

Overcoming the “Oxidant Problem”: Strategies to Use O₂ as the Oxidant in Organometallic C–H Oxidation Reactions Catalyzed by Pd (and Cu)

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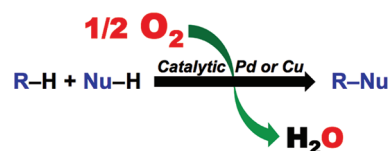
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CONSPECTUS

Oxidation reactions are key transformations in organic chemistry because they can increase chemical complexity and incorporate heteroatom substituents into carbon-based molecules. This principle is manifested in the conversion of petrochemical feedstocks into commodity chemicals and in the synthesis of fine chemicals, pharmaceuticals, and other complex organic molecules. The utility and function of these molecules correlate directly with the presence and specific placement of oxygen and nitrogen heteroatoms and other functional groups within the molecules.

Methods for selective oxidation of C–H bonds have expanded significantly over the past decade, and their role in the synthesis of organic chemicals will continue to increase. Our group's contributions to this field are linked to our broader interest in the development and mechanistic understanding of aerobic oxidation reactions. Molecular oxygen (O₂) is the ideal oxidant. Its low cost and lack of toxic byproducts make it a highly appealing reagent that can address key “green chemistry” priorities in industry. With strong economic and environmental incentives to use O₂, the commodity chemicals industry often uses aerobic oxidation reactions. In contrast, O₂ is seldom used to prepare more-complex smaller-volume chemicals, a limitation that reflects, in part, the limited synthetic scope and utility of existing aerobic reactions.

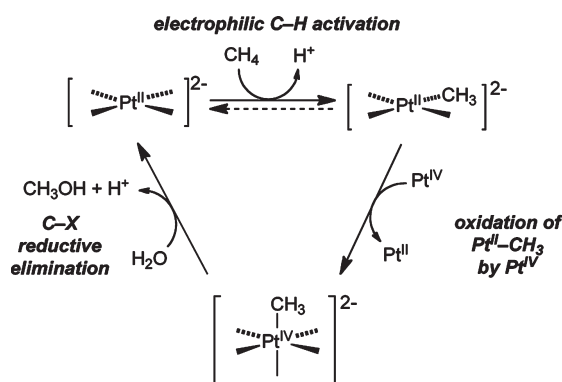
Pd-catalyzed reactions represent some of the most versatile methods for selective C–H oxidation, but they often require stoichiometric transition-metal or organic oxidants, such as Cu^{II}, Ag^I, or benzoquinone. This Account describes recent strategies that we have identified to use O₂ as the oxidant in these reactions. In Pd-catalyzed C–H oxidation reactions that form carbon-heteroatom bonds, the stoichiometric oxidant is often needed to promote difficult reductive elimination steps in the catalytic mechanism. To address this challenge, we have identified new ancillary ligands for Pd that promote reductive elimination, or replaced Pd with a Cu catalyst that undergoes facile reductive elimination from a Cu^{III} intermediate. Both strategies have enabled O₂ to be used as the sole stoichiometric oxidant in the catalytic reactions. C–H oxidation reactions that form the product via β-hydride or C–C reductive elimination steps tend to be more amenable to the use of O₂. The use of new ancillary ligands has also overcome some of the limitations in these methods. Mechanistic studies are providing insights into some (but not yet all) of these advances in catalytic reactivity.



1. Introduction

Over the past decade, catalytic C–H functionalization reactions have begun to emerge as viable alternatives to traditional synthetic methods in organic chemistry. These methods exhibit substantial diversity, with mechanisms ranging from hydrogen-atom abstraction and C–H insertion (e.g., by carbenes, carbenoids, and related species) to organometallic C–H activation.¹ The mechanistic variations lead to unique selectivity patterns, with important implications for organic synthesis.²

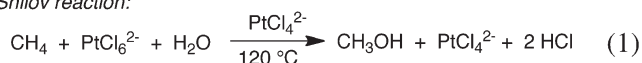
Organometallic C–H oxidation and oxidative-coupling reactions offer important advantages over widely used catalytic cross-coupling methods and traditional C–C and C–X (X = heteroatom) bond-forming reactions. By eliminating the requirement for prefunctionalized substrate(s), such as alkyl/aryl halides or organometallic reagents, these methods offer the prospect of broader substrate scope and improved atom-economy. In order for these benefits to be fully realized, however, at least two conditions must be met: (1) the reaction must achieve site-selective functionalization of a C–H bond in an organic

SCHEME 1. Proposed Catalytic Mechanism of the Shilov Reaction

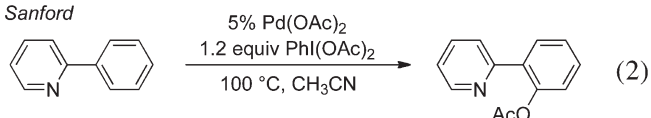
substrate, and (2) the cost and/or waste associated with the stoichiometric oxidant should not offset the benefits of using a less-functionalized substrate. Aerobic oxidative-coupling reactions that proceed with high chemo-, regio-, and stereoselectivity represent near-ideal embodiments of these criteria.

Platinum-catalyzed oxidation of methane, reported by Shilov et al. nearly four decades ago, provides historical context for the field of organometallic C–H oxidation.³ This reaction achieves selective oxidation of methane to methanol (and methyl chloride) in aqueous solution, with $\text{Pt}^{\text{II}}\text{Cl}_6^{2-}$ as the catalyst and $\text{Pt}^{\text{IV}}\text{Cl}_6^{2-}$ as the stoichiometric oxidant (eq 1). The mechanism involves three key steps (Scheme 1):⁴ (1) electrophilic C–H activation of methane by Pt^{II} , (2) two-electron oxidation of a $\text{Pt}^{\text{II}}\text{--CH}_3$ intermediate by Pt^{IV} , and (3) nucleophilic attack of water on the resulting $\text{Pt}^{\text{IV}}\text{--CH}_3$ species, formally an $\text{S}_{\text{N}}2$ -type reductive elimination, to afford CH_3OH . This so-called "Shilov reaction" is one of the earliest catalytic demonstrations of organometallic C–H oxidation, and it continues to serve as a paradigm for new developments in the field. For example, $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ -catalyzed C–H oxidation reactions (e.g., eqs 2 and 3)⁵ proceed by a mechanism that closely resembles Scheme 1, involving sequential C–H activation, oxidation, and C–X reductive elimination steps.

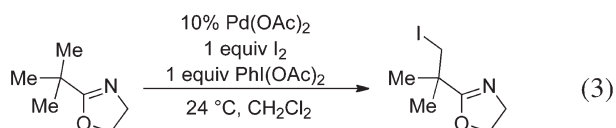
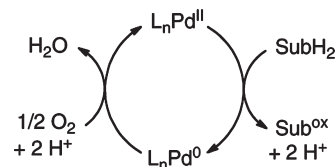
Shilov reaction:



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**SCHEME 2.** Simplified Catalytic Cycle for $\text{Pd}^{\text{II}}/\text{Pd}^0$ -Catalyzed Aerobic Oxidation Reactions

The use of Pt^{IV} as a stoichiometric oxidant in the Shilov reaction represents a significant drawback that has been difficult to address.⁶ Oxidants that are commonly used in $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ -catalyzed reactions, such as $\text{PhI}(\text{OAc})_2$, diaryliodonium salts, *N*-bromosuccinimide, and electrophilic fluorine reagents,⁷ are more user-friendly (e.g., soluble in organic solvents) and less expensive than $\text{Pt}^{\text{IV}}\text{Cl}_6^{2-}$; however, their use still contributes to lower atom economy, and reduces the appeal of these reactions vis-à-vis traditional cross-coupling methods and hinders large-scale applications. Separately, many recently reported Pd^{II} -catalyzed C–H oxidation reactions employ stoichiometric benzoquinone, Cu^{II} , or Ag^{I} as stoichiometric oxidants.⁷ As this field expands and the opportunities afforded by these reactions impact mainstream organic synthesis, the importance of addressing this "oxidant problem" will become increasingly apparent.

Our research group has had a long-standing interest in Pd-catalyzed aerobic oxidation reactions.⁸ These reactions typically proceed via a $\text{Pd}^{\text{II}}/\text{Pd}^0$ pathway and differ from Shilov and $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ -catalyzed C–H oxidations in that the stoichiometric oxidant (O_2) does not participate directly in the substrate oxidation step(s) (Scheme 2). Important early precedents exist for C–H oxidation reactions of this type. For example, Pd^{II} -catalyzed homocoupling of arenes was first reported in the mid-1960s (eq 4).⁹ These reactions received little attention relative to the more-selective, nonoxidative cross-coupling reactions of aryl halides; however, the growing importance of C–H functionalization reactions and environmentally benign methods for chemical synthesis provides strong motivation to reinvestigate reactions of this type. Such efforts will benefit from four decades of advances in mechanistic characterization of organometallic reactions (including C–H activation), insights into ancillary ligand effects in catalysis, and principles of O_2 activation and reduction by transition metals.

