# Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions

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## 1. Introduction

### 1.1. Introduction to Pd-Catalyzed Directed C−H Functionalization

The development of methods for the direct conversion of carbon−hydrogen bonds into carbon−oxygen, carbon−halogen, carbon−nitrogen, carbon−sulfur, and carbon−carbon bonds remains a critical challenge in organic chemistry. Mild and selective transformations of this type will undoubtedly find widespread application across the chemical field, including in the synthesis of pharmaceuticals, natural products, agrochemicals, polymers, and feedstock commodity chemicals. Traditional approaches for the formation of such functional groups rely on

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prefunctionalized starting materials for both reactivity and selectivity. However, the requirement for installing a functional group prior to the desired C−O, C−X, C−N, C−S, or C−C bond adds costly chemical steps to the overall construction of a molecule. As such, circumventing this issue will not only improve atom economy but also increase the overall efficiency of multistep synthetic sequences.

Direct C−H bond functionalization reactions are limited by two fundamental challenges: (i) the inert nature of most carbon−hydrogen bonds and (ii) the requirement to control site selectivity in molecules that contain diverse C−H groups. A multitude of studies have addressed the first challenge by demonstrating that transition metals can react with C−H bonds to produce C−M bonds in a process known as "C−H activation".[1] The resulting C−M bonds are far more reactive than their C−H counterparts, and in many cases they can be converted to new functional groups under mild conditions.

The second major challenge is achieving selective functionalization of a single C−H bond within a complex molecule. While several different strategies have been employed to address this issue, the most common (and the subject of the current review) involves the use of substrates that contain coordinating ligands. These ligands (often termed "directing groups") bind to the metal center and selectively deliver the catalyst to a proximal C−H bond. Many different transition metals, including Ru, Rh, Pt, and Pd, undergo stoichiometric ligand-directed C−H activation reactions (also known as cyclometalation).[2,3] Furthermore, over the past 15 years, a variety of catalytic carbon−carbon bond-forming processes have been developed that involve cyclometalation as a key step.[1b−d,4]

The current review will focus specifically on ligand-directed C−H functionalization reactions catalyzed by palladium. Palladium complexes are particularly attractive catalysts for such transformations for several reasons. First, ligand-directed C−H functionalization at Pd centers can be used to install many different types of bonds, including carbon−oxygen, carbon−halogen, carbon−nitrogen, carbon−sulfur, and carbon−carbon linkages. Few other catalysts allow such diverse bond constructions,[5−7] and this versatility is predominantly the result of two key features: (i) the compatibility of many Pd$^{II}$ catalysts with oxidants, and (ii) the ability to selectively functionalize cyclopalladated intermediates. Second, palladium participates in cyclometalation with a wide variety of directing groups and, unlike many other transition metals, readily promotes C−H activation at both sp$^2$ and sp$^3$ C−H sites. Finally, the vast majority of Pd-catalyzed directed C−H functionalization reactions can be performed in the presence of ambient air and moisture, making them exceptionally practical for applications in organic synthesis.

While several accounts have described recent advances, this is the first comprehensive review encompassing the large body of work in this field over the past 5 years (2004−2009). Both synthetic applications and mechanistic aspects of these transformations are discussed where appropriate, and the review is organized on the basis of the type of bond being formed.

Thomas Lyons was born in Ottawa, IL, in 1983. He received his B.S. degree with honors in Chemistry from DePaul University in 2005 under the mentorship of Professor Matthew Dintzner. He is currently a Ph.D. candidate in Professor Melanie Sanford's research laboratory, where he is studying regioselective oxidative coupling reactions.

Melanie Sanford received her B.S. and M.S. degrees at Yale University, where she carried out undergraduate research in the laboratory of Professor Robert Crabtree. She pursued graduate studies at the California Institute of Technology working with Professor Robert Grubbs. Following postdoctoral work at Princeton University with Professor John Groves, she joined the faculty at the University of Michigan in the summer of 2003 as an Assistant Professor of Chemistry. In spring 2007 she was promoted to her current position of Associate Professor of Chemistry. She has been recognized with a number of awards, including a Presidential Early Career Award in Sciences and Engineering, an Arthur Cope Scholar award from the American Chemical Society, and the BASF catalysis award. Research in the Sanford group focuses broadly on the development and mechanistic study of new transition-metal-catalyzed reactions for applications in organic synthesis. The group is working to develop a diverse set of transformations for the direct conversion of unactivated carbon−hydrogen bonds into new functional groups with high levels of chemo-, regio-, and stereoselectivity.

## 1.2. Mechanistic Manifolds

In general, ligand-directed C−H activation takes place at $Pd^{II}$ centers to afford cyclopalladated intermediates of general structure **A**. Complex **A** can then undergo functionalization by two distinct mechanistic manifolds. The first involves a $Pd^{II/0}$ pathway (Scheme 1), where functionalization occurs via a reductive process (typically reductive elimination or $\beta$-hydride elimination/deprotonation) to release the product. The resulting $Pd^0$ intermediate is then oxidized to regenerate the $Pd^{II}$ catalyst.

A second pathway involves functionalization of palladacycle **A** with an electrophilic reagent. Such reagents can react by several distinct mechanisms, including (i) direct electrophilic cleavage of the Pd−C bond without a change in oxidation state at the metal center (Scheme 2), (ii) one-electron oxidation of palladacycle **A** (Scheme 3), or (iii) two-electron oxidation of the palladacyclic complex (Scheme 4). In the latter case, two-electron oxidation could proceed to generate a $Pd^{IV}$ intermediate (**B**, Scheme 4) or a $Pd^{III} \sim Pd^{III}$ dimer (**C**, Scheme 4), depending on the nature of the ancillary ligands at the metal center. Notably, the reactions in Schemes 1−4 all show delivery of the functional group from an external reagent; however, intramolecular functionalization can also occur in these systems.

## 2. Carbon−Oxygen Bond Formation

A variety of different oxidants have been used to effect Pd-catalyzed *ortho*-oxygenation reactions. This section details the current state of the art in terms of reaction scope and mechanism for each class of oxygenation reagent.

## 2.1. Iodine(III) Oxidants

The first examples of Pd-catalyzed ligand-directed $sp^2$ C−H bond oxygenation used $PhI(OAc)_2$ as a stoichiometric oxidant in conjunction with catalytic $Pd(OAc)_2$.[8] A variety of pyridine derivatives served as excellent directing groups, and the reactions produced *ortho*-acetoxylated products in yields ranging from 54% to 88% (Scheme 5). Other nitrogen-based directing groups, including imines, oxime ethers, azobenzene derivatives, and nitrogen heterocycles (e.g., pyrazoles and isoxazolines) were also effective; furthermore, amides, which contain relatively basic oxygen atoms, could be used to direct these reactions.[9,10] In contrast, simple ketones and aldehydes did not undergo *ortho*-acetoxylation under these conditions, presumably because these are relatively poor ligands for $Pd^{II}$. This is a limitation of the vast majority of Pd-catalyzed reactions discussed in this review.[11]

These transformations are typically conducted without any special purification of solvents or reagents, and all of the *ortho*-oxygenation reactions in this section were similarly tolerant of ambient air and moisture. Many common functional groups are stable under the reaction conditions, including aryl halides, ethers, benzylic hydrogens, nitro groups, and enolizable ketones, oximes, and amides. A systematic study of *meta*-substituted arylpyridines and arylpyrrolidinones revealed that Pd-catalyzed $sp^2$ C−H acetoxylation occurs selectively at the less hindered *ortho* site, regardless of the electronic character or potential chelating ability of the *meta* substituent.[9] This selectivity appears to be general for most Pd-catalyzed C−H functionalization reactions of *meta*-substituted arenes (vide infra for examples).

Polymer-immobilized $ArI(OAc)_2$ has also been used for the Pd-catalyzed acetoxylation of many of the substrates shown in Scheme 5 and afforded the products in comparable yields to $PhI(OAc)_2$.[12] This oxidant offers the advantage that it can be readily recovered from the reaction mixture and recycled (eq 1).

**Scheme 1. Reductive Functionalization Pathway: $Pd^{II/0}$ Catalytic Cycle**
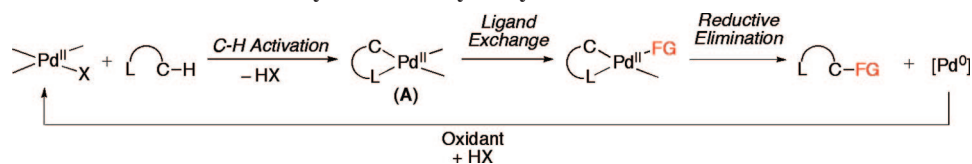
**Scheme 2. Electrophilic Functionalization Pathway (Mechanism i): Direct Electrophilic Functionalization of Palladacycle A**
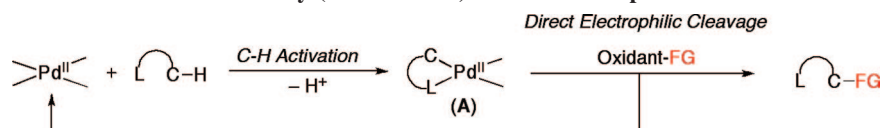


**Scheme 3. Electrophilic Functionalization Pathway (Mechanism ii): One-Electron Oxidation of Palladacycle A**
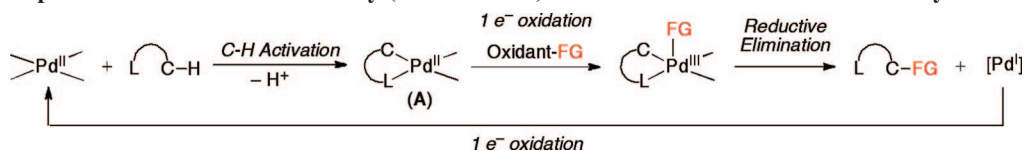


**Scheme 4. Electrophilic Functionalization Pathway (Mechanism iii): Two-Electron Oxidation of Palladacycle A**
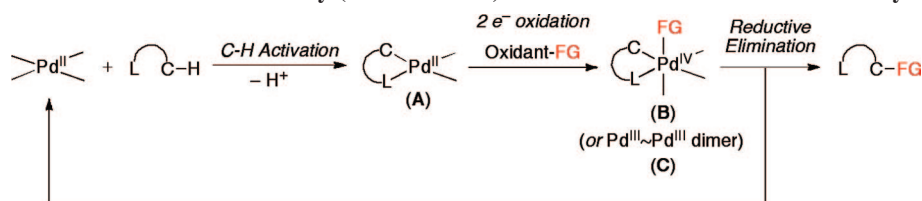


**Scheme 5. Pd(OAc)$_2$-Catalyzed sp$^2$ C−H Acetoxylation with PhI(OAc)$_2$[8−10]**
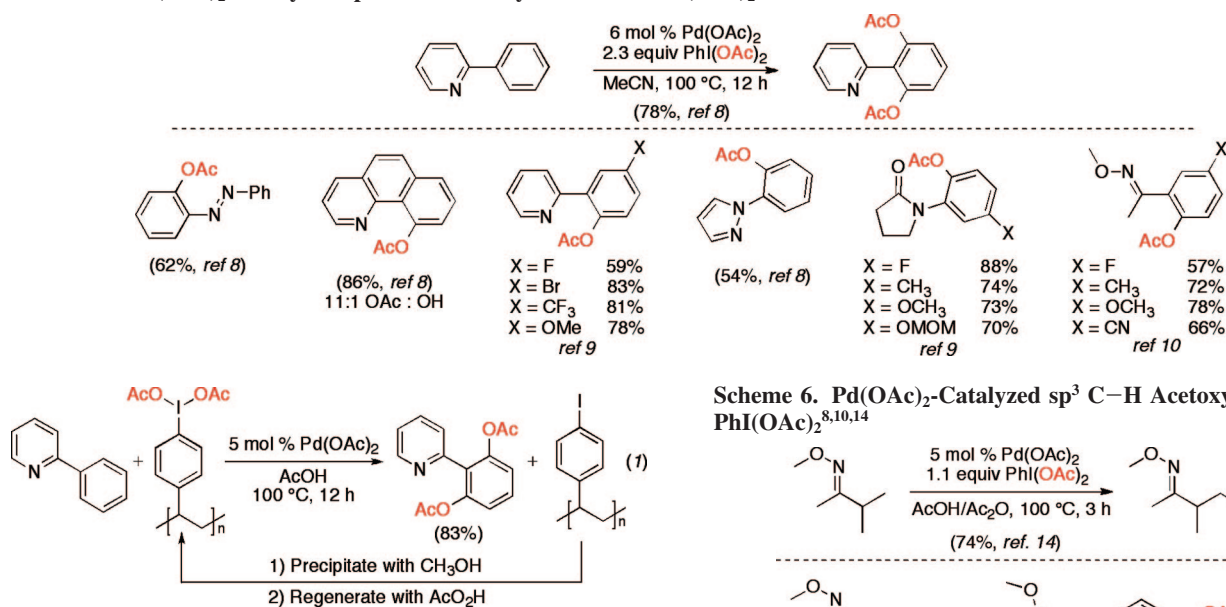


When the solvent for these reactions was changed from AcOH to an alcohol (ROH), aryl ether products were formed in high yields.[8] For example, the Pd-catalyzed reaction of benzo[*h*]quinoline with PhI(OAc)$_2$ in ROH could be used to prepare methyl, ethyl, isopropyl, and trifluoroethyl ethers (eq 2). The in situ reaction of the alcohol solvent with PhI(OAc)$_2$ to afford PhI(OR)$_2$[13] is believed to be a key step in these transformations.
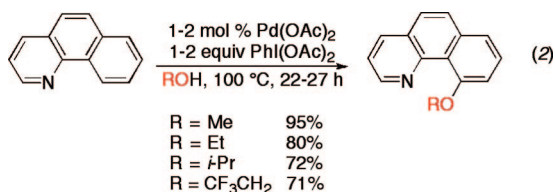


The first report of Pd-catalyzed ligand-directed sp$^3$ C−H bond oxygenation also used PhI(OAc)$_2$ as the terminal oxidant. As summarized in Scheme 6, both benzylic[8] and unactivated sp$^3$ C−H bonds[14] were readily converted to OAc

**Scheme 6. Pd(OAc)$_2$-Catalyzed sp$^3$ C−H Acetoxylation with PhI(OAc)$_2$[8,10,14]**
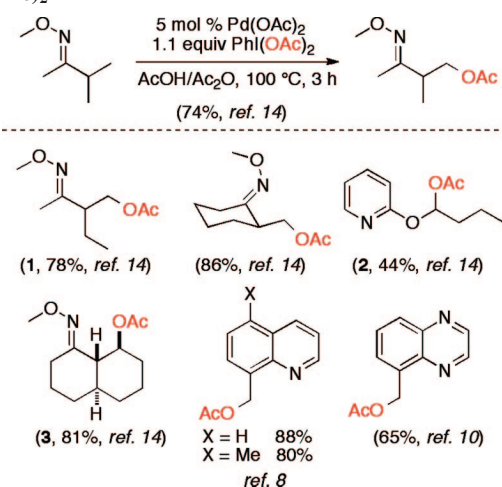


groups. Oxime ether and pyridine directing groups could be utilized for these transformations, and no products of $\beta$-hydride elimination were observed, presumably due to the rigidity of the palladacyclic intermediates.

In general, sp$^3$ C−H acetoxylation proceeds with very high selectivity for functionalization of 1° (versus 2°) C−H bonds and for the formation of 5-membered (versus 6-membered) palladacycles. A good example of this selectivity can be seen in the synthesis of product **1** (Scheme 6), which was formed with high (>95%) selectiv-

**Scheme 7. Proposed Mechanism for Pd(OAc)$_2$-Catalyzed C−H Acetoxylation with PhI(OAc)$_2$[8,15]**
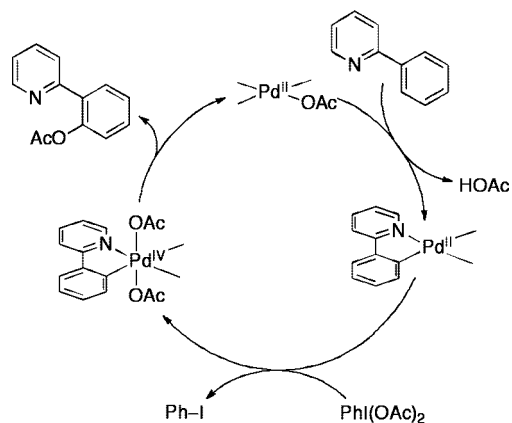


ity in the presence of numerous different types of proximal C−H bonds. While this high selectivity is advantageous for many applications, a current limitation of this chemistry (as well as of many related Pd-catalyzed ligand-directed C−H functionalization reactions) is that the activation of 2° and 3° sp$^3$ C−H bonds remains challenging. Acetoxylation at 2° sites with PhI(OAc)$_2$ has only been achieved in substrates containing adjacent activating groups (for example, the oxygen in **2**) or in highly rigid molecules such as **3** (Scheme 6).

