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Organotrifluoroborate Hydrolysis: Boronic Acid Release Mechanism and an Acid–Base Paradox in Cross-Coupling**

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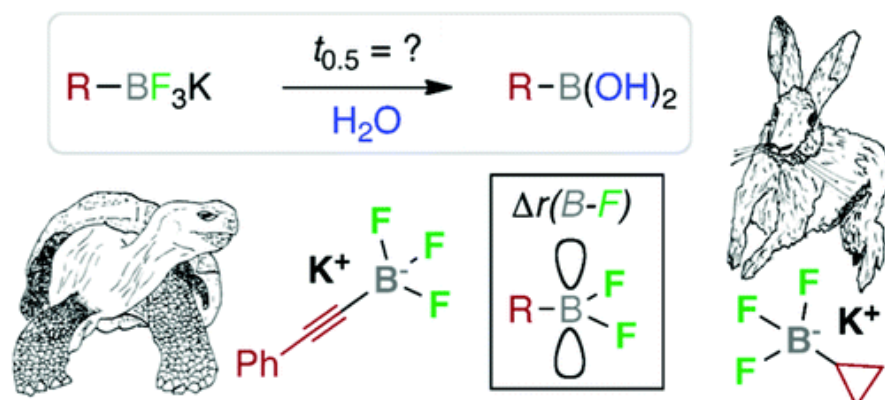
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Supporting information:

Detailed procedures of all reactions and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>

Graphical abstract:



Abstract

The hydrolysis of potassium organotrifluoroborate (RBF_3K) reagents to the corresponding boronic acids ($\text{RB}(\text{OH})_2$) has been studied in the context of their application in Suzuki–Miyaura coupling. The “slow release” strategy in such SM couplings is only viable if there is an appropriate gearing of the hydrolysis rate of the RBF_3K reagent with the rate of catalytic turnover. In such cases, the boronic acid $\text{RB}(\text{OH})_2$ does not substantially accumulate, thereby minimizing side reactions such as oxidative homocoupling and protodeboronation. The study reveals that the hydrolysis rates (THF, H_2O , Cs_2CO_3 , $55\text{ }^\circ\text{C}$) depend on a number of variables, resulting in complex solvolytic profiles with some RBF_3K reagents. For example, those based on *p*-F-phenyl, naphthyl, furyl, and benzyl moieties are found to require *acid* catalysis for efficient hydrolysis. This acid–base paradox assures their slow hydrolysis under *basic* Suzuki–Miyaura coupling conditions. However, partial phase-splitting of the THF/ H_2O induced by the Cs_2CO_3 , resulting in a lower pH in the bulk medium, causes the reaction vessel shape, material, size, and stirring rate to have a profound impact on the hydrolysis profile. In contrast, reagents bearing, for example, isopropyl, β -styryl, and anisyl moieties undergo efficient “direct” hydrolysis, resulting in fast release of the boronic acid while reagents bearing, for example, alkynyl or nitrophenyl moieties, hydrolyze extremely slowly. Analysis of B–F bond lengths (DFT) in the intermediate difluoroborane, or the Swain–Lupton resonance parameter (\mathfrak{R}) of the R group in RBF_3K , allows an a priori evaluation of whether an RBF_3K reagent will likely engender “fast”, “slow”, or “very slow” hydrolysis. An exception to this correlation was found with vinyl- BF_3K , this reagent being sufficiently hydrophilic to partition substantially into the predominantly aqueous minor biphasic phase, where it is rapidly hydrolyzed.

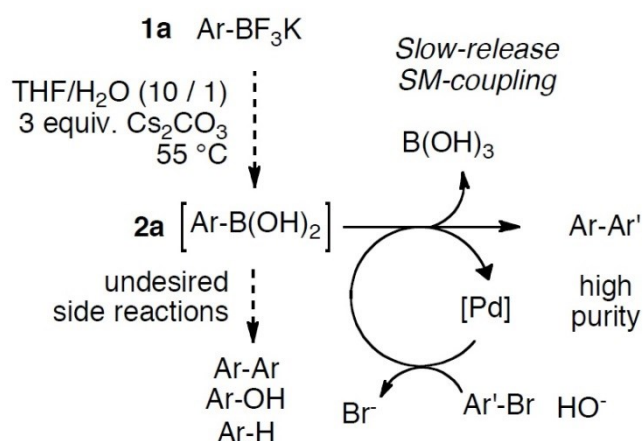
Introduction

The Suzuki–Miyaura (SM) cross-coupling reaction^[1] is one of the most important transition metal-catalyzed reactions to have been developed for organic synthetic application. The broad applicability of the reaction class has arisen through key advances in the design and development of optimized precatalyst,^[2] ligand,^[3] and boronate coupling partners.^[4] These developments have been particularly important in cases where specific classes of boronic acid are prone to side reactions such as oxidation, homocoupling, and protodeboronation. Indeed, this sensitivity has led to major efforts being made in the development of suitable protecting groups, resistant to all of the degradation pathways, but able to release^[5] the requisite boronic acid *in situ* under the SM coupling conditions. These considerations are especially salient in medicinal chemistry where biaryl moieties are ubiquitous but the heteroaromatic boronic acid reagents can readily undergo protodeboronation.

Two particularly successful examples of this mode of reactivity in SM coupling^[5] are *N*-methyliminodiacetic acid (MIDA) boronates^[6] and organotrifluoroborates ($[\text{RBF}_3]$).^[7, 8] Many examples of both reagent classes are now commercially available and are being widely applied in synthesis and in process development. The

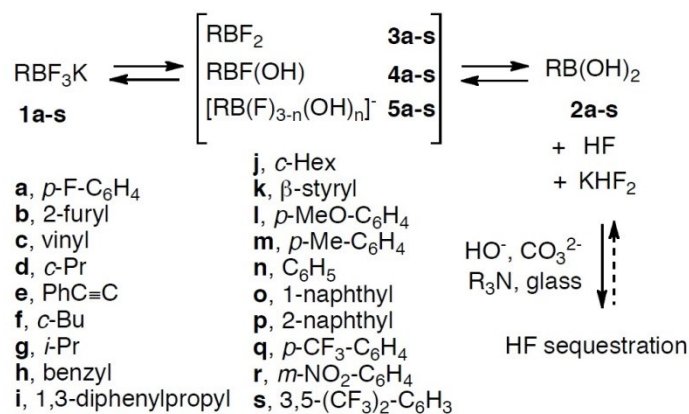
MIDA boronates were developed by Burke for the coupling of unstable boronic acids^[6] and as reagents for iterative synthesis.^[9] A simple and readily controlled hydrolysis allows MIDA boronates to undergo efficient Pd-catalyzed cross-coupling with a wide spectrum of substrates. The use of organotrifluoroborates as alternative reagents for SM couplings and other processes^[10] was pioneered by Genet,^[7a-7c] Molander,^[7d, 7e] and Batey.^[8]

In addition to undergoing clean and efficient coupling, the potassium salts are stable, crystalline, easily handled solids. We recently reported^[11] on the mechanism of SM coupling of ArBF_3K reagents (**1a**, $\text{Ar} = p\text{-F-C}_6\text{H}_4$) under the exceptionally effective general conditions developed by Molander.^[12] Reactions proceed *via* ArBF_3K hydrolysis^[8, 11, 12n-12p] and generate the biaryl coupling product ($\text{Ar-Ar}'$) in very high purity, Scheme 1.^[12]



Scheme 1. Suzuki–Miyaura coupling of ArBF_3K reagents (**1**), *via* ArB(OH)_2 (**2**),^[11] under Molander’s conditions.^[12]

Based on NMR and DFT studies, we concluded that it is an *in situ* slow release^[5, 6] of ArB(OH)_2 (**2a**) and fluoride,^[13] from the ArBF_3K reagent (**1a**), that attenuates many of the side reactions that arise on *direct* use of the aryl boronic acid.^[11] With certain substrate classes, minimization of these side reactions can be of paramount importance, and conditions that release the boronic acid at a rate that is appropriate to catalytic turnover are of significant benefit. To engender slow-^[5a, 5b] or fast-release^[5c] conditions requires an understanding of the factors affecting the solvolysis rate of organotrifluoroborates in general, as well as how their relative lability varies as a function of the organic moiety (R in RBF_3K). Herein we report on the rates and mechanisms of hydrolysis of RBF_3K salts **1a–s** (Scheme 2) under the aqueous basic conditions pertinent to SM coupling, where the half-lives range from minutes to months.



Scheme 2. Hydrolytic equilibrium of 1 with 2, via 3–5, and overall driving force of hf sequestration by base or glass.

