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Can Palladium Acetate Lose Its "Saltiness"? Catalytic Activities of the Impurities in Palladium Acetate

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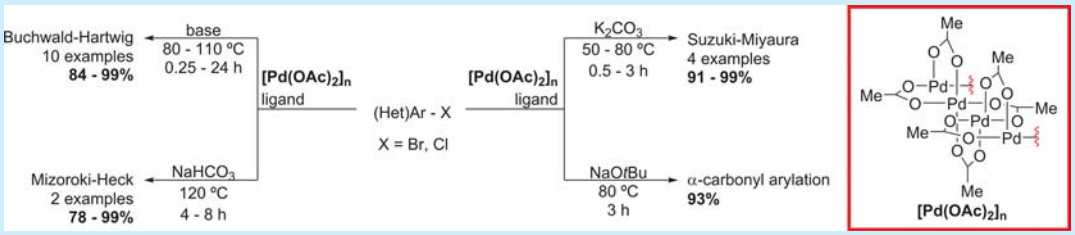
Supporting Information



ABSTRACT: Commercially available palladium acetate often contains two major impurities, whose presence can impact the overall catalytic efficacy. This systematic study provides a comparison of the differences in catalytic activity of pure palladium acetate, $Pd_3(OAc)_6$, with the two impurities: $Pd_3(OAc)_5(NO_2)$ and polymeric $[Pd(OAc)_2]_n$ in a variety of cross-coupling reactions. The solid state ^{13}C NMR spectra of all three compounds in conjunction with DFT calculations confirm their reported geometries.

The biblical quote, "...but if the salt loses its saltiness, how can it be made salty again? It is no longer good for anything, except to be thrown out and trampled underfoot."[1] is very much applicable to some commercial samples of palladium acetate, $Pd_3(OAc)_6$ (**1**), which can be substantially contaminated with variable amounts of two impurities, $Pd_3(OAc)_5(NO_2)$ (**2**) and polymeric $[Pd(OAc)_2]_n$ (**3**) (Figure 1), while employing the well-practiced classical synthesis

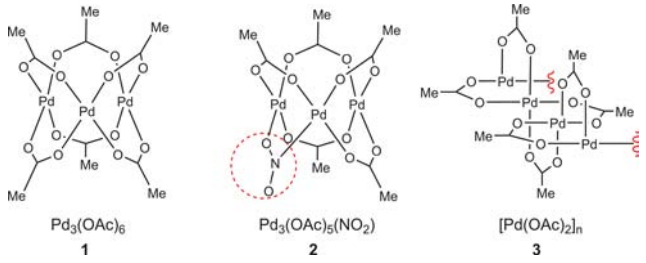


Figure 1. Structures of $Pd_3(OAc)_6$ (**1**), $Pd_3(OAc)_5(NO_2)$ (**2**), and $[Pd(OAc)_2]_n$ (**3**).

protocol developed by Wilkinson.[2] Palladium acetate is an extremely popular catalyst used in multi-kg to ton quantities for organic transformations such as C−H activation,[3] cross-coupling,[4] and precatalyst manufacture.[5] Examples of its commercial uses include multi-ton manufacture of pharmaceutical and agrochemical molecules such as montelukast,[6] eletriptan,[7] and boscalid.[8]

The formation and amount of byproducts **2** and **3** can be correlated to the concentration of NO_x[9,10] and water present,[10] respectively, during the traditional preparation of catalyst **1**. Although the amount of impurity **3** observed in commercially available palladium acetate appears to be minimal in recent years, by employing analytical techniques such as IR spectroscopy and insol tests, it has been reported to contain up to 20 mol % of **2**.[10] Recently, there have been reports on the benefits of recrystallized **1**[11] demonstrating its improved reactivity in catalysis and precatalyst formation, although this requires the use of carcinogenic solvents such as benzene. However, a recent report by Fairlamb et al. demonstrated that **1** and **2** may share similar catalytic efficacy in C−H arylation using precatalysts derived from both palladium sources where the NO_2^- ion was considered to be a spectator ligand.[5b] To the best of our knowledge, it has been assumed that **3** is inactive as a catalyst as there are no reports of its use, although its synthesis and characterization are reported in detail.[10,12] Herein, we report the synthesis of pure **1**−**3** (see Supporting Information) to compare their activities in a variety of cross-coupling reactions. The unexpected activity of polymeric **3** in many cross-coupling reactions and the limitations of **2** and **3** in certain chemistries, especially precatalyst formation will be discussed.

