

Aryltrifluoroborate Hydrolysis | Hot Paper |

Dynamic Ion Speciation during the Hydrolysis of Aryltrifluoroborates**

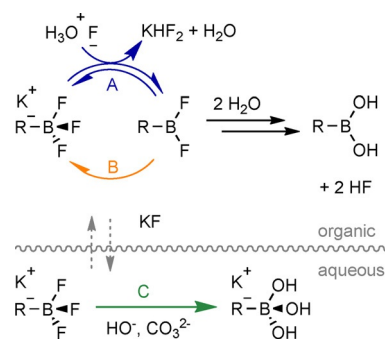
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Abstract: Organotrifluoroborates serve as coupling partners during transmetalation in the Suzuki–Miyaura reaction but require hydrolysis prior to the coupling reaction. Their anionic nature allows study of their hydrolysis by electrospray ionization mass spectrometry (ESI-MS) through real-time monitoring, complemented by pH analysis. The induction period

varied according to the borates employed, and a dynamic series of equilibria for numerous ions was observed during hydrolysis. We found that the induction periods and reaction rates were sensitive to the R group of the borates, the shape of the reaction vessel, and stir rate.

Introduction

Many organoboronic acids are known to be inherently unstable to oxidation or protolytic deboronation; making their benchtop handling and storage difficult.^[1,2] As an alternative, chemists sometimes use stable, easy-to-handle organoborate salts. Thus, organotrifluoroborates, along with *N*-methylimidodiacetic acid (MIDA) boronates,^[3–6] have become common organoboron sources in the Suzuki–Miyaura reaction.^[7–16] They require hydrolysis^[17–19] prior to the coupling reaction, and the Lloyd-Jones research group has extensively studied this hydrolysis reaction by nuclear magnetic resonance (NMR).^[20–22] They proposed that in THF/water (including a base), a biphasic system with three mechanisms of hydrolysis is at work (Scheme 1). The hydrolysis is catalyzed in path A by acid and is correspondingly retarded by base.^[20] Fluoride dissociation by path B is accelerated by base, and a third path C is active in the aqueous phase for hydrophilic substituents and is accelerated by base.^[20] They noticed that the biphasic system needed to reach a critical pH (induction period) for the reaction to start through path A.^[20] Considering that organotrifluoroborates are anionic, we were interested to see whether we could observe the dynamics of any of these ions (i.e., $[\text{RBF}_n(\text{OH})_{3-n}]^-$, $n = 0–3$) by methods developed in our laboratory, namely pressurized sample infusion (PSI) coupled with electrospray ionization mass spectrometry (ESI-MS).^[23,24] This sample introduction



Scheme 1. Trifluoroborate hydrolysis pathways proposed by Lloyd-Jones and Perrin (R = alkyl, aryl).^[20,40]

method enables real-time analysis of a complex reacting solution.^[25–39] In addition, changes in pH due to speciation during hydrolysis could be measured in parallel using a pH meter.

Results and Discussion

We settled on investigating five organotrifluoroborate potassium salts: *p*-tolyltrifluoroborate, *p*-methoxyphenyltrifluoroborate, cyclohexyltrifluoroborate, isopropyltrifluoroborate and phenyltrifluoroborate. The first four borates were shown by Perrin^[40] and Lloyd-Jones^[20] to be the fastest hydrolyzing examples, and therefore were the best match for our methodology (PSI-ESI-MS gathers spectra on a timescale of seconds, so dense data can be collected in minutes). However, we also explored the reactivity of phenyltrifluoroborate (found to be a slow hydrolyzing example by Perrin^[40] and Lloyd-Jones^[20]), for an insight into its rate of hydrolysis using our technique. The hydrolysis was studied with a 1:3 ratio of organotrifluoroborate to base (Cs_2CO_3) and a THF/ H_2O ratio of 10:1. In order to avoid saturation issues in our mass spectrometer, the concentration of the borate was kept at 1.8 mM. We examined the reaction

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[**] A previous version of this manuscript has been deposited on a preprint server (<https://doi.org/10.26434/chemrxiv.12724724.v1>)

Supporting information and the ORCID identification numbers for the authors of this article can be found under:
<https://doi.org/10.1002/chem.202004726>

at slow (≈ 168 rpm) and fast (≈ 600 rpm) stir rates, and in both a round-bottomed flask and in a Schlenk tube. Reactions were also monitored separately using a pH meter.

