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

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1. Introduction

• Suzuki-Miyaura (SM) cross-coupling reaction is one of the most important reactions in organic chemistry.

• Protecting groups for boronic acids, such as trifluoroborates and MIDA boronates, have been developed (Figure 1).[1] Organotrifluoroborate (RBF_3K) reagents are easily prepared, air-stable and easy to handle.

• The in situ *slow-release* of $ArB(OH)_2$ (**2**) and fluoride from the $ArBF_3K$ reagent (**1**) reduces the side reactions (homocoupling, oxidation, protodeboronation) observed when aryl boronic acid is directly used (Scheme 1).[2]

Problem: solvolysis of RBF_3K is rather complex, making the "slow-release" strategy not viable in some cases.

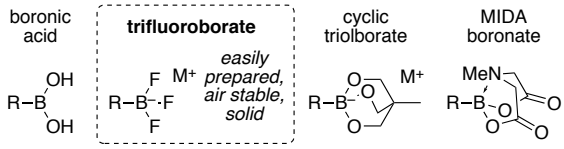
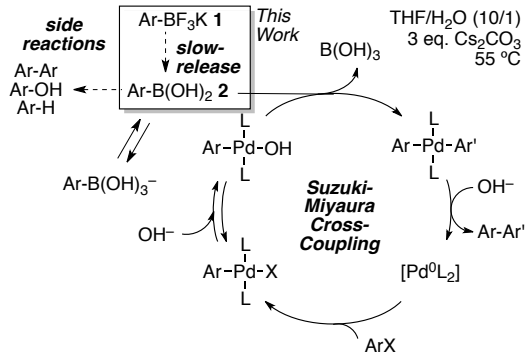


Figure 1. Chemical structures of boronic acid and derivatives.

Scheme 1. Suzuki-Miyura Coupling of $ArBF_3K$ Reagents (**1**) via $ArB(OH)_2$ (**2**).



This Work: factors that affect the hydrolysis of RBF_3K reagents were investigated. Analysis of the B–F bond allows a priori evaluation whether RBF_3K will engender a "slow-" or "fast-release".

2. Results and Discussion

2.1. Hydrolysis Mechanism of Aryltrifluoroborate 1a (R = *p*-F-C_6H_4) (Environmental Factor)

2.1.1. Hydrolitic Equilibrium and Effect of Glass (Reaction Vessel)

• The shape and size of the glass reaction vessel showed large effect in the hydrolytic half-life $t_{1/2}$ of **1a** under SM-coupling conditions (Figure 2). The question is *WHY?*

• [^{10}B]-**1a** and [$^2H_4$]-**2a** under standard SM-coupling conditions do not undergo Ar/B exchange (Scheme 2a).

=> F/OH ligand-exchange via intermediates **3a**–**5a** should allow the equilibrium between **1a** and **2a**.

=> *Fluoride sequestration* ultimately drives the equilibrium to the side of **2a** (Scheme 2b).

• *Glass acting as a fluorophile* can explain the effect of the reaction vessel.

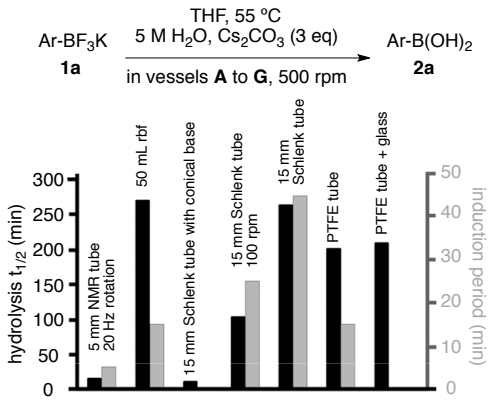
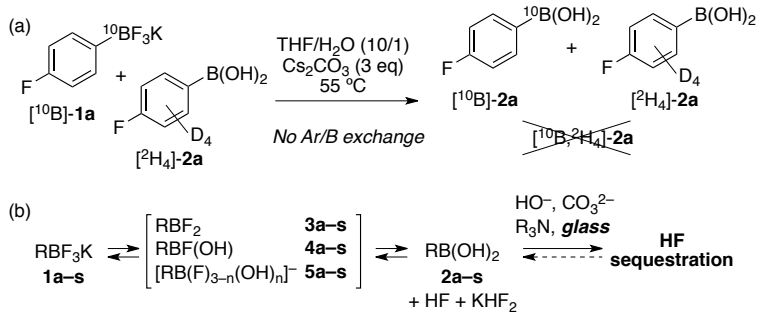


Figure 2. (a) Hydrolytic half-life of **1a** (8 mM) to **2a** in reaction vessels **A**-**G**; magnetic stirring rate 500 rpm unless noted. Determined by ^{19}F NMR.

