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C−H Bond Activation at Palladium(IV) Centers

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Supporting Information

ABSTRACT: This communication describes the first observation and study of C−H activation at a Pd^{IV} center. This transformation was achieved by designing model complexes in which the rate of reductive elimination is slowed relative to that of the desired C−H activation process. Remarkably, the C−H activation reaction can proceed under mild conditions and with complementary site selectivity to analogous transformations at Pd^{II}. These results provide a platform for incorporating this new reaction as a step in catalytic processes.

Over the past decade, high oxidation state palladium catalysis has found increasingly diverse applications in organic synthesis.[1] The development of new transformations in this area has been guided by fundamental studies of Pd^{III} and Pd^{IV} model complexes, which have provided key insights into the unique reactivity and mechanisms accessible at high valent palladium centers.[1,2] To date, these model studies have focused primarily on reductive elimination from Pd^{III} and/or Pd^{IV} species.[1,2] In contrast, the possibility of other organometallic transformations at high oxidation state Pd has not been explored in detail. This is likely due to the assumption that reductive elimination occurs much faster than competing reactions.

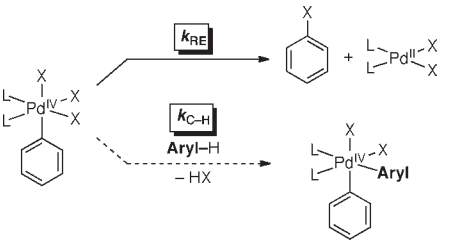
Very recently, several groups have proposed a new reaction, C−H activation at a transient Pd^{IV} intermediate, as a key step in catalysis.[3−7] This novel mode of reactivity has been implicated in four different catalytic contexts: (*i*) C−H oxidative coupling reactions,[3] (*ii*) the carboamination of olefins,[4] (*iii*) the acetoxylation of allylic C−H bonds,[5] and (*iv*) the C−H arylation of naphthalene.[6,7] Remarkably, many of these catalytic reactions proceed under unusually mild conditions[3−5] and/or exhibit unprecedented site selectivities.[3,4,6] These results suggest that harnessing C−H activation at Pd^{IV} could provide opportunities for achieving distinct and complementary reactivity relative to analogous (and much more common) transformations at Pd^{II} centers.

While the reports described above have proposed C−H activation at Pd^{IV} during catalysis, there is currently no literature precedent for such a transformation. As such, we sought to design model systems to demonstrate the viability of this reaction and to probe reactivity and site selectivity in this context.[8,9] This communication demonstrates that, with the appropriate choice of supporting ligands, C−H activation at a Pd^{IV} center can proceed rapidly at room temperature. Furthermore, we show that the site selectivity of this transformation can be dramatically different from that at analogous Pd^{II} complexes. These results provide a platform for incorporating this reaction as a step in new catalytic processes.

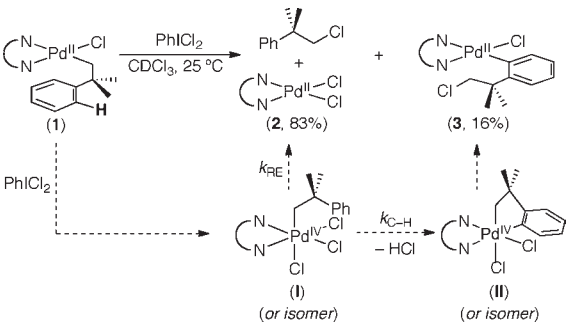
In order to observe and study C−H activation at Pd^{IV}, it is critical to slow competing C−X bond-forming reductive elimination (k_{RE}) while increasing the relative rate of the desired C−H activation process (k_{C-H}) (Scheme 1). On the basis of these considerations, we initiated investigations of oxidatively induced C−H activation at complex **1** (Scheme 2). This Pd^{II} starting material contains a rigid bidentate sp^2 N-donor ligand [2,2′-bis(4-*tert*-butylbipyridine (dtbpy)] and a chloride. Both of these ligands are known to slow reductive elimination (k_{RE}) from high valent Pd intermediates,[11−13] often enabling detection/isolation of Pd^{III} or Pd^{IV} species.[1,2,11−13] In addition, the tethered aryl C−H bond could undergo sp^2 C−H activation to afford a five-membered palladacycle. The intramolecular nature of this C−H cleavage event is expected to increase k_{C-H}.[10]

We first examined the oxidation of **1** with $PhICl_2$, since this reagent is known to react with Pd^{II} starting materials to yield

Scheme 1. Competing Reductive Elimination versus C−H Activation at Pd^{IV}



Scheme 2. Oxidation of 1 with $PhICl_2$: Formation of 2 and 3 (N∼N = dtbpy)



