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Controlling Site Selectivity in Palladium-Catalyzed C–H Bond Functionalization

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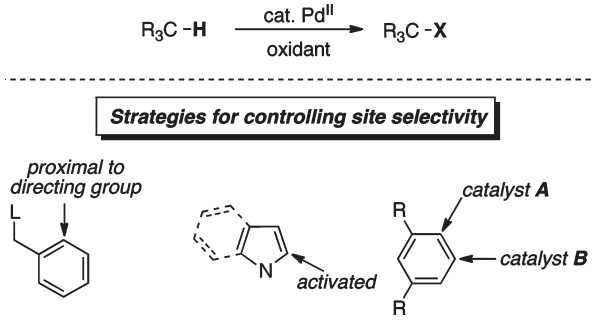
CONSPECTUS

Effective methodology to functionalize C–H bonds requires overcoming the key challenge of differentiating among the multitude of C–H bonds that are present in complex organic molecules. This Account focuses on our work over the past decade toward the development of site-selective Pd-catalyzed C–H functionalization reactions using the following approaches: substrate-based control over selectivity through the use of directing groups (approach 1), substrate control through the use of electronically activated substrates (approach 2), or catalyst-based control (approach 3). In our extensive exploration of the first approach, a number of selectivity trends have emerged for both sp^2 and sp^3 C–H functionalization reactions that hold true for a variety of transformations involving diverse directing groups. Functionalizations tend to occur at the less-hindered sp^2 C–H bond *ortho* to a directing group, at primary sp^3 C–H bonds that are β to a directing group, and, when multiple directing groups are present, at C–H sites proximal to the most basic directing group. Using approach 2, which exploits electronic biases within a substrate, our group has achieved C-2-selective arylation of indoles and pyrroles using diaryliodonium oxidants. The selectivity of these transformations is altered when the C-2 site of the heterocycle is blocked, leading to C–C bond formation at the C-3 position. While approach 3 (catalyst-based control) is still in its early stages of exploration, we have obtained exciting results demonstrating that site selectivity can be tuned by modifying the structure of the supporting ligands on the Pd catalyst. For example, by modulating the structure of N–N bidentate ligands, we have achieved exquisite levels of selectivity for arylation at the α site of naphthalene. Similarly, we have demonstrated that both the rate and site selectivity of arene acetoxylation depend on the ratio of pyridine (ligand) to Pd. Lastly, by switching the ligand on Pd from an acetate to a carbonate, we have reversed the site selectivity of a 1,3-dimethoxybenzene/benzo[*h*]quinoline coupling. In combination with a growing number of reports in the literature, these studies highlight a frontier of catalyst-based control of site-selectivity in the development of new C–H bond functionalization methodology.



Introduction

C–H bonds are truly ubiquitous, an attribute that makes them attractive starting materials for the elaboration of complex molecules. However, this same characteristic is also a great impediment to developing practical methods for C–H bond functionalization. To achieve useful yields of a single product, functionalization must occur with high site selectivity for one C–H bond over the others within a complex molecule. Finding a solution to this challenge has been a driving force for much of the research in our laboratory over the past decade. This Account describes our work on the development of Pd-catalyzed C–H bond functionalization reactions, with a particular focus on strategies for achieving site selectivity in these transformations.

Background. Our overall goal has been to develop selective methods for oxidatively transforming C–H bonds embedded in complex molecules into a wide variety of other functional groups (e.g., C–O, C–S, C–halogen, C–N, and C–C bonds; Scheme 1). Our first efforts (initiated in 2003) focused on identifying a competent catalyst for these diverse transformations. We noted a number of literature reports demonstrating Pd^{II}-mediated oxidative functionalization of benzene and simple derivatives thereof. These typically employed $Pd(OAc)_2$ in conjunction with an oxidant to effect C–heteroatom[1] or C–C bond formation.[2,3]

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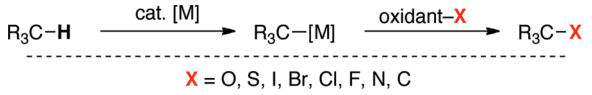
SCHEME 1. Transformation of C–H Bonds into Diverse Functional Groups



However, these methods were typically limited by high catalyst loadings (TON ≈ <1–10), modest substrate scope (typically electron-neutral or electron-rich aromatics), and formation of mixtures of product isomers.

In 1996, Crabtree demonstrated that $Pd(OAc)_2$-catalyzed arene oxidation could be accomplished with substantially lower catalyst loading (TON = 19–127) using $PhI(OAc)_2$ as the terminal oxidant.[4] However, like the earlier work discussed above, the transformation proceeded with poor site selectivity and both alkanes and electron-deficient arenes showed low reactivity. Motivated by this precedent, we initiated studies to address these key limitations.

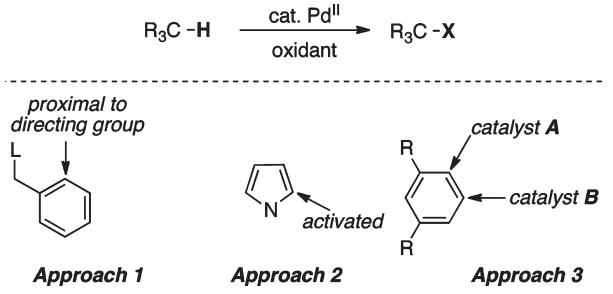
Strategies for Control of Selectivity. Using the combination of Pd^{II} catalysts and oxidants, we have developed a wide variety of C–H functionalization reactions. We have taken three basic strategies to achieve site selectivity (Scheme 2) that involve both "substrate-based control" (approaches 1 and 2) and "catalyst-based control" over selectivity (approach 3). Approach 1 employs substrates that contain coordinating functional groups to direct C–H activation and subsequent functionalization to a proximal site. Approach 2 involves the use of heterocyclic substrates that contain highly activated C–H sites. Finally, approach 3 involves the design of ligands for the Pd catalyst that exert control over site selectivity in C–H functionalization. Each of these approaches is discussed in detail below.

