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The ubiquitous cross-coupling catalyst system ‘Pd(OAc)2’/2PPh3 forms a unique dinuclear PdI complex: an important entry point into catalytically competent cyclic Pd3 clusters

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Palladium(II) acetate ‘Pd(OAc)2’/*n*PPh3 is a ubiquitous precatalyst system for cross-coupling reactions. It is widely accepted that reduction of *in situ* generated *trans*-[Pd(OAc)2(PPh3)2] affords [Pd0(PPh3)n] and/or [Pd0(PPh3)2(OAc)]- species which undergo oxidative addition reactions with organohalides – the first committed step in cross-coupling catalytic cycles. In this paper we report for the first time that reaction of Pd3(OAc)6 with 6 equivalents of PPh3 (*i.e.* a Pd/PPh3 ratio of 1:2) affords a novel dinuclear PdI complex [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] as the major product, the elusive species resisting characterization until now. While unstable, the dinuclear PdI complex reacts with CH2Cl2, *p*-fluoroiodobenzene or 2-bromopyridine to afford Pd3 cluster complexes containing bridging halide ligands, *i.e.* [Pd3(X)(PPh2)2(PPh3)3]X, carrying an overall 4/3 oxidation state (at Pd). Use of 2-bromopyridine was critical in understanding that a putative 14-electron mononuclear ‘PdII(R)(X)(PPh3)’ is released on forming [Pd3(X)(PPh2)2(PPh3)3]X clusters from [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2]. Altering the Pd/PPh3 ratio to 1:4 forms Pd0(PPh3)3 quantitatively. In an exemplar Suzuki-Miyaura cross-coupling reaction, the importance of the ‘Pd(OAc)2’/nPPh3 ratio is demonstrated; catalytic efficacy is significantly enhanced when n = 2. Employing ‘Pd(OAc)2’/PPh3 in a 1:2 ratio leads to the generation of [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] which upon reaction with organohalides (i.e. substrate) forms a reactive Pd3 clusters species. These higher nuclearity species are the cross-coupling catalyst species, when employing a ‘Pd(OAc)2’/PPh3 of 1:2, for which there are profound implications for understanding downstream product selectivities, chemo-, regio- and stereoselectivities., particularly when employing PPh3 as the ligand.

Introduction

Palladium(II) acetate ‘Pd(OAc)2’ is commonly used in combination with tertiary phosphine ligands, *e.g.* PPh3, to generate active catalyst species for an eclectic array of cross-coupling reactions,1 where it is universally accepted that ‘Pd0(PPh3)n’ species are formed.2 Such species enter into oxidative reactions with organohalides, *e.g.* iodobenzene to generate *trans*-[Pd(I)(Ph)(PPh3)2].3 Considerable and notable efforts have been made by Amatore and Jutand4 to understand how varying the ‘Pd(OAc)2’/nPPh3 ratio affects the generation of reduced palladium species in both THF and DMF. Following extensive NMR spectroscopic and electrochemical measurements, conclusions were drawn implicating phosphine-induced reduction of ‘Pd(OAc)2’/nPPh3 mixtures, via *trans*-[Pd(OAc)2(PPh3)2], by an intramolecular process (independent of phosphine concentration, once the latter complex is formed).4 The global findings from Amatore and Jutand are detailed in Scheme 1, showing the key intermediate species observed by 31P NMR spectroscopic studies. Comparisons of these data were made with complexes generated from [Pd(PPh3)4] in the presence of *n*-Bu4NOAc,4a under electrochemical conditions. The conclusions were that ‘Pd0(PPh3)n’ species are generated *in situ* from the reaction of Pd(OAc)2’/2PPh3 mixtures.4a Later studies showed that increasing the Pd/PPh3 ratio to 1:3 and above led to the clean generation of [Pd0(PPh3)n(OAc)]– species (n = 2 or 3), with O=PPh3 being a key side product, *i.e.* formed during the formal PdII→Pd0reduction process.4b,4c Both ‘Pd0(PPh3)2’ and [Pd0(PPh3)2(OAc)]– species react in by oxidative addition with organohalides.

