Fluorination in Flow

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Accelerating Palladium-Catalyzed C–F Bond Formation: Use of a Microflow Packed-Bed Reactor**

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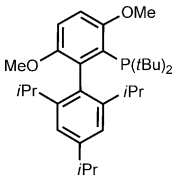
The aryl fluoride motif is a mainstay in a variety of disciplines, most notably pharmaceuticals, agrochemicals, and in positron emission tomography (PET). A large number of clinically approved pharmaceuticals contain this substituent due to its importance in tailoring the properties of organic molecules.[1] While numerous methods have been developed to construct aromatic C–F bonds, most, if not all, suffer from at least one drawback with regard to safety, practicality, and/or substrate scope.[2] Recently, there has been an increase in the number of new methods, particularly in the use of metal-catalyzed or -mediated processes. In particular, work by the groups of Grushin,[3] Sanford,[4] Ritter,[5] Yu,[6] and others[7] have both increased the number of synthetically useful aryl C–F bond-forming reactions as well as deepened our understanding of the underlying challenges inherent in such processes. The state of the art of these methodologies, however, are far from ideal especially when compared to other aryl carbon–heteroatom bond forming reactions.[8]

We recently described the catalytic conversion of aryl triflates to aryl fluorides using CsF as the fluoride source and a Pd-catalyst based on *t*BuBrettPhos (**1**).[9] This fluorination reaction utilized readily available "F^-" sources as the fluorine atom donor. Owing to the exceedingly low solubility of anhydrous CsF in the non-polar solvents typically employed for this transformation (e.g., toluene, cyclohexane) the reaction is visibly saturated with fluoride, yet increasing the amount of CsF increases the rate of C–F bond formation (Figure 1).[10] While short reaction times can be attained using large excesses of CsF, the amount of waste makes this strategy unattractive. Moreover, efficient mixing becomes increasingly difficult when dealing with large quantities of insoluble fluoride. These drawbacks in the batch process make this heterogeneous fluorination reaction an ideal candidate for microflow technology. Compared to batch processes, microfluidics offer the advantage of enhanced heat- and mass-transfer characteristics, high surface-to-volume ratio, safety of operation at elevated temperatures and pressures, precise control over residence (reaction) times and isolation of sensitive reactions from air and moisture.[11] Herein, we describe the development of a CsF packed-bed reactor for the Pd-catalyzed conversion of aryl triflates to aryl fluorides in flow.



*t*BuBrettPhos (**1**)

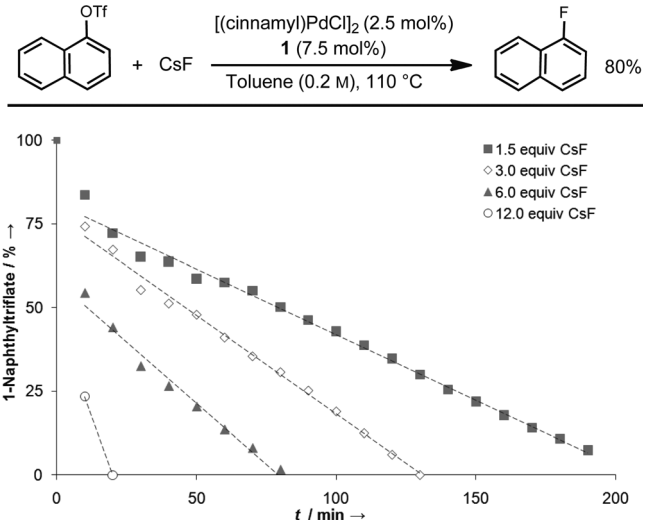


Figure 1. Conversion dependence on CsF loading in batch.

We chose to initiate our investigation by modifying our stainless steel packed-bed reactor design, which has proven effective for both C–N and C–C bond-forming processes in flow.[12] We anticipated that by replacing the stainless steel packing with CsF, we could utilize large amounts of fluoride, as well as capitalize on the excellent mixing that this design provides. In such a packed-bed reactor, the interfacial area is governed by the porosity of the packing, and the mean particle size. To achieve a more uniform flow distribution in the packed bed, the microreactor was filled with finely ground CsF that had been filtered to obtain a uniform particle size distribution of approximately 45–106 μm (see Supporting Information for details). The typical amount of CsF in one reactor corresponds to approximately 35 equivalents of fluoride (based on a 1 mmol scale reaction).

Due to the hygroscopic nature of CsF, the reactor was packed in a nitrogen-filled glovebox, and then transferred and

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stored on the benchtop. A microfluidic system was assembled as shown in Figure 2. Notably, all reagent solutions were prepared on the bench top and then loaded into a reagent loop. The reagents were subsequently introduced in the reactor through a single syringe pump.