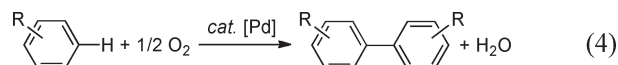


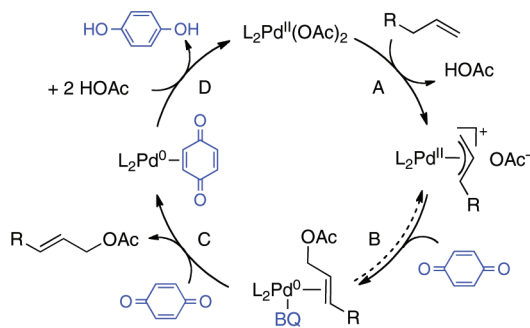
TABLE 1. Representative Pd-Catalyzed Oxidation Reaction and the Identity of the Product-Forming Step in the Catalytic Mechanism^a

Oxidative Transformation	Product-Forming Step
A. Alcohol Oxidation $\text{R-CH}_2\text{-OH} \xrightarrow[\text{O}_2]{\text{cat. [Pd]}} \text{R-CHO}$	β-Hydride Elimination
B. Wacker-Type Oxidative Cyclization $\text{HNu-CH}_2\text{-CH=CH}_2 \xrightarrow[\text{O}_2]{\text{cat. [Pd]}} \text{Nu-CH}_2\text{-CH}_2\text{-CH=CH}_2$	
C. Aza-Wacker $\text{R}_2\text{N-H} + \text{R}'\text{-CH=CH}_2 \xrightarrow[\text{O}_2]{\text{cat. [Pd]}} \text{R}'\text{-CH=CH-NR}_2$	
D. Oxidative Heck Coupling $\text{R-Ar-H} + \text{Z-CH=CH}_2 \xrightarrow[\text{O}_2]{\text{cat. [Pd]}} \text{R-Ar-CH=CH-Z}$	
<hr/>	
E. Oxidative Biaryl Coupling $\text{R-Ar-H} + \text{R}'\text{-Ar'-H} \xrightarrow[\text{O}_2]{\text{cat. [Pd]}} \text{R-Ar-Ar'-R}'$	Reductive Elimination
F. Allylic C–H Oxidation $\text{R-CH}_2\text{-CH=CH}_2 + \text{Nu-H} \xrightarrow[\text{O}_2]{\text{cat. [Pd]}} \text{R-CH=CH-CH}_2\text{-Nu}$	
G. Oxidative Heterofunctionalization of Arenes $\text{R-Ar-H} + \text{Nu-H} \xrightarrow[\text{O}_2]{\text{cat. [Pd]}} \text{R-Ar-Nu}$	

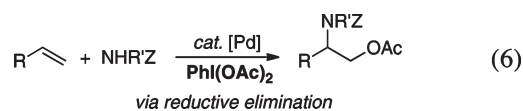
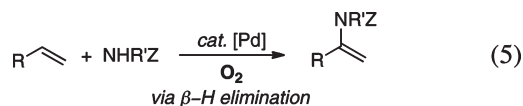
^aNu = heteroatom nucleophile; Z = electron-withdrawing group.

2. Pd-Catalyzed Aerobic Oxidation Reactions: β-Hydride versus Reductive Elimination Reactions

Pd-catalyzed oxidation reactions that proceed via a Pd^{II}/Pd⁰ cycle can be divided into two general classes, distinguished by the product-forming step in the catalytic mechanism: β-hydride elimination versus reductive elimination. Examples of the former class include alcohol oxidation and oxidative-coupling reactions of alkenes (Table 1, reactions A–D), and the latter class includes oxidative-coupling reactions of arenes and allylic oxidation reactions (Table 1, Reactions E–G). A survey of the literature^{7,8,10} reveals that Pd^{II}-catalyzed oxidation reactions that proceed via β-hydride elimination are often compatible with O₂ as the oxidant, whereas reactions that proceed via reductive elimination typically employ alternative oxidants, such as benzoquinone, Cu^{II}, and Ag^I, among others. Such trends are evident in our studies of Pd-catalyzed oxidative amination of alkenes:^{8c} aza-Wacker reactions that form enamide products via β-hydride elimination from an alkyl-Pd^{II} intermediate are compatible with O₂

SCHEME 3. Proposed Mechanism for Pd-Catalyzed Allylic Acetoxylation Using BQ as the Oxidant

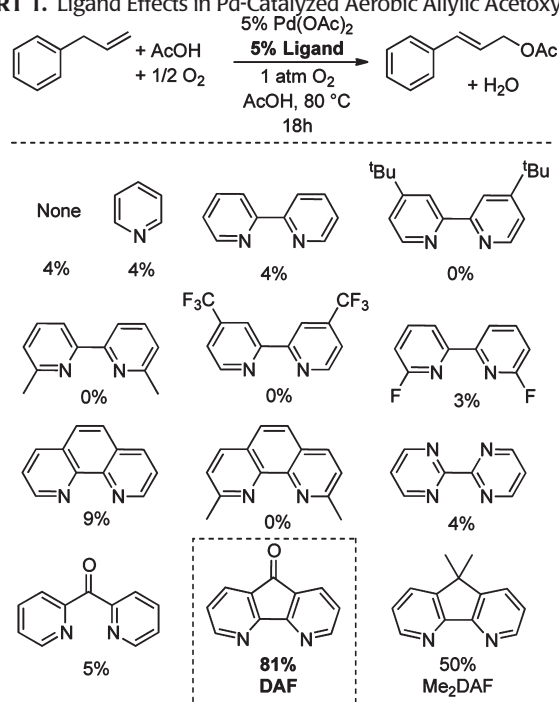
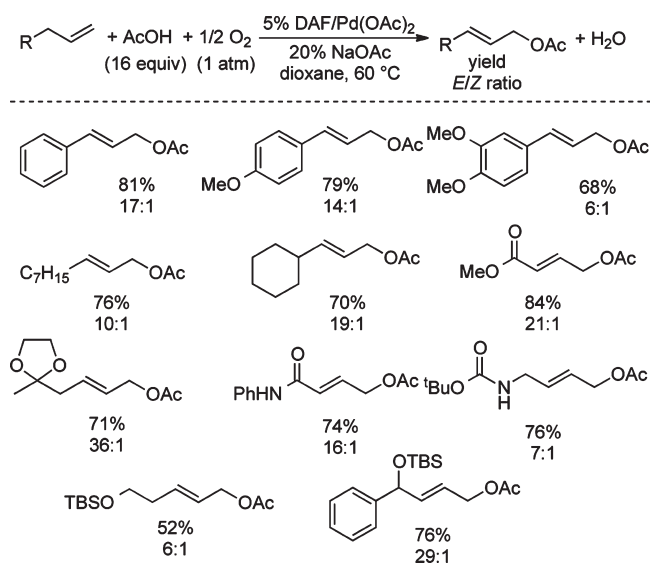
(eq 5), but the aminoacetoxylation of alkenes requires PhI(OAc)₂ (eq 6), reflecting the need to oxidize a Pd^{II}(alkyl)-(OAc) intermediate to a higher oxidation state to promote C–O reductive elimination.



β-Hydride and reductive elimination steps are quite different with respect to the redox changes that take place at Pd. β-Hydride eliminations from Pd^{II}-alkoxide or -alkyl intermediates generate Pd^{II}-hydrides, which involves no formal change in the Pd^{II} oxidation state. In contrast, reductive eliminations from Pd^{II}(Ar)(Ar') or Pd^{II}(Ar)(Nu) intermediates afford Pd⁰, reflecting two-electron reduction of the Pd center. If the Pd^{II} center in these catalytic intermediates is not sufficiently oxidizing, the reductive elimination step may be slow or even thermodynamically unfavorable. In many cases, oxidation of the organopalladium(II) intermediate (e.g., to a Pd^{III} or Pd^{IV} species) is needed to promote reductive elimination.¹¹ Our studies of aerobic C–H oxidation reactions presented below address both classes of reactions (β-hydride and reductive elimination).

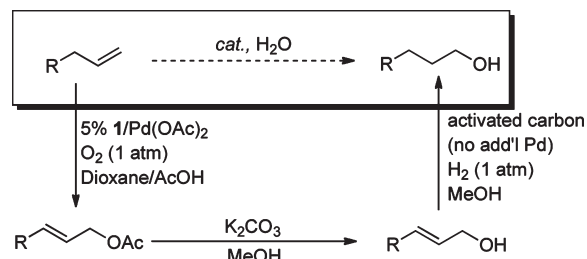
3. Allylic C–H Acetoxylation: A Ligand-Based Strategy to Replace Benzoquinone with O₂

Pd-catalyzed oxidative heterofunctionalization of allylic and aromatic C–H bonds (cf. Table 1, F and G) are rarely compatible with O₂.¹² Allylic C–H oxidation reactions commonly employ benzoquinone (BQ) as the stoichiometric oxidant.¹³ BQ has been shown to promote the product-forming reductive elimination step,¹⁴ which involves inner-sphere or outer-sphere

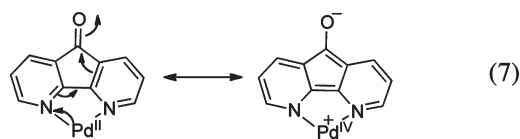
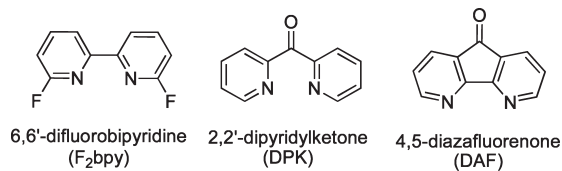
CHART 1. Ligand Effects in Pd-Catalyzed Aerobic Allylic Acetoxylation**CHART 2.** Aerobic Allylic Acetoxylation of Terminal Alkenes

nucleophilic attack on an allyl-Pd^{II} intermediate, and it also serves as the stoichiometric oxidant in the conversion of Pd⁰ to Pd^{II} (Scheme 3).¹⁵ We speculated that an ancillary ligand could be used to destabilize the allyl-Pd^{II} intermediate and enable reductive elimination to occur in the absence of BQ. If the same ligand could promote oxidation of Pd⁰ to Pd^{II} with O₂,¹⁶ it should be possible to achieve aerobic allylic C–H oxidation reactions.¹⁷

Nitrogen-based ligands are common in Pd-catalyzed aerobic oxidation reactions, and we reasoned that electron-deficient

SCHEME 4. Net Anti-Markovnikov Hydration of Terminal Alkenes Involving Aerobic Allylic Acetoxylation, Acetate Cleavage, Alkene Hydrogenation Sequence

ligands would increase the Pd^{II}/Pd⁰ reduction potential and thereby facilitate reductive elimination. Three of our initial ideas included 6,6'-difluorobipyridine (6,6'-F₂bpy), 2,2'-dipyridylketone (DPK), and 4,5-diazafluorenone (DAF). The fluorine substituents of 6,6'-F₂-bpy significantly reduce the basicity of the nitrogen lone pair via their inductive effect, while the carbonyl groups in DPK and DAF could remove electron density on Pd^{II} center via π -backbonding, formally leading to a Pd^{IV} resonance contribution (eq 7).



