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Catalyst Activation

The Impact of Palladium(II) Reduction Pathways on the Structure and Activity of Palladium(0) Catalysts**

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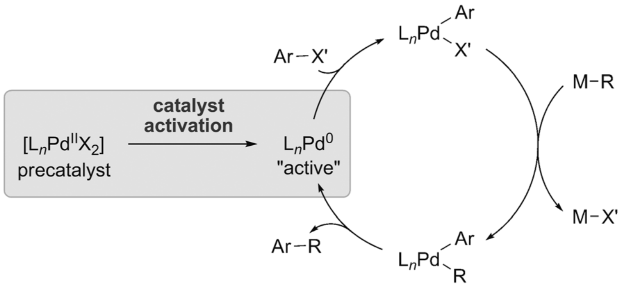
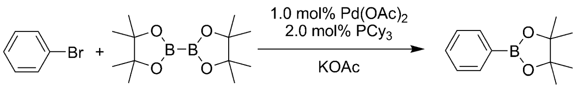
Over the past decade, the scientific community has witnessed a dramatic increase in the number of catalytic transformations promoted by palladium complexes.[1] At the same time, continued improvements to both new and existing Pd-catalyzed reactions have resulted in milder conditions and greater substrate generality. These developments in Pd catalysis can be largely attributed to an increased understanding of the individual steps involved in catalytic reactions, particularly oxidative addition,[2] transmetalation,[3] and reductive elimination.[4] Because these elementary processes factor prominently in most catalytic cycles, improvements to palladium-catalyzed reactions have mainly focused on altering the electronic and steric properties of ligands coordinated to the Pd center to accelerate one or more of these steps.[5]

However, a key step that remains poorly understood, yet directly impacts the overall rate and performance of a Pd^0-catalyzed transformation, is the catalyst activation step. This step involves the reduction of a stable Pd^{II} precursor to an active, zero-valent palladium catalyst and must occur prior to entering the catalytic cycle (Scheme 1). Despite the obvious implications of catalyst activation on a palladium-catalyzed reaction, there is a scarcity of detailed studies concerning the mechanism and efficiency of this reduction process.[6] Herein, we present studies that provide an in depth understanding of the in situ generation of $\{L_nPd^0\}$ ($n = 1$ or 2) catalysts under the standard conditions of a common Pd-catalyzed transformation, the Miyaura borylation [Eq. (1)]. Two pathways for catalyst activation were identified, which provide distinct $\{L_nPd^0\}$ complexes: (1) a bisphosphine Pd^0 species resulting from the diboron-mediated reduction of $\{L_2Pd^{II}\}$ and (2) a monophosphine Pd^0 species resulting from the base-promoted reduction of $\{L_2Pd^{II}\}$ by a ligated phosphine. Direct comparison of the catalytic activity of the resulting $\{L_nPd\}$ species reveals the impact that catalyst activation has on both the identity and reactivity of a palladium catalyst.



Scheme 1. Role of palladium(II) catalyst activation in palladium-catalyzed reactions.

 (1)

We began our studies by determining the reagent(s) responsible for the reduction of a Pd^{II} precatalyst to an active Pd^0 species during the Miyaura borylation. The air-stable catalyst precursor $[(Cy_3P)_2Pd(OAc)_2]$ (**1**),[7] which is readily formed from the combination of $Pd(OAc)_2$ and 2.0 equiv PCy_3, was chosen for these investigations owing to its widespread application in the borylation of aryl halides.[8] A series of stoichiometric reactions were conducted between **1** and the typical reagents utilized in the borylation reaction to determine the effectiveness of each reagent towards the reduction of **1** (Table 1).

