

^{18}F -Labeling of Aryl- SCF_3 , $-\text{OCF}_3$ and $-\text{OCHF}_2$ with $[\text{F}^{18}]\text{Fluoride}^{**}$

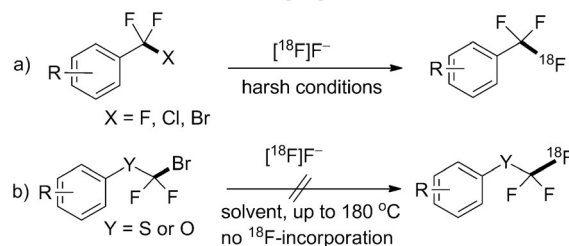
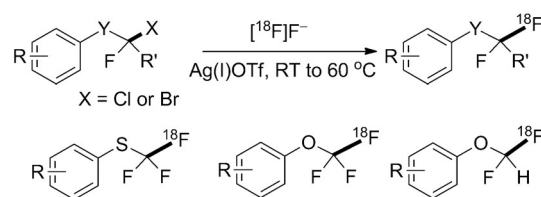
Tanatorn Khotavivattana, Stefan Verhoog, Matthew Tredwell, Lukas Pfeifer,

Samuel Calderwood, Katherine Wheelhouse, Thomas Lee Collier, and Véronique Gouverneur*

Abstract: We report that halogenophilic silver(I) triflate permits halogen exchange (halex) nucleophilic ^{18}F -fluorination of aryl- OCHFCl , $-\text{OCF}_2\text{Br}$ and $-\text{SCF}_2\text{Br}$ precursors under mild conditions. This Ag^{I} -mediated process allows for the first time access to a range of ^{18}F -labeled aryl- OCHF_2 , $-\text{OCF}_3$ and $-\text{SCF}_3$ derivatives, inclusive of $[\text{F}^{18}]\text{riluzole}$. The ^{18}F -labeling of these medically important motifs expands the radiochemical space available for PET applications.

Positron emission tomography (PET) is a non-invasive quantitative imaging technology assessing biological and biochemical processes in living subjects.^[1] This imaging modality enhances our understanding of disease states and drug activity during both preclinical and clinical development. The success of PET and renewed interest in ^{18}F -radiochemistry led to creative methods to incorporate ^{18}F into molecules of increasing complexity.^[2] Despite these advances, clinically useful radiotracers lie within a narrow accessible space with $[\text{F}^{18}]\text{fluoroalkanes}$ and $[\text{F}^{18}]\text{fluoroarenes}$ at the forefront. Many potentially high-value PET ^{18}F -labeled tracers and drugs lie outside this radiochemical space, and the ability to test tracers not amenable to traditional or newly developed ^{18}F -labeling intervention would be a major boost for PET imaging. A more diverse range of ^{18}F -tags could serve medicinal chemists by informing the selection of lead compounds much earlier in the drug discovery pipeline. Drug developers have employed di- and trifluoromethyl ether, as well as thioether substitution to tune conformation on demand, or modulate physicochemical parameters such as lipophilicity.^[3] Pharmaceutical drugs that have benefited from these substitutions are the CF_3O -containing 2-amino benzo-thiazole riluzole, the first drug approved for the treatment of

amyotrophic lateral sclerosis,^[4] or the CF_3S -substituted 2-phenylethylamine tiflorex, which possesses anorectic activity.^[5] To date, there is no method available to label trifluoromethyl ethers or thioethers. The prospect of providing ^{18}F -labeled aryl- OCF_3 , $-\text{OCHF}_2$ and $-\text{SCF}_3$ applying a common methodology led us to consider halogen exchange ^{18}F -fluorination (Figure 1). Halogen exchange (halex) applied

I. Thermal activation for halex $[\text{F}^{18}]\text{fluorination}$

II. Metal activation for halex $[\text{F}^{18}]\text{fluorination}$ (this work)


Broad applicability: novel $[\text{F}^{18}]\text{tags}$ of medicinal relevance and expansion of radiochemical space for PET applications

