a. PRF# 56849-ND1
b. Organotrifluoroborates as fluoride ion sources in cationic fluorination for the preparation of fluorinated organics
c. PI: David M. Perrin, Chemistry Department, University of British Columbia, Vancouver, Canada
d. co-PI: Emmanuel Gras, Laboratoire de Chimie de Coordination – CNRS, Toulouse, France

Fluorine is unknown in feed stocks commonly produced by the petrochemical industry yet features prominently in molecules of high added value for agrochemicals and pharmaceuticals. An ever-increasing demand for fluorinated aromatics for use in materials, pharmaceuticals, agrochemicals, and radiotracers continues to drive innovation in forming aryl C-F bonds. Examples include new metal mediated processes, deoxy-fluorination reactions, hypervalent iodine mediated oxidations, and halogen exchange processes. While there is surging interest in new methods including elegant metal-catalyzed reactions new applications of electrophilic fluorinating reagents, most industrial processes still rely on either halogen exchange (halex) processes, use of either nucleophilic fluoride or HF in addition reactions, or the Balz-Schiemann reaction. Indeed, the canonical Balz-Schiemann reaction, first reported in 1927 and featured in all modern organic chemistry textbooks, is used to synthesize fluorinated aromatics, including radiofluorinated ones. Nevertheless, generally harsh conditions and high temperatures are required to react a diazonium-tetrafluoroborate salt ($ArN_2^+BF_4^-$).

Our previous work on organotrifluoroborates that afforded a formal analysis of structure-activity relationships relating to the rate solvolytic defluorination led us to posit that organotrifluoroborates, which are much more soluble in organic solvents than is BF_4^-, may competently serve as fluoride-ion sources in Balz-Schiemann type reactions. Hence, we envisioned that an organotrifluoroborate would enable the use of milder conditions for the formation of aryl fluorides as well as the possibility of transferring fluoride ions to latent carbocations in an intra/intermolecular fashion. It is this hypothesis, now tested in the context of the Balz-Schiemann reaction, that forms the basis of this New Directions Grant. In this second-year report, we are pleased to report that funds were used directly towards proposed research; here we are pleased to report considerable success in driving new research in our labs, including the publication of a full article in this year (Mohy el Dine, Sadek, *et al*. *Chem. Eur. J.* 2018). Therein, we show that commonly available RBF_3^-s serve as fluoride ion sources for fluoro-dediazoniation under very mild conditions (Figure 1), thereby identifying a new substrate class for this venerated reaction. More importantly, we extend this application to a one-pot reaction where the ArN_2^+ is generated *in situ*, thus avoiding the need to isolate potentially explosive diazonium salts. Our findings now expand the substrate scope of the historic Balz-Schiemann reaction after ninety years.

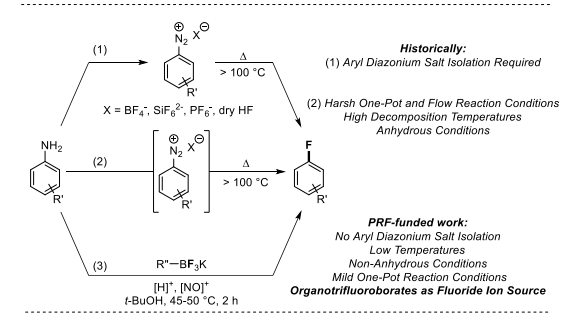

Figure 1: (1) and (2): previous developments in the Balz-Schiemann reaction. (3): PRF-funded work.

As reported at the end of year-1, our investigation had started with the observation that mesityl-diazonium tosylate reacted cleanly with phenyltrifluoroborate in a Balz-Schiemann type reaction run in THF at 50 deg for 2 hr in yields of 57% (n=3). Following up on these very positive results in year-2, we tested other solvents. Strikingly, CH_2Cl_2 and tBuOH supported similar reaction albeit with slightly depressed yields. Not surprisingly, when the reaction was run in water or primary alcohols (e.g. MeOH) respectively, the phenol and methyl ether were recovered. Reaction in MeCN gave the acetanilide upon aqueous work-up via a presumed Ritter-type reaction whereas reaction in DMSO gave the phenol and the arene along with other unidentified by-products. Non-polar solvents e.g. xylene, cyclohexane and toluene gave little if any product, attributed to the lack of solubility of the starting materials in these solvents. Notably, these solvents are often used in standard Balz-Schiemann reactions however the aryldiazonium "ate" salt is insoluble and the reaction is run biphasically in these solvents where the starting material is heated in an aspersion.

Based on these results, we established that the fluorination can be accomplished in a single one-pot-two-step manner starting with the aniline and the organotrifluoroborate per Figure 2. As with the aforementioned dediazoniation reaction, we were pleased to find that the same reaction can be run directly on the aniline in the presence of dry acid in non-aqueous solvents such as CH_2Cl_2, tBuOH, and THF. Having established success in direct fluorination in solution, we investigated the acid source; testing AcOH, HCl, HNO_3, H_2SO_4, TosOH, and H_3PO_4, we found that all acids, except for AcOH, provided good-to-excellent yields while surprisingly H_3PO_4 provided the highest yields.

