^{18}F-Fluorination

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Synthesis of ^{18}F-Difluoromethylarenes from Aryl (Pseudo) Halides

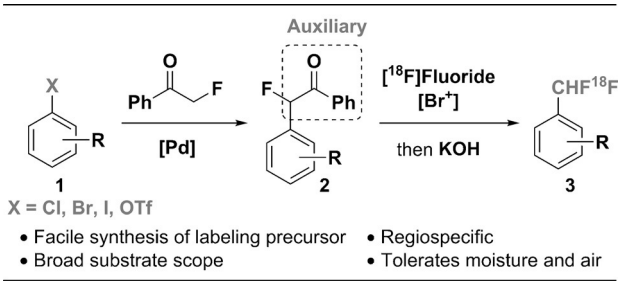
Hang Shi, Augustin Braun, Lu Wang, Steven H. Liang, Neil Vasdev,* and Tobias Ritter**

Abstract: *A general method for the synthesis of [^{18}F]difluoromethylarenes from [^{18}F]fluoride for radiopharmaceutical discovery is reported. The method is practical, operationally simple, tolerates a wide scope of functional groups, and enables the labeling of a variety of arenes and heteroarenes with radiochemical yields (RCYs, not decay-corrected) from 10 to 60 %. The ^{18}F-fluorination precursors are readily prepared from aryl chlorides, bromides, iodides, and triflates. Seven ^{18}F-difluoromethylarene drug analogues and radiopharmaceuticals including Claritin, fluoxetine (Prozac), and [^{18}F]DAA1106 were synthesized to show the potential of the method for applications in PET radiopharmaceutical design.*

Fluorine-18 (^{18}F) is the most commonly used radionuclide for molecular imaging by positron emission tomography (PET).[1] Over the past five years, several modern fluorination reactions have been developed with ^{18}F, many of which are achieved with high specific activity (SA) [^{18}F]fluoride.[2] The development of modern ^{18}F-multi-fluoromethylation reactions, for example to incorporate ^{18}F into trifluoromethyl groups, is now also addressed, due to the prospects of making more labeled chemotypes available for imaging.[3] A challenge in the preparation of ^{18}F-labeled compounds that contain more than one fluorine atom, especially when located on the same carbon atom, is the probability of isotope exchange, which can substantially lower the specific activity. Here we describe a general method for [^{18}F]CHF_2-arenes from [^{18}F]fluoride. The method is practical and general over a wide variety of arenes and heteroarenes. On a fundamental level, the crucial but unusual C–F bond formation occurs by nucleophilic substitution on a fully substituted carbon.

The most extensive work to date on multi-fluorinated ^{18}F-labeled molecules has been directed at the synthesis of ^{18}F-trifluoromethyl groups:[3] Gouverneur and co-workers have established a practical method based on [^{18}F]$CuCF_3$ species, with a large substrate scope.[3f] A year later, three other groups independently reported different methods to prepare [^{18}F]$CuCF_3$, which was also explored for the [^{18}F]trifluoromethylation of aryl boronic acids.[3g–i] Groves and co-workers have reported a direct C–H to C–^{18}F transformation based on Mn-salen-catalyzed benzylic fluorination with [^{18}F]fluoride,[2j] which was also extended to ^{18}F-trifluoromethylarenes.[3j] [^{18}F]CHF_2 arenes, such as [^{18}F]4-(difluoromethyl)-1,1′-biphenyl, can be synthesized through decarboxylative ^{18}F-fluorination with [^{18}F]Selectfluor generated from [^{18}F]F_2 or Ag^I-mediated halogen-exchange with the [^{18}F]fluoride ion.[3e,k] Gouverneur's group improved the substrate scope of Ag^I-mediated halogen-exchange; but the CHFCl-arene starting materials still require several synthetic steps for preparation.[3m] To date, no method has been reported for the ^{18}F-labeling of difluoromethylarenes with a high specific activity. Here, we describe progress toward the goal of high-specific-activity difluoromethylation in a practical and general reaction.

To overcome the challenge of C–F bond formation to achieve ^{18}F-difluoromethylation from [^{18}F]fluoride, we have designed an ^{18}F-difluoromethylation reaction that features a benzoyl auxiliary, which controls the chemoselectivity of the C–H functionalization; this results in [^{18}F]fluoride introduction being observed only at the desired benzylic position. The auxiliary can be installed from aryl (pseudo) halides and quickly cleaved in situ after radio-fluorination to generate ^{18}F-difluoromethylarenes (Scheme 1).



