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Anionic Pd(0) and Pd(II) Intermediates in Palladium-Catalyzed Heck and Cross-Coupling Reactions

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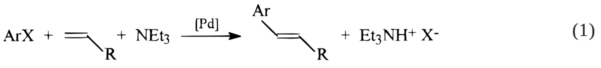
ABSTRACT
The anions of $PdCl_2L_2$ and $Pd(OAc)_2$, precursors of palladium(0) used in cross-coupling and Heck reactions, play a crucial role in these reactions. Tricoordinated anionic complexes $Pd^0L_2Cl^-$ and $Pd^0L_2(OAc)^-$ are the effective catalysts instead of the usually postulated Pd^0L_2 complex. The anion ligated to the palladium(0) affects the kinetics of the oxidative addition to ArI as well as the structure and reactivity of the arylpalladium(II) complexes produced in this reaction. Thus, pentacoordinated anionic complexes are formed, $ArPdI(Cl)L_2^-$ or $ArPdI(OAc)L_2^-$, the precursor of neutral *trans*-$ArPd(OAc)L_2$, instead of the usually postulated *trans*-$ArPdIL_2$ complex ($L = PPh_3$).

Palladium-catalyzed Heck reactions (eq 1)[1a,b,d,e] or cross-coupling reactions between aryl halides and nucleophiles (eq 2)[1b−h] have been intensively developed for their important synthetic applications.

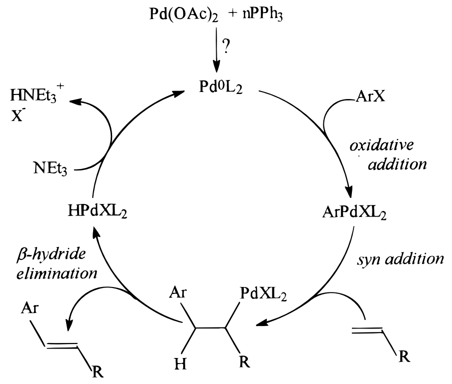


(1)

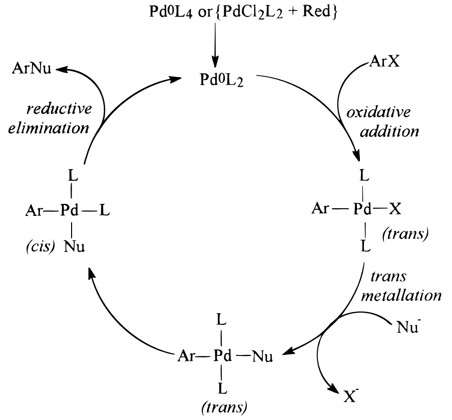
$$ArX + mNu \xrightarrow{[Pd]} ArNu + mX \qquad (2)$$

In both cases, the first step of the catalytic cycle is an oxidative addition of the aryl halide to the usually supposed 14-electron complex Pd^0L_2 ($L =$ monodentate phosphine ligand) to afford a σ-arylpalladium(II) complex, *trans*-$ArPdXL_2$ (Schemes 1 and 2). The second step is a nucleophilic attack on *trans*-$ArPdXL_2$, either a *syn*-addition (Heck reactions, Scheme 1) or a transmetalation (cross-coupling reactions, Scheme 2). The final product is generated by either β-hydride elimination (Heck) or reductive elimination (cross-coupling).

Scheme 1. "Textbook" Mechanism for Heck Reactions



Scheme 2. "Textbook" Mechanism for Cross-Coupling Reactions



In the very first mechanistic approaches, these elemental steps have been investigated separately and under stoichiometric conditions, starting from isolated stable complexes: either palladium(0) complexes (for the oxidative addition)[2] or *trans*-$ArPdXL_2$ complexes (for the *syn*-addition of olefins[3] or transmetalation of nucleophiles[4]) or mixed complexes $RPdR'L_2$ (for the reductive elimination).[5] Thanks to these studies, fundamental results are available on these elemental steps, e.g., influence of the ligand (basicity, cone angle) on the rate of oxidative addition or reductive elimination as well as influence of the nucleophile in the transmetalation or in the *syn*-addition step. However, in most studies, the mechanistic investigations have not been performed in the context of a real catalytic cycle, i.e., starting from the precursor of the palladium(0) or from the real arylpalladium(II) complex involved in the nucleophilic attack. Working on isolated putative catalytic cycle segments and thus with stable complexes is risky because the real elemental

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catalytic steps, which generally involve an energetic and thus unstable complex, may proceed quite differently. Moreover, the role of presumed “innocent” anions, cations, or protons, which may be present in catalytic reactions but absent in the isolated investigated step, is thus deliberately omitted. This is probably why some reported mechanisms appear inconsistent, unexpected, or not understood. For example, why are nucleophilic attacks on *trans*-$ArPdIL_2$ complexes slower than the overall catalytic reaction? Why are PdX_2L_2 complexes more specific to cross-coupling whereas $Pd(OAc)_2$ and phosphines mixtures are more specific to Heck reactions, although in both cases Pd^0L_2 is supposed to be the common effective catalyst and *trans*-$ArPdXL_2$ the unique and common complex formed in the oxidative addition of ArX to Pd^0L_2?

Mechanistic investigations require kinetic data. Long time scales ($t_{1/2}$ greater than a few minutes) are accessible to analytical techniques such as UV or NMR spectroscopy. However, these techniques are not adapted to the short times required for investigating short-lived species. Electrochemical techniques fill in this gap. Short-lived species can be generated by reduction/oxidation of known compounds in transient cyclic voltammetry or chronoamperometry performed at steady disk electrodes and their reactivity monitored by evolution of their reduction/oxidation current versus scan rate or duration of potential steps. Time scales from 10^{-1} to 10^{-8} s are thus available. Electrochemistry is then used for both its *synthetic* and *analytical* abilities. Reactivity of stable compounds can be monitored electrochemically since currents are proportional to concentrations. Electrochemistry is then simply used as an *analytical* technique, and time scales higher than mixing times can be explored. However, electrochemical techniques cannot afford structural information (except oxidation state of the metal) unless by comparison to authentic samples. When authentic samples are not available, association of electrochemical approaches which provide kinetic and mechanistic data with structure-determining techniques such as ^{31}P NMR spectroscopy is thus advantageous for the investigation of any reaction of electroactive complexes, even when no electron-transfer steps are involved.

