J|A|C|S
ARTICLES

Published on Web 09/28/2010

On the Mechanism of Palladium-Catalyzed Aromatic C−H Oxidation

David C. Powers, Daphne Y. Xiao, Matthias A. L. Geibel, and Tobias Ritter*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

Received June 21, 2010; E-mail: ritter@chemistry.harvard.edu

Abstract: The mechanism of Pd-catalyzed aromatic C−H oxidation chemistry continues to be vigorously discussed. Historically, Pd(II)/Pd(IV) catalysis cycles have been proposed. Herein, we present a detailed study of $Pd(OAc)_2$-catalyzed aromatic C−H chlorination and propose dinuclear Pd(III) complexes as intermediates. We have identified a succinate-bridged dinuclear Pd(II) complex, which self-assembles during catalysis, as the catalyst resting state. In situ monitoring of catalysis has revealed that chlorination proceeds with turnover-limiting oxidation of a dinuclear resting state, and that acetate ions, liberated during the formation of the catalyst resting state, catalyze the bimetallic oxidation. Informed by reaction kinetics analysis, relevant dinuclear Pd(III) complexes have been prepared and observed to undergo selective C−Cl reductive elimination. Based on the combination of kinetic data obtained during catalysis and explicit structural information of relevant intermediates, we propose a $Pd(II)_2/Pd(III)_2$ catalysis cycle for $Pd(OAc)_2$-catalyzed aromatic C−H chlorination.

Introduction

Palladium typically undergoes two-electron redox chemistry.[1] C−H functionalization reactions catalyzed by palladium are commonly proposed to proceed via either Pd(0)/Pd(II) or Pd(II)/Pd(IV) redox cycles.[2] Pd(IV) intermediates have been suggested in Pd-catalyzed aromatic C−H oxidation reactions since 1971,[3] and Pd(II)/Pd(IV) catalysis cycles have subsequently become generally accepted as the operative mechanisms for a large class of Pd-catalyzed oxidation reactions. Over the past 5 years, many synthetically useful Pd-catalyzed oxidation reactions have been developed.[4−6] Discussion of the mechanisms of these oxidation reactions has often been based on stoichiometric organometallic reactions of isolated Pd(IV) model complexes.[4g] Experimental support for the viability of Pd(IV) intermediates during catalysis, however, has not yet been reported,[4e] and the relevance of the isolated Pd(IV) complexes to catalysis has not yet been demonstrated.

In this article we report kinetic data obtained during catalysis, which implicate a dinuclear palladium complex in oxidation. Informed by the kinetic data, we have identified and evaluated a dinuclear Pd(III) complex implicated in catalysis. Interpretation of relevant kinetic data has been possible because we have identified, isolated, and characterized the previously unanticipated catalyst resting state: a succinate-bridged dinuclear Pd(II)

---

(1) Negishi, E. I., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons, Inc.: New York, 2002.

(2) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041–4047.

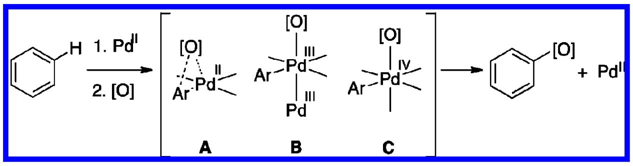
(3) Henry, P. M. *J. Org. Chem.* **1971**, *36*, 1886–1890.

(4) For recent reviews, see (a) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924–1935. (b) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412–9423. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (d) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (e) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, 712–733. (f) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824–889. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.

(5) For directed C−H oxidations to form C−C bonds, see (a) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046–4048. (b) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047–14049. (c) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066–6067. (d) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554–5558. (e) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118. (f) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473–1476. (g) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097–6100. (h) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648–3649. (i) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. C−O bonds, see: (j) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543. (k) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (l) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141–1144. (m) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285–13293. (n) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717–4720. (o) Zhang, J.; Khaskin, E.; Anderson, N. P.; Zavalij, P. Y.; Vedernikov, A. N. *Chem. Commun.* **2008**, 3625–3627. (p) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174–3177. C−N bonds, see (q) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049. (r) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184–16186. (s) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806–10807. (t) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892–6895. For C−halogen bonds, see (u) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134–7135. (v) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416–7417. (w) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483–11498. (x) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523–2526. (y) Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008**, *64*, 6979–6987. (z) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215–5219. (aa) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, *131*, 11310–11311. (bb) Arnold, P. L.; Sanford, M. S.; Pearson, S. M. *J. Am. Chem. Soc.* **2009**, *131*, 13912–13913.

10.1021/ja1054274

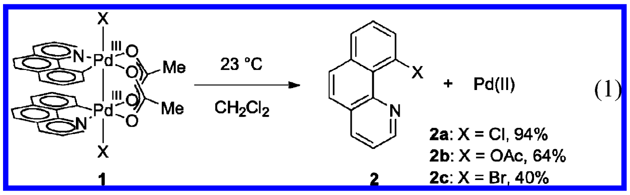
Scheme 1. Oxidative Functionalization of the C−H Bond Could Proceed via Direct Electrophilic Substitution (**A**, redox neutral at Pd), Oxidative Addition To Afford a Dinuclear Pd(III) Complex Followed by Bimetallic Reductive Elimination (**B**), or Oxidative Addition To Afford a Mononuclear Pd(IV) Complex (**C**) Followed by Monometallic Reductive Elimination



complex. The combination of kinetic and structural information has allowed, for the first time in the field of Pd-catalyzed aromatic C−H oxidation, discussion of both structure and oxidation state of the high-valent palladium complexes relevant to redox catalysis. We propose a mechanism for Pd(OAc)$_2$-catalyzed C−H chlorination, which accounts for previously reported results, including minor byproduct formation (<1%). Our results suggest that dinuclear Pd(III) intermediates are relevant in reactions previously believed to proceed via Pd(IV) complexes.