The intramolecular reduction of the related complex $[(Ph_3P)_2Pd(OAc)_2]$ to form an anionic Pd^0 species and triphenylphosphine oxide has been reported by Amatore[9] and others.[10] However, we found that prolonged heating of **1** at 70 °C in toluene,[11] either alone or with added PCy_3, gave no observable formation of a Pd^0 species based on ^{31}P NMR spectroscopy, indicating that such a mechanism is not operative for **1** (Table 1, entries 1 and 2). Reports by Ozawa and Hayashi,[12] and more recently by Buchwald,[13] indicate that in many cases water can promote the reduction of $[L_nPd(OAc)_2]$ to $\{L_nPd^0\}$ and phosphine oxide. After heating **1** for 5 h at 70 °C in the presence of 5.0 equiv H_2O, less than 5% conversion of **1** was observed, suggesting that the predominant pathway for activation of the PCy_3-ligated Pd^{II} precatalyst is not solely mediated by adventitious water.

Other reported methods for the generation of L_nPd^0 include the treatment of $[L_nPdCl_2]$ with aqueous alkaline base (KOH) to give phosphine oxide and the $\{L_nPd^0\}$ species.[14] As the weak base KOAc is commonly used for

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Table 1: Evaluation of various reagents for the reduction of **1** to **2**.

$$\underset{\mathbf{1}}{[(Cy_3P)_2Pd^{II}(OAc)_2]} \xrightarrow[\text{toluene, 70 °C}]{\text{reagent}} \underset{\mathbf{2}}{[(Cy_3P)_2Pd^0]}$$

Entry	Reagent	Equiv	*t*	Yield [%][a]
1	None		5 h	0
2	PCy_3	1.0	5 h	0
3	H_2O	5.0	5 h	4
4	KOAc	10.0	5 h	3
5	TBAOAc	10.0	5 h	12
6	TBAOAc[b]	10.0	20 min	47
7	$TBABF_4$	10.0	1 h	0
8	TBAOTf	10.0	1 h	3
9	KOH[c]	1.1	1 h	49
10	TBAOH	1.1	20 min	50
11	B_2pin_2	10.0	10 min	96
12	B_2pin_2	1.1	16 h	84

[a] Yield determined by ^{31}P NMR spectroscopy with triphenylphosphine oxide as an internal standard. [b] Addition of 1.0 equiv of H_2O. [c] Addition of 2.0 equiv of [18]crown-6.

the Pd-catalyzed borylation of aryl halides, we evaluated the possibility that the acetate base in the reaction could promote catalyst activation. However, heating **1** and excess KOAc in toluene gave only trace reduction after 5 h (Table 1, entry 4). Owing to the poor solubility of KOAc in toluene, we also evaluated the more soluble base, tetrabutylammonium acetate (TBAOAc). The reaction of **1** and excess oven-dried TBAOAc stalled at 30 % conversion of the Pd^{II} complex into $[Pd(PCy_3)_2]$ (**2**, 12 %), with concomitant formation of phosphine oxide and Pd black (entry 5). As trace amounts of water are typically present in catalytic reactions containing base,[15] we allowed **1** to react with TBAOAc in the presence of 1.0 equiv H_2O. Under these conditions, complete reduction of **1** was observed to give 50 % yield of **2** along with 1.0 equiv of $O{=}PCy_3$ after 20 min at 70 °C (entry 6). Based on our observation that increasing amounts of water enhances the rate of reduction, we hypothesized that hydroxide, rather than ammonium cation or acetate anion, was responsible for promoting the reduction of **1**. Indeed, ammonium salts such as $TBABF_4$ and TBAOTf gave less than 5 % reduction of **1** to **2** (entries 7 and 8), while hydroxide bases such as KOH[16] or TBAOH reduced **1** to a mixture of **2**, phosphine oxide, and Pd black (entries 9 and 10).

Although the experiments summarized in entries 1–10 of Table 1 are consistent with a base-promoted, phosphine-mediated Pd^{II} reduction process, they do not rule out the existence of alternative reduction pathways in the Miyaura borylation. Along with phosphine-mediated reduction, nucleophilic coupling partners such as organolithium reagents,[17] organostannanes,[18] arylboronic acids,[19] alcohols,[20] and amines[21] have also been reported to effect the reduction of Pd^{II} to Pd^0. Therefore, we conducted the reaction of **1** with the diboron reagent, B_2pin_2. Heating **1** with 10 equiv B_2pin_2 led to the quantitative conversion of **1** into $[Pd(PCy_3)_2]$ (**2**) within 10 min at 70 °C (entry 11).[22] Further investigation revealed that only one equivalent of B_2pin_2 is required for complete reduction of **1** to **2**, but the rate of the reduction is slower under these conditions (entry 12). Analysis of the reaction mixture by ^1H and ^{11}B NMR spectroscopy after the reduction of **1** by B_2pin_2 indicated that 2.0 equiv AcOBpin is formed along with the $\{L_2Pd^0\}$ complex, with no detectable formation of phosphine oxide or Pd black.