• Investigation of hydrolysis of **1a** was carried out in a PTFE tube. Without glass or base, the reaction reached a hydrolytic pre-equilibrium. On addition of glass powder, the hydrolysis proceeded with simple pseudo-first-order kinetics, at a rate that was *directly proportional to the glass surface-area* (Figure 3).

Scheme 2. (a) Exchange study between [^{10}B]-**1a** and [$^{2}H_4$]-**2a** under SM cross-coupling conditions.(b) Hydrolytic equilibrium of **1** with **2**, via **3–5**, and overall driving force of HF sequestration by base or glass.



a, *p*-F-C_6H_4 **e**, PhC **i**, 1,3-diphenylpropyl **m**, *p*-Me-C_6H_4 **p**, 2-naphthyl
b, 2-furyl **f**, *c*-Bu **j**, *c*-Hex **n**, C_6H_5 **q**, *p*-CF_3-C_6H_4
c, vinyl **g**, *i*-Pr **k**, b-styryl **o**, 1-naphthyl **r**, *m*-NO_2-C_6H_4
d, *c*-Pr **h**, benzyl **l**, *p*-MeO-C_6H_4 **p**, 2-naphthyl **s**, 3,5-$(CF_3)_2$-C_6H_3

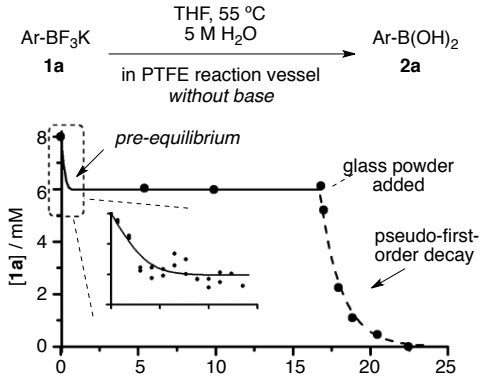


Figure 3. Hydrolysis of **1a** in a PTFE vessel. Lines through data are approach to equilibrium and subsequent pseudo-first order decay after addition of borosilicate glass powder.

2.1.2 Effect of Base: THF/Water Phase-Splitting and pH

• Inorganic bases induce a phase-splitting of water in the homogeneous THF/water medium, although the system may present the visual aspect of a homogeneous medium.

=> Under SM coupling conditions, the majority of the base is present in the minor aqueous phase (pH ≥ 12) rather than in the bulk THF/H_2O phase (pH ≈ 9) (Figure 3a).

• In a pH single-phase basic medium, the boronic acid is predominantly present as $ArB(OH)_3^-$. In contrast, a biphasic system maintains a relatively lower pH in the organic phase, ensuring that a higher proportion of $ArB(OH)_2$, the active transmetalating agent,[3] is present while facilitating the generation of the key complex R-Pd-OH (Figure 3b).

=> *in situ generation of a biphasic medium is benefic to the reaction.*

• Although a base or glass ("HF-sink"), is required to drive the hydrolysis to completion, base in the medium strongly retards hydrolysis (Figures 3c and 3d).

=> hydrolysis of **1a** should proceed by an acid-catalyzed hydrolytic equilibrium (*acid-base paradox*).

