

## Dual role of nucleophiles in palladium-catalyzed Heck, Stille, and Sonogashira reactions\*

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**Abstract:** In palladium-catalyzed Heck, Stille, or Sonogashira reactions, the nucleophiles—respectively, alkenes, vinylstannanes or alkynes—are involved in carbopalladation or transmetallation steps that follow the oxidative addition of an aryl halide or triflate to a Pd<sup>0</sup> complex. As soon as the nucleophiles possess a C=C or a C≡C bond capable of coordinating the Pd<sup>0</sup> complex active in the oxidative addition, they play a dual role since they interfere in the oxidative addition by a decelerating effect due to a partial coordination of the active Pd<sup>0</sup> complex. Indeed, its concentration decreases due to the formation of either unreactive complexes ( $\eta^2\text{-RCH=CH}_2$ )Pd<sup>0</sup>L<sub>2</sub> (R = Ph, CO<sub>2</sub>Et, L = PPh<sub>3</sub>; R = Bu<sub>3</sub>Sn, L = AsPh<sub>3</sub>), ( $\eta^2\text{-RCH=CH}_2$ )Pd<sup>0</sup>L<sub>2</sub>(OAc)<sup>−</sup> (R = Ph, L = PPh<sub>3</sub>), ( $\eta^2\text{-R-C}\equiv\text{CH}$ )Pd<sup>0</sup>L<sub>2</sub> (R = Ph, L = PPh<sub>3</sub>) or more slowly reactive complexes ( $\eta^2\text{-R-C}\equiv\text{CH}$ )Pd<sup>0</sup>L<sub>2</sub> (R = CO<sub>2</sub>Et, L = PPh<sub>3</sub>), ( $\eta^2\text{-RCH=CH}_2$ )Pd<sup>0</sup>L<sub>2</sub> (R = CO<sub>2</sub>Me, L<sub>2</sub> = dppf). Whenever the oxidative addition is faster than the ensuing carbopalladation or transmetallation, the decelerating effect of the nucleophiles in the oxidative addition is in favor of a better efficiency for the catalytic cycle by bringing the rate of the fast oxidative addition closer to that of the slow carbopalladation or transmetallation steps.

### INTRODUCTION

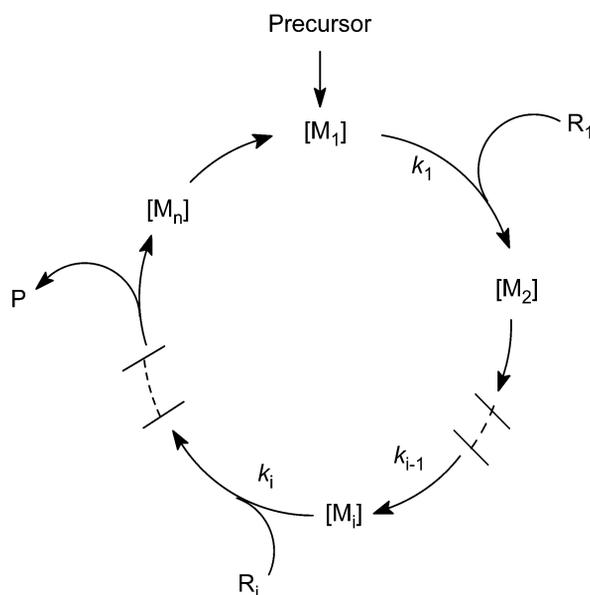
Transition metal-catalyzed reactions involve catalytic cycles which are a succession of elemental steps in which the metal is present as different catalytic species (Scheme 1). When taken independently, each elemental step has its own reaction rate. However, when these elemental steps are involved in a catalytic cycle and when the stationary regime of the catalytic cycle is reached, all steps have the same rate. Indeed, the rate of the elemental chemical step *i* (Scheme 1) is:  $v_i = k_i[R_i][M_i]$ , i.e., the product of its rate constant  $k_i$ , the reagent R<sub>*i*</sub> concentration (whenever R<sub>*i*</sub> is involved in the considered elemental step) and the concentration of the reactive species [M<sub>*i*</sub>]. But the concentration of this latter is modulated, controlled by the rate of the previous reaction (*i*−1) in which it is generated (Scheme 1) [1].

The stationary regime of the catalytic cycle will be then more easily reached if the intrinsic reaction rates of all elemental steps are close as possible to each other. In other words, to increase the efficiency of a catalytic cycle one must: (i) accelerate the rate-determining step (i.e., destabilize stable intermediate complexes) and (ii) decelerate the fast reactions by stabilizing high-energy species [1].

This concept is illustrated by the dual role of nucleophiles in palladium-catalyzed Heck [2–5], Stille [6,7], and Sonogashira [8] reactions. Indeed, the nucleophiles are not only involved in the rate-determining step of the catalytic cycle (carbopalladation or transmetallation) but interfere in the often

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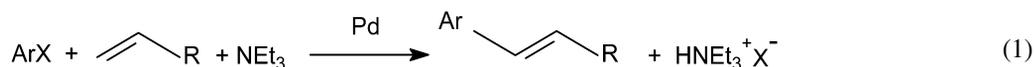
Scheme 1

fast oxidative addition (which precedes the rate-determining step) by a decelerating effect due to their coordination to the  $\text{Pd}^0$  species active in the oxidative addition.

