

An Investigation into the Effects of Pd Speciation on Cross-coupling Reactions

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Abstract

Pd-catalysed cross-coupling reactions form a pillar in modern synthetic organic chemistry. Many Pd-based (pre-)catalysts have been developed for cross-coupling chemistry but understanding what the active Pd catalyst species is under different reaction conditions is critical, particularly since Pd speciation can lead to changes in active catalyst structure and function. Chapter 1 surveys the literature on the relationship between active catalyst speciation and the underlying mechanisms of cross-coupling catalysis. Current mechanistic understanding is underpinned by $[\text{Pd}^0(\text{L})_n]$ -type active species ($\text{L} = \text{e.g.}$ phosphine ligand). In this context, the known mechanistic aspects of the prominent Suzuki-Miyaura reaction (SMCC) are critically discussed. What is known about the formation, propagation and mechanism of action of higher order Pd species, including well defined Pd clusters and nanoparticles which can exhibit unique reactivity, are discussed, with a focus on catalytic applications. The factors that are known to govern site-selectivity at multiply-functionalised starting materials in cross-coupling chemistry are examined.

Chapter 2 details the differences in Pd speciation arising from reacting $[\text{Pd}_3(\text{OAc})_6]$ with varying equivalents of triphenylphosphine (PPh_3). $[\text{Pd}_3(\text{OAc})_6]$ and ≥ 9 equivalents of PPh_3 forms mononuclear $[\text{Pd}^0(\text{PPh}_3)_n]$ complexes ($n \geq 3$). $[\text{Pd}_3(\text{OAc})_6]$ reacts with exactly 6 equivalents of PPh_3 to form a dinuclear Pd^{I} complex $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **I**. **I** reacts with organohalides forming tripalladium clusters: $[\text{Pd}_3(\mu\text{-X})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$ (**Pd₃X·X**) ($\text{X} = \{\text{pseudo}\}\text{halide}$). Reaction of 3 equivalents of PPh_3 with $[\text{Pd}_3(\text{OAc})_6]$ results in the formation of Pd particles.

Chapters 3 and 4 explore the consequences of these findings in terms of cross-coupling catalyst efficacy. Chapter 3 describes the correlation between Pd speciation and catalyst performance in cross-couplings of model mono-brominated heteroaromatic substrates, where, for example, $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ or **Pd₃X·X** ($\text{X} = \text{Cl}$ or Br) or **I** significantly out-performed $[\text{Pd}_3(\text{OAc})_6]/12\text{PPh}_3$ or $[\text{Pd}^0(\text{PPh}_3)_3]$. Chapter 4 describes that $[\text{Pd}_3(\text{OAc})_6]/x\text{PPh}_3$ ratios are critical in determining regioselectivity outcomes in cross-coupling reactions of 2,4-dibromopyridine **III**, with *normal* C2-selectivity being associated with $[\text{Pd}^0(\text{PPh}_3)_n]$ complexes when $x \geq 9$, and *abnormal* C4-selectivity being associated with higher order species when $3 \leq x \leq 6$. A combination of $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ pre-catalyst system and the presence of a quaternary ammonium or imidazolium salt boosted C4-coupling at **III** under SMCC and Kumada reaction conditions.

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Author's Declaration

The author declares that this thesis is an original work and that they are the sole author. This work has not previously been presented for an award at this, or any other, university. All sources are acknowledged as in the References section.

Parts of this work have been published in a peer-reviewed journal, a copy which can be found in Appendix 1:

The ubiquitous cross-coupling catalyst system $\text{Pd}(\text{OAc})_2/2\text{PPh}_3$ forms a unique dinuclear Pd^{I} complex: an important entry point into catalytically competent cyclic Pd_3 clusters. Neil W. J. Scott, Mark J. Ford, Christoph Schotes, Rachel R. Parker, Adrian C. Whitwood and Ian J. S. Fairlamb *Chem. Sci.*, **2019**, *10*, 7898–7906.

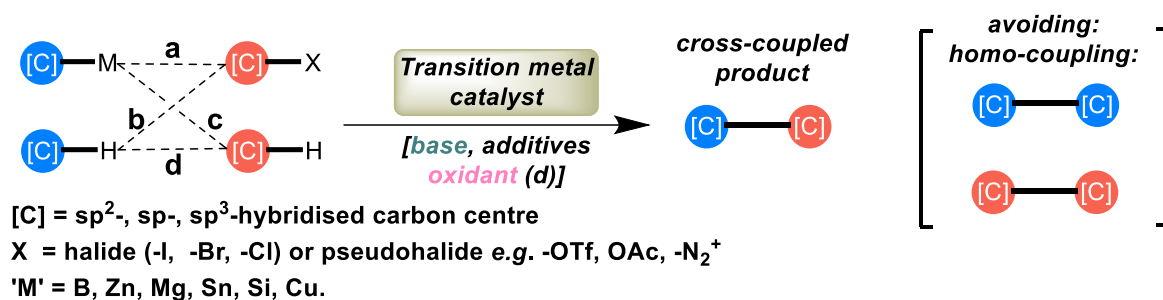
Neil W. J. Scott

January 2021

Chapter 1 – Introduction

1.1. Cross-coupling Reactions – an Overview

Pd-catalysed cross-coupling reactions (Scheme 1) have proven to be the most powerful and versatile methods for the formation of carbon–carbon bonds in chemical synthesis. The importance of cross-coupling reactions was exemplified, when in 2010 the Nobel prize for chemistry was awarded to some of the pioneers of the field: Heck, Negishi and Suzuki.¹



Scheme 1 A generic scheme showing a range of classic cross-coupling possibilities, which can be used to form C–C bonds.

Scheme 1 shows the overall process for four different cross-coupling regimes including classical cross-coupling (**a**) as well as various couplings involving C–H bond activation (**b**, **c** & **d**).² From a straightforward economic assessment, C–H bond functionalisation, either direct (**b** & **c**) or by C–H/C–H *oxidative* coupling (**d**), would appear to be an ideal situation – and a natural successor to classic cross-coupling catalysis, as such a methodology cuts down on potentially wasteful and costly pre-functionalisation of substrates.^{3–4} The field of transition metal- (TM-) catalysed C–H functionalisation is positively burgeoning, with new methodologies being reported weekly, however, unactivated C–H bonds frequently require harsh conditions and high catalyst loadings to facilitate activation.⁵ Such conditions can lead to issues in product selectivity and/or functional group tolerance, hence affecting overall process efficiency. In the case of (**d**), where two C–H bonds are oxidatively coupled, participation of a stoichiometric amount of additive oxidant is necessary, potentially leading to downstream issues in the scale-up of processes. Under the classic cross-coupling regime (**a**), where pre-functionalised organohalides and organometallic substrates are coupled, frequently less harsh conditions are required and hence the catalysts and conditions can be finely tuned to yield the desired result. Indeed, the classical cross-coupling approach is currently the default choice, over C–H functionalisation for most practising synthetic chemists. Site-selectivity and functional group tolerance problems can thus be circumvented, by deploying appropriate pre-functionalised reagents. Furthermore, TM catalyst loadings required under the *classical* cross-coupling regime have potential to be very low, making catalysis cheaper while minimising the potential for toxic metal contamination in

the final products.⁶⁻⁹ Further still, appropriate design can allow for facile recycling of privileged catalysts, thus minimising the waste of precious heavy metals which are embedded in many patents for at least the next 20 to 30 years.¹⁰⁻¹¹ Thus, there is still a strong research drive in the cross-coupling field to hone and enhance the understanding of the classical cross-coupling approach to optimise reactivity and selectivity while keeping TM levels as low as possible in each case. To this end, acquiring a full mechanistic picture for a given cross-coupling process is of crucial importance in understanding the factors governing catalyst efficiency and selectivity. In broad terms, this Thesis explores the benefits of mechanistic understanding in classical cross-coupling processes, particularly with regards to knowledge and control of Pd speciation in applications, with the global aim of improving the environmental friendliness and economic efficiency of cross-coupling processes.

Of the myriad named classical cross-coupling methodologies available (Figure 1), the Suzuki-Miyaura cross-coupling reaction (hereafter SMCC) undoubtedly sees the widest use in both industrial and academic settings and is one of the top 5 reactions used in medicinal chemistry.¹²

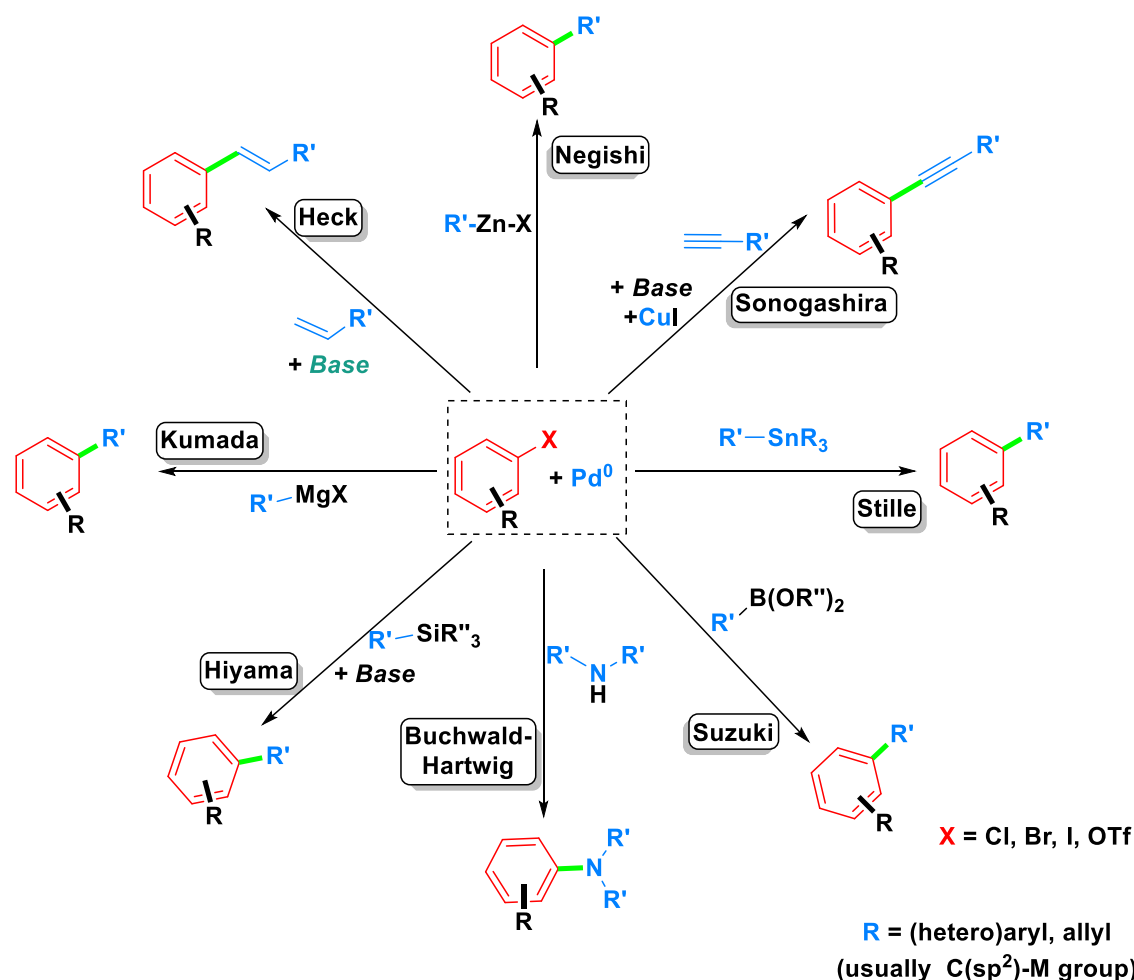


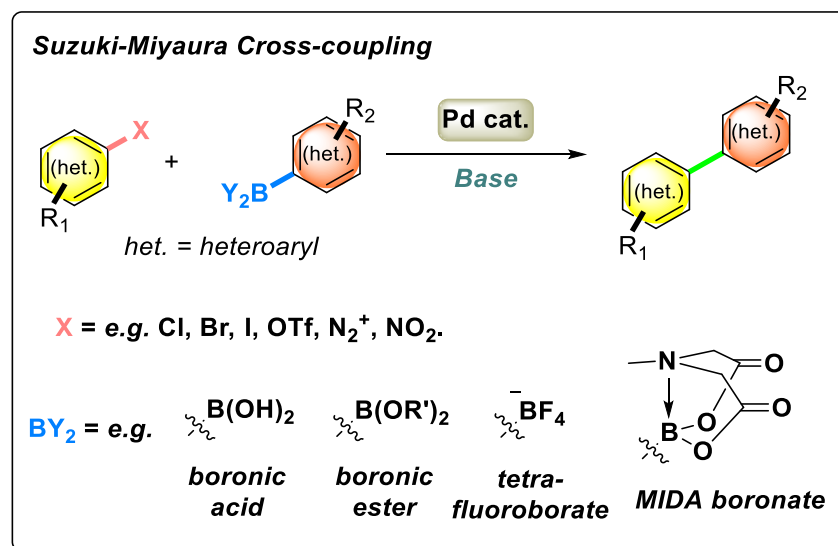
Figure 1 Generalised schemes for eight of the major *named* types of classic C–C bond-forming cross-coupling reactions at organohalide substrates (generic phenyl halide pictured), enabled by Pd-based catalysts.

The prominent synthetic use of the SMCC is a combined result of its reliability, mildness, functional group tolerance, as well as the ease of access and diversity of the relatively stable and environmentally benign boron-based coupling partner.¹³ Indeed it has been argued that the success of SMCCs has directed the course of drug discovery over the last 20 years.¹² In the following section, the SMCC reaction will be used as a case study for exploring accepted mechanistic understanding, as well as the limits thereof, of an apparently well-understood cross-coupling reaction.

1.2. Cross-coupling Reactions – Mechanistic Aspects

1.2.1. The Current Mechanistic Picture of the Suzuki-Miyaura Cross-Coupling Reaction

The SMCC reaction (Scheme 2) employs a TM catalyst, most frequently Pd-based, in the presence of a base to couple together an organoboron compound (*e.g.* a boronic acid, boronic ester or boronamide) with an organohalide or pseudohalide ($X = \text{Cl}, \text{Br}, \text{I}, \text{OTf}, \text{etc.}$).¹³⁻¹⁴ The SMCC is not limited to classical (pseudo)halides; for example, carbonates, carbamates and amides have all been successfully activated and coupled in SMCC processes.¹⁵⁻¹⁶ A significant recent advance in the SMCC reaction is the discovery that the nitro group of nitroarenes could be functionalised for cross-coupling with arylboronic acids, enabled by forcing conditions and highly specialised dialkylbiaryl ligands.¹⁷⁻¹⁸



Scheme 2 A generic Suzuki-Miyaura cross-coupling reaction scheme. Showing the diverse range of (hetero)aryl halides and boron species that can be coupled under SMCC conditions.

Despite its ubiquity in chemical synthesis, only fairly recently has direct evidence been compiled for each step of the SMCC catalytic cycle, giving a complete mechanistic picture for the reaction. A

representation of the classic, and widely accepted, *homogeneous* SMCC reaction mechanism, between a generic aryl halide and phenylboronic acid, involving a mononuclear $[\text{Pd}^0(\text{L})_n]$ -type catalyst (where L = a tertiary organophosphine ligand) and a hydroxide base is shown in Figure 2.

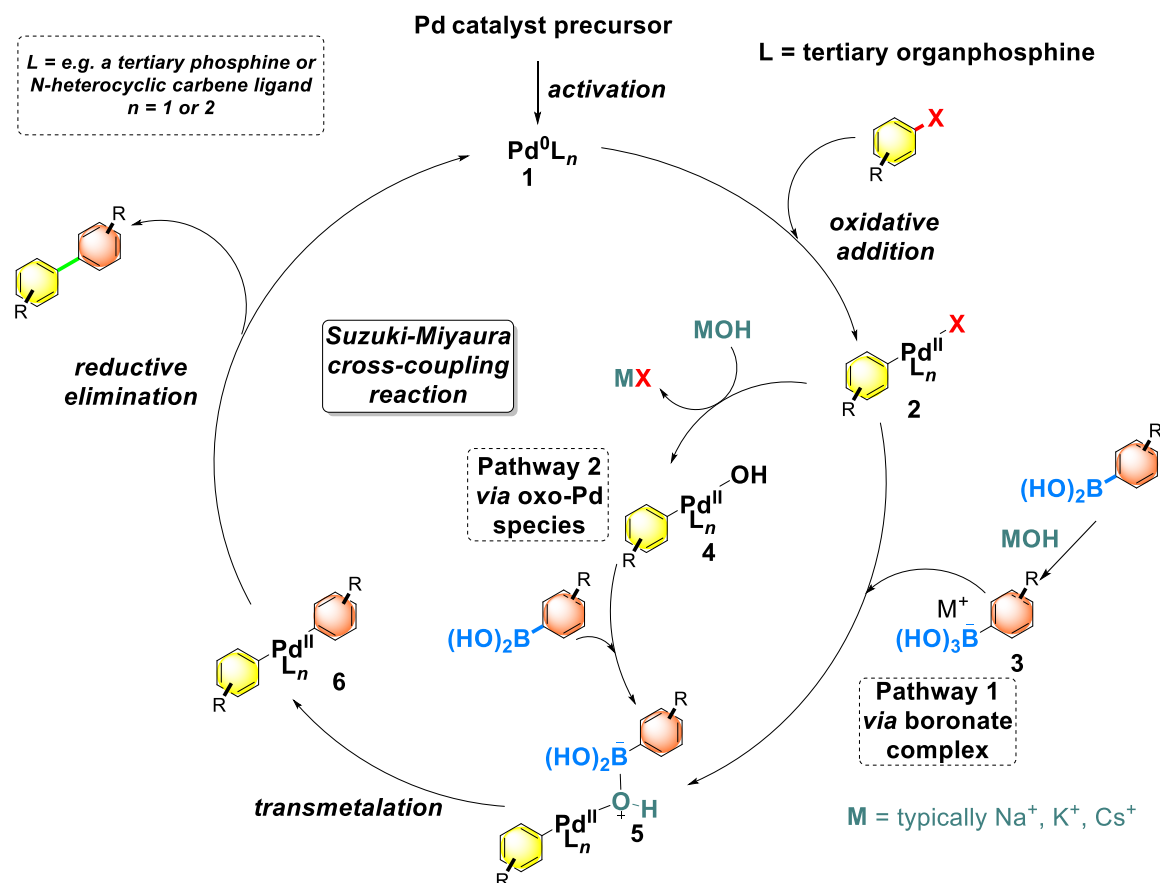


Figure 2 A full mechanistic picture for the Suzuki-Miyaura cross-coupling reaction, showing the two proposed pathways hypothesised to occur prior to the transmetalation event, enabled by a hydroxide base. Strong evidence points towards the mechanism proceeding *via* pathway 2 when a $[\text{Pd}^0(\text{L})_n]$ -type catalyst is used.

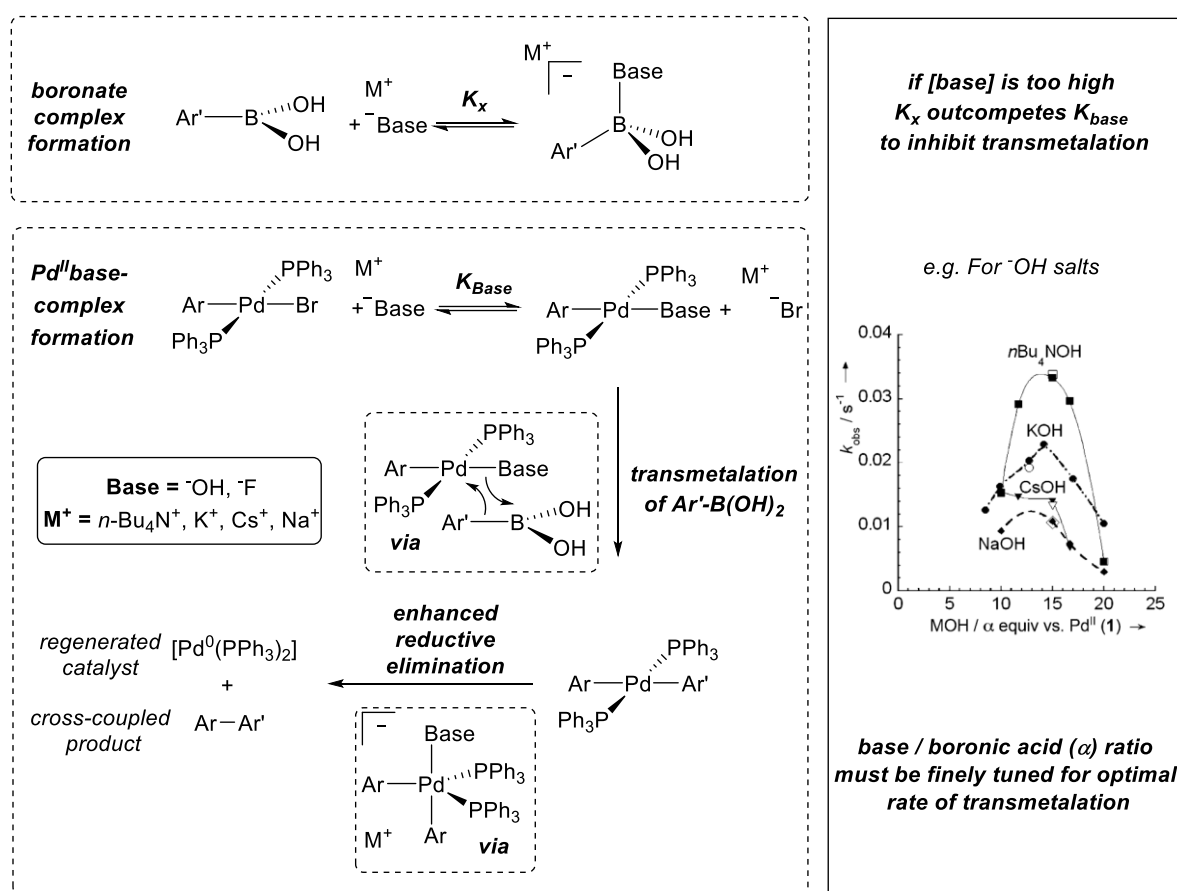
The first step involves activation of a catalyst precursor to a low valent, low oxidation state reactive species, in this case a $[\text{Pd}^0(\text{L})_n]$ complex in the presence of ligands or additives (See section 1.2.2, for a detailed discussion of this step). Once the catalyst is activated, the cross-coupling catalytic cycle commences with the oxidative addition of $[\text{Pd}^0(\text{L})_n]$ ($n=1$ or 2)¹⁹ to the organohalide to form a Pd^{II} complex **2**, stabilised by ancillary ligands.²⁰ The oxidative addition step can be rate determining in cases where unactivated aryl chlorides are used as substrates.²¹⁻²² If using a $[\text{Pd}^0(\text{L})_n]$ -type catalyst, the oxidative addition step can be enhanced (*e.g.* for more challenging C–Cl bond activation) by employing exogenous ligands conducive to the formation of mono-ligated $[\text{Pd}^0(\text{L})_1]$; for example, bulky electron-rich tertiary phosphines such as $\text{P}t\text{Bu}_3$ or alkylbiaryl (Buchwald-type) ligands.²³⁻²⁵ The second step, transmetalation, involves the formal transfer of an organic group from activated boron to the Pd^{II} oxidative addition product complex **2** in exchange for the coordinated halide forming **6**. The final step

then involves reductive elimination at **6**, which proceeds after a *trans-cis* isomerisation, forming the cross-coupled product, while regenerating a $[\text{Pd}^0(\text{L})_n]$ complex which may then be free to enter the catalytic cycle again. Electron-poor, bulky ligands can act to accelerate the reductive elimination step at Pd^{II} complexes.²⁶⁻²⁷ Significant contention has surrounded the role of the base (commonly OH^- or F^-) in the transmetalation step.²⁸ Early theories of the role of its role in the SMCC suggested that the base forms a tetracoordinate ‘boronate’ complex **3** which increases nucleophilicity and thus the ability to coordinate to the intermediate *trans*- $[\text{Ar-Pd}^{\text{II}}(\text{L})_2(\text{X})]$ complex (aryl halide Pd species) **2** forming **5** (Pathway 1, Figure 2).²⁹ Several subsequent observations have suggested that this was not the case. For example, known Lewis bases, *e.g.* Et_3N , were unable to enable transmetalation. Importantly, preformed boronate complexes, in absence of base, were found to produce poor product yields on direct reaction with Pd^{II} oxidative addition complexes.³⁰ It was hence postulated that the transmetalation event could proceed with *trans*- $[\text{Ar-Pd}^{\text{II}}(\text{L})_n(\text{OH})]^a$ (or the dinuclear form *trans*- $[\text{Ar-Pd}^{\text{II}}(\mu\text{-OH})_2(\text{PR}_3)_2]$ (*aryl-oxo-Pd^{II} complexes*), which forms from a salt metathesis reaction between the hydroxide base and the *trans*- $[\text{Ar-Pd}^{\text{II}}(\text{PR}_3)_n(\text{X})]$ (*aryl-halide-Pd^{II} complexes*). It was not until 2011 that two groups independently confirmed the mechanism of transmetalation from such complexes through stoichiometric kinetic studies. Carrow, Hartwig *et al.* employed low temperature ^{31}P NMR-based kinetics experiments to measure rates of depletion of the implicated Pd complex concentrations as transmetalation proceeds. It was found that the rate of transmetalation of arylboronate complexes with aryl-halide- Pd^{II} complexes was slower than the reaction of arylboronic acids with aryl-oxo- Pd^{II} complexes by four orders of magnitude.³¹ In addition, under thermodynamic stoichiometric conditions, the relative populations of the aryl-halide- Pd^{II} complexes: aryl-oxo- Pd^{II} complexes, were roughly equal. Thus, both kinetically and thermodynamically speaking, the reaction between the aryl-halide- Pd^{II} complexes and arylboronic complexes is disfavoured, indicating that the transmetalation step mostly proceeds *via* Pathway 2 (Figure 2) and an *aryl-oxo-Pd^{II} complexes*.

Jutand *et al.* independently reported an important ‘triple role’ for the specific bases $[\text{M}]^+\text{OH}^-$ ³² and $[\text{M}]^+\text{F}^-$,³³ which were found to behave quite analogously, and are frequently used as bases in the transmetalation step of the SMCC reaction.³⁴ The role of base concentration had previously been in question in SMCC chemistry. Importantly, the electrochemical experimental regime deployed by Jutand *et al.* allowed reactions to be carried out with large excesses of arylboronic acid with respect to Pd, thus effectively modelling true catalytic conditions, where concentration of catalytic species is low relative to substrate. Reaction rates for ultimate transmetalation between *trans*- $[\text{Ar-Pd}(\text{Br})(\text{PPh}_3)_2]$ and high excesses of arylboronic acids ($\text{Ar}'\text{-B}(\text{OH})_2$) in the presence of varied concentrations of excess OH^- or F^- (introduced as soluble $[n\text{-Bu}_4\text{N}]\text{OH}/\text{F}$ salts) could be monitored electrochemically (Scheme 3). Under these conditions, varying the ratio of base to arylboronic acid, a bell-curve-type relationship between OH^-/F^- concentration and rate of transmetalation (k_{obs}) was observed, indicating that if the

^a hydroxide can be generated *in situ* from deprotonation of adventitious or additive H_2O by an appropriate base.

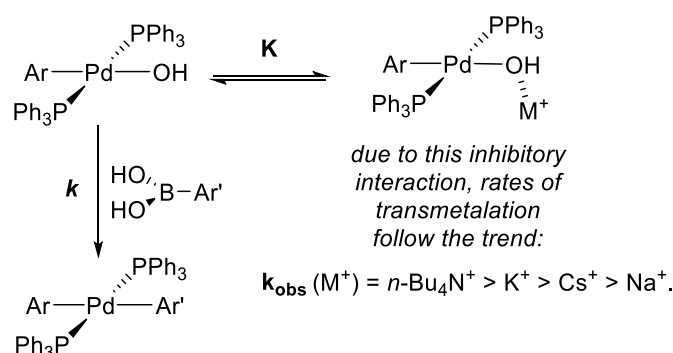
solution concentration of hydroxide or fluoride is too high, above a certain threshold, transmetalation rates are reduced. Crucially, OH^- or F^- bases able to react with arylboronic acids, forming arylboronate complexes, or with $\text{trans-[Ar-Pd(Br)(PPh}_3)_2]$, forming $\text{trans-[Ar-Pd(OH)(PPh}_3)_2]$, in competing equilibria. Thus, if the concentration of hydroxide is too high, the arylboronic acid is converted to the arylboronate complex which was confirmed, in line with observations from Carrow, Hartwig *et al.*, to be unreactive with either $\text{trans-[Ar-Pd(OH)(PPh}_3)_2]$ or $\text{trans-[Ar-Pd(Br)(PPh}_3)_2]$ (graph, Scheme 3). Jutand *et al.* also revealed a third role for the hydroxide base through formation of a base-ligated pentacoordinate post-transmetalation intermediate, forcing the aryl substituents into *cis*-formation, resulting in a promotion of reductive elimination through circumvention of the need for a thermodynamically unfavoured $\text{trans} \rightarrow \text{cis}$ isomerisation reaction (Scheme 3).³²⁻³³



Scheme 3 Summary of the crucial role of equilibria between a Pd oxidative addition product $\text{trans-[Ar-Pd(Br)(PPh}_3)_2]$, or arylboronic acid, and base (OH^- or F^-) in the transmetalation and reductive elimination steps of the SMCC reaction. Equilibria for OH^- or F^- base reaction with boronic acid (upper) and $\text{trans-[Ar-Pd(Br)(PPh}_3)_2]$ (lower). Adapted with permission from *Chem. Eur. J.* 2012, 18, 6616-6625 Copyright 2000 Wiley-VCH Verlag GmbH & Co.

An important message to take from the independent mechanistic work of Hartwig and Jutand is that for transmetalation to proceed with optimal efficiency in SMCC processes, a fine balance of base and boronic acid concentration must be struck. In situations where oxidative addition is not rate-

determining, for example, where aryl bromides and iodides are used as substrates, the rate and overall yield of the reaction could be enhanced by judicious control of the base concentration, to minimise the amount of inhibitory boronate complex in the reaction solution, whilst promoting the formation of the reactive *aryl-oxo-Pd^{II}* complex. Consequently, by optimising the rate of transmetalation, the effects of undesired competitive reaction pathways such as protodeborylation, protodehalogenation and homocoupling may be kept to a minimum.³⁵⁻³⁷ Most bases employed in the SMCC reaction are inorganic salts MX, where X is the basic (anionic) component and M⁺ is a counteranion. The counteranion was found to attenuate transmetalation, *i.e.* reactivity with arylboronic acid, by coordination to the *trans*-[Ar-Pd^{II}(OH)(PPh₃)₂] complex, thus for k_{obs} (transmetalation), an order of reactivity is seen where $n\text{-Bu}_4\text{N}^+ > \text{K}^+ > \text{Cs}^+ > \text{Na}^+$ (Scheme 4).³⁸

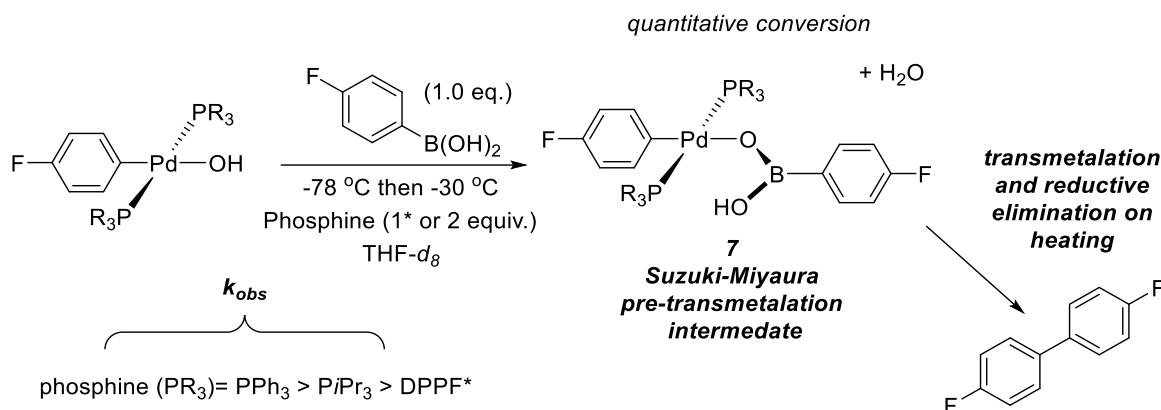


Scheme 4 Rates of transmetalation can be influenced by the identity of the base's counteranion in the SMCC. The metal cation can bind to the pre-transmetalation Pd-hydroxo complex thereby inhibiting and reducing transmetalation k_{obs} .

Therefore, employing weaker-coordinating cations such as $n\text{-Bu}_4\text{N}^+$ acted to enhance transmetalation rates with respect to the alkali-metal counterparts. An additional effect of salts containing bulky $n\text{-Bu}_4\text{N}^+$ cations on the reactivity of heterogeneous cross-coupling catalytic manifolds is discussed in Section 1.3.2.2. Commonly employed bases, such as alkali-metal carbonates, have been found to act to generate OH^- indirectly by *in situ* deprotonation of H_2O (either additive or adventitious). For example, carbonates in anhydrous solutions cannot mediate transmetalation from *e.g.* *trans*-[Ar-Pd(Br)(PPh₃)₂], while acetates can actually compete with OH^- in the pre-transmetalation intermediate *trans*-[Ar-Pd(OH)(PPh₃)₂] thereby inhibiting transmetalation.³⁸

Using low temperature multinuclear NMR spectroscopic techniques, Denmark *et al.* structurally characterised SMCC pre-transmetalation intermediates for the first time. By treating Pd-oxo complexes, *e.g.* *trans*-[Ar-Pd(OH)(PR₃)₂] with *para*-fluorophenylboronic acid in THF-*d*₈ (Scheme 5), quantitative formation of the highly reactive transmetalation intermediate **7** was observed, which was structurally characterised by ¹H, ¹⁹F, ³¹P and ¹¹B (1- and 2-dimensional) NMR spectroscopic methods, prior to observation of biaryl products following reductive elimination.³⁹⁻⁴⁰ Similar rapid and direct

reactivity was seen between arylboronic esters and arylboroxines with *trans*-[Ar-Pd(OH)(PR₃)₂].⁴¹ Additionally, the rate of formation of pre-transmetalation intermediate *e.g.* **7** was found to be faster with the more dissociative ligand, PPh₃, than with electron-rich P*t*Pr₃ and bis-chelating DPPF, underlining the utility of a coordinatively unsaturated, electrophilic Pd^{II} centre to enhance transmetalation.⁴⁰



Scheme 5 One example of a catalytic intermediate **7** which features a Pd–O–B linkage and forms immediately prior to transmetalation in the SMCC reaction.

Notably, while the reaction of *trans*-[Ar-Pd(OH)(PR₃)₂] with arylboronic acids led to quantitative conversion to the P–O–B intermediate **7** (Scheme 5), the same product could arise from the reaction of thallium *para*-fluorophenylboronate with *trans*-[Ar-Pd(I)(PR₃)₂] however with poor conversion. This finding is in-keeping with relatively sluggish reactivity of boronate complexes as observed by the groups of both Hartwig and Jutand (*vide supra*).^{32, 42}

1.2.2. Catalyst Activation of Pd(II) Salts for Cross-coupling Catalysis

It is well established that Pd⁰ species can initiate cross-coupling catalysis *via* activation of a carbon–(pseudo)halide bond by oxidative addition.⁴³ Hence, pre-activated Pd⁰ pre-catalysts such as [Pd⁰(PPh₃)₄] and [Pd₂(dba)₃.solv.] have seen wide utility in all branches of chemical synthesis. The advantage of employing such a catalyst is that it is already in the required low oxidation state and therefore does not necessarily require any redox-based chemical activation.⁴⁴ When employing complexes featuring electron rich Pd⁰, particularly under air,⁴⁵ a balance must be struck between practicalities of storage/handling and catalytic activity. These issues can be somewhat circumvented by employing Pd^{II} complexes such as Pd(OAc)₂ or PdCl₂ as catalyst precursors, which may be activated *in situ* through reduction by appropriate solvents, additives or catalytic substrates. The method of *in situ* reduction (activation) of Pd^{II} salts is attractive as such salts generally show greater thermal and air stability and can thereby be stored for extended periods of time without loss of value.

Amatore, Jutand *et al.* were the first group to show that tertiary phosphine ligands, when deployed in combination with $\text{Pd}(\text{OAc})_2$ do not merely stabilise and modulate the activity of the active Pd catalyst, but can also play a crucial role in reductive activation under mild conditions (see Chapter 2 for further details and work building on this).⁴⁶⁻⁴⁸ It was found that ≥ 4 equivalents of PPh_3 reacts with $\text{Pd}(\text{OAc})_2$ to rapidly form *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$,⁴⁹⁻⁵⁰ which is converted, in an inner sphere intramolecular reduction process, to an active anionic Pd^0 complex $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)]^-$ with concomitant oxidation of 1 equivalent of sacrificial PPh_3 to $\text{O}=\text{PPh}_3$ ($\text{P}^{\text{III}} \rightarrow \text{P}^{\text{V}}$) (lower, Figure 3).⁴⁶ The electronic and steric properties of the phosphine allowed for control of the rate of reduction to the active Pd^0 complex.⁴⁷ The same research group, building on earlier work by Grushin *et al.*,⁵¹ similarly delineated the mechanism of activation of the pre-catalytic complex *trans*- $[\text{PdCl}_2(\text{PPh}_3)_2]$, which exhibits greater robustness in solution than the analogous *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ complex, requiring additive base (often a tertiary amine, *e.g.* under Sonogashira cross-coupling conditions) for reductive activation to the Pd^0 complex $[\text{Pd}^0(\text{PPh}_3)_3]$ (upper, Figure 3).⁵²

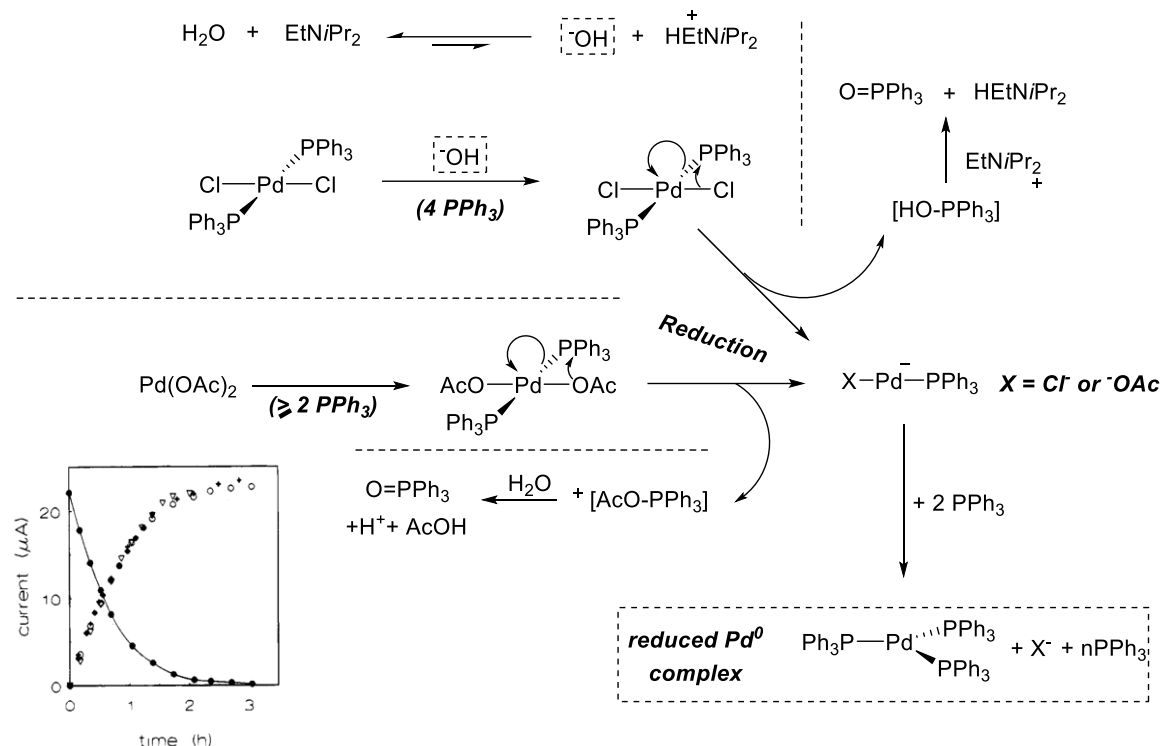


Figure 3 Comparison of the mode of catalyst activation of *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ (below) formed immediately by solubilising $\text{Pd}(\text{OAc})_2$ and ≥ 2 PPh_3 , and *trans*- $[\text{PdCl}_2(\text{PPh}_3)_2]$ (above) to Pd^0 complexes in the presence of high excesses of PPh_3 . The graph (bottom-left) shows the rate of *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ consumption and formation of Pd^0 complexes. In the case of *trans*- $[\text{PdCl}_2(\text{PPh}_3)_2]$, reduction at Pd is facilitated by hydroxide, formed by deprotonation of H_2O by a tertiary amine base. Adapted with permission from *Organometallics* 1995, 14, 1818-1826. Copyright 1995 American Chemical Society.

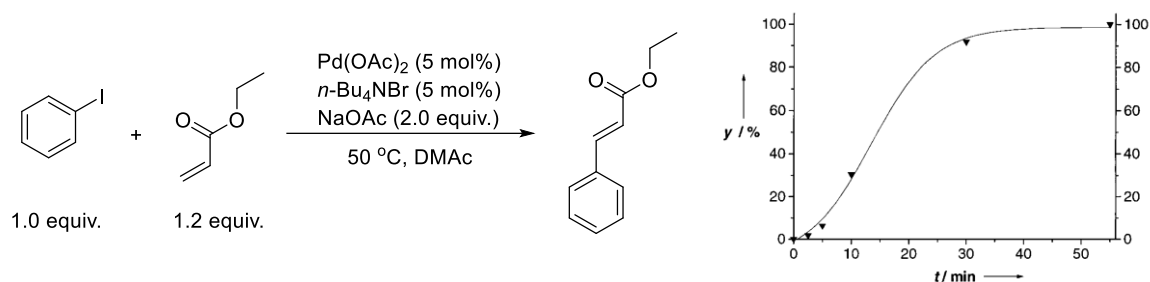
Importantly, in the case of *trans*- $[\text{PdCl}_2(\text{PPh}_3)_2]$, a role of the tertiary amine base (Et_3N) was to form hydroxide *via in situ* deprotonation of trace H_2O , which facilitated reduction to a Pd^0 complex, with concomitant oxidation at phosphorus. Although in this case, the amine was found to act indirectly in

the activation of *trans*-[PdCl₂(PPh₃)₂], there have been reported examples where amines can directly reduce and activate Pd^{II} salts.⁵³⁻⁵⁶ In these cases, where it is noted that phosphines were not present, significantly elevated temperatures (*e.g.* 120-150 °C) were required to activate the Pd pre-catalyst for cross-coupling to take place. This observation indicates that phosphine ligands can significantly decrease the reduction potential of Pd^{II} salts, effectively acting as a mild reducing agent, allowing catalyst activation to proceed at room temperature. Colacot *et al.* examined the analogous catalytic activation of [PdBr₂(cod)] (cod = 1,5-cyclooctadiene) in the presence of ≥ 3 equivalents of the bulky, electron rich P^{*i*}Bu₃ ligand which activates to form [Pd⁰(P^{*i*}Bu₃)₂] with concomitant oxidation of sacrificial P^{*i*}Bu₃ to [BrP^{*i*}Bu₃]⁺Br⁻ (See Chapter 3 for further details).⁵⁷ Cross-coupling substrates such as organoboronic acids have been identified to be able to induce catalyst activation.^{37, 58-59} There are also numerous cases where the rate of activation of pre-catalyst solutions containing Pd(OAc)₂-phosphine complexes can be markedly accelerated by adventitious or additive H₂O.⁶⁰⁻⁶³

While Jutand *et al.* and other groups have demonstrated that monomeric Pd⁰ *can* be generated from Pd^{II} in the presence of tertiary phosphine additives, the vast majority of studies on the mechanism of activation of have been carried out with an excess of phosphine present, thus departing from modelling of practical catalytic conditions, where fewer catalytic equivalents of triarylphosphine are more commonly deployed. Clearly, *e.g.* [Pd⁰(PR₃)₄] is unlikely to be the catalyst resting state under conditions where pre-catalytic Pd^{II}/ 2 PR₃ is employed, as there is simply not enough ligand present to stabilise such a species. Furthermore, it is well-accepted that excesses of donor ligands can have a deleterious effect on catalytic performance.⁶⁴

Under exogenous ligand-free catalytic conditions, Reetz and co-workers discovered that *in situ* activation of Pd(OAc)₂ by an alkylammonium salt additive,^b in DMAc under Heck reaction conditions, sigmoidal kinetics with respect to product formation were observed (Scheme 6).⁶⁵⁻⁶⁶ Pd nanoparticles (PdNPs), sampled from the reaction solution, were characterised by transmission electron microscopy (TEM). This finding showed that, under the reaction conditions, the cross-coupling reaction begins with a slow induction period, followed by an autocatalytic growth phase, indicative of self-proliferative active catalyst formation. In this case, a sigmoidal curve has been fitted, although it is noted that there are not many data points, indicating that there are likely significant errors with this curve fit.

^b See section 1.3.2.2 for a detailed discussion about the effect of salt additives, including alkylammonium salts, on the propagation of Pd in solution.



Scheme 6 (Left) Showing conditions used for the ligand-free Heck coupling of iodobenzene with ethyl acrylate, catalysed by $\text{Pd}(\text{OAc})_2$ alongside additive $n\text{-Bu}_4\text{NBr}$. **(Right)** a kinetic profile for the rate of formation of the cross-coupled product, displaying sigmoidal kinetics. In the graph ‘y’ corresponds to reaction conversion. Reproduced with permission from *Angew. Chem. Int. Ed.* 2000, **39**, 165-168. Copyright 2000 Wiley-VCH Verlag GmbH & Co.

Such a mode of catalytic activation is strongly – although, importantly, not exclusively⁶⁷⁻⁶⁸ – linked to heterogeneous catalytic manifolds (associated with PdNPs), where the autocatalytic phase is achieved when a heterogeneous surface is primed for catalysis (see Section 1.3 for a discussion of the role of such heterogeneous Pd species in catalysis).^{43, 69-71}

It can be seen that the dynamics and nature of activated Pd species can vary as a function of the reaction conditions employed, as summarised in Figure 4.

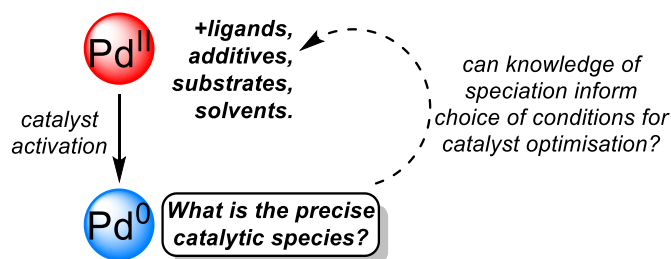


Figure 4 A generalised scheme summarising the factors which influence reduction and activation of Pd^{II} salts for cross-coupling catalysts.

Where an active catalyst is generated *in situ*, control of the catalytic activation step is crucial for controlling the optimal catalytic activity. Further, knowing the precise nature of the formed catalytically active species may inform the choice of pre-catalytic conditions. Under some conditions, contrary to the well-defined Pd^0 species described in the SMCC mechanistic discussion *vide supra*, higher order catalytic species such as Pd clusters and PdNPs can arise. This Thesis presents new evidence for such higher order species arising from simple mixtures of $\text{Pd}^{\text{II}}(\text{OAc})_2$ /tertiary phosphine mixtures, with implications for cross-coupling catalysis.

1.2.3. Cross-coupling Reactivity: A Complete Mechanistic Picture?

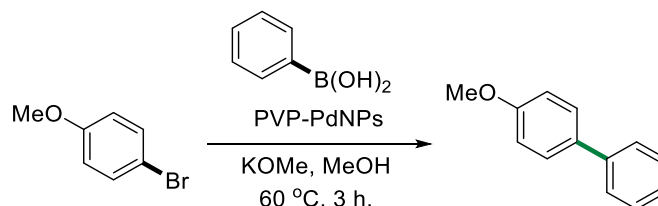
The mechanistic understanding of cross-coupling can inform the synthetic chemist how to select conditions for a given system, allowing them to fine-tune variables such as catalyst identity, base identity and concentration, and ratios of organometallic/organohalide coupling partners, all with a view to enhancing reaction outcomes. These factors can all contribute to reduction both in costs and in unnecessary waste in for a given cross-coupling reaction process. Importantly, however, not all SMCC reactions (or cross-coupling reactions in general) act *via* the homogeneous, phosphine-ligated, mono-nuclear complexes, *e.g.* *trans*-[Ar–Pd(X)(PR₃)₂], the product of oxidative addition of [Pd⁰(PR₃)₂] to Ar–X, that underpin current state-of-the-art understanding of the SMCC mechanism. The field is positively flourishing, however, with examples of cross-coupling being mediated by *e.g.* exogenous ligand-free systems, Pd nanoparticles and ligated Pd cluster catalysts, where a [Pd⁰(L)_n] model catalyst is unlikely to apply or is altogether incompatible. Mechanisms by which cross-coupling catalysis can proceed under such diverse catalytic manifolds are far less well understood although such systems can exhibit powerful and distinctive reactivity. Following sections will highlight current understanding of how these diverse types of catalytic species can operate.

1.3. Pd nanoparticles as (quasi-)Heterogeneous Cross-coupling Catalysts

Pd particles are well known to form under working conditions during many cross-coupling processes, as a result of degradation and precipitation of solvated Pd species. Pd nanoparticles (PdNPs) have been shown to be active and catalytically competent in cross-coupling processes.^{43, 72-73} The benefits of using heterogeneous Pd sources are clear. They can be easily handled and are usually stable under air as well as being relatively easily removed from a reaction and recycled and as result can reduce waste of expensive Pd metal. Consequently, much research goes into the development of supported PdNP heterogeneous catalysts.⁷⁴ There are two broad modes of action whereby a heterogeneous catalyst, *e.g.* supported PdNPs can operate: *true*-heterogeneous: catalysis at particle surface and *quasi*-heterogeneous: where a heterogeneous source acts as a reservoir for a leached active species.⁷² Key pieces of evidence for cross-coupling catalyst action by both *true*- and *quasi*-heterogeneous manifolds are discussed in the next two sections.

1.3.1. Evidence for Heterogeneous Catalytic Behaviour: Surface Catalysis vs. Leaching

Early strong evidence for *true*-heterogeneous cross-coupling catalytic behaviour was reported by Fairlamb and Lee.⁷⁵⁻⁷⁶ In their study, the catalytic action of the heterogeneous catalyst: PdNPs stabilised by a polymer polyvinylpyrrolidone support (PVP-PdNPs), was probed in a model SMCC coupling of 4-bromoanisole and phenylboronic acid (Scheme 7).



Scheme 7 Model reagents and conditions employed in the study by Fairlamb *et al.*, elucidating the heterogeneous nature of the PVP-PdNP active catalyst during Suzuki-Miyaura cross-coupling turnover.

Using a colloidal seeding method, PVP-PdNPs, featuring PdNPs of four distinct and well-defined sizes, were selectively synthesised, with each adopting a truncated cuboctahedra morphology (average size from 1.8 to 4.0 nm, confirmed by TEM imaging). When applied to the model SMCC, catalyst activity (as expressed by TOF) was seen to decrease as the particle size was increased. If, however, the particle size was normalised to the known total number of Pd atoms on *defect sites* of the PdNPs, a linear, unchanging relationship between particle size and TOF was recorded (left, Figure 5). This finding pointed towards the catalytic activity of the surface being governed by the number of low coordination number *defect sites* on the particle. This finding, however, does not necessarily answer the question of whether the reaction is occurring on the PdNP surface, as the noted defect sites could simply be sites at which leaching Pd atoms may be more soluble (accessible to the solution) and hence more likely to leach into the reaction solution and thusly operate homogeneously (*i.e.* by a *quasi*-heterogeneous mode of action). The authors therefore deployed an *in operando* extended X-ray absorption fine structure spectroscopic (EXAFS) technique to monitor the coordination environment of the surface Pd (right, Figure 5) as a function of time. Most importantly, no measurable change in coordination environment on the surface Pd was recorded during the entire reaction process.

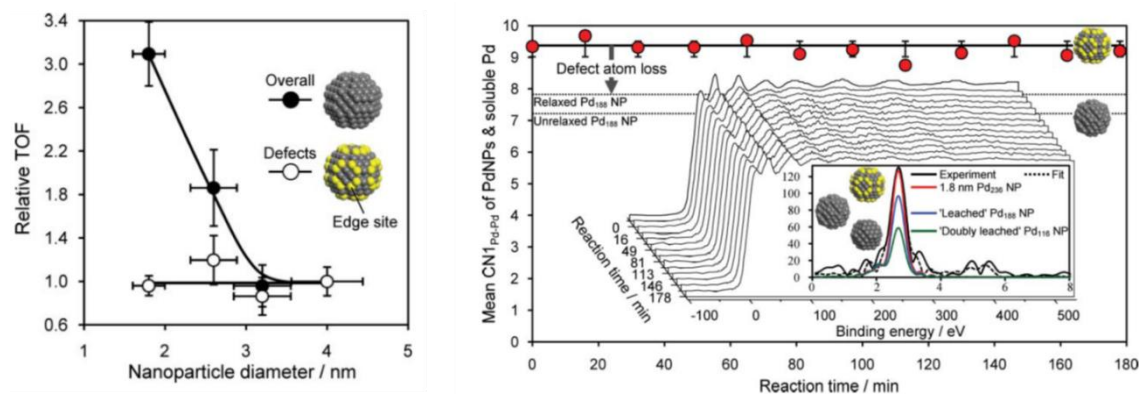


Figure 5 (left) Showing the PVP-PdNPs size-dependence on TOF in a model SMCC, normalised to either total surface Pd atoms (●) or defect surface Pd atoms (○) (right) XAFS data showing that no significant change in surface Pd coordination number as the model SMCC proceeds. Reproduced with permission from *Angew. Chem., Int. Ed.* 2010, 49, 1820-1824. Copyright 2010 Wiley-VCH Verlag GmbH & Co.

An absence of significant leaching of Pd from the PVP-PdNPs was noted. Kinetic analysis of the model SMCC reaction demonstrated no presence of an induction period, indicating that the PVP-PdNPs were not simply acting as a pre-catalyst or a reservoir for a true active species (*vide infra*). Immediate, and complete termination of catalyst activity was observed upon adding elemental Hg (a positive Hg poisoning test).^{69, 77-78} This study provides significant evidence that cross-coupling may occur on the surface of a heterogeneous catalyst. At this stage, however, catalysis by rapid leaching/redeposition events not observable on the EXAFS timescale cannot be ruled out.

Building on these findings, Xie *et al.* recently presented further direct evidence for surface-mediated SMCC reactions.⁷⁹ *Au-Pd core-satellite superstructures* (silica particles coated with a layer of AuNPs and an outer layer of PdNPs) (Figure 6, a and b) were surface-modified with 4-bromothiophenol, which was tethered by chemisorption (*via* a sulfide linker) to the Pd surface outer layer of the nanoparticle. The tethered substrate was able to be cross-coupled with phenylboronic acid (in aqueous K₂CO₃) (Figure 6, c) forming tethered biaryl product. Surface enhanced Raman spectroscopy (SERS) was used to track the depletion of the aryl halide reactants and concomitant formation of the biaryl product, both of which remained anchored to the particle surface throughout the process (Figure 6, d). Using SERS, kinetic reaction profiles of the could be made, demonstrating that smaller nanoparticles (5 nm) reacted faster than larger nanoparticles (15 nm), which was rationalised to be a result of increased exposure of surface Pd (or, as is more likely, increased numbers of low coordination number defect sites). When applying the SERS technique to the reversed-polarity reaction, where the phenylboronic acid was instead tethered to the NP surface, and 4-bromophenol was used as the solution-phase aryl bromide substrate, no turnover was measured.

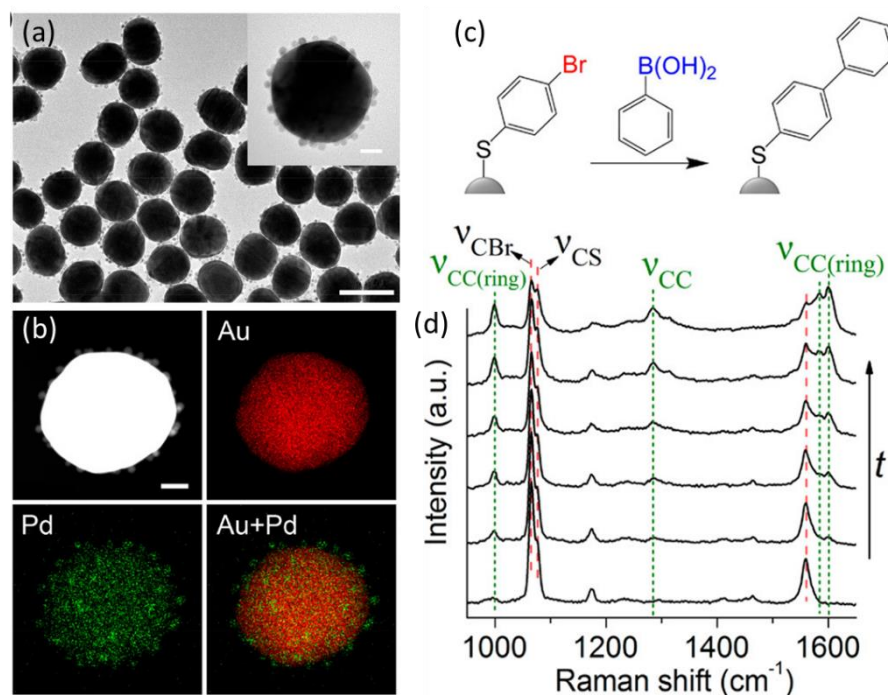


Figure 6 Showing (a) A TEM image of Au-Pd core-satellite superstructures (b) High-angle annular dark field scanning transmission electron microscopy (HAADF-STEM) image showing distribution of different elements on Au-Pd core-satellite superstructures (c) Reaction scheme for proposed surface-catalysed SMCC, showing the tethered bromobenzene reacting in the presence of aqueous phenylboronic acid in the presence of K_2CO_3 (d) Stacked SERS spectra showing conversion of tethered aryl bromide to tethered biaryl as a function of time. Adapted with permission from *J. Phys. Chem. Lett.* 2019, 10, 1286-1291. Copyright 2019 American Chemical Society.

The above findings are in line with the nanoparticle surface being necessary for C–Br bond activation. Further, it was found that when interstitial organic groups were inserted between the tethered bromobenzene moiety and the PdNP surface, the reaction was faster as a function of surface-C–Br-bond proximity. It was found that the shorter the distance of the C–Br bond to the surface, the more likely an interaction with the surface will occur. It was hence reasoned that the C–Br bond of the bromobenzene substrate could meet the catalyst surface for activation by ‘swinging’ or ‘rolling’ around its sulfide anchor.

Leaching of Pd from the AuNP superstructure was however noted, therefore, control experiments were necessary to determine the catalytic contribution of leached Pd to the overall process. The reaction was attempted exclusively employing the 4-bromothiophenol substrate tethered to catalytically inactive Au as the nanoparticle surface, in the presence of a solution containing Pd which had leached from a standard Au-Pd-catalysed post reaction ($\sim 200 \mu\text{g L}^{-1}$ measured by ICP-AES). Since conversion was not observed under these control conditions, the notion that the leached Pd species enabled the cross-coupling reaction was ruled out. This finding was taken to indicate that surface catalysis may occur even if leaching of inactive species from the heterogeneous source occurs. These results provide

another strand of evidence to indicate that a Pd surface can activate an aryl halide to react heterogeneously with arylboronic acid to form a biaryl product. This reaction system does not however discount the possibility, not addressed by the authors, that Pd could be leached onto the tethered aryl halide and ‘hop’ back onto the Pd surface after catalysis. In this situation, the tethered substrate could facilitate efficient reversible shuttling on and off of the support.

Under some cross-coupling conditions, homogeneous species leached from PdNPs have been proven to be responsible for observed catalytic turnover. Rothenberg demonstrated leaching of catalytically-active Pd from relatively large nanoparticles (~ 15 nm), generated from *in situ* reduction and stabilisation of $[\text{Pd}(\text{NO}_3)_2]$ in the presence of a *tetra-n*-octylammonium ammonium glycolate salt.⁸⁰ By design of a special reactor containing a porous membrane which would only allow passage of smaller particles ($< \sim 5$ nm), it was proved that leached species can be active in cross-coupling processes. This finding was not taken, however, to necessarily confirm that the leached species are operating as mono-nuclear catalysts, since particles of this size could theoretically contain several thousand Pd atoms and thus, the reaction could still be occurring on a surface of leached clusters. Baiker *et al.* used X-ray absorption spectroscopic methods to track, *in situ*, the leaching of Pd from a heterogeneous source ($\text{Pd}/\text{Al}_2\text{O}_3$) under Mizoroki-Heck cross-coupling conditions.⁸¹ *In situ* probing also indicated the presence of smaller, colloidal PdNPs as well as anionic mono-nuclear molecular species $[\text{PdBr}_4]^{2-}$ and $[\text{Pd}_2\text{Br}_6]^{2-}$, which had leached into the liquid phase, thus painting a more complicated picture where multiple different types of species can evolve from a single heterogeneous source.

Irreversible leaching from heterogeneous sources can result in loss of expensive metal catalyst, to either waste streams, or to contamination of final products, therefore making chemical processes less economically viable. The problem of leaching is of further significance for the pharmaceutical sector, which sets stringent limits (< 10 ppm for oral consumption) on the trace levels of Pd which can contaminate drug-products.⁸² Thus, there is significant research drive to develop scavenger systems which can efficiently reclaim Pd lost to reaction solutions.⁸³⁻⁸⁴ It is however beneficial to have a heterogeneous catalyst source that is fully recyclable and does not irreversibly leach Pd to the reaction solution on turnover. There are numerous literature-reported cases where catalysis was proven to occur by a leaching-redeposition mechanism, where the heterogeneous Pd source could be recycled and efficiently redeployed in multiple successive reactions.⁸⁵⁻⁸⁶

In 2020, Scaiano and co-workers applied, for the first time, a total internal reflection fluorescence microscopy (TIRFM) technique in approaching the problem of the active phase when a heterogeneous catalyst source is employed. The method involved tracking single cross-coupling events by measuring fluorescence emission events as functions of spacial position and time at a heterogeneous PdNP on TiO_2 catalyst ($\text{Pd}@/\text{TiO}_2$).⁸⁷ By use of a specially engineered BODIPY-based fluorescent aryl bromide

substrate, which could couple with thienyl boronic acid under flow conditions to afford a SMCC product with a very different absorbance and emission spectrum to that of the starting material, fluorescence emission events could be used to track the presences of substrate and products. The method provided direct evidence of a leaching-deposition mechanism under the flow conditions, whereby after initial interaction of the aryl bromide with the PdNPs, reductive elimination and product release was seen to occur at a position distinct to that of initial interaction (b, Figure 7).

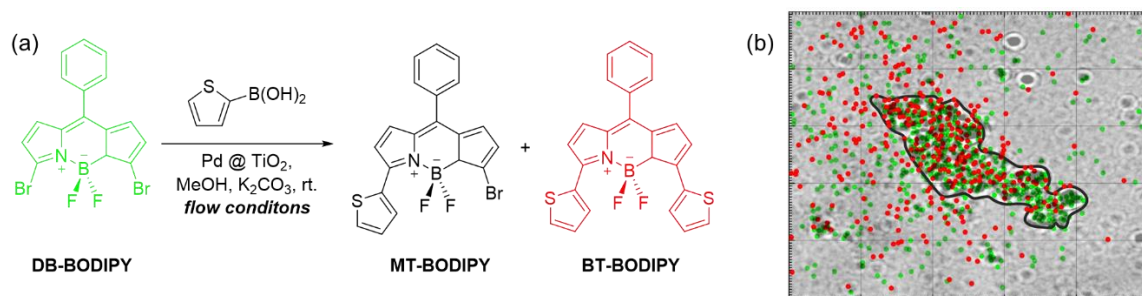
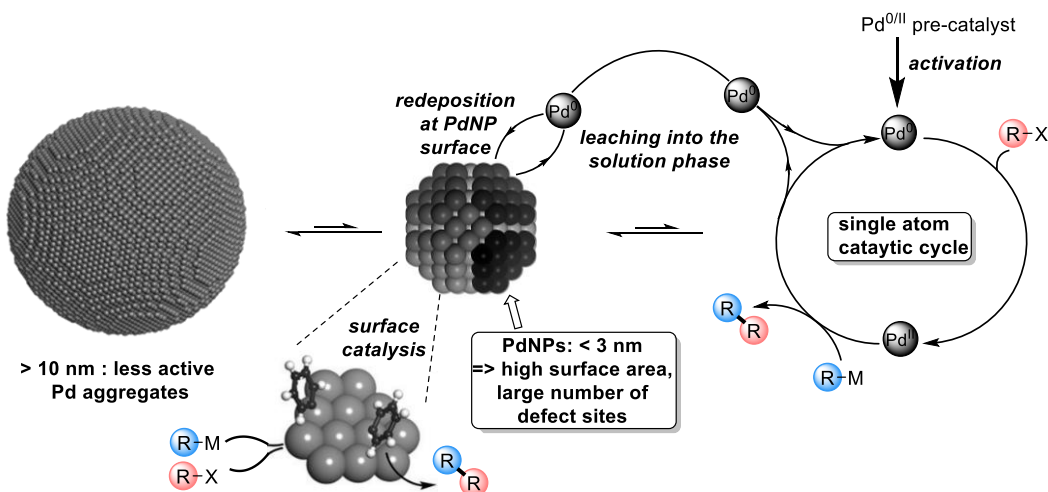


Figure 7 (a) Reaction scheme, including conditions used in the SMCC of the fluorescent aryl bromide substrate DB-BODIPY to form the mono- and bis-arylated products: MT-BODIPY and BT-BODIPY. (b) Overlay TEM image of catalyst with a map of emission events for recorded locations of DB-BODIPY reactant adsorption to the PdNP catalyst (green dots) and BT-BODIPY product formation (red dots). Adapted with permission from Springer/Nature, *Nat. Catal.* 2020, **3**, 427-437. © 2020.

Importantly, the TIRFM method confirmed that the K_2CO_3 base aided in the desorption of the Pd from the catalyst surface, indicating that with this heterogeneous catalyst source, the base played a dual role in facilitating C–Br bond activation in addition to its expected role in the transmetalation event (see Section 1.2.1).

Zeng *et al.* designed an core-shell FeO support for PdNPs, surrounded by a microporous silica ‘membrane’ which precluded interactions between larger substrates and the PdNP surfaces prior to catalyst turnover in the SMCC reaction.⁸⁸ In this case it was determined that oxidative addition of iodobenzene onto the heterogeneous surface caused etching of active Pd and, as a consequence, leaching of Pd resulted in the subsequent C–C bond-forming steps proceeding in the solution phase. Again, redeposition of recycled Pd^0 onto the heterogeneous catalyst surface after complete conversion of iodobenzene substrate allowed for efficient catalyst recycling.

This section has shown that, in a given catalytic system, components of heterogeneous or homogeneous catalytic manifolds could potentially act in concert (summarised in Scheme 8). Homogeneous mono-nuclear Pd is known to aggregate to particles, which can be catalytically active in their own right, either as direct surface catalysts, or by acting as a reservoir for active leached Pd in the solution phase.



Scheme 8 The complex picture for the modes of reactivity of homogeneous and heterogeneous metal species in a given cross-coupling process.

This picture is further complicated by the potential for an additional role for Pd clusters, which bridge the gap between homogeneous and heterogeneous catalyst manifolds.⁸⁹⁻⁹⁰ The catalytic role of such Pd clusters is discussed in Section 1.4.

1.3.2. Stabilisation of Catalytically Relevant PdNPs in Solution

There are many factors that can affect the formation and stability of PdNPs in solution. Solvents, and additives, such as salts, ligands, polymers and surfactants have all been demonstrated to play important roles in cross-coupling catalysis by governing the kinetics and dynamics of PdNP stability and solution propagation.

1.3.2.1. The Role of Solvents on Pd Stabilisation and Propagation

Solvents with high polarities and viscosities, such as polar aprotic solvents *e.g.* DMF, DMAc and NMP, have been classed as ‘*palladaphilic*’, due to their ability to activate and stabilise Pd. There is significant evidence that such solvents influence the stability and propagation dynamics of catalytically active species, including PdNPs.⁹¹ Obora *et al.* reported the synthesis and characterisation of ‘ligandless’ DMF-stabilised PdNPs (1.0-1.5 nm as measured by TEM) which demonstrated extremely high activity (up to 6.0×10^8 {TON}) in SMCC and Heck reaction applications using low catalyst loadings (<12 ppm/Pd).⁹² The PdNPs were synthesised simply by heating a DMF solution of PdCl₂, without any additional additives, under reflux for 6 hours. Analogous DMF-stabilised PdNPs derived from Pd(OAc)₂ exhibited superior TONs to those synthesised from PdCl₂ in SMCC applications, indicating that the acetate anion may play a positive role in catalysis.⁹³ Choi *et al.* developed an HPLC-MS technique to detect small DMF-stabilised PdNPs (Pd₁₀-Pd₂₀ i.e. < 3 nm).⁹⁴ On account of their size

(See Section 1.3.1) such small PdNPs would most likely be catalytically relevant if applied to cross-coupling conditions and may elude characterisation by other methods, *e.g.* TEM.

The known toxicity of polar aprotic solvents such as DMF, DMAc and NMP, should not be overlooked however and alternatives should be sought where possible.⁹⁵⁻⁹⁶ γ -Valerolactone **8** (GVL), a lignocellulose-derived solvent has been put forth as a green alternative to toxic and environmentally damaging polar aprotic solvents (Figure 8).⁹⁷ Computational analysis (DFT) has indicated that GVL has a similar co-ordination affinity to Pd as DMAc, and hence is expected to behave similarly in activation and propagation of PdNPs.⁹⁸ Propylene carbonate **9** has also been demonstrated as a green alternative stabilising medium for catalytic PdNPs (Figure 8).⁹⁹ While such green alternative solvents have been studied as potential replacements for highly toxic polar solvents,¹⁰⁰ further work is needed to validate their performance in cross-coupling under a robust range of conditions.

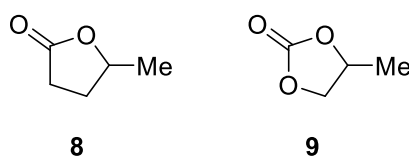
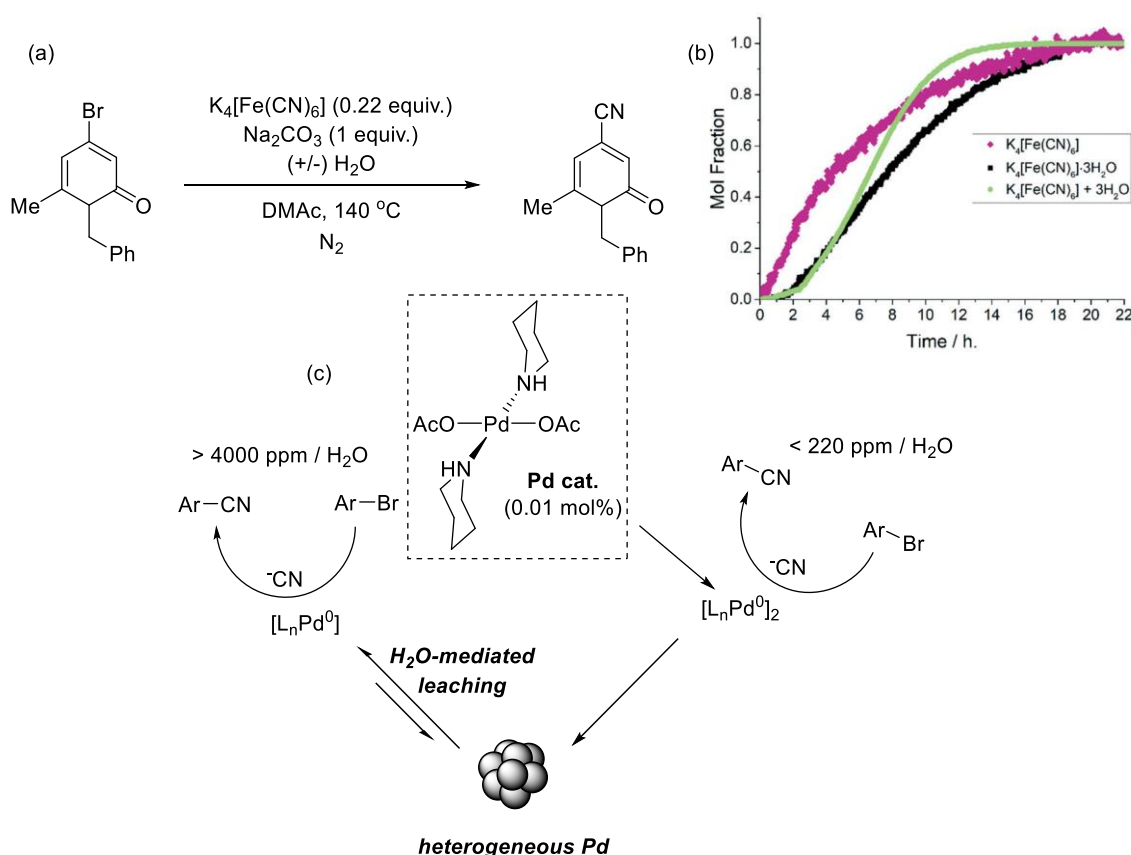


Figure 8 The molecular structures of γ -valerolactone and propylene carbonate, biomass-derived polar aprotic *green* solvents, promoted as alternatives to the highly toxic commonly used solvents such as DMF, DMAc and NMP.

H₂O, a polar protic solvent, is also pervasively exploited in nominal homogeneous as well as heterogeneous Pd-cross-coupling applications. In addition to its role in solubilising base, formation of active hydroxide in SMCC reactions and, more generally, activation of Pd pre-catalysts for cross-coupling processes (see Sections 1.2.1 & 1.2.2), H₂O has been shown to have influence over catalytic speciation and resulting cross-coupling activity. Bedford *et al.* showed that the [Pd₃(OAc)₆] could hydrolyse in the presence of H₂O to form a hydroxide-bridged cluster of the form [Pd₃(μ -OH)(OAc)₅].¹⁰¹ The substitution of acetate anion with H₂O, forming [Pd₃(μ -OH)(OAc)₅], was found to be essentially quantitative in solvents such as THF, acetone and 1,4-dioxane, which demonstrate good H₂O miscibility. Hii *et al.* delineated a crucial, multi-faceted role for H₂O in the activation of [Pd₃(OAc)₆] in SMCC reactions.⁵⁸ An H₂O-mediated dissociation of [Pd₃(OAc)₆] was found to occur prior to reduction to Pd⁰-particles by arylboronic acid, and hence it was reasoned that stoichiometry (relative to Pd) of H₂O present was seen to have direct bearing on the amount of catalytically available Pd⁰ and hence the reaction efficacy. When Corma *et al.* tested a variety of different species of pre-catalysts in a Mozoroki-Heck reaction, it was found that employing monodisperse catalytic PdNPs (*ca.* 3.9 nm) as pre-catalysts, the presence of H₂O was crucial in achieving optimal activity.¹⁰² Furthermore, enhanced reactivity in the presence of H₂O was correlated with the detection of smaller Pd clusters (3 or 4 atoms), stemming from the supported heterogeneous source, as detected by ESI-MS and UV/Vis

methods. Additionally, similar reactivity patterns were observed when using $\text{Pd}(\text{OAc})_2$, palladacyclic complexes and Pd/C pre-catalysts, with H_2O mediating a crucial enhancement of activity, as evident by the elimination of a catalytic induction period in each case.

H_2O has also been shown to play a role in the promotion of leaching from heterogeneous catalyst sources.¹⁰³⁻¹⁰⁴ Working with BayerCropScience, Bray, Ford and Fairlamb discovered a nuanced role for H_2O in catalyst speciation arising from a *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ source in arylcyanation reactions in a DMAc reaction medium (Scheme 9).¹⁰⁵ It was found that the H_2O quantity present had a marked influence on catalytic performance, with the presence of >4000 ppm of H_2O resulting in a heterogeneous-rooted catalytic manifold. However, carrying out the reaction under drier conditions (220 ppm H_2O) resulted in higher activity and a homogeneous catalytic manifold. In the case of the heterogeneous catalytic system formed with H_2O >4000 ppm, H_2O was determined to enable leaching of Pd^0 species from the heterogeneous PdNP source. At <220 ppm H_2O , a reaction order of 2 in Pd was recorded, implicating a bimetallic $[\text{Pd}^0(\text{L})_n]_2$ ($\text{L} = \text{N-piperidyl}$) active species.

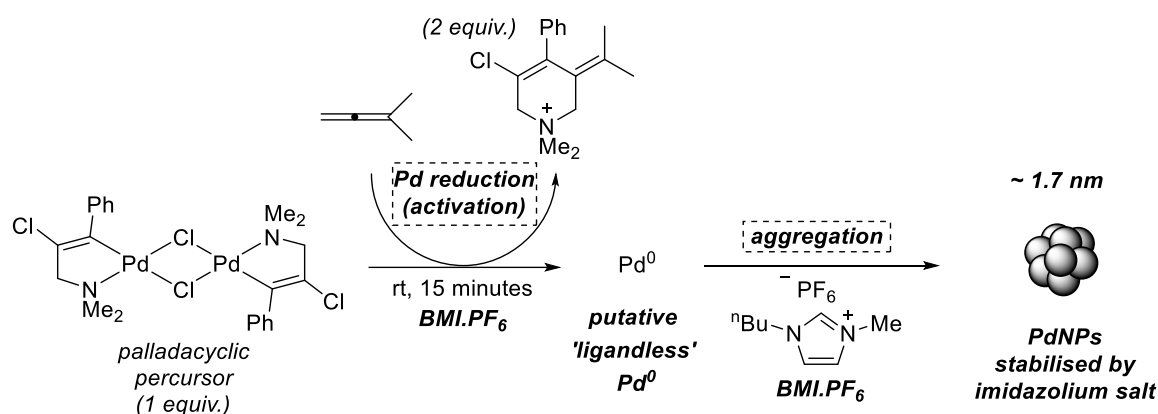


Scheme 9 Findings concerning the Pd speciation arising from *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ during catalytic arylcyanation reactions, (a) reaction conditions used, (b) how the reaction kinetics vary as a function of H_2O present, (c) Summary of findings regarding Pd speciation under the presence of different quantities of H_2O . Adapted from *React. Chem. Eng.* 2019, 4, 122-130.¹⁰⁵

In summation, polar aprotic solvents and H₂O have been demonstrated to play a clear role in the activation and stabilisation of catalytically relevant Pd species which can be derived from Pd^{II} salt-based pre-catalytic sources, including Pd(OAc)₂.

1.3.2.2. The Role of Additives in Pd Stabilisation and Propagation

Dupont *et al.* found that PdNPs, generated from the room temperature reaction between a palladacyclic precursor and dimethylallene, could be stabilised by an imidazolium hexafluorophosphate ionic liquid (**BMI.PF₆**) (Scheme 10).¹⁰⁶ When PPh₃ was added during the activation process, [Pd⁰(PPh₃)₄] was detected. This observation was taken to indicate that bare, atomic Pd⁰ is generated from the reaction, which, in the absence of PPh₃, aggregates to the observed stabilised PdNPs, in the ionic liquid. The **BMI.PF₆**-stabilised PdNPs, were determined by TEM to be irregular shaped particles which measured at 1.7 ± 0.3 nm and demonstrated good activity in a model Mizoroki-Heck coupling reaction.

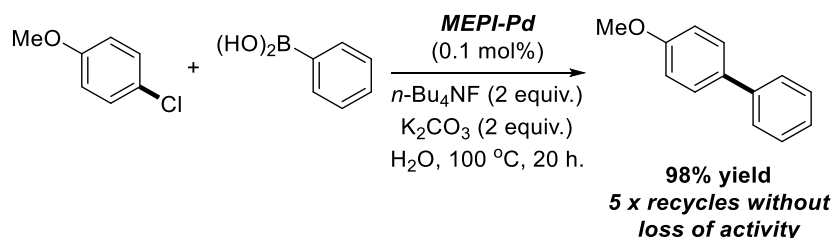


Scheme 10 Findings by Dupont *et al.*, that a palladacyclic Pd^{II} complex can reduce to Pd⁰, and subsequently PdNPs stabilised by the ionic liquid BMI.PF₆ as the reaction medium.

Using UV-Vis spectroscopic analysis, Rothenberg *et al.* monitored the formation of valence-conduction bands (λ_{abs} 370–390 nm), corresponding to PdNP surface plasmon resonances¹⁰⁷ to track the dynamics of formation and growth of *in situ* formed PdNPs on reduction (activation) of homogeneous sources.¹⁰⁸ In this case PdCl₂, Pd(OAc)₂ and Pd(NO₃)₂ in DMF, were used as PdNP sources, in the presence of stabilising *tetra-n*-octylammonium salts, featuring acetate, formate or glycolate counteranions. A combination of PdCl₂, as the PdNP precursor, and *tetra-n*-octylammonium formate proved to be optimal for rapid precursor conversion. Polymers such as PVP are frequently used to stabilise catalytic nanoparticles, either as part of the pre-catalytic system, or used *in situ*.^{109–110} In a remarkably simple and robust synthetic methodology, Doubleday *et al.* reported the use of polyethylene glycol (PEG) for enhancement of 'ligandless' Pd(OAc)₂-catalysed Suzuki coupling of a vast range of substituted (hetero)aryl bromides.¹¹¹ PEG-2000 was determined to be the optimal polymeric molecular weight in conditions screening for a model reaction. After stirring under working

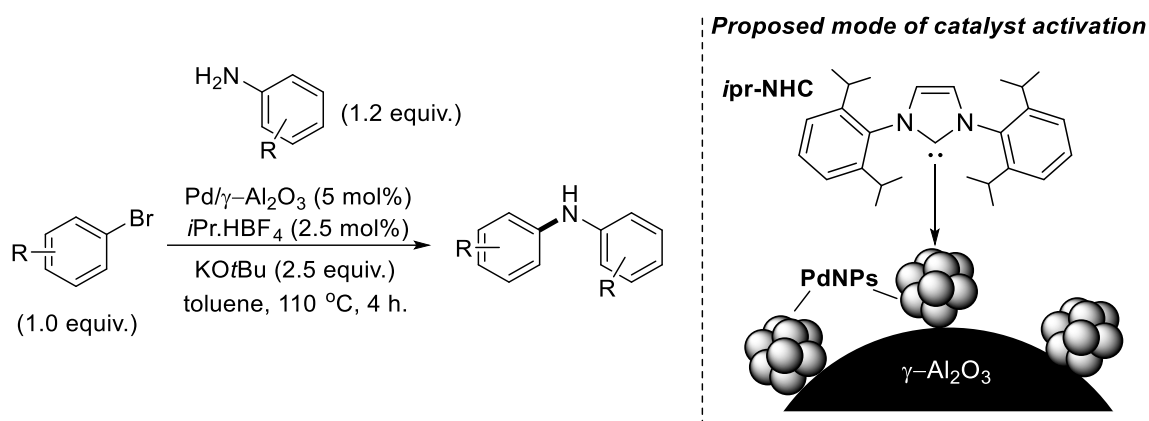
reaction conditions for 1 minute, PdNPs were seen to derive *in situ* from Pd(OAc)₂ and grow larger as a function of time exposed to the reaction conditions (as measured by TEM). Indeed the supramolecular structure of such polyol reaction media has been widely exploited in the stabilisation of highly active catalytic metal nanoparticles.¹¹²

Through coordinative co-evolution of [NH₄]₂[PdCl₄], poly-*N*-vinylimidazole and *N*-isopropylacrylamide in the presence of a NaBH₄ reducing agent, Uozumi *et al.* prepared a highly active polymer-supported heterogeneous catalytic system: **MEPI-Pd**.¹¹³ XPS analysis indicated that both Pd⁰ and Pd^{II} species remained in the final material which, when employed as a heterogeneous pre-catalyst, enabled high activity and recyclability in SMCC applications at aryl chloride substrates, with a H₂O reaction medium (Scheme 11). Notably, additive *tetra-n*-butylammonium fluoride (*n*-Bu₄NF) was necessary, in addition to the K₂CO₃ base, for efficient catalytic turnover in couplings of the unactivated aryl chlorides. A discussion of the role of these separate base systems was however lacking in the report.



Scheme 11 Conditions and reagents used by Uozumi *et al.* in SMCC reactions catalysed by **MEPI-Pd**: a polymer-supported heterogeneous Pd catalyst.

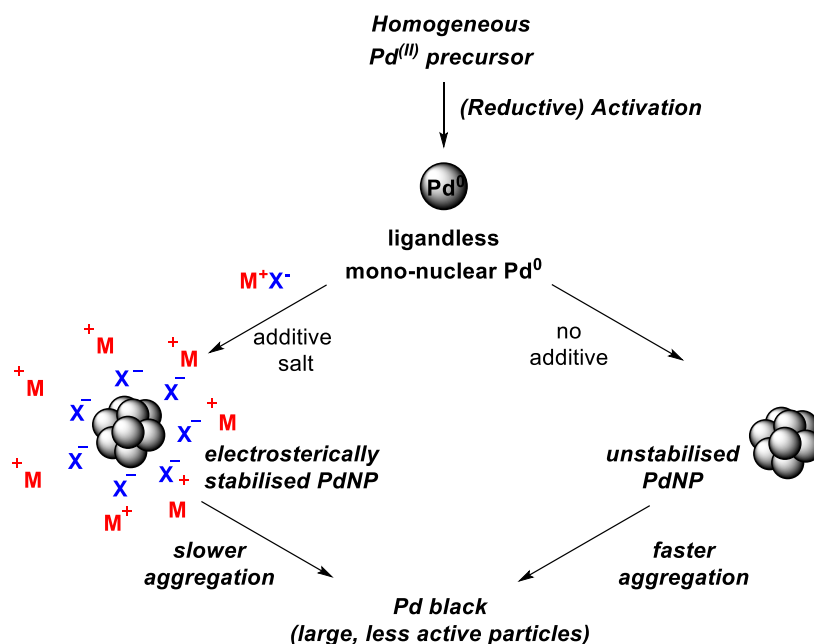
PdNPs stabilised by organophosphines (*e.g.* PPh₃, P(*n*-octyl)₃ or BINAP) have been prepared and characterised by TEM microscopic and ³¹P NMR analyses.¹¹⁴ Other donor ligand types such as NHCs, *e.g.* those derived by deprotonation of imidazolium salts, can be used as stabilising ligands for PdNPs. *N*-heterocyclic carbenes (NHCs) are prime candidates as effective ligands for cross-coupling catalysis because of their strong σ -electron-donating capabilities, as well as their highly tuneable steric properties.¹¹⁵⁻¹¹⁶ Fairlamb *et al.* examined the generation of *N*-heterocyclic carbene stabilised Pd- and Au-NPs by simple ligand exchange from tertiary phosphine or thioether-stabilised nanoparticles.¹¹⁷ It was found that the NHC-stabilised NPs generated were not very stable and led to rapid formation of larger particles. The observation that strongly σ -electron donating, poorly π -accepting NHCs did not stabilise PdNPs as effectively as tertiary phosphines suggests a π -accepting component to the stabilisation of PdNPs by tertiary phosphines, or that strong donation by NHCs may destabilise PdNPs. Glorius *et al.* have shown that NHCs (derived *in situ* by deprotonation of imidazolium salts) can have a powerful role in the activation of a heterogeneous Pd/ γ -Al₂CO₃ catalyst to enable challenging Buchwald-Hartwig amination reactions between aryl bromides and a range of substituted anilines (Scheme 12).¹¹⁸



Scheme 12 Reaction conditions for the Buchwald-Hartwig amination of aryl bromides with anilines. The *i*Pr-NHC (derived *in situ* from *i*Pr.HBF₄) was postulated to enhance catalysis by electron donation to the surface of a PdNP affixed to a heterogeneous $\gamma\text{-Al}_2\text{CO}_3$ source.

Standard heterogeneity tests on the working Buchwald-Hartwig amination reaction (Scheme 12) indicated that the active catalyst remained heterogeneous in nature during turnover. In this case, surface analytical techniques along with computational methods indicated that the NHC could bind and ‘inject’ electron density into the heterogeneous Pd, thereby activating the catalyst. This mode of heterogeneous catalyst activation was subsequently employed by the Glorius group in RhNP-catalysed *cis*-selective hydrogenation of polyfluorinated arenes, enabled by cyclic(alkyl)(amino)carbenes (CAACs).¹¹⁹

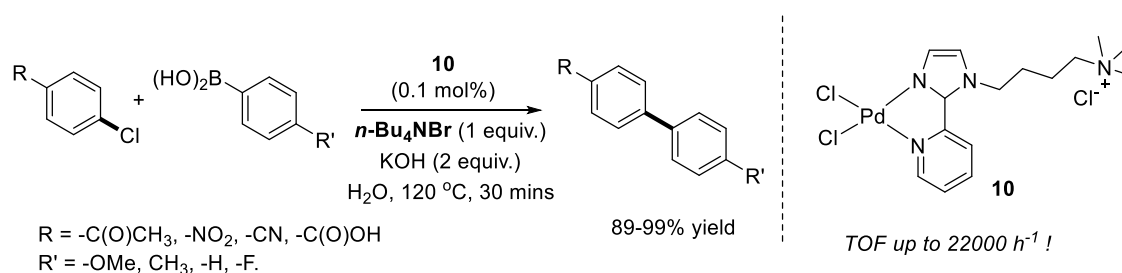
Throughout the history of TM catalysis, salt additives have been postulated to play an important role in stabilisation of active TM-containing nanoparticles. As early as 1979, Gratzel *et al.* found that employing quaternary ammonium salts acted to stabilise and boost the reactivity of PtNPs in the electrochemical reduction of H₂O.¹²⁰ Reetz *et al.* discovered that PdNPs could arise, and be stabilised by additive *tetra-n*-butylammonium bromide (*n*-Bu₄NBr), after *in situ* reduction and activation of Pd(OAc)₂ during Mirozoki-Heck cross-coupling reactions between iodobenzene and ethyl acrylate, at 50 °C, in DMAc.⁶⁵⁻⁶⁶ Finke *et al.* were instrumental in the preliminary understanding of the mechanism of stabilisation of catalytically active nanoparticles by additive salts.¹²¹ In a close analogy to the electrical double layer which forms at an electrode surface, in presence of a salt, the electropositive outer surface of a PdNP can be stabilised by coordination by a diffuse inner layer of anions which are transiently stabilised by an outer layer of cations (Scheme 13).¹²² The steric and electronic properties of cations and anions which compose a given salt can influence the degree of transient stability as a particle grows in solution. Such an influence has been proposed to have an effect on catalyst efficacy in cross-coupling reactions.^{8, 123} This type of stabilisation, known as *electrosteric* stabilisation, where *electronic* and *steric* stability can be conferred to PdNPs by additive salts after Pd pre-catalyst activation is summarised in Scheme 13.



Scheme 13 *Electrosteric* stabilisation of Pd nanoparticles by additive salts after activation from a homogeneous Pd precursor complex/salt.

Electrosteric stabilisation is most likely responsible for the stabilisation of PdNPs generated in the ionic liquid (**BMI**.PF₆) as reported by Dupont *et al.* (*vide supra*), however in this case the salt also acts as the bulk reaction medium.¹⁰⁶ Finke *et al.* discovered a powerful role for anions in the presence of [*n*-Bu₄N]⁺ counteranions in stabilising IrNPs in the hydrogenation of cyclohexene in an acetone medium.¹²¹ They found that hydrogenation rates were enhanced by large, polyoxometalate [(P₂W₁₅Nb₃O₆₁)₂O]¹⁶⁻ anions, featuring multiple negative charge sites which were proposed to more effectively stabilise catalytically active IrNPs than, for example, citrate or chloride.¹²¹ The same group later found that the simple, widely available salt [*n*-Bu₄N]₂[HPO₄] was superior in the stabilisation of PdNPs derived from Pd(acac)₂ in the same reaction, with propylene carbonate as the reaction medium.¹²⁴

Zhou *et al.* carried out SMCC reactions at activated aryl chloride substrates using a PdCl₂-based pre-catalyst featuring a bidentate 2-(2-pyridyl)-imidazole ligand **10**, containing a quaternary trimethylammonium cation attached *via* a butyl chain (Scheme 14).¹²⁵



Scheme 14 Conditions used for the SMCC reaction of activated aryl chlorides catalysed by a 2-(2-pyridyl) imidazolium palladium trichloride pre-catalyst **10**, in the presence of *n*-Bu₄NBr.

The pre-catalyst, which was activated *in situ*, exhibited extremely high activity (TOF up to 22000 h⁻¹ with a catalyst loading of 0.001 mol%). Activity in the SMCC reaction at aryl chloride substrates was only possible when the quaternary ammonium chloride pre-catalyst was deployed in concert with *n*-Bu₄NBr as an additive. The activity of the catalytic system in this case was attributed to the stabilisation of small, highly active PdNPs formed *in situ* and stabilised by the salts present in the system. This observation mirrors the examples reported by Uozumi *et al.* where activation of aryl chlorides required the presence of additive *n*-Bu₄NF (*vide supra*).

Pleixats and Shafrir assessed a series of three tris-imidazolium-salt-supported PdNPs as pre-catalysts (**2a-Pd**, **2b-Pd** and **3a-Pd**) for the SMCC reaction (Figure 9).¹²⁶

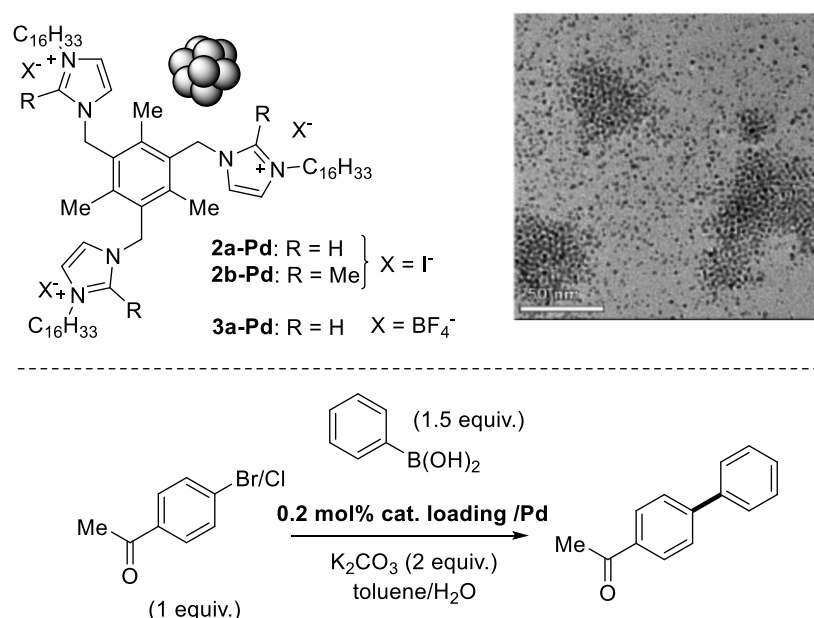


Figure 9 Showing catalyst constituents alongside a TEM image, used to determine PdNP size and size-distribution after catalyst synthesis, and generalised SMCC conditions deployed in the assessment of catalytic applications of tris-imidazolium-salt-supported PdNPs. Image reproduced with permission from *Adv. Synth. Catal.* 2012, 354, 651-662. Copyright 2012 Wiley-VCH Verlag GmbH & Co.

In a design which was inspired by ionic liquids, the imidazolium salt-based stabilising ligands featured three ionic sites rendered bulky and organic-soluble *via* 16-carbon atom aliphatic chains (Figure 9). The catalysts were prepared by hydrogenic reduction of [Pd⁰₂(dba)₃.solv.] in the presence of the ligands, in an apparently unoptimized Pd:ligand ratio of 1:1 and subsequent TEM analysis indicated a PdNP size of 2.9–4.2 nm. Crucially, while all Pd-catalysts were tested in the more challenging C–Cl bond activation at 4-chloroacetophenone, only the catalyst which featured a tris-imidazolium ligand that was unsubstituted in the C2-position (**2a-Pd**, Figure 9) was able to mediate cross-coupling. It was hence hypothesised that deprotonation of the imidazolium C2–H under the basic conditions allowed for

NHC carbene formation, thereby boosting PdNP catalytic activity. There have been many published examples of highly active NHC-Pd-mediated cross-coupling reaction; for example, the PEPPSI class of catalysts designed by Organ *et al.* are well-established in synthetic applications.¹²⁷⁻¹²⁸ This hypothesis was supported by solid-state ^{13}C NMR studies on the catalytic material, which indicated a carbene-type resonance indicative of ligation to PdNPs. The two ligands which were methyl-substituted in the C2-position and hence unable to allow access to a carbene (**2b-Pd** and **3a-Pd**) did not show as high catalytic activity or indeed a carbenic-type ^{13}C NMR signal under solid-state NMR analysis. It was additionally noted that, under optimised reaction conditions for the I^- -containing catalyst, the $[\text{BF}_4]^-$ -containing catalyst performed significantly poorer, indicating that the enhanced basicity of I^- *vs.* $[\text{BF}_4]^-$ acted to boost catalyst activity. The optimised system **2a-Pd** proved to be a versatile catalyst and was additionally applied to Mizoroki-Heck-, Sonogashira- and Hiyama-type cross-coupling applications, demonstrating high catalyst turnovers and good functional group tolerance.¹²⁹ Willans *et al.*, prepared a somewhat analogous *tris*-imidazol-2-ylidene (*N*-heterocyclic carbene)-supported Pd^{II} precatalyst in site-selective SMCC reactions at the dihalogenated heteroaromatic compound 2,4-dibromopyridine (see Section 4.1 for further details on this process).¹³⁰

Astruc *et al.* exploited *electrosteric stabilisation* by employing relatively large, supramolecular ‘dendrimer’-type agents.⁸ For example, an elaborate dendrimer-stabilised material containing PdNPs (DSN-G0, Figure 10) furnished with sodium sulfonate groups was synthesised and employed in cross-coupling reactions.¹³¹ Such dendrimeric superstructures are designed to combine aspects of polymer-stabilisation with electrosteric salt stabilisation.

Employing the dendrimer-stabilised DSN-G0 (Figure 10) catalyst, high yields (>90%) and TONs (960 - 9400) were observed in SMCC reactions at activated iodobenzenes proceeding at room temperature. However, in order to get bromobenzene cross-couple with boronic acids, a higher temperature of 100 °C was required. The relatively sluggish catalytic behaviour of this highly engineered system compared to that of more simple electrosterically stabilised PdNP systems (*vide supra*) may indicate that there are limits of positive effects conferred by such elaborate systems and careful, structurally informed design may be necessary for optimal catalyst activity.

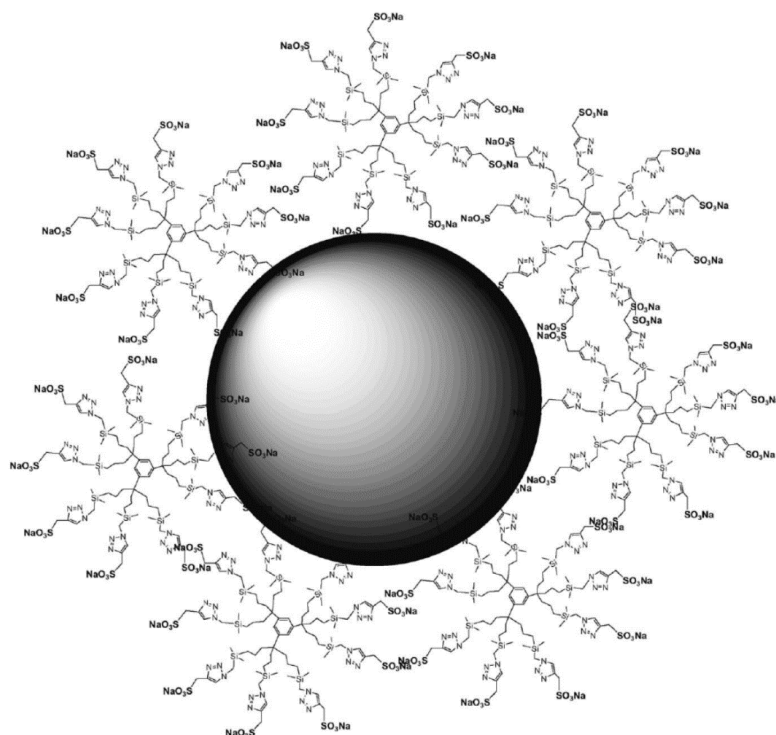


Figure 10 A schematic of DSN-G0, a PdNP (centre) stabilised within a dendrimer superstructure containing sodium sulfonate groups, realised by Astruc *et al.* Such systems have seen catalytic application in SMCC and hydrogenation applications. Reproduced with permission from *Adv. Synth. Catal.* 2008, 350, 837 – 845. Copyright 2008 Wiley-VCH Verlag GmbH & Co.

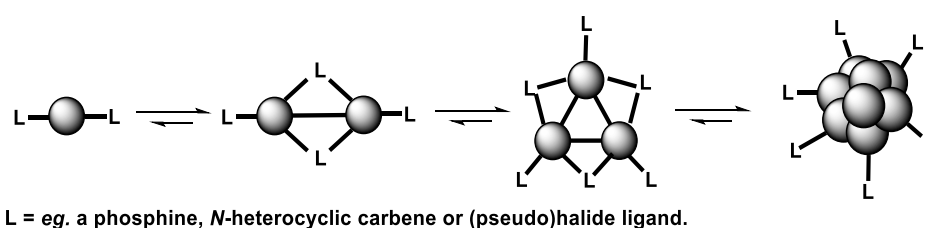
The electronics and sterics of the stabilisation agent are crucial to the catalytic activity of electrosterically-stabilised catalytic PdNPs, however, when generated from Pd^{II} precursors. The nature of the reductant can also have influence, particularly pertaining to the size and morphology and hence surface activity of both *in situ*-generated and pre-fabricated PdNPs for cross-coupling applications. *Marcus theory* states that differences in electrical potential between that of the reductant and the metal ion precursor can dictate the rate of the reduction, with higher potential differences resulting in more rapid reduction and activation.¹³² The rate of reduction can thus be controlled by the identity of reductant or rate of addition of the reductant to the process. Therefore for optimal PdNP catalyst activity, when generated *in-* or *ex-situ*, a balance must be struck between the reduction rate and the efficiency of the stabiliser.^{8, 123} To this end, tuning of the combination of Pd precursor, salt stabiliser and method of Pd reduction may contribute to optimal catalytic activity in a given reaction system.

Electrosterically-stabilised PdNPs can thus be highly active in cross-coupling processes, allowing for efficient bond activation/functionalisation at, at times, extremely low catalyst loadings. Understanding the factors that confer and optimise activity could be of key value for industrial cross-coupling processes, not only for efficient activation of more challenging C–Cl bonds but also with a view to keeping Pd catalyst loadings as low as possible, reducing unnecessary waste of the precious metal. Fine-

tuning of the electrosteric properties of additive salts, may allow access to a universally applicable, highly active catalyst system where Pd loading can be kept to a minimum. The uncertainty concerning the active catalytic phase, be it *true*- or *quasi*-heterogeneous (as detailed in Section 1.3.1) applies under an *electrosteric stabilisation* regime, and it is most likely that the active phase varies depending on specific reaction conditions.

1.4. Pd Clusters – from Structural Curios to Uniquely-Active Catalysts

Section 1.3.1 described the complicated picture whereby homogeneous Pd species may give rise to heterogeneous catalytic species and *vice versa*. The precise mechanism by which homogeneous, mononuclear ligated Pd⁰ monomers can convert to Pd particles is not well known. One hypothesis for this process is that it occurs *via* incremental aggregation of homogeneous ligated clusters containing metal–metal bonds (Scheme 15).⁸⁹ In this context, the definition of a cluster includes dimeric (/dinuclear) complexes.



Scheme 15 Catalytic Pd tends to aggregate during a cross-coupling process. Schematic showing a mechanistic picture for the incremental aggregation of monomeric Pd to a Pd particle, *via* ligated Pd dimer and tripalladium clusters.

Koningsberger *et al.* presented time resolved UV-visible spectroscopic and EXAFS evidence for Pd dimers and trimers forming *en route* to PdNPs during catalytic turnover.¹³³ Such clusters may act to bridge the gap between homogeneous and heterogeneous catalysis, with potential for both ligand–metal and metal–metal cooperation to influence catalytic activity.⁹⁰ An important question in understanding the holistic picture is: can multinuclear ligated clusters contribute to the catalytic activity of the reaction in question? Hence, if so, can the reactivity of such clusters be exploited to change the outcomes of cross-coupling reactions for the better? Down the years there have been numerous reports of cluster complexes containing Pd–Pd bonds which have been structurally characterised and, in some cases, have had their reactivity with small molecules probed.^{134–138} Recently however there have been increasing reports of ligated Pd clusters which have demonstrated unique catalytic activity, not seen with traditional homogenous or heterogenous catalytic precursors. This section highlights structural aspects as well as catalytic applications of ligated cluster complexes containing Pd–Pd bonds.

The simplest type of Pd–Pd-bonded cluster systems are dinuclear complexes. There is a wide variety of different types of Pd dimeric complexes, which have been structurally interrogated and have seen catalytic application. Han *et al.* synthesised an acetonitrile-ligated Pd^I dimer [Pd^I(NCMe)₃]₂[SbF₆]₂ (**11a**, Figure 11) *via* direct reaction of [Pd⁰₂(dba)₃.solv.] with [Pd^{II}(NCMe)₄][SbF₆]₂.¹³⁹⁻¹⁴⁰ This solvent-stabilised complex showed activity in SMCC reactions at aryl chlorides and bromides and is particularly remarkable for having a very short Pd^I–Pd^I interatomic distance of 2.4878(7) Å, indicative of a relatively strong Pd–Pd interaction for this class of compound. The complex is also notable for being a rare case of a Pd^I dimer featuring no bridging ligands. Significantly, the addition of phosphines (PPh₃, dppf) acted to enhance the performance of **11a** as a cross-coupling catalyst in the SMCC reaction at aryl bromides and chlorides. Analogous Pd^I dinuclear cationic structures featuring methyl isocyanide (**11b**) and PMe₃ (**11c**) ligands, have been reported, also exhibiting short Pd–Pd interactions.¹⁴¹⁻¹⁴² Upon treatment of **11a** with dialkylbiaryl (Buchwald) ligands, Spokoyny *et al.* isolated and characterised a dinuclear Pd^I complex, stabilised by two coordinating dialkylbiaryl ligands and bridged by phenyl groups (representative structure of the JohnPhos analogue shown: **12**, Figure 11), with the charge balanced by two un-coordinated [BF₄][–] anions.¹⁴³ The complex exhibited competence as a pre-catalyst in Buchwald-Hartwig amination reactions at aryl chlorides and bromides. Very recently, dinuclear Pd^I complexes have been discovered and invoked as catalytic species derived from a direct reaction between Pd(OAc)₂ and dialkylbiaryl phosphines. During the course of *this work*, Bedford *et al.* reported that Pd(OAc)₂ could react with *ortho*-substituted dialkylbiaryl ligands to form cationic dicyclohexylphosphido bridged Pd^I dinuclear complexes (**13a & b**, Figure 11).¹⁴⁴ The structure of **13a** and **13b** were somewhat analogous to **12**, however a dicyclohexylphosphido ligand, formed through cleavage of a biaryl group from the dicyclohexylbiaryl phosphine, was seen to coordinate and bridge the Pd^I dimer and the X-ray crystal structure showed one phosphine ligand to bridge *via* aryl–metal interactions. ³¹P NMR spectroscopic analysis indicated fluxional interchange between the two phosphine environments in solution. Isolated Pd complex **13a**, was successfully employed in Buchwald-Hartwig aryl amination reactions and performed on a par with Pd(OAc)₂/SPhos or Ruphos pre-catalytic systems. Grimaud *et al.* found that a Pd^I dimer of the form [Pd^I(OAc)(XPhos)]₂ (XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) forms upon direct reaction between Pd(OAc)₂ and XPhos, however the specific coordination structure was not defined in this case.¹⁴⁵

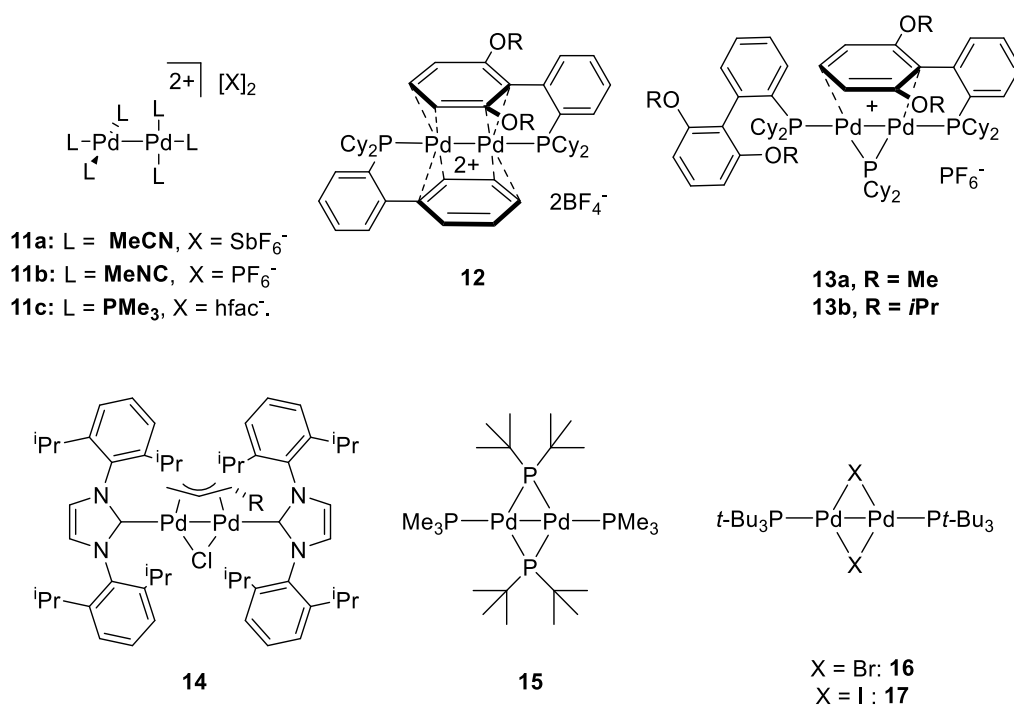
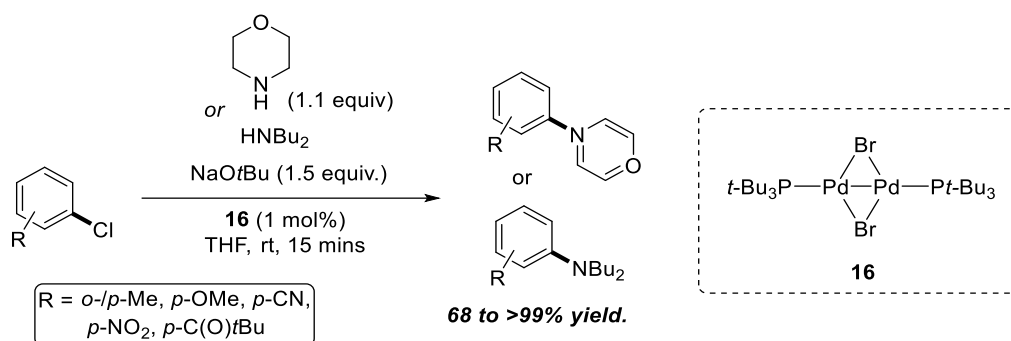


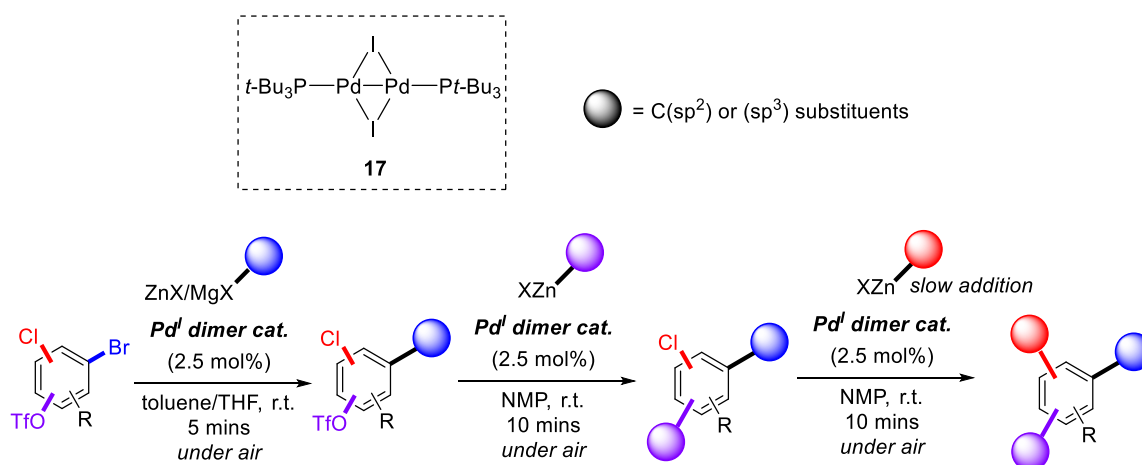
Figure 11 Selected structures of known Pd dinuclear complexes which have interesting properties and/or have been reported in cross-coupling applications.

Hazari *et al.* synthesised an allyl- and halide-bridged, NHC-stabilised Pd^I dimeric complex, which formed *in situ* after the reduction of Pd^{II} complexes of the form [Pd^I(NHC)(η^3 -allyl)Cl] (**14**, Figure 11).¹⁴⁶ In this case, the Pd^I dimeric catalyst was determined to be a source for catalytically active Pd⁰ upon disproportionation during the SMCC reaction between aryl chlorides and arylboronic acids. Jones *et al.* discovered that a CO-ligated tripalladium cluster [Pd₃(μ -P*t*Bu₂)₂(κ -CO)₂(κ -Cl)], bridged by *tert*-butylphosphido groups could fragment, and the CO ligands fully substitute after treatment with σ -electron-donating PMe₃ to form the phosphido-bridged Pd^I dimeric species [Pd^I(μ -P*t*Bu₂)(PMe₃)]₂ **15** (Figure 11).¹⁴⁷ This discovery indicated that a higher order tripalladium cluster can be converted to a lower order Pd^I dimer. The overall reverse of process this has been observed and is discussed *vide infra*. Vilar *et al.* discovered that μ -halide-bridged Pd^I dimers of the form [Pd^I(μ -X)(P*t*Bu₃)]₂ (**16** {X=Br}, **17** {X=I}, Figure 11) could be synthesised by reaction of [Pd⁰₂(dba)₃·C₆H₆] with P*t*Bu₃ in the presence of CHX₃.¹⁴⁸⁻¹⁴⁹ In 2002, Hartwig *et al.* found **16** to be a highly active cross-coupling catalyst, being able to efficiently activate aryl chlorides for Buchwald-Hartwig amination reactions at room temperature – the cutting edge for cross-coupling catalyst efficacy at the time (Scheme 16).¹⁵⁰



Scheme 16 Conditions and reagents employed in the Buchwald-Hartwig amination reaction of aryl chlorides, catalysed by the Pd^I dimer complex (**16**).

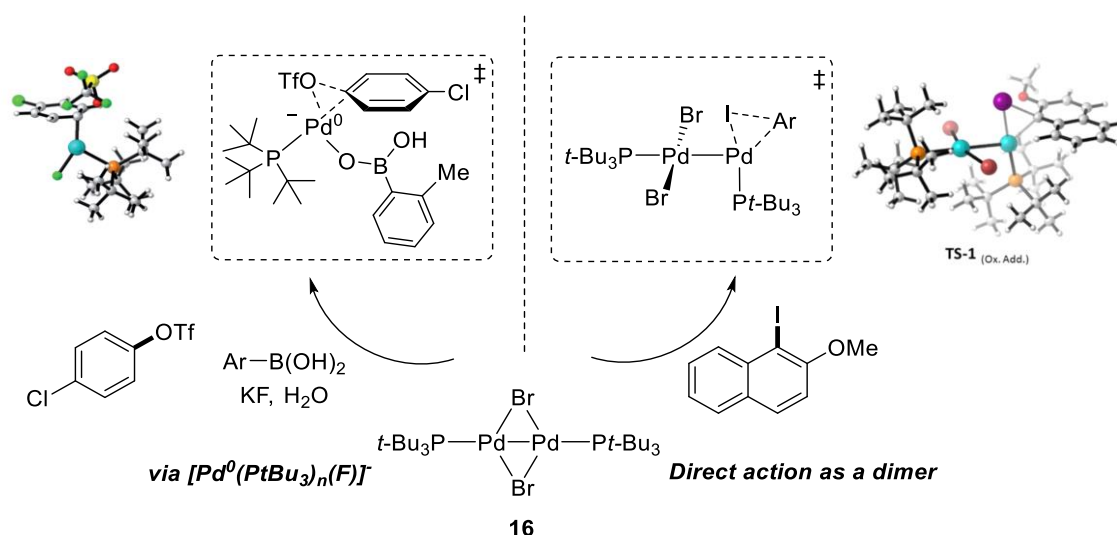
Colacot and Schoenebeck found that the dinuclear Pd^I complex [Pd^I(μ-Br)(P*t*Bu₃)₂] **16** could be formed simply, by direct reaction between P*t*Bu₃ and [Pd^{II}(Br)₂(cod)] (cod = 1,5-cyclooctadiene), with profound implications being uncovered for resulting catalyst activity depending on the pre-catalytic Pd:P ratio (See Section 3.1 for further details on this study).⁵⁷ When applied to the SMCC reaction, the dinuclear Pd^I complex **16** was shown to be able to effectively and chemoselectively cross-couple aryl chlorides over triflates, as exemplified by the chemoselective C–Cl bond functionalisation of 4-chlorophenyl triflate (see Section 1.5.1, for further details on this substrate). Schoenebeck *et al.* subsequently found that deploying the air stable iodide-bridged analogue [Pd^I(μ-I)(P*t*Bu₃)₂] **17**, C(sp²)–Br sites could undergo Negishi, or Kumada cross-coupling, with high chemoselectivity over C–OTf and C–Cl bonds on the same compounds.¹⁵¹ Notably, using the same pre-catalyst, with the crucial use of NMP as the reaction solvent, fully site-selective Negishi cross-coupling could be realised at C–OTf over C–Cl sites.¹⁵² Subsequently, slow addition of an organozinc reagent in NMP under an atmosphere of argon allowed for a high yielding Negishi-type couplings at aryl chlorides.¹⁵² This methodology allowed for a high-precision, triply selective sequence, allowing for highly selective, and rapid functionalisation of multiply (pseudo)halogenated arene substrates (Scheme 17).



Scheme 17 Showing the application of (**17**) in successive, chemoselective cross-coupling catalytic applications, allowing for rapid diversification of a range of tri(pseudo) halogenated substrates, featuring C(sp²) bromides·chlorides and triflates.

Schoenebeck *et al.* subsequently found a positive raft of additional and novel applications of **17**,¹⁵³ proving the robust, air stable catalyst to be effective and selective in a wide variety of novel synthetic reactions including C(sp²)–S¹⁵⁴ and C(sp²)–Se¹⁵⁵ bond formation (avoiding catalytic deactivation by Pd–S/Se interactions), α -arylation of esters¹⁵⁶, efficient synthesis of conjugated polymers *via* a Negishi-type approach¹⁵⁷ and germylation of sulfonium salts.¹⁵⁸

A major question surrounding the [Pd^I(μ -X)(P*t*Bu₃)]₂ dimer catalyst (X = Br or I, **16** and **17** respectively) is its mode of activity, specifically whether it acts as a bimetallic dimer or whether it acts as a source of a monomeric Pd⁰ active species. The reality appears to be that the mode of activity varies as a function of the conditions deployed. Using experimental and computational means, Schoenebeck *et al.* determined that under cross-coupling conditions **16** disproportionates to [Pd⁰(P*t*Bu₃)₂] and subsequently low-phosphine-ligated [Pd⁰(P*t*Bu₃)] and [Pd⁰(X)(P*t*Bu₃)][–], which were reasoned to be the active species (where X = Br[–], F[–] or [Ar–B(OH)(O)][–]: anions deemed to be present under working SMCC conditions).¹⁵⁹ It was later found that the base (*e.g.* KOH, KF or KO*t*Bu₃) could induce the Pd^I–Pd^I cleavage with the nucleophilicity and concentration of the base employed in SMCC reactions, influencing the degree of cleavage.^{160–161} Additional phosphine is known to cleave Pd^I–Pd^I bonds.^{57, 162} It was hence found, for optimal release of catalytically active Pd⁰ into the solution, a balance had to be struck – if the base system was not strong enough, it would not be able to cleave the Pd^I–Pd^I bond to release sufficient quantities of Pd⁰ for catalysis, but if too-strong a base system was used, the catalyst would deactivate to aggregated bulk Pd metal due to high concentrations of Pd⁰ in solution.¹⁶¹ Thus, **16** can act as an efficient precursor for highly catalytically active Pd⁰ monomers in solution, in the presence of inorganic bases or phosphines. Some experiments have indicated that the Pd^I complex **16** can react as a dinuclear species, *i.e.* by *bimetallic* catalysis. For example, catalytic I/Br exchange reactions were successfully mediated at aryl iodides using **16**, with a low activation barrier for direct bimetallic oxidative addition (C–I bond activation), an outcome supported by computational methods (DFT).¹⁶³ ³¹P NMR spectroscopic analysis during turnover showed no other Pd species than the dinuclear Pd^I complex in the reaction mixture. Kinetic data on such reactions supported a 1st order reaction profile with respect to both dinuclear Pd^I (pre)-catalyst and aryl iodide.¹⁶⁴



Scheme 18 Findings from Schoenebeck *et al.* regarding the action of the $[\text{Pd}^{\text{I}}(\mu\text{-X})(\text{P}t\text{-Bu}_3)]_2$ ($\text{X} = \text{Br}$ or I) catalyst (**16**). Under SMCC conditions, the dimer dissociates to a mono-nuclear Pd^0 complex which activates an aryl triflate by oxidative addition. In reaction with an aryl iodide, the complex remains intact during oxidative addition. Showing the transition states of activation as determined by DFT analysis. Adapted with permission from Ref. 164 and with permission from *Angew. Chem. Int. Ed.* 2011, *50*, 8192-8195. Copyright 2019 Wiley-VCH Verlag GmbH & Co.

The same group showed that reacting the iodide-bridged dimer **17** with diphenylphosphine resulted in the formation of a novel *tripalladium* cluster complex $[\text{Pd}_3(\mu\text{-PPh}_2)_3(\text{PPh}_3)_3]\text{I}$ **18**, which exhibited differing reactivity to its precursor (Figure 12, a).¹⁶⁵ It is notable that **18** was formed quantitatively; indicating that, in the cluster forming reaction, the strongly σ -donating $\text{P}t\text{Bu}_3$ ligand of the precursor is fully substituted by the less σ -donating and π -accepting PPh_2 ligand.¹⁶⁶ The fate of the $\text{P}t\text{Bu}_3$ ligand during this process was not, however, reported. The catalyst showed strong chemoselectivity for $\text{C}(\text{sp}^2)\text{-I}$ bonds over $\text{C}(\text{sp}^2)\text{-Br}$ and $\text{C}(\text{sp}^2)\text{-Cl}$ (Figure 12, b) in Kumada cross-couplings. The chemoselectivity of **18**, whether used as an isolated catalyst, or generated *in situ*, was superior to that of other catalyst systems such as its precursor compound **17**, $[\text{Pd}^0(\text{PPh}_3)_4]$, $[\text{Pd}^0_2(\text{dba})_3]$, $[\text{Pd}^0_2(\text{dba})_3]/\text{JohnPhos}$ or $\text{Pd}(\text{OAc})_2$ alone. Using DFT, the activation barriers ($\Delta G^\ddagger$) for oxidative addition of a single Pd atom of trimer **18** was accordingly calculated to be significantly higher with Ph-Br (38.8 kcal mol⁻¹) and Ph-Cl (45 kcal mol⁻¹), than with Ph-I (30.7 kcal mol⁻¹), thus rationalising the site-selectivity to be controlled by the oxidative addition step (Figure 12, c).

Converting the Pd^{I} complex **17** to Pd_3 complex **18** resulted in more controlled reactivity – effectively the reactivity has been tempered such that the trimer cannot activate more challenging C-Br over C-Cl bonds. This allowed for efficient coupling at a single halogen site, facilitating controlled and efficient diversification of a multi-halogenated substrate. In this case, direct reaction between the Pd_3 cluster **18** with the model substrate 4-iodoacetophenone resulted in the formation of another Pd_3 cluster of the form $[\text{Pd}_3(\mu\text{-I})_3(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{I}^-$ (**d**, Figure 12).

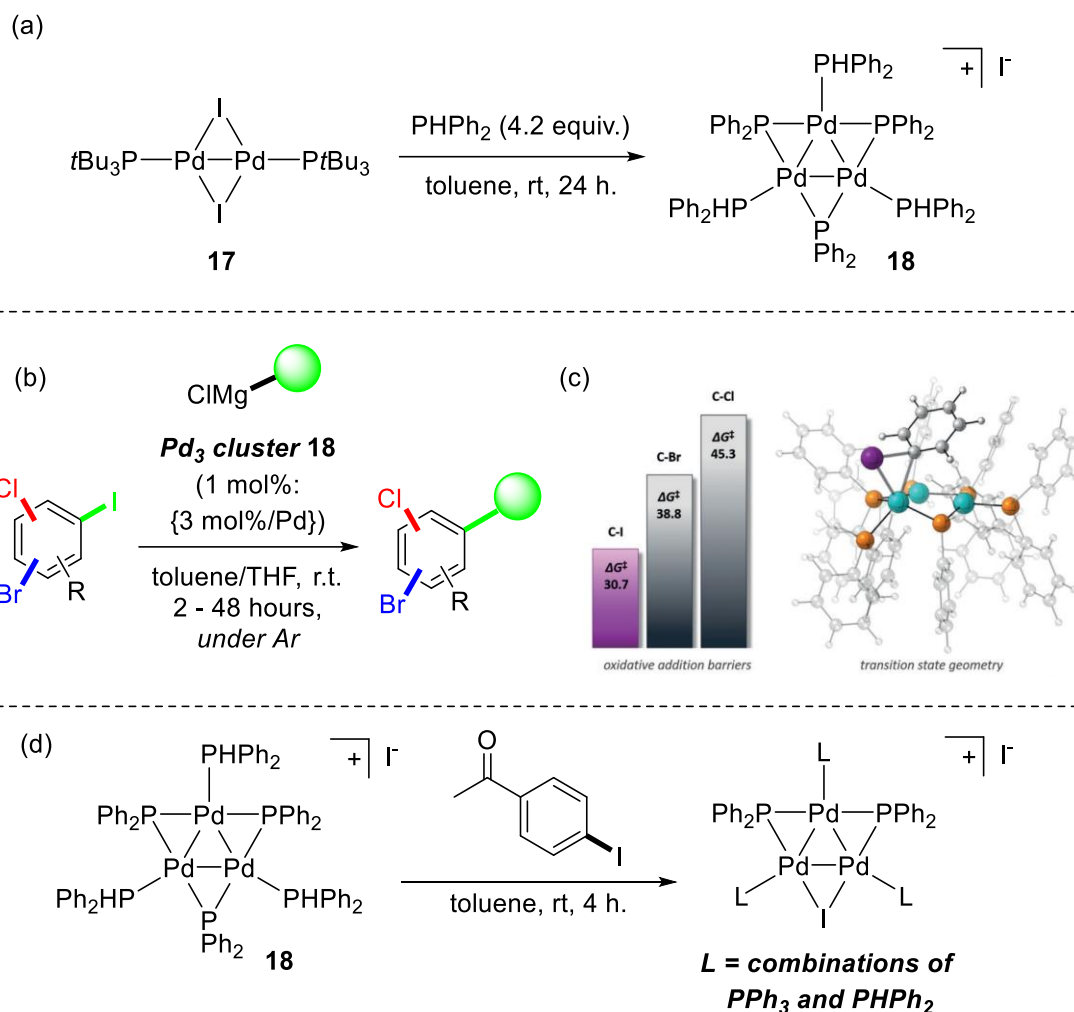
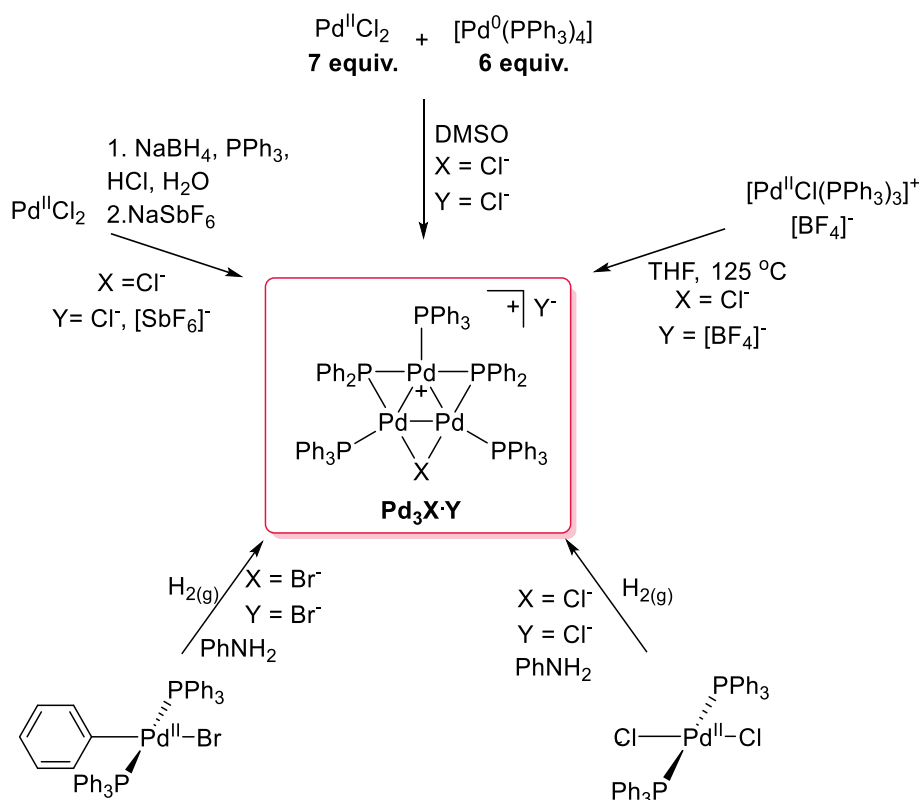


Figure 12 (a) Showing the process for the conversion of the Pd^I dimer $[Pd^I(\mu-I)(PtBu_3)]_2$ (17) to the Pd_3 cluster (18) (b) Application of cluster (18) for chemoselective $C(sp^2)-I$ Kumada cross-coupling reactions. (c) The DFT-modelling for the oxidative addition of 18 to halobenzenes: showing the relative energies (in $kcal.mol^{-1}$) of oxidative addition (bar graph) and the optimised geometry transition state. Adapted with permission from *Angew. Chem. Int. Ed.* 2019, 58, 211-215 Copyright 2019 Wiley-VCH Verlag GmbH & Co.

This conversion on exposure to 4-iodoacetophenone points towards a different, albeit related, tripalladium species being present after the first catalytic turnover, under cross-coupling conditions.

The $[Pd_3(\mu-X)(\mu-PPh_2)_2(PPh_3)_3]^+Y^-$ motif (herein abbreviated as $Pd_3X \cdot Y$ {X, Y = halide or pseudohalide}), where an approximately equilateral triangular Pd core, featuring an oxidation state of 4/3 per Pd, is stabilised by two μ -phosphido ligands, a μ -halide ligand and three κ -arylphosphine ligands has featured prominently in the literature over the years (Scheme 19).¹⁶⁷



Scheme 19 Showing the variety of different ways that tripalladium clusters adopting the motif $[\text{Pd}_3(\mu\text{-X})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+[\text{X}]^-$ may be synthesised by reductive activation of simple Pd^{II} salts.

As early as 1968, Coulson *et al.* found that a direct reaction between PdCl_2 and $[\text{Pd}^0(\text{PPh}_3)_4]$ resulted in the formation of the tripalladium cluster of the form $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$.¹⁶⁸ Dixon *et al.* later confirmed its precise structure, by use of ^{31}P NMR spectroscopic and X-ray diffraction analysis.^{167, 169} In this case, $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ was synthesised by reacting $[\text{PdCl}(\text{PPh}_3)_2]^+[\text{BF}_4]^-$ in superheated THF (125 °C) for 50 hours (Caution! Such a procedure should only be carried out using a reaction vessel that can withstand the high vapour pressures involved). Moiseev *et al.* found that hydrogenation of $[\text{PdCl}_2(\text{PPh}_3)_2]$, $[\text{PdCl}_2(\text{PPh}_3)]_2$ or $[\text{PdBr}(\text{Ph})(\text{PPh}_3)_2]$ with molecular hydrogen in the presence of an organic amine solvent resulted in the formation of $\text{Pd}_3\text{X}\cdot\text{X}$ ($\text{X} = \text{Cl}$ or Br).¹⁷⁰ The same group similarly discovered that $[\text{Pd}_3(\text{OAc})_6]$ salts could be hydrogenated to form a variety of different Pd clusters, the structures of some of which were not at the time fully characterised.¹⁷¹ These syntheses show that higher order Pd cluster structures readily form as stable species under reducing (hydrogenic) conditions, from simple Pd precursor complexes.¹³⁷ It was not until 2017 that Li *et al.* reported a catalytic application of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$, finding it to be a highly active catalyst in SMCC reactions at aryl bromide substrates (Figure 13, a).¹⁷² Furthermore, a study into its stoichiometric activity, showed that the Pd cluster, which was reported to remain intact throughout the catalytic process, was not able to react directly with bromobenzene in an oxidative addition-type process. Evidence was however presented for reactivity between the Pd_3 cluster and boronic acid in the presence of a K_2CO_3 base. The $[\text{Pd}_3(\mu\text{-$

$\text{Ph})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$ ion was detected by ESI-MS, and supported by EXAFS data. Based on the findings that $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ could not react with aryl bromides, but appeared to react with arylboronic acids while remaining intact during reaction turnover, a mechanism whereby the initial steps of the SMCC were inverted and transmetalation occurred prior to C–Br bond activation was postulated (Figure 13, b)

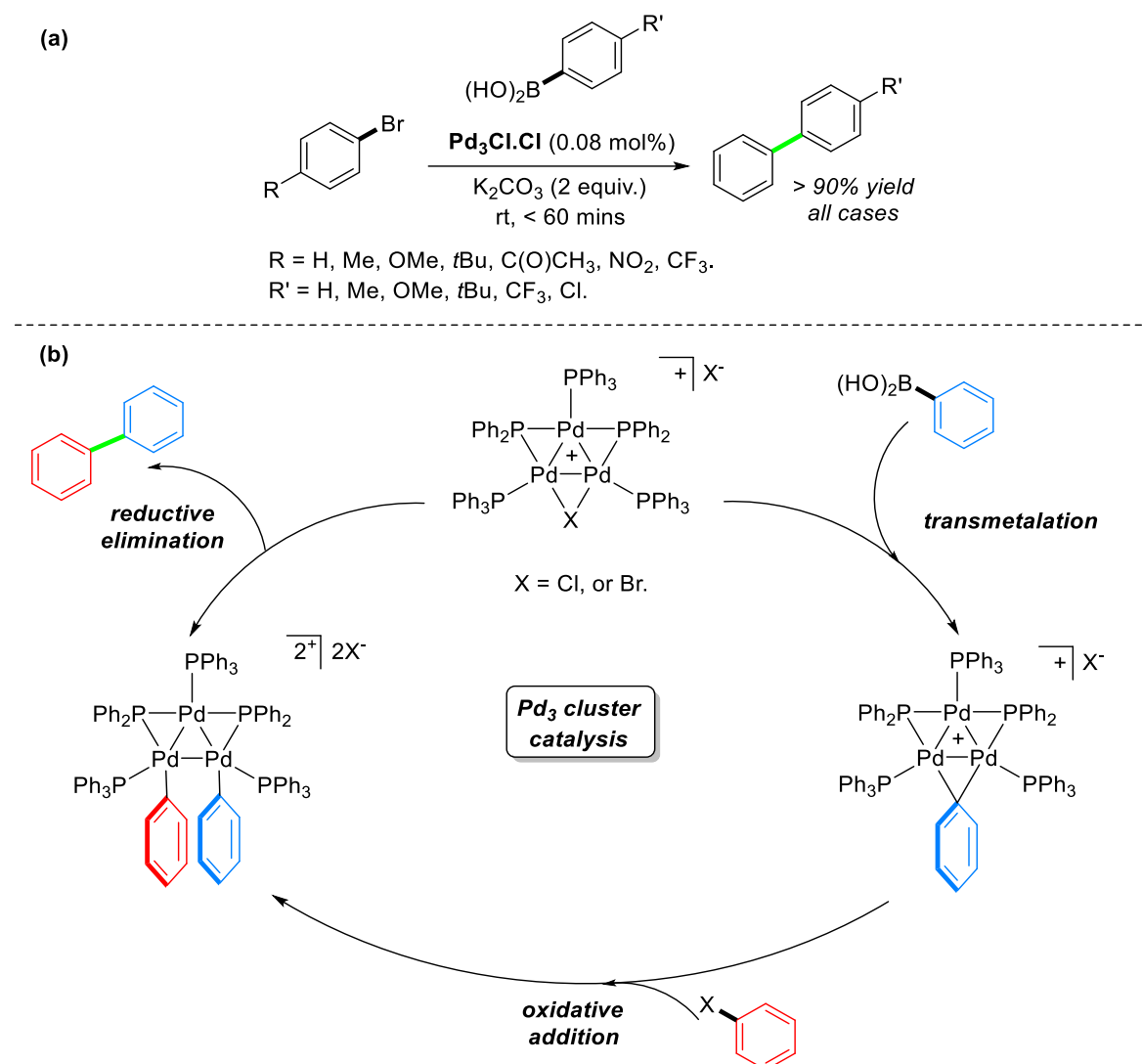


Figure 13 Showing the extraordinary reactivity of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ as reported by Li *et al.* (a) powerful reactivity at low catalyst loadings in SMCC applications. No oxidative addition-type C–Br bond activation of bromobenzene was noted, however, direct reactivity between the cluster and phenylboronic acid was observed in the presence of base. On the basis of these findings, the above catalytic cycle (b) was proposed.

Subsequently, the Zhu group successfully tethered the $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$ catalyst to an $\gamma\text{-Al}_2\text{O}_3$ support for application in the selective reductive coupling of benzaldehyde with nitrobenzene to form benzalaniline (imine product) over the undesired over-reduced product benzyaniline (secondary amine product).¹⁷³

Within the Fairlamb group, Dr. Kate M. Appleby found that simple hydrogenic reduction of $[\text{Pd}(\text{OTf})_2(\text{PPh}_3)_2]$ in CH_2Cl_2 resulted in the formation of a *linear* Pd_3 cluster complex $[\text{Pd}_3(\text{PPh}_3)_4][\text{OTf}]_2$ **19**.¹⁷⁴⁻¹⁷⁵ It is notable that the linear structure evident by X-ray crystallographic analysis, was also present in solution, as confirmed by ^1H NMR spectroscopic analysis, which indicated $\eta^2\text{-Ar-Pd}$ interactions by upfield shifting of ^1H resonances (Figure 14).

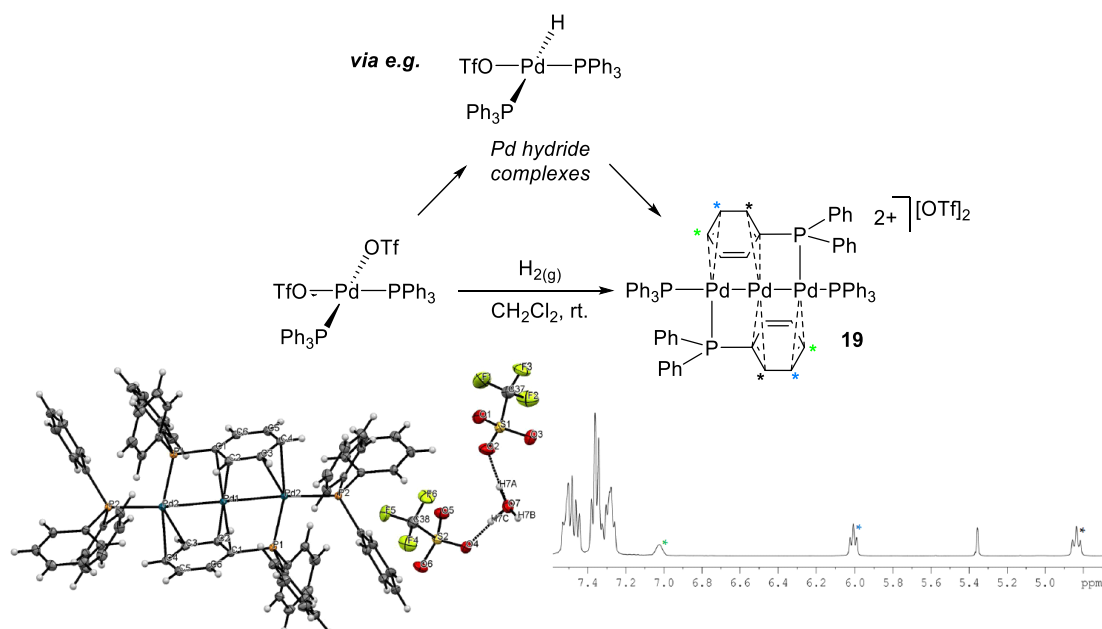
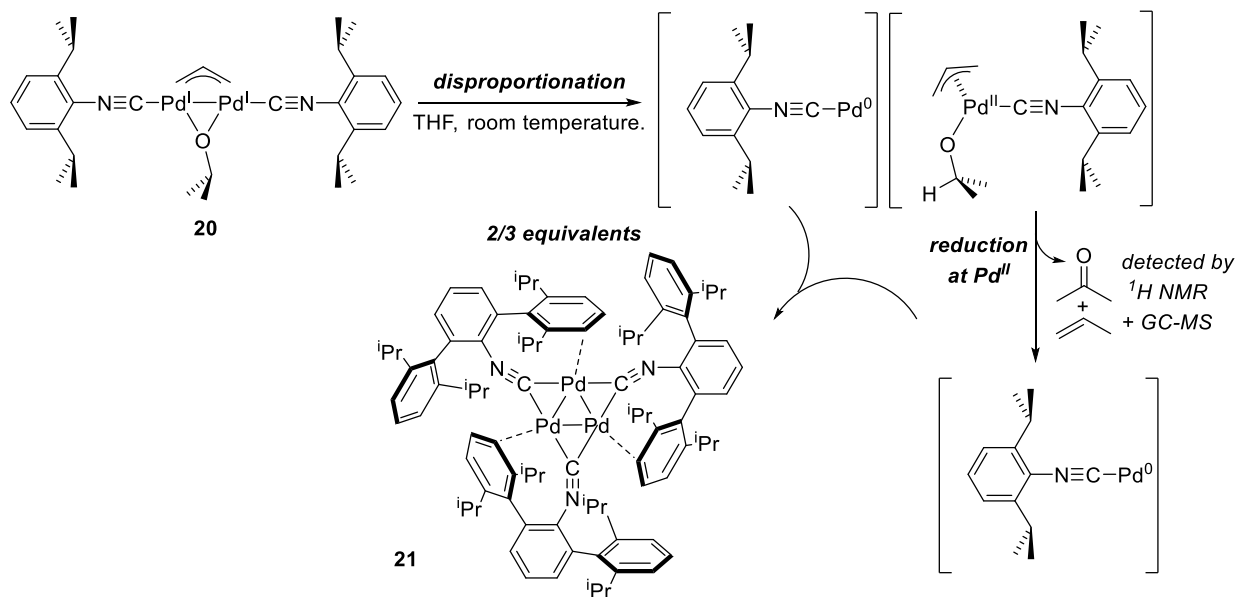


Figure 14 (a) Single crystal X-ray structure of $[\text{Pd}_3(\text{PPh}_3)_4][\text{OTf}]_2$ (**19**), showing linear arrangement of Pd atoms **(b)** ^1H NMR spectrum, with assignment of shielded ^1H resonances of η^2 -coordinated bridging phenyl interaction from PPh_3 ligand. Images adapted from Dr. Kate M. Appleby's PhD thesis.¹⁷⁴

A $[\text{Pd}_3(\text{PPh}_3)_4][\text{BF}_4]_2$ analogue was independently synthesised¹⁷⁵ and found to be of similar catalytic competence as its $[\text{Pd}(\text{OTf})_2(\text{PPh}_3)_2]$ precursor complex, and higher catalytic competence than $[\text{Pd}^0(\text{PPh}_3)_4]$, in the SMCC reaction between 6-methyl-4-(4-methylphenyl)-pyran-2-one and 4-tolylboronic acid.

In 2017, while investigating the role of bulky, π -accepting isocyanide-containing ligands ($\text{CNAr}^{\text{Dipp}2}$)¹⁷⁶ in Pd cross-coupling catalysis, Figueroa *et al.* isolated the remarkable tripalladium cluster $[\text{Pd}_3(\eta^2\text{-Dipp-}\mu\text{-CNAr}^{\text{Dipp}2})_3]$ **21** (Scheme 20).¹⁷⁷ The cluster was observed to form after a room temperature reductive disproportionation of an allyl and alkoxide-bridged Pd^{I} dinuclear complex $[(\mu\text{-C}_3\text{H}_5)(\mu\text{-X})\text{Pd}^{\text{I}}(\text{CNAr}^{\text{Dipp}2})_2]$ **20**, eliminating propene and acetone (detected by ^1H NMR and GC-MS). As a result, each Pd atom was seen to exhibit a formal oxidation state of zero. Thus, in essence, the cluster is a trimer of three mono-ligated $[\text{Pd}^0(\text{CNAr}^{\text{Dipp}2})_1]$ complexes, stabilised by bridging, π -accepting isocyanide ligands in addition to $\eta^2\text{-C,C}$ interactions from the phenyl groups to the Pd centres (Pd–Pd bond distance = 2.6353(5)). The cluster **21** was found to be competent in SMCC reactions at aryl

bromides at room temperature, performing superiorly to the Pd^I precursor complex **20** under the same conditions, but slightly worse than the independently synthesised bis-ligated Pd⁰ complex [Pd⁰(CNArDipp)₂].



Scheme 20 The reductive disproportionation of an isocyanide stabilised Pd^I dimer (**20**) forming Pd₃ cluster (**21**).

The above work shows that an unstable dinuclear Pd^I complex can convert to a stabilised Pd₃ cluster, demonstrating that low-coordinate Pd may be stabilised by aggregation to structurally well-defined ligated clusters. In this case it is likely that further aggregation, which may have occurred with analogous unprotected electron rich Pd complexes, was prevented by the bulky and π -electron accepting quality of the coordinated isocyanide ligand.

Kurosawa *et al.* found that reaction between [Pd⁰₂(dba)₃] and tetraphenylphosphonium chloride in the presence of a [C₇H₇][BF₄]⁻ source yielded a cluster complex (**22**) featuring a chloride-capped triangular Pd₃ anion (**22**), sandwiched between two cycloheptatrienyl cations (Figure 15).¹⁷⁸⁻¹⁷⁹ It was subsequently found that related, well defined aryl-sandwiched complexes could catalyse the intramolecular cyclisation reaction between 2-phenylethynylaniline to 2-phenylindole (Figure 15) whereas [Pd⁰₂(dba)₃] or Pd(OAc)₂ could not under the same conditions.¹⁸⁰

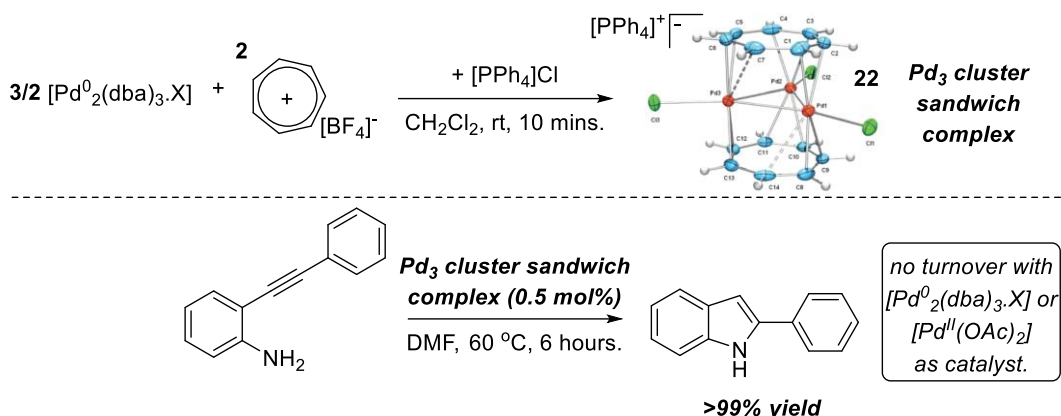


Figure 15 Schemes showing (above) the synthesis of a cycloheptatrienyl Pd_3 sandwich complex and (below) application as a catalyst in a cycloisomerisation reaction forming 2-phenylindole.

Malacria and Maestri *et al.* reported the unique activity of a C3-symmetric sulfide-bridged cluster complex of the form $[\text{Pd}_3(\mu\text{-SR})_3(\text{PR}'_3)_3]^+\text{X}^-$ (X^- = non-coordinating anion, R = aryl group)(Figure 16).¹⁸¹ With this compound, analogously to the $\text{Pd}_3\text{X}\cdot\text{X}$ cluster motif discussed *vide supra*, the Pd_3 core is ligated by three κ -organophosphine ligands, however the Pd centres are bridged by organosulfide ligands. Notably, contrary to highly planar structure of the $\text{Pd}_3\text{X}\cdot\text{X}$ motif as highlighted above, generally, the S- and P-atoms of $[\text{Pd}_3(\mu\text{-SR})_3(\text{PR}'_3)_3]^+\text{X}^-$ each sit out of the Pd_3 plane, adopting a proximally alternating staggered conformation.

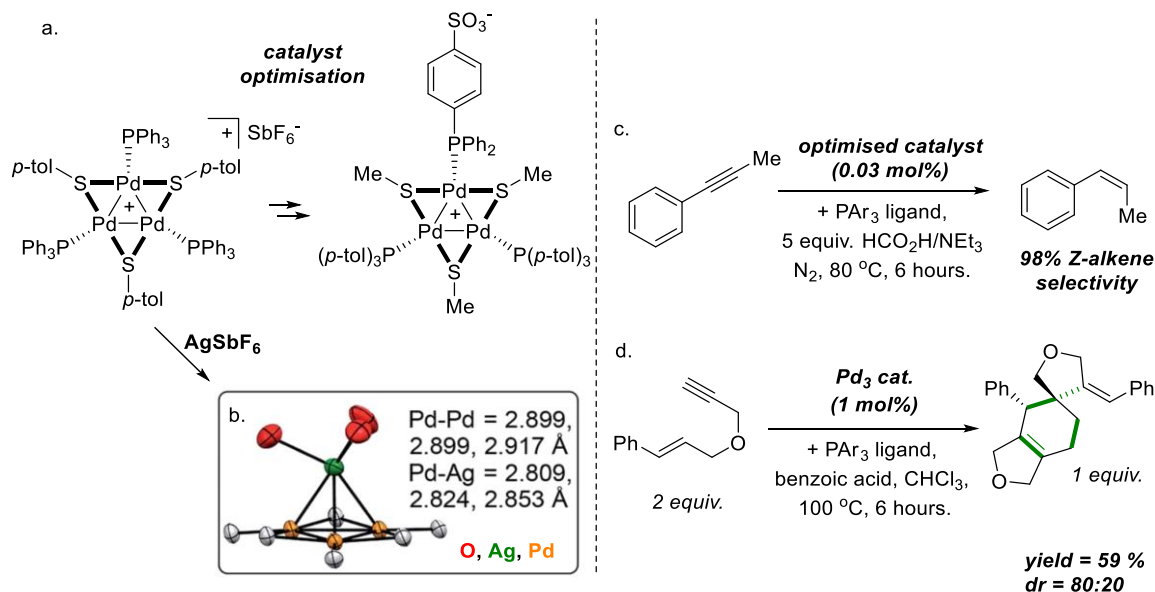


Figure 16 (a) Showing structures of the Pd_3 cluster catalyst of the form $[\text{Pd}_3(\mu\text{-SR})_3(\text{PR}'_3)_3]^+\text{X}^-$ prior to, and after, catalyst optimisation. (b) Crystallographic evidence for the cluster's reactivity with a Lewis acid, forming a tetranuclear Pd_3Ag cluster dicationic core, showing metal-metal bond lengths (O-based ligands, H_2O and THF have been represented as their co-ordinating O-atoms, organic groups and $[\text{SbF}_6]^-$ anions were omitted for clarity). Synthetic applications of the $[\text{Pd}_3(\mu\text{-SR})_3(\text{PR}'_3)_3]^+\text{X}^-$ cluster complex: (c) An example of an application of optimised conditions for the catalytic semi-reduction of internal alkynes, (d) Pd_3 -catalysed cyclisation reaction. Adapted from *Chem. Sci.*, 2017, 8, 7394; licenced under Creative Commons, published by the Royal Society of Chemistry.