The anionic speciation profile of the reaction mixture prior to addition of base and water was simple, showing signals only for $[\text{ArBF}_3]^-$ (Figure 1A) and its corresponding aggregate ion $[(\text{ArBF}_3)_2\text{K}]^-$ (generated due to an increase in concentration of the borate in the droplet formed during the electrospray ionization process^[41–43]). Addition of base and water soon resulted in a profusion of new peaks (Figure 1B). These peaks could be assigned to partially hydrolyzed, dehydrated, and aggregate ions.

We expected to observe each progressive species in the conversion from $[\text{RBF}_3]^-$ (1) through to $[\text{RB}(\text{OH})_3]^-$ (7; Scheme 2), but the equilibria are more complex than we had first guessed. We observed aggregates, such as $[(\text{RBF}_3)_2\text{M}]^-$ ($\text{M}=\text{K}$ or Cs), dehydrated species, such as $[\text{RBO}_2\text{H}]^-$ (8) and $[\text{R}_2\text{B}_2\text{O}_3\text{H}]^-$ (9); and mixed dimers, such as $[\text{R}_2\text{B}_2\text{O}_3\text{H}_2\text{F}]^-$ (10). Given that dehydrated boronic acids are known to adopt cyclic structures,^[44–47] we assigned a hydrogen-bond stabilized boroxine-type structure for 9.

Species 8 is of relevance for a Suzuki–Miyaura reaction, as it is structurally part of a pre-transmetalation intermediate proposed by Denmark.^[48,50] For substrates with electron-withdrawing R groups,^[40] such as phenyltrifluoroborate, *p*-methoxyphenyltrifluoroborate or *p*-tolyltrifluoroborate, the formation of 8 will be more favored (due to $\text{RB}(\text{OH})_2$ being less stabilized^[20]) than for the cyclohexyltrifluoroborate and isopropyltrifluoro-

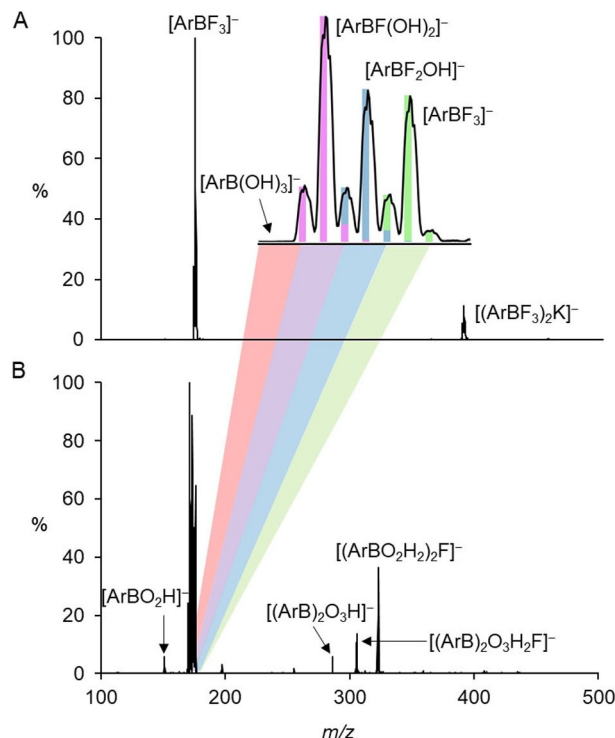
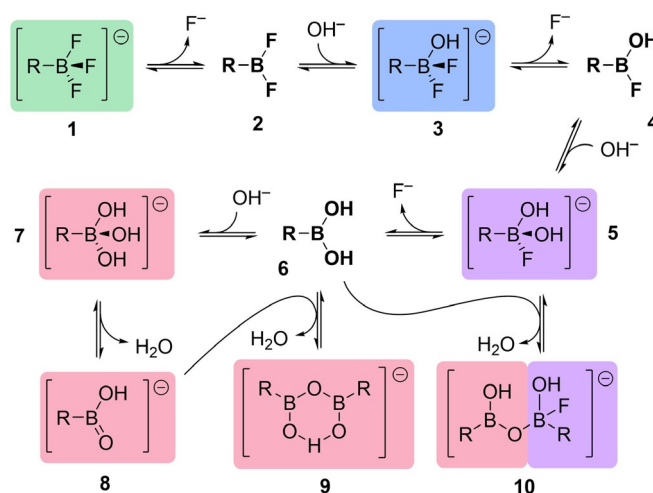


Figure 1. A) Negative-ion mass spectrum of KArBF_3 in THF. B) Negative-ion mass spectrum of the same solution 20 minutes after the addition of water and Cs_2CO_3 . Inset: magnification of the $[\text{ArBF}_n(\text{OH})_{3-n}]^-$ ($n=0-3$) region of the spectrum at $t=20$ min.



