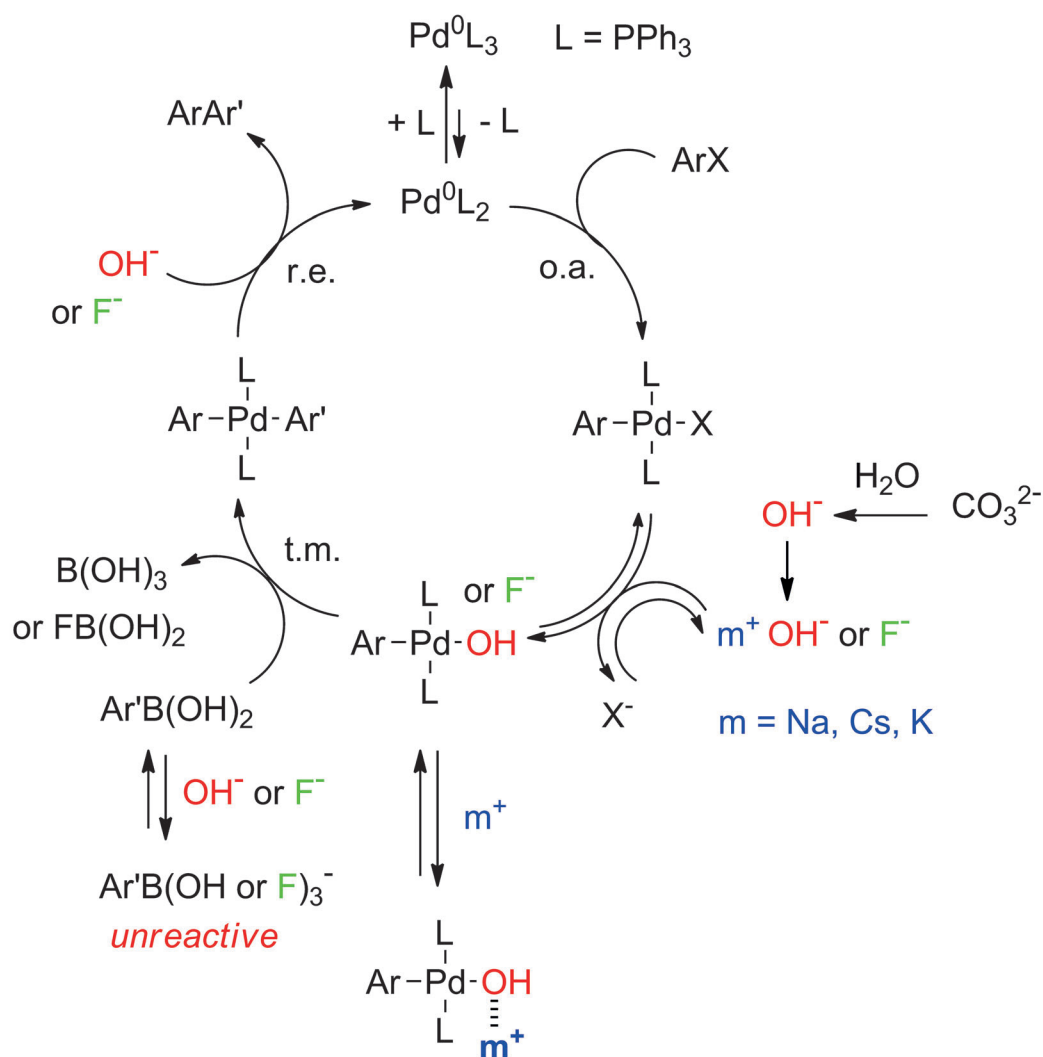


# Mechanism of Palladium-Catalyzed Suzuki–Miyaura Reactions: Multiple and Antagonistic Roles of Anionic “Bases” and Their Counteranions

**Christian Amatore,\* Gaëtan Le Duc, and Anny Jutand\*<sup>[a]</sup>**

*In honour of Professor Irina Beletskaya's birthday and in recognition of her seminal and continuous contributions to organometallic catalysis*



Four kinetically antagonistic roles for the "base" ( $\text{OH}^-$ ,  $\text{F}^-$ ,  $\text{CO}_3^{2-}$ ) and its counter cation  $\text{m}^+$

Rate of the rds transmetallation controlled by the ratio:

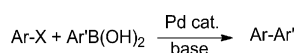
$$\frac{[\text{OH}^-] \text{ or } [\text{F}^-]}{[\text{Ar}'\text{B}(\text{OH})_2]}$$

**Abstract:** In Suzuki–Miyaura reactions, anionic bases  $F^-$  and  $OH^-$  (used as is or generated from  $CO_3^{2-}$  in water) play multiple antagonistic roles. Two are positive: 1) formation of *trans*-[Pd(Ar)F(L)<sub>2</sub>] or *trans*-[Pd(Ar)-(L)<sub>2</sub>(OH)] (L = PPh<sub>3</sub>) that react with Ar'B(OH)<sub>2</sub> in the rate-determining step (rds) transmetallation and 2) catalysis of the reductive elimination from intermediate *trans*-[Pd(Ar)(Ar')(L)<sub>2</sub>]. Two roles are negative: 1) formation of unreactive arylborates (or fluoroborates) and 2) complexation of the OH group of [Pd(Ar)(L)<sub>2</sub>(OH)] by the counteraction of the base (Na<sup>+</sup>, Cs<sup>+</sup>, K<sup>+</sup>).

**Keywords:** bases • kinetics • palladium • reaction mechanisms • Suzuki–Miyaura reactions

## Introduction

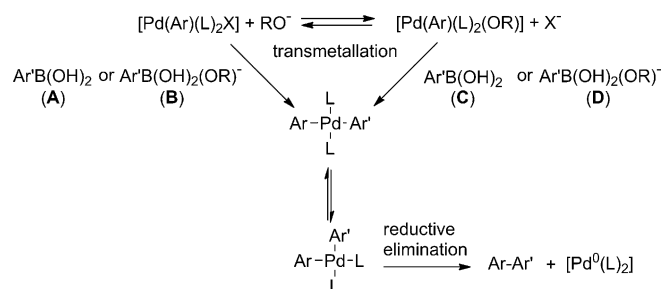
The palladium-catalyzed Suzuki–Miyaura reaction is one of the most efficient reactions for the synthesis of unsymmetrical biaryls Ar–Ar' from aryl halides ArX (X = I, Br, Cl) and arylboronic acids Ar'B(OH)<sub>2</sub> (Scheme 1).<sup>[1–3]</sup> The first re-



Scheme 1. Suzuki–Miyaura reaction.

ported reactions by Suzuki et al. in 1981 insisted on the presence of a base, even if no proton was exchanged.<sup>[2]</sup> This was later on confirmed and various bases have been used: MeO<sup>−</sup>, EtO<sup>−</sup>, OH<sup>−</sup>, CO<sub>3</sub><sup>2−</sup>, and F<sup>−</sup> associated with counteranions, such as Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>, Li<sup>+</sup>, *n*Bu<sub>4</sub>N<sup>+</sup>, Ag<sup>+</sup>, or Tl<sup>+</sup>.<sup>[1–5]</sup>

Such a requirement for a base was intriguing and has led to various mechanistic interpretations. The first hypothesis proposed by Suzuki et al. involved the reaction of alkoxides RO<sup>−</sup> (R = Me, Et) with arylboronic acids to generate anionic arylborates Ar'B(OH)<sub>2</sub>(OR)<sup>−</sup> thought to be more active than Ar'B(OH)<sub>2</sub> in the transmetallation with the complexes [Pd(Ar)(L)<sub>2</sub>X] generated in the oxidative addition of ArX to [Pd<sup>0</sup>(L)<sub>n</sub>] (pathways B and A, respectively, Scheme 2, R = OEt). The same authors have also proposed X/OR exchange in [Pd(Ar)(L)<sub>2</sub>X] to generate [Pd(Ar)(L)<sub>2</sub>(OR)] that would react with Ar'B(OH)<sub>2</sub>(OR)<sup>−</sup> (pathway D in Scheme 2, R = OEt).<sup>[1i,4]</sup> The reaction of [Pd(Ar)(L)<sub>2</sub>X] with Ar'B(OH)<sub>3</sub><sup>−</sup> (generated in the presence of OH<sup>−</sup>) was proposed by Smith et al. as the major reaction (pathway B, R = H).<sup>[5a]</sup> Path-



Scheme 2. Postulated (R = alkyl, H, L = PPh<sub>3</sub>) and computed pathways (R = H, L = PH<sub>3</sub>, PR''<sub>3</sub>) for the mechanism of the Suzuki–Miyaura reaction.