After a significant rational optimisation by both sulfide and triarylphosphine ligand substitution, application of the Pd₃ catalyst in highly efficient and selective semi-reduction reactions at internal alkynes was possible under transfer-hydrogenation conditions (c. Figure 16). The successful catalyst optimisation for hydrogenation demonstrated the scope for modulation of such catalyst activity by tuning the cluster's steric and electronic properties through simple phosphine or sulfide ligand exchange processes. Intriguingly, the Pd₃ cluster was confirmed to be aromatic and isoelectronic with the cyclopropenyl cation. Aromaticity was probed by a variety of means including SQUID magnetometry, which found the electrons within d_{x²-y²} atomic orbitals to be fully delocalised, which was supported by computational MO analyses (NBO and AdNDP).¹⁸² The Pd₃ structure was reactive as a Lewis base with other metal complexes after reaction with Ag salts (*e.g.* AgSbF₆), through the cluster's fairly unhindered, delocalised d-orbital π -system, forming a 3-dimensional pyramidal, aromatic structure, with Ag capping the Pd₃ plane.(b, Figure 16).¹⁸³ This finding hints at the potential reactivity mode of these Pd₃ clusters and might inform how the analogous [Pd₃(μ -Cl)(μ -PPh₂)₂(PPh₃)₃]⁺Cl⁻ cluster may react. The optimised catalyst system was applied to the diastereoselective synthesis of tricyclic cyclohexene architectures, showing that the cluster could be used for the bespoke synthesis of complex pharmaceutically-relevant molecular scaffolds (d. Figure 16).¹⁸⁴ Such transformations could not be realised using simple Pd(OAc)₂ or [Pd₂(dba)₃.solv.] catalyst systems.

When computationally modelling the oxidative addition step, involving less well-defined Pd₃ sub-nanometre clusters derived from a heterogeneous source to aryl halides, Corma *et al.* noted that the exposed metal atoms 'cooperate' to lower the barrier for the C–X bond activation (where X = I, Br, Cl), even for more challenging aryl chloride bond activations, in various cross-coupling processes.¹⁸⁵ This finding further indicates that an extremely small catalytic cluster can behave in ways distinct from that of mono-nuclear Pd species, which is often the only active species modelled in cross-coupling mechanistic studies.

This section has shown that Pd clusters demonstrate privileged stoichiometric and catalytic reactivity, frequently outperforming common precatalysts such as [Pd⁰(PPh₃)₄], [Pd⁰₂(dba)₃] and Pd(OAc)₂. From the examples selected it has been demonstrated that both high catalyst activity as well as site-control can be realised using well-defined Pd clusters. A common feature of all of the Pd cluster catalysts presented is that their preparation is lengthy and expensive and therefore unlikely to be economical in a large-scale industrial setting. A key question that *this study* wishes to address is whether such unique Pd cluster catalysis be accessed from simple, relatively inexpensive, Pd precursors, thereby forgoing the need for such demanding catalyst syntheses.

1.5. Site-selectivity in Cross-coupling Reactions at Multiply (pseudo)Halogenated (hetero)Aromatic Compounds

The exceptional synthetic utility of cross-coupling chemistry means that site-selective cross-coupling reactions can be a vital tool for the rapid parallel diversification of dihalogenated (hetero)aromatic compounds, allowing for highly efficient construction of compound libraries for drug and agrochemical discovery applications.¹⁸⁶⁻¹⁸⁸ Therefore, if two or more couplings at different (pseudo)halide sites on a single substrate are to be realised as part of a chemical synthesis, to maximise efficiency and to avoid the formation of unwanted by-products, command of site-selectivity is of significant value to small molecule discovery. The prevalence of aromatic heterocyclic moieties in pharmaceuticals and agrochemicals highlights a particular need for designing site-selective reactions for these types of compounds. Several reviews have been written on the subject, however a full understanding of the factors that control site-selectivity in cross-coupling reactions has not yet been achieved.¹⁸⁶⁻¹⁸⁸ In this context, Pd speciation has not been widely considered as a variable which may control site-selectivity. Since cross-coupling reactions can be robust and tolerant to a broad range of functional groups, the ability to choose which site of, for example, a di-halogenated heteroaromatic compound is to be cross-coupled may give flexibility in a given multi-step synthesis. This section discusses the factors that are known to control cross-coupling site-selectivity, then goes on to give synthetic examples where control of site-selective (both *chemo* and *regio*) cross-coupling has been achieved.

1.5.1. Factors that Control Site-selectivity in Cross-coupling Reactions

Understanding the mechanistic factors that determine cross-coupling site-selectivity is of significant importance, with the ultimate challenge being, given any particular dihalogenated substrate, to be able to select catalytic conditions that can bring about total selectivity at a site of choice. In a situation where there are multiple (pseudo)halides present in a (hetero)aromatic substrate, the relative ease of oxidative addition at such a site is generally accepted to be the primary determinant of site-selectivity.¹⁸⁶⁻¹⁸⁷ In most reports, the active Pd species modelled to participate in the site-determining oxidative addition step is a phosphine-ligated Pd⁰ complex of the form [Pd⁰(L)_n] (typically L = a phosphine ligand and n = 1 or 2). Such a complex will generally have a preferred position of bond activation by oxidative addition, with Pd generally adding to the more electrophilic site. It is important to note that, in some cases, the electronic and steric nature of the Pd⁰ complex can additionally influence site-selectivity outcomes, and thus these factors will be discussed *vide infra*.

Spivey *et al.* compiled a review¹⁸⁸, following an earlier review by Fairlamb *et al.*¹⁸⁷, that utilised both Pfizer's global chemistry RKB and CAS Scifinder® databases to empirically survey trends in regioselectivity in SMCC reactions at common dihalogenated heteroaromatic compounds. Their work demonstrated

that, across the board in literature, dihalogenated heteroaromatic substrates tend to couple at one specific preferred position in the SMCC. It was shown, for each of the 4505 common dihalogenated heteroarenes examined, how many SMCC reactions coupled at a preferred site (4340) and how many went against anticipated reactivity (165).

The bond dissociation energy (BDE) of the C–X (X = {pseudo}halide) bond of an aryl halide substrate can be a predictor of the site of oxidative addition, *i.e.* the lower the bond dissociation energy of a given site, the easier oxidative addition can proceed at that site over another site with a higher BDE.¹⁸⁷ For *chemoselective* reactions, where two or more *different* halides are present within the same substrate, BDE varies quite predictably in the order F >> Cl > Br > I. Hence, for example, a C–I bond would typically be selectively cross-coupled over a C–Br bond within the same substrate. Where the *regioselective* cross-coupling question arises for two or more of the *same* type of (pseudo)halide is present in the substrate of interest, the preferred site can be less clear-cut. Broadly speaking, the preferred site of oxidative addition at multiply halogenated heteroaromatic compounds is influenced by electronic effects from substituents (*e.g.* electron withdrawing effects of heteroatoms) proximal to the C–X sites, thus reflecting similar trends in nucleophilic aromatic substitution (S_NAr) chemistry.¹⁸⁷

On the other hand, using NMR spectroscopy, chemical shift (δ) values can be used to predict electrophilicities (and therefore the propensity to undergo site-selective oxidative addition) of the different halogenated carbon atoms of heteroaromatic substrates. For example, Handy and Zhang showed that the proton chemical shifts (δ_{H}) of *parent non-halogenated* heteroaromatic compounds could be used to predict the preferred (electrophilic) site for cross-coupling.¹⁸⁹ Generally, the larger the δ_{H} of the site (*i.e.* the further downfield in the ¹H NMR spectrum), the more intrinsically electrophilic the site will be. Consequently, oxidative addition will be more likely at that site (Figure 17, 23–27).

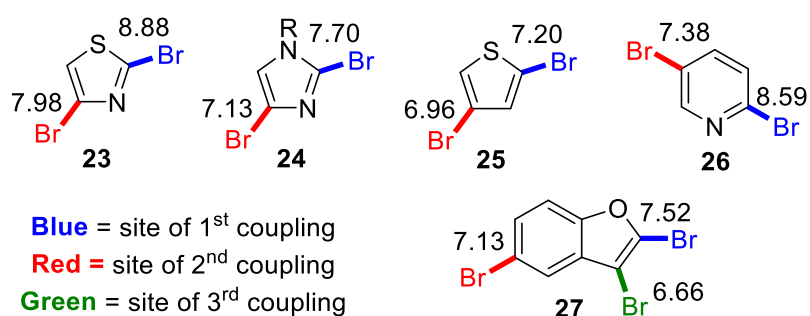
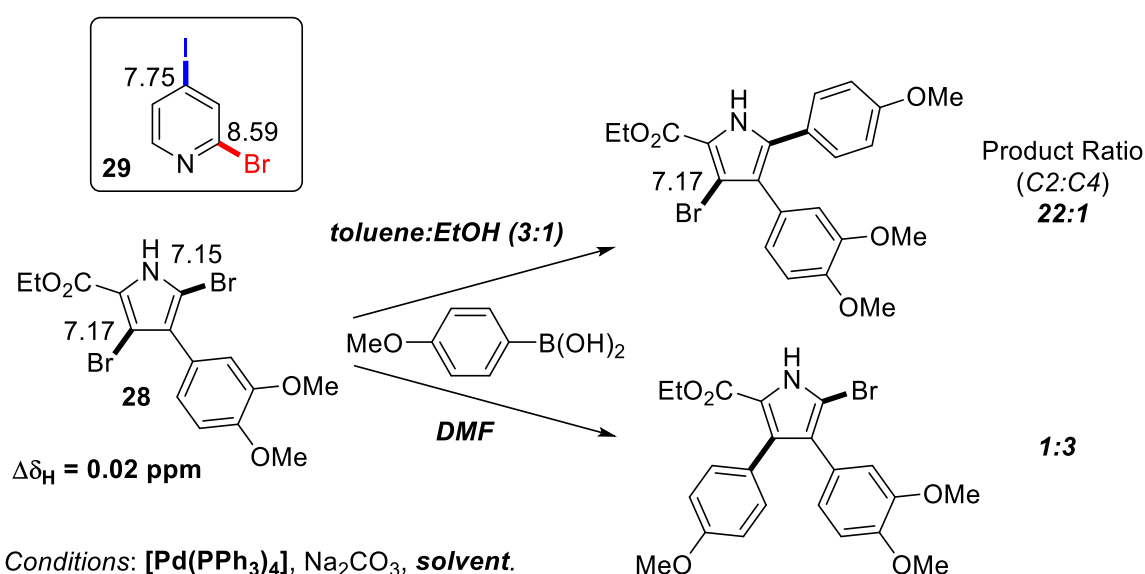


Figure 17 Showing a selection of multiply brominated heterocyclic compounds for which observed SMCC site-preference agrees with Handy and Zhang's ¹H NMR spectroscopic method for predicting site-selectivity. ¹H NMR chemical shifts (δ_{H}) of the parent non-halogenated heterocycle for each example are displayed next to their respective site.

In each case (Figure 17, **23–27**) the highest value of δ_{H} correlates with the site of preferential cross-coupling. In the case of triply brominated 2,3,6-tribromobenzofuran **27**, the sequence of cross-coupling follows that indicated by the order of δ_{H} chemical shift values of the three respective proton signals of the parent compound. There are, however, examples of regioselective cross-couplings where this NMR-based predictor is invalid, particularly in cases where the parent compound ^1H chemical shift differences ($\Delta\delta_{\text{H}}$) are less than 0.3 ppm.¹⁹⁰⁻¹⁹¹ For example, under otherwise identical conditions, a mere change of the solvent system from DMF to a toluene and EtOH mixture results in a switch in preference from overall C2 to C4 selectivity in SMCCs at a substituted 2,4-dibromopyrrole **28** (Scheme 21).¹⁹² This site-selectivity switch suggests that other changes to the reaction conditions can lead to the dichotomous outcomes.

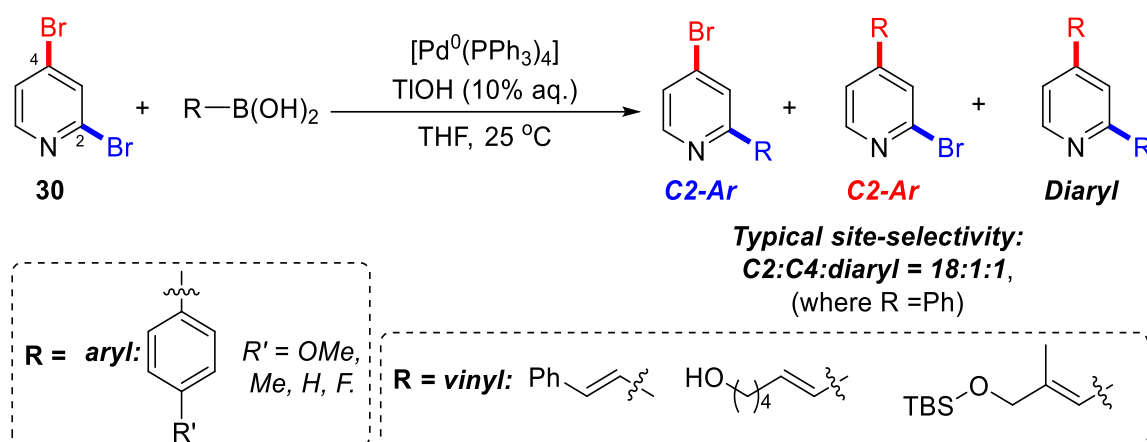


Scheme 21 Situations where the Handy-Zhang ^1H NMR based method for predicting site-selectivity breaks down. A SMCC reaction where there is minute difference in $\Delta\delta$ in the parent compound, a change in solvent conditions leads to site-selectivity reversal. Top-left: the structure of 2-bromo-4-iodopyridine (**29**).

In *chemoselective* cross-couplings however this predictor, perhaps expectedly, cannot be applied as the identity of the (pseudo)halides involved influences BDE to a greater extent than the electronic influence of proximal heteroatoms. For example, at 2-bromo-4-iodopyridine **29** (Scheme 21) cross-coupling occurs preferentially at the C4–I position, while the ^1H resonance of the parent pyridine would suggest coupling at the C2–Br position.

A prominent example of regioselective cross-coupling occurring at an *expected* site of a dihalogenated heteroaromatic was reported by Cid *et al.*, when exploring SMCC reactions of 2,4-dibromopyridine **30**.¹⁹³ Under the applied conditions, using $[\text{Pd}^0(\text{PPh}_3)_4]$ as a catalyst, cross-coupling of a variety of aryl

and alkenyl boronic acids invariably occurred at the C2–Br site, producing the C4- and di-arylated product as minor products (Scheme 22).



Scheme 22 Showing the organoboronic acid substrates, conditions and reagents used for the site-selective SMCC reactions at the dihalogenated heteroaromatic substrate 2,4-dibromopyridine (**30**).

This observed site-selectivity was rationalised to be a result of the electrophilicity of the C2–Br site, enhanced by a proximal nitrogen. The C2 site-selectivity additionally conformed to expectations based on the Handy-Zhang method detailed above.¹⁹⁴ Substrate **30** features prominently in Chapter 4 of this Thesis, as it has proven to be an excellent model substrate for probing site-selective SMCC reactions.

In some cases, the BDE of different C–X sites at a multiply (pseudo)halogenated substrate fails as a predictive method for the site of cross-coupling as subtle factors pertaining to how the activated complex forms *en route* to the oxidative addition products are not factored in. Computational modelling has shown that the preferred site of oxidative addition by $[Pd^0(L)_n]$ (where $n = 1$ or 2) to multiply halogenated heteroaromatic substrates to be a combination of intrinsic electronic effects at the substrate's sites and how these factors interact with the sterics and electronics of the catalyst.¹⁹⁵⁻¹⁹⁶ Site-selective oxidative addition reactions to multiply halogenated heterocycles featuring halides of the same type was investigated computationally by Houk, Schoenebeck *et al.* using $[Pd^0(PH_3)_2]$ as a fixed model Pd species. The overall activation energy $\Delta E^\ddagger$ for the oxidative addition reaction was modelled as the difference between energy of *distortion* $\Delta E^\ddagger_{dist}$, an aggregate of the energy required to stretch the C–X bond and bend $[Pd^0(L)_2]$ into the transition state, and the energy of *interaction* between such distorted reactants: $\Delta E^\ddagger_{int}$. a. Figure 18 shows how modelling of $\Delta E^\ddagger_{int}$ is determined computationally, with a model 2-halopyridine substrate.

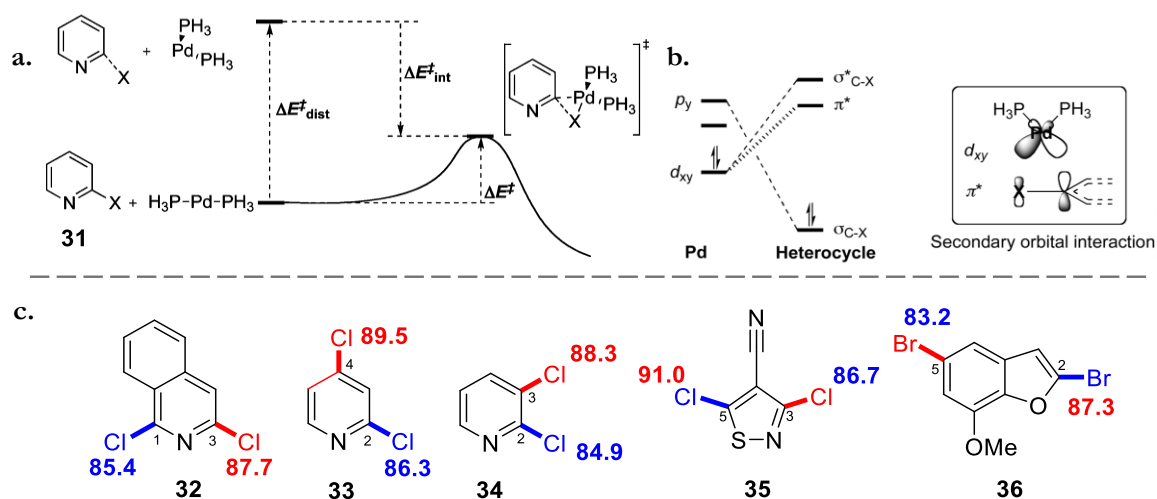
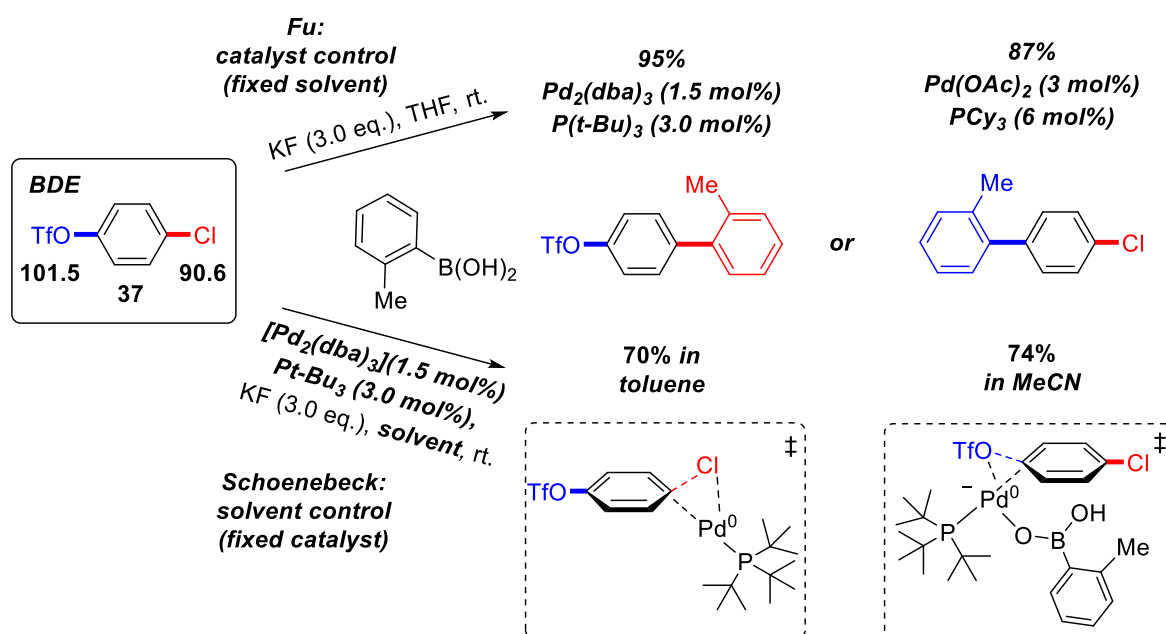


Figure 18 a. Graphical depiction of energetic considerations employed when calculating $\Delta E^\ddagger$ for oxidative addition reactions between $[\text{Pd}^0(\text{PH}_3)_2]$ and (di)halogenated heteroaromatic compounds. b. An FMO diagram showing orbital interactions involved for the situation at 31 where oxidative addition is controlled by $\Delta E^\ddagger_{\text{int}}$. c. Examples of structures calculated where the C–X site (coloured blue) is the site of first oxidative addition. Numbers coloured blue show the sites where BDE is higher and red where BDE is lower (BDE values in units of kcal mol⁻¹). Incidences where the colours mismatch indicate cases where site-selectivity is not merely a direct result of higher BDE (related to $E^\ddagger_{\text{dist}}$) but controlled by interaction energy due to secondary MO effects. Adapted with permission from *J. Am. Chem. Soc.* 2007, 129, 12664-12665. Copyright (2007) American Chemical Society.

It was found that the BDE of the carbon–halogen bond did not necessarily parallel the computed site of oxidative addition. For the different compounds modelled, it was found that $\Delta E^\ddagger_{\text{dist}}$ was strongly related to the BDE, however $\Delta E^\ddagger_{\text{int}}$ could overcome high $\Delta E^\ddagger_{\text{dist}}$, under certain conditions. Analysis of the frontier molecular orbitals (FMO) allowed for rationalisation of why oxidative addition can occur preferentially at sites with higher BDE. Donation of π -electron density from the electron-rich d_{xy} -HOMO orbital of $[\text{Pd}^0(\text{L})_2]$ into the π^* -LUMO orbital (b., Figure 18) of the heteroarene effectively acts to increase $\Delta E^\ddagger_{\text{int}}$ resulting in a lowered overall $\Delta E^\ddagger$ for oxidative addition. In other words, electronic population of π^* -LUMO orbital on the heteroarene is a secondary molecular orbital interaction which results in a weakening of the C–X bond and, hence, a lower $\Delta E^\ddagger$. Hence, the more electron-rich the phosphine, the higher in energy d_{xy} -HOMO and the larger the $\Delta E^\ddagger_{\text{int}}$. A wide range of oxidative additions to dihalogenated heteroarenes were modelled, some of which contravened expected site-selectivity for oxidative addition, based on BDE arguments alone. For example (c. Figure 18), with compounds **32–34** the site of oxidative addition was correctly predicted based on BDE, while with compounds **35** and **36**, an interaction component was needed for correct prediction of site-selectivity.

Fu *et al.* discovered a remarkable catalyst-mediated switch in site-selectivity at the substrate 4-chlorophenyltriflate **37** when investigating bulky and electron rich tertiary phosphine ligands at Pd catalysts applied to SMCC reactions (upper fork, Scheme 23).¹⁹⁷ The experimentally-derived order of

reactivity of (pseudo)halides follows the trend $I > Br \approx OTf \gg Cl$, hence, generally cross-coupling would be expected to occur preferentially at a C–OTf site over a C–Cl site.¹⁹⁸ Employing pre-catalytic $Pd(OAc)_2/2PCy_3$ ($Pd:P = 1:2$), expected C–OTf selectivity was observed, however employing the bulkier $Pt-Bu_3$ introduced in mixtures of $[Pd_2(dba)_3]/2Pt-Bu_3$ ($Pd:P = 1:1$), resulted in a remarkable switch to selective cross-coupling at the less activated C–Cl site. The notion that the two, very different pre-catalytic systems could lead to very different active species was not discussed in this case. Subsequently, Schoenebeck *et al.* found that, in addition to ligand choice, solvent polarity could be pivotal in determining site-selectivity in SMCCs at **37** using a fixed pre-catalyst system: $[Pd_2(dba)_3]/2Pt-Bu_3$ ($Pd:P = 1:1$), with C–Cl-selectivity in toluene, and C–OTf-selectivity in more polar MeCN (lower fork, Scheme 23).¹⁵⁹



Scheme 23 Showing how site-selectivity at 4-chlorophenyltriflate (**37**) can be switched using catalyst choice (upper conditions, Fu *et al.*) or solvent modulation of catalyst behaviour (lower conditions, Schoenebeck *et al.*). BDE of C–Cl and C–OTf of **37** are shown.

Houk *et al.* computationally^c investigated oxidative addition reactions to **37**, mirroring experimental observations by Fu *et al.*, employing $[Pd^0(PMe_3)_n]$ ($n = 1, 2$) as a model catalyst, the bis-ligated species ($n = 2$) was selective for the C–OTf bond at **37**, while the mono-ligated species ($n = 1$) was selective for the C–Cl bond.¹⁹⁹ In the oxidative addition reaction between C–Cl (which has a lower BDE than C–OTf) and $[Pd^0(PMe_3)_2]$ significantly less $\Delta E^\ddagger_{dist}$ is required to achieve the transition state than with $[Pd^0(PMe_3)]$, however interaction energy is not significantly different. At C–OTf, the $\Delta E^\ddagger_{dist}$ is higher, on account of the stronger C–O bond than C–Cl, however, in the distorted transition state, the π^* -

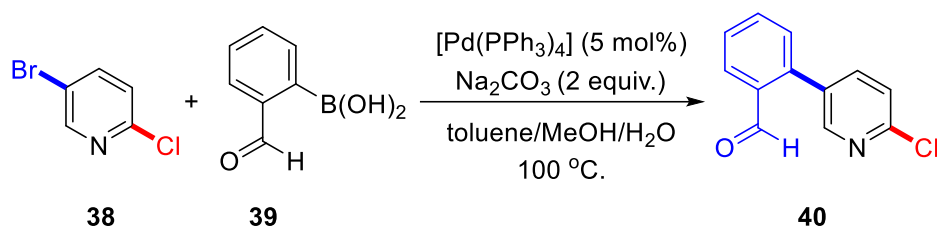
^c Using DFT methods: Gaussian09, revision A.01, B3LYP/6-31+G(d)1 using ECP for Pd [LANL2DZ] level of theory, for gas phase calculations.

LUMO energy is lowered. Bis-ligated Pd^0 is more electron-rich, leading to higher energy d_{xy} -HOMO. The decreased HOMO-LUMO gap in this case lowered $\Delta E^\ddagger$ for $[\text{Pd}^0(\text{PMe}_3)_2]$. Therefore, in the case of bis-ligated Pd^0 , the regioselectivity is *interaction*-controlled and mono-ligated Pd^0 the regioselectivity is *distortion*-controlled. Follow-up computational work by Schoenebeck *et al.* further investigated the solvent-induced inversion of catalyst-selectivity at **37**, this time using a fixed pre-catalytic system: $[\text{Pd}_2(\text{dba}_3)]/2\text{P}^t\text{Bu}_3$ (Pd:P = 1:1) (lower fork, Scheme 23) and found that, here, the difference in reactivity in polar MeCN (C–OTf-selective) was not, as was first hypothesised, due to solvent stabilisation of monoligated Pd^0 (*i.e.* $[\text{Pd}^0(\text{P}^t\text{Bu})_3(\text{NCMe})]$ complexes). It was however determined that the solvent acted to allow stabilisation and solvation of anionic Pd^0 -complexes of the form $[\text{Pd}^0(\text{P}^t\text{Bu})_3(\text{X})]^-$, where X^- was experimentally reasoned to be either F^- or $[\text{Ar}-\text{B}(\text{OH})\text{O}]^-$, which were deemed to be available under working SMCC conditions. Such anionic species, analogous to having extra phosphine ligand, were confirmed to result in *interaction*-control in couplings at the C–OTf site of **37**. Anionic Pd species have been shown experimentally to be able to accelerate oxidative addition in other work by the Jutand^{48, 200} and Hartwig groups.²⁰¹ Modulation of catalyst identity and conditions can thus lead to striking changes in site-selectivity. On the other hand, bulky ligands are known to be able to stabilise mono-ligated Pd^0 .¹⁹⁸ Taken together, selective oxidative addition at C–Cl by mono-ligated Pd^0 , stabilised by P^tBu_3 is the reason for Fu’s observed C–Cl site selectivity at **37** (upper fork, Scheme 23).¹⁹⁷ Likewise, Houk and Schoenebeck’s calculations explain observed C–OTf site-selectivity when a catalytic system that is more likely to generate bis-ligated Pd^0 complexes is employed. Thus, by understanding electronics of multiply halogenated substrates along with judicious design of the catalytic system, in theory, site-selective C–X bond functionalisation is feasible.

1.5.2. Examples of Site-control in Cross-coupling Chemistry

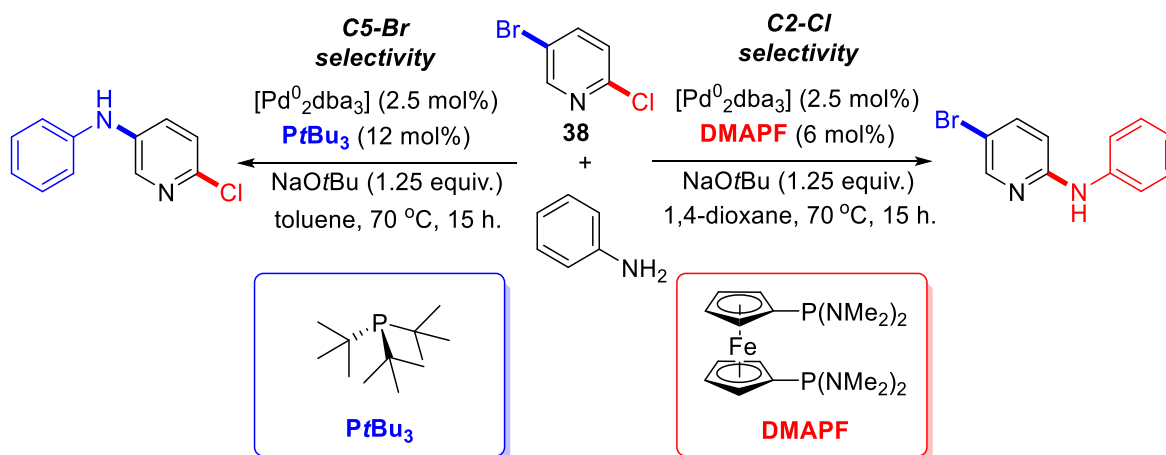
The following examples detail experimental studies where control has been achieved in site-selectivity (either *chemo*- or *regio*-selectivity) in cross-coupling reactions. Where applicable, reported mechanistic reasoning for observed site-selectivity is discussed.

Employing the mixed dihalogenated heteroarene 2-chloro, 5-bromochloropyridine **38** and *ortho*-formylphenylboronic acid **39**, SMCC coupling was realised at the C5-position giving **40**, exploiting the relatively low BDE of Br compared with Cl (Scheme 24).²⁰²



Scheme 24 The conditions used in SMCC coupling of the mixed halide 5-bromo, 2-chloropyridine (**38**), using $[\text{Pd}^0(\text{PPh}_3)_4]$ as a pre-catalyst, which resulted in selective reaction at the C5–Br position.

The above case therefore contravenes the outcome that would be predicted by the Handy-Zhang method (*vide supra*). The selective arylation at the C5–Br site of **38** allows for the C2–Cl functionality being available for downstream chemical reactions. 2-Chloro-5-bromo-pyridine **38** is a particularly interesting substrate with which to test site-selectivity as two factors that influence site control – bond dissociation energy and intrinsic polarity, stand in opposition. The site with the higher BDE is situated next to a site of increased electrophilicity (C2–Cl-position), proximal to the nitrogen. On the other hand, the bond with the lower dissociation energy (C5–Br) is situated at a site which is not subjected to increased polarity due to electronic effects from the pyridyl nitrogen. In a more recent study by Sigman *et al.*, additive ligand effects at $[\text{Pd}^0_2(\text{dba})_3]$ allowed for a subversion of this chemoselectivity in Buchwald-Hartwig amination reactions at **38** (Scheme 25).²⁰³



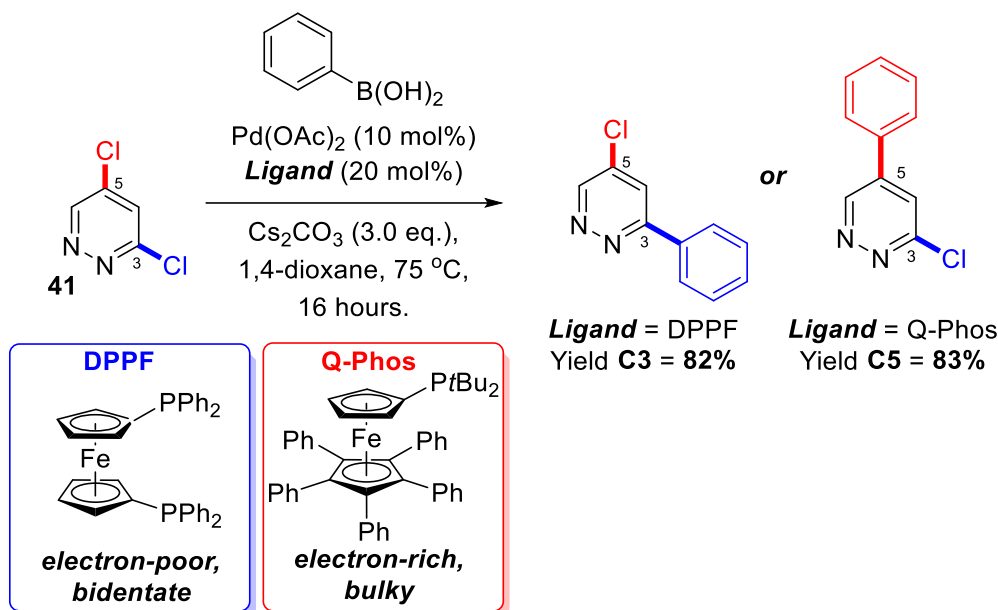
Scheme 25 The conditions employed by Sigman *et al.* for the chemoselective Buchwald-Hartwig amination reaction between 2-chloro-5-bromopyridine (**38**) with aniline, where employing bidentate DMAPF allows C2–Cl site-selectivity, while PtBu_3 results in C5–Br site-selectivity.

In toluene, employing bulky, electron-rich phosphine ligands (*e.g.* PtBu_3) which give rise to mono-ligated Pd^0 complexes, the C5–Br position could be selectively aminated. In more polar dioxane, the DMAPF ligand and other related bidentate, electron-rich but π -electron-accepting ligands were optimal for activation of the challenging C2–Cl bond. This phenomenon was rationalised to be an effect of the

enhanced nucleophilicity, a result of the electron-rich bis-ligated bidentate Pd complex, which increases interaction energy ($\Delta E_{\text{int}}^{\ddagger}$), therefore compensating for an increased distortion barrier ($\Delta E_{\text{dist}}^{\ddagger}$) required to break the C–Cl bond.

The above are examples of control of *chemoselectivity* through judicious control of the catalytic system. A significant problem with this approach is that the synthesis of substrates featuring mixed halides can often be synthetically non-trivial, potentially reducing the aggregate efficiency of a process. In terms of type of site-selectivity, *regioselectivity*, is generally considered to be more of a challenge, in addition to being more synthetically attractive than that of *chemoselectivity*. There have nevertheless been numerous examples of site-control at dihalogenated (hetero)aromatic compounds featuring multiple halides of the same type.

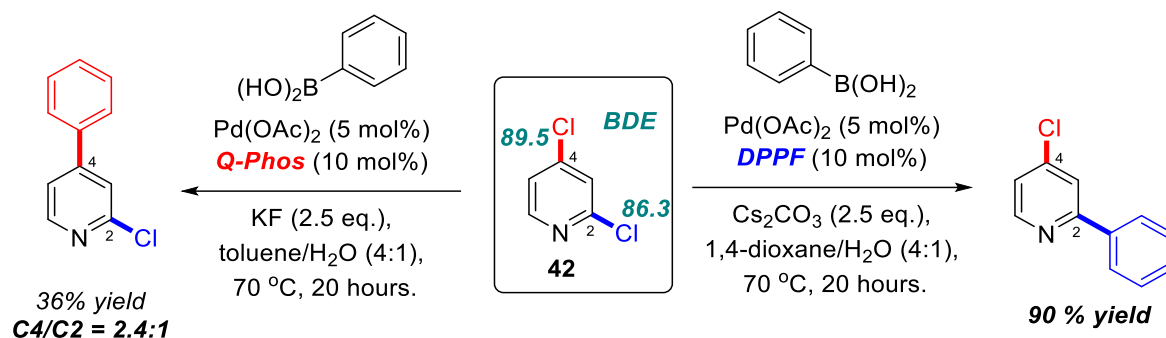
Nargund *et al.* reported an example of a catalyst-mediated switch in regioselectivity in SMCC reactions at between 3,5-dichloropyridazine **41** and phenylboronic acid (Scheme 26).²⁰⁴ Employing catalytic mixtures of Pd(OAc)₂ and bidentate DPPF, optimal selectivity was achieved at the C3-position of **41**.



Scheme 26 Showing conditions used by Nargund *et al.* to control the site-selectivity at the substrate 3,5-dichloropyridazine (**41**).

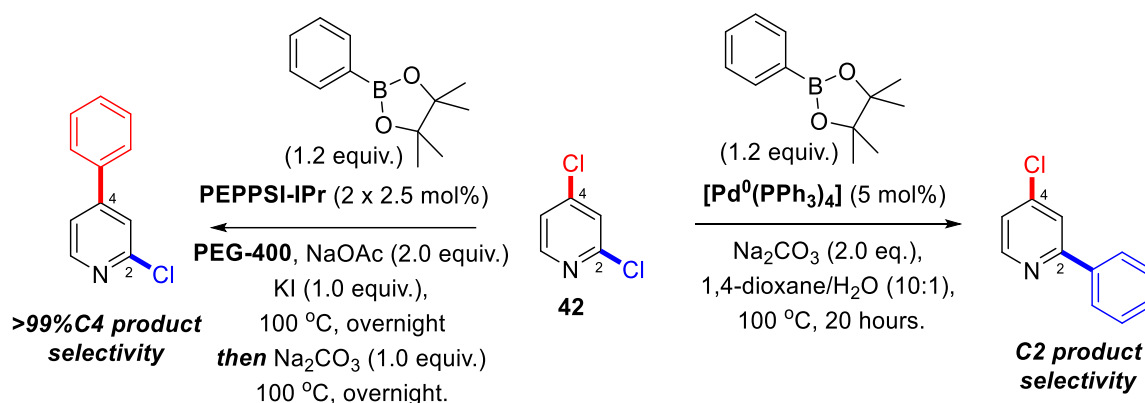
On the other hand, the employment of the bulky, electron rich monodentate QPhos ligand, allowed for selective coupling at the challenging C5-position. Other bulky, electron-rich phosphines such as P^tBu₃, AmPhos, and cataCXium®A, also showed preference for the C5-product. Less electron-rich ligands PPh₃, Xantphos and DPPP, enabled C3-selectivity. Dialkylbiaryl ligands Ruphos, XPhos and SPhos (*Buchwald-type*) gave the bis-arylated product as the major cross-coupled product. Employing an analogous methodology, the same group were able to achieve some selectivity in SMCC reactions

between 2,4-dichloropyridine **42** and phenylboronic acid, with site-selectivity for the C2–Cl and C4–Cl being most efficient using DPPF and Q-Phos, respectively, as additive ligands (Scheme 27). The C4-selective reaction, however, was quite modest, with C4:C2 = 2.4:1. It is of note that, in addition to ligand identity, other aspects of the reaction conditions were changed for the optimised selectivity. A less polar solvent mixture (toluene/H₂O) along with KF base was used for the C4-selective reaction while the more polar solvent system of dioxane/H₂O and Cs₂CO₃ was used for the C2-selective reaction. Details of how this optimisation was performed were not reported.



Scheme 27 Showing conditions used by Nargund *et al.* to control the site-selectivity at the substrate 2,4-dichloropyridine (**42**). BDEs displayed for the substrate were reported by Houk *et al.*¹⁹⁶

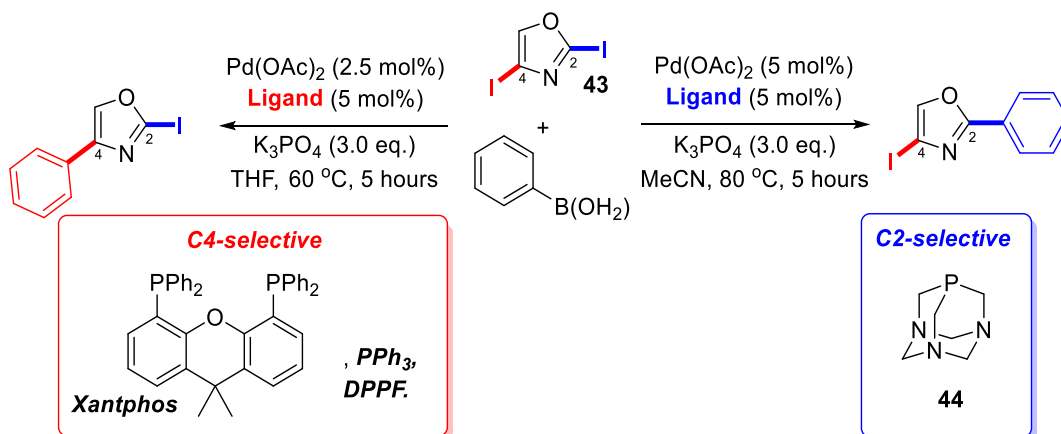
Crucially, in both cases, with substrates **41** and **42**, by employing the bulky, electron rich ligand Q-phos, which is likely to give rise to mono-ligated Pd⁰ complexes, the more challenging C–Cl site (featuring the higher BDE) was able to be selectively coupled. Yang *et al.* recently reported the first highly C4-selective SMCC between 2,4-dichloropyridine **42** and a variety of arylboronic pinacol esters (Scheme 28).²⁰⁵



Scheme 28 Conditions used by Yang *et al.* to realise the C4-selective SMCC between 2,4-dichloropyridine (**42**) and phenylboronic acid pinacol ester. [Pd⁰(PPh₃)₄] enabled cross-coupling at the C2 position.

Unprecedented C4-selectivity was realised at **42** using a PEPPSI-*i*pr pre-catalyst along with a mixture of KI (additive) and NaOAc/Na₂CO₃ base system, which brought about optimised 99:1 (C4:C2) selectivity in a PEG-400 reaction medium, at elevated temperatures of 100 °C. [Pd⁰(PPh₃)₄] was seen to select for the C2 product while electron-rich catalyst systems such as [Pd⁰(P^tBu₃)₂] and BrettPhos-Pd-G3 and cataCXium®A-Pd-G3 demonstrated overall preference for the C4 product. Although no reference was made to the supposed nature of the active catalytic species exhibiting optimised selectivity, under such reaction conditions, *i.e.* a polar polymeric reaction medium with salt additives and elevated temperatures, often give rise to PdNPs (see Section 1.3.2.2).

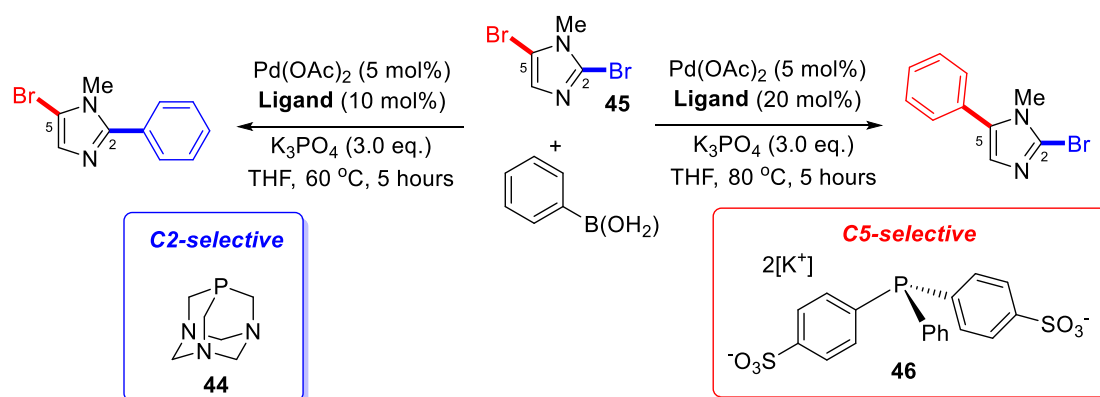
Steves *et al.* investigated site-selective SMCC reactions at dihalogenated oxazoles, imidazoles and thiazoles and discovered another example of catalyst-control in site-selectivity (Scheme 29 & Scheme 30).¹⁹⁰ Here, site-selectivity could be switched by changing the ligand in pre-catalytic Pd(OAc)₂/tertiary organophosphine mixtures. It was found that, employing structurally diverse phosphines such as PPh₃, Xantphos and DPPF, contrary to expectations based on the Handy-Zhang method (*vide supra*), the preferred site for reaction at 2,4-diiodooxazole **43** was the C4 site (Scheme 29). Optimal site-selectivity at the C2-position could be achieved using the strong-electron donor phosphine ligand 1,3,5-triaza-7-phosphaadamantane **44**. Problematically, in addition to being the only ligand to enable the challenging C2-selectivity, this was the only reaction that was reported employing MeCN as the reaction solvent (and an elevated temperature), thus raising the question of whether the observed selectivity was due to a solvent polarity effect rather than a ligand effect.



Scheme 29 Showing optimal conditions reported for site-selectivity in the SMCC between 2,4-diiodooxazole (**43**) and phenylboronic acid.

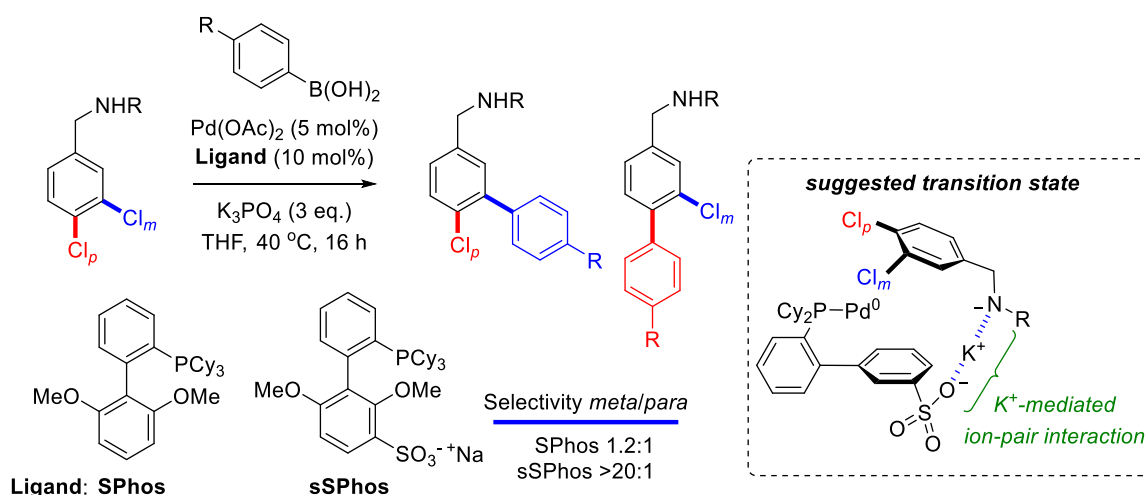
In applying similar conditions to the substrate 2,5-dibromo-1-methylimidazole **45** (Scheme 30), where the C2 position is the predicted site of cross-coupling, the C2–I bond proved quite challenging to selectively activate, with most phosphine ligands tested showing selectivity for the C5-position. On the other hand, optimal C5-site selectivity was achieved using the dianionic triarylphosphine phosphine

ligand **46**. Optimal selectivity for the C2-position, in this case, could be realised by employing **44** as a ligand.



Scheme 30 Showing optimal conditions reported for the selectivity in the SMCC between 2,5-dibromo-1-methylimidazole (**45**) and phenylboronic acid.

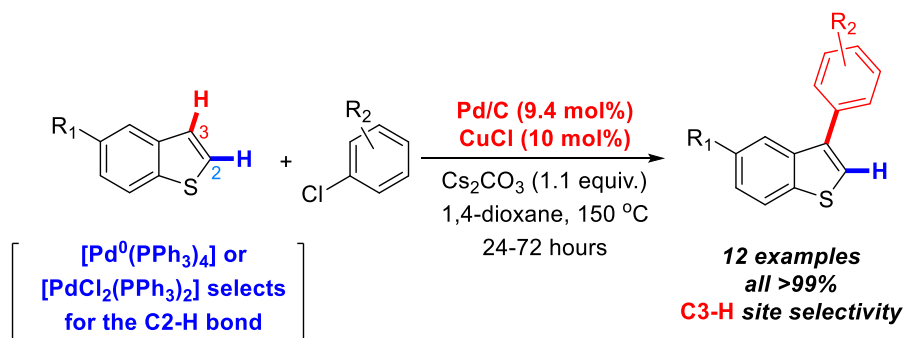
Thus far, examples reported herein have involved exploiting intrinsic electronic differences at sites to control selectivity outcomes. One way in which such intrinsic reactivity can be overcome is to utilise a directing group to exploit steric or electronic properties of intramolecular substituents to force coupling at a desired site. A significant downside of such an approach is that the potentially synthetically non-trivial addition and removal of directing groups (if, as is most likely, it is undesired in the product) would be likely to increase the cost and decrease the efficiency of the process. Such a strategy is frequently deployed in overcoming site-selectivity issues in C–H functionalisation chemistry.²⁰⁶⁻²⁰⁸ Phipps *et al.* have established an elegant, novel method for *remote direction* in SMCC site-selectivity in challenging, electronically non-differentiated chlorine sites in substituted aromatic compounds.²⁰⁹ Employing conventional dialkylbiaryl ligands (*e.g.* SPhos, XPhos), no preferential site-selectivity was observed at either C–Cl_{meta/para} site at *N*-substituted-3,4-dichlorobenzylamines which were proven to be deprotonated (anionic) under working catalytic conditions. However, when anionic sulfonated ligand variants (*e.g.* sSPhos and sXPhos) were employed, a remarkable increase in site-selectivity for the C–Cl_{meta} position was observed (Scheme 31).



Scheme 31 Reagents and conditions used for site-selective SMCC at N-substituted-3,4-dichlorobenzylamines, mediated by dialkylbiaryl ligands. Putative transition state prior to oxidative addition (site-selectivity determining step) involving $[Pd^0(sSPPhos)]$ and aryl chloride substrates is highlighted, which brings together Pd^0 and $C-Cl_{meta}$ prior to oxidative addition.

A dependence of K^+ ion present in solution (derived from the base additive) on site-selectivity was noted. Hence, a putative K^+ -bridging electrostatic interaction, bringing together anionic catalyst and substrate immediately prior to a regioselectivity-determining oxidative addition event at $C-Cl_{meta}$, was hypothesised, to result in the observed regioselectivity (Scheme 31). Implicit in this hypothesis was that such a transition state, resulting in bond activation at $C-Cl_{para}$ would be of higher energy and thus disfavoured. Increased site-selectivity was observed with a range of similarly remote directing substrates, under analogous conditions in both Sonogashira and Buchwald-Hartwig amination reactions. Such long-range directing capability was previously unknown and has revealed a new mode of directed regioselectivity, however, the generality of such remote direction in other types of substrates is untested at this stage.

Glorius *et al.* reported a site-selective direct C–H arylation reaction where aryl chlorides were used to arylate benzo[*b*]thiophene substrates (Scheme 32).²¹⁰



Scheme 32 Showing the conditions employed for the C3 site-selective direct C–H arylation of benzo[*b*]thiophenes.

A dual catalytic system of Pd/C and CuCl (a proposed Lewis acidic co-catalyst) enabled almost exclusive reactivity at the C3 position of benzo[*b*]thiophene substrates, while nominal homogeneous pre-catalysts $[\text{Pd}^0(\text{PPh}_3)_4]$ and $[\text{PdCl}_2(\text{PPh}_3)_2]$ brought about coupling at the C2 position.²¹⁰ Although an example of a C–H bond activation/functionalisation, this finding is particularly notable as it constitutes the first example of a switch in site-selectivity as a direct result of use of a heterogeneous catalyst.

A common feature of most reported examples of site-control in Pd-catalysed cross-coupling reactions is the application of often highly engineered ligands with which an often putative, $[\text{Pd}^0(\text{L})_n]$ (where, usually, $n = 1$ or 2) active species is frequently invoked. There are few examples reported in the literature where changes in gross catalyst speciation results in changes in cross-coupling site-selectivity, with the C–H functionalisation of benzo[*b*]thiophenes reported by Glorius *et al.* (Scheme 32) being a notable exception. The notion that different types of species, other than $[\text{Pd}^0(\text{L})_n]$ can be responsible for differences in site-selectivity outcomes is not widely discussed, despite higher order species such as clusters and nanoparticles being known to be important catalytically active species under cross-coupling conditions and being known to behave differently to their homogeneous counterparts (see Section 1.3).^{43, 76, 79, 165, 211–212} The work presented in Chapters 3 & 4 provides evidence that higher order species can be responsible for different outcomes in cross-coupling reactions.

1.6. Concluding Remarks

This introductory chapter has presented the case considering the importance of higher order species (clusters and nanoparticles) in cross-coupling catalysis. A summary of what is known about the mechanism of the SMCC reaction was presented. The diverse modes action of catalytic PdNPs was discussed along with what is known about their stabilisation and propagation under cross-coupling conditions. What is known about the at times privileged catalytic activity of well-defined ligated Pd clusters has been examined. The factors that may control site-selectivity in cross-coupling reactions have been discussed with an emphasis on mechanistic knowledge concerning the proposed catalytically active Pd species.

Arguments were made throughout the discussion that the precise Pd catalyst speciation is often not discussed in scientific papers, particularly in catalytic systems where the conditions used are conducive to the formation of higher order species such as PdNPs and clusters. This is exemplified by the fact that $[\text{Pd}^0(\text{L})_n]$ is most often used as a modelled active catalyst (where L is an introduced ligand), with changes in L and n at a monomeric Pd^0 species often taken to account for changes in reactivity. In some cases, this model could be an oversimplification, considering what is known about higher order

catalyst speciation under different cross-coupling conditions. *This work* provides further evidence that higher order Pd species can enable distinctive reactivity, with the potential to improve the greenness and efficiency of cross-coupling processes through more detailed understanding about the pre-catalyst activation step.

1.7. Project Aims and Objectives

1.7.1. Aims

- To understand the formation and reactivity of catalytic species arising from simple $\text{Pd}(\text{OAc})_2/\text{nPPh}_3$ catalytic mixtures.
- To exploit knowledge of such active speciation to better control cross-coupling reactivity, thereby unlocking previously unrealised potential of simple Pd catalyst precursors.
- To understand how the knowledge gained from studying Pd catalyst speciation can be utilised to control site-selective cross-coupling reaction outcomes.

1.7.2. Objectives

- To investigate the direct reactions between $\text{Pd}(\text{OAc})_2$ -based catalysts and varying quantities of PPh_3 , by characterisation of the reaction products. (Chapter 2)
- Assess the reactivity of isolated products of $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ mixtures and varying quantities of PPh_3 with key components of cross-coupling reactions, *e.g.* 2-bromopyridine and additional PPh_3 . (Chapter 2)
- To assess the catalytic differences in Pd speciation arising from different $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ mixtures by assessing their performance in model Suzuki-Miyaura cross-coupling reaction. (Chapter 3)
- Examine benchmark site-selective cross-coupling reactions of 2,4-dibromopyridine to determine differences in catalyst efficacy for different catalytic species arising from $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ mixtures. (Chapter 4)
- Determine the impact of reaction additives (namely alkylated-N-containing salts) which are key to observed control in site-selectivity control in cross-coupling reactions of 2,4-dibromopyridine. (Chapter 4)

Chapter 2 – Palladium(II) acetate / Tertiary Phosphine Ratios: The Effect of Stoichiometry on Speciation Events

2.1. Introduction

Palladium(II) acetate $\{\text{Pd}(\text{OAc})_2\}^{\text{d}}$ is the most widely used precursor to catalytic Pd for use in cross-coupling applications. Such ubiquity is a direct result of its relative cheapness, ease of handling and solubility in organic solvents.²¹³⁻²¹⁴ Although $\text{Pd}(\text{OAc})_2$ can be activated for cross-coupling reactivity, by the reaction solvent, in absence of additive ligand (see Section 1.2.2),^{7, 58, 66, 215} many powerful catalyst systems can be derived *in situ* from mixtures of $\text{Pd}(\text{OAc})_2$ and tertiary phosphines.^{62, 145, 197, 216} Undoubtedly the cheapest and most widely available such tertiary phosphine is triphenylphosphine (PPh_3). Considering the low cost and ubiquity of the $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ pre-catalyst/ligand combination it would be of great value to fully understand its activation, with the ultimate goal of the chemical industry utilising this knowledge to optimise reactivity, and the potential enhancement of kilogram to tonne scale agrochemical and pharmaceutical processes in mind.

This Chapter begins by highlighting what is known in the literature about the activation of $\text{Pd}(\text{OAc})_2$ by triarylphosphines forming species active for cross-coupling catalysis. The subsequent subsections build on this work and disclose new findings concerning the formation and stoichiometric reactivity of the active species formed from $\text{Pd}(\text{OAc})_2$ and varying equivalences of PPh_3 .

2.2. Prior Literature: $\text{Pd}(\text{OAc})_2$ Activation in the Presence of Tertiary Phosphines

By 1992 it was widely accepted that Pd^0 (*i.e.* zero-valent Pd) could activate organohalides (*e.g.* aryl and vinyl halides) hence mediating cross-coupling processes.²¹⁷⁻²¹⁹ However, the mechanism by which $\text{Pd}(\text{OAc})_2$, as a Pd^{II} complex, could catalyse cross-coupling reactions was still in question (*e.g.* in the SMCC and the Mizoroki-Heck alkenylation reactions). Amatore and Jutand *et al.* performed pioneering studies elucidating, in significant detail, the mechanism by which $\text{Pd}(\text{OAc})_2^{\text{e}}$ converts, in the presence

^d Palladium(II) acetate $\{\text{Pd}(\text{OAc})_2\}$ may exist in multiple polymorphic forms, including a loosely-bound Pd_3 trimeric form, as $[\text{Pd}_3(\text{OAc})_6]$ and polymeric form *e.g.* $[\text{Pd}(\text{OAc})_2]_n$. In this work, nitrite-free $[\text{Pd}_3(\text{OAc})_6]$ has been employed exclusively.

^e In the work by Amatore, Jutand *et al.*, the form of $\text{Pd}(\text{OAc})_2$ (*e.g.* the trimeric or polymeric forms) was not specified thus, in this segment, the generic term ' $\text{Pd}(\text{OAc})_2$ ' will be used to describe whatever polymorph was used by the authors.

of tertiary phosphines, to an active and reduced form.^{46-48, 200} The evidence presented for this process is examined below, with the key findings summarised in Scheme 34 (page 94).

In the ground-breaking studies by Amatore and Jutand (briefly introduced in Section 1.2.2), electrochemical and ^{31}P NMR methods were employed to analyse mixtures of $\text{Pd}(\text{OAc})_2$ and PPh_3 in THF and DMF. Stirred mixtures of $\text{Pd}(\text{OAc})_2$ and ≥ 2 equivalents of PPh_3 were shown to generate *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** immediately, as evidenced by an electrochemical reduction peak and a ^{31}P NMR singlet, reported at δ_{P} 14.4 ppm (THF). In the presence of a high excess of PPh_3 (8 equivalents), *in situ* formed **47** was seen to convert to a mixture of species at room temperature. On tracking the reaction process electrochemically, an oxidation peak, indicative of a reduced Pd^0 species was detected. A new broad ^{31}P NMR singlet at δ_{P} -4.7 ppm, in THF, was assigned as a Pd^0 complex in exchange with the high excess of free PPh_3 . ^{31}P NMR analysis also indicated the presence of $[\text{Ph}_3\text{P}-\text{OAc}]^+\text{X}^-$ and $\text{O}=\text{PPh}_3$, forming at the expense of the signal representing **47**. AcOH was also formed as a product of the process.

The $\text{O}=\text{PPh}_3$ and AcOH were rationalised as hydrolysis products of $[\text{Ph}_3\text{P}-\text{OAc}]^+\text{X}^-$ by adventitious H_2O , present in the solvent which would formally balance the reaction equation with release of 1 equivalent of H^+ into the reaction solution.⁴⁷ After addition of an excess of iodobenzene to solutions containing the Pd^0 complex generated from reaction of $\text{Pd}(\text{OAc})_2$ and 10 equivalents of PPh_3 , a recorded electrochemical oxidation peak was seen to rapidly disappear and a new reduction peak was observed. ^{31}P NMR spectroscopic analysis confirmed the presence of *trans*- $[\text{Ph}-\text{Pd}(\text{I})(\text{PPh}_3)_2]$, as a major solution species as validated against an authentic sample. From these findings, it was concluded that the overall reaction process involved an inner-sphere redox process at Pd, where the phosphine is oxidised ($\text{P}^{\text{III}} \rightarrow \text{P}^{\text{V}}$) to the $\text{O}=\text{PPh}_3$ and $[\text{Ph}_3\text{P}-\text{OAc}]^+\text{X}^-$ species observed as the Pd is reduced ($\text{Pd}^0 \leftarrow \text{Pd}^{\text{II}}$).⁴⁸ Indeed the overall redox process was determined to be driven by the thermodynamically favourable oxidation of PPh_3 .

Subsequent kinetic analysis revealed that the activation of **47** is governed by two rate constants, representative of two distinct processes: the inner-sphere redox process (k_1), forming $\text{X}^+[\text{Pd}(\text{OAc})(\text{PPh}_3)]^-$, the *rate determining step*, followed by a faster step (k_2), where any remaining free phosphine quickly ligates to stabilise the reduced Pd^0 complex. The same group compared the properties of the reduced species generated from $\text{Pd}(\text{OAc})_2/5$ equivalents of PPh_3 , with that of $[\text{Pd}^0(\text{PPh}_3)_4]$.²⁰⁰ As quantitative reduction of mixtures of $\text{Pd}(\text{OAc})_2$ and 5 equivalents of PPh_3 to a Pd^0 complex was found to result in 1 equivalent of oxidised phosphine, $\text{O}=\text{PPh}_3$, the resulting complex was initially postulated to have a Pd: PPh_3 ratio of 1:4, *i.e.* $[\text{Pd}^0(\text{PPh}_3)_4]$. However, electrochemical analysis of both complexes showed differing oxidation potentials, indicating that the major species in solution was not $[\text{Pd}^0(\text{PPh}_3)_4]$. The difference was thus determined to be due to the presence of the

acetate ligand in the solution, which acted to render the Pd^0 complex anionic. Additionally, after oxidative addition of the reduced species to iodobenzene, presence of $[\text{Ph-Pd}(\text{OAc})(\text{PPh}_3)_2]$ was evident, as opposed to $[\text{Ph-Pd}(\text{I})(\text{PPh}_3)_2]$, indicating that acetate outcompetes iodide at the complex (Figure 19, B. lower).²⁰⁰ This effect is likely due to steric reasons. The rate of oxidative addition of *in situ* generated $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_2]^-$ to iodobenzene was found to be 3.4 times faster than that with $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_3]^-$. The result confirmed that the additional phosphine ligand acted to slow down the rate of oxidative addition. Further kinetic data supported a transient pentacoordinate, anionic Pd^{II} intermediate which neutralises upon release of an iodide, forming $[\text{Ph-Pd}(\text{OAc})(\text{PPh}_3)_2]$ as the major solution species (Figure 19, C.). The presence of this oxidative addition complex not only confirmed the presence of the Pd^0 complex, but also demonstrated that the formed Pd^0 complex can participate in oxidative addition, the first committed step in cross-coupling reactions.

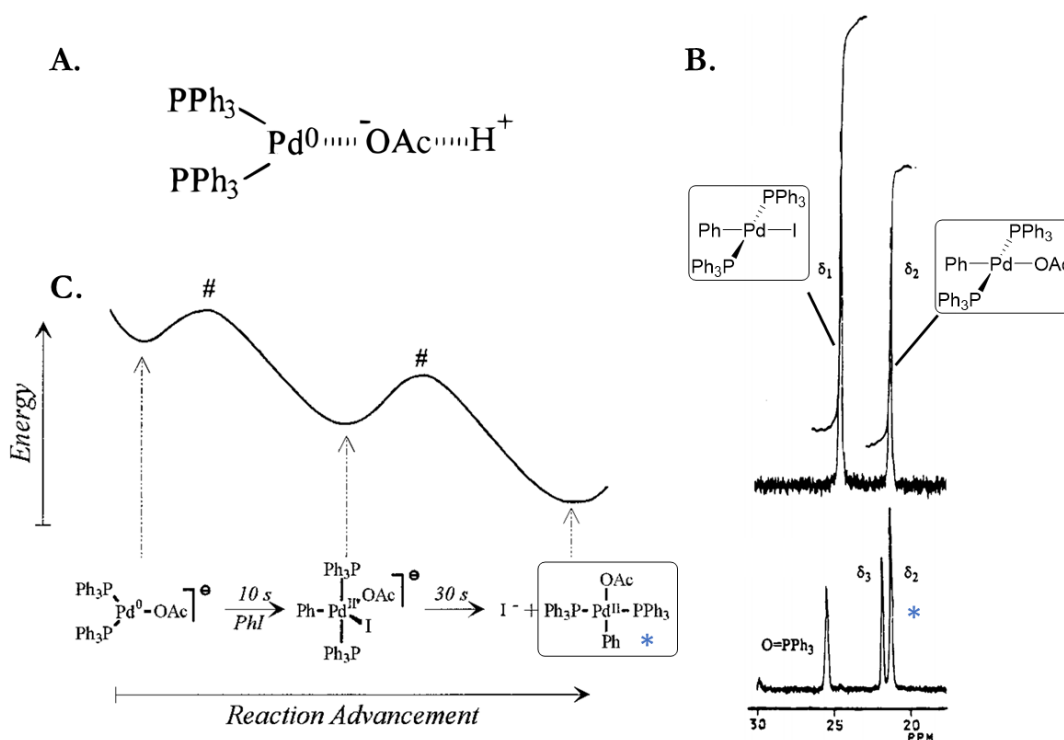
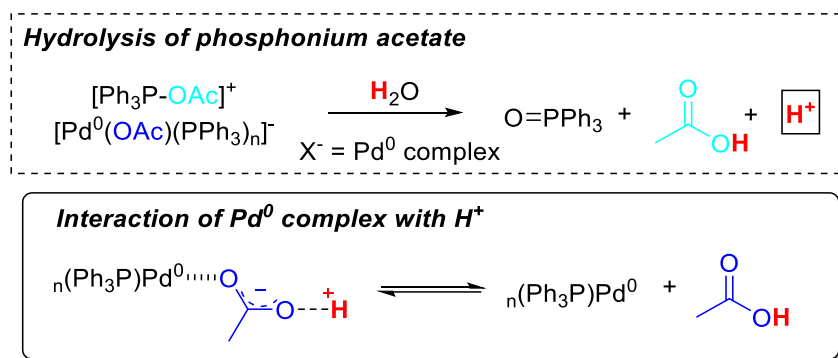


Figure 19 Participation of acetate ligands in the oxidative addition reaction of $[\text{Pd}(\text{OAc})(\text{PPh}_3)_n]^-$ with iodobenzene, also showing: a. the final conclusion, that H^+ acts as a participatory cation, stabilising acetate-ligated active anionic species. b. Showing ^{31}P NMR evidence for the participation of $-\text{OAc}$ in the oxidative addition of $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$ to iodobenzene; a qualitative energy surface diagram detailing the conclusion that a pentacoordinate anionic species forms after oxidative addition of $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$ to iodobenzene, which then releases an iodide anion, forming neutral tetracoordinate species 47. Adapted with permission from Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A.; Meyer, *Organometallics* 1995, 14, 5605-5614. Copyright (1995) American Chemical Society.

The conclusion was made that acetate-ligated anionic Pd^0 species, *e.g.* $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_2]^-$, are responsible for Pd cross-coupling catalysis when employing $[\text{Pd}(\text{OAc})_2]/>3 \text{ PPh}_3$.²²⁰ Therefore, when $n\text{PPh}_3 \geq 3$, the catalytic species which forms from the quantitative reaction of $\text{Pd}(\text{OAc})_2$ with $n\text{PPh}_3$

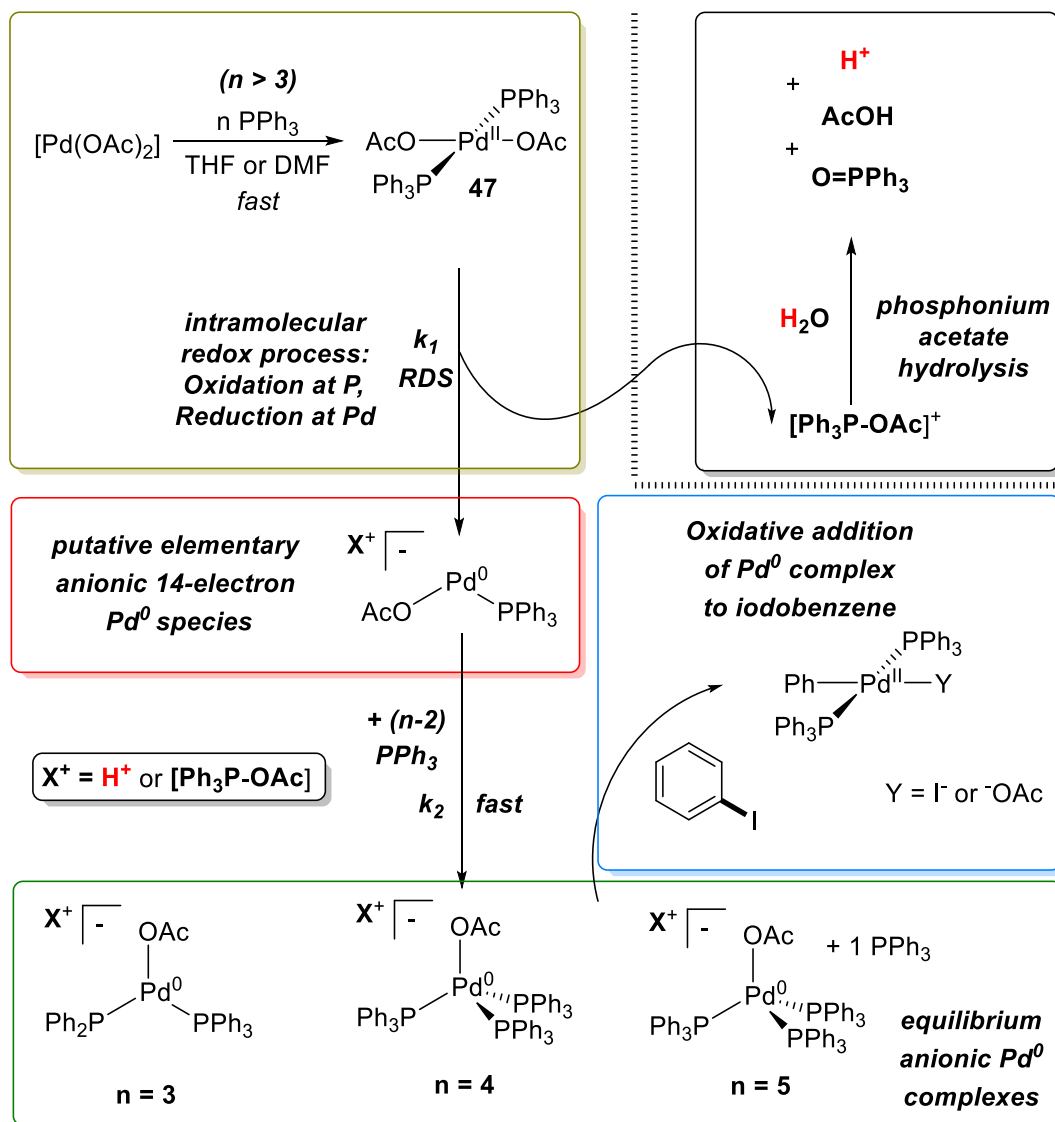
in THF and DMF is $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_{n-1}]^-$, with 1 equivalent of PPh_3 being lost as oxidised phosphorus species ($\text{O}=\text{PPh}_3$ or $[\text{Ph}_3\text{P}-\text{OAc}]^+\text{X}^-$). The hydrolysis of $[\text{Ph}_3\text{P}-\text{OAc}]^+\text{X}^-$ yields a proton, in addition to one equivalent of AcOH and $\text{O}=\text{PPh}_3$ and this proton may protonate basic sites within the system and hence compete with Pd^0 for the acetate ligand as depicted by Amatore and Jutand (Figure 19, A.). The equilibrium involved is summarised in Scheme 33.



Scheme 33 The equilibrium between acetate-ligated $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$ anionic and a neutral state, in solutions generated from $\text{Pd}(\text{OAc})_2$ and ≥ 3 PPh_3 . Based on the finding by Jutand *et al.* that acetate anions participate in stabilisation and reactivity, and the finding that a ‘free’ proton is present in solution.

Further information on this process was gained by measuring the reaction kinetics of *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** activation under a variety of conditions.⁴⁷ It was found that the rate of formation of $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_2]^-$ (the species formed from **47** where Pd:P is 1: ≥ 4) was independent of PPh_3 concentration. Additionally, the disappearance of **47** followed that of a simple first order process. However, the appearance of the signal representative of the reduced product $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_2]^-$ did not. This discrepancy pointed towards an intermediate species being involved. Noting that a change in temperature acted to increase the reaction rate, an Eyring analysis was carried out examining the thermodynamics of activation, and $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were determined as $+65 \text{ kJ mol}^{-1}$ and $-94 \text{ J mol}^{-1} \text{ K}^{-1}$, respectively. The negative $\Delta S^\ddagger$ value implies a highly-ordered transition state, compared to that of the precursor complex **47**. This finding constituted support for the hypothesis that reduction proceeds *via* an inner-sphere mechanism at Pd. Later, Kollár *et al.* similarly investigated the reaction of $\text{Pd}(\text{OAc})_2/n\text{PPh}_3$ in DMF, amongst other phosphines, further validating that $\text{Pd}^0(\text{PPh}_3)_n$ species are formed under ambient reaction conditions.²²¹ It was subsequently shown by Kohler *et al.* that carrying out these reactions under a visible-light-irradiation source ($\lambda = 400\text{-}700 \text{ nm}$) significantly boosts the rate of the intramolecular reduction reaction, by increasing the rate of inner sphere electron transfer to Pd.²²² Increased rates of reductive activation, enabled by visible irradiation were implicated in increased Heck cross-coupling reaction rates under similar irradiative conditions.

The combined key findings about the activation of $\text{Pd}(\text{OAc})_2$ by ≥ 3 PPh_3 , as delineated by Amatore and Jutand *et al.*, are summarised in Scheme 34, overleaf.



Scheme 34 A summary of the findings by Amatore, Jutand *et al.* on the activation of $\text{Pd}(\text{OAc})_2$ to a Pd^0 species, upon reaction with ≥ 3 equivalents of PPh_3 . Here, the Pd^{II} complex **47** is reduced to $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)]^-$, which may be stabilised by excess free PPh_3 in solution. Concomitantly $\text{P}^{\text{III}}\text{Ph}_3$ is oxidised to the P^{V} species: $[\text{AcO}-\text{PPh}_3]^+\text{X}^-$, which hydrolyses in the presence of trace water to $\text{O}=\text{PPh}_3$, AcOH and H^+ . $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)]^-$ is able to then oxidatively add to iodobenzene.

Critically, the identity of the species involved *e.g.* $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)]^-$ and $[\text{Ph}-\text{Pd}(\text{OAc})(\text{PPh}_3)_2]$ was often not directly structurally characterised but reasoned by circumstantial arguments, on the basis of electrochemical observations and ^{31}P NMR singlets, compared against authentic samples. Results detailed in Section 2.3 build on the understanding of speciation arising from $\text{Pd}(\text{OAc})_2/\geq 3$ equivalents of PPh_3 , using $[\text{Pd}_3(\text{OAc})_6]$, and provide further evidence for the characterisation of these species.

The effect of *para*-substituents on the phenyl groups of triphenylphosphines on both the rate of Pd^{II} reduction to Pd⁰ and the subsequent oxidative addition with iodobenzene was investigated kinetically.⁴⁷ Similarly to PPh₃ systems, triphenylphosphines of the form P(*p*-C₆H₄-Z)₃ (Z = -OMe, -Me, -Cl, -CF₃) were shown to instantaneously form *trans*-[Pd^{II}(OAc)₂(P(*p*-C₆H₄-Z)₃)₂] on exposure to DMF or THF solutions of Pd(OAc)₂ (Figure 20, Left). Notably, the more electron-withdrawing the *para*-substituent, the lower its measured electrochemical reduction potential and the faster the spontaneous formation of the Pd⁰ species from *trans*-[Pd^{II}(OAc)₂(P(*p*-C₆H₄-Z)₃)₂]. As with *trans*-[Pd^{II}(OAc)₂(PPh₃)₂] **47**, solutions of *trans*-[Pd^{II}(OAc)₂(P(*p*-C₆H₄-Z)₃)₂] resulted in the formation of Pd complexes over time. A positive linear Hammett relationship was recorded, with a reduction rate dependence measured to be proportional to the electron-withdrawing nature of the phosphine (*i.e.* rate, ν -CF₃ > -OMe), with a ρ -value of +0.9 (Figure 20). The positive ρ -value is indicative of a build-up of negative charge in the reduction rate-determining step,²²³ an observation consistent with attack of the phosphine by acetate during the process.

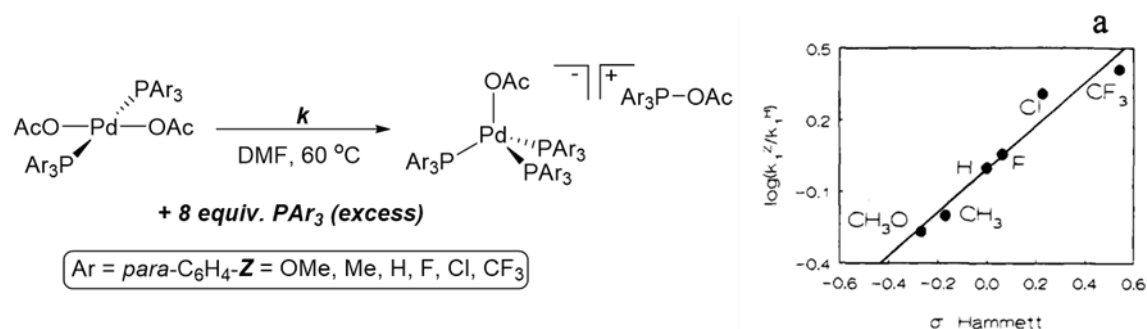


Figure 20 A positive linear Hammett correlation was observed between substituent and rate of formation of a Pd⁰ complex from [Pd^{II}(OAc)₂(P(*p*-C₆H₄-Z)₃)₂] which was generated from Pd(OAc)₂ and 10 equivalents P(*p*-C₆H₄-Z)₃. Reprinted with permission from Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A, *Organometallics* 1995, **14**, 1818-1826. Copyright 1995 American Chemical Society.

The effect of each *para*-substituent on the rate of oxidative addition reaction of the Pd⁰ complex to iodobenzene (Figure 21, Left) was measured. In this case, a negative linear Hammett correlation was made ($\rho = -2.4$, Figure 21), consistent with a build-up of positive charge in the transition state. Therefore, the more electron-rich the triarylphosphine used, the faster the rate of oxidative addition, a result of a more electron-rich Pd⁰-centre, due to σ -electron-donation from the more electron rich triarylphosphine ligands.

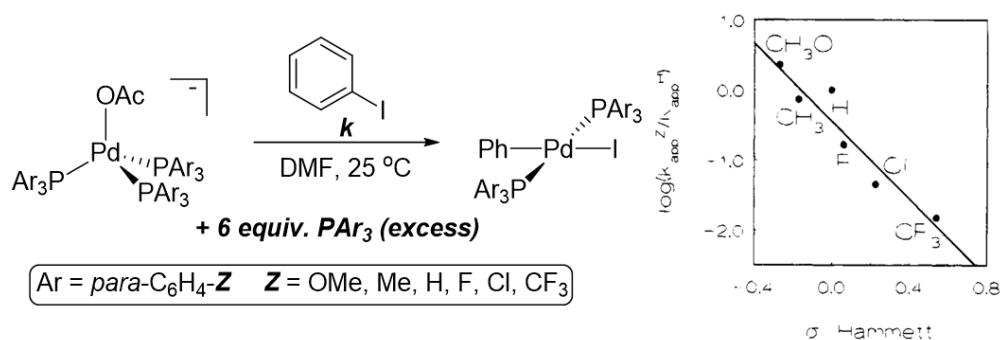


Figure 21 A linear Hammett correlation between substituent and rate of formation of a Pd^0 complex from $[\text{Pd}^{\text{II}}(\text{OAc})_2(\text{P}(\text{p-C}_6\text{H}_4\text{-Z})_3)_2]$. . Reprinted with permission from Amatore, C.; Carre, E.; Jutand, A.; M'Barki, *Organometallics* 1995, 14, 1818-1826. Copyright 1995 American Chemical Society.

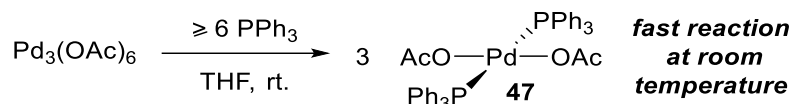
The acetate-assisted intramolecular reduction of tertiary phosphine ligated Pd^{II} complexes is a general phenomenon, occurring with related Pd^{II} complexes containing bidentate DPPP and BINAP ligands,⁶⁰⁻⁶¹ or dialkylbiaryl phosphine ligands.^{62, 145} Indeed, such activations have also been reported for other carboxylate-containing Pd^{II} salts, including $\text{Pd}(\text{acac})_2$, $\text{Pd}(\text{OTf})_2$ and $\text{Pd}(\text{TFA})_2$.²²⁴⁻²²⁷

The vast majority of Amatore and Jutand's studies were confined to systems using high ligand excesses (≥ 5 equivalents) relative to Pd. The report from 1992 showed, on reaction of $\text{Pd}(\text{OAc})_2$ with one equivalents of PPh_3 , that a clearly different species was formed, characterised by two sharp peaks in the ^{31}P NMR spectrum.⁴⁶ This species was formulated as $[\text{Pd}_2(\text{PPh}_3)_2(\text{OAc})_2\text{S}_y]^{n-}$, with 'solvent molecules (S_y) and acetate anions as ligands'. Other than the two ^{31}P NMR signals, no structural evidence, was presented to support this claim. However, this new species exhibited an electrochemical reduction peak, and could react with iodobenzene. Prior to *this research* there was no significant work done to investigate the activation of $\text{Pd}(\text{OAc})_2$ by one equivalent of PPh_3 . Thus, the situation where $\text{Pd}(\text{OAc})_2$ is activated by one or two equivalents of PPh_3 was hitherto not well understood. This observation is puzzling since many reported examples of catalytic $\text{Pd}(\text{OAc})_2 / n\text{PPh}_3$ applications in cross-coupling use a Pd: PPh_3 ratio of 1:2 – the primary reason for this is most likely due to a handing down of practical knowhow and experience from research groups involved in completed target-oriented syntheses.^{59, 197, 228-230} In order to get a better understanding of the formation, nature and reactivity of the catalytically-relevant species generated from $\text{Pd}(\text{OAc})_2/n\text{PPh}_3$ mixtures, it was decided to systematically investigate the effect of varying the Pd: PPh_3 ratio (*i.e.* the values of n) on active Pd speciation.

Results & Discussion

2.3. Reaction of Palladium(II) Acetate with ≥ 3 equivalents of Triphenylphosphine

Reaction of $[\text{Pd}_3(\text{OAc})_6]$ with six equivalents or greater of PPh_3 ($\text{Pd:P} = 1:\geq 2$) causes fast dissociation of the weakly-bound trimeric cluster to form *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** (Scheme 35).^{46, 49-50}



Scheme 35 Reaction of $[\text{Pd}_3(\text{OAc})_6]$ with ≥ 6 equivalents of PPh_3 results in its rapid phosphinolysis, forming *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** immediately at room temperature.

This was confirmed by immediate ^{31}P NMR spectroscopic analysis of THF- d_8 solutions of $[\text{Pd}_3(\text{OAc})_6]$ and 6, 9, 12 or 15 equivalents of PPh_3 , where a singlet resonance at δ_{P} 15.1 ppm was observed in each case (see below for further details).⁴⁶ Complex **47** appears as a yellow-green solid and is partially soluble in THF on formation from $[\text{Pd}_3(\text{OAc})_6]$ and ≥ 6 equivalents of PPh_3 . From a crude reaction solution of $[\text{Pd}_3(\text{OAc})_6]$ and exactly 6 equivalents of PPh_3 in THF, crystals of **47** grew, one of which was subjected to single crystal X-ray diffraction analysis (Figure 22).

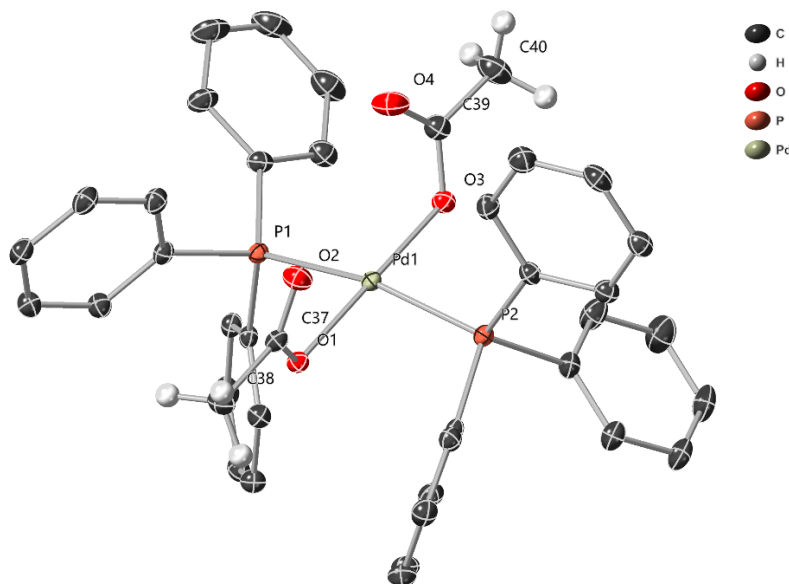
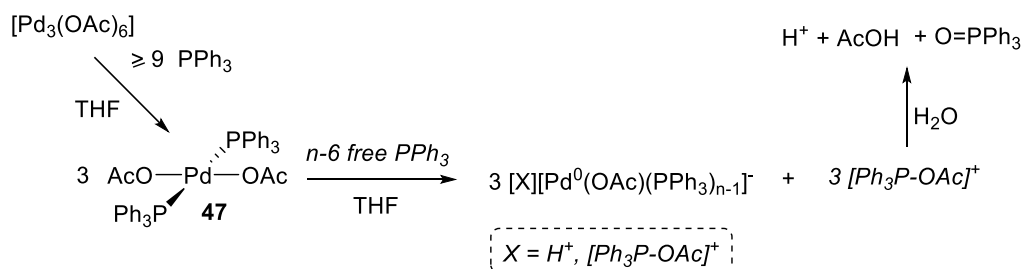


Figure 22 Structure of *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** obtained *via* XRD of a single crystal. Thermal ellipsoids set to 30% probability and the hydrogen atoms from the PPh_3 ligands have been omitted for clarity. Selected interatomic distances /Å: Pd1–P2 = 2.3414(6), P1–Pd1 = 2.3218(6) Pd1–O1 = 2.0249(18), Pd1–O3 = 2.0274(19). Selected interatomic angles /°: P1–Pd1–P2 = 168.25(2), O1–Pd1–O3 = 177.81(7), O1–Pd1–P1 = 84.77(5), O3–Pd1–P2 = 90.89(5), O3–Pd1–P1 = 93.93(6).

It can be seen (Figure 22) that **47** is a monomeric, approximately square planar Pd^{II} complex featuring two *trans*-acetate and two *trans*-PPh₃ ligands, although it is notable that the P-atoms lie slightly out with the Pd–O–P plane (P1–Pd1–P2 = 168.25(2)°), giving the structure a ‘butterfly’ conformation. It is of note that in **47** the Ph groups of the PPh₃ ligands are staggered around the P–Pd–P-bond axis. The acetate ligands lie on the same (*syn*) side of the square plane and are slightly staggered: dihedral angle C37–O1–O3–C39 = –25.664°. The mean Pd–P and Pd–O bond lengths of **47** lengths were 2.33 and 2.03 Å respectively. The Pd–P bond lengths parallel that of the bond length of the square planar complex *trans*-[PdCl₂(PPh₃)₂] (2.3399(9) Å).²³¹ *trans*-[Pd(OAc)₂(3,3,1-PPBN)₂] (PPBN = 9-phenyl-9-phosphabicyclononane), another approximately square planar *trans*-bis(phosphine)-Pd(OAc)₂ complex, reported by Edwards *et al.* contained slightly longer P–O (2.064(13) Å) and Pd–P (2.3483(13) Å) bond distances than **47**.²³² In that case, it is notable that, in contrast with **47**, the acetate ligands are orientated on opposite sides of the square plane, adopting an *anti*-conformation

While the next subsection (Section 2.4) deals with novel findings concerning speciation events when [Pd₃(OAc)₆] is reacted with exactly 6 equivalents of PPh₃ *i.e.* where no excess of PPh₃ is present relative to the *in situ*-generated **47**, this subsection discusses the reactivity of **47** generated by treatment of [Pd₃(OAc)₆] with ≥ 9 equivalents of PPh₃, from which stabilised Pd⁰ complexes are known to arise. A summary, as discovered by Amatore and Jutand, for the process whereby Pd⁰ complexes are formed from [Pd₃(OAc)₆] in the presence of ≥ 9 equivalents of PPh₃ is shown in Scheme 36 (see the previous section (2.2) for a more detailed discussion of prior literature concerning this process).



Scheme 36 Summary scheme for the formation of reduced (activated) species upon mixing [Pd₃(OAc)₆] and ≥ 9 equivalents of PPh₃ in THF.

Reaction of [Pd₃(OAc)₆] with 9 or 12 equivalents of PPh₃ at room temperature in dry THF-*d*₈ for 16 hours resulted in conversion of *in situ* formed **47** to a variety of species, as evident by ³¹P NMR spectroscopic analysis (Figure 23).

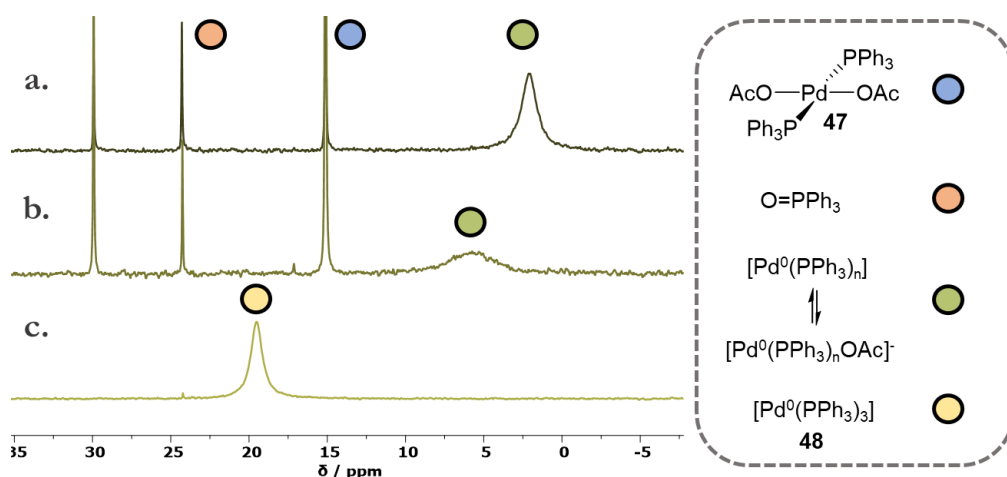
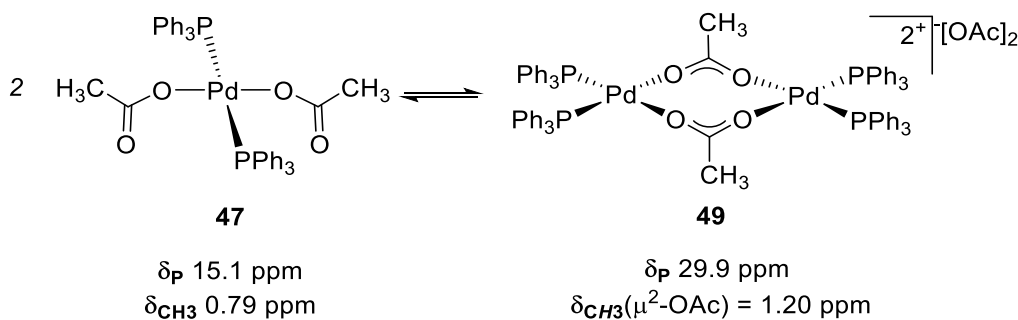


Figure 23 A stack of ^{31}P NMR spectra (202.5 MHz, 256 scans, referenced to 85% $\text{H}_3\text{PO}_4\{\text{aq}\}$) of the crude $\text{THF}-d_8$ reaction solution of $[\text{Pd}_3(\text{OAc})_6]$ with n equivalents of PPh_3 after 16 hours. (a.) $n = 12$ ($\text{Pd}:\text{P} = 1:4$). (b.) $n = 9$ ($\text{Pd}:\text{P} = 1:3$). (c.) A sample of authentic $[\text{Pd}^0(\text{PPh}_3)_3]$, isolated from complete reaction of $[\text{Pd}_3(\text{OAc})_6]$ and 12 PPh_3 .

In line with the findings by Amatore and Jutand (Section 2.2), a sharp ^{31}P NMR resonance at δ_{P} 15.1 ppm, representing unreacted **47**, was initially present under both regimes, indicating incomplete activation, under the conditions (a. & b., Figure 23).^{46, 233} Both reactions additionally featured broad resonances upfield of **47**, characterised as $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$, in exchange with free PPh_3 reproducing findings by Amatore and Jutand *et al.*^{46, 200} The $[\text{Pd}_3(\text{OAc})_6]/12 \text{ PPh}_3$ reaction mixture (a. Figure 23) exhibited a peak at δ_{P} 2.0 ppm ($\Delta\nu_{1/2} = 228 \text{ Hz}$), while the $[\text{Pd}_3(\text{OAc})_6]/9 \text{ PPh}_3$ mixture exhibited a broader peak at δ_{P} 5.7 ppm ($\Delta\nu_{1/2} = 666 \text{ Hz}$). It is clear therefore that greater excesses of PPh_3 result in more upfield ^{31}P NMR chemical shifts for PPh_3 , moving towards that of free PPh_3 ($\delta_{\text{P}} -4.6 \text{ ppm}$ in $\text{THF}-d_8$), a result of exchange between the Pd^0 -ligated and free PPh_3 environment.

Authentic $[\text{Pd}^0(\text{PPh}_3)_3]$ **48**, synthesised and isolated from the reaction of $[\text{Pd}_3(\text{OAc})_6]$ with 12 equivalents of PPh_3 (*vide infra*), could be used as a reference with which to compare the chemical shift of a relatively low coordinate Pd^0 - PPh_3 exchange (c. Figure 23). The resonance at δ_{P} 24.2 ppm was verified as $\text{O}=\text{PPh}_3$ by spiking the post-reaction solution with an authentic sample. Acetic acid (AcOH) was also evident in the post-reaction mixture, as validated by comparison with literature reported ^1H NMR data in $\text{THF}-d_8$.^{46, 234} A major singlet at δ_{P} 29.9 ppm (Figure 23) was tentatively assigned as the dicationic dimer of **47**, namely $[\text{Pd}(\mu_2\text{-OAc})(\text{PPh}_3)_2][\text{OAc}]_2$ **49** (Scheme 37). Although not reported by Jutand *et al.* this resonance has been reported by other workers investigating this system.²²¹⁻²²² It appears that **49** is favoured when there is less free PPh_3 present in the mixture, as the reaction proceeds, and the formation of monomeric **47** is disfavoured. If, however, the reaction is allowed to go to completion, both signals at δ_{P} 15.1 (**47**) and at δ_{P} 29.9 ppm were lost (below, Figure 25), indicating they are related and are both converted into the observed new species.



Scheme 37 Proposed structure of a Pd^{II} dimer complex: [Pd(μ²-OAc)(PPh₃)₂][OAc]₂ (**49**), likely participates in equilibrium with (**47**), as represented by observed ³¹P, ¹H NMR chemical shifts in a THF-*d*₈ solution.

The integration of a broad ¹H aliphatic-type resonance (δ_{H} 1.20 ppm) changes proportionally with that of the ³¹P resonance (δ_{P} 24.2 ppm) over the course of the reaction, supporting the notion that both resonances were on the same molecule. The broadness of this ¹H resonance at δ_{H} 1.20 ppm ($\Delta\nu_{1/2} = 8.4$ Hz), as well as that of the free acetate ¹H resonance at δ 1.90 ppm ($\Delta\nu_{1/2} = 10.2$ Hz), may indicate exchange with free acetate anions in solution. The chemical shift δ_{H} 1.20 ppm of this peak is characteristic of bridging acetate ligands in Pd^{II}-PPh₃-containing triaryl phosphine complexes.²³⁵

It is important to emphasise that both the reactions discussed above (Figure 23) were carried out in rigorously dried THF-*d*₈ and both feature an excess of free PPh₃ as a consequence of incomplete conversion of Pd^{II} to Pd⁰, which resulted in broadened, high-field resonances representing the Pd⁰ complexes in exchange with free PPh₃. Further light could be shed on this reactivity by monitoring the reaction by ³¹P NMR as a function of time. It was found that over time the integration of the peak representing **47** decreased over time, with this decrease ceasing approximately 140 minutes after reaction initiation. Simultaneously, the δ_{P} of the Pd⁰ complex was seen to increase as a function of the same time. This indicates that the reaction had reached equilibrium under the conditions after the time period. The integration of the peak at δ_{P} 15.1 ppm, representative of **47**, normalised relative to the first recorded spectrum (initially recorded *ca.* 8 minutes after mixing of [Pd₃(OAc)₆]/12 equivalents of PPh₃) was plotted against $\Delta\delta_{\text{P}}$ as a function of the time {Figure 24}).

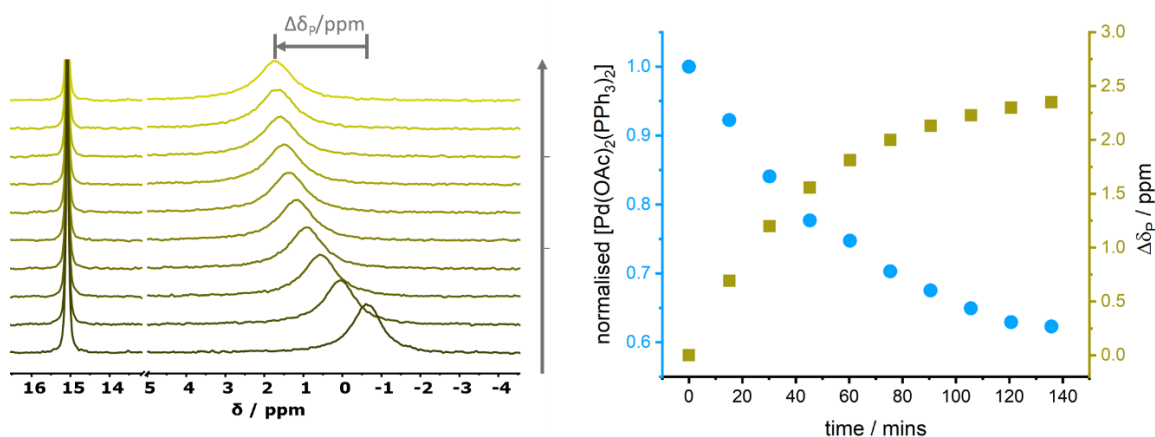


Figure 24 (Left) Stack of ^{31}P NMR (202.5 MHz, $\text{THF}-d_6$, 298 K) spectra collected from the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and PPh_3 (12 equiv.) showing change in *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ (**47**) and δ_{P} as functions of time. Note the excised region of the ^{31}P spectra between ~ 5 and 13 ppm. (Right) Graph of **47**, normalised to initial integral value and $\Delta\delta_{\text{P}}$ as functions of time.

The observation outlined above indicates that the ^{31}P chemical shift change is proportional to the concentration of ligated Pd^0 present in solution. The conventional way of quantifying a species by NMR, *i.e.* integration of a representative peak, is not valid in this case as the Pd^0 complex is in dynamic exchange with a fixed amount of PPh_3 in solution at 298 K. This reaction has shown that δ_{P} of an evolving Pd^0 complex in the presence of an excess of PPh_3 carries information concerning how far the reduction reaction has proceeded. Therefore, tracking reaction conversion by following changes in δ_{P} could potentially be of use for direct quantification the amount of Pd^0 in a solution under such a regime. It has also shown that under the dry conditions tested, the conversion of **47** to Pd^0 is incomplete after 140 minutes (see below for a discussion of the influence of the reaction conditions on the full conversion of **47**).

The reaction between $[\text{Pd}_3(\text{OAc})_6]$ and 9 equivalents of PPh_3 (three equivalents of phosphine *per* Pd) was heated to 60 °C in THF for 16 hours. Under these conditions, decomposition was evident by ^{31}P NMR spectroscopic analysis and a black suspension of Pd particles was observed. If, on the other hand, the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and 12 equivalents of PPh_3 (4 equivalents of phosphine *per* Pd) was similarly heated to 60 °C in THF for 16 hours, no visible Pd black particles were observed and the reaction solution appeared as a bright lemon-yellow solution, with the presence of $[\text{Pd}(\text{OAc})(\text{PPh}_3)_3]^-$ evident by ^{31}P and ^1H NMR. Clearly, at 60 °C, in THF, the reduced reaction product of $[\text{Pd}_3(\text{OAc})_6]$ with 12 equivalents of PPh_3 is more stable than that with 9 equivalents of PPh_3 . This is a result of the increased stability of the *tris*- PPh_3 -ligated complex $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_3]^-$ complex *vs.* that of the *bis*- PPh_3 -ligated complex $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_2]^-$. ^{31}P NMR spectroscopic analysis of this solution showed near complete consumption of **47** and a broad peak at δ_{P} 20.4 ppm, representing the $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_3]^-$ species as well as $\text{O}=\text{PPh}_3$ (Figure 25).

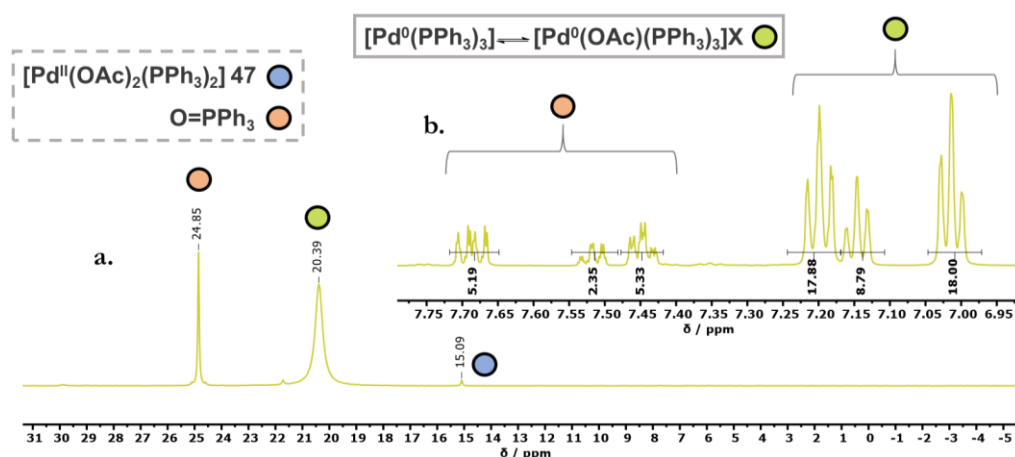


Figure 25 NMR spectroscopic analysis of a solution of $[\text{Pd}_3(\text{OAc})_6]$ and 12 PPh_3 which had been stirred overnight at room temperature at 60 °C. (a.) ^{31}P NMR (202.5 MHz) (b) ^1H NMR (500 MHz) expansion of the aromatic region.

Notably, integration of the phenyl resonance in the ^1H NMR spectrum showed a ratio of approximately 1:1 with respect to the amount of $\text{O}=\text{PPh}_3$ to $[\text{Pd}^0(\text{PPh}_3)_3(\text{OAc})^-]$, confirming the concomitant formation of approximately one equivalent of $\text{O}=\text{PPh}_3$ *per* reduced Pd atom.⁴⁶ Layering the THF reaction solution with hexane (1:4 THF/hexane) and overnight storage at $-18\text{ }^\circ\text{C}$, under an atmosphere of N_2 , resulted in formation of large bright yellow crystals (up to 1 mm diameter). These single crystals were subjected to X-ray diffraction analysis which showed them to be the neutral, 16-electron Pd^0 complex $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** (Figure 26).

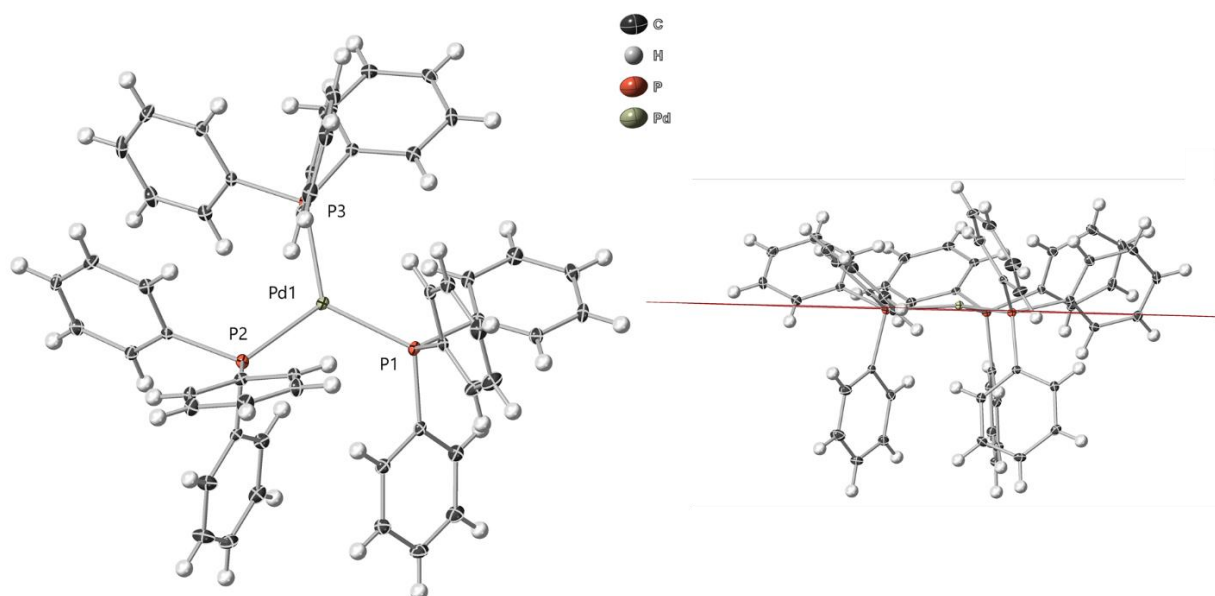
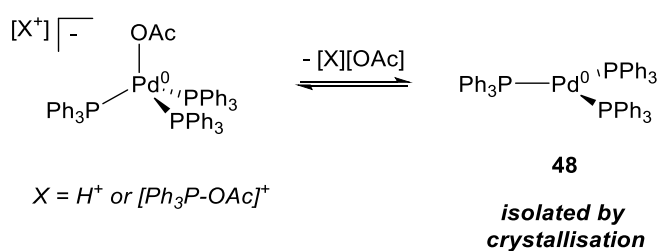


Figure 26 Two different perspectives of the X-ray diffraction structure of a single crystal of $[\text{Pd}^0(\text{PPh}_3)_3]$ **48**, obtained from the complete reaction of $[\text{Pd}_3(\text{OAc})_6]$ with 12 equivalents of PPh_3 . (Left) View from along the principle axis, (Right) view across a calculated plane through the Pd and P atoms. Thermal ellipsoids have been set to 30% and hydrogen atoms have been modelled as spheres. Two molecules of THF and one molecule of hexane have been omitted for clarity. Selected interatomic distances /Å $\text{Pd1-P3} = 2.3119(6)$, $\text{P1-P2} = 2.3156(6)$, $\text{Pd1-P1} = 2.3084(6)$. Selected interatomic angles /°: $\text{P3-Pd1-P2} = 114.88(2)$, $\text{P1-Pd1-P3} = 126.09(2)$, $\text{P1-Pd1-P2} = 117.11(2)$.

The crystal structure of **48** (Figure 26) shows the PPh₃ ligands to be arranged in a trigonal conformation around the Pd centre, in line with previous crystallographic data for this complex.²³⁶ As demonstrated by the high variation in P–Pd–P bond angle away from 120°, and the significant error in the calculation of a plane through the Pd and P atoms (0.02578 Å² n), the complex deviates slightly from planarity, towards a trigonal pyramidal geometry. Interestingly, this slight deviation from planarity is not present in the analogous, Pd⁰ complexes: [Pd⁰(P(3,5-(CF₃)₂C₆H₃)₃)₃], [Pd⁰(P(2-*thienyl*)₃)₃] or [Pd⁰(PCyPh₂)₃].²³⁷⁻²³⁹ There is a relatively short distance between modelled ortho-hydrogen atoms of the phenyl rings and the Pd centre (2.9500 Å), blocking its face on one side of the Pd-3P plane. The adjacent phenyl groups of the proximal PPh₃ ligands are facially aligned in propeller-blade-like solid-state structure. The Pd–P bond length (2.3120(6) Å) is notably shorter than that of the related tetrahedral complex [Pd⁰(PPh₃)₄] (2.430(±0.14) Å).²⁴⁰

Compound **48** was isolated from the [Pd₃(OAc)₆]/12 PPh₃ mixture by crystallisation and hence characterised by other means. ³¹P NMR analysis indicated a singlet at δ 19.5 ppm in THF-*d*₈. LIFDI mass spectral analysis of the isolated material showed presence of [Pd(PPh₃)₃]⁺ (m/z 892.1772) as well as the elusive 14 electron-bis-phosphine-ligated complex [Pd⁰(PPh₃)₂]⁺ (m/z 630.0835), both featuring the expected isotopic distribution pattern, indicating the presence of both species in solution.

Although the species isolated by crystallisation was [Pd⁰(PPh₃)₃] **48**, this does not rule out the observation by Amatore and Jutand, that acetate plays a role at the complex under this regime (see Section 2.2).²⁰⁰ It is likely that in solution, the acetate ligand is in dynamic equilibrium with the protons which are released after hydrolysis of phosphonium acetate, thus, during crystallisation, **48** is trapped out and removed from this equilibrium, leaving acetic acid in the mother liquor. (Scheme 38).



Scheme 38 Equilibrium structures of reduced Pd⁰ species formed after full reaction of [Pd₃(OAc)₆] with 12 PPh₃.

Reaction of [Pd₃(OAc)₆] with 15 equivalents of PPh₃ in THF under rigorous Schlenk conditions, with freshly distilled and rigorously dried THF resulted in only minimal conversion to the [Pd⁰(OAc)(PPh₃)_n][−] complex as observed by ³¹P NMR spectroscopy, even after seven days of reaction at reflux (upper spectrum, Figure 27, below). Indeed, undissolved yellow-green **47** powder was clearly visible in the stirred suspension after this time. The reaction mixture was cooled to 23 °C, deoxygenated

H₂O (ca. 20 μ L, 5.5 equivalents, with respect to Pd) was added and the resulting mixture was stirred at room temperature for a further 3 hours. After this time the reaction appeared as a yellow solution and ³¹P NMR spectral analysis showed complete conversion of **47** to [Pd⁰(OAc)(PPh₃)_n][–] complex as evident by a broad peak at 13.5 ppm. (lower spectrum, Figure 27). O=PPh₃ was again observed as the major biproduct of the redox process under these conditions.^f

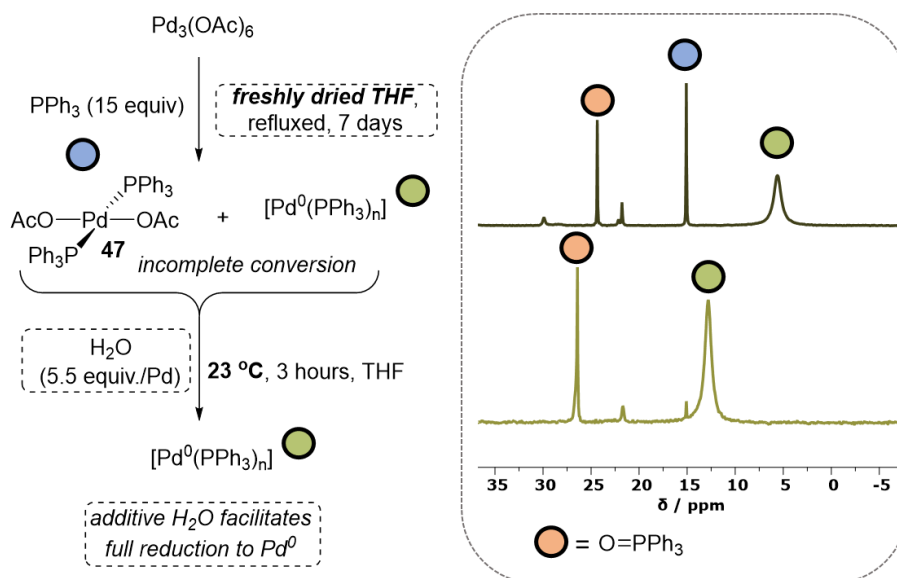


Figure 27 Reaction of [Pd₃(OAc)₆] with 15 PPh₃ in freshly dried and distilled THF. ³¹P NMR analysis (upper in stack: 202.5 MHz, 256 scans THF, unlocked) of a sample taken after 7 days showed incomplete conversion of *in situ*-formed **47**. (lower stack) After addition of H₂O and subsequent analysis of a sample, near complete conversion of **47** to [Pd⁰(PPh₃)_n(OAc)][–] was evident after 3 hours. O=PPh₃ was seen as a major biproduct of the redox process.

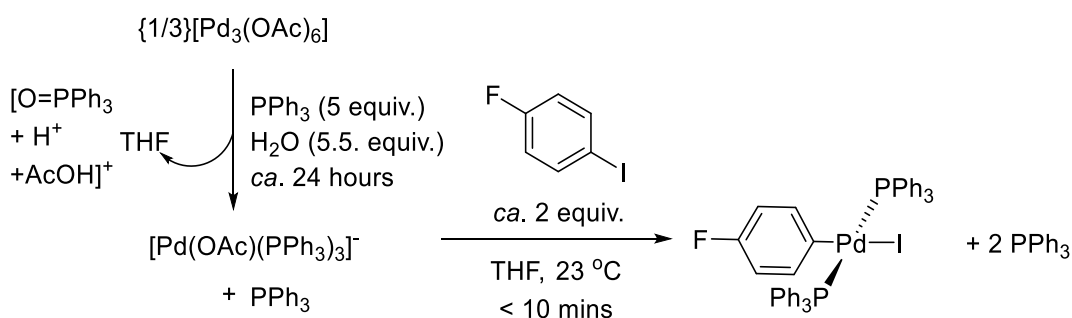
This finding indicates that H₂O (either adventitious or additive) can have a crucial role in the reduction of [Pd(OAc)₂(PPh₃)₂] **47** to [Pd⁰(PPh₃)_n(OAc)][–], likely by driving the process of oxidation of PPh₃ to O=PPh₃, *via* [Ph₃P–OAc]⁺, during the intramolecular reduction.⁶¹ It is therefore likely that the incomplete reactions reported in Figure 23 Figure 24 (*vide supra*), which were carried out in rigorously dried THF-*d*₈ were limited by the quantity of trace adventitious H₂O. The finding that H₂O can enhance reduction and activation of Pd^{II} salts is in line with studies on reduction and activation of other Pd^{II} complexes. Shortly after Amatore and Jutand's initial study of Pd(OAc)₂ activation by PPh₃, Ozawa *et al.* found additive, known amounts of H₂O to be required for the analogous reduction/activation of Pd(OAc)₂ by BINAP in benzene.⁶⁰ In the same study it was demonstrated, using isotopic labelling, that O from additive H₂O directly oxidised the phosphine. Subsequently, Amatore, Jutand *et al.* discovered an accelerative role of H₂O in analogous activation of Pd(OAc)₂ by the bidentate phosphine DPPP.⁶¹ The same group found that trace H₂O in the reaction system was necessary for the room temperature

^f The ³¹P NMR chemical shift of O=PPh₃ was demonstrated to migrate to lower field as a function of the quantity of H₂O present. This phenomenon is likely a result of hydrogen-bonding interaction between H₂O and the oxide resulting in a change in the electronic environment at phosphorus.²⁴¹

reduction of $[\text{PdCl}_2(\text{PPh}_3)_2]$ to $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** under Sonogashira-type cross-coupling reaction conditions, in the presence Hünig's base (See section 1.2.2 for further details).⁵¹⁻⁵² It is therefore a fairly general observation that H_2O can have a crucial accelerative effect on Pd^{II} complex reduction and catalyst activation in the presence of tertiary phosphines. Future work might elucidate the precise role of H_2O in the activation of **47**. The reason why this critical role for H_2O was not previously delineated is unclear, however the majority of reactions performed by Amatore and Jutand were performed in DMF and with additive salts (used as electrolytes) both of which can be quite challenging to get rigorously dry. It is therefore likely the reaction systems they used were contaminated with significant quantities of adventitious H_2O .^{46-47, 200}

The Oxidative Addition Reaction of $[\text{Pd}^0(\text{PPh}_3)_3(\text{OAc})]^-$ and *para*-Fluoroiodobenzene

To further confirm the presence of a Pd^0 complex, *para*-fluoroiodobenzene (*ca.* 2 equivalent excess with respect to Pd initially added) was added to the crude solution of $[\text{Pd}^0(\text{PPh}_3)_3(\text{OAc})]^-$ (Figure 27), generated from the complete reaction of $[\text{Pd}_3(\text{OAc})_6]$ with 15 equivalents of PPh_3 (Pd:P = 1:5) at room temperature in the presence of additive H_2O (Scheme 39).



Scheme 39 Conditions for the reaction of the crude mixture of $[\text{Pd}^0(\text{PPh}_3)_3(\text{OAc})]^-$, generated from complete reaction of $[\text{Pd}_3(\text{OAc})_6]$ with 15 equivalents of PPh_3 , and *para*-fluoroiodobenzene.

This process resulted in a facile oxidative addition reaction (complete in < 8 minutes) of the Pd^0 centre complex into the C–I bond, forming *trans*- $[(4\text{-F-C}_6\text{H}_4)\text{Pd}^{\text{II}}\text{I}(\text{PPh}_3)_2]$ **51** with release of free PPh_3 into the solution, as evident by ^{31}P NMR and ^{19}F spectroscopic analysis (a, Figure 28). $\text{O}=\text{PPh}_3$, a remnant from the redox activation of $[\text{Pd}_3(\text{OAc})_6]$ to active Pd^0 was additionally present in solution.

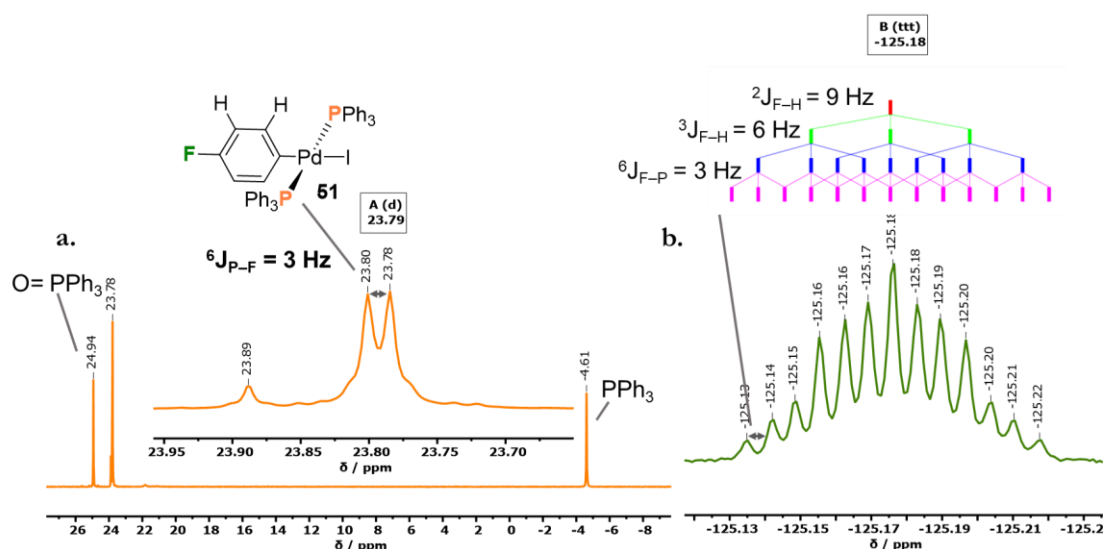


Figure 28 NMR spectra as collected after addition of *para*-fluoroiodobenzene (*ca.* 2 equiv.) to a solution of [Pd(OAc)(PPh₃)₃][−] and *para*-fluoroiodobenzene in THF. ³¹P NMR externally referenced to H₃PO₄ in H₂O (85% [w/v]). (a.) ³¹P NMR spectrum (202.5 MHz) unlocked and externally referenced to H₃PO₄ in H₂O showing an expansion of peak representing **51** (b.) ¹⁹F NMR (476 MHz) expansion of peak representing **51**, accounting for observed multiplicity.

The ³¹P NMR spectrum (202.5 MHz) of the crude reaction mixture showed a doublet, indicating P–F coupling with a J_{P-F} of 3.4 Hz. Matched J -values for $^6J_{P-F}$ and $^6J_{F-P}$ indicates through bond coupling between P and F. Analysis of the same solution by ¹⁹F NMR (476 MHz) resonances showed a multiplet signal (δ_F −125.2 ppm), featuring an intensity pattern of 13 members of the form 1:2:3:6:7:8:10:8:7:6:3:2:1, each separated by 3 Hz (Figure 28). This 13-membered intensity pattern stems from coincident coupling constants of arising from $^2J_{F-H} = 9$ Hz, $^3J_{F-H} = 6$ Hz and $J_{F-P} = 3$ Hz (see J -coupling tree, b. Figure 28). Matched J -values for $^6J_{P-F}$ and $^6J_{F-P}$ (3 Hz) confirms the presence of long-range coupling between P and F in this compound. This observation is in line with the structure of the oxidative addition product being *trans*-[(4-F-C₆H₄)Pd^{II}(I)(PPh₃)₂] **51**. Indeed, a single crystal of **51** was grown from the crude THF solution by carefully layering it with hexane (1:5 THF/hexane [v/v]) (Figure 29).

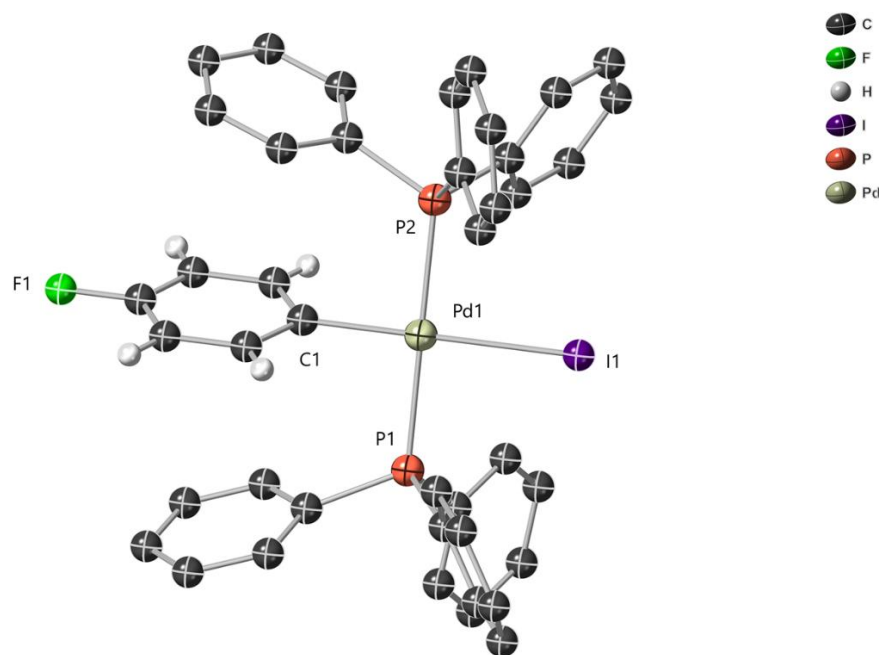


Figure 29 Structure, obtained by X-ray diffraction, of a single crystal of *trans*-[(4-F-C₆H₄)Pd^{II}(I)(PPh₃)₂] (**51**) obtained from the complete reaction of [Pd(OAc)(PPh₃)₃][−] and *para*-fluoroiodobenzene. Thermal ellipsoids set at 30%. Selected interatomic distances/Å: Pd1–P1 = 2.3176(5), Pd1–I1 = 2.7084(3), C1–Pd1 = 2.029(3). Selected interatomic angles/°: P1–Pd1–I1 = 89.857(14), C1–Pd1–P1 = 90.143(14).

The crystal structure showed that the complex was almost perfectly square planar around the Pd centre and featured an iodide ligand trans to a *para*-fluoroiodobenzene ligand, supporting the ³¹P and ¹⁹F NMR data collected. The crystal structure of **51** was isostructural to the related *trans*-[(Ph)Pd^{II}(I)(PPh₃)₂], reported by Grushin *et al.*, which featured similar bond lengths and angles with Pd–I, Pd–C and Pd–P bond lengths being 2.7011(8), 2.029(4) and 2.338(1) Å, respectively, indicating that the *para*-fluorine substituent on the phenyl ligand does not significantly influence the structure.²⁴² On close examination of the extended crystal structure, it was seen that F and I were perfectly aligned intermolecularly along the I–Pd–F axis (interatomic distance 3.995 Å) indicating some interaction between F and I during the crystallisation process: P–Pd = 2.7011(8). The oxidative addition product **51** mirrors previous observations by Amatore and Jutand on the facile formation of *trans*-[(Ph)Pd^{II}(I)(PPh₃)₂] upon adding iodobenzene to solutions of Pd⁰ complexes generated from a complete reaction of [Pd(OAc)₂] with 10 equivalents of PPh₃.⁴⁶

The Reaction Between [Pd₃(OAc)₆] and 9 Equivalents of PPh₃ (Pd:P = 1:3)

Attempts were made to isolate and characterise the Pd⁰ complex formed from reaction of [Pd₃(OAc)₆] and 9 equivalents of PPh₃ (Pd:P = 1:3), which was described by Amatore and Jutand as [Pd⁰(PPh₃)₂(OAc)][−].⁴⁸ To this end, [Pd₃(OAc)₆] was stirred with 9 equivalents of PPh₃ in THF, before

H₂O (20 µL, 5.5 eq / Pd) was added (to accelerate Pd⁰ complex formation, *vide supra*) and the resulting mixture was stirred at room temperature for 2 hours. After this time, a sample of the reaction mixture was subjected to ³¹P NMR spectroscopic analysis (Figure 30).

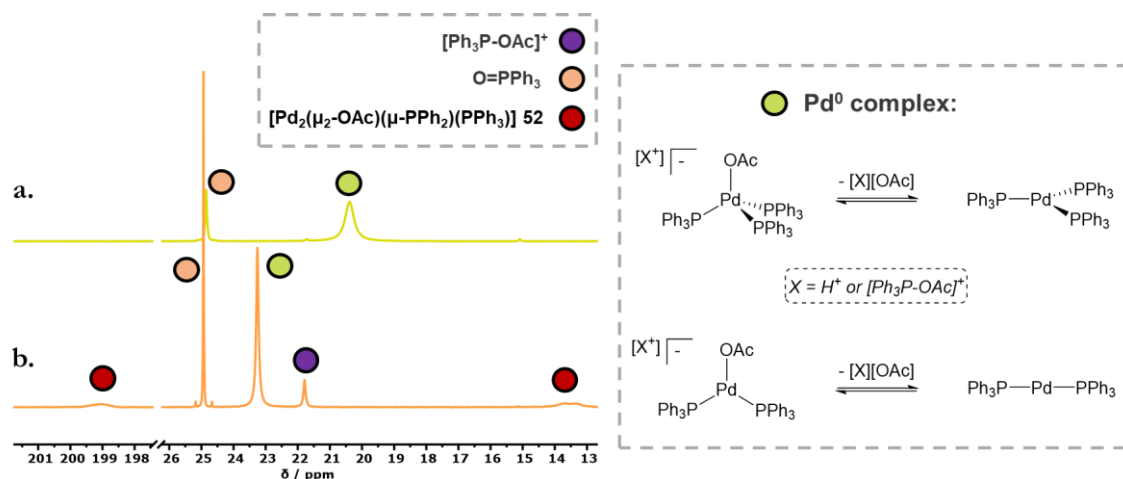


Figure 30 ³¹P NMR spectra (202.5 MHz, unlocked, THF, externally referenced to H₃PO₄ in H₂O {85% w/v}) of samples taken directly from solutions of [Pd₃(OAc)₆]/nPPH₃ after 2 hours of reaction at room temperature. (a.) Where n = 12, a [Pd⁰(PPh₃)_n] complex arises, δ_P of which is upfield of that in (b.) where n = 9.

It can be seen (Figure 30, b.) that *in situ*-formed **47** had completely disappeared (no peak evident at δ_P 15.1 ppm) and a broad peak at δ_P 23.3 ppm (Δν_{1/2} = 16.9 Hz) had appeared, which was assigned as the Pd⁰ complex [Pd⁰(PPh₃)₂(OAc)]⁻. This resonance is significantly downfield with respect to the resonance for the Pd⁰ complex generated from [Pd₃(OAc)₆] and 12 equivalents of PPh₃ where δ_P = 23.3 ppm (Δν_{1/2} = 64.8 Hz) (Pd:P = 1:4) (a. Figure 30). The reduced peak broadness and increased chemical shift in the [Pd₃(OAc)₆]/ 9 equivalents of PPh₃ system, compared with that of the [Pd₃(OAc)₆]/ 12 equivalents of PPh₃ system is consistent with the lack of exchange with free PPh₃. This observation, taken with the known starting stoichiometry points supports the identity of this species being the low coordinate complex [Pd⁰(PPh₃)₂], or that in exchange with an acetate anion [Pd⁰(PPh₃)₂(OAc)]⁻, after full conversion of **47**. Concomitant formation of O=PPh₃ was observed in addition to [Ph₃P–OAc]⁺ were represented by peaks at δ 24.9 and 21.8 ppm, respectively. Two minor, broad resonances, at δ_P 199.1 and 13.5 ppm species respectively represent the Pd^I dinuclear complex [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52**.^g

The diradical cation of m/z [Pd(PPh₃)₂(OAc)]⁺ [M-2e]⁺ was observed by LIFDI mass spectral analysis (m/z 689.06, with the expected isotopic distribution pattern) supporting ligation by acetate in solution.^h

^g **52** is a newly characterised molecular species and it is discussed in detail in Section 2.4.

^h Signals representing [Pd⁰(PPh₃)₃] were observed in the same LIFDI-MS spectrum. [Pd^{II}(OAc)(PPh₃)₂]⁺ could form by loss of acetate from trace, unreacted *trans*-[Pd^{II}(OAc)₂(PPh₃)₂] **47**, however a similarly conducted LIFDI-MS analysis of an authentic sample of **47** did not lead to detection of [Pd(OAc)(PPh₃)₂]⁺.

Robust efforts were made to isolate the major Pd⁰ species by crystallisation and thus interrogate the structure of this species. Upon carefully layering the post reaction THF solution with hexane and storing at –18 °C, overnight, a single yellow crystal was picked from the dark red mixture. The crystal was subjected to X-ray diffraction analysis, however, and thusly identified as [Pd⁰(PPh₃)₃] **48**. The observation of **48** may indicate that the low-coordinate Pd⁰ complexes [Pd⁰(OAc)(PPh₃)₂][–] or [Pd⁰(PPh₃)₂] are too unstable in solution even at –18 °C to be isolated under these conditions. The solution complex may undergo disproportionation to Pd aggregates, or the Pd^I dinuclear complex (a solution component, as detected by ³¹P NMR) **52** and stable **48** (Figure 31).

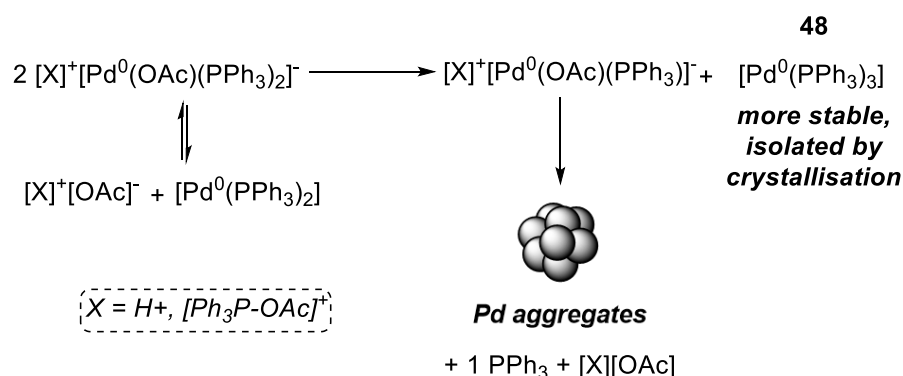


Figure 31 A plausible mechanism by which [Pd⁰(PPh₃)₃] could form *via* disproportionation of *e.g.* two equivalents of [Pd⁰(OAc)(PPh₃)₂][–] to form one equivalent of [Pd(OAc)(PPh₃)₂][–] which may rapidly degrade to Pd particles.

The work reported in this section has built on the findings by Amatore and Jutand *et al.* concerning the formation and reactivity of Pd⁰ complexes generated from reactions of [Pd₃(OAc)₆] and ≥ 9 equivalents of PPh₃. The crystal structure of the complex *trans*-[Pd(OAc)₂(PPh₃)₂] **47**, formed by PPh₃-induced dissociation of [Pd₃(OAc)₆] was recorded for the first time. Mixing [Pd₃(OAc)₆] and 9, 12 or 15 equivalents of PPh₃ results in formation of [Pd⁰(OAc)(PPh₃)_{*n*-3}][–]-type complexes as characterised by ³¹P NMR spectroscopic analysis and, for the first time in these systems, LIFDI-MS. ³¹P NMR was also used to track the progress of Pd⁰ complex formation at expense of its precursor **47**. [Pd⁰(OAc)(PPh₃)₃][–], generated from full reaction of [Pd₃(OAc)₆] with 15 PPh₃ was shown to undergo rapid oxidative addition into the C–I bond of *para*-fluoroiodobenzene to form *trans*-[(4-F-C₆H₄)Pd^{II}(I)(PPh₃)₂] **51**, which was characterised by multinuclear NMR spectroscopy and a single crystal X-ray diffraction study. [Pd⁰(PPh₃)₃] **48** was isolated and characterised by X-ray crystallography after quantitative reaction of [Pd₃(OAc)₆] and 12 equivalents of PPh₃. For the first time, evidence was presented for the necessity for H₂O, either adventitious or purposely added, to be present for this intramolecular reduction and activation to occur. [Pd⁰(OAc)(PPh₃)₂][–], the reduced product of the reaction of [Pd₃(OAc)₆] and 9 equivalents of PPh₃ (Pd:P = 1:3) was characterised in solution by ³¹P NMR spectroscopic analysis for the first time.

2.4. Reaction of Palladium(II) Acetate with Exactly 2 Equivalents of Triphenylphosphine per Palladium

Stark qualitative differences in speciation behaviour were realised when $[\text{Pd}_3(\text{OAc})_6]$ was treated with 6 equivalents of PPh_3 (*i.e.* a Pd:P ratio of 1:2), compared to the reactions of $[\text{Pd}_3(\text{OAc})_6]$ with ≥ 9 equivalents of PPh_3 . A variety of different molecular species were identified to arise during this process. Treatment of $[\text{Pd}_3(\text{OAc})_6]$ with 6 equivalents of PPh_3 at 25 or 40 °C in dry $\text{THF-}d_8$ was seen to result in the formation of an altogether different reduced (activated) species. After 16 hours at 25 °C, for example, the solution was interrogated by ^{31}P NMR spectroscopy (Figure 32, c.). Analogous reactions between $[\text{Pd}_3(\text{OAc})_6]$ with 9 and 12 equivalents of PPh_3 (performed under otherwise identical conditions) are given, for comparison (Figure 32, a and b). Under the conditions, unreacted *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** (δ_{P} 15.1 ppm) remained, along with $\text{O}=\text{PPh}_3$ (δ_{P} 24.2 ppm, validated by spiking the mixture an authentic sample) and $[\text{Ph}_3\text{P}-\text{OAc}]^+[\text{X}]^-$ (δ_{P} 21.8 ppm).⁴⁶ The resonance at δ_{P} 29.9 ppm has been tentatively assigned as **49** the dimer of **47**: $[\text{Pd}^{\text{II}}(\mu_2-\text{OAc})_2(\text{PPh}_3)_2][\text{OAc}]_2$.ⁱ In this case, broad resonances representing $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$ -type complexes, as observed in the reaction of $[\text{Pd}_3(\text{OAc})_6]$ with ≥ 9 equivalents of PPh_3 , were notably absent.

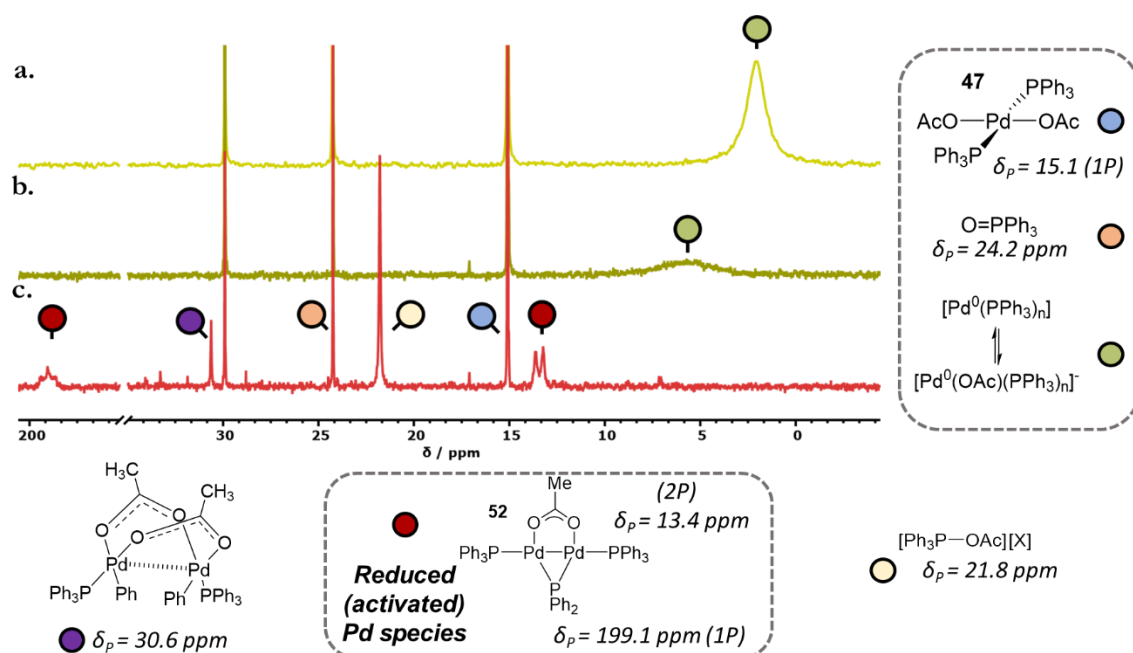


Figure 32 Stack of ^{31}P NMR spectra (202.5 MHz, 256 Sc, $\text{THF-}d_8$ referenced to an external sample of H_3PO_4 {aq, 85% [w/v]}) of the crude reaction mixtures of $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ under the same conditions, after a 16 hour reaction time at 25 °C (a.) $[\text{Pd}_3(\text{OAc})_6]/12\text{PPh}_3$ (b.) $[\text{Pd}_3(\text{OAc})_6]/9\text{PPh}_3$ and (c.) $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$, showing the identities different species in each respective mixture.

ⁱ See the previous section for a discussion concerning the tentative structural assignment of **49**.

A major new species was evident by an intriguing phosphido-type, low-field resonance (δ_P 199.1 ppm), coupled to a higher field phosphine-type doublet (δ_P 13.4 ppm). This species was subsequently characterised as the Pd^I dinuclear complex $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** (see section 2.4.1 for a deeper discussion of the characterisation of this complex). Additionally, the singlet at δ_P 30.6 ppm was characterised as the phenyl-ligated Pd^{II}-dimer complex $[\text{Pd}^{\text{II}}(\mu_2\text{-O}_2\text{-OAc})(\text{Ph})(\text{PPh}_3)]_2$ **53** (see section 2.4.1 for discussion on the characterisation of this complex).

The influence of the piperidyl ligand in the formation and behaviour of **52** from the piperidyl derivative of $[\text{Pd}_3(\text{OAc})_6]$: *trans*- $[\text{Pd}^{\text{II}}(\text{OAc})_2(\text{N-piperidyl})_2]$ in the presence of PPh_3 is discussed in section 2.4.3.

A GC-EI mass spectrometric analysis was carried out on an aliquot of the same crude post reaction solution, which detected benzene, biphenyl, and *ortho*-terphenyl as products of this reaction (Figure 33). The phenyl group observed in benzene, biphenyl and *ortho*-terphenyl have most likely been formed by protonation or reductive elimination of Pd-Ph complexes formed after the cleavage of PPh_3 which had occurred during the formation of the phosphido-ligand of **52**.

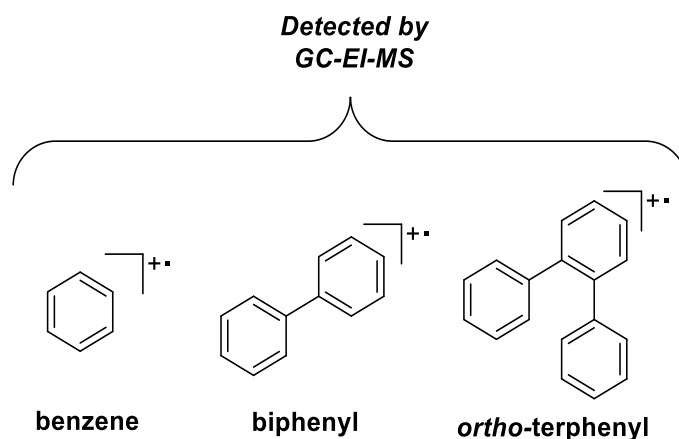


Figure 33 Structures of organic phenyl-containing compounds detected by GC-EI-MS from the $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ crude, post-reaction mixture.

2.4.1. Isolation and Characterisation of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52**

After complete consumption of *trans*- $[\text{Pd}^{\text{II}}(\text{OAc})_2(\text{PPh}_3)_2]$ **47**, when generated from $[\text{Pd}_3(\text{OAc})_6]$ with 2 equivalents of PPh_3 , the THF reaction solution was carefully layered with hexane (THF/hexane = 1:4 [v/v]) and subsequently stored at -18°C resulting in the growth of bright red single crystals which were subjected to X-ray crystallographic analysis. The single crystal's structure was confirmed as a Pd^I dinuclear species $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** (Figure 34).

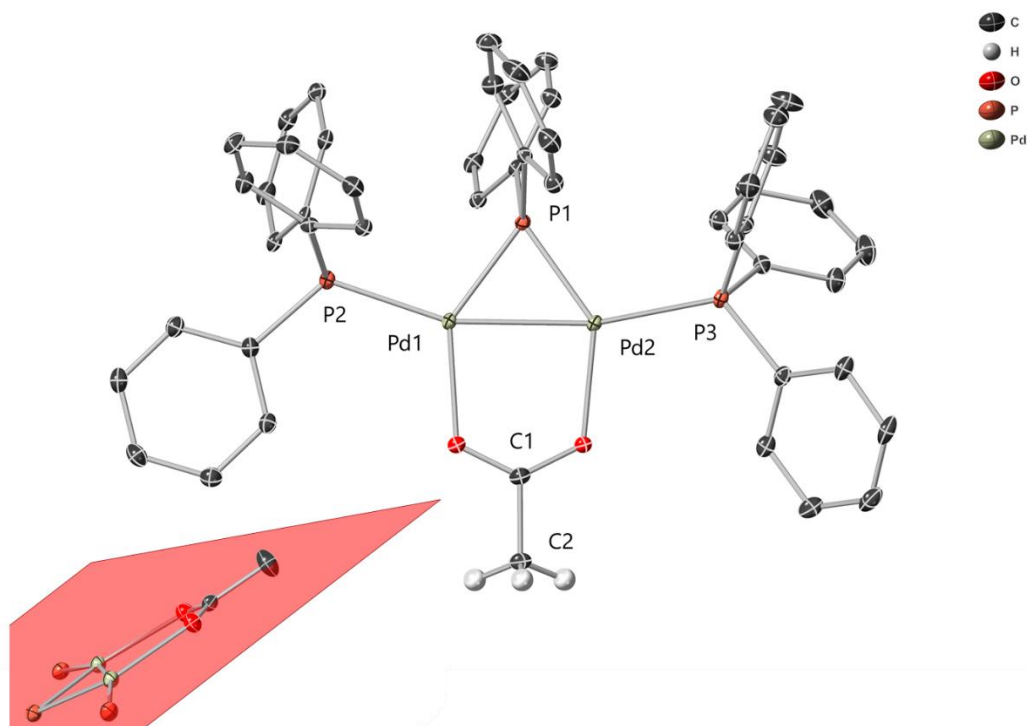


Figure 34 Structure, obtained by single crystal X-ray diffraction of the Pd^I dinuclear complex [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52**. Thermal ellipsoids set to 30%. H-atoms of PPh₃ ligands have been omitted for clarity. Selected interatomic distances /Å Pd1–Pd2=2.5958(3), P1–Pd1=2.2083(7), P1–Pd2=2.2062(7), P2–Pd1=2.3003(7) P3–Pd2=2.3001(7), O1–Pd1=2.2069(18) O2–Pd2=2.1764(18). Selected interatomic angles /°: Pd2–P1–Pd1=72.03(2), P2–Pd1–Pd2=162.041(19), P3–Pd2–Pd1=167.21(2), O2–Pd2–Pd1=85.35(5). Bottom-left: showing a plane (pink) calculated through Pd, P, C and O atoms of the complex (sum-of-squares error for the plane 0.04423 Å²/n.)

It can be seen that the crystal structure **52** is a Pd dimer, with the two Pd centres bridged by one μ-diphenylphosphido and one μ₂-1,3-acetato ligand and each Pd capped with a κ-PPh₃ ligand. Although each of the two Pd atoms of **52** are formally in the +1-oxidation state, the complex is diamagnetic, as a result of a bonding interaction between Pd^I centres. A Pd–Pd bond is indicated by the Pd distance being 2.5958(3) Å, which is shorter than the sum of two Pd van der Waals radii²⁴³ and typical of Pd^I–Pd^I bonding interactions.^{146, 148, 244–245} For example, a comparable dicyclohexylphosphido-bridged, dicyclohexylbiaryl ligand-stabilised Pd^I dinuclear complex **13b** reported by Bedford *et al.* has a Pd^I–Pd^I distance of 2.6076(4) Å (Figure 35).¹⁴⁴ Similarly di-*tert*-butylphosphido bridged Pd^I dimer **13**, reported by Jones *et al.* features a Pd^I–Pd^I bond length of 2.571(2) Å (Figure 35).¹⁴⁷

Diamagnetism, and the presence of a Pd^I–Pd^I bonding interaction in **52** was additionally supported by DFT calculations (Figure 38, below). The Pd and P atoms, as well as the core of the μ₂-1,3-acetato ligand (O and C atoms) lie, to a fair approximation, on the same plane (sum-of-squares error for the plane: 0.04423 Å²/n) (Figure 34). Additionally, the Pd–Pd bond length is significantly shorter than the

two μ_2 -1,3-acetato-bridged Pd^{II} dimeric complexes **53** (Section 2.4.2) and **64** (Section 2.6): 3.0610(3) & 3.0115(4) Å, respectively.

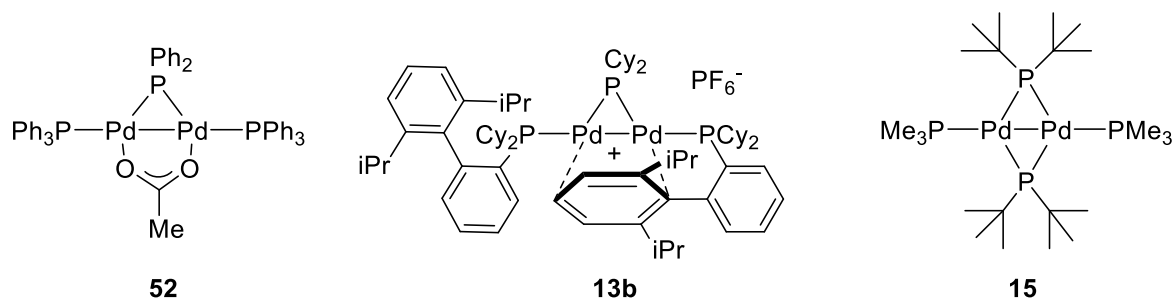


Figure 35 The chemical structure **52**, shown alongside that of two other previously reported diorganophosphido-bridged Pd^I dinuclear complexes.

The bridging nature of the anionic diphenylphosphido ligand in **52**, is a fairly common binding mode for phosphido ligands in TM complexes.²⁴⁶⁻²⁴⁸ As a result of the bridging interaction, the diphenylphosphido ligand features approximately tetrahedral geometry with respect to the coordinated atoms around the P centre. The two Pd–PPh₂ distances of **52**, as well as that of the Pd–PPh₃ bonds are remarkably similar, reflective of the high symmetry over the C₂ axis.

When the crude reaction mixture, formed upon mixing [Pd₃(OAc)₆] with 6 equivalents of PPh₃ at room temperature was subjected to LIFDI mass spectral analysis, a peak at exact mass *m/z* 980.056 was detected, with an isotopic distribution conforming to the [Pd₂(μ_2 -OAc)(μ -PPh₂)(PPh₃)₂]⁺ radical cation, representative of **52** (Figure 36).

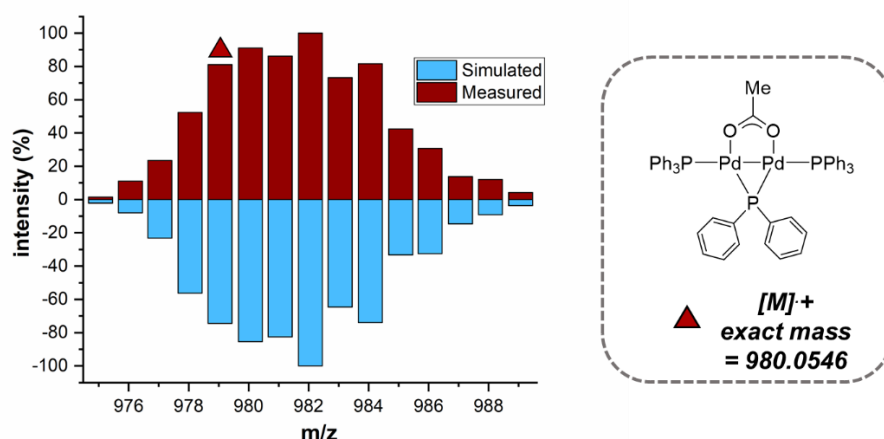


Figure 36 Isotopic distribution (simulated vs. measured) alongside atomic connectivity of the [Pd₂(μ_2 -OAc)(μ -PPh₂)(PPh₃)₂]⁺ radical cation, observed by LIFDI-MS, analysis of the reaction solution of [Pd₃(OAc)₆] and 6 equivalents of PPh₃.

It was subsequently realised that **52** could be synthesised on-scale by complete reaction of [Pd₃(OAc)₆] with 6 equivalents of PPh₃ in THF with additive deoxygenated H₂O (*ca.* 5 equivalents *per* Pd was added).

The additive H₂O was found to have an accelerative effect on the intermolecular reduction reaction, leading to full conversion of **47**, analogous to that discussed in Section 2.3 with [Pd(OAc)₆] / ≥ 9 PPh₃ systems. The product could be rapidly precipitated from the reaction mixture by cooling the post-reaction THF solution to 0 °C and adding hexane while stirring (THF:hexane 1:4 [v/v]). The resulting precipitate was then further purified by crystallisation from a THF solution layered with hexane, after storage overnight at –18 °C. The isolated material appeared as a dark reddish-purple powder and a 31% yield was recorded. The structure of the isolated material was then further interrogated by both ³¹P NMR and ¹H spectroscopic analyses (Figure 37). The ³¹P NMR spectrum of isolated **52** (a. Figure 37) shows two resonances: a PPh₃ doublet (δ_P 13.4 ppm) coupled to the low field, diphenylphosphido triplet (δ_P 199.1 ppm) with a matched ²J_{P-P} coupling constant of 85.5 Hz (*i.e.* a simple AB₂-type spin system) with respective integrations of 2:1. This spectrum hence conforms to the structure observed by XRD analysis of the crystal obtained from the same reaction (Figure 34), which implies two approximately chemically equivalent phosphino P atoms orthogonal to a bridging phosphido P atoms.

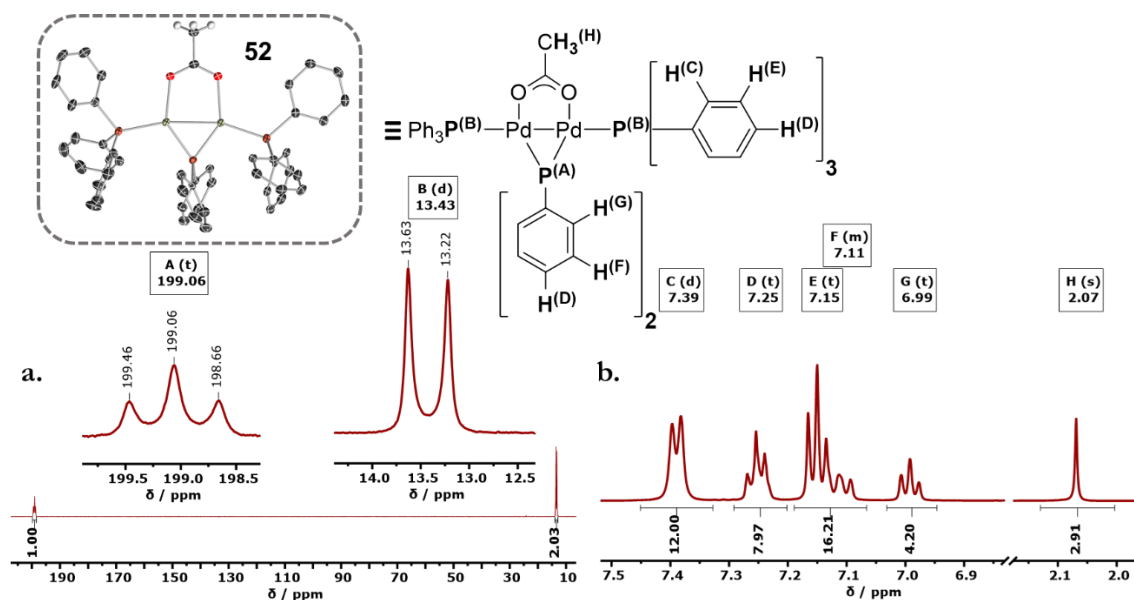


Figure 37 NMR spectral assignment of resonances of [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] (**52**) in THF-*d*₈ (a.) ³¹P NMR (202.5 MHz, 512 scans) **52**, with an expansion of the two resonances. (b.) ³¹P NMR (500 MHz, 64 scans) spectrum of isolated **52** note the excised region of the spectrum, between *ca.* δ_H 2.15-6.85 ppm.

