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## Chelating N-Heterocyclic Carbene Alkoxide as a Supporting Ligand for Pd<sup>II/IV</sup> C-H Bond Functionalization Catalysis\*\*

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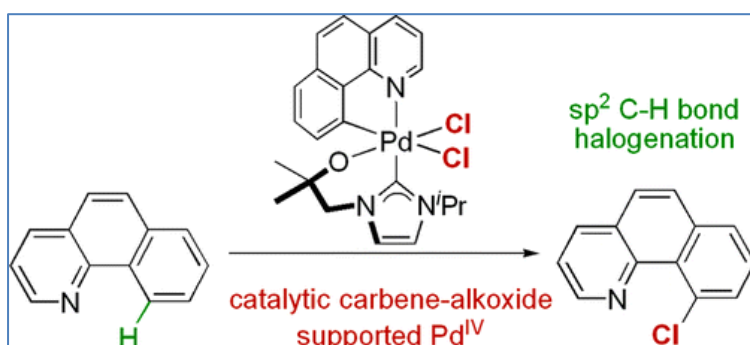
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**Supporting information available:** Full experimental details and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>

**Graphical abstract:**



**Keywords:**

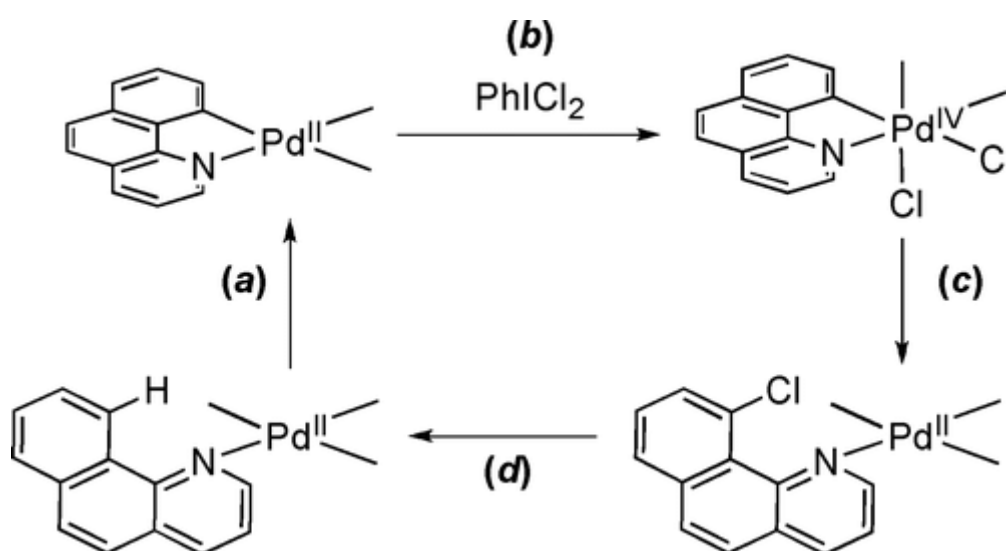
forming reductive elimination; carbon-hydrogen bonds; palladium complexes; alkenes; pd(ii); reactivity; fluoride

## Abstract

A Pd<sup>IV</sup> complex that represents a viable catalytic intermediate in Pd-catalyzed C-H bond halogenation reactions has been isolated and structurally characterized. It contains the first examples of both a Pd<sup>IV</sup> NHC bond and a Pd<sup>IV</sup> alkoxide bond, and serves as a pre-catalyst for C-H bond halogenation. As such, this represents a new class of tunable supporting ligand systems in Pd<sup>IV</sup> catalysis.