Approach 1. Substrate-Based Control of Selectivity through the Use of Directing Groups

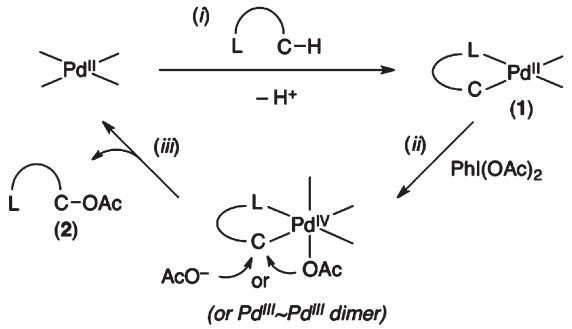
Catalytic Reaction Development. Our initial efforts focused on developing a ligand-directed version of Crabtree's $Pd(OAc)_2$-catalyzed arene acetoxylation with $PhI(OAc)_2$.[4] We aimed to capitalize on the well-known cyclopalladation reaction (stoichiometric ligand-directed C–H bond activation at Pd^{II}) to achieve site-selective C–H cleavage (Scheme 3, step i).[5] Subsequent reaction between the cyclopalladated intermediate **1** and $PhI(OAc)_2$ could then release the desired acetoxylated product **2** (steps ii, iii).[2,5,6]

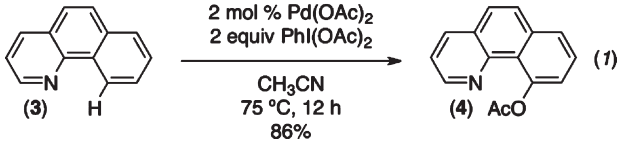
We first pursued the $Pd(OAc)_2$-catalyzed C–H acetoxylation of benzo[*h*]quinoline (**3**). Gratifyingly, C–H oxygenation occurred in high yield to afford **4** as a single isomer (eq 1).[7a] Notably, this transformation (like nearly all of those described in this Account) can be conveniently carried out on the benchtop without exclusion of ambient air or moisture.

SCHEME 2. Strategies for Controlling Site Selectivity



SCHEME 3. Catalytic Cycle for Ligand-Directed C–H Acetoxylation

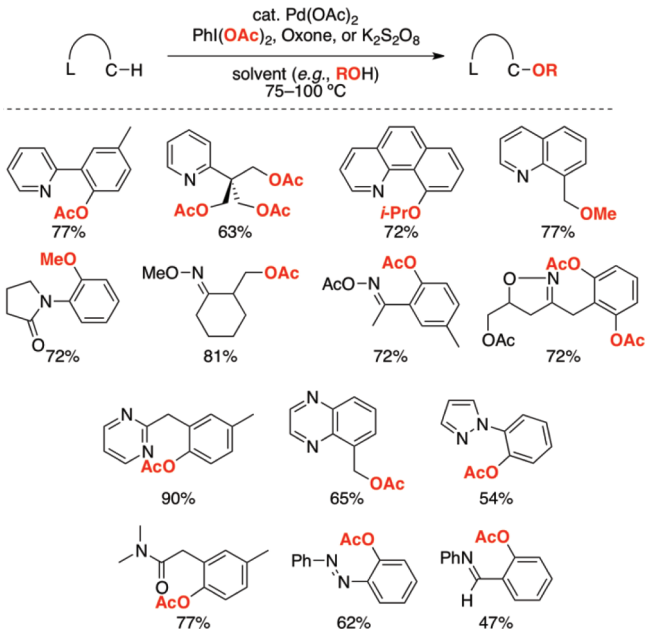




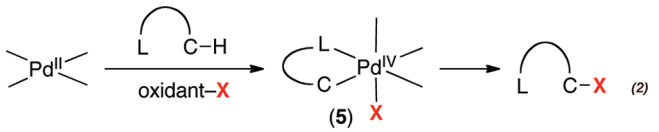
The $Pd(OAc)_2$-catalyzed ligand-directed C–H acetoxylation could be accomplished at both sp^2- and sp^3-C–H bonds. Diverse directing groups including pyridine, pyrimidine, pyrazine, pyrazole, azobenzene, imine, pyrrolidinone, oxime ether and acetate, isoxazoline, and amide derivatives were all effective in providing high selectivity for a proximal C–H site (Scheme 4).[7] Substrates containing two or three identical sites for functionalization could be di- or trioxygenated by using multiple equivalents of oxidant. With many substrates, C–H acetoxylation also proceeds in high yield with polymer-immobilized iodine(III) reagents,[7e] Oxone,[7d] or $K_2S_2O_8$[7d] as oxidants. Furthermore, conducting these reactions in alcohol solvents (e.g., MeOH, ^{i}PrOH, CF_3CH_2OH) results in C–H etherification.[7a,d] Other groups have subsequently demonstrated related Pd-catalyzed C–H oxygenation reactions directed by carboxylic acids, oxazolines, anilides, and amidoquinolines.[8]

Mechanistic studies are consistent with the catalytic cycle depicted in Scheme 3.[4,7a,9] This mechanism suggests that

SCHEME 4. Representative Products of Ligand-Directed C–H Oxygenation



the use of oxidants that could transfer alternative groups to the Pd center (oxidant–X in eq 2) should generate high-valent Pd complexes of general structure **5**. These, in turn, could undergo C–X bond-forming reductive elimination to generate diverse functionalized products.

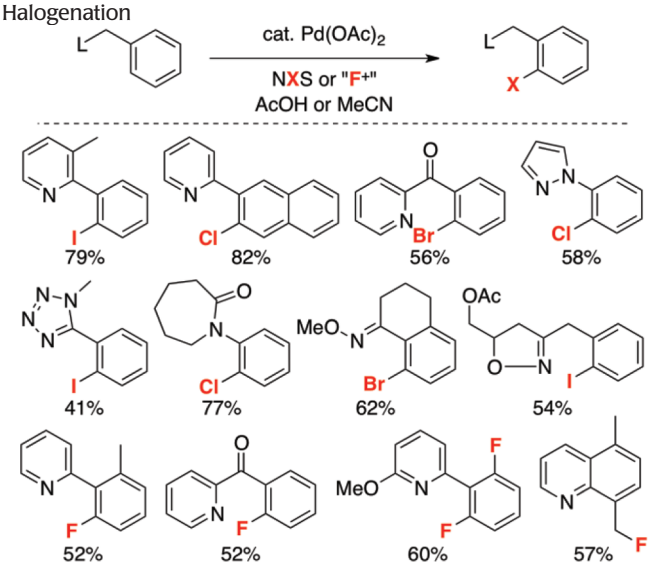


(or Pd^{III}~Pd^{III})

