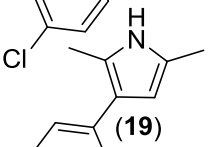
We next evaluated the scope of this transformation with respect to the hypervalent iodine coupling partner. A series of diverse reagents of general structure Ar_2IBF_4 were prepared from the corresponding ArI and $ArB(OH)_2$ in a versatile one pot procedure developed by Olofsson and coworkers.[21] As summarized in Table 2.3, these reagents were effective for the 3-arylation of 1,2-dimethyl-5-phenyl pyrrole, 1,2,5-trimethylpyrrole, and 2,5-dimethylpyrrole. Remarkably, chloride, bromide, and iodide substituents were all well-tolerated on the oxidant (entries 1, 2, and 7). These serve as valuable synthetic handles for manipulating the products further. In addition, good to excellent yields of C–H

arylation products were obtained with Ar_2IBF_4 containing electron donating methyl and methoxy substituents (entries 4 and 5). This reactivity is in marked contrast to the Doucet/Santelli system,[13] which requires electron deficient aryl bromide electrophiles. Finally, even the highly sterically congested *ortho*-methyl substituted iodine(III) reagent provided a modest yield of C–H arylated product **17** (entry 6).

Table 2.3. Scope of Arylating Reagents[a]



entry	pyrrole	product	yield (%)
1		 (**12**)	88
2		 (**13**)	53
3		 (**14**)	74
4		 (**15**)	73

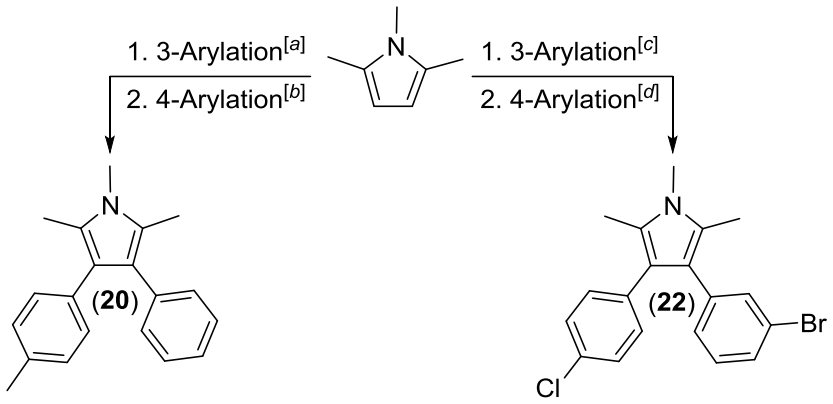
entry	pyrrole	product	yield (%)
5		 (**16**)	39
6		 (**17**)	34
7		 (**18**)	58
8		 (**19**)	49

[a]1 equiv (1.0 mmol) of pyrrole, 1 equiv (1.0 mmol) of Ph_2IBF_4, 2.5 mol% of $(MeCN)_2PdCl_2$ in 2.5 mL of DCE at 84 ºC for 2 h. All results are an average of 2 runs. Moderate yields can be accounted for by competing oligimerization of pyrrole starting material. Excess hypervalent iodine reagent leads to decrease in yields.

A final set of investigations focused on further functionalizing the 3-arylated pyrrole products. Specifically, we sought to examine whether these species underwent Pd-catalyzed C4-arylation with Ar_2IBF_4 to generate 1,2,3,4,5-substituted pyrrole derivatives. We were pleased to find that reacting **14** and **21** with Ar_2IBF_4 in the presence of 5 mol % of $(MeCN)_2PdCl_2$ at 84 ºC in DCE provided penta-substituted pyrroles **20** and **22** in 44% and 32% yield, respectively (Scheme 2.3). Despite the relatively modest yields, this type of reaction is quite valuable because it provides access to pyrroles with different

aryl groups at the 3- and 4-positions, a difficult substitution pattern to achieve using the Paal-Knorr synthesis.

Scheme 2.3. Sequential Diarylation to Form Pentasubstituted Pyrroles



[*a*] 2.5 mol % $(MeCN)_2PdCl_2$, 1 equiv $[(4\text{-}MeC_6H_4)_2I]BF_4$, DCE, 84 ºC, 2 h; (73%, **14**)
[*b*] 5 mol % $(MeCN)_2PdCl_2$, 1 equiv $[Ph_2I]BF_4$, DCE, 84 ºC, 2 h; (44%, **20**)
[*c*] 2.5 mol % $(MeCN)_2PdCl_2$, 1 equiv $[(4\text{-}ClC_6H_4)_2I]BF_4$, DCE, 84 ºC, 2 h; (38%, **21**)
[*d*] 5 mol % $(MeCN)_2PdCl_2$, 1 equiv $[(4\text{-}BrC_6H_4)_2I]BF_4$, DCE, 84 ºC, 2 h; (32%, **22**)

2.3 Conclusion

In conclusion, this paper demonstrates the Pd-catalyzed mono- and sequential di-arylation of 2,5-substituted pyrrole derivatives with Ar_2IBF_4. These reactions provide an attractive and selective method for synthesizing polysubstituted pyrroles under mild conditions in a short amount of time.

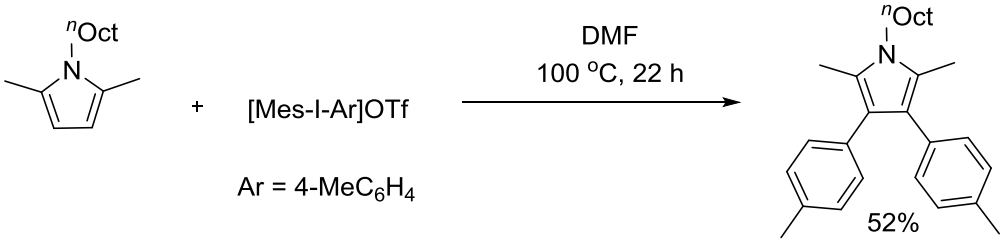
2.4 Updates

Since publishing this method in the beginning of 2011, functionalization at the 2- and/or 5-position of pyrroles has remained a hot topic of research;[22] a number of advances in generating multiply substituted pyrroles via multi-component systems have been reported,[23] and two new direct C–H arylation

reactions at the 3-position of pyrroles and pyrrole derivatives have been accomplished.

In 2011, Ackermann and coworkers reported the metal-free arylation of indoles and 1,2,5-substituted pyrroles.[24] While the primary focus of this paper was on the 3-arylation of indoles, there is one example which demonstrates the 3,4-diarylation of N-octyl 2,5-dimethyl pyrrole using mesityl aryl iodonium trifluoromethanesulfonate at 100 ^{o}C in DMF (Scheme 2.4). This research represents an advance because it does not require any transition-metal catalyst. However, the main drawbacks to this work include the necessity of an inert, nitrogen atmosphere, moderate yields, and the fast di-arylation of both the 3- and 4- positions of pyrroles concurrently (with the same aryl group).

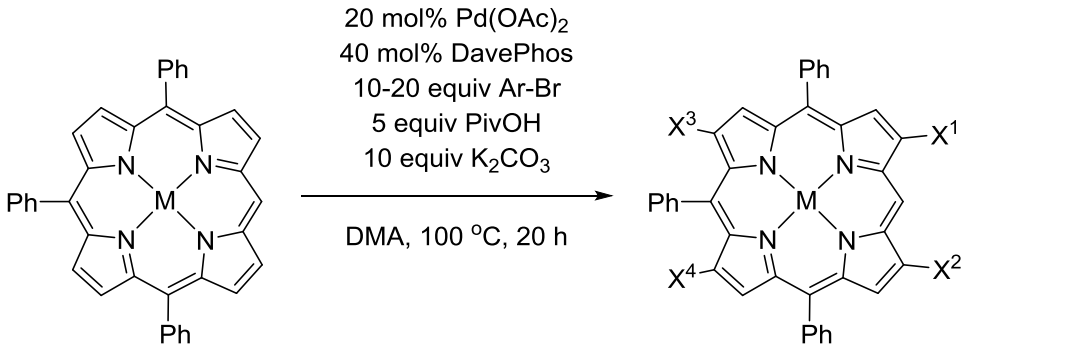
Scheme 2.4. Metal-free 3-Arylation of N-Octyl 2,5-Dimethyl Pyrrole



Also in 2011, Osuka, Yorimitsu and coworkers described a rare, selective β-arylation of porphyrins via a direct C–H arylation with aryl bromides.[25] Zinc and nickel complexes of 5,10,15-tris(3,5-di-tert-butylphenyl)porphyrin could be selectively mono-, di-, or tetra-arylated at the β-position (Scheme 2.5). The extent of arylation was dictated by the identity of the metal associated with the

porphyrin as well as the amount of aryl bromide used. This reaction allows rapid access to β-arylated porphyrins which may have useful properties in functional materials and supramolecular chemistry.

Scheme 2.5. Selective β-Arylation of Metal Porphyrin Complexes



[M] = Ni or Zn

Ni (10 eq. Ar-Br) - X^1/X^2 = Ar, X^3/X^4 = H (80%)
Ni (20 eq. Ar-Br) - $X^1/X^2/X^3/X^4$ = Ar (33%)
Zn (10 eq. Ar-Br) - X^1 = Ar, $X^2/X^3/X^4$ = H (91%)

2.5 Experimental

General Procedures: NMR spectra were recorded on a Varian MR400 (400.52 MHz for ^{1}H; 100.71 for ^{13}C, 376.87 MHz for ^{19}F) NMR spectrometer with the residual solvent peak ($CDCl_3$: ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm) as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as an external reference at 0.00 ppm. Multiplicities are reported as follows: br s (broad singlet), app (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants *J* are reported in Hz. Flash chromatography was performed on EM Science silica gel 60 (0.040-0.063 mm particle size, 230-400 mesh). Thin layer chromatography

was performed on Merck TLC plates pre-coated with silica gel 60 F_{254}. High resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Gas chromatography was carried out on a Shimadzu 17A using a Restek Rtx®-5 (Crossbond 5% diphenyl – 95% dimethyl polysiloxane; 15 m, 0.25 mm ID, 0.25 µm df) column.

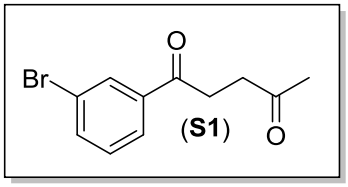
Materials and Methods: Substrates **P8** and **P11** were obtained from commercial sources and were used as received. Substrates **P1-P6, P9** and **P10** were prepared by cyclizing the corresponding diones with methylamine using sulfamic acid as the catalyst.[19b] Substrate **P7** was prepared by cyclizing the dione with magnesium nitride.[26] The diones were prepared according to a literature procedure.[27] The aryliodonium salts Ar_2IBF_4 with Ar = *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-IC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *o*-FC_6H_4 and *o*-MeC_6H_4 were prepared via literature method using the corresponding aryl iodide and arylboronic acid in the presence of *m*-CPBA.[21] Ph_2IBF_4 was synthesized from $PhB(OH)_2$ and $PhI(OAc)_2$ in the presence of BF_3•OEt_2.[28] $Pd(Cl)_2(MeCN)_2$ was prepared by the reacting $PdCl_2$ in acetonitrile at room temperature.[18] Other palladium catalysts were obtained from commercial sources (Strem or Pressure Chemicals) and used as received. Solvents were obtained from Fisher Chemical and used without further purification. Flash chromatography was performed on EM Science silica gel 60 (0.040-0.063 mm particle size, 230-400 mesh) and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel

60 F254. Control reactions (in the absence of Pd catalyst or in the absence of oxidant) showed no reaction under our standard conditions.

2.6 Synthesis and Characterization

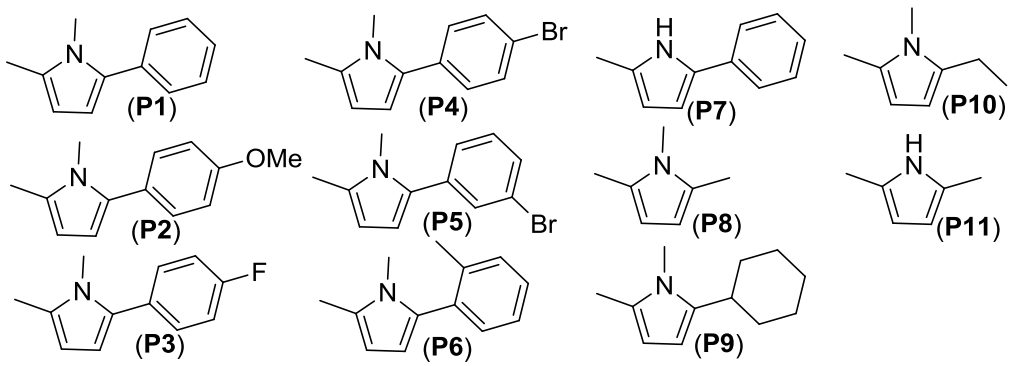
2.6.1 Dione Precursors

Dione precursors to substrates **P1-P7, P9** and **P10** were synthesized as described in ref. 27. Characterization data for the precursors to **P1-P4, P6, P7, P9** and **P10** matched that reported in the literature.[27] The characterization of previously unknown compound **S1** is reported below.

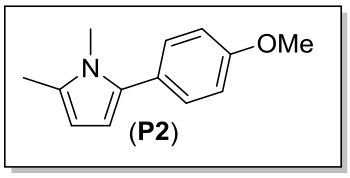


Methyl vinyl ketone (2.50 mL, 1 equiv, 30 mmol), 3-bromobenzaldehyde (3.5 mL, 1 equiv, 30 mmol), triethylamine (6.6 mL, 1.6 equiv, 48 mmol) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (1.16 g, 0.15 equiv, 4.5 mmol) were combined according to ref. 27, yielding a clear brown liquid (5.50 g, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.90 (d, J = 7.0 Hz, 1H), 7.69 (d, J = 10.0 Hz, 1H), 7.35 (app. t, J = 8.0 Hz, 1H), 3.23 (t, J = 6.3 Hz, 2H), 2.90 (t, J = 6.3 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 206.4, 196.5, 138.0, 135.3, 130.4, 129.7, 126.1, 122.3, 36.4, 31.9, 29.4. HRMS electrospray (m/z): [M+] calcd for $C_{11}H_{11}BrO_2$, 276.9840; found, 276.9830.

2.6.2 Pyrrole Substrates

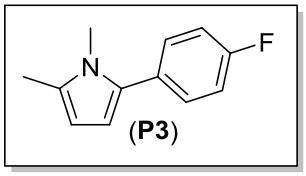


Pyrrole substrates **P8** and **P11** were purchased from Aldrich and used as received. Substrates **P1-P6, P9** and **P10** were synthesized as described in ref.19b.[29] Substrate **P7** was synthesized as described in ref. 26. Characterization data for **P1** and **P7** matched that reported in the literature.[30,31] The characterization of previously unknown pyrroles **P2-P6, P9** and **P10** is reported below.



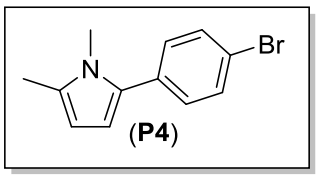
1-(4-Methoxyphenyl)pentane-1,4-dione (1.8 g, 1 equiv, 8.7 mmol), methylamine (33 wt % in absolute ethanol, 2.2 mL, 2 equiv, 17.4 mmol) and sulfamic acid (0.084 g, 0.1 equiv, 0.87 mmol) were used to yield **P2** as a white solid (1.33 g, 76% yield). Mp = 55.3-56.6 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 6.5, 2.0 Hz, 2H), 6.93 (dd, *J* = 6.5 Hz, 2.0 Hz, 2H), 6.05 (d, *J* = 3.5 Hz, 1H), 5.94 (dd,

J = 3.5, 0.5 Hz, 1H), 3.84 (s, 3H), 3.48 (s, 3H), 2.29 (d, *J* = 0.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 133.7, 130.2, 129.7, 126.6, 113.7, 106.6, 106.0, 55.2, 31.5, 12.7. HRMS EI+ (m/z): [M+] calcd for $C_{13}H_{15}NO$, 201.1153; found, 201.1157.



(**P3**)

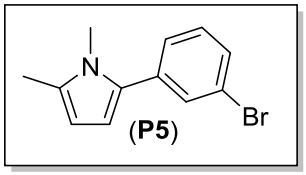
1-(4-Fluorophenyl)pentane-1,4-dione (0.39 g, 1 equiv, 2 mmol), methylamine (33 wt % in absolute ethanol, 0.5 mL, 2 equiv, 4 mmol) and sulfamic acid (0.019 g, 0.1 equiv, 0.2 mmol) were used to yield **P3** as a white solid (0.29 g, 76% yield). Mp = 70.9-74.7 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 2H), 7.07 (m, 2H), 6.09 (d, *J* = 3.5 Hz, 1H), 5.95 (d, *J* = 3.5 Hz, 1H), 3.48 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7 (d, *J* = 245 Hz), 133.0, 130.3 (d, *J* = 8 Hz), 130.1, 130.0, 115.2 (d, *J* = 22 Hz), 107.3, 106.2, 31.5, 12.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ 116.1 (m, 1H). HRMS EI+ (m/z): [M+] calcd for $C_{12}H_{12}FN$, 189.0954; found, 189.0953.



(**P4**)

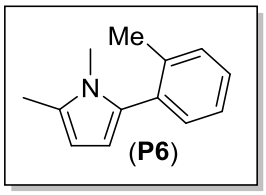
1-(4-Bromophenyl)pentane-1,4-dione (2.0 g, 1 equiv, 8 mmol), methylamine (33 wts % in absolute ethanol, 2.0 mL, 2.5 equiv, 16 mmol) and sulfamic acid (0.078

g, 0.1 equiv, 0.8 mmol) were used to yield **P4** as a white solid (1.36 g, 68% yield). Mp = 61.6-62.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 2H), 6.13 (d, *J* = 3.5 Hz, 1H), 5.96 (d, *J* = 3.5 Hz, 1H), 3.51 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.8, 131.4, 131.1, 130.0, 120.3, 107.7, 106.5, 31.7, 12.7 (two aromatic signals are coincidentally overlapping). HRMS electrospray (m/z): [M+] calcd for $C_{12}H_{12}BrN$, 250.0231; found, 250.0232.



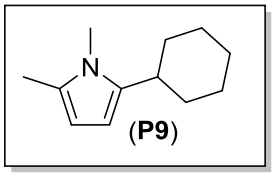
(**P5**)

1-(3-Bromophenyl)pentane-1,4-dione (2.0 g, 1 equiv, 8 mmol), methylamine (33 wt % in absolute ethanol, 2.0 mL, 2.5 equiv, 16 mmol) and sulfamic acid (0.078 g, 0.1 equiv, 0.8 mmol) were used to yield **P5** as a yellow oil (1.79 g, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.40 (d, *J* = 6.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.25 (m, 1H), 6.15 (d, *J* = 3 Hz, 1H), 5.97 (d, *J* = 3 Hz, 1H), 3.52 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 132.2, 131.0, 129.7, 129.0, 126.8, 122.2, 108.1, 106.6, 31.6, 12.6 (two aromatic signals are coincidentally overlapping). HRMS electrospray (m/z): [M+] calcd for $C_{12}H_{12}BrN$, 250.0231; found, 250.0234.



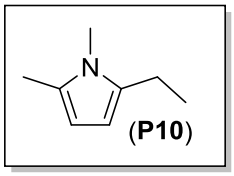
(**P6**)

1-(2-Tolyl)-pentane-1,4-dione (1.5 g, 1 equiv, 8 mmol), methylamine (33 wt % in absolute ethanol, 2.0 mL, 2.5 equiv, 16 mmol) and sulfamic acid (0.078 g, 0.1 equiv, 0.8 mmol) were used to yield **P6** as a yellow oil (1.41 g, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23-7.85 (multiple peaks, 4H), 5.97 (app. s, 2H), 3.27 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 133.7, 132.4, 131.2, 129.8, 128.6, 127.6, 125.3, 106.9, 105.4, 30.8, 20.0, 12.5. HRMS EI (m/z): [M+] calcd for $C_{13}H_{15}N$, 185.1204; found, 185.1207.



(**P9**)

1-Cyclohexylpentane-1,4-dione (2.3 g, 1 equiv, 13 mmol), methylamine (33 wt % in absolute ethanol, 4.0 mL, 2.5 equiv, 32.5 mmol) and sulfamic acid (0.126 g, 0.1 equiv, 1.3 mmol) were used to yield **P9** as white solid (1.82 g, 79% yield). Mp = 47.7-48.9 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (d, *J* = 3 Hz, 1H), 5.78 (d, *J* = 3 Hz, 1H), 3.41 (s, 3H), 2.47 (m, 1H), 2.22 (s, 3H), 1.96 (m, 2H), 1.82 (m, 2H), 1.74 (m, 1H), 1.34-1.40 (multiple peaks, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 127.6, 104.8, 101.6, 36.1, 33.4, 29.9, 26.7, 26.2, 12.5. HRMS EI (m/z): [M+] calcd for $C_{12}H_{19}N$, 177.1517; found, 177.1522.

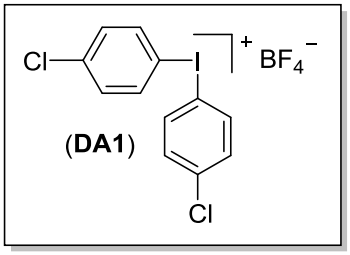


(**P10**)

Heptane-2,5-dione (1.6 g, 1 equiv, 12.6 mmol), methylamine (33 wt % in absolute ethanol, 3.1 mL, 2.5 equiv, 25 mmol) and sulfamic acid (0.12 g, 0.1 equiv, 1.3 mmol) were used to yield **P10** as a clear oil (1.35 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83-5.85 (multiple peaks, 2H), 3.43 (s, 3H), 2.59 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.7, 127.3, 104.4, 102.6, 29.4, 19.6, 12.5, 12.0. HRMS EI (m/z): [M+] calcd for $C_8H_{13}N$, 123.1048; found, 123.1046.

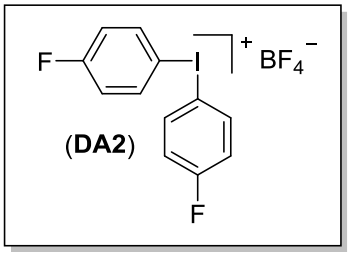
2.6.3 Diaryliodonium Salts

The aryliodonium salts Ar_2IBF_4 with Ar = *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-IC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *o*-FC_6H_4 and *o*-MeC_6H_4 were prepared from their corresponding aryl boronic acid and aryl iodide as described in ref. 21. Characterization data for compounds with Ar = *p*-MeC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, *o*-FC_6H_4 and *o*-MeC_6H_4 matched that reported in the literature.[21] The characterization of previously unknown diaryliodionium salts **DA1-DA3** is reported below.



(**DA1**)

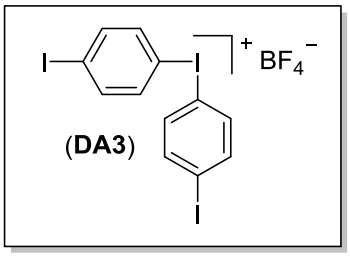
1-Chloro-4-iodobenzene (0.72 g, 1 equiv, 3 mmol), *m*-CPBA (0.57 g, 1.1 equiv, 3.3 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 0.94 mL, 2.5 equiv, 7.5 mmol), and 4-chlorophenylboronic acid (0.47 g, 1 equiv, 3 mmol) in CH_2Cl_2 (12 mL) were used to yield **DA1** a white solid (0.67 g, 51% yield). Mp = 155.1-158.9 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.24 (d, J = 9 Hz, 2H), 7.62 (d, J = 9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 137.5, 137.0, 131.8, 114.7. ^{19}F NMR (376 MHz, DMSO-d_6): δ –148.3 (d, J = 20 Hz). HRMS cation (m/z): [M+] calcd for $C_{12}H_8BCl_2F_4I$, 348.9042; found, 348.9041.



(**DA2**)

1-Fluoro-4-iodobenzene (0.42 mL, 1 equiv, 3 mmol), *m*-CPBA (0.57 g, 1.1 equiv, 3.3 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 0.94 mL, 2.5 equiv, 7.5 mmol), and 4-fluorophenylboronic acid (0.42 g, 1 equiv, 3 mmol) in CH_2Cl_2 (12 mL) were used to yield **DA2** a white solid (0.69 g, 56% yield). Mp = 103.2-105.5 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.31 (d, J = 8.5 Hz, 2H), 7.41 (t, J = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.0 (d, J = 250.6 Hz), 138.0 (d, J = 8.8 Hz),

119.3 (d, *J* = 22.5 Hz), 111.2. ^{19}F NMR (376 MHz, DMSO-d_6): δ –148.3 (d, *J* = 20 Hz), –106.6 (q, *J* = 3.8 Hz). HRMS cation (m/z): [M+] calcd for $C_{12}H_8BF_6I$, 316.9633; found, 316.9629.



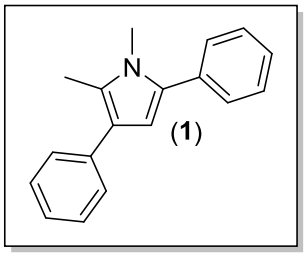
(**DA3**)

1,4-Diiodobenzene (0.99 g, 1 equiv, 3 mmol), *m*-CPBA (0.57 g, 1.1 equiv, 3.3 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 0.94 mL, 2.5 equiv, 7.5 mmol), and 4-iodophenylboronic acid (0.74 g, 1 equiv, 3 mmol) in CH_2Cl_2 (12 mL) yielded **DA3** an off-white solid (1.0 g, 55% yield). Mp = 184.2-191.4 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 140.4, 136.8, 116.1, 100.4. ^{19}F NMR (376 MHz, DMSO-d_6): δ –148.4 (d, *J* = 20 Hz). HRMS cation (m/z): [M+] calcd for $C_{12}H_8BF_4I_3$, 532.7755; found, 532.7748.

2.6.4 C–H Arylation

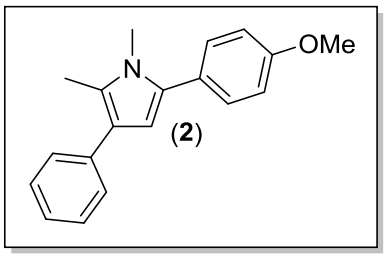
General procedure**:** In a 20 mL scintillation vial, the appropriate pyrrole (1 equiv) and $PdCl_2(MeCN)_2$ (2.5 mol %) were dissolved in DCE at room temperature to make a 0.2 M solution. The resulting mixture was stirred at room temperature for 5 min. The appropriate diaryliodonium salt (1 equiv) was added, the vial was sealed with a Teflon-lined cap, and the reaction was stirred at 84 ºC for 2 h. The

reaction mixture was cooled to room temperature and washed with $NaHCO_3$ (2 x 30 mL). The organic layer was then dried with $MgSO_4$ and concentrated *in vacuo*, and the product was purified by chromatography on silica gel. Reported yields for each product are an average of two runs.



(**1**)

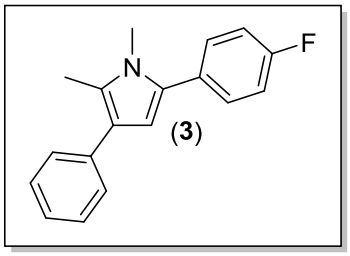
The general procedure was followed, using 1,2-dimethyl-5-phenylpyrrole (171.2 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **1** was purified by chromatography on silica gel (R_f = 0.6 in 85% hexanes/15% EtOAc) and was obtained as an off-white solid (200 mg, 81% yield). Characterization data for compound **1** matched that reported in the literature.[32]



(**2**)

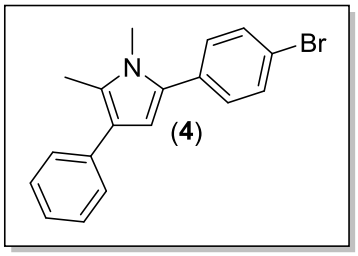
The general procedure was followed, using 1,2-dimethyl-5-*p*-methoxyphenylpyrrole (201.2 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **2** was purified by

chromatography on silica gel (R_f = 0.6 in 85% hexanes/15% EtOAc) and was obtained as an off-white solid (141 mg, 51% yield). Mp = 126.8-131.5 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.34-7.39 (multiple peaks, 4H), 7.24 (m, 1H), 6.96 (d, *J* = 7.0 Hz, 2H), 6.27 (s, 1H), 3.85 (s, 3H), 3.54 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 137.3, 133.5, 130.2, 128.3, 128.1, 126.1, 125.1, 121.7, 113.8, 107.3, 55.3, 31.9, 11.4 (two aromatic signals are coincidentally overlapping). HRMS electrospray (m/z): [M+] calcd for $C_{19}H_{19}NO$, 278.1545; found, 278.1545.



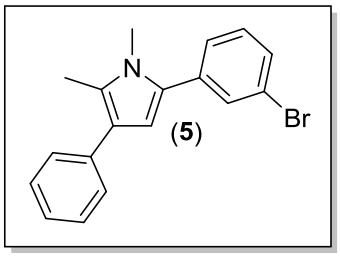
(**3**)

The general procedure was followed, using 1,2-dimethyl-5-*p*-fluorophenylpyrrole (189.2 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **3** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as a white solid (191 mg, 72% yield). Mp = 117.4-120.9 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.41 (multiple peaks, 6H), 7.24 (m, 1H), 7.10 (m, 2H), 6.29 (s, 1H), 3.54 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.9 (d, *J* = 144.5 Hz), 137.1, 132.7, 130.5, 130.4, 129.6, 128.2 (d, *J* = 34 Hz), 126.7, 125.3, 121.9, 115.3 (d, *J* = 21.4 Hz), 108.0, 31.9, 11.4. ^{19}F NMR (376 Mz, $CDCl_3$): δ –116.0 (m, 1H). HRMS electrospray (m/z): [M+] calcd for $C_{18}H_{16}FN$, 266.1345; found, 266.1347.



