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Silver-Mediated ^{18}F-Labeling of Aryl-CF_3 and Aryl-CHF_2 with ^{18}F-Fluoride

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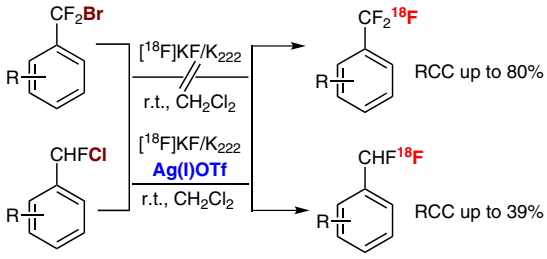
In celebration of Prof. Steven Ley's 70th birthday



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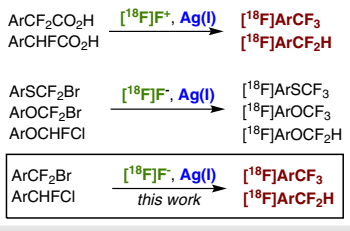
Abstract We report the synthesis of [^{18}F]arylCF_3 and [^{18}F]arylCHF_2 derivatives from arylCF_2Br and arylCHFCl precursors applying a silver-mediated halogen exchange with [^{18}F]fluoride. In the absence of Ag(I)OTf, no reaction takes place at room temperature for both classes of substrates; this result demonstrates the beneficial role of silver(I) as a means to induce ^{18}F-incorporation under very mild conditions.

Key words radiochemistry, halogen exchange, silver, fluoride, trifluoromethylarenes, difluoromethylarenes

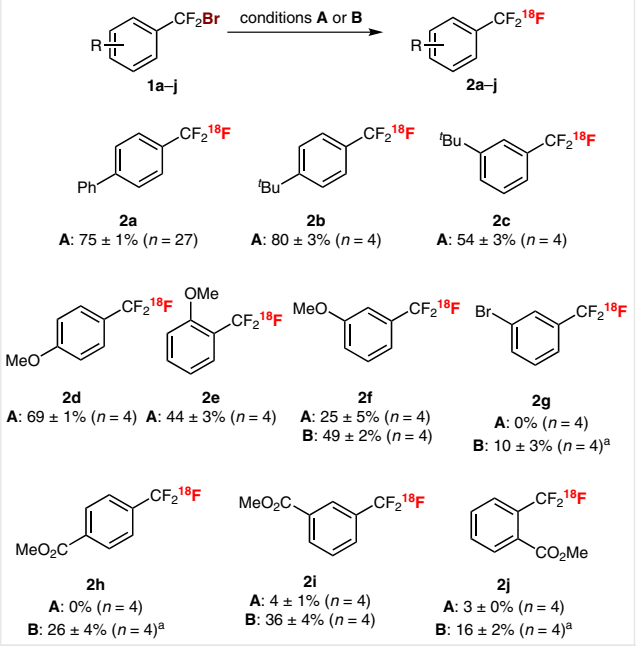
The importance of positron emission tomography (PET) as a noninvasive imaging technique for the assessment of disease state and for drug development has caused a great demand for novel strategies enabling ^{18}F incorporation.[2] As a result, numerous methods for ^{18}F-labeling have been developed in recent years,[3] and their value discussed in authoritative reviews.[4] Despite these advances, radiochemists could benefit from a much more diverse range of ^{18}F-tags and ^{18}F-labeling methods to support their (pre)clinical programs. With these considerations in mind, one approach is to develop radiochemical methods that are applicable to the synthesis of various ^{18}F-labeled motifs. One such example is the silver(I)-mediated decarboxylative ^{18}F-fluorination with [^{18}F]Selectfluor bis(triflate) of α,α-difluoro- and α-fluoroarylacetic acids, a process leading to [^{18}F]arylCF_3 and [^{18}F]arylCF_2H, respectively;[5] this method requires access to [^{18}F]F_2 to prepare [^{18}F]Selectfluor bis(triflate),[6] a limitation encouraging the development of an alternative strategy using readily available [^{18}F]fluoride. Recently, we reported that silver(I)-mediated halogen exchange (halex) with [^{18}F]F^- affords three novel ^{18}F-labeled motifs of medicinal relevance, specifically [^{18}F]arylSCF$_3$, [^{18}F]arylOCF$_3$, and [^{18}F]arylOCHF$_2$.[7] In this Letter, we report that this silver(I)-mediated halogen-exchange strategy is applicable to a range of arylCF_2Br and arylCHFCl precursors affording [^{18}F]arylCF_3 and [^{18}F]arylCHF_2 in good radiochemical conversions (RCC);[8] a notable characteristic of this process is the very mild reaction conditions applied for ^{18}F-incorporation compared to alternative methods (Scheme 1).



