

Synthetic and Mechanistic Studies of Pd-Catalyzed C–H Arylation with Diaryliodonium Salts: Evidence for a Bimetallic High Oxidation State Pd Intermediate

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Abstract: This contribution describes the substrate scope and mechanism of Pd-catalyzed ligand-directed C–H arylation with diaryliodonium salts. This transformation was applied to the synthesis of a variety of different biaryl products, using directing groups including pyridines, quinolines, pyrrolidinones, and oxazolidinones. Electronically and sterically diverse aryl groups (Ar) were transferred in high yield using iodine(III) reagents of general structure [Mes–I–Ar]BF₄. Mechanistic investigations have been conducted that establish the kinetic order of the catalytic reaction in each component, determine the resting state of the catalyst and the iodine(III) reagent, quantify the electronic influence of the arylating reagent on the reaction rate, and establish the intra- and intermolecular 1° H/D kinetic isotope effect. On the basis of these studies, this transformation is proposed to proceed via turnover-limiting oxidation of the Pd dimer [Pd(N~C)(OAc)]₂ (N~C = 3-methyl-2-phenylpyridine) by [Mes–I–Ph]BF₄. This mechanism implicates a bimetallic high oxidation state Pd species as a key catalytic intermediate. The significance of this and other aspects of the proposed mechanism are discussed in detail.

Introduction

Biaryls are important synthetic targets, as they serve as key structural motifs of diverse natural products, pharmaceuticals, agrochemicals, and conjugated materials. The most common method for forming biaryl linkages involves transition metal-catalyzed cross coupling (*e.g.*, Suzuki–Miyaura, Stille, Hiyama, Sonogashira, Kumada, and Negishi reactions).¹ While these transformations have found widespread application, they suffer from the disadvantage that they require the use of two prefunctionalized starting materials. As such, each coupling reagent must be independently prepared, which adds one or more additional steps to a synthetic sequence.

More recent efforts have begun to explore metal-catalyzed C–H arylation as an alternative strategy for the construction of biaryls.^{2–6} This approach is attractive because it allows direct replacement of an Ar–H bond with an Ar–Ar' bond, eliminating the need for a preinstalled functional group. In addition, appropriate ligands can be used to direct highly site selective C–H arylation within complex organic molecules. In recent years, there has been a flurry of activity in this field, and ligand-directed C–H arylation methods have been reported with various late transition-metal catalysts.^{2–6}

Our group has been particularly interested in developing Pd-catalyzed ligand-directed C–H arylation reactions using [Ar–I^{III}–Ar']X reagents.^{5,6} These iodine(III) compounds were selected on the basis of significant evidence that they could

- (1) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, 50, 1. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, 576, 147. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, 100, 3009. (f) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, 58, 9633. (g) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, 35, 835. (h) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, 219, 131. (i) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, 103, 1979.
- (2) For recent reviews that discuss C–H arylation, see: (a) Campeau, L. C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Yu, J. Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, 4, 4041. (d) Godula, K.; Sames, D. *Science* **2006**, 312, 67. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, 107, 174. (f) Beccalli, E. M.; Brogini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, 107, 5318. (g) Ackermann, L. *Synlett* **2007**, 507. (h) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, 36, 1036. (i) Campeau, L. C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, 36, 1058. (j) Catellani, M.; Motti, E.; Della Ca, N. *Acc. Chem. Res.* **2008**, 41, 1512. (k) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (l) Li, B. J.; Yand, S. D.; Shi, Z. J. *Synlett* **2008**, 949. (m) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, DOI: 10.1039/b805701j.

- (3) For examples of ligand-directed Ar–H oxidative coupling, see: (a) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, 128, 14047. (b) Xia, J. B.; You, S. L. *Organometallics* **2007**, 26, 4869. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, 129, 11904. (d) Li, B. J.; Tian, S. L.; Fang, Z.; Shi, Z. J. *Angew. Chem., Int. Ed.* **2008**, 47, 1115. (e) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, 10, 2207.
- (4) For other proposals of Pd-catalyzed ligand-directed C–H arylation via a Pd^{IV} mechanism, see ref 5a and: (a) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, 7, 3657. (b) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, 127, 13154. (c) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, 8, 3391. (d) Giri, R.; Mangel, N.; Li, J. J.; Wang, D. H.; Breazzano, S. P.; Saunders, L. B.; Yu, J. Q. *J. Am. Chem. Soc.* **2007**, 129, 3510. (e) Chiong, H. A.; Pham, Q. N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, 129, 9879. (f) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2008**, 47, 9462. (g) Yang, F.; Wu, Y.; Zhu, Z.; Zhang, J.; Li, Y. *Tetrahedron* **2008**, 64, 6782. (h) Yang, F.; Wu, Y.; Li, Y.; Wang, B.; Zhang, J. *Tetrahedron* **2009**, 65, 914.
- (5) (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, 127, 7330. (b) Deprez, N. R.; Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, 128, 4972.

Table 1. Products of Pd-Catalyzed Directed C–H Phenylation with $[\text{Ph}_2\text{I}]\text{BF}_4^a$

Entry	Product	Yield	Entry	Product	Yield	Entry	Product	Yield	Entry	Product	Yield
1		91%	4		72% ^c	7		75% ^e	10		83% ^e
2		74%	5		60% ^d	8		84% ^e	11		49% ^b
3		51% ^b	6		58% ^b	9		78%	12		67%

^a Conditions: 1 equiv of substrate, 1.1–2.5 equiv of $[\text{Ph}_2\text{I}]\text{BF}_4$, 5 mol % of $\text{Pd}(\text{OAc})_2$ in AcOH , $\text{AcOH}/\text{Ac}_2\text{O}$, benzene, or toluene, 100 °C, 8–24 h.

^b The balance of material was starting material (entry 11) or a mixture of starting material and diarylated product (entries 3 and 6). ^c Conditions: 2 equiv of 8-methylquinoline, 1 equiv of $[\text{Ph}_2\text{I}]\text{BF}_4$. ^d Approximately 16% of the product in entry 5 was formed in the absence of $\text{Pd}(\text{OAc})_2$. ^e 1.2–2 equiv of NaHCO_3 was added.