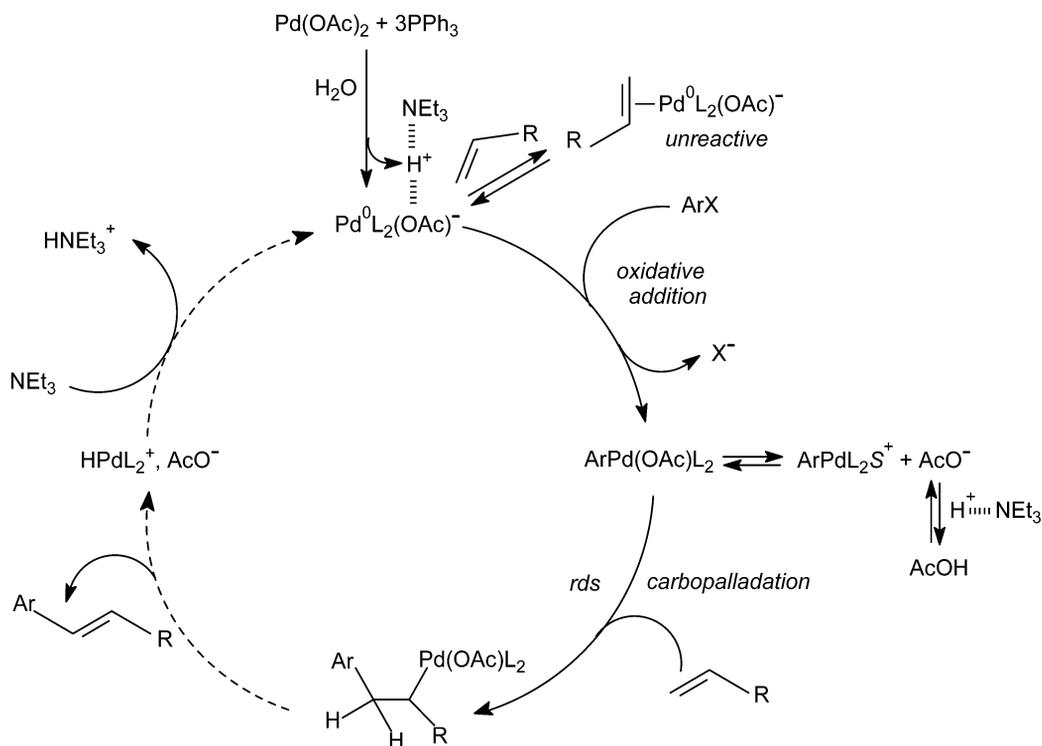
## THE DUAL ROLE OF NUCLEOPHILES IN PALLADIUM-CATALYZED HECK REACTIONS

### Monodentate ligand

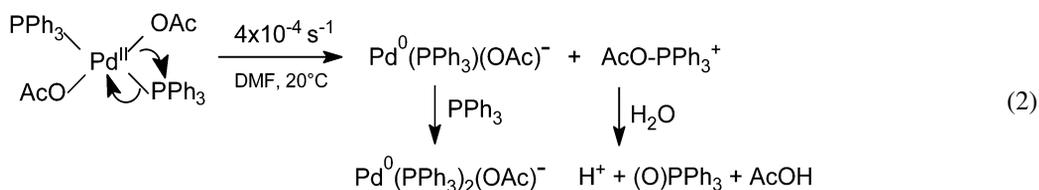
The mechanism of the Heck reaction (eq. 1) [2–5], when the catalytic precursor is  $\text{Pd}(\text{OAc})_2$  associated with  $n\text{PPh}_3$  ( $n \geq 3$  equiv), is given in Scheme 2 [9–12]. Before we examine the dual role of the nucleophile, it is worthwhile to recall the dual role of the base (e.g.,  $\text{NEt}_3$ ), which illustrates the concept exposed in the introduction. Indeed, in DMF at 25 °C, in the presence of the base: (i) the oxidative addition is slower (e.g., for  $\text{PhI}$ :  $k = 140 \text{ M}^{-1}\text{s}^{-1}$  vs.  $65 \text{ M}^{-1}\text{s}^{-1}$  in the presence of 3 equiv  $\text{NEt}_3$  [11]) and (ii) the carbopalladation step is faster (e.g., for  $\text{PhCH}=\text{CH}_2$ ,  $k = 8.5 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$  vs.  $1.7 \times 10^{-4} \text{ M}^{-1}\text{s}^{-1}$  in the presence of 3 equiv  $\text{NEt}_3$  [11]). This dual effect is rationalized as followed [12]. Protons are generated together with the  $\text{Pd}^0$  complex through the hydrolysis of the phosphonium salt formed in the intramolecular reduction of  $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$  by the phosphine (eq. 2) [9]. Interaction of the protons with the acetate ion of the reactive  $\text{Pd}^0\text{L}_2(\text{OAc})^-$  would result in the formation of the high-energy  $\text{Pd}^0\text{L}_2$  species. By neutralizing these protons, the contribution of the base is the stabilization of the very reactive  $\text{Pd}^0\text{L}_2$  under the less reactive anionic form  $\text{Pd}^0\text{L}_2(\text{OAc})^-$ , resulting then in a slower oxidative addition. Similarly, in the carbopalladation step, neutralization of protons by the base results in a shift of the equilibrium between  $\text{PhPd}(\text{OAc})(\text{PPh}_3)_2$  and  $\text{PhPd}(\text{PPh}_3)_2(\text{DMF})^+$  (Scheme 1) toward  $\text{PhPd}(\text{OAc})(\text{PPh}_3)_2$ , the most reactive complex in the slow carbopalladation step.



In the presence of the base, the fast oxidative addition (when performed from aryl iodides or activated aryl bromides) is slower and the slow carbopalladation step with the alkene is faster. Both effects favor the efficiency of the catalytic reaction by bringing the rate of the oxidative addition and that of the carbopalladation closer to each other.