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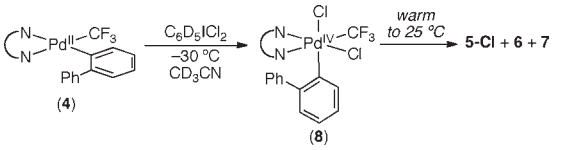
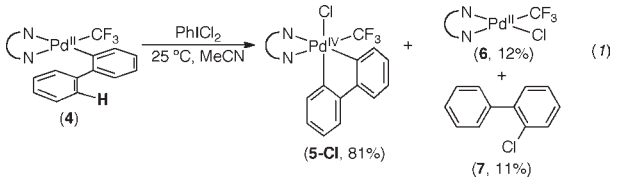
Scheme 3. Low Temperature NMR Study of Reaction of 4 with d_5-$PhICl_2$



isolable Pd^{IV} products.[13] As shown in Scheme 2, the reaction produced two major inorganic compounds: $Pd^{II}Cl_2(dtbpy)$ (**2**, 83% yield) and complex **3** (16% yield). Both **2** and **3** are Pd^{II} species rather than the desired Pd^{IV} products; however, **3** is remarkable in that it contains a σ-aryl rather than a σ-alkyl ligand bound to Pd. We hypothesized that **2** and **3** might be formed from transient Pd^{IV} intermediate **I**, which could undergo competing sp^3-C−Cl bond-forming reductive elimination (to liberate **2**) and C−H activation/sp^3-C−Cl bond formation to generate **3**. While these were promising initial results, complex **3** remained a minor side product under all conditions examined. Additionally, efforts to observe putative Pd^{IV} intermediates **I** and/or **II** were unsuccessful in this system.

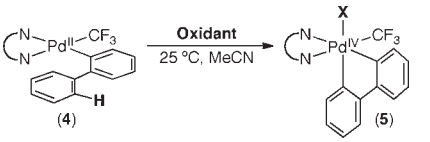
The results in Scheme 2 suggest that k_{RE} is significantly faster than k_{C-H} for intermediate **I**. We reasoned that this problem could be addressed by (1) replacing the chloride with an X-type ligand that is less prone to reductive elimination and (2) limiting the conformational flexibility of the tethered C−H substrate. As such, we next targeted $Pd^{II}(CF_3)(2\text{-}PhC_6H_4)$-(dtbpy) (**4**) as our Pd^{II} starting material. The incorporation of the CF_3 ligand was a particularly important design feature, since several recent reports have shown that $Pd^{IV}(CF_3)$(Aryl) complexes can be stable to reductive elimination at or above room temperature.[14] Complex **4** was prepared in 58% yield by the reaction of $Pd^{II}(I)(2\text{-}PhC_6H_4)$(dtbpy) with CsF/$TMSCF_3$ in THF.

The treatment of **4** with 1 equiv of $PhICl_2$ in MeCN at 25 °C for 35 min resulted in a color change from pale yellow to dark yellow along with the formation of products **5-Cl**, **6**, and **7** in 81%, 12%, and 11% yield as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (eq 1). Complex **5-Cl** was isolated in 77% yield by recrystallization from CH_2Cl_2/Et_2O. Characterization of **5-Cl** by NMR spectroscopy, mass spectrometry, and X-ray crystallography (of a close analogue, *vide infra*) revealed that this is an octahedral Pd^{IV} complex containing a cyclometalated biphenyl ligand. This indicates that the desired C−H activation event has occurred.



In order to gain insights into the mechanism of the C−H activation process, we monitored the reaction of **4** with $C_6D_5ICl_2$ at −30 °C in CD_3CN (Scheme 3). ^{1}H and ^{19}F NMR analysis showed fast consumption of starting material and the formation of transient intermediate **8**.[15] Upon warming to RT, this intermediate decayed over 35 min with first-order kinetics to form mixture of **5-Cl** and **6** (final ratio of **5-Cl**:**6** = 1.0:0.27 under these conditions). Intermediate **8** shows resonances associated with

Table 1. Variation of Oxidant (N∼N = dtbpy)



Entry	Oxidant	X (Product)	Yield (%)
1	$PhICl_2$	Cl (**5-Cl**)	77
2	$PhI(TFA)_2$	TFA (**5-TFA**)	73
3	$PhI(OAc)_2$	OAc (**5-OAc**)	nr[a]
4	NFTPT	OTf (**5-OTf**)	86

[a] No reaction observed after 12 h at 25 °C.

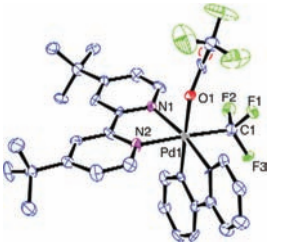


Figure 1. ORTEP plot of **5-TFA**.