Later, Koller *et al.* examined the reaction of ‘Pd(OAc)2’/nPPh3 in DMF,5 amongst other phosphines, concluding that ‘Pd0(PPh3)n’ species are formed under ambient reaction conditions. Taken together these studies suggest that a Pd/PPh3 ratio of 1:3 is necessary for satisfactory catalytic cross-coupling performance.

Over the last 17 years we have regularly debated the differences in cross-coupling catalyst system performance on changing the Pd/PPh3 ratio from 1:2 to 1:3.6 When papers are reported employing a Pd/PPh3 ratio of 1:2 we have asked the why, as 1:3 would be ideal based on the outcomes of previous studies;.4 in other words, optimal conditions for forming catalytically active [Pd0(PPh3)n(OAc)]– species requires ≥3 equivalents of PPh3 per Pd, “not 2 equivalents”, when ‘Pd(OAc)2’ is used as the initial PdII precatalyst.

A superb recent example is found in the high-throughput automated reaction screening study conducted by a team from Pfizer,7 where a Pd/PPh3 ratio of 1:2 was used for 480 Suzuki-Miyaura cross-coupling (SMCC) reactions, involving changes in solvent and base, against relatively minor changes in substrate structure, correlated alongside many other phosphine ligands (over 5760 reactions in total). Cronin *et al.* further applied a machine learning algorithm based on the product percentage yields.8 With such important developments being made in automation, reaction optimization and machine learning,9 knowing precisely the reactive Pd species, formed under working reaction conditions, has never been more important. Thus, herein we report that the reaction of Pd3(OAc)6 with 6 equivalents of PPh3 (Pd:PPh3, 1:2), in both THF and DMF, generates a well-defined [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] complex **II**. The formation of this unusual species adds to the mechanistic debate concerning the activation pathways for Pd(II) precatalysts, particularly papers reported by: (a) Balcells and Hazari10a showing formation of PdI dimers with NHC ligands and bridging allyl and chloride ligands (eq. 1); (b) Colacot and Schoenebeck10b showing formation of PdI dimers with phosphines and bridging bromide ligands (eq. 2); (c) Bedford10c showing SPhos activation on reaction with Pd(OAc)2 (eq. 3); (d) Jutand and Grimaud10d showing XPhos reactions with Pd(OAc)2 leading to a proposed PdI dimer (eq. 4).



Scheme 1 Reactions of ‘Pd(OAc)2’ with PPh3 (1:2 ratio). 31P NMR spectral data are taken from reference 4a.

The stability and reactivity of these PdI dimers appear to be critical in understanding the delivery of active ‘L-Pd0’ species, a process dependent on L/Pd ratios and additives. From our study we find that [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] **II**, exhibits unique reactivity toward organohalides, *e.g.*CH2Cl2 **1a**, *p*-fluoro-iodobenzene **1b** and 2-bromopyridine **1c**, which affordsPd3 cluster species, namely [Pd3(X)(µ-PPh2)2(PPh3)3]X **VII** (later referred to as **Pd3X•X**, where X = Cl, Br, I or OAc). Our results naturally connect to a recent report showing that **Pd3Cl•Cl** is a highly active catalyst for SMCC reactions, including the activation of substrates containing harder to activate C-Cl bonds.11 **Pd3Cl•Cl** invokes an unusual switch in cross-coupling steps from oxidative addition then transmetallation to transmetallation and then oxidative addition.11



Results and Discussion

The reaction of ultra-pure Pd3(OAc)6 (>99% purity) with PPh3, in varying ratios, in THF-d8 were conducted at room temperature (25 ºC) and monitored by 1H and 31P NMR spectroscopic analysis (where [Pd] = 20 mM; *T* = 298 K, external reference = 85% H3PO4 in H2O). A wide spectral window (–50 to +250 ppm) was required to allow full characterization of the array of phosphorus signals and associated species formed under these reaction conditions (Figs. 1 and 2).

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Figure 1 The room temperature formation of dinuclear PdII complexes from *trans*-Pd(OAc)2(PPh3)2 in THF. The Pd0 species Pd0(PPh3)3 **IX** and[Pd0(PPh3)3OAc]– **IX'** are indicated by cyan circles (appearing as coincident signals by 31P NMR spectroscopic analysis when present together – compare top two 31P NMR spectra in Fig. 2 with the authentic sample of Pd0(PPh3)3 **IX**, bottom spectrum, Fig. 2).

