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# Highly Regioselective Catalytic Oxidative Coupling Reactions: Synthetic and Mechanistic Investigations

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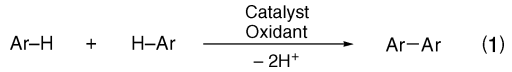
Biaryl linkages are key features of diverse natural products, pharmaceuticals, materials, and many other important organic molecules.[1] The most common method for biaryl C−C bond construction is metal-catalyzed cross-coupling between two functionalized starting materials.[1] More recently, several groups have developed C−H activation/C−C bond forming reactions that use an arene C−H bond as one of the coupling partners, offering the advantages of enhanced efficiency and decreased byproduct formation.[1,2] However, from the perspectives of operational simplicity, availability of starting materials, and atom economy, an even more attractive approach to biaryls would be the direct oxidative coupling of two unfunctionalized arenes (eq 1).[1,3,4] In such a transformation, both starting materials could be used directly without prior functionalization, and the sole byproduct would be 2 equiv of $H^+$. As such, the development of catalytic and highly regioselective methods for the oxidative coupling of substituted arenes remains an ongoing synthetic challenge.[3,4]




$Pd^{II}$ salts in conjunction with terminal oxidants, such as $O_2$ and $Ag^I$, are well-known to promote the oxidative coupling of arenes/heteroarenes to produce mixtures of biaryl products.[1,4−6] However, to date, the utility of these transformations has remained limited due to slow reaction rates, low conversions/yields, and lack of selectivity (substituted arenes typically afford complex mixtures of regioisomeric and oligomeric products).[4,5] We reasoned that the efficiency and selectivity of these processes might be rendered synthetically useful by incorporating appropriate directing groups into the arene substrates.[6] Importantly, a similar approach has been used for the selective functionalization of *ortho*-C−H bonds in other Pd-catalyzed C−H activation/oxidation reactions.[6,7] We report herein that 2-arylpyridines undergo highly regioselective Pd-catalyzed oxidative C−C coupling *at room temperature* with Oxone as a terminal oxidant. Furthermore, we provide preliminary mechanistic evidence that these transformations proceed by a new, highly unusual mechanism involving two different C−H activation steps—one at $Pd^{II}$ and one at $Pd^{IV}$.

Our initial investigations focused on the dimerization of 2-*o*-tolylpyridine. After surveying a variety of oxidants, solvents, and catalysts (Tables S1−S3), we found that 5 mol % of $Pd(OAc)_2$ and 2 equiv of Oxone in *i*-PrOH at room temperature served as optimal conditions for this transformation, providing product **1** in 86% isolated yield (eq 2).[8] Importantly, **1** was obtained cleanly as a single regioisomeric product, presumably due to the directing ability of the pyridine substituent. Oxidants that have been used previously for $Pd^{II/0}$-catalyzed oxidative couplings (e.g., air, AgF, AgOAc) did not afford any of product **1**, suggesting that the current reactions are not operating within a traditional $Pd^{II/0}$ mechanistic manifold.[4−6]

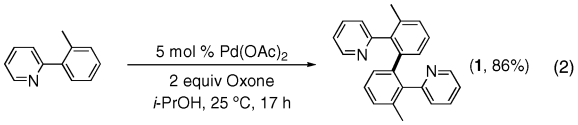
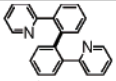
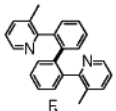
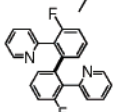
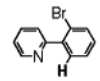
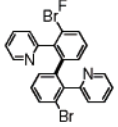
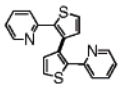
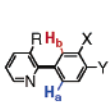
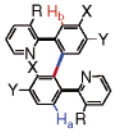