The mechanism of Pd-catalyzed C−H oxygenation with PhI(OAc)$_2$ has been explored in some detail. Initial work showed that these reactions proceed with similar rates using either Pd(OAc)$_2$ or palladacycle **4** (eq 3) as the catalyst.[8] In addition, **4** was shown to react directly with PhI(OAc)$_2$ to afford acetoxylated product **5** (eq 3).[8] The former result suggests that **4** is a kinetically competent intermediate, while the latter provides evidence against a Pd$^{II/0}$ process. On this basis, the catalytic cycle in Scheme 7 was proposed for this transformation (shown with 2-phenylpyridine as a representative substrate). This cycle involves the following steps: (i) ligand-directed C−H activation to generate a cyclopalladated intermediate, (ii) two-electron oxidation of the palladacycle to generate a Pd$^{IV}$ species, and, finally, (iii) C−O bond-forming reductive elimination to release the product.[8,15] Notably, the other ancillary ligands on Pd during the catalytic cycle are not currently known and are represented as sticks in Scheme 7. More recent studies have suggested the possibility of a closely related two-electron mechanism involving dimeric Pd$^{III}$∼Pd$^{III}$ intermediates in related transformations.[16−18]
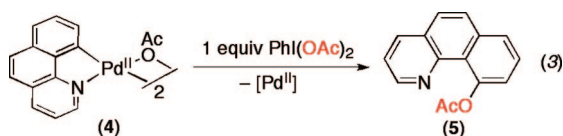


With both 2-benzylpyridine and 2-*ortho*-tolylpyridine as substrates, these transformations showed a zero-order dependence on [PhI(OAc)$_2$] in several different solvents (benzene, AcOH/Ac$_2$O, and MeCN).[19,20] In addition, large 1° intermolecular kinetic isotope effects (between 3.58 and 4.3) were observed (eqs 4 and 5). These studies indicate that cyclopalladation is the rate-limiting step of the catalytic cycle.
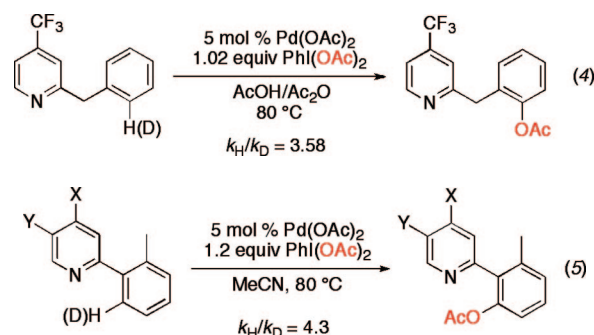


More detailed studies of the turnover-limiting step were recently conducted on the Pd(OAc)$_2$-catalyzed acetoxylation of 2-*ortho*-tolylpyridine (tolpy) in MeCN.[20] This transformation showed a Hammett $\rho$ value of +0.89 upon substitution of X and Y (eq 5) as well as an inverse first-order dependence on [tolpy] and a 1.5-order dependence on [Pd]. On the basis of these studies, the catalyst resting state was proposed to be *trans*-(tolpy)$_2$Pd$^{II}$(OAc)$_2$ (**6**) and cyclopalladation was proposed to proceed by two competing mechanisms that both involve pre-equilibrium dissociation of the tolpy ligand (Scheme 8).[20]

Because cyclopalladation is turnover limiting, it has proven challenging to directly investigate the proposed oxidation and C−O bond-forming reductive elimination steps of the catalytic cycle in Scheme 7. Thus, studies in this area have focused on the generation of stable model complexes to assay the feasibility of both (1) the two-electron oxidation of Pd$^{II}$ to Pd$^{IV}$ with PhI(OAc)$_2$ as the well as (2) C−O bond-forming reactions from high oxidation state Pd centers.[18,21−23] These studies have shown that PhI(OAc)$_2$ reacts with bis-cyclometalated model complex **7** to afford stable Pd$^{IV}$ species **8** (Scheme 9). Further, upon heating, complex **8** undergoes clean and quantitative C−O bond-forming reductive elimination to form **9**. Detailed mechanistic studies of this process (including Hammett plots, Eyring analysis, crossover studies, and investigations of the influence of solvent and additives) indicate that reductive elimination proceeds by an ionic mechanism involving initial carboxylate dissociation followed by C−O coupling from a 5-coordinate cationic intermediate (Scheme 9).[23,24] Although **8** is not an actual catalytic intermediate, these studies provide insights into the reactivity of high oxidation state palladium centers, which may be relevant to catalytic reactions.

**Scheme 8. Proposed Competing Mechanisms of Rate-Limiting Cyclopalladation during Pd(OAc)$_2$-Catalyzed C−H Acetoxylation[20]**
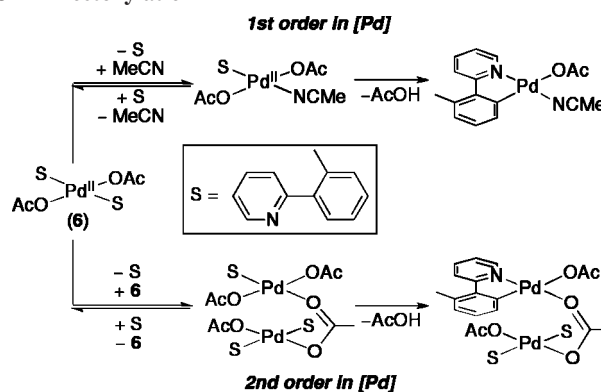
**Scheme 9. Formation and Reactivity of Model Pd$^{IV}$ Complex 8[23]**
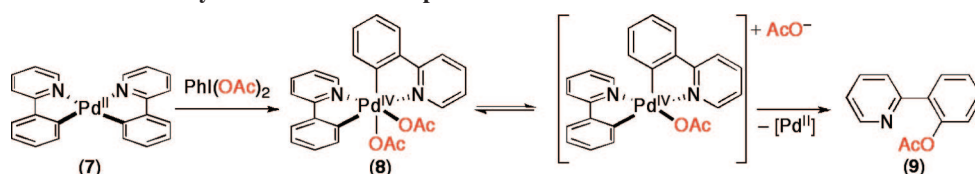


**Scheme 10. Pd(OAc)$_2$-Catalyzed sp$^2$ C−H Bond Oxygenation with Inorganic Peroxides[10,26]**
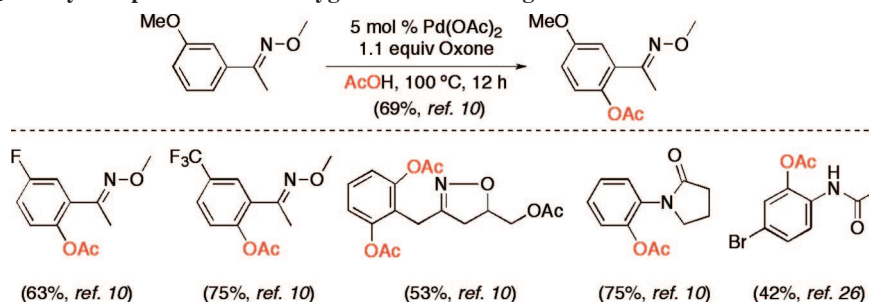


**Scheme 11. Acetoxylation of sp$^3$ C−H Bonds with Oxone[28]**
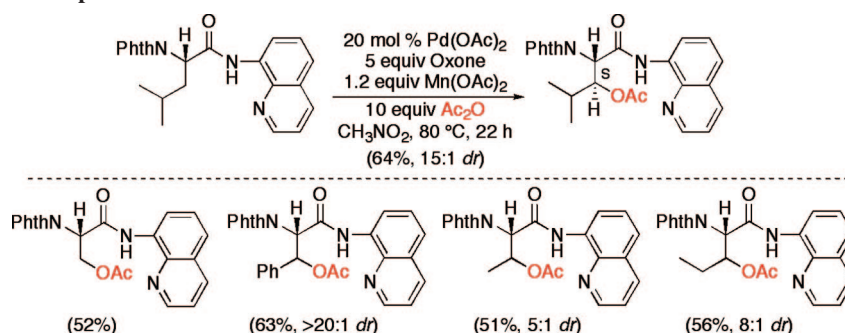


## 2.2. Iodine(I) Oxidants

The iodine(I) reagent IOAc has been successfully utilized for the Pd(OAc)$_2$-catalyzed acetoxylation of methyl groups in Boc-protected N-methylamine derivatives (eq 6).[25] The IOAc is generated in situ by reaction of I$_2$ with either PhI(OAc)$_2$ or AgOAc. Interestingly, no reaction was observed when either PhI(OAc)$_2$ or I$_2$ was used independently. Various alkyl N-methylamines and N-methylanilines underwent C−H acetoxylation in good to excellent yields, and remarkably high selectivity was observed for functionalization of N-CH$_3$ over N-aryl substituents. The mechanism was proposed to involve the following sequence of steps: (i) amide-directed C−H activation, (ii) oxidation to Pd$^{IV}$, (iii) C−I bond-forming reductive elimination, and, finally, (iv) nucleophilic displacement of I$^-$ by OAc$^-$ under the reaction conditions. However, generation of the products via direct C−OAc bond-forming reductive elimination (as proposed in Scheme 7) could not be ruled out.
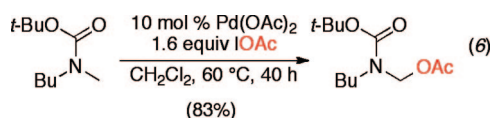


## 2.3. Peroxide Oxidants

Peroxide oxidants are attractive alternatives to costly iodine-based reagents for Pd-catalyzed ligand-directed C−H oxygenation. The Pd-catalyzed oxygenation of sp$^2$ C−H bonds has been achieved using inorganic peroxides such as Oxone or K$_2$S$_2$O$_8$ in AcOH or MeOH (Scheme 10).[10] In this system, the inorganic peroxide serves as the terminal oxidant (proposed to promote oxidation of Pd$^{II}$ to Pd$^{IV}$) while the solvent acts as the source of the oxygen functionality. Substrates containing a variety of directing groups including oxime ethers, amides, and isoxazolines react to afford both aryl esters[10,26] and aryl ethers.[10] Additionally, 2-arylpyridines can be converted directly to phenols using Oxone in conjunction with t-BuOH and PEG-3400.[27]

While Oxone and K$_2$S$_2$O$_8$ were highly effective reagents for oxygenation of sp$^2$ C−H bonds, early studies reported only moderate yields with sp$^3$ C−H substrates (eq 7).[10] However, subsequent work showed that the combination of Oxone and Mn(OAc)$_2$ promotes efficient acetoxylation of unactivated 2° sp$^3$ C−H bonds in amidoquinolines (Scheme 11).[28] The X-ray structure of a cyclopalladated amidoquinoline showed that both the amide and the quinoline moieties were bound to the metal, which may facilitate activation of 2° sp$^3$ C−H bonds. The reaction was applied to a number of amino-acid-derived substrates and generally proceeded in good yield (51−63%) and with high levels of diastereoselectivity (5:1 to >20:1). The authors propose that Mn(OAc)$_2$ reacts with Oxone to afford Mn$_3$O(OAc)$_7$, which then functions as a Lewis acid to increase the reactivity of the Pd$^{II}$ catalyst.
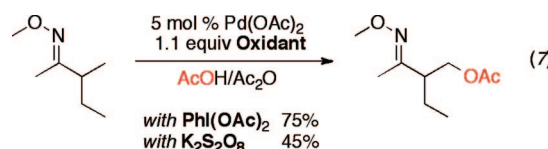


Efficient Pd(OAc)$_2$-catalyzed oxygenation of sp$^3$ C−H bonds has also been achieved using MeCO$_2$O-t-Bu or lauroyl

**Scheme 12. Oxazoline-Directed sp³ C—H Acetoxylation with MeCO₂O-t-Bu or Lauroyl Peroxide[29]**
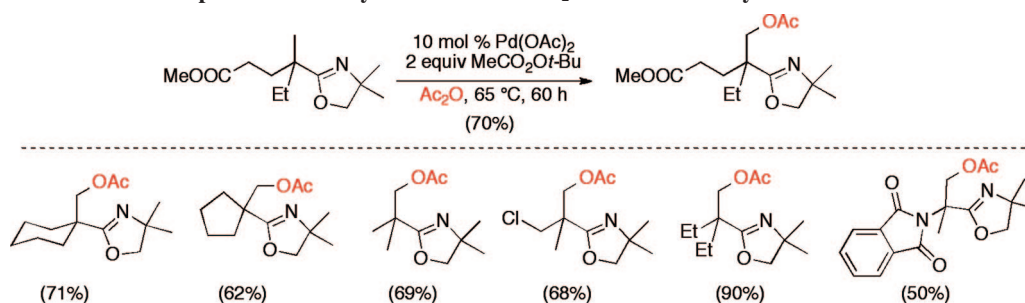


peroxide (Scheme 12).[29] The presence of acetic anhydride was essential in this system and was proposed to promote catalytic turnover. Oxazolines were employed as directing groups, and the reaction conditions were compatible with ketals, imides, esters, and alkyl chlorides. Substrates containing diastereotopic methyl groups proximal to a chiral oxazoline directing group afforded acetoxylated products with modest to excellent levels of diastereoselectivity (ranging from 56:44 to 91:9 dr) (eq 8). Again, a Pd[II/IV] mechanism was proposed for this system.
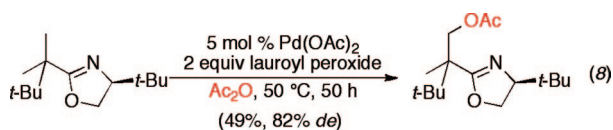


## 2.4. Dioxygen as a Terminal Oxidant

The Pd-catalyzed quinoline-directed acetoxylation of benzylic C—H bonds has recently been achieved using dioxygen as a terminal oxidant (eq 9).[30] This transformation proceeds with Pd(acac)₂ as the catalyst in conjunction with a 2,6-pyridinedicarboxylate ligand (H₂hpda in eq 9) in AcOH/Ac₂O under an atmosphere of O₂. While the reaction is currently restricted to 8-methylquinoline-derived substrates, it is an exciting advance because O₂ is readily available and inexpensive. Furthermore, it raises the intriguing question of whether O₂ can be used to generate high oxidation state palladium intermediates.
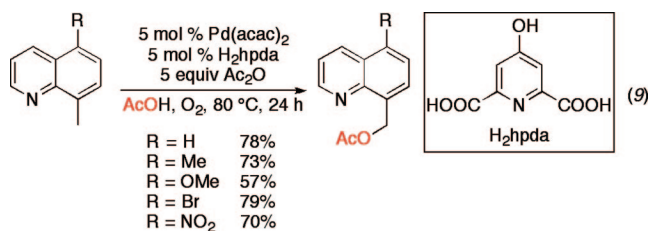


## 3. Carbon—Sulfur Bond Formation

Palladium-catalyzed ligand-directed formation of carbon—sulfur bonds remains relatively rare, and most examples involve intramolecular reactions to generate the C—S linkage. The first report of this type of transformation involved Pd(cod)Cl₂-catalyzed conversion of electronically diverse thioenols to substituted benzothiophenes (eq 10).[31] While the detailed mechanism remains to be elucidated, the authors invoked the involvement of a disulfide intermediate (formed in situ by oxidation of the starting material with DMSO).[32,33] This disulfide was then proposed to undergo oxidative addition to Pd⁰, cyclometalation at Pd[II], and finally C—S bond-forming reductive elimination to release the product. The proposed mechanism is supported by the observation

of traces of disulfides in the final reaction mixture as well as by the demonstration that independently prepared disulfides undergo smooth Pd-catalyzed annulation to form benzothiophene products.
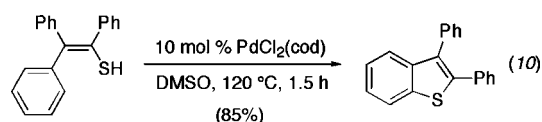


A similar intramolecular C—S bond-forming reaction has been applied to the synthesis of benzothiazoles from thiobenzanilides using catalytic Pd(cod)Cl₂ in combination with CuI and Bu₄NBr (eq 11).[34] While the role of the additives is not well understood, dramatically lower yields were obtained in their absence (35% without CuI and 3% without NBu₄Br). More recently, the related transformation of N-arylthioureas to 2-aminobenzothiazoles was reported using catalytic Pd(PPh₃)₄ along with O₂/MnO₂ as oxidants.[35] In both cases, Pd[II/0] mechanisms were proposed, but further studies will be required to delineate the details.
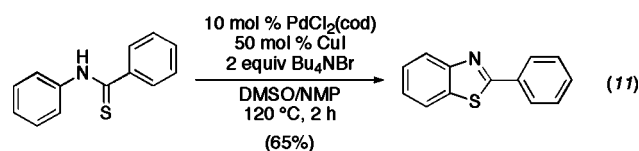


To date, the only example of intermolecular Pd-catalyzed C—H activation/C—S bond formation employed ArSO₂Cl as the sulfonating reagent.[36] Arylpyridine, arylpyrazole, and aryloxime ether substrates were converted to diarylsulfones using catalytic Pd(MeCN)₂Cl₂ and stoichiometric ArSO₂Cl (Scheme 13). The reaction was tolerant of electron-donating (p-MeO) and electron-withdrawing (p-CF₃) substituents on both the organic substrate and the sulfonyl chloride; however, aliphatic sulfonyl chlorides decomposed under the reaction conditions. Interestingly, tuning of the solvent, cocatalyst, and reaction temperature led to competing C—H chlorination and/or arylation (vide infra). Both Pd[II/0] and Pd[II/IV] mechanisms are plausible for this transformation.