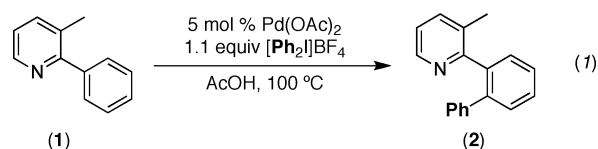
promote biaryl formation via an unusual $\text{Pd}^{\text{II/IV}}$ catalytic cycle.^{7,8} We anticipated that a $\text{Pd}^{\text{II/IV}}$ pathway for C–H arylation would be highly complementary to related reactions in the literature, particularly those involving more common $\text{Pd}^{\text{0/II}}$ mechanisms. For example, $\text{Pd}^{\text{II/IV}}$ sequences should tolerate important functional groups (*e.g.*, aryl halides and enolizable ketones) that can be reactive with the low-valent Pd intermediates and/or strong bases often required in $\text{Pd}^{\text{0/II}}$ processes. In addition, high oxidation state Pd species are known to be stable toward air and moisture,^{7,8} obviating the need for special glassware and/or for rigorous purification of solvents and reagents. Finally, since $\text{Pd}^{\text{II/IV}}$ -catalyzed reactions remain relatively rare,^{2,4–8} we reasoned that mechanistic studies could provide novel insights that might be broadly applicable to this class of transformations.

We report herein a detailed investigation of the substrate scope and mechanism of $\text{Pd}(\text{OAc})_2$ -catalyzed ligand-directed C–H arylation with $[\text{Ar}^-\text{I}-\text{Ar}^+]\text{BF}_4$.^{5a} Studies of reaction order in each component, Hammett analysis, kinetic isotope effect data, and equilibrium investigations have all been used to interrogate the resting state of the catalyst and the oxidant under the reaction conditions. These investigations provide strong evidence for oxidation as the turnover-limiting step and suggest the formation of a dimeric high oxidation state Pd complex as

a key catalytic intermediate. The potential implications of these findings are discussed.

Results and Discussion

Synthetic Scope. Initial studies examined the $\text{Pd}(\text{OAc})_2$ -catalyzed ortho-phenylation of 3-methyl-2-phenylpyridine (**1**) with the hypervalent iodine reagent $[\text{Ph}_2\text{I}]\text{BF}_4$.^{5a} This reaction afforded the monophenylated product **2** in a variety of common solvents, with the optimal conditions being 1.1 equiv of $[\text{Ph}_2\text{I}]\text{BF}_4$ and 5 mol % of $\text{Pd}(\text{OAc})_2$ at 100 °C in AcOH (eq 1). Notably, this reaction proceeded efficiently in the presence of ambient moisture and air, and no special purification of solvents or reagents was required.

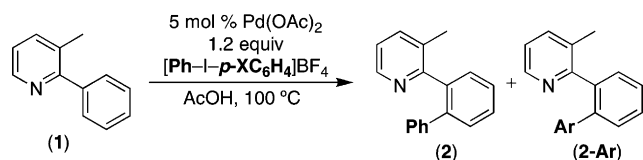


Numerous directing groups, including pyridines, quinolines, pyrrolidinones, and oxazolidinones, were also effective at promoting both aromatic and benzylic C–H phenylation with $[\text{Ph}_2\text{I}]\text{BF}_4$ (Table 1).^{5a} This transformation tolerated the presence of enolizable ketones, aldehydes, ethers, amides, benzylic hydrogens, and aryl halides within the organic substrate. Good to excellent yields were obtained regardless of the electronic nature of the aromatic compound. Further, excellent (>20:1) site selectivity was observed when a meta-substituent was present on the arene undergoing functionalization.⁹

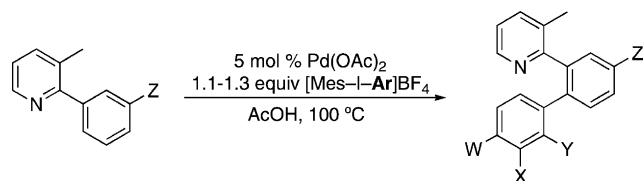
To further expand the utility of this methodology, we explored the installation of diverse arenes (*Ar*). We initially reasoned that selective transfer of different aryl groups might be achieved based on electronic preferences, and thus, a series of electronically unsymmetrical iodine(III) reagents $[\text{Ph}-\text{I}-p\text{-XC}_6\text{H}_4]\text{BF}_4$ was examined. As summarized in Table 2, these reagents underwent preferential transfer of the most electron-deficient aromatic group; however, the levels of selectivity were only modest, with ratios of **2:2-Ar** ranging from 2.6:1 to 1:0.31.

(9) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.

- (6) For other examples of the use of $[\text{Ar}_2\text{I}]\text{X}$ in C–H arylation, see: (a) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (b) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (c) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.
- (7) (a) Bayler, A.; Canty, A. J.; Ryan, J. H.; Skelton, B. W.; White, A. H. *Inorg. Chem. Commun.* **2000**, *3*, 575. (b) Canty, A. J.; Rodemann, T. *Inorg. Chem. Commun.* **2003**, *6*, 1382. (c) Canty, A. J.; Patel, J.; Rodemann, T.; Ryan, J. H.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 3466. (d) Canty, A. J.; Rodemann, T.; Skelton, B. W.; White, A. H. *Inorg. Chem. Commun.* **2005**, *8*, 55. (e) Canty, A. J.; Rodemann, T.; Skelton, B. W.; White, A. H. *Organometallics* **2006**, *25*, 3996. (f) Chaudhuri, P. D.; Guo, R.; Malinakova, H. C. *J. Organomet. Chem.* **2007**, *693*, 567.
- (8) For other examples of the oxidation of Pd^{II} to Pd^{IV} with an iodine(III) reagent, see: (a) Lagunas, M. C.; Gossage, R. A.; Spek, A. L.; van Koten, G. *Organometallics* **1998**, *17*, 731. (b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (c) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (d) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, ASAP article.

