FULL PAPER

### Mechanistic Origin of Antagonist Effects of Usual Anionic Bases (OH<sup>-</sup>, CO<sub>3</sub><sup>2-</sup>) as Modulated by their Countercations (Na<sup>+</sup>, Cs<sup>+</sup>, K<sup>+</sup>) in Palladium-Catalyzed Suzuki–Miyaura Reactions

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Abstract: The mechanism of the reaction of *trans*-ArPdBrL<sub>2</sub> (Ar = p-Z- $C_6H_4$ , Z=CN, H; L=PPh<sub>3</sub>) with  $Ar'B(OH)_2$  ( $Ar' = p - Z' - C_6H_4$ , Z' = H, CN, MeO), which is a key step in the Suzuki-Miyaura process, has been established in N,N-dimethylformamide (DMF) with two bases, acetate  $(nBu_4NOAc)$  or carbonate  $(Cs_2CO_3)$ and compared with that of hydroxide  $(nBu_4NOH)$ , reported in our previous work. As anionic bases are inevitably introduced with a countercation M+ (e.g.,  $M^+OH^-$ ), the role of cations in the transmetalation/reductive elimination has been first investigated. Cations  $M^+$  (Na<sup>+</sup>, Cs<sup>+</sup>, K<sup>+</sup>) are not innocent since they induce an unexpected decelerating effect in the transmetalation via their complexation to the OH ligand in the reactive ArPd(OH)L<sub>2</sub>, partly inhibiting its transmetalation with Ar'B(OH)<sub>2</sub>. A decreasing reactivity

### Introduction

The cross-coupling of aryl halides (ArX) with arylboronic acids (Ar'B(OH)<sub>2</sub>) or aryltrifluoroborates (Ar'BF<sub>4</sub><sup>-</sup>) is catalyzed by palladium in the presence of a base (NaOH, TlOH, KOH, R<sub>4</sub>NOH, TlOEt, Ag<sub>2</sub>O, K<sub>3</sub>PO<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, Tl<sub>2</sub>CO<sub>3</sub>)<sup>[1]</sup> (Scheme 1). This reaction is a key step in the total synthesis of natural products.<sup>[2]</sup>

$$ArX + \begin{cases} Ar'B(OH)_2 & Pd cat. \\ Ar'BF_3^- & base \end{cases} Ar-Ar'$$

Scheme 1. Suzuki-Miyaura reaction.

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order is observed when M<sup>+</sup> is associated with OH<sup>-</sup>:  $nBu_4N^+ > K^+ > Cs^+ >$ Na<sup>+</sup>. Acetates lead to the formation of trans-ArPd(OAc)L<sub>2</sub>, which does not undergo transmetalation with Ar'B(OH)<sub>2</sub>. This explains why acetates are not used as bases in Suzuki-Miyaura reactions that involve  $Ar'B(OH)_2$ . Carbonates (Cs<sub>2</sub>CO<sub>3</sub>) give rise to slower reactions than those performed from nBu<sub>4</sub>NOH at the same concentration, even if the reactions are accelerated in the presence of water due to the generation of OH-. The mechanism of the reaction with carbonates is then similar to that established for  $nBu_4NOH$ , involving ArPd(OH)L<sub>2</sub> in the transmetalation with Ar'B(OH)<sub>2</sub>.

**Keywords:** anionic bases • arylboronic acid • cations • reaction mechanisms • palladium

Due to the low concentration of OHgenerated from CO32- in water, both transmetalation and reductive elimination result slower than those performed from nBu<sub>4</sub>NOH at equal concentrations as Cs<sub>2</sub>CO<sub>3</sub>. Therefore, the overall reactivity is finely tuned by the concentration of the common base OH- and the ratio [OH<sup>-</sup>]/[Ar'B(OH)<sub>2</sub>]. Hence, the anionic base (pure OH<sup>-</sup> or OH<sup>-</sup> generated from CO32-) associated with its countercation (Na<sup>+</sup>, Cs<sup>+</sup>, K<sup>+</sup>) plays four antagonist kinetic roles: acceleration of the transmetalation by formation of the reactive ArPd(OH)L<sub>2</sub>, acceleration of the reductive elimination, deceleration of the transmetalation by formation of unreactive Ar'B(OH)3and by complexation of ArPd(OH)L<sub>2</sub> by M<sup>+</sup>.

We recently reported kinetic data on the transmetalation/ reductive elimination steps of Suzuki–Miyaura reactions, thus revealing an unprecedented triple role of the base OH<sup>-</sup> (Scheme 2).<sup>[3]</sup> Two of them are positive: 1) formation of the



Scheme 2. Mechanism of the Suzuki–Miyaura reaction when the base is  $OH^-$  associated with  $nBu_4N^{+,[3]}$ 

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reactive *trans*-ArPd(OH)L<sub>2</sub> (L=PPh<sub>3</sub>) involved in the ratedetermining transmetalation with Ar'B(OH)<sub>2</sub> and 2) acceleration of the reductive elimination from *trans*-ArPdAr'L<sub>2</sub> (Scheme 2). The third role is negative: 3) formation of intrinsically unreactive aryl borates Ar'B(OH)<sub>3</sub><sup>-</sup> leading to two kinetically antagonist effects of hydroxide, controlled by the ratio [OH<sup>-</sup>]/[Ar'B(OH)<sub>2</sub>].<sup>[3]</sup> The reactivity of Ar'B(OH)<sub>2</sub> with ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> and lack of reactivity of Ar'B(OH)<sub>3</sub><sup>-</sup> with ArPdX(PPh<sub>3</sub>)<sub>2</sub> evidenced in our previous work<sup>[3]</sup> was soon after confirmed by Carrow and Hartwig.<sup>[4]</sup> We recently established that fluoride anions play the same three roles as those established for hydroxides, with ArPdF-(PPh<sub>3</sub>)<sub>2</sub> as the key complex involved in the transmetalation with Ar'B(OH)<sub>2</sub>.<sup>[5]</sup>

The role of the base (e.g., carbonates) in reactions involving  $\operatorname{Ar'BF_4}^-$  has been studied. Batey and Quach have made the hypothesis that anionic  $\operatorname{Ar'BF_3}_ (OH)_n^-$  (n=1, 2) must be formed from  $\operatorname{Ar'BF_3}^-$  in the presence of hydroxides generated from the base.<sup>[6a]</sup> The successive basic hydrolysis of  $\operatorname{Ar'BF_3}^-$  to eventually  $\operatorname{Ar'B(OH)_2}$  was established by Molander,<sup>[6b-d]</sup> Hutton,<sup>[6e]</sup> Lloyd-Jones,<sup>[6f]</sup> and their co-workers. The latter proposed a reaction of  $\operatorname{Ar'B(OH)_2}$  with  $\operatorname{ArPd(OH)L}$  species in a transmetalation step.<sup>[6f]</sup>

The role of cations (Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>, Ag<sup>+</sup>, Tl<sup>+</sup>) introduced as counterions of anionic bases or with  $Ar'BF_3^-$  (mainly K<sup>+</sup> ) has not been fully investigated. We used  $nBu_4NOH$  to voluntarily by-pass the role of cations and to focus on the role of the base. nBu<sub>4</sub>NOH is indeed fully dissociated in DMF into OH<sup>-</sup> and the innocent nBu<sub>4</sub>N<sup>+</sup>.<sup>[3]</sup> As pioneered by Kishi,<sup>[7a]</sup> some countercations of bases, Ag<sup>+</sup> in Ag<sub>2</sub>O or more interestingly Tl<sup>+[7]</sup> in TlOH, TlOEt, and Tl<sub>2</sub>CO<sub>3</sub> have a beneficial effect on Pd-catalyzed Suzuki reactions, compared with KOH. This is rationalized by the formation of insoluble AgX or TIX in THF/H2O, inducing a shift of the equilibrium ArPdXL<sub>2</sub>/ArPd(OH)L<sub>2</sub> (Scheme 2) towards the reactive ArPd(OH)L<sub>2</sub> whose concentration increases, leading to a faster reaction. Some anionic bases as carbonates<sup>[1]</sup> are often introduced with other countercations (e.g., Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, or Cs<sub>2</sub>CO<sub>3</sub>) whose influence on the mechanism of the catalytic reaction has never been investigated.