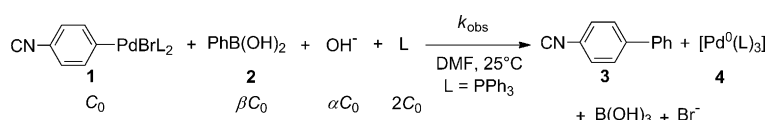
ways B or C were also proposed by Matos and Soderquist in cross-coupling reactions of PhBr with alkylboranes or alkylboronates, respectively, in reactions performed in the presence of NaOH.<sup>[5b]</sup> Indeed, R'B(R<sup>1</sup>)<sub>2</sub>(OH)<sup>−</sup> was formed and reacted with [PdBr(L)<sub>2</sub>(Ph)] (pathway B) whereas R'B-(OR<sup>2</sup>)(R<sup>1</sup>) were found to react with [Pd(OH)(Ph)(PPh<sub>3</sub>)<sub>2</sub>] (pathway C).<sup>[5b]</sup> Later on, DFT calculations were published with OH<sup>−</sup> as the base. Two pathways were computed to be operating for the transmetallation: reaction of [Pd(OH)(L)<sub>2</sub>(Ph)] (L = PH<sub>3</sub>) with PhB(OH)<sub>2</sub> (pathway C, Scheme 2, R = H)<sup>[6a]</sup> or reaction of PhB(OH)<sub>3</sub><sup>−</sup> with [PdBr(Ph)(L)<sub>n</sub>] (n = 1, 2; L = PH<sub>3</sub>, PR''<sub>3</sub>, pathway B).<sup>[6a,b,c]</sup> In all cases, the transmetallation leads to *trans*-[Pd(Ar)-(Ar')(L)<sub>2</sub>] complexes<sup>[7]</sup> that deliver the biaryl Ar–Ar' and [Pd<sup>0</sup>(L)<sub>2</sub>] in the same reductive elimination step. Those steps may become rate-determining when the oxidative addition is fast enough. However, no kinetic data on the transmetallation and reductive elimination were available from the literature, hence impeding definitive conclusions.

This was the state of the art in 2009 when we decided to investigate the mechanism of Suzuki–Miyaura reactions, focussing on the role of the bases in the transmetallation and reductive elimination steps. We report in this review the mechanistic role of anionic bases, such as hydroxides,<sup>[8]</sup> carbonates,<sup>[9]</sup> and fluorides,<sup>[10]</sup> associated with counteranions that do not have any affinity for halide anions in polar solvents, such as sodium, potassium, and cesium.<sup>[9]</sup> Unexpected multiple and antagonistic roles of the anionic bases and their counteranions have been established by kinetic data.<sup>[8–10]</sup>

## Three Antagonistic Roles for Hydroxide Ions

The mechanistic role of hydroxide ions was investigated in reactions of arylboronic acids with isolated *trans*-[Pd(Ar)(L)<sub>2</sub>X] (X = I, Br, or Cl; L = PPh<sub>3</sub>) formed by oxidative addition of ArX to [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>4</sub>],<sup>[11]</sup> a catalyst used in reported catalytic reactions.<sup>[1–5]</sup> Electrochemical techniques have been mainly used to follow the reactions. Indeed, the reagents, intermediates, and products of the reactions have been characterized by their reduction or oxidation potential, whereas the evolution of their concentration in the reaction

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Scheme 3.

has been followed by the evolution with time of their reduction or oxidation current ( $i$ ) always proportional to their concentration  $C_i$  at any time ( $i = AC_i$ ).<sup>[12]</sup>

The mechanism of the reaction in Scheme 3 has been first investigated as a model one.<sup>[8]</sup> Reactions were performed in DMF, often used in catalytic reactions<sup>[1–5]</sup> and in the presence of excess PPh<sub>3</sub> (2 equiv) to observe the formation of a stable [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>].<sup>[13]</sup> Hydroxide ion was associated to the innocent counteranion  $n\text{Bu}_4\text{N}^+$  to minimize the possible cation influence (vide infra).<sup>[8]</sup>

Complex **1** was characterized by its reduction peak  $R_1$  (Figure 1a) with a reduction peak current proportional to its initial concentration  $C_0$  (1.9 mM). Addition of a large excess of PhB(OH)<sub>2</sub> **2** (up to  $\beta=30$  equiv) to model real catalytic conditions (low catalyst concentration and much higher reagent concentration) did not modify the reduction peak current of **1** even at long times, providing evidence that no reaction took place between **1** and **2** at 25°C. It is only after

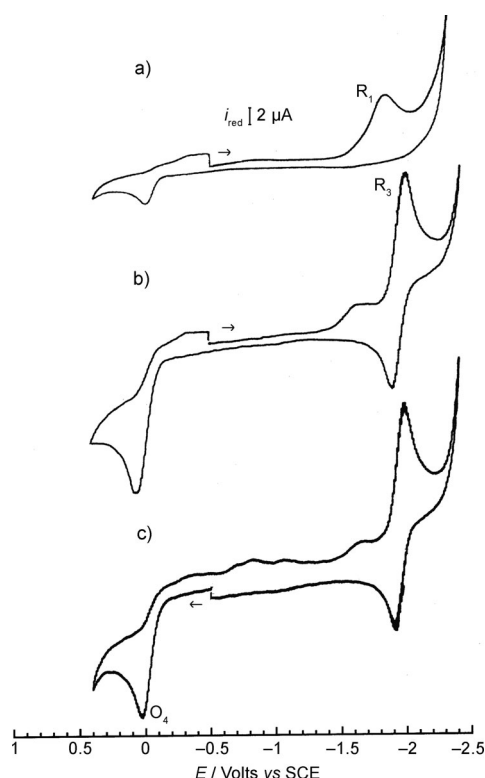


Figure 1. Cyclic voltammetry performed at a gold disk electrode ( $d=1$  mm) in DMF containing  $n\text{Bu}_4\text{NBF}_4$  (0.3 M) with a scan rate of  $0.5 \text{ V s}^{-1}$ , at 25°C, in the presence of PPh<sub>3</sub> (3.8 mM). a) Reduction at  $R_1$  of  $\text{trans}[\text{PdBr}(p\text{-CN-C}_6\text{H}_4)(\text{PPh}_3)_2]$  (**1**;  $C_0=1.9$  mM). b) Reduction at  $R_3$  of  $p\text{-CN-C}_6\text{H}_4\text{-Ph}$  (**3**) formed by addition of PhB(OH)<sub>2</sub> **2** (20 equiv) to **1** ( $C_0=1.9$  mM), followed by OH<sup>−</sup> (10 equiv) after 400 s. c) Oxidation at  $O_4$  of [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>] formed together with  $p\text{-CN-C}_6\text{H}_4\text{-Ph}$  as in b.

addition of excess hydroxide ( $\alpha=10$  for  $\beta=20$ ) that the reduction peak of **1** disappeared, leading to the new reversible reduction peak  $R_3$  of the biaryl **3** (Figure 1b) and the oxidation peak  $O_4$  of [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>] (Fig-

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Christian Amatore 61, is Member of the French Académie des Sciences and of Academia Europaea, President Elect of the International Society of Electrochemistry (ISE), Honorary Fellow of the Royal Society of Chemistry, Honorary Fellow of the Chinese Chemical Society, Fellow of ISE, Honorary Member of the Israeli Chemical Society, Editor of ChemPhysChem and served as one of the twenty members of the High Council of Science and Technology which advised the French Presidents on scientific matters. He is Honorary Professor of many major universities around the world. He received numerous national and international awards and medals and has been knighted in the French Orders of Meritus and of Légion d'Honneur. Christian Amatore provided electrochemists with instrumental and conceptual means enabling them to tackle with important problems in organic, inorganic, and organometallic chemistry, catalysis as well as in biology and nanosciences. All together this work corresponds to more than 400 primary research publications cumulating in 15,600 citations with a "h-index" of 63.



Anny Jutand has studied Chemistry at ENSCP/University Paris 6 (France). She obtained the "Doctorat d'Etat" (PhD) under the guidance of Prof. J. F. Fauvarque at the University Paris 13 in 1980. After a postdoctoral stay with Prof. B. Åkermark at the Royal Institute of Technology in Stockholm, she moved back to the University Paris 13. She then joined Dr. C. Amatore group at the Ecole Normale Supérieure in Paris in 1985. She became Research Director at CNRS (equivalent to full Professor) in 1992. She received the award of the Organic Chemistry Division of the French Chemical Society in 2003 and the "Grand Prix de l'Etat" of the French Academy of Sciences in 2008. Her current research interest is transition-metal catalysis (Pd, Ru, Cu, Fe ...), focussing on mechanistic investigation by means of electrochemical techniques.



ure 1c). Addition of a known amount of the authentic samples **3** and **4** allowed the determination of the yield of **3** (95 %) and **4** (98 %) from the increase of their respective reduction and oxidation current. This simple study by cyclic voltammetry showed that  $\text{OH}^-$  anions are required in the reaction that delivers the expected products **3** and  $[\text{Pd}^0(\text{PPh}_3)_3]$  in quantitative yield at 25 °C (Scheme 3). The biaryl **3** and  $[\text{Pd}^0(\text{PPh}_3)_3]$  are formed at the same rate in the same reductive elimination step (Scheme 2). It was thus decided to follow the kinetics of the formation of  $[\text{Pd}^0(\text{PPh}_3)_3]$  by chronoamperometry at a rotating disk electrode polarized at +0.05 V on the oxidation wave of  $[\text{Pd}^0(\text{PPh}_3)_3]$  ( $\text{O}_4$ ). As observed in Figure 2a, the oxidation current  $i$  of  $[\text{Pd}^0(\text{PPh}_3)_3]$