Scheme 2. Proposed equilibria for trifluoroborate hydrolysis. Highlighted species are ionic and observable by ESI-MS. Structural connectivity is proposed based on structures of these molecular formulae in the literature.^[22,48,49]

rate ($\text{RB}(\text{OH})_2$ is more stabilized due to π -donation or hyperconjugation^[20]) salt hydrolysis. We found that the ratio of intensities for ions 7:8 varied for each different R group of the borates in all reactions, and also varied with pH (see the Supporting Information). No species corresponding to $[\text{KF}_2]^-$, $[\text{CsF}_2]^-$, $[\text{BF}_4]^-$, or $[\text{B}(\text{OH})_4]^-$ was observed. $[\text{KF}_2]^-$ and $[\text{CsF}_2]^-$ are by-products of path A,^[20] and $[\text{BF}_4]^-$ and $[\text{B}(\text{OH})_4]^-$ are protodeboronation by-products.^[51]

All numbered species exhibited dynamic behavior and could be classified into different types according to their degree of hydrolysis. All species related to each $[\text{ArBF}_{3-n}(\text{OH})_n]^-$ ($n=0-3$, i.e., 1, 3, 5 and 7, respectively) through aggregation or dehydration were grouped together for the sake of simplicity of interpretation. As different ions provide different ESI-MS response,^[52] and neutrals are not detected at all (unless associated with a charged entity), traces of species in this study do not directly correspond to concentrations. Rather, they indicate the approximate proportion of the charged components of a mixture that can be attributed to a particular ion (or group of related ions). A composite presentation of a representative data set is shown in Figure 2, for the hydrolysis of potassium *p*-methoxyphenyltrifluoroborate in a Schlenk tube at a slow stir rate.

In Figure 2, the combination of pH measurements with ESI-MS confirmed the relation between pH and the system's dynamics. Upon addition of a base to a THF solution of the trifluoroborates, the pH increased immediately from approximately 7 to 10 with a brief induction period (induction period is the interval between the time when the base is added to the system and the time when the substrate begins to decay); this agreed with the ESI-MS result (Figure 2); however, other cases showed long induction periods under same reaction conditions (see the Supporting Information). The end of the induction period was indicated by an abrupt pH drop for most substrates (Figure 2 and the Supporting Information), possibly due to mopping up of HF by the base.^[20] After the pH drop, there

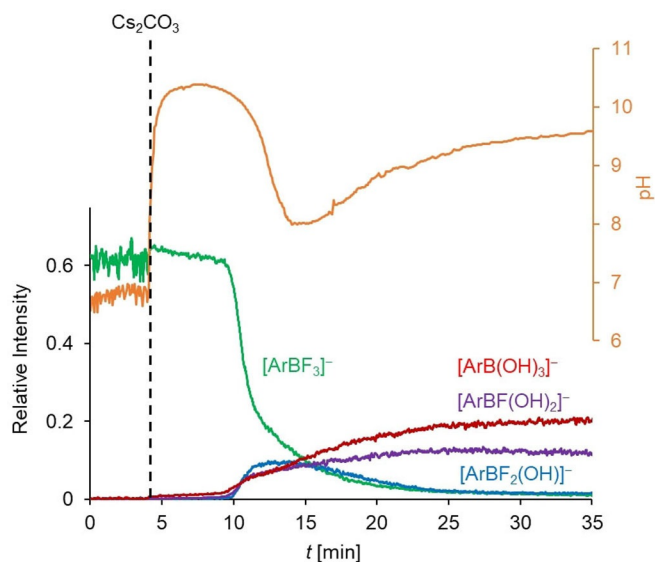


Figure 2. Relative species intensity and pH values for the hydrolysis of potassium *p*-methoxyphenyltrifluoroborate in THF (55 °C) performed in a Schlenk tube at a slow stir rate. Cs_2CO_3 in H_2O was added at 4 min. The $[\text{ArB}(\text{OH})_3]^-$ trace is a sum of intensities of all species with $F=0$, that is, $7 + 8 + 9 + \frac{1}{2}10$.

was a slow pH recovery and expansion as shown in Figure 2 and the Supporting Information. Although a base is necessary for hydrolysis, it also hinders full hydrolysis. This explains the increase in pH after the induction period.^[40] Parallel analysis with ESI-MS indicated in Figure 2 showed a first-order decay in trifluoroborate at the end of the induction period (see the Supporting Information) as well as evolution of hydrolyzed species which reached equilibrium with the substrate after 22 minutes of base addition. Further, the pH recovery seen in Figure 2 notably started where the trace of $[\text{ArBF}_3]^-$ crossed that of $[\text{ArBF}_2(\text{OH})]^-$. This probably indicates that the main contributor to the pH drop involves the consumption of $[\text{ArBF}_3]^-$.