We report herein kinetic data which show that less halophilic cations, such as Na<sup>+</sup>, K<sup>+</sup>, and Cs<sup>+</sup> (associated to  $OH^-$ ) also play an important but decelerating role in the transmetalation step of Suzuki–Miyaura reactions. The mechanistic role of another anionic base such as carbonate (always associated with those countercations) has been investigated as well.

### **Results and Discussion**

The present mechanistic investigations were performed by means of electrochemistry<sup>[8]</sup> associated with NMR spectroscopy, as in our previous work dealing with the role of hydroxide anion (from  $nBu_4NOH$ ) in the Suzuki–Miyaura reactions.<sup>[3]</sup> The simultaneous use of the two methods allows the characterization of the reactive ArPd<sup>II</sup> complex generated from ArPdX(PPh<sub>3</sub>)<sub>2</sub>, the intermediate ArPd<sup>II</sup>Ar' and the cross-coupling product ArAr', all exhibiting a known characteristic reduction signal.<sup>[3]</sup> The palladium(0) formed in the reaction was characterized by its oxidation signal. Moreover, the rate of formation of the palladium(0) was monitored by an electrochemical technique that takes advantage of the fact that the oxidation current is proportional to the concentration.<sup>[3]</sup> The present experiments were performed under conditions representative of one cycle of a real catalytic sequence. Indeed, the kinetics were investigated from *trans*-ArPdX(PPh<sub>3</sub>)<sub>2</sub> complexes in the presence of large excesses of Ar'B(OH)<sub>2</sub> (from 10 to 100 equiv vs. Pd<sup>II</sup>) and a base to mimic catalytic reactions involving 10 to 1 mol% catalyst, respectively.

**Decelerating effect of cations**: To compare the kinetics of the transmetalation performed in the presence of bases MOH ( $M^+=Na^+$ ,  $K^+$ ,  $Cs^+$ ) to that performed in the presence of  $nBu_4NOH$  in our previous work,<sup>[3]</sup> the same reagents were investigated: *trans*-4-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub> (1) ( $C_0$ = 1.9 mM) and PhB(OH)<sub>2</sub> (2) ( $\beta C_0$ ) (Scheme 3). mOH was in-



Scheme 3.

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troduced at  $\alpha C_0$  concentration (in the range 14–40 mM) from mother solutions in methanol (1 M), as for  $nBu_4NOH$ .<sup>[3]</sup> The reactions were performed at 25 °C, in DMF (a solvent which is used in catalytic reactions,<sup>[1j–1,2,7d]</sup> as well as methanol<sup>[1]</sup>), in the presence of excess PPh<sub>3</sub> (2 equiv) to observe the formation of a stable and soluble Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>, characterized by an oxidation wave ( $E_{1/2} = +0.1$  V vs. SCE) at a rotating disk electrode whose oxidation plateau current was proportional to the Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> concentration at any time.

Figure 1 a exhibits the kinetics of formation of  $Pd^{0}(PPh_{3})_{3}$ in a reaction involving **1** (1.9 mM), **2** ( $\beta$ =20 equiv), and NaOH ( $\alpha$ =10 equiv).  $Pd^{0}(PPh_{3})_{3}$  (characterized by its oxidation signal and quantified from the value of the current at the oxidation peak) was formed in 94% yield. The crosscoupling product 4-CN-C<sub>6</sub>H<sub>4</sub>-Ph, (characterized by its reduction peak potential at -2.01 V and quantified from the value of the current at the reduction peak) was formed in 95% yield.

As it was established in our previous work,<sup>[3]</sup> Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> is formed in a reductive elimination from intermediate *trans*-ArPdAr'(PPh<sub>3</sub>)<sub>2</sub>, which is faster in the presence of OH<sup>-</sup> than the rate-determining transmetalation reaction, in which *trans*-ArPdAr'(PPh<sub>3</sub>)<sub>2</sub> is formed (Scheme 2). Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> and ArAr' (here 4-CN-C<sub>6</sub>H<sub>4</sub>-Ph) were thus formed at the same rate as the rate-determining transmetalation step. In other words, Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> was formed at the same rate as **1** disappeared in the transmetalation. The plot of lnx versus time was linear (Figure 1 b)  $(x = (i_{lim} - i_i)/i_{lim}$  where  $i_{lim} =$  final oxi-



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Figure 1. Kinetics of the reaction of *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub> (1.9 mM) with PhB(OH)<sub>2</sub> (20 equiv) in the presence of PPh<sub>3</sub> (2 equiv) and NaOH (10 equiv). a) Variation of the oxidation current *i* of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> versus time: *i* was determined by chronoamperometry at a rotating gold disk electrode (d=2 mm) polarized at +0.05 V. b) Plot of lnx versus time:  $x = (i_{lim} - i_t)/i_{lim}$ ;  $i_{lim} =$  final oxidation current of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>;  $i_t$ = oxidation current at time *t*. c) Comparison with the reaction involving *n*Bu<sub>4</sub>NOH (10 equiv)<sup>[3]</sup> instead of NaOH. All reactions were performed in DMF containing *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.3 M) at 25 °C.

dation current of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>,  $i_t$  = oxidation current at time *t*). The value of the observed rate constant  $k_{obs}$  of the transmetalation was obtained from the slope of the straight plot: lnx =  $-k_{obs}t$  (Figure 1 b).  $k_{obs}$  = 0.0096 s<sup>-1</sup> ( $\beta$  = 20,  $\alpha$  = 30, DMF, 25 °C).

A comparison of the kinetic curves obtained in the presence of NaOH (Figure 1b) or  $nBu_4NOH$  (Figure 1c) at the same initial concentrations reveals a slower reaction in the presence of NaOH. The decelerating effect of cations  $M^+ =$ Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup> is a general feature (Figure 2a). The antagonist effect of OH<sup>-</sup> due to the competitive formation of the reactive ArPd(OH)(PPh\_3)<sub>2</sub> and the unreactive Ar'B(OH)<sub>3</sub><sup>-</sup>, that results in the bell-shaped variation of  $k_{obs}$  versus the OH<sup>-</sup> concentration (evidenced in our previous work),<sup>[3]</sup> was still observed for all investigated bases (Figure 2a). When considering the maximum value of  $k_{obs}$  for each cation, a decreasing reactivity order was established:

 $nBu_4NOH > KOH > CsOH > NaOH$ 

As  $H_2O$  could be introduced via the base (e.g., CsOH·H<sub>2</sub>O), the effect of  $H_2O$  on the kinetics of the transmetalation was tested, leading to nonsignificant effects (Figure 2 a, open symbols).