A visual comparison of the two methods of catalyst activation is shown in Figure 1. As previously indicated, the base-promoted reduction of **1** leads to significant formation of Pd black and only 50 % net conversion of the Pd^{II} source into $[Pd(PCy_3)_2]$ (pathway A), whereas the B_2pin_2-mediated reduction of **1** leads to the quantitative formation of $[Pd(PCy_3)_2]$ (pathway B). In the former pathway, one phosphine ligand coordinated to the Pd^{II} center is converted into the corresponding phosphine oxide, leaving an unstable monophosphine $\{L_1Pd^0\}$ species that undergoes rapid disproportionation to $\{L_2Pd^0\}$ and Pd black. Owing to the oxidation of one equivalent of phosphine during the base-mediated reduction, standard preparations of $\{L_nPd^0\}$ complexes from $[L_nPdCl_2]$ and KOH typically require the addition of excess free phosphine.[14a,c]

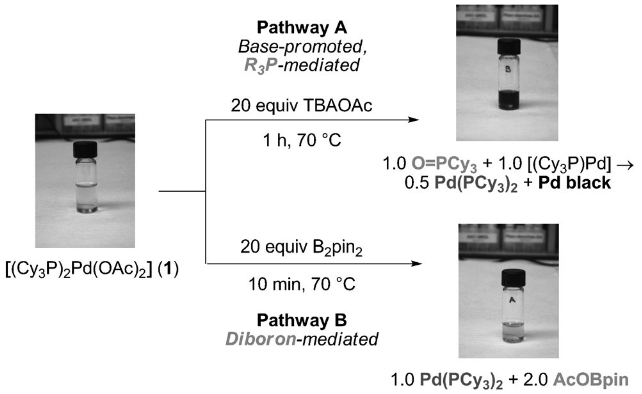


Figure 1. Reduction of **1** by TBAOAc (pathway A)[15] and by B_2pin_2 (pathway B).

In the case of B_2pin_2-mediated reduction, no phosphine oxide is formed; therefore, catalyst activation through this pathway proceeds cleanly and forms the Pd^0 complex **2** in high yield. To determine the generality of using a diboron species as a reductant for $\{L_nPd^{II}\}$, we examined the reduction of $[L_nPd(OAc)_2]$ complexes of $P(iPr)_3$, $P(tBu)_3$, $PPhCy_2$, and A-taPhos as well as the analogous dichloride Pd^{II} complex $[(Cy_3P)_2PdCl_2]$. For each of the acetoxy–Pd^{II} complexes, full conversion into the corresponding $[(R_3P)_2Pd^0]$ species was observed after 1 h at 70 °C using 10 equiv B_2pin_2. In contrast, $[(Cy_3P)_2PdCl_2]$ proved unreactive under these conditions, suggesting that acetoxy groups on the Pd^{II} center are necessary for the reduction to occur.

Based on our understanding of the available pathways for Pd^{II} reduction, we next examined the impact of catalyst activation on the Pd/PCy_3-catalyzed borylation of bromobenzene (Figure 2). Using a standard “dump-and-stir” procedure, wherein all reagents are charged simultaneously with no prior catalyst pre-aging, the borylation of PhBr catalyzed by 0.2 mol % **1** formed the corresponding phenylboronate ester (PhBpin) in 84 % yield after 5 h at 70 °C (condition A).