¹H NMR spectroscopic analysis (b. Figure 37) shows the correct number of aromatic environments (6), with integrations correctly representing the relative number of protons present for assignment as **52**. All aromatic signals in the ¹H NMR spectrum of **52** were broad, indicating solution exchange processes. The aromatic region was assigned using a combination of ¹³C, and 2D-COSY, HSQC and HMBC spectra. Additionally, a peak at δ_H 2.07, representative of the CH₃ group of the bridging acetate ligand was evident. Infrared spectroscopic analysis of **52** showed an absorbance band at 1532 cm⁻¹, and three absorbance bands at 1479, 1435 and 1401 cm⁻¹. These sets of absorbances were assigned as the

symmetric (ν_{sym}) and asymmetric (ν_{asym}) CO stretching frequencies of the bridging carboxylato ligand, which are in-keeping with other analogous μ_2 -1,3-carboxylato-bridged Pd^I dimers²⁴⁵ and, more generally, with other μ_2 -1,3-carboxylato-bridged Pd^{II} complexes.²⁴⁹

Computational modelling of the structure of **52** was carried out by Prof. Ian J. S. Fairlamb, using density functional theory (DFT) calculations at the B3LYP/DEF2SVP-D3 level of theory with an implicit solvent (THF) modelled. The modelled HOMO and LUMO orbitals are shown in Figure 38. The results revealed a bond length of 2.58 Å, which is close to the bond length observed crystallographically 2.5958(3) Å, supporting the complex's diamagnetic properties and the presence of a Pd–Pd bonding interaction. The modelling showed that the HOMO resides over the Pd–Pd bond and the LUMO resides at the phosphorus atom of the bridging diphenylphosphido ligand. The HOMO and LUMO may potentially provide clues to the mode of reactivity of the complex with electrophiles or nucleophiles.

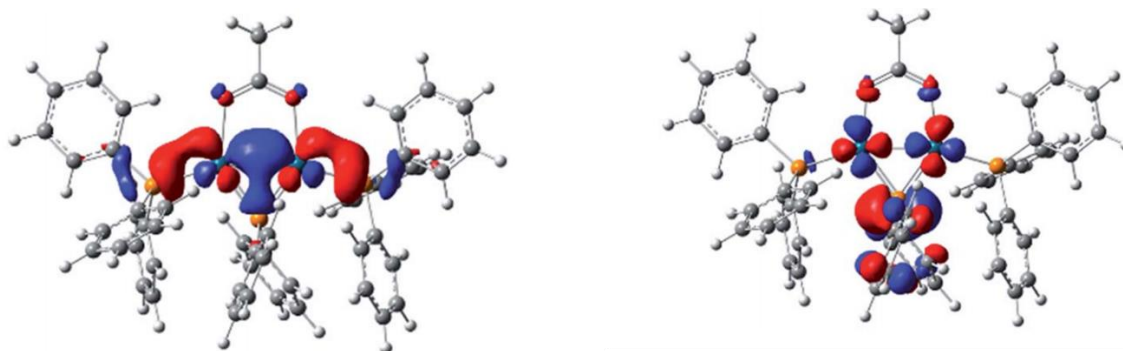


Figure 38 The structures of the HOMO (left) and LUMO (right) of **52** computed by density functional theory (B3LYP/DEF2SVP functional/basis set used for optimization, single point orbital and total energies: CPCM implicit solvent (tetrahydrofuran) and Grimme's D3 empirical correction used. Calculations by Prof. Ian J. S. Fairlamb.

Analogous conversion of **47** to **52**, upon treatment of $[\text{Pd}_3(\text{OAc})_6]$ with 6 equivalents of PPh_3 , was also realised in $\text{DMF-}d_7$ and $\text{benzene-}d_6$ solvents. **52** was seen to exhibit a low stability in solution – THF solutions were observed to decompose at to a black solution (most likely Pd metal particles) at 22–25 °C, over the course of 5–7 days. An analogous Pd^I dinuclear complex: $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-P(4-C}_6\text{H}_4\text{OMe)}_2\text{)(P(4-C}_6\text{H}_4\text{OMe)}_3)_2]$ was able to be synthesised by reacting $[\text{Pd}_3(\text{OAc})_6]$ with 6 equivalents of $\text{P(4-C}_6\text{H}_4\text{OMe)}_3$ in THF. When $[\text{Pd}_3(\text{OAc})_6]$ was reacted with 6 equivalents of the electron-poor substituted triphenylphosphine: $\text{P(4-C}_6\text{H}_4\text{CF}_3)_3$, an analogous Pd^I dinuclear structure did not form and decomposition to Pd black occurred after the same reaction time (16 hours) as that used for the synthesis of **52**.

When the crude post-reaction mixture of $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 in THF was analysed using ESI-MS, an intriguing cluster molecular ion was detected (Figure 39).

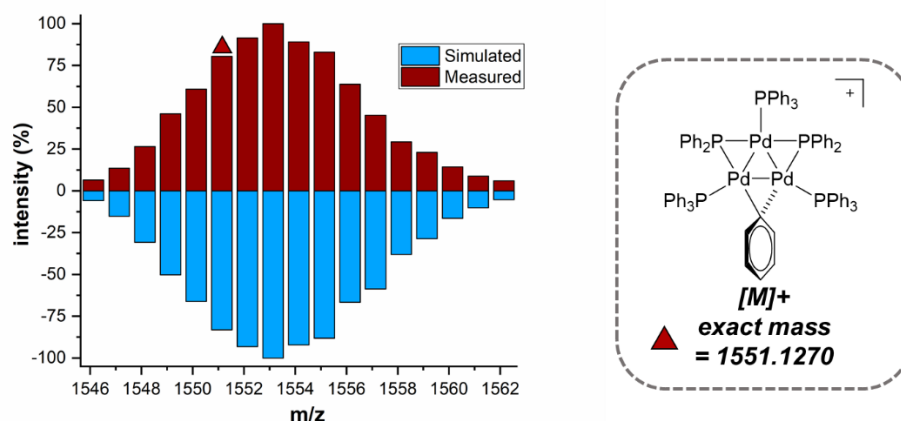


Figure 39 Isotopic distribution (simulated vs. measured) alongside proposed atomic connectivity of the $[\text{Pd}_3(\mu\text{-Ph})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$ cation, detected by ESI-MS analysis of the reaction of $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 . Also showing the likely structure of this complex ion.¹⁷²

This m/z and isotopic distribution fits that of the $[\text{Pd}_3(\mu\text{-Ph})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$, adopting the coordination motif that is shown to readily arise from reaction of Pd^{I} phosphido-ligated and organohalides *vide infra* (Section 2.5.1) and is relatively common in published literature (Section 1.4). The structure of the complex has therefore been assigned as $[\text{Pd}_3(\mu\text{-Ph})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$ (right, Figure 39), a tripalladium cluster featuring bridging diphenylphosphido ligands, and, intriguingly, a phenyl ligand. This precise tripalladium cluster complex has been detected by ESI-MS before, by Li *et al.*, who suggested that it forms directly from a proposed transmetalation of a phenyl group from phenylboronic acid to $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$ under alkaline conditions (Section 1.4, Page 69).¹⁷² The detection of this $[\text{Pd}_3(\mu\text{-Ph})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$ species indicates that, upon mixing $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 under these conditions, further clustering to higher order multinuclear Pd species is possible, as the system tends towards the Pd black thermodynamic product.

Complex **52** was subsequently found to exhibit novel reactivity, contrasting with that of the $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$ active complex formed from the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and ≥ 9 equivalents of PPh_3 (Section 2.3).^{46-48, 200} For example, it is able to activate organohalides to yield well-defined, tripalladium cluster species of the form $[\text{Pd}_3(\mu\text{-X})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$ (section 2.5.1). Additionally, reaction of **52** with additional PPh_3 resulted in further novel reactivity (section 2.5.3).

2.4.2. Isolation and Characterisation of $[\text{Pd}(\mu_2\text{-OAc})(\text{Ph})(\text{PPh}_3)]_2$ **53**

After crystallisation of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52**, from the complete reaction between $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 , the mother liquor was filtered off and stored under N_2 at -18°C . From this solution, a beige precipitate formed which was subjected to NMR spectroscopic analysis (*vide infra*). Additionally, single crystals were grown from a THF solution of this material by layering with hexane (THF/hexane 1:4 [v/v]). X-ray diffraction analysis confirmed the crystals to be the dimeric phenyl-ligated Pd^{II} dimer complex $[\text{Pd}(\mu_2\text{-OAc})(\text{C}_6\text{H}_5)(\text{PPh}_3)]_2$ **53** (Figure 40).

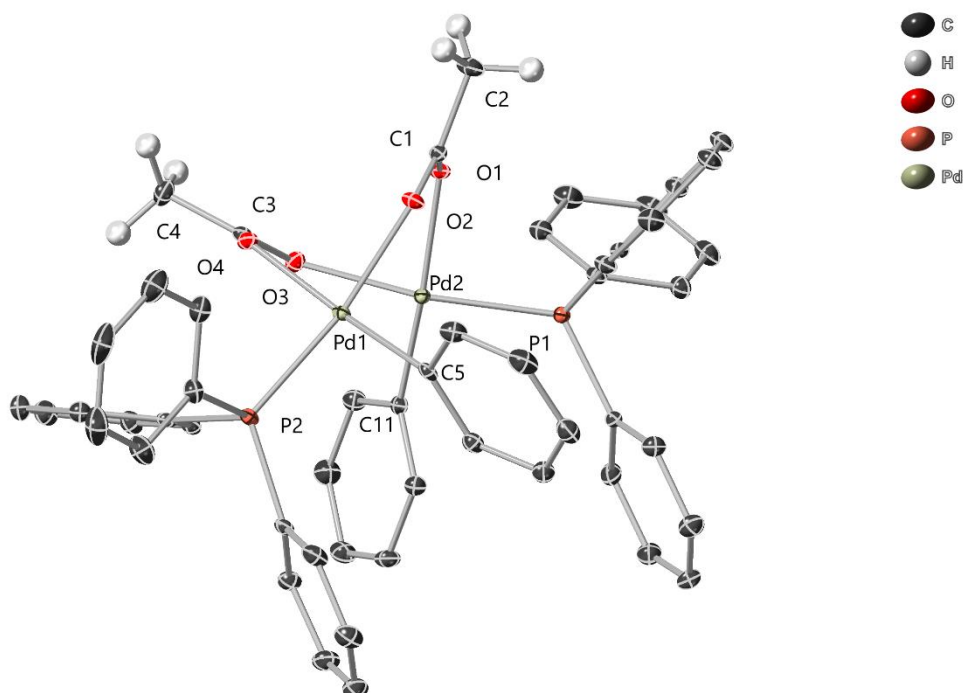


Figure 40 Structure, obtained by single crystal X-ray diffraction of the Pd^{II} dimeric complex $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\text{Ph})(\text{PPh}_3)]_2$ (**53**). H-atoms of PPh_3 ligands omitted for clarity. Selected interatomic distances /Å: $\text{Pd1-Pd2}=3.0610(3)$, $\text{Pd1-P2}=2.2239(7)$, $\text{Pd2-P1}=2.2196(6)$, $\text{Pd1-C5}=1.991(2)$, $\text{O1-Pd2}=2.1432(17)$. Selected interatomic angles /°: $\text{C5-Pd1-O3}=88.28(9)$, $\text{C5-Pd1-P1}=91.44(7)$, Selected torsion angles /°: $\text{P1-Pd1-Pd2-P2}=115.363$, $\text{C5-Pd1-Pd2-C11}=84.851$, $\text{C5-Pd1-Pd2-P1}=14.673$.

The X-ray crystallographic analysis (Figure 40) revealed the structure to be that of a dimer of two Pd^{II} centres, each adopting a square planar conformation, bridged by two μ_2 -1,3-acetato ligands, adopting a ‘clam-shell’-type structure, with κ -phenyl and κ - PPh_3 ligands (Figure 40). The crystal structure of **53** is isostructural to that previously reported X-ray crystal structure data.²⁵⁰ Pd-Pd interatomic distance $3.0610(3)$ Å is longer than that of the $\text{Pd}^{\text{I}}\text{-Pd}^{\text{I}}$ bond of **52** ($2.5958(3)$), however, this distance is less than the sum of the Pd Van der Waals radii.²⁵¹ The Pd-PPh_3 bond distances are notably significantly

shorter than that observed with monomeric Pd^{II}-P containing complexes **47** (*vide supra*), **64** (Section 2.6) and **OA_{C2-Br}** (Section 4.2.2) (range ~2.318 - 2.342 Å).

The ³¹P {¹H} NMR analysis of **53**, in THF-*d*₈, showed a single resonance at δ_P 30.6 ppm (a. Figure 41) thus identifying it as a minor species, observed in crude reaction mixture (Figure 32, page 110). The isolated material was subjected to LIFDI mass spectral analysis, which confirmed presence of [(Pd(μ₂-OAc)(Ph)(PPh₃))₂]⁺, the radical cation of **53**, with an isotopic distribution pattern close to that of the theoretical simulated pattern for the chemical formula (Figure 41).

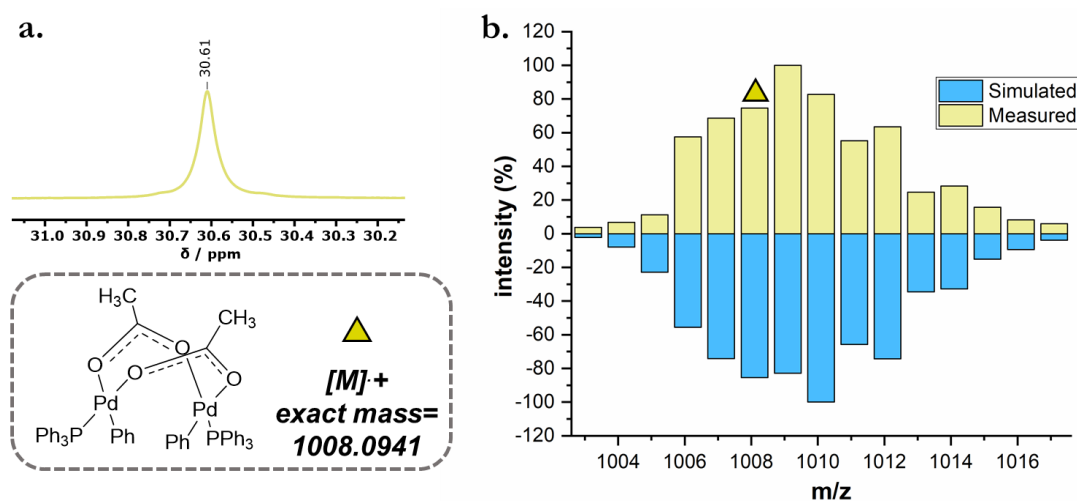


Figure 41 (a.) ³¹P NMR resonance (202.5 MHz, 256 Sc, THF-*d*₈) and (b.) LIFDI-mass spectral isotopic distribution pattern for **53**, which was isolated from the reaction between [Pd₃(OAc)₆] and 6 equivalents of PPh₃.

The acquired data for [(Pd(μ₂-OAc)(C₆H₅)PPh₃)₂] **53** matches literature reported characterisation data, including a which had previously prepared in a 41% yield by reaction of [Pd₃(OAc)₆] with 8.6 equivalents of PPh₃, under air in refluxing methanol.²⁵⁰

2.4.3. Influence of the Piperidyl Ligand on Pd(OAc)₂ Speciation Events

Trans-[Pd(OAc)₂(*N*-piperidyl)₂] **54**, which was originally developed by the Fairlamb group in York, has been employed as an effective pre-catalyst for various transformations in this work (see Sections 4.3 & 4.4) and in reported literature.^{54, 105, 252} Employing the [Pd₃(OAc)₆]-derived complex **54** (Figure 42) in a reaction with *n* equivalents of PPh₃ led to differing reactivity to that of the analogous reaction between [Pd₃(OAc)₆] and 3*n* equivalents of PPh₃.

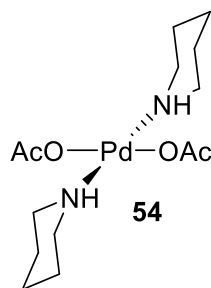


Figure 42 The structure of *trans*-[Pd(OAc)₂(*N*-piperidyl)₂] (**54**).

When **54** was treated with 2 equivalents of PPh₃, in a reaction equivalent in terms of Pd:PPh₃ ratio to the reaction between [Pd₃(OAc)₆] and 6 equivalents of PPh₃ with the Pd:P ratio being 1:2, the Pd dinuclear species **52** does not form. This was indicated by no resonance being detected at δ 199 and 13 ppm in the ³¹P NMR spectrum of the reaction solution, after a 16-hour reaction at 40 °C (Figure 43).

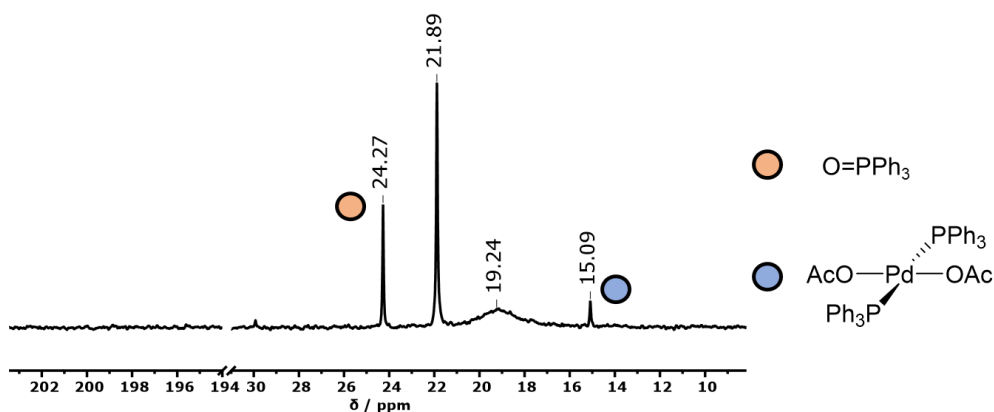


Figure 43 ³¹P NMR spectrum recorded after reaction of **54** with PPh₃ (2 equivalents) (202.5 MHz, THF, unlocked, externally referenced to H₃PO₄ [in H₂O 85% w/v]). Showing the low field phosphido region of the spectrum, for comparison with content from Figure 44.

The phosphine oxide, O=PPh₃ (δ_P 24.3 ppm, identified by comparison with an authentic sample), and a broad resonance at δ_P 19.24 ppm (Δν_{1/2} = 371.48 Hz) were identified by ³¹P spectral analysis in the reaction solution after 16 hours, along with a major peak at δ 21.9 ppm. The integration of the peak at δ_P 21.9 ppm was found to decrease as the broad resonance migrated downfield (δ_P 17.5 → 19.3 ppm). A trace amount of **47** (δ_P 15.1 ppm) was also detected. By analogy with the [Pd₃(OAc)₆]/≥ 9 equivalents of PPh₃ reaction system, where a Pd^{II}-PPh₃ complex **47** converts to a broad Pd⁰-PPh₃ complex [Pd⁰(OAc)(PPh₃)_n]⁻ (Section 2.3), the resonance at δ_P 21.9 ppm was assigned as a mixed piperidyl/PPh₃ ligated complex of the formula [Pd^{II}_v(OAc)_x(PPh₃)_y(*N*-piperidyl)_z] which could be formed *in situ*, *via* direct reaction between **54** and two equivalents of PPh₃. Likewise, due to the migratory nature of the peak at δ_P 19.24 (Figure 43), as well its broadness, and in analogy with the piperidyl-ligand free system (Section 2.3) has been assigned as a piperidine/PPh₃-ligated Pd⁰ complex of the form [Pd⁰(PPh₃)_n(piperidyl)_m] (most likely in exchange with free acetate in solution, in line with Amatore and

Jutand's studies (discussed in Section 2.2).²⁰⁰ This observation also suggests that the piperidyl ligand plays a stabilising role and prevents the formation of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** by competing with PPh_3 to stabilise any formed Pd^0 complex.

When **54** was treated with 1 equivalent of PPh_3 in THF at 40 °C, a broad PPh_3 -type resonance (δ_{P} 13.4 ppm) and a low field resonance (δ_{P} 197.9 ppm) was detected after 16 hours. Despite a lack of coupling detectable by 1D ^{31}P NMR spectroscopy (a. Figure 44), these two resonances were confirmed to be coupled by use of ^{31}P – ^{31}P COSY (b. Figure 44). Due to the similarities in chemical shifts observed between this species and **52** (Section 2.4.1) it is most likely that this species is a closely related Pd^{I} dinuclear complex, with broadened resonances due to chemical exchange between PPh_3 and liberated piperidine.

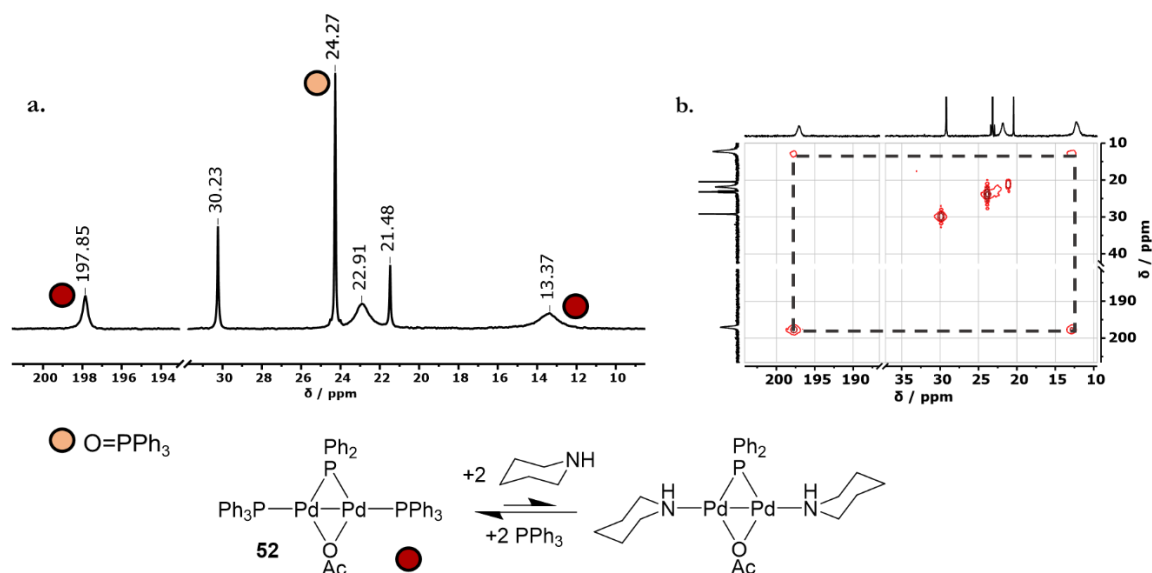
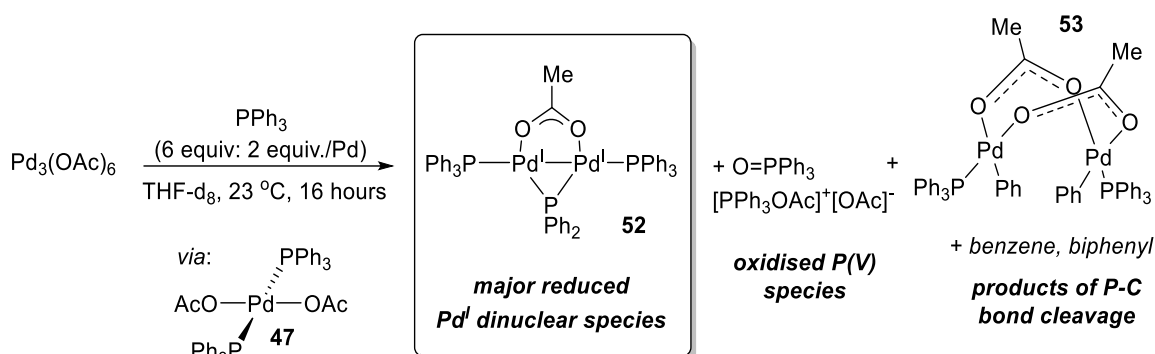


Figure 44 (a.) ^{31}P NMR (202.5 MHz, THF, unlocked, externally referenced to H_3PO_4 [in H_2O 85% w/v]) evidence for of **52**, arising in a THF solution of **54** and 1 equivalent of PPh_3 . (b.) A ^{31}P – ^{31}P COSY spectrum of the same solution, showing correlation between PPh_3 - and phosphido-type(PPh_2) resonances, indicating coupling between these resonances.

A key message from this study is that the Pd^{I} dinuclear complex **52** arises as a reduced species from the reaction between *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ **54** and 1 equivalent of PPh_3 . When formed in this way, **52** is in chemical exchange with piperidine released by **54** which would likely influence reactivity. Complex **52** does not form on reaction of **54** with 2 equivalents of PPh_3 . This observation indicates that piperidine, as a σ -electron-donor ligand, can prevent formation of Pd^{I} by ligating and stabilising the putative Pd^0 complex in the same way that PPh_3 can (Sections 2.2 & 0). This finding on the speciation of *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ *vs.* $[\text{Pd}_3(\text{OAc})_6]$ in the presence of $n\text{PPh}_3$ is in line with trends in the catalytic activity of *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ *vs.* $[\text{Pd}_3(\text{OAc})_6]$ when employed alongside $n\text{PPh}_3$ (see Section 4.4) under SMCC reaction conditions.

2.4.4. Summary and Discussion: The Reaction of $\text{Pd}_3(\text{OAc})_6$ with 6 Equivalents of PPh_3

When $[\text{Pd}_3(\text{OAc})_6]$ is treated with exactly 6 equivalents of PPh_3 , multiple species are formed. After initial formation of *trans*- $[\text{Pd}^{\text{II}}(\text{OAc})_2(\text{PPh}_3)_2]$ **47**, the major reduced (activated) species is a Pd^{I} dinuclear complex $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** (Scheme 40). This species stands in contrast with the $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$ active complex formed from the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and ≥ 9 equivalents of PPh_3 (Section 2.3).^{46–48, 200}

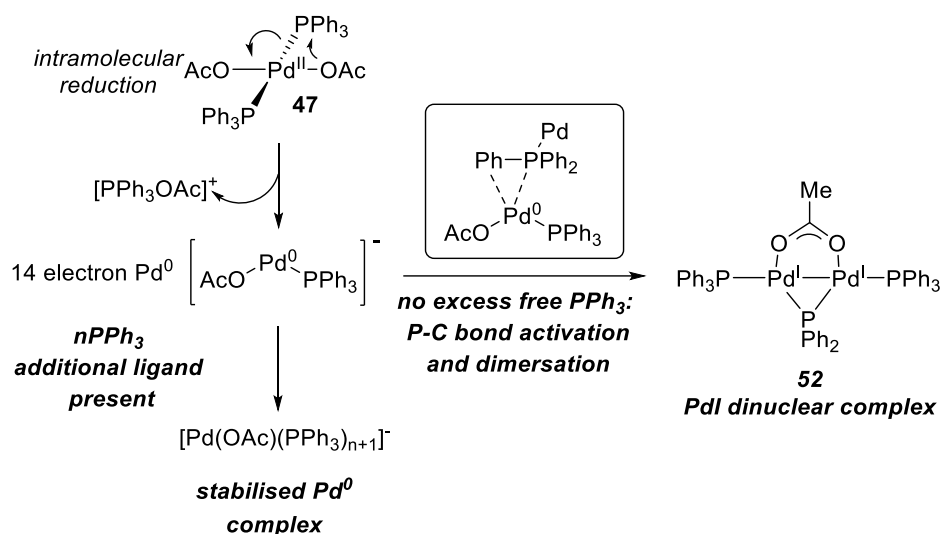


Scheme 40 Summary scheme showing the products now known to arise from the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 as evidenced (*vide supra*).

The activated Pd^{I} dinuclear complex **52** is bridged by a μ_1 -diphenylphosphido- and a μ_2 -1,3-acetato ligand. Both $\text{O}=\text{PPh}_3$ and $[\text{Ph}_3\text{P}-\text{OAc}]^+$ were detected as the oxidised (P^{V}) side-products of the intramolecular redox activation process. The phenyl-containing side products Pd^{II} dimer complex were **53**, benzene, biphenyl, and a trace amount of *ortho*-terphenyl were detected, which account for the loss of a phenyl moiety in formation of the diphenylphosphido bridging ligand. The presence of a diphenylphosphido ligand alongside the phenyl-containing compounds indicates that P-C bond cleavage has occurred at a PPh_3 ligand (*e.g.* through an oxidative addition reaction) followed by dimerisation (Scheme 41).

P-C bond scission by Pd complexes has been reported in literature,^{253–254} including during the analogous reaction between $\text{Pd}(\text{OAc})_2$ and the dialkylbiaryl ligand MePhos at $85\text{ }^\circ\text{C}$ in MeOH , forming a Pd^{I} dinuclear complex-bridging dicyclohexylphosphido ligand.¹⁴⁴ In this case however, the fate of the cleaved biaryl moiety was not reported. Girolami *et al.* reported that the thermolysis of $[\text{Pd}^{\text{I}}(\text{PMe}_3)_3][\text{hfac}]_2$ at $100\text{ }^\circ\text{C}$ and 10^{-3} Torr led to the formation of $[\text{Pd}^{\text{II}}\text{Me}(\text{PMe}_3)_3]^+[\text{hfac}]^-$, where the Me ligand is proposed to form *via* oxidative addition of *in situ* formed Pd^0 species to PMe_3 .^{142, 255} Indeed,

a $\text{Pd}(\text{OAc})_2$ -catalysed olefin arylation reaction has been realised, with PPh_3 as a phenylating agent, deployed alongside stoichiometric AgOAc (oxidant) and AcOH additives.²⁵⁶



Scheme 41 Formation of reduced (active) species **52** upon reacting $[\text{Pd}_3(\text{OAc})_6]$ with exactly 2 equivalents of PPh_3 .

The following is a rationalisation of the observation of the difference in speciation observed in the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 *vs.* $[\text{Pd}_3(\text{OAc})_6]$ and ≥ 9 equivalents of PPh_3 . Under the $[\text{Pd}_3(\text{OAc})_6]$ and ≥ 9 equivalents of PPh_3 regime, the Pd^{II} complex **47** quickly forms and then converts to $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$ *via* a highly reactive 14-electron Pd^0 species $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)]^-$. This is aided by ligation by *n* equivalents of available PPh_3 in solution.⁴⁷ Under the $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 regime, however, after formation of **47**, there is no excess of phosphine present to stabilise formed $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)]^-$, thus the reactive 14-electron Pd^0 complex activates ligated PPh_3 and dimerises, furnishing the observed complex **52**. The precise mechanism for this process is currently unproven, however, based on extrapolation of events in systems with excess PPh_3 present it is most likely that the highly reactive 14-electron elementary species $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)]^-$ (See Section 2.2) may activate P–C bond of a PPh_3 within unreacted free **47** *via* oxidative addition *en route* to the Pd^{I} dinuclear complex. Other previously reported Pd^{I} dinuclear complexes have been synthesised by direct reaction of Pd^0 with Pd^{II} complexes.^{139, 142, 244} Acetoxybenzene, which was hypothesised as a by-product, formed *via* reductive elimination of phenyl and acetate ligands of **53** (a hypothesised intermediate *en route* to **52**) was not detected by GC-MS analysis of the crude reaction product. Notwithstanding, the reduced species that forms from the reaction of $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 , the Pd^{I} dimeric complex **52**, is distinctly different from that which arises from the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and ≥ 9 equivalent of PPh_3 , monomeric $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$ -type complexes. Hence, as a result of the difference in the amount of available ligand, a difference in speciation is evident. As this overarching study proceeded, it was clear that Pd/PPh_3 ratios in pre-catalytic $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ systems induces

profound implications on reactivity (Section 2.5), catalyst efficacy (Chapter 3) and site-selectivity (Chapter 4) in cross-coupling reactions. It was hence decided to test the reactivity of **52** with species relevant to cross-coupling catalysis, namely organohalides (Section 2.5.1) and additional PPh₃ (Section 2.5.3).

2.5. Reactivity of the Novel Pd^I Dinuclear Complex: [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52**

In this section, work done towards investigating the reactivity of the newly discovered Pd^I nuclear complex [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52** is reported. Complex **52** was shown to react with the organohalides (electrophiles) CH₂Cl₂, *para*-fluoroiodobenzene and 2-bromopyridine to produce a tripalladium cluster complex of the form [Pd₃(μ-X)(μ-PPh₂)₂(PPh₃)₃]⁺Y⁻ (where X and Y are anionic ligands and counterions, respectively). Complex **52** was shown to disproportionate upon treatment with PPh₃ (nucleophile) to form a new diphenylphosphinito bridged Pd^I complex (**58**) and [Pd⁰(PPh₃)₃] **48** which were both characterised in solution. Upon treatment of this solution with 2-bromopyridine **55**, the Pd⁰ complex **48** was shown to undergo oxidative addition, while the diphenylphosphinito fragment underwent conversion to [Pd₃(μ-Br)(μ-PPh₂)₂(PPh₃)₃]⁺X⁻ complex. A diphenylphosphinato-bridged Pd^I complex **62** was additionally isolated from this mixture and characterised crystallographically.

2.5.1. Reactivity of [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52** with Organohalides

The isolated Pd^I dinuclear complex **52**, formed from reaction of [Pd₃(OAc)₆] with 6 equivalents of PPh₃ proved to be able react with dichloromethane solvent. Over the course of 14 hours, **52** was seen to fully react at 25 °C in a mixture of *ca.* 60 equivalents of CD₂Cl₂ and THF-d₈ (2:3 v/v ratio, respectively) (a. Figure 45). After 14 hours, the same reaction was sampled in CD₂Cl₂ and a new species was identified by ³¹P NMR spectroscopy (b. Figure 45).

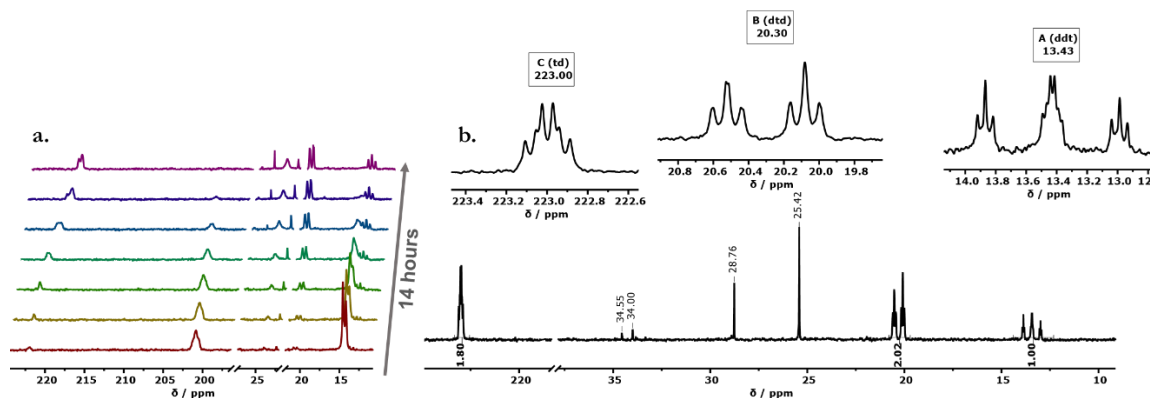


Figure 45 ^{31}P NMR data for the reaction between the $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52**, and CD_2Cl_2 . a. (202.5 MHz, THF- d_8) a time course for the 14 hour the reaction between **52** and CD_2Cl_2 ($\text{CD}_2\text{Cl}_2\text{:THF-}d_8 = 2\text{:}3$) Spectra shown at time intervals of 2 hours from reaction commencement. b. (202.5 MHz, CD_2Cl_2) spectrum of the post reaction solution showing expansions of resonances form the $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$ ($\text{Pd}_3\text{Cl}\cdot\text{X}$) cluster product.

Three major coupled resonances were seen to arise at expense of **52** as a function of time. Careful analysis of ^{31}P NMR spectral data, presented by Li *et al.* for the cationic tripalladium cluster complex of the form $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$, showed matching ^{31}P NMR data (Figure 45), indicating that the same cluster species is formed in this case.¹⁷² The $[\text{Pd}_3(\mu\text{-X})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Y}^-$ (**Pd₃X·Y**)ⁱ motif was first discovered by Coulson, and has been reported several times in the literature (See Section 1.4)¹⁶⁷⁻¹⁶⁸ Indeed, an efficient and direct route to the dichloride complex **Pd₃Cl·Cl** was published by Moiseev *et al.* in 1982.¹⁷¹ An authentic sample was hence synthesised by the same method, which provided supporting evidence that this complex had formed (See section 2.5.2 for discussion of synthesis and characterisation of **Pd₃X·X**). Comparison of the NMR spectroscopic data of the sample, and the standard, from which a single crystal X-ray structure was obtained, provided conclusive proof of the structure and connectivity of the cluster. Additionally, ESI-Mass spectral analysis confirmed the presence of the $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$ cation in the post-reaction solution (Figure 46).

ⁱ For the abbreviation **Pd₃X·Y**, representing the $[\text{Pd}_3(\mu\text{-X})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Y}^-$ salt, **X** represents the bridging (coordinated) halide ligand, and **Y** represents the non-coordinating counteranion.

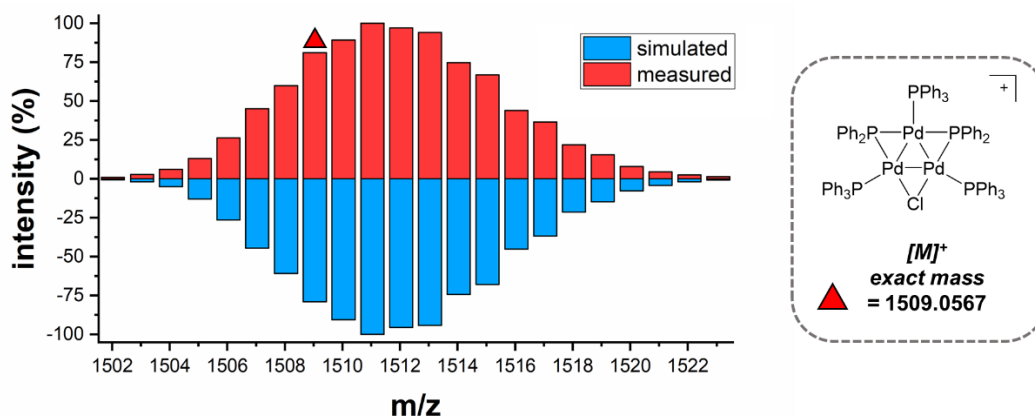


Figure 46 m/z and Isotopic distribution pattern of the cation detected by ESI-MS analysis for complex $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$ detected from the reaction of **52** and dichloromethane.

Based on the above data, it is clear that one of the major products of the reaction between **52** and CH_2Cl_2 is the trinuclear cluster $\text{Pd}_3\text{Cl}\cdot\text{X}$. In this case, the counteranion for the complex cluster cation is most likely acetate or chloride, which are species known to be present in the mixture. A reaction time course, carried out in CH_2Cl_2 , indicated that two equivalents of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** converted to one molecule of $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$. Other unidentified singlet resonances were also present in the ^{31}P NMR spectrum, indicating that other unidentified phosphorus-containing species were being produced during the reaction.

After establishing that $\text{Pd}_3\text{Cl}\cdot\text{X}$ can be generated from the complete reaction of **52** with CD_2Cl_2 , it was decided to examine the reactivity of **52** with aryl halides, which are frequently used as substrates in cross-coupling reactions. Different observations were made in the reaction between $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** and *para*-fluoroiodobenzene in THF. Here, $[\text{Pd}_3(\mu\text{-I})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{X}$ was not detected by ^{31}P NMR spectroscopic analysis, which showed multiple resonances indicating that significant decomposition of P-containing species had occurred. The $[\text{Pd}_3(\mu\text{-I})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$ ion was however detected by ESI-MS (Figure 47), demonstrating that this cluster can form to some extent from the reaction between $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ and *para*-fluoroiodobenzene. Upon mixing the reactants, a colour change from dark red transparent solution to dark brown opaque solution was observed, indicating decomposition of Pd-containing species to bulk metal particles.

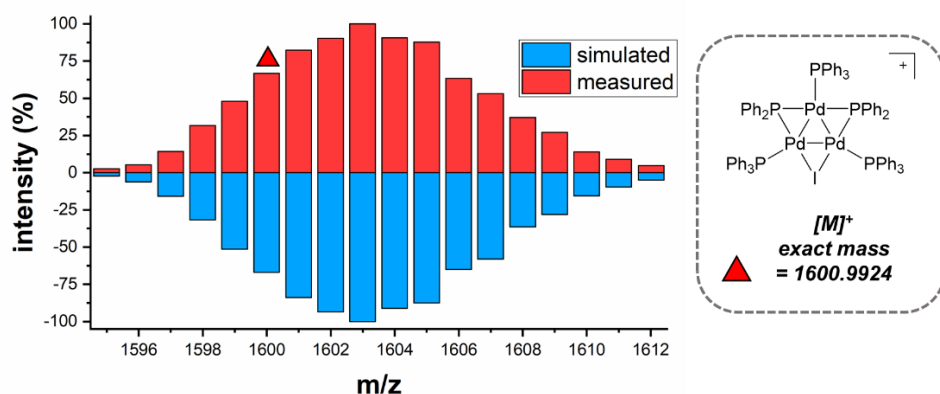


Figure 47 m/z and isotopic distribution pattern of the cation detected by ESI-MS analysis for complex $[\text{Pd}_3(\mu\text{-I})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$ detected from the reaction of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** with *para*-fluoroiodobenzene.

In order to shed further light on the reactivity of **52** with aryl halides, the heterocyclic aryl halide, 2-bromopyridine **55** was employed. It was envisaged that the N-heteroatom, situated proximal to the C–Br site may act to stabilise the reaction system, which decomposed in the case of reaction between **52** with *para*-fluoroiodobenzene. 2-bromopyridine **55** was hence added to a $\text{THF-}d_8$ solution of **52** at room temperature. After *ca.* 45 minutes under these conditions, ^{31}P NMR spectral analysis of the post-reaction solution ($\text{THF-}d_8$) indicated full conversion to a range of products (Figure 48).

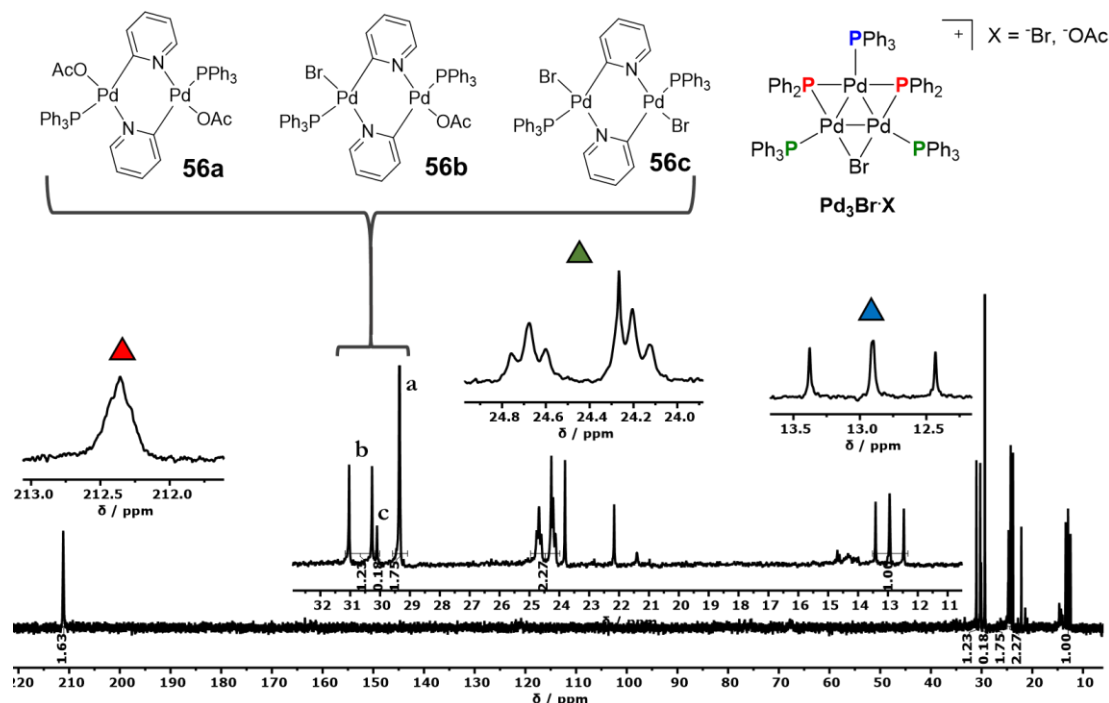


Figure 48 ^{31}P NMR spectra (202.5 MHz, $\text{THF-}d_8$), confirming the presence of the tripalladium cluster complex $\text{Pd}_3\text{Br}\cdot\text{X}$ in solution after treatment of **52** with 2-bromopyridine **55**. The products, *trans*-(P,N)- $[\text{Pd}(\text{X})(\mu\text{-pyridyl-C}^2, \text{N})(\text{PPh}_3)]$ ($\text{X} = \text{Br}^-$ and/or OAc^- , **56a**, **56b** and **56c**) were also shown to be present in solution (see below).

The tripalladium cluster **Pd₃Br·X** was evident by a low field phosphido resonance at δ_P 212.4 ppm and two high-field PPh₃-type resonances at δ_P 24.4 and 12.9 ppm (see Section 2.5.2 for synthesis and detailed structural characterisation of a **Pd₃Br·Br** standard). ESI-MS analysis confirmed the presence of the [Pd₃(μ -Br)(μ -PPh₂)₂(PPh₃)₃]⁺ cation as indicated by NMR analysis (Figure 49).

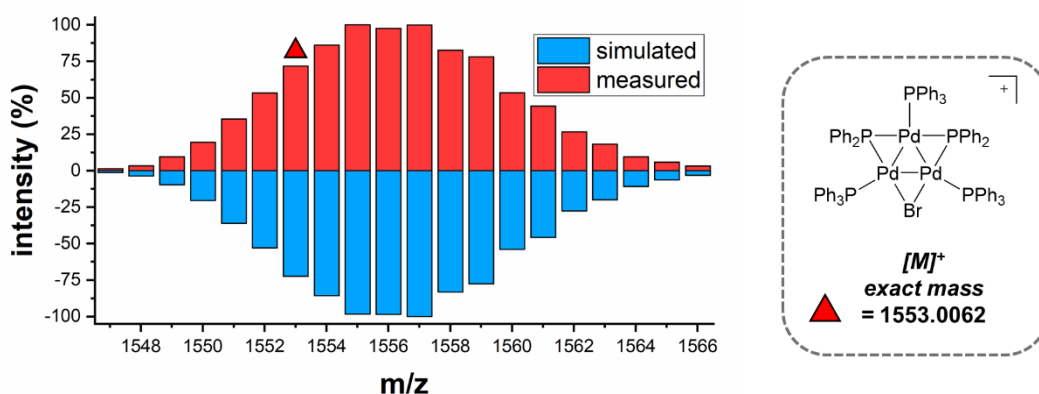
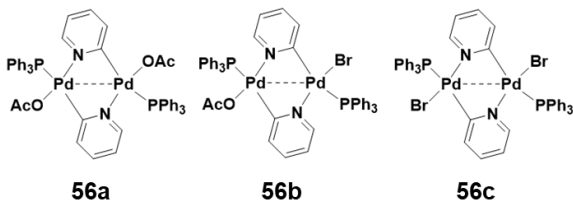


Figure 49 m/z and isotopic distribution pattern of the cation detected by ESI-MS analysis for the cationic complex [Pd₃(μ -Br)(μ -PPh₂)₂(PPh₃)₃]⁺ detected from the reaction of **52** with 2-bromopyridine.

The presence of three variants of the Pd^{II} dimer complex *trans*-(P,N)-[Pd(X)(μ -pyridyl-C², N)(PPh₃)₂]: **56a**, **56b** and **56c** (where X = all three combinations of -Br or -OAc) were also evident (Figure 48) by ³¹P and ¹H NMR and mass spectral analysis. Only a trace amount of the related *bis*-phosphine ligated monomeric complex *trans*-[Pd^{II}(Br)(C²-pyridyl)(PPh₃)₂] **57** was present (δ_P 22.1 ppm) and this amount did not vary with time.^k LIFDI-MS analysis of the crude reaction mixture showed presence of three metal complexes found to be Pd^{II} dimer complexes: **56a** ([M]⁺ exact mass m/z = 1010.08, **56b** ([M]⁺ exact mass m/z = 1029.99 Da) and **56c** ([M]⁺ exact mass m/z = 1049.89 Da), in addition to the formed [Pd₃(μ -Br)(μ -PPh₂)₂(PPh₃)₃]⁺ ([M]⁺ exact mass m/z = 1553.01 Da), as observed by ESI-MS (Figure 49).

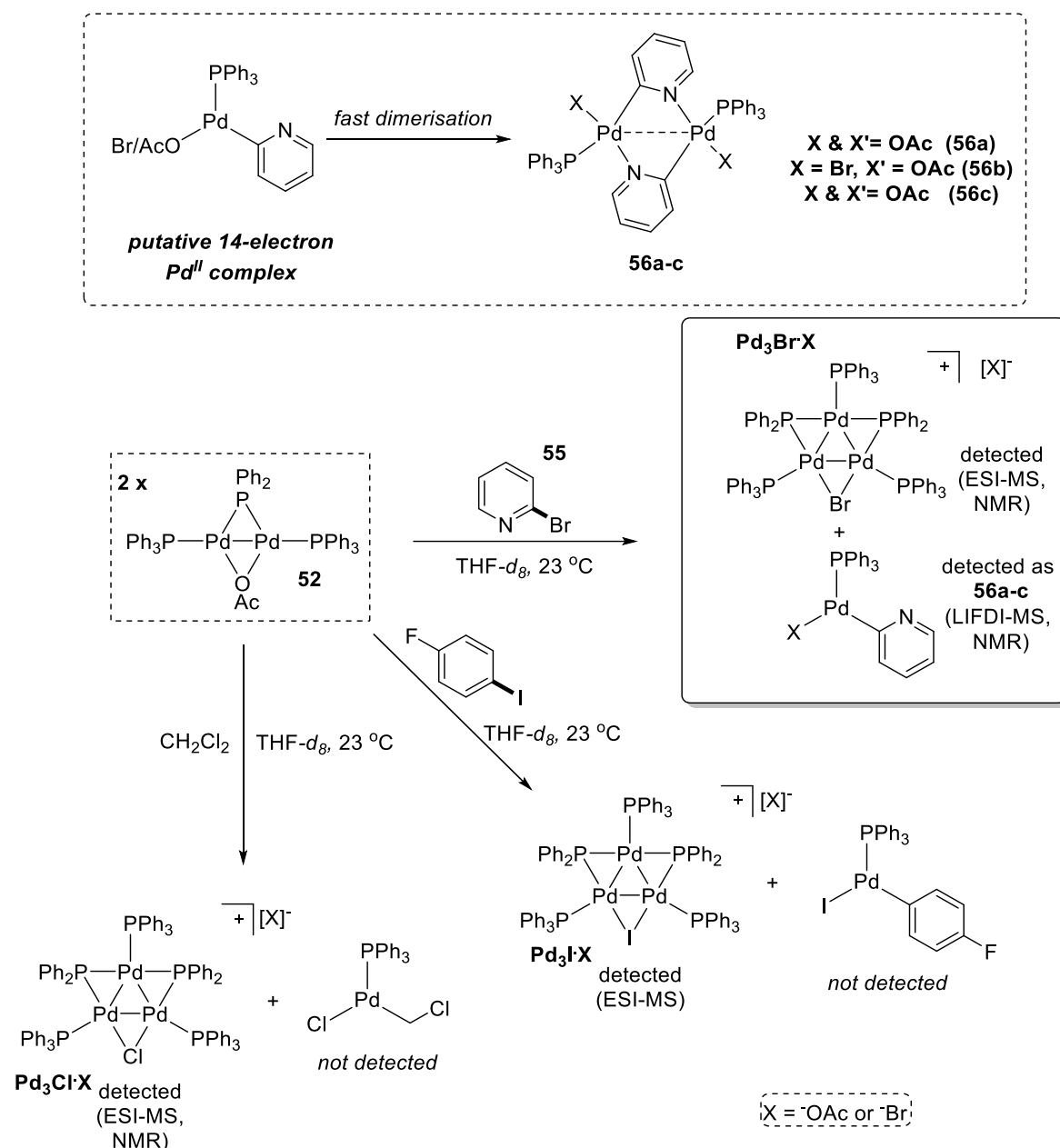
^k The identity of compound *trans*-(P,N)-[PdBr(μ -pyridyl-C², N)(PPh₃)₂] **56c** was confirmed by generating an authentic sample *via* oxidative addition of [Pd⁰(PPh₃)₄] to 2-bromopyridine. The related monomer *trans*-[Pd^{II}(Br)(C²-pyridyl)(PPh₃)₂] **57** is now known to exist in equilibrium with **56c**. See section 2.5.3.2.1, for details.



Notably, **52** did not react analogously with the heteroaryl compound 6-bromoquinoline. Treating a THF solution of **52** with 6-bromoquinoline resulted in decomposition of **52** to a black solution and no observable oxidative addition-type product or **Pd₃X·Y** cluster complex during a 16-hour timecourse. This is most likely that the lack of reactivity of **52** with 6-bromoquinoline was due to the relatively unactivated nature of the C–Br bond in this case, giving some indication of the limits to the reactivity of complex **52** with C–X bonds.

To summarise, the Pd^I dinuclear complex **52** is able to react with dichloromethane, *para*-fluoroiodobenzene and 2-bromopyridine **55** to produce tripalladium clusters of the form, [Pd₃(μ-X)(μ-PPh₂)₂(PPh₃)₃]⁺Y[–] (X = Cl, I and Br) in all cases, and stabilised Pd^{II} dimeric complexes **56a–c** in the latter case. These reactive events are highlighted in Scheme 42.

The reaction between **52** and **55** aided in elucidating the likely reactive events between **52** and CH₂Cl₂ and *para*-fluoroiodobenzene. The characterisation of **56a–c** complexes indicated that the C–Br bond had been activated, most likely in an oxidative addition-type reaction, by a [Pd⁰(OAc)(PPh₃)][–] fragment of **52** to the C–Br bond of **55**, forming a reactive monomeric 14-electron Pd^{II} complex, upon cleavage of the Pd^I dimer. The putative 14-electron complex would then be stabilised by self-dimerisation through the pyridyl N-atom, forming the observed 16-electron Pd^{II} dimeric complex **56a–c** (Scheme 42). The mechanism of **Pd₃Br·X** formation, at this stage is unclear, however after the oxidative addition and dimerisation process, the remaining fragment of **52** ([Pd^{II}(PPh₂)(PPh₃)]⁺) could feasibly form the [Pd₃(μ-Br)(μ-PPh₂)₂(PPh₃)₃]⁺ cluster complex motif through reaction with another equivalent of the Pd^I dimeric complex **52** and bridging Br, liberated from **55**.



Scheme 42 Summary of findings and conclusions regarding the reactivity of [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52 with organohalides.**

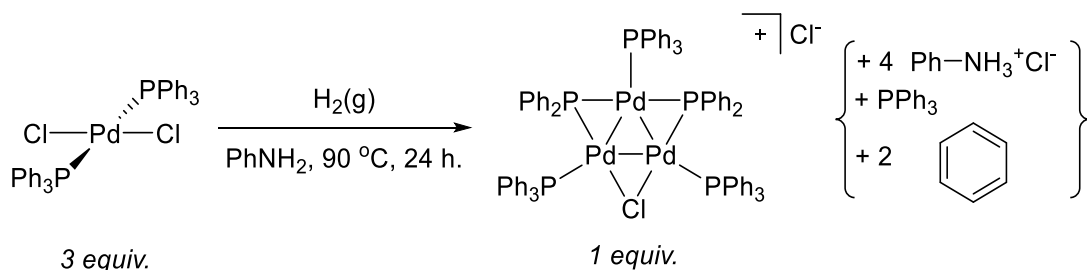
In the case of the reaction between **52** and *para*-fluoroiodobenzene, it is likely that an analogous oxidative addition occurs, affording a highly reactive 14-electron Pd^{II} complex and the observed cluster **Pd₃I·X**, which was observable by ESI-MS. In this case, however, due to the reactivity of the 14-electron complex, and absence of stabilising N-donor atoms which are present in **55**, the system quickly decomposes, as observed in the rapid formation many multiple unassignable ³¹P NMR resonances and the observed formation of Pd black. In the case of the reaction between **52** and dichloromethane, the post-reaction system was clearly more stabilised than in the case of the reaction with *para*-fluoroiodobenzene, as evident by the presence of **Pd₃Cl·X** and the relatively few species observed in the

resulting ^{31}P NMR spectrum, however, despite best efforts, a formal, putative, CH_2Cl^+ fragment could not be traced in this reaction system.

In each of these cases, however, the formation of the cluster complex of the form $[\text{Pd}_3(\mu\text{-X})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$ (**Pd₃X·X**) was evident in post-reaction solutions of **52** with organohalides. The clusters exhibit an average formal oxidation state of 4/3 per Pd. It is important to note that these clusters, which have been shown in other work to be active as (pre-)catalysts in cross-coupling reactions,^{162, 172} and can be generated *in situ* by simply allowing complete reaction of $[\text{Pd}_3(\text{OAc})_6]$ with exactly 6 equivalents of PPh_3 (resulting in formation of the Pd^{I} dimeric complex $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52**) then adding appropriate organohalides. Thus, the unique reactivity of **Pd₃Cl·X**-type clusters may be simply accessed *in situ*, thus circumventing the need for their non-trivial synthesis and isolation.^{167, 171} Chapter 3 details comparative studies of authentic **Pd₃Cl·X** *vs.* $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ as (pre)-catalytic systems in a model SMCC reaction.

2.5.2. Synthesis and Characterisation of $[\text{Pd}_3(\mu\text{-X})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{X}$ Clusters

A $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$ **Pd₃Cl·Cl** standard could be prepared by stirring *trans*- $[\text{Pd}^{\text{II}}\text{Cl}_2(\text{PPh}_3)_2]$ in aniline, under an atmosphere of H_2 (Scheme 43).



Scheme 43 Scheme detailing the procedure used to synthesise authentic standards of the cluster complex $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$ by hydrogenation of *trans*- $[\text{Pd}^{\text{II}}\text{Cl}_2(\text{PPh}_3)_2]$ in the presence of aniline.

The above procedure was adapted from a method first published in 1982 by Moiseev *et al.*¹⁷⁰ Benzene was reported to form as the by-product resulting from the cleavage of triphenylphosphine, leading to formation of the diphenylphosphido ligands during this process.

Notably, in *this study*, when the same reaction was attempted in piperidine, instead of aniline, Pd black formed within *ca.* 10 minutes, at 90°C . No **Pd₃Cl·Cl** was characterised under these conditions. This observation may indicate that employing the stronger piperidine base instead of aniline as the reaction medium, provides a higher reduction potential, leading to formation of bulk Pd metal instead of the **Pd₃Cl·Cl**, which is evidently thermodynamically stable at 90°C in aniline.

From a CDCl_3 solution of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$, layered with petroleum ether, a bright red crystal was grown at room temperature which was subjected to X-ray crystallographic analysis, allowing for elucidation of the structure (Figure 51).

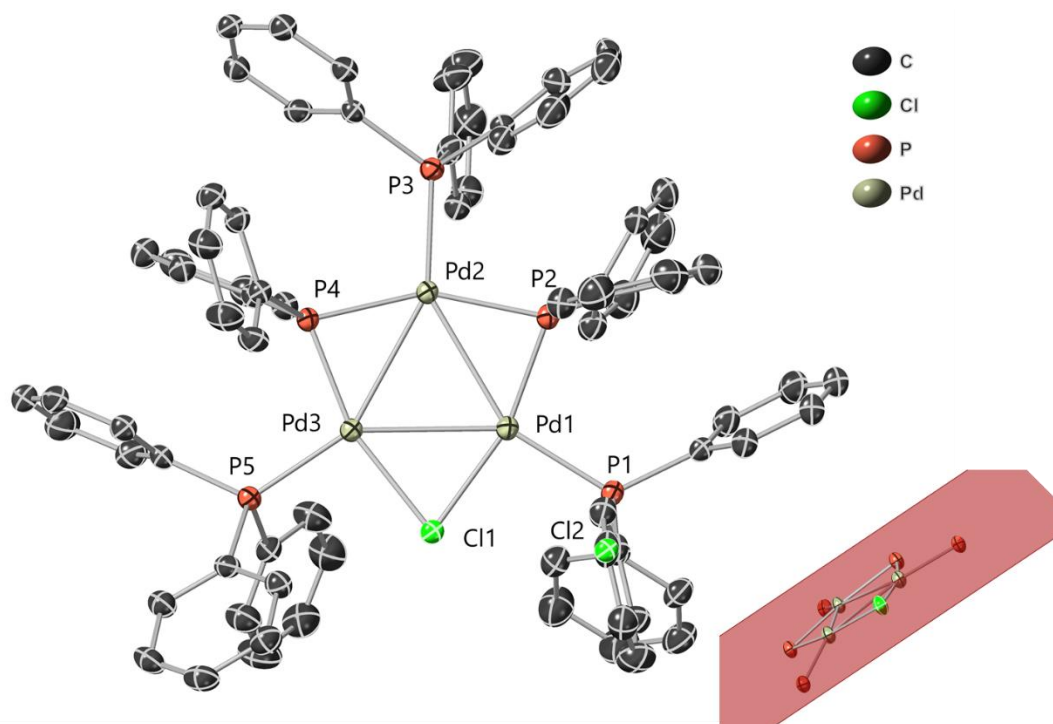


Figure 51 Structure, obtained by single crystal XRD for $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$ ($\text{Pd}_3\text{Cl}\cdot\text{Cl}$) Bottom-right: A plane calculated through the Pd, $\text{P}(\text{PR}_2)$ and Cl atoms Sum-of-squares error: $0.00780 \text{ \AA}^2/\text{n}$. Seven molecules of CHCl_3 , present within the unit cell were omitted for clarity. Note the non-coordinating Cl^- counteranion ($\text{Cl}2$), which sits in front of one of the $\text{P}(1)\text{PPh}_3$. Thermal ellipsoids have been set at 50%. Hydrogen atoms have been omitted for clarity. Selected bond distances / $\text{\AA}$: $\text{Cl}1\text{-Pd}=2.3828(8)$, $\text{Cl}1\text{-Pd}3=2.4002(8)$, $\text{P}1\text{-Pd}1=2.2837(8)$, $\text{P}2\text{-Pd}1=2.1905(8)$, $\text{P}2\text{-Pd}2=2.2775(8)$, $\text{P}3\text{-Pd}2=2.3034(8)$, $\text{P}4\text{-Pd}2=2.2670(8)$, $\text{P}4\text{-Pd}3=2.1967(8)$, $\text{P}5\text{-Pd}3=2.2913(8)$, $\text{Pd}1\text{-Pd}2=2.9138(3)$, $\text{Pd}1\text{-Pd}3=2.8882(3)$, $\text{Pd}2\text{-Pd}3=2.9127(3)$. Selected interatomic angles / $^\circ$: $\text{Pd}3\text{-Pd}2\text{-Pd}1=59.432(8)$, $\text{Pd}1\text{-P}2\text{-Pd}2=81.38(3)$, $\text{Pd}1\text{-Cl}1\text{-Pd}3=74.29(2)$.

This is the first time that the $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ cluster (*i.e.* featuring a Cl^- non-coordinating counteranion) has been characterised crystallographically, however it is highly comparable with reported X-ray crystal structures for the related complexes $\text{Pd}_3\text{Cl}\cdot\text{SbF}_6$ and $\text{Pd}_3\text{Cl}\cdot\text{BF}_4$, which both feature different (non-nucleophilic) counteranions.^{169,172} In the case of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ (Figure 51), the triangular Pd core which is – to a close approximation equilateral – lies on the same plane as the $\mu\text{-Cl}$ (plane sum of least squares error = $0.00780 \text{ \AA}^2/\text{n}$). The three Pd–Pd interactions are approximately equal in length (E.S.D = 0.0003 $\text{\AA}$ for each) and longer than that measured for the Pd^{I} dimers reported in this work: **52** (2.5958(3) $\text{\AA}$), **58** (2.5680(10) $\text{\AA}$) and **62** (2.6140(5) $\text{\AA}$). The Pd–Pd bond length is also in line with reported bond lengths (2.928, 2.894 & 2.935 $\text{\AA}$) for the related cluster $[\text{Pd}(\mu\text{-Cl})(\mu\text{-PPh}_2)(\text{PEt}_3)_3]^+[\text{BF}_4]^-$, which features the stronger σ -electron donor ligand PEt_3 instead of PPh_3 .²⁵⁸ The two $\text{PPh}_2\text{-Pd}$ bridging bond distances

are significantly different for each diphenylphosphido ligand making the bridging interaction asymmetric, in line with that of the PPh_2 ligands in Pd^{I} dimers **52** and **58**, reported *vide infra*. The three $\kappa\text{-PPh}_3$ ligands lie slightly out of this plane in a *syn* orientation (sum of least squares error = $0.20092 \text{ \AA}^2$, if phosphine P atoms are included in the calculation of the plane). The second Cl_2 anion does not co-ordinate directly to the tripalladium metal core. The Pd-P-Cl -containing core of the molecule exhibits C_{2v} symmetry, around an axis defined by the line through the *Cl1*, *Pd2* and *P3* atoms. Each Pd atom within the cluster displays a formal oxidation state of $4/3$.

For the purpose of discussion, the two inequivalent phosphine environments have been named in terms of their distance from the *Cl1* ion (which disrupts the symmetry), *P1* and *P5* have been defined as *proximal*, while the *P3* has been defined as *distal*.

^{31}P NMR spectroscopic analysis proved useful for rationalising the structure of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ in solution. Coupling was evident between phosphorus resonances in $\text{THF-}d_8$ (Figure 52).

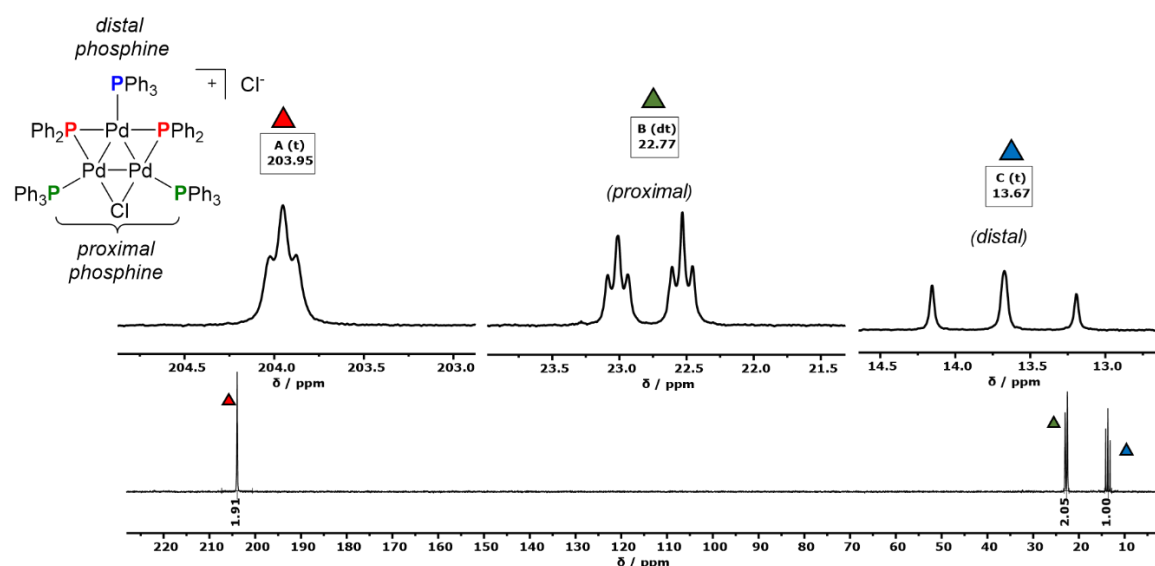


Figure 52 ^{31}P NMR spectrum (202.5 MHz, $\text{THF-}d_8$) of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$, showing expansions of the three chemical shifts representative of the three phosphorus environments, displayed alongside a representation of the structure.

There are three resonances in the ^{31}P NMR spectrum of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ (recorded in $\text{THF-}d_8$): a low field phosphido resonance which appeared as a triplet at δ 203.0 ppm (2P), peaks in a region for Pd-coordinated PPh_3 which appeared as a doublet of triplets at δ 22.8 ppm (2P), and another, PPh_3 -type resonance at δ 13.7 ppm appeared as a triplet. Coupling between the *distal* and *proximal* phosphine environments was evident, with matched high-magnitude coupling constants of $^3J_{\text{P-P}} = 97 \text{ Hz}$. This relatively large coupling constant value is consistent with the 3J *trans*-orientation between the *distal* and *proximal* phosphines across the tripalladium core. Due to relative integration values, the phosphine

shifts at δ 22.8 (2P) and 13.7 ppm (1P) were assigned as the *proximal* and *distal* phosphines, respectively. Coupling between phosphido and *proximal* phosphines was evident by a matched coupling-constant $^2J_{P-P}$ = 16 Hz. In THF- d_8 coupling between *distal* and phosphide resonances was not evident under these conditions. This NMR data matches data obtained from the reaction between **52** and CH₂Cl₂. ESI-mass spectral analysis of authentic **Pd₃Cl·Cl** showed a peak at exact mass m/z 1553.0062, with the expected isotopic distribution, representative of the [Pd₃(μ -Cl)(μ -PPh₂)₂(PPh₃)₃]⁺ ion, as was observed by ESI-MS of the reaction between **52** and CH₂Cl₂ a peak at **Pd₃Cl·Cl**.

In an adapted procedure, originally published by Dixon *et al.* in 1978, [Pd₃(μ -Cl)(μ -PPh₂)₂(PPh₃)₃]⁺Cl[−] (**Pd₃Cl·Cl**) was treated with a high excess of KBr to convert it to [Pd₃(μ -Br)(μ -PPh₂)₂(PPh₃)₃]⁺Br[−] (**Pd₃Br·Br**).¹⁶⁷ Single crystals could be grown by slow evaporation of THF, from which the **Pd₃Br·Br** structure was revealed by single crystal X-ray diffraction analysis (Figure 53).

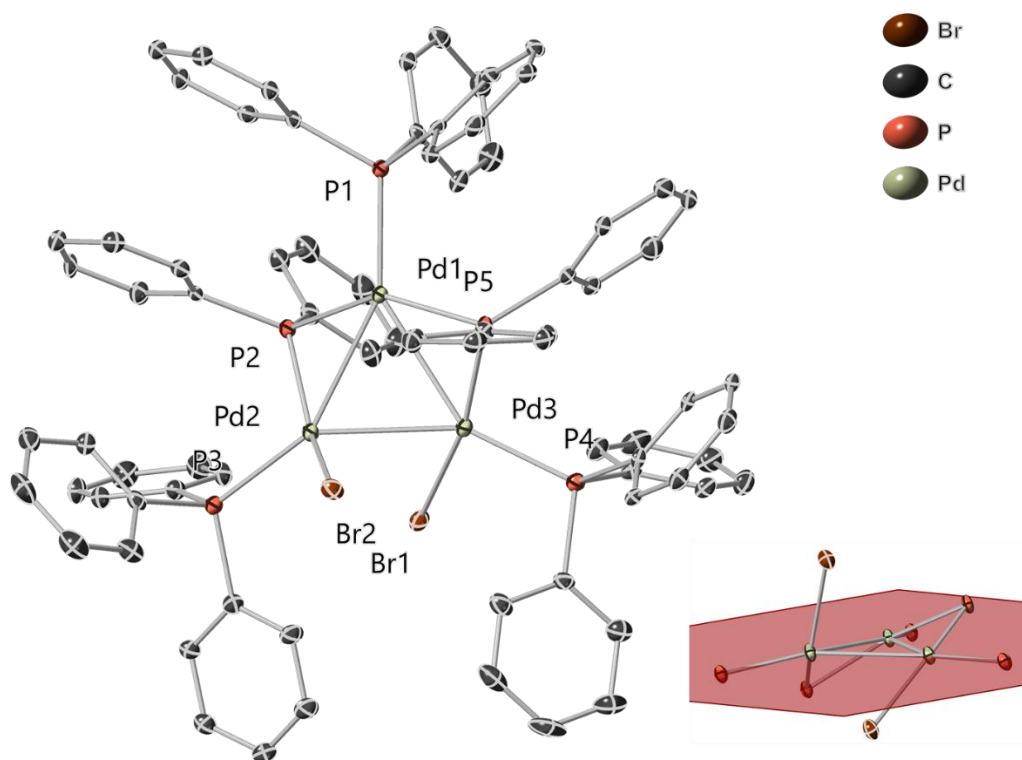


Figure 53 Structure, obtained by single crystal X-ray diffraction for [Pd₃(μ -Br)(μ -PPh₂)₂(PPh₃)₃]⁺Br[−] (**Pd₃Br·Br**). Hydrogen atoms have been omitted for clarity. One THF molecule of crystallisation has been omitted for clarity. Bottom-right: A plane (pink) calculated through the Pd, P (PPh₃) atoms and Cl atoms Sum-of-squares error: 0.05895 Å²/n. Selected interatomic distances /Å: 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–P3=2.299(3), Pd1–P1=2.299(2) Pd2–P2=2.210(2), Pd1–P2=2.262(2). Selected interatomic angles /°: 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).

It should be noted that the R1 factor for the diffraction data of **Pd₃Br·Br** (Figure 53) = 7.04%, precluding a detailed quantitative comparison to that of **Pd₃Cl·Cl** (Figure 51, R1 factor = 3.58%). Some significant qualitative observations can be made, however. One notable difference is that, instead of the counteranion being non-coordinating, as was the case with **Pd₃Cl·Cl**, with **Pd₃Br·Br** neither bromide anion is bridging and both are κ -coordinated to proximal Pd ions, with one pointing up and one pointing down. Additionally, in the case of **Pd₃Br·Br**, the cluster is twisted, with P(Ph₂) atoms being staggered, with one pointing up and one pointing down while the triangular Pd core lies on approximately the same plane as the P(Ph₃) atoms (Sum-of-squares error: 0.05895 Å²/n). This observation indicates that there is steric hindrance at the PPh₃ and PPh₂ ligands, which, in turn is likely caused by hindrance from the coordination of the two Br⁻ anions. The coordination of the two Br⁻ anions in **Pd₃Br·Br** indicates that generally Br⁻ anions can coordinate better with the Pd₃ core than Cl⁻, in spite of the increased size of Br⁻ relative to Cl⁻,²⁵⁹ apparently resulting in steric hindrance at the complex. This phenomenon may be due the softer nature of the Br⁻ ions relative to Cl⁻, perhaps allowing for better orbital overlap with the Pd₃ core. The observed stark differences in solid-state structure between **Pd₃Cl·Cl** and **Pd₃Br·Br** could point towards differences in reactivity between the two complexes, however there was only a very marginal difference observed in the catalytic competence of **Pd₃Br·Br** *vs.* **Pd₃Cl·Cl** in a model SMCC reaction (see Section 3.2.2).

This constitutes the first time that the **Pd₃Br·Br** cluster complex has been interrogated crystallographically, however a single crystal X-ray structure has been recorded for a [Pd₃(μ -Br)(μ -PPh₂)₂(PPh₃)₃]⁺X⁻-type complex by Aldridge *et al.*²⁶⁰, who isolated an analogous cluster complex featuring a mixed occupancy bridging halide site (Cl or Br) (Figure 54). Similarly, substitution of one of the bromides with the non-coordinating [SbF₆]⁻ anion, as reported by Li *et al.* also leads to formation of the mono- μ -Br-bridged complex.

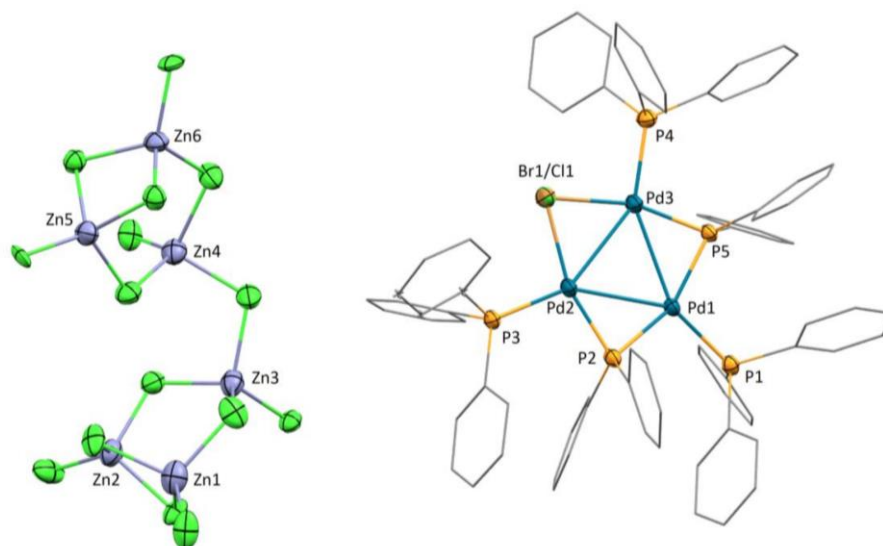


Figure 54 The crystal structure of $[\text{Zn}_6\text{Cl}_{15}][\text{Pd}_3\text{X}]_3$ ($\text{X} = \text{Cl}^-$ & Br^-) as reported by Aldridge *et al.*, featuring a mixed-occupancy bridging chloride and bromide ligand in the presence of a non-coordinating $[\text{Zn}_6\text{Cl}_{15}]^{3-}$ anion. Reproduced with permission from *Chem. Eur. J.* 2017, 23, 12655-12667. Copyright 2017 Wiley-VCH Verlag GmbH & Co.

In this case (Figure 54), very bulky, non-coordinating counter-anions $[\text{Zn}_6\text{Cl}_{15}]^{3-}$ (1/3 equivalent per Pd_3Br^+) were present and the halide, P and Pd atoms were seen to lie in the same plane. It is therefore likely that the coordinating nature of the second Br^- ion $\text{Pd}_3\text{Br}\cdot\text{Br}$ has a significant effect on the cluster structure, causing the observed steric clashes within of the core structure, as observed in the crystal structure of $\text{Pd}_3\text{Br}\cdot\text{Br}$ obtained in this work (Figure 53).

As with $\text{Pd}_3\text{Cl}\cdot\text{Cl}$, three resonances were evident in the ^{31}P NMR spectrum of $\text{Pd}_3\text{Br}\cdot\text{Br}$ (Figure 55), at δ 210.6 ppm (triplet, 2PPh_2), δ 24.0 ppm (2PPh_3) and 12.4 ppm (1PPh_3).

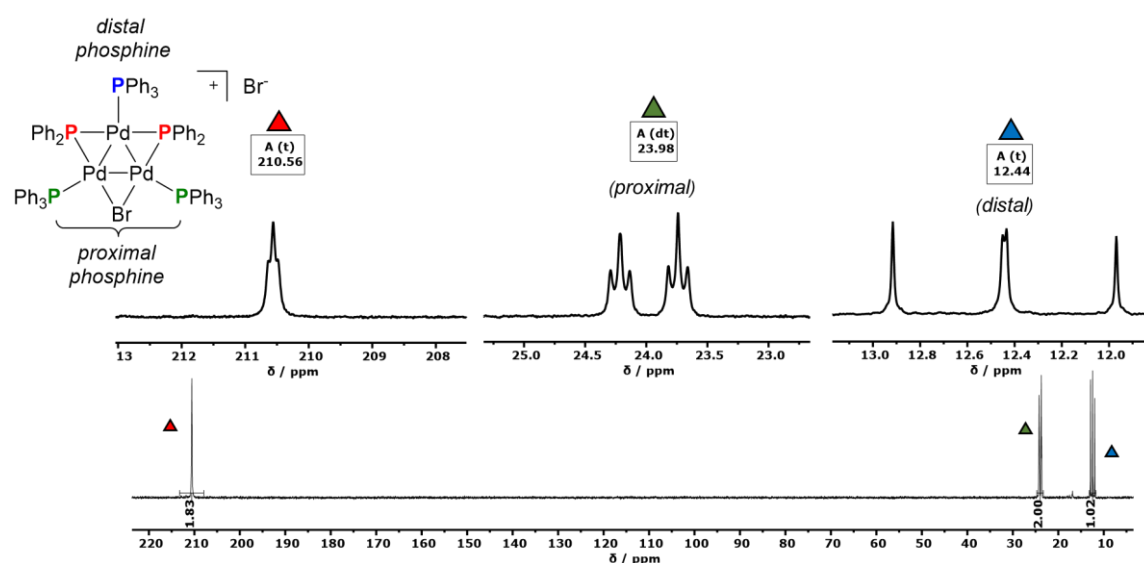


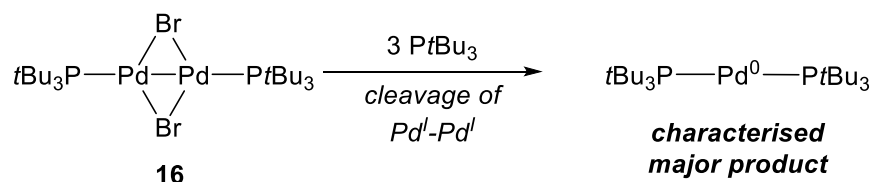
Figure 55 ^{31}P NMR spectrum (202.5 MHz, $\text{THF}-d_8$) of $\text{Pd}_3\text{Br}\cdot\text{Br}$, showing expansions of the three shifts representative of the three phosphorus environments, displayed alongside a labelled representation of the structure.

A large coupling ($^3J_{P-P} = 97$ Hz) was measured between the two PPh_3 (*proximal* and *distal*) environments of **Pd₃Br·Br**, which was similar to that of **Pd₃Cl·Cl**. Additionally, a smaller coupling ($^2J_{P-P} = 16$ Hz) was measured between PPh_2 and the *proximal* phosphine. It is of note that, although the solid-state structure of **Pd₃Br·Br** indicates two coordinating, bromide ligands, if this phenomenon is present in CD_2Cl_2 solution, it does not significantly perturb the structure enough in the solution phase to change the ^{31}P NMR spectrum compared with **Pd₃Cl·Cl**. This ^{31}P NMR data matches these data obtained from the reaction between Pd^I dinuclear complex **52** and 2-bromopyridine **55**, further confirming that the **Pd₃Br·Br** cluster arises from this reaction mixture. Additionally, ESI-mass spectral analysis of authentic **Pd₃Br·Br** showed a peak at exact mass, 1553.0062, with the correct isotopic distribution, representative of the $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+$ ion.

This section reported data which characterised authentic samples of **Pd₃Cl·Cl** and **Pd₃Br·Br**, confirming the presence of these complexes in reactions between **52** and organohalides (Section 2.5).

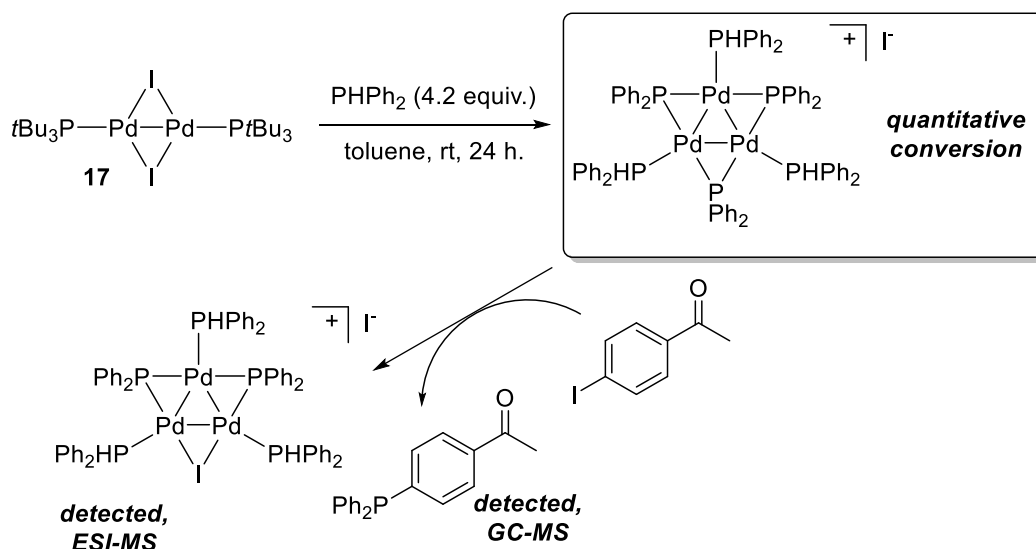
2.5.3. Reactivity of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** with Additional PPh_3

The reactivity of Pd^I dinuclear complexes with additional phosphine ligand is not well understood in the literature. Colacot and Schoenebeck stated that treatment of the Pd^I dimer complex $[\text{Pd}(\mu\text{-Br})(\text{PtBu}_3)]_2$ **16** with an additional 3 equivalents of PtBu_3 ‘provided mostly $(\text{PtBu}_3)_2\text{Pd}$ ’ (Scheme 44).⁵⁷



Scheme 44 Colacot and Schoenebeck indicated that the major product from the reaction between $[\text{Pd}^{\text{I}}(\mu\text{-Br})(\text{PtBu}_3)]_2$ (**16**) was the Pd^0 complex $[\text{Pd}^0(\text{PtBu}_3)_2]$. The authors did not state what conditions were used (*e.g.* solvent) nor give any details of mass balance.

A straightforward rationalisation of the observation of the formation of $[\text{Pd}^0(\text{PtBu}_3)_2]$ in this case would be that a PtBu_3 -induced disproportionation of the $\text{Pd}^{\text{I}}\text{-Pd}^{\text{I}}$ bond of **16** occurred to abstract the Pd^0 complex. If this is the case, then the question arises: what happens to the remaining putative Pd^{II} fragment ‘ $[\text{Pd}^{\text{II}}(\text{Br})_2(\text{PtBu}_3)]$ ’, which must form in order to balance the reactivity? Schoenebeck *et al.* published, while *this project* was in progress, that the reaction of the related, iodide-bridged dimer $[\text{Pd}^{\text{I}}(\mu\text{-I})(\text{PtBu}_3)]_2$ **17** with diphenylphosphine (PPh_2), in toluene at room temperature resulted in a quantitative conversion to the trinuclear Pd_3 complex $[\text{Pd}_3(\mu\text{-PPh}_2)_3(\text{PPh}_2)_3]^+\text{I}^-$ (Scheme 45, see Section 1.4 for further details).¹⁶²



Scheme 45 Reaction of **17** with diphenylphosphine (4.2 equivalents) yields the trinuclear Pd cluster $[\text{Pd}_3(\mu\text{-PPh}_2)_3(\text{PhPPh}_2)_3]^+\text{I}^-$ which reacts with *para*-iodoacetophenone to yield the trinuclear Pd cluster complex $[\text{Pd}_3(\mu\text{-I})(\mu\text{-PPh}_2)_2(\text{PhPPh}_2)_3]^+\text{I}^-$.

An increase in overall formal oxidation state *per* Pd ($1 \rightarrow 4/3$) occurred during the process of forming $[\text{Pd}_3(\mu\text{-PPh}_2)_3(\text{PhPPh}_2)_3]^+\text{I}^-$. It is of note that the PhPPh_2 completely displaced P^tBu_3 from the its precursor complex (**17**), indicating that the π -accepting ligand PhPPh_2 forms a more favourable interaction than the strong σ -donor phosphine P^tBu_3 .²⁶¹ Furthermore, upon treatment of this cluster complex with *para*-iodoacetophenone, C–I bond activation proceeded resulting in conversion to a tripalladium cluster complex adopting the **Pd₃I·X** motif (see Section 1.4, Scheme 19).¹⁶⁸ Similar treatment of $[\text{Pd}_3(\mu\text{-PPh}_2)_3(\text{PhPPh}_2)_3]^+\text{I}^-$ with *para*-bromo- or chloro- acetophenone did not result in C–X bond activation, an observation which was correlated with the ability of $[\text{Pd}_3(\mu\text{-PPh}_2)_3(\text{PhPPh}_2)_3]^+\text{I}^-$ to chemoselectively activate C–I bonds over C–Br and C–Cl bonds in Kumada cross-coupling applications. This work demonstrated that, by exploring the fundamental stoichiometric reactivity of the I-bridged Pd^I dimer **17**, access to a uniquely active catalyst exhibiting a finely tuned activity could be achieved. Figueroa *et al.* reported that the allyl- and alkoxy-bridged Pd^I dimer **20**, featuring isocyanide ligands, spontaneously disproportionates to Pd⁰ and Pd^{II} components, resulting in the formation of a zero-valent tripalladium complex **21** after an intramolecular reduction at a Pd^{II} complex (See Section 1.4, Scheme 20).¹⁷⁷ A similar cleavage of $[\text{Pd}^{\text{I}}_2(\text{PMe}_3)_6]^{2+}[\text{hfac}]^{2-}$ by disproportionation was hypothesised as an intermediate step *en route* to the formation of observed $[\text{PdMe}(\text{PMe}_3)_3]^+[\text{hfac}]^-$ was postulated by Girolami *et al.*, however in this case the evidence presented was not sufficient to prove this pathway of reactivity.¹⁴² In this section, work is presented towards understanding of the reactive events when the novel Pd^I dinuclear complex $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** is treated with additional PPh_3 .

2.5.3.1. Characterisation of the Reaction Between $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** and nPPh_3

$[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52**, isolated from the reaction of $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 , was reacted with 1 equivalent of PPh_3 in THF-d_8 , at room temperature. After *ca.* 30 minutes ^{31}P NMR spectral analysis (298 K) revealed several new features (b., Figure 56), which could be compared with an authentic sample of **52** (a., Figure 56). A broad peak at δ_{P} 199.6 ppm was assigned as unreacted **52** (PPh_2 resonance). Loss of resolution of this triplet was evident, in addition to a slight shift to a lower field (δ_{P} 199.1 $\rightarrow$ 199.6 ppm), which is likely a result of the complex's participation of exchange equilibria associated with the presence of added PPh_3 . Two new low-field resonances at δ_{P} 122.6 and 77.3 ppm appeared with doublet (*d*) and doublet of doublet (*dd*) multiplicities, respectively, which integrated with a ratio of 1:1. A major, broad resonance at δ_{P} 23.9 ppm was evident. Two broad, unresolved resonances at approximately δ_{P} 26.0 and 15.0 ppm (PPh_3 -type chemical shifts) were also observed.

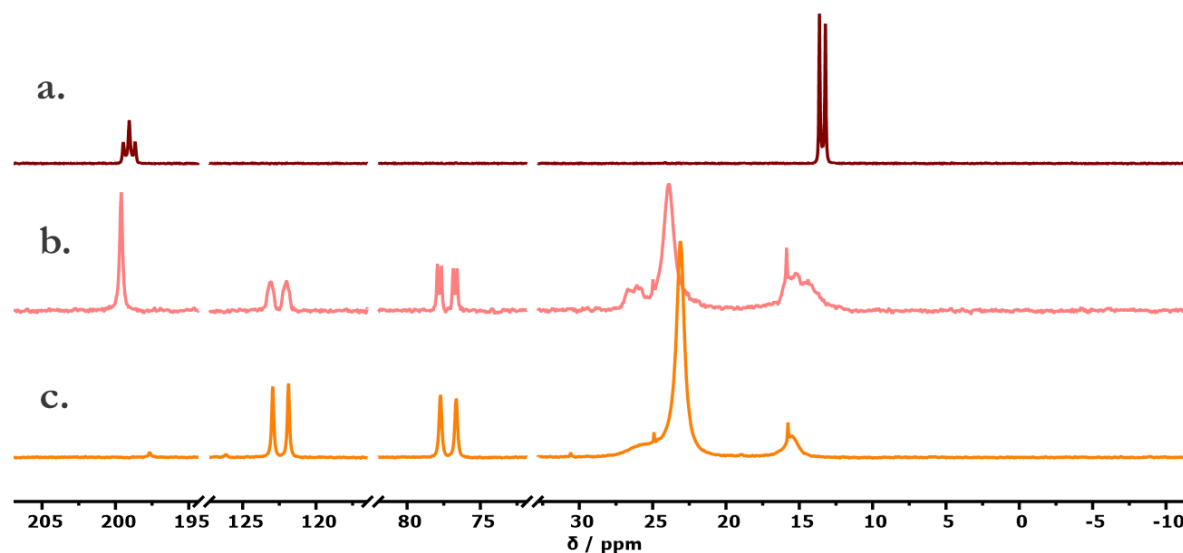


Figure 56 ^{31}P NMR spectra (202.5 MHz, 512 Sc, 298 K) showing the reaction of **52** with additional PPh_3 , at 25 °C in THF-d_8 after *ca.* 30 mins. a.) authentic sample of **52**, presented for comparison with: (b.) Reaction mixture of **52** with 1 equivalent of PPh_3 and (c.) Reaction mixture of **52** with 2 equivalents of PPh_3 . Note the excised regions of the spectra, between *ca.* 127-195 and 32-82 ppm, done so that the resonances could be shown together.

The presence of the PPh_2 ^{31}P NMR resonance at 199.6 ppm, upon treatment of **52** with 1 equivalent of PPh_3 indicated the presence of **52** in the post-reaction solution (Figure 56), suggesting that the reaction had gone to partial completion. Hence, upon reacting **52** with 2 equivalents of PPh_3 at room temperature, in THF-d_8 , further reaction progression was evident by ^{31}P NMR analysis (c. Figure 56) after *ca.* 30 mins, compared with the equivalent reaction with 1 equivalent of PPh_3 (b. Figure 56). Complete loss of **52** was evident by the disappearance of its PPh_2 resonance. Low-field resonances at δ_{P} 122.6 and 77.3 ppm were again present, but had appeared to broaden out, with both appearing as

doublets. The major, broad resonance had appeared to shift upfield (δ_P 23.9→23.1 ppm) in this case. Broad resonances at δ_P 25.6 and 15.6 ppm were evident, and had broadened out, indicating exchange processes between PPh_3 ligands. Reacting **52** with 10 equivalents of PPh_3 resulted in complete disappearance of these resonances and a movement of the major singlet far upfield to 7.25 ppm (THF as solvent, externally referenced to $H_3PO_4(aq)$ 85% w/w). The observation is analogous with that observed upon treating a $[Pd^0(PPh_3)_n]$ complex with additional PPh_3 (see Section 2.3, for further details on this phenomenon).^{46, 221}

Mass spectral analysis of the same solution provided evidence towards the identity of the species present. LIFDI-MS showed a peak at m/z 892.1769 conforming to the radical cation $[Pd(PPh_3)_3]^+$ with the correct isotopic distribution pattern, indicating the presence of $[Pd^0(PPh_3)_3]$ **48** in solution, (right, Figure 57). LIFDI-MS indicated presence of a prominent cation at m/z 1122.0882 (left, Figure 57). ESI-MS corroborated this finding, detecting the corresponding $[M+H]^+$ cation (m/z 1123.0960) with the correct isotopic distribution. Structures that fit the exact masses and isotopic distributions (and later confirmed to be major species in the solution) are given in Figure 57.

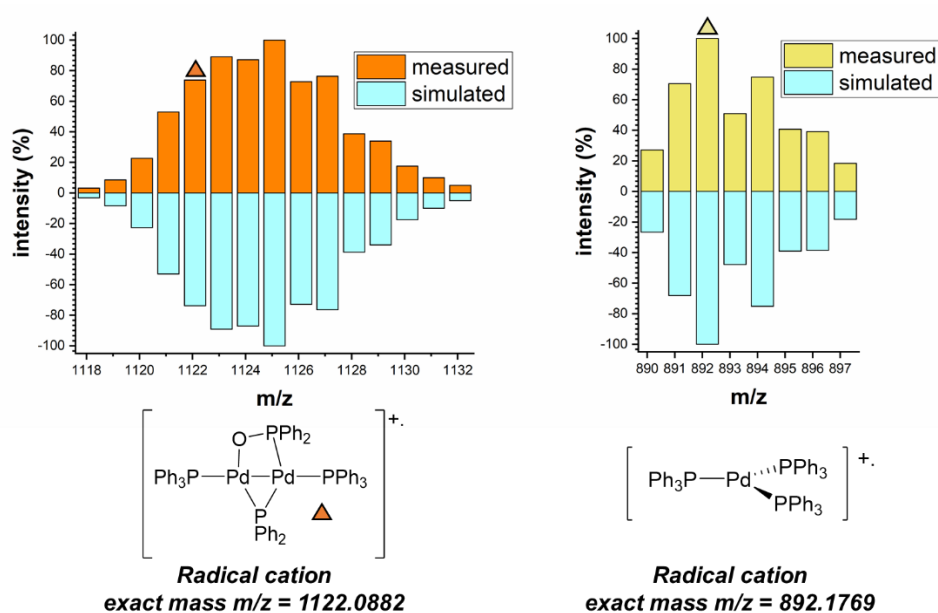


Figure 57 LIFDI-MS spectral analysis of the reaction between **52** and 2 equivalents of PPh_3 , showing exact masses and isotopic distributions of peaks, displayed alongside representative structural formulae.

Bright red single crystals were grown from a THF- d_8 solution of **52** and 2 equivalents of PPh_3 after overnight storage at $-18^\circ C$. One such crystal was subjected to X-ray diffraction, confirming the structure to be a new Pd^I - Pd^I dinuclear complex $[Pd^I_2(\mu-PPh_2)\{\kappa_2-P,O-\mu-P(O)Ph_2\}(\kappa-PPh_3)_2]$ **58**, bridged by one μ_2 -dihphenylphosphido ligand and one diphenylphosphinito (κ_2 - $(P,O)-\mu_2$ - $P(O)Ph_2$) ligand, which bridges the Pd centres through one P and one O atom (Figure 58). The calculated exact

mass and isotopic distribution (m/z) of the structure of **58**, as obtained by single crystal X-ray diffraction fitted with the cation observed by LIFDI-MS (Figure 57).

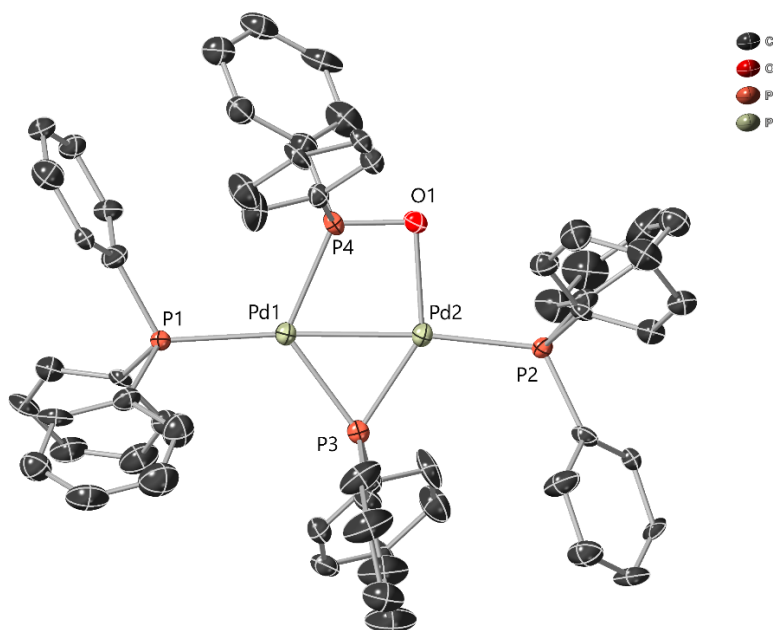
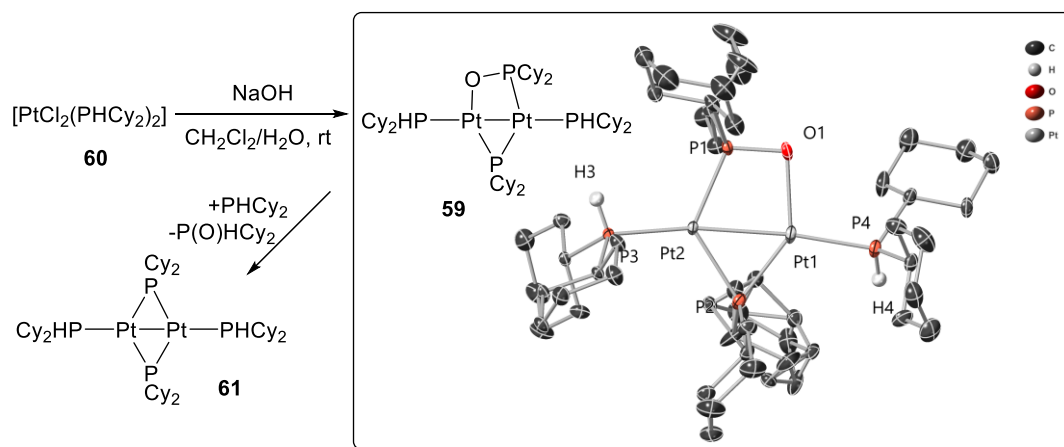


Figure 58 Molecular structure of $[\text{Pd}^{\text{I}}_2(\mu\text{-PPh}_2)\{\kappa_2\text{-P,O-}\mu\text{-P(O)Ph}_2\}(\kappa\text{-PPh}_3)_2]$ (**58**), obtained *via* X-ray diffraction of a single crystal grown from THF- d_8 reaction solution of **52** with 2 equivalents of PPh_3 . Hydrogen atoms have been omitted for clarity. Thermal ellipsoids set at 30% probability. Selected interatomic distances /Å: Pd1–Pd2=2.5680(10), Pd1–P1=2.360(9) Pd2–P2=2.275(9), Pd1–P3=2.316(3), Pd2–P3=2.210(3) P1–P4=2.328(3), P4–O1=1.550(8), P2–O1=2.150(7). Selected interatomic angles /°: Pd1–P3–Pd2=69.093, Pd1–Pd2–O1=86.162, Pd2–O1–P4=93.688.

The X-ray diffraction data (Figure 58) showed the structure of **58** to be similar to other $\text{Pd}^{\text{I}}\text{--Pd}^{\text{I}}$ structures, such as **52** (*vide supra*). The Pd–Pd bond length was 2.5680(10) Å: *ca.* 1.1 % shorter than the phosphido-bridged $\text{Pd}^{\text{I}}\text{--Pd}^{\text{I}}$ complex **52** (2.5958(3) Å), and characteristic of a $\text{Pd}^{\text{I}}\text{--Pd}^{\text{I}}$ bonding interaction.^{146, 148, 244-245} The Pd– $\text{PPh}_2(\text{O})$ bond length was measured at 2.328(3) Å, which was longer than that of the P– PPh_2 (diphenylphosphido) bond lengths measured in this complex, as well as **52** (and **62** *vide infra*). The P–O bond (1.550(8) Å) of the PPh_2 ligand has significant double bond-character, being close in length to that of $\text{O}=\text{PPh}_3$ (P–O bond length is 1.479(2) Å).²⁶² The P–O bond length is in line with a known bridging phosphinito Pd^{II} dimer complex.²⁶³ The complex was significantly desymmetrised along the $\text{Ph}_3\text{P--Pd--Pd--PPh}_3$ bond axis, with the Pd1–P1 interaction (2.360(9) Å) being approximately 4% longer than that of Pd2–P2 (2.275(9) Å). For comparison, the C2 symmetrical complex **52** exhibits Pd– PPh_3 bond distances of 2.3002(7) and 2.3001(7) Å, which were both intermediate in value to the Pd– PPh_3 bond distances measured crystallographically for **58**. The Pd– PPh_2 bond lengths were accordingly distorted: with the P1–P3 and Pd2–P3 bond lengths being 2.316(3) and 2.210(3) Å, respectively, contrasting with that of the symmetrical diphenylphosphido ligand in **52**, whose analogous bond lengths were remarkably similar. The Pd–Pd bond length was 2.5680(10) Å: *ca.* 1.1 % shorter than the phosphido-bridged $\text{Pd}^{\text{I}}\text{--Pd}^{\text{I}}$ complex **52** (2.5958(3) Å).

To the author's knowledge this structure constitutes the first example of a Pd^I–phosphinito complex, however an analogous Pt complex is known – [Pt₂(μ-PCy₂){κ₂-P,O-μ-P(O)Cy₂}(κ-PCy₃)₂] **59**, which was synthesised by Mastroilli *et al.* by treating [PdCl₂(PHCy₂)₂] **60** with hydroxide base (Scheme 46) in a CH₂Cl₂/H₂O mixture at room temperature.²⁶⁴ In this case, the P–O bond length of the bridging phosphinito ligand was 1.556(4) Å, which is the same as the P–O bond length in **58** however still indicative of double bond character.



Scheme 46 Synthesis of [Pt₂(μ-PCy₂)(κ₂-P,O-μ-Cy₂PO)(κ-Cy₂PH)₂] **59** and its reactivity with additional dicyclohexylphosphine. Crystal structure image produced on Crystallmaker® software, using XRD data published by Mastroilli *et al.* *Inorg. Chem.* 2008, 47, 4785-4795.²⁶⁵

Reaction of **59** with excess PHCy₂ ligand resulted in protonation and dissociation of the phosphinito ligand and conversion to the C₂-symmetric *bis*-dicyclohexylphosphido-bridged Pt^I–Pt^I dimer [Pt(μ-PCy₂)(PHCy₂)₂] **61** (Scheme 46).²⁶⁵ Subsequent studies on the reactivity of **59** with small molecules found the complex to be amphiphilic in nature, being able to react with both Brønsted acids (electrophiles) and nucleophiles.^{246, 266} The calculated exact mass and isotopic distribution (*m/z*) of the structure of **58**, obtained by single crystal X-ray, diffraction fitted with the cation observed by LIFDI-MS (Figure 57).

To reduce the effect of the observed exchange processes and hence confirm the contents of solution species by ³¹P NMR spectroscopy, the reaction between **52** and 2 equivalents of PPh₃ was subjected to low temperature ³¹P NMR analysis (173 K) (Figure 59).

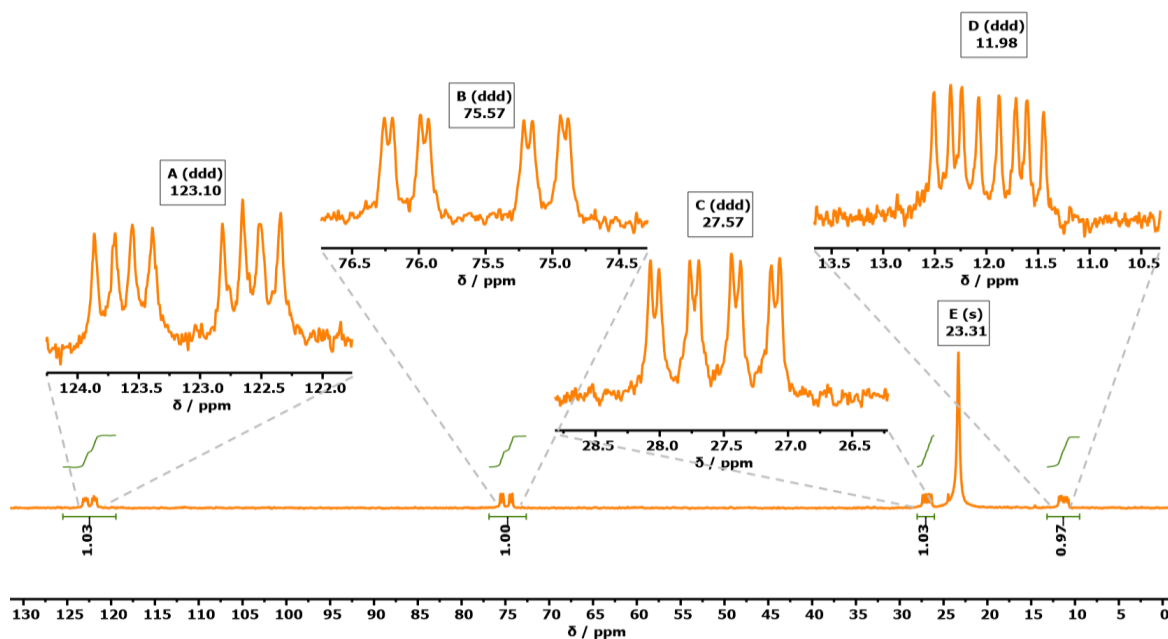


Figure 59 ^{31}P NMR (202.5 MHz, THF-d_8 , 173 K 512 Scans), using low temperature to slow down chemical exchange processes, allowing for resolution of multiplets. Showing expansions of peaks representative of **58**, as assigned on the basis of this, and other, data (Figure 60).

Upon cooling the THF-d_8 solution to 173 K ($\Delta T = -125$ K *cf.* Figure 56), the resonances were seen to clearly resolve (Figure 59). The low-field resonances as observed at 298 K were marginally shifted to δ_{P} 123.1 and 75.6 ppm, resolved as doublet of doublet of doublets (*ddd*). The two high field (PPh_3 -type) chemical shifts at δ_{P} 27.6 and 12.0 ppm were seen to fully resolve, also revealing *ddd* multiplicities. Coupling constants indicated that these four resonances were all mutually $J_{\text{P-P}}$ coupled (See Table a., Figure 60 and accompanying text for structural assignment of resonances). This mutual coupling was further supported by ^{31}P – ^{31}P COSY analysis (b., Figure 60). A prominent, broad PPh_3 -type chemical shift was again present at δ_{P} 23.3 ppm at 173 K. Significant sharpening of this resonance was apparent [$\Delta\nu_{1/2}$ 129→66 Hz (298→173 K)] pointing towards it being in fast chemical exchange with other PPh_3 -type resonances at 298 K. Due to the variable nature of this chemical shift in response to varying amounts of PPh_3 , along with the presence of the $[\text{Pd}(\text{PPh}_3)_3]^+$ radical cation detected by LIFDI-MS (Figure 57) in the post-reaction solution, this major species was assigned as $[\text{Pd}^0(\text{PPh}_3)_3]$ **48**. The clear sharpening of this resonance at 173 K points towards the existence of chemical exchange between P nuclei (of PPh_3 -type ligands) at 298 K. The presence of **48** was additionally confirmed through the detection of the oxidative addition product: *trans*- $[\text{Pd}^{\text{II}}(\text{Br})(\text{C}^2\text{-pyridyl})(\text{PPh}_3)_2]$ **57**, by ^{31}P NMR at expense of **48**, upon treatment of the system with 2-bromopyridine **55**, liberating PPh_3 (Section 2.5.3.2.1 *vide infra*).

The coupling constants for the four *ddd* peaks (A, B, C and D, Figure 59), observed in the ^{31}P NMR spectrum of the crude reaction solution are tabulated (a. Figure 60) and assigned to the P atoms as

obtained from the crystal structure of **58** (Figure 58). All four peaks were seen to integrate to a ratio of 1:1:1:1. High-magnitude coupling (217.2 Hz) was observed between the two lower field resonances (δ_P 123.1 and 75.6 ppm), consistent with $^2J_{P-P}$ (*trans*) coupling of the phosphido ligands. A large coupling constant (131.5 Hz) was also observed between the two PPh_3 -type resonances, **C** and **D**: consistent with longer range $^3J_{P-P}$ (*trans*)-coupling. Coupling constants in line with $^2J_{P-P}$ (*cis*) coupling were observed between **A** and **C** (61.5 Hz), and **A** and **D** (33.6 Hz), showing that phosphine **C** and **D** experience comparable magnetic influence from **A**. **B** on the other hand couples to **D** in line with $^2J_{P-P}$ (*cis*) (55.8), however a much smaller coupling constant (15.8 Hz), indicative of $^2J_{P-P}$ (*cis*), was observed between **B** and **C**. This lower coupling constant indicates that an atom lies between **B** and **C**, consistent with the presence of the O atom between **B** and **C**.

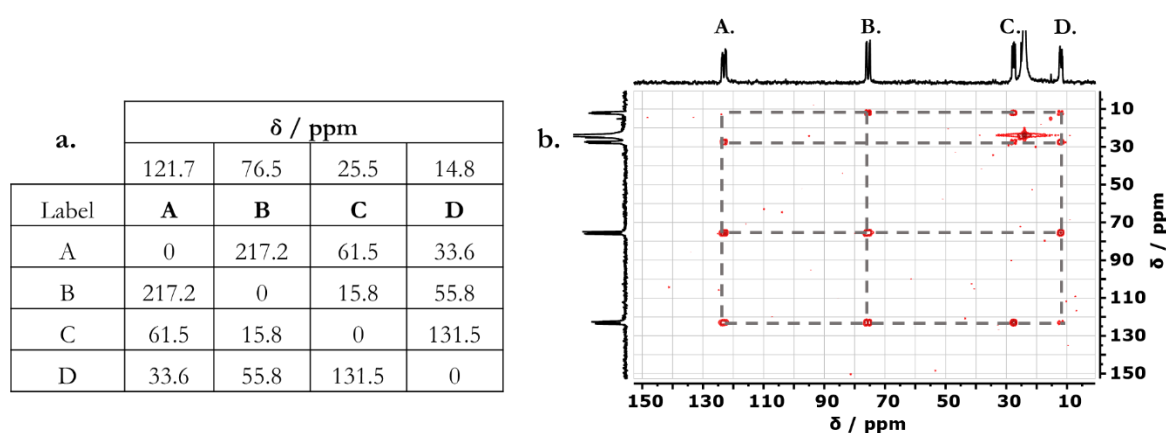


Figure 60 J_{P-P} coupling constants between resonances of **58** in the reaction between **52** and 2 equivalents of PPh_3 . (a.) table displaying couplings observed between chemical shifts, extracted from spectral data as displayed in Figure 59. (b.) ^{31}P - ^{31}P COSY spectrum confirming coupling between assigned resonances.

This ^{31}P NMR data are in full agreement with what would be anticipated on the basis of the connectivity of the crystal structure (Figure 58) and the radical cation $[Pd^I_2(\mu-PPh_2)\{\kappa_2-P,O-\mu-P(O)Ph_2\}(\kappa-PPh_3)_2]^+$ as indicated by MS analysis (Figure 57). The assignment of the ^{31}P NMR spectrum of this species, with reference to the coupling data (a, Figure 60), is shown below (Figure 61).

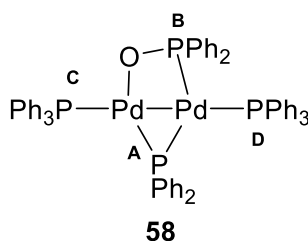


Figure 61 The structure of **58** with phosphorus atoms labelled as assigned from the ^{31}P NMR spectrum recorded at 173 K (Figure 59 & Table a., Figure 60).

Thus, the two major Pd–P-containing species observed in the ^{31}P NMR spectrum of the reaction between $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** and 2 equivalents of PPh_3 are $[\text{Pd}^{\text{I}}_2(\mu\text{-PPh}_2)\{\kappa_2\text{-P,O-}\mu\text{-P(O)Ph}_2\}(\kappa\text{-PPh}_3)_2]$ **58** and $[\text{Pd}^0(\text{PPh}_3)_3]$ **48**.

Analysis of the same THF- d_8 post-reaction solution by ^1H NMR spectroscopy showed a single major *acetate* ($-\text{CH}_3$)-type resonance at δ_{H} 2.15 ppm (Figure 62). Additionally, $^{13}\text{C}\{^1\text{H}\}$ NMR analysis showed a *carbonyl* ($\text{R}-\text{C}(\text{O})-\text{R}$)-type singlet at δ 166.2 ppm and an *acetate* ($-\text{CH}_3$)-type singlet at δ 20.9 ppm. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR analysis of an authentic sample of acetic anhydride in THF- d_8 showed exactly the same chemical shifts, demonstrating acetic anhydride (Ac_2O) to be a major product of the reaction. It was additionally evident by comparative integration of ^1H signal of an assigned *ortho*-H of the diphenylphosphido ligand peak on **58** and the ($-\text{CH}_3$) peak of acetic anhydride, that **58** and Ac_2O are present in the reaction solution in an approximate molecular ratio of 1:1, respectively.

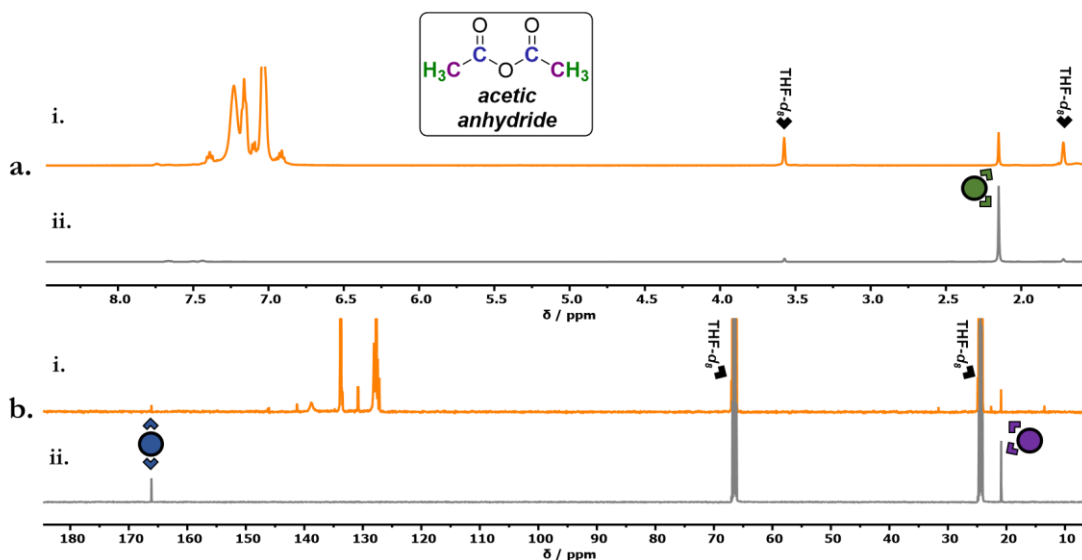


Figure 62 NMR evidence for the presence of Ac_2O in the post-reaction solution (THF- d_8). (a.) ^1H NMR (500 MHz) (i.) post-reaction solution (ii.) authentic Ac_2O (b.) $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz) (i.) post-reaction solution (ii.) authentic Ac_2O .

One other species was characterised in the reaction mixture between **52** and 2 equivalents of PPh_3 . A single dark red crystal was grown by careful layering of a THF post-reaction solution with hexane followed by storage under argon at -18°C . X-ray diffraction analysis showed it to be another Pd^{I} dinuclear complex, namely $[\text{Pd}^{\text{I}}_2(\mu\text{-PPh}_2)\{\kappa_2\text{-O,O-}\mu\text{-P(O)}_2\text{Ph}_2\}(\kappa\text{-PPh}_3)_2]$ **62** (Figure 63).

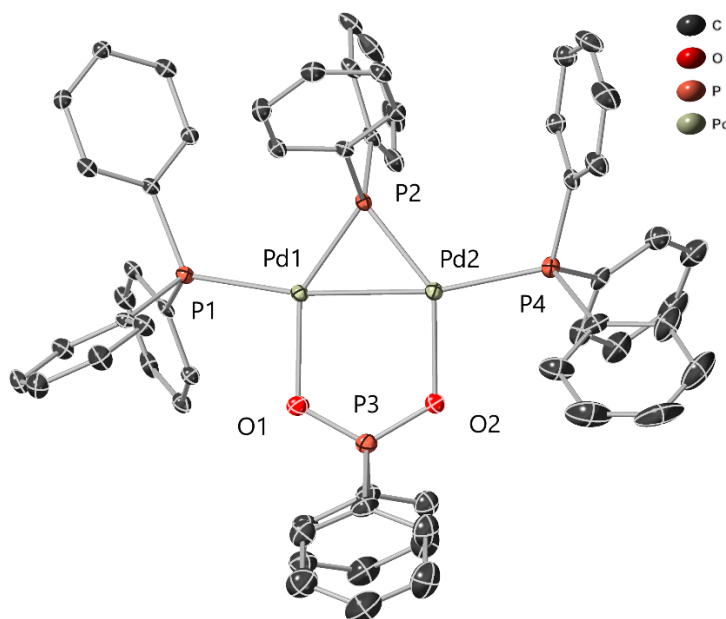
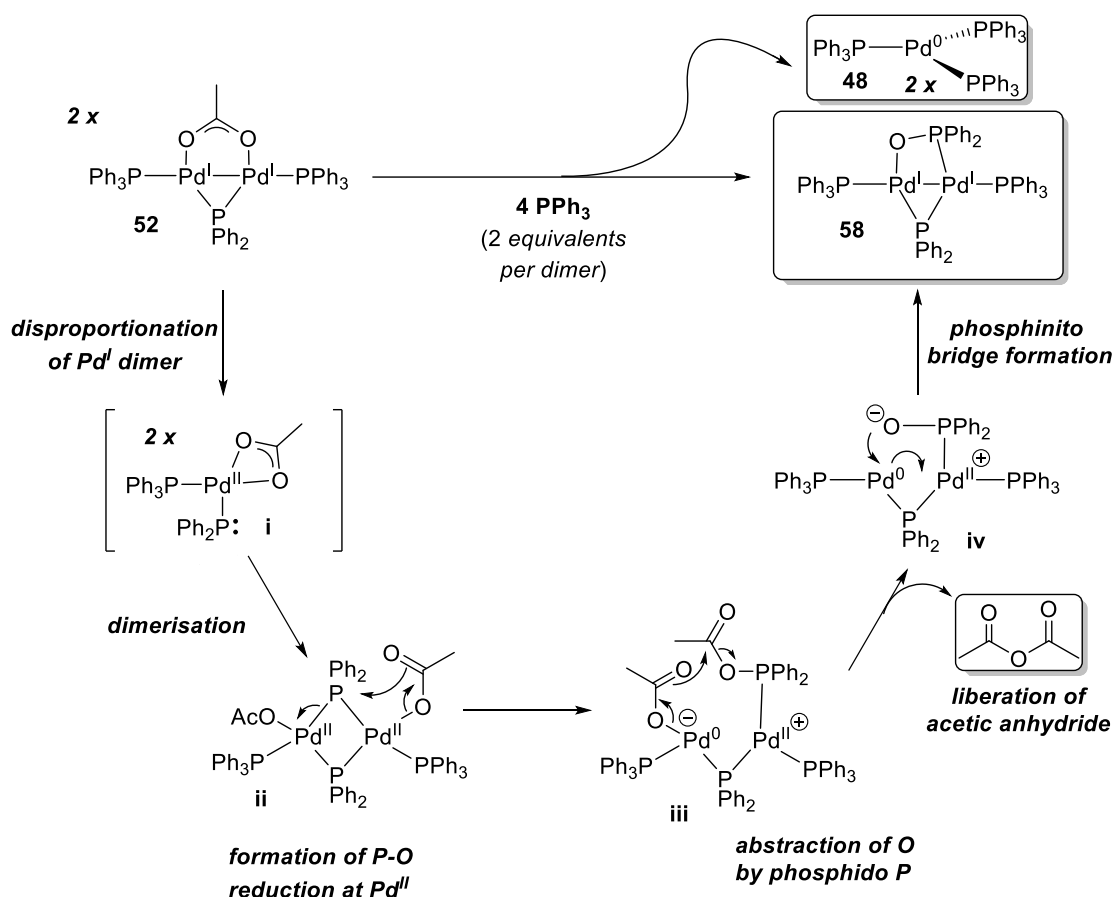


Figure 63 The structure of $[\text{Pd}^{\text{I}}_2(\mu\text{-PPh}_2)\{\kappa_2\text{-O,O-}\mu\text{-P(O)}_2\text{Ph}_2\}(\kappa\text{-PPh}_3)_2]$ (**62**) obtained *via* X-ray diffraction of a single crystal grown from a THF- d_8 reaction solution of **52** with 2 equivalents of PPh_3 . Two molecules of THF and all hydrogen atoms have been omitted for clarity. Thermal ellipsoids have been set at 30% probability. Selected bond distances /Å: $\text{Pd1-Pd2} = 2.6140(5)$, $\text{P1-Pd1} = 2.2901(12)$, $\text{Pd2-P4} = 2.3095(12)$, $\text{P2-Pd1} = 2.1810(12)$, $\text{P2-Pd2} = 2.1888(12)$, $\text{Pd1-O1} = 2.162(4)$, $\text{Pd2-O2} = 2.186(4)$, $\text{O1-P3} = 1.507(4)$, $\text{O2-P3} = 1.529(4)$. Selected interatomic angles /°: $\text{O1-P3-O2} = 120.7(2)$, $\text{Pd1-P2-Pd2} = 73.48(4)$.

Analogous to the Pd dinuclear complex **58**, this complex **62** is bridged by a single κ_2 -diphenylphosphido ligand, however, the secondary bridge in this case is a diphenylphosphinito ligand, which bridges the two Pd^{I} centres through a $\kappa_2\text{-O-}\mu_2$ interaction (Figure 63). The Pd1-Pd2 bond distance ($2.6140(5)$ Å) of **62** is slightly longer than that of both analogous Pd^{I} dinuclear complexes **52** ($2.5958(3)$ Å) and **58** ($2.5680(10)$ Å) as disclosed in this work, but is still characteristic of an, albeit weaker, $\text{Pd}^{\text{I}}\text{-Pd}^{\text{I}}$ bonding interaction.^{146, 148, 244-245} All Pd, P, and O atoms lie on, to a close approximation, the same plane in line with the structure of complexes **58** and **52**. Both the P3-O1 and O1-Pd1 bonds of **62** are close in length, respectively, giving the structure a C_2 symmetry element. The diphenylphosphinito ligand exhibits two short P–O bonds $1.507(4)$ and $1.529(4)$ Å which are both indicative of significant double bond character (P–O bond lengths of O=PPh_3 and P(OPh)_3 are $1.479(2)$ and ~ 1.600 Å, respectively).^{262, 267} The two Pd–O bond lengths ($2.162(4)$ and $2.186(4)$ Å) between the $\mu(\kappa\text{-O})_2$ -diphenylphosphinito ligand and the two Pd^{I} centres are comparable to that of the Pd–O bond lengths in the $\mu(\kappa\text{-O})_2$ -acetato ligand of the $\text{Pd}^{\text{I}}\text{-Pd}^{\text{I}}$ dimer **52** ($2.1764(18)$ and $2.2069(18)$ Å). To the author's knowledge, this structure constitutes the first example of a diphenylphosphinito-bridged Pd^{I} complex. One literature precedent of a reported diphenylphosphinito-bridged Pd complex, **63**, is known, which is formed from hydrogenation of the Pd^{II} complex, $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{PPh}_3)_2]$ **64** (Figure 64, *vide infra*). Although numerous metal phosphinato complexes are known, examples of multinuclear complexes bridged by such ligands are rare.²⁶⁸⁻²⁷⁰ There are examples in the literature of

diphenylphosphinato-bridged organotin complexes.²⁷¹ Additionally, the phosphinato ligand is known to bridge tin and boron in bimetallic dimeric compounds.²⁷² No trace of this phosphinato-bridged Pd^I dimer species **62** was observed in the ³¹P NMR spectrum of the post-reaction solution, pointing towards it being a relatively minor solution species.

To summarise the results thus far, addition of 2 equivalents of PPh₃ to [Pd^I₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52** results in full conversion to the Pd^I dinuclear complex [Pd^I₂(μ-PPh₂){κ₂-P,O-μ-P(O)Ph₂}(κ-PPh₃)₂] **58**, [Pd⁰(PPh₃)₃] **48** and acetic anhydride within 30 minutes, at room temperature. On the other hand, reaction of **52** with one equivalent of PPh₃ resulted in only partial conversion of **52** to **48** and **58**. This demonstrated that, in order to fully cleave the Pd^I–Pd^I bond, abstraction of a [Pd⁰(PPh₃)₃] **48** monomer by two equivalents of PPh₃ was necessary. In other words, the bis-ligated complex [Pd⁰(PPh₃)₂] was not sufficiently stable to trap out Pd⁰ in a dynamic reversible process. The clear presence of **48** as a major Pd⁰ species in the post-reaction mixture indicated that Pd^I–Pd^I bond cleavage by disproportionation has occurred, which would formally yield a Pd^{II} species as the other product upon Pd^I–Pd^I bond cleavage. The other Pd-containing product, however, is a Pd^I dinuclear species **58**, which shows that a clean formal reduction at Pd occurred as part of the reaction process. The presence of Ac₂O in the post-reaction mixture points towards the fate of bridging acetate ligand from complex **52**. Furthermore, the presence of Ac₂O, must have formed from two acetate ligands, eliminating an O atom, thus indicating that one acetate has transferred its oxygen atom from acetate to a diphenylphosphido ligand, leading to the observed diphenylphosphinito ligand and a concomitant formal reduction at Pd. The resulting acyl moiety could then react with another equivalent of acetate to form the observed Ac₂O. This process accounts for the formation of the observed Pd^I dinuclear **58** species in the reaction product. A tentative mechanism for the process, based on the observed products of the reaction mixture, is detailed below (Scheme 47).



Scheme 47 Proposed mechanism of formation of **58**, showing gross movement of electron pairs (represented by curly arrows) for observations associated with the reaction between **52** and 2 equivalents of PPh₃, accounting for the contents of the observed crude reaction solution.

Upon treatment of **52** with 2 equivalents of PPh₃ a stable Pd⁰ complex [Pd⁰(PPh₃)₃], as observed, might be abstracted upon cleavage of the Pd^I-Pd^I bond of the dinuclear complex **52**. Such disproportionation of the dimer would thus yield one equivalent of the putative Pd^{II} complex (**ii**, Scheme 47), which may be transiently stabilised by the acetate ligand adopting a η^2 -OAc binding mode.²⁷³ Dimerisation of this complex might enhance system stability *via* bridging interactions from the highly nucleophilic diphenylphosphido ligand,²⁷⁴ yielding a Pd^{II} dimer intermediate (**iii**, Scheme 47). Hence, a situation where acetate and a diphenylphosphido ligand lie in close proximity, which could facilitate the formation of a P-O interaction leading to formal reduction at the proximal Pd (Pd^{II}→Pd⁰). Subsequent nucleophilic attack by the acetate ligand at a formed diphenylphosphinic acid anhydride ligand could result in release of Ac₂O as observed, and formation of a phosphonito ligand which could then stabilise the dimer by bridging through O (**iv**, Scheme 47). This redox process would likely be driven by the formation of a strong P-O interaction, much like in the formation of Pd⁰ from phosphine-ligated Pd^{II} acetate complexes (as discussed *vide supra*).^{46, 48, 262} Such a strong P-O bond is evident in the short P-O bond distance as observed in the diphenylphosphinito ligand of the product **58** (Figure 58).

This is not the first-time oxygen has evidently transferred from a carboxylato ligand to a diphenylphosphido moiety. Moissev *et al.* observed the formation of diphenylphosphinato-bridged Pd^{II} complex, formed *via* the reaction of [Pd^{II}(μ₂-OAc)(κ-OAc)(PPh₃)₂] **64**, (see Section 2.6 for more details on the reactivity of this complex) with molecular hydrogen in the presence of formic acid.²⁷⁵ The complex [Pd^{II}(κ₂-O,O-μ-P(O)₂Ph₂)(Ph)(PPh₃)₂] **63**, which was structurally interrogated by single crystal XRD analysis (Figure 64), was postulated to form *via* transfer of oxygen from formic acid after cleavage of PPh₃ to PPh₂.

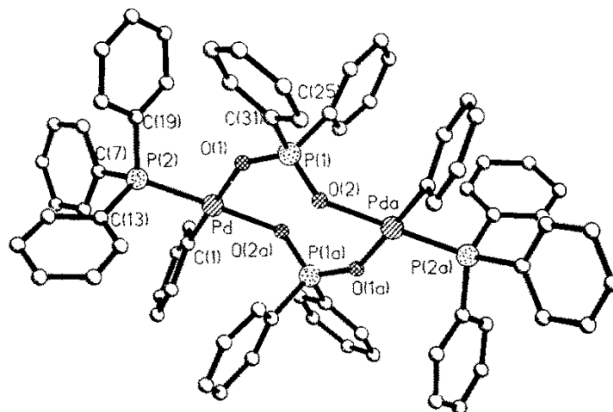


Figure 64 ORTEP Representation of the crystal structure of the μ₂-O₂-phosphinato-bridged Pd^{II} complex **63**. Reprinted with permission from *Springer Nature, J. Clust. Sci.* 1992, **3**, 411-421 © 1992.

2.5.3.2. Reaction of the [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52** / 2PPh₃ Mixture with 2-bromopyridine **55**

Efforts to isolate [Pd₂(μ-PPh₂){κ₂-P,O-μ-P(O)Ph₂}(κ-PPh₃)₂] **58** from [Pd⁰(PPh₃)₃] **48** and the remaining reaction mixture ultimately failed, however, to examine the reactivity of **58**, 2-bromopyridine **55** was directly added to the reaction solution generated from [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52** and 2 equivalents of PPh₃ (*vide supra*), in THF-*d*₈ at room temperature.³¹P NMR was initially used to track the reaction progress (Figure 65).

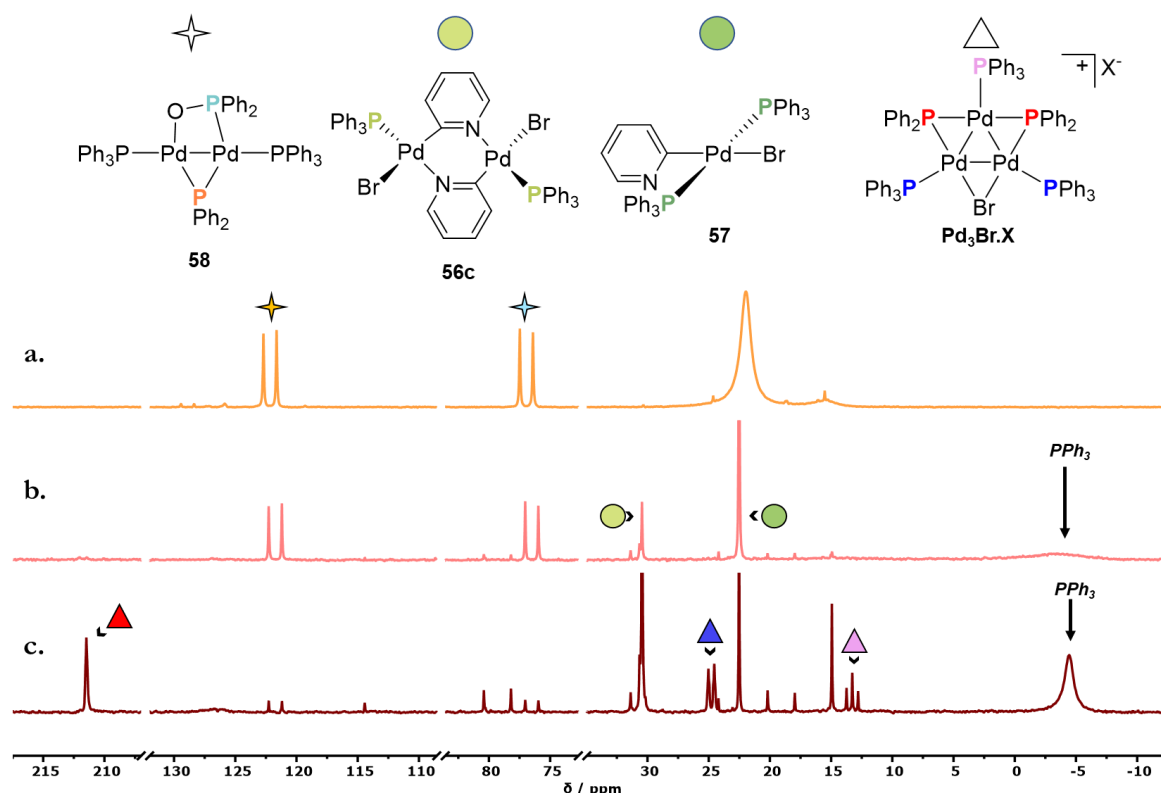


Figure 65 ^{31}P NMR (202.3 MHz, $\text{THF-}d_8$) stack, tracking the reaction in the solution generated from (a.) **58** and 2 equivalents of PPh_3 , (b.) 20 minutes and (c.) 13 hours after adding 2-bromopyridine (**55**).

Structural assignment was possible for some of the ^{31}P -containing reaction products which were seen to evolve over the 13-hour reaction period (Figure 65). After approximately 20 minutes (b. Figure 65), the broad peak representing the $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** (δ_{P} 22.0 ppm) component was completely lost at expense of resonances at δ_{P} 22.5 and 30.5 ppm, along with a broad peak at δ_{P} -4.4 ppm which was assigned as liberated PPh_3 (by comparison with an authentic sample in $\text{THF-}d_8$). A background reaction between the complex $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** and **55** was carried out, which confirmed the identity of the resonances at 22.5 and 30.5 ppm as the oxidative addition complexes *trans*- $[\text{Pd}^{\text{II}}(\text{Br})(\text{C}^2\text{-pyridyl})(\text{PPh}_3)_2]$ **57** and *trans*-(P,N)- $[\text{PdBr}(\mu\text{-pyridyl-C}^2, \text{N})(\text{PPh}_3)_2]$ **56c** (See section 2.5.3.2.1 for further details).¹ ESI-MS analysis confirmed the presence of the complexes **57** and **56c** in the post-reaction solution on the basis of observation of the respective $[\text{M-Br}]^+$ cations. LIFDI-MS analysis additionally showed a peak at m/z 708.1216, corroborating the solution presence of the monomeric *trans*- $[\text{Pd}^{\text{II}}(\text{Br})(\text{C}^2\text{-pyridyl})(\text{PPh}_3)_2]$ **57** complex (b. Figure 66).

During the 13-hour reaction process, **57** was seen to convert into **56c** as noted by the decrease of the integration of δ_{P} 22.5 ppm at expense of increase of the resonance at 30.5 ppm (c. Figure 65). This

¹ The Pd^{II} dimer complex *trans*-(P,N)- $[\text{PdBr}(\mu\text{-pyridyl-C}^2, \text{N})(\text{PPh}_3)_2]$ **56c** along with related species **36a** and **36b** were also seen to form directly from the reaction between $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **58** and **55** (see section 2.5.1).

dimerisation was confirmed as a background process, occurring spontaneously, leading to the formation of **56c** as the thermodynamic product of the reaction between $[\text{Pd}^0(\text{PPh}_3)_3]$ and 2-bromopyridine (See Section 2.5.3.2.1). Additionally, **58** was observed to slowly convert to a cluster complex of the type $[\text{Pd}_3(\mu\text{-X})(\mu\text{-PPh}_2)(\text{PPh}_3)_3]^+\text{X}^-$ (**Pd₃X·X**) over time. This complex adopts the same structural motif as that which forms from direct reaction of **52** with **55** (see Section 2.5.1 for details), and has previously been shown form from a variety of routes (see Section 1.4). Identification of the cluster complex as **Pd₃Br·X** complex was confirmed by detection of the $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)(\text{PPh}_3)_3]^+$ cation by ESI-MS with the correct isotopic distribution (c. Figure 66) and by ^{31}P NMR spectroscopic analysis (a, Figure 66) from which comparison against an authentic standard of **Pd₃Br·Br** showed resonances with the correct splitting pattern for the $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)(\text{PPh}_3)_3]^+$ ion (see Section 2.5.2 for discussion of the ^{31}P NMR characteristic of this complex).¹⁶⁷

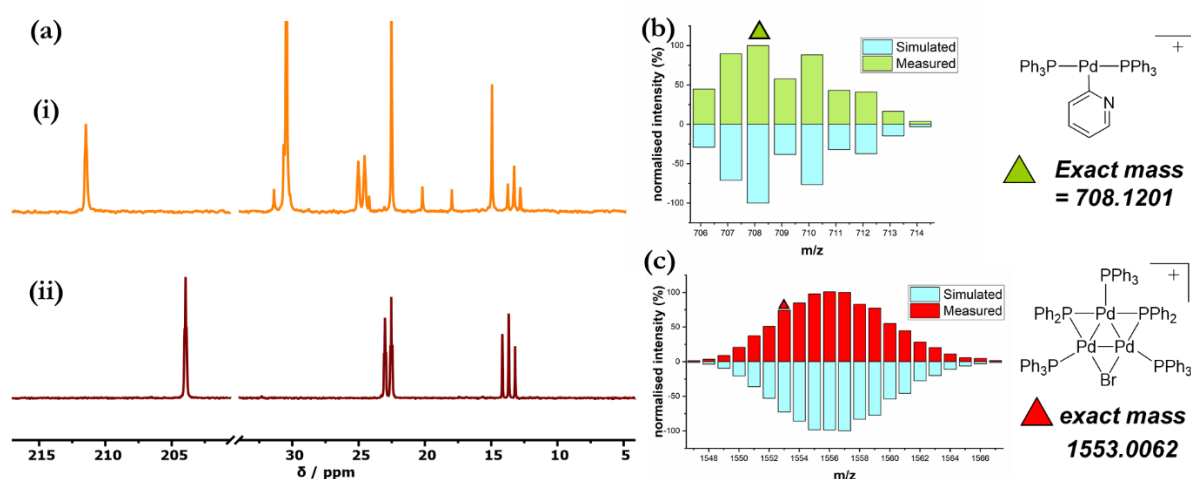


Figure 66 Data identifying species formed from the crude reaction mixture following addition of 2-bromopyridine (**55**) to a solution generated from mixing of **55/** with 2 PPh_3 in $\text{THF-}d_8$. (a) a stack of (i) the ^{31}P spectrum recorded after the 13-hour reaction period, overlaid with (ii) a ^{31}P spectrum of authentic $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)(\text{PPh}_3)_3]^+\text{Br}^-$. (b) ESI-MS evidence for formation of $[\text{Pd}(\text{C}^2\text{-pyridyl})(\text{PPh}_3)]^+$ motif (**57** and **56c**)

Comparison of the reaction data with the ^{31}P NMR spectrum of $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)(\text{PPh}_3)_3]^+\text{Br}^-$, shows significantly shifted resonances for the phosphide ligand (δ_{P} 204.0 $\rightarrow$ 211.5 ppm), and *proximal* PPh_3 (δ_{P} 22.8 $\rightarrow$ 24.8 ppm) ^{31}P resonances, with respect to the standard, indicating that dynamic processes were likely occurring within the mixture, affecting the NMR shift frequencies. Alternatively, the counterion for the **Pd₃Br⁺** cluster moiety, which is unidentified at this stage may influence P chemical shifts of the cluster. Some other ^{31}P resonances in the mixture remain unidentified, including resonances at δ_{P} 17.5, 20.1 and 31.8 ppm revealing that other more minor species form as a result of this process. Unreacted Ac_2O was evident by ^1H NMR (singlet at δ_{H} 2.15 ppm) after the reaction time, indicating that this species, left over from the reaction of **52** with PPh_3 , most likely does not participate in the reaction process.

2.5.3.2.1. Delineating the Background Oxidative Addition Reaction Between $[\text{Pd}^0(\text{PPh}_3)_3]$ and 2-Bromopyridine

In order to confirm the identity of the suspected oxidative addition products of $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** to 2-bromopyridine **55** in the reaction of the solution derived from the disproportionation of **52** after treatment with 2 equivalents of additional PPh_3 , the oxidative addition of the related complex $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** to **55** was tracked using ^{31}P NMR spectroscopic analysis as a function of time (Figure 67). Soon after (addition of 2.2 equivalents of PPh_3 to a solution of **65** in $\text{THF-}d_8$ ca. 20 minutes), a major peak at δ_{P} 22.5 ppm was evident, in addition to a peak at δ_{P} -4.4 ppm which was assigned as liberated PPh_3 (b. Figure 67). A minor peak (δ_{P} 30.5 ppm) was identified as the Pd^{II} dinuclear complex *trans*-(P,N)- $[\text{PdBr}(\mu\text{-pyridyl-C}^2, \text{N})(\text{PPh}_3)]_2$ **56c**, with reference to an authentic sample.²⁵⁷

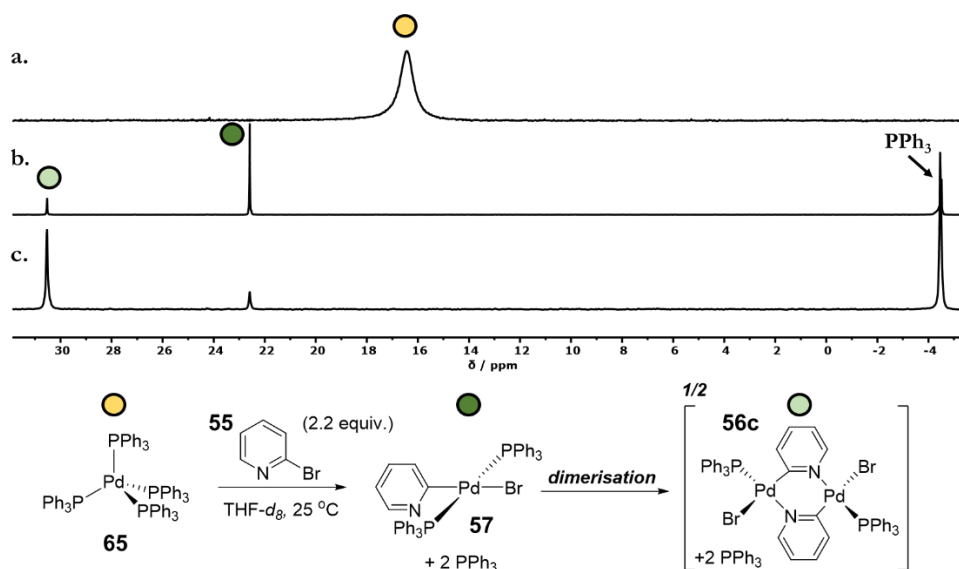


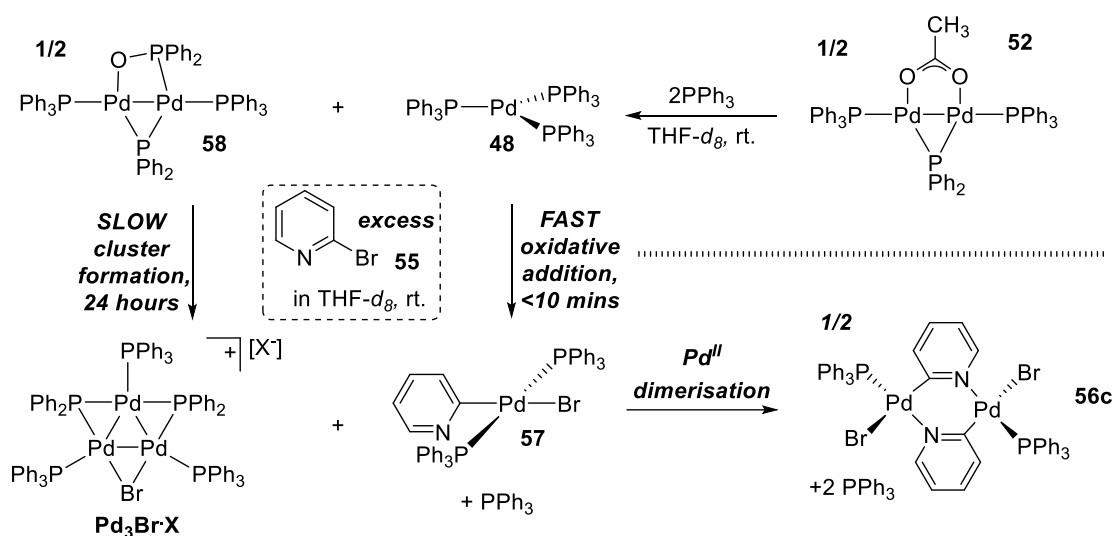
Figure 67 ^{31}P NMR (202.5 MHz, 298 K) tracking of the room temperature reaction between $[\text{Pd}^0(\text{PPh}_3)_4]$ (**65**) and 2-bromopyridine (**55**) in $\text{THF-}d_8$. (a.) **65** in absence of **55**. (b.) ca. 20 minutes after addition of **55** (2.2 equivalents) (c.) 48 hours after addition of **55**.

Upon allowing the solution to react at room temperature for 48 hours, the integration of the peak at δ_{P} 30.5 ppm was seen to increase at expense of that at δ_{P} 22.5 ppm (b. Figure 67). Accordingly, the integration of the peak representative free PPh_3 at δ_{P} -4.4 ppm was seen to increase. The peak at δ_{P} 22.5 ppm was hence assigned as the monomeric oxidative addition product *trans*- $[\text{Pd}(\text{Br})(\text{C}^2\text{-pyridyl})(\text{PPh}_3)_2]$ **57**, which was seen to convert to the dimeric complex *trans*-(P,N)- $[\text{PdBr}(\mu\text{-pyridyl-C}^2, \text{N})(\text{PPh}_3)]_2$ **56c** over time, accounting for the observed increase in the quantity of free PPh_3 . This observation was similarly noted as a background reaction in the solution generated from mixing **52** with 2 equivalents of PPh_3 , followed by subsequent addition of 2-bromopyridine **55**, further confirming the presence of the Pd^0 complex $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** in the initial reaction solution (Section 2.5.3.1).

The observation that *trans*-[Pd(Br)(C²-pyridyl)(PPh₃)₂] **57** converts to *trans*-(P,N)-[PdBr(μ-*pyridyl*-C², N)(PPh₃)₂] **56c** over time, at 25 °C, with release of free PPh₃ (see scheme, Figure 67) demonstrates that **56c** is more thermodynamically stable than **57**. This phenomenon may be due to the increased stability of the dimer which forms a 6-membered ring, in a boat conformation.²⁵⁷ There may be also an entropic contribution to this stability due to the increased solution disorder as, during the process, molecules of monomer create one dimer releasing 2 equivalents of PPh₃ *per* dimerization reaction (2 molecules → 3 molecules). In any case, it is interesting that the more thermodynamically stable dimeric complex features substitution of, harder dative bonds from the pyridine donor at expense of PPh₃.²⁷⁶

2.5.3.3. Summary of Findings

In summary (Scheme 48), on exposure of **52** to 2 equivalents of additional PPh₃ in THF, the Pd^I-Pd^I complex disproportionates to [Pd⁰(PPh₃)₃] **48** and a novel phosphinito and phosphide-bridged Pd^I dimer complex [Pd₂(μ-PPh₂){κ²-P,O-μ-P(O)Ph₂}(κ-PPh₃)₂] **58** (Scheme 48). The presence of acetic anhydride (a biproduct of the process) indicated that the phosphinito ligand had formed by abstraction of an oxygen atom *via* a mechanism involving formal acyl transfer to acetate. The phosphinato-bridged Pd^I dimer [Pd₂(μ-PPh₂){κ²-O,O-μ-P(O)₂Ph₂}(κ-PPh₃)₂] **62**, a minor reaction species, was crystallised from the same solution. When the crude solution of **58** and Pd⁰ complex **48** was reacted with 2-bromopyridine **55**, **48** reacted rapidly to produce the oxidative addition product *trans*-[Pd^{II}(Br)(C²-*pyridyl*)(PPh₃)₂] **57** which was seen to slowly dimerise to *trans*-(P,N)-[PdBr(μ-*pyridyl*-C², N)(PPh₃)₂] **56c** over time. **58**, on the other hand was seen to slowly convert to the [Pd₃(μ-Br)(μ-PPh₂)₂(PPh₃)₃]⁺X⁻ (**Pd₃Br·X**) cluster complex. The identity of the X⁻ counteranion for [Pd₃(μ-Br)(μ-PPh₂)₂(PPh₃)₃]⁺X⁻ is currently unknown, but could feasibly be phosphinite (Ph₂PO⁻), or Br⁻, the known anionic species in the mixture.



Scheme 48 Summary of the overall process found to occur upon treating a THF-*d*₈ solution containing **58** and **48**, generated from reaction of **52** and PPh₃ (2 equivalents) and **55**. X⁻ is unidentified but most likely [Ph₂PO]⁻, or Br⁻: anions present in the system.

The above findings, as summarised in Scheme 48, could be relevant to catalysis in the case of the degradation of Pd^I dimers in the presence of aryl halides (*e.g.* **55**) and phosphines (PPh₃) under working cross-coupling conditions. If, for example, catalytic Pd^I dimer degraded in solution, this could leave an excess of PPh₃ which could cleave the remaining dimer, and cause the disproportionation to mononuclear Pd⁰ complex, which are generally less active in cross-coupling (See chapters 3 & 4).⁵⁷ Such a phenomenon could partially account for decreased catalytic activity in the latter stages of reactions. More generally these findings show the potential for interconversion between different higher-order Pd species when exposed to chemicals often present during cross-coupling catalytic turnover.

2.6. Reaction of Palladium(II) Acetate with 1 Equivalent of PPh₃ per Palladium

When [Pd₃(OAc)₆] was treated with 3 equivalents of PPh₃ (*i.e.* a Pd to P ratio of 1:1), major qualitative differences in product speciation were observed, compared with that observed in the reactions of [Pd₃(OAc)₆] with either 6 or ≥ 9 equivalents of PPh₃ (Sections 2.3 & 2.4, respectively). Upon treating [Pd₃(OAc)₆] with 3 equivalents of PPh₃ in rigorously dry THF-*d*₈, ¹H and ³¹P NMR spectra were collected (Figure 68).

