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Mechanistic Studies on Direct Arylation of Pyridine *N*-Oxide: Evidence for Cooperative Catalysis between Two Distinct Palladium Centers

Yichen Tan, Fabiola Barrios-Landeros,[‡] and John F. Hartwig*

Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801, United States
Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: Direct arylations of pyridine *N*-oxide (PyO), a convenient method to prepare 2-arylpyridines, catalyzed by $Pd(OAc)_2$ and $PtBu_3$ have been proposed to occur by the generation of a $PtBu_3$-ligated arylpalladium acetate complex, $(PtBu_3)Pd(Ar)(OAc)$ (**1**), and the reaction of this complex with PyO. We provide strong evidence that **1** does not react directly with PyO. Instead, our data imply that the cyclometalated complex $[Pd(OAc)(tBu_2PCMe_2CH_2)]_2$, which is generated from the decomposition of **1**, reacts with PyO and serves as a catalyst for the reaction of PyO with **1**. The reaction of PyO with **1** occurs with an induction period, and the reaction of **1** with excess PyO in the presence of $[Pd(OAc)(tBu_2PCMe_2CH_2)]_2$ is zeroth-order in **1**. Moreover, the rates of reactions of PyO with bromobenzene catalyzed by $[Pd(OAc)(tBu_2PCMe_2CH_2)]_2$ and $[Pd(PtBu_3)_2]$ depend on the concentration of $[Pd(OAc)(tBu_2PCMe_2CH_2)]_2$ but not on the concentration of $[Pd(PtBu_3)_2]$. Finally, the reaction of **1** with a model heteroarylpalladium complex containing a cyclometalated phosphine, $[(PEt_3)Pd(2\text{-benzothienyl})(tBu_2PCMe_2CH_2)]$, rapidly formed the arylated heterocycle. Together, these data imply that the rate-determining C−H bond cleavage occurs between PyO and the cyclometalated $[Pd(OAc)(tBu_2PCMe_2CH_2)]_2$ rather than between PyO and **1**. In this case, the resulting heteroarylpalladium complex transfers the heteroaryl group to **1**, and C−C bond-formation occurs from $(PtBu_3)Pd(Ar)$(2-pyridyl oxide). This mechanism proposed for the direct arylation of PyO constitutes an example of C−H bond functionalization in which C−H activation occurs at one metal center and the activated moiety undergoes functionalization after transfer to a second metal center.

Direct arylation, the reaction of aryl halides with arenes or heteroarenes to form biaryl or aryl-heteroaryl products, is an attractive alternative to traditional cross-coupling because it occurs without the need to prepare organometallic or main-group reagents.[1] For example, the direct arylation of pyridine *N*-oxide (PyO) with aryl halides,[2] the subject of the mechanistic studies in this paper, leads to the selective formation of 2-arylpyridine derivatives after reduction to the pyridine. This sequence occurs without 2-pyridyl organometallic reagents, which are often unstable and difficult to synthesize. The scope of direct arylation has broadened to encompass various heteroarenes,[3] arenes with directing groups,[4] electron-deficient arenes,[5] and even simple arenes such as benzene[6] as coupling partners.

However, little experimental information on the mechanism of direct arylations is available, especially on the mechanism by which the aryl or heteroaryl C−H bond is cleaved. Phosphine-ligated arylpalladium carboxylate complexes $LPd(Ar)(OC(O)R)$ are typically proposed to react with heteroarenes or arenes to form biarylpalladium complexes through a concerted metalation−deprotonation pathway,[7] but we recently reported that a "ligandless" species is involved in the direct arylation of benzene,[8] not the proposed phosphine-ligated complex.

In contrast, DFT calculations suggested that phosphine-ligated arylpalladium acetates are competent to undergo C−H bond cleavage with various heteroarenes, including PyO's.[7c] A recent experimental study showed that the reaction of isolated $(PtBu_3)Pd(Ph)(OAc)$ with 4-nitro-PyO formed the arylated product, but the yield of this reaction (48%) was lower than that for the analogous catalytic process.[9] Thus, the detailed mechanism of the cleavage of the aromatic C−H bonds in the direct arylation of PyO's remains uncertain.