(**4**)

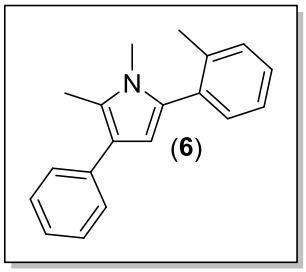
The general procedure was followed, using 1,2-dimethyl-5-*p*-bromophenylpyrrole (250.3 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **4** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as a white solid (232 mg, 71% yield). Mp = 110.6-113.4 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.5 Hz, 2H), 7.36-7.40 (m, 4H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.25 (m, 1H), 6.32 (s, 1H), 3.56 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 132.3, 131.5, 130.2, 130.0, 128.3, 128.1, 127.3, 125.3, 122.4, 120.6, 108.3, 32.0, 11.4. HRMS Electrospray (m/z): [M+] calcd for $C_{18}H_{16}BrN$, 326.0544; found, 326.0531.



(**5**)

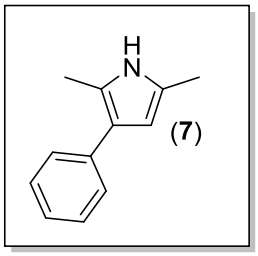
The general procedure was followed, using 1,2-dimethyl-5-*m*-bromophenylpyrrole (250.3 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **5** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as a white solid (200 mg, 61% yield). Mp = 84.3-87.8 ºC. ^{1}H NMR (500

MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.35-7.43 (multiple peaks, 5H), 7.21-7.29 (multiple peaks, 3H), 6.34 (s, 1H), 3.58 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 135.5, 132.2, 131.4, 129.9, 129.5, 128.4, 128.1, 127.5, 127.1, 125.4, 122.4, 122.2, 108.7, 32.1, 11.4. HRMS electrospray (m/z): [M+] calcd for $C_{18}H_{16}BrN$, 326.0544; found, 326.0542.



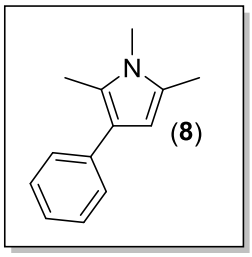
(**6**)

The general procedure was followed, using 1,2-dimethyl-5-*o*-tolylpyrrole (185.2 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **6** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as a white solid (218 mg, 83% yield). Mp = 65.7-68.7 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (m, 2H), 7.38 (m, 2H), 7.20-7.26 (multiple peaks, 5H), 6.21 (s, 1H), 3.34 (s, 3H), 2.44 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 137.4, 133.3, 132.2, 131.3, 130.0, 128.2, 127.8, 127.8, 125.4, 125.0, 124.9, 121.1, 107.6, 31.2, 20.2, 11.3. HRMS Electrospray (m/z): [M+] calcd for $C_{19}H_{19}N$, 262.1596; found, 262.1595.



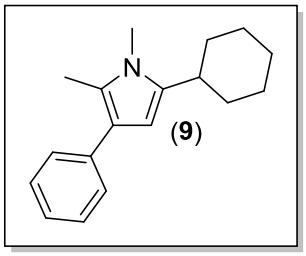
(**7**)

The general procedure was followed, using 2,5-dimethylpyrrole (157.2 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **7** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as an off-white solid (37 mg, 16% yield). Characterization data for compound **7** matched that reported in the literature.[33]

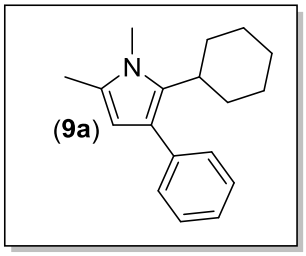


(**8**)

The general procedure was followed, using 1,2,5-trimethylpyrrole (135.3 mL, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **8** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as a brown oil (98 mg, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.40 (multiple peaks, 4H), 7.21 (m, 1H), 6.03 (s, 1H), 3.46 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 128.2, 128.0, 127.7, 124.9, 124.3, 120.5, 105.7, 30.3, 12.4, 11.2. HRMS EI (m/z): [M+] calcd for $C_{13}H_{15}N$, 185.1205; found, 185.1208.

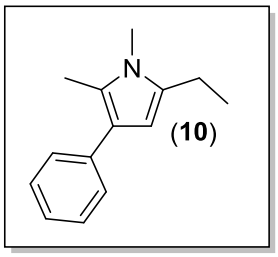


The general procedure was followed, using 2-cyclohexyl-1,5-dimethylpyrrole (177.3 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **9** was purified by chromatography on silica gel (R_f = 0.6 in 85% hexanes/15% EtOAc) and was obtained as an inseparable mixture of **9** : **9a** (12 : 1 ratio). This mixture was obtained as a yellow oil (184 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8 Hz, 2H), 7.43 (t, *J* = 8 Hz, 2H), 7.24 (m, 1H), 6.10 (s, 1H), 3.54 (s, 3H), 2.61 (m, 1H), 2.42 (s, 3H), 2.08 (m, 2H), 1.94 (m, 2H), 1.86 (m, 1H), 1.38-1.55 (multiple peaks, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 137.7, 128.1, 127.9, 124.7, 124.0, 120.4, 102.7, 35.8, 33.4, 30.1, 26.7, 26.2, 11.0. HRMS EI (m/z): [M+] calcd for $C_{18}H_{23}N$, 253.1830; found, 253.1837.



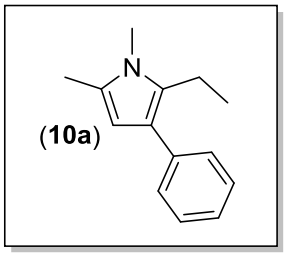
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.44 (multiple peaks, 4H), 7.21 (m, 1H), 6.02 (s, 1H), 3.50 (s, 3H), 2.53 (m, 1H), 2.36 (s, 3H), 2.02 (m, 2H), 1.87 (m, 2H), 1.78 (m, 1H), 1.34-1.48 (multiple peaks, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2,

137.7, 128.1, 128.0, 124.8, 124.0, 120.7, 102.7, 36.0, 33.4, 30.2, 26.7, 26.2, 12.0.

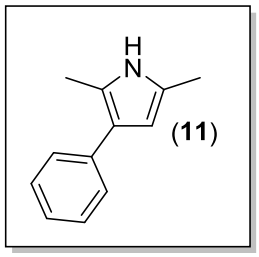


(**10**)

The general procedure was followed, using 2-ethyl-1,5-dimethylpyrrole (123.2 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **10** was purified by chromatography on silica gel (R_f = 0.6 in 85% hexanes/15% EtOAc) and was obtained as an inseparable mixture of **10** : **10a** (1.4 : 1 ratio) as a yellow oil (112 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.42 (multiple peaks, 4H), 7.21 (m, 1H), 6.05 (s, 1H), 3.48 (s, 3H), 2.62 (q, *J* = 7 Hz, 2H), 2.37 (s, 3H), 1.32 (t, *J* = 7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 134.1, 128.2, 128.0, 127.8, 124.8, 120.4, 103.9, 30.2, 19.9, 12.7, 11.1. HRMS EI (m/z): [M+] calcd for mixture of $C_{14}H_{17}N$, 199.1361; found, 199.1370.

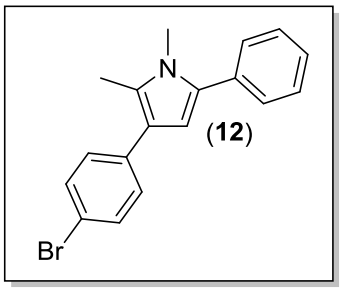


An authentic sample of product **10a** was prepared as described in ref. 1, using 4-phenylheptane-2,6-dione (1.77 g, 1 equiv, 8.7 mmol), methylamine (33 wt % in absolute ethanol, 2.7 mL, 2.5 equiv, 21.8 mmol), and sulfamic acid (84 mg, 0.1 equiv, 0.87 mmol) to afford **10a** as a yellow solid (1.18 g, 59% yield). Mp = 53.9-55.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.41 (multiple peaks, 4H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.03 (s, 1H), 3.50 (s, 3H), 2.75 (q, *J* = 7 Hz, 2H), 2.28 (s, 3H), 1.27 (t, *J* = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 130.3, 128.2, 127.9, 127.8, 125.9, 120.2, 106.0, 30.2, 18.2, 15.0, 12.3. HRMS EI (m/z): [M+] calcd for $C_{14}H_{17}N$, 199.1372; found, 199.1370.



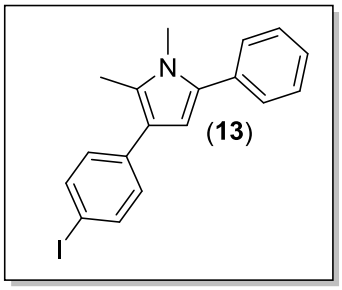
The general procedure was followed, using 2,5-dimethylpyrrole (103.0 mL, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **11** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc). The mono-arylated product was further separated from a diarylated side product by sublimation (50 ºC at 23 torr). Compound **11** was

obtained as a white solid (94 mg, 55% yield). Characterization data for **11** matched that reported in the literature.[34]

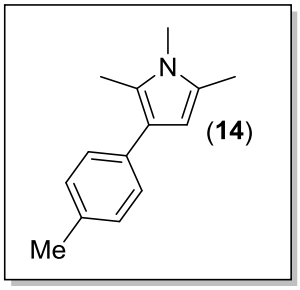


(**12**)

The general procedure was followed, using 1,2-dimethyl-5-phenylpyrrole (171.2 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[(p\text{-}BrC_6H_4)_2I]BF_4$ (525.7 mg, 1.0 mmol). Product **12** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as a white solid (279 mg, 86% yield). Mp = 114.9-119.9 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.0 Hz, 2H), 7.41-7.42 (multiple peaks, 4H), 7.26-7.28 (multiple peaks, 3H), 6.29 (s, 1H), 3.57 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2, 134.1, 133.3, 131.4, 129.6, 128.8, 128.4, 126.9, 120.7, 118.9, 107.7, 32.1, 11.4 (overlapping signals). HRMS electrospray (m/z): [M+] calcd for $C_{18}H_{16}BrN$, 326.0544; found, 326.0535.

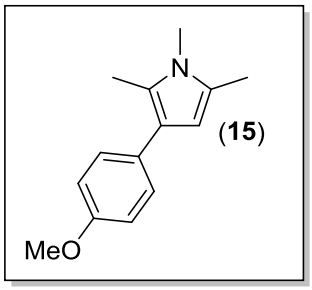


The general procedure was followed, using 1,2-dimethyl-5-phenylpyrrole (171.2 mg, 1.0 mmol) and $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[(p\text{-}IC_6H_4)_2I]BF_4$ (619.1 mg, 1.0 mmol). Product **13** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as an off-white solid (207 mg, 55% yield). Mp = 124.2-128.9 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8 Hz, 3H), 7.41-7.42 (multiple peaks, 4H), 7.17 (d, *J* = 8 Hz, 2H), 6.29 (s, 1H), 3.57 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.3, 136.7, 134.0, 133.2, 129.9, 128.8, 128.6, 128.4, 128.3, 126.9, 120.8, 107.6, 30.1, 11.4. HRMS electrospray (m/z): [M+] calcd for $C_{18}H_{16}IN$, 374.0406; found, 374.0392.



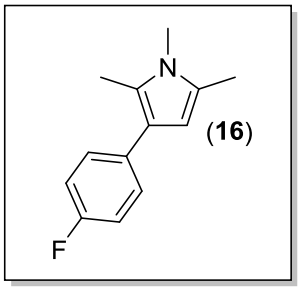
The general procedure was followed, using 1,2,5-trimethylpyrrole (135.3 □L, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[(p\text{-}MeC_6H_4)_2I]BF_4$ (396.0 mg, 1.0 mmol). Product **14** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as a yellow solid (146 mg, 73%

yield). Mp = 39.8-42.1 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8 Hz, 2H), 7.16 (d, *J* = 8 Hz, 2H), 5.98 (s, 1H), 3.44 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.7, 134.3, 128.9, 127.9, 127.5, 124.0, 120.4, 105.6, 30.3, 21.0, 12.3, 11.1. HRMS EI+ (m/z): [M+] calcd for $C_{14}H_{17}N$, 199.1361; found, 199.1368.

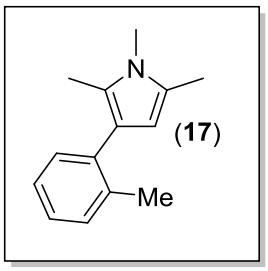


(**15**)

The general procedure was followed, using 1,2,5-trimethylpyrrole (135.3 □L, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and [(*p*-$MeOC_6H_4)_2I$]BF_4 (428.0 mg, 1.0 mmol). Product **15** was purified by chromatography on silica gel (R_f = 0.5 in 85% hexanes/15% EtOAc) and was obtained as an off-white solid (171 mg, 75% yield). Mp = 37.9-40.9 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8 Hz, 2H), 5.95 (s, 1H), 3.82 (s, 3H), 3.44 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2, 130.2, 129.0, 127.5, 123.7, 120.0, 113.7, 105.6, 55.2, 30.3, 12.3, 11.1. HRMS electrospray (m/z): [M+] calcd for $C_{14}H_{17}NO$, 216.1388; found, 216.1393.

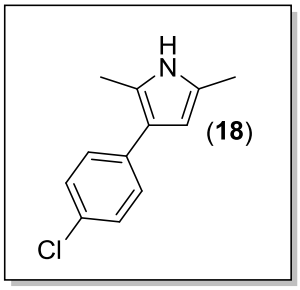


The general procedure was followed, using 1,2,5-trimethylpyrrole (135.3 □L, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[(p\text{-}FC_6H_4)_2I]BF_4$ (403.9 mg, 1.0 mmol). Product **16** was purified by chromatography on silica gel (R_f = 0.6 in 85% hexanes/15% EtOAc) and was obtained as a white crystalline solid (82 mg, 41% yield). Mp = 62.3-65.8 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 2H), 7.03 (m, 2H), 5.95 (s, 1H), 3.44 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8 (d, *J* = 240.6 Hz), 133.6, 129.3 (d, *J* = 6.3 Hz), 127.7, 124.1, 119.6, 115.0 (d, *J* = 20.9 Hz), 105.6, 30.3, 12.3, 11.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ –116.7 (m, 1H). HRMS EI+ (m/z): [M+] calcd for $C_{13}H_{14}FN$, 203.1110; found, 203.1113.



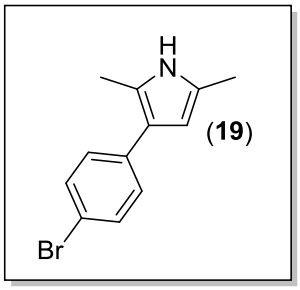
The general procedure was followed, using 1,2,5-trimethylpyrrole (135.3 □L, 1.0 mmol), $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and $[(o\text{-}MeC_6H_4)_2I]BF_4$ (396.0 mg, 1.0 mmol). Product **17** was purified by chromatography on silica gel (R_f = 0.7 in

85% hexanes/15% EtOAc) and was obtained as a red oil (72 mg, 36% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 1H), 7.20-7.23 (multiple peaks, 2H), 7.07-7.12 (m, 1H), 5.91 (s, 1H), 3.49 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.2, 136.7, 130.9, 129.8, 126.7, 125.9, 125.2, 124.5, 119.7, 106.8, 30.3, 20.6, 12.4, 11.0. HRMS EI+ (m/z): [M+] calcd for $C_{14}H_{17}N$, 199.1361; found, 199.1363.

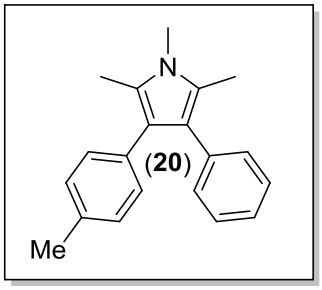


(**18**)

The general procedure was followed, using 2,5-dimethylpyrrole (103.0 □L, 1.0 mmol) and $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and [(*p*-$ClC_6H_4)_2I$]BF_4 (436.8 mg, 1.0 mmol). Product **18** was purified by chromatography on silica gel (R_f = 0.4 in 85% hexanes/15% EtOAc) and was obtained as a white solid (94 mg, 46% yield). Mp = 101.2-104.2 ºC. ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 9.62 (br. s, 1H), 7.38 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 5.92 (s, 1H), 2.33 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 130.4, 128.5, 128.4, 126.0, 122.6, 119.8, 106.1, 12.8, 12.6. HRMS electrospray (m/z): [M+] calcd for $C_{12}H_{12}ClN$, 206.0737; found, 206.0738.

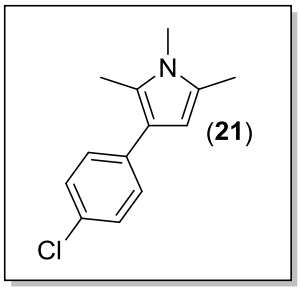


The general procedure was followed, using 2,5-dimethylpyrrole (103.0 □L, 1.0 mmol) and $PdCl_2(MeCN)_2$ (65.0 mg, 0.025 mmol), and [(*p*-$BrC_6H_4)_2I$]BF_4 (525.7 mg, 1.0 mmol). Product **19** was purified by chromatography on silica gel (R_f = 0.3 in 85% hexanes/15% EtOAc) and was obtained as a white solid (112 mg, 45% yield). Mp = 113.5-116.4 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (br. s, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 5.98 (s, 1H), 2.35 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.1, 131.3, 128.9, 126.0, 122.6, 119.8, 118.4, 106.0, 12.8, 12.6. HRMS electrospray (m/z): [M+] calcd for $C_{12}H_{12}BrN$, 250.0231; found, 250.0225.



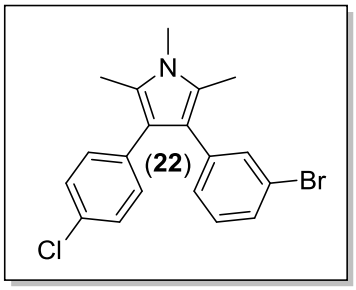
The general procedure was followed, using **14** (199.3 mg, 1.0 mmol), $PdCl_2(MeCN)_2$ (1.30 mg, 0.05 mmol), and $[Ph_2I]BF_4$ (367.9 mg, 1.0 mmol). Product **20** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc) and was obtained as a white solid (121 mg, 44% yield). Mp

= 100.8-103.2 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (m, 2H), 7.13 (m, 2H), 7.07 (d, *J* = 7 Hz, 1H), 7.02 (m, 2H), 6.95 (d, *J* = 6.4 Hz, 2H), 3.52 (s, 3H), 2.28-2.30 (multiple peaks, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 134.4, 133.3, 130.4, 130.2, 128.5, 127.7, 125.0, 124.9, 124.8, 120.1, 119.9, 30.6, 29.7, 21.1, 10.9. HRMS electrospray (m/z): [M+] calcd for $C_{20}H_{21}N$, 275.1674; found, 275.1666.



(**21**)

The general procedure was followed, using 1,2,5-trimethylpyrrole (135.3 mL, 1.0 mmol), $PdCl_2(MeCN)_2$ (1.30 mg, 0.025 mmol) and $[(p ClC_6H_4)_2I]BF_4$ (436.8 mg, 1.0 mmol). Product **21** was purified by chromatography on silica gel (R_f = 0.7 in 85% hexanes/15% EtOAc), and was obtained as an off-white solid (220 mg, 38% yield). Mp = 48.8-52.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.27 (multiple peaks, 4H), 5.96 (s, 1H), 3.43 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 130.5, 129.1, 128.3, 128.0, 124.4, 119.4, 105.5, 30.4, 12.4, 11.1. HRMS electrospray (m/z): [M+] calcd for $C_{13}H_{14}ClN$, 219.0815; found, 219.0809.



The general procedure was followed, using **21** (109.9 mg, 0.5 mmol), $PdCl_2(MeCN)_2$ (65 mg, 0.025 mmol), and $[(m\text{-}BrC_6H_4)_2I]BF_4$ (525.7 mg, 0.5 mmol). Product **22** was purified by chromatography on silica gel (R_f = 0.6 in 85% hexanes/15% EtOAc) and was obtained as an off-white solid (60 mg, 32% yield). Mp = 110.6-113.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.29 (multiple peaks, 2H), 7.20 (d, *J* = 7 Hz, 2H), 7.06 (m, 1H), 6.79 (d, *J* = 7 Hz, 2H), 6.89 (m, 1H), 3.53, (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 134.4, 132.9, 131.5, 131.0, 129.4, 129.1, 128.2, 128.1, 125.5, 125.3, 121.9, 118.9, 118.7, 30.6, 10.8, 10.8. HRMS electrospray (m/z): [M+] calcd for $C_{19}H_{17}BrClN$, 373.0233; found, 373.0226.

2.7 Additional Experiments

2D ^{1}H correlation experiments to determine the major regioisomer:

For unsymmetrical products **1-5, 12**, and **13**, the identity of the major regioisomer was determined by aryl-methyl (H_b to H_c and H_a to H_i) and aryl-pyrrole (H_g to H_h and H_i to H_h) NOE correlations as determined by 2D NOESY experiments (Figure 2.2). Determinative correlations for **9** and **6**, which are highly analogous to those in products **1-5, 12** and **13**, are shown in Figure 2.3 and Figure 2.4, respectively.

It is also interesting to note that there was a through bond correlation (as determined by a COSY) between methyl protons (H_a) and pyrrole proton (H_h) in all pyrrole products.

Figure 2.2. NOESY correlation for **1-5**, **12**, and **13**

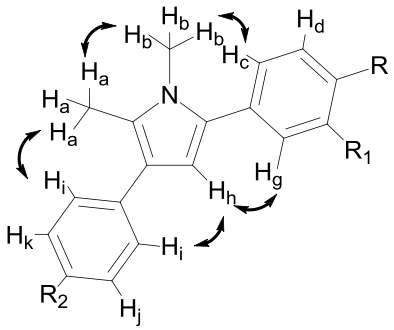


Figure 2.3. NOESY correlations for **6**

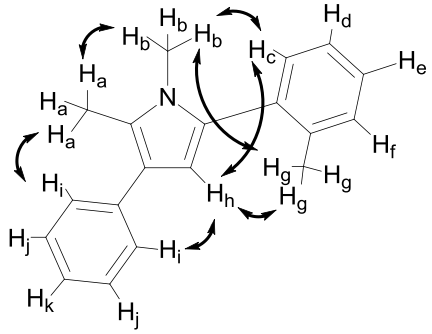
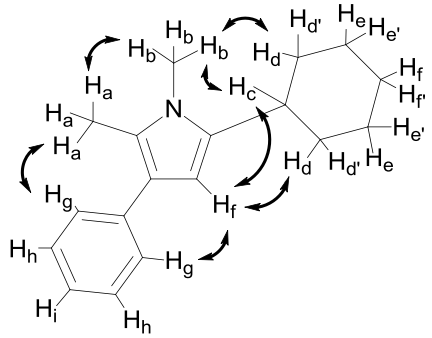


Figure 2.4. NOESY correlations for **9**



2.8 References

[1] Adapted with permission from Wagner, A. M.; Sanford, M. S. Palladium-Catalyzed C−H Arylation of 1,2,5-Substituted Pyrroles. *Org. Lett*. **2011**, *13*, 288-291. Copyright © 2011, American Chemical Society.

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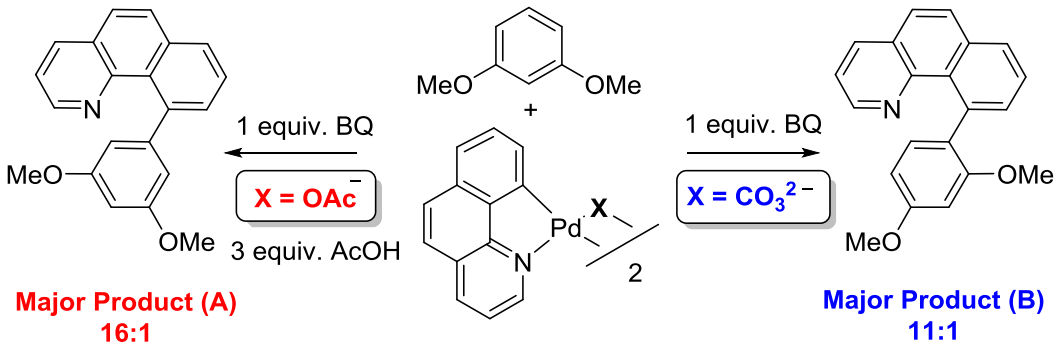
Chapter 3. Oxidative Cross-Coupling of Benzo[*h*]quinoline and 1,3-Dimethoxybenzene[1]

3.1 Introduction

In 2011, the Sanford group reported the palladium-mediated oxidative cross-coupling of 1,3-dimethoxybenzene and benzo[*h*]quinoline (bzq).[2a] Through stoichiometric studies, it was discovered that adding different anions, OAc^- and CO_3^{2-}, led to different selectivities in the undirected arylation (Scheme 3.1). In the system in which the benzo[*h*]quinoline acetate-bridged dimer, $[Pd(Bzq)(OAc)]_2$, was used in the presence of AcOH, high selectivity for the *meta/meta*, isomer **A** was observed (**A**-selective). When the benzo[*h*]quinoline chloride-bridged dimer, $[Pd(Bzq)(Cl)]_2$, was used in the presence of Cs_2CO_3, the *ortho/para*, isomer **B** was formed preferentially (**B**-selective). **B**-selectivity is attributed to the *in situ* generation of the benzo[*h*]quinoline carbonate-bridged dimer, $[Pd(Bzq)(CO_3)]_2^{2-}$, in the presence of the carbonate salt. $[Pd(Bzq)(Cl)]_2$ was found to be unreactive in this system in the absence of other anions. This example represents one of few known catalyst-controlled, site-selective C–H arylation reactions.

Scheme 3.1. Anionic Ligand Effect on Selectivity



While **A**-selectivity was hypothesized to be due to steric effects,[2] the origin of **B**-selectivity was more difficult to determine. One hypothesis was that the **B**-selective system proceeds through an electrophilic aromatic substitution (S_EAr) type mechanism. The greater nucleophilicity of the carbon connected to H_b, by virtue of it being *ortho* and *para* to the OMe substituents, would account for the observed selectivity. To test this hypothesis density functional theory (DFT) calculations were performed to assess the relative energies of a variety of 1,2- and 1,2,3- substituted arenes. Calculations did not support this hypothesis.[2]

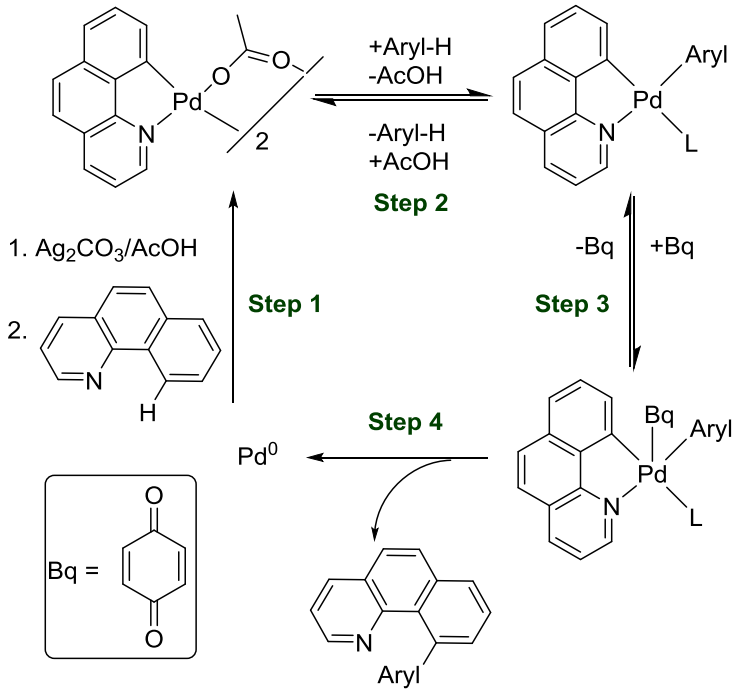
A second hypothesis was that C–H acidity, which has been shown to play a large role in reactivity and selectivity,[3] could be responsible for the observed selectivity. DFT calculations were performed to determine the relative acidities of H_a and H_b, pKa(H_a) and pKa(H_b), for a series of 1,2- and 1,2,3- substituted arenes. No clear relationship between bond acidity and selectivity was discovered. [2]

This chapter discusses the continued use of computational chemistry to gain an understanding of factors that contribute to selectivity in the oxidative cross-coupling of benzo[*h*]quinoline and 1,3-dimethoxybenzene. Further, experimental results that provide evidence for the proposed mechanism of selectivity and the development of a catalytic variant of this reaction are also examined.

