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Aryl Trifluoroborates in Suzuki–Miyaura Coupling: The Roles of Endogenous Aryl Boronic Acid and Fluoride**

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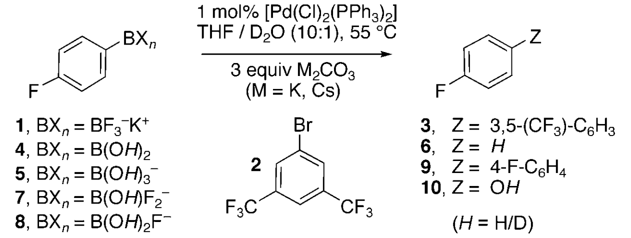
A wide range of organoboron reagents can be used as alternative reagents to boronic acids in Suzuki–Miyaura (SM) coupling reactions.[1] The readily prepared,[2] convenient to handle potassium trifluoroborates, RBF$_3$K, which have been developed by the groups of Genet[3] and Molander,[4] are often the reagents of choice for these transformations. Although extensive optimization of the base, solvent, and temperature is required for each class of substrate,[4,5] their utility in SM coupling reactions has led to their widespread commercial availability. Apart from a preliminary study in 2003,[5a] their mode of action has not been investigated in detail, and the origin of their efficacy[4,5a] remains to be elucidated. Herein, we report the SM coupling of aryl trifluoroborate **1** with aryl bromide **2** to generate biaryl[5a,j] **3** (Scheme 1). We show that endogenous aryl boronic acid **4** and fluoride, both arising from **1**, play key roles in the coupling reaction, being involved at all stages: from catalyst activation and catalytic turnover, through to the inhibition of side reactions. Collectively, these phenomena result in the exceptional performance of the reagent in the SM coupling.[4]

The SM coupling of **1** with **2** was studied in a toluene/water (3:1)[5b–e] biphasic solution, and in a tetrahydrofuran/water (10:1)[5f–i] solution, both systems being commonly employed for the SM coupling of trifluoroborates.[5] The reactions in toluene/water, failed to go to completion: turnover ceased after 6 hours, affording 55% of the base-catalyzed[6] protodeboronation product **6**[7] and $\leq 32\%$ of coupling product **3**. In aqueous tetrahydrofuran (Scheme 1) the reaction proceeded much more efficiently (5.5 h; $>95\%$ yield of **3**), with few side products (≤ 0.1–2%), even when the reaction was performed in air.

In contrast, reaction of the boronic acid (**4**) under identical conditions, gave **3** in variable yield, and afforded substantially more of side products **9**/**10** (2–40%), compared to trifluoroborate substrate **1**.



Scheme 1. SM coupling of trifluoroborate **1** with bromide **2** to generate biaryl **3** together with the three major side products arising from protodeboronation (**6**), homocoupling (**9**), and oxidation (**10**).

The performance of aryl boronic acid reagents can be improved by the addition of KF,[8] whereas trifluoroborate reagents require aqueous solvent systems for SM coupling with standard substrates.[9–11] This observation has led to suggestions that mixed borates, $[\mathrm{RBF}_{(3-n)}(\mathrm{OH})_n]^-$,[12,13] are the true transmetalating species.[4b,5a,10,13b] Base titration of **1** in a solely aqueous medium (D$_2$O) was monitored by ^{19}F and ^{11}B NMR spectroscopy. Trifluoroborate **1** underwent hydrolysis via boronic acid **4** to give boronate **5**; the transformation required approximately three equivalents of K$_2$CO$_3$ or Cs$_2$CO$_3$, or six equivalents of KOH to proceed to completion. At ambient temperature, boronate **5** slowly gave rise to fluorobenzene **6** by protodeboronation;[6] the process was substantially faster at 55 °C. Rapid equilibrium between **4** and **5** gave rise to time-averaged ^{19}F NMR chemical shifts (*p*-F-Ar nuclei), from which analysis of $\Delta\delta_F$ values versus [base] was used to establish the mol% of boronate **5** (e.g. Figure 1a).