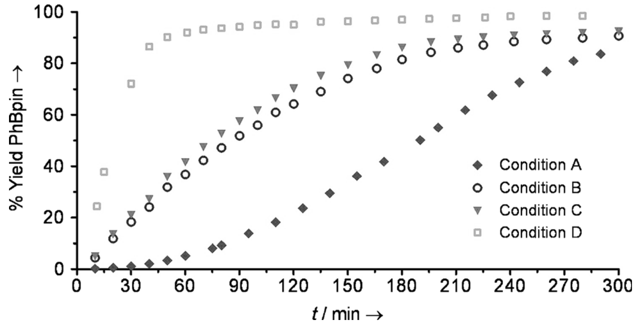


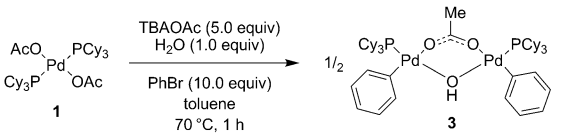
Figure 2. Kinetic experiments comparing different reaction setups for the Pd/PCy$_3$-catalyzed borylation of PhBr using 1.1 equiv B$_2$pin$_2$ and 2.0 equiv TBAOAc at 70 °C. Condition A: "dump-and-stir" with 0.2 mol% **1**; condition B: pre-age 0.2 mol% **1** with B$_2$pin$_2$ in toluene for 10 min at 70 °C, then add PhBr and TBAOAc; condition C: 0.2 mol% **2**; condition D: pre-age 0.2 mol% **1** with PhBr and TBAOAc in toluene for 1 h at 70 °C, then add B$_2$pin$_2$. All of the reactions were monitored by HPLC using 1,3,5-trimethoxybenzene as an internal standard.

Although this reaction gave a high yield of the aryl boronate, a significant induction period was observed during the course of the reaction. This induction period could be eliminated by pre-aging the Pd^{II} precatalyst **1** with B$_2$pin$_2$ for 10 min at 70 °C, followed by subsequent addition of the aryl halide and TBAOAc (condition B). The reaction rates and profiles obtained from this pre-aging procedure were identical to that obtained from using 0.2 mol% **2** (condition C), consistent with our observation that the Pd^0 species obtained from pre-aging **1** with B$_2$pin$_2$ is **2**.

In contrast to these results, an alternative pre-aging procedure that involved heating **1** with TBAOAc prior to addition of PhBr and B$_2$pin$_2$ gave inconsistent reaction rates, occasional reaction stalling, and greater amounts of biphenyl by-product. These observations are consistent with the presence of ligandless Pd species in the reaction mixture, which can participate in the catalytic reaction but are often less reliable and generate greater impurities than ligated Pd complexes.[23] To stabilize the transient monophosphine {L$_1$Pd^0} species and to prevent the formation of ligandless Pd, an additional equivalent of free phosphine could be added to form a more stable bisphosphine {L$_2$Pd^0} species. However, we reasoned that the reactive {L$_1$Pd^0} species should also undergo rapid oxidative addition of an aryl halide to form an [L$_1$Pd^{II}(Ar)X] complex. As aryl halides are substrates for a variety of Pd-catalyzed reactions, the activation of a Pd^{II} precatalyst in the presence of base and aryl halide would be an attractive method for converting an [L$_2$Pd(OAc)$_2$] species such as **1** into a catalytically active Pd complex.

The reaction of **1** with TBAOAc and PhBr at 70 °C led to the generation of a colorless solution with no observable formation of Pd black.[24] Subsequent addition of B$_2$pin$_2$ and further heating at 70 °C provided a 92% yield of PhBpin after 1 h (condition D).[25] Notably, this catalyst activation procedure provided a significantly faster reaction than the analogous reaction using [Pd(PCy$_3$)$_2$] as catalyst, which required approximately 4 h to reach completion.

To identify the Pd species generated from the reduction of **1** by TBAOAc in the presence of PhBr, we conducted the stoichiometric reaction of **1** with 5.0 equiv TBAOAc and 10 equiv of PhBr [Eq. (2)].[26] After 1 h at 70 °C, the Pd^{II} complex **1** was fully converted into a single species that exhibited a ^{31}P peak at 33.9 ppm along with one equivalent of tricyclohexylphosphine oxide (45.8 ppm). The chemical shift at 33.9 ppm was comparable to the 30–37 ppm chemical shifts previously reported for monophosphine dimers [{(R$_3$P)Pd(Ph)(μ-OH)}$_2$][14b] and [{(R$_3$P)Pd(Ph)(μ-OAc)}$_2$].[27] Subsequent isolation from acetone gave the air-stable, crystalline monophosphine phenyl Pd^{II} complex **3** in 59% yield (Figure 3).