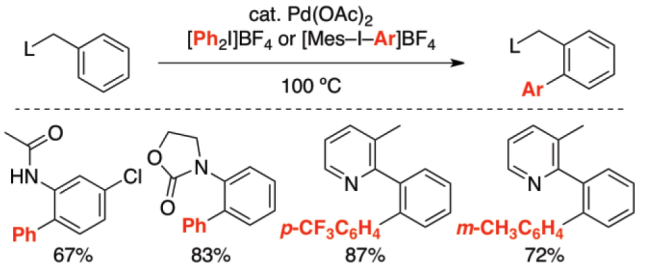
Consistent with this hypothesis, we found that *N*-halosuccinimides are effective oxidants for Pd-catalyzed ligand-directed C–H halogenations to generate C–Cl, C–Br, and C–I bonds[7g,10] and that *N*-fluoropyridinium oxidants can be utilized for related C–H fluorination reactions (Scheme 5).[11] Other research groups have reported related C–H halogenation reactions using CuX_2,[12c,e] IOAc,[12a,b,d] and *N*-fluoropyridinium reagents.[13]

This strategy has also proven successful for achieving ligand-directed C–H arylation. We have shown that either diaryliodonium salts (Ar_2I^+, Scheme 6) or *in situ* generated Ph• can be used as oxidants to effect the selective Pd-catalyzed C–H arylation of a variety of substrates.[9c,14,15] Numerous related Pd-catalyzed ligand-directed C–H arylation reactions (typically with aryl halide oxidants) have been reported in the literature using diverse directing groups including anilides, pyridines, benzoxazoles, carboxylic acids, amides, oxime ethers, aminoquinolines, and picolinamides.[8b,16]

SCHEME 5. Representative Products of Ligand-Directed C–H Halogenation



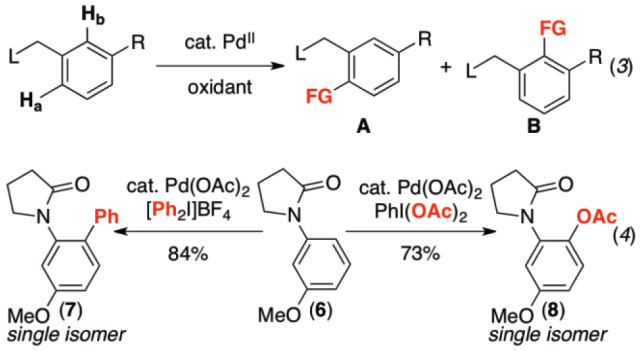
SCHEME 6. Representative Products of Ligand-Directed C–H Arylation



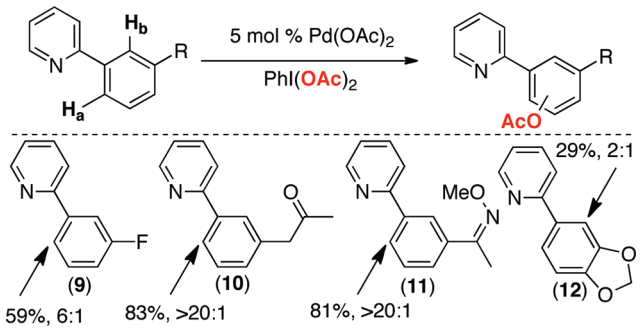
Selectivity Trends for Ligand-Directed C–H Functionalization. Selectivity in Ligand-Directed sp^2-C–H Functionalization. Pd-catalyzed ligand-directed arene C–H functionalization reactions generally afford products functionalized exclusively *ortho* to the directing group. This selectivity is dictated by the C–H activation step, because only a palladacycle containing a Pd–C_{ortho} bond is geometrically feasible.[5] Arene functionalization most commonly occurs via five- or six-membered palladacycles, although reactions proceeding via seven-membered and larger palladacyclic intermediates have also been reported.[17]

When two sterically inequivalent *ortho* C–H sites are available, high selectivity is typically observed for functionalization at the less hindered site (eq 3, product **A**).[7c] This selectivity stands in contrast to directed *ortho*-lithiation (DoL). When R can act as a secondary binding site for Li^+ (e.g., R = OMe, OMOM), DoL leads to functionalization at the site between the two substituents.[18] In contrast, the Pd-catalyzed functionalization of substrate **6** yields

products **7** or **8** without detectable formation of isomers (eq 4).[7c,14]



SCHEME 7. Major Site for C–H Acetoxylation of 3′-Substituted 2-Arylpyridines

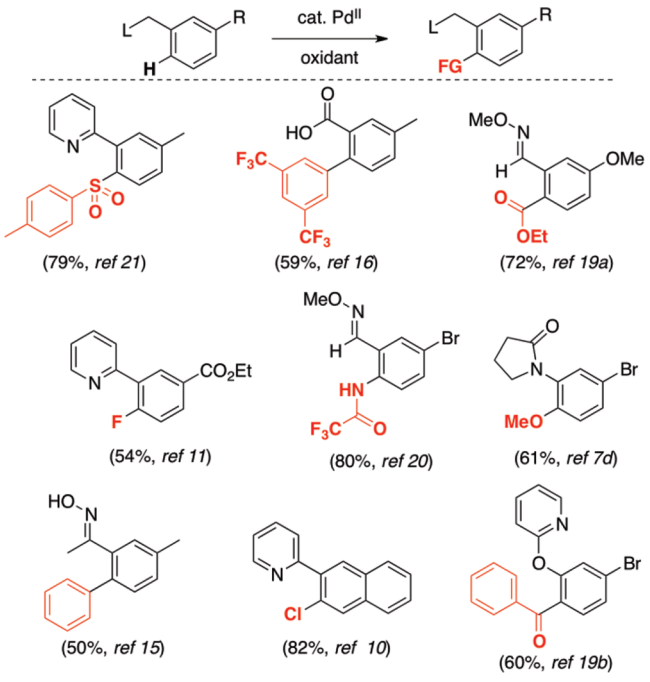


In an attempt to test the limits of this selectivity, we devised a number of substrates that might be biased toward acetoxylation at the more sterically hindered *ortho* site (Scheme 7).[7c] Substrate **9** contains a *meta*-fluorine substituent, which is comparable in size to hydrogen, thereby potentially ameliorating the steric bias. Substrates **10** and **11** contain *meta* ketone/oxime ether moieties, which could act as secondary ligands for Pd. However, remarkably all of these substrates still provided moderate (6:1) to excellent (>20:1) preference for **A**. Indeed, only one substrate was identified (**12**) that afforded modest selectivity for **B** (2:1).

