Site Selectivity in Palladium-Catalyzed Oxidative Functionalization Reactions

by

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To Dr. Sanford, Lopa
and my grandmother

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Abstract

Carbon-hydrogen bonds are ubiquitous in nature. The development of transformations for selective and functional group tolerant methods for the direct functionalization of C–H bonds is an important challenge in organic chemistry. Recent work in our group has shown that $Pd(OAc)_2$ in conjunction with $PhI(OAc)_2$ serves as an efficient catalyst for ligand-directed palladium-catalyzed C–H activation/acetoxylation reactions. These reactions are believed to proceed via a $Pd^{II/IV}$ catalytic cycle.

In order to expand the scope of these oxygenation reactions we sought to explore whether high and predictable levels of site selectivity could be achieved for the functionalization of meta-substituted arenes. These substrates consist of two different C–H bonds that could undergo chelate-directed functionalization. In general, our results show that the palladium-catalyzed C–H activation/acetoxylation of *meta*-substituted arenes occurs preferentially at the less congested position.

Additionally, we desired to install other functionalities such as halogen and aryl groups in the final products using electrophilic halogenating and arylating reagents as terminal oxidants. A detailed exploration of palladium-catalyzed chelate-directed chlorination, bromination, and iodination of arenes using *N*-halosuccinimides as terminal oxidants has been conducted. These halogenation reactions often lead to products complementary to those obtained by traditional electrophilic aromatic substitution reactions. Additionally, we have shown that diaryl iodonium salts can be used as oxidants for site selective C–H activation/arylation reactions in the presence of $Pd(OAc)_2$ as the catalyst. Preliminary results suggest that the mechanism of this reaction involves a Pd^{II}/Pd^{IV} catalytic cycle, which is of interest because nearly all palladium mediated C–C bond forming reactions proceed via a Pd^{0}/Pd^{II} cycle.

Finally, we have applied the insights gained from the aforementioned oxidation reactions towards the functionalization of Pd^{II} intermediates generated through organometallic transformations different from C-H activation. In this regard, a methodology for the oxidative halogenation of Pd^{II}-alkyl complexes generated via olefin insertion into Pd-aryl bonds to form 1,2-arylhalogenated products has been developed. Interestingly, the isomeric 1,1-arylhalogenated products could also be obtained in high selectivity just by tuning the reaction conditions.

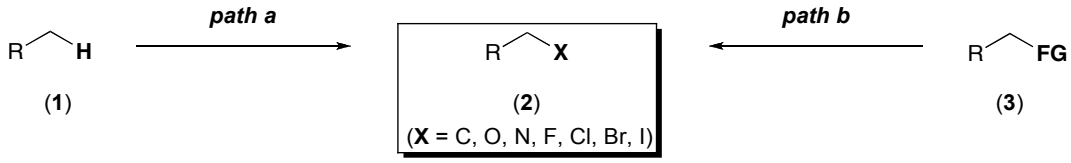
In all, this thesis describes a variety of site selective palladium-catalyzed oxidative functionalization reactions. These include palladium-catalyzed chelate-directed C–H activation/C–X (X = C, O, Cl, Br, I) bond formation and the palladium-catalyzed difunctionalization of olefins. The $Pd^{II/IV}$ catalytic cycle proposed for many of these transformations has allowed for bond formations (e.g., carbon-halogen) that previously proved challenging via traditional $Pd^{0/II}$ catalytic cycles. The generality, high selectivity, and functional group tolerance of these reactions make them attractive for the functionalization, late stage derivatization, and the synthesis of complex biologically active molecules.

Chapter 1

Introduction

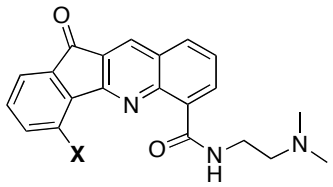
The development of site selective, chemoselective and functional group tolerant methods for the direct conversion of C–H bonds to more versatile C–X (X = O, C, N, F, Cl, Br, I) bonds remains an important challenge in contemporary chemistry (Scheme 1, path a). [1-7] Such an approach would preclude the need for pre-functionalized starting materials (**3**) (Scheme 1, path b) that are often not readily accessible for the assembly of complex molecules.

Scheme 1: Strategies for Constructing Diverse C-X Bonds



New methodologies for the direct functionalization of C–H bonds have the potential to dramatically change retrosynthetic strategies for the synthesis of complex molecules. Additionally, they might expedite the process of structure activity relationship (SAR, studies of change in activity of a drug based on small structural modifications) in the pharmaceutical industry by allowing for late stage derivatization of biologically active molecules. For example, indeno-quinoline-6-carboxamide (**4**) is a cytotoxic reagent whose activity (IC_{50}) is highly dependent on the **X** substituent (Scheme 2). [8,9]

Scheme 2: Structure Activity Relationship for **4**

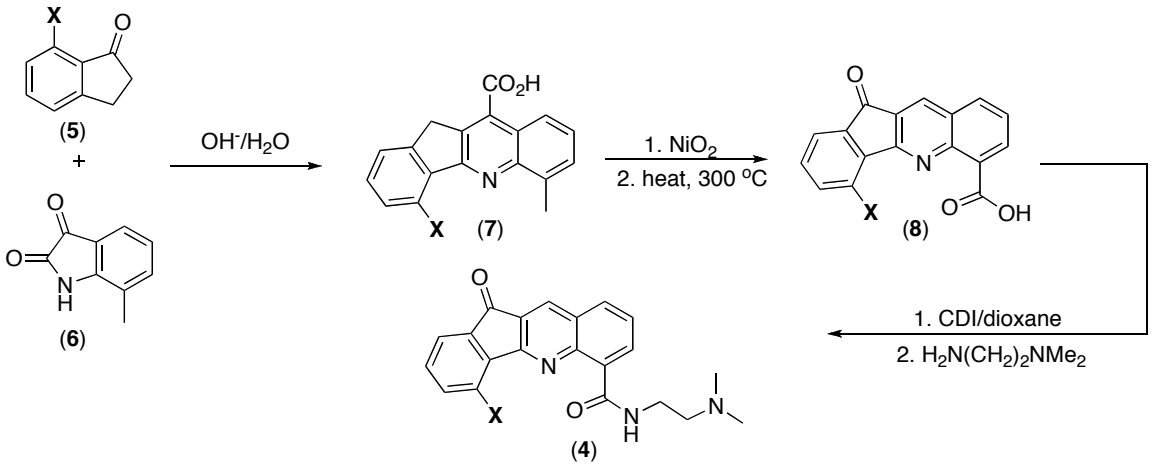


(**4**)

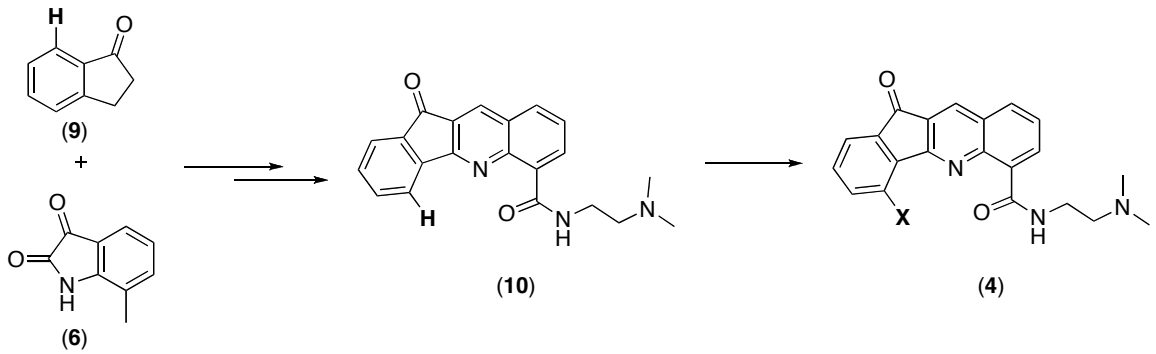
Entry	X	IC_{50}
1	**H**	**91**
2	**OMe**	**23**
3	**Me**	**15**
4	**Cl**	**8.2**

Current methods of synthesizing analogues of **4** with different **X** groups require at least four steps starting from functionalized reactants **5** and **6** (Scheme 3). [8,9] The proposed direct C–H bond functionalization strategy (Scheme 1, pathway a) could significantly shorten the synthesis by allowing the installation of the **X** groups at an advanced intermediate **10** (Scheme 4). Importantly, it would eliminate the need to start with the **X** functionality in the reactant **5**.

Scheme 3: Current Method for Synthesizing Derivatives of **4**

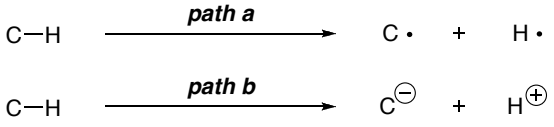


Scheme 4: Proposed Strategy for Synthesizing Derivatives of **4**



While an attractive strategy, there are several challenges that need to be considered to develop methodologies for the direct functionalization of C–H bonds. First, there is a significant kinetic barrier associated with the homolytic or heterolytic cleavage of C–H bonds (**Challenge 1**). [1,2,5,10] The splitting of C–H bonds can occur in two different ways to generate radicals, or carbanions (Scheme 5). The difficulty of splitting C–H bonds homolytically (Scheme 5, path a) can be thought of in terms of their large bond dissociation energies (90-110 kcal mol^{-1}). The unfavorable heterolytic cleavage (Scheme 5, path b) of C–H bonds is exemplified by the high pK_a values of the conjugate acids of unstabilized carbanions (pK_a ~ 40-50). These physical properties of C–H bonds can be attributed to (i) their nonpolar nature and (ii) their low energy HOMOs and high energy LUMOs. Both of these characteristics render the C–H bond inert towards reactions with most common electrophiles or nucleophiles. Hence, the traditional methods of functionalizing C–H bonds have relied on the use of highly reactive species such as super acids, carbenes, nitrenes, and free radicals. However, the low regio- and chemoselectivities of these transformations has limited their widespread applicability.[5]

Scheme 5: Homolytic and Heterolytic Cleavage of C–H Bonds

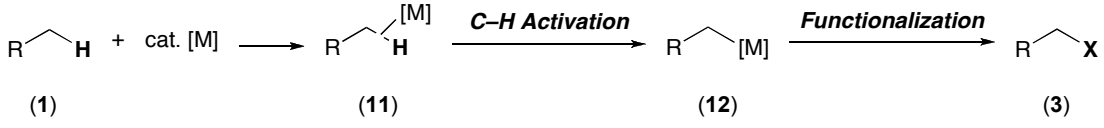


The second challenge entails achieving site selectivity in functionalization of structurally complex molecules that bear many different C–H bonds of comparable strengths and reactivity (**Challenge 2**). For example, most organic molecules contain both aromatic and alkyl C–H bonds, both of which have very similar bond dissociation energies and pK_a's. Hence, the selective functionalization of one over the other is often difficult.

Finally, and perhaps the most important challenge in terms of synthetic utility, is the ability to install diverse functional groups in the final product (**Challenge 3**). As discussed above, one potential application of direct C–H bond functionalization is expediting SAR investigations of pharmaceuticals. However, for this to be realized, a method must be developed that has the ability to transform the C–H bond in advanced intermediates such as **10** (Scheme 4) to a variety of functionalities.

Challenge 1 can be addressed by the use of transition metals. The binding of a C–H bond to a transition metal leads to the formation of a σ complex **11** (Scheme 6).[11] This metal/C–H interaction leads to weakening of the C–H bond due to (i) donation of electron density from the metal dπ orbital to the σ* orbital of the C–H bond and (ii) delocalization of the electrons in the bonding orbital of the C–H bond onto the metal. This weakening of the C–H bond renders it more susceptible to cleavage with concomitant formation of a M–C bond (as in **12**, Scheme 6). The M–C bond thus generated is more reactive than the C–H bond and can subsequently be functionalized to afford the desired product **3**.

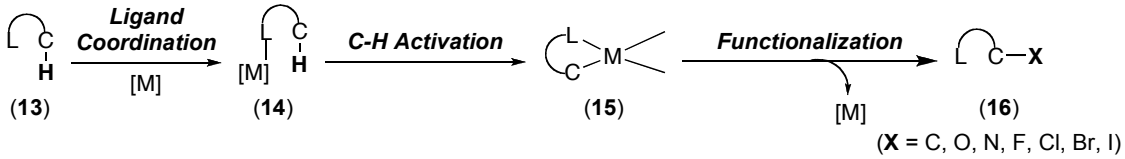
Scheme 6: Transition Metal Mediated C–H Bond Functionalization



In order to take advantage of transition metal assisted activation of C–H bonds to selectively functionalize one of the many C–H bonds present in molecules (**Challenge 2**), researchers have employed a chelate-directed strategy (Scheme 7). [12-19] This approach involves the use of substrates **13** bearing appropriate coordinating moieties (L). As shown in Scheme 7, the binding of the metal to the ligand (L) directs the metal to activate the

proximal C–H bond to afford the cyclometallated complex **15**. Subsequent functionalization of **15** would occur selectively at the carbon bonded to the metal. This leads to the site selective installation of the desired functional group X proximal to the ligand (as in **16**) with concomitant regeneration of the catalyst [M].

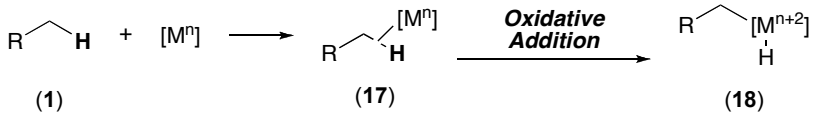
Scheme 7: Chelate Directed C–H Activation/Functionalization of C–H Bonds



Judicious choice of the transition metal catalyst is critical to achieve a viable catalytic cycle that can realize **Challenge 3**, namely diverse functionalization of C–H bonds. The key features of the desired catalytic cycle that are dictated by the metal of choice are (i) the metal must have the ability to undergo facile cyclometallation of **13**, (ii) the C–M bond in **15** must have the potential to be converted to diverse C–X bonds (**Challenge 3**), (iii) the metal species **14** that will undergo cyclometallation must be sufficiently stable towards oxidants (necessary for carbon-heteroatom bond formation since C–H to C–heteratom results in a net oxidation at the carbon atom) and (iv) the C–X bonds in the product (**16**) must be inert towards further activation by the metal catalyst.

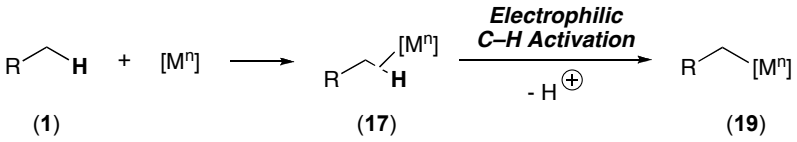
Several transition metals are known to effect cyclometallation of substrates **13**. Of these metals however, only a few are amenable to the functionalization reaction shown in Scheme 7 for many reasons. First, most metals (e.g., Ru^0, Rh^I, Ir^I) activate C–H bonds via an oxidative addition pathway, which results in an increase in oxidation state at the metal center upon cyclometallation (Scheme 8).[5] As such, this process often requires metals in low oxidation states that are generally unstable under the oxidizing conditions necessary for carbon-heteroatom bond formation. Additionally, oxidative addition into the C–X (X = Cl, Br, I) bonds in the product is very facile at most low valent metal centers, which could lead to undesired side reactions.

Scheme 8: C–H Activation via an Oxidative Addition Mechanism

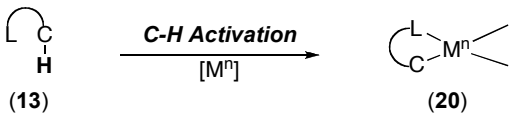


On the other hand, some high oxidation state metal complexes (e.g., Rh^{III} and Ir^{III}) undergo C–H activation by an electrophilic mechanism (with no change of oxidation state at the metal center) instead of oxidative addition (Scheme 9).[5] However, the resulting cyclometallated complexes **20** generated via ligand directed electrophilic C–H activation (Scheme 10) are usually resistant to further functionalization by either inner sphere or outer sphere oxidants (due to being coordinatively saturated and being stable toward ligand substitution).

Scheme 9: C–H Activation via an Electrophilic Mechanism



Scheme 10: Ligand-Directed Electrophilic C–H Activation

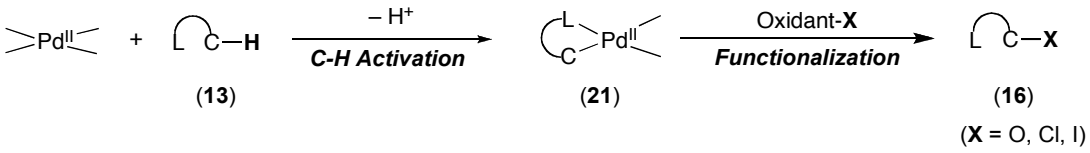


In this regard, group 10 metals in the +2 or +4 oxidation states (Pd^{II}, Pt^{II} and Pt^{IV}) are the most suitable for the development of the desired diverse C–H bond functionalization reactions (Scheme 7) for several reasons: (i) Pd^{II} and Pt^{IV} are less susceptible to oxidation (by two electron oxidants) prior to cyclometallation, (ii) C–M bonds in the cyclometallated complexes generated by Pd^{II}-, Pt^{II}- and Pt^{IV}-mediated C–H activation, can be transformed into a variety of C–X (X = O, Cl, I) bonds and (iii) C–X bonds in the functionalized products are resistant to further activation by the metal catalyst. Pd (price/mole of $PdCl_2$ = \$5188) is significantly less expensive than Pt

(price/mole of $PtCl_2$ = \$17074); hence, Pd^{II} catalysts have attracted enormous attention for the desired C–H bond functionalization reactions.

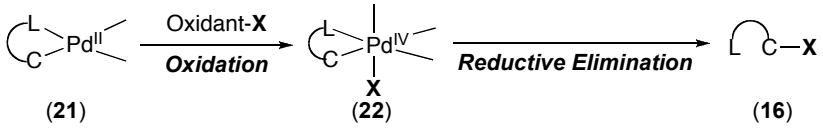
Indeed, over the past 40 years organic chemists have found that Pd^{II} complexes can undergo stoichiometric ligand-directed C–H activation to afford cyclopalladated complexes **21** (Scheme 11).[20] Furthermore, **21** is now known to undergo reactions with a variety of electrophilic oxidants, which transform the C–Pd bond (in **21**) into diverse C–X (X = O, Cl, I) bonds (Scheme 11). The overall two-step process depicted in Scheme 11 thus constitutes the desired site selective functionalization of a C–H bond adjacent to the ligand in the substrate (**13**), albeit with stoichiometric amounts of the metal.

Scheme 11: Stoichiometric Cyclopalladation/Oxidation Sequence



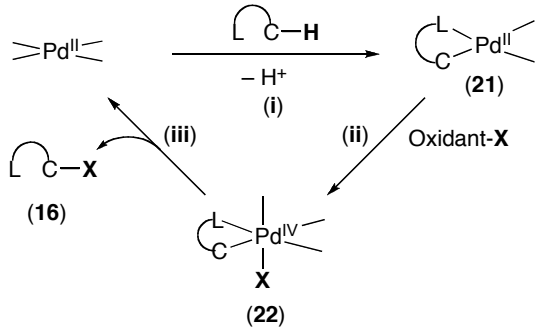
Importantly, the key product-forming step in these reactions is proposed to involve C–X bond-forming reductive elimination from a transient Pd^{IV} intermediate **22** (Scheme 12). The intermediacy of such Pd^{IV} species in these transformations is proposed to be critical in achieving bond constructions (e.g., C–H to C–Cl) that could not previously be realized.[20]

Scheme 12: Oxidation of Cyclopalladated Complexes via Pd^{IV} Intermediates



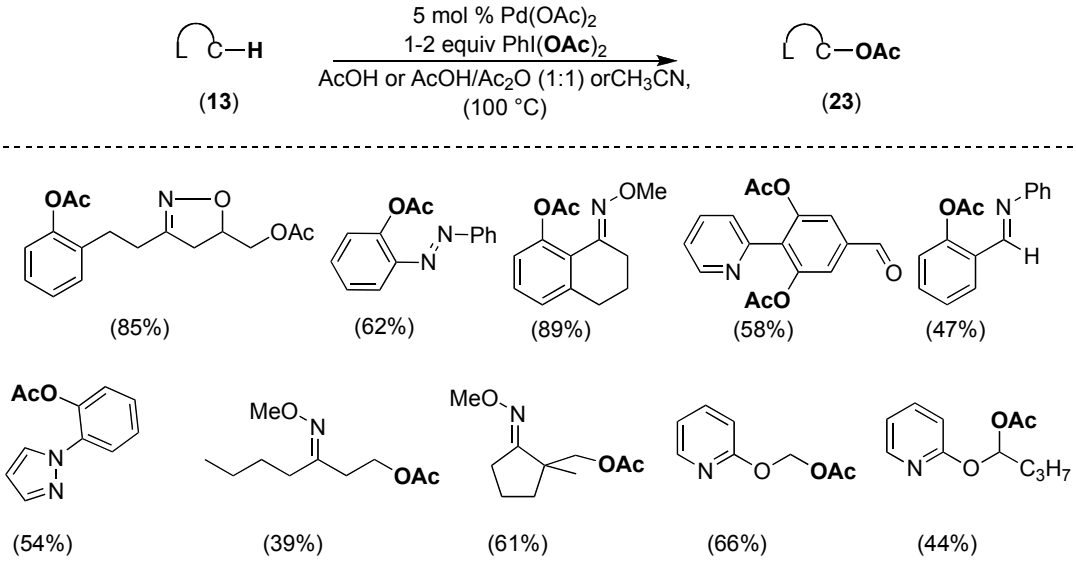
Our group sought to exploit this unique stoichiometric cyclopalladation/oxidation sequence via Pd^{IV} intermediates (Scheme 11) for the development of palladium-catalyzed (Scheme 13) functionalization of C–H bonds. In particular, we wanted to explore and harness the mechanisms and reactivity available to Pd^{IV} complexes like **22** for the discovery of novel C–H functionalization reactions.

Scheme 13: Proposed $Pd^{II/IV}$ Catalytic Cycle for C–H Bond Functionalization



In 2004, our group reported the palladium-catalyzed ligand directed acetoxylation of both sp^2 and sp^3 C–H bonds using $Pd(OAc)_2$ as the catalyst and $PhI(OAc)_2$ as the oxidant (Scheme 14).[21] Importantly, these reactions are believed to proceed via a $Pd^{II/IV}$ catalytic cycle (Scheme 13) and do not require the exclusion of air or moisture. The oxidant $PhI(OAc)_2$ is the source of the acetate in the final product **20**.

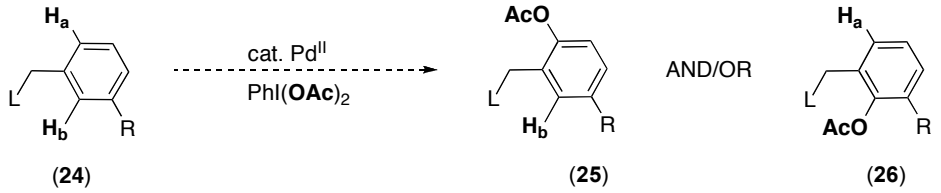
Scheme 14: Pd-Catalyzed C–H Activation/Acetoxylation



With these results in hand, we wanted to expand the scope of these oxygenation reactions. In this context, ***Chapter 2*** details our studies towards the acetoxylation of *meta*

substituted arenes of general structure **24** (Scheme 15). These substrates contain two different C–H bonds (C–H_a and C–H_b) that could undergo chelate-directed functionalization to afford **25** and **26**, respectively. Hence, we sought to explore whether high and predictable levels of site selectivity could be achieved for the functionalization of **24**.[22]

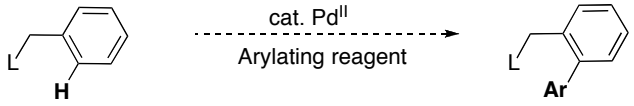
Scheme 15: Site Selectivity in Pd-Catalyzed Acetoxylation of *m*-Substituted Arenes



(**24**) (**25**) (**26**)

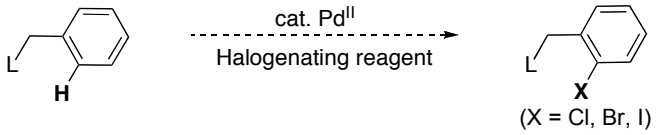
Additionally, we desired to install other functionalities such as halogen and aryl groups in the final products using electrophilic halogenating and arylating reagents as terminal oxidants. ***Chapters 3 and 4*** describe our efforts towards the development of Pd-catalyzed carbon-carbon and carbon-halogen bond-forming reactions, respectively (Schemes 16 and 17). Interestingly, the $Pd^{II/IV}$ reaction manifold for the C–C bond forming reactions allows for functional group tolerance and selectivities that are different from other widely used $Pd^{0/II}$-catalyzed cross coupling strategies (Scheme 16). [23] Furthermore, the halogenation reactions presented in ***Chapter 4*** lead to products complementary to those obtained by traditional electrophilic aromatic substitution reactions (Scheme 17).[24,25]

Scheme 16: $Pd^{II/IV}$-Catalyzed C–H Activation/Arylation



(**27**) (**28**)

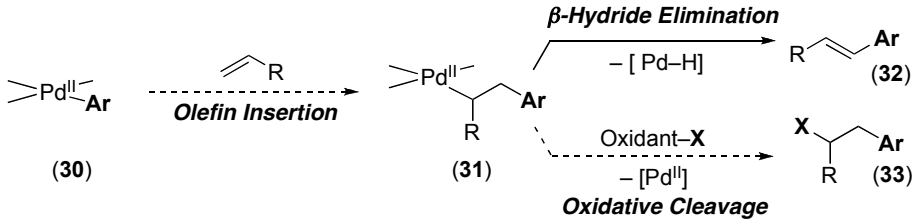
Scheme 17: Pd-Catalyzed C–H Activation/Halogenation



(**27**) (**29**)

As discussed above, ***Chapters 2, 3*** and ***4*** present our explorations of Pd-catalyzed ligand directed C–H activation/C–X (X = C, O, Cl, Br, I) bond-forming reactions. The key product-forming step in these reactions involves oxidative functionalization of the Pd–C bond of the cyclopalladated Pd^{II} complex **21** via Pd^{IV} intermediates (Scheme 13). Based on these results, we reasoned that other Pd^{II} σ alkyl or aryl intermediates (formed by organometallic transformations different from C–H activation) generated in the presence of strong oxidants might undergo functionalization to generate novel products. In particular, we envisioned that Pd-alkyl complexes **31** formed via olefin insertion into Pd-aryl bonds could be intercepted with oxidants to afford product **33** (Scheme 18). However, Pd^{II}-σ-alkyl species **31** is well known to undergo ß-hydride elimination under traditional $Pd^{0/II}$ catalysis to form alkenes such as **32**.[26] Nonetheless, we anticipated that under oxidative conditions, **31** could competitively react with the oxidant to afford the desired functionalized product **33**.

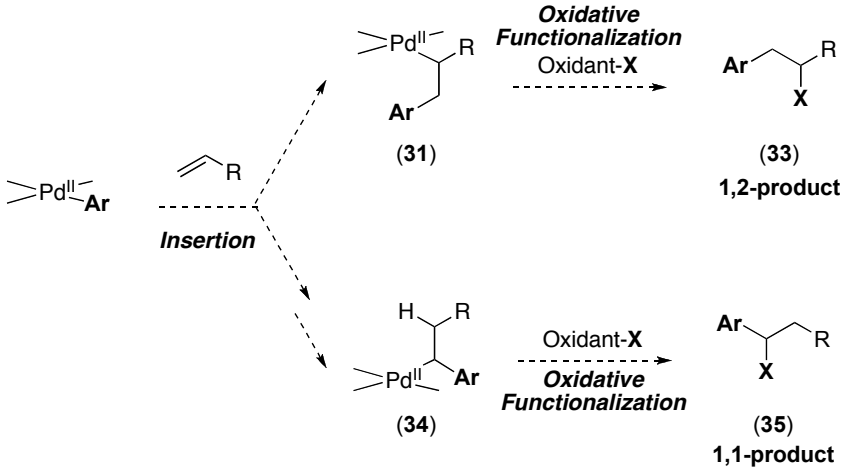
Scheme 18: Oxidatively Intercepting Pd-Alkyl Intermediates



(**30**) (**31**) (**32**) (**33**)

In this regard, ***Chapter 5*** details our efforts towards the oxidative halogenation of alkenes to form 1,2-arylhalogenated products **33** (Scheme 19). Interestingly, we also found that 1,1-arylhalogenated products **35** could also be obtained in high selectivity just by tuning the reaction conditions.[27]

Scheme 19: Pd-Catalyzed Arylhalogenation of Alkenes



In conclusion, this thesis describes a variety of site selective palladium-catalyzed oxidative functionalization reactions. These include palladium-catalyzed chelate-directed C–H activation/C–X (X = C, O, Cl, Br, I) bond formation and the palladium-catalyzed difunctionalization of olefins. The $Pd^{II/IV}$ catalytic cycle proposed for many of these transformations has allowed for bond formations (e.g., carbon-halogen) that previously proved challenging via traditional $Pd^{0/II}$ catalytic cycles. The generality, high selectivity, and functional group tolerance of these reactions make them attractive for the functionalization, late stage derivatization, and the synthesis of complex biologically active molecules.

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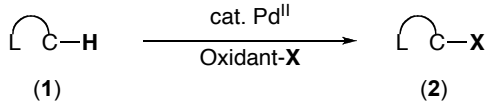
Chapter 2

Site Selectivity in Palladium-Catalyzed C-H Activation/Acetoxylation Reactions

2.1 Background and Significance

Palladium-catalyzed chelate-directed C–H activation/oxidation reactions have emerged as a powerful methodology for the direct conversion of C–H bonds to a variety of C–X (X = O,[1-6] N,[7-9] C,[10-34] F,[35] Cl, Br, I [2, 6, 36-43]) bonds. Importantly, the chelate-directed approach allows for the site selective functionalization of a C–H bond proximal to a directing group (L in Scheme 1).

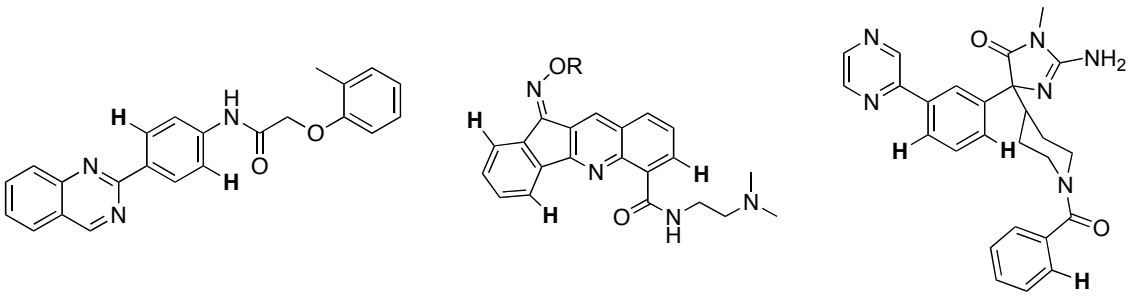
Scheme 1: Palladium-Catalyzed Ligand-Directed C–H Activation/Functionalization



(**1**) (**2**)

We and others have shown that this methodology is very general with respect to directing groups such as pyridines, oxime ethers, pyrazoles, isoxazolines, quinolines, tetrazoles, amides and azo linkages. Importantly, these chelating functionalities are widely prevalent in a variety of pharmaceutical candidates (Scheme 2).[44-47] Hence, palladium-catalyzed ligand-directed oxidative functionalization reactions could potentially expedite the process of SAR studies by allowing for diverse functionalization of C–H bonds at late stages of the synthesis of drug molecules.

Scheme 2: Examples of Biologically Active Molecules



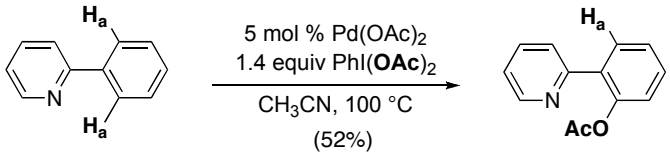
(**3**)
CETP Inhibitor

(**4**)
Cytotoxic

(**5**)
β-Secretase Inhibitor

Our group has demonstrated that $Pd(OAc)_2$ in conjunction with $PhI(OAc)_2$ serves as an efficient catalyst for the ligand-directed acetoxylation of arene C–H bonds in substrates containing appropriate chelating groups. For example, the reaction of 2-phenylpyridine (**6**) under our optimal acetoxylation conditions leads to the formation of the oxygenated product **7** in 52% isolated yield (Scheme 3).[1, 2]

Scheme 3: Palladium-Catalyzed Acetoxylation of 2-Phenylpyridine

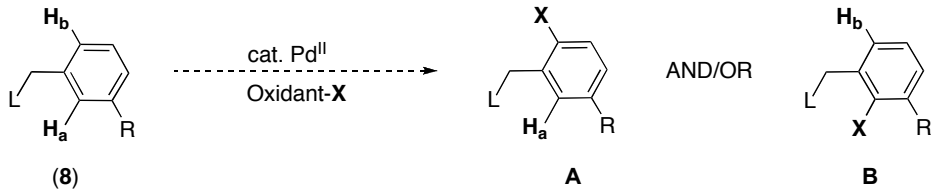


(**6**) (**7**)

Notably, the two *ortho* C–H bonds (C–H_a) in **6** and most other substrates explored by our group are chemically equivalent. Hence, the oxygenation of either of the two C–H_a bonds in these substrates affords the same product **7** (Scheme 3). In contrast, substrates of general structure **8** (Scheme 4), bearing a substituent *meta* to the directing group, contain two chemically inequivalent *ortho* C–H bonds: C–H_a and C–H_b (Scheme 4). Palladium-catalyzed ligand-directed C–H activation/oxygenation of these substrates could potentially lead to two isomeric products **A** and **B** via acetoxylation of either C–H_a or C–H_b. We sought to explore the oxygenation of this important class of substrates in order to further expand the synthetic utility of the acetoxylation reactions developed by

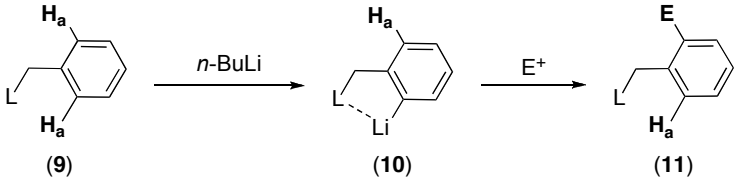
our group. In particular, we wanted to study how the electronic and steric nature of the substituent R (Scheme 4) affected site selectivity of these transformations.[48]

Scheme 4: Palladium-Catalyzed Ligand Directed C–H Activation/Functionalization



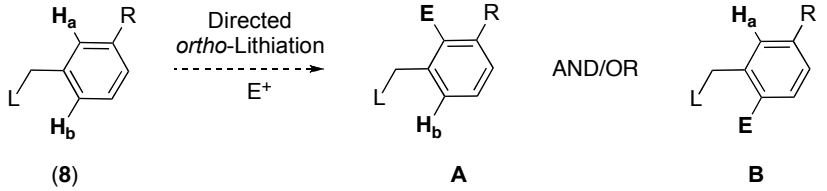
The site selectivity of functionalization of *meta*-substituted arenes has been explored systematically for a number of other reactions in the literature (e.g., directed *ortho*-lithiation and ruthenium-catalyzed C–H activation/olefin coupling) that involve chelate-directed functionalization. Directed *ortho*-lithiation reactions involve ligand directed deprotonation of the *ortho* protons (C–H_a, Scheme 5) by a strong base like *n*-BuLi to generate intermediate **10**.[49] Subsequent reaction of **10** with an electrophile (E^+) affords the *ortho* functionalized product **11**.

Scheme 5: Directed *ortho*-Lithiation



The influence of *meta* substituents on site selectivity has been studied extensively for directed *ortho*-lithiation of substrates **8** (Scheme 6).[4] In these reactions, selectivity is dictated by two factors: (i) the ability of the *meta* substituent to coordinate to the lithium ion and/or (ii) the inductive effects of the substituents R.

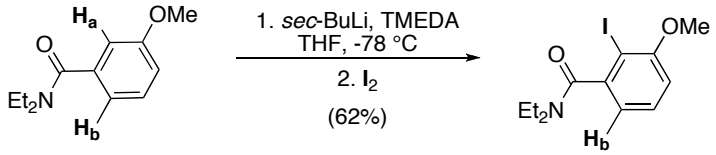
Scheme 6: Site Selectivity in Directed *ortho*-Lithiation



(**8**) **A** **B**

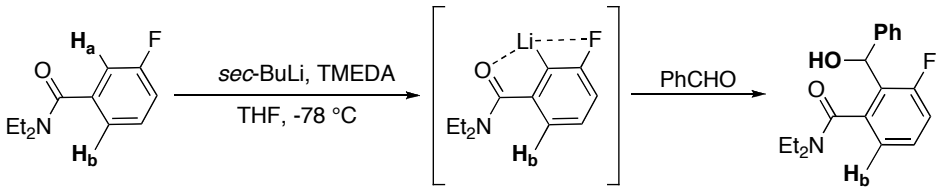
For example, reaction of substrates **12** (Scheme 7) and **14** (Scheme 8) bearing *meta* substituents such as OMe or F leads to isomer **B** (Scheme 6) as the major product with >20:1 selectivity via cooperation between the amide ligand and the OMe or F group.

Scheme 7: Directed *ortho*-Lithiation of **12**



(**12**) (**13**)

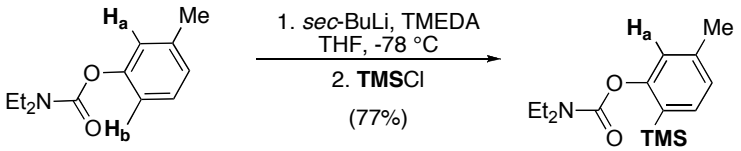
Scheme 8: Directed *ortho*-Lithiation of **14**



(**14**) (**15**) (**16**)

The preference for isomer **B** (Scheme 6) with substrate **12** is attributed to the *ortho* directing effect of the amide and the increased acidity of the C–H_a because of the inductively electron withdrawing OMe group (Scheme 7). However for **14**, both the dual chelation of the ligand and F to the Li atom and the increased acidity of the C-H_a proton are believed to be important in imparting the observed selectivity (Scheme 8).[49, 50] In contrast, isomer **A** (Scheme 6) is the predominant product in the reaction of substrates containing non-coordinating and inductively electron donating substituents like CH_3 (Scheme 9).[49]

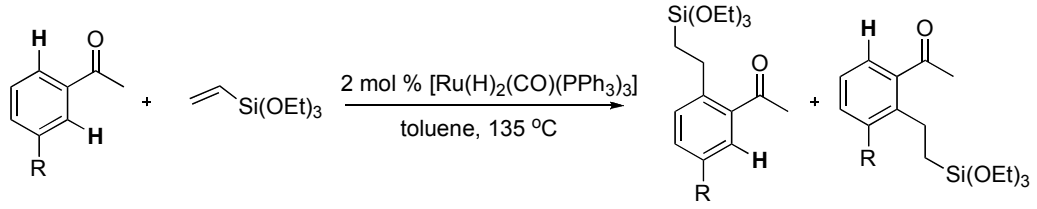
Scheme 9: Directed *ortho*-Lithiation of **17**



(**17**) (**18**)

Such studies on site selectivity have also been conducted for ligand-directed ruthenium-catalyzed C–H activation/olefin coupling of a variety of *meta*-substituted aryl ketones (Scheme 10).[51-57] In these reactions, dual chelation of the ligand and the R group to ruthenium directs C–C bond formation to the more sterically congested position when R is a coordinating *meta* substituent (e.g., F and OMe) (Scheme 10, entries 4 and 5). On the other hand, **A** is the major product with other substituents, R (e.g., CN, Me and CF_3) that are either sterically hindered or have relatively poor ligand affinities for ruthenium in selectivities ranging from 2.7:1 (Scheme 10, entry 3) to >20:1 (Scheme 10, entries 1 and 2).

Scheme 10: Ruthenium-Catalyzed C–H Activation/Olefin Coupling



(**19**) **19-A** **19-B**

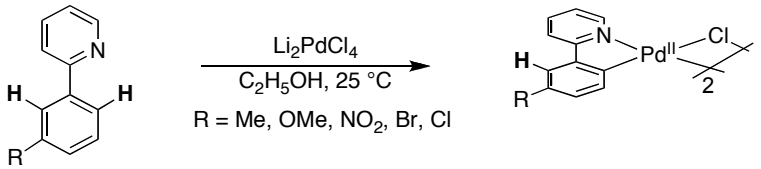
Entry	R	Yield	19-A:19-B
1	CF_3	82%	only A
2	Me	96%	30:1
3	CN	97%	2.7:1
4	OMe	93%	1:8.3
5	F	80%	1:26

In contrast to the reactions depicted in Schemes 7–10 above, investigations of site selectivity for functionalization of *meta*-substituted arenes in Pd^{II}-catalyzed C–H activation/C–heteroatom bond forming reactions were very sporadic and not very

extensive when we began our explorations.[16, 58-61] However, several stoichiometric examples of palladium mediated C–H activation of *meta*-substituted arenes had been documented.

For instance, Gutierrez and coworkers studied the reaction of a variety of *meta*-substituted 2-phenylpyridine derivatives (**20**) with stoichiometric amounts of Li_2PdCl_4 in EtOH at room temperature (Scheme 11).[62, 63] They demonstrated that cyclopalladation of **20** proceeds via activation of the less sterically congested C–H bond regardless of the electronic and the steric nature of the *meta* substituent.

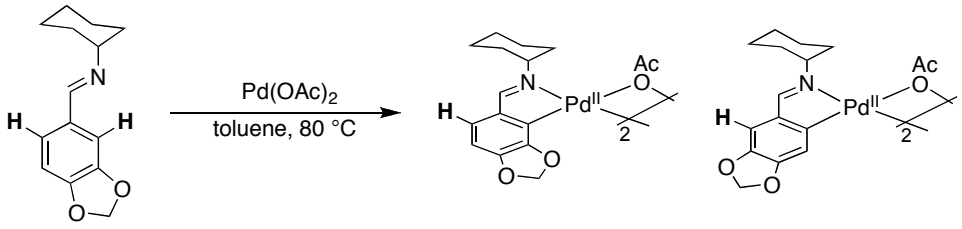
Scheme 11: Stoichiometric Cyclopalladation of 2-Phenylpyridine Derivatives



(**20**) (**21**)

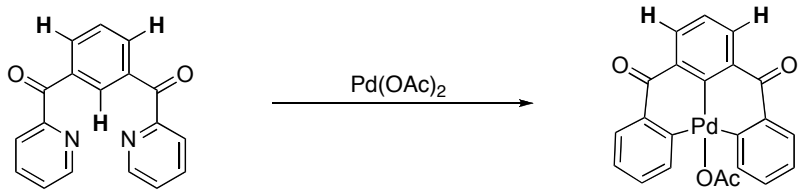
Less common are reports of cyclopalladation at the more sterically congested site. As shown in Scheme 12, the cyclopalladation of substrate **22** bearing the methylenedioxy *meta* substituent affords **22-B** as the major product albeit with only modest selectivity (2:1).[64] Additionally, the reaction of **23** with $Pd(OAc)_2$ leads to complex **24** as the major product (Scheme 13).[65]

Scheme 12: Cyclopalladation of **22** Containing Methylenedioxy Substituent



(**22**) (**22-B**) 2:1 (**22-A**)

Scheme 13: Stoichiometric Cyclopalladation of **23**



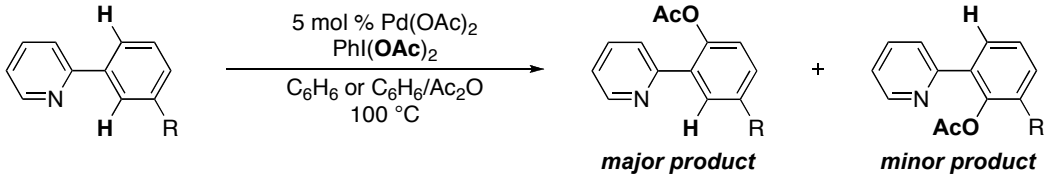
(**23**) (**24**)

Although the stoichiometric examples in the literature suggest that cyclopalladation reactions most commonly proceed via activation of the less sterically hindered C–H bond (with the exception substrates **22** and **23**), the relevance of these results to catalytic C–H activation/functionalization reactions was not clear. In particular, it is not known if the selectivity in stoichiometric reactions is a manifestation of kinetic or thermodynamic control. Hence, we sought to systematically explore the reactions of *meta*-substituted arenes in palladium-catalyzed C–H activation/acetoxylation reactions developed by our group. Importantly, the insights gained from this study could potentially be applied to other Pd-mediated carbon-heteroatom bond forming transformations.

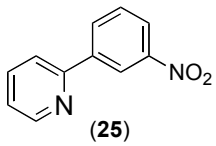
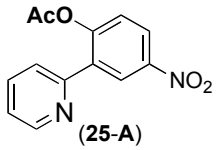
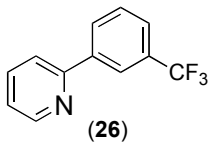
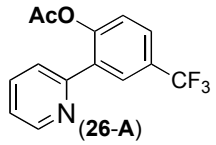
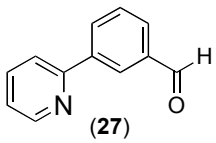
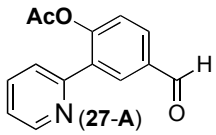
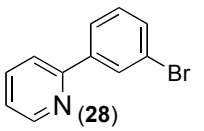
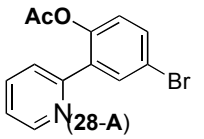
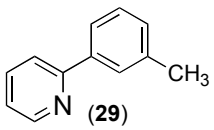
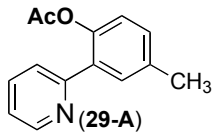
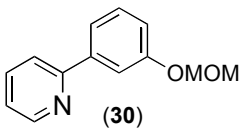
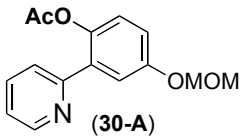
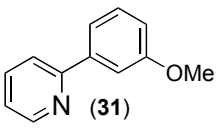
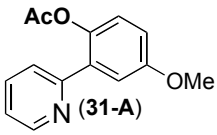
2.2 Results and Discussion

We began our study with a variety of *meta*-substituted 2-(3-substituted phenyl) pyridine derivatives (**25**–**31**) (Table 2.1). We were pleased to find that the reaction of substrates **25**–**31** with 1.1 to 3.0 equiv of $PhI(OAc)_2$ in the presence of 5 mol % $Pd(OAc)_2$ afforded the mono acetoxylated products in good yields (Table 2.1). Importantly, only trace amounts of diacetoxylation were observed in these transformations. The reaction is compatible with a variety of functional groups including ethers (Table 2.1, entries 6, 7), halides (Table 2.1, entry 4), and benzylic hydrogens (Table 2.1, entry 5). Additionally, these reactions proceeded in comparable times for substrates bearing electron rich (0.5 h to 1.5 h, Table 2.1, entries 5-7) and electron deficient arenes (45 min to 3 h, Table 2.1, entries 1-4).

Table 2.1: Acetoxylation of 2-Phenylpyridine Derivatives



(**25**-**31**) (**25**-**31**)-**A** (**25**-**31**)-**B**

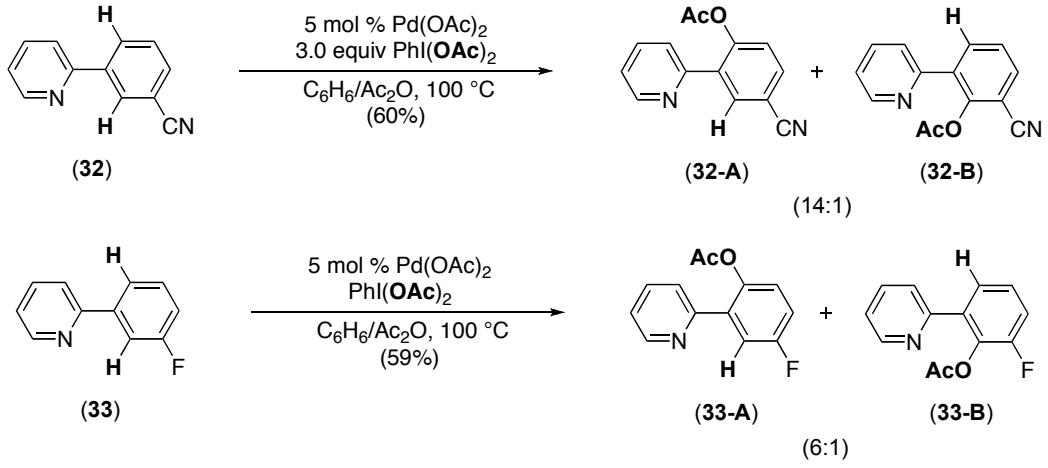
Entry	Substrate	Major Product	Yield[a]	A:B	Time
1	 (**25**)	 (**25-A**)	60%	>100:1[b]	3 h
2	 (**26**)	 (**26-A**)	81%	>20:1[c]	45 min
3	 (**27**)	 (**27-A**)	61%	>20:1[c]	1.5 h
4	 (**28**)	 (**28-A**)	83%	>100:1[b]	1.5 h
5	 (**29**)	 (**29-A**)	77%	138:1	0.5 h
6	 (**30**)	 (**30-A**)	76%	>20:1[c]	1 h
7	 (**31**)	 (**31-A**)	78%	60:1	1.5 h

[a]Reaction Conditions: 5 mol% $Pd(OAc)_2$, 1.1-3.0 equiv $PhI(OAc)_2$, C_6H_6 or C_6H_6/Ac_2O, 100 °C. [b]Selectivities reported as >100:1 because only one product peak observed by GC. [c]Selectivities reported as >20:1 because other little peaks were observed by GC that might or might not be the minor isomer.

Both ^{1}H NMR spectroscopy and gas chromatography (GC and GCMS) were employed to assess the site selectivity in these reactions. In most cases ^{1}H NMR spectra and COSY analysis confirmed the structures of the major isomers. Authentic samples of the acetoxylated products were synthesized through an alternate route in cases for which the structure of the major isomer could not be assigned based on the ^{1}H NMR spectra of the oxygenated compounds. The selectivities (**A**:**B**) reported in Table 2.1 were obtained by GC analysis of the crude reaction mixtures.

In general, the major product (isomer **A**, Table 2.1) in these reactions resulted from C–H activation/oxygenation of the less sterically hindered C–H bond regardless of the electronic nature of the *meta* substituent, with >20:1 selectivity. These results are consistent with the site selectivities observed for the stoichiometric reactions of 2-phenyl pyridine derivatives mentioned in section 2.1.[62] However, the site selectivities are somewhat attenuated for substrates **32** and **33** bearing relatively smaller cyano (14:1) and fluoro (6:1) groups as the *meta* substituents (Scheme 14).

Scheme 14: Palladium-Catalyzed Acetoxylation of **32** and **33**

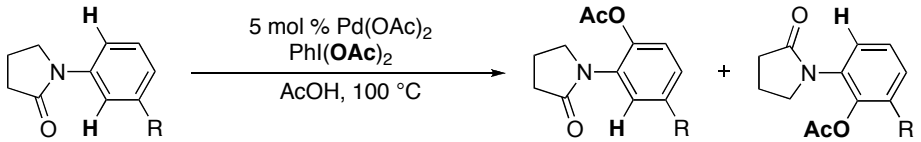


Notably, the observed site selectivity with substrates bearing coordinating *meta* substituents such as F (Scheme 14) and OMe (Table 2.1, entry 7), is complementary to that obtained in the directed *ortho*-lithiation[49] and ruthenium-catalyzed C–H activation/olefin coupling reactions[51] described in section 2.1. Furthermore, the

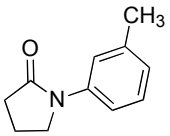
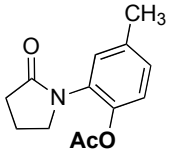
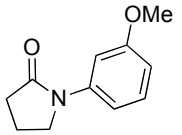
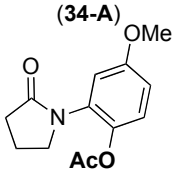
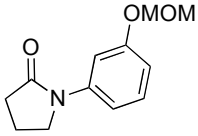
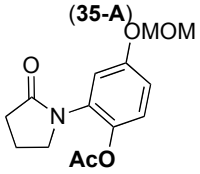
selectivity (14:1) observed with the small cyano group as the *meta* substituent (Scheme 14) is significantly higher than that observed for the Ru-catalyzed reactions (2.7:1) (Scheme 10, entry 3). Finally, the result with substrate **33** (Scheme 14), which shows a modest preference for functionalization adjacent to H over F, is particularly remarkable, since these two atoms are sterically quite similar.[66]

We next desired to explore the effect of the directing group on the reactivity and the site selectivity of C–H activation/oxygenation of *meta*-substituted arenes. Hence we studied the reaction of a series of *meta*-substituted 2-phenylpyrrolidinone derivatives (**34**–**36**) (Table 2.2). Unlike the phenylpyridine derivatives (**25**–**31**) (Table 2.1 and Scheme 14), the reactivity of these substrates was highly dependent on the electronics of the arene ring being functionalized. Under the optimal conditions (5 mol % $Pd(OAc)_2$, 1.1-3.0 equiv $PhI(OAc)_2$, AcOH, 100 °C) the palladium-catalyzed acetoxylation of substrates (**34**–**36**) bearing electron rich arenes afforded the oxygenated products in good yields (Table 2.2).

Table 2.2: Acetoxylation of 2-Phenylpyrrolidinone Derivatives



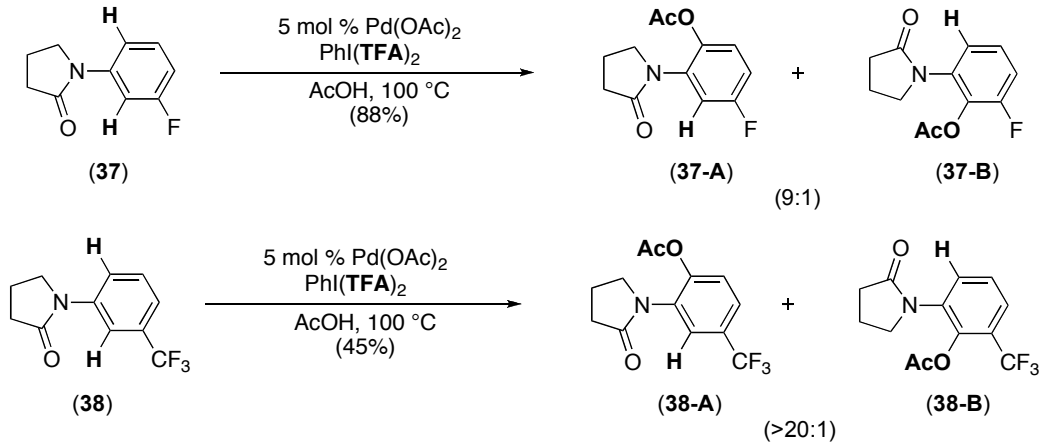
(**34-36**) (**34-36**)-**A** (**34-36**)-**B**

Entry	Substrate	Major Product	Yield[a]	A:B[b]
1	 (**34**)	 (**34-A**)	74%	>20:1
2	 (**35**)	 (**35-A**)	73%	>20:1
3	 (**36**)	 (**36-A**)	70%	>20:1

[a]Reaction Conditions: 5 mol% $Pd(OAc)_2$, 1.1-3.0 equiv $PhI(OAc)_2$, $AcOH/Ac_2O$, 100 °C. [b]Selectivities determined by crude GC; >20:1 means that there were other little peaks observed by GC that might be the minor product but the ratio of the major peaks to these little peaks was at least >20:1

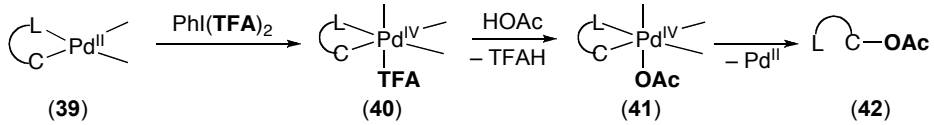
In contrast, the reaction of substrate **37** bearing an electron withdrawing fluorine substituent afforded low yield (45% based on GC conversion) with $PhI(OAc)_2$ as the oxidant (Scheme 15). The modest yield of the oxygenated products was partly due to the low reactivity of the substrate since significant amounts of the starting material (55% based on GC conversion) remained at the end of the reaction. However, gratifyingly, the oxygenated products **37-A** and **37-B** could be obtained in excellent yield (88%) using a more reactive iodine(III) reagent ($PhI(TFA)_2$) as the terminal oxidant (Scheme 15). Analogous to **37**, the reaction of **38** bearing the CF_3 substituted arene also led to higher yield (45%) of the acetoxylated product **38-A** with $PhI(TFA)_2$ (Scheme 15) than with $PhI(OAc)_2$ (~10%).

Scheme 15: Palladium-Catalyzed Acetoxylation of **29** and **30**

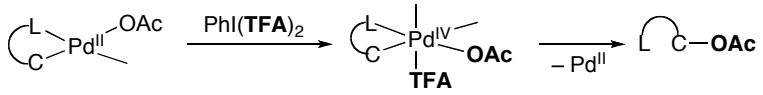


In these reactions the highly reactive $PhI(TFA)_2$ oxidant might be accelerating the oxidative functionalization of the electron deficient cyclopalladated intermediates generated via C–H activation of **37** and **38**, thereby facilitating catalytic turnover and leading to superior yields of the acetoxylated products. However, we were intrigued by the exclusive formation of the acetate products **37-A**/**37-B** and **38-A** despite the presence of two different carboxylate ions, OAc and $OCOCF_3$ in the reaction mixture. None of the corresponding trifluoroacetate products were obtained from these reactions. There are atleast two possible rationales for the selective formation of acetate products in these reactions.[67] One possibility is that upon oxidation of **39** to **40** (Scheme 16)**,** the trifluoroacetate group in **40** might be displaced by the acetate from the AcOH solvent to afford a more stable Pd^{IV} intermediate **41**. C–O bond forming reductive elimination from **42** would then afford the acetate products (Scheme 16). Alternatively, at the Pd^{IV} intermediate **44**, C–OAc reductive elimination is more facile than the C–TFA coupling (Scheme 17). At this time these two possibilities cannot be distinguished.

Scheme 16: Carboxylate Exchange at Pd^{IV}



Scheme 17: Competitive Reductive Elimination of OAc versus TFA at Pd^{IV}

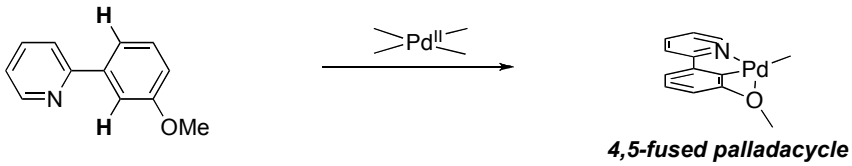


(**43**) (**44**) (**42**)

While the reactivity of the phenylpyrrolidinone substrates was significantly influenced by the electronics of the arene moiety, site selectivity was relatively unaffected by the nature of the *meta* substituent. Analogous to the phenylpyridine derivatives, isomers **34-A**–**38-A** were the major products in these reactions with a selectivity of >20:1 resulting from oxygenation of the less hindered C–H bond (Table 2 and Scheme 15). The fluoro-substituted substrate **37** also underwent functionalization at the less sterically congested C–H bond, albeit with more modest selectivity (9:1) (Scheme 15).

As mentioned above, functionalization of the less congested C–H bond occurs regardless of the nature of the *meta* substituents or the directing groups in Pd-catalyzed C–H activation/acetoxylation reactions. However, we wanted to further probe the system to see if we could override these steric effects and find a way to effect oxygenation of the more hindered C–H bond. We hypothesized that the lack of secondary directing effects by coordinating *meta* substituents such as OMe might be attributed to the formation of unfavorable 4,5-membered palladacyclic intermediates upon dual chelation assisted cyclopalladation (Scheme 18).

Scheme 18: Formation of Unfavorable Palladacycles Upon C–H Activation

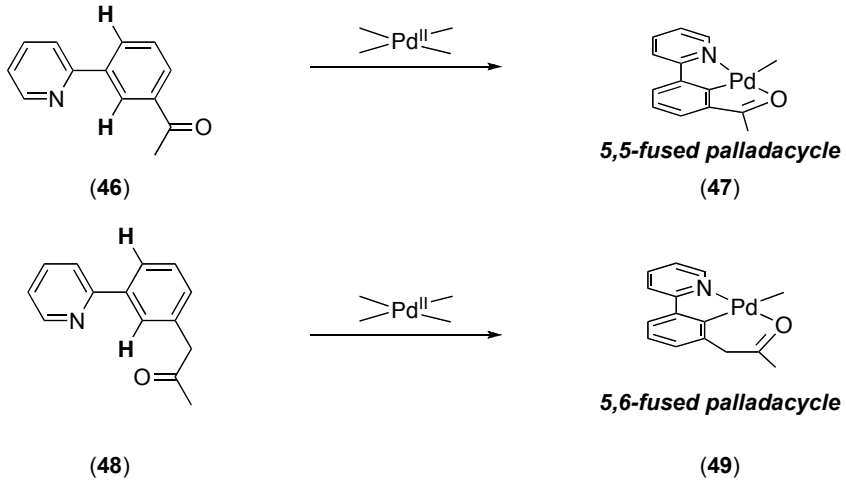


(**31**) (**45**)

Hence, we designed substrates **46** and **48** bearing the ketone moiety as the *meta* substituent. In these substrates, C–H activation via dual chelation of the pyridine and the carbonyl would afford favorable 5,5- or 5,6-membered palladacyclic intermediates **47**

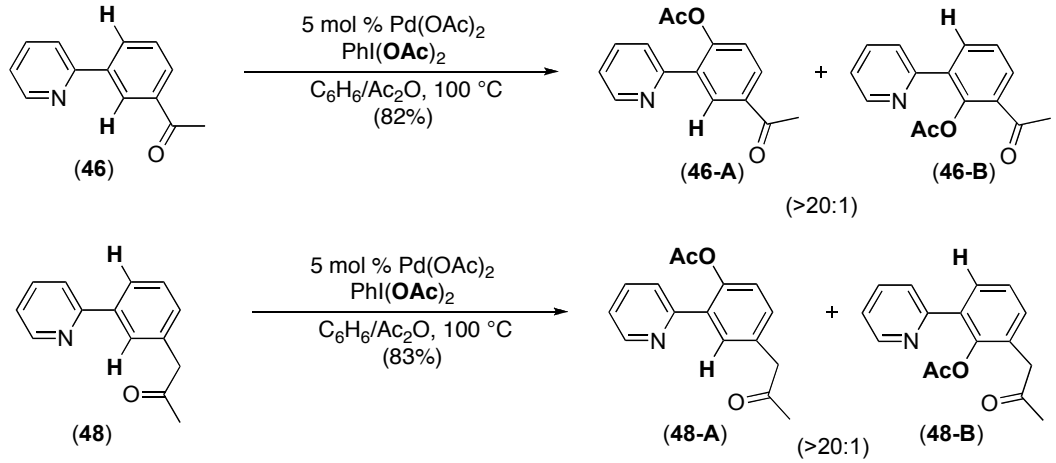
and **49** (Scheme 19). Importantly, ketones have been proposed to act as L type ligands for Pd^{II} in other Pd-catalyzed C–C bond forming reactions.[68, 69]

Scheme 19: Formation of Favorable 5,5- and 5,6-Fused Palladacycles



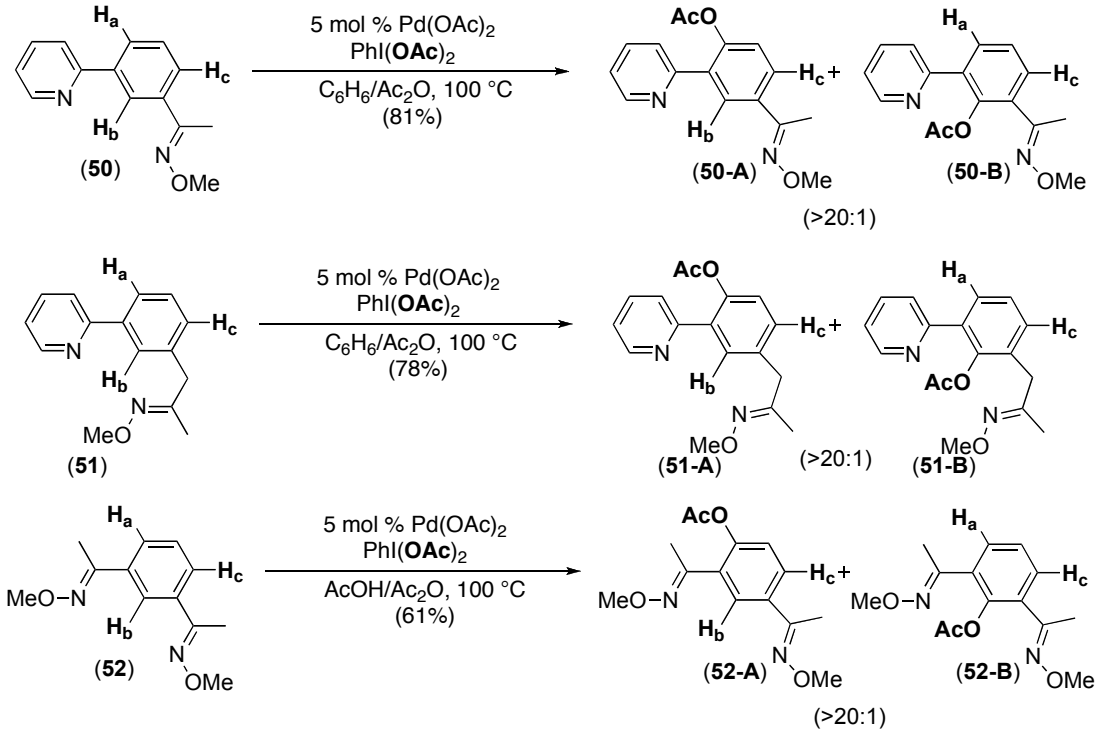
As shown in Scheme 20, the reaction of substrates **46** and **48** under our optimal conditions afforded the acetoxylated products in good yields. However, the product was formed via acetoxylation of the C–H bond *para* to the ketone substituent in both cases, implicating a lack of secondary directing effects of the carbonyl moiety under our reaction conditions.

Scheme 20: Palladium-Catalyzed Acetoxylation of **46** and **48**



Based on the results described above, we surmised that the lack of dual chelation in the systems discussed above might arise due to the poor ligand abilities of the *meta* substituents for Pd^{II}. Hence, in an effort to bias toward functionalization at the more congested C–H bond, we next considered substrates **50**–**52** containing two strongly coordinating ligands (pyridine and oxime ether) *meta* to each other (Scheme 21). Notably, our group has previously shown that both oxime ethers and pyridines independently serve as effective directing groups in palladium-catalyzed C–H activation/acetoxylation reactions. Interestingly, however, the reaction of substrates **50**–**52** still led to the ligand directed oxygenation of the less sterically hindered C–H bond affording products **50-A**–**52-A** with >20:1 selectivity.

Scheme 21: Palladium-Catalyzed Acetoxylation of **50–52**

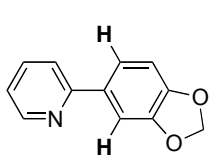


Substrates **50**–**52** contain of three C–H bonds (C–H_a, C–H_b and C–H_c) that could potentially be functionalized via the ligand directed strategy (Scheme 16). The pyridine moiety could direct oxygenation of C–H_a in **50**–**51**. The oxime ether and/or the pyridine could promote the functionalization of C-H_b in **50**–**52** and, finally, the oxime ether could independently direct acetoxylation of C-H_c in **50**–**52**. However, the exclusive formation

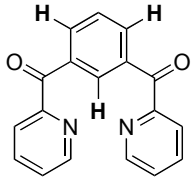
of **50-A**–**52-A** indicates that in substrates containing multiple chelating groups, the palladium-catalyzed C–H activation/functionalization is selectively directed by the most dominant ligand (e.g., pyridine in **50** and **51**) at the less sterically hindered position.

In a final effort to bias oxygenation to the more congested C–H bond, we investigated the reaction of substrates **53** and **23** (Scheme 22) that contain *meta* substituents for which secondary directing effects have been observed in stoichiometric cyclopalladation reactions (Schemes 12 and 13).[64, 65]

Scheme 22: Substrates Containing Methylenedioxy and Benzoyl Pyridine Groups



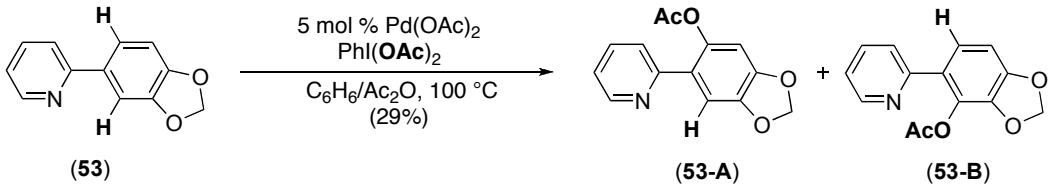
(**53**)



(**23**)

As shown in Scheme 23 below, the reaction of **53** afforded a mixture of the acetoxylated products **53-A** and **53-B** in 29% yield. The low yield in this reaction is due to significant formation of the di-oxidized (67% based on GC conversion) products. However, consistent with the stoichiometric cyclpalladation reaction described in Scheme 12 above, the major product from the reaction of **53** formed via oxygenation of the more sterically hindered C–H bond albeit with modest selectivity (**53-A**:**53-B** = 1:2).[59] In this case, the cyclic nature of the -OCH_2O- group might decrease the effective size of the *meta* substituent, hence allowing for oxygenation at the more congested position. Additionally, the conformational constraint of the five membered ether ring might render the lone pair of the oxygen more accessible for coordination to the palladium center.

Scheme 23: Palladium-Catalyzed Acetoxylation of **53**

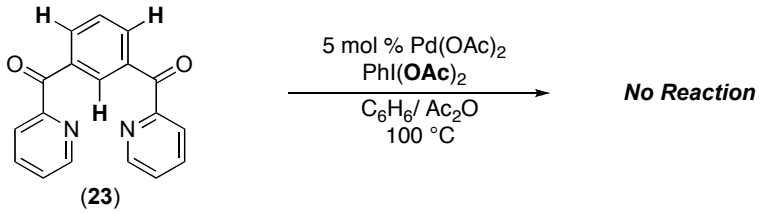


(**53**) (**53-A**) (**53-B**)

(1:2)

We next subjected substrate **23** to our standard conditions for acetoxylation. However, as shown in Scheme 24, no oxygenated product was obtained from this reaction. We were surprised by this result because **23** is known to undergo stoichiometric cyclopalladation to afford complex **24** (Scheme 13). We reasoned that the two symmetrically disposed strongly coordinating pyridine ligands might be hindering the oxidative functionalization of the cyclopalladated complex **24** (generated upon C–H activation), hence preventing the formation of the acetoxylated product.

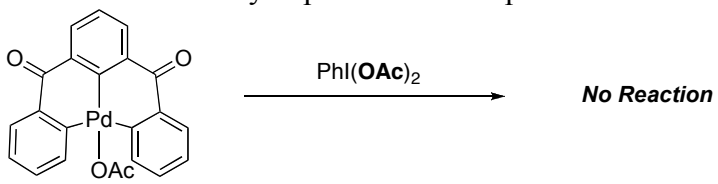
Scheme 24: Palladium-Catalyzed Acetoxylation of **23**



(**23**)

In order to probe this hypothesis, we conducted the reaction of complex **24** with stoichiometric amounts of $PhI(OAc)_2$. As depicted in Scheme 25, this reaction did not afford the oxygenated product. These results indicate that the presence of two strongly coordinating pyridine ligands is necessary for selective dual chelation assisted cyclopalladation to occur with high selectivity in *meta*-substituted arenes (Scheme 13). However, in such cases, the oxidative functionalization of the cyclopalladated complex **24** does not proceed.

Scheme 25: Reaction of Cyclopalladated Complex **24** with $PhI(OAc)_2$

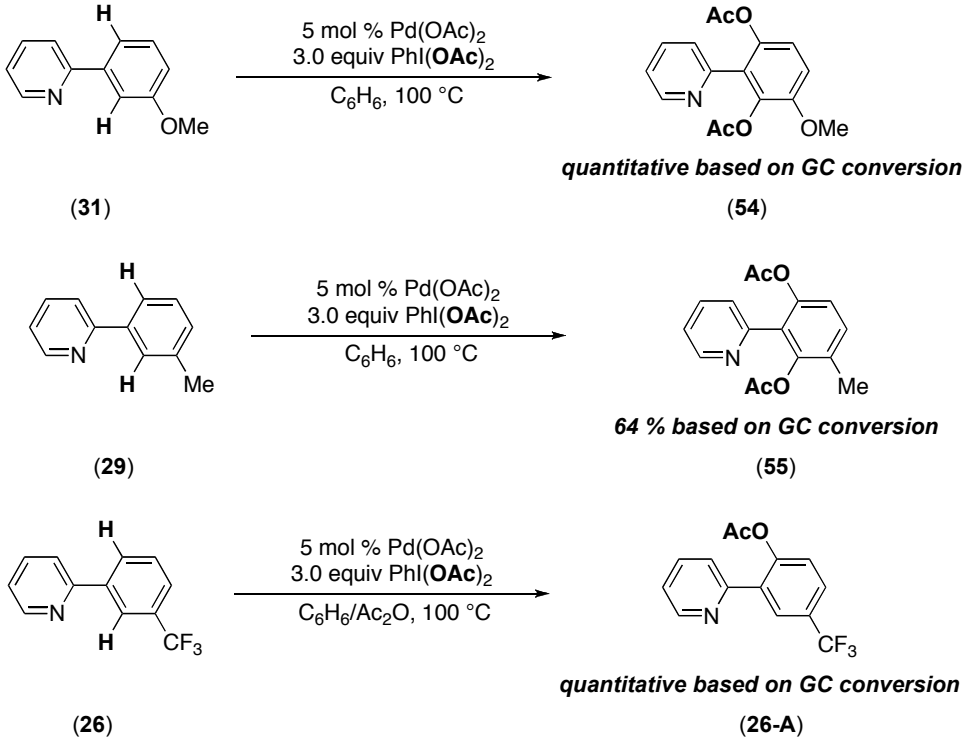


(**24**)

As discussed above, the palladium-catalyzed acetoxylation of *meta*-substituted arenes leads to the clean formation of the monoxygenated products via functionalization of the less sterically hindered C–H bond. However, the use of super stoichiometric

amounts of $PhI(OAc)_2$ revealed that the dioxygenated products can form depending on the electronic nature of the arene being functionalized (Scheme 26). For example the reaction of substrate **31** containing an electron rich methoxy substituent, with 3.0 equiv of $PhI(OAc)_2$ led to the formation of the diacetoxylated product **54** quantitatively (based on GC conversion). Under similar reaction conditions, substrate **29** bearing an electron neutral methyl substituent afforded only 64% of the diacetoxylated product **55**. Finally, the reaction of substrate **26** containing an electron poor trifluoromethyl group led to only the monoacetoxylated product **26-A** even with 3.0 equiv of the oxidant.

Scheme 26: Reaction of **31**, **29** and **26** with excess $PhI(OAc)_2$



These results suggest that the palladium-catalyzed C–H activation/acetoxylation of the more sterically hindered C–H bond is possible under our reaction conditions, but only after the formation of the monofunctionalized products. This along with the fact that the selectivity determining C–H activation step is not reversible and is rate determining for these reactions (found by other members of the group), we surmise that the

monooxygenated products obtained via preferential functionalization of the less sterically hindered C–H bond are the kinetic products.

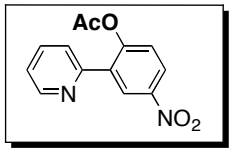
2.3 Conclusions

In summary, we have conducted the first comprehensive study of site selectivity for *meta*-substituted arenes in palladium-catalyzed ligand-directed C–H activation/functionalization reactions. In general, our results show that the palladium-catalyzed C–H activation/acetoxylation of *meta*-substituted arenes occurs preferentially at the less congested position. The similar results observed for the 2-phenylpyridine and the phenylpyrrolidinone derivatives indicate that site selectivities reported herein might be general for a wide variety of directing groups. Additionally, as will be detailed in subsequent chapters (***Chapters 3 and 4***), the observed sensitivity to the steric environment of the arene ring for the acetoxylation reactions appears to be general for a wide variety of Pd-catalyzed C–H activation/functionalization reactions. Indeed, subsequent or concurrent to our work several reports have shown similar results for palladium-catalyzed oxidative functionalization of C–H bonds with pyridine, amide, oxime ether, and carboxylic acid directing groups. Furthermore, the modest selectivity for functionalization adjacent to H versus fluorine suggests that Pd^{II}-mediated C–H activation reactions might be very sensitive to slight steric perturbations in the system. Importantly, our results suggest that the site selectivities for palladium-catalyzed C–H activation/functionalization reactions might often be different and complementary to those obtained for directed *ortho*-lithiation or ruthenium-catalyzed C–H activation reactions. Finally, the predominant functionalization occurs adjacent to the more strongly coordinating ligand (e.g., pyridine) at the less sterically crowded C–H bond in substrates containing multiple chelating groups. This result is particularly exciting because it suggests the possible application of our methodology towards selective functionalization of the C–H bond proximal to the dominant directing group in complex biologically active molecules comprising multiple chelating moieties.