Where the ratio of Pd:PPh3 was 1:1, degradation of Pd3(OAc)6, leading to the formation of large perfectly spherical Pd particles (sized ~ 0.1-0.4 μm, by TEM) and many P-containing species (by 31P NMR) was observed. Alteration of the Pd/PPh3 ratio to 1:2 led to the formation of a major new phosphorus-containing species at δ 199.01 (t, 1P) and δ 13.41 (d, 2P), with a 2*J*PP coupling constant of 83.5 Hz (*i.e.* an AX2 type spin system). The high 31P chemical shift of δ 199.01 indicates that the PPh3 ligand has been activated by *P*-*C* bond-cleavage to give a bridging phosphido-group at Pd, with concomitant loss of ‘C6H5’. The 1H NMR spectrum shows a methyl resonance at δ 2.08 (s, 3H), due to a bridging acetoxy ligand, which balances with aromatic proton integrals (40 H). Running the reaction at lower Pd3(OAc)6 concentration (between 3 and 20 mM) allowed this speciesto be isolatedin a form that could be crystallized. X-ray diffraction analysis of dark red single crystals of this speciesconfirmed its structure as [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] **II**, possessing both bridging µ2-acetoxy and µ-phosphido ligands and terminal-capping PPh3 ligands. The Pd-Pd bond distance was found to be 2.5958(3) Å, which is in-keeping with other dinuclear PdI complexes with bridging µ-acetoxy ligands known in the literature (typical Pd-Pd distances 2.532 to 2.711 Å), and shorter than a related structure, [Pd2(η3-allyl)(µ-OC(O)*i*-Bu)(PPh3)2] where the Pd…Pd bond distance equals 2.6267(3).12

A scaled-up synthesis of **II** was found possible from Pd3(OAc)6 /6PPh3, formed in 31% yield (Note: some Pd is lost as large particles during its preparation), which was fully characterized. Interestingly, the LIFDI-MS data showed that the dinuclear PdI complex was present in solution (M+· = *m/z* 982, with the correct isotopic distribution). The reference 31P NMR spectrum for purified **II** is given in Fig. 2 (externally-referenced to H3PO4). GC-MS analysis of the crude reaction mixture containing **II** indicated that benzene and biphenyl were present, the former most likely derived from protonation of ‘Pd-Ph’ species by adventitious water/AcOH and the latter by reductive elimination. Acetoxybenzene, a possible reductive elimination product, was not detected by GC-MS analysis. These species are accompanied by O=PPh3 **III**, [Ph3P(OAc)]X **IV** and another dinuclear PdII species **VIII**, the latter only in minor amounts. Complex **VIII** was previously reported as a major product of a reaction of ‘Pd(OAc)2’ with 2 equivalents of PPh3 on heating in methanol (41% yield).13 It is worth noting that complex **II** is stable in dry THF solutions over 12 hours, which allows for its spectroscopic characterization, but decomposition is seen after *ca.* 5 days at 22-25 °C.

On changing the Pd/PPh3 ratio to 1:3 complex **II** was not formed, simply a broad resonance at δ 5.71 (FWHM ca. 550 Hz) characterized as Pd0(PPh3)n / [Pd0(PPh3)n(OAc)]P(OAc)Ph3 (n = 1, 2 or 3). The chemical shift alters with time, with concomitant formation of O=PPh3, by hydrolysis of [Ph3P(OAc)]X **IV**, yielding AcOH also. Heating this mixture to 60 ºC, over 16 h, eventually ended in decomposition to form large Pd black particles. Indeed, similar 31P NMR spectra were seen on changing the Pd/PPh3 ratio to 1:4, leading to a mixture of Pd0(PPh3)3 **IX** and [Pd0(OAc)(PPh3)3]– **IX'**. At the same Pd/PPh3 ratio, subsequent heating to 60 ºC resulted in clean conversion of **II** into Pd0(PPh3)3 (**IX**), O=PPh3 (**III**) and 2AcOH, quantitatively, as shown by both 31P and 1H NMR spectra. Layering this solution with hexane, after *t* = 16 h, led to the formation of yellow-orange crystals, which were found suitable for X-ray diffraction, establishing the compound as Pd0(PPh3)3 (**IX**) (Fig. 2). It is worthy of note that **IX** is a relatively stable Pd0 complex in the solid-state (note: discoloration is noted in air after ~1 day).