We also observed that different reaction vessels (Schlenk tube vs. round-bottomed flask) and changes in stirring rate could substantially affect the reaction rate. For example, in Figure 3, reactions conducted in a Schlenk tube mostly had relatively low rates of hydrolysis compared with a round-bottomed flask. Lloyd-Jones^[20] and Hartwig^[53] determined that in a Schlenk tube better phase contact is achieved between the bulk solvent and the basic aqueous solution. The rate of base transfer into the bulk medium is comparatively increased in a Schlenk tube, which could suppress hydrolysis;^[20] but herein, hydrolysis of $\text{K}[p\text{-MeOC}_6\text{H}_4\text{BF}_3]$ and $\text{K}[\text{CyBF}_3]$ in a Schlenk tube at fast and slow stir rates, respectively, did not show any change in the rate of hydrolysis. In addition, changes in stirring rate affected the induction periods (Figure 4 and the Supporting Information). Figure 4A shows an example in which hydrolysis of potassium *p*-tolyltrifluoroborate at a fast stir rate never reached the catalytic regime; whereas at a slow stir rate (Figure 4B), a gradual conversion was observed with an induction time of approximately 10 minutes, followed by catalytic hydrolysis. With increased stir rates, Lloyd-Jones and co-workers found that the transfer of base from aqueous to organic phase is possibly facilitated; this could retard acid catalytic activity by

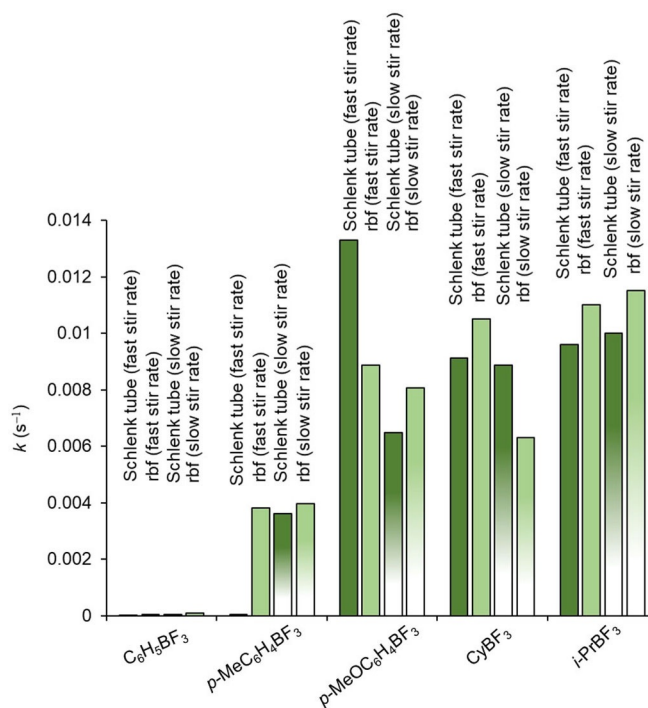


Figure 3. Representation of rate constants for the hydrolysis of potassium salts of phenyltrifluoroborate, *p*-tolyltrifluoroborate, *p*-methoxyphenyltrifluoroborate, cyclohexyltrifluoroborate and isopropyltrifluoroborate in THF/ H_2O (10:1) containing Cs_2CO_3 . The reaction was conducted in a Schlenk tube and a round-bottomed flask at fast and slow stir rates. Rate constants were determined by linear regression of $\ln(\text{relative intensity})$ versus time (see the Supporting Information).