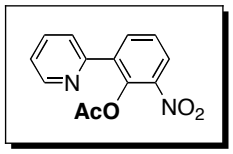
2.4 Experimental Procedure

General Procedures: NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C) or a Varian Inova 400 (399.96 MHz for ^{1}H; 100.57 MHz for ^{13}C; 376.34 MHz for ^{19}F) spectrometer. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin-Elmer "Spectrum BX" FT-IR spectrometer.

Materials and Methods: Pyridine substrate **31** was prepared by Suzuki cross-coupling of 3-methoxyphenyl boronic acid with 2-bromopyridine according to a literature procedure. Pyridine substrates **25–30**, **32**, **33**, **46, 48,** and **53** were prepared by Stille cross-coupling of 2-tributylpyridyltin with the corresponding aryl bromides. Substrates **50–52** were synthesized by reaction of the corresponding ketones with methoxylamine hydrochloride using a known procedure for making oxime ethers. Amide substrates **34–38** were prepared by palladium-catalyzed arylation of the corresponding lactam. Substrate **23** was prepared by coupling 2-lithiopyridine with *N,N,N,N,*-tetraethylisopthalamide according to a literature procedure. The authentic compounds were prepared by Stille cross-coupling. Cyclopalladated complex **24** was prepared according to a literature procedure. $Pd(OAc)_2$ was obtained from Pressure Chemical and used as received, and $PhI(OAc)_2$ and $PhI(TFA)_2$ were obtained from Acros 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 F_{254}. Control reactions (in the absence of Pd catalyst) were run for each substrate, and generally showed no reaction under our standard conditions.



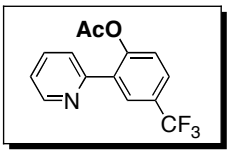
Substrate **25** (132 mg, 0.66 mmol, 1 equiv), $PhI(OAc)_2$ (637 mg, 2.0 mmol, 3.0 equiv), and $Pd(OAc)_2$ (7.38 mg, 0.03 mmol, 0.05 equiv) were combined in C_6H_6 (2.2 mL) and Ac_2O (2.2 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 3 h. The solvent was removed under vacuum, and the resulting yellow solid was purified by chromatography on silica gel (R_f = 0.24 in 65% hexanes/35% ethyl acetate). The product **25-A** was obtained as a pale yellow solid (101 mg, 60% yield); mp = 98-99 °C. ^{1}H NMR (d_6-acetone): δ 8.75-8.73 (m, 1H), 8.71 (d, J = 2.8 Hz, 1H), 8.33 (dd, J = 8.9, 2.8 Hz, 1H), 7.95-7.91 (m, 1H), 7.85-7.82 (m, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.44-7.41 (m, 1H), 2.26 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 168.98, 154.01, 153.93, 150.80, 146.74, 137.71, 135.14, 126.86, 126.03, 125.23, 124.56, 124.17, 20.90. IR (thin film): 3098, 1760, 1591, 1531, 1353 cm^{-1}. Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47, H, 3.90, N, 10.85; Found: C, 60.34, H, 3.66, N, 10.53. Retention time (GC): 10.1 min. Only one isomer is observed by GC and ^{1}H NMR.



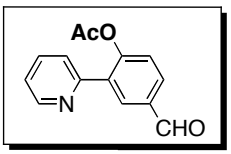
2-Bromo-6-nitrophenol (506 mg, 2.30 mmol, 1 equiv), Ac_2O (4.6 mL) and pyridine (0.88 mL) were combined in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with H_2O (3 x 15 mL) and brine (1 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product, 1-bromo-2-acetoxy-3-nitrobenzene was obtained as a yellow oil (559 mg, 93% yield).

Under a nitrogen atmosphere, 1-bromo-2-acetoxy-3-nitrobenzene (559 mg, 2.1 mmol, 1 equiv), and $Pd(PPh_3)_4$ (124 mg, 0.11 mmol, 0.05 equiv) and tributylpyridyltin (870 mg, 2.4 mmol, 1.1 equiv) were combined in toluene (5 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 110 ºC for 12 h. The

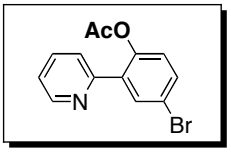
reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite, and washed with copious ethyl acetate. The washings were combined and concentrated under vacuum. The crude product was dissolved in ethyl acetate and extracted with 1M aqueous KF (4 x 30 mL). The combined organic layers were then extracted with brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The resulting brown oil was purified by chromatography on silica gel (R_f = 0.25 in 65% hexanes/35% ethyl acetate). The product **25-B** was obtained as a yellow solid (30.0 mg, 5% yield). ^{1}H NMR (d_6-acetone): δ 8.73-8.71 (m, 1H), 8.34 (td, J = 7.9, 1.5 Hz, 1H), 8.18 (dd, J = 8.1, 1.6 Hz, 1H), 7.94 (td, J = 7.8, 1.7 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.67 (t, J = 8.1 Hz, 1H), 7.45-7.42 (m, 1H), 2.22 (s, 3H). Retention time (GC): 9.42 min.



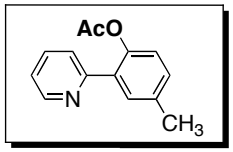
Substrate **26** (208 mg, 0.93 mmol, 1 equiv), $PhI(OAc)_2$ (450 mg, 1.40 mmol, 1.5 equiv), and $Pd(OAc)_2$ (10.4 mg, 0.05 mmol, 0.05 equiv) were combined in C_6H_6 (3 mL) and Ac_2O (3 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 45 min. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.30 in 75% hexanes/25% ethyl acetate). The product **26-A** was obtained as a pale yellow oil (211 mg, 81% yield). ^{1}H NMR (d_6-acetone): δ 8.73-8.72 (m, 1H), 8.19 (s, 1H), 7.89 (td, J = 8.0, 1.8 Hz, 1H), 7.84-7.79 (multiple peaks, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.42-7.38 (m, 1H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 169.11, 154.36, 151.98, 150.58, 137.46, 134.74, 128.61 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 128.51 (q, $^2J_{C\text{-}F}$ = 33 Hz), 127.10 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 125.63, 124.89 (q, $^1J_{C\text{-}F}$ = 271 Hz), 124.39, 123.77, 20.74. IR (KBr): 1768, 1597 cm^{-1}. Anal. Calcd for $C_{14}H_{10}F_3NO_2$: C, 59.79, H, 3.58, N, 4.98; Found: C, 60.14, H, 3.68, N, 5.25. Only one isomer is observed by GC and ^{1}H NMR.



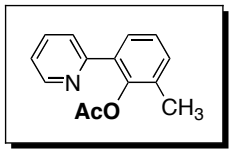
Substrate **27** (214 mg, 0.88 mmol, 1 equiv), $PhI(OAc)_2$ (1094 mg, 3.40 mmol, 3.0 equiv), and $Pd(OAc)_2$ (12.7 mg, 0.06 mmol, 0.05 equiv) were combined in C_6H_6 (3.6 mL) and Ac_2O (3.6 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 1.5 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.27 in 60% hexanes/50% ethyl acetate). The product **27-A** was obtained as a pale yellow oil (171 mg, 61% yield). ^{1}H NMR (d_6-acetone): δ 10.12 (s, 1H), 8.73 (d, J = 4.0 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.4, 2.0 Hz, 1H), 7.91 (td, J = 8.0, 2.0 Hz, 1H), 7.77 (dd, J = 8.0, 0.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.39 (ddd, J = 8.0, 5.2, 1.2 Hz, 1H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 191.99, 169.30, 155.14, 153.85, 150.72, 137.64, 135.69, 134.89, 133.53, 130.91, 125.73, 124.54, 123.84, 21.03. HRMS electrospray (m/z): [M^+] calcd for $C_{14}H_{11}NO_3$, 241.0739; found, 241.0741.



Substrate **28** (206 mg, 0.88 mmol, 1 equiv), $PhI(OAc)_2$ (312 mg, 0.97 mmol, 1.1 equiv), and $Pd(OAc)_2$ (9.85 mg, 0.04 mmol, 0.05 equiv) were combined in C_6H_6 (2.8 mL) and Ac_2O (2.8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 1.5 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.25 in 80% hexanes/20% ethyl acetate). The product **28-A** was obtained as a pale yellow oil (213 mg, 83% yield). ^{1}H NMR (d_6-acetone): δ 8.69 (ddd, J = 4.8, 1.8, 0.9, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.89 (td, J = 7.5, 1.8 Hz, 1H), 7.73 (dt, J = 8.0, 1.0 Hz, 1H), 7.63 (dd, J = 8.6, 2.5 Hz, 1H), 7.38 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 169.45, 154.65, 150.69, 148.66, 137.58, 136.09, 134.20, 133.21, 126.78, 124.50, 123.83, 119.53, 20.97. IR (KBr): 1764, 1585 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45, H, 3.45, N, 4.79; Found: C, 53.34, H, 3.51, N, 4.83. Only one isomer is observed by GC and ^{1}H NMR.



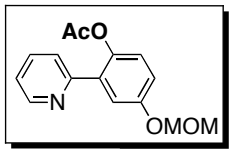
Substrate **29** (214 mg, 1.26 mmol, 1 equiv), $PhI(OAc)_2$ (448 mg, 1.39 mmol, 1.1 equiv), and $Pd(OAc)_2$ (14.2 mg, 0.06 mmol, 0.05 equiv) were combined in C_6H_6 (8.2 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 0.5 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.32 in 70% hexanes/30% ethyl acetate). The product **29-A** was obtained as a yellow oil (219 mg, 77% yield) as a 27:1 (by GC) mixture of regioisomers. ^{1}H NMR (d_6-acetone): δ 8.68-8.66 (m, 1H), 7.83 (td, *J* = 7.5, 1.9, 1H), 7.65 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 7.31 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.25 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 2.39 (s, 3H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 169.79, 156.48, 150.43, 147.28, 137.23, 136.47, 133.71, 132.02, 130.90, 124.34, 124.26, 123.14, 21.01, 20.92. IR (thin film): 2922, 1763, 1586 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99, H, 5.77, N, 6.16; Found: C, 73.85, H, 6.04, N, 6.01. Retention time (GC): 7.84 min (major) 7.58 min (minor).



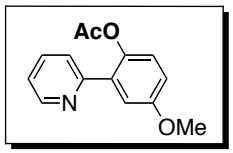
2-Bromo-6-methyphenol[vii] (500 mg, 2.70 mmol, 1 equiv), Ac_2O (5.30 mL) and pyridine (1.11 mL) were combined in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with H_2O (3 x 15 mL) and brine (1 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product, 1-bromo-2-acetoxy-3-methylbenzene was obtained as a yellow oil (499 mg, 81% yield).

Under a nitrogen atmosphere, 2-acetoxy-1-bromo-3-methylbenzene (500 mg, 2.18 mmol, 1 equiv), and $Pd(PPh_3)_4$ (252 mg, 0.22 mmol, 0.10 equiv) were combined in toluene (11 mL), and 2- tributylpyridyltin (883 mg, 2.40 mmol, 1.1 equiv) was then added. The reaction mixture was refluxed for 12 h, then diluted with ethyl acetate (30 mL), filtered

through a pad of silica gel and washed with copious ethyl acetate. The washings were combined, concentrated under vacuum, and, purified by column chromatography on silica gel (R_f = 0.20 in 75% hexanes/25% ethyl acetate). The product **29-B** was obtained as a pale yellow solid (238 mg, 48% yield). ^{1}H NMR (d_6-acetone): δ 8.67-8.65 (m, 1H), 7.85 (td, *J* = 7.5, 1.9 Hz, 1H), 7.63 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.35-7.31 (multiple peaks, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 2.22 (s, 3H), 2.17 (s, 3H). Retention time (GC): 7.58 min.

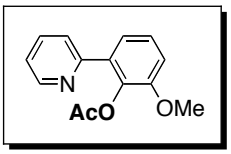


Substrate **30** (214 mg, 1.30 mmol, 1 equiv), $PhI(OAc)_2$ (448 mg, 1.40 mmol, 1.1 equiv), and $Pd(OAc)_2$ (14.1 mg, 0.06 mmol, 0.05 equiv) were combined in C_6H_6 (8.2 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100 ºC for 0.5 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.32 in 70% hexanes/30% ethyl acetate). The product **30-A** was obtained as a yellow oil (219 mg, 77% yield). ^{1}H NMR (d_6-acetone): δ 8.68-8.67 (m, 1H), 7.84 (td, *J* = 8.0, 1.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50-7.49 (m, 1H), 7.34-7.31 (m, 1H), 7.13-7.12 (m, 1H), 5.25 (s, 2H), 3.46 (s, 3H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 169.94, 156.09, 156.02, 150.50, 143.74, 137.32, 134.85, 125.37, 124.32, 123.37, 118.73, 118.16, 95.46, 56.17, 20.97. IR (thin film): 2956, 1763, 1586 cm^{-1}. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{15}H_{15}NO_4$, 296.0899; found, 296.0903. GC analysis (RESTEK Rtx®-5, FID detector): 100% integration. Only one isomer is observed by GC and ^{1}H NMR.



Substrate **31** (201 mg, 1.08 mmol, 1 equiv), $PhI(OAc)_2$ (384 mg, 1.19 mmol, 1.1 equiv), and $Pd(OAc)_2$ (12.1 mg, 0.05 mmol, 0.05 equiv) were combined in C_6H_6 (7 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at

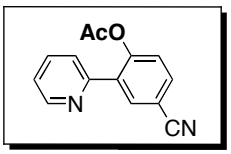
100ºC for 1.5 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.27 in 60% hexanes/40% ethyl acetate). The product **31-A** was obtained as a yellow oil (206 mg, 78% yield) as a 60:1 (by GC) mixture of regioisomers. ^{1}H NMR (d_6-acetone): δ 8.69-8.67 (m, 1H), 7.84 (td, *J* = 7.6, 1.9 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 3.1 Hz, 1H), 7.31 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.85 (s, 3H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 169.70, 158.11, 155.87, 150.17, 142.57, 136.99, 134.45, 125.07, 124.05, 123.02, 115.69, 115.58, 55.73, 20.67. IR (thin film): 2940, 1760, 1585 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12, H, 5.39, N, 5.76; Found: C, 69.33, H, 5.08, N, 5.72. Retention time (GC): 8.85 min (major) 8.56 min (minor).



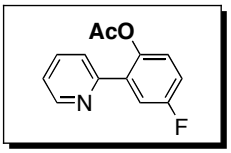
2-Bromo-6-methoxyphenol[viii] (500 mg, 2.46 mmol, 1 equiv), Ac_2O (4.7 mL) and pyridine (4.7 mL) were combined in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with H_2O (3 x 15 mL) and brine (1 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product, 1-bromo-2-acetoxy-3-methoxybenzene was obtained as a yellow oil (542 mg, 90% yield).

Under a nitrogen atmosphere, 1-bromo-2-acetoxy-3-methoxybenzene (542 mg, 2.21 mmol, 1 equiv), and $Pd(PPh_3)_4$ (255 mg, 0.22 mmol, 0.10 equiv) were combined in toluene (11 mL), and 2- tributylpyridyltin (895 mg, 2.43 mmol, 1.1 equiv) was added. The reaction mixture was refluxed for 12 h, then diluted with ethyl acetate (30 mL), filtered through a pad of silica, and washed with copious ethyl acetate. The washings were combined, concentrated under vacuum, and purified by chromatography on silica gel (R_f = 0.25 in 65% hexanes/35% ethyl acetate). The product **31-B** was obtained as a pale yellow solid (182 mg, 34% yield). ^{1}H NMR (d_6-benzene): δ 8.55 (d, *J* = 4.8 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.9

Hz, 1H), 6.64-6.61 (m, 1H), 6.53 (d, J = 8.2, Hz, 1H), 3.28 (s, 3H), 1.91 (s, 3H). Retention time (GC): 8.56 min.

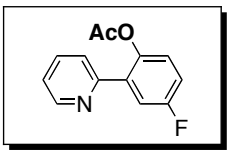


Substrate **32** (207 mg, 1.15 mmol, 1 equiv), $PhI(OAc)_2$ (1110 mg, 3.45 mmol, 3.0 equiv), and $Pd(OAc)_2$ (12.9 mg, 0.06 mmol, 0.05 equiv) were combined in C_6H_6 (3.7 mL) and Ac_2O (3.7 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100 ºC for 3.0 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.32 in 60% hexanes/40% ethyl acetate). The product **32-A** was obtained as a yellow oil (163 mg, 60% yield). ^{1}H NMR (d_6-acetone): δ 8.72 (m, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.88 (td, J = 6.8, 2.0 Hz, 2H), 7.77 (d, J = 6.8 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.39 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 2.22 (s, 3H)..



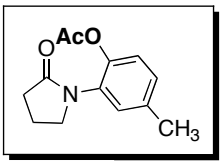
Substrate **33** (207 mg, 1.20 mmol, 1 equiv), $PhI(OAc)_2$ (462 mg, 1.4 mmol, 1.2 equiv), and $Pd(OAc)_2$ (13.4 mg, 0.06 mmol, 0.05 equiv) were combined in C_6H_6 (7.7 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 4 h. ^{1}H NMR analysis of the crude reaction mixture showed a 6:1 mixture of regioisomers. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.26 in 70% hexanes/30% ethyl acetate). The product **33-A** was obtained as a pale yellow oil (163 mg, 59% yield) as a 6:1 (by NMR) mixture of regioisomers. ^{1}H NMR (d_6-acetone) (major isomer): δ 8.70-8.69 (m, 1H), 7.88 (td, J = 7.6, 1.8 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.61-7.58 (m, 1H), 7.38-7.35 (m, 1H), 7.26-7.23 (multiple peaks, 2H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone) (major isomer): δ 169.76, 161.18 (d, $^1J_{CF}$ = 241 Hz), 154.97, 150.66, 145.50, 137.56, 135.79 (d, $^3J_{CF}$ = 8.34 Hz), 126.40 (d, $^3J_{CF}$ = 8.4 Hz), 124.40, 123.80, 117.66 (d, $^2J_{CF}$ = 24 Hz),

116.93 (d, $^2J_{CF}$ = 24 Hz), 20.94. ^{19}F NMR ($CDCl_3$): -116.27 to -116.32 (m), -128.33 to -128.37 (m). IR (thin film): 1766, 1462 cm^{-1}. Anal. Calcd for $C_{13}H_{10}FNO_2$: C, 67.53, H, 4.36, N, 6.06; Found: C, 67.19, H, 4.16, N, 6.04. The isomers do not separate by GC.



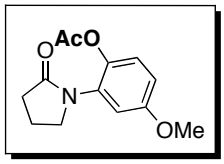
2-Bromo-4-fluorophenol (1.00 g, 5.20 mmol, 1 equiv), Ac_2O (10.5 mL) and pyridine (2.0 mL) were combined in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and extracted with H_2O (3 x 30 mL) and brine (1 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product, 1-acetoxy-2-bromo-4-fluorobenzene was obtained as a yellow oil (946 mg, 77% yield).

Under a nitrogen atmosphere, 1-acetoxy-2-bromo-4-fluorobenzene (500 mg, 2.10 mmol, 1 equiv), and $Pd(PPh_3)_4$ (248 mg, 0.21 mmol, 0.10 equiv) were combined in toluene (11 mL), and 2- tributylpyridyltin (869 mg, 2.36 mmol, 1.1 equiv) was added. The reaction mixture was refluxed for 12 h, then diluted with ethyl acetate (30 mL), filtered through a pad of silica, and washed with copious ethyl acetate. The washings were combined, concentrated under vacuum, and purified by chromatography on silica gel (R_f = 0.24 in 75% hexanes/25% ethyl acetate). The product (**33-A**) was obtained as pale yellow oil (248 mg, 50% yield). ^{1}H NMR (d_6-acetone): δ 8.70-8.68 (m, 1H), 7.89 (td, J = 8.0, 1.8 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.60-7.57 (m, 1H), 7.39-7.36 (m, 1H), 7.26-7.24 (multiple peaks, 2H), 2.18 (s, 3H).

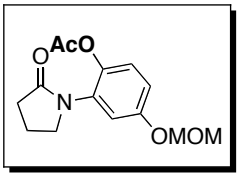


Substrate **34** (201 mg, 1.15 mmol, 1 equiv), $PhI(OAc)_2$ (665 mg, 2.06 mmol, 1.8 equiv), and $Pd(OAc)_2$ (12.8 mg, 0.06 mmol, 0.05 equiv) were combined in AcOH (13.5 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at

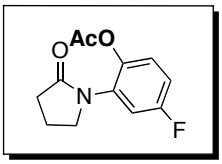
100ºC for 12 h. The reaction mixture was filtered through a plug of glass wool and washed with copious ethyl acetate. The solvent was removed under vacuum, and the resulting black oil was purified by chromatography on silica gel (R_f = 0.22 in 20% hexanes/80% ethyl acetate). The product **34-A** was obtained as a pale yellow oil (197 mg, 74% yield). ^{1}H NMR (d_6-acetone): δ 7.18 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 8.3, 2.1 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 3.72 (t, J = 7.0 Hz, 2H), 2.38 (t, J = 8.0 Hz, 2H), 2.31 (s, 3H), 2.20 (s, 3H), 2.18-2.10 (multiple peaks, 2H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 173.97, 169.25, 144.91, 136.61, 132.55, 128.77, 128.59, 124.16, 50.47, 31.58, 20.97, 20.79, 20.02. IR (thin film): 2954, 1763, 1699, 1425 cm^{-1}. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{13}H_{15}NO_3$, 256.0950; found, 256.0952. GC analysis (RESTEK Rtx®-5, FID detector): 99.5% integration. Only one isomer is observed by GC and ^{1}H NMR.



Substrate **35** (202 mg, 1.05 mmol, 1 equiv), $PhI(OAc)_2$ (510 mg, 1.58 mmol, 1.5 equiv), and $Pd(OAc)_2$ (11.8 mg, 0.05 mmol, 0.05 equiv) were combined in AcOH (12.4 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 3.0 h. The reaction mixture was filtered through a plug of glass wool and washed with copious ethyl acetate. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.20 in 20% hexanes/80% ethyl acetate). The product **35-A** was obtained as a pale brown solid (193 mg, 73% yield); mp = 96.5-97.5ºC. ^{1}H NMR (d_6-acetone): δ 7.09 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 2.9 Hz, 1H), 6.86 (dd, J = 8.9, 3.0 Hz, 1H), 3.78 (s, 3H), 3.73 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 8.1 Hz, 2H), 2.19 (s, 3H), 2.17-2.09 (multiple peaks, 2H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 173.97, 169.48, 158,32, 140.64, 133.59, 124.99, 113.47, 113.29, 56.06, 50.48, 31.61, 20.93, 20.02. IR (KBr): 2960, 1759, 1690, 1605 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64, H, 6.07, N, 5.62; Found: C, 62.46, H, 5.72, N, 5.59. Only one isomer is observed by GC and ^{1}H NMR.

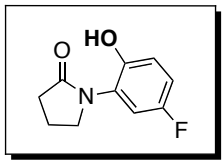


Substrate **36** (202 mg, 0.91 mmol, 1 equiv), $PhI(OAc)_2$ (530 mg, 1.64 mmol, 1.8 equiv), and $Pd(OAc)_2$ (10.2 mg, 0.04 mmol, 0.05 equiv) were combined in AcOH (5.4 mL) and Ac_2O (5.4 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 6.5 h. The reaction mixture was filtered through a plug of glass wool and washed with copious ethyl acetate. The solvent was removed under vacuum, and the resulting brown oil was purified by chromatography on silica gel (R_f = 0.20 in 20% hexanes/80% ethyl acetate). The product **36-A** was obtained as a light brown oil (179 mg, 70% yield). ^{1}H NMR (d_6-acetone): δ 7.10 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 2.9 Hz, 1H), 6.97 (dd, J = 8.9, 2.9 Hz, 1H), 5.18 (s, 2H), 3.73 (t, J = 6.8 Hz, 2H), 3.43 (s, 3H), 2.39 (t, J = 8.1 Hz, 2H), 2.19 (s, 3H), 2.18-2.10 (multiple peaks, 2H). $^{13}C\{^1H\}$ NMR (d_6-acetone): δ 173.99, 169.42, 155.95, 141.54, 133.58, 125.02, 115.84, 115.79, 99.51, 56.19, 50.47, 31.58, 20.94, 20.02. IR (thin film): 2956, 1762, 1699, 1504 cm^{-1}. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{14}H_{17}NO_5$, 302.1004; found, 302.1001. GC analysis (RESTEK Rtx®-5, FID detector): 99.4% integration. Only one isomer is observed by GC and ^{1}H NMR.

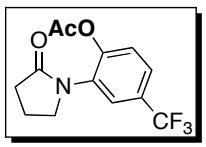


Substrate **37** (205 mg, 1.14 mmol, 1 equiv), $PhI(TFA)_2$ (1.08 g, 2.52 mmol, 2.2 equiv), and $Pd(OAc)_2$ (12.8 mg, 0.05 mmol, 0.05 equiv) were combined in AcOH (7.0 mL) and Ac_2O (7.0 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 3.5 h. GCMS analysis of the crude reaction mixture showed a 14:1 mixture of regioisomers. The reaction mixture was filtered through a plug of glass wool and washed with copious ethyl acetate. The solvent was removed under vacuum, and the resulting black oil was purified by chromatography on silica gel (R_f = 0.26 in 20% hexanes/80% ethyl acetate). The product **37-A** was obtained as a brown solid

(239 mg, 88% yield); mp = 49.9-52.0 ºC as a 20:1 (by GCMS) mixture of regioisomers. ^{1}H NMR (d_6-acetone): δ 7.26-7.21 (multiple peaks, 2H), 7.11-7.06 (m, 1H), 3.78 (t, J = 6.9 Hz, 2H), 2.41 (t, J = 7.7 Hz, 2H), 2.23 (s, 3H), 2.16 (quin, J = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 174.30, 169.23, 160.55 (d, $^{1}J_{CF}$ = 242 Hz), 143.08 (d, $^{4}J_{CF}$ = 3.0 Hz), 134.19 (d, $^{3}J_{CF}$ = 11 Hz), 125.89 (d, $^{3}J_{CF}$ = 9.9 Hz), 114.69 (d, $^{2}J_{CF}$ = 25 Hz), 114.60 (d, $^{2}J_{CF}$ = 23 Hz), 50.33, 31.51, 20.93, 19.96. ^{19}F NMR ($CDCl_3$): -114.96 to -115.01 (m). IR (thin film): 2984, 1766, 1702, 1503 cm^{-1}. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{12}H_{12}FNO_3$, 260.0699; found, 260.0703. GC analysis (RESTEK Rtx®-5, FID detector): 100% integration (two regioisomers).

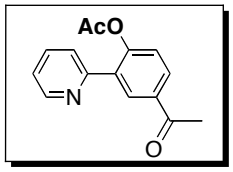


The regioselectivity of this reaction could not be determined definitively from the ^{1}H NMR spectrum of **37-A**. As a result, **37-A** was hydrolyzed to the phenol according to the following procedure in order to assess the regioselectivity. Product **37-A** (144 mg, 0.61 mmol, 1 equiv) and K_2CO_3 (12.7 mg, 0.09 mmol, 0.15 equiv) were combined in MeOH (1.3 mL) in a 20 mL vial, and the reaction was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with H_2O (3 x 15 mL) and brine (1 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product was obtained as a white solid (83 mg, 70% yield). ^{1}H NMR (C_6D_6): δ 9.28 (s, 1H), 7.02 (dd, J = 8.9, 5.6 Hz, 1H), 6.67-6.63 (m, 1H), 6.33 (dd, J = 9.9, 2.9 Hz, 1H), 2.61 (t, J = 6.9 Hz, 2H), 1.79 (t, J = 7.9 Hz, 2H), 1.020-0.939 (multiple peaks, 2H).

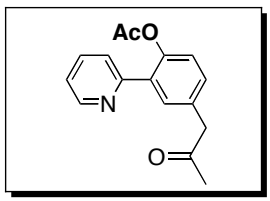


Substrate **38** (204 mg, 0.89 mmol, 1 equiv), $PhI(TFA)_2$ (1913 mg, 4.40 mmol, 5.0 equiv), and $Pd(OAc)_2$ (9.90 mg, 0.04 mmol, 0.05 equiv) were combined in AcOH (10.5 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at

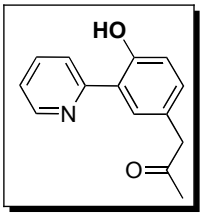
100ºC for 12 h. The reaction mixture was filtered through a plug of glass wool and washed with copious ethyl acetate. The solvent was removed under vacuum, and the resulting brown oil was purified by chromatography on silica gel (R_f = 0.29 in 30% hexanes/70% ethyl acetate). The product **38-A** was obtained as a light brown oil (115 mg, 45% yield). ^{1}H NMR (d_6-acetone): δ 7.81 (d, J = 2.0 Hz, 1H), 7.66 (dd, J = 8.4, 2.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 3.84 (d, J = 6.8 Hz, 2H), 2.44 (t, J = 8.0 Hz, 2H), 2.28 (s, 3H), 2.19 (quin, J = 7.6 Hz, 2H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 173.50, 167.78, 148.77, 132.86, 127.49 ($^2J_{C\text{-}F}$ = 32 Hz), 124.88, 124.58 ($^3J_{C\text{-}F}$ = 12 Hz), 124.02 ($^3J_{C\text{-}F}$ = 15 Hz), 123.88 ($^1J_{C\text{-}F}$ = 270 Hz), 49.34, 30.47, 20.02, 19.07.



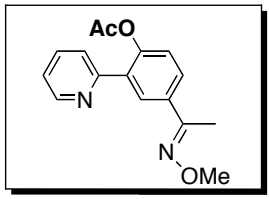
Substrate **46** (202 mg, 1.02 mmol, 1 equiv), $PhI(OAc)_2$ (396 mg, 1.23 mmol, 1.2 equiv), and $Pd(OAc)_2$ (11.5 mg, 0.05 mmol, 0.05 equiv) were combined in C_6H_6 (3.3 mL) and Ac_2O (3.3 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100 ºC for 0.5 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.20 in 55% hexanes/45% ethyl acetate). The product **46-A** was obtained as a yellow oil (213 mg, 82% yield). ^{1}H NMR (d_6-acetone): δ 8.73-8.71 (m, 1H), 8.43 (d, J = 2.3 Hz, 1H), 8.07 (dd, J = 8.4, 2.3 Hz, 1H), 7.89 (td, J = 7.5, 1.9 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.39-7.35 (multiple peaks, 2H), 2.64 (s, 3H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 196.99, 169.36, 155.47, 152.85, 150.63, 137.54, 136.16, 134.22, 132.01, 130.29, 124.99, 124.50, 123.65, 26.85, 21.01. IR (thin film): 3005, 1766, 1684, 1587 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58, H, 5.13, N, 5.49; Found: C, 70.44, H, 5.17, N, 5.39. Only one isomer is observed by GC and ^{1}H NMR.



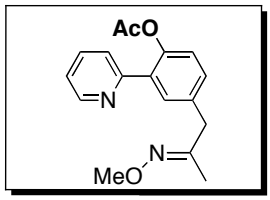
Substrate **48** (207 mg, 0.98 mmol, 1 equiv), $PhI(OAc)_2$ (473 mg, 1.47 mmol, 1.5 equiv), and $Pd(OAc)_2$ (10.9 mg, 0.05 mmol, 0.05 equiv) were combined in C_6H_6 (3.2 mL) and Ac_2O (3.2 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100 ºC for 1.5 h**.** The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.32 in 70% hexanes/30% ethyl acetate). The product **48-A** was obtained as a yellow oil (204 mg, 77% yield). ^{1}H NMR (d_6-acetone): δ 8.68-8.66 (m, 1H), 7.84 (td, *J* = 8.0, 1.9 Hz, 1H), 7.68-7.66 (multiple peaks, 2H), 7.34-7.29 (multiple peaks, 2H), 7.15 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 2H), 2.18 (s, 3H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 205.56, 169.70, 156.22, 150.48, 148.19, 137.29, 134.00, 133.87, 132.84, 131.64, 124.45, 124.38, 123.25, 49.94, 29.63, 21.01. IR (thin film): 3004, 1763, 1714, 1586 cm^{-1}. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{16}H_{15}NO_3$, 292.0950; found, 292.0949. GC analysis (RESTEK Rtx®-5, FID detector): 100% integration. Only one isomer is observed by GC and ^{1}H NMR.



The regioselectivity of this reaction could not be determined definitively from the ^{1}H NMR spectrum of **48-A**. As a result, **48-A** was hydrolyzed to the phenol according to the following procedure in order to assess the regioselectivity. Product **48-A** (100 mg, 0.37 mmol, 1 equiv) and HCl (1ml) were combined in MeOH (2.0 mL) in a 20 mL vial, and the reaction was stirred for 8 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with H_2O (3 x 15 mL) and brine (1 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product was obtained as a orange oil (60.0 mg, 71% yield). ^{1}H NMR (d_6-acetone): δ 8.63-8.61 (m, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.04-7.99 (m, 1H), 7.86 (d, *J* = 2.1 Hz, 1H), 7.44-7.40 (m, 1H), 7.17 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 2H), 2.14 (s, 3H).

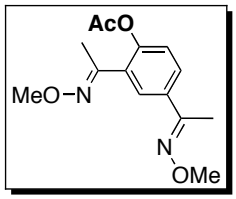


Substrate **50** (182 mg, 0.80 mmol, 1 equiv), $PhI(OAc)_2$ (388 mg, 1.20 mmol, 1.5 equiv), and $Pd(OAc)_2$ (8.99 mg, 0.04 mmol, 0.05 equiv) were combined in C_6H_6 (2.6 mL) and Ac_2O (2.6 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 0.5 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.20 in 75% hexanes/25% ethyl acetate). The product **50-A** was obtained as a yellow oil (177 mg, 77% yield) as a single isomer. ^{1}H NMR (d_6-acetone): δ 8.69 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.13 (d, *J* = 2.3 Hz, 1H), 7.88 (td, *J* = 7.9, 1.9 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.36 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 3.96 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 169.54, 155.93, 153.95, 150.52, 149.93, 137.35, 135.34, 133.96, 129.22, 127.83, 124.57, 124.43, 123.39, 62.25, 20.99, 12.42. IR (KBr): 2936, 1765, 1593 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59, H, 5.67, N, 9.85; Found: C, 67.39, H, 5.71, N, 9.75. Only one isomer is observed by GC and ^{1}H NMR.

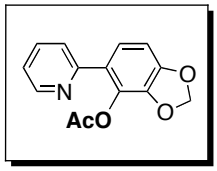


Substrate **51** (200 mg, 0.83 mmol, 1 equiv), $PhI(OAc)_2$ (402 mg, 1.25 mmol, 1.5 equiv), and $Pd(OAc)_2$ (9.32 mg, 0.04 mmol, 0.05 equiv) were combined in C_6H_6 (2.7 mL) and Ac_2O (2.7 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 1.0 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.24 in 60% hexanes/40% ethyl acetate). The product **51-A** was obtained as a yellow oil (182 mg, 74% yield) as a 2:1 mixture of oxime isomers. ^{1}H NMR ($CDCl_3$ with a few drops of C_6D_6) (major isomer): δ 8.50 (d, *J* = 4.8 Hz, 1H), 7.49 (td, *J* = 7.6, 1.8 Hz, 1H), 7.40 (d, *J*

= 2.2 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.02-6.99 (m, 1H), 6.93 (d, 8.2 Hz, 1H), 3.70 (s, 3H), 3.34 (s, 2H), 1.95 (s, 3H), 1.59 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) (mixture of isomers): δ 169.90, 168.40, 155.15, 150.49, 150.43, 150.35, 149.21, 146.76, 141.16, 137.36, 137.26, 129.15, 124.48, 124.22, 123.99, 122.92, 122.90, 109.91, 106.98, 105.54, 103.48, 103.16, 41.13, 20.99, 20.53. IR (KBr): 2937, 1767, 1586 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_3$ (mixture of oxime isomers): C, 68.44, H, 6.08, N, 9.39; Found: C, 68.28, H, 6.26, N, 9.23. Retention time (GC): 10.9 min (major oxime) and 10.7 min (minor oxime). Regioisomers not observed by GC or ^{1}H NMR.

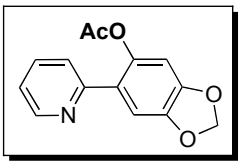


Substrate **52** (200 mg, 0.908 mmol, 1 equiv), $PhI(OAc)_2$ (351 mg, 1.09 mmol, 1.2 equiv), and $Pd(OAc)_2$ (10.2 mg, 0.04 mmol, 0.05 equiv) were combined in AcOH (2.9 mL) and Ac_2O (2.9 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 12 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.20 in 90% hexanes/10% ethyl acetate). The product **52-A** was obtained as a yellow oil (153 mg, 61% yield). ^{1}H NMR ($CDCl_3$): δ 7.65 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.25 (s, 3H), 2.17, (s, 3H), 2.12 (s, 3H).



Substrate **53** (150 mg, 0.75 mmol, 1 equiv), $PhI(OAc)_2$ (291 mg, 0.90 mmol, 1.2 equiv), and $Pd(OAc)_2$ (8.43 mg, 0.04 mmol, 0.05 equiv) were combined in C_6H_6 (4.9 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100 ºC for 10 h. The solvent was removed under vacuum, and the resulting orange oil was purified by chromatography on silica gel (R_f = 0.29 in 70% hexanes/30% ethyl acetate).

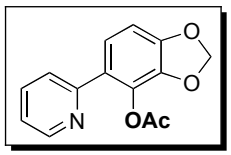
The product **53-B** was obtained as a yellow oil (55.5 mg, 29% yield) as a 2:1 mixture of regioisomers. ^{1}H NMR (d_6-acetone) (major isomer): δ 8.64-8.62 (m, 1H), 7.82 (td, J = 7.6, 1.9 Hz, 1H), 7.59 (dt, J = 8.0, 1.0 Hz, 1H), 7.32-7.27 (multiple peaks, 2H), 6.89 (d, J = 8.2 Hz, 1H), 6.11 (s, 2H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone) (mixture of isomers): δ 169.90, 168.39, 156.15, 150.43, 150.35, 149.21, 146.76, 144.05, 141.16, 137.37, 137.27, 132.96, 129.16, 124.47, 124.22, 123.99, 122.93, 109.91, 106.98, 105.55, 103.49, 103.16, 20.99, 20.52. IR(thin film): 2901, 1765, 1567 cm^{-1}. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{14}H_{11}NO_4$, 280.0586; found, 280.0585. GC analysis (RESTEK Rtx®-5, FID detector): 65.8% integration (major isomer), 34.2% integration (minor isomer). Retention time (GC): 9.37 min (major) and 9.60 min (minor).



Bromosesamol[ix] (500 mg, 2.30 mmol, 1 equiv), Ac_2O (4.6 mL) and pyridine (0.88 mL) were combined in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with H_2O (3 x 15 mL) and brine (1 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product, 1-acetoxy-2-bromo-4,5-methylenedioxybenzene was obtained as a orange solid (594 mg, 99% yield).

Under a nitrogen atmosphere, 1-acetoxy-2-bromo-4,5-methylenedioxybenzene (501 mg, 1.93 mmol, 1 equiv), and $Pd(PPh_3)_4$ (112 mg, 0.10 mmol, 0.05 equiv) were combined in toluene (10 mL), and 2- tributylpyridyltin (783 mg, 2.13 mmol, 1.1 equiv) was added. The reaction mixture diluted with ethyl acetate, filtered through a pad of Celite, and washed with copious ethyl acetate. The washings were combined and concentrated under vacuum. The crude product was dissolved in ethyl acetate (30 mL), extracted with 1M aqueous KF (4 x 30 mL). The combined organic layers were then extracted with brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The resulting yellow oil was purified by chromatography on silica gel (R_f = 0.29 in 70% hexanes/30% ethyl acetate).

The product **53-A** was obtained as a pale yellow solid (103 mg, 21% yield). ^{1}H NMR (d_6-acetone): δ 8.65-8.62 (m, 1H), 7.82 (td, J = 8.0, 1.9 Hz, 1H), 7.64 (dt, J = 8.0, 1.1 Hz, 1H), 7.31-7.26 (multiple peaks, 2H), 6.75 (s, 1H), 6.10 (s, 2H), 2.15 (s, 3H). Retention time (GC): 9.60.



2-bromo-5,6-methylenedioxyphenol[ix, x] (350 mg, 1.60 mmol, 1 equiv), Ac_2O (3.2 mL) and pyridine (0.61 mL) were combined in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with H_2O (3 x 15 mL) and brine (1 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The product, 1-acetoxy-6-bromo-2,3-methylenedioxybenzene was obtained as a orange solid (337 mg, 81% yield).

Under a nitrogen atmosphere, 1-acetoxy-6-bromo-2,3-methylenedioxybenzene (337 mg, 1.30 mmol, 1 equiv), and $Pd(PPh_3)_4$ (75.1 mg, 0.06 mmol, 0.05 equiv) were combined in toluene (10 mL), and 2- tributylpyridyltin (718 mg, 1.95 mmol, 1.5 equiv) was added. The reaction mixture diluted with ethyl acetate (30 mL), filtered through a pad of Celite, and washed with copious ethyl acetate. The washings were combined and concentrated under vacuum. The crude product was dissolved in ethyl acetate, extracted with 1M aqueous KF (4 x 30mL). The combined organic layers were then extracted with brine (1 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The resulting yellow oil was purified by chromatography on silica gel (R_f = 0.29 in 70% hexanes/30% ethyl acetate). The product **53-B** was obtained as a yellow oil (58.0 mg, 17% yield). ^{1}H NMR (d_6-acetone): δ 8.63-8.62 (m, 1H), 7.84-7.61 (m, 1H), 7.59 (dt, J = 8.0, 1.1 Hz, 1H), 7.32-7.28 (multiple peaks, 2H), 6.89 (d, J = 8.2, 1H), 6.11 (s, 2H), 2.21 (s, 3H). Retention time (GC): 9.37.

Reaction with substrate 23: Substrate **23** (20.0 mg, 0.07 mmol, 1 equiv), $PhI(OAc)_2$ (33.5 mg, 0.10 mmol, 1.5 equiv), and $Pd(OAc)_2$ (0.78 mg, 0.003 mmol, 0.05 equiv) were combined in AcOH (0.45 mL), AcOH/Ac_2O (0.23/0.23 mL), C_6H_6 (0.45 mL), C_6H_6/Ac_2O (0.23/0.23 mL), CH_2Cl_2 (0.45 mL) or CH_3CN (0.45 mL) in a 4 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 12 h. The reaction was cooled to room temperature and analyzed by gas chromatography, which showed only starting material.

Reaction with complex 24: Complex **24** (20.0 mg, 0.04 mmol, 1 equiv) and $PhI(OAc)_2$ (17.1 mg, 0.05 mmol, 1.2 equiv) were combined in AcOH (0.28 mL), AcOH/Ac_2O (0.14/0.14 mL), C_6H_6 (0.28 mL), C_6H_6/Ac_2O (0.14/0.14 mL), CH_2Cl_2 (0.28 mL) or CH_3CN (0.28 mL) in a 4 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 12 h. The reaction was cooled to room temperature and analyzed by ^1H NMR spectroscopy and gas chromatography, which showed no formation of the acetoxylated product.

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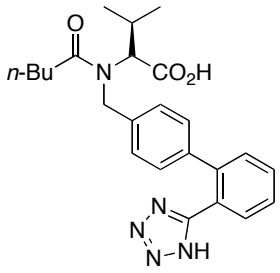
Chapter 3

Palladium-Catalyzed C-H Activation/C-C Bond Formation

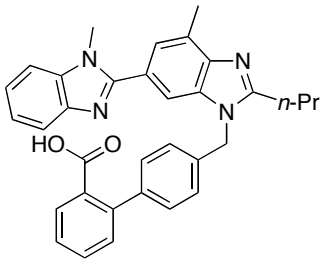
3.1 Background and Significance

Biaryl subunits are widely prevalent in pharmaceuticals and agrochemicals (Scheme 1).[1] Additionally, they serve as integral components of semiconductors and liquid crystals. Hence, the formation of biaryl linkages is very important in synthetic organic chemistry, and as a result, a large number of metal-catalyzed reactions have been developed for this transformation.

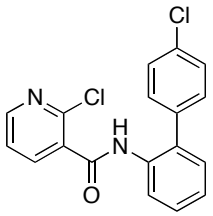
Scheme 1: Biaryl Units as Components of Pharmaceuticals and Agrochemicals



(**1**)
Angiotensin II receptor antagonist



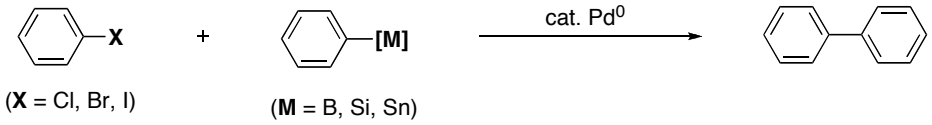
(**2**)
Angiotensin II receptor antagonist



(**3**)
Complex II inhibitor

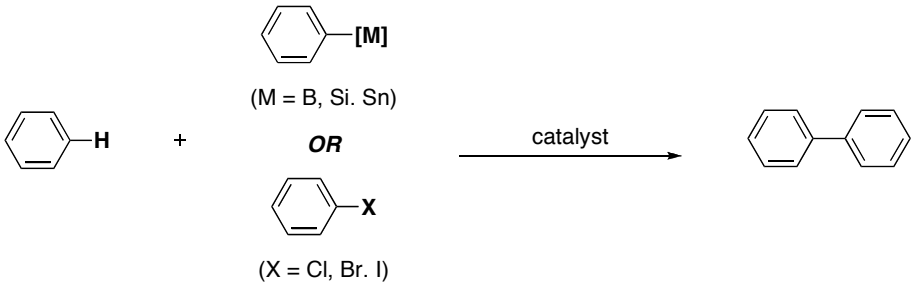
Among these, $Pd^{0/II}$-catalyzed cross-coupling reactions between organic halides (or triflates) and organometallic reagents (e.g., boronic acids, stannanes, silanes) have been demonstrated to have widespread synthetic utility (Scheme 2).[2]

Scheme 2: $Pd^{0/II}$ Cross Coupling Reactions



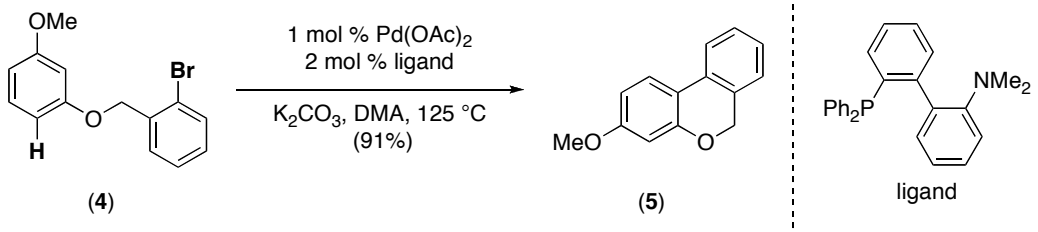
However, these methods do have two significant disadvantages. These are: (i) the requirement for two functionalized starting materials that might not always be accessible in the context of complex molecule synthesis and (ii) the generation of undesired salt byproducts that necessitate tedious and expensive purification processes. Hence, significant research efforts have recently focused on the transition metal-catalyzed direct arylation of arene C–H bonds with organometallic reagents (or aryl halides) as a more attractive alternative (Scheme 3). This approach would employ more ubiquitous C–H bonds in lieu of one of the functionalized reactants and would lead to less byproduct formation, thus rendering the process more atom economical. However, one of the key challenges associated with this strategy is the achievement of site selective and chemoselective arylation of the desired C–H bond in a complex molecule.

Scheme 3: Direct Arylation of Arenes



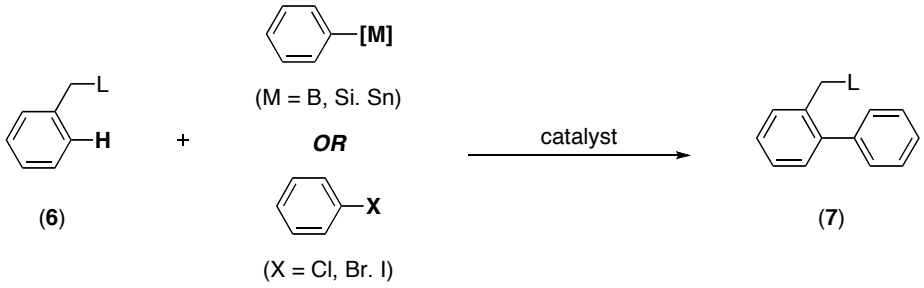
One approach to achieve site selectivity in direct arylation reactions has been the intramolecular coupling of a C–H bond with an appropriate arylating reagent. Several palladium-catalyzed transformations of this type have been reported.[3,4] For example, Fagnou and coworkers have shown that **4** can be converted to **5** in the presence of catalytic $Pd(OAc)_2$ (Scheme 4).[3] However, these reactions are inherently limited by the requirement for the C–H bond and the aromatic coupling partner to be present in the same molecule.

Scheme 4: Example of an Intramolecular Direct Arylation Reaction



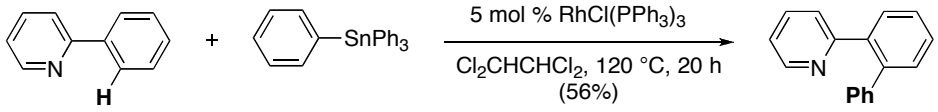
A more general strategy employed for achieving site selective arylation of C–H bonds involves chelate-directed C–H activation/C–C bond formation. This approach allows for the selective installation of an aryl group proximal to the directing ligand (L) (Scheme 5).

Scheme 5: Chelate Assisted Direct Arylation Reactions



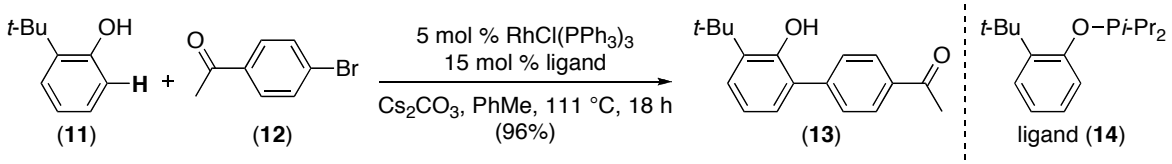
Prior to our investigations in this field, there were several reports of ligand directed C–H activation/arylation reactions catalyzed by Ru and Rh complexes. For example, Rh^{I}-catalyzed ligand directed arylation of 2-phenylpyridine **8** was reported with aryl stannanes (Scheme 6).[5] However, the use of toxic stannane **9** limits the practical applicability of this reaction. Additionally, Bedford and coworkers had demonstrated the *ortho* arylation of phenols using aryl bromides and a rhodium catalyst (Scheme 7).[6] However, only *ortho* substituted phenols could be efficiently arylated using this method.

Scheme 6: Rhodium-Catalyzed Pyridine Directed Arylation



(**8**) (**9**) (**10**)

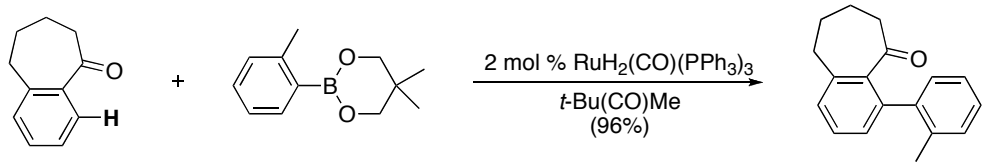
Scheme 7: Rhodium-Catalyzed Phenol Directed Arylation



(**11**) (**12**) (**13**) ligand (**14**)

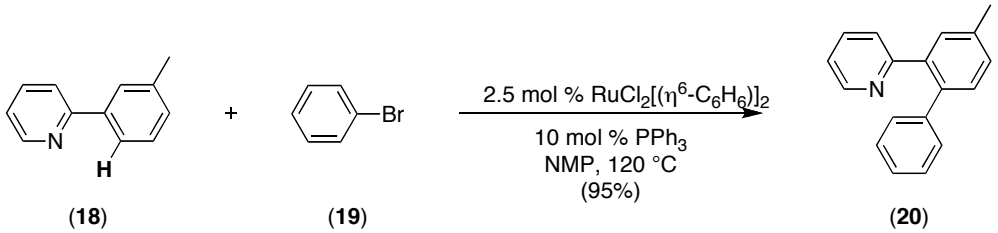
A ruthenium-catalyzed approach for ketone-directed arylation of arenes was developed using arylboronates. A variety of electronically diverse aromatic ketones and arylboronates were used in these transformations (Scheme 8).[7,8] Subsequently, Oi reported a methodology for the ruthenium-catalyzed arylation of phenylpyridines with aryl bromides (Scheme 9).[9,10] However, these transformations were not expanded to the use of other directing groups.

Scheme 8: Ruthenium-Catalyzed Ketone Directed Arylation



(**15**) (**16**) (**17**)

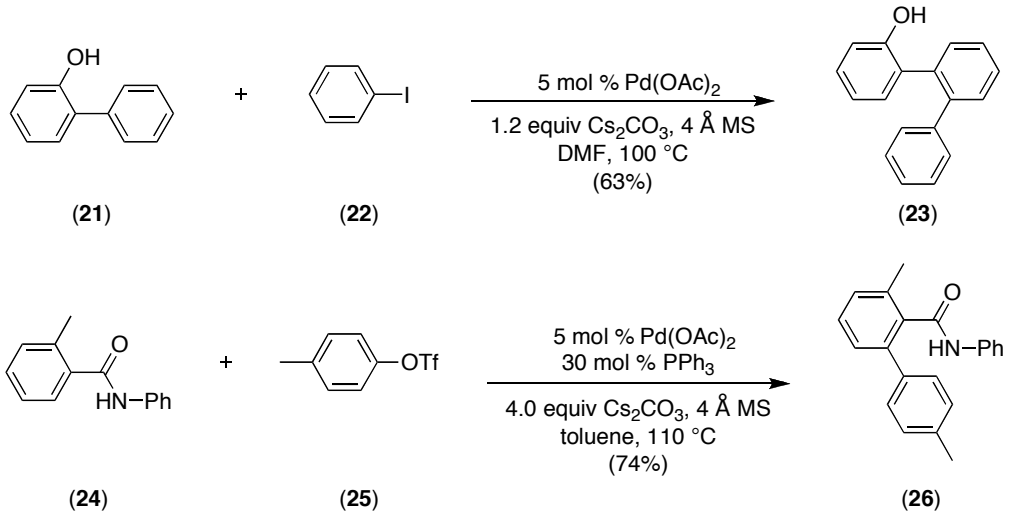
Scheme 9: Ruthenium-Catalyzed Pyridine Directed Arylation



(**18**) (**19**) (**20**)

Finally, Miura demonstrated phenol and amide directed $Pd^{0/II}$-catalyzed arylation reactions using aryl halides and triflates. As illustrated in Scheme 10, the palladium-catalyzed reaction of **21** with phenyl iodide leads to the arylated product **23** in 76% isolated yield.[11-13] Similarly, the arylated product **26** was obtained in 74% yield from the reaction of anilide **24** with PhOTf.[14]

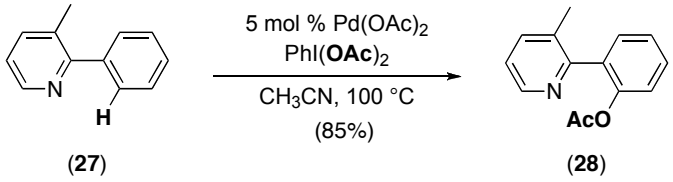
Scheme 10: $Pd^{0/II}$-Catalyzed Direct Arylation Reactions



While all the aforementioned examples demonstrated the feasibility of direct arylation reactions, they exhibit a limited scope of directing groups. More importantly, functionalities such as aryl halides are not tolerated in the methodologies described above. Hence the development of direct arylation reactions with a broad scope and functional group compatibility remains an area of current interest.

Our group has demonstrated a general palladium-catalyzed ligand-directed acetoxylation of C–H bonds using $PhI(OAc)_2$ as the terminal oxidant for substrates bearing a wide variety of directing groups.[15-18] For example, the palladium-catalyzed reaction of 3-methyl-2-phenylpyridine **27** with $PhI(OAc)_2$ in AcOH affords the acetoxylated product **28** in 85% isolated yield (Scheme 11).

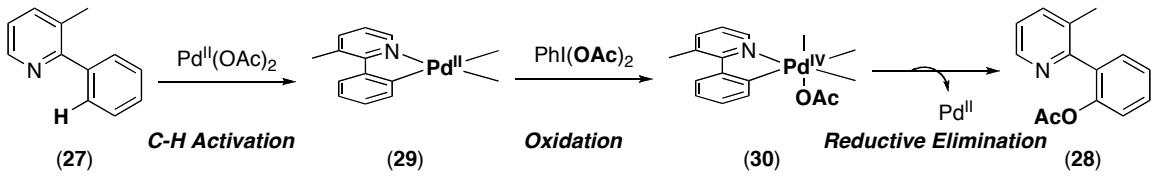
Scheme 11: Palladium-Catalyzed Ligand Directed Acetoxylation



(**27**) (**28**)

As shown in Scheme 12, the proposed mechanism of this reaction involves (i) ligand-directed C–H activation to afford **29**, (ii) oxidation of **29** to the Pd^{IV} intermediate **30** by $PhI(OAc)_2$ and finally (iii) C–O bond forming reductive elimination from **30**. Importantly, $PhI(OAc)_2$ is believed to be the source of the acetate in the the Pd^{IV} intermediate **30** and hence in the final product.

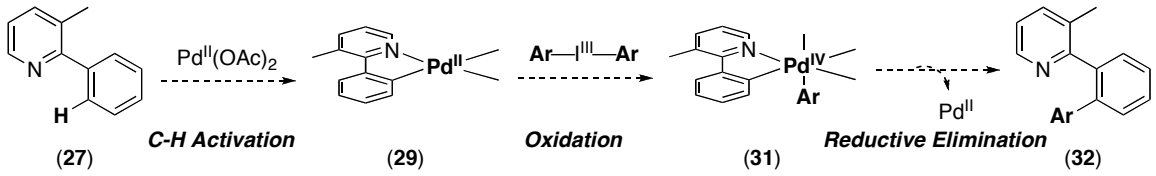
Scheme 12: Proposed Mechanism for Palladium-Catalyzed Acetoxylation



(**27**) (**29**) (**30**) (**28**)

Based on this mechanistic manifold, we reasoned that the use of diaryl iodonium salts $[Ar–I–Ar]BF_4$, in place of $PhI(OAc)_2$ might allow us to access the Pd^{IV} aryl intermediate **31** (Scheme 13). C–C reductive elimination from **31** would then afford the desired arylated product **32**.[19]

Scheme 13: Proposed Palladium-Catalyzed Direct Arylation



(**27**) (**29**) (**31**) (**32**)

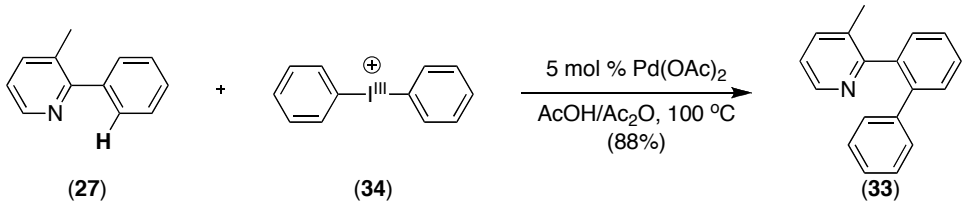
Overall this process would allow for the palladium-catalyzed ligand-directed site selective arylation of C–H bonds in substrates containing appropriate chelating groups. Additionally, the proposed $Pd^{II/IV}$ catalytic cycle for this reaction is highly unusual and mechanistically distinct from the $Pd^{0/II}$-catalyzed C–C bond forming reactions. We were

excited about the implications of the $Pd^{II/IV}$ manifold with respect to the synthetic utility of these direct arylation reactions. Based on the ambient reaction conditions and the stability of functional groups such as aromatic bromides to the $Pd^{II/IV}$-catalyzed acetoxylation reactions developed by our group, we envisioned that the proposed C–H activation/C–C bond forming transformation might exhibit a broad and complementary scope to traditional cross-coupling methodologies and to the other directed C–H arylation reactions described above.

3.2 Synthetic Scope

We began our studies with 3-methyl-2-phenylpyridine (**27**) as the substrate and $[Ph–I–Ph]BF_4$ as the oxidant. After some optimization, my colleague Nick Deprez found that the palladium-catalyzed reaction of **27** with $[Ph–I–Ph]BF_4$, in AcOH afforded the phenylated product **33** in 88% isolated yield (Scheme 14). Importantly, the C–H bond adjacent to the pyridine directing group was selectively phenylated in this system (Scheme 14).

Scheme 14: Palladium-Catalyzed Direct Arylation of **27**

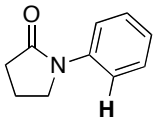
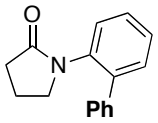
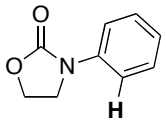
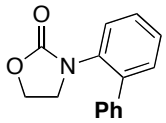
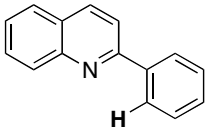
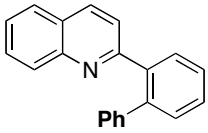
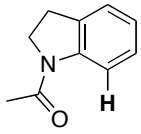
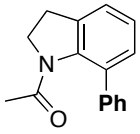


(**27**) (**34**) (**33**)

In conjunction with Lopa Desai, we have shown that the palladium-catalyzed phenylation of a variety of other substrates could also be achieved. Varying the solvent (typically between AcOH, $AcOH/Ac_2O$, C_6H_6 and toluene) and the equivalents of oxidant between 1.1 and 2.5 was necessary to obtain optimal conditions for each substrate. In addition, the use of $NaHCO_3$ as an additive led to improved yields for the phenylation of certain amide substrates. In these cases, the improved yields were attributed to the neutralization of the strong acid, HBF_4 generated in these arylation reactions. Directing groups such as pyridines, amides, quinolines, and oxazolidinones could be effectively

used in these transformations (Table 3.1). Importantly, these ligands are widely prevalent in important biologically active molecules. Hence, this methodology could potentially be used to arylate C–H bonds proximal to chelating groups in late stages of the synthesis of pharmaceutical candidates.

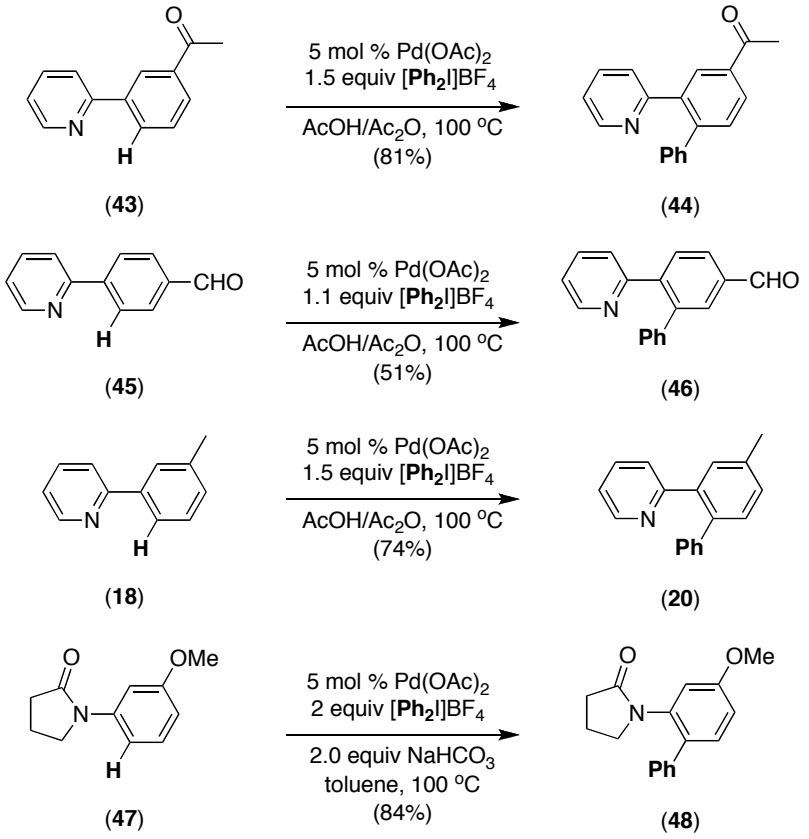
Table 3.1: Scope of Directing Groups

Entry	Substrate	Product	Yield[a]
1	 (**35**)	 (**36**)	75%[b]
2	 (**37**)	 (**38**)	84%[b]
3	 (**39**)	 (**40**)	58%
4	 (**41**)	 (**42**)	49%

[a]Reaction Conditions: 1 equiv of substrate, 1.1-2.5 equiv $[Ph_2I]BF_4$, 5 mol % $Pd(OAc)_2$ in AcOH, AcOH/Ac_2O, C_6H_6 or toluene, 100 C, 8 - 24 h.
[b] $NaHCO_3$ (1.5 - 2.0 equiv) added.

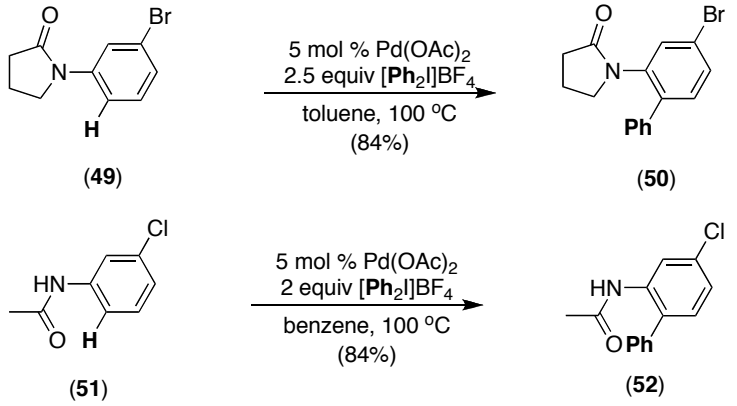
This phenylation reaction is also tolerant of a number of common functional groups. For example, enolizable ketones (**43**), aromatic aldehydes (**45**) and benzylic hydrogens (**18**) are well tolerated under the reaction conditions (Scheme 15).

Scheme 15: Functional Group Tolerance for Direct Phenylation



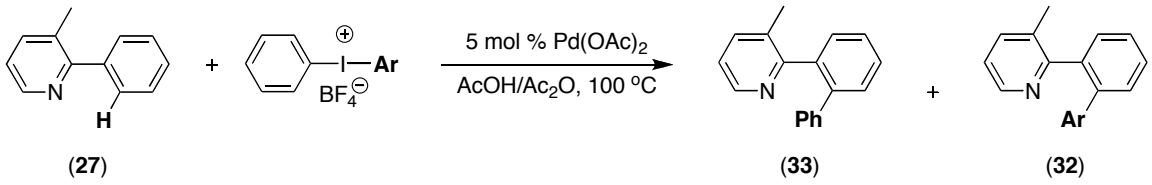
Furthermore, both electron rich (substrates **43** and **47**, Scheme 15) and electron poor arenes can be effectively phenylated to afford products in good yields. Analogous to the acetoxylation reactions described in ***Chapter 2***, substrates **43, 18**, and **47** bearing *meta*-substituted arenes undergo phenylation at the less sterically congested C-H bond with >20:1 selectivity.[18] Finally and most importantly, these reactions exhibit functional group tolerance complementary to traditional $Pd^{0/II}$-catalyzed cross-coupling methodologies. For example, aromatic bromides in substrates **51** (which are reactive with Pd^0 intermediates) are completely stable under our oxidative catalytic conditions (Scheme 16).

Scheme 16: Tolerance of Aromatic Halides

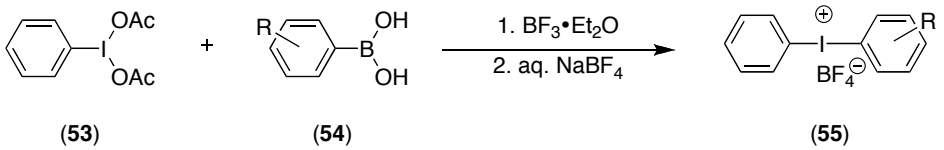


In order to further expand the synthetic utility of these transformations, we next desired to incorporate diverse aryl groups into the final products. We began these studies by investigating the reaction of 3-methyl-2-phenylpyridine **27** with a variety of mixed iodonium salts [Ph–I–Ar]BF_4. In these reactions, one could obtain the phenylated product **33** and/or the arylated product **32** via transfer of either the phenyl (Ph**)** or the aryl (Ar) group from the oxidant (Scheme 17). Hence we wanted to assess the effect of the electronic and steric nature of Ar on the ratio of **33** to **32**. Importantly, the mixed oxidants [Ph–I–Ar]BF_4 are easily accessible by the reaction of $PhI(OAc)_2$ with $ArB(OH)_2$ in the presence of BF_3•Et_2O (Scheme 18).

Scheme 17: Direct Arylation with Mixed Oxidants

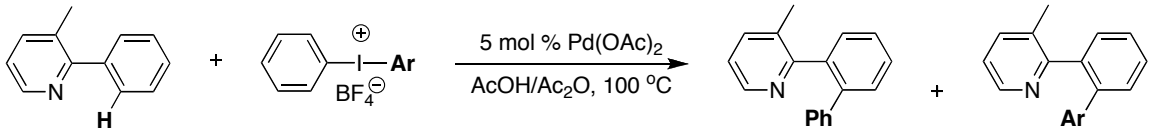


Scheme 18: Synthesis of Mixed Oxidants

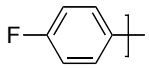
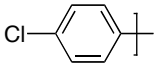
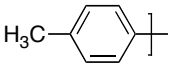
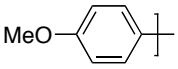
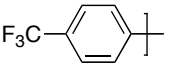


We were pleased to find that the $Pd(OAc)_2$-catalyzed reaction of **27** with the mixed iodine(III) reagents resulted in selective arylation of the C–H bond adjacent to the pyridine group (Table 3.2). A variety of functional groups including aromatic halides (Table 3.2, entries 1 and 2) and benzylic hydrogens (Table 3.2, entry 3.3) were well tolerated on the arene component (Table 3.2). However, the desired arylated products **B** were obtained only as mixtures with the analogous phenylated product **A**.

Table 3.2: Scope of Arylation of **27** with Mixed Oxidants



(**27**) (**A**) (**B**)

Entry	Ar	A:B[a]
1		3:1
2		1.2:1
3		1.4:1
4		3:1
5		1:2.6

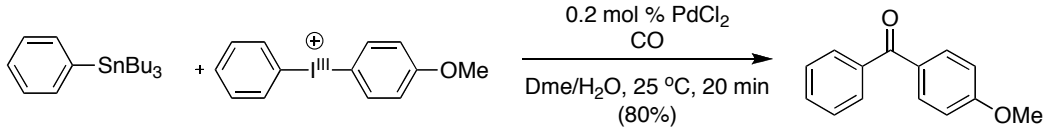
[a]Reaction Conditions: 5 mol % $Pd(OAc)_2$, 1.1 equiv [Ph—I—Ar]BF_4, AcOH, 12 h 100 °C.

Notably, the electronic properties of the aryl group had a significant influence on the product distribution (Table 3.2). For example, the reaction of **27** with [Ph–I–(*p*-CF_3Ph)] led to **B** as the major product (Table 3.2, entry 5). In contrast, the use of [Ph–I–(*p*-OMePh)], which contains an electron rich arene, afforded **A** and **B** in a ratio of 3:1 favoring the phenylated product (Table 3.2, entry 4). Hence, electron deficient aryl

groups transfer with greater facility than electron rich arenes under our reaction conditions.

In contrast, most $Pd^{0/II}$ cross-coupling reactions with $[Ph–I–Ar]BF_4$ show high selectivity for the transfer of electron rich arenes.[20] This is illustrated by the carbonylative Stille coupling of $PhSnBu_3$ with $[p\text{-}OMePh–I–Ph]BF_4$ shown in Scheme 19. Here, the electron rich methoxy substituted benzophenone **58** is the exclusive product (Scheme 19).[21]

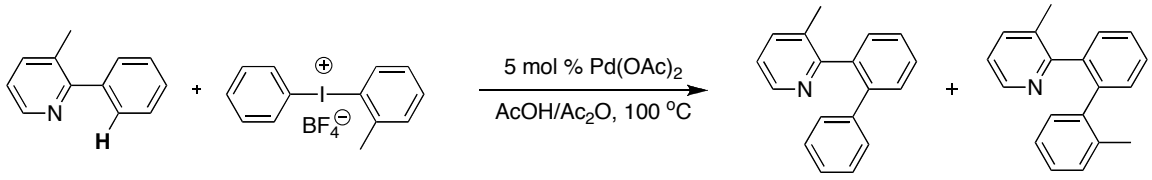
Scheme 19: Electronic Effects of the Oxidant in Carbonylative Stille Coupling



(**56**) (**57**) (**58**)

The steric properties of the oxidant also affected the product distribution in these direct arylation reactions. The yield of the arylated product decreased with increasing size of the **Ar** group. This is exemplified by the reaction of **27** with $[Ph–I–(o\text{-}CH_3Ph)]$ depicted in Scheme 20. In this system, the phenylated product **33** was formed preferentially over **60** with ~3:1 selectivity (Scheme 20).

Scheme 20: Steric Effects of the Oxidant



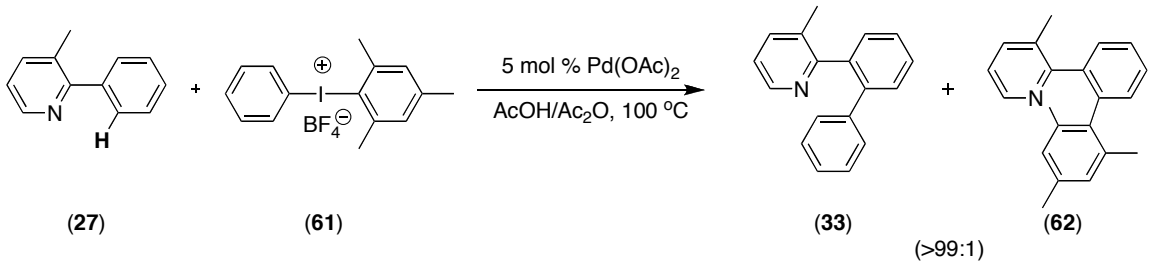
(**27**) (**59**) (**33**) (**60**)

(**3:1**)

This steric effect was most striking when $[Ph–I–mesityl]BF_4$ was employed as the oxidant. In this system, the phenylated product **33** was formed exclusively in 85% isolated yield. None of the product **62** with the bulky mesityl group was observed in this

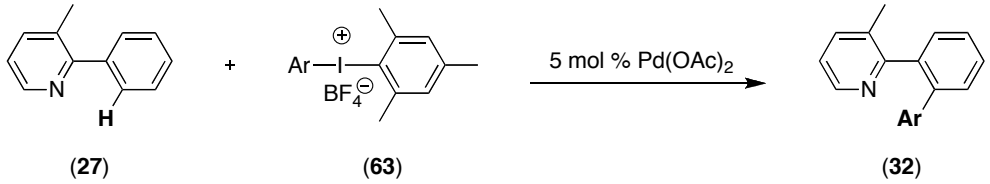
reaction (Scheme 21). Importantly, similar steric effects have been reported for $Pd^{0/II}$-catalyzed C–C bond forming reactions.[20]

Scheme 21: Phenylation of **27** with [Ph–I–Mesityl]BF_4



We envisioned that, analogous to the reaction with [mesityl–I–Ph]BF_4 (Scheme 21), the use of [mesityl–I–Ar]BF_4 might lead to the exclusive transfer of the smaller aryl groups (Scheme 22). Hence, this approach might allow for the formation of desired arylated products **32** in more synthetically useful selectivities than those obtained using [Ar–I–Ph]BF_4.