Computational studies using DFT calculations with [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] **II** at the B3LYP/DEF2SVP-D3 level of theory. The calculations reveal a short Pd-Pd bond (2.58 Å), supporting its diamagnetic properties. The HOMO resides primarily on the Pd-Pd centers, whereas the LUMO can be found over the phosphide and Pd-Pd centers (Fig. 3). The HOMO/LUMO provide potential clues about the underlying reactivity of [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] toward other species such as electrophiles and nucleophiles.

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Figure 2 Top: Single crystal X-ray diffraction structures of **II**, **VIII** and **IX** are shown (thermal ellipsoids shown at 50%, H-atoms and solvent of crystallization not shown, for clarity). Bottom: 31P{1H} NMR (202 MHz) spectra of mixtures of ‘Pd(OAc)2’ with nPPh3 (n = 1 to 4) in THF at 23 ºC for 16 h, showing differences in phosphorus speciation. Reference spectra are given for **II** (green), **VIII** (blue) and **IX** (cyan); other species are OPPh3 (pink), [AcOPPh3]X (yellow, where X is likely the OAc anion) and *trans*-Pd(OAc)2(PPh3)2 **I** (red). Several phosphorus species are uncharacterized for the Pd(OAc)2/1PPh3 experiment (also resulting in PdNP formation). For the equilibrium shown against the ratio of Pd(OAc)2/4PPh3 spectral data, acetate anion and free PPh3 are involved, explaining the substantially lower chemical shift (compare also the reference spectrum of pure Pd0(PPh3)3 **IX** – bottom**)**.



Figure 3 The HOMO (left) and LUMO (right) for [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] **II**, computed by Density Functional Theory (b3lyp/def2svp functional/basis set used for optimization, single point orbital and total energies; CPCM implicit solvent and Gimme’s D3 empirical correction used).

We believe that the mechanism for formation of **II** is different to the PdI dimer stabilised by a bridging arene, as reported by Bedford.10c  In the latter case a sequential reaction in methanol was used, followed by treatment with a non-coordinating anion leaves a suitably-disposed arene to stabilise the cationic PdI dimer species, though Pd-π-arene interactions. In **II** acetate takes on that role.

**Reactivity of II towards organohalides.** The reaction of [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] **II** with CH2Cl2 **1a** (~10-fold excess) occurred at room temperature to afford a new Pd species, which was identified as [Pd3(Cl)(PPh2)2(PPh3)3]OAc **Pd3Cl·OAc** by ESI studies (+ve mode, detected by the [M-OAc]+ ion) (Fig. 4).14 Real-time reaction monitoring by 31P NMR spectroscopic analysis showed that **Pd3Cl·OAc** formed over several hours at the expense of **II**.The data for **Pd3Cl·OAc** closely matches the data obtained from the independent synthesis of [Pd3(Cl)(µ-PPh2)2(PPh3)3]Cl **Pd3Cl·Cl**, starting from PdCl2(PPh3)2 in aniline under H2(g) at 90 ºC, for which an X-ray structure of a single crystal was determined (Fig. 5).15 We were unable to trace the ‘CH2Cl’ fragment derived from CH2Cl2, ‘Pd(PPh3)1’ and acetate anion required to balance the overall chemical reaction. However, balance of overall charge and mass allows one to postulate a putative 14-electronic PdII species **Xa**. Similarly, reaction of **II** with *p*-fluoro-iodobenzene **1b** afforded [Pd3(I)(µ-PPh2)2(PPh3)4]OAc **Pd3I·OAc**,as shown by31P NMR and ESI data (as the [M-OAc]+ ion), which degraded rapidly to form Pd black. As with the reaction of **II** with CH2Cl2 **1a**,the ‘*p*-F-C6H4-’ fragment derived from **1b**, ‘Pd(PPh3)1’ and OAc anion could not be fully traced (PdII species **Xb** is postulated).