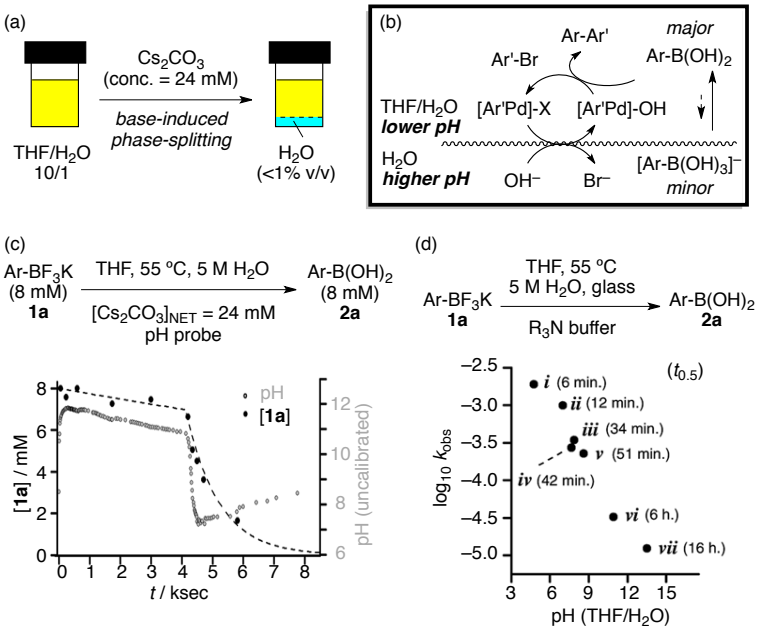


Figure 3. (a) Phase-splitting of THF/H_2O solution (10/1) under basic conditions. (b) SM coupling in a biphasic system. (c) Hydrolysis of **1a** under basic heterogeneous conditions and the accompanying change in pH of the bulk phase. (d) Hydrolysis of **1a** under different base/buffer conditions.i: MOPS 50 and 100 mM ii: no buffer, iii: TRIS, iv: Et_3N, v: *i*-Pr_2-NEt, vi: DBU, vii: *t*-Bu-P_4.

Conclusion in Section 1a: under the basic THF/H_2O conditions, the base-mediated suppression of solvolysis of **1a** counts for the variability in the induction period and solvolytic decay. pH buffering ability of the bulk phase depends on three processes:

(i) the rate of hydrolytic equilibrium of **1a**, to liberate HF/KHF_2 <= *depends on R*

(ii) the rate of sequestration of the HF/KHF_2 <= *depends on vessel and base*

(iii) the interfacial transfer rate of hydroxide or carbonate from the strongly basic minor biphase into the bulk medium (the major biphase) <= *depends on mixing efficiency*

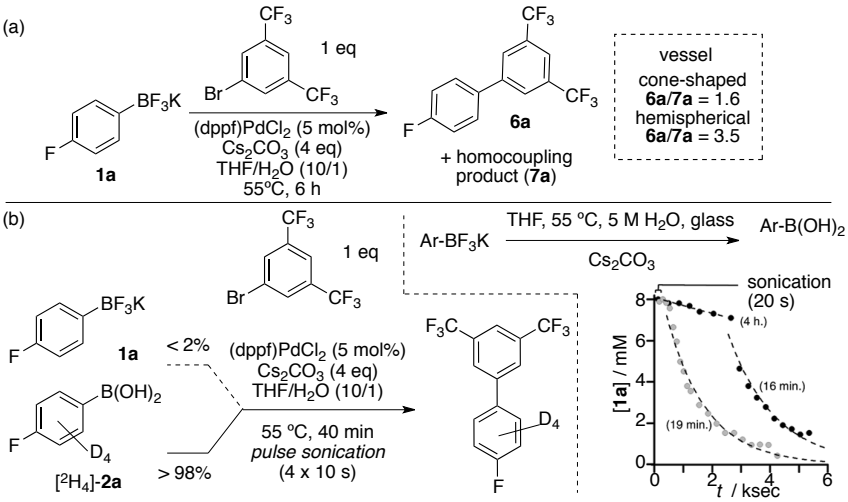
(ii) and (iii) => Reaction environment is an important factor!

Examples

1) Mixing: inefficient mixing may result in etching of the vessel glass by HF, KHF_2.

2) Reaction vessel shape: a cone-shaped base vessel resulted in poor phase contact of the bulk solvent with the basic minor split phase, resulting in faster hydrolysis and higher amount of homo-coupling product when compared to a hemispherical base vessel (Scheme 3a).