We review here our mechanistic investigations on palladium-catalyzed Heck and cross-coupling reactions. These have been studied in the context of their real catalytic cycles, i.e., starting from real precursors of the palladium(0), respectively $\{Pd(OAc)_2 + nL\}$, mixtures in DMF or PdX_2L_2 (X = Cl, Br) in THF. The unexpected ability of anions, halides, and acetate (delivered by the precursor) to coordinate both palladium(0) and arylpalladium(II) complexes to form previously unsuspected tri- or pentacoordinated anionic intermediates is shown to be crucial because it governs the whole catalytic process. Since the mechanisms presented are quite intricate, we preferred to use a transversal presentation, focused on the role of the non classical tri- and pentacoordinated anionic intermediates which will be discussed in each reaction.

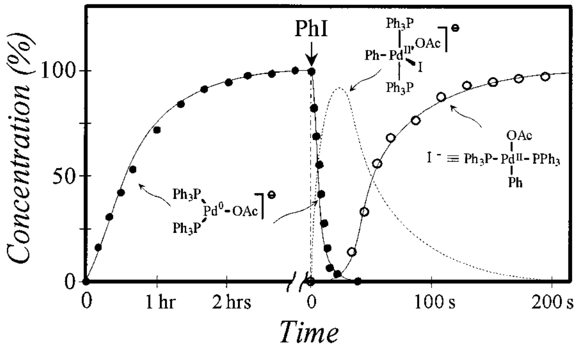
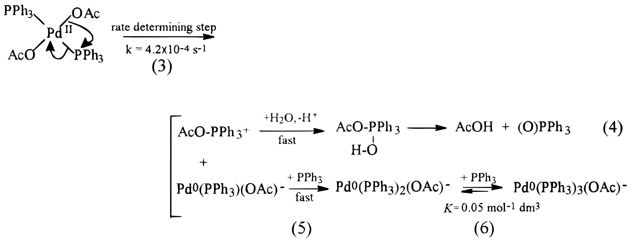


FIGURE 1. Schematic representation of the in situ formation of $Pd^0(OAc)(PPh_3)_2^-$ (solid symbols) from a mixture of $Pd^{II}(OAc)_2$ and PPh_3 (left part of diagram), followed by its fast oxidative addition upon addition of PhI (right part of diagram). On the right part of the diagram is represented the slower apparition of iodide ions (open symbols), which is tantamount to the formation of the *trans*-$PhPd^{II}(OAc)(PPh_3)_2$ final product. The complement at 100% of the sum of iodide ion and $Pd^0(PPh_3)_2(OAc)^-$ is shown by the dashed curve and represents the time variations of the transient anionic pentacoordinated species $PhPd^{II}I(OAc)(PPh_3)_2^-$. This sequence of events is reconstructed from real experiments (25 °C, DMF, 0.3 mol dm^{-3} n-Bu_4NBF_4) in which the $Pd^0(PPh_3)_2(OAc)^-$ (solid symbols) and iodide ions (open symbols) concentrations were followed chronoamperometrically at the rotating disk electrode.[7–8,10] Each relative concentration relates to the overall concentration of $Pd(OAc)_2$ (2 mmol dm^{-3}) introduced initially. PhI (20 mmol dm^{-3}) was added at the moment indicated by the arrow, when the formation of $Pd^0(PPh_3)_2(OAc)^-$ from $Pd(OAc)_2$ (2 mmol dm^{-3}) and PPh_3 (20 mmol dm^{-3}) was almost complete.

Tricoordinated Anionic Palladium(0) Intermediates in Oxidative Additions

Coordination of Palladium(0) by Acetate Anions. $\{Pd^{II}(OAc)_2 + nL\}$ ($n \geq 2$) mixtures are usual catalytic systems for Heck reactions (eq 1).[1a,b,d,e,6] Although the real catalyst was supposed to be Pd^0L_2, its formation in situ remained a mystery. In DMF, $\{Pd(OAc)_2 + nPPh_3\}$ ($n \geq 2$) mixtures rapidly lead to $Pd(OAc)_2(PPh_3)_2$, which can be detected on the basis of its reduction peak.[7,8] This reaction is followed by slow formation of a palladium(0) complex, which can be detected on the basis of its oxidation peak, and of phosphine oxide $(O)PPh_3$.[7,9] The kinetics of this spontaneous reaction was monitored by amperometry, by recording the decay of the reduction current of $Pd(OAc)_2(PPh_3)_2$ (proportional to its concentration) versus time as well as the increase of the oxidation current of the palladium(0) (proportional to its concentration) formed in situ (Figure 1). The reaction order is zero in PPh_3 and one in $Pd(OAc)_2$. The palladium(0) is produced by an intramolecular reduction, which is the rate-determining step of the overall process (eq 3).[8] The palladium(0) formed in situ from the $\{Pd(OAc)_2 + 10PPh_3\}$ mixture exhibits a broad ^{31}P NMR signal in DMF. Despite the excess of PPh_3, the signal for free PPh_3 is not detected, which indicates that PPh_3 is involved in at least one equilibrium. In DMF, the broad ^{31}P NMR signal of $Pd^0(PPh_3)_4$ which characterizes the equilibrium between palladium(0) complexes and PPh_3 [$Pd^0(PPh_3)_3 \leftrightarrows Pd^0(PPh_3)_2 + PPh_3$] is shifted but remains broad after addition of n-Bu_4NOAc. This indicates that AcO^- ions interfere in



