The Impact of Precatalyst Oxidation State in C–N Cross Couplings with 2-Phosphinoimidazole-Derived Bimetallic Pd(I) and Pd(II) Complexes

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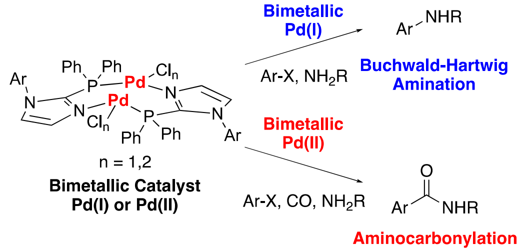
ABSTRACT: We report the catalytic activity of two phosphinoimidazole-derived bimetallic palladium complexes in Pd-catalyzed amination reactions. Our studies demonstrate that the starting oxidation state (Pd(I) or Pd(II)) of the dimeric complex has a significant impact on the efficiency of the catalytic reaction. The corresponding Pd(I) complex shows higher reactivity in Buchwald-Hartwig aminations, while the Pd(II) complex is much more reactive in carbonylative amination reactions. These new dimeric palladium complexes provide good to excellent reactivity and yields in the amination reactions tested.



Palladium-catalyzed C–N cross couplings are among the most efficient and selective methods for generating carbon nitrogen bonds in synthetic and medicinal chemistry.[1] Recent advances in the development of Pd catalysts for cross couplings have led to the discovery of various dimeric Pd(I) and Pd(II) catalysts that are highly effective at C–N bond formation, as well as for C–C, C–O, and C–S couplings (Figure 1a).[2–5] In many cases, these dimeric catalysts serve as precatalysts to monometallic Pd(0) reaction pathways. Schoenebeck and others have demonstrated that in some cases the intact dimeric structure of the bimetallic palladium complex can in fact be essential to high reactivity via cooperative catalytic effects.[6] These cooperative effects can include binding substrates across both metals, or accessing unique oxidation states that are not achievable with monometallic Pd catalysts. Dimeric palladium complexes have also been identified in palladium-catalyzed oxidation reactions, where the dimeric catalyst structure helps stabilize higher oxidation state Pd(III) intermediates.[7]

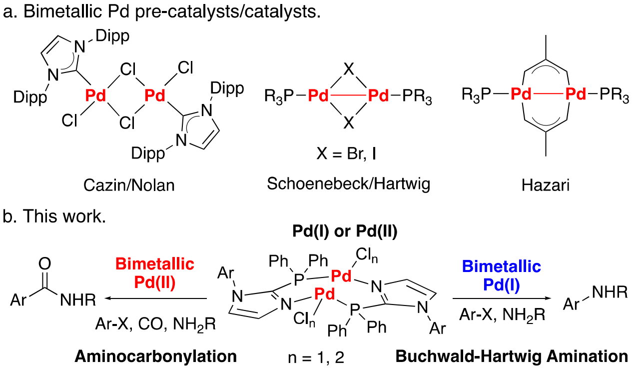
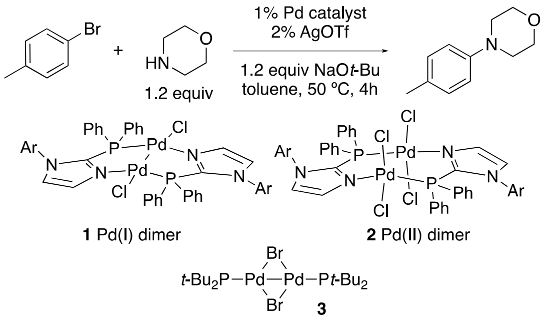


Figure 1. a) Common bimetallic Pd precatalysts and catalysts. b) Aminocarbonylations and Buchwald-Hartwig aminations with bimetallic Pd catalysts.