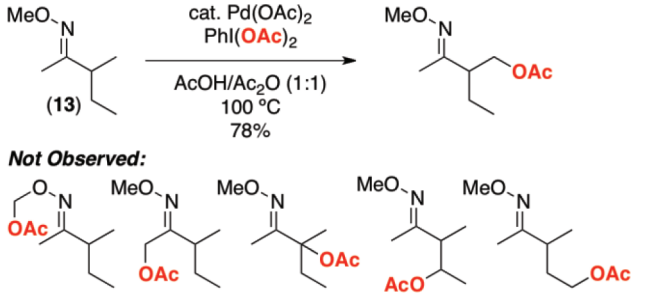
Analogous selectivity trends have been reported for many other Pd-catalyzed ligand-directed arene C–H oxidations[10,11,12a,16,19–21] with substrates bearing diverse directing groups and aromatic ring substituents (Scheme 8).[22]

Selectivity in Ligand-Directed sp^3 C–H Functionalization. Ligand-directed sp^3-C–H functionalization typically proceeds with high selectivity for primary over secondary C–H bonds.[5,7b,7g] In addition, selectivity is observed for C–H bonds that are β versus α or γ to the directing group (i.e, five-membered palladacycles are strongly favored over their four- or six-membered counterparts). These trends are illustrated by the C–H acetoxylation of **13** (Scheme 9), which

SCHEME 8. Selectivity for Isomer A in Diverse C–H Functionalizations



SCHEME 9. Selectivity in Ligand-Directed sp^3-C–H Acetoxylation



provides a single detectable product derived from functionalization at the primary β-C–H site.[7b] With few exceptions (*vide infra*), secondary sp^3 C–H bonds do not undergo functionalization even in the absence of more preferable sites for oxidation [e.g., substrate **14** (Figure 1)].[7b]

The selectivity for primary C–H oxidation stands in contrast to free radical or electrophilic C–H oxidation reactions.[23] These typically afford functionalization at electron-rich C–H sites; as such, the opposite order of C–H bond

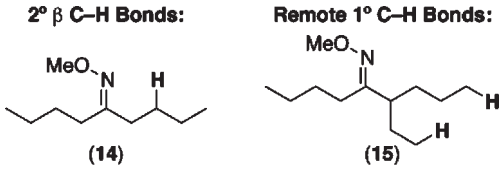


FIGURE 1. Unreactive substrates for sp^3-C–H oxygenation.

reactivity is observed (tertiary > secondary > primary). The difference between the selectivities in Pd-catalyzed versus radical/electrophilic mechanisms likely reflects the strong influence of sterics and of C–H bond pK_a[24] on the palladation step.

Five-membered palladacyclic intermediates are typically important for achieving high-yielding sp^3 C–H functionalization. For example, substrates such as **15** showed no reactivity in the presence of $Pd(OAc)_2$/$PhI(OAc)_2$ (Figure 1).[7b] The markedly higher reactivity of β-C–H bonds is likely due to the more favorable energy requirements for forming a five-membered palladacycle.[5]

To date, there are only a few examples of Pd-catalyzed ligand-directed C–H functionalization at secondary sp^3-C–H sites (Figure 2). These reactions typically occur in substrates that have steric constraints/geometric biases or are electronically activated. One example involves *trans*-decalone methyl oxime ether, whose rigid conformation positions the equatorial secondary β-C–H bond near the coordinated Pd^{II}, leading to product **16** with high selectivity.[7b] In a second example, an amidoquinoline ligand binds to Pd in a bidentate fashion, thereby placing a secondary C–H site in close proximity to the Pd center to afford product **17**.[8b] Electronic activation likely contributes to the facility of secondary sp^3-C–H acetoxylation to form **18** (α to an activating oxygen atom)[7b] and arylation to form **19** (benzylic C–H site).[14] Finally, secondary C–H bonds on cyclopropanes are often amenable to functionalization (e.g., to afford **20**[12b] and **21**[25]), likely due to the diminished steric requirements for C–H activation, the high rigidity of the substrate, and/or the increased s character of cyclopropyl C–H bonds.

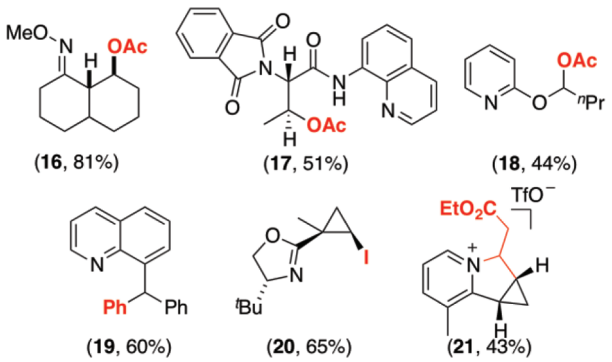
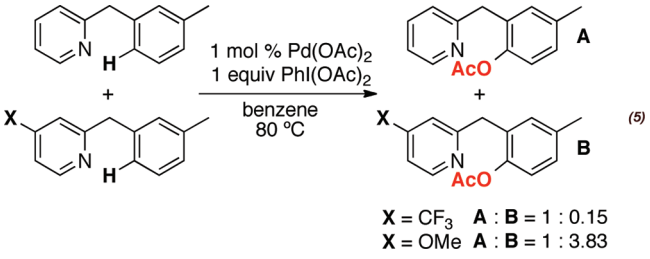
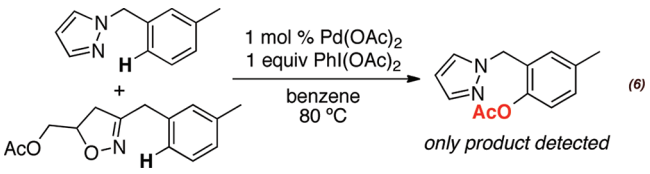


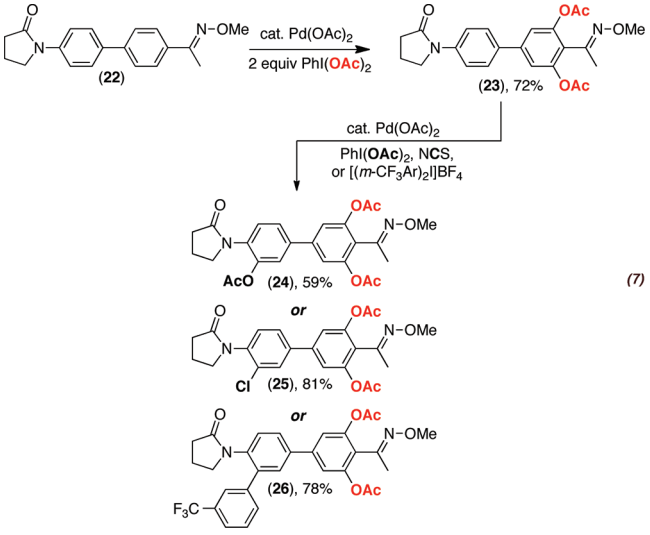
FIGURE 2. Products of secondary sp^3-C–H functionalization.

