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January 2017

The final published version of this article can be found at:

<https://doi.org/10.1039/C6CC08824D>

Citation for this paper:

Janusson, E., Zijlstra, H.S., Nguyen, P.P.T., MacGillivray, L. Martelino, J. & McIndoe, J.S. (2017). Real-time analysis of $\text{Pd}_2(\text{dba})_3$ activation by phosphine ligands. *Chemical Communications*, 53(5), 854-856.

<https://doi.org/10.1039/C6CC08824D>

Real-Time Analysis of Pd₂(dba)₃ Activation by Phosphine Ligands

Eric Janusson,^a Harmen S. Zijlstra,^a Peter P. T. Nguyen,^a Landon MacGillivray,^a Julio Martelino,^a and J. Scott McIndoe^{*a}

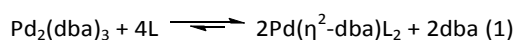
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A combination of UV-Vis spectroscopy and electrospray ionization mass spectrometry is used for real-time monitoring of Pd₂(dba)₃ activation with sulfonated versions of PPh₃ and a Buchwald-type ligands. This provides insight into the effect of ligand and preparation conditions on activation and allows for establishment of rational activation protocols.

Palladium-based catalysts are amongst the most important and widely used transition-metal complexes in catalysis and are used in numerous coupling reactions.¹ The active Pd catalyst is often obtained by *in situ* activation of a precatalyst with a triaryl phosphine. The outcome of the activation process can depend on the source of the precatalyst,² order of addition, and chosen reaction conditions.³ Recently, several reports on the activation chemistry of Pd(II) precursors have appeared,⁴ but investigations regarding the activation of zero valent Pd precursors remain limited.^{5–12} Pd₂(dba)₃ is the most frequently employed source of Pd(0),¹³ but despite its popularity the actual nature of the catalytically relevant species and the influence of reaction conditions on its activation are incompletely understood. *In situ* activation is often carried out using a Pd₂(dba)₃ solution which is either preheated or stirred for an extended period of time followed by addition of two equivalents (relative to Pd) of ligand of choice.^{5–7,14} This general process is often portrayed as a simple ligand exchange (eqn 1) but is actually more complicated, because the free dba remains in solution to compete for coordination to palladium.



Depending on the ligand used and the reaction conditions chosen the activity of the catalyst varies significantly.^{14,15}

Reports on the effect of changes in parameters during activation are in some cases contradictory.¹⁶ Heating of precatalyst and ligand prior to the addition of substrates has been suggested as a means to ensure reproducible reaction rates;^{17–19} however, others question the benefits of this precaution.^{2,3,20} Depending on the precatalyst and ligand used, long stirring times may be unnecessary or may even change catalyst speciation which further complicates the activation. A further complicating factor is the non-innocence of the dba ligand leading to the presence of Pd(dba)_xL_y type complexes.^{5,8,21} The occurrence of such species in different solvents have not been investigated in detail and may play a significant role in the catalytic process.^{22–24} On top of that, the choice of Pd₂(dba)₃ supplier or storage may influence catalytic activity as minor impurities and the presence of nanoparticles in individual samples of Pd₂(dba)₃ may further influence the activation and activity.^{2,25}

It is important to understand the activation of Pd₂(dba)₃ under various conditions to get a clear picture of the process and to optimize the formation of active catalyst. Real-time monitoring of catalyst activation assists in the elucidation of the various species formed and pathways taken during this process. Electrospray ionization mass spectrometry (ESI-MS) has previously been shown to be a valuable tool in understanding catalytic reactions and charge-tagged phosphine ligands (*vide infra*) have been established as a useful means of enabling real-time ESI-MS investigations using a normally neutral catalyst.^{26–30} Using only ESI-MS, neutral Pd₂(dba)₃ and other neutral species cannot be observed. To overcome this limitation and obtain richer information we have paired ESI-MS with UV-Vis spectroscopy. This set up allows for monitoring of the complete activation and provides deeper understanding of the processes involved.

