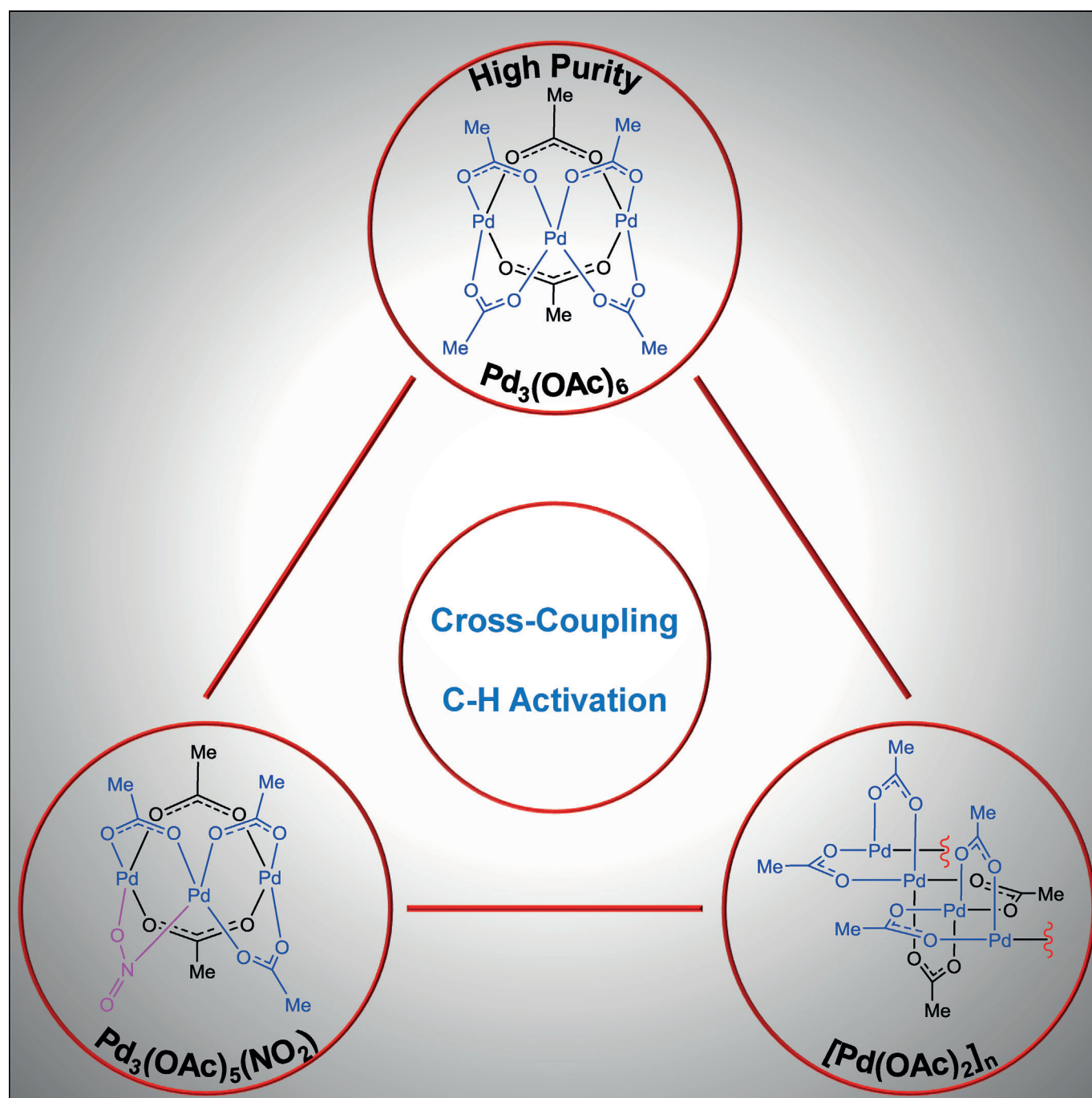


Palladium Complexes

Understanding Palladium Acetate from a User Perspective

William A. Carole and Thomas J. Colacot^{*,[a]}



Abstract: The behavior of palladium acetate is reviewed with respect to its synthesis, characterization, structure (in both solution and solid state), and activation pathways. In addition, comparisons of catalytic activities between pure palladium acetate and two common byproducts,

$\text{Pd}_3(\text{OAc})_5(\text{NO}_2)$ and polymeric $[\text{Pd}(\text{OAc})_2]_n$, typically present in commercially available material are reviewed. Hence, this minireview serves as a concise guide for the users of palladium acetate from both academia and industry.

1. Introduction

Cotton's description of the "non-trivial" behavior^[1] of the widely used commodity chemical, palladium acetate, $\text{Pd}_3(\text{OAc})_6$ (**1**), with respect to its characterization and impurities has been apt until recently. Palladium acetate is one of the most popular Pd precursors in metal-catalyzed organic synthesis, particularly for cross-coupling reactions,^[2] based on the number of publications and patents.^[3] Many blockbuster drugs such as singulair,^[4] losartan,^[5] eletriptan,^[6] naproxen,^[7] and agrochemicals such as prosulfuron^[8] and boscalid^[9] utilize ton quantities of **1** as a catalyst precursor. The monomer Cyclotene, which is used as a coating and adhesive for a variety of electronics applications, is made by a Heck reaction using palladium acetate.^[10,11] Palladium acetate has also been used to make small-molecule electron donors for heterojunction solar cells via Suzuki–Miyaura coupling.^[12] In addition, **1** is used in the synthesis of various precatalysts for cross-coupling.^[13]