Pd-catalyzed C−H oxidation reactions are commonly initiated by C−H metalation to form a Pd−C bond.[7] Conceptually, subsequent oxidative functionalization of the nascent Pd−C bond can proceed by several different mechanisms (Scheme 1). Direct electrophilic Pd−C bond cleavage via intermediate **A** would proceed without oxidation state change at palladium.[8] Alternatively, metal-centered oxidation would afford a high-valent Pd complex, such as dinuclear Pd(III) intermediate **B** or mononuclear Pd(IV) intermediate **C**, which would afford the observed products via reductive elimination.

Mononuclear Pd(IV) intermediates in Pd-catalyzed C−H oxidation chemistry were first proposed by Henry in 1971.[3] Stock,[9] Crabtree,[10] and Sanford[5k] proposed similar Pd(II)/Pd(IV) redox mechanisms for Pd-catalyzed aromatic C−H oxidations. Each of the three fundamental steps of the proposed Pd(II)/Pd(IV) redox mechanisms—palladation of aromatic C−H bonds by Pd(II) to afford Pd(II) aryl complexes,[11] oxidation of Pd(II) aryl complexes to afford Pd(IV) complexes,[12] and reductive elimination of C−C,[13] C−O,[14] C−Cl,[15] and C−F[16] bonds from Pd(IV) complexes—have been independently documented in stoichiometric organometallic reactions. However, the relevance of the reported stoichiometric reactions of Pd(IV) complexes to catalysis has not yet been established by in situ study of catalysis.



(1)

In 2009, we reported C−Cl, C−Br, and C−O reductive elimination reactions from well-defined dinuclear Pd(III) complexes (**1**) and proposed that reductive elimination from related dinuclear Pd(III) complexes may be the product-forming step in a variety of palladium-catalyzed oxidative C−H functionalizations (eq 1).[17] Deprez and Sanford reported a study of Pd(OAc)$_2$-catalyzed oxidative C−C bond-forming reactions and implicated dinuclear Pd intermediates.[18] On the basis of these studies, mechanisms involving dinuclear Pd(III) intermediates in catalysis are emerging as a viable alternative to previously accepted mononuclear Pd(IV)-based mechanisms.

Herein, we report an investigation of the mechanism of Pd(OAc)$_2$-catalyzed acetoxylation and chlorination of 2-phenylpyridine derivatives. We discuss the difficulties inherent in choosing appropriate model complexes for discussion of the mechanism of catalysis and present data obtained under conditions relevant to catalysis. Observation and isolation of the catalyst resting state of chlorination, combined with measurements of reaction kinetics *during catalysis* has implicated the intermediacy of dinuclear complexes in the redox cycle of catalysis. Informed by results obtained by in situ monitoring of

---

(6) For olefin oxidations, see (a) Vicente, J.; Saura-Llamas, I.; Bautista, D. *Organometallics* **2005**, *24*, 6001–6004. (b) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691. (c) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181. (d) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836–5837. (e) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542–14543. (f) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737–5740. (g) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906–4907. (h) Liu, H.; Yu, J.; Wang, L.; Tong, X. *Tet. Lett.* **2008**, *49*, 6924–6928. (i) Tang, S.; Peng, P.; Wang, Z.-Q.; Tang, B.-X.; Deng, C.-L.; Li, J.-H.; Zhong, P.; Wang, N.-X. *Org. Lett.* **2008**, *10*, 1875–1878. (j) Hövelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K. *Chem. Commun.* **2008**, 2334–2336. (k) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763–773. (l) Tang, S.; Peng, P.; Pi, S.-F.; Liang, Y.; Wang, N.-X.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1179–1182. (m) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962–2964. (n) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442–5445. (o) Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Am. Chem. Soc.* **2009**, *131*, 3452–3453. (p) Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846–3847. (q) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520–7521. (r) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466–3467.

(7) Kalyani, D.; Sanford, M. S. *Top. Organomet. Chem.* **2007**, *24*, 85–116.

(8) (a) Alibrandi, G.; Minniti, D.; Romeo, R.; Uguagliati, P.; Calligaro, L.; Belluco, U. *Inorg. Chim. Acta* **1986**, *112*, L15–L16. (b) Hill, G. S.; Rendina, L. M.; Puddephatt, R. J. *Organometallics* **1995**, *14*, 4966–4968. (c) Kalberer, E. W.; Houlis, J. F.; Roddick, D. M. *Organometallics* **2004**, *23*, 4112–4115.

(9) Stock, L. M.; Tse, K.-T.; Vorvick, L. J.; Walstrum, S. A. *J. Org. Chem.* **1981**, *46*, 1757–1759.

(10) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A: Chem.* **1996**, *108*, 35–40.