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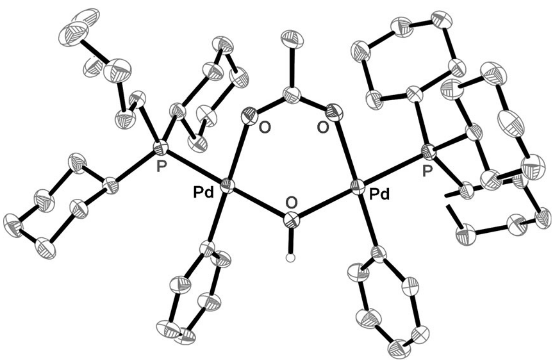

Figure 3. ORTEP diagram of the complex [(Cy$_3$P)$_2$Pd$_2$Ph$_2$(μ-OH)(μ-OAc)] (**3**) with ellipsoids set at 35% probability (hydrogen atoms, except for the bridging OH group, are omitted).

As transmetalation during the Miyaura borylation is commonly proposed to occur between B$_2$pin$_2$ and a [L$_2$Pd(Ar)(OAc)] species, we sought to determine whether one or both Pd centers of the acetoxo-, hydroxo-bridged dimer **3** would undergo reaction with the diboron reagent. The reaction of **3** and 2.0 equiv B$_2$pin$_2$ at room temperature resulted in the immediate formation of Pd black and 2.0 equiv PhBpin, indicating that both of the oxo-bound Pd centers undergo transmetalation with B$_2$pin$_2$. To determine if **3** is a competent catalyst for the Miyaura borylation, we conducted the borylation of PhBr with B$_2$pin$_2$ using 0.1 mol% **3** (0.2 mol% Pd). The reaction proceeded rapidly and led to a 93% yield of PhBpin after 1 h at 70 °C. No induction period was observed during this reaction, and the reaction rate was identical to that of a reaction using 0.2 mol% **1** pre-aged with TBAOAc and PhBr. The precipitation of Pd black was not observed until the end of these reactions, indicating that under the conditions of the catalytic reaction the oxidative addition of an aryl halide to {(Cy$_3$P)Pd^0} is faster than disproportionation to form [Pd(PCy$_3$)$_2$] and Pd black.

Although monophosphine {L$_1$Pd} complexes are commonly proposed to be more reactive than analogous bisphosphine {L$_2$Pd} complexes owing to the presence of an additional open coordination site on the metal center,[28] to the best of our knowledge a direct comparison of an {L$_1$Pd} complex and an {L$_2$Pd} complex containing the same dative ligand has not been reported. This is partially due to the instability of monophosphine {L$_1$Pd^0} complexes, which precludes their direct comparison with {L$_2$Pd^0} species, and the preference of Pd^{II} complexes to contain either one or two phosphines based on the steric properties of the ligand. For example, Pd^{II} complexes containing unhindered trialkyl- or triarylphosphine ligands, such as PCy$_3$ and PPh$_3$, typically exist as bisphosphine [L$_2$Pd(Ar)X] species, whereas Pd^{II} complexes containing bulky phosphines, such as P(*t*Bu)$_3$ and Q-Phos, typically exist as three-coordinate [L$_1$Pd(Ar)X] complexes.[29] As the monophosphine Pd^{II} pseudodimer **3**, containing a single PCy$_3$ ligand on each Pd center, was determined to be a competent catalyst for Miyaura borylation, we sought to compare the catalytic activity of **3** with the analogous bisphosphine Pd^{II} complex [(Cy$_3$P)$_2$Pd(Ph)(OAc)] (**4**). A comparison of the rate of borylation of PhBr using 0.1 mol% **3** versus 0.2 mol% **4** demonstrates that the reaction catalyzed by monophosphine Pd^{II} species **3** is approximately four-fold faster than the analogous reaction catalyzed by bisphosphine Pd^{II} species **4** (Figure 4).