Figure 1. ^{18}F -Labeling of aryl- SCF_3 , $-\text{OCF}_3$ and $-\text{OCHF}_2$. I.a) Thermal activation for halex ^{18}F -fluorination of aryl- CF_2X precursors employs harsh conditions. I.b) Thermal activation is not suitable for the ^{18}F -labeling of aryl- SCF_3 or aryl- OCF_3 by halex ^{18}F -fluorination. II. $\text{Ag}^{\text{I}}\text{OTf}$ mediated ^{18}F -halex occurs under mild conditions and allows access to new ^{18}F -labeled motifs of medicinal significance including $[\text{F}^{18}]\text{aryl-SCF}_3$, $-\text{OCF}_3$ and $-\text{OCHF}_2$.

to ^{18}F -labeling relies on thermal activation only;^[6] this method has met with limited success for aryl- CF_2X precursors since the presence of two α -fluorine severely inhibits substitution with fluoride (Figure 1, Ia).^[7] In preliminary work, we found that thermal activation does not permit ^{18}F -incorporation to label aryl- OCF_3 or aryl- SCF_3 derivatives by halogen exchange ^{18}F -fluorination (see below and Figure 1, Ib). These difficulties prompted us to identify a metal-based activation approach for halex ^{18}F -fluorination of RCF_2X precursors under mild reaction conditions; such an advance may be transformational to access medically important ^{18}F -labeled motifs that are currently not within reach (Figure 1, II).

Silver is used in homogeneous catalysis owing to its Lewis acidity, its halide affinity or as a powerful 1e^- oxidant.^[8] We

[*] T. Khotavivattana,^[†] S. Verhoog,^[†] Dr. M. Tredwell, L. Pfeifer, S. Calderwood, Prof. V. Gouverneur
University of Oxford, Chemistry Research Laboratory
Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: veronique.gouverneur@chem.ox.ac.uk

Dr. T. Lee Collier
Advion BioSystems
10 Brown Road, Suite 101, Ithaca, NY 14850 (USA)
Dr. K. Wheelhouse
Medicines Discovery & Development, GlaxoSmithKline R&D
Gunns Wood Road, Stevenage, Hertfordshire, SG1 2NY (UK)

[†] These authors contributed equally to this work.

[**] Financial support was provided by the EPSRC (S.V., M.T.), GSK (S.V.), the CRUK (M.T.), the Royal Thai Government (T.K.), the EU (FP7-PEOPLE-2012-ITN-RADIOMI-316882 to L.P.), the MRC (S.C.) and Advion. V.G. holds a Royal Society Wolfson Research Merit Award (2013-2018).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201504665>.

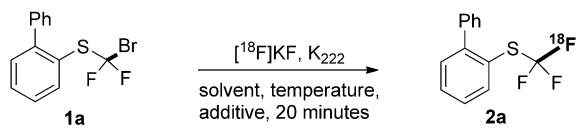
employed Ag^I salts and [¹⁸F]selectfluor bis(triflate)^[9] for the ¹⁸F-fluorination of arylstannanes^[9] and arylboronic acids,^[10] and to induce the ¹⁸F-fluorodecarboxylation of 2,2-difluoro-2-arylacetic acid derivatives.^[11] In this study, we considered that the affinity of Ag^I salts for halide may facilitate halogen exchange nucleophilic ¹⁸F-fluorination under mild reaction conditions; this characteristic of Ag^I-based chemistry has never been considered as a generic activation manifold to promote halox ¹⁸F-fluorination.^[12] Here, we report that silver(I) triflate allows for RCF₂-Br bond displacement with [¹⁸F]fluoride under mild conditions. The method offers, for the first time, access to ¹⁸F-labeled aryl-OCF₃ and -SCF₃ motifs, and was successfully extended to [¹⁸F]aryl-OCHF₂ (Figure 1, II).

We focused in the first instance on the ¹⁸F-labeling of trifluoromethyl thioethers, a class of compounds characterized by high lipophilicity (Hansch constant $\pi = 1.44$); for drug discovery, this property allows effective transport of drug molecules through lipid membranes and improves bioavailability.^[3] The ¹⁸F-labeling of trifluoromethyl thioethers has not been reported despite the impressive number of methods developed in recent years permitting aryl-SCF₃ or aryl-SCF₃ bond construction.^[3,13] In the context of radiochemistry, these methods would require ¹⁸F-reagents suitable for [¹⁸F]CF₃ or [¹⁸F]SCF₃ incorporation. The conversion of ArSCCl₃ into ArSCF₃ with excess SbF₃ is the oldest method for the synthesis of perfluoroalkylsulfide and is still commercially significant.^[14] Recent variants of Swarts-type fluorination create an arylSCF₂-F bond from arylSCF₂-Br precursors in the presence of SbF₃ at 160 °C,^[15] or with AgBF₄.^[16] These reagents are not suitable for ¹⁸F-labeling due to the risk of isotope exchange. For preliminary studies, we prepared [1,1'-biphenyl]-4-yl(bromodifluoromethyl)-sulfane (**1a**),^[17] a model difluorinated precursor requiring single ¹⁸F-fluorination to afford [¹⁸F]arylSCF₃ (**2a**) (Table 1).