These ligands were screened together with other nitrogen-based ligands in an effort to achieve allylic C–H acetoxylation of allyl benzene under 1 atm O₂ (Chart 1). Traditional ligands, including pyridine, bipyridine, and phenanthroline, were almost completely ineffective. Bipyrimidine, which is effective in BQ-promoted allylic acetoxylation,^{13b} 6,6'-F₂-bpy, and DPK were also unsuccessful. Diazafluorenone (DAF) proved to be uniquely successful, enabling an 81% yield of cinnamyl acetate. We also tested 9,9-dimethyl-4,5-diazafluorenone (Me₂DAF) and obtained a 50% yield. The latter result is not better than that observed with DAF, but the improved results relative to all other ligands suggests that the beneficial effect of DAF reflects the unique geometry of the diazafluorenone structure. The DAF-Pd(OAc)₂ catalyst system was successfully applied to aerobic acetoxylation of a number of terminal alkenes, including those bearing synthetically useful functional groups (Chart 2). Linear allylic

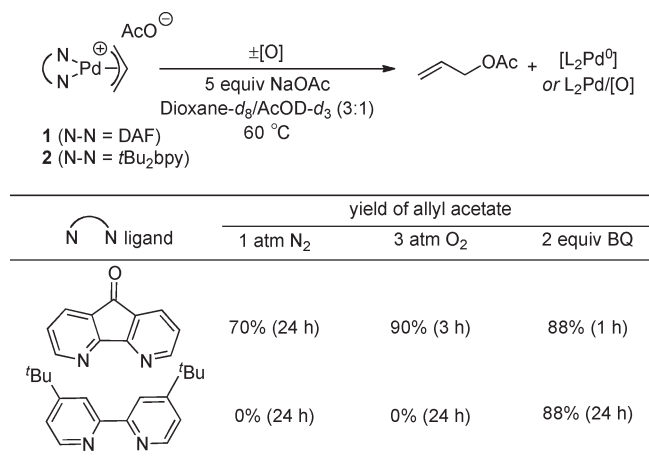


FIGURE 1. Ligand effects on stoichiometric acetoxylation of π -allyl-Pd complexes.

acetates were obtained exclusively, with a strong preference for the *E* stereoisomer. This reactivity was implemented to achieve net anti-Markovnikov hydration of terminal alkenes via sequential aerobic acetoxylation, alcoholysis of the acetate and hydrogenation of the allylic alcohol (Scheme 4). In this one-pot sequence, the heterogeneous Pd catalyst for the hydrogenation step was formed in situ by adding activated carbon to the crude reaction mixture and placing the vessel under an atmosphere of hydrogen gas.

Mechanistic studies have begun to provide insights into the ability of the diazafluorenone ligand to support aerobic, BQ-free catalytic turnover. Initial studies confirmed that DAF promotes reductive elimination from Pd^{II}. The reactivity of two [(L)Pd^{II}(η^3 -allyl)]OAc complexes, **1** (L = DAF) and **2** (L = *t*Bu₂bpy), toward reductive elimination was investigated under three different conditions: in the absence of oxidant and in the presence of O₂ or BQ (Figure 1). The DAF-ligated complex **1** formed allyl acetate under all three conditions, and the rate was faster in the presence of an oxidant. The *t*Bu₂bpy-ligated complex **2** was completely unreactive, except in the presence of BQ, demonstrating that BQ can induce acetoxylation of an otherwise unreactive π -allyl-Pd^{II} complex and that O₂ cannot serve as a direct surrogate for BQ. The C–O reductive elimination step was shown to be reversible with **1**, as revealed by the incorporation of deuterium-labeled acetate into cinnamyl acetate in the presence of 25 mol % [(DAF)Pd^{II}(allyl)]OAc (Figure 2A). Analogous exchange was not observed in the presence of the *t*Bu₂bpy complex **2**. A mechanism that accounts for these observations is shown in Figure 2B. Reductive elimination of allyl acetate initially affords an Pd⁰-alkene adduct, and this species can revert to the allyl-Pd^{II} species (*k*_{rev}), undergo alkene exchange (*k*_{exch}), or react with

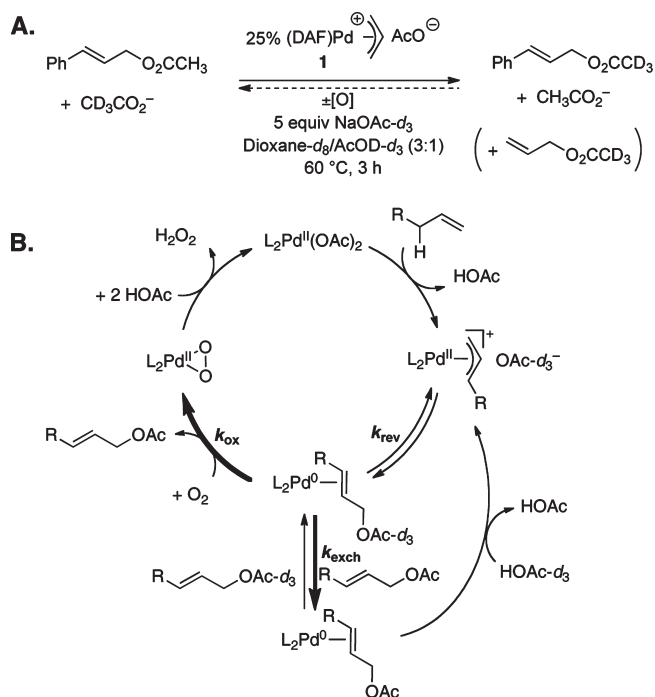
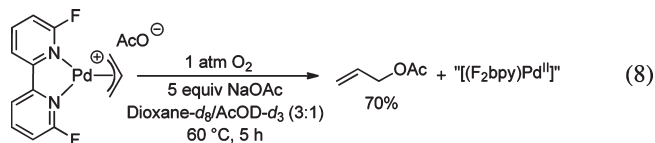


FIGURE 2. Evidence for reversible C–O reductive elimination from (DAF)Pd(η^3 -allyl) complexes (A), and mechanistic rationale for (L)Pd(η^3 -allyl)-catalyzed acetate exchange in cinnamyl acetate and the influence of an oxidant on the extent of exchange (B).

an oxidant (*k*_{ox}). Evidence for competition between the *k*_{ox} and *k*_{exch} steps was evident from reduced isotopic exchange at elevated O₂ pressures. The ability of an oxidant to compete with the *k*_{rev} step explains the faster rate of allyl acetate reductive elimination from **1** in the presence of an oxidant.

Additional studies reveal that ligand-promoted reductive elimination is not sufficient to achieve aerobic catalytic acetoxylation. [(6,6'-F₂bpy)Pd^{II}(allyl)]OAc undergoes stoichiometric reductive elimination of allyl acetate under aerobic conditions (eq 8), but the 6,6'-F₂bpy ligand does not support aerobic catalytic turnover (Chart 1). These observations suggest the ancillary ligand influences other steps in the catalytic mechanism (e.g., C–H activation). Additional mechanistic studies will be needed to fully elucidate the unique influence of DAF on catalytic reactivity.

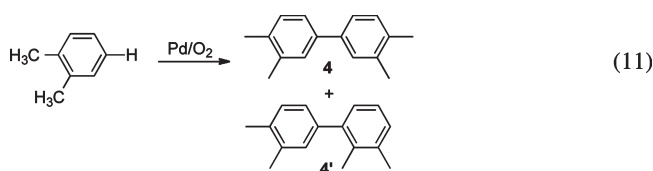
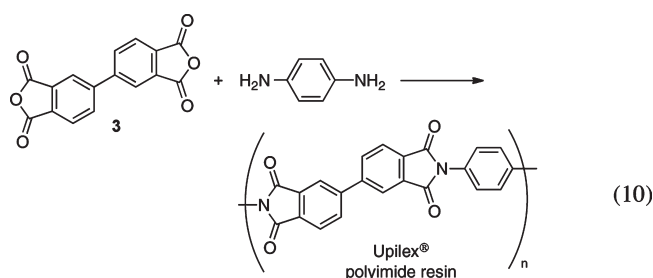
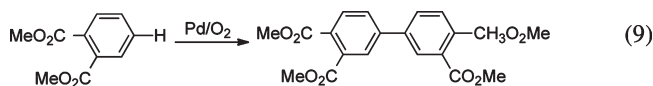


4. Regioselective Aerobic Oxidative Coupling of Arenes without Directing Groups

Pd-catalyzed methods for oxidative homocoupling of arenes were among the first examples of aerobic

organometallic C–H oxidation (eq 4).⁹ The synthetic utility of these methods were limited by low regioselectivity, however. Here, we summarize two recent studies that address issues of regioselectivity while incorporating the use O₂ as the oxidant.