(11) (a) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272–3273. (b) Ryabov, A. D. *Synthesis* **1985**, 233–252. (c) Fuchita, Y.; Hiraki, K.; Kamogawa, Y.; Suenaga, M. *J. Chem. Soc., Chem. Commun.* **1987**, 941–942. (d) Fuchita, Y.; Oka, H.; Okamura, M. *Inorg. Chim. Acta* **1992**, *194*, 213–217.

(12) (a) Uson, R.; Fornies, J.; Navarro, R. *J. Organomet. Chem.* **1975**, *96*, 307–312. (b) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83–90.

(13) Byers, P. K.; Canty, A. J.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1986**, 1722–1724.

(14) (a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790–12791. (b) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974–10983.

(15) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142–15143.

(16) (a) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061. (b) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793–3807.

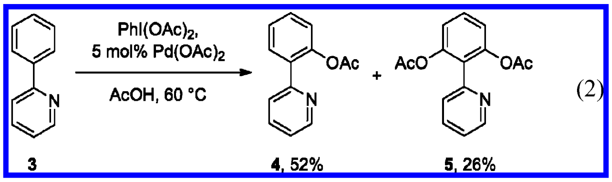
(17) (a) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302–309. (b) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050–17051.

(18) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241.

catalysis, we have studied the organometallic chemistry of dinuclear Pd(III) complexes relevant to catalysis.

Results and Discussion

$Pd(OAc)_2$-Catalyzed Aromatic Acetoxylation. Palladium-catalyzed acetoxylation of benzene was first reported in 1966.[19] In 1971, Henry proposed Pd(IV) intermediates in aromatic acetoxylation with $K_2Cr_2O_7$.[3] Reports by Stock[9] and Crabtree[10] also entertained the possibility of Pd(IV) intermediates in aromatic acetoxylation reactions. Aromatic C−H palladation is rate determining in the $Pd(OAc)_2$-catalyzed acetoxylation of benzene by $PhI(OAc)_2$ reported by Crabtree.[10] Kinetic data obtained from the Crabtree reaction, therefore, provides information regarding the mechanism of metalation, not the mechanism of oxidation; the identity of potential high-valent intermediates during catalysis could not be probed. The observed reactivity was most easily interpreted as an operating Pd(II)/(IV) redox cycle. In 2004, Sanford disclosed the regioselective ortho-oxidation of 2-phenylpyridine derivatives (eq 2).[5k] Sanford proposed Pd(IV) intermediates during catalysis and put forth a mechanism involving cyclometalation at Pd(II), oxidation of the resulting Pd-aryl complex to Pd(IV), followed by product-forming reductive elimination from Pd(IV).[5j,k]

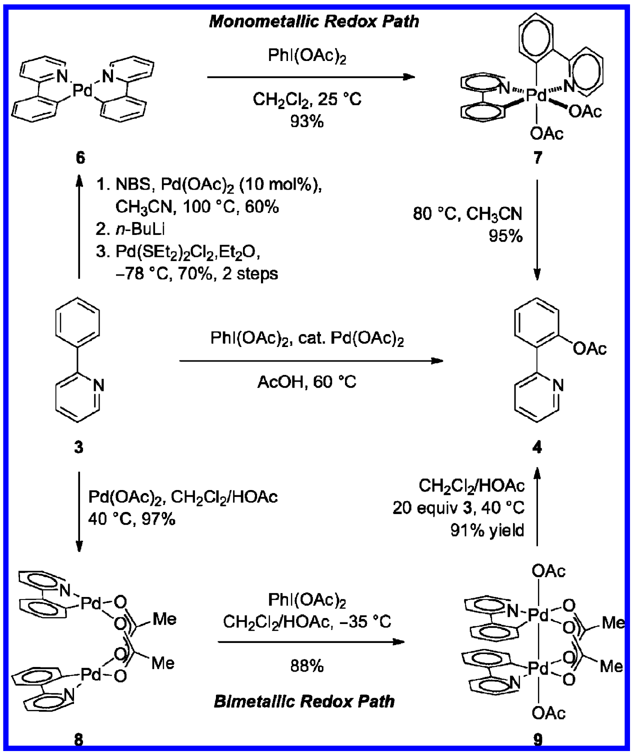


(2)

Pd(IV) complex **7** has been studied as a model complex of the proposed Pd(IV) intermediates in acetoxylation (Scheme 2).[14] Upon thermolysis, Pd(IV) complex **7** undergoes product-forming C−O reductive elimination. The original authors discussed **7** as a model complex and did not propose it to be an intermediate in catalysis.[4g] Subsequently, we have shown that **7** is not a kinetically competent intermediate for catalysis.[17b]

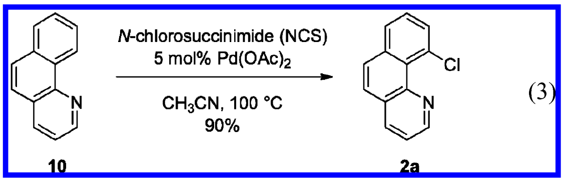
We selected dinuclear Pd(II) complex **8** as a starting point for our own investigation of C−H acetoxylation (Scheme 2),[17b] because it is the product of cyclometalation of 2-phenylpyridine (**3**) with $Pd(OAc)_2$.[20] Treatment of **8** with $PhI(OAc)_2$ afforded dinuclear Pd(III) complex **9**. Subsequent thermolysis of **9** in the presence of 20 equiv of 2-phenylpyridine (**3**)—pseudocatalytic conditions—resulted in the formation of **4** in 91%. Evaluation of dinuclear Pd(III) complex **9** during catalysis revealed that **9** is a kinetically competent catalyst for acetoxylation.

