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Citation

Powers, David C., Matthias A. L. Geibel, Johannes E. M. N. Klein, and Tobias Ritter. 2009. Bimetallic palladium catalysis: Direct observation of Pd(III)–Pd(III) intermediates. *Journal of the American Chemical Society* 131(47): 17050–17051.

Published version

<https://doi.org/10.1021/ja906935c>

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Bimetallic Palladium Catalysis: Direct Observation of Pd(III)–Pd(III) Intermediates

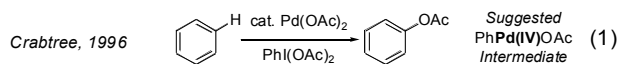
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Pd(II)/Pd(IV) redox cycles have been proposed for a variety of palladium-catalyzed transformations since 1971.^{1,2} In 2009, bimetallic Pd(III) intermediates were put forth as a mechanistic alternative to the frequently invoked Pd(II)/Pd(IV) redox cycles.³ Our account disclosed previously unrecognized reactions from organometallic Pd(III) complexes, but did not provide evidence for the generality of bimetallic Pd(III) intermediates in catalysis. Here we report the first direct observation of bimetallic Pd(III) complexes in C–H acetoxylation reactions. The Pd(III) intermediates are obtained by oxidation of Pd(II) catalysts with one of the most common oxidants for oxidative palladium catalysis—PhI(OAc)₂. Our results demonstrate that bimetallic Pd(III) complexes should be considered as relevant reaction intermediates in a class of Pd-catalyzed reactions previously suggested to proceed via Pd(II)/Pd(IV) redox cycles.²

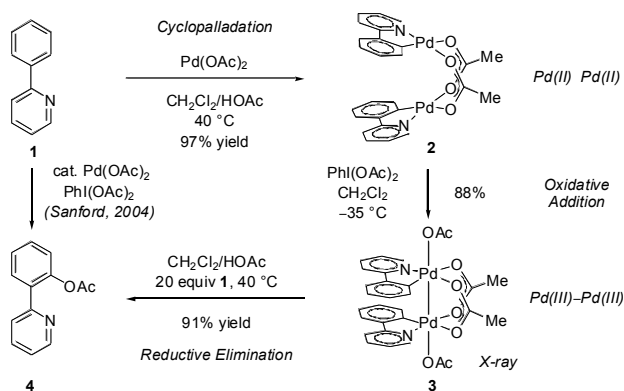
Pd-catalyzed aromatic C–H acetoxylation was first reported in 1966.⁴ In acetic acid, oxidants such as K₂Cr₂O₇, Pb(OAc)₄, and N₂O₂ oxidize benzene to phenyl acetate under Pd catalysis.⁵ Stock proposed a Pd(II)/Pd(IV) mechanism for this class of reactions in 1981.⁶ Crabtree reported the first Pd(OAc)₂-catalyzed acetoxylation of arenes with the terminal oxidant PhI(OAc)₂ (eq 1).⁷ Since 2004, Sanford⁸ and Yu⁹ have pioneered practical, directed C–H acetoxylation reactions that also employ Pd(OAc)₂ as catalyst. Reductive elimination from well-defined Pd(IV) complexes, shown for C–C bond formation by Canty¹⁰ and for C–O bond formation by Sanford,¹¹ has been observed. However, the relevance of Pd(IV) complexes to Pd-catalyzed acetoxylation has not been established.



While several bimetallic complexes of Pt(III) have been reported,¹² only few organometallic Pd(III) complexes have been described: five paddlewheel complexes by Cotton and Lahuerta,¹³ and five carboxylate-bridged bimetallic complexes by us.³ We have shown that reductive elimination from bimetallic Pd(III) complexes can form carbon–heteroatom bonds, and implicated bimetallic palladium complexes in catalysis through kinetic analysis. However, when oxidants such as NCS were employed, proposed bimetallic Pd(III) complexes were not observed during catalysis. To evaluate the potential generality of bimetallic Pd(III) complexes as intermediates in catalysis, we studied the oxidation of Pd(II) catalysts with PhI(OAc)₂, one of the most common oxidants for Pd-catalyzed C–H bond functionalizations.²

Cyclopalladation, first reported by Cope in 1965,¹⁴ of 2-phenylpyridine (**1**) with Pd(OAc)₂, afforded the bimetallic Pd(II) complex **2**, in which the two palladium nuclei are held in proximity by bridging acetate ligands (Scheme 1). When bimetallic Pd(II) complex **2** was treated with PhI(OAc)₂ at

Scheme 1. Discrete Bimetallic Pd(III) Intermediate in Acetoxylation.