To avoid the formation of **2** and **3** completely during the synthesis of pure **1**, we report a new method that involves a ligand exchange with palladium pivalate. In this process, commercially available $Pd_3(OPiv)_6$[13] is heated with excess acetic acid to form high purity **1** (eq 1). The nitrito complex, **2**,

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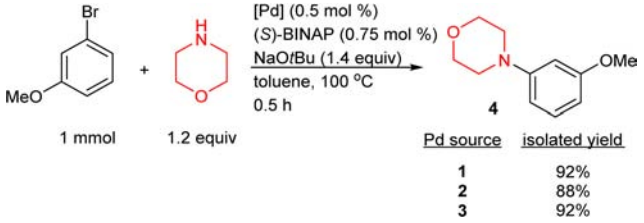
and polymeric **3** were obtained in high purity via modifications to the traditional synthesis (see Supporting Information).

$$Pd_3(OPiv)_6 \xrightarrow[100\ ^\circ C, 5\ h]{HOAc} Pd_3(OAc)_6 \quad (1)$$

Although **1** and **2** can be characterized by solution phase ^1H NMR spectroscopy under careful conditions,[9] polymer **3** proved more challenging to characterize because of its high insolubility in most organic solvents. Thus, we utilized solid-state ^{13}C NMR for analyzing **1**−**3** to identify their differences. Pure **1** contains both methyl (20−25 ppm) and carbonyl sites (185−195 ppm) which were fit to 12 pseudo-Voigt profiles of approximately equal area and was therefore consistent with the reported trimeric structure of **1**. Because of the small separations in the spectrum, however, assignment of the individual peaks was not possible. A similar analysis was conducted for **2** and **3**. Polymer **3** exhibits two peaks in both the methyl and carbonyl regions, which is consistent with the linear polymer crystal structure. Nitrito complex **2** also contains two resolvable peaks in each region and their relative intensities allow the material to be easily distinguished from the polymer. Subsequent DFT calculations were in agreement with the observed spectra and were also consistent with a trimeric structure (see Supporting Information).

To understand the activities of **1**−**3**, initially, we examined their use in the Buchwald-Hartwig amination of 3-bromoanisole with morpholine (Scheme 1). Surprisingly, all three species

Scheme 1. Buchwald−Hartwig Amination of 3-Bromoanisole with Morpholine Using 1−3

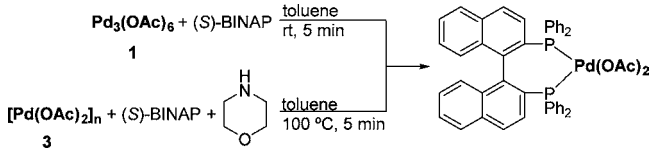


were equally effective in forming the desired product at 100 °C. The activity of **3** was highly unexpected considering its insolubility in most organic solvents.