4.1. Selective Homocoupling of *o*-Xylene. A rare, commercially important application of Pd-catalyzed homocoupling of arenes is the reaction of dimethyl-*ortho*-phthalate (eq 9). This reaction is employed in the commercial synthesis of 4,4'-bipthalic anhydride (**3**),¹⁸ a monomer for the high-performance polyimide resin, Upilex (eq 10).¹⁹ The production of **3** originates with *o*-xylene and requires five overall steps including esterification and alcoholysis/hydrolysis reactions. This route potentially could be streamlined by the development of a selective method for direct oxidative coupling of *o*-xylene (eq 11).²⁰ The best reported conditions for this reaction employ a Pd(OAc)₂/1,3-cyclohexanedione catalyst system at 140 °C.^{20b} The reaction exhibits modest regioselectivity (**4**/**4'** = 3.3:1), but low overall chemoselectivity (40%), with significant formation of higher-molecular-weight oligomers. Prompted by recent industrial interest in improved arene homocoupling methods,²¹ we decided to explore this reaction further, with the hypothesis that higher regio- and chemoselectivity could be achieved by developing a more active catalyst that operates at lower temperatures.²²



Our initial screening studies focused on the oxidative coupling of *o*-xylene (eq 11) at 80 °C, 60 °C lower than the previously optimized conditions. A variety of oxidatively

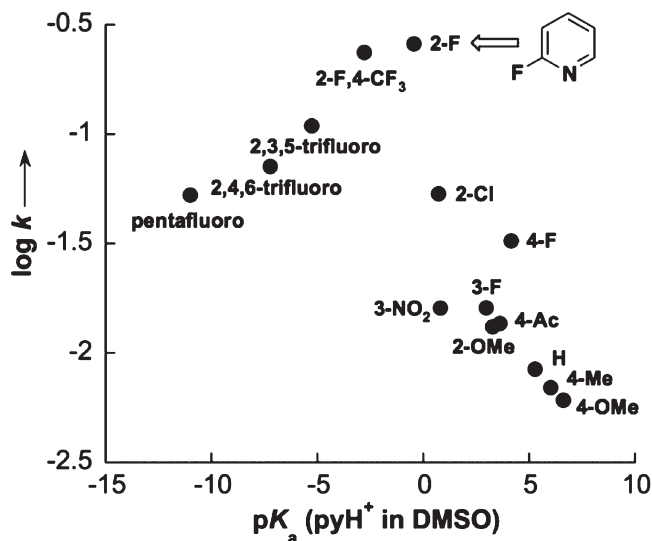
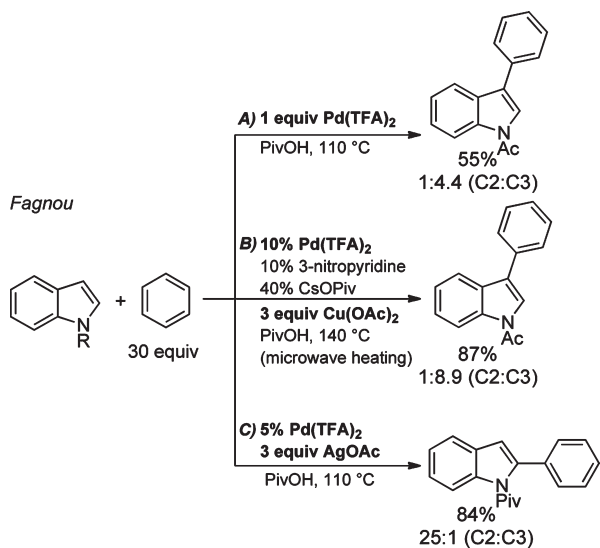


FIGURE 3. Dependence of the rate of *o*-xylene homocoupling on the identity of the ancillary pyridine ligands. The pK_a values correspond to those for the pyridinium ions in DMSO.

stable nitrogen ligands were tested in combination with Pd(OAc)₂ or Pd(TFA)₂ (TFA = trifluoroacetate). Chelating ligands such as bipyridine and phenanthroline, the latter of which is used in the oxidative coupling of dimethyl *o*-phthalate, inhibited the oxidative coupling of *o*-xylene. Monodentate pyridine derivatives, especially electron-deficient derivatives were promising, and the best results were obtained with 2-fluoropyridine (^{2F}py). The identity of the anionic ligand also influenced the reaction, with a 1:1 ratio of acetate and trifluoroacetate (TFA) anions being optimal, and cocatalytic Cu(OTf)₂ (Pd/Cu = 1:1) improved the results at low catalyst loading. Unpublished mechanistic data suggest Cu^{II} influences multiple steps in the catalytic mechanism, including C–H activation, transmetalation of aryl ligands between Pd^{II} centers, and, potentially, biaryl reductive elimination and reoxidation of Pd⁰. Further investigation of these fundamental steps is ongoing. With the optimized reaction conditions [4.4 M *o*-xylene in AcOH, 0.1% Pd(OAc)(TFA)/0.2% ^{2F}py, 0.1% Cu(OTf)₂, 1 atm O₂, 80 °C], the oxidative coupling of *o*-xylene proceeded with improved regioselectivity (7.3:1) and much higher chemoselectivity (94%) relative to the previous results.

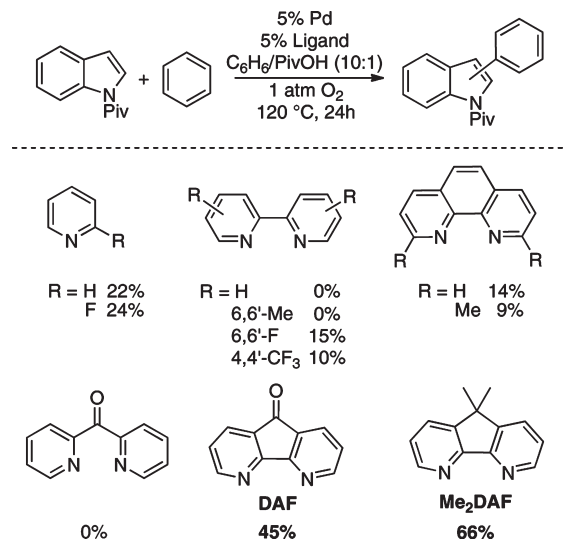
Systematic analysis of ancillary ligand effects on this reaction provided valuable insights. Initial rates of the oxidative coupling reactions were obtained with a wide range of substituted-pyridine ligands, and the log of the rate constant was plotted vs the pyridinium pK_a. This analysis revealed a "volcano plot" in which ^{2F}py is at the peak (Figure 3). Pyridines more basic than ^{2F}py appear to attenuate the

SCHEME 5. Oxidative Cross-Coupling of Indoles and Benzene with Stoichiometric Transition-Metal Oxidants²⁶

electrophilicity of the Pd catalyst and reduce catalyst activity. In contrast, ¹H NMR spectroscopic studies showed that pyridines less basic than ²Fpy are poor ligands and appear to be unable to activate the catalyst, for example, by breaking up binuclear and trinuclear aggregates of Pd-carboxylates.

A large deuterium kinetic isotope effect, $k_H/k_D = 10.7(2.0)$, observed in a competition experiment with *o*-xylene/*o*-xylene-*d*₁₀ (1:1), is consistent with C–H activation of *o*-xylene as the turnover-limiting step of the catalytic mechanism. Electron-deficient ligands, such as ²Fpy and TFA, should enhance the electrophilicity of the Pd^{II} catalyst and facilitate C–H activation. The beneficial effect of acetate (1 equiv relative to Pd) on the reaction can be rationalized within the framework of a “concerted metalation-deprotonation” (CMD) pathway for Pd^{II}-mediated C–H activation,²³ wherein a basic ligand, such as acetate, participates in deprotonation of a C–H bond as the Pd–C_{aryl} bond is forming.

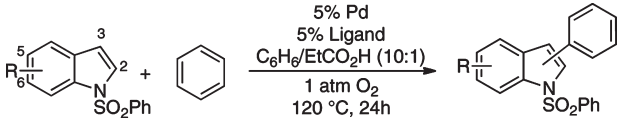
Overall, this work led to a significantly improved method for aerobic oxidative coupling of *o*-xylene, and it highlights the influence of electron-deficient ligands in promoting Pd-catalyzed oxidation reactions. The ability of *N*-donor ligands to stabilize Pd catalysts in aerobic oxidation reactions is widely recognized, but they also typically diminish catalytic activity.²⁴ In the present case, however, the electron-deficient ancillary donor ligand *enhances* the catalyst activity.²⁵ The identification of oxidatively stable ligands that support aerobic catalytic turnover and also enhance Pd-catalyst activity has important implications for the development of improved C–H oxidation reactions.

