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Catalytic Decarboxylative Fluorination for the Synthesis of Tri- and Difluoromethyl Arenes

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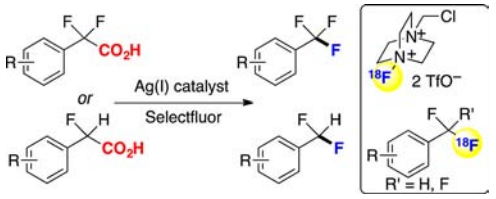
ABSTRACT



Treatment of readily available α,α-difluoro- and α-fluoroarylacetic acids with Selectfluor under Ag(I) catalysis led to decarboxylative fluorination. This operationally simple reaction gave access to tri- and difluoromethylarenes applying a late-stage fluorination strategy. Translation to [^{18}F]labeling is demonstrated using [^{18}F]Selectfluor bis(triflate), a reagent affording [^{18}F]tri- and [^{18}F]difluoromethylarenes not within reach with [^{18}F]F_2.

Arenes bearing trifluoromethyl groups are important structural motifs found in medicinal compounds.[1] The CF_3 group can enhance efficacy by encouraging electrostatic interactions with targets, improving cellular membrane permeability, and augmenting resistance toward oxidative metabolism of the drug.[2] As a result, tremendous effort has been directed toward the formation of aryl C−CF_3 using trifluoromethylating reagents.[3] Strategies relying on an aryl CF_2−F bond disconnection are less common, despite the potential value of this approach to access [^{18}F]-labeled biomarkers for applications in positron emission tomography (PET). This functional imaging technology, which is used to probe biological processes in vivo, can facilitate clinical diagnosis and is a valuable tool as quantitative biomarker in drug development.[4] Since the half-life of ^{18}F is relatively short (110 min), the late-stage fluorination of aryl [^{18}F]CF_3 is best performed through aryl CF_2-[^{18}F]F bond construction.[5] Difluoromethylene

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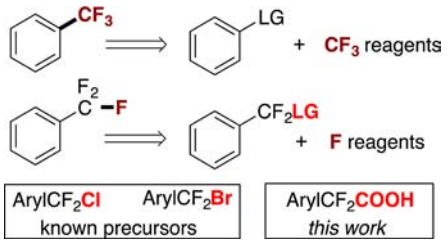
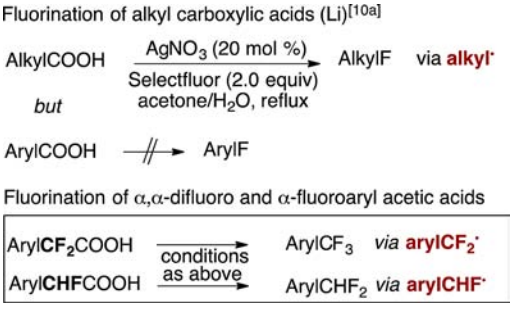
Scheme 1. Retrosynthesis of Aryl CF_3 (LG = Leaving Group)



precursors armed with a suitable leaving group have been considered to access the aryl [^{18}F]CF_3 motif. More commonly, bromide, chloride, and fluoride are displaced in halex exchange processes with [^{18}F]fluoride; these reactions require harsh reaction conditions and could suffer from narrow substrate scope and low specific activity, especially for radiotracers obtained by isotopic exchange or carrier-added methods.[6] Given the importance of decarboxylative fluorination to access alkyl fluorides, we were surprised that the displacement of a carboxylic acid functionality has never been considered for the construction of trifluoromethylated arenes from α,α-difluoroaryl acetic acid precursors (Scheme 1).