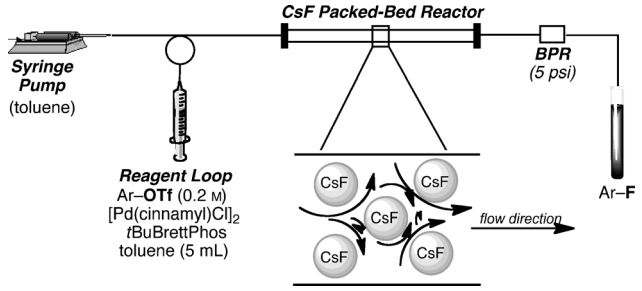


Figure 2. Schematic representation of the microreactor setup for the fluorination of aryl triflates in flow.

We began by examining the conversion of 1-naphthyltriflate to 1-fluoronaphthalene in flow (Figure 3). Utilizing conditions similar to that in Figure 1 (5 mol% Pd, 0.2 M ArOTf in toluene, 110 °C), we were pleased to find that full conversion was achieved with a residence time of only 10 min.

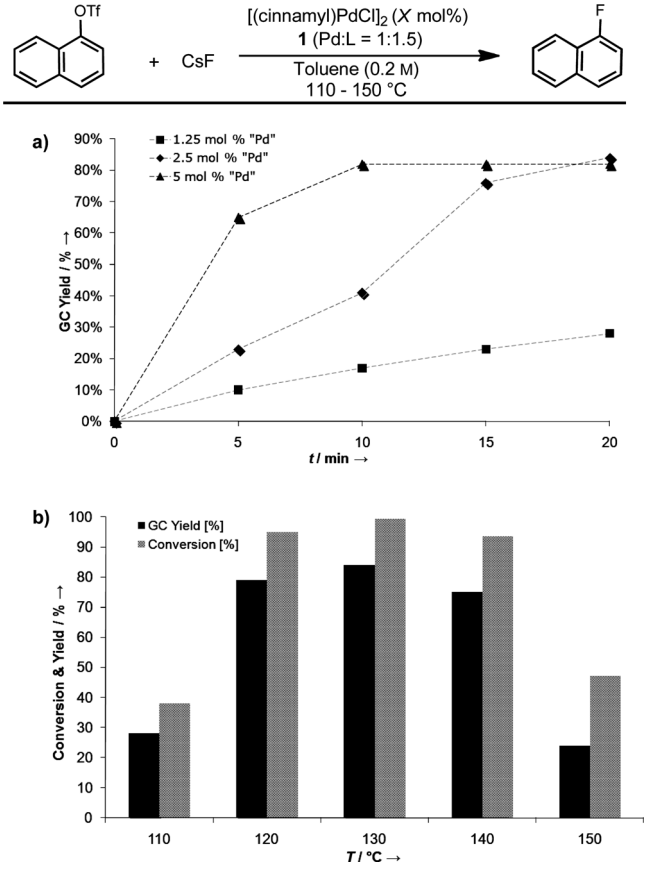
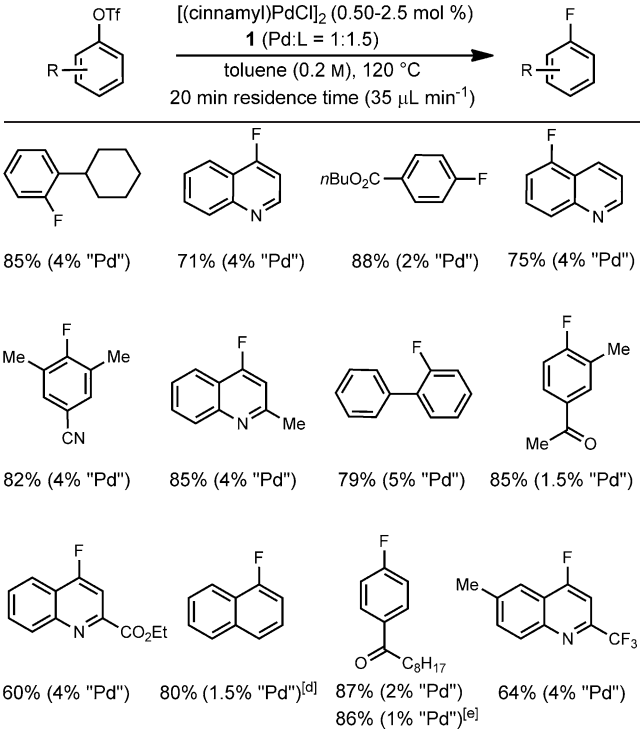


Figure 3. Pd-catalyzed fluorination of 1-naphthyltriflate in flow: a) Catalyst loading and residence time comparison at 110 °C. b) Temperature dependence with low catalyst loading (1.25 mol% Pd, 20 min residence time).