Figure 2. a) Kinetics of the reaction of *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub> **1** ( $C_0$ =1.9 mM) with PhB(OH)<sub>2</sub> (20 equiv) in the presence of PPh<sub>3</sub> (2 equiv) and MOH ( $\alpha$  equiv) (M=nBu<sub>4</sub>N,<sup>[3]</sup> K, Cs, Na). Plots of  $k_{obs}$ versus  $\alpha$  (note that  $k_{obs}$  was plotted versus the value of the initial amount of hydroxides introduced into the medium). Effect of H<sub>2</sub>O: ( $\Box$ ) 30 equiv added to nBu<sub>4</sub>NOH; ( $\odot$ ) 15 equiv added to KOH and ( $\nabla$ ) 30 equiv added to CsOH. ( $\diamond$ ): reaction performed in the presence of nBu<sub>4</sub>NOH (15 equiv) and NaBF<sub>4</sub> (15 equiv). b) Kinetics of the reaction of *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub> ( $C_0$ =1.9 mM) with PhB(OH)<sub>2</sub> (20 equiv) in the presence of PPh<sub>3</sub> (2 equiv), nBu<sub>4</sub>NOH (15 equiv) and  $\alpha'$  equiv of ( $\blacktriangle$ ) KBF<sub>4</sub>, or ( $\blacklozenge$ ) NaBF<sub>4</sub> (concentration range for MBF<sub>4</sub>: 0-42 mM). Plot of 1/  $k_{obs}$  versus [MBF<sub>4</sub>] expressed in equiv ( $\alpha'$ ) versus Pd<sup>II</sup> complex **1**. All reactions were performed in DMF containing nBu<sub>4</sub>NBF<sub>4</sub> (0.3 M) at 25 °C.

Interestingly, the value of  $k_{obs}$  obtained for the reaction of **1** with **2** (20 equiv) in the presence of  $nBu_4NOH$  (15 equiv) and NaBF<sub>4</sub> (15 equiv) was similar to that obtained for the same reaction performed in the presence of NaOH (15 equiv);  $k_{obs} = 0.0104$  and  $0.0109 \text{ M}^{-1} \text{s}^{-1}$ , respectively (Figure 2a), thus confirming the specific deceleration effect of Na<sup>+</sup>. This was further confirmed in reactions performed with  $nBu_4NOH$  (15 equiv) as the base, in the presence of increasing amounts ( $\alpha'$  equiv) of KBF<sub>4</sub> or NaBF<sub>4</sub> (free ions in DMF) in the range 0–42 mM (Figure 2b). The decelerating effect of the cations Na<sup>+</sup> and K<sup>+</sup> was definitively established by linear plots of  $1/k_{obs}$  versus the concentration of M<sup>+</sup> (Figure 2b):  $1/k_{obs} = a + b\alpha' = a + b[M<sup>+</sup>]/C_0$ .

A decrease of the concentration of the active ArPd(OH)-(PPh<sub>3</sub>)<sub>2</sub> (in equilibrium with ArPdBr(PPh<sub>3</sub>)<sub>2</sub>, Scheme 2) must be at the origin of the decelerating effect exerted by cations. Cations<sup>[9]</sup> might interfere in the kinetics of the transmetalation via formation of ion pairs (in equilibrium with free ions) such as [M<sup>+</sup>OH<sup>-</sup>]. This would decrease the concentration of the active ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> and consequently slow down the transmetalation. Cations may also ion-pair with the anions released during the reaction, such as [M<sup>+</sup>

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Br<sup>-</sup>], leading to increased concentrations of the active ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> and consequently in accelerating the transmetalation. Ion pairs are not expected to be formed in polar DMF. Nevertheless, the conductivity of MOH and MBr was measured in DMF at 25 °C. The conductivity of MOH (M<sup>+</sup>=Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>) increased linearly with its concentrations (in the range: 0–35 mM; see Figures S1–S3 in the Supporting Information); the conductivity of MBr (M<sup>+</sup>=Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>) as well for concentrations in the range: 0–120 mM (Figures S4–S6 in the Supporting Information). This means that only free ions were present in solution, M<sup>+</sup> +OH<sup>-</sup> and M<sup>+</sup>+Br<sup>-</sup>, respectively. The decelerating effect of cations M<sup>+</sup> by formation of ion pairs was thus ruled out.

The <sup>1</sup>H NMR spectrum of Ar'B(OH)<sub>2</sub> (Ar'=p-CN-C<sub>6</sub>H<sub>4</sub>, Ph) in [D<sub>7</sub>]DMF was not affected by addition of NaBF<sub>4</sub> (5 equiv), thus ruling out any interaction of Na<sup>+</sup> with Ar'B(OH)<sub>2</sub>. The aromatic protons of Ar'B(OH)<sub>3</sub><sup>-</sup>, nBu<sub>4</sub>N<sup>+</sup> (Ar'=p-CN-C<sub>6</sub>H<sub>4</sub>, Ph) in [D<sub>7</sub>]DMF were slightly shifted after addition of NaBF<sub>4</sub> (5 equiv) but a similar shift was observed upon addition of nBu<sub>4</sub>NBF<sub>4</sub> (5 equiv), therefore evidencing that the shift was not due to Na<sup>+</sup> but to a ionic strength on the charged borate.

Alkali cations are known to bind oxygen centers as in alcohols.<sup>[10]</sup> The decelerating effect of the cations in the transmetalation might be due their complexation to the hydroxide of ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> (**3**) to form **3-M**<sup>+</sup> [Eq. (1)]. This would decrease the concentration of the active ArPd(OH)-(PPh<sub>3</sub>)<sub>2</sub> involved in the rate-determining transmetalation step.

The complexation of ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> by cation M<sup>+</sup> would thus be in competition with its transmetalation by Ar'B(OH)<sub>2</sub> (Scheme 4). Higher the affinity of the cation for ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub>, slower the transmetalation. From the kinetic curves in Figure 2a, one predicts that the affinity of the cations for the OH group of ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> must decrease in the order: Na<sup>+</sup> > Cs<sup>+</sup> > K<sup>+</sup>, which is in agreement with the decreasing affinity order of cations for alcohols:



Scheme 4. Competitive complexation/transmetalation in the presence of cations  $M^+$  (Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>) in DMF (solvent voluntarily omitted).<sup>[9]</sup>

 $Na^+ > K^+$  established by DFT calculations (however performed in the gas phase).<sup>[10b]</sup> Theoretical data for the affinity of Cs<sup>+</sup> for alcohols are not available.