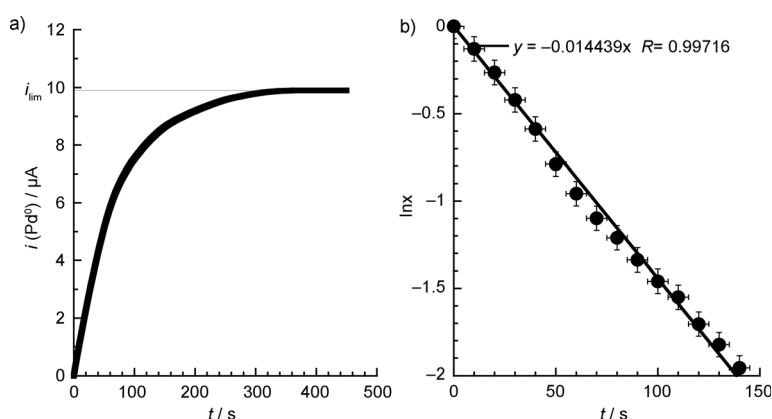


Figure 2. a) Kinetics of the reaction of *trans*-[PdBr(*p*-CN-C<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>] (**1**) ( $C_0 = 1.9 \text{ mM}$ ) with PhB(OH)<sub>2</sub> ( $\beta = 20$  equiv) in the presence of PPh<sub>3</sub> (2 equiv) and  $\text{OH}^-$  ( $\alpha = 10$  equiv). Evolution of the oxidation current  $i_t$  of  $[\text{Pd}^0(\text{PPh}_3)_3]$  (proportional to its concentration  $C_t$ ) versus time. b) Plot of  $\ln x$  versus time:  $x = (i_{\text{lim}} - i_t)/i_{\text{lim}}$ ;  $i_{\text{lim}}$ : final oxidation current of  $[\text{Pd}^0(\text{PPh}_3)_3]$ ;  $i_t$ : oxidation current of  $[\text{Pd}^0(\text{PPh}_3)_3]$  at time  $t$  (see Figure 2a).  $\ln x = -k_{\text{obs}}t$ .

was null in the absence of  $\text{OH}^-$  but increased with time after addition of  $\text{OH}^-$  ( $\alpha = 10$  for  $\beta = 20$ ) to reach a limit ( $i_{\text{lim}}$ ) corresponding to the quantitative formation of  $[\text{Pd}^0(\text{PPh}_3)_3]$  at the end of the reaction. Since the current  $i_t$  is proportional to the concentration  $C_t$  of **4**, the kinetic curve in Figure 2a characterizes the kinetics of the formation of  $[\text{Pd}^0(\text{PPh}_3)_3]$  in the reaction of Scheme 3.

At that stage, two kinetic behaviors could be envisioned. Either the transmetalation is faster than the reductive elimination, which is thus rate-determining with a zero-order reaction for the formation of the Pd<sup>0</sup> complex **4**, or the transmetalation is rate-determining (i.e. affected by the concentrations of **2** and  $\text{OH}^-$ ) followed by a faster reductive elimination. In that case, the rate of formation of the Pd<sup>0</sup> complex should be affected by the concentrations of **2** and  $\text{OH}^-$  with reaction orders for the formation of Pd<sup>0</sup> different from zero. It will be established in the following that the rate of formation of the Pd<sup>0</sup> complex **4** is affected by the concentrations of **2** and  $\text{OH}^-$ , which indicates that the transmetalation step is rate-determining (rds). In other words,  $[\text{Pd}^0(\text{PPh}_3)_3]$  appears at the same rate as the Pd<sup>II</sup> complex **1** disappears and the kinetic curve in Figure 2a characterizes the rds transmetalation step. The corresponding logarithmic

plot against time was linear (Figure 2b) and the slope of the straight line gave the value of the observed rate constant  $k_{\text{obs}}$  of the transmetalation step ( $k_{\text{obs}} = 0.015 \text{ s}^{-1}$  when  $\alpha = 10$ ,  $\beta = 20$ ). It is worthwhile to note that the reaction was pretty fast since it took place within less than 400 s (Figure 2a). The electrochemical technique was thus well adapted to the timescale of the transmetalation and this analytical technique has been always used in the following experiments to get kinetic data on the transmetalation step.

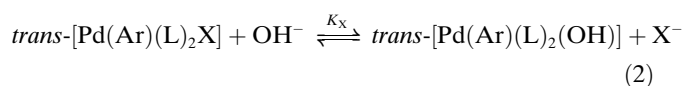
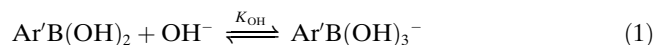
The influence of the concentrations of PhB(OH)<sub>2</sub> (**2**) and  $\text{OH}^-$  on the rate of the transmetalation was then investigated. In a first approach, the concentration of  $\text{OH}^-$  was maintained constant ( $\alpha = 10$  equiv) and  $k_{\text{obs}}$  was determined in the presence of various amounts of **2** ( $\beta$  equiv). Surprisingly, the plot of  $k_{\text{obs}}$  versus  $\beta$  was not linear as expected for a first-order reaction but exhibited a maximum (Figure 3a).<sup>[8]</sup> Interestingly, it was observed that the reaction became very slow when the concentration of **2** exceeded the concentration of  $\text{OH}^-$  (Figure 3a), which suggested that at high concentrations of **2**, the hydroxide ions required for the reaction, were quenched by **2** to form an unreactive species. In a second approach, the concentration of **2** was maintained constant and  $k_{\text{obs}}$  was determined in the presence of various amounts of  $\text{OH}^-$  ( $\alpha$  equiv). The plots of  $k_{\text{obs}}$

versus  $\text{OH}^-$  exhibited a maximum whatever the selected concentration of **2** (Figure 3b).<sup>[8]</sup>

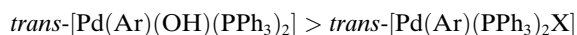
Therefore, hydroxide ions are involved in two kinetically antagonistic effects. Hydroxides are required for the reaction but it becomes slower and slower at too high  $\text{OH}^-$  concentrations. As a result, the rate of the transmetalation is controlled by the ratio  $[\text{OH}^-]/[\text{PhB(OH)}_2]$  that must be smaller than one in the present case (Figure 3c). This antagonistic effect is very general and happens for various substituted Ar'B(OH)<sub>2</sub> (Figure 3d), substituted  $[\text{Pd}(\text{Ar})\text{Br}(\text{PPh}_3)_2]$  (Figure 3e), and for X in  $[\text{Pd}(\text{Ar})(\text{PPh}_3)_2\text{X}]$  (Figure 3f) for which the variations of  $k_{\text{obs}}$  versus the hydroxide concentration were always bell-shaped.<sup>[8]</sup>

<sup>11</sup>B NMR spectra was used to characterize the reversible formation of aryltrihydroxyborates (called arylborates in the following) upon addition of hydroxide ions to solutions of arylboronic acids in DMF [Eq. (1)]. The equilibrium constants  $K_{\text{OH}}$  were quite high (e.g.,  $K_{\text{OH}} > 10^3 \text{ M}^{-1}$ , Ar' = Ph, DMF, 27 °C).<sup>[8]</sup> <sup>31</sup>P NMR spectra was used to characterize the reversible formation of *trans*-[Pd(Ar)(OH)(PPh<sub>3</sub>)<sub>2</sub>] upon addition of hydroxide ions to solutions of *trans*-[Pd(Ar)(PPh<sub>3</sub>)<sub>2</sub>X] in DMF [Eq. (2)], in agreement with reactions performed in THF.<sup>[5b,14a]</sup> The equilibrium constants  $K_X$  were

calculated from the NMR spectroscopic data (e.g.,  $K_X=5$ , Ar=Ph, X=Br).<sup>[8]</sup> Therefore, hydroxide ions are present in two equilibria involving two arylboron derivatives [Eq. (1)] and two aryl-Pd<sup>II</sup> complexes [Eq. (2)] at the origin of the four hypothetical pathways previously proposed for the transmetallation (Scheme 2). The purpose was to find out experimentally which one is dominant.



The influence of bromide ions released in the equilibrium in Equation (2) on the rate of the transmetallation was first tested ( $\alpha=15$ ,  $\beta=20$ ). Bromide ions (introduced as *n*Bu<sub>4</sub>NBr) exerted a decelerating effect, as proven by the inverse relationship between  $k_{\text{obs}}$  and Br<sup>−</sup> concentration (Figure 4). This implies that *trans*-[Pd(Ar)(OH)(PPh<sub>3</sub>)<sub>2</sub>], the concentration of which decreases in the presence of increasing bromide concentrations [Eq. (2)], is more reactive in the transmetallation than *trans*-[Pd(Ar)Br(PPh<sub>3</sub>)<sub>2</sub>]:



The complex *trans*-[Pd(OH)(Ph)(PPh<sub>3</sub>)<sub>2</sub>] (**5**) was quantitatively generated in situ by reacting PPh<sub>3</sub> (6 equiv) with the dimers