The treatment of **1a** with [¹⁸F]KF/K₂₂₂ in a range of solvents and at temperatures up to 180 °C did not permit ¹⁸F-incorporation (Table 1, entries 1–5). A series of Ag^I salts were considered to promote halox ¹⁸F-fluorination (entries 6–9). The presence of Ag⁺OTf (1 equiv) in DCM or DCE afforded [¹⁸F]arylSCF₃ **2a** in 60% and 79% radiochemical yield (RCY),^[18] respectively (entries 9 and 10). At 60 °C in DCE with 2 equiv of AgOTf, the RCY increased to 81% (entry 11). A lower 10 mol% loading of Ag^I salt permits halox ¹⁸F-fluorination in DCM at room temperature but the RCY dropped to 34% (entry 12). Changing the amount of precursor or concentration had no beneficial effect (entries 13 and 14). Acetonitrile, dimethylformamide or diethyl ether are not suitable solvents for this transformation (RCY < 5%), a result best rationalized referring to the calculated bonding enthalpies of these solvents to Ag⁺ (entries 15–17).^[19] The use of AgNTf₂ with a weakly coordinating triflimide counteranion was also effective, affording **2a** in 74% RCY (entry 18). Experiments using LiOTf or Cu(OTf)₂ instead of Ag⁺OTf confirmed that Ag^I is the critical entity permitting halogen exchange (entries 19 and 20).

Various arylSCF₃ **2a-i** were ¹⁸F-labeled applying reaction conditions **A** (1 equiv AgOTf, DCM, RT) or **B** (2 equiv AgOTf, DCE, 60 °C); the RCYs are higher under conditions

Table 1: ¹⁸F-Fluorination of the arylSCF₂Br precursor **1a**.^[a]

				
Entry	Solvent ^[b]	Additive	Temp.	RCY [%] ^[c]
1	MeCN	–	80 °C	0 (<i>n</i> = 2)
2	DMF	–	110 °C	0 (<i>n</i> = 2)
3	DMA	–	150 °C	0 (<i>n</i> = 2)
4	NMP	–	180 °C	0 (<i>n</i> = 2)
5	DMSO	–	180 °C	0 (<i>n</i> = 2)
6	DCM	Ag ₂ O	RT	0 (<i>n</i> = 2)
7	DCM	AgNO ₃	RT	0 (<i>n</i> = 2)
8	DCM	Ag ₂ CO ₃	RT	0 (<i>n</i> = 2)
9	DCM	AgOTf	RT	60 ± 4 (<i>n</i> = 10)
10	DCE	AgOTf	RT	79 ± 3 (<i>n</i> = 2)
11	DCE	AgOTf ^[d]	60 °C	81 ± 3 (<i>n</i> = 4)
12	DCM	AgOTf ^[e]	RT	34 ± 9 (<i>n</i> = 2)
13 ^[f]	DCM	AgOTf	RT	31 ± 2 (<i>n</i> = 2)
14 ^[g]	DCM	AgOTf	RT	44 ± 3 (<i>n</i> = 2)
15	MeCN	AgOTf	RT	0 (<i>n</i> = 2)
16	DMF	AgOTf	RT	0 (<i>n</i> = 2)
17	Et ₂ O	AgOTf	RT	0 (<i>n</i> = 2)
18	DCM	AgNTf ₂	RT	74 ± 3 (<i>n</i> = 2)
19	DCM	LiOTf	RT	0 (<i>n</i> = 2)
20	DCM	Cu(OTf) ₂	RT	0 (<i>n</i> = 2)