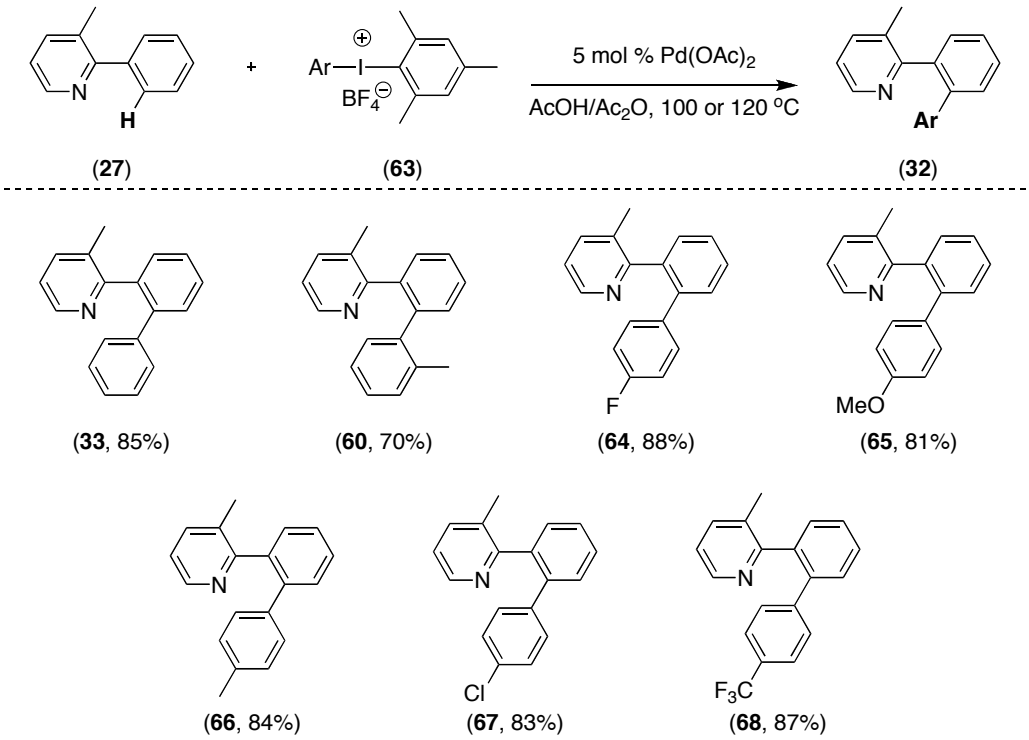
Scheme 22: Arylation of **27** with [Ar-I-Mesityl]BF_4



We were delighted to find that the use of [mesityl–I–Ar]BF_4 under our standard reaction conditions exclusively effected transfer of the Ar group in good to excellent yields (Scheme 23). The products **33**, **60**, and **64-68** were obtained with >20:1 selectivity regardless of the electronic nature of the aryl group. Furthermore, a variety of functional groups including aromatic halides (**64** and **67**) were well tolerated on the arene component. Additionally, the sterically hindered *o*-tolyl group was also incorporated in the final product (**60**) with high (>20:1) levels of selectivity. Interestingly, the reactions to form **33**, **60**, **64** and **66-68** showed complete consumption of **27** in 12 h at 100 °C. However, the reaction of **27** with the electron rich oxidant [mesityl–I–(*p*-OMePh)]BF_4 to

form **65** required 120 °C to afford complete conversion. This effect of the oxidant electronics on the reaction rate suggests that oxidation by [Ar–I–mesityl]BF_4 occurs at or before the rate-limiting step.

Scheme 23: Scope of Arylation of **27** with [Ar-I-Mesityl]BF_4



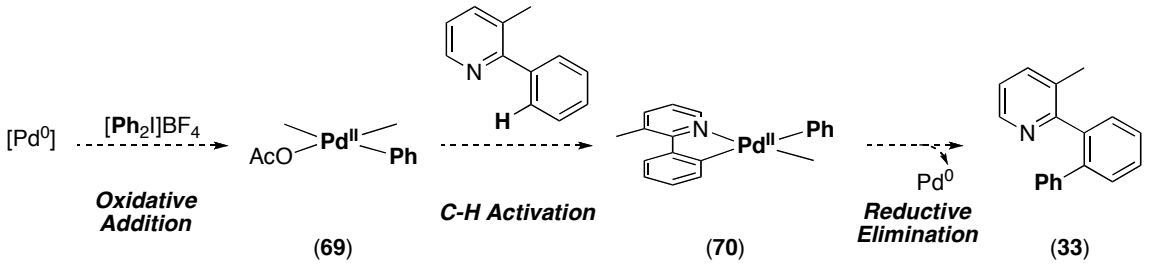
3.3 Mechanistic Investigations

Having explored the synthetic scope of these arylation reactions, we next turned our focus towards investigating the mechanism. As will be detailed below, we considered mechanisms involving $Pd^{0/II}$ and $Pd^{II/IV}$ catalytic cycles.

We first considered the most widely invoked mechanism for $Pd^{0/II}$-catalytic cycles (mechanism 1, Scheme 24) using I^{III} reagents.[20] This mechanism begins with oxidative addition of Pd^0 (generated via in situ reduction of $Pd(OAc)_2$) into the Ph–I bond of the oxidant to afford **69**. Subsequent ligand directed C–H activation followed by C–C bond

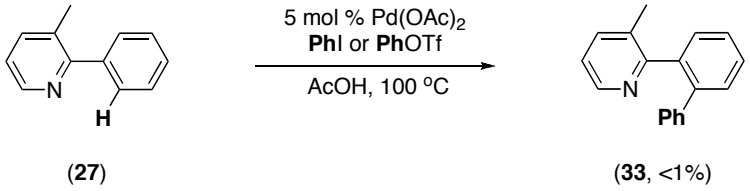
forming reductive elimination could then release the product and regenerate the Pd^0 catalyst.

Scheme 24: Mechanism 1



We reasoned that if our arylation reactions proceeded via mechanism 1, then the use of conventional $Pd^{0/II}$ oxidants such as ArI in place of $[Ar–I–Ar]BF_4$ should afford the arylated products. However, as shown in Scheme 25, the palladium-catalyzed reaction of **27** with PhI or PhOTf as oxidants afforded <1% of the phenylated product **33**. This result strongly suggests against mechanism 1 being operative under our catalytic conditions.

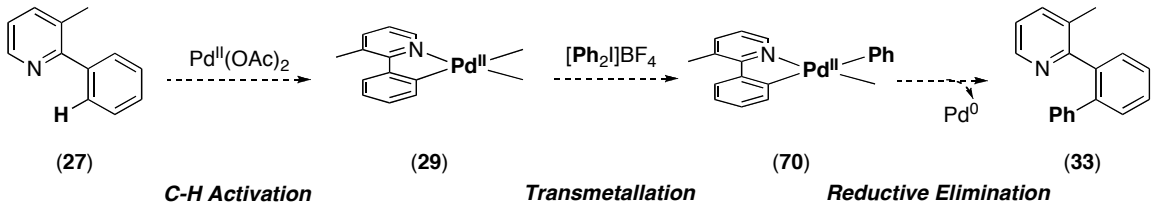
Scheme 25: Reaction of **27** with PhI and PhOTf



(**27**) (**33**, <1%)

We next considered an alternative $Pd^{II/0}$ mechanism that commences with Pd^{II} mediated C–H activation to afford the cyclopalladated complex **29** (Scheme 26).[20] Transmetallation of the aryl group (Ar) from the iodine(III) reagent onto **29** with subsequent C–C reductive elimination leads to the arylated product **33**. The first step of this mechanism, namely cyclopalladation, is well documented. In contrast, there is relatively little precedent for the transmetallation between a Pd-aryl species and $[Ph–I–Ph]BF_4$, although a report by Moriarty did suggest this mechanistic possibility in cross coupling reactions.[22]

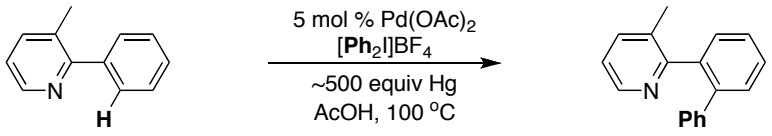
Scheme 26: Mechanism 2



It is well known that transmetallation of electron rich arenes to Pd^{II} intermediates is more facile than their electron poor counterparts. Hence, if mechanism 2 were operative for our arylation reactions, we would expect the selective transfer of the more electron rich aryl group. However, as discussed in section 3.2 above, the palladium-catalyzed reaction of **27** with [*m*-CF_3Ph–I–Ph]BF_4 led to the preferential transfer of the electron poor trifluoromethyl substituted arene, suggesting against mechanism 2 (Table 2, entry 5).

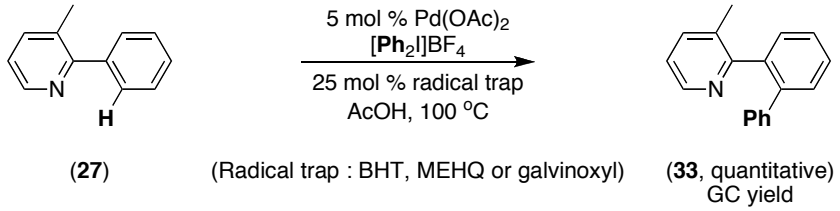
We next desired to probe the involvement of Pd nanoparticles or free radicals under our reaction conditions, as both of these have been proposed previously for $Pd^{0/II}$ catalyzed reactions. Importantly, a number of Heck reactions that were initially proposed to proceed via $Pd^{II/IV}$-catalytic cycles have now been shown to be catalyzed by palladium nanoparticles.[23] In order to test for the participation of Pd nanoparticles in our reactions, **27** was subjected to the standard reaction conditions in the presence of Hg. Notably, Hg is known to act as a potent poison for heterogeneous catalysis by forming an amalgam with Pd nanoparticles. However, as shown in Scheme 27, the arylation of **27** was unaffected by the presence of Hg, suggesting strongly against nanoparticle assisted catalysis.

Scheme 27: Phenylation of **27** in the Presence of Hg



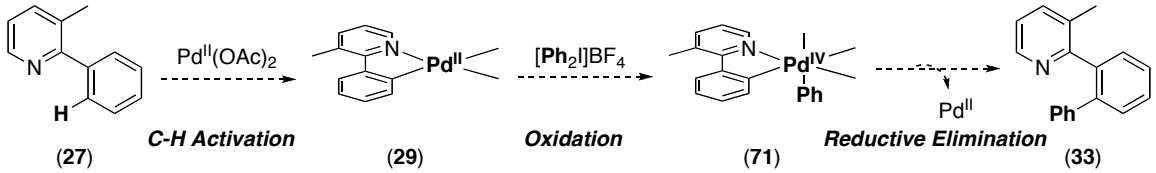
In order to probe for the involvement of radicals, we conducted the reaction of **27** with [Ph–I–Ph]BF_4 in the presence of radical inhibitors. The data presented in Scheme 28 suggests against any radical intermediates, as the reaction was unaffected by the presence of BHT (butylated hydroxytoluene), MEHQ (hydroquinone monomethyl ether) or galvinoxyl.

Scheme 28: Phenylation of **27** in the Presence of Radical Inhibitors



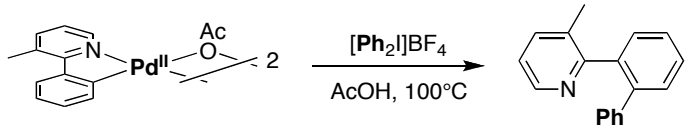
Finally, we wanted to directly investigate the viability of a $Pd^{II/IV}$ catalytic manifold for the palladium-catalyzed ligand directed arylation reactions (Scheme 29). More specifically, we wanted to probe the intermediacy of (i) the cyclopalladated complex **29** and (ii) the proposed Pd^{IV} species **71**.

Scheme 29: Mechanism 3



In order to explore the former, we first examined the stoichiometric reaction of **72** with [Ph–I–Ph]BF_4. As shown in Scheme 30 below, this reaction led to the desired phenylated product **33**, albeit in much lower yield (20%) than that obtained (88%) in the catalytic phenylation of **27** (Scheme 14). However, analysis of the crude reaction by ^1H NMR spectroscopy and electrospray mass spectrometry revealed a complex mixture of additional high molecular weight organic products, and the MS data is consistent with the formation of a mixture of polyphenylated momomers and dimers of **27**.

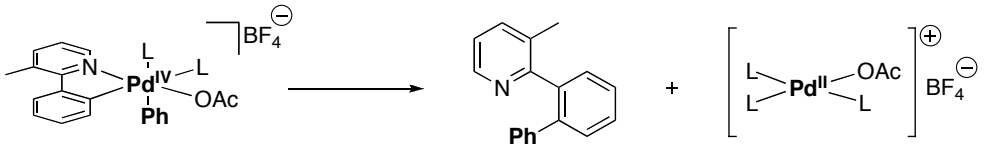
Scheme 30: Stoichiometric Phenylation of the Cyclopalladated Complex



(**72**) (**33**, 20%)

While the origin of these products and the details of this reactivity are not known, we speculated that the highly reactive cationic palladium species **73** generated after initial C–C bond forming reductive elimination may be responsible for producing these polyphenylated products (Scheme 31). Notably, under the catalytic conditions, a large excess of substrate is present relative to catalyst, so such a reactive species is expected to be trapped rapidly in a productive manner.

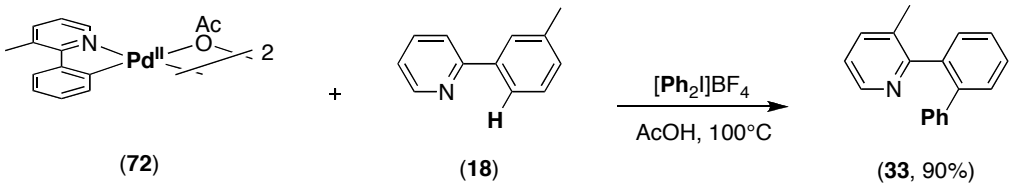
Scheme 31: Generation of Cationic Pd^{II} upon Reductive Elimination



(**71**) (**33**) (**73**)

Hence, we theorized that the addition of free ligand to the stoichiometric reaction might attenuate the reactivity of **73** and allow the stoichiometric arylation reaction to proceed in higher yield without the formation of polyarylated side products. In order to probe this hypothesis, we investigated the stoichiometric reaction of **72** with [Ph–I–Ph]BF_4 in the presence of *meta*-methyl-2-phenylpyridine **18** (Scheme 32). Importantly, **18** (which is electronically and structurally similar to **27**) was used as the free ligand in place of **27** to allow us to quantify the yield of the arylation of **72** without complications from the arylation of the free ligand. Gratifyingly, these conditions led to the formation of the arylated product in 90% GC yield. This result supports the proposed oxidative arylation of **29** in Scheme 30.

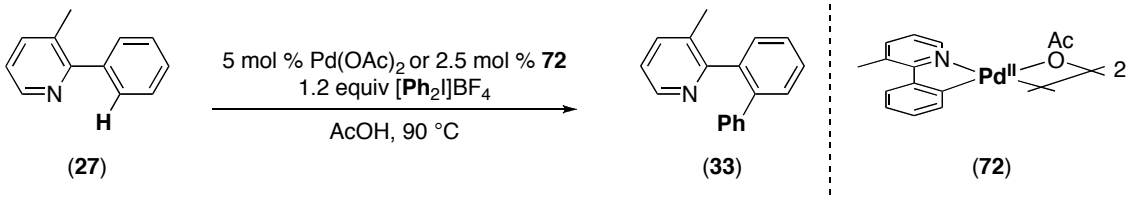
Scheme 32: Stoichiometric Phenylation of **72** in the Presence of Free Ligand



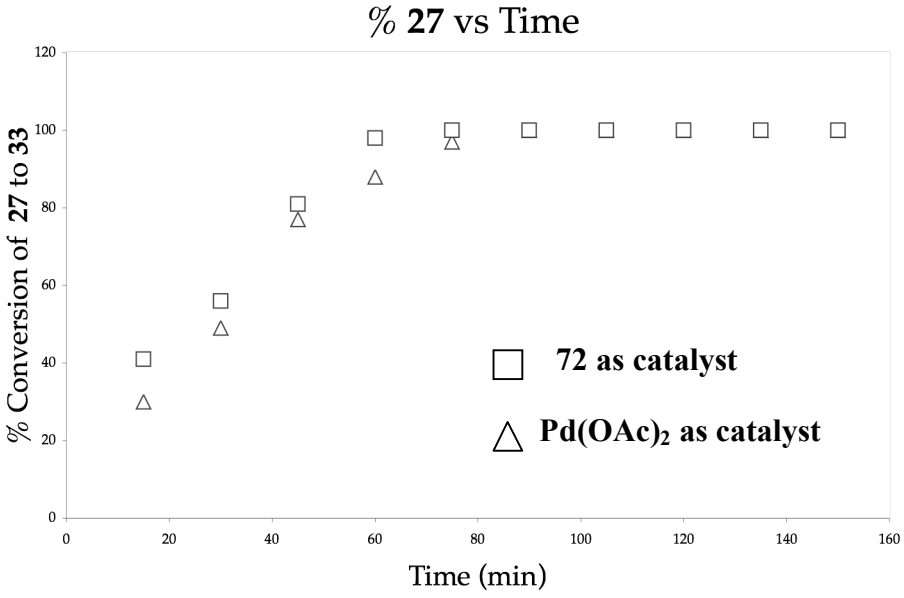
(**72**) (**18**) (**33**, 90%)

Furthermore, as depicted in Scheme 33, the cyclometallated complex **72** catalyzed the arylation reaction of **27** at rates comparable to that of $Pd(OAc)_2$. The phenylation reaction was complete in about 1.5 h using either **72** or $Pd(OAc)_2$ as the catalyst at 90 °C. Taken together, the data in Schemes 32 and 33 suggest that the cyclopalladated complex **72** is a kinetically competent intermediate for our direct arylation reactions.

Scheme 33: Time Course of Phenylation of **27** with $Pd(OAc)_2$ versus **72** as Catalyst

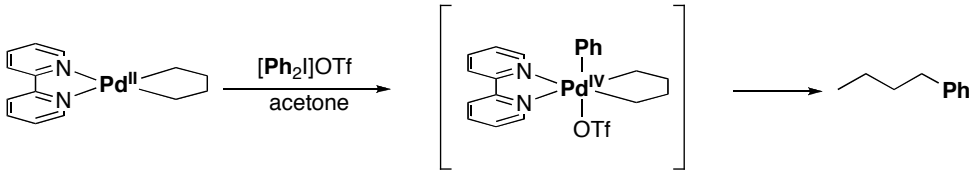


(**27**) (**33**) (**72**)



In order to gain further support for the proposed $Pd^{II/IV}$ mechanism, we explored the reaction of palladacycle **72** with traditional $Pd^{0/II}$ oxidants in place of $[Ph–I–Ph]BF_4$. While Canty has shown that $[Ph–I–Ph]BF_4$ can oxidize Pd^{II} to Pd^{IV} (Scheme 34),[24] there are no reports suggesting the accessibility of high oxidation state Pd^{IV} species with oxidants such as PhI and PhOTf.

Scheme 34: Oxidation of Pd^{II} to Pd^{IV} by [PhIPh]OTf

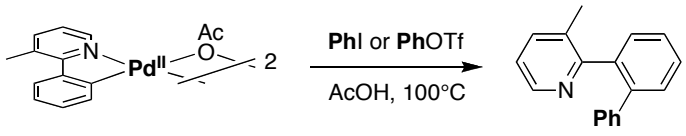


(**74**) (**75**) (**76**, 22%)

Observed by ^{1}H NMR at -50 °C

As shown in Scheme 35, the phenylated product **33** was not formed in the stoichiometric reaction of **72** with PhI or PhOTf. However, as mentioned above (Scheme 31 and 33), **72** reacts with $[Ph–I–Ph]BF_4$ to afford **33**. These results lend further credence to the intermediacy of Pd^{IV} species in the catalytic oxidative arylation reactions.

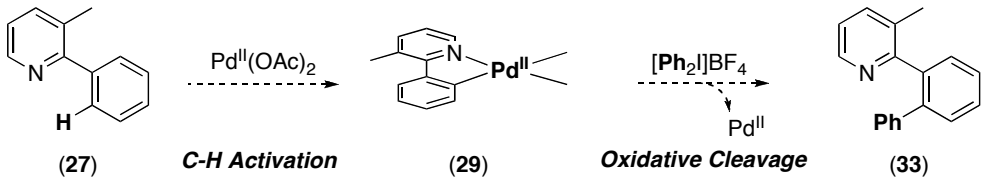
Scheme 35: Reaction of the Cyclopalladated Complex **72** with PhI or PhOTf



(**72**) (**33**, < 1%)

Based on these preliminary mechanistic investigations, we surmise that the $Pd^{II/IV}$ catalytic manifold depicted in Scheme 29 is operative for the palladium-catalyzed ligand directed C–H activation/arylation reactions. However, at this time we cannot exclude a mechanism involving direct electrophilic cleavage of the Pd-aryl bond in **29** by $[Ph–I–Ph]BF_4$ (Scheme 36). This alternative mechanism would constitute a $Pd^{II/II}$ catalytic regime with no change of oxidation state at the palladium center.

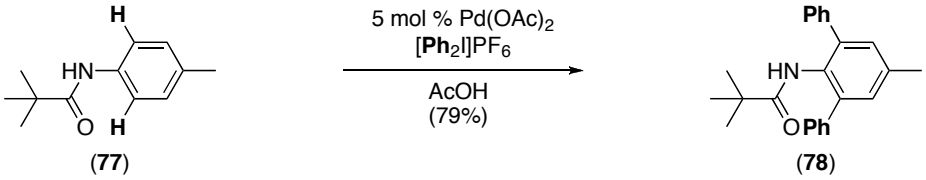
Scheme 36: Possible Mechanism Involving a $Pd^{II/II}$ Catalytic Cycle



3.4 Subsequent Examples

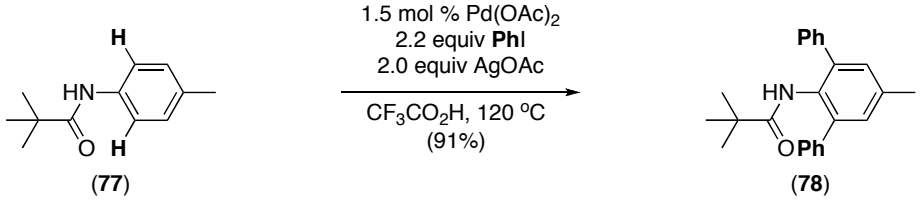
There have been several publications on palladium-catalyzed ligand-directed C-H activation/arylation reactions to form biaryl linkages since our initial work in 2005. In particular there have been reports on carboxylic acid and anilide directed arylations of arenes that proceed via $Pd^{0/II}$ catalytic cycles with boronates or silanes as the arylating reagents.[25, 26] However, the most interesting reactions in the context of our work are the arylations proposed to proceed via a $Pd^{II/IV}$ catalytic manifold.[27-32] Daugulis and coworkers reported a palladium-catalyzed *ortho*-diarylation of anilides using [Ph–I–Ph]PF_6 as the oxidant (Scheme 37). Notably, these reaction conditions are very similar to those reported by our group. However, only one substrate (**77**) was examined using Daugulis' methodology.[27]

Scheme 37: Palladium-Catalyzed Diphenylation of Anilide



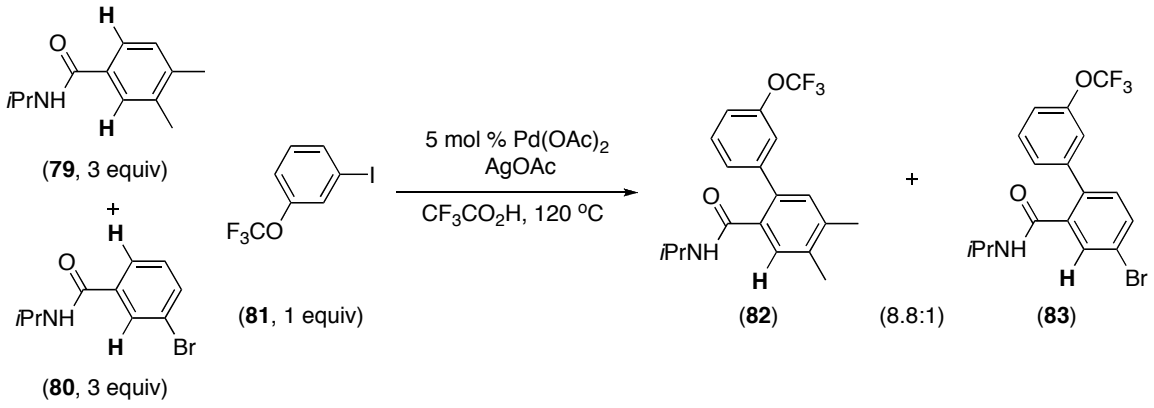
Additionally, Daugulis and coworkers have demonstrated that these arylation reactions can proceed using aryl iodides instead of [Ph–I–Ph]PF_6 as the arylating reagents in the presence of stoichiometric amounts of silver salts (Scheme 38).[27] These reactions have been subsequently expanded to the use of other directing groups such as benzyl amines, pyridines, acetinilides, quinolines and carboxylic acids.[28-32]

Scheme 38: Palladium-Catalyzed Diphenylation of Anilide using Iodoarene

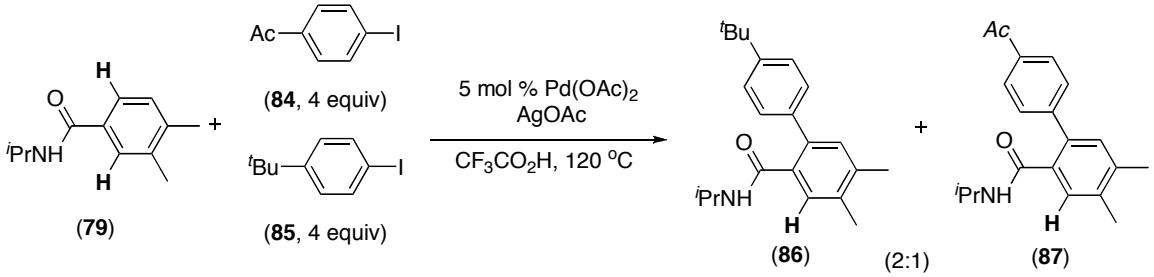


A variety of electronically diverse substrates can be used in these reactions. Furthermore, a number of moderately electron poor and electron rich aryl iodides serve as effective arylating reagents. However, the use of aryl iodides containing strongly electron donating (4-iodoanisole)[29] or electron withdrawing (*p*-trifluoromethyliodobenzene)[28] groups leads to diminished yields of the arylated products. Additionally, *ortho*-substituted aryl iodides are unreactive under these reaction conditions.[32] As exemplified by the competition reaction depicted in Scheme 39 below, arylation of electron rich arenes is relatively faster than arylation of electron poor arenes.[29] Interestingly, these transformations proceed faster with electron rich aryl iodides than with their electron poor counterparts.[29] For example, the reaction of **79** with equimolar quantities of **84** and **85** led to products **86** and **87** in a 2:1 ratio (Scheme 40). In contrast, as mentioned in section 3.2, the transfer of electron poor arenes was more facile in our arylation reactions.

Scheme 39: Effects of Substrate Electronics in Phenylation of Anilide

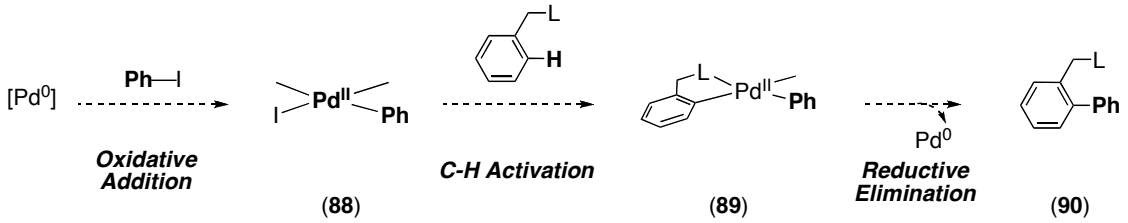


Scheme 40: Electronic Effects of the Iodoarene in Diphenylation of Anilide

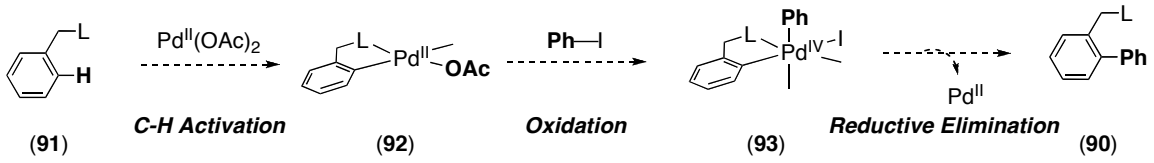


Detailed mechanistic studies have not been performed for these transformations. However, the authors have speculated on two possible mechanisms for these arylations. The first (Scheme 41) involves a $Pd^{0/II}$ catalytic cycle while the second (Scheme 42) proceeds via a $Pd^{II/IV}$ manifold.[31]

Scheme 41: Possible $Pd^{0/II}$ Mechanism for Daugulis' Arylations



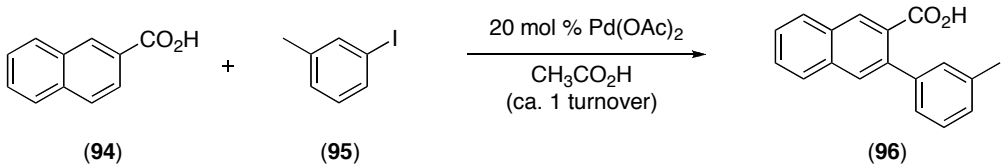
Scheme 42: Possible $Pd^{II/IV}$ Mechanism for Daugulis' Arylations



In order to distinguish between these mechanistic regimes, the reaction of 2-naphthoic acid (**94**) with 3-iodotoluene (**95**) was conducted with either a Pd^0 or a Pd^{II} catalyst in the absence of AgOAc (which is believed to be important for catalytic turnover). As shown in Schemes 43 and 44, one turnover to the arylated product was observed with $Pd(OAc)_2$ while no product was obtained with Pd^0 sources such as $Pd_2(dba)_3$ and $Pd(P^tBu_3)_2$. Based on these results along with the observed stability of aryl bromides and chlorides under the reaction conditions, the authors propose that the $Pd^{II/IV}$

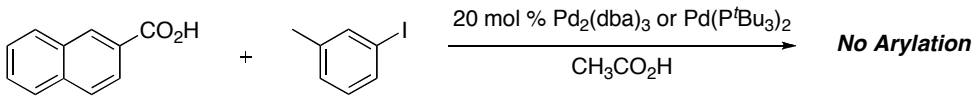
reaction manifold is operative for their arylations. In particular, the authors suggest that the aryl iodide oxidizes the cyclopalladated complex (generated upon C–H activation) to a Pd^{IV} species. Furthermore, AgOAc is proposed to regenerate the $Pd(OAc)_2$ catalyst via iodide exchange for an acetate at the Pd^{II} species formed upon reductive elimination.

Scheme 43: Arylation of 2-Naphthoic Acid with a Pd^{II} Catalyst



(**94**) (**95**) (**96**)

Scheme 44: Arylation of 2-Naphthoic Acid with Pd^0 Catalysts



(**94**) (**95**)

As described above, Daugulis and coworkers have developed a methodology for the direct arylation of arenes. The key difference between these reactions and those developed by our group is the use of ArI instead of $[Ar–I–Ar]BF_4$ as the arylating reagent. Analogous to our reactions, aromatic chlorides and bromides are stable under Daugulis' reaction conditions. However, functional group tolerance is somewhat limited for these transformations due to the use of strongly acidic trifluoroacetic acid as the solvent in many cases. Additionally, as mentioned above, the scope of these reactions is subject to both electronic and steric limitations on the aryl iodide. This is in contrast to our reactions, in which both electron rich (*p*-OMePh) and electron poor (*p*-CF_3Ph) as well as sterically hindered (*o*-tolyl) aryl groups can be efficiently incorporated into the final products. Finally, the key step leading to the arylated products is proposed to involve oxidation of the cyclometallated complex by the arylating reagent via a Pd^{IV} intermediate. While the oxidation of Pd^{II} to Pd^{IV} using [Ph–I–Ph]OTf by Canty (Scheme 34) supports the feasibility of Pd^{IV} species in our reactions, there are no literature reports suggesting the accessibility of high oxidation state Pd^{IV} complexes using aryl iodides. Hence, a more

detailed mechanistic investigation with systematic exploration of different reaction variables is necessary in order to propose the $Pd^{II/IV}$ catalytic cycle for arylation reactions developed by Daugulis.

3.5 Conclusions

In summary, we have shown that diaryl iodonium salts can be used as oxidants for site selective C–H activation/arylation reactions in the presence of $Pd(OAc)_2$ as the catalyst. Preliminary results suggest that the mechanism of this reaction involve a Pd^{II}/Pd^{IV} catalytic cycle, which is of interest because nearly all palladium mediated C–C bond forming reactions proceed via a Pd^0/Pd^{II} cycle.

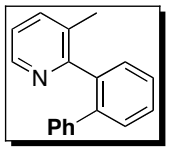
3.6 Experimental Procedure

General Procedures: NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^1H; 125.70 MHz for ^{13}C) or a Varian Inova 400 (399.96 MHz for ^1H; 100.57 MHz for ^{13}C) spectrometer. ^1H NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m), and broad resonance (br).

Materials and Methods: Substrates **35**, **37**, **39**, **41**, **45**, and **51** were obtained from commercial sources and used as received. Substrate **27** was prepared by Suzuki cross-coupling of phenyl boronic acid and 2-bromo-3-methylpyridine according to a literature procedure.[33] Pyridine substrates **18** and **43** were prepared by Stille cross-coupling of 2-tributylpyridyltin with the corresponding aryl bromides.[34] Amide substrates **47** and **49** were prepared by palladium-catalyzed arylation of the corresponding lactam.[35] Phenyl iodonium salts were prepared by the reaction of $PhI(OAc)_2$ with $ArB(OH)_2$ in the presence of $BF_3{\bullet}Et_2O$ (for $[Ph_2I]BF_4$, $[Ph–I–p\text{-}FC_6H_4]BF_4$, $[Ph–I–p\text{-}ClC_6H_4]BF_4$, $[Ph–I–o\text{-}CH_3C_6H_5]BF_4$, $[Ph–I–p\text{-}CH_3C_6H_5]BF_4$)[36] or trifluoromethanesulfonic acid (for [Ph–I–*p*-

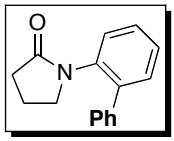
$MeOC_6H_4]BF_4$ and [Ph–I–thienyl]BF_4).[37] Mesityl iodonium salts were prepared by the reaction of $MesI(OAc)_2$[38] with $ArB(OH)_2$ in the presence of BF_3•Et_2O (for [Mes–I–*p*-$FC_6H_4]BF_4$, [Mes–I–*p*-$ClC_6H_4]BF_4$, [Mes–I–*o*-$CH_3C_6H_5]BF_4$, [Mes–I–*p*-$CH_3C_6H_5]BF_4$, [Mes–I–(1-naphthyl)]BF_4, by reaction of $PhI(OAc)_2$ with mesitylene in H_2SO_4,[39] or by reaction of $MesI(OAc)_2$ with anisole in CH_2Cl_2/trifluoroacetic acid.[40] $Pd(OAc)_2$ was obtained from Pressure Chemical and used as received and $PhI(OAc)_2$ was obtained from Acros and used as received. Mercury (electrochemical grade, 99.9999%) was obtained from Aldrich 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 F_{254}. Control reactions (in the absence of Pd catalyst) were run for each substrate, and generally showed no reaction under our standard conditions. In general, crude reaction mixtures were filtered through glass wool or Celite to remove insoluble materials that form at the end of the reaction before workup.

I. Experimental Procedures

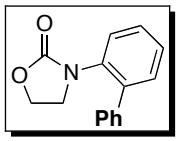


Substrate **27** (200 mg, 1.18 mmol, 1 equiv), $[Ph_2I]BF_4$ (500 mg, 1.36 mmol, 1.15 equiv) and $Pd(OAc)_2$ (13.2 mg, 0.059 mmol, 5 mol %) were combined in acetic acid (10 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred at 100°C for 12 hours. The reaction mixture was filtered through a plug of Celite and then concentrated under vacuum. The resulting crude oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.2 in 95% CH_2Cl_2/5% ethyl acetate). The product **33** was obtained as a viscous yellow oil (255 mg, 88% yield); ^1H NMR (d_6-acetone): δ 8.47 (d, *J* = 4.8 Hz, 1H), 7.55-7.43 (multiple peaks, 3H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.37-7.35 (m, 1H), 7.21-7.10 (multiple peaks, 6H), 1.75 (s, 3H). $^{13}C\{^1H\}$

NMR (d_6-acetone): δ 161.29, 148.19, 142.99, 142.40, 141.62, 139.03, 133.06, 131.80, 131.32, 130.92, 130.04, 129.58, 128.98, 128.48, 124.00, 19.95. Anal. Calcd for $C_{18}H_{15}N$: C, 88.13, H, 6.16, N, 5.71; Found: C, 88.15, H, 6.17, N, 5.43. IR (thin film) 1418 cm^{-1}.

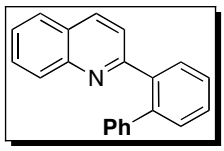


Substrate **35** (152 mg, 0.94 mmol, 1 equiv), $[Ph_2I]BF_4$ (521 mg, 1.41 mmol, 1.5 equiv), $NaHCO_3$ (119 mg, 1.14 mmol, 1.5 equiv) and $Pd(OAc)_2$ (11.9 mg, 0.053 mmol, 5 mol %) were combined in toluene (8 mL) in a 20 mL vial fitted with a Teflon lined cap, and the reaction was stirred at 100°C for 24 hours. The reaction mixture was filtered through a plug of Celite and concentrated under vacuum to afford a yellow oil, which was purified by chromatography on silica gel (R_f = 0.1 in 50% ethyl acetate/50% hexanes). The product **36** was obtained as an orange oil (170 mg, 75% yield). ^{1}H NMR ($CDCl_3$): δ 7.44-7.35 (multiple peaks, 6H), 7.34-7.33 (m, 2H), 7.32 (t, J = 1.7 Hz, 1H), 3.21 (t, J = 7.0 Hz, 2H), 2.43 (t, J = 8.1 Hz, 2H), 1.90-1.83 (m, 2H). $^{13}C\{^1H\}$ NMR (d_6-acetone): δ 174.18, 140.09, 140.03, 137.60, 130.95, 129.13, 128.78, 128.59, 128.44, 127.71, 127.59, 49.65, 31.06, 18.99. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98, H, 6.37, N, 5.90; Found: C, 80.67, H, 6.46, N, 5.67. IR (thin film) 1715, 1377 cm^{-1}.

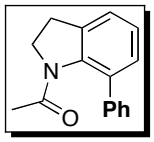


Substrate **37** (150 mg, 0.92 mmol, 1 equiv), $[Ph_2I]BF_4$ (676 mg, 1.84 mmol, 2 equiv), $Pd(OAc)_2$ (10.2 mg, 0.046 mmol, 5 mol %) and $NaHCO_3$ (155 mg, 1.84 mmol, 2 equiv) were combined in benzene (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap and the reaction was heated at 100ºC for 12 hours. The reaction mixture was filtered through a plug of Celite and then evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.23 in

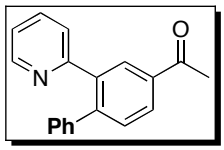
97.5% CH_2Cl_2/2.5% ethyl acetate). The product **38** was obtained as a yellow solid (182 mg, 83% yield); mp 107-109 ºC. ^{1}H NMR (C_6D_6): δ 7.38 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.32-7.30 (m, 2H), 7.14-7.12 (m, 1H), 7.10-7.06 (multiple peaks, 3H), 7.05-6.99 (m, 2H) 3.24 (dd, *J* = 8.6, 7.2 Hz, 2H), 2.55 (dd, *J* = 8.5, 7.2 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 157.78, 139.62, 139.00, 135.08, 131.10, 128.89, 128.87, 128.58, 128.41, 128.25, 127.99, 62.43, 47.13. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30, H, 5.48, N, 5.85; Found: C, 75.50, H, 5.66, N, 5.68. IR (KBr) 1740, 1483 cm^{-1}.



Substrate **39** (200 mg, 0.97 mmol, 1 equiv), $[Ph_2I]BF_4$ (428 mg, 1.16 mmol, 1.2 equiv), and $Pd(OAc)_2$ (10.9 mg, 0.054 mmol, 5 mol %) were combined in AcOH (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC overnight. GC analysis at the completion of the reaction showed 19% starting material (**39**), 71% mono-arylated product (**40**) and 10% of the analogous diarylated product. The reaction mixture was filtered through a plug of Celite and then evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). The organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford a yellow oil, which was purified by chromatography on silica gel (R_f = 0.22 in 94% hexanes/6% ethyl acetate). The product **40** was obtained as a pale yellow solid (157 mg, 58% yield); mp 134-138 ºC. ^{1}H NMR (C_6D_6): δ 8.38 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 7.60, 1.45, 1H), 7.39-7.34 (m, 2H), 7.31-7.28 (m, 2H), 7.26-7.16 (multiple peaks, 6H), 6.95-6.90 (m, 2H), 6.88-6.86 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 159.60, 147.94, 140.86, 140.46, 139.45, 134.43, 130.62, 130.21, 129.52, 129.26, 129.06, 128.62, 128.04, 127.88, 127.59, 127.18, 126.60, 126.27, 123.13. HRMS-electrospray (*m/z*): [M^+ – H] calcd for $C_{21}H_{15}N$, 280.1126; found, 280.1127. IR (KBr) 1699, 1589 cm^{-1}.



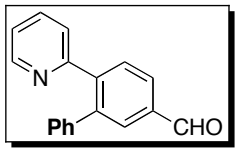
Substrate **41** (150 mg, 0.93 mmol, 1 equiv), $[Ph_2I]BF_4$ (685 mg, 1.86 mmol, 2 equiv), and $Pd(OAc)_2$ (10.4 mg, 0.047 mmol, 5 mol %) were combined in AcOH (5 mL) and Ac_2O (5 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC overnight. GC analysis at the completion of the reaction showed 29% starting material (**41**) and 71% of the mono-arylated product (**42**). Notably, attempts to optimize the reaction conditions did not lead to further conversion with this substrate. The reaction mixture was evaporated to dryness, and the remaining solid residue was taken up in MeOH (20 mL) and filtered through a plug of Celite. The methanol was removed under vacuum and the solids were taken up in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (3 x 30 mL). The organic extracts were concentrated under vacuum to afford a red oil, which was purified by chromatography on silica gel (R_f = 0.2 in 70% hexanes/30% ethyl acetate). The product **42** was obtained as pale yellow solid (108 mg, 49% yield); mp 117-119 ºC. ^{1}H NMR (d_6-acetone): δ 7.52-7.14 (multiple peaks, 8H), 4.23 (t, J = 7.2 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 1.50 (br s, 3H). $^{13}C\{^1H\}$ NMR (d_6-acetone): δ 141.58, 129.77, 128.16, 127.78, 126.02, 124.67,51.15, 22.89. (The ^{13}C NMR peaks of **12a** are broad and several are missing, presumably as a result of fluxional motion of the amide.) Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98, H, 6.37, N, 5.90; Found: C, 80.89, H, 6.52, N, 5.58. IR (KBr) 1648 cm^{-1}.



Substrate **43** (150 mg, 0.76 mmol, 1 equiv), $[Ph_2I]BF_4$ (420 mg, 1.14 mmol, 1.5 equiv), and $Pd(OAc)_2$ (8.5 mg, 0.038 mmol, 5 mol %) were combined in acetic acid (6 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap and the reaction was heated at 100ºC for 2 days. The reaction mixture was filtered through a plug of Celite and then evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). The organic layer was

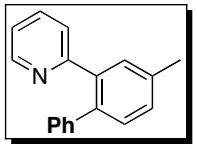
dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.25 in 88% CH_2Cl_2/12% ethyl acetate). The product **44** was obtained as an orange/brown solid (189 mg, 91% yield); mp 77-78ºC. ^{1}H NMR (acetone-d_6): δ 8.59-8.57 (m, 1H), 8.07 (dd, *J* = 8.0, 1.9 Hz, 1H), 8.24 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 8.0, 1H), 7.50 (td, *J* = 7.7, 1.8 Hz, 1H), 7.26-7.25 (m, 3H), 7.21-7.18 (m, 1H), 7.16-7.13 (m, 2H), 6.96-6.93 (m, 1H), 2.63 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 197.80, 158.50, 149.81, 145.36, 140.37, 139.93, 136.43, 135.63, 131.12, 129.64, 128.44, 128.18, 127.64, 125.49, 122.99, 26.96. HRMS-electrospray (*m/z*): [M^+ + H] calcd for $C_{19}H_{15}NO$, 274.1232; found, 274.1233. Anal. Calcd for $C_{19}H_{15}NO$: C, 83.94, H, 5.53, N, 5.12; Found: C, 83.56, H, 5.45, N, 5.04. IR (KBr) 1683, 1586 cm^{-1}.

The regioselectivity of this reaction could not be definitively determined from the ^{1}H NMR spectrum of **44** due to overlapping aromatic resonances. As a result, a deuterated version of this product was prepared by reaction of **43** with [Mes–I–C_6D_5]BF_4 under analogous conditions to those described above. The ^{1}H NMR data for the deuterated product (**43-*d*$_5$**) was as follows: ^{1}H NMR (d_6-acetone): δ 8.69-8.67 (m, 1H), 8.30 (d, *J* = 2.0 Hz, 1H), 8.17 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.68 (d, *J* = 8 Hz, 1H), 7.63 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.34-7.32 (m, 1H), 7.15-7.13 (m, 1H).

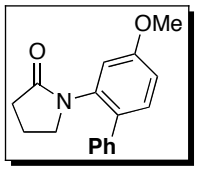


Substrate **45** (200 mg, 1.09 mmol, 1 equiv), [Ph_2I]BF_4 (441 mg, 1.20 mmol, 1.1 equiv), and $Pd(OAc)_2$ (12.2 mg, 0.054 mmol, 5 mol %) were combined in AcOH (9 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC overnight. GC analysis at the completion of the reaction showed 11% starting material (**45**), 67% mono-arylated product (**46**) and 21% of the analogous diarylated product. The reaction mixture was filtered through a plug of Celite and evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). The organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford a yellow oil, which was purified by chromatography on silica gel (R_f = 0.25 in 65% hexanes/35% ethyl acetate). The product

46 was obtained as pale yellow solid (142 mg, 51% yield); mp 90-94 ºC. ^{1}H NMR (C_6D_6): δ 9.71 (s, 1H), 8.51-8.49 (m, 1H), 7.87 (d, *J* = 9.7 Hz, 1H), 7.74 (d, *J* = 1.5 Hz, 1H), 7.61 (dd, *J* = 7.9, 1.5, 1H), 7.04-7.01 (m, 2H), 6.99-6.96 (multiple peaks, 3H), 6.74-6.66 (m, 2H), 6.52-6.28 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 191.60, 157.49, 149.32, 144.64, 141.15, 139.63, 135.77, 135.11, 131.60, 131.08, 129.17, 128.14, 127.97, 127.01, 124.97, 121.78. HRMS-electrospray (*m/z*): [M^+ – H] calcd for $C_{18}H_{13}NO$, 258.0919; found, 258.0922. IR (KBr): 1696, 1585 cm^{-1}.

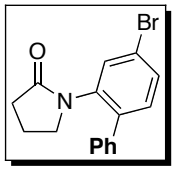


Substrate **18** (150 mg, 0.89 mmol, 1 equiv), $[Ph_2I]BF_4$ (489 mg, 1.33 mmol, 1.5 equiv), and $Pd(OAc)_2$ (9.9 mg, 0.044 mmol, 5 mol %) were combined in acetic acid (4 mL) and acetic anhydride (4 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap and the reaction was heated at 100ºC for 12 hours. The reaction mixture was filtered through a plug of Celite and then evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil, which was purified by chromatography on silica gel (R_f = 0.24 in 97.5% CH_2Cl_2/2.5% ethyl acetate). The product **20** was obtained as a brown solid (156 mg, 74% yield); mp 80-84 ºC . ^{1}H NMR (C_6D_6): δ 8.58 (d, *J* = 4.8 Hz, 1H), 7.79 (s, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.22-7.20 (m, 2H), 7.04-6.95 (multiple peaks, 4H), 6.83-6.79 (m, 2H), 6.77-6.75 (m, 1H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 158.88, 148.94, 140.85, 138.76, 137.36, 136.92, 134.68, 130.66, 130.03, 129.28, 128.86, 127.59, 126.08, 125.04, 120.84, 20.66. HRMS-electrospray (*m/z*): [M^+ + H] calcd for $C_{18}H_{15}N$, 246.1283; found, 246.1290. IR (KBr) 1584 cm^{-1}.



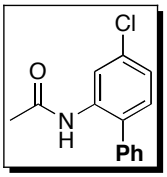
Substrate **47** (180 mg, 0.94 mmol, 1 equiv), $[Ph_2I]BF_4$ (692 mg, 1.88 mmol, 2 equiv), $Pd(OAc)_2$ (10.5 mg, 0.047 mmol, 5 mol %) and $NaHCO_3$ (158 mg, 1.88 mmol, 2 equiv) were combined in toluene (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap and the reaction was heated at 100ºC for 12 hours. The reaction mixture was evaporated to dryness, and the residue was redissolved in CH_2Cl_2 and filtered through a plug of Celite. The solution was concentrated to afford a yellow oil, which was purified by chromatography on silica gel (R_f = 0.25 in 70% ethyl acetate/30% hexanes). The product **48** was obtained as a yellow solid (211 mg, 84% yield); mp 61-64 ºC. ^{1}H NMR (C_6D_6): δ 7.41-7.39 (m, 2H), 7.18-7.16 (m, 1H), 7.14-7.05 (multiple peaks, 4H), 6.73 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.30 (s, 3H), 2.78 (t, *J* = 6.9 Hz, 2H), 2.03 (t, *J* = 8.0 Hz, 2H), 1.19-1.12 (m, 2H). ^{13}C{H} NMR ($CDCl_3$): δ 175.15, 159.10, 138.41, 136.62, 131.46, 131.09, 127.92, 127.89, 126.74, 113.70, 112.89, 54.95, 49.66, 30.74, 18.46. HRMS-electrospray (*m/z*): [M^+ + Na] calcd for $C_{17}H_{17}NO_2$, 290.1157; found, 290.1167. IR (KBr) 1687, 1609 cm^{-1}.

The regioselectivity of this reaction could not be definitively determined from the ^{1}H NMR spectrum of **48** due to overlapping aromatic resonances. As a result, a deuterated version of this product was prepared by reaction of **47** with $[Mes–I–C_6D_5]BF_4$ under analogous conditions to those described above. The ^{1}H NMR data for the deuterated product (**48-*d*$_5$**) was as follows: ^{1}H NMR (d_6-acetone): δ 7.31 (d, *J* = 8.5 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 3.84 (s, 3H), 3.26 (t, *J* = 6.9 Hz, 2H), 2.26 (t, *J* = 8.0 Hz, 2H), 1.91-1.84 (m, 2H).



Substrate **49** (180 mg, 0.75 mmol, 1 equiv), $[Ph_2I]BF_4$ (689 mg, 1.87 mmol, 2.5 equiv), and $Pd(OAc)_2$ (8.4 mg, 0.038 mmol, 5 mol %) were combined in toluene (6.25 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap and the reaction was heated at 100ºC for 12 hours. The reaction mixture was filtered through a plug of Celite and then evaporated to dryness. The resulting oil was dissolved in methylene chloride and extracted with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). The

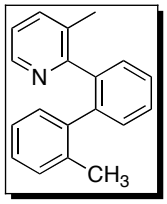
organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.23 in 96% CH_2Cl_2/4% ethyl acetate). The product **50** was obtained as an orange-brown solid (180 mg, 78% yield); mp 116-118 ºC. ^{1}H NMR (C_6D_6): δ 7.52 (s, 1H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.13-7.06 (multiple peaks, 4H), 6.79 (d, *J* = 8.1 Hz, 1H), 2.59 (t, *J* = 6.8 Hz, 2H), 1.93 (t, *J* = 8.0 Hz, 2H), 1.13-1.06 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 175.39, 138.49, 137.84, 137.38, 131.89, 131.26, 130.90, 128.39, 127.93, 127.75, 121.44, 49.77, 30.85, 18.79. Anal. Calcd for $C_{16}H_{14}BrNO$: C, 60.78, H, 4.46, N, 4.43; Found: C, 61.08, H, 4.66, N, 4.19. IR (KBr) 1697, 1413 cm^{-1}.



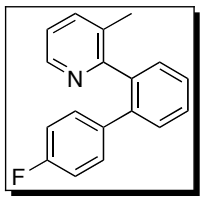
Substrate **51** (250 mg, 1.47 mmol, 1 equiv), $[Ph_2I]BF_4$ (1.08 g, 2.95 mmol, 2 equiv), and $Pd(OAc)_2$ (16.5 mg, 0.074 mmol, 5 mol %) were combined in benzene (12 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap and the reaction was heated at 100ºC for 12 hours. The reaction mixture was filtered through a plug of Celite and then evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.28 in 55% diethyl ether/45% hexanes). The product **52** was obtained as an orange-brown solid (240 mg, 67% yield); mp 125-126 ºC. ^{1}H NMR (C_6D_6): δ 9.02 (s, 1H), 7.10-7.05 (multiple peaks, 3H), 6.97-6.95 (m, 2H), 6.91 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.64 (s, 1H), 1.25 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 167.96, 136.65, 135.27, 133.40, 130.55, 130.19, 128.82, 128.66, 127.88, 123.94, 121.24, 24.04. Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.44, H, 4.92, N, 5.70; Found: C, 68.38, H, 4.99, N, 5.47. IR (KBr) 3224, 3026, 1648, 1532 cm^{-1}.

The regioselectivity of this reaction could not be definitively assigned from the ^{1}H NMR spectrum of **52** due to overlapping aromatic resonances. As a result, a deuterated

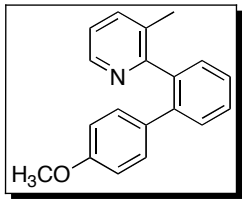
version of this product was prepared by reaction of **51** with [Mes–I–C_6D_5]BF_4 under analogous conditions to those described above. The ^{1}H NMR data for the deuterated product (**52-*d*$_5$**) was as follows: ^{1}H NMR (C_6D_6): δ 9.02 (br. s, 1H), 6.92 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.64 (br. s, 1H), 1.25 (s, 3H).



Substrate **27** (150 mg, 0.89 mmol, 1 equiv), [Mes–I–*p*-$CH_3C_6H_5$]BF_4 (489 mg, 1.15 mmol, 1.3 equiv) and $Pd(OAc)_2$ (10 mg, 0.044 mmol, 5 mol %) were combined in acetic acid (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred at 100°C for 12 hours. The reaction mixture was filtered through a plug of glass wool and concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.25 in 80% hexanes/20% ethyl acetate). The product **60** was obtained as a white solid (165 mg, 72% yield**);** mp 73-77 ºC. ^{1}H NMR (*d*$_6$-acetone): δ 8.30 (d, *J* = 3.6 Hz, 1H), 7.48-7.44 (multiple peaks, 2H), 7.39-7.36 (multiple peaks, 2H), 7.32-7.30 (m, 1H), 7.10-7.03 (multiple peaks, 3H), 6.96-6.92 (multiple peaks, 2H), 2.16 (s, 3H), 1.95 (s, 3H). ^{13}C{^{1}H} NMR (*d*$_6$-acetone): δ 160.12, 147.01, 141.58 (br), 141.42, 137.95, 136.67 (br), 131.97, 131.13, 130.67, 130.63, 128.35, 127.81, 125.53, 122.81, 20.74, 19.34. (Several of the ^{13}C NMR peaks of **1h** are broad and three are missing – this is believed to be the result of fluxional motion about the aryl-aryl bonds.) Anal. Calcd for $C_{18}H_{14}FN$: C, 87.99, H, 6.61, N, 5.40**;** Found: C, 88.09, H, 6.51, N, 5.24. IR (KBr) 1418 cm^{-1}.

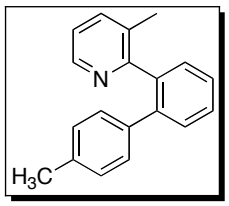


Substrate **27** (153 mg, 0.91 mmol, 1 equiv), [Mes–I–*p*-FC_6H_5]BF_4 (446 mg, 1.04 mmol, 1.15 equiv) and $Pd(OAc)_2$ (10.1 mg, 0.043 mmol, 5 mol %) were combined in acetic acid (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred at 100°C for 12 hours. The reaction mixture was filtered through a plug of glass wool and concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.3 in 75% hexanes/25% ethyl acetate). The product **64** was obtained as a yellow solid (210 mg, 88% yield); mp 135-137 ºC. ^{1}H NMR (d_6-acetone): δ 8.43 (d, J = 4.0 Hz, 1H), 7.57-7.32 (multiple peaks, 5H), 7.22-7.12 (multiple peaks, 3H), 6.97-6.93 (m, 2H), 1.77 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 162.60 (d, $^1J_{CF}$ = 243 Hz), 160.15, 147.34, 140.76, 140.35, 138.29 (d, $^4J_{CF}$ = 3.0 Hz), 138.12, 131.99, 131.82 (d, $^3J_{CF}$ = 7.6 Hz), 130.79, 130.30, 129.07, 128.16, 123.10, 115.35 (d, $^2J_{CF}$ = 21 Hz), 18.91**.** Anal. Calcd for $C_{18}H_{14}FN$: C, 82.11, H, 5.36, N, 5.32**;** Found: C, 81.86, H, 5.52, N, 5.15. IR (KBr) 1482 cm^{-1}.

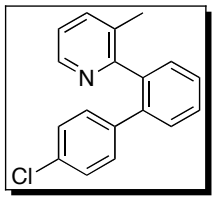


Substrate **27** (150 mg, 0.89 mmol, 1 equiv), [Mes–I–*p*-$MeOC_6H_5$]BF_4 (449 mg, 1.02 mmol, 1.1 equiv) and $Pd(OAc)_2$ (10 mg, 0.044 mmol, 5 mol %) were combined in acetic acid (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred at 120°C for 12 hours. The reaction mixture was filtered through a plug of glass wool and concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.20 in 80% hexanes/20% ethyl acetate). The product **65** was obtained as a clear oil (197 mg, 81% yield); ^{1}H NMR (d_6-acetone): δ 8.42 (d, J = 4.4 Hz, 1H), 7.46-7.28 (multiple peaks, 5H), 7.14-7.11 (m, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 3.68 (s, 3H), 1.70 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 159.73,

158.68, 146.42, 140.22, 139.73, 137.18, 133.40, 131.17, 130.17, 129.94, 129.33, 128.13, 126.68, 122.12, 113.22, 54.49, 18.09. HRMS (electrospray) [M^+] calcd for $C_{19}H_{19}NO$, 275.1310; found, 275.1303. IR (KBr) 1609, 1516 cm^{-1}.

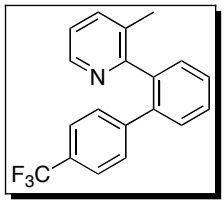


Substrate **27** (150 mg, 0.89 mmol, 1 equiv), [Mes–I–*p*-$CH_3C_6H_5$]BF_4 (432 mg, 1.02 mmol, 1.15 equiv) and $Pd(OAc)_2$ (10 mg, 0.044 mmol, 5 mol %) were combined in acetic acid (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred at 100°C for 12 hours. The reaction mixture was filtered through a plug of glass wool and concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.25 in 80% hexanes/20% ethyl acetate). The product **66** was obtained as a yellow solid (193 mg, 84% yield); mp 59-62 ºC. ^{1}H NMR (d_6-acetone): δ 8.45 (d, *J* = 4.4 Hz, 1H), 7.50-7.43 (multiple peaks, 3H), 7.39-7.33 (multiple peaks, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.04-6.98 (multiple peaks, 4H), 2.23 (s, 3H), 1.74 (s, 3H). $^{13}C\{^1H\}$ NMR (d_6-acetone): δ 159.68, 146.39, 140.49, 139.81, 138.29, 137.15, 136.14, 131.16, 129.95, 129.43, 128.98, 128.46, 128.13, 126.91, 122.12. Anal. Calcd for $C_{18}H_{14}FN$: C, 87.99, H, 6.61, N, 5.40**;** Found: C, 87.73, H, 6.45, N, 5.11. IR (KBr) 1449 cm^{-1}.



Substrate **27** (150 mg, 0.89 mmol, 1 equiv), [Mes–I–*p*-ClC_6H_5]BF_4 (453 mg, 1.02 mmol, 1.15 equiv) and $Pd(OAc)_2$ (10 mg, 0.044 mmol, 5 mol %) were combined in acetic acid (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was

stirred at 100°C for 12 hours. The reaction mixture was filtered through a plug of glass wool and concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.25 in 75% hexanes/25% ethyl acetate). The product **67** was obtained as a yellow solid (205 mg, 83% yield); mp 106-107 ºC. ^{1}H NMR (d_6-acetone): δ 8.42 (dd, J = 4.8, 1.2 Hz, 1H), 7.55-7.46 (multiple peaks, 3H), 7.43 (dt, J = 7.5, 0.8 Hz, 1H), 7.38-7.36 (m, 1H), 7.21-7.12 (multiple peaks, 5H), 1.79 (s, 3H). ^{13}C{^{1}H} NMR (d_6-acetone): δ 160.11, 147.48, 140.84, 140.82, 140.25, 138.31, 133.25, 132.12, 131.71, 130.95, 130.39, 129.25, 128.81, 128.53, 123.27, 19.07. Anal. Calcd for $C_{18}H_{14}FN$: C, 77.28, H, 5.04, N, 5.01**;** Found: C, 77.59, H, 4.91, N, 4.63. IR (KBr) 1477, 1449 cm^{-1}.



Substrate **27** (150 mg, 0.89 mmol, 1 equiv), [Mes–I–p-$CF_3C_6H_5$]BF_4 (466 mg, 0.98 mmol, 1.1 equiv) and $Pd(OAc)_2$ (10 mg, 0.044 mmol, 5 mol %) were combined in acetic acid (8 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred at 100°C for 12 hours. The reaction mixture was filtered through a plug of glass wool and concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford an orange oil, which was purified by chromatography on silica gel (R_f = 0.25 in 75% hexanes/25% ethyl acetate). The product **68** was obtained as a yellow oil (242 mg, 87% yield). ^{1}H NMR (d_6-acetone): δ 8.42 (d, J = 4.2 Hz, 1H), 7.57-7.53 (multiple peaks, 5H), 7.46-7.40 (multiple peaks, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.18 (dd, J = 8.0 Hz, 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (d_6-acetone): δ159.83, 147.84, 146.27, 140.87, 140.13, 138.42, 132.21, 131.06, 130.76, 130.59, 129.34, 129.08 (d, J = 32 Hz), 128.99, 125.59 (q, J = 4 Hz), 124.43 (q, 270 Hz), 123.39, 19.08. Anal. Calcd for $C_{18}H_{14}FN$: C, 72.83, H, 4.50, N, 4.47**;** Found: C, 72.53, H, 4.60, N, 4.36.

Reaction of 27 with Ph–I. Substrate **27** (15.0 mg, 0.09 mmol, 1 equiv), Ph–I (21.7 mg, 0.11 mmol, 1.20 equiv), and $Pd(OAc)_2$ (1.00 mg, 0.004 mmol, 5 mol %) were combined in AcOH (1.04 mL) in a 2 mL vial equipped with a small magnetic stir bar. The vial was sealed with a Teflon-lined cap and heated at 100ºC for 12 hr. The reaction was cooled to room temperature and analyzed by gas chromatography, which showed only starting material and Ph–I with <1% of product **33**.

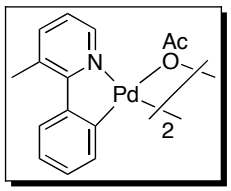
Reaction of 27 with Ph–OTf. Substrate **27** (15.0 mg, 0.09 mmol, 1 equiv), Ph–OTf (24.1 mg, 0.11 mmol, 1.20 equiv), and $Pd(OAc)_2$ (1.00 mg, 0.0044 mmol, 5 mol%) were combined in AcOH (1.04 mL) in a 2 mL vial equipped with a small magnetic stir bar. The vial was sealed with a Teflon-lined cap and heated at 100ºC for 12 hr. The reaction was cooled to room temperature and analyzed by gas chromatography, which showed only starting material (**27**) and Ph–OTf with <1% of product **33**.

Reaction of 27 with $[Ph_2I]BF_4$ in the Presence of Hg. Substrate **27** (10.0 mg, 0.059 mmol, 1 equiv), $[Ph_2I]BF_4$ (26.1 mg, 0.071 mmol, 1.20 equiv), and $Pd(OAc)_2$ (0.700 mg, 0.0031 mmol, 5 mol%) were combined in AcOH (0.50 mL) in a 2 mL vial equipped with a small magnetic stir bar. Metallic Hg (>500 equiv) was added to the reaction mixture, and the vial was sealed with a Teflon-lined cap and heated at 100ºC for 12 hr. The reaction was cooled to room temperature and analyzed by gas chromatography, which revealed quantitative conversion to product **33**. **SAFETY NOTE: These reactions should be handled with extreme caution, as the reaction of excess $[Ph_2I]BF_4$ is known to generate highly toxic phenyl mercury compounds!**[41]

Reaction of 27 with $[Ph_2I]BF_4$ in the Presence of MEHQ. Substrate **27** (10.0 mg, 0.059 mmol, 1 equiv), $[Ph_2I]BF_4$ (26.1 mg, 0.071 mmol, 1.20 equiv), and $Pd(OAc)_2$ (0.700 mg, 0.0031 mmol, 5 mol%) were combined in AcOH (0.50 mL) in a 2 mL vial equipped with a small magnetic stir bar. MEHQ (1.83 mg, 0.015 mmol, 25 mol%) was added to the reaction mixture, and the vial was sealed with a Teflon-lined cap and heated

at 100ºC for 12 hr. The reaction was cooled to room temperature and analyzed by gas chromatography, which revealed quantitative conversion to product **33**.

Reaction of 27 with $[Ph_2I]BF_4$ in the Presence of Galvinoxyl. Substrate **27** (10.0mg, 0.059 mmol, 1 equiv), $[Ph_2I]BF_4$ (26.1 mg, 0.071 mmol, 1.20 equiv), and $Pd(OAc)_2$ (0.700 mg, 0.0031 mmol, 5 mol %) were combined in AcOH (0.50 mL) in a 2 mL vial equipped with a small magnetic stir bar. Galvinoxyl (6.23 mg, 0.015 mmol, 25 mol%) was added to the reaction mixture, and the vial was sealed with a Teflon-lined cap and heated at 100ºC for 12 hr. The reaction was cooled to room temperature and analyzed by gas chromatography, which revealed quantitative conversion to product **33**.



Synthesis of Palladacycle 72. Substrate 1 (1.07 g, 6.30 mmol, 1.4 equiv), and $Pd(OAc)_2$ (1.01 g, 4.50 mmol, 1 equiv) were combined in MeOH (63 mL) in a 200 mL flask equipped with a magnetic stir bar and stirred at room temperature for 12 hr. The reaction mixture was then filtered, and the precipitate was washed with diethyl ether (100 mL), collected and dried. The product was obtained as a yellow solid (918 mg, 61% yield). ^{1}H NMR (d_6-acetone): δ 7.92 (d, J = 5.2 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 7.5 Hz, 2H), 6.94 (d, J = 7.4 Hz, 2H), 6.88-6.78 (multiple peaks, 4H), 6.53 (dd, J = 7.6, 2.0 Hz, 2H), 2.44 (s, 6H), 2.09 (s, 6H). Anal. Calcd for $C_{28}H_{26}N_2O_4Pd_2$: C, 50.39, H, 3.93, N, 4.20; Found: C, 50.27, H, 3.98, N, 4.10.

Stoichiometric Reaction of 72 with $[Ph_2I]BF_4$. Complex **72** (15.0 mg, 0.02 mmol, 1 equiv), $[Ph_2I]BF_4$ (61.1 mg, 0.17 mmol, 3.2 equiv per Pd), and **18** (19.0 mg, 0.11 mmol, 2.5 equiv per Pd) were combined in AcOH (0.37 mL) in a 2 mL vial equipped with a small magnetic stir bar. The vial was sealed with a Teflon-lined cap and heated at 100ºC for 12 hr. The reaction was cooled to room temperature and analyzed by gas chromatography, which showed 90 % yield of **33** (determined relative to an internal

standard). Significant quantities of phenylated **18** (product **20**) were also observed by GC (as expected since an excess of oxidant was utilized). Importantly, when $[Ph_2I]BF_4$ was replaced with Ph–I or Ph–OTf under otherwise identical conditions <1% of product **33** was observed by GC.

When the stoichiometric reaction between **72** and $[Ph_2I]BF_4$ reaction was conducted in the absence of added substrate **18** (under the following conditions: complex **72** (1 equiv, 0.02 mmol), $[Ph_2I]BF_4$ (1.2 equiv per Pd, 0.05 mmol), AcOH (0.37 mL), 12 hr, 100ºC) product **33** was obtained in 20% yield (determined relative to an internal standard) as the major product detectable by GC analysis. ^{1}H NMR spectroscopy and electrospray mass spectrometry revealed a complex mixture of additional high molecular weight organic products, and the MS data is consistent with the formation of a mixture of polyphenylated momomers and dimers of **27**. While the origin of these products and the details of this reactivity remains under investigation, we hypothesize that added **18** may act to trap reactive cationic palladium species (generated after initial C–C bond forming reductive elimination) that may be responsible for producing these polyphenylated products. Notably, under catalytic conditions, a large excess of substrate is present relative to catalyst, so such reactive species are expected to be trapped rapidly in a productive manner.

II. Reactions with Mixed Iodonium Reagents [Ph–I–Ar]BF_4

Reaction of 27 with [Ph–I–Ar]BF_4. Substrate **27** (10.0 mg, 0.059 mmol, 1 equiv), [Ph–I–Ar]BF_4 (0.071 mmol, 1.20 equiv), and $Pd(OAc)_2$ (0.700 mg, 0.0031 mmol, 5 mol %) were combined in AcOH (0.49 mL) in a 2 mL vial equipped with a small magnetic stir bar. The vial was sealed with a Teflon-lined cap and heated at 100ºC for 12 hr. The reaction was cooled to room temperature and analyzed by gas chromatography. The yields of the products were determined by integration relative to a GC standard (2-phenylpyridine) and are ± approximately 10%.

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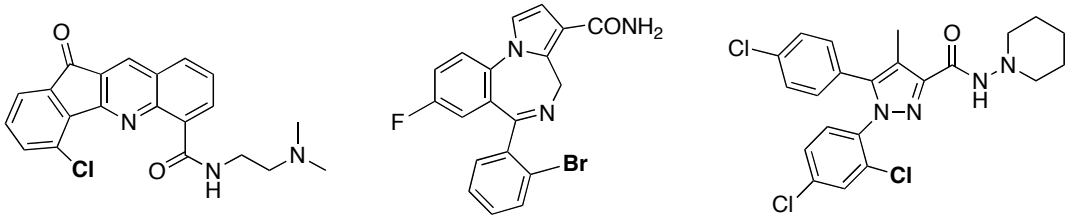
Chapter 4

Palladium-Catalyzed Ligand-Directed Halogenation of Arenes

4.1 Background and Significance

Halogenated arenes are widely prevalent in a variety of biologically active molecules and pharmaceutical agents (Scheme 1).[1] Aryl halides also serve as important precursors to organolithium[2] and Grignard reagents.[3] Furthermore, aryl halides have been employed as substrates for nucleophilic aromatic substitution[4] and for benzyne generation. [5] Additionally, aryl halides have found widespread utility as reactants for a variety of cross coupling reactions. As a result of the diverse potential applications of aromatic halides, the development of new site selective, chemoselective, and functional group tolerant approaches to the synthesis of these molecules remains an important challenge.

Scheme 1: Biologically Active Molecules Containing Aryl Halides



(**1**)
Cytotoxic

(**2**)
Convulsion

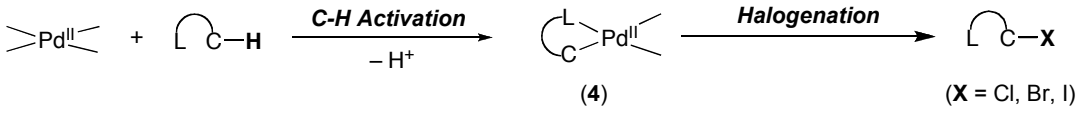
(**3**)
CB1 Receptor blocker

Current methods for the synthesis of aryl halides include electrophilic aromatic substitution (EAS)[6, 7] and directed *ortho*-lithiation.[8] While these transformations have

been widely used, they have several disadvantages. First, these reactions in general require the use of strong acids (EAS) and bases (directed *ortho*-lithiation) that might not be compatible with many commonly used functional groups. Second, they often lead to a mixture of isomeric halogenated products that might be difficult and tedious to separate. Additionally, benzylic halogenation and overhalogenation are a very common consequence of these methods. Finally, there are significant limitations in the substrate scope of these transformations. For example, EAS most commonly requires electron rich arenes. Due to the clear limitations of the current methods, the development of new, simple and complementary methodologies for the synthesis of halogenated arenes is highly desirable.

Our group has recently developed several palladium-catalyzed methods for the chelate-directed oxidative functionalization of C–H bonds using hypervalent iodine(III) reagents as terminal oxidants. For example, the reaction of diverse organic substrates with $PhI(OAc)_2$[9-12] or $[Ph_2I]BF_4$[13,14] in conjunction with a Pd^{II} catalyst leads to the ligand-directed conversion of sp^2 and sp^3 C–H bonds to C–O and C–C bonds, respectively. These results suggested the possibility of an analogous Pd-catalyzed transformation for the direct conversion of C–H bonds to C–X (X = Cl, Br, I) bonds using electrophilic halogenating reagents such as $PhICl_2$ (Scheme 2). We envisioned that such a reaction would provide the desired products with complete site selectivity and without the requirement for electron rich substrates or strong acids/bases.

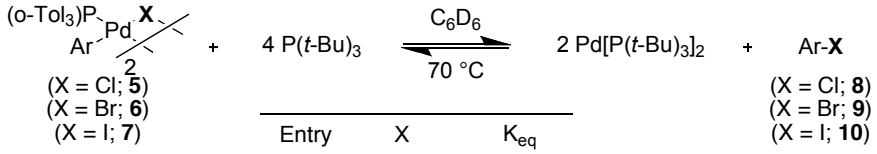
Scheme 2: Proposed Palladium-Catalyzed Directed C–H Bond Halogenation



A key step in the proposed palladium-catalyzed directed C–H activation/halogenation reactions would require the conversion of the C–Pd bond in **4** to a C–X bond in the product (Scheme 1). This transformation is well known to be challenging from Pd^{II} (and most other metal complexes) because its microscopic reverse – the oxidative addition of aryl/vinyl/alkyl halides to Pd^0 – is highly thermodynamically and kinetically favored relative to the desired reductive elimination reaction. For

example, Roy and Hartwig have shown that the K_{eq} for direct reductive elimination of haloarenes from Pd^{II} ranges from ~10^{-5} (for Ar–I) to ~10^{-2} (for Ar–Cl) (Scheme 3).[14] Additionally, the rate constant for the reductive elimination from **5** to form **8** ranges from 10^{-4} to10^{-5} s^{-1} at 65 °C (Scheme 4). As a result, the desired reaction is not amenable to catalysis via a traditional $Pd^{II/0}$ catalytic cycle.[15]

Scheme 3: K_{eq} for Carbon-Halogen Reductive Elimination at Pd^{II}

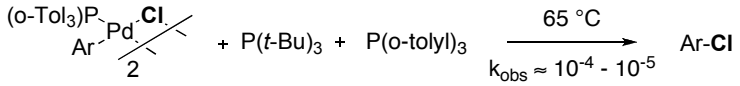


(X = Cl; **5**)
(X = Br; **6**)
(X = I; **7**)

(X = Cl; **8**)
(X = Br; **9**)
(X = I; **10**)

Entry	X	K_{eq}
1	Cl	9×10^{-2}
2	Br	2.3×10^{-3}
3	I	3.7×10^{-5}

Scheme 4: Rate Constant for Carbon-Halogen Reductive Elimination at Pd^{II}

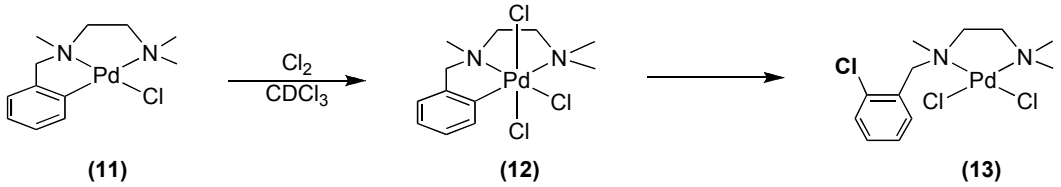


(**5**) (**8**)

However, recent work from our group has shown that reductive elimination reactions from Pd^{IV} have very different electronic requirements than those from Pd^{II}, [16] indicating that the desired carbon–halogen coupling could be facile from this oxidation state. A number of literature reports further supported the potential viability of this approach. For example, van Koten and Elsevier have directly observed transient Pd^{IV} intermediates in the oxidation of Pd^{II} complexes with molecular halogens or $PhICl_2$.[17, 18] As shown in Scheme 5, the reaction of cyclopalladated complex **11** with Cl_2 affords the Pd^{IV} intermediate **12** (Scheme 5), which was moderately stable and could be characterized by ^1H NMR spectroscopy at room temperature. However, it decomposed over time to afford halogenated product **13**. While the mechanism of formation of **13** was not studied in detail, it presumably involves C–Cl bond forming reductive elimination at

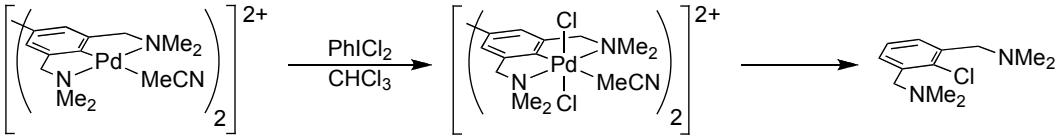
Pd^{IV}. Elsevier and coworkers reported a similar reaction between the cationic complex **14** and $PhICl_2$ (Scheme 6).