*cis/trans*-[Pd( $\mu$ -OH)(Ph)(PPh<sub>3</sub>)<sub>2</sub>]<sub>2</sub> (0.95 mM), as was reported by Grushin and Alper.<sup>[14b]</sup> The hydroxo complex **5** (1.9 mM) was characterized by its reduction peak at R<sub>5</sub> (Figure 5a). It disappeared when **5** was reacted with PhB(OH)<sub>2</sub> (10 equiv) but surprisingly, [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>] was not formed (Figure 5b). Instead a reduction peak was observed at R<sub>6</sub> attesting to the formation of an intermediate Pd<sup>II</sup> complex. Previous studies have shown that this intermediate complex was *trans*-[Pd(Ph)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (**6**).<sup>[7b]</sup> Similarly, *trans*-[Pd(*p*-CN-C<sub>6</sub>H<sub>4</sub>)(Ph)(PPh<sub>3</sub>)<sub>2</sub>] was formed upon reacting *p*-CN-C<sub>6</sub>H<sub>4</sub>-B(OH)<sub>2</sub> with **5**.<sup>[7b,8]</sup> Those *trans* complexes were quite stable and could be characterized by <sup>1</sup>H and <sup>31</sup>P NMR spectroscopy.<sup>[7b]</sup> It is only after addition of OH<sup>−</sup> (5 equiv) that the *trans*-[Pd(Ar)(Ar')(L)<sub>2</sub>] complexes disappeared (attested by the decay of their reduction peak R<sub>6</sub>) leading to the formation of Ar–Ar' and [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>] (**4**) observed through its oxidation peak at O<sub>4</sub> (Figure 5c). Intermediate *trans*-[Pd(Ar)(Ar')(L)<sub>2</sub>] complexes slowly evolved to the formation of **4** in the absence of OH<sup>−</sup> when one of the aryl groups was substituted by an electron-donating group, such as MeO, which favored the reductive elimination. Nevertheless, the reductive elimina-

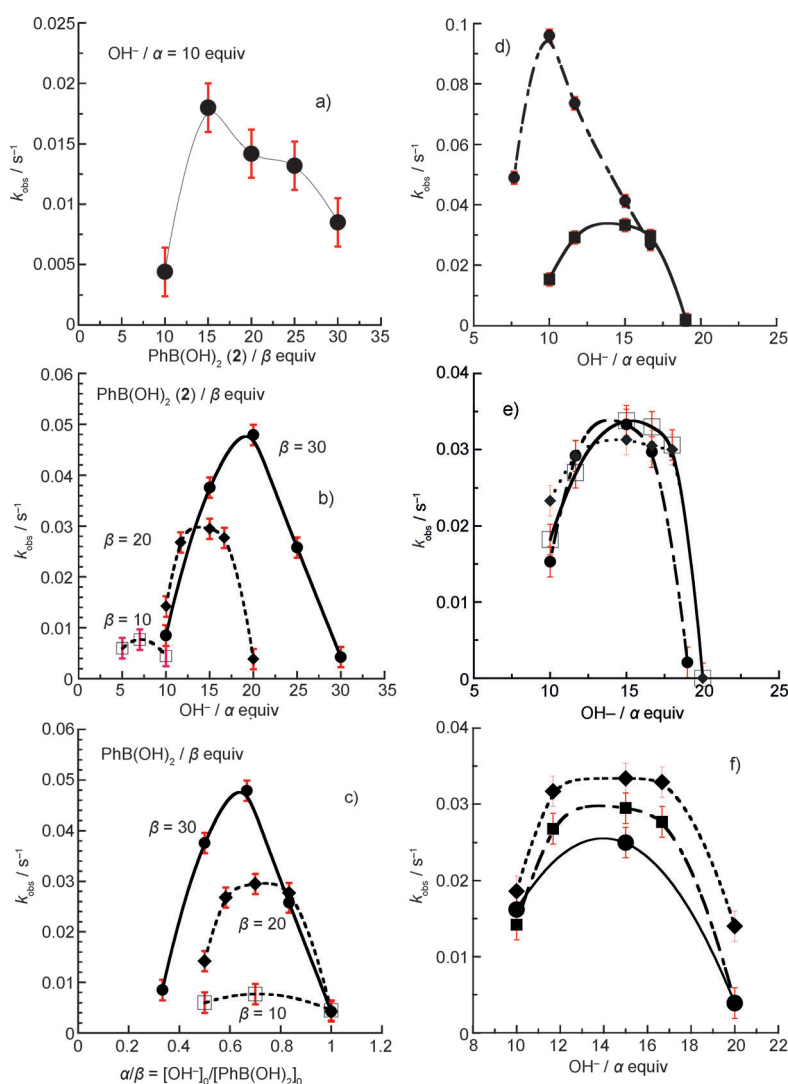


Figure 3. Reactions performed in DMF in the presence of PPh<sub>3</sub> (2 equiv) at 25°C. a) Reaction of PhB(OH)<sub>2</sub> **2** ( $\beta$  equiv) with [PdBr(*p*-CN-C<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>] (**1**) ( $C_0=1.9$  mM) and OH<sup>−</sup> ( $\alpha$  equiv). Plot of  $k_{\text{obs}}$  versus  $\beta$  for  $\alpha=10$ . b) Same reagents: plot of  $k_{\text{obs}}$  versus  $\alpha$  for  $\beta=10, 20, 30$ . c) Same reagents. Plot of  $k_{\text{obs}}$  versus  $\alpha/\beta$ . d) Influence of the substituent Z' of *p*-Z'-C<sub>6</sub>H<sub>4</sub>-B(OH)<sub>2</sub> (**2**) (20 equiv) on the rate of its reaction with [PdBr(*p*-CN-C<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>] (**1**) ( $C_0=1.9$  mM) in the presence of  $\alpha$  equiv of OH<sup>−</sup> (■: H, ●: *p*-MeO). Plot of  $k_{\text{obs}}$  versus  $\alpha$ . e) Influence of the substituent Z of [PdBr(*p*-Z-C<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>] ( $C_0=1.9$  mM) on the rate of its reaction with PhB(OH)<sub>2</sub> **2** (20 equiv) in the presence of  $\alpha$  equiv of OH<sup>−</sup>. Plot of  $k_{\text{obs}}$  versus  $\alpha$  (●: *p*-CN, □: H, ◆: *p*-F). f) Influence of the halide X of [Pd(*p*-CN-C<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>X] ( $C_0=1.9$  mM) on the rate of its reaction with PhB(OH)<sub>2</sub> (20 equiv) in the presence of  $\alpha$  equiv of OH<sup>−</sup> (●: Cl, ■: Br, ◆: I). Plot of  $k_{\text{obs}}$  versus  $\alpha$ .

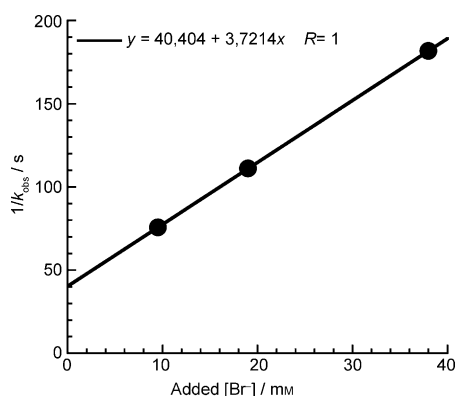


Figure 4. Influence of the bromide concentration on the kinetics of the reaction of *trans*-[PdBr(*p*-CN-C<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>] (**1**) (*C*<sub>0</sub> = 1.9 mM) with PhB(OH)<sub>2</sub> (**2**) (20 equiv) in the presence of PPh<sub>3</sub> (2 equiv) and OH<sup>−</sup> (15 equiv). Plot of 1/*k*<sub>obs</sub> versus bromide concentration (introduced via *n*Bu<sub>4</sub>NBr).

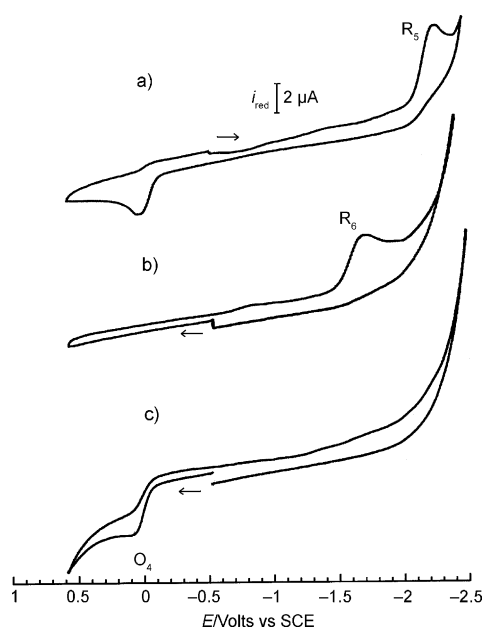


Figure 5. Cyclic voltammetry performed at a gold disk electrode (*d* = 1 mm) in DMF containing *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.3 M) with a scan rate of 0.5 Vs<sup>−1</sup>, at 25°C, in the presence of PPh<sub>3</sub> (3.8 mM). a) Reduction at R<sub>5</sub> of *trans*-[Pd(OH)(Ph)(PPh<sub>3</sub>)<sub>2</sub>] (**5**) (1.9 mM) generated by reaction of PPh<sub>3</sub> (5.7 mM) to [Pd(μ-OH)(Ph)(PPh<sub>3</sub>)<sub>2</sub>] (0.95 mM). b) Reduction at R<sub>6</sub> of *trans*-[Pd(Ph)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (**6**) formed by reaction of PhB(OH)<sub>2</sub> (19 mM) to *trans*-[Pd(OH)(Ph)(PPh<sub>3</sub>)<sub>2</sub>]. c) Oxidation at O<sub>4</sub> of [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>] formed after addition of OH<sup>−</sup> (9.5 mM) to *trans*-[Pd(Ph)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] generated as in Figure 5b.

tion was again faster upon addition of OH<sup>−</sup>. This means that *trans*-[Pd(Ar)(Ar')(PPh<sub>3</sub>)<sub>2</sub>] complex might be stable (supported by DFT calculations)<sup>[6a]</sup> and unexpectedly, OH<sup>−</sup> catalyzes the reductive elimination from the *trans* complex via a pentacoordinated complex;

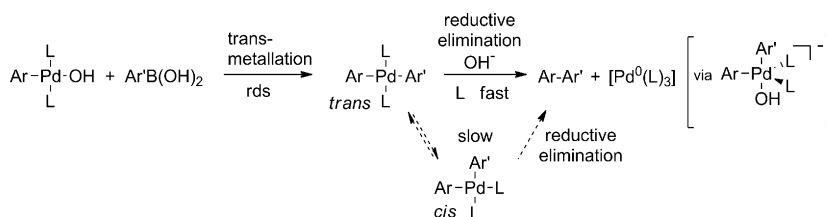
OH<sup>−</sup> playing the well-known role of a fifth ligand on the Pd<sup>II</sup> center<sup>[15]</sup> (Scheme 4). The classical reductive elimination proceeding through the *cis* complex, which is slow due to the endergonic *trans*/*cis* isomerization is then bypassed (Scheme 4).