The complexation of the OH group of trans-ArPd(OH)-(PPh<sub>3</sub>)<sub>2</sub> by Na<sup>+</sup> was evidenced by NMR.<sup>[11a]</sup> The <sup>1</sup>H NMR spectrum of *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-Pd(OH)(PPh<sub>3</sub>)<sub>2</sub> (**3a**) (20 mM) in [D<sub>7</sub>]DMF exhibited the two doublets of the aryl group (see the Supporting Information). After addition of NaBF<sub>4</sub> (7.5 equiv, 150 mm), the two doublets were slightly shifted downfield and two new doublets appeared upfield assigned to the complex 3a-Na<sup>+</sup> (Equation (1), see Experimental Section). A new broad singlet for the OH proton of 3a-Na<sup>+</sup> was observed at -2.58 ppm. The <sup>31</sup>P NMR singlet of **3a** (14 mm) was shifted downfield after addition of NaBF<sub>4</sub> ( $\alpha'$  = 2 equiv, 28 mm) while a new singlet appeared at upper field assigned to 3a-Na<sup>+</sup> (Figure S7 in the Supporting Information). The magnitude of its singlet increased at the expenses of the magnitude of the singlet of 3a after successive addition of NaBF<sub>4</sub> up to 105 mм (Figure S7).<sup>[11b]</sup> Therefore, Na<sup>+</sup> did effectively interact with ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> by reversible complexation of its hydroxide [Eq. (1)]. The equilibrium constant  $K_{\text{Na}} = x/[C_0(1-x)(\alpha'-x)]$  was calculated from the slope of the linear plot of x/(1-x) versus  $(\alpha'-x)$  where x/(1-x)(1-x) was given by the NMR ratio of the singlets of 3a-Na<sup>+</sup> and 3a, respectively (Figure S8 in the Supporting Information). This led to  $K_{\rm Na} = 75 \pm 5 \,{\rm m}^{-1}$  (DMF, 27 °C). Since CsBF<sub>4</sub> is not commercially available, the complexation of trans-PhPd(OH)(PPh<sub>3</sub>)<sub>2</sub> (**3b**) by Cs<sup>+</sup> was evidenced by <sup>31</sup>P NMR in the reaction of CsOH with *trans*-PhPdBr(PPh<sub>3</sub>)<sub>2</sub> in [D<sub>7</sub>]DMF (22.66 ppm for **3b–Cs<sup>+</sup>** vs. 22.41 ppm for **3b**). The experimental decelerating effect of the cation Cs<sup>+</sup> on the kinetics of the transmetalation  $(Na^+ > Cs^+ > K^+)$  was found to be inverted with respect to the expected one based on its ionic radius (Na<sup>+</sup> >K<sup>+</sup> >Cs<sup>+</sup>). No simple explanation seems available other than invoking specific interactions of Cs<sup>+</sup> with the DMF solvent.<sup>[11c]</sup>

The new kinetic law that takes into account the new equilibrium constant  $K_{\rm M}$  (Scheme 5) is displayed in Equa-



Scheme 5. Role of the countercation  $M^+$  (Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>) of the base OH<sup>-</sup> in the mechanism of the Suzuki–Miyaura reaction (the solvent DMF is voluntarily omitted).<sup>[9]</sup>

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tion (2).<sup>[12]</sup> Due to the excess of MOH, the concentration  $[M^+]$  may be considered as constant all along the reaction under these catalytic-like conditions (rate =  $k_{obs}[Pd^{II}]_{total}$ ).

$$k_{\rm obs} = k_{\rm tm} \beta C_0 \left( \frac{1}{1 + K_{\rm OH} [\rm OH^-]} \right) \left( \frac{K_{\rm x} [\rm OH^-]}{[\rm X^-] + K_{\rm x} [\rm OH^-] (1 + K_{\rm M} [\rm M^+])} \right)$$
(2)

The theoretical variation of  $k_{obs}$  versus [OH<sup>-</sup>] exhibits a maximum, as experimentally observed in Figure 2a. The position of the maximum [Eq. (3)] and the value of  $k_{obs}^{max}$ depend on the concentration of the cation and the value of  $K_{M}$ .

$$[OH^{-}]^{max} = \left(\frac{[X^{-}]}{K_{x}K_{OH}(1 + K_{M}[M^{+}])}\right)^{1/2}$$
(3)

The theoretical hyperbolic decay of  $k_{obs}$  versus [M<sup>+</sup>] [Eq. (4)] is in agreement with the decelerating effect of M<sup>+</sup> observed in Figure 2 b, being consistent with our mechanism.

$$\frac{1}{k_{obs}} = \left(\frac{1 + K_{OH}[OH^{-}]}{k_{m}\beta C_{0}}\right) \left(1 + \frac{[X^{-}]}{K_{x}[OH^{-}]}\right) + \frac{(1 + K_{OH}[OH^{-}])}{k_{m}\beta C_{0}} \times K_{M}[M^{+}] = a' + b'[M^{+}]$$
(4)

Scheme 5 updates our former mechanism of the Suzuki-Miyaura reaction through including the role of cations  $M^+$ =Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup> (counterions of the anionic base, here OH<sup>-</sup>) which in contrast to Ag<sup>+</sup> or Tl<sup>+</sup> are at the origin of a decelerating transmetalation via their complexation to the reactive ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub>. Hence, the base not only plays a role via the ratio [OH<sup>-</sup>]/[Ar'B(OH)<sub>2</sub>] but also via its associated countercation M<sup>+</sup>. Moreover, other sources of cations need to be considered with care, e.g., K<sup>+</sup> when Ar'BF<sub>3</sub><sup>-</sup>K<sup>+</sup> are used as precursors of Ar'B(OH)<sub>2</sub>.<sup>[6]</sup>

**Carbonate as base**: Carbonate ions are often used as bases in Suzuki–Miyaura reactions involving arylboronic acids.<sup>[1,13a,b]</sup> They are mainly introduced with a countercation, as in Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, or Na<sub>2</sub>CO<sub>3</sub> and are moderately soluble even in sufficiently polar solvents such as DMF.<sup>[13c]</sup> Their low solubility is often compensated by the introduction of a small amount of water.<sup>[1,13b]</sup> As  $(nBu_4N)_2CO_3$  was not available, Cs<sub>2</sub>CO<sub>3</sub>.<sup>[13c]</sup> However, one has to keep in mind that that Cs<sup>+</sup> exerts a decelerating effect in the transmetalation by a factor of about 2.4 when comparing  $nBu_4NOH$ and CsOH at similar concentrations (compare the respective values of  $k_{obs}^{max}$  in Figure 2 a).

The reaction of "dry"  $Cs_2CO_3$  (10 equiv) with *trans*-PhPdBr(PPh<sub>3</sub>)<sub>2</sub> (5 mM) was followed by <sup>31</sup>P and <sup>1</sup>H NMR in [D<sub>7</sub>]DMF. No reaction took place, the singlet of *trans*-PhPdBr(PPh<sub>3</sub>)<sub>2</sub> (24.06 ppm) remained unchanged. It was only after addition of water (10% in volume) that the two singlets characteristic of *cis* (32.94 ppm) and *trans* (32.4 ppm) [PhPd( $\mu$ -OH)(PPh<sub>3</sub>)]<sub>2</sub> appeared whereas *trans*-



Scheme 6.