However, researchers from both academia and industry have expressed frustration from time to time, as they have encountered problems with reproducibility, activity, and selectivity from batch to batch, supplier to supplier, and also moving from lab to production scale when utilizing commercially available palladium acetate. This is, in part, due to the absence of a uniform analytical approach to determine the purity of **1**. In addition there can be inconsistencies due to a variety of factors including particle size,^[14] reaction solvent, and the conditions employed.^[15] Two common impurities often present in commercially available **1** include $\text{Pd}_3(\text{OAc})_5(\text{NO}_2)$ (**2**)^[16] and the insoluble, polymeric $[\text{Pd}(\text{OAc})_2]_n$ (**3**) (Figure 1), whose influence in catalysis and precatalyst formation was recently investigated.^[13k,15] Although **1** is believed to be an air- and moisture-stable compound, it has been shown to react readily with trace amounts of water (**4**)^[1,17] and certain alcohols (**5**)^[17] to generate new species in solution which adds further complexity to its characterization and activity studies. In addition, Bedford and co-workers recently demonstrated that **1** will slowly convert to **4** (34%) when left exposed to air for eight days, highlighting the importance of storage conditions due to its water sensitivity in the solid state.^[17a]

Nevertheless, **1** can be considered superior to its alternatives, such as $\text{Pd}(\text{dba})_2$, $\text{Pd}_2(\text{dba})_3$, or $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ as a cata-

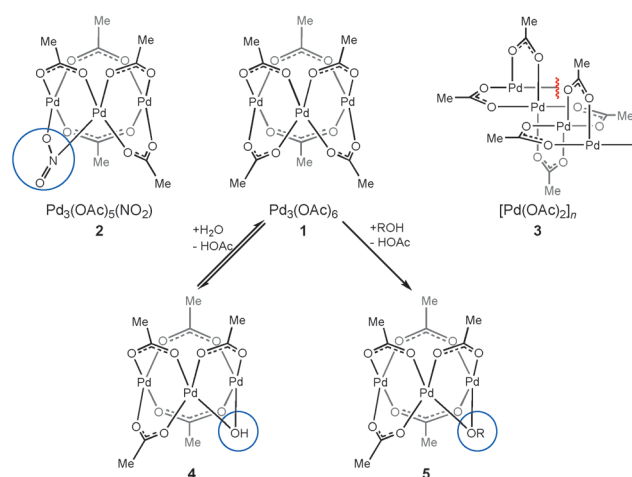


Figure 1. $\text{Pd}_3(\text{OAc})_6$ (**1**), $\text{Pd}_3(\text{OAc})_5(\text{NO}_2)$ (**2**), $[\text{Pd}(\text{OAc})_2]_n$ (**3**), hydrolysis product (**4**), and alcoholysis product (**5**).

lyst precursor from a stability and process economics point of view. Although the $\text{Pd}_x(\text{dba})_y$ catalyst family is utilized in a variety of organic transformations, some reports have demonstrated that free dba can interfere with the active L_nPd^0 species, hindering oxidative addition.^[18] Fairlamb et al. have reported that for some reactive organohalides (i.e. Ar-Br) free dba can be beneficial by limiting the availability of the active L_nPd^0 species, thereby reducing the formation of inactive Pd clusters.^[18c,19] In a recent, widely publicized report, Ananikov and Zaleskiy stated that routine testing of $\text{Pd}_2(\text{dba})_3$ is required due its tendency to decompose into nano-Pd.^[20] Therefore, "the content of catalytically active species may significantly vary, thus leading to estimation of incorrect values of mol%, TON and TOF actually employed in the reaction."^[20] Having said that, Fairlamb and Reay have shown that nano-Pd can be useful in cross-coupling reactions with less challenging substrates such as aryl bromides and iodides.^[21] Thus, due to the innate instability of $\text{Pd}_x(\text{dba})_y$ catalysts and potential interference of free dba, use of a stable palladium precursor, such as palladium acetate can be more practical in several organic transformations.

The purpose of this minireview is not to provide an exhaustive account of palladium acetate or its applications but to consolidate many of the reported syntheses and characterization and application studies of **1** in a concise manner and provide insight into the purity determination and the subsequent use of a given sample of palladium acetate in comparison to byproducts **2** and **3**. By providing these guidelines for the general use of **1**, we hope that its users can minimize potential

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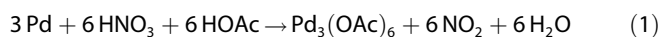
errors while conducting reactions either in an R&D or commercial setting.

2. Review on Synthesis, Purity and Characterization

The following section is intended to critically analyze the reported syntheses of palladium acetate and provide recommendations for the synthesis of high purity palladium acetate, **1**. We will also outline how its purity can be determined using simple techniques from a user perspective.

2.1. Synthesis of high purity palladium acetate

The synthesis of palladium acetate was first reported by Wilkinson et al.,^[22] where glacial acetic acid containing palladium powder is heated at reflux with a minimal amount of nitric acid until the generation of brown NO_x fumes ceases [Eq. (1)]. Although this is a relatively old method, it is still the most commercially employed route for the synthesis of **1**, considering the process economics. Since then, several modified methods have been reported in the literature,^[1,16,23,24] however, depending on how the reactions are conducted (e.g. mole ratio, order of reagent addition, reaction time, temperature, etc.), two impurities (**2** and **3**, Figure 1) can be obtained in variable amounts. As mentioned in the introduction, **1** is known to react with trace amounts of water to form the hydrolysis product, **4**, which can further complicate its isolation and characterization. This observation is supported by our own experiences in this area as well as the characterization studies by Cotton in 2005,^[1] and more recently by Stolyarov,^[16] Fairlamb,^[13k] Bedford,^[17a] and Nosova.^[17b]



Two modified methods reported by Hausman and co-workers to avoid the formation of **2** and/or **3** include reacting palladium hydroxide in acetic acid^[23a,b] or dissolving palladium metal in acetic acid in the presence of other strong acids under a positive pressure of oxygen.^[23c] An attempt by Stolyarov et al.^[16] to repeat the former method led to incomplete conversion with a tedious work-up, involving multiple extractions and solvent removal steps. We also encountered similar issues while repeating this same procedure. The latter method can be potentially hazardous as palladium acetate solid is known to explode when grinding in air at higher temperatures. In addition the process may lead to the formation of polymeric palladium acetate, **3**.