sequestering HF .^[20] However, in this study, we observed that the rates of hydrolysis for $\text{K}[p\text{-MeOC}_6\text{H}_4\text{BF}_3]$ and $\text{K}[\text{CyBF}_3]$ increased under fast stirring conditions, which was unexpected (Figure 3 and the Supporting Information). This discrepancy with their findings could be attributed to differences in reaction vessels (PTFE vs. glass vessel), stirring rate (100 vs. 168 rpm for slow stirring and 500 vs. 600 rpm for fast stirring), and the concentration of the reagents used (8 vs. 1.8 mM for the borates and 24 vs. 5.5 mM for the base). Nonetheless, it was generally observed that the rate of hydrolysis was inversely proportional to the pH of the system after addition of the base (see the Supporting Information). This implies that a brief induction period (as shown in the pH analysis, see the Supporting Information) and a drop in pH can be indicators of increased rate of solvolysis leading to consumption of $[\text{ArBF}_3]^-$, and sequestering of HF .^[20] Also, a further drop in pH, could be attributed to less retardation of hydrolysis by the base, and vice versa (see the Supporting Information). In respect of this, the fast hydrolysis of $\text{K}[p\text{-MeOC}_6\text{H}_4\text{BF}_3]$ in a Schlenk tube at fast stir rate could be explained by the further drop in pH (pH dropped from ≈ 10.5 to ≈ 7.2 at the end of the induction period), as compared with the hydrolysis at slow stirring rate (pH dropped from ≈ 10.5 to ≈ 8 at the end of the induction period, see the Supporting Information). Also, the increased rate of hydrolysis at fast stirring conditions for $\text{K}[\text{CyBF}_3]$ can be explained by the slow pH recovery which indicates less hindrance by the base (see the Supporting Information).

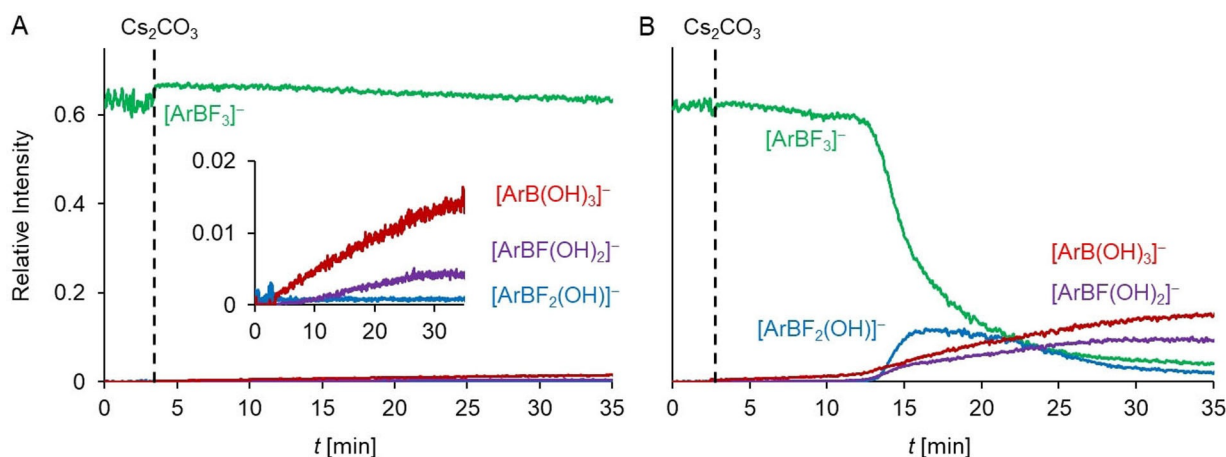


Figure 4. Relative species intensity and pH values for the hydrolysis of potassium *p*-tolyltrifluoroborate in THF/H₂O (10:1) containing Cs₂CO₃; performed at A) a fast stir rate (see Figure S5 for duplicate chronogram) and B) a slow stir rate. Inset: hydrolyzed species; the [ArB(OH)₃][−] trace is a sum of intensities of all species with *F* = 0.

As expected, the R group had a significant effect on the conversion rate of the trifluoroborates. As shown in Figure 3, the reaction rate for phenyltrifluoroborate was slower than that of *p*-tolyltrifluoroborate, *p*-methoxyphenyltrifluoroborate, cyclohexyltrifluoroborate and isopropyltrifluoroborate; and as well, the induction period was relatively longer for the same substrate (see the Supporting Information). This implied that the phenyl group could stabilize the borate better than the R group of the other substrates,^[40] hence the order of reactivity was C₆H₅BF₃K < *p*-MeC₆H₄BF₃K < *p*-MeOC₆H₄BF₃K < CyBF₃K ≈ *i*PrBF₃K. These results are consistent with previous studies.^{[20,40]88888}

Conclusions

Real-time analysis of the hydrolysis of aryltrifluoroborates using ESI-MS confirms many of the behaviors previously revealed by ¹⁹F NMR, including sensitivity to stir rates and flask geometry and the existence of significant induction periods following the addition of base. ESI-MS reveals additional details: the presence of a complex soup of reaction products, including not just partially hydrolyzed products, but also dehydrated products and aggregate species thereof. The system eventually settles into a complex equilibrium in which a wide array of species is simultaneously present. This complex speciation points to an equally complex system when aryltrifluoroborates are used as an aryl source in Suzuki–Miyaura reactions; what seems on paper to be a single-component addition might instead have a complicated effect on the catalytic system. The next step will be to consider how this complex mixture is perturbed by the introduction of cross-coupling partners and ultimately which components most readily undergo transmetalation.