Scheme 2. On the Basis of Stoichiometric Model Complexes, Either Pd(II)/Pd(IV) or $Pd(II)_2/Pd(III)_2$ Redox Couples Can Be Formulated for Pd-Catalyzed C−H Acetoxylation



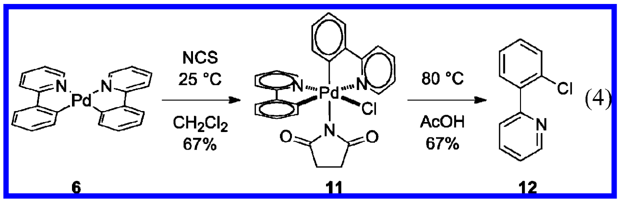
Based on the stoichiometric organometallic reactions shown in Scheme 2, synthesis cycles involving either mononuclear Pd(IV) or dinuclear Pd(III) intermediates have been formulated.[14b,17a] Which of these synthesis cycles most resembles the operative catalysis cycle cannot be determined with currently available data. Determination of the redox couple relevant during catalysis is not possible for the reaction shown in eq 2 because, like in the acetoxylation of benzene reported by Crabtree,[10] C−H metalation is the turnover-limiting step during acetoxylation of **3** (see Supporting Information).[17b,21] The nuclearity[22] of the palladium intermediates relevant to redox chemistry in the catalytic cycle can only be probed when the turnover-limiting step does not precede the redox chemistry. The results presented in Scheme 2 therefore have no demonstrated relevance to catalysis and there is no basis for discrimination between potential mechanisms involving electrophilic M−C cleavage (redox neutral at Pd; **A**, Scheme 1), oxidation to a dinuclear Pd(III) intermediate (bimetallic redox path; Scheme 2), or the intermediacy of a mononuclear Pd(IV) complex (monometallic redox path).

$Pd(OAc)_2$-Catalyzed Aromatic Chlorination. In 1970, Fahey reported the directed chlorination of palladated azobenzene using Cl_2,[23] and in 2004, Sanford reported the Pd-catalyzed chlorination of 2-phenylpyridine derivatives using *N*-chlorosuccinimide (NCS) as the terminal oxidant (eq 3).[5k]



(3)

Analogous to Pd(IV) model complex **7**, isolated by oxidation of **6** with $PhI(OAc)_2$, Pd(IV) chloride model complex **11** has been isolated upon oxidation of **6** with NCS and observed to undergo C−Cl reductive elimination upon thermolysis (eq 4).[15]



(4)

---

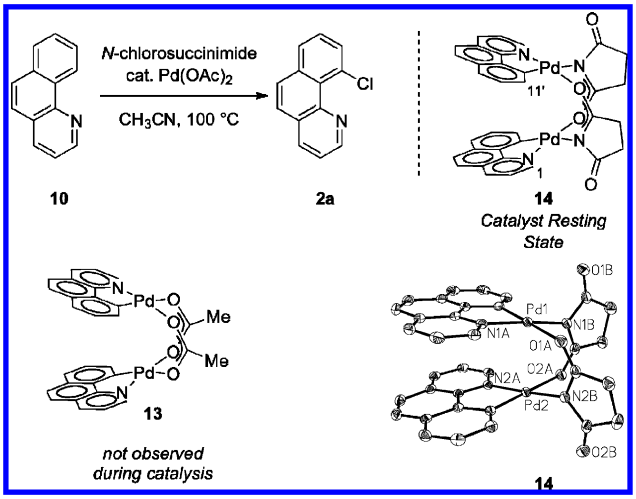
[19] (a) Davidson, J. M.; Triggs, C. *Chem. Ind. (London)* **1966**, 457. (b) Tisue, T.; Downs, W. J. *J. Chem. Soc. D* **1969**, 410.

[20] Gutierrez, M. A.; Newkome, G. R.; Selbin, J. *J. Organomet. Chem.* **1980**, *202*, 341–350.

[21] Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584–4587.

[22] Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092−14103.

Scheme 3. Resting State of Pd-Catalyzed Chlorination of Benzo[*h*]quinoline (**10**) Is Succinate-Bridged Dinuclear Pd Complex **14**, Not Acetate-Bridged Complex **13**[a]



[a] ORTEP drawing of **14** with ellipsoids drawn at 50% probability (hydrogen atoms omitted for clarity). Pd1−Pd2 distance in **14**: 2.8628(4) Å.

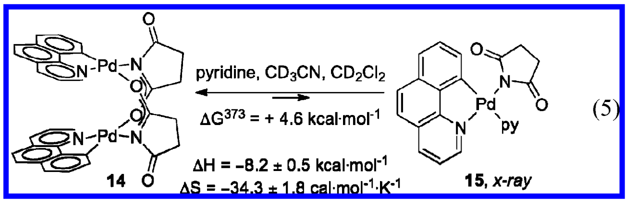
Unlike Pd(OAc)$_2$-catalyzed acetoxylation, which proceeds with turnover-limiting metalation, we have found that the Pd(OAc)$_2$-catalyzed chlorination of **10** with NCS (eq 3) proceeds with turnover-limiting oxidation. Turnover-limiting oxidation was implied by the observation of zero-order kinetic dependence on substrate and first-order kinetic dependence on NCS. Rate-determining oxidation allowed direct interrogation of the catalyst structure during the redox cycle operative in catalysis, which is not possible for transformations in which metalation is turnover limiting.