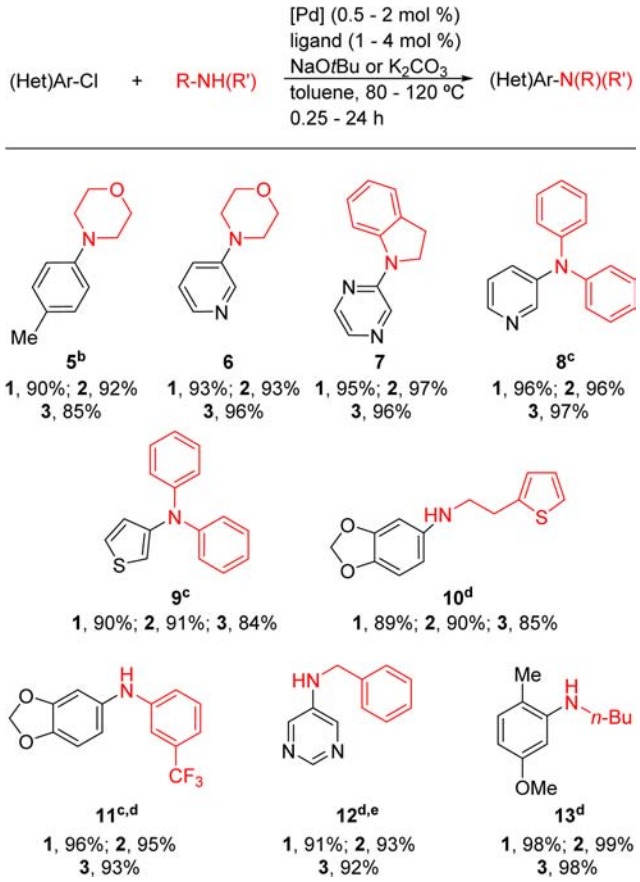
In an effort to understand the unexpected activity of polymer **3**, we examined the reaction conditions leading to its "depolymerization". Heating **3** in toluene at 100 °C resulted in no change of the catalyst. The addition of 1 equiv of morpholine led to the formation of a palladium mirror at 100 °C. When mixing **3** with (*S*)-BINAP, we noted low conversion of 25% to the preformed complex, [(*S*)-BINAP]Pd(OAc)$_2$ by ^{31}P NMR spectroscopy after 18 h at 100 °C. Interestingly, mixing 1 equiv of both morpholine and (*S*)-BINAP with **3** at 100 °C led immediately to a homogeneous red solution, which contained [(*S*)-BINAP]Pd(OAc)$_2$[14] with a small amount of unreacted ligand. The use of different amines such as *n*-butylamine, aniline, or piperidine in place of morpholine afforded similar results. On the contrary, [(*S*)-BINAP]Pd(OAc)$_2$ was readily formed on mixing **1** with (*S*)-BINAP at room temperature without the presence of an amine (Scheme 2).

Following this observation, we expanded our scope of Buchwald−Hartwig amination to include a variety of primary and secondary amines using **1**−**3** (Scheme 3). Under these conditions, all three catalysts provided similar activity, affording

Scheme 2. Synthesis of [(*S*)-BINAP]Pd(OAc)$_2$



Scheme 3. Buchwald−Hartwig Amination Using 1−3[a]



[a]Reaction conditions: Pd catalyst (0.5−2.0 mol %), RuPhos (1.0−4.0 mol %), aryl chloride (1 mmol), amine (1.2 mmol), NaO*t*Bu (1.4 mmol), toluene (2 mL/mmol), 80−120 °C, isolated yields reported. [b]JohnPhos ligand used. [c]5 mol % H_2O added. [d]BrettPhos ligand used. [e]Aryl bromide used and K_2CO_3 as base.

the desired products in good yield. The polymer **3** provided comparable results even at low loadings (0.5 mol % Pd) and short reaction times (<15 min) (**7**). Challenging partners such as diphenylamine (for making **8**, **9**) and 3-trifluoroaniline (for making **11**) were also coupled, although the reactions required a small amount of water to reach full conversion. Buchwald et al. have reported the importance of water in C−N cross-coupling reactions to aid the reduction of Pd(II) to the active Pd(0) species when palladium acetate was used.[15]

Intrigued by these results, we next examined a Suzuki-Miyaura coupling at room temperature (Figure 2). Using modified literature conditions at 30 °C,[16] **1** and **2** provided full conversion to **14** in 2 h, whereas **3** gave only 82%. Further reducing the temperature to 20 °C resulted in a drastic decrease in conversion using **3** (27%), whereas the activity of **1** and **2** remain unchanged. Interestingly, **2** appears to be slightly more active than **1** for this particular coupling, presumably because of