***Table 1.*** Substrate Scope of Oxidative Coupling Reactions[a]

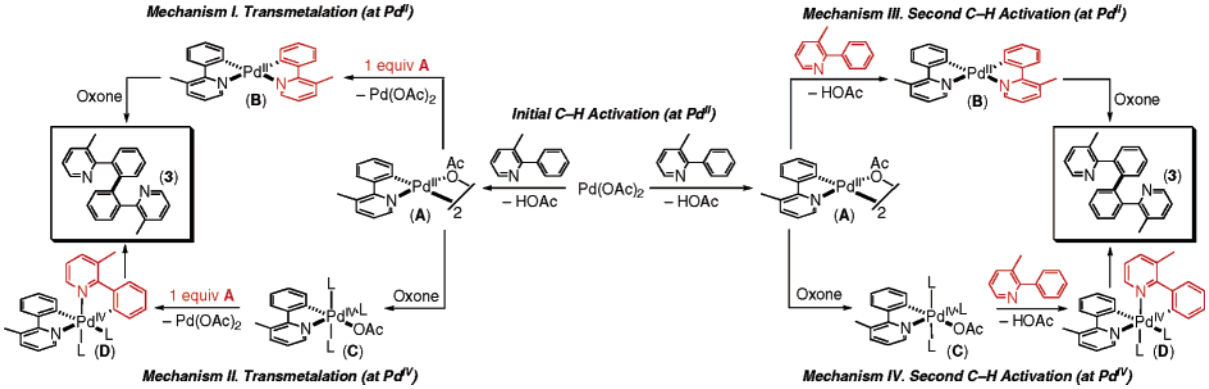
| entry | substrate | product | product #, yield[b] |
|---|---|---|---|
| 1 |  |  | **2**, 41% |
| 2 |  |  | **3**, 86% |
| 3 |  |  | **4**, 82% |
| 4 |  |  | **5**, 67% |
| 5 |  |  | **6**, 44% |

| entry | substrate | product (isomer a) | product (isomer b) | yield (ratio a : b)[b] |
|---|---|---|---|---|
| |  |  |  | |
| 6 | X=$CF_3$; Y=H; R=H | **7-a** | **7-b** | 44% (1.7 : 1) |
| 7 | X=OMe; Y=H; R=Me | **8-a** | **8-b** | 76% (1 : 1.3) |
| 8 | X=Cl; Y=Cl; R=H | **9-a** | **9-b** | 58% (1.1 : 1) |

[a] Conditions: 5−10 mol % of $Pd(OAc)_2$, 2 equiv of Oxone in MeOH, *i*-PrOH, $CF_3CH_3OH$, or $MeNO_2$ at 25−60 °C for 17 h. [b] Isolated yield (average of two runs).

Oxidative coupling was effective and highly regioselective for a variety of other 2-arylpyridine derivatives (Table 1). With 2-phenylpyridine (entry 1), dimer **2** was obtained in significantly lower yield than **1**, due to further oligomerization of the product. This competing oligomerization could be attenuated by placing a substituent at the 3-position of the pyridine (entry 2) or by blocking one of the *ortho* sites on the arene (entries 3−5), which both serve to inhibit subsequent directed C−H activation reactions.[7] Notably, a variety of arene substituents, including Me, OMe, F, and Br, were well tolerated in these transformations. The lack of side reactions with aryl bromides, even when placed at the *ortho*-position (entry 4), is particularly remarkable and is in contrast to traditional

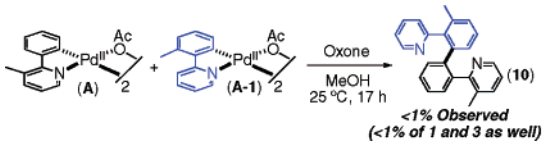
***Scheme 1.*** Possible Mechanisms for Oxidative Coupling




Ullmann-type reactions for arene coupling.[1] Interestingly, 2-(2-thienyl)pyridine underwent clean pyridine-directed coupling at the $\beta$-position; in contrast, most Cu-, Fe-, and Pd-mediated couplings of thiophene derivatives are highly selective for reaction at $C_\alpha$.[1,5,9]

Substrates containing *meta*-substituents (X) on the arene ring reacted to form mixtures of two isomeric dimers (entries 6−8). The two regioisomers—one symmetrical (resulting from bis coupling at the less sterically hindered *ortho*-site) and one unsymmetrical—were typically obtained in close to a 1:1 ratio, although the product distribution did vary somewhat as a function of X.[10] Intriguingly, these modest selectivities are in sharp contrast to previous studies of directed C−H activation at $Pd^{II}$, in which the less hindered *ortho*-C−$H_a$ bond is activated with high—typically >20:1—selectivity.[7c] These unexpected results provided initial evidence that a novel mechanism might be operating in the current reactions.

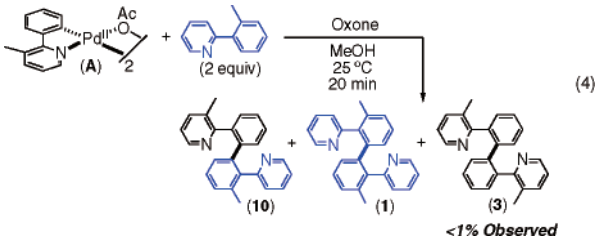
As summarized in Scheme 1, we considered four potential mechanisms for these transformations, all of which begin with palladation of the arylpyridine substrate to produce $Pd^{II}$ complex **A**. Mechanisms I and II then involve transmetalation from **A** (either to a second equivalent of **A** or to a transient $Pd^{IV}$ species **C**) followed by C−C coupling to release **3**. (Notably, such transmetalation/disproportionation reactions have been proposed as key steps in many previously reported $Pd^{II}$-catalyzed oxidative coupling processes.)[4e,5] In contrast, mechanisms III and IV proceed via a second C−H activation step (occurring either at $Pd^{II}$ complex **A** or at $Pd^{IV}$ complex **C**), followed by C−C coupling to form **3**.[11]




