Suzuki–Miyaura Reactions

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The Triple Role of Fluoride Ions in Palladium-Catalyzed Suzuki–Miyaura Reactions: Unprecedented Transmetalation from [ArPdFL$_2$] Complexes**

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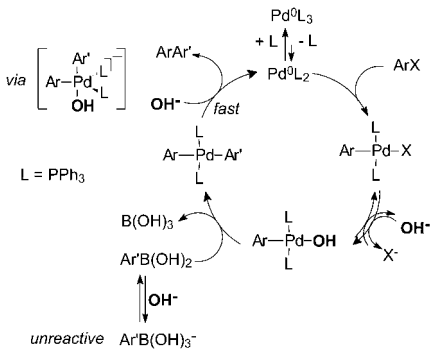
Palladium-catalyzed Suzuki–Miyaura reactions between aryl boronic acids (Ar′B(OH)$_2$) and aryl halides (ArX) to generate ArAr′ require a base,[1] such as hydroxide,[2] carbonate, or fluoride. The mechanism of the reaction has been thoroughly established for cases in which the base employed is OH$^-$ associated with nBu$_4$N$^+$, an innocent counter cation (Scheme 1).[2] The hydroxide ions play three roles. Two are antagonistic in the rate-determining trans-



Scheme 1. Catalytic cycle of the Suzuki–Miyaura reaction performed in the presence of hydroxide (nBu$_4$NOH) as a base.

metalation: 1) formation of *trans*-[ArPd(OH)L$_2$] (L = PPh$_3$), which reacts with Ar′B(OH)$_2$; and 2) formation of unreactive Ar′B(OH)$_3^-$. The third role is positive: fast promotion of reductive elimination from the *trans*-[ArPdAr′L$_2$] intermediate (Scheme 1). The overall reaction rate is thus controlled by the ratio [OH$^-$]/[Ar′B(OH)$_2$].[2] The higher reactivity of Ar′B(OH)$_2$ with [ArPd(OH)(PPh$_3$)$_2$] versus Ar′B(OH)$_3^-$ with [ArPdX(PPh$_3$)$_2$] shown in our previous work[2] was later confirmed by Hartwig and Carrow.[3]

Herein we present kinetic and mechanistic data on the role of fluoride anions in Suzuki–Miyaura reactions.[1,4] Three roles for F$^-$ were determined, including an unprecedented transmetalation from [ArPdFL$_2$] complexes.

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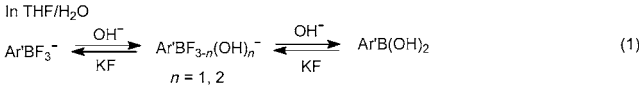
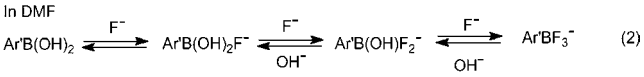
Fluoride ions have a strong affinity for aryl boron moieties owing to the stability of Ar′BF$_3^-$.[1,5] Batey and Quach have hypothesized that anionic Ar′BF$_2$(OH)$^-$ or Ar′BF(OH)$_2^-$ must be formed from Ar′BF$_3^-$ in the presence of a base.[5a] The successive basic hydrolysis of Ar′BF$_3^-$ into Ar′B(OH)$_{3-n}$F$_n^-$ (n = 1–3) and, ultimately, Ar′B(OH)$_2$ was established by Molander et al.[5b–d] Hutton et al.,[5e] and Lloyd-Jones et al,[5f] who also demonstrated that fluoride ions react reversibly with aryl boronic acids to eventually generate Ar′BF$_3^-$[5f] [Eq. (1)].