3.2 Results and Discussion

The overall proposed mechanism of this oxidative C–H functionalization reaction, which is laid out in Scheme 3.2, consists of cyclopalladation of bzq (Step 1), followed by reversible C–H insertion into the aryl–H bond (Step 2). C–H insertion is then followed by benzoquinone (BQ) binding to the Pd-center (Step 3) which facilitates irreversible reductive elimination (Step 4). Importantly, the reductive elimination step is greatly facilitated by the presence of BQ.[2,4] Detailed experimental mechanistic studies suggest that BQ promotes reductive elimination via its coordination to a Pd-intermediate (Step 2), and this hypothesis is supported by recent computational studies of an oxidative Heck reaction.[5] In addition to facilitating the reductive elimination, the concentration of benzoquinone can also affect site-selectivity under some conditions. For example, when acetate is the anionic ligand, a high concentration of BQ (10 equiv.) gives rise to much lower selectivity (**A** : **B**, 1 : 1). Interestingly, and in marked contrast, with carbonate as the counterion, the **A/B** selectivity is independent of BQ concentration.

Scheme 3.2. Catalytic Cycle for Oxidative Cross-Coupling



On the basis of this general mechanism, Italo Sanhueza of the Schoenebeck group (formerly at ETH Zurich, now at RWTH Aachen University) performed DFT calculations using Gaussian09.[6] The goals of his computational experiments were (i) to determine the mechanism and selectivity of the C–H activation with the different anionic ligands, (ii) to determine the mechanism and selectivity of the BQ-promoted reductive elimination with the different anionic ligands, and then (iii) to calculate the transition states and relevant intermediates for each anionic ligand and model these on a reaction coordinate to determine why different selectivities are observed.

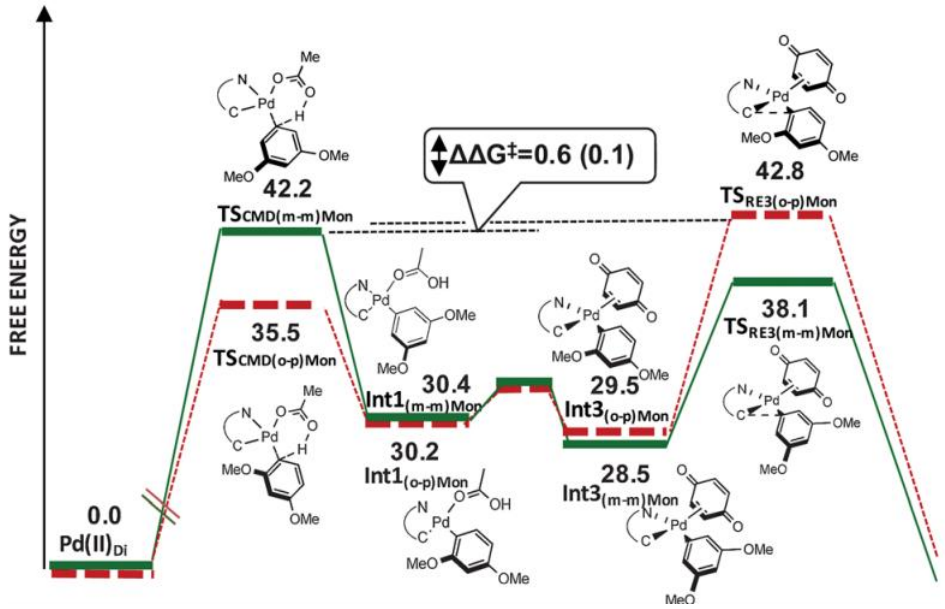
Based on the computational experiments, it was determined that (i) both anionic ligands promote C–H activation of the simple arene through a concerted

cyclometalation-deprotonation mechanism, favoring the electronically activated *ortho/para* product **B**, and (ii) both anionic ligands provide the same selectivity for the reductive elimination step, favoring the less sterically hindered *meta/meta* product **A**.

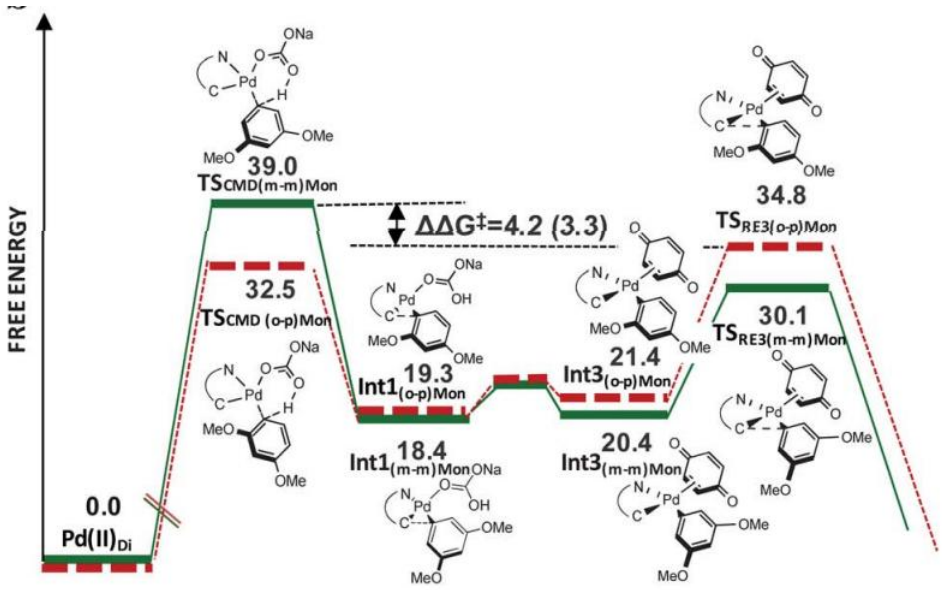
Thus, the observed change in selectivity must originate from a change in rate- and selectivity-determining step when either acetate or carbonate is the ligand. Accordingly, it was determined that reductive elimination is the rate- and selectivity determining step when acetate is the ligand (Step 4, *meta/meta,* **A**-selective,) and C–H activation is the rate- and selectivity determining step when carbonate is the ligand (Step 2, *ortho/para,* **B**-selective). This selectivity is also illustrated on the reaction coordinates shown in Figure 3.1a for acetate and Figure 3.1b for carbonate.

Figure 3.1. Reaction Coordinate Diagrams for Acetate and Carbonate[a]

a) Acetate



b) Carbonate

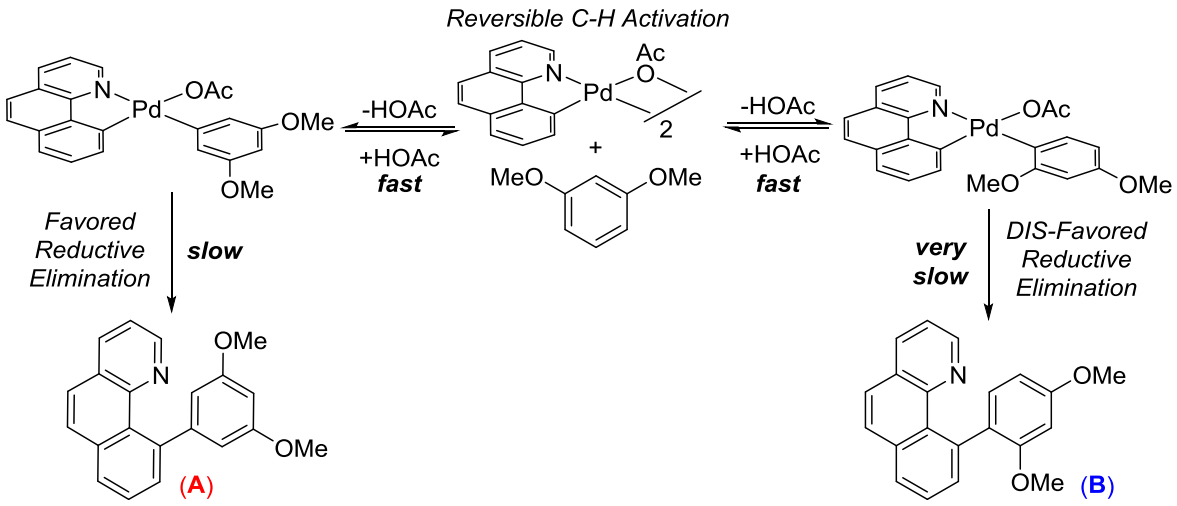


[a]Overview of selectivity controlling steps for the acetate and carbonate system, considering monometallic pathways; calculated at COSMO-RS (DMSO/DMB = 50 : 300) M06L/def2-TZVPP. Free energies illustrated in kcal mol^{-1}.[7]At COSMO-RS (DMSO/DMB = 50 : 300) M06L/6-31++G (d,p) (SDD for Pd & Na), the selectivity is 5.0 kcal mol^{-1}. Energies in parenthesis are based on B3LYP geometries [COSMO-RS (DMSO/DMB = 50 : 300) M06L/6-31++G(d,p) (SDD for Pd & Na)//B3LYP/6-31++G(d) (withLANL2DZ for Pd & Na)].

Based on these conclusions, a number of experiments were designed and performed to test the computationally derived mechanism. Under the original conditions when acetate is the anionic ligand, reductive elimination is the selectivity determining step and the reaction is *meta/meta,* **A-**selective. According to the calculations, this selectivity is observed because the C–H activation and reductive elimination are nearly equal in energy in this system (compared to the carbonate system when C–H activation is much higher in energy, see Figure 3.1a and b ΔΔG values). Thus, *meta/meta* selectivity is observed in the acetate system because the reversible C–H activation step can equilibrate while the

relatively slow reductive elimination selectively and irreversibly generates the less sterically-hindered product **A** (Scheme 3.3).

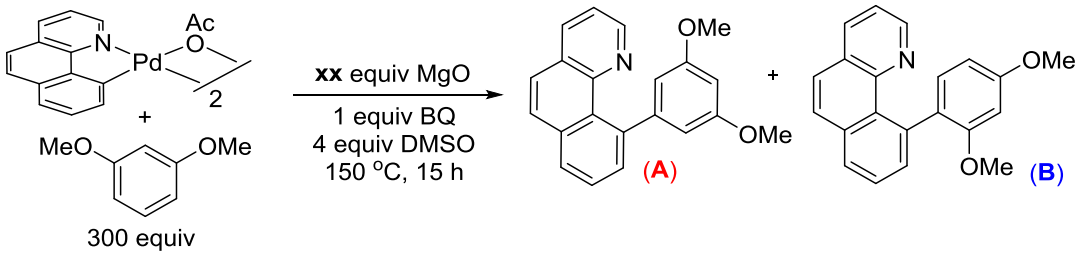
Scheme 3.3. Acetate System: C–H Activation and Reductive Elimination



It has previously been shown that adding acetic acid to this system increases the reversibility of the C–H activation, thus providing faster equilibration and higher *meta/meta* **A**-selectivity.[2a] It was hypothesized that by adding a base to these conditions and thereby removing acetic acid, the C–H activation should become less reversible and the *meta/meta* **A** product, should therefore be less favored. Gratifyingly, when MgO, an insoluble base that should not interact with the catalytic intermediates,[8] is added, in fact less *meta/meta* **A** product is observed (Table 3.1).

Next, it was hypothesized that adding external acid to the MgO/acetate system should reverse these effects by restoring reversibility at the

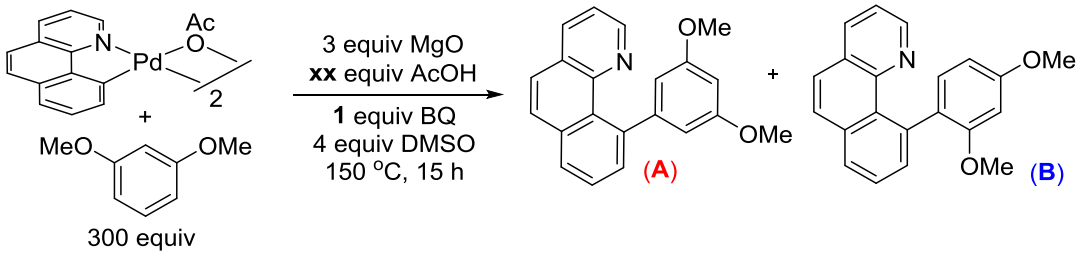
Table 3.1. Effect of MgO on Selectivity under Acetate Conditions[a]



entry	equiv MgO	yield (%)[b]	ratio A : B[c]
1	0	91	6.3 : 1
2	8	100	5.0 : 1
3	15	100	3.3 : 1

[a]1 equiv (0.02 mmol) $[(Bzq)PdOAc]_2$, 300 equiv (6 mmol) 1,3-dimethoxybenzene, 1 equiv (0.02 mmol) benzoquinone, 4 equiv (0.08 mmol) DMSO, 0-15 equiv (0-0.3 mmol) MgO at 150 °C for 15h. [b]GC yields based on an average of two runs with nonadecane as the standard. [c]Ratio of isomers determined based on analysis of the crude reaction mixture by GC.

Table 3.2. Effect of Exogeneous Acid under MgO/Acetate Conditions[a]

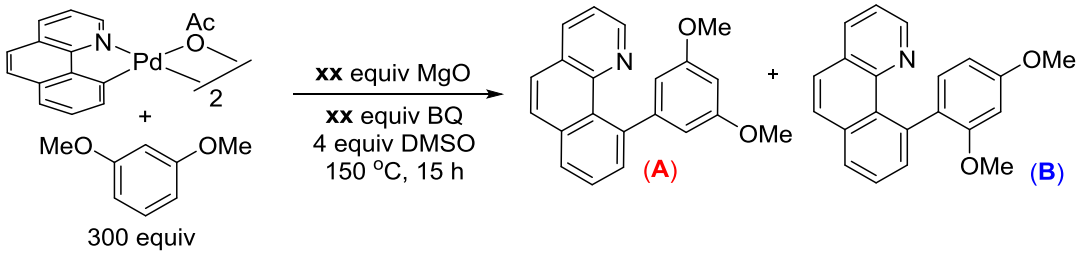


entry	equiv AcOH	yield (%)[b]	ratio A : B[c]
1	0	100	5.8 : 1
2	0.5	100	9.7 : 1
3	1	100	12.8 : 1
4	3	100	13.2 : 1
5	5	100	14.2 : 1

[a]1 equiv (0.02 mmol) $[(Bzq)PdOAc]_2$, 300 equiv (6 mmol) 1,3-dimethoxybenzene, 1 equiv (0.02 mmol) benzoquinone, 4 equiv (0.08 mmol) DMSO, 3 equiv (0.06 mmol) MgO, 0-5 equiv (0-0.1 mmol) AcOH at 150 °C for 15h. [b]GC yields based on an average of two runs with nonadecane as the standard. [c]Ratio of isomers determined based on analysis of the crude reaction mixture by GC.

C–H insertion step. This trend is demonstrated in Table 3.2, which shows that upon adding more equivalents of exogeneous acid greater *meta/meta,* **A**-selectivity is obtained.

Table 3.3. Effect of BQ on Selectivity under MgO/Acetate Conditions[a]



		8 equiv MgO		15 equiv MgO	
entry	**equiv BQ**	**yield (%)[b]**	**ratio A : B [c]**	**yield (%)[b]**	**ratio A : B [c]**
1	1	100	5.0 : 1	100	3.3 : 1
2	3	100	2.5 : 1	100	2.0 : 1
3	5	100	1.8 : 1	100	1.3 : 1
4	7	100	1.4 : 1	100	1.0 : 1
5	10	100	1.1 : 1	100	0.8 : 1

[a]1 equiv (0.02 mmol) $[(Bzq)PdOAc]_2$, 300 equiv (6 mmol) 1,3-dimethoxybenzene, 1-10 equiv (0.02-0.2 mmol) benzoquinone, 4 equiv (0.08 mmol) DMSO, 8 or 15 equiv (0.16 or 0.3 mmol) MgO at 150 °C for 15h. [b]GC yields based on an average of two runs with nonadecane as the standard. [c]Ratio of isomers determined based on analysis of the crude reaction mixture by GC.

Finally, it has also been shown that under acetate conditions, BQ can accelerate the rate of reductive elimination, allowing less time for equilibration at the C–H activation step and thus less *meta/meta* **A**-selectivity. Further experiments varied the concentration of BQ under the conditions with added MgO (Table 3.3). These studies support the change in selectivity determining

step from C–H activation to reductive elimination under the acetate conditions with MgO as an added base. However, it should be noted that adding MgO to the acetate conditions may not lead to a completely irreversible system. A completely irreversible system should have selectivities similar to those seen under carbonate conditions (**A** : **B** = 1 : 11). However, adding more MgO does lead to more *ortho/para* **B**-product.

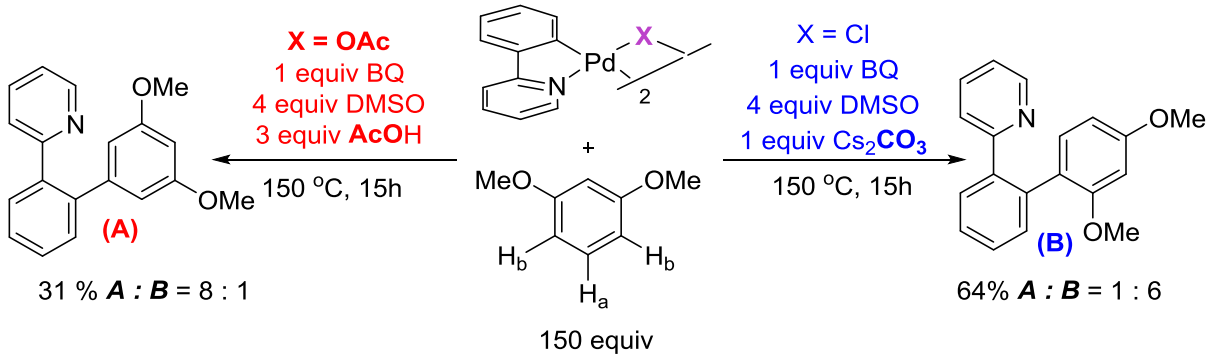
With a detailed picture of the selectivity- and rate-determining steps, the next step was to develop a catalytic variant of these oxidative cross-coupling reactions. To this end, preliminary studies of the catalytic reactions between 2-phenylpyridine[9] and 1,3-dimethoxybenzene were performed. It should be noted that the stoichiometric reaction of the phenylpyridine pallacycle and 1,3-dimethoxybenzene provides moderate yields and analogous selectivity to the benzo[*h*]quinoline reactions (Scheme 3.4a vs.Scheme 3.1).

Scheme 3.4b shows a potential set of reaction conditions that may allow for selective catalytic reactions. In these studies, acetate based catalysts and oxidants could be utilized in the **A**-selective reaction and carbonate salts or oxidants could be employed in the **B**-selective reaction. These reactions should proceed through a similar mechanism to that laid out in Scheme 3.2.

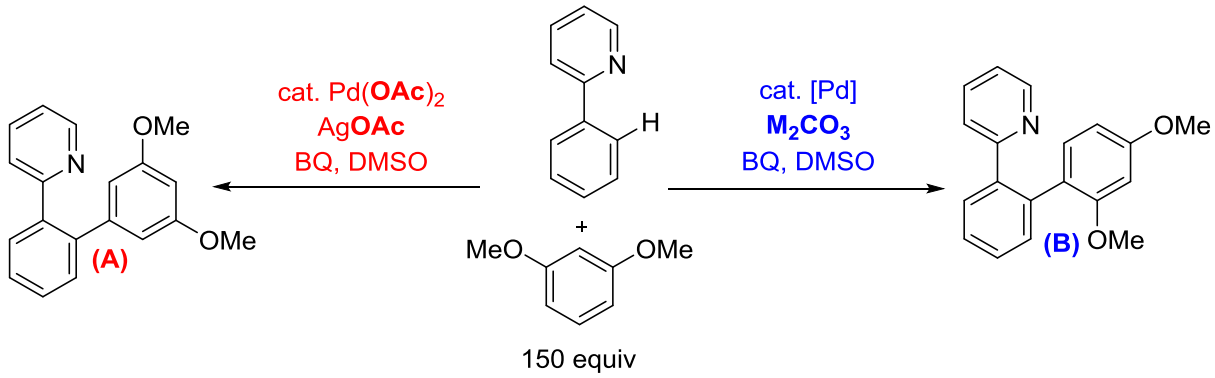
While favorable results were obtained for the **A**-selective reaction using the above hypothesized conditions, none of the conditions screened for the **B**-selective reaction afforded more than one catalytic turnover (Scheme 3.5). This lack of reactivity could potentially be due to the inability of the palladium catalyst

Scheme 3.4. Selectivity in the Phenylpyridine System

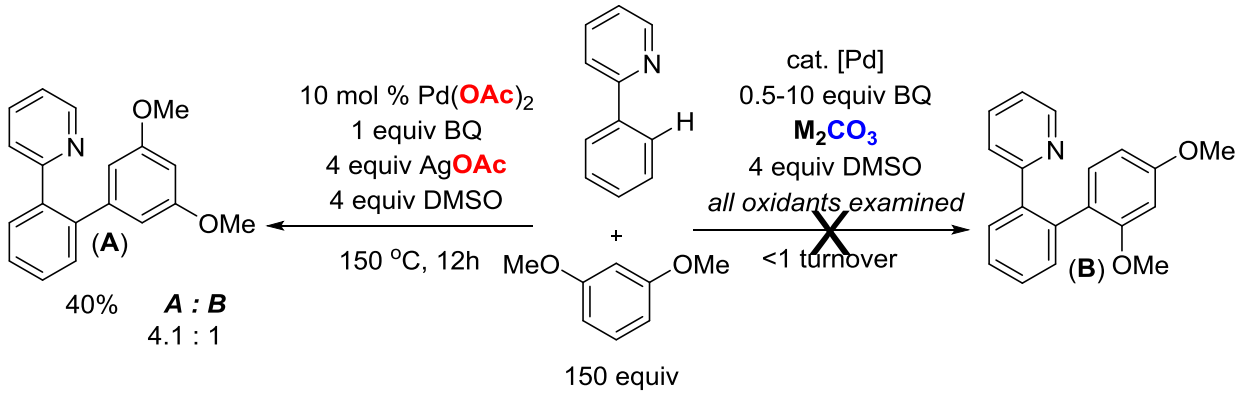
a) Stoichiometric



b) Proposed Catalytic



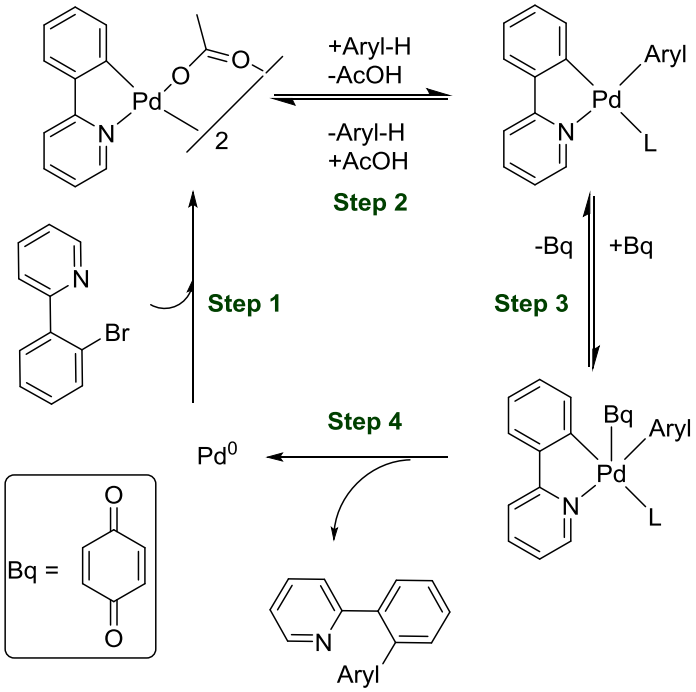
Scheme 3.5. Unsuccessful Catalytic Oxidative Cross-Coupling



to be reoxidized in the absence of acetate and thus its inability to reenter the catalytic cycle.[10]

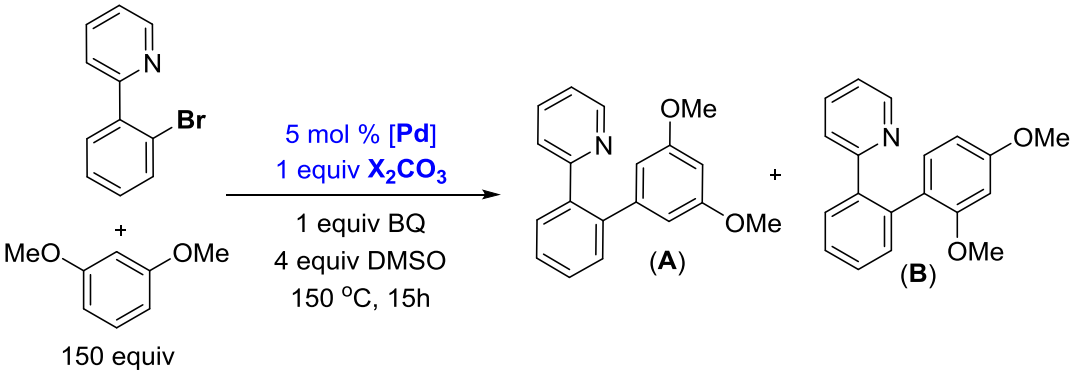
In order to bypass issues in the reoxidation step, use of a halide substituted analog of 2-phenylpyridine, 2-(2-bromophenyl)pyridine, was proposed (Scheme 3.6). Using this brominated analog would allow the palladium catalyst to reenter the catalytic cycle through oxidative addition into the aryl-halide bond instead of requiring an external oxidant (Scheme 3.6, Step 1 vs Scheme 3.2, Step 1), allowing the selectivity of the undirected arene to be probed in a catalytic reaction.

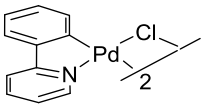
Scheme 3.6. Proposed Catalytic Cycle for Oxidative Addition then C–H Activation



Initial studies focused on optimizing catalytic conditions for the **A**- and **B**-selective direct C–H arylation reactions. The principal challenge was determining whether the **B**-selective system was catalytically viable with 2-(2-bromophenyl)pyridine (Table 3.4). When using $[Pd(PhPy)(Cl)]_2$ as the catalyst and Cs_2CO_3 as the salt – conditions analogous to the stoichiometric reaction in Scheme 3.1a - less than one catalytic turnover was observed (Table 3.4, entry 1). Excitingly, exchanging Cs_2CO_3 with Ag_2CO_3 led to a moderate yield and good selectivity (entry 2). It is hypothesized that the use of a silver salt is necessary because it facilitates the oxidative addition of the starting aryl bromide, producing silver bromide as an insoluble byproduct. Upon further catalyst screens, Pd_2dba_3

Table 3.4. Catalytic B-Selective, Carbonate Condition Optimization[a]



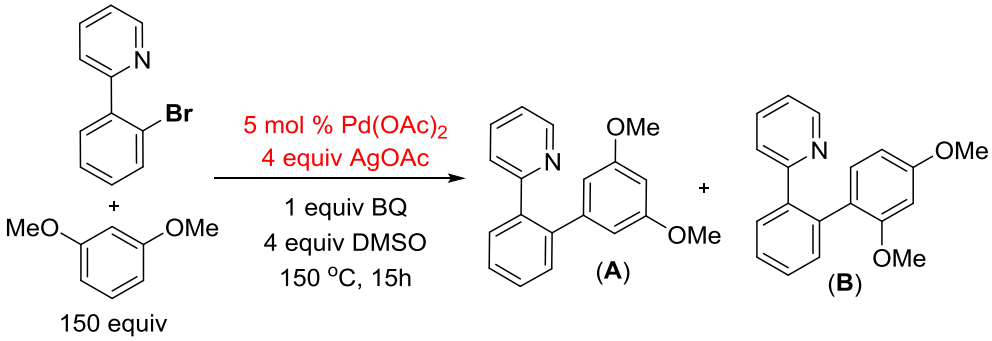
entry	catalyst	additive	yield (%)[b]	ratio A : B[c]
1		Cs_2CO_3	<1 turnover	--
2		Ag_2CO_3	59	1 : 8.8
3	Pd_2dba_3	Ag_2CO_3	77	1 : 20

[a]5 mol% (4 μmol) [Pd], 150 equiv (12 mmol) 1,3-dimethoxybenzene, 1 equiv (0.08 mmol) 2-(2-bromophenyl)pyridine, 1 equiv (0.08 mmol) X_2CO_3, 1 equiv (0.08 mmol) benzoquinone, 4 equiv (0.32 mmol) DMSO at 150 °C for 15h. [b]GC yields based on an average of two runs with nonadecane as the standard. [c]Ratio of isomers determined based on analysis of the crude reaction mixture by GC.

was found to give a good yield and excellent selectivity for the **B**-selective reaction (entry 3). Pd_2dba_3 may be the optimal catalyst for this transformation due the weakly bound dba ligands, which may allow for facile *in situ* formation of $[Pd(PhPy)(CO_3)]_2$.[11]

Next, catalytic acetate conditions were investigated (Table 3.5). First, reaction conditions very similar to the ones used in the catalytic oxidative cross-coupling were attempted (Scheme 3.5), and it was found that these did provide catalytic turnover in the system as well as modest **A**-selectivity (Table 3.5, entry

Table 3.5. Catalytic A-Selective, Acetate Condition Optimization[a]



entry	additive (equiv)	yield (%)[b]	ratio A : B[c]
1	--	31	3.1 : 1
2	AcOH (1)	9	4.0 : 1
3	NaOH (1)	7	1.3 : 1
4	MgO (3)	37	3.1 : 1
5	MgO (6)	49	2.7 : 1

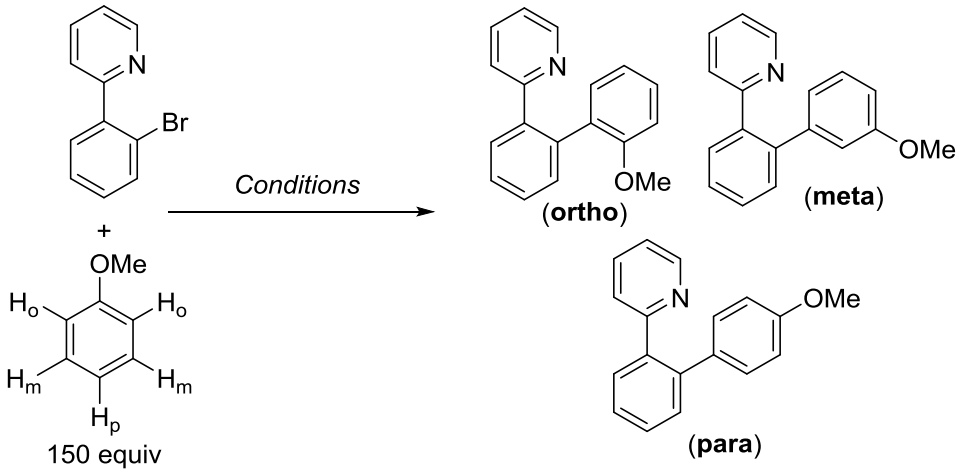
[a]5 mol% (4 μmol) $Pd(OAc)_2$, 150 equiv (12 mmol) 1,3-dimethoxybenzene, 1 equiv (0.08 mmol) 2-(2-bromophenyl)pyridine, 4 equiv (0.032 mmol) AgOAc, 1 equiv (0.08 mmol) benzoquinone, 4 equiv (0.32 mmol) DMSO at 150 °C for 15h. [b]GC yields based on an average of two runs with nonadecane as the standard. [c]Ratio of isomers determined based on analysis of the crude reaction mixture by GC.