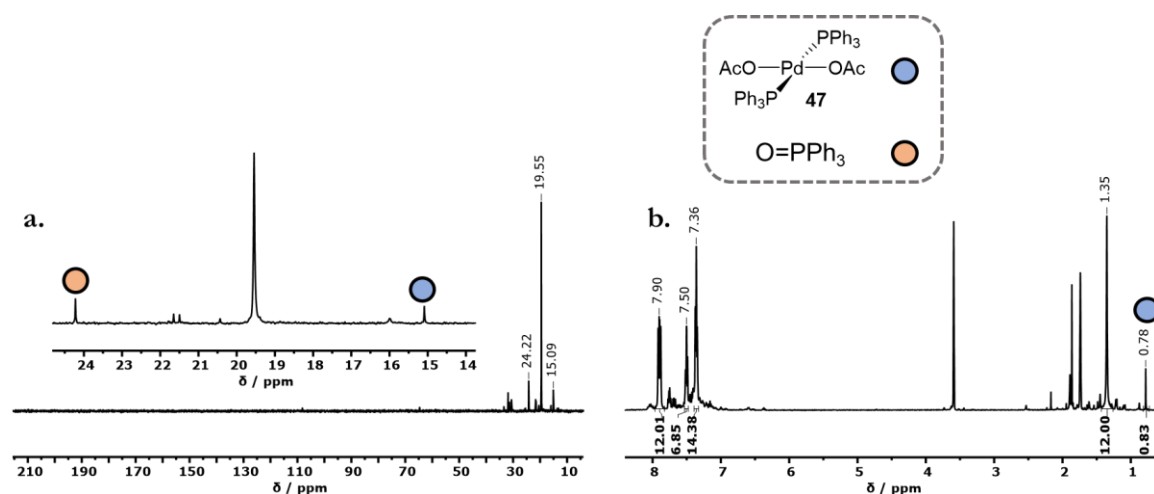


Figure 68 NMR spectra recorded in THF-*d*₈ of the mixture of [Pd₃(OAc)₆] and 3 PPh₃. (a.) ³¹P NMR (202.5 MHz), showing a singlet representative of a major new species 64 at δ_P 19.6 ppm. (a.) ¹H NMR (500 MHz) showing proton resonances. The singlet at δ_H 1.35 ppm has been assigned to represent an equilibration of the -CH₃ environments bridging and terminal acetate ligands (see discussion *vide infra*), both spectra were recorded within 1 hour of mixing at room temperature.

Both spectra indicate that significant degradation, in the form of many unidentified resonances, had occurred, at room temperature, in the interval between mixing and analysis (Figure 68). ^{31}P NMR spectroscopic analysis of the reaction after 30 minutes at 25 °C indicated a major singlet at δ_{P} 19.6 ppm, representing a species not observed under the $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ reaction regimes reported *vide supra*. Similarly, at approximately the same time after mixing, a major acetate($-\text{CH}_3$)-type singlet was observed by ^1H NMR spectroscopy at δ_{H} 1.35 ppm. Peaks at δ_{P} 15.1 ppm and δ_{H} 0.79 ppm indicated a trace amount of *trans*- $[\text{Pd}^{\text{II}}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** to be present in solution. An orange crystal was grown by layering of one such THF solution, prepared at 0 °C, with cold hexane (THF:hexane = 1:4 [v/v]) after subsequent storage for 4 days at –18 °C. This crystal was subjected to X-ray diffraction analysis which identified it as $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{PPh}_3)_2]$ **64**: a clam-shell-type μ_2 -acetate-bridged Pd^{II} dimer complex featuring two bridging acetates, two terminal acetates and two PPh_3 ligands (Figure 69).

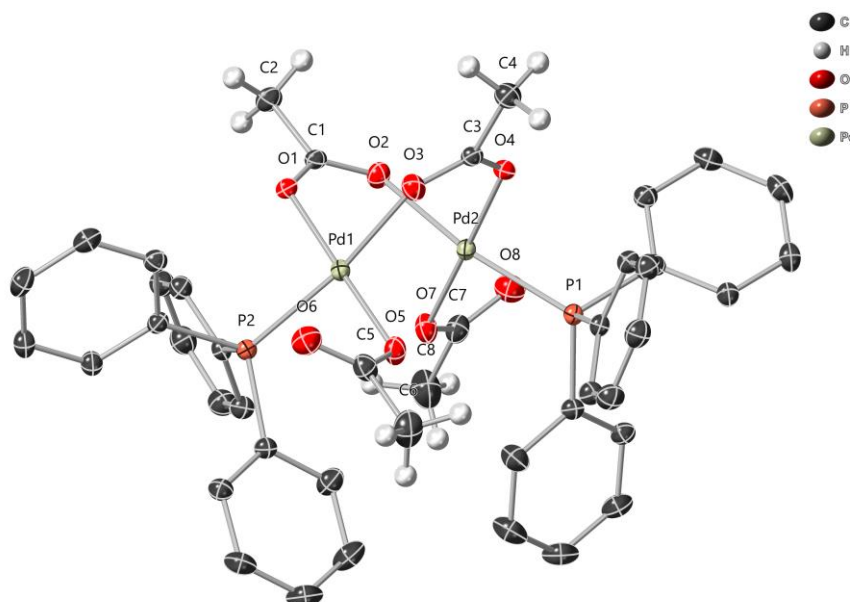


Figure 69 Structure obtained by X-ray diffraction analysis of a single crystal of $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{PPh}_3)_2]$ (**64**). Thermal ellipsoids were set at 50% probability. Selected interatomic distances /Å: Pd1–P2 = 2.2329(7), Pd1–O1 = 2.0209(18), Pd1–O3 = 2.1062(19), Pd1–O5 = 1.999(2), Pd1–Pd2 = 3.0115(4). Selected interatomic angles /°: P2–Pd1–O1 = 88.62(5), O1–Pd1–O3 = 89.61(8) P2–Pd1–O5 = 92.11(6), O3–Pd1–O5 = 89.83(8). Torsion angles /°: O5–Pd1–Pd2–O7 = 89.766, O5–Pd1–Pd2–P1 = –4.867, P2–Pd1–Pd1–P2 = –99.500.

This constitutes the first time an X-ray crystal structure for **64** has been collected. The crystal structure of **64** indicates that the Pd complex-to-acetate-to- PPh_3 ratio (Pd:OAc:Pd = 1:2:1) has been conserved. **64** has been synthesised by a similar approach, and structurally interrogated before however, most notably by infrared spectroscopic analysis by Wilkinson *et al.*²⁷⁷ It has been noted to be an unstable compound, observed to blacken under air in the solid state over a several days, corroborating its demonstrated instability reported herein. The two Pd^{II} centres show an approximate square planar geometry with respect to the three Pd–O bonds and single Pd–P bond *per* monomer. The PPh_3 ligands

lie *anti* across the Pd–Pd bond with respect to each other, as do the κ -acetato ligands. The structure of **64** invites comparison with that of **53**, the phenyl-ligated clam-shell type Pd^{II} dimer complex which forms as one of the products of the reaction of [Pd₃(OAc)₆] with exactly 6 equivalents of PPh₃ (Section 2.4.2). The Pd–Pd interatomic distance of **64** is 3.0115(4) Å which is 1.6% shorter than that of **53** (3.0610(3) Å), however some bonding character is implied by this distance being lower than that of the sum of the Van der Waals radii for Pd.²⁵¹ It of note that the two acetate bridged Pd^{II} complexes **53** and **64** feature Pd–P bond distances (range ~2.220–2.233 Å) that are significantly shorter than that observed with monomeric Pd^{II}–P containing complexes **47**, **53** and **OA_{C2-Br}** (see section 4.2.2, *vide infra*) (range ~2.3176 – 2.342 Å).

It is of note that in contrast to **64**, which decomposes quite rapidly in solution (*vide infra*), **53** was seen to be stable in solution for >2 weeks, without any observable decomposition products by ³¹P NMR analysis, indicting the extra acetate ligands have some role in the observed instability of **64**.

Infrared spectral analysis (ATR) showed four peaks representative of the two acetate binding modes of **64**. Bands at 1628 and 1309 cm⁻¹, represented the ν_{asym} and ν_{sym} CO stretches of the κ -acetato ligand respectively, while bands 1564 and 1409 cm⁻¹ were representative of the ν_{asym} and ν_{sym} CO stretches of the μ -acetato ligand, respectively. This data matches previously recorded IR data for **64**, which was until this work, the only characterisation data of this compound.²⁷⁷ Presence of **64** was additionally evident by detection of [Pd^{II}(μ_2 -OAc)(κ -OAc)(PPh₃)₂]₂ as an [M–OAc]⁺ cation, m/z = 913.01877, by LIFDI-MS after immediate analysis of the reaction solution upon mixing [Pd₃(OAc)₆] and 3 PPh₃. The major singlet at δ_P 19.6 ppm in the ³¹P NMR spectrum was assigned to the two identical chemical environments in the **64** dimer (a. Figure 68, page 154). Upon close analysis of the THF-*d*₈ reaction solution by ¹H NMR spectroscopy (b. Figure 68, page 154), comparison of the major ¹H resonances phenyl integrals with that of the acetate CH₃ resonance shows the correct number of acetate (CH₃) protons *per* phenyl for **64**. However, here only one acetate (CH₃) environment is present as a broad resonance at δ_H 1.35 ppm $\Delta\nu_{1/2}$ = 5.66 Hz – significantly broader than the signal representing the CH₃ resonance of *trans*-[Pd(OAc)₂(PPh₃)₂] **47** ($\Delta\nu_{1/2}$ = 1.90 Hz). Two acetate (CH₃) environments would be expected from the structure obtained by X-ray diffraction. It is therefore likely, in solution at 25 °C, that the acetato ligands are in rapid chemical exchange between the bridged and terminal state. A tentative mechanism, potentially explaining the exchange at room temperature, based on the crystal structure of **64** is presented in Figure 70.

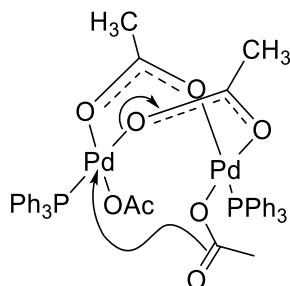
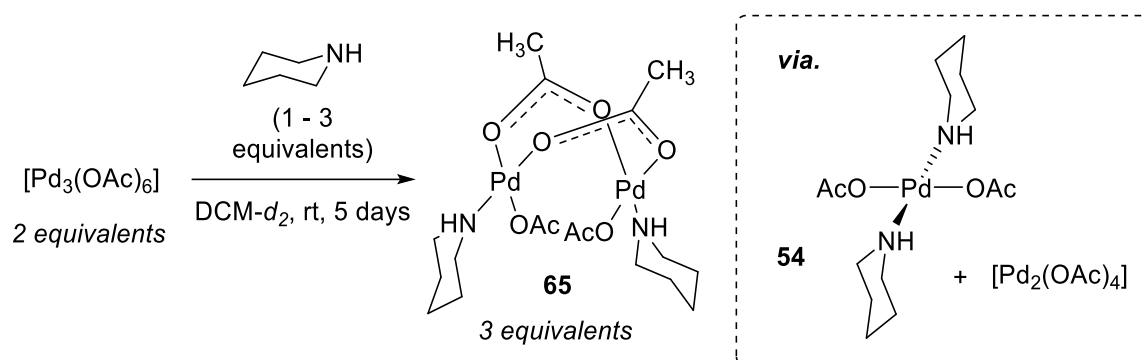


Figure 70 Hypothesised dynamic exchange mechanism, accounting for the single acetate (CH_3) environment detected in the ^1H NMR spectrum of **64** which was formed after reaction between $[\text{Pd}_3(\text{OAc})_6]$ and 3 equivalents of PPh_3

The observation that **64**, a clam-shell-type $\mu_2\text{-CO}_2$ diacetate-bridged complex of the general structure $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{L})]_2$, mirrors the type of complex that arises from the aminolysis of $[\text{Pd}_3(\text{OAc})_6]$ by 1 - 3 equivalents of piperidine, as investigated in our group by Bray, Fairlamb and Ford (Scheme 49).²⁷⁸



Scheme 49 The experimental conditions used and findings by Dr. Joshua T. W. Bray on the aminolysis of $[\text{Pd}_3(\text{OAc})_6]$ with 1-3 equivalents of piperidine forming a structure analogous to **64**.

Bray *et al.* observed that on reaction of $[\text{Pd}_3(\text{OAc})_6]$ with 1-3 equivalents of piperidine, the clam shell complex $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{N-piperidyl})]_2$ **65** is formed as the thermodynamic product of the reaction, with full conversion after *ca.* 5 days (Scheme 49). Intriguingly, the monomeric *trans*- $[\text{Pd}^{\text{II}}(\text{OAc})_2(\text{N-piperidyl})_2]$ **54** complex was noted to form *en route* to the dimer, meaning that initial cleavage of the $[\text{Pd}_3(\text{OAc})_6]$ trimer by piperidine abstracts a monomer yielding **54** and a putative $[\text{Pd}_2(\text{OAc})_4]$ dimer as intermediate, kinetically stable, complex. A heterobimetallic variant of $[\text{Pd}_2(\text{OAc})_4]$: the paddlewheel-type complex $[\text{Pd}(\mu_2\text{-OAc})_4\text{Ni}(\text{OH}_2)]\cdot\text{AcOH}$ has been isolated and characterised by Moiseev *et al.*²⁷⁹ By extrapolation of this process, the analogous reaction of $[\text{Pd}_3(\text{OAc})_6]$ with 3 PPh_3 may similarly form **64** *via* **47** and $[\text{Pd}_2(\text{OAc})_4]$ albeit on a far faster timescale (complete formation of **64** in < 20 mins, as observed by ^{31}P NMR) as a result of the higher affinity of

PPh_3 than the σ -electron donating piperidine for the Pd^{II} nucleus. Further studies would be needed to confirm this hypothesis.

Under dry conditions, in a $\text{THF-}d_8$ solution, the reaction of $[\text{Pd}_3(\text{OAc})_6]$ and 3 equivalents of PPh_3 was monitored by ^{31}P NMR spectroscopy as a function of time, at 25 °C (Figure 71). This kinetic tracking of the reaction showed that the integration of the *in situ* formed **64** (δ_{P} 19.6 ppm) was seen to depreciate over time (NMR stack (a.) & Graph (b.), Figure 71).

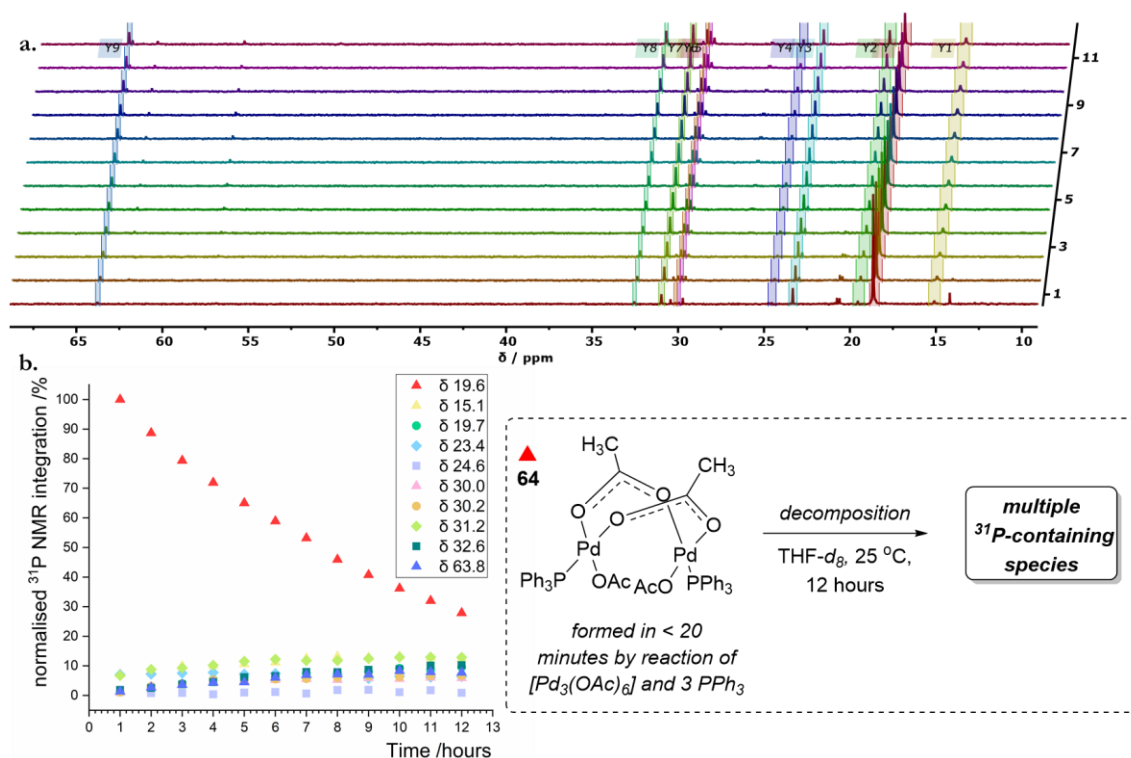


Figure 71 ^{31}P NMR (202.5 MHz $\text{THF-}d_8$) spectroscopic tracking of the depreciation of the integration of $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{PPh}_3)]_2$ **64** (δ_{P} 19.6 ppm) and formation multiple unidentified P-containing species over a 12 hour time-course at 25 °C. (a.) Stack of ^{31}P NMR spectra showing integrations of the more prominent resonances. (b.) A graph of the selected integration values, normalised to the initial integration value of **64** vs. time.

Many ^{31}P containing species were seen to evolve over the 12-hour time-course, at 25 °C, indicating significant decomposition of **64** (δ_{P} 19.6 ppm) to many P-containing molecular species. This observation contrasts with situations where $[\text{Pd}_3(\text{OAc})_6]$ was treated with 6 or ≥ 9 equivalents of PPh_3 , where well defined Pd^{I} or Pd^0 species were seen to arise (Sections 2.3 & 2.4). Additionally, in this case it is notable that $\text{O}=\text{PPh}_3$ was only a minor product of this decomposition process (δ_{P} 23.4 ppm). Indeed, no major ^{31}P species were seen to arise after degradation of **64**.

^1H NMR spectroscopic analysis of the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and 3 PPh_3 in $\text{THF-}d_8$, as with ^{31}P NMR, indicated significant degradation to acetate and phenyl-containing products. Analysis of the ^1H NMR spectrum of the post reaction solution showed the presence of a major singlet at δ_{H} 2.15

ppm, representing the CH_3 environment of acetic anhydride (Ac_2O), which was authenticated by comparison with an authentic standard of Ac_2O in $THF-d_8$ (Figure 72). Acetic acid ($AcOH$) was also detected as a major singlet at δ_H 1.89 ppm²³⁴ (representative of the CH_3 environment), indicating it to be a by-product of the process of the decomposition of **64**.

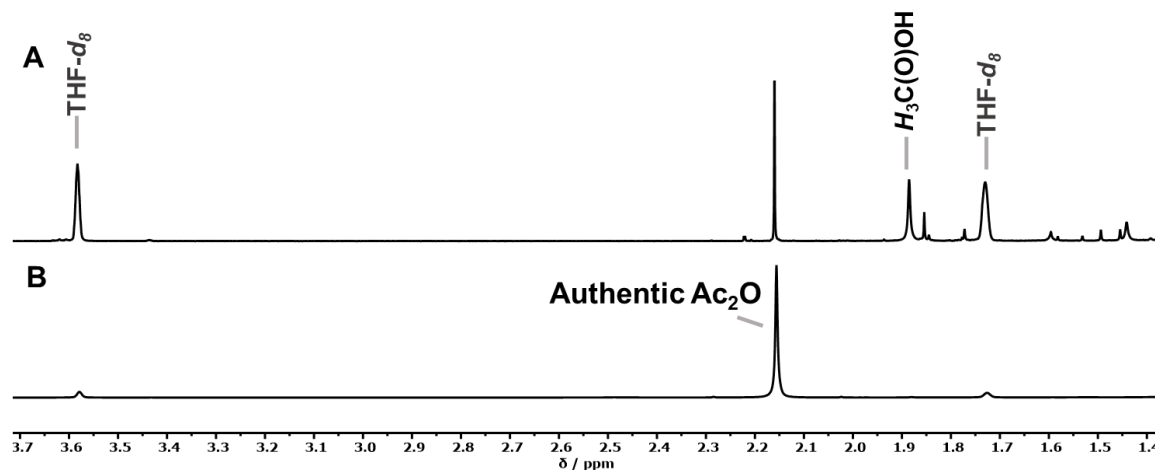


Figure 72 Evidence for acetic anhydride (Ac_2O) in the post reaction solution. Expanded 1H NMR stack of: (A.) the post-reaction solution of $[Pd_3(OAc)_6]/3PPh_3$ (*ca.* 12 hours after mixing) with that. (B.) of an authentic sample of Ac_2O acetic anhydride, both in $THF-d_8$.

Comparison of the two CH_3 -type integrals representing acetate-containing species Ac_2O and $AcOH$ (Figure 72), indicated that their presence in the post-reaction solution in a molecular ratio of 1:3 ($Ac_2O:AcOH$). This observation is in-keeping with one acetate being acylated *per* degradation of a molecule of $[Pd^{II}(\mu_2-OAc)(\kappa-OAc)(PPh_3)_2]$ **64**, and the remaining three acetates abstracting protons from the reaction mixture and thusly converting to $AcOH$.

The observation of acetic anhydride as a by-product of the reaction between of $[Pd_3(OAc)_6]$ and 3 equivalents of PPh_3 stands in contrast to the decomposition of *trans*- $[Pd^{II}(OAc)_2(PPh_3)_2]$ **47** (forming from solutions of $[Pd_3(OAc)_6]$ and 6 or ≥ 9 equivalents PPh_3), which forms $O=PPh_3$ and $AcOH$ concomitantly with formation of reduced Pd^0 or Pd^I species (as discussed in Sections 2.2, 2.3 & 2.4 *vide supra*).⁴⁶

The reaction solution transformed from a brown-orange solution to an opaque black solution indicating the formation of Pd black, over the course of *ca.* 1 hour. Transmission electron microscopic (TEM) analysis of aliquots of the solution after *ca.* 18 hours indicated the presence of large, perfectly spherical Pd particles, ranging in size from *ca.* 20–500 nm (Figure 73). The particles observed by TEM in this case are most likely aggregates of reduced Pd^0 formed from an intramolecular reduction process which bears analogy to that observed in the reaction between $[Pd_3(OAc)_6]$ and ≥ 6 of PPh_3 .

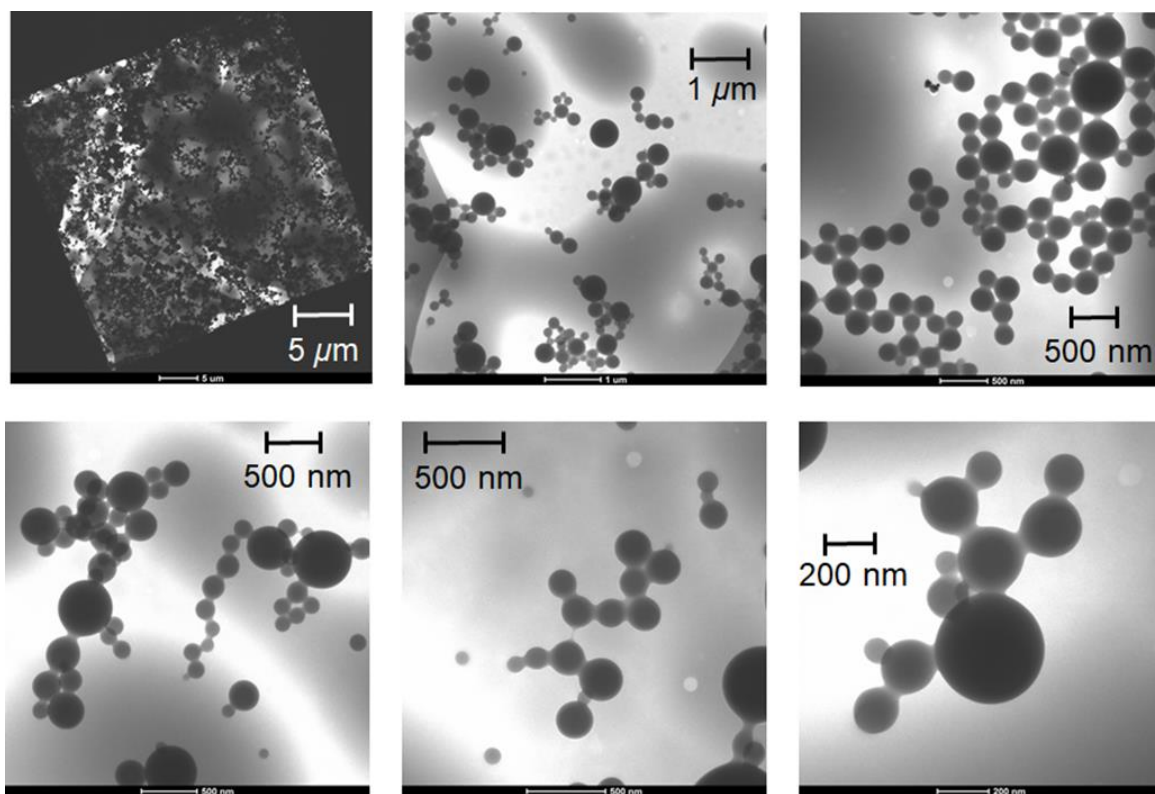
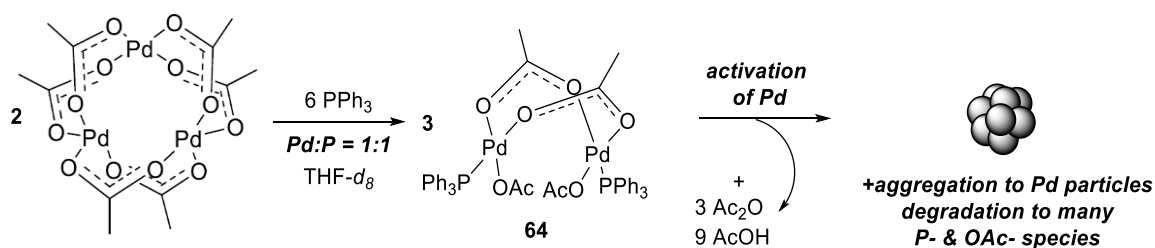


Figure 73 Images, obtained by TEM, of aliquots of a THF solution, generated from the reaction $[\text{Pd}_3(\text{OAc})_6]$ with 3 equivalents of PPh_3 ($\text{Pd}:\text{PPh}_3=1:1$) *ca.* 18 hours at room temperature.

These relatively large particles (*ca.* 20–500 nm) (Figure 73) likely form as a result of growth from smaller particles *i.e.* diffusional growth and aggregation of PdNPs (Ostwald ripening).²⁸⁰

The process for the reaction between $[\text{Pd}_3(\text{OAc})_6]$ and three equivalents of PPh_3 at room temperature in $\text{THF-}d_8$, as determined in this section, is summarised in Scheme 50.



Scheme 50 Showing Pd speciation, determined in this work to arise from treating $[\text{Pd}_3(\text{OAc})_6]$ with 3 equivalents of PPh_3 .

The formation of acetic anhydride in the post-reaction solution may have implications for the activated Pd speciation. Ac_2O would most likely form under these conditions by transfer of an acyl group to acetate. This assumption raises the question of the fate of the eliminated oxygen atom. One possibility

is that the oxygen could have transferred onto Pd during the process, and, as a result, O may be present embedded within and/or on the surface of the formed Pd particles. Transfer of the oxygen could be responsible for the reduction (electron transfer) to particulate Pd. To determine the elemental composition of the Pd surface, XAS methods could be deployed. This finding could be compared to bulk elemental analysis (*e.g.* ICP-AES or ICP-MS) which could reveal how the surface and bulk elemental composition compares. Indeed, the presence of oxides in PdNP catalysts has previously been noted to influence reactivity in Suzuki-Miyaura cross-coupling reactions.²⁸¹⁻²⁸³

The reaction process, as determined in this section is summarised in Scheme 50. When $[\text{Pd}_3(\text{OAc})_6]$ is reacted with 3 equivalents of PPh_3 (Pd:P = 1:1) a Pd^{II} dimeric complex $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{PPh}_3)]_2$ **64** forms. This complex differs with that which forms when $[\text{Pd}_3(\text{OAc})_6]$ is reacted with 6 or ≥ 9 equivalents of PPh_3 , where the monomeric complex *trans*- $[\text{Pd}^{\text{II}}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** is known to form and Pd activates by reduction at expense of concomitant oxidation of PPh_3 (Sections 2.2, 2.3 & 2.4). In solution $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{PPh}_3)]_2$ **64** is unstable, and degrades over the course of 12-18 hours to Pd particles and a range of unidentified P-containing species, releasing Ac_2O and AcOH as by-products. The major Pd-containing product after *ca.* 18 hours was Pd particles (20-500 nm, observed by TEM). The presence Ac_2O as a major by-product of the Pd activation process and the absence of significant amounts of $\text{O}=\text{PPh}_3$ suggests a difference in the mechanism of activation of Pd^{II} to the observed Pd particles under the $[\text{Pd}_3(\text{OAc})_6]/3 \text{ PPh}_3$ regime, compared to that of $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ or $\geq 9 \text{ PPh}_3$. This finding does not rule out a role for the electronic influence of PPh_3 in the mechanism of activation of **64**, however the absence of oxidised phosphine in the post-reaction solution indicates that acetate, instead of PPh_3 , is the agent which facilitates the conversion of Pd^{II} to Pd particles. It is notable that the difference in mechanism of activation of Pd^{II} most likely stems from structural differences between the *in situ*-formed $\text{Pd}^{\text{II}}\text{-PPh}_3$ complex (**47** or **64**) under the different $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ regimes.

2.7. Palladium(II) acetate activation with PPh₃: Summary of Key Results and Perspectives

[Pd₃(OAc)₆] reacts with varying quantities of PPh₃ to yield activated Pd species. This chapter has shown that different ratios of [Pd₃(OAc)₆] to PPh₃ result in clear differences in the nature of the activated species.

When [Pd₃(OAc)₆] is reacted with ≥ 9 equivalents of PPh₃ (Pd:P = 1: ≥ 3), stabilised mono-nuclear Pd complexes [Pd⁰(PPh₃)_n] ultimately form, which are in equilibrium with free [OAc]⁻ present in solution.^{46, 200} [Pd⁰(PPh₃)₃] **48** was isolated by crystallisation from a complete reaction of [Pd₃(OAc)₆] with 12 equivalents of PPh₃ mixture. The *in situ*-formed Pd⁰ complexes can undergo oxidative addition, the first committed step in cross-coupling, into *para*-fluoroiodobenzene. H₂O was found to be a crucial ingredient for full conversion of [Pd₃(OAc)₆] to Pd⁰ complexes.

When [Pd₃(OAc)₆] is reacted with exactly 6 equivalents of PPh₃ (Pd:P = 1:2) a novel Pd^I dinuclear complex arises [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52**, stabilised by bridging interactions through one μ-phosphido and one μ₂-CO₂-acetato ligand. The structure and reactivity of **52** was investigated. **52** was shown to react with organohalides to afford Pd₃ clusters of the form [Pd₃(μ-X)(μ-PPh₂)₂(PPh₃)₃]⁺X⁻ **Pd₃X·X** (X = halide anions present) which are known to be active cross-coupling catalysts. **52** reacted with 2-bromopyridine **55** to form [Pd₃(μ-Br)(μ-PPh₂)₂(PPh₃)₃]⁺X⁻ alongside Pd^{II} dimer complexes *trans*-(P,N)-[PdX(μ-*pyridyl*-C², N)(PPh₃)₂] **56a**, **56b**, **56c** (where here X = three combinations of Br⁻ and OAc⁻). Chapter 3 (Section 3.2.1) reports that **52** is a competent pre-catalyst for a model SMCC reaction, demonstrating reactivity on a par with the [Pd₃(OAc)₆]/ 6 PPh₃ pre-catalytic mixture.

On treatment with further PPh₃, **52** immediately disproportionates at room temperature to form a novel Pd^I dinuclear complex [Pd₂(μ-PPh₂){κ²-P,O-μ-P(O)Ph₂}(κ-PPh₃)₂] **58**, stabilised by μ-phosphido and a μ₂-phosphinito ligands, alongside [Pd⁰(PPh₃)₃] **48**. This system was shown to react with **55** to form a **Pd₃Br·X**-type cluster complex and the product of oxidative addition of **48** to **55** *trans*-[Pd^{II}(Br)(C²-pyridyl)(PPh₃)₂] **57** which converted over time to *trans*-(P,N)-[PdX(μ-*pyridyl*-C², N)(PPh₃)₂] **56c**.

When [Pd₃(OAc)₆] was treated with 3 equivalents of PPh₃ (Pd:P = 1:1) at room temperature, the dimeric Pd^{II} complex [Pd^{II}(μ₂-OAc)(κ-OAc)(PPh₃)₂] **64** rapidly forms and the system subsequently degrades to particles alongside decomposition to many PPh₃-containing species over the course of 12 hours, with formation of Ac₂O and AcOH.

An important general message from this work is that higher order species can evolve from solutions of $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ when low amounts of PPh_3 are present relative to $[\text{Pd}_3(\text{OAc})_6]$. For example, when $[\text{Pd}_3(\text{OAc})_6]$ is treated with 6 equivalents of PPh_3 , a Pd:P of 1:2, an insufficient quantity of PPh_3 is available to stabilise Pd^0 and the system is stabilised by Pd^{I} dimer **52** formation by cleavage of PPh_3 (with loss of Ph) and aggregation of two Pd centres. **52** is quickly converted into well-defined multinuclear Pd_3 (**$\text{Pd}_3\text{X}\cdot\text{X}$**) complexes in the presence of organohalides. When $[\text{Pd}_3(\text{OAc})_6]$ is mixed with exactly 3 equivalents of PPh_3 (Pd:P = 1:1), upon activation in absence of stabilising ligand, Pd particles arise as the major activated Pd species. The natures of these species lie in stark contrast to the mononuclear Pd^0 complexes which are well known to form when $[\text{Pd}_3(\text{OAc})_6]/\geq 9\text{PPh}_3$ (Pd:P = 1: ≥ 3). The observation that different types of activated species evolve from different stoichiometric ratios of $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$, correlates with different catalytic performances when the $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ system is applied as a pre-catalyst mixture in cross-coupling reactions at mono- and di-halogenated heteroaromatic substrates (Chapters 3 & 4). Further discussion of the impact of this work is highlighted in Chapter 5: Conclusions & Future Work.

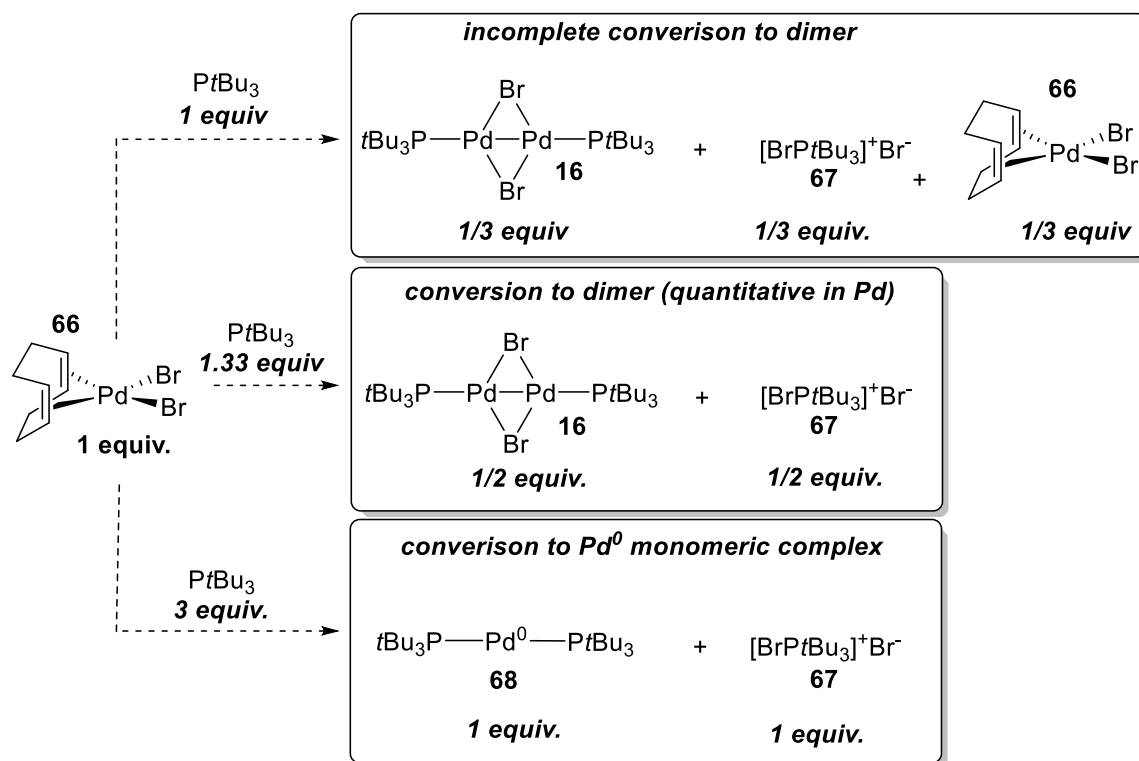
Chapter 3 – The Influence of Catalytic Speciation on Cross-coupling Reactions at Mono-halogenated Substrates

3.1. Introduction

In this section, the knowledge gained regarding Pd speciation arising from $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ mixtures was put to the test in two different model Suzuki-Miyaura cross-coupling reactions. Chapter 2 demonstrated that simple differences in $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ ratios resulted in stark differences in the speciation of the activated Pd. With these findings in mind and as reduced (activated) Pd species are known to participate in catalytic cross-coupling reactions (Section 1.2.2),^{44, 48, 62} it was decided to assess the effect of differing pre-catalytic ratios of $[\text{Pd}_3(\text{OAc})_6]$ and PPh_3 in model Suzuki-Miyaura cross-coupling (SMCC) reactions. Catalyst performances of $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ in model SMCC reactions were compared with those species shown in Chapter 2 to form from different $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ ratios. Similar effects of Pd speciation on site-selective cross-coupling reactions at a multiply halogenated heteroaryl substrate are explored in Chapter 4.

In an important literature precedent for *this work*, Colacot and Schoenebeck *et al.* investigated the reductive activation of $[\text{PdBr}_2(\text{cod})]$ **66** (cod = 1,5-cyclooctadiene) in the presence of various quantities of the strongly donating, and sterically demanding phosphine P^tBu_3 .⁵⁷ The effect of the pre-catalytic ratios on catalytic efficacy in several different cross-coupling reactions was then assessed. In the presence of varying equivalents of P^tBu_3 (Scheme 51) different activated Pd species were seen to arise from **66** in toluene at room temperature. Under the conditions, **66** reacted with 1 equivalent of P^tBu_3 to form a 1/3 equivalent of the Pd^{I} dimeric complex $[\text{Pd}^{\text{I}}(\mu\text{-Br})(\text{P}^t\text{Bu}_3)]_2$ **16^m** at expense of 1/3 equivalents of formed bromo(tri-*tert*-butyl) phosphonium bromide $[\text{BrP}^t\text{Bu}_3]^+\text{Br}^-$ **67**. When 1.33 equivalents of P^tBu_3 was reacted with **66** under the same conditions, complete conversion to a 1/2 equivalent of **16** was evident, with concomitant formation of a 1/2 equivalent of **67**. Treatment of **66** with a higher excess of P^tBu_3 (3 equivalents) resulted in quantitative formation of the mononuclear Pd^0 complex $[\text{Pd}^0(\text{P}^t\text{Bu}_3)_2]$ **68**.

^m See Section 1.4 for a detailed discussion of the diverse reactivity of $[\text{Pd}^{\text{I}}(\mu\text{-Br})(\text{P}^t\text{Bu}_3)]_2$ **16** and related Pd^{I} dimers complexes.



Scheme 51 Showing the variety of species generated from reductive activation of $[\text{Pd}^{\text{II}}(\text{Br})_2(\text{cod})]$ **66** to Pd^{I} and Pd^0 complexes at room temperature, in toluene, which were shown to have a bearing on cross-coupling activity.

The finding that Pd^{II} can be reduced to Pd^{I} or Pd^0 complexes with the speciation changing as a function of relative Pd/phosphine stoichiometry (Scheme 51) is highly analogous to $[\text{Pd}_3(\text{OAc})_6]$ activation by PPh_3 (See Chapter 2).⁴⁶⁻⁴⁸ Furthermore, each equivalent of reduced Pd complex is accompanied by oxidation of a single equivalent of phosphine ($\text{P}^{\text{III}} \rightarrow \text{P}^{\text{V}}$), to form **67**, in a process comparable to the oxidation of PPh_3 by O in the Pd^{II} -acetate-based systems.⁵⁷ It was noted that PdBr_2 (*i.e.* not containing the cod ligand) could not undergo the same transformation to **16** under the same conditions. This difference was taken to stem from the reduced solubility of $\text{Pd}^{\text{II}}\text{Br}_2$ *vs.* **66**, as any direct participation of cod in the reduction mechanism was ruled out. One significant difference between the $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ and $[\text{PdBr}_2(\text{cod})]/n\text{P}^t\text{Bu}_3$ systems is that $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ ($\text{Pd}:\text{L} = 1:1$) degrades to Pd particles while $[\text{PdBr}_2(\text{cod})]/1\text{P}^t\text{Bu}_3$ ($\text{Pd}:\text{L} = 1:1$) system merely undergoes incomplete conversion to well-defined molecular species **16** and **17**. The strong electron-donating ability of the phosphine was rationalised to facilitate Pd reduction. The relevance of such speciation to catalytic performance in Buchwald-Hartwig aminations, SMCC reactions and α -arylation of acetophenone with *ortho*-chlorotoluene was investigated, as summarised in Figure 74.

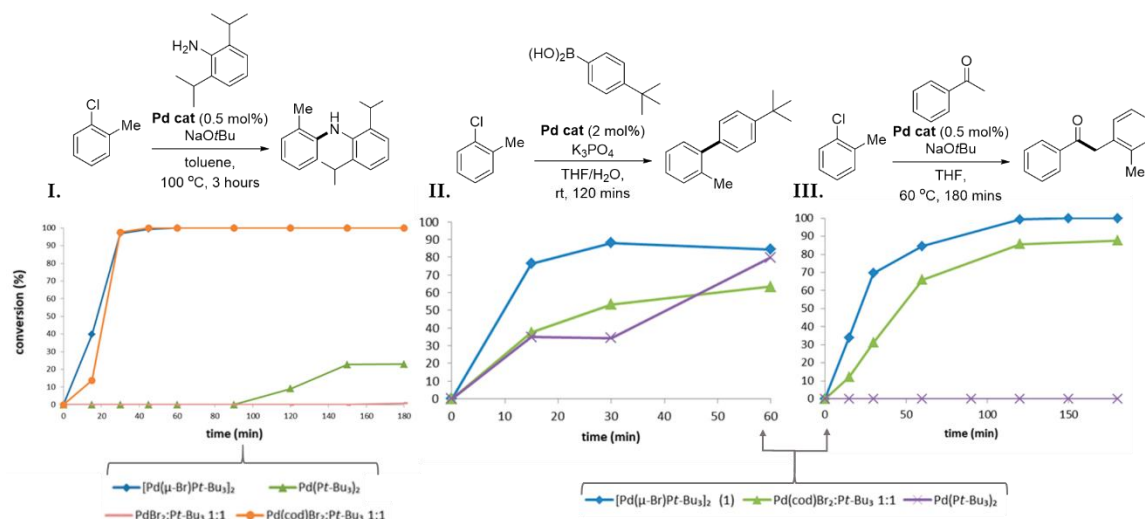


Figure 74 The effects of different catalytic species on a range of three different cross-coupling reactions, all featuring *ortho*-chlorotoluene as the aryl halide substrate: I. Buchwald-Hartwig amination II. α -Arylation of acetophenone, III. Suzuki-Miyaura cross-coupling. Adapted with permission from *J. Am. Chem. Soc.* 2017, **139**, 5194-5200. Copyright 2017 American Chemical Society.

In the three reported cross-coupling applications (Figure 74), with the Pd loading kept fixed, the isolated Pd^I dimer $[\text{Pd}^{\text{I}}(\mu\text{-Br})(\text{P}^t\text{Bu}_3)]_2$ **16** exhibited higher reaction rates and ultimate conversions of *ortho*-chlorotoluene than that of $[\text{Pd}(\text{Br})_2(\text{cod})]$ **66**/1 P^tBu_3 , $\text{Pd}^{\text{II}}\text{Br}_2$ /1 P^tBu_3 , $[\text{Pd}^0(\text{P}^t\text{Bu}_3)_2]$ **68** pre-catalytic systems. It was therefore reasoned that, the Pd^I dimer **16** is a significantly more active catalyst than the mononuclear Pd⁰ complex **68**. Additionally, based on the observed speciation events (summarised in Scheme 51) the active species generated *in situ* from **66**/1 P^tBu_3 , forms 0.33 equivalents of activated **16**, this was taken to account for the decreased activity of the $[\text{Pd}^{\text{II}}(\text{Br})_2(\text{cod})]$ /1 P^tBu_3 system compared with when authentic **16** was deployed.

An important message from this work is that the catalytic activity of Pd^I dinuclear complex **16** (either generated *in situ* or employed as an isolated catalyst) is higher than that of the Pd⁰ complex **68**. This is a striking result as **68** is known to be a source of mono-ligated $[\text{Pd}^0(\text{P}^t\text{Bu}_3)]$, which is known to be highly active in the activation of C–Cl bonds, after dissociation of a single P^tBu_3 ligand.^{23,284} This work additionally shows that access to a catalyst of higher activity than **68** can be achieved by merely varying the ratio of pre-catalytic **66** and 1 P^tBu_3 . Hence, the issues associated with the thermal instability and air sensitivity of expensive **68** may be circumvented. This chapter reports a similar approach to assessing cross-coupling efficacy of active species generated from simple $[\text{Pd}_3(\text{OAc})_6]/n$ PPh_3 mixtures.

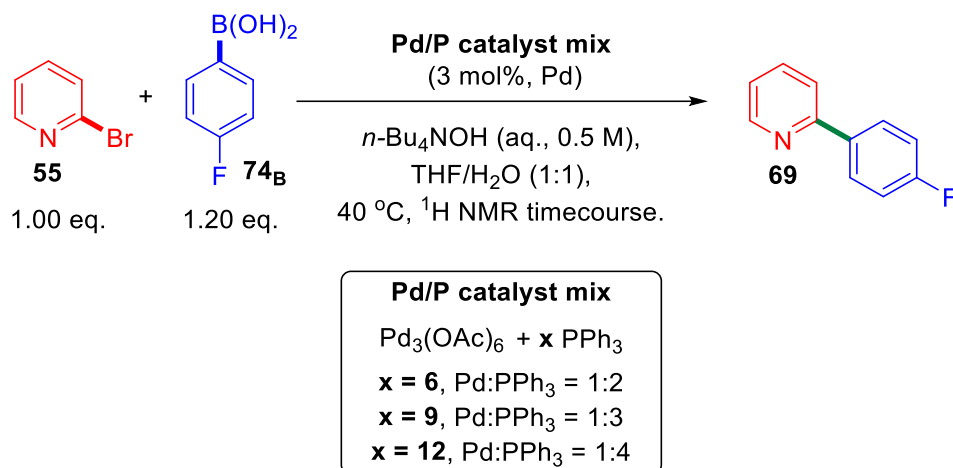
Results & Discussion

3.2. The Influence of Pd Speciation on Reaction Rates in a Model Suzuki-Miyaura Cross-coupling Reaction

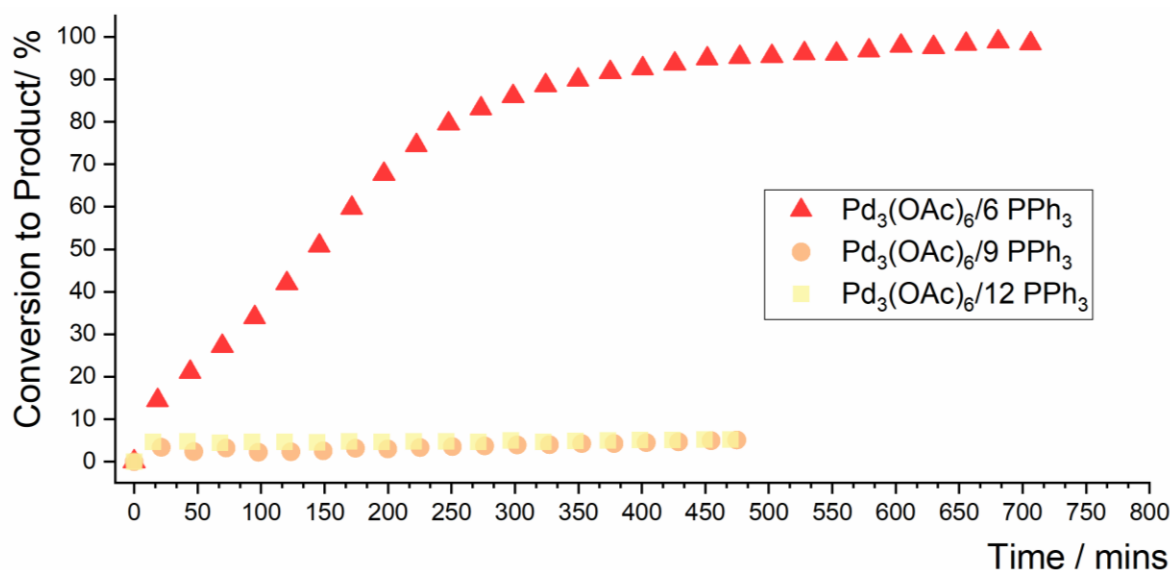
An *in operando* ^1H NMR-based kinetic assay was designed to track the model SMCC reaction of 2-bromopyridine **55** with *para*-fluorophenyl boronic acid **74_B** forming 2-(*para*-fluorophenyl)pyridine **69**. *n*-Bu₄NOH (aq.) was employed as a hydroxide base system, which promoted a single-phase reaction which could be tracked by *in operando* ^1H NMR spectroscopic analysis (see experimental section for details). Notably, this base was also used to mirror conditions reported for the site-selective reactions at 2,4-dibromopyridine as reported in Chapter 4.

3.2.1. $[\text{Pd}_3(\text{OAc})_6]/n \text{PPh}_3$ Effects on SMCC Catalysis

Initially, the effects of pre-catalytic $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ ratios on catalyst efficacy in the model SMCC reaction of **55** with *para*-fluorophenyl boronic acid **74_B** to form 2-(*para*-fluorophenyl)pyridine **69**. The relative rates of reactions (Graph 1), catalysed by mixtures of $[\text{Pd}_3(\text{OAc})_6]$ and 6, 9 and 12 equivalents of PPh_3 , were assessed in this model SMCC reaction (Scheme 52).



Scheme 52 Conditions for the model Suzuki-Miyaura cross-coupling reaction of 2-bromopyridine **55** with *para*-fluorophenylboronic acid **74_B** forming **69**, catalysed by mixture of $[\text{Pd}_3(\text{OAc})_6]$ and PPh_3 at three different specified ratios.



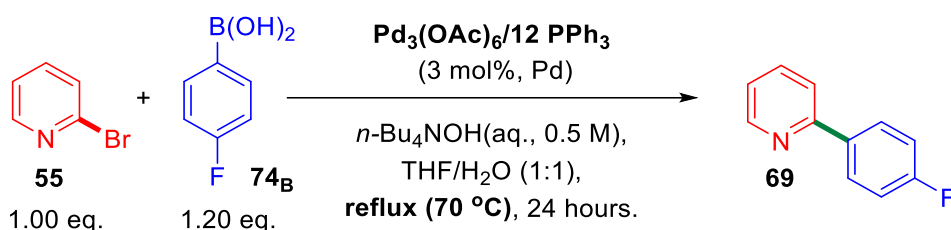
Graph 1 Showing differences in catalyst efficacy in the coupling of 2-bromopyridine **55** with *para*-fluorophenyl boronic acid, forming 2-(*para*-fluorophenyl)pyridine **69** cross-coupled product over time as a function of the pre-catalytic $[\text{Pd}_3(\text{OAc})_6]/n \text{ PPh}_3$ ratio ($n = 6, 9$ and 12).

Graph 1 shows significant differences in catalyst performance as a function of $[\text{Pd}_3(\text{OAc})_6]/n$ equivalents of PPh_3 ratio under conditions highlighted in Scheme 52. With a final conversion of 98% to **69** after *ca.* 12 hours, the $[\text{Pd}_3(\text{OAc})_6]/6$ equivalents of PPh_3 ($\text{Pd}:\text{P} = 1:2$) pre-catalyst system performs markedly better than that with 9 or 12 equivalents of PPh_3 , which achieved 3 and 5 % conversion to **69**, respectively. The $[\text{Pd}_3(\text{OAc})_6]/9$ or 12 equivalents of PPh_3 pre-catalytic system was in line with the use of $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** as a pre-catalyst under the same conditions (*vide infra*).

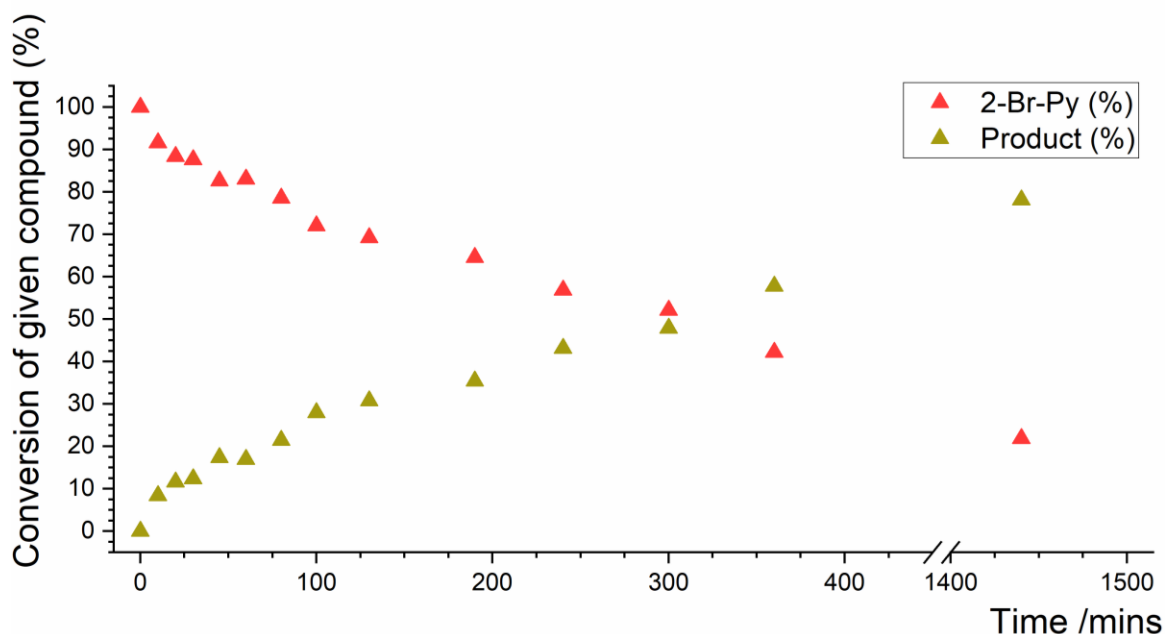
With the $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ catalyst system, the conversion to **69** initially rises in an approximately linear fashion, indicating a linear non-exponential, zero-order kinetic regime *i.e.* the reaction rate is independent of the concentration of **55**, as the reaction progresses. Such a zero-order profile finding has been observed by Schoenebeck *et al.* in the Kumada cross-coupling reactions, using a the dimeric $[\text{Pd}^{\text{I}}(\mu\text{-I})\text{P}(\text{tBu}_3)_2]_2$ **17** catalyst.²⁸⁵ This observation could be indicative of an autocatalytic manifold. After approximately 250 minutes, however this linear growth of product switches to more of a first order profile. The observed switch in reaction kinetics may indicate a change mechanism in the latter stages of the reaction, perhaps due to catalyst degradation, as the substrate **55** is consumed. Such a profile would fit with a heterogeneous reaction mechanism, in line with expectations from understanding of the catalytic speciation arising from $[\text{Pd}_3(\text{OAc})_6]/6$ equivalents of PPh_3 , which quickly forms visible Pd particles on exposure to the reaction base $n\text{-Bu}_4\text{NOH}$ (aq).²⁸⁶ Under a heterogeneous catalytic regime, later-stage deactivation can arise as a result of aggregation, leading to a reduction in activity. Further tests, which would certainly need to be performed to prove this hypothesis, are discussed in the *Future Work* section (Chapter 5).⁶⁹ It is additionally of note that the reaction rate was faster at the very beginning. This phenomenon was rationalised as being due to a measured exotherm (around 2 °C) as

a result of solvation of the reaction participants upon reaction initiation by introduction of the *n*-Bu₄NOH (aq.) base. Indeed, the recorded conversion to product in the [Pd₃(OAc)₆]/9 and 12 equivalents of PPh₃-catalysed reactions is likely a result of this exotherm upon reaction initiation.

Graph 1 shows that [Pd₃(OAc)₆]/9 or 12 PPh₃ pre-catalytic systems performed sluggishly compared to [Pd₃(OAc)₆]/6 PPh₃. By increasing the temperature of the reaction catalysed by [Pd₃(OAc)₆]/12PPh₃ to reflux under otherwise analogous conditions (Scheme 53), it was demonstrated that a higher final conversion was able to be reached with this pre-catalytic system (Graph 2).^a



Scheme 53 Conditions for the Suzuki-Miyaura cross-coupling reaction of 2-bromopyridine **55** with *para*-fluorophenylboronic acid, **74_B** forming **69**, catalysed by a pre-stirred mixture of [Pd₃(OAc)₆] and 12 PPh₃. Analysed by an *ex situ* sampling method.



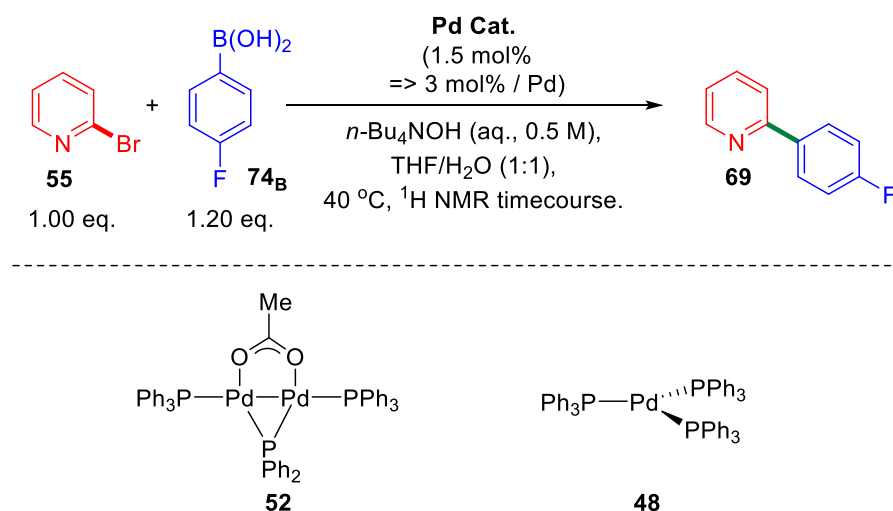
Graph 2 Kinetic plot of the SMCC between of 2-bromopyridine **55** with *para*-fluorophenylboronic acid, catalysed by [Pd₃(OAc)₆]/12 PPh₃, set up according to conditions highlighted in Scheme 53. Note the cut made to the time axis, which allows the conversion after 24 hours to be displayed.

^a Due to the issues associated with following reactions under reflux using NMR spectroscopy, an *ex situ* sampling method was developed to follow this reaction kinetically.

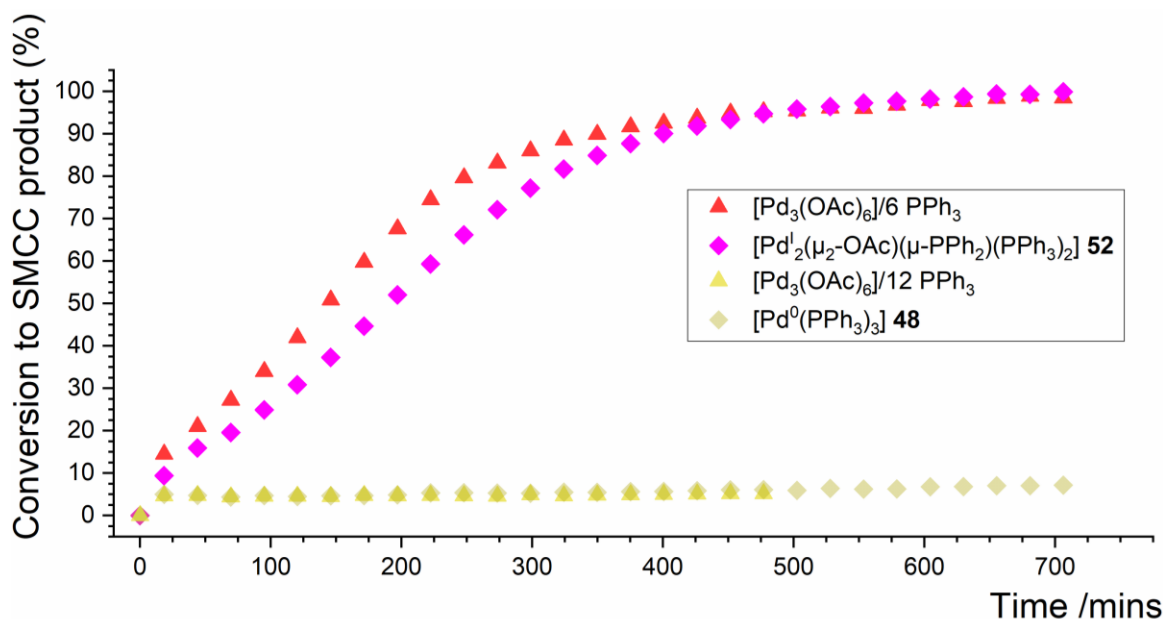
Graph 2 shows that over a 360-minute time-course, a significantly higher conversion to **69** (58%) could be realised. After 24 hours, a conversion of 78% was recorded. This result confirms the catalytic competency of the $[\text{Pd}_3(\text{OAc})_6]/12 \text{ PPh}_3$ catalytic mixture under the conditions, at more elevated temperatures. The observed reactivity in this case reflects that previously reported in the SMCC reaction between 2-bromopyridine and phenylboronic acid, catalysed by $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** in THF/ H_2O (2:1), using Na_2CO_3 (aq.) as a base at 80 °C.²⁵⁷

The differences in reactivity between $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ and that of $[\text{Pd}_3(\text{OAc})_6]/9$ or 12 equivalents of PPh_3 reflect the differences in types of species that can arise from these respective ratios. It was demonstrated in Chapter 2 that $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ forms the reactive, higher order, dinuclear $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** species when reacted in THF (Section 2.4). Under equivalent conditions, $[\text{Pd}_3(\text{OAc})_6]/9$ and 12 PPh_3 catalyst systems have been shown in *this work* (Sections 2.2 & 0) and in literature, to form stabilised Pd^0 complexes.^{46-48, 200}

To confirm the catalyst efficacy of **52**, the reduced species generated from the mixture of $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ (Pd:P = 1:2), was applied as a (pre-)catalyst under the model SMCC conditions (Scheme 54). The Pd-loading was fixed at 3 mol% to provide a direct comparison with $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ *vide supra*. $[\text{Pd}_3(\text{OAc})_6]$ and 9 or 12 equivalents of PPh_3 are known to form monomeric Pd^0 complexes $[\text{Pd}^0(\text{PPh}_3)_n]$ ($n = 2$ or 3, with a potential contribution to stability from solvated acetate). Therefore, for comparison, authentic $[\text{Pd}^0(\text{PPh}_3)_3]$ **48**, which is related to the catalytic species formed from the direct $[\text{Pd}_3(\text{OAc})_6]/12 \text{ PPh}_3$ reaction was also tested as a (pre-)catalyst in the model SMCC.



Scheme 54 Application of **52** and **48** as catalysts in the model SMCC of **55** and **74B**.



Graph 3 Comparison of the kinetics of the model SMCC reaction (details in Scheme 54), catalysed by **52** vs. [Pd₃(OAc)₆]/6PPh₃. The performance of Pd⁰ complex **48** and vs. [Pd₃(OAc)₆]/12PPh₃ in the same reaction is also given, for comparison.

As anticipated, **52** proved to be able to mediate the SMCC reaction, with a comparable kinetic profile to pre-catalytic [Pd₃(OAc)₆]/6 PPh₃ (Graph 3). The initial rate of the [Pd₃(OAc)₆]/6 PPh₃ SMCC reaction is slightly faster than that catalysed by [Pd₃(OAc)₆]/6PPh₃, however, both catalytic systems reach quantitative conversion after approximately 600 minutes (10 hours). This appears to be a result of the deactivation rate being slower with the **52** catalyst than with the [Pd₃(OAc)₆]/6 equivalents of PPh₃. The similarity of these kinetic profiles may indicate that both reactions are occurring by similar mechanisms. A quantitative yield (> 99%) of isolated product **69** was obtained from this reaction, after column chromatography.

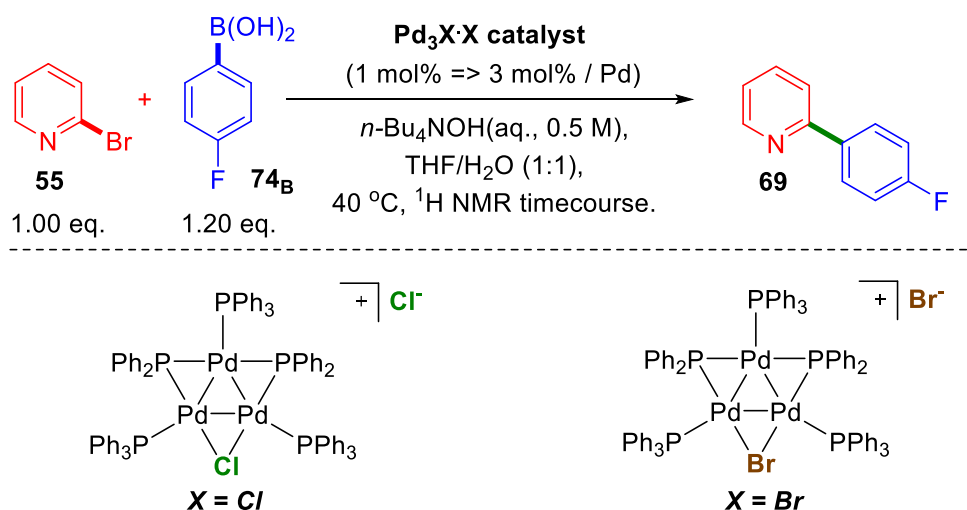
Graph 3 also shows kinetic traces showing the performance of both the [Pd₃(OAc)₆]/12 PPh₃ pre-catalytic mixture and that of authentic monomeric complex Pd⁰ complex, [Pd⁰(PPh₃)₃] **48** isolated from a complete reaction of [Pd₃(OAc)₆] and 12 PPh₃ (see Section 2.3) under like conditions. These systems, which are both expected to act *via* a [Pd⁰(L)₂] active species (L = PPh₃ or ·OAc),^{46-47, 200} were seen to perform similarly sluggishly under the model SMCC reaction conditions at 40 °C.

To sum up this subsection, employing [Pd₃(OAc)₆]/ 6 PPh₃ as a pre-catalytic mixture performs similarly to the Pd^I dimeric complex, which is the reduced (activated) product of the reaction of [Pd₃(OAc)₆] and 6 PPh₃ under identical model SMCC conditions. On the other hand, the [Pd₃(OAc)₆]/ 12 PPh₃ system, performs sluggishly when applied the same model SMCC, as does the authentic Pd⁰ complex **48**, which can be generated from direct reaction between [Pd₃(OAc)₆] and 12 equivalents of PPh₃.

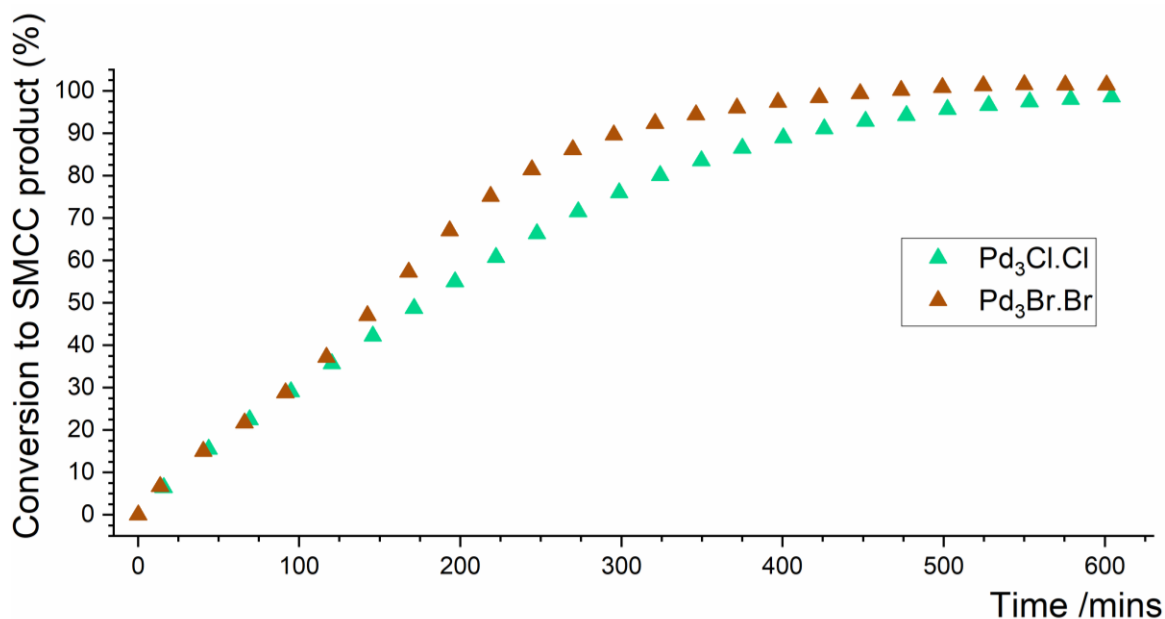
3.2.2. $\text{Pd}_3\text{X}\cdot\text{X}$ Cluster Catalytic Performance

Chapter 2 showed that the direct reaction of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** with 2-bromopyridine **55** resulted in formation of the tripalladium cluster complex $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$ (**$\text{Pd}_3\text{Br}\cdot\text{X}$**) and a mixture of dimeric Pd^{II} complexes *trans*-(P,N)- $[\text{PdBr}(\mu\text{-pyridyl-C}^2, \text{N})(\text{PPh}_3)_2]$ (combinations of $\text{X} = \text{Br}^-$ and OAc^-) **56a-c**. In 2017 Li *et al.* determined that the cluster complex, $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$ (**$\text{Pd}_3\text{Cl}\cdot\text{Cl}$**), which adopts analogous atomic connectivity as **$\text{Pd}_3\text{Br}\cdot\text{X}$** , to be a highly active catalytic species in SMCC reactions (Section 1.4).¹⁷² Fairlamb *et al.* found **56c** to be a competent catalyst in the SMCC reactions at aryl bromides; for example, it enabled coupling of 2-bromopyridine **55** with phenylboronic acid, producing 2-phenylpyridine in a 68% yield.²⁵⁷

To confirm catalytic efficacy and assess the halide-influence on reactivity of Pd clusters which adopt the **$\text{Pd}_3\text{X}\cdot\text{X}$** motif, authentic samples of **$\text{Pd}_3\text{Cl}\cdot\text{Cl}$** and **$\text{Pd}_3\text{Br}\cdot\text{Br}$** , synthesised by the methods highlighted in Section 2.5.2, were employed as (pre-)catalysts under the model SMCC conditions (Scheme 55 & Graph 4). Catalyst loadings were set at 1 mol%, to provide overall Pd loadings of 3 mol%, thus allowing for comparison with the reactions reported *vide supra*.



Scheme 55 Reagents and conditions used for the $\text{Pd}_3\text{X}\cdot\text{X}$ ($\text{X} = \text{Cl}$ or Br) cluster-catalysed model SMCC between **55** and **74_B**, comparing the effects of the halide anion (both coordinating and non-coordinating) in **$\text{Pd}_3\text{Br}\cdot\text{Br}$** and **$\text{Pd}_3\text{Cl}\cdot\text{Cl}$** .

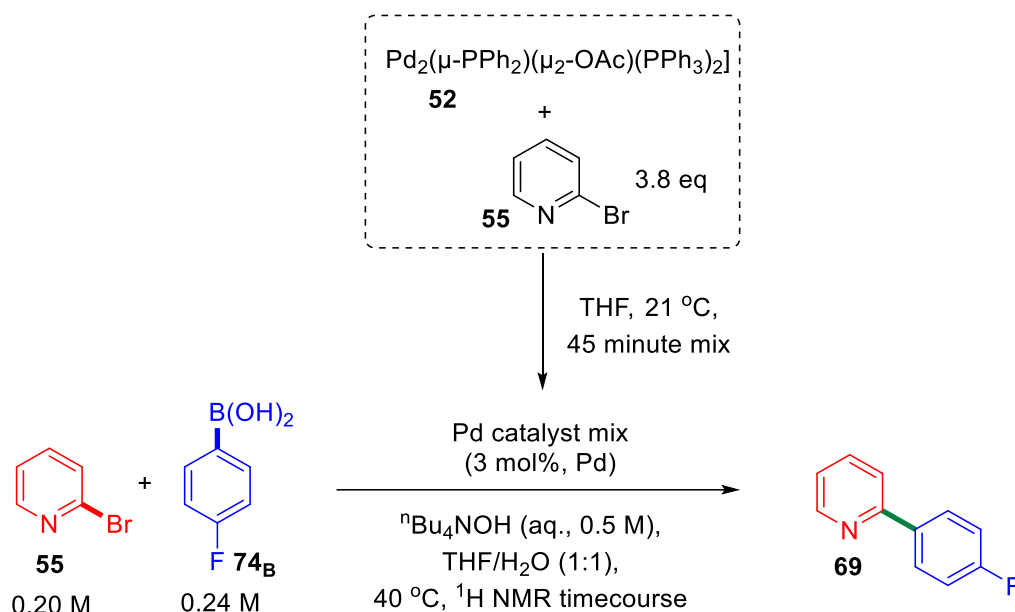


Graph 4 Comparison of the catalytic activity of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ vs. $\text{Pd}_3\text{Br}\cdot\text{Br}$ in the model SMCC reaction **55** with *para*-fluorophenylboronic acid (Scheme 55).

Graph 4 indicates that both cluster complexes $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ and $\text{Pd}_3\text{Br}\cdot\text{Br}$ are catalytically competent, with activities comparable to that of both $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ and **52**. The comparison presented in **Graph 4** constitutes the first time that halide effects of $\text{Pd}_3\text{X}\cdot\text{X}$ catalysts on cross-coupling kinetics have been assessed. Overall, $\text{Pd}_3\text{Br}\cdot\text{Br}$ showed broadly similar reactivity to that of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$. This similarity reflects similarities in overall structure of the two cluster complexes, indicating that the catalytic performance is not significantly dependent on the identity of the halide anions (where $\text{X} = \text{Br}$ or Cl). Despite broadly comparable initial rates, the rate of product conversion remains relatively high with $\text{Pd}_3\text{Br}\cdot\text{Br}$ however the rate gradually slows in the case of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$. Both $\text{Pd}_3\text{Br}\cdot\text{Br}$ - and $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ -catalysed reactions reach quantitative conversion at approximately 473 and 604 minutes, respectively. Hence $\text{Pd}_3\text{Br}\cdot\text{Br}$ performs better than $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ as a catalyst, in terms time taken to reach quantitative conversion. Based on the kinetic profiles, the rate of the $\text{Pd}_3\text{Br}\cdot\text{Br}$ -catalysed reaction is sustained for a longer time during the reaction. This may indicate that the Br^- anions introduced with the $\text{Pd}_3\text{Br}\cdot\text{Br}$ catalyst confer greater activity or stability on the active catalyst during turnover.

To recap, **52** was shown to be a competent (pre-)catalyst in the above SMCC reaction (Graph 3) and able to react with 2-bromopyridine **55**. As both product classes of the reaction between **52** and **55** ($\text{Pd}_3\text{Br}\cdot\text{X}$ and *trans*-(P,N)- $[\text{PdBr}(\mu\text{-pyridyl})\text{-C}^2, \text{N}](\text{PPh}_3)_2$ { $\text{X} = \text{Br}^-$ or $-\text{OAc}$ } **56a-c**), are established as competent SMCC catalysts it was decided react Pd^{I} dinuclear **52** complex with 2-bromopyridine **55**, allowing $\text{Pd}_3\text{Br}\cdot\text{X}$ and **56a-c** to form *in situ*, immediately prior to addition of the mixture as a catalyst in the model SMCC reaction (Scheme 56) at **55**. Activity of the *in situ*-generated mixture could thus be

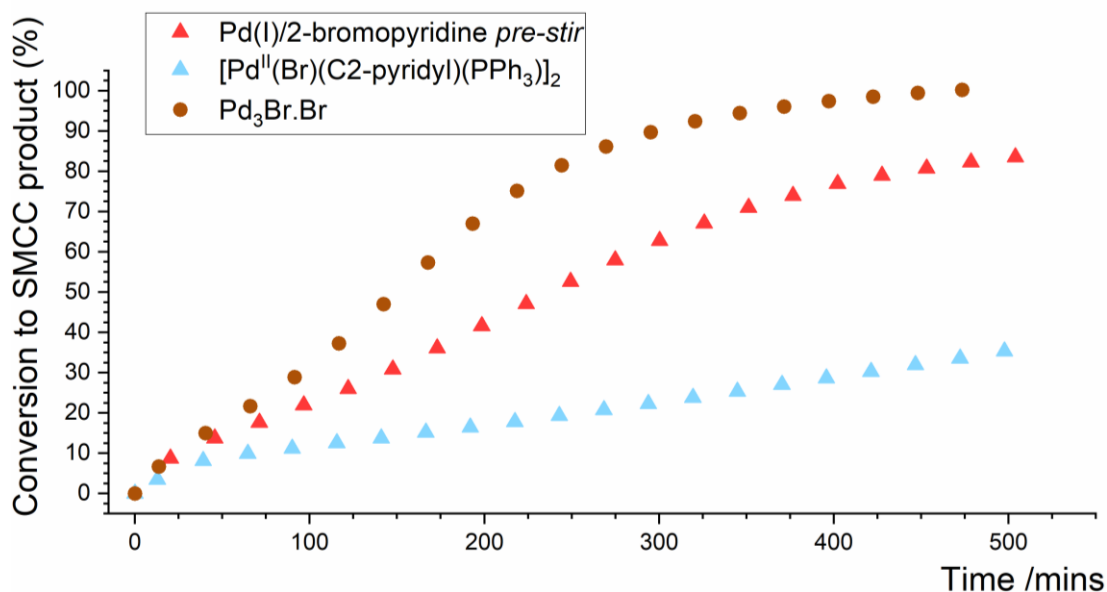
compared with that of authentic **Pd₃Br·Br** and **56c**^o (0.5 mol% {1 mol% with respect to active Pd}) to approximate the amount of **56a-c** being generated *in situ*, and in doing so, allow for the delineation of the relative reactivity of the efficacy of each species generated in the model SMCC reaction.



Scheme 56 Reaction setup for the *in situ* generation of a catalytic mixture from reaction of **52** with **55** and subsequent addition of this mixture to the model SMCC between **55** and *para*-fluorophenylboronic acid forming **69**.

Based on knowledge of the reaction time required, **52** was treated with **55** (Section 2.5.1) and stirred at room temperature for 45 minutes, allowing for full conversion to **Pd₃Br·Br** and **56a-c**, after which time this entire reaction solution was transferred to the catalytic reaction substrates, and the model SMCC was initiated (Scheme 56). The measured kinetic profile of this reaction was then compared against profiles of the same reaction, catalysed by authentic **Pd₃Br·Br** and **56c**.

^o For this experiment, the assumption was made that anion effects (Br⁻, ⁻OAc⁻) **56a-c** would not significantly influence reactivity – the *in situ*-generated mixture was compared against the bromide-containing catalyst variants: **Pd₃Br·Br** and **56c**.



Graph 5 Comparison of kinetic profiles of the stirred mixture of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** and 2-bromopyridine **55** (Scheme 56) with that of authentic $\text{Pd}_3\text{Br}\cdot\text{Br}$ and $[\text{Pd}^{\text{II}}(\text{Br})(\text{C2-pyridyl})(\text{PPh}_3)_2]$ **56c**.

Graph 5 allows for comparison of the catalytically active species generated from reactivity with **55**, a component of the model SMCC reaction. When adjusted approximately for catalyst loading, $\text{Pd}_3\text{Br}\cdot\text{Br}$ was indicated to exhibit higher reactivity in the model SMCC reaction, when compared to the catalyst mixture generated from mixing **52** with **55**. Both catalyst systems performed better than **56c**, establishing that the Pd_3 cluster component of the *in situ*-generated mixture is more active than species **56a-c** which were shown to be less active in this SMCC. In other words, these experiments indicate that, while the two known products of the reaction of **52** and **55** are catalytically active, the Pd_3 cluster component ($\text{Pd}_3\text{Br}\cdot\text{X}$) contributes more significantly to the catalyst activity than the Pd^{II} complex under the conditions examined.

3.2.3. Perspectives

This section highlights the pivotal effect of Pd:P-ligand ratio in pre-catalytic $[\text{Pd}_3(\text{OAc})_6]/n$ equivalents of PPh_3 mixtures, with $n = 6$ performing markedly better as a catalyst than when $n = 9$ or $n = 12$, under otherwise fixed SMCC conditions. The comparable catalytic performances of $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ and $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52**, $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ and $\text{Pd}_3\text{Br}\cdot\text{Br}$: species determined in Chapter 2 to arise from intramolecular reduction of $[\text{Pd}_3(\text{OAc})_6]$ by 6 equivalents of PPh_3 , the latter two form on exposure to organohalides including 2-bromopyridine **55**, supports their catalytic action by a like mechanism. As similar kinetic activity derives from $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ as with the higher order clusters **52** and $\text{Pd}_3\text{Br}\cdot\text{Br}$, and **52** converts to $\text{Pd}_3\text{Br}\cdot\text{X}$ on exposure to certain

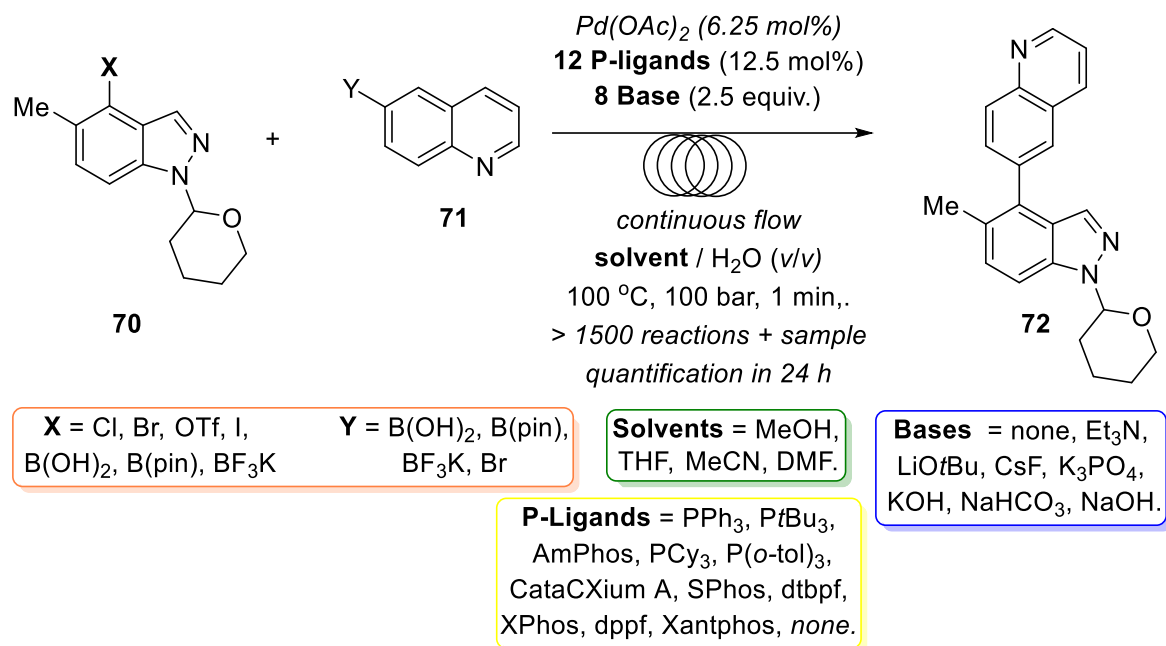
organohalides (*e.g.* 2-bromopyridine **55**) it is likely that related higher order species are involved as the active species under cross-coupling conditions, where organohalide is present, however further work would be required in order to confirm this hypothesis (See Section 5.2.2, Future work).

This result highlights the importance of the selection of pre-catalytic conditions, as, for example an extra equivalent of PPh_3 *per* Pd can result in a completely different reaction outcome. These observations broadly agree with findings reported in Chapter 4, where increased reaction rates (notwithstanding changes in site-selectivity) at the dihalogenated substrate 2,4-dibromopyridine (**30**) when $[\text{Pd}_3(\text{OAc})_6]/3$ or 6 PPh_3 are deployed as pre-catalytic systems, compared with when $[\text{Pd}_3(\text{OAc})_6]/\geq 9 \text{ PPh}_3$ are deployed. These results complement findings by Colacot *et al.* on the $[\text{Pd}^{\text{II}}(\text{Br})_2(\text{cod})]/\text{nP}^t\text{Bu}_3$ catalytic system (*vide supra*) where lower equivalents of P^tBu_3 phosphine were seen to result in faster, more efficient cross-coupling.⁵⁷ These catalytic findings were similarly linked back to the stoichiometric speciation as a function of Pd:P ratio, where higher order Pd^{I} dinuclear species $[\text{Pd}^{\text{I}}\text{Br}(\text{P}^t\text{Bu}_3)]_2$ arose when lower equivalences of phosphine (≤ 1.3 equivalents per Pd) were employed, and mono-nuclear $[\text{Pd}^0(\text{P}^t\text{Bu}_3)_2]$ arose when higher equivalents of phosphine (≥ 3 equivalents per Pd) were employed.

3.3. Influence of Catalytic Speciation on Efficacy in a Pharmaceutically Relevant Cross-coupling Reaction

3.3.1. Introduction

The application of high-throughput studies, historically the mainstay of lead compound screening drug discovery, has found powerful application in synthetic chemistry. A key desirable aspect of high-throughput studies in synthetic chemistry is that many more reactions can be done in a given time, thus freeing up chemical researchers' time for high quality experimental analysis and judicious design of future experiments. With the simultaneous burgeoning of integrable technologies such as machine learning and robotics, novel high-throughput synthetic technologies and methodologies are rightly on the cutting edge of current chemical research.²⁸⁷ In one prominent example, Sach *et al.*, working for the pharmaceutical company Pfizer, reported an automated, flow chemistry-based high-throughput approach to the optimisation of a challenging Suzuki-Miyaura cross-coupling for the pharmaceutically relevant cross-coupling of an indazole derivative **70** with a quinoline moiety **71** forming **72** (Scheme 57).²²⁸



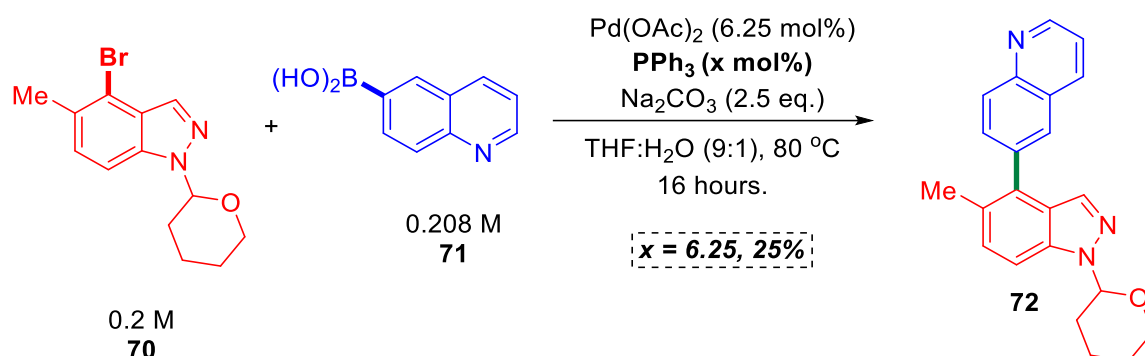
Scheme 57 Showing the conditions used for the mmol-scale high-throughput approach to reaction optimisation by Sach *et al.* at Pfizer for optimised access to a pharmaceutically relevant target *via* a SMCC reaction.

Employing this approach, conditions (with variables changed highlighted in **Bold**, Scheme 57) could be rapidly changed, allowing for a total of 5760 reactions, assessing the effect of many combinations of modified variables on product yield. Astonishingly, an optimised maximum rate of >1500 reactions *per* 24 hours could be achieved, with quantitative reaction analysis (LC-MS) built into the method. Indeed, the data set was so rich that it was taken up by Cronin *et al.* as a basis for machine learning with application in experimental design.²⁸⁸⁻²⁸⁹ The optimised high yielding catalytic conditions were successfully transferred to 200 mg-scale batch processes.

It is notable from the reported results, which exclusively involved Pd(OAc)₂ as the Pd catalyst source, and despite the use of heavily engineered, expensive tertiary phosphine ligands such as CataCXium A, DTBPF and SPhos, some of the best yields under these conditions could be achieved with the simplest and cheapest tertiary organophosphine, PPh₃.²⁰³ Indeed, in many cases PPh₃ worked well while other ligands performed poorly under otherwise identical conditions. This observation highlights an important point that, using simple, cheap Pd(OAc)₂/ 2 PPh₃ pre-catalytic mixture, activated *in situ* under the appropriate conditions, high reactivity, can be achieved, surpassing that of expensive, engineered ligands. In this high-throughput study, many phosphine ligands were examined, however, and notably in all cases the Pd(OAc)₂/phosphine ratio was fixed at 1:2. With these observations in mind, and knowledge of optimised conditions taken from *this study* in hand, it was decided to test the effect of known Pd speciation arising from different ratios of Pd(OAc)₂/PPh₃- pre-catalytic mixtures on SMCC outcomes.

3.3.2. Results and Discussion

Primarily, in this study, optimised conditions, published by Sach *et al.* for the SMCC reaction of 4-bromo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **70** with 6-quinoline boronic acid **71** were adapted to determine whether changing the ratio of Pd(OAc)₂ (introduced here again as [Pd₃(OAc)₆]) to PPh₃ would affect the reaction outcome (Scheme 58).²²⁸ The solvent system (THF/H₂O {9:1}) and the base, Na₂CO₃ were selected due to their optimised performance with the Pd(OAc)₂/2PPh₃ catalyst system as reported by Sach *et al.* in their high-throughput synthetic study.²²⁸



Scheme 58 Conditions used for a SMCC reaction between **70** and **71** catalysed by varying pre-catalytic ratios of [Pd₃(OAc)₆] and PPh₃. Conditions were adapted from a high-throughput flow reaction study by Sach *et al.*.

For each reaction, conversions were comparison of ¹H NMR integrations of the starting material and the product against a 1,3,5-trimethoxybenzene internal standard, as tabulated below. By comparison of the ¹H NMR spectrum of the crude post-reaction mixture, no homocoupled or protodeborylated products were observed in the post-reaction mixture under these conditions.

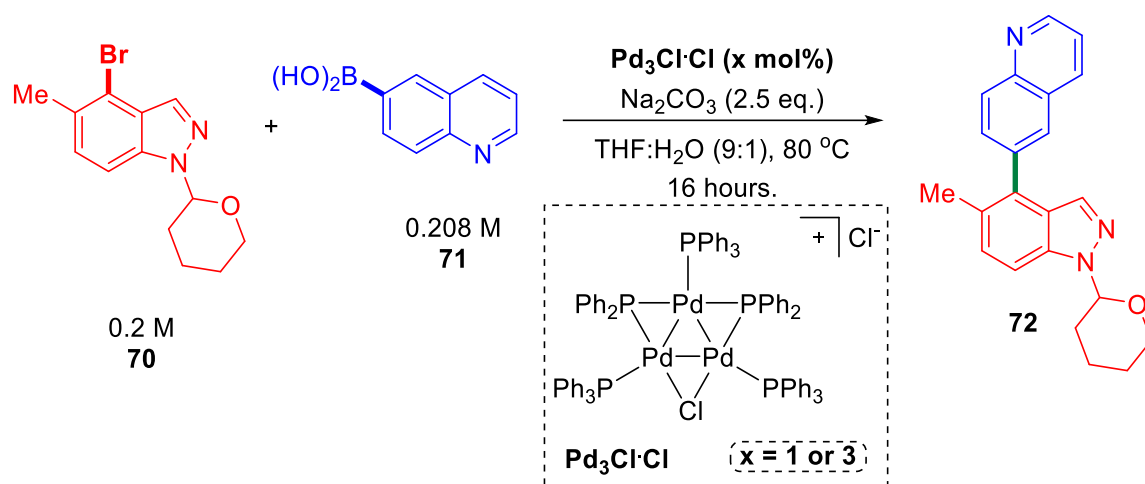
Table 1 Results showing the effect of changing the pre-catalytic $[\text{Pd}_3(\text{OAc})_6]/\text{PPh}_3$ ratio on conversion outcomes in the SMCC reaction as detailed in Scheme 58. Conversion determined by ^1H NMR analysis of the crude, post-reaction solution (validated against 1,3,5-trimethoxybenzene).

Pd:P	Conversion to SMCC product /%
1:1	72 ^p
1:2	88
1:4	55

These results show that varying the $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ ratio resulted in significant change in conversion to products, with $[\text{Pd}_3(\text{OAc})_6]/3$ and 6PPh_3 performing better than $[\text{Pd}_3(\text{OAc})_6]/12\text{PPh}_3$, in terms of conversion to the SMCC product **72**. This indicates that the additional pre-catalytic PPh_3 has a deleterious effect on catalytic efficacy. Notably $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ resulted in a lower conversion than when employing $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ as the pre-catalyst system, contrasting with observations on site-selective cross-coupling reactions at 2,4-dibromopyridine **30**, where the former catalyst system resulted in higher conversion than the latter in the conditions highlighted in Section 4.4. These results were additionally repeated and validated in the group by Aaron Aspell,²⁹⁰ who additionally showed that, employing $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$, lowering the Pd catalyst loading resulted in an increase in reaction conversion and turnover. Such an observation, where there is an inverse relationship between catalyst loading and conversion has been recorded before and can be associated with the formation of PdNPs as the active catalyst species.^{7, 72, 291}

Reactions were set up under identical conditions, instead employing the trinuclear Pd cluster **$\text{Pd}_3\text{Cl}_2\text{Cl}$** as the catalyst under different catalyst loadings (Scheme 59).

^p Result obtained by Aaron Aspell, MChem student and member of the Fairlamb group from Sept 2019-May 2020.



Scheme 59 Conditions for a SMCC reaction between **70** and **71**, forming **72** catalysed by $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ (against 1,3,5-trimethoxybenzene).

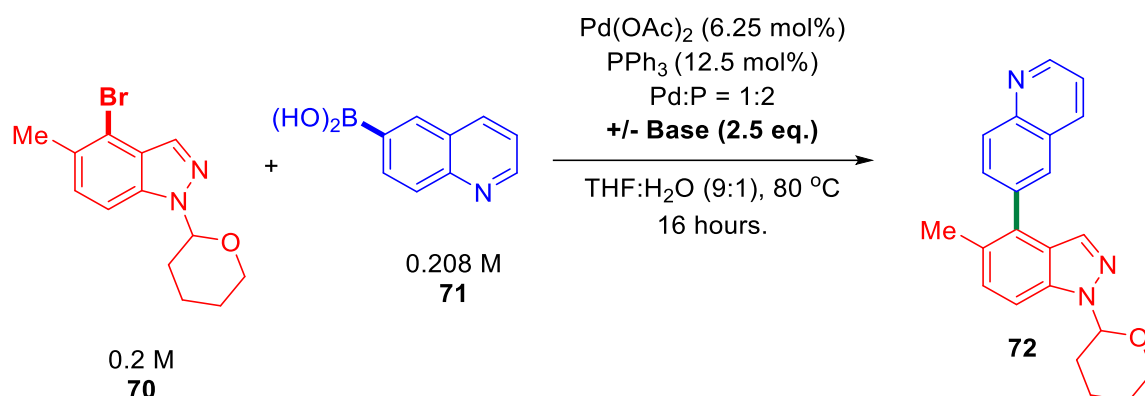
Results for reactions as from Scheme 59 are tabulated in Table 2. Here, catalyst loading has been expressed in terms of molecular loading *i.e.* 1 mol% of the $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ trinuclear catalyst means a 3 mol% in terms of Pd loading.

Table 2 Showing the effect of changing the $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ (pre-)catalyst loading on conversion outcomes in the SMCC reaction as detailed in Scheme 59. Conversion determined by ^1H NMR analysis of the crude, post reaction solution (validated against 1,3,5-trimethoxybenzene).

Cat. Loading (x mol%)	Conversion /%
1	35
3	78

Table 2 shows that the Pd_3 cluster is efficacious in this pharmaceutically relevant cross-coupling reaction, however, it performs worse as a catalyst than pre-catalytic $[\text{Pd}_3(\text{OAc})_6]/3$ or 6 PPh_3 . As might be conventionally anticipated, in this case, a higher loading of $\text{Pd}_3\text{Cl}\cdot\text{Cl}$ catalyst results in a higher conversion to the cross-coupled product.

A base screening was performed, with a view to replicating results obtained by Sach *et al.* using a $[\text{Pd}_3(\text{OAc})_6]/6$ PPh_3 pre-catalytic system. Of particular interest is the transferability of reaction data from the reported flow process to the batch process, as would be carried out under normal laboratory conditions. Hence, three reactions were set up, featuring bases that were high-, medium- and low-performing, according to Sach's flow data (Scheme 60).²²⁸ The flow system reported temperatures of 100 °C and pressures of 100 bar. Such extreme conditions are not feasible and/or sufficiently safe to employ in a normal synthetic laboratory environment, so instead a reaction temperature of 80 °C within a sealed pressure tube was used.



Scheme 60 Conditions used for the base screening of the SMCC between **70** and **71** forming **72**, carried out to validate the transferability of reaction outcomes from batch to flow.

The conversions to the SMCC product as a function of the base employed are displayed in Table 3.

Table 3 Showing the effect of changing the base identity on conversion outcomes in the SMCC reaction as detailed in Scheme 60. Conversion determined by ¹H NMR analysis of the crude, post reaction solution (validated against 1,3,5-trimethoxybenzene). The result for the same cross-coupling reaction, carried out under flow conditions as provided by Sach *et al.* is detailed, for comparison.

Base	Conversion /%	Conversion /%
	<i>This work</i>	<i>Sach conditions^a</i>
NaHCO ₃	88	66
KOH	12	45
none	4	26

In under both sets of conditions, flow reported by Sach *et al.*, and batch reported in Table 3, NaHCO₃ exhibited the highest performance of the bases tested. Under batch conditions, KOH resulted in a poor conversion of 12% – significantly lower than that reported under flow conditions by Sach *et al.* (45%). Performing the reaction with no added base resulted in a 4% conversion to product, indicating that the basicity of the indazole or quinoline functionalities of the substrates were sufficient to facilitate some degree of cross-coupling under the reaction conditions. This effect was clearly accentuated under the flow conditions as reported by Sach *et al.*, with a conversion of 26% observed in the absence of additive base. The overall trend observed in *this work* under batch conditions, mirrors the trend analogous reactions carried out in flow, however, under batch conditions, the conversion using NaHCO₃ is increased, compared with that carried out in flow. In the cases of the less active KOH system or that

^a As Scheme 60 except under flow conditions T = 100 °C, P = 100 bar

carried out without additive base, the flow conditions resulted in an increased conversion compared with batch.

3.4. Conclusions and Perspectives

Knowledge regarding active speciation stemming from $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ mixtures reported in Chapter 2 has been put to the test two model SMCC reactions at mono-brominated heteroaromatic substrates under two distinctly different sets of SMCC conditions. In the simple SMCC between 2-bromopyridine **55** and *para*-fluorophenylboronic acid **74B**, the $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ catalyst system markedly outperformed that of $[\text{Pd}_3(\text{OAc})_6]/9\text{PPh}_3$ or 12PPh_3 at 40°C , the latter system required elevated temperatures to induce catalytic turnover. Similarly, in the pharmaceutically relevant cross-coupling of 4-bromo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **70** and 6-quinoline boronic acid **71**, $[\text{Pd}_3(\text{OAc})_6]/6\text{PPh}_3$ out-performed that of $[\text{Pd}_3(\text{OAc})_6]/12\text{PPh}_3$ in terms of conversion to product. The summary regarding the correlation between known active catalyst speciation and catalyst efficacy of $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ mixtures (where $n \geq 6$) is shown in Figure 75.

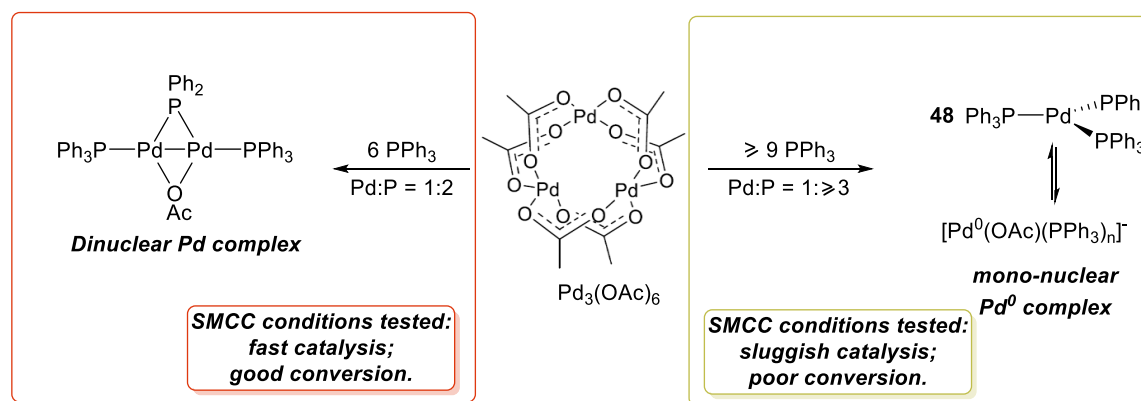


Figure 75 The observed dichotomy of catalyst activity, when employing different $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ pre-catalytic systems, which can be related back to catalyst speciation.

Differences in catalytic activity correlate well with differences in catalytic speciation arising from $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ mixtures. When $[\text{Pd}_3(\text{OAc})_6]$ is mixed stoichiometrically with ≥ 9 equivalents of PPh_3 , a mono-nuclear Pd^0 complex arises of the form $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_n]^-$. When such systems are applied to the model SMCC reactions (*vide supra*), relatively low catalyst turnover was observed. On the other hand, stoichiometric mixtures of $[\text{Pd}_3(\text{OAc})_6]$ and 6 PPh_3 do not form a mononuclear Pd^0 complex but a higher order dimeric species: $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52**. When **52** or $[\text{Pd}_3(\text{OAc})_6]$ and 6 equivalents of PPh_3 are applied to model SMCC reaction, similar faster kinetics and good conversions were recorded. This dichotomy in reactivity under both stoichiometric and SMCC catalytic conditions must stem from the quantity of pre-catalytic PPh_3 deployed: when there is less than or equal to 2 pre-catalytic equivalents of PPh_3 ligand *per* Pd^{II} centre, or, once activated, 1 PPh_3 *per* reduced Pd centre (considering that 1 equivalent of PPh_3 is oxidised during the catalyst activation process {Section

2.4}), higher order species arise. These species form as a result of the putative Pd⁰ centre⁴⁷ forming without the potential for stabilisation by excess ligand, thus resulting in aggregation.

As exposure of **52** to organohalide forms the $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$ **Pd₃Br·X**, which itself is catalytically active,^{162, 172} and shows similar catalytic competence as **52** when used as a pre-catalyst for a model SMCC reaction at 2-bromopyridine **55**, it is likely that this – or related higher order species – are responsible for reactivity under the $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ catalytic regime. A role for other contents of the SMCC reaction (*e.g.* the *n*-Bu₄NOH base) on the speciation of the active catalyst under these conditions should not, however, be ruled out and this notion is elaborated on in Chapter 4. To further assess the scope of this effect, the catalyst $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ would need to be compared against $[\text{Pd}_3(\text{OAc})_6]/\geq 9 \text{ PPh}_3$ catalyst systems in a wider variety of substrates of cross-coupling conditions. One could envisage a scenario, *e.g.* harsh temperatures where a $[\text{Pd}^0(\text{L})_n]$ -type active species could perform better than a less protected catalyst system, which may be prone to deactivation by aggregation. Hence in future studies, along the lines of the high-throughput reaction screening by Sach *et al.*, in addition to pre-catalyst/ ligand additive identity, the relative quantities of catalyst and additive ligand components could be tested as an important reaction variable.

The results reported in *this chapter*, taken with findings reported in Chapter 2 contribute to understanding why, despite mechanistic understanding of active species arising from $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ being limited to the situation where high excesses of PPh_3 are used ($n \geq 12$)⁴⁶⁻⁴⁸ generally speaking, synthetic organic applications of this system usually deploys a Pd:P ratio of 1:2. A low ratio of PPh_3 to Pd results in different, higher order species, with enhanced reactivity compared to monomeric Pd^0 complexes. This is exemplified by the fact that a $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ ratio of 1:2 was used as an exclusive pre-catalyst/phosphine ligand by Sach *et al.* in their high-throughput, flow-based reaction approach (as discussed *vide supra*).²²⁸ From a practical standpoint this chapter shows that the precise control of the ratio of $[\text{Pd}_3(\text{OAc})_6]/n \text{ PPh}_3$ can be crucial for resulting cross-coupling activity. It is important, for example, that the intended quantity of pre-catalyst and additive ligand is judiciously weighed as small errors in weighing *e.g.* in the reaction in Section 3.2, a weighing error of $\sim 50\%$ of 7.9 mg (PPh_3) could essentially bring about a shutdown of catalysis. High accuracy and precision in weighing of pre-catalyst components is especially important when carrying out reactions on the very small scale, *e.g.* in high throughput robotic reaction setups, the weighing apparatus must be appropriately calibrated to allow accurate weighing in order to access the optimal catalyst species. In a similar vein, the purity of Pd precatalysts – in this case $[\text{Pd}_3(\text{OAc})_6]$ – is important to be known so that the correct Pd:ligand ratio can be introduced, for optimal activity of the *in situ* formed active catalyst. This is particularly important with $[\text{Pd}_3(\text{OAc})_6]$, commercial batches of which are subject to drastic variation in purity.^{r,54, 101, 214, 292}

^r Commercial batches of $[\text{Pd}_3(\text{OAc})_6]$ are frequently contaminated with nitrito-ligated $[\text{Pd}_3(\text{OAc})_5(\mu_2\text{-}\kappa\text{-O}, \kappa\text{-N-NO}_2)]$, which is a by-product of its synthesis from $\text{Pd}(\text{NO}_3)_2$.

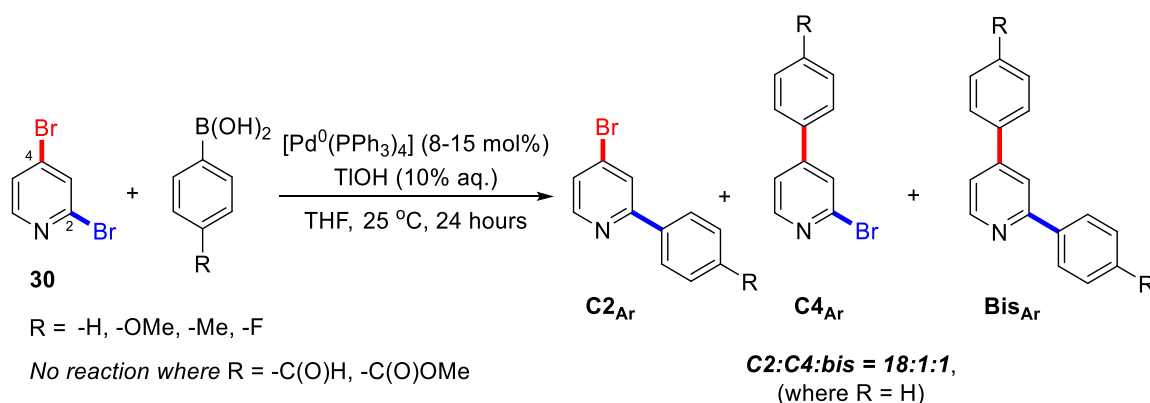
The results reported in this Chapter complement those described in Chapter 4 regarding the speciation effects on cross-coupling reactivity and site-selectivity at a model dihalogenated heteroaromatic compound. The observation that the ratio of $[\text{Pd}_3(\text{OAc})_6]$ to PPh_3 is important to catalyst speciation and hence catalyst efficacy most likely extends to other $\text{Pd}^{\text{II}}/\text{L}$ pre-catalytic systems, and potential future work to assess these effects are discussed in Chapter 5 (*Future Work*).

Chapter 4 – Exploiting Pd-catalyst Speciation for Regiocontrol in Cross-coupling Reactions at Dihalogenated Heteroaromatic Compounds

4.1. Background – Site-selectivity in Cross-coupling Reactions at 2,4-Dibromopyridine

This chapter documents the applied knowledge of the prior chapters to site-selectivity in cross-coupling reactions using 2,4-dibromopyridine **30**, a compound that has received considerable synthetic attention, with 35 published reactions at this compound reported in the literature. Very recently, structures possessing the 2,4-pyridyl substitution pattern have shown promise as drug candidates, and thus have been the subject of synthetic studies involving various cross-coupling reactions.²⁹³⁻²⁹⁵ Additionally, 2,4-diarylated pyridines have shown to show promise as biocompatible, low toxicity push-pull UV fluorescence emitters for *in vivo* imaging applications.²⁰⁵

Cid *et al.*, after publication of a novel, efficient synthesis of the compound,²⁹⁶ were the first group to examine site-selective Suzuki-Miyaura cross-coupling (SMCC) reactions at 2,4-dibromopyridine **30**.¹⁹³ In a somewhat sporadic catalyst/reaction conditions screening study, it was found that using [Pd⁰(PPh₃)₄] **65** as a catalyst along with aqueous TlOH (base) at 25 °C in THF resulted in optimal C2/C4 site-selectivity (18:1). Such conditions were successfully employed in the efficient synthesis of the natural product visual pigment A2E, using a vinylboronic acid substrate.²⁹⁷ The use of **65**, along with aqueous K₂CO₃ base, in THF gave a lower C2/C4 ratio (6:1), indicating that the TlOH base used had a significant bearing on the site-selectivity under the optimised conditions identified within the study. It should be noted that the Tl⁺ cation can be toxic, even at low doses, and therefore, where possible, any application of TlX salts in chemical processes should be avoided.²⁹⁸ Additionally, using the [Pd₂(dba)₃]/PCy₃ (Pd:ligand ratio not specified by the authors) pre-catalyst system, with K₃PO₄ as a base, in toluene at 25 °C, a high C2-regioselectivity was achieved. This C2 site-selectivity, the site proximal to the electronegative N atom, is in accordance with that which would be predicted by a Handy-Zhang analysis (see Section 1.5.1) where the ¹H NMR chemical shifts of the of the parent compound (simple pyridine), $\delta_{\text{H}}(\text{C}_2\text{-H}/\text{C}_6\text{-H})$ and $\delta_{\text{H}}(\text{C}_4\text{-H})$ are 8.6 and 7.7. ppm, respectively, predicting that coupling would occur preferentially at the C2 position, followed by the C4 position.¹⁸⁹



Scheme 61 Optimised conditions reported by Cid *et al.* for the C2-selective SMCC between 2,4-dibromopyridine **30** and a variety of arylboronic acids, forming three products: C2-arylated (C2_{Ar}), C4-arylated (C4_{Ar}) and diarylated (Bis_{Ar}), with good selectivity for C2_{Ar} .

It is curious that phenylboronic acids containing electron-withdrawing *para*-substituents ($-\text{C(O)H}$, and $-\text{C(O)OMe}$) could not be cross-coupled under these conditions. In an effort to understand the observed C2-site-selectivity, a direct reaction between $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** and **30** was conducted. Analysis of the post-reaction solution by ^{31}P NMR spectroscopy indicated the presence of a major product along with two other minor products. This major product was assigned as the monomeric C2-oxidative addition product $\text{OA}_{\text{C2-Br}}$, however notably they did not gain conclusive proof that a C2-arylated product derived from the major oxidative addition product. Notwithstanding, the appearance of a major species in the ^{31}P NMR spectrum indicated that there was a site-preference for oxidative addition, thus providing a tentative explanation for the observed overall C2-site-selectivity in the SMCC reaction. A single crystal, grown from the reaction mixture was subjected to X-ray diffraction analysis, which proved that one of the minor species was the dimeric complex *trans*-(P,N)-[PdBr(μ -2-4-bromopyridyl)-C 2 , N](PPh $_3$) $_2$ $\text{OA}_{\text{C2-Br-dinuc}}$ (Figure 76).

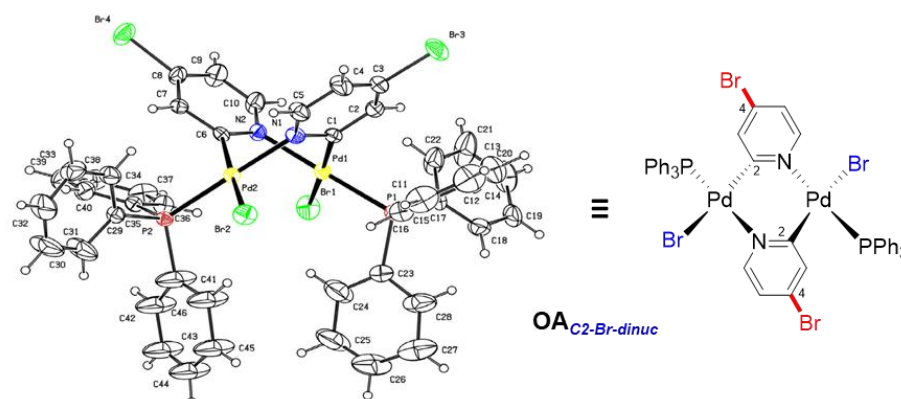


Figure 76 ORTEP representation of the crystal structure of the dimer of the C2-oxidative addition product to 2,4-dibromopyridine **30**, $\text{OA}_{\text{C2-Br-dinuc}}$. Reprinted from *Tetrahedron* 2006, **62**, 11063-11072. Copyright (2006), adapted with permission from Elsevier.

This complex is analogous to the product of oxidative addition of **65** to the mono-brominated analogue, 2-bromopyridine **55**: *trans*-[PdBr(μ_2 -pyridyl-C², N)(PPh₃)₂] **56c** reported earlier by Fairlamb, Beeby *et al.*²⁵⁷ Despite this finding, it was shown that the dimeric complex **65** was unreactive with arylboronic acids, even at elevated temperatures and thus not a direct participant in the catalytic cycle. The group hence reasoned that the monomeric species: *trans*-[PdBr(μ_2 -4-bromopyridyl-C², N)(PPh₃)₂] (**OA_{C2-Br}**) as the participant in the transmetalation reaction, resulting in the production of the C2-arylated cross-coupled product (**C2_{Ar}**). Therefore, it was indicated that oxidative addition to the C2 site of **30**, **OA_{C2-Br}**, was the size-selectivity determining step in the SMCCs under the assessed conditions. It was also posited that the formation of the dimeric species **OA_{C2-Br-dinuc}**, which was found to be stable to transmetalation, may explain the relatively low catalyst turnover numbers observed in the catalytic SMCC reactions.

There have been a few other reported examples of selective cross-coupling reactions involving 2,4-dibromopyridine **30**. Jiang *et al.* employed ‘pre-catalytic’ Pd(OAc)₂/4PPh₃ systems for C2-selective SMCCs at **30**, at elevated temperatures.^{295, 299} High C2-selectivity at **30** was realised by Zhou *et al.* in Sonogashira-type cross-couplings, using Pd(TFA)₂/2PPh₃ as their optimised catalyst system.³⁰⁰ A C4-site-selective cross-coupling reaction was reported by Rao *et al.*, where a sub-stoichiometric amount of a Bi-based organometallic substrate was cross-coupled selectively at **30**, albeit in an expectedly poor yield.³⁰¹ C4-selective Suzuki-Miyaura cross-couplings at **30** were unreported in literature until 2019, when Hardie, Willans *et al.* examined the catalytic activity of a cyclotrimeratrylene-tethered trinuclear Pd^{II}-NHC complex **73** (Figure 77).³⁰²

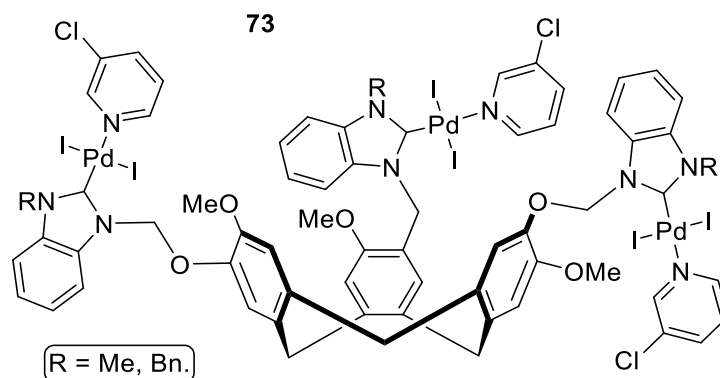


Figure 77 Showing the generic structure of the cyclotrimeratrylene-tethered trinuclear Pd^{II}-NHC complex (**73**), used as a catalyst for the first C4-selective SMCC reaction, at the substrate 2,4-dibromopyridine (**30**) as reported by Willans and Hardy.³⁰²

Here, using **73** as a pre-catalyst, good conversions and high site-selectivities at **30**, superior to that of Pd(OAc)₂/2PPh₃, were recorded, however significant formation of the bis-arylated product was observed in all examples (See Section 4.5 for further discussion of this work).

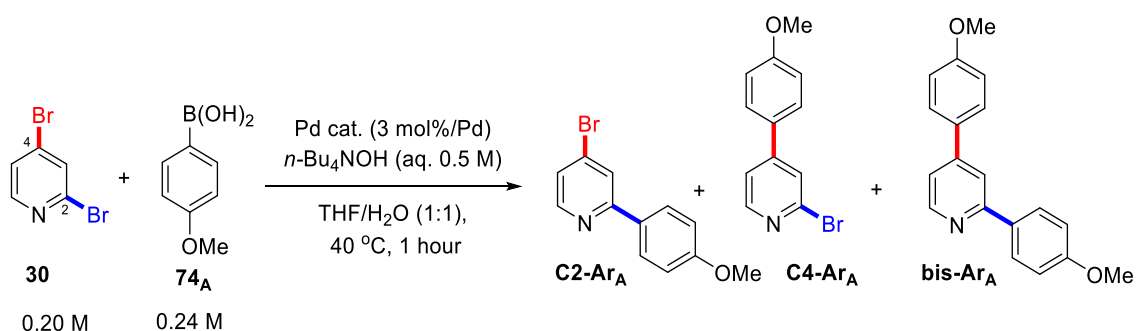
In absence of any reported examples subverting C2 site-selectivity at 2,4-dibromopyridine at the time of commencing the project, **30** was selected as a dihalogenated heteroaromatic compound (featuring two halides of the same type) with which to test catalyst speciation effects on site-selectivity.

Results & Discussion

4.2. Pd⁰-catalysts in Site-selective Suzuki-Miyaura Cross-coupling Reactions at 2,4-Dibromopyridine

4.2.1. [Pd⁰(PPh₃)₄] and [Pd⁰(dba)₃·CHCl₃]/ 1 or 2 PPh₃ Precatalysts Enable C2-selective Suzuki-Miyaura Coupling at 2,4-Dibromopyridine

This study began by reconstructing the conditions reported by Cid *et al.*¹⁹³ which selected for the C2-arylated product in site-selective SMCC reactions at 2,4-dibromopyridine **30**. **30** and *para*-anisylboronic acid **74_A** were chosen as model coupling partners and [Pd⁰(PPh₃)₄] **65** was used as the catalyst (Scheme 62). Due to the high toxicity associated with TIOH, it was decided that this compound should not be used as a base in this study.^{298, 303} Aqueous *tetra-n*-butylammonium hydroxide (*n*-Bu₄NOH aq.) was selected as a substitute for TIOH because of its high hydroxide solubility in organic solvents, and known ability to enhance transmetalation and reductive elimination steps in the SMCC catalytic cycle,^{s, 38, 304} A 1:1 mixture of THF and H₂O was employed as the reaction medium, which formed a single-phase solution under the reaction conditions.



Scheme 62 Conditions employed for the [Pd⁰(PPh₃)₄] **65**-catalysed SMCC between 2,4-dibromopyridine **30** and *para*-anisylboronic acid **74_A**.

Table 4 Results for the [Pd⁰(PPh₃)₄]-catalysed SMCC between **30** and **74_A** under conditions reported above, showing overall conversion (%), along with relative amounts of SMCC products C2-Ar_A, C4-Ar_A and bis-Ar_A. [*THF/H₂O (1:1) refluxing temperature, under the

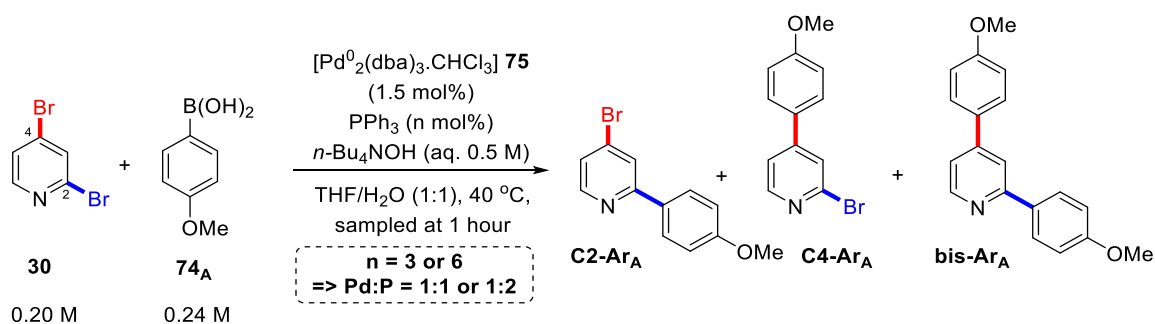
^s *n*-Bu₄NOH, can be beneficial over *e.g.* KOH, CsOH or NaOH. Due to the non-coordinating nature of the *n*-Bu₄N⁺ is does not have such an inhibitory effect on transmetalation in the SMCC reaction. This phenomenon has been observed with alkali metal counteranions See Section 1.1 for a more detailed discussion of this effect.

conditions]. Product conversions were determined by ^1H NMR analysis of crude reaction samples taken at 24 hours.

Temperature (T, °C)	Conversion (%)	C2-Ar _A (%)	C4-Ar _A (%)	bis-Ar _A (%)	C2/C4
40	35	65	27	8	2.4
68*	100	70	15	15	4.7

[Pd⁰(PPh₃)₄] **65** was thus found to be a sluggish catalyst under these conditions, indeed elevated temperatures were required for the reaction to go to completion (Table 4). Raising the temperature to reflux (68 °C) resulted in not only an increase in conversion, but also an increase in site-selectivity. In both cases, C4 and bis-arylated products are formed, however a mostly C2-selective SMCC at **30** was achievable under more forcing temperatures under like conditions. This mirrors the sluggish reactivity observed with the related pre-catalytic complex [Pd⁰(PPh₃)₃] **48** in analogous cross-coupling reactions of 2-bromopyridine **55** the mono-halogenated analogue of **30** (Section 3.2.1).

Employing another Pd⁰ precursor source, namely [Pd⁰₂(dba)₃·CHCl₃] **75** (dba = dibenzylideneacetone) along with additive nPPh₃ ligand was tested under the analogous conditions (Scheme 63). One molecule of **75** contains two atoms of Pd, and the complex is known to dissociate *in situ* in the presence of PPh₃, to the ligated mono-nuclear Pd⁰ complex [Pd⁰(η²-dba)_{3-n}(PPh₃)_n] (n = 1 or 2), where dba is known to be non-innocent.³⁰⁵⁻³⁰⁶ Therefore, a catalyst loading of 1.5 mol% of **75** was employed in the reaction to allow comparable catalyst loadings to the [Pd(PPh₃)₄]-catalysed reaction (both at 3 mol%/Pd). By varying the relative ratio of Pd:P in the pre-catalyst system, optimal activity could be assessed.



Scheme 63 Conditions employed for the [Pd₂(dba)₃·CHCl₃] **75**/nPPh₃-catalysed SMCC between **30** and **74_A**.

Table 5 Results for the $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]/\text{nPPh}_3$ -catalysed SMCC between **30 and **74_A** under conditions reported above, showing overall conversion (%), along with relative amounts of SMCC products C2-**Ar_A**, C4-**Ar_A** and bis-**Ar_A**. Conversions and relative amounts of products were determined by ^1H NMR analysis of crude samples of the reaction, taken 1 hour after the reaction start.**

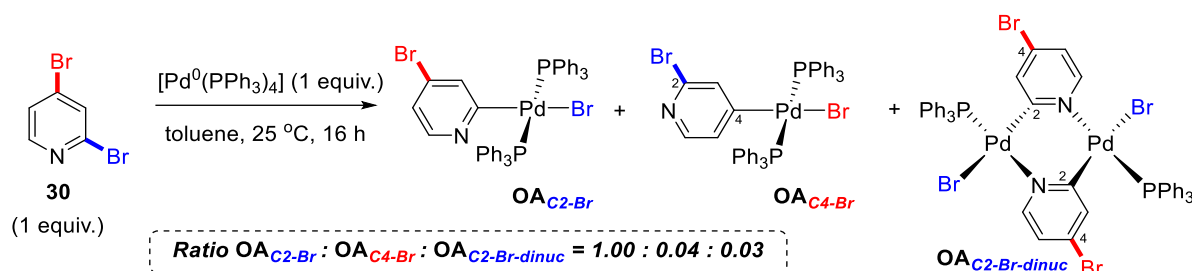
Pd:P	Conversion (%)	C2-Ar_A (%)	C4-Ar_A (%)	bis-Ar_A (%)	C2/C4
1:1	100	65	9	26	2.4
1:2	76	59	11	4	4.7

The results for the $[\text{Pd}^0_2(\text{dba})_3 \cdot \text{CHCl}_3]/\text{nPPh}_3$ -catalysed SMCC reaction (Table 5) show that, under both pre-catalytic catalyst-phosphine loadings reported, at 40 °C, this system is far more active than that $[\text{Pd}^0(\text{PPh}_3)_4]$, under equivalent conditions. The pre-catalytic ratio where Pd:P = 1:1 notably exhibits higher activity and C2/C4-selectivity than the Pd:P = 1:2 example. However, it was noted that in the more active system (Pd:P = 1:1), significant conversion to undesired diarylated **bis-Ar_A** product was observed.

Notwithstanding the potential for participation of dba as a non-innocent ligand when employing **75** as a catalyst system,³⁰⁷⁻³⁰⁸ the presence of additional phosphine clearly has a detrimental effect on catalytic activity in this reaction. The two *in situ* generated $[\text{Pd}^0(\eta^2\text{-dba})_{3-n}(\text{PPh}_3)_n]$ ($n = 1$ or 2) and $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** catalyst systems all demonstrated C2-selectivity in SMCC reactions at 2,4-dibromopyridine **30**, in line with the findings of Cid *et al.* using **65** under their reported conditions.¹⁹³

4.2.2. Further Work on Site-selectivity of the Oxidative Addition Reaction of $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** to 2,4-Dibromopyridine

Stoichiometric studies were subsequently carried out in order to gain further information on why ' $\text{Pd}^0(\text{L})_n$ ' catalyst systems exhibit C2-selectivity in SMCC reactions at 2,4-dibromopyridine **30**. $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** (1 equivalent) was treated with 2,4-dibromopyridine **30** (1 equivalent) at room temperature, in toluene with stirring overnight, according to the experimental method previously reported by Cid *et al.* (Scheme 64).¹⁹³



Scheme 64 Conditions used for the oxidative addition reaction between $[Pd^0(PPh_3)_4]$ and **30**.

After removing the toluene solvent *in vacuo* and washing the residue with diethyl ether, ^{31}P spectroscopic analysis of a CD_2Cl_2 solution of the crude reaction product (a. Figure 78) confirmed the site-selectivity of the oxidative addition, with singlet peaks at δ_P 22.8, 24.3 and 27.6 ppm respectively representing OA_{C2-Br} , OA_{C4-Br} and $OA_{C2-Br-dinuc}$ in a respective ratio of 1.00 : 0.04 : 0.03 (verified against data reported by Cid *et al.*).¹⁹³ Therefore, according to ^{31}P NMR spectroscopy the C2/C4-selectivity for the oxidative addition is approximately 25:1, accounting for the overall C2-selectivity observed in the SMCC reactions involving $[Pd^0(PPh_3)_4]$ **65** (Scheme 62).

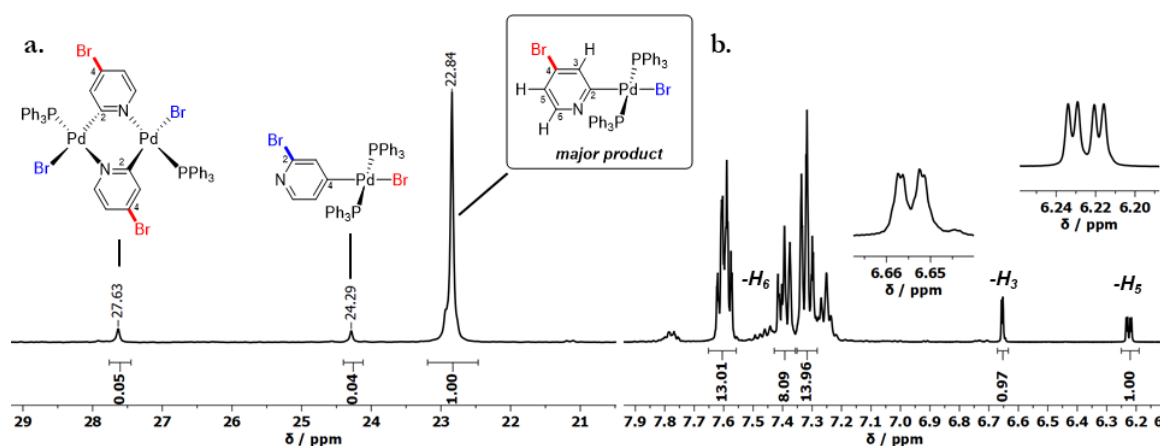


Figure 78 (a.) ^{31}P NMR spectrum (162 MHz, 256 scans, CD_2Cl_2), showing the distribution of the products of oxidative addition of $[Pd^0(PPh_3)_4]$ **65** to **30**. (b.) 1H NMR spectrum of the same sample (400 MHz, 64 scans, CD_2Cl_2), showing OA_{C2-Br} as the major species, H_3 and H_5 protons on the 4-bromopyridyl ligand have been assigned.

Green-yellow crystals were grown by carefully layering the CD_2Cl_2 solution of the crude reaction product with pentane and cooling to -18 °C under an atmosphere of argon. X-ray diffraction analysis of a single crystal proved the structure to be that of OA_{C2-Br} : the C2 monomeric oxidative addition product, a *trans*-complex which is a novel crystal structure. The ^{31}P NMR singlet at δ_P 22.84 ppm was thus identified as the phosphorus resonance of OA_{C2-Br} (Figure 78).

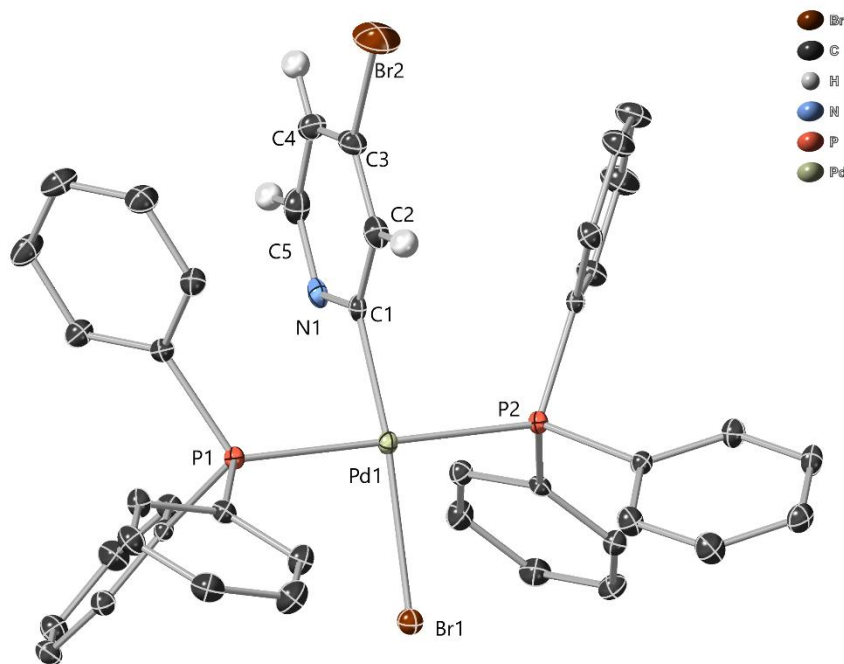
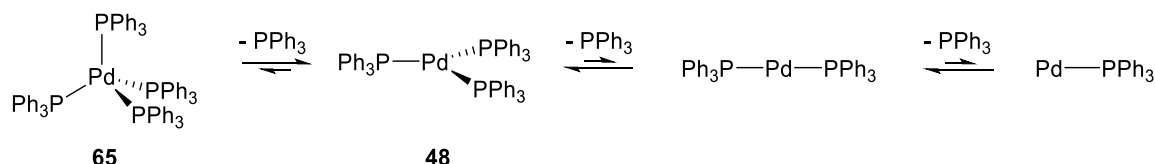


Figure 79 Structure, obtained by X-ray diffraction, of a single crystal of **OA_{C2-Br}**, obtained from the direct stoichiometric reaction between **[Pd⁰(PPh₃)₄]** **65** and **30**. Ellipsoids have been set at 50 % probability. H-atoms of PPh₃ ligands and three molecules of dichloromethane have been omitted for clarity. Selected interatomic distances /Å: P1–Pd1 = 2.3330(9), C1–Pd1 = 1.987(6), Br1–Pd1 = 2.5193(7). Selected interatomic angles /°: C1–Pd1–Br = 166.36(18), P1–Pd1–P2 = 177.28(5), P1–Pd1–Br1 = 90.94(2), C1A–Pd1–P1 = 89.17(3).

The crystal structure is approximately square planar; however, the bromide ion sits slightly outside this plane (C1–Pd1–Br = 166.36(18)° *vs.* the P1–Pd1–P2: 177.28(5)°). The Pd–P bond distance of **OA_{C2-Br}** (2.3330 Å) is in line with that of the other Pd^{II}–PPh₃ containing complexes in this work: *trans*-[Pd(OAc)₂(PPh₃)₂] **47** and *trans*-[(4-F-Ph)Pd(I)(PPh₃)₂] **51** (Pd–P = 2.3414 and 2.3176 Å, respectively). The Pd–Br bond, is close in length to that found in the *trans*-[(Ph)Pd(Br)(PPh₃)₂] complex (Pd–Br = 2.532(1) Å) reported by Grushin *et al.*²⁴²

¹H NMR analysis of a CD₂Cl₂ solution of the crude reaction product, showed significantly shielded aromatic resonances, at δ_H 6.65 and 6.23 ppm (b. Figure 78), which were assigned as –H₃ and –H₅ protons on the 4-bromopyridyl ligand of **OA_{C2-Br}** on the basis of their coupling constants. The upfield-shifting of these resonances is likely a result of shielding interactions from ring currents of proximal phenyl moieties. Such an interaction is supported by the crystal structure, which indicates an interfacial π-stacking interaction – the 4-bromopyridyl ligand is sandwiched between two phenyl groups from the two PPh₃ ligands, providing further evidence that the crystal obtained is the major species as observed in the ¹H NMR spectrum. In light of the findings in Chapter 2 (see Section 2.5.3.2.1) that the oxidative addition product to 2-bromopyridine **55** slowly dimerises, similarly, over time **OA_{C2-Br}** is predicted be able undergo the same transformation.

It is known, based on kinetic examination of the rate of oxidative addition of $[\text{Pd}^0(\text{PPh}_3)_4]$ to aryl halides in solution, that $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** is mostly dissociated to $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** and free PPh_3 ,³⁰⁹ which, in turn, is in equilibrium with the bis-ligated complex $[\text{Pd}^0(\text{PPh}_3)_2]$.⁶⁴ It is known the low-coordinate species $[\text{Pd}^0(\text{PPh}_3)_2]$ or $[\text{Pd}^0(\text{PPh}_3)]$ are the active species in oxidative addition reactions involving **65**. In cross-coupling reactions, **65** essentially acts as a pre-catalyst for a lower-ligated active species. The reactivity of $[\text{Pd}^0(\text{PPh}_3)_4]$ is hence governed by the three equilibria which release **48**, $[\text{Pd}^0(\text{PPh}_3)_2]$ and $[\text{Pd}^0(\text{PPh}_3)_1]$ into solution (Scheme 65).



Scheme 65 The equilibria that govern the speciation of $[\text{Pd}^0(\text{PPh}_3)_4]$ (**65**) in solution. Equilibrium Pd–P coordination environments are given.

The dynamic exchange processes of a solution of $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** were examined by variable temperature ^{31}P NMR spectroscopic analysis. As evident in the ^{31}P NMR spectrum of $[\text{Pd}^0(\text{PPh}_3)_4]$, which shows a broad singlet at δ_{P} 16.4 ppm ($\Delta\nu_{1/2} = 178.8$ Hz) in $\text{THF}-d_8$ at 298 K, this exchange is faster than can be resolved on the NMR timescale at this temperature. Hence, by slowing down the rate of exchange, by incremental cooling of the $\text{THF}-d_8$ solution of $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** (Figure 80), it was assessed whether this exchange between $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** and PPh_3 could be resolved using ^{31}P NMR at 202.5 MHz.

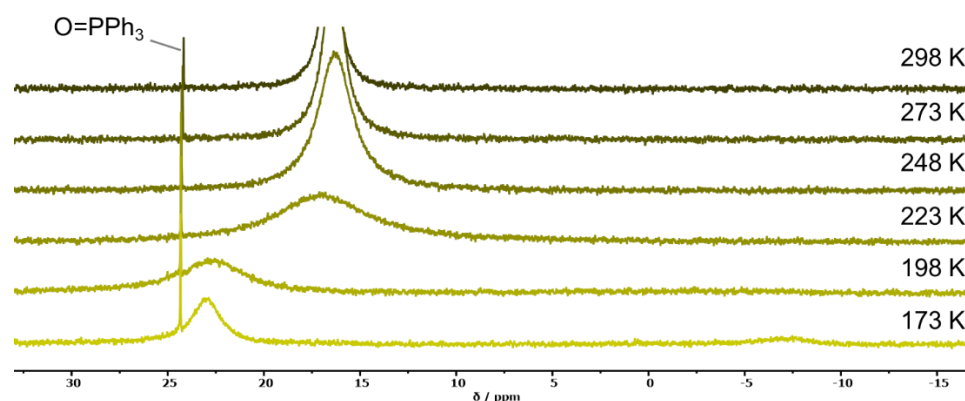


Figure 80 A stack of ^{31}P NMR spectra (202.5 MHz, 256 Scans), showing the effects of incremental cooling of a solution of $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** in $\text{THF}-d_8$ from 298–173 K.

As the THF-*d*₈ solution of [Pd⁰(PPh₃)₄] was incrementally cooled, the rate of chemical exchange was resultantly slowed. The peak representing Pd⁰-ligated PPh₃ was seen to broaden significantly, from $\Delta\nu_{1/2}$ 182 to 1241 Hz over the 75 K temperature range (Figure 80). By 173 K, the spectrum was seen to exhibit two broad peaks, still in intermediate exchange, however the resonance representing the Pd⁰–P exchange had sharpened considerably to $\Delta\nu_{1/2}$ 341 and another broad peak had appeared. The two chemical shifts were in line with that of free PPh₃ (δ_P –7.5 ppm) and a lower ligated Pd⁰-PPh₃ complex [Pd⁰(PPh₃)₃] (δ_P 23.0 ppm). Thus, it can be seen that the slowing of exchange between [Pd⁰(PPh₃)₃] and PPh₃ has been observed by ³¹P NMR at 173 K, allowing resolution of the respective peaks. Further cooling of the solution was not possible due to the temperature becoming close to that of the freezing point of THF. As a result of the limited solubility of [Pd⁰(PPh₃)₄] **65** in THF-*d*₈ it is certain that the concentration of **65** is not constant throughout the cooling process, therefore a reduction of signal/noise may be partially due to a reduction of solution concentration of the Pd complex upon its precipitation.

Maes *et al.* have investigated the mechanism of oxidative addition of [Pd⁰(PPh₃)₄] **65** to the C2-Br-site of 2-bromopyridine **55**.³¹⁰ It was found that the rate of [Pd⁰(PPh₃)₂] (derived from **65**) oxidative addition to **55** ($k_{obs} = 3.3 \times 10^{-3} \text{ s}^{-1}$) was ~1000 times faster than the same addition to bromobenzene ($k_{obs} = 3.0 \times 10^{-6} \text{ s}^{-1}$) in DMF. The C2–Br bond of 2-bromopyridine **55** is thus easier to activate than the C–Br bond of bromobenzene, as is predictable from bond dissociation energy arguments.¹⁹⁵ Furthermore, by comparing rates of oxidative addition of [Pd⁰(PPh₃)₂] to C5-substituted 2-chloro-, 2-bromo- and 2-iodopyridine, and comparison of resulting linear Hammett plots, further information about the activation of these pyridines was gained. Rates were significantly increased when employing electron-withdrawing substituents at 2-bromopyridines ($\rho = 4.12$) and 2-chloropyridines ($\rho = 3.88$) whereas with 2-iodopyridine ($\rho = 2.84$) only moderately so. This data, along with supporting computational analysis, indicated that 2-bromopyridine and 2-chloropyridine involve an S_NAr-type mechanism where charge (which is stabilised by electron withdrawing substituents) is built up in the transition state, whereas 2-iodopyridine, along with bromo- and iodobenzene proceed *via* a concerted mechanism (Figure 81).³¹¹⁻

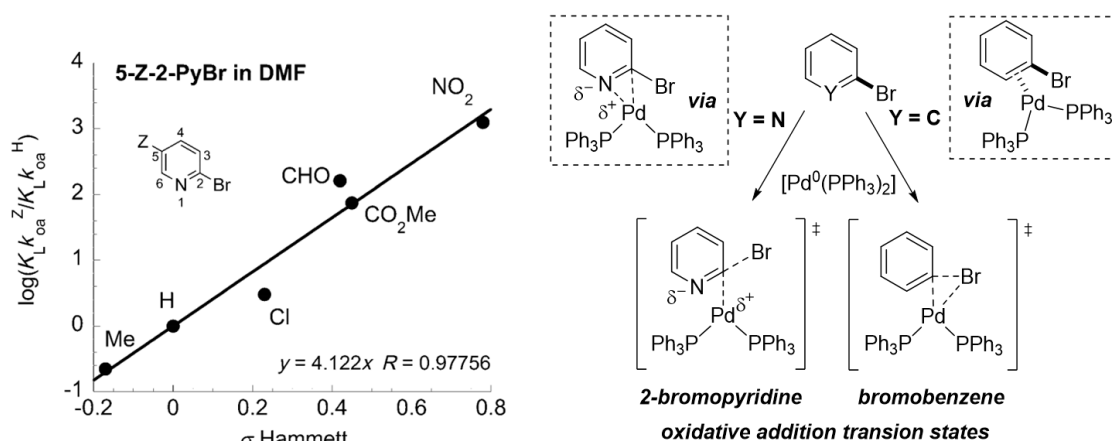


Figure 81 Showing (a.) A linear Hammett plot for the oxidative addition reaction of $[\text{Pd}^0(\text{PPh}_3)_2]$ to C5-substituted 2-bromopyridines, indicating build-up of negative charge in the transition state of the rate-determining step. (b.) Calculated (by DFT[e 6-31+G(d) basis set, hybrid exchange correlation functional: PBE0]) transition state mechanisms for $[\text{Pd}^0(\text{PPh}_3)_2]$ oxidative addition into C–Br sites of 2-bromopyridine, by an $\text{S}_{\text{N}}\text{Ar}$ -type mechanism (left pathway), and bromobenzene, by a classical concerted mechanism (right pathway). Adapted from *Chem. Eur. J.* 2015, 21, 7858-7865. Copyright 2015 Wiley-VCH Verlag GmbH & Co.

This data indicates that unconventional $\text{S}_{\text{N}}\text{Ar}$ -type oxidative addition occurs at 2-bromopyridine **55**. It is most likely, due to structural similarities between 2-bromopyridine and 2,4-dibromopyridine that $[\text{Pd}^0(\text{PPh}_3)_2]$ oxidative addition to the C2–Br position at 2,4-dibromopyridine (Scheme 64) occurs by this mechanism.

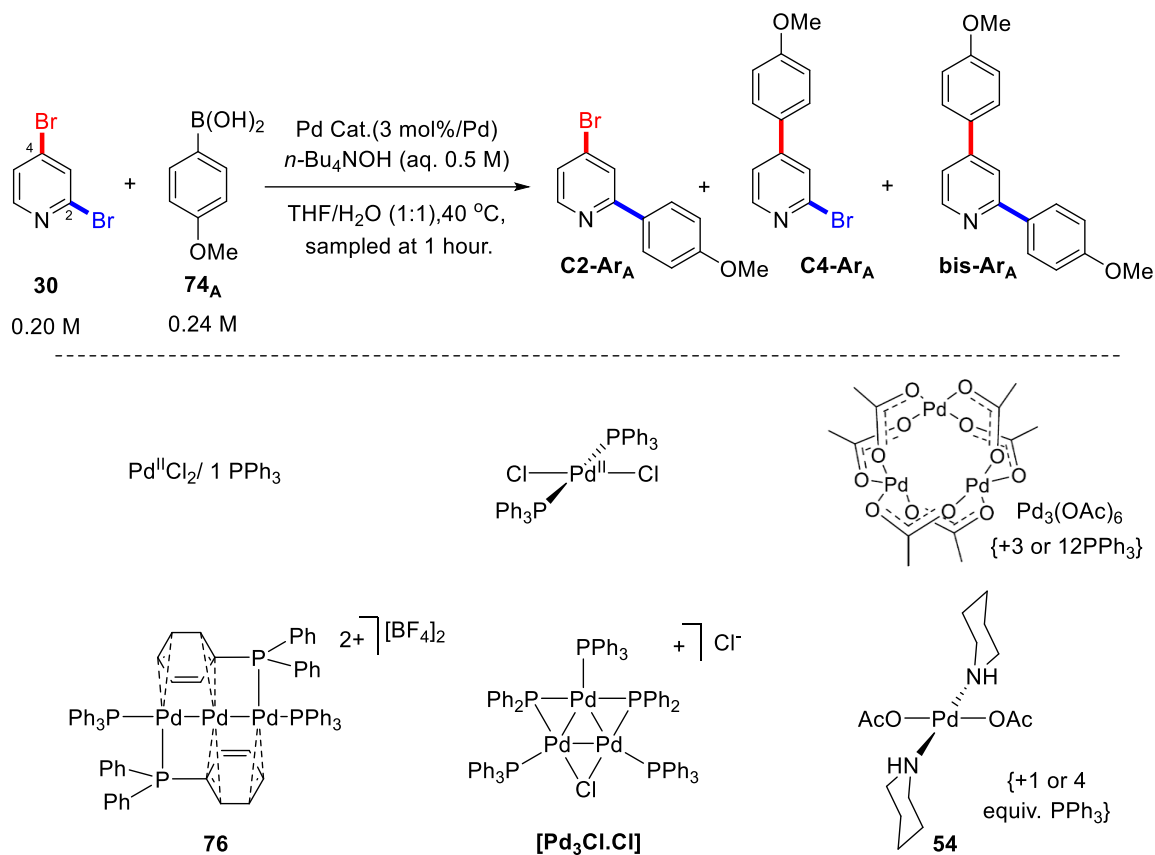
4.3. Switching Site-control in Suzuki-Miyaura Cross-coupling Reactions at the Substrate 2,4-Dibromopyridine

4.3.1. C4-site-selectivity at 2,4-Dibromopyridine: Screening of Pd_3 Cluster and Pd^{II} Salt-based Pre-catalysts

The previous section showed that the Pd^0 -based pre-catalysts $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]/\text{nPPh}_3$ and $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** demonstrated *normal* C2-site-selectivity under the reported SMCC conditions at 2,4-dibromopyridine **30**. Upon testing a range of higher oxidation state pre-catalyst systems under the same conditions however, unexpected selectivity for the *abnormal* C4–Br site in SMCC reactions at **30** was registered (Scheme 66, Table 6)

Henceforth ‘*standard conditions*’, as outlined in Scheme 66, employ THF/ H_2O as the solvent system, stirred at 40°C , with $n\text{-Bu}_4\text{NOH}$ (aq.) as the base, which forms a homogeneous solution. Comparative catalyst loadings were based on molar Pd loadings and were fixed at 3 mol%. Catalysts examined were

PdCl_2 with 1 additive equivalent of PPh_3 ($\text{PdCl}_2/1\text{PPh}_3$), *trans*- $[\text{PdCl}_2(\text{PPh}_3)_2]$, *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ **54** alone, or with 1 or 4 equivalents of PPh_3 , $[\text{Pd}_3(\text{OAc})_6]$ alone, or with 3 equivalents of PPh_3 ($\text{Pd}:\text{P} = 1:1$). Two different Pd_3 cluster complexes were additionally examined as pre-catalysts in this reaction: triangular $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{Cl}^-$ (**$\text{Pd}_3\text{Cl}\cdot\text{Cl}$**) (see Sections 1.4, 2.5.1 & 3.2.2)^{167-168, 172} and linear $[\text{Pd}_3(\text{PPh}_3)_4][\text{BF}_4]_2$ **76** (Section 1.4).¹⁷⁴⁻¹⁷⁵

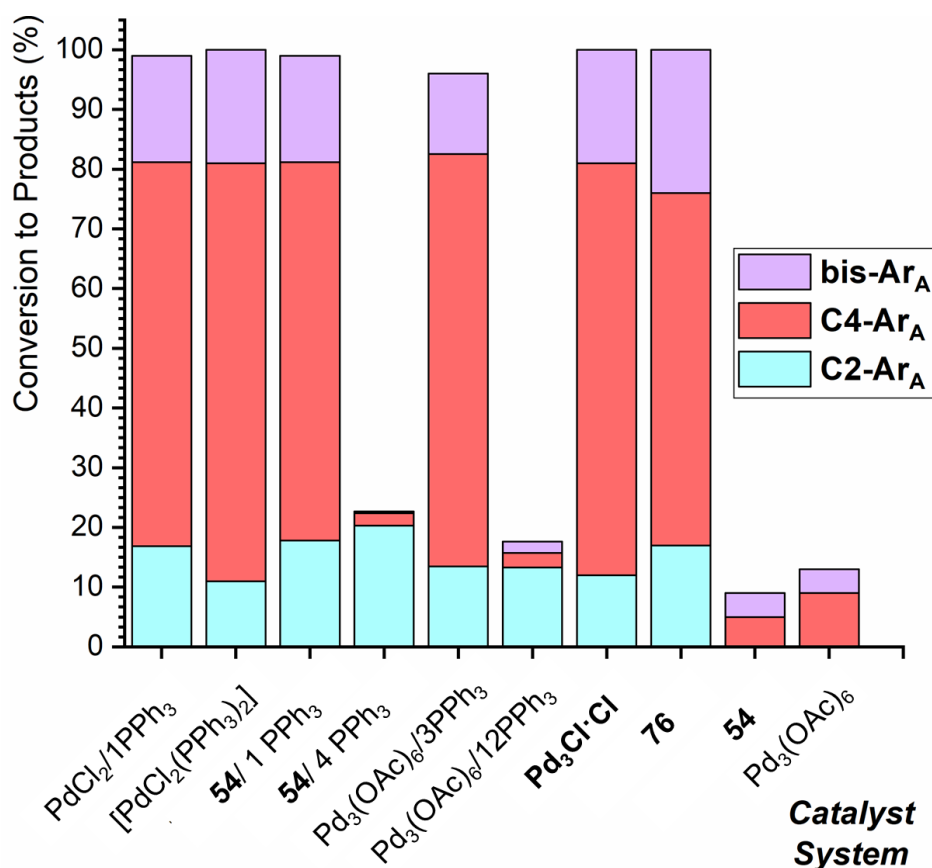


Scheme 66 Conditions employed, and structures of pre-catalysts used in the catalyst screening in the SMCC reaction between 2,4-dibromopyridine (**30**) and *para*-anisylboronic acid (**74_A**).

The results for the above catalytic experiments are displayed in Table 6 as well as being collated in a stacked bar chart, to show the distribution of converted products of **30**: C2-**Ar_A**, C4-**Ar_A** and bis-**Ar_A** (Graph 6).

Table 6 Showing the performance of the above Pd catalysts in the model SMCC reaction between 30 and 74_A. Conversions and relative amounts of products were determined by ¹H NMR analysis of a crude sample of the reaction, taken 1 hour after the reaction initiation.

Entry	Pre-catalyst	Conversion (%)	C2-Ar _A (%)	C4-Ar _A (%)	bis-Ar _A (%)	Pd:PPh ₃ Ratio	C4/C2
1	PdCl ₂ /1PPh ₃	99	17	64	18	1:1	3.76
2	[PdCl ₂ (PPh ₃) ₂]	100	11	70	19	1:2	6.36
3	54/1PPh ₃	99	18	64	17	1:1	3.58
4	54/4PPh ₃	29	70	7.2	0.8	1:4	0.10
5	[Pd ₃ (OAc) ₆]/3 PPh ₃	96	13	70	13	1:1	5.52
6	[Pd ₃ (OAc) ₆]/6 PPh ₃	100	13	65	23	1:2	5.00
7	Pd ₃ Cl ₂ ·Cl	100	12	69	19	1:1	5.65
8	76	100	17	59	25	1:1.33	3.54
9	Pd ₃ (OAc) ₆	12	0	9	4	N/A	N/A
10	54	9	0	5	4	N/A	N/A



Graph 6 Stacked bar chart showing overall conversions and product distributions in the SMCC reaction of **30** with *para*-anisylboronic acid **74_A**.