(1)

We have tested the effect of fluoride ions introduced as nBu$_4$NF (3 equiv) on p-FC$_6$H$_4$B(OH)$_2$ in DMF. As reported for KF in THF/H$_2$O,[5f] in the ^{19}F NMR spectrum, the singlet of p-FC$_6$H$_4$B(OH)$_2$ at −112.11 ppm disappeared and led to a complex mixture of signals. In the presence of excess nBu$_4$NF (> 3 equiv), p-FC$_6$H$_4$BF$_3^-$ was detected at −136.31 ppm (BF$_3^-$) and −116.89 ppm (p-F), in agreement with literature values.[5f]

Consequently, in the presence of a large amount of F$^-$, the major reagent must be Ar′BF$_3^-$ [Eq. (2)]. Batey and Quach[5a] observed that no reaction took place between PhBF$_3^-$Cs$^+$ and



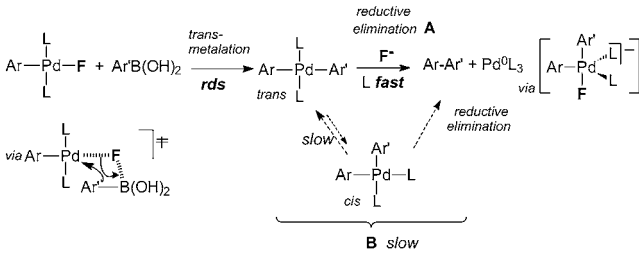
(2)

p-CHOC$_6$H$_4$Br in the presence of [Pd^0(PPh$_3$)$_4$] (3 mol%) in DMF and in the absence of a base, whereas the same reaction involving PhB(OH)$_2$ and CsF (3 equiv) proceeded, establishing that PhBF$_3^-$ was not the reactive species.[6] Lloyd-Jones et al. have also established that Ar′BF$_3^-$ ions are quite unreactive in the absence of a base. However, in the presence of OH$^-$ (generated from Cs$_2$CO$_3$ in THF/H$_2$O), Ar′BF$_3^-$ is partly converted to Ar′B(OH)$_2$, which reacts with an [ArPd(OH)L] species in a transmetalation step.[5f] We have also observed that no p-NCC$_6$H$_4$Ph was formed after two hours when p-[NCC$_6$H$_4$PdI(PPh$_3$)$_2$] (1.9 mM) was combined with PhBF$_3^-$ (20 equiv) in DMF at RT, once more confirming that aryltrifluoroborates are not reactive.[5] This suggests another role for fluoride ions that could promote the formation of [ArPdFL$_2$] as the reactive species.

The substitution of other halides by fluorides in *trans*-[$ArPdX(PPh_3)_2$] was also investigated. Grushin et al. have reported the synthesis of one fluorinated aryl complex, *trans*-[$PhPdF(PPh_3)_2$], by reacting *trans*-[$PhPdI(PPh_3)_2$] with AgF in benzene.[7] We first synthesized an authentic sample of *trans*-*p*-[$NCC_6H_4PdF(PPh_3)_2$] by reacting excess AgF with [{*p*-$NCC_6H_4Pd(\mu\text{-}I)(PPh_3)$}$_2$] in the presence of PPh_3 (2 equiv) in toluene. *trans*-[*p*-$NCC_6H_4PdF(PPh_3)_2$] was isolated in 66% yield and characterized by NMR (Supporting Information, Figure S1). In the ^{31}P NMR spectrum, a doublet was observed at 19.38 ppm (d, $J_{FP} = 12$ Hz; Figure S1a) and the ^{19}F NMR spectrum revealed a broad, poorly defined signal. Gratifyingly, a more defined ^{19}F signal structure was observed at −281.67 ppm (tt, $J_{FP} = 12$ Hz, $J_{FH} = 2$ Hz; Figure S1b) in the presence of excess PPh_3 (4 equiv). This improvement was most likely due to a *trans*/*cis* equilibrium that lies in favor of the *trans* complex in the presence of excess PPh_3. When nBu_4NF (1 equiv) was added to *trans*-[*p*-$NCC_6H_4PdI(PPh_3)_2$] (5.8 μmol) in 0.5 mL of DMF/[D_7]DMF containing PPh_3 (2 equiv),[8] the doublet of [*p*-$NCC_6H_4PdF(PPh_3)_2$] was observed in the ^{31}P NMR spectrum together with the singlet of the starting complex in a ratio of 61:39, respectively. The ratio was 94:6 in the presence of nBu_4NF (2 equiv). Consequently, fluoride ions exchanged with the original halide of *trans*-[$ArPdX(PPh_3)_2$] to generate *trans*-[$ArPdF(PPh_3)_2$] through the equilibrium given in Equation (3). The equilibrium constant was estimated from the ^{31}P NMR data: $K_X = 5 \pm 1$ (X = I, Ar = *p*-NCC_6H_4, DMF, 27 °C).