CHART 3. Identification of a Ligand for Aerobic Pd-Catalyzed Indole-Arene Cross-Coupling

4.2. Regioselective Oxidative Cross-Coupling of Indoles and Benzene.

The synthesis of biaryls via direct oxidative cross-coupling of two arenes represents a near-ideal transformation; however, such reactions face major challenges associated with regioselectivity, homo- vs cross-coupling, and the identity of the oxidant. Fagnou and co-workers reported an important breakthrough in this area in the Pd-catalyzed coupling of indoles and arenes (Scheme 5).²⁶ Good control over regioselectivity was achieved by the choice of oxidant: Cu(OAc)₂ favored C3 arylation and AgOAc favored C2 arylation of the indole. One-electron oxidants such as Cu^{II} and Ag^I can promote C–C reductive elimination from Pd^{II},²⁷ but the oxidative cross-coupling of indole and benzene was also possible with stoichiometric Pd^{II} (Scheme 5A). These observations prompted us to consider whether similar oxidative coupling reactions could be achieved with O₂ as the oxidant, ideally while retaining control over the reaction regioselectivity.²⁸

A number of ligands were evaluated in the Pd-catalyzed oxidative cross-coupling of *N*-pivaloyl indole with benzene under 1 atm O₂ (Chart 3). Most ligands performed poorly; however, respectable product yields were obtained with DAF and Me₂DAF (45% and 66%, respectively). Further optimization studies revealed that the identities of the ancillary ligand (DAF vs Me₂DAF) and anionic ligands affected the product regioselectivity. Selectivities were observed as high as 5:1 favoring the C2 isomer with a Pd(TFA)₂/Me₂DAF catalyst system, and 5.8:1 favoring the C3 isomer with a Pd(OPiv)₂/DAF catalyst system (Table 2). In all cases, O₂ served as the

TABLE 2. Regioselective Oxidative Cross-Coupling of Indole with Simple Arenes


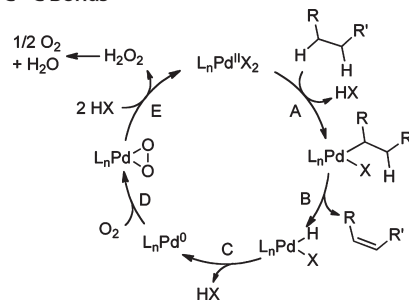
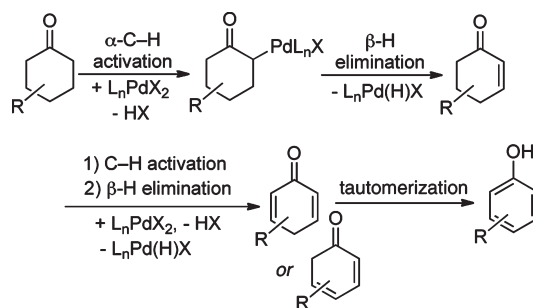
R	catalyst	yield	C2:C3 selectivity
H	Pd(TFA) ₂ /Me ₂ DAF Pd(OPiv) ₂ /DAF	66% 76%	1:5.8 2:1
5-Cl	Pd(TFA) ₂ /Me ₂ DAF Pd(OPiv) ₂ /DAF	71% 68%	1:1.3 5:1
6-Cl	Pd(TFA) ₂ /Me ₂ DAF Pd(OPiv) ₂ /DAF	71% 66%	1.4:1 3.7:1
5-OMe	Pd(TFA) ₂ /Me ₂ DAF Pd(OPiv) ₂ /DAF	54% 71%	1:3.9 2.3:1
6-OMe	Pd(TFA) ₂ /Me ₂ DAF Pd(OPiv) ₂ /DAF	70% 65%	1:1.3 2.6:1

sole stoichiometric oxidant with no additional transition metal additive or cocatalyst (Table 2).²⁸

Modest primary deuterium kinetic isotope effects ($k_H/k_D = 2.8-3.8$) were observed in competition experiments with 1:1 C₆H₆/C₆D₆. These values are smaller than observed in the homocoupling of *o*-xylene, but they are consistent with rate-limiting C–H activation. Additional studies will be needed to gain further insights into the catalytic mechanism. For example, these reactions could involve C–H activation of the two substrates at different Pd^{II} centers, followed by transmetalation, to afford a Pd^{II}(Ph)(indolyl) intermediate. Or the same intermediate could form via sequential C–H activation at a single Pd^{II} center. The biaryl product can be generated via C–C reductive elimination from this intermediate. More work is also required to understand the origin of the reaction regioselectivity. Experimental and computational studies to probe these issues are ongoing. Despite such uncertainties, the catalytic results highlight the potential ability of ancillary ligands to support regioselective aerobic oxidative cross-coupling of arenes.

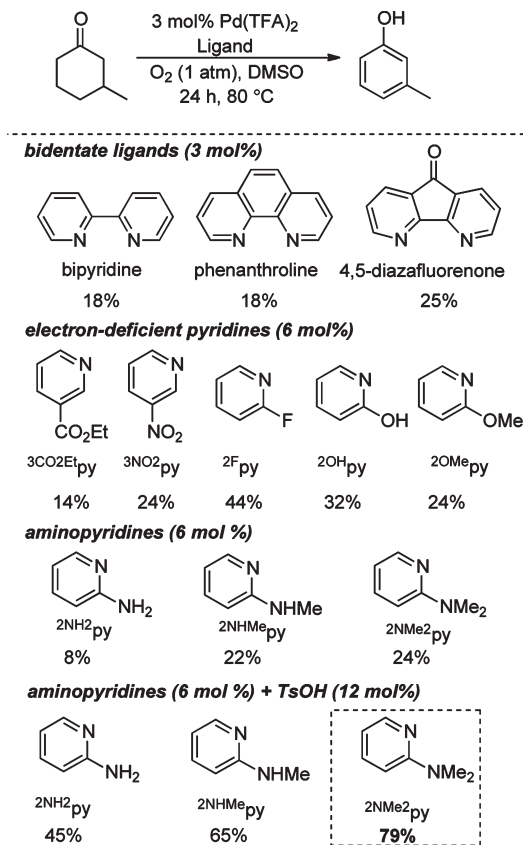
5. Aerobic Dehydrogenation of Cyclohexanones to Phenols

Conversion of saturated carbon–carbon bonds to alkenes is an important class of C–H functionalization.²⁹ The recognition that Pd-catalyzed reactions involving β -hydride elimination are often compatible with O₂ (see section 2) prompted us to begin exploring this class of reactions. Such reactions

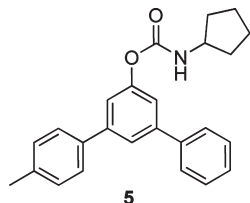
SCHEME 6. Proposed Mechanism for Pd^{II}-Catalyzed Dehydrogenation of Saturated C–C Bonds**SCHEME 7.** Stepwise Sequence of Pd^{II}-Mediated Dehydrogenation of Cyclohexanones

could proceed via Pd^{II}-mediated C–H activation and β -hydride elimination (Scheme 6, steps A and B), followed by aerobic oxidation of the resulting Pd^{II}–H (Scheme 6, steps C–E).³⁰ If successful, such methods could provide environmentally benign alternatives to commonly used stoichiometric dehydrogenation reagents, such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and IBX (2-iodoxybenzoic acid). Our initial studies focused on aerobic dehydrogenation of cyclohexanones to phenols (Scheme 7).³¹

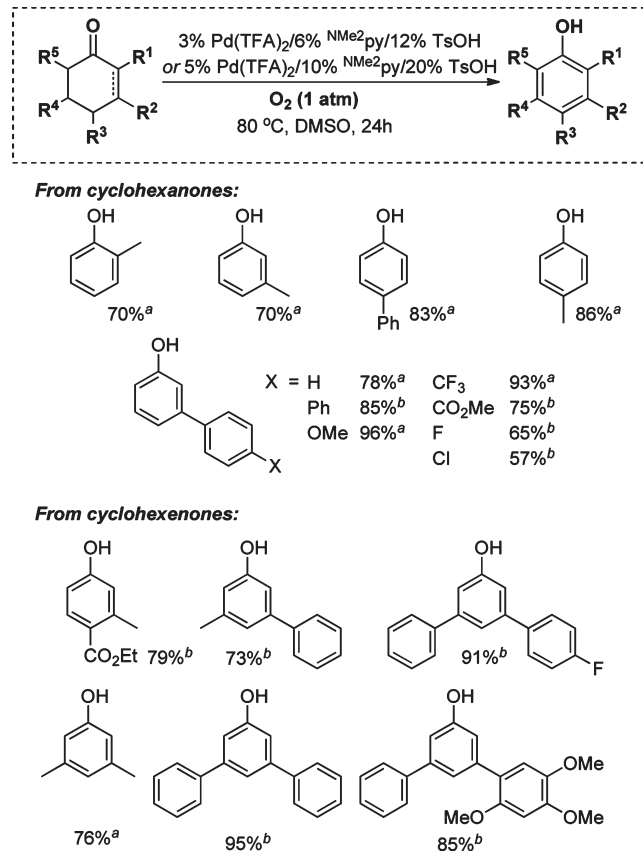
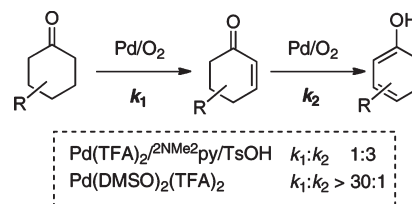
3-Substituted cyclohexanones and cyclohexanones are readily accessible, and their dehydrogenation leads to *meta*-substituted phenols that can be difficult to access by traditional aromatic substitution reactions. 3-Methylcyclohexanone was one of the substrates used in our catalyst screening efforts, which evaluated a number of Pd^{II} sources and ancillary ligands under 1 atm O₂ (Chart 4). We examined a number of pyridine-derived ligands, including electron-deficient derivatives similar to those described above. Moderate success was observed with 2-fluoropyridine (44%), but even better results were obtained when 2-dimethylaminopyridine (²NMe₂py) was used in combination with *p*-toluenesulfonic acid (TsOH). The mechanistic basis for this success is still under investigation, but our working hypothesis is that the pyridine nitrogen coordinates to Pd and the tertiary amine is protonated to afford a