The study reveals that, unlike the MIDA boronates,^[6b] the hydrolysis of RBF₃K salts is dependent on a number of variables, sometimes resulting in complex solvolytic profiles. Moreover, the solvolysis mechanism, and thus rate, is highly dependent on the organic moiety (R). Indeed, some RBF₃K reagents require *acid* catalysis for hydrolysis under the nominally *basicSM* coupling conditions, Scheme 1. This acid–base paradox is the origin of a dramatic impact of the reaction vessel shape, material, size, and stirring rate on the hydrolysis profile. In contrast, other RBF₃K reagents do not require acid catalysis and hydrolyze rapidly, resulting in release of the boronic acid far faster than the cross-coupling catalyst can turnover. This then renders the accumulating boronic acid potentially susceptible to undesired degradation pathways. To aid a more rational design and optimization of RBF₃K coupling reactions under solvolytic conditions,^[7, 10, 12] we develop an a priori evaluation of whether the “R” moiety will engender “fast”, “slow”, or “very slow” hydrolysis and discuss the scope and limitations for control of boronic acid release rates.

Results and Discussion

We began with a more detailed evaluation of the hydrolysis of the aryltrifluoroborate **1a**, under the conditions of Scheme 1^[11, 12] but without the Pd catalyst or SM coupling partner (3,5-(CF₃)₂-C₆H₃Br). ArBF₃K hydrolysis has previously been studied in aqueous buffer (pH 6.9–7.0) by Perrin,^[14] with LFER analysis suggesting a rate-limiting loss of KF, followed by a rapid cascade of associative exchange of F for OH,^[15, 16] to yield the arylboronic acid **2a**. Intermediate species (e.g., **3a–5a**, Scheme 2) were not detected (¹⁹F NMR) by Perrin under buffered aqueous conditions^[14] nor by us under the SM coupling conditions of Scheme 1.^[11] However, low concentrations of some intermediates are detected (¹⁹F-EXSY NMR/ESI-MS),^[16, 17] along with BF₄⁻ and BF₃(OH)⁻ ions,^[18] in a solely aqueous medium (no organic co-solvent).

1. Hydrolysis of 1a. Under the conditions of Scheme 1, boronic acid **2a** and trifluoroborate **1a** undergo degenerate interconversion. To confirm that this arises solely through F/OH ligand-exchange, either directly or *via* solvent,^[16] rather than by Ar/B exchange,^[19] we hydrolyzed [¹⁰B]-**1a** (99% ¹⁰B) in the presence of [²H₄]-**2a** with 5 M H₂O in THF (as Scheme 1, no ArBr or Pd) at 55 °C. EI-MS analysis indicated that no [²H₄,¹⁰B]-**1a/2a** species were generated in excess of natural abundance (20% ¹⁰B). Thus, under the SM coupling conditions, one or more intermediates of type **3a–5a** are readily accessible, albeit in low concentrations, allowing equilibrium between **1a** and **2a**. This equilibrium is then coupled to one or more subsequent processes that remove fluoride. It is this fluoride sequestration that ultimately drives the equilibrium to lie completely on the side of **2a**, Scheme 2.

A prominent feature of the hydrolyses conducted in aqueous basic THF, Scheme 1, was that the reaction kinetics (**1a**→**2a**; ¹⁹F NMR) were dependent on the vessel size and shape, the order of addition of components, and the rate of stirring and proceeded after a variable induction period; see A–G, Figure 1.

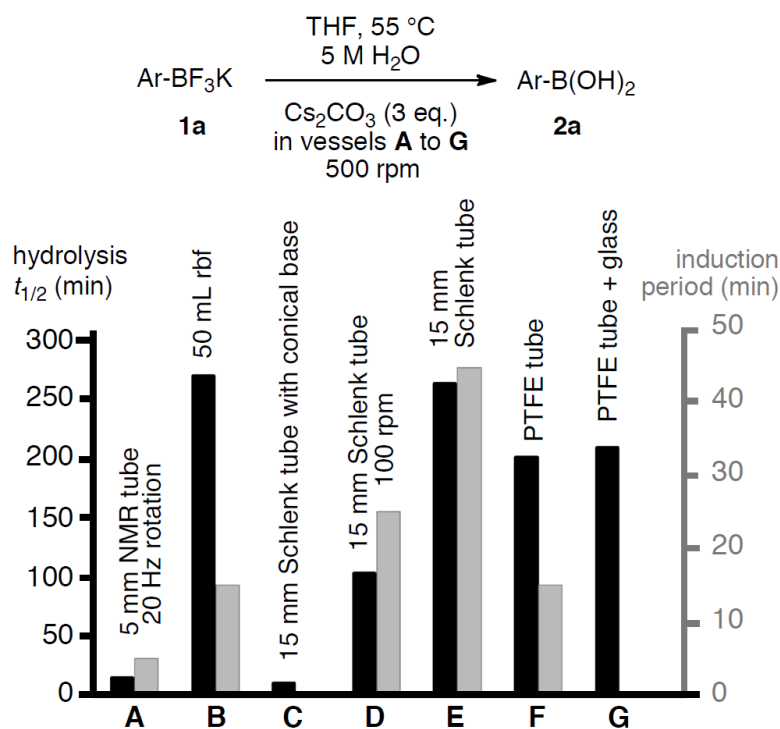


Figure 1. Hydrolytic half-life of **1a** (8 mM) to **2a** in THF containing 5 M water and Cs₂CO₃ (24 mM net) in reaction vessels A–G; magnetic stirring rate 500 rpm unless noted. Data determined by ¹⁹F NMR monitoring *in situ* or after sampling; k_{obs} and thus $t_{1/2}$ determined by linear regression of $\ln([\mathbf{1a}]_0/[\mathbf{1a}]_t)$ versus t . In most reactions there was a significant negative deviation from first order decay beyond ca. 2–3 half-lives, due to HF sequestration causing rate suppression, *vide infra*.

Hydrolytic Equilibrium of 1a and the Effect of Glass. The known instability of RBF_3K species to silica gel,^[20] silyl compounds,^[17] and alumina^[21] suggested that under certain conditions, glass reaction vessels were acting as fluorophiles. On switching to PTFE-lined NMR tubes and PTFE Schlenk tubes, and conducting the reactions in the *absence* of base, but with addition of powdered glass,^[22] hydrolysis proceeded with simple pseudo-first-order kinetics, at a rate that was directly proportional to the glass surface-area (see Supporting Information). Moreover, the reactions proceeded without an induction period. In the absence of glass, there was a rapid hydrolytic pre-equilibrium ($t_{1/2} \leq 180$ s), giving rise to **1a** and **2a** and a mildly acidic solution (pH = 5; glass electrode, uncalibrated). On addition of glass powder to these equilibrium mixtures, smooth pseudo-first-order decays in **1a** were observed, e.g., Figure 2.

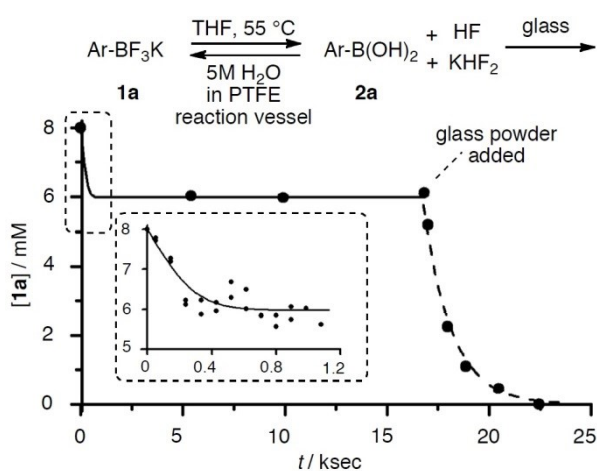


Figure 2. Hydrolysis of ArBF_3K **1a** in 10/1 (v/v) of THF/water (5 M H_2O) in a PTFE vessel. Lines through data are approach to equilibrium (solid line; see inset for data and kinetic fit^[23, 24]) and subsequent pseudo-first-order decay to $[\mathbf{1a}] = 0$ (dashed line) after addition of “grade 3” borosilicate glass powder.^[22]

The pre-equilibrium, which is difficult to characterize in the presence of glass, was analyzed in detail by ^{11}B and ^{19}F NMR, Figure 3. Simulations were consistent with a process of the type: $\mathbf{1a} + 2\text{H}_2\text{O} \leftrightarrow \mathbf{2a} + \text{KHF}_2 + \text{HF}$.^[23, 24] As a result of the large excess of water over **1a**, the forward term is pseudo-first-order while the reverse is third-order. This results in increasing concentrations of trifluoroborate **1a** liberating smaller proportions of boronic acid **2a** at equilibrium, Figure 3, graph A. For example, a 1 mM sample of **1a** liberates 73% **2a** whereas a 100 mM sample liberates just 5% **2a**. Moreover, increasing concentrations of water stabilize the trifluoroborate, possibly *via* aqueous solvation of the K^+ counterion, so as to counteract the equilibration process, Figure 3, graph B. Both features may be important in the optimization of couplings of organotrifluoroborates that liberate unstable boronic acids.