Selectivity between Directing Groups. Many substrates of interest contain multiple basic groups that could potentially bind to the Pd center and direct C–H functionalization. We conducted systematic competition studies to assess the relative propensities of different N- and O-donor groups to direct Pd-catalyzed C–H acetoxylation.[7f] These investigations revealed a strong correlation between the basicity of the directing group and the relative rate of C–H functionalization proximal to that group. This is exemplified by competition experiments between electronically varied benzylpyridine substrates (eq 5), as well as those between different heterocyclic directing groups (eq 6).





Scheme 10 summarizes the relative reactivity of directing groups in competition studies. Importantly, the trends derived from these experiments have predictive power. For example, they correctly predicted that substrate **22** would undergo selective C–H acetoxylation adjacent to the oxime ether group (eq 7). The resulting product **23** could then be further elaborated to afford products **24**–**26** via amide-directed oxygenation, chlorination, or arylation.

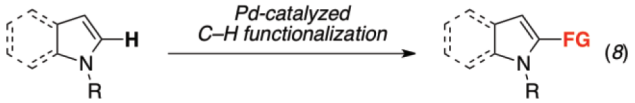


Catalyzed versus Uncatalyzed Selectivity. With many aromatic substrates, arene C–H functionalization with an electrophilic oxidant can occur by either a Pd-catalyzed

pathway or an uncatalyzed electrophilic aromatic substitution (EAS). In certain cases, these two pathways afford different and complementary site selectivity (Scheme 11). Some examples of this phenomenon include the halogenation of electron-rich oxime ether **27** (which selectively affords **28** in the absence of Pd and **29** under Pd catalysis), pyrazole **30** (forming **31** and **32**, respectively), and quinoline **33** (generating **34** and **35**).[10]

Approach 2. Substrate-Based Control of Selectivity through the Use of Electronically Activated Substrates

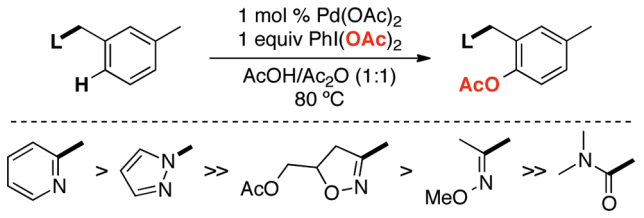
A second strategy for obtaining site selectivity in Pd-catalyzed C−H functionalization is to utilize substrates that have a significant electronic or steric bias for palladation at a specific site. Electron-rich heterocycles are particularly common targets for this approach. For example, many research groups have demonstrated modest to high site selectivity for Pd-catalyzed C−H functionalization at C-2 of indole and C-2/C-5 of pyrrole derivatives (eq 8).[26] This selectivity is believed to derive from an electronic preference for generating Pd−σ-heteroaryl complexes at C-2 (either by initial palladation at this site or by palladation at C-3 followed by palladium migration).[26] This area has been the subject of several reviews,[26] and this section focuses just on our group's contributions in this area.



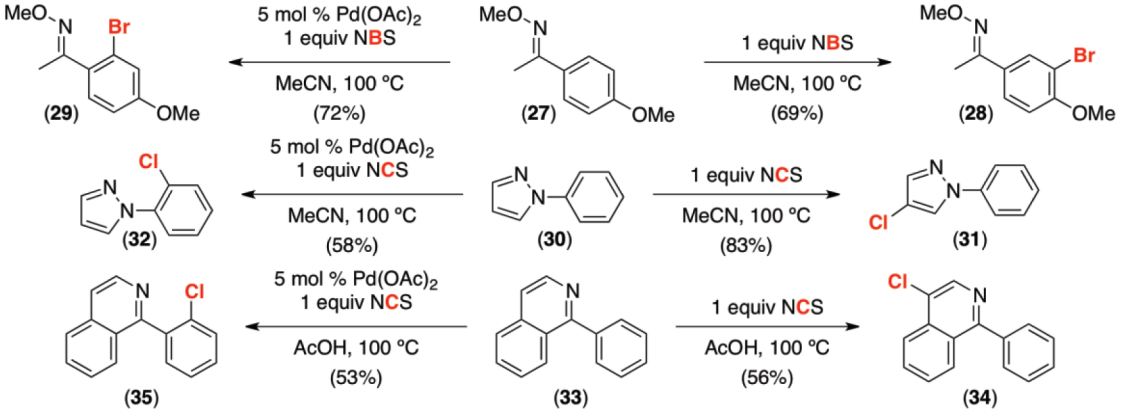
Our initial studies focused on the Pd-catalyzed reaction between indole and $[Ph_2I]BF_4$ (the oxidant used previously for ligand-directed C−H arylation). $(IMes)Pd(OAc)_2(H_2O)$ [IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] proved to be the optimal catalyst, providing 2-phenylindole in excellent (81%) yield with >20:1 selectivity for functionalization at C-2.[27] Comparable yields and site selectivities were obtained with a variety of substituted indole substrates (Scheme 12). Arylation was exclusively observed at C-2 except when this site was blocked (e.g., 1,2-dimethylindole). In the latter case, a modest yield of the C-3 arylation product **36** was obtained.

The C-2 arylation of pyrroles also proceeded with high site selectivity under these conditions (e.g., **37**). Blocking C-2/C-5 of pyrrole (as in 2,5-dimethylpyrrole) significantly diminished reactivity. Under our original conditions, only 12% yield of **38** was obtained; however, the use of $PdCl_2(MeCN)_2$ at an elevated temperature (84 °C) enabled high yielding C-3 phenylation of this substrate.[28] Other 2,5-disubstituted pyrroles also underwent arylation under these conditions, and selectivity appears to be dictated by the relative size of the 2- and 5-substituents (Scheme 13). For example, 2-cyclohexyl-1,5-dimethylpyrrole underwent highly selective (29:1) arylation at the less hindered C-4 to form **39**. However, when cyclohexyl was replaced by a smaller ethyl group, selectivity for C-4 arylation decreased to 2:1 (**40**).