CHART 4. Ligand Effects for Aerobic Dehydrogenation of 3-Methyl Cyclohexanone

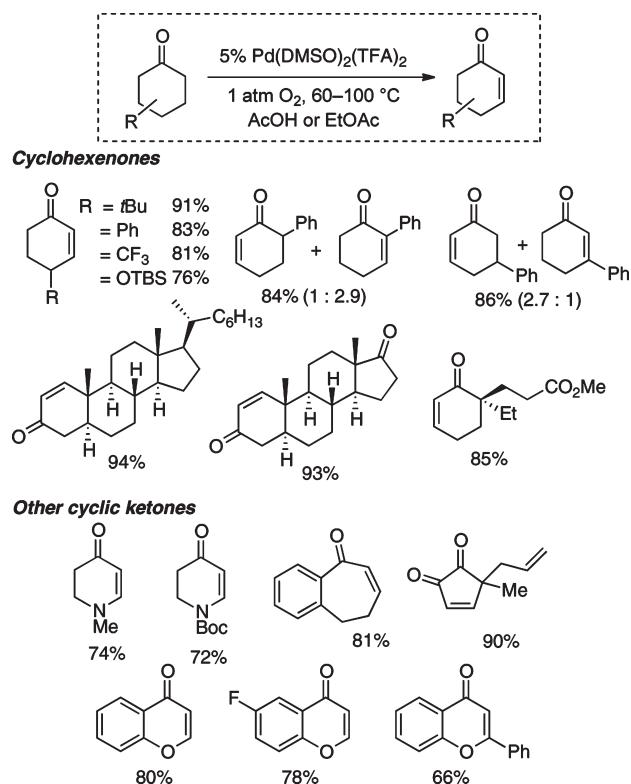
more electron-deficient ligand. A ligand with a quaternary ammonium substituent, [2-Me₃Npy]⁺, is also effective (63%, unpublished), but not as good as the ²NMe₂py/TsOH combination. The optimized catalyst system was effective in the dehydrogenation of a number of substituted cyclohexanone and cyclohexenone substrates (Chart 5). Dehydrogenation reactions of this type represent efficient alternatives to traditional cross-coupling reactions in the preparation of substituted aromatic molecules. This prospect was illustrated in an efficient route to the phenolic fragment of an allosteric inhibitor of the luteinizing hormone receptor (**5**), which had been prepared previously by a sequence of low-yielding cross-coupling reactions.³¹



The time course of cyclohexanone dehydrogenation reveals the intermediate formation of cyclohexenone, which

CHART 5. Phenols Prepared via Dehydrogenation of Cyclohexanone or Cyclohexenone Derivatives**SCHEME 8.** Aerobic Dehydrogenation Provides Access to Phenols or Cyclohexenones

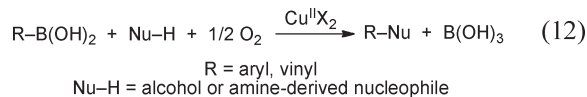
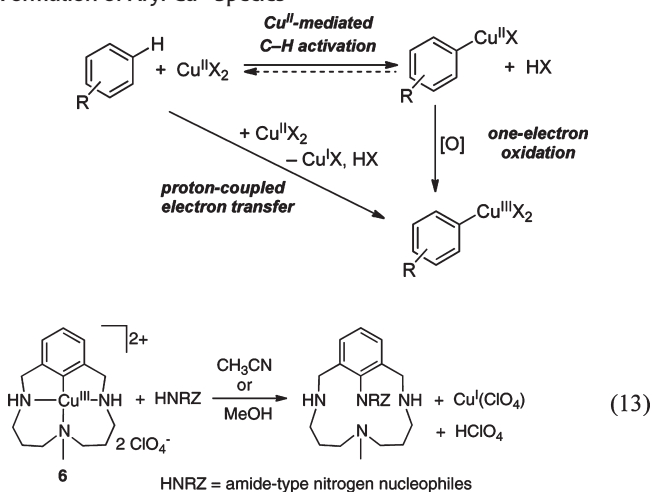
rapidly converts to phenol under the reaction conditions. Kinetic analysis reveals the second dehydrogenation step is approximately 3-fold faster than the first ($k_2 \approx 3k_1$, Scheme 8). Recent studies have led to a new catalyst system [Pd(DMSO)₂(TFA)₂/AcOH] that achieves "interrupted" dehydrogenation of cyclohexanone, in which the first dehydrogenation step proceeds much faster than the second. Kinetic simulation of the reaction time course reveals that $k_1:k_2 > 30:1$ (Scheme 8). This catalytic method has been applied to a number of synthetically useful targets (Chart 6).³² Further development of these and other aerobic dehydrogenation reactions, together with mechanistic characterization of these

CHART 6. Enones Prepared via Dehydrogenation of Cycloketone Derivatives

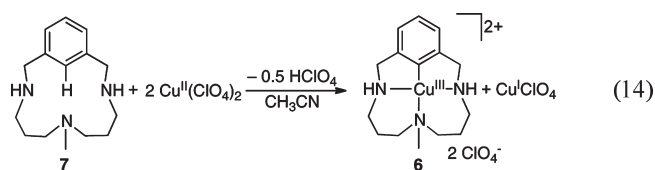
new reactions, represent important goals of future studies. Overall, these results support the analysis in section 2 that C–H functionalization reactions that proceed via β -hydride elimination are particularly amenable to the use of O₂ as the terminal oxidant.

6. Copper(II)-Catalyzed Aerobic C–H Oxidation

Recent advances in copper catalysis have introduced new opportunities to achieve aerobic C–H oxidation.^{8d,33} Our work in this area originated with a mechanistic study of Cu-catalyzed methods for aerobic oxidative coupling of arylboronic acids and heteroatom nucleophiles ("Chan–Lam reactions"; eq 12), in which aryl-copper(III) species have been proposed as intermediates.^{34,35} We also investigated C–N reductive elimination reactions involving a well-defined macrocyclic aryl-copper(III) species **6** (eq 13).^{36,37} Reductive elimination from Cu^{III} is extremely facile, rivaling (or surpassing) the ease of reductive elimination from Pd^{IV}, and our recent studies suggest that such reactions may play a key role in aerobic C–H oxidations.³⁸

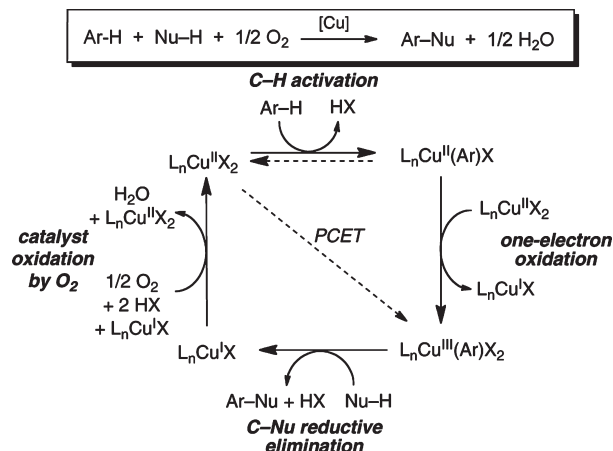
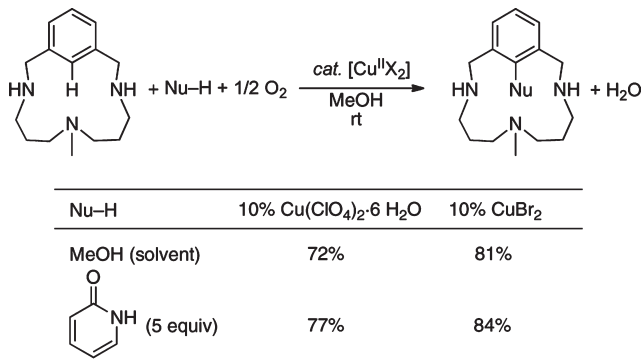
**SCHEME 9.** Possible Mechanisms for Cu^{II}-Mediated C–H Activation and Formation of Aryl-Cu^{III} Species

The mechanism by which organocopper(III) intermediates could form in Cu^{II}-catalyzed C–H oxidation reactions is not necessarily obvious, but recent studies reveal that Cu^{II}-mediated C–H activation can proceed via disproportionation of Cu^{II} into Cu^I and an organocopper(III) species,³⁹ illustrated in the synthesis of the aryl-Cu^{III} complex **6**, reported by Ribas et al. (eq 14).⁴⁰ Reactions of this type have been shown to proceed via one of two possible pathways: (1) stepwise C–H activation by Cu^{II} followed by oxidation to the aryl-Cu^{III} species, or (2) concerted, proton-coupled electron transfer (Scheme 9).^{39,41}



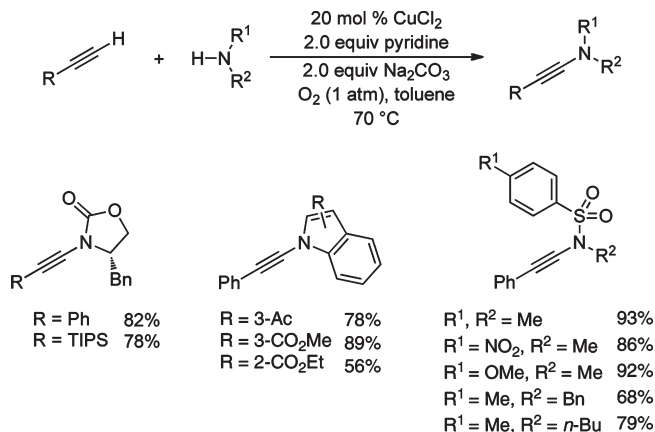
In the course of our work, we recognized that Cu-mediated C–H activation and reductive elimination steps (e.g., eqs 14 and 13) could be combined with aerobic oxidation of Cu^I to provide a catalytic pathway for aerobic C–H oxidation (Scheme 10). This concept was demonstrated in the Cu-catalyzed oxidative functionalization of arene **7** under 1 atm O₂, using methanol and pyridone as the heteroatom nucleophiles (Scheme 11).³⁸ Kinetic and spectroscopic studies of the catalytic reaction provided direct evidence for the intermediacy of the aryl-Cu^{III} complex **6**, supporting the mechanism in Scheme 10.