## Main text

Palladium(IV) complexes have been proposed as key intermediates in the catalytic ligand-directed functionalization of arene and alkane C-H bonds.<sup>1</sup> The best current methods for CH halogenation reactions of this type employ Pd(OAc)<sub>2</sub> as a catalyst in conjunction with a terminal oxidant such as PhICl<sub>2</sub> or an *N*-halosuccinimide.<sup>2</sup> In the proposed Pd<sup>II</sup>/Pd<sup>IV</sup> cycle for these transformations, ligand-directed C-H activation - step a in Scheme 1 - is followed by oxidation of Pd<sup>II</sup> to Pd<sup>IV</sup> in the presence of a strong oxidant (step b). The resulting Pd<sup>IV</sup> complex can then undergo C-Cl bond-forming reductive elimination (step c) to generate the product. Recently, similar Pd<sup>IV</sup> or closely related dimeric Pd<sup>III</sup> intermediates have been proposed in many different Pd-catalyzed reactions, including C-H functionalizations, aminofunctionalizations of alkenes, the construction of cyclopropanes from enynes, and the arylhalogenation of olefins.<sup>3</sup>



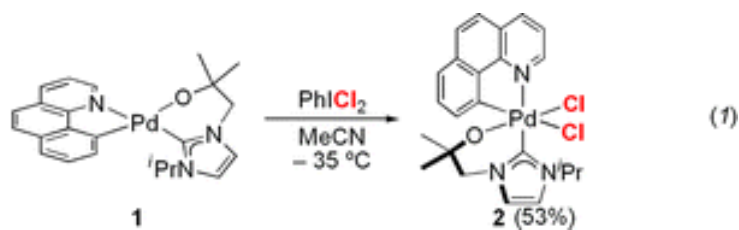
**Scheme 1.** Pd(OAc)<sub>2</sub> catalyzed chlorination of benzo[*h*]quinoline. a) ligand directed C-H activation; b) oxidation of Pd<sup>II</sup> to Pd<sup>IV</sup> by PhICl<sub>2</sub>; c) C-Cl bond-forming reductive elimination; d) ligand exchange.

While Pd<sup>II/IV</sup>-catalyzed processes are efficient and selective for certain classes of substrates, significant challenges remain in this field. In particular, the development of novel catalysts with enhanced activity, broader scope, and chiral ligand environments would be highly desirable. However, catalyst design for this mechanistic manifold has been extremely limited due to the relatively small subset of ancillary ligands (predominantly sp<sup>2</sup> N donors and carboxylates)<sup>4,5</sup> that are known to support high oxidation state Pd<sup>II/IV</sup> centers. This communication describes the first implementation of robust, modular chelating N-heterocyclic carbene ligands for Pd<sup>II/IV</sup> catalyzed processes.

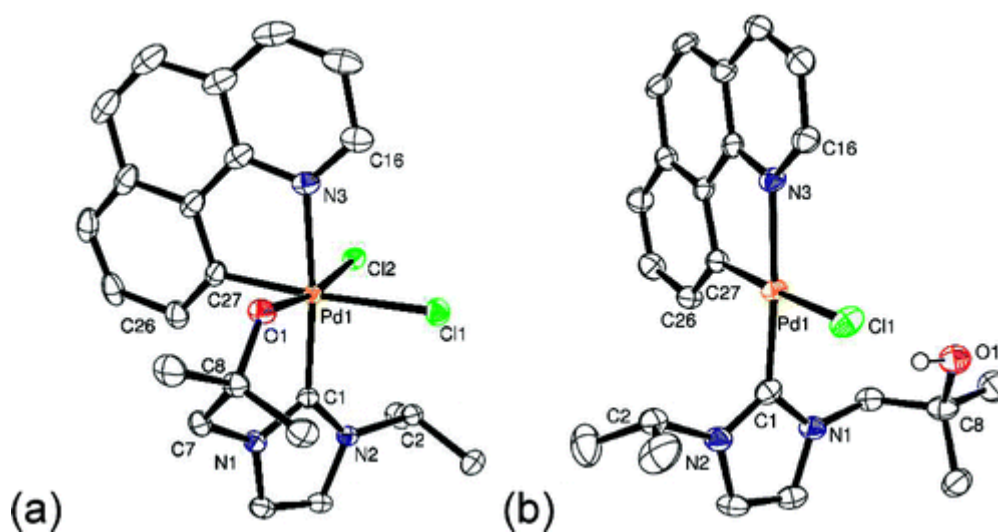
Several key features must be considered in the design of ancillary ligands for these oxidative transformations. First, suitable ligands should be strong  $\sigma$ -donors (it is unlikely that a d<sup>6</sup> Pd<sup>IV</sup> center has orbitals low enough in energy to accept electrons *via*  $\pi$ -donation) and sufficiently bulky and/or chelating to help stabilize the higher palladium oxidation states.<sup>4,5</sup> Second, the ligands must be resistant to decomposition under the highly oxidizing reaction conditions. Third, it is essential that the supporting ligands do not participate in reductive elimination reactions that compete with functionalization of the desired substrate. Finally, the ideal ancillary ligands would be modular, in order to facilitate the design of new catalysts for regio- and stereoselective reactions.<sup>6</sup>