Scheme 3. (a) Effect of shape of reaction vessel in SM coupling. (b) Chemoselective SM coupling via sonication. (Inset) Effect of 20s of sonication pulse on the hydrolysis of **1a** in a heterogeneous media.



3) Chemoselective Cross-Coupling: Highly efficient phase contact can be produced by sonication. Under pulse sonication conditions, the boronic acid-derived cross-coupling product was generated with high selectivity (Scheme 3b).

2.2. Hydrolysis of 1b–s (R Factor)

2.2.1. Hydrolytic Equilibrium in 1a–i and Base-Mediated Hydrolysis of 1a–s

- Range of k_{obs} in glass- or base-mediated hydrolysis of **1a–s** was very large (> 10^5).
- *Rationalization of the trend*:

- slow hydrolysis: stabilization of RBF_3K form by the s-character of C at the B–C bond, e.g, **1e**

- fast hydrolysis: stabilization of $RB(OH)_2$ form by π-donation (**1c**,**1d**) or hyperconjugation (**1g**)

=> B–F bond length, an indicator of the ability of R to donate into the vacant p-orbital on B, should correlate with the hydrolysis (k_{obs}) of RBF_3K.

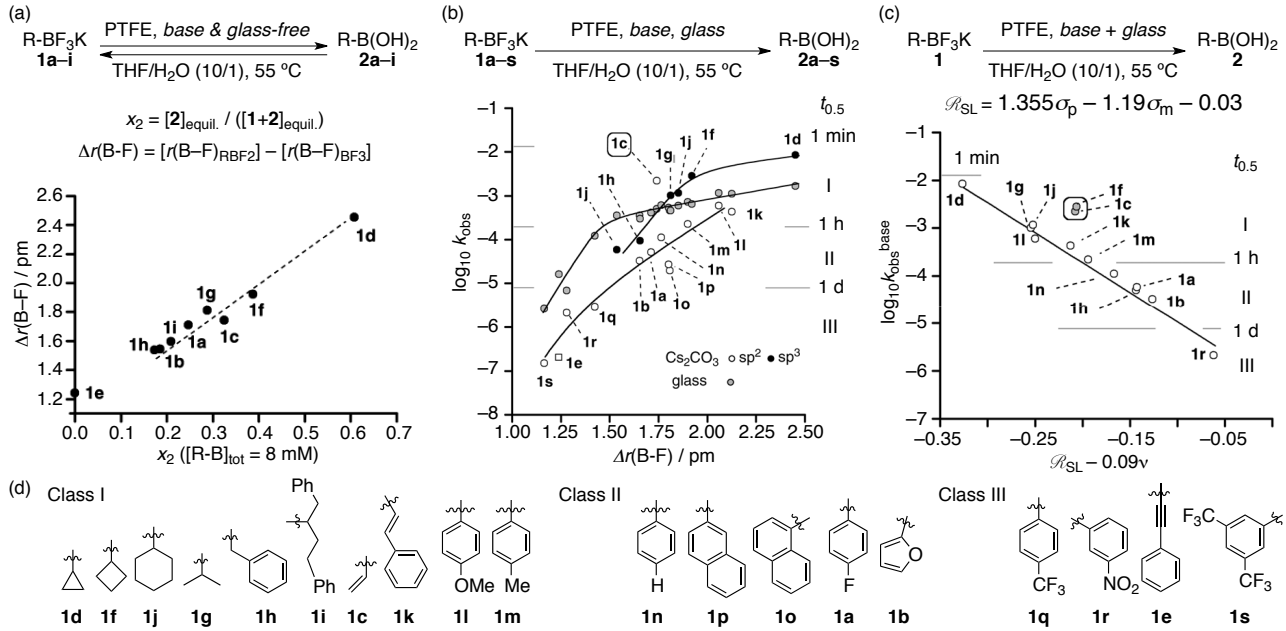
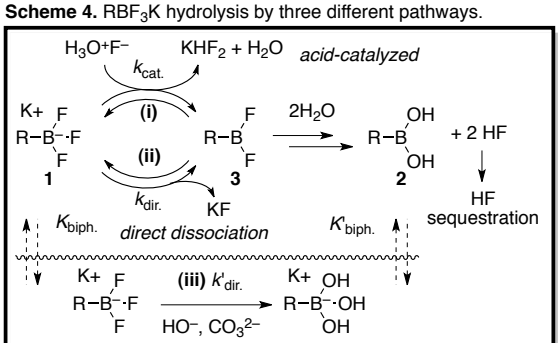