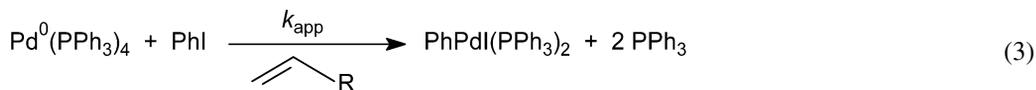


Scheme 2

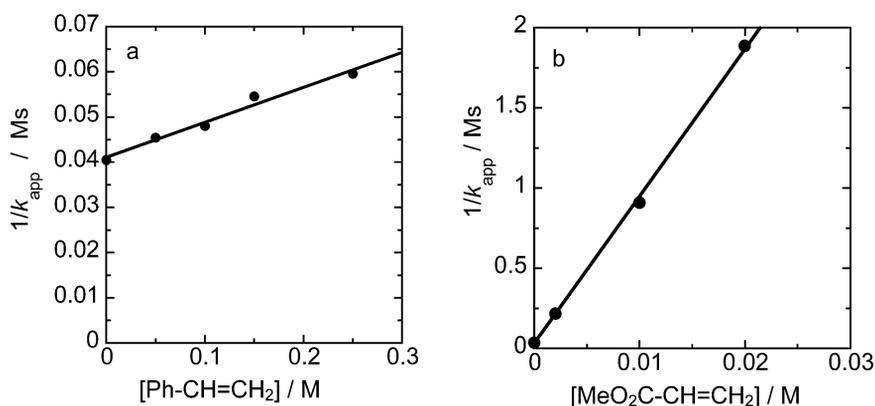


Since Pd<sup>0</sup> complexes ligated by alkenes (dba [13–15], norbornene [16], ethylene [16,17], diethyl fumarate [18], etc.), are well known, it was of interest to investigate whether the alkenes involved as reagents in Heck reactions [2–5] would coordinate the active Pd<sup>0</sup> complex and consequently would interfere in the kinetics of the oxidative addition.

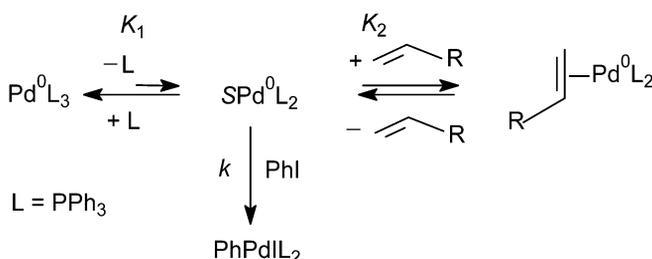
A decelerating effect of alkenes RCH=CH<sub>2</sub> (R = Ph, CO<sub>2</sub>Me) was first observed in the oxidative addition of PhI to Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>4</sub> in DMF (eq. 3) [19].



The oxidative addition is slower and slower when performed in the presence of increasing amounts of styrene. This decelerating effect is more pronounced for methyl acrylate. The rate constant  $k_{\text{app}}$  is inversely proportional to the styrene or methyl acrylate concentration (Figs. 1a,b). This suggests that the concentration of the reactive Pd<sup>0</sup>L<sub>2</sub> complex [20] decreases due to its complexation by the alkene to form unreactive complexes ( $\eta^2\text{-RCH=CH}_2$ )Pd<sup>0</sup>L<sub>2</sub> (R = Ph, CO<sub>2</sub>Me). This is in agreement with the mechanism reported in Scheme 3 and with the ensuing expression of  $k_{\text{app}}$  (eq. 4) [19].



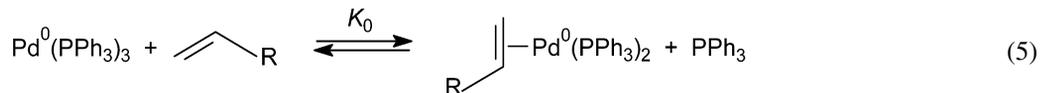
**Fig. 1** Oxidative addition of PhI to  $\text{Pd}^0(\text{PPh}_3)_4$  in DMF at 25 °C in the presence of an alkene. Plot of  $1/k_{\text{app}}$  vs.: (a) the styrene concentration (eq. 4); (b) the methyl acrylate concentration (eq. 4).



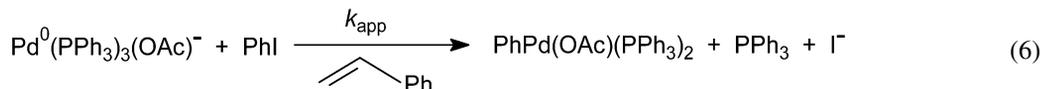
**Scheme 3**

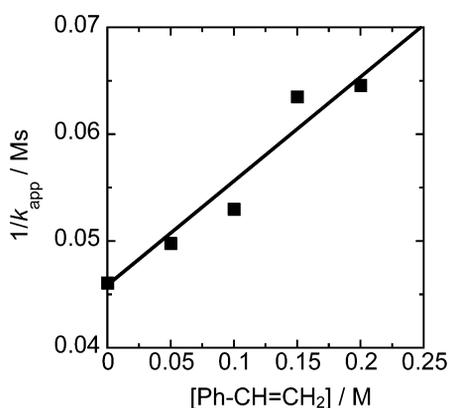
$$\frac{1}{k_{\text{app}}} = \frac{[\text{L}]}{kK_1} + \frac{K_2[\text{RCH}=\text{CH}_2]}{k} \quad (4)$$

The value of  $K_0 = K_1K_2$  of the overall equilibrium in eq. 5 is calculated from the slope and intercept of the straight lines in Fig. 1a for styrene ( $K_0 = 4.8 \times 10^{-3}$ ) and in Fig. 1b for methyl acrylate ( $K_0 = 7.5$ ) in DMF at 25 °C. As expected, the affinity of the electron-deficient methyl acrylate for the electron-rich  $\text{Pd}^0\text{L}_2$  is higher than that of styrene. The ratio of their respective equilibrium constant  $K_2$  is provided by the ratio of their respective equilibrium constant  $K_0$  and is equal to 1560, in favor of the complexation by the methyl acrylate. This explains why, for identical concentration of styrene and methyl acrylate, the observed decelerating effect on the oxidative addition is much more important for methyl acrylate than for styrene (Figs. 1a,b).