Several groups have made seminal contributions toward fluorodecarboxylation of carboxylic acids with F_2[7] and XeF_2.[8] Following these discoveries, Sammis and co-workers established that milder reagents can be used for the fluorination of alkyl radicals via the decomposition of *tert*-butyl peresters of carboxylic acids; these reagents include NFSI (*N*-fluorobenzenesulfonimide) and Selectfluor (1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)).[9] More recently, Li and co-workers[10a] have shown that aliphatic carboxylic acids underwent fluorodecarboxylation with Selectfluor under $AgNO_3$ catalysis, a reaction involving a putative radical intermediate via Ag(III)-assisted single-electron transfer followed by fluorine atom transfer.[11] This method tolerates a range of functional groups but is not applicable to aryl carboxylic acids. We questioned whether the incorporation of a difluoromethylene unit between the aryl group and the carboxylic acid functionality could lead to a new class of reactive substrates since the α,α-difluorobenzyl radical is a well characterized aryl-stabilized species known to adopt an all planar geometry.[12] Herein, we report that α,α-difluoroaryl acetic acids respond to silver-catalyzed fluorodecarboxylation in the presence of Selectfluor; this method, which offers access to aryl CF_3 through late-stage fluorination, was extended to the preparation of difluoromethylated arenes and was found suitable for [^{18}F]-labeling using [^{18}F]Selectfluor bis(triflate) (Scheme 2).

Scheme 2. Ag-Catalyzed Fluorodecarboxylation of Carboxylic Acids



We initiated our studies with the fluorodecarboxylation of biphenyl-4-yl(difluoro)acetic acid **1a**, a substrate readily prepared in two steps from the corresponding aryl iodide and ethyl bromodifluoroacetate adapting a literature procedure (Table 1).[13,14] Gratifyingly, exposure of **1a** to $AgNO_3$ (20 mol %) and 2 equiv of Selectfluor, in 1:1 (v/v) acetone/H_2O under reflux, gave the trifluoromethylated arene **2a** in >95% yield (entry 1). The reaction monitored by ^{19}F NMR was completed within 1 h (100% conversion of **1a**); it required $AgNO_3$ to proceed (entry 2) and was found to be equally successful using Selectfluor bis(triflate) (entry 3). Alternative reagents were not suitable. The use of NFSI gave no reaction under the standard reaction conditions and the use of 5 equiv of NFSI in MeCN at 100 °C afforded the acyl fluoride **3a**[15] in 30% yield along with trace amount of **2a** (entries 4 and 5). The treatment of **1a**

(5) For methods toward [^{18}F]CF_3 and [^{18}F]CF_2CF_3, see: (a) Josse, O.; Labar, D.; Georges, B.; Grégoire, V.; Marchand-Brynaert, J. *Bioorg. Med. Chem.* **2001**, *9*, 665–675. (b) Dolbier, W. R., Jr.; Li, A.-R.; Koch, C. J.; Shiue, C.-Y.; Kachur, A. V. *Appl. Radiat. Isot.* **2001**, *54*, 73–80. (c) Riss, P. J.; Aigbirhio, F. I. *Chem. Commun.* **2011**, *47*, 11873–11875. (d) Riss, P. J.; Ferrari, V.; Brichard, L.; Burke, P.; Smith, R.; Aigbirhio, F. I. *Org. Biomol. Chem.* **2012**, *10*, 6980–6986.

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(10) (a) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404. For an early example of Ag(I)-catalyzed oxidative decarboxylation of acids by peroxydisulfate, see: (b) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 1651–1659.

(11) For a recent account on free-radical approaches for Csp^3–F bond formation, see: Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3570–3572.

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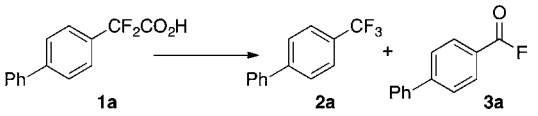
(14) Details provided in the Supporting Information.

(15) The formation of benzoyl fluoride upon fluorodecarboxylation of benzoic acid has been reported. See ref 8.

with XeF_2 in DCM at room temperature gave **2a** and the acyl fluoride **3a** in 23% and 11% yield, respectively (entry 6).