We report the synthesis and full characterization of the $PtBu_3$-ligated arylpalladium acetate complex $(PtBu_3)Pd(Ar)(OAc)$ (**1**)[10] and detailed mechanistic studies of the direct arylation of PyO with this isolated complex. Inconsistent with previous proposals, the direct reaction of isolated **1** with PyO does not form arylated products. Instead, the cyclometalated complex $[Pd(OAc)(tBu_2PCMe_2CH_2)]_2$ generated via decomposition of **1** catalyzes the reaction between **1** and PyO to form the arylated product. Our data imply that this cyclometalated complex directly reacts with PyO to cleave the aromatic C−H bond. Thus, our data imply that this reaction occurs by a cooperative C−H bond functionalization process in which one metal fragment cleaves the C−H bond and a second fragment functionalizes the moiety resulting from this C−H bond cleavage event.

The synthesis of **1** is outlined in Scheme 1. The reaction of $Pd(PtBu_3)_2$ with 3-(fluoromethyl)phenyl iodide in the presence of AgOAc formed **1** in acceptable yield for our studies. Complex **1** was characterized by elemental analysis and NMR spectroscopy. The fluoromethyl moiety allowed us to monitor reactions by ^{19}F NMR spectroscopy. The F atom does not affect the catalytic process; the reaction of 3-(fluoromethyl)-phenyl bromide with PyO catalyzed by $Pd(OAc)_2$ and $PtBu_3$ formed the 2-aryl-PyO in good yield (77%).

In contrast to the 77% yield of the catalytic reaction, the stoichiometric reaction of isolated **1** with PyO at 120 °C in toluene formed the arylated PyO in a lower 52% yield. This observation was consistent with a previous report in which a similar difference in yield was obtained between the stoichiometric reaction of an isolated $PtBu_3$-ligated arylpalladium acetate complex $(PtBu_3)Pd(Ph)(OAc)$

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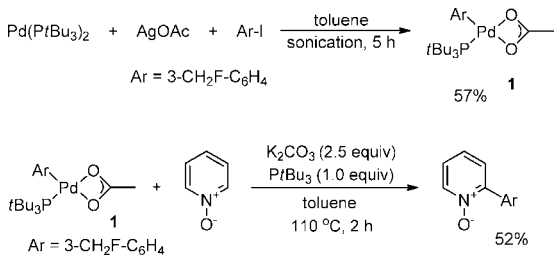
Scheme 1. Synthesis of 1 and Its Reaction with PyO under the Previously Reported Conditions[a]



[a]Yield of arylated product determined by ^{19}F NMR.

with 4-nitro-PyO and the catalytic reaction of Ph-Br with 4-nitro-PyO.[9]

These differences in yield between the catalytic and stoichiometric reactions led us to study the reaction of isolated acetate **1** in more detail. Figure 1 shows the profile of the decay of **1** during the

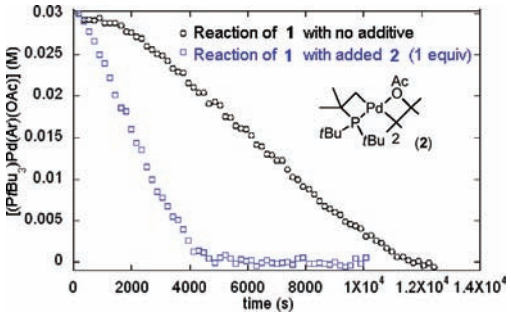
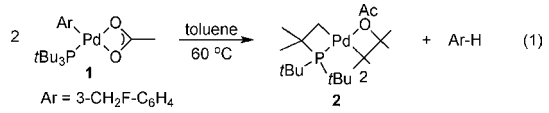


Figure 1. Decay of $(PtBu_3)Pd(Ar)(OAc)$ (**1**) in toluene at 60 °C in the presence of 20 equiv of PyO, 1.0 equiv of $PtBu_3$, and 2.5 equiv of K_2CO_3 with no additive (black) or with 1 equiv of added **2** (blue).

