ORGANIC LETTERS

2009
Vol. 11, No. 20
4584−4587

Mechanistic Comparison between Pd-Catalyzed Ligand-Directed C−H Chlorination and C−H Acetoxylation

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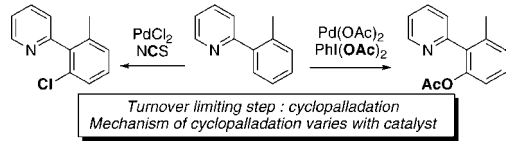
Received August 6, 2009

ABSTRACT



This communication describes detailed investigations of the mechanism of the Pd-catalyzed C−H chlorination and acetoxylation of 2-*o*-tolylpyridine. Under the conditions examined, both reactions proceed via rate-limiting cyclopalladation. However, substrate and catalyst order as well as Hammett data indicate that the intimate mechanism of cyclopalladation differs significantly between $PdCl_2$-catalyzed chlorination and $Pd(OAc)_2$-catalyzed acetoxylation.

Palladium-catalyzed ligand-directed C−H bond functionalization has become a valuable synthetic method for the selective oxidation of organic molecules.[1] Over the past 5 years, numerous Pd-catalyzed reactions have been developed for the directed oxygenation,[2] halogenation,[3] amination,[4] sulfonylation,[5] and arylation[1b−e] of both sp^2 and sp^3 C−H bonds. Furthermore, these transformations have been applied to structurally diverse organic scaffolds, including amino acid derivatives[2c] and drug substrates.[6]

While significant progress has been made in the development of new reactions, detailed mechanistic studies in this area have received considerably less attention.[7,8] An improved mechanistic understanding could facilitate (i) the development of new catalysts with improved catalytic activity and substrate scope as well as (ii) the rational implementation of strategies for controlling the chemo-, diastereo-, enantio-, and site-selectivity of C−H functionalization reactions. This communication describes an investigation of the mechanism of pyridine-directed C−H bond chlorination with *N*-chlorosuccinimide (NCS). We report on the optimization of the

(1) For reviews, see: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Li, B. J.; Yang, S. D.; Shi, Z. J. *Synlett* **2008**, 949. (e) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(2) For examples, see: (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (b) Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (c) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.

(3) For examples, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Giri, R.; Chen, X.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (c) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. (d) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (e) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (f) Wang, X.; Mei, T. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.

(4) For examples, see: (a) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Jordon-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (c) Mei, T. S.; Wang, X.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.

(5) Zhao, X.; Dimitrijevic, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466.

(6) Wasa, M.; Engle, K. M.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886.

(7) (a) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *128*, 14047. (b) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651. (d) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974. (e) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234.

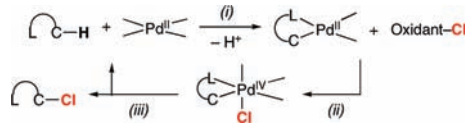
(8) (a) Chiong, H. A.; Pham, Q. N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (b) Li, J. J.; Giri, R.; Yu, J. Q. *Tetrahedron* **2008**, *64*, 6979. (c) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302.

10.1021/ol901820w CCC: $40.75
Published on Web 09/15/2009

catalyst, elucidation of the turnover-limiting step, and mechanistic comparison to related Pd-catalyzed C−H acetoxylation reactions.

Pd-catalyzed C−H chlorination has been proposed to proceed by the general catalytic cycle outlined in Scheme 1.[3,8c,9,10] This cycle begins with ligand directed C−H

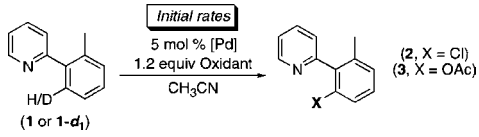
Scheme 1. General Mechanism for C−H Chlorination[9]



activation (i), which is followed by two-electron oxidation of the resulting palladacycle to a monomeric Pd^{IV} species (or a closely related $Pd^{III}-Pd^{III}$ dimer) (ii).[8c] Finally, C−Cl bond-forming reductive elimination (iii) regenerates the catalyst and releases the functionalized product. Previous studies have demonstrated that electrophilic chlorinating reagents like *N*-chlorosuccinimide (NCS)[10] and $PhICl_2$[8c,10] can promote the stoichiometric two-electron oxidation of cyclometalated Pd(II) complexes, demonstrating the potential viability of step (ii) of the proposed catalytic cycle. However, detailed investigations of the turnover-limiting step, the kinetic isotope effect, and the electronic requirements of C−H chlorination have thus far not been explored.