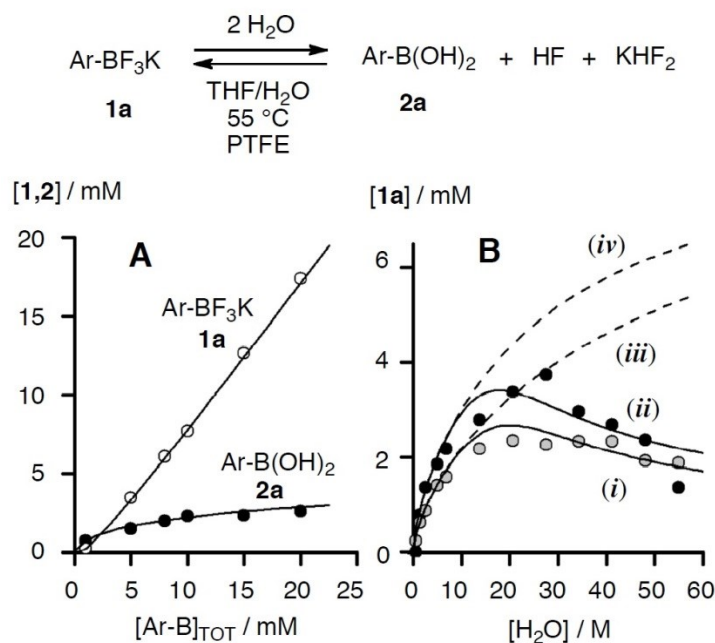


Figure 3. Equilibrium concentrations of trifluoroborate **1a** and boronic acid **2a** in THF/H₂O, as a function of [Ar-B]_{TOT} (graph A, [H₂O] = 5M, at 55 °C) and [H₂O] (graph B, [1a]₀ = 8 mM, at 25 °C and at 55 °C) in a PTFE vessel. Solid lines through data points are simulations of **1a** + 2H₂O ↔ **2a** + KHF₂ + HF, where $K = 5.5 \times 10^{-8}$ (55 °C) and 1.8×10^{-8} (25 °C) coupled to a solvation equilibrium: **1a** + 4H₂O ↔ [1a·4H₂O]; $K = 6.3 \times 10^{-6} \text{ M}^{-4}$ (25 °C, *i*) and $9.9 \times 10^{-6} \text{ M}^{-4}$ (55 °C, *ii*). Dashed lines are simulations at 25 °C (*iii*) and 55 °C (*iv*) without the additional solvation model.

Phase-Splitting and the Effect of pH. Returning to trifluoroborate hydrolyses conducted in the presence of Cs₂CO₃, measurement of the pH in the bulk medium in the PTFE vessel at the beginning of the reaction showed that it was only mildly basic (pH = 9, uncalibrated) despite the full dissolution of 3 equiv of Cs₂CO₃ and no detectable hydrolysis of **1a** (¹⁹F NMR). This initially confusing result arises from the inorganic base inducing a phase-split in the homogeneous THF/water medium, as recently noted by Hartwig.^[25] Under the SM coupling conditions of Scheme 1 (net 24 mM Cs₂CO₃), the minor phase represents ≤1% of the total volume, Figure 4. Moreover, although the system can present the visual aspect of a homogeneous medium, the majority of the base is present in the minor phase (pH >12), rather than in the bulk (pH ≈ 9).^[26]

Amatore and Jutand,^[27a] Hartwig,^[25] and Schmidt^[27b] have independently demonstrated that the boronic acid ArB(OH)₂, not the trihydroxyboronate species ([ArB(OH)₃]⁻), is the active transmetalating agent in SM coupling. This highlights an important benefit that arises from the *in situ* generation of a biphasic medium (see inset to Figure 4), an aspect that to the best of our knowledge has not been noted previously. In a high pH single-phase medium, the boronic acid is predominantly present as the trihydroxyboronate. In contrast, a biphasic system maintains a relatively lower pH in the organic phase, ensuring that a higher proportion of boronic acid

coupling partner is present^[28] while still facilitating generation of the key transmetalating complex R–Pd–OH^[25, 27] from the oxidative addition product R–Pd–X. This phenomenon may account for the extensive use of biphasic conditions in SM coupling.^[29]

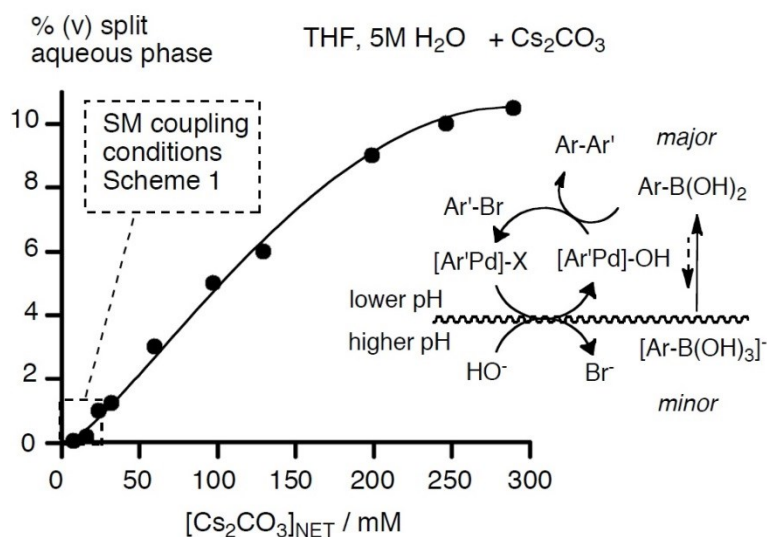


Figure 4. Volume (% of total) of minor biphasic (pH >12) as a function of [Cs₂CO₃]_{net} in solution in 10/1 (v/v) of THF/water (5 M H₂O). The line through the data is solely a guide to the eye. Inset: SM coupling in a biphasic medium.

Simultaneous monitoring of the pH and the extent of hydrolysis of **1a** (¹⁹F NMR) in the bulk phase proved informative. On addition of THF/water (10/1) to anhydrous mixtures of **1a** and Cs₂CO₃, the pH rose rapidly as the base dissolved and, on a few occasions, trifluoroborate hydrolysis displayed long induction periods, e.g., Figure 5A. During the induction period, **1a** underwent very slow hydrolysis and the pH gradually decreased. After reaching a critical point, a much more rapid first-order hydrolytic decay in **1a** ensued, accompanied by a precipitous drop in the pH. More often, the initial rise in pH was smaller and the induction period was much shorter, e.g., Figure 5B, but again the end of induction was signaled by a rapid drop in pH. In all cases, the pH reached a minimum of ca. 7 (uncalibrated) before slowly rising again to ca. 9, accompanied by a progressive negative deviation from first-order solvolytic decay in **1a**.