In 2005 Cotton's group reported a modification to Wilkinson's method in which nitrogen gas was bubbled through the reaction mixture to rapidly sweep the NO_x fumes generated during the distillation of excess acetic acid to prevent the formation of **2** and **3**.^[1] Although this preparation is reported to produce pure **1** in high yield (94%), we were unable to reproduce this result. Stolyarov's attempt afforded results similar to ours, obtaining a mixture of **1** and **2** with 70% overall yield.^[16] A minor deviation in our attempt to repeat the experiment in-

volved the use of commercially manufactured palladium sponge versus Pd sponge obtained via reduction of Na₂PdCl₄ as outlined by Cotton.^[1] After multiple attempts to mimic the system, full conversion of the palladium sponge was never realized. This may highlight the importance of the palladium source used in the synthesis of **1**.

More recently, Stolyarov et al. reported a new route where palladium nitrate crystal is reacted with sodium or potassium acetate in aqueous acetic acid at room temperature for 24 h.^[16] The alkali metal acetate acts as a scrubbing agent to bind any free NO₃⁻ ions thus suppressing the formation of **2** and **3**. The amount of water used was crucial as the reaction in glacial acetic acid yielded only **3**, however, when conducted in water alone, a low yield (32%) was obtained, presumably due to the hydrolysis of **1**.^[16] Although we were able to reproduce this method in our lab to afford **1**, incomplete conversion was observed even after 24 h.

Inspired by Wilkinson's comment on the carboxylate exchange (transesterification) on Pd, we recently reported a method which, thus far, has produced very pure palladium acetate (>99.8%) without trace formation of **2** or **3** by conversion of palladium(II) pivalate to **1** through ligand exchange [Eq. (2)].^[15,25] This method avoids the use of water which may lead to reduced yield by forming the hydrolysis product **4**. In addition, it eliminates the use of strong acids, which are known to catalyze the formation of **3**.^[16] To date we believe that this is the best method to obtain high purity **1**, as recryst-

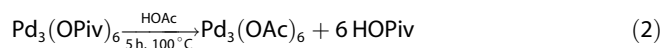
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tallization of impure **1** made via the traditional synthesis is not practical due to the use of large quantities of hazardous solvents, such as benzene.^[26]



2.2. Characterization and purity of palladium acetate

Determining the purity of palladium acetate can be a complicated task and is a prime factor in Cotton's description of its "non-trivial" behavior. Although several analytical methods exist to characterize **1**, traditional approaches include infrared (IR) spectroscopy and elemental (C,H,N) analysis.^[22] More recently a method was developed using solution-phase ¹H NMR spectroscopy under rigorous anhydrous conditions.^[1] While all of these methods are practical, we have observed that a combination of the available methods can be devised to determine the purity of **1** accurately.

Although IR and elemental analysis remain the most widely reported tests to determine the purity of **1**, they do not provide an accurate picture of purity. While IR spectroscopy provides a qualitative estimate of sample purity, quantitative analysis can be difficult due to non-linear effects with respect to sample concentration. In our lab, we performed diffuse reflectance IR spectroscopy on pure samples of **1–3** in the solid state.^[27] Spectra obtained for **1** and **2** correlated well with previously reported values.^[1,16,22] While the presence of **2** and **3** can be detected by IR spectroscopy, > 1–2 mol% of either impurity is required due to the limits of detection.^[28] As **1** and **3** share identical chemical composition, elemental analysis cannot be used to differentiate the two, however, to a certain extent it can be used to determine the amount of **2** present in a sample by accurately measuring the nitrogen content.

Other methods to assess sample purity include melting point analysis and solubility (Table 1). The decomposition point of pure **1** is reported to be 205 °C.^[22] High purity material generated in-house provided similar results degrading between 203–205 °C. Impurities **2** and **3** appeared to be more stable, decomposing at temperatures above 222 °C. Solubility, however, can be used to quantitatively determine the amount of **3** present. While **2** is more soluble than **1**, the nearly insoluble nature of **3** (Table 1) allows it to be separated with ease followed by IR and elemental analysis for full characterization.^[29]

Table 1. Melting point and solubility data for **1–3**.

Compound	Decomp range [°C] ^[a]	Solubility [mg mL ⁻¹]			
		toluene	acetone	THF	DMF
1	203–205	13.2	19.2	20.0	41.7
2	222–228	13.9	25.0	71.4	100
3	222–224	insol.	insol.	insol.	insol.

[a] All samples decomposed in the range specified and were not observed to melt. The range provided is the point at which decomposition was first noted and when the sample fully decomposed.

Until Cotton's report in 2005, NMR spectroscopy was ineffective, as commercial samples often contained multiple peaks (Figure 2) instead of a single peak as expected for pure **1**.^[1] Due to the facile hydrolysis of palladium acetate in a solution containing trace amounts of water, the spectrum is often complicated by the appearance of four additional resonances (Figure 2, **1**), which are interestingly not observed for complex

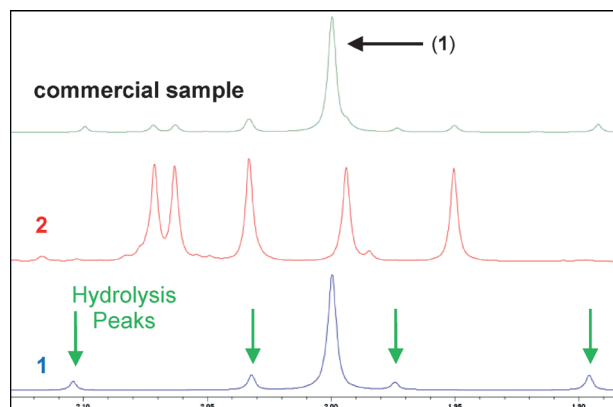


Figure 2. ¹H NMR spectra using non-anhydrous CDCl₃ for **1** and **2**.^[31]