PhPd(OH)(PPh<sub>3</sub>)<sub>2</sub><sup>[14]</sup> was formed in the presence of excess PPh<sub>3</sub> (2 equiv; Scheme 6). This evidences that in the presence of water, Cs<sub>2</sub>CO<sub>3</sub> generated low concentrations of OH<sup>-</sup> (Equation (5) in Scheme 6)<sup>[6,13b]</sup> which played the same role vis à vis ArPdXL<sub>2</sub> as  $nBu_4NOH$  did.<sup>[3]</sup>

Smith et al.<sup>[13b]</sup> reported that  $K_2CO_3$  in THF/H<sub>2</sub>O generates OH<sup>-</sup> which reacts with Ar'B(OH)<sub>2</sub> to generate Ar'B(OH)<sub>3</sub><sup>-</sup>. An acceleration of a Suzuki–Miyaura reaction between ArCl and Ar'B(OH)<sub>2</sub> was observed upon increasing the amount of water.<sup>[13b]</sup> At that time (1994), the accelerating effect was explained by the formation of Ar'B(OH)<sub>3</sub><sup>-</sup> which was supposed to be more reactive than Ar'B(OH)<sub>2</sub>. However, we established in 2011 that Ar'B(OH)<sub>3</sub><sup>-</sup> is intrinsically unreactive.<sup>[3]</sup> Hence, the cause of the accelerating effect must be rather found in the formation of reactive ArPd(OH)L<sub>2</sub> as evidenced above (Schemes 1 and 6).

As established in previous works,<sup>[3,15]</sup> trans-PhPd(OH)- $(PPh_3)_2$  (1.9 mM) reacts with p-CN-C<sub>6</sub>H<sub>4</sub>-B(OH)<sub>2</sub> (5 equiv) in the presence of  $PPh_3$  (2 equiv) to generate the stable complex trans-p-CN-C<sub>6</sub>H<sub>4</sub>-Pd-Ph(PPh<sub>3</sub>)<sub>2</sub> detected in cyclic voltammetry by its reduction signal ( $E^{p}_{red} = -1.47 \text{ V}$ ). The addition of "dry" Cs<sub>2</sub>CO<sub>3</sub> (2.5 equiv) resulted in the slow formation of  $Pd^{0}(PPh_{3})_{3}$  ( $t_{1/2}=1$  h 30) together with the cross-coupling product p-CN-C<sub>6</sub>H<sub>4</sub>-Ph, both detected by their oxidation and reduction signals, respectively. The reaction was considerably slower than that observed when *n*Bu<sub>4</sub>NOH was added to the same intermediate *trans-p*-CN- $C_6H_4$ -Pd-Ph(PPh<sub>3</sub>)<sub>2</sub> ( $t_{1/2}=2$  min).<sup>[3]</sup> This suggests that  $CO_3^{2-1}$ may favor the reductive elimination from trans-p-CN-C<sub>6</sub>H<sub>4</sub>-Pd-Ph(PPh<sub>3</sub>)<sub>2</sub>, most probably via  $OH^{-}$  generated by reaction of carbonates with water traces [Eq. (5)], through formation anionic pentacoordinated bisaryl-Pd<sup>II</sup> complexes of (Scheme 7).<sup>[16]</sup> This by-passed the classical overall slow reductive elimination due to the endergonic formation of cis-ArPdAr'L<sub>2</sub> from *trans*-ArPdAr'L<sub>2</sub>.<sup>[3]</sup>



Scheme 7. Transmetalation and  $OH^-$ -assisted reductive elimination from trans-ArPdAr'L<sub>2</sub>.

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It was therefore of interest to investigate the kinetics of the reaction of *trans*-ArPdX(PPh<sub>3</sub>)<sub>2</sub> with arylboronic acids,  $Ar'B(OH)_2$  in DMF in the presence of "dry" Cs<sub>2</sub>CO<sub>3</sub> and then in the presence of increasing amounts of added water (Scheme 8).

The kinetics of the formation of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> was followed by chronoamperometry at a rotating gold disk electrode (see above). The evolution of the oxidation current of Pd<sup>0</sup>- $(PPh_3)_3$  (proportional to its concentration) was recorded with time after addition of 2 (20 equiv) to a solution containing 1 ( $C_0 = 1.9 \text{ mM}$ ), PPh<sub>3</sub> (2 equiv) and Cs<sub>2</sub>CO<sub>3</sub> ( $\alpha$  equiv). The reaction was first performed with "dry"  $Cs_2CO_3$  (15 equiv) in the absence of water. Whereas the same reaction performed in the presence of nBu<sub>4</sub>NOH (15 equiv) led to the formation of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> and p-CN- $C_6H_4$ -Ph with a half-reaction time of  $t_{1/2} = 10 \text{ s}^{[3]}$  no formation of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> was observed in the presence of "dry"  $Cs_2CO_3$  (15 equiv), even after long duration times (>3 h). In the presence of higher amounts of PhB(OH)<sub>2</sub> (50 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (25 equiv), a slow reaction took place  $(t_{1/2} = 14300 \text{ s};$ Figure 3 a). The reaction was accelerated  $(t_{1/2} = 3250 \text{ s})$  by increasing both concentrations:  $PhB(OH)_2$  (100 equiv) and  $Cs_2CO_3$  (50 equiv) while keeping the same ratio  $\alpha/\beta$  (Figure 3b). Though, the reaction remained slower than those performed with  $nBu_4NOH^{[3]}$  instead of dry Cs<sub>2</sub>CO<sub>3</sub> at the same concentration.



Figure 3. Evolution of the molar fraction x' of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> versus time in the reaction of *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub> **1** (1.9 mM) with: a) PhB(OH)<sub>2</sub> (50 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (25 equiv); b) PhB(OH)<sub>2</sub> (100 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (50 equiv). Both reactions were performed in DMF containing *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.3 M) in the presence of PPh<sub>3</sub> (2 equiv) at 25 °C. Molar fraction of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>:  $x' = i_t/i_{lim}$  ( $i_t$ =oxidation current of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> (proportional to its concentration) at time *t*,  $i_{lim}$ =final oxidation current). The currents were determined at a rotating gold disk electrode (*d*=2 mm) polarized at +0.05 V versus SCE.

Interestingly, the formation of  $Pd^{0}(PPh_{3})_{3}$  exhibited an induction period (Figure 3) which evidenced the formation of an intermediate complex, such as *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-Pd-Ph-(PPh\_{3})<sub>2</sub> (see above). The latter evolved at longer times to

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afford  $Pd^0(PPh_3)_3$  and the coupling product *p*-CN-C<sub>6</sub>H<sub>4</sub>-Ph. This indicates that in the presence of "dry" Cs<sub>2</sub>CO<sub>3</sub>, under our experimental conditions, the time scales of the transmetalation and the reductive elimination were close to each other

and that the reductive elimination was not considerably faster than the transmetalation, in contrast to what was observed when  $nBu_4NOH$  was used as the base.<sup>[3]</sup>

When the same reaction was performed in the presence of added H<sub>2</sub>O ( $\delta$ =25 equiv), the induction period was shortened (compare Figure 4a and b) and the Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> formation became faster. Both effects were reinforced in the presence of a larger amount of water ( $\delta$ =1750 equiv; Figure 4c).