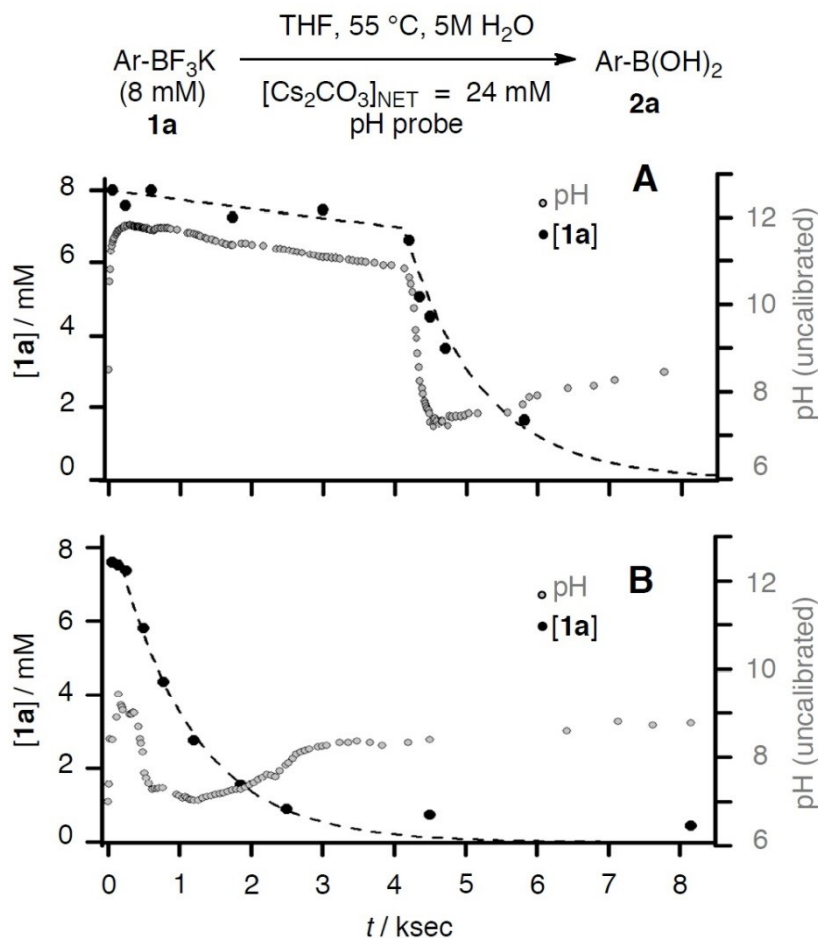


Figure 5. Examples of long (A) and short (B) induction periods in the hydrolysis of **1a** (8 mM) under basic heterogeneous conditions (3 equiv of Cs_2CO_3) in 10/1 (v/v) of THF/water (5 M H_2O) at 55 °C and the accompanying change in pH. $t = 0$ is defined as the point when all solids had dissolved after addition of preheated solvent to an anhydrous mixture of **1a**/ Cs_2CO_3 . The dashed lines are first-order decays in **1a** ($k_{\text{obs}} = 3.34 \times 10^{-5} \text{ s}^{-1}$ and $9.34 \times 10^{-4} \text{ s}^{-1}$) during and after induction.

These results suggested that although a base, or other “HF-sink”, is required to drive the hydrolysis (**1a** to **2a**) to completion,^[14, 17, 20, 21] somewhat paradoxically, base in the bulk medium strongly retards hydrolysis of **1a** by suppressing an *acid*-catalyzed hydrolytic equilibrium. An important ramification of this is that for RBF_3K reagents that display analogous acid-catalyzed hydrolytic profiles, *vide infra*, the final stages of SM coupling may take a disproportionately long time to complete due to the pH approaching or exceeding a critical value (see for example the decay of **1a** after 2.5 ks in Figure 5B). Hydrolysis of trifluoroborate **1a** under *homogeneous* (single phase) conditions, employing organic bases/buffers (i to vii, Figure 6A) in place of the

Cs₂CO₃, support the conclusion that the equilibrium between **1a** and **2a** is (specific) acid-catalyzed, with solvolysis rates inversely proportional to the pH.

Buffering, Induction Periods, Sonication, and Chemoselective Coupling. For hydrolyses conducted in THF/water mixtures with an inorganic base (e.g., Cs₂CO₃) that induces phase-splitting (Figure 4), the base-mediated suppression of solvolysis of **1a** also accounts for the substantial variability in the induction period and ensuing solvolytic decay. The situation arises because the pH buffering ability of the bulk phase is dependent on at least three processes: (i) the rate of hydrolytic equilibrium of **1a**, to liberate HF/KHF₂; (ii) the rate of sequestration of the HF/KHF₂ by base or the glass surface of the reaction vessel; (iii) the interfacial transfer rate of hydroxide or carbonate from the strongly basic minor biphasic into the bulk medium (the major biphasic). Because process (ii) depends on the vessel surface, both its area and its identity, while process (iii) depends on phase mixing efficiency, the reaction environment becomes an important component.

These observations have significant implications for SM coupling of RBF₃K reagents under aqueous basic conditions.^[25, 27] First, if mixing is not efficient, then base-induced phase-splitting may result in the etching of glass or metal reactors through liberation of HF/KHF₂ in the bulk phase; under such conditions the addition of sacrificial glass might be considered.

Second, as noted above, the slow-release^[5] of RB(OH)₂ can reduce side reactions, such as O₂-mediated homocoupling to generate R–R,^[11] and thus even apparently small changes in reaction conditions can have a significant impact. For example, SM couplings of **1a** (Scheme 1) conducted under air in Schlenk tubes that differed only by the shape of the base of the tube proceeded quite differently, despite identical reaction volumes, magnetic stirring rates, and negligible stirring vortices. In a tube with a cone-shaped base, which resulted in poor phase contact of the bulk solvent with the basic minor split phase, fast hydrolysis of **1a** to **2a** occurred (*t*_{1/2} 10 min), and a cross-coupled/homocoupled product ratio (4-fluoro-3,5-bis(trifluoromethyl)-biphenyl/4,4'-difluorobiphenyl) of 1.6 was obtained. In contrast, a tube with a hemispherical base resulted in better phase contact, slower release rate (*t*_{1/2} 4.4 h), and less oxidative homocoupling (ratio = 3.5).

Highly efficient phase contact can be engendered by ultrasound. Under the standard hydrolytic conditions (Scheme 1), just 20 s sonication, before and after the addition of **1a**, reproducibly extended induction periods to over 45 min, during which there was >96% rate suppression,^[30] Figure 6, graph B. This phenomenon can be exploited in the context of chemoselective cross-couplings.^[31] Thus, under optimized pulse sonication conditions, Scheme 3, the boronic acid-derived cross-coupling product was generated with high selectivity (>98%) from a reaction mixture containing equimolar trifluoroborate **1a** and deuterated boronic acid [²H₄]-**2a**.^[11] With RBF₃K reagents that can undergo slow release, *vide infra*, this technique has the potential for stepwise liberation of a boronic acid from an organotrifluoroborate,^[32] allowing telescoped processes and iterative synthesis with different electrophiles.^[9, 33, 34]

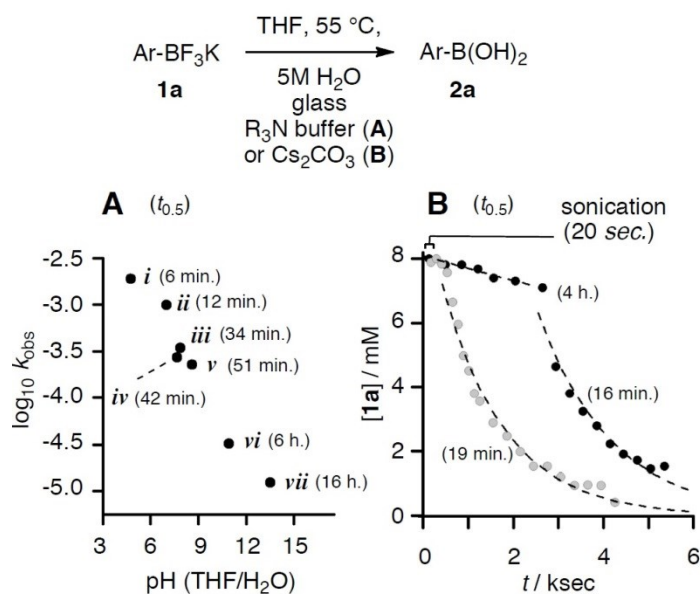
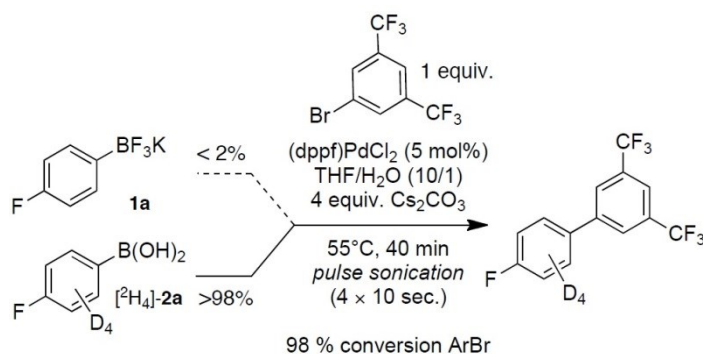


Figure 6. Graph A: Hydrolysis of **1a** (base/buffer employed: (i) MOPS 50 and 100 mM [partial phase-splitting]; (ii) no buffer; (iii) TRIS; (iv) Et₃N; (v) *i*-Pr₂NEt; (vi) DBU; (vii) *t*-Bu-P₄); the pH values (glass electrode; $t = 0$) are normalized to ii = pH 7. Graph B: the effect of a 20 s. sonication pulse on the hydrolysis of **1a** in a heterogeneous medium of 10/1 (v/v) THF/water (5 M H₂O) with 3 equiv of Cs₂CO₃. Dashed lines are first-order decays in **1a**.