1). In the stoichiometric study, it was found that adding acetic acid led to increased **A**-selectivity.[2] However, upon addition of acetic acid to the direct C–H arylation, the reactivity was dramatically decreased with only a slight increase in selectivity (entry 2). If adding acid inhibits the reaction, it was thought that adding base may promote it. Homogeneous bases such as sodium hydroxide also stalled the reaction (entry 3), however going back to the stoichiometric studies, heterogeneous bases such as magnesium oxide were able to remove the generated acetic acid without negatively affecting the catalyst (entries 4 and 5). It should be noted that modest **A**-selectivity is observed under the acetate conditions in the presence of magnesium oxide. However, in accordance with the stoichiometric experimental investigations, more magnesium oxide, while leading to higher yields, also provides poorer **A**-selectivity.

With optimized conditions in hand, the cross-coupling of anisole and 2-(2-bromophenyl)pyridine under acetate and carbonate conditions, were performed to determine if the same factors that dictate selectivity in the stoichiometric reaction are also responsible for selectivity in this catalytic system (Table 3.6). In the stoichiometric reaction under acetate conditions, when reductive elimination is the rate- and selectivity-determining step, the main factor in determining selectivity was sterics – with 1,3-dimethoxybenzene, the *meta/meta* **A**-product was the major product. In the catalytic reaction between anisole and 2-(2-bromophenyl)pyridine, the same trend is observed. The *meta*- and *para*- C–H activation products, which have similar steric properties, are the major products. The sterically hindered *ortho*-product is the minor product (entry 1).

In the stoichiometric reaction under the carbonate conditions, when C–H activation is the rate- and selectivity-determining step, the main factor in determining selectivity was electronics – with 1,3-dimethoxybenzene, the *ortho/para* **B**-product was the major product. Similarly, in the catalytic cross-coupling of anisole and 2-(2-bromophenyl)pyridine, the electronically activated *ortho*- and *para*-substituted biaryls are the major products. The minor product is generated from activation of the less electron-rich *meta*-position.

Table 3.6. Cross-coupling of Anisole and 2-(2-bromophenyl)pyridine

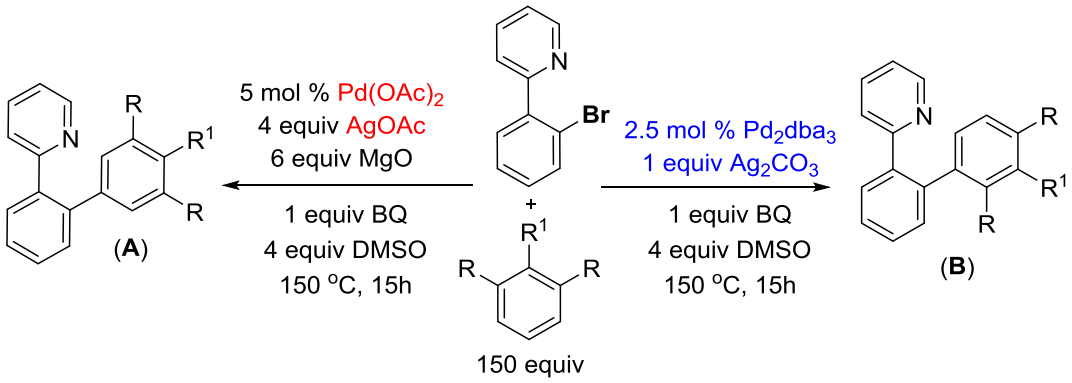


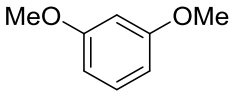
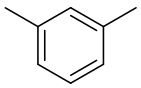
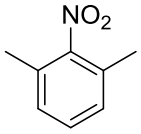
entry	conditions[a,b]	ortho[c]	meta	para
1	acetate	1	4	4
2	carbonate	2	1	2

[a]Acetate conditions: 5 mol% (4 μmol) $Pd(OAc)_2$, 150 equiv (12 mmol) anisole, 1 equiv (0.08 mmol) 2-(2-bromophenyl)pyridine, 4 equiv (0.032 mmol) AgOAc, 1 equiv (0.08 mmol) benzoquinone, 6 equiv (0.48 mmol) MgO, 4 equiv (0.32 mmol) DMSO at 150 °C for 15h. [b]Carbonate conditions: 2.5 mol% (2 μmol) $Pd_2(dba)_3$, 150 equiv (12 mmol) arene, 1 equiv (0.08 mmol) 2-(2-bromophenyl)pyridine, 4 equiv (0.032 mmol) Ag_2CO_3, 1 equiv (0.08 mmol) benzoquinone, 4 equiv (0.32 mmol) DMSO at 150 °C for 15h. [c]Ratio of isomers determined based on analysis of the crude reaction mixture by GC.

Finally, a number of di- and tri- substituted undirected arenes, including *m*-xylenes and 2,6-dimethylnitrobenzene, were tested in these catalytic direct C–H arylation reactions (Table 3.7). Under the **A**-selective acetate conditions, all arenes tested showed high selectivity for the *meta/meta* **A**-isomer (Table 3.7, entries 1, 3 and 5). According to the computational studies, under acetate

Table 3.7. Scope of Catalytic Conditions



entry	arene	conditions[a,b]	yield (%)[c]	ratio A : B[d]
1		acetate	49	2.7 : 1
2		carbonate	82	1 : 17.2
3		acetate	44	13.8 : 1
4		carbonate	25	1 : 1
5		acetate	22	24.2 : 1
6		carbonate	30	1.4 : 1

[a]Acetate conditions: 5 mol% (4 μmol) $Pd(OAc)_2$, 150 equiv (12 mmol) arene, 1 equiv (0.08 mmol) 2-(2-bromophenyl)pyridine, 4 equiv (0.032 mmol) AgOAc, 1 equiv (0.08 mmol) benzoquinone, 6 equiv (0.48 mmol) MgO, 4 equiv (0.32 mmol) DMSO at 150 °C for 15h. [b]Carbonate conditions: 2.5 mol% (2 μmol) $Pd_2(dba)_3$, 150 equiv (12 mmol) arene, 1 equiv (0.08 mmol) 2-(2-bromophenyl)pyridine, 4 equiv (0.032 mmol) Ag_2CO_3, 1 equiv (0.08 mmol) benzoquinone, 4 equiv (0.32 mmol) DMSO at 150 °C for 15h. [c]GC yields based on an average of two runs with nonadecane as the standard. [d]Ratio of isomers determined based on analysis of the crude reaction mixture by GC.

conditions, **A**-selectivity is dictated by steric preference thus *meta/meta* selectivity is the expected result. Higher **A**-selectivity may be observed in these less electronically biased systems (entries 3 and 5, compared to 1,3-dimethoxybenzene) because the *ortho/para* **B**-selective C–H activation step, which is dictated by electronics and has an influence on selectivity under the acetate conditions, provides less bias (Scheme 3.3, Table 3.1). This lack of strong electronic bias may also be the reason that under the **B**-selective carbonate conditions, though the arenes provided a less dramatic selectivity in favor of the **A**-isomer, no switch in selectivity was observed (entries 2, 4 and 6). Lastly, electron rich arenes gave greater yields (entries 1, 2, 3 and 4) than electron poor arenes (entries 5 and 6) probably due to their increased ability to react with the electrophilic palladium catalyst.

3.3 Conclusion

Overall, combining theory and experiment allowed us to develop a detailed mechanistic picture for the origin of site-selectivity in the stoichiometric catalyst-controlled oxidative cross-coupling of benzo[*h*]quinoline and 1,3-dimethoxybenzene. The information gleaned from the stoichiometric studies was then applied to the analogous catalytic direct C–H arylation of 2-(2-bromophenyl)pyridine and a number of different electronically substituted arenes. The same factors that were found to dictate selectivity in the stoichiometric reaction were also shown to be responsible for selectivity in the catalytic reaction, providing evidence that the Pd-mediated and Pd-catalyzed reactions proceed through similar mechanisms. In the future, it is hoped that the mechanistic insight

from these computations and experiments will assist in the development of further catalyst-controlled C–H activation reactions.

3.4 Experimental

General Procedures: Gas chromatography was carried out on a Shimadzu 17A using a Restek Rtx®-5 (Crossbond 5% diphenyl – 95% dimethyl polysiloxane; 15 m, 0.25 mm ID, 0.25 μm df) column. GC calibrated yields and selectivities are reported relative to nonadecane as an internal standard.

Materials and Methods: MgO (Alfa Aesar), DMSO (Acros Organics), 1,3-dimethoxybenzene (Alfa Aesar) and AcOH (Fisher Scientific) were obtained from commercial sources and used as received. Benzoquinone (BQ) was obtained from Acros Organics and further purified by vacuum sublimation. $[(Bzq)PdOAc]_2$ was prepared via the C–H activation of 7,8-benzo[*h*]quinoline with $Pd(OAc)_2$.[12] Authentic samples of C–H activation products for GC calibration and comparison were prepared and isolated according to reference.[2a]

3.5 Synthesis and Characterization

3.5.1 Stoichiometric Reactions

General Procedure: $[(Bzq)PdOAc]_2$ (0.0137 g, 0.02 mmol, 1 equiv), benzoquinone (0-0.0432 g, 0-0.4 mmol, 0-10 equiv) and MgO (0-0.024 g, 0-0.6 mmol, 0-15 equiv) were weighed into a 4 mL glass scintillation vial. Appropriate amount of DMSO, 1,3-dimethoxybenzene (1.6 mL, 12 mmol, 300 equiv), and

AcOH (0-0.11 mL, 0-0.20 mmol, 0-5 equiv) were added, and the vial was sealed with a Teflon-lined cap. The vial was placed into a well of a 150 ºC preheated aluminum block and heated for 15 h. The crude reaction mixture was filtered through a plug of Celite (washing with dichloromethane). The reaction was monitored by GC using nonadecane as the standard.

3.5.2 Catalytic Reactions

General Procedure: [Pd] (2 or 4 μmol, 5 mol%), 2-phenylpyridine (11 μL, 0.08 mmol, 1 equiv) or 2-(2-bromophenyl)pyridine (13 mL, 0.08 mmol, 1 equiv), benzoquinone (8.6 mg, 0.08 mmol, 1 equiv), AgOAc (53.4 mg, 0.32 mmol, 4 equiv) or X2CO3 (0.08 mmol, 1 equiv) and MgO (0-0.19.3 mg, 0-0.32 mmol, 0-6 equiv) and were weighed into a 4 mL glass scintillation vial. Appropriate amount of DMSO (23 μL, 0.32 mmol, 4 equiv), arene (12 mmol, 150 equiv), and AcOH (0-5 μL, 0-0.08 mmol, 0-1 equiv) were added, and the vial was sealed with a Teflon-lined cap. The vial was placed into a well of a 150 ºC preheated aluminum block and heated for 15 h. The crude reaction mixture was filtered through a plug of Celite (washing with dichloromethane). The reaction was monitored by GC using nonadecane as the standard.

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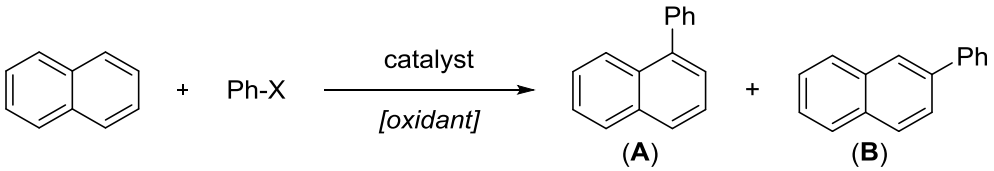
Chapter 4. Platinum-Catalyzed C–H Arylation of Simple Arenes[1]

4.1 Introduction

Transition metal catalyzed C–H arylation reactions have emerged as valuable synthetic methods for constructing biaryl linkages.[2] Over the past 15 years, there have been tremendous advances in this field, particularly in ligand-directed C–H arylation[3,4] and in the C–H arylation of heterocyclic scaffolds.[5] In contrast, the C–H arylation of simple aromatic substrates (lacking directing or activating groups) remains challenging.[4,6] While some high yielding transformations of this type have been developed,[7,8] it remains difficult to achieve high site-selectivity as well as to predictably tune selectivity in these reactions.[9]

These challenges are exemplified by the C–H arylation of the simple arene naphthalene, which can provide two isomeric products, **A** and **B**. As summarized in Table 4.1, most previously reported catalysts for this transformation provide modest selectivity for isomer **A**.

Table 4.1. Metal-Catalyzed C–H Arylation of Naphthalene

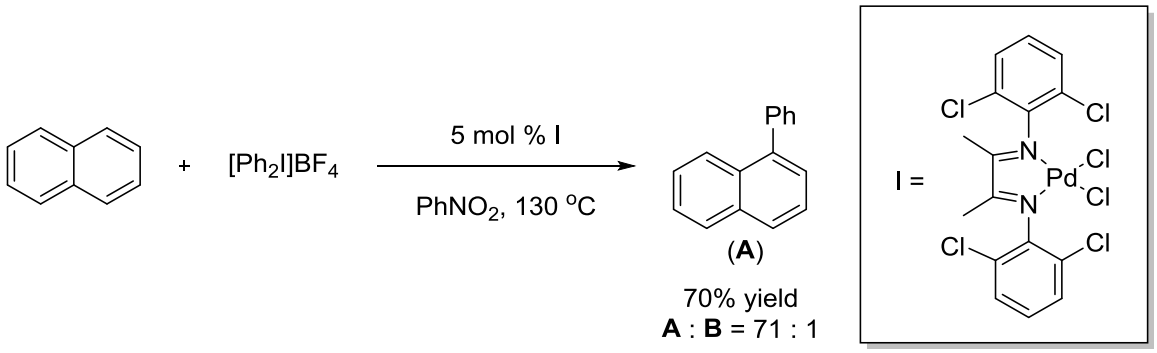


entry	Ph–X	catalyst	yield (%)	A : B
1[9]	PhH	$Pd(OAc)_2$	32[a]	>20 : 1
2[10]	$PhSnCl_3$	$PdCl_2$	40[a]	4 : 1
3[11]	$PhSiMe_3$	$PdCl_2$	38[a]	7 : 1
4[12]	PhI	$Pd(OAc)_2$	72[b]	3 : 1
5[13]	PhBr	Cp_2Ni	70[b]	2 : 1
6[14]	Ph_2IBF_4	Pd(II)@MOF-5(O_h)	64[b]	3 : 1
7[15]	Ph_2IOTf	$[Pd(OAc)(C\sim P)]_2$[c]	47[b]	1 : 1

[a]Based on naphthalene. [b]Based on Ph–X. [c]Herrmann-Beller catalyst; (C~P) = $CH_2C_6H_4P(o\text{-Tol})_2$.

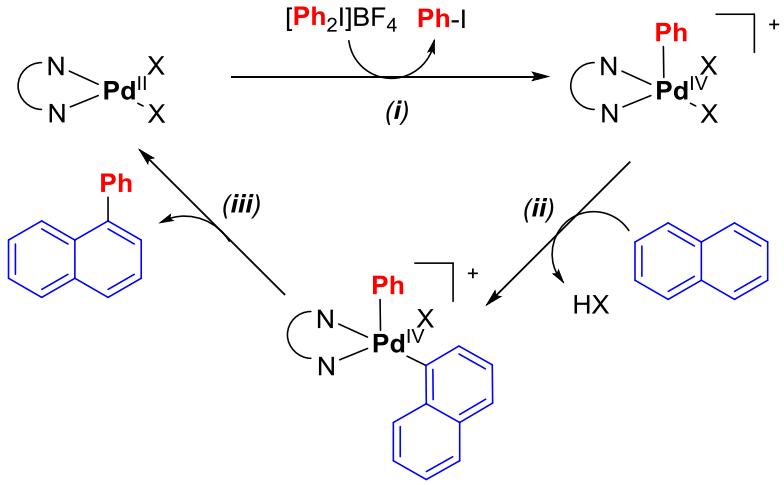
We recently demonstrated that diimine-ligated Pd catalyst **I** affords high selectivity for product **A** in the C–H arylation of naphthalene with Ph_2IBF_4 (70% yield, 71 : 1 ratio of **A** to **B**, Scheme 4.1).[10] This reaction represents a promising example of catalyst-modulated selectivity in C–H arylation.[9] However, this method remains limited by a poor substrate scope (only naphthalene underwent high-yielding and site-selective C–H arylation). Furthermore, while highly **A**-selective catalysts have been identified, **B**-selectivity remains elusive in most of these transformations.

Scheme 4.1. Diimine-$PdCl_2$-Catalyzed Naphthalene Arylation



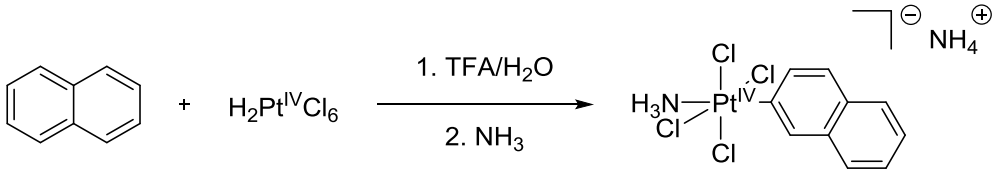
The mechanism of **I**-catalyzed naphthalene arylation with Ph_2IBF_4 is proposed to involve three key steps: (i) rate-limiting oxidation of Pd^{II} catalyst **I** to Pd^{IV} by Ph_2IBF_4, (ii) C–H activation of naphthalene at this Pd^{IV} intermediate, and (iii) C–C bond-forming reductive elimination from Pd^{IV} to release the biaryl product (Table 4.2).[10]

Scheme 4.2. Proposed Mechanism of $Pd^{II/IV}$ Catalyzed Naphthalene Arylation



On the basis of this mechanism, we hypothesized that many of the prior limitations of this method could be addressed by changing the metal catalyst from Pd to Pt. Pt^{II} is generally easier to oxidize than Pd^{II},[11] which could potentially lead to an acceleration of the rate-limiting step of the catalytic cycle. Additionally, there is significant literature precedent for stoichiometric activation of electronically diverse arenes at Pt^{IV} centers (example with naphthalene,[12] Scheme 4.3).[13] In these stoichiometric reactions, the selectivity of C–H cleavage is primarily dictated by steric factors, supporting the feasibility of achieving high **B**-selectivity in Pt-catalyzed naphthalene arylation. However, a key challenge for this approach is that there are not, to our knowledge, any examples of Pt-catalyzed intermolecular C–H arylation in the literature[14] (in marked contrast to the hundreds of such transformations catalyzed by Pd).[2-6] This void is likely due to the relatively high barrier for reductive elimination from Pt^{IV} compared to that from Pd^{IV}.[15]

Scheme 4.3. Naphthalene C–H Activation by Pt^{IV}



stoichiometric C-H activation at Pt^{IV}

single isomer

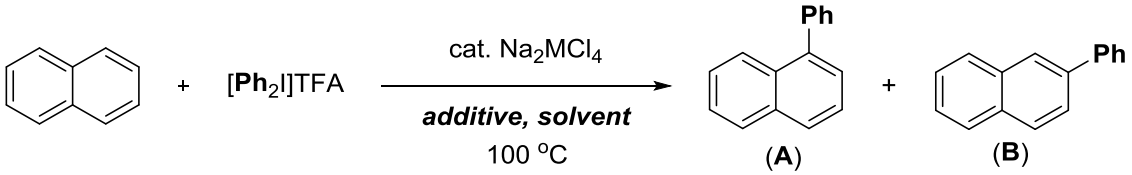
This chapter discusses the development of a new Pt-catalyzed C–H arylation of naphthalene and other simple arenes. Remarkably, a complete

reversal in selectivity for naphthalene arylation is observed upon substituting Pt for Pd under otherwise identical reaction conditions. Details on the scope and mechanism of this new transformation are presented.

4.2 Results and Discussion

Our initial studies focused on the C–H arylation of naphthalene with Ph_2ITFA (TFA = trifluoroacetate) catalyzed by Pd and Pt salts in trifluoroethanol (TFE) at 100 ºC.[16] As anticipated based on our previous report,[10] the Pd catalyst Na_2PdCl_4 afforded the biaryl product with good selectivity for isomer **A** over **B** (Table 4.2, entry 1). However, remarkably, under otherwise identical conditions, changing the catalyst to the analogous platinum salt (Na_2PtCl_4) resulted in a complete reversal in selectivity (**A** : **B** = 1 : 10, entry 2). Optimizing the Pt-catalyzed reaction, it was found that the highest yields are obtained in neat naphthalene in the presence of 5 equiv of NBu_4OTf. The tetrabutylammonium salt additive is hypothesized to limit catalyst degradation to Pt-black over the course of the reaction. Ionic liquids, including tetrabutylammonium salts, are known to inhibit this type of catalyst degradation via solvation effects.[17] The Pt catalyst loading could be lowered to 2.5 mol %, and the product was obtained in 65% yield with 35 : 1 selectivity for isomer **B** (entry 4).

Table 4.2. Optimizing Naphthalene Phenylation

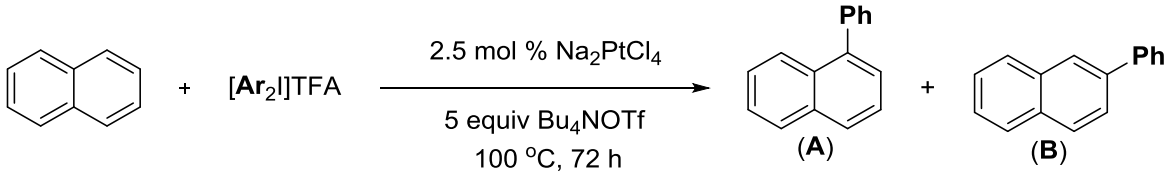


entry	[M]	solvent	additive	yield (%)[c]	A : B
1[a]	Pd	TFE	none	65	25 : 1
2[a]	Pt	TFE	none	31	1 : 10
3[a]	Pt	TFE	Bu_4NOTf	48	1 : 18
4[b]	Pt	none	Bu_4NOTf	65	1 : 35

[a]Conditions: Ph_2ITFA (1 equiv), naphthalene (30 equiv), [M] (10 mol %), additive (15 equiv), TFE (0.14 M), 100 ºC, 24 h. [b]Conditions: Ph_2ITFA (1 equiv), naphthalene (60 equiv), Bu4NOTf (5 equiv), [Pt] (2.5 mol %), 100 ºC, 72 h. [c]GC yield based on hexadecane as a standard.

The Pt-catalyzed reaction could be used to couple naphthalene with a variety of substituted aryliodonium salts. High **B**-selectivity (>20:1) was observed in all cases. Both electron-donating (Table 4.3, entries 1–3) and electron-withdrawing substituents (entries 4–7) on Ar_2ITFA were well-tolerated. A carbonyl-containing aryliodonium salt afforded lower yield, possibly due to competing ligation and deactivation of the Pt-catalyst (entry 8). *Ortho*-substitution (as in (*o*-tolyl)$_2$ITFA) had a minimal deleterious effect on the reaction yield (compare entries 2 and 3); however, the selectivity for isomer **B** was considerably enhanced in this system (**A** : **B** > 1 : 100). This result suggests that the Ar group may be ligated to Pt during the C–H cleavage step and that the steric environment at the Pt center plays a role in selectivity.

Table 4.3. Scope of Ar_2ITFA Reagents[a]

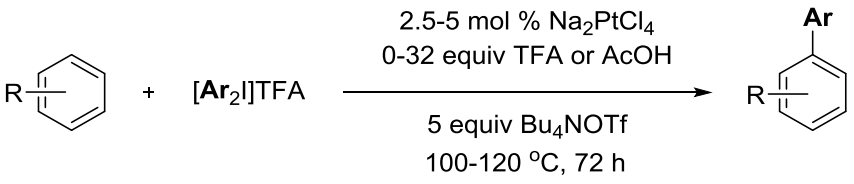


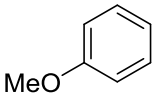
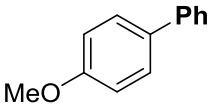
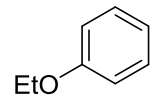
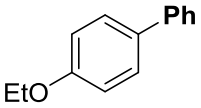
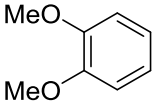
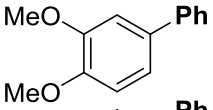
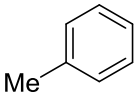
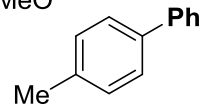
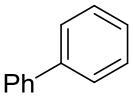
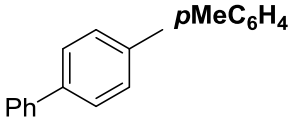
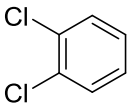
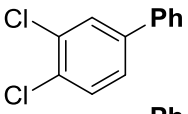
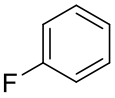
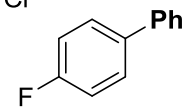
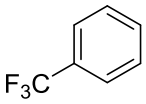
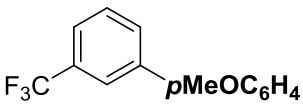
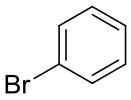
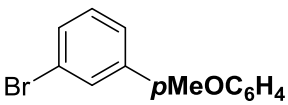
entry	Ar	yield (%)[b,c]	A : B[d]
1	*p*-$MeOC_6H_4$	84	1 : 25
2	*p*-MeC_6H_4	85	1 : 24
3	*o*-MeC_6H_4	72	>1 : 100
4	*p*-FC_6H_4	61	1 : 34
5	*p*-BrC_6H_4	57	1 : 27
6	*m*-BrC_6H_4	63	1 : 41
7	*p*-$CF_3C_6H_4$	53	1 : 30
8	*p*-AcC_6H_4	19	1 : 21

[a]Conditions: Ar_2ITFA (1 equiv), naphthalene (60 equiv), Na_2PtCl_4 (2.5 mol %), Bu_4NOTf (5 equiv), 100 ºC, 72 h. [b]Isolated yield based on an average of two runs. [c]Mass balance is the corresponding Ar–Cl. [d]Ratio of isomers determined based on analysis of the crude reaction mixture by GC.

The scope of this transformation was next evaluated with respect to the arene coupling partner. As shown in Table 4.4, electronically diverse arenes were found to participate in Pt-catalyzed C–H arylation with Ar_2ITFA. Steric factors dominate the site-selectivity of these transformations.[8] Most notably, products of *ortho*-arylation were generally not detected in these systems. Additionally, di-substituted arenes reacted with high selectivity at the less hindered 4-position (entries 3 and 6).