## 4. Carbon—Halogen Bond Formation (Halogen = Cl, Br, I)

An early report of Pd-catalyzed ligand-directed C—H halogenation involved the *ortho*-chlorination of azobenzene with Cl₂.[37] As shown in eq 12, this reaction afforded a mixture of mono-, di-, tri-, and tetra-chlorinated products. While this work from 1970 elegantly demonstrated the viability of such transformations, the requirement for Cl₂ as the oxidant limited its widespread application in organic synthesis. As such, recent work has focused on the use of more practical halogenating

**Scheme 13. Intermolecular C−S Bond Formation with ArSO₂Cl³⁶**
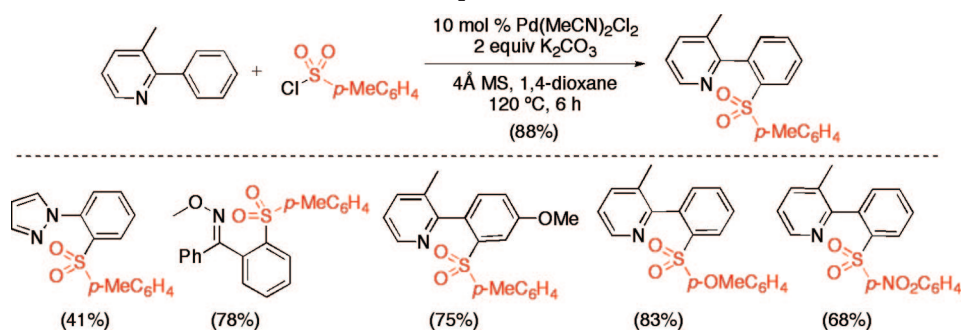


**Scheme 14. Halogenation of sp² C−H Substrates with N-Halosuccinimides⁴⁰**
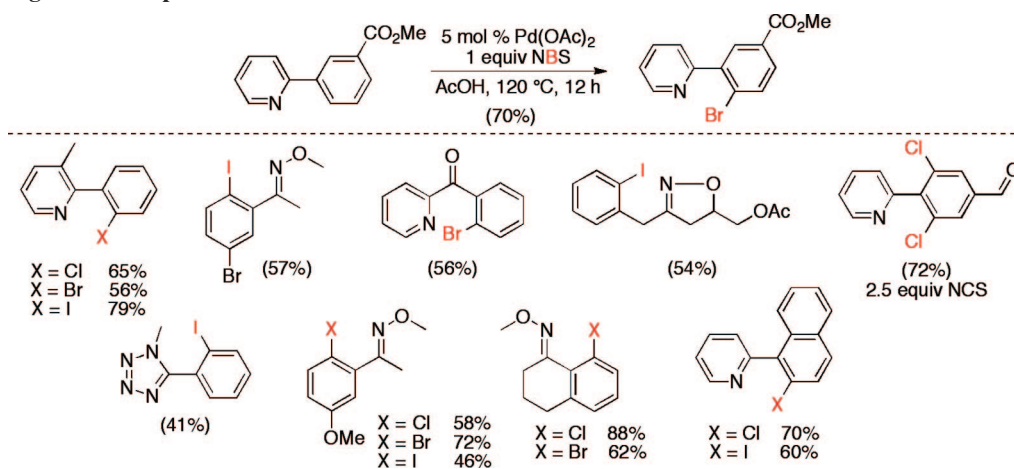


reagents (X⁺).³⁸ These transformations are described below and are organized based on the X⁺ reagent used in the reaction.
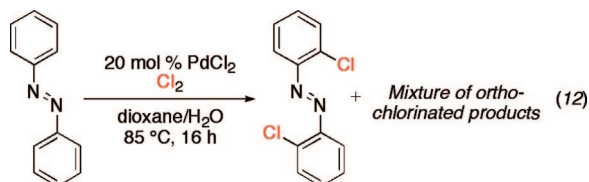


## 4.1. N-Halosuccinimides

A 2001 patent by Kodama and co-workers demonstrated that the combination of Pd(OAc)₂ and N-iodosuccinimide promotes the *ortho*-iodination of benzoic acids.³⁹ In 2004, similar conditions were applied to the directed chlorination and bromination of benzo[h]quinoline (eq 13, *i*). Interestingly, use of the more reactive "Cl⁺" source PhICl₂ led to chlorination at the 5-position (eq 13, *ii*) in lieu of the quinoline-directed transformation.⁸,⁴⁰
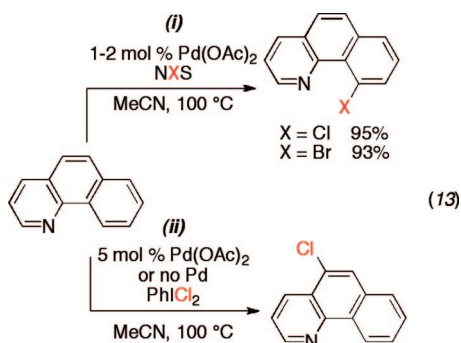


Pd-catalyzed directed sp²-halogenation with N-halosuccinimides has subsequently been expanded to a wider variety of directing groups, including pyridines, oxime ethers, isoquinolines, amides, and isoxazolines (Scheme 14).⁴⁰,⁴¹ In substrates with two available *ortho* C−H bonds, modest yields were obtained and competitive di-*ortho*-halogenation was typically observed. The di-*ortho*-halogenated products could generally be formed in high yields by utilizing excess oxidant (2.5 equiv), unless a steric bias was introduced into the substrate (for example, the 3-methyl group in 3-methyl-2-phenylpyridine).

The utility of this methodology is highlighted by substrates that afford different halogenated products in the presence versus the absence of a Pd catalyst.⁴⁰ For example, with **10**−**12**, *ortho*-halogenated products were obtained selectively under Pd catalysis (Scheme 15, *i*). However, in the absence of Pd, products of electrophilic aromatic substitution or benzylic halogenation were generated (Scheme 15, *ii*). This demonstrates the complementarity of Pd-catalyzed C−H functionalization to more traditional organic halogenation processes.

Kinetic studies of the PdCl₂-catalyzed chlorination of 2-*ortho*-tolylpyridine (tolpy) in MeCN showed that the reaction is first order in [Pd] and zero order in both [tolpy] and [NCS].²⁰ In addition, a large intermolecular kinetic isotope effect ($k_H/k_D = 4.4$) was observed (Figure 1). On the basis of this data, *trans*-Pd(tolpy)₂(Cl)₂ was proposed as the catalyst resting state and cyclopalladation was proposed to be the turnover-limiting step. The zero-order dependence on [tolpy] is in interesting contrast to the analogous C−H acetoxylation reactions (Scheme 8).²⁰ This result suggests that cyclopalladation occurs at Pd centers with different ligand environments in these two reactions.

**Scheme 15. Complementary Halogenation Products in the Presence/Absence of Pd[40]**
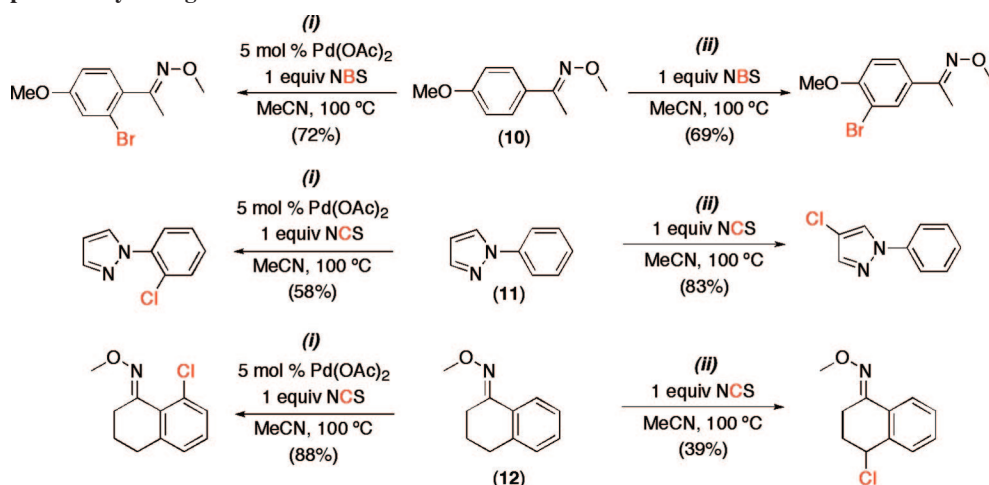


Model studies have been conducted to gain insights into the steps after cyclopalladation in the catalytic cycle. For example, the stoichiometric oxidation of Pd[II] model complex (phpy)$_2$Pd[II] with NCS afforded the Pd[IV] oxidative addition adduct **13**. Furthermore, complex **13** underwent C—Cl bond-forming reductive elimination to form **14** at 80 °C (Scheme 16).[42] These experiments demonstrate that NCS is a sufficiently strong and kinetically reactive oxidant to promote the oxidation of Pd[II] to Pd[IV] in this model system. In addition, these studies illustrate the viability of C—Cl bond-forming reductive elimination from Pd[IV].

More recent investigations have examined the oxidation of cyclometalated benzo[*h*]quinoline dimer **4**, a proposed intermediate in Pd-catalyzed C—H chlorination.[18] Reaction of **4** with PhICl$_2$ resulted in a net two-electron oxidation reaction to form symmetrical Pd[III]~Pd[III] dimer **15** (Scheme 17). Additionally, this dimer underwent C—Cl bond-forming reductive elimination in high yield at room temperature. While PhICl$_2$ is not a useful oxidant for catalytic C—H chlorination, complex **15** was also shown to be kinetically competent for the Pd-catalyzed chlorination of benzo-[*h*]quinoline with NCS. This report, along with a number of other recent studies,[16,17,20,43,44,48] suggests that dimeric or multimeric high oxidation state Pd intermediates are possible in C—H oxidation reactions, particularly when bridging carboxylate ligands are available.
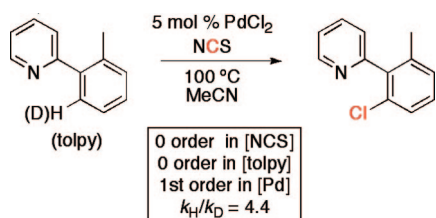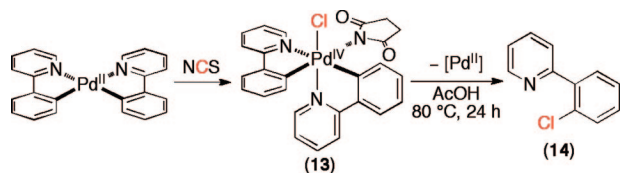


**Figure 1.** Key mechanistic data for PdCl$_2$–catalyzed chlorination of 2-*ortho*-tolylpyridine with NCS.[20]

**Scheme 16. Oxidation with *N*-Chlorosuccinimide and C—Cl Bond-Forming Reductive Elimination from a Pd[IV] Model Complex[42]**



## 4.2. CuX$_2$ (X = Cl, Br)

Pd-catalyzed sp$^2$ C—H halogenation has also been achieved using copper halides as terminal or co-oxidants. An early study showed that 3-methyl-2-phenylpyridine reacts with CuCl$_2$ in MeCN at 100 °C to afford *ortho*-chlorinated product **16** in modest (30%) yield (eq 14).[41] More recently, the combination of CuCl$_2$/Cu(OAc)$_2$ has been used for the Pd-catalyzed *ortho*-chlorination of acetanilides.[45] While unselective chlorination of these electron rich substrates was observed with NCS (eq 15, *i*), the use of CuCl$_2$/Cu(OAc)$_2$ afforded selective *ortho*-functionalization for various substituted anilides (eq 15, *ii*). A two-electron Pd[II/IV] mechanism similar to that in Scheme 7 was suggested, based on the observed catalytic and stoichiometric reactivity of an isolable palladacycle of acetanilide. The formation of related Pd[III]~Pd[III] dimers could also be considered in this system,[16,17,20,43,44,48] as well as a one-electron oxidation mechanism involving monomeric Pd[III] intermediates (Scheme 2).[46]
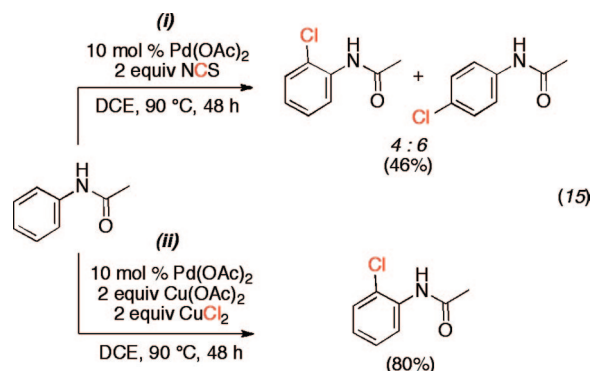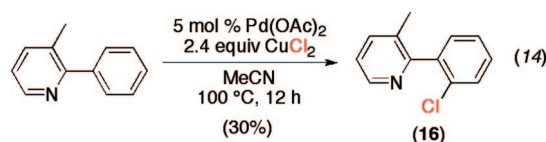


Pyridine-directed chlorination with CuCl$_2$ has also been achieved using catalytic Pd(MeCN)$_2$Cl$_2$ and stoichiometric ArSO$_2$Cl in DMF (eq 16).[36] Though only four arylpyridine substrates were examined, all underwent *ortho*-chlorination in high yield (71−85%). Mechanistic studies are not yet available, but the authors speculate that ArSO$_2$Cl reacts with

**Scheme 17.  Oxidation of 4 with PhICl₂[18]**



*Kinetically competent for Pd(OAc)₂ catalyzed C−H chlorination with NCS*
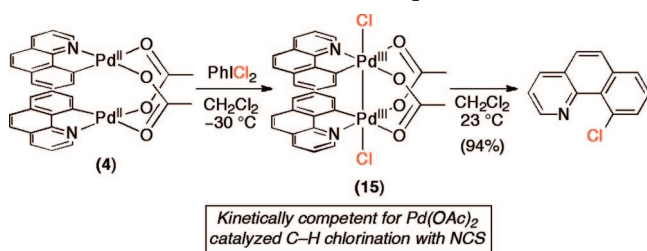
**Scheme 18.  sp³ C−H Iodination with IOAc (formed in situ from PhI(OAc)₂/I₂)[48]**
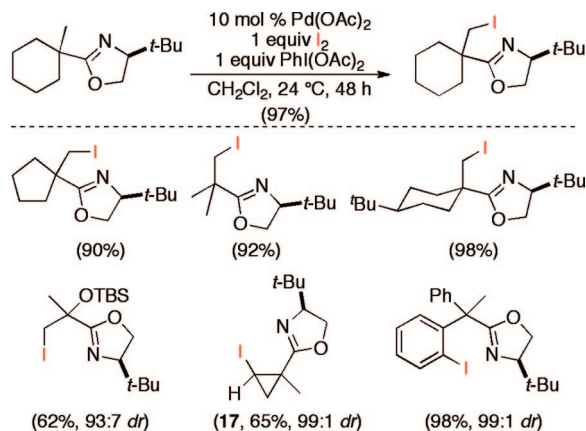


DMF to form an amidinium arenesulfonate salt,[47] which may play a role in the chlorination reaction.
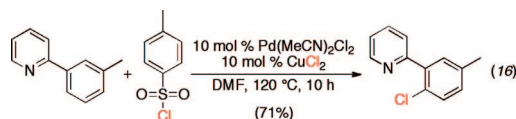


## 4.3. Suárez (XOAc) Reagents (X = Br, I)

Suárez-type reagents (XOAc) have also been employed for the halogenation of sp² and sp³ C−H bonds. The use of these reagents was pioneered by Yu, who initially demonstrated that the combination of I₂ and PhI(OAc)₂ (which generates IOAc in situ) is effective for Pd(OAc)₂-catalyzed oxazoline-directed iodination of unactivated alkyl groups (Scheme 18).[48] When different types of sp³ C−H bonds were proximal to the directing group, iodination generally occurred selectively at 1° sites, similar to the acetoxylation reactions discussed above. Cyclopropane-containing molecules like **17** were a notable exception to this trend and reacted at a 2° sp³ C−H bond on the ring. The use of chiral directing groups provided iodinated products with good to excellent levels of diastereoselectivity (ranging from 91:9 to 99:1 dr).