Our mechanistic investigation focused on the Pd-catalyzed functionalization of 2-*o*-tolylpyridine (**1**) with NCS and $PhI(OAc)_2$ to form **2** and **3**, respectively (Table 1). Substrate

Table 1. Intermolecular Kinetic Isotope Effect Data



entry	catalyst	oxidant	k_H/k_D
1	$PdCl_2$	NCS	4.4 ± 0.2
2	$Pd(OAc)_2$	$PhI(OAc)_2$	4.3 ± 0.5

1 possesses several desirable features. First, it undergoes selective monofunctionalization. Second, it participates cleanly in both C−H chlorination and C−H acetoxylation reactions, thus allowing direct comparison of these two transformations. Finally, the pyridine ring is readily modified, which facilitates analysis of electronic effects in these systems.[11] Our studies began with conditions analogous to those in the literature: 5 mol % of $Pd(OAc)_2$ and 1.2 equiv of NCS in CH_3CN with [**1**] = 0.12 M.[3c] However, at this concentration the reactions did not remain homogeneous, which led to inconsistent kinetics; furthermore, when [**1**] was lowered, competing formation of acetoxylated product **3** was observed,[12] which complicated kinetic analysis.

Based on these preliminary studies, we surveyed a variety of alternative Pd sources (Table S2, Supporting Information) and identified $PdCl_2$ as an optimal catalyst for the chlorination of **1** in MeCN. Further optimization revealed that 5 mol % of $PdCl_2$ is required to achieve full conversion and that the highest yield (80%) is obtained at concentrations between 0.048 and 0.024 M. Importantly, these conditions also worked well for the $Pd(OAc)_2$-catalyzed *ortho*-acetoxylation of **1**, providing **3** in 77% yield.

With optimal conditions for the chlorination and acetoxylation of **1** in hand,[13] we first examined the intermolecular kinetic isotope effect (KIE) for the two reactions. The Pd-catalyzed functionalizations of **1** and **1-*d*$_1$** were monitored by GC, and the method of initial rates was used to determine the rate at each [oxidant]. As shown in Table 1, a large primary isotope effect was observed in both systems, with $k_H/k_D = 4.4 \pm 0.2$ for chlorination and $k_H/k_D = 4.3 \pm 0.5$ for acetoxylation.[14]

We next established the kinetic order in each reaction component, starting with the oxidant. As shown in Figure 1,

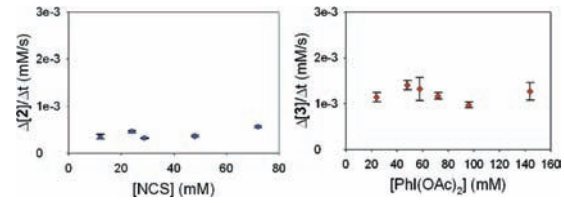


Figure 1. Order in oxidant for C−H chlorination (blue) and acetoxylation (red).

for both NCS and $PhI(OAc)_2$ the initial rate was independent of [oxidant] over a wide range of concentrations (12−144 mM or 0.5−3.0 equiv of oxidant relative to substrate).

The kinetic order in palladium was next determined for each transformation by varying the catalyst loading from 2.5 to 10 mol % ([Pd] = 0.6−4.8 mM) under otherwise identical conditions. As shown in Figure 2, chlorination showed a first-order dependence on [Pd] over this catalytically relevant concentration range. In contrast, for the C−H acetoxylation reaction, a plot of initial rate versus [Pd] was clearly not linear. A weighted nonlinear least-squares fit of the data to

(9) The identity of the ancillary ligands in the catalytic intermediates is not known; as a result, these ligands are represented as sticks.

(10) For the oxidation of a Pd^{II} model complex to Pd^{IV} with NCS, see: Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.