Overall reaction:

$$Pd(OAc)_2 + 4PPh_3 + H_2O \longrightarrow Pd^0(PPh_3)_2(OAc)^- + AcOH + (O)PPh_3 + H^+ \quad (7)$$

this equilibrium by forming anionic species $Pd^0(PPh_3)_n(OAc)^-$ (eq 6).[10] Even in the presence of excess PPh_3, the intramolecular reduction of $Pd(OAc)_2(PPh_3)_2$ affords anionic palladium(0) complexes ligated by acetate and involved in an equilibrium with PPh_3 (eqs 5 and 6). Noticeably, the overall reaction (eq 7) affords protons resulting from the hydrolysis to $(O)PPh_3$ of the phosphonium salt formed with the palladium(0) (eqs 3 and 4).[10]

The formation of palladium(0) from $Pd(OAc)_2$ and para-substituted triarylphosphines is faster when the phosphine is substituted by an electron-withdrawing group and follows a Hammett correlation ($\rho = +2.4$ at 25 °C).[8] No palladium(0) was spontaneously generated from $Pd(OAc)_2$ and tri(*o*-tolylphosphine), in agreement with the reported formation of a palladacycle by insertion of palladium(II) into the C−H methyl bond of tri(*o*-tolylphosphine).[11a]

The kinetics of the oxidative addition of PhI to the anionic palladium(0) generated in situ from $Pd(OAc)_2$ and $nPPh_3$ ($n \geq 3$) mixtures in DMF is monitored by recording the decay of the oxidation current of the palladium(0) versus time (Figure 1). The reaction rate is not affected by acetate concentration but decreases with increasing phosphine concentration (Table 1). This indicates that the reactive species is generated by an uphill equilibrium involving PPh_3 but not AcO^- (eq 6). The 16-electron complex $Pd^0(PPh_3)_2(OAc)^-$ is the only possible candidate.[10] Surprisingly, the $\{Pd(OAc)_2 + 5PPh_3\}$ mixture, after evolution to palladium(0) and concomitant oxidation of one phosphine to $(O)PPh_3$, is more reactive than $\{Pd^0(PPh_3)_4 + AcO^-\}$ (Table 1, entries 2 and 3), although both systems formally give rise to the same species in solution, i.e., $Pd^0(PPh_3)_3(OAc)^-$ in equilibrium with the reactive $Pd^0(PPh_3)_2(OAc)^-$ and PPh_3. However, this formal identity neglects that protons are formed together with the palladium(0) when generated from $Pd(OAc)_2$ (eq 7). Proton interaction with the acetate of $Pd^0(PPh_3)_2(OAc)^-$ affords a more "naked" and thus more reactive complex **1**, being closer to $Pd^0(PPh_3)_2$. Addition of a base (required in Heck reaction) such as NEt_3, which neutralizes protons, slows the oxidative addition (Table 1, entries 3 and 4), and the rate becomes thus very similar to that of the proton-free system $\{Pd^0(PPh_3)_4 + 1AcO^-\}$ (Table 1, entries 2 and 4).[10] In agreement with this view, the $\{Pd(OAc)_2 + 3PPh_3\}$ mixture, which leads to the quantitative formation of the most reactive species $Pd^0(PPh_3)_2(OAc)^-$, is the most reactive system, and the decelerating effect of NEt_3 on the oxidative addition rate is again visible (Table 1, entries 5 and 6).

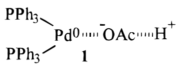


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Table 1. Reactivity of Palladium(0) Complexes in Oxidative Addition to Phenyl Iodide as a Function of Precursors (L = PPh_3)[a]

no.	precursor of Pd^0 (2 mmol dm^{-3})	reactive species[b] (S = solvent)	k_{app} ($M^{-1}\,s^{-1}$) in THF (DMF)
1	Pd^0L_4	SPd^0L_2[c]	16^d $(16)^d$ $(25)^e$
2	$Pd^0L_4 + AcO^-$	$Pd^0L_2(OAc)^-$	$(21)^e$
3	$Pd(OAc)_2 + 5L$	$Pd^0L_2(OAc)^-,H^+$	$(41)^e$
4	$Pd(OAc)_2 + 5L + 3NEt_3$	$Pd^0L_2(OAc)^-$	$(22)^e$
5	$Pd(OAc)_2 + 3L$	$Pd^0L_2(OAc)^-,H^+$	$(140)^e$
6	$Pd(OAc)_2 + 3L + 3NEt_3$	$Pd^0L_2(OAc)^-$	$(65)^e$
7	$PdBr_2L_2 + 2e$	$Pd^0L_2Br^-$	400^d
8	$PdCl_2L_2 + 2e$	$Pd^0L_2Cl^-$	530^d
9	$PdCl_2L_2 + 2e + 50Li^+$	Pd^0L_2Cl,Li	1320^d
10	$PdCl_2L_2 + 2e + 1Zn^{2+}$	$Pd^0L_2Cl,ZnCl$	1480^d

[a] "$Pd^0L_nL'_{n'}$" + PhI $\xrightarrow{k_{app}}$ "$PhPdXL_2$" + $(n - 2)L + n'L'$. [b] Present at stoichiometric concentration relative to the precursor except when otherwise noted. [c] Transient species present at traces under steady state. [d] 20 °C. [e] 25 °C.

In summary, PPh_3 reduces $Pd(OAc)_2$ to palladium(0) with three important consequences: $Pd^0(PPh_3)_2$ is not formed in a quantitative amount because one acetate ion remains ligated to the palladium(0), affording anionic complexes; $Pd^0(PPh_3)_2(OAc)^-$ is the reactive species in oxidative addition; and its reactivity is increased by the protons which are generated concomitantly.

This example shows that evolution of a precursor system as well as formation and further evolution of the true catalytic species can be monitored by electrochemistry as an analytical technique, in conjunction with spectroscopy, provided that reaction rates are not too fast. Investigation of more reactive species requires their generation by transient cyclic voltammetry, as illustrated in the next section.