Experimental Section

Reagents were purchased from Sigma–Aldrich and were used without further purification. Gases used were purchased from Airgas.

Tetrahydrofuran was distilled over CaH₂ and stored under an inert atmosphere prior to use. The instrument used for all monitored reactions was a Waters Acquity Triple Quadrupole Detector. All ESI experiments were performed in the negative ion mode. ESI source parameters were as follows: capillary voltage was held at 3 kV, cone voltage at 12.0 V, and extraction cone at 1 V. The following settings were used to obtain optimal desolvation conditions: desolvation gas flow rate 200 Lh^{−1}, cone gas flow rate 100 Lh^{−1}, source temperature 100 °C, desolvation temperature 180 °C. The detector gain was set to an optimal voltage of 470 V. Scan time was set to 1 s, with an inter-scan time of 0.1 s. The collision gas flow (high-purity argon) was switched off except in tandem mass spectrometric experiments (MS/MS). MS/MS experiments were conducted with a collision energy between 2–15 V. Predicted isotope pattern was overlaid on the experimental isotope pattern (see the Supporting Information) using an isotope pattern overlay python script.^[54,55] IKA RCT B hot plate magnetic stirrer was used for all experiments. The pH measurements were recorded with an HI 2020-01 pH meter equipped with HI 10430 digital pH electrode.

A typical reaction for trifluoroborate hydrolysis is as follows. A PSI-ESI(−)-MS setup was prepared under an inert atmosphere with a potassium trifluoroborate salt (12 μmol, 1 equiv) in tetrahydrofuran in a Schlenk tube and a round-bottom style flask. The reaction mixture temperature was raised to 55 °C, stirring rate was set identically to all other experiments (≈168 and ≈600 rpm for slow and fast stir rate experiments, respectively). The reaction mixture was connected to the ESI source by a piece of FEP tubing, and acquisition was initiated. Cesium carbonate (36 μmol, 3 equiv) was dissolved in distilled water and injected into the reaction mixture (tetrahydrofuran/water ratio 10:1). Prior to addition of the base at both stir rates, there is no phase separation. After addition of the base at both stir rates, there is a brief phase separation (lasts for about 5 s or less) which disappears (solution looks well mixed). The capillary sampling the solution is close to the bottom of the flask (≈5–10 mm above the stirrer bar). Reactions were carried out for potassium salts of *p*-tolyltrifluoroborate (*p*-MeC₆H₄BF₃), *p*-methoxyphenyltrifluoroborate (*p*-MeOC₆H₄BF₃), cyclohexyltrifluoroborate (CyBF₃), phenyltrifluoroborate (C₆H₅BF₃), and isopropyltrifluoroborate (*i*PrBF₃). Real-time pH experiments were also carried out separately following the same procedure as described for the ESI-MS experiments. The reaction monitoring technique employed in this study followed a conventional approach whereby the distance be-

tween the spray emitter and the MS inlet is fixed at ≈ 5 mm, hence the MS results shown are a reflection of the composition of the bulk reaction mixture, and not influenced by the rate acceleration in the ESI source as observed by Cooks and co-workers when the distance between the spray emitter and the MS inlet is greater than a centimeter.^[56,57] We see good agreement between MS and other methods of analysis when using this approach.^[58,59] Methodological optimization and careful experimental technique were required to obtain reliable equilibrium behavior between reactions, but the observed hydrolysis species were consistent between reactions and across substrates.

Acknowledgements

J.S.M. thanks the NSERC Discovery Grant Program for operational funding and CFI, BCKDF, and the University of Victoria for infrastructural support.

Conflict of Interests

The authors declare no conflict of interests.

Keywords: aryltrifluoroborates · hydrolysis · ion speciation · pH analysis · real-time monitoring

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Manuscript received: October 27, 2020

Revised manuscript received: November 16, 2020

Accepted manuscript online: November 23, 2020

Version of record online: January 18, 2021