We recently reported the synthesis of new bimetallic palladium complexes scaffolded on a 2-phosphinoimidazole ligand that can be isolated at either the Pd(I) or Pd(II) oxidation states (Figure 2b).[8] Mechanistic experiments and DFT calculations confirmed the thermodynamic stability of the dimeric Pd complex with respect to the monomeric form and suggested that the Pd complex stays intact during catalysis. Because either the bimetallic Pd(I) or Pd(II) complex can be selectively isolated, we wondered if the starting oxidation state of the palladium complex would have a significant impact on the reactivity of the catalyst in cross coupling reactions. We chose to investigate the reactivity of our bimetallic catalysts in C–N bond forming reactions due to the precedence for Pd(I) and Pd(II) complexes to participate in many of these catalytic reactions.[3-5] In this report, we demonstrate that our bimetallic Pd(I) catalyst has much higher reactivity in Buchwald-Hartwig aminations than the corresponding Pd(II) complex, which is consistent with previous results with dimeric Pd(I) precatalysts in this transformation.[6a] We also demonstrate that the corresponding dimeric Pd(II) catalyst is much more active for aminocarbonylation reactions with aryl iodides and amines in the presence of CO. The ability to selectively modify the starting oxidation state of the metal catalyst in this manner on the same ligand framework provides a unique method for optimizing catalytic activity with bimetallic complexes that is hard to achieve with monometallic catalysts.

We previously reported the catalytic activity of bimetallic complexes **1** and **2** in a newly discovered naphthalene synthesis reaction that occurs via tandem ketone arylation and cyclization.[8] In that study, we found that Pd(II) complex **2** had slightly higher reactivity than the Pd(I) complex. This result suggested to us that the starting oxidation state of our bimetallic complexes could have an important impact on catalytic efficiency and that there may be reactions where either the Pd(I) or Pd(II) complex would be more active. To test this, we started by screening our complexes in the Buchwald-Hartwig amination reaction seen in Table 1. The addition of AgOTf as co-catalyst led to a slight increase in reactivity in all cases. We found that while the dimeric Pd(I) complex **1** had excellent reactivity, the Pd(II) catalyst **2** reacted sluggishly (Table 1, entries 1–2). This trend is consistent with previous reports of the high activity of dimeric Pd(I) catalysts over Pd(II) catalysts in Suzuki reactions and Buchwald-Hartwig aminations, where the Pd(I) dimer can act as a source for monoligated Pd(0)L catalysts.[3] Alternatively, the Pd(I) dimer could remain intact and benefit from being at a lower oxidation state than the corresponding Pd(II) complex, facilitating faster oxidative addition (*vide infra*). We also compared catalyst **1** with other palladium catalyst systems and found that our bimetallic catalyst had similar or better reactivity to optimized catalysts including Pd_2dba_3/RuPhos,[9a-c] RuPhos Pd G3,[9d] and Pd(I) dimer **3** (entries 3–5).[3c, 9e] However, our goal in this work is to demonstrate that these bimetallic Pd catalysts are reactive in C–N bond forming reactions and that the starting oxidation state of the catalysts can be important for catalysis. Based on this excellent reactivity, we further optimized the reaction parameters and found that *in situ* formation of the Pd(I) dimer with $Pd(OAc)_2$ led to only modest reactivity (entry 6). Either palladium acetate by itself (entry 7), or the phosphinoimidazole ligand with no palladium (entry 8) led to only 5% or no product, respectively. We also found that the reaction performed equally well in dioxane solvent and that KO*t*Bu as base led to lower conversions (entries 9–10). Finally, we can drop the temperature of the reaction to room temperature and still obtain nearly full conversion after 15 hours. We have not extensively investigated the optimization of this or the following reaction, as there are other more reactive catalysts capable of performing these reactions as well as or better than our bimetallic complex.

Table 1. Optimization of Buchwald-Hartwig amination reaction with palladium dimers.



entry[a]	catalyst	% Conv.[b]
1	**1**	100 (90)
2	**2**	42
3	Pd_2dba_3/RuPhos	97
4	RuPhos Pd G3	87
5	**3**	99
6[c]	**1**	68
7	$Pd(OAc)_2$	5
8	Ligand	1
9[d]	**1**	93
10[e]	**1**	54
11[f]	**1**	92

[a] Reaction run with 2% palladium or 1% dimer (0.01 mmol), silver triflate (0.02 mmol), iodobenzene (0.1 mmol, 1 eq), morpholine (0.12 mmol, 1.2 eq), and sodium tert-butoxide in 0.2 mL toluene at 50 °C for 4 hours. [b] Conversion determined by ^1H NMR analysis of the crude reaction mixture. Isolated yield is shown in parentheses. [c] Ligand and $Pd(OAc)_2$ were pre-stirred in a 0.1 M solution of toluene for 15 minutes. [d] With dioxane. [e] With KO*t*Bu (1.2 equiv). [f] Run at room temperature for 15 h.