When the dibasic nature of M$_2$CO$_3$ was taken into account, there was no significant difference in the curve

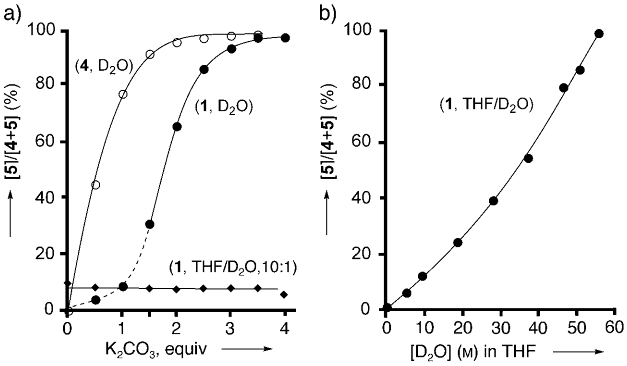


Figure 1. a) Titration of **1** and **4** with K$_2$CO$_3$ in D$_2$O (71 mM) and in THF/D$_2$O (8 mM). There is no significant difference in using Cs$_2$CO$_3$ or KOH as the base. b) The effect of D$_2$O concentration on the fraction of **5** (mol%) in **4**/**5**, generated from **1**+4 equiv K$_2$CO$_3$ in THF.

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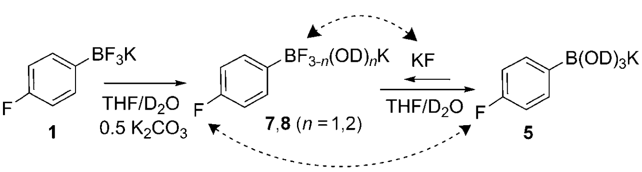
obtained with K_2CO_3, Cs_2CO_3, or KOH, and after addition of the theoretical amount of base required to replace the three fluoride ions in **1**, the shape of the curve was identical to that observed for the boronic acid **4**. At low concentrations of base, the effect of additional fluoride (4, 8, and 12 equiv KF) on the titration of **1** with K_2CO_3 was to slightly increase the proportion of **5**, because of the slight increase in the pH value caused by the aqueous fluoride. However, under the concentrations of base employed for the SM coupling, the effect was negligible (Scheme 1).

Protodeboronation to give **6** is the major pathway for the inefficient SM coupling of **1** in a toluene/water biphase,[7] but is not detected under the standard aqueous tetrahydrofuran conditions[5f–i] (see Scheme 1). The effect of tetrahydrofuran on homogeneous solutions of **5**, generated in situ from **1** with 4 equivalents K_2CO_3 in D_2O, was studied by ^{19}F NMR spectroscopy. As the D_2O concentration was reduced from 55 M (100% D_2O) to 0 M (100% THF; see Figure 1b), the equilibrium population shifted from $\geq 98\%$ boronate (**5**) to $\geq 98\%$ boronic acid (**4**), thereby resulting in complete suppression of the protodeboronation reaction (**5**→**6**). In 5.1 M D_2O (10:1 THF/water, Scheme 1),[5f–i] where the equilibrium population of **5** is almost independent of base concentration (Figure 1a), protodeboronation is negligible: $< 0.1\%$ **6** was generated in 12 days, as opposed to 46% **6** in 47 M D_2O.

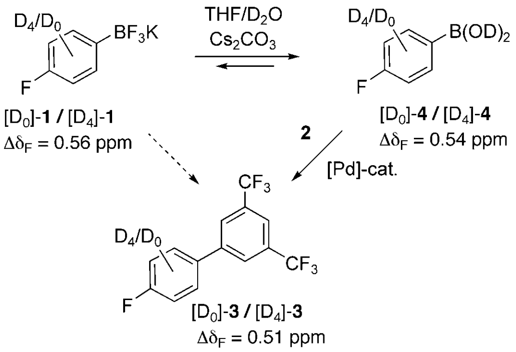
^{19}F NMR analysis of the SM coupling reaction confirmed that **1** undergoes hydrolysis,[13–15] but the growth in biaryl product (**3**) was substantially in advance of the boronic acid **4** for the first 20–30 turnovers. No intermediate mixed species (**7**, **8**, or the related neutral intermediates, $ArBX_2$; X = F,OH,OD) were observed under these conditions.[13a] However, at higher water concentrations, an intermediate was detected, reaching a maximum (8% of the total Ar–B species) when 0.5 equivalents K_2CO_3 was added in a THF/D_2O (1:10, 45 M D_2O) solution (Scheme 2).