In parallel with these fundamental studies, we developed a Cu-catalyzed method for aerobic oxidative amidation of

SCHEME 10. Stepwise Mechanism for Cu-Catalyzed Aerobic C–H Oxidation**SCHEME 11.** Oxidative Functionalization of **6** Catalyzed by Cu^{II}

terminal alkynes. The combination of 20 mol % CuCl₂ with 2 equiv pyridine and 2 equiv Na₂CO₃ in toluene under 1 atm O₂ enables oxidative coupling of terminal alkynes with a variety of nitrogen nucleophiles (Scheme 12).⁴² Numerous related Cu-catalyzed aerobic C–H oxidation methods of this type have been published recently by others.^{8d} The mechanisms of these reactions, including those in Scheme 12, are poorly understood and generally remain unexplored. The results described above, however, suggest that a catalytic mechanism involving an organocopper(III) intermediate may be a plausible pathway.

The mechanism in Scheme 10 exhibits an intriguing relationship to the Shilov mechanism presented in the Introduction (Scheme 1). Both reactions feature C–H activation steps initiated by a divalent metal ion (Cu^{II} or Pt^{II}) and the resulting organometallic intermediate must be oxidized to a higher-valent species (Cu^{III}–Ar and Pt^{IV}–CH₃) before C–X reductive elimination takes place. Both reactions utilize a metal-based oxidant, Cu^{II}, or Pt^{IV}, to oxidize the organometallic intermediate. A key difference between the two

SCHEME 12. Aerobic Copper-Catalyzed Synthesis of Ynamides from Terminal Alkynes

reactions, however, is the nature of the reduced metal byproduct. Cu^I, which forms in the C–H activation process and upon reductive elimination from Cu^{III}, can react readily with O₂ to regenerate the active Cu^{II} catalyst. In contrast, Pt^{II} is kinetically inert toward reaction with O₂. This difference enables copper catalysts to overcome the "oxidant problem" experienced by many Pt and Pd catalysts. Future work will undoubtedly clarify the scope and limitations of this reactivity.

7. Conclusion

The results presented here highlight a number of different strategies to address the "oxidant problem" in Pd-catalyzed C–H oxidation reactions. A common theme throughout these studies is the important role of the ancillary ligands in promoting aerobic catalytic turnover. Such ligands can promote reductive elimination, thereby avoiding the need for BQ or other undesirable stoichiometric oxidants to promote the reductive elimination step. In other cases, ligands facilitate key C–H activation or β -hydride elimination steps and/or contribute to regioselective C–H functionalization. The mechanistic basis for these ligand effects is not yet fully understood, but the empirical results described here point to the abundant opportunities to develop new aerobic C–H oxidation reactions. Finally, Cu-catalyzed aerobic oxidation reactions appear to provide a mechanistically novel strategy to address some of the most challenging C–H oxidation reactions that proceed via C–X reductive elimination.

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BIOGRAPHICAL INFORMATION

Alison Campbell received a B.S. in biochemistry from Lafayette College in 2004 and a Ph.D. in 2009 from the University of North Carolina under the supervision of Professor Michel R. Gagné. She was then an NIH Postdoctoral Fellow at the University of Wisconsin with Professor Shannon S. Stahl studying new methods for palladium-catalyzed aerobic C–H oxidations, and she recently joined the process research group at Eli Lilly (Indianapolis, IN).

Shannon Stahl is a Professor of Chemistry at the University of Wisconsin—Madison. He was an undergraduate at the University of Illinois at Urbana–Champaign, and subsequently attended Caltech (Ph.D., 1997), where he was an NSF predoctoral fellow with Prof. John E. Bercaw. From 1997 to 1999, he was an NSF postdoctoral fellow with Prof. Stephen J. Lippard at MIT.