Figure 4. Evolution of the molar fraction x' of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> versus time formed in the reaction of *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub> **1** (1.9 mM) with PhB(OH)<sub>2</sub> (50 equiv) in the presence of Cs<sub>2</sub>CO<sub>3</sub> (25 equiv) and PPh<sub>3</sub> (2 equiv): a) without any water, b) in the presence of H<sub>2</sub>O (25 equiv), c) in the presence of H<sub>2</sub>O (1750 equiv). All reactions were performed in DMF containing *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.3 M) at 25 °C. Molar fraction of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>:  $x' = i/i_{lim} = final$  oxidation current of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> (proportional to its concentration),  $i_{lim} = final$  oxidation current). The current intensities were determined at a rotating gold disk electrode (d=2 mm) polarized at +0.05 V versus SCE.

All these experiments established that the transmetalation resulted very slow in the presence of "dry" Cs<sub>2</sub>CO<sub>3</sub> because of the lack of a significant concentration of OH<sup>-</sup> which consequently led to a low concentration of the reactive trans-p- $CN-C_6H_4-Pd(OH)(PPh_3)_2$ . The reductive elimination was also slow due to the lack of OH-. The half-reaction time of the reductive elimination was estimated to  $t_{1/2} = 7 \times 10^3$  s by considering the part of the kinetic curve at longest times in Figure 4a. In the presence of increasing amounts of water, i.e., in the presence of increasing amounts of OH<sup>-</sup> [Eq. (5)], the transmetalation was accelerated through increasing  $ArPd(OH)(PPh_3)_2$  concentration. The reductive elimination was accelerated as well because promoted by OH- (compare the kinetic curves at long times in Figure 4). Nevertheless, reactions involving Cs<sub>2</sub>CO<sub>3</sub>, even in the presence of large amounts of water, were considerably slower than those involving  $nBu_4NOH$  at equal concentrations. This cannot be attributed to the decelerating effect of the cation Cs<sup>+</sup> (a de-

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celerating effect of a factor 2.4 was expected, see Figure 2a) but to the low concentration of hydroxides generated from  $Cs_2CO_3$  in water [Eq. (5)]. Once again, the rates of the transmetalation and reductive elimination were controlled by the concentration of hydroxides. However, accurate kinetic data could not be obtained since the concentration of hydroxides generated from  $Cs_2CO_3$  could not be evaluated with certainty.<sup>[6f]</sup> Moreover, reaction rates were found to be very dependent on the quality of  $Cs_2CO_3$ , "dry" or not, bought from different companies, a feature already observed by Meyers et al. in palladium-catalyzed C–N cross-coupling reactions.<sup>[17]</sup>

Therefore, Suzuki–Miyaura reactions performed in the presence of 'dry" carbonates as base are considerably slower even in the presence of water than those performed in the presence of hydroxide ( $nBu_4NOH$ ) at identical concentrations. However, the mechanism remains similar, involving the same reactive ArPd(OH)L<sub>2</sub> (Scheme 9). The reactions are slower due to the low concentration of OH<sup>-</sup> generated from carbonates which is at the origin of 1) a slow transmetalation because of the low concentration of the reactive ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> and 2) a slow reductive elimination because promoted by hydroxides present at low concentrations (Scheme 9).



Scheme 9. Mechanism of the Suzuki–Miyaura reaction when the base is carbonate in DMF/water. The role of the countercation (here  $Cs^+$ ) is not mentioned in this Scheme (see Scheme 5 for the role of the countercation).

Acetate as base: Acetate ions are used as base in cross-coupling reactions of aryl halides ArX and  $(RO)_2B$ -B $(OR)_2$  leading to Ar-B $(OR)_2$ .<sup>[1c]</sup> Miyaura and Suzuki reported that the reaction of *trans*-PhPdBr $(PPh_3)_2$  with  $(RO)_2B$ -B $(OR)_2$  ( $(RO)_2$ =pinacolato)<sup>[1c,f]</sup> which generates PhB $(OR)_2$  was accelerated in the presence of acetate ions (KOAc in DMSO), via the formation of *trans*-PhPd $(OAc)(PPh_3)_2$  by Br/OAc exchange.<sup>[1c,f,18]</sup> A transmetalation of *trans*-PhPd $(OAc)(PPh_3)_2$  by (RO)<sub>2</sub>B-B $(OR)_2$  was supposed to generate *trans*-PhPd-B $(OR)_2(PPh_3)_2$  and then PhB $(OR)_2$  by subsequent reductive elimination. Surprisingly, PhB $(OR)_2$  did not further couple with *trans*-PhPd $(OAc)(PPh_3)_2$  to generate PhPh,<sup>[1c,f]</sup> as it

should do in a classical Suzuki–Miyaura reaction. According to other authors, an extra base as  $OH^-$  is required to perform the second cross-coupling, suggesting that acetates are not a good base for cross-coupling of  $Ar'B(OR)_2$ .<sup>[Ic,19,20a]</sup> Up to our knowledge, acetates are not an efficient base for the Suzuki–Miyaura reaction performed from  $Ar'B(OH)_2$ .<sup>[19,20b]</sup> This incited us to investigate the role of acetates in Suzuki– Miyaura reactions. They were introduced as  $nBu_4NOAc$  in order to by-pass the role of countercations as Na<sup>+</sup> or K<sup>+</sup> (see above).

The formation of *trans*-PhPd(OAc)(PPh<sub>3</sub>)<sub>2</sub> by reversible reaction of  $nBu_4NOAc$  with *trans*-PhPdX(PPh<sub>3</sub>)<sub>2</sub> (X=I, Br, Cl) has been already evidenced in our group [Eq. (6)] and the equilibrium constant  $K_{X/OAc}$  determined in DMF.<sup>[18]</sup>

$$Ar - Pd - X + AcO^{-} \xrightarrow{K_{X/OAc}} Ar - Pd - OAc + X^{-} (6)$$

$$Ar - Pd - OAc + Ar'B(OH)_{2} \xrightarrow{K} Ar - Pd - Ar' (7)$$

$$Ar - Pd - Ar' + AcO^{-} \xrightarrow{L} Ar - Ar' + PdL_{3} (8)$$

As observed in our previous work,<sup>[3]</sup> no reaction took place between *trans*-PhPdBr(PPh<sub>3</sub>)<sub>2</sub> (1.9 mM) and *p*-MeO-C<sub>6</sub>H<sub>4</sub>-B(OH)<sub>2</sub> ( $\beta$ =20 equiv) in the presence of PPh<sub>3</sub> (2 equiv) in DMF at 25 °C. Addition of *n*Bu<sub>4</sub>NOAc (from  $\alpha$ =10 to 50 equiv) did not lead to the formation of the coupling product *p*-MeO-C<sub>6</sub>H<sub>4</sub>-Ph neither at 25 °C, nor at 50 °C (Scheme 10). Similarly, no reaction took place between

trans-ArPdXL<sub>2</sub> + Ar'B(OH)<sub>2</sub> + 
$$nBu_4NOAc$$
 + 2 L   
 $C_0 \quad \beta C_0 \quad \alpha C_0$ 
DMF, 25 °C
  
 $L = PPh_3$ 
ArAr' + Pd<sup>0</sup>L<sub>3</sub>

Scheme 10.

*trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub> (1.9 mM), PhB(OH)<sub>2</sub> (from 10 to 20 equiv) in the presence of PPh<sub>3</sub> (2 equiv) and  $nBu_4NOAc$  (from to 10 to 50 equiv) in DMF at 25°C (Scheme 10).