Scheme 2. ^{19}F EXSY contacts (----- $\tau = 25$–40 ms) observed between **7**,**8** and **5** on hydrolysis of [d_0]-**1** in 1:10 THF/D_2O (45 M D_2O).

^{19}F EXSY analysis showed that this species, tentatively assigned by integration as $[ArBF_2(OD)]^-K^+$ (**8**),[16] was in rapid equilibrium ($\tau \leq 40$ ms) with boronate **5** and KF, but not with trifluoroborate **1**. However, reversible generation of trifluoroborate **1** was confirmed under the SM coupling conditions from the observation of a smooth equilibration between [D_0]-**1** and [D_4]-**4** with [D_4]-**1** and [D_0]-**4**, respectively (Scheme 3).

In parallel with F/OH exchange at boron, fluoride sequestration by the base and the glassware[15] progressively drove the equilibrium towards the boronic acid **4** (> 98%). No intermediate species were detected by ^{11}B or ^{19}F NMR spectroscopy, although they must be present, albeit at low concentrations (≤ 60 μM), to facilitate the indirect equilibrium between **1** and **4**. To contribute significantly to the catalytic flux for SM coupling, these mixed species, such as **7** and **8**, need to be exceptionally active towards transmetalation. To assess this aspect, we studied (B3LYP/6-31G*,lacv3p)[16] phenyl transfer from $[PhBX_3]^-$ (X = F, OH) to $[Pd(Br)Ar(L)_n]$ (L = PPh_3; $n = 1,2$), generated by oxidative addition of PhBr to $[Pd(PPh_3)_2]$, in tetrahydrofuran. As illustrated in Figure 2, the energy barrier towards transmetalation increases with increasing ligation of boron by fluoride, consistent with the decreasing ability of the boron reagent to complex to Pd (intermediate **IA2**) and the reduced nucleophilicity of the phenyl moiety (transition state **TSA2**). We expect catalytic flux to proceed almost exclusively through phenyl transfer from $PhB(OH)_2$ (cf **4**) to $[Pd(OH)(PPh_3)(Ph)]$, or from $[PhB(OH)_3]^-$ (cf **5**$^-$) to $[Pd(PPh_3)(Ph)]^+$; without significant contribution from **1**, **7**, or **8**.



Scheme 3. Interconversion of [D_4]-**4**/[D_0]-**1** with [D_0]-**4**/[D_4]-**1** in 10:1 THF/D_2O (5.1 M D_2O) with 3 equiv Cs_2CO_3 at 55 °C. Also shown is the palladium-catalyzed SM coupling with **2**; see Figure 3a.

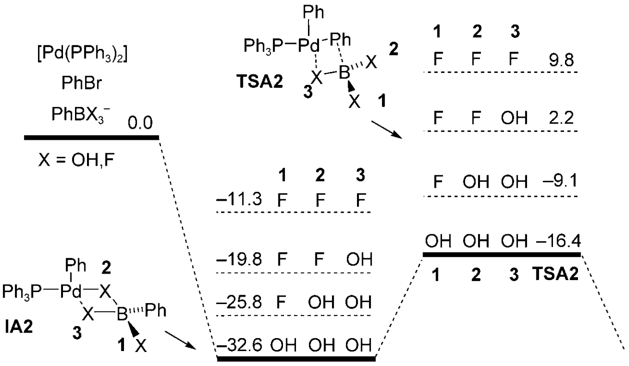


Figure 2. Energies (kcal mol^{-1}) for Ph transfer to $[Pd(Br)Ar(L)_n]$ from $[PhBX_3]^-$ (X = F, OH; L = PPh_3); lower energy ($n = 1$) complexes are shown; ($n = 2$) follows the same order, but are ca. 20 kcal mol^{-1} higher: **IA2**/**TSA2** = −33.9:5.5); −31.9:13.2; −31.2:17.6; −26.9:10.9.[16]

This conclusion was tested by performing the SM coupling reactions of mixtures of [D_0]-**1** and [D_4]-**4**, in initial ratios 90:10, 70:30, 50:50, 30:70, and 10:90 (Figure 3a).[16] Catalytic turnover (**2**→**3**) proceeded in parallel with the equilibration