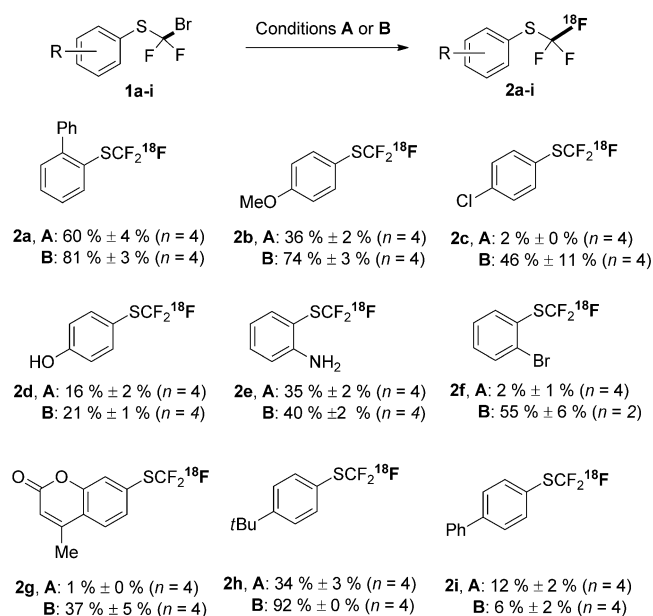
[a] **1a** (0.04 mmol), solvent (300 μL), additive (0.04 mmol), 20 min.

[b] DMF = *N,N*-dimethylformamide; DMA = *N,N*-dimethylacetamide; NMP = *N*-methyl-2-pyrrolidone; DMSO = dimethylsulfoxide; DCM = dichloromethane; DCE = 1,2-dichloroethane. [c] Radiochemical yield determined by radio-TLC and repeated *n* times. [d] 0.08 mmol.

[e] 0.004 mmol. [f] **1a** (0.02 mmol), AgOTf (0.02 mmol). [g] **1a** (0.02 mmol), AgOTf (0.02 mmol), 150 μL of DCM.

B, with the exception of **1i**. The reaction tolerates alkyl, ethers, esters, aryl and halogens on the aryl core, as well as unprotected amine and alcohol positioned *ortho* or *para* with respect to the thioether functionality (Scheme 1).

The successful labeling of trifluoromethyl thioethers **2a-i** encouraged further investigation with the ¹⁸F-fluorination of two additional motifs of medicinal importance. Trifluoromethyl ethers are within reach by halox fluorination upon treatment of aryl trichloromethyl ethers with HF, SbF₃, SbF₅ (Swart's reagent) in the presence of SbCl₅ or MoF₆.^[20] Alternative methods employ aryl fluoroformates or aryl xanthates reacting with SF₄/HF at 160 °C or with HF-pyridine and an oxidant, respectively.^[21] These syntheses requiring sequential fluorination are not ideal for ¹⁸F-labeling, hence 4-(bromodifluoromethoxy)-1,1'-biphenyl **3a** was selected as model substrate for ¹⁸F-incorporation. Experiments probing the reactivity of **3a** with [¹⁸F]KF and Kryptofix.222 did not lead to product formation in the absence of Ag^I salt. Extensive optimization indicated that ¹⁸F-fluorination of this substrate is challenging, and we were therefore delighted to obtain **4a** in RCY averaging 24% (*n* = 4) when the reaction was conducted in DCE at 60 °C with AgOTf (2 equiv). The reaction did not proceed in acetonitrile but gave 18% RCY in toluene at 100 °C. Decreasing the amount of Ag^I or the temperature had a detrimental effect on the RCY. Other Ag^I salts gave traces of the product with the exception of AgBF₄