Resting State of Pd(OAc)$_2$-Catalyzed C−H Chlorination. Inspection of the ^{1}H NMR spectra of the chlorination reaction shown in eq 3 during catalysis revealed that benzo[*h*]quinolyl palladium acetate dimer **13**, formed by reaction of **10** with Pd(OAc)$_2$, was not present in the reaction mixture (Scheme 3). Instead, we found that succinate-bridged dinuclear palladium(II) complex **14**, was the only observable palladium-containing compound present during chlorination. Resting state **14** self-assembles from Pd(OAc)$_2$, benzo[*h*]quinoline (**10**), and succinimide, which is generated by reduction of NCS, and was isolated and characterized as a moisture and air stable crystalline solid.[24]

The dinuclear structure of **14** in the solid state was established by single crystal X-ray diffraction. Complex **14** contains two palladium nuclei held in proximity by bridging succinate ligands,[25] and is structurally similar to acetate-bridged derivatives, such as **13**. The Pd−Pd distance in **14** is 2.8628(4) Å, which is 0.02 Å longer than the corresponding distance in acetate-bridged complex **13**.

NMR and UV−vis spectroscopy have been used to establish that resting state **14** is dinuclear in solution. The ^{1}H NMR signals of the benzo[*h*]quinolinyl ligands are shifted upfield versus the corresponding shifts for benzo[*h*]quinoline, characteristic of dimeric complexes in which the aromatic ligands are held in proximity to one another.[20,26] In addition, an NOE between H-1 and H-11′ was observed, indicating that the two ligand planes are held in proximity relative to one another in solution. Possible aggregation of resting state **14** in solution to form higher order aggregates was excluded by linear concentration-dependent UV−vis spectra of **14** (up to 0.3 mM).[27] On the basis of these data, the structure of **14** in solution resembles the dinuclear solid-state structure.

Dinuclear palladium complexes can exist as an equilibrium mixture of mono- and dinuclear complexes in the presence of nitrogenous ligands due to *N*-coordination to the metal center.[28] It has been postulated that, in the presence of arylpyridine derivatives, Pd should be sequestered in mononuclear complexes.[21] We have examined the potential monomer−dimer equilibrium of succinate-bridged complex **14** and have experimentally shown that dinuclear palladium complex **14** is favored over mononuclear complex **15**, derived from *N*-coordination of pyridine at elevated temperatures (eq 5). Examination of the equilibrium between **14** and the corresponding pyridine-ligated mononuclear complex (**15**; for X-ray, see Supporting Information) as a function of temperature revealed that dimer formation, with concurrent expulsion of 2 equiv of nitrogenous ligand is entropically favored ($\Delta S = -34.3$ cal·mol^{-1}·K^{-1}) relative to related monomeric complexes (eq 5).



(5)

Rate Law for Chlorination of Benzo[*h*]quinoline Catalyzed by 14. Resting state **14** is a *chemically* competent catalyst for the chlorination of benzo[*h*]quinoline with NCS; chlorination proceeds in 84% isolated yield with 5 mol % **14**. Resting state **14** is not a *kinetically* competent catalyst for the reaction shown in eq 3; when isolated complex **14** is used as catalyst, the rate of chlorination was approximately 1/4 the rate of chlorination when Pd(OAc)$_2$ was employed as catalyst.

When isolated and purified resting state **14** is employed as catalyst, acetate ions, which are generated by acetate-for-

---

(23) (a) Fahey, D. R. *Chem. Commun.* **1970**, 417. (b) Fahey, D. R. *J. Organomet. Chem.* **1971**, *27*, 283–292.

(24) By ^{1}H NMR, resting state **14** is the exclusive Pd-containing compound present during the chlorination of benzo[*h*]quinoline. As the NCS employed is not contaminated by succinimide (^{1}H NMR) and the resting state is formed prior to the observation of any C−Cl bond formation, the succinimide content of the resting state comes neither from an impurity nor from succinimide produced during the first catalyst turnover of chlorination. Currently, the mechanism of formation of resting state **14** from benzo[*h*]quinoline, Pd(OAc)$_2$, and NCS is not known.

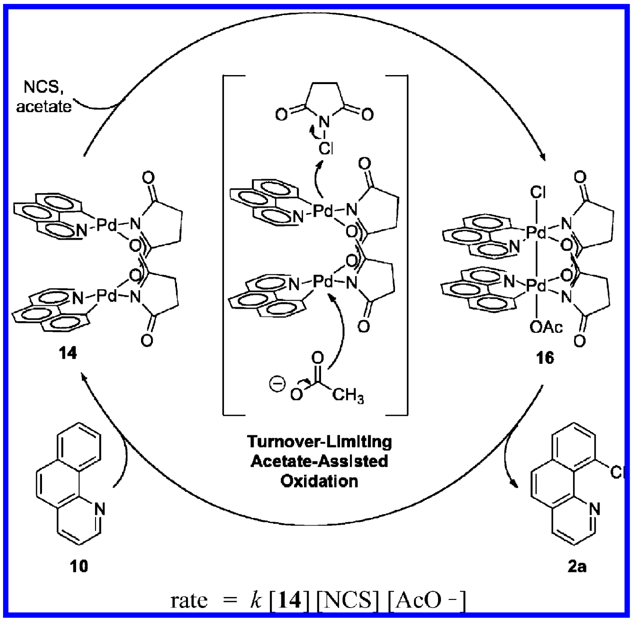
(25) (a) Serrano, J. L.; García, L.; Pérez, J.; Pérez, E.; Vives, J.; Sánchez, G.; López, G.; Molins, E.; Orpen, A. G. *Polyhedron* **2002**, *21*, 1589–1596. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; Sánchez, G.; López, G.; Serrano, J. L.; García, L.; Pérez, J.; Pérez, E. *J. Chem. Soc., Dalton Trans.* **2004**, 3970–3981. (c) Crawforth, C. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Serrano, J. L.; Taylor, R. J. K.; Sánchez, G. *Adv. Synth. Catal.* **2006**, *348*, 405–412.