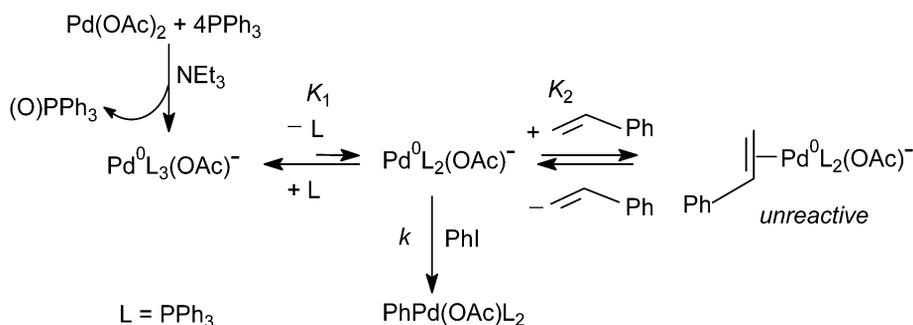
The decelerating effect of an alkene (styrene) on the rate of the oxidative addition of PhI to the  $\text{Pd}^0$  complexes generated from  $\text{Pd}(\text{OAc})_2$  and 4 equiv  $\text{PPh}_3$  is also observed (eq. 6, Fig. 2) [19]. The kinetics are performed in the presence of a base ( $\text{NET}_3$ , 3 equiv) to avoid any interference of protons (vide supra).





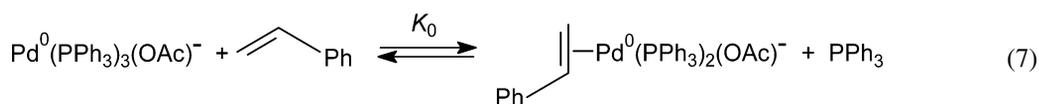
**Fig. 2** Oxidative addition of PhI to  $\text{Pd}^0(\text{PPh}_3)_3(\text{OAc})^-$  generated from  $\text{Pd}(\text{OAc})_2$  (2 mM) and  $\text{PPh}_3$  (10 mM) in DMF at 25 °C in the presence of styrene and  $\text{NEt}_3$  (6 mM). Plot of  $1/k_{\text{app}}$  vs. the styrene concentration (eq. 4).

The reciprocal of the apparent rate constant  $k_{\text{app}}$  varies linearly with the styrene concentration (Fig. 2, eq. 4), as observed for  $\text{Pd}^0(\text{PPh}_3)_4$ . This establishes that the anionic complex  $\text{Pd}^0(\text{PPh}_3)_2(\text{OAc})^-$ —generated from  $\text{Pd}^0(\text{PPh}_3)_3(\text{OAc})^-$ —which is the reactive species in the absence of any styrene [11,12] also coordinates the styrene to generate the unreactive complex  $(\eta^2\text{-PhCH=CH}_2)\text{Pd}^0(\text{PPh}_3)_2(\text{OAc})^-$  (Scheme 4), which results in a slower oxidative addition.



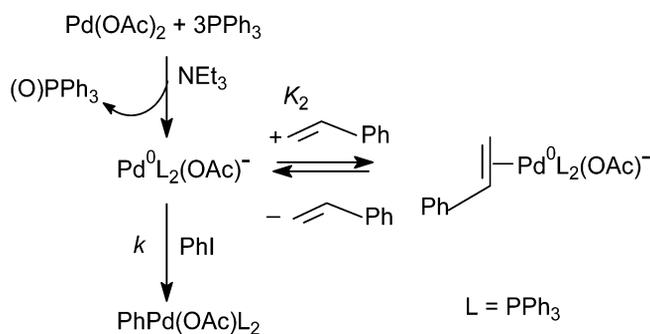
**Scheme 4**

The equilibrium constant  $K_0$  in eq. 7 is calculated from the slope and intercept of the straight line in Fig. 2:  $K_0 = 5.5 \times 10^{-3}$  (DMF, 25 °C).



Since the value of  $K_1$  ( $9 \times 10^{-4}$  M) is known from an earlier work [12], the value of the equilibrium constant  $K_2$  (Scheme 4) can be determined:  $K_2 = 61 \text{ M}^{-1}$  (DMF, 25 °C).

When the catalytic precursor of a Heck reaction is  $\text{Pd}(\text{OAc})_2$  associated with 3 equiv  $\text{PPh}_3$ , the active species is  $\text{Pd}^0(\text{PPh}_3)_2(\text{OAc})^-$ , generated in stoichiometric amount (Scheme 5) [11]. In the presence of styrene, the mechanism of the oxidative addition to PhI involves then the only right part of Scheme 4, as now expressed in Scheme 5, in which the values of  $k$  and  $K_2$  are known. If the concentration in styrene is 100 times higher than the  $\text{Pd}^0$  concentration, which is usual in catalytic reactions, then the oxidative addition of PhI is 13 times slower.



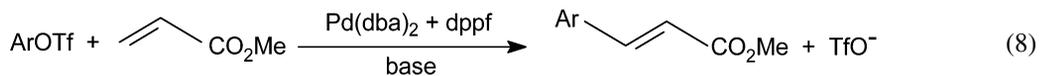
Scheme 5

Consequently, in Heck reactions when the catalytic precursor is  $\text{Pd}(\text{OAc})_2$  associated with  $\text{PPh}_3$ , the alkene play a dual role. Indeed, increasing the alkene concentration results in: (i) a slower oxidative addition because part of the active  $\text{Pd}^0$  complex is stocked under an unreactive form  $(\eta^2\text{-RCH=CH}_2)\text{Pd}^0(\text{PPh}_3)_2(\text{OAc})^-$  and (ii) a faster carbopalladation (usual effect of concentration in the kinetics of the reaction), as illustrated in Scheme 1.