Based on the excellent reactivity observed in Table 1, we decided to explore the substrate scope of complex 1 in Buchwald-Hartwig aminations (Figure 2). Both aryl bromides and iodides undergo amination in good yield (**4a-4b**, **4h-4i, 4m-4n**), although aryl bromides often required longer reaction times. When multiple halides are present, reaction with an aryl iodide is preferred over reaction with a bromide or chloride within the same molecule (**4c-4d**). Aryl iodides containing both electron donating and withdrawing groups could undergo the reaction, with donating groups providing higher yields (**4e-4k**). More sterically hindered aryl iodides (**4j-4k**) could also give good yields, as well as heteroaryl halides (**4l-4n**). We also investigated additional amine coupling partners and found that while more electron-rich, disubstituted amines worked well (**4o, 4q, 4s**), primary amines gave lower yields of product (**4p, 4r**).

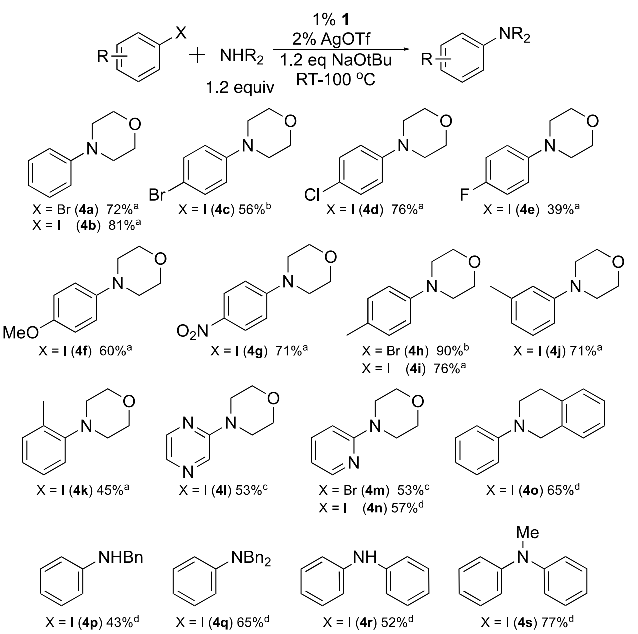


Figure 2. Substrate scope of Buchwald-Hartwig aminations. Yields are isolated yield of the product after purification. [a] Reaction run at 40 °C. [b] Reaction run at room temperature. [c] Reaction run at 60 °C. [d] Reaction run at 100 °C.

Our next goal was to investigate the reactivity of our two dimeric Pd complexes in an additional amination reaction. To this end, we began by screening our catalyst in carbonylative aminations of aryl halides, as seen in Figure 3.[10] In this reaction, the addition of AgOTf as a co-catalyst had no impact on the rate of the reaction, and thus was omitted. For the carbonylative amination, Pd(I) dimer **1** gave very low conversion to product, while Pd(II) dimer **2** reached 100% conversion in just 90 minutes. This difference in reactivity confirms our hypothesis that changing the starting oxidation state in our bimetallic complexes can lead to a dramatic shift in reactivity, and that different reactions benefit from different oxidation states of the same catalyst. We hypothesize that the Pd(I) dimer is less active because it may bind more strongly to CO than the Pd(II) dimer. A recent study by Hartwig showed that in the aminocarbonylation reaction, an off-cycle Pd(I) dimer containing a bridging CO led to catalyst deactivation, which may explain the difference in reactivity we observed.[11] While we were unable to observe any change in the structure of complexes **1** or **2** (via ^{31}P NMR) in the presence of CO, this does not necessarily mean that a non-active CO adduct of **1** does not form during the reaction. Finally, we tested a variety of aryl iodide and amine coupling partners (**5a-5e**). As with the

Buchwald-Hartwig amination, use of 1-bromo-4-iodobenzene gave only activation of the iodide bond (**5b**). Primary and secondary amines worked equally well in the reaction (**5a**–**5c**), and more electron-rich amines provided higher yields of the amide product (**5d**, **5e**).