Coordination of Palladium(0) by Halide Anions. Cross-coupling reactions (eq 2) are catalyzed by $Pd^0(PPh_3)_4$.[1b−f,4a] It has been established that $Pd^0(PPh_3)_2$, formed after two successive decomplexations of PPh_3, is the transient reactive species in the oxidative addition to ArX.[2a] However, its concentration is extremely low because it is involved in an endergonic equilibrium with the major but unreactive species $Pd^0(PPh_3)_3$. Reducible palladium(II) complexes such as $Pd^{II}Cl_2(PPh_3)_2$ have been considered as better precursors since their reduction in situ (either by nucleophiles[4a] or by independent reducers[12]) was expected to yield quantitatively the reactive $Pd^0(PPh_3)_2$. Although such precursors are frequently used synthetically,[1b,d,f] the reactivity of the ensuing palladium(0) complexes had never been fully examined.

$PdX_2(PPh_3)_2$ (X = Cl, Br, I) complexes are reduced in THF in a single overall bielectronic process, affording palladium(0) complexes characterized by their oxidation peak, which is detected on the reverse scan (Figure 2).[13] When $PdX_2(PPh_3)_2$ reduction is performed in the presence of PhI (1 equiv), the oxidation peak of the electrogenerated palladium(0) is no longer detected (Figure 2), showing that the oxidative addition to PhI occurs and is complete in

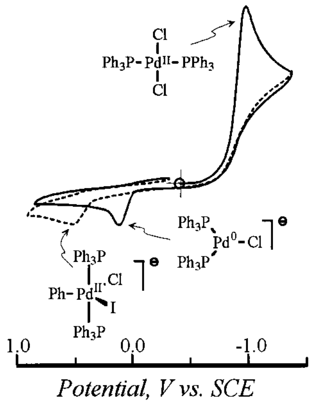
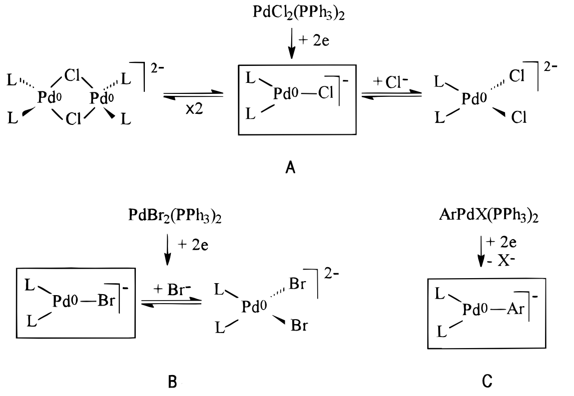


FIGURE 2. Cyclic voltammograms obtained for the reduction of $Pd^{II}Cl_2(PPh_3)_2$ (2 mmol dm^{-3}) in THF, 0.3 mol dm^{-3} n-Bu_4NBF_4, in the absence (solid curve) or in the presence of PhI (20 mmol dm^{-3}) (dashed curve). The solid anodic trace shows the oxidation peak of $Pd^0Cl(PPh_3)_2^-$ formed by the overall bielectronic reduction of $PdCl_2(PPh_3)_2$, whereas in the presence of PhI (dashed curve) the oxidation wave of species is absent because it has reacted within a few milliseconds to afford the anionic pentacoordinated species $PhPd^{II}I(Cl)(PPh_3)_2^-$, whose oxidation peak is observed at more positive potentials (dashed curve). Steady gold disk electrode (0.5 mm diameter) at a 0.2 V s^{-1} scan rate; 20 °C.

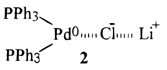
Scheme 3



much less than a second. The palladium(0) oxidation peak is progressively restored upon decreasing the time scale, i.e., by increasing the scan rate. The oxidative addition rate constants, whose high values preclude their determination by usual spectroscopic techniques, are then readily determined from variations of oxidation peak current versus scan rate.[13b] The oxidative addition rate slows as the palladium(II) concentration is decreased or the chloride ion concentration increased (added as n-Bu_4NCl), suggesting that chloride ions interfere in the oxidative addition by ligation of the electrogenerated palladium(0). After an exhaustive electrolysis of $PdCl_2(PPh_3)_2$ (2 F/mol), the solution exhibits three ^{31}P NMR signals featuring palladium(0) complexes, whose relative magnitude depends on chloride concentration. A detailed kinetic study establishes that chloride ions coordinate the palladium(0) center to form three anionic complexes, including one dimer and involved in two equilibria (Scheme 3A) which are fast versus the voltammetry time scale but slow versus the ^{31}P NMR time scale.[13b] The dimer is the most reactive species, but under usual conditions ($[Pd^0] \approx 2$ mmol dm^{-3}) its concentration is too low to account significantly in catalytic cycles compared to $Pd^0(PPh_3)_2Cl^-$, which is thus the main palladium(0) species (Table 1, entry 8). Reduction of $PdBr_2(PPh_3)_2$ affords two mononuclear complexes (Scheme 3B), with $Pd^0(PPh_3)_2Br^-$ being the most reactive one.[13b] In the absence of added halides, under the usual concentration of 2 mmol dm^{-3}, $Pd^0(PPh_3)_2Cl^-$ and $Pd^0(PPh_3)_2Br^-$ are formed from $PdCl_2(PPh_3)_2$ and $PdBr_2(PPh_3)_2$, respectively. $Pd^0(PPh_3)_2Cl^-$ is the most reactive complex (Table 1, entries 7 and 8).[13b]

Consequently, $Pd^0(PPh_3)_2$ does not exist in solution when generated in the presence of halide anions (delivered by precursors $PdX_2(PPh_3)_2$) because halide anions coordinate the palladium(0) center to form anionic species. This coordination is not restricted to halides (or acetate, see above) since the bielectronic reduction of $ArPd^{II}X(PPh_3)_2$ complexes (X = Cl, Br, I) affords anionic complexes $Pd^0(PPh_3)_2(Ar)^-$, in which Ar^- anions coordinate the palladium(0) center (Scheme 3C).[14] These anionic palladium(0) complexes are key intermediates in the palladium-catalyzed homocoupling of aryl halides since they undergo oxidative addition to ArX.[14]