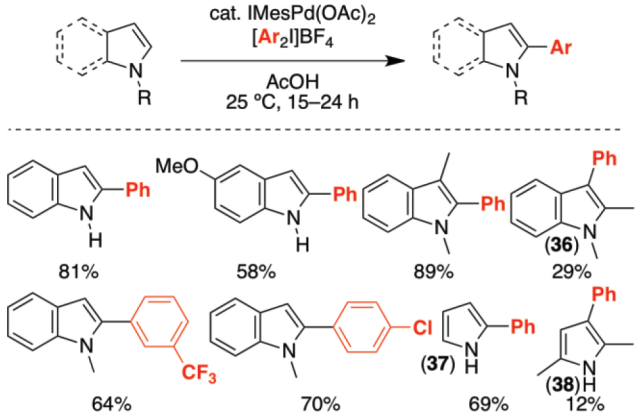
SCHEME 10. Relative Reactivity of Directing Groups toward C−H Acetoxylation in Competition Studies



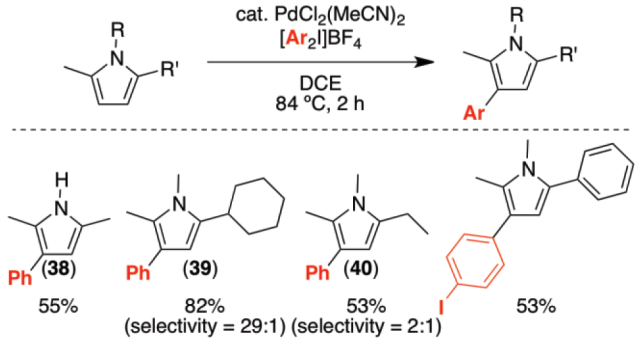
SCHEME 11. Complementary Site Selectivity of Halogenation in the Presence and Absence of Pd



SCHEME 12. Pd-Catalyzed C-2 Arylation of Indoles and Pyrroles with $[Ar_2I]BF_4$



SCHEME 13. Pd-Catalyzed C-3 Arylation of 2,5-Disubstituted Pyrroles

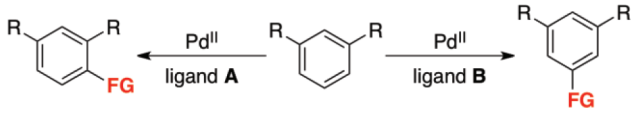


Approach 3. Catalyst-Based Control of Selectivity

In addition to substrate-based control strategies, the site selectivity of C–H functionalization can be controlled via modification of the Pd catalyst structure. This approach targets C–H substrates that lack directing or activating groups, with the ultimate goal of achieving selective formation of different isomeric products by simply changing the ligands at the Pd center (Scheme 14). This has historically proven difficult because the vast majority of Pd-catalyzed C–H functionalization reactions proceed most efficiently under "ligandless conditions" (involving simple Pd salts like $Pd(OAc)_2$ as catalysts). *As such, a key challenge has been to identify ligands that both accelerate these reactions and modulate their site selectivity.*

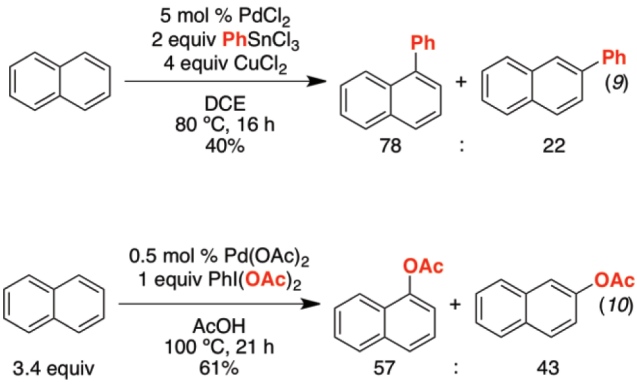
This section discusses catalyst control over selectivity in the context of three different C–H oxidation reactions. Research in all three of these areas remains in its infancy, and in most cases the mechanistic origin of the observed selectivity remains to be elucidated. Nonetheless, these efforts represent an exciting frontier for the development

SCHEME 14. Catalyst Control of Selectivity with Ancillary Ligands



of practical and selective Pd-catalyzed C–H functionalization reactions without the requirement for activating or directing groups.

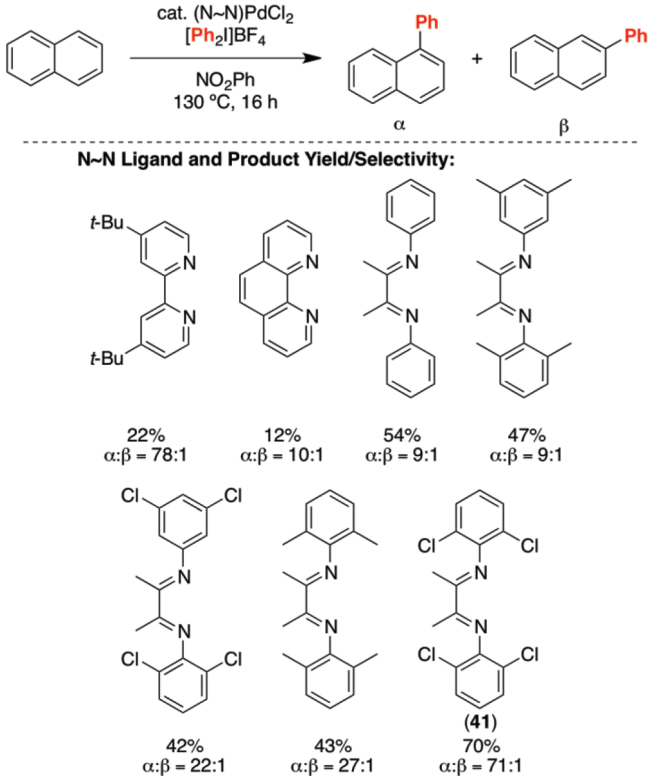
Naphthalene Arylation. Naphthalene has historically proven a challenging substrate for selective C–H functionalization. For example, the $PdCl_2$-catalyzed C–H arylation of naphthalene with $PhSnCl_3$ proceeds with only modest α selectivity (78:22, eq 9).[29] Furthermore, the $Pd(OAc)_2$-catalyzed C–H acetoxylation of naphthalene with $PhI(OAc)_2$ affords a nearly statistical distribution of isomeric products ($\alpha/\beta = 57{:}43$, eq 10).[4]



We chose the Pd-catalyzed C–H arylation of naphthalene with diaryliodonium salts as a platform for investigating catalyst control over site selectivity. A survey of Pd sources and ligands revealed that the combination of $PdCl_2$ and bidentate N–N donors (e.g., bipyridine and diimines) afforded catalysts with enhanced reactivity relative to $PdCl_2$ alone. Furthermore, modification of the N–N ligand resulted in significant changes in selectivity (Scheme 15). While no clear trends were observed as a function of the steric/electronic properties of the N–N ligand, catalyst **41** was found to be uniquely effective for this transformation, affording 70% yield with remarkably high site selectivity ($\alpha/\beta = 71{:}1$).[30]

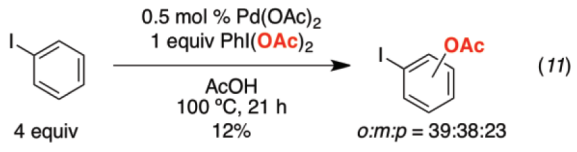
Mechanistic studies of this reaction suggest an unusual pathway in which palladation of naphthalene occurs at a highly electrophilic Pd^{IV} center.[30] This provides a potential explanation for the high selectivity for phenylation at the most nucleophilic α-site. Further studies will be required to obtain insights into the central role that the 2,6-dichlorodiimine ligand plays in enhancing this α-selectivity. Current

SCHEME 15. Catalyst Control of Selectivity in Napthalene Arylation



efforts are aimed at identifying catalysts capable of reversing the selectivity of this transformation to afford high selectivity for the β-arylated product. In addition, the identification of catalysts that show broader substrate scope is another important future goal.