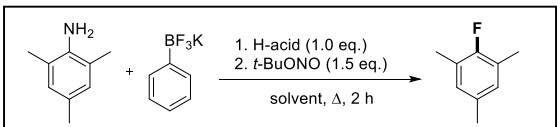

Figure 2: direct fluorination starting with aniline

To address the mechanism of this reaction, we considered a standard heterolytic mechanism ascribed to the Balz-Schiemann reaction as well as a hemolytic (radical) mechanism reminiscent of the Sandmeyer reaction. Addition of TEMPO had little effect while sodium ascorbate provided inconsistent results as yields were either unaffected or greatly

diminished. As O_2 may also intercept radical intermediates, a lower yield in the presence of O_2 often suggests radical processes. Though degassing slightly improved yields somewhat, such improvement was not found to be substantial enough to implicate a radical intermediate *en route* to the fluoro-arene. To further exclude the possibility of a radical mechanism, we added cuprous ion ($CuCO_3$ or $Cu(MeCN)_4PF_6$) or $SnCl_2$ to the reaction; all additives eroded fluorination yields. Hence, fluoro-dediazoniation likely proceeds by the well-accepted heterolytic mechanism involving an ion pair, with little evidence to suggest a radical mechanism. Finally, it's important to note that the organoboronic acid was incapable of serving catalyticaly as a fluoride-ion transfer reagent to the aryl cation; indeed, 0.5-1 eq. of the organotrifluoroborate are required.

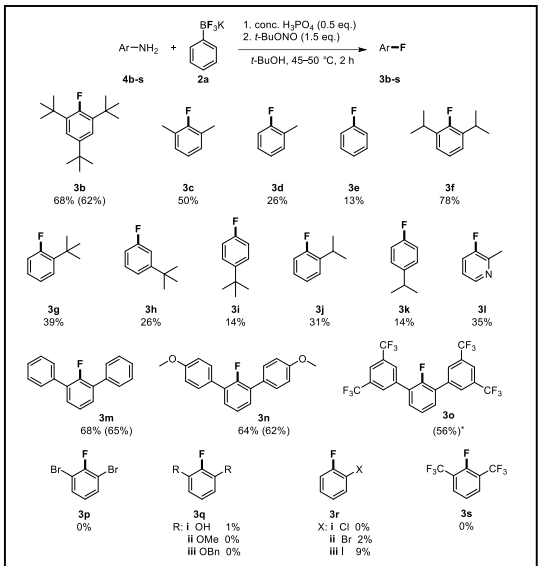

Figure 3: substrate scope for aryl fluorination.

The substrate scope of this reaction was then addressed (Figure 3). Generally, fluoro-arenes were obtained in moderate to high yields. Sterically hindered anilines were efficiently fluorinated (**3b**, **3c**, **3f**, **3g**). Removing steric bulk from one or both *ortho* positions of the aniline reduced yields: **3b** was produced in 68% yield, *ortho-t*-butylaniline was fluorinated in 39% yield (**3g**). Progressively moving the alkyl substituent to the *meta* and then *para* positions further diminished yields to 26% (**3h**) and 14% (**3i**), respectively. The same trend holds for **3f** (78%), **3j** (31%), and **3k** (14%). The effect of *ortho* steric bulk is evidenced by decreasing yields between di- and mono-*ortho* substituted anilines; yields are halved when comparing **3c** (50%) to **3d** (26%), and degrade further when comparing **3f** (78%) to **3j** (31%). To address the role of steric bulk at *ortho* positions, three anilines were synthesized and fluorinated in good yields (**3m**-**3o**) thus showing tolerance of halogen and ether functionalities on the parent aniline. The reaction conditions also allowed the fluorination of heterocycle **3l** in moderate yield. Heteroatom substituents at *ortho* positions gave trace amounts of product (**3p**-**3r**). Unfortunately, to date we have not been able to extend the substrate scope substantially beyond that which is featured in Figure 3.

In the second year of support, we have extended this work to the use of solid-supported organotrifluoroborates as originally proposed. Also of interest, we have found equally promising results using monofluoroborates, which also provide competent for fluoride ion transfer. In light of this limited substrate scope, we have been investigating several other substrates that will lend mechanistic insight into the specific role of the trifluoroborate as a source of fluoride ion transfer while extending this reaction manifold to other carbocations. Representative substrates are shown in Figure 4 that will test intramolecular delivery of fluoride. Surprising, in our hands, these gave very low fluorination yields. In addition, the synthesis of the corresponding boronic acids is less trivial than initially anticipated. We have also begun to investigate acyl-trifluoroborates as fluoride ion sources in Balz-Schiemann-type reactions. An acylboronate represents a rare constellation of atoms, which until recently has not been easily prepared. We have recently reported an effective methodology for synthesizing acylboronates starting with an alkyne that is boronated to give the 2-vinyl-MIDA-boronate which is then dihydroxylated, cleaved by IO_4^- treatment and converted to the trifluoroborate.

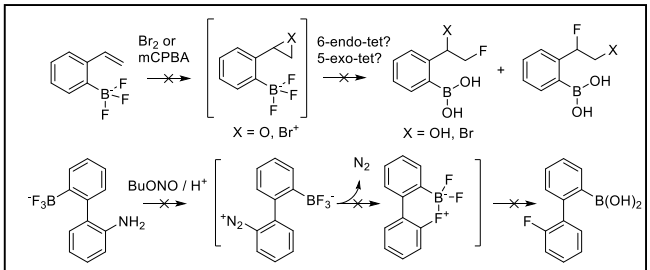

Figure 4: representative substrates for intramolecular F-anion delivery.

Career impact of research. This New Directions grant from the PRF was instrumental in supporting the above research. It supported several students and one postdoctoral fellow along with support for materials and conference attendance. This work has enabled my trainees to pursue new synthetic methodology towards the production of fluorinated organics while pursuing testing fundamental precepts of trifluoroborates as reservoirs of fluoride ion that may be delivered to incipient carbocations. A clear outcome of this funding has been the successful publication of the bulk of this work in 2018 and we anticipate publication of at least two related publications. Trainees supported by these funds have gained valuable training in new methods development and has enabled them to pursue chemical research in my lab or in others.