Negishi et al. have proposed that anionic palladium(0) complexes $Li_nX_nPd^0(PPh_3)_2$ (X = Cl, Br) are formed by chemical reduction of $PdX_2(PPh_3)_2$ by organolithium reagents.[15a] However, their reactivity in oxidative addition with PhI is too high to be monitored by classical methods such as ^{31}P NMR spectroscopy.[15] It is possible to mimic the formation of such palladium(0) complexes by reducing $PdX_2(PPh_3)_2$ at the electrode in the presence of free cations, Li^+ or Zn^{2+}—introduced as $LiBF_4$ and $Zn(BF_4)_2$—and to investigate their reactivity with PhI. The oxidative addition is faster in the presence of metal cations (Table 1, entries 8–10).[13b] This shows that cations interact with the halide anions ligated to the palladium(0) by ion pairing, affording a more "naked" and thus more reactive palladium(0) complex closer to $Pd^0(PPh_3)_2$, as in compounds **2** and **3**. Cations play the same role for $Pd^0(PPh_3)_2Cl^-$ as protons do for $Pd^0(PPh_3)_2(OAc)^-$ (compound **1**).



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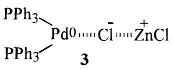

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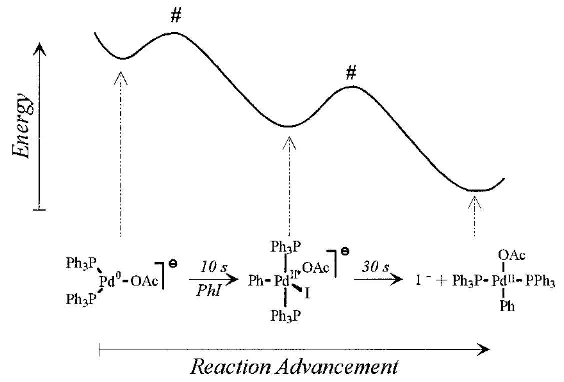
In summary, halides, acetate, and aryl anions coordinate $Pd^0(PPh_3)_2$ to form anionic tricoordinated complexes $Pd^0(PPh_3)_2(X')^-$, which undergo oxidative addition to aryl halides. The oxidative addition kinetics depends on the anion (released by palladium(II) precursors or by aryl halides during the reaction) but also on cations (delivered by nucleophiles or reducers) and protons (released during Heck reactions or reduction procedures). Anions ligated to the palladium(0) also affect both the structure of arylpalladium(II) complexes formed by oxidative additions and their reactivity with nucleophiles.

Anionic Pentacoordinated Arylpalladium(II) Complexes

Heck Reactions. When generated in situ from {$Pd(OAc)_2 + nPPh_3$} ($n \geq 3$) mixtures, the palladium(0) catalyst is

Scheme 4



an anionic species, $Pd^0(PPh_3)_2(OAc)^-$. Its oxidative addition to PhI affords not $PhPdI(PPh_3)_2$, as postulated (Scheme 1), but a new complex, *trans*-$PhPd^{II}(OAc)(PPh_3)_2$.[10] The mechanism of its formation was investigated by amperometry at a rotating disk electrode polarized on the plateau of the oxidation wave of $Pd^0(PPh_3)_2(OAc)^-$. Addition of PhI results in a fast decay of the oxidation current (Figure 1) and provides kinetic data on the oxidative addition rate (Scheme 4). However, at longer times, the oxidation current rises again (Figure 1). This rising current characterizes iodide ions, quantitatively released in solution after the oxidative addition. This indicates that $PhPd(OAc)(PPh_3)_2$ is formed ultimately and that the reaction proceeds in two separate steps via an intermediate short-lived anionic pentacoordinated complex, $PhPdI(OAc)(PPh_3)_2^-$, in which both acetate and iodide ions remain coordinated to the palladium(II) center (Scheme 4, [Pd] = 2 mmol dm^{-3}).[10] Its short half-life (30 s) precludes ^{31}P NMR characterization. $PhPd(OAc)(PPh_3)_2$ is also involved in a slow endergonic equilibrium with a cationic complex, $PhPd(PPh_3)_2^+$, and AcO^- (eq 8).[10] Therefore, the acetate

$$PhPd(OAc)(PPh_3)_2 \rightleftharpoons PhPd(PPh_3)_2^+ + AcO^- \qquad K = 1.4 \times 10^{-3}\ \text{mol dm}^{-3} \qquad (8)$$

ion borne by the palladium(0) remains ligated to two different phenylpalladium(II) complexes, one anionic and the other neutral. Moreover, through equilibrium (8), it regulates the formation of a cationic phenylpalladium(II). The interplay between these different phenylpalladium(II) complexes which are formed in Heck reactions is finely tuned by acetate ions delivered by $Pd(OAc)_2$.