Lowering the catalyst loading to 2.5 mol% allowed for full conversion within 20 min, however unsatisfactory results were obtained at 1.25 mol% Pd loading (Figure 3a). It is worth noting that the infusion of stainless steel spheres into the reactor matrix was also investigated, due to presumed increases in heat transfer,[13] but gave no advantage over a pure CsF packing in terms of residence times or product yield. As stated, one of the major advantages of flow chemistry is the ability to "superheat" solvents above their boiling point in a safe and controlled manner by employing a backpressure regulator (BPR).[14] Figure 3b depicts the temperature dependence of the Pd-catalyzed fluorination of 1-naphthyltriflate in flow employing low catalyst loadings (1.25 mol% Pd). Although low conversions and yields were obtained at 110 °C, excellent conversions and yields were obtained at temperatures between 120–140 °C with 130 °C being optimum.

The substrate scope of the process is shown in Table 1. For simplicity of experimental set-up, we utilized a standard temperature of 120 °C and residence time of 20 min for all

Table 1: Substrate scope of the Pd-catalyzed fluorination of aryl triflates in flow.[a–c]



[a] Reaction conditions: ArOTf (1 mmol), [(cinnamyl)PdCl]$_2$ (0.50–2.5 mol%), *t*BuBrettPhos (**1**) (Pd:L = 1:1.5), toluene (5 mL), 120 °C, 35 μL min^{-1} flow rate, 20 min residence time. [b] Yields of isolated products, average of two runs. [c] mol% of palladium equivalents ("Pd"). [d] Yield for 3 mmol experiment = 80% (8 h experiment). [e] T = 130 °C.

substrates. A single reactor was used to process the substrates in groups of two or three (1 mmol each) with an intermittent wash step of the reactor (using anhydrous toluene) between runs. Importantly, this demonstrated that the reactor could be re-used multiple times. Excellent results were obtained for a

wide variety of substrates. Aryl triflates bearing esters, ketones, and cyano groups were well tolerated, as well as a variety of heteroaryl triflates. A number of electron-deficient substrates could be fluorinated using relatively low catalysts loadings (1.5–2.0 mol% Pd) and by employing higher temperatures (i.e. 130 °C), 4-nonanoylphenyl triflate could be converted to its corresponding fluoride in 86% yield using only 1 mol% Pd. These results represent some of the lowest catalyst loadings reported for any aryl C–F bond forming reaction. The reactors performance for continuous, longer experiments was also examined. We were pleased to find that 3 mmol of 1-naphthyltriflate could be fluorinated without a decrease in yield and without any noticeable microreactor clogging during the 8 h experiment. Similar to the batch process,[9] electron-rich aryl triflates, especially those lacking *ortho* substituents, were problematic. The requirement of full dissolution of the starting materials in toluene also represents a known technical limitation of the described chemistry, although conducting the reaction under dilute conditions can partially circumvent this problem.

In summary, we have described the first aryl C–F bond forming reaction in flow.[15] A packed-bed reactor design allowed for easy handling of large quantities of insoluble CsF with excellent mixing, precise control over reaction times, and the ability to safely handle elevated temperatures and pressures. Moreover the reusability of the reactor design was demonstrated as well as its capacity to handle longer experiments. The apparent complexity of many microfluidic systems can be overwhelming at times to users unfamiliar with such equipment. The system described herein, however, is operationally simple—only a single syringe pump is required. Vital to the success of this technology is the exceedingly low solubility of CsF in the reaction medium thus preventing simple dissolution of the reactor.[16] While efforts to improve the batch process with respect to substrate scope are ongoing, we feel the results reported herein will allow for smooth transfer of future enhancements to flow.

Experimental Section

A toluene solution of the aryl triflate (0.2 M), $[(\text{cinnamyl})\text{PdCl}]_2$ (1–5 mM), and *t*BuBrettPhos (3–15 mM) was injected into a reagent loop (5 mL). This solution was delivered to a packed-bed reactor (700 μL, packed with anhydrous, ground CsF (particle size 45–106 μm) at 120 °C using a single Harvard Apparatus syringe pump (35 $\mu L\,min^{-1}$). Next, the sample was collected, which corresponded to exactly 1 mmol. Further details on the equipment setup and workup procedures can be found in the Supporting Information.

Sample analysis: GC analysis and ^{19}F NMR spectroscopy were used to determine the conversions. NMR and IR spectroscopies were used to identify the products.

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[16] We flowed ca. 20 mL of anhydrous toluene through the reactor (T = 120 °C) and then evaporated the resulting solution to dryness; no solid CsF was detected.