Table 2. Arylation of 3-Methyl-2-phenylpyridine

entry	X	2:2-Ar
1	CF ₃	2.6 : 1
2	F	1 : 0.33
3	Cl	1 : 0.83
4	CH ₃	1 : 0.71
5	OMe	1 : 0.31

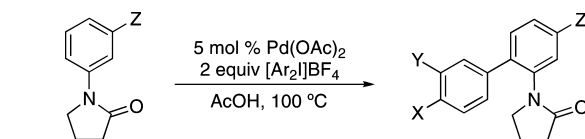
Table 3. Pd-Catalyzed Arylation of 3-Methyl-2-arylpyridines with [Mes-I-Ar]BF₄

entry	W	X	Y	Z	yield (%)
1	H	H	H	H	85
2	CF ₃	H	H	H	87
3	F	H	H	H	88
4	Cl	H	H	H	83
5	Me	H	H	H	84
6	OMe	H	H	H	81 ^a
7	C(O)Me	H	H	H	81
8	H	C(O)Me	H	H	81
9	H	CHO	H	H	88
10	H	H	Me	H	72
11	CF ₃	H	H	OMe	81 ^b
12	Cl	H	H	OMe	79 ^b
13	F	H	H	OMe	79 ^b
14	Me	H	H	OMe	78 ^b
15	OMe	H	H	OMe	56 ^{b,c}

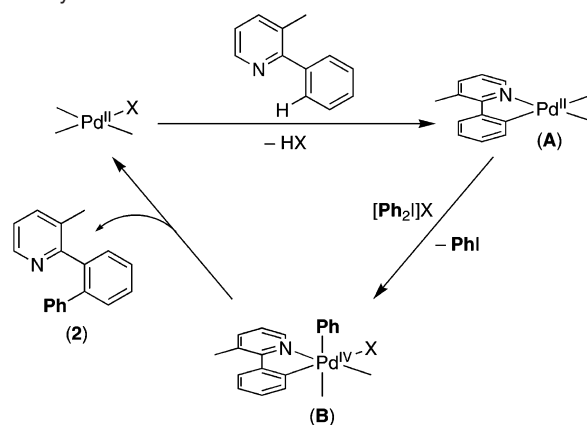
^a Reaction carried out at 120 °C. ^b Traces of the Mes addition product were observed, but selectivity was generally >12:1. See Supporting Information for further details. ^c With 2 equiv of [Mes-I-(*p*-MeOC₆H₄)]BF₄.

We next sought to sterically differentiate the two Ar groups on iodine(III), reasoning that smaller groups should transfer more rapidly. Gratifyingly, the mesityl/aryl-substituted reagents [Mes-I-Ar]BF₄ reacted to transfer the smaller Ar group with high selectivity. As summarized in Tables 3 and 4, pyridine and pyrrolidinone products containing both electron-rich and electron-deficient Ar could be prepared in high yield using these reagents. Many substituents were tolerated on the aryl ring being transferred, including enolizable ketones, ethers, benzylic hydrogens, and halogens. Further, these reagents were effective for the selective installation of relatively large aryl groups such as *o*-tolyl.

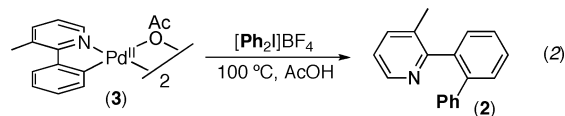
Mechanistic Investigations. We next sought to gain a detailed mechanistic understanding of this Pd-catalyzed C–H arylation. Our previous investigations showed that the reaction is unaffected by the addition of 500 equiv of Hg⁰ or 25 mol % of the free radical inhibitors MEHQ and galvinoxyl.^{5a} These results suggest against mechanisms involving palladium nanoparticles¹⁰ or free radical intermediates.¹¹ In addition, palladacycle **3** was shown to be an effective catalyst, with a comparable kinetic profile to Pd(OAc)₂. Further, the stoichiometric reaction between **3** and

Table 4. Pd-Catalyzed Arylation of 2-Aryl Pyrrolidinones with [Ar-I-Ar]BF₄

entry	X	Y	Z	yield (%)
1	Me	H	MeO	83
2	H	CF ₃	MeO	84
3	Me	H	H	81

Scheme 1. Originally Proposed Catalytic Cycle for Pd-Catalyzed C–H Arylation^{5a}

[Ph₂I]BF₄ cleanly afforded the *ortho*-arylated product **2** (eq 2).^{5a} In contrast, more traditional Pd^{0/II} electrophiles like PhI and PhOTf were ineffective phenylating reagents under both catalytic and stoichiometric reaction conditions. Finally, Canty and Malinakova have both demonstrated the stoichiometric oxidation of Pd^{II} model complexes with [Ar₂I]X reagents to form observable monomeric Pd^{IV} species.⁷ On the basis of all of these results, the general catalytic cycle shown in Scheme 1 was proposed, involving (i) ligand-directed C–H activation to afford palladacycle **A**, (ii) oxidation of **A** with [Ph₂I]BF₄ to generate a Pd^{IV} intermediate of general structure **B**, and finally, (iii) C–C bond-forming reductive elimination to afford the arylated product **2**.



These preliminary studies left several key outstanding questions regarding the C–H arylation mechanism. For example, the turnover-limiting step of this catalytic cycle remained to be established. In addition, detailed information about the ligand environment of the proposed Pd^{IV} intermediate **B** was not available from the initial investigations. Finally, the effect of electronic modification of the oxidant on the rates of these reactions was poorly understood. To gain further mechanistic insights, we

- (10) Heck reactions catalyzed by palladacycles were originally proposed to proceed via a Pd^{II/IV} catalytic cycle; however, more recent studies have shown the reactions are most likely catalyzed by Pd⁰ nanoparticles. For a review, see: Weck, M.; Jones, C. W. *Inorg. Chem.* **2007**, *46*, 1865.
- (11) Kraatz, H. B.; van der Boom, M. E.; Ben-David, Y.; Milstein, D. *Isr. J. Chem.* **2001**, *41*, 163.

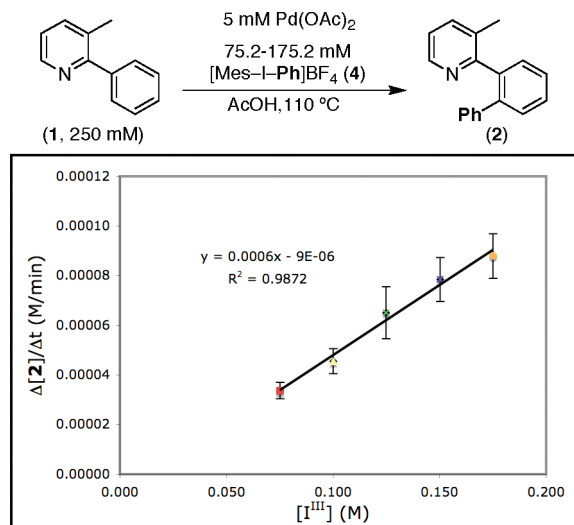


Figure 1. Plot of initial rate ($\Delta[2]/\Delta t$) versus $[I^{III}]$ showing first-order kinetics in I^{III} reagent.

have undertaken detailed studies to establish (1) the kinetic order in each component of the catalytic reaction, (2) the resting state of the catalyst and iodonium reagent, (3) the electronic influence of the iodonium reagent on the reaction rate, and (4) the intra- and intermolecular 1° H/D kinetic isotope effects.