(11) 2-Benzylpyridines were used in a previous mechanistic study of Pd-catalyzed C−H acetoxylation (ref 7b). However, these substrates reacted with NCS to form undesired benzylic chlorination side products.

(12) The OAc is presumably derived from the $Pd(OAc)_2$ catalyst.

(13) The kinetic studies were run at different concentrations (0.024 M for chlorination versus 0.048 M for acetoxylation) because the data for each reaction was significantly more reproducible under these conditions. However, the same kinetic orders and analogous Hammett trends were observed for chlorination at 0.048 M. See the Supporting Information.

(14) Intermolecular primary KIE values between 3.58 and 1.85 were observed in the Pd-catalyzed C−H acetoxylation of 2-benzylpyridines (ref 7b).

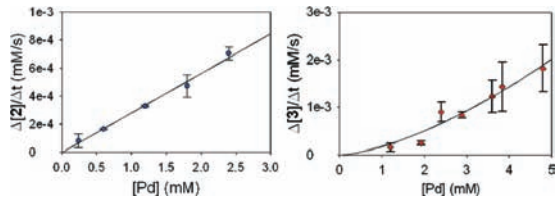


Figure 2. Order in [Pd] for C−H chlorination (blue) and acetoxylation (red).

the equation: $f(x) = a[\mathrm{Pd}]^n$ provided an order (n) of 1.5 ± 0.2 (Figure 2).

Finally, the order in substrate **1** was examined, using 0.25−2.5 equiv of **1** relative to oxidant ([**1**] = 6−120 mM). Again, the chlorination and acetoxylation reactions showed different results (Figure 3). For chlorination, a plot of initial

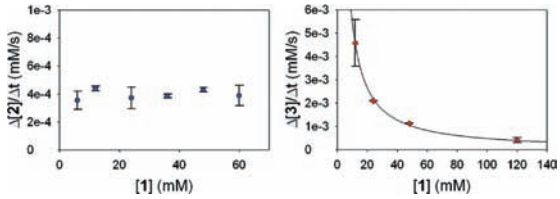


Figure 3. Order in [**1**] for C−H chlorination (blue) and acetoxylation (red).

rate versus [**1**] showed that the rate was independent of [**1**]. In contrast, the acetoxylation reactions showed an inverse first-order dependence on [**1**].

To gain insight into the electronic requirements of these reactions, we next probed the initial rate of C−H functionalization with a series of electronically different 2-*o*-tolylpyridines. As shown in Figure 4, Hammett plots for both

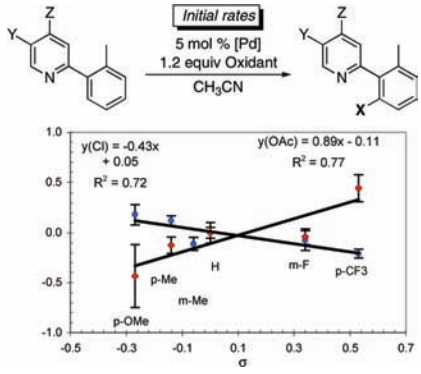


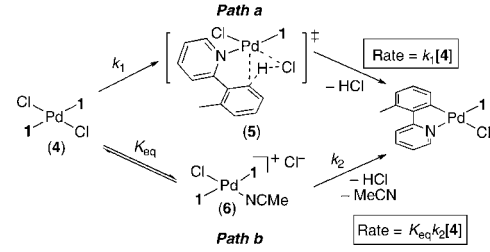
Figure 4. Hammett plot for C−H chlorination (blue) and C−H acetoxylation (red).