Scheme 3. Chemoselective SM coupling *via* sonication.

2. Hydrolysis of Trifluoroborates 1b–s. To investigate the generality of our observations on the solvolysis of **1a**, *vide supra*, we studied the hydrolysis of an additional 18 potassium organotrifluoroborates (**1b–s**). We began by comparing hydrolytic pre-equilibria (PTFE, no fluorophile) and then the effect of glass and base (heterogeneous and homogeneous) on the rates of hydrolysis of **1b–i**, Figure 7. The reactions were conducted

with carefully controlled magnetic stirring rates in the same PTFE vessel, with identical glass surface area/reaction volume ratios, and were found to be reproducible within these limits.

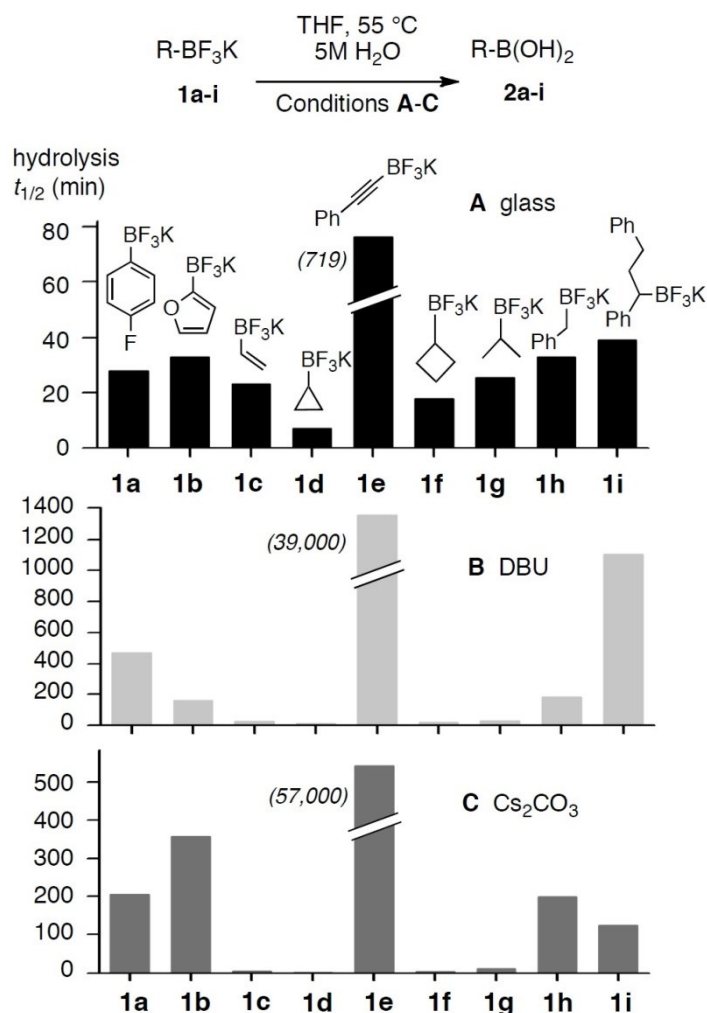


Figure 7. Hydrolytic half-lives for trifluoroborates **1a–i**, 8 mM in 10/1 (v/v) of THF/water (5 M H₂O) at 55 °C in the presence of grade 3 glass powder (**A**), 3 equiv of DBU (**B**), and 3 equiv of Cs₂CO₃ (**C**). Bar heights for the very slowly hydrolyzed alkynyl substrate **1e** have been scaled down by approximately 10, 28, and 100 in **A**, **B**, and **C**, respectively; in these cases, the approximate half-lives are indicated in parentheses.

Hydrolytic Equilibria in 1a–i and Glass-Mediated Hydrolysis. Under base-free conditions, glass powder induced pseudo-first-order hydrolyses ($k_{\text{obs}}^{\text{glass}}$) in substrates **1a–i** ($[\mathbf{1}]_0 = 8 \text{ mM}$) with no induction period and without evidence for the rapid pre-equilibria observed in the absence of glass. The least reactive substrate was the phenylethynyl trifluoroborate **1e** ($t_{1/2} = 12 \text{ h}$), for which we were unable to detect a hydrolytic pre-equilibrium in the absence of glass; the most reactive substrate was the cyclopropyl trifluoroborate **1d** ($t_{1/2} = 7$

min). The hydrolytic equilibrium (x_2)^[35] correlates with the rate of glass-mediated hydrolysis,^[36, 37] consistent with the glass exerting a constant fluorophilic capacity, thus driving the overall hydrolysis, but simultaneously buffering the acid catalysis.

Whilst the range of $k_{\text{obs}}^{\text{glass}}$ values is small (ca. 10^2) compared to that with base ($>10^5$), *vide infra*, we sought to elucidate whether there was a simple structural origin for the trends observed. In a qualitative sense, increasing s-character at the carbon bound to boron, e.g., alkynyl substrate **1e**, would be expected to stabilize the borate (RBF_3K) form.^[38] In contrast, substrates that are able to engage in π -donation, e.g., vinyl **1c** and cyclopropyl **1d**, or in hyperconjugation, e.g., isopropyl **1g**, would be expected to stabilize the borane form (R-BX_2 , X = OH, F), leading to larger values of x_2 . Seeking a more quantitative analysis, we surveyed single-crystal X-ray structures of potassium trifluoroborates (20 examples, predominantly aryl and alkenyl: see Supporting Information). The trends in this data suggested that B–F bond lengths might be used as a probe for x_2 and the variation in relative $k_{\text{obs}}^{\text{glass}}$ values between substrates.

We thus optimized structures for the difluoroboranes^[39] (RBF_2 ; **3a–i**) using DFT (6-31+G(d) B3LYP; THF continuum) with the expectation that an increase in the ability of “R” to donate into the vacant p-orbital on boron should be signaled by an increase in the B–F bond length. The resulting data were normalized against BF_3 , such that $\Delta r(\text{B–F}) = [r(\text{B–F})_3] - [r(\text{B–F})_{\text{BF}_3}]$,^[40] and found to correlate with the experimentally determined hydrolytic equilibrium (x_2) for **1a–i**, Figure 8.

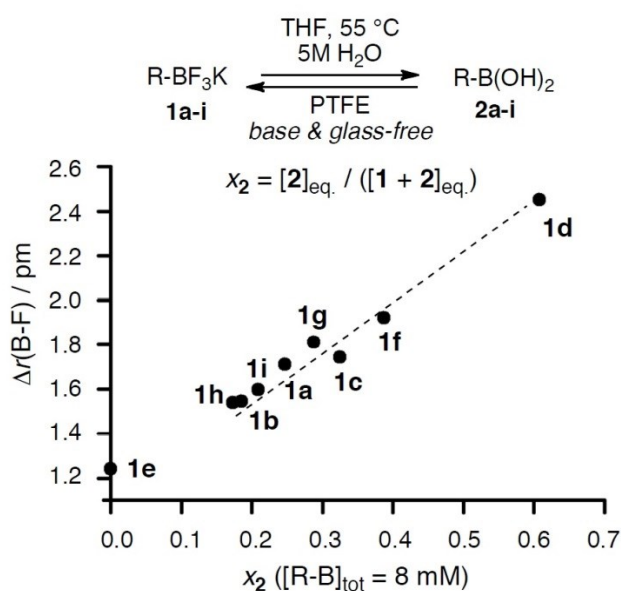


Figure 8. Variation in B–F bond length ($\Delta r(\text{B–F})$, by DFT) in RBF_2 (**3a–i**) with hydrolytic equilibrium (x_2)³⁵ for RBF_3K (**1a–i**) \rightarrow RB(OH)_2 (**2a–i**) at $[\text{RB}]_{\text{TOT}} = 8$ mM; x_2 for **1e** was not determined.^[37] $\Delta r(\text{B–F}) = 0.0018 \ln K + 0.0474$.

Base-Mediated Hydrolysis of 1a–s and Generalized Mechanistic Regimes. Under SM coupling conditions, Scheme 1, where a base is required to facilitate transmetalation with RB(OH)_2 ,^[25, 27] the prediction of hydrolysis rates becomes significantly more complex than Figure 8 might suggest. Indeed, for **1a–i**, the rates spanned over 5 orders of magnitude. The substrates fall broadly into two classes, with the base causing either rate enhancement or rate retardation, relative to $k_{\text{obs}}^{\text{glass}}$. Thus, analogous to **1a**, the rates of hydrolysis of 2-furanyl (**1b**), benzyl (**1h**), and 1,3-diphenylpropyl (**1i**) trifluoroborates were strongly retarded by base (Cs_2CO_3 and DBU), and alkynyl trifluoroborate **1e** was almost inert, with a half-life of about 40 days. In contrast, Cs_2CO_3 induced substantial acceleration in the hydrolysis of the vinyl (**1c**), cyclopropyl (**1d**), cyclobutyl (**1f**), and isopropyl (**1g**) trifluoroborates; see bottom bar chart in Figure 7.