The Arnold group has previously used N-heterocyclic carbene (NHC) ligands functionalized with tethered anionic alkoxy or amido groups to stabilize high oxidation state metal cations.<sup>7</sup> Such ligands are attractive candidates for accessing the target Pd<sup>IV</sup> species because NHC-Pd<sup>II</sup> complexes are known to be stable in acidic reaction media and in the presence of strong oxidants.<sup>8</sup> Based on these considerations, we set out to synthesize Pd<sup>II</sup> complexes containing chelating carbene ligands that could participate in key steps of the catalytic cycle in Scheme 1.

Complex **1** PdL(bzq) (L = OCMe<sub>2</sub>CH<sub>2</sub>(1-C{NCHCHN<sup>t</sup>Pr}); bzq = benzo[*h*]quinoline) (eq. 1) can be envisioned as the product of ligand-directed C-H activation (step a in Scheme 1). Here, it was prepared in 88% yield by treatment of [Pd(bzq)Cl]<sub>2</sub><sup>9a</sup> with KL<sup>9b</sup> in THF at -35 °C. It is an orange solid and has been fully characterized. The metal-bound carbene is evident in the <sup>13</sup>C NMR spectrum from the deshielded resonance at 174.1 ppm.



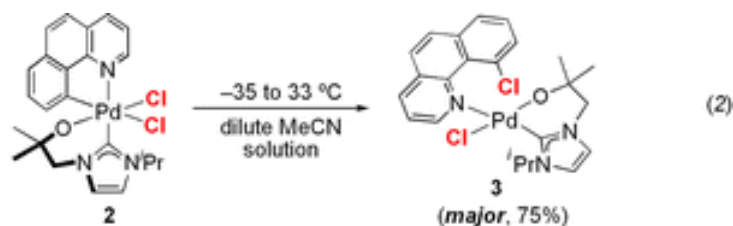
Treatment of **1** with equimolar  $\text{PhICl}_2$  in  $\text{MeCN-}d_3$  at  $-35\text{ }^\circ\text{C}$  results in the oxidative addition of two chloride ligands to the Pd center to give **2** (eq. 1), step b in Scheme 1. Rapid, essentially quantitative formation of **2** can be observed by  $^1\text{H}$  NMR spectroscopy. Complex **2** is stable in the solid state for at least one week and has been fully characterized. The resonance for the proton on C16 (Figure 1a) is shifted to higher frequency (9.80 ppm), and the carbene resonance is now observed at 150.6 ppm in the  $^{13}\text{C}$  NMR spectrum. To the best of our knowledge, **2** is the first  $\text{Pd}^{\text{IV}}$ -NHC and also the first isolated  $\text{Pd}^{\text{IV}}$  alkoxide.



**Figure 1.** Molecular structure of **2** (a) and **4** (b). Ellipsoids drawn at the 50% probability level. Hydrogen atoms except alcohol omitted for clarity. Selected bond lengths ( $\text{\AA}$ ) and angles (deg) **2**: Pd1-C1 1.993(2), Pd1-O1 1.993(1), Pd1-N3 2.105(2), Pd1-C27 2.045(2), Pd1-Cl1 2.464(2), Pd1-Cl2 2.342(1); C27-Pd1-C1-N1 60.4(2); **4**: Pd1-C1 1.981(3), Pd1-N3 2.085(3), Pd1-C27 2.000(3), Pd1-Cl1 2.413(4); C27-Pd1-C1-N1 92.8(2).