C−H chlorination and C−H acetoxylation showed a modest correlation with the σ values of the Y and Z substituents. Very different ρ values were obtained for the two reactions, with $\rho = -0.43$ for chlorination and $\rho = +0.89$ for acetoxylation.[15]

The data presented here offer valuable insights into the mechanistic similarities and differences between the Pd-catalyzed chlorination and acetoxylation of substrate **1**. The large primary intermolecular KIE coupled with the zero-order dependence on [oxidant] provide strong evidence that both transformations proceed via turnover-limiting cyclopalladation. This is in interesting contrast to the C−H arylation of 3-methyl-2-phenylpyridine with $[Ar_2I]BF_4$, which was proposed to involve turnover-limiting oxidation of a cyclometalated Pd(II) dimer.[7e]

While the rate-determining step appears to be the same in both of the current systems, the different kinetic orders in [Pd] and in [**1**] as well as the different Hammett ρ values are consistent with different mechanisms for cyclopalladation in the $PdCl_2$ versus $Pd(OAc)_2$-catalyzed reactions. Significant literature precedent has shown that PdX_2 (X = OAc or Cl) reacts rapidly and quantitatively with excess amine or pyridine derivatives (L) to form monomeric complexes of general structure $Pd(X)_2(L)_2$.[16] For example, $Pd(OAc)_2(ba)_2$ (ba = benzylamine) has been directly observed in the $Pd(OAc)_2$-mediated cyclometalation of benzylamine in MeCN.[17] As such, we propose that the catalyst resting state during both C−H functionalizations is most likely $Pd(X)_2(\mathbf{1})_2$ (X = Cl, **4**; X = OAc, **7**) (Schemes 2 and 3).[18]

Scheme 2. Two Possible Mechanisms for the Turnover-Limiting Step of C−H Chlorination (**1** = 2-*o*-Tolylpyridine)



In the chlorination reaction, the observed zero-order dependence on [**1**] suggests that cyclometalation at

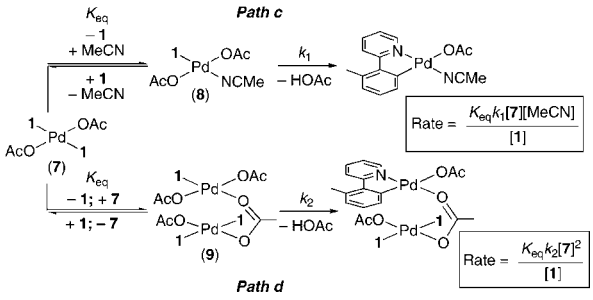
(15) Interpretation of the Hammett data is somewhat complicated by the conjugated biaryl system in **1**, since substitution of Y and Z can influence the electronics of both the pyridine (which binds to the metal) and the *ortho*-C−H bond (which undergoes activation). We note that the observed ρ value for C−H acetoxylation (+0.89 in MeCN) is reasonably similar to that reported for benzylpyridines (+1.40 in benzene, ref 7b), where the pyridine and aryl group are electronically isolated. Thus, we hypothesize that the effect observed here is predominantly due to pyridine electronics.

(16) For examples, see: (a) Deeming, A. J.; Rothwell, I. P. *J. Organomet. Chem.* **1981**, *205*, 117. (b) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629. (c) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403, and references therein.

(17) Kurzeev, S. A.; Kazankov, G. M.; Ryabov, A. D. *Inorg. Chim. Acta* **2002**, *340*, 192.

(18) A dimeric resting state followed by C−H activation at a dimeric intermediate is also possible based on the kinetic data for C−H chlorination. However, literature reports suggest that dimeric complexes like $Pd_2(X)_4(L)_2$ only predominate in solution under conditions where L:[Pd] < 2:1. Vicente, J.; Saura-Llamas, I. *Comments Inorg. Chem.* **2007**, *28*, 39.

Scheme 3. Possible Competing Mechanisms for the Turnover-Limiting Step of C−H Acetoxylation (**1** = 2-*o*-Tolylpyridine)



$Pd(Cl)_2(\mathbf{1})_2$ (**4**) proceeds by either (a) direct C−H activation via a five-coordinate transition state such as **5**[19] or (b) pre-equilibrium chloride dissociation followed by C−H activation at cationic complex **6**.[20] Paths a and b are both consistent with the observed kinetic orders of 1 in [Pd] and 0 in [**1**].[18] Furthermore, both mechanisms have been proposed for related cyclometalation reactions in the literature.[19,20] We tend to favor path b, as it offers a better explanation for the Hammett ρ value of −0.43. The latter can be rationalized on the basis of increased lability of Cl^- (at complex **4**) and MeCN (at complex **6**) with more electron-releasing pyridine ligands. This would lead to an increase in both K_{eq} and k_2, thereby affording faster reactions with electron rich pyridines.