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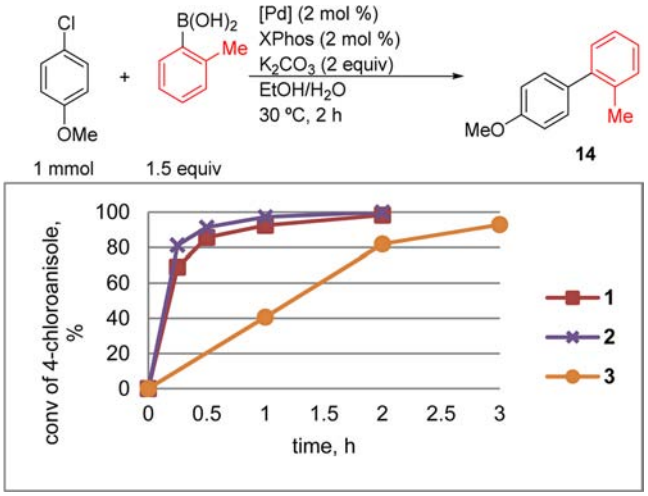
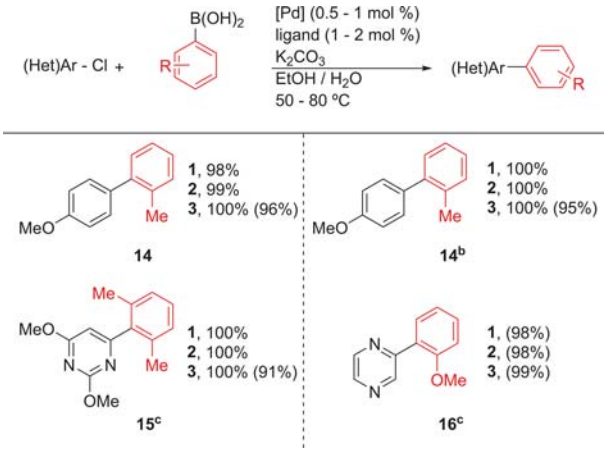


Figure 2. Calibrated GC conversion of 4-chloroanisole.

its higher solubility. However, **1**–**3** afforded similar yield of **14** at 50 °C (Scheme 4, top left). This demonstrates that under the

Scheme 4. Suzuki–Miyaura Coupling Using 1–3[a]



[a]Reaction conditions: Pd catalyst (0.5–1.0 mol %), XPhos (1–2 mol %), aryl halide (1.0 mmol), boronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), EtOH (2 mL), H_2O (2 mL), 50–80 °C, NMR yield reported using 1,3,5-trimethoxybenzene or mesitylene as internal standard. isolated yield in parentheses. [b]Aryl bromide used, PPh_3 as ligand. [c]AmPhos as ligand.

Suzuki conditions, slightly elevated temperatures minimize the differences between the three palladium sources. Similar activities were observed at 50 °C for both aryl and heteroaryl halides, even when a less electron-rich ligand, such as PPh_3, was employed (**14**, Scheme 4, top right).

Moving forward with our investigation, we examined a reported ligandless α-carbonyl arylation at 80 °C (Table 1).[4g] We observed 100% NMR yield of aryl ketone **17** using **1** and **2**; however, only 39% was afforded using polymeric **3** (Table 1). Further increasing the reaction time using **3** provided a moderate increase in yield to 51%. However, the addition of 2 mol % of JohnPhos with **3** gave 93% yield. This further demonstrates that the ligand could play a role in assisting **3** to form an active catalytic species efficiently.

To expand the name reaction scope further, we compared the activities of catalysts **1**–**3** in the Mizoroki–Heck reaction of

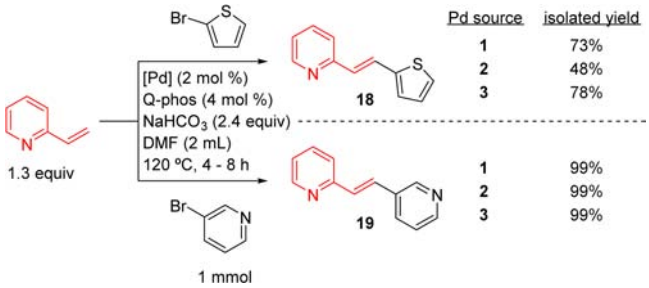
Table 1. Ligandless α-Carbonyl Arylation Using 1–3

entry	Pd source	NMR yield (%)[a]
1	**1**	100
2	**2**	100
3	**3**	39
4[b]	**3**	51
5[c]	**3**	93

[a]NMR yields obtained using 1,3,5-trimethoxybenzene as internal standard. [b]22 h reaction time. [c]Added 2 mol % JohnPhos ligand to reaction.