Scheme 5: Stoichiometric Chlorination of Cyclopalladated Complex **11** with Cl_2



(11) **(12)** **(13)**

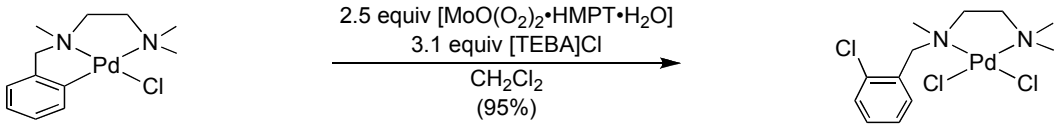
Scheme 6: Stoichiometric Chlorination of Cyclopalladated Complex **14** with $PhICl_2$



(14) **(15)** **(16)**

van Koten's research group has also demonstrated that the halogenation of cyclopalladated Pd^{II} complexes can be achieved using a combination of a non-halogenating oxidant and a chloride ion source.[19] For example, the reaction of complex **17** with $MoO(O_2)_2$•HMPT•H_2O leads to the halogenated organic product **18**. Notably the yield of **18** increases in the presence of (triethyl)(benzyl)ammonium chloride ([TEBA]Cl) as the chloride ion source (Scheme 7).

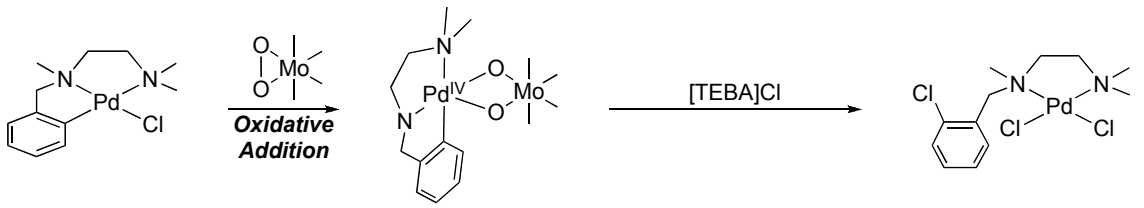
Scheme 7: Stoichiometric Chlorination with Molybdenum Peroxide



(17) **(18)**

The mechanism of this reaction is proposed to involve oxidation of **17** to a Pd^{IV} aryl intermediate **19**. Subsequent attack of the chloride ions on this Pd^{IV}-aryl species leads to **18** (Scheme 8).

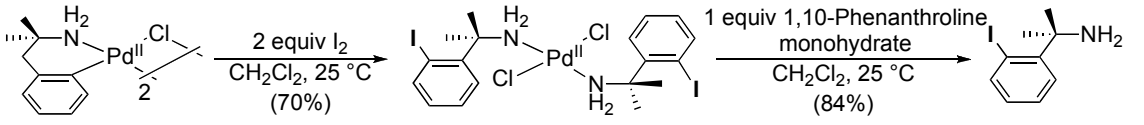
Scheme 8: Mechanism of Stoichiometric Chlorination with Molybdenum Peroxide



(17) (19) (18)

There have also been reports of stoichiometric iodinations of cyclopalladated compounds using I_2 as the oxidant. For example, the reaction of **20** with I_2 leads to the formation of **21** (Scheme 9). The treatment of **21** with 1,10-phenanthroline monohydrate releases the organic product.[20]

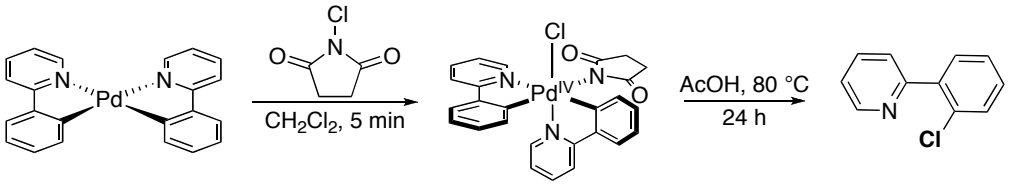
Scheme 9: Stoichiometric Iodination with I_2



(20) (21) (22)

Very recently, our group has demonstrated that *N*-chlorosuccinimide (NCS) can oxidize Pd^{II} to Pd^{IV}.[21] Specifically, we have shown that the reaction of the biscyclometallated Pd^{II} complex **23** with NCS affords an isolable Pd^{IV} complex **24**. Furthermore, thermolysis of **24** in a variety of solvents cleanly affords the chlorinated product **25** via C–Cl bond forming reductive elimination (Scheme 10).

Scheme 10: Stoichiometric Chlorination with NCS

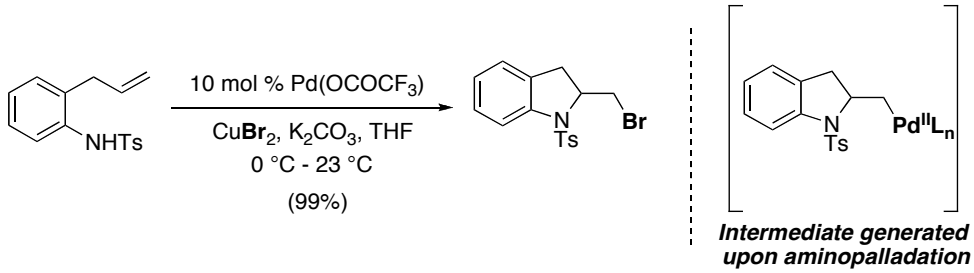


(23) (24) (25)

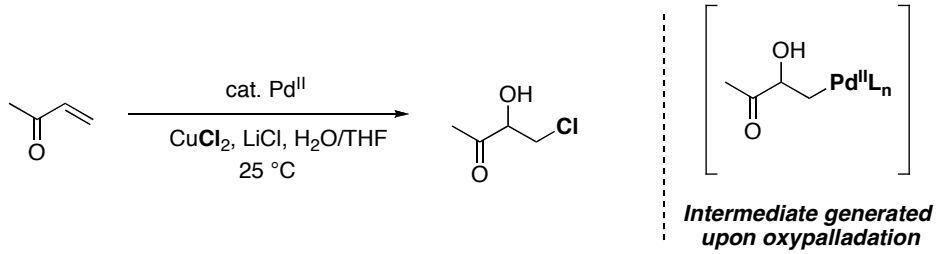
In addition, several groups have reported that intermediates generated upon aminopalladation (Scheme 11), oxypalladation (Scheme 12), and halopalladation

(Scheme 13) of alkenes at Pd^{II} can undergo C–X (X = Cl, Br) bond formation with oxidants such as Br_2, $CuCl_2$, mixtures of peroxides and halide salts, or $PhICl_2$.[22-25]

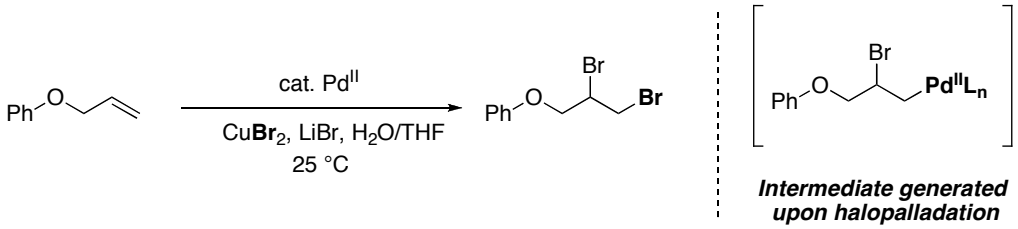
Scheme 11: Aminopalladation/Halogenation of Alkenes



Scheme 12: Oxypalladation/Halogenation of Alkenes

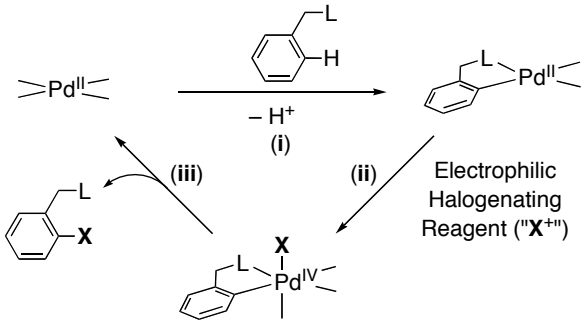


Scheme 13: Halopalladation/Halogenation of Alkenes



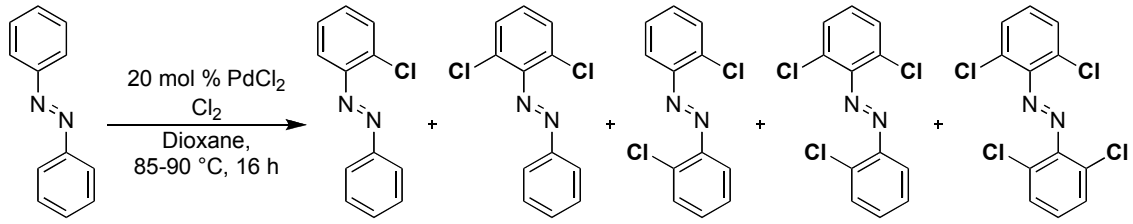
Based on this precedent, we felt that Pd-catalyzed C–H bond halogenation could proceed by a catalytic cycle involving: (i) ligand-directed C–H activation at a Pd^{II} center,[26-29] (ii) oxidation of the resulting palladacycle to Pd^{IV}, and (iii) carbon–halogen bond-forming reductive elimination to form the desired product and regenerate the catalyst (Scheme 14). Importantly, based on the stoichiometric examples described above, a variety of electrophilic halogenating reagents such as Cl_2, $PhICl_2$, I_2, and NCS could potentially be used for these reactions.

Scheme 14: Proposed Catalytic Cycle for Directed C–H Bond Halogenation



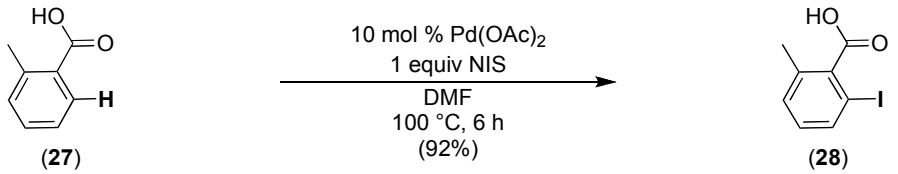
There were a few early reports of palladium-catalyzed chelate-directed halogenation of arenes proceeding via the mechanism depicted in Scheme 11 prior to our work. Fahey demonstrated that the $PdCl_2$-catalyzed reaction of azobenzene with Cl_2 affords the *ortho*-chlorinated azobenzene **26-Cl** in 8% isolated yield (Scheme 15).[30] The low yield of **26-Cl** in this reaction is partly due to the formation of di-, tri-, and tetrachlorinated products **26-Cl_2**, **Iso-26-Cl_2**, **26-Cl_3**, and **26-Cl_4,** respectively. While this transformation demonstrated the feasibility of palladium-catalyzed chelate-directed halogenation of arenes, it was not applied to the chlorination of other substrates or toward the incorporation of other halogens into the products. Additionally, the formation of mixtures of products and the use of Cl_2 as the oxidant severely limits the practical applicability of this reaction.

Scheme 15: Palladium-Catalyzed Halogenation of Azobenzene



In 2001, Kodama and coworkers reported the palladium-catalyzed *ortho*-iodination of benzoic acid derivatives using $Pd(OAc)_2$ as the catalyst and *N*-iodosuccinimide (NIS) as the terminal oxidant. This methodology was limited to C–I bond formation and carboxylic acids as the directing group (Scheme 16).[31]

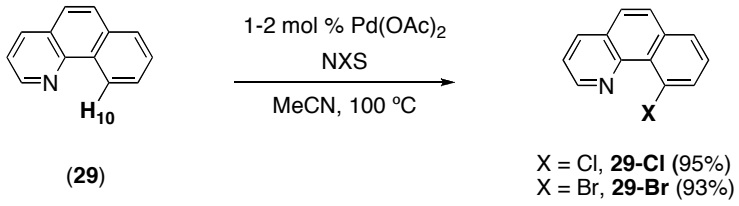
Scheme 16: Palladium-Catalyzed Iodination of Benzoic Acid Derivatives



While all the aforementioned examples of palladium-catalyzed ligand-directed halogenation of C–H bonds represent a remarkable advancement in the field of site selective halogenation of arenes, they are limited with respect to the scope of directing groups and substrates. Additionally, none of these methods represent a general method for the incorporation of a variety of halogens (Cl, Br, and I) under a similar set of reaction conditions.

More recently Allison Dick, a former member of our group, showed that the $Pd(OAc)_2$-catalyzed reaction of benzo[*h*]quinoline (**29**) and *N*-chlorosuccinimide (NCS) affords **29-Cl** in 95% yield via chelate-directed halogenation of the $C–H_{10}$ bond (Scheme 17). In addition, the corresponding brominated product **29-Br** could be obtained in excellent yield (93%) using NBS as the stoichiometric oxidant. Importantly, these reactions showed exclusive selectivity for halogenation of the $C–H_{10}$ bond proximal to the chelating group.[12]

Scheme 17: Palladium-Catalyzed Halogenation of Benzo[*h*]quinoline

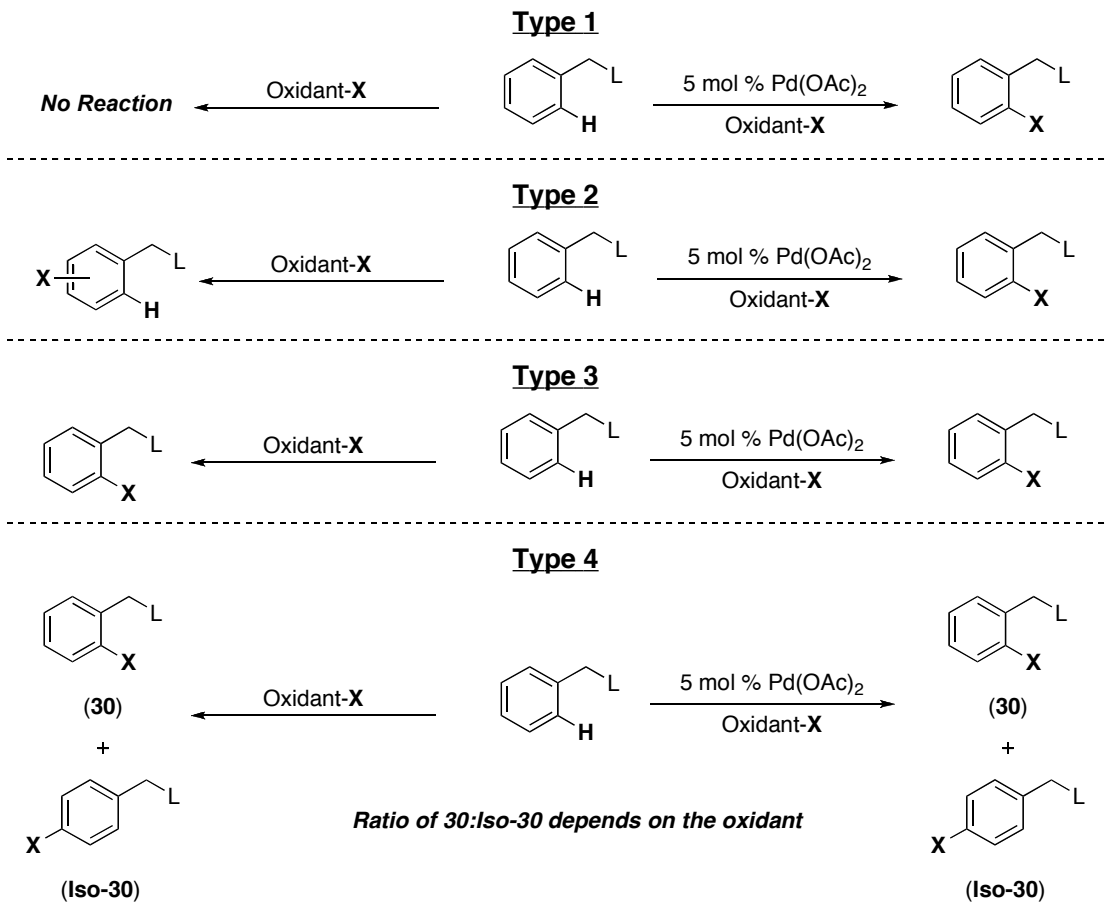


With these preliminary results from our group, we desired to undertake a comprehensive exploration of the palladium-catalyzed ligand-directed C–H activation/halogenation reactions. Specifically, we wanted to develop reaction conditions that are general with respect to directing groups and arenes and would allow the incorporation of diverse (Cl, Br ,and I) halogens into the final products.[32, 33]

4.2 Initial Results

Our initial experimentation revealed that there was no universal set of reaction conditions for these transformations, and that varying the solvent (typically between MeCN and AcOH), temperature (ranging from 100 – 120 ºC), and oxidant (between NXS and CuX_2) was necessary in order to obtain the optimal conditions for each substrate. Additionally, substrates with different substitution patterns on the aryl ring and with different directing groups showed dramatically different reactivities. In general, the substrates could be divided into four types (Scheme 18) based on their reactivity in the presence and absence of palladium as follows: (i) substrates for which the Pd-catalyzed reaction results in chelate-directed halogenation, while the control (without Pd catalyst) affords no halogenated products (**Type 1**), (ii) substrates for which the Pd-catalyzed and control reactions afford different halogenated products (**Type 2**), (iii) substrates for which the catalyzed and the uncatalyzed reactions afford the same product or mixtures of products (**Type 3**), and (iv) substrates for which the similarity/difference in reactivity between the Pd-catalyzed and control reactions is dictated by the nature of the oxidant (**Type 4**). A detailed discussion of each of these types of substrates follows below.

Scheme 18: Types of Substrates for Halogenation Reactions

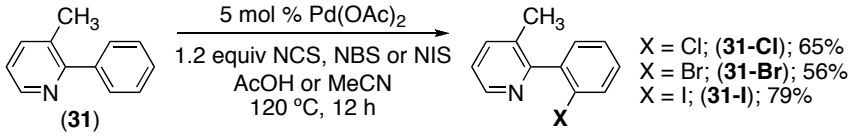


4.3 Type 1 Substrates

Type 1 substrates generally contain electron withdrawing directing groups such as pyridines, oxime ethers, isoxazolines, quinolines, and tetrazoles; furthermore, the arene ring that undergoes halogenation is typically electron-neutral or electron-deficient (containing substituents such as halides, oxime ethers, ketones and aldehydes) and hence not activated towards EAS. Substrates containing such structural motifs possess a wide range of potential applications. For example, isoxazolines serve as useful precursors to β-amino acids,[34] while pyridines and tetrazoles are important components of diverse drug molecules.[35] Tetrazole derivatives can also be used as trigger explosives and serve as components of mixed propellants.[35]

3-Methyl-2-phenylpyridine (**31**) represents a prototypical **Type 1** substrate. Thus palladium-catalyzed halogenation of **31** was studied using a variety of electrophilic halogenating reagents in AcOH and MeCN. Under all of the conditions examined, **31** afforded <5% halogenated products in the absence of the palladium catalyst. In contrast, in the presence of $Pd(OAc)_2$, most of the reagents screened afforded significant quantities of the *ortho*-halogenated products **31-Cl**, **31-Br**, or **31-I**. In general, the *N*-halosuccinimides proved to be superior oxidants, providing the highest isolated yields of **31-Cl** (65 %), **31-Br** (56 %) and **31-I** (79 %) (Scheme 19).

Scheme 19: Palladium-Catalyzed Halogenation of 3-Methyl-2-Phenylpyridine



Among the other oxidants examined (Table 4.1), a number of notable observations were made. Consistent with the C–H activation/acetoxylation reactions using $PhI(OAc)_2$ as the terminal oxidant, the use of the analogous iodine(III) reagent $PhICl_2$ afforded the desired product **31-Cl**, albeit in only 32% yield (Table 4.1, entry 5). The low yield of this transformation can most likely be attributed to the instability of $PhICl_2$ at the elevated temperatures (100 ºC) utilized for these transformations[36] (at room temperature no product formed and only unreacted substrate was seen by crude GC). Interestingly, neither Br_2 nor I_2 afforded substantial quantities of halogenated products (Table 4.1, entries 11 and 17, respectively), despite the fact that these reagents are highly effective for the stoichiometric halogenation of Pd^{II} alkyl,[37] aryl,[30, 38] and vinyl[39] species. This may be due to the decreased reactivity and/or solubility of PdX_2 (presumably formed *in situ* from the reaction of $Pd(OAc)_2$ with halide ions) in these reactions.[40] In contrast, $CuCl_2$ was an effective reagent for transforming **31** to **31-Cl** in 30% GC yield under standard conditions (Table 4.1, entry 6). This result is particularly remarkable because $CuCl_2$ could potentially be utilized in catalytic quantities with readily available and inexpensive dioxygen as the ultimate terminal oxidant.[41-44]

Table 4.1. Palladium-Catalyzed Reaction of **31** with Electrophilic Halogenating Reagents

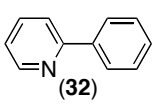
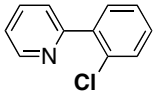
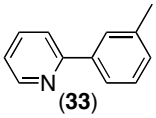
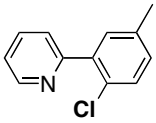
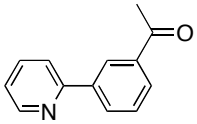
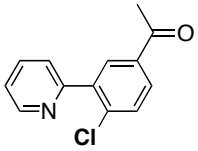
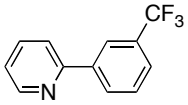
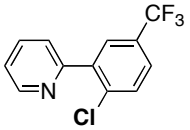
Entry	Halogenating Reagent	Product	GC yield in AcOH	GC yield in MeCN
1	NCS	(**31-Cl**)	60%	56%
2	$Pb(OAc)_4$/LiCl[c]	(**31-Cl**)	63%	51%
3	Chloramine-T	(**31-Cl**)	56%	36%
4	$K_2Cr_2O_7$/LiCl[c]	(**31-Cl**)	42%	0%
5	$PhICl_2$	(**31-Cl**)	32%	15%
6	$CuCl_2$	(**31-Cl**)	21%[a]	30%[a]
7	NBS	(**31-Br**)	53%	44%
8	Br_2/$PhI(OAc)_2$	(**31-Br**)	39%	24%
9	$Pb(OAc)_4$/LiBr[c]	(**31-Br**)	32%	42%
10	$K_2Cr_2O_7$/LiBr[c]	(**31-Br**)	15%	8%
11	Br_2	(**31-Br**)	0%	26%
12	$CuBr_2$	(**31-Br**)	0%[a]	15%[a]
13	NIS	(**31-I**)	64%	87%
14	I_2/$PhI(OAc)_2$	(**31-I**)	64%	71%
15	$K_2Cr_2O_7$/LiI[c]	(**31-I**)	44%	0%
16	$Pb(OAc)_4$/LiI[c]	(**31-I**)	37%	0%
17	I_2	(**31-I**)	0%	40%

[a] 2.4 equiv halogenating reagent; [b] Isolated yields from reactions carried out at 120 ºC; [c] 2 equiv LiX.

A number of other **Type 1** substrates were identified, and the results of their Pd-catalyzed reactions with *N*-halosuccinimides are summarized in Tables 4.2, 4.3, and 4.4. As discussed above, all these substrates afforded <5% of halogenated products in the absence of palladium. However, in the presence of the palladium catalyst, the ligand-directed *ortho*-halogenated products were obtained in modest to good yields. All of these transformations (and those described throughout this chapter) are completely tolerant of ambient air and moisture and were typically conducted on the bench-top using commercial solvents and reagents. Furthermore, the safe and inexpensive nature of these transformations makes them easily scalable, and relatively large-scale reactions (11 to 82 mmol) typically afforded comparable yields to those carried out with 0.5-1.5 mmol of

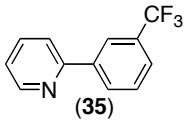
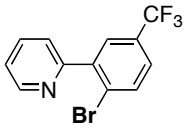
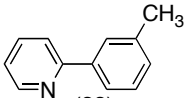
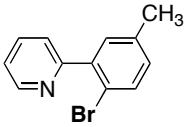
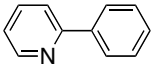
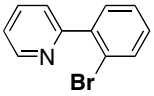
material. This is exemplified by substrate **33** (Table 4.3), for which Allison Dick has shown that reactions performed at 17 mmol and 1.4 mmol scales afforded product **33-Br** in nearly identical 51% isolated yield. In addition, the use of 1 mol % catalyst afforded comparable yields in similar reaction times to 5 mol % $Pd(OAc)_2$; for example, **31-Cl**, **31-Br** and **31-I** were obtained in 71%, 54%, and 90% GC yields, respectively, after 12 h with 1 mol % Pd. Further reduction of the catalyst load (to 0.5 mol %) typically resulted in some (~20%) diminishment in yield. The easy and practical scale up along with the low catalyst loadings should make these halogenation reactions very attractive for diverse applications.

Table 4.2. Palladium-Catalyzed Chlorination of **Type 1** Substrates[a]

Entry	Substrate	Product	Product #, Yield
1	 (**32**)		**32-Cl**, 55%
2	 (**33**)		**33-Cl**, 63%
3	 (**34**)		**34-Cl**, 30%
4	 (**35**)		**35-Cl**, 41%

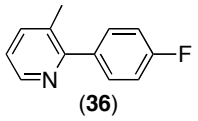
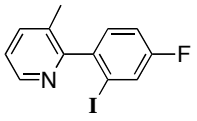
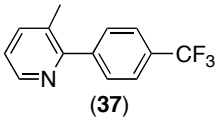
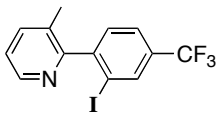
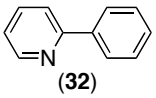
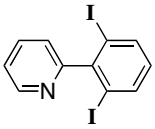
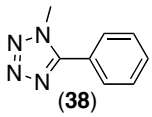
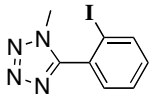
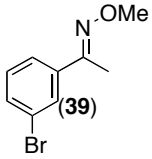
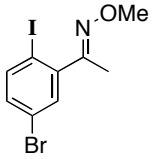
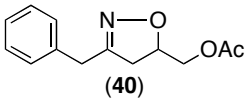
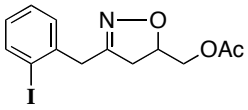
[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.1-1.2 equiv NCS, 100-120 ºC, 12 h, MeCN or AcOH.

Table 4.3. Palladium-Catalyzed Bromination of **Type 1** Substrates[a]

Entry	Starting Material	Product	Product #, Yield
1	 (**35**)		**35-Br**, 63%
2	 (**33**)		**33-Br**, 51%
3	 (**32**)		**32-Br**, 63%

[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.2-2.0 equiv NBS, 100-120 ºC, 12 h, MeCN or AcOH.

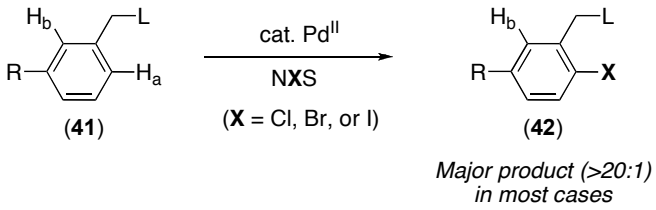
Table 4.4 Palladium-Catalyzed Iodination of **Type 1** Substrates[a]

Entry	Substrate	Product	Product #, Yield
1	 (**36**)		**36-I**, 70%
2	 (**37**)		**37-I**, 78%
3	 (**32**)		**32-I$_2$**, 41%
4	 (**38**)		**38-I**, 41%
5	 (**39**)		**39-I**, 57%
6	 (**40**)		**40-I**, 54%

[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.05-2.1 equiv NIS, 100-120 ºC, 12 h, MeCN or AcOH;
[b] 3.0 equiv NIS.

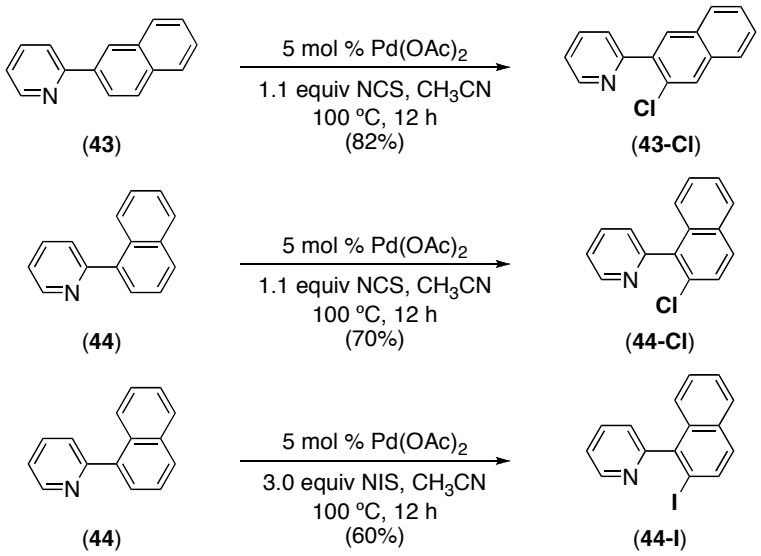
In reactions of *meta*-substituted arene substrates **41**, which bear two chemically inequivalent *ortho* C–H bonds, the less hindered position was usually halogenated with high selectivity (Scheme 20).[45] Further, the site selectivity of these reactions was general for different directing groups. For example, the reactions of pyridine and oxime ether substrates resulted in halogenation *para* to the *meta* substituent (Table 4.4, entry 5).

Scheme 20: Site Selectivity for Halogenation of *Meta*-Substituted Arenes



In naphthyl substituted substrates **43** and **44**, Waseem Anani, a former undergraduate in our group, demonstrated that the less sterically congested 3' *ortho*-C–H bond was selectively halogenated, despite the fact that the 1' position is more nucleophilic (Scheme 21). This sensitivity to the steric environment of the arene ring is analogous to the Pd-catalyzed C–H activation/functionalization reactions described in ***Chapters 2 and 3***.[9, 13, 45]

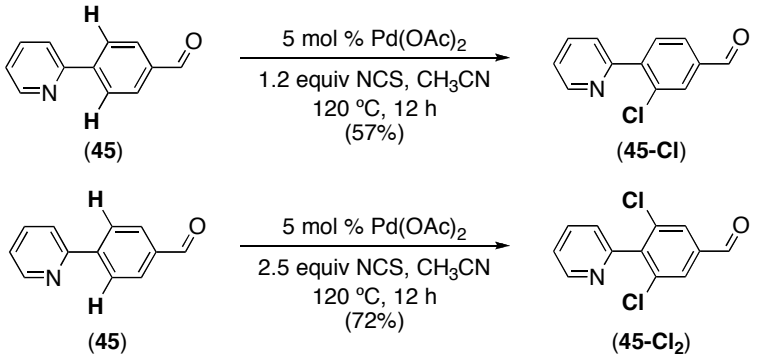
Scheme 21: Palladium-Catalyzed Halogenation of **44** and **45**



C–H activation/halogenation reactions of **Type 1** substrates containing two readily accessible, chemically equivalent C–H bonds generally led to modest yields of the monohalogenated products due to competitive formation of the corresponding difunctionalized compounds. Tuning the stoichiometry of the oxidant in these systems allowed for the formation of dihalogenated products in good yields. For example, the

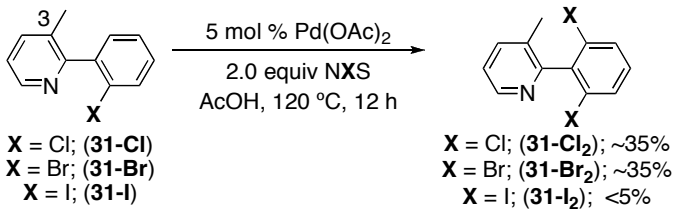
palladium-catalyzed chlorination of **45** afforded the monochlorinated product **45-Cl** in 57% yield. However, the use of excess oxidant in this reaction afforded the dichlorinated product **45-Cl$_2$** in 72% yield (Scheme 22).

Scheme 22: Palladium-Catalyzed Halogenation of **46**



Several approaches can be taken to attenuate the extent of dihalogenation in these systems if it is not desired. For example, as discussed above, the incorporation of a *meta*-substituent generally decreased the formation of dihalogenated side-products, presumably by reducing the rate of a second C–H activation at the more sterically hindered site (Scheme 20). Additionally, dihalogenation could be minimized in phenylpyridine derivatives by placing a substituent at the 3-position of the pyridine moiety (for example, substrate **31** in Scheme 19). As shown in Scheme 23, the extent of dihalogenation in these systems decreases with increasing size of the halogen on the arene counterpart. This is illustrated by the fact that ~35% of the difunctionalized products were formed when **31-Cl** and **31-Br** were subjected to forcing reaction conditions (5 mol % Pd(OAc)$_2$, 2 equiv NXS, AcOH, 120 °C), while only traces (<5%) of the diiodinated product was observed in the analogous reaction of **31-I** with NIS (Scheme 23). In these systems, the unfavorable steric interactions between the *ortho*-halogen of the mono-functionalized arene and the 3-substituent on the pyridine ring make it difficult to achieve coplanarity between the aryl rings, which is necessary for the second C–H activation/functionalization to occur.[46, 47]

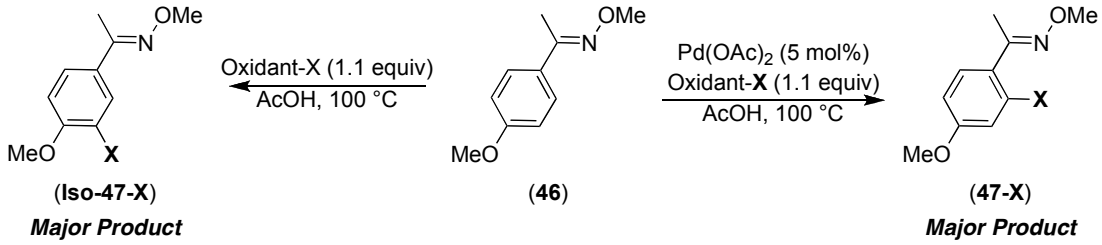
Scheme 23: Effect of the Halogen Size on Dihalogenation



4.4 Type II Substrates

Type 2 substrates are generally activated towards EAS and hence undergo halogenation in the absence of the Pd catalyst. However, in these cases there is a difference in the products favored by the catalyzed reaction versus by electrophilic aromatic substitution; therefore, the products obtained with Pd are complementary to those obtained in the control reactions. Oxime ether substrate **46** exemplifies this class of substrates (Scheme 24).

Scheme 24: Pd-Catalyzed versus Uncatalyzed Halogenation of **46**



(**Iso-47-X**) (**46**) (**47-X**)

Major Product ***Major Product***

The arene ring of **46** is activated at the 3-position toward EAS due to the electron-donating methoxy substituent. Hence, the major product (**Iso-46-X**) in these reactions without palladium resulted from halogenation *ortho* to the activated methoxy substituent. As shown in Table 5, the reaction of **46** afforded significant quantities of the halogenated products with a variety of halogenating reagents both in the presence and absence of the palladium catalyst. While the control reactions with NXS in AcOH cleanly afforded the 3-substituted products **Iso-46-X** (Table 4.5, entry 1), other oxidants such as $PhICl_2$, Chloramine-T and Br_2 led to mixtures of **46-X** and **Iso-46-X** via unselective halogenation.

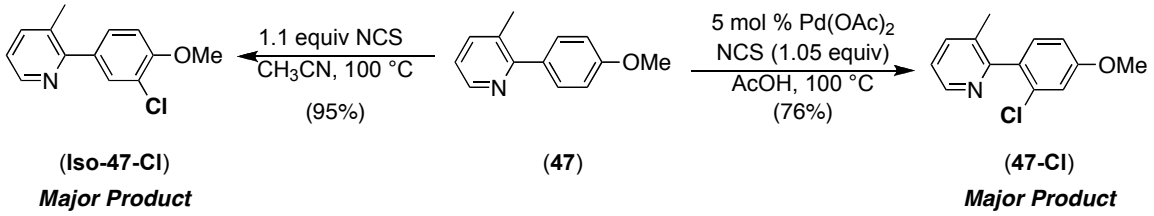
Table 4.5: Palladium-Catalyzed Reaction of **46** with Diverse Halogenating Reagents

Entry	Halogenating Reagent	X	GC yield *with* Pd		GC yield *without* Pd	
			46-X	**Iso-46-X**	**46-X**	**Iso-46-X**
1	NCS	**Cl**	87%	<5%	<5%	64%
2	Chloramine-T	**Cl**	42%	25%	36%	56%
3	$PhICl_2$	**Cl**	<5%	52%	13%	50%
4	$CuCl_2$	**Cl**	16%[a]	<5%[a]	0%[a]	0%
5	NBS	**Br**	72%	<5%	0%	9%
6	$Br_2/PhI(OAc)_2$	**Br**	0%	0%	0%	0%
7	Br_2	**Br**	11%	8%	13%	15%
8	$CuBr_2$	**Br**	0%	0%	0%	0%
9	NIS	**I**	48%	6%	<5%	47%
10	$I_2/PhI(OAc)_2$	**I**	0%	0%	0%	67%
11	I_2	**I**	0%	0%	0%	0%

In the presence of 5 mol % $Pd(OAc)_2$, the catalyzed reaction in general out-competed EAS affording *ortho*-halogenated compounds **46-Cl**, **46-Br**, and **46-I** as the predominant products in most cases. Interestingly, however, the use of the highly reactive iodine(III) reagent $PhICl_2$ as the oxidant led solely to the EAS product **Iso-46-Cl** even in the presence of the palladium catalyst. Other oxidants such as Br_2 and Chloramine-T afforded mixtures of products favoring the desired ligand-directed *ortho*-halogenated isomer with only modest selectivity. Gratifyingly, the palladium-catalyzed reaction of **46** with *N*-halosuccinimides (NXS) as the terminal oxidants led to the exclusive formation of the desired chelate-directed products in GC yields ranging from 48-87%. Under these optimal conditions, the products **46-Cl**, **46-Br** and **46-I** were isolated in 58%, 72% and 46% yields respectively.

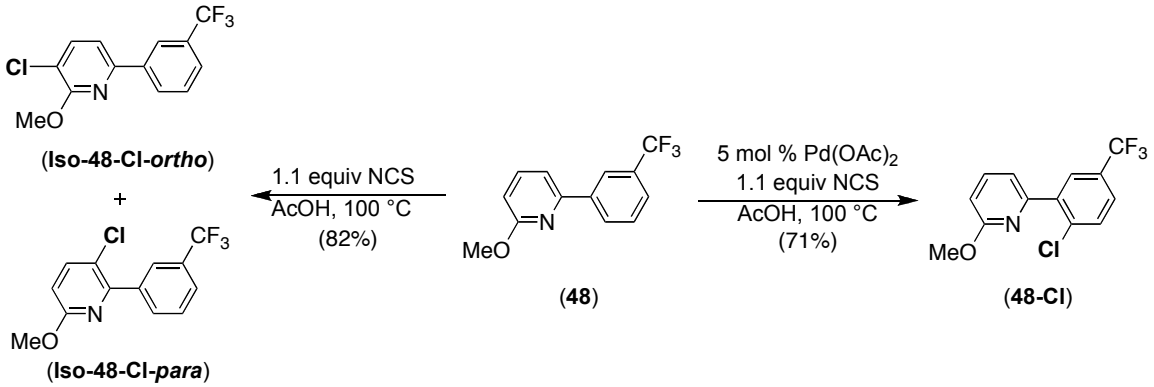
Similar results were observed in analogous **Type 2** substrates with different directing groups. For example, 3-methyl-2-(4-methoxyphenyl)pyridine (**47**) afforded **47-Cl** in 76% isolated yield in the Pd-catalyzed reaction, while only **Iso-47-Cl** was obtained in the control (Scheme 25).

Scheme 25: Catalyzed versus Uncatalyzed Chlorination of **47**



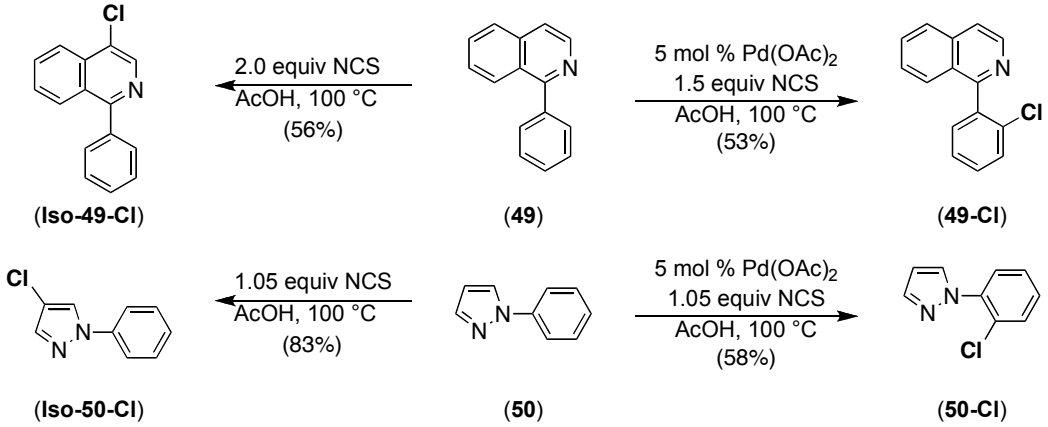
Substrate **48**, which contains a methoxy substituent on the ring of the pyridine directing group, showed comparable behavior (Scheme 26). In the absence of Pd, a mixture of regioisomeric products was obtained with Cl incorporated *ortho* (**Iso-48-Cl-*ortho***) and *para* (**Iso-48-Cl-*para***) to the methoxy substituent on the electron rich pyridine ring. However, in the presence of 20 mol % $Pd(OAc)_2$, the directed chlorination product **48-Cl** was obtained cleanly in 71% yield (Scheme 26).

Scheme 26: Catalyzed versus Uncatalyzed Chlorination of **48**



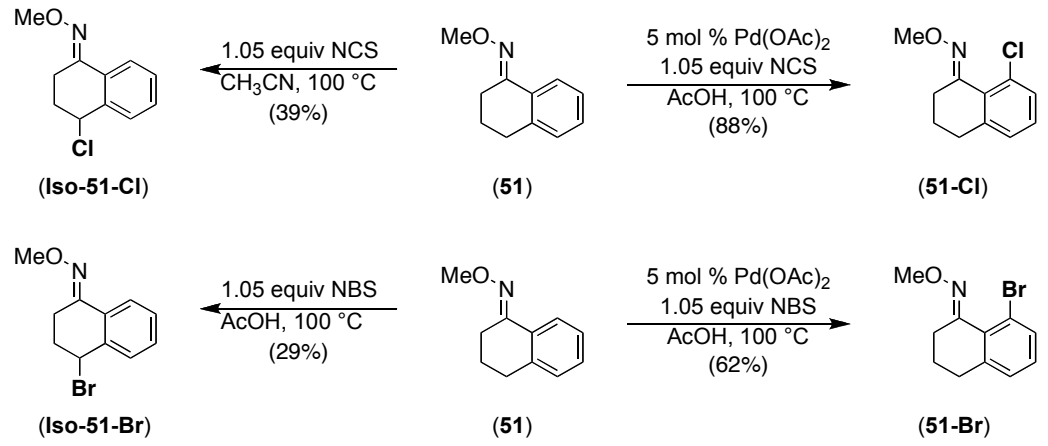
Other substrates that fall into **Type 2** are those containing the heterocyclic directing groups isoquinoline (**49**) and pyrazole (**50**) (Scheme 27). Without added palladium, these substrates underwent chlorination on the heterocyclic ring; however, in the presence of 5 mol % $Pd(OAc)_2$, Pd-catalyzed directed C–H activation/chlorination out-competed EAS, and the *ortho*-chlorinated products **49-Cl** and **50-Cl** were obtained in 53% and 58% isolated yields, respectively.

Scheme 27: Chlorination of Substrates **49** and **50**



Another **Type 2** substrate is the oxime ether **51** (Scheme 28). The 2º benzylic position of **51** is highly activated towards benzylic halogenation with NCS or NBS, and, in the absence of Pd-catalyst, the benzylic halides **Iso-51-Cl** and **Iso-51-Br** were obtained as the major products (albeit in modest yields – Scheme 28). However, in the Pd-catalyzed process, chelate-directed halogenation was fast relative to benzylic oxidation, and haloarenes **51-Cl** and **51-Br** were obtained in 88% and 62% isolated yields, respectively.

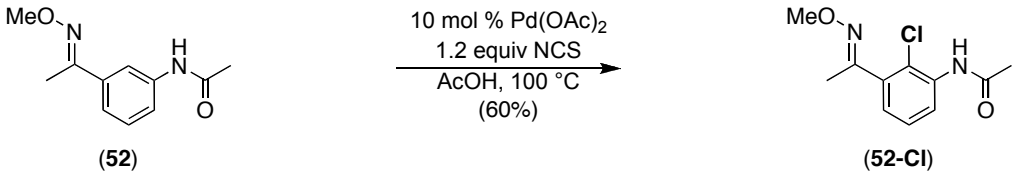
Scheme 28: Chelate-Directed versus Benzylic Halogenation



A final **Type 2** compound is the *meta*-substituted oxime ether **52** which possesses three potential sites for directed C–H activation (Scheme 29). In contrast to the substrates discussed in section 4.3 above, **52** underwent Pd-catalyzed chlorination with high (>20:1)

selectivity for the more hindered 2-position of the arene. This may be the result of the cooperative coordination of both the amide and the oxime directing groups to the Pd-center during the C–H activation step of this reaction.[9] However, the reaction of **52** with NCS in the absence of palladium afforded a complex mixture of isomeric chlorinated products.

Scheme 29: Palladium-Catalyzed Chlorination of **52**

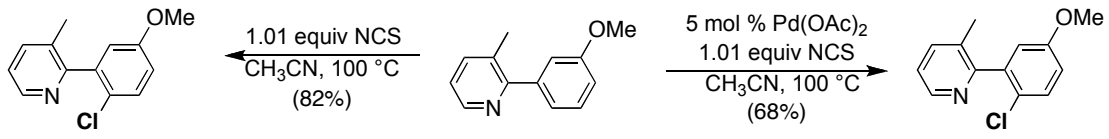


(**52**) (**52-Cl**)

4.5 Type 3 Substrates

Type 3 substrates are activated towards EAS at the same position (in the molecule) as the palladium-catalyzed ligand-directed halogenation reactions. As such, these compounds favor the same product or mixtures of products both in the presence and absence of palladium. Hence, unless otherwise noted, the use of a palladium catalyst offers no significant advantage in terms of the yield, purity or selectivity of reactions with these substrates. For example, **53**, containing a highly electron donating arene substituent (*e.g.,* OMe) at the position *meta*- to the directing group, is a representative member of this type. In this compound, both the catalyzed and the uncatalyzed processes afforded halogenation *para* to the substituent. Thus, the use of a palladium catalyst was not necessary to obtain the "chelate-directed" *ortho*-halogenated product **53-Cl** in high yields (Scheme 30).

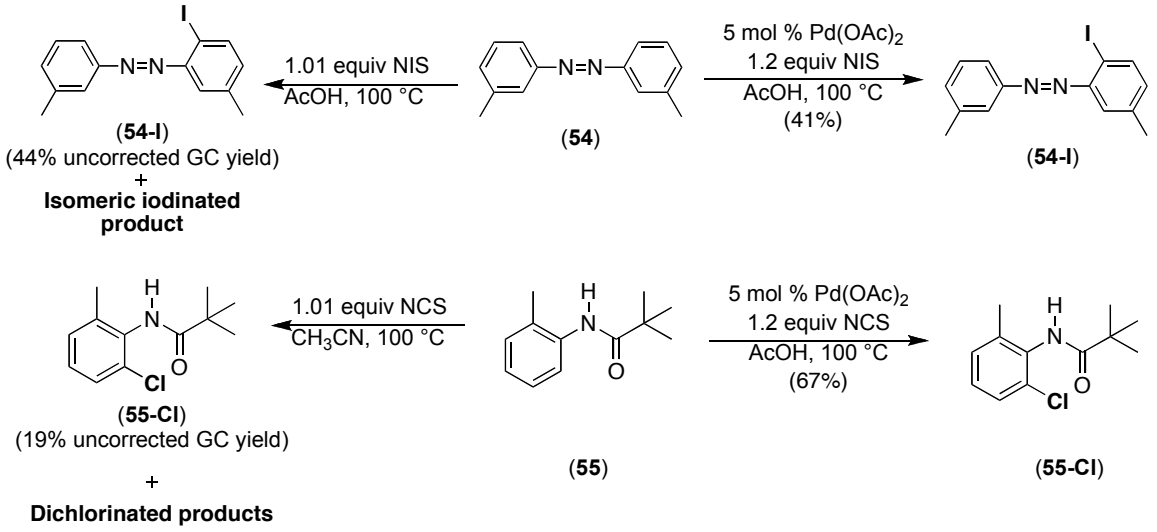
Scheme 30: Chlorination of **53**



(**53-Cl**) (**53**) (**53-Cl**)

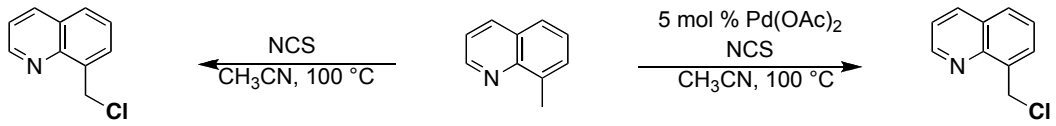
Azobenzene **54** also falls under **Type 3**, as both the catalyzed and the uncatalyzed reactions afford the *ortho*-iodinated product **54-I** as the major product (Scheme 31). However, in this case the use of palladium affords the desired chelate directed product in higher yields because the reaction in the absence of palladium affords a 4:1 mixture of isomeric iodinated products. Similarly, the reaction of pivalamide **55** with NCS afforded significant quantities of the *ortho*-chlorinated product **55-Cl** with or without palladium (Scheme 31). However, in this case, the catalyzed reaction provided **55-Cl** in higher yield and selectivity, as it suppressed formation of dichlorinated side-products, which were produced in ~50% yield in the control reaction. Thus for substrates **54** and **55**, the addition of Pd could be advantageous for applications where high material throughput and facile isolation/purification steps are necessary.

Scheme 31: Halogenation of Substrates **54** and **55**



Type 3 substrates are not limited to those undergoing arene C–H functionalization. For example, Waseem Anani demonstrated that 8-methylquinoline (**56**) reacts with NCS to afford the benzylic chloride **56-Cl** with or without palladium (Scheme 32). However, interestingly, with $CuCl_2$ as the oxidant, this product is formed only in the Pd-catalyzed transformation, and not in the control. Hence, **56** represents a **Type 3** substrate with NCS while it is a **Type 1** substrate with $CuCl_2$.

Scheme 32: Chlorination of 8-Methylquinoline



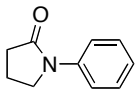
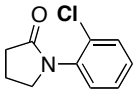
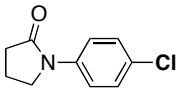
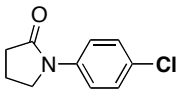
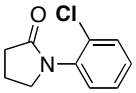
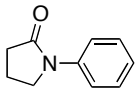
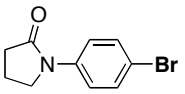
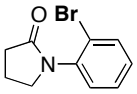
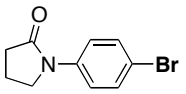
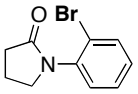
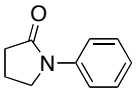
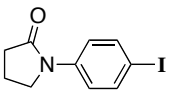
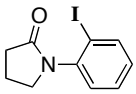
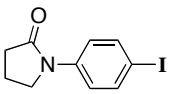
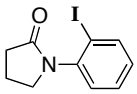
(**56-Cl**) (**56**) (**56-Cl**)

4.6 Type 4 Substrates

Type 4 substrates are those in which there is a delicate balance between the catalyzed and uncatalyzed processes, such that the nature of the oxidant dictates which product predominates. In general, the chlorination of **Type 4** substrates with NCS was most amenable to palladium catalysis, and they typically reacted to form different major mono-chlorinated products in Pd-catalyzed versus control reactions. In contrast, halogenating reagents such as NIS generally afforded identical results with and without Pd.

This **Type 4** behavior is clearly illustrated by the reactivity profile of pyrrolidinone substrate **57** (Table 4.6). As shown in Table 4.6, the control reaction with NCS afforded an approximately 1:1 mixture of *ortho* and *para*-chlorinated products (**57-Cl** and **Iso-57-Cl**, respectively), while the *ortho*-chlorinated product **57-Cl** predominated in the Pd-catalyzed reaction. In contrast, the reaction of **57** with NBS provided a mixture of *ortho* and *para* brominated products **57-Br** and **Iso-57-Br** both in the presence and absence of palladium. Finally, the reaction of **57** with NIS afforded exclusively the *para* iodinated product **Iso-57-I** in both the catalyzed and the uncatalyzed reactions.

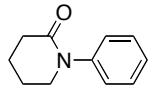
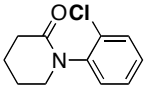
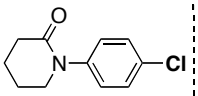
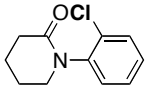
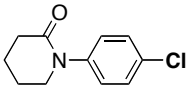
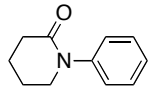
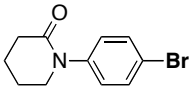
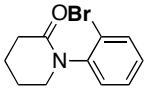
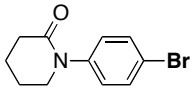
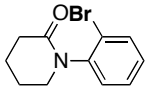
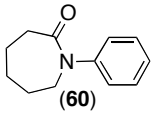
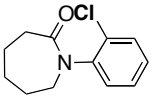
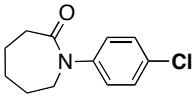
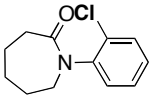
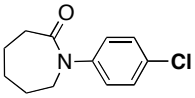
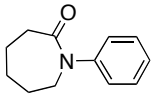
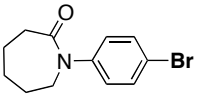
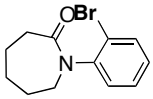
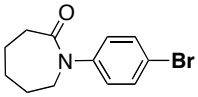
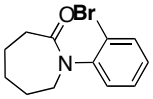
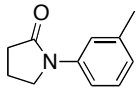
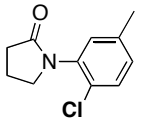
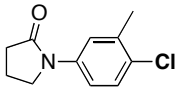
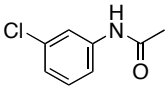
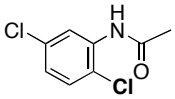
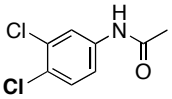
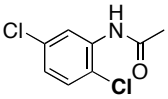
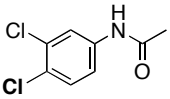
Table 4.6: Palladium-Catalyzed versus Uncatalyzed Halogenation of **57**

Entry	Starting Material	Oxidant	Major Product with Pd Catalyst	Minor Product with Pd Catalyst	Major Product without Pd Catalyst	Minor Product without Pd Catalyst
1	 (**58**)	NCS	 (**57-Cl**, 77%)	 (**Iso-57-Cl**, <5%)	 (**Iso-57-Cl**, 50%)[b]	 (**57-Cl**, 50%)[b]
2	 (**58**)	NBS	 (**Iso-57-Br**, 75%)[b]	 (**57-Br**, 17%)[b]	 (**Iso-57-Br**, 73%)[b]	 (**57-Br**, 19%)[b]
3	 (**58**)	NIS	 (**Iso-57-I**, 80%)	 (**57-I**, <5%)	 (**Iso-57-I**, 80%)	 (**57-I**, <5%)

[a] 1.5-1.8 equiv NXS, 100 ºC, 12 h, AcOH; [b]Uncorrected yields as determined by GC and GCMS.

Similarly, control reactions of pyrrolidinones **58, 59** and **60** (Table 4.7) as well as the acetanilide **61** with NCS afforded a mixture of chlorinated products, while the analogous Pd-catalyzed reactions afforded **58-Cl**, **59-Cl, 60-Cl** and **61-Cl** in 58%, 77%, 81%, and 70% isolated yields respectively, along with only traces of the undesired isomeric products. Again, the corresponding bromination reactions of **58** and **59** afforded approximately 3:1-4:1 mixture of regioisomeric brominated products both in the presence and the absence of palladium.

Table 4.7: Palladium-Catalyzed versus Uncatalyzed Halogenation of **58-61**

Entry	Starting Material	Oxidant	Major Product with Pd Catalyst	Minor Product with Pd Catalyst	Major Product without Pd Catalyst	Minor Product without Pd Catalyst
1	 (**59**)	NCS	 (**58-Cl**, 57%)	 (**Iso-58-Cl**, <5%)	 (**58-Cl**, 45%)[b]	 (**Iso-58-Cl**, 41%)[b]
2	 (**59**)	NBS	 (**Iso-58-Br**, 63%)	 (**58-Br**, 37%)	 (**Iso-58-Br**, 81%)[b]	 (**58-Br**, 19%)[b]
3	 (**60**)	NCS	 (**59-Cl**, 77%)	 (**Iso-59-Cl**, <5%)	 (**59-Cl**, 41%)[b]	 (**59-Cl**, 28%)[b]
4	 (**60**)	NBS	 (**Iso-59-Br**, 60%)[b]	 (**59-Br**, 40%)[b]	 (**Iso-59-Br**, 77%)[b]	 (**59-Br**, 23%)[b]
5	 (**61**)	NCS	 (**60-Cl**, 81%)	 (**Iso-60-Cl**, <5%)	Complex mixture of products	
6	 (**62**)	NCS	 (**61-Cl**, 70%)	 (**Iso-61-Cl**, 17%)	 (**61-Cl**, 43%)	 (**Iso-61-Cl**, 39%)

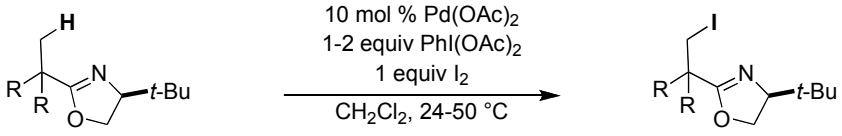
The reactivity of **Type 4** substrates represents a competition between the palladium-catalyzed reaction and electrophilic aromatic substitution. The results in Tables 4.6 and 4.7 suggest that changing the oxidants alters the relative rates of the catalyzed and the uncatalyzed processes. Current efforts in our group are directed towards delineating the effect of the oxidants on the relative contributions of the catalyzed and the noncatalyzed reaction pathways.

4.7 Subsequent Examples

Subsequent to the preliminary communication from our group, Yu and coworkers demonstrated that oxazolines can serve as efficient directing groups for the Pd-catalyzed

C–H activation/iodination of sp^3 C–H bonds using I_2 as the electrophilic iodinating reagent in conjunction with stoichiometric amounts of $PhI(OAc)_2$ (Scheme 33).[48-50] The authors believe that $PhI(OAc)_2$ serves as the source of the acetate to regenerate the $Pd(OAc)_2$ catalyst in these reactions. In general, these reactions were selective for the iodination of primary over secondary C–H bonds. Additionally the efficiency of these transformations was very sensitive to the size of the substituent at the 4-position of the oxazoline moiety. The yields of the iodinated products decreased when the *t*-butyl group was replaced with relatively smaller Ph, *i*-Pr or Me groups.

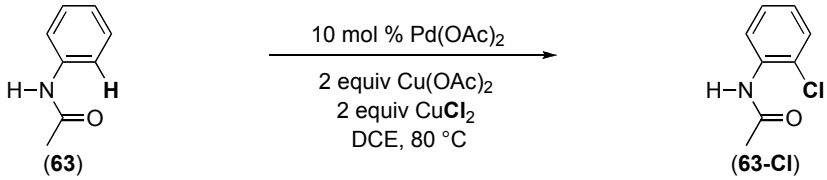
Scheme 33: Palladium-Catalyzed Oxazoline-Directed sp^3 C–H Bond Iodination



(62) **(62-Cl)**

Concurrent with our work, Shi and coworkers reported the palladium-catalyzed chelate-directed halogenation of acetanilide derivatives using CuX_2 (X= Cl, Br) as the oxidant in conjunction with stoichiometric quantities of $Cu(OAc)_2$ (Scheme 34). This methodology was very sensitive to the nature of the nitrogen protecting group. The desired halogenated product was only obtained with *N*-acetyl, *N*-pivolyl and N-(3'-phenylpropionyl) amides. Substrates bearing formyl, benzoyl, tosyl, and trifluoroacetyl protecting groups exhibited low reactivity. Furthermore, the yield of the chlorinated product diminished significantly with decreasing electron density on the arene.

Scheme 34: Palladium-Catalyzed *Ortho* Chlorination of Acetanilides



(**63**) (**63-Cl**)

4.8 Conclusions

In summary, we have conducted the first detailed exploration of palladium-catalyzed chelate-directed chlorination, bromination, and iodination of arenes using *N*-halosuccinimides as terminal oxidants. Preliminary results demonstrate that the halogenation of benzylic sp^3 C–H bonds can also be achieved using this methodology. These reactions were generally tolerant of a variety of functional groups and showed wide scope with respect to directing groups. Furthermore, the reactivity trends of the various compounds greatly depended on the substitution pattern/electronics of the substrate as well as the ligand abilities of the directing group. Hence, the products obtained from these reactions are often different from and highly complementary to those obtained via traditional methods, such as electrophilic aromatic substitution and benzylic halogenation. The broad scope and often orthogonal nature of these Pd-catalyzed halogenation reactions should make them a valuable synthetic tool for accessing a more diverse array of halogenated organic molecules.

4.9 Experimental Procedure

General: NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C), a Varian Inova 400 (399.96 MHz for ^{1}H; 100.57 MHz for ^{13}C; 376.34 MHz for ^{19}F), or a Varian Mercury 300 (300.07 MHz for ^{1}H NMR, 75.45 MHz for ^{13}C; 282.35 MHz for ^{19}F) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), triplet of doublets (td), triplet of triplets (tt), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer. Melting points were determined with a Mel-Temp 3.0, a Laboratory Devices Inc, USA instrument and are uncorrected. HRMS data were obtained on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Gas Chromatography was performed on a Shimadzu GC-17A equipped with a Restek Rtx©-5 column (15m,

0.25 mm 1D, 0.25 μm df) and a FID detector. GC yields are reported as corrected GC yields based on a calibration curve against naphthalene as an internal standard. Typical errors associated with GC yields is approximately +/- 5%. GCMS analysis was performed on a Shimadzu GCMS QP-5000 equipped with a Restek Rtx©-5 column (30m, 0.25 mm 1D, 0.25 μm df). Reactions with $CuCl_2$ were not conducive to GC analysis directly from the crude reaction mixture because a large amount of the desired product remained coordinated to the copper. To correct for this, pyridine was added to each crude reaction mixture (1/2 the total volume of the reaction for small scale screenings) to liberate the product prior to GC analysis.

Materials and Methods: All reactions were performed with magnetic stirring in scintillation vials or thick-walled glass pressure-resistant vessels sealed with a Teflon bushing. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation and then at ca. 10 mtorr (vacuum pump). 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.Pyridine substrates **31**, **36**, **37**, **43**, **44**, **47**, **48**, **49 and 52** were prepared by Suzuki coupling of the corresponding arylboronic acid with 2-bromo-3-picoline, 2-bromopyridine, or 1-chloroisoquinoline.[51] Substrates **33**, **34** and **35** were prepared by Stille coupling of 2-tributylpyridyltin with the corresponding aryl bromides.[52] Oxime substrates **39**, **46**, **51**, and **52** were prepared as previously reported,[11] and tetrazole[53] and azobenzene[54] substrates **38** and **54** were prepared according to literature procedures. Amide substrates **57-60** was synthesized via arylation of the corresponding lactams.[55, 56] The remainder of the substrates were obtained from commercial sources (typically Acros Organics, Aldrich, or Lancaster) and were used without further purification. $Pd(OAc)_2$ was obtained from Pressure Chemical and used as received. NCS and NBS were obtained from Acros, while NIS was obtained from Oakwood Products, and all were used without further purification. Solvents were obtained from Fisher Chemical and used as received.

General Procedure for Palladium-Catalyzed Halogenationn of C–H bonds: Procedure A. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial or a

larger pressure vessel. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC (unless otherwise noted) for 12 h. The solvent was removed under vacuum, and the resulting residues were purified by chromatography on silica gel.

Procedure B. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC (unless otherwise noted) for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL). An aqueous solution of Na_2CO_3 (10 mL) was then added dropwise to this mixture until the effervescence ceased. The organic and aqueous layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was then purified by chromatography on silica gel.

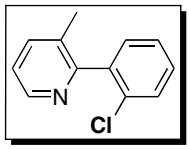
Procedure C. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC (unless otherwise noted) for 12 h. The solvent was removed under vacuum. The crude residue was dissolved in CH_2Cl_2 (15 mL) and washed with $NaHCO_3$ (1 x 15mL). The aqueous layer was washed with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated. The resulting oil was purified by chromatography on silica gel.

Procedure D. A solution of the oxidant in the reaction solvent was added slowly with stirring to a solution of the substrate in the same solvent. The resulting mixture was stirred at room temperature for 1 h, then the solvent was evaporated. The crude residue was extracted between CH_2Cl_2 and H_2O to remove the succinimide byproduct. The organic layer was washed with brine, filtered, and concentrated to afford the product.

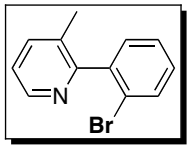
Procedure E. The substrate and CuX_2 were dissolved in MeCN and heated to 120 ^oC for 12 h. After evaporation of the solvent, the resulting material was taken up in CH_2Cl_2 and

washed several times with an equal volume of a solution of 5% pyridine in water, until the aqueous layer was no longer a bright blue color. The organic layer was then washed with brine, dried with $MgSO_4$, filtered and condensed to give the crude product, liberated from most of the copper oxidant.

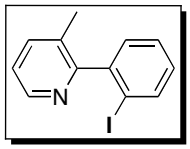
Procedure F. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum. The crude residue was dissolved in CH_2Cl_2 (15 mL) and washed with a solution of 5% pyridine in water (3 x 15mL) followed by washing with brine (1 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated. The resulting oil was purified by chromatography on silica gel.



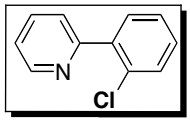
Substrate **31** (100 mg, 0.591 mmol, 1 equiv), NCS (86.8 mg, 0.650 mmol, 1.10 equiv), and $Pd(OAc)_2$ (6.6 mg, 0.029 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (4.9 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 120 ºC for 12 h. The solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2, filtered through a pad of silica and washed with a 50/50 mixture of hexanes/ethyl acetate (300 mL). The filtrate was concentrated and the resulting oil was purified by chromatography on silica gel (R_f = 0.3 in 5% EtOAc/95% CH_2Cl_2). Product **31-Cl** was isolated as a clear oil (78 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.48-7.46 (m, 1H), 7.36-7.30 (multiple peaks, 3H), 7.26-7.23 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.03, 146.61, 139.35, 137.85, 132.75, 132.23, 130.38, 129.47, 129.39, 126.90, 122.90, 18.77. Anal. Calcd for $C_{12}H_{10}ClN$: C, 70.77, H, 4.95, N, 6.88; Found: C, 70.83, H, 4.77, N, 6.80.



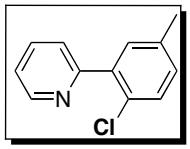
Substrate 3**1** (100 mg, 0.591 mmol, 1 equiv), NBS (126 mg, 0.709 mmol, 1.20 equiv), and $Pd(OAc)_2$ (6.6 mg, 0.029 mmol, 5 mol%) were combined in a 20 mL vial. AcOH (4.9 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 120 ºC for 12 h. The solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2, filtered through a pad of silica and washed with a 50/50 mixture of hexanes/ethyl acetate (300 mL). The filtrate was concentrated and the resulting oil was purified by chromatography on silica gel (R_f = 0.3 in 5% EtOAc/95% CH_2Cl_2). Product **31-Br** was isolated as a clear oil (82 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.40 (td, *J* = 7.5, 1.2 Hz, 1H), 7.31-7.24 (multiple peaks, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.47, 146.58, 141.41, 137.79, 132.59, 131.83, 130.20, 129.46, 127.46, 122.91, 122.51, 18.88. Anal. Calcd for $C_{12}H_{10}BrN$: C, 58.09, H, 4.06, N, 5.65; Found: C, 58.29, H, 4.29, N, 5.62.



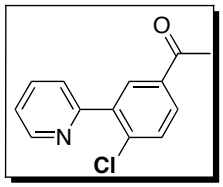
Substrate 3**1** (50.0 mg, 0.295 mmol, 1 equiv), NIS (79.8 mg, 0.354 mmol, 1.20 equiv), and $Pd(OAc)_2$ (3.3 mg, 0.015 mmol, 5 mol %) were combined in a 20 mL vial. CH_3CN (2.5 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2, filtered through a pad of silica and washed with a 50/50 mixture of hexanes/ethyl acetate (150 mL). The filtrate was concentrated and the resulting oil was purified by chromatography on silica gel (R_f = 0.3 in 5% EtOAc/95% CH_2Cl_2). Product **31-I** was isolated as a clear oil (69 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54-8.52 (m, 1H), 7.93 (ddd, *J* = 8.0, 1.2, 0.38 Hz, 1H), 7.60 (ddd, *J* = 7.7, 1.6, 0.71 Hz, 1H), 7.43 (td, *J* = 7.5, 1.2 Hz, 1H), 7.27-7.24 (multiple peaks, 2H), 7.09 (td, *J* = 7.7, 1.7 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.90, 146.59, 145.25, 138.93, 137.93, 131.29, 129.39, 129.17, 128.22, 122.99, 97.63, 19.09. Anal. Calcd for $C_{12}H_{10}IN$: C, 48.84, H, 3.42, N, 4.75; Found: C, 49.05, H, 3.32, N, 4.67.



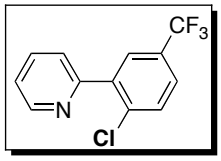
Substrate **32** (206 mg, 1.33 mmol, 1 equiv), NCS (213 mg, 1.59 mmol, 1.20 equiv), and $Pd(OAc)_2$ (14.9 mg, 0.066 mmol, 5 mol %) were combined in a 20 mL vial. CH_3CN (8.6 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2, filtered through a pad of celite and washed with copius CH_2Cl_2. The filtrate was concentrated and the resulting oil was purified by chromatography on silica gel (R_f = 0.32 in 10% EtOAc/90% hexanes). Product **32-Cl** was isolated as a clear oil (138 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 5.6 Hz, 1H), 7.73 (td, *J* = 7.6, 2.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.56 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.44 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.35-7.29 (multiple peaks, 2H), 7.25 (ddd, *J* = 7.2, 5.2, 0.8 Hz, 1H).



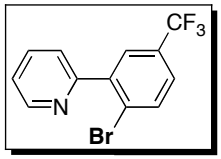
Substrate **33** (204 mg, 1.20 mmol, 1 equiv), NCS (193 mg, 1.40 mmol, 1.20 equiv), and $Pd(OAc)_2$ (13.5 mg, 0.060 mmol, 5 mol %) were combined in a 20 mL vial. CH_3CN (7.8 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 120 ºC for 12 h. The solvent was removed under vacuum and the resulting oil was purified by chromatography on silica gel (R_f = 0.2 in 10% EtOAc/90% hexanes). Product **33-Cl** was isolated as a clear oil (154 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H), 7.75 (td, *J* = 7.6, 1.6 Hz, 1H), 7.65 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.28 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.14 (dd, *J* = 8.4, 2.4 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.91, 149.46, 138.68, 136.87, 135.72, 132.05, 130.30, 129.78, 128.94, 124.88, 122.26, 20.75. Anal. Calcd for $C_{12}H_{10}ClN$: C, 70.77, H, 4.95, N, 6.88; Found: C, 70.94, H, 5.02, N, 6.67.



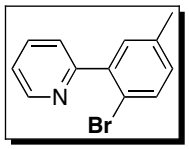
Substrate **34** (202 mg, 1.00 mmol, 1 equiv), NCS (247 mg, 1.80 mmol, 1.80 equiv), and $Pd(OAc)_2$ (11.5 mg, 0.051 mmol, 5 mol %) were combined in a 20 mL vial. CH_3CN (6.6 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 120 ºC for 12 h. The solvent was removed under vacuum and the resulting oil was purified by chromatography on silica gel (R_f = 0.12 in 20% EtOAc/80% hexanes). Product **34-Cl** was isolated as a clear oil (78 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (ddd, *J* = 5.2, 2.0, 1.2 Hz, 1H), 8.16 (d, *J* = 1.2 Hz, 1H), 7.92 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.78 (td, *J* = 7.6, 2.0 Hz, 1H), 7.65 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.32 (ddd, J = 7.6, 5.2, 1.6 Hz, 1H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.99, 156.09, 149.91, 139.60, 137.49, 136.29, 136.06, 131.96, 130.75, 129.16, 125.03, 123.03, 26.86.



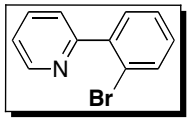
Substrate **35** (199 mg, 0.890 mmol, 1 equiv), NCS (239 mg, 1.70 mmol, 2.0 equiv), and $Pd(OAc)_2$ (10.0 mg, 0.044 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (5.8 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was stirred at 120 ºC for 12 h. The solvent was removed under vacuum, and the resulting crude material was purified by chromatography on silica gel (R_f = 0.28 in 8% EtOAc/92% hexanes). Product **35-Cl** was isolated as a tan oil (94 mg, 41% yield). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.49 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H), 7.97 (br s, 1H), 7.23 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.05 (td, *J* = 8.0, 2.0 Hz, 1H), 6.99-6.97 (multiple peaks, 2H), 6.62 (ddd, *J* = 7.6, 4.8, 0.8 Hz, 1H).



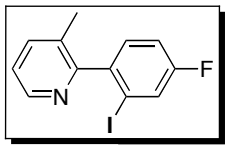
Substrate **35** (150 mg, 0.672 mmol, 1 equiv), NBS (239 mg, 1.344 mmol, 2.0 equiv), and $Pd(OAc)_2$ (7.5 mg, 0.034 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (5.6 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was stirred at 120 ºC for 12 h. The solvent was removed under vacuum, and the resulting crude material was purified by chromatography on silica gel (R_f = 0.23 in 5% EtOAc/95% hexanes). Product **35-Br** was isolated as a tan oil (128 mg, 63% yield). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.73 (ddd, J = 4.5, 1.5, 1.0 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.95 (td, J = 8.0, 1.5 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.76 (dt, J = 8.0, 1.0 Hz, 1H), 7.71 (ddd, J = 8.0, 2.5, 0.5 Hz, 1H), 7.47 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.68, 149.48, 141.73, 136.18, 133.94, 130.00 (q, $^2J_{C\text{-}F}$ = 33 Hz), 128.32 (q, $^3J_{C\text{-}F}$ = 4 Hz), 126.19 (q, $^3J_{C\text{-}F}$ = 4 Hz), 125.68 (q, $^4J_{C\text{-}F}$ = 1 Hz), 124.68, 123.68 (q, $^1J_{C\text{-}F}$ = 273 Hz), 123.02. ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.67. Anal. Calcd for $C_{12}H_7BrF_3N$: C, 47.71, H, 2.34, N, 4.64; Found: C, 47.64, H, 2.16, N, 4.54.



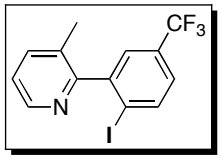
Procedure A was followed at 120 °C, utilizing substrate **33** (201 mg, 1.20 mmol, 1 equiv), NBS (254 mg, 1.40 mmol, 1.2 equiv), $Pd(OAc)_2$ (13.3 mg, 0.06 mmol, 5 mol %), and CH_3CN (7.7 mL). Product **33-Br** was isolated as a clear oil (151 mg, 51% yield, R_f = 0.10 in 95% hexanes/5% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 4.9 Hz, 1H), 7.75 (td, J = 7.6, 1.8 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.29 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 7.07 (dd, J = 8.1, 2.3 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 149.3, 140.8, 137.5, 135.7, 132.9, 132.1, 130.5, 124.8, 122.3, 118.3, 20.8. Anal. Calcd for $C_{12}H_{10}BrN$: C, 58.09, H, 4.06, N, 5.65; Found: C, 57.90, H, 3.90, N, 5.49.