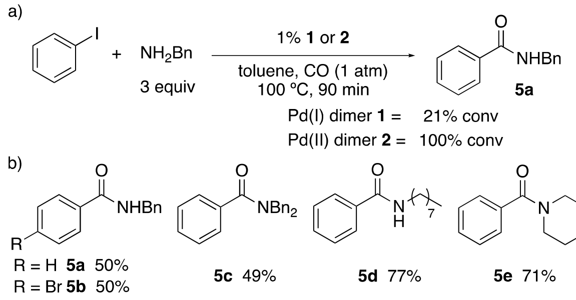


Figure 3. a) Performance of palladium dimers in aminocarbonylation reaction. b) Substrate scope for carbonylative amination of aryl iodides.

For the two amination reactions above, we wondered whether the palladium catalysts (**1** or **2**) remained intact throughout the reaction, or if they undergo decomposition to more active monometallic forms or nanoparticles.[3b,12] For both catalytic systems, we tracked the reaction by ^{31}P NMR and mass spectrometry. For the Buchwald-Hartwig reaction, we see only a slight shift in the ^{31}P NMR spectra for complex **1** and a small amount of free ligand (3.5:1 ratio **1** to free ligand)**.** The phosphorus shift for complex **1** is likely the result of chloride exchange.[13] In addition, the mass spectrum (MS) of the crude reaction mixture shows mainly dimeric palladium species, suggesting that catalyst breakdown to a monometallic species is not particularly preferred. This result is in direct contrast with Schoenebeck’s results that show that Pd(I) dimer $\{[PtBu_3]PdBr\}_2$ rapidly undergoes conversion to monometallic $Pd(0)(PtBu_3)_2$ in Suzuki-Miyaura cross couplings.[3b] While a catalytically-active monometallic complex cannot be ruled out, the evidence at hand suggests that the bimetallic Pd complex may be responsible for the observed catalysis. The presence of free ligand in the reaction suggests that some of the catalyst may decompose to nanoparticles or monometallic complexes. The addition of mercury to a Buchwald-Hartwig amination reaction with complex **1** gave 87% conversion in 4 hours. This result suggests that nanoparticles do not play a significant role in this reaction, although this effect cannot be ruled out completely. For complex **2**, we observed similar results by ^{31}P and mass spectrometry in the Buchwald Hartwig reaction. Thus, we believe the enhanced reactivity for complex **1** when compared with complex **2** may result from its lower starting oxidation state, which could accelerate oxidative addition or lead to a more stable bimetallic catalyst due to the presence of the metal–metal bond.

For the aminocarbonylation reaction with catalysts **1** and **2**, we observed the formation of a significant amount of free ligand by ^{31}P NMR. This suggested the formation of nanoparticles in the reaction and so we ran the mercury drop test to investigate this possibility.[12] When excess mercury was added to the aminocarbonylation reaction with **1** or **2**, <5% conversion was achieved in 90 minutes. This suggests that nanoparticles may play a significant role in catalyzing this reaction, especially considering the high temperature.[14] Under these reaction conditions, **1** and **2** likely break down to catalytically active phosphine-stabilized Pd^0 nanoparticles. It follows that catalyst **1** likely forms nanoparticles at a slower rate than catalyst **2** and therefore provides lower yields and conversions in high-temperature aminocarbonylation reactions. At this stage we can only hypothesize that the lower reactivity of complex **1** and its proposed slower rate of nanoparticle formation may be due to possible formation of off-cycle Pd(I) dimer CO complexes, as previously observed,[11] that slow the decomposition rate. This hypothesis is supported by the large number of unidentified peaks in the ^{31}P NMR of complex **1** (see Supporting Information). Less electronic density on the Pd(II) centers in **2** may limit the formation of similar CO-bound complexes and allow for quicker ligand loss and formation of nanoparticles.

In conclusion, we have demonstrated that the beginning oxidation state of 2-phosphinoimidazole-derived bimetallic palladium complexes can have a dramatic impact on catalytic efficiency in palladium-catalyzed amination reactions. In the Buchwald-Hartwig amination reaction, the Pd(I) dimer had higher reactivity, while the Pd(II) dimer performed more efficiently in the carbonylative amination reaction. Additional studies show that the Pd(I) dimer complex remains largely intact throughout the Buchwald-Hartwig amination reaction and may be important for the high catalytic efficiency observed. For the aminocarbonylation reaction, we demonstrate that nanoparticle formation likely is responsible for catalysis and hypothesize that the faster rate of decomposition from the Pd(II) dimer may explain the observed differences in catalysis. Ongoing studies in our laboratory with these complexes are investigating both experimentally and with DFT calculations the importance of the bimetallic catalyst structures during catalysis.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures, characterization data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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