$$trans\text{-}[ArPdXL_2] + F^- \underset{}{\overset{K_X}{\rightleftharpoons}} trans\text{-}[ArPdFL_2] + X^- \quad (3)$$

Having the isolated *trans*-[*p*-$NCC_6H_4PdF(PPh_3)_2$] in hand, its reactivity with $PhB(OH)_2$ could be directly tested in DMF. The reaction was followed by cyclic voltammetry (see the Supporting Information). Gratifyingly, the known complex *trans*-[*p*-$NCC_6H_4PdPh(PPh_3)_2$][2,9] was formed and detected by its reduction peak in cyclic voltammetry (see the Supporting Information) upon reacting [*p*-$NCC_6H_4PdF(PPh_3)_2$] (1.9 mM) with $PhB(OH)_2$ (5 equiv) in the presence of PPh_3 (2 equiv) in DMF at room temperature. Also, as observed in our previous work, *trans*-[*p*-$NCC_6H_4PdPh(PPh_3)_2$] was quite stable.[2] It is only after the addition of CsF (8 equiv) that [$Pd^0(PPh_3)_3$] and *p*-NCC_6H_4Ph (characterized by their oxidation and reduction peak respectively,[2] see the Supporting Information) were generated together in a fast reaction ($t_{1/2}$ = ca. 2 min). It is thus shown for the first time that [$ArPdFL_2$] undergoes transmetalation with $Ar'B(OH)_2$, as a consequence of the fluorophilicity of the boron center (Scheme 2).[10] Furthermore, F^- promotes the reductive elimination from stable *trans*-[$ArPdAr'L_2$] complexes (path A in Scheme 2), bypassing the classical path B in which the rate of the reductive elimination from the related *cis*-complex is retarded by slow *trans*/*cis* isomerization (Scheme 2). By analogy to the proposed formation of an anionic five-coordinate species involving OH^- as the fifth ligand (Scheme 1),[2] the formation of an anionic five-coordinate[11] species involving F^- as the fifth ligand is now proposed to explain the promotion of the

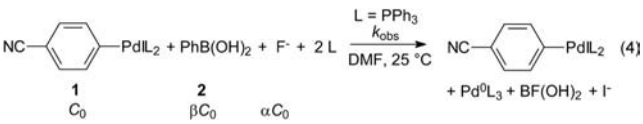


Scheme 2. Mechanistic pathways in the Suzuki–Miyaura reaction performed in the presence of fluoride anions.

reductive elimination from the *trans*-complex (path A in Scheme 2). Indeed, it is reported that a fifth ligand on square-planar four-coordinate *trans* d^{10} complexes favors reductive elimination.[12] In the case of F^-, the lifetime of the five-coordinate species is too short to be observed.

However, as indicated above, F^- reacted with $PhB(OH)_2$ to release OH^- [Eq. (2)], which also favors the reductive elimination in path A (Scheme 1).[2] In actual catalytic reactions involving $Ar'B(OH)_2$ and F^-, F^- and OH^- (released from $Ar'B(OH)_2$) are always present in large amounts. Whatever the anion, F^- or OH^-, that promotes the reductive elimination, the key point is that the resulting process is always faster than the transmetalation in the presence of those anions.

The kinetics of the reaction of *trans*-[*p*-$NCC_6H_4PdI(PPh_3)_2$] (**1**) with $PhB(OH)_2$ (**2**) were then investigated in DMF at 25 °C in the presence of PPh_3 (2 equiv) and nBu_4NF (α equiv) introduced from a 1M stock solution in THF [Eq. (4)].