reaction of **1** with PyO at 60 °C in toluene, as measured by ^{19}F NMR spectroscopy. This reaction exhibited an induction period followed by a relatively linear decay of **1**. The ^{19}F NMR yield of the arylated product was 55% at the end of the reaction. Further analysis of the NMR data showed that <1% of the arylated product was formed during the induction period. Instead, fluoromethylbenzene and the cyclometalated complex $[Pd(\mu^2\text{-OAc})(\kappa^2\text{-}tBu_2PCMe_2CH_2)]_2$ (**2**)[11] were formed during this period (eq 1). Cyclometalated **2** forms from decomposition of **1**; heating **1** in toluene for 8 h at 60 °C gave **2** in 92% yield.



The formation of cyclometalated **2** during the induction period suggested that this complex could be involved in the reaction of acetate **1** with PyO. To test this hypothesis, the reaction of **1** with PyO and 1 equiv of added **2** was conducted. No induction period was observed during this process, and the yield of 2-aryl-PyO (84%) was as high as that of the catalytic process. Moreover, a zeroth-order decay of **1** was observed in the reaction with added **2**, suggesting that the rate-determining step[12] occurred without the involvement of **1**. Finally, the concentration of **2** was constant during this reaction, making **2** a catalyst for the stoichiometric reaction of PyO with **1**.

To assess whether the C−H cleavage step occurs by reaction of PyO with **2**, the order of the reaction in each reagent was

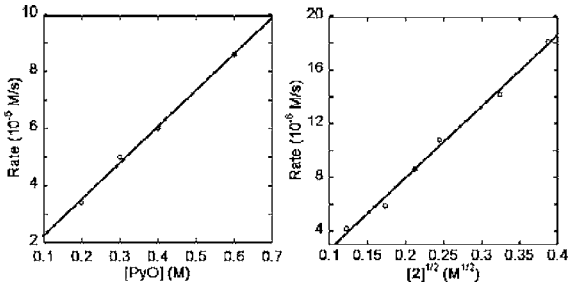
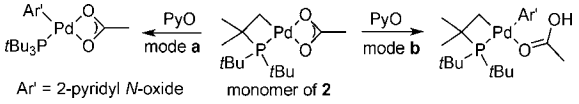


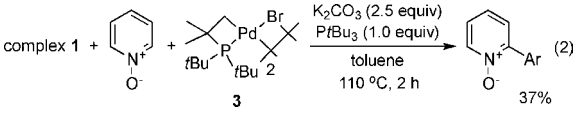
Figure 2. Plots of rate vs [PyO] and $[\mathbf{2}]^{1/2}$ in toluene at 60 °C for the reaction of **1** with PyO.

measured. Figure 2 shows plots of the reaction rate versus [PyO] and $[\mathbf{2}]^{1/2}$. The linear fit of the rate vs the concentration of PyO from 0.2 to 0.6 M showed that the reaction is first-order in PyO. A linear fit of the rate vs $[\mathbf{2}]^{1/2}$ and a nonlinear fit of the rate vs [**2**] revealed a half-order, or at least partial order, dependence on [**2**] from 0.015 to 0.15 M. This partial order in [**2**] implies that the reaction occurs by a pre-equilibrium between the observed dimeric **2** and a catalytically active monomer before the rate-determining C−H bond cleavage step. These results, along with the zeroth-order dependence on [**1**], clearly support the proposal that the C−H cleavage occurs by reaction of PyO with **2** rather than **1**.