Table 4.4. Scope of Arene Substrates[a]



entry	substrate	major product	yield (%)[b,c]	selectivity[d]
1[f]			83	single isomer
2[f]			85	single isomer
3[f]			48	single isomer
4[e,f]			46	2.4 : 1 (*p : m*)
5[e]			42	1.2 : 1 (*p : m*)
6[g]			48	20 : 1
7[e]			52	6 : 1 (*p : m*)
8[g]			53	1.4 : 1 (*m : p*)
9[g]			59	2.5 : 1 (*m : p*)

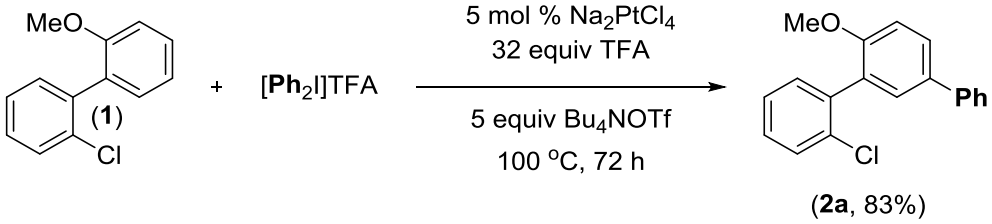
[a]Conditions: Ar_2ITFA (1 equiv), arene (30-60 equiv), Na_2PtCl_4 (2.5 mol %), Bu_4NOTf (5 equiv), TFA or AcOH (0 or 32 equiv), 100-120 ºC, 72 h. [b]Isolated yield based on an average of two runs. [c]Mass balance is the corresponding Ar-Cl. [d]Ratio of isomers determined based on analysis of the crude reaction mixture by GC. [e]With 10 mol % Na_2PtCl_4. [f]With TFA. [g]With AcOH.

Electronic effects also play a role, particularly with mono-substituted arenes, where the *meta* and *para* sites are essentially sterically equivalent. With these substrates, modest to high selectivity was observed for reaction at the more electron rich of the two sites. For example, the best selectivities were obtained with anisole and ethoxybenzene (entries 1 and 2). In these cases, only products derived from *para*-arylation were detected. It should be noted that in the case of electron-rich arenes, adding TFA significantly improves the yield and *para*-selectivity of the reaction. The presence and amount of TFA has been shown previously to have a drastic effect on selectivity and reactivity in the palladium-catalyzed oxidative cross-coupling of simple arenes.[18] Electron-neutral arenes displayed modest selectivity for the *para* product over the *meta* product (entries 4 and 5). Finally, the inductively withdrawing trifluoromethyl substituent afforded a slight preference for C–C bond formation at the *meta* site over the *para* position (*m* : *p* = 1.4 : 1, entry 8). Interestingly, the selectivity for C–H arylation of halide-substituted arenes varied with the halide (entries 7 and 9).[19] Acetic acid was used as an additive for a number of reactions with electron-poor arenes because it improved the reproducibility of these reactions.

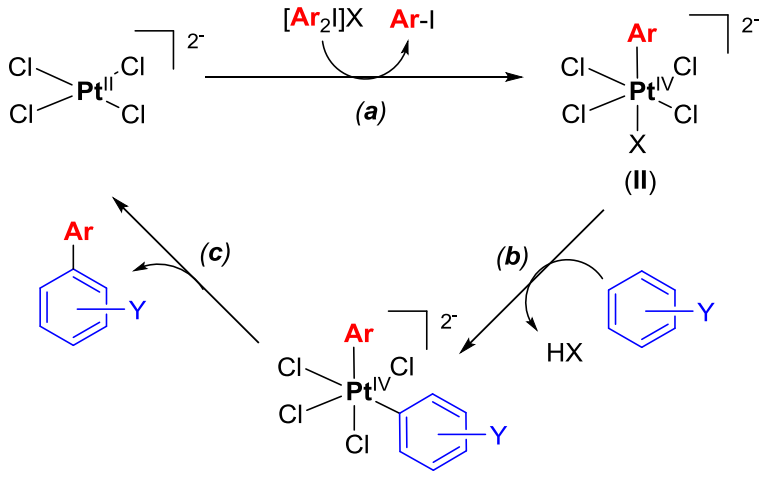
To probe the role of substrate electronics on the relative rates of these reactions, we conducted an intramolecular competition experiment. When TFA was used as an additive, Pt-catalyzed arylation of substrate **1** with Ph_2ITFA proceeded with >100:1 selectivity on the more electron rich ring (*para* to the methoxy substituent), providing **2a** as the only detectable product (Scheme 4.4, 83% yield). This selectivity demonstrates that with TFA, the reaction is

significantly faster with electron rich arene substrates. In the absence of TFA, a complex mixture of phenylation products, (*meta* and *para* to both the methoxy and chloro substituents) was observed.

Scheme 4.4. Electronic Effect on Arylation



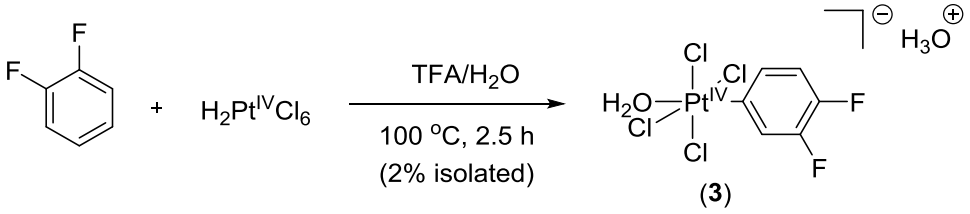
Scheme 4.5. Proposed Mechanism



A plausible mechanism for this transformation is shown in Scheme 4.5 and is similar to the mechanism proposed for the related Pd-catalyzed transformation in Scheme 4.2.[10] To probe the viability of the first step (***a*** in Scheme 4.5) we examined the stoichiometric reaction between Na_2PtCl_4 and Ar_2ITFA (Ar = 3,4-difluorophenyl). ^{19}F and ^{195}Pt NMR spectrum analysis showed

that a new Pt-aryl product was formed after 8 min at 100 ºC in anisole. This species showed ^{19}F NMR resonances at –143.3 and –148.1 ppm, a ^{195}Pt NMR resonance at –724.8 ppm, and HRMS data consistent with a Pt^{IV} intermediate of general structure **II**.[12] However, this species proved challenging to isolate. As a result, we pursued the synthesis of a close analogue of **II** using a modification of Shul'pin's procedure for stoichiometric C–H activation at $H_2Pt^{IV}Cl_6$.[13] The reaction of $H_2Pt^{IV}Cl_6$ with 1,2-difluorobenzene followed by purification via preparative TLC afforded the anionic aqua-Pt^{IV}Ar complex **3** (Scheme 4.6). Complex **3** was characterized by ^{1}H, ^{13}C, ^{19}F, and ^{195}Pt NMR spectroscopy, mass spectrometry and elemental analysis. The ^{19}F and ^{195}Pt NMR spectrum chemical shifts as well as the HRMS data of **3** are nearly identical to those of the stoichiometric oxidation product **II** discussed above.

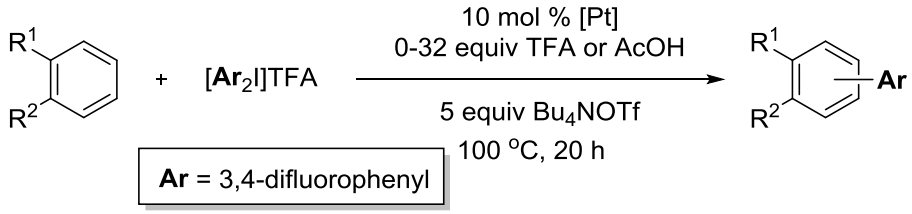
Scheme 4.6. Preparing the Pt^{IV}-Aryl Complex

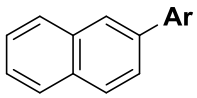
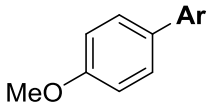
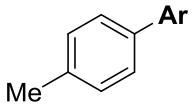
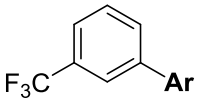
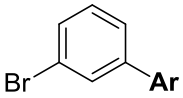


We further tested the ability of complex **3** to catalyze the arylation of a variety of substrates with Ar_2ITFA (Ar = 3,4-difluorophenyl). Table 4.5 presents a comparison of this reaction to the reaction catalyzed by the platinum salt, Na_2PtCl_4, under identical conditions. In general, the two catalysts provided comparable yields and nearly identical selectivities for a range of C–H

substrates. These results provide further support for the proposal that Pt^{IV}–aryl species **3**, or a close analogue thereof, is an intermediate in Na_2PtCl_4-catalyzed C–H arylation reactions.

Table 4.5. Comparison of C–H Arylation Catalyzed by Na_2PtCl_4 or **3**[a]



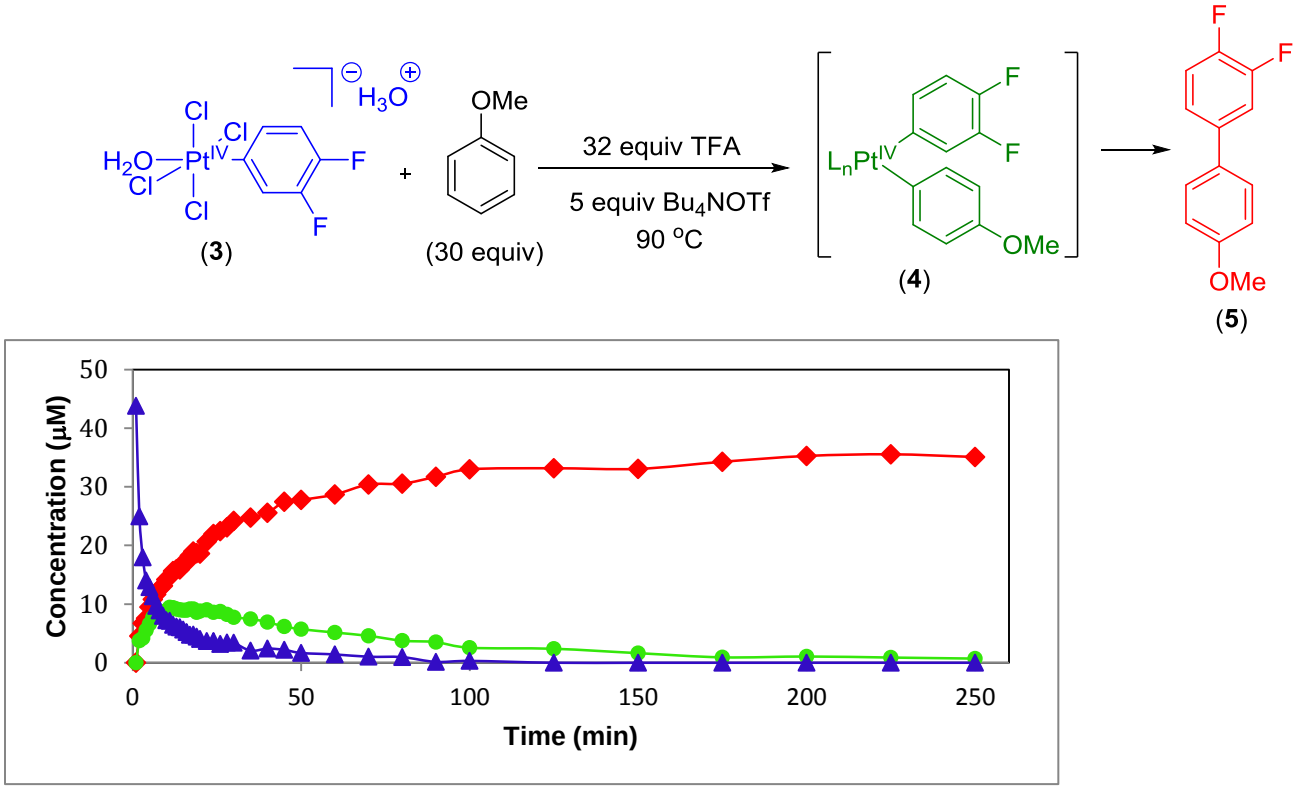
entry	major product	yield (%) (Na_2PtCl_4)[b]	selectivity (%) (Na_2PtCl_4)[c]	yield (%) (**3**)[b]	selectivity (%) (**3**)[c]
1		56	20 : 1	51	20 : 1
2[d,e]		47	single isomer	30	single isomer
3[e]		37	3.5 : 1 (*p* : *m*)	33	2.9 : 1 (*p* : *m*)
4[f]		16	1.7 : 1 (*m* : *p*)	18	1.4 : 1 (*m* : *p*)
5[f]		25	2.5 : 1 (*m* : *p*)	25	2.5 : 1 (*m* : *p*)

[a]Conditions: Ar_2ITFA (1 equiv), arene (30 or 60 equiv), TFA or AcOH (0 or 32 equiv), Na_2PtCl_4 or **3** (10 mol %), Bu_4NOTf (5 equiv), 100 ºC, 20 h. [b]Yields determined by GC. [c]Ratio of products determined by GC. [d]With 30 equiv of arene. [e]With TFA. [f]With AcOH.

With Pt^{IV} aryl complex **3** in hand as a close analogue of **II**, we investigated the final two steps of the proposed catalytic cycle (***b*** and ***c*** in Scheme 4.5). As anticipated, **3** (blue triangles in Figure 4.1) reacted with anisole over 6 h at 90 ºC

to form the biaryl product **5** (red diamonds in Figure 4.1). Furthermore, when this reaction was followed by ^{19}F NMR spectroscopy, an intermediate (green circles in Figure 4.1) was observed to form and then decay with concomitant appearance of product **5**. We hypothesize that this intermediate may be a diaryl Pt^{IV} species (**4**, analogue of **III** in Scheme 4.5).[20] Observing such an intermediate preliminarily suggests that reductive elimination is the rate-determining step in this Pt-catalyzed reaction.

Figure 4.1. Reaction Profile for the Arylation of Anisole with **3** (concentrations determined by ^{19}F NMR Spectroscopy). ▲ = **3**; ♦ = **5**; ● = intermediate (proposed to be **4**).



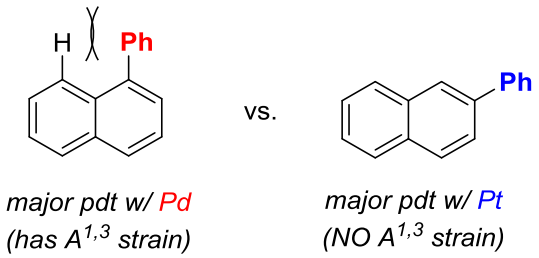
We have conducted a number of additional studies to further probe the reaction mechanism. For example, both the C–H arylation of naphthalene and the C–H arylation of anisole were found to be zero order in Ph_2I^+. Furthermore, comparison of the initial rate of naphthalene to that of naphthalene-d_8 showed a k_H/k_D value of 1. An identical result was obtained with anisole/anisole-d_8. These data suggest that neither oxidation nor C–H cleavage are the rate-determining step of the catalytic reaction. These results are consistent with the proposal (above) of C–C bond-forming reductive elimination as the rate-determining step in the Pt-catalyzed reaction.

The platinum-catalyzed arylation of naphthalene, which favors product **B**, and the analogous palladium-catalyzed arylation of naphthalene, which favors product **A**, are proposed to proceed through the mechanisms presented in Scheme 4.5 and Scheme 4.2, respectively. Based on these mechanisms, either C–H activation or reductive elimination is the selectivity-determining step for these systems. It was previously determined that the rate-determining step for the palladium-catalyzed reaction is oxidation[10] while the above experiments provide evidence that the rate-determining step for the platinum-catalyzed reaction is reductive elimination. The difference in selectivity for the palladium- and platinum-catalyzed systems may be a consequence of the difference in the rate- and/or selectivity-determining step for each reaction.

In the platinum-catalyzed system, where reductive elimination is the rate-determining step, it is hypothesized that C–H activation is the selectivity-determining step. In this system, reductive elimination is slow, thus it is proposed

that the C–H activation is comparatively fast and potentially *reversible*. If C–H activation is reversible and selectivity-determining, product **B**, the thermodynamically favored regioisomer of phenylnaphthalene, due to the lack of $A^{1,3}$ strain in the product (Figure 4.2), would be favored.

Figure 4.2. Thermodynamic Regioisomer of Phenylnaphthalene

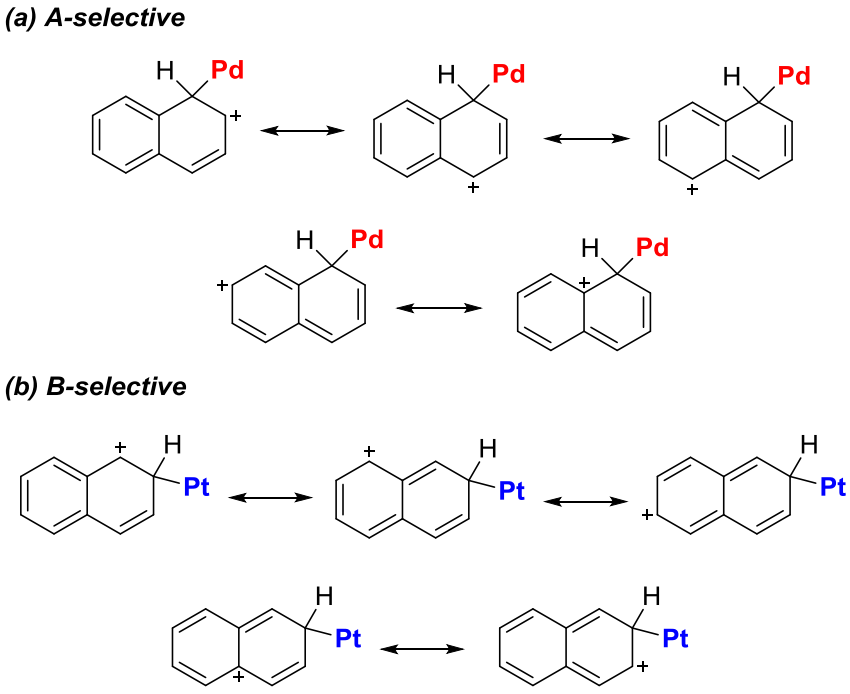


In the palladium-catalyzed system, where oxidation is the rate-determining step, it is hypothesized that either C–H activation or reductive elimination may be the selectivity-determining step. In this system, oxidation is slow, thus it is proposed that fast C–H activation is followed by fast reductive elimination. If C–H activation is followed by fast reductive elimination, C–H activation will be relatively *irreversible.*

Due to the electrophilic nature of palladium (and platinum) and the electron rich nature of naphthalene, C–H activation for both reactions is proposed to proceed via an electrophilic aromatic substitution (EAS) mechanism. For the EAS of naphthalene, the cationic intermediates that lead to product **A** are more stable because these intermediates have more resonance structures that retain aromaticity (Figure 4.3a) than the intermediates that lead to product **B** (Figure

4.3b). If C–H activation is irreversible and selectivity-determining, product **A**, the kinetically favored regioisomer of phenylnaphthalene, which is obtained from the pathway with the most stable intermediates, would be favored.

Figure 4.3. Kinetic Regioisomer of Phenylnaphthalene



If reductive elimination is the selectivity-determining step for the palladium-catalyzed system the more sterically encumbered product will be favored. Organometallic principles dictate that complexes with increased steric hindrance will undergo reductive elimination more quickly than less sterically hindered complexes. Thus, product **A** which has $A^{1,3}$ strain would be favored over product **B** if reductive elimination is the selectivity-determining step in the palladium-catalyzed system (Figure 4.2).

4.3 Conclusion

In summary, this paper demonstrates the first example of intermolecular $Pt^{II/IV}$-catalyzed direct C–H arylation of simple arenes. The use of Na_2PtCl_4 in conjunction with diaryliodonium oxidants enables arylation of diverse substrates, with predominantly sterically-controlled site-selectivity. Preliminary mechanistic studies suggest that the transformation proceeds through a Pt^{II}/Pt^{IV} catalytic cycle, and that reductive elimination may be rate limiting. Compared to analogous Pd-catalyzed arylation reactions, in which oxidation is rate limiting, the Pt-catalyzed conditions are effective for a much broader scope of substrates. Furthermore, the site-selectivity of Pt-catalyzed naphthalene arylation is complementary to that observed with Pd catalysis. As such, this work represents an important step toward assembling a set of general, tunable catalysts for site-selective C–H functionalization of simple arenes.

4.4 Experimental

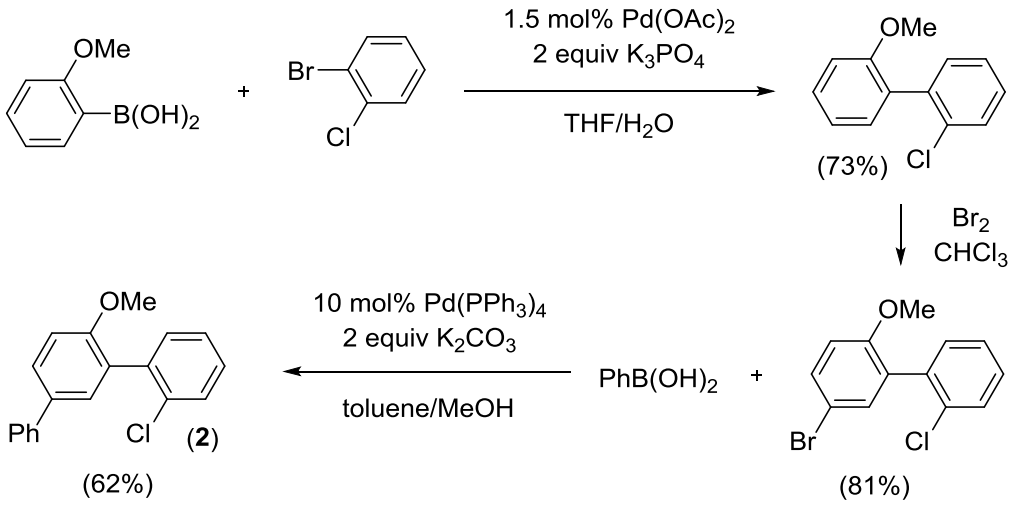
General Procedures: NMR spectra were recorded on a Varian vnmrs 700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C), a Varian vnmrs 500 (500.10 MHz for ^{1}H; 125.75 MHz for ^{13}C, 470.56 MHz for ^{19}F), a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C), or a Varian MR400 (400.52 MHz for ^{1}H; 100.71 for ^{13}C, 376.87 MHz for ^{19}F) NMR spectrometer with the residual solvent peak ($CDCl_3$: ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm) as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as an external reference at 0.00 ppm. Multiplicities are reported as follows: br s (broad singlet), app (apparent), s (singlet), d (doublet), t (triplet), q

(quartet), m (multiplet). Coupling constants *J* are reported in Hz. Flash chromatography was performed either on EM Science silica gel 60 (0.040-0.063 mm particle size, 230-400 mesh) or on a Biotage Isolera Flash Purification System using normal-phase 50 mm particle size silica. Thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F_{254}.High resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Gas chromatography was carried out on a Shimadzu 17A using a Restek Rtx®-5 (Crossbond 5% diphenyl – 95% dimethyl polysiloxane; 15 m, 0.25 mm ID, 0.25 µm df) column. GC calibrated yields and selectivities are reported relative to hexadecane as an internal standard.

Materials and Methods: Simple arenes (naphthalene, anisole, phenetol, veratrole, trifluorotoluene, 1,2-dichlorobenzene and bromobenzene), boronic acids, iodoarenes and solvents were obtained from commercial sources and used without further purification. H_2PtCl_6 (Pressure Chemical) and Na_2PtCl_4 (Sigma Aldrich and Alfa Aesar) were obtained from commercial sources and used as received. Tetrabutylammonium triflate (Aldrich), trifluoroacetic acid (Oakwood products) and acetic acid (Fisher Chemical) were obtained from commercial sources and used without further purification. Authentic samples of biaryl compounds were prepared via Suzuki-Miyaura cross-coupling reactions between commercially available aryl bromides and aryl boronic acids.[21,22] The authentic competition cross-coupling product **2** was prepared by a sequence

comprising a Suzuki cross-coupling,[21] a bromination using Br_2[23], and a final Suzuki cross-coupling (Scheme 4.7).[22]

Scheme 4.7. Synthesis of biaryl **2**



All reactions were conducted on the bench top without precautions to exclude air or moisture. For all C–H arylations reactions, no product was detected under control conditions in the absence of Pt catalyst or in the absence of oxidant.

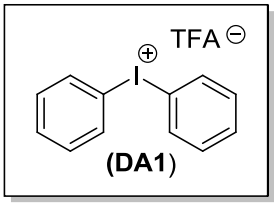
4.5 Synthesis and Characterization

4.5.1 Diaryliodonium Salts:

General Procedure**:** Diaryliodonium trifluoroacetate salts were prepared from their corresponding tetrafluoroborate salts, which were synthesized according to literature procedures: Ph_2IBF_4 was prepared by reacting $PhI(OAc)_2$ with $PhB(OH)_2$ in the presence of BF_3•OEt_2.[24] Other aryliodonium salts Ar_2IBF_4 (Ar =

p-FC_6H_4, *p*-$CF_3C_6H_4$, *p*-BrC_6H_4, *m*-BrC_6H_4, *p*-MeC_6H_4, *o*-MeC_6H_4 and *p*-$OMeC_6H_4$) were prepared by reacting the corresponding aryl iodide and arylboronic acid with *m*-CPBA in the presence of BF_3•OEt_2.[25]

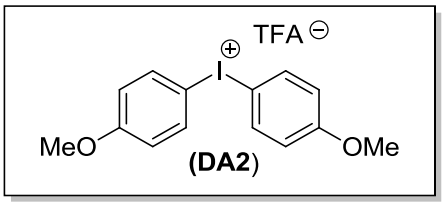
Diaryliodonium tetrafluoroborate salts were then dissolved in dichloromethane and allowed to stir with a saturated aqueous solution of sodium trifluoroacetate for 1–3 h. Water was then added and the aqueous layer was extracted three times with dichloromethane. The combined dichloromethane layers were again stirred with saturated aqueous sodium trifluoroacetate solution for 1-3 hours to ensure complete conversion to the desired TFA salt. Water was added and the aqueous layer was extracted three times with dichloromethane. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting solids were recrystallized from dichloromethane and ether.



(DA1)

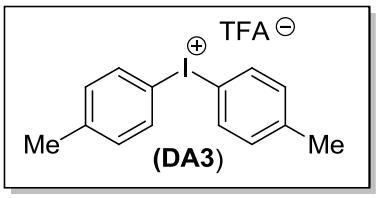
The general procedure was followed utilizing phenylboronic acid (5.25 g, 1.05 equiv, 43.0 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 5.7 mL, 1.10 equiv, 45.0 mmol), and $PhI(OAc)_2$ (13.2 g, 1 equiv, 41.0 mmol) in dry CH_2Cl_2 (550 mL), with subsequent treatment with saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA1** as a white solid [14.1 g, 87% yield, mp = 195-196 ^oC (lit. 197-198 ^oC)].[26] ^{19}F NMR (376 MHz, DMSO-d_6): δ –73.4. HRMS $[M–TFA]^+$ calcd for $C_{12}H_{10}I$:

280.9822; Found: 280.9819. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[26]



(**DA2**)

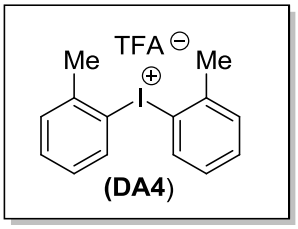
The general procedure was followed utilizing 4-iodoanisole (3.51 g, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 4-methoxyphenylboronic acid (2.50 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA2** as a white solid (2.18 g, 32% yield, mp = 129-130 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (d, J = 9 Hz, 4H), 7.05 (d, J = 9 Hz, 4H), 3.79 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.8, 158.3 (q, $^{2}J_{C–F}$ = 31 Hz, TFA), 136.9, 117.3, 117.3 (q, $^{1}J_{C–F}$ = 299 Hz, TFA), 106.3, 55.7. ^{19}F NMR (376 MHz, DMSO-d_6): δ –73.4. HRMS $[M–TFA]^+$ calcd for $C_{14}H_{14}IO_2$: 341.0033; Found: 341.0036.



(**DA3**)

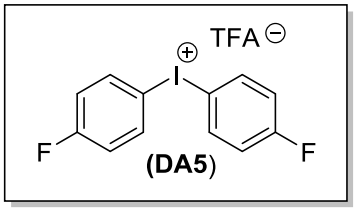
The general procedure was followed utilizing 4-iodotoluene (3.27 g, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 4-tolylboronic acid (2.24 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with saturated sodium

trifluoroacetate (2 x 100 mL) to yield **DA3** as a white solid (2.65 g, 42 % yield, mp = 177-179 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, J = 8 Hz, 4H), 7.32 (d, J = 8 Hz, 4H), 2.33 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.2 (q, $^{2}J_{C–F}$ = 31 Hz, TFA), 142.3, 135.0, 132.2, 117.2 (q, $^{1}J_{C–F}$ = 299 Hz, TFA), 113.3, 20.8. ^{19}F NMR (376 MHz, DMSO-d_6): δ –73.4. HRMS $[M–TFA]^+$ calcd for $C_{14}H_{14}I$: 309.0135; Found: 309.0137.



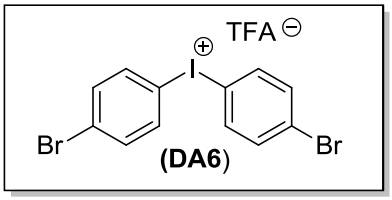
(DA4)

The general procedure was followed utilizing 2-iodotoluene (1.91 mL, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 2-tolylboronic acid (2.24 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA4** as a white solid (2.41 g, 38% yield, mp = 170-172 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (d, J = 8 Hz, 2H), 7.60-7.55 (multiple peaks, 4H), 7.30 (m, 2H), 2.60 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.1 (q, $^{2}J_{C–F}$ = 31 Hz, TFA), 140.6, 137.2, 132.6, 131.5, 129.2, 120.8, 117.2 (q, $^{1}J_{C–F}$ = 300 Hz, TFA), 25.0. ^{19}F NMR (376 MHz, DMSO-d_6): δ –73.4. HRMS $[M–TFA]^+$ calcd for $C_{14}H_{14}I$: 309.0135; Found: 309.0138.