Table 1. Fluorodecarboxylation of **1a**



entry	fluorine source[a]	reaction conditions	yield of **2a**[b] (%)	yield of **3a**[b] (%)
1	**I** (2 equiv)	20 mol % of $AgNO_3$, acetone/H_2O (1:1), 55 °C, 1 h	>95	
2	**I** (2 equiv)	acetone/H_2O (1:1), 55 °C, 1 h		
3	**II** (2 equiv)	20 mol % of $AgNO_3$, acetone/H_2O (1:1), 55 °C, 1 h	>95	
4	**III** (2 equiv)	20 mol % of $AgNO_3$, acetone/H_2O (1:1), 60 °C, 1 h		
5	**III** (5 equiv)	20 mol % of $AgNO_3$, MeCN, 100 °C, 1 h	<5	30
6	**IV** (1 equiv)	DCM, rt, 30 min	23	11

[a] **I** = Selectfluor; **II** Selectfluor bis(triflate); **III** *N*-fluorobenzenesulfonimide (NFSI); **IV** XeF_2. [b] Determined by ^{19}F NMR with 1-fluoro-3-nitrobenzene as internal standard.

Next, substrates **1a**–**q** were prepared[14] and transformed into trifluoromethylated arenes by applying the optimized conditions (Scheme 3). The efficiency of the reaction was dependent on the electronic properties of the aryl motif. The fluorination of the methoxy-substituted carboxylic acids **1b**–**d** gave the desired isolated products **2b**–**d** with yields superior to 80%. The reaction scale was increased from 0.2 to 2.0 mmol for the synthesis of **2a** and **2c** with no erosion of yield. The reaction did not allow access to **2e** indicating that more electron-rich precursors are not suitable due to competitive fluorination of the aromatic ring. Various functional groups are well tolerated inclusive of ether, halide, ketone, alkyl, and amide. Double *ortho*-substitution of the aromatic ring with methyl groups did not affect reactivity as shown with the fluorination of **1h** leading to **2h** in 56% yield. The yield of **2l** was improved from 33% to 49% using 4 equiv of Selectfluor. Fluoxetine **2m**, an antidepressant acting as a selective serotonin reuptake inhibitor[16] was prepared in 59% yield as a trifluoroacetic acid salt using the *N*-Boc protected precursor and applying the standard protocol followed by *N*-Boc deprotection with TFA.[14] The chemoselective formation of **2n** informed that the aryl carboxylic acid group is inert under the reaction conditions. For substrate **1o** featuring two benzylic carboxylic acid groups, the fluorination led to 17% of the trifluoromethylated product **2o** along with a large amount of unreacted starting material (57%). The side products **4o** (double fluorodecarboxylation) and **5o** (fluorodecarboxylation at the nonfluorinated benzylic position) were formed in 24% and 2% yield, respectively.

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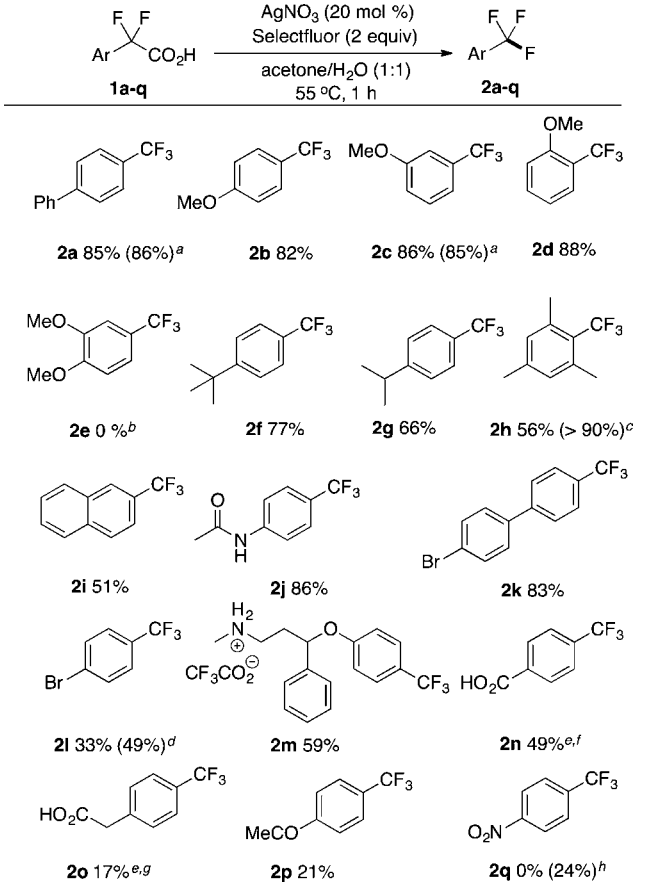
Scheme 3. Fluorination of α,α-Difluoroaryl Acetic Acids