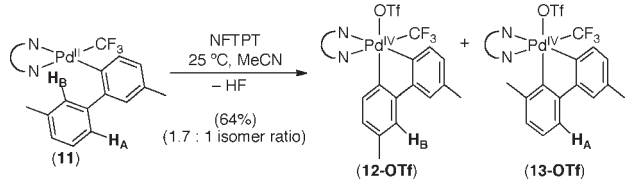
15 aromatic protons, and a ^{1}H−^{1}H COSY allowed assignment of five distinct protons on the pendant phenyl ring.[16] This indicates that the ring is not yet cyclometalated (and also shows that rotation about the aryl−aryl bond is slow on the NMR time scale). ^{19}F−^{13}C HBMC further confirmed that **8** contains a single σ-aryl ligand, as the CF_3 fluorines showed only one correlation with an aromatic carbon. In contrast, two ^{19}F−^{13}C HMBC correlations were observed for the cyclometalated product **5-Cl**. Finally, a DOSY experiment showed that **5-Cl** and **8** have nearly identical diffusion coefficients at −15 °C, indicating that these complexes have similar hydrodynamic radii. This is consistent with the formulation of **8** as a monomeric octahedral complex.

Mass spectrometry experiments provided further insights into the molecular structure of **8**. ESI-MS showed a peak at 631.1312, which corresponds to the mass of $[Pd(CF_3)(2\text{-}PhC_6H_4)(Cl)$-$(dtbpy)]^+$. Notably, electrospray ionization commonly results in loss of one X-type ligand from Pd^{IV} complexes.[2g] For example, ESI-MS of **5-Cl** affords a peak at 595.1560, corresponding to the mass of $[\mathbf{5\text{-}Cl}-Cl]^+$. MALDI, a softer ionization technique, resulted in a peak at 667.1, which corresponds to $[Pd(CF_3)$ $(2\text{-}PhC_6H_4)(Cl)_2(dtbpy)+H]^+$.

All of the NMR and MS data presented above are consistent with formulation of intermediate **8** as a Pd^{IV} complex of general structure $Pd^{IV}(CF_3)(2\text{-}PhC_6H_4)(Cl)_2(dtbpy)$. The diamagnetic nature of this complex clearly indicates that it is not a monomeric Pd^{III} species. The NMR diffusion experiment along with MALDI MS data provide evidence against alternative formulations as a Pd^{III} dimer or a square planar Pd^{II} complex.[17] *Overall, the characterization data are fully consistent with the C−H activation event occurring at Pd^{IV} intermediate* **8**, thereby representing the first demonstration that high oxidation state Pd can mediate this transformation.

We next explored the reaction of **4** with other $2e^-$ oxidants. While no reaction was observed with iodobenzene diacetate

Scheme 4. Site Selectivity of C−H Activation at Pd^{IV}



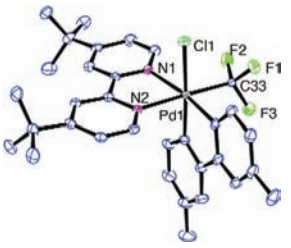
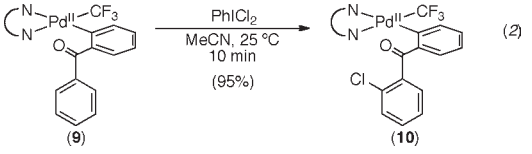


Figure 2. ORTEP plot of **12-Cl**.

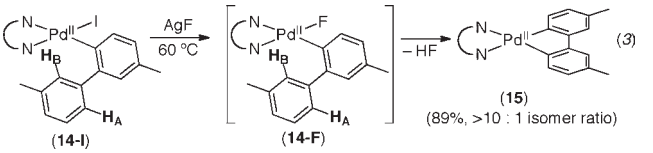
$(PhI(OAc)_2$, Table 1, entry 3),[2g] both iodobenzene bistrifluoroacetate $PhI(TFA)_2$ and *N*-fluoro-2,4,6-trimethylpyridinium triflate (NFTPT)[14] reacted with **4** within 10 min at RT to afford cyclometalated Pd^{IV} complexes where X = trifluoroacetate and triflate (**5-TFA** and **5-OTf**, respectively). The structure of the trifluoroacetate complex was confirmed by X-ray crystallography, and an ORTEP picture of **5-TFA** is shown in Figure 1. Consistent with the solution NMR data, the crystal structure shows an unsymmetrical ligand environment around the octahedral Pd^{IV} center, with the trifluoroacetate group *trans* to one σ-aryl ligand and the trifluoromethyl group *trans* to one N of the dtbpy (Figure 1).