Kinetic Order of the Reaction. We first sought to determine the turnover-limiting step of this transformation by establishing the kinetic order of C–H arylation in each reaction component. These studies focused on the $Pd(OAc)_2$ -catalyzed ortho-phenylation of 3-methyl-2-phenylpyridine (**1**) with $[Mes-I-Ph]BF_4$ (**4**).¹² We first examined the order of this transformation in the I^{III} reagent by combining 3-methyl-2-phenylpyridine (250 mM), $Pd(OAc)_2$ (5 mM), and varying concentrations of **4** (75.2 to 175.2 mM) in AcOH at 110 °C. The reactions were monitored by gas chromatography, and the initial rates method was used to determine the rate at each $[I^{III}]$. As shown in Figure 1, a plot of initial reaction rate ($\Delta[2]/\Delta t$) versus $[I^{III}]$ was linear, indicating a first-order dependence on the I^{III} reagent.¹³ This result suggests that the iodine(III) oxidant is involved in the turnover-limiting step. Notably, this is in contrast to most other Pd-catalyzed ligand-directed C–H functionalization reactions, where cyclopalladation is typically rate limiting.¹⁴

The order in $[Pd]$ was next determined using an analogous procedure, with 3-methyl-2-phenylpyridine (250 mM), $[Mes-I-Ph]BF_4$ (100 mM), and varying concentrations of $Pd(OAc)_2$ (3.8 to 10 mM) in AcOH at 110 °C.¹² The data from these experiments were subjected to a nonlinear least-squares fit to the equation: $f(x) = a[Pd]^n$. This fit provided an order (n) of 2.09 ± 0.08 (Supporting Information, Figure S7), which was also reflected in a linear plot of initial rate versus $[Pd]^2$ (Figure 2). This second-order dependence on $[Pd]$ is consistent with a monomeric catalyst resting state that is in equilibrium with a dimeric active catalyst (*vide infra*).

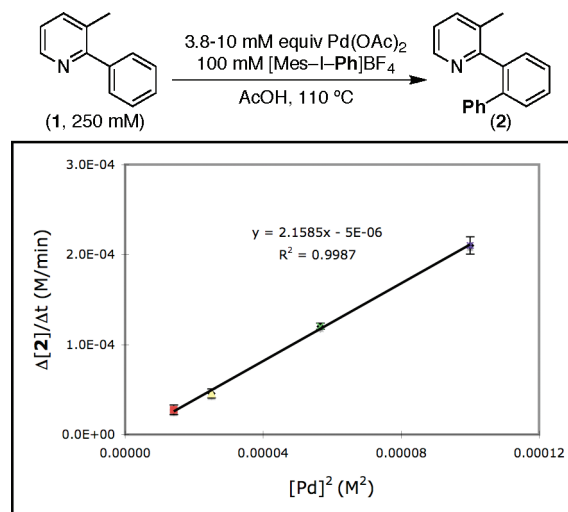


Figure 2. Plot of initial rate ($\Delta[2]/\Delta t$) versus $[Pd]^2$ showing second-order kinetics in $[Pd]$.

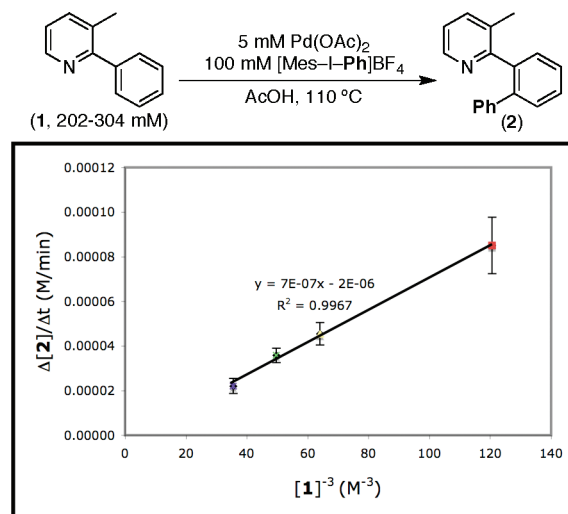


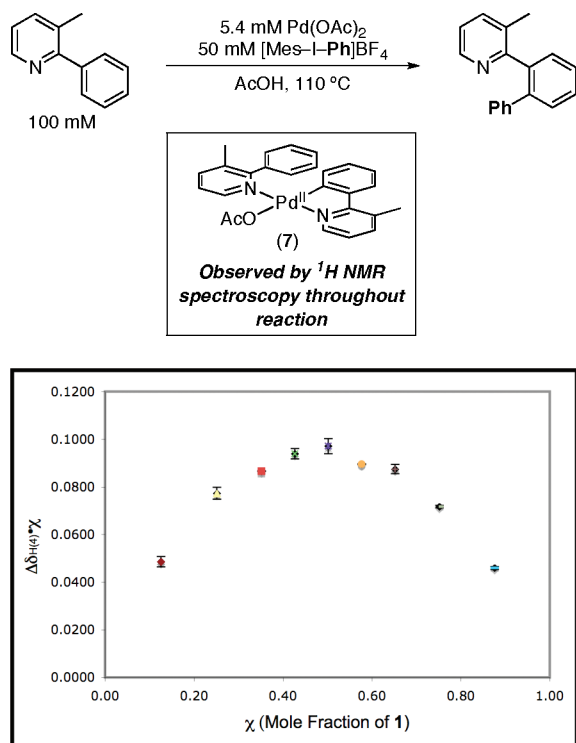
Figure 3. Plot of initial rate ($\Delta[2]/\Delta t$) versus $[1]^{-3}$ showing inverse third-order kinetics in **1**.