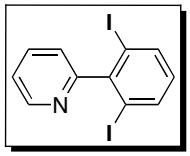
Procedure A was followed at 120 °C, utilizing substrate **32** (2.17 g, 14.0 mmol, 1 equiv), NBS (2.99 g, 16.8 mmol, 1.2 equiv), $Pd(OAc)_2$ (156 mg, 0.70 mmol), and CH_3CN (200 mL). Product **32-Br** was isolated as a yellow oil (2.07 g, 63% yield, R_f = 0.05 in 95% hexanes/5% EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H), 7.77 (td, *J* = 8.0, 2.0 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.61 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.41 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.30 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 7.27-7.24 (m (obscured by solvent), 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 149.5, 141.3, 135.9, 133.3, 131.5, 129.8, 127.6, 124.8, 122.5, 121.8. HRMS EI (m/z): $[M]^+$ Calcd for $C_{11}H_8BrN$: 232.9840; Found: 232.9839.



Substrate **36** (150 mg, 0.801 mmol, 1 equiv), NIS (216 mg, 0.961 mmol, 1.20 equiv), and $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (6.7 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2, filtered through a pad of silica and washed with a 50/50 mixture of hexanes/ethyl acetate (300 mL). The filtrate was concentrated and the resulting solid was purified by chromatography on silica gel (R_f = 0.3 in 5% EtOAc/95% CH_2Cl_2). Product **36-I** was isolated as a clear oil (175 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.66 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.27-7.21 (multiple peaks, 2H), 7.16 (td, *J* = 8.2, 2.5 Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.47 (d, $^1J_{C\text{-}F}$ = 251 Hz), 159.98, 146.62, 141.47, 138.11, 131.63, 130.03 (d, $^3J_{C\text{-}F}$ = 7.4 Hz), 125.89 (d, $^2J_{C\text{-}F}$ = 24 Hz), 123.21, 115.45 (d, $^2J_{C\text{-}F}$ = 21 Hz), 97.15 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 19.10. ^{19}F NMR (376 MHz, $CDCl_3$): d –112.77. Anal. Calcd for $C_{12}H_9FIN$: C, 46.03, H, 2.90, N, 4.47; Found: C, 46.31, H, 2.90, N, 4.20.



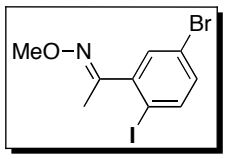
Procedure B was followed, utilizing substrate **37 (**150 mg, 0.633 mmol, 1 equiv), NIS (171 mg, 0.759 mmol, 1.2 equiv), $Pd(OAc)_2$ (7.1 mg, 0.032 mmol, 5 mol %) and CH_3CN (5.3 mL). Product **37-I** was isolated as a light yellow viscous oil with gradient elution from 100% CH_2Cl_2 to 95% CH_2Cl_2/5% EtOAc (179 mg, 78% yield, R_f = 0.22 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 3.6 Hz, 1H), 8.19 (s, 1H), 7.71 (d, *J* = 6.0 Hz, 1H), 7.64 (d, *J* = 6.4 Hz, 1H), 7.38 (d, *J* = 6.4 Hz, 1H), 7.30 (dd, *J* = 6.2, 3.8 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 148.9, 146.8, 138.1, 135.8 (q, J_{CF} = 4.4 Hz), 131.4 (q, J_{CF} = 33 Hz), 131.1, 129.5, 125.2 (q, J_{CF} = 3.6 Hz), 123.5, 122.8 (q, J_{CF} = 272 Hz), 97.5, 18.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.7 (s). Anal. Calcd for $C_{13}H_9F_3IN$: C, 43.00, H, 2.50, N, 3.86; Found: C, 43.41, H, 2.57, N, 3.86.



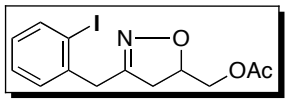
Procedure A was followed, utilizing substrate **32** (150 mg, 0.966 mmol, 1 equiv), NIS (457 mg, 2.03 mmol, 2.1 equiv), $Pd(OAc)_2$ (10.8 mg, 0.048 mmol, 5 mol %), and AcOH (8.1 mL). Product **32-I_2** was isolated as a light brown solid (162 mg, 41% yield, mp = 122.7-124.2 ºC, R_f = 0.29 in 90% hexanes/10% EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (d, *J* = 4.5 Hz, 1H), 7.93 (d, *J* = 8 Hz, 2H), 7.83 (t, *J* = 8 Hz, 1H), 7.36 (m, 1H), 7.26 (d, *J* = 8 Hz, 1H), 6.75 (t, *J* = 8 Hz, 1H). ^{13}C NMR (100 MHz): δ 164.2, 149.2, 148.2, 139.0, 136.6, 131.1, 124.1, 123.2, 96.9. Anal. Calcd for $C_{11}H_7I_2N$: C, 32.46, H, 1.73, N, 3.44; Found: C, 32.71, H, 1.66, N, 3.50.

Procedure A was followed, utilizing substrate **38** (150 mg, 0.936 mmol, 1 equiv), NIS (442 mg, 1.97 mmol, 2.1 equiv), $Pd(OAc)_2$ (20.9 mg, 0.094 mmol, 10 mol %), and AcOH

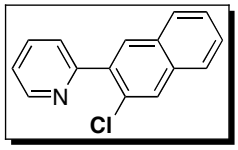
(7.8 mL). Product **38-I** was isolated as a viscous milky white oil (111 mg, 41% yield, R_f = 0.23 in 98.5% toluene/1.5% MeCN). The calibrated GC yield (against naphthalene as the internal standard) of the reaction was 41%. Note: the sample obtained from column chromatography was contaminated with approximately 50% of the starting material. Samples for HRMS, NMR analysis and calibrated GC yields were obtained after further purification by HPLC (95% hexanes/5% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). mp = 71.8-72.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46 (td, *J* = 7.8, 1.6 Hz, 1H), 7.16 (td, *J* = 7.8, 1.5 Hz, 1H), 4.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 140.7, 132.4, 131.2, 131.1, 128.2, 95.6, 39.7. HRMS EI (m/z): [M^+] Calcd for $C_8H_7IN_4$, 285.9715; Found, 285.9720.



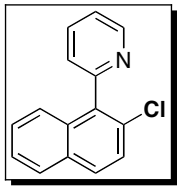
Substrate **39** (150 mg, 0.657 mmol, 1 equiv), NIS (177 mg, 0.789 mmol, 1.20 equiv), and $Pd(OAc)_2$ (7.4 mg, 0.033 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (5.5 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting brown solids were purified by chromatography on silica gel (R_f = 0.2 in 25% CH_2Cl_2/75% hexanes). Product **39-I** was isolated as a white solid as a 4:1 mixture of E:Z oxime isomers (133 mg, 57% yield); mp = 67.0-68.0 °C. Major oxime isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.99 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.32, 144.37, 140.79, 132.98, 132.46, 122.50, 93.93, 62.07, 16.51. Minor oxime isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.8 Hz, 1H), 7.16-7.14 (multiple peaks, 2H), 3.83 (s, 3H), 2.14 (s, 3H). Anal. Calcd for C_9H_9BrNO: C, 30.54, H, 2.56, N, 3.96; Found: C, 30.51, H, 2.62, N, 3.96.



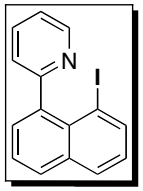
Substrate **40** (121 mg, 0.519 mmol, 1 equiv), NIS (140 mg, 0.623 mmol, 1.20 equiv), and $Pd(OAc)_2$ (5.8 mg, 0.025 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (4.3 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting brown solids were purified by chromatography on silica gel (R_f = 0.26 in 2% EtOAc/98% CH_2Cl_2). Product **40-I** was isolated as a clear viscous oil (101 mg, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.32 (td, *J* = 7.4, 1.2 Hz, 1H), 7.28 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.97 (td, *J* = 7.9, 1.9 Hz, 1H), 4.81-4.76 (m, 1H), 4.13 (dd, *J* = 11.8, 4.1 Hz, 1H), 4.06 (dd, *J* = 11.8, 5.8 Hz, 1H), 3.89 (d, *J* = 15.4 Hz, 1H), 3.85 (d, *J* = 15.4 Hz, 1H), 3.00 (dd, *J* = 17.3, 10.9 Hz, 1H), 2.67 (dd, *J* = 17.3, 7.1 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.72, 156.62, 139.81, 138.78, 129.97, 129.03, 128.78, 100.59, 77.46, 65.03, 38.92, 38.79, 20.74. IR (thin film): 1741, 1233 cm^{-1}. HRMS electrospray (m/z): [M+] calcd for $C_{13}H_{14}INO_3$, 359.0018; found, 359.0000. GC analysis (Restek Rtx$^{@}$-5, FID detector): 100% integration.



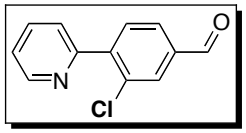
Substrate **43** (100 mg, 0.487 mmol, 1 equiv), NCS (71.5 mg, 0.536 mmol, 1.1 equiv), and $Pd(OAc)_2$ (8.4 mg, 0.024 mmol, 5 mol %) were combined in a 20 mL vial. CH_3CN (4.0 mL) was added, the vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting yellow/brown solid was purified by chromatography on silica gel (R_f = 0.18 in 25% EtOAc/75% toluene). Product **43-Cl** was isolated as a light yellow solid (96 mg, 82% yield); mp = 78.2-79.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79-8.77 (m, 1H), 8.09 (s, 1H), 7.99 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.81-7.79 (multiple peaks, 2H), 7.74-7.71 (m, 1H), 7.56-7.48 (multiple peaks, 2H), 7.36-7.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.75, 149.31, 136.11, 133.67, 131.85, 131.16, 129.67, 128.40, 128.25, 127.39, 126.70, 126.58, 125.21, 122.51. Two carbon resonances appear to be coincidently overlapping. HRMS electrospray (m/z): [M+] calcd for $C_{15}H_{10}ClN$, 239.0502; found, 239.0499. GC analysis (Restek Rtx$^{@}$-5, FID detector: 100% integration.



Procedure A was followed, utilizing substrate **44** (100 mg, 0.487 mmol, 1 equiv), NCS (72 mg, 0.536 mmol, 1.1 equiv), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol, 5 mol %), and CH_3CN (4.0 mL). Product **44-Cl** was isolated as a yellow solid (81 mg, 70% yield, mp = 85.7-86.4 ºC, R_f = 0.11 in 95% toluene/5% EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 8.80-8.79 (m, 1H), 8.03-7.97 (multiple peaks, 3H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.58-7.49 (multiple peaks, 3H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz): δ 157.4, 150.6, 137.6, 137.3, 134.2, 133.1, 131.0, 130.7, 129.0, 128.1, 127.8, 127.1, 126.7, 126.6, 123.7. HRMS EI (m/z): [M^+] Calcd for $C_{15}H_{10}ClN$, 239.0502; Found, 239.0499.

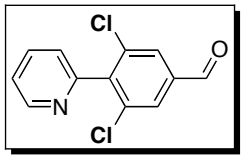


Procedure A was followed, utilizing substrate **44** (100 mg, 0.487 mmol, 1 equiv), NIS (329 mg, 1.46 mmol, 3.0 equiv), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol, 5 mol %), and CH_3CN (4.0 mL). Product **44-I** was isolated as a yellow solid (97 mg, 60% yield, mp = 85.9-87.0 ºC, R_f = 0.19 in 97.5% Toluene/2.5% EtOAc). ^1H NMR (400 MHz, acetone-d_6): δ 8.78 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 8.03-7.97 (multiple peaks, 3H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.58-7.49 (multiple peaks, 2H), 7.44-7.42 (multiple peaks, 2H), 7.26 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 161.8, 150.5, 144.4, 137.5, 136.3, 133.9, 131.1, 130.6, 129.0, 127.9, 127.4, 127.1, 126.3, 123.9, 97.1. HRMS EI (m/z): [M^+] Calcd for $C_{15}H_{10}IN$, 330.9858; Found, 330.9857.

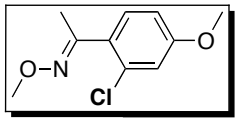


Substrate **45** (100 mg, 0.546 mmol, 1 equiv), NCS (87.5 mg, 0.655 mmol, 1.20 equiv), and $Pd(OAc)_2$ (6.1 mg, 0.027 mmol, 5 mol %) were combined in a 20 mL vial. CH_3CN

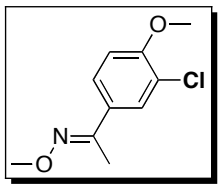
(4.5 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 120 ºC for 12 h. The solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2, filtered through a pad of silica and washed with a 50/50 mixture of hexanes/ethyl acetate (300 mL). The filtrate was concentrated and the resulting solid was purified by chromatography on silica gel (R_f = 0.2 in 5% EtOAc/95% CH_2Cl_2). Product **45-Cl** was isolated as a white solid (67 mg, 57% yield); mp = 67.2-67.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.0 (s, 1H), 8.77-8.75 (m, 1H), 8.00 (d, *J* = 1.6 Hz, 1H), 7.88 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.82 (td, *J* = 7.6, 1.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.71 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.36 (ddd, *J* = 7.6, 4.9, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.57, 155.52, 149.78, 144.45, 137.08, 136.05, 133.29, 132.39, 131.11, 127.91, 124.82, 123.09. IR (KBr): 2922, 1697 cm^{-1}. HRMS electrospray (m/z): [M+] calcd for $C_{12}H_8ClNO$, 217.0294; found, 217.0289. GC analysis (Restek Rtx$^{@}$-5, FID detector): 100% integration.



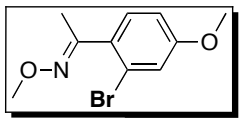
Substrate **45** (100 mg, 0.546 mmol, 1 equiv), NCS (182 mg, 1.364 mmol, 2.5 equiv), and $Pd(OAc)_2$ (6.1 mg, 0.027 mmol, 5 mol %) were combined in a 20 mL vial. CH_3CN (4.5 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 120 ºC for 12 h. The solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2, filtered through a pad of silica and washed with a 50/50 mixture of hexanes/ethyl acetate (300 mL). The filtrate was concentrated and the resulting solid was purified by chromatography on silica gel (R_f = 0.3 in 5% EtOAc/95% CH_2Cl_2). Product **45-Cl$_2$** was isolated as a white solid (99 mg, 72% yield); mp = 106.6-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.78 (d, *J* = 4.9 Hz, 1H), 7.91 (s, 2H), 7.86 (td, *J* = 7.7, 1.8 Hz, 1H), 7.41-7.38 (m, 1H), 7.35 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.22, 154.45, 149.82, 143.48, 137.28, 136.61, 135.94, 128.88, 124.60, 123.44. IR (KBr): 2852, 1692, 1546 cm^{-1}. Anal. Calcd for $C_{12}H_7Cl_2NO$: C, 57.17, H, 2.80, N, 5.56; Found: C, 57.01, H, 2.92, N, 5.47.



Procedure A was followed, utilizing substrate **46** (100 mg, 0.558 mmol, 1 equiv), NCS (81.9 mg, 0.614 mmol, 1.1 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH (4.6 mL). Product **46-Cl** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (69 mg, 58% yield, R_f = 0.20 in 55% hexanes/45% CH_2Cl_2). Major oxime isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.99 (s, 3H), 3.82 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 155.8, 133.4, 130.9, 129.3, 115.3, 112.8, 61.8, 55.6, 16.5. Minor oxime isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.84 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 2.20 (s, 3H). HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{12}ClNO_2$, 213.0557; Found, 213.0563.

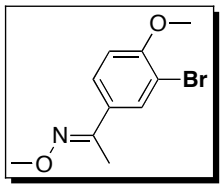


Procedure A was followed, utilizing substrate **46** (100 mg, 0.558 mmol, 1 equiv), NCS (89.4 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product **Iso-46-Cl** was isolated as a white solid as a single oxime isomer (62 mg, 53% yield, mp = 60.2-61.6 ºC, R_f = 0.25 in 60% hexanes/40% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 152.9, 130.0, 127.8, 125.4, 114.0, 111.5, 61.9, 56.2, 12.3. HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{12}ClNO_2$, 213.0557; Found, 213.0562.

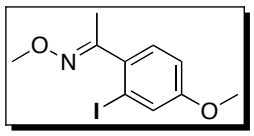


Procedure A was followed, utilizing substrate **46** (100 mg, 0.558 mmol, 1 equiv), NBS (109 mg, 0.614 mmol, 1.1 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH

(4.6 mL). Product **46-Br** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (105 mg, 72% yield, R_f = 0.30 in 55% hexanes/45% CH_2Cl_2). Major oxime isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 2.8 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.97 (s, 3H), 3.80 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 156.7, 131.3, 130.9, 122.2, 118.3, 113.3, 61.8, 55.6, 16.7. HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{12}BrNO_2$, 257.0051; Found, 257.0056. Minor oxime isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.87 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.15 (s, 3H). HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{12}BrNO_2$, 257.0051; Found, 257.0057.

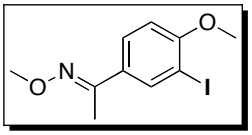


Procedure A was followed, utilizing substrate **46** (100 mg, 0.558 mmol, 1 equiv), NBS (119 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product **Iso-46-Br** was isolated as a white solid as a single oxime isomer (99 mg, 69% yield, mp = 70.2-71.1 ºC, R_f = 0.30 in 55% hexanes/45% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 2.4 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 152.9, 130.9, 130.4, 126.2, 111.7, 111.4, 61.9, 56.3, 12.35. HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{12}BrNO_2$, 257.0051; Found, 257.0056.

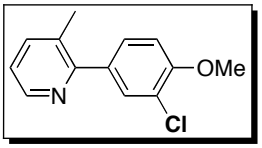


Procedure A was followed, utilizing substrate **46** (100 mg, 0.558 mmol, 1 equiv), NIS (151 mg, 0.669 mmol, 1.2 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH (4.6 mL). Product **46-I** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (78 mg, 46% yield, R_f = 0.29 in 55% hexanes/45% CH_2Cl_2). Major oxime isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 2.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.89 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.98 (s, 3H), 3.79 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):

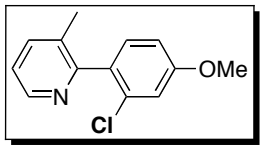
δ 159.7, 158.2, 135.2, 129.9, 124.7, 114.1, 96.0, 61.8, 55.6, 16.9. Minor oxime isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 2.2 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.92 (dd, J = 8.4, 2.1 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.14 (s, 3H). HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{12}INO_2$, 304.9913; Found, 304.9909.



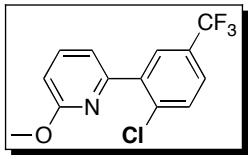
Procedure A was followed, utilizing substrate **46** (100 mg, 0.558 mmol, 1 equiv), NIS (151 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product **Iso-46-I** was isolated as a light yellow solid as a single oxime isomer (81 mg, 47% yield, mp = 65.0-66.4 ºC, R_f = 0.29 in 55% hexanes/45% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 2.4 Hz, 1H), 7.59 (dd, J = 8.4, 2.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 152.8, 137.0, 131.0, 127.3, 110.3, 86.0, 61.9, 56.4, 12.4. HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{12}INO_2$, 304.9913; Found, 304.9916.



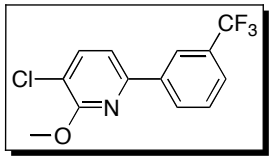
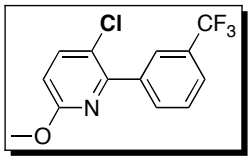
Substrate **47** (150 mg, 0.753 mmol, 1 equiv) and NCS (111 mg, 0.828 mmol, 1.1 equiv) were combined in a 20 mL vial. CH_3CN (7 mL) was added, the vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting yellow/brown solid was purified by chromatography on silica gel (R_f = 0.40 in 90% CH_2Cl_2/10% EtOAc). Product **Iso-47-Cl** was isolated as a clear oil (167 mg, 95% yield). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.45 (d, J = 4.8 Hz, 1H), multiple peaks (7.65-7.63, 2H), 7.52 (dd, J = 8.4, 2.0 Hz, 1H), 7.21 (dd, J = 7.6, 4.8 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 157.34, 155.57, 147.78, 139.38, 135.00, 131.59, 131.34, 129.73, 122.92, 122.19, 112.47, 56.48, 20.29. Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81, H, 5.18, N, 5.99; Found: C, 66.85, H, 5.22, N, 6.01.



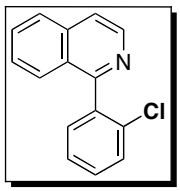
Substrate **47** (150 mg, 0.753 mmol, 1 equiv), NCS (105 mg, 0.791 mmol, 1.05 equiv), and $Pd(OAc)_2$ (8.4 mg, 0.038 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (7 mL) was added, the vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting yellow/brown solid was purified by chromatography on silica gel (R_f = 0.40 in 85% CH_2Cl_2/15% EtOAc). Product **47-Cl** was isolated as a clear oil (133 mg, 76% yield). ^{1}H NMR (400 MHz, acetone-d_6): d 8.45 (d, J = 4.8 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 8.0, 4.8 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.99 (dd, J = 8.4, 2.4 Hz, 1H), 3.87 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): d 160.88, 157.82, 147.39, 138.26, 133.74, 133.09, 132.95, 132.14, 123.56, 115.05, 113.87, 55.97, 18.90. Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81, H, 5.18, N, 5.99; Found: C, 66.85, H, 5.28, N, 5.94.



Procedure B was followed, utilizing substrate **48** (100 mg, 0.395 mmol, 1 equiv), NCS (58 mg, 0.434 mmol, 1.1 equiv), $Pd(OAc)_2$ (17.7 mg, 0.079 mmol, 20 mol %), and AcOH (3.3 mL). Product **48-Cl** was isolated as a clear oil (81 mg, 71% yield, R_f = 0.35 in 98% hexanes/2% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.01-7.98 (m, 1H), 7.83 (dd, J = 8.1, 7.2 Hz, 1H), 7.82-7.75 (multiple peaks, 2H), 7.37 (dd, J = 10.0, 0.8 Hz, 1H), 6.86 (dd, J = 11.0, 1.2 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 164.8, 153.4, 140.8, 140.1, 137.1, 132.3, 129.9 (q, J_{CF} = 32.2 Hz), 129.3 (q, J_{CF} = 4.05 Hz), 127.2 (q, J_{CF} = 3.7 Hz), 124.9 (q, J_{CF} = 272 Hz), 118.5, 111.4, 53.8. ^{19}F NMR (282 MHz, acetone-d_6): δ –63.1 (s) Anal. Calcd for $C_{13}H_9ClF_3NO$: C, 54.28, H, 3.15, N, 4.87; Found: C, 54.37, H, 3.01, N, 4.80.

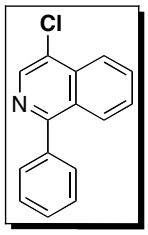



Procedure B was followed, utilizing substrate **48** (100 mg, 0.395 mmol, 1 equiv), NCS (58 mg, 0.434 mmol, 1.1 equiv), and AcOH (3.3 mL). GC analysis of the crude reaction mixture showed 3:1 mixture of regioisomeric mono-chlorinated products. Isomer **Iso-48-Cl-ortho** was isolated as a clear oil (36 mg, 32% yield, R_f = 0.18 in 98% hexanes/2% toluene). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.44 (s, 1H), 8.40 (d, J = 7.7 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.79-7.73 (multiple peaks, 2H), 7.68 (d, J = 8.0 Hz, 1H), 4.12 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 159.74, 151.80, 140.43, 139.86, 131.55 (q, J_{CF} = 32 Hz), 131.17, 130.70, 125.37 (q, J_{CF} = 271 Hz), 126.57 (q, J_{CF} = 3.8 Hz), 124.03 (q, J_{CF} = 3.8 Hz), 118.28, 115.13, 54.59. ^{19}F NMR (376 MHz, $CDCl_3$): δ –62.72 (s). HRMS EI (m/z): [M^+] Calcd for $C_{13}H_9ClF_3NO$, 287.0325; Found, 287.0318. Isomer **Iso-48-Cl-para** was isolated as a clear oil (57 mg, 50% yield, R_f = 0.13 in 98% hexanes/2% toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (multiple peaks, 2H), 7.73-7.64 (multiple peaks, 2H), 7.59 (t, J = 7.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.30, 151.8, 142.2, 140.1, 134.2, 130.8 (q, J_{CF} = 32 Hz), 129.1, 126.9 (q, J_{CF} = 3.7 Hz), 126.3 (q, J_{CF} = 3.6 Hz), 125.3 (q, J_{CF} = 271 Hz), 122.3, 112.8, 54.2. ^{19}F NMR (376 MHz, $CDCl_3$):δ –62.6 (s). HRMS EI (m/z): [M^+] Calcd for $C_{13}H_9ClF_3NO$, 287.0325; Found, 287.0316.

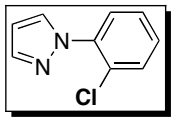


Substrate **49** (150 mg, 0.731 mmol, 1 equiv), NCS (146 mg, 1.096 mmol, 1.5 equiv), and $Pd(OAc)_2$ (8.2 mg, 0.036 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (6.1 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was stirred at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting crude material was purified by chromatography on silica gel (R_f = 0.33 in 5% EtOAc/95% hexanes). Product **49-Cl** was isolated as a light yellow semisolid (93 mg, 53% yield). ^{1}H

NMR (300 MHz, acetone-d_6): δ 8.60 (dd, J = 5.7, 2.7, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.87 (dd, J = 5.7, 2.5 Hz, 1H), 7.81-7.75 (m, 1H), 7.65-6.49 (multiple peaks, 6H). ^{13}C NMR (75 MHz, acetone-d_6): δ 159.34, 143.02, 139.54, 137.07, 133.66, 132.27, 131.06, 130.81, 130.23, 128.37, 127.89, 127.82, 127.49, 121.34. Two carbon resonances appear to be coincidently overlapping. HRMS electrospray (m/z): [M+] calcd for $C_{15}H_{10}ClN$, 239.0502; found, 239.0490. GC analysis (Restek Rtx$^{@}$-5, FID detector): 100% integration.

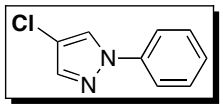


Procedure A was followed, utilizing substrate **49** (100 mg, 0.487 mmol, 1 equiv), NCS (130 mg, 0.974 mmol, 2.0 equiv), and AcOH (4.0 mL). Product **Iso-49-Cl** was isolated as a white solid (66 mg, 56% yield, mp = 129.7-130.3 ºC, R_f = 0.29 in 90% hexanes/10% CH_2Cl_2). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.65 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.94 (dt, J = 6.8, 1.2 Hz, 1H), 7.74 (dt, J = 6.8, 1.2 Hz, 1H), 7.70-7.68 (multiple peaks, 2H), 7.58-7.53 (multiple peaks, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 160.5, 141.7, 139.9, 134.7, 132.3, 130.8, 129.6, 129.3, 129.1, 128.7, 128.2, 127.6, 124.1. Anal. Calcd for $C_{15}H_{10}ClN$: C, 75.16, H, 4.21, N, 5.84; Found: C, 74.48, H, 4.19, N, 5.65.

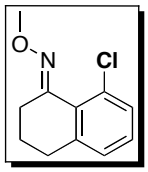


Procedure B was followed, utilizing substrate **50** (150 mg, 1.04 mmol, 1 equiv), NCS (146 mg, 1.09 mmol, 1.05 equiv), $Pd(OAc)_2$ (23.3 mg, 0.104 mmol, 10 mol %), and AcOH (8.7 mL). Product **50-Cl** was isolated as a clear oil (108 mg, 58% yield, R_f = 0.12 in 60% hexanes/40% CH_2Cl_2). The calibrated GC yield (against naphthalene as the internal standard) of the reaction was 72%. Note: the sample obtained from column chromatography was contaminated with approximately 13% of the starting material.

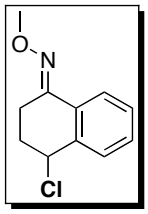
Samples for microanalysis were obtained after further purification by HPLC (98% hexanes/2% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 3.2 Hz, 1H), 7.75 (s, 1H), 7.58 (dd, J = 10.4, 2.0 Hz, 1H), 7.52 (dd, J = 10.2, 2.6 Hz, 1H), 7.42-7.30 (multiple peaks, 2H), 6.48 (t, J = 2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 131.3, 130.6, 128.9, 128.3, 127.8, 127.6, 106.6. Two carbon resonances are coincidently overlapping. HRMS EI (m/z): [M^+] Calcd for $C_9H_7ClN_2$, 178.0298; Found, 178.0299.



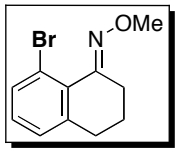
Procedure B was followed, utilizing substrate **50** (150 mg, 1.04 mmol, 1 equiv), NCS (146 mg, 1.09 mmol, 1.05 equiv), and AcOH (8.7 mL). Product **Iso-50-Cl** was isolated as a clear oil (154 mg, 83% yield, mp = 72.5-74.3 ºC, R_f = 0.26 in 70% hexanes/30% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.64-7.62 (multiple peaks, 3H), 7.45 (t, J = 7.4 Hz, 2H), 7.31(tt, J = 7.4, 1.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 139.4, 129.5, 126.9, 124.8, 118.9, 112.3. HRMS EI (m/z): [M^+] Calcd for $C_9H_7ClN_2$, 178.0298; Found, 178.0297.



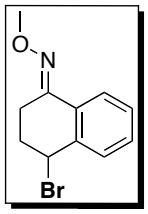
Procedure A was followed, utilizing substrate **51** (150 mg, 0.856 mmol, 1 equiv), NCS (120 mg, 0.899 mmol, 1.05 equiv), $Pd(OAc)_2$ (9.6 mg, 0.043 mmol, 5 mol %), and AcOH (7 mL). Product **51-Cl** was isolated as a clear oil (179 mg, 88% yield, R_f = 0.3 in 75% hexanes/25% CH_2Cl_2). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.32 (dd, J = 7.8, 1.5 Hz, 1H), 7.23-7.13 (multiple peaks, 2H), 3.96 (s, 3H), 2.72 (t, J = 6.6 Hz, 2H), 2.65 (t, J = 6.0 Hz, 2H), 1.76-1.67 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6): δ 152.9, 144.8, 132.3, 130.3, 129.8, 129.7, 127.4, 62.3, 31.3, 25.3, 21.7. Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01, H, 5.77, N, 6.68; Found: C, 63.05, H, 5.83, N, 6.70.



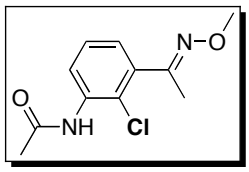
Procedure A was followed, utilizing substrate **51** (150 mg, 0.856 mmol, 1 equiv), NCS (120 mg, 0.899 mmol, 1.05 equiv), and CH_3CN (7 mL). Product **Iso-51-Cl** was isolated as a clear oil (70 mg, 39% yield, R_f = 0.3 in 75% hexanes/25% CH_2Cl_2). Note: product **Iso-51-Cl** was isolated in higher yield (66%) from the analogous reaction in AcOH; however, the isolated product from this reaction was contaminated with traces of isomeric chlorinated impurities. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.98 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 6.4 Hz, 1H), 7.25-7.22 (m, 2H), 5.63 (t, J = 2.8 Hz, 1H), 4.02 (s, 3H), 3.26-3.17 (m, 1H), 2.80-2.76 (m, 1H), 2.30-2.15 (multiple peaks, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 151.7, 138.3, 130.4, 129.8, 128.6, 127.3, 125.0, 62.8, 47.9, 30.7, 24.4. Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01, H, 5.77, N, 6.68; Found: C, 63.11, H, 5.88, N, 6.68.



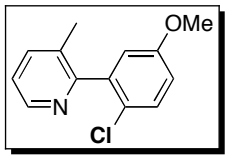
Substrate **51** (150 mg, 0.856 mmol, 1 equiv), NBS (160 mg, 0.899 mmol, 1.05 equiv), and $Pd(OAc)_2$ (9.6 mg, 0.043 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (7 mL) was added, the vial was sealed with a Teflon lined cap, and mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting brown solids were purified by chromatography on silica gel (R_f = 0.3 in 75% hexanes/25% CH_2Cl_2). Product **51-Br** was isolated as a clear oil (135 mg, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.7 Hz, 1H), 4.04 (s, 3H), 2.76 (t, J = 6.9 Hz, 2H), 2.62 (t, J = 6.1 Hz, 2H), 1.75 (quin, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.03, 143.84, 133.20, 130.79, 128.98, 126.94, 120.33, 62.19, 30.93, 24.79, 21.01. Anal. Calcd for $C_{11}H_{12}BrNO$: C, 51.99, H, 4.94, N, 5.51; Found: C, 51.78, H, 4.67, N, 5.35.



Procedure A was followed, utilizing substrate **51** (150 mg, 0.856 mmol, 1 equiv), NBS (160 mg, 0.899 mmol, 1.05 equiv), and AcOH (7.1 mL). Product **Iso-51-Br** was isolated as a clear oil (64 mg, 29% yield, R_f = 0.3 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.30-7.14 (multiple peaks, 3H), 5.63 (t, *J* = 2.7 Hz, 1H), 4.06 (s, 3H), 3.34-3.27 (m, 1H), 2.76 (app d, *J* = 16 Hz, 1H), 2.32-2.24 (m, 1H), 2.19-2.08 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5, 137.1, 129.5, 128.9, 127.7, 126.5, 124.5, 62.7, 37.9, 30.6, 25.3. HRMS EI (m/z): [M^+] Calcd for $C_{11}H_{12}BrNO$, 253.0102; Found, 253.0106.



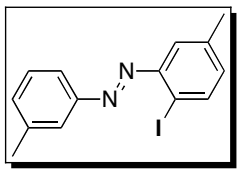
Procedure C was followed, utilizing substrate **52** (150 mg, 0.727 mmol, 1 equiv), NCS (116 mg, 0.872 mmol, 1.2 equiv), $Pd(OAc)_2$ (16.3 mg, 0.072 mmol, 10 mol %), and AcOH (6.1 mL) Product **52-Cl** was isolated as a light yellow solid as a 4:1 mixture of oxime isomers (105 mg, 60% yield, mp = 123.9-125.3 ºC, R_f = 0.20 in 70% hexanes/30% EtOAc). Major oxime isomer:^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.1 Hz, 1H), 7.64 (br s, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 3.94 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz): δ 168.2, 155.4, 137.2, 135.0, 128.4, 127.5, 125.0, 121.7, 61.9, 24.9, 16.3. Minor oxime isomer:^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 7.9 Hz, 1H), 7.67 (br s, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 3.80 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H). IR (KBr): 1654 cm^{-1}. HRMS EI (m/z): [M^+] Calcd for $C_{11}H_{13}ClN_2O_2$, 240.0666; Found, 240.0662.The reaction in the absence of palladium showed a complex mixture of isomeric chlorinated products by GC analysis.



Procedure with Pd Catalyst: Substrate **53** (150 mg, 0.753 mmol, 1 equiv), NCS (102 mg, 0.760 mmol, 1.01 equiv), and $Pd(OAc)_2$ (8.4 mg, 0.038 mmol, 5 mol%) were combined in a 20 mL vial. CH_3CN (7 mL) was added, the vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting yellow/brown solid was purified by chromatography on silica gel (R_f = 0.31 in 90% CH_2Cl_2/10% EtOAc). Product **53-Cl** was isolated as a light yellow solid (120 mg, 68% yield).

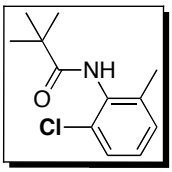
Procedure without Pd Catalyst: Substrate **53** (150 mg, 0.753 mmol, 1 equiv) and NCS (102 mg, 0.760 mmol, 1.01 equiv), were combined in a 20 mL vial. CH_3CN (7 mL) was added, the vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting yellow/brown solid was purified by chromatography on silica gel (R_f = 0.31 in 90% CH_2Cl_2/10% EtOAc). Product **53-Cl** was isolated as a light yellow solid (144 mg, 82% yield). The products with and without Pd were identical by GC and ^{1}H NMR analysis.

Mp = 77.9-79.0 ºC. ^{1}H NMR (300 MHz, acetone-d_6): δ 8.45 (d, J = 4.5 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.32-7.27 (m, 1H), 7.00 (dd, J = 8.7, 3.0 Hz, 1H), 6.88 (d, J = 2.7 Hz, 1H), 3.82 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 158.61, 157.13, 146.62, 140.83, 137.46, 131.70, 129.98, 123.51, 122.95, 115.69, 115.23, 55.14, 17.92. Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81, H, 5.18, N, 5.99; Found: C, 66.90, H, 5.30, N, 5.89. GC analysis of the isolated product showed 6% of the regioisomer.

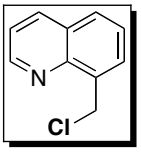


Procedure A was followed, utilizing substrate **54** (100 mg, 0.475 mmol, 1 equiv), NIS (160 mg, 0.713 mmol, 1.5 equiv), $Pd(OAc)_2$ (5.3 mg, 0.024 mmol, 5 mol %), and AcOH

(4.0 mL). Product **54-I** was isolated as an orange solid (65 mg, 41% yield, mp = 64.6-66.0 ºC, R_f = 0.20 in 98% hexanes/2% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.81-7.79 (multiple peaks, 2H), 7.45-7.39 (multiple peaks, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.01 (dd, *J* = 8.0, 2.4 Hz, 1H), 2.48 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 151.1, 139.4, 139.1, 139.0, 133.1, 132.3, 128.9, 123.9, 120.8, 117.8, 98.4, 21.4, 20.9. HRMS EI (m/z): [M^+] Calcd for $C_{14}H_{13}IN_2$, 336.0123; Found, 336.0123. The reaction in the absence of palladium showed a 4:1 mixture of isomeric iodinated products.

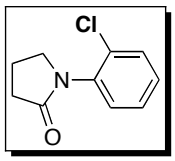


Procedure A was followed, utilizing substrate **55** (150 mg, 0.784 mmol, 1 equiv), NCS (126 mg, 0.941 mmol, 1.2 equiv), $Pd(OAc)_2$ (8.8 mg, 0.039 mmol, 5 mol %) and AcOH (6.5 mL). Product **55-Cl** was isolated as a white solid (118 mg, 67% yield, mp = 158.4-160.0 ºC, R_f = 0.20 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.31 (br s, 1H), 7.28 (dd, *J* = 7.4, 2.4 Hz, 1H), 7.21-7.14 (multiple peaks, 2H), 2.22 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6): δ 176.9, 139.9, 135.4, 133.5, 129.7, 128.6, 127.7, 39.9, 27.9, 18.8. IR (KBr): 1654 cm^{-1}. Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.85, H, 7.14, N, 6.21; Found: C, 63.71, H, 7.30, N, 5.84.

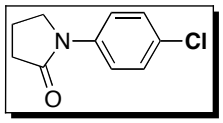


Procedure F was followed, utilizing substrate **56** (110 mg, 0.768 mmol, 1 equiv), $CuCl_2$ (413 mg, 3.07 mmol, 4.0 equiv), $Pd(OAc)_2$ (8.6 mg, 0.038 mmol, 5 mol %), and CH_2Cl_2 (6.4 mL). Product **56-Cl** was isolated as a yellow solid (118 mg, 86% yield, R_f = 0.21 in 95% hexanes/5% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.79-7.87 (multiple peaks, 2H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.3, 146.1,

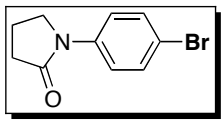
136.6, 135.8, 130.3, 128.9, 128.5, 126.5, 121.7, 42.6. Anal. Calcd for $C_{10}H_8ClN$: C, 32.46, H, 1.73, N, 3.44; Found: C, 32.71, H, 1.66, N, 3.50.



Procedure C was followed, utilizing substrate **57** (209 mg, 1.29 mmol, 1 equiv), NCS (208 mg, 1.55 mmol, 1.2 equiv), $Pd(OAc)_2$ (14.5 mg, 0.064 mmol, 5 mol %), and AcOH (8.4 mL). Product **57-Cl** was isolated as an off-white solid (197 mg, 77% yield, mp = 40.9-42.4 ºC, R_f = 0.30 in 60% hexanes/40% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.51 (d, J = 7.3 Hz, 1H), 7.39-7.32 (multiple peaks, 3H), 3.77 (t, J = 6.92 Hz, 2H), 2.43 (t, J = 7.2Hz, 2H), 2.22 (q, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 174.7, 138.2, 132.9, 130.9, 130.8, 129.8, 128.7, 50.5, 31.4, 19.9. IR (KBr): 1698 cm^{-1}. HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{10}ClNO$, 195.0451; Found, 195.0450.

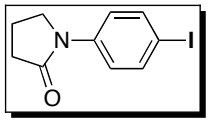


Procedure C was followed, utilizing substrate **57** (203 mg, 1.26 mmol, 1 equiv), NCS (202 mg, 1.51 mmol, 1.5 equiv), and AcOH (8.1 mL).) Product **Iso-57-Cl** was isolated as a white solid (142 mg, 58% yield, mp = 95.5-96.6 ºC, R_f = 0.44 in 60% hexanes/40% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 9.2 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 3.84 (t, J = 7.2 Hz, 2H), 2.62 (t, J = 8 Hz, 2H), 2.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 137.9, 129.4, 128.7, 120.8, 48.6, 32.6, 17.8. IR(KBr): 1679 cm^{-1}. HRMS EI (m/z): [M^+] Calcd for $C_{10}H_{10}ClNO$, 195.0451; Found, 195.0445.

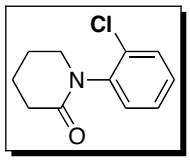


Procedure A was followed, utilizing substrate **57** (150 mg, 0.930 mmol, 1 equiv), NBS (199 mg, 1.12 mmol, 1.2 equiv), $Pd(OAc)_2$ (10.4 mg, 0.046 mmol, 5 mol %), and AcOH (7.7 mL). Product **Iso-57-Br** was isolated as a white solid (156 mg, 70% yield, R_f = 0.30

in 60% hexanes/40% EtOAc). The NMR data was identical to that reported previously for this compound.

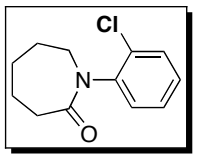


Procedure with palladium catalyst: Procedure A was followed, utilizing substrate **57** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.9 mg, 0.031 mmol, 5 mol %), and AcOH (5.2 mL). Product **Iso-57-I** was isolated as a light yellow solid (141 mg, 80% yield, mp = 140.0-141.6 ºC, R_f = 0.28 in 60% hexanes/40% EtOAc). *Procedure without palladium catalyst*: Procedure A was followed, utilizing substrate **59** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), and AcOH (5.2 mL). Product **Iso-57-I** was isolated as a light yellow solid (141 mg, 80% yield, mp = 140.0-141.6 ºC, R_f = 0.28 in 60% hexanes/40% EtOAc). The products with and without Pd were identical by GC and ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 3.81 (t, *J* = 7.2 Hz, 2H), 2.59 (t, *J* = 8.1 Hz, 2H), 2.19-2.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 139.1, 137.7, 121.5, 87.9, 48.4, 32.7, 17.8. IR (KBr): 1684 cm^{-1}. Anal. Calcd for $C_{10}H_{10}INO$: C, 41.83, H, 3.51, N, 4.88; Found: C, 41.82, H, 3.62, N, 4.71.

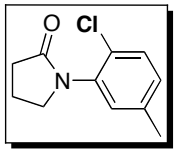


Procedure C was followed, utilizing substrate **58** (100 mg, 0.571 mmol, 1 equiv), NCS (114 mg, 0.856 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.39 mg, 0.028 mmol, 0.05 mol equiv), and AcOH (8.4 mL). Product **58-Cl** was isolated as an off-white solid (68.0 mg, 57% yield, mp = 55.9-56.9 ºC, R_f = 0.18 in 90% CH_2Cl_2/10% EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.32 (td, *J* = 7.5, 1.5 Hz, 1H), 7.29-7.25 (multiple peaks, 2H), 3.60 (m, 1H), 3.49 (m, 1H), 2.64-2.52 (multiple peaks, 2H), 2.02-1.93 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 140.6, 132.2, 130.4, 129.4, 128.9,

127.9, 50.9, 32.5, 23.4, 21.4. IR (KBr): 2921, 1652 cm^{-1}. HRMS EI (m/z): [M+Na^+] Calcd for $C_{11}H_{12}ClNO$, 232.0505; Found, 232.0505.

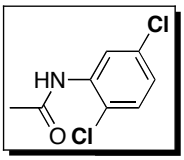


Substrate **59** (100 mg, 0.528 mmol, 1 equiv), NCS (106 mg, 0.793 mmol, 1.50 equiv), and $Pd(OAc)_2$ (5.92 mg, 0.026 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (4.4 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum. The crude was dissolved in CH_2Cl_2 (15mL) and washed with $NaHCO_3$ (1 x 15mL). The aqueous layer was washed with CH_2CL_2 (2 x 15mL). The combined organic layers were dried over $MgSO_4$, filtered and the concentrated. The resulting oil was purified by chromatography on silica gel (R_f = 0.21 in 40% EtOAc/60% hexanes). Product **59-Cl** was isolated as a milky white viscous oil (91.0 mg, 77 % yield). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.46 (dd, J = 7.7, 1.7 Hz, 1H), 7.31-7.27 (m, 1H), 7.26-7.21 (multiple peaks, 2H), 3.77 (dd, J = 14.4, 8.3 Hz, 1H), 3.56 (dd, J = 14.0, 7.6 Hz, 1H), 2.78-2.67 (m, 2H), 1.98-1.74 (multiple peaks, 6H). ^{13}C NMR (100 MHz, acetone-d_6): δ 175.61, 142.22, 132.06, 130.34, 129.36, 128.45, 127.79, 52.77, 37.49, 30.13, 28.68, 23.37. IR (thin film): 2927, 1662, 1478 cm^{-1}. HRMS electrospray (m/z): [M+$Na]^+$] calcd for $C_{12}H_{14}ClNO$, 246.0662; found, 246.0658. GC analysis (Restek Rtx$^@$-5, FID detector): 100% integration.

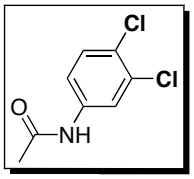


Substrate **60** (201 mg, 1.147 mmol, 1 equiv), NCS (230 mg, 1.721 mmol, 1.50 equiv), and $Pd(OAc)_2$ (12.8 mg, 0.057 mmol, 5 mol %) were combined in a 20 mL vial. AcOH (13 mL) was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 ºC for 12 h. The solvent was removed under vacuum, and the resulting brown solids were purified by chromatography on silica gel (R_f = 0.14 in 40% EtOAc/60% hexanes). Product **60-Cl** was isolated as a light brown oil (194 mg, 81%

yield). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.37 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.15 (dd, J = 8.2, 2.1 Hz, 1H), 3.74 (t, J = 6.7 Hz, 2H), 2.42 (t, J = 8.1 Hz, 2H), 2.32 (s, 3H), 2.21 (quin, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 174.86, 139.18, 138.19, 131.53, 130.88, 130.81, 130.05, 50.79, 31.74, 21.05, 20.26. IR (KBr): 2951, 1700, 1487 cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01, H, 5.77, N, 6.68; Found: C, 62.86, H, 5.64, N, 6.57. The control reaction with substrate **2** (in the absence of Pd catalyst) showed multiple mono-chlorinated products, indicative of unselective chlorination of the arene ring.



Procedure A was followed, utilizing substrate **61** (150 mg, 0.884 mmol, 1 equiv), NCS (212 mg, 1.59 mmol, 1.8 equiv), $Pd(OAc)_2$ (9.90 mg, 0.044 mmol, 5 mol %), and AcOH (7.4 mL). Product **61-Cl** was isolated as a white solid (126 mg, 70% yield, mp = 133.4-133.9 ºC, R_f = 0.28 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.74 (br s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 8.4, 2.4 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 169.7, 137.6, 133.3, 131.3, 125.3, 123.l, 122.8, 24.3. IR (KBr): 1666 cm^{-1}. HRMS EI (m/z): [M^+] Calcd for $C_8H_7Cl_2NO$, 202.9905; Found, 202.9896.



Procedure A was followed, utilizing substrate **61** (150 mg, 0.884 mmol, 1 equiv), NCS (142 mg, 1.06 mmol, 1.2 equiv), and AcOH (7.4 mL). Product **61-Cl** was isolated as a white solid (77 mg, 43% yield, mp = 133.4-133.9 ºC, R_f = 0.28 in 80% hexanes/20% EtOAc). The NMR data was identical to that reported above for the reaction with palladium. The Product **Iso-61-Cl** was isolated as a white solid (70 mg, 39% yield, mp = 121.9-123.3 ºC, R_f = 0.24 in 60% hexanes/40% EtOAc).^{1}H NMR (400 MHz, acetone-d_6):

δ 7.78 (br s, 1H), 7.73 (d, J = 1.8 Hz, 1H), 7.35-7.29 (multiple peaks, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 137.3, 132.7, 130.4, 127.5, 121.6, 119.1, 24.5. IR (KBr): 1665 cm^{-1}. HRMS EI (m/z): [M^+] Calcd for $C_8H_7Cl_2NO$, 202.9905; Found, 202.9904.

4.10 References

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26. Interestingly, such high selectivity for the functionalization of the more sterically hindered C–H bond was previously observed only with OH as a *meta* substituent (see ref. 10a) suggesting that the –OH and –NH functionalities might be playing a role in imparting this selectivity.

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31. 20 mol% palladium was required for this substrate to avoid the formation of the uncatalyzed products.

32. Substrates containing unactivated sp^3 substrates did not afford the products of directed halogenation under our standard reaction conditions in the presence of a variety of different halogenating reagents. Ongoing efforts aim to develop methods for the halogenation of this class of substrates.

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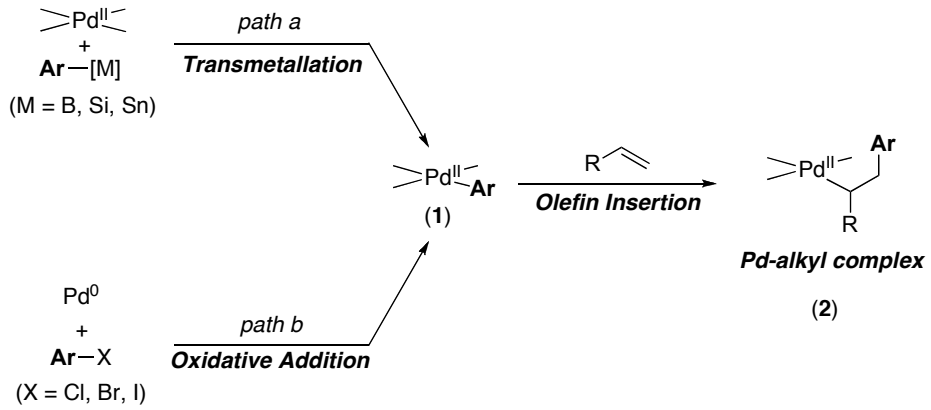
Chapter 5

Palladium-Catalyzed Arylhalogenation of Alkenes

5.1 Background and Significance

Palladium-catalyzed cascade reactions are widely used for the assembly of complex organic molecules.[1] These transformations frequently involve σ-alkyl-Pd^{II} complexes that are formed by olefin insertion into a Pd-aryl bond (**2** in Scheme 1).[1] The Pd-aryl species **1** in these transformations can be generated by oxidative addition of Pd^0 into aryl halides or through transmetallation of aryl metal reagents (Ar-[M]) onto Pd^{II}.

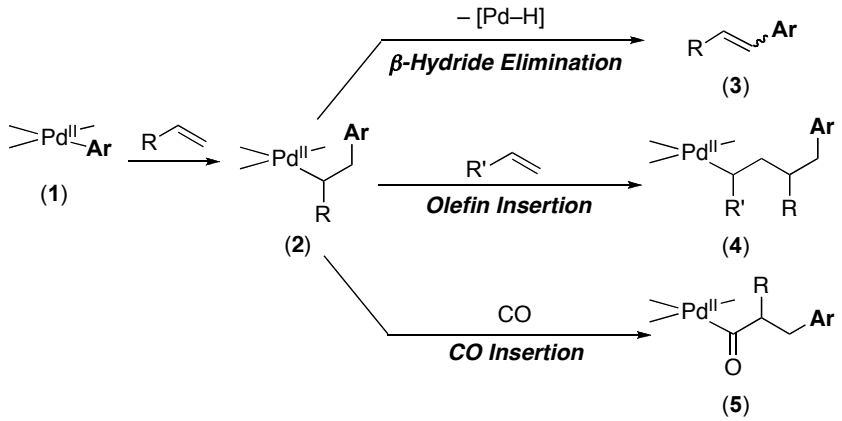
Scheme 1: Generation of Pd-alkyl Complexes



Intermediates such as **2** have been shown to undergo a variety of reactions to afford valuable functionalized products. For example, **2** is known to undergo β-hydride elimination to afford alkene products **3**.[2] The olefin insertion/β-hydride elimination sequence depicted in Scheme 2 is the well-known Mizoroki-Heck Reaction.

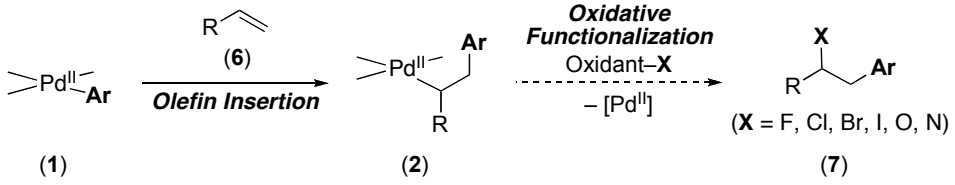
Alternatively, **2** can be intercepted by olefin/alkyne insertion or by CO insertion to afford **4** and **5**, respectively.[3]

Scheme 2: Reactions of Pd-alkyl Complexes



In contrast, selective and high yielding approaches to the oxidative functionalization of σ-alkyl-Pd^{II} intermediates such as **2** remain rare (Scheme 3). These reactions would lead to the formation of a C–C bond and a C–X bond (X = Cl, Br, I, F, O, N) with concomitant generation of a stereocenter in a single transformation. Additionally, the direct conversion of the Pd–C bond of **2** into a variety of C–X bonds would make these transformations very valuable for the diverse functionalization of easily accessible α-olefins.

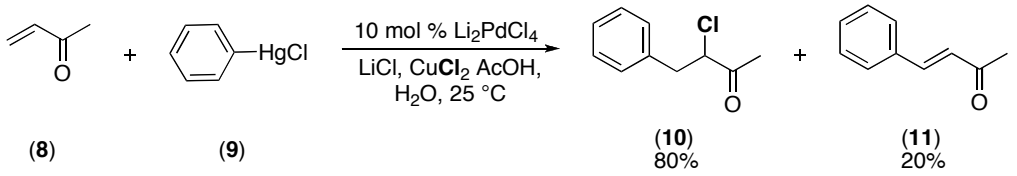
Scheme 3: Oxidative Interception of Heck Intermediates



An early report by Heck described the oxidative halogenation of intermediates of general structure **2** to form 1,2-arylhalogenated compounds.[4,5] For example, the palladium-catalyzed reaction of **8** with **9** as the arylating reagent and $CuCl_2$ as the terminal oxidant afforded product **10** in 80% yield (Scheme 4). However, competing

formation of alkene product **11** (via β-hydride elimination) along with the requirement of toxic aryl mercury reagent **9** severely limited the scope, yields, and overall synthetic utility of these transformations.

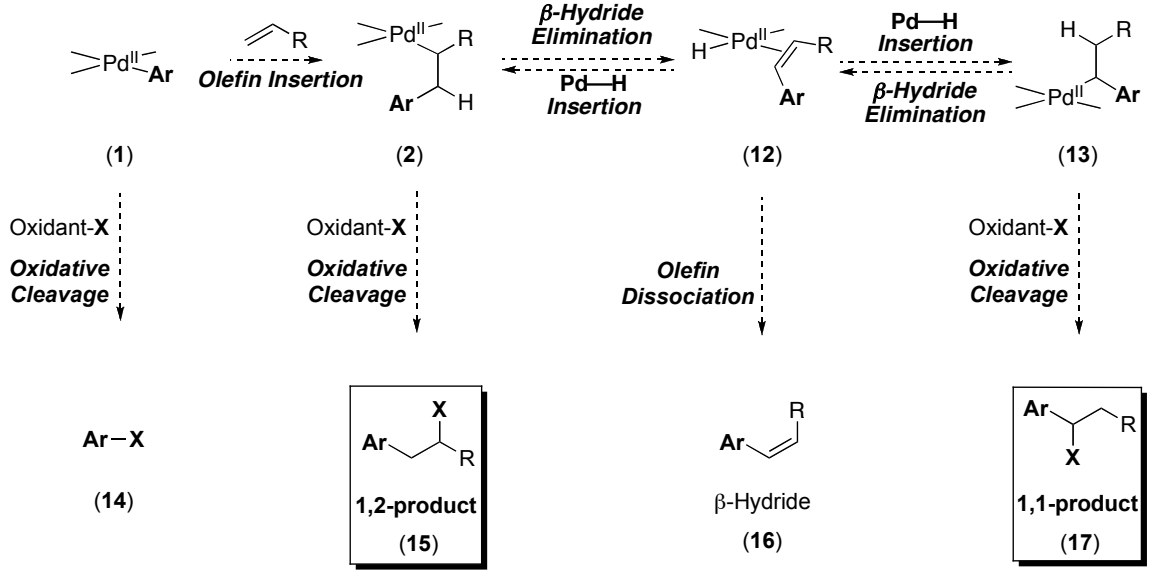
Scheme 4: 1,2-Arylchlorination of **8**



(**8**) (**9**) (**10**) 80% (**11**) 20%

In order to develop general, high yielding and selective methods for the diverse oxidative functionalization of intermediates like **2**, several challenges need to be addressed (Scheme 5). First, the Pd-aryl intermediate **1** has the potential to undergo oxidative cleavage prior to olefin insertion, affording substituted arenes **14** rather than the desired functionalized product **15**. Secondly, Heck-type chemistry could occur, in which the σ-alkyl-Pd species formed upon olefin insertion into the Pd-C bond of **2** undergoes β-hydride elimination/olefin dissociation to yield alkene products **16**. Finally, complex **12**, generated upon β-hydride elimination might undergo olefin insertion into the Pd-H bond to form either of the two isomeric σ-alkyl-Pd intermediates **2** or **13**. Subsequent oxidative cleavage of the Pd-C bonds of **2** and **12** would afford mixtures of the vicinal and geminal difunctionalized products **15** (1,2-isomer) and **17** (1,1-isomer), respectively. Hence, reaction conditions must be rationally designed to obtain either the 1,2-product **15** or the 1,1-product **17**. Importantly, the selective formation of either the 1,1- or the 1,2-isomers from the same α-olefin reactant would significantly enhance the synthetic applicability of these reactions by allowing access to a wider array of difunctionalized products.

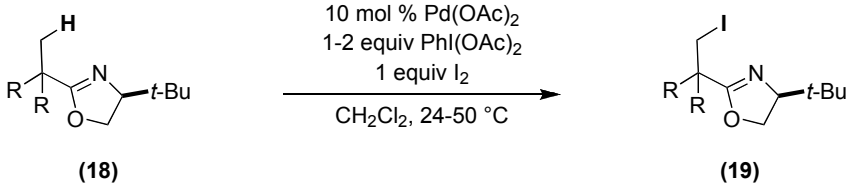
Scheme 5: Challenges Associated with Oxidative Functionalization of Heck Intermediates



With these considerations in mind, we initiated investigations towards oxidative functionalization of Heck intermediates using electrophilic halogenating reagents (halogen = Cl, Br) as the terminal oxidants to obtain the arylhalogenated products **15** and **17**. We anticipated that the wide variety of readily accessible halogenating oxidants[6] with different reactivities would enable us to have the versatility to design reaction conditions to obtain either the 1,1- or the 1,2-arylhalogenated products selectively. In order to obtain the 1,2-products selectively, careful control of the relative rate of olefin insertion versus oxidation of **2** as well as the relative rate of oxidation of **2** versus β-hydride elimination would be essential. We reasoned that the use of solvents that are not employed in Heck reactions might assist in preventing β-hydride elimination processes. Heck reactions are most commonly conducted in polar solvents such as DMF and DMA. Hence, we thought that the use of non-polar solvents such as Et_2O or CH_2Cl_2 might limit β-hydride elimination/dissociation processes. More importantly, we hypothesized that selectivity could be achieved by using an oxidant that is sufficiently reactive to out-compete β-hydride elimination from **2**, yet attenuated to allow olefin insertion prior to oxidation of **1**.

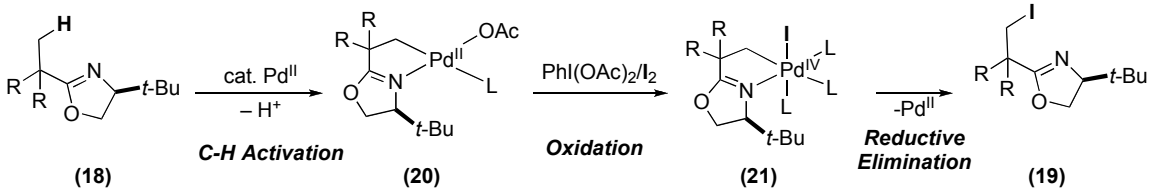
Recent work has demonstrated that σ-Pd-alkyl species generated through C–H activation can undergo oxidative halogenation using hypervalent iodine(III) reagents.[6-9] For example, Yu and coworkers have shown that the palladium-catalyzed reaction of **18** with a combination of I_2 and $PhI(OAc)_2$ leads to the iodinated product **19** (Scheme 6).[8] These transformations are proposed to involve C–I reductive elimination from transient Pd^{IV} intermediates at the key product-forming step. The high reactivity of iodine(III) oxidants allows for a faster rate of oxidation of σ-Pd-alkyl intermediate **20** to the corresponding Pd^{IV} species **20**, versus β-hydride elimination.[10-13] The resistance of these Pd^{IV} complexes toward β-hydride elimination allows for the functionalization of **21** in the subsequent step with little to no formation of alkene byproducts.

Scheme 6: $Pd^{II/IV}$-Catalyzed Oxazoline-Directed C–H Activation/Iodination



(18) **(19)**

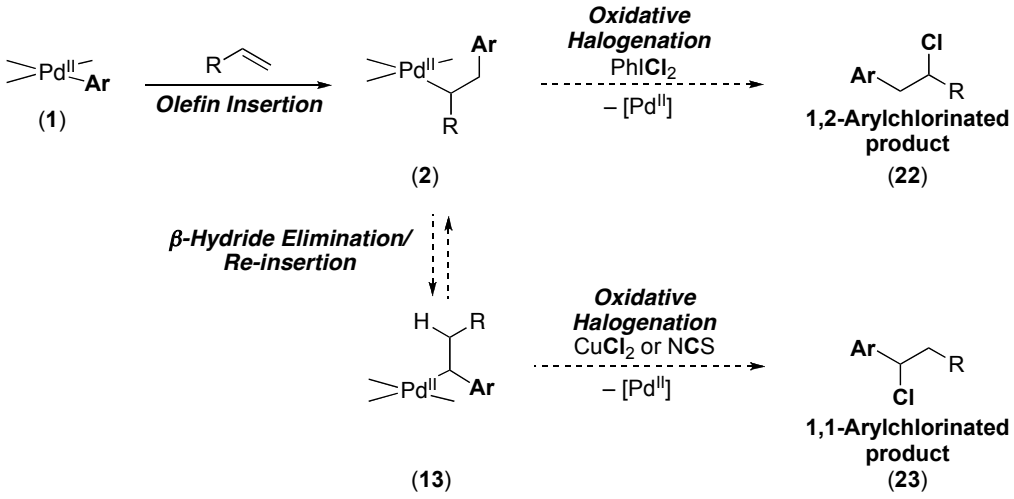
Scheme 7: Proposed Mechanism of Oxazoline-Directed C–H Activation/Iodination



(18) **(20)** **(21)** **(19)**

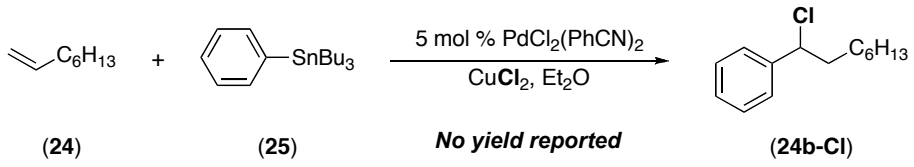
Based on this work, we reasoned that the iodine(III) oxidant $PhICl_2$ might have the potential to outcompete β-hydride elimination from palladium alkyl intermediates, and allow the formation of the 1,2-arylchlorinated product **22** (Scheme 8).[14] Importantly, van Koten has demonstrated that high oxidation state Pd^{IV} intermediates are accessible using $PhICl_2$ as the oxidant.[15]

Scheme 8: Proposed Arylhalogenation Reactions

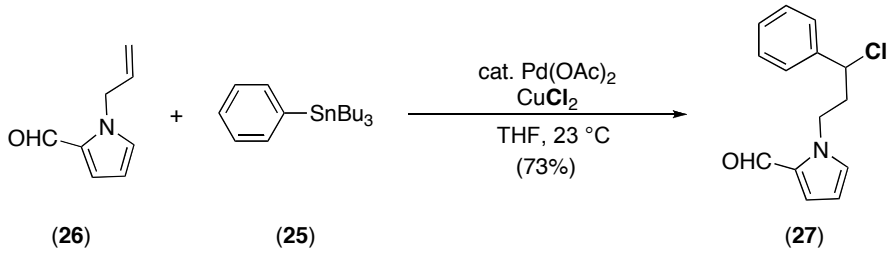


Conversely, we envisioned that the use of less reactive oxidants could allow access to both the σ-Pd-alkyl and the Pd-benzyl intermediates **2** and **13**, respectively, via β-hydride elimination/reinsertion processes from **2**. In these systems, mixtures of 1,1- and 1,2-products would be expected if there were no preference for oxidative functionalization of **2** versus **13**. However, sporadic literature reports have suggested selectivity for the reaction of Pd-benzyl intermediates in the presence of other equilibrating isomeric σ-Pd-alkyl species.[16-20] For example, Tamaru and coworkers demonstrated the palladium-catalyzed 1,1-phenylchlorination of 1-octene (Scheme 9).[17] However, the yield for this transformation was not reported and 1-octene was the only substrate examined. More recently, a similar 1,1-phenylchlorination reaction was demonstrated for substrate **26** with $CuCl_2$ as the oxidant (Scheme 10).[16] Based on these reports, we speculated that the use of less reactive oxidants such as $CuCl_2$[6, 21-25] and NCS under reaction conditions that favor the oxidative cleavage of **13** versus **2**, could potentially afford the 1,1-products selectively.

Scheme 9: 1,1-Arylchlorination of 1-Octene



Scheme 10: 1,1-Arylchlorination of **26**



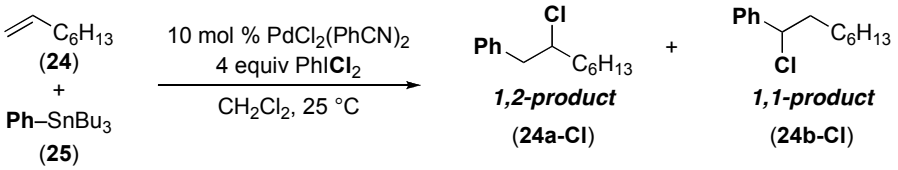
(**26**) (**25**) (**27**)

5.2 Synthetic Scope of Arylchlorinations

Our studies began by investigating the Pd-catalyzed reaction of 1-octene with $PhSnBu_3$ in the presence of $PhICl_2$ as the terminal oxidant. As discussed above, we envisioned that the use of $PhICl_2$ would limit β-hydride elimination from **2** and allow for the selective formation of the 1,2-product **22** (Scheme 8). We chose $PhSnBu_3$ as the arylating reagent because it is known to transmetallate to Pd^{II} to generate phenyl palladium species under relatively mild reaction conditions.

As shown in Table 5.1, we were pleased to find that the desired 1,2-product was formed in a number of different solvents at room temperature. Although the 1,1-isomer was the major product in most solvents, the 1,2-product was indeed favored in the reaction in CH_2Cl_2, albeit with low selectivity (entry 10). Gratifyingly, lowering the reaction temperature to –78 °C afforded the 1,2-product in good selectivity. However, the yield of the product was still modest (entry 11).

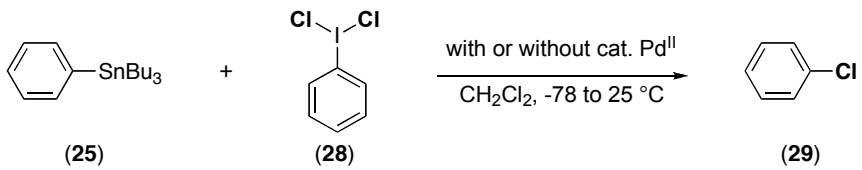
Table 5.1: Solvent Study for 1,2-Arylchlorination with $PhICl_2$



Entry	Solvent	Temperature	NMR yield	1,2:1,1
1	Dioxane	25 °C	57%	1:56
2	THF	25 °C	18%	1:17
3	Et_2O	25 °C	38%	1:6
4	C_6H_6	25 °C	27%	1:3
5	$PhCF_3$	25 °C	39%	1:3
6	DCE	25 °C	26%	1:1
7	DMF	25 °C	trace product	
8	CH_3CN	25 °C	trace product	
9	AcOH	25 °C	10%	2:1
10	**CH_2Cl_2**	**25 °C**	**25%**	**2:1**
11	**CH_2Cl_2**	**-78 °C to 25 °C**	**48%**	**15:1**

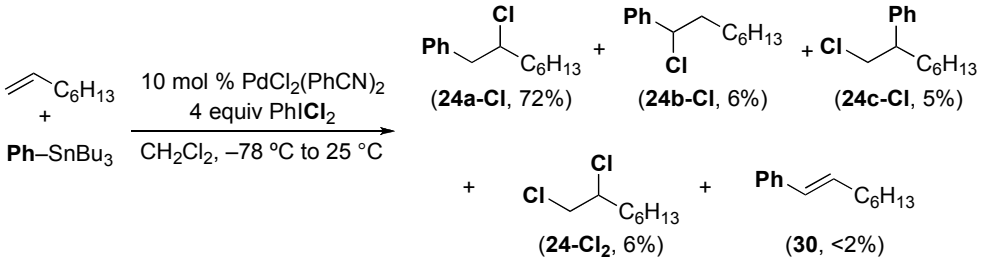
Gas chromatographic analysis of the crude reaction mixture revealed the formation of chlorobenzene as a side product. Based on the proposed mechanism in Scheme 5, we theorized that the formation of chlorobenzene might be a result of oxidative cleavage of the Pd-aryl complex **1** (generated upon transmetallation) by $PhICl_2$ prior to olefin insertion. Interestingly, a control experiment showed that this side product actually results from the direct reaction of $PhICl_2$ with $PhSnBu_3$ in the absence of the palladium catalyst (Scheme 11).

Scheme 11: Reaction of $PhSnBu_3$ with $PhICl_2$



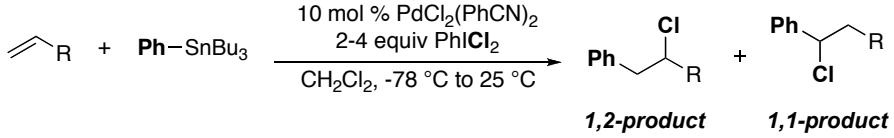
This side reaction could then be responsible for the low yield of the desired 1,2-product, since only a small excess (1.3 equiv) of $PhSnBu_3$ was being used. Consistent with this hypothesis, the yield of the 1,2-product increased significantly when an additional 1.3 equiv of $PhSnBu_3$ was added one hour after the start of the reaction (to make up for the loss due to the side reaction). Hence, under the optimal conditions (10 mol % $PdCl_2(PhCN)_2$, 4 equiv $PhICl_2$, 2.6 equiv of $PhSnBu_3$, CH_2Cl_2 –78 °C to 25 °C), the palladium-catalyzed phenylchlorination of 1-octene (**24**) afforded the 1,2-product **24a-Cl** in 72% yield and the corresponding 1,1-isomer **24b-Cl** in 6% yield (as determined by ^1H NMR spectroscopy) (Scheme 12). Additionally, very small amounts of 2,1-phenylchlorinated product **24c-Cl** (5%) and dichlorinated product **24-Cl_2** (4%) were also formed in this reaction. Gratifyingly, only trace (<2%) of the alkene product **30** generated via β-hydride elimination was observed in the crude reaction mixture.

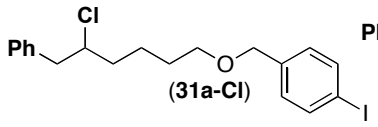
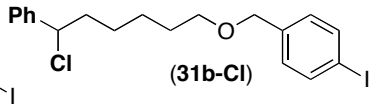
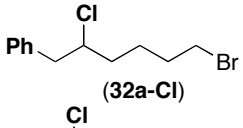
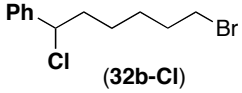
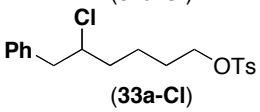
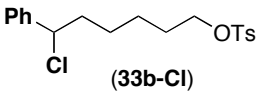
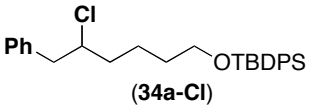
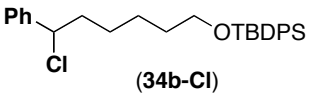
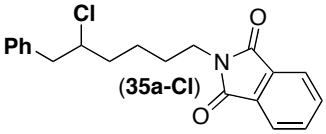
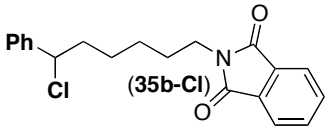
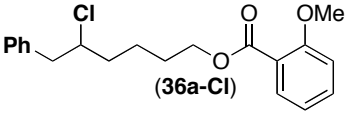
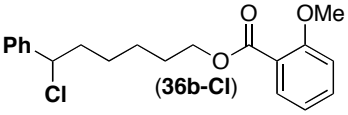
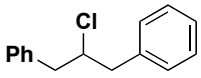
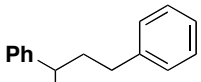
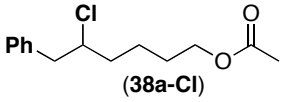
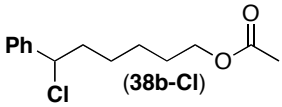
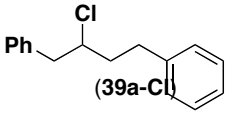
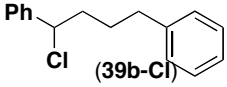
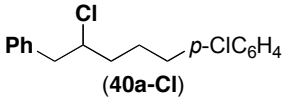
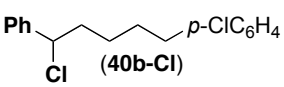
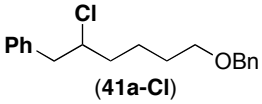
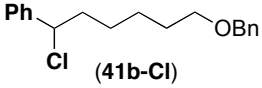
Scheme 12: Palladium-Catalyzed 1,2-Arylchlorination of 1-Octene



As shown in Table 5.2, these conditions for the formation of the 1,2-phenylchlorinated products could be applied to a number of different α-olefins. These reactions were tolerant of a wide variety of common functional groups such as esters, aromatic and alkyl halides, benzylic hydrogens, amides, silyl ethers, and both electron rich and electron poor aryl groups. In all cases, the products were obtained in good to excellent yields with good selectivity for the 1,2-isomer.