The kinetics of the formation of [$Pd^0(PPh_3)_3$] were followed by chronoamperometry using a rotating disk electrode polarized at +0.05 V (oxidation potential of [$Pd^0(PPh_3)_3$]). The increase in its oxidation current (proportional to its concentration) was then recorded with time (Figure 1a) after addition of nBu_4NF (20 equiv) to a solution containing **1** ($C_0 = 1.9$ mM), **2** (20 equiv), and PPh_3 (2 equiv). The plot of $\ln x$ with time was linear (Figure 1b). The value of $k_{obs} = 0.032\ s^{-1}$ was determined from the slope of the linear correlation (Figure 1b).

The variation of k_{obs} versus the amount of fluoride (α equiv) exhibited a bell-shaped maximum (Figure 2a), as previously observed for hydroxides,[2] although the phenomenon was less accurate than for OH^-. The same behavior was observed in the reaction of *trans*-[$PhPdBr(PPh_3)_2$] (1.9 mM) with $PhB(OH)_2$ (20 equiv) performed in the presence of nBu_4NF (α equiv; Figure 2b). The dependence on the F^- concentration reveals that k_{obs} describes the kinetics of the rate-determining transmetalation.

Therefore, as with hydroxides, fluorides are involved in two kinetic antagonist effects: F^- ions are required to

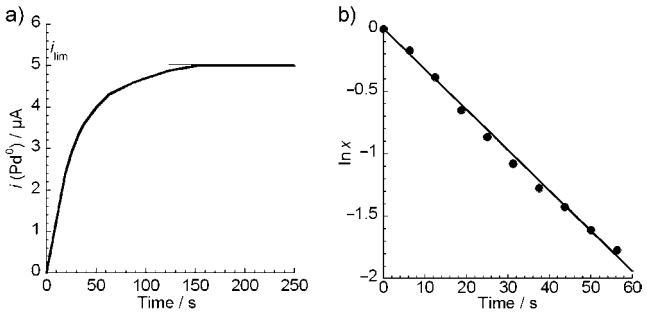


Figure 1. Kinetics of the reaction of *trans*-[*p*-$NCC_6H_4PdI(PPh_3)_2$] (1.9 mM) with $PhB(OH)_2$ (20 equiv) in the presence of PPh_3 (2 equiv) and nBu_4NF (20 equiv) in DMF at 25 °C. a) Evolution of the oxidation current of [$Pd^0(PPh_3)_3$] (proportional to its concentration) measured by chronoamperometry using a rotating gold disk electrode ($d = 2$ mm) polarized at 0.05 V. b) Variation of ln$x$ versus time ($x = (i_{lim} - i_t)/i_{lim}$, where i_{lim} = final value of the oxidation current of [$Pd(PPh_3)_3$] and i_t = oxidation current at t). $y = -0.032367x$ $R = 0.99788$.

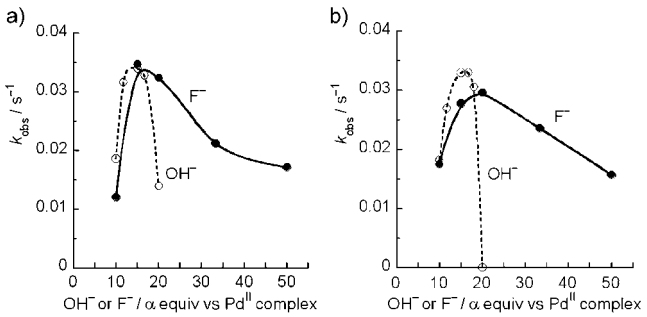
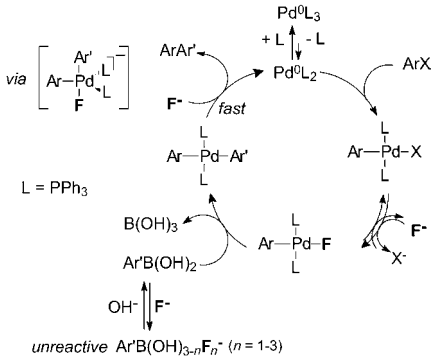