In the cases (Table 6 & Graph 6) where SMCC reactions were carried out using [Pd₃(OAc)₆] or **54** without PPh₃ (entries 9 & 10, Table 6) conversions were found to be very low. This is most likely because, under the conditions, the catalyst [Pd₃(OAc)₆], or its piperidyl-ligated derivative *trans*-[Pd(OAc)₂(*N*-piperidyl)₂] **54**, cannot reduce and activate efficiently to produce a sufficiently active cross-coupling catalyst (Section 1.2.2). In some cases, usually where high temperatures are employed, such Pd catalysts are able to be activated by the reaction solvent and proceed *via* phosphine 'ligand-free' catalysis.^{7, 66, 102, 105, 185, 313} When the reaction temperature was raised to reflux however, such catalysts in absence of PPh₃ additive did not enable significantly higher conversions; for example, [Pd₃(OAc)₆] alone resulted in <20% conversion to products at 68 °C. If, however, the same catalysts were employed alongside 1 equivalent (or greater) of PPh₃ (entries 3 - 6), a remarkable increase in catalyst efficacy was observed, with near complete conversion of **30** observed within 1 hour at 40 °C in each case.

Most notably, in these cases (entries 1-8, Table 6 & Graph 6), *abnormal* C4-site-selectivity at **30** was observed. In the case of the reactions carried out with one or greater equivalent of added PPh₃, the PPh₃ has potential to act as a reductant, with concomitant formation of oxidised PPh₃ (1 equivalent per Pd), leading to catalyst activation (see 1.2.2 & Chapter 2).^{46, 48, 52} Taken together, these results

demonstrate that the additive PPh_3 vastly enhances the catalytic efficacy of the $\text{Pd}(\text{OAc})_2$ -containing pre-catalysts $[\text{Pd}_3(\text{OAc})_6]$ and **54**.

Pd-cluster pre-catalysts, **$\text{Pd}_3\text{Cl}\cdot\text{Cl}$** and **76** (entries 7 & 8, Table 6), both gave good conversions and overall C4-selective reaction outcomes at **30**. Initially, in this study, it was postulated that such cluster pre-catalysts were privileged in enabling the observed C4-site-selectivity, however it later became clear that other, more simple, Pd^{II} precatalysts using additive PPh_3 , also enabled somewhat enhanced C4-selectivity compared with the Pd_3 cluster pre-catalysts examined (*vide supra*).

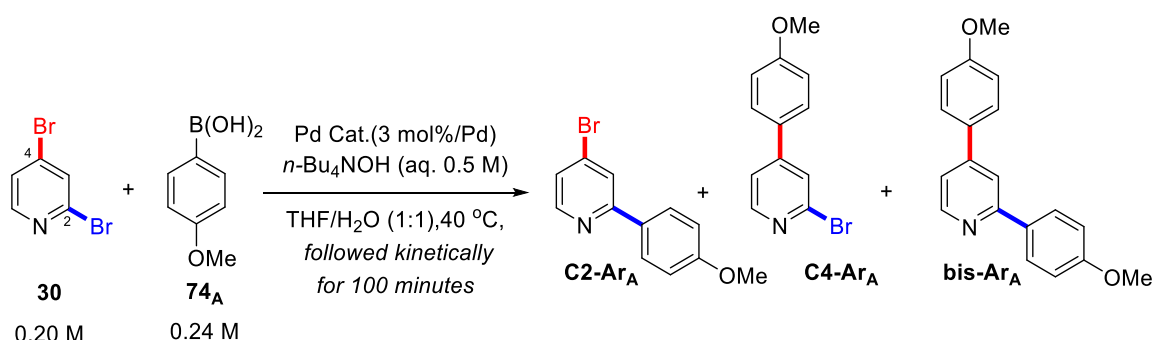
Each catalyst examined in this series which featured a pre-catalytic formal oxidation state >0 , and featuring less than two phosphine ligands *per* $\text{Pd}(\text{OAc})_2$ displayed high activity and overall C4-site-selectivity towards **30**. It is also of significance that the highest recorded site-selectivity under these conditions was with the simple $[\text{Pd}_3(\text{OAc})_6]/3 \text{ PPh}_3$ catalyst system (where $\text{Pd}:\text{P} = 1:1$): the cheapest and most easily accessed of the Pd- PPh_3 -containing catalysts tested. On the other hand, when $[\text{Pd}_3(\text{OAc})_6]/12 \text{ PPh}_3$ was examined as a pre-catalyst under the same conditions, ‘normal’ C2-selectivity, and a significant reduction in conversion of **30** to products was observed with $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$. The observation of this dichotomy of site-selectivity under different $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ ratio regimes, which is further examined and discussed in Section 4.4, was crucial to the decision to probe the behaviour of solutions of $[\text{Pd}_3(\text{OAc})_6]/n \text{ PPh}_3$ closely (Chapter 2).

The - catalyst system generated *in situ* from $\text{PdCl}_2/1 \text{ PPh}_3$ ($\text{Pd}:\text{P} = 1:1$) gave lower C4/C2 site-selectivity at **30** than pre-synthesised *trans*- $[\text{PdCl}_2(\text{PPh}_3)_2]$, which indicates a practical role for the extra catalytic equivalent of phosphine in this case (entries 1 & 2). This observation stands in contrast with $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ ($\text{Pd}:\text{P} = 1:1$), where both conversion and site-selectivity were enhanced using a lower quantity of PPh_3 per Pd (≥ 1 per Pd, See Section 4.4 for further details). The role of the extra equivalent of PPh_3 is likely for the stabilisation of the activated catalytic species, preventing its degradation under the reaction conditions, however a detailed investigation of the catalytic speciation of the $\text{PdCl}_2/1\text{PPh}_3$ *vs.* that of *trans*- $[\text{PdCl}_2(\text{PPh}_3)_2]$ would be required to fully delineate the reasons for the catalytic difference observed (See Future Work – Section 5.2.1)

Several entries in Table 6 constitute rare examples of selective C4-activation of **30** (unprecedented at the time of the initial discovery). Later in the study it became clear that, in addition to the pre-catalytic identity, another aspect of the SMCC conditions, the nature of the *n*- Bu_4NOH (aq) base, proved to be a key factor in the observed site-selectivity. The subsequent sections of this chapter disclose the results of investigations into the factors that can lead to the reversal of conventional site-selectivity of **30**.

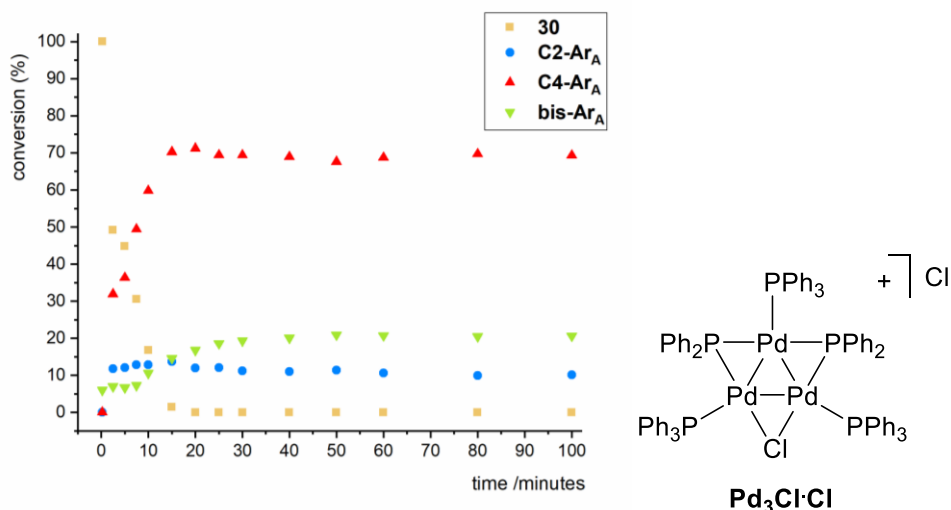
4.3.2. Product Evolution Analysis of C4-selective Cross-coupling Catalysis

In order to understand the change in site-selectivity as a function of time, a kinetic product evolution assay was designed, examining a selected range of precatalysts which had displayed C4-selectivity in SMCC reactions at 2,4-dibromopyridine **30** (*vide supra*). The C4-selective pre-catalysts: $\text{Pd}_3\text{Cl}\cdot\text{Cl}$, $[\text{Pd}_3(\text{PPh}_3)_4][\text{BF}_4]_2$ **76**, *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ **54** / 1 PPh_3 and $[\text{Pd}_3(\text{OAc})_6]/3 \text{ PPh}_3$ were examined in the coupling of **30** with *para*-anisylboronic acid **74_A** under *standard conditions* (Scheme 67 & Graphs 7-10, respectively). To this end, an *ex situ* NMR-based kinetic product evolution assay was developed to show how the rate and the site-selectivity of the SMCC reaction varied over time.

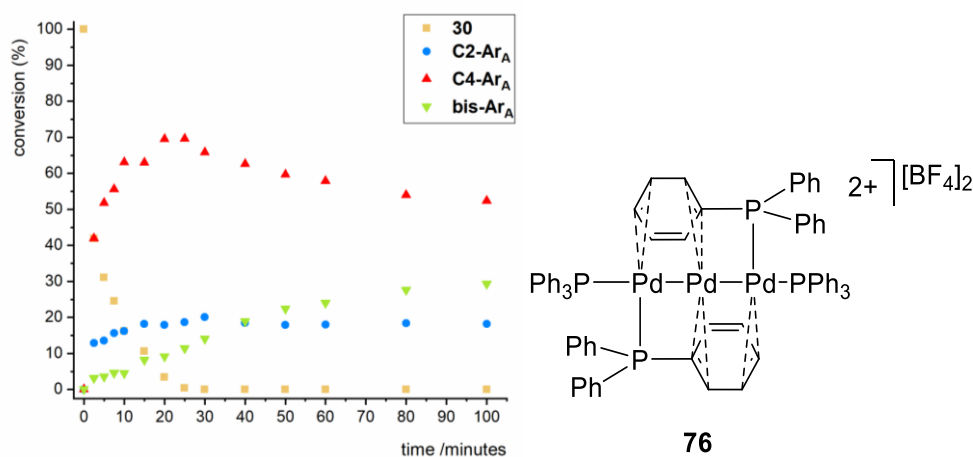


Scheme 67 Conditions employed in kinetic assays of the SMCC between **30** and *para*-anisylboronic acid **74_A**. Structures of precatalysts used are shown in Graphs 7-10 below.

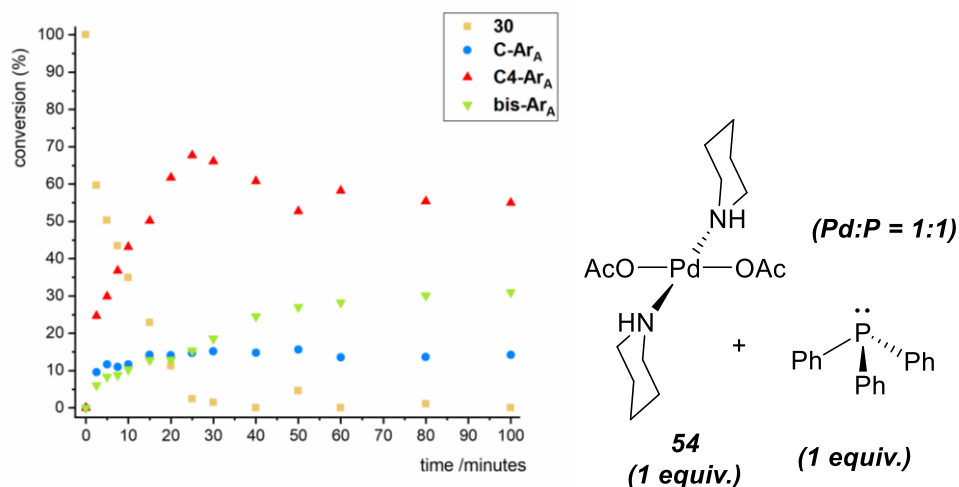
The reaction temperature was internally measured *via* a thermocouple throughout each process, with controlled magnetic stirring at 40 °C (± 0.5 °C). In all cases, however, a spike in temperature of 2-3 °C was recorded upon addition of the *n*-Bu₄NOH (aq) base solution, which had been validated to initiate the reaction. This measured exotherm is most likely a result of the combined effects of THF/H₂O mixing, arylboronic acid/hydroxide reaction (Lewis acid/base reaction) and is expected to account for the increased conversion recorded in the early stages of the reaction. The assay involved taking samples at 0, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 40, 50, 60, 80 and 100 minutes after reaction initiation by adding *n*-Bu₄NOH (aq) base solution. Each sample, after extraction from the reaction solution, was quickly quenched by dilution in CH₂Cl₂ and worked up, producing crude products which were examined by ¹H NMR spectroscopic analysis. Product evolution curves were hence produced which showed changes to the distribution of 2,4-dibromopyridine **30** starting material, and the three pyridine-containing products: C2-Ar_A, C4-Ar_A and bis-Ar_A with time (Graph 7-Graph 10).



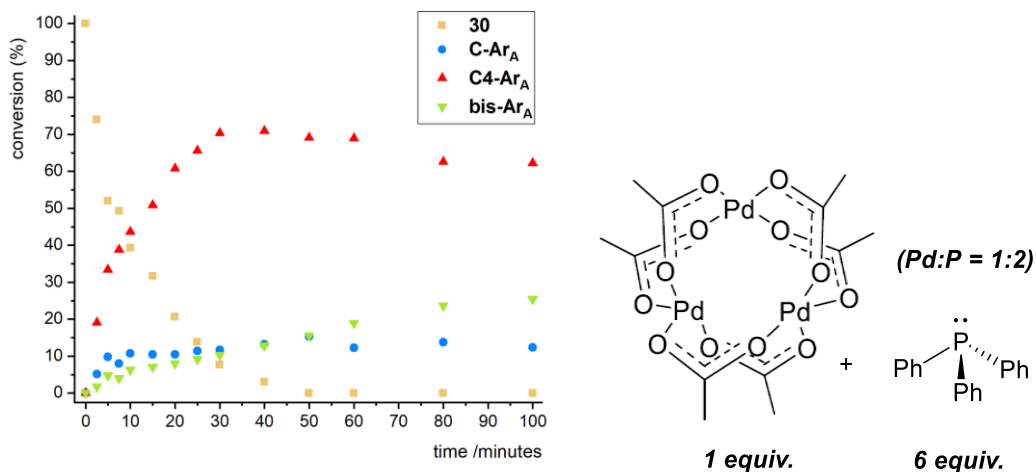
Graph 7 A plot of conversion of **30** to products against time in the SMCC reaction between **30** (S.M.) and **74_A**, catalysed by $\text{Pd}_3\text{Cl}\cdot\text{Cl}$



Graph 8 A plot of conversion of **30** to products against time in the SMCC reaction between **30** (S.M.) and **74_A**, catalysed by **76**.



Graph 9 A plot of conversion of **30** to products against time in the SMCC reaction between **30** (S.M.) and **74_A**, catalysed by **54**/1 PPh_3 ($\text{Pd:P} = 1:1$).



Graph 10 A plot of conversion of **30** to products against time in the SMCC reaction between **30** (S.M.) and **74_A**, catalysed by [Pd₃(OAc)₆] / 6PPh₃ (Pd:P = 1:2)

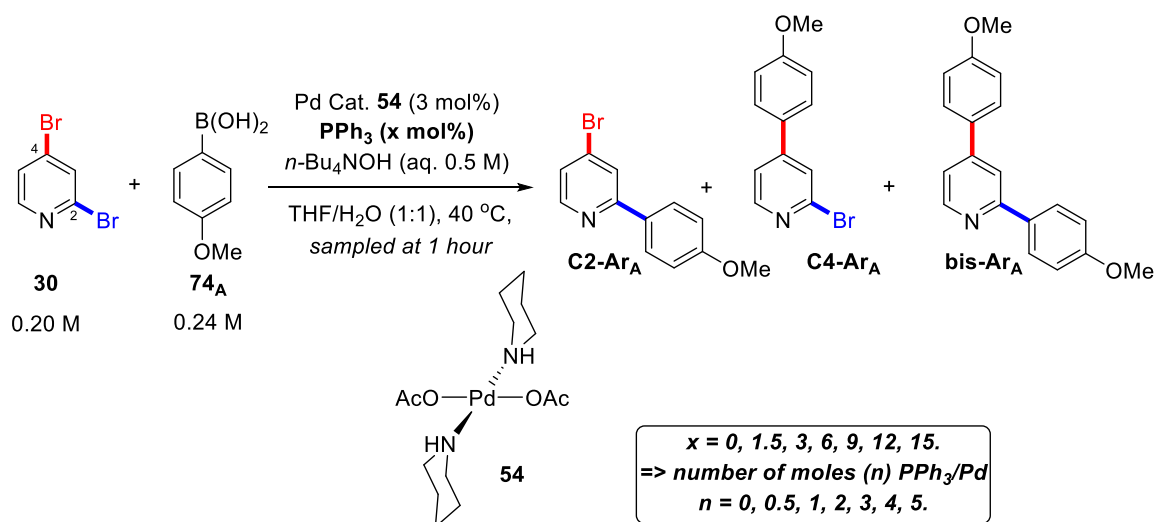
Under these conditions, with each kinetic assay, the **C4-Ar_A** product was the major product from the start and throughout the reaction. At the point at which the starting material **30** was consumed, the amount of the C4-arylated product slowly depreciated over time resulting from the excess **74_A** (0.2 equivalents) which enabled cross-coupling at the second C2–Br site, forming the di-arylated product **bis-Ar_A**. The curve conclusively shows that the diarylated product, **bis-Ar_A**, forms from a second coupling at the C2 site of the **C4-Ar_A** product. This is notable since the catalyst system selects for the C4-position. This would indicate that under the conditions arylation at the C4 position activates the C2 position more than arylation of the C2 position activates the C4 position. The slow conversion of **C4-Ar_A** to **bis-Ar_A** is reflective of the lower ability of the catalyst to cross-couple at the C2–Br site of **30**. These catalytic assays also indicated that under the conditions, from a synthetic utility standpoint, where the maximum quantity of the *abnormal* **C4-Ar_A** product and minimal formation **C2-Ar_A** and **bis-Ar_A** would be desired, the best time at which to stop the reaction was between 20 and 30 minutes after initiation. Therefore, quenching the reaction at this point would allow for the production of a maximum quantity of the *abnormal* C4-arylated product, whilst minimising the formation of the undesired by-products.

The Pd catalyst loading was fixed in each of these kinetic assays. Broadly, there is similar pattern of reactivity between these four examples. It could be posited, that despite the differing pre-catalyst sources, convergence to a similar active catalytic species could have been occurring. Such an observation has been made previously by Reay and Fairlamb *et al.* when closely investigating the kinetics of C–H bond activation from significantly divergent homogeneous and heterogeneous catalyst sources.³¹⁴ One technique that could be utilised in future work to explore this hypothesis is EXAFS. Using *in operando* EXAFS analysis, similarities between the X-ray absorption signature of Pd species present could be assessed under working catalytic conditions and would point towards whether

structurally similar active species are operating under the conditions (See Chapter 5 – *Future Work* section for discussion of ways that the active catalytic species could be further probed under the reported reaction conditions).

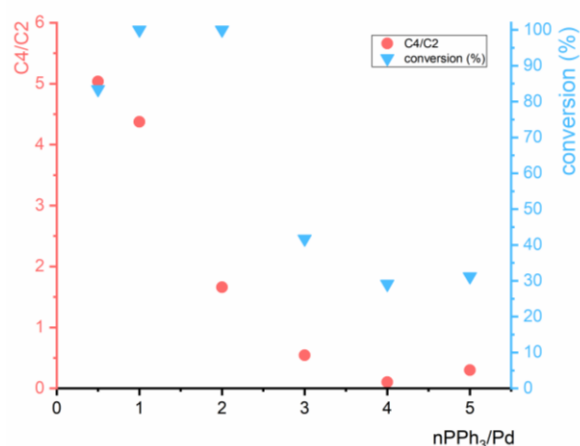
4.4. Effects of Pd/PPh₃ Pre-catalytic Ratios on Catalytic Site-selectivity and Catalyst Efficacy

Intrigued by the stark differences in site-selectivity and conversion of 2,4-dibromopyridine (**30**) in reactions where Pd(OAc)₂ complexes were employed alongside different equivalents of PPh₃ as catalysts systems (Table 6 & Graph 6), it was decided to closely investigate the effect of Pd(OAc)₂/nPPh₃ pre-catalytic ratios arising from **54** and [Pd₃(OAc)₆] as Pd(OAc)₂ sources. At the first instance **54** was used as a pre-catalyst, alongside varying equivalences of PPh₃ under conditions derived from the SMCC *standard conditions* (Scheme 68).

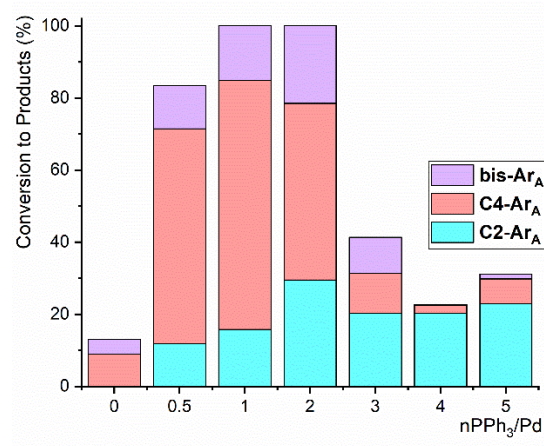


Scheme 68 Conditions and reagents used for the SMCC reaction between **30** and **74_A**, catalysed by **54** employed alongside varying equivalents of PPh₃. Conversions and site-selectivities were determined by analysing ¹H NMR spectra of crude samples taken after 1 hour.

Both conversion and C₄/C₂, a measure of C₄ selectivity over C₂ selectivity, were plotted against number of equivalents of PPh₃ *per* Pd (introduced as **54**) (Graph 11). Additionally, the conversion and distribution of the three observed products (C2-Ar_A, C4-Ar_A and bis-Ar_A) are presented in Graph 12.



Graph 11 Showing C4/C2 (left-hand Y-axis and conversion (%), right hand Y-axis) plotted as a function of nPPh₃/54 for the SMCC between **30 and **74_A**.**

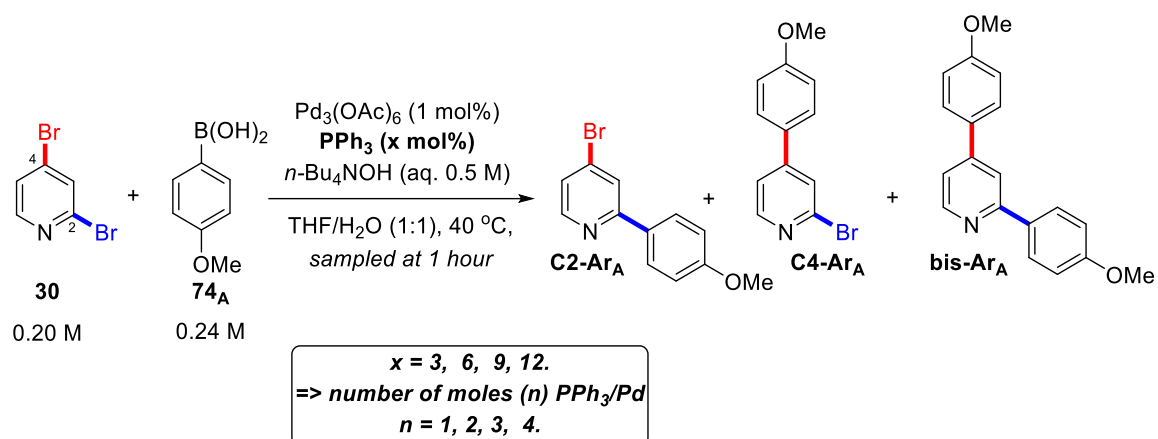


Graph 12 Showing product distributions of C2, C4 and bis-Arylated products, for the SMCC reaction, as a function of nPPh₃/ 54.

It can be seen (Graph 11 & Graph 12) that both conversion of **30** and C4/C2 site-selectivity are markedly affected by pre-catalytic equivalents of PPh₃ to Pd. As PPh₃/Pd is increased incrementally, C4/C2 selectivity begins at a maximum where PPh₃/Pd = 0.5:1, and depreciates significantly between 1 and 2 PPh₃/Pd. At PPh₃/Pd = 3 the C4/C2 site-selectivity dips below 1, indicating an overall switch to C2-site-selectivity. Further increasing the PPh₃/Pd ratio results in minor increases of C2 (over C4) site-selectivity. For the entry where no PPh₃ used (Graph 12), the reactivity is very different, with a poor conversion of **30** (9%). Nevertheless, it is notable that in this case an almost exclusive C4/C2 site-selectivity was recorded.

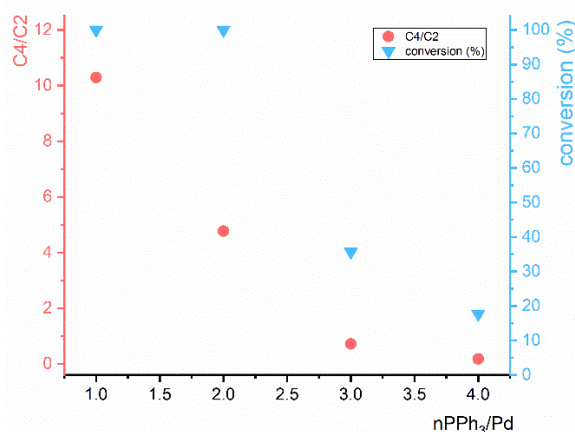
Table 6 showed that [Pd₃(OAc)₆] / 3 PPh₃ could enable higher C4/C2-selectivity **54**/nPPh₃ (C4/C2 = 5.5 *vs.* 3.6 for [Pd₃(OAc)₆] and **54** respectively). For this reason, reactions featuring four different [Pd₃(OAc)₆]/nPPh₃ ratios were performed under the exactly the same conditions as the above but for the change of the 'Pd(OAc)₂' precursor complex from **54** to [Pd₃(OAc)₆] (Scheme 69).[†] The same catalytic loading, with respect to Pd loading, of 3 mol% was used as with **54**.

[†] These reactions were carried out by Pablo Garcia-Thomas, an MChem student, who was under the supervision of the author of this work from September 2018 to April 2019.

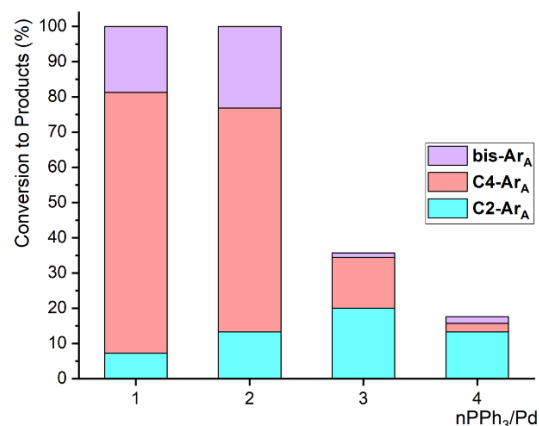


Scheme 69 Conditions and reagents used for the SMCC reaction between **30** and **74_A**, catalysed by $[\text{Pd}_3(\text{OAc})_6]$ with varying equivalents of additive PPh_3 . Conversions and site-selectivities were determined by analysing ^1H NMR spectra of crude samples taken after 1 hour.

This reaction series served to allow for direct comparison of $[\text{Pd}_3(\text{OAc})_6]$ and **54** catalytic precursors, each in the presence of varying quantities of PPh_3 as an additive ligand. In terms of the overall trends in conversion and site-selectivity as a function of Pd:P ratios, $[\text{Pd}_3(\text{OAc})_6]$ performed similarly to that of **54**, as can be viewed in Graph 13 and Graph 14.



Graph 13 Showing C4/C2 (left-hand Y-axis) and conversion (%; right hand Y-axis) plotted as a function of nPPh₃/Pd for the Pd₃(OAc)₆/nPPh₃-catalysed SMCC between **30** and **74_A**

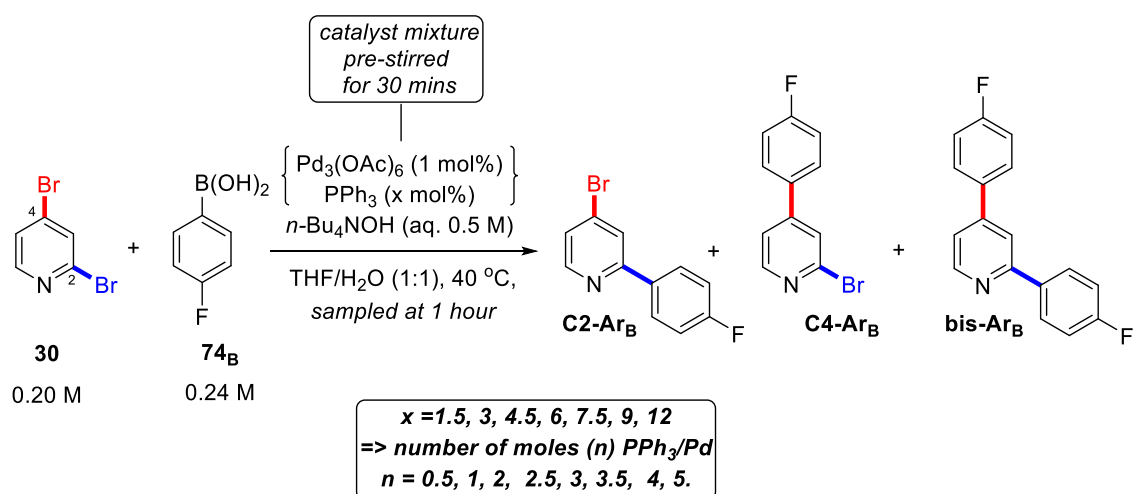


Graph 14 Showing product distributions of C2, C4 and bis-Arylated products, for the SMCC reaction, catalysed by Pd₃(OAc)₆/nPPh₃.

With [Pd₃(OAc)₆], as with **54**, conversions and C4/C2 selectivities were highest when 1 equivalent of PPh₃ per 'Pd(OAc)₂' unit were employed. Importantly, in the case of Pd₃(OAc)₆/3 PPh₃ (PPh₃/Pd = 1:1), the C4/C2 selectivity was 10.3 – more than twice the selectivity of the analogous **54**/1 PPh₃ system. Conversion remained high (100%) when 2 PPh₃/Pd were used, however the recorded C4/C2 selectivity was seen to drop significantly, from 10.3 to 4.8, in this case. On employing ≥ 3 PPh₃/Pd, again, a marked drop in conversion, along with a switch to an overall C2-selectivity was recorded. The C2(/C4) selectivity was seen to increase greatly, when going from 3 to 4 PPh₃/Pd (C2/C4 = 1.4 to 5.5), concurrently with a further drop in overall conversion. A key difference in the reactivity of the [Pd₃(OAc)₆] and **54** catalyst systems however is, when 2 PPh₃/Pd was employed, C4-site-selective reactions are more pronounced: with C4/C2 = 4.8 and 1.7 for [Pd₃(OAc)₆] and **54** respectively. Similarly, *normal* C2-selectivities of the ≥ 3 PPh₃/Pd regimes are higher with [Pd₃(OAc)₆] than with **54**. In summary, pre-catalytic [Pd₃(OAc)₆]/nPPh₃ is a higher performing catalyst system, in terms of site-selectivity than **54**/nPPh₃, with a 1:1 ratio of Pd:P being optimal in terms of both C4 site-selectivity and conversion.

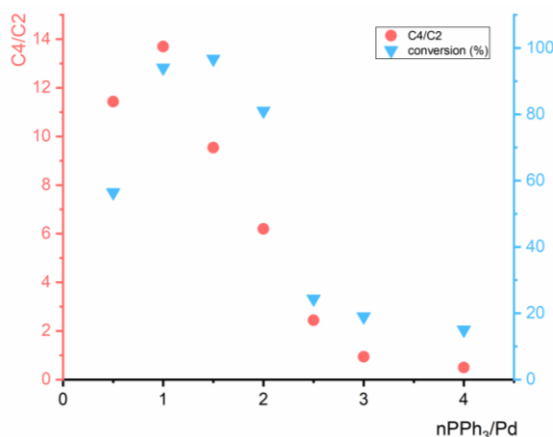
Hence, it was decided to investigate the effect of a range of [Pd₃(OAc)₆]/nPPh₃ ratios on the SMCC of **30** under conditions as detailed in Scheme 69. Here, *para*-fluorophenylboronic acid **74_B** was used instead of *para*-anisylboronic acid **74_A** (Scheme 70). This modification was made in light of knowledge of the effect of phenylboronic acid *para*-substituents on reactivity (Section 4.6). It was anticipated that due to the reduced reactivity of *para*-fluorophenylboronic acid **74_B** compared with *para*-anisylboronic acid **74_A**, experimental errors associated with the fast reactivity could be mitigated, allowing for a more accurate investigation into [Pd₃(OAc)₆]/nPPh₃ ratio effects on catalyst efficacy. Additionally, it was found that a 30 minute catalyst pre-stir (of 'Pd(OAc)₂'/nPPh₃), prior to introduction to the substrates

and base resulted in a marginal improvement in measured site-selectivity, therefore this procedure was utilised throughout this reaction series.

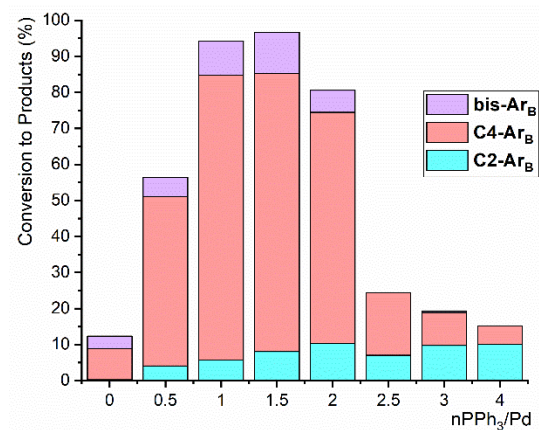


Scheme 70 Showing the conditions and reagents used for the SMCC between **30** and *para*-fluorobenzeneboronic acid **74_B**. Conversions and site-selectivities were determined by analysing the ¹H NMR spectra of crude samples taken after 1 hour.

Again, in this reaction series, both conversion and C4/C2 ratio, were plotted against number of equivalents of PPh_3 per Pd (Graph 15) and a stacked column graph was constructed to show the change in product distribution changed as the ratio of PPh_3 per Pd was varied (Graph 16).



Graph 15 Showing C4/C2 (left-hand Y-axis and conversion (%), right hand Y-axis) plotted as a function of $n\text{PPh}_3/\text{Pd}$ for the $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ -catalysed SMCC between **30** and **74_B** (Scheme 70).



Graph 16 Showing product distributions of C2, C4 and bis-Arylated products, for the SMCC reaction under the conditions detailed in Scheme 70, catalysed by $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$.

Similar overall trends in site-selectivity and conversion in SMCC reactivity between **30** and *para*-fluorophenylboronic acid **74_B** enabled by $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ as with *para*-anisylboronic acid catalysed

by **54**/ $n\text{PPh}_3$ or $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$. Upon changing the ratio of Pd to PPh_3 however, under these conditions, selectivity for a given C–Br site was higher under each ratio regime. Using 1 equivalent of PPh_3 per Pd, optimal site-selectivity ($\text{C4/C2} = 13.7$) and high activity (94% conversion of **30**) could be achieved. However, using a sub-stoichiometric quantity of PPh_3 per Pd (0.5 PPh_3/Pd), a significant drop in C4 site-selectivity and conversion was observed ($\text{C4/C2} = 11.4$, 56% conversion). Increasing the amount of PPh_3 to 1.5/Pd resulted in a marginal increase in conversion, but with a loss of C4 site-selectivity (97% conversion, $\text{C4/C2} = 9.5$). Reduced site-selectivity and reduced conversion of **30** were recorded when PPh_3 was increased to 2 PPh_3/Pd ($\text{C4/C2} = 6.2$, 81% conversion). Again, a dramatic change in catalytic performance was observed. However, when the amount of PPh_3 was increased to 2.5, with a marked decrease in overall C4-selectivity and conversion of **30** recorded ($\text{C4/C2} = 2.4$, 24% conversion). A further decrease in conversion was recorded when 3 PPh_3/Pd was employed, along with a switch to an overall C2-selectivity (19% conversion, $\text{C4/C2} = 0.94$). Increasing PPh_3/Pd to 4, resulted in higher C2 product formation and a lower overall conversion of **30** (15% conversion, $\text{C4/C2} = 0.5$).

Clearly, upon changing the ratio of $[\text{Pd}_3(\text{OAc})_6]$ to PPh_3 similar overall trends were recorded in terms of product selectivity and conversion using **74A** acid and **74B**, however, it is noted that in the latter case, that the *abnormal* C4 site-selectivity was more significant. Additionally, product conversions were generally slightly lower with **74B** than with **74A** after 1 hour of reactivity under the conditions. These phenomena are in line with the relative nucleophilicities of the activated substrates, as a result of electronic effects arising from the *para*-phenyl substituents.³¹⁵ A detailed investigation of the effect of the *para*-substituents on site-selectivity and reaction conversion in SMCC reactions at **30** is reported in Section 4.6.

Taken together, the results disclosed in this section demonstrate that the catalytic performance of a system can be significantly modified by changing the pre-catalytic $\text{Pd}(\text{OAc})_2:\text{PPh}_3$ ratio for $[\text{Pd}_3(\text{OAc})_6]$ and *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ **54**. In terms of reaction conversions, broadly speaking, these results mirror what was observed in kinetic studies at the mono-brominated analogue of **30**: 2-bromopyridine **55**, where reaction rates were found to be enhanced when a lower equivalence of PPh_3/Pd was employed (Section 0.). Here, the SMCC conversion and site-selectivity at **30** is changed significantly by modifying the pre-catalytic PPh_3/Pd ratio under the analogous conditions. To the knowledge of the author, this is the first time that such a switch in cross-coupling site-selectivity has been observed by merely changing the pre-catalyst/ligand additive ratio.

The following discussion centres around correlations between species arising from $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ mixtures and the application of this system as a pre-catalyst for SMCC reactions. A discussion about

the reasons for the observed differences such correlations in the activity of related *trans*-[Pd(OAc)₂(N-piperidyl)₂] **54** is featured subsequently.

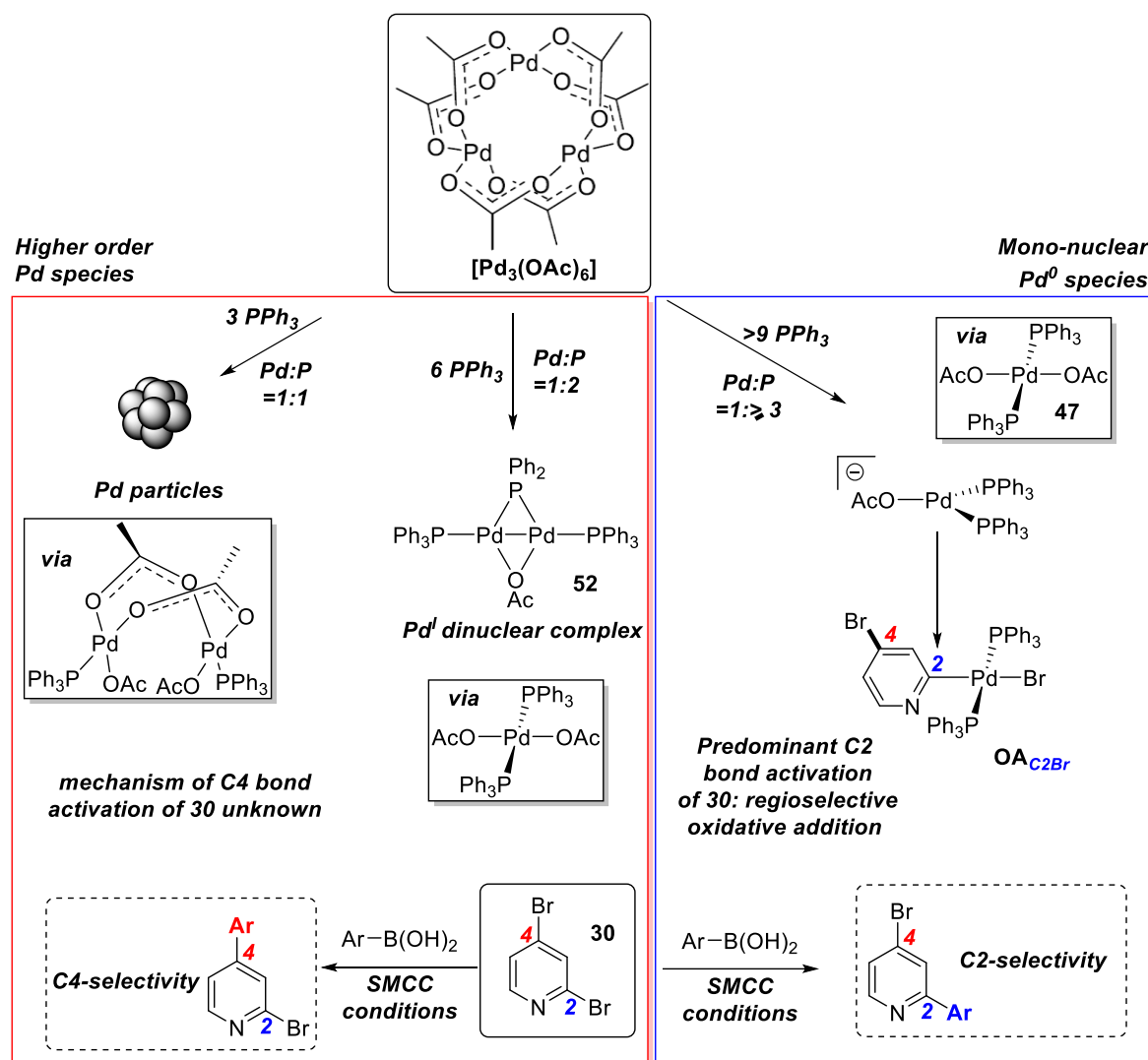
Importantly, as with the observations in Chapter 3 that the rates of SMCC reactions at 2-bromopyridine **55** can be markedly increased by employing a [Pd₃(OAc)₆]/6 PPh₃ instead of a [Pd₃(OAc)₆]/9 or 12 equivalents of PPh₃, observations of site-selectivity under otherwise identical catalytic conditions is strongly correlated with stoichiometric Pd speciation discoveries reported in Chapter 2 and reported in literature.^{46-47, 200}

Chapter 2 built on previously published literature^{46-48, 200} to show that when [Pd₃(OAc)₆] reacts with ≥ 9 equivalents of PPh₃, monomeric [Pd⁰(PPh₃)_n] complexes are formed which react directly with aryl halides to form oxidative addition products (Section 0). Section 4.2.2 showed that the closely related Pd monomeric complex [Pd⁰(PPh₃)₄] **65**²⁰⁰ reacts directly with **30** to form the C2-oxidative addition product (**OA_{C2-Br}**) predominantly. The sluggish catalyst system that forms when greater than 9 equivalents of PPh₃ are employed *per* [Pd₃(OAc)₆] (Pd:P = 1: ≥ 3) exhibits C2-site-selectivity at **30**, and shows overall reactivity in line with that observed with the Pd⁰ pre-catalyst [Pd⁰(PPh₃)₄] (Section 4.2.1).

On the other hand, crucially, Chapter 2 showed that treating [Pd₃(OAc)₆] with 3 or 6 equivalents of PPh₃ (Pd:PPh₃ = 1:1 or 1:2) resulted in starkly different Pd speciation, compared with the Pd⁰ monomers that form when [Pd₃(OAc)₆] activates in the presence of ≥ 9 equivalents of PPh₃ (Pd:P = 1: ≥ 3). When [Pd₃(OAc)₆] was reacted with 3 PPh₃ (Pd:PPh₃ = 1:1) Pd particles were seen to form. When exactly 6 equivalents of PPh₃ is deployed *per* Pd (Pd:PPh₃ = 1:2) the dinuclear Pd^I complex [Pd₂(μ -PPh₂)(μ -OAc)(PPh₃)₂] **52** evolves after reductive activation. Furthermore, when **52** is treated with organohalides (R-X), higher order trinuclear cluster complexes of the form [Pd₃(μ -Br)(PPh₂)₂(PPh₃)₃]⁺X⁻ (**Pd₃X·X**) arise. At this stage it is unclear to what extent that **Pd₃X·X**-type clusters can participate in the cross-coupling catalytic cycles, however **Pd₃Cl·Cl** it reported in the literature and *this work* to be an active catalyst for the SMCC reaction.¹⁷² Control experiments showed that this cluster aggregates to particles on treatment directly with the reaction base *n*-Bu₄NOH (aq.). Generally, if there is not enough free PPh₃ ligand present to stabilise mono-nuclear Pd⁰, there is a tendency for higher order Pd species to form and propagate.

This chapter has demonstrated a dichotomy in SMCC catalytic efficacy and site-selectivity. High activity and C4 selectivity in SMCC reactions at **30** is observed in 'Pd(OAc)₂'/*n*PPh₃ catalyst systems where *n* = 1 or 2 and lower activity and C2 selectivity is observed when *n* = ≥ 3 . These observations correlate well with differences in speciation between higher order species formed from ([Pd₃(OAc)₆]/3 or 6 PPh₃, Pd:P = 1:1 or 1:2): the Pd^I dinuclear complex **52** or Pd particles, and mono-nuclear Pd⁰ complexes (arising from ([Pd₃(OAc)₆]/ ≥ 9 PPh₃, Pd:P = 1: ≥ 3), under stoichiometric conditions. It

was therefore concluded that C2 selectivity observed arises as a result of the formation of monomeric $[\text{Pd}^0(\text{PPh}_3)_n]$ complexes, where the site-selectivity is determined by selective oxidative addition reaction to the C2–Br site to **30**. The mechanism of the observed C4 selectivity where $[\text{Pd}_3(\text{OAc})_6]/3$ or 6 PPh_3 is employed is unclear at this stage, however it is most likely that higher order species, which form as a result of the pre-catalytic Pd:P ratio, are involved. The conclusions involving $[\text{Pd}_3(\text{OAc})_6]$ as a pre-catalyst in the presence of varying equivalences of PPh_3 are summarised in Scheme 71.



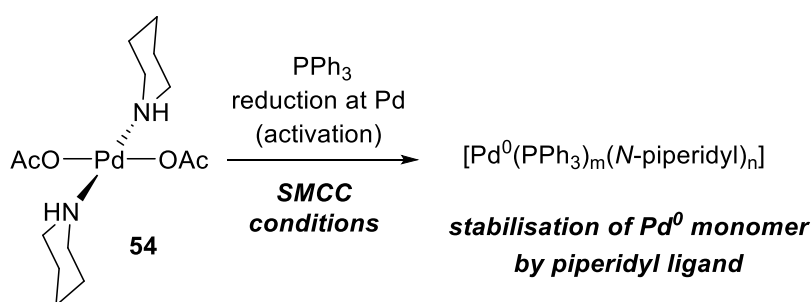
Scheme 71 Showing the correlation made between the formation, of higher order species vs. mono nuclear Pd^0 species, from differing ratios of $[\text{Pd}_3(\text{OAc})_6]$ and PPh_3 , and site-selectivity in SMCC reactions at 30.

Jutand *et al.* showed that for activation of ‘Pd(OAc)₂’ in the presence of tertiary phosphines, one equivalent of PPh₃ is required for full conversion to a Pd⁰ complex.⁴⁶⁻⁴⁸ The reduced activity observed when less than one equivalent, *e.g.* 0.5 equivalents, of PPh₃ are employed for each pre-catalytic ‘Pd(OAc)₂’ unit (from [Pd₃(OAc)₆] or **54**), is likely a result of the Pd present being only partially reduced

to the active catalytic species, thusly reducing the effective catalyst loading of the species which exhibited high reactivity and C4-selectivity at **30**. Colacot *et al.*, as discussed in Chapter 3, made similar observations when employing $[\text{Pd}^{\text{II}}\text{Br}_2(\text{cod})]$ **66** as a pre-catalyst in tandem with 1 equivalent of $\text{P}t\text{Bu}_3$, in cross-coupling reactions which was demonstrated to result in partial conversion to a $[\text{Pd}^{\text{I}}(\mu\text{-Br})(\text{P}t\text{Bu}_3)]_2$ (**16**) active species, which was reasoned to account for reduced cross-coupling reaction rates.⁵⁷

Differences Between *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ / $n\text{PPh}_3$ **54** vs. $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ Catalytic Performance

As was observed with $[\text{Pd}_3(\text{OAc})_6]$, with *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$ **54** and $n\text{PPh}_3$ as pre-catalysts for SMCC reactions at **30**, the highest activity and selectivity for the C4 arylated product was recorded when low relative amounts of PPh_3 (1 or 2 equivalents *per* Pd) were employed. The C4 site-selectivity was, however, significantly higher with $[\text{Pd}_3(\text{OAc})_6]$ than with **54**. This difference in activity may be explained by considering the presence of two equivalents of piperidyl ligand, in addition to additive PPh_3 , per Pd introduced as part of the **54** pre-catalyst. In Chapter 2 (Section 2.4.3), it was indicated that whether 2 or 1 equivalents of PPh_3 is mixed with **54** in THF, activation to Pd^0 $[\text{Pd}^0(\text{PPh}_3)_n(\text{piperidyl})_m]$ or the Pd^{I} dimeric complex, $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ occurred, respectively, with both featuring PPh_3 ligands in exchange with free piperidine. It is most likely, therefore, considering the tempered reactivity of the piperidine-containing catalyst systems, compared with that derived from $[\text{Pd}_3(\text{OAc})_6]$ alone that the extra piperidyl ligand contributes to the stability of *in situ* formed Pd^0 (Scheme 72) and, to an extent prevents the formation of the highly active and selective catalytic species that enabled C4 arylation at **30**, favouring a mono-nuclear Pd^0 -mediated, C2-selective pathway.



Scheme 72 A hypothesis for observed active speciation arising from **54**. Both PPh_3 and piperidine are present and available to stabilise less active Pd^0 monomer catalysts.

It is known that amines such as piperidine can bring about reduction (activation) of $\text{Pd}(\text{OAc})_2$ via a mechanism involving concomitant amine β -hydride elimination.^{105, 252, 316} If both piperidine and added PPh_3 may be involved in $\text{Pd}(\text{OAc})_2$ reduction (activation), that would imply that a lower fraction of the present PPh_3 would be consumed upon complete reduction at Pd, thus the excess PPh_3 would

be free, in addition to available piperidine, to aid in the stabilisation of the less active Pd⁰ monomers. The prevalence of Pd⁰ monomeric complexes stabilised by piperidyl and PPh₃ ligands may thus explain the observed lower activity of **54** vs. [Pd₃(OAc)₆] in the site-selective SMCC reactions at **30**.

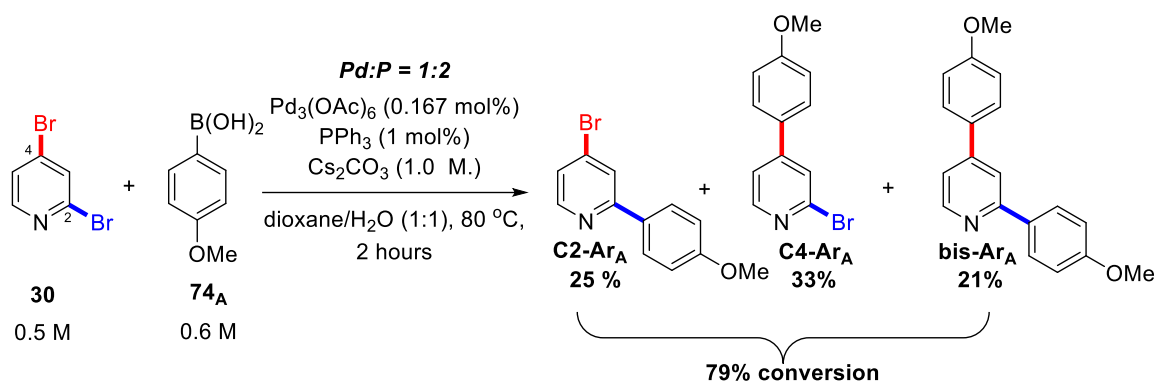
A key finding, elucidated from this section is that, under the SMCC conditions explored, the optimal catalyst ratio of 'Pd(OAc)₂'/PPh₃ (introduced from either [Pd₃(OAc)₆] or **54**) is 1:1, in terms of both activity and site-selectivity for the *abnormal* C4-position in SMCCs at the model substrate **30**. This result was not anticipated, as in most catalytic examples involving Pd(OAc)₂-containing pre-catalysts, two or more equivalents of triarylphosphine per Pd(OAc)₂ are used. Indeed, mechanistic understanding of catalyst speciation in [Pd₃(OAc)₆]/PPh₃ was until now limited to situations where an excess (≥ 4 equivalents) of PPh₃/Pd is used.^{46-48, 200} The next section explores the factors that lead to the abnormal C4-selectivity in cross-coupling reactions at **30**, focusing on the privileged pre-catalyst system [Pd₃(OAc)₆]/3 PPh₃.

4.5. Alterations to the Cross-coupling Conditions: Additive and Base Effects

4.5.1. Effect of Quaternary Ammonium Cations on Site-control in Suzuki-Miyaura Cross-coupling Reactions

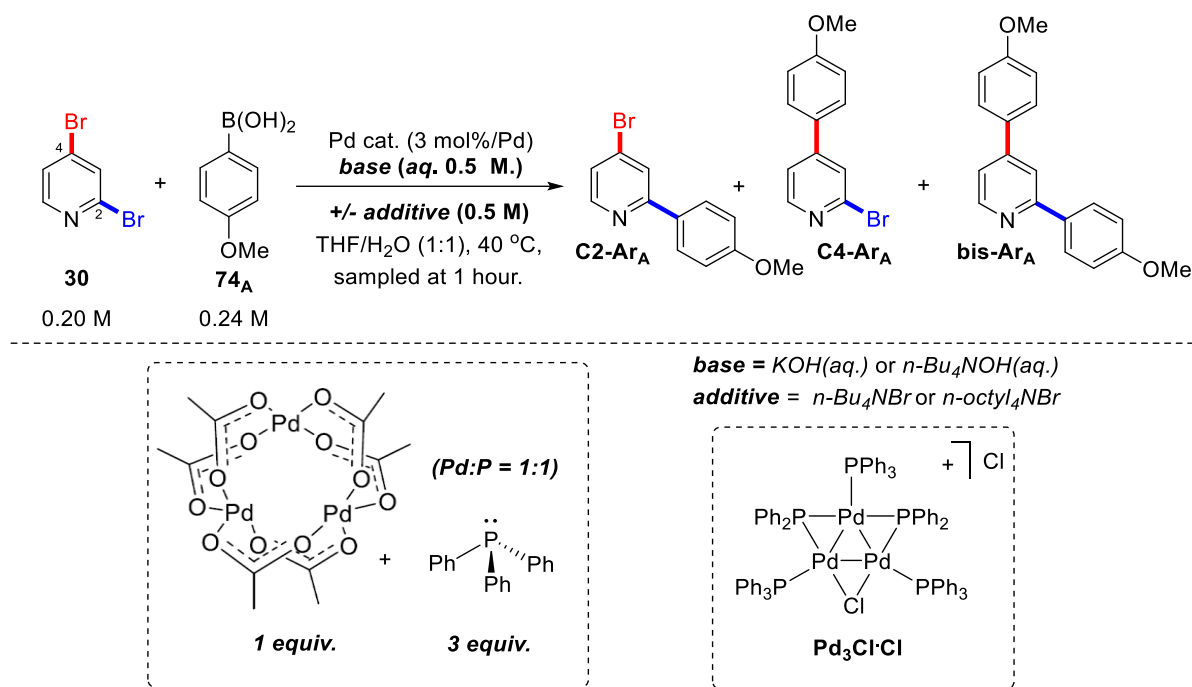
Armed with the knowledge that, employing 'Pd(OAc)₂'-containing complexes alongside 1 catalytic equivalent of PPh₃ per Pd, an optimal outcome of catalytic site-selectivity and reactivity at 2,4-dibromopyridine **30** could be achieved, it was decided to test whether other aspects of the model SMCC conditions examined could be contributing to the catalyst efficacy.

In a relevant literature precedent, Hardie, Willans *et al.* reported the SMCC reaction between **30** and *para*-anisylboronic acid **74A** (Scheme 73).³⁰²



Scheme 73 Conditions, reagents, and conversion and site-selectivity outcomes reported by Willans *et al.*, for the $\text{Pd}_3(\text{OAc})_6/6\text{PPh}_3$ -catalysed site-selective SMCC between **30** and **74_A**.

In the above case (Scheme 73), a pre-catalytic system of $[\text{Pd}_3\text{OAc}]_6/6\text{PPh}_3$ (Pd:P = 1:2) was employed. Notably, in this case, a pre-catalytic Pd:P ratio of 1:2 led to a conversion of 79% and a very slight preference for the C4-arylated product over the C2 product: C4/C2 = 1.3. This lack of site-selectivity is curious as it stands in contrast with the substantially higher C4-selectivity observed in the analogous coupling of **30** with **74_A** under *standard conditions* C4/C2 = 10.3 (Graph 13 & Graph 14, *vide supra*). Important deviations in the above conditions (Scheme 73) from the site-selective ‘*standard conditions*’ reported in this work are catalyst loading, temperature, solvent system and identity of the base. Perhaps the most significant difference between the above conditions and *standard conditions*, however, may be the identity of the base: Cs_2CO_3 . The *standard conditions* used in *this study*, involve a strong, organic- and water-soluble base, *tetra-*n*-butylammonium* hydroxide (*n*-Bu₄NOH) which is not very frequently deployed in Suzuki-Miyaura cross-coupling catalysis. It was therefore decided to test our conditions in absence of this highly soluble, highly dissociated source of hydroxide.³⁴ To test the effect of this base, and in particular the effect of the bulky, non-coordinating cation: *n*-Bu₄N⁺, a series of reactions were carried out according to the conditions presented in Scheme 74.



Scheme 74 Conditions, reagents and additives, alongside the structures of the two pre-catalytic systems used in experiments assessing the effect of the quaternary ammonium cation/hydroxide base system on site-selectivity and efficacy in the SMCC between **30** and **74_A**.

The *n*-Bu₄N⁺ increases the effective alkalinity of the reaction by fully dissolving into solution with a high degree of ion dissociation.³⁸ By modifying the base and additives, the effects of the *n*-Bu₄N⁺ cation on reaction outcomes could be assessed. Two different pre-catalytic systems were used in this study: [Pd₃(OAc)₆]/3 PPh₃ and the tripalladium cluster complex **Pd₃Cl·Cl** – both of which had shown good site-selectivity and conversion under *standard conditions* (*vide supra*). **Pd₃Cl·Cl** was used as it had been found to form stoichiometrically from mixtures [Pd₃(OAc)₆]/6 PPh₃ in the presence of organohalide (See Section 2.5.1), and showed comparable catalytic activity to [Pd₃(OAc)₆] and 3 or 6 equivalents of PPh₃ (Table 6, *vide supra*). The effect of the additive/base changes on conversion and site-selectivity in a 1 hour reaction time are highlighted in (Table 7). Entry 1 (Table 7) shows the reactivity of [Pd₃(OAc)₆]/3 PPh₃ under benchmark standard conditions, for comparison with subsequent entries (Scheme 67). Entry 2 shows a reaction where aqueous KOH was used, directly replacing aqueous *tetra*-*n*-butylammonium hydroxide as reaction base. In this case, it can be seen that, while overall conversion is still quite high (89%), the site-selectivity of the system is drastically reduced (C4/C2 = 1.8:1), with only a minor preference for the C4-product recorded, in line with Willans' conditions, using Cs₂CO₃ (C4/C2 = 1.3).

Table 7 A summary of results, including C4/C2 site-selectivity and conversions for experiments assessing additive/base effects for SMCC reactions as detailed in Scheme 74 (Conv. = Conversion of **30** after a 1 hour reaction time).

Pre-catalyst	Entry	Base	Additive	Conv.*/%	C2-Ar _A : C4-Ar _A : bis-Ar _A
[Pd ₃ (OAc) ₆]/ 3 PPh ₃	1	n-Bu ₄ NOH	none	100	10:70:20
	2	KOH	none	89	26:46:28
	3	KOH	<i>n</i> -Bu ₄ NBr	88	3:70:26
[Pd ₃ (OAc) ₆]/ 6 PPh ₃	4	n-Bu ₄ NOH	none	100	18:58:24
	5	KOH	<i>n</i> -Bu ₄ NBr	100	8:79:6
Pd ₃ Cl ₂ ·Cl	6	n-Bu ₄ NOH	none	100	15:69:16
	7	KOH	none	92	38:38:24
	8	KOH	<i>n</i> -Bu ₄ NBr	94	9:82:10
	9	KOH	<i>n</i> -Octyl ₄ NBr	100	7:90:3

When KOH was used in concert with additive *tetra-n*-butylammonium bromide (*n*-Bu₄NBr) (Entry 3, Table 7), however, C4-selectivity increased to a remarkable C4:C2 = 23:1 along with slightly decreased conversion of **30** to products in the reaction time when compared with using *n*-Bu₄NOH alone as the base. In this case (Entry 3) it was noted that a significant quantity of diarylated **bis-Ar_A** product was seen to arise. When using [Pd₃(OAc)₆]/6 PPh₃ as the pre-catalyst system, with KOH/*n*-Bu₄NBr additives (Entry 5) similarly resulted in increased C4/C2 selectivity compared with using *n*-Bu₄NOH (Entry 4). Additionally, [Pd₃(OAc)₆]/6 PPh₃ with KOH/*n*-Bu₄NBr resulted in high overall conversion of **30** and decreased formation **bis-Ar_A**. This phenomenon is the result of this system being less active at the C4–Br position of **30**, rendering **30** the limiting reagent. In the case of [Pd₃(OAc)₆]/3 PPh₃ with KOH/*n*-Bu₄NBr (Entry 3) formed **C2-Ar_A** is rapidly converted to **bis-Ar_A** and **74_A** becomes the limiting reagent, leaving unreacted **30**.

Parallel observations were made with **Pd₃Cl₂·Cl** as a pre-catalyst, for which the benchmark performance under *standard conditions* is detailed in entry 6 (Table 7). When using KOH (Entry 7, Table 7) in absence of any other additive, C4-site-selectivity was lower (C4/C2 = 1.0) however where *n*-Bu₄NBr and KOH were employed together (Entry 8), high C4 site-selectivity was replenished (C4/C2 = 9.8). Notably, when the bulkier, longer-chained quaternary ammonium *tetra-n*-octylammonium bromide (*n*-Octyl₄NBr, entry 9) was deployed, alongside KOH, an even higher C4/C2 site-selectivity (C4:C2 = 12.9:1) was achieved.

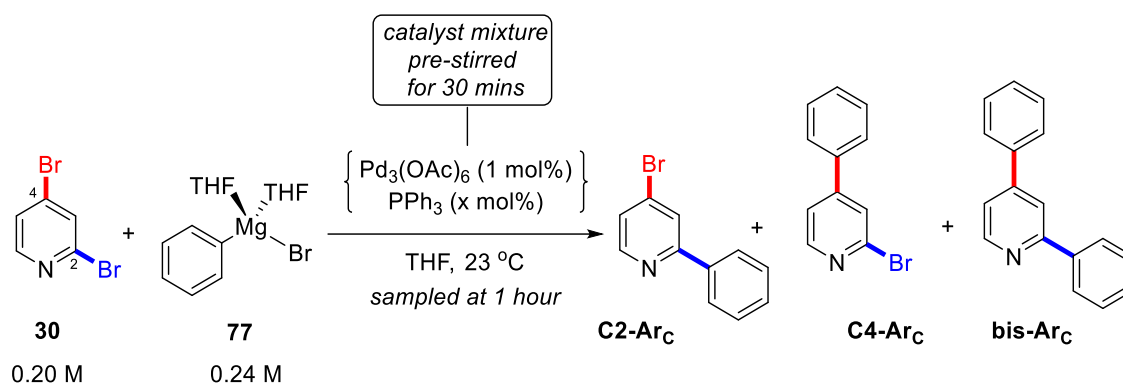
Importantly, this study shows that absence of the *n*-R₄N⁺ ion, in reactions mediated by KOH, site-selectivity preference is lost. When *n*-R₄N⁺ is introduced to the reaction as the *n*-R₄NBr salt, where

KOH is the base, the C4-selectivity was reinstated. This observation implicates the $n\text{-R}_4\text{N}^+$ cation as having a powerful role in forming or stabilising a catalyst system which is both more active (resulting in higher conversion) and exhibits an increased C4-site-selectivity in SMCCs at **30**. It was reported in Chapter 2 (Section 2.6) that the $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ pre-catalyst system forms Pd particles which were determined to form as a result of a lack of stabilising agent for the activated Pd. In addition, **Pd₃Cl·Cl** was noted to form visible Pd particles in presence of hydroxide (introduced as $n\text{-Bu}_4\text{NOH}$ {aq}) in absence of other substrates. The precise nature of the active catalyst is at this stage unproven, nevertheless, since it is known that both pre-catalytic species tested break down to particles in absence of stabilising ligands, it is highly likely that the additive $n\text{-R}_4\text{NX}$ exhibits an *electrosteric stabilising* effect on an *in situ*-generated particulate active species (*e.g.* a PdNP). In other words it is hypothesised that under the conditions, pre-catalytic systems: $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ and **Pd₃Cl·Cl** form particles which are stabilised by the additive $n\text{-Bu}_4\text{X}$ salt ($\text{X} = \text{Br}^-$ or OH^-), and this catalytic species is responsible for the C4-Ar selectivity observed in SMCC reactions at **30**. This hypothesis is supported by the observation that the larger $n\text{-Octyl}_4\text{NBr}$ salt, which could provide enhanced *steric* protection for an active particle, enabled an increased site-selectivity at **30** (See Section 1.3.2.2 and discussions *vide infra* for further details).

4.5.2. Effect of Pd/PPh₃ Ratios and Quaternary Ammonium Cations on Site-control in Kumada Cross-coupling Reactions

This study has disclosed that privileged catalytic conditions can be employed to control site-selectivity in SMCC reactions at 2,4-dibromopyridine **30**. In order to assess the scope of applications of such catalyst systems, it was decided to test them in a different type of cross-coupling reaction, namely the Kumada-Corriu (hereafter Kumada) cross-coupling reaction. Notably, Kumada cross-couplings do not require addition of a formal base and are usually performed under anhydrous conditions. Hence, the effect of hydroxide and water on cross-coupling outcomes could be tested.

Initially, the effect of changing the ratios of pre-catalytic $[\text{Pd}_3(\text{OAc})_6]$ and PPh_3 on the Kumada cross-coupling reaction between **30** and the Grignard reagent phenylmagnesium bromide **77** in dry THF was assessed, in the absence of any further additive. The catalytic conditions were based on the SMCC ‘*standard (SMCC) conditions*’ (see Scheme 66, section 4.3.1) with substrate equivalences, substrate concentrations and catalytic loadings being conserved (Scheme 75).



Scheme 75 Conditions and reagents used for the site-selective Kumada-Corriu cross-coupling between 2,4-dibromopyridine **30** and phenylmagnesiumbromide **77**. Reactions were analysed by ^1H analysis of crude samples, taken after 1 hour.

Important differences between the above conditions and the SMCC *standard conditions* are that reactions were kept rigorously dry and were performed at room temperature (as opposed to 40 °C) in absence of any additive base or water. To allow for catalyst activation prior to cross-coupling initiation, the $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ pre-catalyst system was pre-stirred for 30 minutes in THF. Results concerning conversion and cross-coupled product distribution as a function of $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ are detailed in Table 8.

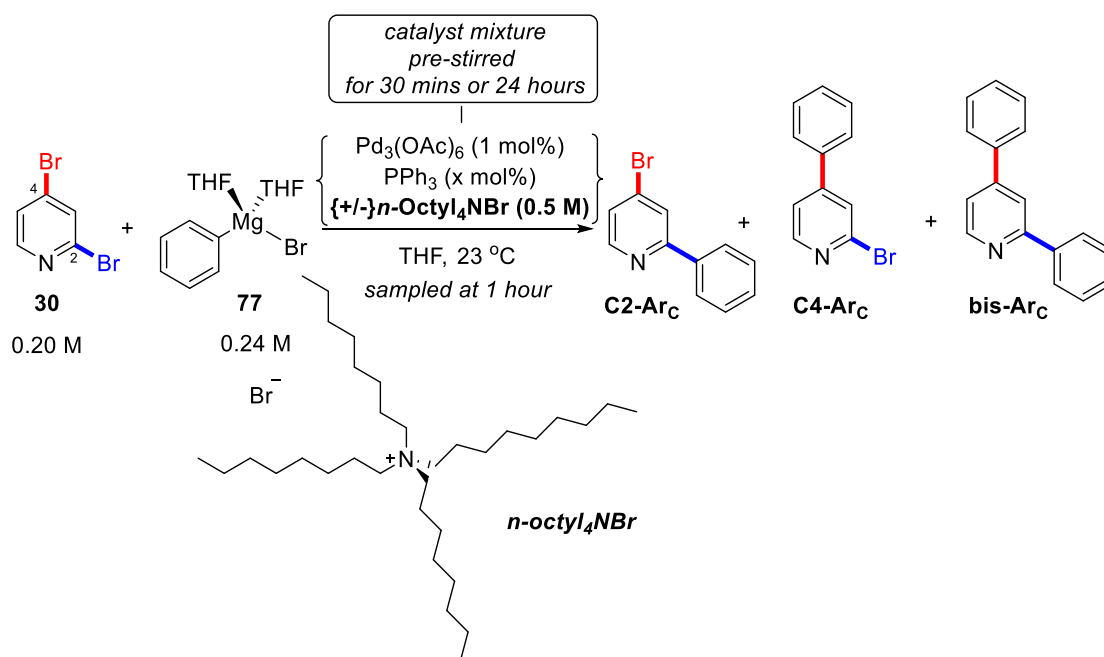
Table 8 Showing conversions, product distributions and C2/C4 site-selectivities, for Kumada reactions catalysed by $\text{Pd}_3(\text{OAc})_6/\text{nPPh}_3$ mixtures, in absence of quaternary ammonium salt additives. Reactions were analysed by ^1H analysis of crude samples, taken after 1 hour.

nPPh ₃ /Pd	Conversion /%	C2-Ar _C :C4-Ar _C :bis-Ar _C	C4/C2
[No Pd or PPh ₃]	None	N/A	N/A
3	99	84:6:9	1:14
6	100	91:3:6	1:30
12	100	83:0:17	1:>100

Mirroring SMCC *standard conditions*, it can be seen (Table 8) that in absence of any Pd catalyst, no formation of products was evident and 2,4-dibromopyridine **30** starting material could be reclaimed, indicating that no observable $\text{S}_{\text{N}}\text{Ar}$ -type chemistry was occurring in the background under the reported conditions. The $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ catalyst system resulted in conversion of **30** to C2-Ar_C, C4-Ar_C and bis-Ar_C products. Employing the $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ pre-catalyst mixture, high conversion and C2-selectivity was registered, with a C2/C4 ratio = 14. This observation stands in contrast to SMCC chemistry where, if catalysed by $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ under *standard conditions* as detailed above (Scheme

66), C4-selectivity was observed. Using higher amounts of PPh_3/Pd (2 or 4 *per* Pd) resulted in similarly high catalyst activity, with 100% conversion to products and an increase in overall C2-site-selectivity, with $[\text{Pd}_3(\text{OAc})_6]/12\text{PPh}_3$ showing no measurable presence of the C4-product by ^1H NMR in the sample taken. As the samples taken were snapshots of the state of the reaction after 1 hour, the possibility that any C4-product formed could have formed and been rapidly converted to **bis-Ar_C** cannot be ruled out in the above cases.

Thus, under Kumada conditions, cross-coupling at **30** is overwhelmingly C2-site-selective, regardless of the Pd:P ratio when using $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ as pre-catalytic systems. It was therefore decided to test whether adding the quaternary ammonium salt, *n*-Octyl₄NBr, could have an effect on the reaction outcomes, as the *n*-R₄N⁺ cation had previously proved to be crucial for C4 site-selectivity under SMCC *standard conditions*. *n*-Octyl₄NBr in particular was selected as a quaternary ammonium salt additive, over *e.g.* *n*-Bu₄NBr, as it had previously demonstrated the ability to form a catalyst system with a higher C4-site-selectivity in SMCC reactions at **30** (Table 7). The effect of the length of pre-stirring time of the pre-catalytic mixture in presence and absence of *n*-Octyl₄NBr was also assessed. Conditions employed in this study are shown in Scheme 76.



Scheme 76 Conditions and reagents used for the site-selective Kumada cross-coupling between **30** and **77** in the presence or absence of additive *n*-Octyl₄NBr. $\text{Pd}_3(\text{OAc})_6/n\text{PPh}_3$ pre-catalyst systems with variable equivalents of PPh_3 . Catalyst pre-stir length was also varied. Reactions were analysed by ^1H analysis of crude samples, taken after 1 hour.

The *n*-Octyl₄NBr additive concentration (0.5 M: 2.5 equivalents *vs.* **30**) was chosen to reflect the that of *n*-Bu₄N⁺ introduced as *n*-Bu₄NOH (aq) under the *standard* SMCC conditions. Conversion and site-selectivity results under the conditions highlighted (Scheme 76) are collated in Table 9.

Table 9 Showing results for the reactions Kumada cross-coupling reactions with Pd₃(OAc)₆/nPPh₃ catalyst pre-stirring time in presence and absence *n*-Octyl₄NBr, the conditions for which are detailed (Scheme 76).

Entry	Pre-stir time /h	Additive (+/-)	PPh ₃ /Pd	conversion/%	C2-Arc:C4-Arc:bis-Arc (%)	C4:C2
1	0.5	-	1	99	84:6:9	1:14
2	24	-	1	85	80:11:8	1:6.8
3	0.5	+	1	83	21:68:12	3.1:1
4	24	+	1	96	15:77:8	5.1:1
5	0.5	+	4	96	67:26:7	1:2.6

Entry 2 (Table 9) shows that, after a 24-hour pre-stir, the [Pd₃(OAc)₆]/3 PPh₃ catalyst results in C2 cross-coupling site-selectivity at **30**. It can be seen that the pre-stirring length has a detrimental effect on both conversion of **30** and C2-site-selectivity (entries 1 & 2, Table 9). This observation indicates that under the conditions, during a lengthy pre-stir, the catalytic Pd present becomes less active, perhaps by aggregation to large Pd particles.²⁸⁰ Entry 3 shows that when employing [Pd₃(OAc)₆]/3PPh₃ (Pd:P = 1:1) the Kumada cross-coupling reaction can be forced to switch to overall C4-site-selectivity in the presence of an *n*-Octyl₄NBr additive. Entry 4 demonstrates that if the pre-stirring time of the pre-catalyst mixture is increased to 24 hours, an increase in both C4/C2-site-selectivity and reaction conversion was recorded. This observation indicates that catalyst efficacy is enhanced as a result of increasing the pre-stirring period in the presence of additive *n*-Octyl₄NBr. Entry 5 shows that if a high ratio PPh₃/Pd is employed, as in pre-catalytic [Pd₃(OAc)₆]/12 PPh₃, overall C2-site-selectivity is retained, in the presence of the *n*-Octyl₄NBr additive. It is significant, however, that C2 site-selectivity with a [Pd₃(OAc)₆]/12 PPh₃ pre-catalyst is markedly reduced in the presence of the *n*-Bu₄NBr additive (C4:C2 = 1:2.6) *vs.* an absence of the additive (C4:C2 = 1:>100).

As these Kumada-type conditions were kept rigorously water-free, it is clear that the presence of water or hydroxide is not necessary for the site-selective cross-coupling at **30**. These results underline that a combination of both a low phosphine/Pd ratio, generated from a [Pd₃(OAc)₆]/nPPh₃ system *and* the additive *n*-Octyl₄NBr are required to bring about optimal C4 site-selectivity at 2,4-dibromopyridine **30** under the reported Kumada conditions. These findings are in line with SMCC reactivity under the analogous conditions as reported *vide supra*, however in absence of quaternary ammonium salt additive,

Kumada reactions are strongly C2 selective, whereas under SMCC conditions (with KOH(aq.) as the base), neither the C4- nor the C2-product is preferentially selected for.

A discussion of the potential mechanistic reasons for the dichotomy of catalyst selectivity at **30**, from the point of view of active catalyst speciation, is presented in Section 4.7. As the presence of an alkylammonium salt additive was necessary for the formation of the C4-selective cross-coupling products at **30**, the following section reports the design of a bespoke salt additive in effort to enhance the selectivity of the reaction.

4.5.3. Design of a Tris-imidazolium Tribromide Salt and its Application in the Suzuki-Miyaura Cross-coupling Reaction.

This Section has reported that a quaternary ammonium salt was a crucial ingredient for achieving optimal C4 site-selectivity in cross-coupling reactions (SMCC and Kumada) at 2,4-dibromopyridine **30**, using catalysts derived from [Pd₃(OAc)₆]/3PPh₃ or **Pd₃Cl·Cl**. In light of this finding, it was decided to further test this hypothesis by engineering a quaternary ammonium salt envisaged to boost the theorised *electrosteric stabilisation* of the active catalyst (see Sections 1.3.2.2 & 4.7).

A novel tris-imidazolium tribromide salt **TrisImid·3Br** (Figure 82) was synthesised, imbued with properties hypothesised to better optimise C4-selectivity at **30** and, in doing so, test the hypothesis that the C4-selective active species is stabilised by an electrosteric mode (Sections 1.3.2.2).^u The compound's design was inspired by cyclotrimeratrylene-tethered trinuclear Pd^{II}-NHC complex **73**, an imidazolium-based Pd^{II} pre-catalyst reported by Willans *et al.* (Figure 77)³⁰² and a related imidazolium-containing compound class investigated by Pleixats and Shafir for the stabilisation of catalytic PdNPs in cross-coupling applications (Chapter 1, Figure 9).^{126, 317} The novel tris-imidazolium compound **TrisImid·3Br** features a 2,4,6-triethylbenzene core. Each 2,4,6-position of the triethylbenzene core was substituted with 2-methylimidazolium rings-tethered through their N3-atoms to the core *via* methylene carbon centres. The N1-positions of the three imidazolium groups were each quaternarised with amyl groups, rendering the compound tri-cationic, with enhanced steric bulk around N: the site of positive charge.

^u Practical work on the synthesis and application of **TrisImid·3Br** to principally carried out by Anthony Eyles: an MChem student under the supervision of the author from 09.2019-04.2020.

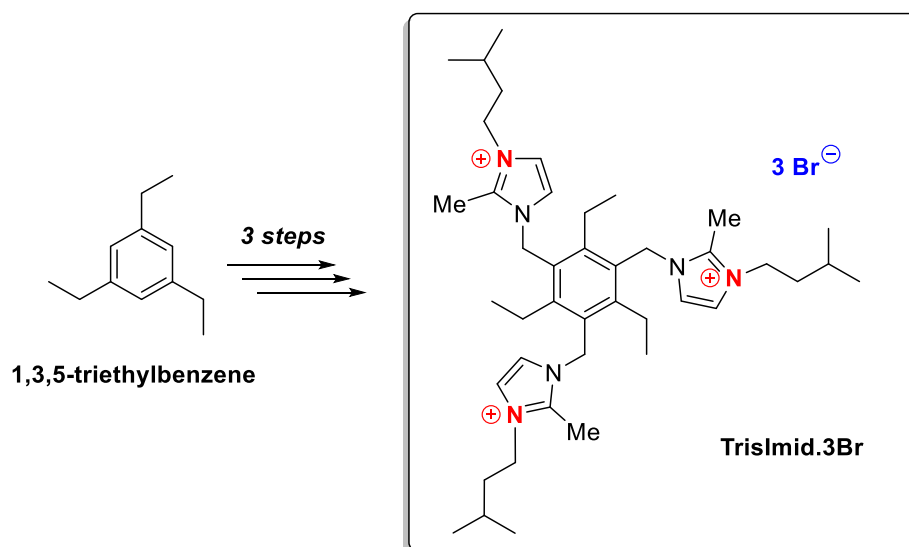
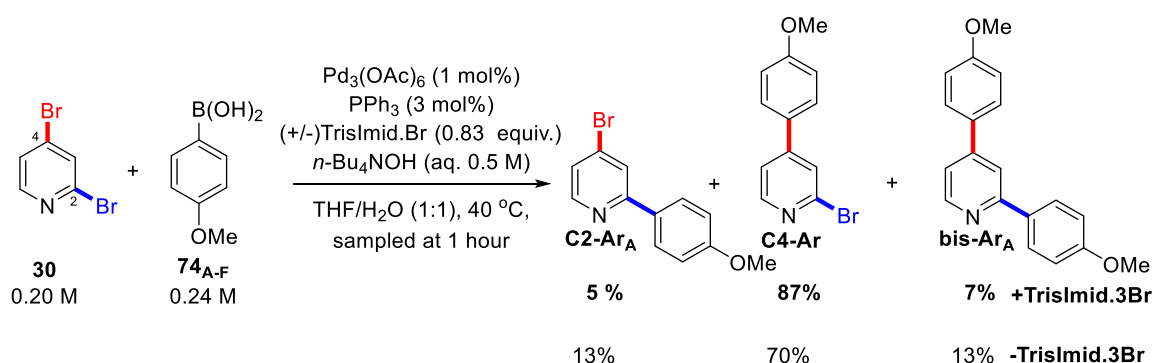


Figure 82 Showing the structure of the tris-imidazolium tribromide (**Trisimid·3Br**) compound designed and to enhance site-selectivity in cross-coupling reactions at 30 and to test the hypothesis that the catalyst that exhibits C4-selectivity at 30 is particulate in nature and stabilised by *electrosteric effects* of cationic ligands.

A SMCC reaction was performed (Scheme 77) to assess the catalytic performance, in terms of site-selectivity and conversion, using $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ in the SMCC reaction between 30 and 74_A in the presence of **Trisimid·3Br**. *N*-Bu₄NOH (aq.) was used as the base. 0.83 equivalents of **Trisimid·Br** were used to normalise to the number of ionic sites, thus introducing the same number of quaternary nitrogen sites and bromide anions, in effort to allow for a comparable setup to previous reactions.^v



Scheme 77 Conditions and reagent used for the SMCC reaction, catalysed by $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ in the presence of **Trisimid·3Br** (Figure 82) between 30 and 74_A. Conversions and site-selectivities were determined by ¹H NMR analysis of a sample of the reaction mixture taken after 1 hour.

It can be seen (Scheme 77) that the activity of the catalyst system with additive **Trisimid·3Br** is high, with 99% conversion after 1 hour. Most intriguingly at 18.3:1, the site-selectivity was a significant

^v 2.5 equivalents have previously been used, since **Trisimid·3Br** contains three anions and cations *per* molecule $2.5/3 = 0.83$, therefore 0.83 equivalents of this compound were used.

improvement on the background reaction in absence of **TrisImid·3Br** which exhibits a C4:C2 of 5.4:1. It also is of added note that the high selectivity for **C4-Ar_A**, accompanied by relatively low conversion to **C2-Ar_A** and **bis-Ar_A** compared to like reactions previously reported (*vide supra*). This finding supports the theory that bulky, cationic N⁺-containing salts enhance C4-selectivity in cross-couplings at **30**.

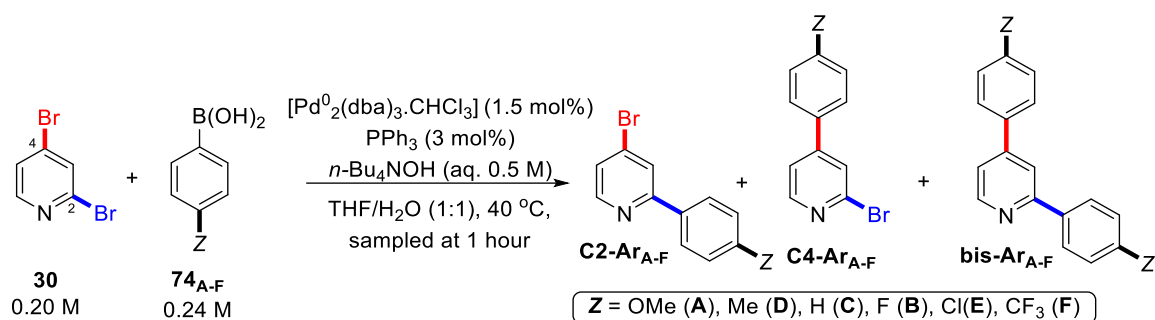
To summarise this section, C4 site-selectivity in SMCC reactions under the model conditions at 2,4-dibromopyridine **30** is enhanced by use of bulky quaternary ammonium/imidazolium salts, including the novel salt **TrisImid·3Br**. Such additives can be applied to both Suzuki-Miyaura and Kumada cross-couplings to improve yields of the *abnormal* C4-product. Section 4.7 section brings together findings from this chapter, and the preceding chapters, and discusses mechanistic reasoning behind the observed site-selectivity at this model reaction system.

4.6. Phenylboronic Acid *Para*-substituent Effects on Suzuki-Miyaura Site-selectivity

Considering the impact and ubiquitous application of the SMCC reaction in organic synthesis, there have been surprisingly few systematic investigations into the effects of phenylboronic *para*-substituents on site-selectivity in SMCC outcomes at dihalogenated aromatic substrates. To gain further understanding of the catalytic systems that showed *abnormal* C4 site-selectivity in Suzuki-Miyaura cross-coupling reactions at 2,4-dibromopyridine **30**, it was decided to investigate how changing the electronic properties of the phenylboronic acid coupling partner affects catalytic reaction outcomes. To do this, the performance of three model Pd-PPh₃-containing catalyst systems were tested in six different SMCC reactions at **30**, in each reaction the electronics of the *para*-(Z)-substituent of the phenylboronic acid was incrementally varied under *standard conditions*. The pre-catalyst systems examined under *standard conditions* at **30** were [Pd⁰₂(dba)₃·CHCl₃]/2PPh₃: a benchmark active C2-selective catalytic system which was tested against the C4-selective systems: [Pd₃(μ-Cl)(μ-PPh₂)₂(PPh₃)₃]⁺Cl⁻ (**Pd₃Cl·Cl**) and [Pd₃(OAc)₆]/3PPh₃. Hence, with each pre-catalytic system, the electronic effect of the *para*-substituted phenylboronic acids **74_{A-F}** on SMCC performance could be assessed (Scheme 78-Scheme 80). In each series of *para*-substituted boronic acids investigated, *standard* SMCC conditions were used and the Pd loading was kept constant (3 mol%) for each catalyst system used.

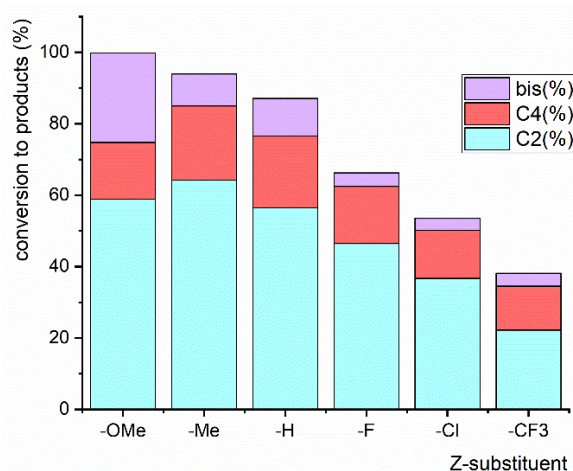
The setup for the [Pd⁰₂(dba)₃·CHCl₃]/2PPh₃-catalysed reaction series, which investigated *para*-substituent effects of phenylboronic acids under *standard conditions* is shown below (Scheme 78). The [Pd₂(dba)₃·CHCl₃]/2PPh₃ to Pd:PPh₃ ratio was selected as a benchmark C2-selective system, as it showed better conversion and a higher C2/C4 selectivity at **30** (than with *e.g.* [Pd₂(dba)₃·CHCl₃]/4

PPh₃, or with [Pd(PPh₃)₄] **65**) when using *para*-anisyl boronic acid **74_A** as the coupling partner at **30** under *standard conditions* (Table 5, Section 4.2.1)

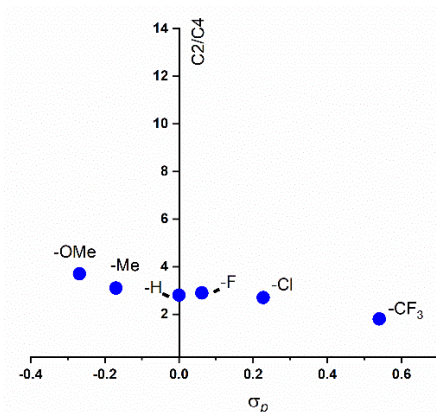


Scheme 78 Conditions employed for the [Pd₂(dba)₃·CHCl₃]/2 PPh₃-catalysed SMCC between 2,4-dibromopyridine **30** and *Z*-substituted phenylboronic acids **74_{A-F}**.

Results, obtained *via* ¹H NMR spectroscopic analysis of the crude reaction product, detailing the observed product distribution of C2-, C4- and bis-arylated product varied with the *Z*-substituent of the phenylboronic acid employed are presented in a column graph (Graph 17). A scatter plot showing general trend of how C2/C4 site-selectivity varied with σ_p -Hammett parameter, a measure of electron donor/withdrawal ability of each *Z*-substituent, is additionally shown (Graph 18).



Graph 17 Showing C2-, C4, and bis-arylated product distributions, adding up to the total reaction conversion in the reaction series investigating phenylboronic acid *para*-substituent effects on the SMCC reaction at **30**, catalysed by [Pd₂(dba)₃·CHCl₃]/2PPh₃].

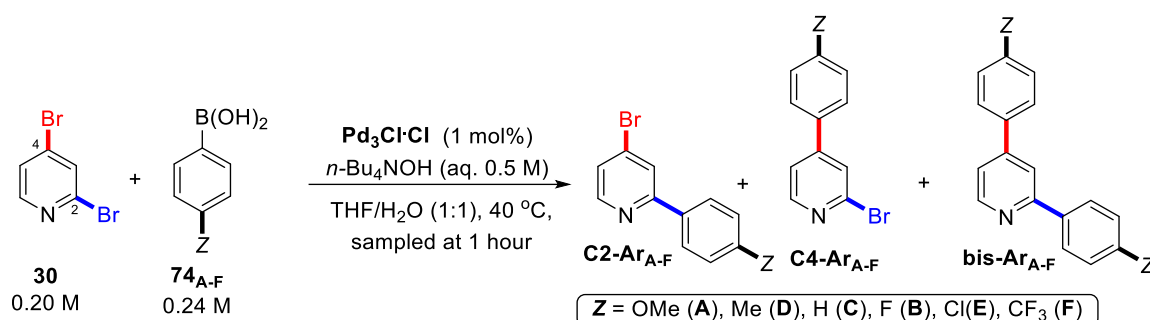


Graph 18 Showing how C2/C4 site-selectivity varies with σ_p -value effects from the boronic acid substrate in the SMCC reaction at **30** catalysed by [Pd₂(dba)₃·CHCl₃]/2PPh₃].

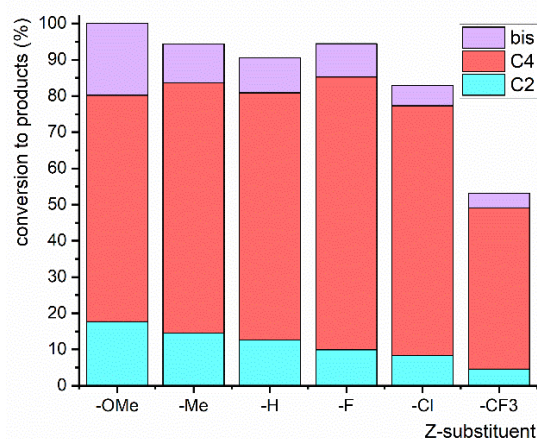
It can be seen that all reactions in this series showed overall C2 site-selectivity, forming C4 and bis-arylated products as side-products. *Para*-substituted phenylboronic acid substrates featuring electron-releasing or electron-withdrawing substituents were all able to convert **30** to products within the 1-

hour reaction time, however electron-withdrawing phenylboronic acids showed reduced reactivity, as exemplified by lower conversions, within the 1-hour reaction time. Notably, the preference for the C2-position is reduced as more electron-withdrawing substituents are employed. Under the C2-selective conditions reported by Cid *et al.*, electron-withdrawing phenylboronic acids were unable to be coupled at **30**,¹⁹³ indicating that the above conditions are superior in terms of boronic acid substrate scope.

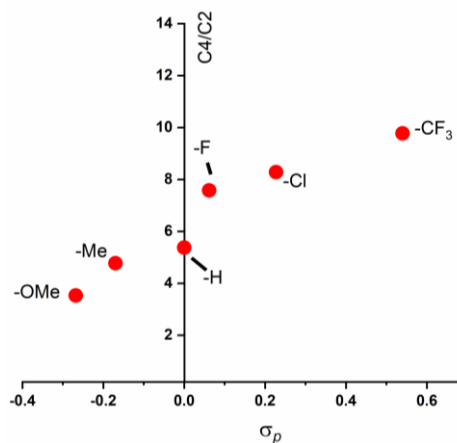
Employing **Pd₃Cl₂Cl** as a pre-catalyst for SMCC for the same series of *para*-substituted phenylboronic acids with **30** (Scheme 79) afforded the **C4-Ar** product as the major product in all cases, with **C2-Ar** and **bis-Ar** products present in the crude reaction product after 1 hour (Graph 19).



Scheme 79 Conditions employed for the Pd₃Cl₂Cl-catalysed SMCC reactions between **30** and Z-substituted phenylboronic acids **74_{A-F}**.



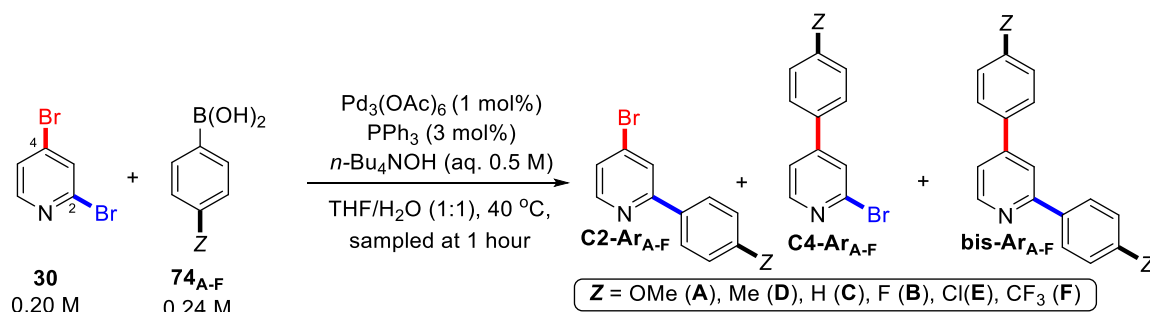
Graph 19 Showing C2-, C4, and bis-arylated product distributions, adding up to the total reaction conversion in the reaction series investigating phenylboronic *para*-substituent effects on the SMCC reaction at **30**, catalysed by Pd₃Cl₂Cl.



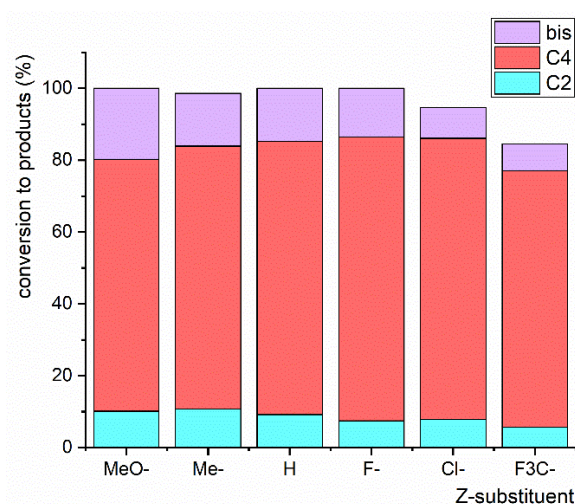
Graph 20 Showing how C2/C4 site-selectivity varies with σ_p -value effects from the phenylboronic acid substrate in the SMCC reaction at **30** catalysed by Pd₃Cl₂Cl.

Similarly to [Pd₂(dba)₃·CHCl₃]/2PPh₃, using **Pd₃Cl₂Cl** as the catalyst, the best conversions were recorded with the more electron-donating phenylboronic acids, however, in this case, overall preference for the C4-position was observed, which was enhanced as a function of the increased

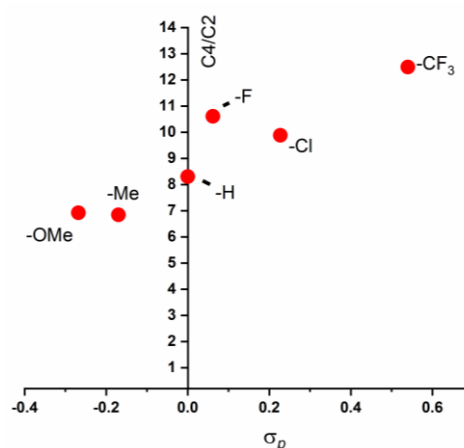
electron-withdrawing character (σ_p) of each para-substituted phenylboronic acid. Analogous, but more marked effects as with **Pd₃Cl₂Cl** were observed with the [Pd₃(OAc)₆]/3PPh₃ pre-catalytic system (Scheme 80).



Scheme 80 Conditions employed for the [Pd₃(OAc)₆]/3PPh₃ -catalysed SMCC between **30** and **Z**-substituted phenylboronic acids **74_{A-F}**.



Graph 21 Showing C2-, C4, and bis-arylated product distributions, adding up to the total reaction conversion in the reaction series investigating phenylboronic acid para-substituent effects in the SMCC reaction at **30**, catalysed by [Pd₃(OAc)₆]/3PPh₃



Graph 22 Showing how C2/C4 site-selectivity varies with σ_p -value effects from the phenylboronic acid substrate in the SMCC reaction at **30**, catalysed by [Pd₃(OAc)₆]/3PPh₃.

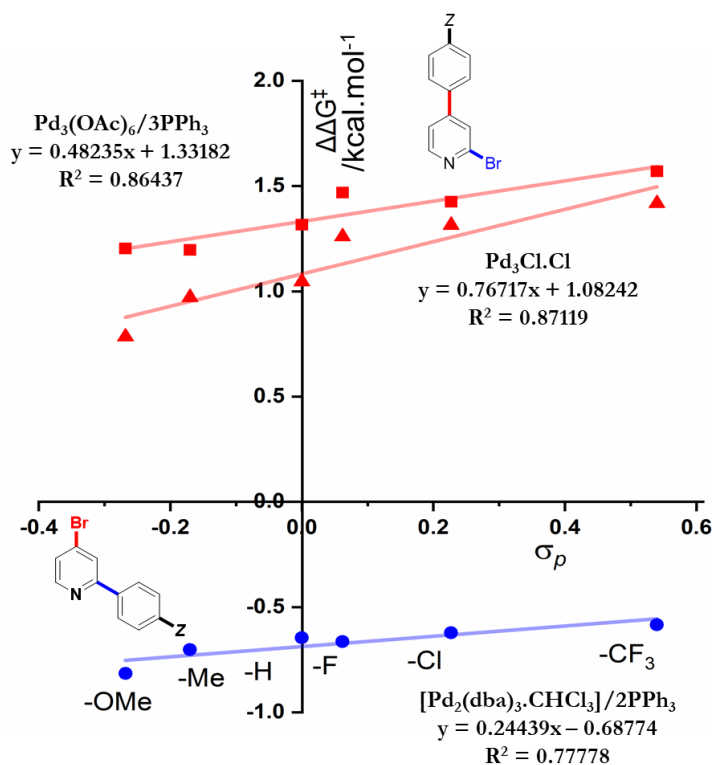
As with **Pd₃Cl₂Cl**, [Pd₃(OAc)₆]/3PPh₃ enabled higher conversion when more electron-releasing *para*-substituents were employed but good conversions of **30** were observed after 1 hour in all cases (Graph 21 & Graph 22). Again, the more electron-withdrawing the substituent, the higher the recorded C4/C2 selectivity. More electron-withdrawing *para*-substituents on the phenylboronic acids resulted in higher overall C4/C2 site-selectivity, in spite of the lower conversions observed. From a synthetic standpoint, in terms of both C4 site-selectivity and conversion of **30**, [Pd₃(OAc)₆]/3PPh₃ performed better than **Pd₃Cl₂Cl**, allowing efficient and selective coupling of an electronically diverse range of phenylboronic acids, forming 2-bromo-4-arylpyridines in good conversions.

According to transition state theory, the product ratio of C4-Ar and C2-Ar is proportional to differences in activation energy ($\Delta\Delta G^\ddagger$) between the competing transition states of the two mono-arylated products (Equation 1).³¹⁸

$$\Delta\Delta G^\ddagger = -RT \ln \frac{n(\text{C4-Ar})}{n(\text{C2-Ar})}$$

Equation 1 The relationship between product selectivity and differences in activation energy ($\Delta\Delta G^\ddagger$) for C4-Ar vs. C2-Ar sites at **30**. R = gas constant, T = reaction temperature (323 K).

Graph 23 shows the $\Delta\Delta G^\ddagger$ (kcal.mol⁻¹), calculated for the C4 and the C2 SMCC products of cross-coupling at **30** under each catalyst manifold as shown above, plotted as a function of the Hammett parameter (σ_p) for each boronic acid *para*-substituent. As expected, a positive linear relationship was evident as a function of σ_p which indicates that site-selectivity is sensitive to the *para*-substituent, which provides stability to small amount of negative charge build-up in the site-selectivity determining step. This plot facilitates comparison of all three tested pre-catalytic manifolds in terms of the $\Delta\Delta G^\ddagger$ and σ_p .



Graph 23 Showing how $\Delta\Delta G^\ddagger$ of the C4-position over the C2-position in SMCC reactions varies with σ_p (electronic parameter for para-substituted boronic acid {74_{A-F}}) with specified pre-catalytic systems. $\Delta\Delta G^\ddagger = 0.001986 \text{ kcal.K}^{-1}.\text{mol}^{-1} \times 315 \text{ K} \times \ln(\text{conversion}\{\text{C4-Ar}\}/\text{conversion}\{\text{C2-Ar}\})$.

The above reactions show a clear effect of each *para*-substituted phenylboronic acid electronics on SMCC reactivity at **30** under the conditions tested. As the Z-substituent in the arylboronic acid is varied, the catalyst used has a marked bearing on the overall site-selectivity outcomes of these reactions. In each case, the more electron withdrawing the substituent, the higher the C4/C2 selectivity and the lower the conversion of **30**. The $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]/2 \text{ PPh}_3$ catalyst system, despite showing overall C2 site-selectivity, showed a loss of selectivity, with higher functionalisation of the C4 position of **30** as the electron-withdrawing nature of the *para*-substituents was increased. This observation may point towards multiple species operating in a single catalytic reaction. Under the reported conditions PdNPs have been associated with C4-selectivity at **30**, in line with that seen with the other two catalyst systems, while homogeneous Pd⁰ monomeric catalysts have been linked to C2-selectivity. $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$ is well known to be a source Pd⁰ monomeric complexes upon exposure to triarylphosphines, but may also act as a source of PdNPs under a variety of condition.^{126, 306, 319} It is thus reasonable to assert that mono-nuclear $[\text{Pd}^0(\eta^2\text{-dba})_3\text{-n}(\text{PPh}_3)_n]$ ($n = 1$ or 2) species may be operating as well as PdNPs, which might show opposing site-selectivity at **30**. Kinetic analysis of the reactions would indicate how the rates of C2 and C4 product formation change over time, and it may be anticipated that PdNPs, which would likely form as the reaction proceeds, concordantly increasing the rate of C4 product later in the reaction. Recharging the reaction with substrates after initial consumption of **30** and assessing the

subsequent site-selectivity could also indicate whether a change in catalytic speciation had occurred over time. Additionally, tracking the evolution of $[\text{Pd}^0_2(\text{dba})_3 \cdot \text{CHCl}_3]/2\text{PPh}_3$ mixtures over time, by ^{31}P NMR analysis (probing degradation of homogenous species) and *e.g.* TEM analysis (probing growth of formed PdNPs) could be used to gauge how speciation changes with the passage of time.

In the conventionally accepted cross-coupling catalytic cycle, oxidative addition occurs first and is usually characterised as being irreversible. Under such a scenario, the site of oxidative addition is the determinant of cross-coupling site-selectivity (See Chapter 1).^{187-188, 195} Assuming reactivity *via* a *conventional* reductive cross-coupling catalytic cycle, in order for the boronic acid substrate to have the observed bearing on site-selectivity during its participation in the transmetalation step, the oxidative addition step must be reversible. Alternatively, if the transmetalation reaction was to occur prior to the oxidative addition step, as had been reported with employing **Pd₃Cl₂Cl** clusters in SMCC applications¹⁷² (see Section 1.4), and the boronic acid substrate reacts first with the cluster, prior to an oxidative addition-type event, a different preference for the site of C–Br bond activation at **30** may prevail. Indeed, arylboronic acids have previously been reported to be activated by PdNP surfaces.³²⁰ The reason, however for the observed effect of phenylboronic acid *para*-substituent effects on site-selectivity, at this stage, has not been delineated, however with better knowledge of precise catalyst identity in the reaction under the reported conditions (as discussed in the Future Work section: 5.2.2), mechanistic reasons for these observations could perhaps be rationalised.

This study has uncovered a rare case where phenylboronic acid *para*-substituents have a bearing on product selectivity in a site-selective SMCC reaction at the dihalogenated heteroarene **30**. Generally, the site-selectivity of a SMCC process is thought to be not dependent on the electronic properties of the arylboronic acid.¹⁸⁸ To the knowledge of the author, such reactivity, as observed, where site-selectivity is dependent on the electronics of the arylboronic acid coupling partner has not been reported. Ultimately, this work has shown that catalyst speciation has a profound role on product selectivity, with *normal* C2-selectivity being associated with monomeric $[\text{Pd}^0(\text{PPh}_3)_n]$ active catalysts and *abnormal* C4-selectivity being associated with higher order Pd aggregates – these species appear to show significant deviations in behaviour from the textbook, monomeric, $[\text{Pd}^0(\text{L})_n]$ -type catalytic species.

4.7. Bringing Together the Results

This chapter has shown that different types of catalytic species can have a marked effect on site-selectivity outcomes in cross-coupling reactions at the dihalogenated heteroaromatic compound 2,4-dibromopyridine **30**. Employing $[\text{Pd}^0_2(\text{dba})_3 \cdot \text{CHCl}_3]/2$ or 4 equivalents PPh_3 of $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** as pre-catalysts resulted in *normal* C2 site-selectivity in SMCCs at **30** under selected conditions. When employing 'Pd(OAc)₂' / $n\text{PPh}_3$ -type catalytic systems, derived from $[\text{Pd}_3(\text{OAc})_6]$ or *trans*- $[\text{Pd}(\text{OAc})_2(\text{N-piperidyl})_2]$, when 'Pd(OAc)₂' / 1 or 2 PPh_3 is employed the Pd^{II} is activated forming particles which can be stabilised by the additive quaternary ammonium salt. When higher amounts of PPh_3/Pd are introduced: $\text{Pd}(\text{OAc})_2 / \geq 3 \text{ PPh}_3$, the stabilised Pd^0 complex: $[\text{Pd}^0(\text{L})_n]$ (where $\text{L} = \text{OAc}, \text{PPh}_3$) can form which are stabilised and selectively activate the C2-position of **30**, consequently exhibit C2-selectivity as a catalyst in cross-coupling at this substrate (Sections 2.2, 2.3, 4.2 & 4.2.1).^{46-47, 193, 200} Notably, under otherwise identical conditions, employing different pre-catalytic $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ ratios resulted in vastly different SMCC site-selectivities, with 1:1 or 1:2 (Pd:P) ratios selecting for the *abnormal* C4 site at **30**. By performing appropriate control experiments, it was found that the $n\text{-Bu}_4\text{N}^+$ cation of the $n\text{-Bu}_4\text{N}^+\text{X}^-$ base/additive ($\text{X} = \text{Br}^-/\text{-OH}$), in concert with the Pd:P ratio was responsible for the in the *abnormal* C4 selectivity in SMCC/Kumada cross-couplings at **30**.

Under both Suzuki- and Kumada cross-coupling conditions tested, in the presence of bulky, soluble quaternary ammonium salts ($n\text{-alkyl}_4\text{NBr}$), *abnormal*, C4-selectivity and high activity at **30** can be achieved. The work presented in Chapter 2 showed that mixing $[\text{Pd}_3(\text{OAc})_6]$ in the presence of 3 equivalents of PPh_3 (Pd:P = 1:1) results in the formation of Pd particles as analysed by TEM analysis. If the SMCC reactions are carried out in absence of $n\text{-alkyl}_4\text{NX}$ ($\text{X} = \text{Br}^-$ or -OH), the *abnormal* C4 selectivity is lost. Pd nanoparticles are generally accepted to either act as surface catalysts in their own right, or as reservoirs for leached active species, which may act as true catalysts (Section 1.3.1). If these findings are to be combined, it points towards a particulate Pd active species, the reactivity of which being strongly influenced by the presence of the quaternary ammonium salt.

The presence of quaternary ammonium salts under working catalytic conditions has been shown in the literature to influence the reactivity of such catalytically relevant Pd nanoparticles (Section 1.3.2.2). There is a wealth of literature that explores the stabilisation and enhancement of reactivity by additive salts. Finke *et al.* defined that the electropositive outer surface of a nanoparticle can be stabilised through ligation by anions,¹²¹ which, in turn, are stabilised transiently by coordination with cations, in a situation analogous to an the electrical double layer.¹²² Dupont and co-workers reported that *in situ* reduction (activation) of palladacyclic precursor complexes in the presence of an imidazolium-based ionic liquid (BMI.PF_6) led to the formation of Pd^0 which were seen to aggregate to small PdNPs active in the Mizoroki-Heck alkenylation.¹⁰⁶ Astruc *et al.* explored the stabilisation of catalytic Pd

nanoparticles by design of elaborate supramolecular structures called dendrimers which could be cationic in nature. Such salts are hypothesised to stabilise *via* an *electrosteric stabilisation* regime.^{8, 131}

Thus, a reasonable hypothesis for the observed *abnormal* reactivity observed is that a PdNP active, catalyst, generated from $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ or $\text{Pd}_3\text{Cl}\cdot\text{Cl}$, is stabilised electrosterically by an *n*-alkyl₄NBr salt, under working cross-coupling conditions (Figure 83). Alternatively, the stabilised PdNP could act as a catalytically relevant reservoir for, a highly active homogeneous species, able to activate the challenging C4–Br site of **30**.

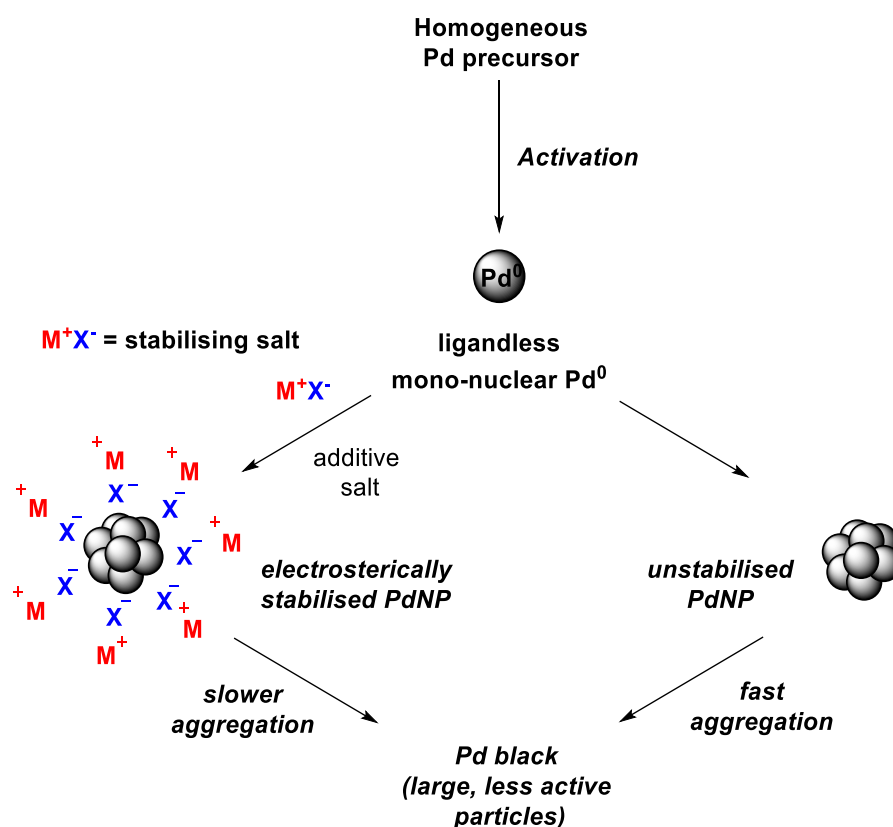


Figure 83 Hypothesised formation and subsequent *electrosteric stabilisation* by additive salt of the outer surface of a PdNP generated from $\text{Pd}_3(\text{OAc})_6$ after activation by 3 PPh_3 .

The novel **TrisImid·3Br** compound was designed to be able to *electrosterically* stabilise catalytic Pd-nanoparticles by introducing and allowing coordination an inner-layer of bromide anions with three cations, through a cooperative chelate-type effect. Such effects were envisioned to stabilise an active PdNP species better than mono-nuclear quaternary ammonium salts, which would be more transiently bound. Indeed, deploying **TrisImid·3Br** in the model SMCC at **30** resulted in almost exclusive cross-coupling at its C4 position. Thus, the compound was expected to have improved on the PdNP stabilising/activating ability of *n*-R₄NX (X = –OH or Br[–]), through the dual properties of being both bulky and able to stabilise the Pd-nanoparticle architecture in three positions (Figure 84).

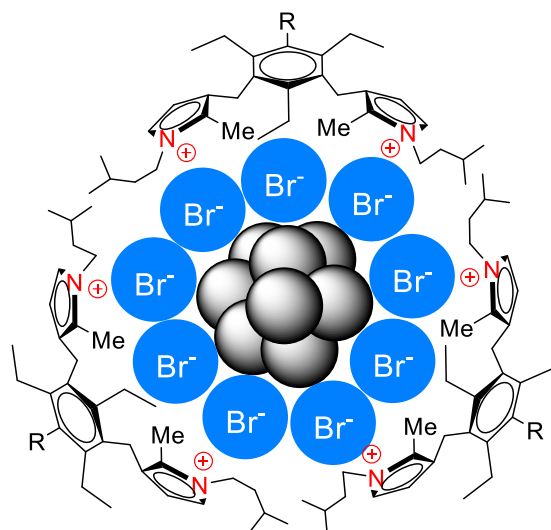


Figure 84 Showing how two arms of tris-imidazolium outer-shell of TrisImid.Br might interact with a bromide inner-shell of a Pd nanoparticle, exhibiting the ability to stabilise the nanoparticle electrosterically R = the third imidazolium arm of the molecule, omitted for clarity.

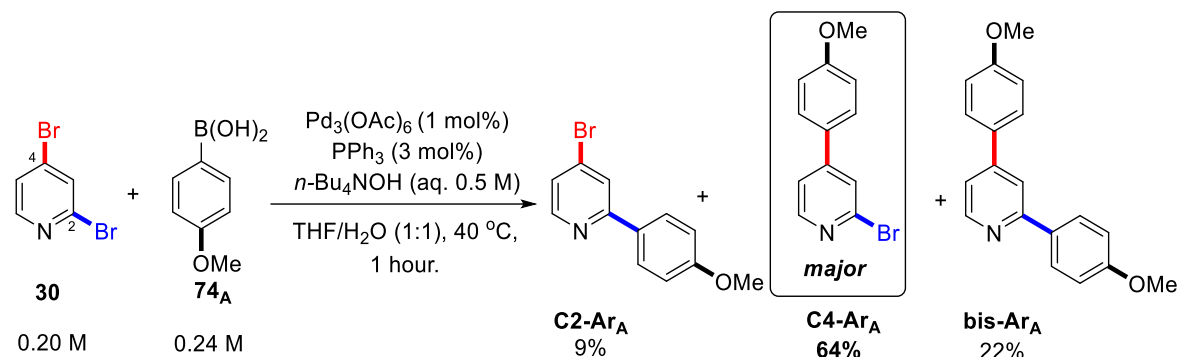
The Future Work section discusses experiments designed to confirm the electrosteric hypothesis of catalyst activity as highlighted in this section. Further work would probe further structural aspects of this hypothesis and explore ideas which may further boost the reactivity of such a catalyst system, *e.g.*, the screening of variable anionic components of additive salts in an effort to boost catalyst activity and selectivity (see Section 5.2.3).

4.8. Application of Site-control for the Benefit of Chemical Synthesis

Control of site-selectivity at dihalogenated heteroaromatic compounds has potential applications in agrochemical/pharmaceutical discovery and process chemistry. It was highlighted in Chapter 1 that site-selectivity: chemoselectivity, and, less often, regioselectivity can be controlled by optimising catalyst systems. For example, by employing highly engineered phosphine ligand/catalyst combinations that enhance the selectivity for one site over another (Section 1.5). This work shows that using simple, ubiquitous $[\text{Pd}_3(\text{OAc})_6]$ in concert with the one of the cheapest and most widely available tertiary phosphines, PPh_3 , along with tuning wider catalytic conditions, desired site-selectivity can, in principle, be optimised for a given site. This finding underlines the need for further understanding of what mechanistic factors can control catalyst speciation so that, from the simplest catalyst precursors, a broad diversity of powerful reactivity can be accessed.

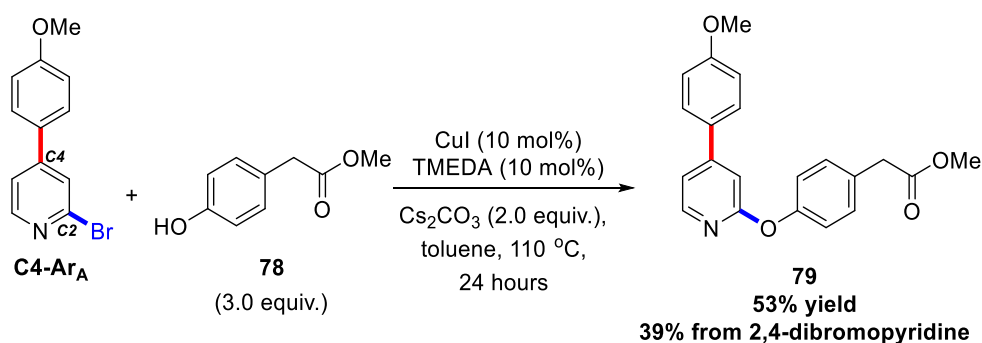
One application of the optimised catalyst conditions, as delineated *vide supra*, is for the rapid diversification of structures for small molecule discovery. For example, using the *standard conditions* for

SMCC reactions at 2,4-dibromopyridine **30**, selection for the C4-product 2-bromo,4(*para*-anisyl)pyridine (**C4-Ar_A**) is possible, which could be isolated in a 64% yield, after column chromatography (Scheme 81).



Scheme 81 Conditions used for the C4-site-selective SMCC at 2,4-dibromopyridine. Yields of isolated product are shown.

The above SMCC reaction constitutes the first time that **C4-Ar_A** has been made in one step from **30** in a good yield. This product could now be used for further diversification, by reaction at the C2–Br site, as a whole host of potential chemical reactions could be performed at this site, allowing for the exploration of further new chemical space. One example of which is the Ullman-type etherification reaction allowing access to the novel compound **79** (Scheme 82, Ullman conditions were adapted from a method published by Zhou *et al.*).³⁰⁰



Scheme 82 Conditions and reagents used for the Ullman coupling reaction between 2-bromo, 4-(*para*-anisyl)pyridine and methyl hydroxyphenylacetate.

This is an example of a novel compound that has been created through exploitation of knowledge of factors that control site-selectivity in cross-coupling. This study has also shown that using the presented conditions, both electron-rich and electron-poor arylboronic acids can be coupled selectively at **30** (Section 4.6), allowing access to previously undiscovered 2-bromo,4-arylpyridines potentially opening the door for efficient further diversification of the simple ‘2-bromo, 4-arylpyridyl’ motif.

4.9. Concluding Remarks

In conclusion, control of site-selectivity at 2,4-dibromopyridine **30** has been facilitated by investigating Pd catalytic speciation events and interactions between catalysts and additives present under cross-coupling conditions. Indeed, **30**, has been used as a tool to probe differences in mechanism arising from differing pre-catalytic sources.

Crucially, this work has identified two sets of optimised conditions for efficient site-control of SMCC reactions at **30**, allowing access to mono-arylated products in cross-couplings of **30** at the site of choice. Employing a simple $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ pre-catalytic mixture, under the conditions provided efficient access to 2-bromo-4-arylpyridine compounds by C4-selective cross-coupling at **30**. This C4 site-selectivity could be boosted by employing the novel **TrisImid.3Br** salt as an additive. On the other hand, using $[\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3]/2\text{PPh}_3$ as a pre-catalyst, gave predominant access to a wide variety of 4-bromo-2-arylpyridine products under otherwise identical conditions. Both methods employed either *n*-Bu₄NOH(aq.) or *n*-Bu₄NBr/KOH(aq.) as the base system: an improvement, in terms of individual and environmental safety, on the previously published methodology for the C2-selective arylation functionalisation of **30**,¹⁹³ which employed highly toxic TIOH(aq.).³⁰³

Employing $[\text{Pd}_3(\text{OAc})_6]$, a synergistic combination of $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ ratio ($3 \leq n \leq 6$) and the presence of an N-alkyl-quaternarised organic salt proved to be key for *abnormal* C4-selectivity observed in SMCC and Kumada cross-coupling reactions. These findings prove that there is scope for seriously modulating the activity and selectivity of seemingly straightforward, relatively cheap, catalyst systems generated *in situ* from pre-catalytic mixtures such as $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$, by informed choice of appropriate salt additives. Such command of control of site-selectivity in cross-coupling reactions at multiply halogenated (hetero)aromatics would be of key utility in the synthetic chemist's toolkit for both small molecule discovery and the streamlining of chemical processes (See Future Work, Section 5.2.3 for a discussion on how catalyst activity could be controlled by salt additives).

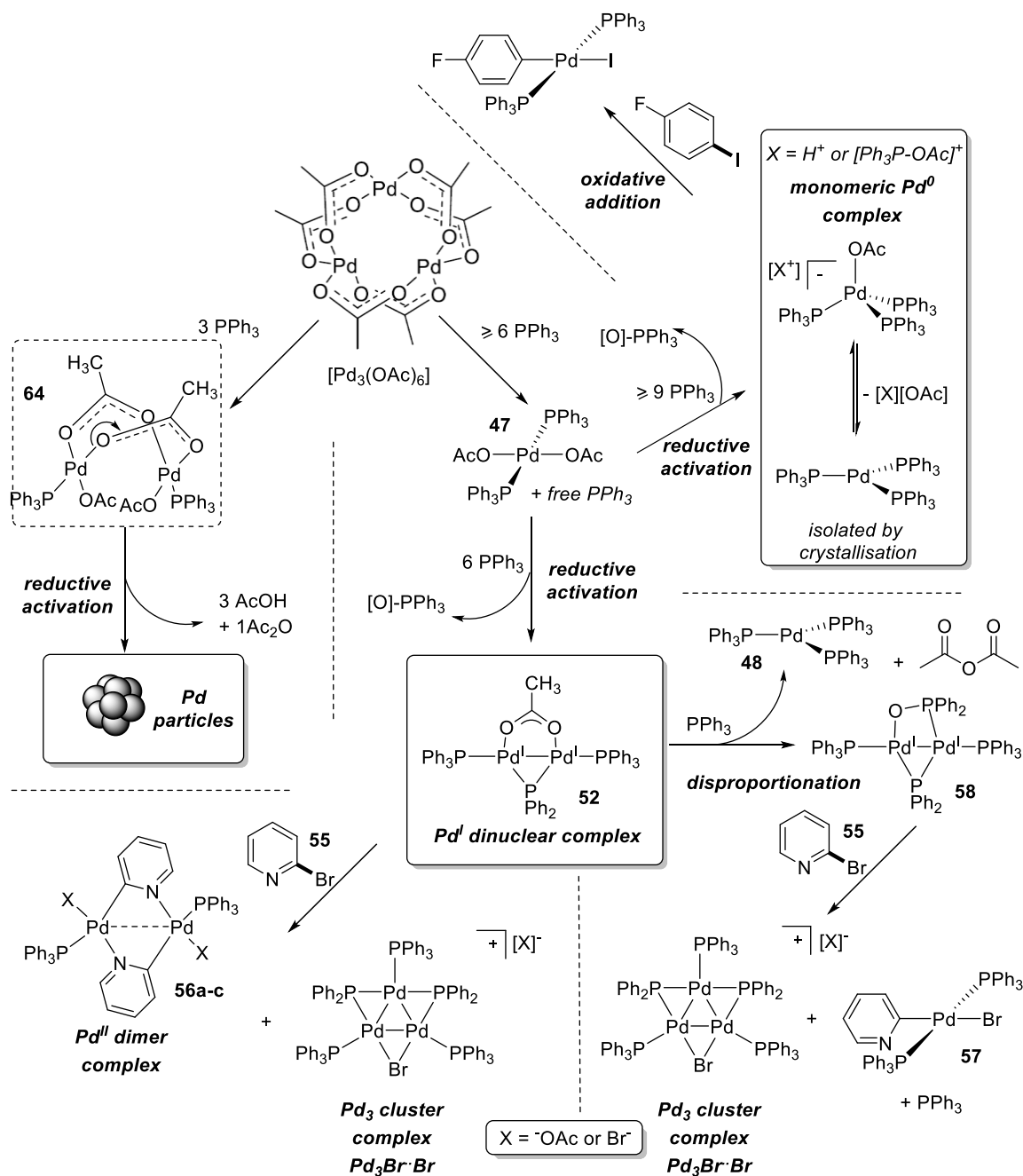
Chapter 5 – Conclusions & Future Work

5.1. Conclusions

The work reported within this Thesis has described the behaviour of the formation as well as the stoichiometric and catalytic reactivity of activated species arising from mixing simple 'Pd(OAc)₂' and PPh₃ in different ratios. Stark differences have been discovered between the stoichiometric and catalytic reactivity of known higher order Pd cluster species versus that of Pd⁰ monomeric species.

It has been established that when [Pd₃(OAc)₆] is treated with ≥ 9 equivalents of PPh₃ in THF, stabilised [Pd⁰(OAc)(PPh₃)_n]⁻ complexes form, from which the complex [Pd⁰(PPh₃)₃] **48** could be isolated (Scheme 83).^{46-48, 200} For the first time, a crucial role for H₂O in the reduction and catalytic activation of [Pd₃(OAc)₆] by PPh₃ has been revealed. Stoichiometric reactions showed [Pd⁰(PPh₃)₄] **65**, which behaves analogously with [Pd⁰(OAc)(PPh₃)_n]⁻,²⁰⁰ to be able to selectively oxidatively add to the C2 position of 2,4-dibromopyridine **30**, indicating that this step is responsible for the observed C2 selectivity when using [Pd⁰(PPh₃)_n] or [Pd₃(OAc)₆]/ ≥ 9 PPh₃ as (pre-)catalysts for cross-coupling.¹⁹³

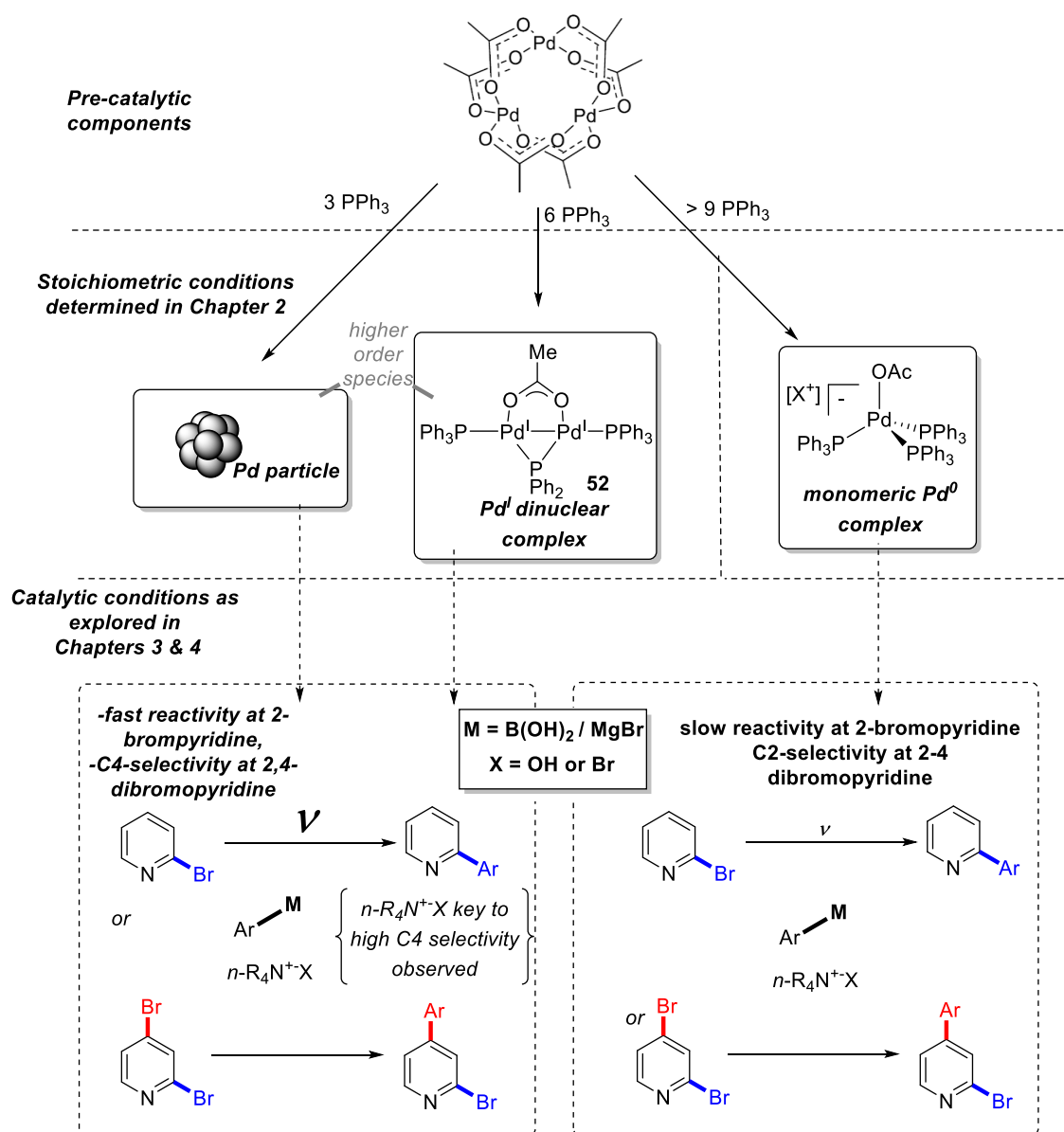
It was revealed that reacting [Pd₃(OAc)₆] with exactly 6 equivalents of PPh₃, in THF, afforded the dinuclear complex [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52** (Scheme 83) which was able to activate organohalides (electrophiles) *e.g.* 2-bromopyridine (**55**) at room temperature to yield tripalladium cluster complexes of the form [Pd₃(μ-X)(μ-PPh₂)(PPh₃)₃] (**Pd₃X·X**) and the Pd dimer complexes *trans*-(P,N)-[Pd(X)(μ-*pyridyl*-C², N)(PPh₃)₂]: **56a**, **56b** and **56c** (where X = combinations of ·Br or ·OAc). Upon addition of further PPh₃ (2 equivalents) to **52** the Pd^I-Pd^I dimer was cleaved in a facile manner, at room temperature, rapidly forming another novel Pd^I dinuclear complex [Pd₂(μ-PPh₂){κ²-P,O-μ-P(O)Ph₂}(κ-PPh₃)₂] **58** and [Pd⁰(PPh₃)₃] **48**. **58** was found to contain a rare bridging μ₂-P,O diphenylphosphinito ligand, formed by oxidation of a diphenylphosphido ligand by acetate, which bridged the Pd^I-Pd^I dimer. On exposure of the post-reaction system containing **58** and **48** to the heteroaryl halide compound **55**, **58** formed a cluster complex of the form **Pd₃Br·X**, while the monomeric Pd⁰ complex **48** oxidatively adds into the C-Br bond yielding *trans*-[Pd(Br)(C²-pyridyl)(PPh₃)₂] **57** which was seen to spontaneously convert under the conditions to *trans*-(P,N)-[PdBr(μ-*pyridyl*-C², N)(PPh₃)₂] **56c**, releasing PPh₃. When treating [Pd₃(OAc)₆] with 3 equivalents of PPh₃, in THF at room temperature, an unstable diacetate-bridged Pd^{II} complex: [Pd^{II}(μ₂-OAc)(κ-OAc)(PPh₃)₂] **64** was immediately formed, which ultimately decomposed, providing a pathway to Pd nanoparticles, with release of AcOH and Ac₂O during the process.



Scheme 83 A summary of the major findings in this work concerning the formation and reactivity of major activated Pd species arising from $[Pd_3(OAc)_6]/n PPh_3$ mixtures in THF.

When employed as a pre-catalytic system in a model SMCC reaction at 2-bromopyridine **55**, $[Pd_3(OAc)_6]/6 PPh_3$, **52** and $Pd_3X \cdot X$ ($X = Cl, Br$) demonstrated comparable catalytic, markedly outperforming pre-catalytic mixtures of $[Pd_3(OAc)_6]/9$ or $12 PPh_3$ ($Pd:P = 1:3$ or $1:4$), under like conditions, as summarised in Scheme 84. Similar trends in catalytic efficacy as a function of $[Pd_3(OAc)_6]/n PPh_3$ ratio was observed in a more synthetically challenging, pharmaceutically relevant SMCC reaction between a bromoindazole **70** and 6-quinoline-boronic acid **71**.

Notably, the $[\text{Pd}_3(\text{OAc})_6]/6 \text{ PPh}_3$ ($\text{Pd}:\text{P} = 1:2$) catalyst system, as well as $\text{Pd}_3\text{Cl}\cdot\text{Cl}$, were shown to exhibit *abnormal* C4-selectivity in model SMCC reactions at the dihalogenated heteroaromatic substrate **30**, contrasting with $[\text{Pd}_3(\text{OAc})_6]/\geq 9 \text{ PPh}_3$ ($\text{Pd}:\text{P} = 1:\geq 3$), $[\text{Pd}^0(\text{PPh}_3)_4]$ **65** catalytic systems which demonstrated *normal* C2-selectivity (Scheme 84) under the same conditions. Optimal site-selectivity at **30** could be realised by employing $[\text{Pd}_3(\text{OAc})_6]/3 \text{ PPh}_3$ ($\text{Pd}:\text{P} = 1:1$) as a catalyst system, implicating a particulate Pd species as being responsible for the *abnormal* C4 site-selectivity observed under the SMCC conditions. Taken together, these results indicate that different catalyst reactivities can be realised from simple changes to $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ ratios, one of the simplest and cheapest Pd pre-catalyst/ligand combinations. Through understanding of how differing catalyst speciation occurs under different $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ regimes, optimal reactivity and site-selectivity could be achieved in under model cross-coupling conditions at **30**.



Scheme 84 Summary of main findings concerning active speciation and resulting catalytic activity from $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ mixtures.

A synergistic combination of $[\text{Pd}_3(\text{OAc})_6]/n\text{PPh}_3$ ratio and additive salt ($n\text{-Bu}_4\text{NOH}/n\text{-Bu}_4\text{NOH}/\text{TrisImid}\cdot\mathbf{3Br}$) was found to be key for both selectivity and activity under SMCC and Kumada reaction conditions. A bespoke *tris*-imidazolium bromide salt **TrisImid·3Br** was hence fruitfully deployed to enhance SMCC site-selectivity, enabling a record high C4-selectivity at **30**. The success of the application of this salt underlines the scope for design of salts for boosting catalyst efficacy.

Para-substituent effects of different phenylboronic acids on site-selectivity at **30** were examined under three different catalytic systems: $[\text{Pd}^0_2(\text{dba})_3\cdot\text{CHCl}_3]/2 \text{ PPh}_3$ (showing C2-selectivity), $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ and **Pd₃Cl·Cl** (showing C4-selectivity) under model SMCC conditions. These experiments demonstrated the synthetic utility of the conditions used, allowing efficient synthesis of compounds which previously couldn't be accessed by SMCC chemistry. Under each catalytic system, the sensitivity of site-selectivity and product conversion to the electronics of phenylboronic the *para*-substituent was observed which indicated that aryl-group transmetalation is crucial to determining site-selectivity under the catalytic conditions.

The above findings have significant implications in understanding control in catalytic processes. This work shows that different types of catalytic species can result in significantly different cross-coupling outcomes. When employing $\text{Pd}(\text{OAc})_2/n\text{PR}_3$ as catalytic systems, the active catalyst is usually accepted to be a $[\text{Pd}^0(\text{L})_n]$ species. Indeed $[\text{Pd}^0(\text{L})_n]$ is often modelled computationally to post-rationalise reaction outcomes, however *this work* has shown that, with $\text{Pd}(\text{OAc})_2/n\text{PPh}_3$ mixtures, such a mono-ligated species only forms, when $\geq 9 \text{ PPh}_3$ is used. In an example highlighted in Chapter 1, Fu *et al.* reported that pre-catalytic $\text{Pd}(\text{OAc})_2/1.2 \text{ PCy}_3$, resulted in good C–OTf site-selectivity, over C–Cl in SMCC reactions.¹⁹⁷ Houk and Schoenebeck later rationalised that this selectivity stems from oxidative addition into the C–OTf by the bis-ligated $[\text{Pd}^0(\text{PCy}_3)_2]$, which was modelled computationally as the species responsible for substrate activation.^{159, 195, 199} *This work* calls into question, however, whether bis-ligated $[\text{Pd}^0(\text{PCy}_3)_2]$ can arise from, mixtures of $\text{Pd}(\text{OAc})_2$ and 1.2 PCy_3 , and points toward this pre-catalytic mixture forming higher order Pd species. Thus, it is likely that the precise species that mediates catalytic transformations may not in all cases have been correctly modelled, and that in some cases higher order species such as Pd clusters and PdNPs may be acting by a significantly different mechanism (see Sections 1.3 & 1.4). Although the species that was modelled allowed for arrival at the correct answer in the above case, such a mono-nuclear species will undoubtedly fail as a model in some cases, particularly in more complicated reaction systems; for example, where more subtle differences in $\Delta G^\ddagger$ are present at competing sites of bond activation. This work underlines the importance of understanding and modelling the correct catalytic species for full and precise understanding of catalytic processes.

5.2. Future Work

5.2.1. Understanding of Catalytic Speciation Events Involving Other Widely Used Catalyst Precursors

In this work, a trend was observed with emergent active Pd speciation as a function of Pd:P ratio with $[\text{Pd}_3(\text{OAc})_6]/\text{nPPh}_3$ mixtures. Broadly speaking, the lower the quantity of PPh_3 ligand available, the less protected the activated Pd, which led to the formation of higher order Pd species, as exemplified by the fact that a dimer forms when $\text{Pd:P} = 1:2$ and particles are formed when $\text{Pd:P} = 1:1$. The observations that different Pd:L ratios result in the evolution of different types of species is most likely not limited to $[\text{Pd}(\text{OAc})_2]/\text{nPPh}_3$ pre-catalytic systems. Future work could determine the generality of this observation with other commonly deployed $\text{Pd}^{\text{II}}/\text{L}$ pre-catalytic systems, in order to better understand speciation events which might, in turn open the door to better control of cross-coupling reactivity and product selectivity. Very little detail is known about the analogous catalytic activation and speciation of other ubiquitous Pd-catalyst sources, and a catch-all $[\text{Pd}^0(\text{L})_n]$ -type species is typically invoked in discussions of the vast majority of catalytic mechanisms.

One pre-catalytic system, which may be a natural progression from $[\text{Pd}_3(\text{OAc})_6]$ (studied extensively in this work) is $[\text{Pd}(\text{NO}_3)_2]$. There is early literature evidence that, analogously with $[\text{Pd}_3(\text{OAc})_6]$ activation by PAr_3 , Pd^0 complexes can be generated by reduction of $[\text{Pd}(\text{NO}_3)_2]$ by PPh_3 .³²¹ No subsequent work has been carried out on *in situ* active catalyst evolution from $[\text{Pd}(\text{NO}_3)_2]$ in the presence of organophosphine and indeed $[\text{Pd}(\text{NO}_3)_2]$ is only rarely used as a pre-catalyst for cross-coupling applications. An example of a hypothetical outcome of such a study, extrapolated from the findings presented in *this work* is shown in Figure 85. A benefit of being able to generate useful catalysts *in situ* directly from $[\text{Pd}(\text{NO}_3)_2]$, is that it could cut out the need for the problematic synthesis of the ubiquitous $[\text{Pd}_3(\text{OAc})_6]$ which is normally realised by reaction of $[\text{Pd}(\text{NO}_3)_2]$ in the presence of excess AcOH .^{54, 214, 292} The known dynamic redox chemistry of NO_x ligands may have to be taken into account if $[\text{Pd}(\text{NO}_3)_2]/\text{nPAr}_3$ reactivity is to be exploited as a pre-catalytic entity for applications in classic cross-coupling or C–H bond activation/functionalisation chemistry.³²²⁻³²³

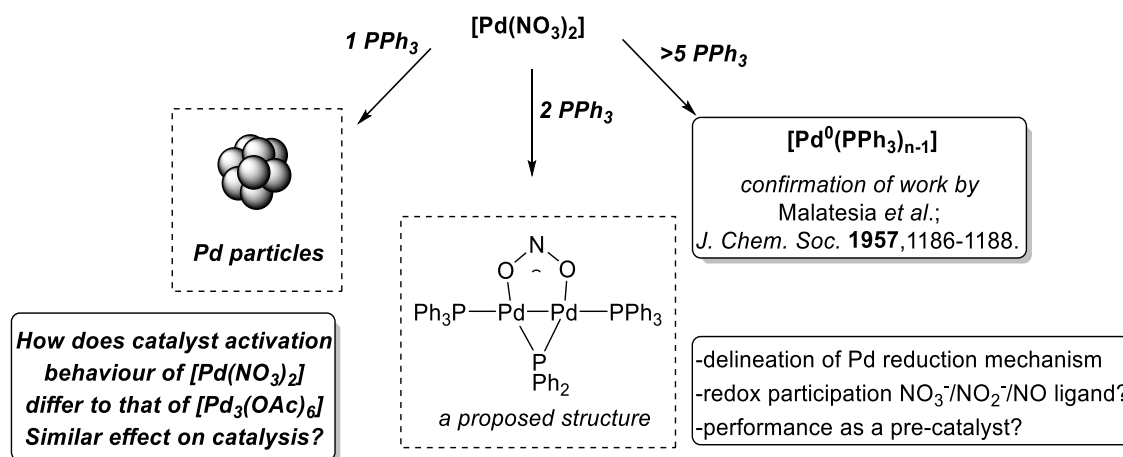


Figure 85 A schematic showing how the emergent speciation upon reaction of $[\text{Pd}(\text{NO}_3)_2]$ with varying quantities of PPh_3 might evolve. $[\text{Pd}(\text{NO}_3)_2]$ is a simple, relatively inexpensive salt and a precursor for $[\text{Pd}_3(\text{OAc})_6]$.

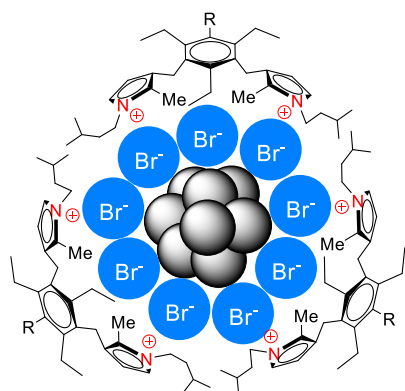
Like $[\text{Pd}_3(\text{OAc})_6]/\geq 12 \text{ PPh}_3$, the $[\text{PdCl}_2(\text{PPh}_3)_2]$ has been demonstrated to form the mononuclear complex $[\text{Pd}^0(\text{PPh}_3)_3]$ in the presence of excess PPh_3 , H_2O and a tertiary amine base (See Section 1.2.2 for further details).⁵² In a study into $[\text{PdCl}_2(\text{PPh}_3)_2]$ activation by Jutand *et al.*, 3 equivalents of PPh_3 were purposely added to stabilise Pd^0 formed *in situ*, thus preventing formation of the actual species which would form under cross-coupling conditions. The question therefore still remains as to what type of species arises from $[\text{PdCl}_2(\text{PPh}_3)_2]$ in absence of additive PPh_3 , under working catalytic conditions. $[\text{PdCl}_2(\text{PPh}_3)_2]$ has seen great success in application as a pre-catalyst in Sonogashira cross-coupling reactions of terminal alkynes with aryl halides, which commonly feature an excess of a Cu^{I} salt additive to enable transmetalation of the alkynyl cross-coupling partner.³²⁴ In absence of any other stabilisation agents, under Sonogashira conditions, putative, elementary, reduced $[\text{X}]^{+/-}[\text{Pd}^0\text{Cl}(\text{PPh}_3)_1]$ species (formed by reduction at Pd, with concomitant oxidation of PPh_3) may achieve some stabilisation by reaction with CuX salts, which are present in relative excess, perhaps leading to a catalytic role for heterometallic Pd–Cu clusters.^{325–326} Another pre-catalyst system where active speciation could be further explored is *trans*- $[\text{PdBr}(\text{N-succinimidyl})(\text{PPh}_3)_2]$,³²⁷ which has recently demonstrated the ability to act as a dual π -acid/cross-coupling catalyst in a one pot spirocyclisation/Heck cross-coupling reaction.³²⁸ In this case, the influence of the succinimidyl anion could be contrasted as a highly electron-poor surrogate for acetate (as studied in *this work*) on the redox activation of Pd^{II} in the presence of PPh_3 . Analogous work to this work could be carried out, investigating the mode of activation and the catalyst speciation of the NHC-ligated PEPPSI pre-catalyst. This could be of particular interest in light of finding by Glorius *et al.* of the powerful role of NHCs in the catalytic activation of Pd surfaces for challenging cross-coupling applications.¹¹⁸ For example, putative $[\text{Pd}^0(\text{NHC})]$ complexes which are thought to derive from PEPPSI-pre-catalysts have not been very well characterised.^{329–330} With an approach based on methods deployed in this work,

similar close analysis of activated PEPPSI systems may yield information as to the true speciation arising from such an extremely electron rich and sterically protecting carbene ligand.

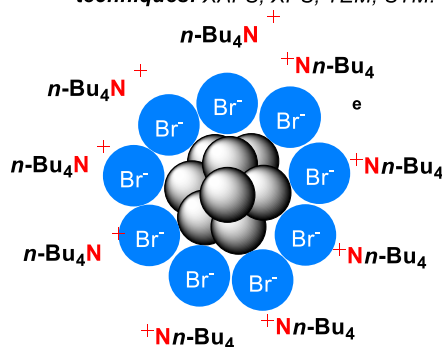
In analogy to the findings presented in this Thesis such knowledge of speciation arising from the above examples could be exploited to get a more precise idea of the nature of the catalyst during cross-coupling turnover, with an ultimate goal of being able to fine-tune and control reactivity for the benefit of organic synthesis.

5.2.2. Further Characterisation of Catalytic Species Arising from $\text{Pd}_3(\text{OAc})_6/3 \text{PPh}_3$ in the Presence of Alkylammonium Salts

Based on known Pd speciation arising from $[\text{Pd}_3(\text{OAc})_6]/3 \text{PPh}_3$ and changes in catalytic behaviour in the presence of additive salts (*e.g.* $n\text{-Bu}_4\text{NBr}$ or **TrisImid·3Br**), an electrosterically stabilised PdNP was circumstantially reasoned to be the highly active and site-selective species under the working cross-coupling conditions reported in this study (Chapters 3 & 4). A range of characterisation techniques could be employed to gain further, direct evidence as to the nature of the active Pd species (summarised in Scheme 85). Primarily, standard tests could be carried out, with appropriate controls, to determine whether a heterogeneous species has a role in catalyst activity. Examples of such tests include the mercury poisoning test,⁷⁷⁻⁷⁸ the hot filtration test and the three-phase-test.⁶⁹ Dynamic light scattering (DLS) could be used to monitor the dynamics of diffusion rate and particle size of particles and associated coordinated salts. Similarly, analysis of solution samples by electron microscopy methods such as SEM/TEM could corroborate how particle size distributions and particle morphology may vary with time under working conditions. Suitable controls, such as quenching the growth of NPs with a polymeric agent (*e.g.* PVP) would be necessary to indicate whether particle size or morphology was compromised during sampling. Higher resolution microscopic imaging techniques, such as STM, could be used to locate potential sites of catalytic activity such as defect sites. Particle size and morphology may prove to have a bearing on the activity of a PdNP active catalyst. X-ray-based methods could also be employed, such as *in operando* EXAFS, which could be used to correlate the coordination geometry of the PdNPs against known standards, after stoichiometric formation, or during catalytic turnover as a function of time.^{76, 331} Using XPS, particle surface composition could be probed, and the presence and nature of salt adsorbates could be tested. Additionally, using this method, the hypothesis could be tested that an O atom is incorporated into a Pd particle surface, when after abstraction from acetate, when particles are generated from $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ mixtures (Section 2.6).

Probing a PdNP active catalyst

-**Heterogeneity tests:** Hg^0 poisoning,
hot filtration, the three phase test
-**Solution dynamics:** DLS, UV-vis
-**Surface characterisation**
techniques: XAFS, XPS, TEM, STM.



Scheme 85 Summarising how a PdNP could be confirmed as a catalytically relevant species and methods by which such as species could be structurally probed.

Once the structure of the active species involved in C4–Br site-selectivity in SMCC reactions at 2,4-dibromopyridine **30** is precisely identified, it could be possible to delineate the mechanistic reasoning for the *abnormal* C4-selectivity observed under the reported conditions using modelling techniques (*e.g.* DFT). For example, using a DFT-modelled species³³² representative of the active species present in solution, the relative energies of transition states and thermodynamic products of reactions between that and *e.g.* **30** or arylboronic acids could be calculated.⁹⁰

Using the aforementioned experimental methods, precise knowledge of the structure of the active species may additionally inform structure-activity-relationships for the design of tailored salt additive a (building on the success with **TrisImid·3Br** as an additive *vide infra* for further discussion on this) and may inform aspects such as optimal Pd catalyst/salt additive ratio with a view to boosting catalytic efficiency and minimising both catalyst and additive loadings. Modelling of PdNP growth in the presence of salt additives (*e.g.* employing molecular dynamics as a simulation method) may aid in finding additive salts which strike the balance between PdNP stability and activity.³³³ Taken together, this method may allow for a tailored approach to the selective activation of a desired C–X site in a dihalogenated aromatic compound.

Finally, following active catalyst identification, after finding a way of isolating it, *e.g.* by nanofiltration or by controlled centrifugation, recyclability tests could be carried out to assess whether the *in situ* generated catalytic species is able to retain its activity/selectivity for subsequent uses. Such a recyclable catalyst, generated from simple $[Pd_3(OAc)_6]/3PPh_3$ in the presence of additive salt would potentially have a high added value and would thus be worthwhile exploring as a patentable, marketable product with a view to reducing the environmental harm and increasing the economic efficiency of future chemical processes.

5.2.3. Application of Findings: Further Exploration and Optimisation of Catalyst Activity and Selectivity in Cross-coupling Applications

A combination of $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ in the presence of alkylammonium salts, which was indicated to lead to the formation of Pd particles, resulted in optimal cross-coupling site-selectivity and efficacy under conditions tested. Thus, an *in situ* derived, salt stabilised PdNP was proposed as the species responsible for the observed powerful activity. This Thesis has shown that by understanding specific speciation events, unexplored catalytic chemical space can be accessed. Despite making significant headway in understanding the variables that lead to enhanced activity of $[\text{Pd}_3(\text{OAc})_6]/\text{PPh}_3$ systems, we have only been able to, at this point, scratch the surface of the exploration of the factors that could build on such observations. For example, it was found that increasing the steric bulk of the cationic portion of the quaternary ammonium bromide additive, site-selectivity in Kumada and Suzuki-Miyaura cross-couplings at 2,4-dibromopyridine **30** was boosted. Building on prior reported literature, incremental tuning of the steric and electronic properties of the additive salt could result in increased reactivity of the proposed PdNP active species, perhaps allowing for efficient activation of more challenging substrates, such as aryl chlorides.^{8, 121, 124} Another future goal might be to assess the effect of lowering (or indeed raising) the catalytic loading of the $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ pre-catalyst mixture, which was kept fixed at 3 mol%/Pd throughout this work. There have been numerous literature examples featuring low Pd loadings which have been shown to exhibit high catalytic turnovers in cross-coupling applications, some of which have been shown to involve a PdNP active species.^{66, 105, 291} The extent to which the catalytic activity could be boosted by changing the properties of the additives and ligands could be further explored by testing optimised conditions on a variety of different substrates and reactions (Figure 86).

When working with an *electrosterically-stabilised* catalyst manifold, the identity of the reducing agent can influence the rate of PdNP formation, with implications for the PdNP size (ideally ~1 – 2 nm), morphology and resultant catalytic activity (Section 1.3.1).^{8, 334} In the case of activation of $[\text{Pd}_3(\text{OAc})_6]$ in the presence of $\geq 4 \text{ PPh}_3$, Jutand *et al.* have shown that electron withdrawing *para*-substituted triphenylphosphines accelerate Pd^{II} reduction, while electron donating *para*-substituents lower the rate of reduction with respect to triphenylphosphine (Section 2.2).⁴⁷ It may therefore be anticipated that the differing electronic nature of *e.g.* *tris-para*-substituted triphenylphosphines may have a bearing on catalyst activity of solutions arising from $[\text{Pd}_3(\text{OAc})_6]/3 \text{P}(\textit{para}\text{-C}_6\text{H}_4\text{-Z})_3$ ($\text{Z} = \textit{e.g.}$ MeO, Me, Cl, CF_3) as a result of changes of the rate of PdNP formation in the presence of a stabilising salt. It could be envisaged that by employing a phosphine which slows the Pd activation step may result in slower PdNP growth. Therefore, by employing a more electron-donating additive phosphine, in concert with an appropriate stabilising salt (see discussion below), a higher catalyst activity might be realised as smaller nanoparticles with a higher prevalence of defect sites may arise (see Section 1.3.1).