2-bromothiophene and 2-vinylpyridine (Scheme 5).[4h] Contrary to our previous observations, **2** gave an inferior yield of 48% in

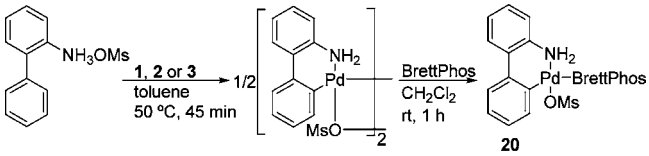
Scheme 5. Mizoroki–Heck Reaction Using 1–3



comparison to pure **1** (73%) or polymeric **3** (78%). However, this did not hold true when the electrophile was changed to 3-bromopyridine under identical conditions. In this example, **1**–**3** display similar activity, giving full conversion with 99% isolated yield in all three cases. It is unclear why **2** gave a lower yield in the prior example.

Finally, we studied the effect of **2** and **3** on the synthesis of a palladacycle precatalyst. Buchwald has used palladium acetate to prepare various preformed catalysts that often exhibit superior activity in cross-coupling reactions. A representative example is the third generation BrettPhos palladacycle (**20**) which is prepared by a cyclometalation reaction of palladium acetate with 2-biphenylammonium mesylate to form the dimeric palladacycle (Scheme 6).[5a]

Scheme 6. Synthesis of Third Generation BrettPhos Palladacycle Using 1–3



Pd source	yield of dimer	yield of **20**
1	98.2%	94%
2	82.6%	87%
3	0%	

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The dimer is further reacted with BrettPhos to yield the desired palladacycle in high yield. Preparation of **20** using **1** proceeded as described in the literature with similar yield and purity. In contrast, when using **3** for the dimer formation, no conversion of the starting material was observed. Although the use of **2** resulted in the formation of **20**, a lower yield (72% overall) with significant unidentified impurities was observed in both the intermediate and final products. Compound **20**, synthesized using **2** gave several impurity peaks by ^{1}H NMR spectroscopy and two additional unidentified peaks by ^{31}P NMR (42.2 and 44.0 ppm). These observations are similar to those reported by Fairlamb during the synthesis of Pd-$(OAc)_2(pip)_2$ (pip = piperidine) using **2**, which led to a complex ^{1}H NMR spectra, although the complex was reported to be catalytically active.[5b] We were unable to isolate the impurity for unambiguous structural assignment. In addition, the product yield for both steps was lower when **2** was used instead of **1**.

In conclusion, this study provides the first systematic investigation of the reactivity of pure palladium acetate in comparison to two common impurities, **2** and polymeric **3**. Although **3** was believed to be inactive, this study demonstrates that at elevated temperatures and slightly modified reaction conditions (e.g., addition of a ligand) it exhibits high levels of reactivity similar to pure **1** in Buchwald–Hartwig, Suzuki–Miyaura and Mizoroki–Heck cross couplings, and in a ketone alpha-arylation example. However, there are exceptions; for example, **3** is inferior for the synthesis of a palladacycle precatalyst and in cross-coupling at reduced temperatures and/or in the absence of a phosphine ligand. On the basis of these differences in reactivity of **2** and **3**, we recommend high purity palladium acetate as a control catalyst when evaluating commercial samples of palladium acetate to ensure reliable and reproducible results.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02835.

Experimental procedures and characterization data including solid-state NMR and DFT calculations (PDF)

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Notes

The authors declare the following competing financial interest(s): High purity palladium acetate and palladium pivalate are commercially available through JMCCT (www.jmcct.com).

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