Finally, the order of the reaction in 3-methyl-2-phenylpyridine (**1**) was examined, using $[Mes-I-Ph]BF_4$ (100 mM) and $Pd(OAc)_2$ (5 mM) along with **1** ranging from 202 to 304 mM in AcOH at 110 °C.¹² Qualitative experiments revealed that the reaction rate slowed dramatically with increasing **1**, suggesting an inverse order dependence on the substrate. The quantitative rate data (initial rate versus $[1]$) were subjected to a nonlinear least-squares fit to the equation: $f(x) = a[1]^n$, which revealed an inverse third-order dependence on **1** ($n = -3.1 \pm 0.2$, Supporting Information, Figure S10). As shown in Figure 3, this is also reflected in the linear fit of the plot of initial rate versus $[1]^{-3}$. This result indicates that 3 equiv of **1** must be lost

(12) All of the order studies were conducted under conditions where $[1] > ([4] + [Pd])$. When $[1] < ([4] + [Pd])$, the kinetics become much more complex, and the order in **1** deviates from inverse third order (see Supporting Information p S16). This is expected based on the proposed mechanism, since under these conditions, the resting state of the oxidant is a mixture of **8** and **4**.

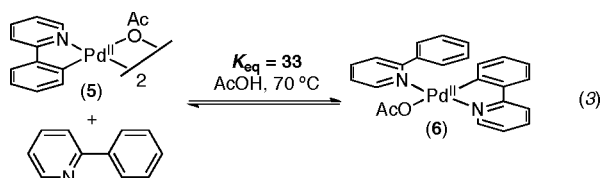
(13) Further confirmation of a first order dependence was provided by a non-linear least squares fit to the eq: $f(x) = a[4]^n$. This provided $n = 1.12 \pm 0.08$ and $a = 6 \pm 1 \times 10^{-4}$.

(14) (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (b) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (c) Giri, R.; Chen, X.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (d) Wang, D. H.; Hao, X. S.; Wu, D. F.; Yu, J. Q. *Org. Lett.* **2006**, *8*, 3387. (e) Chen, X.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (f) Chiong, H. A.; Pham, Q. N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (g) Xia, J. B.; You, S. L. *Organometallics* **2007**, *26*, 4869. (h) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.

Scheme 2. Observation of **7** Under the Catalytic Reaction Conditions**Figure 4.** Job plot of $\Delta\delta_{\text{H}(4)} \cdot \chi$ (mole fraction of substrate) versus χ at 110 °C.

in order to progress from the resting state to the transition state of the reaction.

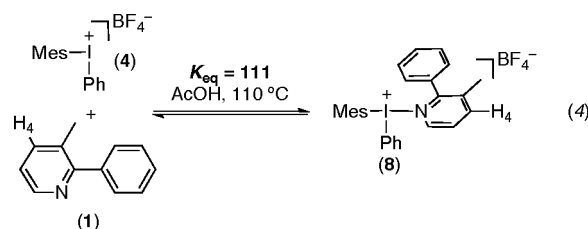
Catalyst Resting State. We next sought to probe the resting state of the [Pd] under the reaction conditions. Since complex **3** was previously shown to serve as an effective catalyst for C–H arylation and underwent stoichiometric reaction with $[\text{Ph}_2\text{I}]\text{BF}_4$ to afford **2** (eq 2),^{5a} we hypothesized that **3** might be a catalytic intermediate. When dimer **3** was combined with 20 equiv of **1** at 110 °C in AcOH (mimicking the catalytic reaction conditions, but in the absence of oxidant), only the corresponding monomer **7** (which shows a diagnostic broad resonance at 6.2 ppm) was observed by ^1H NMR spectroscopy (Scheme 2 and Supporting Information, Figure S19).¹⁵ This is consistent with a literature report by Ryabov showing that the closely related dimer **5** reacts with 2-phenylpyridine to form monomer **6** with K_{eq} of $33 \pm 2 \text{ M}^{-1}$ at 70 °C in AcOH (eq 3).¹⁵ When the catalytic resting state was monitored by ^1H NMR spectroscopy at 110 °C, an identical broad signal at 6.2 ppm was observed throughout this transformation (Scheme 2 and Supporting Information, Figure S19). These experiments collectively suggest that the resting state of the Pd during the catalytic cycle is monomer **7** (Scheme 2).



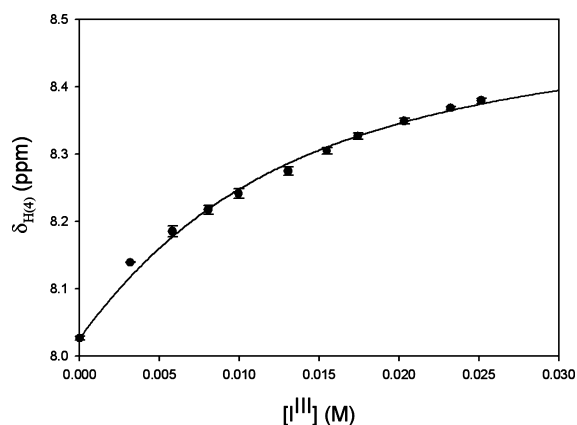
Oxidant Resting State. Several literature reports have demonstrated that pyridine derivatives can coordinate to diaryli-

odonium salts.¹⁶ In a particularly relevant example, Ochiai has shown by ^1H NMR spectroscopy that $[\text{Ph}_2\text{I}]\text{BF}_4$ forms a 1:1 complex with pyridine ($K_{\text{eq}} = 20.2 \text{ M}^{-1}$ at 24 °C in CH_2Cl_2).^{16d} Discrete “bound” and “free” adducts were not observed due to fast exchange on the NMR time scale. Instead, the binding interaction was monitored by changes in the chemical shifts associated with pyridine resonances at varying relative concentrations of pyridine and $[\text{Ph}_2\text{I}]\text{BF}_4$.

We conducted an analogous set of studies to examine the interaction between **1** and $[\text{Mes-I-Ph}]\text{BF}_4$ (**4**) under our catalytic conditions (110 °C in AcOH). First, we used a Job plot to establish the stoichiometry of complexation. A series of solutions with a constant total concentration ($[\text{1}] + [\text{4}] = 23.6 \text{ mM}$ in $\text{CD}_3\text{CO}_2\text{D}$), but with varied mole fractions of the two components, were examined by ^1H NMR spectroscopy at 110 °C.¹⁷ The chemical shift of $\text{H}(4)$ of **1** moved downfield as the mole fraction of **4** increased, and the change in chemical shift relative to free **1** ($\Delta\delta_{\text{H}(4)}$) was used to construct a Job plot (Figure 4). This plot showed a maximum at $\chi = 0.5$, indicating that complexation between **1** and **4** occurs with a 1:1 stoichiometry.^{18,19} These data implicate the formation of iodine(III) adduct **8** under the catalytic reaction conditions (eq 4).