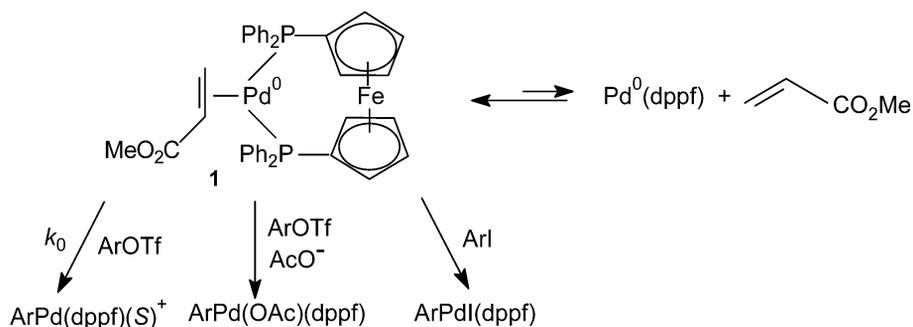
The base and the alkene play then the same dual role in Heck reactions: deceleration of the oxidative addition and acceleration of the slow carbopalladation step. Whenever the oxidative addition is fast (e.g., with aryl iodides or activated aryl bromides), this dual effect will increase the efficiency of the catalytic reaction.

### Bidentate ligand

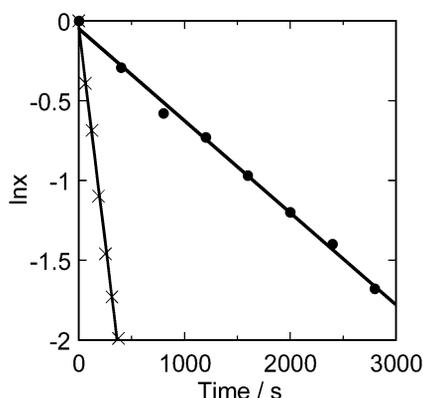
In the course of a Heck reaction between aryl triflates and methyl acrylate with the catalytic precursor consisting of  $\text{Pd}(\text{dba})_2$  and dppf (eq. 8), a new  $\text{Pd}^0$  complex was isolated:  $(\eta^2\text{-MeO}_2\text{C-CH=CH}_2)\text{Pd}^0(\text{dppf})$  **1** [21], instead of the usual  $(\eta^2\text{-dba})\text{Pd}^0(\text{dppf})$  [15].



The contribution of complex **1** in the oxidative addition of  $\text{PhI}$  or  $\text{PhOTf}$  is investigated in THF. It is found to be the unique complex involved in the oxidative addition since no decelerating effect of the methyl acrylate concentration is observed in the kinetics (Scheme 6) [21]. In that case, the concentration of the more reactive complex  $\text{Pd}^0(\text{dppf})$  [15] is maintained very low due to its strong complexation with the methyl acrylate. The rate constant of the oxidative addition  $k_0$  was determined for  $\text{PhI}$  ( $0.0058 \text{ M}^{-1}\text{s}^{-1}$ , Fig. 3) and  $\text{PhOTf}$  ( $0.0011 \text{ M}^{-1}\text{s}^{-1}$ ) in THF at 25 °C [21].



Scheme 6



**Fig. 3** Oxidative addition of PhI (0.1 M) to  $(\eta^2\text{-MeO}_2\text{C-CH=CH}_2)\text{Pd}^0(\text{dppf})$  1 (2 mM) in THF at 25 °C. Variation of  $\ln x$  vs. time (x: molar fraction of 1): (●) in the absence of  $\text{Eu}(\text{OTf})_3$ ,  $\ln x = -k_0[\text{PhI}]t$ ; (×) in the presence of  $\text{Eu}(\text{OTf})_3$  (6 mM).

An acceleration of the oxidative addition by a factor 9 for PhI (Fig. 3) and 8 for PhOTf was observed in the presence of  $\text{Eu}^{3+}$  cations (added as the triflate salt) due to a complexation of the methyl acrylate by the  $\text{Eu}^{3+}$  cations [21]. This results in a shift of the equilibrium in Scheme 6 toward  $\text{Pd}^0(\text{dppf})$ , increasing then the concentration of the more reactive complex.

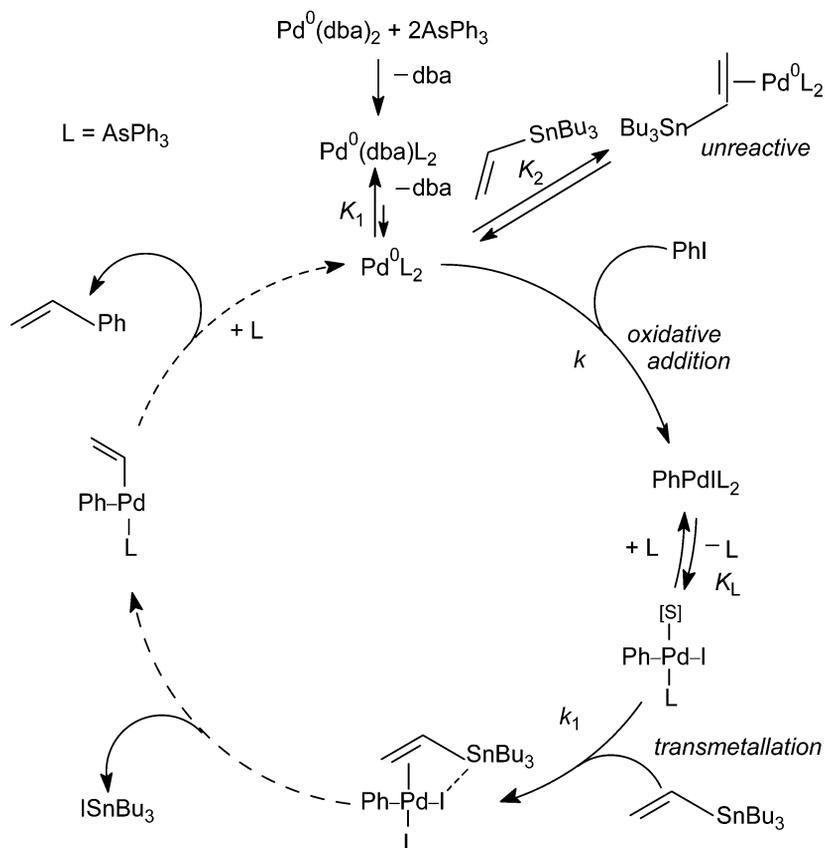
Once again, the alkene of a Heck reaction plays a dual role. Indeed, besides its traditional role in the carbopalladation step, the alkene interferes in the oxidative addition by a decelerating effect due to its complexation to the more reactive  $\text{Pd}^0(\text{dppf})$  complex, which generates a less reactive complex  $(\eta^2\text{-MeO}_2\text{C-CH=CH}_2)\text{Pd}^0(\text{dppf})$ . In that specific case, the oxidative addition may become rate-determining due to the high decelerating effect of the nucleophile.