Table 5.2: Substrate Scope for 1,2-Phenylchlorination

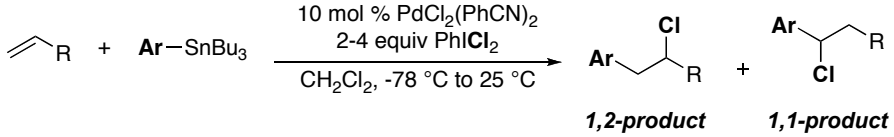


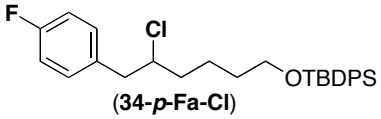
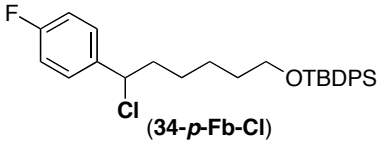
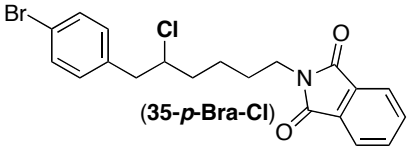
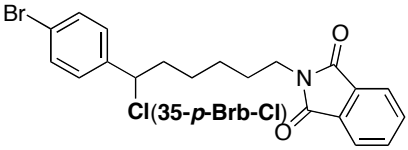
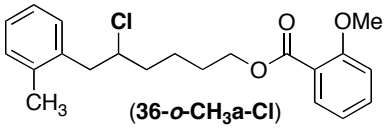
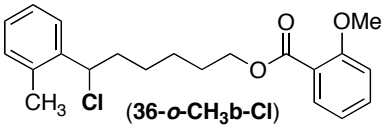
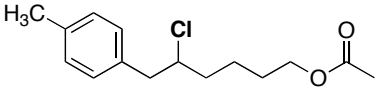
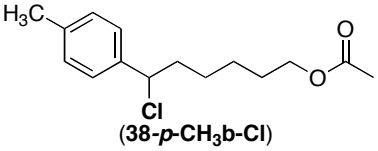
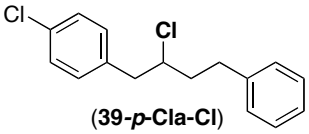
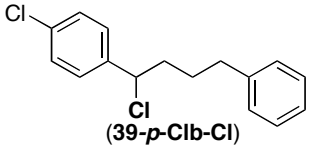
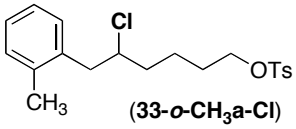
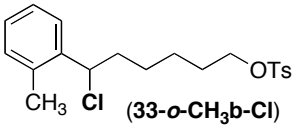
Entry	1,2 Product	1,1 Product	Yield	1,2:1,1
1	 (**31a-Cl**)	 (**31b-Cl**)	72%	8:1
2	 (**32a-Cl**)	 (**32b-Cl**)	84%	13:1
3	 (**33a-Cl**)	 (**33b-Cl**)	96%	9:1
4	 (**34a-Cl**)	 (**34b-Cl**)	92%	11:1
5	 (**35a-Cl**)	 (**35b-Cl**)	85%	6:1
6	 (**36a-Cl**)	 (**36b-Cl**)	86%	8:1
7	 (**37a-Cl**)	 (**37b-Cl**)	68%	6:1
8	 (**38a-Cl**)	 (**38b-Cl**)	86%	10:1
9	 (**39a-Cl**)	 (**39b-Cl**)	75%	14:1
10	 (**40a-Cl**)	 (**40b-Cl**)	89%	3:1
11	 (**41a-Cl**)	 (**41b-Cl**)	83%	12:1

These reactions were also general with respect to the tin reagent. As shown in Table 5.3, electron rich and electron poor substituents, as well as oxidizable

functionalities such as benzylic hydrogens and aromatic halides could be well tolerated on the arylating component. Furthermore, the sterically hindered *o*-tolyl tin reagent could be effectively used in these transformations. However, in these cases significant quantities (12%-14%) of the 2,1-isomer also formed. Interestingly, selectivity for the 1,2-product was much higher (>20:1) with styrene substrates (Table 5.4) than with those depicted in Tables 5.2 and 5.3.

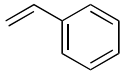
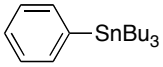
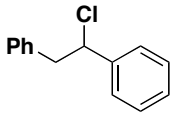
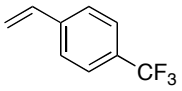
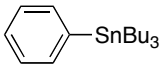
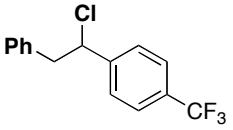
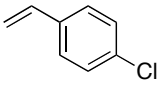
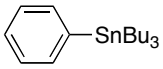
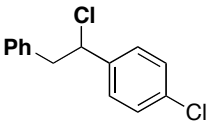
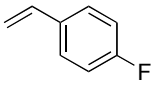
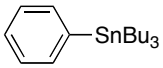
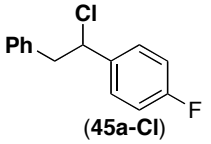
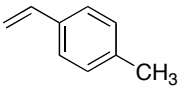
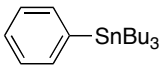
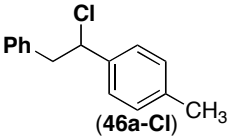
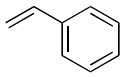
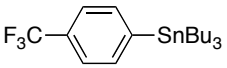
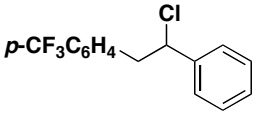
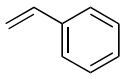
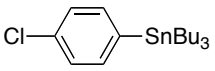
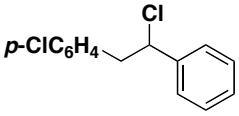
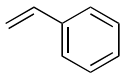
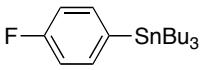
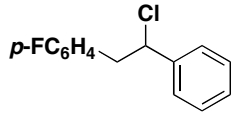
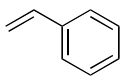
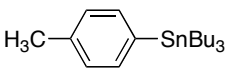
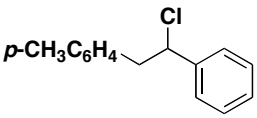
Table 5.3: Substrate Scope for 1,2-Arylchlorination



Entry	1,2 Product	1,1 Product	Yield[a]	1,2:1,1
1	 (**34-*p*-Fa-Cl**)	 (**34-*p*-Fb-Cl**)	84%	11:1
2	 (**35-*p*-Bra-Cl**)	 **Cl**(**35-*p*-Brb-Cl**)	96%	7:1
3	 (**36-*o*-CH$_3$a-Cl**)	 (**36-*o*-CH$_3$b-Cl**)	96%	10:1
4	 (**38-*p*-CH$_3$a-Cl**)	 (**38-*p*-CH$_3$b-Cl**)	66%	5:1
5	 (**39-*p*-Cla-Cl**)	 (**39-*p*-Clb-Cl**)	66%[c]	2:1[b]
6	 (**33-*o*-CH$_3$a-Cl**)	 (**33-*o*-CH$_3$b-Cl**)	86%	11:1

[a] total yield of the 1,2-, 1,1- and the 2,1-isomers. [b]Ratio is 1,2 : (1,1+1,4). [c]Yield is the sum of 1,2-, 1,1-, 1,4-, and 2,1-isomers

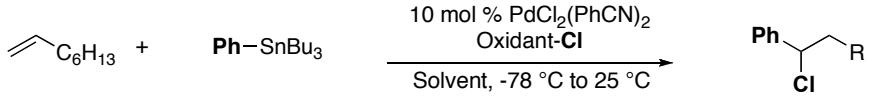
Table 5.4: 1,2-Arylchlorination of Styrene Substrates

Entry	Substrate	Tin Reagent	1,2-Product	yield	1,2:1,1
1	 (**42**)		 (**42a-Cl**)	71%[a]	N/A
2	 (**43**)		 (**43a-Cl**)	78%[b]	>20:1
3	 (**44**)		 (**44a-Cl**)	67%[b]	>20:1
4	 (**45**)		 (**45a-Cl**)	51%[b]	>20:1
5	 (**46**)		 (**46a-Cl**)	51%[b]	>20:1
6	 (**42**)		 (**42-*p*-CF$_3$a-Cl**)	81%[a]	>20:1
7	 (**42**)		 (**42-*p*-Cla-Cl**)	81%[b]	>20:1
8	 (**42**)		 (**42-*p*-Fa-Cl**)	80%[b]	>20:1
9	 (**42**)		 (**42-*p*-CH$_3$a-Cl**)	63%[b]	>20:1

[a] Crude H NMR yields. [b] Isolated yields

Having optimal parameters for the formation of the 1,2-product, we next sought to design reaction conditions to obtain selectivity for the 1,1-arylchlorinated product. As discussed above in Section 5.1, we reasoned that by switching from the highly reactive oxidant $PhICl_2$ to less reactive oxidants such as $CuCl_2$ or *N*-chlorosuccinimide (NCS), we could promote the formation of the 1,1-isomer. We were pleased to discover that under otherwise identical conditions to the $PhICl_2$ reaction, the use of NCS or $CuCl_2$ in the palladium-catalyzed arylchlorination of 1-octene led to exclusive formation of the 1,1-product **24b-Cl**, albeit in low (<5% and 13%) yields (Table 5.5, entries 1 and 4). Gratifyingly, with $CuCl_2$ as the oxidant, ethereal solvents like Et_2O and THF resulted in the 1,1-product in 59% and 60% yield respectively (Table 5.5, entries 5 and 6). As shown in Table 5.6 below, the 1,1-arylchlorination reactions show a substrate scope analogous to the 1,2-reactions discussed above. Notably in all cases, only trace amounts of the β-hydride elimination product are observed, and the 1,1-isomer is obtained in >20:1 selectivity.

Table 5.5: Optimization for 1,1-Phenylchlorination of 1-Octene

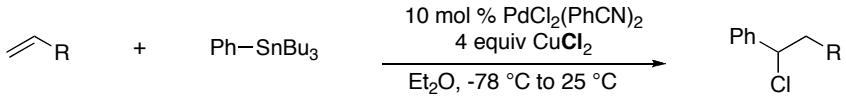


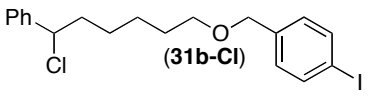
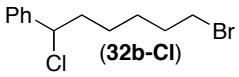
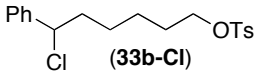
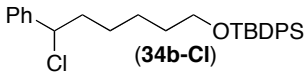
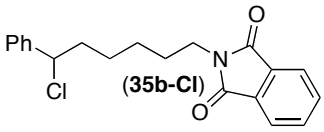
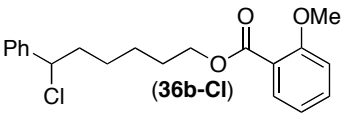
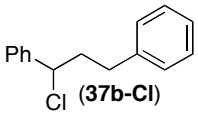
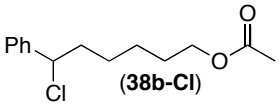
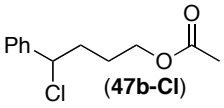
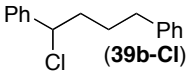
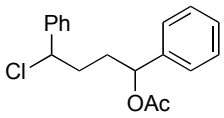
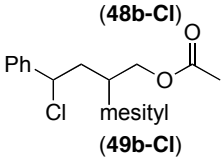
(**24**) (***1,1-product***) (**24b-Cl**)

Entry	Oxidant	Solvent	yield (%)[a]
1	NCS	CH_2Cl_2	<5
2	NCS	Et_2O	26
3	NCS	THF	36
4	$CuCl_2$	CH_2Cl_2	13
5	$CuCl_2$	THF	60
6	$CuCl_2$	Et_2O	59

[a] Yield determined by ^1H NMR spectroscopy of crude reaction mixtures

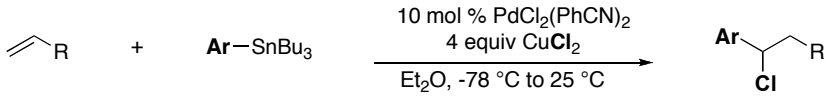
Table 5.6: Substrate Scope for 1,1-Phenylchlorination

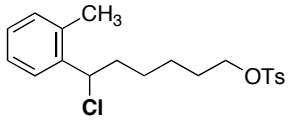
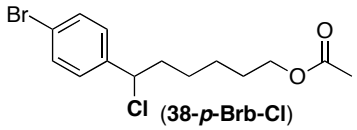
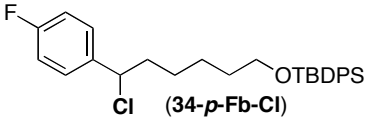
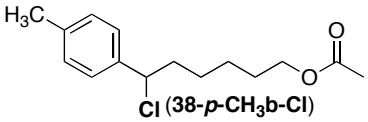
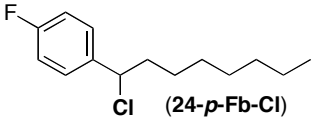
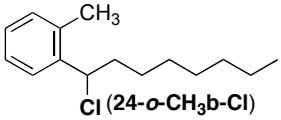
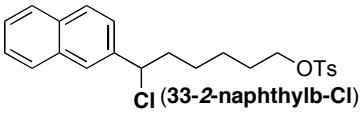
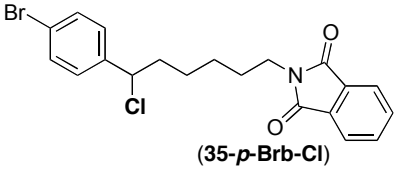


Entry	1,1 Product	Yield	1,1:1,2
1	 (**31b-Cl**)	53%	>20:1
2	 (**32b-Cl**)	54%	>20:1
3	 (**33b-Cl**)	71%	>20:1
4	 (**34b-Cl**)	66%	>20:1
5	 (**35b-Cl**)	71%	>20:1
6	 (**36b-Cl**)	45%	>20:1
7	 (**37b-Cl**)	55%	>20:1
8	 (**38b-Cl**)	71%	>20:1
9	 (**47b-Cl**)	45%	>20:1
10	 (**39b-Cl**)	84%	>20:1
11	 (**48b-Cl**)	70% dr=1:1	>20:1
12	 (**49b-Cl**)	77%	>20:1

Like the 1,2-arylchlorinations, these reactions were also effective with a wide array of different arylating reagents. The 1,1-isomer was obtained in excellent selectivity with electronically and sterically different aryltributyl tin derivatives (Table 5.7).

Table 5.7: Substrate Scope for 1,1-Arylchlorination

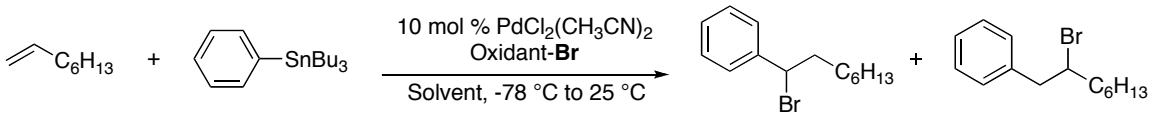


Entry	1,1 Product	Yield	1,1:1,2
1	 (**33-*o*-CH$_3$b-Cl**)	67%	>20:1
2	 (**38-*p*-Brb-Cl**)	71%	>20:1
3	 (**34-*p*-Fb-Cl**)	59%	>20:1
4	 (**38-*p*-CH$_3$b-Cl**)	73%	>20:1
5	 (**24-*p*-Fb-Cl**)	50%	>20:1
6	 (**24-*o*-CH$_3$b-Cl**)	30%	>20:1
7	 (**33-*2*-naphthylb-Cl**)	42%	>20:1
8	 (**35-*p*-Brb-Cl**)	47%	>20:1

5.3 Synthetic Scope of Arylbrominations

Having investigated the scope and selectivity of the arylchlorination reactions we next turned our efforts towards the development of analogous palladium-catalyzed arylbrominations. We reasoned that the use of electrophilic brominating reagents as terminal oxidants in place of $PhICl_2$ or $CuCl_2$ should lead to arylbrominated products under otherwise identical conditions. However, we did not know how closely the trends in site selectivity would compare between the arylchlorinations and arylbrominations. As shown in Table 5.8 below, the use of $CuBr_2$ and NBS as oxidants in the palladium-catalyzed reaction of 1-octene with $PhSnBu_3$ afforded significant quantities of the arylbrominated products in a variety of solvents, and the yields were generally higher with $CuBr_2$. Furthermore, analogous to the arylchlorination reactions, the use of $CuBr_2$ in Et_2O led to the corresponding 1,1-arylbrominated product in good yield (54%) and with excellent selectivity (>20:1).

Table 5.8: Solvent Study for Phenylbromination of 1-Octene



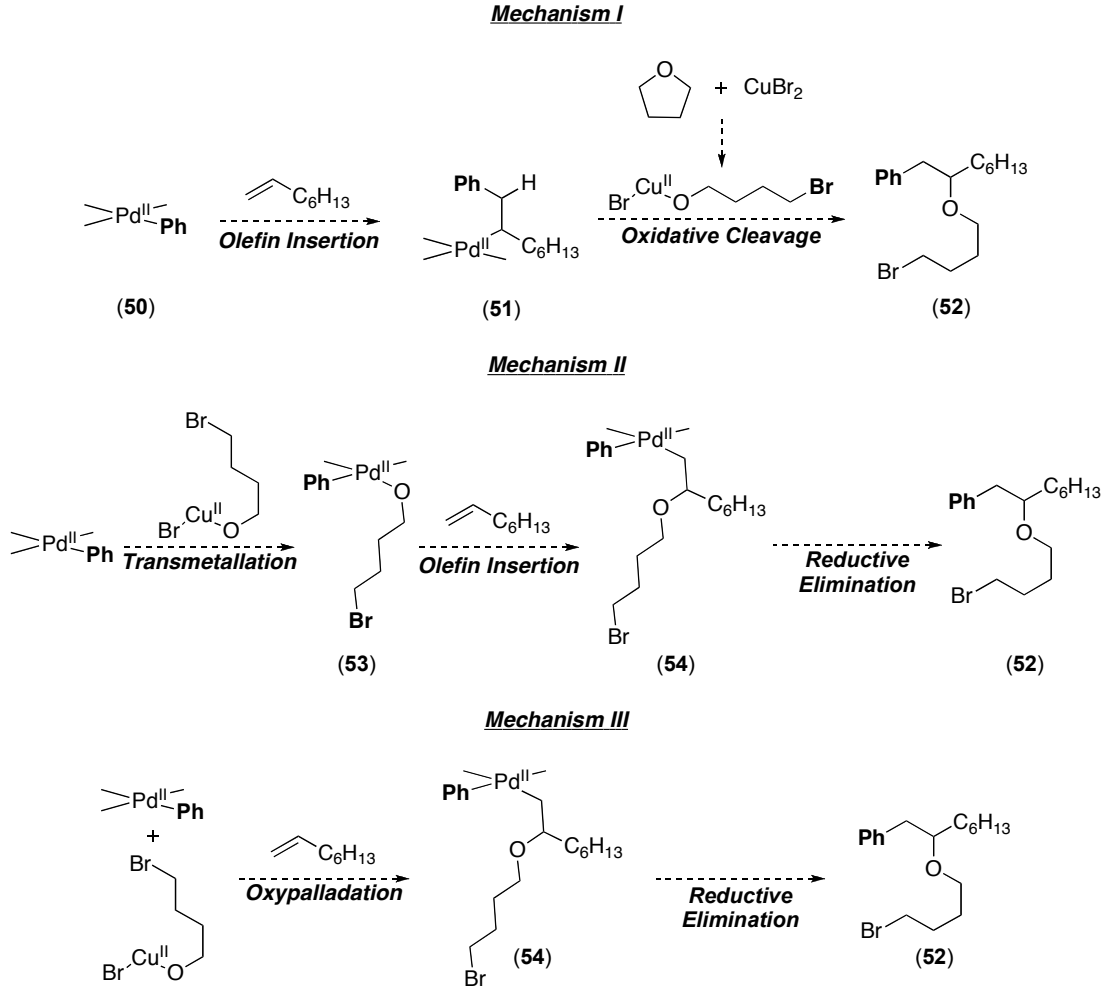
1,1-product (**24b-Br**) ***1,2-product*** (**24a-Br**)

Entry	Oxidant	Solvent	NMR yield	1,1:1,2	[octene]
1	NBS	CH_2Cl_2	trace product	>20:1	0.032 M
2	NBS	Et_2O	13%	>20:1	0.032 M
3	NBS	THF	26%	>20:1	0.032 M
4	$CuBr_2$	CH_2Cl_2	trace product		0.032 M
5	$CuBr_2$	Et_2O	54%	>20:1	0.128 M
6	$CuBr_2$	THF	16%	1:15	0.032 M
7	$CuBr_2$	THF	53%	1:12	0.128 M

Interestingly, the use of $CuBr_2$ in THF instead of Et_2O led to a complete reversal of site selectivity and afforded the 1,2-arylbrominated isomer as the major product (**24a-Br** : **24b-Br** = 15:1), albeit in low (16%) yield (Table 5.8, entry 6). Notably, this is in contrast to the trend observed in the arylchlorinaton reactions, in which the use of $CuCl_2$ in THF favors the formation of the 1,1-arylhalogenated products. Subsequent optimization revealed that that the desired 1,2-phenylbrominated product could be obtained in 53% yield simply by increasing the concentration of the reaction mixture to 0.128 M (Table 5.8, entry 7).

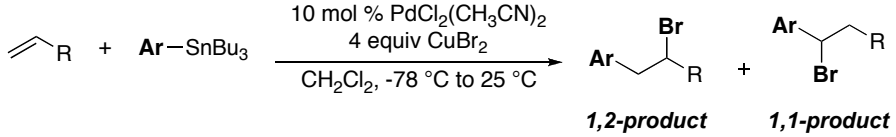
The major side product formed (~15% yield as determined by ^1H NMR spectroscopy) in the 1,2-arylbromination of 1-octene in THF was product **52** resulting from solvent incorporation in the product. Three possible mechanisms depicted in Scheme 13, could account for the formation of **52**.[26] Further studies need to be conducted to elucidate which one of these is operative under our reaction conditions.

Scheme 13: Possible Mechanisms for the Formation of **52**

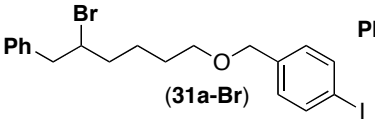
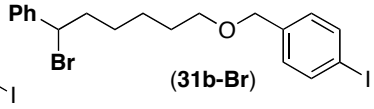
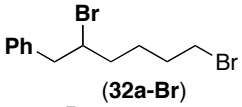
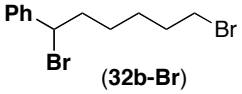
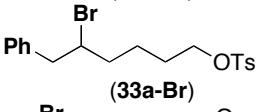
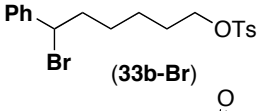
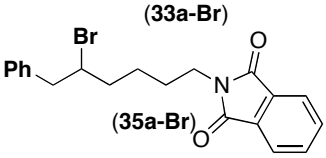
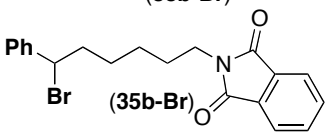
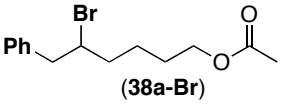
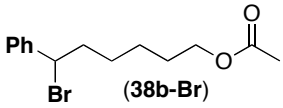
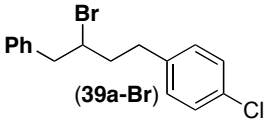
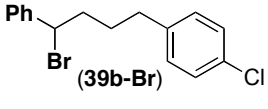
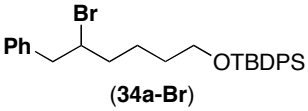
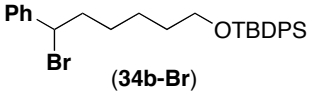
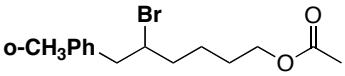
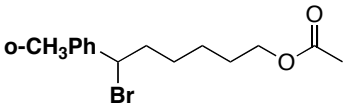


As shown in Tables 5.9-5.11, the optimal reaction conditions for formation of the 1,1- and 1,2-arylbrominated products are general for a variety of α-olefins. These transformations exhibit a scope and functional group tolerance similar to the arylchlorination reactions. Analogous to the 1,2-arylchlorinations with $PhICl_2$, the 1,2-arylbrominations with $CuBr_2$/THF also afford the 1,2-products with much greater selectivity (>20:1) with styrene substrates (Table 5.10) than with those shown in Table 5.9. The low yields of the arylbrominated products with styrene substrates are partly due to the formation of significant quantities (34%–65%) of stilbene derivatives via β-hydride elimination. Additionally, 15%–41% of the unreacted substrate also remained at the end of the reaction.

Table 5.9: Substrate Scope for 1,2-Arylbromination

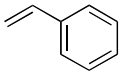
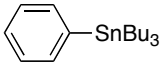
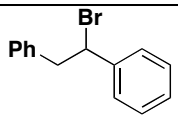
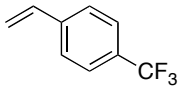
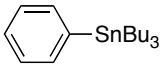
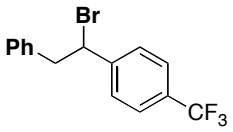
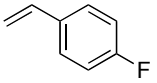
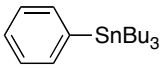
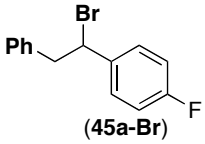
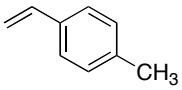
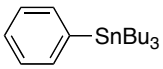
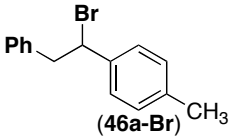
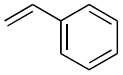
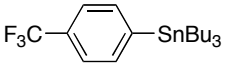
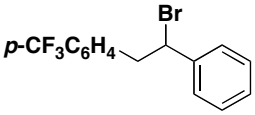
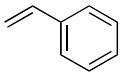
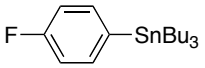
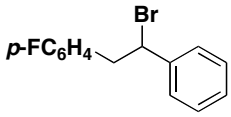
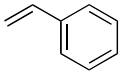
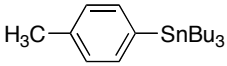
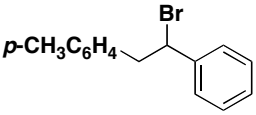


1,2-product *1,1-product*

Entry	1,2 Product	1,1 Product	Yield	1,2:1,1
1	 (**31a-Br**)	 (**31b-Br**)	49%[a]	11:1
2	 (**32a-Br**)	 (**32b-Br**)	55%	15:1
3	 (**33a-Br**)	 (**33b-Br**)	50%	17:1
4	 (**35a-Br**)	 (**35b-Br**)	55%	11:1
5	 (**38a-Br**)	 (**38b-Br**)	62%	15:1
6	 (**39a-Br**)	 (**39b-Br**)	68%	18:1
7	 (**34a-Br**)	 (**34b-Br**)	64%	22:1
8	 (**38-*o*-CH$_3$a-Br**)	 (**38-o-CH$_3$b-Br**)	43%	9:1

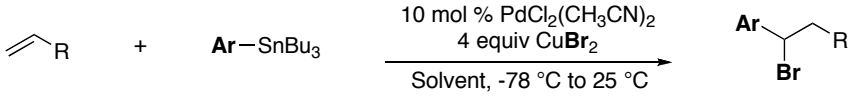
[a]Yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture

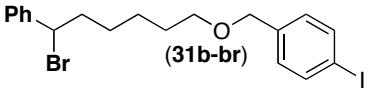
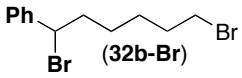
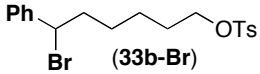
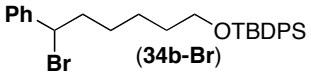
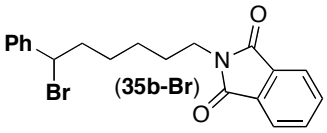
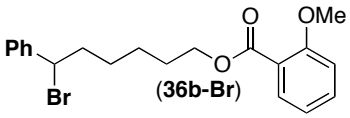
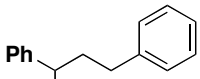
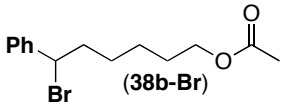
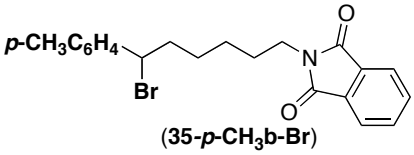
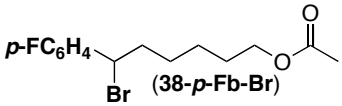
Table 5.10: 1,2-Arylbromination of Styrene Substrates

Entry	Substrate	Tin Reagent	1,2 Product	yield[a,b]	1,2:1,1[b]
1	 (**42**)		 (**42a-Br**)	44%	>20:1
2	 (**43**)		 (**43a-Br**)	23%	>20:1
3	 (**45**)		 (**45a-Br**)	45%	>20:1
4	 (**46**)		 (**46a-Br**)	43%	>20:1
5	 (**42**)		 (**42-*p*-CF$_3$a-Br**)	52%	>20:1
6	 (**42**)		 (**42-*p*-Fa-Br**)	30%	>20:1
7	 (**42**)		 (**42-*p*-CH$_3$a-Br**)	19%	>20:1

[a]Reaction conditions: 10 mol% $PdCl_2(CH_3CN)_2$, 4 equiv $CuBr_2$, 2 equiv *p*-XPhSnBu$_3$ added at the start of the reaction and another 1 equiv added 4 h after the start of the reaction, THF, 0.096 M in substrate, -78 °C - 25 °C. [b] Determined by ^{1}HNMR spectroscopy analysis of the crude reaction mixtures.

Table 5.11: Substrate Scope for 1,1-Arylbromination



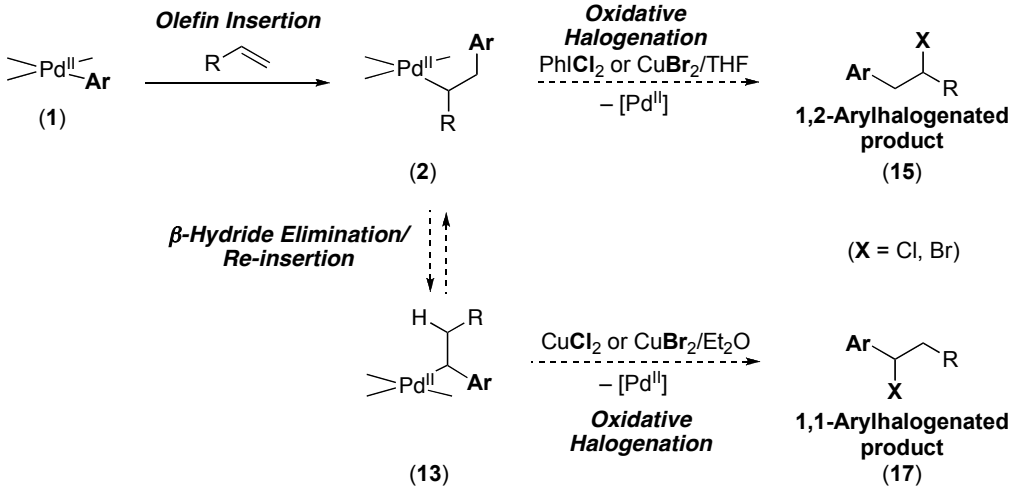
Entry	1,1 Product	Yield	1,1:1,2
1	 (**31b-br**)	57%	>20:1
2	 (**32b-Br**)	71%	>20:1
3	 (**33b-Br**)	68%	>20:1
4	 (**34b-Br**)	61%	>20:1
5	 (**35b-Br**)	70%	>20:1
6	 (**36b-Br**)	41%	>20:1
7	 (**37b-Br**)	37%	>20:1
8	 (**38b-Br**)	68%	>20:1
9	 (**35-*p*-CH$_3$b-Br**)	35%	>20:1
10	 (**38-*p*-Fb-Br**)	49%	10:1

5.4 Mechanistic Investigations of 1,2-Arylhalogenations

We next turned our efforts toward obtaining insight into the mechanism of these arylhalogenation reactions. In particular, we desired to (i) gain evidence for the proposed mechanistic pathway via deuterium labeling studies, (ii) understand the role of the oxidants in imparting the 1,2 versus 1,1 selectivity, (iii) investigate the reasons for the high selectivity for benzylic functionalization with $CuCl_2$ and $CuBr_2$ in Et_2O, and (iv) gain insight into the stereochemical course of these transformations.

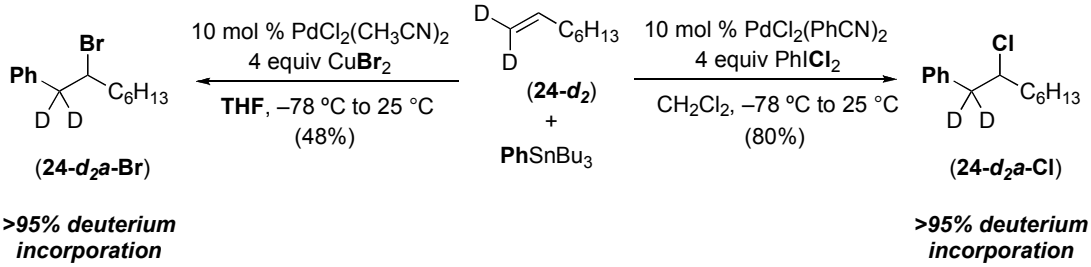
Deuterium Labeling Studies: The key steps of the proposed mechanism for the formation of the 1,2-arylhalogenated product **15** are as follows: (i) transmetallation between $ArSnBu_3$ and the Pd^{II} catalyst to form aryl palladium intermediate **1**, (ii) insertion of alkene into the Pd–C bond of **1** to afford **2**, and (iii) oxidative halogenation of the Pd–C bond in **2** to release the product and regenerate the catalyst (Scheme 14).

Scheme 14: Proposed Mechanism for the Formation of 1,2- and 1,1-Products

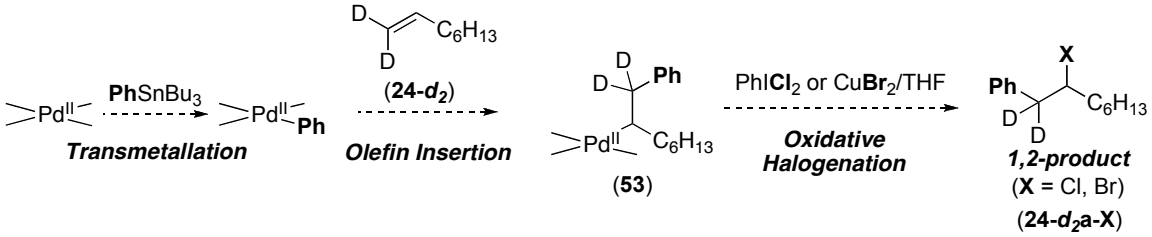


The observed formation of **24-*d*$_2$a-Cl** and **24-*d*$_2$a-Br** in the reaction of 1-octene–(1,1-d_2) under the standard conditions with $PhICl_2$ and $CuBr_2$/THF, respectively strongly supports our mechanistic proposal for the formation of the 1,2-products in these reactions (Schemes 15 and 16).

Scheme 15: Proposed Pathway for the 1,2-Arylhalogenation of 1-Octene-(1,1-d_2)

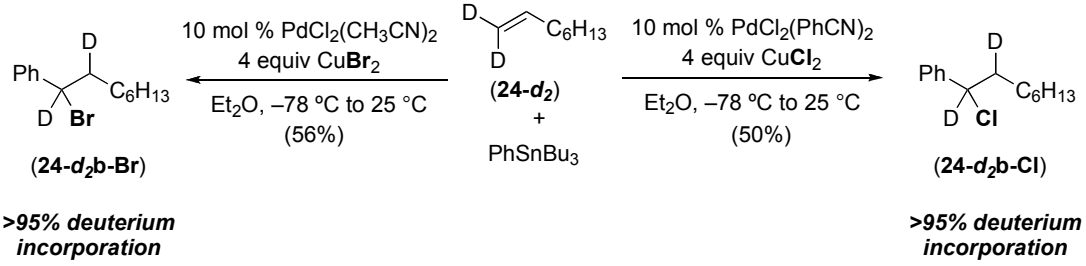


Scheme 16: 1,2-Arylhalogenation of 1-Octene-(1,1-d_2)

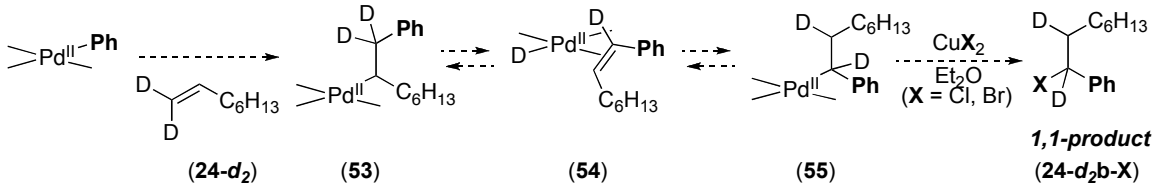


The formation of the 1,1-arylhalogenated products can also be explained based on the mechanistic manifold depicted in Scheme 14. β-Hydride elimination from **2**, followed by fast reinsertion into the Pd–H bond with the opposite regiochemistry, would result in a new Pd-alkyl intermediate **13**. Oxidative halogenation of **13** would lead to the 1,1-product **17** (Eq. 3). Consistent with this mechanistic proposal, the reaction of 1-octene-(1,1-d_2) under the 1,1-arylchlorination and 1,1-phenylbromination conditions affords products **24-*d*$_2$b-Cl** and **24-*d*$_2$b-Br**, respectively, with clean incorporation of deuterium at the 1 and the 2-positions (Schemes 17 and 18).

Scheme 17: Proposed Pathway for the 1,1-Arylhalogenation of 1-Octene-(1,1-d_2)



Scheme 18: 1,1-Arylhalogenation of 1-Octene-(1,1-d_2)



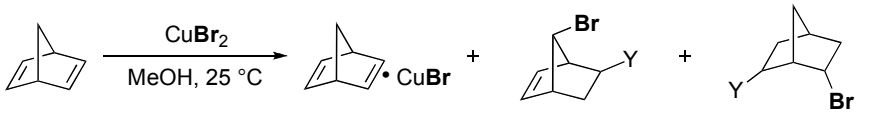
Role of Oxidant in 1,2 versus 1,1 Selectivity: As discussed in Sections 5.2 and 5.3 above, selectivity for the formation of the 1,2- and the 1,1-products is highly dependent on the oxidant and the reaction conditions. The use of $PhICl_2$ or $CuBr_2$/THF leads to the formation of the 1,2-arylchlorinated or 1,2-arylbrominated isomer as the major product. However, the use of $CuCl_2$ and $CuBr_2/Et_2O$ affords the 1,1-products with high selectivity.

In order to explain this selectivity, we hypothesized that, with the highly reactive oxidant $PhICl_2$, the oxidative chlorination of intermediate **2** is significantly faster that β-hydride elimination (Scheme 14). Thus, formation of the 1,2-isomer is favored, and is observed as the predominant product. Conversely, oxidative chlorination of **2** with the less reactive oxidant $CuCl_2$ is slower. This permits equilibration between **2** and **13**. In this scenario, when both intermediates **2** and **12** are accessible, it appears that halogenation of the Pd-benzyl intermediate **13** is more favorable than the halogenation of the Pd-alkyl species **2**. We propose that this accounts for the observed selectivity for the 1,1-arylchlorinated product under these conditions.

The formation of the 1,2-arylbrominated products with $CuBr_2$ in THF is intriguing because the analogous $CuCl_2$ oxidant selectively affords 1,1-arylchlorinated isomers under otherwise identical reaction conditions. Very early reports on Cu^{II}-mediated halogenation reactions suggest that the reactivity of $CuBr_2$ can be altered significantly in the presence of donor solvents or coordinating additives.[27] For example, the halogenation of carbonyl compounds and polynuclear aromatics by $CuBr_2$ require refluxing methanolic solutions for long reaction times (3-100 h) to afford the products in low (8-10%) yields. In contrast, similar brominations of diolefins could be performed at room temperature over 5 – 10 minutes (Scheme 19). This difference in reactivity of $CuBr_2$ toward olefins is attributed to the coordination of the diolefin to the CuBr byproduct of the reaction. The

consumption of CuBr is proposed to be the driving force for these reactions. Notably, however, similar reactions with $CuCl_2$ could only be achieved with strongly coordinating additives like acetonitrile. Based on this precedent we wondered if this reversal of selectivity in THF versus Et_2O with $CuBr_2$ as the oxidant was a result of the different coordinating abilities of the two solvents.

Scheme 19: Cu**Br**$_2$ Mediated Bromination of Diolefins

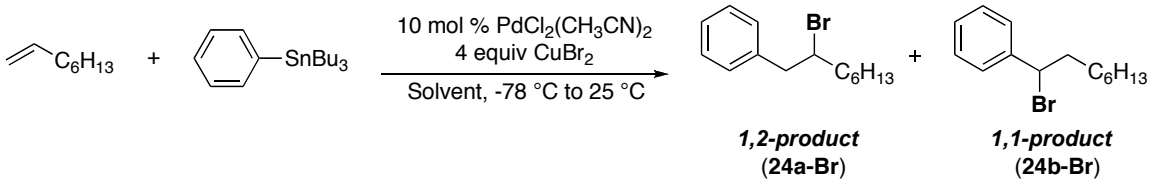


Y = Br (10%)
Y = OCH_3 (32%)

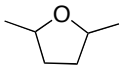
Y = Br (17%)
Y = OCH_3 (41%)

To probe this hypothesis, we subjected 1-octene to the standard reaction conditions with $CuBr_2$ as the oxidant using a series of methyl-substituted tetrahydrofurans as the solvent.[28] Importantly, THF, 2-methyl-THF and 2,5-dimethyl-THF would be expected to differ significantly in their coordinating abilities, but not in their dielectric constants. As shown in Table 5.12, both the yield and the selectivity for the 1,2-product decreased as the steric bulk of the solvent increased. These data imply that solvent coordination (or lack thereof) to $CuBr_2$ is playing a role in imparting the observed site selectivity in the arylbrominations. Thus, although $CuBr_2$ in Et_2O may behave analogously to $CuCl_2$, we propose that solvent (THF) coordination to $CuBr_2$ appears to increase its reactivity, resulting in faster oxidative halogenation. This could explain the selectivity for the 1,2 product in the presence of a coordinating solvent.

Table 5.12: Solvent Steric Effect in 1,2-Arylbrominations

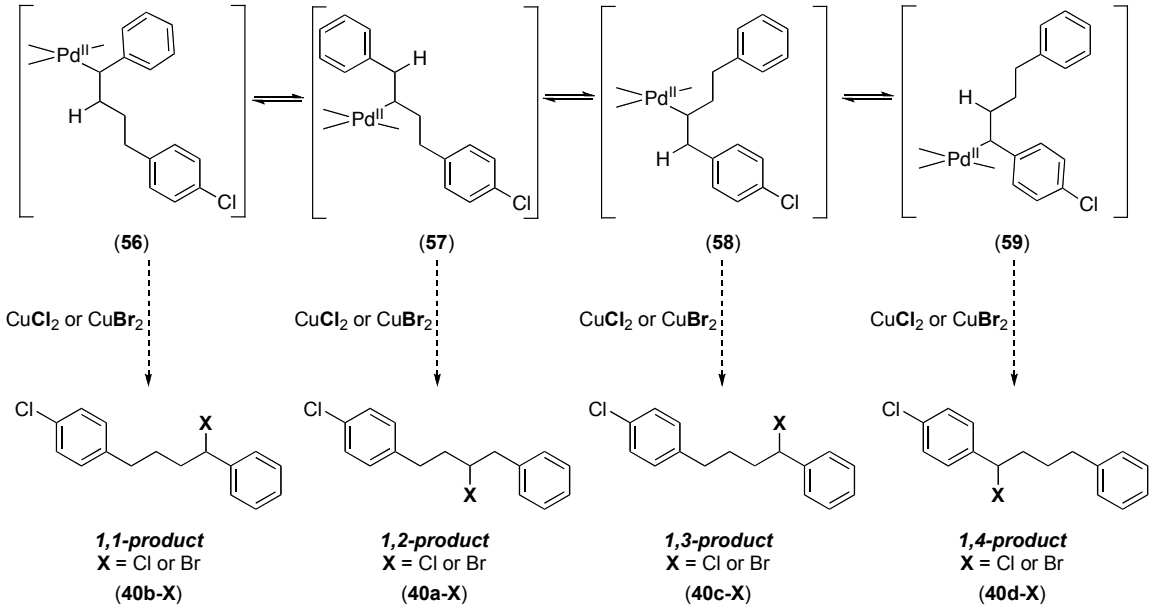


1,2-product (**24a-Br**) *1,1-product* (**24b-Br**)

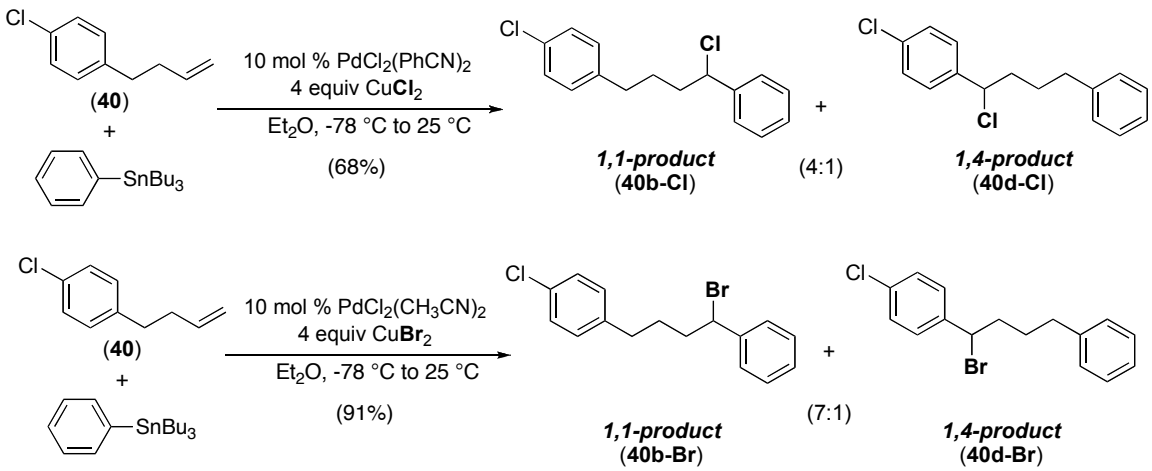
Entry	Oxidant	Solvent	NMR yield	1,2:1,1
1	$CuBr_2$		60%	11:1
2	$CuBr_2$		60%	4.5:1
3	$CuBr_2$		30%	4:1

Benzylic Functionalization with $CuCl_2$ and $CuBr_2$ in Et_2O: As discussed above, the arylhalogenation reactions with $CuCl_2$ or $CuBr_2/Et_2O$ afford the 1,1-arylhalogenated products with high selectivity, presumably via preferential functionalization of the Pd-benzyl intermediate over the equilibrating Pd-alkyl intermediate. Further confirmation of this preference for benzylic functionalization was obtained when we examined the Pd-catalyzed phenylchlorination and phenylbromination of 4-(4-chlorophenyl)-1-butene (**40**). In this homoallyl benzene system, initial olefin insertion of **40** would afford the Pd-alkyl complex **57**. However, subsequent β-hydride elimination/reinsertion processes could lead to isomeric Pd-alkyl complexes **56**–**59**, and hence products **40a-X**–**40d-X** (Scheme 20). As shown in Scheme 21, these reactions afforded two isomeric phenylhalogenated products – 1,1-functionalized **40b-Cl** and **40b-Br** and 1,4-functionalized **40d-Cl** and **40d-Br** – in a 4:1 and a 6:1 ratio respectively. The formation of **40d-Cl** and **40d-Br** (which requires the Pd in **58** to migrate 2 carbons down the alkyl chain) confirms that there are equilibrating β-hydride elimination/reinsertion steps prior to oxidative cleavage. In addition, the sole formation of **40b-Cl**, **40b-Br**, **40d-Cl**, and **40d-Br** (as opposed to isomers resulting from halogenation at other positions along the alkyl chain) supports the proposed selectivity for benzylic functionalization with CuX_2 in Et_2O (Scheme 20).

Scheme 20: Possible Intermediates and Products in the Reaction of **40**

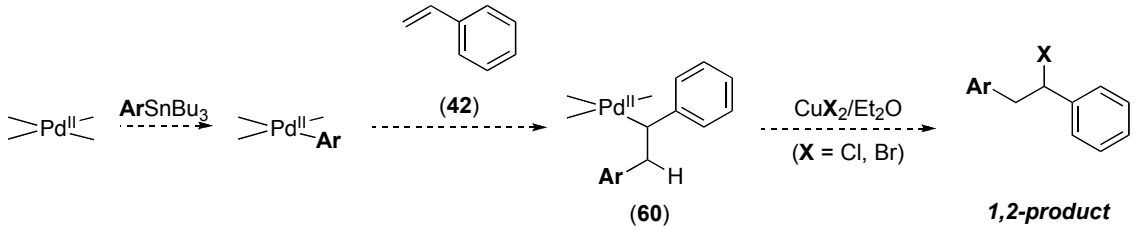


Scheme 21: Arylhalogenation of 4-(4-chlorophenyl)-1-butene



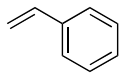
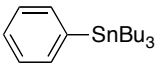
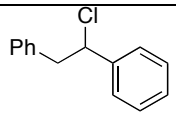
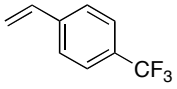
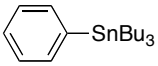
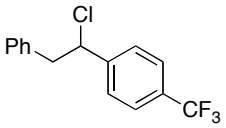
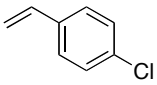
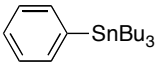
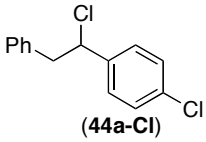
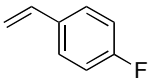
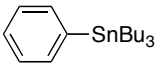
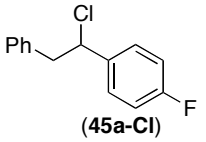
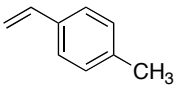
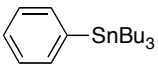
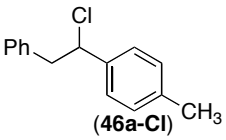
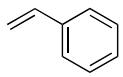
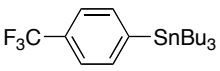
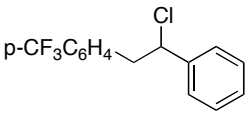
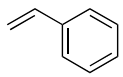
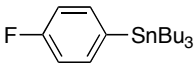
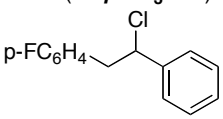
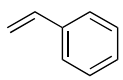
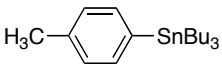
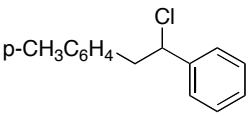
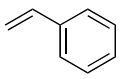
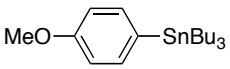
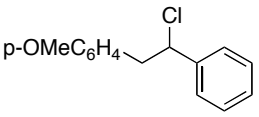
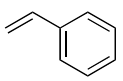
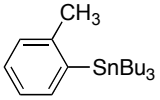
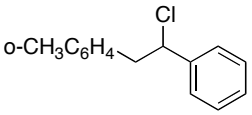
Based on these results, we postulated that CuX_2 in Et_2O should afford 1,2 products for substrates such as styrene for which the Pd-alkyl intermediate formed upon initial olefin insertion consists of a benzylic Pd-C bond (Scheme 22).

Scheme 22: Proposed Formation of 1,2-Products with CuX_2/Et_2O



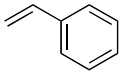
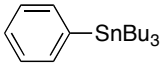
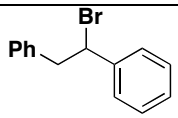
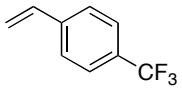
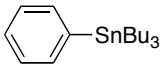
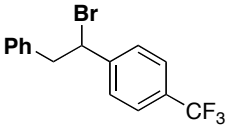
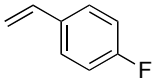
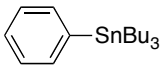
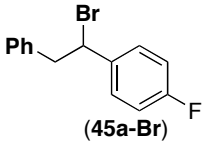
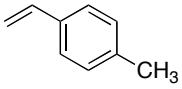
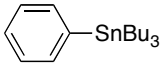
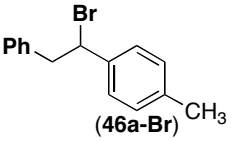
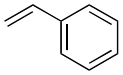
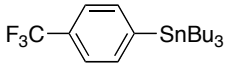
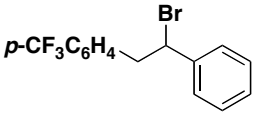
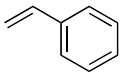
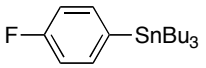
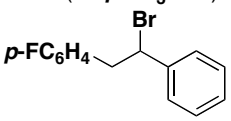
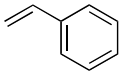
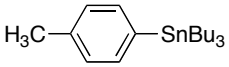
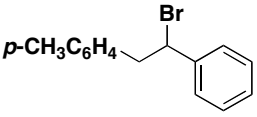
To probe this hypothesis, we subjected styrene to our 1,1-arylhalogenation conditions with a number of electronically different tributylaryltin derivatives. As predicted, the 1,2-product was the major product of this transformation regardless of the electronic nature of the transmetallating reagent or the alkene substrate (Tables 5.13 and 5.14). Similar preference for the 1,2-products was observed when substituted styrenes **43**, **45**, amd **46** were subjected to the 1,1-arylhalogenation conditions with $PhSnBu_3$ as the arylating reagent (Tables 5.13 and 5.14). The yields of the products in these cases are modest due to formation of significant amounts of the β-hydride products (30%–50%) and/or the low reactivity of the substrate (20%–75% of the unreacted substrate was observed by GC in the crude reactions).

Table 5.13: Arylchlorination of Styrene Substrates with $CuCl_2$

Entry	Substrate	Tin Reagent	1,2 Product	yield[a]	1,2:1,1[a]
1	 (**42**)		 (**42a-Cl**)	50%	N/A
2	 (**43**)		 (**43a-Cl**)	49%	1:1
3	 (**44**)		 (**44a-Cl**)	44%[b]	3:1
4	 (**45**)		 (**45a-Cl**)	48%	1.4:1
5	 (**46**)		 (**46a-Cl**)	44%	5:1
6	 (**42**)		 (**42-*p*-CF$_3$a-Cl**)	49%	7.6:1
7	 (**42**)		 (**42-*p*-Fa-Cl**)	50%	2.2:1
8	 (**42**)		 (**42-*p*-CH$_3$a-C**)	38%	2.4:1
9	 (**42**)		 (**42-*p*-OMea-Cl**)	32%[b]	>20:1
10	 (**42**)		 (**42-*o*-CH$_3$a-C**)	43%[b]	6:1

[a]Yields and selectivities determined by ^{1}H NMR Spectroscopy. [b]Isolated yields

Table 5.14: Arylbromination of Styrene Substrates with $CuBr_2$ in Et_2O

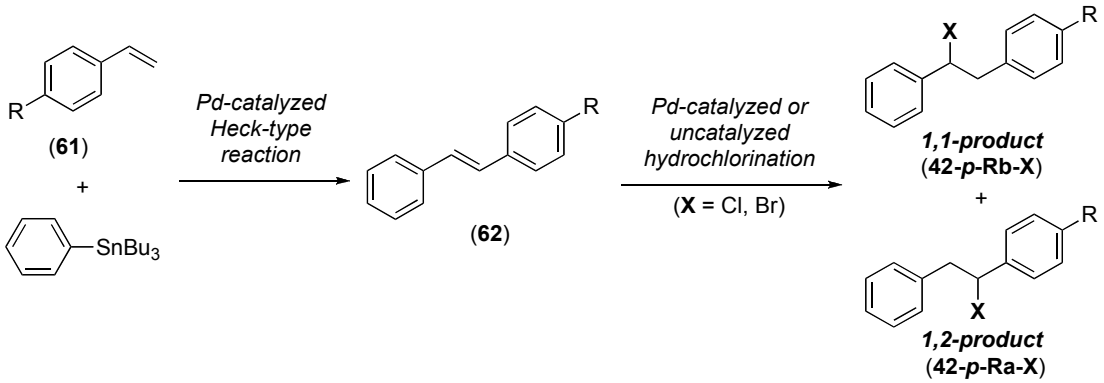
Entry	Substrate	Tin Reagent	1,2 Product	yield[a,b]	1,2:1,1[a]
1	 (**42**)		 (**42a-Br**)	43%	N/A
2	 (**43**)		 (**43a-Br**)	30%	1.5:1
3	 (**45**)		 (**45a-Br**)	52%	7:1
4	 (**46**)		 (**46a-Br**)	44%	>20:1
5	 (**42**)		 (**42-*p*-CF$_3$a-Br**)	4%	>20:1
6	 (**42**)		 (**42-*p*-Fa-Br**)	25%	20:1
7	 (**42**)		 (**42-*p*-CH$_3$a-Br**)	36%	>20:1

[a]Yields and selectivities determined by ^{1}H NMR Spectroscopy. [b]Reaction conditions: 10 mol % $PdCl_2(CH_3CN)_2$, 4 equiv $CuBr_2$, 1.3 equiv $PhSnBu_3$, Et_2O, 0 °C - 25 °C, 0.032 M in substrate

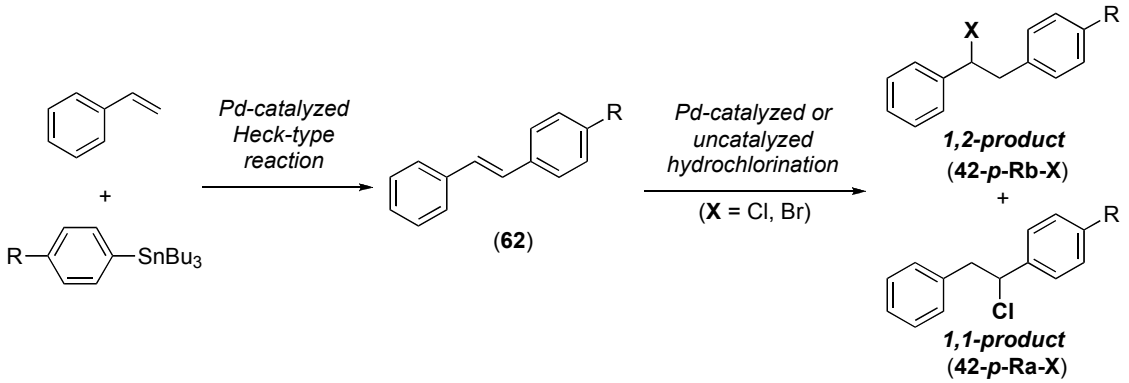
In addition to providing further evidence to support the preference for benzylic functionalization with CuX_2 in Et_2O, the styrene results also help to discount an alternative mechanism for the 1,1-arylhalogenations that would involve a standard Heck-type reaction followed by hydrohalogenation of the resulting olefin **62** (Schemes 23 and 24). If this sequential Heck/hydrohalogenation mechanism were operating, an identical distribution of **42-*p*-Ra-X** and **42-*p*-Rb-X** would be expected for the reactions depicted in

Schemes 22 and 23. However, these transformations afforded very different ratios of **42-*p*-Ra-X** : **42-*p*-Rb-X** (Tables 5.13 and 5.14).

Scheme 23: Possible Heck/Hydrohalogenation Pathway for Substituted Styrenes

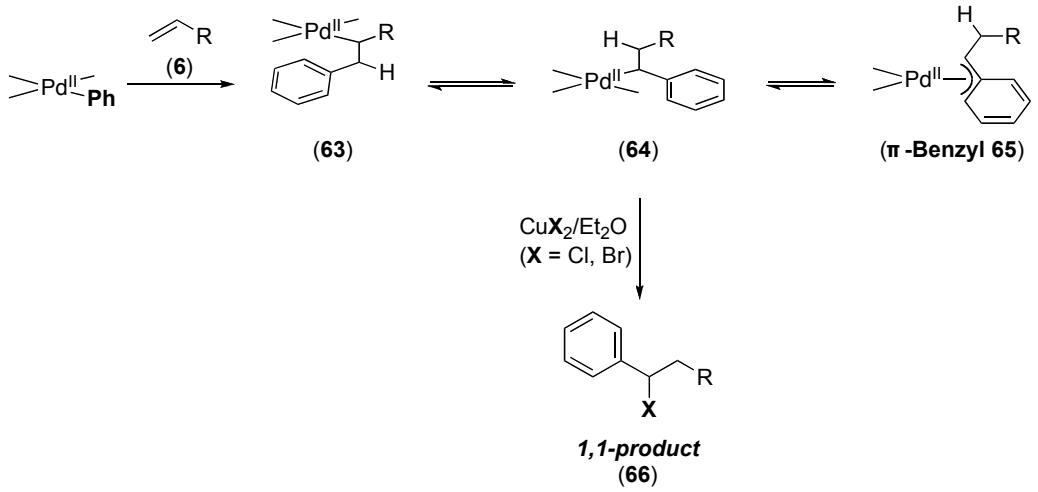


Scheme 24: Possible Heck/Hydrohalogenation Pathway for Styrenes



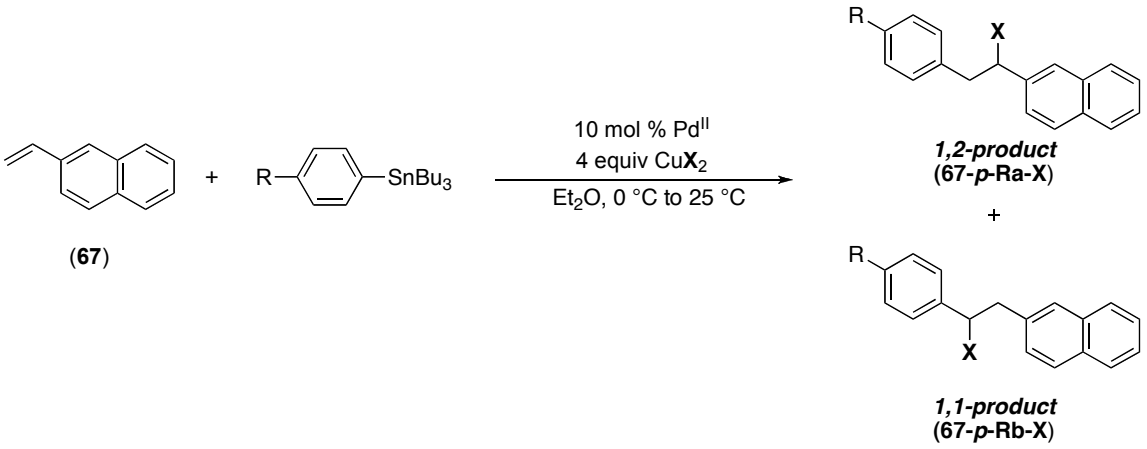
With the styrene and homoallyl benzene results in hand, we next sought to understand the reasons for preferential benzylic functionalization with CuX_2 in Et_2O. We hypothesized that the selectivity for benzylic halogenation might arise from equilibration of σ-benzyl Pd intermediate **64** with a corresponding π-benzyl Pd species (**65**) (Scheme 25).[10] A π-benzyl interaction could lead to increased amounts of the 1,1-product by (i) shifting the equilibrium between σ-alkyl complex **63** and **64**/**65** to the right and/or (ii) increasing the rate of oxidative halogenation of **64**/**65** versus **63**.

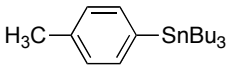
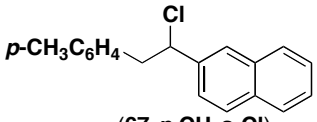
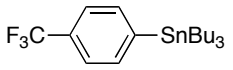
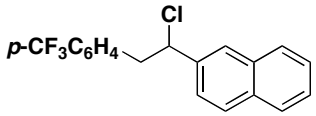
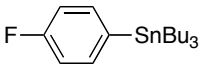
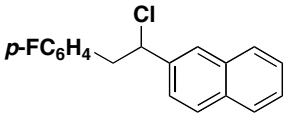
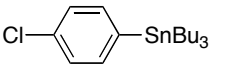
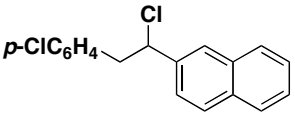
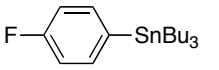
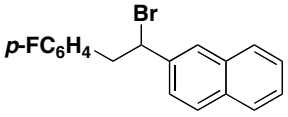
Scheme 25: Proposed Intermediacy of π-Benzyl Species in 1,1-Arylhalogenations



To probe this hypothesis, the Pd-catalyzed reactions of 2-vinylnapthalene (**67**) with a number of electronically different aryltributyltin derivatives and $CuCl_2$ or $CuBr_2$ in Et_2O (Table 5.15) were compared under identical conditions to the styrene reactions in Tables 5.13 and 5.14. In both cases, initial alkene insertion would directly generate a Pd-benzyl or Pd-naphthyl intermediate; therefore, significant quantities of 1,2-arylhalogenated products were expected in both reactions. Indeed, as shown in Tables 5.13-5.15, the expected products were observed. The ratio of 1,2- to 1,1-products with styrene using $CuCl_2$ as the oxidant ranged from 1:1 to 7.6:1 (Table 5.13), while the corresponding reactions with vinylnaphthalene provided a >50:1 ratio of **67-*p*-Ra-X** : **67-*p*-Rb-X** (Table 5.15, entries 1-4). Similarly, the selectivity for the 1,2-product increased from 20:1 (Table 5.14, entry 6) to >50:1 (Table 5.15, entry 5) in going from styrene to vinylnaphthalene with $CuBr_2$ as the oxidant and *p*-fluorophenyltributyl tin as the arylating reagent. Literature reports have shown that π-naphthyl complexes are both more thermodynamically stable and more kinetically reactive than the corresponding π-benzyl species.[19,20,29] As such, this large increase in selectivity between styrene and vinylnaphthalene provides strong support for π-aryl stabilization as a key factor dictating the selectivity of these $CuCl_2$ and $CuBr_2/Et_2O$-mediated arylhalogenations.

Table 5.15: Arylhalogenation of Vinylnaphthalene



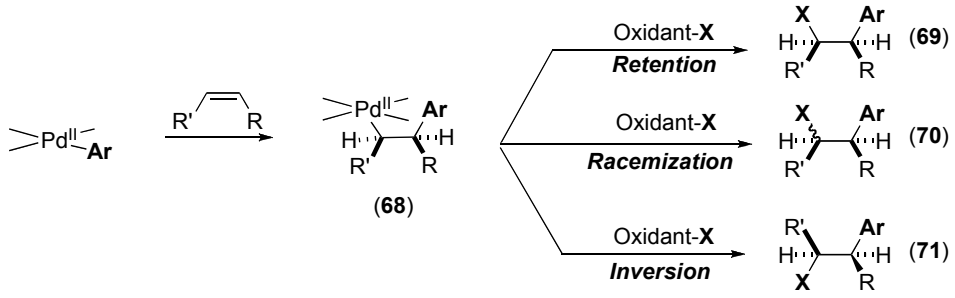
Entry	Oxidant	Tin Reagent	1,2 Product	Yield	1,2:1,1[c]
1	$CuCl_2$		 (67-*p*-CH_3a-Cl)	26%[a]	>50:1
2	$CuCl_2$		 (67-*p*-CF_3a-Cl)	49%[b]	>50:1
3	$CuCl_2$		 (67-*p*-Fa-Cl)	77%[a]	>50:1
4	$CuCl_2$		 (67-*p*-Cla-Cl)	69%[a]	>50:1
5	$CuBr_2$		 (67-*p*-Fa-Br)	48%[a]	>50:1

[a]Yield determined by ^{1}H NMR spectroscopy; [b]Isolated yield; [c]Selectivities determined by ^{1}H NMR spectroscopy

Stereochemistry: Having gained an understanding of the mechanism and selectivities in the arylhalogenation reactions, we next desired to investigate the

stereochemical course of the C–X (X = Cl, Br) bond forming step. The first step of the arylhalogenations described herein is well documented to proceed with *syn* stereochemistry to afford σ-Pd-alkyl intermediates **68** (Scheme 26). In contrast, the subsequent oxidative halogenation of the Pd–C bond in **68** could potentially occur with retention, inversion, or racemization of stereochemistry at the carbon, depending on the substrate, oxidant, and reaction conditions.[30-32] In order, to develop enantioselective arylhalogenation reactions, it would be essential that the oxidative cleavage occurs with either inversion or retention but not racemization. Hence, we wanted to undertake stereochemical studies to gain insight into the product forming oxidative halogenation step in our arylhalogenation reactions.

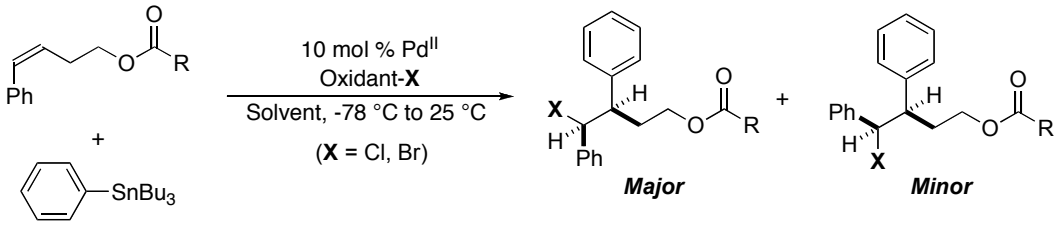
Scheme 26: Possible Stereochemical Outcomes for Arylhalogenations



We began our studies by subjecting the stereochemically pure internal *cis* and *trans* olefin substrates ***cis*-72** and ***trans*-72** to our arylhalogenation conditions with different oxidants. As shown in Tables 5.16 and 5.17, these reactions proceeded to afford significant quantities of the arylhalogenated products under all conditions examined. The reactions with CuX_2 proceed with modest diastereoselectivities. Diastereomer **72a-X** was formed as the major product in the reactions with the olefin ***cis*-72**, and the opposite diastereomer **72b-X** was predominant in reactions with the olefin ***trans*-72** which illustrates that these transformations proceed stereoselectively. Similarly, with $PhICl_2$, the same trend in diastereomer formation was observed with respect to substrate olefin geometry. Interestingly however, in contrast to the reactions with CuX_2, the arylhalogenations of ***cis*-72** and ***trans*-72** with $PhICl_2$ proceeded with excellent levels of diastereoselectivity to afford products **72a-X** and **72b-X** respectively with >20:1

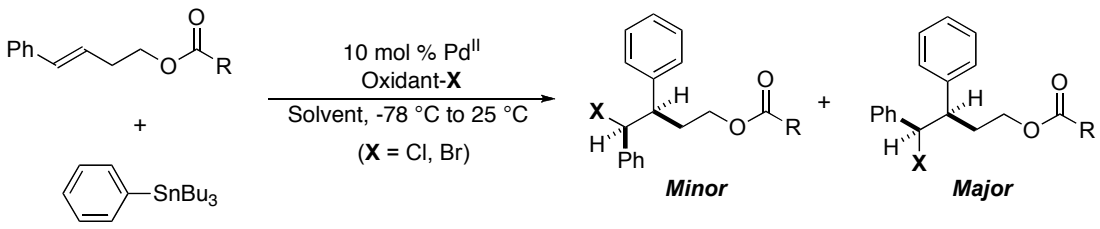
selectivity. Importantly, the relative stereochemistry of product **72a-Cl** was confirmed by X-ray crystallography. The structural assignment for the analogous phenylbrominated product **72a-Br** was made based on the coupling constant analogy between **72a-Cl** and **72a-Br**. However, in order to absolutely confirm the stereochemistry of the products via X-ray crystallography, with $CuBr_2$ as the oxidant the arylbrominations of ***cis*-73** and ***trans*-73** were examined. The stereochemistry of the major diastereomer from the reaction of ***cis*-73** was confirmed using X-ray crystallography analysis.

Table 5.16: Arylhalogenation of *cis*-Olefins



Entry	R	Substrate	Oxidant	Solvent	Yield	Major:Minor
1	biphenyl	***cis*-72**	$CuCl_2$	Et_2O	50%	10:1
2	biphenyl	***cis*-72**	$CuBr_2$	Et_2O	10%	10:1
3	biphenyl	***cis*-72**	$PhICl_2$	CH_2Cl_2	55%	>20:1
4	acetate	***cis*-73**	$CuBr_2$	Et_2O	10%	9:1

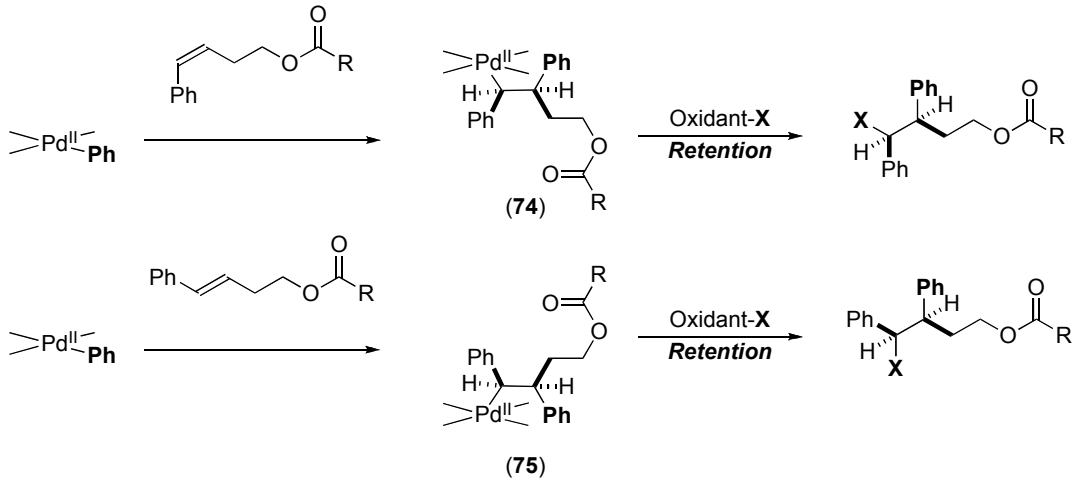
Table 5.17: Arylhalogenation of *trans*-olefins



Entry	R	Substrate	Oxidant	Solvent	Yield	Major:Minor
1	biphenyl	***trans*-72**	Cu**Cl**$_2$	Et_2O	13%	3:1
2	biphenyl	***trans*-72**	Cu**Br**$_2$	Et_2O	13%	2:1
3	biphenyl	***trans*-72**	PhI**Cl**$_2$	CH_2Cl_2	17%	>20:1
4	acetate	***trans*-73**	Cu**Br**$_2$	Et_2O	13%	2:1

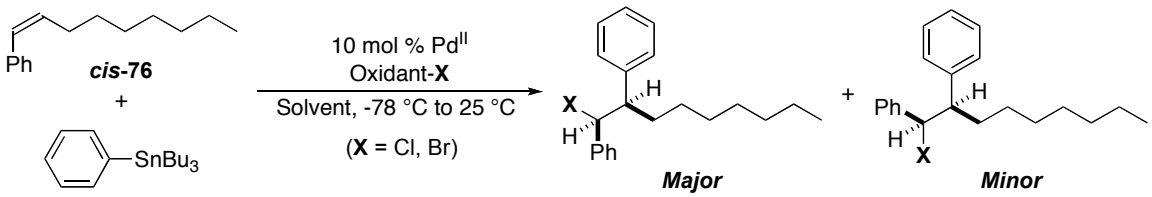
The formation of the major diastereomers in the reactions of ***cis*-72**, ***cis*-73**, ***trans*-73** and ***trans*-72** could be explained by the mechanism depicted in Scheme 27. This mechanism involves transmetallation between $PhSnBu_3$ and the Pd^{II} catalyst to generate the Pd^{II}-phenyl species. *Syn* olefin insertion of the cis or the trans alkenes into the Pd–C bond would then afford intermediates **74** and **75** respectively. The formation of **72a-X** (or **73a-X** for R = acetate) and **72b-X** (or **73b-X** for R = acetate) as the major diastereomers from the reaction of substrates ***cis*-72** (or ***cis*-73**) and ***trans*-72** (or ***trans*-73**), respectively, under our reaction conditions necessitates that the oxidative halogenation of the benzyl Pd-alkyl intermediates **74** and **75** proceeds predominantly with retention of stereochemistry at the carbon.

Scheme 27: Proposed Mechanism for Arylhalogenation of Internal Alkenes



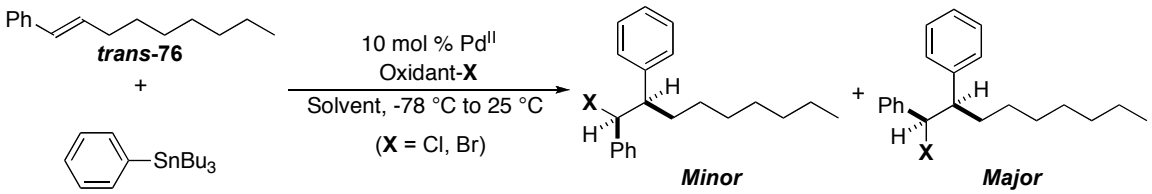
In order to probe whether the carboxylate groups at the terminus of the substrates ***cis*-72**, ***cis*-73**, ***trans*-73** and ***trans*-72** were playing a role in imparting the observed stereoselectivity, we examined the reactions of substrates ***cis*-76** and ***trans*-76**. However, as shown in Tables 5.18 and 5.19, the major diastereomers from the reaction of these substrates also resulted from retention of stereochemistry at oxidative cleavage with all oxidants.