2. The situation is further complicated if impurity **2** is present in large concentrations (Figure 2, commercial sample). Cotton found that by using anhydrous solvent a single peak for **1** can be obtained by ¹H NMR spectroscopy.^[1] While we have found that sodium-dried C₆D₆ stored in a N₂-filled glovebox works best to obtain a single peak for a pure sample of **1** (δ = 1.63 ppm in C₆D₆),^[15] the use of CDCl₃ (stored over K₂CO₃) is more practical in determining the amount of **2** present because of the higher resolution gained between **1** and **2** (Figure 2) in the proton spectrum. Thus, using dried CDCl₃ and an internal standard (1,4-dimethoxybenzene), we developed a simple method to quantitatively measure the concentration of **2** present in a commercial sample (Figure 3).^[30]

In addition to solution-phase ¹H NMR spectroscopy, we recently reported solid-state ¹³C NMR data for **1–3** (Figure 4).^[15] As there are limited methods available to analyze insoluble **3**, this provided an additional technique to characterize the complex, in comparison to **1** and **2**. Each complex was analyzed in a similar manner and the data obtained, in conjunction with DFT calculations, were in agreement with the accepted trimeric structure of **1** and **2** and the reported linear polymer structure of **3** in the solid state. Similar to IR spectroscopy, this technique may be capable of determining if **2** or **3** are present; however, the detection limit is 1–2% of the total signal.

While several methods exist to determine the purity of **1** such as IR spectroscopy, solution-phase ¹H NMR, solid-state ¹³C NMR, and elemental analysis, individually, they do not always provide a quantitative estimate of the levels of byproducts present. However, using a combination of the available methods, including elemental analysis, solution-phase ¹H NMR spectroscopy, and a solubility test can provide a closer esti-

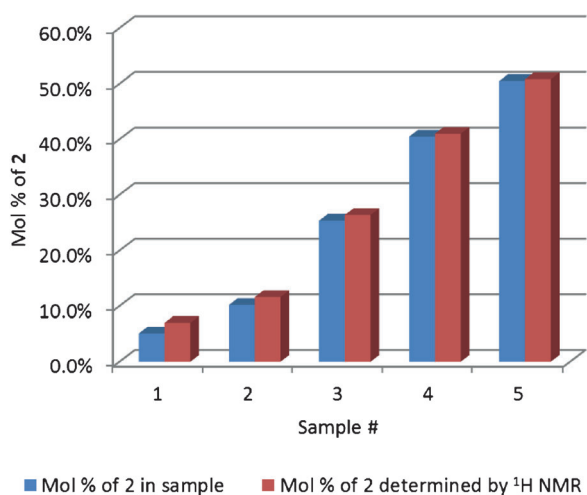


Figure 3. Determination of mol% of **2** present in pre-weighed samples using 1,4-dimethoxybenzene as an internal standard. Concentration of **2** calculated based on comparison of the internal standard to the combined resonances at $\delta = 2.06$ and 2.07 ppm for **2**.

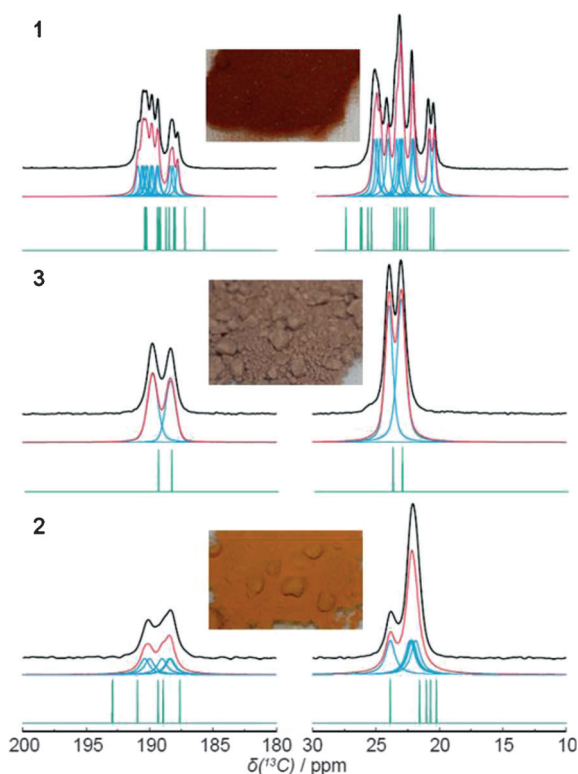


Figure 4. ¹³C CPMAS spectra of $\text{Pd}_3(\text{OAc})_6$, $[\text{Pd}(\text{OAc})_2]_n$ (polymer), and $\text{Pd}_3(\text{OAc})_6(\text{NO}_2)_2$. With the exception of spinning sidebands, no features were present outside of the regions shown. Each spectrum is shown with fitted peaks (blue) and the sum of fitted peaks (red). Schematic spectra (green) show the positions of the calculated chemical shifts.^[15]

mate to the amount of **2** and/or **3** present in any sample of palladium acetate.

3. Structure–Activity Studies of Palladium Acetate

Although there is significant evidence to support the trimeric structure of **1** in the solid state,^[1,22,32] there is still much debate over its structure (or composition) in solution depending on the solvent(s) used. The following section describes the factors affecting the structure–activity relationship in activating the catalyst for organic synthesis applications.

3.1. The structure of palladium acetate in solid versus solution phase

The trimeric structure of **1** in benzene or glacial acetic acid at room temperature, determined by osmometry, was first reported by Wilkinson and co-workers.^[22] We also recently verified the trimeric structure in the solid state through ¹³C NMR solid-state spectroscopy in conjunction with DFT calculations (Figure 5).^[15] This is important as some suppliers incorrectly claim that palladium acetate is monomeric in nature.