(26) Navarro-Ranninger, C.; Zamora, F.; Martínez-Cruz, L. A.; Isea, R.; Masaguer, J. R. *J. Organomet. Chem.* **1996**, *518*, 29–36.

(27) (a) Jennette, K. W.; Gill, J. T.; Sadownick, J. A.; Lippard, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 6159–6168. (b) Bailey, J. A.; Hill, M. G.; Marsh, R. E.; Miskowski, V. M.; Schaefer, W. P.; Gray, H. B. *Inorg. Chem.* **1995**, *34*, 4591–4599. (c) Yam, V. W.-W.; Yu, K.-L.; Cheung, K.-K. *J. Chem. Soc., Dalton Trans.* **1999**, 2913–2915. (d) Wong, K. M.-C.; Zhu, N.; Yam, V. W.-W. *Chem. Commun.* **2006**, 3441–3443. (e) Lo, L. T.-L.; Ng, C.-O.; Feng, H.; Ko, C.-C. *Organometallics* **2009**, *28*, 3597–3600.

(28) (a) Powell, J. *J. Chem. Soc. A* **1971**, 2233–2239. (b) Powell, J.; Jack, T. *Inorg. Chem.* **1972**, *11*, 1039–1048. (c) Jack, T. R.; Powell, J. *Can. J. Chem.* **1975**, *53*, 2558–2574. (d) Ryabov, A. D. *Inorg. Chem.* **1987**, *26*, 1252–1260.

Scheme 4. Proposed Acetate-Assisted Bimetallic Oxidation of **14** Would Afford Dinuclear Pd(III) Complex **16** Immediately Following Oxidation[a]



[a] Oxidation of the dinuclear core of **14** removes the two electrons in the Pd−Pd σ* orbital (HOMO), and thus results in Pd−Pd bond formation.

succinate exchange during catalysis, are not present in the reaction mixture. We postulated that resting state **14** by itself is kinetically incompetent due to potential acetate ion cocatalysis when $Pd(OAc)_2$ is used as catalyst. This hypothesis was confirmed by observation of rate enhancements upon addition of either AcOH or acetate ions ($n Bu_4NOAc$) to the reaction mixture. In the presence of 4.0 equiv of acetic acid with respect to **14**, as is liberated during self-assembly of **14** from $Pd(OAc)_2$ during catalysis, resting state **14** is a kinetically competent catalyst. Examination of the initial rates of chlorination as a function of added acetic acid (or nBu_4NOAc) concentration revealed that chlorination is first order dependent on [AcO^-].

The reaction orders of both oxidant and Pd complex **14** were measured under pseudo-first-order conditions with respect to AcOH. The rate of chlorination is first-order dependent on NCS, consistent with rate-determining oxidation. The rate of chlorination is also first-order dependent on the concentration of dinuclear resting state **14**, consistent with rate-determining oxidation of dinuclear **14** by NCS. The rate of chlorination is zeroth-order in benzo[*h*]quinoline as well as in succinimide, which is generated as a stoichiometric byproduct of oxidation. Hence, identification of the previously unanticipated succinate-bridged dinuclear Pd resting state enabled the determination of a simple rate equation: rate = k [**14**][NCS][AcO^-]. On the basis of the rigid dinuclear structure of the resting state and the measured first-order rate dependence on resting state **14**, acetate, and NCS, we propose turnover-limiting bimetallic oxidation of **14** with nucleophilic assistance[29] by acetate (Scheme 4). An analogous resting state and rate equation was found for chlorination of 2-phenylpyridine (**3**) (see Supporting Information).

In our initial report regarding the mechanism of $Pd(OAc)_2$-catalyzed C−H chlorination of benzo[*h*]quinoline (**10**), we reported a reaction order of 1.5 with respect to $Pd(OAc)_2$.[17a] We interpreted this reaction order as consistent with a catalyst resting state comprised of mono- and dinuclear palladium complexes,[28] and a dinuclear transition state. While the data was correct, our results presented here show that interpretation of a measured reaction order of $Pd(OAc)_2$ could not lead to elucidation of the mechanism: By changing the concentration of $Pd(OAc)_2$, we simultaneously varied both [Pd] and [AcO^-] and therefore unknowingly changed the concentrations of two components appearing in the rate law.