For the acetoxylation reaction, the observed inverse first-order dependence on [**1**] implicates pre-equilibrium dissociation of **1** from $Pd(OAc)_2(\mathbf{1})_2$ prior to C−H activation. As shown in Scheme 3, this could generate monomeric species $Pd(OAc)_2(\mathbf{1})$(MeCN) (**8**) (path c) or an acetate-bridged dimer such as $Pd_2(OAc)_4(\mathbf{1})_3$ (**9**) (path d), and cyclometalation could then occur at either of these intermediates. Path c is expected to show a first order dependence on [Pd], while path d should be second order in [Pd] (Scheme 3). We propose that these (or other closely related) competing first- and second-order mechanisms are likely responsible for the observed 1.5 order dependence on [Pd] in this system.[21] The Hammett ρ value of +0.89 is fully consistent with this mechanistic proposal, as electron-withdrawing substituents on the pyridine ligand should both increase both K_{eq} values and also render complexes **8** and **9** more reactive toward electrophilic C−H activation (thereby increasing both k_1 and k_2).[7b,19b,c] Notably, mechanisms similar to both c[17] and d[18] have been proposed for the stoichiometric cyclometalation of benzylamine at $Pd(OAc)_2$ in MeCN.[17]

There are several important ramifications of these studies. First, it is clear that the ligand environment at Pd during C−H activation is significantly different in these two transformations. If this result proves general, it has potential implications for diastereoselectivity in the C−H functionalization of chiral substrates upon changing the catalyst/oxidant combination. In addition, the structures of the key intermediates (as well as the possibility of competing mechanisms) should inform the selection of chiral ligands for asymmetric C−H functionalization reactions. Finally, the development of more highly active C−H chlorination and acetoxylation catalysts will require accelerating the cyclometalation step of the catalytic cycle. Because most ancillary ligands decrease the rate of directed C−H activation relative to that with simple Pd salts, this is a particularly challenging problem that will likely require the design of novel ligands.

In summary, this paper describes the mechanism of Pd-catalyzed directed C−H chlorination and acetoxylation of **1**. Under the conditions examined, both reactions proceed via turnover-limiting cyclopalladation. However, kinetic order and Hammett data indicate that the intimate mechanism of C−H activation differs significantly between $PdCl_2$-catalyzed chlorination and $Pd(OAc)_2$-catalyzed acetoxylation. Ongoing work seeks to further explore the proposed mechanisms computationally as well as exploit the current results for the development of new C−H functionalization catalysts.

Acknowledgment. We thank the NIH NIGMS (GM-073836) for support of this research. K.J.S. also acknowledges Novartis for a graduate fellowship. Finally, we thank Frontier Scientific for a generous gift of 2-methylboronic acid.

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

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(19) For examples of cyclometalation mechanisms analogous to path a, see ref 16c as well as: (a) Yatsimirsky, A. K. *Zh. Neorg. Khim.* **1979**, *24*, 2711. (b) Yagyu, T.; Aizawa, S.; Funahashi, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 619. (c) Yagyu, T.; Iwatsuki, S.; Aizawa, S.; Funahashi, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1857. (d) Martin-Matute, B.; Mateo, C.; Cardenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2001**, *7*, 2341.

(20) For examples of cyclometalation mechanisms analogous to path b, see: (a) Alsters, P. L.; Engel, P. F.; Hogerheide, M. P.; Copijn, M.; Spek, A. L.; van Koten, G. *Organometallics* **1993**, *12*, 1831. (b) Otto, S.; Chanda, A.; Samuleev, P. V.; Ryabov, A. D. *Eur. J. Inorg. Chem.* **2006**, 2561, and references therein.

(21) An alternative explanation would be that the catalyst resting state is a mixture of monomeric and dimeric Pd species (see ref 8c for a similar proposal). However, we believe that this is unlikely, as literature precedent suggests that the reaction between a large excess of **1** and $Pd(OAc)_2$ to form $Pd(OAc)_2(\mathbf{1})_2$ should to be fast and essentially quantitative, particularly at 70 °C. See refs 16−18.