In the presence of OH<sup>−</sup>, the reductive elimination becomes faster than the rate-determining transmetalation of [Pd(Ar)(L)<sub>2</sub>(OH)] with Ar'B(OH)<sub>2</sub>, as was observed experimentally (Scheme 4). The rate of the transmetalation was not affected by the concentration of added PPh<sub>3</sub> (zero-order reaction),<sup>[8]</sup> which means that the transmetalation does not proceed via a monoligated [Pd(OH)(Ph)(PPh<sub>3</sub>)] or [Pd(μ-OH)(Ph)(PPh<sub>3</sub>)<sub>2</sub>].

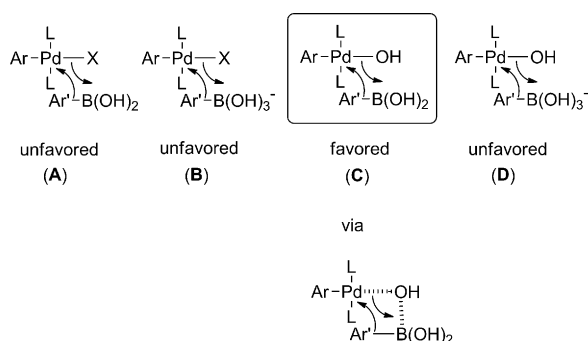
The mechanism of the transmetalation through path C in Scheme 5 is thus well established (vide supra).<sup>[8]</sup> This step is triggered by the oxophilicity of the boron centre that allows a precomplexation of the hydroxo of [Pd(Ar)(L)<sub>2</sub>(OH)], which facilitates the transmetalation (Scheme 5).<sup>[5b, 16]</sup>

The three other pathways A, B, and D in Scheme 5 were then kinetically ruled out. Path A is not favored since no reaction took place in the absence of hydroxide ions (vide supra). Path D is not favored since the reactions became very slow at high hydroxide concentrations in which both [Pd(Ar)(L)<sub>2</sub>(OH)] and Ar'B(OH)<sub>3</sub><sup>−</sup> coexist (Figure 3b). Moreover, no reaction was independently observed when *trans*-[Pd(OH)(Ph)(PPh<sub>3</sub>)<sub>2</sub>] was added to preformed Ar'B(OH)<sub>3</sub><sup>−</sup>.<sup>[8]</sup> Pathway B has also been ruled out. Ar'B(OH)<sub>3</sub><sup>−</sup> is in equilibrium with Ar'B(OH)<sub>2</sub> and OH<sup>−</sup>, which could react with *trans*-[Pd(Ar)(L)<sub>2</sub>X] to generate *trans*-[Pd(Ar)(L)<sub>2</sub>(OH)]. Ar'B(OH)<sub>3</sub><sup>−</sup> could thus react with *trans*-[Pd(Ar)(OH)(L)<sub>2</sub>] via Ar'B(OH)<sub>2</sub> (path C) but in a slow reaction because the equilibrium lays in favor of Ar'B(OH)<sub>3</sub><sup>−</sup> leading to a low concentration of the active Ar'B(OH)<sub>2</sub>. This is why the intrinsic reactivity of Ar'B(OH)<sub>3</sub><sup>−</sup> with *trans*-[Pd(Ar)(L)<sub>2</sub>X] (Path B in Scheme 5) had to be tested in the presence of an excess of halide ions to avoid the substitution X/OH. No reaction was observed, ruling out path B. The predominance of path C over path B was later on confirmed by Carrow and Hartwig.<sup>[17]</sup>

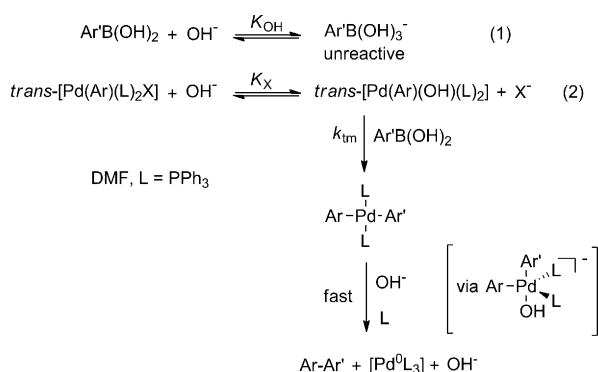
The mechanism of the transmetalation followed by reductive elimination is displayed in Scheme 6. Hydroxide ions exert an antagonistic effect on the rate of the transmetalation because they are involved in two competitive equilibria, one leading to the formation of unreactive arylborates [Eq. (1)] and the second one leading to the reactive species [Pd(Ar)(OH)(PPh<sub>3</sub>)<sub>2</sub>] [Eq. (2)].



Scheme 4. Mechanism of the transmetalation and reductive elimination in the presence of hydroxide ions (see reference [15g] for the species between brackets).



Scheme 5.



Scheme 6.

The related kinetic laws are given in Equations (3) and (4). The theoretical evolution of  $k_{\text{obs}}$  versus  $\text{OH}^-$  concentration [Eq. (4)] exhibits a maximum in agreement with the experimental kinetic curves (Figure 3).

$$\text{rate} = k_{\text{obs}} [\text{Pd}^{\text{II}}]_{\text{total}} \quad (3)$$

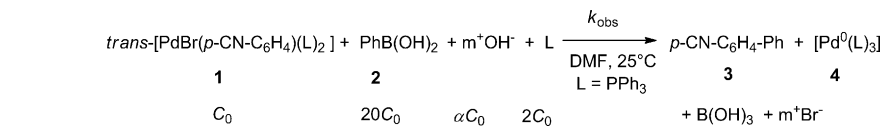
$$k_{\text{obs}} = k_{\text{tm}} \beta C_0 \left( \frac{1}{1 + K_{\text{OH}} [\text{OH}^-]} \right) \left( \frac{K_X [\text{OH}^-]}{[\text{X}^-] + K_X [\text{OH}^-]} \right) \quad (4)$$

The mechanism of the Suzuki–Miyaura reaction is presented in Scheme 7, including the three antagonistic kinetic roles of the hydroxides: 1) formation of the reactive *trans*-[Pd(Ar)(L)<sub>2</sub>(OH)] in the rds transmetallation with Ar'B(OH)<sub>2</sub> the rate of which is controlled by the ratio:  $[\text{OH}^-]/[\text{Ar'B(OH)}_2]$ , 2) catalysis of the reductive elimination from *trans*-[Pd(Ar)(Ar')(L)<sub>2</sub>], and 3) formation of unreactive Ar'B(OH)<sub>3</sub><sup>−</sup>. The hydroxide ions do not play the role of a base but are ligands of aryl–Pd<sup>II</sup> complexes.

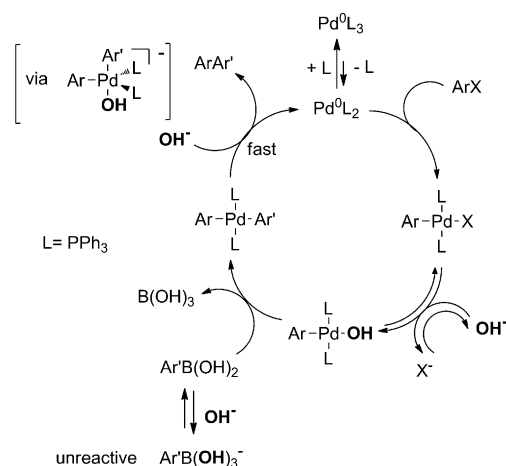
Further work on the mechanism of the ligand-less Suzuki–Miyaura also stressed on the nonreactivity of aryltri-hydroxyborates.<sup>[18]</sup>

#### Fourth antagonistic kinetic role

due to the counteraction of hydroxide: The counteraction of hydroxide investigated in Scheme 7 was the innocent *n*Bu<sub>4</sub>N<sup>+</sup>.<sup>[8]</sup> However, some



Scheme 8.