The phosphine ligands used in this study were chosen because they can be seen as the charge-tagged derivatives of two commonly used neutral phosphine ligands (Fig. 1). The [PPN]⁺[TPPMS][−] (1), was chosen as an analogue of

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† Electronic Supplementary Information (ESI) available: Experimental details and additional mass spectra. See DOI: 10.1039/x0xx00000x

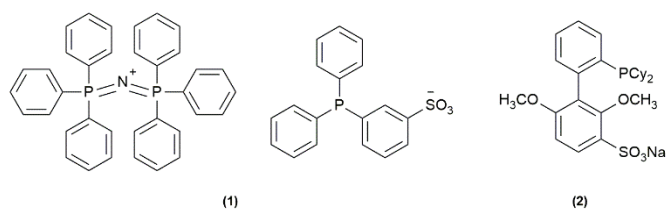


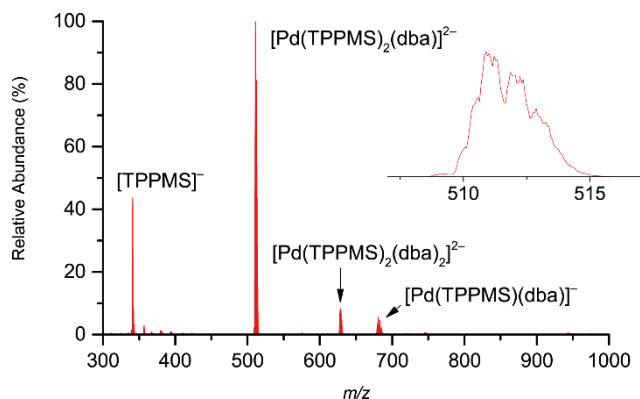
Fig. 1 Sulfonated phosphine ligands used in this work: [PPN]⁺[TPPMS][−] (**1**); Na⁺[sSPhos][−] (**2**).

triarylphosphines (PAr₃); Na⁺[sSPhos][−] (**2**) is a Buchwald-type ligand. In a typical reaction, a custom-made flask was equipped with a septum and fiber optic UV-Vis probe (see Supplemental Information). The flask was evacuated and filled with degassed solvent that was fed into the ESI-MS using the pressurized sample infusion (PSI) methodology.^{31,32} Precatalyst and ligand were injected following common protocols and allowed to react. Initially only the neutral Pd₂(dba)₃ is present, and detectable only by UV-Vis. In methanol, it exhibits an absorbance at 532 nm (d-d) along with another absorbance at 345 nm (n-π*) owing to the presence of free dba that is common in commercial samples.^{2,8} Upon addition of ligand, free ligand and ligated palladium species (both charged) appear which are easily identifiable using ESI-MS. Careful optimization of the MS cone voltage prevents fragmentation of these delicate species (Figure S1). Combining both these methods gives for a convenient way to monitor the conversion of Pd₂(dba)₃ into the charged catalyst.

Activation of Pd₂(dba)₃ in MeOH at room temperature (21°C) with **1** yields [Pd(TPPMS)₂(dba)]^{2−} as the major product, along with the two minor species [Pd(TPPMS)₂(dba)₂]^{2−} and [Pd(TPPMS)(dba)][−] (Fig. 2). The speciation is similar to that observed previously using DMF or THF and Pd(dba)₂/PPh₃.⁷ It is interesting to note that the sensitivity of ESI-MS also allows for observation of species not registered by other methods.

A closer look at the real-time UV-Vis and ESI-MS data shows that the reaction takes only about 1.5 minutes to reach equilibrium (Fig. 3), despite activation procedures often calling for much longer stirring times or heat in other solvents.^{14,33}

If the precatalyst/ligand mixture was heated instead of stirred at room temperature, catalytic oxidation of [TPPMS][−] was observed. Oxidation of the phosphine ligand has been



reported Fig. 2 ESI-MS spectrum of activation of Pd₂(dba)₃ with [TPPMS][−] in MeOH