Scheme 1. Auxiliary-facilitated [^{18}F]difluoromethylarene formation.

The labeling procedure entails the following steps: 1) C–H bromination to α-Br-α-F-acetophenone; 2) in situ halogen-exchange with [^{18}F]fluoride; and 3) benzophenone cleavage.[4] The treatment of aryl acetophenones **2** with *N*-bromophthalimide and [^{18}F]fluoride in the presence of tetraethylammonium bicarbonate (TEAB) in chlorobenzene and acetonitrile

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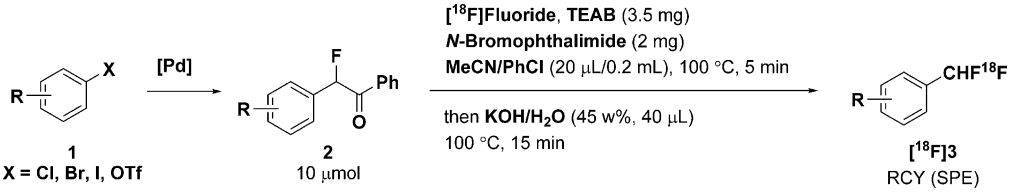
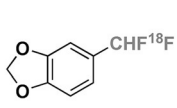
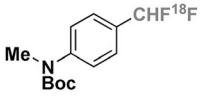
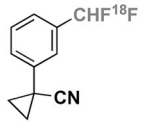
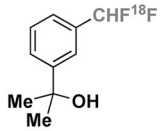
Table 1: ^{18}F-Difluoromethylarene formation of aryl-acetophenones.[a]

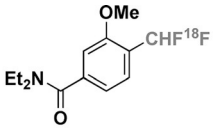


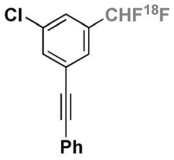

[^{18}F]3a
29% ± 2% (*n* = 3)

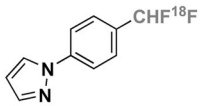

[^{18}F]3b
29% ± 1% (*n* = 3)

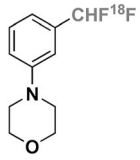

[^{18}F]3c
54% ± 3% (*n* = 3)

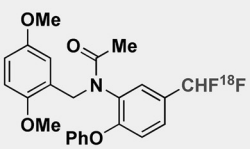

[^{18}F]3d
36% ± 3% (*n* = 3)

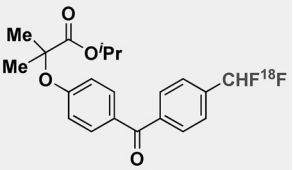

[^{18}F]CHF$_2$-Analepticon
11% ± 1% (*n* = 3)

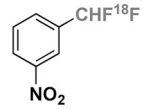

[^{18}F]3e
61% ± 2% (*n* = 3)

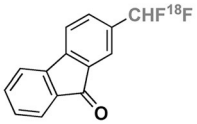

[^{18}F]3f
50% ± 1% (*n* = 3)

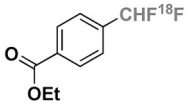

[^{18}F]3g[b]
16% ± 2% (*n* = 3)

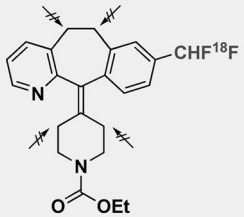

[^{18}F]CHF$_2$-DAA1106
36% ± 5% (*n* = 3)

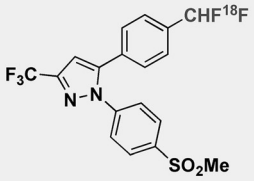

[^{18}F]CHF$_2$-Fenofibrate
47% ± 3% (*n* = 3)
39% RCY (HPLC)

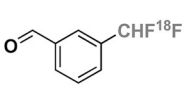

[^{18}F]3h
47% ± 3% (*n* = 3)

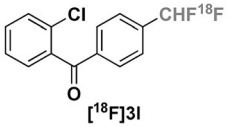

[^{18}F]3i
41% ± 1% (*n* = 3)

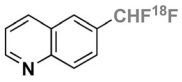

[^{18}F]3j[c]
26% ± 2% (*n* = 3)

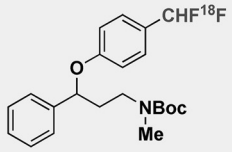

[^{18}F]CHF$_2$-Claritin[c]
21% ± 2% (*n* = 3)