Scheme 7. Mechanism of the Suzuki–Miyaura reaction when the base is *n*Bu<sub>4</sub>NOH.<sup>[8]</sup>

counteractions, such as Ag<sup>+</sup> or Tl<sup>+</sup>, were reported to accelerate Suzuki–Miyaura reactions performed in THF, as was pioneered by Kishi et al.<sup>[19]</sup> This is now rationalized by a shift of the equilibrium *trans*-[Pd(Ar)(L)<sub>2</sub>X]/*trans*-[Pd(Ar)(L)<sub>2</sub>(OH)] by quenching the halide ion to form insoluble AgX or TlX in THF. As a result, the concentration of *trans*-[Pd(Ar)(L)<sub>2</sub>(OH)] should increase, making the transmetallation faster. It was thus of interest to investigate the effect of counteractions that do not have any affinity for halide ions ( $\text{m}^+ = \text{Na}^+, \text{Cs}^+, \text{K}^+$ ) in a polar solvent, such as DMF.<sup>[9]</sup>

The observed rate constant  $k_{\text{obs}}$  of the reaction in Scheme 8 was determined in the presence of *m*OH ( $\alpha$  equiv).

Whatever the counteractions, the variation of  $k_{\text{obs}}$  versus  $\text{OH}^-$  concentration always resulted in a bell-shaped curve (Figure 6a), which confirmed the kinetically antagonistic effect of hydroxide ions. However, a decelerating effect of the cations was observed relative to *n*Bu<sub>4</sub>N<sup>+</sup> (Figure 6a) since the maximum value of  $k_{\text{obs}}$  decreased in the order:<sup>[9]</sup> *n*Bu<sub>4</sub>N<sup>+</sup> > K<sup>+</sup> > Cs<sup>+</sup> > Na<sup>+</sup>

The decelerating effect of the counteractions was confirmed in reactions performed in the presence of *n*Bu<sub>4</sub>NOH (15 equiv) and increasing amounts of KBF<sub>4</sub> or NaBF<sub>4</sub>. There is indeed an inverse relationship between  $k_{\text{obs}}$  and the concentration of the counteraction (Figure 6b):  $1/k_{\text{obs}} = a + b[\text{m}^+]$ .

After having checked by conductivity measurements that all *m*OH and *m*Br were fully dissociated in DMF,<sup>[9]</sup> a complexation of the cation  $\text{m}^+$  with the OH group of *trans*-[Pd(Ar)(OH)(PPh<sub>3</sub>)<sub>2</sub>] (Ar = Ph) was evidenced by <sup>1</sup>H and <sup>31</sup>P NMR spectra.<sup>[9]</sup> Through this complexation, the concen-

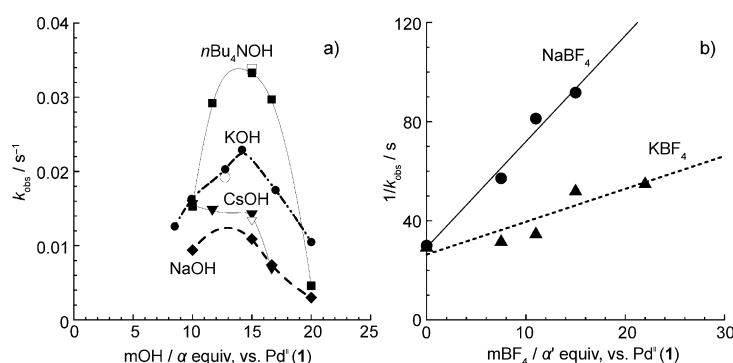
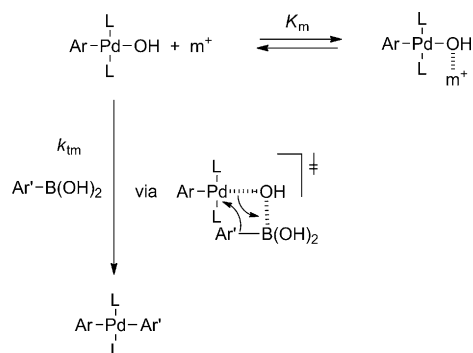


Figure 6. All reactions were performed in DMF containing  $n\text{Bu}_4\text{NBF}_4$  (0.3 M) in the presence of  $\text{PPh}_3$  (2 equiv) at 25 °C. a) Kinetics of the reaction of  $\text{trans}[\text{PdBr}(p\text{-CN-C}_6\text{H}_4)(\text{PPh}_3)_2]$  (**1**) ( $C_0 = 1.9 \text{ mM}$ ) with  $\text{PhB}(\text{OH})_2$  (20 equiv) and  $m\text{OH}$  ( $\alpha$  equiv) ( $m = n\text{Bu}_4\text{N}$ , K, Cs, Na). Plots of  $k_{\text{obs}}$  versus  $\alpha$  (initial amount of  $m\text{OH}$  introduced into the medium). Non effect of  $\text{H}_2\text{O}$ :  $\square$ : 30 equiv added to  $n\text{Bu}_4\text{NOH}$ ;  $\circ$ : 15 equiv added to  $\text{KOH}$ , and  $\nabla$ : 30 equiv added to  $\text{CsOH}$ . b) Kinetics of the reaction of  $\text{trans}[\text{PdBr}(p\text{-CN-C}_6\text{H}_4)(\text{PPh}_3)_2]$  (**1**) ( $C_0 = 1.9 \text{ mM}$ ) with  $\text{PhB}(\text{OH})_2$  (20 equiv) in the presence of  $n\text{Bu}_4\text{NOH}$  (15 equiv) and  $\alpha'$  equiv of  $\text{KBF}_4$  ( $\blacktriangle$ ) or  $\text{NaBF}_4$  ( $\bullet$ ) (concentration range for  $m\text{BF}_4$ : 0–42 mM). Plot of  $1/k_{\text{obs}}$  versus  $[m\text{BF}_4]$  expressed in equiv ( $\alpha'$ ) versus  $\text{Pd}^{\text{II}}$  complex **1** (-----:  $y = 26.463 + 1.3243x$ ,  $R = 0.90711$ ; —:  $29.286 + 4.2709x$ ,  $R = 0.98981$ ).

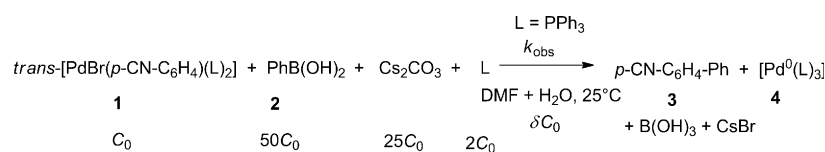


Scheme 9. Competitive complexation/transmetalation in the presence of cations  $m^+$  ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cs}^+$ ) in DMF (solvent voluntarily omitted).

tration of  $[\text{Pd}(\text{Ar})(\text{OH})(\text{PPh}_3)_2]$  decreased and the competitive transmetalation became slower (Scheme 9).

The new expression of  $k_{\text{obs}}$  (derived from Equations (3) and (4)), which includes the effect of the counteranions by its concentration  $[m^+]$  and the equilibrium constant  $K_m$  is given in Equation (5). The theoretical variation of  $k_{\text{obs}}$  versus  $[\text{OH}^-]$  exhibits a maximum [Eq. (5)], as experimentally observed in Figure 6a. The value and the position of  $k_{\text{obs}}^{\text{max}}$  depend on both the concentration of the cation and the value of  $K_m$  [Eq. (6)]. Moreover, there is an inverse relationship between  $k_{\text{obs}}$  and the concentration of the counteranion [Eq. (7)], as observed experimentally (Figure 6b).<sup>[9]</sup>

Scheme 11.

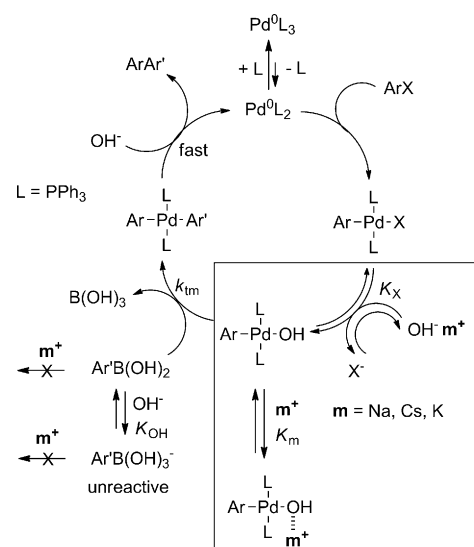


$$k_{\text{obs}} = k_{\text{tm}}\beta C_0 \left( \frac{1}{1 + K_{\text{OH}}[\text{OH}^-]} \right) \left( \frac{K_X[\text{OH}^-]}{[\text{X}^-] + K_X[\text{OH}^-](1 + K_m[m^+])} \right) \quad (5)$$

$$[\text{OH}^-]^{\text{max}} = \left( \frac{[\text{X}^-]}{K_X K_{\text{OH}}(1 + K_m[m^+])} \right)^{1/2} \quad (6)$$

$$\frac{1}{k_{\text{obs}}} = \left( \frac{1 + K_{\text{OH}}[\text{OH}^-]}{k_{\text{tm}}\beta C_0} \right) \left( 1 + \frac{[\text{X}^-]}{K_X[\text{OH}^-]} \right) + \frac{(1 + K_{\text{OH}}[\text{OH}^-])}{k_{\text{tm}}\beta C_0} x K_m[m^+] = a' + b'[m^+] \quad (7)$$

The mechanism of the Suzuki reactions involving the role of the counteranions may be disclosed as in Scheme 10.<sup>[9]</sup>



Scheme 10. Role of the counteranion of the base  $m^+$  in the Suzuki–Miyaura reaction (the solvent DMF around the cations is voluntarily omitted).<sup>[9]</sup>