Reactions with IOAc are also proposed to proceed via a Pd^{II/IV} mechanism with the key step involving C−I bond-forming reductive elimination from Pd^{IV}. The stoichiometric oxidation of Pd^{II} species with IOAc has not been studied in detail. However, mechanistic studies of the catalytic iodination of **18** revealed a modest intramolecular 1° kinetic isotope effect ($k_H/k_D = 1.5$) and a Hammett $\rho$ value of −1.6 upon substitution of X (eq 17).[49] On this basis, C−H bond cleavage was proposed to proceed via an electrophilic mechanism.
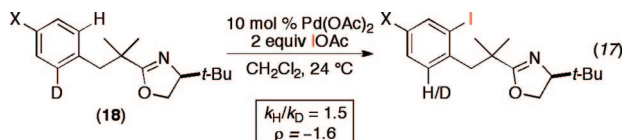


A similar protocol was developed for the carboxylic-acid-directed iodination and bromination of sp² C−H bonds with XOAc.[50] In the presence of catalytic Pd(OAc)₂ and 2 equiv of IOAc, substrates with two available *ortho*-C−H bonds underwent dihalogenation in high yields (eq 18, *ii*). The addition of tetraalkylammonium salts could be used to curb this reactivity, and selective monohalogenation was achieved in the presence of 1 equiv of Bu₄NX (X = I, Br) (eq 18, *i*). The tetrabutylammonium carboxylate ion pair is believed to be crucial for reactivity and selectivity in this reaction; however, the exact nature of its interaction with the Pd catalyst has yet to be elucidated.
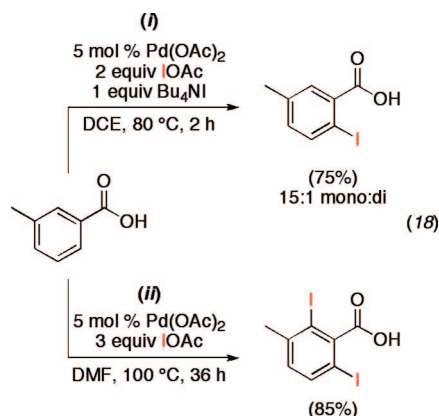


## 4.4. Electrochemical Oxidation

Electroorganic synthesis techniques have also been utilized to achieve selective halogenation of aryl C−H bonds.[51] This method of oxidation utilizes aqueous HX as the halogen source in a divided cell with two platinum electrodes. A variety of arylpyridine and arylpyrimidine substrates underwent PdX₂-catalyzed chlorination and bromination (X = Cl or Br, respectively) to afford *ortho*-halogenated products in excellent yields, and the organic products could be isolated in pure form by a simple extraction process. With highly electron-rich substrates like 2-(2-methoxyphenyl)pyridine, the site selectivity of halogenation could be controlled by tuning the electric current (and thereby the rate of X⁺ generation).
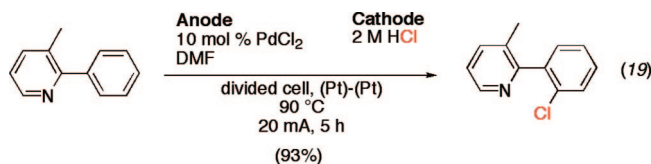


## 5. Carbon−Fluorine Bond Formation

Only two examples of Pd-catalyzed ligand-directed C−H fluorination have been reported to date.[52,53] The first study demonstrated that Selectfluor, *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, *N*-fluoropyridinium tetrafluoroborate, 4-iodotoluenedifluoride, and *N*-fluorodisulfonamide could all be used for the Pd(OAc)₂-catalyzed benzylic fluorination of 8-methylquinoline (Scheme 19). Extensive optimization revealed that *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate was the best electrophilic fluorinating reagent for this transformation and that microwave heating decreased the reaction time and minimized formation of undesired side products (eq 20). An analogous transformation (using *N*-fluoropyridinium

**Scheme 19. Electrophilic Fluorinating Reagents for the Benzylic Fluorination of 8-Methylquinoline[52]**
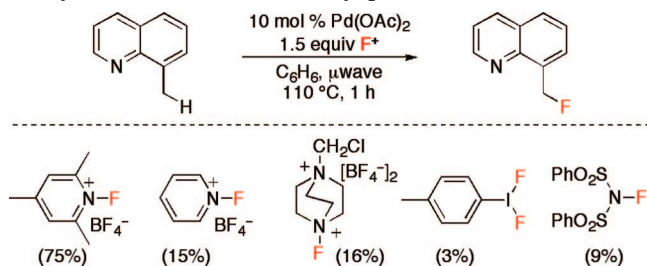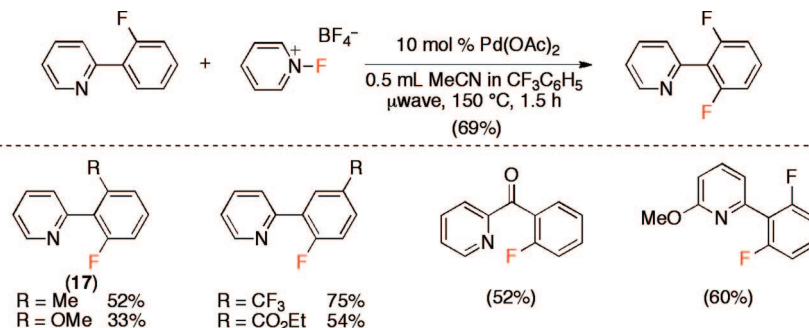


tetrafluoroborate) was developed for the *ortho*-fluorination of 2-arylpyridines (Scheme 20).
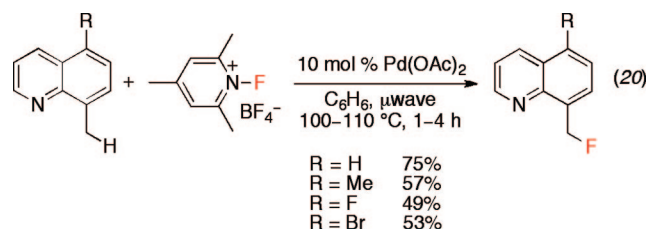


More recent work expanded the scope of catalytic C–H fluorination to benzylamine-based substrates.[53] *N*-Fluoro-2,4,6-trimethylpyridinium triflate was used as the "F⁺ source" along with *N*-methylpyrrolidinone (NMP) as a key promoter for the Pd(OTf)₂-catalyzed fluorination of triflamide-protected benzylamines (eq 21). This is a valuable development because triflamides can be converted to a broad range of synthetically useful functional groups including benzaldehydes, benzylamines, nitriles, and benzylmalonates, thereby providing access to a variety of functionalized aryl fluoride-containing products.
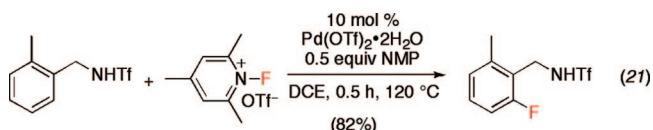


Both of these reports suggested that C–F bond formation might proceed via a Pd$^{II/IV}$ mechanism similar to that in Scheme 7, and subsequent work has provided evidence supporting the viability of such a pathway.[54,55] These studies demonstrated the stoichiometric oxidation of Pd$^{II}$ aryl model complexes with electrophilic fluorinating reagents. In both cases, stable Pd$^{IV}$ products (**19** in eq 22[54] and **20** in eq 23[55]) were isolated and characterized by X-ray crystallography. Furthermore, both species underwent C–F bond formation under conditions milder than those in the catalytic reaction. While **19** and **20** are clearly model complexes (rather than

actual catalytic intermediates in the C–H fluorination reactions above), these studies offer evidence for the feasibility of both the oxidation and the C–F bond-forming steps of a Pd$^{II/IV}$ catalytic cycle for C–H fluorination.
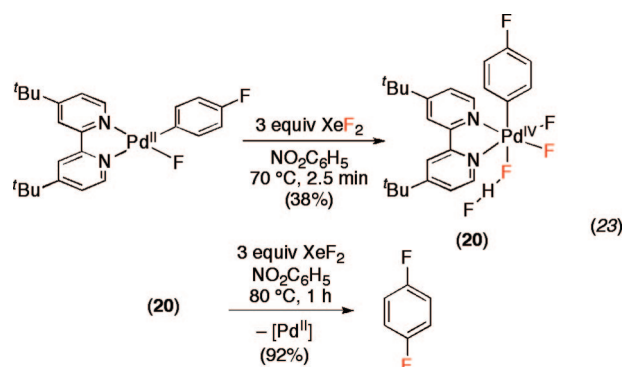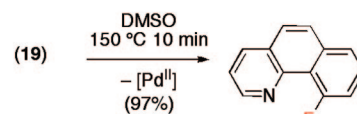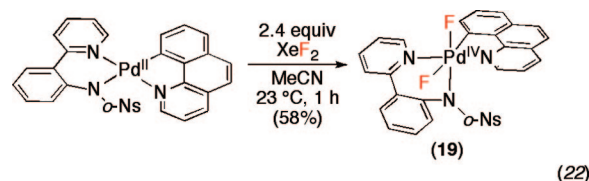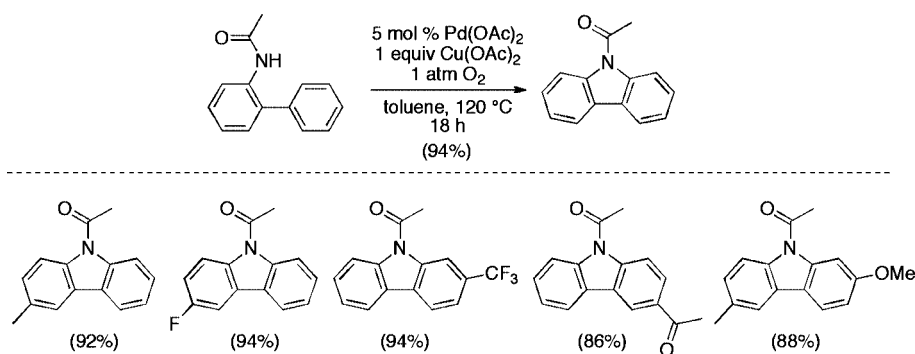




## 6. Carbon–Nitrogen Bond Formation

Palladium-catalyzed ligand-directed C–H functionalization has also been utilized for the construction of C–N bonds, which are important features of many biologically active molecules.[56,57] Reactions in this class of bond formation fall into two general categories: those where the C–N bond is formed intramolecularly to generate a heterocycle and those where the nitrogen group is delivered from an external reagent.

### 6.1. Intramolecular C–N Bond Formation

An early example of Pd-catalyzed directed C–H amination involved the construction of carbazoles via intramolecular C–N coupling.[58] 2-Phenylacetanilides underwent Pd(OAc)₂-catalyzed cyclization with Cu(OAc)₂/O₂ (in toluene)[58] or O₂ (in DMSO)[59] as the oxidant (Scheme 21). An acetyl protecting group on the amine was generally necessary for efficient reaction, although modest yield (12%) was recently reported for a similar reaction with a simple aniline using Pd/C as the catalyst.[60]

Two possible Pd$^{II/0}$ mechanistic pathways were proposed for this carbazole synthesis (Scheme 22). The first involves

**Scheme 20. Pd(OAc)₂-Catalyzed *ortho*-Fluorination of 2-Arylpyridines with *N*-Fluoropyridinium Tetrafluoroborate[52]**

**Scheme 21. Intramolecular C−H Amination To Form Carbazoles[58]**



**Scheme 22. Proposed Pd[II/0] Mechanisms for Carbazole Formation[58],**
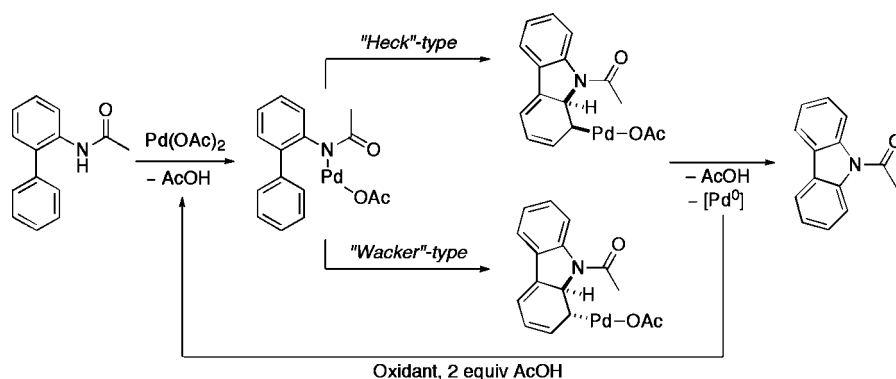


coordination of Pd to the amide nitrogen followed by a Heck-type cyclization/$\beta$-hydride elimination sequence. A second proposed pathway proceeds via amide-directed Wacker-type cyclization/$\beta$-hydride elimination to generate the carbazole.