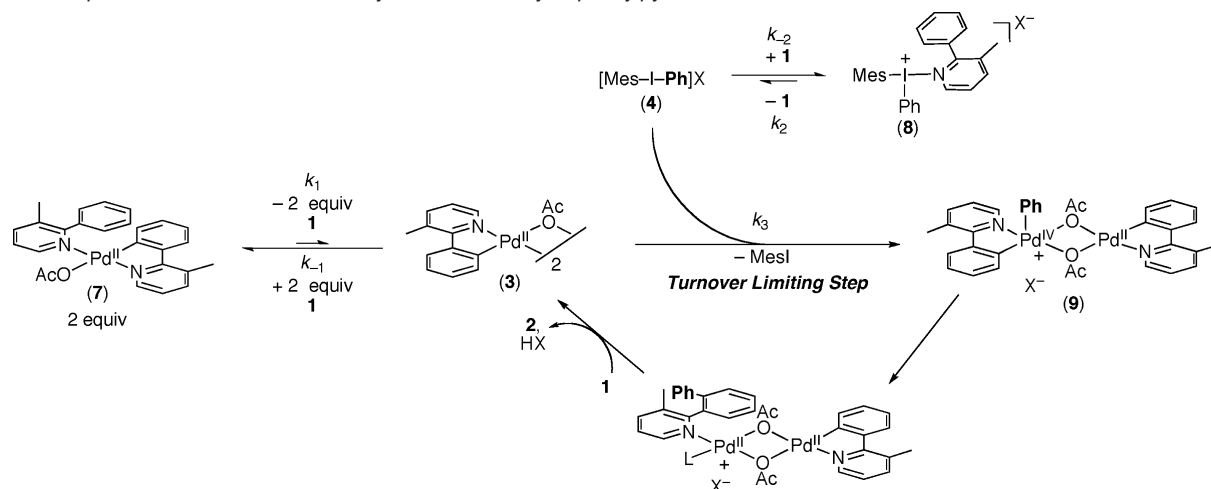


The equilibrium constant for the reaction in eq 4 was next established by measuring $\delta_{\text{H}(4)}$ while titrating in increasing $[\text{Mes-I-Ph}]\text{BF}_4$ in $\text{CD}_3\text{CO}_2\text{D}$ at 110 °C (Figure 5). The resulting curve was fitted to a 1:1 binding model,²⁰ and the nonlinear least-squares fit afforded an equilibrium constant of $111 \pm 18 \text{ M}^{-1}$. This value of K_{eq} is consistent with complex **8** (eq 4) as the resting state of the oxidant under the catalytic conditions.¹²

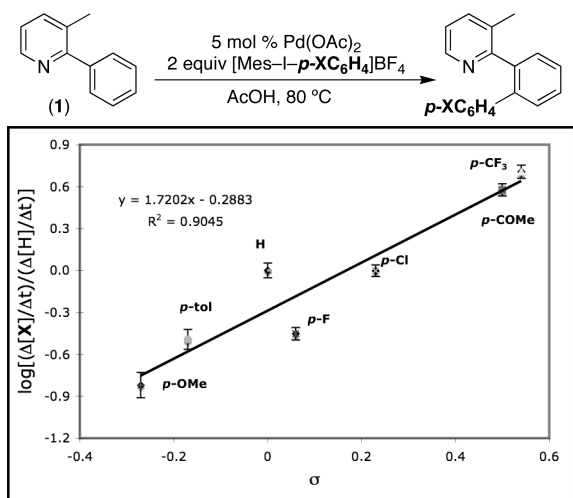
**Figure 5.** $\delta_{\text{H}(4)}$ as a function of $[\text{I}^{\text{III}}]$ at 110 °C. The line depicts a nonlinear least-squares fit to a 1:1 binding model, which showed that $K_{\text{eq}} = 111 \pm 18 \text{ M}^{-1}$.

Hammett Study. The rate of the $\text{Pd}(\text{OAc})_2$ -catalyzed reaction between 3-methyl-2-phenylpyridine (**1**) and $[\text{Mes-I-}p\text{-XC}_6\text{H}_4]\text{BF}_4$ was next examined as a function of the substituent

(15) Ryabov, A. D. *Inorg. Chem.* **1987**, *26*, 1252.

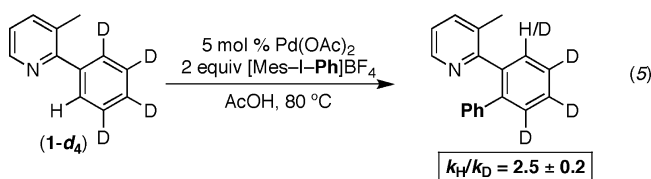
Scheme 3. Proposed Mechanism for C–H Arylation of 3-Methyl-2-phenylpyridine

X. Substrate **1** (100 mM) was combined with $\text{Pd}(\text{OAc})_2$ (5 mM) and the appropriate oxidant $[\text{Mes}-\text{I}-(p\text{-XC}_6\text{H}_4)]\text{BF}_4$ (200 mM) in AcOH at 80 °C, and the initial reaction rate was measured with each iodine(III) reagent. A Hammett plot of the resulting data provided a ρ value of $+1.7 \pm 0.2$ (Figure 6). This indicates that C–H arylation is strongly accelerated by electron-withdrawing groups on the iodine(III) reagent.²¹