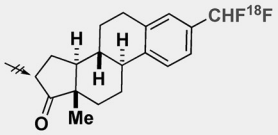

[^{18}F]CHF$_2$-SC-58125
47% ± 2% (*n* = 3)
37% RCY (HPLC)

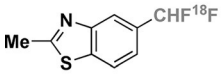

[^{18}F]3k
13% ± 2% (*n* = 3)

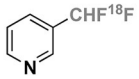

[^{18}F]3l
46% ± 2% (*n* = 3)

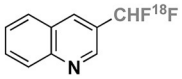

[^{18}F]3m
49% ± 3% (*n* = 3)
47% ± 2% (*n* = 3)[d]
43% RCY (HPLC)
SA = 0.49 mCi/μmol


[^{18}F]CHF$_2$-Boc-Fluoxetine[c,e]
17% ± 2% (*n* = 3)


[^{18}F]CHF$_2$-Estrone[c,e]
11% ± 1% (*n* = 3)

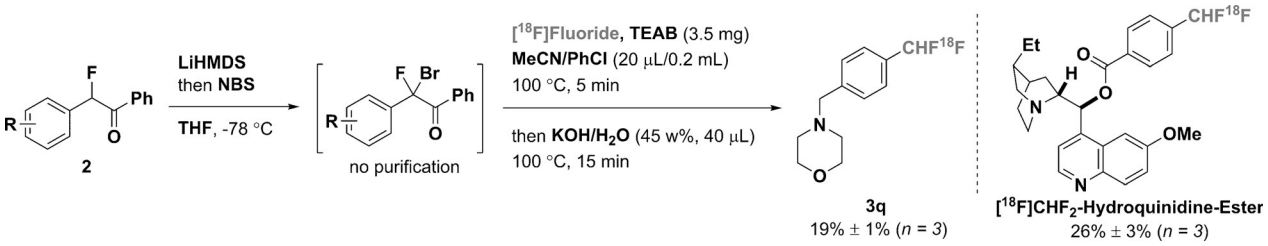

[^{18}F]3n
37% ± 1% (*n* = 3)


[^{18}F]3o
40% ± 3% (*n* = 3)


[^{18}F]3p
47% ± 3% (*n* = 3)

General conditions: [a] arene **2** (10 μmol), *N*-bromophthalimide (2.0 mg), TEAB (3.5 mg), chlorobenzene (0.2 mL), MeCN (20 μL), 100 °C, 5 min, then KOH aqueous solution (45 w%, 40 μL), 100 °C, 15 min. [b] *N*-Bromophthalimide (4.2 mg), then $Na_2S_2O_3{\cdot}5\,H_2O$ (5.0 mg) was added in the second step. [c] KOH aqueous solution (45 w%, 60 μL). [d] Chlorobenzene was replaced by water-saturated chlorobenzene (0.2 mL). [e] Chlorobenzene was replaced by benzene (0.2 mL). Yield ranges are provided; *n* = number of independent reactions; RCY (SPE): reaction mixture was purified by solid-phase extraction (SPE); RCY (HPLC): reaction mixture was purified by semipreparative HPLC.[6]

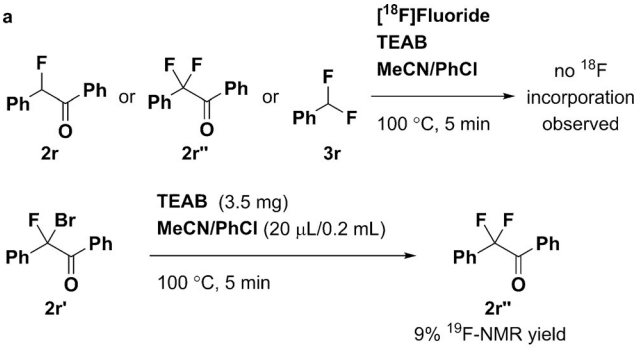
at 100 °C,[5] followed by the addition of an aqueous KOH solution after 5 min, gave [^{18}F]CHF$_2$-arenes **3** (Table 1). The procedure was successfully applied to the ^{18}F-difluoromethylation of a wide range of substrates, including both electron-deficient and electron-rich aromatics. The radiochemical yields (RCYs, not decay-corrected, relative to the starting [^{18}F]fluoride) range from 10 to 60 %.[6] Halide, alcohol, ether, aldehyde, ketone, ester, amide, carbamate, cyanide, nitrate, cyclopropane, and alkyne functional groups are tolerated. The method is also compatible with heterocycles (for example, **3m**–**p**). Moisture is tolerated; water-saturated chlorobenzene gave the same radiochemical yield within error ([^{18}F]**3m**, 47 % versus 49 % RCY). For the aniline derivative **2g**, the expected product was not generated under the standard conditions; we surmised that the basic nitrogen was oxidized by *N*-bromophthalimide instead of the α-CH bond of acetophenone. Given that bromo-arylaminium can be reduced to aniline, after ^{18}F-labeling of **2g**, the addition of sodium thiosulfate to the reaction mixture afforded [^{18}F]CHF$_2$-aniline ([^{18}F]**3g**) in 16 % RCY.