An alternative approach to carbazoles involves the Pd(OAc)$_2$-catalyzed cyclization of *N*-alkylanilines in the presence of PhI(OAc)$_2$ (eq 24).[61] In contrast to the reactions in Scheme 21, this transformation proceeds efficiently at room temperature and its substrate scope is highly complementary, allowing synthesis of both *N*-alkyl and *N*-allylcarbazoles containing diverse aromatic substituents including aryl iodides (eq 24). These distinguishing features are believed to result from a difference in mechanism, and a Pd[II/IV] pathway involving intermediate **21** (eq 24) was proposed.
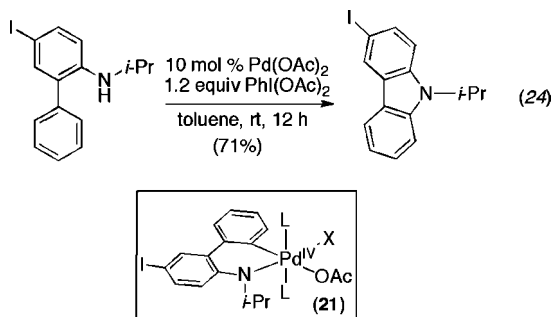


Tosylhydrazones have been used to direct intramolecular *ortho*-amination to form indazoles.[62] In these systems, Pd(OAc)$_2$ served as the catalyst in conjunction with 1 equiv of Cu(OAc)$_2$ and 2 equiv of AgO$_2$CCF$_3$ (eq 25). In substrates with two electronically distinct aryl rings, modest to excellent selectivity was observed for cyclization on the more electron-rich arene. Interestingly, *meta*-Br substitution was well tolerated; however, substrates containing *ortho*-Br groups

underwent facile Ar−Br oxidative addition. A similar enamine-directed intramolecular C−H amination was utilized to construct diarylindoles (eq 26).[63] In both of these reactions, Pd[II/0] pathways are likely.
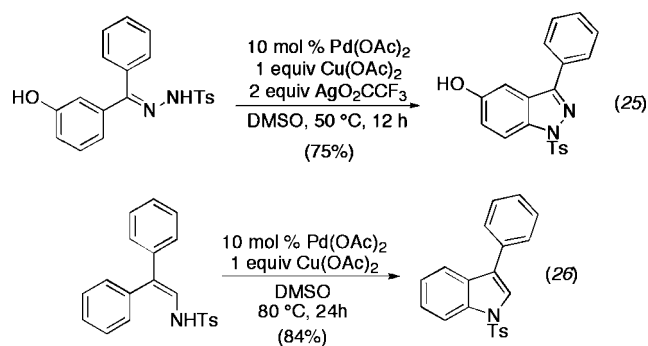


Very recently, phenethyltriflamides have been used as precursors to indolines (eq 27).[64] *N*-Fluoro-2,4,6-trimethylpyridinium triflate was employed as the terminal oxidant for these cyclizations, leading to high yields of aminated products and minimal competing fluorination. The reaction showed good functional group compatibility, tolerating halogen, acetyl, cyano, and nitro substituents on the aromatic ring. However, attempts to prepare the corresponding 6-membered tetrahydroquinolines via analogous cyclizations resulted in low yields (28−30%).
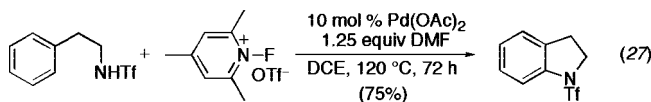


Finally, lactams have been prepared via intramolecular amination with amides (Scheme 23).[65] This reaction required the use of

**Scheme 23. Intramolecular C−H Amination to Form Lactams[63]**



(88%)   (96%)   (72%)   (78%)
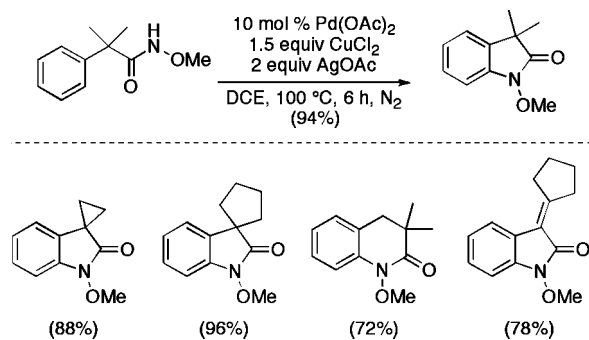
catalytic Pd(OAc)$_2$ in combination with 1.5 equiv of CuCl$_2$ and 2 equiv of AgOAc. Diverse β-, γ-, and δ-lactams were formed in high yields; however, the reaction was limited to substrates with a high degree of substitution α to the amide-directing group, suggesting that the Thorpe−Ingold effect may play a key role in cyclization. Preliminary investigations implicated a Pd$^{II/IV}$ catalytic cycle; however, further studies will be required to obtain a complete mechanistic picture.

## 6.2. Intermolecular C−N Bond Formation

The only example of Pd-catalyzed intermolecular directed C−H amination reported to date involves the functionalization of sp$^2$ and sp$^3$ C−H bonds in pyridine and oxime ether substrates (Scheme 24).[66] In this system, Pd(OAc)$_2$ served as the catalyst and a combination of K$_2$S$_2$O$_8$ and NH$_2$R was used to introduce the nitrogen functionality. Electron-deficient primary amides including carbamates, acetamides, and sulfonamides all proved effective as "NHR" sources.

Mechanisms involving cyclopalladation followed by either direct nitrene insertion or oxidation to a Pd$^{IV}$ imido intermediate were proposed. To probe the possibility of a transient nitrene intermediate, benzamide was submitted to the reaction conditions in the presence of MeOH (eq 28). The major organic product was methyl-N-(2-methoxyphenyl)carbamate (**23**), which is consistent with a sequence involving (i) initial generation of a nitrene, (ii) Curtius rearrangement to form

the corresponding isocyanate, (iii) trapping with MeOH to generate methyl carbamate **22**, and, finally, (iv) Pd-catalyzed directed C−H oxygenation[10] to form **23** (eq 28). This experiment suggested the viability of a nitrene mechanism; however, the possible intermediacy of a Pd$^{IV}$ imido complex (which has been suggested in related stoichiometric reactions of palladacycles)[67] could not be excluded.



(28)
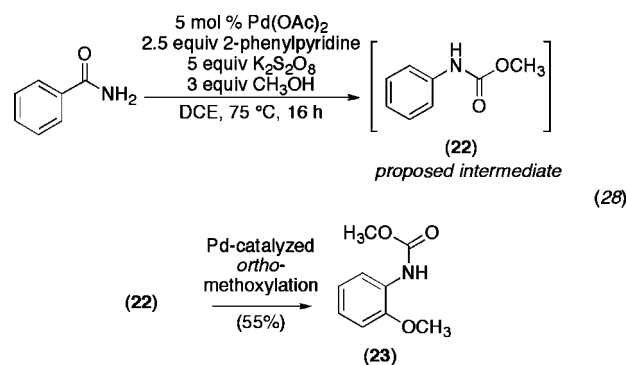
## 7. Carbon−Carbon Bond Formation

The most widely studied area in this field is Pd-catalyzed ligand-directed C−H activation followed by C−C coupling to afford ortho-arylated, alkenylated, alkylated, or carbonylated products. Pioneering studies between 1997 and 2004 demonstrated that alcohols, amides, and aldehydes could serve as directing groups for Pd$^{II/0}$ catalyzed ortho-arylation, -alkenylation, and -alkylation. This and related early work has been extensively reviewed;[68−70] therefore, the current discussion focuses on advances in the field starting in 2005.

## 7.1. C−H Arylation with Prefunctionalized Arylating Reagents

A first key development in 2005 was the demonstration that Pd(OAc)$_2$ catalyzes the ortho-phenylation of diverse arylpyridines, quinolines, pyrrolidinones, oxazolidinones, and benzodiazepines with diphenyliodonium salts (Scheme 25).[71−73] The unsymmetrical mesityl/aryl-substituted iodonium reagents [Mes−I−Ar]BF$_4$ could be used to install different

**Scheme 24. Intermolecular Amination of Pyridines and Oxime Ethers[66]**



(92%)   (87%)   (83%)   (93%)   (76%)
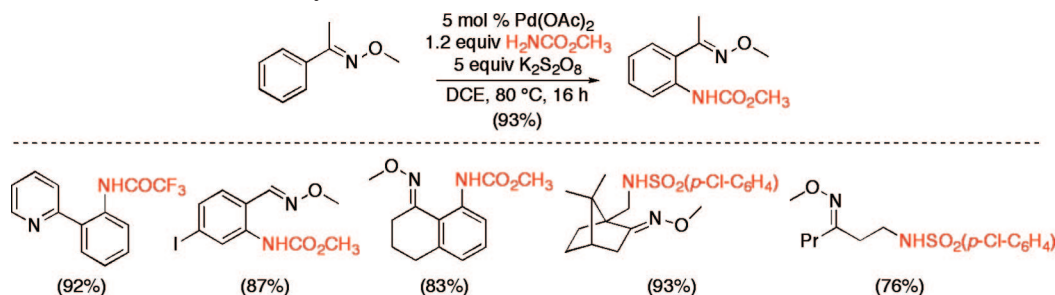
**Scheme 25. Pd(OAc)$_2$-Catalyzed sp$^2$ C−H Phenylation with [Ph$_2$I]BF$_4$[71]**



(91%)   (51%)   (72%)   (78%)   (48%)   (67%)
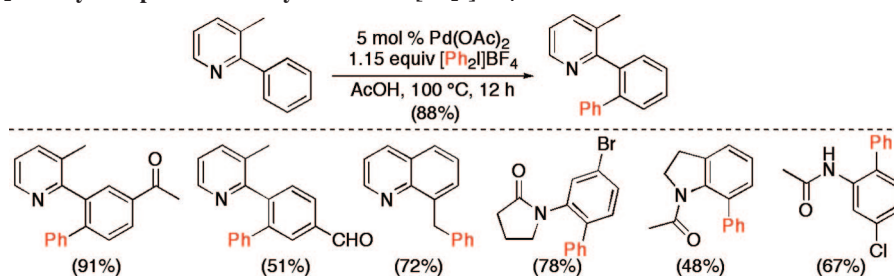
**Scheme 26. Key Steps in the Proposed Mechanism of sp² C−H Arylation with [Mes−I−Ph]BF₄[17]**
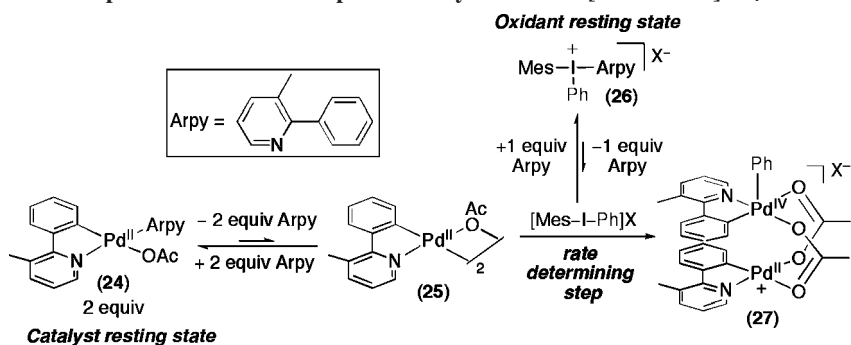


**Scheme 27. Pd(OAc)₂-Catalyzed sp² C−H Arylation with AgOAc/Ar−I[72,76−79]**
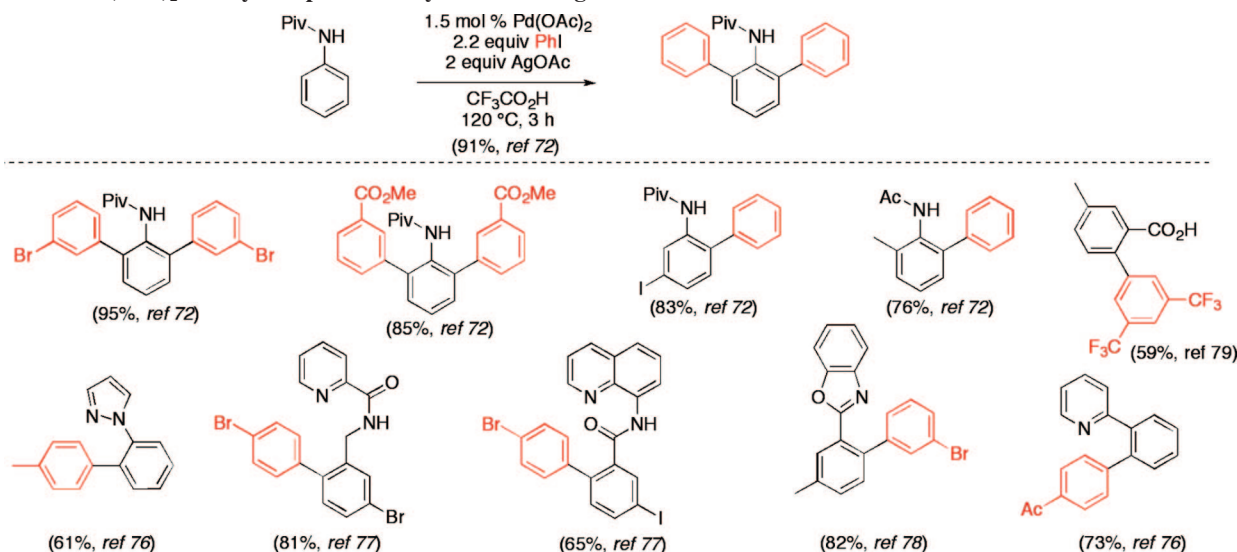


aryl groups (eq 29). The large mesityl substituents served as "dummy ligands" on the iodine(III), and the smaller aryl group was transferred with high selectivity (>99:1 in most cases). Generally, faster reaction rates and higher yields were observed with electron-deficient aryl groups.
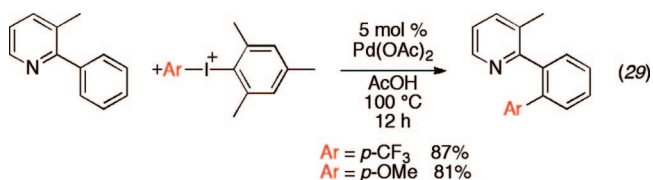


These reactions were initially proposed to proceed by a Pd$^{II/IV}$ mechanism analogous to that in Scheme 7.[71] Subsequent studies provided more detailed insights into the catalyst resting state, the turnover-limiting step, and the ligand environment of high oxidation state Pd intermediates in this transformation (Scheme 26).[17] These investigations showed that with 3-methyl-2-phenylpyridine as the substrate, the catalyst resting state is monomeric Pd$^{II}$ species **24** and the oxidant resting state is arylpyridine-coordinated iodine(III) reagent **26**. Pre-equilibrium dissociation of the arylpyridine from both **24** and **26** produces cyclometalated dimer **25** and free [Mes−I−Ph]BF₄. The turnover-limiting step was then proposed to proceed via oxidation of **25** by [Mes−I−Ph]BF₄ to afford dimeric Pd$^{IV}$∼Pd$^{II}$ adduct **27** (alternatively formulated as a Pd$^{III}$∼Pd$^{III}$ species, depending on the nature of the Pd−Pd interaction).[74] Carbon−carbon bond-forming reductive elimination, ligand exchange, and cyclometalation complete the proposed catalytic cycle.

Several key experiments provided support for the mechanism in Scheme 26.[17] First, the catalytic reaction showed a first-order dependence on [I$^{III}$] (**26**), a second-order dependence on [Pd], and an inverse third-order dependence on [arylpyridine] (all consistent with the rate law derived for the sequence in Scheme 26). Second, Hammett studies with *para*-substituted I$^{III}$ reagents showed a ρ value of +1.7, consistent with turnover-limiting oxidative addition. Finally, substitution of the *ortho*-C−H bond with a C−D bond resulted in an intra- but not an intermolecular kinetic isotope effect, indicating that C−H activation occurs after the turnover-limiting step.

A related Pd(OAc)₂-catalyzed sp² C−H arylation was developed using stoichiometric AgOAc in conjunction with 2−9 equiv of Ar−I.[72,75] This method has been applied to the arylation of substituted anilides,[72] 2-arylpyridines,[75−77] benzoxazoles,[75,78] and benzoic acid derivatives (Scheme 27 and eq 30).[79] Amide and oxime ether-directed versions have also been used as the first step in tandem sequences to generate fluorenones (eq 31 and 32).[80,81] All of these transformations show broad scope and functional group compatibility; most notably, aryl iodides are well tolerated in the cyclometalating substrate.