The nature of the stabilising salt could also be further modulated and enhanced, and its identity potentially informed by structural characterisation of the active catalyst species (see above), with a view to further boosting the catalytic performance of $[\text{Pd}_3(\text{OAc})_6]/3 \text{ PPh}_3$ mixtures. Chapter 4 highlighted the design of a tricationic tris-imidazolium tribromide salt (**TrisImid·3Br**) which was found to enhance site-selectivity in an SMCC reaction at 2,4-dibromopyridine **30**. Further modulation of the structure may increase steric bulk and organic solvent solubility, perhaps by deploying a longer alkyl chain at the cationic sites, potentially allowing for greater steric protection of the proposed PdNP species. To knowledge of the author, there has not been a systematic study on the dual effect of the cation and anion on the stability and catalytic activity of an *in situ*-generated PdNP catalyst in cross-coupling or C–H activation/functionalising chemistry. In *this work* focus was placed on modification of the *cation*, *e.g.* by increasing the alkyl chain size of *n*- R_4NBr and design of a tricationic tris-imidazolium tribromide salt. Modification of the *anion*, which directly coordinates to the PdNP surface, may also act to stabilise and enhance catalysis under and *electrosteric* NP stabilisation model. The sterics and basicity of the anion has been shown to have a role in the stabilisation of catalytic NPs.³³⁵ Finke *et al.* and deployed a well-defined, bulky, multi-anionic polyoxometalate cluster $[(\text{P}_2\text{W}_{15}\text{Nb}_3\text{O}_{61})_2\text{O}]^{16-}$ in the stabilisation of IrNPs for powerful applications in alkene hydrogenation reactions.¹²¹ The same group also employed the tridentate hydrogen phosphate anion $[\text{HPO}_3^{2-}]$ to enhance activity of PdNPs for an analogous application.¹²⁴ Future work could test the effect of the basicity of the anion on catalytic activity *e.g.* halide anions: F^- *vs.* Cl^- *vs.* Br^- *vs.* I^- or, for carboxylate anions: pivalate *vs.* acetate *vs.* trifluoroacetate *vs.* triflate (Figure 86). Ideally the additive salt must not negatively interfere with any other aspects of the mechanism. The potential for the basicity of the anion to interfere other aspects of the cross-coupling reactions must be considered. For example, acetates have been shown to be able inhibit transmetalation of aryl groups on boronic acids to *trans*- $[\text{Ar-Pd}(\text{OH})(\text{PPh}_3)_2]$ in the SMCC reaction (Section 1.2.1), so care must be taken to choose anions which stabilise the active species but do not adversely affect catalytic turnover in other ways.³⁴

Salts composed of varying combinations of cations and anions could be synthesised and systematically screened in the model cross-coupling at **30**. In each case, balance must be struck between often competing factors of stability and reactivity of the active catalyst. Another reaction variable which could be assessed is the loading of the additive salt, with particular attention to the Pd/additive salt ratio. The quantities of additive salt under the conditions explored in this work were rather high, generally set at 2.5 equivalents per aryl halide substrate (~ 83 equivalents *per* Pd). Future work could explore whether this quantity could be reduced, ideally to catalytic-type quantities, without loss of catalyst activity/selectivity, or whether a high concentration of salt is necessary for the observed interesting activity. The above factors involving changes to catalytic conditions, which could be potentially explored in future work are summarised in Figure 86.

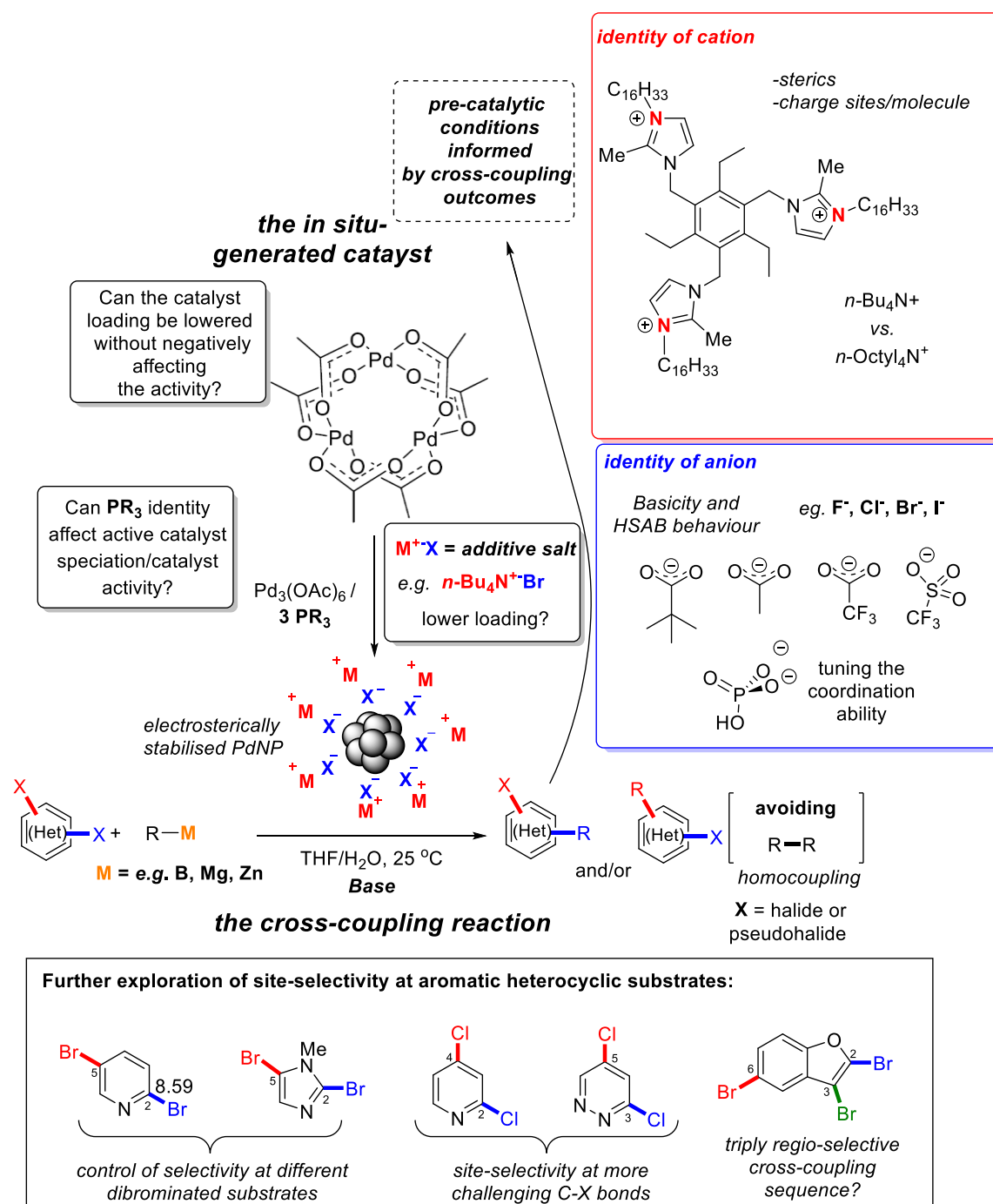


Figure 86 Showing variables of pre-catalytic conditions that could be modified, as part of a high-throughput study, to optimise reactivity and site-selectivity at a range of substrates and in various cross-coupling reactions. Control of active catalyst speciation by influencing $[\text{Pd}_3(\text{OAc})_6]/3\text{PPh}_3$ activation in the presence of additive salts may be key to controlling resulting reactivity as was found in *this work*.

Once an optimally active catalyst system has been achieved under SMCC conditions, approximations of the optimised conditions used to generate the catalyst system could be assessed in other types of cross-coupling reactions, e.g. Kumada-Corriu, Negishi, Sonogashira, Mizoroki-Heck and Hiyama reactions (Figure 86). In each case, attention could be paid to cross-coupling product selectivity and

minimisation of the formation of by-products, such as homo-coupled and protodeborylated products. Optimised catalyst conditions could then be applied to different types of dihalogenated heteroaromatic compounds, under different cross-coupling regimes. A natural progression from the 2,4-dibromopyridine **30** substrate, which was extensively studied in this work, might be 2,5-dibromopyridine as the unactivated C5–Br site is more challenging to functionalise than the C4–Br site of **30**.¹⁸⁹ The catalytic conditions employed in this work could be applied to regioselective cross-coupling at another type of aromatic heterocycle for, which site-control has been previously realised, such as 2,5-dibromo-1-methylimidazole.¹⁹⁰ It would be of particular value in this context to be able to bypass the use of elaborate/expensive ligand architectures previously used to achieve selectivity at such substrates (Section 1.5). Applying the understanding reported in this work to cross-coupling at more synthetically challenging, but more easily accessed, *dichlorinated* heteroaromatics such as 2,4-dichloropyridine or 3,5-dichloropyridazine may similarly avoid the use of elaborate ligands and harsh reaction conditions as reported in previous site-selective examples (Section 1.5.2).^{204–205} Finally, if regiocontrol is possible at a given dihalogenated heteroaromatic compound, a further challenge may be to assess catalyst selectivity at a *trihalogenated heteroaromatic*, featuring three carbon–halogen bonds of the same type. A triply *regio*-selective cross-coupling sequence at a tribrominated compound 2,3,6-tribromobenzoxazole (Figure 86) would allow for further rapid diversification of potentially biologically relevant heteroaromatic compounds for agrochemical or pharmaceutical applications. This strategy would build on the triply *chemo*-selective cross-coupling sequence reported by Schoenebeck *et al.*¹⁵²

The use of an automated robotic platform would be an ideal approach for a systematic high-throughput screening of factors identified as important for enhancing cross-coupling catalysts arising from simple $\text{Pd}_3(\text{OAc})_6/3\text{PR}_3$ catalyst precursors (*vide supra*) (Figure 86). Controllable variables such as the organophosphine additive identity, the identity of the cation and anion within the salt additive, substrate and type of cross-coupling reaction could thus be efficiently systematically and incrementally modified to assess the scope of activity of the $[\text{Pd}_3(\text{OAc})_6]/3\text{PR}_3$ pre-catalytic system. Using this method, it may be possible to determine whether there is a universally active, isolable and marketable, catalytic species that forms from an optimised $[\text{Pd}_3(\text{OAc})_6]/3\text{PR}_3$ pre-catalytic mixture, or as is more likely in the opinion of the author, that conditions need to be adjusted to generate an optimal catalyst suitable for particular substrate and reaction combinations.

Chapter 6 – Experimental Section

6.1. General Details of In-laboratory Analysis

Solvents and Reagents

Generally, reagents were purchased from *Sigma-Aldrich*, *Alfa Aesar*, *Acros Organics* or *Fluorochem* and used as received unless otherwise stated. Specifically, boronic acids were purchased from *Tokyo Chemical Industries* or *Fluorochem* and used as received. 2,4-Dibromopyridine **30** was purchased from *Fluorochem* and used as received. The purity of **30** was verified (>99%) against a 1,3,5-trimethoxybenzene standard, using ^1H NMR spectroscopy. $\text{Pd}(\text{OAc})_2$ (>99% purity) was obtained from *Precious Metals Online* and used as received. Triphenylphosphine (PPh_3) was purchased from *Fischer* and purified by recrystallization from hot ethanol, under an atmosphere of N_2 , dried under high vacuum and subsequently stored over P_2O_5 . 6-Quinoline boronic acid **71** was purchased from *Alfa Aesar* and used as received. 2-Bromopyridine **55** (*Tokyo Chemical Industries*) was degassed by the freeze-pump-thaw method and stored under nitrogen. Any trace copper (chip) in *para*-fluoriodobenzene (*Tokyo Chemical Industries*) was removed by washing with pyridine/water (1:3, v/v, $\{3 \times 10 \text{ mL}\}$) then with water ($2 \times 10 \text{ mL}$) and brine ($1 \times 10 \text{ mL}$), before drying over MgSO_4 (subsequently removed by filtration). The filtrate was then concentrated *in vacuo* before being distilled into an ampoule on a high vacuum line. Aniline (*Sigma-Aldrich* {*Merck*}) was dried overnight over CaH_2 before being distilled by high vacuum, transferred into an ampoule and deoxygenated by bubbling through with N_2 . 4-Bromo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **70** was synthesised by Dr. James D. Firth, using an established literature procedure.²²⁸ *Tetra-n*-butyl ammonium hydroxide (*n*- Bu_4NOH {aq.}) (*Merck*) was purchased as a 1.5 M aqueous solution, diluted to 1.0 M with deionised water before being transferred into an ampoule and deoxygenated by bubbling through with N_2 from a Schlenk line. KOH (aq., 1.0 M) was prepared and degassed by bubbling through with N_2 and stored in a J.Youngs tap-sealed ampoule. Phenylmagnesium bromide solution **77** (1.2 mL, 1.0 M in THF) was purchased from Merck. After receipt, **77** was transferred *via* cannula, driven by N_2 balloon pressure, into an oven dried ampoule, sealed with a J.Youngs tap, for storage under ‘Schlenk conditions’ *tetra-n*-butyl ammonium bromide and *tetra-n*-butyl ammonium bromide were purchased from Merck and used as delivered, taking care to minimise exposure to air, due to the hygroscopicity of these compounds.

THF was dried by heating to reflux over sodium metal pieces (2 days) before being distilled, transferred to an ampoule and subsequently deoxygenated by bubbling with argon *via* cannula for *ca.* 30 min. THF- d_8 and benzene- d_6 were dried over potassium metal pieces for two days. CD_2Cl_2 was dried over CaH_2 for two days. THF- d_8 , benzene- d_6 and CD_2Cl_2 were freeze-pump-thaw-degassed before being distilled

for storage in an ampoule under argon. Petroleum ether (petrol) refers to the fraction of petroleum that distils between 40-60 °C. Brine refers to a saturated, aqueous solution of NaCl.

[Pd⁰(PPh₃)₄] **65** was prepared, using an established literature procedure by Coulson, and stored in an Ar glovebox at –30 °C.³³⁶ [Pd₃(PPh₃)₄][BF₄]₂ was synthesised by a method first reported by Kannan *et al.*¹⁷⁵ and adapted by Dr Kate Mary Appleby.¹⁷⁴ *trans*-[Pd^{II}(OAc)₂(N-piperidyl)₂] **54** was synthesised according to an adapted literature procedure.^{252, 278}

Room temperature upper and lower limits are stated as 13-25 °C, but typically 21 °C was recorded. Inert techniques (Schlenk and glovebox) were used for chemical reactive operations. Schlenk techniques/conditions refers to the use of high vacuum, liquid nitrogen trap on a standard in-house built dual line manifold {vacuum and N₂}. Sampling for NMR spectroscopic analysis, under Schlenk conditions, was carried out using a NMR-Schlenk adapter, allowing syringed samples to be introduced into a J. Youngs NMR tube under a flow of N₂.

Instrumentation and In-laboratory Analysis

Chromatographic Details

Thin layer chromatography (TLC) was carried out using Merck 5554 aluminium backed silica plates (silica gel 60 F254) and spots were visualized using UV light (at 254 nm) or by standard staining methods. Retention factors (R_f) are reported in parentheses along with the solvent system used. Flash column chromatography was performed using Sigma-Aldrich 60 Å silica gel (particle size 40–63 µm) and a solvent system as reported in the text.

Nuclear Magnetic Resonance Spectroscopy

NMR spectra were obtained in the solvent indicated, using a Bruker AVIIIHD 500 instrument (500 MHz [¹H], 470 MHz [¹⁹F], 203 MHz [³¹P] 125 MHz [¹³C]), JEOL ECX400 or JEOL ECS400 spectrometer (400 MHz [¹H], 376 MHz [¹⁹F], 162 MHz [³¹P] 101 MHz [¹³C]). Chemical shift frequencies are reported in parts per million (ppm). ¹H and ¹³C NMR were referenced to the residual non-deuterated solvent of the deuterated solvent used (CHCl₃ δ_H = 7.26 ppm: δ_C = 77.16 ppm (CDCl₃), CD₂HCl₂ δ_H = 5.31 ppm and δ_C = 54.0 ppm (CD₂Cl₂). ³¹P NMR chemical shifts were externally calibrated against a H₃PO₄ solution (aq. 85%), the singlet resonance of which was set to 0 ppm. Generally, spectra were typically collected at a temperature of 298 K (25 °C). All ³¹P or ¹³C NMR spectra were obtained with ¹H decoupling unless otherwise stated. NMR spectra were processed using MestReNova software (versions 5.3, 7.03 and 8.1) as required and were exported as .TIF or .PNG files

in and inserted directly into the document. Multiplicities are described as *e.g.* singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m), apparent (app.) and broad (br). The matched *J*-coupling constants have been quoted to ± 0.1 Hz. ^1H NMR chemical shifts are quoted to 2 decimal places. Copies of recorded NMR spectra for all isolated organometallic compounds are given in Section 6.3, below. Spectra for all isolated organic compounds (products of catalysis) are given in Appendix 3.

Mass Spectrometry

ESI mass spectra were measured using a Bruker Daltonics microTOF instrument, Agilent series 1200LC with electrospray ionisation or on a Thermo LCQ using electrospray ionisation, with <5 ppm error recorded for all HRMS samples. LIFDI mass spectrometry was carried out using a JEOL AccuTOF GCx-plus instrument (JMS-T200GC), fitted with a probe produced by Linden CMS. The probe was equipped with 13 μm emitters on an AccuTOF instrument. Alternatively, LIFDI-MS was carried out using a Waters GCT Premier MS Agilent 7890A GC instrument.

Mass spectral data is quoted as the m/z ratio of the exact mass. Mass to charge ratios (m/z) are reported in Daltons. High resolution mass spectra (HRMS) are reported with <5 ppm error (ESI and LIFDI). For clarity, ESI and LIFDI data are reported for ^{106}Pd , the most abundant natural isotope of Pd (the ‘exact mass’).

Single Crystal X-Ray Diffraction

Suitable single crystals were selected, and diffraction data were collected at 110 K on an Oxford Diffraction SuperNova diffractometer with Cu- K_α radiation ($\lambda = 1.54184 \text{ \AA}$) using a EOS CCD camera. Diffractometer control, data collection, initial unit cell determination, frame integration and unit-cell refinement was carried out with “CrysAlis”.³³⁷ Using OLEX2³³⁸ software, the structure was solved with the ShelXS327 structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimisation. Within OLEX2, the algorithm used for structure solution was “ShelXT dual-space”.³³⁹ Crystallmaker® software was used to visualise structures as well as for generating the figures presented herein. Generally, solvent molecules and counterions have generally been omitted for clarity), alongside crystallographic data.

Infrared Spectroscopy

Infrared spectra were obtained using a Bruker ALPHA-Platinum FTIR Spectrometer with a platinum-diamond ATR sampling module. Solid-state IR spectra were collected using an ATR probe. Solution-phase IR were recorded in an NaCl window solution cell.

Elemental Analysis (CHN)

Samples were prepared using a Sartorius SE2 high precision analytical balance. Samples were analysed in duplicates. An Exeter Analytical CE-440 elemental analyser was used to collect all elemental analysis data, which was calibrated against acetanilide standards. Samples were run as duplicates. Herein, the amounts of carbon (C), hydrogen (H), and nitrogen (N) are given as mean percentages of the two runs.

Melting Points

Melting points were recorded using a Stuart digital SMP3 melting point analysis machine. A ramp rate of 4.0 °C.min⁻¹ was generally used.

6.2. Experimental Procedures

6.2.1. Reactions Involving Stoichiometric Reactions of Pd-containing Complexes (Chapters 2 & 4)

NMR Scale Reactions Between Pd₃(OAc)₆ with 6, 9 or 12 Equivalents of PPh₃ (Sections 2.3 & 2.4)

The [Pd₃(OAc)₆] (2.3 mg, 3.3 μmol) and PPh₃ (amount specified in Table 10, below) were weighed and transferred into a J. Youngs NMR tube (in an Ar-filled glovebox). THF-*d*₈ (0.5 mL) was added and the resultant mixture was shaken vigorously before the sample was introduced to an NMR spectrometer where data was collected (within *ca.* 15 minutes).

Table 10 Amounts (+ masses) used for the stoichiometric reactions between [Pd₃(OAc)₆] and varying quantities of PPh₃ in THF-*d*₈.

Equivalents of PPh ₃ used per Pd ₃ (OAc) ₆	Equivalents of PPh ₃ used per Pd	Amount of Pd ₃ (OAc) ₆ used / μmol	Amount of PPh ₃ used / μmol	Mass of PPh ₃ used/ mg	<i>Labbook Reference #</i>
6	2	3.3	20	5.2	NWJS-4-291
9	3	3.3	30	7.9	NWJS-4-290
12	4	3.3	40	10.5	NWJS-4-304

A $^{31}\text{P}\{^1\text{H}\}$ spectrum (203 MHz, 128 scans) was additionally recorded after 16 h, showing how the system had evolved after this time (a final data point). All spectra were recorded at 298 K (25 °C). After the 16-hour reaction time, ^{31}P NMR spectra of each reaction mixture was externally referenced by inserting phosphoric acid solution (85% in H_2O {w/w}) sealed within a capillary tube, the resonance of which was set to δ 0.0 ppm. The spectra used in the thesis (Figure 32) were taken *ca.* 16 hours from reaction initiation.

Reaction of *in situ*-Generated $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_3]^-$ with *para*-Fluoroiodobenzene (Section 2.3)

A solution of $[\text{Pd}^0(\text{OAc})(\text{PPh}_3)_3]^-$ was generated from reacting $\text{Pd}_3(\text{OAc})_6$ with 15 equiv. of PPh_3 Pd:P in THF. A Schlenk tube was charged with $\text{Pd}_3(\text{OAc})_6$ (44.9 mg, 0.067 mmol, 1 equiv.) and PPh_3 (262.3, 1.00 mmol, 15 equiv.) was sealed (Suba-seal®). After evacuating and backfilling the flask, dry THF (5 mL) was added and the mixture was heated to reflux with magnetic stirring, under a cold finger condenser and an atmosphere of N_2 for 24 hours. At this point, the mixture was cooled to room temperature and ^{31}P spectroscopic analysis showed only partial conversion of *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** to Pd^0 complex. After 2 hours at room temperature, two drops of H_2O (*ca.* 5.5 equiv. w.r.t. Pd) were added to the solution (to accelerate the reduction {activation} process) and the solution was then stirred for a further 2 hours under N_2 at room temperature. After this time a sample was taken, which was subjected to ^{31}P NMR spectroscopic analysis, confirming complete conversion to the Pd^0 complex. *para*-Fluoroiodobenzene (88.8 mg, 46 μL , 0.40 mmol) was added dropwise to the bulk solution with magnetic stirring at room temperature. A sample (0.5 mL) was immediately drawn out under Schlenk conditions and subjected to NMR analysis as detailed in Section 2.3. After NMR analysis, a sample was carefully layered with hexane and stored at -18°C which resulted in growth of crystals suitable for X-Ray crystallographic analysis.

See Appendix 4 for X-Ray Crystallographic Data (ijsf1913).

Labook Reference Number: NWJS-4-341.

Reactivity of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** with Organohalides (Section 2.5.1.)

Reaction of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** with CD_2Cl_2

In an Ar-filled glovebox, to an NMR tube was added $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]$ **52** (5.0 mg, 5.0 μmol , 1.0 equiv.), which was dissolved in THF (0.3 mL). CD_2Cl_2 (0.2 mL) was added dropwise and the NMR tube was sealed, shaken and then introduced to the NMR spectrometer, where ^{31}P NMR spectra were collected to monitor the reaction over time (298 K). The reaction was found to go to completion after 14 hours. Other species were observed by ^{31}P NMR spectroscopic analysis, which could not be characterised (as detailed in the paper, and in more detail *vide infra*). A sample was analysed by ESI-MS

(10 μL , 5 hours after reaction initiation), which confirmed conversion to the $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$

Labbook Reference Number: NWJS-4-266.

Reaction of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** with 2-bromopyridine **55**

In an Ar-filled glovebox, in a J. Young's NMR tube **52** (5.0 mg, 5.0 μmol , 1.0 equiv.) was dissolved in THF- d_8 (0.3 mL). A THF- d_8 (0.2 mL) solution of **55** (3.3 mg, 2 μL , 0.021 mmol, 0.105 M, 4.1 equiv.) was added dropwise and the NMR tube was sealed, shaken, and introduced to an NMR spectrometer, where ^{31}P NMR spectra were collected to track the reaction over time (at 298 K {25 $^\circ\text{C}$ }). An aliquot of the NMR sample was analysed by ESI-MS (10 μL) after 45 minutes, which confirmed the presence of $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]^+\text{X}^-$.

Labbook Reference Number: NWJS-4-313.

Reactions of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** with PPh_3 (Section 2.5.3)

*Reaction between $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]$ **52** and 1 equivalent of PPh_3*

In an Ar glovebox, $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** (5.0 ± 0.05 mg, 5.1 μmol , 1.0 equiv.) was weighed into a vial and a solution of PPh_3 (1.4 ± 0.05 mg, 5.3 μmol , 1.04 equiv.) in THF- d_8 (0.5 mL) was added dropwise. The entire solution was transferred into a J. Youngs NMR tube. A colour change from dark red to bright red-orange was immediately observed upon shaking the NMR tube at room temperature. The NMR sample was swiftly introduced to an NMR spectrometer for ^{31}P spectroscopic analysis.

Labbook Reference Number: NWJS-6-350.

*Reaction between **52** and 2 equivalents of PPh_3*

In an Ar-glovebox $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** (10.0 ± 0.05 mg, 10.2 μmol , 1.0 equiv.) was weighed into a vial and a solution of PPh_3 (5.4 ± 0.05 mg, 20.6 μmol : 2.08 equiv.) in THF- d_8 (0.5 mL) was added dropwise the resulting solution was transferred into a J. Youngs NMR tube. A colour change from dark red to bright red-orange was again immediately observed upon shaking the tube at room temperature. This post-reaction solution was sampled for LIFDI- and ESI-mass spectral analysis by removing a liquid sample in an Ar-glovebox and transferring into a crimp-sealed vial (1 mL capacity). For LIFDI-MS-sampling, *ca.* 0.2 mL of the THF- d_8 was extracted with a syringe and needle and the vial was quickly sealed under Argon. For ESI-MS-sampling, a small sample (5 μL) of the THF solution was diluted in toluene 1 mL before being injected directly into the mass spectrometer for analysis.

Labbook Reference Number: NWJS-5-365, NWJS-5-420, NWJS-5-426.

Crystallisation of $[\text{Pd}_2(\mu\text{-PPh}_2)\{\kappa\text{-P,O-}\mu\text{-P(O)Ph}_2\}(\kappa\text{-PPh})_2]$ **52 & $[\text{Pd}_2(\mu\text{-PPh}_2)\{\kappa\text{-2O,O-}\mu\text{-P(O)}_2\text{Ph}_2\}(\kappa\text{-PPh}_3)_2]$ **62**:** Crystals of **58** were grown from this solution THF- d_8 solution by careful layering with pentane (THF- d_8 /pentane = 1:4) and subsequent storage over *ca.* 2 days at -18°C , under an atmosphere of argon. Red crystals formed alongside a yellow precipitate most likely $[\text{Pd}^0(\text{PPh}_3)_3]$, which was observed as a major solution species. Red crystals were purposely selected and subjected to X-ray crystallographic analysis. Red crystals of $[\text{Pd}_2(\mu\text{-PPh}_2)\{\kappa\text{-2 O,O-}\mu\text{-P(O)}_2\text{Ph}_2\}(\kappa\text{-PPh}_3)_2]$ **62** (*phosphinato*-bridged complex) were grown from a similar solution by layering with dry hexane (THF- d_8 /hexane = 1:4) and subsequent storage over *ca.* 7 days at -18°C .

See Appendix 4 for X-Ray Crystallographic Data (ijsf 1920 {**58**}), (ijsf 1916 {**62**}).

Labbook Reference Number: NWJS-5420.

^1H NMR spectral analysis: evidence for 1:1 ratio of acetic anhydride: Due to overlap of peaks of **58** and $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** it was challenging to get an idea of the comparative stoichiometry of species **58** and acetic anhydride (Ac_2O) from the ^1H NMR spectrum of the crude reaction mixture. The peak at 6.92 ppm has been assigned as the PCC H {ortho proton} of the bridging diphenylphosphido ligand of **58**, based on to chemical shift similarities with the bridging diphenylphosphido ligand of the starting material Pd^{I} dimer **52** (*vide infra*). When the Ac_2O peak was set as 6H, an integration of 6.44 H was measured for the peak at 6.92 ppm, which is higher than the 4H which would be expected. This higher than expected is clearly a result of the peaks location next to a large broad resonance from the phenyl resonances of **48**. It can be reasoned from this observation is that the relative amount of **58** to Ac_2O is, to an approximation, 1:1.

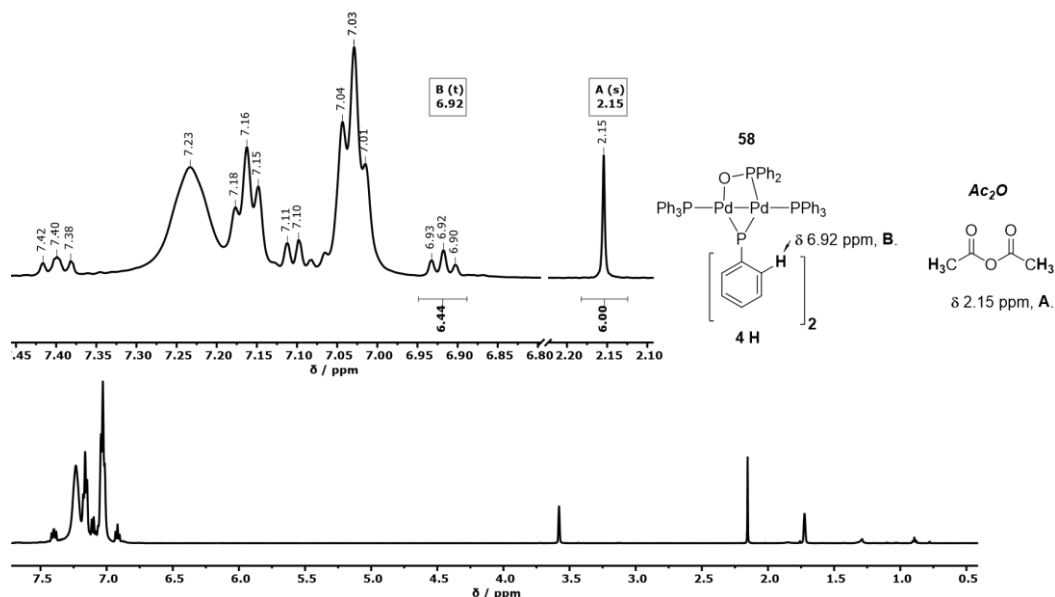


Figure 87 ^1H NMR spectrum of the **52**/ 2PPh_3 post-reaction solution. Showing expansion of the aromatic region (6.8–7.45 ppm) showing acetic anhydride. Integrations of the peaks assigned as the ortho protons of the μ -phosphido ligand of **58** and the methyl peaks of Ac_2O have been compared.

Reaction of the Mixture Generated from $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ (**52**) and 2 PPh_3 with Excess 2-bromopyridine (Section 2.5.3.2)

Procedure: The reaction between $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** and 2 PPh_3 was carried out as outlined *vide supra*. In an Ar glovebox, the solution was treated with 2-bromopyridine **55** (5 μL , 8.25 mg, 0.052 mmol $\Rightarrow$ 5 equiv.) *via* a microsyringe within 24 hours of generation of the stable solution of **52** and $[\text{Pd}^0(\text{PPh}_3)_3]$. The evolution of the resulting red solution was monitored over the course of 13 hours by ^{31}P NMR spectroscopy.

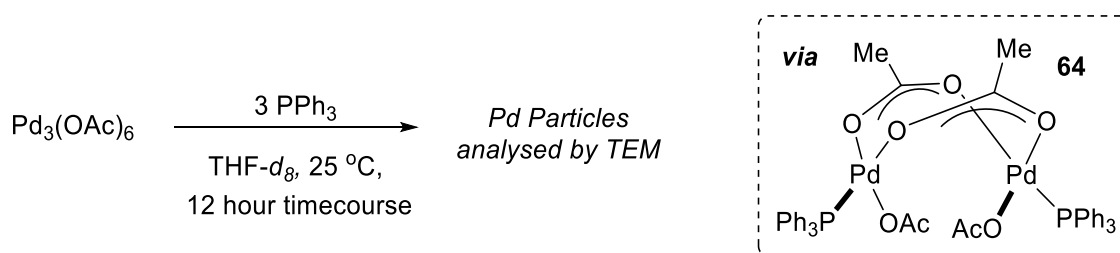
Labbook Reference Number: NWJS-5-426.

Analysis of the Background Reaction: Treatment of $[\text{Pd}^0(\text{PPh}_3)_4]$ with 2-Bromopyridine (Section 2.5.3.2.1)

Carried out for the confirmation of NMR identification of products of the oxidative addition of $[\text{Pd}^0(\text{PPh}_3)_3]$ (generated *in situ* by disproportionation of **52** after addition of PPh_3). Here, $[\text{Pd}^0(\text{PPh}_3)_4]$ was used as a proxy for $[\text{Pd}^0(\text{PPh}_3)_3]$ (in solution, $[\text{Pd}^0(\text{PPh}_3)_4]$ is known to lose a PPh_3 ligand, readily forming $[\text{Pd}^0(\text{PPh}_3)_3]$ **48** (and, to a lesser extent, $[\text{Pd}^0(\text{PPh}_3)_2]$).³⁰⁹ In an argon-filled glovebox, $[\text{Pd}^0(\text{PPh}_3)_4]$ (10 mg, 8.7 μmol) dissolved in 0.5 mL of $\text{THF-}d_8$. 2-Bromopyridine (3.0 mg, 19.1 μmol , 2.2 equiv.) was added dropwise *via* a microsyringe. The mixture was transferred into a J. Youngs NMR tube before being sealed and introduced to an NMR spectrometer for *in operando* ^{31}P spectroscopic analysis (298 K).

Labbook Reference Number: NWJS-5-367.

Reaction between $[\text{Pd}_3(\text{OAc})_6]$ and 3 PPh_3 (Section 2.6)



Scheme 86 Conditions used for the reaction between $\text{Pd}_3(\text{OAc})_6$ and 3 PPh_3 ($\text{Pd:P} = 1:1$) in $\text{THF-}d_8$

NMR tracking of the reaction: The $[\text{Pd}_3(\text{OAc})_6]$ (2.25 ± 0.05 mg, 3.3 μmol) and PPh_3 (2.60 ± 0.05 mg) were weighed and transferred into a J. Youngs NMR tube (in an Ar-filled Glove box). $\text{THF-}d_8$ (0.5 mL) was added and the sample was swiftly introduced to an NMR spectrometer where data was collected (within *ca.* 15 minutes). ^{31}P and ^1H NMR spectra were recorded at this point. Hence, a ^{31}P NMR time

course was recorded, tracking the degradation of **64** with time, along with the formation of many unidentified products. Integration data as a function of time was recorded using MestReNova ‘data analysis’ function and graphed using OriginPro 2018 software (Figure 71).

Imaging of aliquots of the post reaction solution was carried out thereafter, by pipetting a drop of the reaction solution onto a mesh grid which was examined by TEM microscopy. Representative images are presented in Figure 73.

64 was not isolated from solution due to its instability (*vide supra* and discussion in the main paper). The following data is presented for its characterisation in solution after direct reaction between $\text{Pd}_3(\text{OAc})_6$ and 3 PPh_3 , in THF-d_8 as highlighted above.

^1H NMR (500 MHz, THF-d_8) δ 7.90 (m, 12H, *phenyl-H*), 7.54 – 7.46 (br. m, 6H, *phenyl-H*), 7.36 (m, 12H, *phenyl-H*), 1.35 (s, 12H, OC(O)CH_3).

^{31}P NMR (203 MHz, THF-d_8) δ 19.55 (s).

LIFDI-MS Data (+ve mode) mode: Found 913.0309 $[\text{M-OAc}]^+$ Calc. (for $\text{C}_{42}\text{H}_{39}\text{O}_6\text{P}_2\text{Pd}_2$) 913.0188.

IR (v/cm^{-1} , ATR): 1628 ($\kappa\text{-CO}_{2\text{asym}}$), 1564 ($\mu\text{-CO}_{2\text{asym}}$), 1409 ($\mu\text{-CO}_{2\text{sym}}$), 1309 ($\kappa\text{-CO}_{2\text{sym}}$).²⁷⁷

Labbook reference number: NWJS-4-292 (NMR analysis + timecourse), NWJS-4-310 (TEM imaging).

Isolation of a single crystal of $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{PPh}_3)]_2$: A Schlenk tube was charged with $\text{Pd}_3(\text{OAc})_6$ (6.7 mg, 0.01 mmol) and 1 PPh_3 ({7.9 mg, 0.03 mmol} $\Rightarrow$ Pd:P = 1:1). The Schlenk tube atmosphere was evacuated and backfilled with N_2 before being put on ice. THF (2.5 mL $\Rightarrow$ 0.01 M, pre-cooled to 0 °C) was added and the resulting mixture was stirred at 0 °C for 5 minutes, appearing as a brownish-red solution. A sample (0.5 mL) was taken *via* a syringe and added to an NMR tube under Schlenk conditions, on ice. The mixture was then carefully layered with pre-cooled hexane (at 0 °C) and swiftly stored at –18 °C.

See Appendix 4 for X-Ray Crystallographic Data (ijsf1908).

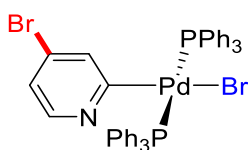
Labbook reference number: NWJS-4-328.

The Oxidative Addition Reaction of $[\text{Pd}^0(\text{PPh}_3)_4]$ to 2,4-Dibromopyridine (Section 4.2.2)

$[\text{Pd}(\text{PPh}_3)_4]$ (200 mg, 0.173 mmol) was treated with 2,4-dibromopyridine **30** (41.0 mg, 0.173 mmol) at 23 °C, in toluene (0.5 mL; dry, degassed) with stirring for 16 hours, according to the experimental method previously reported by Cid and co-workers.¹⁹³ After removing the toluene solvent *in vacuo* and washing the residue with Et_2O (3 $\times$ 0.5 mL; dry, degassed), ^{31}P spectroscopic analysis of a CD_2Cl_2

solution of the crude reaction product (Figure 78) confirmed the site-selectivity of the oxidative addition reaction. Crystals were grown by layering the above CD₂Cl₂ solution with an excess of excess dry, degassed hexane (1:3 CD₂Cl₂/ hexane v/v). The crystalline product could therefore be isolated for further characterisation (*vide infra*) in a 26% yield of isolated **OA_{C2-Br}** product (an unoptimised crystallisation process).

Characterisation Data for Bromo(4-bromo-C2-pyridinyl), bis(triphenylphosphine) Palladium(II) (OA_{C2-Br})¹⁹³



N.B. in solution **OA_{C2-Br}** converts over time to the dimer product **OA_{C2-Br-dinuc}** with release of uncoordinated PPh₃, therefore after isolation by crystallisation during solution characterisation of **OA_{C2-Br}** (by *e.g.* NMR spectroscopy) a mixture of the three species rapidly arises.

³¹P NMR (202 MHz, CD₂Cl₂) δ 22.84 (s) ppm. ¹H NMR (500 MHz, CD₂Cl₂) δ 7.64 – 7.54 (m, 12H, PPh₃), 7.44 – 7.36 (m, 7H, PPh₃ {6H} + *pyridyl*-C₆-H {1H}), 7.35 – 7.28 (m, 12H), 6.66 (d, *J* = 1.9 Hz, 1H, *pyridyl*-C₃-H), 6.23 (dd, *J* = 5.3, 1.9 Hz, 1H, *pyridyl*-C₅-H) ppm.

ESI-MS Data (+ve mode) mode: Found 786.0328 [M-Br]⁺ Calc. (for C₄₂H₃₉O₆P₂Pd₂) 786.0301.

IR (*ν*/cm⁻¹, ATR): 3049 (w, C-H), 1589 (m), 1535 (m), 1525 (m), 1480 (m), 1433 (s), 1346 (m), 1186 (m), 1094 (m), 998 (m), 807 (m), 740 (br, m), 690 (br, s), 517 (br, s), 499 (s).

Elemental analysis (% CHN), calculated for C₄₁H₃₃Br₂NP₂Pd: C, 56.74; H, 3.83; N, 1.61; Found: C, 56.55; H, 3.79; N, 1.61.

See Appendix 4 for X-Ray Crystallographic Data (ijsf1805).

Labbook Reference Number NWJS-3-183, NWJS-6-490.

6.2.2. Procedures for Cross-coupling Reactions at Mono-halogenated Heteroaromatic Substrates (Chapter 3)

Sampling and *In-operando* ¹H NMR Kinetic Analysis Method for SMCC Processes

Sampling Method: A sample (0.5 mL) was taken by syringe and added to an NMR tube (J. Youngs), which was subsequently sealed (inert conditions were maintained by use of a Schlenk NMR adapter). The sample was swiftly introduced into a Bruker AVIIIHD 500 MHz NMR spectrometer (the probe

was pre-heated to 40 °C). After tuning and shimming, the first spectrum was recorded (at $t = 8$ -12 mins).

Kinetic Analysis: For ^1H NMR in operando kinetic analysis, a Bruker AVIIIHD 500 MHz NMR spectrometer was programmed to record one spectrum (32 scans) every 5 minutes. These spectra could be stacked and, using ‘Mestrenova Data analysis’ software, reactions could be monitored, following a given compound proton integral as a function of time. The pyridine- H_6 signal for each compound were integrated for both product and starting material (δ 8.64 and 8.38 ppm respectively, in THF:H₂O {1:1, v/v}). These proton integrals were used to gauge the relative amounts of these compounds throughout the reaction time-course. The data was then graphed using OriginPro 2018 software. A guide to the method of data processing is highlighted in Figure 88 below.

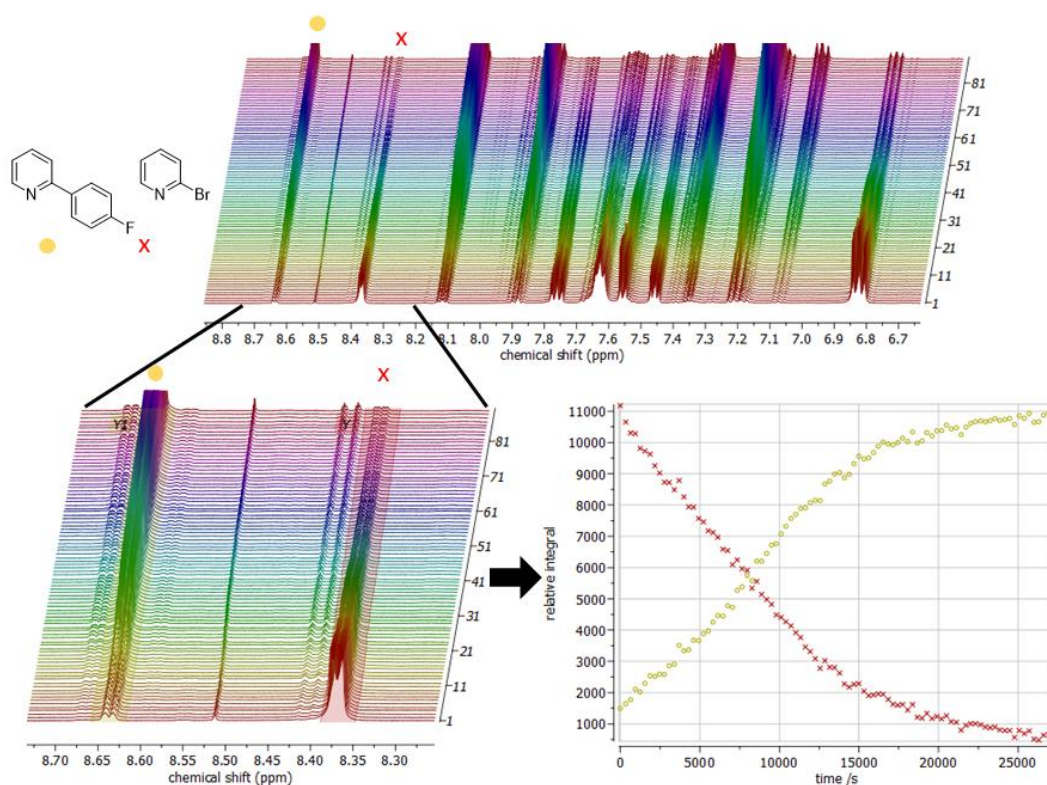


Figure 88 Graphical summary of the method used for extracting kinetic data using ‘Mestrenova Data Analysis’. A stack of the entire time-course was generated, showing the reaction profile with time (top), could be integrated (shown bottom left) giving a raw data plot (bottom right) for the relevant starting materials and products

The time scale was converted from seconds to minutes. There was a period, typically 8-12 minutes where no spectra were recorded (involving transferring the NMR sample from the reaction flask into the NMR spectrometer probe, and shimming), this time-period was adjusted on each plot. Every 5 data points, for time and integral, were averaged (using a 5-point average). A plot was thus constructed showing relative integral (%) of the starting material and products change over time. Data was truncated at the point at which the reaction was judged to be complete.

Model Suzuki-Miyaura Cross-coupling Reactions at 2-bromopyridine **55** (Chapter 3)

General Procedure A: Varying the Ratio of Pd₃(OAc)₆/nPPh₃ – Pd:PPh₃ 1:2 vs. 1:4: Comparative Catalytic Activity in a Model Suzuki-Miyaura Cross-coupling Reaction

An oven-dried Schlenk flask (*flask A*), charged with Pd₃(OAc)₆ (6.7 mg, 0.01 mmol) and PPh₃ (Table 11) was evacuated and backfilled with N₂. THF (2.5 mL; dry, degassed) was added *via* a syringe the resulting solution was stirred for 30 minutes in a pre-heated oil bath (40 °C). Meanwhile, another oven-dried Schlenk flask (*Flask B*) was charged with *para*-fluorophenylboronic acid **74B** (167.9 mg, 1.20 mmol), before being evacuated and backfilled with N₂. This flask was charged with 2-bromopyridine **55** {95 µL, 158.0 mg, 1.00 mmol, previously degassed). After the stirring period, the contents of *Flask A* were transferred to *Flask B* *via* cannula, the mixture was subsequently stirred at 40 °C for 5 minutes. Degassed *tetra-n*-butylammonium hydroxide (aq. 2.5 mL, 1.0 M) was added *via* a syringe (marking the *t*₀ time point) and allowed to mix to form a homogenous solution for 30 seconds, with stirring at 40 °C. The reaction was sampled and a timecourse analysed according to the general method detailed above. *Note:* the background reaction in absence of added *tetra-n*-butylammonium hydroxide was proven minimal: negligible conversion was observed under these reaction conditions

Table 11 Quantities: moles, masses and equivalents for the amount of Pd₃(OAc)₆ used relative to PPh₃.

Pd:PPh ₃	Pd ₃ (OAc) ₆ moles / mmol	Pd ₃ (OAc) ₆ mass / mg	Equiv. of PPh ₃	PPh ₃ /mmol	PPh ₃ /mg	Labbook Reference Number
1:2	0.01	6.7	6	0.06	15.7	NWJS-4-300/303
1:3	0.01	6.7	9	0.09	23.6	NWJS-4-311
1:4	0.01	6.7	12	0.12	31.4	NWJS-4-309

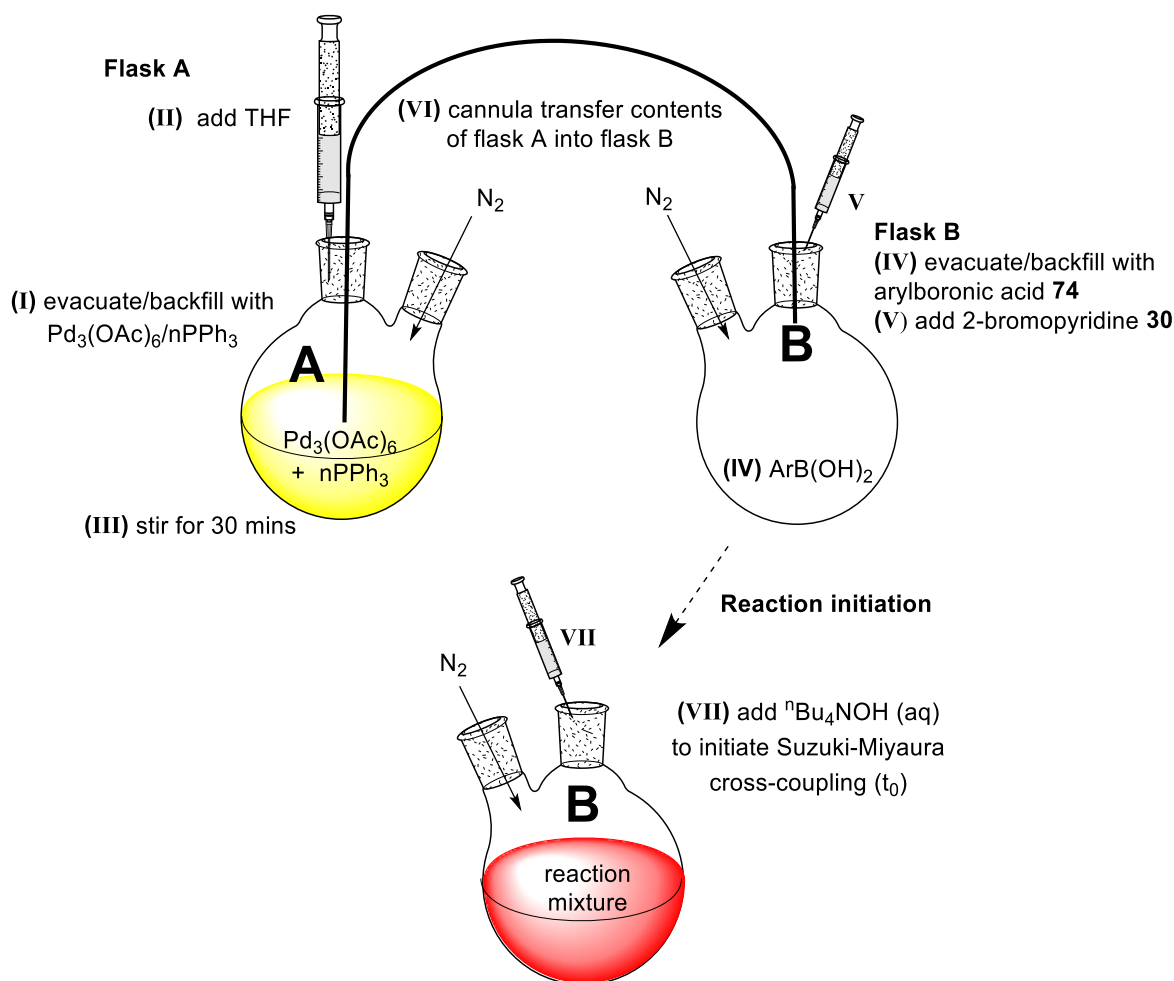


Figure 89 Highlighting the practical steps involved with reaction setup (General Procedure A) an adapted method was used for General Procedure B.

General Procedure B: The Use of Miscellaneous Isolated Molecular Species as Catalysts Under Model Suzuki-Miyaura Cross-coupling Conditions

An oven-dried Schlenk flask (*flask A*) charged with **Pd Catalyst** (See Table 12 for quantities used) was evacuated and backfilled with N_2 . Another oven-dried Schlenk flask (*flask B*) was charged with *para*-fluorophenylboronic acid **74B** (167.9 mg, 1.20 mmol) and subsequently evacuated and backfilled with N_2 . This flask was then injected with 2-bromopyridine (95 μL , 158.0 mg, 1.00 mmol, previously degassed). THF (2.5 mL; dry, degassed) was added *via* a syringe to *Flask A* which stirred at 40 $^\circ\text{C}$ for 1 minute. The contents of *Flask A* were transferred to into *Flask B* *via* a cannula, this mixture was stirred in a pre-heated oil bath 40 $^\circ\text{C}$ for 5 mins. *Tetra-n*-butylammonium hydroxide (aq., 2.5 mL, 1.0 M) was added *via* a syringe (marking t_0) and allowed to mix to form a homogenous solution by stirring for 30 seconds at 40 $^\circ\text{C}$. The reaction was sampled and a timecourse analysed according to the general method reported above.

Table 12 Quantities, moles, mass equivalents for the amount of Pd catalyst used relative to PPh₃ for experiments following procedure B

Pd Catalyst	Loading(x) mol%	Pd loading /mol%	Mass used / mg	<i>Labbook Reference Number</i>
[Pd ₂ (μ ₂ -OAc)(μ-PPh ₂)(PPh ₃) ₂] (52)	1.5	3	14.7	NWJS-4-319
[Pd ₃ (μ-Cl)(μ-PPh ₂) ₂ (μ-PPh ₃) ₃]Cl	1	3	15.5	NWJS-4-324
[Pd ₃ (μ-Br)(μ-PPh ₂) ₂ (μ-PPh ₃) ₃]Br	1	3	16.4	NWJS-4-327
[Pd(Br)(N,C ² -pyr)(PPh ₃) ₂] (56c)	0.5	3	5.3	NWJS-4-326
[Pd ⁰ (PPh ₃) ₃] (48)	3	3	26.7	NWJS-4-315

General Procedure C: Model Suzuki-Miyaura Cross-coupling Reaction, Catalysed by a Solution Formed From the Mixture of [Pd₂(μ-PPh₂)(μ₂-OAc)(PPh₃)₂] with 2-Bromopyridine

In an Ar-filled glovebox, a solution of 2-bromopyridine (3.0 mg, 0.019 mmol, 3.8 equiv.) in THF (0.85 mL; dry, degassed) was added to an oven-dried Schlenk flask (*Flask A*) charged with [Pd₂(μ-PPh₂)(μ₂-OAc)(PPh₃)₂] **52** (5.0 mg, 0.005 mmol, 1 equiv.). This solution was sealed before being removed from the glovebox, applied to Schlenk conditions and allowed to equilibrate with magnetic stirring at room temperature for 45 minutes.^w Meanwhile, another Schlenk flask (*Flask B*) was charged with *para*-fluorophenylboronic acid **74_B** (52.0 mg, 0.40 mmol) before being evacuated and backfilled with N₂. This flask was then injected with 2-bromopyridine **55** (95 μL, 158.0 mg, 1.00 mmol, previously degassed). The contents of *Flask A* were transferred into *Flask B* and the resultant solution was stirred in a pre-heated 40 °C oil bath for 5 minutes. *Tetra-n*-butylammonium hydroxide (aq., 0.85 mL, 1.0 M) was added *via* a syringe (marking t₀) and allowed to mix to form a homogenous solution by stirring for 30 seconds at 40 °C. The reaction was sampled according to the general method reported above.

Labbook Reference Number: NWJS-4-320.

^w ³¹P NMR spectroscopic analysis showed that full conversion of **52** to [Pd₃(μ-Br)(μ-PPh₂)₂(PPh₃)₃]X and other resonances (as detailed in Section 2.5.1) had occurred after this time.

High Temperature Model Suzuki-Miyaura Cross-coupling Reaction, Catalysed by Pre-stirred Pd₃(OAc)₆/12PPh₃: *Ex Situ* NMR analysis

An oven-dried Schlenk flask (*Flask A*) charged with Pd₃(OAc)₆ (6.7 mg, 0.01 mmol) and PPh₃ (31.4 mg, 0.12 mmol) was evacuated and backfilled with N₂. THF (2.5 mL; dry, degassed) was added *via* a syringe and the immediately-formed greenish-yellow fine suspension of *trans*-[Pd(OAc)₂(PPh₃)] **47** was stirred for 30 minutes in an oil bath which was pre-heated to 40 °C. Meanwhile, another oven-dried Schlenk flask (*Flask B*) was charged with *para*-fluorophenylboronic acid **74B** (167.9 mg, 1.20 mmol) and subsequently evacuated and backfilled with N₂. This flask was injected with 2-bromopyridine **55** (95 µL, 158.0 mg, 1.00 mmol, previously degassed). After the stirring period, the contents of *Flask A* were transferred to into *Flask B* *via* a cannula, this mixture was subsequently stirred at 70 °C for 5 minutes. *Tetra-n*-butylammonium hydroxide (aq. 2.5 mL, 1.0 M) was added *via* a syringe (marking t₀) and the subsequent solution was stirred at 70 °C.

An *ex situ* analysis method was developed to sample this reaction. Samples were taken at t = 10, 20, 30, 45, 60, 80, 100, 130, 150, 190, 240, 300, 360 and 1440 minutes. Each sample (100 µL) was quenched with dppe solution (2 mL, 2 mg.mL⁻¹). Each solution was then filtered through Celite before being concentrated *in vacuo*. The resulting orange oil was then dissolved in CDCl₃ (0.5 mL) and subjected to ¹H NMR analysis. From this data, the relative amounts of starting material and converted product could be plotted see chapter

Labbook Reference Number: NWJS-4-318.

General Procedure D: SMCC of Bromoindazole 70 and 6-quinolineboronic Acid 71

The procedure for each catalytic reaction was adapted from a method by Sach *et al.*²²⁸ A pressure tube equipped with a magnetic stirring bar was charged with 4-bromo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **70** (59.0 mg, 0.2 mmol), 6-quinoline boronic acid **71** (0.208 mmol, 36.0 mg), base (0.5 mmol, 2.5 eq: Na₂CO₃ {42.0 mg} or KOH {28.5 mg}), 1,3,5-trimethoxybenzene (56.0 mg) and Pd catalyst (See Table 13). The pressure tube was tightly sealed and THF (0.9 mL) and H₂O (0.1 mL) was added (forming a 1.0 mL, 0.2 M solution with respect to **70**). The pressure tube was then placed within an aluminium heating block and the temperature raised to reflux (~80 °C). Upon reaching 80 °C, the reaction was stirred at that temperature for 16 hours. The reaction mixture was quenched by addition of NH₄Cl (sat. aq., 1 mL). Organics were extracted with EtOAc (3 × 2 mL) and combined before being dried over MgSO₄ and concentrated in vacuum. Characterisation data for the product **72** is reported in Section 6.4.1.

Table 13 Catalyst identities and loadings – General Procedure D.

Catalyst	mol / %	n / mmol	m / mg	Labbook Reference Number
Pd(OAc)₂/ 2 PPh₃	6.25 / 12.5	0.0125/0.00250	2.8 / 6.6	NWJS-6-445
Pd₃(OAc)₆/12 PPh₃	6.25 / 25	0.00125/0.0050	2.8 / 13.1	NWJS-6-446
Pd₃Cl₂·Cl	1	0.002	3.1	NWJS-5-436
Pd₃Cl₂·Cl	3	0.006	9.3	NWJS-5-437

6.2.3. Procedures for Site-selective Cross-coupling Reactions (Chapter 4)

General Procedure E: Product Evolution Curves (Section 4.3.2) for Site-selective SMCC Reactions at 2,4-Dibromopyridine **30**

To an oven dried Schlenk tube, 2,4-dibromopyridine **30** (473 mg, 2.0 mmol, 1.0 equiv.), *para*-anisylboronic acid acid **74_A** (365 mg, 2.4 mmol, 1.2 eq) and ‘Pd catalyst’ (3 mol%/Pd) were added. The flask was sealed (Suba-seal®), THF (2.5 mL; dry, degassed) was added using a syringe and the resulting mixture was magnetically stirred for 5 minutes, in a pre-heated oil bath. After this time, all solids were seen to have dissolved into a clear solution and the temperature of the reaction was measured to be 40 ± 0.5 °C using an internal thermocouple. The cross-coupling reaction was then initiated by addition of *tetra-n*-butylammonium hydroxide solution (aq. 2.5 mL, 1.0 M→0.5 M, 2.5 equiv.) which was added by a rapid injection using a syringe over the Suba-seal®. The reaction was stirred, and samples were taken at the 0^x, 2.5, 5, 7.5, 10, 15, 20, 25, 20, 40, 50, 60, 80 and 100 minutes. Samples (*ca.* 100 uL), taken at the specified times *via* a 1000 µL syringe were rapidly quenched by dissolution in CH₂Cl₂ before being filtered through a pipette fitted with a Celite® plug (*ca.* 1 cm depth) (to get rid of any particulate Pd). Each filtrate was concentrated in vacuum to reveal a reddish-brown oil which was dissolved in CDCl₃ (0.5 mL) for NMR sampling. NMR spectra were analysed according to the method reported below.

^x The zero datapoint was taken as quickly as possible, the time at which it was taken was recorded and considered accurately in the analysis of the data.

Table 14 Catalysts, loadings and masses used for the product evolution assays. **54** = *trans*-[Pd(OAc)₂(*N*-piperidyl)]

Pd Catalyst	mol / %	n / mmol	m / mg	Labbook Reference Number
[Pd ₃ (μ-Cl)(μ-PPh ₂) ₂ (μ-PPh ₃) ₃]Cl	1	0.02	30.9	NWJS-2-160
[Pd ₃ (PPh ₃) ₄][BF ₄] ₂	1	0.03	30.8	NWJS-1-34
54 / {PPh ₃ } (1:1)	3/ {3}	0.06/ {0.06}	31.0	NWJS-2-84
Pd ₃ (OAc) ₆ / {2PPh ₃ }	1/ {6}	0.02/ {0.012}	13.5/ {31.5}	NWJS-5-432

General Procedure F: The Effect of Pre-catalytic *trans*-[Pd(OAc)₂(*N*-piperidyl)] **54 /nPPH₃ Ratio on Site-selective SMCC Reactions at 2,4-dibromopyridine **30****

To an oven dried Schlenk tube, equipped with a stirrer bar, 2,4-dibromopyridine **30** (237 mg, 1.0 mmol, 1 equiv.) was added along with *para*-anisylboronic acid **74_A** (182 mg, 1.2 mmol, 1.2 equiv.), *trans*-[Pd(OAc)₂(*N*-piperidyl)] **54** (11.7 mg, 3 mol%, 0.03 mmol with respect to Pd) and a variable amount of PPh₃ (see Table 15 below) . The flask was then sealed (Suba-seal®) before being evacuated and backfilled with N₂ three times. THF (5 mL; dry, degassed) was added and the resulting mixture was stirred for 5 minutes, after which time all solids were seen to have dissolved into a light-yellow solution. To this solution, a sonically degassed (*ca.* 20 minutes) aqueous solution of *tetra-n*-butylammonium hydroxide (2.5 mL, 1.0 M→0.5 M, 2.5 equiv.) was added by rapid injection, using a syringe. Samples (*ca.* 100 μL), taken at the specified times using a 1000 μL syringe were rapidly quenched by dissolution in CH₂Cl₂ solution before being filtered through a pipette fitted with a Celite plug (*ca.* 1 cm depth) (filter out any large particulate Pd). The filtrate was concentrated in vacuum to reveal a reddish-brown oil which was dissolved in CDCl₃ (0.5 mL) for NMR sampling. The samples were analysed according to the method reported below.

Table 15 Detailing ratio of Pd 54 to PPh₃ alongside the quantity (mmol and mg) of PPh₃ used in this study.

TomCat:PPh ₃ ratio (by mole) Pd:P	Amount of PPh ₃ /mmol	Mass of PPh ₃ /mg	Labbook Reference Number
1:0.5	0.015	3.9	NWJS-2-94
1:1	0.03	7.9	NWJS-2-89
1:2	0.06	15.7	NWJS-2-92
1:3	0.09	23.6	NWJS-2-91
1:4	0.12	31.5	NWJS-2-85
1:5	0.15	39.3	NWJS-2-93

General Procedure G: The Effect of Pre-catalytic Pd₃(OAc)₆/nPPh₃ Ratio on Site-selective SMCC Reactions at 2,4-dibromopyridine **30**

An oven-dried Schlenk flask (*Flask A*) charged with [Pd₃(OAc)₆] (6.7 mg, 0.03 mmol {3 mol%/Pd}) and PPh₃ (Table 16) was sealed (Suba-seal®), before being evacuated and backfilled with N₂. THF (2.5 mL; dry, degassed) was added *via* a syringe and the immediately formed greenish-yellow suspension was stirred in an oil bath which was pre-heated to 40 °C. Another oven-dried Schlenk flask (*Flask B*) was charged with 2,4-dibromopyridine **30** (236.9 mg, 1.00 mmol, 1.0 equiv.) and *para*-fluorophenylboronic acid **74B** (167.9 mg, 1.20 mmol), sealed (Suba-seal®), and subsequently evacuated and backfilled with N₂. After 30 minutes of stirring, the contents of *Flask A* were transferred into *Flask B* *via* a cannula and the resulting mixture was allowed to stir for 5 mins in order to thermally equilibrate as a solution at 40 °C. Aqueous *tetra-n*-Butylammonium hydroxide (aq., 1.0 M, 2.5 mL, degassed) was then added (*t*₀) to commence the reaction. Samples (*ca.* 125 µL), taken at the specified times using a 1000 µL syringe were rapidly quenched by dissolution in CH₂Cl₂ before being filtered through a Pasteur pipette which was fitted with a Celite plug (*ca.* 1 cm depth) (to remove large Pd particles). The filtrate was concentrated in vacuum to reveal a reddish-brown oil which was dissolved in CDCl₃ (0.5 mL) for NMR sampling. The samples were analysed according to the method reported below.

Table 16 Detailing the ratio of Pd₃(OAc)₆ to PPh₃ alongside the quantity (mmol and mg) of PPh₃ used in each reaction.

Pd ₃ (OAc) ₆ :PPh ₃ /mol%:mol%	Pd:P ratio	Amount of PPh ₃ /mmol	Mass of PPh ₃ /mg	Labbook Reference Number
1:0	1:0	N/A	N/A	NWJS-5-417
1:1.5	1:0.5	0.015	3.9	NWJS-5-418
1:3	1:1	0.03	7.9	NWJS-4-307
1:4.5	1:1.5	0.045	11.8	NWJS-5-419
1:6	1:2	0.06	15.7	NWJS-4-306
1:7.5	1:2.5	0.075	19.7	NWJS-5-414
1:9	1:3	0.09	23.6	NWJS-4-308
1:12	1:4	0.12	31.5	NWJS-5-401

General Procedure H: Base and Additive Effects on Site-selectivity in SMCC reactions at 2,4-dibromopyridine **30**

An oven-dried Schlenk flask charged with 2,4-dibromopyridine **30** (236.9 mg, 1.0 mmol), *para*-anisylboronic acid **74A** (182.4 mg, 1.2 mmol) Pd Cat. (3 mol% Pd loading, see Table 17 for specific quantities used) was sealed (Suba-seal®), evacuated and backfilled with N₂. Depending on the reaction, the additive was added at this point (See Table 18 for specific amounts used). The flask's atmosphere was then evacuated and backfilled with N₂ before THF (2.5 mL; dry, degassed) was added *via* a syringe and the resulting mixture, which appeared as a solution, was stirred for 5 minutes at 40 °C (pre-heated oil bath). After this time, aqueous **base** (2.5 mL, 1.0 M, degassed) was added (*t*₀) to commence the reaction. The resulting reaction solution was hence stirred at 40 °C. Samples (*ca.* 125 uL), taken at the specified times using a 1000 µL syringe were rapidly quenched by dissolution in CH₂Cl₂ solution before being filtered through a Pasteur pipette fitted with a Celite plug (*ca.* 1 cm depth) (to get rid of any particulate Pd). The filtrate was concentrated in vacuum to reveal a reddish-brown oil which was dissolved in CDCl₃ (0.5 mL) for NMR sampling. The samples were analysed according to the method reported below.

Table 17 Catalyst amounts used in additive study.

Pd Cat.	mass / mg	amount / mmol
$\text{Pd}_3(\text{OAc})_6$ / 3 {PPh ₃ }	6.7 / {7.9}	0.01 / {0.03}
$\text{Pd}_3(\text{OAc})_6$ / 6 {PPh ₃ }	6.7 / {15.5}	0.01 / {0.06}
$[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$	15.5	0.01

Table 18 Additive amounts used in additive study.

Additive	m / mg	amount / mmol
<i>n</i> -Bu ₄ NBr	805	2.5
<i>n</i> -Octyl ₄ NBr	1367	2.5

Labbook Reference Numbers (Chapter 4, Table 7): NWJS-5-392 (Entry 1), NWJS-2-119 (Entry 2), NWJS-6-487 (Entry 3), NWJS-6-432 (Entry 4), LMS-1-34 (Entry 5), NWJS-2-160 (Entry 6), LMS-1-002 (Entry 7), LMS-1-006 (Entry 8), LMS-1-033 (Entry 9).

General Procedure I: Site-selective Kumada-Corriu Cross-couplings at 2,4-Dibromopyridine **30**

A Schlenk flask (*Flask A*) was charged with $\text{Pd}_3(\text{OAc})_6$ (6.7 mg, 0.01 mmol, 1 mol%, Table 19) and PPh₃ (3, 6, or 12 mol%, Table 19), (+/-) *tetra-n*-octylammonium bromide (805.92 mg, 1.5 equiv.) and sealed (Suba-seal®) before being evacuated and backfilled with N₂ three times. THF (2.5 mL; dry, deoxygenated) was added and the resulting mixture was stirred at 23 °C for 0.5 or 24 hours.

A second Schlenk flask (*Flask B*) was charged with 2,4-dibromopyridine **30** before being evacuated and backfilled with N₂ three times. THF (1.3 mL) was added and the resulting clear solution was stirred at room temperature. After the specified premixing time, the contents of *Flask A* were transferred *via* cannula into *Flask B*. The resulting mixture was allowed to equilibrate for 1 minute with magnetic stirring, after which time phenylmagnesium bromide **77** solution (1.2 mL, 1.0 M in THF => total volume of 5 mL) was added in a rapid injection. The subsequent solution was stirred for one hour. The needle, containing excess **77** solution could be quenched with isopropyl alcohol, then washed through with H₂O.

A sample (125 µL) was taken *via* a syringe and quickly quenched by addition to a vial containing 100 µL of NH₄Cl solution (*aq.*, sat.) and 1 mL of H₂O. EtOAc (2 mL) was added and the resulting mixture was vigorously shaken. The EtOAc layer was removed using a pipette and the aqueous layer was

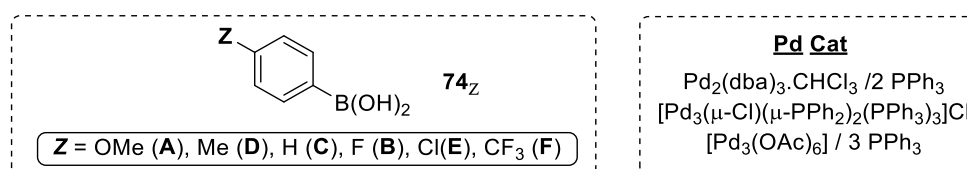
extracted with another two aliquots of EtOAc (2 mL). The combined organics were filtered through an MgSO₄ plug (*ca.* 1 cm depth) and washed through with EtOAc (1 mL). The filtrate was concentrated *in vacuo* to afford a yellow oil which was dissolved in CDCl₃ and subjected to ¹H NMR analysis (*vide infra*).

Table 19 Detailing ratio of Pd₃(OAc)₆ to PPh₃ alongside the quantity (mmol and mg) of PPh₃ used in this study.

Pd ₃ (OAc) ₆ :PPh ₃ /mol%:mol%	Pd:P ratio	Amount of PPh ₃ /mmol	Mass of PPh ₃ /mg
1:3	1:1	0.03	7.9
1:6	1:2	0.06	15.7
1:12	1:4	0.12	31.5

Labbook Reference Numbers (*Chapter 4*); Table 8: NWJS-4-342 (*Entry 1*), NWJS-4-342 (*Entry 2*), NWJS-4-340 (*Entry 3*), NWJS-5-399 (*Entry 4*); Table 9: NWJS-4-342 (*Entry 1*), NWJS-5-343 (*Entry 2*), NWJS-6-346 (*Entry 3*), NWJS-4-333 (*Entry 4*), NWJS-5-351 (*Entry 5*).

General Procedure J: *Para*-substituent Effect on Catalyst Site-selectivity



Scheme 87 Cat and conditions used for investigating boronic acid *para*-substituent effects on the site-selective SMCC reaction at 1.

An oven-dried Schlenk tube, charged with a Pd catalyst (3 mol%/Pd, see Table 20 for details), 2,4-dibromopyridine **30** (236.9 mg, 1.0 mmol), *para*-substituted phenylboronic acid **74_{A-F}** (1.2 mmol, Scheme 87) was sealed (Suba-seal®) before being evacuated and backfilled with N₂. THF (2.5 mL; dry, degassed) was added *via* a syringe (over the Suba-seal®) and the resulting mixture was allowed to magnetically stir for 5 minutes in an oil bath which was pre-heated to 40 °C, to allow for full dissolution and thermal equilibration. *Tetra-n*-butylammonium hydroxide solution (2.5 mL, 1.0 M, degassed) was then added (*t*₀) to commence the reaction.

Samples (*ca.* 125 μ L), taken at 1 hour using a 1 mL syringe, were rapidly quenched by dissolution in CH_2Cl_2 before being filtered through a pipette fitted with a Celite[®] plug (*ca.* 1 cm depth) (to get rid of any particulate Pd). The filtrate was then concentrated *in vacuo* to reveal a reddish-brown oil which was dissolved in CDCl_3 (0.5 mL) for NMR sampling. The samples were analysed according to the method reported below.

Table 20 Catalyst amounts used for *Para*-substituent effect on catalyst site-selectivity study

Pd Cat.	mass /mg	amount / mmol
$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 \{2\text{PPh}_3\}$	16.5 {7.9}	0.015 {0.03}
$[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$	15.5	0.01
$\text{Pd}_3(\text{OAc})_6 \{ \text{PPh}_3 \}$	6.7 {7.9}	0.01 {0.03}

General Workup Procedure for Site-selective SMCC and Kumada reactions

The above cross-coupling reactions involving 2,4-dibromopyridine **30** (both SMCC and Kumada) could be worked up using the following procedure. After the reaction time the reaction solution was quenched using a of NH_4Cl (sat. aq). The organics were then extracted using EtOAc (4×10 mL) and combined before drying over MgSO_4 and subsequently concentrated *in vacuo*. The resulting residue, which generally appeared as a reddish-brown oil, could be purified by column chromatography (SiO_2) using a hexane or petroleum ether/EtOAc solvent system. See Section 6.4.2 for details on the purification of the specific compounds.

¹H NMR Analysis of NMR Samples of Site-selective Cross-coupling Reactions

The reaction conversion and site-selectivity of cross-coupling reactions at 2,4-dibromopyridine **30** were generally determined using a ¹H-NMR spectroscopy-based assay of crude reaction samples. Crude samples were prepared according to the relevant method (*vide supra*). Products were identified in the crude reaction solution by reference to literature-published data or, if the product was not reported, comparison to characterisation data from the isolated product (See section 6.4.2 for specific data). The pyridyl- H_6 protons of the starting materials and products were generally well-resolved, due to the significant deshielding (proximity to electronegative N atom), thus, integration of these protons was generally used to determine the relative amounts of starting material and products: **C2-Ar**, **C4-Ar** and **diaryl**.

The errors for ^1H NMR (400 MHz) integration for measurements taken in site-selective cross-coupling reactions at **30** are within a $\pm < 2\%$ confidence limit. This value was obtained by measuring the variance (%) in a reaction run in triplicate. The amount of sample taken (125 μL , from the 0.2 M reaction mixtures) was kept constant and 32 scans were recorded in each NMR experiment, allowing for comparable signal/noise ratios. Increasing the relaxation delay (D_1) between scans made no appreciable difference in relative ratio of the peaks.

An example of how the products could be identified and quantified in the crude, post-reaction mixture is shown below. The quantification method was validated by use of an internal standard (*vide infra*).

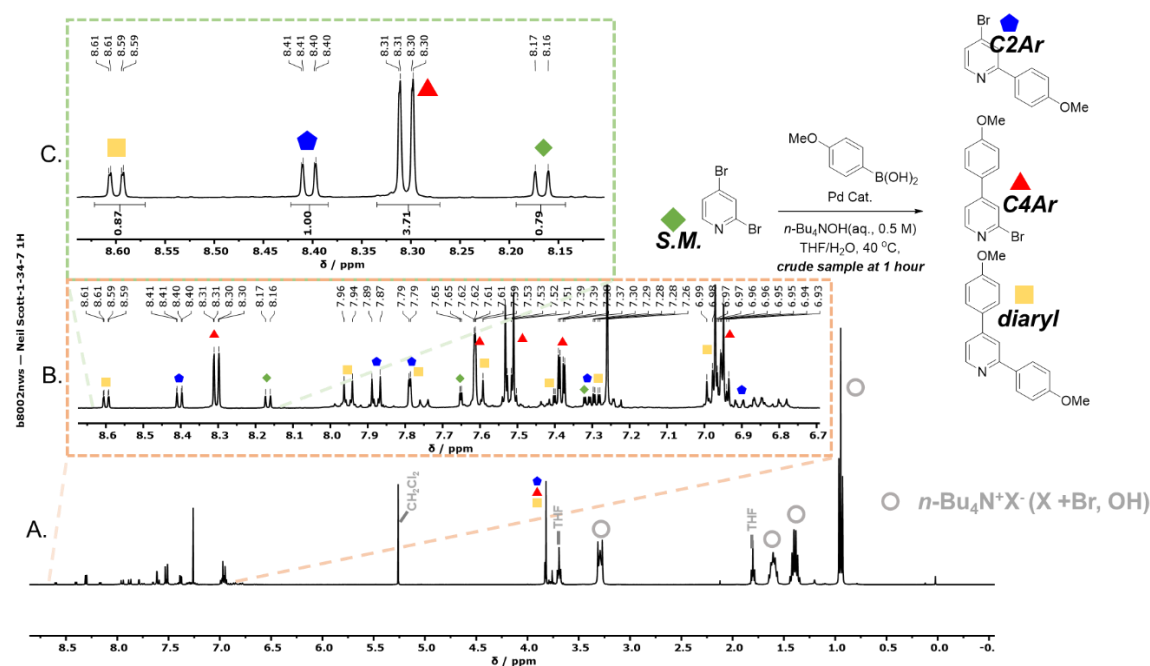


Figure 90 Method used for identifying and quantifying products of site-selective cross-coupling reactions at **30** by ^1H NMR spectroscopy. A) crude NMR spectrum, B) expansion of aromatic region, allowing for the characterisation of products, C) Expansion of the pyridine- H_6 region, integration of which allowed for determination of reaction conversion and site-selectivity of the reaction.

How conversion and site-selectivity data was obtained:

$$\text{Overall Conversion (\%)} = \frac{\text{integration C2+C4+diaryl}}{\text{integration S.M. +C2+C4+diaryl}} \times 100 = \mathbf{87.6\%}$$

$$\text{Conversion of given product e.g. C2-Ar (\%)} = \frac{\text{integration C2}}{\text{integration S.M. +C2+C4+diaryl}} \times 100 = \mathbf{15.7\%}$$

Using this method was therefore processed as highlighted in Table 21.

Table 21 General method for processing of data to quantify overall conversion, and site-selectivity in cross-coupling reactions at 2,4-dibromopyridine (**30**).

	S.M. (30)	C2-Ar	C4-Ar	diaryl
Integral	0.79	3.71	1.00	0.87
Conversion (%)	12.4	58.2	15.7	13.7

The above method was validated against an internal standard, 1,3,5-trimethoxybenzene. To do this, 1,3,5-trimethoxybenzene (56.0 mg, 0.333 mmol) was added as a solid, alongside the other solids of the reaction mixture ($\text{Pd}(\text{OAc})_2/1\text{PPh}_3$), 2,4-dibromopyridine **30** (1.0 mmol) and the *para*-substituted phenylboronic acid (**74**_{A-F}, 1.20 mmol). The reaction was carried out and sampled as highlighted in General Procedure F (*vide supra*). The sample was subjected to by ^1H NMR spectroscopic analysis (see Section 6.4.2 below for details of product identification and characterisation).

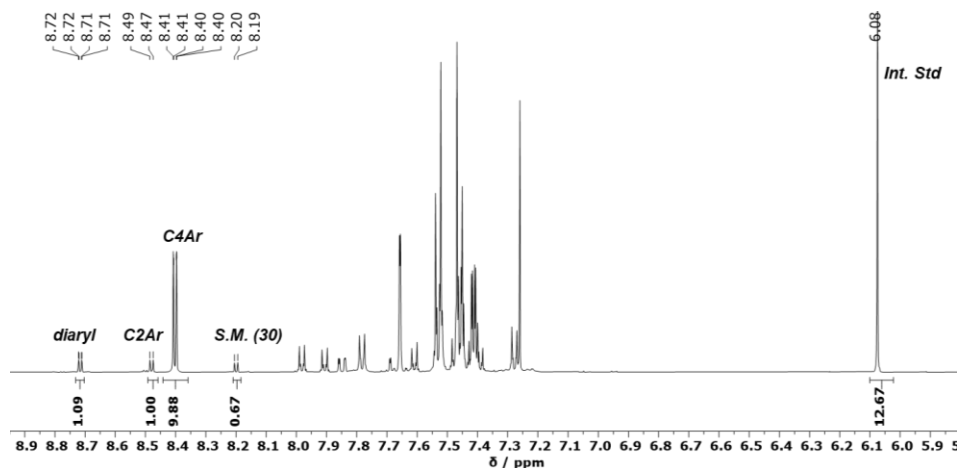


Figure 91 A ^1H NMR spectrum (400 MHz, CDCl_3), showing how the pyridyl- H_6 peaks representing **30** and the three SMCC products were quantified against the *aryl*-H (3H) resonance of 1,3,5-trimethoxybenzene internal standard ('Int Std') in a crude reaction sample.

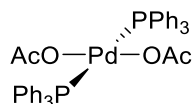
The products could then be quantified against the internal standard as follows (Table 22), indicating a quantitative method.

Table 22 An example of how the method of analysis of the crude SMCC reaction mixture was validated by use of a 1,3,5-trimethoxybenzene internal standard. *Internal standard = Peak at δ_{H} 6.08 ppm, representing $3 \times \text{Aryl-H}$ protons was used for integral comparison.

	S.M. (30)	C4-Ar	C2-Ar	diaryl	Int Std*
Integration	0.67	9.88	1.00	1.09	12.67
Conversion (%)	5.3	78.2	7.9	8.6	N/A
Conversion (%) against Int Std*	5.3	78.0	8.0	8.6	N/A

6.3. Synthesis and Characterisation of Organometallic Compounds

***Bis*(triphenylphosphine)palladium(II) diacetate 47 from Pd₃(OAc)₆**



A Schlenk tube was charged with Pd₃(OAc)₆ (50.0 mg, 0.074 mmol) and PPh₃ (233.7 mg, 0.446 mmol, 6 equiv.), before being sealed (Suba-seal®) and evacuated and backfilled with N₂ (three times). The flask was cooled to 0 °C and cold THF (5.5 mL; dry, degassed) was added *via* a syringe over the Suba-seal®, with magnetic stirring. The resulting mixture was magnetically stirred for 5 minutes, generating a stirred suspension of a bright green-yellow solid. THF was removed *in vacuo* (Schlenk), keeping cool at 0 °C. The residue was washed with Et₂O (3 × 2 mL; dry, degassed) and the residue was dried under high vacuum. The product appeared as a greenish-yellow powder which darkened under air. The compound was sparingly soluble in THF and benzene but showed better solubility in DMF. A quantitative yield was obtained from the procedure; however, the compound was not characterised in a pure form in the solution phase, owing to the complex's inherent instability (see Section 2.4). The compound data matches that reported in literature.^{46, 50}

³¹P NMR (203 MHz, THF-*d*₈) δ 15.09 ppm

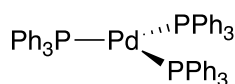
¹H NMR (500 MHz, THF-*d*₈) δ 7.75 (q, *J*_{HH} = 5.6 Hz, 12, PCCH), 7.41 (t, *J*_{HH} = 7.3 Hz, 6H, PCCHCHCH), 7.35 (t, *J* = 7.3 Hz, 12H, PCCHCH), 0.77 (s, 6H, -C(O)CH₃) ppm.

IR data (ν/cm⁻¹, ATR) 1636 (*br. s.*, C=O *ν*_{asym} stretch), 1625(s), 1570 (s), 1482 (s), 1434 (s), 1536.0 (s), 1299 (s, C=O *ν*_{sym} stretch), 1070 (s), 743 (m), 690 (vs), 520 (s), 507 (vs), 494 (s).

See Appendix 4 for X-Ray Crystallographic Data (ijsf1807a).

Labbook Reference Number: NWJS-4-298.

***Tris*(triphenylphosphine) Palladium(0) 48 from Pd₃(OAc)₆**



Pd₃(OAc)₆ (44.2 mg, 0.656 mmol) and PPh₃ (209.8 mg, 0.800 mmol) were added to an oven-dried Schlenk flask which was evacuated and backfilled with N₂ (three times) THF (10 mL; dry, degassed) was added *via* syringe and the reaction temperature was raised to 60 °C. The solution was stirred at 60

°C overnight, under an atmosphere of N₂. After 16 hours, a sample was taken (using Schlenk techniques) which showed some remaining *trans*-[Pd(OAc)₂(PPh₃)₂] **47** (³¹P NMR singlet at δ 15.1 ppm). The reaction was then brought to reflux (66 °C) for 30 minutes after which time complete consumption of **47** was seen to have occurred. At this point ¹H NMR spectroscopy showed complete conversion of **47** to Pd⁰(PPh₃)₃, with one equivalent of O=PPh₃ and 2 equivalents of acetic acid.

The reaction mixture was then allowed to cool to room temperature and filtered to remove a small amount of formed Pd black. The solvent was removed *in vacuo* and the residual bright yellow solid was washed with Et₂O (3 × 2 mL; dry, degassed), to remove excess PPh₃. This residue was dried *in vacuo*. Yield: 55 mg, 34 %. This residue was purified by recrystallisation from a THF solution (10 mg.ml⁻¹), layered with hexane (THF/hexane, *ca.* 1/5 {v/v}) under a N₂ atmosphere at 18 °C. Crystals suitable for X-ray diffraction studies were isolated from this solution. [Pd⁰(PPh₃)₃] complex is reported in and matches literature data.^{19, 340}

¹H NMR (500 MHz, THF-*d*₈) δ 7.19 (*br. t*, *J* = 8.1 Hz, 18H, PCCH), 7.15 (*br. t*, *J* = 7.4 Hz, 9H, PCCHCHCH), 7.03 (*br. t*, *J* = 7.4 Hz, 18H, PCCHCHCH).

³¹P NMR (203 MHz, THF-*d*₈) δ 19.54 (s, 3P).

¹³C NMR (126 MHz, THF-*d*₈) δ 140.2 (d, ¹*J*_{C-P} = 14.1 Hz, PCCH), 134.8 (d, ²*J*_{C-P} = 17.4 Hz, PCCH), 129.0 (s, PCCHCHCH), 128.8 (d, ³*J* = 8.1 Hz, PCCHCHCH).

Elemental analysis (CHN) for 7Pd(PPh₃)₃:1Pd: (calc.) C, 71.39; H, 4.99; (found) C, 71.44 H, 5.13. The trace Pd metal contaminant present in this sample is estimated at 1.7 wt.%. It is noted that [Pd(PPh₃)₃] is an inherently unstable species (16e⁻ Pd⁰ complex), thus its decomposition to Pd metal in the solid state is expected.

LIFDI-MS Data (+ve mode) mode: Found 892.17723 (M⁺); Calc. (for C₅₀H₄₃O₂P₃Pd₂) 892.17635.

See Appendix 4 for X-Ray Crystallographic Data (ijsf1821).

Labbook reference number: NWJS-4-293, NWJS-4-312.

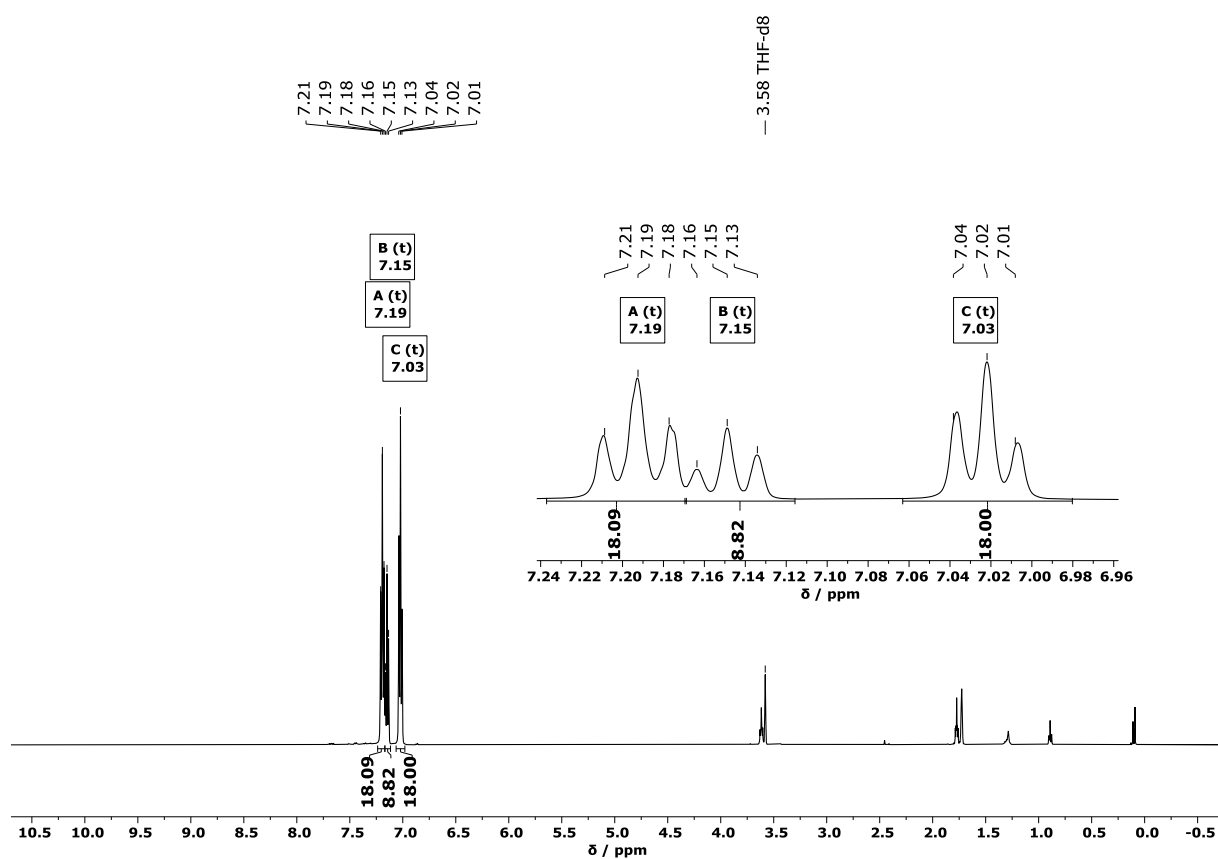


Figure 92 ^1H NMR Spectrum (500 MHz, $\text{THF-}d_8$) of $[\text{Pd}^0(\text{PPh}_3)_3]$ 48.

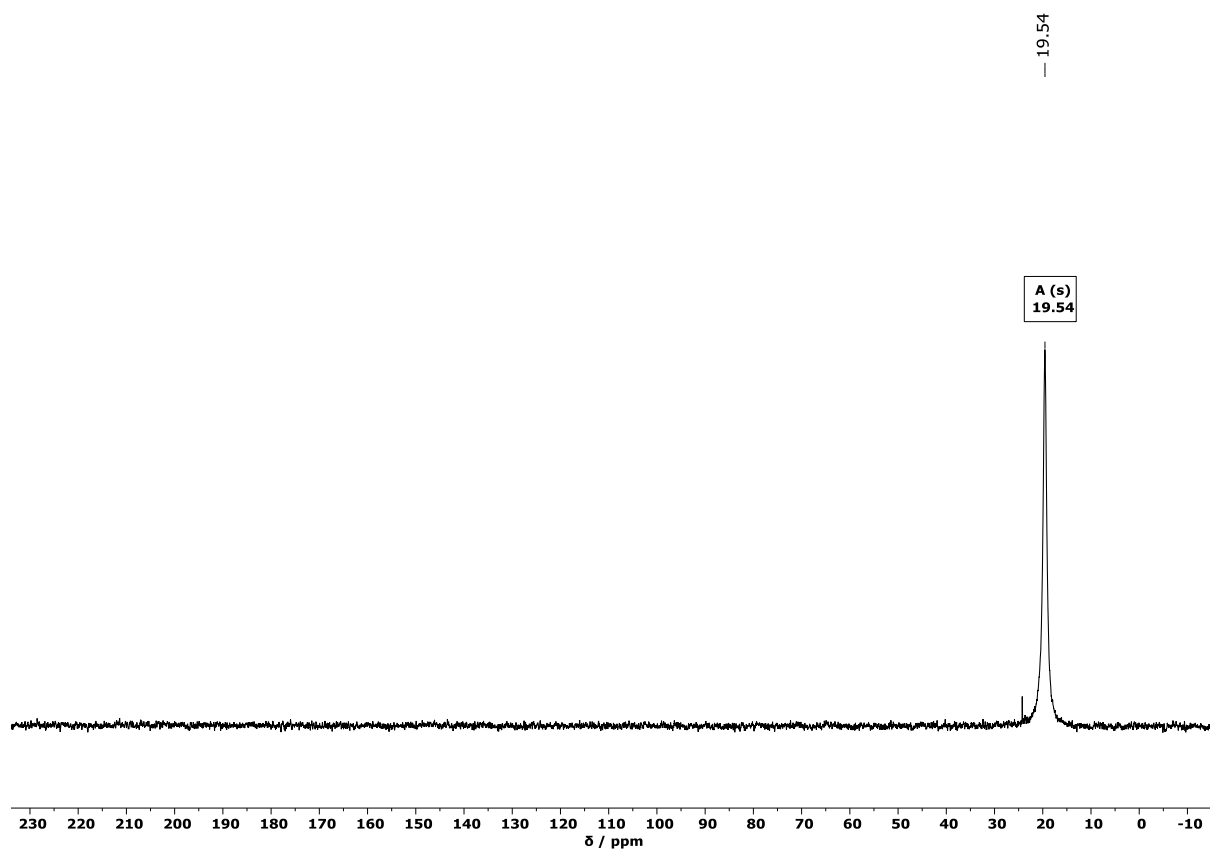


Figure 93 ^{31}P NMR Spectrum (203 MHz, $\text{THF-}d_8$) of $[\text{Pd}^0(\text{PPh}_3)_3]$ 48.

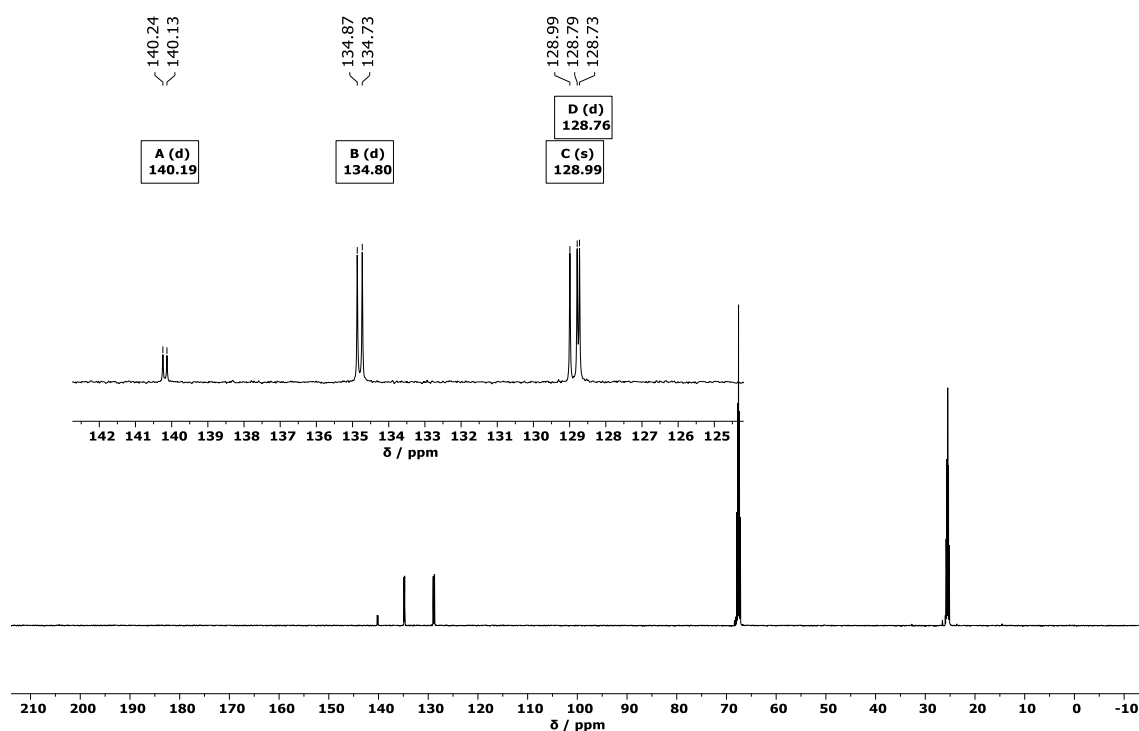
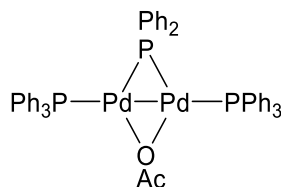


Figure 94 ^{13}C NMR Spectrum (126 MHz, $\text{THF-}d_8$) of $[\text{Pd}^0(\text{PPh}_3)_3]$ **48**.

$[\text{Pd}^{\text{I}}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** from $\text{Pd}_3(\text{OAc})_6$



$[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52** was first observed by ^{31}P NMR (wide spectral window, +250 to –50 ppm) spectroscopic analysis of the $\text{Pd}_3(\text{OAc})_6$ / 6 PPh_3 crude reaction mixture which showed an intriguing phosphido-type low-field resonance (δ 199.06 ppm $\text{THF-}d_8$) coupled to a higher field phosphine-type resonance (δ 13.43 ppm). The structure of this species was first postulated upon close analysis of a LIFDI-MS spectrum (detection of the radical cation) of this crude reaction mixture, subsequently by X-ray diffraction analysis of a single crystal of the dinuclear Pd^{I} complex **52**.

The following preparative method was devised for the synthesis of and isolation of $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]$ **52**. $\text{Pd}_3(\text{OAc})_6$ (100 mg, $673.5 \text{ g}\cdot\text{mol}^{-1}$, 148 μmol) and PPh_3 (233.7 mg, 891 μmol) were added to a Schlenk flask which subsequently evacuated and backfilled with N_2 . THF (65 mL, giving a 3.4 mM final concentration; dry, degassed,) was added slowly *via* a cannula, with vigorous stirring, until all instantaneously formed *trans*- $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ **47** had fully dissolved into a pale green-yellow

solution. Stirring was halted {to minimise metal particle growth from competing reduction of Pd^{II} to Pd⁰} and the solution of **47** was left standing at 23 °C. Samples could be taken to monitor the conversion of **47** to **52** using ³¹P NMR spectroscopy (sampling from the Schlenk flask under inert {N₂} atmosphere conditions). After three hours, **47** had been fully consumed, thusly the solution was concentrated *in vacuo* from 3.4 mM to 22 mM (with respect to the amount of Pd). The solution was filtered to remove small amounts of formed Pd black. The filtrate was cooled to 0 °C and hexane (*ca.* 40 mL => ~1:4 THF/hexane {v/v}) was added *via* cannula, with stirring. Stirring was halted once the solutions were fully mixed and the solution was left to precipitate for *ca.* 2 hours. The solid was then isolated *via* filtration (using Schlenk techniques) and residual solvent was then removed *in vacuo* to give the product as a dark red-purple powder (67 mg, 31% yield). The mother liquor yielded a precipitate of [Pd₂(μ-OAc)₂(C₆H₅)₂(PPh₃)₂] **53** after standing at room temperature for *ca.* 3 days (*vide infra*). Crystals suitable for X-ray diffraction were produced by layering a THF solution of the crude reaction mixture of Pd₃(OAc)₆ with 6 equivalents of PPh₃ with hexane, (THF/hexane, {1:5, v/v}, after total consumption of *trans*-[Pd(OAc)₂(PPh₂)₂] **47**).

¹H NMR (500 MHz, THF-*d*₈) δ 7.39 (*br. d*, *J* = 7.5 Hz, 12H, PCCH of PPh₃), 7.25 (*br. t*, 8H { *t*, *J* = 7.1 Hz, 8H, PCCHCHCH of PPh₃ } + PCCHCHCH of PPh₂ (2H), almost completely buried), 7.15 (*t*, *J* = 7.6 Hz, 12H, PCCHCH of PPh₃), 7.10 (*app. t*, *J* = 9.7 Hz, 4H, PCCHCH of PPh₂), 6.99 (*t*, *J* = 7.5 Hz, 4H, PCCH), 2.07 (*s*, 3H OCOCH₃).

³¹P NMR (203 MHz, THF-*d*₈); ³¹P NMR AB₂ spin system; δ 199.06 (*t*, *J* = 82.0 Hz, **A**, 1P, PPh₂), 13.43 (*d*, *J* = 82.0 Hz, 2P, **B**₂, 2PPh₃).

¹³C NMR (126 MHz, THF-*d*₈) δ 187.9 (OC(O)CH₃), 141.38 (*d*, ¹*J*_{C-P} = 8.0 Hz, PCCH of PPh₂), 136.6 (*br. s*, PCCH of PPh₃), 134.6 (*s*, PCCHCH of PPh₃), 133.5 (*d*, ²*J*_{C-P} = 14.9 Hz, PCCHCH of PPh₂), 129.8 (*br. s*, PCCHCHCH of PPh₃), 129.3 (*s*, PCCHCHCH of PPh₂), 128.7 (*br. s*, PCCH of PPh₃), 128.3 (*d*, *J* = 9.1 Hz, PCCHCH of PPh₂).

IR {*ν*, in THF (5.1 mM), cm⁻¹} 1532 (*ν*_{asym}), 1479, 1435, 1401 (*ν*_{sym}); *ν*_{asym} – *ν*_{sym} = 131 cm⁻¹. Calculated (DFT): *ν*_{asym}CO₂ = 1589 (rel. int. set to 1); *ν*_{sym}CO₂ = 1455 (rel. int. = 0.34) & 1429 (rel. int. = 0.47); *ν*_{asym}CO₂(calc.) – *ν*_{sym}CO₂(calc.,ave.) = 147 cm⁻¹. The experimental and calculated stretching frequencies for *ν*_{asym}CO₂ and *ν*_{sym}CO₂ are in-keeping with those reported for a related Pd^I complex containing a μ₂-1,3-carboxylato ligand,²⁴⁵ and comparable more general to related metal complexes containing μ₂-1,3-carboxylato ligands.²⁴⁹

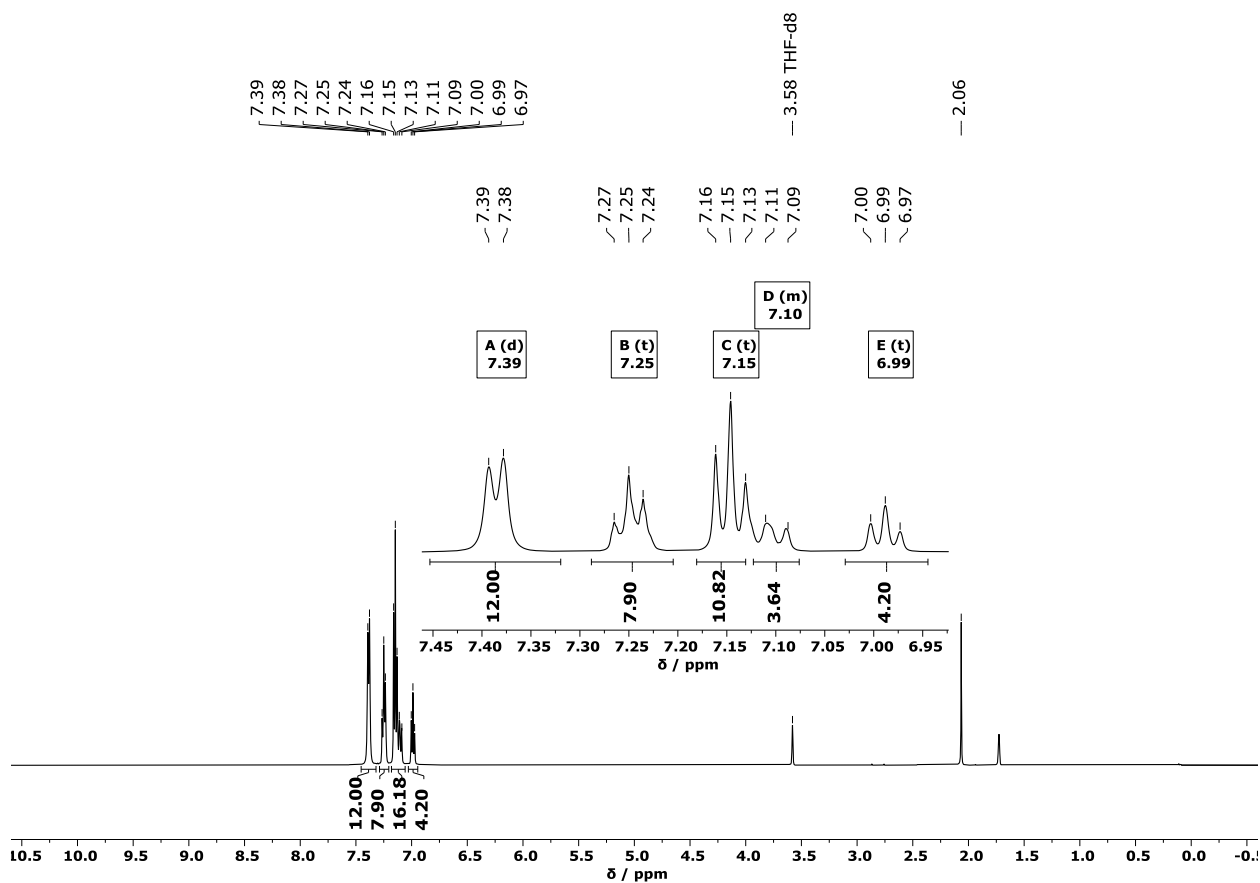
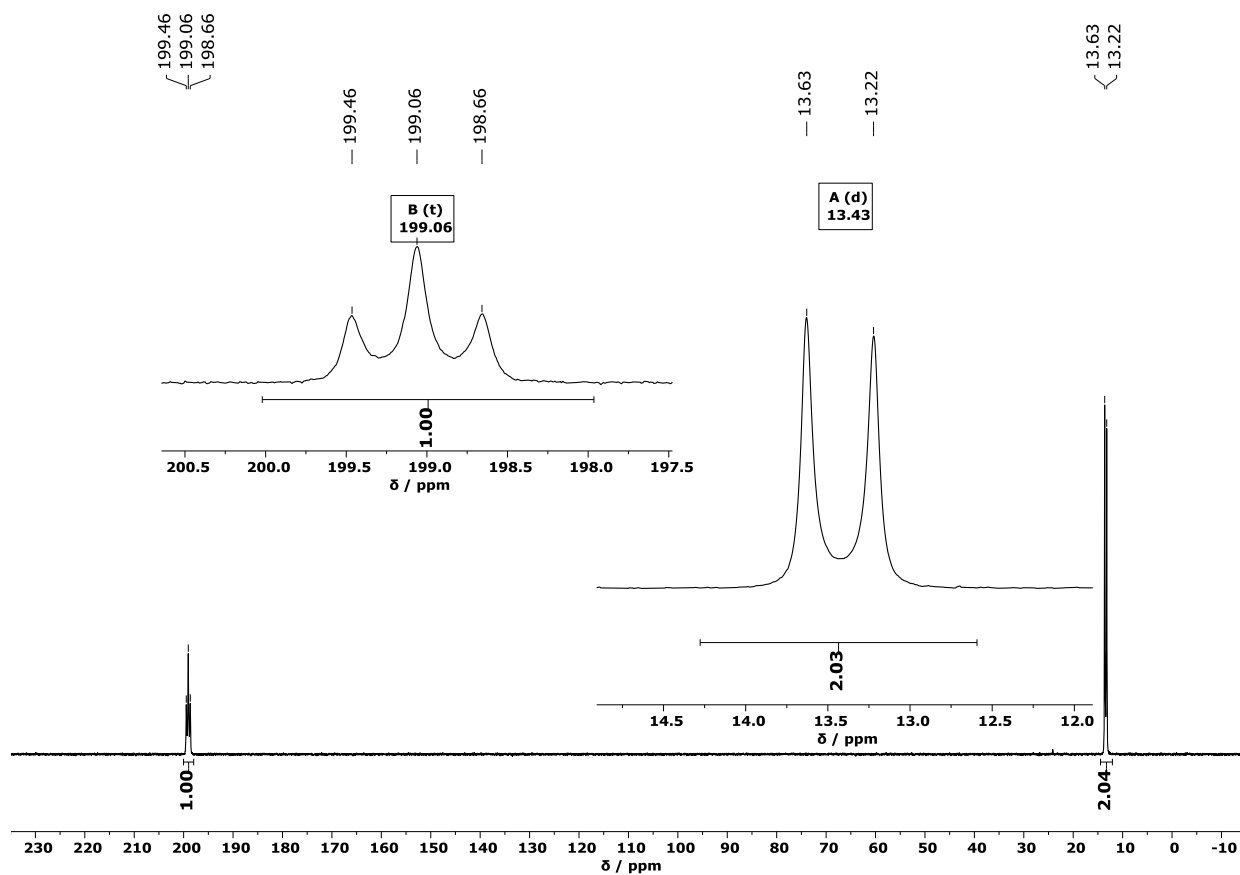
LIFDI-MS (+ve mode) mode: Found 980.05517 (M⁺); Calc. (for C₅₀H₄₃O₂P₃Pd₂) 980.05401.

Elemental analysis (CHN) for C₅₀H₄₃O₂P₃Pd₂: Calc. for 61.18 H, 4.42; Found C, 61.53 H, 4.44.

MP – 112-114 °C (decomposition in sealed capillary tube under Ar).

See Appendix 4 for X-Ray Crystallographic Data (ijsf 1817).

Labbook Reference Number: NWJS-6-473, NWJS-6-316, NWJS-6-440.

Figure 95 ¹H NMR spectrum (500 MHz, THF-*d*₈) of [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] 52Figure 96 ³¹P NMR spectrum (203 MHz, THF-*d*₈) of [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] 52

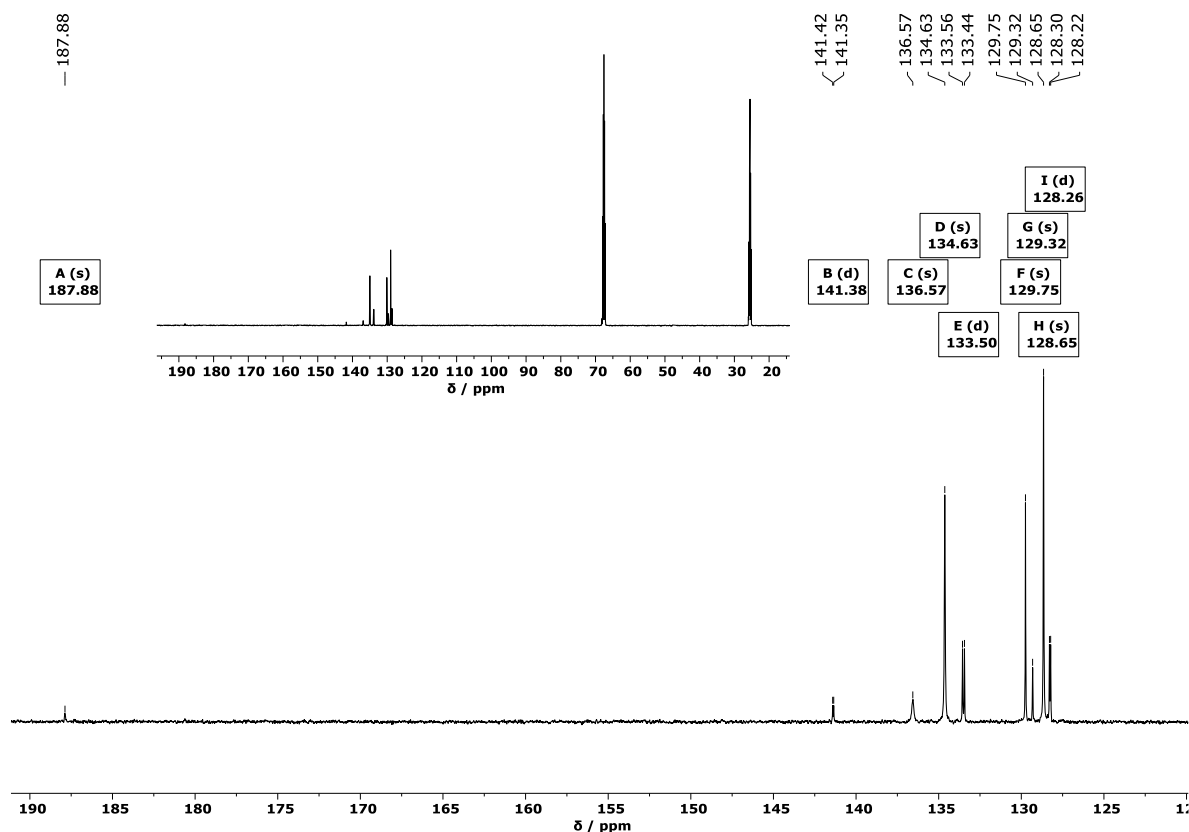
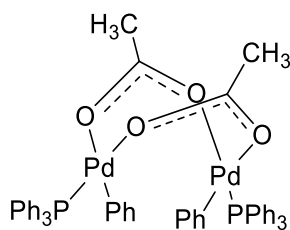


Figure 97 ^{13}C NMR spectrum (126 MHz, $\text{THF-}d_8$) of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ **52**.

bis[μ -(Acetato- $\kappa\text{-O},\kappa\text{-O}'$)]diphenylbis(triphenylphosphine)dipalladium **53**
 isolated from $\text{Pd}_3(\text{OAc})_6/6 \text{ PPh}_3$



53

The mother liquor isolated from the solid precipitate of the reaction forming **52** (*vide supra*) was left standing for *ca.* 3 days at room temperature under an atmosphere of N_2 . From this solution, a clump of off-white precipitate of **53** was observed, which was filtered off before being recrystallised (by layering a THF solution of **53** with hexane {1:5, v/v}). A single crystal was selected for X-ray crystallography, confirming the structure and molecular connectivity of the title compound. This data matched that which had been previously reported in literature.²⁵⁰

^1H NMR (500 MHz, $\text{THF-}d_8$) δ 7.33 – 7.20 (m, 22H, PPh_3 + PdPCH), 7.09 (br. t, $J = 6.7$ Hz, 12H PPh_3), 6.81 (br. t, $J = 7.1$ Hz, 2H, Pd-CCHCHCH), 6.68 (br. t, $J = 7.4$ Hz, 4H, PdCCHCHCH), 1.13 (br. s, 6H, OC(O)CH_3).

^{31}P NMR (203 MHz, $\text{THF-}d_8$) δ 30.70 (s, 2P) ppm.

^{13}C NMR (126 MHz, $\text{THF-}d_8$) δ 179.8 (s, OC(O)CH_3), 150.2 ($\text{CCH}\{\textit{phenyl}\}$), 138.5 ($\text{CCH}\{\textit{phenyl}\}$), 135.6 (d, $^1J_{\text{C-P}} = 11.4$ Hz,), 131.3 (d, $^2J_{\text{C-P}} = 50.8$ Hz, PCCH), 130.8 (s, $\text{CCHCH}\{\textit{phenyl}\}$), 128.6 (d, $^3J_{\text{C-P}} = 10.6$ Hz, PCCHCH), 127.4 (s, PCCHCHCH), 123.7, 24.2 (s, OC(O)CH_3) ppm.

LIFDI-MS Data (+ve mode) mode: Found 1008.09216 (M^{+}); Calc. (for $\text{C}_{52}\text{H}_{46}\text{O}_4\text{P}_2\text{Pd}_2$) 1008.09355.

See Appendix 4 for X-Ray Crystallographic Data (ijsf 1818).

Labbook Reference Number: NWJS-4-273

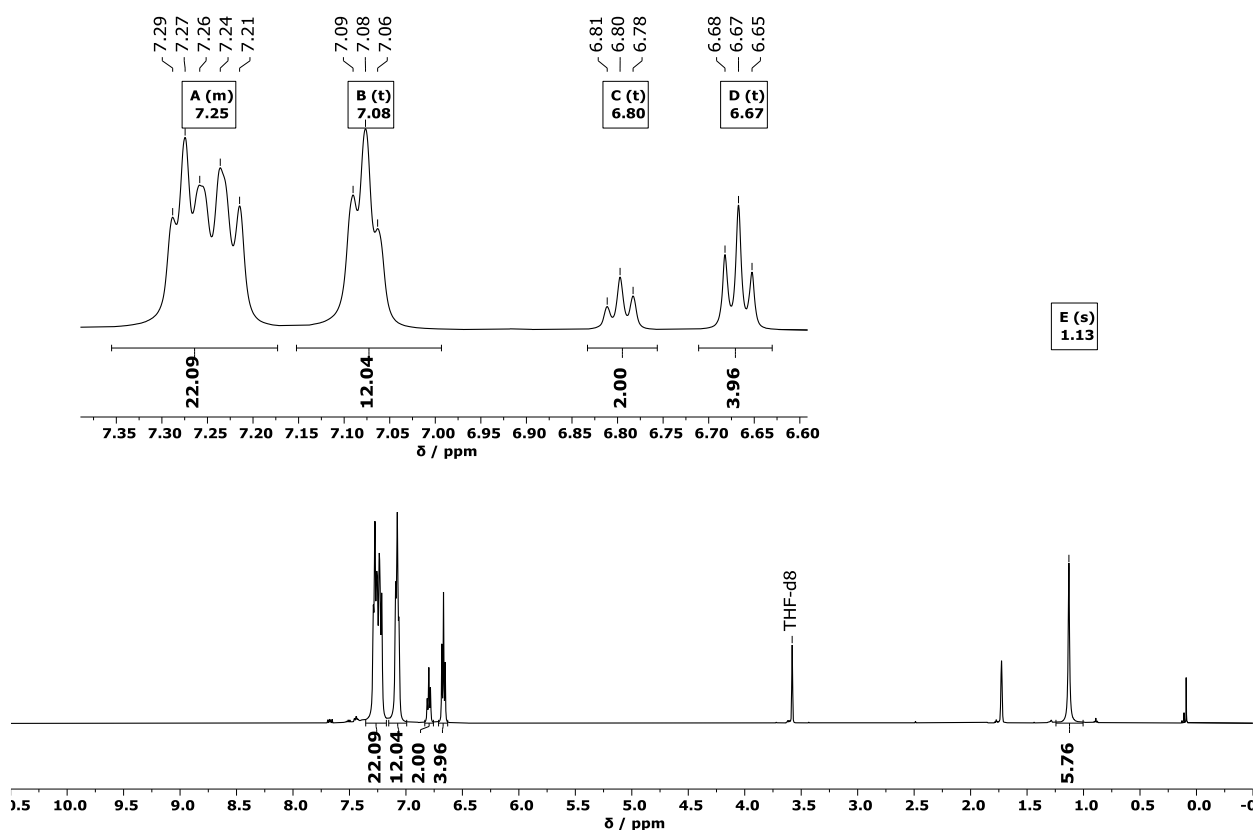
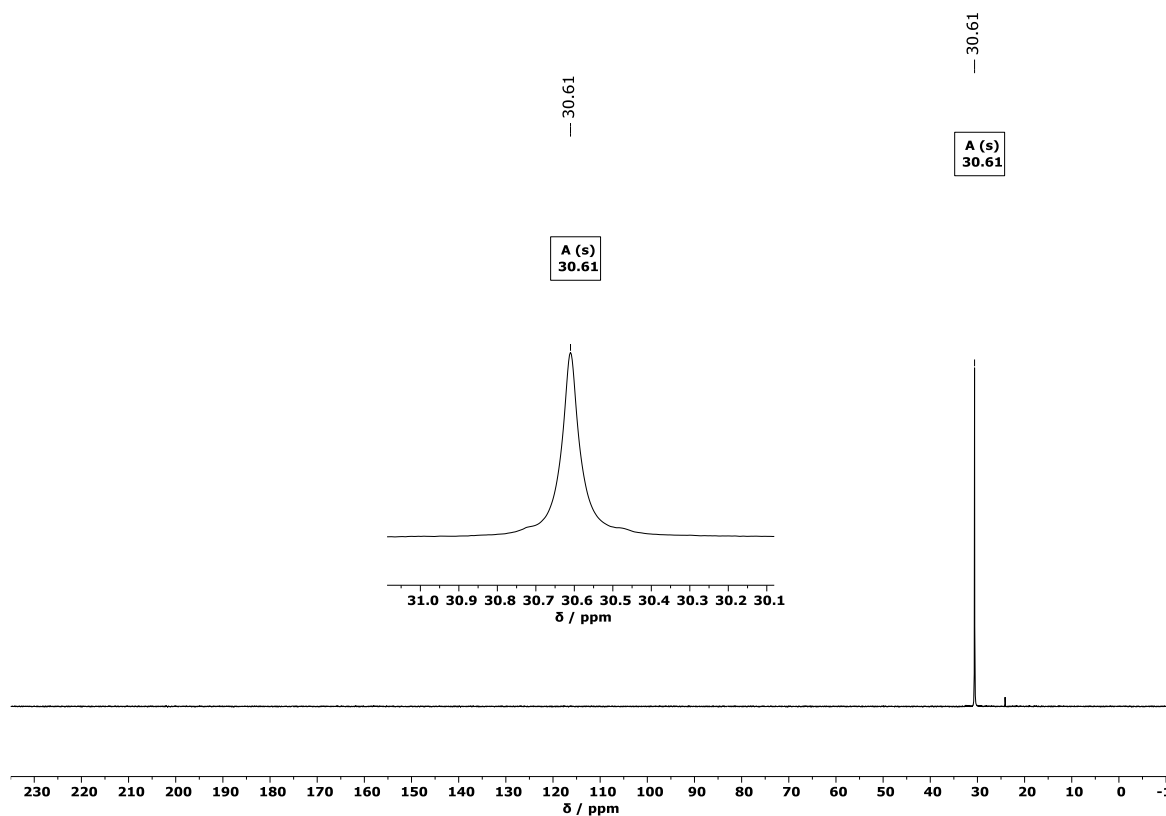
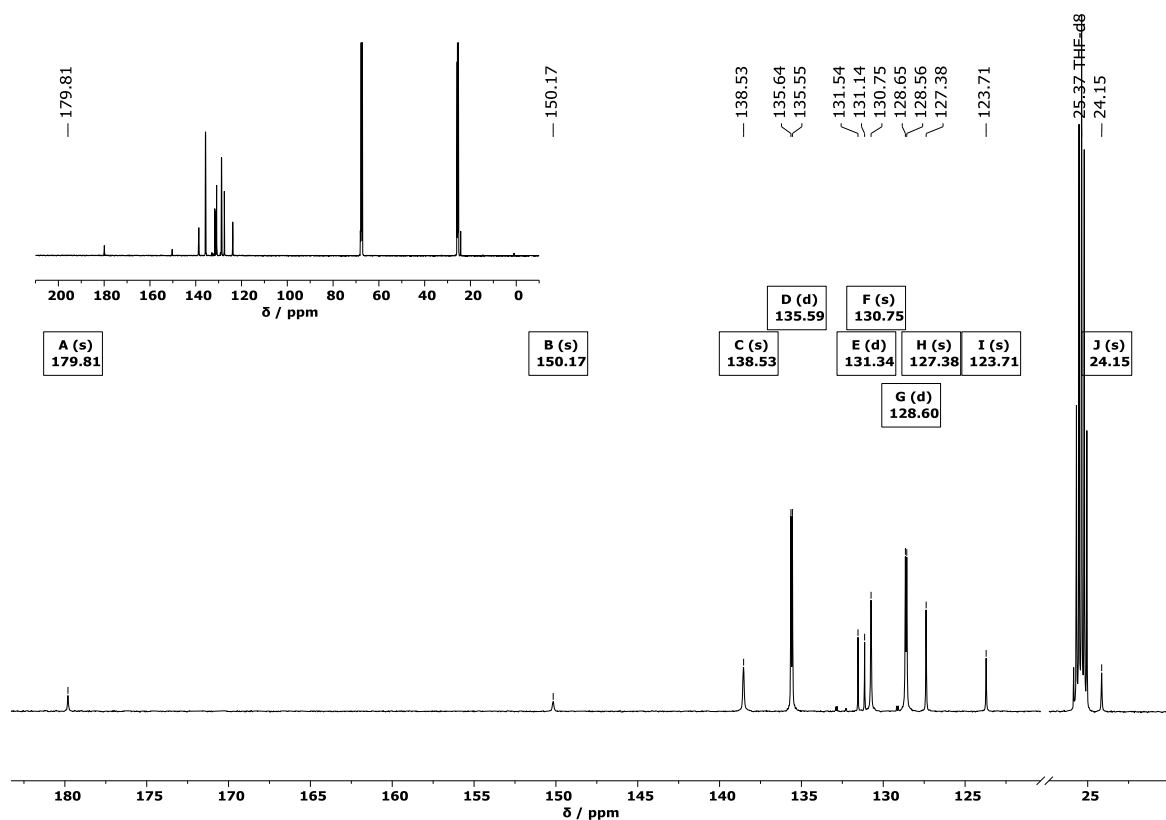
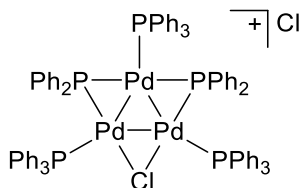


Figure 98 ^1H NMR spectrum (500 MHz, $\text{THF-}d_8$) of $[\text{Pd}_2(\mu_2\text{-OAc})_2(\text{C}_6\text{H}_5)_2(\text{PPh}_3)_2]$ 53.

Figure 99 ^{31}P NMR spectrum (203 MHz, $\text{THF-}d_8$) of $[\text{Pd}_2(\mu_2\text{-OAc})_2(\text{C}_6\text{H}_5)_2(\text{PPh}_3)_2]$ 53.Figure 100 ^{13}C NMR spectrum (126 MHz, $\text{THF-}d_8$) of $[\text{Pd}_2(\mu_2\text{-OAc})_2(\text{C}_6\text{H}_5)_2(\text{PPh}_3)_2]$ 53.

Synthesis of $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$ ($\text{Pd}_3\text{Cl}\cdot\text{Cl}$) – the ‘Coulson Cluster’



$[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$ (**$\text{Pd}_3\text{Cl}\cdot\text{Cl}$**), first reported by D. R. Coulson in 1968.¹⁶⁸ This work has established that authentic **$\text{Pd}_3\text{Cl}\cdot\text{Cl}$** is best prepared by an adapted procedure, which was reported by Moiseev *et al.*¹⁷¹

Adapted procedure: $[\text{PdCl}_2(\text{PPh}_3)_2]$ (1.0 g, 0.701 mmol) was added to a Schlenk flask which was sealed (by Suba-Seal®) and evacuated and backfilled with N_2 three times. Dry, distilled and degassed aniline (20 mL) was added *via* cannula. The subsequent reaction mixture was heated to 90 °C, with magnetic stirring. At this point the $[\text{PdCl}_2(\text{PPh}_3)_2]$ had fully dissolved, giving an orange solution. The headspace was carefully evacuated, and the Schlenk flask sealed (under vacuum) and filled with H_2 (by balloon; replenished when necessary, during complete reaction). This system was magnetically stirred at 90 °C for 24 hours. After *ca.* 30 minutes, the solution had turned from bright orange to dark red. After the reaction time, the H_2 balloon was removed, and the solution was allowed to cool to room temperature. The solution was transferred *via* cannula to a distillation apparatus and distilled to dryness. With care, the resulting dark red solid was thoroughly extracted with benzene (3×10 mL; dry, degassed; *note toxicity hazard for benzene*). The benzene extract was concentrated *in vacuo*, then the solid residue was washed with Et_2O (3×10 mL) and hexane (2×10 mL). The resulting dark red solid was recrystallised from CHCl_3 and hexane (1/5, *v/v*). To obtain crystals suitable for single-crystal X-ray diffraction studies, $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$ was crystallised by layering a CDCl_3 solution with petroleum ether (*ca.* 1/5, *v/v*) in an NMR tube. This data matched that reported in the literature.^{167, 171} Yield = 446 mg (62% assuming 3 mol of starting material $\rightarrow$ 1 mol of product).¹⁷¹

^1H NMR (500 MHz, $\text{THF-}d_8$) δ 7.52 (br. q, $J_{\text{H-H}} = 6.6$ Hz, 12H), 7.22 (br. t, $J_{\text{H-H}} = 7.5$ Hz, 6H), 7.14 – 6.97 (m, 28H), 6.91 – 6.81 (m, 12H), 6.78 (t, $J_{\text{H-H}} = 7.5$ Hz, 8H).

^{31}P NMR (203 MHz, $\text{THF-}d_8$) $^{167}\text{AB}_2\text{X}_2$ spin system, (where A = phosphine *distal* to Cl, B = phosphine *proximal* to Cl, X = μ -phosphido ligands). δ 203.95 (t, $J = 15.2$ Hz, $\mu\text{-PPh}_2$), 22.77 (dt, $J = 97.6, 15.2$ Hz, *proximal*- PPh_3), 13.67 (t, $J = 97.6$ Hz, *distal*- PPh_3).

^{13}C NMR (126 MHz, $\text{THF-}d_8$) δ 139.41 (t, $J_{\text{C-P}} = 8.8$ Hz, C_q), 136.21 (t, $J_{\text{C-P}} = 6.0$ Hz, C–H), 135.42 (t, $J_{\text{C-P}} = 19.6$ Hz, C_q), 135.16, 135.01 – 134.80 (m), 134.70 (d, $J_{\text{C-P}} = 13.9$ Hz, C–H), 130.10 (s, C–H), 129.83 (s, C–H), 129.17 (s, C–H), 128.74 (d, $J_{\text{C-P}} = 9.8$ Hz, C–H), 128.28 (t, $J_{\text{C-P}} = 4.8$ Hz, C–H), 128.00 (br. s, C–H).

ESI-MS Data (+ve mode) mode: Found 1511.0577(M⁺); Calc. (for C₇₈H₆₅ClP₅Pd₃) 1511.0576.

IR (ν/cm⁻¹, ATR, solid state): 3048(w), 1478 (m), 1432 (m), 1091 (m), 737 (m) 688 (s), 522 (s), 510 (s), 488(s), 449 (m).

MP – 164-166 °C (decomposition to black material).

See Appendix 4 for X-Ray Crystallographic Data (ijsf 1804).

Labbook Reference Number: NWJS-3-243, NWJS-4-288.

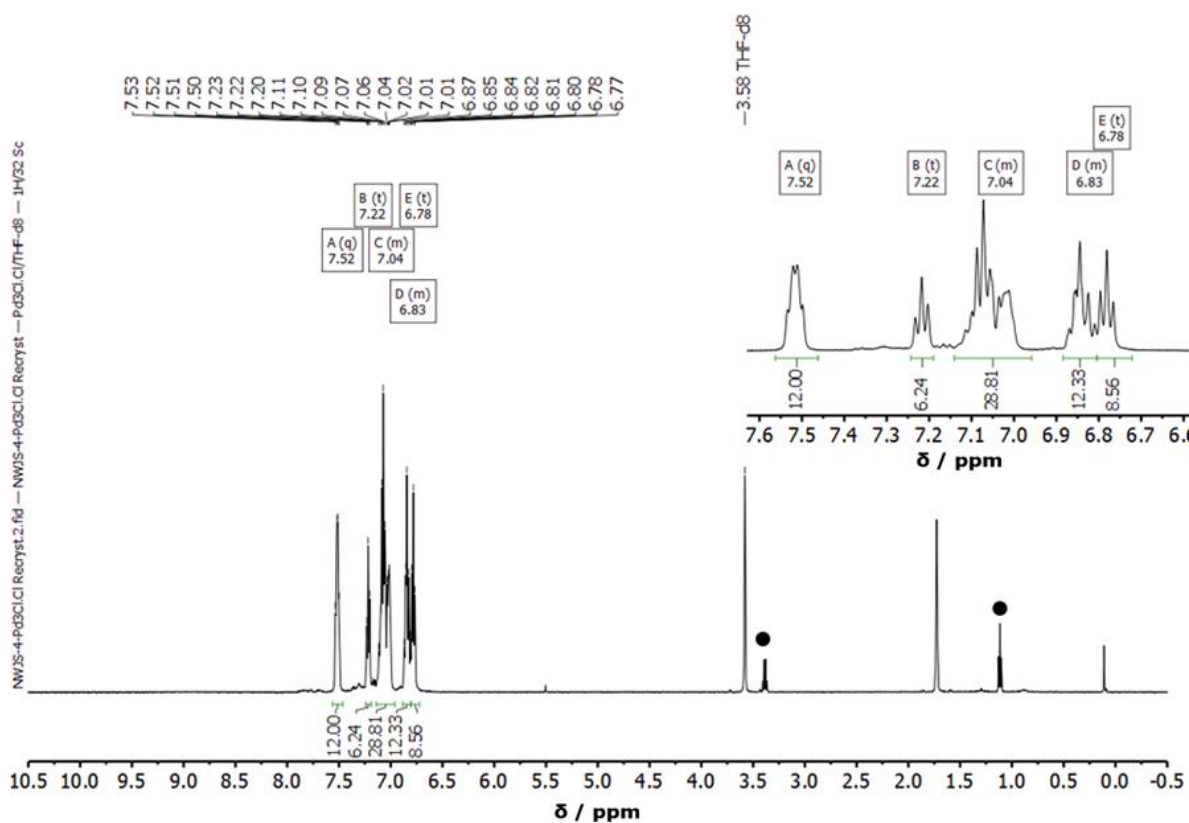


Figure 101 ¹H NMR spectrum (500 Hz, THF-*d*₈) of [Pd₃(μ-Cl)(μ-PPh₂)₂(PPh₃)₃]Cl (Pd₃Cl·Cl). circles = Et₂O (solvent of crystallisation).

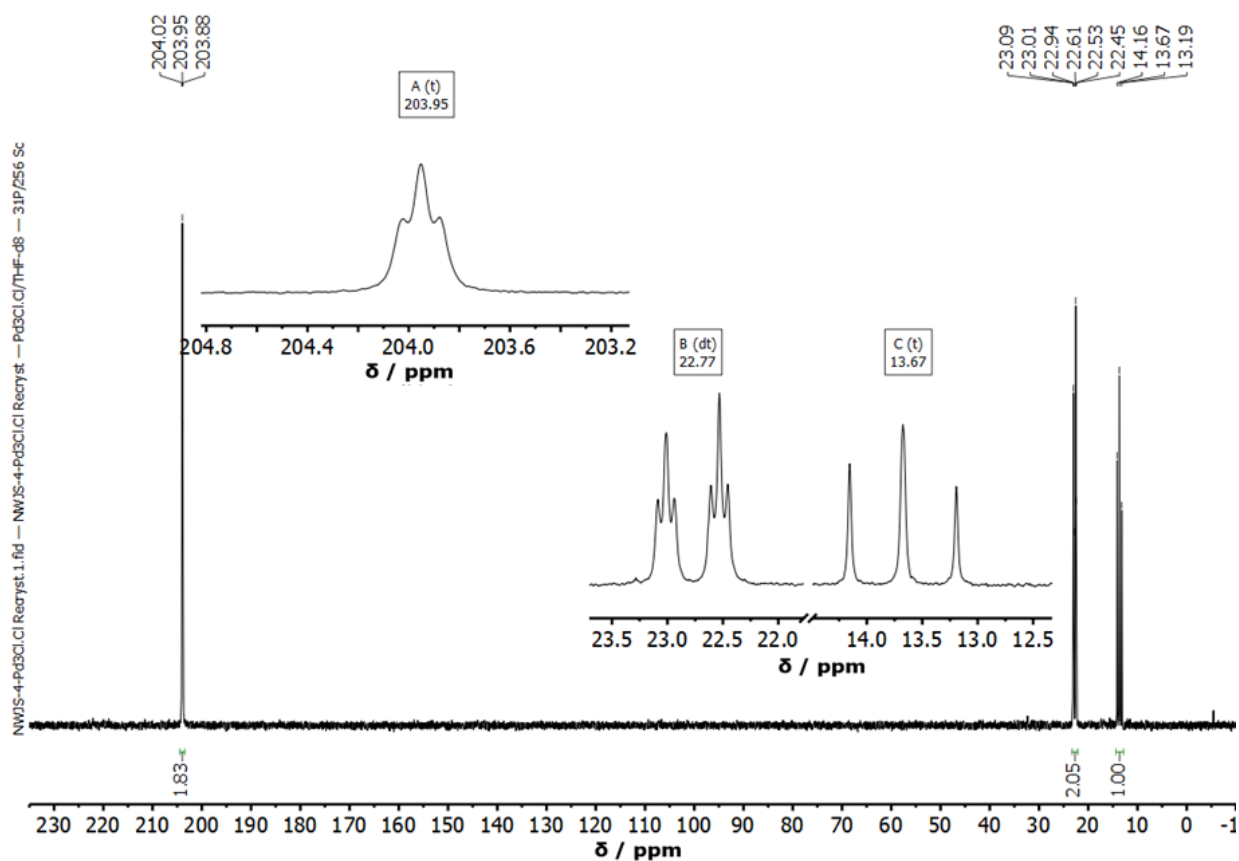


Figure 102 ^{31}P NMR (203 MHz, $\text{THF-}d_8$) spectrum of $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$ ($\text{Pd}_3\text{Cl}\cdot\text{Cl}$)

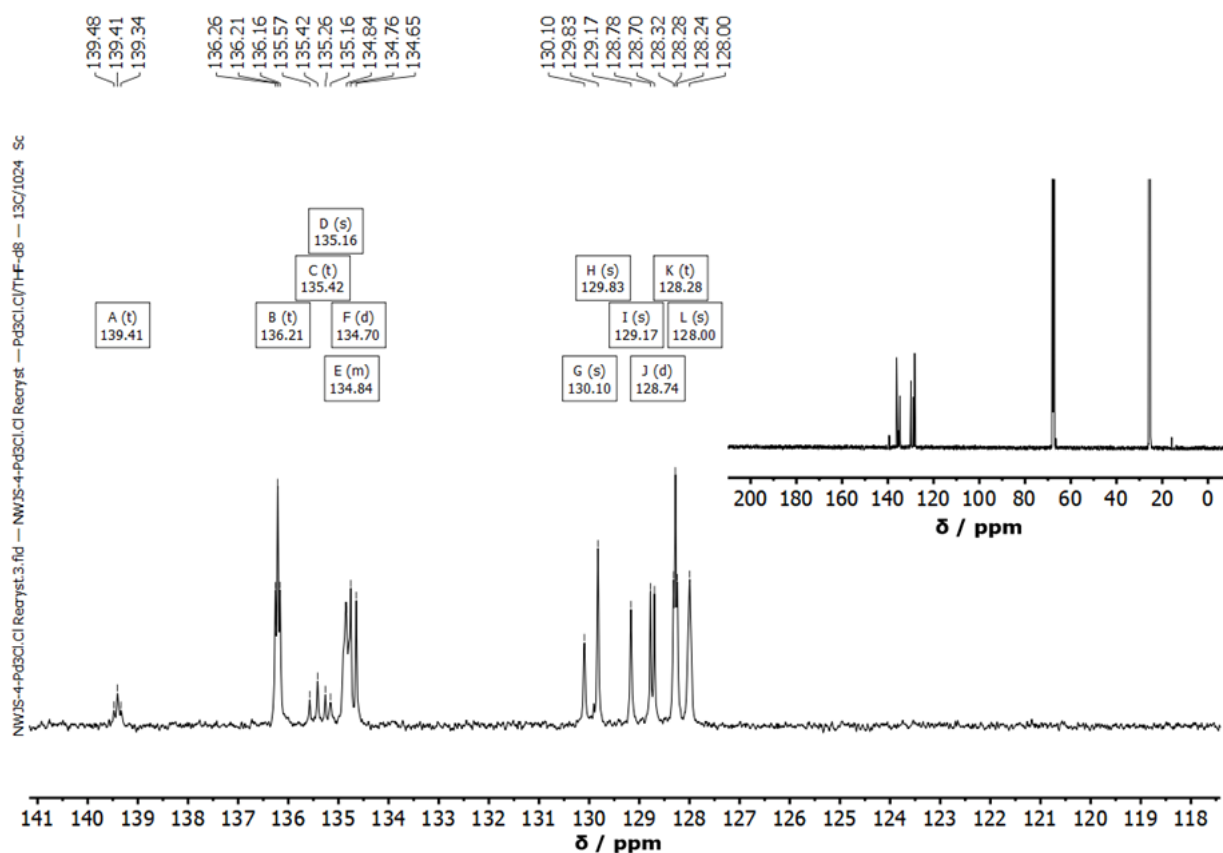
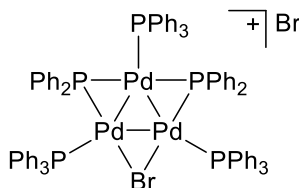


Figure 103 ^{13}C NMR spectrum (126 MHz, $\text{THF-}d_8$) of $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$ ($\text{Pd}_3\text{Cl}\cdot\text{Cl}$)

Synthesis of $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)_2(\mu\text{-PPh}_3)_3]\text{Br}$ Cluster $\text{Pd}_3\text{Br}\cdot\text{Br}$



Adapted from a procedure from Dixon *et al.*¹⁶⁷ A Schlenk flask charged with $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\mu\text{-PPh}_3)_3]\text{Cl}$ was evacuated and backfilled three times. Acetone (10 mL; dry, degassed) was added *via* a syringe and the $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\mu\text{-PPh}_3)_3]\text{Cl}$ ($\text{Pd}_3\text{Cl}\cdot\text{Cl}$) was seen to dissolve into a dark red solution. KBr (aq., 1 mL, 0.5 g.mL⁻¹, 4.2 M, {previously degassed by bubbling through with N₂ for *ca.* 30 mins, with sonication}) was added dropwise to the $[\text{Pd}_3(\mu\text{-Cl})(\mu\text{-PPh}_2)_2(\mu\text{-PPh}_3)_3]\text{Cl}$ solution. A colourless precipitate was seen to precipitate immediately upon addition of KBr (aq.). Hence, the resulting reaction mixture was a dark red solution with a colourless sediment. After stirring the reaction mixture for 1 hour at 23 °C, degassed water (2 mL) was added, bringing the colourless precipitate back into solution. This solution was transferred *via* cannula into another Schlenk flask containing a solution of KBr (aq. 50 mL, 0.5 g.mL⁻¹, 4.2 M) where a dark red precipitate quickly formed upon contact. The solid precipitate was isolated from the mother liquor *via* cannula filtration and dried *in vacuo*. Leaving a dark red residue (with a colourless co-precipitate {KBr/KCl}). The dark red residue was dissolved in dry CH₂Cl₂ (2 × 2 mL) and transferred into a fresh Schlenk flask *via* cannula filtration (leaving behind co-precipitated KBr/KCl salt). The combined filtrate was carefully layered with dry degassed Et₂O (20 mL, CH₂Cl₂/Et₂O 1:5 {v/v}). Dark red crystals were seen to grow in the flask over the course of *ca.* 72 hours. The crystals were removed by filtration, giving an isolated yield of recrystallised product 78 mg (37%). Compound data agreed with that reported in literature.¹⁶⁷ Single crystals suitable for XRD were grown by slow evaporation of a 10 mg.mL⁻¹ CH₂Cl₂ solution of **Pd₃Br·Br** at room temperature, under an atmosphere of N₂.

¹H NMR (500 MHz, THF-*d*₈) δ 7.51 (*p*-q, $J_{\text{H-H}} = 6.3, 5.8$ Hz, 12H), 7.22 (br. t, $J_{\text{H-H}} = 7.4$ Hz, 6H), 7.17 – 7.01 (m, 20H), 7.00 – 6.92 (m, 8H), 6.91 – 6.81 (m, 12H), 6.77 (br. t, $J_{\text{H-H}} = 7.7$ Hz, 8H).

³¹P NMR (203 MHz, THF-*d*₈) AB₂X₂ spin system¹⁶⁷ (where A = phosphine *distal* to Br, B = phosphine *proximal* to Br, X = μ -phosphido ligands). δ 210.56 (t, $J = 14.8$ Hz), 23.98 (dt, $J = 95.9, 14.8$ Hz), 12.44 (t, $J = 95.9$ Hz).

¹³C NMR (126 MHz, THF-*d*₈) δ 140.12 – 139.69 (m, C_q), 136.41 (t, $J_{\text{C-P}} = 5.9$ Hz, C–H), 135.98 – 135.56 (m, C_q), 135.05, 134.99 – 134.80 (m), 134.71 (d, $J = 13.8$ Hz), 130.12, 129.80, 129.15, 128.77 (d, $J = 10.0$ Hz), 128.18 (t, $J = 5.0$ Hz), 127.93 (t).

ESI-MS Data (+ve mode) mode: Found 1553.0088(M⁺); Calc. (for C₇₈H₆₅BrP₅Pd₃) 1553.0062.

IR{ ν , ATR, solid state, cm^{-1} }: 3049 (w), 1477 (m), 1431 (m), 736 (m) 689 (s), 522 (s), 507 (s), 487 (s), 420 (m).

MP – 158-160 °C (decomposition to black material).

See Appendix 4 for X-Ray Crystallographic Data (*ijsf* 1905).

Labbook reference number: NWJS-4-325.

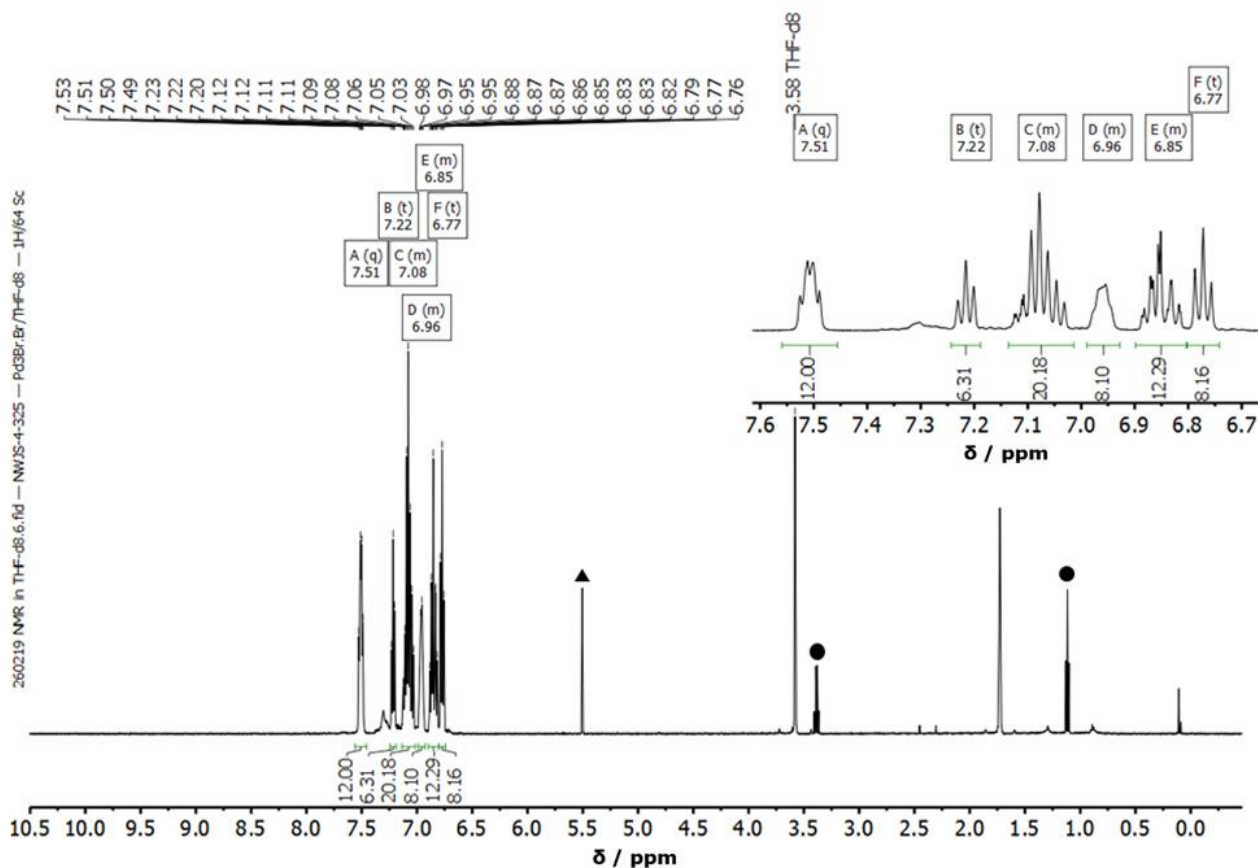


Figure 104 ^1H NMR spectrum (500 MHz, $\text{THF-}d_8$) of $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)_2(\mu\text{-PPh}_3)_3]\text{Br}$ $\text{Pd}_3\text{Br}\cdot\text{Br}$. Triangle = CH_2Cl_2 , circles = Et_2O (solvent of crystallisation).

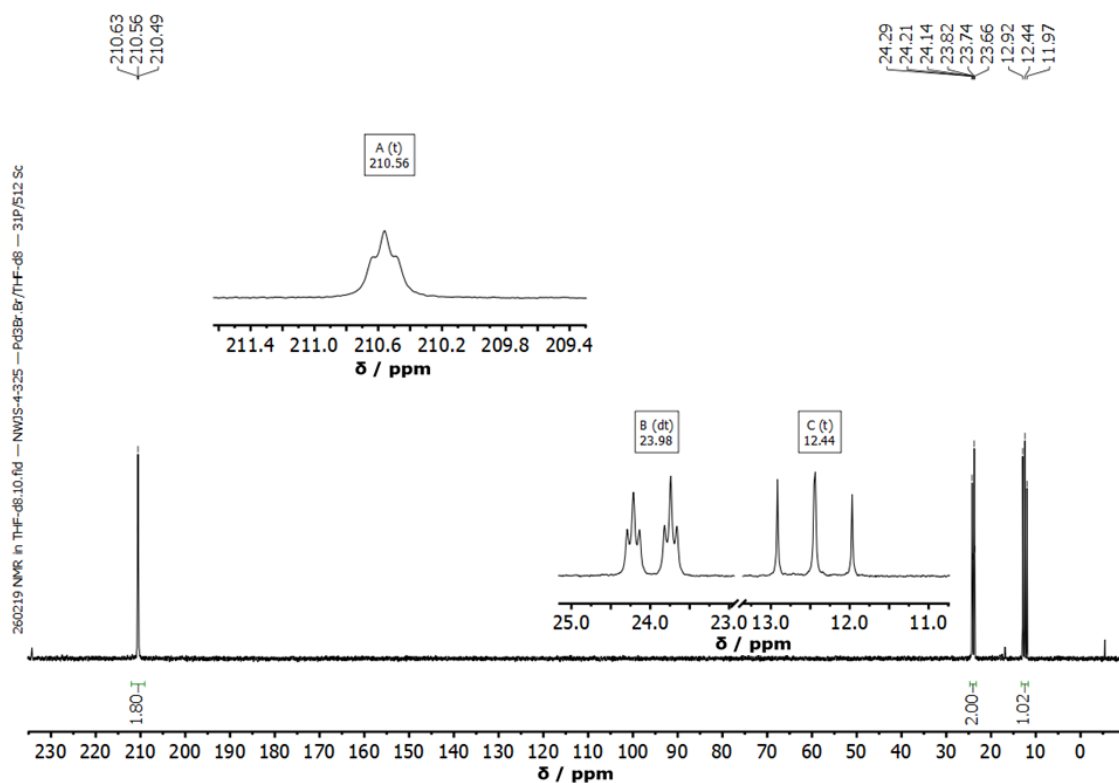


Figure 105 ^{31}P NMR (203 MHz, $\text{THF-}d_8$) spectrum of $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Br}$ ($\text{Pd}_3\text{Br}\cdot\text{Br}$)

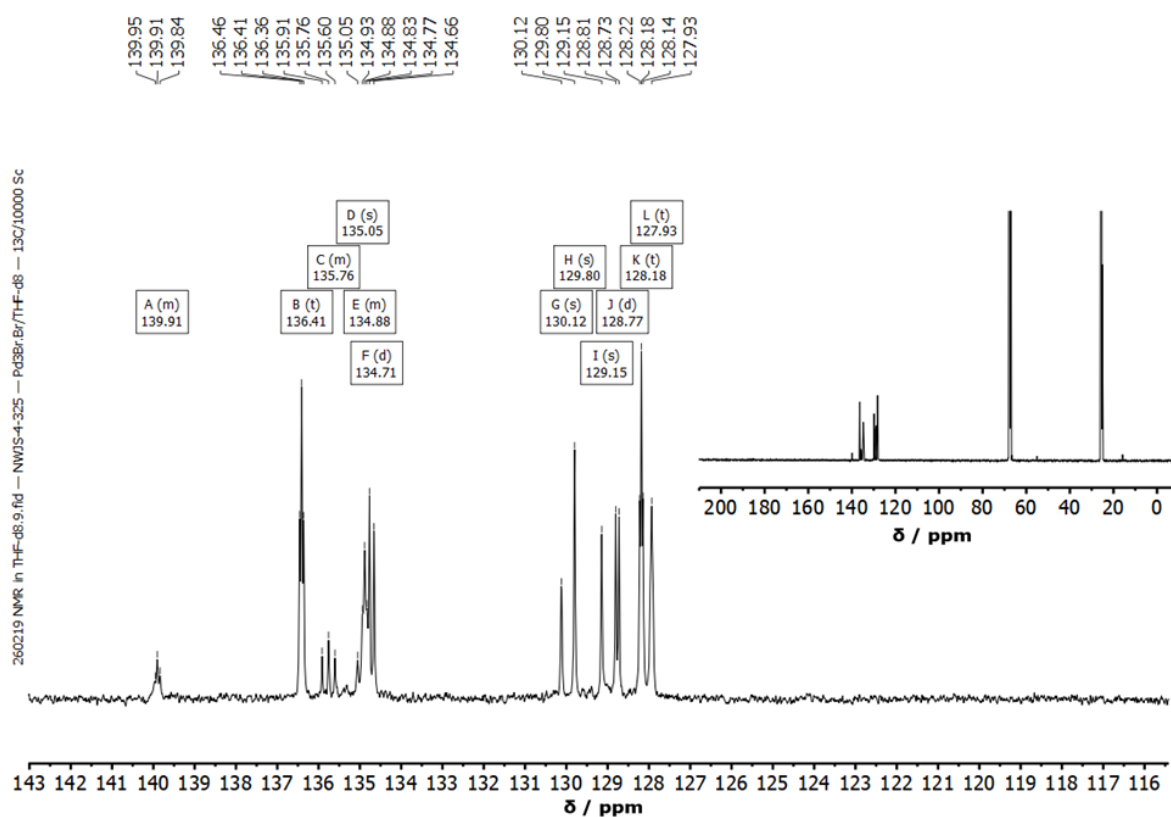
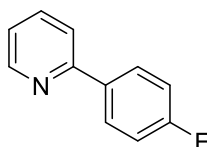


Figure 106 ^{13}C NMR (126 MHz, $\text{THF-}d_8$) spectrum of $[\text{Pd}_3(\mu\text{-Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Br}$ ($\text{Pd}_3\text{Br}\cdot\text{Br}$).