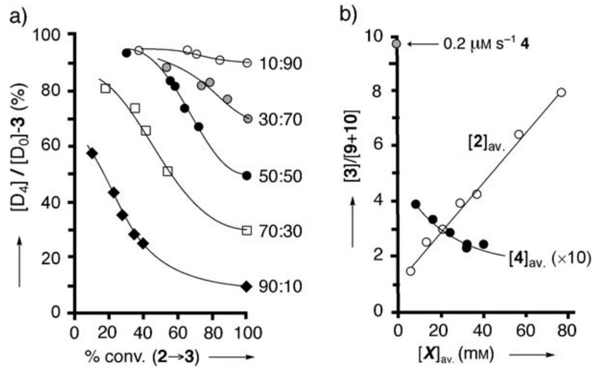


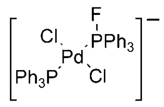
Figure 3. a) Isotope distribution (% [D_4]) in **3** as a function of the conversion of **2**, during coupling with [D_0]-**1**/[D_4]-**4** in the initial ratios indicated. b) SM coupling efficiency ([**3**]/[**9**+**10**]) as a function of [**2**]$_{av.}$ and [**4**]$_{av.}$ in reactions conducted in air. Solid lines are solely as a guide for the eye.[16]

between **1** and **4**, and, after complete conversion of **2**, the isotope distribution in the SM coupling product **3** (%[D_4]), reflects the initial [D_0]/[D_4] ratio of **1**:**4**. However, prior to full equilibration, the isotope distribution in the evolving SM coupling product **3** reflects the isotope distribution in the reactive component. The product that was initially generated was predominantly [D_4]-**3**, even if the mixture of boron reagents contained just 10% [D_4]-**4**, thus confirming that boronic acid **4** is the dominant transmetalating species. These results reinforce the conclusion that **1** serves as a reservoir for **4**, via an unobserved intermediate species, such as **7** and **8**, which themselves do not contribute directly to the SM coupling.

The question then arises as to why the indirect reaction, that is, starting from **1** rather than **4**, is more efficient. The significant difference lies not in the rate, but in the substantial decrease in the amount of side products obtained with trifluoroborate **1**. Indeed, reactions starting directly from boronic acid **4** proceeded to completion faster than reactions starting from **1**; predominantly because the slow and somewhat variable[15] rate of hydrolysis (**1**→**4**) can limit the rate of catalytic turnover.

For SM coupling in aqueous tetrahydrofuran, the rate of protodeboronation (**5**→**6**) is negligible, and thus only two of the three side products (**6**, **9**, and **10**) differentiate the use of trifluoroborate reagent **1** from boronic acid **4**. Under routine synthetic conditions, that is, reagents and solvents that have not been rigorously purified, the SM coupling of **2** with **4** in aqueous tetrahydrofuran generated **9** and **10** in two stages: rapid initial production followed by a progressive accumulation during the catalytic turnover. As shown below, these side products arise from three different processes: one generates **9**, one generates **10**, and one generates both. All three processes are substantially suppressed in reactions starting from **1**, in which **4** is generated in situ.

In reactions that employ **4** directly, the precatalyst, [$PdCl_2(PPh_3)_2$], is reductively activated by a two-stage transmetalation/reductive elimination sequence to generate [$Pd(PPh_3)_2$] and homocoupled product **9**. The latter is detected by ^{19}F NMR spectroscopy immediately after turnover begins, and its stoichiometry is in direct proportion to the catalyst loading.[16] However, in reactions employing trifluoroborate **1**, which generates **4** in situ, there is no trace of **9** (< 0.1%), even with high catalyst loadings (5 mol%). The quantitative reduction of [$PdCl_2(PPh_3)_2$] must therefore take place before any significant build up[17] of **4** has occurred. Endogenous[18] fluoride can catalyze[19] the reduction[20] of the precatalyst, [$PdCl_2(PPh_3)_2$], for example, by hydrolysis of a fluorophosphonium species generated from a phosphorane[21] complex (**11**). ^{31}P NMR spectroscopic analysis of the SM coupling of **1** in THF/$^{18}OH_2$ (10:1) confirmed that hydrolytic catalyst activation generates $Ph_3P{=}^{18}O$ ($\Delta\delta_P = 0.04$ ppm), and, nominally, a monophosphane Pd^0 complex.[22]