**Figure 6.** Hammett plot for Pd-Catalyzed C–H arylation of **1** with $[\text{Mes}-\text{I}-\text{Ar}]\text{BF}_4$.

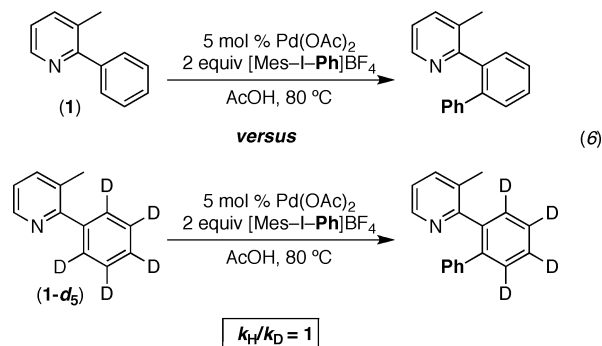
Kinetic Isotope Effect. Finally, the 1° intra- and intermolecular kinetic isotope effects ($k_{\text{H}}/k_{\text{D}}$) for this C–H phenylation reaction

were determined. As shown in eq 5, the intramolecular 1° $k_{\text{H}}/k_{\text{D}}$ for substrate **1-d₄** was 2.5 ± 0.2 , based on ^1H NMR



spectroscopic analysis of the isolated product. This is similar to that seen in other Pd-catalyzed ligand-directed C–H functionalization reactions, which typically show 1° intramolecular KIE values ranging from 2.2 to 6.7.²²

The intermolecular kinetic isotope effect was determined by comparing the initial reaction rate of 3-methyl-2-phenylpyridine (**1**) to that of 3-methyl-2-(*d*₅)-phenylpyridine (**1-d₅**) (eq 6). In this system, $k_{\text{H}}/k_{\text{D}}$ was determined to be 1. The observed lack of an intermolecular KIE implies that C–H bond cleavage occurs after the rate-determining step of the reaction.



- (16) (a) Weiss, R.; Seubert, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 891. (b) Zhdankin, V. V.; Kuposov, A. Y.; Yashin, N. V. *Tetrahedron Lett.* **2002**, *43*, 5735. (c) Ochiai, M.; Suefuji, T.; Miyamoto, K.; Shiro, M. *Chem. Commun.* **2003**, 1438. (d) Suefuji, T.; Shiro, M.; Yamaguchi, K.; Ochiai, M. *Heterocycles* **2006**, *67*, 391.
- (17) A Job plot at 80 °C also displayed a maximum at 0.5 and is available in the Supporting Information.
- (18) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626.
- (19) Job, A. *Ann. Chem.* **1928**, *9*, 113.
- (20) (a) Funasaki, N.; Ishikawa, S.; Neya, S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 719. (b) Bisson, A. P.; Hunter, C. A.; Morales, J. C.; Young, K. *Chem. Eur. J.* **1998**, *4*, 845. (c) Fielding, L. *Tetrahedron* **2000**, *56*, 6151.

- (21) Anslyn, E. K.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; p 447.
- (22) For recent selected examples of intramolecular kinetic isotope effects in Pd-catalyzed ligand-directed C–H functionalization reactions, see refs 14b, d, e, and f as well as: (a) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (b) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554. (c) Li, J. J.; Giri, R.; Yu, J. Q. *Tetrahedron* **2008**, *64*, 6979. (d) Kirchberg, S.; Vogler, T.; Studer, A. *Synlett* **2008**, 2841.

Summary of Mechanistic Data. The data assembled above allow us to formulate a complete mechanistic picture of the catalytic C–H arylation reaction. As shown in Scheme 3, we propose that the resting state of the catalyst is the monomeric Pd^{II} species **7**, and the resting state of the oxidant is the pyridine-coordinated iodine(III) reagent **8**. This proposal is consistent both with the values of K_{eq} from eq 3 and Figure 5, as well as with the direct observation of **7** under the catalytic reaction conditions (Scheme 2). To enter the catalytic cycle, free oxidant **4** is generated by dissociation of 1 equiv of **1** from **8**. In addition, the Pd dimer **3** is formed by the combination of 2 equiv of monomer **7**, with concomitant dissociation of 2 equiv of **1**. The reaction between **3** and **4** to afford high oxidation state dimeric intermediate **9** is then proposed to be the turnover-limiting step of the catalytic cycle, which is followed by C–C bond formation, ligand exchange, and cyclometalation to return to the catalyst resting state. The rate equation shown in eq 7 can be derived on the basis of the proposed mechanism, and application of the pre-equilibrium approximation for [**3**] and [**4**] affords the rate expression shown in eq 8.

$$\text{rate} = k_3[\mathbf{3}][\mathbf{4}] \quad (7)$$

$$\text{rate} = \frac{k_1 k_2 k_3 [\mathbf{7}]^2 [\mathbf{8}]}{k_{-1} k_{-2} [\mathbf{1}]^3} \quad (8)$$

The proposed mechanism is supported by all of the data presented above. For example, eq 8 predicts that the reaction will be first order in [I^{III}], second order in [Pd], and inverse third order in **1**, consistent with the experimental observations. In addition, the Hammett ρ value of 1.7 ± 0.2 is consistent with oxidative addition as the turnover-limiting step. This value is comparable to that observed in Pd^{0/II} oxidative addition reactions.²³ Finally, the observation of an intra- but not an intermolecular kinetic isotope effect is consistent with C–H activation occurring during the catalytic cycle but after the turnover-limiting step.

There are several notable features of the mechanism proposed in Scheme 3. First, the observed second-order dependence on [Pd] implicates bimetallic acetate-bridged Pd complex **9** as a key intermediate in this process. This dimer can be viewed as a Pd^{IV} species attached to a bridging Pd^{II} complex (as drawn in Scheme 3 and also **9a** in Figure 7). Alternatively, if there is significant bonding between the two Pd centers, this may be considered a Pd^{III}–Pd^{III} dimer (**9b**, Figure 7). This latter

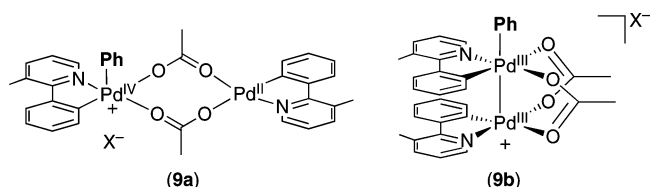


Figure 7. Two possible formulations for intermediate **9**: Pd^{IV}/Pd^{II} (**9a**) versus Pd^{III}~Pd^{III} (**9b**).

possibility is particularly interesting given the proximity of the palladium centers in crystal structures of **5**.²⁴ In addition, Cotton and more recently Ritter have reported the formation of related symmetrical Pd^{III}–Pd^{III} dimers **11** and **13** by oxidation of