Single crystals of **2** suitable for X-ray analysis were grown by diffusion of pentanes into an acetone solution of **2** at  $-35\text{ }^\circ\text{C}$ ; the molecular structure is shown in Figure 1(a). The palladium center in **2** is

approximately octahedral. The Pd–C<sub>carbene</sub> bond is long (1.981(3) Å), and comparison of the Pd–C<sub>aryl</sub>, Pd–O, and Pd–Cl distances with those in a handful of other Pd<sup>IV</sup> complexes suggests that they are also long in **2**,<sup>4,5,10</sup> in accordance with significant steric congestion at the octahedral metal centre. The high frequency chemical shift of the proton on C26 in the <sup>1</sup>H NMR spectrum of **2** (6.12 ppm) as well as nOe interactions between it and the *iso*-propyl and methyl protons on the alkoxy-carbene ligand suggest that the solid state structure is retained in solution.



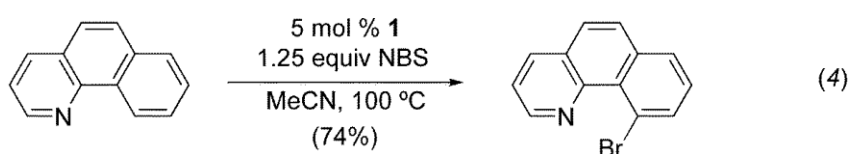
While **2** is stable at –35 °C in acetonitrile and at room temperature in the solid state, we were delighted to find that it undergoes C–Cl bond-forming reductive elimination upon warming in solution. As shown in eq. 2, warming a 5.3 x 10<sup>–4</sup> M solution of **2** in MeCN from –30 to 33 °C over 24 h afforded yellow **3** as the major product in 75% isolated yield. This represents a rare example of directly observable carbon-halogen bond-forming reductive elimination from a Pd<sup>IV</sup> complex.<sup>5</sup> Notably, we did not detect reductive elimination products containing the carbene ligand under any conditions. This is remarkable because many side reactions (*e.g.*, C<sub>carbene</sub>–C<sub>bzq</sub>, C<sub>bzq</sub>–O, or C<sub>carbene</sub>–Cl bond-forming reductive elimination) are possible in this system.



Interestingly, changing the reaction concentration had a significant impact on the products resulting from thermal decomposition of **2**. When the reaction was conducted at a higher concentration (1.1 x 10<sup>–2</sup> M), product **3** was formed as only 46 % of total Pd-containing products, along with equimolar quantities of **4** and a complex assigned as **3'** (eq. 3). The ratio of these two products was readily

determined by integration of the diagnostic  $^1\text{H}$  NMR resonances for the proton vicinal to N3 (9.03 ppm and 9.42 ppm, respectively), and **4** was further characterized by single crystal X-ray analysis; the structure is shown in Figure 1(b). Complex **4** can also be converted back to **1** by the addition of base, for example KHMDS (see SI). The formation of **3'** and **4** suggests that intermolecular decomposition pathways (presumably involving electrophilic aromatic substitution on the bzq ligand and protonolysis of the alkoxide) can be competitive for  $\text{Pd}^{\text{IV}}$  complex **2** under some conditions. This is particularly interesting because intramolecular C–X bond forming reductive elimination from  $\text{Pd}^{\text{IV}}$  has typically been assumed to be fast in such systems.<sup>4,5</sup>