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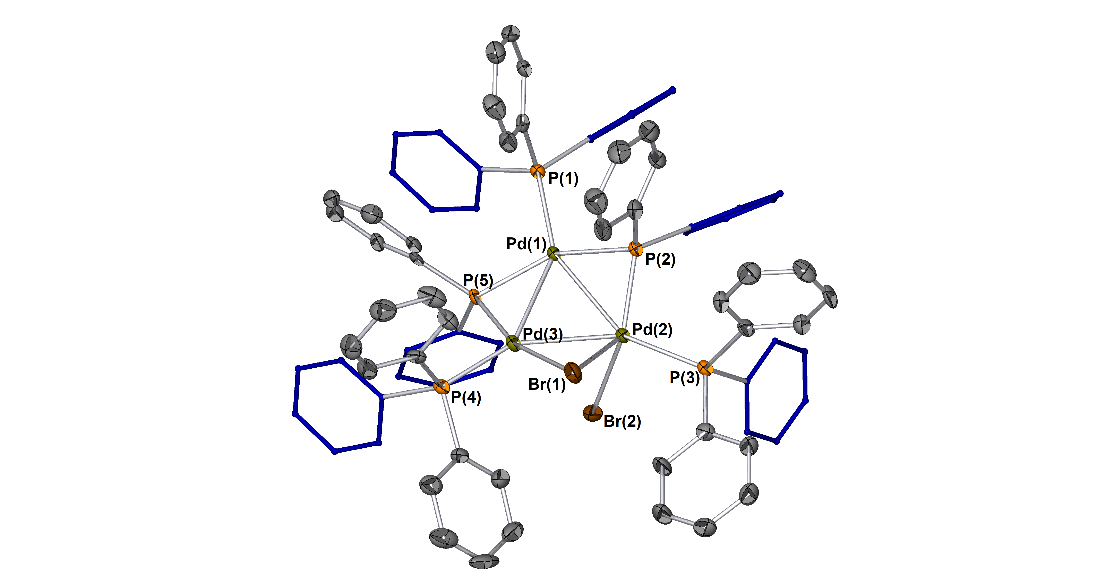
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Figure 5 The single crystal X-ray diffraction structures for [Pd3(X)(PPh2)2(PPh3)3]X (Top, X = Cl, **Pd3Cl•Cl**; Bottom, X = Br, **Pd3Br•Br**); H-atoms and solvent of crystallization are not shown and thermal ellipsoids are set at 50% probability. For **Pd3Cl•Cl** the non-coordinating chloride anion is not shown. Selected bond lengths (Å) and angles (⁰) for: **Pd3Cl•Cl** Cl1–Pd1 = 2.3828(8); Cl1–Pd3 = 2.4002(8); Pd1–Pd2 = 2.9138(3); Pd1–Pd3 = 2.8882(3); Pd2–Pd3 = 2.9127(3); Pd1–Cl1–Pd3 = 74.29(2); Pd1–P2–Pd2 = 81.38(3); Pd3–P4–Pd2 = 81.45(3); Cl1–Pd1–Pd2 = 113.303(19); Cl1–Pd1–Pd3 = 53.130(18); Pd3–Pd1–Pd2 = 60.265(8). **Pd3Br•Br** Pd1–Pd2 = 2.8355(10); Pd2–Br1 = 2.9423(13); Pd2–Br2 = 2.5698(13); Pd3–Br1 = 2.5490(13); Pd1–Pd3 = 2.8808(10); Pd2–Pd3 = 2.8240(10); Pd2–Pd1–Pd3 = 59.21(2), Pd3–Pd2–Pd1 = 61.20(2), Pd2–Pd3–Pd1 = 59.60(2); Pd3–Br1–Pd2 = 61.40(3); Br2–Pd2–Pd1 = 101.20(4); Br2–Pd2–Pd3 = 76.91(3); Br2–Pd2–Br1 = 96.67(4).

To reveal whether putative 14-electron PdII species were being formed in the reactions of **II** with organohalides (R–X) we hypothesized that a reaction with 2-bromopyridine **1c** might enable characterization by the stabilization conferred by *N*-coordination from the pyridine ring, leading to formation of a stable 16-electron dinuclear PdII species (*i.e.* **4a-c**, Fig. 4**)**.