## THE DUAL ROLE OF NUCLEOPHILES IN PALLADIUM-CATALYZED STILLE REACTIONS

The Stille reaction [6,7] between PhI and the vinyltin derivative  $\text{CH}_2=\text{CH-SnBu}_3$  is catalyzed by  $\text{Pd}^0$  complexes (eq. 9).

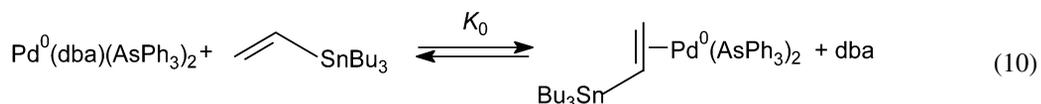


When the catalytic precursor is of  $\text{Pd}^0(\text{dba})_2$  associated to  $\text{AsPh}_3$ , the catalytic reaction is 1000 times faster than with  $\text{PPh}_3$ . The origin of the higher efficiency of  $\text{AsPh}_3$  comes from the rate-determining transmetallation step [22–24] in the course of which one  $\text{AsPh}_3$  of the complex  $\text{PhPdI}(\text{AsPh}_3)_2$  (generated in the fast oxidative addition of PhI [22,25,26]) is substituted by the vinyltin (Scheme 7). The reaction of the nucleophile in the transmetallation step may proceed either after the prior dissociation of one  $\text{AsPh}_3$  in DMF (Scheme 8) [24] or before dissociation when polyfluorinated aryl iodides are considered, in THF [23].



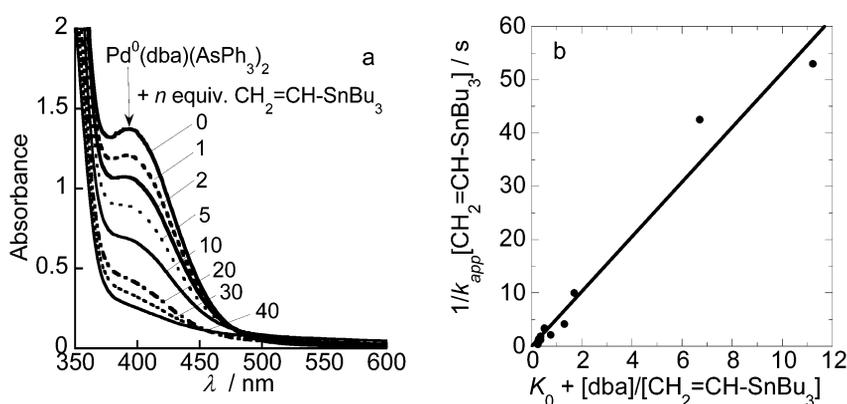
Scheme 7

The mechanism of the fast oxidative addition has been investigated in details and the minor complex Pd<sup>0</sup>(AsPh<sub>3</sub>)<sub>2</sub> is found to be the reactive species in the oxidative addition of PhI, whereas as the major complex Pd<sup>0</sup>(dba)(AsPh<sub>3</sub>)<sub>2</sub> is unreactive [26]. However, in the presence of the nucleophile CH<sub>2</sub>=CH-SnBu<sub>3</sub>, a new complex is formed as evidenced by UV spectroscopy (Fig. 4a), in which the C=C bond of the nucleophile coordinates the Pd<sup>0</sup> complex: ( $\eta^2$ -CH<sub>2</sub>=CH-SnBu<sub>3</sub>)Pd<sup>0</sup>(AsPh<sub>3</sub>)<sub>2</sub> in a reversible reaction (eq. 10) with  $K_0 = 0.21$  in DMF and 0.06 in THF at 25 °C [26].

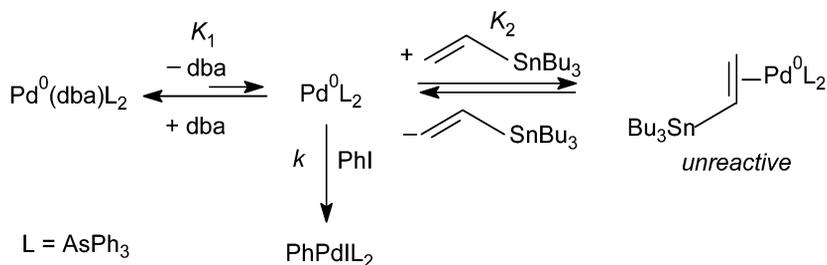


In DMF, at 25 °C, if the concentration of CH<sub>2</sub>=CH-SnBu<sub>3</sub> is 50 times higher than that of Pd<sup>0</sup>(dba)(AsPh<sub>3</sub>)<sub>2</sub>, as in a catalytic reaction, then the concentration of ( $\eta^2$ -CH<sub>2</sub>=CH-SnBu<sub>3</sub>)Pd<sup>0</sup>(AsPh<sub>3</sub>)<sub>2</sub> is 10 times higher than that of Pd<sup>0</sup>(dba)(AsPh<sub>3</sub>)<sub>2</sub>, which becomes thus the minor complex.