Scheme 1 Silver(I)-mediated radiochemical methods using [^{18}F]F^+ and [^{18}F]F^- sources allow access to a range of diverse ^{18}F-motifs

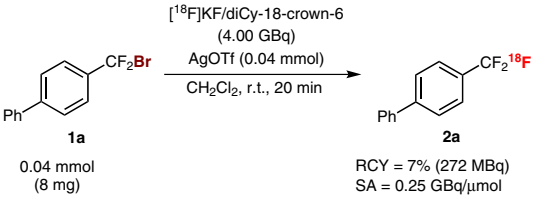
Halex reactions for the synthesis of arylCF_3 derivatives require harsh reaction conditions.[9] α-Bromo-α,α-difluorotoluene precursors do not react with [^{18}F]fluoride at room temperature; however, ^{18}F-incorporation occurs with [^{18}F]KF/K_{222} in sulfolane at 160 °C or with [^{18}F]TBAF in DMSO at 135 °C. We consider metal activation with Ag(I)OTf as an alternative to thermal activation which may allow for this process to proceed under much milder condi-

tions. Pleasingly, we found that the treatment of 4-(bromodifluoromethyl)-1,1′-biphenyl (**1a**) with [^{18}F]KF/K_{222} and one equivalent of AgOTf in CH_2Cl_2 at room temperature afforded [^{18}F]4-(trifluoromethyl)-1,1′-biphenyl {[^{18}F]**2a**} in 75% (n = 27) RCC (Scheme 2).[10] This method proved successful for arylCF$_2$Br precursors **2b**–**f** with alkyl, aryl, and methoxy substituents located *ortho*, *meta*, or *para* relative to the CF_3 group being tolerated. For the most challenging substrates **1g**–**j** bearing electron-withdrawing substituents, no or only trace amount of product could be detected at room temperature; ^{18}F-labeling was, however, observed by employing [^{18}F]KF/K_{222} and Ag(I)OTf (2 equiv) in DCE at 60 °C. The *m*-bromoarene **1f** led to [^{18}F]**2f** in 10% RCC, and the ester-substituted precursors **1h**–**j** responded to ^{18}F-fluorination in RCC in the range of 25%. The ester-substituted arenes **1h** and **1j** were more problematic as [^{18}F]**2h** and [^{18}F]**2j** were formed along labeled side products, possibly ^{18}F-labeled acyl fluoride (vide infra), and nucleophilic participation of the *ortho*-positioned ester functionality for [^{18}F]**2j**. Finally, this set of conditions increased the yield of the *m*-methoxy-substituted product [^{18}F]**2f**. Control experiments with **1a** confirm that, in the absence of Ag(I)OTf, no ^{18}F-labeling takes place at room temperature in CH_2Cl_2, and a trace of product [^{18}F]**2a** (< 5%, complex mixture) was detected at 60 °C in DCE.[10] These results suggest that the use of Ag(I)OTf is beneficial for ^{18}F-incorporation for this class of brominated substrates.



Scheme 2 Silver(I)-mediated halex ^{18}F fluorination towards [^{18}F]aryl-CF_3. Conditions A: [^{18}F]KF/K_{222}, AgOTf (1.0 equiv), CH_2Cl_2, r.t., 20 min. Conditions B: [^{18}F]KF/K_{222}, AgOTf (2.0 equiv), DCE, 60 °C, 20 min. [a] RCC of ^{18}F-labeled product shown; this reaction leads to ^{18}F-labeled side products. *n* = number of experiments.