The data presented herein suggests that **L** could be a viable supporting ligand for catalytic halogenation reactions involving  $\text{Pd}^{\text{IV}}$  intermediates. Due to the low thermal stability of  $\text{PhICl}_2$ ,<sup>2</sup> we examined the activity of **1** in directed C–H bromination used *N*-bromosuccinimide as the electrophilic halogenating reagent. We were pleased to find that **1** is an effective pre-catalyst for the bromination of benzo[*h*]quinoline, providing 10-bromobenzo[*h*]quinoline in 74% yield after 48 h at 100 °C in MeCN (eq. 4). Additional arylpyridine derivatives also undergo *ortho*-bromination in good yield with this catalyst and two other  $\text{Pd}^{\text{IV}}$  bromide complexes relevant to the catalytic systems have also been characterized (see SI). Notably, these reactions are slow relative to those catalyzed by  $\text{Pd}(\text{OAc})_2$ , which are complete within 12 h under identical conditions. This is not unexpected since the current system was optimized for the stabilization of  $\text{Pd}^{\text{IV}}$ , and cyclopalladation (typically the rate determining step) is expected to be sluggish at a more electron rich  $\text{Pd}^{\text{II}}$  center.<sup>11</sup> Importantly, at the end of catalytic reactions, no protonated/unbound carbene ligand was observed by  $^1\text{H}$  NMR spectroscopy (see SI for details), suggesting the stability of the Pd–carbene bond to prolonged heating under oxidizing conditions.



In conclusion, this communication describes the synthesis of a new  $\text{Pd}^{\text{IV}}$  complex that undergoes C–Cl bond-forming reductive elimination and serves as an effective pre-catalyst for the selective halogenation of C–H bonds. Complex **2** is, to the best of our knowledge, the first example of a  $\text{Pd}^{\text{IV}}$ -NHC or  $\text{Pd}^{\text{IV}}$ -alkoxide adduct. The complex contains tuneable ligands that appear to be inert to the strongly oxidizing reaction conditions, implying that related systems that can impart regio- or stereocontrol over the C–H functionalization reaction should be accessible. Investigation into the use of the pendant alcohol to facilitate substrate activation, the use of other oxidants, and the design of asymmetric ligand structures is ongoing and will be reported in due course.

## References:

1. (a) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382. (b) Yu, J. Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (d) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A.* **1994**, *108*, 35.
2. With  $\text{PhICl}_2$  and N-halosuccinimides: (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. (b) Kodama, H.; Katsuhira, T.; Nishida, T.; Hino, T.; Tsubata, K. *Chem. Abstr.* **2001**, *135*, 344284. With  $\text{XOAc}$ : Li, J. J.; Giri, R.; Yu, J. Q. *Tetrahedron* **2008**, *64*, 6979.
3. For some recent examples, see: (a) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. (b) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302. (c) Lyons, T. W.; Sanford, M. S. *Tetrahedron* **2009**, *65*, 3211. (d) Muniz, K.; Hovelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (e) Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 2150. (f) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962. (g) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.
4. Canty, A. J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons, Inc.: Hoboken, 2002; Vol. 1, p 189 and references therein.
5. (a) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974. (b) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796. (c) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (d) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.
6. (a) Asymmetric Pd-catalyzed C–H functionalization: Shi, B. F.; Mangel, N.; Zhang, Y. H. Yu, J. Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (b) The first asymmetric  $\text{Pd}^{\text{II/IV}}$ -catalyzed process: Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Am. Chem. Soc.* **2009**, *131*, 3452.
7. (a) Arnold, P. L.; Casely, I. J. *Chem. Rev.* **2009**, doi:10.1021/cr8005203. (b) Arnold, P. L.; Mungur, S. A.; Blake, A. J.; Wilson, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5981.
8. (a) Meyer, D.; Taige, M. A.; Zeller, A.; Hohlfeld, K.; Ahrens, S.; Strassner, T. *Organometallics* **2009**, *28*, 2142 and references therein. (b) Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752.
9. (a) Pugliese, T.; Godbert, N.; Aiello, I.; Ghedini, M.; La Deda, M. *Inorg. Chem. Commun.* **2006**, *9*, 93. (b) Arnold, P. L.; Rodden, M.; Wilson, C. *Chem. Commun.* **2005**, 1743.
10. Canty, A. J.; Patel, J.; Pfeffer, M.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta* **2002**, *327*, 20.
11. For example, see: Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285 and references therein.