Scheme 2. Two Possible Modes for C−H Bond Cleavage by the Cyclometalated Palladium Acetate Complex



To determine whether the cyclometalated $PtBu_3$ ligand or the acetate ligand is involved in the cleavage of the aromatic C−H bond (Scheme 2, pathway **a** vs **b**), an analogous cyclometalated palladium bromide complex, $[PdBr(tBu_2PCMe_2CH_2)]_2$ (**3**), was added to the reaction of **1** and PyO (eq 2). The yield of the arylated product from this reaction (37%) was even lower than that from the reaction between **1** and PyO with no additives. Moreover, no deuterium incorporation into $PtBu_3$ was observed in the reaction of **2** with PyO-d_5. These results imply that the acetate ligand in the cyclometalated complex is involved in the C−H bond cleavage.



If the rate-determining C−H bond cleavage step occurs between PyO and **2**, then the catalytic reactions of bromoarenes with PyO should depend on the concentration of **2** but not on the concentration of **1**. To test this prediction, reactions of 3-bromotoluene with PyO catalyzed by **2** and $Pd(PtBu_3)_2$ were conducted with different amounts of **2** and $Pd(PtBu_3)_2$ (Table 1). The $Pd(PtBu_3)_2$ component, along with the combination of HOAc and base, provides access to intermediate **1**. A series of reactions was conducted with identical amounts of $Pd(PtBu_3)_2$ and varying amounts of **2** (entries 1−3). The reactions with higher concentrations of **2** were faster than those with lower concentrations of **2**, and the dependence on [**2**] was half-order. Reactions with the same amount of **2** but varying amounts of $Pd(PtBu_3)_2$ were also conducted (entries 3−5). The rate of these reactions did not depend measurably on the concentration of $Pd(PtBu_3)_2$. These

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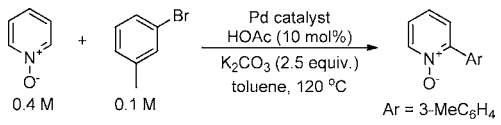
Table 1. Reactions of PyO with 3-Bromotoluene with Varied Amounts of the Two Pd Cocatalysts



	Pd catalyst amounts (mol %)		
entry	**2**	$Pd(PtBu_3)_2$	initial rate (M/s)[a]
1	1	5	2.8×10^{-6}
2	2	5	5.3×10^{-6}
3	5	5	8.5×10^{-6}
4	5	2	7.7×10^{-6}
5	5	1	8.2×10^{-6}

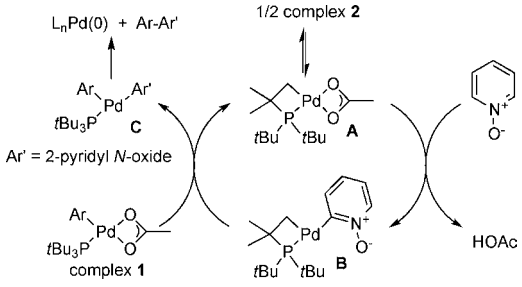
[a]Calculated by monitoring the reaction by GC during the first hour (estimated errors are $\pm 0.3 \times 10^{-6}$ M/s)

results further support our assertion that the C−H bond cleavage occurs by the reaction of PyO with the monomeric form of **2**.

To assess the differences in barriers for cleavage of the C−H bond in PyO by complexes **1** and **2**, we used density functional theory (DFT) to compute the barriers for the reaction of PyO with $(PtBu_3)Pd(Ph)(OAc)$ and $PdOAc(tBu_2PCMe_2CH_2)$. The calculated $\Delta G^{\ddagger}$ at 25 °C for the reaction of $Pd(OAc)$-$(tBu_2PCMe_2CH_2)$ with PyO was found to be 27 kcal/mol, whereas that for the reaction of $(PtBu_3)Pd(Ph)(OAc)$ with PyO was found to be 33 kcal/mol (see the Supporting Information for details). The calculated barrier for the reaction of PyO with **2** matches well with the experimental barrier (27 kcal/mol) obtained from the kinetic data and is much lower than the barrier computed for the reaction of $(PtBu_3)Pd(Ph)(OAc)$ with PyO. These computed barriers are, again, consistent with our proposal that PyO reacts with **2** rather than with **1**.

On the basis of these studies, we propose that the reaction of PyO with **1** occurs by the catalytic cycle shown in Scheme 3.