To further explore this issue, we studied the hydrolysis of RBF_3K reagents **1j–s**. Analysis of the expanded data set confirms that the glass-mediated hydrolyses correlate well with $\Delta r(\text{B–F})$ in RBF_2 (**3**) above 1.5 pm; below this threshold, the rates of hydrolysis drop precipitously, Figure 9. Due to the glass surface area dependence, $k_{\text{obs}}^{\text{glass}}$ is relative rather than absolute. Nonetheless, the correlation acts as a useful reference curve for analysis of the rates under the heterogeneous basic conditions induced by Cs_2CO_3 ($k_{\text{obs}}^{\text{base}}$).

Under basic conditions, while the heterogeneity introduces greater rate variation, $\log_{10}k_{\text{obs}}^{\text{base}}$ correlates reasonably smoothly with $\Delta r(\text{B–F})$, with differentiation according to whether R is sp^2 or sp^3 ; see lines through data, Figure 9. Vinyl reagent **1c** is clearly an outlier from the correlation, *vide infra*. When $\Delta r(\text{B–F})$ in RBF_2 (**3**) is below ca. 1.5 pm, the rates of hydrolysis are very slow, with half-lives in the range of days (**1q**) to over a month (**1s**). Above $\Delta r(\text{B–F}) \approx 1.5$ pm, $k_{\text{obs}}^{\text{base}}$ increases approximately exponentially, with a half-life of just 1.4 min found for **1d**, where $\Delta r(\text{B–F}) \approx 2.5$ pm. Around the region where $\Delta r(\text{B–F})$ is 1.7 to 2.0 pm, some substrates (e.g., **1n** and **1m**) are found to be very sensitive to mixing efficiency, this being signaled for example by abrupt rate accelerations when reaction sampling is insufficiently frequent.

Overall these features are readily interpreted if the hydrolysis is considered to arise *via* two general processes, Scheme 4: (i) acid-catalyzed^[41] loss of MF from **1** and (ii) a direct equilibrium dissociation of MF ($\text{M} = \text{K}$ or Cs), as proposed by Perrin,^[41] from **1** to liberate **3**.

For substrates where $\Delta r(\text{B–F})$ ^[40] is below approximately 1.75 pm, the R group is insufficiently stabilizing in **3** to facilitate efficient hydrolysis by the direct dissociation pathway (ii). Instead, the acid-catalyzed pathway (i) is dominant, resulting in strong rate suppression on addition of base. Of course, inefficient transit *via* pathway (ii) still occurs in the presence of base, and this accounts for example for the slow background hydrolysis observed after sonication in Cs_2CO_3 -mediated hydrolysis of **1a**, Figure 6B. In contrast, for substrates where $\Delta r(\text{B–F})$ is above this threshold, R is better able to stabilize RBF_2 (**3**), e.g., by π -overlap or hyperconjugation with the vacant p-orbital on B, allowing efficient hydrolysis by pathway (ii). Pathway (ii) can only be accelerated by base to the point at which the rate-limiting step becomes k_{dir} . Indeed, increasing concentrations

of DBU had no effect on the rate of hydrolysis of **1d** and **1f**. This then suggests that Cs_2CO_3 is able to assist dissociation, e.g., by interaction of OH^- or CO_3^{2-} with M^+ , similar to the process proposed by Hutton.^[17]

As noted above, the hydrolysis of vinyl trifluoroborate (**1c**) proceeds nearly 2 orders of magnitude faster under base-mediated conditions than predicted by its $\Delta r(\text{B-F})$ value. In contrast, the rate with styryl **1k** was “normal”, as was $k_{\text{obs}}^{\text{glass}}$ for both species, suggesting a unique mechanism for hydrolysis of **1c** with base. After excluding various catalyzed mechanisms,^[42] we took a selection of reagents (**1a**, **1c**, **1o**, **1g**, and **1j**) and analyzed the separated bulk and minor biphases by ^{11}B NMR after 5 min hydrolysis at 20 °C. This confirmed (see Supporting Information) that when R is small enough (**1c** and **1g**) the ionic RBF_3K reagent is sufficiently hydrophilic to partition extensively into the predominantly aqueous minor biphasis. For isopropyl **1g**, this partitioning has little impact, as hydrolysis *via* pathway (ii) is already reasonably efficient. For vinyl reagent **1c**, the process ($K_{\text{biph.}}$) induces a significant increase in hydrolysis rate, *via* pathway (iii).^[11]

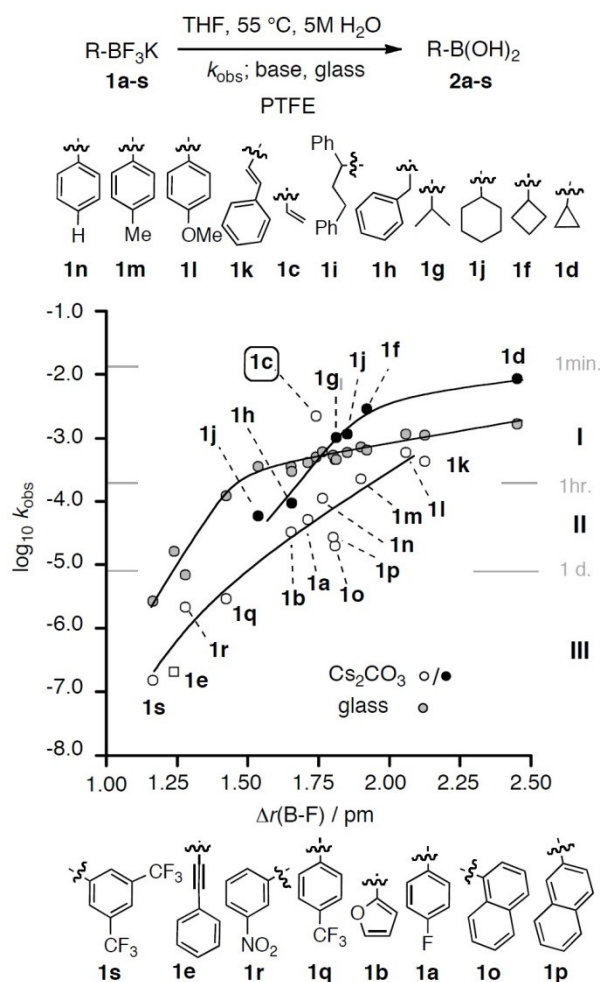
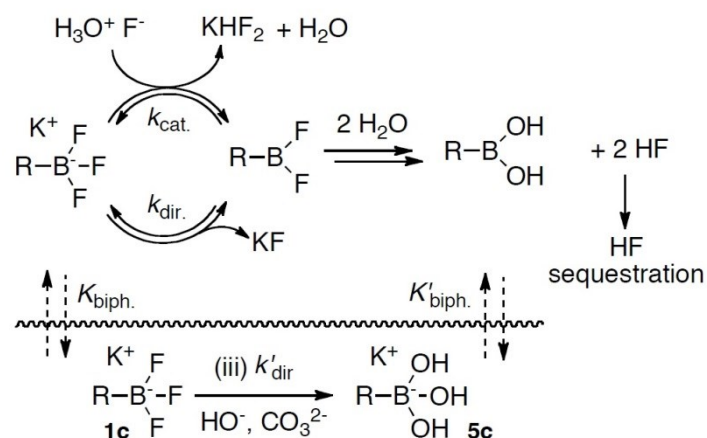


Figure 9. Bond elongation ($\Delta r(\text{B-F})$)^[39] in RBF_2 (**3a-s**) versus $\log_{10} k_{\text{obs}}$ (s^{-1}) for hydrolysis of **1a-s** (8 mM) mediated by glass powder and by Cs_2CO_3 in 10/1 (v/v) of THF/water (5 M H_2O) at 55 °C in a PTFE vessel with 500 rpm magnetic stirring. Lines through data are a solely a guide to the eye. Reagents classed by $t_{0.5}$ in base (I, ≤ 1 h; II 1 h-24 h; III ≥ 1 day).



Scheme 4. Dichotomous RBF₃K hydrolysis^a.