Table 5.18: Arylhalogenation of ***cis*-76**



Entry	Oxidant	Solvent	Yield	Major:Minor
1	Cu**Cl**$_2$	Et_2O	55%	9:1
2	Cu**Br**$_2$	Et_2O	30%	7:1
3	PhI**Cl**$_2$	CH_2Cl_2	59%	12:1

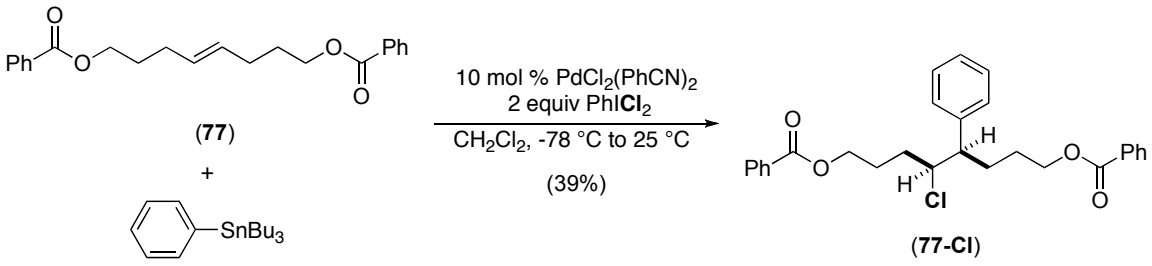
Table 5.19: Arylhalogenation of ***trans*-76**



Entry	Oxidant	Solvent	Yield	Major:Minor
1	Cu**Cl**$_2$	Et_2O	37%	1.3:1
2	Cu**Br**$_2$	Et_2O	15%	2:1
3	PhI**Cl**$_2$	CH_2Cl_2	24%	3:1

Finally, we desired to assess whether these stereochemical results were unique to substrates (such as ***cis*-72**, ***cis*-73**, ***cis*-76**, ***trans*-72**, ***trans*-73** and ***trans*-76**) for which oxidative cleavage occurs at a benzylic position. Hence we studied the arylchlorination of substrate **77** with $PhICl_2$ as the oxidant. As shown in Scheme 28 the reaction of **77** afforded product **77-Cl** in 39% NMR yield as the only diastereomer. X-ray crystallography analysis of the product confirmed that this reaction proceeds with retention of stereochemistry at the carbon at oxidative cleavage.

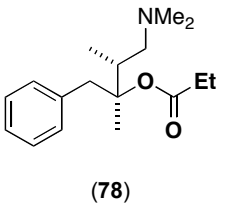
Scheme 28: Arylchlorination of Olefin **77**



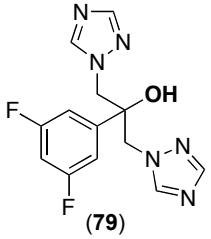
5.5 Conclusions

In summary, we have developed Pd-catalyzed reactions for the arylchlorination and the arybromination of α-olefins by oxidatively intercepting Heck intermediates. Depending on the nature of the oxidant and the reaction conditions, both 1,1- and 1,2-arylhalogenated products can be obtained in good yield and with good to excellent selectivity. The selectivity of these reactions can be tuned rationally (i) by controlling the relative rates of oxidative functionalization versus β-hydride elimination from equilibrating Pd^{II}-alkyl species and (ii) by π-benzyl stabilization of Pd intermediates. Importantly, these reactions form the mechanistic basis for the future development of more synthetically useful aryloxygenated, arylaminated and arylfluorinated products using a broad scope of oxidants and transmetalating reagents. Additionally, the insights gained from the arylhalogenation reactions will be applied toward the development of enantioselective versions of these reactions and for the synthesis of complex biologically active molecules such as **78** and **79** (Scheme 29).

Scheme 29: Examples of Drug Molecules Bearing 1,2- and 1,1-Aryloxygenated Motifs



(**78**)
Darvocet-N
analgesic



(**79**)
Fluconazole
antifungal

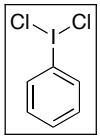
5.6 Experimental Procedure

General Procedures: NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C), a Varian Inova 400 (399.96 MHz for ^{1}H; 100.57 MHz for ^{13}C; 376.34 MHz for ^{19}F), or a Varian Mercury 300 (300.07 MHz for ^{1}H NMR, 75.45 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of

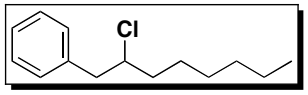
doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer.

Materials and Methods: Substrates **31,**[1] **33,**[2] **34,**[3] **35**[4] and **36**[5] were prepared using literature procedures.[1] Substrate **38** was synthesized by reaction of 5-hexen-1-ol with Ac_2O in pyridine. Substrates **24**, **32**, **37**, **39**, **40**, **42**, **43**, **44**, **45**, **46**, **24-*d*$_2$** and **67** were obtained from commercial sources and used as received. $PhSnBu_3$,[6] *p*-$XPhSnBu_3$ (X = Cl, F, H, CF_3, CH_3 and OMe),[6] 2-naphthylSnBu$_3$,[6] PdCl2$(CH_3CN)_2$ and $PdCl_2(PhCN)_2$[7] were prepared using literature procedures. $PhICl_2$ was prepared via a modification of a literature procedure,[8] was stored at –30 ºC under inert atmosphere, and was prepared fresh every three weeks. NCS and $CuCl_2$ were obtained from Acros Organics and Strem Chemicals and used without further purification. CH_2Cl_2 was obtained from Fisher Chemical and used without further purification. Diethyl ether was purified using an Innovative Technology (IT) solvent purification system composed of activated alumina, copper catalyst, and molecular sieves. 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. HPLC was performed on a Varian ProStar 210 HPLC using Waters µ-Porasil 10µm silica (19 x 300 mm) columns. Melting points were determined with a Mel-Temp 3.0, a Laboratory Devices Inc, USA instrument and are uncorrected. Control reactions (in the absence of Pd catalyst) were run with 1-octene and styrene, with both $PhICl_2$ and $CuCl_2$ and showed none of the desired products. In addition, reactions of **30**, *cis*-stilbene and *trans*-stilbene with either $PhICl_2$, $CuCl_2$ or $CuBr_2$ did not lead to any of the desired products.

Experimental Procedures

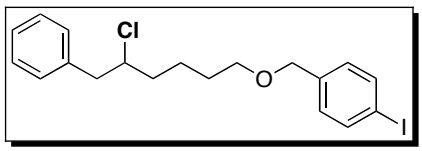


A solution of iodobenzene (4 mL) in CH_2Cl_2 (80 mL) was cooled to 0 ºC. Chlorine gas was bubbled through this solution for 10 min, and the resulting reaction mixture was stirred at 0 ºC for an additional 0.5 h. The yellow solid that precipitated during the reaction was collected on a frit and washed with copious hexane. $PhICl_2$ was obtained as a light yellow solid (9.53 g, 97% yield).



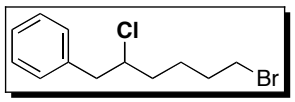
$PdCl_2(PhCN)_2$ (34.2 mg, 0.089 mmol, 10 mol %) was weighed into a 50 mL Schlenk flask. $PhICl_2$ (980 mg, 3.56 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate (100 mg, 0.891 mmol, 1.00 equiv) in CH_2Cl_2 (28 mL) was added. $PhSnBu_3$ (425 mg, 1.159 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (425 mg, 1.158 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 10 : 1 ratio of **24a-Cl** : **24b-Cl**. The product was purified by chromatography on silica gel using 0.5% Et_3N in hexanes. The product was isolated as a clear oil (140 mg, 71% yield, R_f = 0.43 in hexanes). Note: The isolated product contained 88% of **24a-Cl** and 7% of **24b-Cl** (13 : 1 ratio of **24a-Cl** : **24b-Cl**) as well as traces of the 2,1 isomer (4%) and the 1,3 isomer (1%). Samples of **24a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters µ-porasil 19.1 mm). ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (t, J = 7.50 Hz, 2H), 7.29-7.23 (multiple peaks, 3H), 4.15-4.10 (m, 1H), 3.07 (d, J = 7.00 Hz, 2H), 1.83-1.77 (m, 1H),

1.75-1.67 (m, 1H), 1.64-1.57 (m, 1H), 1.48-1.40 (m, 1H), 1.37-1.26 (multiple peaks, 6H), 0.91 (t, J = 7.00 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.11, 129.34, 128.36, 126.69, 64.06, 45.03, 37.68, 31.68, 28.74, 26.41, 22.56, 14.04. HRMS EI (m/z): [M^+] Calcd for $C_{14}H_{21}Cl$, 224.1332; Found, 224.1337.

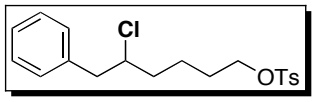


$PdCl_2(PhCN)_2$ (12.1 mg, 0.032 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (348 mg, 1.27 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **31** (100 mg, 0.316 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) was added. $PhSnBu_3$ (150.9 mg, 0.411 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (150.9 mg, 0.411 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 10 : 1 ratio of **31a-Cl** : **31b-Cl**. The product was purified by chromatography on silica gel using 1.5% ethyl acetate/98.5% hexanes. The product was isolated as a clear oil (96.5 mg, 72% yield, R_f = 0.13 in 2% ethyl acetate/98% hexanes). Note: The isolated product contained 80% of **31a-Cl** and 10% of **31b-Cl** (8 : 1 ratio of **31a-Cl** : **31b-Cl**) as well as traces of the 2,1 isomer (6%) and the 1,3 isomer (4%). Samples of **31a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (1.5% ethyl acetate/98.5% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 8.50 Hz, 2H), 7.31 (t, J = 7.49 Hz, 2H), 7.26-7.23 (m, 1H), 7.20 (d, J = 7.75 Hz, 2H), 7.07 (d, J = 8.00 Hz, 2H), 4.42 (s, 2H), 4.12-4.06 (m, 1H), 3.44 (t, J = 6.25 Hz, 2H), 3.05 (dd, J = 14.24, 7.24 Hz, 1H), 3.01 (dd, J = 14.00, 6.50 Hz, 1H), 1.82-1.75 (m, 1H), 1.73-1.47 (multiple peaks, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.31, 137.98, 137.46, 129.46, 129.34, 128.41, 126.75, 92.88, 72.22, 70.22, 63.76,

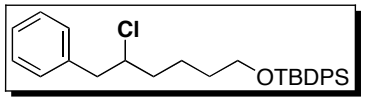
45.04, 37.36, 29.15, 23.21. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{19}H_{22}IClO$, 451.0302; Found, 451.0315.



$PdCl_2(PhCN)_2$ (23.5 mg, 0.061 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (675 mg, 2.45 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **32** (100 mg, 0.613 mmol, 1.00 equiv) in CH_2Cl_2 (9.6 mL) was added. $PhSnBu_3$ (293 mg, 0.797 mmol, 1.3 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (293 mg, 0.797 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 12 : 1 ratio of **32a-Cl** : **32b-Cl**. The product was purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. The product was isolated as a clear oil (140 mg, 84% yield, R_f = 0.18 in hexanes). Note: The isolated product contained 80% of **32a-Cl** and 6% of **32b-Cl** (13 : 1 ratio of **32a-Cl** : **32b-Cl**) as well as traces of the 2,1 isomer (6%) and the 1,3 isomer (8%). Samples of **32a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.74 Hz, 2H), 7.25 (t, *J* = 7.74 Hz, 1H), 7.21 (t, *J* = 8.00 Hz, 2H), 4.12-4.07 (m, 1H), 3.39 (t, *J* = 6.75 Hz, 2H), 3.07 (dd, *J* = 14.24, 7.74 Hz, 1H, approximate values due to second order effects), 3.03 (dd, *J* = 14.50, 6.99 Hz, 1H, approximate values due to second order effects), 1.92-1.67 (multiple peaks, 5H), 1.60-1.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.78, 129.33, 128.45, 126.83, 63.43, 44.97, 36.62, 33.34, 32.19, 25.14. HRMS EI (m/z): $[M^+]$ Calcd for $C_{12}H_{16}ClBr$, 274.0124; Found, 274.0118.

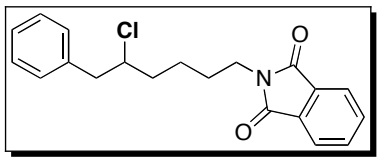


$PdCl_2(PhCN)_2$ (15.0 mg, 0.039 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (432 mg, 1.57 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **33** (100 mg, 0.393 mmol, 1.00 equiv) in CH_2Cl_2 (6.1 mL) was added. $PhSnBu_3$ (188 mg, 0.511 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (188 mg, 0.511 mmol, 1.3 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a >20 : 1 ratio of **33a-Cl** : **33b-Cl**. The product was purified by chromatography on silica gel using 8% ethyl acetate/92% hexanes. The product was isolated as a clear viscous oil (137 mg, 96% yield, R_f = 0.20 in 8% ethyl acetate/92% hexanes). Note: The isolated product contained 84% of **33a-Cl** and 9% of **33b-Cl** (9 : 1 ratio of **33a-Cl** : **33b-Cl**) as well as traces of the 2,1 isomer (7%). Samples of **33a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (3% ethyl acetate/97% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.00 Hz, 2H), 7.35-7.30 (muliple peaks, 4H), 7.27-7.23 (m, 1H), 7.18 (d, *J* = 8.50 Hz, 2H), 4.05-4.00 (multiple peaks, 3H), 3.02 (dd, *J* = 14.24, 7.24 Hz, 1H), 2.97 (dd, *J* = 14.00, 6.49 Hz, 1H), 2.45 (s, 3H), 1.76-1.56 (multiple peaks, 5H), 1.46-1.39 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.74, 137.73, 133.11, 129.84, 129.29, 128.45, 127.89, 126.83, 70.20, 63.35, 44.95, 36.82, 28.33, 22.48, 21.64. IR (thin film): 2952, 1358, 1176 cm^{-1}. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{19}H_{23}ClO_3S$, 389.0954; Found, 389.0959.



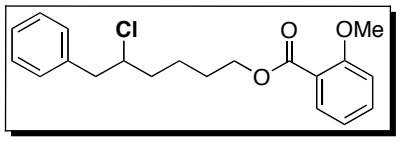
$PdCl_2(PhCN)_2$ (11.3 mg, 0.029 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (325 mg, 1.18 mmol, 4.00 equiv) was added to this flask in the glove box.

The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **34** (100 mg, 0.295 mmol, 1.00 equiv) in CH_2Cl_2 (9.2 mL) was added. $PhSnBu_3$ (141 mg, 0.384 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (141 mg, 0.384 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 10 : 1 ratio of **34a-Cl** : **34b-Cl**. The product was purified by chromatography on silica gel using 1% ethyl acetate/99% hexanes. The product was isolated as a clear oil (122 mg, 92% yield, R_f = 0.15 in 1% ethyl acetate/99% hexanes). Note: The isolated product contained 89% of **34a-Cl** and 8% of **34b-Cl** (11 : 1 ratio of **34a-Cl** : **34b-Cl**) as well as traces of the 2,1 isomer (3%). Samples of **34a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (0.4% ethyl acetate/99.6% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, J = 7.80, 1.40 Hz, 4H), 7.42-7.32 (multiple peaks, 6H), 7.28 (dd, J = 7.20, 1.40 Hz, 2H), 7.22 (dd, J = 6.00, 1.40 Hz, 1H), 7.17 (d, J = 7.20 Hz, 2H), 4.08-4.01 (m, 1H), 3.62 (t, J = 6.20 Hz, 2H), 2.99 (d, J = 6.80 Hz, 2H), 1.75-1.44 (multiple peaks, 6H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.04, 135.58, 134.03, 129.54, 129.36, 128.38, 127.60, 126.71, 63.87, 63.61, 44.96, 37.35, 31.96, 26.89, 22.79, 19.22. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{28}H_{35}ClOSi$, 473.2043; Found, 473.2057.



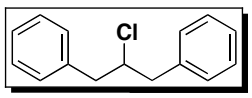
$PdCl_2(PhCN)_2$ (8.36 mg, 0.022 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (120 mg, 0.436 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **35** (50.0 mg, 0.218 mmol, 1.00 equiv) in CH_2Cl_2 (3.4 mL) was added. $PhSnBu_3$ (104 mg, 0.284 mmol, 1.30 equiv) was added,

and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (104 mg, 0.284 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 6 : 1 ratio of **35a-Cl** : **35b-Cl**. The product was purified by chromatography on silica gel using 1% ethyl acetate/99% hexanes. The product was isolated as a clear viscous oil (62.4 mg, 85% yield, R_f = 0.14 in 8% ethyl acetate/92% hexanes). Note: The isolated product contained 80% of **35a-Cl** and 13% of **35b-Cl** (6 : 1 ratio of **35a-Cl** : **35b-Cl**) as well as traces of the 2,1 isomer (2%) and the 1,3 isomer (5%). Samples of **35a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (2% ethyl acetate/98% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, *J* = 6.00, 3.20 Hz, 2H), 7.86 (dd, *J* = 6.00, 3.60 Hz, 2H), 7.31-7.11 (multiple peaks, 5H), 4.07-4.00 (m, 1H), 3.64 (t, *J* = 6.80 Hz, 2H), 3.01 (dd, *J* = 14.00, 7.60 Hz, 1H), 2.97 (dd, *J* = 14.00, 6.80 Hz, 1H), 1.83-1.75 (m, 1H), 1.72-1.56 (multiple peaks, 4H), 1.50-1.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.39, 137.88, 133.90, 132.12, 129.32, 128.41, 126.77, 123.21, 63.51, 45.04, 37.73, 37.07, 28.04, 23.76. IR (thin film): 2928, 1716, 1371 cm^{-1}. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{20}H_{20}ClNO_2$, 364.1080; Found, 364.1074.



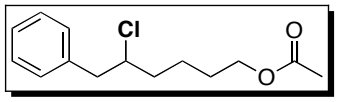
$PdCl_2(PhCN)_2$ (16.4 mg, 0.043 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (469 mg, 1.71 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **36** (100 mg, 0.427 mmol, 1.00 equiv) in CH_2Cl_2 (13 mL) was added. $PhSnBu_3$ (204 mg, 0.555 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (204 mg, 0.555 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room

temperature over 5 h and stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 8 : 1 ratio of **36a-Cl** : **36b-Cl**. The product was purified by chromatography on silica gel using 8% ethyl acetate/92% hexanes. The product was isolated as a clear viscous oil (126 mg, 86% yield, R_f = 0.19 in 8% ethyl acetate/92% hexanes). Note: The isolated product contained 85% of **36a-Cl** and 10% of **36b-Cl** (8 : 1 ratio of **36a-Cl** : **36b-Cl**) as well as traces of the 2,1 isomer (5%). Samples of **36a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (3% ethyl acetate/97% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 7.79, 1.80 Hz, 1H), 7.46 (m, 1H), 7.30 (t, *J* = 7.20 Hz, 2H), 7.26-7.20 (multiple peaks, 3H), 6.98 (ddd, *J* = 8.00, 4.40, 1.19 Hz, 2H), 4.29 (t, *J* = 6.19 Hz, 2H), 4.15-4.08 (m, 1H), 3.90 (s, 3H), 3.07 (dd, *J* = 14.00, 7.20 Hz, 1H), 3.03 (dd, *J* = 14.00, 6.40 Hz, 1H), 1.88-1.69 (multiple peaks, 5H), 1.64-1.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.30, 159.12, 137.87, 133.41, 131.54, 129.33, 128.42, 126.78, 120.31, 120.10, 112.00, 64.53, 63.69, 55.95, 45.03, 37.17, 28.20, 23.09. IR (thin film): 2922, 1723, 1249 cm^{-1}. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{20}H_{23}ClO_3$, 369.1233; Found, 369.1228.



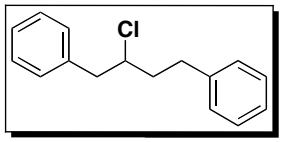
$PdCl_2(PhCN)_2$ (32.4 mg, 0.085 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (931 mg, 3.38 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **37** (100 mg, 0.846 mmol, 1.00 equiv) in CH_2Cl_2 (13 mL) was added. $PhSnBu_3$ (404 mg, 1.10 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (404 mg, 1.10 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$,

filtered, and concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 5 : 1 ratio of **37a-Cl** : **37b-Cl**. The product was purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. The product was isolated as a clear oil (131 mg, 68% yield, R_f = 0.25 in hexanes). Note: The isolated product contained 80% of **37a-Cl** and 14% of **37b-Cl** (6 : 1 ratio of **37a-Cl** : **37b-Cl**) as well as traces of the 2,1 isomer (6%). Samples of **37a-Cl** for HRMS and NMR analysis were obtained upon further purification of the isolated product by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.19 (multiple peaks, 10H), 4.33-4.26 (m, 1H), 3.10 (dd, *J* = 14.40, 5.60 Hz, 2H), 3.00 (dd, *J* = 14.00, 8.00 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.84, 129.33, 128.42, 126.80, 63.95, 44.29. HRMS EI (m/z): [M^+] Calcd for $C_{15}H_{15}Cl$, 230.0862; Found, 230.0860.



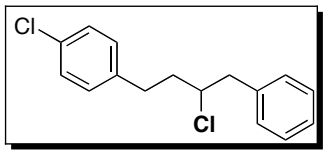
$PdCl_2(PhCN)_2$ (26.9 mg, 0.070 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (387 mg, 1.41 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **38** (100 mg, 0.704 mmol, 1.00 equiv) in CH_2Cl_2 (11 mL) was added. $PhSnBu_3$ (336 mg, 0.915 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (336 mg, 0.915 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 10 : 1 ratio of **38a-Cl** : **38b-Cl**. The product was purified by chromatography on silica gel using 3% ethyl acetate/97% hexanes. The product was isolated as a clear oil (152 mg, 86% yield, R_f = 0.13 in 3% ethyl acetate/97% hexanes). Note: The isolated product contained 85% of **38a-Cl** and 9% of **38b-Cl** (10 : 1 ratio of **38a-Cl** : **38b-Cl**) as well as traces of the 2,1 isomer (6%). Samples of **38a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (1.5% ethyl acetate/98.5% hexanes, 20

mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.40 Hz, 2H), 7.23-7.21 (m, 1H), 7.17 (d, *J* = 7.20 Hz, 2H), 4.08-4.00 (m, 1H), 4.01 (t, *J* = 6.20 Hz, 2H), 3.03 (dd, *J* = 13.79, 7.00 Hz, 1H, approximate values due to second order effects), 2.98 (dd, *J* = 14.20, 6.59 Hz, 1H, approximate values due to second order effects), 2.00 (s, 3H), 1.80-1.42 (multiple peaks, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.14, 137.84, 129.31, 128.42, 126.80, 64.21, 63.58, 45.04, 37.11, 28.05, 22.98, 20.97. IR (thin film): 2923, 1741, 1238 cm^{-1}. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{14}H_{19}ClO_2$, 277.0971; Found, 277.0958.

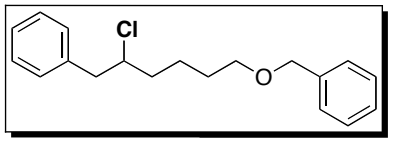


$PdCl_2(PhCN)_2$ (29.0 mg, 0.076 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (832 mg, 3.02 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **39** (100 mg, 0.756 mmol, 1.00 equiv) in CH_2Cl_2 (12 mL) was added. $PhSnBu_3$ (361 mg, 0.983 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (361 mg, 0.983 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 11 : 1 ratio of **39a-Cl** : **39b-Cl**. The product was purified by chromatography on silica gel using 0.5% Et_3N in hexanes. The product was isolated as a clear oil (137 mg, 75% yield, R_f = 0.23 in hexanes). Note: The isolated product contained 86% of **39a-Cl** and 6% of **39b-Cl** (14 : 1 ratio of **39a-Cl** : **39b-Cl**) as well as traces of the 2,1 isomer (6%) and the 1,2-dichloro product (1%). Samples of **39a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.14 (multiple peaks, 10H), 4.11-4.03 (m, 1H), 3.09-3.00 (multiple peaks, 2H), 2.95-2.89 (m, 1H), 2.76-2.69 (m, 1H), 2.11-1.92

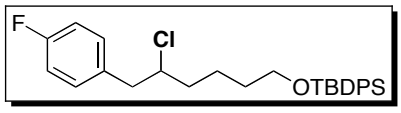
(multiple peaks, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.96, 137.74, 129.34, 128.50, 128.45, 128.39, 126.77, 126.05, 62.95, 44.97, 39.21, 32.63.



$PdCl_2(PhCN)_2$ (23.0 mg, 0.060 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (660 mg, 2.40 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **40** (100 mg, 0.600 mmol, 1.00 equiv) and CH_2Cl_2 (9.4 mL) were added. $PhSnBu_3$ (286 mg, 0.780 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (286 mg, 0.780 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 3 : 1 ratio of **40a-Cl** : **40b-Cl**. The product was purified by chromatography on silica gel using 1% Et_3N/99% hexanes. The product was isolated as a clear oil (147 mg, 89% yield, R_f = 0.33 in hexanes). Note: The isolated product contained 71% of **40a-Cl** and 22% of **40b-Cl** (3 : 1 ratio of **40a-Cl** : **40b-Cl**) as well as traces of the 2,1 isomer (7%). Samples of **40a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.18 (multiple peaks, 5H), 7.14 (d, J = 8.8 Hz, 4H), 7.04 (d, J = 8.8 Hz, 4H), 4.03-3.96 (m, 1H), 3.05 (dd, J = 14.0, 7.2 Hz, 1H), 2.99 (dd, J = 14.0, 6.4 Hz, 1H), 2.89-2.82 (m, 1H), 2.71-2.64 (m, 1H), 2.05-1.86 (multiple peaks, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.37, 137.61, 131.82, 129.85, 129.32, 128.56, 128.44, 126.85, 62.66, 45.01, 38.99, 31.97. HRMS EI (m/z): $[M]^+$ Calcd for $C_{16}H_{16}Cl_2$, 278.0629; Found, 278.0634.

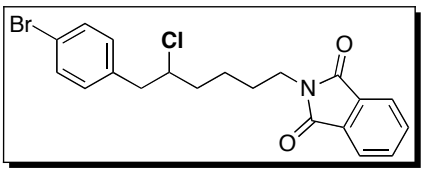


$PdCl_2(PhCN)_2$ (20.1 mg, 0.052 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (289 mg, 1.05 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **41** (100 mg, 0.525 mmol, 1.00 equiv) and CH_2Cl_2 (8.2 mL) were added. $PhSnBu_3$ (251 mg, 0.766 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (251 mg, 0.766 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 7:1 ratio of **41a-Cl** : **41b-Cl**. The product was purified by chromatography on silica gel using 2% EtOAc/1% Et_3N/97% hexanes. The product was isolated as a clear oil (131 mg, 83% yield, R_f = 0.14 in 2% EtOAc/98% hexanes). Note: The isolated product contained 88% of **41a-Cl** and 7% of **41b-Cl** (12 : 1 ratio of **41a-Cl** : **41b-Cl**) as well as traces of the 2,1 isomer (5%). Samples of **41a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (0.2% EtOAc/99.8% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.19 (multiple peaks, 8H), 7.17 (d, J = 7.2 Hz, 2H), 4.45 (s, 2H), 4.10-4.02 (m, 1H), 3.43 (t, J = 6.4 Hz, 2H), 3.00 (d, J = 6.8 Hz, 2H), 1.80-1.44 (multiple peaks, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.52, 137.98, 129.32, 128.37, 128.35, 127.62, 127.51, 126.71, 72.91, 70.05, 63.83, 44.98, 37.39, 29.17, 23.21.



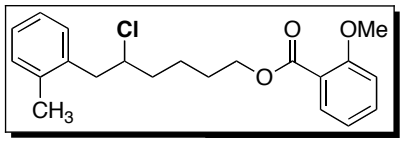
$PdCl_2(PhCN)_2$ (11.3 mg, 0.030 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (162 mg, 1.182 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **34** (100 mg, 0.295 mmol, 1.00 equiv) in CH_2Cl_2 (4.6 mL) was added. *p*-$FPhSnBu_3$ (148 mg, 0.384 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of *p*-$FPhSnBu_3$ (148 mg, 0.384 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was

filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 10:1 ratio of **34-*p*-F-a-Cl** : **34-*p*-F-b-Cl**. The product was purified by chromatography on silica gel using 0.5% EtOAc/0.5% Et_3N/99% hexanes. The product was isolated as a clear oil (116 mg, 84% yield, R_f = 0.37 in 1% EtOAc/99% hexanes). Note: The isolated product contained 81% of **34-*p*-F-a-Cl** and 7% of **34-*p*-F-b-Cl** (11 : 1 ratio of **34-*p*-F-a-Cl** and **34-*p*-F-b-Cl**) as well as the 2,1 isomer (7%) and the 1,2-dichloro product (5%). Samples of **34-*p*-F-a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (0.2 % EtOAc/99.8% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.67-7.64 (multiple peaks, 4H), 7.44-7.35 (multiple peaks, 6H), 7.18-7.14 (multiple peaks, 2H), 6.98 (tt, J = 8.40, 3.2 Hz, 2H), 4.05-3.99 (m, 1H), 3.65 (t, J = 6.40 Hz, 2H), 3.02-2.93 (multiple peaks, 2H), 1.75-1.49 (multiple peaks, 6H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.75 ($^1J_{C\text{-}F}$ = 243 Hz), 135.56, 133.98, 133.65 ($^4J_{C\text{-}F}$ = 3.0 Hz), 130.81 ($^3J_{C\text{-}F}$ = 8.5 Hz) 129.55, 127.60, 115.17 ($^2J_{C\text{-}F}$ = 21Hz) 63.83, 63.55, 43.99, 37.31, 31.90, 26.86, 22.78, 19.20. ^{19}F NMR (376 MHz, $CDCl_3$): δ -116.05 – -116.34. HRMS EI (m/z): $[M+H]^+$ Calcd for $C_{28}H_{34}ClFOSi$, 469.2129; Found, 469.2113.



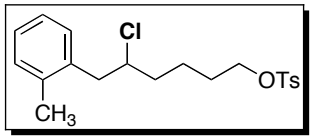
$PdCl_2(PhCN)_2$ (16.7 mg, 0.044 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (240 mg, 0.872 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **35** (100 mg, 0.436 mmol, 1.00 equiv) in CH_2Cl_2 (6.8 mL) was added. *p*-$BrPhSnBu_3$ (252 mg, 0.567 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (252 mg, 0.567 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 8 : 1 ratio

of **35-*p*-Br-a-Cl** : **35-*p*-Br-b-Cl**. The product was purified by chromatography on silica gel using 7% EtOAc/1% Et_3N/92% hexanes. The product was isolated as a clear viscous oil (178 mg, 96% yield, R_f = 0.12 in 8% EtOAc/92% hexanes). Note: The isolated product contained 75% of **35-*p*-Br-a-Cl** and 11% of **35-*p*-Br-b-Cl** (7 : 1 ratio of **35-*p*-Br-a-Cl** and **35-*p*-Br-b-Cl**) as well as traces of the 2,1 isomer (5%) and the 1,2-dichloro product (9%). Samples of **35-*p*-Br-a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (5% EtOAc/95% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (br s, 2H), 7.70 (br s, 2H), 7.40 (d, *J* = 8.40 Hz, 2H), 7.06 (d, *J* = 7.60 Hz, 2H), 4.06-3.96 (m, 1H), 3.66 (t, *J* = 6.80 Hz, 2H), 3.01-2.91 (multiple peaks, 2H), 1.81-1.60 (multiple peaks, 5H), 1.50-1.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.39, 136.78, 133.92, 132.09, 131.49, 131.05, 123.21, 120.71, 63.07, 44.28, 37.65, 37.13, 27.96, 23.70. HRMS Electrospray: $[M+Na]^+$ Calcd for $C_{20}H_{19}BrClNO_2$, 442.0185; Found, 442.0200.



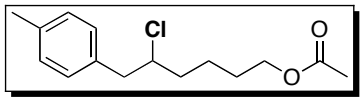
$PdCl_2(PhCN)_2$ (9.05 mg, 0.024 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (130 mg, 0.472 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **36** (55.3 mg, 0.236 mmol, 1.00 equiv) in CH_2Cl_2 (3.7 mL) was added. *o*-$CH_3PhSnBu_3$ (117mg, 0.307 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (117mg, 0.307 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 10:1 ratio of **36-*o*-CH_3a-Cl** : **35-*o*-CH_3b-Cl**. The product was purified by chromatography on silica gel using 7% EtOAc/1% Et_3N/92% hexanes. The product was isolated as a clear viscous oil (60.3 mg, 96% yield, R_f = 0.12 in 8% EtOAc/92% hexanes). Note: The isolated product contained 80% of **36-*o*-CH_3a-Cl** and 8% of **36-*o*-CH_3b-Cl** (10 : 1 ratio

of **36-*o*-CH_3a-Cl** : **36-*o*-CH_3b-Cl**) as well as the 2,1 isomer (12%) and the 1,2-dichloro product (0.3%). Samples of **36-*o*-CH_3a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (5% EtOAc/95% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 7.80, 1.60 Hz, 1H), 7.47-7.42 (m, 1H), 7.15-7.12 (multiple peaks, 4H), 6.98-6.94 (multiple peaks, 2H), 4.28 (t, *J* = 6.80 Hz, 2H), 4.12-4.05 (m, 1H), 3.88 (s, 3H), 3.10 (dd, *J* = 14.00, 7.60 Hz, 1H), 3.02 (dd, *J* = 14.00, 6.80 Hz, 1H), 2.31 (s, 3H), 1.90-1.60 (multiple peaks, 6H). No further characterization was obtained because the 1,2-product was contaminated with significant amounts of the corresponding 2,1-isomer.

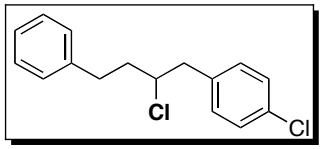


$PdCl_2(PhCN)_2$ (7.50 mg, 0.019 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (108 mg, 0.393 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **33** (50.0 mg, 0.196 mmol, 1.00 equiv) in CH_2Cl_2 (3.1 mL) was added. *o*-$CH_3PhSnBu_3$ (97.4 mg, 0.256 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (97.4 mg, 0.256 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 7 : 1 ratio of **33-*o*-CH_3a-Cl** : **33-*o*-CH_3b-Cl**. The product was purified by chromatography on silica gel using 8% EtOAc/1% Et_3N/91% hexanes. The product was isolated as a clear viscous oil (64.9 mg, 86% yield, R_f = 0.24 in 8% EtOAc/92% hexanes). Note: The isolated product contained 79% of **33-*o*-CH_3a-Cl** and 7% of **33-*o*-CH_3b-Cl** (11 : 1 ratio of **33-*o*-CH_3a-Cl** : **33-*o*-CH_3b-Cl**) as well as significant quantities of the 2,1 isomer (14%). Samples of **33-*o*-CH_3a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (3% EtOAc/97% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.00 Hz, 2H), 7.35 (d, *J* = 7.50 Hz,

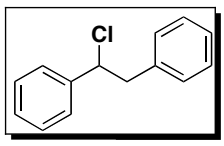
2H), 7.20-7.19 (multiple peaks, 4H), 4.05-4.00 (m, 1H), 3.08 (dd, J = 14.00, 7.50 Hz, 2H), 2.99 (dd, J = 14.50, 6.50 Hz, 1H), 2.46 (s, 3H), 2.33 (s, 3H), 1.78-1.60 (multiple peaks, 5H), 1.50-1.40 (m, 1H). Carbon was not obtained because the 1,2-product was contaminated with significant quantities of the corresponding 2,1-isomer.



$PdCl_2(PhCN)_2$ (26.9 mg, 0.070 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (387 mg, 1.41 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and a solution of substrate **38** (100 mg, 0.703 mmol, 1.00 equiv) in CH_2Cl_2 (11 mL) was added. *p*-$CH_3PhSnBu_3$ (349 mg, 0.914 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (349 mg, 0.914 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 5 : 1 ratio of **38-*p*-CH$_3$a-Cl** : **38-*p*-CH$_3$b-Cl**. The product was purified by chromatography on silica gel using 1.5% EtOAc/1% Et_3N/98% hexanes. The product was isolated as a clear viscous oil (121 mg, 66% yield, R_f = 0.11 in 2.5% EtOAc/97.5% hexanes). Note: The isolated product contained 73% of **38-*p*-CH$_3$a-Cl** and 15% of **38-*p*-CH$_3$b-Cl** (5 : 1 ratio of **38-*p*-CH$_3$a-Cl** : **38-*p*-CH$_3$b-Cl**) as well as traces of the 2,1 isomer (10%) and the β-hydride product (3%). Samples of **38-*p*-CH$_3$a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (1% EtOAc/99% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.06 (multiple peaks, 4H), 4.08-4.01 (multiple peaks, 3H), 3.04-2.93 (multiple peaks, 2H), 2.31 (s, 3H), 2.02 (s, 3H), 1.80-1.43 (multiple peaks, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.15, 136.37, 134.77, 129.18, 129.12, 64.25, 63.78, 44.63, 37.06, 28.07, 22.99, 21.06, 20.97. HRMS EI (m/z): [M^+] Calcd for $C_{15}H_{21}ClO_2$, 268.1230; Found, 268.1232.

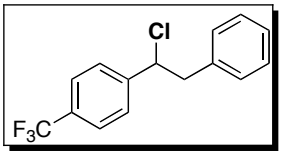


$PdCl_2(PhCN)_2$ (29.0 mg, 0.060 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (832 mg, 3.02 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **39** (100 mg, 0.980 mmol, 1.00 equiv) and CH_2Cl_2 (12 mL) were added. *p*-$ClPhSnBu_3$ (395 mg, 0.980 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of *p*-$ClPhSnBu_3$ (395 mg, 0.980 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 2 : 1 ratio of **39-*p*-Cla-Cl**: (**39-*p*-Clb-Cl** + **39-*p*-Cld-Cl)**. The product was purified by chromatography on silica gel using 1% Et_3N/99% hexanes. The product was isolated as a clear oil (137 mg, 66% yield, R_f = 0.33 in hexanes). Note: The isolated product contained 68% of **39-*p*-Cla-Cl** and 29% of **39-*p*-Clb-Cl** + **39-*p*-Cld-Cl** (2 : 1 ratio of **39-*p*-Cla-Cl**: (**39-*p*-Clb-Cl** + **39-*p*-Cld-Cl**) as well as traces of the 2,1 isomer (3%). Samples of **39-*p*-Cla-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.18 (multiple peaks, 5H), 7.14 (d, *J* = 8.8 Hz, 4H), 7.04 (d, *J* = 8.8 Hz, 4H), 4.03-3.96 (m, 1H), 3.05 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.99 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.89-2.82 (m, 1H), 2.71-2.64 (m, 1H), 2.05-1.86 (multiple peaks, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.37, 137.61, 131.82, 129.85, 129.32, 128.56, 128.44, 126.85, 62.66, 45.01, 38.99, 31.97. HRMS EI (m/z): $[M]^+$ Calcd for $C_{16}H_{16}Cl_2$, 278.0629; Found, 278.0642.



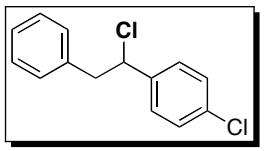
$PdCl_2(PhCN)_2$ (18.4 mg, 0.050 mmol, 5 mol %) was weighed into a 25 mL Schlenk flask. $CuCl_2$ (516 mg, 3.84 mmol, 4.00 equiv) was added to this flask in the glove box. The

flask was sealed with a rubber septum. The flask was cooled to 0 °C, and substrate **42** (100 mg, 0.960 mmol, 1.00 equiv) and Et_2O (30 mL) was added. $PhSnBu_3$ (458 mg, 1.25 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was extracted with 1 M aqueous KF solution. The organic layers were extracted once with brine, dried over MgSO4 and filtered. The filtrate was concentrated and purified by chromatography on silica gel using hexanes. The product **42a-Cl** was isolated as a clear oil (126 mg, 60% yield, R_f = 0.16 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.18 (multiple peaks, 8H), 7.08 (dd, J = 8.4, 2.0 Hz, 2H), 5.02 (t, *J* = 7.6 Hz, 1H), 3.37 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.32 (dd, *J* = 14.0, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.11, 137.43, 129.39, 128.53, 128.30, 127.11, 126.80, 64.12, 46.47. One of the carbons is coincidentally overlapping. HRMS EI (m/z): $[M]^+$ Calcd for $C_{14}H_{13}Cl$, 216.0706; Found, 216.0703.

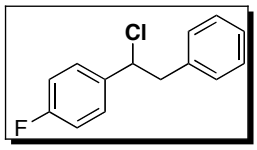


$PdCl_2(PhCN)_2$ (22.2 mg, 0.058 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (319 mg, 1.16 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **43** (100 mg, 0.581 mmol, 1.00 equiv) and Et_2O (18 mL) was added. $PhSnBu_3$ (277 mg, 0.755 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. The product **43a-Cl** was isolated as a clear oil (127 mg, 78% yield, R_f = 0.21 in hexanes). ^{1}H NMR (400 MHz, acetone *d*$_6$): δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.28-7.20 (multiple peaks, 3H), 7.08 (d, *J* = 7.2 Hz, 2H), 5.07 (t, *J* = 7.2 Hz, 1H), 3.40 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.30 (dd, *J* = 14.0, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.90, 136.71, 130.39 ($^2J_{C\text{-}F}$ = 32 Hz), 129.37, 128.44,

127.58, 127.07, 125.50 ($^3J_{C\text{-}F}$ = 3.7 Hz), 123.91 ($^1J_{C\text{-}F}$ = 270 Hz), 62.86, 46.40. HRMS EI (m/z): $[M]^+$ Calcd for $C_{15}H_{12}ClF_3$, 284.0580; Found, 284.0581.

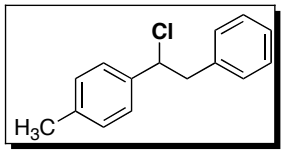


$PdCl_2(PhCN)_2$ (27.7 mg, 0.072 mmol, 10 mol %) and $PhICl_2$ (397 mg, 1.44 mmol, 2.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (20 mL) was added in the glove box, and the flask was cooled to 0 °C. Substrate **44** (100 mg, 0.721 mmol, 1.00 equiv) and $PhSnBu_3$ (344 mg, 0.938 mmol, 1.30 equiv) in dry Et_2O (2 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **44a-Cl** was isolated as a clear oil (121 mg, 67% yield, R_f = 0.20 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.29 (multiple peaks, 7H), 7.04 (d, *J* = 7.34 Hz, 2H), 4.98 (t, *J* = 7.39 Hz, 1H), 3.35 (dd, *J* = 13.79, 7.39 Hz, 1H), 3.25 (dd, *J* = 14.00, 7.20 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.56, 136.97, 134.03, 129.38, 128.69, 128.55, 128.40, 126.96, 63.08, 46.48. HRMS EI (m/z): $[M]^+$ Calcd for $C_{14}H_{12}Cl_2$, 250.0316; Found, 250.0324.

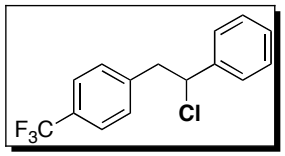


$PdCl_2(PhCN)_2$ (31.4 mg, 0.082 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (450 mg, 1.64 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **45** (100 mg, 0.819 mmol, 1.00 equiv) and Et_2O (25 mL) was added. $PhSnBu_3$ (391 mg, 1.064 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h.

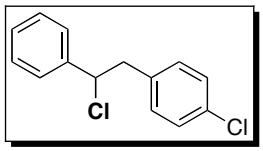
The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. The product **45a-Cl** was isolated as a clear oil (98 mg, 51% yield, R_f = 0.20 in hexanes). ^{1}H NMR (500 MHz, acetone d_6): δ 7.51-7.48 (multiple peaks, 2H), 7.25-7.16 (multiple peaks, 5H), 7.12-7.08 (multiple peaks, 2H), 5.31 (t, J = 6.4 Hz, 1H), 3.42 (dd, J = 14.0, 8.0 Hz, 1H approximate values due to second order effects), 3.38 (dd, J = 14.0, 7.5 Hz, 1H approximate values due to second order effects). ^{13}C NMR (100 MHz, acetone d_6): δ 163.28 ($^1J_{C\text{-}F}$ = 244 Hz), 138.62 ($^4J_{C\text{-}F}$ = 3.0 Hz), 138.56, 130.37 ($^3J_{C\text{-}F}$ = 8 Hz), 130.28, 129.13, 127.59, 116.08 ($^2J_{C\text{-}F}$ = 22 Hz), 64.02, 46.73. HRMS EI (m/z): $[M]^+$ Calcd for $C_{14}H_{12}ClF$, 234.0612; Found, 234.0613.



$PdCl_2(PhCN)_2$ (32.4 mg, 0.085 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (465 mg, 1.69 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **46** (100 mg, 0.846 mmol, 1.00 equiv) and Et_2O (36 mL) was added. $PhSnBu_3$ (404 mg, 1.100 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The crude NMR showed a 83% yield of **46a-Cl** and a >20:1 ratio of **46a-Cl : 46b-Cl**. The filtrate was concentrated and purified by chromatography on silica gel using 1% pyridine/99% hexanes. A second column was done with 0.5% pyridine/99.5% hexanes. The product **46a-Cl** was isolated as a clear oil (97 mg, 51% yield, R_f = 0.24 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.21 (multiple peaks, 5H), 7.16-7.12 (multiple peaks, 4H), 5.05 (t, J = 7.2 Hz, 1H), 3.40 (dd, J = 14.0, 8.0 Hz, 1H), 3.35 (dd, J = 13.6, 6.6 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.22, 138.14, 137.60, 129.38, 129.20, 128.28, 127.01, 126.75, 64.12, 46.38, 21.15. HRMS EI (m/z): $[M]^+$ Calcd for $C_{15}H_{15}Cl$, 230.0862; Found, 230.0866.

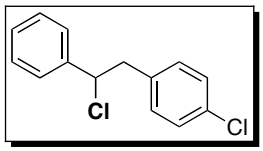


$PdCl_2(PhCN)_2$ (18.4 mg, 0.048 mmol, 5 mol %) was weighed into a 25 mL Schlenk flask. $CuCl_2$ (516 mg, 3.84 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum. The flask was cooled to 0 °C, and substrate **42** (100 mg, 0.960 mmol, 1.00 equiv) and Et_2O (19 mL) was added. *p*-$CF_3PhSnBu_3$ (543 mg, 1.248 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was extracted with 1 M aqueous KF solution (2 x 100 mL) and once with brine (1 x 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by chromatography on silica gel using hexanes. The product was isolated as a clear oil (197 mg, 73% yield, R_f = 0.24 in hexanes) as a mixture of 1,1 ans 1,2-isomers. Samples of **42-*p*-CF_3a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.34-7.29 (multiple peaks, 5H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.03 (t, *J* = 6.8 Hz, 1H), 3.42 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.37 (dd, *J* = 14.0, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.37, 140.59, 129.78, 129.14 ($^2J_{C\text{-}F}$ = 32 Hz), 128.67, 128.57, 127.03, 125.24 ($^3J_{C\text{-}F}$ = 3.6 Hz), 124.14 ($^1J_{C\text{-}F}$ = 272 Hz), 62.86, 46.40. HRMS EI (m/z): $[M]^+$ Calcd for $C_{15}H_{12}ClF_3$, 284.0580; Found, 284.0576.

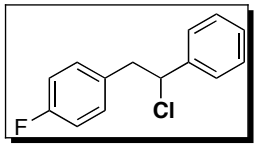


$PdCl_2(PhCN)_2$ (18.4 mg, 0.048 mmol, 5 mol %) and $CuCl_2$ (258 mg, 1.92 mmol, 4.00 equiv) were weighed into a 50 mL Schlenk flask. Dry Et_2O (15 mL) was added in the glove box, and the flask was cooled to 0 °C. Substrate **42** (50.0 mg, 0.480 mmol, 1.00 equiv) and *p*-$ClPhSnBu_3$ (251 mg, 0.624 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h.

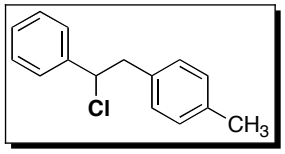
The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 3 : 1 ratio of **42-*p*-Cla-Cl** : **42-*p*-Clb-Cl**. The crude product was purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. The product was isolated as a clear oil as a 2 : 1 mixture of **42-*p*-Cla-Cl** and **42-*p*-Clb-Cl** (52 mg, 44% yield, R_f = 0.20 in hexanes). Since **42-*p*-Cla-Cl** and **42-*p*-Clb-Cl** were inseparable, samples of **42-*p*-Cla-Cl** and **42-*p*-Clb-Cl** for HRMS and NMR analysis were obtained from the reactions of styrene and *p*-chlorostyrene, respectively, with $PhICl_2$. These results are detailed below.



$PdCl_2(PhCN)_2$ (36.8 mg, 0.096 mmol, 10 mol %) and $PhICl_2$ (528 mg, 1.92 mmol, 2.00 equiv) were weighed into a 50 mL Schlenk flask. Dry Et_2O (28 mL) was added in the glove box, and the flask was cooled to 0 °C. Substrate **42** (100 mg, 0.960 mmol, 1.00 equiv) and *p*-$ClPhSnBu_3$ (501 mg, 1.25 mmol, 1.30 equiv) in dry Et_2O (2 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **42-*p*-Cla-Cl** was isolated as a white solid (195 mg, 81% yield, R_f = 0.26 in hexanes, mp = 76.0-76.7 ºC). ^1H NMR (500 MHz, $CDCl_3$): δ 7.35-7.29 (multiple peaks, 5H), 7.23 (d, *J* = 8.00 Hz, 2H), 7.03 (d, *J* = 8.50, 2H), 5.00 (t, *J* = 7.24 Hz, 1H), 3.37 (dd, *J* = 14.00, 8.00 Hz, 1H), 3.30 (dd, *J* = 13.75, 6.74 Hz, 1H). ^{13}C NMR (100 MHz, Acetone-d_6): δ 142.06, 137.61, 132.84, 132.05, 129.32, 129.15, 128.98, 128.11, 64.51, 45.75. HRMS EI (m/z): $[M]^+$ Calcd for $C_{14}H_{12}Cl_2$, 250.0316; Found, 250.0326.

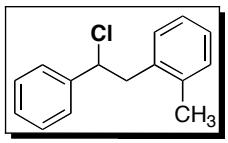


$PdCl_2(PhCN)_2$ (36.8 mg, 0.096 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (528 mg, 1.92 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **42** (100 mg, 0.96 mmol, 1.00 equiv) and Et_2O (30 mL) was added. *p*-$FPhSnBu_3$ (481 mg, 1.06 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. The product **42-*p*-Fa-Cl** was isolated as a clear oil (177 mg, 80% yield, R_f = 0.24 in hexanes). ^{1}H NMR (500 MHz, acetone *d*$_6$): δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.37-7.22 (multiple peaks, 5H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.25 (t, *J* = 7.6 Hz, 1H), 3.40 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.37 (dd, *J* = 14.0, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, acetone *d*$_6$): δ 162.60 ($^1J_{C\text{-}F}$ = 242 Hz), 142.19, 134.78 ($^4J_{C\text{-}F}$ = 2.9 Hz), 132.16 ($^3J_{C\text{-}F}$ = 8 Hz), 129.38, 129.18, 128.17, 115.67 ($^2J_{C\text{-}F}$ = 21 Hz), 64.88, 45.77. ^{19}F NMR (376 MHz, acetone-*d*$_6$): δ -117.58 – -117.66. HRMS EI (m/z): $[M]^+$ Calcd for $C_{14}H_{12}ClF$, 234.0612; Found, 234.0615.

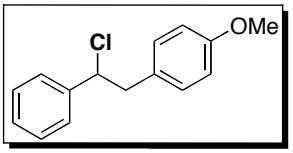


$PdCl_2(PhCN)_2$ (36.8 mg, 0.096 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (528 mg, 1.92 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to -78 °C. Et_2O (28 mL) was added. A solution of substrate **42** (100 mg, 0.96 mmol, 1.00 equiv) in dry Et_2O (1 mL) and *p*-$CH_3PhSnBu_3$ (475 mg, 1.25 mmol, 1.30 equiv) in dry Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and

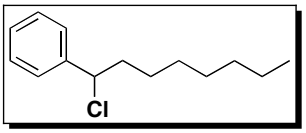
purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **42-*p*-CH_3a-Cl** was isolated as a clear oil (137 mg, 63% yield, R_f = 0.24 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (multiple peaks, 5H), 7.08 (d, *J* = 7.6 Hz,1H), 7.02 (d, *J* = 8.0 Hz, 1H), 5.04 (t, *J* = 7.6 Hz, 1H), 3.41-3.30 (multiple peaks, 2H) 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.24, 136.35, 134.39, 129.25, 129.00, 128.50, 128.25, 127.14, 64.28, 46.04, 21.05. HRMS EI (m/z): $[M]^+$ Calcd for $C_{15}H_{15}Cl$, 230.0862; Found, 230.0860.



$PdCl_2(PhCN)_2$ (18.4 mg, 0.050 mmol, 5 mol %) and $CuCl_2$ (516 mg, 3.84 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to 0 °C. Et_2O (30 mL) was added at 0 °C. Substrate **42** (100 mg, 0.960 mmol, 1.00 equiv) in Et_2O (1 mL) and *o*-$CH_3PhSnBu_3$ (476 mg, 1.25 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was extracted with 1 M aqueous KF solution (2 x 100 mL) and once with brine (1 x 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated. The crude ^{1}H NMR spectrum of this reaction mixture showed a 6:1 ratio 6:1. The crude product was purified by chromatography on silica gel using hexanes. Product **42-*o*-CH_3a-Cl** was isolated as an oil (95 mg, 43% yield, R_f = 0.13 in hexanes) as a mixture of **42-*o*-CH_3a-Cl** and **42-*o*-CH_3b-Cl**. Samples of **42-*o*-CH_3a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (multiple peaks, 5H), 7.11-7.00 (multiple peaks, 4H), 5.02 (t, *J* = 8.0 Hz, 1H), 3.40 (dd, *J* = 14.4, 8.0 Hz, 1H), 3.28 (dd, *J* = 14.0, 6.8 Hz, 1H).

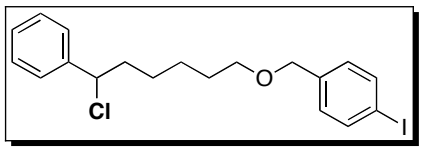


$PdCl_2(PhCN)_2$ (18.4 mg, 0.050 mmol, 5 mol %) and $CuCl_2$ (516 mg, 3.84 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to 0 °C. Et_2O (30 mL) was added at 0 °C. Substrate **42** (100 mg, 0.960 mmol, 1.00 equiv) in Et_2O (1 mL) and *p*-$OMePhSnBu_3$ (496 mg, 1.25 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The filtrate was extracted with 1 M aqueous KF solution (2 x 100 mL) and once with brine (1 x 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The crude product was purified by chromatography on silica gel using a gradient of hexanes to 1% EtOAc/99 % hexanes to 2% EtOAc/98% hexanes. Product **42-*p*-OMea-Cl** was isolated as an oil (75 mg, 32% yield, R_f = 0.20 in 2% EtOAc/98% hexanes). Samples of **42-*p*-OMea-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (2% EtOAc/98% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.26 (multiple peaks, 5H), 6.99 (d, J = 7.6 Hz, 2H), 6.78 (d, J = 7.2 Hz, 2H), 4.98 (t, J = 7.2 Hz, 1H), 3.74 (s, 3H), 3.32 (dd, J = 14.4, 8.0 Hz, 1H), 3.26 (dd, J = 14.4, 7.2 Hz, 1H).

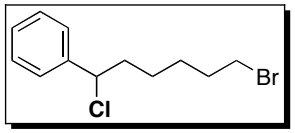


$PdCl_2(PhCN)_2$ (34.2 mg, 0.089 mmol, 10 mol %) and $CuCl_2$ (479 mg, 3.565 mmol, 4.00 equiv) were weighed into a 50 mL Schlenk flask. Dry Et_2O was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Substrate **24** (100 mg, 0.891 mmol, 1.00 equiv) and $PhSnBu_3$ (425 mg, 1.158 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and

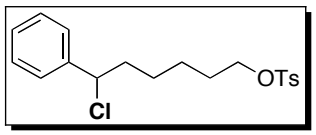
the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel that was pre-wetted with 0.5% Et_3N in hexanes. Product **24b-Cl** was isolated as a clear oil (98.0 mg, 50% yield, R_f = 0.53 in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.24 (multiple peaks, 5H), 4.85 (dd, *J* = 8.00, 6.79 Hz, 1H), 2.17-1.98 (multiple peaks, 2H), 1.51-1.41 (m, 1H), 1.37-1.20 (multiple peaks, 9H), 0.87 (t, *J* = 6.40 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.01, 128.56, 128.15, 126.92, 63.89, 39.99, 31.73, 29.08, 28.97, 27.08, 22.61, 14.07. HRMS EI (m/z): $[M^+]$ Calcd for $C_{14}H_{21}Cl$, 224.1332; Found, 224.1343.



$PdCl_2(PhCN)_2$ (12.1 mg, 0.032 mmol, 10 mol %) and $CuCl_2$ (170 mg, 1.27 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (8 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **31** (100 mg, 0.316 mmol, 1.00 equiv) in dry Et_2O (2 mL) and $PhSnBu_3$ (150.9 mg, 0.411 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel. Product **31b-Cl** was isolated as a clear oil (70.9 mg, 53% yield, R_f = 0.13 in 1.5% ethyl acetate/98.5% hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.00 Hz, 2H), 7.37-7.28 (multiple peaks, 5H), 7.07 (d, *J* = 7.50 Hz, 2H), 4.84 (t, *J* = 7.00 Hz, 1H), 4.42 (s, 2H), 3.43 (t, *J* = 6.00 Hz, 2H), 2.17-2.09 (m, 1H), 2.06-1.99 (m, 1H), 1.59 (quin, *J* = 6.87 Hz, 2H), 1.53-1.46 (m, 1H), 1.44-1.28 (multiple peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.87, 138.33, 137.39, 129.40, 128.56, 128.16, 126.88, 92.83, 72.13, 70.27, 63.68, 39.90, 29.46, 26.83, 25.60. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{19}H_{22}IClO$, 451.0302; Found, 451.0318.

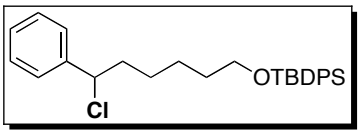


$PdCl_2(PhCN)_2$ (23.5 mg, 0.061 mmol, 10 mol %) and $CuCl_2$ (330 mg, 2.45 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (17 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **32** (100 mg, 0.613 mmol, 1.00 equiv) in dry Et_2O (2 mL), and $PhSnBu_3$ (292.7 mg, 0.797 mmol, 1.3 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 0.5% triethylamine/99.5% hexanes. Product **32b-Cl** was isolated as a clear oil (100 mg, 60% yield, R_f = 0.21 in hexanes). Note: The isolated product also contained 11% of the 1,6 isomer. Samples of **32b-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.28 (multiple peaks, 5H), 4.86 (dd, *J* = 8.00, 6.40 Hz, 1H), 3.39 (t, *J* = 6.60 Hz, 2H), 2.20-2.00 (multiple peaks, 2H), 1.86 (quin, *J* = 7.00 Hz, 2H), 1.58-1.45 (multiple peaks, 3H), 1.41-1.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.74, 128.63, 128.25, 126.88, 63.55, 39.77, 33.61, 32.47, 27.50, 26.22. HRMS EI (m/z): [M^+] Calcd for $C_{12}H_{16}ClBr$, 274.0124; Found, 274.0114.



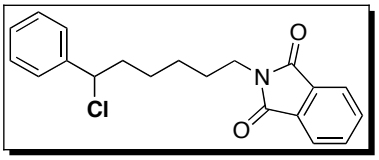
$PdCl_2(PhCN)_2$ (13.7 mg, 0.036 mmol, 10 mol %) and $CuCl_2$ (192 mg, 1.43 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (9 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **33** (90.7 mg, 0.357 mmol, 1.00 equiv) in dry Et_2O (2 mL) and $PhSnBu_3$ (188 mg, 0.511 mmol, 1.30 equiv) were added, and the

reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 8% ethyl acetate/92% hexanes. Product **33b-Cl** was isolated as a viscous clear oil (91.5 mg, 71% yield, R_f = 0.18 in 8% ethyl acetate/92% hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.49 Hz, 2H), 7.37-7.28 (multiple peaks, 7H), 4.79 (dd, *J* = 8.24, 6.24 Hz, 1H), 4.01(t, *J* = 6.24 Hz, 2H), 2.44 (s, 3H), 2.10-2.03 (m, 1H), 2.00-1.93 (m, 1H), 1.63 (quin, *J* = 6.87 Hz, 2H), 1.48-1.22 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.69, 141.69, 133.15, 129.82, 128.64, 128.28, 127.87, 126.85, 70.29, 63.49, 39.70, 28.62, 26.40, 24.81, 21.63. IR (thin film): 2940, 1358, 1175 cm^{-1}. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{19}H_{23}ClO_3S$, 389.0954; Found, 389.0945.

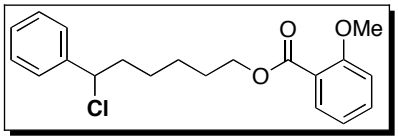


$PdCl_2(PhCN)_2$ (11.3 mg, 0.029 mmol, 10 mol %) and $CuCl_2$ (159 mg, 1.18 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (7 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **34** (100 mg, 0.295 mmol, 1.00 equiv) in dry Et_2O (2 mL) and $PhSnBu_3$ (141 mg, 0.384 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 1% ethyl acetate/99% hexanes. Product **34b-Cl** was isolated as a clear oil (86.7 mg, 66% yield, R_f = 0.18 in 1% ethyl acetate/99% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 7.80, 1.40 Hz, 4H), 7.45-7.28 (multiple peaks, 11H), 4.83 (dd, *J* = 8.00, 6.40 Hz, 1H), 3.65 (t, *J* = 6.40 Hz, 2H), 2.17-1.98 (multiple peaks, 2H), 1.59-1.26 (multiple peaks, 6H), 1.05 (s, 9H). ^{13}C NMR (100

MHz, $CDCl_3$): δ 141.92, 135.55, 134.03, 129.51, 128.58, 128.17, 127.58, 126.91, 63.77, 63.67, 39.96, 32.27, 26.86, 26.82, 25.21, 19.20. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{28}H_{35}ClOSi$, 473.2043; Found, 473.2042.

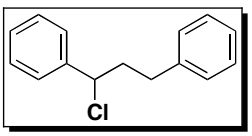


$PdCl_2(PhCN)_2$ (16.7 mg, 0.044 mmol, 10 mol %) and $CuCl_2$ (235 mg, 1.74 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (12 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **35** (100 mg, 0.436 mmol, 1.00 equiv) in dry Et_2O (2 mL) and $PhSnBu_3$ (208 mg, 0.567 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 8% ethyl acetate/92% hexanes. Product **35b-Cl** was isolated as a clear viscous oil (106 mg, 71% yield, R_f = 0.20 in 8% ethyl acetate/92%hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 5.40, 3.00 Hz, 2H), 7.70 (dd, *J* = 5.60, 2.80 Hz, 2H), 7.37-7.25 (multiple peaks, 5H), 4.83 (dd, *J* = 8.00, 6.40 Hz, 1H), 3.66 (t, *J* = 7.20 Hz, 2H), 2.19-1.98 (multiple peaks, 2H), 1.67 (quin, *J* = 7.40 Hz, 2H), 1.58-1.49 (m, 1H), 1.43-1.31 (multiple peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.42, 141.77, 133.88, 132.10, 128.59, 128.20, 126.89, 123.17, 63.59, 39.78, 37.83, 28.39, 26.64, 26.27. IR (thin film): 2938, 1709, 1395 cm^{-1}. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{20}H_{20}ClNO_2$, 364.1080; Found, 364.1072.



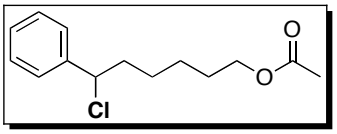
$PdCl_2(PhCN)_2$ (16.4 mg, 0.043 mmol, 10 mol %) and $CuCl_2$ (229 mg, 1.71 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (11 mL) was added in the

glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **36** (100 mg, 0.427 mmol, 1.00 equiv) in dry Et_2O (2 mL) and $PhSnBu_3$ (204 mg, 0.555 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 8% ethyl acetate/92% hexanes. Product **36b-Cl** was isolated as a clear viscous oil (98.0 mg, 67% yield, R_f = 0.20 in 8% ethyl acetate/92% hexanes). Note: The isolated product also contained 4% of the 1,6 isomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 7.74, 1.74 Hz, 1H), 7.46 (td, *J* = 7.49 1.50 Hz, 1H), 7.38-7.28 (multiple peaks, 5H), 6.99-6.96 (multiple peaks, 2H), 4.85 (dd, *J* = 8.00, 6.49 Hz, 1H), 4.28 (t, *J* = 6.50 Hz, 2H), 3.89 (s, 3H), 2.20-2.12 (m, 1H), 2.09-2.02 (m, 1H), 1.75 (quin, *J* = 6.99 Hz, 2H), 1.58-1.54 (m, 1H), 1.53-1.46 (multiple peaks, 2H), 1.43-1.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.26, 159.10, 141.81, 133.38, 131.48, 128.61, 128.23, 126.89, 120.33, 120.09, 112.00, 64.64, 63.64, 55.93, 39.90, 28.51, 26.74, 25.51. IR (thin film): 2938, 1723, 1490 cm^{-1}. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{20}H_{23}ClO_3$, 369.1233; Found, 369.1241.

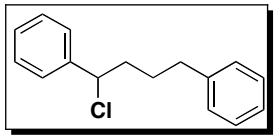


$PdCl_2(PhCN)_2$ (2.90 mg, 0.008 mmol, 10 mol %) and $CuCl_2$ (40.6 mg, 0.302 mmol, 4.00 equiv) were weighed into a 4 mL scintillation vial. Et_2O (1.2 mL) and CH_3NO_2 (1.2 mL) was added, and the vial was cooled to 0 °C. Substrate **37** (8.92 mg, 0.075 mmol, 1.00 equiv) and $PhSnBu_3$ (36.0 mg, 0.098 mmol, 1.30 equiv) were added, and the vial was sealed with a Teflon lined cap. The reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. Ten identical reactions were set up and then combined for purification. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated,

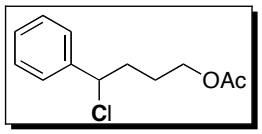
and purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. Product **37b-Cl** was isolated as a clear oil (94.4 mg, 55% yield, R_f = 0.21 in hexanes). ^{1}H NMR (400 MHz, acetone d_6): δ 7.45 (d, J = 8.00 Hz, 2H), 7.38 (t, J = 7.40 Hz, 2H), 7.32 (dt, J = 7.20, 2.00 Hz, 1H), 7.28 (t, J = 7.40 Hz, 2H), 7.22-7.17 (multiple peaks, 3H), 4.99 (dd, J = 8.20, 6.20 Hz, 1H), 2.84-2.77 (m, 1H), 2.70-2.63 (m, 1H), 2.48-2.31 (multiple peaks, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 142.68, 141.73, 129.48, 129.29, 129.24, 129.14, 127.92, 126.89, 63.86, 42.24, 33.82. HRMS EI (m/z): [M^+] Calcd for $C_{15}H_{15}Cl$, 230.0862; Found, 230.0863.



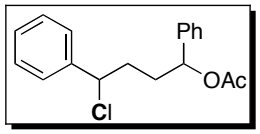
$PdCl_2(PhCN)_2$ (26.9 mg, 0.070 mmol, 10 mol %) and $CuCl_2$ (378 mg, 2.81 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (20 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **38** (100 mg, 0.704 mmol, 1.00 equiv) in dry Et_2O (2 mL) and $PhSnBu_3$ (336 mg, 0.915 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 2.5% ethyl acetate/0.5% Et_3N/97% hexanes. Product **38b-Cl** was isolated as a clear oil (126 mg, 71% yield, R_f = 0.13 in 3% ethyl acetate/97% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (multiple peaks, 5H), 4.84 (dd, J = 8.19, 6.59 Hz, 1H), 4.04 (t, J = 6.80 Hz, 2H), 2.19-1.98 (multiple peaks, 2H), 2.04 (s, 3H), 1.62 (quin, J = 7.00 Hz, 2H), 1.55-1.48 (m, 1H), 1.44-1.31 (multiple peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.14, 141.78, 128.60, 128.22, 126.86, 64.31, 63.60, 39.85, 28.37, 26.69, 25.38, 20.96. IR (thin film): 2939, 1737, 1240 cm^{-1}. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{14}H_{19}ClO_2$, 277.0971; Found, 277.0962.



$PdCl_2(PhCN)_2$ (14.5 mg, 0.038 mmol, 10 mol %) and $CuCl_2$ (203 mg, 1.51 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (10 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **39** (50.0 mg, 0.378 mmol, 1.00 equiv) in dry Et_2O (2 mL) and $PhSnBu_3$ (181 mg, 0.492 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite, and the pad was washed with Et_2O (2 x 100 mL). The filtrate was concentrated and purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. Product **39b-Cl** was isolated as a clear oil (76 mg, 84% yield, R_f = 0.23 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.24 (multiple peaks, 7H), 7.20-7.14 (multiple peaks, 3H), 4.87 (t, *J* = 7.20 Hz, 1H), 2.65 (t, *J* = 7.60 Hz, 2H), 2.22-2.02 (multiple peaks, 2H), 1.90-1.79 (m, 1H), 1.71-1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.74, 141.70, 128.60, 128.35, 128.22, 126.90, 125.88, 63.59, 39.43, 35.19, 28.73. HRMS EI (m/z): [M+] Calcd for $C_{16}H_{17}Cl$, 244.1019; Found, 244.1014.

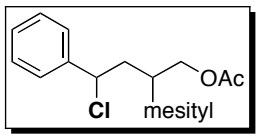


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.30 (multiple peaks, 5H), 4.89 (t, *J* = 6.5 Hz, 1H), 4.14-4.06 (multiple peaks, 2H), 2.24-2.08 (multiple peaks, 2H), 2.06 (s, 3H), 1.93-1.83 (m, 1H), 1.74-1.65 (m, 1H).

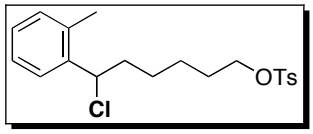


^{1}H NMR (500 MHz, $CDCl_3$) (mixture of diastereomers): δ 7.36-7.30 (multiple peaks, 10H), 5.80-5.75 (m, 1H), 4.87-4.82 (m, 1H), 2.21-1.82 (multiple peaks, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereomers): δ 171.81, 41.31, 141.30, 140.03, 140.00,

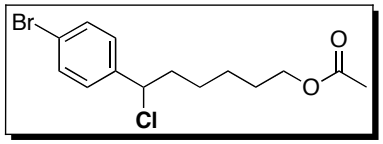
128.66, 128.65, 128.52, 128.36, 128.34, 128.04, 126.82, 126.37, 75.28, 74.99, 63.27, 63.02, 35.87, 35.76, 33.81, 33.68, 21.19.



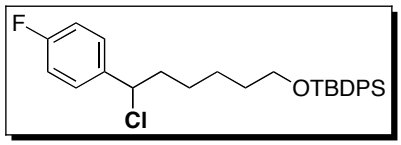
^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers): δ 7.32-7.23 (multiple peaks, 8H), 7.17-7.15 (multiple peaks, 2H), 6.82-6.74 (multiple peaks, 4H), 4.70 (t, *J* = 8.0 Hz, 1H), 4.58 (t, *J* = 7.2 Hz, 1H), 4.37-4.19 (multiple peaks, 4H), 3.76 (quin, *J* = 7.6 Hz, 1H), 3.40 (quin, *J* = 8.0 Hz, 1H), 2.70-2.57 (multiple peaks, 2H), 2.52 (t, *J* = 6.8 Hz, 2H), 2.35 (s, 3H), 2.28 (s, 3H), 2.23 (s, 6H), 2.22 (s, 6H), 2.02 (s, 3H), 1.99 (s, 3H).



$PdCl_2(PhCN)_2$ (7.54 mg, 0.020 mmol, 10 mol %) and $CuCl_2$ (106 mg, 0.786 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (4.1 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **33** (50.0 mg, 0.197 mmol, 1.00 equiv) in dry Et_2O (1 mL) and *o*-$CH_3PhSnBu_3$ (97.4 mg, 0.256 mmol, 1.30 equiv) in dry Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 7% ethyl acetate/1% Et_3N/92% hexanes. Product **33-*o*-CH_3b-Cl** was isolated as a viscous clear oil (50.0 mg, 67% yield, R_f = 0.15 in 8% ethyl acetate/92% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.00 Hz, 2H), 7.42 (d, *J* = 7.20 Hz, 1H), 7.43 (d, *J* = 8.00 Hz, 2H), 7.23-7.12 (multiple peaks, 3H), 5.05 (dd, *J* = 8.80, 6.00 Hz, 1H), 4.00 (t, *J* = 6.40 Hz, 2H), 2.43 (s, 3H), 2.35 (s, 3H), 2.14-2.04 (m, 1H), 2.01-1.93 (m, 1H), 1.63 (quin, *J* = 6.87 Hz, 2H), 1.52-1.25 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.70, 139.55, 133.14, 133.14, 130.55, 129.82, 128.07, 127.86, 126.56, 126.33, 70.28, 59.55, 38.50, 28.63, 26.54, 24.90, 21.62, 19.01. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{20}H_{25}ClO_3S$, 403.1111; Found, 403.1122.

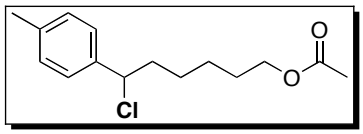


$PdCl_2(PhCN)_2$ (13.5 mg, 0.035 mmol, 10 mol %) and $CuCl_2$ (189 mg, 1.41 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (9 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **38** (50.0 mg, 0.352 mmol, 1.00 equiv) in dry Et_2O (1 mL) and *p*-$BrPhSnBu_3$ (203 mg, 0.457 mmol, 1.30 equiv) in dry Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1.5% ethyl acetate/1% Et_3N/97.5% hexanes. Product **38-*p*-Brb-Cl** was isolated as a viscous clear oil (63.0 mg, 54% yield, R_f = 0.11 in 2.5% ethyl acetate/97.5% hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 6.80 Hz, 2H), 7.23 (d, *J* = 6.40 Hz, 2H), 4.77 (t, *J* = 7.6 Hz, 1H), 4.02 (t, *J* = 6.80 Hz, 2H), 2.13-1.90 (multiple peaks, 2H), 1.63-1.56 (m, 1H), 1.52-1.27 (multiple peaks, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.13, 140.81, 131.75, 128.59, 122.08, 64.25, 62.61, 39.76, 28.35, 26.60, 25.35, 20.96. HRMS EI (m/z): $[M]^+$ Calcd for $C_{14}H_{18}BrClO_2$, 332.0179; Found, 332.0183.

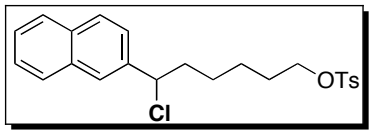


$PdCl_2(PhCN)_2$ (6.11 mg, 0.016 mmol, 10 mol %) and $CuCl_2$ (85.6 mg, 0.637 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (3.0 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **34** (53.9 mg, 0.159 mmol, 1.00 equiv) in dry Et_2O (1 mL) and *p*-$FPhSnBu_3$ (79.7 mg, 0.207 mmol, 1.30 equiv) in dry Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by

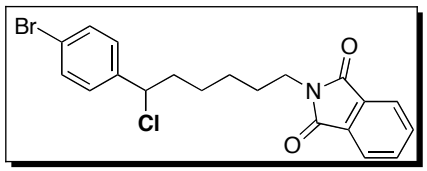
chromatography on silica gel using 0.5% ethyl acetate/0.5% Et_3N/99% hexanes. Product **34-*p*-Fb-Cl** was isolated as a viscous clear oil (43.0 mg, 59% yield, R_f = 0.33 in 1% ethyl acetate/99% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (multiple peaks, 4H), 7.45-7.32 (multiple peaks, 8H), 7.03 (tt, *J* = 8.8, 2.0 Hz, 2H), 4.81 (t, *J* = 8.00 Hz, 1H), 3.65 (t, *J* = 6.00 Hz, 2H), 2.15-1.93 (multiple peaks, 2H), 1.58-1.20 (multiple peaks, 6H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.36 (J_{C-F} = 246.75 Hz), 137.80 (J_{C-F} = 3.12 Hz), 135.55, 134.03, 129.52, 128.65 (J_{C-F} = 8.56 Hz), 127.58, 115.48 (J_{C-F} = 21.75 Hz), 63.63, 62.88, 40.04, 32.24, 26.86, 26.77, 25.18, 19.20. ^{19}F NMR (376.34 MHz, $CDCl_3$): δ -113.78. HRMS EI (m/z): $[M+NH_4]^+$ Calcd for $C_{28}H_{34}ClFOSi$, 486.2395; Found, 486.2397.



$PdCl_2(PhCN)_2$ (13.5 mg, 0.035 mmol, 10 mol %) and $CuCl_2$ (189 mg, 1.41 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (9 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **38** (50.0 mg, 0.352 mmol, 1.00 equiv) in dry Et_2O (1 mL) and *p*-$CH_3PhSnBu_3$ (174 mg, 0.457 mmol, 1.30 equiv) in dry Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1.5% ethyl acetate/1% Et_3N/97.5% hexanes. Product **38-*p*-CH$_3$b-Cl** was isolated as a viscous clear oil (68.0 mg, 73% yield, R_f = 0.11 in 2.5% ethyl acetate/97.5% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.4, 2H), 7.15 (d, *J* = 7.6, 2H), 4.82 (t, *J* = 7.20 Hz, 1H), 4.04 (t, *J* = 6.40 Hz, 2H), 2.34 (s, 3H), 2.19-1.98 (multiple peaks, 2H), 2.02 (s, 3H), 1.61 (quin, *J* = 6.80 Hz, 2H), 1.54-1.46 (m, 1H), 1.42-1.30 (multiple peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.18, 138.87, 138.10, 129.29, 126.80, 64.35, 63.63, 39.80, 28.40, 26.77, 25.41, 21.14, 20.98.