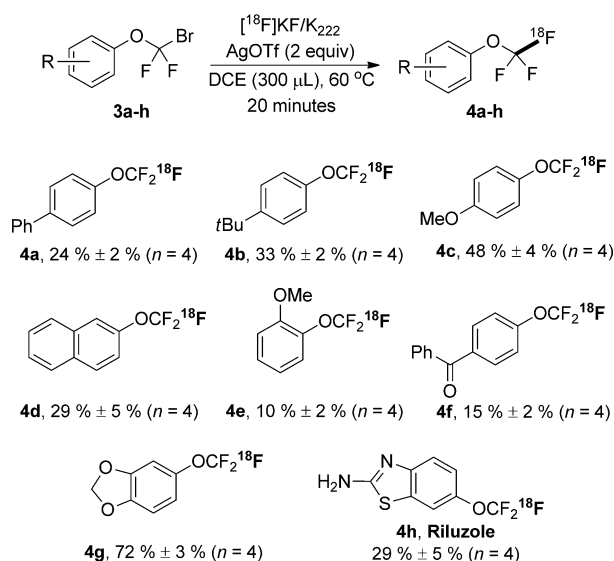
Scheme 1. Ag^I-Mediated halex ¹⁸F-fluorination towards [¹⁸F]aryl-SCF₃. Conditions **A**: AgOTf (1 equiv), DCM, RT, 20 min. Conditions **B**: AgOTf (2 equiv), DCE, 60 °C, 20 min. DCM = dichloromethane; DCE = 1,2-dichloroethane.

(9 % RCY at room temperature), but this reagent was not retained due to the risk of isotope scrambling.^[22] Applying the protocol optimized for this class of substrates (2 equiv of AgOTf, DCE, 60 °C, 20 min), the labeled products **4a–g** were obtained with RCY reaching 72 %. The method gave [¹⁸F]riluzole **4h** in 29 % RCY from the N-unprotected precursor **3h**. For this target, the use of the mono- or bis-protected *N*-Boc precursor was not advantageous (Scheme 2, I).

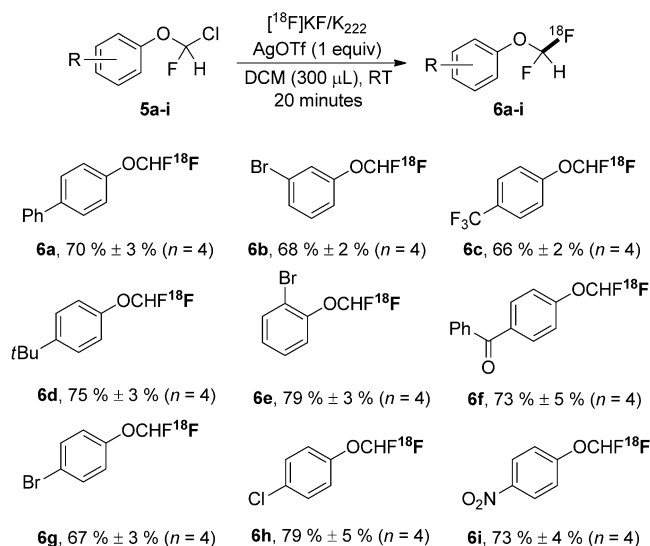
The reactivity of 4-(chlorofluoromethoxy)-1,1'-biphenyl **5a**, a substrate which upon ¹⁸F-fluorination could afford the [¹⁸F]difluoromethoxyarene **6a**, was examined next (Scheme 2, II). 4-(Bromofluoromethoxy)-1,1'-biphenyl was not considered as this precursor was difficult to prepare and purify. The difluoromethoxy group is an important motif for medicinal chemists due to its non-isotropic shape and electrostatic potential. This group can adopt two interconverting conformations of different lipophilicity, a property enabling this unit to adjust to polarity changes of the molecular environment.^[23] Early experiments reveal that **5a** responded to halex ¹⁸F-fluorination at room temperature in the absence of Ag^I salt affording **6a** in low RCY (19 %), but the RCY increased to 70 % when AgOTf was added to the reaction vial. The RCYs obtained with precursors **5a–i** ranged from 66 % to 79 %. These data indicate that halex ¹⁸F-fluorination is more facile for this class of substrates, with both electron withdrawing and donating substituents well tolerated on the arene.