To verify findings concerning formation of [Pd3(Br)(µ-PPh2)2(PPh3)3]OAc (**Pd3Br·OAc**) *vide supra*, a closely related sample was prepared by treatment of [Pd3(Cl)(µ-PPh2)2(PPh3)3]Cl (**Pd3Cl·Cl**)with excess KBr in CH2Cl2, giving [Pd3(Br)(µ-PPh2)2(PPh3)3]Br (**Pd3Br·Br**).16 The latter material possessed identical 31P NMR and MS data to that seen for **Pd3Br·OAc** from the reaction of **II** with 2-bromopyridine **1c**. A reasonable single crystal X-ray diffraction structure for **Pd3Br·Br** was further determined(Fig. 5). Whilst a detailed comparison between **Pd3Cl·Cl** and **Pd3Br·Br** cannot be made (*R*1 factors for **Pd3Cl·Cl** = 3.58% and **Pd3Br·Br** = 7.04%), there are striking structural differences that necessitate additional comment. The cyclic 6-membered ‘Pd-P-Pd-Cl-Pd-P’ fragment is essentially flat in **Pd3Cl·Cl**, leaving the second chloride anion as non-coordinating. However, in **Pd3Br·Br** we see something quite different – the cyclic 6-membered ‘Pd-P-Pd-Br-Pd-P’ fragment is highly twisted, which is associated with an interacting second bromide anion.



Figure 4 Reactions of dinuclear PdI complex II with organohalides (**1a-c**), leading to formation of Pd3 clusters Pd3X•OAc. The X anions in these clusters are likely acetate (mass balance is formally correct using acetate for all Pd species formed), although mixtures of different anions cannot be ruled out for species generated in situ. The MS ions are all observed by ESI (+ve mode) as molecular cations, the data for which is presented (real – in blue; simulated – in red). The 31P{1H} NMR spectrum for species generated from the reaction of 2-bromopyridine 1c with II illustrates the formation of Pd3Br•OAc and species **4a-c** (note a cut // in the 31P NMR spectrum is made between 40 and 190 ppm, due to the wide spectral range, for ease of viewing – full 31P NMR spectra are shown in the Supporting Information).

It is tempting to draw an analogy here to a bromonium ion interacting with a bromide anion (*i.e.* reactions of alkenes with bromide proceeding via bromonium ion intermediates). The structural differences between **Pd3Cl·Cl** and **Pd3Br·Br** suggest that they could be distinctly different in how they operate in catalysis.

The relevance of our findings concerning reaction of **II** with organohalides requires contextualisation with the results recently reported by Schoenebeck and co-workers.17 It has been shown that [Pd(µ-I)P(t-Bu)3]2 reacts with PHPh2 (slight excess relative to the PdI dimer) in toluene at room temperature to give a Pd3 cluster containing three bridging phosphide ligands (Fig. 6). Subsequent reaction with an aryl halide then delivers a Pd3-type cluster containing a bridging iodide ligand, similar to the **Pd3X.X** clusters *vide supra*. The pathways to these Pd3 clusters are not the same. Complex **II** reacts directly with organohalides to give **Pd3X.X** clusters (where X = Cl, Br or I), *i.e.* additional phosphine is not necessary at this point. Indeed, if additional PPh3 (2 equiv.) is reacted with **II** (1 equiv.) in THF at room temperature we see the generation of Pd(PPh3)n species (where n = 3, this species was detected by LIFDI-MS, see ESI). This finding is in-keeping with what was observed when Pd3(OAc)6 was reacted with nine equivalents of PPh3 (*i.e.* Pd/PPh3 ratio of 1:3, Fig. 2). We expect that Pd0 complexes are generated from disproportionation of the PdI dinuclear complex **II**, upon addition of PR3, akin to the observations reported by Schoenebeck and Colacot.10b



Figure 6. Schoenebeck’s findings17 on the formation of a Pd3-type cluster from an electron-rich PdI dimer species.