(31)



(79%)



(32)

(90%)
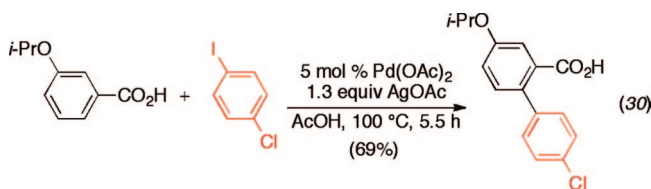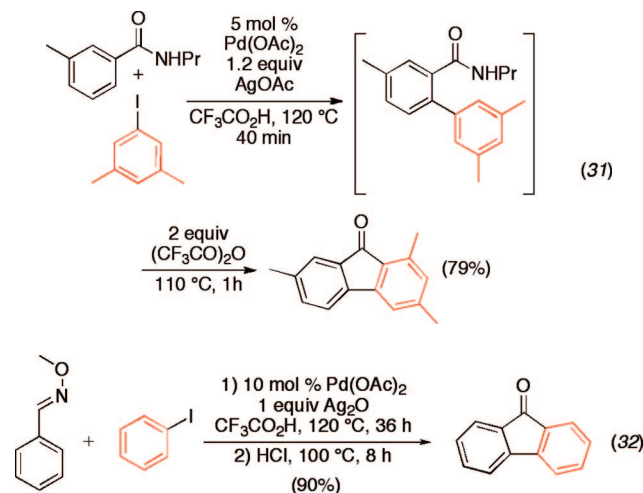
The combination of AgOAc and Ar−I has also been utilized for the Pd-catalyzed arylation of unactivated sp³ C−H bonds (Scheme 28).[76,77,28] Directing groups including pyridines, aminoquinolines, and picolinamides were used, and arylation occurred at both 1° and 2° sp³ C−H sites. In substrates containing diastereotopic 2° C−H positions, only one stereoisomer of the product was reported.[28]

The coupling of aryl iodides with sp³ C−H bonds in carboxylic acid derivatives has also been achieved using a slight modification of the above conditions (eq 33).[82] In this system, $Ag_2CO_3$ was used as the $Ag^I$ source in combination with 2 equiv of NaOAc and 1 equiv of $K_2HPO_4$. While the reaction yields were generally high, mixtures of mono- and diarylated products (ranging between 3:1 and 5:1) were observed in all cases.



(33)

4 : 1
(72%)
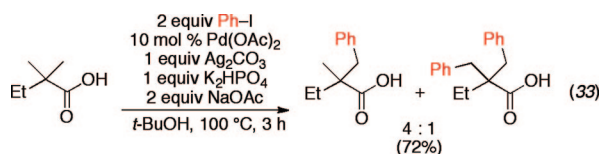
All of these $Pd(OAc)_2$-catalyzed reactions with $Ag^I$/ArI have been proposed to proceed by the $Pd^{II/IV}$ mechanism outlined in Scheme 29. The only mechanistic studies to date have been conducted with benzoic acid substrates. In these systems, neither of the $Pd^0$ sources $Pd_2(dba)_3$ or $Pd(^tBu_3P)_2$ promoted arylation (eq 34).[79] Furthermore, in the absence of AgOAc, a single turnover was observed (eq 34), suggesting that the silver salt serves to regenerate the Pd catalyst, rather than activate the Ar−I toward oxidative

addition. Intriguingly, qualitative studies also showed that electron-rich aryl iodides react faster, which is in contrast to the $[Ar_2I]BF_4$ chemistry described above.[72,77,83] Though a $Pd^{II/IV}$ mechanism was suggested, $Pd^{III}$ radical intermediates have been proposed under similar conditions and cannot be ruled out at this time.[83,84]



(34)
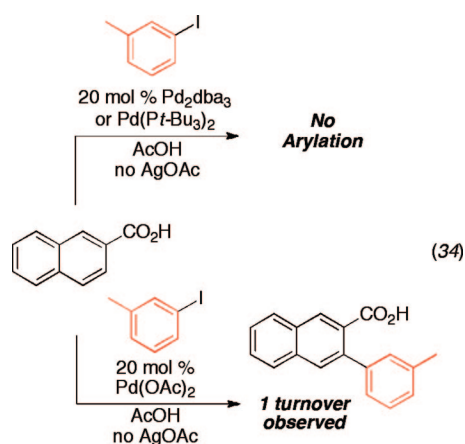
Several $Pd^{II/0}$-catalyzed *ortho*-arylation methods have also been reported since 2005. For example, the *ortho*-arylation of benzoic acids with aryl chlorides has been achieved using 5 mol % of $Pd(OAc)_2$, 10 mol % of *n*-BuAd$_2$P, and 2.2 equiv of $Cs_2CO_3$ (Scheme 30). High yields were obtained with electron-deficient Ar−Cl and ArCO$_2$H; however, competitive decarboxylation and/or hydrodechlorination was observed with more electron-rich benzoic acids and aryl chlorides. A $Pd^{II/0}$ mechanism was proposed involving the following steps: (i) oxidative addition of the Ar−Cl to $Pd^0$, (ii) ligand exchange of chloride for benzoate, (iii) directed C−H activation, and (iv) C−C bond-forming reductive elimination to generate the product. A similar procedure has also recently been applied to the *ortho*-arylation of benzaldehydes with aryl chlorides using catalytic $Pd(OAc)_2$, an *N*-heterocyclic carbene ligand, and stoichiometric $Cs_2CO_3$ as a base.[85]

The arylation of sp³ C−H bonds with aryl iodides has been reported using $Pd^{II/0}$ catalysis and phosphine ligands (Scheme 31).[86] $Pd(OAc)_2$ was employed as a precatalyst in conjunction with Cy-JohnPhos and CsF to arylate an α-methyl group in *N*-(perfluorophenyl)acetamides. At least one additional α-substituent (either an alkyl or an aryl group) was generally required to achieve efficient catalysis in these transformations (Scheme 31).

**Scheme 28. Pd(OAc)₂-Catalyzed sp³ C−H Arylation with AgOAc/Ar−I[77,28]**
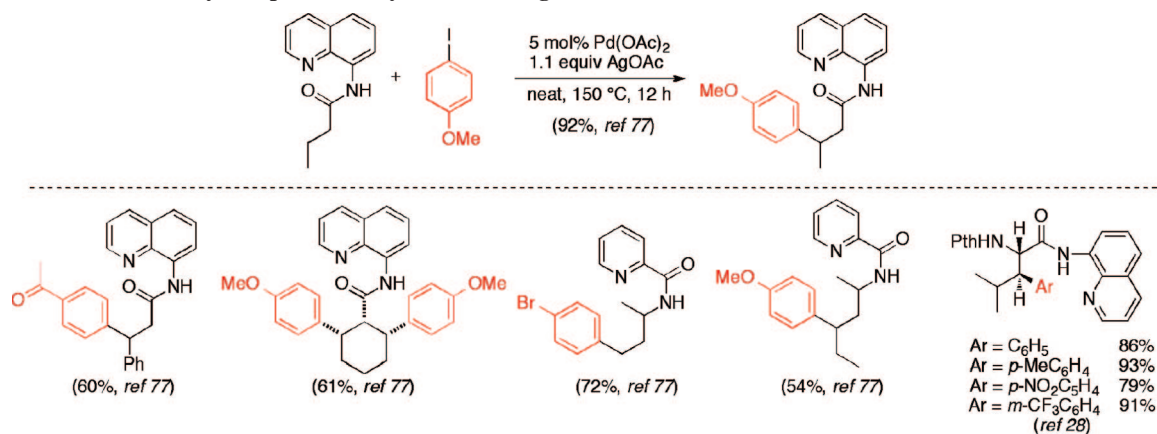
**Scheme 29. Proposed Mechanism for Pd-Catalyzed Directed Arylation with Ag$^I$/Ar−I[79]**
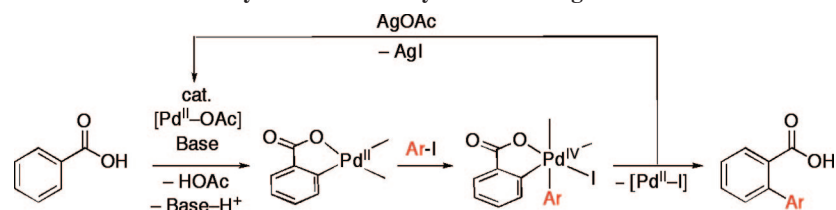


**Scheme 30. Pd$^{II/0}$-Catalyzed *ortho*-Arylation of Benzoic Acids with Ar−Cl[79]**
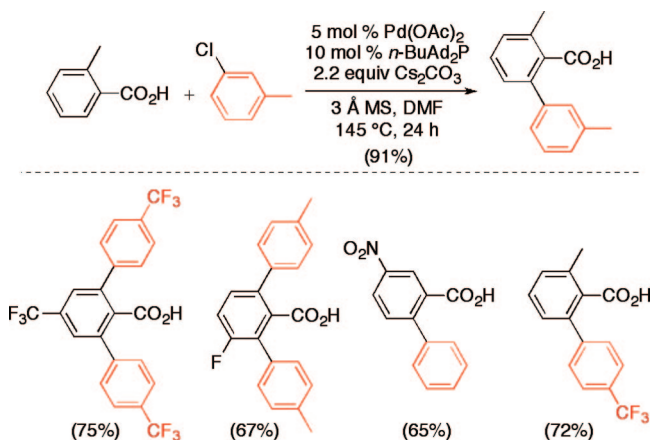


Pd$^{II/0}$-catalyzed sp$^3$ C−H arylation of carboxylic acids has been achieved with arylboronic esters.[82] Pd(OAc)$_2$ was used as the catalyst with benzoquinone (BQ) as an additive along with 1.5 equiv of K$_2$HPO$_4$ and 1 equiv of Ag$_2$CO$_3$ (eq 35). Interestingly, extensive screening revealed that alternative silver oxidants (e.g., Ag$_2$O or AgOAc) and bases (e.g., Na$_2$CO$_3$) afforded <5% yield of the arylated products. While excellent (>98%) selectivity for monoarylation was observed, the yields were generally modest (20−38%).
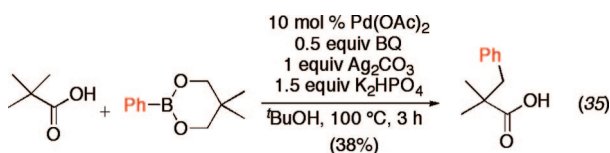


Boronic acids have also been studied as coupling partners in the Pd-catalyzed *ortho*-arylation of *N*-alkyl acetanilides using Cu(OTf)$_2$ as the oxidant and Ag$_2$O as a key additive (eq 36).[87] A number of commercially available boronic acids proved effective as arylating reagents, particularly those containing electron-donating groups. In contrast, the presence of electron-withdrawing substituents or *ortho*-substitution on the boronic acid resulted in lower yields. A similar reaction with boronic acids was later applied to 2-arylpyridines using 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as the oxidant.[88]
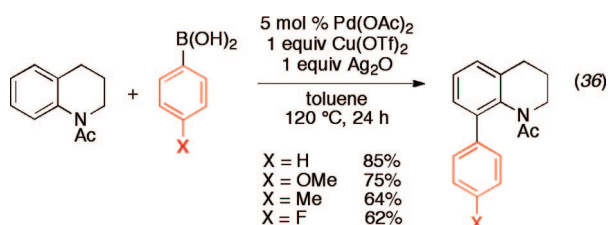


Arylsilylethers are another class of transmetalating reagents that can be utilized for directed C−H arylation reactions.[89,90]

For example, the combination of catalytic Pd(OAc)$_2$, 2 equiv of AgF, and 2 equiv of Cu(OTf)$_2$ resulted in clean *ortho*-arylation of acetanilide substrates with ArSi(OMe)$_3$ (eq 37). These reactions were proposed to proceed through a Pd$^{II/0}$ manifold. While only trimethoxyphenylsilanes were examined with acetanilides, a variety of different aryl silicon reagents proved effective for the related Pd-catalyzed *ortho*-arylation of enamides.[90]
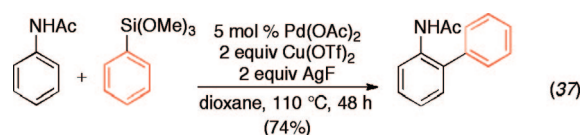


Finally, aryl acylperoxides have been used to effect pyridine-, quinoline-, oxime ether-, and oxazoline-directed *ortho*-arylation (eq 38).[91] A mechanism involving decarboxylation to generate aryl radicals (Ar•) followed by reaction of Ar• with cyclopalladated intermediates was proposed. Consistent with this pathway, conducting the catalytic reactions in the presence of ascorbic acid (a potential radical scavenger) led to dramatically decreased conversions to product.
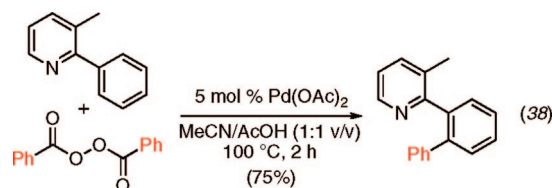


## 7.2. C−H Arylation without Prefunctionalized Arylating Reagents

A second strategy for Pd-catalyzed ligand-directed C−H arylation involves the direct oxidative coupling of L∼C−H with an Ar−H substrate *without the requirement for prefunctionalization of either reagent*. An early example of this approach involved the Pd(OAc)$_2$-catalyzed dimerization of 2-arylpyridine derivatives using Oxone as the stoichiometric oxidant (eq 39).[92] This homocoupling proceeded in modest to good yield with substituted arylpyridines. With *meta* substituents on the aryl ring, low site selectivity was observed, which is in sharp contrast to typical directed C−H activation reactions at Pd$^{II}$.
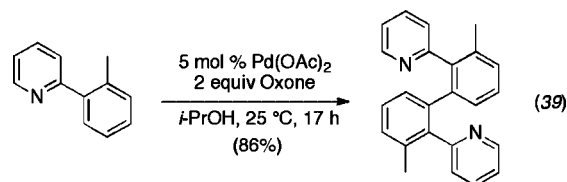


This unusual selectivity suggested the possibility of an unconventional reaction mechanism. Indeed, detailed investigations provided evidence for a pathway involving the following sequence of steps: (i) initial cyclometalation at Pd$^{II}$, (ii) oxidation of this Pd$^{II}$ intermediate to Pd$^{IV}$, (iii) a second

**Scheme 31. Pd$^{II/0}$-Catalyzed sp$^3$ C−H Arylation of Alkylamides with Ar−I[86]**
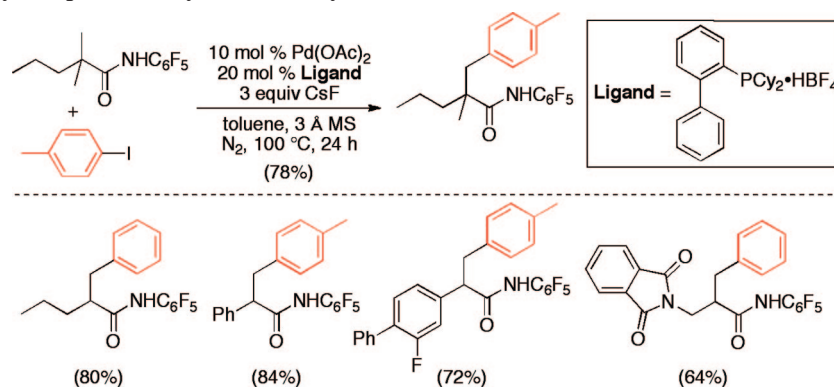


**Scheme 32. Proposed Mechanism for Pd$^{II/IV}$ Homocoupling of Arylpyridines[92]**
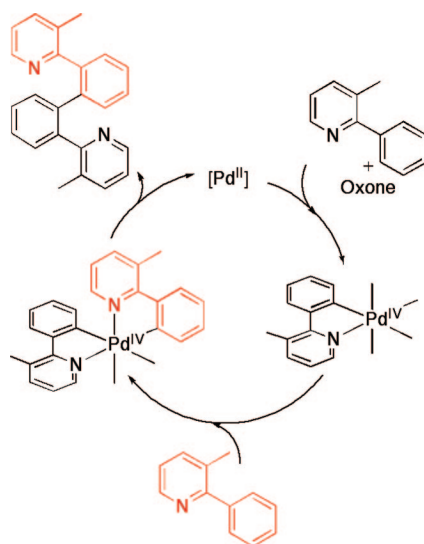


cyclometalation at Pd$^{IV}$, and, finally, (iv) C−C bond-forming reductive elimination to produce the dimeric product (Scheme 32). This appears to be the first example where strong evidence is available in support of C−H activation occurring at a high oxidation state Pd center.