(3)

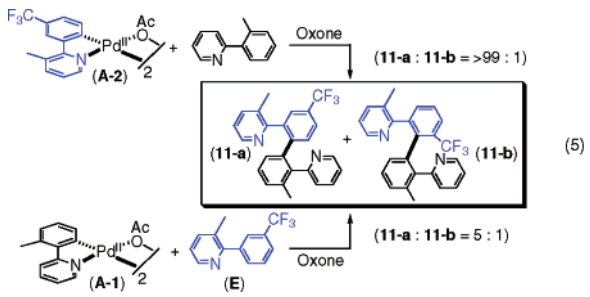
Our investigations began by probing the viability of the two transmetalation mechanisms I and II. Both require that cyclometalated ligands from two different $Pd^{II}$ complexes exchange between metal centers prior to C−C bond formation. Therefore, a coupled product resulting from crossover between **A** and **A-1** (where **A-1** contains 2-*o*-tolylpyridine as the cyclometalated ligand) would be expected for both mechanisms. However, as shown in eq 3, stoichiometric reactions between **A** and **A-1** yielded <1% of the anticipated crossover product, **10**.

We reasoned that the presence of free arylpyridine substrate (which is in large excess under the catalytic conditions) might be required for transmetalation, and therefore crossover, to occur. As such, we also explored the stoichiometric reaction of **A** with 2 equiv of free 2-*o*-tolylpyridine (eq 4). However, <1% of product **3** (which would be formed from transmetalation between 2 equiv of **A**) was observed in this reaction, providing additional evidence against mechanisms I or II.



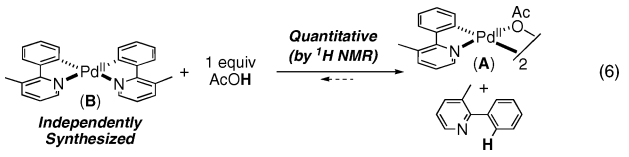

(4)

Significant support for a mechanism involving two discrete C−H activation steps (rather than transmetalation between Pd centers) was obtained from the experiments outlined in eq 5. Complex **A-2** (which is palladated with >20:1 selectivity at the less hindered *ortho*-position) reacted with 2-*o*-tolylpyridine to afford a single observable heterodimer **11-a**. In contrast, complex **A-1** reacted with 3-methyl-2-(3-trifluoromethyl)phenylpyridine (**E**) to produce a 5:1 mixture of regioisomeric heterodimers **11-a** and **11-b**. These data strongly suggest that **E** is introduced onto the Pd center in two discrete C−H activation steps *with vastly different degrees of selectivity* (mechanisms III or IV), rather than via transmetalation from a single common cyclopalladated intermediate **A-2**.

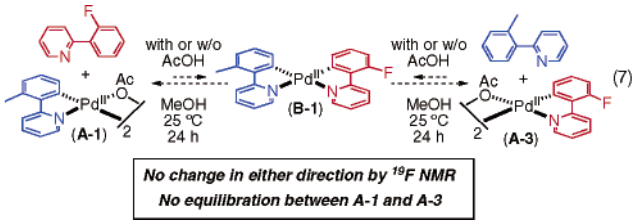



(5)

Our studies next sought to distinguish between mechanisms III and IV. As shown in Scheme 1, mechanism III involves C−H activation of a second equiv of substrate at $Pd^{II}$ intermediate **A** to form the biscyclometalated complex **B**. To study this mechanism, we independently prepared a sample of **B**[12] and treated it with 1 equiv of AcOH (which would be present in the reaction mixture following the second C−H activation event). This reaction resulted in the quantitative formation of 1 equiv of **A** and 1 equiv of free 2-phenyl-3-methylpyridine (eq 6), indicating that any equilibrium between **A** and **B** should lie far to the left. On the basis of this result, mechanism III would require fast equilibration between **A** and **B**, followed by trapping of the transient intermediate **B** with oxidant.[12]




We probed for the possible intermediacy of biscyclometalated analogues of **B** by studying equilibration between two slightly differentiated complexes **A-1** and **A-3** and the corresponding free arylpyridines (eq 7). If traces of biscyclometalated intermediate **B-1** were formed under the reaction conditions, it should undergo protonation by AcOH to produce mixtures of **A-1** and **A-3**, thereby resulting in equilibration between these two species. However, attempts to approach this equilibrium from either side at 25 °C over 24 h resulted in no observable reaction, providing strong evidence against the participation of mechanism III in these reactions.[13−15]