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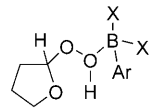

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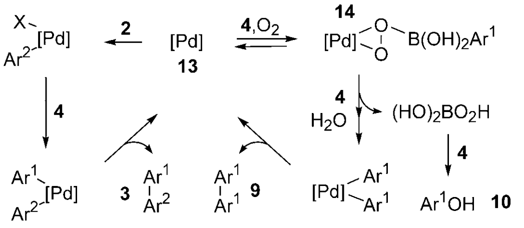
Phenol **10** is also produced (observed by ^{19}F NMR spectroscopy) at the beginning of SM coupling reactions in which **4** is employed directly, and in quantities that depend on the purity of the tetrahydrofuran. However, phenol **10** is absent in reactions that employ **1** to generate **4** in situ. A tetrahydrofuran-derived oxidant[23] is thus consumed by a non-phenolic pathway, prior to significant hydrolysis of **1**. Control experiments confirmed that at 55 °C, trifluoroborate **1** is able to mediate the decomposition of aqueous tetrahydrofuran solutions of tetrahydrofuran-2-hydroperoxide.[23] In contrast, boronic acid **4** is efficiently oxidized[24] into phenol **10** under the same conditions. The difference in outcome between **1** and **4** may arise from a bifurcation in the conventional oxidation pathway (**12**, X = OH), in which an [1,2]-Ar shift leads to **10**. The increased Lewis acidity of the boron center (X = F) would both reduce the migratory aptitude of the Ar group, and affect the polarity of the O–O moiety, for example, to induce its regioisomeric cleavage via a [1,2]-H/CH_2 shift from the tetrahydrofuran ring,[25a] or an α-CH elimination.[25b]

In the SM coupling of boronic acid **4**, incomplete degassing of the aqueous tetrahydrofuran solvent prior to reaction, or an ingress of air during sampling of the reaction, results in the generation of side products **9** and **10** in a 1:1 ratio throughout catalytic turnover. This process is almost absent when **1** is employed, even though the reactions proceed through **4**.[26] The mechanism of the palladium-catalyzed aerobic oxidative homocoupling[27] of aryl boronic acids has been shown by Amatore, Jutand, and co-workers[28] to involve a peroxo intermediate [$Pd(\kappa^2\text{-}O_2)$]. This species reacts with two molecules of aryl boronic acid and water to generate a biaryl species (cf **9**) and perboric acid, $B(OH)_2OOH$. The latter oxidizes a third molecule of aryl boronic acid to the phenol (**10**).

Consideration of a mechanism for SM coupling in competition with oxidative homocoupling (Scheme 4) suggests that a Pd^0 intermediate (**13**) is partitioned between oxidative addition of the aryl bromide (**2**) versus reaction with oxygen and the boronic acid to form **14**.



Scheme 4. Schematic mechanism for the SM coupling of ArBr **2** (by oxidative addition of **2** to Pd^0 complex **13** leading to biaryl **3**) versus the oxidative homocoupling of **4** with O_2 via **14**, which leads to biaryl **9** and phenol **10**. [Pd] = *cis/trans* $[Pd(PPh_3)_n]$, where $n = 0,1,2$; X = Br, OH.

Conducting the SM coupling of **4** under air, so that $[O_2]$ is approximately constant, confirmed a linear relationship between [**2**] and [**3**]/([**9**] + [**10**]), see the open circles in Figure 3b. An analogous, but inverse relationship was found for the boronic acid ([**3**]/([**9**] + [**10**]) $\propto$ [**4**]$^{-1}$), thus suggesting a reversible,[29] or boronic acid facilitated O_2 addition (**13**→**14**, via $[Pd(\kappa^2\text{-}O_2)]$). The high sensitivity of the oxidative pathway to the concentration of boronic acid is key to the efficiency of the indirect process that starts from trifluoroborate **1**: slow hydrolysis[30] of **1** relative to turnover keeps the concentration of **4** low, thus reducing the partitioning of **13** via the $[Pd(\kappa^2\text{-}O_2)(\mathbf{4})]$ intermediate **14**. This conclusion was tested by syringe-pump addition ($0.2\ \mu\text{M}\,s^{-1}$)[16] of a THF/H_2O (10:1) solution of **4** + Cs_2CO_3 to an SM coupling of **2** that was conducted under air. The effect was substantial, affording a [**3**]/([**9**] + [**10**]) ratio of > 9.5, as compared to a ratio of only 3.5 with **1** under the standard conditions (Scheme 1).