Addition of  $nBu_4NOAc$  (5 equiv) to p-CN-C<sub>6</sub>H<sub>4</sub>-PdBr-(PPh<sub>3</sub>)<sub>2</sub> (1.9 mM) before introduction of PhB(OH)<sub>2</sub> (10 equiv) did not lead to any reaction, despite the detection of the complex p-CN-C<sub>6</sub>H<sub>4</sub>-Pd(OAc)(PPh<sub>3</sub>)<sub>2</sub> formed by reaction of AcO<sup>-</sup> with p-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub>, as attested by their reduction peak potentials ( $E^{p}_{red} = -1.91$  V and -1.80 V respectively) [Eq. (6)]. The intermediate complex *trans*-ArPdAr'L<sub>2</sub> (Ar=p-CN-C<sub>6</sub>H<sub>4</sub>, Ar'=Ph) was not formed since its reduction peak (at  $E^{p}_{red} = -1.47$  V, see above) was not observed. Consequently, *trans*-ArPd(OAc)(PPh<sub>3</sub>)<sub>2</sub> did

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not undergo any transmetalation with  $Ar'B(OH)_2$  [Eqs. (6)–(7)].

Even if the intermediate trans-ArPdAr'L<sub>2</sub> was not formed [Eq. (7)], it was nevertheless of academic interest to test the effect of AcO<sup>-</sup> on the fate of this stable intermediate that easily undergoes reductive elimination in the presence of OH<sup>-</sup>, as evidenced in our previous work.<sup>[3]</sup> The complex trans-p-CN-C<sub>6</sub>H<sub>4</sub>-Pd-Ph(PPh<sub>3</sub>)<sub>2</sub> was generated by reacting *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-Pd(OH)(PPh<sub>3</sub>)<sub>2</sub> (1.9 mM) with PhB(OH)<sub>2</sub> (10 equiv) in the presence of PPh<sub>3</sub> (2 equiv) (Figure S9). No Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> was formed upon addition of *n*Bu<sub>4</sub>NOAc (15 equiv) after 1 h. It is only after addition of nBu<sub>4</sub>NOH (15 equiv) that  $Pd^{0}(PPh_{3})_{3}$  and p-CN-C<sub>6</sub>H<sub>4</sub>-Ph were formed, in agreement with our previous results (Figure S9 in the Supporting Information).<sup>[3]</sup> Therefore, even if the intermediate complex trans-ArPdAr'L<sub>2</sub> were formed in the transmetalation, it did not undergo any reductive elimination in the presence of acetate ions [Eq. (8)]. This definitively explains why acetates are not good bases for Suzuki-Miyaura reactions performed from arylboronic acids.[19,20c]

### Conclusion

Cations M<sup>+</sup> (Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>) inevitably introduced as countercations of anionic bases in palladium-catalyzed Suzuki– Miyaura reactions exert an unexpected decelerating effect in the transmetalation step (a key step in Suzuki–Miyaura reactions) with the following decreasing reactivity order:  $nBu_4NOH > KOH > CsOH > NaOH$ . This results from a complexation of the hydroxoligand of the reactive ArPd(OH)(PPh\_3)<sub>2</sub> complex by the cation M<sup>+</sup> (Scheme 5). Though decreased, the overall reactivity remains finely tuned by the concentration of the base OH<sup>-</sup> and the ratio [OH<sup>-</sup>]/[Ar'B(OH)<sub>2</sub>].

The mechanism of the transmetalation/reductive elimination already established when the base is  $nBu_4NOH$  has been investigated for other bases, carbonates and acetates. Acetates (from  $nBu_4NOAc$ ) are not an efficient base. Indeed, they react with *trans*-ArPdX(PPh\_3)<sub>2</sub> to form *trans*-ArPd(OAc)(PPh\_3)<sub>2</sub> which did not transmetalate with Ar'B(OH)<sub>2</sub>. This explains why acetates are not used in Suzuki–Miyaura reactions performed from ArB(OH)<sub>2</sub>.

Even if the reactions are accelerated upon addition of water, carbonates (from  $Cs_2CO_3$ ) lead to much slower reactions than those performed from  $nBu_4NOH$  at the same concentration. However, they proceed through a similar mechanism, that is via the formation of the reactive *trans*-ArPd(OH)(PPh\_3)<sub>2</sub> from hydroxide ions generated through the reaction of carbonates with water (Scheme 9 to be compared with Scheme 1). Carbonates (via hydroxides) promote the reductive elimination from intermediate *trans*-ArPdAr'-(PPh\_3)<sub>2</sub>. However, due to the relatively low concentration of hydroxide ions generated from carbonates in water, both transmetalation and reductive elimination result slower than those performed in the presence of  $nBu_4NOH$  (at the same concentration as carbonate). Noteworthy, this deceleration

results more intense on the reductive elimination leading to the observation of an induction period for the generation of  $Pd^{0}(PPh_{3})_{3}$ .

In Suzuki–Miyaura reactions involving a fast oxidative addition (aryl iodides and bromides), one needs to increase the rate of the rate-determining transmetalation. This requires: 1) to select the best base:  $OH^- > CO_3^{2-} \gg AcO^-$ , 2) to optimize the ratio  $[OH^-]/[Ar'B(OH)_2]$ , and 3) to select the best countercation of the anionic base:  $TI^+$  or  $Ag^+ > nBu_4N^+ > K^+ > Cs^+ > Na^+$ . This optimization is of course less crucial if the oxidative addition is rate determining as for aryl chlorides. However, the mechanism of the transmetalation/reductive elimination, elucidated in the present work for carbonates and in our previous work for hydroxides<sup>[3]</sup> remains valid.

### **Experimental Section**

Reaction of NaBF<sub>4</sub> with *trans-p*-CN-C<sub>6</sub>H<sub>4</sub>-Pd(OH)(PPh<sub>3</sub>)<sub>2</sub> (3a) as Monitored by <sup>1</sup>H NMR (250 MHz, [D<sub>7</sub>]DMF) and <sup>31</sup>P NMR (101 MHz, [D<sub>7</sub>]DMF): The two doublets at 7.16 and 6.72 ppm of the aryl group of *p*-CN-C<sub>6</sub>H<sub>4</sub>-Pd(OH)(PPh<sub>3</sub>)<sub>2</sub> (3) (10 µmol, 20 mM) in 0.5 mL of [D<sub>7</sub>]DMF (see the Supporting Information) were slightly shifted of 0.025 ppm downfield after addition of 8 mg (75 µmol, 7.5 equiv) of NaBF<sub>4</sub>. Two new doublets appeared at upfield at 7.01 ppm (d,  $J_{HH}$ =8 Hz) and 6.63 ppm (d,  $J_{HH}$ =8 Hz), assigned to the complex **3a–Na<sup>+</sup>**, formed by complexation of the OH of **3a** by Na<sup>+</sup> [Eq. (1)]. The OH singlet in **3a–Na<sup>+</sup>** was observed at –2.58 ppm.