–35 °C, the thermally sensitive bimetallic Pd(III) complex **3** was observed, and could be isolated in 88% yield. Complex **3** is stable in solution and in the solid state below –10 °C and was characterized crystallographically (Figure 1).

Bimetallic **3** is not the catalyst resting state and cannot be observed during catalysis. However, we observed the formation and reaction of **3** under pseudocatalytic conditions by sequential addition of reagents at controlled temperatures. We treated Pd(OAc)₂ with excess substrate **1** and observed the dimer **2** in the presence of five equivalents of **1**.¹⁵ Subsequent addition of five equivalents PhI(OAc)₂ at –10 °C afforded the Pd(III) dimer **3** in 66% yield.¹⁶ Upon warming the purified intermediate **3** in the presence of 20 equiv of substrate **1** to 40 °C, bimetallic reductive elimination occurred to afford product **4** in 91% yield. Reductive elimination from **3** in the absence of **1** afforded product **4** in only 6% yield. Likewise, the Pd(OAc)₂-catalyzed reaction **1** → **4** with 100 mol% Pd did not afford **4** upon heating at 80 °C for 12 h. Both results suggest the consumption of product **4** by Pd after reductive elimination.¹⁷

After reductive elimination from **3** in the presence of **1**, the bimetallic Pd(II) complex **2** was observed by ¹H NMR. Reductive elimination by first order kinetics in bimetallic Pd(III) complex was established by following product formation from a methylated analog of **3** for accurate ¹H NMR integration. All reactions shown in Scheme 1 can be carried out in CH₂Cl₂ or AcOH or a mixture thereof. The isolation of **3**, however, required addition of CH₂Cl₂ because **3** was not stable at the freezing point of AcOH (17 °C) or above. Observation of both oxidation of **2** with PhI(OAc)₂ and reductive elimination from **3** to **4** is consistent with the participation of bimetallic Pd(III) intermediates in the Pd-catalyzed C–H functionalization of arenes with the oxidant PhI(OAc)₂.

Discrete monometallic Pd(IV) complexes such as **5** (Figure 1) have been considered as models for the high-valent palladium complexes, from which C–O reductive elimination could occur during catalysis.^{11b} We measured the initial rate of the reaction

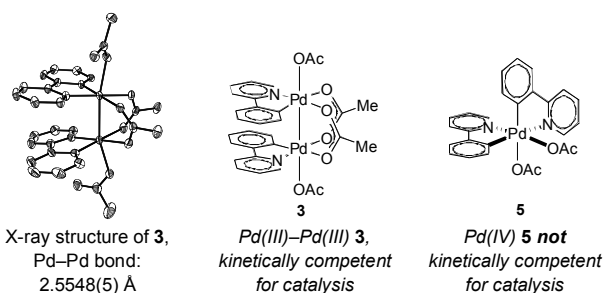
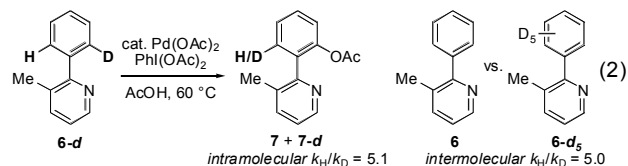


Figure 1. ORTEP diagram of Pd(III) **3** with ellipsoids drawn at 50% probability level; kinetic competence of **3** and **5**.

from **1** to **4** (shown on the left of Scheme 1) catalyzed by 8 mol% Pd(OAc)₂, 8 mol% monometallic Pd(IV) **5**, and 4 mol% bimetallic Pd(III) **3**, respectively. The initial rate of product formation with catalyst **5** was half as fast as the initial rate with Pd(OAc)₂ as catalyst. Therefore, the Pd(IV) complex **5** is not kinetically competent for catalysis. The initial rate of product formation with bimetallic Pd(III) complex **3** is faster than the rate observed with Pd(OAc)₂, which demonstrates that **3** is kinetically competent for catalysis. Observation and kinetic competence of **3**, as well as the kinetic incompetence of **5**, cannot exclude the potential transient intermediacy of Pd(IV) complexes other than **5**. For example, our data cannot rule out the formation and relevance to catalysis of monoaryl Pd(IV) complexes.