6.4. Synthesis and Characterisation of Organic Products

6.4.1. Products of Cross-coupling Reactions at Mono-halogenated Heteroaromatic Compounds

2-(4-Fluorophenyl)-pyridine 69



The title compound was synthesised using General Procedure B (2.6 6.2.2.). The combined crude reaction solution was quenched by addition to NH_4Cl (aq. sat, 5 mL). The organic layer was collected, and the aqueous layer was washed with EtOAc (3×5 mL). The organics were combined, dried over MgSO_4 and filtered through a Celite plug (1 cm depth), to remove large black particles formed after the quench (likely the product of catalyst decomposition after the quench). The filtrate was concentrated in vacuo. The residue was then adsorbed to silica and hence purified *via* column chromatography on SiO_2 (petroleum ether/EtOAc, 95:5 (v/v), $R_f = 0.1$). Appeared as a colourless solid, Yield = 171.7 mg (quant. %).

^1H NMR (400 MHz, Chloroform-*d*) δ 8.67 (ddd, $J = 4.9, 1.9, 1.0$ Hz, 1H, *pyridyl*-C₆-H), 8.05 – 7.90 (m, 2H, *phenyl*-C₂'H), 7.74 (m, $J = 7.3, 1.9, 1.0$ Hz, 1H, *pyridyl*-C₄-H), 7.68 (dt, $J = 8.0, 1.1$ Hz, 1H, *pyridyl*-C₃-H), 7.22 (ddd, $J = 7.4, 4.8, 1.2$ Hz, 1H, *pyridyl*-C₅-H), 7.20 – 7.08 (m, 2H, *phenyl*-C₃'H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.6 (d, $^1J_{\text{C-F}} = 248.3$ Hz C₄'-F), 156.6 (C_q¹), 149.8 (C₆), 136.9 (C₄), 135.7 (d, $^4J_{\text{C-F}} = 3.1$ Hz, C_q¹'), 128.8 (d, $^3J_{\text{C-F}} = 8.4$ Hz, C₂'), 122.2 (C₅), 120.3 (C₃), 115.8 (d, $^2J_{\text{C-F}} = 21.6$ Hz, C₃').

^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.06 (tt, $J_{\text{F-H}} = 9.3, 5.4$ Hz).

IR (ν/cm^{-1} , ATR): 3053 (w), 3010 (w), 1583 (m), 1567 (m), 1509 (m), 1464 (m), 1298 (w), 1218 (m), 1099 (m), 1058 (m), 1010 (w), 989 (w), 844 (m), 826 (m), 771 (a), 736 (m), 569 (m), 475 (m).

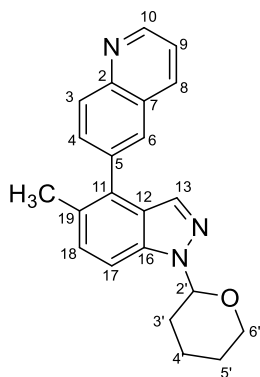
ESI-MS $m/z = 174.0713$ $[\text{M}+\text{H}]^+$: $\text{C}_{11}\text{H}_9\text{FN}$ requires 174.0714

Melting point - 39-41°C

R_f (TLC, petroleum ether/EtOAc, 95:5 {v/v}) = 0.10.

Compound characterisation data agrees with that previously reported in literature. ³⁴¹

Labbook Reference Number: NWJS-4-319

6-[5-Methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]quinolone 72

The title compound was prepared using General Procedure D (*vide supra*). It was isolated from combined crude materials from multiple in order to get characterisation of the final product of SMCC reactions reported in Section 3.3. The combined products was purified by flash chromatography (SiO₂), running a solvent system of petroleum ether/EtOAc, 9:1 (v/v) (to elute the bromoindazole starting material) before gradually increasing the gradient to 2:8 (v/v), which resulted in elution of the title compound **72**. Yields for individual reactions are detailed Section 3.3.2. Appearance: colourless, viscous, gel-like oil.

¹H NMR (400 MHz, Methanol-*d*₄) δ 8.91 (dd, *J* = 4.3, 1.7 Hz, 1H, C₁₀-H), 8.44 (d, *J* = 8.4 Hz, 1H, Ar), 8.17 (d, *J* = 8.8 Hz, 1H, Ar), 7.97 (d, *J* = 2.0 Hz, 1H, Ar), 7.82 (dd, *J* = 8.7, 2.0 Hz, 1H, Ar), 7.68 – 7.57 (m, 3H, Ar), 7.43 (d, *J* = 8.8 Hz, 1H, Ar), 5.82 (dd, *J* = 9.9, 2.6 Hz, 1H, C_{2'}), 4.07 – 3.98 (m, 1H, C-H_{aliph}), 3.83 (ddd, *J* = 11.5, 10.6, 3.1 Hz, 1H, C-H_{aliph}), 2.56 – 2.44 (m, 1H C-H_{aliph}), 2.35 (s, 3H, CH₃), 2.17 – 2.07 (m, 1H), 2.07 – 1.99 (m, 1H), 1.91 – 1.62 (m, 3H).

¹³C NMR (101 MHz, Methanol-*d*₄) δ 151.6 (C-H), 148.0 (C_q), 139.9 (C_q), 138.8 (C_q), 138.6 (C-H), 134.0 (C-H), 133.6 (C_q), 133.2 (C-H), 131.4 (C-H), 129.9 (C_q), 129.8 (C-H), 129.4, 129.3 (C-H), 126.4 (C_q), 123.1 (C-H), 110.8 (C-H), 86.5 (C-H), 68.7 (C-H), 30.7 (C-H), 26.3 (C-H), 23.8 (C-H), 19.4 (C-H). IR (*ν*/cm⁻¹, ATR): 2935 (w), 2856 (w), 1734 (w), 1592 (w), 1494 (m), 1421 (m), 1181 (m), 1161 (m), 1080 (s), 1041 (s), 997 (s), 909 (m), 837 (s), 797 (s).

MS Analysis GC-EI *m/z* = 343.1689 [M]⁺ C₂₂H₂₁N₃O requires 343.1685.

R_f(TLC, PET/EtOAc, 2:8 {v/v}) = 0.31.

Compound data matches that previously reported in literature.²²⁸

6.4.2. Products of Cross-coupling Reactions at Di-halogenated Heteroaromatic Compounds

Products of cross-coupling at 2,4-dibromopyridine **30** were at least characterised as part of the crude reaction mixture (^1H or ESI-MS) solution or after isolation by column chromatography (SiO_2). The collated data is presented below.

SMCC of 2,4-Dibromopyridine **30** with 4-Anisyl Boronic Acid **74_A**

Products could be identified from crude reaction mixtures (Figure 107). Characterisation data matched that reported in the literature,¹⁹³ and/or with data collated for isolated compounds reported *vide infra*.

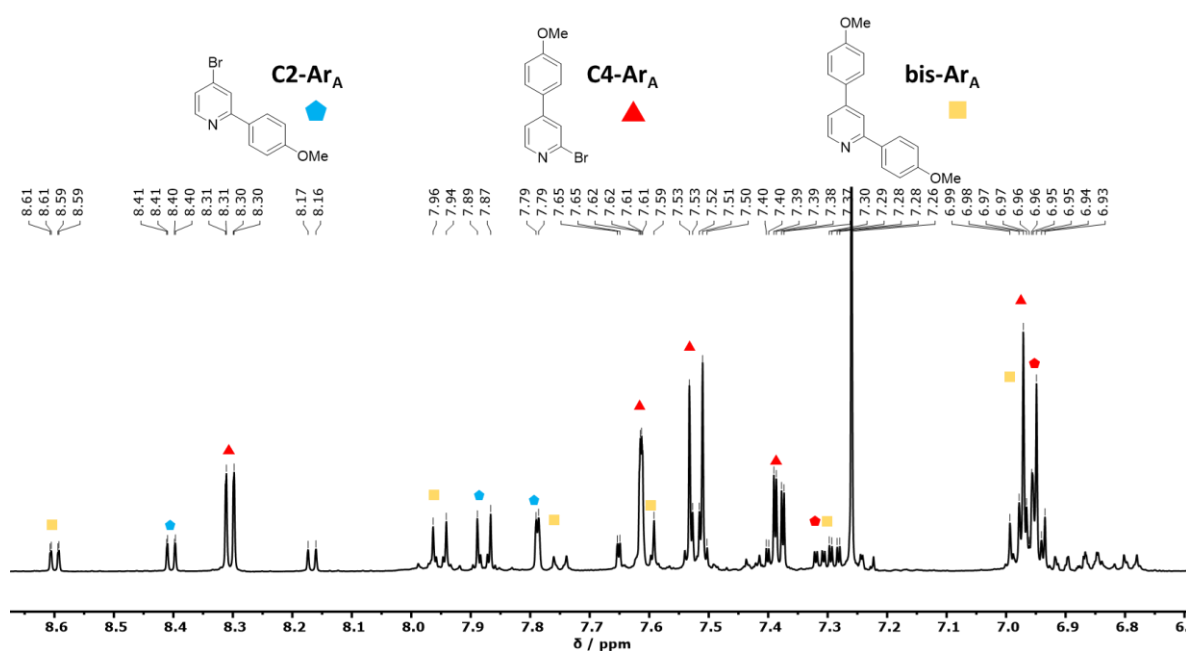
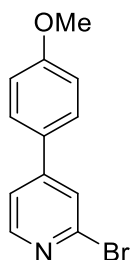


Figure 107 ^1H NMR spectrum (400 MHz, CDCl_3) showing C4-Ar_A, C2-Ar_A and bis-Ar_A product identification as part of a crude reaction mixture.

2-Bromo-4-(4-anisyl)-pyridine (C4-Ar_A)

Compound characterisation data agrees with that previously reported in literature.¹⁹³ It was isolated from the reaction mixture using a hexane/EtOAc, 85:15 (*v/v*) solvent system, which was run with a gradient, starting from neat hexane. Yield from the model SMCC, General Procedure F, 710.7 mg, 3.0 mmol scale in 2,4-dibromopyridine **30**, catalysed by Pd₃(OAc)₆/3PPh₃ = 510.5 mg (64 %). Appearance: colourless powder. Melting point – 55.5-56.9 °C (57 °C lit.).¹⁹³

¹H NMR (400 MHz, Chloroform-*d*) δ 8.37 (dd, *J* = 5.3, 0.7 Hz, 1H, *pyridyl*-C₆-H), 7.68 (dd, *J* = 1.7, 0.7 Hz, 1H, *pyridyl*-C₃-H), 7.62 – 7.53 (m, 2H, *aryl*), 7.44 (dd, *J* = 5.3, 1.7 Hz, 1H, *pyridyl*-C₅-H), 7.05 – 6.97 (m, 2H, *aryl*), 3.87 (s, 3H, OCH₃) ppm.

¹³C NMR (101 MHz, Chloroform-*d*) δ 161.2 (C), 151.2 (C), 150.2 (C–H), 142.8 (C), 128.9 (C), 128.45(2C–H), 125.3 (C–H), 120.4 (2C–H), 114.9 (C–H), 55.6 (C–OCH₃) ppm.

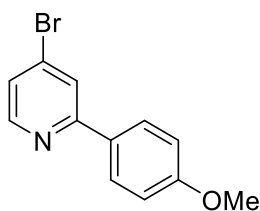
IR (ν, ATR): 3045 (w, C–H), 2935 (w, C–H), 2832 (w, C–H), 1609 (m), 1586 (s), 1515(s), 1457(m), 1429 (m), 1418(m), 1375 (m), 1292 (m), 1247 (vs), 1126 (m), 1082 (m), 1045 (m), 1018 (m), 986 (m), 815 (vs), 755 (m), 685 (m), 568 (m), 435 (m).

HRMS ESI-MS *m/z* = 264.0018 [M+H]⁺ : C₁₂H₁₁⁷⁹BrNO requires 264.0019

Elemental analysis (% CHN), calculated for C₁₂H₁₀BrNO: C, 54.57; H, 3.82; N, 5.30; Found: C, 54.48; H, 3.88; N, 5.13.

R_f (TLC, Petroleum ether/EtOAc, 85:15) = 0.10.

Labbook Reference Number: NWJS-6-448.

4-Bromo-2-(4-anisyl)-pyridine (C2-Ar_A)

Compound characterisation data agrees with that previously reported in literature.¹⁹³ It was isolated from the reaction mixture using a hexane/EtOAc 85:5 (*v/v*) solvent system, which was run with a gradient, starting from neat hexane. Yield from the model SMCC, General Procedure F, 3.0 mmol scale in 2,4-dibromopyridine **30**, catalysed by Pd₃(OAc)₆/3PPh₃ = 72.9 mg (9 %). Appearance: colourless powder.

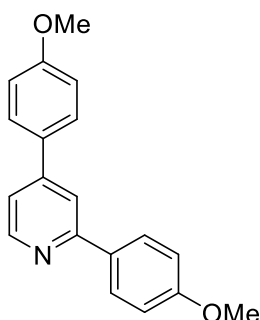
¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (d, *J* = 5.3 Hz, 1H, *pyridyl*-C₆H), 7.97 – 7.89 (m, 2H, *aryl*), 7.84 (d, *J* = 1.8 Hz, 1H, *pyridyl*-C₃H), 7.34 (dd, *J* = 5.3, 1.8 Hz, 1H, *pyridyl*-C₅H), 7.04 – 6.95 (m, 2H, *aryl*), 3.87 (s, 3H, OCH₃) ppm.

¹³C NMR (101 MHz, Chloroform-*d*) δ 161.0 (C), 158.6 (C), 150.3 (C–H), 133.6 (C), 130.6 (C), 128.5 (C–H), 124.6 (C–H), 123.2 (C–H), 114.3 (C–H), 55.5 C–OCH₃.

HRMS ESI-MS *m/z* = 264.0019 [M+H]⁺: C₁₂H₁₁⁷⁹BrNO requires 264.0019.

R_f (TLC, Petroleum ether/EtOAc, 85:15) = 0.27.

Labbook Reference Number: NWJS-6-448.

2,4-bis-(4-anisyl)-pyridine (bis-Ar_A)

Compound characterisation data agrees with that previously reported in literature.¹⁹³ It was isolated from the reaction mixture using a hexane/EtOAc 85:5 (*v/v*) solvent system, which was run with a gradient, starting from neat hexane. Yield from the model SMCC, General Procedure F, 710 mg, 3.0 mmol scale in 2,4-dibromopyridine **30**, catalysed by Pd₃(OAc)₆/3PPh₃ = 98.0 mg (11%). Appearance: colourless powder.

^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (dd, J = 5.2, 0.8 Hz, 1H, *pyridyl*-C₆H), 8.04 – 7.94 (m, 2H, *aryl*), 7.83 (dd, J = 1.8, 0.8 Hz, 1H *pyridyl*-C₃H), 7.68 – 7.58 (m, 2H, *aryl*), 7.36 (dd, J = 5.2, 1.8 Hz, 1H, *pyridyl*-C₅H), 7.01 (dd, J = 8.8, 3.4 Hz, 4H, *aryl*), 3.86 (s, 6H, OCH₃, *overlapping*) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.6 (2C), 157.6 (C), 149.7 (C), 149.0 (C–H), 132.0 (C), 130.9 (C), 128.4 (C–H), 128.4 (C–H), 119.2 (C–H), 117.6 (C–H), 114.6 (C–H), 114.2 (C–H), 55.5 (C–CH₃), 55.5 (C–OCH₃) ppm.

HRMS ESI-MS m/z = 292.1332 [M+H]⁺ : C₁₁H₉FN requires 292.1338.

R_f (TLC, Petroleum ether/EtOAc, 85:15) = 0.07.

Labbook Reference Number: NWJS-6-448.

SMCC of 2,4-Dibromopyridine 30 with *para*-Fluorophenylboronic Acid 74_B

Products could be identified from crude reaction mixtures (Figure 108). Characterisation data matched that reported in the literature,^{193, 342} and/or with data collated for the isolated compounds reported *vide infra*.

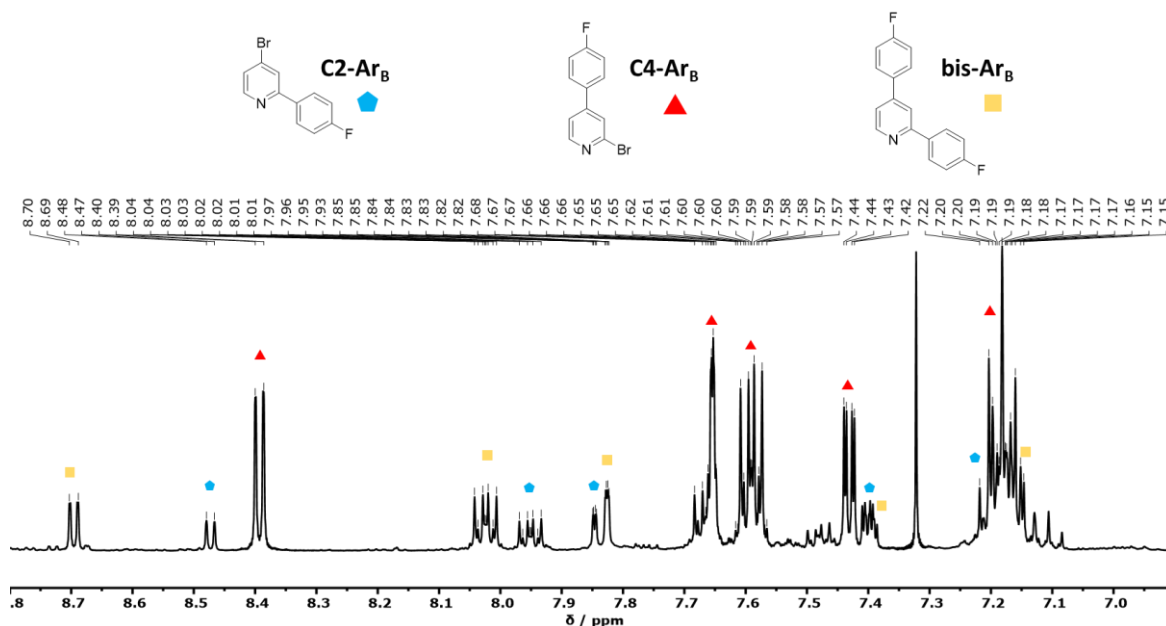
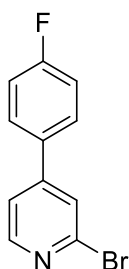


Figure 108 ^1H NMR spectrum (400 MHz, CDCl₃) showing C4-Ar_B, C2-Ar_B and bis-Ar_B product identification as part of a crude reaction mixture.

2-Bromo-4-(4-fluorophenyl)pyridine (C4-Ar_B)

Although the title compound is commercially available, no literature data was found for its characterisation or any alternative syntheses. It was isolated from the reaction mixture using column chromatography (SiO₂) with a hexane/EtOAc (95:5) solvent system run with a gradient, starting from neat hexane. Yield from the model SMCC, catalysed by **Pd₃Cl·Cl** (General Procedure J) = 161.9 mg (65 %). Appeared as a colourless solid. Melting point – 157.0-158.9 °C.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 (dd, *J* = 5.2, 0.7 Hz, 1H, *pyridyl*-C₆-H), 7.66 (dd, *J* = 1.6, 0.7 Hz, 1H, *pyridyl*-C₃-H), 7.63 – 7.54 (m, 2H, *aryl*), 7.41 (dd, *J* = 5.2, 1.6 Hz, 1H, *pyridyl*-C₅-H), 7.24 – 7.13 (m, 2H) ppm.

¹³C NMR (101 MHz, Chloroform-*d*) δ 163.8 (d, ¹*J*_{C-F} = 250.4 Hz, C–F), 150.6 (C), 150.2 (C–H), 143.1 (C), 132.9 (d, ⁴*J*_{C-F} = 3.3 Hz, *aryl*-C_q), 129.0 (d, ³*J* = 8.3 Hz, *aryl*-C–H), 125.8 (C–H), 120.8 (C–H), 116.4 (d, ²*J*_{C-F} = 21.7 Hz, *aryl*-C–H) ppm.

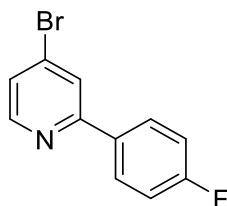
¹⁹F NMR (376 MHz, Chloroform-*d*) δ –111.18 (ddd, *J* = 13.7, 8.3, 5.2 Hz) ppm.

IR (ν/cm⁻¹, ATR): 3051 (w), 1587 (m), 1528 (m), 1512 (m), 1455 (m), 1370 (m), 1300 (m), 1223 (m), 1159 (m), 1126 (m), 1102 (m), 1080 (m), 1040 (m), 986 (m), 963 (m), 883 (m), 822 (vs), 754 (m), 685 (m), 593 (m), 554 (s), 517 (m), 434 (m).

HRMS ESI-MS *m/z* = 251.9816 [M+H]⁺ : C₁₁H₈BrFN requires 251.9824

*R*_f (hexane/EtOAc 95:5) = 0.11

Labbook Reference Number: NWJS-3-232.

4-Bromo-2-(4-fluorophenyl)pyridine (C2-Ar_B)

Compound characterisation data agrees with that previously reported in literature.¹⁹³ It was isolated from the reaction mixture using column chromatography (SiO₂) with a hexane/EtOAc (95:5) solvent

system run with a gradient, starting from neat hexane. Yield from the model SMCC (General Procedure J), catalysed by **Pd₃Cl₂·Cl** = 21 mg (8%). Appeared as a colourless oily film.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.49 (d, *J* = 5.3 Hz, 1H, *pyridyl*-C₆H), 8.01 – 7.91 (m, 2H, *aryl*), 7.86 (d, *J* = 1.8 Hz, 1H, *pyridyl*-C₃H), 7.40 (dd, *J* = 5.3, 1.8 Hz, 1H, *pyridyl*-C₅H), 7.22 – 7.11 (m, 2H, *aryl*) ppm.

¹³C NMR (101 MHz, Chloroform-*d*) δ 164.0 (d, ¹*J*_{C-F} = 249.5 Hz, C_q), 157.9 (C), 150.5 (C–H), 134.3 (C), 133.8 (C), 129.1 (d, ³*J*_{C-F} = 8.5 Hz), 125.4 (C–H), 123.8 (C–H), 116.0 (d, ²*J*_{C-F} = 21.8 Hz) ppm.

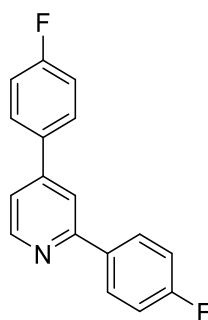
¹⁹F NMR (376 MHz, Chloroform-*d*) δ –111.70 ppm.

HRMS ESI-MS *m/z* = 251.9814[M+H]⁺ : C₁₁H₈BrFN requires 251.9824.

R_f (TLC, hexane/EtOAc 95:5) = 0.29

Labbook Reference Number: NWJS-3-232.

2,4-*bis*-(4-Fluorophenyl) pyridine (bis-Ar_B)



Compound characterisation data agrees with that previously reported in literature.³⁴² It was isolated from the reaction mixture using column chromatography, with a hexane/EtOAc (95:5) solvent system, run with a gradient, starting from neat hexane. Yield from an SMCC reaction (General Procedure J), catalysed by **Pd₃Cl₂·Cl** = 50.0 mg (19 %). Appearance: colourless powder.

δ ¹H NMR (400 MHz, Chloroform-*d*) δ 8.71 (dd, *J* = 5.1, 0.8 Hz, 1H, *pyridyl*-C₆H), 8.07 – 7.99 (m, 2H, *aryl*), 7.82 (dd, *J* = 1.7, 0.8 Hz, 1H, *pyridyl*-C₃H), 7.69 – 7.62 (m, 2H, *aryl*), 7.39 (dd, *J* = 5.1, 1.7 Hz, 1H, *pyridyl*-C₅H), 7.23 – 7.12 (m, 4H, *aryl*) ppm.

¹³C NMR (101 MHz, Chloroform-*d*) δ 164.1 (d, ¹*J*_{C-F} = 249.8 Hz, C_q-F), 163.6 (d, ¹*J*_{C-F} = 250.6 Hz, C_q-F), 157.3 (CH, 150.3, 148.5, 135.7 (d, ³*J*_{C-F} = 3.1 Hz, *aryl*-C–H), 134.7 (d, ³*J*_{C-F} = 3.3 Hz *aryl*-C–H), 129.1 – 128.6 (m), 120.2 (C), 118.4 (C), 116.3 (d, ²*J*_{C-F} = 21.7 Hz, *aryl*-C–H), 115.9 (d, *J* = 21.6 Hz, *aryl*-C–H) ppm.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ –112.35 (ddd, *J* = 13.3, 8.3, 5.2 Hz), –112.72 (ddd, *J* = 14.0, 8.6, 5.2 Hz) ppm.

HRMS ESI-MS *m/z* = 268.0932 [M+H]⁺ : C₁₇H₁₂F₂N requires 268.0938

R_f (TLC, hexane/EtOAc 95:5) = 0.05.

Labbook Reference Number: NWJS-3-232

SMCC of 2,4-Dibromopyridine 30 with Phenylboronic Acid 74c

Products could be identified from crude reaction mixtures (Figure 109). Characterisation data matched that reported in the literature,¹⁹³ and/or with data collated for isolated compounds reported *vide infra*.

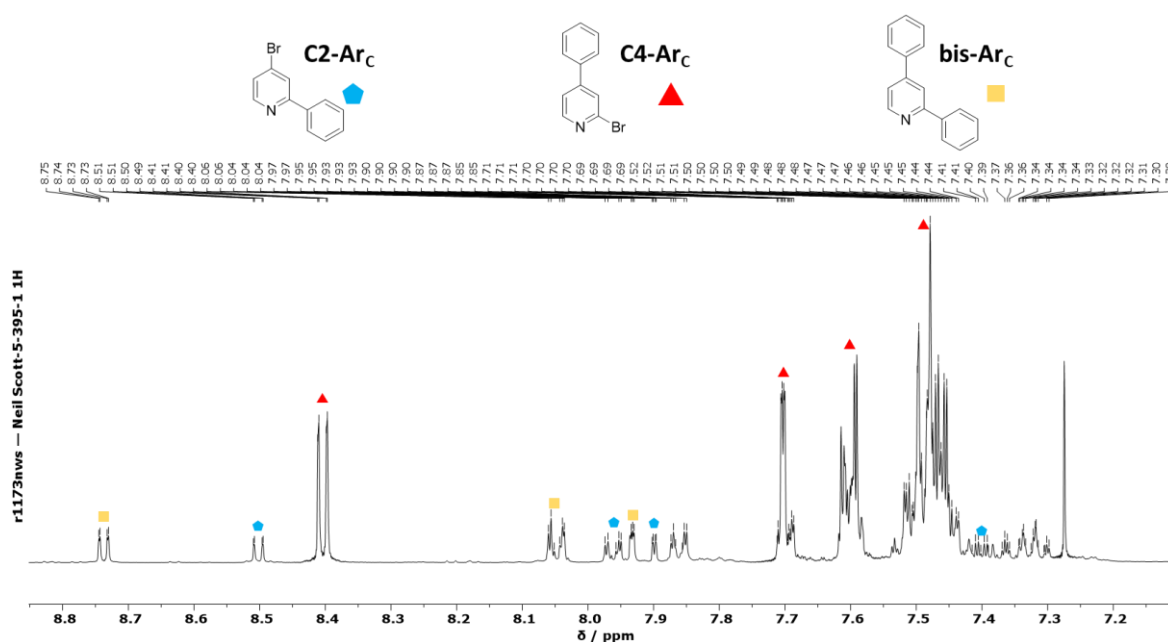
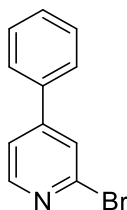


Figure 109 ¹H NMR spectrum (400 MHz, CDCl₃) showing C2-Arc, C4-Arc and bis-Arc products as part of a crude reaction solution.

2-Bromo-4-phenylpyridine (C4-Arc)



Compound characterisation data agrees with that previously reported in literature.¹⁹³ It was isolated from the reaction mixture, catalysed by **Pd₃Cl₂Cl** (General Procedure J) using a hexane/EtOAc (95:5) solvent system, which was run with a gradient, starting from neat hexane. Yield = 145.5 mg (61%) Appearance: colourless powder. Melting point – 65.0-67.1 °C.¹⁹³

^1H NMR (400 MHz, Chloroform-*d*) δ 8.41 (dd, $J = 5.2, 0.7$ Hz, 1H, *pyridyl*-C₆-H), 7.70 (dd, $J = 1.7, 0.7$ Hz, 1H *pyridyl*-C₃-H), 7.65 – 7.56 (m, 2H, *aryl*), 7.54 – 7.42 (m, 4H, *pyridyl*-C₅-H {1H}, *aryl*{3H}) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.5 (C), 150.5 (C–H), 143.0 (C), 136.8 (C), 129.8 (*aryl*-C–H), 129.4 (*aryl*-C–H), 127.2 (*aryl*-C–H), 126.0 (C–H), 121.0 (C–H) ppm.

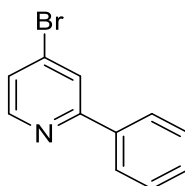
IR (ν/cm^{-1} , ATR): 3057 (d, C–H), 1584 (m), 1526 (m), 1502 (m), 1454 (m), 1444 (m), 1369 (m), 1335 (w), 1317 (w), 1135 (m), 858 (m), 755 (m), 698, (m), 690 (s), 611 (m), 599 (m).

HRMS ESI-MS $m/z = 232.1122$ $[\text{M}+\text{H}]^+$: C₁₇H₁₄⁷⁹BrN requires 232.1121.

Elemental analysis (% CHN), calculated for C₁₁H₈BrN: C, 56.44; H, 3.44; N, 5.98 Found: C, 56.48; H, 3.51; N, 5.89.

Labbook Reference Number: NWJS-3-195.

4-Bromo-2-phenylpyridine (C2-Arc)

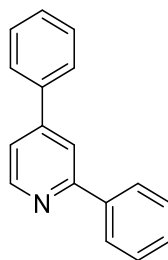


Reaction data for this compound, characterised as part of the crude post-reaction mixture, matched that previously reported in literature (see Figure 110 above).¹⁹³

^1H NMR (400 MHz, Chloroform-*d*) δ 8.49 (d, $J = 5.2$ Hz, 1H, *pyridyl*-C₆-H), 7.95 (m, 2H, *aryl*), 7.88 (dd, $J = 1.8, 0.6$ Hz, 1H, *pyridyl*-C₃-H), 7.65 – 7.54 (m, 2H, , *aryl*). 7.39 (dd, $J = 5.2, 1.8$ Hz, 1H, *pyridyl*-C₅-H) ppm.

HRMS ESI-MS $m/z = 232.1122$ $[\text{M}+\text{H}]^+$: C₁₇H₁₄N requires 232.1121.

Labbook Reference Number: NWJS-3-195.

2,4-*bis*-Phenylpyridine (bis-Ar_C)

Reaction data for this compound, characterised as part of the crude post-reaction mixture, matched that previously reported in literature (see Figure 110 above).¹⁹³

¹H NMR (400 MHz, Chloroform-*d*) δ 8.75 (d, *J* = 5.1 Hz, 1H, *pyridyl*-C₆H), 8.09 – 8.02 (m, 2H, *aryl*), 7.94 (dd, *J* = 1.8, 0.8 Hz, 1H, *pyridyl*-C₃H), 7.74 – 7.67 (m, 2H, *aryl*), 7.56 – 7.40 (m, 7H, *aryl* {6H}, *pyridyl*-C₅H {1H}) ppm.

HRMS ESI-MS *m/z* = 233.9912 [M+H]⁺ : C₁₁H₉⁷⁹BrN requires 233.9913.

Labbook Reference Number: NWJS-3-195.

SMCC of 2,4-dibromopyridine 30 with *para*-Tolyl Boronic acid 74_D

Products could be identified from crude reaction mixtures (Figure 110). Characterisation data matched that reported in the literature,^{193, 293, 343} and/or with data collated for isolated compounds reported *vide infra*.

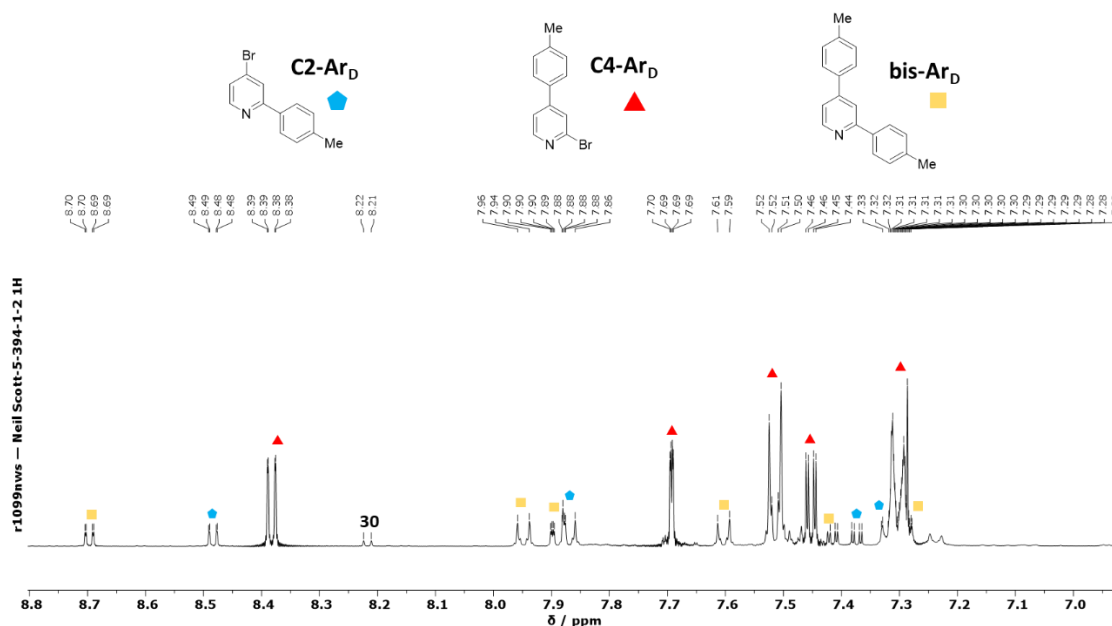
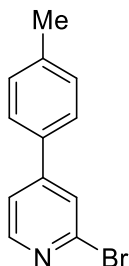


Figure 110 ¹H NMR spectrum (400 MHz, CDCl₃) showing C4-Ar_D, C2-Ar_D and bis-Ar_D product identification as part of a crude reaction mixture.

2-Bromo,4-(4-tolyl)-pyridine (C4-Ar_D)

Compound characterisation data agrees with that previously reported in literature.^{293, 344} It was isolated from the reaction mixture, General Procedure J, catalysed by **Pd₃Cl₂Cl**) using a hexane/EtOAc, 95:5 (v/v) solvent system, which was run with a gradient, starting from neat hexane. Yield = 133.7 mg (54%). Appearance: colourless powder. Melting point – 72.5-72.9 °C (68-70 °C lit.).³⁴⁴

¹H NMR (400 MHz, Chloroform-*d*) δ 8.38 (dd, *J* = 5.2, 0.7 Hz, 1H, *pyridyl*-C₆H), 7.69 (dd, *J* = 1.7, 0.7 Hz, 1H, *pyridyl*-C₃H), 7.53 – 7.48 (m, 2H, *aryl*), 7.44 (dd, *J* = 5.2, 1.7 Hz, 1H, *pyridyl*-C₅H), 7.33 – 7.27 (m, 2H, *aryl*), 2.42 (s, 3H, CH₃) ppm.

¹³C NMR (101 MHz, Chloroform-*d*) δ 151.4 (C), 150.4 (C–H), 143.0 (C–H), 140.2 (C), 133.8 (C), 130.1 (C–H), 127.0 (C–H), 125.7 (C–H), 120.7 (C), 21.4 (C–CH₃) ppm.

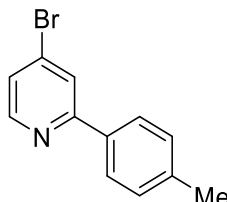
IR (ν/cm⁻¹, ATR): 3011 (w, C–H), 2912 (w, C–H), 1571 (m), 1543 (m), 1511 (m), 1450 (m), 1106 (m), 1042 (m), 984 (m), 866 (m), 802 (vs), 751 (m), 681 (m), 502 (m), 424 (s).

HRMS ESI-MS *m/z* = 248.0067 [M+H]⁺ : C₁₂H₁₁⁷⁹BrN requires 248.0069.

Elemental analysis (% CHN), calculated for C₁₂H₁₀BrN: C, 58.09; H, 4.06; N, 5.65, Found: C, 57.89; H, 4.08; N, 5.54.

R_f (TLC, hexane/EtOAc 95:5 (*v/v*)) = 0.17.

Labbook Reference Number: NWJS-3-194.

4-Bromo-2-(4-tolyl)-pyridine (C2-Ar_D)

Compound characterisation data agrees with that previously reported in literature.¹⁹³ It was isolated from the reaction mixture, General Procedure J, catalysed by **Pd₃Cl₂Cl**) using a hexane/EtOAc 95:5

(v/v) solvent system, which was run with a gradient starting from neat hexane. Yield = 28.3 mg (11%).
Appearance: colourless oil.

^1H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, J = 5.3 Hz, 1H, *pyridyl*-C₆-H), 7.88 (s, 1H, *pyridyl*-C₃-H), 7.87–7.84 (m, 1H, *aryl*), 7.37 (dd, J = 5.3, 1.8 Hz, 1H, *pyridyl*-C₅-H), 7.32–7.27 (m, 2H, *aryl*), 2.41 (s, 3H, CH₃) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.0 (C), 150.4 (C–H), 139.9 (C), 135.3 (C), 133.5 (C), 129.7 (C–H), 127.0 (C–H), 125.0 (C–H), 123.7 (C–H), 21.4 (C–CH₃) ppm.

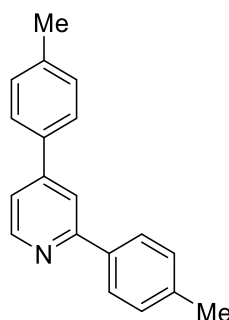
IR (ν/cm^{-1} , ATR): 3009 (w, C–H) 2959 (br,w, C–H), 2852 (w, C–H), 1569 (m), 1542 (m), 1510 (m), 1468 (m), 1448 (m), 1408 (m), 1374 (m), 1314 (m), 1260 (m), 1091 (m), 1044 (m), 1015 (m), 807 (vs), 749 (m), 731 (m), 660 (m), 585 (m), 426 (m).

HRMS ESI-MS m/z = 248.0067 $[\text{M}+\text{H}]^+$: C₁₂H₁₁⁷⁹BrN requires 248.0069.

R_f (TLC, hexane/EtOAc 95:5 (v/v)) = 0.28

Labbook Reference Number: NWJS-3-194.

2,4-bis(4-Tolyl)-pyridine (bis-Ar_D)



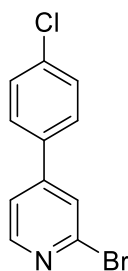
Compound characterisation data agrees with that previously reported in literature.³⁴³ It was isolated from the mixture, General Procedure J, catalysed by **Pd₃Cl₂·Cl**, using a hexane/EtOAc (95:5) solvent system, which was run with a gradient starting from neat hexane. Appeared as a colourless powder.

^1H NMR (400 MHz, Chloroform-*d*) δ 8.70 (dd, J = 5.2, 0.8 Hz, 1H, *pyridyl*-C₆-H), 8.02 – 7.93 (m, 2H, *aryl*), 7.90 (dd, J = 1.7, 0.8 Hz, 1H *pyridyl*-C₃-H), 7.70 – 7.55 (m, 2H, *aryl*), 7.41 (dd, J = 5.2, 1.7 Hz, 1H, *pyridyl*-C₅-H), 7.26–7.35 (m, 4H, *aryl*), 2.43 (s, 6H, 2 × CH₃ {overlapping}).

HRMS ESI-MS m/z = 260.1437 $[\text{M}+\text{H}]^+$: C₁₉H₁₈N requires 260.1434.

R_f (TLC, hexane/EtOAc 95:5 (v/v)) = 0.10.

Labbook Reference Number: NWJS-3-194.

[illegible]2-Bromo-4-(4-chlorophenyl)pyridine (C4-Ar_E)

299

^1H NMR (400 MHz, Chloroform-*d*) δ 8.41 (dd, $J = 5.2, 0.7$ Hz, 1H, *pyridyl*-C₆-H), 7.66 (dd, $J = 1.7, 0.7$ Hz, 1H, *pyridyl*-C₃-H), 7.57 – 7.50 (m, 2H, *aryl*), 7.50 – 7.44 (m, 2H, *aryl*), 7.42 (dd, $J = 5.2, 1.7$ Hz, 1H, *pyridyl*-C₅-H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.7 (*pyridyl*-C–H), 150.1 (C), 143.2 (C), 136.1 (C), 135.2 (C), 129.6 (*aryl*-C–H), 128.4 (*aryl*-C–H), 125.8 (*pyridyl*-C–H), 120.7 (*pyridyl*-C–H) ppm.

IR (ν/cm^{-1} , ATR): 3053 (w, C–H), 3018(w, C–H), 1586 (s), 1525 (m), 1496 (m), 1454 (m), 1406 (m), 1370 (m), 1093(s), 1081 (m), 1043 (m), 1012 (m), 792 (s), 760 (s), 509 (m), 475 (m), 422 (m).

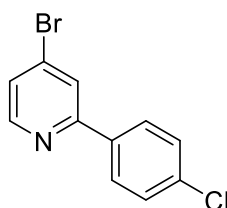
HRMS ESI-MS $m/z = 267.9519$ $[\text{M}+\text{H}]^+$: C₁₁H₈⁷⁹BrClN requires 267.9523

Elemental analysis (% CHN), calculated for C₁₁H₇BrClN: C, 49.20; H, 2.63; N, 5.22; Found: C, 49.05; H, 2.54; N, 5.03.

R_f (TLC, PET/EtOAc, 98:2, $\{v/v\}$) = 0.33.

Labbook Reference Number: NWJS-3-198.

4-Bromo-2-(4-chlorophenyl)pyridine (C2-Ar_E)



Compound characterisation data agrees with that previously reported in literature.³⁴⁶ It was isolated from the reaction mixture (General Procedure J, catalysed by **Pd₃Cl·Cl**) using a hexane/EtOAc (98:2) solvent system, which was run with a gradient, starting from neat hexane. Yield from reaction catalysed by **Pd₃Cl·Cl** = 34.7 mg (12.9 %). Appearance: Colourless powder.

^1H NMR (400 MHz, Chloroform-*d*) δ 8.49 (dd, $J = 5.3, 0.6$ Hz, 1H, *pyridyl*-C₆-H), 7.98 – 7.88 (m, 2H, *aryl*), 7.87 (dd, $J = 1.8, 0.6$ Hz, 1H, *pyridyl*-C₃-H), 7.54 – 7.37 (m, 5H, aryl{4H} *pyridyl*-C₅-H {1H}) ppm.

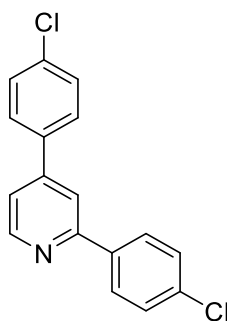
^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.8 (C), 150.6 (*pyridyl*-C–H), 136.6 (C), 136.0 (C), 133.8, (C), 129.2 (*aryl*-C–H), 128.4 (*aryl*-C–H), 125.7 (*pyridyl*-C–H), 123.9 (*pyridyl*-C–H) ppm.

IR (ν/cm^{-1} , ATR): 2957(w), 2920 (w), 2852 (w), 1586 (m), 1570 (m), 1542 (m), 1455 (m), 1372 (m), 1076 (m), 1041 (m), 1015 (m), 985 (m), 802 (vs), 750 (m), 681 (m), 574 (m), 556 (m), 526 (m), 501 (m), 473 (m), 424 (m).

HRMS ESI-MS $m/z = 267.9518$ $[\text{M}+\text{H}]^+$: C₁₁H₈⁷⁹BrClN requires 267.9523

R_f (TLC, PET/EtOAc 98:2, $\{v/v\}$) = 0.22.

Labbook Reference Number: NWJS-3-198.

2, 4-*bis*(4-Chlorophenyl)pyridine (bis-Ar_E)

Compound characterisation data agrees with that previously reported in literature.³⁴³ It was isolated from the reaction mixture, General Procedure J, catalysed by **Pd₃Cl·Cl** using a hexane/EtOAc (98:2) solvent system, which was run with a gradient, starting from neat hexane. Yield from reaction catalysed by **Pd₃Cl·Cl** = 22.9 mg (8%). Appearance: Colourless powder.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.73 (dd, *J* = 5.1, 0.8 Hz, 1H, *pyridyl*-C₆-H), 8.04 – 7.93 (m, 2H, *aryl*), 7.85 (dd, *J* = 1.7, 0.8 Hz, 1H, *pyridyl*-C₃-H), 7.67 – 7.56 (m, 2H, *aryl*), 7.53 – 7.43 (m, 4H, *aryl*), 7.42 (dd, *J* = 5.1, 1.7 Hz, 1H, *pyridyl*-C₅-H) ppm.

¹³C NMR (101 MHz, Chloroform-*d*) δ 157.16 (C), 150.46 (*pyridyl*-C-H), 148.38 (C), 137.84 (C), 136.93 (C), 135.57 (C), 135.47 (*aryl*-C-H), 129.54 (*aryl*-C-H), 129.14 (*aryl*-C-H), 128.50 (*aryl*-C-H), 128.44 (*aryl*-C-H), 120.40 (*pyridyl*-C-H), 118.40 (*pyridyl*-C-H) ppm.

HRMS ESI-MS *m/z* = 300.0338 [M+H]⁺ : C₁₇H₁₂Cl₂N requires 300.0347.

R_f (TLC, PET/EtOAc, 98:2 {v/v}) = 0.11.

Labbook Reference Number: NWJS-3-198.

SMCC of 2,4-Dibromopyridine **30** with *para*-Trifluoromethylphenyl Boronic Acid **74_F**

Products could be identified from crude reaction mixtures (Figure 112). Characterisation data matched that reported in the literature,^{343, 347} and/or with data collated for isolated compounds reported *vide infra*.

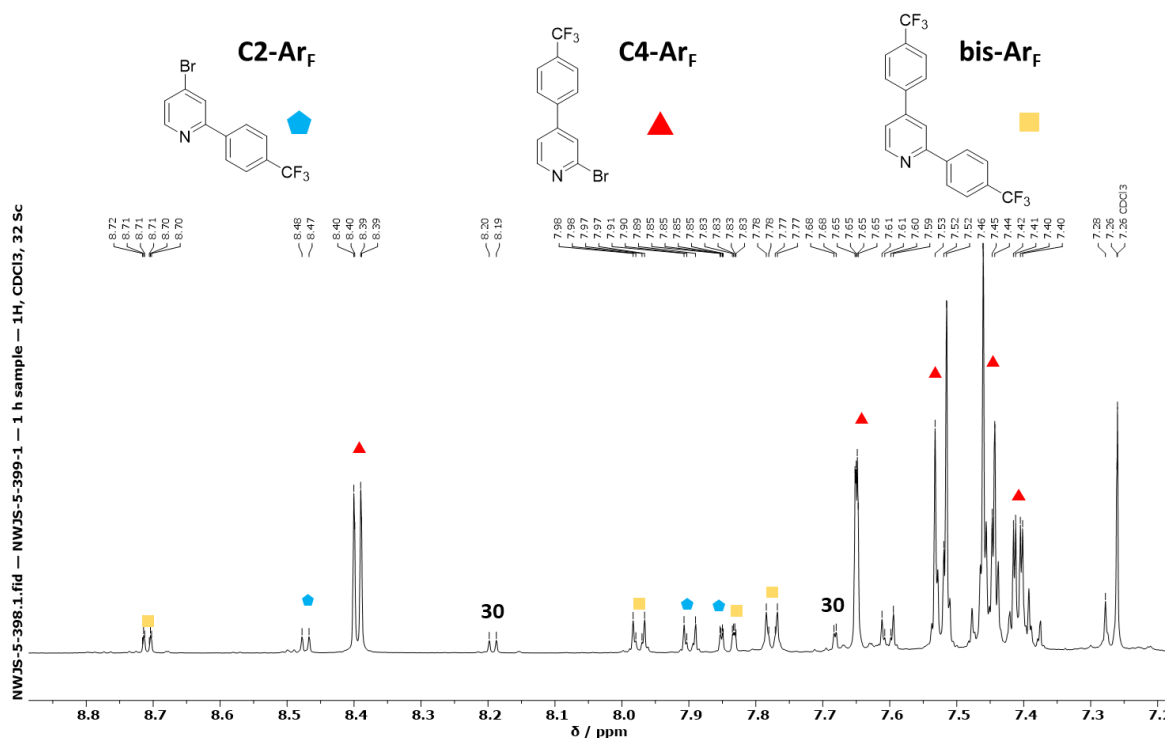
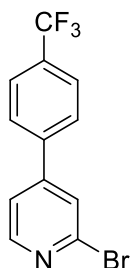


Figure 112 ¹H NMR spectrum (500 MHz, CDCl₃) showing C4-Ar_F, C2-Ar_F and bis-Ar_F compound identification as part of a crude reaction mixture.

2-Bromo-4-(4-trifluoromethylphenyl)pyridine (C4-Ar_F)

Compound characterisation data agrees with that previously reported in literature.³⁴⁷ It was isolated from a reaction mixture, General Procedure J using a hexane/EtOAc, 98:2 (v/v) solvent system, which was run with a gradient, starting from neat hexane. Yield from reaction catalysed by **Pd₃Cl·Cl** = 141.3 mg (47%). Appearance: colourless powder. Melting point – 115.0-117 °C (123.5-124.5 °C lit.).³⁴⁷

^1H NMR (500 MHz, Chloroform-*d*) δ 8.46 (dd, $J = 5.2, 0.6$ Hz, 1H, *pyridyl*-C₆-H), 7.74 – 7.79 (m, 2H, *aryl*), 7.73 – 7.66 (m, 2H, *aryl*) + {*pyridyl*-C₃-H}, 7.47 (dd, $J = 5.2, 1.6$ Hz, 1H, *pyridyl*-C₅-H) ppm.

^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.4 (*pyridyl*-C-H), 149.5 (C), 142.9 (C), 140.0 (C), 131.4 (q, $^2J_{\text{C-F}} = 33.0$ Hz *aryl*-C₄'), 127.3 (*aryl*-C-H) 126.0 (q, $^3J_{\text{C-F}} = 3.7$ Hz, *aryl*-C₃'-H), 125.8 (C-H), 123.6 (q, $J = 272.4$ Hz; $^1J_{\text{C-F}}$ CF₃) 120.7 (C-H) ppm.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.65 ppm.

IR (v/cm⁻¹, ATR): 3019(w), 2981(w), 2831(w), 1608(m), 1585(m), 1515(s), 1457(m), 1429.42(m), 1374.92(m), 1292.08(m), 1184.00 (m), 1017.76(m), 814.70(s), 574.42(m), 567.88(m), 519.79(m).

HRMS ESI-MS $m/z = 301.9773$ [M+H]⁺ : C₁₂H₈⁷⁹BrF₃N requires 301.9787.

Elemental analysis (% CHN), calculated for C₁₂H₇BrF₃N; C 47.71; H, 2.34; N, 4.64 Found: C, 48.09; H, 2.63; N, 4.12.

R_f (TLC, Hexane/EtOAc, 98:2 {v/v}) = 0.12.

XRD analysis (*ijsf1803*):

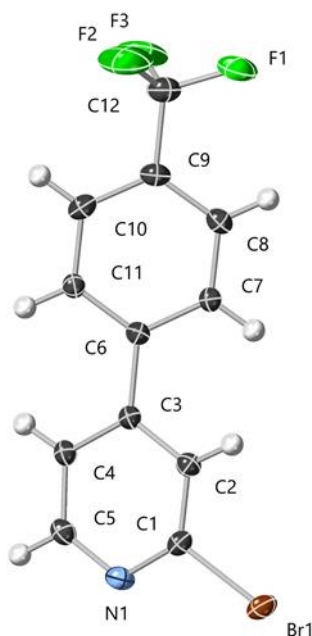


Figure 113 Structure obtained from X-ray diffraction analysis of a single crystal of 2-bromo, 4-(4-trifluoromethylphenyl)pyridine (C4-Ar_F).

A crystal of **C4-Ar_F** was grown by vapour diffusion of pentane in the presence of a CH₂Cl₂ solution containing **C4-Ar_F**. The exact crystal run (by XRD) was subjected to ^1H NMR spectroscopic analysis (700 MHz) which matched data of that of the isolated material (*vide supra*). This conclusively confirms the identity of the NMR characterised species as the C4-arylated product. X-ray crystallographic analysis shows significant distortion of the pyridine ring as evidenced with disparities in bond lengths and deviations away from 120° (Table 23 & Table 24).

Table 23 Analysis of selected bond angles from XRD analysis of a crystal of C4-Ar_F

Angle sweep	$\theta / ^\circ$	deviation from 120°
C(5)–N(1)–C(1)	115.21	4.79
N(1)–C(1)–C(2)	126.02	-6.02
N(1)–C(5)–C(4)	124.25	-4.25
C(1)–C(2)–C(2)	118.01	1.99
C(5)–C(4)–C(2)	119.17	0.83
C(2)–C(4)–C(4)	117.3	2.7

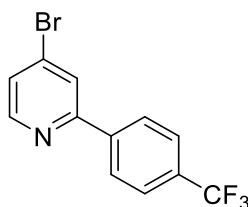
Table 24 Analysis of selected bond lengths from XRD analysis of a crystal of C4-Ar_F

Bond	Bond length / Å
N(1)–C(1)	1.323(3)
N(1)–C(5)	1.347(3)
C(1)–C(2)	1.381(3)
C(5)–C(4)	1.378(3)
C(2)–C(4)	1.396(3)
C(4)–C(2)	1.398(3)
C(1)–Br(1)	1.906(2)

See Appendix 4 for X-Ray Crystallographic Data (ijsf1803).

Labbook Reference Number: NWJS-3-167, NWJS-3-223.

4-Bromo-2-(4-trifluoromethylphenyl)pyridine (C2-Ar_F)



To the knowledge of the author, data for this compound was not previously reported within literature. It was isolated from the crude reaction mixture, catalysed by **Pd₃Cl₂·Cl** (General Procedure J) using PTLC with a hexane/EtOAc (98:2) solvent system. Multiple solvent elutions were needed to allow for separation. Yield from reaction catalysed by **Pd₃Cl₂·Cl** = 3.7 mg (1 %). Appearance: colourless powder.

^1H NMR (400 MHz, Chloroform-*d*) 8.54 (dd, $J = 5.2, 0.6$ Hz, 1H; *pyridyl*-C₆-H), 8.07 – 8.13 (m, 2H, *aryl*), 7.94 (dd, $J = 1.8, 0.6$ Hz, 1H, *pyridyl*-C₃-H), 7.71 – 7.76 (m, 2H, *aryl*), 7.47 (dd, $J = 5.2, 1.8$ Hz, 1H, *pyridyl*-C₅-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.4 (C), 150.7 (C-H), 141.4 (C), 133.9 (C), 131.6 (q, $^2J_{\text{CF}} = 32.6$ Hz, C₄'), 127.5 (C-H), 126.3 (C-H), 126.0 (q, $^3J_{\text{CF}} = 3.8$ Hz, C₃'-H), 124.4 (C-H), 124.2 (q, $^1J_{\text{CF}} = 272.2$, CF₃).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.56 ppm.

HRMS ESI-MS $m/z = 301.9773$ [M+H]⁺ : C₁₂H₇⁷⁹BrF₃N requires 301.9787.

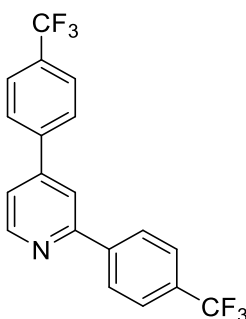
IR (v/cm⁻¹, ATR): 3071 (w), 3054 (w), 2934 (w), 1616 (w), 1566 (m), 1548 (m), 1466 (m), 1376 (m), 1323 (s), 1263 (m), 1169 (s), 1110 (s), 1091 (s), 1070 (s), 1042 (m), 1011 (m), 851 (s), 824 (s), 754 (m), 687 (m), 606 (s), 434 (s).

Elemental analysis (% CHN), calculated for C₁₂H₇⁷⁹BrF₃N; C 47.71; H, 2.34; N, 4.64 Found: C, 47.15; H, 2.37; N, 4.56.

R_f (TLC, Hexane/EtOAc, 98:2 {v/v}) = 0.33.

Labbook Reference Number: NWJS-3-167, NWJS-6-480.

Bis-2,4-(4-trifluoromethylphenyl)pyridine (bis-Ar_F)



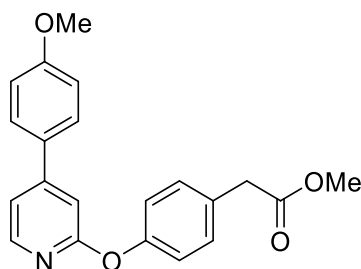
Identified in the crude reaction mixture by comparison to literature reported ^1H NMR spectroscopic data (see Figure 112 above).³⁴³

^1H NMR (400 MHz, Chloroform-*d*) δ 8.80 (dd, $J = 5.1, 0.8$ Hz, 1H, *pyridyl*-C₆-H), 8.18 – 8.14 (m, 2H, *aryl*), 7.50 (dd, $J = 5.1, 1.7$ Hz, 1H, *pyridyl*-C₆-H) ppm. {partial data, from crude ^1H NMR}

^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.47, -62.55 ppm. {partial data, from crude ^{19}F NMR}

HRMS ESI-MS $m/z = 368.0858$ [M+H]⁺ : C₁₉H₁₂F₆N requires 368.0868.

Labbook Reference Number: NWJS-3-167.

Benzeneacetic acid 4[4-anisyl, 2-pyridinyl] oxy]-methyl ester 79

Synthesised in 2 steps from 2,4-dibromopyridine 30.

Step 1 Site-selective SMCC at 2,4-dibromopyridine 30: 2-Bromo,4-(4-anisyl)pyridine (**C4-Ar_A**) was synthesised using a method derive from model C4-selective reaction conditions Pd₃(OAc)₆/3PPh₃ (General Procedure G) as the catalyst system. An oven-dried Schlenk flask (Flask A) charged with Pd₃(OAc)₆ (23.6 mg, 0.03 mmol {3 mol%/Pd}) and PPh₃ (23.6 mg, 0.03 mmol) was evacuated and backfilled with N₂. THF (2.5 mL; dry, degassed) was added *via* a syringe and the immediately formed greenish-yellow suspension was stirred in an oil bath which was pre-heated to 40 °C. Another oven-dried Schlenk tube (Flask B) was charged with 2,4-dibromopyridine (710 mg, 3.00 mmol, 1 equiv.) and *para*-anisylboronic acid **74_A** (479 mg, 3.15 mmol) and subsequently evacuated and backfilled with N₂. After 30 minutes of stirring, the contents of *Flask A* were transferred into *Flask B* *via* a cannula and the resulting mixture was allowed to stir for 5 mins in order to thermally equilibrate at 40 °C. Aqueous *tetra-n*-butylammonium hydroxide (2.5 mL, 1.0 M, degassed) was then added (*t*₀) to commence the reaction. The reaction was stirred overnight at 40 °C. After the reaction time the reaction solution was quenched using a of NH₄Cl (sat. aq). The organics were extracted using EtOAc (4 × 10 mL) before being combined and dried over MgSO₄ and subsequently concentrated in vacuum. The resulting residue, which appeared as a reddish-brown oil was adsorbed to silica and purified by flash chromatography (SiO₂) using a Hexane or petroleum ether/EtOAc(85:15) solvent system to give the product which appeared as a colourless oil (550 mg, 69%).

Step 2 Ullman Coupling at C4-Ar_A: Adapted from a procedure published by Zhao *et al.*²⁹⁴ A Schlenk tube, charged with CuI (18.6 mg, 0.1 mmol) and TMEDA (11.4 mg, 0.1 mmol) were evacuated and backfilled (three times), before being dissolved in dry, degassed toluene (5 mL) and subsequently stirred for 30 min at 23 °C. Cesium carbonate (638.6 mg, 2 mmol) and methyl (4-hydroxyphenyl)-acetate (166.2 mg, 1.00 mmol, 1.32 equiv.) were added into the mixture (as solids) and stirred at room temperature for another 4 h. Finally, solution of 2-bromo,4(4-anisyl)-pyridine (**C4-Ar_A**) (200 mg, 0.758 mmol) in dry toluene (3 mL) was added (total volume = 8 mL => 0.125 M {respect to pyridine substrate}). The reaction mixture was placed in oil-bath which was preheated to 110 °C (refluxed, using a cold finger) under a nitrogen atmosphere for 24 hours. Reaction progress was monitored by TLC

(85:15 {v/v} petroleum ether/ EtOAc). On completion, the reaction mixture was cooled to room temperature. The solvent was evaporated under vacuum (Schlenk) before the residue was dissolved in CH₂Cl₂ (20 mL) and filtered (sinter funnel) and concentrated in vacuum to afford the crude product which appeared as a colourless powder, 264 mg (53%) yield of the title isolated product (Step 2). Melting point – 103.2-104.0 °C.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 5.3 Hz, 1H, *pyridyl*-C₆-H), 7.59 (d, *J* = 8.8 Hz, 2H, *aryl*), 7.33 (d, *J* = 8.5 Hz, 2H, *aryl*), 7.19 (dd, *J* = 5.3, 1.6 Hz, 1H, *pyridyl*-C₅-H), 7.13 (d, *J* = 8.5 Hz, 2H, *aryl*), 7.09 (d, *J* = 1.5 Hz, 1H, *pyridyl*-C₅-H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H, CH₃), 3.71 (s, 3H, CH₃), 3.64 (s, CH₂).

¹³C NMR (101 MHz, Chloroform-*d*) δ 172.6 (C), 165.0 (C), 161.2 (C), 154.0 (C), 152.3 (C), 148.5 (C-H), 130.7 (C-H), 130.2 (C-H), 128.8 (C-H), 121.8 (C-H), 117.1 (C-H), 115.1 (C-H), 109.1 (C-H), 55.5 (CH_{aliph}), 52.2 (CH_{aliph}), 40.7 (CH_{aliph}).

IR (ν/ cm⁻¹, ATR): 3038 (w, C-H), 2953 (w, C-H), 2895 (w, C-H), 2842 (w, C-H), 1734 (m, C=O stretch), 1601 (m), 1393.9 (m), 1217 (m), 1164 (br. m), 1028 (m), 812 (s).

HRMS ESI-MS [M+H] *m/z* = 350.1387: C₂₁H₂₀NO₄ requires 350.1391.

R_f (TLC, PET/EtOAc, 85:15 {v/v}) = 0.15.

Abbreviation List

Ac	acetyl
acac	acetylacetate
AdNDP	adaptive natural density partitioning
AmPhos	(4-(<i>N,N</i> -Dimethylamino)phenyl)di- <i>tert</i> -butyl phosphine
ATR	attenuated total reflectance
BDE	bond dissociation energy
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Bu	butyl
CataCXium® A	di(1-adamantyl)- <i>n</i> -butylphosphine
COSY	correlation spectroscopy
Cy	cyclohexyl
dba	dibenzylideneacetone
DFT	density functional theory
Dipp	2,6-diisopropylphenyl
DLS	dynamic light scattering
DMAc	<i>N,N</i> -dimethylacetamide
DMAPF	1,1'-bis[di-(dimethylamino)phosphino]ferrocene
DMF	<i>N,N</i> -dimethylformamide
DTBPF	1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene
EI	electron ionisation
Equiv.	equivalents
Et	ethyl
EXAFS	extended x-ray absorption fine structure spectroscopy
CAAC	cyclic(alkylamino)carbene
CataXium	di(1-adamantyl)- <i>n</i> -butylphosphine
<i>ca.</i>	<i>circa</i>

Cod	1,5-cyclooctadiene
Cy	cyclohexyl
DPPP	1,2-bis(diphenylphosphino)propane
DPPE	1,2-bis(diphenylphosphino)ethane
EtOH	ethanol
EI	electron ionisation
ESI	electrospray ionisation (MS)
FMO	frontier molecular orbital
FWHM ($\Delta_{1/2}$)	full peak width at half of the maximum peak intensity
GC-MS	gas chromatography – mass spectrometry
GVL	gamma(γ)-valerolactone
hfac	hexafluoroacetylacetone
HOMO	highest occupied molecular orbital
ICP-AES	inductively coupled plasma atomic emission spectroscopy
<i>i</i> pr	isopropyl
IR	infrared spectroscopy
JohnPhos	(2-biphenyl)di-tert-butylphosphine
LC-MS	liquid chromatography – mass spectrometry
LIFDI	liquid injection field desorption ionisation
LUMO	lowest unoccupied molecular orbital
[M] ⁺	molecular ion (MS)
Me	methyl
MeCN	acetonitrile
MeNC	methyl isocyanide
MePhos	2-dicyclohexylphosphino-2'-methylbiphenyl
MIDA	methyliminodiacetic acid (boronic ester)
m.p.	melting point
MS	mass spectrometry

m/z	mass to charge ratio
NBO	natural bond orbital
NHC	<i>N</i> -heterocyclic carbene
NMP	<i>N</i> -methylpyrrolidone
NMR	nuclear magnetic resonance
OAc	acetate
OTf	trifluorotoluenesulfonate (triflate) functional group
Pd/C	Pd on a carbon support
PdNP	Pd nanoparticle
PEG	polyethylene glycol
PEPPSI	pyridine-enhanced pre-catalyst preparation stabilization and initiation
Ph	phenyl
pin	pinacolato
PPBN	9-phenyl-9-phosphabicyclononane
ppm	parts per million
PVP	polyvinylpyrrolidone (polymer)
QPhos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
rt	room temperature
S.M	starting material
SEM	scanning electron microscopy
SERS	surface enhanced Raman spectroscopy
SMCC	Suzuki-Miyaura cross-coupling
solv.	solvent of crystallisation
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
sSPhos	sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate
STM	scanning tunnelling electron microscopy
<i>t</i> -	tertiary

T.E.M.	transmission electron microscopy
TFA	trifluoroacetate/trifluoroacetic acid
T.I.R.F.M	total internal reflection fluorescence microscopy
THF	tetrahydrofuran
T.M.	transition metal
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TOF	(catalyst) turnover frequency
TON	(catalyst) turnover number
Ts	toluenesulfonyl (tosylate) functional group
UV	ultraviolet
Vis	visible
w.r.t.	with respect to
XAS	X-ray absorption spectroscopy
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XP	X-Ray Photoelectron Spectroscopy
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XRD	X-Ray diffraction

Appendix 1 – Published Paper

Part of this work has been published in the following paper.³⁴⁸ A copy is featured below.

Scott, N. W. J.; Ford, M. J.; Schotes, C.; Parker, R. R.; Whitwood, A. C.; Fairlamb, I. J. S., The ubiquitous cross-coupling catalyst system 'Pd(OAc)₂'/2PPh₃ forms a unique dinuclear Pd^I complex: an important entry point into catalytically competent cyclic Pd₃ clusters. *Chem. Sci.* **2019**, *10*, 7898-7906.

Additionally, a book chapter was written reviewing the field of heterogeneous catalysis in C–H activation/functionalisation chemistry:³⁴⁹

Fairlamb, I. J. S.; Scott, N. W. J., Pd Nanoparticles in C–H Activation and Cross-coupling Catalysis. In *Nanoparticles in Catalysis*, Kobayashi, S., Ed. Springer International Publishing: Cham, 2020.

Cite this: *Chem. Sci.*, 2019, 10, 7898

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

Neil W. J. Scott,^a Mark J. Ford,^b Christoph Schotes,^c Rachel R. Parker,^a Adrian C. Whitwood^a and Ian J. S. Fairlamb^{a*}

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 Pd^I complex [Pd₂(μ-PPh₂)(μ₂-OAc)(PPh₃)₂] as the major product, the elusive species resisting characterization until now. While unstable, the dinuclear Pd^I complex reacts with CH₂Cl₂, *p*-fluoriodobenzene 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 'Pd^{II}(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'/*n*PPh₃ 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 cluster 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 and chemo-, regio- and stereoselectivities, particularly when employing PPh₃ as the ligand.

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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'/*n*PPh₃

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'/*n*PPh₃ 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 Pd^{II} → Pd⁰ reduction process.^{4bc} Both 'Pd⁰(PPh₃)₂' and [Pd⁰(PPh₃)₂(OAc)][−] species react by oxidative addition with organohalides.

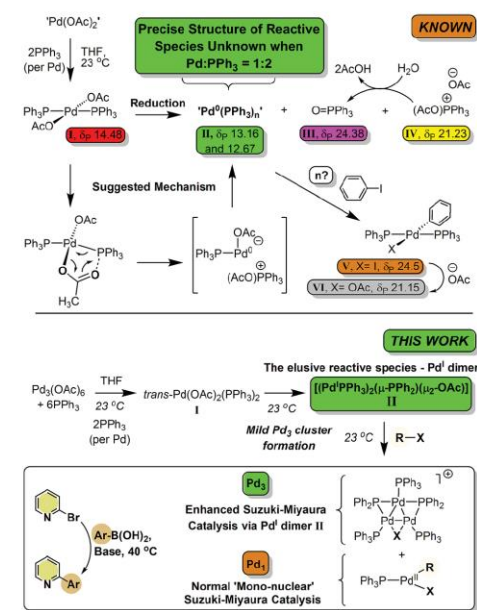
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† Electronic supplementary information (ESI) available: Full experimental details and characterization data for all compounds is provided, including NMR spectra, X-ray diffraction data and computational data (as a PDF file). CCDC 1894927–1894931 and 1901195. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc01847f





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

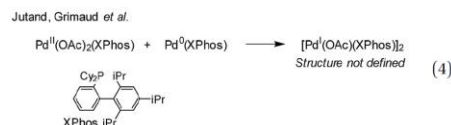
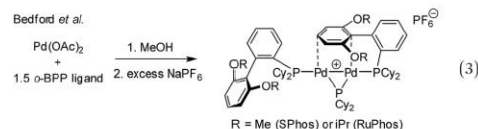
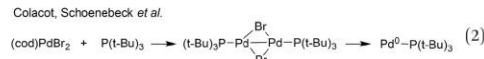
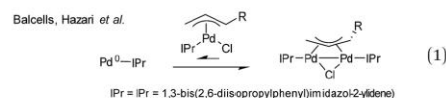
Later, Kollár *et al.* examined the reaction of 'Pd(OAc)₂'/nPPh₃ in DMF,⁵ amongst other phosphines, concluding that 'Pd⁰(PPh₃)_n' species are formed under ambient reaction conditions. Taken together these studies suggest that a Pd/PPh₃ ratio of 1 : 3 is necessary for satisfactory catalytic cross-coupling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

Over the last 20 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 Pd^{II} 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 Hazari^{10a} showing formation of Pd^I dimers with NHC ligands and bridging allyl and chloride ligands (eqn (1)); (b) Colacot and Schoenebeck^{10b} showing formation of Pd^I dimers with phosphines and bridging bromide ligands (eqn (2)); (c) Bedford^{10c} showing SPhos activation on reaction with Pd(OAc)₂ (eqn (3)); (d) Jutand and Grimaud^{10d} showing XPhos reactions with Pd(OAc)₂ leading to a proposed Pd^I dimer (eqn (4)).

The stability and reactivity of these Pd^I 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*-fluoriodobenzene **1b** and 2-bromopyridine **1c**, which affords Pd₃ 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 transmetalation to transmetalation and then oxidative addition.¹¹



Results and discussion

The reaction of ultra-pure $\text{Pd}_3(\text{OAc})_6$ (>99% purity) with PPh_3 , in varying ratios, in THF- d_8 were conducted at room temperature (25 °C) and monitored by ^1H and ^{31}P NMR spectroscopic analysis (where $[\text{Pd}] = 20 \text{ mM}$; $T = 298 \text{ K}$, external reference = 85% H_3PO_4 in H_2O). 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 (Fig. 1 and 2).

Where the ratio of $\text{Pd}:\text{PPh}_3$ was 1 : 1, degradation of $\text{Pd}_3(\text{OAc})_6$, leading to the formation of large perfectly spherical Pd particles (sized ~0.1–0.4 μm , by TEM) and many P-containing species (by ^{31}P NMR) was observed (Fig. 1(a)). Alteration of the Pd/PPh_3 ratio to 1 : 2 (Fig. 1(b)) 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 $^2J_{\text{PP}}$ coupling constant of 83.5 Hz (*i.e.* an AX_2 type spin system). The high ^{31}P chemical shift of δ 199.01 indicates that the PPh_3 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 (40H). Running the reaction at lower $\text{Pd}_3(\text{OAc})_6$ concentration (between 3 and 20 mM) allowed this species to be isolated in a form that could be crystallized. X-ray diffraction analysis of dark red single crystals of this species confirmed its structure as $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]$ **II**, possessing both bridging μ_2 -acetoxy and μ -phosphido ligands and terminal-capping PPh_3 ligands. Complex **II** is a diamagnetic species. The Pd–Pd bond distance was found to be 2.5958(3) Å, which is in-keeping with other dinuclear Pd^{I} 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, $[\text{Pd}_2(\eta^3\text{-allyl})(\mu\text{-OC(O)i-Bu})(\text{PPh}_3)_2]$ where the $\text{Pd}\cdots\text{Pd}$ bond distance equals 2.6267(3).¹²

A scaled-up synthesis of **II** was found possible from $\text{Pd}_3(\text{OAc})_6/6\text{PPh}_3$, 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 Pd^{I} complex was present in solution ($M^+ = m/z$ 982, with the correct isotopic distribution). The reference ^{31}P NMR spectrum for purified **II** is given in Fig. 2 (externally-referenced to H_3PO_4). 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. Acetobenzene, a possible reductive elimination product, was not detected by GC-MS analysis. These species are accompanied by $\text{O}=\text{PPh}_3$ **III**, $[\text{Ph}_3\text{P}(\text{OAc})]\text{X}$ **IV** and another dinuclear Pd^{II} 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 PPh_3 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/PPh_3 ratio to 1 : 3 complex **II** was not formed, simply a broad resonance at δ 5.71 (FWHM *ca.* 550 Hz) characterized as $\text{Pd}^{\text{I}}(\text{PPh}_3)_n/[\text{Pd}^{\text{I}}(\text{PPh}_3)_n(\text{OAc})]\text{P}(\text{OAc})\text{Ph}_3$ ($n = 1, 2$ or 3), see Fig. 1(c). The chemical shift alters with time, with concomitant formation of $\text{O}=\text{PPh}_3$, by hydrolysis of $[\text{Ph}_3\text{P}(\text{OAc})]\text{X}$ **IV**, yielding AcOH also. Heating this mixture to 60 °C, over 16 h, eventually ended in decomposition to form large Pd black particles. Indeed, similar ^{31}P NMR spectra were seen on changing the Pd/PPh_3 ratio to 1 : 4, see Fig. 1(d), leading to a mixture of $\text{Pd}^{\text{I}}(\text{PPh}_3)_3$ **IX** and $[\text{Pd}^{\text{I}}(\text{OAc})(\text{PPh}_3)_3]^-$ **IX'**. At the same Pd/PPh_3 ratio, subsequent heating to 60 °C resulted in clean conversion of **IX** into $\text{Pd}^{\text{I}}(\text{PPh}_3)_3$ (**IX**), $\text{O}=\text{PPh}_3$ (**III**) and 2AcOH, quantitatively, as shown by both ^{31}P and ^1H NMR spectra. Layering this solution with hexane, after $t = 16 \text{ h}$, led to the formation of yellow-orange crystals, which were found suitable for X-ray diffraction, establishing the compound as

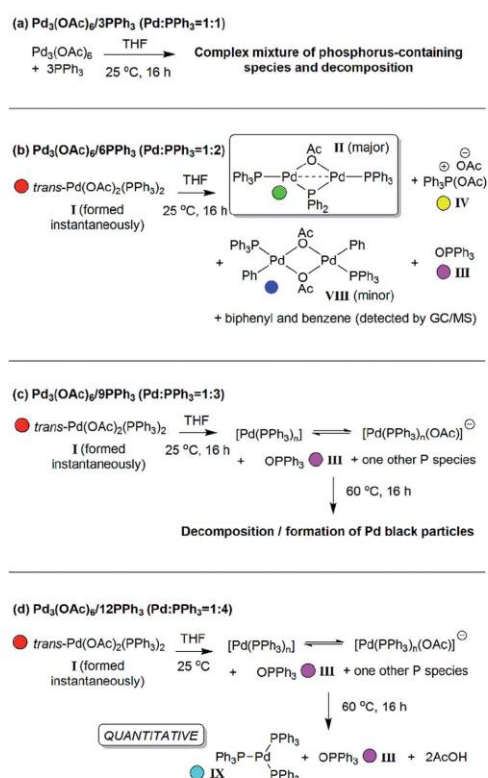


Fig. 1 The room temperature formation of dinuclear Pd^{II} complexes from $\text{trans-Pd}(\text{OAc})_2(\text{PPh}_3)_2$ in THF. (a) Ratio of $\text{Pd}:\text{PPh}_3 = 1:1$; (b) ratio of $\text{Pd}:\text{PPh}_3 = 1:2$; (c) ratio of $\text{Pd}:\text{PPh}_3 = 1:3$; (d) ratio of $\text{Pd}:\text{PPh}_3 = 1:4$. The Pd^{I} species $\text{Pd}^{\text{I}}(\text{PPh}_3)_3$ **IX** and $[\text{Pd}^{\text{I}}(\text{PPh}_3)_3(\text{OAc})]^-$ **IX'** are indicated by cyan circles (appearing as coincident signals by ^{31}P NMR spectroscopic analysis when present together – compare top two ^{31}P NMR spectra in Fig. 2 with the authentic sample of $\text{Pd}^{\text{I}}(\text{PPh}_3)_3$ **IX**, bottom spectrum, Fig. 2).

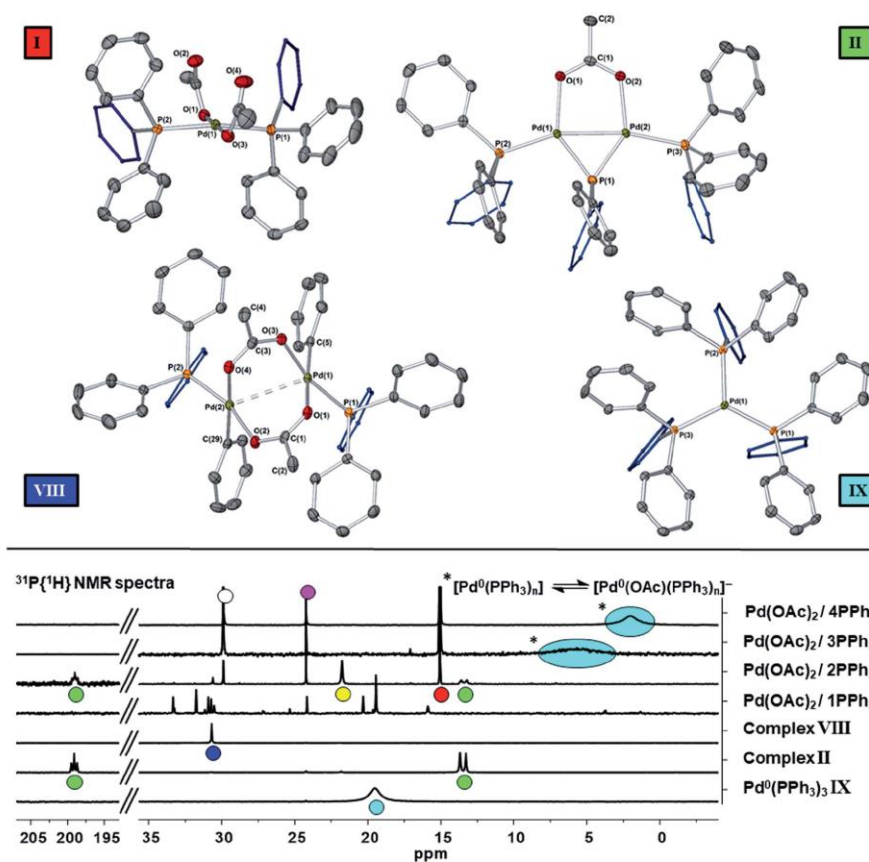


Fig. 2 Top: Single crystal X-ray diffraction structures of II, VIII and IX are shown (thermal ellipsoids shown at 50%, H-atoms and solvent of crystallization not shown, for clarity). Bottom: $^{31}\text{P}\{^1\text{H}\}$ NMR (202 MHz) spectra of mixtures of $\text{Pd}(\text{OAc})_2$ with $n\text{PPh}_3$ ($n = 1$ to 4) in THF at 23°C for 16 h, showing differences in phosphorus speciation. Reference spectra are given for II (green), VIII (blue) and IX (cyan); other species are OPPh_3 (pink), $[\text{AcOPPh}_3]\text{X}$ (yellow, where X is likely the OAc anion) and $\text{trans-Pd}(\text{OAc})_2(\text{PPh}_3)_2$ I (red). Several phosphorus species are uncharacterized for the $\text{Pd}(\text{OAc})_2/1\text{PPh}_3$ experiment (also resulting in PdNP formation). For the equilibrium shown against the ratio of $\text{Pd}(\text{OAc})_2/4\text{PPh}_3$ spectral data, acetate anion and free PPh_3 are involved, explaining the substantially lower chemical shift (compare also the reference spectrum of pure $\text{Pd}^0(\text{PPh}_3)_3$ IX – bottom).

$\text{Pd}^0(\text{PPh}_3)_3$ (IX) (Fig. 2). It is worthy of note that $\text{Pd}^0(\text{PPh}_3)_3$ IX is a relatively stable Pd^0 complex in the solid-state (note: discoloration is noted in air after ~ 1 day).

Computational studies using DFT calculations with $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]$ 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 $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]$ toward other species such as electrophiles and nucleophiles.

We believe that the mechanism for formation of II is different to the Pd^{I} 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 Pd^{I} dimer species, though Pd– π -arene interactions. In II acetate takes on that role.

Reactivity of II towards organohalides

The reaction of $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]$ II with CH_2Cl_2 1a (~ 10 -fold excess) occurred at room temperature to afford a new

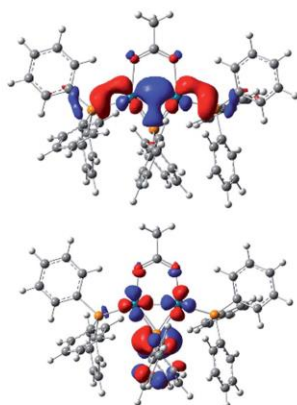


Fig. 3 The HOMO (left) and LUMO (right) for $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu_2\text{-OAc})(\text{PPh}_3)_2]\text{II}$, computed by density functional theory (b3lyp/def2svp functional/basis set used for optimization, single point orbital and total energies; CPCM implicit solvent (tetrahydrofuran) and Gimme's D3 empirical correction used).

Pd species, which was identified as $[\text{Pd}_3(\text{Cl})(\text{PPh}_2)_2(\text{PPh}_3)_3]\text{OAc}$ **Pd₃Cl·OAc** by ESI studies (+ve mode, detected by the $[\text{M} - \text{OAc}]^+$ 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 $[\text{Pd}_3(\text{Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$ **Pd₃Cl·Cl**, starting from $\text{PdCl}_2(\text{PPh}_3)_2$ in aniline under $\text{H}_{2(\text{g})}$ at 90 °C, 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 CH_2Cl_2 , '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 Pd^{II} species **Xa**. Similarly, reaction of **II** with *p*-fluoro-iodobenzene **1b** afforded $[\text{Pd}_3(\text{I})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_4]\text{OAc}$ **Pd₃I·OAc**, as shown by ³¹P NMR and ESI data (as the $[\text{M} - \text{OAc}]^+$ ion), which degraded rapidly to form Pd black. As with the reaction of **II** with CH_2Cl_2 **1a**, the '*p*-F-C₆H₄-' fragment derived from **1b**, 'Pd(PPh₃)₁' and OAc anion could not be fully traced (Pd^{II} species **Xb** is postulated).

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

To verify findings concerning formation of $[\text{Pd}_3(\text{Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{OAc}$ (**Pd₃Br·OAc**) *vide supra*, a closely related sample was prepared by treatment of $[\text{Pd}_3(\text{Cl})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Cl}$ (**Pd₃Cl·Cl**) with excess KBr in CH_2Cl_2 , giving $[\text{Pd}_3(\text{Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{Br}$ (**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.

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 $[\text{Pd}(\mu\text{-I})\text{P}(t\text{-Bu})_3]_2$ reacts with PPh_2 (slight excess relative to the Pd^I 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 PPh_3 (2 equiv.) is reacted with **II** (1 equiv.) in THF at room temperature we see the generation of $\text{Pd}(\text{PPh}_3)_n$ species (where *n* = 3, this species was detected by LIFDI-MS, see ESI†). This finding is in-keeping with what was observed when $\text{Pd}_3(\text{OAc})_6$ was reacted with nine equivalents of PPh_3 (*i.e.* Pd/ PPh_3 ratio of 1 : 3, Fig. 2). We expect that Pd⁰ complexes are generated from disproportionation of the Pd^I dinuclear complex **II**, upon addition of PR_3 , akin to the observations reported by Schoenebeck and Colacot.^{10b}

Importance of our findings in an exemplar SMCC reaction

To better understand the importance of the 'Pd(OAc)₂/*n*PPh₃' ratio in catalysis, the cross-coupling of 2-bromopyridine **1c** with *p*-fluorophenylboronic acid **2** to give 2-arylpyridine **3** was examined,^{6b} using 1 M *n*-Bu₄NOH as the base, in a THF/water mixture (1 : 1, v/v) at 40 °C. We carefully selected 1 M *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/*n*PPh₃' (*n* = 6 and 12, *i.e.* Pd/ PPh_3 = 1 : 2 or 1 : 4



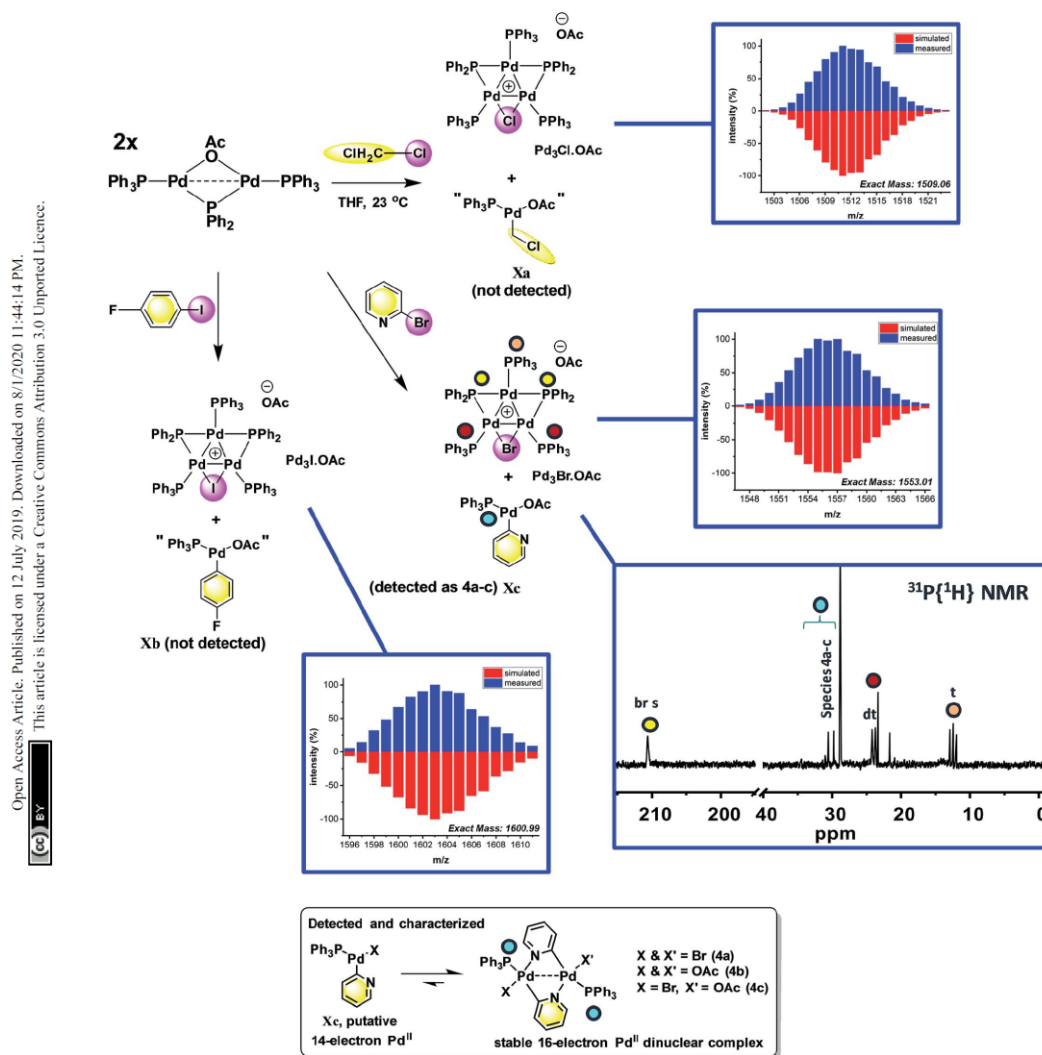


Fig. 4 Reactions of dinuclear Pd complex **II** with organohalides (**1a-c**), leading to formation of Pd₃ clusters Pd₃X·OAc. The X anions in these clusters are likely acetate (mass balance is formally correct using acetate for all Pd species formed), although mixtures of different anions cannot be ruled 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 (measured – 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 ESI†).

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 °C {Fig. 7(A)} –

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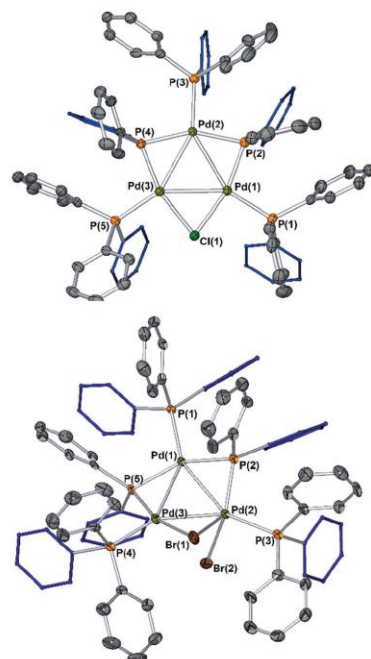


Fig. 5 The single crystal X-ray diffraction structures for $[\text{Pd}_3(\text{X})(\text{PPh}_2)_2(\text{PPh}_3)_3]\text{X}$ (top, $\text{X} = \text{Cl}$, $\text{Pd}_3\text{Cl} \cdot \text{Cl}$; bottom, $\text{X} = \text{Br}$, $\text{Pd}_3\text{Br} \cdot \text{Br}$); H-atoms and solvent of crystallization are not shown and thermal ellipsoids are set at 50% probability. For $\text{Pd}_3\text{Cl} \cdot \text{Cl}$ the non-coordinating chloride anion is not shown. Selected bond lengths (Å) and angles (°) for: $\text{Pd}_3\text{Cl} \cdot \text{Cl}$ $\text{Cl1-Pd1} = 2.3828(8)$; $\text{Cl1-Pd3} = 2.4002(8)$; $\text{Pd1-Pd2} = 2.9138(3)$; $\text{Pd1-Pd3} = 2.8882(3)$; $\text{Pd2-Pd3} = 2.9127(3)$; $\text{Pd1-Cl1-Pd3} = 74.29(2)$; $\text{Pd1-Pd2-Pd3} = 81.38(3)$; $\text{Pd3-Pd1-Pd2} = 81.45(3)$; $\text{Cl1-Pd1-Pd2} = 113.303(19)$; $\text{Cl1-Pd1-Pd3} = 53.130(18)$; $\text{Pd3-Pd1-Pd2} = 60.265(8)$. $\text{Pd}_3\text{Br} \cdot \text{Br}$ $\text{Pd1-Pd2} = 2.8355(10)$; $\text{Pd2-Br1} = 2.9423(13)$; $\text{Pd2-Br2} = 2.5698(13)$; $\text{Pd3-Br1} = 2.5490(13)$; $\text{Pd1-Pd3} = 2.8808(10)$; $\text{Pd2-Pd3} = 2.8240(10)$; $\text{Pd2-Pd1-Pd3} = 59.21(2)$; $\text{Pd3-Pd2-Pd1} = 61.20(2)$; $\text{Pd2-Pd3-Pd1} = 59.60(2)$; $\text{Pd3-Br1-Pd2} = 61.40(3)$; $\text{Br2-Pd2-Pd1} = 101.20(4)$; $\text{Br2-Pd2-Pd3} = 76.91(3)$; $\text{Br2-Pd2-Br1} = 96.67(4)$.

there is an exotherm during initial catalyst turnover (*ca.* 4 turnovers) which is associated with full dissolution of aqueous 1 M *n*-Bu₄NOH (into THF – overall concentration equals 0.5 M *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 $\text{Pd}_3(\text{OAc})_6/12\text{PPh}_3$ (1 : 4, Pd/PPh_3) led to a poor catalyst system for reaction $1\text{c} + 2 \rightarrow 3$ at 40 °C (Fig. 7(C), curves illustrated by diamonds). This catalyst system exhibited higher catalyst efficacy at 70 °C. Thus, additional phosphine slows down catalysis in the reaction of $1\text{c} + 2 \rightarrow 3$, at 40 °C, which is

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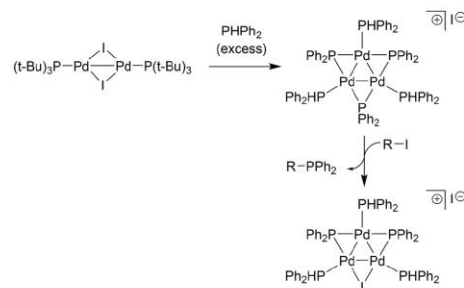


Fig. 6 Schoenebeck's findings¹⁷ on the formation of a Pd_3 -type cluster from an electron-rich Pd^{I} dimer species.

an outcome consistent with our previous studies on SMCCs involving **1c**.^{6b}

With the finding that $[\text{Pd}_2(\mu\text{-PPh}_2)(\mu\text{-OAc})(\text{PPh}_3)_2]$ **II** reacts with 2-bromopyridine **1c** to give $[\text{Pd}_3(\text{Br})(\mu\text{-PPh}_2)_2(\text{PPh}_3)_3]\text{OAc}$ ($\text{Pd}_3\text{Br} \cdot \text{OAc}$) and $[\text{Pd}(\text{X}/\text{X}')(\text{N},\text{C}^2\text{-pyr})(\text{PPh}_3)_2]$ (**4a-c**), additional catalytic experiments were devised to test the importance of such species in the SMCC reaction $1\text{c} + 2 \rightarrow 3$ (Fig. 8). Two control experiments, with different Pd catalysts, were conducted: (a) to establish the catalytic competency of $\text{Pd}_3\text{Br} \cdot \text{Br}$;¹⁹ (b) to assess the catalytic activity of $[\text{Pd}(\text{Br})(\text{N},\text{C}^2\text{-pyr})(\text{PPh}_3)_2]$ **4a**, under comparable reaction conditions. The reaction of $1\text{c} + 2 \rightarrow$

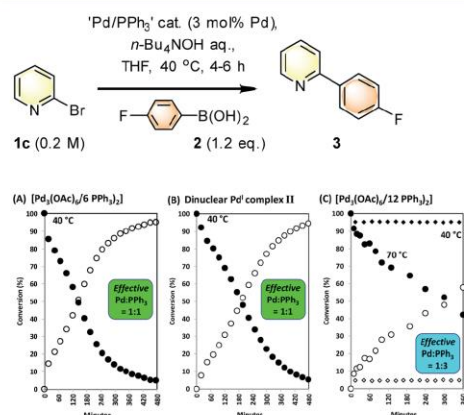


Fig. 7 Kinetic profiles for the SMCC reaction of $1\text{c} + 2$ to give **3**, mediated by $\text{Pd}(\text{OAc})_2/n\text{PPh}_3$ ($n = 2$ and 4) and dinuclear Pd^{I} complex **II**. (A) Reaction mediated by $\text{Pd}_3(\text{OAc})_6/6\text{PPh}_3$; (B) reaction mediated by dinuclear Pd^{I} complex **II**; (C) reaction mediated by $\text{Pd}_3(\text{OAc})_6/12\text{PPh}_3$. Reactions were monitored by ^1H NMR spectroscopic analysis in a J. Young's NMR tube (spinning). The effective $\text{Pd} : \text{PPh}_3$ ratio takes into account that one equivalent of PPh_3 is required to reduce Pd^{II} to Pd^0 , with concomitant formation of one equivalent of $\text{O}=\text{PPh}_3$. For complex **II**, two PPh_3 ligands are present overall, i.e. one per Pd ; in this respect the ' PPh_2 ' group was treated as an anionic ligand.

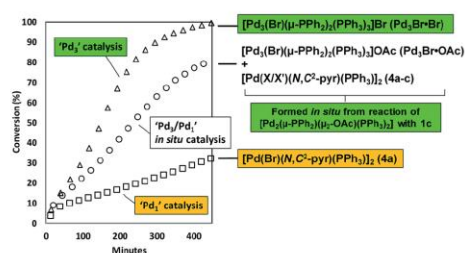


Fig. 8 Overlay of kinetic curves for the SMCC reaction of **1c** + **2** $\rightarrow$ **3**, mediated by **Pd₃Br-Br** (1 mol%), **4a** (0.5 mol%) and **II** (1.5 mol%), generating **Pd₃Br-OAc**, **4a-c** *in situ*; other reaction conditions identical to Fig. 6. Reactions were monitored by ¹H NMR spectroscopic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

3, mediated by **Pd₃Br-Br** (1 mol%, giving 1 mol% active Pd – the cluster being treated as a well-defined catalyst species⁴¹) gave **3** with full conversion after ca. 7.5 h at 40 °C (Fig. 8). The same reaction mediated by an authentic sample of **4a** (0.5 mol% giving 1 mol% active Pd⁴⁶) 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** $\rightarrow$ **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,C²-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,C²-pyr)(PPh₃)₂ 4a]**.

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 Pd^I complex, **[Pd₂(μ-PPh₂)(μ₂-OAc)(PPh₃)₂ 11]**. Species **11** 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.⁴⁶ An important discovery was the finding that **11** 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)₃X]**, carrying an overall 4/3 oxidation state. Use of 2-bromopyridine **1c** was critical in understanding that a putative 14-electron mononuclear 'Pd^{II}(R)(X)(PPh₃)' is released on forming **[Pd₃(X)(PPh₂)₂(PPh₃)₃X]** clusters from **11**. 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** $\rightarrow$ **3**. Near identical catalytic efficacy was seen for a reaction mediated by either 1Pd(OAc)₂/

2PPh₃ or **11**, whereas the 1Pd(OAc)₂/4PPh₃ catalyst system was significantly less effective, requiring a higher temperature (70 rather than 40 °C) 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 11]** can form, *i.e.* when a ratio of Pd/PPh₃ 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 Pd^{II} species (*i.e.* oxidative addition products). If the relative amount of PPh₃ ligand to Pd is low, then 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 of 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 Pd⁰ species in text book mechanisms.

Understanding how **[Pd₃(X)(μ-PPh₂)₂(PPh₃)₃X]** clusters activate aryl/heteroaryl halides and organometallic coupling partners, *e.g.* aryl boronic acids,⁴¹ 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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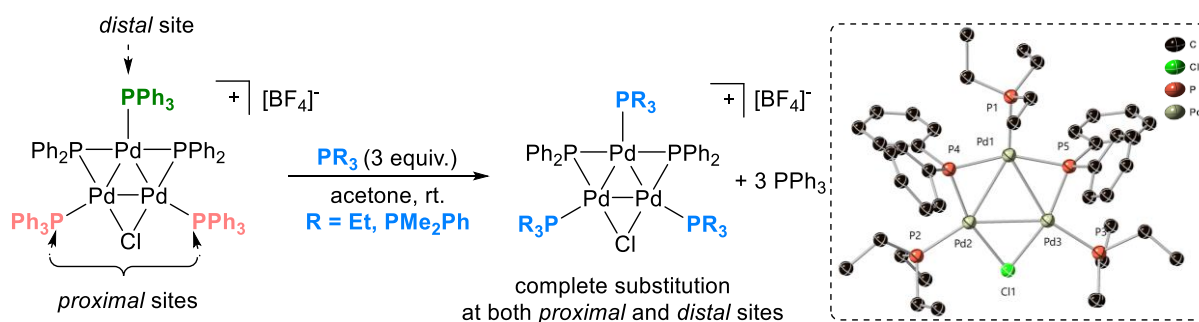


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- 19 Pd₃Br·Br was selected for control experiments as we hypothesized that excess bromide would be generated the SMCC reaction, *i.e.* bromide would be liberated during each catalyst turnover.
- 20 A catalyst loading approximation (1.5 mol% of **II**) was made for comparison of catalytic activity for the *in situ* generation of Pd₃Br·OAc and **4a**, which takes into consideration that degradation of **II** is expected under the real working reaction conditions.
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Appendix 2 – The Reactivity of Pd₃Cl·Cl with PCy₃

Chapter 2 showed that clusters of the form [Pd₃(μ-X)(μ-PPh₂)₂(PPh₃)₃]X⁻ (**Pd₃X·X**, X = Cl, Br, I) could form by treatment the Pd^I dimer complex [Pd₂(μ₂-OAc)(μ-PPh₂)(PPh₃)₂] **52**, which arises upon mixing [Pd₃(OAc)₆] with 6 equivalents of PPh₃ in THF, with organohalides. Clusters adopting the **Pd₃X·X** structural motif have been reported to form *via* a diverse array of pathways (See Section 1.4). **Pd₃X·X** motif has been shown to be catalytically relevant in both *this Thesis* (Chapters 3 & 4) and in published literature.^{162, 172} Details on the structural characterisation of **Pd₃X·X**-type clusters involved in *this work* can be found in Section 2.5.3. Dixon *et al.* demonstrated that treatment of **Pd₃Cl·BF₄** with an excess of PEt₃ in acetone, at room temperature, resulted in full substitution of both *proximal* and *distal* PPh₃ ligands, yielding a [Pd₃(μ-Cl)(μ-PPh₂)₂(PEt₃)₃]⁺[BF₄]⁻ product (Scheme 88).^{167, 258} Likewise, substitution of the *proximal* and *distal* sites was shown to be possible with PMe₂Ph. These reactions demonstrated that full substitution of PPh₃ ligands can occur at both the *proximal* and *distal* sites of the **Pd₃Cl**⁺ cation when treated with these less sterically demanding and more strongly σ-donating tertiary phosphine ligands that of PPh₃.^{166, 261}



Scheme 88 Conditions used by Dixon *et al.* for the ligand substitution reaction between **Pd₃Cl·BF₄** and **PR₃**. Crystallographic data for [Pd₃(μ-Cl)(μ-PPh₂)₂(PEt₃)₃]X⁻, collected by Dixon *et al.*²⁵⁸, was obtained from the Cambridge Crystallographic Data Centre (CCDC). Selected bond distances /Å: Pd2–Pd3 = 2.894, Pd1–Pd2 = 2.94, Pd2–Cl1 = 2.412, Pd2–P2 = 2.300, Pd1–P4 = 2.272 P3–Pd5 = 2.227.

Substitutions of tertiary phosphine ligands have been known to lead to changes in catalytic activity of Pd cluster complexes. For example, Schoenebeck *et al.* recently synthesised the Pd^I dimer complex [Pd^I(μ-I)(P/BuC₂)₂]₂, the P/BuC₂-substituted derivative of [Pd^I(μ-X)(P/Bu₃)₂] **17** (Section 1.4).³⁵⁰ On application in an olefin migration synthetic methodology, [Pd^I(μ-I)P/Bu₃Cy₂]₂ significantly outperformed **17** as a pre-catalyst. Thus, there is scope for modulating the reactivity of cluster catalyst systems simply, by modulating the steric and electronic properties of co-ordinated ligands.

With a view to preparing novel catalyst systems, it was decided to explore substitution of PPh₃ ligands at the **Pd₃Cl**⁺ cation with the bulkier, more electron-rich ligand PCy₃.^{166, 261} **Pd₃Cl·Cl** was, for the first

time, treated with three equivalents of PCy_3 in CD_2Cl_2 . After *ca.* 20 minutes of reactivity at room temperature in CD_2Cl_2 , ^{31}P NMR spectroscopic analysis of the crude-post reaction solution showed disappearance of the ^{31}P signals indicated that the complex had converted fully into a new species (Figure 114, A.).

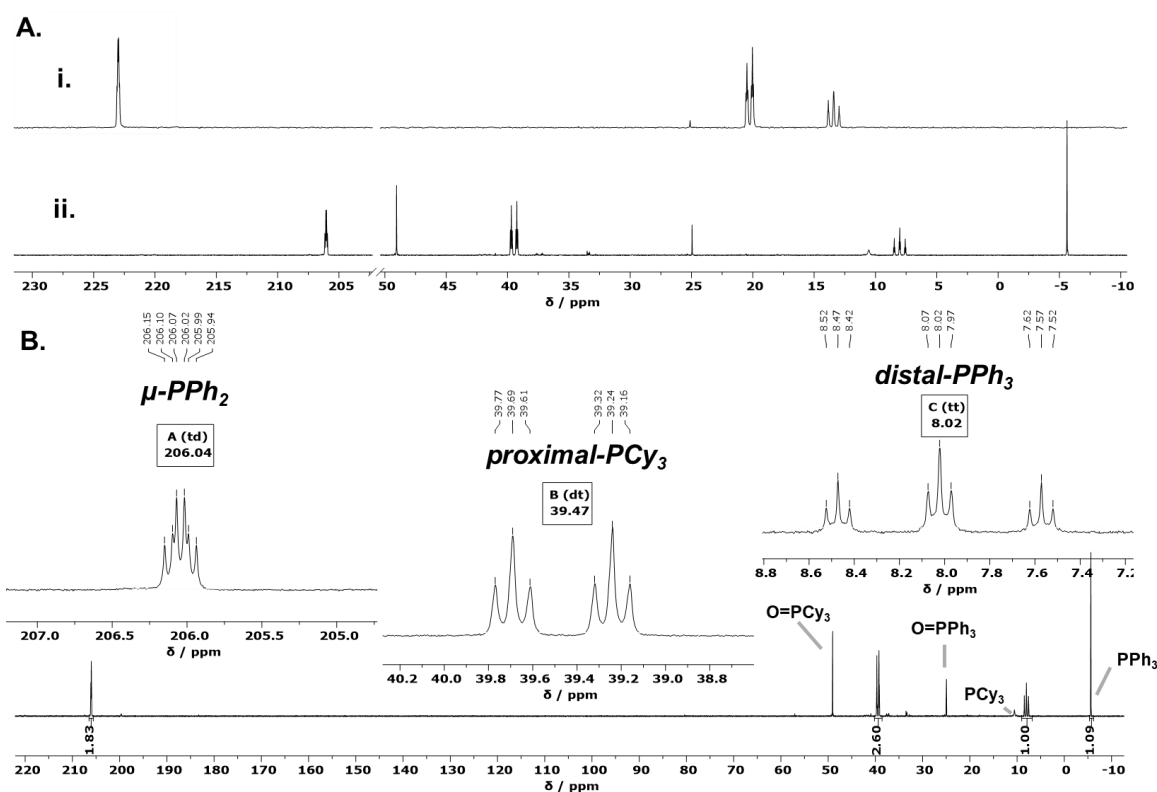


Figure 114 ^{31}P NMR (202 MHz, CD_2Cl_2 , 256 scans, 298K). (A.) Stack of (i.) $\text{Pd}_3\text{Cl}_2\text{Cl}$ starting material. (ii.) The crude reaction product after reacting $\text{Pd}_3\text{Cl}_2\text{Cl}$ with 3 equiv. of PCy_3 . (B.) The whole spectrum of (ii) with expansions showing peak multiplicities of the major product.

In the CD_2Cl_2 solvent, ^{31}P NMR signals representative of $\text{Pd}_3\text{Cl}_2\text{Cl}$ had been replaced with signals of broadly the same peak shape and multiplicity (Section 2.5.2), indicating that a similarly structured cluster motif had appeared in their place (Figure 114).²⁵⁸ The phosphido resonance had been replaced with a triplet of doublets (td) at δ_{P} 206.0 ppm: *ca.* $\Delta\delta_{\text{P}}$ 17 ppm upfield of that of $\text{Pd}_3\text{Cl}_2\text{Cl}$, suggestive of a more electron-rich phosphido environment. The product's doublet of triplets (dt) resonance, representative of the *proximal* P-environment of the product, at δ_{P} 39.5 ppm, appeared significantly downfield ($\Delta\delta_{\text{P}}$ 19.2 ppm) of that of the starting material (δ_{P} 20.3 ppm). The chemical shift of the *distal* ^{31}P -environment is indicative of a PCy_3 -Pd interaction and is downfield of the region where Pd-coordinated PPh_3 ligands generally resonate.³⁵¹⁻³⁵³ The *distal* resonance, a triplet of triplets (tt), at δ_{P} 8.0 ppm, appeared slightly upfield ($\Delta\delta_{\text{P}}$ 5.4 ppm) of that of the $\text{Pd}_3\text{Cl}_2\text{Cl}$ starting material (δ_{P} 13.4 ppm). The above NMR data indicates that complete conversion of $\text{Pd}_3\text{Cl}_2\text{Cl}$ to another cluster adopting a similar structural motif had occurred. The formed cluster, however, showed a significant change in chemical environment at the *proximal* positions and a less significant change at the *distal* position with

respect to **Pd₃Cl·Cl**, pointing towards substitution having occurred exclusively at the *proximal* position. The presence of liberated PPh₃ (δ_P –5.6 ppm) demonstrated that some ligand substitution of PPh₃ had taken place. O=PPh₃ (δ_P 25.0 ppm) tricyclohexylphosphine oxide (O=PCy₃, δ_P 49.0 ppm) and a small amount of unreacted PCy₃ (δ_P 10.6 ppm) were additionally present in solution. The oxidised and free PCy₃ may account for the one equivalent of unreacted PCy₃ which would be present after substitution of two *proximal* sites. There was however an issue with ³¹P integrations not matching as anticipated, indicating significant difference in ³¹P relaxation times between PPh₃ and PCy₃ environments. This issue could have potentially been resolved by increasing the time delay between NMR scans, allowing full relaxation before electromagnetic-induced excitement.

Matched coupling constants indicated *J*-coupling between nearby ³¹P environments (Figure 114). High-magnitude coupling (91.4 Hz, ³*J*_{P-P}) was measured between the *distal* ³¹P resonance (δ_P 8.0 ppm) and the two-equivalent *proximal* ³¹P environments, indicative of their *trans*-like relative orientations across the molecule. Coupling between the phosphido resonance and the two phosphine resonances was additionally evident, with ²*J*_{P-P} being measured at 10.5 and 16.2 Hz for phosphido-*distal* and phosphido-*proximal* coupling, respectively.

To gain more structural evidence for the species present, an aliquot of the crude reaction solution was subjected to ESI mass spectral analysis (Figure 115).

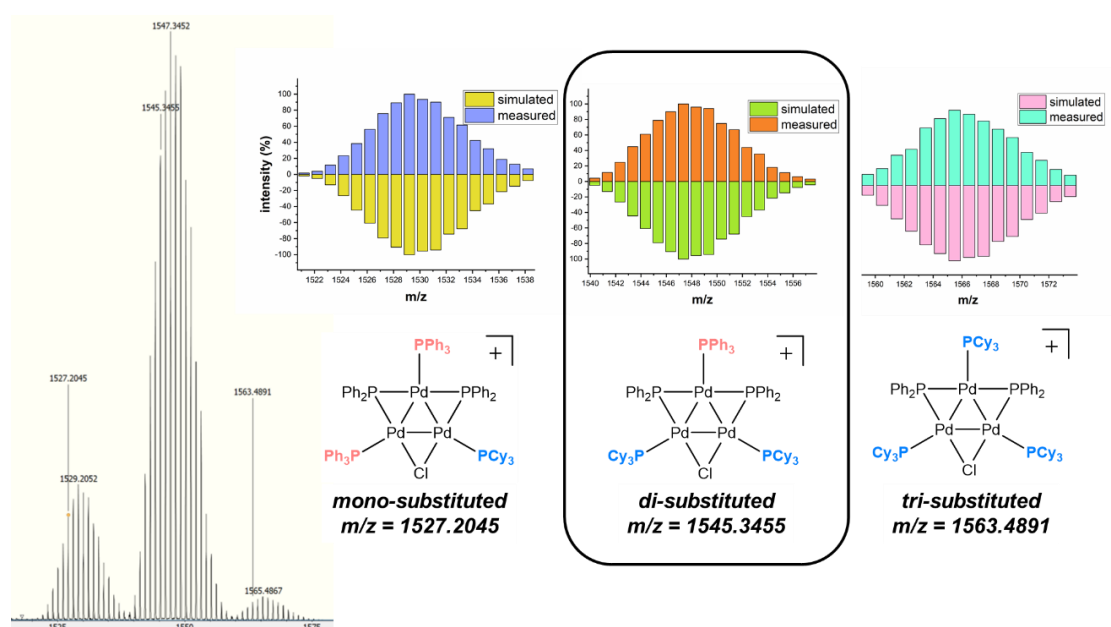


Figure 115 A section of the ESI-mass spectrum of the post-reaction solution. Showing the presence of three different Pd₃ cluster cations. Inset: stacked bar charts showing the isotopic distribution (simulated vs. measured) and exact masses (*m/z*) of the three cations: mono-substituted, di-substituted and tri-substituted with PCy₃.

Three different isotopic distributions (Figure 115), representative of Pd₃ clusters adopting the same bonding motif as **Pd₃Cl₂Cl** but with differing levels of substitution with PCy₃; namely, mono-substituted, di-substituted and tri-substituted products. The mass ion of the di-substituted complex (exact mass $m/z = 1545.3455$ Da), the most intense peak in the mass spectrum, corresponds with the structure the major solution cluster species as observable by NMR, with two *proximal* positions being substituted by PCy₃ ligands. The cluster compound featuring di-substitution of both *proximal* positions, [Pd₃(μ-Cl)(μ-PPh₂)(*distal*-PPh₃)(*proximal*-PCy₃)₂]Cl has thus been named **Diprox**. The structure of the mono-substituted complex (exact mass $m/z = 1527.2045$ Da) as observed by ESI-MS has been presented as mono-*proximal* substituted as the above NMR evidence would suggest that the *proximal*-PPh₃ positions are more easily substituted by PCy₃ than the *distal*-PPh₃ positions. The tri-substituted cluster complex [Pd₃(μ-Cl)(μ-PPh₂)₂(PCy₃)₃]Cl is also observable by ESI-MS. Neither the di- or tri-substituted cluster was observable by ³¹P NMR spectroscopic analysis and therefore are not expected to be significant solution species.

A single crystal, grown by vapour diffusion of pentane onto a CD₂Cl₂ solution of the post-reaction product. XRD analysis of the single crystal (Figure 116) confirmed the structure of the major product of the reaction to be that of the *proximally*-substituted Pd₃ cluster complex **Diprox**, as predicted from combined NMR and MS analyses (*vide supra*).^y

^y The crystal was grown by Nick Heywood, an *MChem* student who was working under the supervision of the author from 09.2018-04.2019.

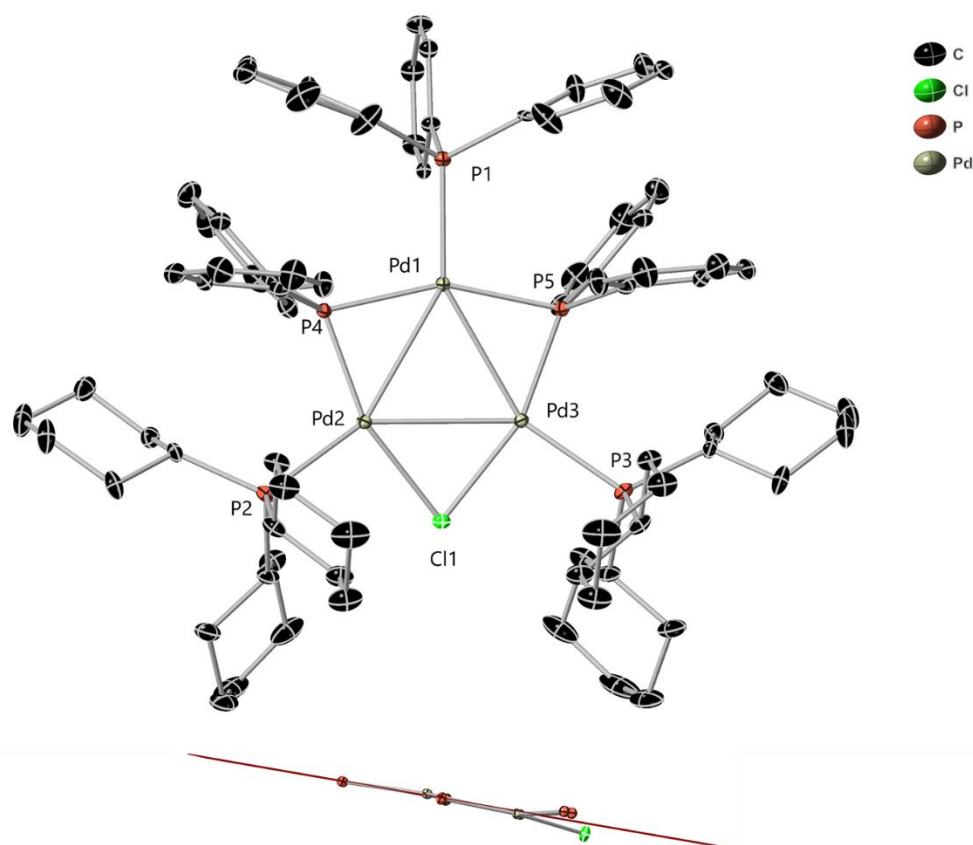
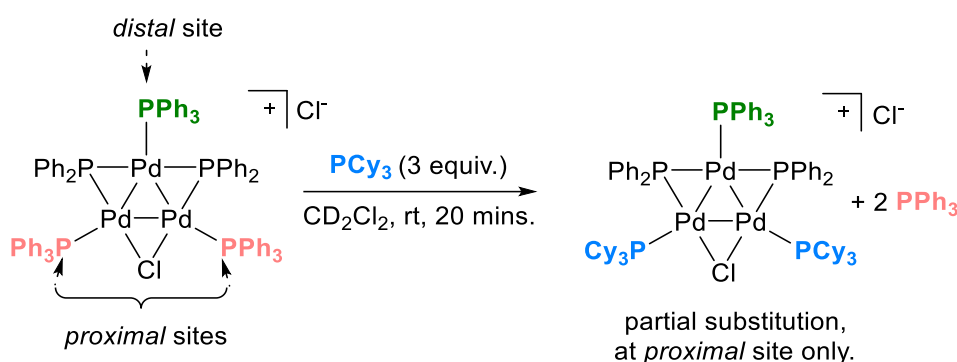


Figure 116 XRD structure, generated from a single crystal of [Pd₃(μ-Cl)(μ-PPh₂)(PPh₃)(PCy₃)₂]⁺ (**Diprox**) Hydrogen atoms omitted for clarity. Ellipsoids set at 50% probability. Complex model is C₂ symmetric along the P1–Pd1–Cl axis. Bottom-right: a plane calculated through the Pd, P and Cl atoms. Sum-of-squares error = 0.18402 Å²/n. Selected interatomic distances /Å: Pd1–Pd2 = 2.9272(7), Pd2–Pd3 = 2.9373(5), Pd1–P1 = 2.3146(17), Pd2–P2 = 2.3054(12), Pd2–P4 = 2.2011(12), Pd2–P4 = 2.2699(12). Pd2–Cl1 = 2.3774(13). Selected interatomic angles /°: Pd3–Pd1–Pd2 = 59.773, Pd1–Pd2–Pd3 = 60.113, Pd1–P4–Pd1 = 82.127, Pd2–Cl1–Pd3 = 75.996.

It is of note that in the above crystal structure of **Diprox**, the non-coordinating Cl[–] ligand, which was present in Pd₃Cl·Cl, was found in the unit cell, and hence only the cationic cluster portion of the complex is shown. Much like Pd₃Cl·Cl and Pd₃Br·Br, the **Diprox** cluster contains a tripalladium centre, bridged by μ-diphenylphosphido and μ-chloro ligand. This data fits well with the above ³¹P NMR spectrum (Figure 114), and, in turn correlates with the predicted structure of **Diprox** observed by ESI-MS (Figure 116). Whilst the Pd₃ core, and the P-atoms of the two μ-PPh₂ and the *distal* PPh₃ ligand essentially sit on the same plane, the P-atoms of the two PCy₃ ligands and the μ-Cl atom sit above and below the plane, respectively. This stands in contrast with this cluster's precursor, Pd₃Cl·Cl, which exhibits a significantly higher planarity, and Pd₃Br·Br where planarity only exists in the Pd₃ core (CR). This solid-state comparison suggests that planarity is lost as a result of steric hindrance between the bulky PCy₃ ligands and the μ-Cl ligand. Broadly speaking, the Pd–PCy₃ (*proximal*) and Pd–PPh₃ (*distal*) sites of **Diprox** are similar respective lengths as the Pd–PPh₃ (*proximal* and *distal*) sites of Pd₃Cl·Cl. The Pd2–Pd3 bond (the bond Pd–Pd interaction directly adjacent to both *proximal* PCy₃

ligands) was measured to be *ca.* 1.7% longer than the analogous bond in $\text{Pd}_3\text{Cl}_2\text{Cl}$. The Pd1–Pd2 bond length (2.9272 Å), on the other hand, is on a par, if slightly longer than the analogous bond length in $\text{Pd}_3\text{Cl}_2\text{Cl}$. This observation suggests that the *proximal* stronger electron donor ligand causes a destabilisation of the complex by lengthening, perhaps as a result of electron donation from the stronger σ -donor PCy_3 .³⁵⁴

It has been concluded, based on the above ^{31}P NMR, MS and crystallographic evidence, that the major product of the reaction between $\text{Pd}_3\text{Cl}_2\text{Cl}$ and 3 equivalents of PCy_3 was the disubstituted complex **Diprox**, where the two *proximal* PPh_3 ligands of $\text{Pd}_3\text{Cl}_2\text{Cl}$ have been quantitatively substituted with two PCy_3 ligands, liberating two equivalents of PPh_3 (Scheme 89).

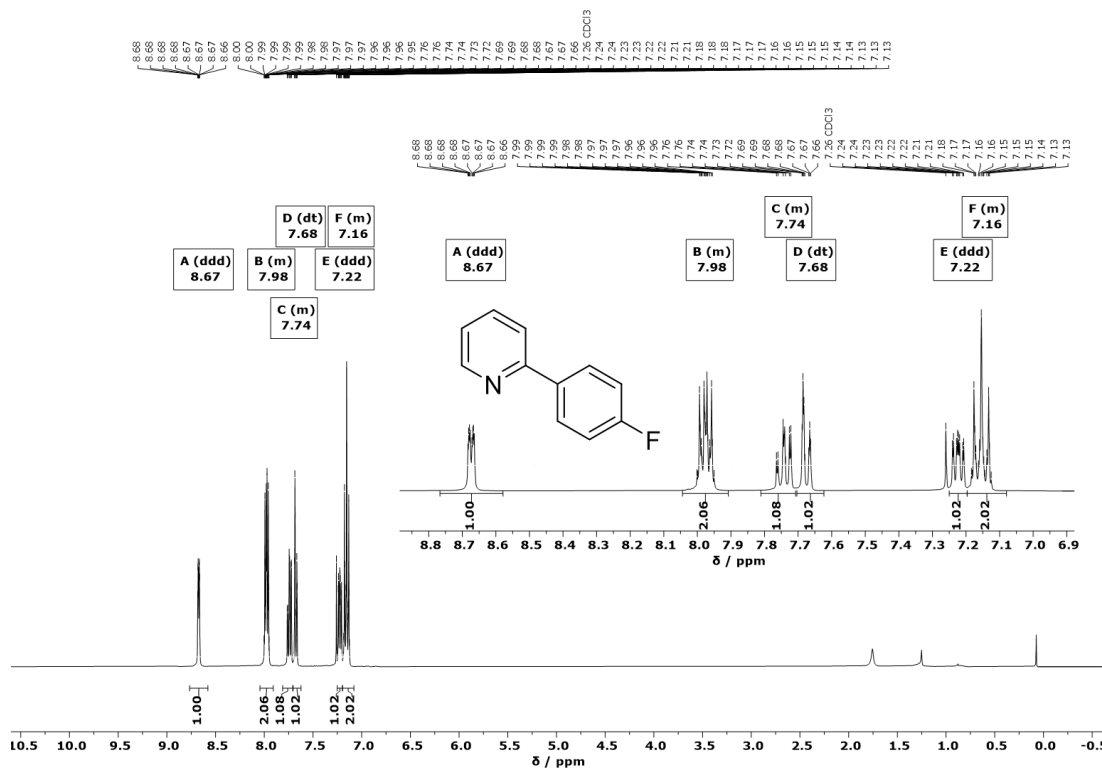
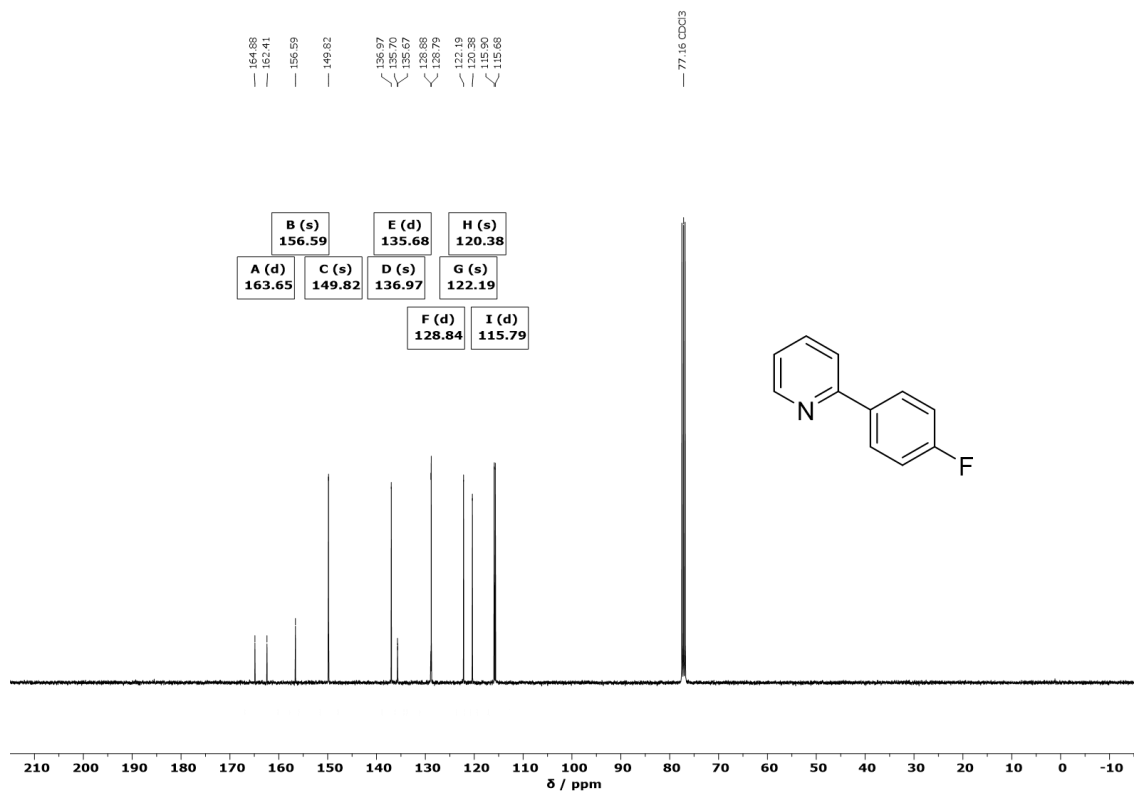


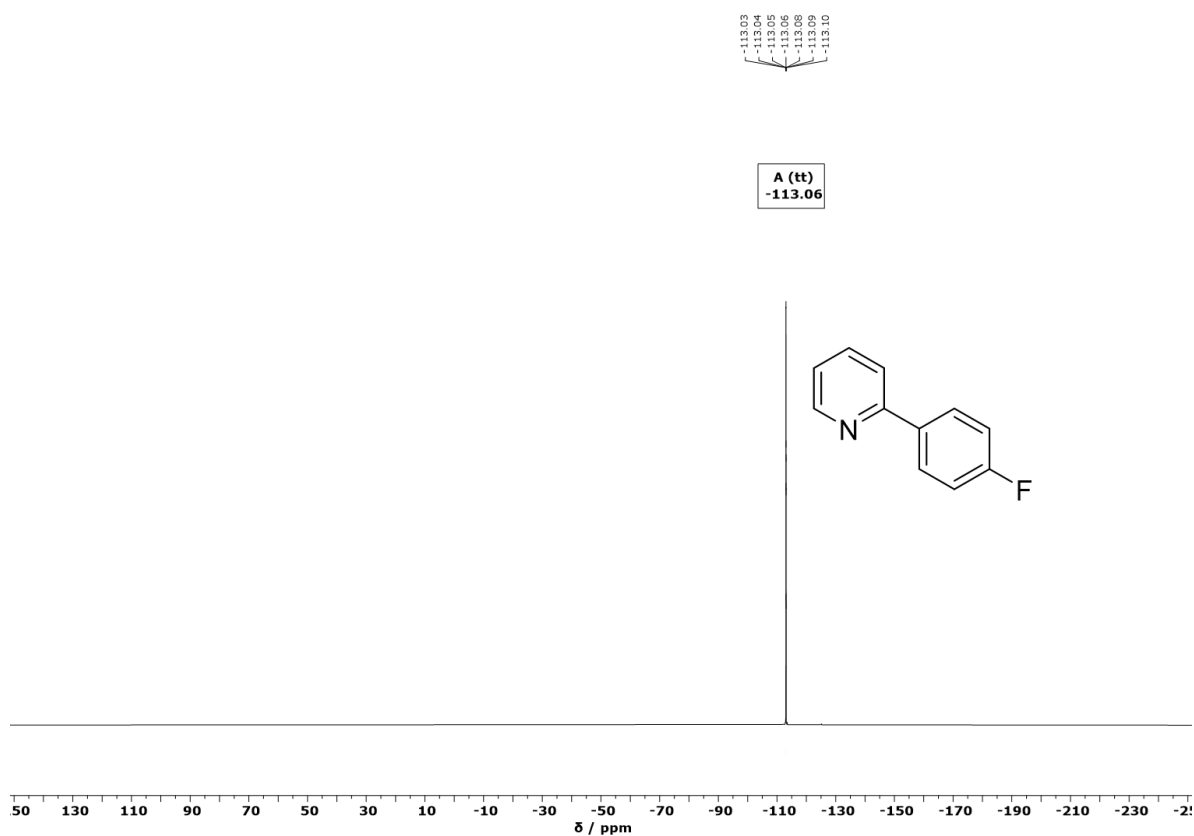
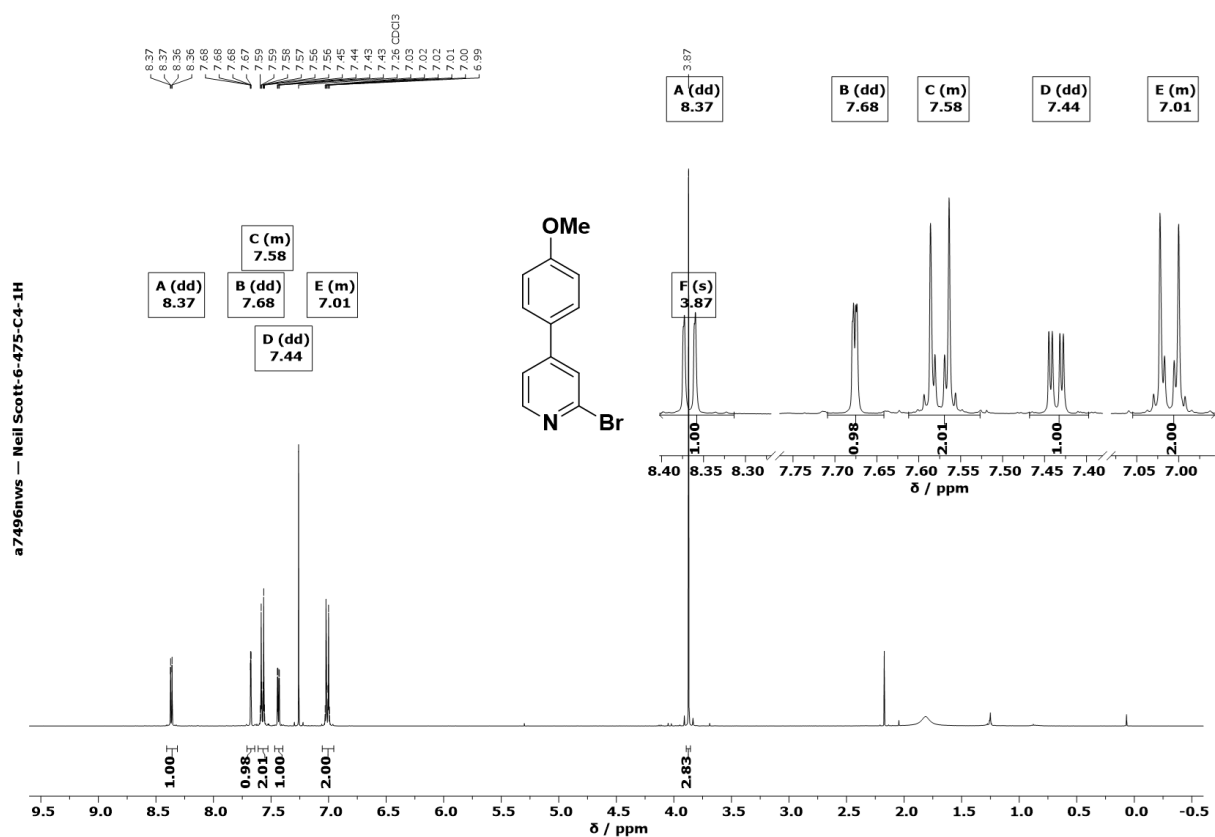
Scheme 89 Synthesis of the disubstituted cluster complex **Diprox** by ligand substitution of $\text{Pd}_3\text{Cl}_2\text{Cl}$ with PCy_3 .

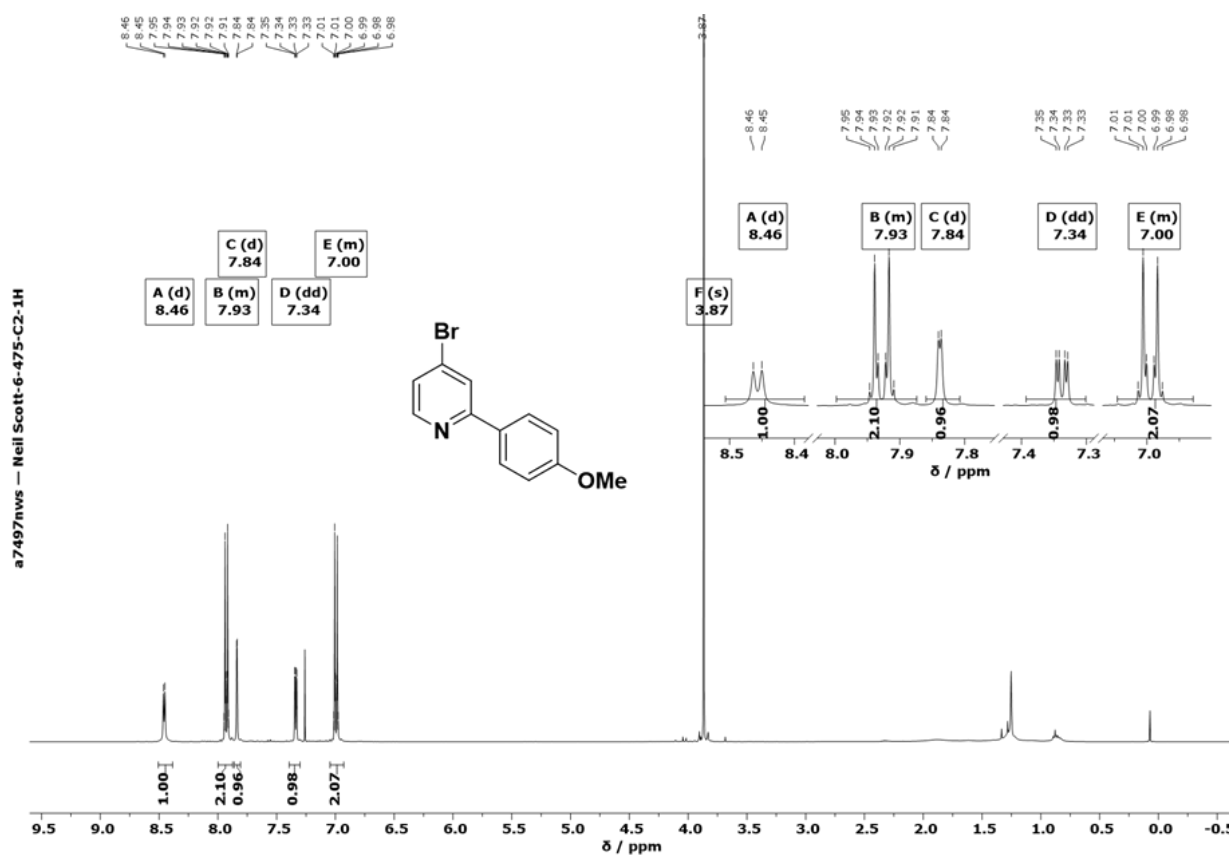
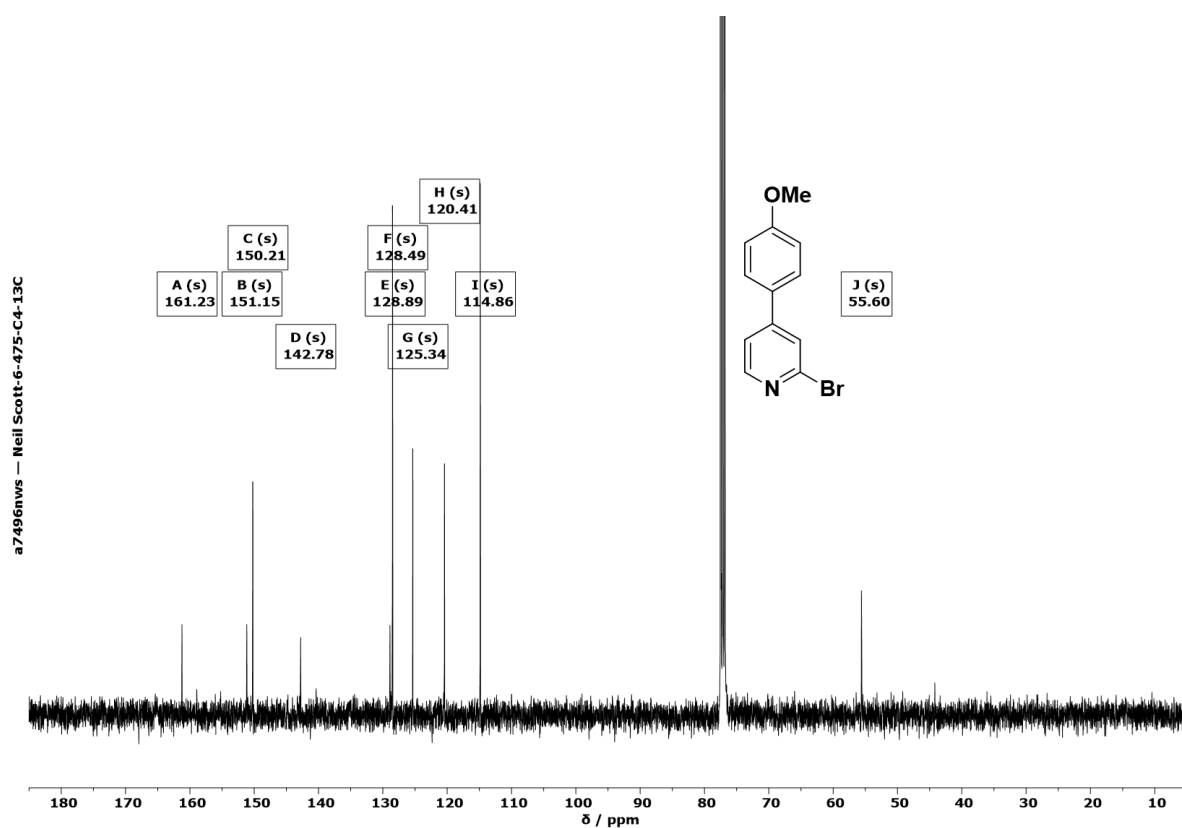
This result stands in stark contrast to substitution of $\text{Pd}_3\text{Cl}_2\text{BF}_4$ with PEt_3 or PMe_2Ph , for which full substitution at both *distal* and *proximal* sites occurs (Scheme 88).

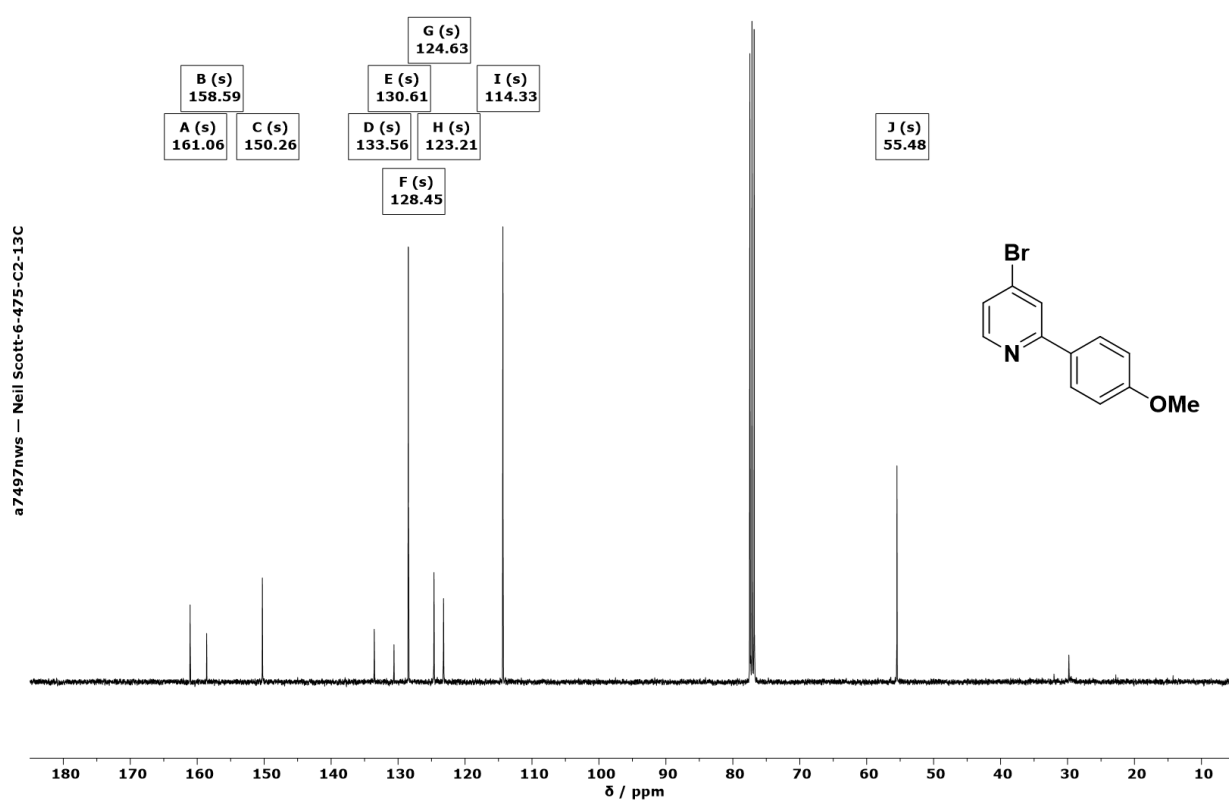
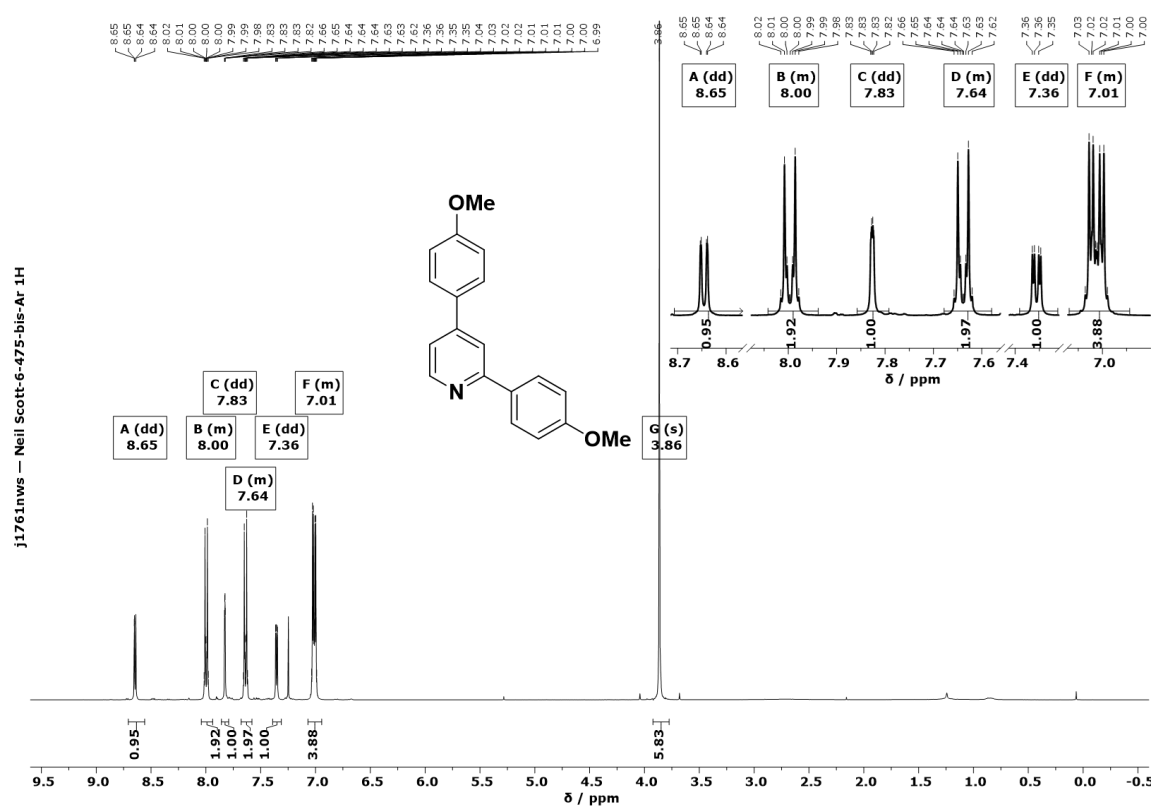
At this stage, efficient isolation of **Diprox** has not been realised, however if that is possible, future work could employ it in catalytic applications against the $\text{Pd}_3\text{Cl}_2\text{Cl}$ benchmark. For example, the competency of **Diprox** could be tested against $\text{Pd}_3\text{Cl}_2\text{Cl}$ in cross-coupling reactions at 2,4-dibromopyridine **30** as reported in Chapter 4. If a difference in the respective clusters' catalytic performance is measured, the aspect of the structural differences which led to this difference in function could be in turn investigated.