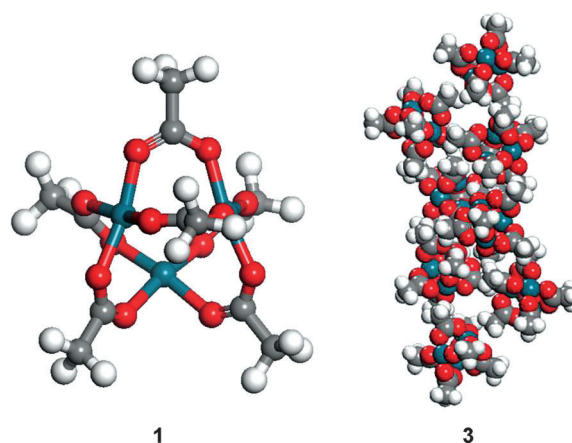


Figure 5. Optimized trimeric structure of **1** and the linear polymeric structure of **3** based on solid-state ¹³C NMR spectroscopy and DFT calculations.^[15]

Since the original report by Wilkinson and co-workers,^[22] there have been several publications suggesting a variety of solution states for **1** including a monomer, dimer, aggregates of trimers, or various polymeric chains (e.g. $[\text{Pd}(\text{OAc})_2]_n$, $n = 1, 2, 3$, etc.) depending on the solvent, concentration, and temperature. Complex **1** has been observed to retain its trimeric structure at ambient temperature in a concentrated solution of chloroform.^[33] However, upon diluting the mixture, the presence of a new linear dimer structure in equilibrium with the trimer was observed using IR spectroscopy. The addition of trace acetic acid was found to shift the equilibrium in favor of the trimer, even at dilute concentrations. Hii et al.^[34] showcased the propensity of **1** to dissociate into monomers in solution, which increases with the dipole moment of the solvent. Even in less polar solvents such as toluene, up to 21% of **1** was found to be monomeric, whereas in N-methylpyrrolidinone (NMP) this increased to 100% (see Table 2) and was consistent with earlier reports.^[35] Compound **1** has also been shown to

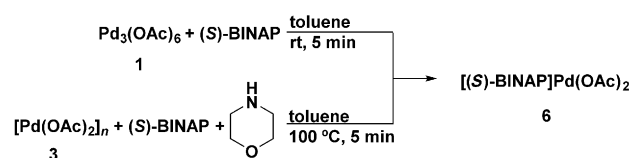
Table 2. Percent dissociation of **1** into monomers in solution.^[34]

Solvent	Dipole moment	% Monomers
benzene	0.00	0
toluene	0.36	21
DMF	3.86	42
NMP	4.09	100

react readily with water^[1] or alcohols where one acetate group is substituted by a solvent molecule (**4** and **5**, Figure 1) while retaining its trimeric structure.^[17] While in the presence of water, equilibrium between species **1** and **4** in solution is observed; in MeOH, **1** will react irreversibly to form complex **5**.^[17b] Therefore, as Bedford et al. suggested,^[17a] reactions conducted in the presence of water or alcohols should be based on species **4** or **5**, and not on **1** alone.

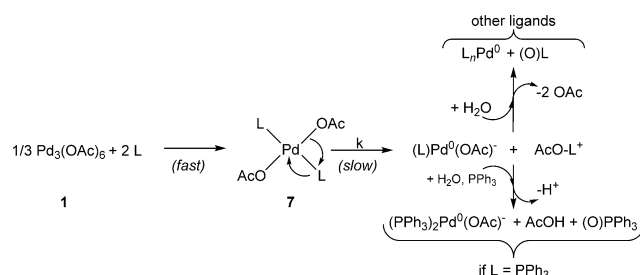
3.2. Activation of palladium acetate

Ozawa and Hayashi were the first group to propose a reduction pathway for **1** in the Mizoroki–Heck reaction using excess (*R*)-BINAP in the presence of Et₃N.^[36] The preformed complex, [(*R*)-BINAP]Pd(OAc)₂ was observed to form spontaneously in solution followed by slow reduction to give the inactive 18-electron species, [(*R*)-BINAP]₂Pd and one equivalent of [(*R*)-BINAP]-monoxide. These observations mirrored our own, where [(*S*)-BINAP]Pd(OAc)₂ (**6**) was formed within 5 min at room temperature in the absence of an amine. However, the addition of an amine was crucial to break up polymeric **3**, which later underwent reduction to form the same active catalytic species (Scheme 1).^[15]



Scheme 1. Reaction of **1** or **3** with (*S*)-BINAP.^[15]

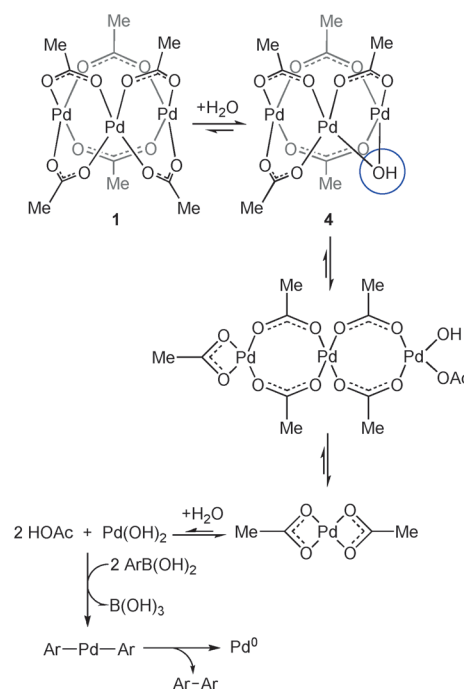
Similar observations were reported by Amatore et al. while using PPh₃ or 1,3-bis(diphenylphosphino)propane (dppp) in DMF (Scheme 2).^[37] In each case a sacrificial equivalent of ligand was required to reduce the Pd^{II} precursor to form the catalytically active Pd⁰ species. Without the added equivalent of ligand, no reduction was observed, however, in the case of bidentate ligands such as dppp, addition of a third equivalent of ligand afforded the inactive 18-electron species, (dppp)₂Pd⁰. Notably, one equivalent of water was necessary to fully form Pd⁰ by shifting the equilibrium away from the thermodynamically favored L_nPd(OAc)₂ (**7**) species, where L_n can be two monodentate phosphines or a single bidentate phosphine ligand.^[37] Buchwald and co-workers have also commented on the importance of water to efficiently form Pd⁰ in the absence