Arene Acetoxylation. As discussed above, the $Pd(OAc)_2$-catalyzed C–H acetoxylation of arenes with $PhI(OAc)_2$ was initially reported by Crabtree in 1996.[4] When applied to substituted aromatic substrates, this original system afforded low yields and poor site selectivity (e.g., eq 11). Our objective was to identify ligands for Pd that could both enhance reactivity and control the site selectivity of these transformations.



Crabtree's early studies showed that the vast majority of common ligands (e.g., pyridine, 1,10-phenanthroline, acetylacetone) dramatically slow the rate of this reaction (eq 12).[4] However, we noted that Crabtree had explored all of the ligands in ratios such that they would generate coordinatively saturated complexes with Pd (e.g, 4 mol % $Pd(OAc)_2$/9 mol % pyridine, eq 12). We reasoned that coordinatively unsaturated Pd complexes [e.g., (pyridine)-$Pd(OAc)_2$] should be more reactive[1b,31] and thus explored the influence of L/Pd ratio on catalytic activity with L = pyridine.[32] Gratifyingly, moving from L/Pd = 2:1 to 1:1 led to a dramatic rate acceleration for this transformation, demonstrating the feasibility of ligand-accelerated catalysis (Figure 3).

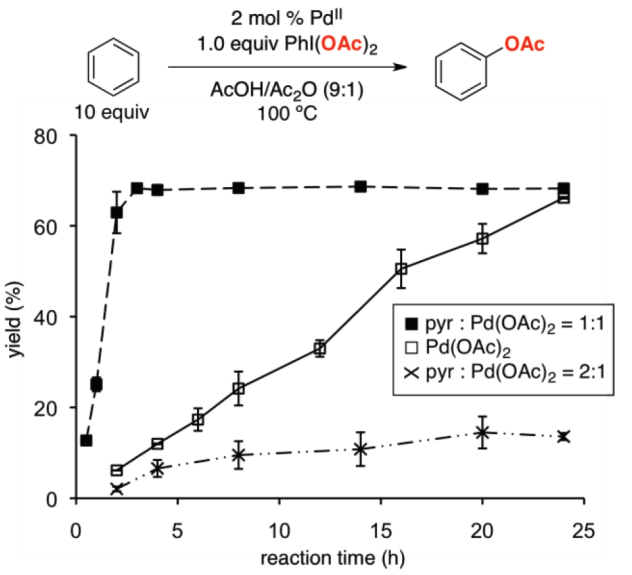
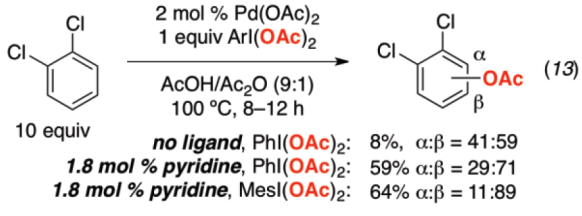


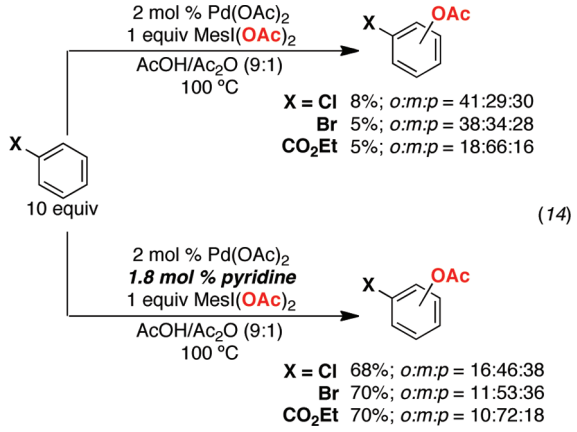
FIGURE 3. Influence of pyridine (pyr) to $Pd(OAc)_2$ ratio on the rate of benzene acetoxylation.

The pyridine ligand also had a significant influence on the site selectivity with substituted arene substrates. For example, the α/β selectivity of the $Pd(OAc)_2$-catalyzed acetoxylation of 1,2-dichlorobenzene changed from 41:59 without pyridine to 29:71 upon the addition of 0.9 equiv of pyridine relative to Pd. Selectivity for the less hindered β site could be further enhanced by employing the bulky oxidant $MesI(OAc)_2$ in place of $PhI(OAc)_2$, resulting in an α/β ratio of 11:89 (eq 13).



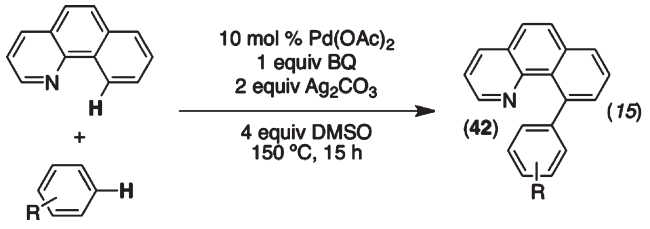
A similar trend was observed for other aromatic substrates, where the addition of 0.9 equiv of the pyridine ligand

in conjunction with $MesI(OAc)_2$ enhanced selectivity for acetoxylation of the less sterically hindered aromatic C–H sites (eq 14).[32]