Pd-catalyzed ligand-directed oxidative cross-coupling reactions have also been described. For example, ferrocenyl oxazolines were selectively *ortho*-arylated using Pd(OAc)$_2$ as the catalyst, Cu(OAc)$_2$ as the terminal oxidant, K$_2$CO$_3$ as a base, and an arene substrate as the solvent (eq 40).[93]
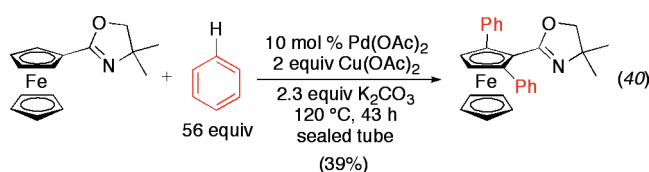


A more general Pd(OAc)$_2$-catalyzed oxidative cross-coupling between L∼C−H (L = pyridine, quinoline, pyrimidine, and pyrazole) and Ar−H was subsequently reported (Scheme 33).[94] In these transformations, benzoquinone was required as a promoter and Ag$_2$CO$_3$ was employed as a stoichiometric oxidant. For many 1,2-, 1,3-, and 1,2,3-substituted aromatic substrates, Ar−H activation proceeded with high selectivity at the least sterically hindered site. Site selectivity could be tuned further by changing the structure of the quinone promoter (Scheme 34).

Similar transformations have also been applied to acetanilides and pivalanilides.[95,96] These substrates underwent Pd-catalyzed *ortho*-arylation with an electronically diverse set of Ar−H using either Cu(OTf)$_2$/O$_2$ (in EtCO$_2$H)[95] (Scheme 35) or O$_2$ (in TFA)[96] as the oxidant (Scheme 36). No additional promoter was required, and the site selectivity of Ar−H activation appeared to be dominated

**Scheme 33. Pd-Catalyzed Benzoquinone-Promoted Oxidative L∼C−H/Ar−H Cross-Coupling[94]**
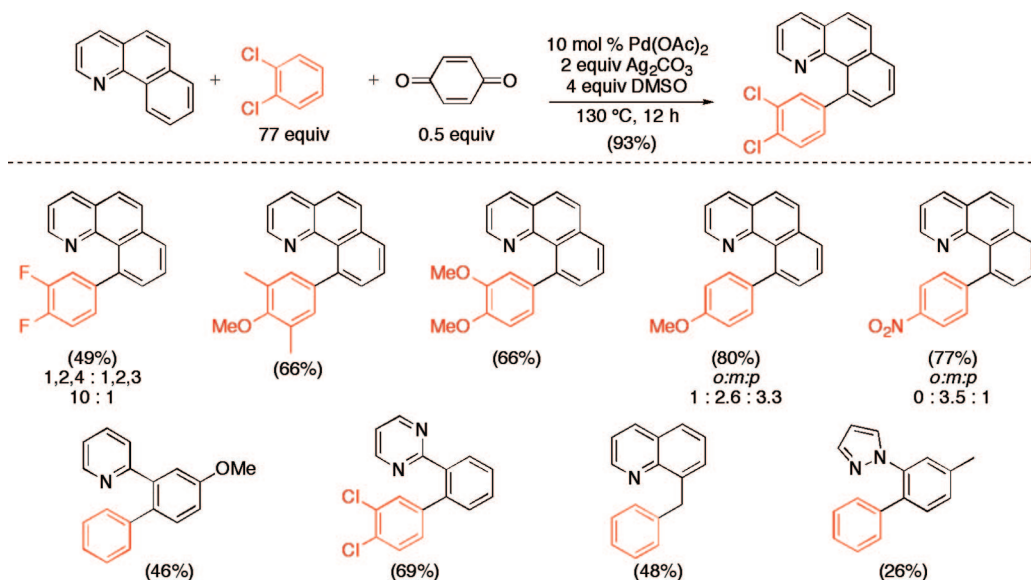
**Scheme 34. Tuning Site-Selectivity of L∼C−H/Ar−H Cross-Coupling by Variation of Quinone Promoter[94]**



| R | R[1] | yield | o : m : p |
|---|---|---|---|
| H | H | 88% | 1 : 2.9 : 3.3 |
| Me | H | 51% | 1 : 15.9 : 6.7 |
| Me | Me | 35% | 1 : 18.1 : 6.5 |
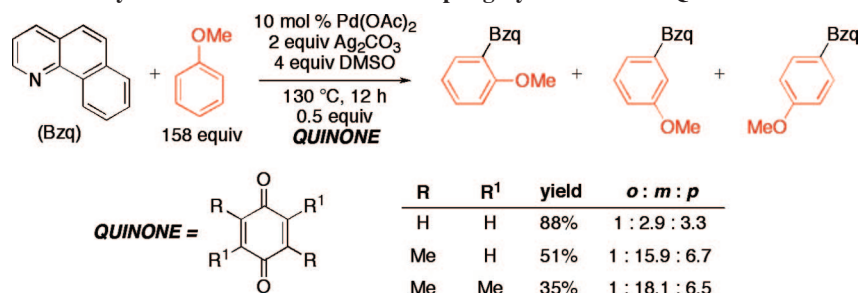
**Scheme 35. Oxidative Cross-Coupling of Amide Derivatives with Aryl−H using Cu(OTf)$_2$/O$_2$ as Oxidant[95]**
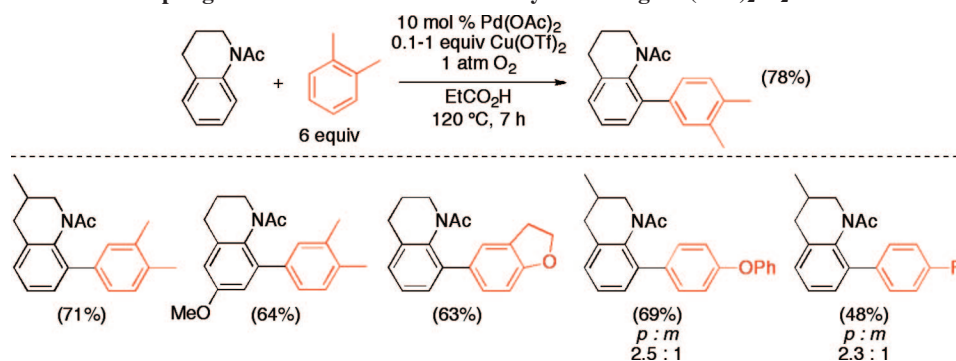


**Scheme 36. Oxidative Cross-Coupling of Amide Derivatives with Ar−H using O$_2$ as Oxidant[96]**
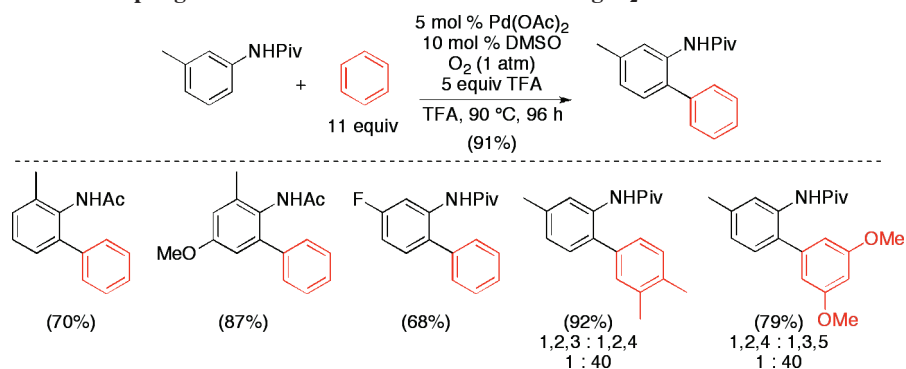


**Scheme 37. Proposed Mechanism for L̃C−H/Ar−H Cross-Coupling[94−97]**
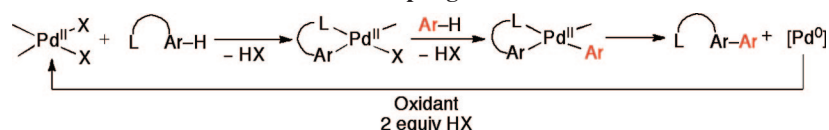


by steric factors. This methodology was applied to the total synthesis of 4-deoxycarbomycin B (eq 41).
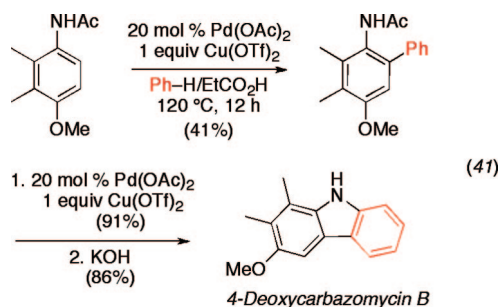


The mechanism proposed for all of these L∼C−H/Ar−H cross-coupling reactions involves the following steps: (i) cyclopalladation of L∼C−H, (ii) Ar−H activation at the resulting cyclopalladated intermediate, (iii) C−C bond-forming reductive

elimination, and (iv) oxidation of the resulting Pd$^0$ center to Pd$^{II}$ (Scheme 37). In the systems where benzoquinone is required, this promoter is believed to facilitate the C−C bond-forming reductive elimination step of the catalytic cycle.[94,97] The effect of BQ on site selectivity appears to be due to selective promotion of reductive elimination at less sterically hindered Pd$^{II}$(Ar)(Ar$^1$) complexes.

## 7.3. C−H Alkenylation

An early example of Pd-catalyzed directed C−H alkenylation involved the coupling of acetanilides with acrylates (eq 42).[98] Benzoquinone was used as the terminal oxidant, and a solvent mixture of TsOH, N-methylpyrrolidinone, and acetic acid was required for efficient turnover. A variety of acetanilides were effective substrates for *ortho*-alkenylation with *n*-butylacrylate, although those bearing electron-withdrawing substituents or *ortho*-substitution afforded lower

**Scheme 38.** *ortho*-Alkenylation of Benzylamines with α,β-Unsaturated Esters and Amides[101]
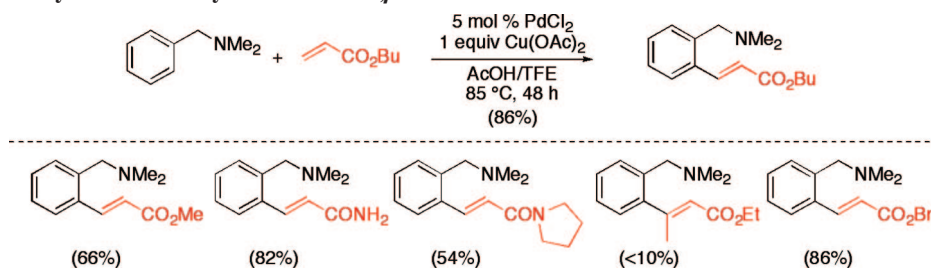


yields. Additionally, no reaction was observed with *N*-methylacetanilide. More recently, an analogous transformation has been reported using $O_2$/Cu(OAc)$_2$ as the oxidant.[99] *N*-(2-Pyridyl)sulfonyl-protected indoles and pyrroles also show similar reactivity with alkenes using Cu(OAc)$_2$·$H_2O$ as the oxidant and Pd(MeCN)$_2$Cl$_2$ as the catalyst.[100]
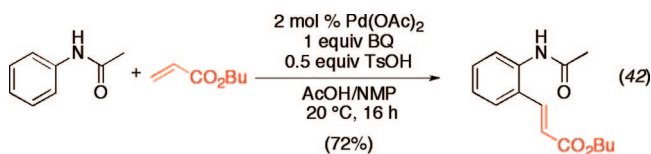


The Pd$^{II/0}$-catalyzed *ortho*-alkenylation of *N,N*-dimethylbenzylamines with electron-deficient alkenes has also been achieved.[101] In this system, catalyst optimization required careful tuning of the electrophilicity of the Pd center as well as the extent of protonation of the directing group, giving the optimal conditions of catalytic PdCl$_2$ in conjunction with 1 equiv of Cu(OAc)$_2$ in acetic acid/trifluoroethanol. Terminal α,β-unsaturated esters and amides served as good substrates (Scheme 38); however, substitution at the β-position shut down the reaction. The products could be reduced in one pot to afford *ortho*-alkylated toluenes, enhancing the synthetic utility of this transformation (eq 43).
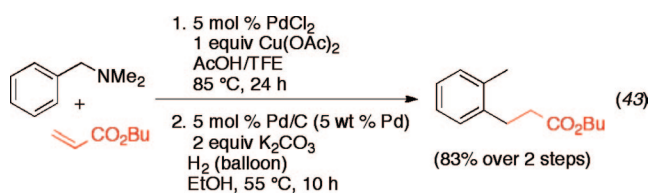


An alternative approach to Pd-catalyzed *ortho*-alkenylation of acetanilides precludes the requirement for a stoichiometric oxidant (eq 44).[102] In this system, 3-haloacrylates were used as alkene substrates and the Pd$^{II}$ catalyst was regenerated directly via β-halogen elimination. Though *trans*-bromo esters provided the highest yields, other haloolefins were also successfully coupled with an observed order of reactivity as follows: *cis*-chloro < *trans*-chloro ≈ *cis*-iodo < *cis*-bromo < *trans*-bromo.



Finally, a Pd$^{II/0}$-catalyzed alkyne-directed 5-*exo-dig* intramolecular C–H alkenylation reaction has been developed for the synthesis of fluorenes (eq 45).[103] This transformation proceeded efficiently with both electron-rich and electron-deficient arenes using 5 mol % of Pd(OAc)$_2$ in conjunction

**Scheme 39.** *ortho*-Alkylation of Oxazolines with SnR$_4$[104]



with 7 mol % of 1,1′-bis(diisopropylphosphino)ferrocene (*i*-Prpf). The authors propose a Pd$^{II/0}$ mechanism involving alkyne-directed C–H activation, migratory insertion, and protonation of the resulti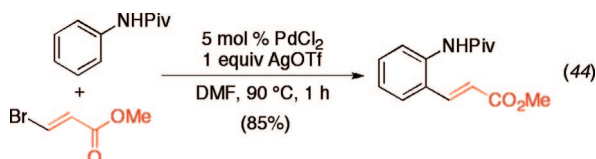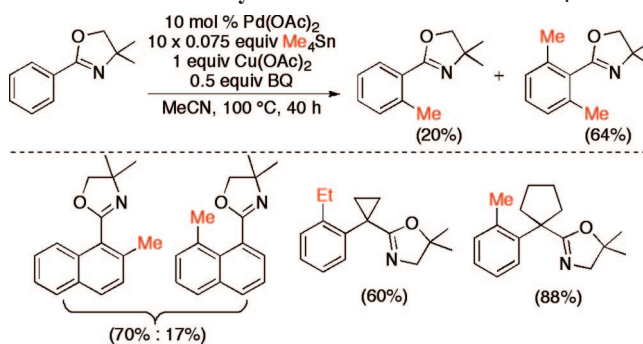ng Pd–C bond as key steps. Electrophilic attack by the aryl ring on a Pd–alkyne complex was ruled out on the basis of the alkene geometry in the product.
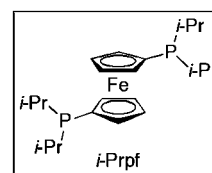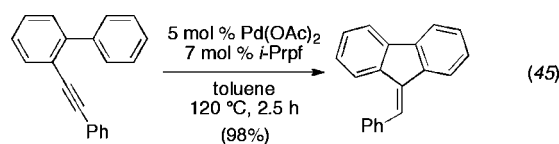


## 7.4. C–H Alkylation

The Pd(OAc)$_2$-catalyzed *ortho*-alkylation of aryl oxazolines has been accomplished using SnR$_4$ (R = Me or Et) (Scheme 39).[104] In these systems, Cu(OAc)$_2$ was used as the terminal oxidant and benzoquinone was a key promoter, believed to accelerate both cyclopalladation and C–C bond formation. Batchwise addition of the stannane was required to avoid competing alkyl–alkyl coupling. Standard heating protocols resulted in slow reaction (40 h); however, microwave irradiation could be used to reduce the reaction time to 10 h.