Scheme 2. Reduction of **1** to Pd⁰ as proposed by Amatore et al.^[37]

of other reducing agents such as arylboronic acids or amines which are subject to β-hydride elimination.^[38]

As stated earlier, the presence of a phosphine ligand in solution readily breaks up trimeric **1** into the monomeric species, even in non-polar solvents such as benzene or toluene, which can further undergo reduction enhanced by the presence of water. Hii et al., found that excess water and a reducing agent, such as ArB(OH)₂ could facilitate the reduction of trimeric palladium acetate, **1**, in the absence of a phosphine ligand in a less polar solvent.^[34] Interestingly, there is no reduction of **1** to Pd⁰ when only two equivalents of ArB(OH)₂ are present in anhydrous THF or toluene; however, switching to a 25% H₂O–THF system led to the formation of a key intermediate, Pd(OH)₂, generated from **4**,^[17] which further undergoes reduction in the presence of the arylboronic acid (Scheme 3). It is important to note that Hii et al. originally reported a hydrolyzed palladium acetate^[34] intermediate similar to what Cotton et al.^[1] reported in 2005. However, recent studies by Bedford and Nosova and co-workers have shown that the complex formed from reaction with water is actually **4**.^[17]



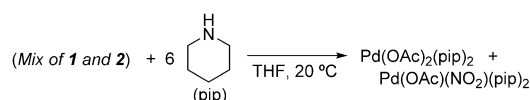
Scheme 3. Reduction of **1** to Pd⁰ using ArB(OH)₂ assisted by water.^[34]

3.3. Activity studies of pure palladium acetate (1) versus its two impurities (2,3)

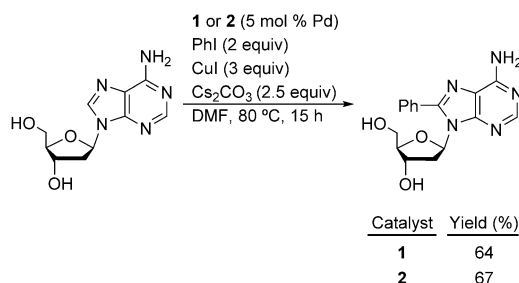
Although there are a significant number of publications on the use of **1** in precatalyst formation^[13] and cross-coupling including, but not limited to, Suzuki–Miyaura,^[39] Buchwald–Hartwig,^[40] Mizoroki–Heck,^[41] and C–H activation^[42] only limited information has been reported on the impact of impurities **2** and **3**. As palladium acetate is a widely used catalyst and commercial samples may contain up to 20 mol% **2**,^[16] one may consider the impact of the nitrite ion to be minimal. However, an older example involving the catalytic oxidation of methane provides some insight on its potential effect in certain chemical transformations. One such example involving the oxidation of methane to methyl trifluoroacetate using palladium acetate afforded the desired product in 60% yield in four days.^[43] Later attempts to reproduce these results using pure **1** were unsuccessful, suggesting impurity **2** or the presence of NO₂[−] may promote this catalysis, although its exact role is unclear.^[13k, 44] In a more recent example, Fairlamb and co-workers reported on the impact of **2** in the formation of a precatalyst and in the direct arylation of 2'-deoxyadenosine (Scheme 4), which identified the nitrite ion to be a spectator ligand in this particular reaction.^[13k] A recent minireview article by Fairlamb et al. provides additional discussion of the possible roles of NO_x ligands in Pd catalysis.^[45]

Recently our group has undertaken a closer examination of the impurities **2** and **3** to determine their impact, if any, as compared to pure palladium acetate, **1** (Table 3).^[15] To our surprise, the presumably inactive polymer, **3**, was found to be

Precatalyst Formation



Use in Catalysis

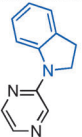
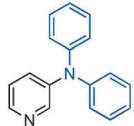
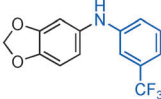
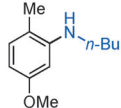
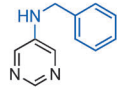
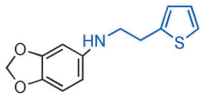

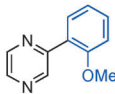
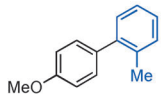
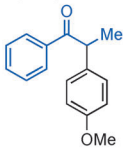


Scheme 4. Fairlamb's study on the synthesis of Pd(OAc)₂(pip)₂ and the direct arylation of 2'-deoxyadenosine^[13k, 45]

active in certain chemical transformations depending on the reaction conditions. Under our conditions, the Buchwald–Hartwig arylation of both 1° and 2° amines with aryl and heteroaryl halides afforded the desired products in good yield for catalysts **1–3**. For amines lacking a β-hydrogen, addition of water was essential to enhance the reaction rate, presumably by promoting the reduction of **1** which correlates with previous reports by Buchwald,^[38] Ozawa^[36] and Amatore (Scheme 2).^[37]

The Suzuki–Miyaura coupling of aryl and heteroaryl halides also gave the desired products in comparable yield at elevated

Table 3. Cross-couplings using **1–3**.^[15]

(Het)ArX X = Br, Cl		+	Nu-R R = H, B(OH) ₂	1, 2 or 3 conditions	(Het)Ar-Nu
Buchwald-Hartwig Amination^[a]					
					
1 , 95%; 2 , 97% 3 , 96% ^[b]	1 , 96%; 2 , 96% 3 , 97% ^[c]	1 , 96%; 2 , 95% 3 , 93% ^[d]	1 , 98%; 2 , 99% 3 , 98% ^[e]	1 , 91%; 2 , 93% 3 , 92% ^[f]	1 , 89%; 2 , 90%; 3 , 85% ^[g]
Suzuki-Miyaura Cross-Coupling^[h]					
					