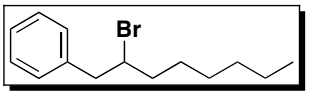


$PdCl_2(PhCN)_2$ (7.54 mg, 0.020 mmol, 10 mol %) and $CuCl_2$ (106 mg, 0.786 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (4.1 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **33** (50.0 mg, 0.197 mmol, 1.00 equiv) in dry Et_2O (1 mL) and *2*-naphthylPhSnBu_3 (107 mg, 0.256 mmol, 1.30 equiv) in dry Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 8% ethyl acetate/1% Et_3N/91% hexanes. Product **33-2-naphthylb-Cl** was isolated as a viscous clear oil (34.4 mg, 42% yield, R_f = 0.19 in 8% ethyl acetate/92% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.74 (multiple peaks, 6H), 7.49-7.45 (multiple peaks, 3H), 7.30 (d, *J* = 8.0, 2H), 4.95 (t, *J* = 6.40 Hz, 1H), 3.99 (td, *J* = 8.40, 2.00 Hz, 2H), 2.42 (s, 3H), 2.20-2.01 (multiple peaks, 2H), 1.61 (quin, *J* = 6.40 Hz, 2H), 1.46-1.29 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.69, 138.85, 133.15, 133.0, 129.81, 128.72, 128.02, 127.85, 127.68, 126.45, 126.40, 125.88, 124.46, 70.28, 63.73, 39.57, 28.62, 26.45, 24.85, 21.62. Two carbons are coincidentally overlapping. HRMS EI (m/z): [M+] Calcd for $C_{23}H_{25}ClO_3S$, 416.1213; Found, 416.1211.



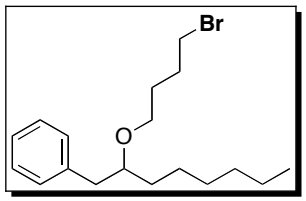
$PdCl_2(PhCN)_2$ (8.40 mg, 0.022 mmol, 10 mol %) and $CuCl_2$ (117 mg, 0.872 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (4.8 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **35** (50.0 mg, 0.218 mmol, 1.00 equiv) in dry Et_2O (1 mL) and *p*-BrPhSnBu_3 (126 mg, 0.284 mmol, 1.30 equiv) in dry Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then

stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 8% ethyl acetate/1% Et_3N/91% hexanes. Product **35-*p*-Brb-Cl** was isolated as a viscous clear oil (43 mg, 47% yield, R_f = 0.20 in 8% ethyl acetate/92% hexanes). However, the yield is approximate because the ^1H NMR of the isolated product contained some aromatic impurity. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84-7.74 (multiple peaks, 6H), 7.49-7.45 (multiple peaks, 3H), 7.30 (d, *J* = 8.0, 2H), 4.95 (t, *J* = 6.40 Hz, 1H), 3.99 (td, *J* = 8.40, 2.00 Hz, 2H), 2.42 (s, 3H), 2.20-2.01 (multiple peaks, 2H), 1.61 (quin, *J* = 6.40 Hz, 2H), 1.46-1.29 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.40, 140.79, 133.88, 132.08, 131.74, 128.60, 123.17, 122.06, 62.58, 39.66, 37.76, 28.32, 26.50, 26.19. HRMS EI (m/z): [M+] Calcd for $C_{20}H_{19}BrClNO_2$, 419.0288; Found, 419.0293.

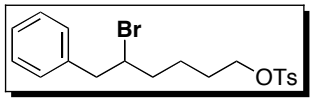


$PdCl_2(CH_3CN)_2$ (23.1 mg, 0.089 mmol, 10 mol %) and $CuBr_2$ (796 mg, 3.56 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (7 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Substrate **24** (100 mg, 0.891 mmol, 1.00 equiv) $PhSnBu_3$ (425 mg, 1.159 mmol, 1.30 equiv) and CuBr (128 mg, 0.891 mmol, 1.00 equiv) in THF were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the crude product was purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. Product was isolated as a viscous clear oil (124.0 mg, 53% yield, R_f = 0.80 in hexanes) as a 10:1 mixture of **24a-Br**:**24b-Br**. Samples of **24a-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.18 (multiple peaks, 5H), 4.19 (m, 1H), 3.16 (multiple peaks, 2H), 1.87-1.74 (multiple peaks, 2H), 1.59 (m, 1H), 1.40 (m, 1H), 1.32-1.26 (multiple peaks, 5H), 0.87 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 138.66, 129.20, 128.38, 126.72, 57.83, 45.72, 38.18, 31.63, 28.60, 27.51, 22.54, 14.02. HRMS EI (m/z): $[M]^+$ Calcd for $C_{14}H_{21}Br$, 268.0827; Found, 268.0823.

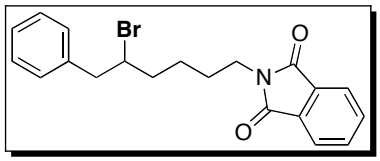


52 was the major side product isolated from the 1,2-phenylbromination of 1-octene. After the desired product from the 1,2-arylbromination of 1-octene was isolated, the column was eluted with 100 % EtOAc and the eluent collected and concentrated and then chromatographed using 2% EtOAc/98% hexanes to obtain product **52** (R_f = 0.54 in 5% EtOAc/95% hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.16 (multiple peaks, 5H), 3.44-3.30 (multiple peaks, 5H), 2.76 (dd, *J* = 13.60, 6.80 Hz, 1H), 2.69 (dd, *J* = 13.20, 5.60 Hz, 1H), 1.83 (quin, *J* = 7.2 Hz, 2H), 1.60 (quin, *J* = 5.6 Hz, 2H), 1.45-1.14 (multiple peaks, 10H), 0.86 (t, *J* = 6.80 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.39, 129.43, 128.16, 125.98, 81.14, 68.29, 40.95, 34.18, 33.83, 31.85, 29.63, 29.41, 28.66, 25.46, 22.61, 14.08. HRMS EI (m/z): $[M+NH_4]^+$ Calcd for $C_{18}H_{29}BrO$, 358.1746; Found, 358.1758.



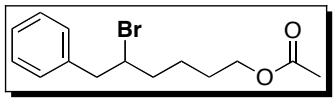
$PdCl_2(CH_3CN)_2$ (5.10 mg, 0.020 mmol, 10 mol %) and $CuBr_2$ (175 mg, 0.786 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (1 mL) was added at -78 °C. A solution of substrate **33** (50.0 mg, 0.197 mmol, 1.00 equiv) in THF (0.53 mL) and $PhSnBu_3$ (93.8 mg, 0.256 mmol, 1.30 equiv) were added sequentially, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the crude product was purified by chromatography on silica gel using 8% EtOAc/1% Et_3N/91% hexanes. Product was isolated as a viscous clear oil (40.0 mg, 50% yield, R_f = 0.18 in 8% EtOAc/92% hexanes)

as a 17:1 mixture of **33a-Br** and **33b-Br**. Samples of **33a-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (3% EtOAc/97% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.35-7.23 (multiple peaks, 5H), 7.17 (d, *J* = 8.8 Hz, 2H), 4.12 (m, 1H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.17 (dd, *J* = 14.40, 7.60 Hz, 1H), 3.09 (dd, *J* = 14.00, 6.8 Hz, 1H) 2.44 (s. 3H), 1.83-1.57 (multiple peaks, 5H), 1.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.74, 138.29, 133.09, 129.85, 129.15, 128.47, 127.89, 126.87, 70.16, 56.80, 45.65, 37.31, 28.21, 23.62, 21.64. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{19}H_{23}BrO_3S$, 433.0449; Found, 433.0446.

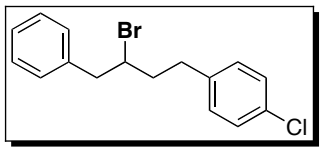


$PdCl_2(CH_3CN)_2$ (11.3 mg, 0.044 mmol, 10 mol %) and $CuBr_2$ (390 mg, 1.74 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (2.4 mL) was added at -78 °C. A solution of substrate **35** (100 mg, 0.436 mmol, 1.00 equiv) in THF (1 mL) and $PhSnBu_3$ (208 mg, 0.567 mmol, 1.30 equiv) were added sequentially, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^{1}H NMR spectrum of this crude reaction mixture showed a 9 : 1 ratio of **35a-Br** : **35b-Br**. The crude product was purified by chromatography on silica gel using 8% EtOAc/1% Et_3N/91% hexanes. Product was isolated as a viscous clear oil (91 mg, 55% yield, R_f = 0.16 in 8% EtOAc/92% hexanes) as a 11:1 mixture of **35a-Br**:**35b-Br**. Samples of **35a-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (3.5% EtOAc/96.5% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.71 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.32-7.18 (multiple peaks, 5H), 4.18 (m, 1H), 3.67 (t, *J* = 7.2 Hz, 2H), 3.19 (dd, *J* = 14.40, 8.00 Hz, 1H), 3.12 (dd, *J* = 14.00, 6.4 Hz, 1H), 1.91-1.60 (multiple peaks, 5H), 1.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.38, 138.43, 133.90, 132.11, 129.17, 128.44, 126.80,

123.21, 57.02, 45.75, 37.69, 37.55, 27.88, 24.89. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{20}H_{20}BrNO_2$, 408.0575; Found, 408.0577.

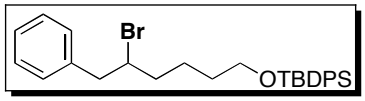


$PdCl_2(CH_3CN)_2$ (18.2 mg, 0.070 mmol, 10 mol %) and $CuBr_2$ (628 mg, 2.81 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (4.5 mL) was added at -78 °C. A solution of substrate **38** (100 mg, 0.703 mmol, 1.00 equiv) in THF (1 mL) and $PhSnBu_3$ (336 mg, 0.914 mmol, 1.30 equiv) were added sequentially, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^1H NMR spectrum of this crude reaction mixture showed a 9 : 1 ratio of **38a-Br** : **38b-Br**. The crude product was purified by chromatography on silica gel using 2.5% EtOAc/1% Et_3N/96.5% hexanes. Product was isolated as a viscous clear oil (128 mg, 62% yield, R_f = 0.11 in 2.5% EtOAc/97.5% hexanes) as a 15:1 mixture of **38a-Br** : **38b-Br**. Samples of **38a-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (1.5% EtOAc/98.5% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.22 (multiple peaks, 3H), 7.18 (d, J = 8.0 Hz, 2H), 4.17 (m, 1H), 4.03 (t, J = 6.0 Hz, 2H), 3.20 (dd, J = 14.40, 7.60 Hz, 1H), 3.12 (dd, J = 14.40, 7.2 Hz, 1H), 2.02 (s, 3H), 1.87-1.55 (multiple peaks, 5H), 1.48 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.13, 138.43, 129.18, 128.47, 126.85, 64.19, 57.11, 45.76, 37.62, 27.94, 24.13, 20.97. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{14}H_{19}BrO_2$, 321.0466; Found, 321.0467.



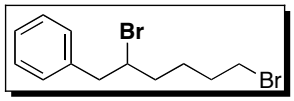
$PdCl_2(CH_3CN)_2$ (15.5 mg, 0.060 mmol, 10 mol %) and $CuBr_2$ (536 mg, 2.40 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (4.7 mL) was

added at -78 °C. Substrate **40** (100 mg, 0.600 mmol, 1.00 equiv) and $PhSnBu_3$ (286 mg, 0.780 mmol, 1.30 equiv) were added sequentially, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^1H NMR spectrum of this crude reaction mixture showed a 14 : 1 ratio of **40a-Br** : **40b-Br**. The crude product was purified by chromatography on silica gel using 1% pyridine/99% hexanes. Product was isolated as a viscous clear oil (130 mg, 68% yield, R_f = 0.26 in hexanes) as a 18:1 mixture of **40a-Br**:**40b-Br**. Note: The isolated product also contained approximately 4.5% of the 2,1 phenylhalogenated (Cl or Br) product. Samples of **40a-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.25-7.15 (multiple peaks, 5H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.06 (m, 1H), 3.16 (dd, *J* = 14.00, 7.20 Hz, 1H), 3.08 (dd, *J* = 14.40, 6.8 Hz, 1H), 2.84 (m, 1H), 2.65 (m, 1H), 2.07-1.92 (multiple peaks, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.19, 138.17, 131.84, 129.85, 129.17, 128.56, 128.46, 126.89, 56.18, 45.70, 39.41, 33.04. HRMS EI (m/z): $[M]^+$ Calcd for $C_{16}H_{16}BrCl$, 322.0124; Found, 322.0115.

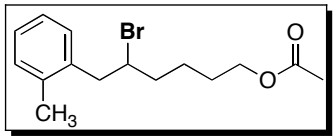


$PdCl_2(CH_3CN)_2$ (7.70 mg, 0.029 mmol, 10 mol %) and $CuBr_2$ (264 mg, 1.18 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (1.3 mL) was added at -78 °C. A solution of substrate **34** (100 mg, 0.295 mmol, 1.00 equiv) in THF (1 mL) and $PhSnBu_3$ (141 mg, 0.384 mmol, 1.30 equiv) were added sequentially, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^1H NMR spectrum of this crude reaction mixture showed a 14 : 1 ratio of **34a-Br** : **34b-Br**. The crude product was purified by chromatography on silica gel using 0.5% EtOAc/0.5% Et_3N/99% hexanes. Product was isolated as a clear oil (92.2 mg, 64% yield, R_f = 0.22 in 1% EtOAc/99%

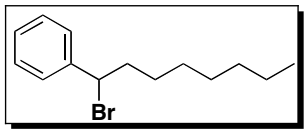
hexanes) as a 22:1 mixture of **34a-Br** : **34b-Br**. Samples of **34a-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (0.2% EtOAc/99.8% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.63 (multiple peaks, 4H), 7.43-7.34 (multiple peaks, 6H), 7.32-7.23 (multiple peaks, 3H), 7.19-7.17 (multiple peaks, 2H), 4.20-4.13 (m, 1H), 3.63 (t, *J* = 6.40 Hz, 2H), 3.19-3.09 (multiple peaks, 2H), 1.84-1.45 (multiple peaks, 6H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.58, 135.57, 134.00, 129.53, 129.20, 128.40, 127.60, 126.75, 63.56, 57.60, 45.70, 45.64, 37.84, 31.82, 26.87, 23.93, 19.20. HRMS EI (m/z): $[M+H]^+$ Calcd for $C_{28}H_{35}BrOSi$, 495.1719; Found, 495.1710.



$PdCl_2(CH_3CN)_2$ (15.9 mg, 0.061 mmol, 10 mol %) and $CuBr_2$ (548 mg, 2.45 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (4.8 mL) was added at -78 °C. Substrate **32** (100 mg, 0.613 mmol, 1.00 equiv) and $PhSnBu_3$ (293 mg, 0.797 mmol, 1.30 equiv) were added sequentially, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^{1}H NMR spectrum of this crude reaction mixture showed a 17 : 1 ratio of **32a-Br** : **32b-Br**. The crude product was purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product was isolated as a clear oil (107 mg, 55% yield, R_f = 0.23 in hexanes) as a 15:1 mixture of **32a-Br** : **32b-Br**. Samples of **32a-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, *J* = 8.00 Hz, 2H), 7.29-7.21 (multiple peaks, 3H), 4.23-4.18 (m, 1H), 3.40 (t, *J* = 6.50 Hz, 2H), 3.23 (dd, *J* = 14.0, 7.50 Hz, 2H), 3.16 (dd, *J* = 14.0, 6.80 Hz, 2H), 1.93-1.75 (multiple peaks, 5H), 1.64-1.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.35, 129.18, 128.47, 126.87, 56.87, 45.68, 37.11, 33.28, 32.05, 26.26. HRMS EI (m/z): [M+] Calcd for $C_{12}H_{16}Br_2$, 317.9619; Found, 317.9620.

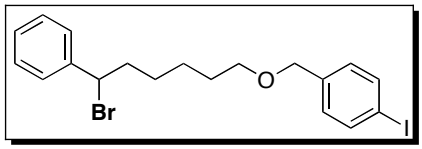


$PdCl_2(CH_3CN)_2$ (18.2 mg, 0.070 mmol, 10 mol %) and $CuBr_2$ (628 mg, 2.81 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (3.5 mL) was added at -78 °C. A solution of substrate **38** (100 mg, 0.703 mmol, 1.00 equiv) in THF (1 mL) and a solution of *o*-$CH_3PhSnBu_3$ (348 mg, 0.914 mmol, 1.30 equiv) were added sequentially, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^1H NMR spectrum of this crude reaction mixture showed a 12 : 1 ratio of **38-*o*-CH_3a-Br** : **38-*o*-CH_3b-Br**. The crude product was purified by chromatography on silica gel using 2.5% EtOAc/ 1%Et_3N/96.5% hexanes. Product was isolated as a clear oil (93.1 mg, 43% yield, R_f = 0.17 in 2.5% EtOAc/97.5% hexanes) as a 9:1 mixture of **38-*o*-CH_3a-Br** : **38-*o*-CH_3b-Br**. Samples of **38-*o*-CH_3a-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (2% EtOAc/98% hexanes, 20 mL/min, Waters µ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 7.15-7.12 (multiple peaks, 4H), 4.20-4.13 (m, 1H), 4.03 (t, *J* = 6.00 Hz, 2H), 3.26 (dd, *J* = 14.40, 7.20 Hz, 1H), 3.12 (dd, *J* = 14.40, 7.20 Hz, 1H), 2.32 (s, 3H), 2.03 (s, 3H), 1.87-1.42 (multiple peaks, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.13, 136.81, 136.20, 130.52, 129.96, 126.97, 125.95, 64.20, 56.35, 43.19, 37.81, 27.95, 24.32, 20.97, 19.57. HRMS CI with ammonia (m/z): $[M+NH_4]^+$ Calcd for $C_{15}H_{21}BrO_2$, 330.1068; Found, 330.1069.

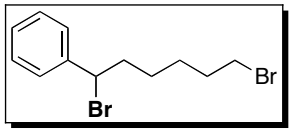


$PdCl_2(CH_3CN)_2$ (11.5 mg, 0.045 mmol, 10 mol %) and $CuBr_2$ (398 mg, 1.78 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (14 mL) was added at -78 °C. Substrate **24** (50.0 mg, 0.445 mmol, 1.00 equiv) and $PhSnBu_3$ (213 mg, 0.579

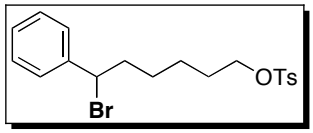
mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 0.5% pyridine/99.5% hexanes. Product **24b-Br** was isolated as a clear oil (54 mg, 46% yield, R_f = 0.57 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.24 (multiple peaks, 5H), 4.94 (t, *J* = 7.2 Hz, 1H), 2.31-2.23 (m, 1H), 2.16-2.08 (m, 1H), 1.49-1.40 (m, 1H), 1.39-1.15 (multiple peaks, 9H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.33, 128.64, 128.23, 127.24, 55.83, 39.99, 31.72, 29.04, 28.86, 28.24, 22.59, 14.05. HRMS EI (m/z): $[M^+]$ Calcd for $C_{14}H_{21}Br$, 268.0826; Found, 268.0830.



$PdCl_2(CH_3CN)_2$ (4.10 mg, 0.016 mmol, 10 mol %) and $CuBr_2$ (141 mg, 0.633 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (3.9 mL) was added at -78 °C. Substrate **31** (50.0 mg, 0.158 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (75.5 mg, 0.206 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1% EtOAc/1% Et_3N/98% hexanes. Product **31b-Br** was isolated as a viscous clear oil (42.0 mg, 57% yield, R_f = 0.13 in 2% ethyl acetate/99% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 8.8, 2.8 Hz, 2H), 7.38-7.24 (multiple peaks, 5H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.93 (t, *J* = 8.0 Hz, 1H), 4.40 (s, 2H), 3.41 (t, *J* = 6.0 Hz, 2H), 2.32-2.23 (m, 1H), 2.17-2.08 (m, 1H), 1.58 (quin, *J* = 6.8 Hz, 2H), 1.54-1.24 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.19, 138.30, 137.41, 129.43, 128.66, 128.28, 127.21, 92.87, 72.16, 70.25, 55.57, 39.90, 29.45, 28.01, 25.51. HRMS CI with ammonia (m/z): $[M+NH_4]^+$ Calcd for $C_{19}H_{22}BrIO$, 490.0242; Found, 490.0242.

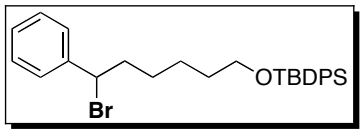


$PdCl_2(CH_3CN)_2$ (7.95 mg, 0.031 mmol, 10 mol %) and $CuBr_2$ (274 mg, 1.23 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (9.6 mL) was added at -78 °C. Substrate **32** (50.0 mg, 0.307 mmol, 1.00 equiv) and $PhSnBu_3$ (146 mg, 0.399 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **32b-Br** was isolated as a viscous clear oil (68.5 mg, 71% yield, R_f = 0.23 in hexanes). Note: The isolated product also contained 7% of the product where the terminal bromine was replaced with a phenyl group. Samples of **32b-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.25 (multiple peaks, 5H), 4.93 (t, *J* = 7.2 Hz, 1H), 3.37 (t, *J* = 6.4 Hz, 1H), 2.33-2.23 (m, 1H), 2.17-2.10 (m, 1H), 1.83 (quin, *J* = 6.8 Hz, 2H), 1.54-1.43 (multiple peaks, 5H), 1.37-1.24 (m, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 143.33, 129.45, 129.10, 128.19, 56.52, 40.43, 34.53, 33.29, 28.04, 27.96. HRMS EI (m/z): [M+] Calcd for $C_{12}H_{16}Br_2$, 317.9619; Found, 317.9614.

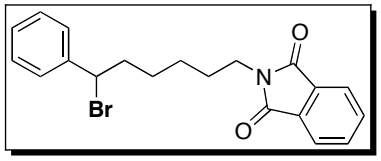


$PdCl_2(CH_3CN)_2$ (5.1 mg, 0.020 mmol, 10 mol %) and $CuBr_2$ (175 mg, 0.786 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (5.1 mL) was added at -78 °C. A solution of substrate **33** (50.0 mg, 0.197 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (93.8 mg, 0.256 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150

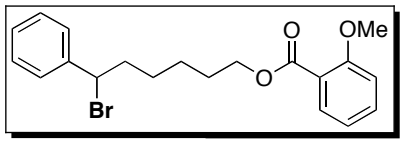
mL). The filtrate was concentrated and purified by chromatography on silica gel using 7% ethyl acetate/1% Et_3N/92% hexanes. Product **33b-Br** was isolated as a viscous clear oil (54.3 mg, 68% yield, R_f = 0.18 in 8% ethyl acetate/92% hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.36-7.24 (multiple peaks, 7H), 4.87 (t, *J* = 7.2 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H), 1.61 (quin, *J* = 6.8 Hz, 2H), 1.48-1.20 (multiple peaks, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.74, 138.29, 133.09, 129.85, 129.15, 128.47, 127.89, 126.87, 70.16, 56.80, 45.65, 37.31, 28.21, 23.62, 21.64. HRMS EI (m/z): $[M+NH_4]^+$ Calcd for $C_{19}H_{23}BrO_3S$, 428.0895; Found, 428.0888.



$PdCl_2(CH_3CN)_2$ (3.83 mg, 0.015 mmol, 10 mol %) and $CuBr_2$ (132 mg, 0.591 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (3.6 mL) was added at -78 °C. A solution of substrate **34** (50.0 mg, 0.148 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (70.5 mg, 0.192 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 0.5% ethyl acetate/1% Et_3N/98.5% hexanes. Product **34b-Br** was isolated as a viscous clear oil (43.6 mg, 61% yield, R_f = 0.30 in 1% ethyl acetate/99% hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 4H), 7.42-7.24 (multiple peaks, 11H), 4.91 (t, *J* = 8.4 Hz, 1H), 3.62 (td, *J* = 6.4, 1.2 Hz, 2H), 2.29-2.06 (multiple peaks, 2H), 1.56-1.18 (multiple peaks, 6H), 1.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.25, 135.56, 134.05, 129.52, 128.65, 128.26, 127.58, 127.24, 120.30, 120.09, 111.99, 63.65, 55.65, 39.97, 32.25, 27.97, 26.86, 25.12, 19.21. HRMS EI (m/z): $[M+NH_4]^+$ Calcd for $C_{28}H_{35}BrOSi$, 512.1984; Found, 512.1979.

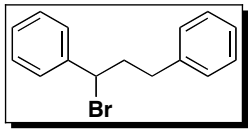


$PdCl_2(CH_3CN)_2$ (5.65 mg, 0.022 mmol, 10 mol %) and $CuBr_2$ (194 mg, 0.872 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (5.8 mL) was added at -78 °C. A solution of substrate **35** (50.0 mg, 0.218 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (104 mg, 0.284 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 7% ethyl acetate/1% Et_3N/92% hexanes. Product **35b-Br** was isolated as a viscous clear oil (58.5 mg, 70% yield, R_f = 0.17 in 10% ethyl acetate/90% hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.84-7.79 (multiple peaks, 2H), 7.71-7.67 (multiple peaks, 2H), 7.37-7.22 (multiple peaks, 5H), 4.91 (t, *J* = 7.2 Hz, 1H), 3.64 (t, *J* = 6.8 Hz, 2H), 2.30-2.21 (m, 1H), 2.15-2.07 (m, 1H), 1.65 (quin, *J* = 7.2 Hz, 2H), 1.58-1.46 (m, 1H), 1.40-1.31 (multiple peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.40, 142.09, 133.87, 132.09, 128.65, 128.28, 127.20, 123.16, 55.40, 39.77, 37.80, 28.35, 27.79, 26.16. HRMS EI (m/z): $[M+NH_4]^+$ Calcd for $C_{20}H_{20}BrNO_2$, 403.1021; Found, 403.1015.

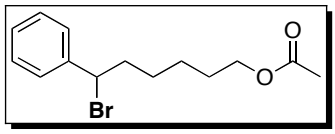


$PdCl_2(CH_3CN)_2$ (5.54 mg, 0.021 mmol, 10 mol %) and $CuBr_2$ (191 mg, 0.854 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (5.7 mL) was added at -78 °C. A solution of substrate **36** (50.0 mg, 0.213 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (102 mg, 0.277 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using

8% ethyl acetate/1% Et_3N/91% hexanes. Product **36b-Br** was isolated as a viscous clear oil (34 mg, 41% yield, R_f = 0.20 in 8% ethyl acetate/92% hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (dt, *J* = 8.0, 2.8 Hz, 1H), 7.49-7.25 (multiple peaks, 6H), 6.99-6.95 (multiple peaks, 2H), 4.95 (td, *J* = 8.0, 2.0 Hz, 1H), 4.27 (td, *J* = 6.8, 2.8 Hz, 2H), 3.89 (s, 3H), 2.33-2.26 (m, 1H), 2.20-2.11 (m, 1H), 1.74 (quin, *J* = 6.0 Hz, 2H), 1.58-1.30 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.25, 159.11, 142.13, 133.40, 131.49, 128.68, 128.32, 127.21, 120.30, 120.09, 111.99, 64.61, 55.94, 55.46, 39.89, 28.49, 27.91, 25.39. HRMS EI (m/z): $[M+H]^+$ Calcd for $C_{20}H_{23}BrO_3$, 391.0909; Found, 391.0904.

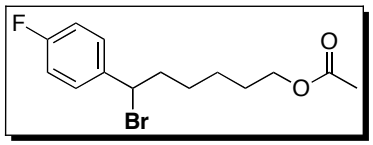


$PdCl_2(CH_3CN)_2$ (10.9 mg, 0.042 mmol, 10 mol %) and $CuBr_2$ (132 mg, 0.591 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (13 mL) was added at -78 °C. Substrate **37** (50.0 mg, 0.423 mmol, 1.00 equiv) and $PhSnBu_3$ (202 mg, 0.55 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **37b-Br** was isolated as a clear oil (42 mg, 37% yield, R_f = 0.13 in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.13 (multiple peaks, 10H), 4.90 (td, *J* = 8.0, 1.2 Hz, 1H), 2.84-2.57 (multiple peaks, 3H), 2.48-2.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.92, 140.42, 128.73, 128.51, 128.40, 127.87, 127.30, 126.20, 54.64, 41.30, 34.18.



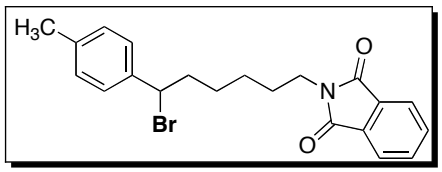
$PdCl_2(CH_3CN)_2$ (9.12 mg, 0.035 mmol, 10 mol %) and $CuBr_2$ (314 mg, 1.41 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (10 mL) was added

at -78 °C. A solution of substrate **38** (50.0 mg, 0.352 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (167 mg, 0.457 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1.5% ethyl acetate/1% Et_3N/97.5% hexanes. Product **38b-Br** was isolated as a viscous clear oil (71.0 mg, 68% yield, R_f = 0.11 in 2% ethyl acetate/98% hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.26 (multiple peaks, 5H), 4.94 (t, *J* = 7.2 Hz, 1H), 4.03 (td, *J* = 6.8, 0.8 Hz, 2H), 2.34-2.24 (m, 1H), 2.18-2.11 (m, 1H), 2.03 (s, 3H), 1.65-1.29 (multiple peaks, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.13, 142.10, 128.66, 128.30, 127.17, 64.28, 55.39, 39.83, 28.34, 27.86, 25.26, 20.97. HRMS EI (m/z): $[M+NH_4]^+$ Calcd for $C_{14}H_{19}BrO_2$, 316.0912; Found, 316.0912.

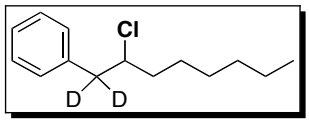


$PdCl_2(CH_3CN)_2$ (9.12 mg, 0.035 mmol, 10 mol %) and $CuBr_2$ (314 mg, 1.41 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (10 mL) was added at -78 °C. A solution of substrate **38** (50.0 mg, 0.352 mmol, 1.00 equiv) in Et_2O (1 mL) and *p*-$FPhSnBu_3$ (176 mg, 0.457 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1.5% ethyl acetate/1% Et_3N/97.5% hexanes. Product **38-*p*-Fb-Br** was isolated as a viscous clear oil (52.5 mg, 49% yield, R_f = 12 in 2% ethyl acetate/98% hexanes) as a 10:1 ratio of 1,1:1,2 isomers. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.31 (multiple peaks, 2H), 7.00 (t, *J* = 8.8 Hz, 2H), 4.90 (t, *J* = 7.2 Hz, 1H), 4.02 (t, *J* = 6.8 Hz, 1H), 2.29-2.20 (m, 1H), 2.13-2.03 (m, 1H), 2.01 (s, 3H), 1.60 (quin, *J* = 6.8 Hz, 2H), 1.53-1.44 (m, 1H), 1.41-1.23 (multiple peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.13, 162.32 (J_{C-F} = 247.65 Hz), 138.07 (J_{C-F} = 3.12 Hz), 128.97, 115.59 (J_{C-F} = 21.75 Hz), 64.24, 54.34,

39.99, 28.35, 27.84, 25.23, 20.95. HRMS EI (m/z): $[M+NH_4]^+$ Calcd for $C_{14}H_{18}BrFO_2$, 334.0818; Found, 334.0825.

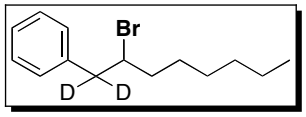


$PdCl_2(CH_3CN)_2$ (11.3 mg, 0.044 mmol, 10 mol %) and $CuBr_2$ (390 mg, 1.745 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (1.8 mL) was added at -78 °C. A solution of substrate **35** (100 mg, 0.436 mmol, 1.00 equiv) in Et_2O (1 mL) and a solution of *p*-$CH_3PhSnBu_3$ (216 mg, 0.567 mmol, 1.30 equiv) in Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 8% ethyl acetate/1% Et_3N/91% hexanes. Product **35-*p*-CH$_3$b-Br** was isolated as a viscous clear oil (60 mg, 35% yield, R_f = 0.24 in 8% ethyl acetate/92% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.80 (multiple peaks, 2H), 7.71-7.67 (multiple peaks, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 4.91 (t, *J* = 7.6 Hz, 1H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 2.30-2.20 (m, 1H), 2.15-2.02 (m, 1H), 1.65 (quin, *J* = 7.2 Hz, 2H), 1.52-1.25 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.41, 139.18, 138.20, 133.88, 132.12, 129.35, 127.10, 123.18, 55.61, 39.78, 37.83, 28.37, 27.84, 26.18, 21.16.

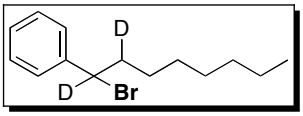


$PdCl_2(PhCN)_2$ (24.0 mg, 0.063 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (689 mg, 2.51 mmol, 4.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **24-*d*$_2$** (71.5 mg, 0.626 mmol, 1.00 equiv) and CH_2Cl_2 (19 mL) were added. $PhSnBu_3$ (299 mg, 0.814 mmol, 1.30 equiv) was added, and the

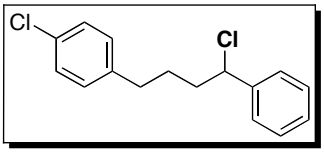
resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (299 mg, 0.814 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a >20 : 1 ratio of **24-*d*$_2$a-Cl** : **24-*d*$_2$b-Cl**. The product was purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. The product was isolated as a clear oil (113 mg, 80% yield, R_f = 0.33 in hexanes). Note: The isolated product contained 91% of **24-*d*$_2$a-Cl** and 4% of **24-*d*$_2$b-Cl** (23 : 1 ratio of **24-*d*$_2$a-Cl** : **24-*d*$_2$b-Cl**) as well as traces of the 2,1 isomer (5%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.38-7.21 (multiple peaks, 10H), 4.10 (dd, *J* = 9.0, 4.0 Hz, 1H), 1.81-1.55 (multiple peaks, 3H), 1.45-1.38 (m, 1H), 1.32-1.27 (multiple peaks, 6H), 0.89 (t, *J* = 7.0 Hz, 3H).



$PdCl_2(CH_3CN)_2$ (11.4 mg, 0.044 mmol, 10 mol %) and $CuBr_2$ (391 mg, 1.75 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (3.4 mL) was added at -78 °C. Substrate (50.0 mg, 0.438 mmol, 1.00 equiv) and $PhSnBu_3$ (209 mg, 0.570 mmol, 1.30 equiv) were added sequentially, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^1H NMR spectrum of this crude reaction mixture showed a 20 : 1 ratio of **24-*d*$_2$a-Br** : of **24-*d*$_2$b-Br**. The crude product was purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product was isolated as a viscous clear oil (83.7 mg, 72% yield, R_f = 0.80 in hexanes) as a >20:1 mixture of **24-*d*$_2$a-Br**: **24-*d*$_2$a-Br**. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.21 (multiple peaks, 5H), 4.22-4.19 (m, 1H), 1.87-1.75 (multiple peaks, 2H), 1.65-1.56 (m, 1H), 2.33-2.24 (m, 1H), 1.47-1.38 (m, 1H), 1.38-1.28 (multiple peaks, 6H), 0.91-0.88 (multiple peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.57, 129.18, 128.37, 126.73, 57.67, 38.09, 31.64, 28.60, 27.51, 22.55, 14.03. HRMS EI (m/z): $[M]^+$ Calcd for $C_{14}H_{19}D_2Br$, 270.0952; Found, 270.0952.

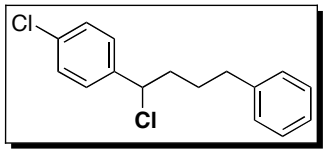


$PdCl_2(CH_3CN)_2$ (11.4 mg, 0.044 mmol, 10 mol %) and $CuBr_2$ (391 mg, 1.75 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (14 mL) was added at -78 °C. Substrate **24-*d*$_2$** (50.0 mg, 0.438 mmol, 1.00 equiv) and $PhSnBu_3$ (209 mg, 0.57 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **24-*d*$_2$b-Br** was isolated as a clear oil (49 mg, 42% yield, R_f = 0.74 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.25 (multiple peaks, 5H), 2.24-2.10 (m, 1H), 1.50-1.40 (m, 1H), 1.65-1.56 (m, 1H), 2.33-2.24 (m, 1H), 1.47-1.38 (m, 1H), 1.36-1.20 (multiple peaks, 9H), 0.87 (t, *J* =5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.27, 128.65, 128.24, 127.23, 39.48, 31.73, 29.05, 28.85, 28.11, 22.60, 14.06.

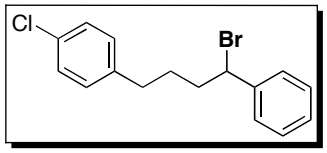


$PdCl_2(PhCN)_2$ (23.0 mg, 0.060 mmol, 10 mol %) and $CuCl_2$ (322 mg, 2.40 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (17 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. A solution of substrate **40** (100 mg, 0.600 mmol, 1.00 equiv) in dry Et_2O (2 mL) and $PhSnBu_3$ (286 mg, 0.780 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, and concentrated. The ^{1}H NMR spectrum of this crude reaction mixture showed a 5 : 1 ratio of **40a-Cl** : **40d-Cl**. The crude product was purified by chromatography on silica gel using 0.5% Et_3N/99.5%

hexanes. The product was isolated as a clear oil as a 4: 1 mixture of **40a-Cl** and **40d-Cl** (113 mg, 68% yield, R_f = 0.34 in hexanes). Samples of **40a-Cl** and **40d-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.28 (multiple peaks, 5H), 7.26-7.22 (multiple peaks, 2H), 7.07 (dd, *J* = 8.49, 2.00 Hz, 2H), 4.84 (td, *J* = 7.24, 2.00 Hz, 1H), 2.61 (t, *J* = 7.50 Hz, 2H), 2.18-2.10 (m, 1H), 2.07-2.00 (m, 1H), 1.86-1.77 (m, 1H), 1.67-1.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.64, 140.10, 131.62, 129.70, 128.65, 128.46, 128.30, 126.88, 63.49, 39.33, 34.52, 28.64. HRMS EI (m/z): $[M]^+$ Calcd for $C_{16}H_{16}Cl_2$, 278.0629; Found, 278.0637.

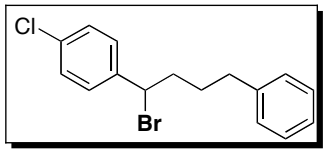


^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.27 (multiple peaks, 6H), 7.20 (t, *J* = 7.50 Hz, 1H), 7.16 (d, *J* = 7.00 Hz, 2H), 4.83 (dd, *J* = 8.00, 6.50 Hz, 1H), 2.66 (t, *J* = 7.50 Hz, 2H), 2.19-2.11 (m, 1H), 2.08-2.00 (m, 1H), 1.88-1.79 (m, 1H), 1.69-1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.56, 140.28, 133.99, 128.81, 128.42, 128.36, 128.32, 125.98, 62.58, 39.39, 35.17, 28.64. HRMS EI (m/z): $[M]^+$ Calcd for $C_{16}H_{16}Cl_2$, 278.0629; Found, 278.0626.

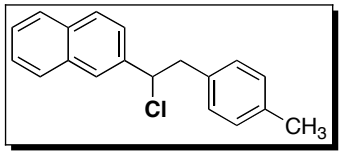


$PdCl_2(CH_3CN)_2$ (15.5 mg, 0.060 mmol, 10 mol %) and $CuBr_2$ (536 mg, 2.40 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (19 mL) was added at -78 °C. Substrate **40** (100 mg, 0.600 mmol, 1.00 equiv) and $PhSnBu_3$ (286 mg, 0.78 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 0.5% pyridine/99.5%

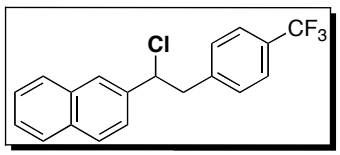
hexanes. The ^{1}H NMR spectrum pf this crude reaction mixture showed a 7:1 ratio of **40a-Br** : **40d-Br**. Product was isolated as a clear oil (150 mg, 91% yield, R_f = 28 in hexanes) as a 7:1 mixture of **40a-Br** : **40d-Br**. The clean product was rechromatographed to obtain a sample of pure **40a-Br** by collecting individual fractions. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.24 (multiple peaks, 5H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.93 (t, *J* = 7.2 Hz, 1H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.32-2.23 (m, 1H), 2.17-2.08 (m, 1H), 1.85-1.74 (m, 1H), 1.64-1.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.95, 140.02, 131.64, 129.69, 128.71, 128.47, 128.37, 127.19, 55.19, 39.31, 34.41, 29.79. HRMS EI (m/z) for loss of HBr: Calcd for $C_{16}H_{16}BrCl$, 242.0862; Found, 242.0866.



$PdCl_2(CH_3CN)_2$ (19.6 mg, 0.076 mmol, 10 mol %) and $CuBr_2$ (676 mg, 3.02 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (24 mL) was added at -78 °C. Substrate **39** (100 mg, 0.756 mmol, 1.00 equiv) and *p*-$ClPhSnBu_3$ (395 mg, 0.98 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^{1}H NMR spectrum of this crude reaction mixture showed a 3:1 ratio of **40d-Br** : **40a-Br**. The crude product purified by chromatography on silica gel using 0.5% pyridine/99.5% hexanes. Product was isolated as a clear oil (93 mg, 45% yield, R_f = 26 in hexanes) as a 3:1 mixture of **40d-Br** : **40a-Br**. The clean product was rechromatographed to obtain a sample of pure **40d-Br** by collecting individual fractions. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.13 (multiple peaks, 9H), 4.91 (t, *J* = 8.0 Hz, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.34-2.24 (m, 1H), 2.18-2.09 (m, 1H), 1.87-1.76 (m, 1H), 1.67-1.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.48, 140.59, 133.98, 128.87, 128.60, 128.41, 128.34, 125.98, 53.99, 39.35, 35.04, 29.82. HRMS EI (m/z) for loss of Br: Calcd for $C_{16}H_{16}BrCl$, 243.0940; Found, 243.0931.

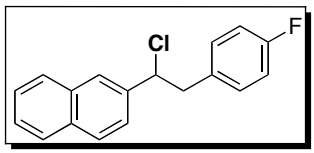


$PdCl_2(PhCN)_2$ (24.9 mg, 0.065 mmol, 10 mol %) and $CuCl_2$ (579 mg, 2.59 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (18 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and cooled to 0 °C. A solution of substrate **67** (100 mg, 0.649 mmol, 1.00 equiv) in dry Et_2O (1 mL) and *p*-$CH_3PhSnBu_3$ (321 mg, 0.843 mmol, 1.30 equiv) in dry Et_2O (1 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **67-*p*-CH$_3$a-Cl** was isolated as a white solid (65.0 mg, 36% yield, R_f = 0.15 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.76 (multiple peaks, 3H), 7.71 (br s, 1H), 7.54 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.48-7.45 (multiple peaks, 2H), 7.04-7.00 (multiple peaks, 4H), 5.19 (t, *J* = 7.2 Hz, 1H), 3.47-3.37 (multiple peaks, 2H) 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.46, 136.41, 134.35, 133.16, 132.98, 129.25, 129.07, 128.56, 128.07, 127.68, 126.35, 126.34, 126.28, 124.76, 64.58, 45.86, 21.04. HRMS EI (m/z): $[M]^+$ Calcd for $C_{19}H_{17}Cl$, 280.1019; Found, 280.1022.

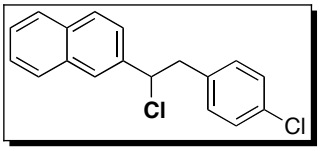


$PdCl_2(PhCN)_2$ (24.8 mg, 0.065 mmol, 10 mol %) and $CuCl_2$ (349 mg, 2.59 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to 0 °C. Et_2O (18 mL) was added at 0 °C. Substrate **67** (100 mg, 0.649 mmol, 1.00 equiv) in Et_2O (2 mL) and *p*-$CF_3PhSnBu_3$ (367 mg, 0.843 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the crude product was purified by chromatography on silica gel

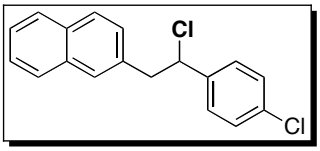
using a 1% Et_3N/99% hexanes. Product **67-*p*-CF_3a-Cl** was isolated as a white solid (105 mg, 49% yield, R_f = 0.15 in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86-7.81 (multiple peaks, 2H), 7.79-7.77 (m, 1H), 7.71 (br s, 1H), 7.54-7.47 (multiple peaks, 5H), 7.23 (d, *J* = 8.8 Hz, 2H), 5.21 (t, *J* = 7.6 Hz, 1H), 3.52 (dd, *J* = 14.0, 7.6 Hz, 1H approximate values due to second order effects), 3.47 (dd, *J* = 14.5, 7.6 Hz, 1H approximate values due to second order effects). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.35, 137.81, 133.22, 132.93, 129.78, 129.18 ($^2J_{C\text{-}F}$ = 32 Hz), 128.79, 128.06, 127.71, 126.59, 126.56, 126.23, 125.29 ($^4J_{C\text{-}F}$ = 3.0 Hz), 124.47, 124.16, ($^1J_{C\text{-}F}$ = 270 Hz), 63.74, 45.96. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.44.



$PdCl_2(PhCN)_2$ (24.8 mg, 0.065 mmol, 10 mol %) and $CuCl_2$ (349 mg, 2.59 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to 0 °C. Et_2O (18 mL) was added at 0 °C. Substrate **67** (100 mg, 0.649 mmol, 1.00 equiv) in Et_2O (2 mL) and *p*-$FPhSnBu_3$ (325 mg, 0.843 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the crude product was purified by chromatography on silica gel using a 1% Et_3N/99% hexanes. Product **67-*p*-Fa-Cl** was isolated as a white solid (141 mg, 77% yield, R_f = 0.15 in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92-7.89 (multiple peaks, 2H), 7.86-7.83 (m, 1H), 7.77 (br s, 1H), 7.60 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.58-7.54 (multiple peaks, 2H), 7.14-7.12 (multiple peaks, 2H), 6.99 (t, *J* = 9.5 Hz, 2H), 5.24 (t, *J* = 7.5 Hz, 1H), 3.52 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.46 (dd, *J* = 14.5, 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.77 ($^1J_{C\text{-}F}$ = 243 Hz), 138.01, 133.13, 133.02 ($^4J_{C\text{-}F}$ = 3.0 Hz), 132.90, 130.89 ($^3J_{C\text{-}F}$ = 8 Hz), 128.61, 128.02, 127.66, 126.44, 126.25, 124.58, 115.14 ($^2J_{C\text{-}F}$ = 21 Hz), 64.31, 45.42. One of the carbons is coincidentally overlapping. ^{19}F NMR (376 MHz, $CDCl_3$): -115.71 – -115.78.

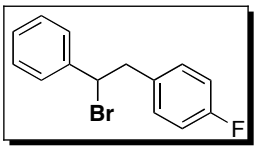


$PdCl_2(PhCN)_2$ (24.9 mg, 0.065 mmol, 10 mol %) and $CuCl_2$ (349 mg, 2.59 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (16 mL) was added in the glove box, and the flask was cooled to 0 °C. A solution of substrate **67** (100 mg, 0.649 mmol, 1.00 equiv) in dry Et_2O (2 mL) and *p*-$ClPhSnBu_3$ (338 mg, 0.843 mmol, 1.30 equiv) in dry Et_2O (2 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **67-*p*-Cla-Cl** was isolated as a white solid (133 mg, 69% yield, R_f = 0.35 in hexanes, mp = 120.9-121.6 ºC). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87-7.83 (multiple peaks, 2H), 7.80-7.78 (m, 1H), 7.71 (s, 1H), 7.55-7.48 (multiple peaks, 3H), 7.21 (d, *J* = 8.50 Hz, 2H), 7.06 (d, *J* = 8.99 Hz, 2H), 5.18 (t, *J* = 7.25 Hz, 1H), 3.46 (dd, *J* = 14.00, 7.49 Hz, 1H), 3.41 (dd, *J* = 14.25, 7.25 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.91, 135.76, 133.15, 132.90, 132.73, 130.75, 128.67, 128.49, 128.04, 127.68, 126.49, 126.47, 126.26, 124.54, 64.04, 45.59. HRMS EI (m/z): $[M]^+$ Calcd for $C_{18}H_{14}Cl_2$, 300.0472; Found, 300.0458.



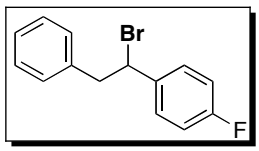
Product **67-*p*-ClbCl** was isolated from the Pd-catalyzed reaction of *p*-chlorostyrene with 2-naphthyl$SnBu_3$ and $PhICl_2$, because the reaction with $CuCl_2$ led to an inseparable mixture of **67-*p*-ClaCl** and **67-*p*-ClbCl**. $PdCl_2(PhCN)_2$ (27.9 mg, 0.072 mmol, 10 mol %) and $PhICl_2$ (397 mg, 1.44 mmol, 2.00 equiv) were weighed into a 25 mL Schlenk flask. Dry Et_2O (20 mL) was added in the glove box. The flask was sealed with a rubber septum that was secured with copper wire and the flask was cooled to –78 °C. *p*-chlorostyrene (100 mg, 0.721 mmol, 1.00 equiv) and 2-naphthyl$SnBu_3$ (391 mg, 0.938 mmol, 1.30

equiv) in dry Et_2O (2 mL) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was gravity filtered through a pad of silica pre-wetted with a 1% solution of Et_3N in Et_2O, and the pad was washed with 1% Et_3N in Et_2O (2 x 100 mL). The filtrate was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel using 1% Et_3N/99% hexanes. Product **67-*p*-ClbCl** was isolated as a white solid (121 mg, 56% yield, R_f = 0.35 in hexanes, mp = 130.9-132.3 ºC). ^{1}H NMR (500 MHz, acetone-d_6): δ 7.83 (d, J = 8.99 Hz, 1H), 7.79 (d, J = 8.00 Hz, 2H), 7.73 (s, 1H), 7.51 (dt, J = 8.49, 2.24 Hz, 2H), 7.48-7.42 (multiple peaks, 2H), 7.37 (td, J = 8.50, 2.00 Hz, 3H), 5.44 (t, J = 7.50 Hz, 1H), 3.59 (dd, J = 14.24, 7.74 Hz, 1H), 3.55 (dd, J = 14.00, 7.49 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.56, 134.47, 134.08, 133.33, 132.37, 128.72, 128.56, 128.20, 128.02, 127.62, 127.38, 126.11, 125.75, 62.99, 46.60. One of the carbon resonances is coincidently overlapping. HRMS EI (m/z): $[M]^+$ Calcd for $C_{18}H_{14}Cl_2$, 300.0472; Found, 300.0474.

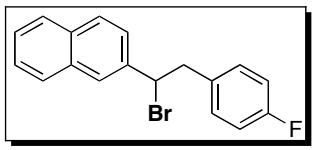


Pd(acac) (14.6 mg, 0.048 mmol, 10 mol %) and $CuBr_2$ (429 mg, 1.92 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (5 mL) was added at -78 °C. Substrate **42** (50.0 mg, 0.480 mmol, 1.00 equiv) and *p*-FPhSnBu_3 (240 mg, 0.57 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^{1}H NMR of the crude reaction mixture showed a >20:1 ratio of **42-*p*-FaBr**: **42-*p*-FbBr**. The crude product was purified by chromatography on silica gel using 0.5% pyridine/99.5% hexanes. Product **42-*p*-FaBr** was isolated as a clear oil (13 mg, 10% yield, R_f = 0.27 in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (multiple peaks, 5H), 7.05-7.01 (multiple peaks, 2H), 6.91 (tt, J = 8.40, 3.20 Hz, 2H), 5.05 (t, J = 7.60 Hz, 1H), 3.51 (dd, J = 14.00, 7.20 Hz, 1H), 3.43 (dd, J = 14.40, 7.60 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):

δ 161.77 ($^1J_{C\text{-}F}$ = 243 Hz), 141.21, 133.76 ($^4J_{C\text{-}F}$ = 3.1 Hz), 130.72 ($^3J_{C\text{-}F}$ = 8.5 Hz), 128.64, 128.47, 127.48, 115.20 ($^2J_{C\text{-}F}$ = 21 Hz), 55.32, 45.62. HRMS EI (m/z) for loss of Br: Calcd for $C_{14}H_{12}BrF$, 199.0923; Found, 199.0928.

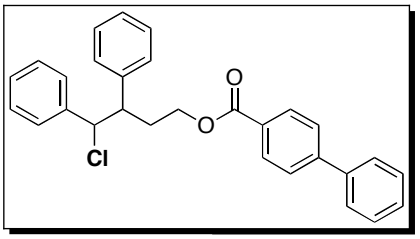


Pd(acac) (12.5 mg, 0.041 mmol, 10 mol %) and $CuBr_2$ (429 mg, 1.92 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (4.3 mL) was added at -78 °C. *p*-F-styrene (50.0 mg, 0.409 mmol, 1.00 equiv) and $PhSnBu_3$ (195 mg, 0.532 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^1H NMR of the crude reaction mixture showed a >20:1 ratio of **45a-Br** to **45b-Br**. The crude product was purified by chromatography on silica gel using 0.5% pyridine/99.5% hexanes. Product **45a-Br** was isolated as a clear oil (73 mg, 65% yield, R_f = 0.29 in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (multiple peaks, 5H), 7.05-7.01 (multiple peaks, 2H), 6.91 (tt, *J* = 8.40, 3.20 Hz, 2H), 5.05 (t, *J* = 7.60 Hz, 1H), 3.51 (dd, *J* = 14.00, 7.20 Hz, 1H), 3.43 (dd, *J* = 14.40, 7.60 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.35 ($^1J_{C\text{-}F}$ = 246 Hz), 137.80, 137.34 ($^4J_{C\text{-}F}$ = 3.9 Hz), 129.27 ($^3J_{C\text{-}F}$ = 8.5 Hz), 129.18, 128.42, 126.93, 115.52 ($^2J_{C\text{-}F}$ = 22 Hz), 54.28, 46.67. ^{19}F NMR (376 MHz, $CDCl_3$): δ -113.10 – -113.17. HRMS EI (m/z) for loss of Br: Calcd for $C_{14}H_{12}BrF$, 199.0923; Found, 199.0925.



Pd(acac) (9.9 mg, 0.032 mmol, 10 mol %) and $CuBr_2$ (289 mg, 1.30 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (2.4 mL) was added at -78 °C.

A solution of vinylnaphthalene (50.0 mg, 0.324 mmol, 1.00 equiv) in Et_2O (1 mL) and *p*-F-$PhSnBu_3$ (162 mg, 0.422 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated and the ^1H NMR of the crude reaction mixture showed a >20:1 ratio of **67-*p*-Fa-Br** to **67-*p*-Fb-Br**. The crude product was purified by chromatography on silica gel using 1% pyridine/99% hexanes. Product **67-*p*-Fa-Br** was isolated as a white solid (38 mg, 36% yield, R_f = 0.24 in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.50 Hz, 1H), 7.85 (t, *J* = 6.00 Hz, 1H), 7.79 (t, *J* = 6.00 Hz, 1H), 7.72 (br s, 1H), 7.60 (dd, *J* = 9.00, 2.00 Hz, 1H), 7.53-7.50 (multiple peaks, 2H), 7.11-7.09 (multiple peaks, 2H), 6.93 (t, *J* = 8.50 Hz, 2H), 5.28 (t, *J* = 7.00 Hz, 1H), 3.64 (dd, *J* = 14.00, 7.50 Hz, 1H), 3.58 (dd, *J* = 14.50, 7.50 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.77 ($^1J_{C\text{-}F}$ = 243 Hz), 138.38, 133.73 ($^4J_{C\text{-}F}$ = 3.1 Hz), 133.17, 132.92, 130.72 ($^3J_{C\text{-}F}$ = 8.5 Hz), 128.75, 128.05, 127.69, 126.56, 126.50, 126.39, 125.12, 115.25 ($^2J_{C\text{-}F}$ = 22 Hz), 55.72, 45.43. ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.73 – -115.80. HRMS EI (m/z): $[M]^+$ Calcd for $C_{18}H_{14}BrF$, 328.0263; Found, 328.0267.



$PdCl_2(CH_3CN)_2$ (11.7 mg, 0.030 mmol, 10 mol %) and $CuCl_2$ (164 mg, 1.218 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (8.5 mL) was added at -78 °C. A solution of substrate ***cis*-72** (100 mg, 0.304 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (145 mg, 0.396 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The crude ^1H NMR spectrum of this reaction mixture showed a 10:1 ratio **72a-Cl** : **72b-Cl**. The crude product was purified by chromatography

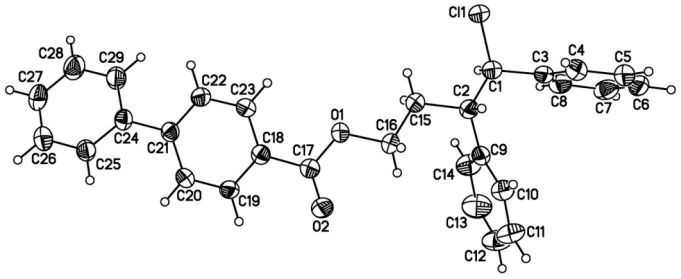
on silica gel using 4% EtOAc/0.5% Et_3N/95.5% hexanes. Product **72a-Cl** was isolated as an oil (66 mg, 50% yield, R_f = 0.15 in 5% EtOAc/95% hexanes) as a mixture of diastereomers. Samples of **72a-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (2%EtOAc/98% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$) (major diastereomer): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.64 (td, *J* = 7.2, 1.6 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.19-7.10 (multiple peaks, 8H), 7.04 (d, *J* = 7.6 Hz, 2H), 5.05 (d, *J* = 8.8 Hz, 1H), 4.29-4.23 (m, 1H), 4.15-4.08 (m, 1H), 3.42 (td, *J* = 10.4, 3.2 Hz, 1H), 2.88-2.80 (m, 1H) 2.32-2.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer): δ 166.26, 145.59, 140.09, 140.00, 139.50, 130.04, 128.92, 128.89, 128.49, 128.45, 128.13, 128.11, 127.91, 127.56, 127.27, 127.08, 126.99, 68.17, 63.18, 51.64, 31.84. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{29}H_{25}ClO_2$, 463.1441; Found, 463.1432.

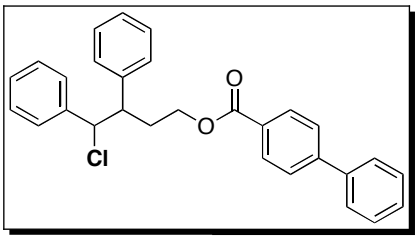
Structure Determination.

Colorless plates of **72a-Cl** were grown by diffusion of pentane into a chlorobenzene solution at 25 deg. C. A crystal of dimensions 0.18 x 0.16 x 0.08 mm was mounted on a Bruker SMART APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube (l = 0.71073 A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 180(1) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 4095 frames were collected with a scan width of 0.5° in w and 0.45° in phi with an exposure time of 30 s/frame. The integration of the data yielded a total of 77825 reflections to a maximum 2q value of 54.74° of which 10525 were independent and 7708 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9856 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group P1bar with Z = 4 for the formula $C_{29}H_{25}O_2Cl$. There are two crystallographically independent molecules in the asymmetric unit. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0417 and wR2 = 0.1013 [based on I

> 2sigma(I)], R1 = 0.0657 and wR2 = 0.1141 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file.

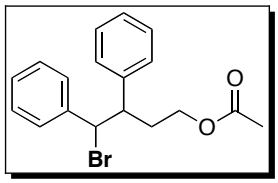
Sheldrick, G.M. SHELXTL, v. 6.12; Bruker Analytical X-ray, Madison, WI, 2001.
Sheldrick, G.M. SADABS, v. 2007/4. Program for Empirical Absorption Correction of Area Detector Data, University of Gottingen: Gottingen, Germany, 2007.
Saint Plus, v. 7.34, Bruker Analytical X-ray, Madison, WI, 2006.





$PdCl_2(CH_3CN)_2$ (14.0 mg, 0.037 mmol, 10 mol %) and $CuCl_2$ (196 mg, 1.46 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. THF (10 mL) was added at 0 °C. A solution of substrate ***trans*-72** (120 mg, 0.365 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (174 mg, 0.475 mmol, 1.30 equiv) were added. The reaction was stirred at 0 °C for 1 hour after which another aliquot of $PhSnBu_3$ (174 mg, 0.475 mmol, 1.30 equiv) was added. The resulting reaction mixture was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The crude ^1H NMR spectrum of this reaction mixture showed a 3:1 ratio diastereomers. The crude product was purified by chromatography on silica gel using 4% EtOAc/0.5% Et_3N/95.5% hexanes. Product was isolated as an oil (69 mg, 43% yield, R_f =

0.15 in 5% EtOAc/95% hexanes) as a mixture of diastereomers. Samples of **72b-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (2% EtOAc/98% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$) (minor diastereomer): δ 8.01 (dt, *J* = 8.5, 2.0 Hz, 8H), 7.21-7.18 (tt, *J* = 8.5, 1.5 Hz, 4H), 7.50 (td, *J* = 7.0, 1.5 Hz, 2H), 7.43 (tt, *J* = 7.0, 1.0 Hz, 1H), 7.38-7.29 (multiple peaks, 8H), 7.25 (d, *J* = 7.5 Hz, 2H), 5.11 (d, *J* = 8.5 Hz, 1H), 4.18 (quin, *J* = 6.0 Hz, 1H), 4.06-4.01 (m, 1H), 3.47 (td, *J* = 8.5, 3.5 Hz, 1H), 2.15-2.02 (multiple peaks, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) (minor diastereomer): δ 166.12, 145.64, 139.94, 139.87, 130.00, 128.93, 128.80, 128.59, 128.55, 128.49, 128.16, 127.66, 127.37, 127.26, 127.00, 67.64, 62.89, 51.23, 32.07. One of the carbons is coincidentally overlapping. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{29}H_{25}ClO_2$, 463.1441; Found, 463.1446.



$PdCl_2(CH_3CN)_2$ (40.9 mg, 0.158 mmol, 20 mol %) and $CuBr_2$ (705 mg, 3.15 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (5.2 mL) was added at -78 °C. A solution of substrate ***cis*-73** (150 mg, 0.789 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (354 mg, 0.964 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The crude ^{1}H NMR spectrum of this reaction mixture showed a 5:1 ratio of diastereomers. The crude product was purified by chromatography on silica gel using 4% EtOAc/1% Et_3N/95% hexanes. Product was isolated as an oil (94 mg, 34% yield, R_f = 0.13 in 6% EtOAc/94% hexanes) as a mixture of diastereomers. Samples of **73a-Br** and **73b-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (2% EtOAc/98% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$) (major diastereomer): δ 7.19-7.05 (multiple peaks, 8H), 6.96 (dd, *J* = 6.0, 1.2 Hz, 2H), 5.10 (d, *J* = 10.4 Hz, 1H), 3.99 (ddd, *J* = 11.0, 7.2, 5.0 Hz, 1H),

3.84-3.78 (m, 1H), 3.42 (td, *J* = 10, 3.6 Hz, 1H), 2.82-2.74 (m, 1H), 2.13-2.04 (m, 1H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer): δ 140.62, 139.38, 128.40, 128.26, 128.13, 127.94, 127.87, 127.01, 62.57, 60.51, 51.08, 33.67, 20.86. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{18}H_{19}BrO_2$, 369.0466; Found, 369.0459. ^{1}H NMR (400 MHz, $CDCl_3$) (minor diastereomer): δ 7.37-7.27 (multiple peaks, 8H), 7.21-7.18 (multiple peaks, 2H), 5.09 (d, *J* = 9.6 Hz, 1H), 3.88-3.82 (m, 1H), 3.72-3.65 (m, 1H), 3.43 (td, *J* = 9.6, 4.0 Hz, 1H), 1.94 (s, 3H) 1.92-1.76 (multiple peaks, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) (minor diastereomer): δ 140.82, 140.39, 128.67, 128.51, 128.26, 127.96, 127.42, 62.44, 60.01, 50.97, 32.44, 20.80. One of the carbons is coincidentally overlapping. HRMS EI (m/z): $[M+Na]^+$ Calcd for $C_{18}H_{19}BrO_2$, 369.0466; Found, 369.0458.

Structure Determination.

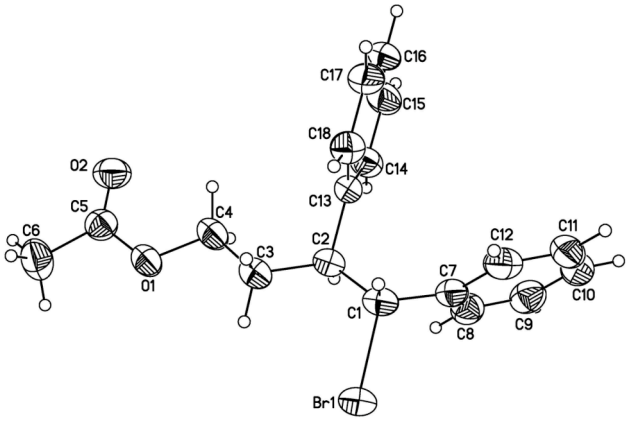
Colorless plates of **73a-Br** were crystallized from a chlorobenzene/pentane solution at 23 deg. C. A crystal of dimensions 0.40 x 0.24 x 0.085 mm was mounted on a standard Bruker SMART-APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube (l = 0.71073 A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 200(2) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 2240 frames were collected with a scan width of 0.5° in w and 0.45° in fwith an exposure time of 30 s/frame. The frames were integrated with the Bruker SAINT software package with a narrow frame algorithm. The integration of the data yielded a total of 33141 reflections to a maximum 2q value of 56.72° of which 4073 were independent and 3316 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9972 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2008/3) software package, using the space group P2(1)/n with Z = 4 for the formula $C_{18}H_{19}O_2Br$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full-matrix least-squares refinement based on F^2 converged at R1 = 0.0300 and wR2 = 0.0726 [based on I > 2sigma(I)], R1 = 0.0405 and wR2 = 0.0784 for

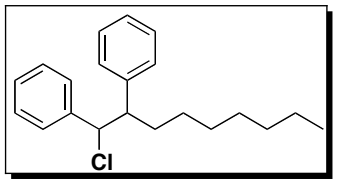
all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file.

Sheldrick, G.M. SHELXTL, v. 2008/3; Bruker Analytical X-ray, Madison, WI, 2008.

Saint Plus, v. 7.53A, Bruker Analytical X-ray, Madison, WI, 2008.

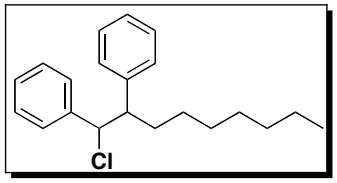
Sheldrick, G.M. SADABS, v. 2008/1. Program for Empirical Absorption Correction of Area Detector Data, University of Gottingen: Gottingen, Germany, 2008.





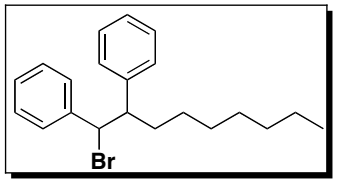
$PdCl_2(PhCN)_2$ (28.4 mg, 0.074 mmol, 10 mol %) and $CuCl_2$ (399 mg, 2.96 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (22 mL) was added at -78 °C. A solution of substrate ***cis*-76** (150 mg, 0.741 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (353 mg, 0.964 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The crude ^1H NMR spectrum of this reaction mixture showed a 9:1 ratio of diastereomers. The crude product was purified by chromatography

on silica gel using 0.5% Et_3N/99.5% hexanes. Product was isolated as an oil (126 mg, 55% yield, R_f = 0.21 in hexanes) as a mixture of diastereomers. However, one set of fractions was just the major diastereomer **76a-Cl** and was used for characterization. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20-7.08 (multiple peaks, 8H), 6.97 (d, *J* = 8.0 Hz, 2H), 4.99 (d, *J* = 9.2 Hz, 1H), 3.16 (td, *J* = 12.0, 3.6 Hz, 1H), 2.31-2.23 (m, 1H), 1.83-1.73 (m, 1H), 1.36-1.06 (multiple peaks, 10H), 0.86 (t, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer): δ 140.75, 140.62, 128.63, 128.03, 127.92, 127.64, 127.62, 126.53, 68.73, 54.41, 32.65, 31.78, 29.47, 29.09, 27.27, 22.59, 14.05. HRMS CI with ammonia: $[M+NH_4]^+$ Calcd for $C_{21}H_{27}Cl$, 332.2145; Found, 332.2149.



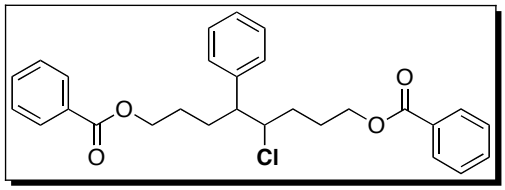
$PdCl_2(PhCN)_2$ (18.9 mg, 0.049 mmol, 10 mol %) and $CuCl_2$ (266 mg, 1.98 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (14 mL) was added at -78 °C. A solution of substrate ***trans*-76** (100 mg, 0.494 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (236 mg, 0.642 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The crude ^1H NMR spectrum of this reaction mixture showed a 2:1 ratio of diastereomers. The crude product was purified by chromatography on silica gel using 0.5% Et_3N/99.5% hexanes. Product was isolated as an oil (57 mg, 37% yield, R_f = 0.19 in hexanes) as a mixture of diastereomers. Samples of **76b-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$) (minor diastereomer): δ 7.34-7.23 (multiple peaks, 8H), 7.16 (d, *J* = 6.8 Hz, 2H), 4.99 (d, *J* = 8.8 Hz, 1H), 3.14 (td, *J* = 8.8, 4.8 Hz, 1H), 1.54-1.44 (multiple peaks, 2H), 1.22-0.96 (multiple peaks, 10H), 0.80 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (minor diastereomer): δ 141.36, 140.60, 128.62, 128.37, 128.16, 128.13, 127.65, 126.82, 68.25, 54.19, 32.98,

31.69, 29.26, 28.97, 27.31, 22.54, 14.02. HRMS CI with ammonia: $[M+NH_4]^+$ Calcd for $C_{21}H_{27}Cl$, 332.2145; Found, 332.2156.



$PdCl_2(CH_3CN)_2$ (38.5 mg, 0.099 mmol, 20 mol %) and $CuBr_2$ (441 mg, 1.98 mmol, 4.00 equiv) were weighed into a 25 mL Schlenk flask. The flask was sealed with a rubber septum that was secured with copper wire and cooled to –78 °C. Et_2O (4.8 mL) was added at -78 °C. A solution of substrate ***cis*-76** (100 mg, 0.494 mmol, 1.00 equiv) in Et_2O (1 mL) and $PhSnBu_3$ (236 mg, 0.642 mmol, 1.30 equiv) were added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The crude ^1H NMR spectrum of this reaction mixture showed a 5:1 ratio of diastereomers. The crude product was purified by chromatography on silica gel using 1% Et_3N/99.5% hexanes. Product was isolated as an oil (52 mg, 19% yield, R_f = 0.21 in hexanes) as a mixture of diastereomers. Samples of **76a-Br** and **76b-Br** for HRMS and NMR analysis were obtained after further purification by HPLC (100% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$) (major diastereomer): δ 7.16-7.03 (multiple peaks, 8H), 6.94 (dd, *J* = 8.0, 1.2 Hz, 2H), 5.09 (d, *J* = 10 Hz, 1H), 3.26 (td, *J* = 10.8, 3.2 Hz, 1H), 2.40-2.32 (m, 1H), 1.79-1.71 (m, 1H), 1.36-1.00 (multiple peaks, 10H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer): δ 141.17, 140.76, 128.45, 128.08, 128.00, 127.65, 126.49, 61.52, 54.10, 34.70, 31.79, 29.43, 29.10, 27.32, 22.60, 14.06. One of the carbons is coincidentally overlapping. HRMS CI with ammonia: $[M+NH_4]^+$ Calcd for $C_{21}H_{27}Br$, 376.1640; Found, 376.1641. ^1H NMR (400 MHz, $CDCl_3$) (minor diastereomer): δ 7.37-7.24 (multiple peaks, 8H), 7.19 (d, *J* = 7.6 Hz, 2H), 5.05 (d, *J* = 10 Hz, 1H), 3.28-3.22 (m, 1H), 1.48-1.41 (multiple peaks, 2H), 1.20-0.92 (multiple peaks, 10H), 0.79 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (minor diastereomer): δ 142.39, 141.10, 128.54, 128.33, 128.20, 127.93, 126.89, 61.02, 54.06, 33.59, 31.67, 29.21, 28.93, 27.48, 22.53,

14.01. One of the carbons is coincidentally overlapping. HRMS CI with ammonia: $[M+NH_4]^+$ Calcd for $C_{21}H_{27}Br$, 376.1640; Found, 376.1651.

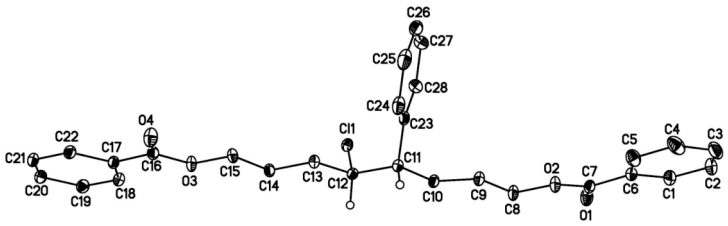


$PdCl_2(PhCN)_2$ (37.5 mg, 0.098 mmol, 10 mol %) was weighed into a 25 mL Schlenk flask. $PhICl_2$ (537 mg, 1.95 mmol, 2.00 equiv) was added to this flask in the glove box. The flask was sealed with a rubber septum that was secured with copper wire. The flask was cooled to –78 °C, and substrate **77** (344 mg, 0.977 mmol, 1.00 equiv) and CH_2Cl_2 (5.7 mL) were added. $PhSnBu_3$ (466 mg, 1.27 mmol, 1.30 equiv) was added, and the resulting mixture stirred at –78 °C for 1 h. A second aliquot of $PhSnBu_3$ (466 mg, 1.27 mmol, 1.30 equiv) was added, and the reaction was allowed to warm to room temperature over 5 h and then stirred for an additional 7 h. The reaction mixture was filtered through a pad of celite and washed with copius Et_2O (150 mL). The filtrate was concentrated. The ^1H NMR spectrum of this crude reaction mixture showed a 39% yield of **77-Cl**. The product was purified by chromatography on silica gel using 9% EtOAc/1% Et_3N/90% hexanes. The product was isolated as a clear oil as a mixture with the corresponding dichloro product. Samples of **77-Cl** for HRMS and NMR analysis were obtained after further purification by HPLC (6% EtOAc/94% hexanes, 20 mL/min, Waters μ-porasil 19.1 mm). ^1H NMR (400 MHz, $CDCl_3$): δ 8.03-7.96 (multiple peaks, 4H), 7.57-7.53 (multiple peaks, 2H), 7.45-7.40 (multiple peaks, 4H), 7.33-7.24 (multiple peaks, 5H), 4.34-4.21 (multiple peaks, 5H), 3.03-2.98 (m, 1H), 2.07-1.99 (multiple peaks, 3H), 1.93-1.82 (multiple peaks, 2H), 1.73-1.59 (multiple peaks, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.53, 166.48, 139.43, 132.89, 132.86, 130.26, 130.18, 129.49, 129.10, 128.32, 128.29, 127.20, 67.00, 64.58, 64.14, 51.37, 32.31, 28.52, 26.72, 26.16. Five carbons are coincidentally overlapping.

Structure Determination.

Colorless plates of **77-Cl** were grown from a chlorobenzene/pentane solution at 25 deg. C. A crystal of dimensions 0.38 x 0.20 x 0.20 mm mounted on a Bruker SMART APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube (l = 0.71073 A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 85(1) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 4530 frames were collected with a scan width of 0.5° in w and 0.45° in phi with an exposure time of 15 s/frame. The integration of the data yielded a total of 93080 reflections to a maximum 2q value of 59.20° of which 6767 were independent and 6209 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9843 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL software package, using the space group P2(1)/c with Z = 4 for the formula $C_{28}H_{29}O_4Cl$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0359 and wR2 = 0.0932 [based on I > 2sigma(I)], R1 = 0.0392 and wR2 = 0.0956 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file.

Sheldrick, G.M. SHELXTL, v. 2008/3; Bruker Analytical X-ray, Madison, WI, 2008.
Sheldrick, G.M. SADABS, v. 2008/1. Program for Empirical Absorption Correction of Area Detector Data, University of Gottingen: Gottingen, Germany, 2008.
Saint Plus, v. 7.34, Bruker Analytical X-ray, Madison, WI, 2006.



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