Seven key points emerging from this study are outlined below. These may also be of importance when considering mechanisms for turnover, for precatalyst activation, and for oxidative side reactions in other areas of transition-metal catalysis that use RBF_3K reagents under aqueous conditions.[2,3,31]

1) Reagent **1** undergoes hydrolytic equilibrium with boronic acid **4**; an accompanying sequestration of fluoride by base and glassware[15] resulted in slow but complete conversion into **4**.
2) Low water concentrations reduce the equilibrium population of borate **5** (Figure 2b), thus suppressing protodeboronation.
3) Mixed intermediates **7** and **8** are not detected (< 60 μM) and computationally (Figure 2) are found to be less efficient than **4** at aryl transfer to Pd^{II} in the transmetalation step.
4) The majority of catalytic turnover proceeds via **4** (Figure 3a).
5) The use of **1** results in fluoride-catalyzed[19] hydrolytic reduction[20] of the precatalyst, possibly via **11**, bypassing the generation of **9**.
6) Trifluoroborate **1** mediates the decomposition of traces of tetrahydrofuran hydroperoxide in the aqueous tetrahydrofuran, possibly via a Lewis acid induced bifurcation in **12**, thus avoiding generation of the phenol **10**.
7) The competing Pd^0-catalyzed aerobic homocoupling via **14**, which consumes three molecules of boronic acid **4** per cycle, is suppressed by high concentrations of **2** and low concentrations of boronic acid **4** (Figure 3b). Slow hydrolysis of trifluoroborate **1** relative to catalytic turnover ensures low concentrations of **4**.[30]

The above factors account for the exceptional performance of the RBF_3K reagent **1** under routine synthetic conditions.[4] This insight will be of use in the scale-up of biaryl SM coupling reactions. For example, the slow addition of boronic acid **4** circumvents prior conversion into trifluoroborate **1**.[2–4] This procedure avoids corrosion of the reaction vessel by fluoride, requires just one equivalent of base instead of three, and still benefits from a hydrolytic Pd^{II} precatalyst activation.[19]

The extensive optimization of base, solvent, and temperature in SM coupling reactions with other trifluoroborates and other organohalides and pseudohalides[4,5] may reflect the requirement to balance the rate of hydrolysis with the rate of catalytic turnover, so that side reactions, such as protodeboronation and oxidative homocoupling, are suppressed.[5a] Our analysis also suggests that partially fluorinated borates ($R\text{-}BF_{3-n}X_n$, X = OH, OR) can participate in the transmetalation event, albeit less efficiently than the boronic acid; however, most studies show that mixed intermediates undergo rapid disproportionation to the fully fluorinated and non-fluorinated species.[5a,12,13]

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Keywords: boron · fluorides · homogeneous catalysis · palladium · reaction mechanisms

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[7] ^{19}F NMR analysis of reactions with $[\mathbf{1}]_0 = 47$ mM (total volume) showed triarylboroxine (generated in situ), **4**, and **2** in the toluene phase, and **5**, 3 KF, and **6** in the aqueous phase. Metastable dispersions of **6** in the aqueous phase migrate slowly into the toluene phase. In more dilute reactions ($[\mathbf{1}]_0 =$ 8 mM), all species except KF were located in the toluene phase. ^{19}F NMR analysis of a reaction conducted without toluene (just water as solvent) yielded < 16 % of SM coupled product (**3**) over a 6 hour period.

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[10] Alcohols are also used as a reaction medium,[5a] but need to be slightly wet (laboratory grade) to be effective. See: T. E. Barder S. L. Buchwald, *Org. Lett.* **2004**, *6*, 2649 – 2652. Analogous effects were found for the SM coupling of **1** with **2**: in laboratory-grade MeOH, the reaction went to completion in ≤ 30 minutes; whereas in anhydrous MeOH, the coupling proceeded to 80 % completion in 9 hours at 80 °C, wherein protonation/decarboxylation of the carbonate base potentially provides a source of water.