A decelerating effect is observed when the oxidative addition is performed in the presence of the nucleophile CH<sub>2</sub>=CH-SnBu<sub>3</sub> (Fig. 4b) with a reaction order of -1 for the nucleophile [26]. The mechanism of the oxidative addition in the presence of the vinyltin is given in Scheme 8. Pd<sup>0</sup>(AsPh<sub>3</sub>)<sub>2</sub> remains the active species but its concentration decreases due to its partial coordination by the vinyltin to form the unreactive complex ( $\eta^2$ -CH<sub>2</sub>=CH-SnBu<sub>3</sub>)Pd<sup>0</sup>(AsPh<sub>3</sub>)<sub>2</sub>.



**Fig. 4** (a) UV spectrum of a solution of  $\text{Pd}^0(\text{dba})_2$  (1 mM) and  $\text{AsPh}_3$  (2 mM) in DMF at 20 °C in a 1-mm path cell in the presence of  $n$  equiv of  $\text{CH}_2=\text{CH-SnBu}_3$ . (b) Oxidative addition of  $\text{PhI}$  to the  $\text{Pd}^0$  complexes generated from  $\text{Pd}^0(\text{dba})_2$  (1 mM) and  $\text{AsPh}_3$  (2 mM) in the presence of various amounts of  $\text{CH}_2=\text{CH-SnBu}_3$  and in the absence or presence of added  $\text{dba}$  (8 mM) in DMF at 20 °C. Plot of  $1/k_{\text{app}}[\text{CH}_2=\text{CH-SnBu}_3]$  vs.  $K_0 + [\text{dba}]/[\text{CH}_2=\text{CH-SnBu}_3]$ .



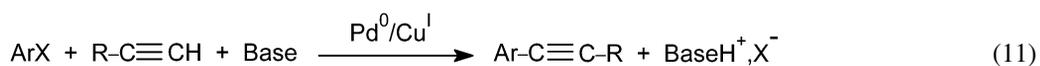
**Scheme 8**

As in Heck reactions, the nucleophile of the Stille reaction plays a dual role since it is involved both in the slow transmetalation step and in the fast oxidative addition with  $\text{PhI}$ , which is then slowed down. This dual effect is in favor of a better efficiency for the catalytic reaction. Such decelerating effect established for  $\text{AsPh}_3$  is dramatically less pronounced for  $\text{PPh}_3$  ( $K_0 = 10^{-4}$  in THF at 28 °C) [26].

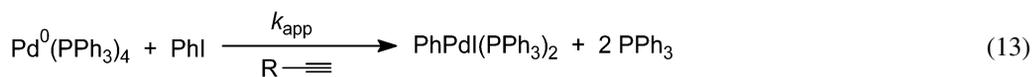
It is worthwhile to note that at least three factors play in favor of a low concentration of the active  $\text{Pd}^0$  complex and consequently slow down the oxidative addition: (i) the ligand  $\text{dba}$ , which stocks part of the  $\text{Pd}^0$  as the stable and unreactive  $\text{Pd}^0(\text{dba})(\text{AsPh}_3)_2$ ; (ii) the nucleophile, which stocks part of the  $\text{Pd}^0$  as the stable and unreactive  $(\eta^2\text{-CH}_2=\text{CH-SnBu}_3)\text{Pd}^0(\text{AsPh}_3)_2$ ; and (iii) probably the product of the Stille reaction (presently the styrene) capable of coordinating the  $\text{Pd}^0$  complex (Scheme 7).

## THE DUAL ROLE OF NUCLEOPHILES IN PALLADIUM-CATALYZED SONGASHIRA REACTIONS

The palladium-catalyzed Sonogashira reactions concern terminal alkynes (eq. 11) [8]. Although the mechanism is not yet clearly established, the alkynes are supposed to be involved in a transmetalation step via an alkynyl-copper generated in situ when a Cu cocatalyst is required (eq. 12) [8].

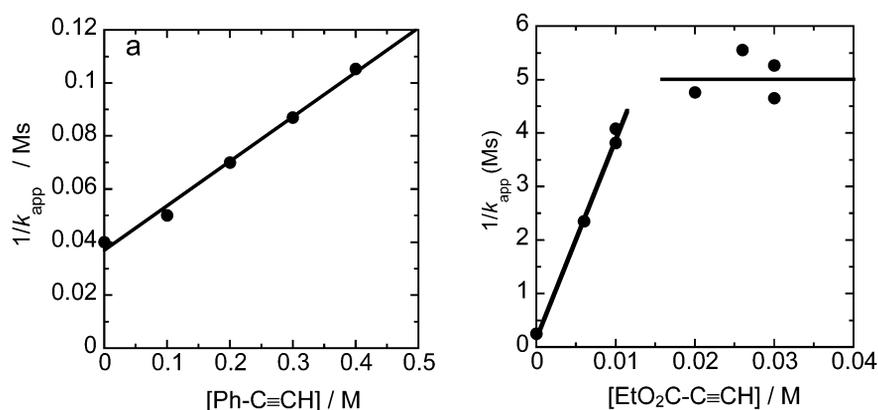


The oxidative of PhI to  $\text{Pd}^0(\text{PPh}_3)_4$  is slower when performed in the presence of terminal alkynes  $\text{RC}\equiv\text{CH}$  ( $\text{R} = \text{Ph}, \text{CO}_2\text{Et}$ ) in DMF (eq. 13) [27].