More recently, Pd-catalyzed pyridine-directed sp$^2$ and sp$^3$ C–H alkylation has been reported with methylboroxines and alkylboronic acids.[105] Under similar conditions to the SnR$_4$ couplings in Scheme 39, both sp$^2$ and sp$^3$ C–H bonds could be methylated with methylboroxine using Cu(OAc)$_2$ as an oxidant and benzoquinone as a promoter (eq 46). Ethyl- and butylboroxines failed to give the desired alkylated products; however, reoptimization of the conditions showed that the

use of a combination of $Ag_2O$ and benzoquinone resulted in high yields for these substrates (eq 47). Analogous conditions have also been developed for the Pd-catalyzed *ortho*-methylation of benzoic acids with methylboronic acids (eq 48).[82]



(46)



(47)



(48)
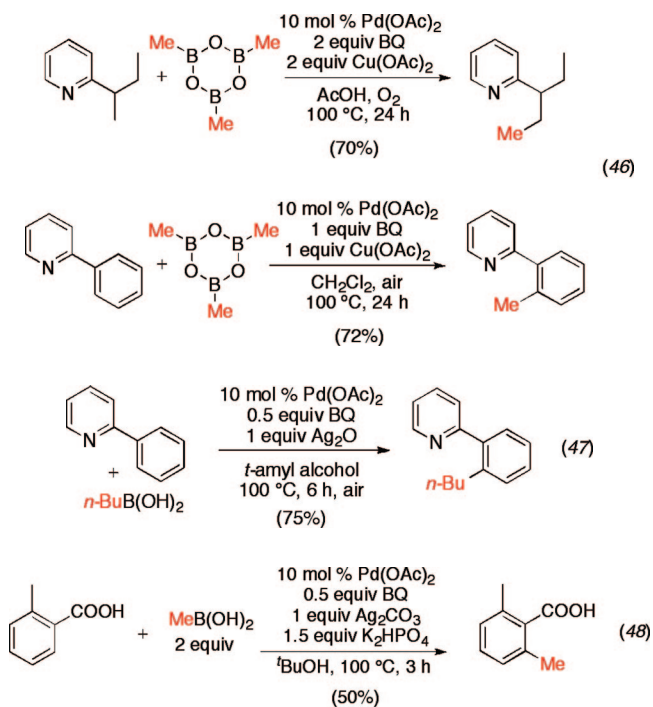
An asymmetric sp$^2$ C−H alkylation reaction has recently been disclosed that uses monoprotected amino acids as chiral ligands and boronic acids as alkylating reagents (eq 49).[106] In this system, (diarylmethyl)pyridine derivatives underwent selective alkylation of one prochiral aryl group in 54−95% ee. A variety of chiral carboxylic acids were screened as ligands, and the best results were obtained with menthoxy-carbonyl-protected L-leucine (L in eq 49). The substrate scope remains somewhat limited; however, these results provide exciting insights for the future development of catalytic asymmetric C−H functionalization reactions.



(49)
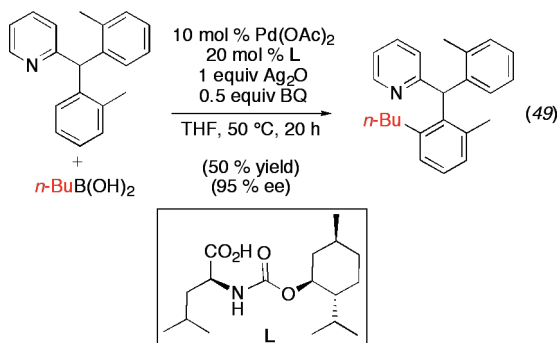
Dicumylperoxide has also been utilized as a reagent for the Pd-catalyzed *ortho*-methylation of 2-arylpyridines.[107] Mixtures of mono- and dimethylated products were obtained with 2 equiv of the peroxide using $Pd(OAc)_2$ as a catalyst (eq 50). Though mechanistic studies were not conducted, a Pd$^{II/0}$ pathway was proposed involving the following sequence: (i) oxidative addition of the peroxide reagent to Pd$^0$, (ii) $\beta$-methyl elimination, (iii) cyclopalladation, and (iv) C−C bond-forming reductive elimination to yield the product.



(50)
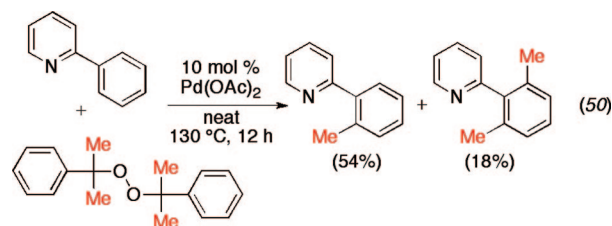
Alkyl halides have also been shown to effect the *ortho*-alkylation of benzoic acids in the presence of catalytic $Pd(OAc)_2$ and a stoichiometric base.[108] In particular, dichloroethane and dibromomethane were effective electrophiles and reacted to form lactone products via an *ortho*-alkylation/$S_N2$ cyclization sequence (eq 51). Competing *O*-alkylation of the carboxylate salts was observed as a side reaction, particularly with electron-rich benzoic acids. However, this undesired transformation could be circumvented by adjusting the temperature along with judicious choice of base (typically $K_2HPO_4$, $KHCO_3$, or $Na_2CO_3$).
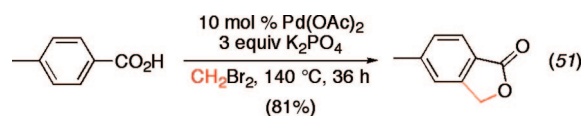


(51)

## 7.5. C−H Alkynylation

The first and only example of Pd-catalyzed directed C−H alkynylation to date involves the reaction of anilides with bromoalkynes.[109] Using catalytic $Pd(OAc)_2$ along with a silyl-protected bromoalkyne, AgOTf, and $K_2CO_3$, a number of substituted anilides could be *ortho*-alkynylated in high yield (eq 52). The mechanism of this transformation was proposed to proceed via the following series of steps: (i) cyclopalladation, (ii) alkyne insertion into the resulting aryl palladium intermediate, (iii) $\beta$-bromide elimination, and (iv) ligand exchange with AgOTf to regenerate the Pd catalyst.



(52)
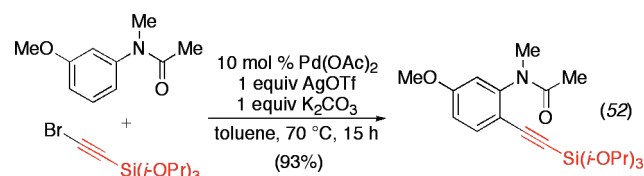
## 7.6. C−H Carbonylation

An early example of Pd-catalyzed directed C−H carbonylation involved the formation of benzolactam derivatives from benzylamines under an atmosphere of CO.[110] $Pd(OAc)_2$ was used as the catalyst, and $Cu(OAc)_2$ and $O_2$ served as co-oxidants (eq 53). Benzylamines underwent significantly faster cyclization than phenethylamines (for example, see substrate **28** in eq 54), presumably because the formation of 5-membered palladacycles is favored over larger rings.



(53)
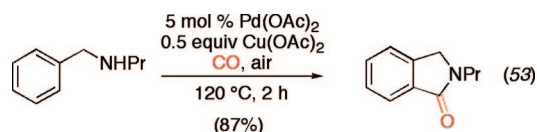
More recently, an analogous urea-directed reaction was utilized to construct cyclic imidates and methyl anthranilates.[111] Benzoquinone was used as the stoichiometric oxidant with $Pd(MeCN)_2(OTs)_2$ as the catalyst. Notably, TsOH (0.5 equiv) was also required to achieve catalyst

(54)
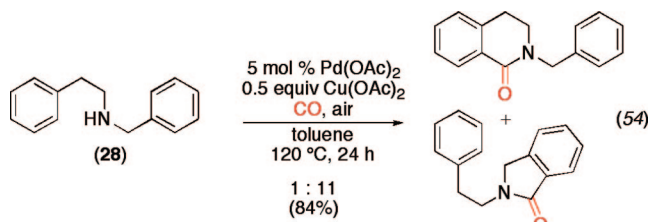
turnover in these systems. In CH$_2$Cl$_2$, cyclic imidates were formed in high yields (eq 55, *ii*); however, when the solvent was changed to THF/MeOH, anthranilate products of methoxycarbonylation were obtained (eq 55, *i*). The latter were proposed to be generated via solvolytic ring opening of the imidates with MeOH.



(55)
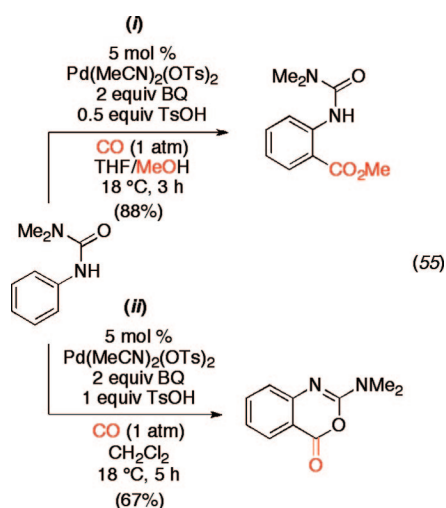
Carboxylate-directed sp$^2$ C–H activation has also been coupled with carbonylation to afford 1,2- and 1,3-dicarboxylic acids.[112] Sodium carboxylates were used to direct cyclopalladation of both benzoic and phenylacetic acids in the presence of catalytic Pd(OAc)$_2$, 2 equiv of NaOAc, and 2 equiv of Ag$_2$CO$_3$ (eq 56). Anhydrides were proposed to be generated as initial intermediates (**29** in eq 56) via intramolecular trapping of a Pd–acyl intermediate. Hydrolysis under the reaction conditions would then afford the observed dicarboxylic acid products.



(56)
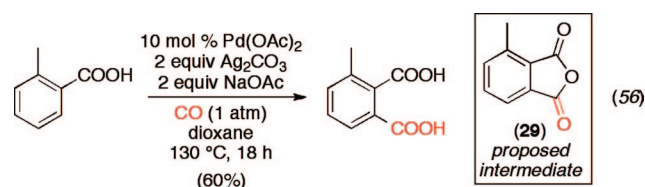
**Scheme 40. Pd-Catalyzed Ethoxycarbonylation with DEAD[113]**
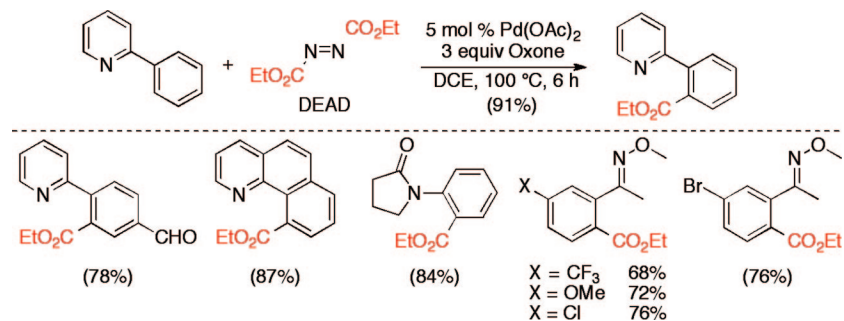


**Scheme 41. Effect of Galvinoxyl on Stoichiometric Ethoxycarbonylation[113]**
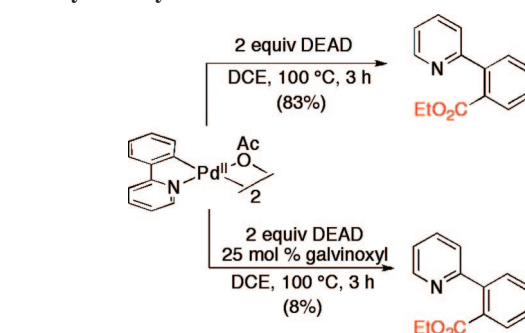


*Ortho*-esters can also be prepared without the requirement for toxic CO. Instead, diethyl azodicarboxylate (DEAD) has been used as a source of an ethoxycarbonyl group.[113] Pyridine-, amide-, and oxime ether-directed ethoxycarbonylation have been achieved with this reagent using Pd(OAc)$_2$ as the catalyst, Oxone as a terminal oxidant, and batchwise addition of DEAD (Scheme 40). The addition of galvinoxyl (a free-radical scavenger) resulted in a dramatically lower yield for the stoichiometric reaction between DEAD and [(phpy)Pd(OAc)]$_2$ (phpy = 2-phenylpyridine) (Scheme 41). On the basis of this result, a mechanism involving reaction of ethoxylacyl radicals with cyclopalladated intermediates was proposed.

Finally, simple aldehydes have recently been shown to be effective reagents for the Pd(OAc)$_2$-catalyzed *ortho*-acylation of 2-arylpyridines (eq 57).[114] Both electron-withdrawing and -donating groups were tolerated on both the arylpyridine- and the aldehyde-coupling partner in this transformation. However, alkyl-substituted aldehydes were unreactive under these conditions. A Pd$^{II/0}$ pathway was proposed for this transformation with aldehyde insertion into a palladacyclic intermediate serving as the key C–C bond-forming step.



(57)

## 8. Conclusions and Future Outlook

The field of Pd-catalyzed ligand-directed C–H functionalization has clearly seen a flurry of activity over the past 5 years, and huge advances have been made in both the development of novel reactions and the mechanistic study of these transformations. The future seems similarly bright as there are many challenges (both short and long term) that

remain to be addressed. For example, it will be important to ascertain whether the reactions described in this review are general with respect to many different directing groups (as each has typically been optimized within a limited class of substrates). Further, it will be synthetically useful to expand the scope of directing groups that can be used in this chemistry to include less basic functionalities like aldehydes, ketones, alcohols, and oxygen heterocycles.[68] More general methods for functionalization at remote positions (via 7-, 8-, 9-membered and larger palladacycles)[49] as well as at 2° and 3° sp³ sites would also greatly expand the utility of these transformations. The application of Pd-catalyzed ligand-directed C−H functionalization to complex, multifunctional substrates also remains a key future objective. The demonstration of efficiency and selectivity in such settings would pave the way for the widespread application of this chemistry for late-stage derivatization of natural products and medical compounds.

Asymmetric catalysis is another clear frontier in this field. Pioneering work by Yu has shown that such reactions are possible.[106] However, the design of asymmetric C−H functionalization reactions that are general with respect to directing group, substrate, and functionalizing reagent remains a critical goal. Such transformations will clearly require significant effort in the area of ligand design.

Finally, the future development of novel reactions in this field will be closely tied to mechanistic investigations. As discussed above, our current mechanistic understanding of these transformations and of the complex interplay between catalyst, ligands, solvent, additives, and substrates remains in its infancy. Mechanistic studies are expected to continue to inform the design and discovery of new highly active and selective catalysts for Pd-catalyzed ligand-directed C−H functionalization processes.

## 9. Abbreviations

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| Ac₂O | acetic anhydride |
| AcOH | acetic acid |
| Ad | adamantyl |
| Ar | aryl |
| atm | atmosphere |
| Boc | *tert*-butoxycarbonyl |
| BQ | benzoquinone |
| Bn | benzyl |
| Bu | butyl |
| cod | cyclooctadiene |
| Cy-JohnPhos | cyclohexyl John Phos ligand |
| DCE | dichloroethane |
| DCM | dichloromethane |
| DEAD | diethyl azodicarboxylate |
| *i*-Prpf | 1,1′-bis(diisopropylphosphino)ferrocene |
| DG | directing group |
| DMF | dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DoL | directed *ortho* lithiation |
| FG | functional group |
| H₂hpda | 4-hydroxypyridine-2,6-dicarboxylic acid |
| L | ligand |
| MOM | methoxymethyl |
| MS | molecular sieves |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |
| NIS | *N*-iodosuccinimide |
| NMP | *N*-methyl-2-pyrrolidone |

| | |
|---|---|
| OAc | acetate |
| OPiv | pivalate |
| Ph | phenyl |
| phpy | phenylpyridine |
| Phth | phthalyl |
| Piv | pivaloyl |
| R | alkyl |
| rt | room temperature |
| TFA | trifluoroacetic acid |
| TFE | trifluoroethanol |
| THF | tetrahydrafuran |
| Ts | tosyl |
| TsOH | *p*-toluenesulfonic acid |
| tolpy | 2-*ortho*-tolylpyridine |
| X | halide |
| μwave | microwave irradiation |

## 10. Acknowledgments

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