Figure 2. Variation of the pseudo first-order rate constant k_{obs} with α equiv of F^- (●) or OH^- (○)[2] for the reaction of $PhB(OH)_2$ (20 equiv) with a) *trans*-[*p*-$NCC_6H_4PdI(PPh_3)_2$] (1.9 mM) and b) *trans*-[$PhPdBr(PPh_3)_2$] (1.9 mM). All of the reactions were performed in the presence of PPh_3 (2 equiv) in DMF at 25 °C.

generate the active *trans*-[$ArPdFL_2$], which reacts with $Ar'B(OH)_2$, as shown above (Scheme 2). However, at sufficiently high concentrations, F^- inhibits the reaction by competitive formation of unreactive $Ar'B(OH)_{3-n}F_n^-$ (n = 1–3) [Eq. (2), Scheme 3]. This confirms the results reported in the literature, which established that $Ar'BF_3^-$ is not reactive in the absence of OH^-.[4d,5] As for OH^-, F^- promotes



Scheme 3. Catalytic cycle of the Suzuki–Miyaura reaction performed in the presence of fluoride anions (nBu_4NF).

the reductive elimination from *trans*-[$ArPdAr'L_2$], making this reaction faster than the transmetalation, which becomes rate-determining (Scheme 2). The rate of the overall reaction is thus controlled by the ratio $[F^-]/[Ar'B(OH)_2]$.

Therefore, we have established that F^- plays the very same three roles already identified for OH^- in the transmetalation and reductive elimination processes (Scheme 3). However, the reaction of F^- with $Ar'B(OH)_2$ is more complex than that of OH^-. Indeed, at least three fluorinated species $Ar'B(OH)_{3-n}F_n^-$ (n = 1–3) may be formed [Eq. (2)] with progressive release of OH^-, which may participate in a catalytic cycle involving OH^- as the base, as in Scheme 1 (see the variation of k_{obs} vs. OH^- concentration in Figure 2). A competitive substitution of I^- in complex **1** by F^- or OH^- was indeed observed (× 2.5 in favor of F^-) when the two anions were added together at the same concentration (14 mM) to **1** (14 mM). As observed in Figure 2, the reaction was less inhibited by high F^- concentrations than by OH^-, suggesting that OH^- ions were more easily trapped by $Ar'B(OH)_2$ than F^- ions (the oxophilicity of boron is higher than its fluorophilicity). Whereas the ratio $[OH^-]/[Ar'B(OH)_2]$ must be lower than 1 to have an efficient reaction, the ratio $[F^-]/[Ar'B(OH)_2]$ may be higher than 1 (Figure 2). Interestingly, the range of the F^- concentrations which led to an efficient reaction appears to be larger than that for OH^- (Figure 2). In other words, the control of the fluoride concentration is not so crucial for an efficient reaction.

In conclusion, the mechanism of the reaction of *trans*-[$ArPdX(PPh_3)_2$] with $Ar'B(OH)_2$, a key step in Suzuki–Miyaura reactions, has been established in DMF in the presence of fluoride anions (Scheme 3) and compared to that reported in our previous work with hydroxide anions (Scheme 1).[2] The formation of [$Pd^0(PPh_3)_3$] and the cross-coupling product $ArAr'$ was followed using electrochemical techniques that provide kinetic data. As with hydroxide ions, fluoride ions play three roles. F^- favors the reaction by: 1) forming *trans*-[$ArPdF(PPh_3)_2$], a key complex that reacts with $Ar'B(OH)_2$ (an unprecedented rate-determining transmetalation) and 2) promoting the reductive elimination from intermediate *trans*-[$ArPdAr'(PPh_3)_2$], which generates $ArAr'$ and active Pd^0. Conversely, F^- disfavors the reaction by the formation of unreactive anionic $Ar'B(OH)_{3-n}F_n^-$ (n = 1–3), leading to the two antagonistic effects of F^- in the transmetalation. Consequently, the overall reactivity is finely tuned by the concentration of F^- and passes through a maximum as F^- concentration increases. Therefore, the rate of the overall reaction is controlled by the ratio [base]/$[Ar'B(OH)_2]$ when the base is either F^- (this work) or OH^-,[2] both associated with the counter cation nBu_4N^+. Work is in progress to expand the scope of the transmetalation of [$ArPdFL_2$] complexes.

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