**Importance of our findings in an exemplar SMCC reaction:** To better understand the importance of the ‘Pd(OAc)2’/nPPh3 ratio in catalysis, the cross-coupling of 2-bromopyridine **1c** with *p*-fluorophenylboronic acid **2** to give 2-arylpyridine **3** was examined,6b using 1M *n*-Bu4NOH as the base, in a THF/water mixture (1:1, *v*/*v*) at 40 ºC. We carefully selected 1M *n*-Bu4NOH as the base, drawing on the recent findings concerning the importance of both the hydroxide anion and cation-type in SMCCs.18 Also pertinent to mention is that our SMCC reaction is homogeneous, *i.e.* not biphasic, simplifying the discussion concerning which phase the Pd catalyst and organoboron species reside in. Furthermore, operationally NMR spectroscopic analysis *in operando* was made feasible by use of aqueous *n*-Bu4NOH in THF.

SMCC reactions of **1c** + **2** → **3** were monitored *in operando* by 1H NMR spectroscopic analysis, allowing pre-stirred mixtures of ‘Pd3(OAc)6’/nPPh3 (n = 6 and 12, *i.e.* Pd/PPh3 = 1:2 or 1:4 respectively) to be compared in THF against a reaction mediated by [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] **II**. The kinetic profiles for the appearance of **3**, with concomitant disappearance of **1c** (pseudo-zero order in **1c**),are shown in Fig. 6. The kinetic profile for the reaction mediated by Pd3(OAc)6/6PPh3 (1:2, Pd/PPh3) indicates that the reaction is efficient at 40 ºC {Fig. 7, (A)} – there is an exotherm during initial catalyst turnover (*ca.* 4 turnovers) which is associated with full dissolution of aqueous 1M *n*-Bu4NOH (into THF – overall concentration equals 0.5M *n*-Bu4NOH). The same reaction mediated by **II** showed a similar kinetic curve {Fig. 7, (B)}, confirming the catalytic competency of this key species isolated earlier. Furthermore, no Pd particles were visibly seen to form during catalysis (the solution appearing completely homogeneous).

Altering the Pd3(OAc)6/12PPh3 (1:4, Pd/PPh3) led to a poor catalyst system for reaction **1c** + **2** → **3** at 40 ºC {Fig. 7, (C), curves illustrated by diamonds}. This catalyst system exhibited higher catalyst efficacy at 70 ºC. Thus, additional phosphine slows down catalysis in the reaction of **1c+2→3**, at 40 ⁰C, which is an outcome consistent with our previous studies on SMCCs involving **1c**.6b





Figure 7 Kinetic profiles for the SMCC reaction of **1c** + **2** to give **3**, mediated by Pd(OAc)2/nPPh3 (n = 2 and 4) and dinuclear PdI complex **II**. Reactions were monitored by 1H NMR spectroscopic analysis in a J. Young’s NMR tube (spinning). The *effective* Pd:PPh3 ratio takes into account that one equivalent of PPh3 is required to reduce PdII to Pd0, with concomitant formation of one equivalent of O=PPh3. For complex **II**, two PPh3 ligands are present overall, *i.e.* one per Pd; in this respect the ‘PPh2’ group was treated as an anionic ligand.

With the finding that [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] **II** reacts with 2-bromopyridine **1c** to give [Pd3(Br)(µ-PPh2)2(PPh3)3]OAc (**Pd3Br•OAc**) and [Pd(X/X')(*N*,*C*2-pyr)(PPh3)]2­ (**4a**-**c**), additional catalytic experiments were devised to test the importance of such species in the SMCC reaction **1c** + **2** → **3** (Fig. 8). Two control experiments, with different Pd catalysts, were conducted: (a) to establish the catalytic competency of **Pd3Br•Br**19; (b) to assess the catalytic activity of [Pd(Br)(*N*,*C*2-pyr)(PPh3)]2­ **4a**, under comparable reaction conditions. The reaction of **1c+2→3**, mediated by **Pd3Br•Br** (1 mol%, giving 1 mol% active Pd – the cluster being treated as a well-defined catalyst species11) gave **3** with full conversion after *ca.* 7.5 h at 40 ºC (Fig. 8). The same reaction mediated by an authentic sample of **4a** (0.5 mol% giving 1 mol% active Pd6b) gave **3** with 32% conversion after *ca.* 7.5 h. These control experiments establish that **Pd3Br•Br** is a significantly more active catalysis species than **4a**. Thus, when generated *in situ*, we expect **Pd3Br+** species to play a more dominant role in terms of the overall catalyst efficacy *vide infra*.