Scheme 2. Stepwise ^{18}F-difluoromethylarene formation of tertiary amines. Reaction conditions: a) arene **2** (10 μmol), LiHMDS (1.0 M in THF, 1.3 equiv), THF (0.25 mL), −78 °C, 45 min, then NBS (1.0 equiv), THF (0.1 mL), −78 °C, 45 min. b) TEAB (3.5 mg), chlorobenzene (0.2 mL), MeCN (20 μL), 100 °C, 5 min, then KOH aqueous solution (45 w%, 40 μL), 100 °C, 15 min.

To demonstrate the potential utility of the ^{18}F-labeling procedure, we examined a variety of well-known biologically active molecule analogues, including fenofibrate (cholesterol scavenger), fluoxetine (selective serotonin reuptake inhibitor), DAA-1106 (translocator protein 18 kDa radiotracer), SC-58125 (COX_2 inhibitor), and analepticon (respiratory stimulant). The labeling method was selective for a claritin derivative, which possesses five benzylic C–H bonds and four allylic C–H bonds. To achieve ^{18}F-labeling of tertiary amines, a stepwise method was developed, with bromination carried out separately, prior to the fluorination (Scheme 2). Specifically, the enolate of precursor **2**, generated by a deprotonation with LiHMDS at low temperature, was trapped by NBS. Without separation, the crude brominated precursor was subjected to a radiofluorination, which afforded the corresponding ^{18}F-labeled amines, including an [^{18}F]CHF_2-hydroquinidine ester in 26% RCY.

Obtaining a high specific activity (SA) is an ongoing challenge for the ^{18}F-labeling of multi-fluoromethyl-compounds due to undesired isotope exchange reactions,[3e–l] with recent progress reported for ^{18}F-trifluoromethylation.[3g] The reactions conditions provided in Table 1 are useful to readily access ^{18}F-labeled difluoromethyl arenes, but only with low specific activity (for example, 0.49 mCi μmol^{-1} for [^{18}F]**3m**). To achieve high specific activity, we attempted to identify the pathway that led to the undesired formation of the non-radioactive compounds **3**. Control experiments showed that ^{19}F/^{18}F isotope exchange did not occur for **2r**, **2r″**, and **3r** in the presence of [^{18}F]fluoride/TEAB at 100 °C (Scheme 3a). In the absence of additional fluoride, the treatment of α-phenyl-α-Br-α-F-acetophenone (**2r′**) with TEAB gave **2r″** in a 9% yield, as determined by NMR spectroscopy. The results demonstrated that decomposition of **2r′** by TEAB released ^{19}F-fluoride ion, which fluorinated **2r′** to form the non-radioactive byproduct **2r″**. However, use of a weaker base, tetrabutylammonium methanesulfonate (TBAOMs), did not decompose α-Br-α-F-acetophenone **2m′**, but ^{18}F-fluorination was not observed when TEAB was replaced by TBAOMs. To increase the nucleophilicity of [^{18}F]fluoride, organic bases such as *N*,*N*-diisopropylethylamine (DIPEA) were explored to promote ^{18}F-fluorination.[7] With 0.5 μmol of precursor **2m′** and a reaction temperature of 80 °C, we determined a specific activity for [^{18}F]**3m** of 81 mCi μmol^{-1} (3.0 GBq μmol^{-1}), with only 39 mCi of starting [^{18}F]fluoride after bombardment (Scheme 3b) for a reaction yielding over 3 mCi of product,