[11] $\mathrm{ArN_2^+BF_4^-}$ (J.-P. Genêt, S. Darses, J.-L. Brayer, J.-P. Demoute, *Tetrahedron Lett.* **1997**, *38*, 4393 – 4396) and $\mathrm{Ar_2I^+BF_4^-}$ (C.-Z. Chen, M. Xia, *Synth. Commun.* **1999**, *29*, 2457 – 2465) salts undergo SM coupling with $\mathrm{ArBF_3K}$ reagents under base-free conditions, probably through competition between $\mathrm{ArBF_3^-}$ and $\mathrm{BF_4^-}$ as a complexed fluoride ligand for coordination to the palladium cation (see Figure 2).

[12] Vedejs et al. noted that aqueous solutions of $\mathrm{PhBF_3K}$ "are somewhat acidic, suggesting the existence of an equilibrium between the tetracoordinated 'ate' species and products of hydrolytic cleavage or ligand exchange." (see Ref. 2 a).

[13] a) R. Ting, C. W. Harwig, J. Lo, Y. Li, M. J. Adam, T. J. Ruth, D. M. Perrin, *J. Org. Chem.* **2008**, *73*, 4662 – 4670; b) R. A. Batey, T. D. Quach, *Tetrahedron Lett.* **2001**, *42*, 9099 – 9103; c) C. A. Hutton, A. K. L. Yuen, *Tetrahedron Lett.* **2005**, *46*, 7899 – 7903.

[14] During the course of this work, the use of wet silica gel to convert $\mathrm{RBF_3K}$ into $\mathrm{RB(OH)_2}$ was reported: G. A. Molander, L. N. Cavalcanti, B. Canturk, P.-S. Pan, L. E. Kennedy, *J. Org. Chem.* **2009**, *74*, 7364 – 7369.

[15] The rate of hydrolysis is unaffected by [**2**] or [Pd], but increases with the glass-surface/reaction-volume ratio. Samples hydrolyze efficiently in the absence of base in a glass vessel, but not at all if conducted in a teflon vessel. In glass vessels, the presence of base caused variable induction periods before the onset of hydrolysis, after which the rates are identical to runs without base present. Solution-phase fluoride (in aq THF) could not be detected by ^{19}F NMR spectroscopy, owing to precipitation (as MF; M = K, Cs) or sequestration by the glass surface.[14]

[16] For full details, see the Supporting Information.

[17] The addition of up to 50 % of **4** to **1** was required to regenerate **9** by transmetalation in the precatalyst activation.

[18] SM coupling of **4** + TBAF (3 equiv) completely suppressed the generation of **9** through activation of a precatalyst. Significant quantities of **1** were generated, together with **8** (7 % Ar), $\mathrm{BF_4K}$ (16 % B), and $\mathrm{B(OH)F_3K}$ (27 % B). Fluoride (exogenous or endogenous) did not inhibit the aerobic oxidative catalytic generation of **9** and **10**. See also: S. Punna, D. D. Diaz, M. G. Finn, *Synlett* **2004**, 2351 – 2354.

[19] If fluoride sources are absent and **4** is in low concentration (<0.4 mM), aqueous basic tetrahydrofuran effects slow hydrolytic precatalyst activation, possibly catalyzed by the glass surface, thus bypassing generation of **9**.

[20] Verkade and co-workers have detailed the fluoride-mediated and -catalyzed reduction of palladium halides by phosphanes: a) M. R. Mason, J. G. Verkade, *Organometallics* **1990**, *9*, 864 – 865; b) M. R. Mason, J. G. Verkade, *Organometallics* **1992**, *11*, 2212 – 2220; c) P. A. McLaughlin, J. G. Verkade, *Organometallics* **1998**, *17*, 5937 – 5940.

[21] S. A. Macgregor, D. C. Roe, W. J. Marshall, K. M. Bloch, V. I. Bakhmutov, V. V. Grushin, *J. Am. Chem. Soc.* **2005**, *127*, 15304 – 15321.