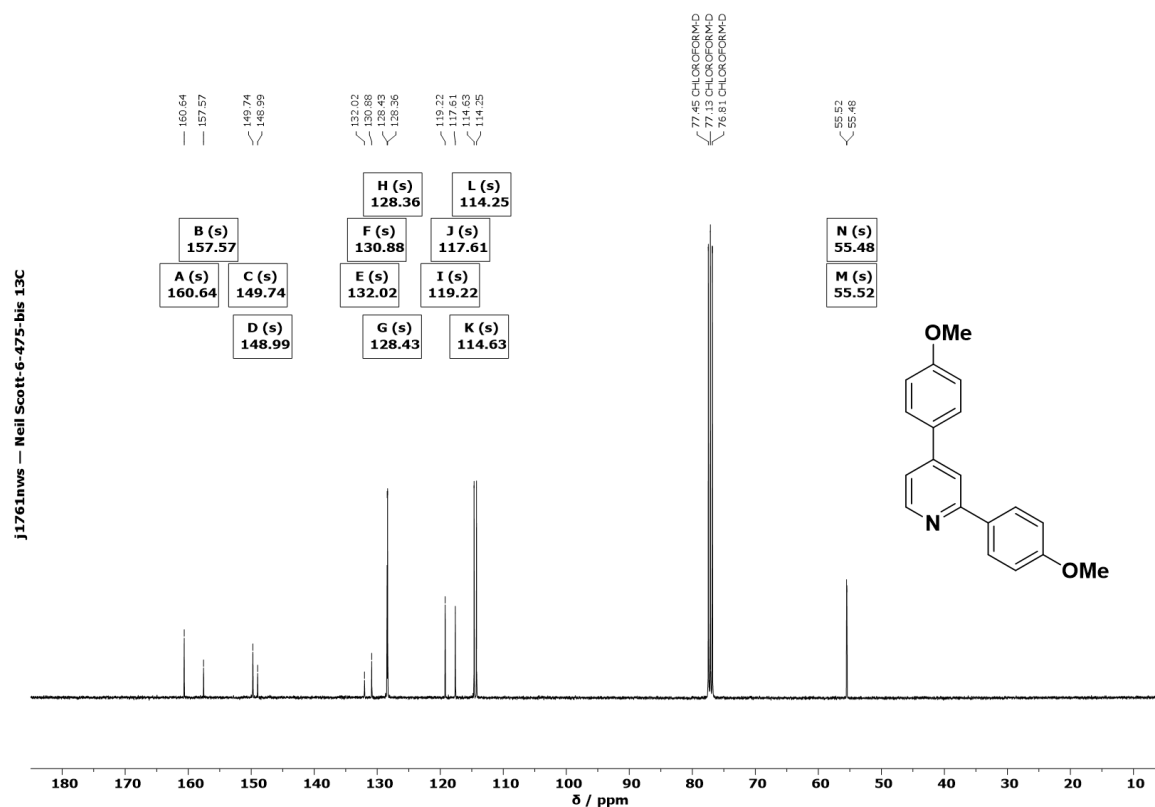
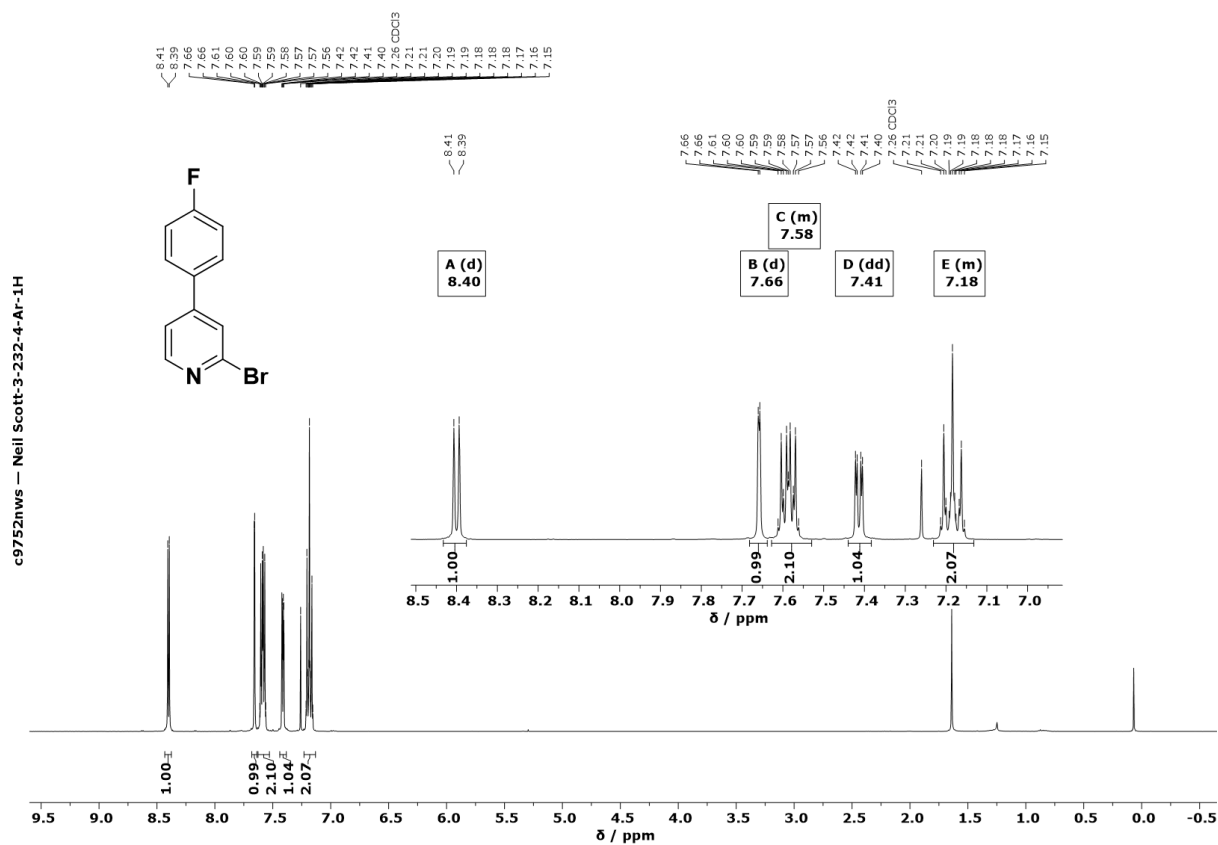
Appendix 3 – NMR Spectra of Organic Compounds

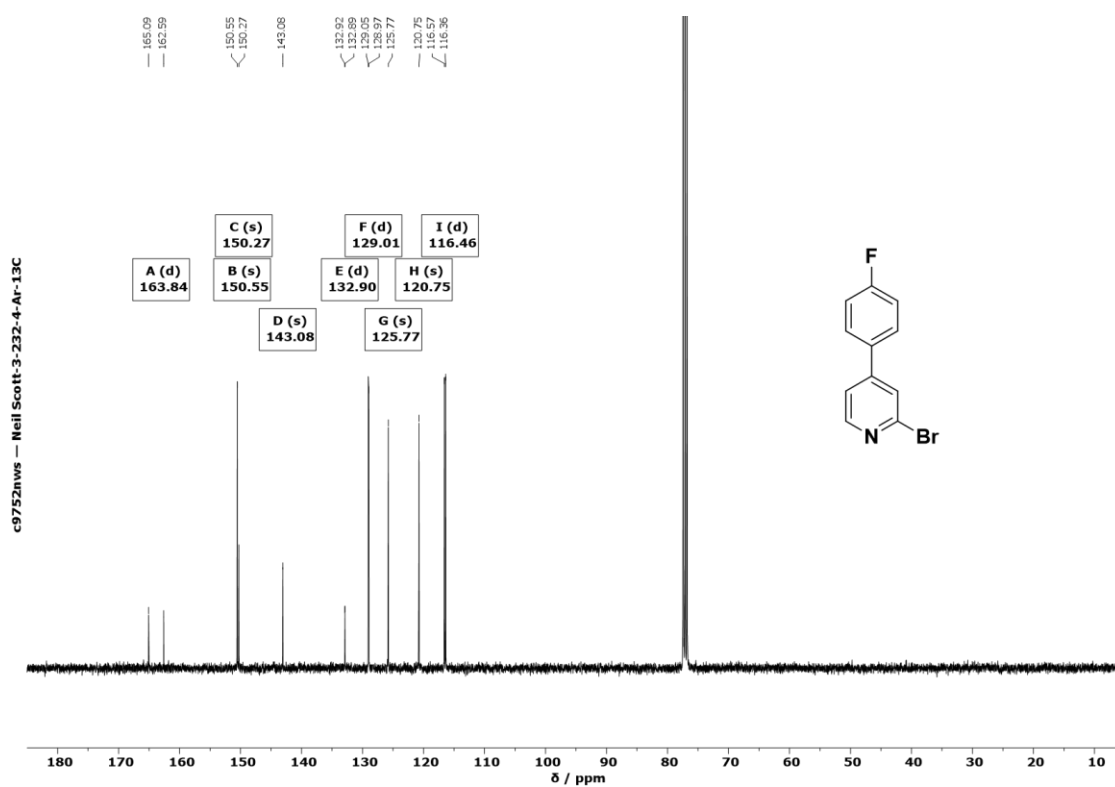
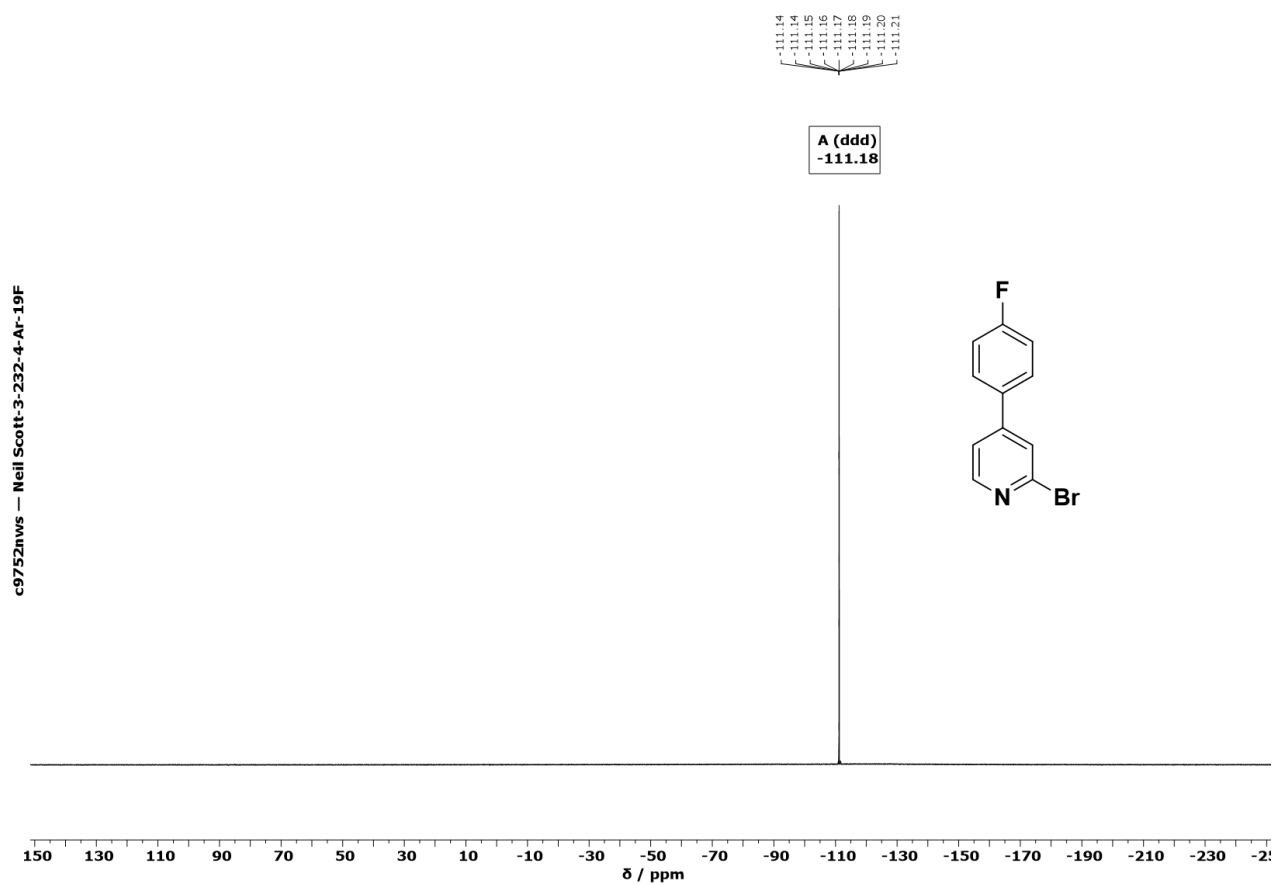
Figure 117 ¹H NMR (CDCl₃, 400 MHz, 32 scans) spectrum of 69.Figure 118 ¹³C NMR (CDCl₃, 101 MHz, 1024 scans) spectrum of 69.

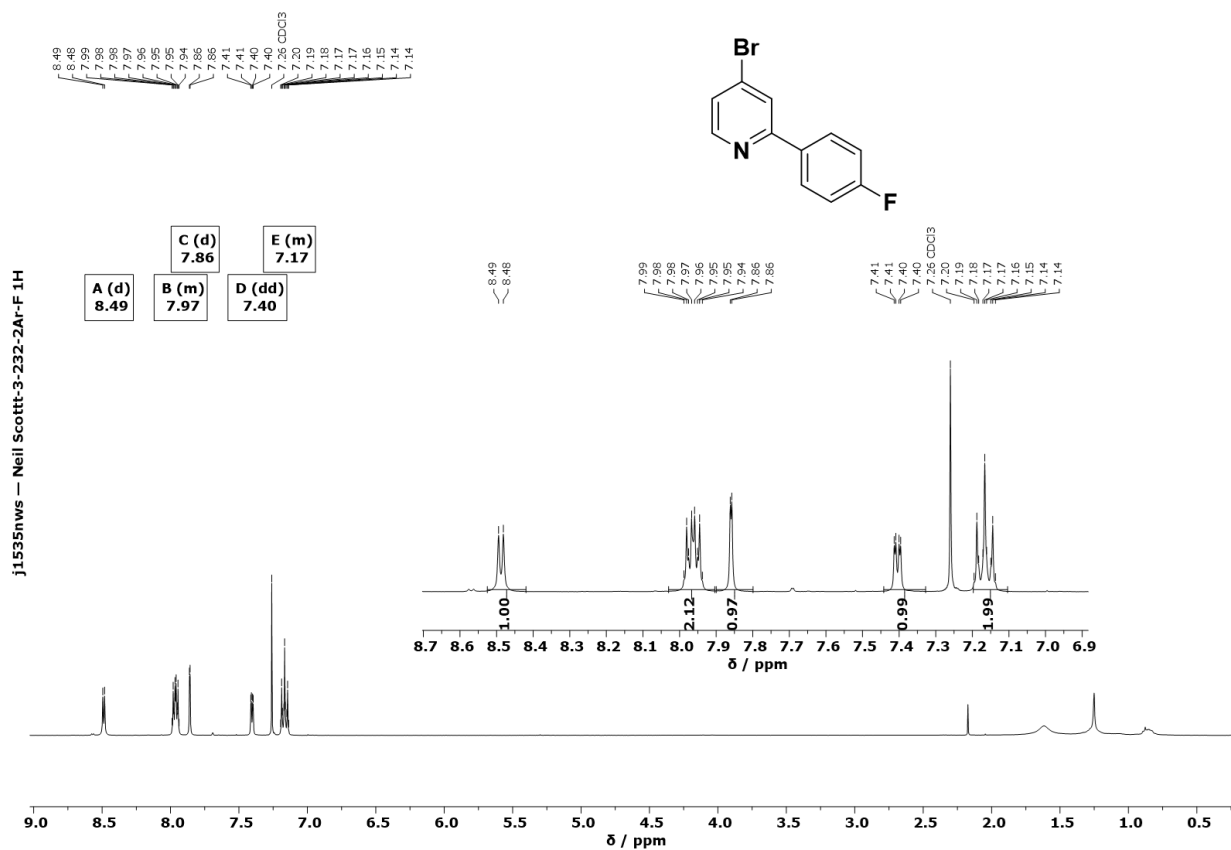
Figure 119 ^{19}F NMR (CDCl_3 , 376 MHz, 128 scans) spectrum of 69.Figure 120 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of C4-Ar_A.

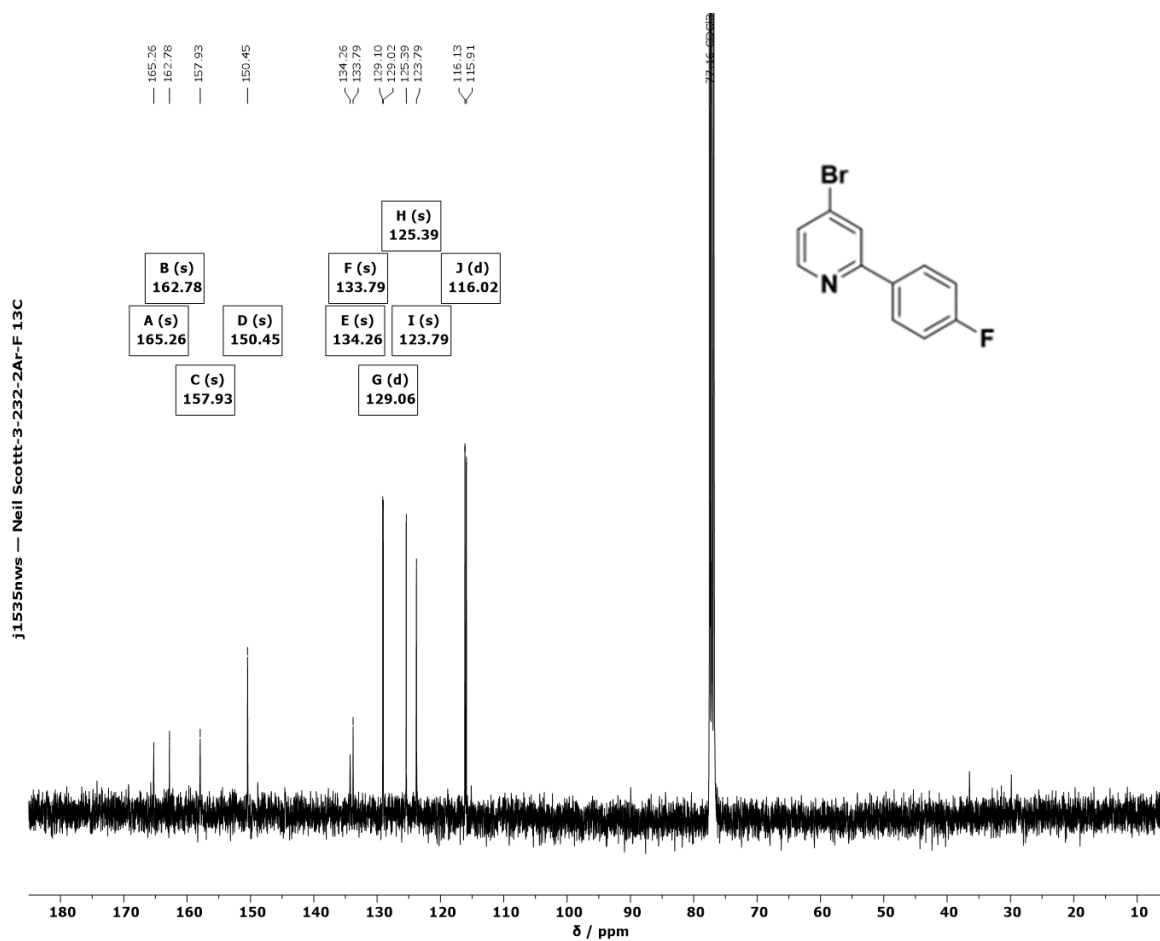


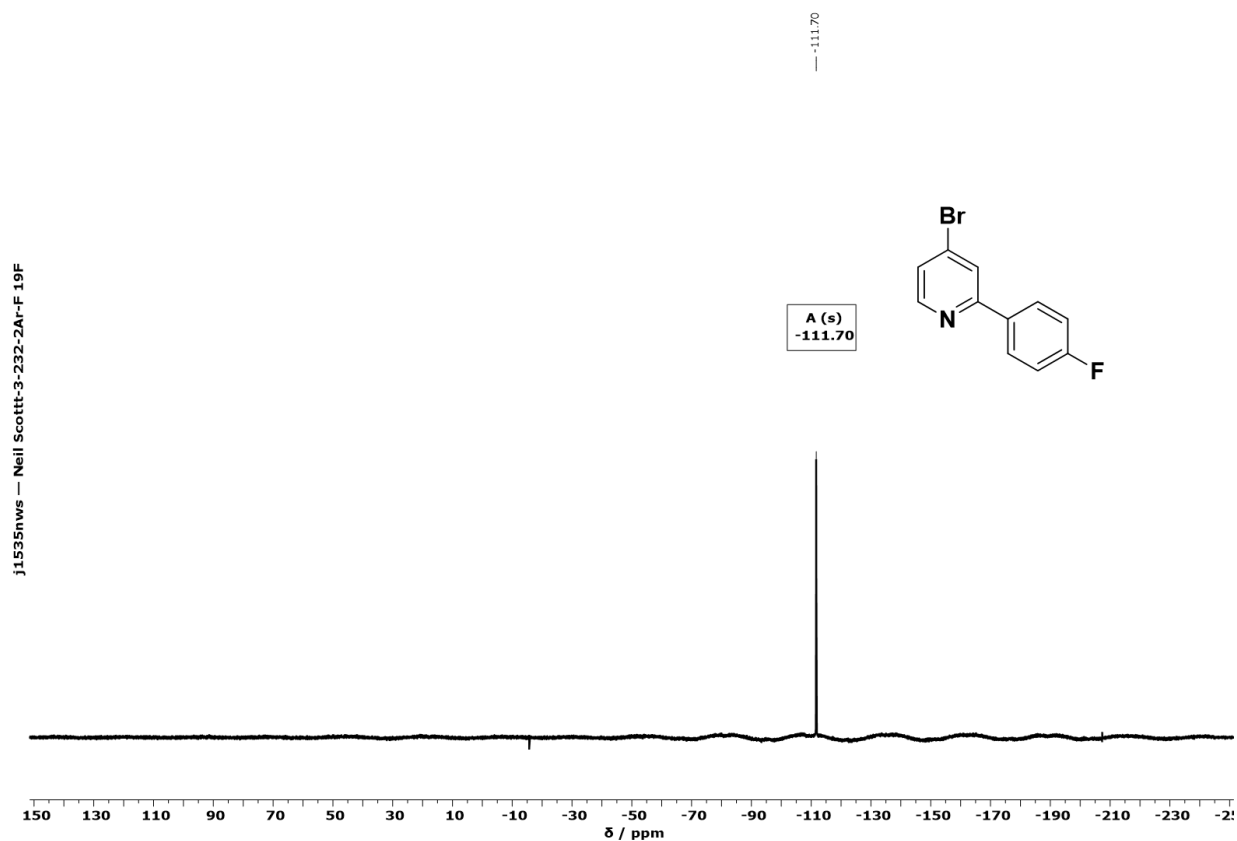
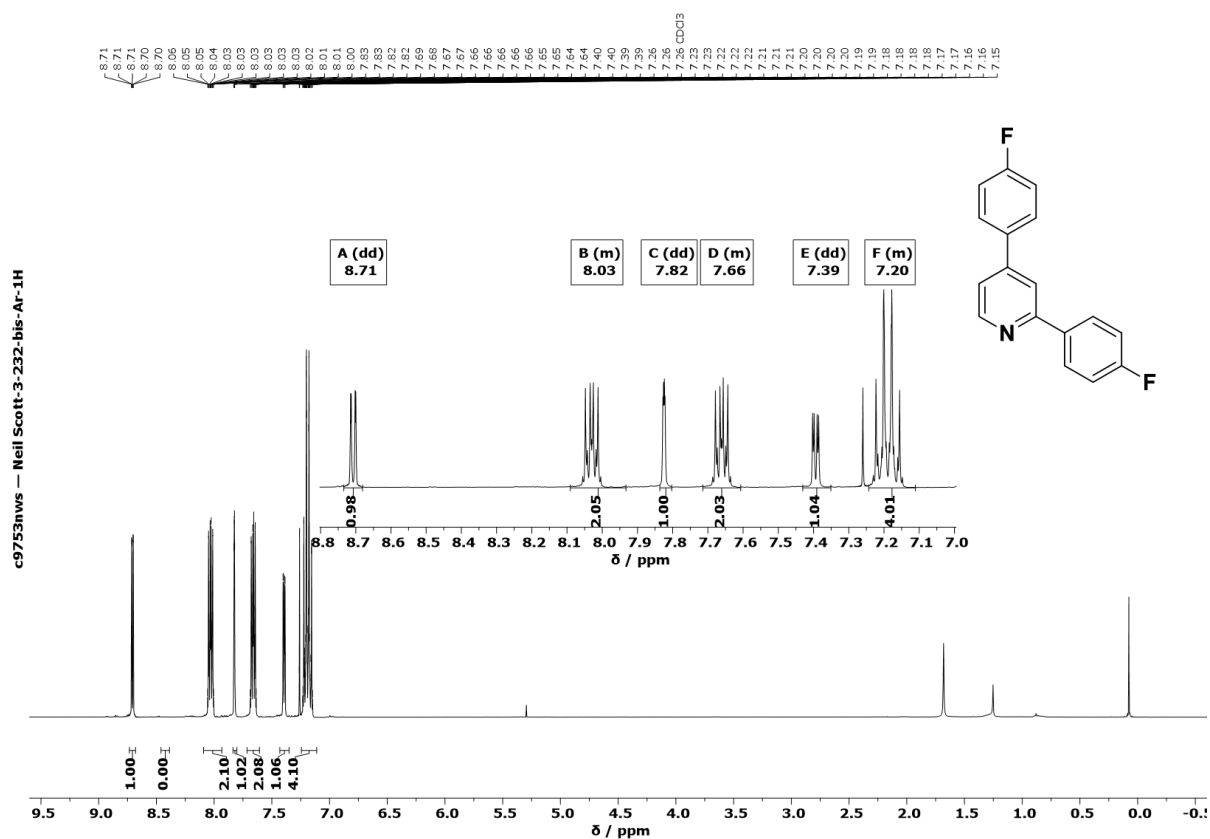
Figure 123 ^{13}C NMR (CDCl_3 , 101 MHz, 1024 scans) spectrum of C2-Ar_A.Figure 124 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of bis-Ar_A.

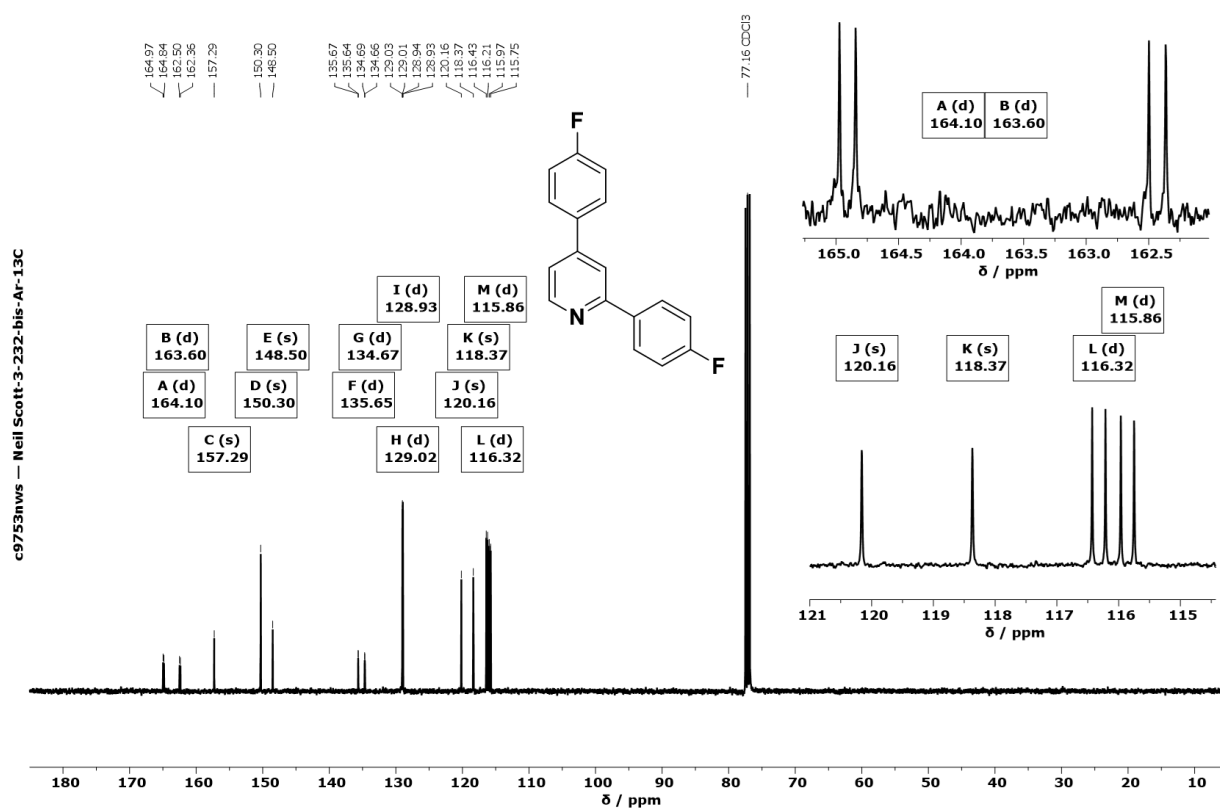
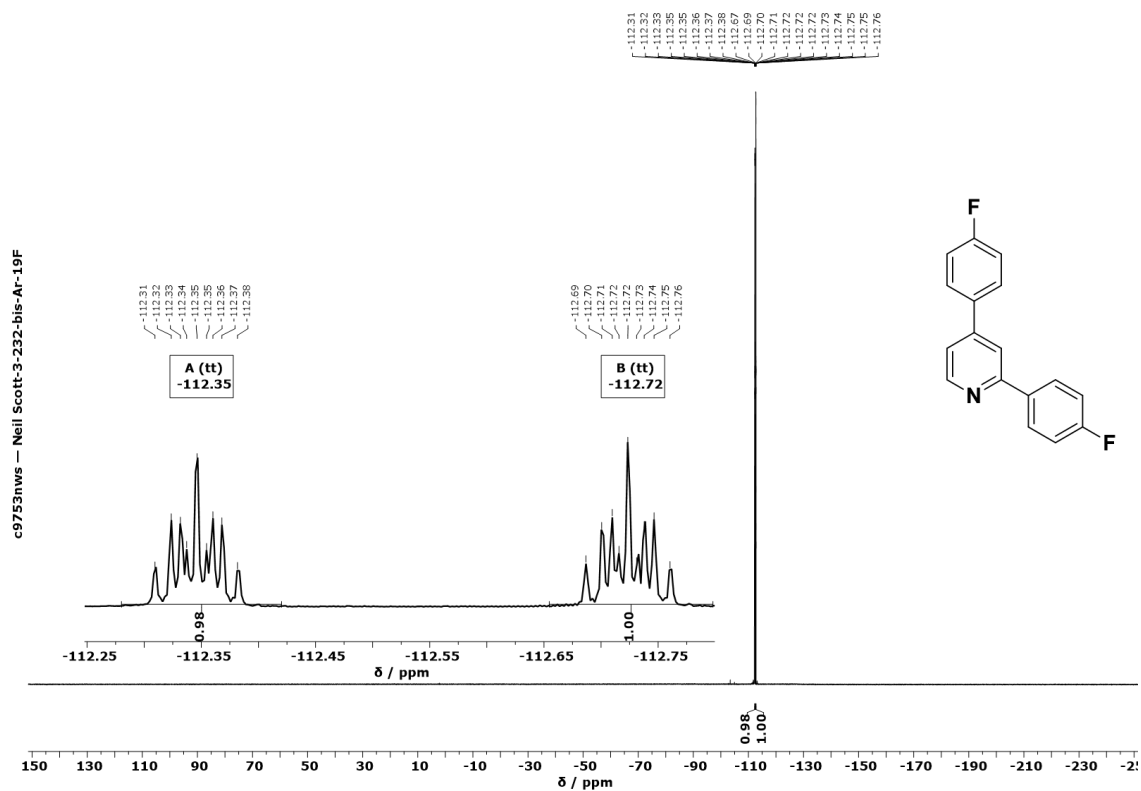
Figure 125 ¹³C NMR (CDCl₃, 101 MHz, 1024 scans) spectrum of bis-Ar_A.Figure 126 ¹H NMR (CDCl₃, 400 MHz, 32 scans) spectrum of C4-Ar_B.

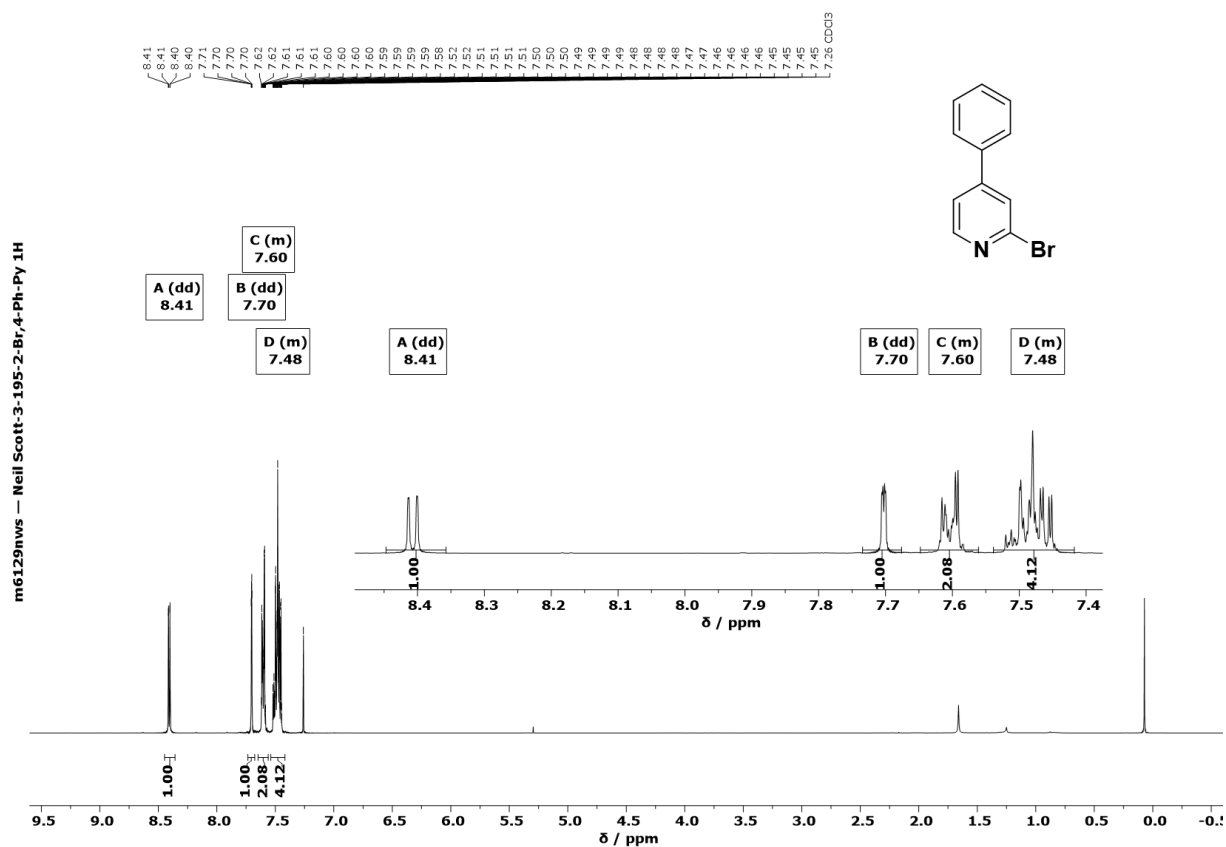
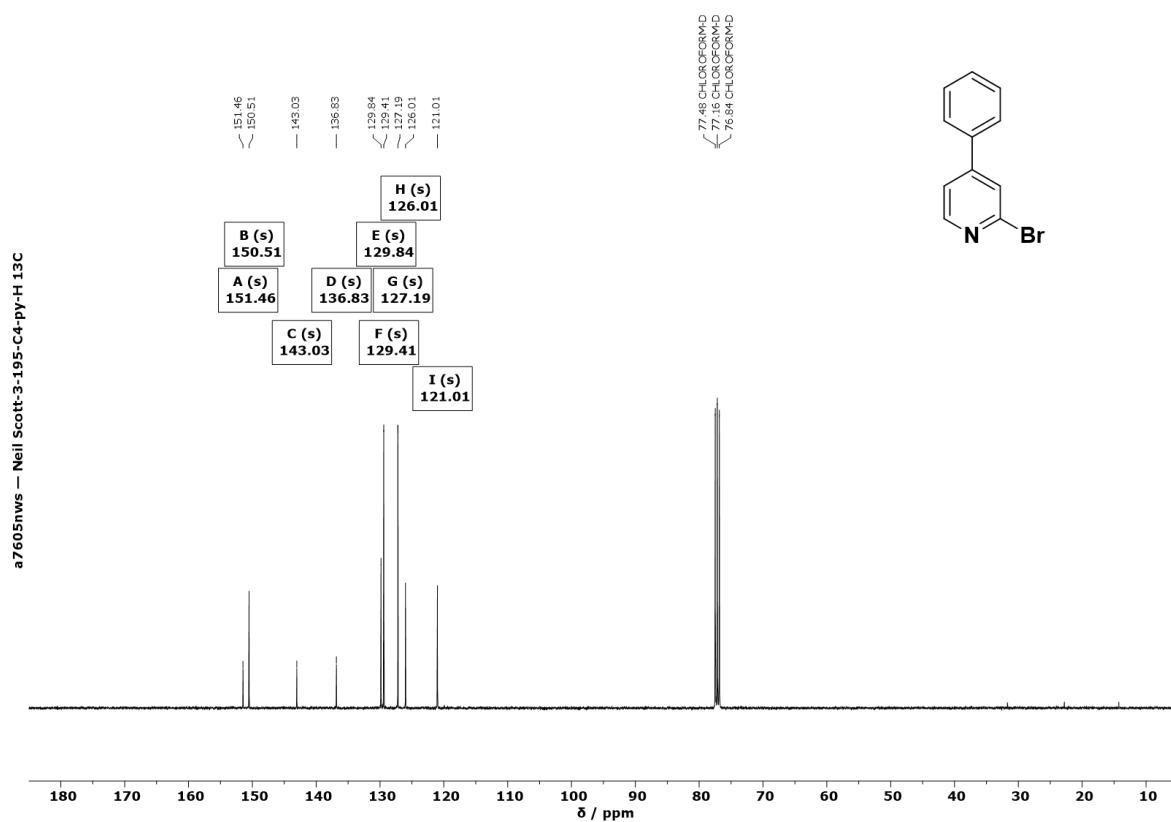
Figure 127 ^{13}C NMR (CDCl_3 , 101 MHz, 2048 scans) spectrum of C4-Ar_B.Figure 128 ^{19}F NMR (CDCl_3 , 376 MHz, 128 scans) spectrum of C4-Ar_B.

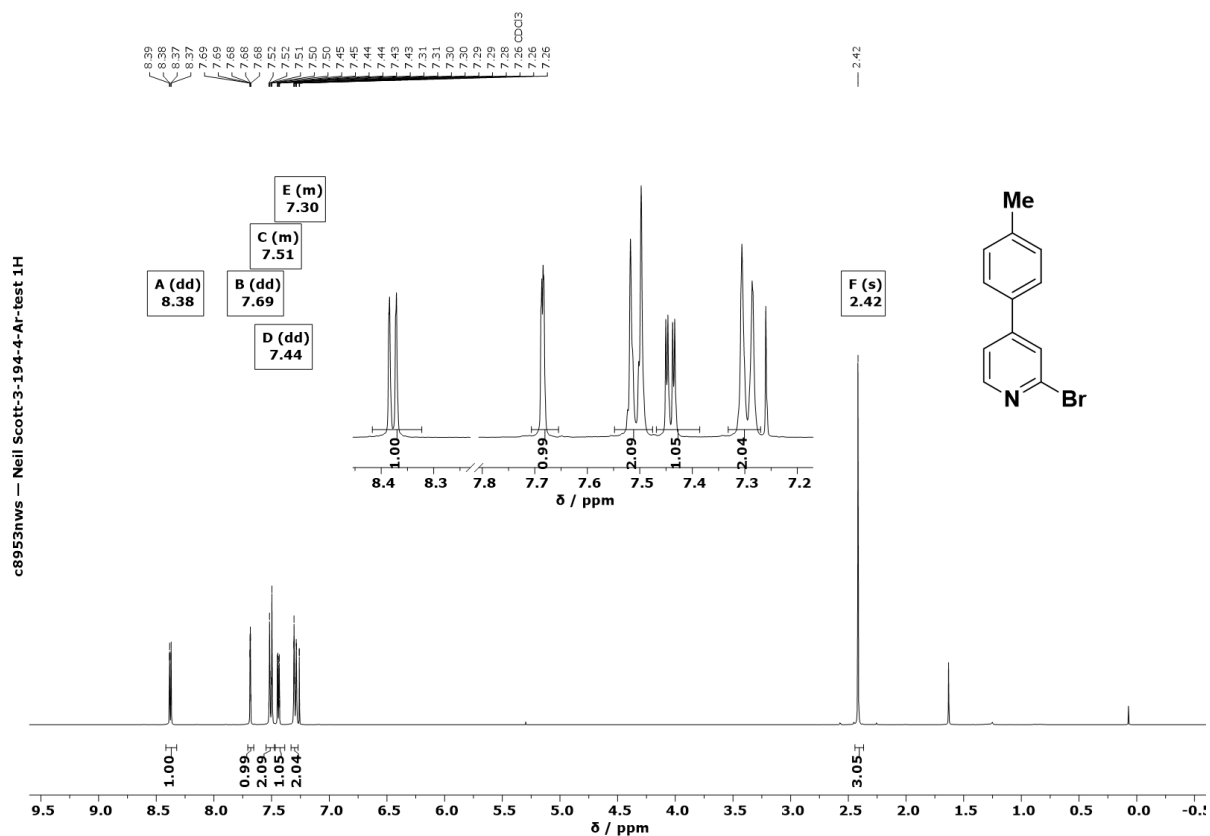
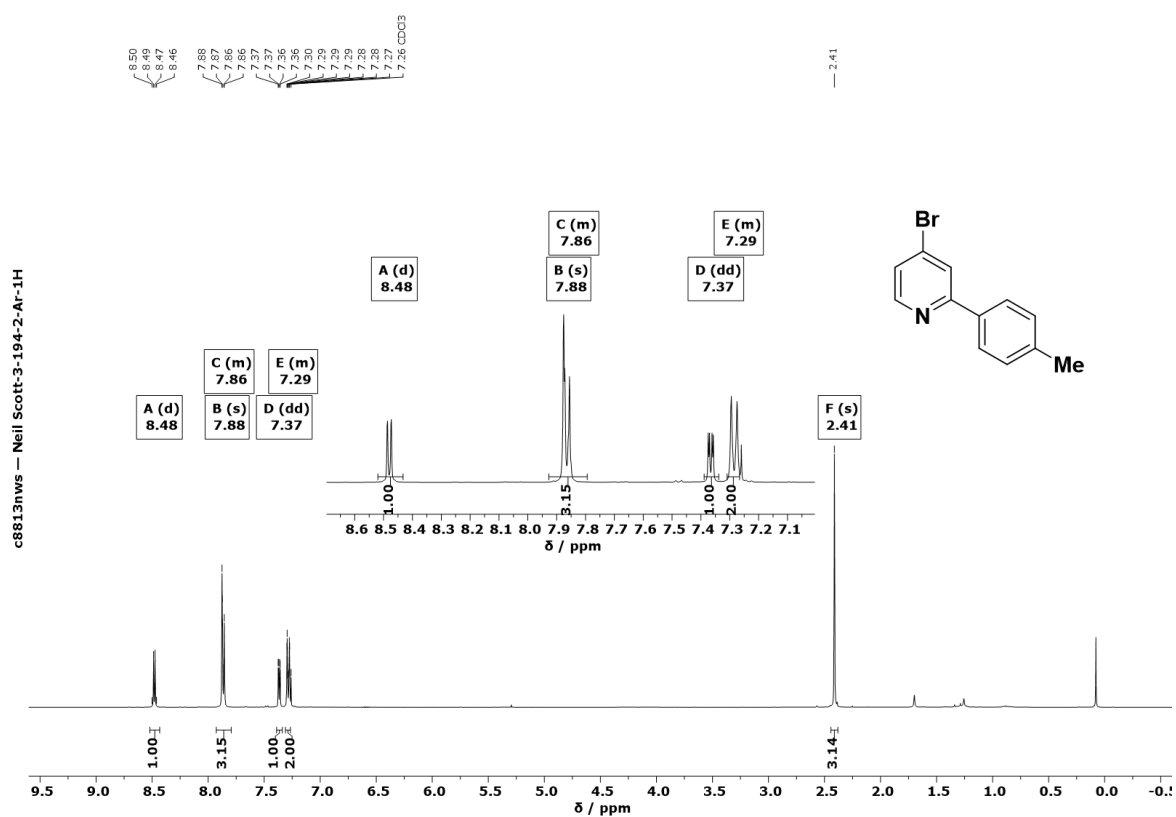
Figure 129 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of C2-Ar_B.

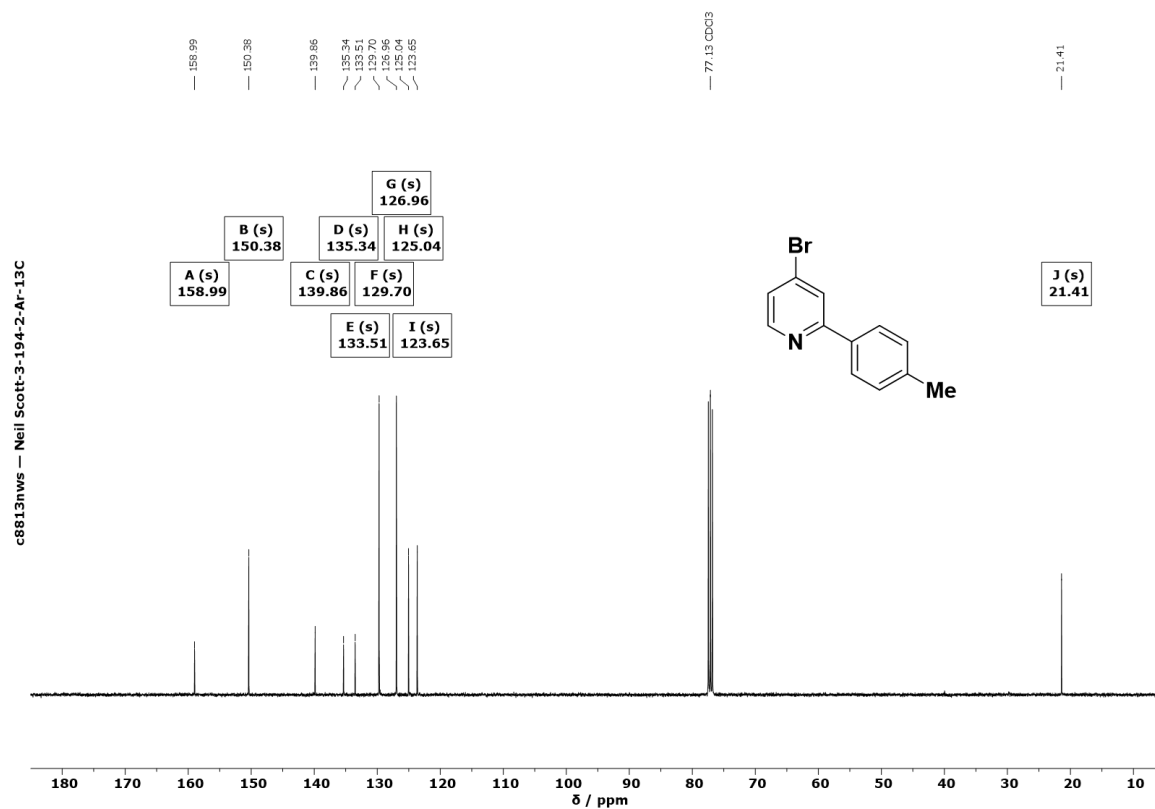
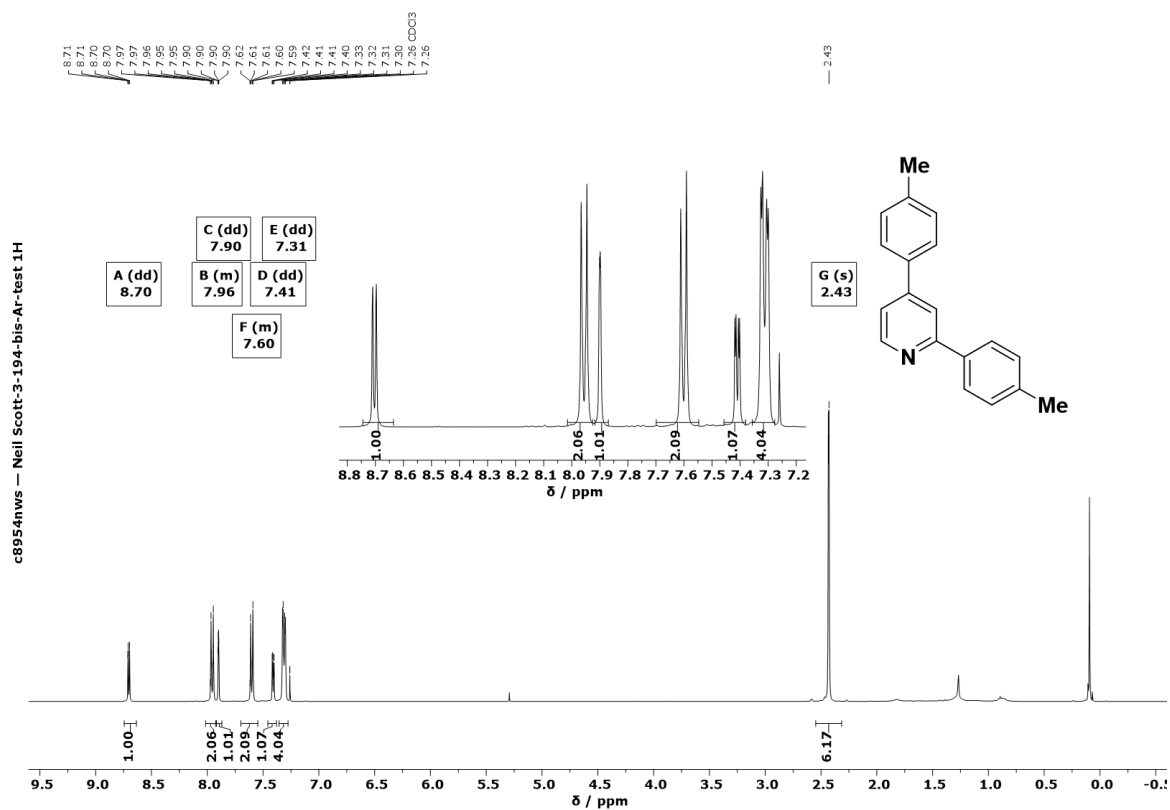
Figure 130 ¹³C NMR (CDCl₃, 101 MHz, 2048 scans) spectrum of C2-Ar_B.

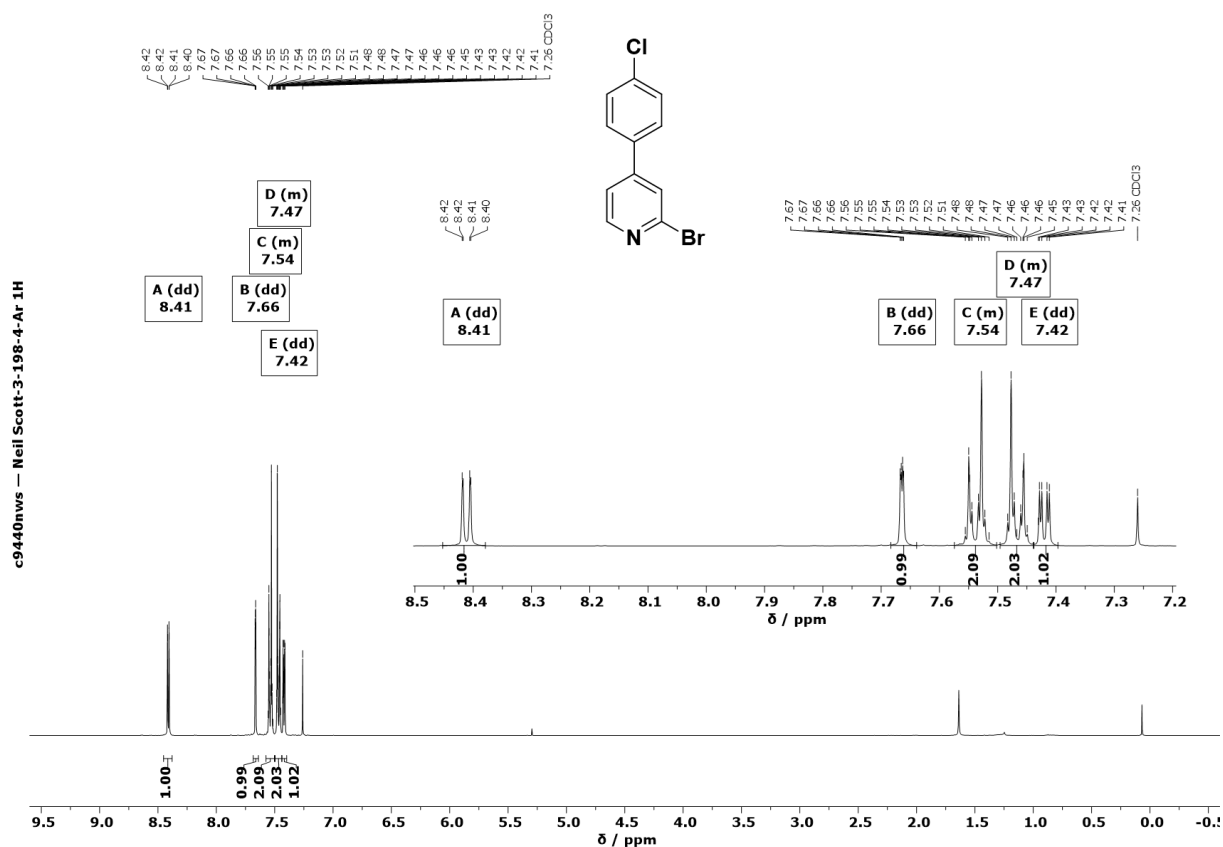
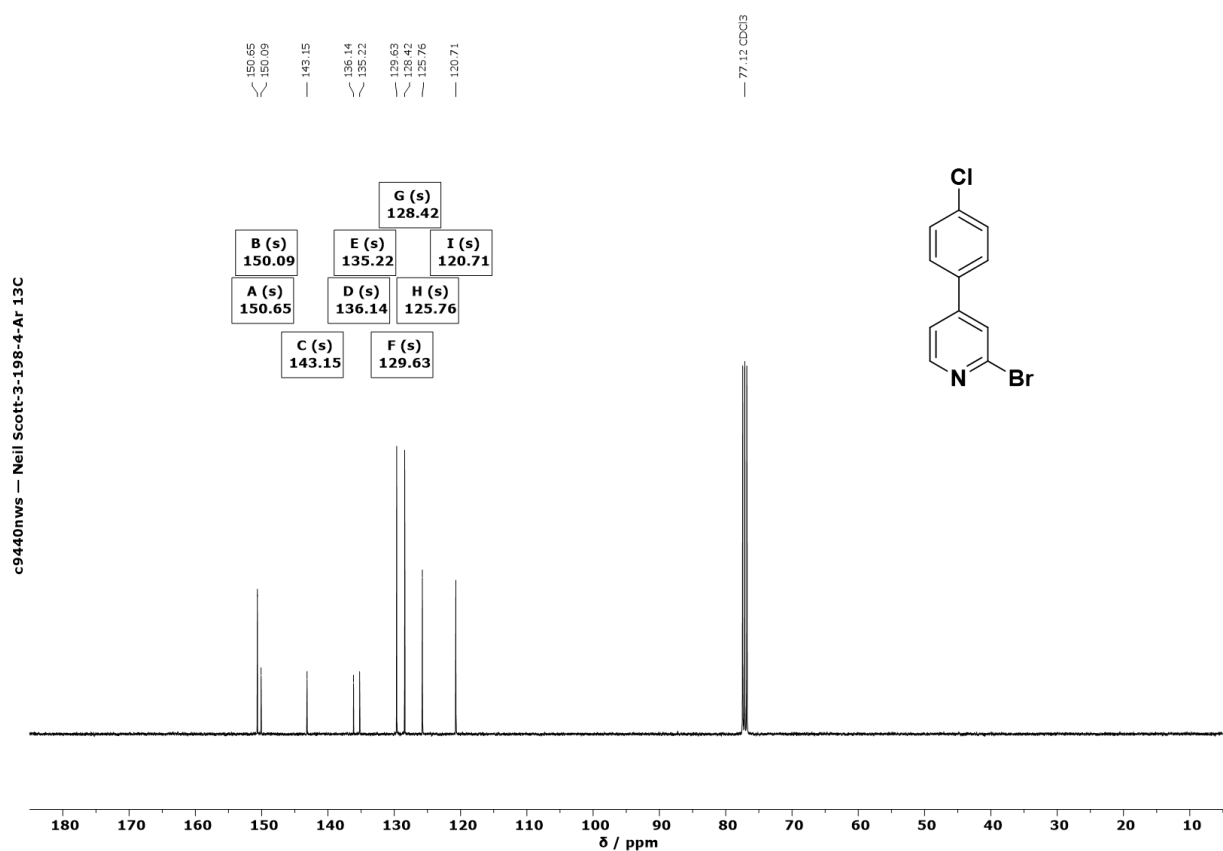
Figure 131 ^{19}F NMR (CDCl_3 , 376 MHz, 128 scans) spectrum of C2-Ar_B.Figure 132 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of bis-Ar_B.

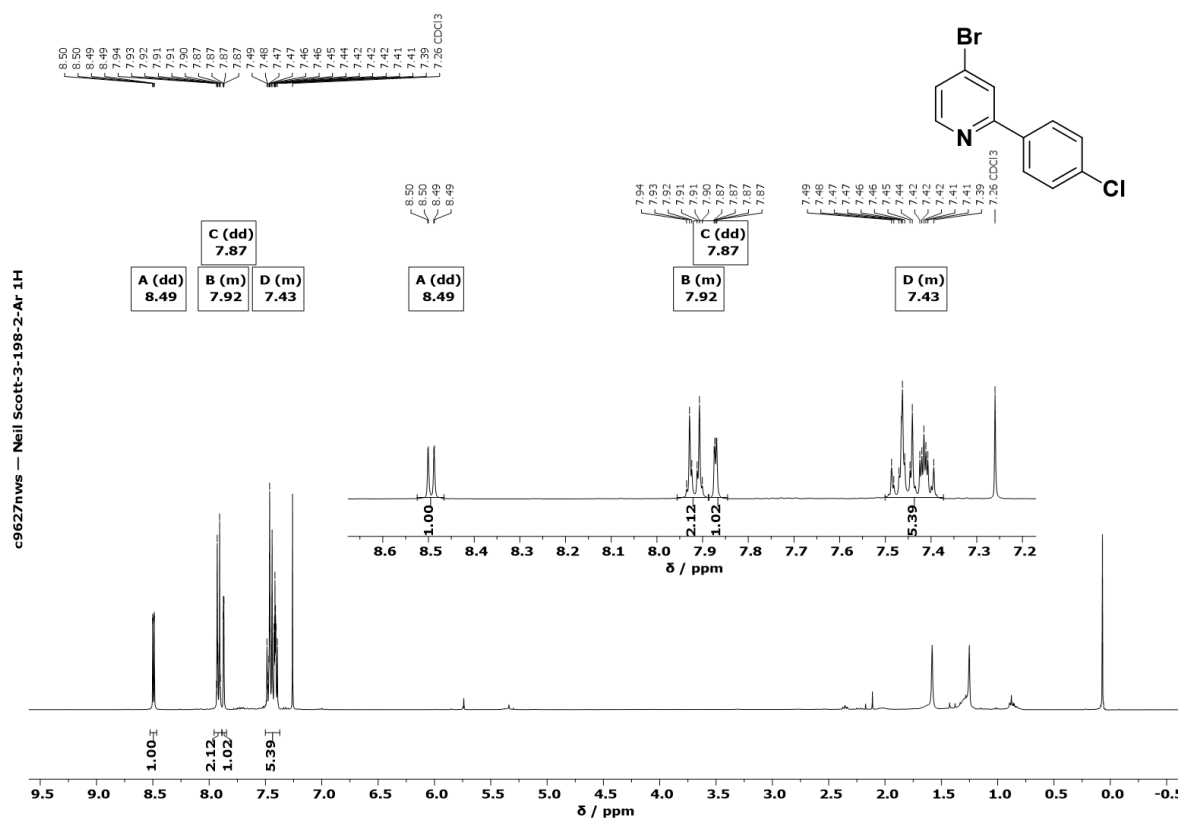
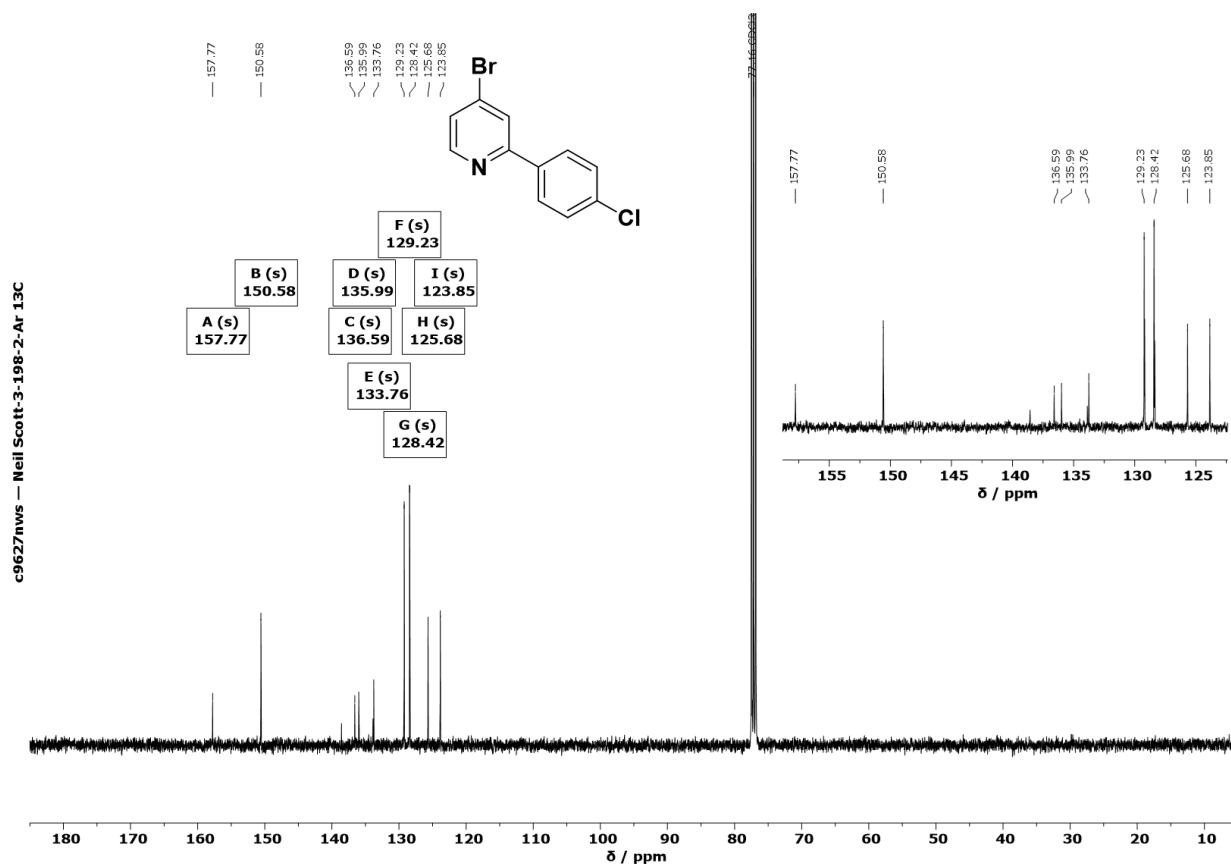
Figure 133 ^{13}C NMR (CDCl_3 , 101 MHz, 2048 scans) spectrum of bis-Ar_B.Figure 134 ^{19}F NMR (CDCl_3 , 376 MHz, 128 scans) spectrum of bis-Ar_B.

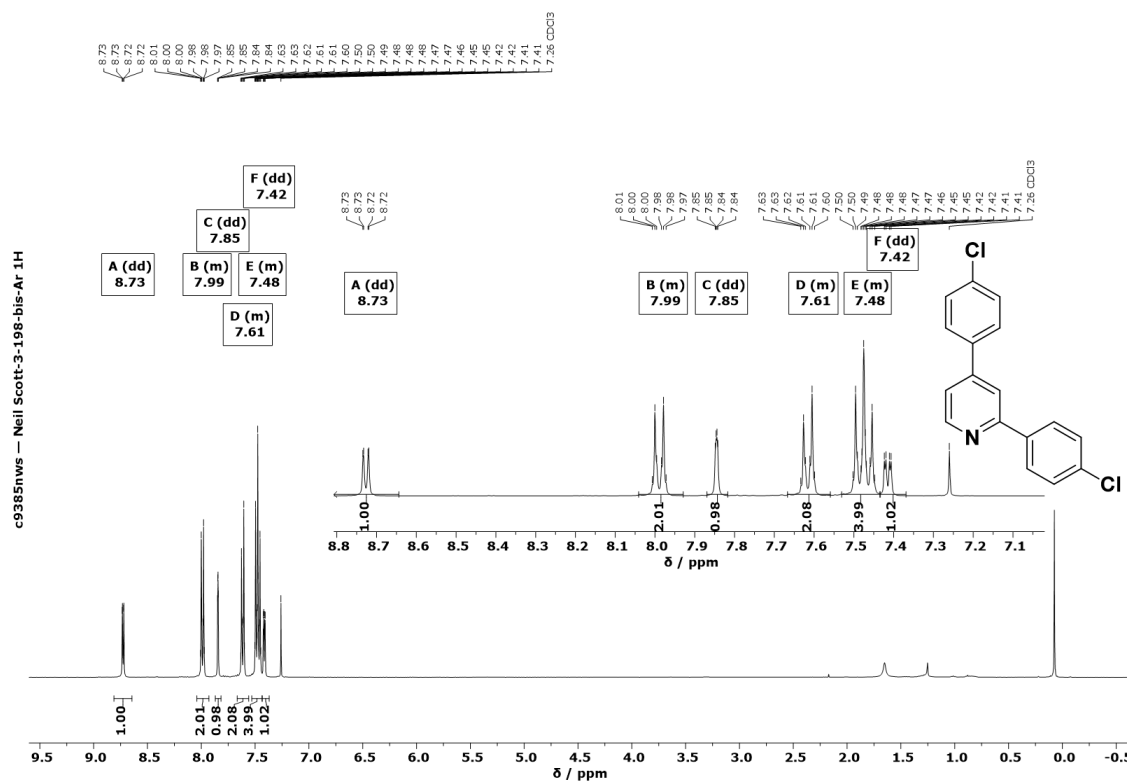
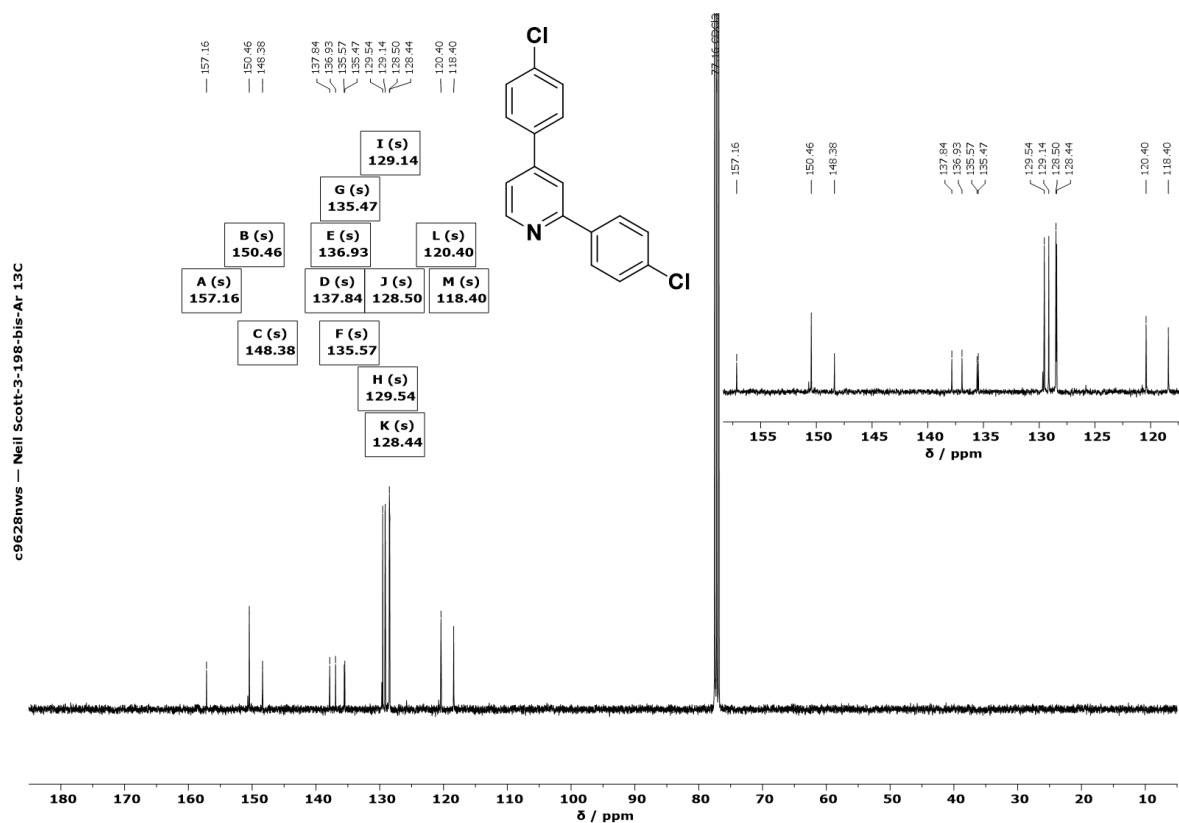
Figure 135 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of C4-Arc.Figure 136 ^{13}C NMR (CDCl_3 , 101 MHz, 1024 scans) spectrum of C4-Arc.

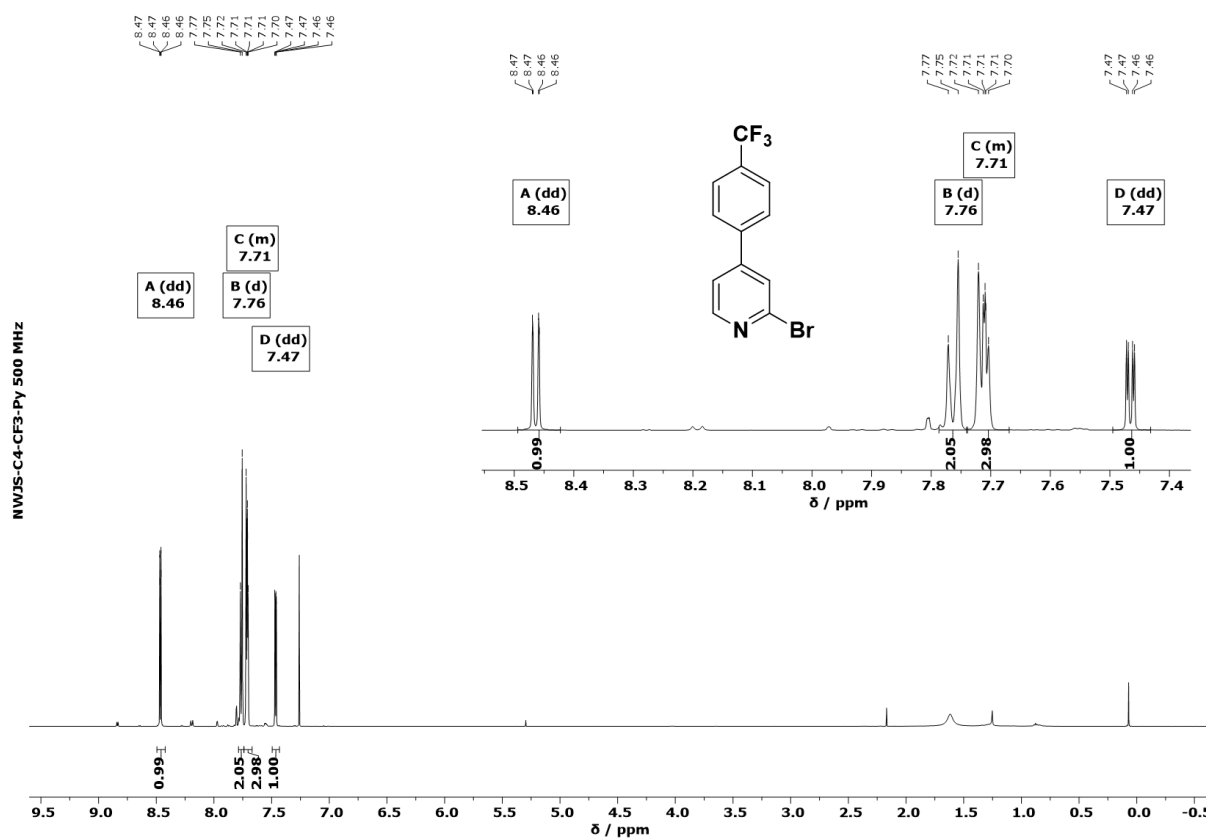
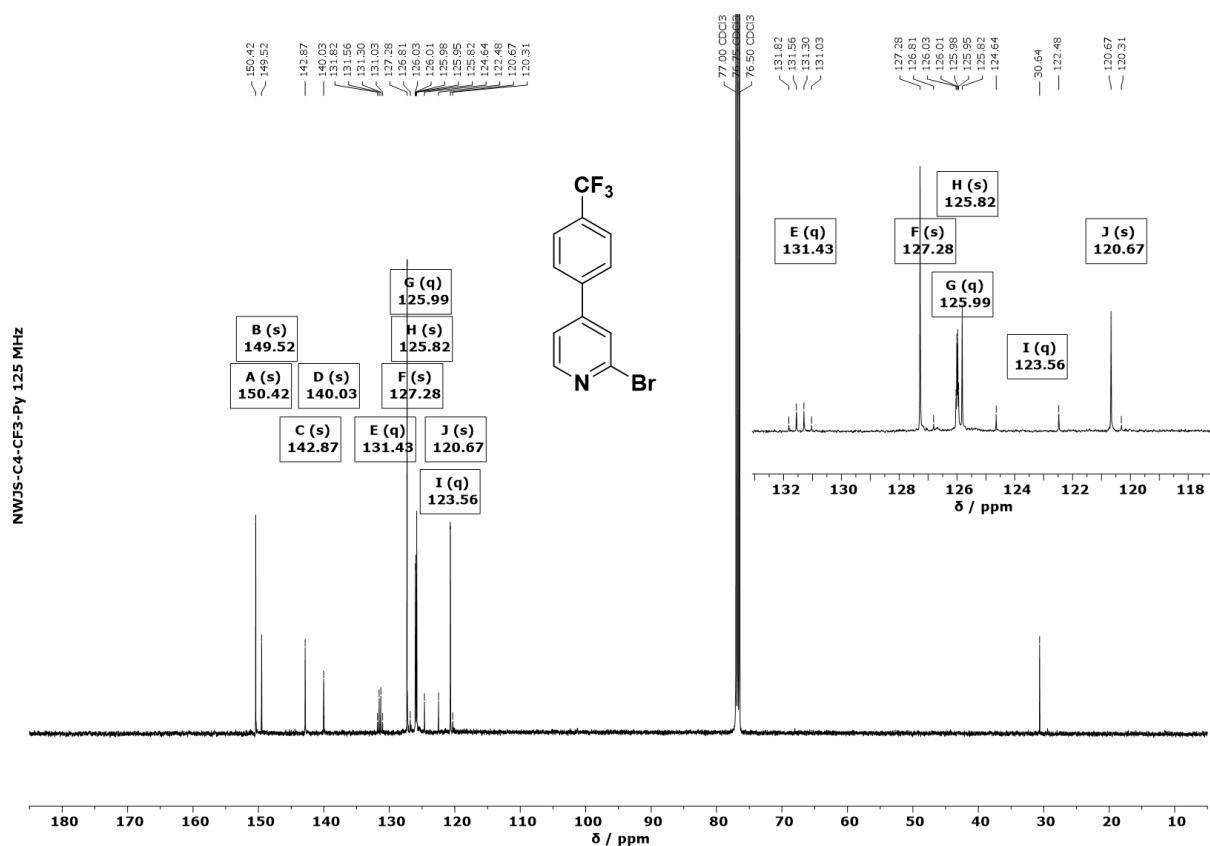
Figure 137 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of C4-Ar_D.Figure 138 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of C2-Ar_D.

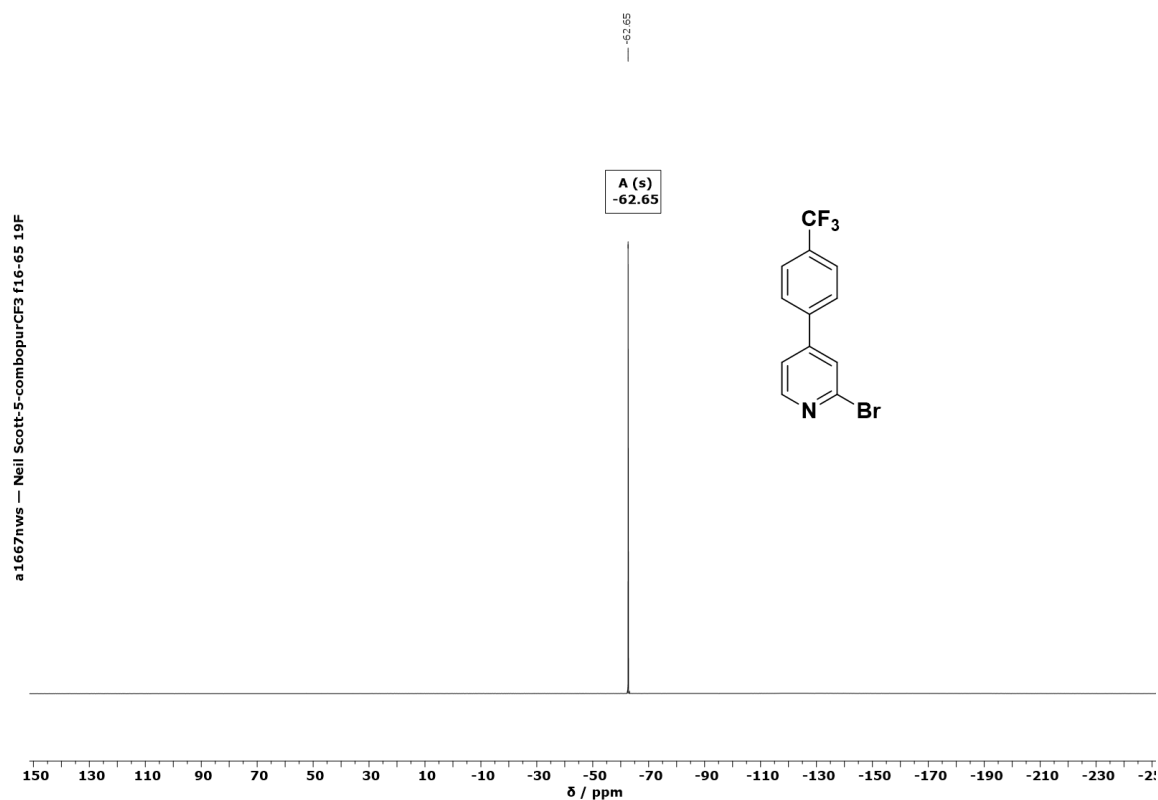
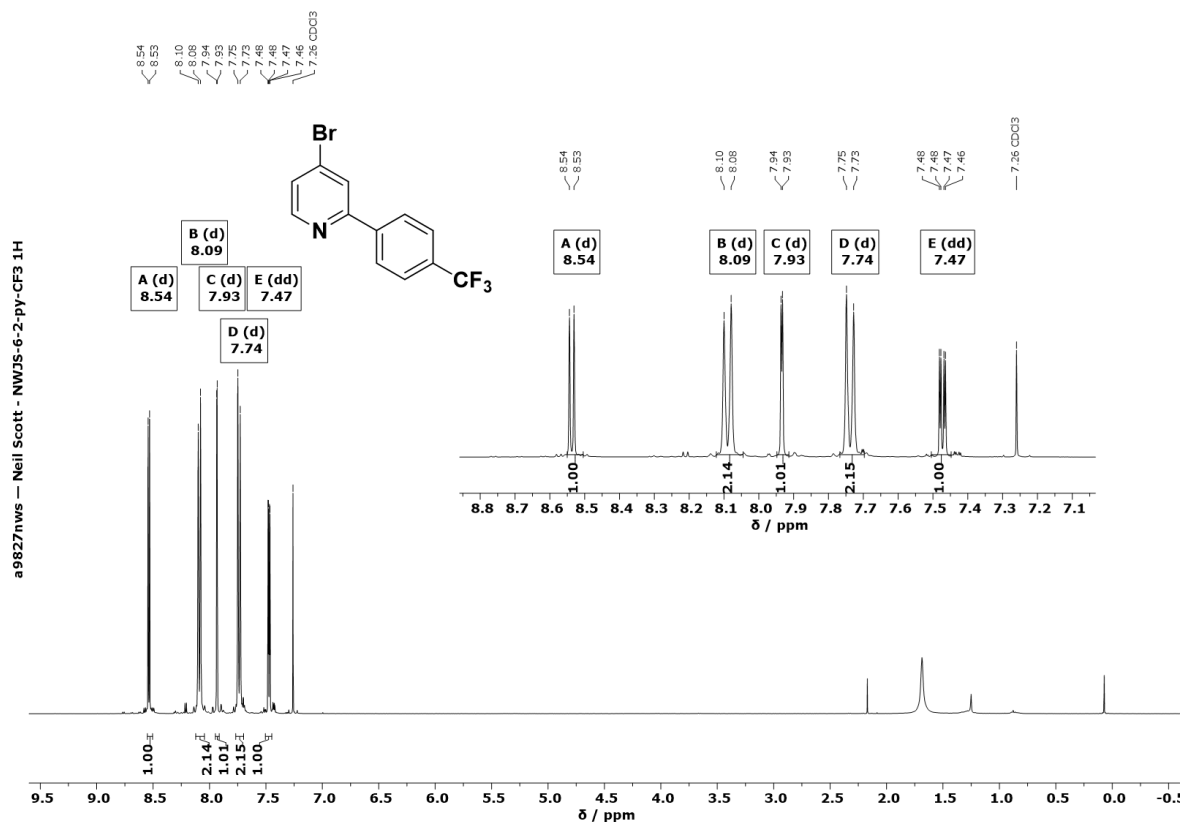
Figure 139 ¹³C NMR (CDCl₃, 101 MHz, 1024 scans) spectrum of C2-Ar_D.Figure 140 ¹H NMR (CDCl₃, 400 MHz, 32 scans) spectrum of bis-Ar_D.

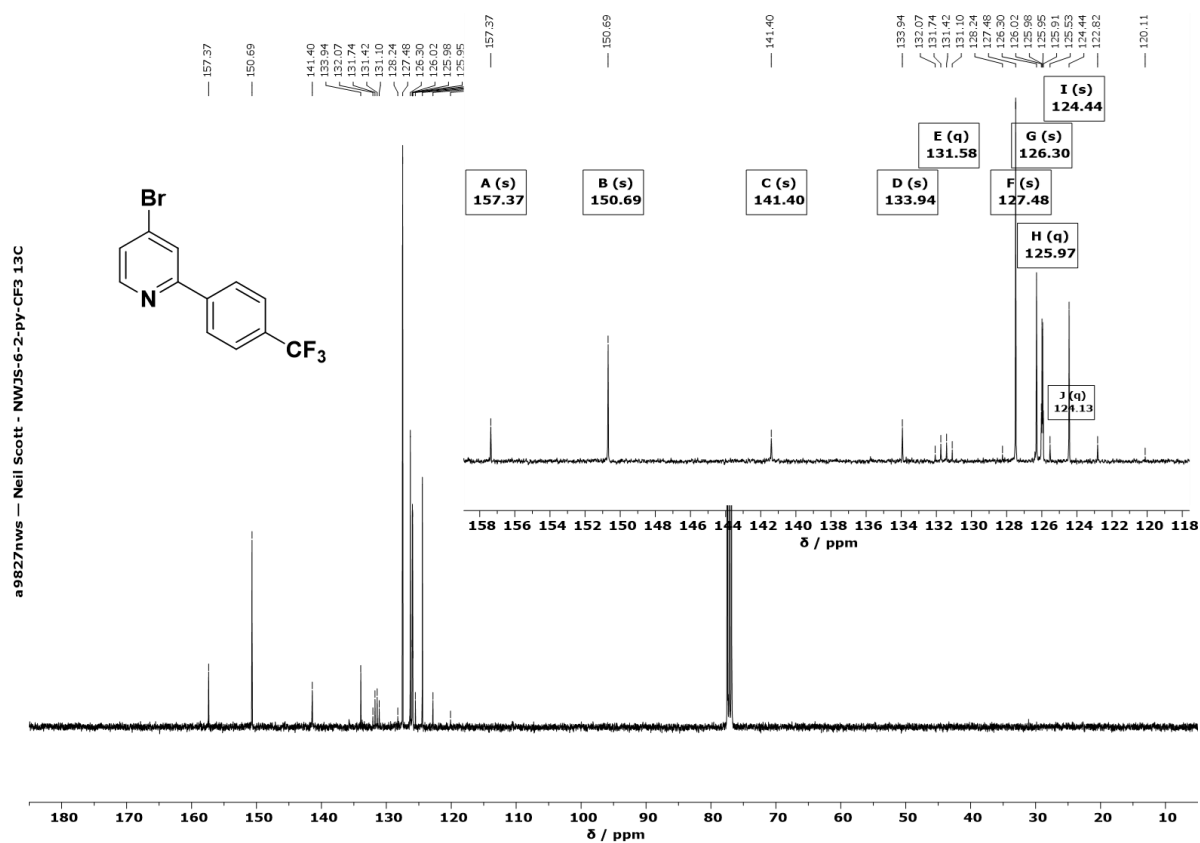
Figure 141 ¹H NMR (CDCl₃, 400 MHz, 32 scans) spectrum of C4-Ar_E.Figure 142 ¹³C NMR (CDCl₃, 101 MHz, 1024 scans) spectrum of C4-Ar_E.

Figure 143 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of C2-Ar_E.Figure 144 ^{13}C NMR (CDCl_3 , 101 MHz, 1024 scans) spectrum of C2-Ar_E.

Figure 145 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of bis-Ar_E.Figure 146 ^{13}C NMR (CDCl_3 , 101 MHz, 1024 scans) spectrum of bis-Ar_E.

Figure 147 ¹H NMR (CDCl₃, 500 MHz, 64 scans) spectrum of C4-Ar_F.Figure 148 ¹³C NMR (CDCl₃, 125 MHz, 1024 scans) spectrum of C4-Ar_F.

Figure 149 ^{19}F NMR (CDCl_3 , 376 MHz, 128 scans) spectrum of C4-Ar_F.Figure 150 ^1H NMR (CDCl_3 , 400 MHz, 32 scans) spectrum of C2-Ar_F.

Figure 151 ¹³C NMR (CDCl₃, 101 MHz, 2048 scans) spectrum of C2-Ar_F.Figure 152 ¹⁹F NMR (CDCl₃, 376 MHz, 128 scans) spectrum of C2-Ar_F.

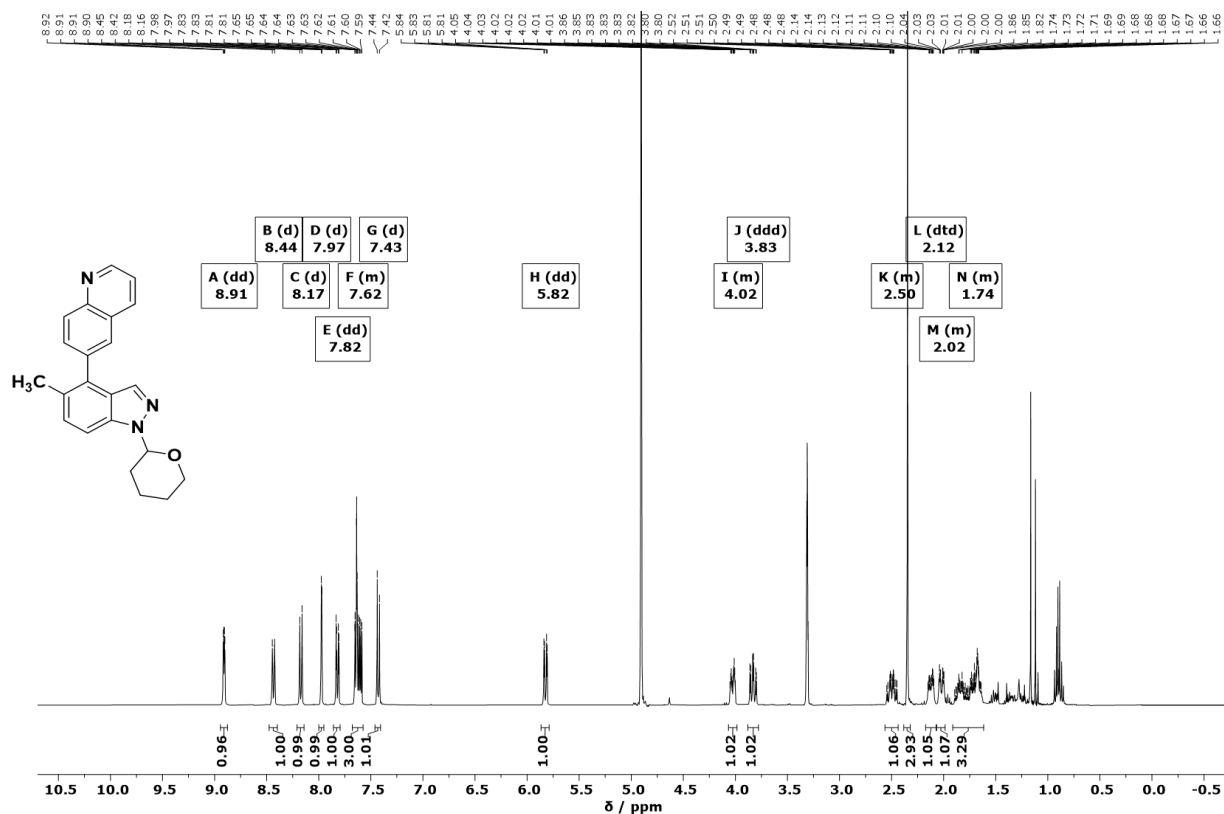


Figure 153 ¹H NMR (methanol-*d*₄, 400 MHz, 32 scans) of 6-[5-Methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]quinolone 72.

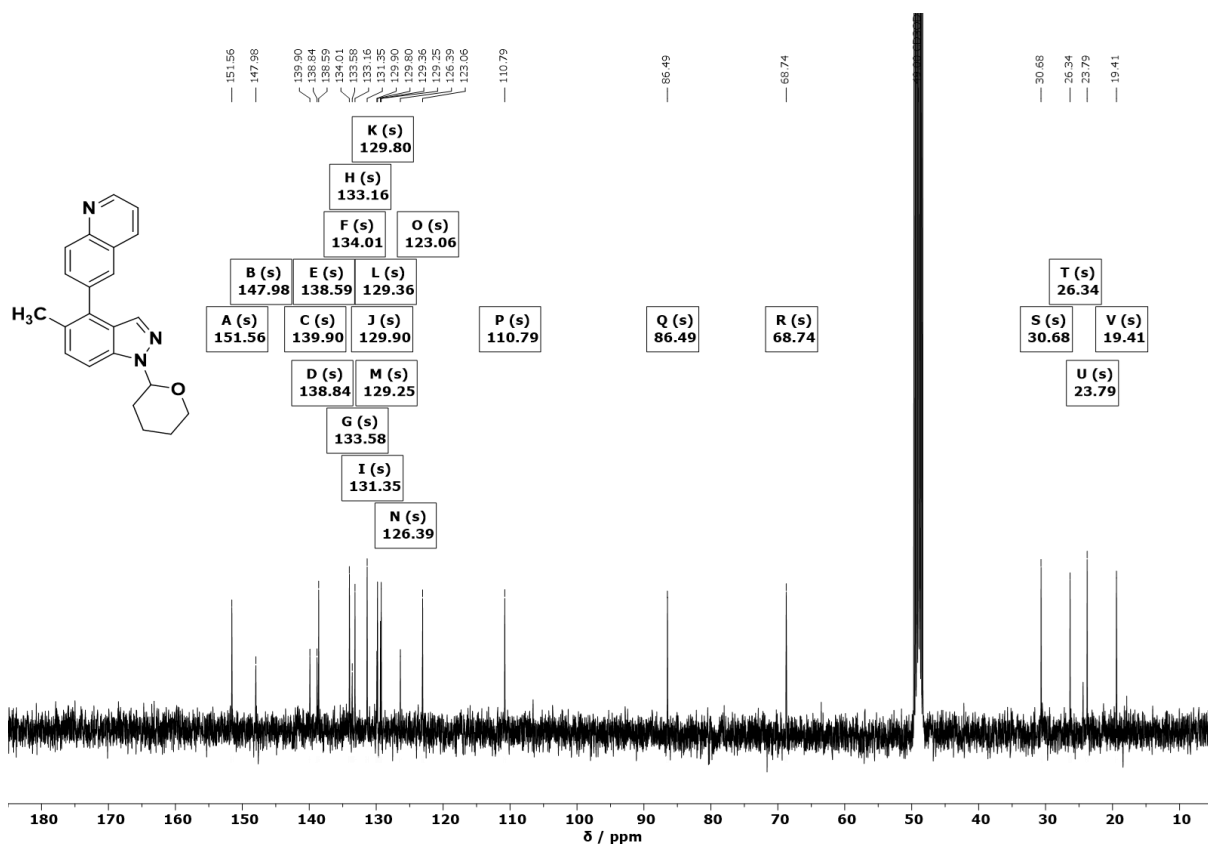


Figure 154 ¹³C NMR (methanol-*d*₄, 101 MHz, 1024 scans) of 6-[5-Methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl]quinolone 72.

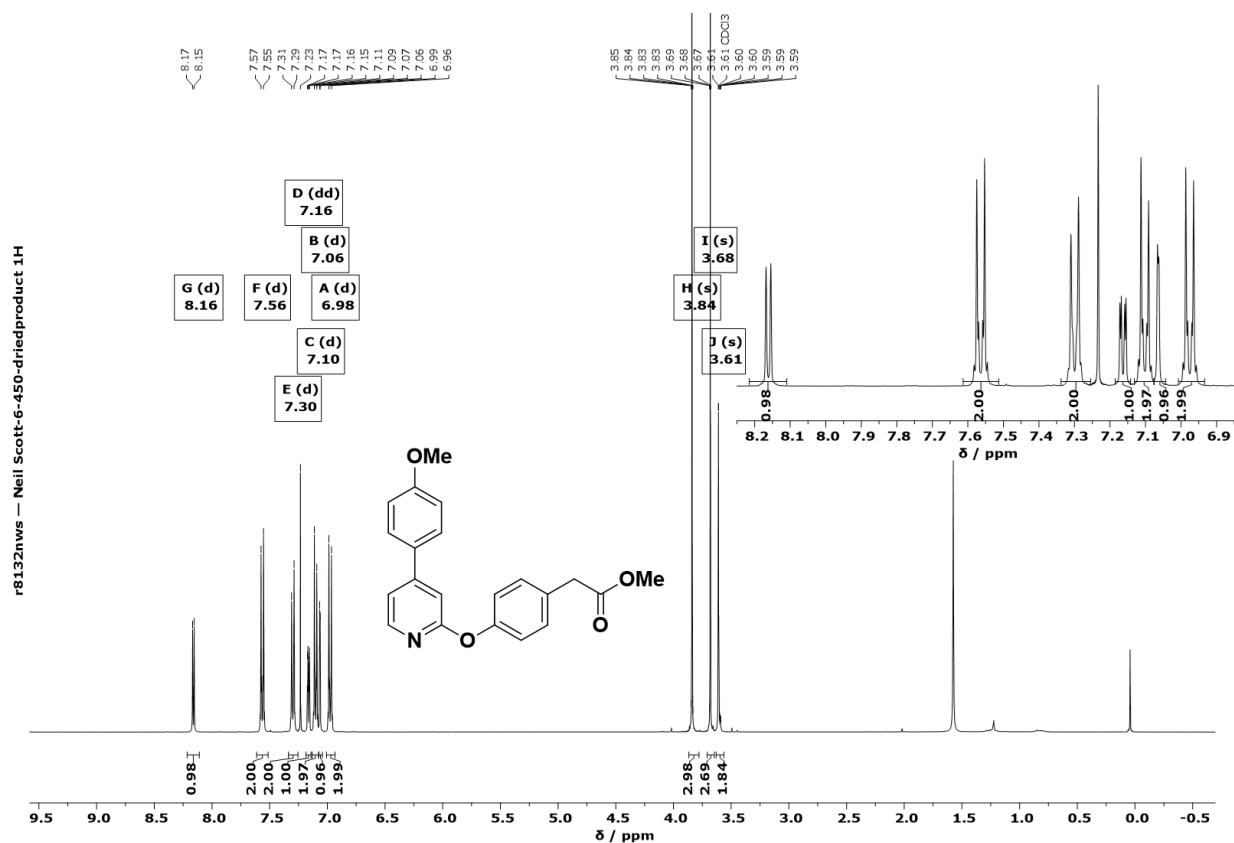


Figure 155 ^1H NMR (CDCl_3 , 400 MHz, 128 scans) of 4[4-anisyl, 2-pyridinyl]oxy]-benzeneacetic acid methyl ester, 79.

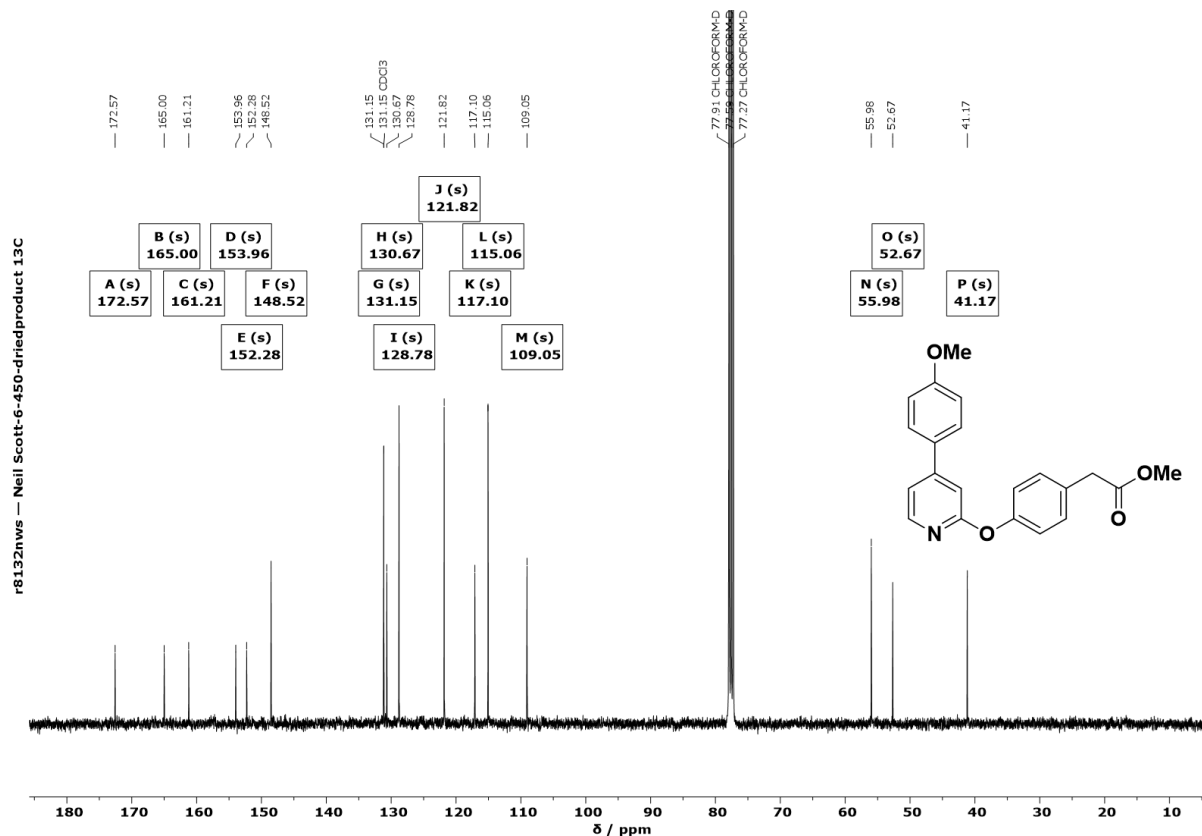


Figure 156 ^{13}C NMR (CDCl_3 , 101 MHz, 2048 scans) of 4[4-anisyl, 2-pyridinyl]oxy]-benzeneacetic acid methyl ester, 79

Appendix 4 – X-Ray Crystallographic Data

Crystallographic Data for Compound 47 (ijsf1807a)

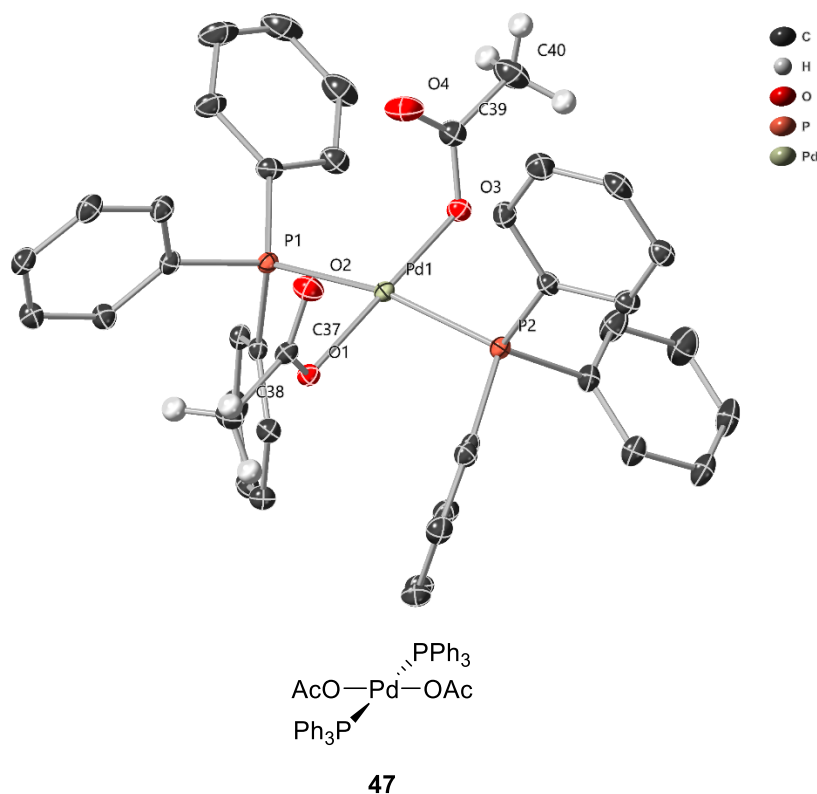


Figure 157 X-ray crystal structure of *trans*-[Pd(OAc)₂(PPh₃)₂] 47. Thermal ellipsoids set to 30% probability and the hydrogen atoms (PPh₃ ligands) have been omitted for clarity. Selected interatomic distances / Å: Pd1–P2 = 2.3414(6), P1–Pd1 = 2.3218(6) P1–O1 = 2.0249(18), P1–O3 = 2.0274(19). Selected bond angles / °: P1–Pd1–P2 = 168.25(2), O1–Pd1–O3 = 177.81(7), O1–Pd1–P1 = 84.77(5), O3–Pd1–P2 = 90.89(5), O3–Pd1–P1 = 93.93(6).

Table 25 Crystal data and structure refinement for ijsf1807a (compound 47).

Identification code	ijsf1807a
Empirical formula	C ₄₀ H ₃₆ O ₄ P ₂ Pd
Formula weight	749.03
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	11.6975(2)

b/Å	15.0053(3)
c/Å	19.3767(3)
α/°	90
β/°	94.765(2)
γ/°	90
Volume/Å³	3389.33(10)
Z	4
ρ_{calc}/cm³	1.468
μ/mm⁻¹	5.641
F(000)	1536.0
Crystal size/mm³	0.193 × 0.127 × 0.094
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.462 to 134.13
Index ranges	-11 ≤ h ≤ 13, -17 ≤ k ≤ 17, -23 ≤ l ≤ 23
Reflections collected	12675
Independent reflections	6044 [R _{int} = 0.0272, R _{sigma} = 0.0364]
Data/restraints/parameters	6044/0/426
Goodness-of-fit on F²	1.043
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0289, wR ₂ = 0.0703
Final R indexes [all data]	R ₁ = 0.0354, wR ₂ = 0.0743
Largest diff. peak/hole / e Å⁻³	0.71/-0.51
Data collected, solved and refined by Rachel R Parker	

Crystallographic Data for Compound 48 (ijsf1821)

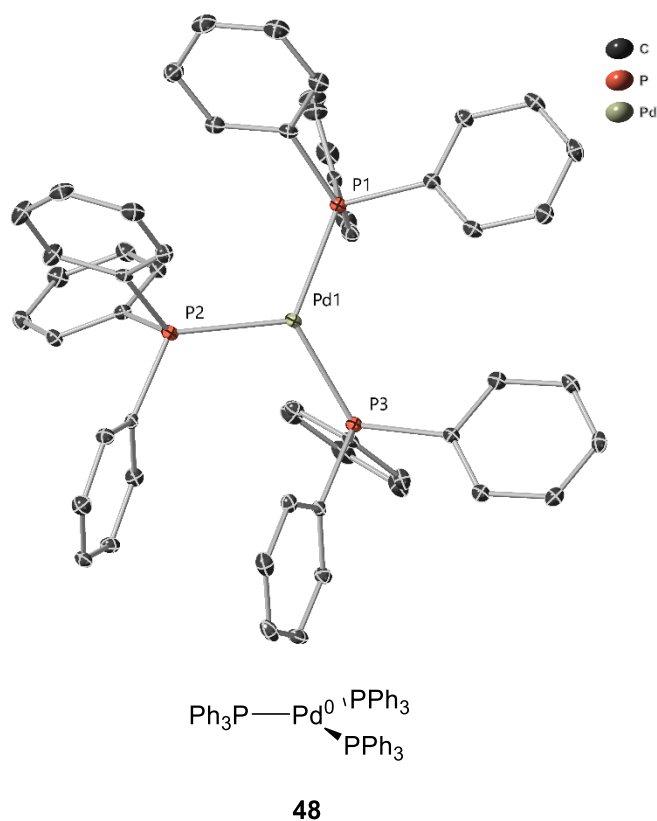


Figure 158 X-ray crystal structure of $[\text{Pd}^0(\text{PPh}_3)_3]$ 48. Thermal ellipsoids have been set to 30%. Hydrogen atoms have been modelled as spheres. Two molecules of THF and one molecule of hexane have been omitted for clarity. Selected interatomic distances /Å Pd1–P3 = 2.3119(6), P1–P2 = 2.3156(6), Pd1–P1 = 2.3084(6). Selected bond angles /°: P3–Pd1–P2 = 114.88(2), P1–Pd1–P3 = 126.09(2), P1–Pd1–P2 = 117.11(2).

Table 26 Crystal data and structure refinement for ijsf1821 (compound 48).

Identification code	ijsf1821
Empirical formula	$\text{C}_{60.39}\text{H}_{59.39}\text{O}_{0.39}\text{P}_3\text{Pd}$
Formula weight	990.70
Temperature/K	110.05(10)
Crystal system	triclinic
Space group	P-1
a/Å	13.5043(4)
b/Å	13.6723(4)
c/Å	14.3402(4)
α /°	92.507(2)
β /°	111.038(2)

$\gamma/^{\circ}$	96.346(2)
Volume/ $\text{\AA}^3$	2446.12(13)
Z	2
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.345
μ/mm^{-1}	0.518
F(000)	1032.0
Crystal size/ mm^3	$0.296 \times 0.122 \times 0.078$
Radiation	MoK α ($\lambda = 0.71073$)
2Θ range for data collection/$^{\circ}$	6.534 to 52.744
Index ranges	$-16 \leq h \leq 16, -17 \leq k \leq 17, -17 \leq l \leq 17$
Reflections collected	20381
Independent reflections	9977 [$R_{\text{int}} = 0.0266, R_{\text{sigma}} = 0.0457$]
Data/restraints/parameters	9977/14/619
Goodness-of-fit on F^2	1.062
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0326, wR_2 = 0.0654$
Final R indexes [all data]	$R_1 = 0.0409, wR_2 = 0.0699$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.47/-0.31
Data collected, solved and refined by Rachel R Parker	

Crystallographic Data for Compound 51 (ijsf1913)

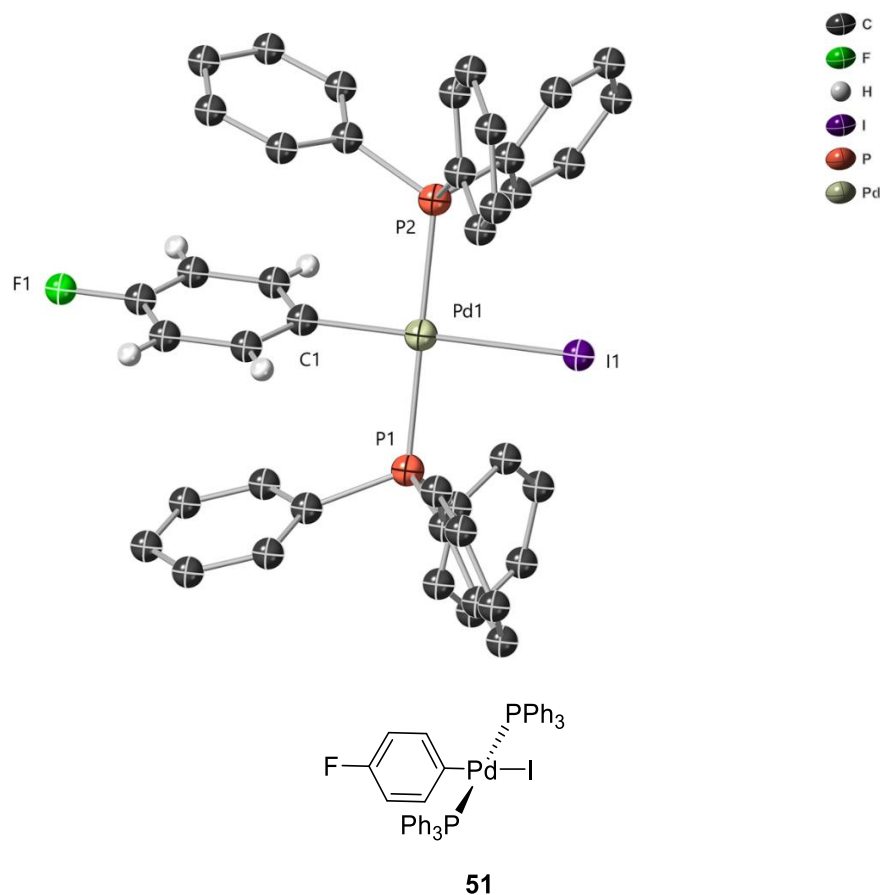


Figure 159 X-ray crystal structure of *trans*-[4-F-C₆H₄)Pd(I)(PPh₃)₂] 51. Thermal ellipsoids have been set at 30%. Hydrogen atoms of the PPh₃ ligands have been removed for clarity. Selected interatomic distances/Å: Pd1–P1 = 2.3176(5), Pd1–I1 = 2.7084(3), C1–Pd1 = 2.029(3). Selected bond Angles/Å: = P1–Pd1–I1 = 89.857(14), C1–Pd1–P1 = 90.143(14).

Table 27 Crystal data and structure refinement for ijsf1913 (compound 51).

Identification code	ijsf1913
Empirical formula	C ₄₂ H ₃₄ FI ₂ Pd
Formula weight	852.93
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	I2/a
a/Å	11.49975(9)
b/Å	12.87789(11)
c/Å	23.42522(16)
α/°	90

$\beta/^\circ$	93.6474(7)
$\gamma/^\circ$	90
Volume/ $\text{\AA}^3$	3462.07(5)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.636
μ/mm^{-1}	12.473
F(000)	1696.0
Crystal size/ mm^3	$0.215 \times 0.112 \times 0.042$
Radiation	CuK α ($\lambda = 1.54184$)
2 θ range for data collection/ $^\circ$	7.564 to 134.154
Index ranges	$-13 \leq h \leq 13, -15 \leq k \leq 15, -27 \leq l \leq 27$
Reflections collected	23869
Independent reflections	3090 [$R_{\text{int}} = 0.0266, R_{\text{sigma}} = 0.0129$]
Data/restraints/parameters	3090/0/215
Goodness-of-fit on F ²	1.050
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0187, wR_2 = 0.0498$
Final R indexes [all data]	$R_1 = 0.0190, wR_2 = 0.0500$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.49/-0.67
Data collected, solved and refined by Adrian C Whitwood	

Crystallographic Data for Compound 52 (ijsf1817)

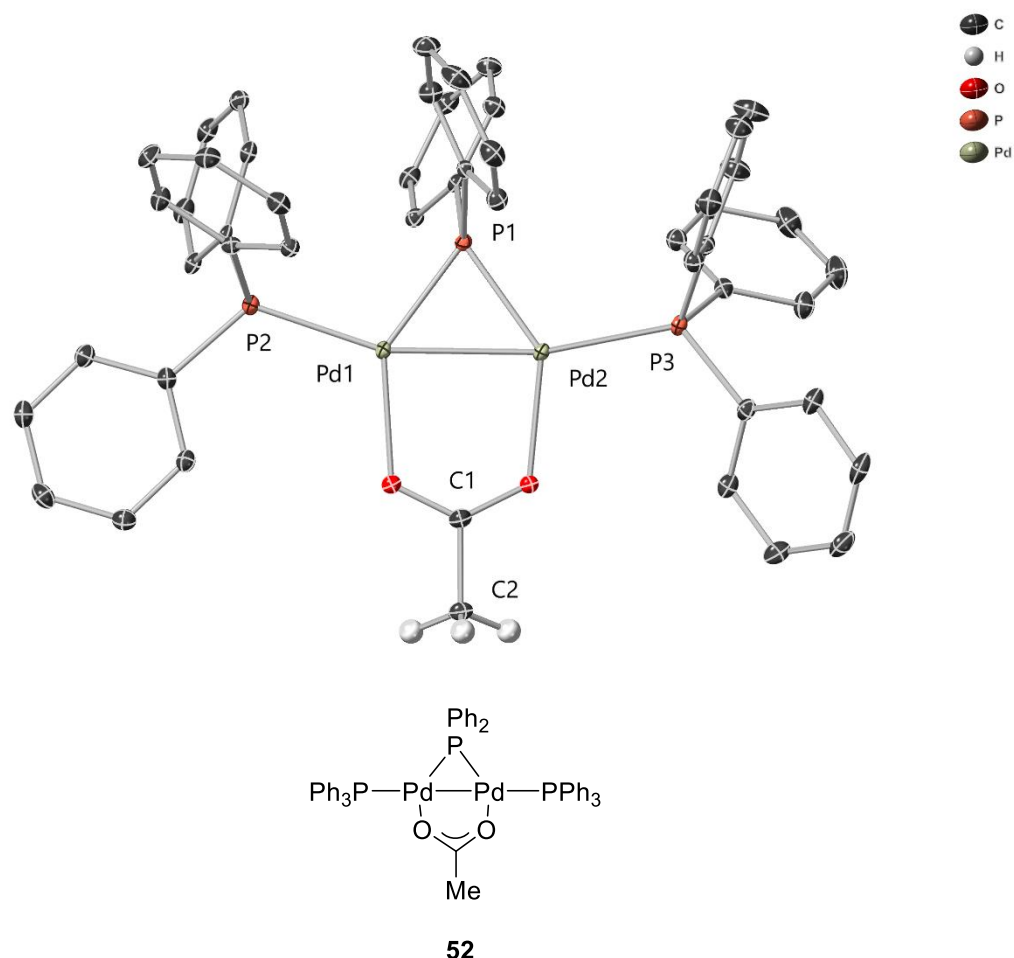


Figure 160 X-ray crystal structure of $[\text{Pd}_2(\mu_2\text{-OAc})(\mu\text{-PPh}_2)(\text{PPh}_3)_2]$ 52. Thermal ellipsoids set at 30%. Hydrogen atoms of the PPh_3 ligands have been removed for clarity. Additionally, one molecule of tetrahydrofuran has been omitted for clarity. Selected interatomic distances /Å: $\text{Pd1-Pd2}=2.5958(3)$, $\text{P1-Pd1}=2.2083(7)$, $\text{P1-Pd2}=2.2062(7)$, $\text{P2-Pd1}=2.3003(7)$, $\text{P3-Pd2}=2.3001(7)$, $\text{O1-Pd1}=2.2069(18)$, $\text{O2-Pd2}=2.1764(18)$. Selected bond angles /°: $\text{Pd2-P1-Pd1}=72.03(2)$, $\text{P2-Pd1-Pd2}=162.041(19)$, $\text{P3-Pd2-Pd1}=167.21(2)$, $\text{O2-Pd2-Pd1}=85.35(5)$.

Table 28 Crystal data and structure refinement for ijsf1817 52.

Identification code	ijsf1817
Empirical formula	$\text{C}_{54}\text{H}_{51}\text{O}_3\text{P}_3\text{Pd}_2$
Formula weight	1053.66
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	$\text{P2}_1/\text{c}$
$a/\text{\AA}$	11.8269(2)

b/Å	29.4867(5)
c/Å	14.1794(2)
$\alpha/^\circ$	90
$\beta/^\circ$	108.7289(19)
$\gamma/^\circ$	90
Volume/Å³	4683.01(14)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.494
μ/mm^{-1}	7.503
F(000)	2144.0
Crystal size/mm³	$0.258 \times 0.093 \times 0.018$
Radiation	CuK α ($\lambda = 1.54184$)
2θ range for data collection/$^\circ$	7.234 to 134.156
Index ranges	$-14 \leq h \leq 12, -19 \leq k \leq 35, -16 \leq l \leq 15$
Reflections collected	17077
Independent reflections	8345 [$R_{\text{int}} = 0.0266, R_{\text{sigma}} = 0.0369$]
Data/restraints/parameters	8345/20/577
Goodness-of-fit on F^2	1.019
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0271, wR_2 = 0.0620$
Final R indexes [all data]	$R_1 = 0.0345, wR_2 = 0.0658$
Largest diff. peak/hole / e Å⁻³	0.49/-0.52
Data collected, solved and refined by Adrian C Whitwood	

Refinement special details

The THF was disordered and modelled in two positions with refined occupancies of 0.919:0.081(3). Equivalent 1-2 and 1,3 distances were restrained to be equal, e.g. C51a-C52a, C51b-C52b, C53a-C54a & C53b-C54b. The ADP of each pair of disordered atoms were constrained to be equal e.g. O3a & O3b.

Crystallographic Data for Compound 53 (ijsf1818)

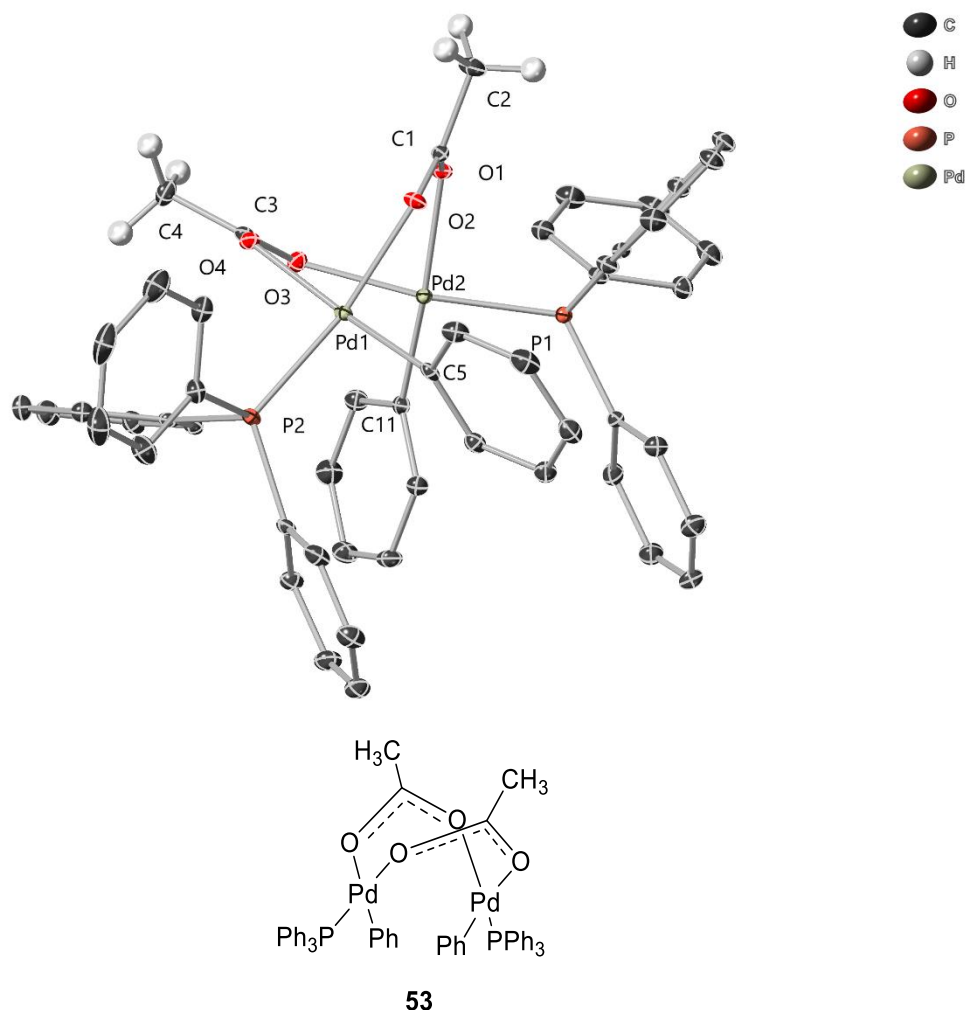


Figure 161 X-ray crystal structure of $[\text{Pd}(\mu_2\text{-OAc})(\text{Ph})(\text{PPh}_3)]_2$ 53. H-atoms of PPh_3 ligands omitted for clarity. Thermal ellipsoids set at 50% probability. Selected interatomic distances /Å: $\text{Pd1-Pd2}=3.0610(3)$, $\text{Pd1-P2}=2.2239(7)$, $\text{Pd2-P1}=2.2196(6)$, $\text{Pd1-C5}=1.991(2)$, $\text{O1-Pd2}=2.1432(17)$. Selected bond angles /°: $\text{C5-Pd1-O3}=88.28(9)$, $\text{C5-Pd1-P1}=91.44(7)$, Selected torsion angles /°: $\text{P1-Pd1-Pd2-P2}=115.363$, $\text{C5-Pd1-Pd2-C11}=84.851$, $\text{C5-Pd1-Pd2-P1}=14.673$.

Table 29 Crystal data and structure refinement for ijsf1818 (compound 53).

Identification code	ijsf1818
Empirical formula	$\text{C}_{52}\text{H}_{46}\text{O}_4\text{P}_2\text{Pd}_2$
Formula weight	1009.63
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	$\text{P2}_1/\text{n}$

a/Å	11.0527(2)
b/Å	23.8864(4)
c/Å	17.0272(2)
$\alpha/^\circ$	90
$\beta/^\circ$	99.5561(16)
$\gamma/^\circ$	90
Volume/Å³	4432.98(13)
Z	4
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.513
μ/mm^{-1}	7.587
F(000)	2048.0
Crystal size/mm³	0.254 × 0.028 × 0.019
Radiation	CuK α (λ = 1.54184)
2Θ range for data collection/$^\circ$	7.402 to 134.138
Index ranges	-13 ≤ h ≤ 13, -25 ≤ k ≤ 28, -20 ≤ l ≤ 14
Reflections collected	16871
Independent reflections	7909 [R_{int} = 0.0250, R_{sigma} = 0.0335]
Data/restraints/parameters	7909/0/543
Goodness-of-fit on F^2	1.034
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0243, wR_2 = 0.0547
Final R indexes [all data]	R_1 = 0.0314, wR_2 = 0.0576
Largest diff. peak/hole / e Å⁻³	0.40/-0.59
Data collected, solved and refined by Adrian C Whitwood	

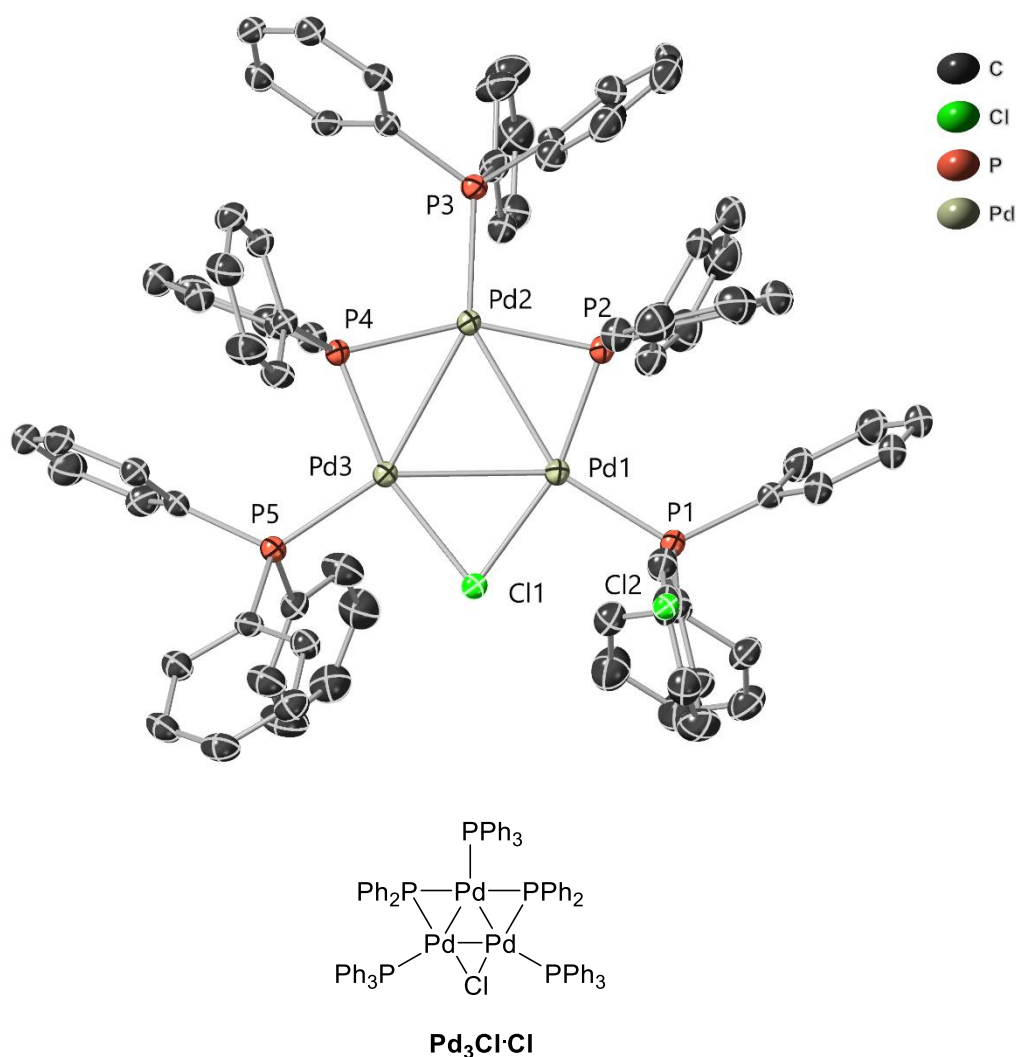
Crystallographic Data for Pd₃Cl·Cl (ijsf1804)

Figure 162 X-ray crystal structure of [Pd₃(μ-Cl)(μ-PPh₂)₂(PPh₃)₃]Cl (Pd₃Cl·Cl). Thermal ellipsoids set at 50%. Hydrogen atoms omitted for clarity. Seven molecules of CHCl₃, present within the unit cell were omitted for clarity. Selected bond distances /Å: Cl1–Pd=2.3828(8), Cl1–Pd3=2.4002(8), P1–Pd1=2.2837(8), P2–Pd1=2.1905(8), P2 – Pd2=2.2775(8), P3–Pd2=2.3034(8), P4–Pd2=2.2670(8), P4–Pd3=2.1967(8), P5–Pd3=2.2913(8), Pd1–Pd2=2.9138(3), Pd1–Pd3=2.8882(3), Pd2–Pd3=2.9127(3). Selected interatomic angles /°: Pd3–Pd2–Pd1=59.432(8), Pd1–P2–Pd2=81.38(3), Pd1–Cl1–Pd3=74.29(2).

Table 30 Crystal data and structure refinement for ijsf1804 (Pd₃Cl·Cl)

Identification code	ijsf1804
Empirical formula	C ₈₃ H ₇₀ Cl ₁₇ P ₅ Pd ₃
Formula weight	2144.09
Temperature/K	110.00(10)

Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	17.6962(2)
b/Å	18.85329(16)
c/Å	29.4453(3)
α/°	90
β/°	106.7594(12)
γ/°	90
Volume/Å³	9406.62(18)
Z	4
ρ_{calc}/g/cm³	1.514
μ/mm⁻¹	10.146
F(000)	4280.0
Crystal size/mm³	0.189 × 0.164 × 0.033
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.014 to 134.154
Index ranges	-21 ≤ h ≤ 21, -22 ≤ k ≤ 21, -35 ≤ l ≤ 21
Reflections collected	51053
Independent reflections	16773 [R _{int} = 0.0356, R _{sigma} = 0.0357]
Data/restraints/parameters	16773/30/1063
Goodness-of-fit on F²	1.033
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0358, wR ₂ = 0.0917
Final R indexes [all data]	R ₁ = 0.0438, wR ₂ = 0.0978
Largest diff. peak/hole / e Å⁻³	1.03/-0.65
Data collected, solved and refined by Adrian C Whitwood	

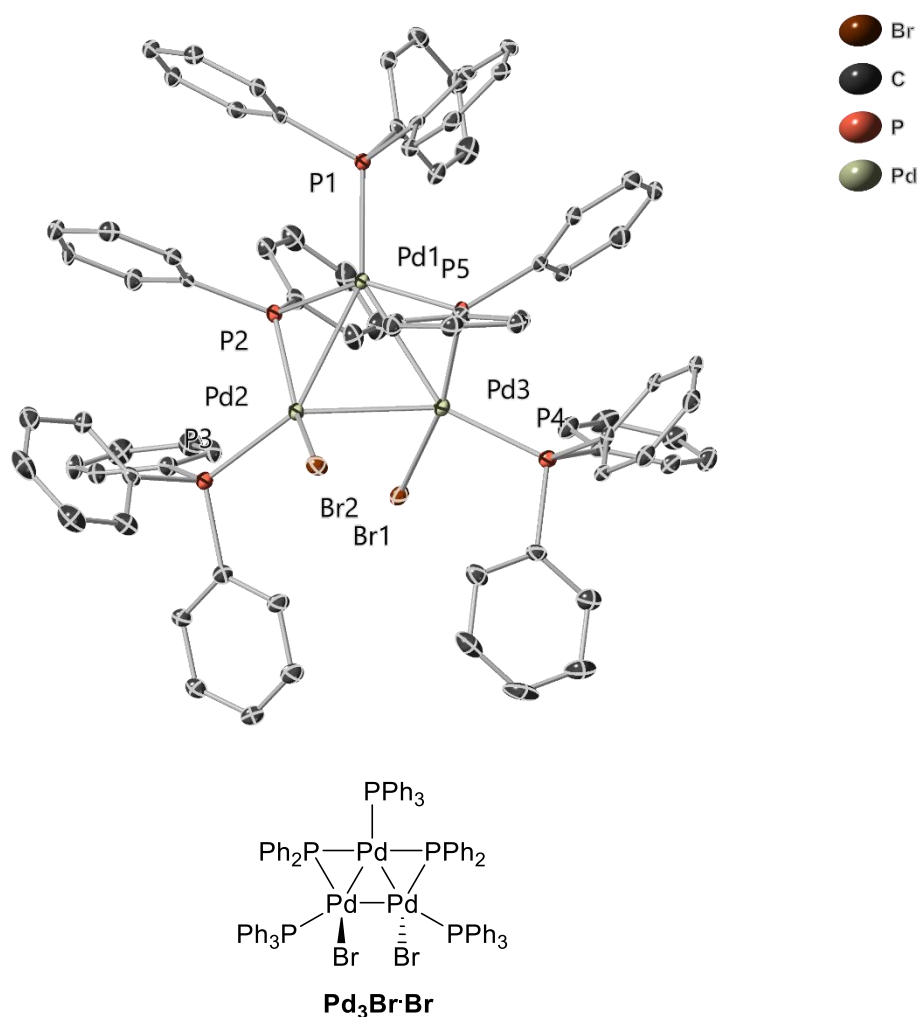
Crystallographic Data for Pd₃Br·Br (ijsf1905)

Figure 163 X-ray crystal structure of [Pd₃(μ-Br)(μ-PPh₂)₂(PPh₃)₃]Br (Pd₃BrBr). Thermal ellipsoids set at 50%. Hydrogen atoms omitted for clarity. One molecule of THF, present in the unit cell, has been omitted for clarity. Selected interatomic distances /Å: 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–P3=2.299(3), Pd1–P1=2.299(2), Pd2–P2=2.210(2), Pd1–P2=2.262(2). Selected interatomic angles /°: 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).

Table 31 Crystal data and structure refinement for ijsf1905 (Pd₃Br·Br)

Identification code	ijsf1905
Empirical formula	C ₈₂ H ₇₃ Br ₂ OP ₅ Pd ₃
Formula weight	1708.27
Temperature/K	110.05(10)
Crystal system	monoclinic

Space group	P2 ₁ /c
a/Å	16.3726(5)
b/Å	23.1564(6)
c/Å	18.9888(4)
α/°	90
β/°	95.645(2)
γ/°	90
Volume/Å³	7164.3(3)
Z	4
ρ_{calc}/g/cm³	1.584
μ/mm⁻¹	8.728
F(000)	3424.0
Crystal size/mm³	0.277 × 0.12 × 0.036
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.804 to 134.156
Index ranges	-19 ≤ h ≤ 17, -15 ≤ k ≤ 27, -22 ≤ l ≤ 20
Reflections collected	24240
Independent reflections	12724 [R _{int} = 0.0403, R _{sigma} = 0.0559]
Data/restraints/parameters	12724/23/845
Goodness-of-fit on F²	1.202
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0704, wR ₂ = 0.1630
Final R indexes [all data]	R ₁ = 0.0884, wR ₂ = 0.1714
Largest diff. peak/hole / e Å⁻³	2.88/-1.58
Data collected, solved and refined by Rachel R Parker	

Crystallographic Data for Compound 58 (ijsf1920)

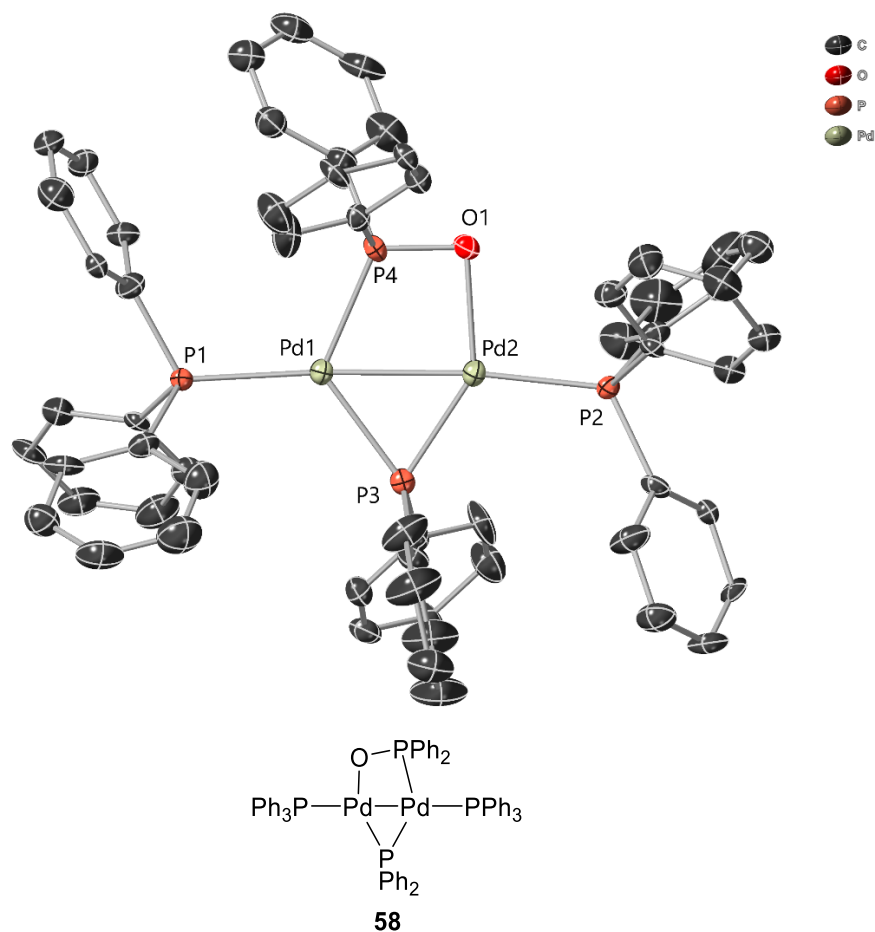


Figure 164 X-ray crystal structure of $[\text{Pd}_2(\mu\text{-PPh}_2)\{\kappa_2\text{-P,O-}\mu\text{-P(O)Ph}_2\}(\kappa\text{-PPh}_3)_2]$ 58. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids set at 30% probability. Selected interatomic distances /Å: Pd1–Pd2=2.5680(10), Pd1–P1=2.360(9), Pd2–P2=2.275(9), Pd1–P3=2.316(3), Pd2–P3=2.210(3), P1–P4=2.328(3), P4–O1=1.550(8), P2–O1=2.150(7). Selected interatomic angles /°: Pd1–P3–Pd2=69.093, Pd1–Pd2–O1=86.162, Pd2–O1–P4=93.688.

Table 32 Crystal data and structure refinement for ijsf1920 58

Identification code	ijsf1920
Empirical formula	$\text{C}_{60}\text{H}_{50}\text{OP}_4\text{Pd}_2$
Formula weight	1123.68
Temperature/K	109.95(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.3916(4)
b/Å	12.1359(5)
c/Å	23.1782(10)

$\alpha/^\circ$	78.881(4)
$\beta/^\circ$	79.050(4)
$\gamma/^\circ$	74.384(4)
Volume/ $\text{\AA}^3$	2469.7(2)
<i>Z</i>	2
$\rho_{\text{calc}}/\text{cm}^3$	1.511
μ/mm^{-1}	7.422
<i>F</i> (000)	1140.0
Crystal size/ mm^3	$0.171 \times 0.066 \times 0.046$
Radiation	CuK α ($\lambda = 1.54184$)
2Θ range for data collection/ $^\circ$	7.65 to 134.16
Index ranges	$-11 \leq h \leq 11, -12 \leq k \leq 14, -21 \leq l \leq 27$
Reflections collected	16496
Independent reflections	8824 [$R_{\text{int}} = 0.0308, R_{\text{sigma}} = 0.0437$]
Data/restraints/parameters	8824/36/793
Goodness-of-fit on F^2	1.228
Final <i>R</i> indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0556, wR_2 = 0.1194$
Final <i>R</i> indexes [all data]	$R_1 = 0.0629, wR_2 = 0.1226$
Largest diff. peak/hole / $\text{e \AA}^{-3}$	0.73/-0.65
Data collected, solved and refined by Adrian C Whitwood	

Refinement Special Details

The asymmetric unit contained two half complexes, each of which were disordered about a centre of inversion. The first complex had a common site for one palladium and one terminal phosphorus (Pd1 & P1), the rest of this complex was modelled in two positions with equal occupancy in each site. All of the phenyl rings were constrained to be regular hexagons with a C-C bond-length of 1.39 angstroms.

Crystallographic Data for Compound 62 (ijsf1916)

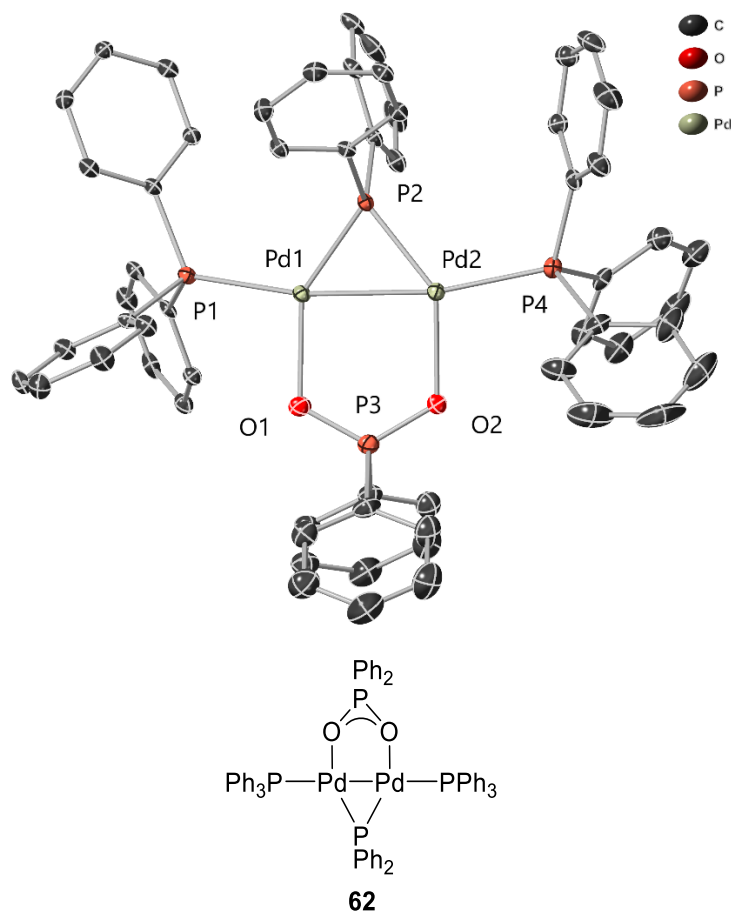


Figure 165 X-ray crystal structure of $[\text{Pd}_2(\mu\text{-PPh}_2)\{\kappa_2\text{-O,O-}\mu\text{-P}(\text{O})_2\text{Ph}_2\}(\kappa\text{-PPh}_3)_2]$ 62 Two molecules of THF and all hydrogen atoms have been omitted for clarity. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids set at 30% probability. Selected bond distances /Å: Pd1–Pd2 = 2.6140(5), P1–Pd1 = 2.2901(12), Pd2–P4 = 2.3095(12), P2–Pd1 = 2.1810(12), P2–Pd2 = 2.1888(12), Pd1–O1 = 2.162(4), Pd2–O2 = 2.186(4), O1–P3 = 1.507(4), O2–P3 = 1.529(4). Selected interatomic angles /°: O1–P3–O2 = 120.7(2), Pd1–P2–Pd2 = 73.48(4).

Table 33 Crystal data and structure refinement for ijsf1916 62

Identification code	ijsf1916
Empirical formula	$\text{C}_{124}\text{H}_{108}\text{O}_5\text{P}_8\text{Pd}_4$
Formula weight	2351.46
Temperature/K	110.05(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.2267(4)
b/Å	13.8505(6)

c/Å	21.9942(11)
$\alpha/^{\circ}$	98.543(4)
$\beta/^{\circ}$	93.796(4)
$\gamma/^{\circ}$	107.503(4)
Volume/Å³	2632.5(2)
Z	1
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.483
μ/mm^{-1}	7.012
F(000)	1196.0
Crystal size/mm³	$0.085 \times 0.031 \times 0.011$
Radiation	CuK α ($\lambda = 1.54184$)
2θ range for data collection/$^{\circ}$	7.29 to 134.158
Index ranges	$-7 \leq h \leq 11, -16 \leq k \leq 16, -25 \leq l \leq 26$
Reflections collected	17507
Independent reflections	9377 [$R_{\text{int}} = 0.0504, R_{\text{sigma}} = 0.0826$]
Data/restraints/parameters	9377/17/658
Goodness-of-fit on F²	1.009
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0435, wR_2 = 0.0841$
Final R indexes [all data]	$R_1 = 0.0697, wR_2 = 0.0944$
Largest diff. peak/hole / e Å⁻³	0.94/-0.89
Data collected, solved and refined by Adrian C Whitwood	

Crystallographic Data for Compound 64 (ijsf1908)

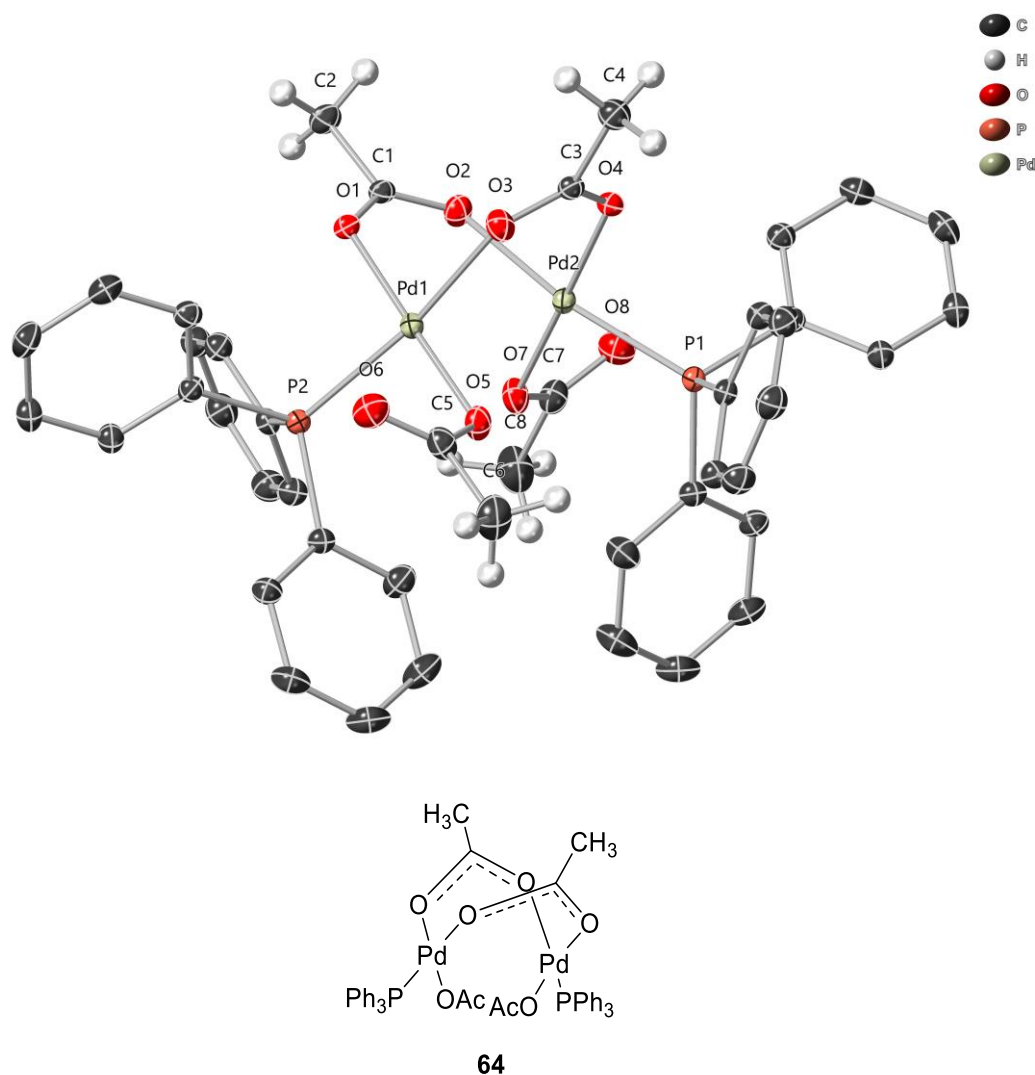


Figure 166 X-ray crystal structure of $[\text{Pd}^{\text{II}}(\mu_2\text{-OAc})(\kappa\text{-OAc})(\text{PPh}_3)]_2$ 64. Thermal ellipsoids were set at 50% probability. Hydrogen atoms from PPh_3 ligands have been removed for clarity. Selected interatomic distances /Å: Pd1–P2 = 2.2329(7), Pd1–O1 = 2.0209(18), Pd1–O3 = 2.1062(19), Pd1–O5 = 1.999(2), Pd1–Pd2 = 3.0115(4). Selected interatomic angles /°: P2–Pd1–O1 = 88.62(5), O1–Pd1–O3 = 89.61(8), P2–Pd1–O5 = 92.11(6), O3–Pd1–O5 = 89.83(8). Torsion angles /°: O5–Pd1–Pd2–O7 = 89.766, O5–Pd1–Pd2–P1 = –4.867, P2–Pd1–Pd1–P2 = –99.500.

Table 34 Crystal data and structure refinement for ijsf1908 64

Identification code	ijsf1908
Empirical formula	$\text{C}_{44}\text{H}_{42}\text{O}_8\text{P}_2\text{Pd}_2$
Formula weight	973.51
Temperature/K	110.05(10)
Crystal system	monoclinic

Space group	C2/c
a/Å	20.9152(4)
b/Å	9.6486(2)
c/Å	22.0620(4)
$\alpha/^\circ$	90
$\beta/^\circ$	113.600(2)
$\gamma/^\circ$	90
Volume/Å³	4079.80(15)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.585
μ/mm^{-1}	8.292
F(000)	1968.0
Crystal size/mm³	0.201 × 0.151 × 0.088
Radiation	CuK α (λ = 1.54184)
2Θ range for data collection/$^\circ$	8.748 to 134.142
Index ranges	-24 ≤ h ≤ 23, -11 ≤ k ≤ 11, -26 ≤ l ≤ 23
Reflections collected	7133
Independent reflections	3635 [R_{int} = 0.0200, R_{sigma} = 0.0234]
Data/restraints/parameters	3635/0/255
Goodness-of-fit on F²	1.058
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0255, wR_2 = 0.0659
Final R indexes [all data]	R_1 = 0.0279, wR_2 = 0.0680
Largest diff. peak/hole / e Å⁻³	0.67/-0.59
Data collected, solved and refined by Rachel R Parker	

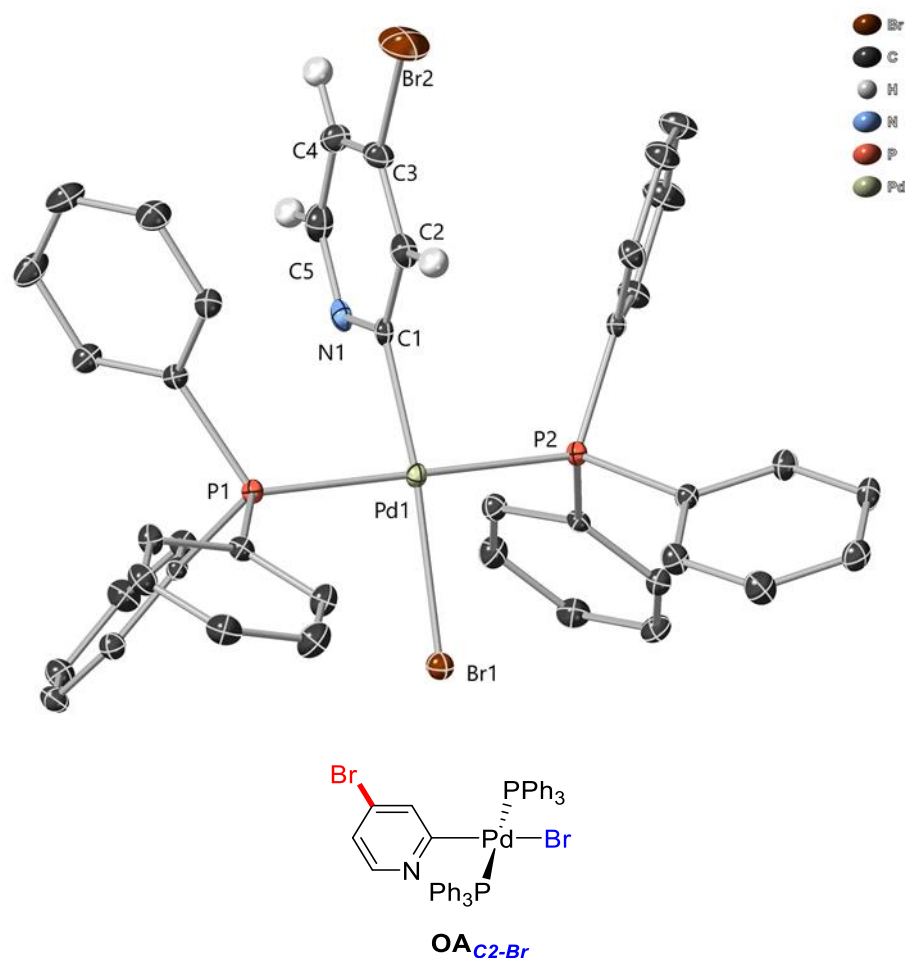
Crystallographic Data for OA_{C2-Br} (ijsf1805)

Figure 167 X-ray crystal structure of *trans*-[Pd(Br)(C²-4-bromopyridyl)(PPh₃)₂] (OA_{C2-Br}). Ellipsoids have been set at 50 % probability. H-atoms of PPh₃ ligands and three molecules of dichloromethane have been omitted for clarity. Selected interatomic distances /Å: P1–Pd1 = 2.3330(9), C1–Pd1 = 1.987(6), Br1–Pd1 = 2.5193(7). Selected interatomic angles /°: C1–Pd1–Br = 166.36(18), P1–Pd1–P2 = 177.28(5), P1–Pd1–Br1 = 90.94(2), C1A–Pd1–P1 = 89.17(3).

Table 35 Crystal data and structure refinement for ijsf1805 (OA_{C2-Br})

Identification code	ijsf1805
Empirical formula	C _{43.5} H ₃₈ Br ₂ Cl ₅ NP ₂ Pd
Formula weight	1080.16
Temperature/K	110.00(10)
Crystal system	monoclinic
Space group	I2/m
a/Å	17.3326(4)
b/Å	14.8308(3)

c/Å	18.9185(4)
$\alpha/^\circ$	90
$\beta/^\circ$	116.862(3)
$\gamma/^\circ$	90
Volume/Å³	4338.4(2)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.654
μ/mm^{-1}	9.392
F(000)	2148.0
Crystal size/mm³	0.205 × 0.125 × 0.025
Radiation	CuK α (λ = 1.54184)
2θ range for data collection/$^\circ$	7.936 to 134.16
Index ranges	-19 ≤ h ≤ 20, -17 ≤ k ≤ 13, -22 ≤ l ≤ 20
Reflections collected	16229
Independent reflections	4047 [R_{int} = 0.0235, R_{sigma} = 0.0185]
Data/restraints/parameters	4047/6/285
Goodness-of-fit on F²	1.164
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0373, wR_2 = 0.0886
Final R indexes [all data]	R_1 = 0.0386, wR_2 = 0.0893
Identification code	ijsf1805
Data collected, solved and refined by Adrian C Whitwood	

Refinement Special Details

The asymmetric unit contained half of the complex plus 1.25 dichloromethanes (as 3 discrete molecules). All were reflected about a central mirror plane parallel to the ac plane. In addition, the quarter dichloromethane was also at an inversion centre.

The complex was disordered with the bromopyridyl ring being modelled in two positions with refined occupancies of 0.858:0.142(2). The ring of the minor form was constrained to be a regular hexagon with bond-lengths of 1.39 angstroms. Several of the atoms of the bromopyridyl were restrained to be in the same plane.

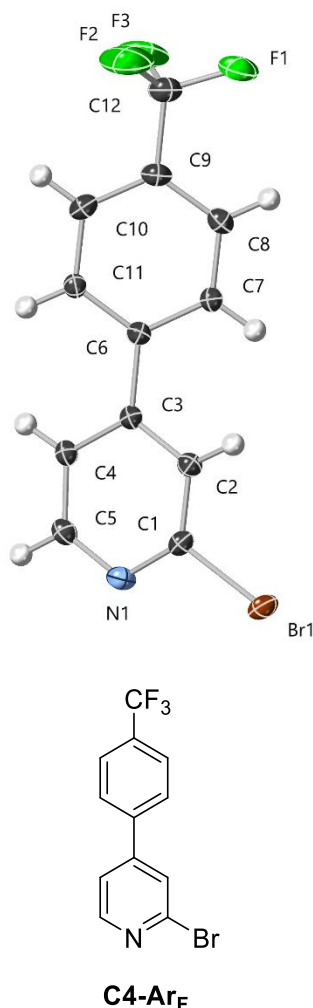
Crystallographic Data for C4-Ar_F (ijsf1803)

Figure 168 X-ray crystal structure of 2-bromo, 4-(4-trifluoromethylphenyl)pyridine (C4-Ar_F). Thermal ellipsoids set at 50%, Hydrogens have been modelled as spheres. Selected interatomic distances /Å: N1 – C1 = 1.323(3), N(1)–C(5) = 1.347(3), C(1)–C(2) = 1.381(3), C(5)–C(4) = 1.378(3), C(2)–C(4) = 1.396(3), C(4)–C(2) = 1.398(3), C(1)–Br(1) = 1.906(2). Selected interatomic angles /°: C(5)–N(1)–C(1) 115.21, N(1)–C(1)–C(2) = 126.02, N(1)–C(5)–C(4) = 124.25, C(1)–C(2)–C(4) = 118.01, C(5)–C(4)–C(2) = 119.17, C(2)–C(4)–C(4) = 117.3. Torsion angle /°: C11–C6–C3–C2 = 29.57.

Table 36 Crystal data and structure refinement for ijsf1803 (C4-Ar_F)

Identification code	ijsf1803
Empirical formula	C ₁₂ H ₇ BrF ₃ N
Formula weight	302.10
Temperature/K	110.05(10)
Crystal system	orthorhombic
Space group	Pbca

a/Å	11.6735(2)
b/Å	6.98840(10)
c/Å	27.1656(4)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/Å³	2216.14(6)
Z	8
$\rho_{\text{calc}}/\text{cm}^3$	1.811
μ/mm^{-1}	5.253
F(000)	1184.0
Crystal size/mm³	$0.307 \times 0.176 \times 0.043$
Radiation	CuK α ($\lambda = 1.54184$)
2θ range for data collection/$^\circ$	9.992 to 142.21
Index ranges	$-14 \leq h \leq 13, -8 \leq k \leq 8, -33 \leq l \leq 26$
Reflections collected	10677
Independent reflections	2118 [$R_{\text{int}} = 0.0343, R_{\text{sigma}} = 0.0200$]
Data/restraints/parameters	2118/36/182
Goodness-of-fit on F^2	1.056
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0283, wR_2 = 0.0756$
Final R indexes [all data]	$R_1 = 0.0311, wR_2 = 0.0782$
Largest diff. peak/hole / e Å⁻³	0.35/-0.39
Data collected, solved and refined by Sam Hart.	

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