## Role of Carbonate Ions

Carbonates,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Cs}_2\text{CO}_3$ ,  $\text{Ag}_2\text{CO}_3$ , and  $\text{Ti}_2\text{CO}_3$  are often used as bases.<sup>[1–4,5a,19a]</sup> The effect of carbonate on the rate of the reaction in Scheme 11 has been tested.  $\text{Cs}_2\text{CO}_3$  has been selected because it is the most soluble salt in DMF.<sup>[20]</sup>

Figure 7a exhibits the kinetics of formation of  $[\text{Pd}^0(\text{PPh}_3)_3]$  versus time for the reaction in Scheme 11, performed in the presence of supposedly “dry”  $\text{Cs}_2\text{CO}_3$  in dry



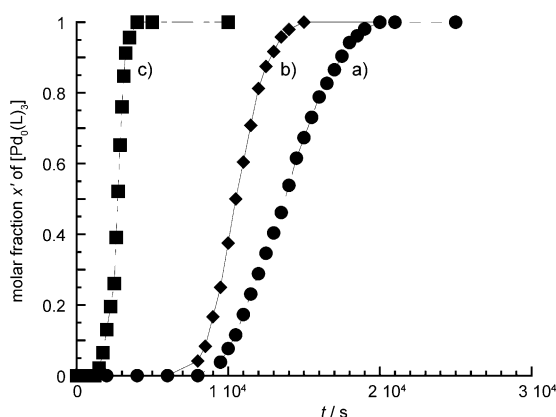
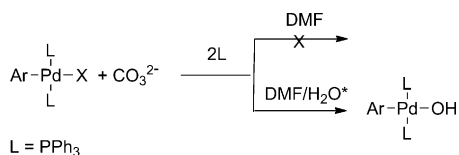


Figure 7. All reactions were performed in DMF containing  $n\text{Bu}_4\text{NBF}_4$  (0.3 M) at 25 °C in the presence of  $\text{PPh}_3$  (2 equiv). Evolution of the molar fraction  $x'$  of  $[\text{Pd}^0(\text{PPh}_3)_3]$  versus time formed in the reaction of  $\text{trans}[\text{PdBr}(p\text{-CN-C}_6\text{H}_4)(\text{PPh}_3)_2]$  (**1**) ( $C_0 = 1.9 \text{ mM}$ ) with  $\text{PhB}(\text{OH})_2$  (50 equiv) in the presence of  $\text{Cs}_2\text{CO}_3$  (25 equiv): a) without any  $\text{H}_2\text{O}$ , b) in the presence of  $\text{H}_2\text{O}$  ( $\delta = 25$  equiv), and c) in the presence of  $\text{H}_2\text{O}$  ( $\delta = 1750$  equiv). Molar fraction of  $[\text{Pd}^0(\text{PPh}_3)_3]$ :  $x' = i/i_{\text{lim}}$  ( $i$ : oxidation current of  $[\text{Pd}^0(\text{PPh}_3)_3]$  (proportional to its concentration  $C_i$ ),  $i_{\text{lim}}$  = final oxidation current). The current intensities were determined at a rotating gold disk electrode ( $d = 2 \text{ mm}$ ) polarized at +0.05 V vs. SCE.

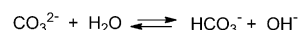
DMF. The reaction was considerably slower than those performed in the presence of  $n\text{Bu}_4\text{NOH}$  under similar conditions. Moreover, a long induction period was observed (Figure 7a) attesting to the accumulation of the intermediate complex  $\text{trans}[\text{Pd}(\text{Ar})(\text{Ar}')(\text{L})_2]$ . This considerably slower reaction was not due to the presence of the  $\text{Cs}^+$  counteranion since the latter exerts a low decelerating effect by a factor two (Figure 6a).<sup>[9]</sup> The reaction was faster and faster in the presence of increasing amounts of water, whereas the induction period was shorter and shorter (Figure 7b,c).<sup>[9]</sup>

There was no reaction of  $\text{CO}_3^{2-}$  with  $\text{trans}[\text{Pd}(\text{Ar})(\text{PPh}_3)_2\text{X}]$  in dry DMF but the introduction of water (10% in volume) led to the formation of  $\text{trans}[\text{Pd}(\text{Ar})(\text{OH})(\text{PPh}_3)_2]$  in the presence of two equivalents of  $\text{PPh}_3$ .<sup>[9]</sup> This was due to the formation of  $\text{OH}^-$  by the reaction of carbonate with water<sup>[5a]</sup> (Scheme 12).

Therefore, water does favor the Suzuki–Miyaura reaction involving carbonates by formation of hydroxide ions.<sup>[5a,9,21]</sup>



\* via  $\text{OH}^-$  from the reaction :



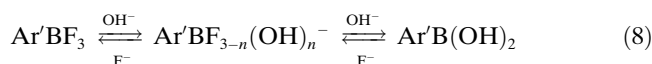
Scheme 12.

The mechanism is thus similar to that reported in Scheme 7. However, a small amount of  $\text{OH}^-$  is generated, controlled by the amount of water. Consequently, relative to pure hydroxides at the same concentration as carbonates, the transmetallation was slower because of the low concentration of  $[\text{Pd}(\text{Ar})(\text{L})_2(\text{OH})]$ . The reductive elimination was also slower due to the low concentration of  $\text{OH}^-$ ; this is why an induction period was observed for the formation of the  $\text{Pd}^0$  by reductive elimination (Figure 7).

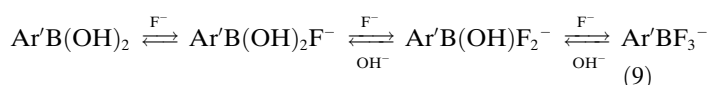
### Three Antagonistic Roles for Fluoride Ions

Fluoride anions are also used as “bases” in Suzuki–Miyaura reactions performed from  $\text{Ar}'\text{B}(\text{OH})_2$ .<sup>[1,22]</sup> Fluorides may also be reversibly generated by reactions of hydroxide ions with  $\text{Ar}'\text{BF}_3^-$  [Eq. (8)] when the latter is used as a reagent in Suzuki–Miyaura reactions,<sup>[1j,k,23,24]</sup> as reported by Batey, Molander, and Lloyd-Jones.<sup>[24]</sup> Consequently, the first expected role of fluoride ions is the formation of mixed anionic arylfluoroborates  $\text{Ar}'\text{B}(\text{OH})_{3-n}\text{F}_n^-$  ( $n = 1-3$ ) [Eq. (9)] reported to be less reactive than  $\text{Ar}'\text{B}(\text{OH})_2$ .<sup>[24a,f,25]</sup>

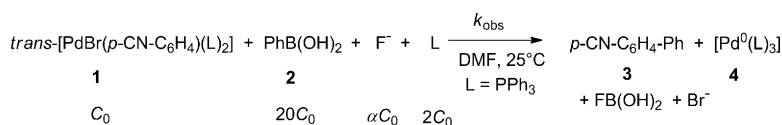
In THF/ $\text{H}_2\text{O}$



In DMF



The influence of fluoride ions on the rate of the reaction in Scheme 13<sup>[10b]</sup> was thus tested in the presence of various



Scheme 13.

amounts of fluorides ( $\alpha$  equiv) added as  $n\text{Bu}_4\text{NF}$  to minimize the role of the counteranion.<sup>[10a]</sup>

Plots of  $k_{\text{obs}}$  versus fluoride concentration exhibited a maximum as for hydroxide ions (Figure 8), which means that  $\text{F}^-$  ions are involved into two kinetically antagonistic effects.<sup>[10a]</sup> Fluoride ions are required but the reactions become slower and slower at high concentrations, which confirms that anionic arylfluoroborates  $\text{Ar}'\text{B}(\text{OH})_{3-n}\text{F}_n^-$  formed at high fluoride concentrations are less reactive than  $\text{Ar}'\text{B}(\text{OH})_2$  in the transmetallation step.<sup>[24f,25]</sup>

Fluoride ions reversibly exchange the halide of  $\text{trans}[\text{Pd}(\text{Ar})(\text{L})_2\text{X}]$  ( $\text{L} = \text{PPh}_3$ ) to generate  $\text{trans}[\text{Pd}(\text{Ar})\text{F}(\text{L})_2]$ ,<sup>[10,26]</sup> as reported by Grushin et al.<sup>[27]</sup>

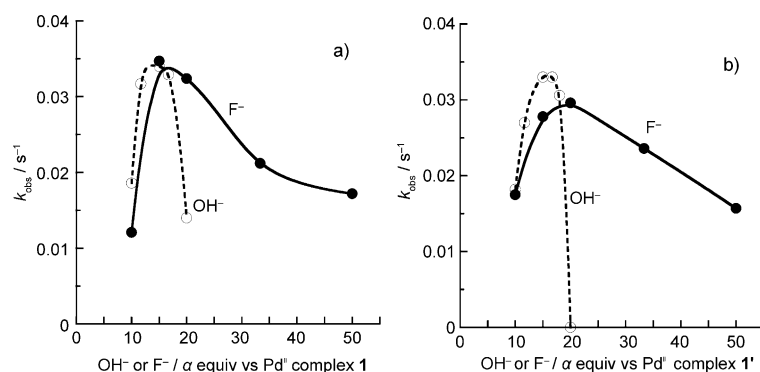
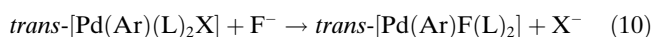
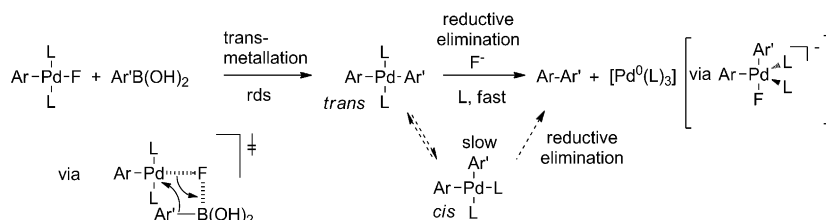


Figure 8. Variation of the pseudo-first order rate constant  $k_{\text{obs}}$  with  $\alpha$  (equiv of F<sup>-</sup> (●) or OH<sup>-</sup> (○)) for the reaction of PhB(OH)<sub>2</sub> (20 equiv) with: a)  $\text{trans-[PdI(p-CN-C}_6\text{H}_4\text{)(PPh}_3\text{)}_2\text{]} \text{ (1)}$  ( $C_0 = 1.9 \text{ mM}$ ); b)  $\text{trans-[PdBr(Ph)(PPh}_3\text{)}_2\text{]} \text{ (1')}$  ( $C_0 = 1.9 \text{ mM}$ ). All reactions were performed in the presence of PPh<sub>3</sub> (2 equiv) in DMF at 25 °C.