[a] Yield in parentheses for the reaction performed on a 2.0 mmol scale. [b] Complex reaction mixture. [c] ^{19}F NMR yield using 1-fluoro-3-nitrobenzene as internal reference is given in parentheses. [d] Yield in parentheses for the reaction performed with 4.0 equiv of Selectfluor in acetone/H_2O 4:1. [e] ^{19}F NMR yield using 1-fluoro-3-nitrobenzene as internal reference. [f] No fluorination at the aryl carboxylic acid. [g] ^{19}F NMR of the crude product revealed **1o** (57%), **2o** (17%), **4o** resulting from double fluorodecarboxylation (24%) and **5o** resulting from fluorination at the nonfluorinated benzylic position (2%) . [h] Yield in parentheses for the reaction performed with F_2 (3 equiv of F_2, 20 mol % of $AgNO_3$, MeCN, −10 °C).

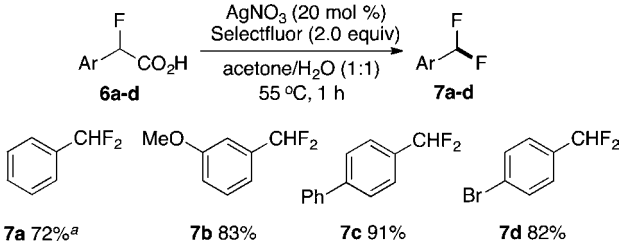
The presence of electron-withdrawing groups on the aryl motif proved detrimental. The acetyl-substituted product **2p** was isolated in only 21% yield, and our standard reaction conditions did not allow for the formation of the nitro-substituted trifluoromethylated arene **2q**. The difficulties encountered with **1q** may originate from the ability of the nitro group to act as a radical quencher.[17] Attempts to promote the fluorodecarboxylation of **1q** using F_2 under optimized conditions (3 equiv of F_2, 20 mol %, MeCN, −10 °C)[14] met with limited success delivering **2q** in 24% (^{19}F NMR). For electron-neutral or electron-rich arenes, F_2 was much less suitable than Selectfluor.[14] The trifluoromethylated arene **2a** was formed in 36% (^{19}F NMR)

(17) Control experiments confirmed that the decarboxylative fluorination of the model substrate **1a** did not proceed when the reaction was performed under the standard conditions in the presence of 1-fluoro-3-nitrobenzene (1 equiv).

when the reaction was conducted using 5 equiv of F_2 in acetonitrile at −35 °C. Arenes **2b** and **2j** could not be prepared with F_2 and **2k** was formed in less than 20% yield (^{19}F NMR).

We next studied the reactivity of α-fluoroaryl acetic acids **6a**−**d** as precursors to access the difluoromethylated arenes **7a**−**d**. The substrates were prepared by electrophilic fluorination of *bis*(silyl)ketene acetals formed in situ from the corresponding aryl acetic acid.[13,14] The fluorodecarboxylation of **6a**−**d** took place under the standard reaction conditions affording the desired difluoromethyl arenes **7a**−**d** in yields ranging from 72% to 91%. The reactivity trends observed for **6a**−**d** appeared to correlate well with the scope and limitation delineated for the decarboxylative fluorination of the corresponding difluorinated aryl acetic acids **1a**−**q** (Scheme 4).