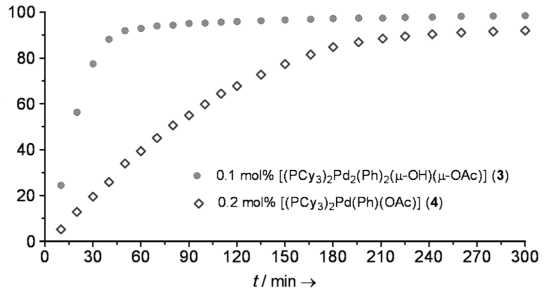

Figure 4. Comparison of the reaction rates for the borylation of PhBr catalyzed by 0.1 mol% **3** (0.2 mol% Pd) and by 0.2 mol% **4** at 70°C. All of the reactions were monitored by HPLC using 1,3,5-trimethoxybenezene as an internal standard.

In summary, our studies of the reduction pathways for Pd^{II} catalyst precursors and the identification of the catalytically active Pd species generated from each of these pathways have yielded new insight into catalyst activation in a widely utilized Pd-catalyzed transformation. Specifically, we identified two distinct pathways for Pd^{II} reduction during the Miyaura borylation reaction: 1) a diboron-mediated pathway, which leads to the formation of a bisphosphine {L$_2$Pd^0} species; and 2) a base-promoted pathway to form a monophosphine {L$_1$Pd^0} complex, which is prone to disproportionation but can be efficiently trapped by oxidative addition of an aryl halide. The fundamental understanding gained from these studies highlights the importance of catalyst activation, not only on the amount of productive Pd species formed in a catalytic reaction, but also on the identity and reactivity of the Pd catalyst.

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Keywords: borylation · catalyst activation · palladium · reaction kinetics · structure elucidation

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[15] In the context of a catalytic reaction in which the base stoichiometry is often two orders of magnitude greater than the catalyst amount, the adventitious water present in the base can be sufficient to promote the reduction. Indeed, using 20 equiv of TBAOAc without prior drying of the base resulted in the full conversion of **1** into [Pd(PCy$_3$)$_2$] and Pd black within 1 h at 70°C.

[16] Addition of 1.0 equiv [18]crown-6 was necessary to increase solubility of KOH in toluene. Without KOH, only trace reduction of **1** occurred in the presence of [18]crown-6.

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[24] In the presence of 2.0 equiv of TBAOAc, full reduction of 0.2 mol% **1** was observed without the addition of water.

[25] The end of the reaction is clearly visualized, because as soon as all the aryl bromide is consumed, colloidal Pd metal precipitates and the clear colorless solution turns black.

[26] As only 5.0 equiv TBAOAc was utilized for the reduction of **1**, an additional equivalent of H$_2$O was necessary to fully convert **1** into the monophosphine Pd^{II} complex **3**. See Table 1, entry 6.

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Communications

Catalyst Activation

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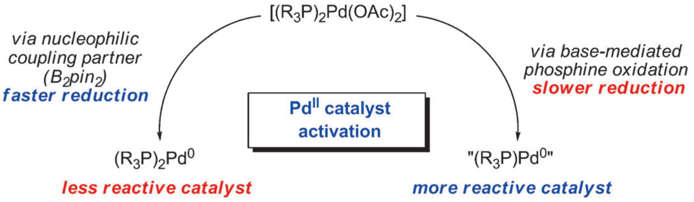
The Impact of Palladium(II) Reduction Pathways on the Structure and Activity of Palladium(0) Catalysts



Two roads diverged: The mechanism of in situ Pd^{II} catalyst activation to generate an active $\{L_nPd^0\}$ catalyst from an air-stable Pd^{II} precursor was examined using the standard conditions of a Miyaura borylation reaction. Two pathways for catalyst activation exist under these conditions, producing two structurally and chemically distinct $\{L_nPd^0\}$ complexes (see scheme).