In order to determine the specific activity (SA), an isolation experiment starting from 4.00 GBq of activity was performed using precursor **1a**. Due to the detrimental effect of increased quantities of K_2CO_3 and Kryptofix on the radiochemical yield (RCY), alternative conditions using $K_2C_2O_4$[11] as base and dicyclohexyl-18-crown-6[12] as the [^{18}F]KF activator were applied. Thereupon, [^{18}F]arylCF$_3$ **2a** was isolated in 7% RCY with a specific activity of 0.25 GBq µmol^{-1} (Scheme 3).[10]

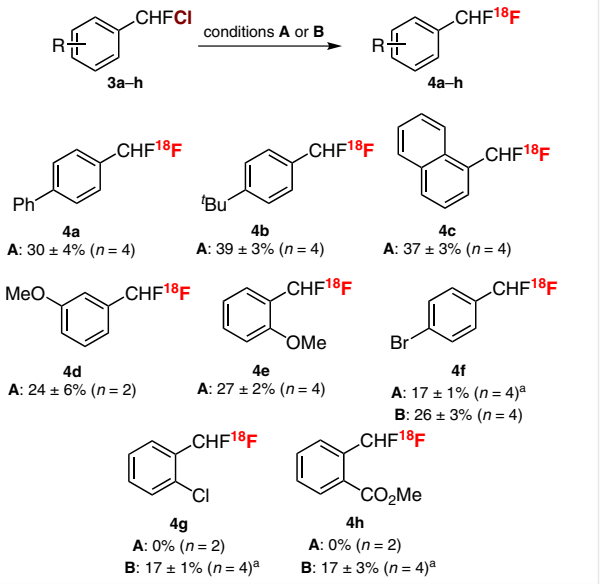


Scheme 3 Specific activity of [^{18}F]**2a**

These values are comparable to those obtained for ^{18}F-labeled arylCF$_3$ applying our [^{18}F]CuCF$_3$-based cross-coupling strategy,[13] and in the same range as those determined for the silver(I)-mediated halex process leading to ^{18}F-labeled arylOCHF$_2$, arylOCF$_3$, and arylSCF$_3$.[7] The low specific activity indicates release of ^{19}F from the substrate. The presence of [^{18}F][1,1′-biphenyl]-4-carbonyl fluoride (<5%) in the crude reaction mixture suggests that a plausible path accounting for ^{19}F release is the attack of adventitious water onto the in situ putatively formed cationic intermediate followed by loss of HF.[10]

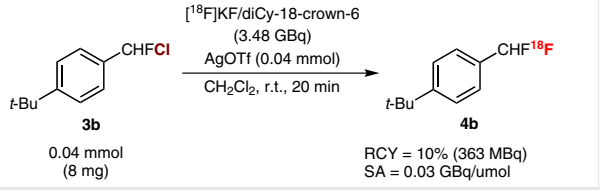
Having investigated the value of this protocol for the synthesis of ^{18}F-labeled arylCF$_3$ groups prompted us to extend this methodology further to arylCHF$_2$, a functionality for which few methods are available for labeling.[5] In drug discovery, the difluoromethyl group (CF$_2$H) is of interest as it is a bioisostere of carbinol,[14] thiol,[15] or hydroxamic acid hydroxyl group.[16] The difluoromethyl group can also act as lipophilic hydrogen-bond donor improving binding selectivity and cell-membrane permeability.[17] The radiosynthesis was undertaken with arylCHFCl precursors which are easier to handle than arylCHFBr (Scheme 4).

The reaction of 4-(chlorofluoromethyl)-1,1′-biphenyl **3a** with [^{18}F]KF/K_{222} in CH_2Cl_2 at room temperature led to trace of the desired product 4-(difluoromethyl)-1,1′-biphenyl (**4a**, 1% RCC, n = 2). When the ^{18}F-labeling was carried out in the presence of Ag(I)OTf, the reaction was successful with alkyl, ether, and bromo substituents all well tolerated; electron-neutral and electron-rich substrates **3a**–**e** are most suitable for these mild conditions. To the best of our knowledge, this method represents the first labeling approach towards [^{18}F]arylCHF$_2$ from [^{18}F]fluoride. Conditions B consisting of using Ag(I)OTf in DCE at 60 °C were beneficial for the bromo-substituted precursor **3f** increasing the RCC of



Scheme 4 Silver(I)-mediated halex ^{18}F-fluorination towards [^{18}F]aryl-CHF_2. Conditions A: [^{18}F]KF/K_{222}, AgOTf (1.0 equiv), CH_2Cl_2, r.t., 20 min. Conditions B: [^{18}F]KF/K_{222}, AgOTf (2.0 equiv), DCE, 60 °C, 20 min. [a] RCC of ^{18}F-labeled product shown; this reaction leads to ^{18}F-labeled side products.