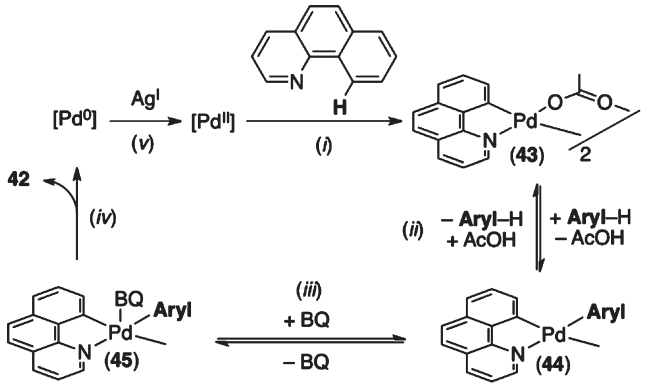
The selectivities remain modest in most of these systems; furthermore, the mechanism by which pyridine/oxidant dictates selectivity requires further investigation. Nonetheless, the demonstration that pyridine ligands, in the correct proportions, can favorably influence activity and selectivity in arene C–H oxidation provides an exciting path forward for the field.[31]

Oxidative Cross-Coupling of Aryl–H with Benzo[*h*]quinoline. Another set of studies has focused on catalyst-controlled selectivity in Pd-catalyzed oxidative cross-coupling reactions.[33] In particular, we have examined the coupling of benzo[*h*]quinoline with aromatic substrates to generate a new biaryl linkage (eq 15). The C–H activation of benzo[*h*]quinoline proceeds with high site selectivity due to the presence of the pyridine directing group, while arene activation is subject to catalyst control.



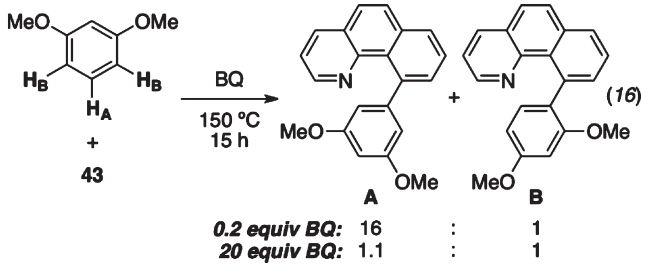
Mechanistic investigations of this transformation implicated a reaction pathway involving (i) ligand-directed C–H activation of benzo[*h*]quinoline to generate dimer **43**, (ii) reversible arene activation to form monomer **44**, (iii) benzoquinone (BQ) complexation to form **45**, (iv) C–C bond-forming reductive elimination to release **42** and Pd^0, and (v) reoxidation of Pd^0 with Ag^I to regenerate the catalyst (Scheme 16).[33b] The rate-limiting step of this sequence changed from ii to iii as a function of the concentration of

SCHEME 16. Proposed Mechanism for Oxidative Coupling between Benzo[*h*]quinoline and Aryl–H



BQ. At low BQ concentration, step iii was rate-determining; however, saturation kinetics were observed at high BQ concentration, suggesting that step ii becomes rate-limiting when BQ is abundant.

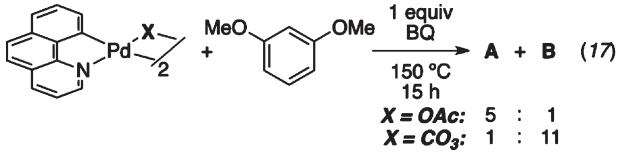
We hypothesized that this change in rate-determining step might result in a change in site selectivity, and this possibility was tested using 1,3-dimethoxybenzene as the arene.[33c,34] With this substrate, functionalization of $C–H_A$ would provide product **A**, while that of $C–H_B$ would afford the isomeric compound **B**. We were pleased to find that the ratio of products **A**/**B** changed from 16:1 to 1.1:1 (eq 16) upon moving from 0.2 equiv of BQ (where step iii is rate-determining) to 20 equiv of BQ (where step ii is rate-limiting).



These results suggest that $Pd(OAc)_2$-mediated C–H activation of DMB (step ii) exhibits low selectivity for $C–H_A$ versus $C–H_B$. In contrast, the BQ-promoted reductive elimination (step iii) appears to be highly selective for **A**. We believe that this is because BQ coordination to Pd^{II} aryl intermediate **44** is very sensitive to sterics.

Further exploration showed that a complete reversal in selectivity to favor isomer **B** could be achieved by simply changing the X-type ligand on Pd.[33c] When carboxylate was replaced with carbonate (eq 17), a strong preference for isomer **B** was observed (**A**/**B** = 1:11). Thus, it appears that although steric effects control the selectivity of arylation under conditions involving a carboxylate ligand, different factors dominate when X = carbonate. Ongoing studies are

directed at elucidating the origin of the **B** selectivity in the carbonate system, but preliminary evidence suggests that the selectivity is not due to an electrophilic palladation step or a thermodynamically controlled deprotonation step.



Summary and Outlook

Substrate-based strategies provide extremely powerful methods for controlling the site selectivity of transition metal-catalyzed C−H bond functionalization and have been extensively explored over the past decade. In contrast, the ability to modulate the site selectivity of a Pd-catalyzed C−H functionalization reaction via variation of the catalyst structure/reaction conditions is an exciting emerging field. Along with the work described above, a number of recent literature reports reflect burgeoning activity in this area. For example, the Pd-catalyzed C−H arylation of *N*-acetylindoles has been demonstrated to occur selectively at C-3 in the presence of $Cu(OAc)_2$ but at C-2 when AgOAc is used as the oxidant.[35a] C−H arylation of azine *N*-oxides has been demonstrated at both sp^2 and sp^3 sites; either site can be accessed selectively depending on the identity of added base.[35b] Finally, a highly *para*-selective C−H arylation is attributed to an $[ArPd^{IV}-F]$ catalytic species formed in the presence of F^+ oxidants.[35c] All of these transformations exemplify the potential power of catalyst control for modulating both reactivity and site selectivity in Pd-catalyzed C−H functionalizations. We anticipate that this will be an area of tremendous growth and activity in the future.

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BIOGRAPHICAL INFORMATION

Sharon R. Neufeldt was born in Tucson, AZ, in 1985. She received her B.S. degree in chemistry from Northern Arizona University, performing research in the laboratory of Professor Clinton F. Lane. She has been working toward her Ph.D. at the University of Michigan under the guidance of Professor Melanie Sanford since 2007, where she is studying ligand-directed Pd-catalyzed C−H and C═C functionalization reactions.

Prof. Melanie S. Sanford was born in New Bedford, MA, in 1975. She received a B.S. and M.S. in chemistry from Yale University in 1996 before obtaining her Ph.D. at California Institute of Technology with Professor Robert Grubbs in 2001. She then completed postdoctoral studies at Princeton University working with Professor John Groves. In 2003, she joined the faculty of the University of Michigan where she is currently the Moses Gomberg Collegiate Professor of Chemistry as well as Arthur F. Thurnau Professor of Chemistry. Her research program focuses on the development of new catalysts and catalytic transformations for applications in the synthesis of useful organic molecules.

FOOTNOTES

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The authors declare no competing financial interest.

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