Participation of **14**, NCS, and acetate during oxidation implies the electronic participation of both metal centers during oxidation (Scheme 4). Whether concerted, simultaneous interaction of acetate ions and NCS with **14**, or pre-equilibrium association of acetate with **14** followed by oxidation, two metal coordination sites are required in order for **14** to interact with both NCS and acetate. In dinuclear Pd(II) complex **14**, one vacant apical coordination site is accessible on each metal. Similar nucleophile-assisted oxidation has been observed during the protonation of Pt(II)−alkyl complexes and has been suggested as evidence for metal-based oxidation as opposed to direct electrophilic M−C bond cleavage.[30]

Previously, we have shown the kinetic advantage of bimetallic reductive elimination over monometallic reductive elimination in related dinuclear Pd(III) complexes.[22] Redox cooperativity between the two metals can reduce the activation barrier to reductive elimination. Our results presented here suggest that bimetallic oxidative addition, the rate-determining step in Pd-catalyzed chlorination with NCS, is also favored over potential monometallic oxidation of a Pd(II) complex to a Pd(IV) complex.

Succinate-Bridged Pd(III) Complexes. Our data implicate acetate-assisted oxidation of dinuclear Pd(II) resting state **14** in rate-determining oxidation. On the basis of the rate law, we propose dinuclear Pd(III) complex **16** as the immediate product of oxidation. Because oxidation is rate determining, we cannot directly observe **16** during catalysis. Resting state **14** is the only observable Pd-containing complex during catalysis.

Because we suggest complex **16** to be on the catalysis cycle, we sought to interrogate whether **16** is a chemically competent intermediate for the chlorination of **10**. Complex **16**, which features one apical acetate ligand and one apical chloride ligand, could potentially participate in either C−Cl or C−O bond formation. Oxidation of Pd(II) complex **14** with acetyl hypochlorite[31] at −78 °C afforded thermally sensitive complex **16**, which could be observed by ^1H NMR spectroscopy at −90 °C (Scheme 5). Warming complex **16** to 23 °C in the presence of 20 equiv of pyridine[32] afforded **2a**, the product of C−Cl bond formation in 84% yield. Compound **2b**, the product of competing C−O reductive elimination, was formed in 0.5% yield (Scheme 5).

The observed predominant, but not exclusive, formation of **2a** from Pd(III) complex **16** is consistent with the product

---

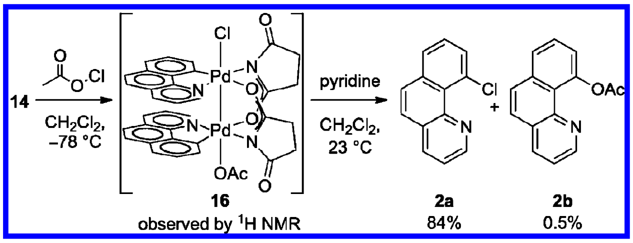
[29] Umakoshi, K.; Ichimura, A.; Kinoshita, I.; Ooi, S. *Inorg. Chem.* **1990**, *29*, 4005–4010.

[30] (a) Belluco, U.; Giustiniani, M.; Graziani, M. *J. Am. Chem. Soc.* **1967**, *89*, 6494–6500. (b) Uguagliati, P.; Michelin, R. A.; Belluco, U. *J. Organomet. Chem.* **1979**, *169*, 115–122. (c) Alibrandi, G.; Minniti, D.; Romeo, R.; Uguagliati, P.; Calligaro, L.; Belluco, U.; Crociani, B. *Inorg. Chim. Acta* **1985**, *100*, 107–113.

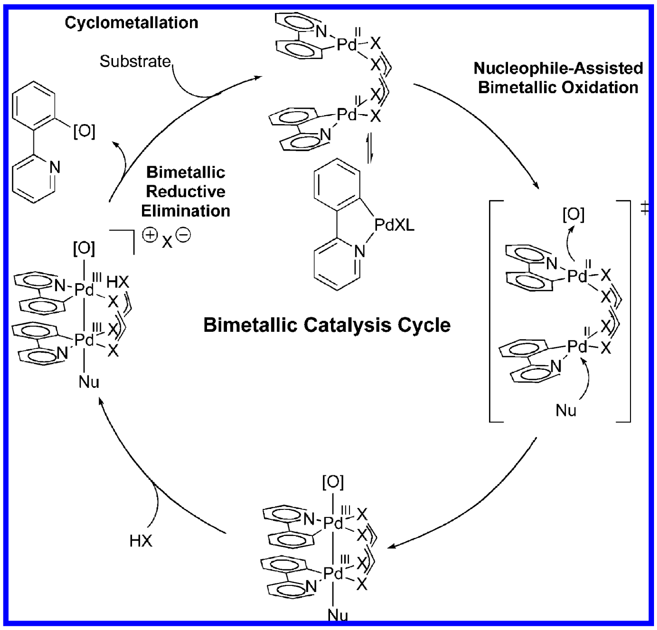
[31] Evans, J. C.; Lo, G. Y.-S.; Chang, Y.-L. *Spectrochim. Acta* **1965**, *21*, 973–979.

[32] Pyridine is added to the reaction mixture because, during examinination of stoichiometric reductive elimination from dinuclear Pd(III) complexes (ref 17), we discovered that a nitrogenous ligand can participate in reductive elimination from dinuclear Pd(III) complexes. Excess nitrogenous ligand is present during catalysis, and thus, the addition of pyridine mimics conditions under which catalysis proceeds.