Scheme 3. Reaction of PyO with 1 Catalyzed by 2

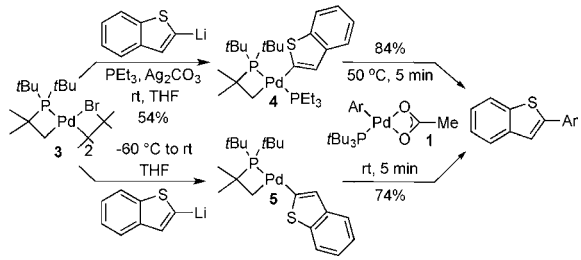


PyO reacts with cyclometalated palladium acetate complex **A** (the monomer of **2**) to generate heteroarylpalladium intermediate **B**, which then reacts with **1** via transfer of the aryl group to form aryl heteroaryl complex **C**. In this mechanism, it is complex **C** that undergoes reductive elimination to form the Pd(0) product and the 2-arylpyridine.

To assess further the proposed pathway, we prepared an example of the proposed heteroarylpalladium intermediate containing the cyclometalated phosphine. With such a complex, we could evaluate whether the reaction of a cyclometalated heteroaryl complex with the arylpalladium carboxylate complex **1** was sufficiently fast to be part of the catalytic cycle. Because of the known difficulty in generating 2-metalated pyridine oxides,[13] which would be used to generate 2-pyridyloxide palladium complexes, in high yield, we conducted studies on 2-benzothienylpalladium complexes. Benzothiophene (BT) undergoes catalytic direct arylation under conditions similar to those of PyO.[3f] To assess more specifically whether studies on the benzothienyl complexes would be relevant to the mechanism of the reaction of PyO, we first assessed whether the mechanistic data implying that the reactions of PyO involve two metal complexes also would be obtained from studies of the reactions of BT. Indeed, the reaction of **1** with BT occurred in a lower yield (64%) than for the catalytic direct arylation of BT (85%), but the rate and yield of the reaction of **1** with BT, like those of **1** with PyO, were much faster and higher (88%) in the presence of added **2.** The yield of the reaction of **1** with BT in the presence of **2** matched that of the direct arylation catalyzed by $Pd(OAc)_2$ and $PtBu_3$. Thus, studies on the transmetalation between **1** and a 2-benzothienylpalladium complex should assess whether transmetalation between two Pd complexes could be part of the reaction of PyO and would assess the scope of our mechanistic conclusions.

PEt_3-stabilized benzothienylpalladium complex **4** containing the cyclometalated phosphine was prepared in acceptable isolated yield by reacting cyclometalated bromide complex **3** with 2-benzothienyllithium in the presence of PEt_3 and Ag_2CO_3 (Scheme 4). This

Scheme 4. Reaction of Complexes 4 and 5 with 1



complex was characterized by ^1H and ^{31}P NMR spectroscopy. A species assigned as the analogous 2-benzothieneyl complex lacking PEt_3 was formed in ~70% yield by the reaction of **3** with 2-benzothienyllithium in the absence of PEt_3 and Ag_2CO_3. This complex was characterized *in situ* by ^1H and ^{31}P NMR spectroscopy.

The reaction of complex **4** with **1** formed the 2-aryl-BT product within 5 min at 50 °C in 84% yield (Scheme 4). The analogous reaction with complex **5** generated *in situ* was even faster, forming the arylated product in 74% yield within 5 min at room temperature. The fast rate and high yield of the reactions of **1** with **4** and **5** containing the cyclometalated phosphine indicate that transmetalation between a heteroarylpalladium intermediate and **1** is kinetically and chemically competent to be part of the mechanism for the stoichiometric reaction of **1** with PyO and BT and the catalytic arylations of these heteroarenes in the presence of $Pd(OAc)_2$ and $PtBu_3$.