Competition experiments were conducted with **1i**, **3a** and **5a** as well as two additional precursors 4-(bromodifluoromethyl)-1,1'-biphenyl **7a** and 4-(chlorodifluoromethyl)-1,1'-biphenyl **9a**; this study provides the ensuing order of reactivity towards ¹⁸F-fluoride: ArOCHFCl > ArCF₂Br ≈

I. [¹⁸F]Labeling of aryl-OCF₃



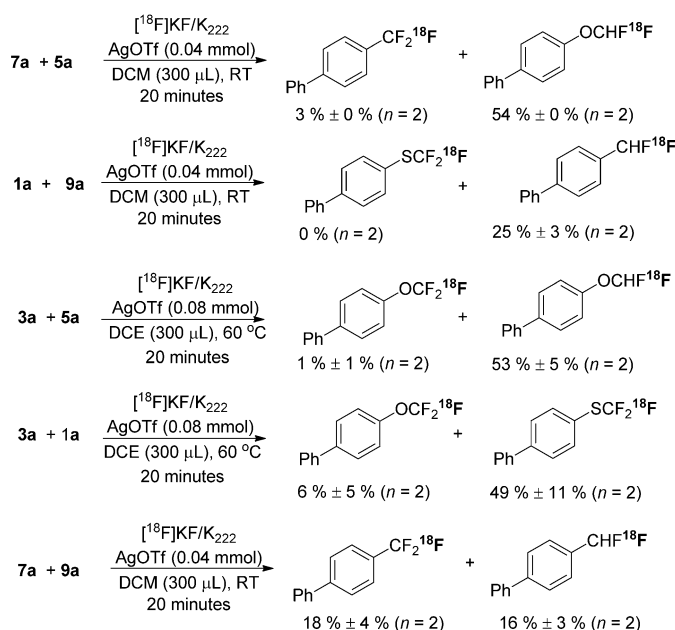
II. [¹⁸F]Labeling of aryl-OCHF₂



Scheme 2. Ag^I-mediated halex ¹⁸F-fluorination towards [¹⁸F]aryl-OCF₃ and -OCHF₂.

ArCHFCl > ArSCF₂Br > ArOCF₂Br (Scheme 3). This order combined with the observation that electron withdrawing groups on the aryl substituent of arylCF₂Br precursors lead to significantly lower RCY,^[17] suggests that cationic intermediates are involved in these Ag^I-mediated ¹⁸F-fluorinations.^[24]

The identification of a robust protocol for the isolation of ¹⁸F-labeled products starting from circa 4 GBq of radioactivity required further tuning since increased quantities of K₂CO₃ and Kryptofix had a detrimental effect on the RCY. These limitations were overcome using potassium oxalate^[25] and dicyclohexyl-18-crown-6^[26] acting as an alternative base and [¹⁸F]KF activator, respectively. Using these modified conditions, the labeled products **2a** ([¹⁸F]arylSCF₃), **4a** ([¹⁸F]arylOCF₃), **6b** and **6f** ([¹⁸F]arylOCHF₂) were isolated



Scheme 3. Competition experiments for Ag^{I} -mediated halogen exchange ^{18}F -fluorination using 0.02 mmol of each starting material.^[17]

after preparative radio-HPLC in 10 % ± 1 % (n = 2), 11 % ± 4 % (n = 2), 34 % ± 1 % (n = 2) and 31 % ± 2 % (n = 2) RCY, respectively. The specific activities (SA)^[27] of **2a**, **4a**, **6b** and **6f** were found to be 0.15 GBq μmol^{-1} , 0.04 GBq μmol^{-1} , 0.04 GBq μmol^{-1} and 0.17 GBq μmol^{-1} , respectively; these values are comparable to those obtained for ^{18}F -labeled aryl- CF_3 applying our ^{18}F - CuCF_3 -based cross-coupling strategy,^[28] and imply that this radiochemical method is best suited to support drug development studies. Control experiments inform that no ^{18}F -incorporation was detectable when subjecting unlabeled **2a**, **4a** or **6a** to the reaction condition applied for Ag^{I} -mediated ^{18}F -fluorination; these results demonstrate that ^{19}F - ^{18}F isotope exchange does not occur on the ^{18}F -labeled product.^[29] The silver content of ^{18}F -radiotracers prepared with our method was considered, although such silver contamination concerns are very different for PET imaging because of the small amount of radiotracer that is required. Inductively coupled plasma atomic emission spectrometry (ICP-AES) analysis was performed on ^{18}F -**6b** and ^{18}F -**4a**, both purified by a conventional HPLC technique. This analysis indicated that Ag^{I} OTf can be removed effectively since the Ag content was found to be < 0.05 $\mu\text{g g}^{-1}$ for ^{18}F -**6b** (n = 2) and 0.02 $\mu\text{g g}^{-1}$ for ^{18}F -**4a** (n = 2); these values are well below any levels of concern.^[30]