Scheme 5. Oxidation of **14** and Subsequent Reductive Elimination from Dinuclear Pd(III) Complex **16**



Scheme 6. Proposed $Pd(II)_2/Pd(III)_2$ Catalysis Cycle[a]



[a] All reactions studied to date, in which oxidation is likely turnover limiting, proceed via dinuclear intermediates.

selectivity during catalysis. Examination of the product mixture of $Pd(OAc)_2$-catalyzed chlorination of benzo[*h*]quinoline (eq 3) by mass spectrometry revealed formation of **2b**, the product of C−O bond formation in 0.5% yield, in addition to **2a** (90% yield).[33] The similarity of product distributions during catalysis and from **16** is consistent with the presence of complex **16** immediately following oxidation during catalysis. Chemoselective reductive elimination, as shown for the preferential formation of **2a** over **2b**, is currently not understood but may be a result of differing propensities of chloride and acetate to dissociate from Pd.

The results reported here support our proposed catalysis cycle for oxidative aromatic C−H functionalization shown in Scheme 6. Following C−H metalation, nucleophile-assisted bimetallic oxidation affords a dinuclear Pd(III) complex. Previously, we have found that acid (for example acetic acid) which is both formed during catalysis by C−H palladation and also often used as reaction solvent, can catalyze reductive elimination from dinuclear Pd(III) complexes.[22] Such acid-catalyzed, bimetallic reductive elimination would generate the observed organic products of catalysis as well as regenerate Pd(II).

Herein, we have been able to correlate relevant structural data of dinuclear Pd intermediates with reaction kinetics, measured during catalysis. Our previous work could provide structural information of dinuclear Pd(III) complexes but could not identify the structures in catalysis.[17] Previous work by Sanford implied dinuclear transition states in Pd-catalyzed oxidative C−C bond formation but could not identify the structure of potential high-valent intermediates; both Pd(III) and Pd(IV) were proposed.[18] While our results were obtained during the study of the chlorination of benzo[*h*]quinoline, they may be relevant to a variety of other C−H oxidation reactions.[4,5] Although experimentation regarding the specific mechanism of individual Pd-catalyzed oxidation reactions is needed, we suggest that mechanisms based on bimetallic Pd(III) chemistry are more common for $Pd(OAc)_2$-catalyzed aromatic C−H oxidation reactions than previously anticipated.

Conclusions

Discussion of high-valent palladium intermediates in Pd-catalyzed aromatic C−H oxidation has been based predominantly on observation of stoichiometric organometallic reactions from isolated model complexes. General consensus regarding the relevance of Pd(II)/Pd(IV) catalysis cycles for aromatic C−H oxidation is evidenced by the frequency with which this proposal is invoked. While evaluation of reductive elimination from Pd(IV) model complexes has allowed the study of the mechanism of reductive elimination from organometallic Pd(IV) complexes, the relevance of the invoked model complexes to catalysis has not yet been established.

We present results that implicate bimetallic oxidation of a dinuclear catalyst resting state to a dinuclear Pd(III) complex during $Pd(OAc)_2$-catalyzed chlorination of benzo[*h*]quinoline. The catalyst resting state has been identified as a succinate-bridged dinuclear Pd(II) complex (**14**), which self-assembles during catalysis. Interpretation of the reaction order of palladium, NCS, and acetate ions, liberated during self-assembly of the catalyst resting state, has revealed unanticipated cocatalysis by acetate ions during rate-limiting bimetallic oxidative addition. Previously, we have shown by experiment and computation that bimetallic redox participation during reductive elimination lowers the energy barrier to reductive elimination.[22] Here, we propose that bimetallic oxidation with simultaneous redox participation of two metals is operative during catalysis. Metal−metal cooperation lowers the activation barrier for both oxidative addition and reductive elimination and favors a $Pd(II)_2/Pd(III)_2$ catalysis cycle for Pd-catalyzed aromatic C−H oxidations.

Historically, analysis of mechanisms of Pd-catalyzed transformations has been dominated by discussion of either Pd(0)/Pd(II) or Pd(II)/Pd(IV) redox cycles. While, in some instances, the intermediacy of discrete monometallic Pd(IV) complexes seems likely,[5bb,34] this should not be the default mechanistic assumption in reactions in which substrate and oxidant are combined with Pd(II) catalysts. Reaction mechanisms involving either redox chemistry at more than one metal center or reactions which proceed without the intermediacy of high-valent palladium are often underappreciated. Based on the similarity of the conditions employed for C−H chlorination with the conditions employed in several Pd-catalyzed oxidative transformations,[5,6] metal−metal cooperation may be much more widespread in catalysis than generally appreciated.

---

(33) The observation of C−O bond formation during C−H chlorination was noted in ref 21.

(34) (a) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1988**, *346*, C27–C30. For discussion of the proposed role of Pd(IV), see (b) Cárdenas, D. J.; Martín-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033–5040. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.

Bimetallic catalysis with metal−metal cooperation is conceptually distinct from Pd(II)/(IV) pathways because cooperative metal−metal redox interaction can lower activation barriers in oxidative palladium catalysis for both oxidative addition and reductive elimination. We anticipate that the mechanism proposed herein will inspire further study to probe the generality of bimetallic redox chemistry in catalysis as well as to allow rational design and development of synthetically viable methods of oxidation chemistry that previously have not been accomplished.

Acknowledgment. We thank the NSF (CHE-0952753) and the NIH-NIGMS (GM088237) for financial support, Dr. Shao-Liang Zheng and Michael Campbell for X-ray crystallographic analysis, and Sanofi Aventis for a graduate fellowship for D.C.P.

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

JA1054274