With the kinetic profiles for the SMCC reaction of **1c+2→3**, mediated by either **Pd3Br•Br** or **4a**, established, we could then qualitatively compare the catalytic activity mediated by **Pd3Br•OAc** and [Pd(X/X')(*N*,*C*2-pyr)(PPh3)]2­ (**4a**-**c**) species, formed *in situ* from the reaction of **II** with **1c**.20 The observed catalyst activity sits between the high reactivity of **Pd3Br•Br** and comparatively lower activity of [Pd(Br)(*N*,*C*2-pyr)(PPh3)]2­ **4a**.



Figure 8 Overlay of kinetic curves for the SMCC reaction of **1c+2→3**, mediated by **Pd3Br•Br** (1 mol%), **4a** (0.5 mol%) and **II** (1.5 mol%, generating **Pd3Br•OAc**, **4a-c** *in situ*); other reaction conditions identical to Fig. 6. Reactions were monitored by 1H NMR spectroscopic analysis in a J. Young’s NMR tube (spinning).

Conclusion

In conclusion we have demonstrated that reaction of Pd3(OAc)6 with 6 equivalents of PPh3, that is in a Pd/PPh3 ratio of 1:2, gives an intriguing dinuclear PdI complex, [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2], **II**. Species **II** is relatively unstable, but characterizable, and we propose it is this species that Amatore and Jutand detected in their early studies, which resisted characterization at that time.4a An important discovery was the finding that **II** reacts relatively cleanly with the organohalides, CH2Cl2 **(1a)**, *p*-fluoroiodobenzene **(1b)** and 2-bromopyridine (**1c**)to afford Pd3 cluster complexes containing bridging halide ligands, *i.e.* [Pd3(X)(PPh2)2(PPh3)3]X, carrying an overall 4/3 oxidation state. Use of 2-bromopyridine **1c** was critical in understanding that a putative 14-electron mononuclear ‘PdII(R)(X)(PPh3)’ is released on forming [Pd3(X)(PPh2)2(PPh3)3]X clusters from **II**. Altering the Pd/PPh3 ratio from 1:2 to 1:4 forms Pd0(PPh3)3 quantitatively, generally in-keeping with Amatore’s and Jutand’s original studies.4 It has been established further that the Pd/PPh3 ratios are important in an exemplar SMCC reaction, Pd/PPh3 ratio Pd/PPh3 reaction, **1c+2→3**. Near identical catalytic efficacy was seen for a reaction mediated by either 1Pd(OAc)2/2PPh3 or **II**, whereas the 1Pd(OAc)2/4PPh3 catalyst system was significantly less effective, requiring a higher temperature (70 rather than 40 ⁰C) for reasonable conversion to product **3** to be observed.

An important take home message from our study is that where [Pd2(µ-PPh2)(µ2-OAc)(PPh3)2] **II** can form, *i.e.* when a ratio of Pd/PPh3 ratio is 1:2 employed in catalysis, reactions with organohalides (common starting materials for cross-coupling catalysis) afford catalytically competent Pd3 cluster complexes *in* *situ*, in addition to other known PdII species (*i.e.* oxidative addition products). A general message is if the relative amount of PPh3 ligand to Pd is low, that Pd clustering tends to occur, to afford either particles (where Pd/PPh3 = 1:1), or ‘ligated clusters’, whereas well-defined dimers and trimers are formed where Pd/PPh3 = 1:2 (the major finding this study) and when there is enough PPh3 ligand around, mono-nuclear Pd0(PPh3)n, *i.e.* n > 2, can be stabilised, aligning with a general understanding of ligated Pd0species in text book mechanisms.

Understanding how [Pd3(X)(µ-PPh2)2(PPh3)3]X clusters activate aryl/heteroaryl halides and organometallic coupling partners, *e.g.* aryl boronic acids,11 will no doubt be important going-forwards, which will enable their catalytic properties to be fully delineated and exploited in chemical synthesis. To emphasize this point further, similar Pd3-type clusters have been studied by Maestri and Malacria in catalysis, particularly hydrogenation.21 Our results, taken together with contributions made by others, show that Pd3-clusters are ripe for exploitation in applied catalysis.

Conflicts of interest

There are no conflicts to declare.

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