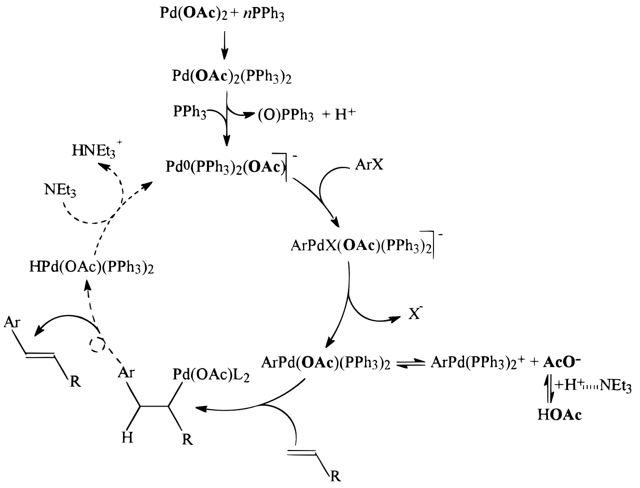
$PhPd(OAc)(PPh_3)_2$ reacts with styrene at room temperature, affording *trans*-stilbene. Yields are higher in the presence of NEt_3 (Table 2, entries 1−3).[10] $PhPdI(OAc)(PPh_3)_2^-$, a negatively charged 18-electron complex, is not prone to be reactive. It was nevertheless tested by addition of styrene to $Pd^0(PPh_3)_2(OAc)^-$ prior to PhI, so that this short-lived intermediate was in contact with styrene as soon as it was generated. No acceleration for the stilbene formation was observed, proving that this intermediate is not the reactive one.

Table 2. Reaction of Styrene with Phenylpalladium(II) Complexes in DMF at 25 °C[a]

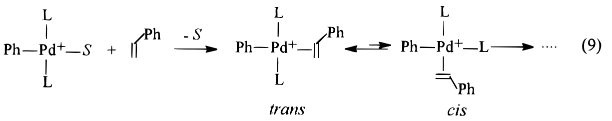
no.	phenylpalladium(II)	NEt_3 (equiv/Pd)	time (h)	(*E*)-stilbene (%)[b]
1	*trans*-$PhPd(OAc)(PPh_3)_2$[c]	0	20	35
2	*trans*-$PhPd(OAc)(PPh_3)_2$[c]	1	17	70
3	*trans*-$PhPd(OAc)(PPh_3)_2$[c]	3	19	75
4	*trans*-$PhPd(PPh_3)_2^+BF_4^-$	0	25	27
5	*trans*-$PhPd(PPh_3)_2^+BF_4^-$	1	18	22
6	*trans*-$PhPdI(PPh_3)_2$	0	24	0
7	*trans*-$PhPdI(PPh_3)_2$ + $2AcO^-$	0	22	57
8	*trans*-$PhPdI(PPh_3)_2$ + $2AcO^-$	1	48	72

[a] Styrene/$PhPdX(PPh_3)_2$ = 100/1. [b] Yields relative to phenylpalladium(II). [c] $PhPd(OAc)(PPh_3)_2$ is formed by reaction of PhI (1 equiv) with the Pd(0) generated from {$Pd(OAc)_2$ + $4PPh_3$}.

Scheme 5. New Mechanism for Palladium-Catalyzed Heck Reactions



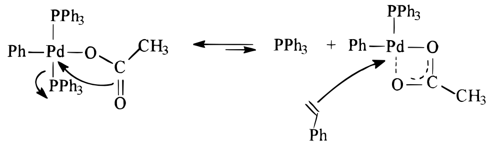
The cationic complex $[PhPd(PPh_3)_2^+BF_4^-]$ reacts with styrene. However, the reaction is slower than that with $PhPd(OAc)(PPh_3)_2$ (Table 2),[10] probably because the solvated cationic *trans*-$PhPd(PPh_3)_2(DMF)^+$ gives a *trans*-adduct which requires an endergonic *trans*−*cis* isomerization to allow *syn*-insertion of the olefin into the Ph-Pd bond (eq 9).



(9)

The *trans*-$PhPdI(PPh_3)_2$ complex does not react sufficiently fast with styrene (Table 2) unless acetate ions are added.[10] This is consistent with the iodide substitution in *trans*-$PhPdI(PPh_3)_2$ into the reactive *trans*-$PhPd(OAc)(PPh_3)_2$.[10] These results definitively rule out the textbook mechanism (Scheme 1) and establish that $PhPd(OAc)(PPh_3)_2$ is the key reactive intermediate in Heck reactions. Its reaction with olefins is the rate-determining step of the catalytic cycle (Scheme 5).

Its reaction with styrene is inhibited by excess phosphine, suggesting that a free coordination site is required to allow olefin coordination. In this context, the higher reactivity of $PhPd(OAc)(PPh_3)_2$ compared to that of $PhPdI(PPh_3)_2$ may arise from the bidentate character of the acetate ligand, which may assist the phosphine release (eq 10). Then, only steric hindrance determines the olefin coordination in a position *cis* to the Ph ligand, which favors the *syn*-addition of the Ph−Pd bond onto the olefin.



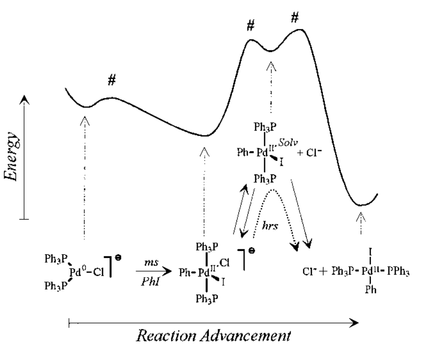
(10)

Role of the Base. The only beneficial effect of the base is observed with $PhPd(OAc)(PPh_3)_2$ (Table 2)[10] generated in situ from $Pd(OAc)_2$ and phosphine, i.e., together with protons (eq 7). The equilibrium between neutral $PhPd(OAc)(PPh_3)_2$ and cationic $PhPd(PPh_3)_2^+$ is affected by protons through interaction with the acetate ligand (Scheme 5). This interaction shifts the equilibrium toward the less reactive cationic complex. Neutralization of protons by a base shifts this equilibrium back to the more reactive $PhPd(OAc)(PPh_3)_2$ and consequently enhances the stilbene formation rate. By neutralizing protons, the base maintains a high concentration of the most reactive complex, $PhPd(OAc)(PPh_3)_2$. Consequently, the role of the base is more subtle than usually considered, viz., only that of recycling the palladium(0) from a palladium(II) hydride (Scheme 1). The base slows the fast oxidative addition with ArX by stabilizing the anionic complex $Pd^0(PPh_3)_2(OAc)^-$ and accelerates the rate-determining step of the catalytic cycle, i.e., the reaction of the olefin with $PhPd(OAc)(PPh_3)_2$ (Scheme 5). This double effect of the base, which tends to accelerate a slow reaction and decelerate a fast reaction, favors a more efficient catalytic cycle by causing all step to occur with comparable rates.