([Eq. (10)], Ar =  $p\text{-CN-C}_6\text{H}_4$ , X = I,  $K_1 = 5$ , DMF, 27 °C from <sup>31</sup>P NMR spectroscopic data).<sup>[28]</sup> The isolated  $\text{trans-[PdF(p-CN-C}_6\text{H}_4\text{)(PPh}_3\text{)}_2\text{]}$  reacts with PhB(OH)<sub>2</sub> to generate the stable intermediate complex  $\text{trans-[Pd(p-CN-C}_6\text{H}_4\text{)(Ph)(L)}_2\text{]}$ , as monitored by cyclic voltammetry. As for hydroxide ions, [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>] and the coupling product **3** were formed after addition of fluoride ions. Consequently, fluoride ions catalyze the reductive elimination from  $\text{trans-[Pd(Ar)(Ar')(L)}_2\text{]}$  by bypassing the conventional *cis* complex



$\text{trans-[Pd(Ar)(L)}_2\text{X]} + \text{F}^- \rightarrow \text{trans-[Pd(Ar)F(L)}_2\text{]} + \text{X}^-$  (10)  
 CN-C<sub>6</sub>H<sub>4</sub>)(PPh<sub>3</sub>)<sub>2</sub>] reacts with PhB(OH)<sub>2</sub> to generate the stable intermediate complex  $\text{trans-[Pd(p-CN-C}_6\text{H}_4\text{)(Ph)(L)}_2\text{]}$ , as monitored by cyclic voltammetry. As for hydroxide ions, [Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>] and the coupling product **3** were formed after addition of fluoride ions. Consequently, fluoride ions catalyze the reductive elimination from  $\text{trans-[Pd(Ar)(Ar')(L)}_2\text{]}$  by bypassing the conventional *cis* complex



Scheme 14. Mechanistic role of fluoride ions in the transmetalation and reductive elimination.

(Scheme 14). The rds transmetalation between  $\text{trans-[Pd(Ar)F(PPh}_3\text{)}_2\text{]}$  and  $\text{Ar'B(OH)}_2$  is triggered by the fluorophilicity of the boron center (Scheme 14).

The mechanism of the Suzuki–Miyaura performed in the presence of fluoride ions is given in Scheme 15.

As for hydroxide ions, fluoride ions play three kinetically antagonistic roles: 1) formation of  $\text{trans-[Pd(Ar)F(L)}_2\text{]}$  reactive in the rds transmetalation with  $\text{Ar'B(OH)}_2$ , 2) catalysis of the reductive elimination from  $\text{trans-[Pd(Ar)(Ar')(L)}_2\text{]}$ , and 3) formation of less or unreactive arylfluoroborates. The rate of the rds transmetalation is then controlled by the ratio  $[\text{F}^-]/[\text{ArB(OH)}_2]$ . Nevertheless, the effective concentration range for which the transmetalation is efficient is wider for fluoride than for hydroxide ions (Figure 8).<sup>[10a]</sup> It is worthwhile to note that the reaction of F<sup>-</sup> with  $\text{ArB(OH)}_2$  may release OH<sup>-</sup> [Eq. (9)] which in turn could be involved

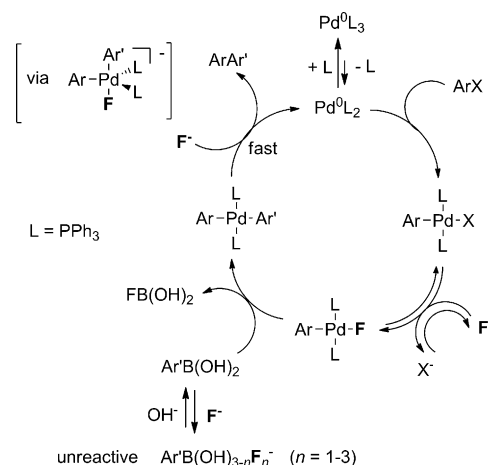
in the catalytic process as in Scheme 7. This may add to the complexity of the process, which may thus intermingle Schemes 7 and 15. However, the competition of F<sup>-</sup> versus OH<sup>-</sup> for the substitution of the iodide ligand in  $\text{trans-[PdI(p-CN-C}_6\text{H}_4\text{)(PPh}_3\text{)}_2\text{]}$  was found to be in favor of F<sup>-</sup>.<sup>[10a]</sup>

## Summary and Outlook

The role of the “base” in Suzuki–Miyaura reactions is fully elucidated. It is established

that anionic bases do not play the role of a base but serve as a ligand for aryl-palladium(II) complexes. Anionic bases, F<sup>-</sup>, OH<sup>-</sup> (when used as is or generated from CO<sub>3</sub><sup>2-</sup> in the presence of water) play multiple kinetically antagonistic roles. Two are positive: 1) formation of the reactive species  $\text{trans-[Pd(Ar)(OH)(PPh}_3\text{)}_2\text{]}$  or  $\text{trans-[Pd(Ar)F(PPh}_3\text{)}_2\text{]}$  in the rate-determining transmetalation step and 2) catalysis of the reductive elimination from intermediate  $\text{trans-[Pd(Ar)(Ar')(PPh}_3\text{)}_2\text{]}$  and two are negative: 1) formation of unreactive aryl borates (or fluoroborates) and 2) complexation of the OH group of  $[\text{Pd(Ar)(OH)(PPh}_3\text{)}_2]$  by the counteraction of the anionic hydroxide.

In Suzuki reactions involving a fast oxidative addition (aryl iodides and activated aryl bromides), one needs to increase the rate of the rate-determining transmetalation. This requires: 1) to select the best base: OH<sup>-</sup> > CO<sub>3</sub><sup>2-</sup><sup>[29]</sup> 2) to optimize the ratio ([OH<sup>-</sup>] or



Scheme 15. Mechanism of the Suzuki–Miyaura reaction in the presence of  $n\text{Bu}_4\text{NF}$ .<sup>[10a]</sup>

$[F^-]/[Ar'B(OH)_2]$ , and 3) to select the best counteraction of the anionic base:  $Tl^+ > Ag^+ > nBu_4N^+ > K^+ > Cs^+ > Na^+$ . This optimization is of course less crucial when the oxidative addition is rds as when aryl chlorides are used. Note that this statement strictly applies only when the oxidative addition is always rate-determining. Yet, its extrapolation to a given aryl halide is rather risky since the bell-shaped kinetics of the transmetallation may make the oxidative addition or transmetallation be the rds, depending on the operative conditions and the degree of advancement of the reaction. Nevertheless, the mechanism of the transmetallation/reductive elimination, elucidated for hydroxide and fluoride ions remains always valid.<sup>[30]</sup>

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- [30] All of what precedes clearly establishes that a deep understanding of such complex organometallic-catalyzed reactions may be achieved only by precise kinetic experiments. Electrochemical methods were shown to be particularly adapted to such purposes when the process takes place under homogeneous conditions mimicking those prevailing during one catalytic cycle. The usefulness of electrochemical approaches may be further extended through their coupling to local microspectroscopy, such as Surface Enhanced Raman Spectroscopy (SERS), for which the catalytic act may proceed at heterogeneous surfaces. For example, we recently investigated through such coupling the mechanism of a Suzuki–Miyaura reaction from 4-MeO-C<sub>6</sub>H<sub>4</sub>-Br and  $\text{PhB}(\text{OH})_2$ , performed in pure water in the presence of  $\text{Cs}_2\text{CO}_3$  as the base and catalytic amounts of  $\text{Pd@Au}$  nanoparticles.<sup>[21]</sup> This study was prompted by literature controversies about the possible catalysis by Pd surface atoms.<sup>[31]</sup> We thus established that the process was fully homogeneous, being triggered by Pd atoms or clusters leaching from the nanoparticles under the action of the base  $\text{OH}^-$  (generated from  $\text{Cs}_2\text{CO}_3$  in water) and/or that of  $\text{PhB}(\text{OH})_3^-$  formed from  $\text{PhB}(\text{OH})_2$ .<sup>[21]</sup>
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