FOOTNOTES

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REFERENCES

- For leading references, see the February 2010 and March 2011 issues of Chem. Rev. and the April 2011 issue of Chem. Soc. Rev.
- Newhouse, T.; Baran, P. S. If C–H Bonds Could Talk: Selective C–H Bond Oxidation. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362–3374.
- Gol'dshleger, N. F.; Es'kova, V. V.; Shteynman, A. A.; Shilov, A. E. Reactions of Alkanes in Solutions of Chloride Complexes of Platinum. *Zh. Fiz. Khim. (Engl. Transl.)* **1972**, *46*, 785–786.
- Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. Homogeneous Oxidation of Alkanes by Electrophilic Late Transition Metals. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180–2192.
- (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. A Highly Selective Catalytic Method for the Oxidative Functionalization of C–H Bonds. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (b) Giri, R.; Chen, X.; Yu, J.-Q. Palladium-Catalyzed Asymmetric Iodination of Unactivated C–H Bonds under Mild Conditions. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112–2115.
- For efforts to replace Pt^{IV}, see the following and references cited therein: (a) Lin, M.; Shen, C.; Garcia-Zayas, E. A.; Sen, A. Catalytic Shilov Chemistry: Platinum Chloride-Catalyzed Oxidation of Terminal Methyl Groups by Dioxygen. *J. Am. Chem. Soc.* **2001**, *123*, 1000–1001. (b) Bar-Nahum, I.; Khenkin, A. M.; Neumann, R. Mild, Aqueous, Aerobic, Catalytic Oxidation of Methane to Methanol and Acetaldehyde Catalyzed by a Supported Bipyrimidylplatinum-Polyoxometalate Hybrid Compound. *J. Am. Chem. Soc.* **2004**, *126*, 10236–10237. (c) Weinberg, D. R.; Labinger, J. A.; Bercaw, J. E. Competitive Oxidation and Protonation of Aqueous Monomethylplatinum(II) Complexes: A Comparison of Oxidants. *Organometallics* **2007**, *26*, 167–172.
- For additional information, see recent reviews of Pd-catalyzed C–H oxidation: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C–H Activation/C–C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (b) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147–1169. (c) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon–Carbon Bonds by Oxidizing Two Carbon–Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215–1292. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. Bond Formation between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions. *Chem. Rev.* **2011**, *111*, 1780–1824.
- For reviews, see: (a) Stahl, S. S. Palladium Oxidase Catalysis: Selective Oxidation of Organic Chemicals by Direct Dioxygen-Coupled Turnover. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Stahl, S. S. Palladium-Catalyzed Oxidation of Organic Chemicals with O₂. *Science* **2005**, *309*, 1824–1826. (c) Kotov, V.; Scarborough, C. C.; Stahl, S. S. Palladium-Catalyzed Aerobic Oxidative Amination of Alkenes: Development of Intra- and Intermolecular Aza-Wacker Reaction. *Inorg. Chem.* **2007**, *46*, 1910–1923. (d) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidative C–H Functionalizations: Recent Trends and Mechanistic Insights. *Angew. Chem., Int. Ed.* **2011**, *47*, 11062–11087.
- (a) Davidson, J. M.; Triggs, C. Reactions of Palladium Complexes with Benzene and Toluene. *Chem. Ind.* **1966**, 457. (b) Davidson, J. M.; Triggs, C. Reaction of Metal Ion Complexes with Hydrocarbons. I. Palladation and Some Other New Electrophilic Substitution Reactions Preparation of Palladium(I). *J. Chem. Soc. (A)* **1968**, 1324–1330.
- Gligorich, K. M.; Sigman, M. S. Recent Advancements and Challenges of Palladium(II)-Catalyzed Oxidation Reactions with Molecular Oxygen as the Sole Oxidant. *Chem. Commun.* **2009**, 3854–3867.
- See the following and references therein: (a) Bäckvall, J.-E.; Bystrom, S. E.; Nordberg, R. E. Stereo- and Regioselective Palladium-Catalyzed 1,4-Diacetoxylation of 1,3-Dienes. *J. Org. Chem.* **1984**, *49*, 4619–4631. (b) Chen, X.; Goodhue, C. E.; Yu, J.-Q. Palladium-Catalyzed Alkylation of sp² and sp³ C–H Bonds with Methylboroxine and Alkylboronic Acids: Two Distinct C–H Activation Pathways. *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635. (c) Lanci, M. P.; Remy, M. S.; Kaminsky, W.; Mayer, J. M.; Sanford, M. S. Oxidatively Induced Reductive Elimination from (tBu₂bpy)Pd(Me)₂: Palladium(IV) Intermediates in a One-Electron Oxidation Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 15618–15620. (d) Khusnutdinova, J. R.; Rath, N. P.; Mirica, L. M. Stable Mononuclear Organometallic Pd(III) Complexes and Their C–C Bond Formation Reactivity. *J. Am. Chem. Soc.* **2010**, *132*, 7303–7306. (e) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A. III.; Ritter, T. Bimetallic Reductive Elimination from Dinuclear Pd(II). *J. Am. Chem. Soc.* **2010**, *132*, 14092–14103.
- Exceptions exist; see, for example: (a) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Convenient and Efficient Pd-Catalyzed Regioselective Oxylfunctionalization of Terminal Olefins by Using Molecular Oxygen as Sole Reoxidant. *Angew. Chem., Int. Ed.* **2006**, *45*, 481–485. (b) Zhang, J.; Khaskin, E.; Anderson, N. P.; Zavalij, P. Y.; Vedernikov, A. N. Catalytic Aerobic Oxidation of Substituted 8-Methylquinolines in Pd(II)-2,6-Pyridinedicarboxylic Acid Systems. *Chem. Commun.* **2008**, 3625–3627. (c) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. Palladium-Catalyzed Method for the Synthesis of Carbazoles Via Tandem C–H Functionalization and C–N Bond Formation. *J. Org. Chem.* **2008**, *73*, 7603–7610. (d) Liu, G.; Yin, G.; Wu, L. Palladium-Catalyzed Intermolecular Aerobic Oxidative Amination of Terminal Alkenes: Efficient Synthesis of Linear Allylamine Derivatives. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733–4736. (e) Zhang, Y.-H.; Yu, J.-Q. Pd(II)-Catalyzed Hydroxylation of Arenes with 1 atm O₂ or Air. *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655.
- See the following and references therein: (a) Chen, M. S.; Prabakaran, N.; Labenz, N. A.; White, M. C. Serial Ligand Catalysis: A Highly Selective Allylic C–H Oxidation. *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971. (b) Lin, B.-L.; Labinger, J. A.; Bercaw, J. E. Mechanistic Investigations of Bipyrimidine-Promoted Palladium-Catalyzed Allylic Acetoxylation of Olefins. *Can. J. Chem.* **2009**, *87*, 264–271.
- For a leading reference, see: Bäckvall, J.-E.; Gogoll, A. Evidence for (π-Allyl)Palladium(II)(Quinone) Complexes in the Palladium-Catalyzed 1,4-Diacetoxylation of Conjugated Dienes. *Tetrahedron Lett.* **1988**, *29*, 2243–2246.
- Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. Acid-Induced Transformation of Palladium(0)-Benzoquinone Complexes to Palladium(II) and Hydroquinone. *Organometallics* **1993**, *12*, 1790–1793.
- Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. Oxygenation of Nitrogen-Coordinated Palladium(0): Synthetic, Structural, and Mechanistic Studies and Implications for Aerobic Oxidation Catalysis. *J. Am. Chem. Soc.* **2001**, *123*, 7188–7189.
- Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. Allylic C–H Acetoxylation with a 4, 5-Diazafluorenone-Ligated Palladium Catalyst: A Ligand-Based Strategy To Achieve Aerobic Catalytic Turnover. *J. Am. Chem. Soc.* **2010**, *132*, 15116–15119.
- For leading references, see: (a) Shiotani, A.; Itatani, H.; Inagaki, T. Selective Coupling of Dimethyl Phthalate with Palladium Catalysts at Atmospheric Pressure. *J. Mol. Catal.* **1986**, *34*, 57–66. (b) Itatani, H.; Yoshimoto, H.; Shiotani, A.; Yokota, A.; Yoshikiyo, M. Process for Producing Biphenyl Compounds. U.S. Patent 4,294,976, 1981.
- Kreuz, J. A.; Edman, J. R. Polyimide Films. *Adv. Mater.* **1998**, *10*, 1229–1232.
- For leading references, see ref **9a** and the following: (a) Yoshimoto, H.; Itatani, H. Palladium-Catalyzed Competitive Reaction of Aromatic Compounds. *J. Catal.* **1973**, *31*, 8–12. (b) Itatani, H.; Shiotani, A.; Yoshimoto, H.; M. Yoshikiyo, Yokota, A. Manufacturing Method of Biphenyl Derivatives. JP Patent 79324, 1980.
- A NineSigma proposal request (#11222-1) was issued in Oct. 2008 by a "a multibillion dollar chemical manufacturer" focused on this topic.
- Izawa, Y.; Stahl, S. S. Aerobic Oxidative Coupling of o-Xylene: Discovery of 2-Fluoropyridine as a Ligand to Support Selective Pd-Catalyzed C–H Functionalization. *Adv. Synth. Catal.* **2010**, *352*, 3223–3229.
- Gorelsky, S. I.; Lapointe, D.; Fagnou, K. Analysis of the Concerted Metalation-Deprotonation Mechanism in Palladium-Catalyzed Direct Arylation Across a Broad Range of Aromatic Substrates. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.
- See, for example: Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. Mechanistic Characterization of Aerobic Alcohol Oxidation Catalyzed by Pd(OAc)₂/Pyridine Including Identification of the

- Catalyst Resting State and the Origin of Nonlinear [Catalyst] Dependence. *J. Am. Chem. Soc.* **2004**, *126*, 11268–11278.
- 25 See also: Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Ligand-Accelerated C–H Activation Reactions: Evidence for a Switch of Mechanism. *J. Am. Chem. Soc.* **2010**, *132*, 14137–14151.
- 26 (a) Stuart, D. R.; Fagnou, K. The Catalytic Cross-Coupling of Unactivated Arenes. *Science* **2007**, *316*, 1172–1175. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073.
- 27 See refs **11c**, **11d**, and references cited therein.
- 28 Campbell, A. N.; Meyer, E. B.; Stahl, S. S. Regiocontrolled Aerobic Oxidative Coupling of Indoles and Benzene Using Pd Catalysts with 4,5-Diazafluorene Ligands. *Chem. Commun.* **2011**, *47*, 10257–10259.
- 29 Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. Dehydrogenation and Related Reactions Catalyzed by Iridium Pincer Complexes. *Chem. Rev.* **2011**, *111*, 1761–1779.
- 30 Konnick, M. M.; Stahl, S. S. Reaction of Molecular Oxygen with a Pd^{II}-Hydride To Produce a Pd^{III}-Hydroperoxide: Experimental Evidence for an HX-Reductive-Elimination Pathway. *J. Am. Chem. Soc.* **2008**, *130*, 5753–5762.
- 31 Izawa, Y.; Pun, D.; Stahl, S. S. Palladium-Catalyzed Aerobic Dehydrogenation of Substituted Cyclohexanones to Phenols. *Science* **2011**, *333*, 209–213.
- 32 Diao, T.; Stahl, S. S. Synthesis of Cyclic Enones via Direct Palladium-Catalyzed Aerobic Dehydrogenation of Ketones. *J. Am. Chem. Soc.* **2011**, *133*, 14566–14569.
- 33 For an important early example, see: Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. Cu(II)-Catalyzed Functionalizations of Aryl C–H Bonds Using O₂ as an Oxidant. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791.
- 34 Qiao, J. X.; Lam, P. Y. S. Copper-Promoted Carbon-Heteroatom Bond Cross-Coupling with Boronic Acids and Derivatives. *Synthesis* **2011**, *2011*, 829–856.
- 35 King, A. E.; Brunold, T. C.; Stahl, S. S. Mechanistic Study of Copper-Catalyzed Aerobic Oxidative Coupling of Arylboronic Esters and Methanol: Insights into an Organometallic Oxidase Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 5044–5045.
- 36 Huffman, L. M.; Stahl, S. S. Carbon-Nitrogen Bond Formation Involving Well-Defined Aryl-Copper(III) Complexes. *J. Am. Chem. Soc.* **2008**, *130*, 9196–9197.
- 37 (a) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. Direct Observation of Cu^I/Cu^{III} Redox Steps Relevant to Ullmann-Type Coupling Reactions. *Chem. Sci.* **2010**, *1*, 326–330. (b) Huffman, L. M.; Casitas, A.; Font, M.; Canta, M.; Costas, M.; Ribas, X.; Stahl, S. S. Observation and Mechanistic Study of Facile C–O Bond Formation between a Well-Defined Aryl-Copper(III) Complex and Oxygen Nucleophiles. *Chem., Eur. J.* **2011**, *17*, 10643–10650.
- 38 King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidative Functionalization of an Arene C–H Bond: Evidence for an Aryl-Copper(III) Intermediate. *J. Am. Chem. Soc.* **2010**, *132*, 12068–12073.
- 39 See section 4 of ref **8d** for a full discussion of this class of reactivity.
- 40 Ribas, X.; Jackson, D. A.; Donnadiou, B.; Mahía, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. Aryl C–H Activation by Cu^{II} to Form an Organometallic Aryl–Cu^{II} Species: A Novel Twist on Copper Disproportionation. *Angew. Chem., Int. Ed.* **2002**, *41*, 2991–2994.
- 41 Ribas, X.; Calle, C.; Poater, A.; Casitas, A.; Gómez, L.; Xifra, R.; Parella, T.; Benet-Buchholz, J.; Schweiger, A.; Mitrikas, G.; Solà, M.; Llobet, A.; Stack, T. D. P. Facile C–H Bond Cleavage Via a Proton-Coupled Electron Transfer Involving a C–H···Cu^{II} Interaction. *J. Am. Chem. Soc.* **2010**, *132*, 12299–12306.
- 42 Hamada, T.; Ye, X.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidative Amidation of Terminal Alkynes: Efficient Synthesis of Ynamides. *J. Am. Chem. Soc.* **2008**, *130*, 833–835.