In summary, acetate ions play a crucial role in Heck reactions. Indeed, one acetate ion delivered by the precursor $Pd(OAc)_2$ is ligated to every palladium(0) or palladium(II) complex of the catalytic cycle, including the key species $ArPd(OAc)(PPh_3)_2$ involved in the rate-determining step (Scheme 5). This explains why $Pd(OAc)_2$ precursors associated with PPh_3 or with triarylphosphines which do not have any substituent in the *ortho* position are efficient catalysts in Heck reactions and proceed via the mechanism of Scheme 5. However, Heck reactions are also catalyzed by $Pd(OAc)_2$ associated with tri(*o*-tolylphosphine). As mentioned above, in that particular case, no palladium(0) complex is formed, but instead a palladacycle involving a palladium(II) is generated[11a] which supposes a different mechanism based on Pd(II)/Pd(IV) complexes.[11a,b] In this perspective, it is worth mentioning that some Heck reactions are performed efficiently with $Pd(OAc)_2$ in the absence of any phosphine,[11c] a situation in which our mechanism (in which the phosphine has a crucial role) cannot apply and specific mechanisms are required.[11b]

Cross-Coupling Reactions. Under usual conditions, the palladium(0) generated by $PdCl_2(PPh_3)_2$ reduction is an anionic complex $Pd^0(PPh_3)_2Cl^-$. Its oxidative addition to PhI affords eventually the expected *trans*-$PhPdI(PPh_3)_2$. However, at shorter times, an intermediate anionic pentacoordinated 18-electron complex, $PhPd^{II}I(Cl)(PPh_3)_2^-$, is formed in which the chloride ion, borne by the palladium(0), remains attached to the palladium(II) center (Scheme 6).[16] The half-life of this anionic complex is long enough to allow its characterization (oxidation peak at +0.405 V in Figure 2 and ^{31}P NMR signal at 33.47 ppm vs H_3PO_4).[16] It is involved in a fast uphill equilibrium in which the chloride ion departs to yield a neutral pentacoordinated complex $PhPdI\mathit{S}(PPh_3)_2$, which affords eventually the *trans*-$PhPdI(PPh_3)_2$ complex (Scheme 6, [Pd] = 2 mmol dm^{-3}, solvent = THF). Chloride ions thus inhibit the *trans*-$PhPdI(PPh_3)_2$ formation, as evidenced by the reciprocal dependence of the overall rate constant versus chloride concentration.[16] Schemes 4 and 6 present some similitude since in both cases the anion ligated to the reacting palladium(0) remains a ligand of the phenylpalladium(II) complex formed by the oxidative addition. But the stability of these anionic pentacoordinated phenylpalladium(II) complexes and their further chemical evolution differ.

Scheme 6



Consequently, chloride ions brought by the palladium(0) finely regulate the formation of three different phenylpalladium(II) complexes. Although nucleophiles react with *trans*-$PhPdI(PPh_3)_2$ to afford cross-coupling products (textbook mechanism, Scheme 2), these reactions are slower than the overall catalytic reaction.[4a,b,16] Moreover, *trans*-$ArPdX(PPh_3)_2$ complexes are formed from $Pd^0(PPh_3)_2Cl^-$ at long times. This establishes that *trans*-$ArPdX(PPh_3)_2$ complexes cannot be intermediates under catalytic conditions. Thus, the nucleophile must attack the intermediate pentacoordinated neutral complex, $ArPdX\mathit{S}(PPh_3)_2$ (Scheme 7, main cycle). This reaction gives an anionic pentacoordinated mixed complex $ArPdX(Nu)(PPh_3)_2^-$, in which the Ar and Nu ligands are now adjacent and so in a favorable position for a fast reductive elimination (Scheme 7)[16] and formation of $Pd^0(PPh_3)_2X^-$, which initiates the second catalytic cycle (Scheme 7, main cycle). As a proof for this new mechanism, the 2-thiophenyl anion reacts overall 2.5 times slower with *trans*-$PhPdI(PPh_3)_2$ (Scheme 2) than with the anionic complex generated by the oxidative addition to $Pd^0(PPh_3)_2Cl^-$ to PhI (Scheme 7).

As catalytic reactions proceed, halide anions and cations are progressively released due to ArX and mNu (m = countercation associated with nucleophiles) conversion. These modifications may induce a progressive transition of the main mechanism in Scheme 7 toward that in Scheme 2. Released ions may be free or ion-paired so that four situations shall be considered:

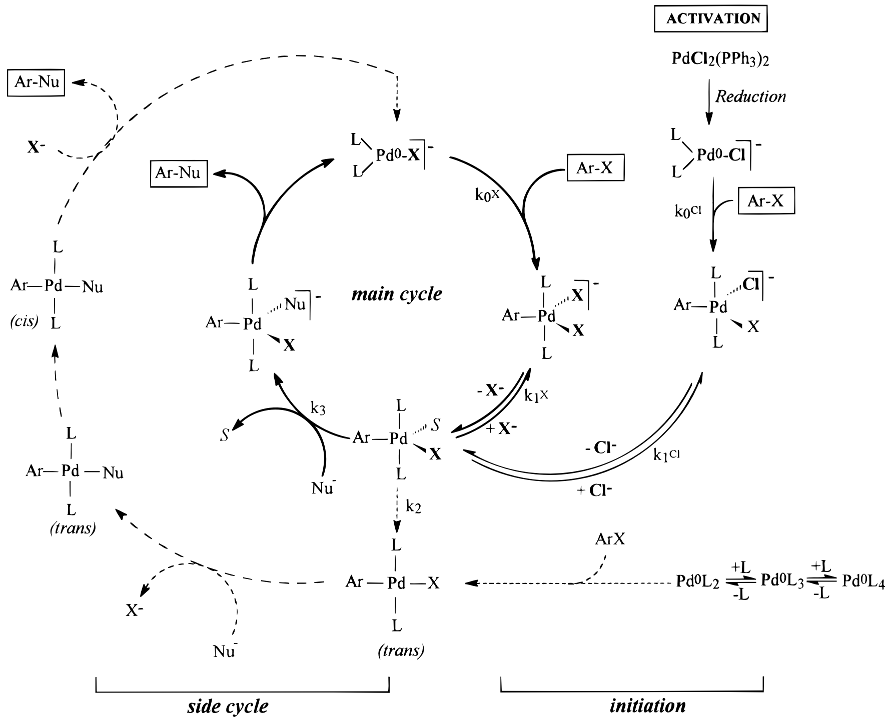
$$\mathrm{ArX} + (\mathrm{m^+Nu^-}) \longrightarrow \mathrm{ArNu} + (\mathrm{m^+X^-}) \tag{11}$$