The pathway in Scheme 5 for the direct arylation of PyO catalyzed by $Pd(OAc)_2$ and $PtBu_3$ is consistent with our mechanistic data on the stoichiometric reaction of PyO with **1**. This catalytic network comprises the cooperation of two distinct metal fragments in two merging catalytic cycles. The left cycle begins with oxidative addition of the aryl bromide to $(PtBu_3)Pd(0)$ to form an arylpalladium(II) intermediate **D**. Exchange of acetate for bromide would generate the arylpalladium acetate intermediate (**1**) proposed previously to cleave the heteroaryl C−H bond. Instead, our data imply that an arylpalladium(II) species undergoes transmetalation with cyclometalated intermediate **B** to form the aryl heteroaryl palladium species **C**. C−C bond-forming reductive elimination would then form the 2-arylpyridine oxide product

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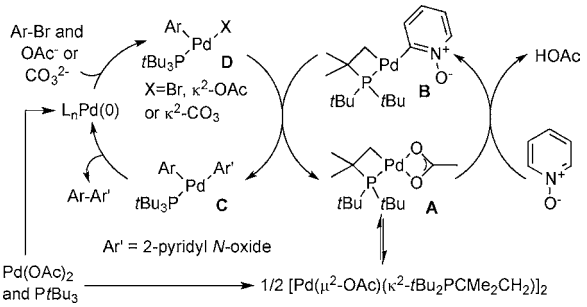
Scheme 5. Revised Mechanism for Direct Arylation of PyO



and regenerate the active Pd(0) catalyst to complete the cycle shown at the left of Scheme 5. In a second cycle, shown at the right of Scheme 5, monomeric Pd(OAc)(tBu$_2$PCMe$_2$CH$_2$) reacts with PyO to cleave the C−H bond and form the complex **B** containing the cyclometalated phosphine.

Our kinetic data imply that the turnover-limiting step in the catalytic direct arylation of PyO occurs between PyO and the monomeric Pd(OAc)(tBu$_2$PCMe$_2$CH$_2$). The equilibrium between the observed dimer **2** and the active monomeric complex **A** is consistent with the partial-order behavior in palladium, and the overall scheme is consistent with the first-order behavior in PyO and zeroth-order behavior in arylpalladium acetate complex **1**. Calculations of the barrier of the reactions of PyO with (PtBu$_3$)Pd(Ph)(OAc) and Pd(OAc)(tBu$_2$PCMe$_2$CH$_2$) with DFT also support the conclusion that the cyclometalated palladium acetate species is more reactive toward C−H bond cleavage than is the arylpalladium acetate intermediate. These data are also consistent with the kinetic data previously obtained on the catalytic process[9] and resolve the inconsistency in the conclusion from these studies of the partial order in palladium and the monomeric nature of the proposed catalyst resting state and the species proposed to react with the pyridine oxide in the turnover-limiting step. Analogous data on the reaction of BT imply that our conclusions pertain to direct arylation reactions beyond PyO.

In summary, detailed kinetic studies on the reactions of the isolated arylpalladium acetate complex **1** with pyridine *N*-oxide in the presence of added cyclometalated palladium acetate complex **2**, along with studies on isolated heteroarylpalladium complex **4** containing a cyclometalated phosphine, have revealed an unexpected mechanism in which the C−H bond of PyO is cleaved by the reaction with cyclometalated complex **2**. We propose that the constrained ring in **2** makes the metal center less hindered and, thereby, allows the reaction of PyO with **2** to occur with a lower barrier than the reaction of PyO with **1**. By the proposed mechanism, one palladium fragment containing P(tBu)$_3$ as ligand adds the aryl halide and forms the C−C bond, but a second fragment containing a cyclometalated phosphine undergoes the C−H bond cleavage step. One can envision many processes for C−H bond functionalization in which one metal cleaves a C−H bond and transfers the resulting hydrocarbyl ligand to a second metal that leads to functionalization, but the demonstration of such a process, other than reactions in which a second metal deprotonates an acidic substrate, is rarely documented.[14] New processes that are based on such a design will be the subject of future studies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

jhartwig@berkeley.edu

Present Address

‡Department of Chemistry, Yeshiva University, New York, NY 10033.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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