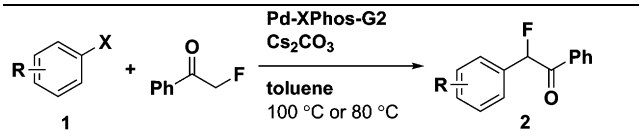
starting radioactivity	[^{18}F]3m	specific activity
12 mCi	1.9 mCi	38 mCi/μmol (1.4 GBq/μmol)
18 mCi	1.3 mCi	64 mCi/μmol (2.4 GBq/μmol)
39 mCi	3.1 mCi	81 mCi/μmol (3.0 GBq/μmol)

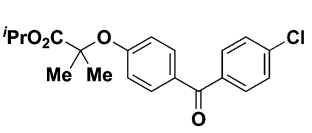
Scheme 3. a) Control experiments. b) Improvement of the specific activity.

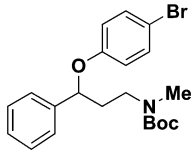
which could be sufficient for preclinical PET imaging studies. Given the anticipated increase of specific activity with larger amounts of starting radioactivity (Scheme 3b), we propose that with appropriate automation specific activities higher than 81 mCi μmol^{-1} (3.0 GBq μmol^{-1}) will be achievable.

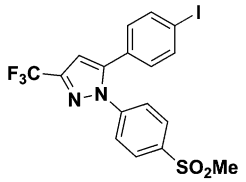
The starting material preparation from aryl halides and pseudo halides is robust and practical. Prior to our work, palladium-catalyzed cross-coupling of aryl halides with α-fluoroacetophenone was not a general reaction and its yields were generally low (for example, 17%).[8] We extended the transformation to be general, from aryl chlorides, bromides, iodides, and triflates, including sterically hindered arenes (the full table of Pd-catalyzed fluoroacetophenonation of arenes is shown in the Supporting Information). To highlight the convenience of the precursor preparation, we show six examples in Table 2.

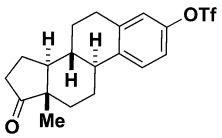
Table 2: Selected examples of Pd-catalyzed fluoroacetophenonation of arenes.[a]

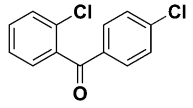


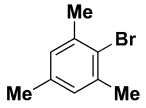

Fenofibrate, 69%


Br-Fluoxetine, 71%


I-SC-58125, 70%


OTf-Estrone, 67%


1l, 50%[b]


1s, 82%[b]

General conditions: [a] arene (1.0 mmol, 1.0 equiv), Pd-XPhos-G2 (3.0 mol%), fluoroacetophenone (1.2 equiv), Cs_2CO_3 (1.5 equiv), toluene (0.2 M), 100 °C. [b] The reactions were carried out at 80 °C.

In conclusion, we have reported a general method for ^{18}F-labeling of difluoromethylarenes vial aryl (pseudo) halides with a broad functional group compatibility. The strategy outlined herein will augment the pool of radiochemical methodologies and enable ^{18}F-labeled difluoromethylarenes to be considered in PET radiotracer design.

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Keywords: aryl (pseudo) halides · difluoromethylarenes · fluorine-18 · positron emission tomography · radiopharmaceuticals

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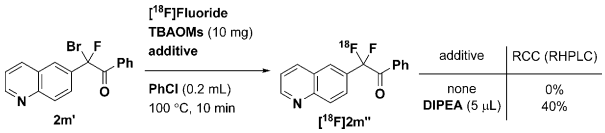
[5] For optimization of labeling conditions, see the Supporting Information, Table S2.

[6] RCY (SPE): reaction mixture was purified by solid-phase extraction (SPE) to separate ^{18}F-labeled product from polar by-products and unreacted [^{18}F]fluoride. The radiochemical yield was measured based on the filtrate, and is reported relative to the starting [^{18}F]fluoride activity. The filtrate was also analyzed by radio-HPLC in conjunction with radio-TLC to determine the radiochemical purity. RCY (HPLC): the reaction mixture was purified by semipreparative HPLC to separate the ^{18}F-labeled product. The radiochemical yield was measured based on the fraction corresponding to the radiolabeled product and is reported relative to the starting [^{18}F]fluoride activity. The filtrate was also analyzed by radio-HPLC. RCY (SPE) and RCY (HPLC) for [^{18}F]difluoromethyl-SC-58125, [^{18}F]6-difluoromethylquinoline, and [^{18}F]difluoromethyl-fenofibrate were consistent (see the Supporting Information, Table S3).

[7] DIPEA used as a base to promote ^{18}F-fluorination:



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