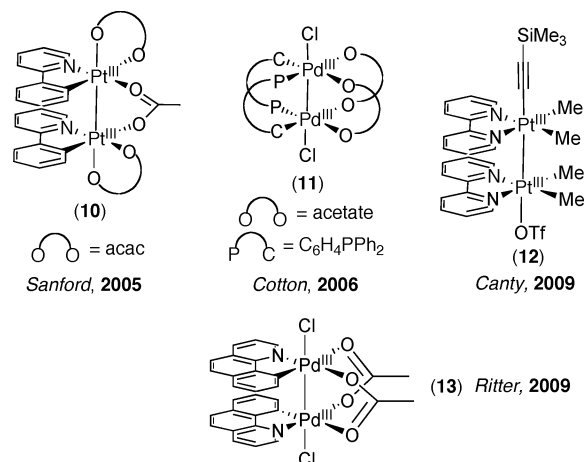


Figure 8. Related Pd^{III}~Pd^{III} and Pt^{III}~Pt^{III} complexes from the literature.

acetate-bridged Pd^{II} complexes with PhICl₂ (Figure 8).^{25–27} Similar Pt^{III}–Pt^{III} dimers have also been formed by reaction of monomeric Pt^{II} starting materials with hypervalent iodine(III) reagents, including PhICl₂,²⁸ PhI(OAc)₂ (**10**),²⁹ and [Ph–I–R]OTf (R = CCSiMe₃) (**12**) (Figure 8).³⁰

Notably, if intermediate **9** is a Pd^{III}–Pd^{III} dimer (**9b**), this complex could undergo direct C–C bond-forming reductive elimination (similar to that depicted in Scheme 3)²⁷ or could disproportionate to Pd^{IV} and Pd^{II} species (either acetate-bridged or unbridged) prior to C–C coupling from Pd^{IV}.^{28,30} In both formulations of the proposed intermediate (**9a** and **9b**), the second Pd center effectively serves as an ancillary ligand to the metal complex that mediates C–C bond formation. As such, an attractive strategy for the development of second-generation C–H arylation catalysts with improved activity and selectivity would involve tuning this organometallic ligand.

It is also interesting to compare the turnover-limiting step of C–H arylation with [Ar₂I]BF₄ to that of C–H acetoxylation with PhI(OAc)₂.^{14h} Remarkably, although both reactions utilize an iodine(III) oxidant and proceed under nearly identical conditions (catalytic Pd(OAc)₂, 100–110 °C in AcOH), the turnover-limiting steps are different. As described above, C–H arylation involves turnover-limiting oxidation. In contrast, Pd-catalyzed C–H acetoxylation shows a zero-order dependence on PhI(OAc)₂ and a large intermolecular 1° H/D kinetic isotope effect, suggesting that cyclopalladation is the turnover-limiting step.³¹ These results have important implications for the application of iodine(III) reagents in other Pd-catalyzed reactions. For example, PhI(OAc)₂ has been used to intercept Pd-alkyl intermediates formed via aminopalladation,³² acetoxyalladation,³³ or carbopalladation³⁴ to generate diverse products.

(23) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.

(24) (a) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Kim, M.; Taylor, T. J.; Gabbai, F. P. *J. Am. Chem. Soc.* **2008**, *130*, 6332.

(25) Cotton, F. A.; Koshevoy, I. O.; Lahuerta, P.; Murillo, C. A.; Sanau, M.; Ubeda, M. A.; Zhao, Q. *J. Am. Chem. Soc.* **2006**, *128*, 13674.

(26) Cotton, F. A.; Gu, J.; Murillo, C. A.; Timmons, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 13280.

(27) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302.

(28) Baxter, L. A. M.; Heath, G. A.; Raptis, R. G.; Willis, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 6944.

(29) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2005**, *24*, 482.

(30) Cauty, A. J.; Gardiner, M. G.; Jones, R. C.; Rodemann, T.; Sharma, M. *J. Am. Chem. Soc.* **2009**, *131*, 7236.

(31) Our initial report on the mechanism of Pd-catalyzed C–H acetoxylation used benzylpyridines as substrates (ref 14h). However, recent studies have shown analogous order and KIE data with 2-phenylpyridine derivatives. Stowers, K. J.; Sanford, M. S. manuscript in preparation.

A key feature of these transformations is that the oxidation of Pd^{II} by $\text{PhI}(\text{OAc})_2$ is faster than competing β -hydride elimination. The current results suggest that analogous oxidations of Pd^{II} -alkyl species with $[\text{Ar}_2\text{I}]\text{BF}_4$ will be significantly slower, which may result in undesired competing processes. Thus, we anticipate that new and more reactive arylating reagents may be required to access chemistry similar to that of $\text{PhI}(\text{OAc})_2$.

Conclusions

In summary, this paper describes detailed synthetic and mechanistic investigations of Pd-catalyzed C–H arylation reactions. The turnover-limiting step of the catalytic cycle involves oxidation of Pd dimer **3** with $[\text{Mes}-\text{I}-\text{Ph}]\text{BF}_4$ (**4**) to form a dimeric high oxidation state Pd intermediate (**9**), which

can potentially be viewed as a mixed-valent $\text{Pd}^{\text{IV}}/\text{Pd}^{\text{II}}$ species or as a $\text{Pd}^{\text{III}}\sim\text{Pd}^{\text{III}}$ dimer. The observed kinetics have important implications for future applications of this chemistry; for example, the second-order dependence on catalyst and inverse third-order dependence on substrate suggest that these transformations will be highly sensitive to reaction concentration and stoichiometry, an important consideration upon scale-up or -down. In addition, the intermediacy of the dimeric species **3** and **9** suggests that catalyst activity and selectivity may be tuned by modification of the tethered metal center. Finally, these investigations raise the larger question of whether similar dimeric intermediates may be involved in other Pd-catalyzed C–H functionalization reactions. Ongoing investigations in our laboratory are seeking to address all of these issues, and the results will be reported in due course.

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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>.

JA904116K

- (32) (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. (b) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (c) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (d) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. (e) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (f) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763.
- (33) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962.
- (34) (a) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906. (b) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836. (c) Liu, H.; Yu, J.; Wang, L.; Tong, X. *Tetrahedron Lett.* **2008**, *49*, 6924. (d) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442. (e) Lyons, T. W.; Sanford, M. S. *Tetrahedron* **2009**, *65*, 3211. (f) Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Am. Chem. Soc.* **2009**, *131*, 3452.