[^{18}F]**4f** from 17% to 26%. For this substrate, whereas conditions A gave multiple ^{18}F-labeled side products, a clean reaction was observed under conditions B; electron-poor substrates **3g** and **3h** that did not react with [^{18}F]KF/K_{222} in the presence of Ag(I)OTf at room temperature were also subjected to heating at 60 °C in DCE. The desired products [^{18}F]**4g** and [^{18}F]**4h** were formed in addition to labeled side products, a factor limiting the radiosynthetic scope of this process. Notably, a control experiment treating **3a** with [^{18}F]KF/K_{222} at 60 °C in DCE in the absence of Ag(I)OTf gave [^{18}F]**4a** in 42% ± 3% (n = 2); this result indicates that for this class of substrates, the presence of Ag(I)OTf is beneficial to induce halogen exchange ^{18}F-fluorination at room temperature only. The specific activity was determined for product **4b** (Scheme 5) starting from 3.48 GBq of activity following the isolation protocol described for **2a** (vide supra). [^{18}F]ArylCHF_2 **4b** was isolated in 10% RCY with a specific activity of 0.03 GBq µmol^{-1}.[10]



Scheme 5 Specific activity of [^{18}F]**4b**

In conclusion, we have studied the silver(I)-mediated halex ^{18}F-fluorination for the synthesis of [^{18}F]arylCF_3 and [^{18}F]arylCHF_2. The use of AgOTf is most beneficial for the labeling of arylCF_2Br precursors, a class of compunds less reactive than arylCHFCl. The current limitation remains the low specific activity, which narrows the range of applications for PET to drug-development activities. The advantage of this process is the mildness of the reaction conditions since ^{18}F-labeling occurs at room temperature for a range of substrates.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560592.

References and Notes

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(2) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem. Int. Ed.* **2008**, *47*, 8998; *Angew. Chem.* **2008**, *120*, 9136.
(3) (a) Huang, X.; Liu, W.; Hooker, J. M.; Grover, J. T. *Angew. Chem. Int. Ed.* **2015**, *54*, 5241; *Angew. Chem.* **2015**, *127*, 5330. (b) Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Grover, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842. (c) Rotstein, B. H.; Stephenson, N.; Nickeisha, A.; Vasdev, N.; Liang, S. H. *Nat. Commun.* **2014**, *5*, 4365. (d) Tredwell, M.; Preshlock, S. M.; Taylor, N. J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2014**, *53*, 7751; *Angew. Chem.* **2014**, *126*, 7885. (e) Van der Born, D.; Sewing, C.; Herscheid, J. D. M.; Windhorst, A. D.; Orru, R. V. A.; Vugts, D. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11046; *Angew. Chem.* **2014**, *126*, 11226. (f) Benedetto, E.; Tredwell, M.; Hollingworth, C.; Khotavivattana, T.; Brown, J. M.; Gouverneur, V. *Chem. Sci.* **2013**, *4*, 89. (g) Gao, Z.; Lim, Y. H.; Tredwell, M.; Li, L.; Verhoog, S.; Hopkinson, M.; Kaluza, W.; Collier, T. L.; Passchier, J.; Huiban, M.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 6733; *Angew. Chem.* **2012**, *124*, 6837. (h) Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456. (i) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639. (j) Hollingworth, C.; Hazari, A.; Hopkinson, M. N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 2613; *Angew. Chem.* **2011**, *123*, 2661.
(4) (a) Jacobson, O.; Kiesewetter, D. O.; Chen, X. *Bioconjugate Chem.* **2015**, *26*, 1. (b) Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. *Chem. Sci.* **2014**, *5*, 4545. (c) Tredwell, M.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 11426; *Angew. Chem.* **2012**, *124*, 11590.