Figure 5. (a) Variation in B–F bond length (Δr(B–F), by DTF) in RBF_2 (**3a–i**) with hydrolitic equilibrium (x_2) for RBF_3K (**1a–i**) ⇌ $RB(OH)_2$ (**2a–i**). (b) Bond elongation (Δr(B–F)) in RBF_2 (**3a–s**) versus $\log_{10}k_{obs}$ (s^{-1}) for hydrolysis of **1a–s** (8 mM). (c) Rates of base-mediated hydrolysis of **1** versus combined resonance ($\mathscr{R}_{SL}$) and steric (ν) parameters. (d) Reagents classified by $t_{0.5}$ in base.

• The calculated Δr(B–F) (variation of B–F bond length from BF_3 to RBF_2, calculated by DFT) correlated well with the experimentally determined hydrolytic equilibrium (x_2) for **1a–i** (Figure 5a).

Scheme 4. RBF_3K hydrolysis by three different pathways.



Hydrolysis via pathway i results in retardation by base. Via pathway ii is accelerated by base. Pathway iii only applies when RBF_3K is sufficiently hydrophilic.

• Under SM-coupling conditions, the prediction of the hydrolysis rate became much more complex. Glass-mediated hydrolyses correlated well with Δr(B–F) above 1.5 pm (Figure 5b). Under basic conditions, $\log_{10}k_{obs}^{base}$ correlated with Δr(B–F), with differentiation whether R is sp^2 or sp^3.

• The large range of k_{obs} was explained by the existence of two pathways for hydrolysis. If Δr(B–F) is below approximately 1.75 pm, the R group is insufficiently stabilizing in **3** to facilitate hydrolysis through direct dissociation pathway (ii). Instead, the acid-catalyzed pathway (i) is dominant, resulting in strong rate suppression on addition of base (Scheme 4).

• Outlier **1c**: R is hydrophilic enough so that the ionic RBF_3K reagent partitions into the aqueous minor biphase via pathway iii.

• However, a more general function than Δr(B–F) should be applied for better application. *Can the R group be treated as if it were a substituent on an aromatic ring ($R\text{-}BF_2 \approx R\text{-}C_{Ar}$)?*

• Swain-Lupton resonance parameter (extension of Hammett equation) (Equation 1) correlated well to Δr(B–F) , and thus to k_{obs}^{glass} (Figure 5c).

$$\mathscr{R}_{SL} = 1.355\sigma_p - 1.19\sigma_m - 0.03 \text{ (Equation 1)}$$

=> Based on these results, trifluoroborates were classified in three groups according to R (Table 1).

Table 1. Classification of trifluoroborate substrates according to hydrolytic haf-life $t_{0.5}$.

class	R	$t_{0.5}$	pathway	misc
I	alkyl, cycloalkyl, electron rich-aryl, alkenyl	< 1 h (fast hydrolysis)	ii (direct dissociation)	Release of boronic acid is faster than its consumption. Advantage is high stability of trifluoro boronate.
II	simple aryl, benzyl, furyl	1 h < $t_{0.5}$ < 24 h (slow hydrolysis)	i (acid catalyzed)	Slow release of boronic acid is feasible.
III	alkynyl, electron-poor aryl	> 24 h (very slow hydrolysis)	i (acid catalyzed)	Transmetalation in SM coupling proceeds via a direct mechanism rather than postsolvolysis

3. Conclusion

• Kinetics of hydrolysis of RBF_3K (**1**) to $RB(OH)_2$ (**2**) was investigated in the presence and absence of base and glass in PTFE vessels for their application in Suzuki-Miyaura coupling.

• Reactions were found to proceed via acid catalysis or direct dissociation of KF.

• Hydrolysis rates (k_{obs}) correlated well with Δr(B–F) and $\mathscr{R}_{SL}$. A priori evaluation can be made to determine whether an RBF_3K will undergo fast or slow hydrolysis.

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