1 , (100%); 2 , (100%) 3 , (100%), 91%	1 , 98%; 2 , 98% 3 , 99%	1 , (98%); 2 , (99%) 3 , (100%), 96% ^[i]	1 , (100%) 2 , (100%) 3 , (39%) 3 , (51%) ^[k] 3 , (93%) ^[l]		
α-Carbonyl Arylation^[j]					

[a] Isolated yields reported, NMR yields in parentheses. General conditions: Aryl chloride (1.0 mmol), amine (1.2 mmol), NaOtBu (1.4 mmol), toluene (2 mL).
 [b] 0.5 mol% Pd catalyst, 1.0 mol% RuPhos, 90 °C, 15 min. [c] 2.0 mol% Pd catalyst, 4.0 mol% RuPhos, 120 °C, 16 h. [d] 2.0 mol% Pd catalyst, 4.0 mol% BrettPhos, 110 °C, 22 h. [e] 0.5 mol% Pd catalyst, 1.0 mol% BrettPhos, 80 °C, 0.5 h. [f] 3.0 mol% Pd catalyst, 6 mol% BrettPhos, K₂CO₃ (1.4 mmol), 110 °C, 24 h. [g] 2.0 mol% Pd catalyst, 4.0 mol% BrettPhos, 110 °C, 1 h. [h] General conditions: Aryl chloride (1.0 mmol), boronic acid (1.5 mmol), K₂CO₃ (2.0 mmol), EtOH (2 mL), H₂O (2 mL), Pd catalyst (1.0 mol%), AmPhos (2.0 mol%), 80 °C, 3 h. [i] 0.5 mol% Pd catalyst, 1.0 mol% XPhos, 50 °C, 1.5 h. [j] General conditions: Aryl bromide (1.0 mmol), ketone (1.2 mmol), NaOtBu (1.3 mmol), Pd catalyst (1.0 mol%), toluene (2 mL), 3 h. [k] 22 h reaction time. [l] Added 2.0 mol% JohnPhos ligand.

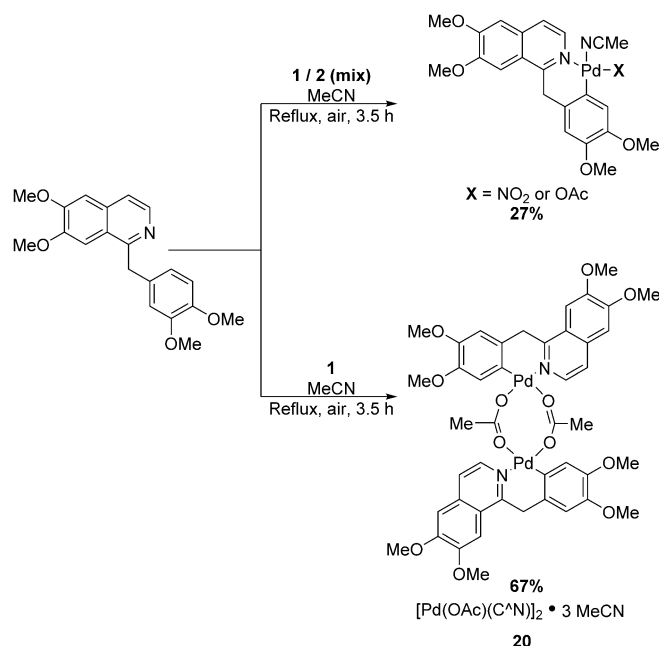
temperatures ($> 50^{\circ}\text{C}$) (Table 3).^[15] At lower temperatures ($< 30^{\circ}\text{C}$), polymeric **3** had significantly diminished activity in the coupling of 4-bromoanisole with *o*-tolylboronic acid (**16**). Interestingly, impurity **2** was slightly more active than **1** in this particular coupling, likely due to higher solubility. Similarly, a noticeable difference was observed in the absence of a phosphine ligand in the α -carbonyl arylation of propiophenone with 4-bromoanisole (**17**). While **1** and **2** gave similar yield, polymeric **3** was far less active (39% yield) under identical conditions even with longer reaction time (51%). However, addition of a phosphine ligand was found to enhance the activity of **3** significantly. This example demonstrates the potential negative impact of polymeric **3** in certain organic transformations depending on the reaction conditions employed.^[15] It was not until the Mizoroki–Heck coupling of 2-vinylpyridine and 2-bromothiophene (**18**) that a negative impact of **2** was observed. While **1** and **3** give comparable yield to the desired product (73–78%), **2** gives only 48%. This result contrasts starkly with the use of 3-bromopyridine (**19**) for the same transformation where all three species were found equally active (Table 4).^[15]

Table 4. Mizoroki–Heck coupling using 1–3. ^{[a] [15]}	
 18 1 , 73%; 2 , 48%; 3 , 78%	 19 1 , 99%; 2 , 99%; 3 , 99%
[a] Isolated yields reported.	

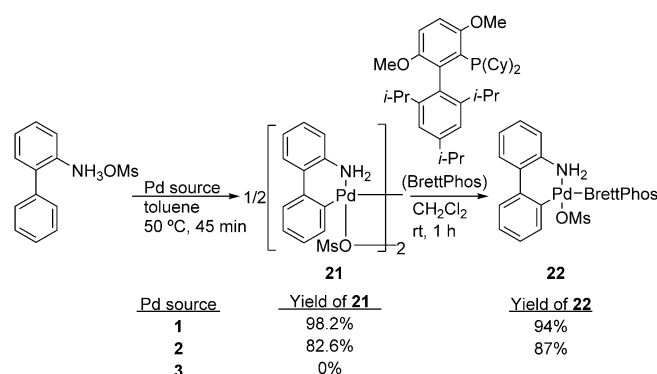
3.4 Impact of impurities in cyclopalladation