Substrate **9** was also examined in order to probe the accessibility of a six-membered palladacycle (eq 2). In this case, reaction with $PhICl_2$ for 10 min at 25 °C returned the *ortho*-chlorinated Pd^{II} product **10** in 95% yield. This result suggests that a six-membered palladacycle was generated but that the resulting Pd^{IV} intermediate underwent rapid C−Cl bond-forming reductive elimination under the reaction conditions.[18]



Finally, we conducted a series of experiments to compare this C−H activation at Pd^{IV} to analogous transformations at Pd^{II} centers. A σ-aryl ligand derived from 2-iodo-3,5′-dimethyl-1,1′-biphenyl (ligand abbreviated σ-DMB) was used, since it contains two sterically and electronically differentiated sites for C−H activation (H_A and H_B). As shown in Scheme 4, the treatment of σ-DMB complex **11** with NFTPT at RT in MeCN produced a 1.7:1 mixture of two isomeric products **12-OTf** and **13-OTf** in 64% yield.[19,20] While **12-OTf/13-OTf** could not be completely separated, the mixture was characterized using a variety of two-dimensional NMR experiments (see Supporting Information for details). In addition, treatment of **12-OTf/13-OTf** with NaCl afforded the corresponding chloride complexes (**12-Cl/13-Cl**), and the structure of the major isomer was definitively established by X-ray crystallography. As shown in Figure 2, the X-ray structure confirms that **12-Cl** (and by analogy **12-OTf**) is the product of C−H activation at H_A.

For comparison, we examined an analogous cyclopalladation reaction at the Pd^{II} σ-DMB complex **14-F** (eq 3), which was generated *in situ* by the treatment of **14-I** with AgF. Cyclopalladation at **14-F** was sluggish at room temperature and required heating to 60 °C in benzene for 4 h to proceed to completion. Furthermore, this reaction afforded >10:1 selectivity for activation of the less sterically hindered C−H bond (H_A).[21] This selectivity is similar to that observed in numerous other cyclopalladation reactions at Pd^{II} centers but very different from that observed in Scheme 4 (1.7:1).[22] The significant difference in both rate and selectivity for this C−H activation at Pd^{II} versus Pd^{IV} highlights the dissimilarity of these processes and demonstrates the potential value of Pd^{IV}-mediated C−H activation in catalysis.



In summary, this communication describes the first observation and study of C−H activation at Pd^{IV}. This transformation was achieved by designing model complexes in which the rate of reductive elimination is slowed relative to that of the desired competing C−H activation process. Remarkably, the C−H activation reaction can proceed under mild conditions and with different site selectivity than analogous transformations at Pd^{II}. Investigations are underway to elucidate the mechanism of C−H activation at Pd^{IV} and to identify further intra- and intermolecular examples of this new reaction. We anticipate that such studies will ultimately enable the rational incorporation of Pd^{IV}-mediated C−H activation into Pd-catalyzed processes.

■ ASSOCIATED CONTENT

Supporting Information. 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.

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(15) When the reaction was conducted at −30 °C, the initial NMR spectrum showed the presence of intermediate **8** along with some of the C−H activation product **5-Cl** (ratio **8**:**5-Cl** = 3:1). The [**8**] did not change over several hours at −30 °C, and this ratio remained constant over that time. Conversion of **8** to a mixture of **5-Cl** and **6** only occurred when the mixture was warmed. These data suggest that the **5-Cl** formed initially in the −30 °C experiment is generated by a different, heretofore undetected intermediate. See Supporting Information for a detailed discussion.

(16) ^{1}H NMR spectroscopic studies of the oxidation of **4-d_5** (in which the pendant phenyl ring is deuterated) further confirmed the assignment of the five aromatic protons of this ring in intermediate **8**.

(17) A key remaining question is the stereochemistry about the octahedral Pd^{IV} center in **8**. We have conducted several experiments to probe this, and they provide tentative support for the structure shown in Scheme 3. See Supporting Information (p S21) for a detailed discussion.

(18) An alternative possible route to **10** would involve electrophilic chlorination of the aromatic ring similar to that described in ref 12a.

(19) Notably, similar selectivity was reported in ref 3, where cyclopalladation at Pd^{IV} is proposed as a key step in catalysis.

(20) The oxidation of **11** with $PhICl_2$ under otherwise identical conditions provided **12-Cl** as the major product with >10: 1 selectivity. This suggests that site selectivity in C−H activation at Pd^{IV} is highly sensitive to the ligand environment at the metal center. More extensive investigations of ligand effects in this system are ongoing.

(21) Under analogous conditions (benzene, 4 h, 60 °C), the reaction of **11** with NFTPT resulted in the same 1.7:1 ratio as observed in Scheme 4.

(22) For examples, see ref 10 as well as: Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.