(5) Mizuta, S.; Stenhagen, I. S. R.; O'Duill, M.; Wolstenhulme, J.; Kirjavainen, A. K.; Forsback, S. J.; Tredwell, M.; Sandford, G.; Moore, P. R.; Huiban, M.; Luthra, S. K.; Passchier, J.; Solin, O.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 2648.
(6) Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2010**, *38*, 6821; *Angew. Chem.* **2010**, *122*, 6973.
(7) Khotavivattana, T.; Verhoog, S.; Tredwell, M.; Pfeifer, L.; Calderwood, S.; Wheelhouse, K.; Collier, T. L.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2015**, *54*, 9991; *Angew. Chem.* **2015**, *127*, 10129.
(8) RCC in this context is determined by radio-TLC (EtOAc–hexane, 1:1) after quenching the reactions with EtOH–H_2O (9:1; 500 µL), multiplying the total amount of incorporated ^{18}F with the radiochemical purity of the product as determined by radio-HPLC.
(9) (a) Angelini, G.; Speranza, M.; Shiue, C.-Y.; Wolf, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, *3*, 113. (b) Ido, T.; Irie, T.; Kasida, Y. *J. Labelled Compd. Radiopharm.* **1979**, *16*, 153. (c) Angelini, G.; Speranza, M.; Wolf, A. P.; Shiue, C.-Y. *J. Labelled Compd. Radiopharm.* **1990**, *28*, 1441. (d) Kilbourn, M. R.; Pavia, M. R.; Gregor, V. E. *Appl. Radiat. Isot.* **1990**, *41*, 823. (e) Hammadi, A.; Crouzel, C. *J. Labelled Compd. Radiopharm.* **1993**, *33*, 703. (f) Das, M. K.; Mukherjee, J. *Appl. Radiat. Isot.* **1993**, *44*, 835. (g) Johnström, P.; Stone-Elander, S. *J. Labelled Compd. Radiopharm.* **1995**, *36*, 537. (h) Prabhakaran, J.; Underwood, M. D.; Parsey, R. V.; Arango, V.; Majo, V. J.; Simpson, N. R.; Van Heertum, R.; Mann, J. J.; Kumar, J. S. D. *Bioorg. Med. Chem.* **2007**, *15*, 1802. (i) Suehiro, M.; Yang, G.; Torchon, G.; Ackerstaff, E.; Humma, J.; Koutcher, J.; Ouerfelli, O. *Bioorg. Med. Chem.* **2011**, *19*, 2287. (j) Lien, V. T.; Riss, P. J. *BioMed Res. Int.* **2014**, 380124.
(10) For details, see the Supporting Information.
(11) (a) Katsifis, A.; Hamacher, K.; Schnitter, J.; Stöcklin, G. *Appl. Radiat. Isot.* **1993**, *44*, 1015. (b) Hamacher, K.; Hamkens, W. *Appl. Radiat. Isot.* **1995**, *46*, 911. (c) Bourdier, T.; Shepherd, R.; Berghofer, P.; Jackson, T.; Fookes, C. J. R.; Denoyer, D.; Dorow, D. S.; Greguric, I.; Gregoire, M.-C.; Hicks, R. J.; Katsifis, A. *J. Med. Chem.* **2011**, *54*, 1860.
(12) (a) Irie, T.; Fukushi, K.; Ido, T.; Nozaki, T.; Kasida, Y. *Int. J. Appl. Radiat. Isot.* **1982**, *33*, 1449. (b) Irie, T.; Fukushi, K.; Ido, T.; Nozaki, T.; Kasida, Y. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 517. (c) Qu, W.; Zha, Z.; Ploessl, K.; Lieberman, B. P.; Zhu, L.; Wise, D. R.; Thompson, C. B.; Kung, H. F. *J. Am. Chem. Soc.* **2011**, *133*, 1122. (d) Ichiishi, N.; Brooks, A. F.; Topczewski, J. J.; Rodnick, M. E.; Sanford, M. S.; Scott, P. J. *Org. Lett.* **2014**, *16*, 3224.
(13) Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. *Nat. Chem.* **2013**, *5*, 941; for a variant giving higher specific activity (up to ~32 GBq/µmol), see ref. 3e.
(14) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626.
(15) Narjes, F.; Koehler, K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Altamura, S.; De Francesco, R.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701.
(16) Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Suresh, M. R.; Knaus, E. E. *J. Med. Chem.* **2009**, *52*, 1525.
(17) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529; and references therein.