^aPredominant transit *via* pathway (i) results in retardation by base. Net hydrolysis *via* pathway (ii) is accelerated by base. Pathway (iii) only applies when RBF₃K is sufficiently hydrophilic.

LFER Analyses of the Hydrolytic Propensity of RBF₃K Reagents: Finally, we considered whether the R group in RBF₂ (**3**) could be treated as though it were a substituent on an aromatic ring (R-Ar), in order to provide a rapid estimate of its ability to conjugate with a π -system on a directly attached sp²-hybridized atom (i.e., R-BF₂ \approx R-C_{Ar}). The Swain–Lupton resonance parameter (\mathfrak{R}_{SL})^[43] was found to provide a useful estimate. To explore the general applicability of this approach, we calculated the $\Delta r(\text{B-F})$ values of 41 examples of **3**, where *R* = aryl, heteroaryl, alkyl, vinyl, and alkynyl, for which \mathfrak{R}_{SL} values were available.^[43] Apart from a few outliers, including sterically hindered *o*-aryl substituents and the 2-pyridyl moiety,^[44] there is a reasonable correlation with \mathfrak{R}_{SL} ; see Supporting Information for full details. There was no correlation found for a series of XBF₂ species where X = halogen, NH₂, SH, SiH₃, H, OH, or OMe.

This LFER type analysis was then applied to the base-mediated hydrolysis of substrates **1a–s**, for which \mathfrak{R}_{SL} values were available.^[43] The initial correlation (see Supporting Information) was slightly improved by a dual-parameter approach, using Charton values (ν) to account for the steric effect of R.^[46] The resulting correlation, Figure 10, allows an a priori assessment of the hydrolytic propensity of RBF₃K reagents under basic aqueous coupling conditions. The RBF₃K reagents can be usefully subdivided according to their $\Delta r(\text{B-F})$ or [$\mathfrak{R}_{\text{SL}} - 0.09\nu$] values. We have subdivided Figures 9 and 10 as **I**, **II**, and **III**, based on the hydrolytic half-lives *under the conditions employed herein*. Class **I** reagents ($t_{0.5} \leq 1$ h) will be prone to direct dissociation (pathway (ii)), thwarting slow release and possibly leading to difficulties in their preparation. Class **II** reagents ($t_{0.5}$ 1–24 h) will predominantly undergo hydrolysis *via* the acid-catalyzed pathway (i), allowing controlled release of boronic acids^[5] under basic conditions provided that phase mixing is efficient or the medium is homogeneous. Class **III** reagents ($t_{0.5} \geq 24$ h) are much more hydrolytically resistant, requiring in some cases days or weeks for substantial conversion to the boronic acid.

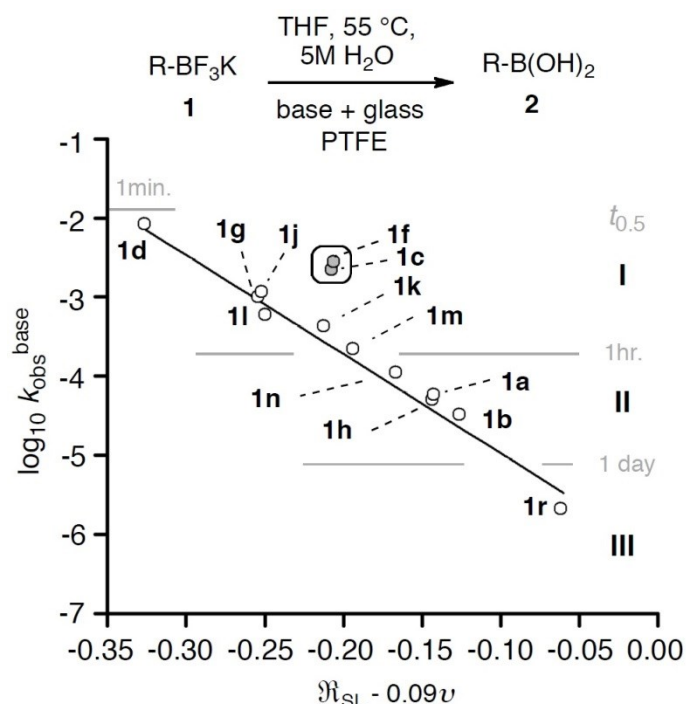


Figure 10. Rates of base-mediated hydrolysis of **1** versus combined resonance (\mathfrak{R}_{SL})^[45] and steric (v)^[46] parameters. Vinyl **1c** is a mechanistic outlier; see text for discussion. The validity of the \mathfrak{R}_{SL} value for cyclobutyl **1f**^[43] is uncertain. Reagents have been classed by $t_{0.5}$ in base (I, ≤ 1 h; II 1–24 h; III ≥ 1 day).

3. Corollaries for the Preparation and Application of Trifluoroborate Reagents in Coupling. The very different behaviors in the range of trifluoroborates studied lead to some important ramifications for their preparation and reaction under basic conditions, e.g., SM coupling, Scheme 1.

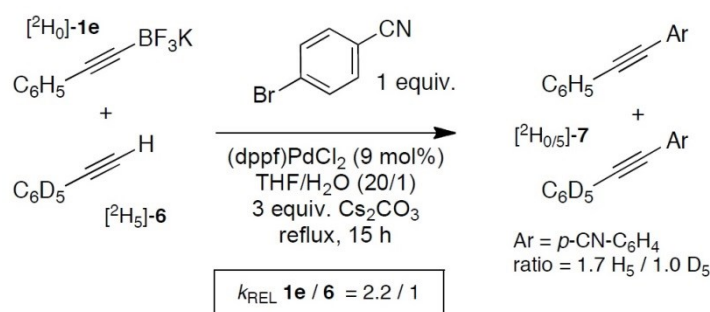
Rapid Hydrolysis and Boronic Acid Stability. Class I trifluoroborates, e.g., isopropyl (**1g**), cyclobutyl (**1f**), and cyclopropyl (**1d**) reagents, as well as pathway (iii) systems such as vinyl (**1c**), undergo such rapid hydrolysis under basic conditions that liberation of the boronic acid is complete in less than 2% of the overall time taken for their SM coupling.^[12b, 12l, 47] Exposure of the cyclopropylboronic acid **2d** to the SM coupling conditions for such an extended period (110 °C, 16 h)^[47] demonstrates that the boronic acid itself is stable toward side reactions such as protodeboronation,^[48] even though its transmetalation with Ar-Pd(L)-OH ^[25, 27] is slow.^[47] Likewise, the cyclobutyl trifluoroborate **1f**, which is not commercially available, is also very rapidly hydrolyzed^[49] to the boronic acid **2f** from which it is derived.^[12l] When we compared the cyclobutyl boronic acid **2f** with trifluoroborate **1f** in parallel SM cross-couplings with $\text{Ar}'\text{-Br}$, we found that they gave identical reaction profiles, albeit both very slow.^[12l, 47] However, a substantial advantage in the use of alkyl trifluoroborates, such as **1d**, **1f**, and **1g**, is their benchtop stability, allowing easy storage and handling. In stark

contrast, many alkyl boronic acids fume in air and require the use of a glovebox for their manipulation. Indeed, hazardously vigorous aerobic oxidation can be exhibited, particularly when samples are anhydrous.^[50]

Slow Hydrolysis and Direct Transmetalation. Class **III** trifluoroborates undergo exceptionally slow hydrolysis in aqueous basic THF. For example, just 18% hydrolysis was detected after 9 days at 55 °C with alkynyl **1e**, while with electron poor aryl **1s**, less than 9% hydrolysis occurred in 2 weeks. Both systems generated the protodeboronated (RH) material rather than the boronic acid. In the case of **1e**, this generates phenylacetylene (**6**), and thus either the trifluoroborate, not the boronic acid **2e**, is the active transmetalating species in its (very slow) SM coupling^[12i] or the process is a copper-free Sonogashira reaction^[51] of alkyne **6**, rather than a genuine SM coupling.

To probe this issue, we competed trifluoroborate **1e** with labeled phenylacetylene ($[^2\text{H}_5]$ -**6**) for limiting *p*-bromobenzonitrile, under Molander's reported coupling conditions,^[12i] Scheme 5.