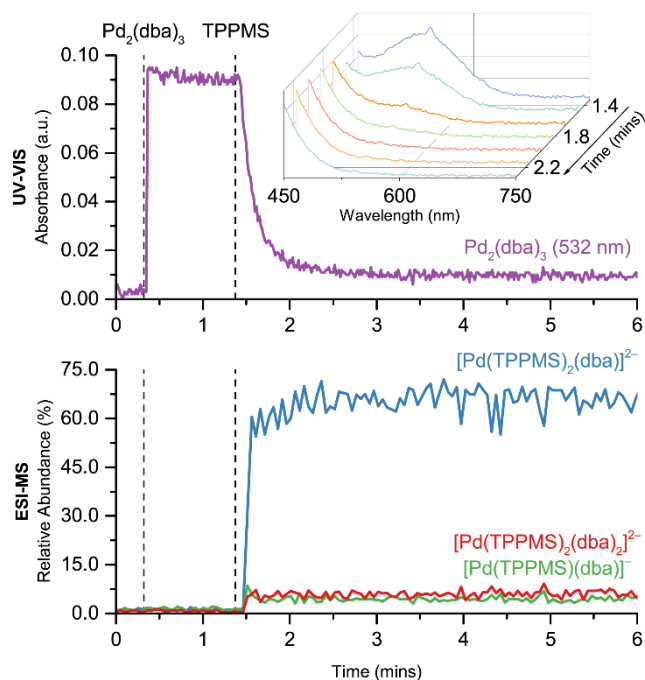


Fig. 3. UV-Vis (top and inset) and ESI-MS (bottom) chromatograms of activation of Pd₂(dba)₃ with [TPPMS][−] in MeOH at room temperature.

to reduce the activity of Pd-based catalysts and is therefore undesirable.^{34,35} While often present in small quantities despite rigorous solvent degasification, heat served to accelerate this decomposition and effectively reduces the concentration of active catalyst in solution. Phosphine oxidation should be considered when preheating is employed while using simple phosphine ligands, though this side reaction can be avoided with oxidation-resistant ligands (*vide supra*).

In the case of DMF there is a clear difference in activation behavior depending on the order of addition. Since it is a coordinating solvent, DMF can replace the Pd-bound dba (see SI Fig. S4).³⁶ To minimize this competition and optimize the amount of active catalyst the phosphine ligand should be present in solution before addition of Pd₂(dba)₃. Conversely, Pd₂(dba)₃ is quite stable in pure MeOH so no such precaution needs to be taken when using that solvent.

Activation of Pd₂(dba)₃ with 2 equivalents **1** in DMF yields [Pd(TPPMS)₂]^{2−} instead of [Pd(TPPMS)₂(dba)]^{2−} as the primary species (Fig. 4), though others have reported that as many as 100 equivalents of ligand are needed to fully replace dba with PPh₃ in DMF as compared to MeOH.^{5,6} Using a Pd:L ratio of 1:2 only Pd(dba)(PPh₃)₂, Pd(PPh₃)₃(DMF) and/or Pd(PPh₃)₂ were reported.⁷

Activation of Pd₂(dba)₃ at room temperature in MeOH or DMF using [sSPhos][−] yields [Pd(sSPhos)(dba)][−] as the only Pd-containing species observable by ESI-MS. The ligand exhibits negligible oxidation following activation even after heating of the mixture showing the robustness of the ligand, as illustrated