Given the importance of **1** for the synthesis of more advanced palladium precatalysts,^[13] effects of **2** or **3** in their synthesis are also of high importance. Fairlamb et al. recently reported on the effects of impurity **2** in a cyclopalladation reaction with papaverine ($\text{C}^{\wedge}\text{N}$) (Scheme 5).^[13k] Following the reaction, a mixture of products was observed, some of which contained a nitrite constituent which was presumed to result from the oxidation of MeCN. However, it was later found that impurity **2** in commercially available palladium acetate was the source of the NO_2^- . Repeating the reaction with pure **1** afforded a novel dimeric complex (**20**) containing three MeCN molecules. Whereas pure **1** provides the desired compound in 67% yield, a mixture of **1** and **2** (~81% **2**) resulted in the formation of byproducts and a lower yield of the palladacycle (27%).^[13k]

Our group has also recently examined the impact of **2** and **3** in cyclopalladation for the formation of the third-generation BrettPhos palladacycle (**22**, Scheme 6).^[15]



Scheme 5. Cyclopalladation with papaverine ($\text{C}^{\wedge}\text{N}$) using **1** or **2**. MeCN molecules for complex **20** structure omitted for clarity. (Structure adapted from Figure 3 of ref. [13k].)



Scheme 6. Synthesis of third-generation BrettPhos palladacycle using 1–3.^[15]

When using **1** the desired products in both steps matched the results reported in the literature. Using **2** gave a lower overall yield (Scheme 6) with various unknown peaks in the ^1H NMR spectrum, similar to what Fairlamb et al. reported in the synthesis of $\text{Pd}(\text{pip})_2(\text{OAc})_2$ and $[\text{Pd}(\text{OAc})(\text{C}^{\wedge}\text{N})]_2$ (**20**).^[13k] Polymeric **3** was completely unreactive for the formation of the precursor dimer complex (**21**). Both of these studies clearly highlight the benefits of using high purity palladium acetate in precatalyst formation, however more studies may be needed to establish generality.^[13k, 15, 45]

4. Summary

In summary, this minireview hopes to provide a user guide on the available synthetic routes for obtaining high purity palladium acetate. Also described are the known methods for deter-

mining a sample's purity with respect to two common byproducts stemming from its traditional synthesis: $\text{Pd}_3(\text{OAc})_5(\text{NO}_2)_2$, **2** and the polymeric palladium acetate, **3**. While several analytical techniques exist, a combination of the available methods provides a more accurate purity estimate. The structure of palladium acetate was reviewed with regards to its composition in both the solid and liquid phase. While in the solid-state **1** exists as a trimer,^[1,22,32] depending on the solvent used and presence of moisture, it has been shown to exist in various forms while in solution.^[33,34] This information is crucial to consider while examining the activity and mechanism when using **1** in catalysis. With regards to activity, it has been demonstrated that impurities **2** and **3** can be as active as **1** in certain chemistries depending on the conditions employed. However, in precatalyst formation, and especially in cyclopalladation, **1** is clearly superior in terms of process yield and purity.^[15] Thus it is important to have access to high purity palladium acetate as a standard when evaluating commercial samples to ensure reproducibility. Despite its early origin, additional investigations are needed including kinetic and detailed mechanistic studies to further understand the differences between the three species of palladium acetate.

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Keywords: cross-coupling • palladium acetate • purity • synthesis

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- [28] By IR spectroscopy the presence of the polymer is indicated by signals appearing at 1486, 1127, and 713 cm^{-1} . Presence of impurity **2** is indicated by signals appearing at 1568, 1515, 1199, and 868 cm^{-1} .
- [29] Solubility test: Dissolve 2 g of sample in 200 mL of acetone and stir for 5 min. Filter sample, and weigh solids collected to determine amount of polymeric palladium acetate present on mass basis.
- [30] With 1,4-dimethoxybenzene as an internal standard, the concentration of the nitrite species was determined at levels as low as 5% by ^1H NMR spectroscopy. In this experiment, pre-weighed samples of both **1** and **2** were added together along with one equivalent of the standard. The samples were then dissolved in dry CDCl_3 and the spectra were collected for each. A comparison of the area of the methoxy groups of the standard to the methyl groups of **1** gave a good estimate of **2** present. However, comparison of the standard to the resonances of **2** at δ = 2.06 and 2.07 ppm, coincided with the actual concentration of **2** present with higher accuracy (less error). This is attributed to the overlap of the main acetate methyl peak of **1** with one of the methyl peaks of **2**

- in chloroform which increases error in the calculation as the concentration of **2** increases in the sample.
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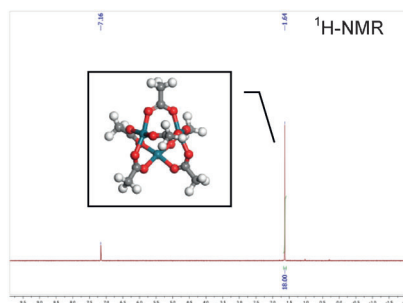
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MINIREVIEW

Palladium acetate, a user perspective!

This minireview provides a concise update on the synthesis, structure, and purity determination of palladium acetate from a user perspective from both academia and industry. Also discussed are the reported activation pathways for pure palladium acetate and the impact of its common impurities in organic synthesis.

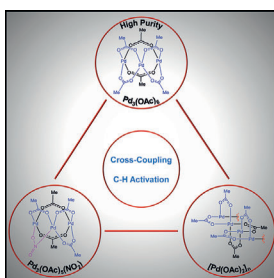


Palladium Complexes

W. A. Carole, T. J. Colacot*

■■ – ■■

Understanding Palladium Acetate from a User Perspective



Palladium Acetate

In their Minireview on page ■■, W. A. Carole, and T. J. Colacot, provide a guide for the users of palladium acetate from both academia and industry, in which they discuss its synthesis, structure, and purity determination. They also give an overview of the reported activation pathways for pure palladium acetate and the impact of its common impurities in organic synthesis.