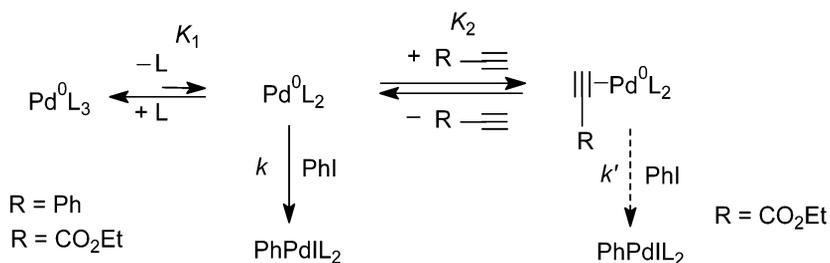


The rate constant of the overall reaction  $k_{\text{app}}$  is inversely proportional to the phenylacetylene concentration (Fig. 5a). Consequently, part of the active  $\text{Pd}^0$  complex is coordinated to  $\text{PhC}\equiv\text{CH}$  to generate the unreactive complex  $(\eta^2\text{-PhC}\equiv\text{CH})\text{Pd}^0(\text{PPh}_3)_2$  (Scheme 9 with  $\text{R} = \text{Ph}$ ) in agreement with eq. 14.

$$\frac{1}{k_{\text{app}}} = \frac{[\text{L}]}{kK_1} + \frac{K_2[\text{RC}\equiv\text{CH}]}{k} \quad (14)$$

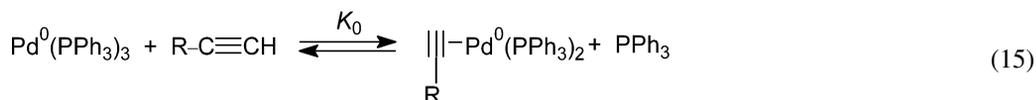


**Fig. 5** Oxidative addition of PhI to  $\text{Pd}^0(\text{PPh}_3)_4$  (2 mM) in DMF at 25 °C in the presence of an alkyne. Plot of  $1/k_{\text{app}}$  vs. (a) the phenylacetylene concentration (eq. 14); (b) the ethyl propiolate concentration (eqs. 16,17). The kinetics is investigated in the presence of excess  $\text{PPh}_3$  (20 mM).



**Scheme 9**

The equilibrium constant of the overall equilibrium in eq. 15 is then calculated from eq. 14 using the slope and intercept of the straight line in Fig. 5a. For  $\text{PhC}\equiv\text{CH}$ :  $K_0 = 0.012$  (DMF, 25 °C) [27].



The situation changes when considering the ethyl propiolate. Indeed, as shown in Fig. 5b, the oxidative addition is slower and slower when the ethyl propiolate concentration increases. However, at

high concentrations the rate of the oxidative addition does not depend on the ethyl propiolate concentration. This means that at high ethyl propiolate concentrations, the equilibrium in eq. 15 is completely shifted towards its right-hand side. The concentration of the active  $\text{Pd}^0(\text{PPh}_3)_2$  complex is then very low, and the only reactive complex is the poor reactive complex  $(\eta^2\text{-EtO}_2\text{C-C}\equiv\text{CH})\text{Pd}^0(\text{PPh}_3)_2$  with the rate constant  $k'$  (Scheme 10, R =  $\text{CO}_2\text{Et}$ ). The new expression of the rate constant  $k_{\text{app}}$  of the overall reaction is given in eq. 16.

$$\frac{1}{k_{\text{app}}} = \frac{[\text{L}]/K_1 + K_2[\text{RC}\equiv\text{CH}]}{k + k'K_2[\text{RC}\equiv\text{CH}]} \quad (16)$$

At high  $\text{EtO}_2\text{C-C}\equiv\text{CH}$  concentrations ( $> 0.02$  M), it simplifies into eq. 17, which allows the determination of  $k' = 0.2 \text{ M}^{-1}\text{s}^{-1}$  (Fig. 5b). At low concentrations ( $< 0.01$  M), eq. 16 simplifies into eq. 14, which allows the determination of  $K_0 = 29$  (DMF,  $25^\circ\text{C}$ ) [27]. The affinity of  $\text{EtO}_2\text{C-C}\equiv\text{CH}$  for  $\text{Pd}^0(\text{PPh}_3)_2$  (expressed by  $K_2$ ) is then 2400 times higher than that of  $\text{PhC}\equiv\text{CH}$ . The reactivity of  $(\eta^2\text{-PhC}\equiv\text{CH})\text{Pd}^0(\text{PPh}_3)_2$  in the oxidative addition was not observed for the investigated range of  $\text{PhC}\equiv\text{CH}$  concentrations ( $< 0.4$  M). However, the contribution of  $(\eta^2\text{-PhC}\equiv\text{CH})\text{Pd}^0(\text{PPh}_3)_2$  as reactive complex in the oxidative addition cannot be excluded for much higher concentrations ( $>> 0.4$  M).

$$\frac{1}{k_{\text{app}}} = \frac{1}{k'} \quad (17)$$

## CONCLUSION

Whatever the palladium-catalyzed Heck, Stille, or Sonogashira reactions, the nucleophiles containing a  $\text{C}=\text{C}$  or  $\text{C}\equiv\text{C}$  bond coordinate the  $\text{Pd}^0$  complex active in the oxidative addition with aryl halides or triflates. As a consequence, the oxidative addition is slower when performed in the presence of the nucleophiles, a situation encountered in catalytic reactions. Whenever the oxidative addition is fast (with aryl iodides, activated aryl bromides, or triflates) compared to the slow carbopalladation or transmetallation steps, the decelerating effect in the oxidative addition due to the nucleophile favors the efficiency of the catalytic reaction by bringing the two rates closer to each other. The stationary regime of the catalytic cycle is then more easily attained. However, whenever the oxidative addition (e.g., of aryl chlorides) is slower than the carbopalladation or transmetallation steps and is consequently the rate-determining step of the catalytic cycle, it will be even slower in the presence of the nucleophile and the catalytic reaction will be then less efficient. Any techniques which allow maintaining a low concentration of the nucleophiles (very slow addition, syringe pump, etc.) would then be beneficial for the efficiency of the catalytic reaction.

This work illustrates the necessity to investigate the mechanism of any elemental step in the context of the real catalytic reaction. As far as the oxidative addition is concerned, its rate and mechanism must be investigated in the presence of all compounds able to coordinate the active  $\text{Pd}^0$  complex, (i) the nucleophile, (ii) dba or acetate ions delivered by the catalytic precursor, and (iii) the product of the catalytic reaction. In the latter situation, the strong complexation of the active  $\text{Pd}^0$  complex by the reaction product when it is highly unsaturated may explain why some catalytic reactions stop before total conversion of the reagents.

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