[22] The generation of nominally different catalysts from the reaction of $\mathrm{[PdCl_2(PPh_3)_2]}$ with **1** versus **4**, did not appear to be the origin of the better performance of **1**. Both systems are phosphane-deficient (^{31}P{^{1}H} NMR analysis with internal standard, $\mathrm{Tol_3P{=}O}$) and gave positive tests for heterogeneous catalysis using the mercury droplet method (C. Pad, W. Hartman, *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 711). Traces of oxidant, such as $\mathrm{B(OH)_2OOH}$, will presumably oxidize the free phosphane ligand. A sample of $\mathrm{Ph_3P^{18}O}$ (0.12 mM, 32 % ^{18}O) was unchanged after heating at 55 °C overnight in 10:1 THF/$\mathrm{H_2[^{18}O_{0.7}]}$ and $\mathrm{Cs_2CO_3}$ (24 mM).

[23] THF undergoes aerobic oxidation, particularly when free of stabilizer, for example, after distillation, and exposed to light or a metal catalyst; a) A. Robertson, *Nature* **1948**, *162*, 153; b) G. I. Nikishin, V. G. Glukhovtsev, M. A. Peikova, A. V. Ignatenko, *Izv. Akad. Nauk SSSR Ser. Khim.* **1971**, *10*, 2323 – 2325; Control experiments confirmed that exposure of aq THF (10:1) to air led to ≥ 8.0 mM hydroperoxide which rapidly oxidizes **4** into **10** at 55 °C. Neither base (e.g. $\mathrm{Cs_2CO_3}$) nor water is required, and neither KF nor TBAF decomposed the peroxide. Use of $[\mathrm{D}]_0$-**1**/$[\mathrm{D}]_4$-**4** mixtures confirmed that **4**, but not **1**, is oxidized into **10**.

[24] a) H. G. Kuivila, *J. Am. Chem. Soc.* **1954**, *76*, 870 – 874; b) H. G. Kuivila, A. G. Armour, *J. Am. Chem. Soc.* **1957**, *79*, 5659 – 5662.

[25] a) W. Ockels, J. Stein, H. Budzikiewicz, *Z. Naturforsch. B* **1984**, *39*, 90 – 94; b) S. J. Blanksby, G. B. Ellison, V. M. Bierbaum, S. Kato, *J. Am. Chem. Soc.* **2002**, *124*, 3196 – 3197.

[26] Control experiments eliminated modification of the glass surface by **1**, the presence of phenol (**10**) as a ligand for palladium, or lower base concentrations as being responsible for this difference.

[27] a) M. Moreno-Mañas, M. Pérez, R. Pleixats, *J. Org. Chem.* **1996**, *61*, 2346 – 2351; b) M. A. Aramendía, F. Lafont, M. Moreno-Mañas, R. Pleixats, A. Roglans, *J. Org. Chem.* **1999**, *64*, 3592 – 3594.

[28] C. Adamo, C. Amatore, I. Ciofini, A. Jutand, H. Lakmini, *J. Am. Chem. Soc.* **2006**, *128*, 6829 – 6836.

[29] Reversible $\mathrm{O_2}$ binding might arise from phosphane deficiency.[21,28]

[30] a) "MIDA" boronates are employed as slow release agents: D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961 – 6963; b) for a recent comparison of the use of "MIDA" boronates with organotrifluoroborates, see: K. Brak, J. A. Ellman, *J. Org. Chem.* **2010**, *75*, 3147 – 3150.

[31] For examples of copper-catalyzed ether formation, see: a) R. A. Batey, T. D. Quach, *Org. Lett.* **2003**, *5*, 1381 – 1384; rhodium-catalyzed 1,2-additions: b) A. Ros, V. K. Aggarwal, *Angew. Chem.* **2009**, *121*, 6407 – 6410; *Angew. Chem. Int. Ed.* **2009**, *48*, 6289 – 6292; rhodium-catalyzed 1,4-additions: c) L. Navarre, M. Pucheault, S. Darses, J.-P. Genet, *Tetrahedron Lett.* **2005**, *46*, 4247 – 4250; d) C. G. Frost, S. D. Penrose, R. Gleave, *Org. Biomol. Chem.* **2008**, *6*, 4340 – 4347.