(DA5)

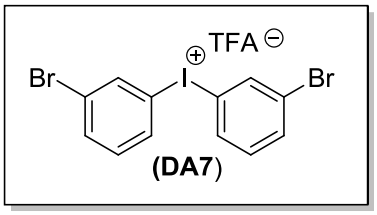
The general procedure was followed utilizing 4-fluoroiodobenzene (1.7 mL, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 4-fluorophenylboronic acid (2.31 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA5** as a white solid (2.71 g, 42% yield, mp = 208-210 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (m, 4H), 7.42 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.9 (d, $^1J_{C–F}$ = 250 Hz), 158.6 (q, $^2J_{C–F}$ = 32 Hz, TFA), 138.0 (d, $^3J_{C–F}$ = 9 Hz), 119.1 (d, $^2J_{C–F}$ = 23 Hz), 116.9 (q, $^1J_{C–F}$ = 297 Hz, TFA), 111.7 (d, $^4J_{C–F}$ = 2.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ –73.4, –106.7. HRMS $[M–TFA]^+$ calcd for $C_{12}H_8F_2I$: 316.9633; Found: 316.9635.



(DA6)

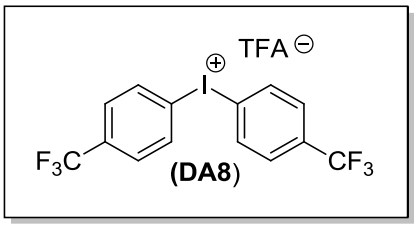
The general procedure was followed utilizing 4-bromoiodobenzene (4.45 g, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 4-bromophenylboronic acid (3.31 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA6** as a white solid (2.81

g, 34% yield, mp = 190-192 ºC). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.17 (d, J = 9 Hz, 4H), 7.75 (d, J = 9 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.6 (q, $^{2}J_{C–F}$ = 32 Hz, TFA), 137.1, 134.5, 126.1, 117.0 (q, $^{1}J_{C–F}$ = 297 Hz, TFA), 116.1. ^{19}F NMR (376 MHz, DMSO-d_6): δ –73.4. HRMS [M–TFA]$^{+}$ calcd for $C_{12}H_8Br_2I$: 436.8032; Found: 436.8029.



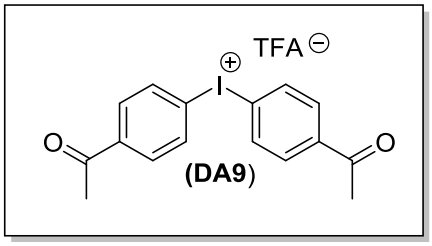
(**DA7**)

The general procedure was followed utilizing 3-bromo-iodobenzene (4.45 g, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 3-bromophenylboronic acid (3.31 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA7** as a white solid (2.98 g, 36% yield, mp = 148-149 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 2H), 8.29 (d, J = 8 Hz, 2H), 7.89 (d, J = 8 Hz, 2H), 7.52 (t, J = 8 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.5 (q, $^{2}J_{C–F}$ = 32 Hz, TFA), 137.0, 134.8, 134.1, 133.2, 123.1, 118.3, 116.8 (q, $^{1}J_{C–F}$ = 298 Hz, TFA). ^{19}F NMR (376 MHz, DMSO-d_6): δ –73.4. HRMS [M–TFA]$^{+}$ calcd for $C_{12}H_8Br_2I$: 436.8032; Found: 436.8027.



(**DA8**)

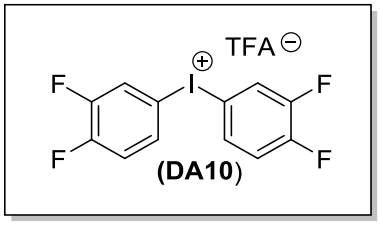
The general procedure was followed utilizing 1-iodo-4-(trifluoromethyl)benzene (2.20 mL, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 4-(trifluoromethyl)phenylboronic acid (3.13 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA8** as a white solid (2.84 g, 36% yield, mp = 199-202 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (d, J = 8 Hz, 4H), 7.93 (d, J = 8 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.8 (q, $^2J_{C–F}$ = 31 Hz, TFA), 136.6, 132.3 (q, $^2J_{C–F}$ = 32 Hz), 128.6, 123.8 (q, $^1J_{C–F}$ = 272 Hz), 122.2, 117.4 (q, $^1J_{C–F}$ = 299 Hz, TFA). ^{19}F NMR (376 MHz, DMSO-d_6): δ –61.7, –73.5. HRMS $[M–TFA]^+$ calcd for $C_{14}H_8F_6I$: 416.9569; Found: 416.9571.



(**DA9**)

The general procedure was followed utilizing 4-iodoacetophenone (3.69 g, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 4-acetylphenylboronic acid (2.71 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with

saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA9** as a brown solid (1.04 g, 15 % yield, mp = 106-109 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, J = 8.4 Hz, 4H), 8.01 (d, J = 8.4 Hz, 4H), 2.58 (s, 6H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 197.4, 157.8 (q, $^{2}J_{C–F}$ = 31 Hz, TFA), 139.0, 135.6, 131.0, 121.8, 117.3 (q, $^{1}J_{C–F}$ = 301 Hz, TFA), 26.9. ^{19}F NMR (376 MHz, DMSO-d_6): δ –73.5. IR (thin film, cm^{-1}): 3019 (w, sp^2 C-H), 2917 (w, sp^2 C-H), 1682 (m, ketone C-O), 1578 (w, aryl C-C), 820 (m, Ar C-H), 802 (w, Ar C-H), 725 (w, Ar C-H).HRMS [M–TFA]$^+$ calcd for $C_{16}H_{14}IO_2$: 365.0033; Found: 365.0037.



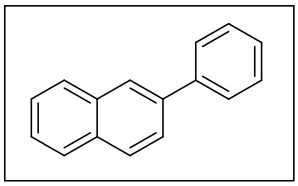
(DA10)

The general procedure was followed utilizing 3,4-difluoroiodobenzene (1.81 mL, 1 equiv, 15.0 mmol), *m*-CPBA (2.85 g, 1.1 equiv, 16.5 mmol), BF_3•Et_2O (48% BF_3 in Et_2O, 4.7 mL, 2.5 equiv, 37.5 mmol), and 3,4-difluorophenylboronic acid (2.61 g, 1.1 equiv, 16.5 mmol) in CH_2Cl_2 (60 mL), with subsequent treatment with saturated sodium trifluoroacetate (2 x 100 mL) to yield **DA10** as a white solid (2.11 g, 32% yield, mp = 211-213 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.56-8.51 (m, 2H), 8.18-8.15 (m, 2H), 7.72-7.65 (m, 2H). ^{13}C NMR (178 MHz, DMSO-d_6): δ 158.7 (q, $^{2}J_{C–F}$ = 30 Hz, TFA), 152.0 (dd, $^{1}J_{C–F}$ = 241 Hz, $^{2}J_{C–F}$ = 13 Hz), 149.8 (dd, $^{1}J_{C–F}$ = 254 Hz, $^{2}J_{C–F}$ = 13 Hz), 133.2 (t, $^{3}J_{C–F}$ = 3 Hz), 125.0 (d, $^{2}J_{C–F}$ = 21 Hz), 120.8 (d, $^{2}J_{C–F}$ = 18 Hz), 117.0 (q, $^{1}J_{C–F}$ = 299 Hz, TFA), 111.5. ^{19}F NMR

(376 MHz, DMSO-d_6): δ –73.5, –131.6 (m), –132.7 (m). HRMS $[M–TFA]^+$ calcd for $C_{12}H_6F_4I$: 352.9445; Found: 352.9443.

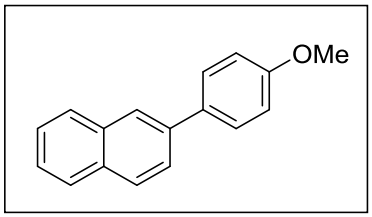
4.5.2 C–H Arylation Products

General Procedure**:** To a 20 mL scintillation vial containing $Na_2PtCl_4•H_2O$ (2.5–10 mol%), tetrabutylammonium triflate (5-15 equiv), and the indicated diaryliodonium salt (1 equiv) was added a simple arene (30-60 equiv) and acid (0 or 32 equiv). The vial was sealed with a Teflon-lined cap, and the reaction was placed into one of the wells of an aluminum block preheated to 100–120 ºC. After stirring for 72 h, the reaction mixture was cooled to room temperature and flushed through silica using hexanes followed by diethyl ether, until arene had been completely eluted, as indicated by TLC. After vacuum concentration, the simple arene was removed by distillation and the remaining residue was purified by automated flash chromatography on a Biotage Isolera Flash Purification System. Yields reported in the manuscript represent an average of two runs.

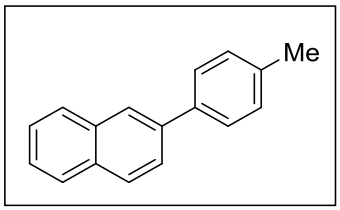


2-Phenylnaphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), [Ph_2ITFA (0.394 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-Phenylnaphthalene was obtained as a white solid [133 mg, 65% yield, R_f = 0.29 in hexanes, mp = 99-101 ºC (lit.[27] 100-101 ºC)]. HRMS EI

[M^+] calcd for $C_{16}H_{12}$, 204.0939; found, 204.0936. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[27]

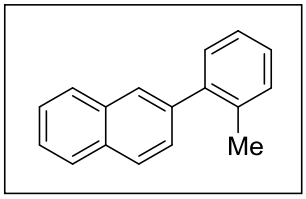


2-(4-Methoxyphenyl)naphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), [(*p*-$OMeC_6H_4)_2$ITFA (0.454 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-(4-Methoxyphenyl)naphthalene was obtained as a white solid [197 mg, 84% yield, R_f = 0.43 in 95% hexanes/5% EtOAc, mp = 134-135 ºC (lit.[27] 135-137 ºC)]. HRMS EI [M^+] calcd for $C_{17}H_{14}O$, 234.1045; found, 234.1046. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[27]

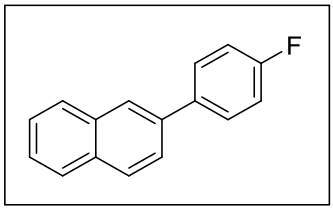


2-(4-Methylphenyl)naphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), [(*p*-$MeC_6H_4)_2$ITFA (0.422 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-(4-Methylphenyl)naphthalene was obtained as a white solid [185 mg, 85% yield, R_f = 0.67 in 95% hexanes/5% EtOAc, mp = 76-78 ºC (lit.[27] 75-78 ºC)]. HRMS EI [M^+] calcd for $C_{17}H_{14}$,

218.1096; found, 218.1092. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[27]

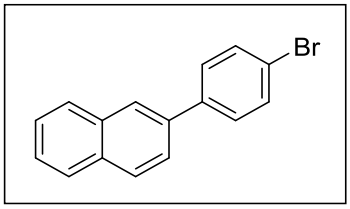


2-(2-Methylphenyl)naphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), [(*o*-$MeC_6H_4)_2$ITFA (0.422 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-(2-Methylphenyl)naphthalene was obtained as a white solid (157 mg, 72% yield, R_f = 0.63 in 95% hexanes/5% EtOAc, mp = 91-92 ºC). HRMS EI [M^+] calcd for $C_{17}H_{14}$, 218.1096; found, 218.1094. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[28]

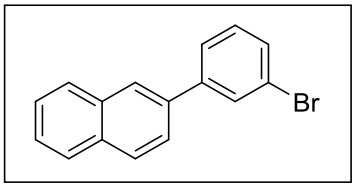


2-(4-Fluorophenyl)naphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), [(*p*-$FC_6H_4)_2$ITFA (0.430 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-(4-Fluorophenyl)naphthalene was obtained as a white solid (135 mg, 61% yield, R_f = 0.27 in hexanes, mp = 100-101 ºC). ^{19}F NMR (376 MHz, $CDCl_3$): δ –115.2. HRMS EI [M^+] calcd for $C_{16}H_{11}F$,

222.0845; found, 222.0845. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[28]

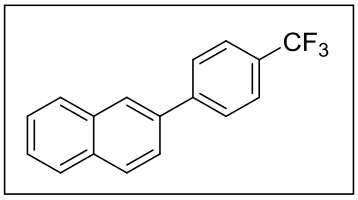


2-(4-Bromophenyl)naphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), [(*p*-$BrC_6H_4)_2$ITFA (0.552 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-(4-Bromophenyl)naphthalene was obtained as a white solid [161 mg, 57% yield, R_f = 0.58 in 97% hexanes/3% EtOAc, mp = 129-130 ºC (lit.[29] 128-129 ºC). HRMS EI [M^+] calcd for $C_{16}H_{11}Br$, 282.0044; found, 282.0044. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[29]

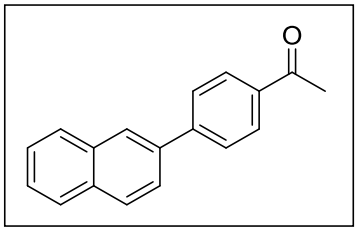


2-(3-Bromophenyl)naphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), [(*m*-$BrC_6H_4)_2$ITFA (0.552 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-(3-Bromophenyl)naphthalene was obtained as a white solid (178 mg, 63% yield, R_f = 0.52 in 97% hexanes/3% EtOAc, mp = 93-95 ºC). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.91-7.86

(multiple peaks, 4H), 7.69 (dd, *J* = 8, 1.5 Hz, 1H), 7.65 (m, 1H), 7.63-7.49 (multiple peaks, 3H), 7.35 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 137.0, 133.5, 132.8, 130.4, 130.3, 130.2, 128.6, 128.2, 127.6, 126.4, 126.3, 126.01, 125.99, 125.2, 123.0. HRMS EI [M^+] calcd for $C_{16}H_{11}Br$: 282.0044; Found: 282.0045.

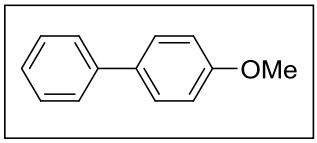


2-(4-(Trifluoromethyl)phenyl)naphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), [(*p*-$CF_3C_6H_4)_2$ITFA (0.552 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-(4-(Trifluoromethyl)phenyl)naphthalene was obtained as a white solid [144 mg, 53% yield, R_f = 0.48 in 97% hexanes/3% EtOAc, mp = 131-132 ºC (lit.[30] 127-129 ºC)]. ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.4. HRMS EI [M^+] calcd for $C_{17}H_{11}F_3$, 272.0813; found, 272.0813. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[30]

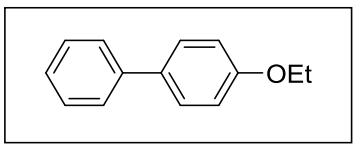


2-(4-Acetylphenyl)naphthalene. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.025 equiv, 0.025 mmol), tetrabutylammonium triflate

(1.96 g, 5 equiv, 5.00 mmol), (p-$COCH_3C_6H_4)_2$ITFA (0.478 g, 1 equiv, 1.00 mmol) and naphthalene (7.69 g, 60 equiv, 60.0 mmol). 2-(4-Acetylphenyl)naphthalene was obtained as an off-white solid [46 mg, 19 % yield, R_f = 0.32 in 90% hexanes/10% EtOAc, mp = 130-133 ºC (lit.[11] 136-139 ºC)]. IR (thin film, cm^{-1}): 2918 (w, sp^2 C-H), 1678 (m, ketone C-O), 1602 (w, aryl C-C), 1580 (w, aryl C-C), 815 (m, Ar C-H), 752 (w, Ar C-H), 725 (w, Ar C-H). HRMS EI [M^+] calcd for $C_{18}H_{14}O$, 246.1045; found, 246.1049. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[31]

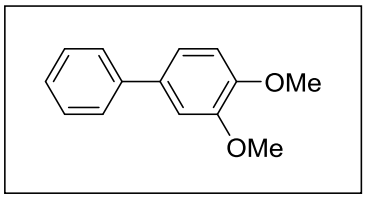


4-Methoxy-1,1'-biphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.020 g, 0.05 equiv, 0.050 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), Ph_2ITFA (0.394 g, 1 equiv, 1.00 mmol), trifluoroacetic acid (2.45 mL, 32 equiv, 32.0 mmol) and anisole (3.26 mL, 30 equiv, 30.0 mmol). 4-Methoxy-1,1'-biphenyl was obtained as a white solid [153 mg, 83% yield, R_f = 0.41 in 95% hexanes/5% EtOAc, mp = 87–91 ºC (lit.[32] 87-88 ºC)]. HRMS EI [M^+] calcd for $C_{13}H_{12}O$, 184.0888; found, 184.0892. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[32]

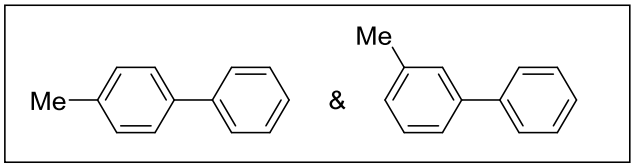


4-Ethoxy-1,1'-biphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.020 g, 0.05 equiv, 0.050 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv,

5.00 mmol), Ph_2ITFA (0.394 g, 1 equiv, 1.00 mmol), trifluoroacetic acid (2.45 mL, 32 equiv, 32.0 mmol) and phenetole (3.79 mL, 30 equiv, 30.0 mmol). 4-Ethoxy-1,1'-biphenyl was obtained as a white solid [168 mg, 85% yield, R_f = 0.45 in 95% hexanes/5% EtOAc, mp = 66–69 ºC (lit.[12] 69–71 ºC)]. HRMS EI [M^+] calcd for $C_{14}H_{14}O$, 198.1045; found, 198.1051. ^1H and ^{13}C NMR spectra matched those reported in the literature.[32]

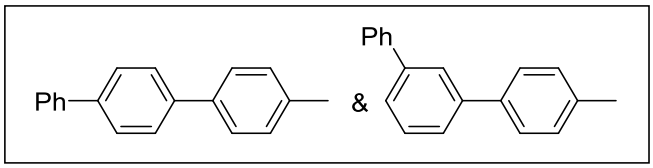


3,4-Dimethoxy-1,1'-biphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.020 g, 0.05 equiv, 0.050 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), Ph_2ITFA (0.394 g, 1 equiv, 1.00 mmol), trifluoroacetic acid (2.45 mL, 32 equiv, 32.0 mmol) and veratrole (3.82 mL, 30 equiv, 30.0 mmol). 3,4-Dimethoxy-1,1'-biphenyl was obtained as a white solid [102 mg, 48% yield, R_f = 0.39 in 95% hexanes/5% EtOAc, mp = 66-67 ºC (lit.[33] 66-67 ºC)]. HRMS EI [M^+] calcd for $C_{14}H_{14}O_2$, 215.1067; found, 215.1073. ^1H and ^{13}C NMR spectra matched those reported in the literature.[33]

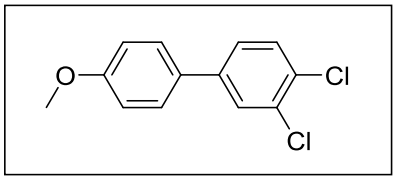


4-Methyl-1,1'-biphenyl and 3-methyl-1,1'-biphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.040 g, 0.1 equiv, 0.100 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), Ph_2ITFA (0.394 g, 1

equiv, 1.00 mmol), trifluoroacetic acid (2.45 mL, 32 equiv, 32.0 mmol) and toluene (6.4 mL, 60 equiv, 60.0 mmol). The product was obtained as a white solid consisting of a 2.4 : 1 mixture of 4-methyl-1,1'-biphenyl : 3-methyl-1,1'-biphenyl (77 mg, 46% yield, R_f = 0.55 in hexanes). HRMS EI [M^+] calcd for $C_{13}H_{12}$, 168.0939; found, 168.0935. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[32]

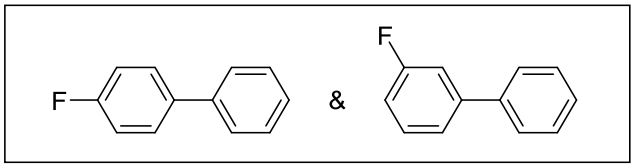


4-Methyl-[1,1':4',1''Terphenyl and 4-methyl-[1,1':3',1''Terphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.040 g, 0.1 equiv, 0.100 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), (p-$MeC_6H_4)_2$ITFA (0.422 g, 1 equiv, 1.00 mmol), and biphenyl (9.25 g, 60 equiv, 60.0 mmol). The product was obtained as a white solid consisting of a 1.2 : 1 mixture of 4-methyl-[1,1':4',1''Terphenyl : 4-methyl-[1,1':3',1''Terphenyl (105 mg, 42% yield, R_f = 0.51 in 95% hexanes/5% EtOAc). HRMS EI [M^+] calcd for $C_{19}H_{16}$, 244.1252; found, 244.1244. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[28,34]

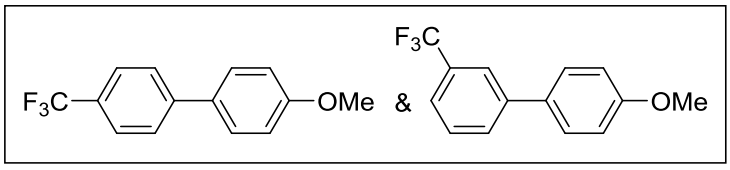


3,4-Dichloro-4'-methoxy-1,1'-biphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.010 g, 0.05 equiv, 0.025 mmol), tetrabutylammonium triflate (2.94 g, 15 equiv, 7.50 mmol), (p-$OMeC_6H_4)_2$ITFA (0.227 g, 1 equiv, 0.500

mmol), acetic acid (0.92 mL, 32 equiv, 16.0 mmol) and 1,2-dichlorobenzene (3.40 mL, 60 equiv, 30.0 mmol). 3,4-Dichloro-4'-methoxy-1,1'-biphenyl was obtained as a white solid (84 mg, 66% yield, R_f = 0.54 in 95% hexanes/5% EtOAc, mp = 42-44 ºC). HRMS EI [M^+] calcd for $C_{13}H_{10}Cl_2O$, 252.0109; found, 252.0112. ^1H and ^{13}C NMR spectra matched those reported in the literature.[35]

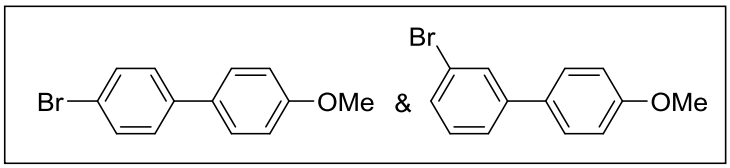


4-Fluoro-1,1'-biphenyl and 3-fluoro-1,1'-biphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.040 g, 0.1 equiv, 0.100 mmol), tetrabutylammonium triflate (1.96 g, 5 equiv, 5.00 mmol), Ph_2ITFA (0.394 g, 1 equiv, 1.00 mmol), and fluorobenzene (5.60 mL, 60 equiv, 60.0 mmol). The product was obtained as a white solid consisting of a 6 : 1 mixture of 4-fluoro-1,1'-biphenyl : 3-fluoro-1,1'-biphenyl (89 mg, 52% yield, R_f = 0.72 in hexanes). HRMS EI [M^+] calcd for $C_{12}H_9F$, 172.0688; found, 172.0684. ^1H and ^{13}C NMR spectra matched those reported in the literature. [32,36]

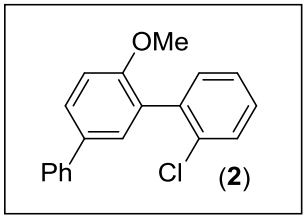


4-Methoxy-4'-(trifluoromethyl)-1,1'-biphenyl and 4'-methoxy-3-(trifluoromethyl)-1,1'-biphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.0050 g, 0.025 equiv, 0.0125 mmol), tetrabutylammonium triflate (2.94 g, 15 equiv, 7.50 mmol), (p-$OMeC_6H_4)_2ITFA$ (0.227 g, 1 equiv, 0.500 mmol), acetic acid (0.92 mL,

32 equiv, 16.0 mmol) and trifluorotoluene (3.68 mL, 60 equiv, 30.0 mmol). The product was obtained as a white solid consisting of a 1 : 1.4 mixture of 4-methoxy-4'-(trifluoromethyl)-1,1'-biphenyl : 4'-methoxy-3-(trifluoromethyl)-1,1'-biphenyl (67 mg, 53% yield, R_f = 0.48 in 95% hexanes/5% EtOAc). ^{19}F NMR (376 MHz, $CHCl_3$): δ –62.3, –72.6. HRMS EI [M^+] calcd for $C_{14}H_{11}F_3O$, 252.0762; found, 252.0771. ^1H and ^{13}C NMR spectra matched those reported in the literature.[37, 28]



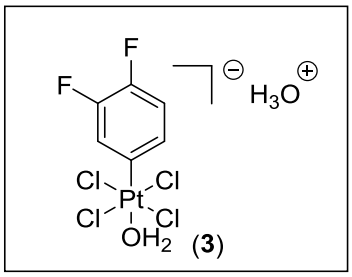
4-Bromo-4'-methoxy-1,1'-biphenyl and 3-bromo-4'-methoxy-1,1'-biphenyl. The general procedure was followed using $Na_2PtCl_4•H_2O$ (0.005 g, 0.025 equiv, 0.0125 mmol), tetrabutylammonium triflate (2.94 g, 15 equiv, 7.50 mmol), (*p*-$OMeC_6H_4)_2ITFA$ (0.277 g, 1 equiv, 0.500 mmol), acetic acid (0.92 mL, 32 equiv, 16.0 mmol) and bromobenzene (3.15 mL, 60 equiv, 30.0 mmol). The product was obtained as a white solid consisting of a 1 : 2.5 mixture of 4-bromo-4'-methoxy-1,1'-biphenyl : 3-bromo-4'-methoxy-1,1'-biphenyl (78 mg, 58% yield, R_f = 0.46 in 95% hexanes/ 5% EtOAc). HRMS EI [M^+] calcd for $C_{13}H_{11}BrO$, 261.9993; found, 261.9984. ^1H and ^{13}C NMR spectra matched those reported in the literature.[38]



(**2**)

The general procedure was followed using $Na_2PtCl_4 \bullet H_2O$ (0.0112 g, 0.05 equiv, 0.028 mmol), tetrabutylammonium triflate (1.08 g, 5 equiv, 2.75 mmol), Ph_2ITFA (0.216 g, 1 equiv, 0.550 mmol), trifluoroacetic acid (1.4 mL, 32 equiv, 18.0 mmol) and 2-chloro-2'-methoxy-1,1'-biphenyl (7.19 g, 60 equiv, 33.0 mmol). Product **2** was obtained as a white solid (135 mg, 83% yield, R_f = 0.39 in 95% hexanes/5% EtOAc, mp = 122-124 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63-7.58 (multiple peaks, 3H), 7.49-7.46 (multiple peaks, 2H), 7.42 (t, *J* = 7 Hz, 2H), 7.37-7.30 (multiple peaks, 4H), 7.06 (d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 140.4, 137.6, 134.0, 133.4, 131.7, 129.8, 129.4, 128.8, 128.7, 128.6, 127.8, 126.8, 126.5, 111.3, 55.8. Two aromatic ^{13}C resonances are coincidentally overlapping. HRMS EI [M^+] calcd for $C_{19}H_{15}ClO$: 294.0811; Found: 294.0810.

*4.5.3. Pt Complex **3***



(**3**)

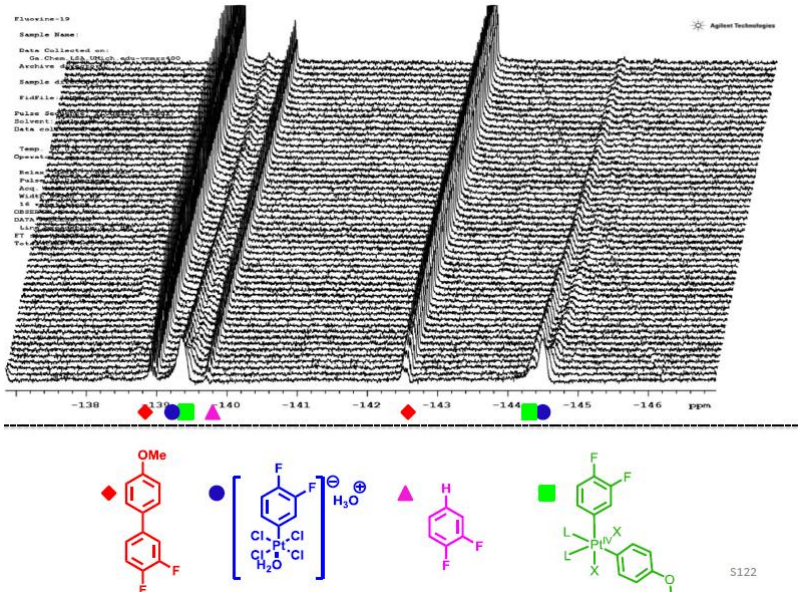
H_2PtCl_6 (0.61 g, 1 equiv, 1.5 mmol), 1,2-difluorobenzene (1.2 mL, 8 equiv, 12 mmol), H_2O (1.8 mL) and trifluoroacetic acid (9 mL) were combined in a 20 mL vial. The vial was sealed with a Teflon-lined cap, and the reaction was stirred at 100 ºC for 2.5 h. The volatiles were removed *in vacuo*, and the remaining residue was dissolved in acetone and applied to a silica gel column. The residue was washed with hexane to remove any aryl byproducts and then flushed through the column with acetone. The acetone was removed *in vacuo*, and the remaining residue was purified by preparatory TLC to provide product **3** as a yellow solid (10 mg, 2% yield, R_f = 0.58 in 2:1 acetone to hexanes). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.28 (m, 1H), 7.16 (m, 1H), 6.75 (m, 1H). ^{13}C NMR (176 MHz, acetone-d_6): δ 149.5 (dd, $^{1}J_{C–F}$ = 240 Hz, $^{2}J_{C–F}$ = 12 Hz), 145.5 (dd, $^{1}J_{C–F}$ = 240 Hz, $^{2}J_{C–F}$ = 12 Hz), 134.7 (m), 126.5 (d, $^{2}J_{C–F}$ = 18 Hz), 112.6 (m), 105.2 (C–Pt). ^{19}F NMR (377 MHz, acetone-d_6): δ –143.9 (m), –148.7 (m).^{195}Pt NMR (150 MHz, acetone-d_6): δ –711.8 (reference Na_2PtCl_6 in acetone set to 0 ppm; ^{195}Pt chemical shift is –227 ppm with respect to H_2PtCl_6 in H_2O). HRMS negative ion electrospray for anionic Pt-complex – H_2O ligand: (m/z) of anion calcd for

$C_6H_3Cl_4F_2Pt$: 447.8589; Found: 447.8614. Anal. Calcd. For $C_6H_8Cl_4F_2O_2Pt$ x 0.75 $CO(CH_3)_2$: C, 18.73; H, 2.10; Found: C, 18.72; H, 2.14.