In another experiments, the <sup>31</sup>P NMR singlet of *p*-CN-C<sub>6</sub>H<sub>4</sub>-Pd(OH)-(PPh<sub>3</sub>)<sub>2</sub> (**3a**) (7 µmol, 14 mM) at 22.41 ppm was shifted to 22.68 ppm after addition of 1.5 mg (14 µmol, 2 equiv, 28 mM) of NaBF<sub>4</sub>, while a new singlet appeared at upper field at 21.82 ppm for complex **3a–Na<sup>+</sup>**, in the ratio **3a–Na<sup>+</sup>/3***a*=0.93 (Figure S7 in the Supporting Information). After addition of again 3.1 mg (total 28 µmol, 4 equiv, 56 mM) of NaBF<sub>4</sub>, the ratio became **3a–Na<sup>+</sup>/3***a*=3.1 (Figure S7). Further addition of 2.7 mg (total 52.5 µmol, 7.5 equiv, 105 mM) of NaBF<sub>4</sub> gave **3a–Na<sup>+</sup>/3***a*=7.39. The equilibrium constant  $K_{\rm M}$  was calculated from the <sup>31</sup>P NMR data (see above and Figure S8 in the Supporting Information).

The same reaction was performed in the presence of 42 mg (125  $\mu$ mol, 250 mM) of  $nBu_4NBF_4$  without any effect on the <sup>1</sup>H NMR, ruling out any effect of the ionic strength.

No significant effect of KBF<sub>4</sub> was observed at 150 mm. This establishes that the affinity of Na<sup>+</sup> for **3a** is considerably higher than that of K<sup>+</sup>, explaining why the rate of the transmetalation was more affected by Na<sup>+</sup> than by K<sup>+</sup> (Figure 2a and b). Experiments with higher amounts of KBF<sub>4</sub> could not be done because of the lack of solubility of KBF<sub>4</sub>.

Typical Procedure for the kinetics of the reaction of p-CN-C<sub>6</sub>H<sub>4</sub>-PdBr-(PPh<sub>3</sub>)<sub>2</sub> with PhB(OH)<sub>2</sub>, in the Presence of MOH, as monitored by chronoamperometry at a rotating disk electrode at 25°C: All experiments were performed under argon atmosphere at 25°C in a thermostated three-electrode cell connected to a Schlenk line. The counterelectrode was a platinum wire of ca. 1 cm<sup>2</sup> apparent surface area; the reference was a saturated calomel electrode (SCE) separated from the solution by a bridge filled with 2 mL of a 0.3 M nBu<sub>4</sub>NBF<sub>4</sub> solution in DMF. 16 mL of degassed DMF containing 0.3 M nBu<sub>4</sub>NBF<sub>4</sub> were poured into the cell, followed by 24 mg (0.03 mmol, 1.9 mm) of p-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub>, 16 mg (0.06 mmol) of PPh3 and 73 mg (0.6 mmol) of PhB(OH)2. The kinetic measurement was performed at a rotating gold disk electrode (d=2 mm, inserted into a Teflon holder, EDI 65109, Radiometer) with an angular velocity of 105 rad.s<sup>-1</sup> (Radiometer controvit) at 25°C. The rotating electrode was polarized at +0.05 V on the oxidation wave of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>. 300 µL (0.3 mmol) of NaOH (1 M in MeOH) was then added into the cell and the increase of the oxidation current of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> was recorded

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versus time up to a constant limit value, attesting to the end of the reaction. The solution turned to yellow, the color of  $Pd^0(PPh_3)_4$  in DMF. A cyclic voltammetry at the same steady electrode was then first performed towards oxidation potentials and revealed the oxidation peak of  $Pd^{0}$ -(PPh\_3)<sub>3</sub>. Its yield (94%) was determined from the increase of its oxidation peak current after addition of 21 mg (0.0185 mmol) of an authentic sample of  $Pd^0(PPh_3)_4$ . A cyclic voltammetry was then performed towards reduction potentials and revealed the reversible reduction peak of *p*-CN-C<sub>6</sub>H<sub>4</sub>-Ph. Its yield (95%) was determined from the increase of its reduction peak current after addition of 6.6 mg (0.037 mmol) of an authentic sample of *p*-CN-C<sub>6</sub>H<sub>4</sub>-Ph (commercially available).

In other experiments, the amount of base was varied and the nature of the base (KOH, CsOH) as well.

Typical procedure for the kinetics of the reaction of p-CN-C<sub>6</sub>H<sub>4</sub>-PdBr-(PPh<sub>3</sub>)<sub>2</sub> with PhB(OH)<sub>2</sub>, in the presence of carbonate (Cs<sub>2</sub>CO<sub>3</sub>), as monitored by chronoamperometry at a rotating disk electrode: The same cell as above was employed. 16 mL of degassed DMF containing 0.3 m nBu<sub>4</sub>NBF<sub>4</sub> were poured into the cell, followed by 24 mg (0.03 mmol, 1.9 mM) of p-CN-C<sub>6</sub>H<sub>4</sub>-PdBr(PPh<sub>3</sub>)<sub>2</sub>, 16 mg (0.06 mmol) of PPh<sub>3</sub> and 244 mg (0.75 mmol) of dry Cs<sub>2</sub>CO<sub>3</sub>. The solution was stirred during 30 min. The rotating gold disk electrode was polarized at +0.05 V on the oxidation wave of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub>. 183 mg (1.5 mmol) of PhB(OH)<sub>2</sub> were then introduced into the cell. The oxidation current of the resulting Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>3</sub> was recorded versus time. After an induction period, the current grew up to a constant limiting value, attesting to the end of the reaction. Mean-while, the solution turned to yellow, the color of Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>4</sub> in DMF.

Similar reactions were performed in the presence of  $13.5 \,\mu\text{L}$  (0.75 mmol) of water introduced just after Cs<sub>2</sub>CO<sub>3</sub>. The amount of water was then increased up to 52.5 mmol.

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# as the catalytic reaction proceeds:<sup>[3]</sup> c) For related proposition of transmetalation of Ar'B(OH)<sub>2</sub> on imine-palladacycle-OH, see: J.L.

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transmetalation of  $Ar'B(OH)_2$  on imine-palladacycle-OH, see: J. L. Serrano, L. García, J. Pérez, E. Pérez, J. García, G. Sánchez, P. Sehnal, S. De Ornellas, T. J. Williams, I. J. S. Fairlamb, *Organometallics* **2011**, *30*, 5095–5109.

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Not that innocent: Unexpectedly, some countercations (Na<sup>+</sup>, Cs<sup>+</sup>, K<sup>+</sup>) of the anionic bases used in the Suzuki– Miyaura reactions decelerate the transmetalation reaction in comparison with inert countercations such as  $nBu_4N^+$ , due to a competitive complexation of the reactive ArPd(OH)(PPh<sub>3</sub>)<sub>2</sub> by M<sup>+</sup> (see scheme).



### **Reaction Mechanisms -**

*C. Amatore,*\* *A. Jutand,*\* *G. Le Duc* ......

Mechanistic Origin of Antagonist Effects of Usual Anionic Bases (OH<sup>-</sup>,  $CO_3^{2-}$ ) as Modulated by their Countercations (Na<sup>+</sup>, Cs<sup>+</sup>, K<sup>+</sup>) in Palladium-Catalyzed Suzuki–Miyaura Reactions