MS analysis indicated the presence of both coupling products in a ratio corresponding to first-order relative rates of 2.2/1, indicative of a *direct* SM coupling of trifluoroborate **1e**, even though the Sonogashira reaction of alkyne **6** does proceed under these conditions. This outcome is fully consistent with the observation that SM coupling of alkynyl trifluoroborates with aryl halides proceeds just as efficiently under anhydrous conditions.^[12i] An analogous direct transmetalation is anticipated for class **III** aryl trifluoroborates, consistent with the use of ethanolic Et_3N , or nonsolvolytic conditions, for the SM coupling of electron-poor aryl reagents, e.g., **1r** and **1s**.^[12n]



Scheme 5. Suzuki–Miyaura versus Sonogashira coupling under conditions reported for SM coupling of **1e**.^[43]

Summary

The kinetics of hydrolysis of RBF_3K reagents (**1**) to the corresponding boronic acids (RB(OH)_2 , **2**), in the context of their application in Suzuki–Miyaura (SM) coupling, have been studied in the presence and absence of base (Cs_2CO_3 and DBU), buffers, and glass, in PTFE vessels. Under Molander’s conditions (aqueous THF, Cs_2CO_3) at 55 °C, Scheme 1,^[12] hydrolysis rates span more than 5 orders of magnitude. Reactions are found to proceed *via* two distinct general mechanisms, one involving acid catalysis (*i*) and the other direct MF dissociation (*ii*), Scheme 4. Vinyl reagent **1c** is anomalous in that it appears to be solvolyzed *via* a hydrophilic mechanism (*iii*). Phase splitting of the THF–water, induced by Cs_2CO_3 (and other inorganics, KF, KOH, K_2CO_3 , etc.), affects the pH buffering in the bulk organic phase, leading to some boronic acid release rates, e.g., anisyl (**1i**), tolyl (**1m**), and cyclohexyl (**1j**), being very sensitive to factors such as the vessel size, shape and material, the order of addition of components, and the rate of stirring.

The hydrolysis rates (k_{obs}) correlate with B–F bond lengths ($\Delta r(\text{B–F})$, by DFT) in the undetected ($^{19}\text{F}/^{11}\text{B}$ NMR) intermediate RBF_2 (**3**), Figure 9, and in the form of a dual-parameter LFER analysis ($\mathfrak{R}_{\text{SL}} - 0.09\text{v}$), Figure 10. Using these correlations an a priori evaluation can be made as to whether an RBF_3K reagent will likely undergo fast (I; $t_{0.5} \leq 1$ h), slow (II; $t_{0.5} = 1\text{–}24$ h), or very slow (III; $t_{0.5} \geq 1$ d) release. Trifluoroborates in class I, R = alkyl, cycloalkyl, and electron -rich aryl and alkenyl, undergo fast or very fast hydrolysis ($t_{0.5} \leq 1$ h) under the basic SM coupling conditions, *via* pathway ii. For these reagents, release of the corresponding boronic acid (**2**) can occur far faster than it is consumed in coupling. Moreover, it is difficult to suppress their hydrolysis other than by using very much lower concentrations of water, as is for example found in “laboratory grade” alcohol.^[52] Class II trifluoroborates, R = simple aryl, benzyl, and furyl, predominantly undergo hydrolysis by the acid-catalyzed pathway i, and *slow release* ($t_{0.5} 1\text{–}24$ h) of the boronic acid is feasible under the basic SM coupling conditions. Finally, class III trifluoroborates, R = alkynyl and electron-poor aryl, are hydrolyzed very slowly ($t_{0.5} > 24$ h), with transmetalation in SM coupling predominantly proceeding *via* a direct mechanism rather than postsolvolytic.

Overall, while all but the very inert class III reagents act as reservoirs for the active RB(OH)_2 reagent,^[8, 11, 12n-12p] with hydrolysis rates strongly depending on R, and cogenerating 3 equiv of fluoride, their stability and crystallinity allows very convenient storage and handling. The latter point is especially pertinent with air-sensitive systems, such as alkyl boronic acids.^[50] We also note that the controlled release of HF/ KHF_2 , under mild hydrolytic conditions from appropriately tuned RBF_3K reagents, has significant potential for application in synthesis and catalysis.

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- [28] For example, titration of THF into an aqueous basic solution (3 equiv of Cs_2CO_3) of **2a** (8 mM) results in a progressive switch in equilibrium from >98% $[\text{ArB}(\text{OH})_3]^-$ through to >98% $\text{ArB}(\text{OH})_2$, with >90% of the latter being present in 10/1 THF/ H_2O . [11]
- [29] A survey of biaryl SM couplings (36976 examples, 1981–2011, SciFinder, Chemical Abstracts Service, Columbus, OH) showed that >53% involved water as a co-solvent, with more than 73% predicted to be biphasic.
- [30] ^{19}F NMR analysis of a solution of **2a** (8 mM) in THF/water (10/1) containing 3 equiv of Cs_2CO_3 , immediately after sonication, confirmed that this does not lead to higher proportions of the “ate” complex $[\text{ArB}(\text{OH})_3]^-$, indicative that sonication does not induce a higher pH in the bulk medium, merely more efficient mass transfer and buffering capacity to neutralize liberated HF or KHF_2 .
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- [34] Catalyst instability resulted in no cross-coupling of $[\text{}^2\text{H}_0]$ -**2a**, liberated by hydrolysis of unreacted $[\text{}^2\text{H}_0]$ -**1a**, with a second electrophile (*p*-anisyl bromide). Homogeneous conditions with an organic base (DBU) also proved to be detrimental to the efficiency of the reaction. However, we did not explore any other ligands or engage in extensive optimization.

- [35] The x_2 values ($x_2 = [\text{RB}(\text{OH})_2]/[\text{R-B}]_{\text{TOT}}$), and thus K_{app} , were most reliably determined by ^{11}B NMR, as ^{19}F NMR analysis required integration of the BF_3K versus the time-averaged signal arising from $\text{KHF}_2 + \text{HF}$, which was sometimes very broad.
- [36] For the conditions explored (20 mg of grade 3 borosilicate glass powder in 6.6 mL of THF/ H_2O (10/1) containing 52.8 μmol of **1**; $[\text{R-B}]_{\text{TOT}} = 8 \text{ mM}$); $\ln k_{\text{obs}}^{\text{glass}} = 0.35 \ln K_{\text{app}} - 1.91$; $R^2 = 0.91$.
- [37] For the exceptionally unreactive alkynyl trifluoroborate **1e**, for which hydrolytic equilibrium was not detected experimentally, the *glass surface area dependent* correlation [36] of rate versus K_{app} predicts x_2 to be 0.01.
- [38] This is consistent with Perrin's conclusions [14] that a slower hydrolysis is observed in ArBF_3K substrates where the aromatic ring is most able to stabilize the negativity of the "ate" complex.
- [39] Normalization against BF_3 ($\Delta r(\text{B-F}) = [r(\text{B-F})_{\text{RBF}_2}] - [r(\text{B-F})_{\text{BF}_3}]$) attenuates DFT parametrization issues. In general, the average $r(\text{B-F})$ value was employed. However, when the BF_2 unit was asymmetric ($\Delta\Delta r(\text{B-F}) > 0.10 \text{ pm}$) and the average significantly deviated from the $\Delta r(\text{B-F})$ versus $\Delta r(\text{B-C})$ correlation (see Supporting Information), the closest value of $\Delta r(\text{B-F})$ to the B-F versus B-C correlation was chosen. We also explored the difference in calculated energies between $[\text{RBF}_3]^-$ and RBF_2 , but no reliable trend emerged.
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- [41] The reverse reaction, i.e., HF-mediated preparation of **1** ($\text{M}^+ = \text{Li}, \text{Na}, \text{K}, \text{Cs}, \text{R}_4\text{N}, \text{R}_4\text{P}$) from **2**, has been reported by Batey [8] and by Matteson: Matteson, D. S.; Maliakal, D.; Pharaazyn, P. S.; Kim, B. J. *Synlett* **2006**, 3501–3503.
- [42] An alkene addition–elimination of MX , where $\text{X} = \text{carbonate or hydroxide}$, for example, was tested by SM coupling of **1c** with Ar-Br in $\text{THF-D}_2\text{O}$, but this did not generate any α -deuterated styrene, as would have been expected for a process formally proceeding *via* an F_2B -stabilized carbanion intermediate in an aqueous medium. Hydrolysis in the presence of $^{10}\text{B}(\text{OH})_3$ resulted in no $^{11}\text{B}/^{10}\text{B}$ exchange, and there was no rate acceleration on addition of KBF_4 .
- [43] For an extensive tabulation of *modified* Swain–Lupton values see: (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, 91, 165–195. Hydrophobic interactions between substituent and aqueous media can strongly affect σ_p/σ_m determinations *via* $\text{p}K_a$ measurements, and thus \mathfrak{R}_{SL} values for such R groups should be viewed as approximate. $\text{p}K_a$ and thus σ_p/σ_m and \mathfrak{R}_{SL} values can be predicted

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