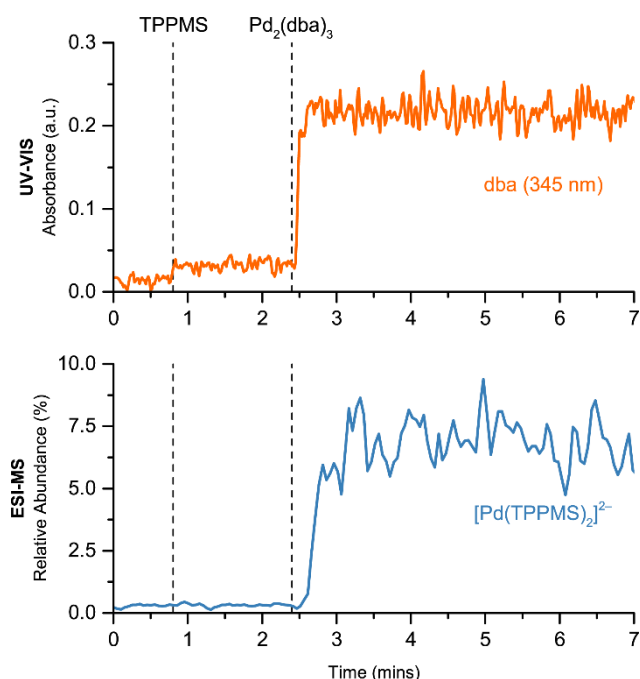
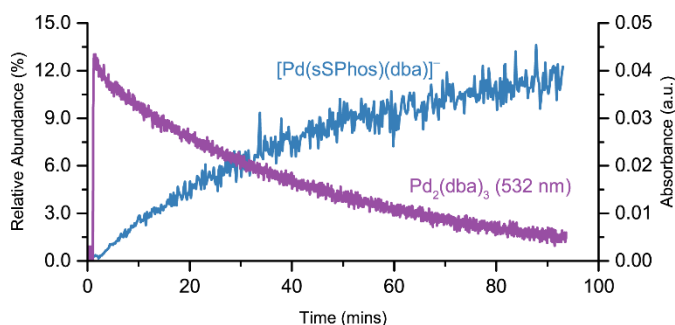


Fig. 4. UV-Vis (top) and ESI-MS (bottom) chromatograms of activation of $\text{Pd}_2(\text{dba})_3$ precatalyst with $[\text{TPPMS}]^-$ in DMF at room temperature.

previously.³⁷ At room temperature in MeOH the catalytically active species is formed relatively slowly, requiring approximately 90 minutes to come to equilibrium. This can be shortened to one minute if the reagents are added to refluxing MeOH, without any change to the speciation observed at lower temperature (see SI Fig. S3). Conversely, the activation with $[\text{sSPhos}]^-$ in DMF proceeds quickly, forming a maximum quantity of $[\text{Pd}(\text{sSPhos})(\text{dba})]^-$ in three minutes. As previously noted, the order of addition is critical and the ligand should be introduced before $\text{Pd}_2(\text{dba})_3$ to optimize the amount of active catalyst produced. The speciation observed with $[\text{sSPhos}]^-$ is similar to the active species, “ L_1Pd ”, reported for Buchwald type ligands in the literature; however, dba does not fully dissociate even with 2 equivalents of $[\text{sSPhos}]^-$ in MeOH or DMF.¹⁴

The combination of UV-Vis and ESI-MS allows for straightforward, real-time monitoring of $\text{Pd}_2(\text{dba})_3$ activation. Using $[\text{TPPMS}]^-$ or $[\text{sSPhos}]^-$ the time needed to achieve equilibrium concentrations of the active catalyst, the influence



of addition order, and effect of preparation conditions on

Fig. 5. Activation of $\text{Pd}_2(\text{dba})_3$ with $[\text{sSPhos}]^-$ in MeOH at room temperature.

activated catalyst in both MeOH and DMF could be obtained. This shows that using orthogonal methods we can observe exactly what is happening in solution and obtain a clear understanding of the *in situ* activation process under a variety of conditions. In most conditions dba is not fully displaced from the active catalytic species by either the simple triarylphosphine ligand (**1**) or a Buchwald-type ligand (**2**); the exception being the activation in DMF with **1**. The techniques used accurately inform us of what these species are and how they behave. Based on these results useful instructions for optimal $\text{Pd}_2(\text{dba})_3$ activation can be prepared. Future work will focus on the activation of different Pd catalyzed systems and the implication of activation protocol on the actual catalysis and catalytic activity.

JSM thanks NSERC (Discovery and Discovery Accelerator Supplements) for operational funding and CFI, BCKDF and the University of Victoria for infrastructural support.

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