Kinetic analysis under conditions of catalysis, isolation of both **2** and **3**, as well as the independent observation of all three fundamental reactions—bimetallic oxidative addition, bimetallic reductive elimination, and cyclometallation—is consistent with the proposed catalytic cycle shown in Figure 2. Measurement of the initial rate of acetoxylation as a function of PhI(OAc)₂ concentration showed a zero order kinetic dependence in oxidant, which precludes rate-determining oxidation. Observation of an intramolecular primary kinetic isotope effect of $k_{\text{H}}/k_{\text{D}} = 5.1$ and an intermolecular primary isotope effect of $k_{\text{H}}/k_{\text{D}} = 5.0$ is consistent with rate-determining cyclopalladation.¹⁸ The isotope effects were determined by acetoxylation of substrate **6-d** and by competing acetoxylation between **6** and **6-d**₅ (eq 2, see Supporting Information). Rate-determining cyclometallation precludes the kinetic implication of bimetallic Pd complexes during oxidation and reductive elimination; however, bimetallic palladium complexes were implicated in the rate-determining step of related C–H oxidations with weaker oxidants than PhI(OAc)₂, in which case cyclopalladation is not rate-determining.^{3,19}

In conclusion, our report discloses the first evidence of bimetallic Pd(III) intermediates in Pd-catalyzed acetoxylation. Based on this evidence and our previous kinetic implication of a bimetallic Pd complex in the rate-determining step of C–H functionalization with NCS, we propose that bimetallic Pd(III) complexes are responsible for a large class of C–H oxidations, previously proposed to proceed via Pd(II)/Pd(IV) redox cycles.

Acknowledgement. We thank Peter Müller for X-ray crystallographic analysis and Sanofi-Aventis for a graduate fellowship for DCP.

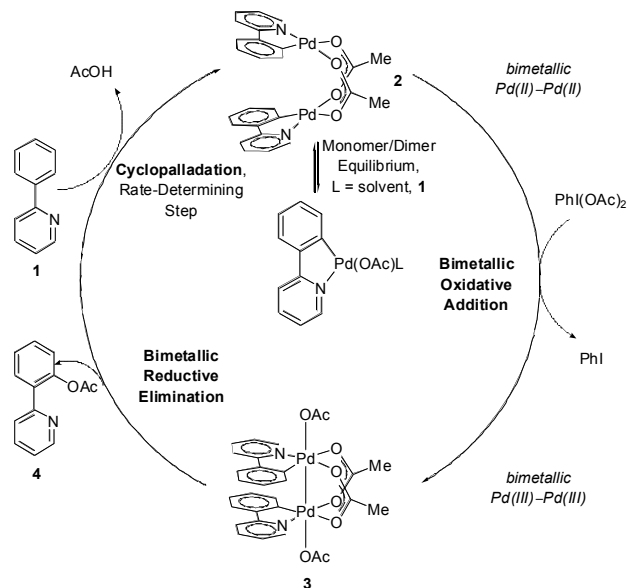
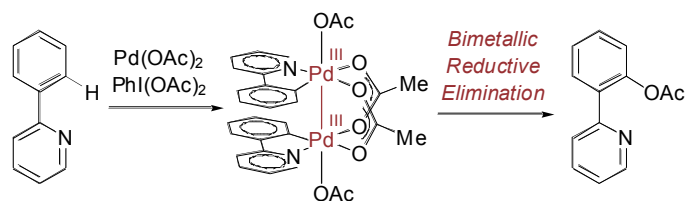


Figure 2. Proposed bimetallic Pd(II)/Pd(III) catalytic cycle.

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>.

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- [17] Acetoxylation of **1** with PhI(OAc)₂ with 100 mol% Pd(OAc)₂ proceeded in 0% yield. The yield of **4** increased when 50 mol% Pd(OAc)₂ was used. The yield of **4** from **3** in the absence of **1** could be increased from 6% to 82% by addition of 20 equiv of pyridine prior to reductive elimination. For details, see Supporting Information.
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$\text{PhI}(\text{OAc})_2$ is a common oxidant for Pd-catalyzed C–H bond functionalizations. Mechanistic hypotheses since the 1960's have suggested a $\text{Pd}(\text{II})/\text{Pd}(\text{IV})$ mechanism. Here we present evidence for the relevance of bimetallic $\text{Pd}(\text{III})$ complexes to catalysis. A bimetallic $\text{Pd}(\text{III})$ acetate was isolated and can afford product by bimetallic reductive elimination.