4.6 Procedure for ^{19}F NMR Spectroscopy Kinetics Experiment Between Pt Complex 3 and Anisole (Figure 4.1)

To a 4 mL glass vial was added **3** (0.0213 g, 1 equiv, 0.0438 mmol), tetrabutylammonium triflate (0.086 g, 5 equiv, 0.220 mmol), anisole (0.29 mL, 60 equiv, 2.60 mmol), trifluoroacetic acid (0.11 mL, 32 equiv, 1.40 mmol), and 1,3,5-trifluorobenzene (2 mL, 0.44 equiv, 0.0193 mmol) as a standard. The solution was transferred to a screw-cap NMR tube, sealed with a Teflon-lined cap, and heated to 90 ºC for 6 h. Over the duration of the experiment, ^{19}F NMR spectra were taken every 60 seconds. This experiment was done in duplicate; a representative array of ^{19}F NMR spectra corresponding to Figure 4.1 is shown below (Figure 4.4).

Figure 4.4. Representative Array of Stoichiometric Arylation Reaction



4.7 Procedure for Catalytic Reactions using Pt Complex 3 (Table 4.5)

Stir bars were treated with aqua regia, washed with water and acetone, and dried before use. To a 4 mL glass vial was added **3** (0.0018 g, 0.1 equiv, 0.0036 mmol), tetrabutylammonium triflate (0.071 g, 5 equiv, 0.180 mmol), 3,4-difluorophenyliodonium trifluoroacetate (0.0168 g, 1 equiv, 0.0168 mmol), a simple arene (30-60 equiv), and acid (32 equiv) as indicated. The vial was sealed with a Teflon-lined cap and stirred for 20 h in a well of an aluminum block preheated to 100–120 °C. The reaction mixture was cooled to room temperature and a hexadecane standard was added. The mixture was flushed through silica using hexanes followed by diethyl ether. Calibrated GC yields reported in the manuscript represent an average of two runs.

4.8 Kinetics Procedures and Representative Kinetic Data

4.8.1 General Information.

Reaction kinetics were measured using the method of initial rates. In each experiment, the appearance of products (A+B) was monitored to ~10% conversion by GCMS. Each experiment was run in triplicate and all kinetic orders represent an average of these three runs. Microsoft Excel was used to fit the data and determine both initial rates and orders.

4.8.2 Kinetics Procedure.

To a 4 mL glass vial was added catalyst, oxidant, tetrabutylammonium salt, arene and trifluoroacetic acid (as indicated). Each vial was heated on a 100 ºC aluminum block for the required time and then quenched immediately by

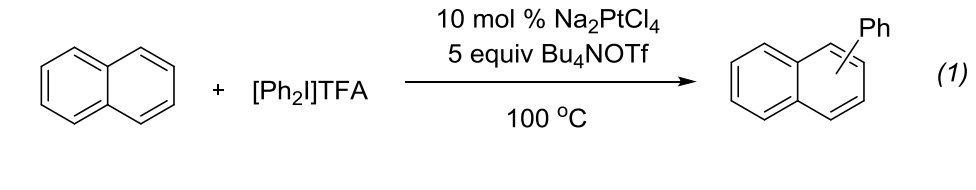
placement in an ice bath. Ether (1.5 mL) and hexanes (1.5 mL) were added to dissolve the remaining arene starting material and phenylated products; this procedure also separated the catalyst and excess oxidant, which are soluble in the tetrabutylammonium salt. Hexadecane (6.9 μL, 0.0235 mmol) was added as an internal standard to each vial, and the solutions were allowed to stir for ~5 min. The hexanes/ether layer was then analyzed by GC.

4.8.3 Kinetic Isotope Effect.

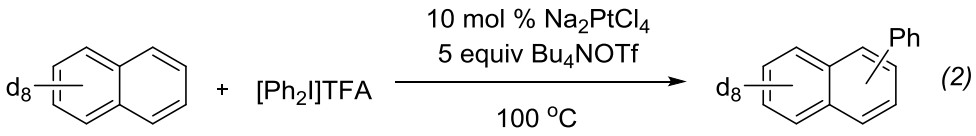
Naphthalene:

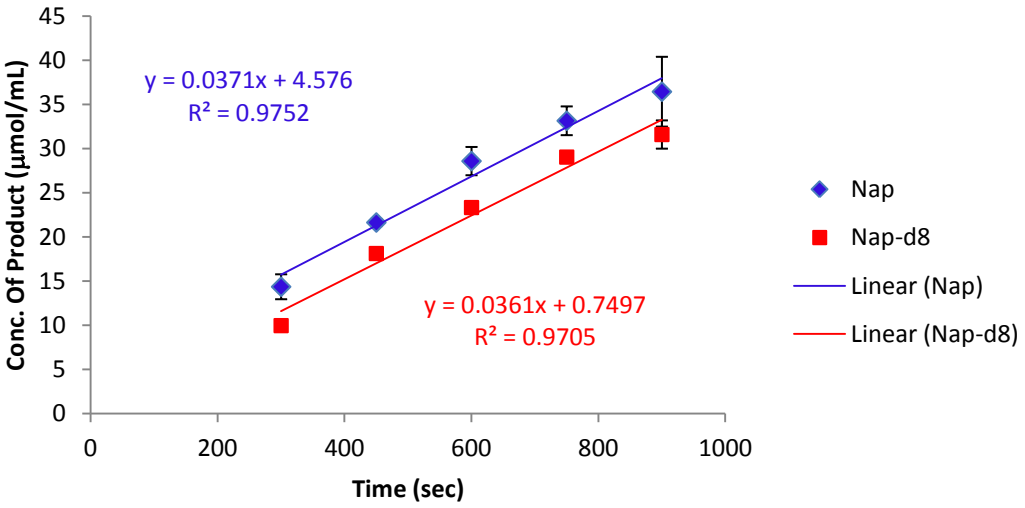
The KIE was determined by comparing the initial reaction rate with naphthalene (eq. 1, Figure 4.5, blue diamonds) with to the initial reaction rate with naphthalene-d_8 (eq. 2, Figure 4.3, red squares). Both reactions were conducted [114] using the standard kinetics procedure above, using arene (1.47 mmol, 30 equiv), Ph_2ITFA (0.049 mmol, 1 equiv), Na_2PtCl_4 (4.9 μmol, 10 mol %), and Bu_4NOTf (0.245 mmol, 5 equiv). Each point is an average of at least 3 runs. These experiments provided a KIE of 1.0 ± 0.1.

Figure 4.5. Initial Rates Data for C–H Phenylation of Naphthalene and Naphthalene-d_8



vs.



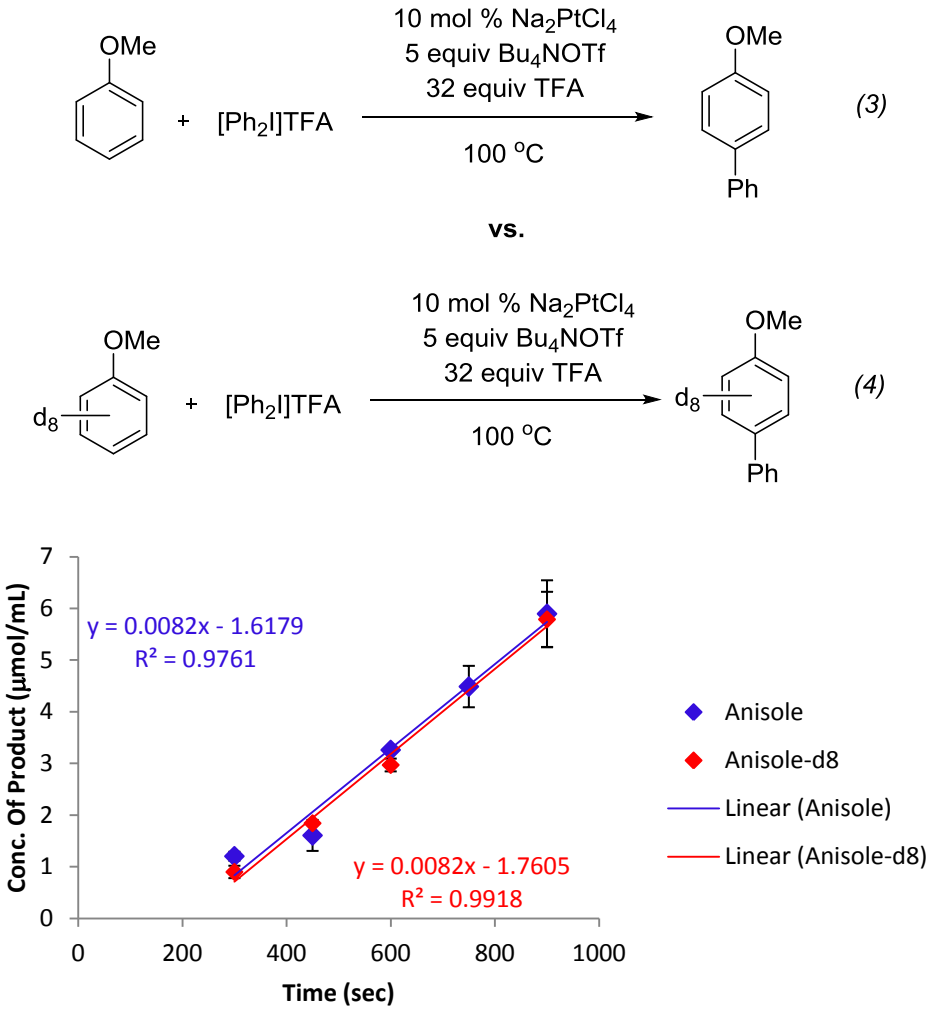


Anisole:

The KIE was determined by comparing the initial reaction rate of anisole (eq. 3, Figure 4.6, blue diamonds) with to the initial reaction rate with anisole-d8 (eq. 4, Figure 4.6, red sqaures). Both reactions were conducted using the standard kinetics procedure above, using arene (1.47 mmol, 30 equiv), Ph_2ITFA (0.049 mmol, 1 equiv), and Na_2PtCl_4 (4.9 µmol, 10 mol %), Bu_4NOTf (0.245 mmol, 5

equiv), and trifluoroacetic acid (1.57 mmol, 32 equiv). Each point is an average of at least 3 runs. These experiments provided a KIE of 1.0 ± 0.0.

Figure 4.6. Initial Rates Data for C–H Phenylation of Anisole and Anisole-d_8

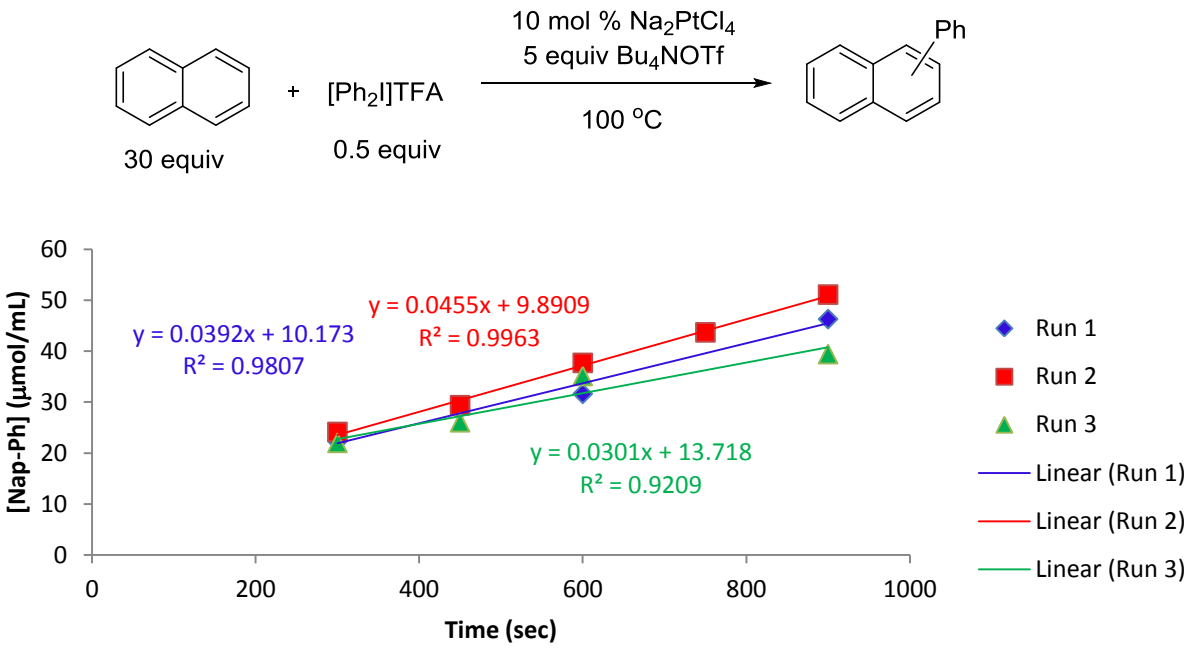


4.8.4 Order in Ph_2ITFA.

General information.The order in Ph_2ITFA was determined by studying the initial rate of C–H phenylation at differing concentrations of Ph_2ITFA with either

naphthalene or anisole. For each data point on the order plots (Figure 4.8 and Figure 4.9), three (3) different kinetic runs were performed and an average of the slopes of those runs ± the standard deviation of those slopes was plotted. For example in Figure 4.8, for the point at Ph_2ITFA = 1.48 μM, the three kinetic runs shown in Figure 4.6 were performed. The average initial rate (38.7 μM/sec, an average of 39.2, 45.5 and 30.1 μM/sec) was plotted in Figure 4.8. The error bars in Figure 4.8 are the standard deviation of these numbers.

Figure 4.7. Initial Rates for 1.48 μM Ph_2ITFA for Figure 4.8

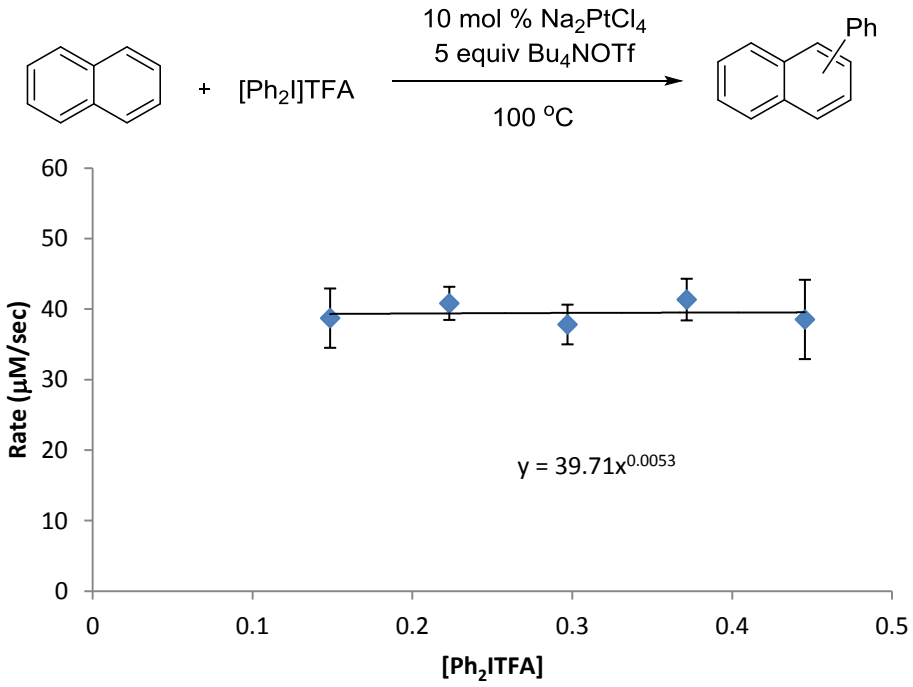


<u>Naphthalene</u>.

Reactions were conducted using the standard kinetics procedure above, using Ph_2ITFA (0.0245-0.0735 mmol, 0.5-1.5 equiv), naphthalene (1.47 mmol, 30

equiv), Na_2PtCl_4 (4.9 µmol, 10 mol %), and Bu_4NOTf (0.245 mmol, 5 equiv). The results of this study, which are an average of three runs, are shown in Figure 4.8. The reaction was fit to y = a*x^b, a=39.7 and b=–5.3*10^{-3} where b is the order in oxidant.

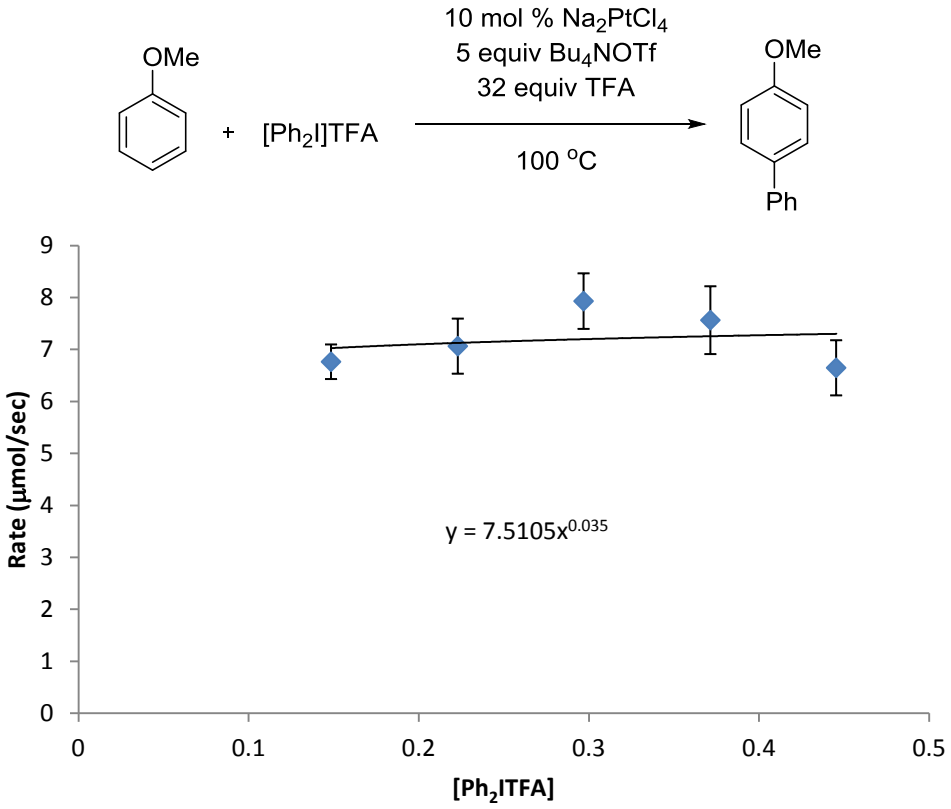
Figure 4.8. Naphthalene: Initial Rates vs. Ph_2ITFA



Anisole.

Reactions were conducted using the standard kinetics procedure above, using Ph_2ITFA (0.0245 to 0.0735 mmol, 0.5 to 1.5 equiv), anisole (1.47 mmol, 30 equiv), Na_2PtCl_4 (4.9 µmol, 10 mol %), Bu_4NOTf (0.245 mmol, 5 equiv) and trifluoroacetic acid (1.57 mmol, 32 equiv). The results of this study, which are an average of three runs, are shown in Figure 4.9. The reaction was fit to y=a*x^b, a = 7.51 and b = 3.5*10^{-2} where b is the order in oxidant.

Figure 4.9. Anisole: Initial Rates vs. Ph_2ITFA



4.9 References

[1] Adapted with permission from Wagner, A. M.; Hickman, A. J.; Sanford, M. S. Platinum-Catalyzed C–H Arylation of Simple Arenes. *J. Am. Chem. Soc.* **2013**, *135*, 15710–15713. Copyright © 2013 American Chemical Society.

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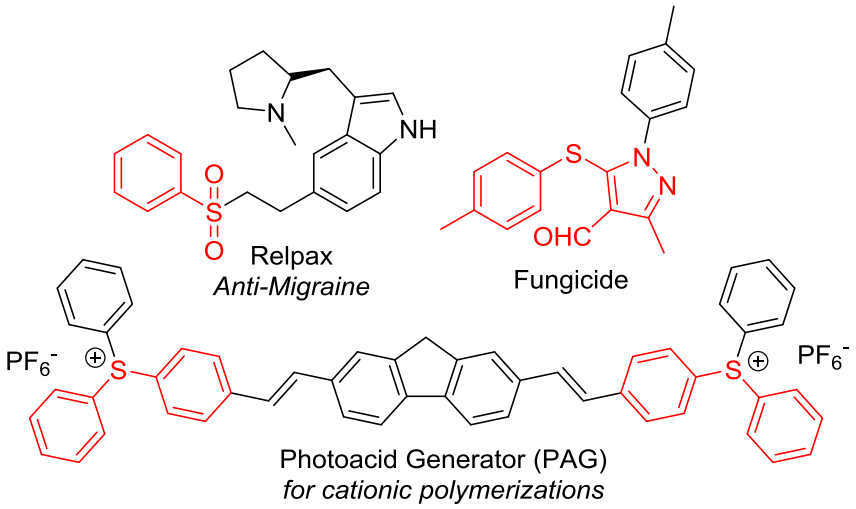
Chapter 5. Transition-Metal-Free Acid-Mediated Synthesis of Aryl Sulfides from Thiols and Thioethers[1]

5.1 Introduction

Preparing aryl sulfides constitutes an active and important area of synthetic organic chemistry due to the extensive biological applications of compounds containing C_{aryl}–S bonds (Figure 5.1).[2] For instance, aryl sulfides, aryl sulfoxides, and aryl sulfones are key components of commercial pharmaceuticals, including Relpax, Lansoprazole, Sulindac, Esomeprazole, and

Figure 5.1. Examples of Aryl Sulfides and Aryl Sulfones



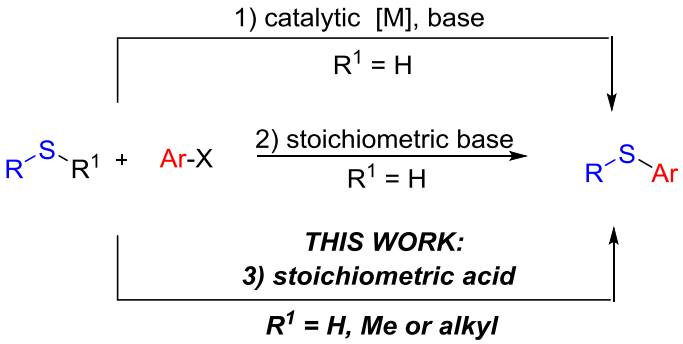
Quetiapine. Aryl sulfides are also present in molecules that are used to treat cancer, inflammation, asthma, Alzheimer's, Parkinson's, and HIV.[3] Finally, aryl sulfides can serve as precursors to photoacid generators (PAGs), which are widely used in paints, anti-corrosives, microelectronics, and coatings.[4]

One of the most common routes to aryl sulfides involves the transition-metal catalyzed cross-coupling of aryl halides or pseudo-halides with thiols under basic conditions.[5] A number of base-mediated, transition-metal free reactions for aryl sulfide synthesis have also been reported.[6] While these represent highly useful transformations, the vast majority of current synthetic methods for aryl sulfide synthesis require at least one of the following: 1) the use of strongly basic media, 2) the use of transition-metal catalysts/mediators, 3) the use of an inert atmosphere, and/or 4) the use of a thiol substrate. These requirements represent disadvantages with respect to functional group tolerance, ease of product purification (particularly for biological applications), and flexibility of synthetic strategies.

The studies in this chapter demonstrate an orthogonal, metal-free method for the synthesis of aryl sulfides that involves reacting either RSH or RSR' with diaryliodonium salts (Scheme 5.1), versatile reagents that have found diverse applications.[7] These reactions proceed under acidic conditions, thereby offering the potential for complementary substrate scope and functional group tolerance relative to base and/or transition-metal catalyzed transformations. This new method offers the additional advantages of compatibility with ambient air and

moisture as well as the flexibility to use either thiols or thioethers as starting materials.

Scheme 5.1. Strategies for Aryl Sulfide Formation

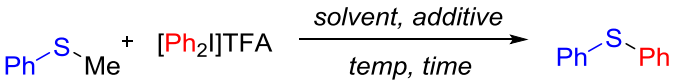


5.2 Results and Discussion

Initial investigations focused on reacting 1 equivalent of thioanisole (PhSMe) with 1 equivalent of diphenyliodonium trifluoroacetate (Ph_2ITFA) to generate diphenyl sulfide (Ph_2S). We were pleased to find that with trifluoroacetic acid (TFA) as the solvent, this reaction provided 26% yield of the desired product after 24 h at 100 ºC (Table 5.1, entry 1). We next examined the reaction in a variety of alternative solvents using 5 equivalents of TFA as an additive. These studies revealed that 1,4-dioxane was the optimal cosolvent (entries 2-5). In dioxane, the reaction proceeded efficiently in the presence of 5 equivalents of either TFA or NaTFA (entries 5 and 6, respectively); however, overall the yields were more reproducible using TFA. Notably, replacing TFA with NaOAc or HOAc resulted in reduced yields (entries 7 and 8). Further optimization of the phenylation reaction showed that the best yields were obtained with 8

equivalents of TFA for 15 h at 110 ºC to provide Ph_2S in 77% yield (entry 9). Finally, because copper has been shown to catalyze reactions between diaryliodonium salts and thiols,[6e] several Cu(I) and Cu(II) salts were tested under our optimal conditions to determine if the reaction could be significantly improved

Table 5.1. Optimizing Thioanisole Phenylation[a]



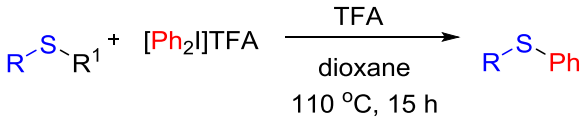
entry	solvent	additive (equiv)	yield (%)[e]
1	TFA	none	26
2	toluene	TFA (5)	36
3	acetic acid	TFA (5)	49
4	DMF	TFA (5)	59
5	1,4-dioxane	TFA (5)	65
6	1,4-dioxane	NaTFA (5)	55
7	1,4-dioxane	NaOAc (5)	3
8	1,4-dioxane	AcOH (5)	13
9	1,4-dioxane	TFA (8)[b]	77
10	1,4-dioxane	TFA (8), [Cu] (0.1)[c]	65-78
11[d]	1,4-dioxane	TFA (8)	83

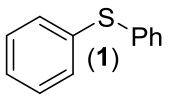
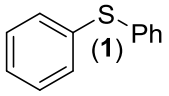
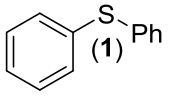
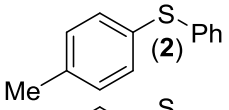
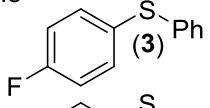
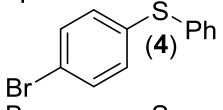
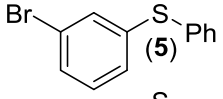
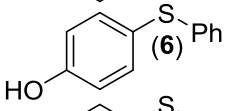
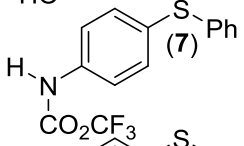
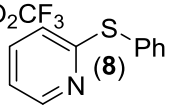
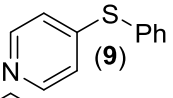
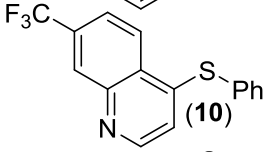
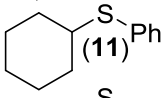
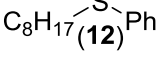
[a]1 equiv (0.093 mmol) of Ph_2ITFA, 1 equiv (0.093 mmol) of thioanisole, 5 equiv (0.47 mmol) of additive, 0.31 M in solvent at 100 ºC for 24 h. [b]8 equiv TFA (0.74 mmol) at 110 ºC for 15 h. [c][Cu] = $Cu(OAc)_2$, $Cu(OTf)_2$, Cu(II) acetylacetonate, $CuCl_2$, CuCN, CuCl. [d]MW conditions: 1.5 h, 120 ºC, 140 W. [e]Yields determined by GC using a hexadecane internal standard.

in the presence of substoichiometric copper additives. As shown in entry 10, adding 0.1 equivalent of copper had minimal impact on the overall reaction yield. Rates in the presence of copper were also similar to the copper-free reaction. The reaction time for this transformation could be reduced from 15 h to 1.5 h by using a microwave reactor (entry 11).