Only mechanism IV, which involves two different C−H activation events—one at $Pd^{II}$ and one at $Pd^{IV}$—is consistent with all of the experiments described above. This mechanism also offers a possible rationale for the low regioselectivity of the second C−H activation step, as a highly electrophilic $Pd^{IV}$ center is likely to be more reactive and therefore less selective in electrophilic C−H activation reactions.[16] Notably, the relative reactivity of $Pd^{II}$ versus $Pd^{IV}$ in C−H activation has not been previously assessed because, to our knowledge, this report represents the first example of C−H activation at a $Pd^{IV}$ center.[17]

In summary, this communication describes a Pd-catalyzed intermolecular oxidative C−C coupling reaction that takes place at room temperature and proceeds with high levels of regioselectivity. Mechanistic studies suggest a previously unprecedented mechanism for this transformation, involving two sequential C−H activation reactions at $Pd^{II}$ and $Pd^{IV}$, respectively. The dramatically different selectivity of the two C−H activation events should be synthetically useful, as it opens the possibility of oxidative cross-coupling reactions between two different C−H substrates. More broadly, this work suggests that $Pd^{IV}$ intermediates are sufficiently long-lived and reactive to participate in fundamental organometallic transformations prior to undergoing reductive elimination. Ongoing studies seek to exploit such transformations for the development of novel catalytic reactions that would not be accessible within traditional $Pd^{II/0}$ reaction manifolds.

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**Supporting Information Available:** Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The $Pd^{II/0}$-catalyzed oxidative coupling of methyl benzoate has been shown to proceed with reasonable (72%) selectivity for the 2,2′-isomer; however, this transformation proceeds with low (~15%) conversion. The selectivity is proposed to result from coordination of the ester moiety to Pd. Lee, S. H.; Lee, K. H.; Lee, J. S.; Jung, J. D.; Shim, J. S. *J. Mol. Catal., A* **1997**, *115*, 241.
(7) For example, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (c) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (d) Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C. Y.; Foxman, B. M.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (e) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141.
(8) In *i*-PrOH and MeOH, significant amounts of *ortho*-ether products were formed as the reaction temperature was increased (see refs 7a,e).
(9) Constable, E. C.; Sousa, L. R. *J. Organomet. Chem.* **1992**, *427*, 125.
(10) Less than 5% of a third possible isomer (resulting from symmetrical coupling at the more hindered *ortho*-position) was observed.
(11) We have reported that $Pd^{IV}$ complexes similar to **D** can be stable at room temperature. However, the reactivity of these compounds is highly dependent on the nature of the anionic ligands (L in complex **D**) and solvent. As such, we believe that derivatives of **D** are plausible intermediates in the current reactions. Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.
(12) We have also examined the direct reaction of **B** with Oxone (a key step of mechanism III) and found that it cleanly affords oxidative coupling product **3**. However, when this same experiment was conducted in the presence of 1 equiv of free 2-*o*-tolylpyridine, a mixture of **3** (42%), **10** (46%), and **1** (12%) was generated. The crossover product—heterodimer **10**—would not be formed if **B** were oxidized directly and quantitatively by Oxone. Instead, it appears to be to be produced via competing protonation of **B** by the moderately acidic oxidant (see eq 6 for a related protonation reaction). (Notably, the pH of a 0.06 M aqueous solution of Oxone is 1.84.) After protonation of **B** to form **A** and 1 equiv of 2-phenyl-3-methylpyridine, the reaction would proceed by analogy to eq 4. As a result, this experiment does not provide definitive data to distinguish mechanisms III and IV. For a more detailed discussion of this experiment, see the Supporting Information.
(13) For further evidence against the formation of **B** (and therefore against mechanism III), see: Ryabov, A. D. *Inorg. Chem.* **1987**, *26*, 1252.
(14) Traces of equilibration products were observed when these reactions were conducted at *significantly* higher temperatures (~100 °C) or when they were carried out in neat AcOH at 60 °C. For a discussion of the mechanism of equilibration under these conditions (which is not believed to involve intermediates analogous to **B-1**), see ref 13.
(15) While we cannot rule out an intermediate with an alternative geometry than **B**/**B-1**, we believe that it should undergo analogous equilibration.
(16) The different selectivities of the two C−H activation steps might also result from the differing steric environments around square planar $Pd^{II}$ versus octahedral $Pd^{IV}$.
(17) For arene C−H activation at $Pt^{IV}$ centers, see ref 4a.

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