Scheme 4. Fluorination of α-Fluoroaryl Acetic Acids[a]



[a] ^{19}F NMR yield using 1-fluoro-3-nitrobenzene as internal reference.

We were poised to investigate the value of the fluorodecarboxylation process for [^{18}F]radiolabeling since [^{18}F]-Selectfluor bis(triflate)[18] is a known [^{18}F]NF reagent[19] proved competent for the [^{18}F]fluorination of a range of substrates (Scheme 5).[18,20] [^{18}F]Selectfluor bis(triflate) [^{18}F]**8** was synthesized as a stock solution in acetone-d_6 from high specific activity [^{18}F]F_2[21] following the protocol reported in the literature.[18] Aliquots of [^{18}F]**8** (220 μL) were added to 100 μL of a stock solution of silver nitrate (2 μmol) and the α,α-difluoro- or α-fluoroaryl acetic acid precursor (10 μmol) in H_2O (10 mL); the solution was then concentrated under a flow of nitrogen at 55 °C. After 30 min, the reaction mixture was analyzed by high performance liquid chromatography (HPLC) to identify and quantify the formation of radiolabeled products. The trifluoromethyl arene [^{18}F]**2a** was formed in 9.1% ± 2.4% RCY with a specific activity (SA) of 3.3 ± 0.2 GBq/μmol. This method was extended to the synthesis of the acetamido-substituted trifluoromethyl arene [^{18}F]**2j** (18% ± 1.5%).

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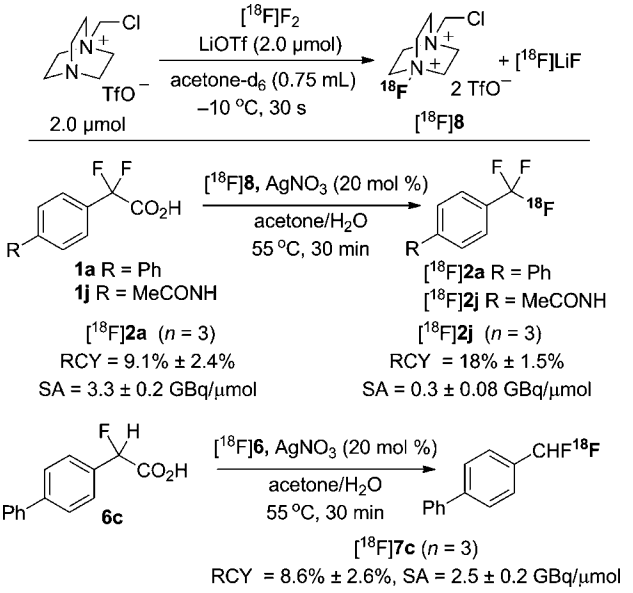
Scheme 5. [^{18}F]Labeling of **1a**, **1j**, and **6a** with [^{18}F]**8**



Pleasingly, the radiosynthesis of the difluoromethyl arene [^{18}F]**7a** was also successful. To the best of our knowledge, this transformation represents the first example of [^{18}F]-labeling of the difluoromethyl group, a new motif now available for PET imaging. Notably, [^{18}F]**2a** could not be prepared from high SA [^{18}F]F_2 in the presence of $AgNO_3$.[14]

In conclusion, we have demonstrated that α,α-difluoro- and α-fluoroarylacetic acids respond to fluorodecarboxylation with Selectfluor under Ag(I) catalysis. This approach to tri- and difluoromethylarenes distinguishes itself from classical methods relying on trifluoromethylating reagents. This novel protocol tolerates various functional groups and allows for the preparation of [^{18}F]labeled tri- and difluoromethylarenes using [^{18}F]Selectfluor bis-(triflate) [^{18}F]**8**. This reagent was found to be advantageous over [^{18}F]F_2, a finding showcasing the benefit of having a range of electrophilic [^{18}F]sources of variable reactivity for applications in [^{18}F]radiochemistry.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.