$$\mathrm{ArX} + \mathrm{m^+} + \mathrm{Nu^-} \longrightarrow \mathrm{ArNu} + (\mathrm{m^+X^-}) \tag{12}$$

$$\mathrm{ArX} + (\mathrm{m^+Nu^-}) \longrightarrow \mathrm{ArNu} + \mathrm{m^+} + \mathrm{X^-} \tag{13}$$

$$\mathrm{ArX} + \mathrm{m^+} + \mathrm{Nu^-} \longrightarrow \mathrm{ArNu} + \mathrm{m^+} + \mathrm{X^-} \tag{14}$$

Scheme 7. New Mechanism for Palladium-Catalyzed Cross-Coupling Reactions



Because of these four possibilities, the metal cation m nature plays a crucial role in the overall mechanism by controlling a possible competition between the main cycle in Scheme 7 and the classical mechanism in Scheme 2. When halide ions are ion-paired (m^+X^-) (eqs 11 and 12), their free concentration does not increase during the conversion of ArX, and no anionic complexes are formed. Whenever free halide ions are not purposely added (e.g., R_4N^+, X^-), the mechanism of Scheme 7 (main cycle) cannot develop, so the cross-coupling reaction presumably proceeds through Scheme 2. Conversely, when halide ions are free (eqs 13 and 14, or free halide ions added), $Pd^0L_2X^-$ and $ArPdX(X)L_2^-$ are formed, so the main cycle of Scheme 7 is expected to dominate. However, the situation is not so simple because Schemes 2 and 7 are interconnected at the level of the intermediate ArPdX(*S*)-L$_2$. The probability of remaining within the main cycle of Scheme 7 is $k_3[Nu^-]/(k_2 + k_3[Nu^-])$. This probability decreases with the conversion since Nu^- is consumed, so Scheme 2 may become increasingly important. However, when halide ions are free (eqs 13 and 14), Scheme 2 is reconnected to Scheme 7 via the formation of $Pd^0L_2X^-$ (left side of Scheme 7), so a new cycle progressively develops (half right part of the "main cycle", left side cycle) at the expense of the initial "main cycle" of Scheme 7. The same situation occurs when the catalysis is initiated by Pd^0L_4 complexes (Scheme 7, bottom).

The ion-paired or free-ion nature of the nucleophile is also crucial in the selection of mechanisms. When nucleophiles are ion-paired, the rate of the nucleophilic attack on ArPdX(*S*)L$_2$ is affected by the metal cation nature because this plays on the value of k_3 and on $[Nu^-]$, so the deviation through the left side cycle is favored. Conversely, when the nucleophile is a free anion (eqs 12 and 14), the metal cation has no influence at all except through that described above, which relates to the availability of free halide ions.

Therefore, the mechanisms in Schemes 2 and 7 are finely tuned by the ion-pairing equilibria involving halide anions and metal cations that are released while the reaction proceeds.

Conclusion

This Account evidences the critical role of anions, halides, and acetate brought by the precursors of palladium(0) used in catalytic Heck and cross-coupling reactions or by aryl halides when the catalytic reaction proceeds. Indeed, Pd^0L_2, postulated as the common catalyst in both catalytic systems, is not formed as a main intermediate. Instead, previously unsuspected reactive anionic species are produced in which the palladium(0) is ligated by a halide ($Pd^0L_2X^-$) or by an acetate ion ($Pd^0L_2(OAc)^-$). The rate of their oxidative addition to aryl halides depends strongly on the anion ligated to the palladium(0) and is respectively accelerated by cations (which destabilize $Pd^0L_2X^-$ by ion-pairing) or by protons (which destabilize $Pd^0L_2(OAc)^-$ by acido-basic reaction). The influence of the anion is not limited to oxidative addition kinetics since the structure and reactivity of the arylpalladium(II) formed in the oxidative addition strongly depend on the anion ligated to the reacting palladium(0). Postulated *trans*-$ArPdI(PPh_3)_2$ complexes are not produced as main intermediates, but instead previously unsuspected complexes are formed: pentacoordinated anionic complexes $ArPdI(Cl)(PPh_3)_2^-$ and $ArPdI(OAc)(PPh_3)_2^-$, and neutral complexes ArPd-(OAc)(PPh$_3$)$_2$, in which the anion ligated to the palladium-(0) remains ligated to the arylpalladium(II) and conditions their intrinsic stability and reactivity with nucleophiles.

The existence of these previously unsuspected intermediates rules out most textbook mechanisms and suggests new catalytic cycles to be considered. They rationalize several empirical findings reported in the literature, concerning reactivity and selectivity which cannot be accounted for by usual mechanisms. They also illustrate the danger of deriving mechanistic information from stoichiometric reactions involving isolated stable complexes expected to be intermediates, without taking into account their real chemical environment in the true catalytic system.[17]

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