As shown in Table 5.2, a variety of thiols and thioanisole derivatives are effective substrates for this transformation. With alkyl aryl sulfides, the C_{sp3}–S bond is cleaved exclusively, resulting in diarylsulfide products (entries 2 and 3). Thioanisoles bearing both electron rich and electron deficient aryl groups showed good reactivity (entries 4-7). Bromide, OH, and NH_2 substituents were tolerated on the thioanisole moiety. Importantly, in the latter two cases, no N- or O-arylation products were detected. However, the aniline functionality underwent trifluoroacetylation under the reaction conditions. Pyridine and quinoline-containing thiols could also be converted to the analogous heterocyclic thioethers using this method (entries 10-12). These types of nitrogen heterocycles are often incompatible with transition-metal catalyzed C–S coupling reactions because of their strong coordinating abilities.

Table 5.2. Scope of Sulfides and Thioethers[a]

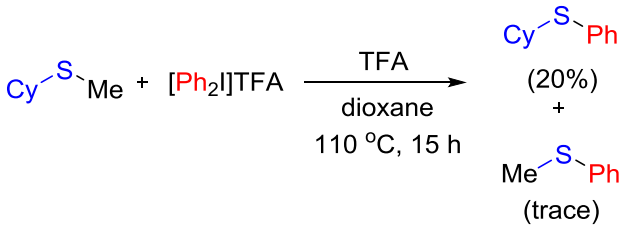


entry	R	R^1	product	yield[b](%)
1	Ph	H	 (**1**)	83
2	Ph	Me	 (**1**)	77
3	Ph	Bu	 (**1**)	79
4	4-MeC_6H_4	Me	 (**2**)	82
5	4-FC_6H_4	Me	 (**3**)	77
6	4-BrC_6H_4	Me	 (**4**)	57
7	3-BrC_6H_4	Me	 (**5**)	54
8	4-HOC_6H_4	Me	 (**6**)	90
9	4-$H_2NC_6H_4$	Me	 (**7**)	38
10	2-C_5H_4N	H	 (**8**)	56
11	4-C_5H_4N	H	 (**9**)	49
12	7-$CF_3C_9H_5N$	H	 (**10**)	69
13	Cy	H	 (**11**)	56
14	Oct	H	 (**12**)	64

[a]1 equiv (0.5 mmol) Ph_2ITFA, 1 equiv (0.5 mmol) thiol or thioether, 8 equiv (4.0 mmol) of TFA, 0.31 M in 1,4-dioxane at 110 ^oC for 15 h. [b]Isolated yields. All results are an average of two runs.

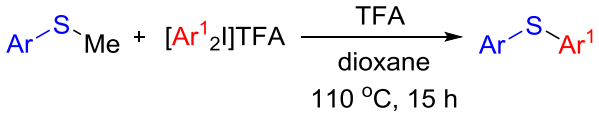
Finally, primary and secondary alkyl thiols are also viable substrates, providing alkyl aryl sulfide products in moderate yields (entries 13 and 14). In contrast, when unsymmetrical primary dialkyl sulfides ($C_{sp3(primary)}$-S-$C_{sp3(primary)}$) were used as starting materials, mixtures of the two possible alkyl aryl products were obtained. In the case of mixed secondary and primary dialkyl sulfides ($C_{sp3(primary)}$-S-$C_{sp3(secondary)}$), there was a preference for forming the secondary alkyl aryl sulfide product. However, again these transformations provided lower yields (Scheme 5.2).

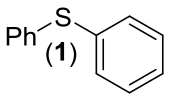
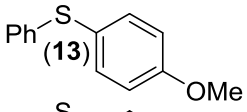
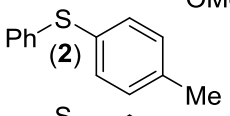
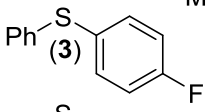
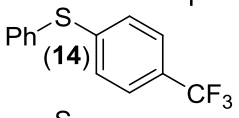
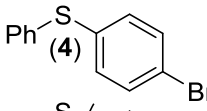
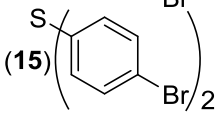
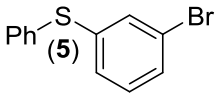
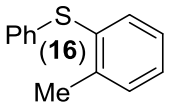
Scheme 5.2. Example of Mixed Alkyl Sulfide in Reaction



The scope of this transformation was next assessed using a series of different hypervalent iodine coupling partners. A series of different Ar_2ITFA reagents were prepared from the corresponding aryl iodide and aryl boronic acid, using a synthesis by Olofsson and coworkers[8] followed by anion exchange.[9] As summarized in Table 5.3, diaryliodonium salts bearing both electron withdrawing and donating groups participate in the thioanisole arylation (entries 2-6). This reaction also tolerates bromine-substituted diaryliodonium salts (entries 6-8). For example, bis(4-bromophenyl) sulfide **15**, which represents a useful precursor to

Table 5.3. Scope of Diaryliodonium Salts[a]



entry	Ar	Ar^1	product	yield[b](%)
1	Ph	Ph		77
2	Ph	4-$MeOC_6H_4$		37
3	Ph	4-MeC_6H_4		85
4	Ph	4-FC_6H_4		78
5	Ph	4-$CF_3C_6H_4$		57
6	Ph	4-BrC_6H_4		70
7	4-BrC_6H_4	4-BrC_6H_4		58
8	Ph	3-BrC_6H_4		55
9	Ph	2-MeC_6H_4		17[c]

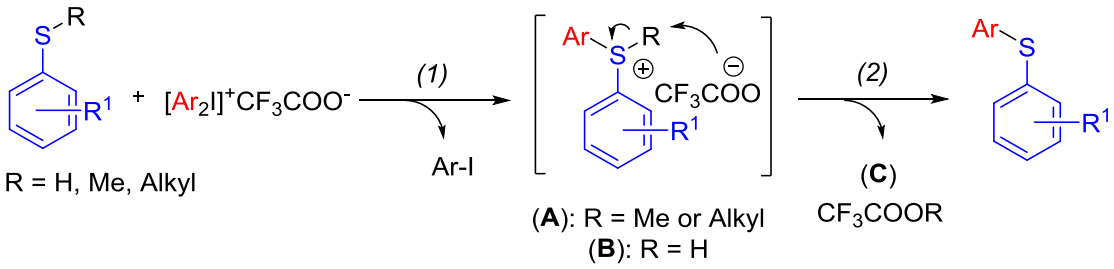
[a]1 equiv (0.5 mmol) Ar^1_2ITFA, 1 equiv (0.5 mmol) thioether, 8 equiv (4.0 mmol) of TFA, 0.31 M in 1,4-dioxane at 110 °C for 15 h. [b]Isolated yields. [c]Yields determined by GC using a hexadecane internal standard. All results are an average of two runs.

photoacid generators, was obtained in high yield through the coupling of 4-bromothioanisole with bis(4-bromophenyl)iodonium trifluoroacetate (entry 7). Finally, this reaction proceeds well using diaryliodonium salts with *meta*-

substitution (entry 8). In contrast, reactions with *ortho*-substituted diaryliodonium salts provided significantly lower yields (entry 9).

We propose that this reaction proceeds via the mechanism proposed in Scheme 5.3. This sequence involves: (1) initial thioether/thiol oxidation with Ar_2ITFA to generate sulfonium salt **A** or **B** followed by (2) nucleophilic substitution with a trifluoroacetate anion to liberate the aryl sulfide product and alkyl ester **C**. Importantly, there is literature precedent supporting the viability of both of these steps. For example, it has been shown that diaryliodonium salts can react with substituted sulfides to produce sulfonium salts, albeit in the presence of a copper catalyst.[6e,10] Furthermore, Takeuchi and coworkers have hypothesized that in a related reaction, a putative amino-sulfonium salt intermediate can undergo nucleophilic substitution with the conjugate base of a strong acid.[11]

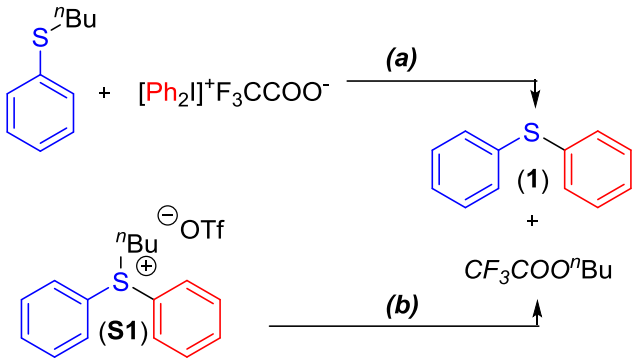
Scheme 5.3. Proposed Mechanism for Thioether Arylation



To test our mechanistic hypothesis, we prepared *n*-butyl phenyl sulfide[12] and after subjecting it to our reaction conditions, observed *n*-butyl trifluoroacetate and diphenyl sulfide by GCMS (Scheme 5.4a). Under these reaction conditions,

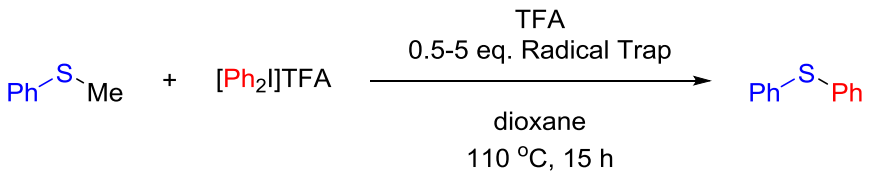
the putative sulfonium intermediate **S1** (analogous to **A**, where R^1 = H, Ar = Ph and R = butyl, in Scheme 5.3) was not detected *in situ* by HRMS thus suggesting that it is short lived and that sulfide oxidation with Ar_2ITFA is likely rate-limiting. We also generated the sulfonium salt, butyl diphenyl sulfonium triflate **S1** (Ph_2SBuOTf)[21] independently and subjected it to our reaction conditions. This sulfonium salt underwent rapid conversion to **1** and F_3CCOO-^{n}Bu (in ≤ 30 min) under our reaction conditions (Scheme 5.4b).[13,14]

Scheme 5.4. Reaction Mechanism Probes



A final set of experiments were done to exclude the possibility of radicals during this reaction because diaryliodonium salts are known to participate in and/or initiate single electron processes.[15] The optimized conditions were performed in the presence of various radical traps and the reactivity was monitored (Table 5.4). The radical traps had minimal effect on reactivity, thus providing further evidence to support our mechanistic proposal and exclude the possibility of a radical mechanism.

Table 5.4. Effect of Radical Traps on Reactivity[a]



entry	radical trap[c]	equiv	yield (%)[b]
1	None	0	77
2	TEMPO	0.5	52
3	TEMPO	1	57
4	TEMPO	5	31
5	BHT	0.5	79
6	BHT	1	75
7	BHT	5	79

[a]1 equiv (0.093 mmol) of Ph_2ITFA, 1 equiv (0.093 mmol) of thioanisole, 8 equiv (0.74 mmol) of CF_3COOH, 0.31 M in solvent at 110 °C for 15 h. [b]Yields determined by GC using hexadecane internal standard. [c]TEMPO = 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl; BHT = butylhydroxytoluene

5.3 Conclusion

In conclusion, this chapter demonstrates thiols and thioether arylation using diaryliodonium salts under acidic conditions and provides evidence for a mechanism that proceeds through a sulfonium salt intermediate. This reaction represents a versatile and robust route to aryl thioether products and is complementary to existing procedures.

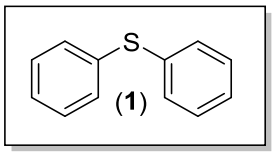
5.4 Experimental

General Procedures: NMR spectra were recorded on a Varian vnmrs 700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C), a Varian vnmrs 500 (500.10 MHz for ^{1}H; 125.75 MHz for ^{13}C, 470.56 MHz for ^{19}F), a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C), or a Varian MR400 (400.52 MHz for ^{1}H; 100.71 for ^{13}C, 376.87 MHz for ^{19}F) NMR spectrometer with the residual solvent peak ($CDCl_3$: ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm) as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as an external reference at 0.00 ppm. Multiplicities are reported as follows: br s (broad singlet), app (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants *J* are reported in Hz. Flash chromatography was performed either on EM Science silica gel 60 (0.040-0.063 mm particle size, 230-400 mesh) or on a Biotage Isolera Flash Purification System using normal-phase 50 mm particle size silica. Thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F_{254}.High resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Gas chromatography was carried out on a Shimadzu 17A using a Restek Rtx®-5 (Crossbond 5% diphenyl – 95% dimethyl polysiloxane; 15 m, 0.25 mm ID, 0.25 µm df) column. GC calibrated yields and selectivities are reported relative to hexadecane as an internal standard.

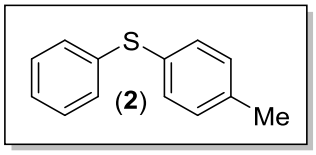
Materials and Methods: All reactions were conducted on the bench top without precautions to exclude air or moisture. All reagents were purchased and used without further purification. Sulfonium salt **S1** was synthesized according to reference 6e. Symmetric iodonium salts were synthesized according to references 8 and 9. Thiol and thioether substrates were obtained from commercial sources and were used as received except n-butyl phenyl sulfide which was prepared from thiophenol and butyl bromide in the presence of n-butyl lithium.[16]

5.5 Synthesis and Characterization

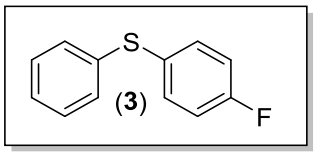
General Procedure for Arylation: To a 20 mL scintillation vial containing Ar_2ITFA (1 equiv, 0.5 mmol) was added a thiol or thioether (1 equiv, 0.5 mmol) and 1,4-dioxane (1.6 mL, 0.31 M). After mixing, trifluoroacetic acid (8 equiv, 4 mmol) was added. The vial was sealed with a Teflon-lined cap, and the reaction was placed into one of the wells of an aluminum block preheated to 110 ºC. After stirring for 15 h, the reaction mixture was cooled to room temperature and water (10 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and the combined organic layers were washed with water (5 mL). The organic layer was then dried over sodium sulfate and concentrated *in vacuo*. The crude reaction mixture was purified by 1) flash column chromatography on silica using hexanes or hexanes/ethyl acetate or 2) vacuum short path distillation followed by passage through a silica plug with ether. Yields reported in the Tables 1-4 represent an average of two runs.



Diphenyl Sulfide (**1**). The crude product was purified by distillation (bp = 296 ºC at 760 torr). Brown oil. From thiophenol and Ph_2ITFA (table 2, entry 1; 77 mg, 83% yield); from thioanisole and Ph_2ITFA (table 2, entry 2 and table 3, entry 1; 72 mg, 77% yield); from butyl phenyl sulfide and Ph_2ITFA (table 2, entry 3; 74 mg, 79% yield). HRMS EI [M^+] calcd for $C_{12}H_{10}S$, 186.0503; found, 186.0500. ^1H and ^{13}C NMR spectra matched those reported in the literature.[17]

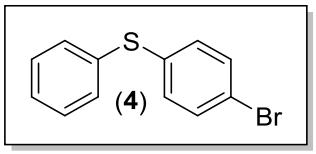


Phenyl p-Tolyl Sulfide (**2**). The crude product was purified by distillation (bp = 308 ºC at 760 torr). Brown oil. From methyl *p*-tolyl sulfide and Ph_2ITFA (table 2, entry 4; 82 mg, 82% yield); from thioanisole and $(4\text{-}MeC_6H_4)_2ITFA$ (table 3, entry 3; 85 mg, 85% yield). HRMS EI [M^+] calcd for $C_{13}H_{12}S$, 200.0600; found, 200.0605. ^1H and ^{13}C NMR data matched those reported in the literature.[17]



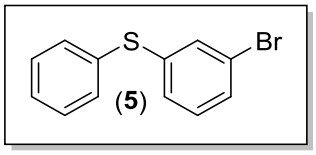
4-Fluorophenyl Phenyl Sulfide (**3**). The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.48 in

hexanes). Colorless oil. From 4-fluorothioanisole and Ph_2ITFA (table 2, entry 5; 79 mg, 77% yield); from thioanisole and $(4\text{-}FC_6H_4)_2ITFA$ (table 3, entry 4; 80 mg, 78% yield). ^{19}F NMR (471 MHz, $CDCl_3$): δ –113.1. HRMS EI [M^+] calcd for $C_{12}H_9FS$, 204.0409; found, 204.0405. ^1H and ^{13}C NMR spectra matched those reported in the literature.[17]



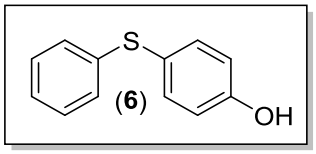
(**4**)

4-Bromophenyl Phenyl Sulfide (**4**). The crude product was purified by distillation (bp = 355 ºC at 760 torr). Brown oil. From 4-bromothioanisole and Ph_2ITFA (table 2, entry 6; 76 mg, 57% yield); from thioanisole and $(4\text{-}BrC_6H_4)_2ITFA$ (table 3, entry 6; 94 mg, 70% yield). HRMS EI [M^+] calcd for $C_{12}H_9BrS$, 263.9608; found, 263.9611. ^1H and ^{13}C NMR spectra matched those reported in the literature.[17]

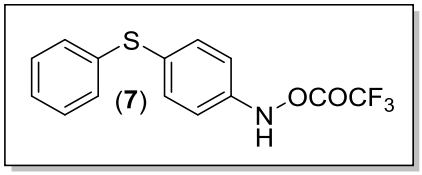


(**5**)

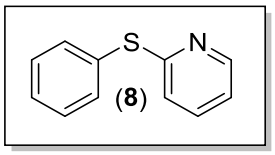
3-Bromophenyl Phenyl Sulfide (**5**). The crude product was purified by distillation (bp = 352 ºC at 760 torr). Brown oil. From 3-bromothioanisole and Ph_2ITFA (table 2, entry 7; 71 mg, 54% yield); from thioanisole and $(3\text{-}BrC_6H_4)_2ITFA$ (table 3, entry 8; 73 mg, 55% yield). HRMS EI [M^+] calcd for $C_{12}H_9BrS$, 263.9608; found, 263.9611. ^1H and ^{13}C NMR spectra matched those reported in the literature.[18]



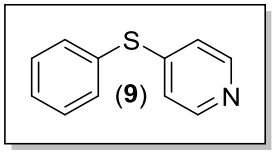
4-Hydroxyphenyl Phenyl Sulfide (**6**). The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.55 in 25% EtOAc/75% hexanes). Brown oil (91 mg, 90% yield). HRMS EI [M^+] calcd for $C_{12}H_{10}OS$, 202.0452; found, 202.0449. ^1H and ^{13}C NMR spectra matched those reported in the literature.[19]



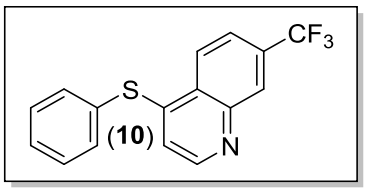
2,2,2-Trifluoro-N-(4-(Phenylthio)Phenyl)Acetamide (**7**). The crude product was purified by flash column chromatography (R_f = 0.23 in 10% EtOAc/90% hexanes). Colorless oil (57 mg, 38% yield). ^1H NMR (700 MHz, $CDCl_3$): δ 9.51 (1H, br s), 7.50-7.51 (m, 2H), 7.25-7.35 (multiple peaks, 7H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 154.7 (q, $J_{C\text{-}F}$ = 37 Hz), 135.0, 134.2, 133.9, 131.6 (q, $J_{C\text{-}F}$ = 26 Hz), 129.3, 127.6, 127.5, 121.1, 115.6 (q, $J_{C\text{-}F}$ = 290 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ –75.7. HRMS electrospray (m/z): [M+H] calcd for $C_{14}H_{11}F_3NOS$, 298.0508; found, 298.0503.



Phenyl 2-Pyridyl Sulfide (**8**). Before extraction with diethyl ether, 2M NaOH was added until the solution was basic. The crude product was purified by distillation (bp = 321 ºC at 760 torr). Brown oil (52 mg, 56% yield). HRMS electrospray (m/z): [M+H] calcd for $C_{11}H_{10}NS$, 188.0528; found, 188.0527. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[6h]

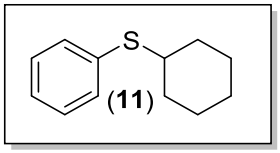


Phenyl 4-Pyridyl Sulfide (**9**). Before extraction with diethyl ether, 2M NaOH was added until the solution was basic. The crude product was purified by column chromatography on an Isolera Flash Purification System (R_f = 0.52 in 50% EtOAc/50% hexanes). Colorless oil (46 mg, 49% yield). HRMS electrospray (m/z): [M+H] calcd for $C_{11}H_{10}NS$, 188.0528; found, 188.0524. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[20]

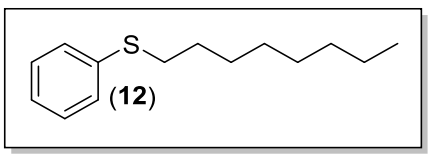


3-(Phenylthio)-7-(Trifluoromethyl)Quinoline (**10**). Before extraction with diethyl ether, 2M NaOH was added until the solution was basic. The crude product was

purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.33 in 25% EtOAc/75% hexanes). Yellowish solid (103 mg, 69% yield, mp = 61-63 ºC). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 6.3 Hz, 1H), 8.38 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.76 (m, 1H), 7.60 (m, 2H), 7.50-7.52 (multiple peaks, 3H), 6.83 (d, *J* = 6.3 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 149.2, 146.6, 135.3, 131.4 (q, $J_{C\text{-}F}$ = 33 Hz), 130.1, 130.0, 128.6, 127.7 (q, $J_{C\text{-}F}$ = 4 Hz), 127.3, 124.8, 123.7 (q, $J_{C\text{-}F}$ = 273 Hz), 121.90 (q, $J_{C\text{-}F}$ = 3 Hz), 119.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ –62.74. HRMS EI [M^+] calcd for $C_{16}H_{10}F_3NS$, 305.0486; found, 305.0485.

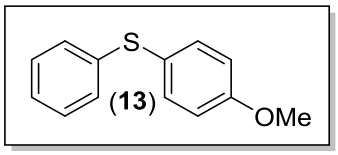


Cyclohexyl Phenyl Sulfide (**11**). The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.52 in hexanes). Colorless oil (54 mg, 56% yield). HRMS EI [M^+] calcd for $C_{12}H_{16}S$, 192.0973; found, 192.0971. ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[17]

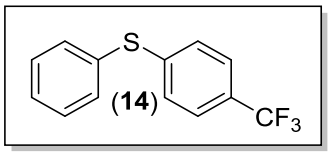


Octyl Phenyl Sulfide (**12**). The crude product was purified by flash column chromatography (R_f = 0.43 in hexanes). Colorless oil (71 mg, 64% yield). HRMS

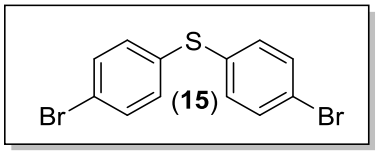
EI [M^+] calcd for $C_{14}H_{22}S$, 222.1442; found, 222.1439. ^1H and ^{13}C NMR spectra matched those reported in the literature.[6h]



4-Methoxyphenyl Phenyl Sulfide (**13**). The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.50 in 10% EtOAc/90% hexanes). Colorless oil (40 mg, 37% yield). HRMS EI [M^+] calcd for $C_{13}H_{12}OS$, 216.0609; found, 216.0607. ^1H and ^{13}C NMR spectra matched those reported in the literature.[17]



Phenyl 4-Trifluoromethylphenyl Sulfide (**14**). The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.53 in hexanes). Colorless oil (72 mg, 57% yield). ^{19}F NMR (377 MHz, $CDCl_3$): δ –62.3. HRMS EI [M^+] calcd for $C_{13}H_9F_3S$, 254.0371; found, 254.0383. ^1H and ^{13}C NMR spectra matched those reported in the literature.[21]



Bis(4-Bromophenyl) Sulfide (**15**). The crude product was purified by distillation (bp = 411 ºC at 760 torr). Clear oil (100 mg, 58% yield). HRMS EI [M^+] calcd for $C_{12}H_8Br_2S$, 341.8713; found, 341.8721. ^1H and ^{13}C NMR spectra matched those reported in the literature.[22]

5.6 References

[1] Adapted with permission from Wagner, A. M.; Sanford, M. S. Acid-Mediated Transition-Metal Free Synthesis of Aryl Sulfides from Thiols or Thioethers and Diaryliodonium Salts. J*. Org. Chem.* **2014**, *79*, 2263-2267. Copyright © 2014, American Chemical Society.

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Chapter 6. Conclusions

The selective activation and coupling of the C–H bonds of simple arenes would provide an efficient way to prepare highly sought after aryl-aryl linkages. In this dissertation, palladium- and platinum-catalyzed C–H arylation reactions were explored to achieve this goal. Specifically, methods of C–H arylation were developed and then studied mechanistically to provide insight into the origin of selectivity. In depth studies of systems that provide contrasting selectivities, like those described above, contribute to an overall understanding of chemical reactivity and represent a step toward the ultimate goal of predicting the outcome of reactions. The over-arching goal of these projects is to understand the factors that contribute to catalyst-controlled site-selectivity in order to eventually develop a suite of synthetically useful reactions that could be used to functionalize any C–H bond in a molecule with high yield and selectivity.

Additionally, a transformation to provide easy and green access to aryl sulfides, which are useful for pharmaceutical and materials applications, was discovered and optimized.

6.1 Studying Metal-Catalyzed C–H Arylation Reactions

In the first part of this dissertation, a series of site-selective C–H arylation reactions, which were catalyzed or mediated by palladium or platinum, were explored.

In chapter 2, the substrate-controlled coupling of 1,3- or 1,2,3-substituted pyrroles with diaryliodonium salts was presented. This method can be used to arylate the unactivated 3- and/or 4-position of substituted pyrroles with moderate to good selectivity for the less sterically hindered position depending on the substitution of the pyrrole substrate. Excitingly, this method can also be used to access 1,2,3,4,5-pentasubstituted pyrroles. Updates on methods for the C–H arylation of pyrroles and pyrroles derivatives since the publication of this paper were also presented. The general interest in this type of arylation since the publication of this method in 2010, including the arylation of interesting porphyrin pyrrole derivatives, demonstrates the utility and impact of this type of methodology.

The majority of this dissertation involves catalyst-controlled arylation reactions. Chapter 3 presented an in depth computational and experimental study of the oxidative cross-coupling of benzo[*h*]quinoline and 1,3-dimethoxybenzene. The insights gleaned from the mechanistic studies were then applied to a catalytic variant, the C–H arylation of 2-(2-bromophenyl)pyridine and 1,3-dimethoxybenzene. The site-selectivity in the catalytic reaction was found to have the same selectivity determining factors as the stoichiometric reaction providing evidence that they go through similar mechanisms.

In chapter 4, the C–H arylation of a variety of simple arenes using a platinum catalyst was discussed. While palladium was found to be unreactive for the coupling of simple arenes (other than naphthalene) with diaryliodonium salts, platinum could perform the coupling of electron rich and electron poor arenes

with moderate to good yields and selectivities. Furthermore, palladium and platinum-catalysts were found to give complementary selectivity for the arylation of naphthalene. Palladium provided good yield and selectivity for the kinetic product, 1-arylnaphthalene, and platinum provided the complementary 2-arylnaphthalene, the thermodynamic product, as the major product. Through mechanistic studies, evidence that this selectivity change is a result of a change in rate-determining-step when either palladium (oxidative addition) or platinum (reductive elimination) was used as the catalyst was also presented.

While platinum has previously been found to activate C–H bonds in numerous stoichiometric systems[1] and is the catalyst used in the famous C_{sp3}–H selective Shilov oxidation system,[2] the method presented in chapter 4 of this dissertation represents a rare example of a C–H functionalization reaction that uses platinum as a *catalyst*. Using this transformation as a framework, one could potentially develop similar platinum-catalyzed C_{sp2}–H and C_{sp3}–H functionalization reactions. It would also be interesting to examine the use of ligands[3,4] in these platinum-catalyzed systems in order to study the effect of ligation on the reactivity, selectivity, and stability of platinum-catalysts.

6.2 Thioarylation

In the final chapter of this dissertation, the metal-free coupling of diaryliodonium salts and thiols or alkyl thioethers was presented. This green method to access the aryl sulfide motif provides complementary reaction conditions and substrate scope to known methods and provides access to numerous aryl sulfides with a diverse array of functional groups in moderate to

good yields. Additionally, this method presents the *metal-free* oxidation of thioethers to sulfonium salts using diaryliodonium salts which has previously only been proposed in the presence of copper catalysts. This mechanism may have implications in the further advancement sulfide chemistry.

6.3. References

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