This work demonstrates that Ag^{I} OTf induces halogen exchange nucleophilic ^{18}F -fluorination under mild reaction conditions and this advance permits for the first time access to medicinally relevant ^{18}F -labeled aryl- OCHF_2 , $-\text{OCF}_3$ and $-\text{SCF}_3$ derivatives. In drug discovery, the concept of chemical space describes the pool of molecules to be considered when searching for new drugs. It is reasonable to predict that major progresses in PET imaging will emerge from a dramatically expanded radiochemical space enabling the synthesis and discovery of radiotracers and radioligands currently not

within reach. This work represents a significant step in this direction.

Experimental Section

General procedure for halogen exchange ^{18}F -fluorination: To a Vial containing Ag^{I} OTf (0.04 mmol) is added ^{18}F - $[\text{K}^{\text{F}}]/\text{K}_{222}$ (≈ 30 MBq) in MeCN (≈ 30 μL). This vial is heated at 100 °C for 2 min under a stream of N_2 . After allowing to cool, substrate (0.04 mmol) in DCM (300 μL) is added to the vial. This mixture is allowed to stir at RT for 20 min, after which time the reaction is quenched by the addition of EtOH/ H_2O (9:1, 500 μL).

Keywords: ^{18}F fluoride · difluoromethyl ethers · halogen exchange · silver triflate · trifluoromethyl ethers

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9991–9995
Angew. Chem. **2015**, *127*, 10129–10133

- [1] a) M. E. Phelps, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9226–9233; b) S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501–1516; c) P. M. Matthews, E. A. Rabiner, J. Passchier, R. N. Gunn, *Br. J. Clin. Pharmacol.* **2012**, *73*, 175–186; d) D. F. Wong, J. Tauscher, G. Gründer, *Neuropsychopharmacology* **2009**, *34*, 187–203.
- [2] For recent reviews, see: a) O. Jacobson, D. O. Kiesewetter, X. Chen, *Bioconjugate Chem.* **2015**, *26*, 1–18; b) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci.* **2014**, *5*, 4545–4553; c) M. Tredwell, V. Gouverneur, *Angew. Chem. Int. Ed.* **2012**, *51*, 11426–11437; *Angew. Chem.* **2012**, *124*, 11590–11602; For selected transformations, see: d) X. Huang, W. Liu, J. M. Hooker, J. T. Groves, *Angew. Chem. Int. Ed.* **2015**, *54*, 5241–5245; *Angew. Chem.* **2015**, *127*, 5330–5334; e) X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker, J. T. Groves, *J. Am. Chem. Soc.* **2014**, *136*, 6842–6845; f) B. H. Rotstein, N. Stephenson, A. Nickeisha, N. Vasdev, S. H. Liang, *Nat. Commun.* **2014**, *5*, 4365; g) M. Tredwell, S. M. Preshlock, N. J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Génicot, V. Gouverneur, *Angew. Chem. Int. Ed.* **2014**, *53*, 7751–7755; *Angew. Chem.* **2014**, *126*, 7885–7889; h) D. van der Born, C. Sewing, J. D. M. Herscheid, A. D. Windhorst, R. V. A. Orru, D. J. Vugts, *Angew. Chem. Int. Ed.* **2014**, *53*, 11046–11050; *Angew. Chem.* **2014**, *126*, 11226–11230; i) E. Benedetto, M. Tredwell, C. Hollingworth, T. Khotavivattana, J. M. Brown, V. Gouverneur, *Chem. Sci.* **2013**, *4*, 89–96; j) Z. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, M. Hopkinson, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban, V. Gouverneur, *Angew. Chem. Int. Ed.* **2012**, *51*, 6733–6737; *Angew. Chem.* **2012**, *124*, 6837–6841; k) E. Lee, J. M. Hooker, T. Ritter, *J. Am. Chem. Soc.* **2012**, *134*, 17456–17458; l) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science* **2011**, *334*, 639–642; m) C. Hollingworth, A. Hazari, M. N. Hopkinson, M. Tredwell, E. Benedetto, M. Huiban, A. D. Gee, J. M. Brown, V. Gouverneur, *Angew. Chem. Int. Ed.* **2011**, *50*, 2613–2617; *Angew. Chem.* **2011**, *123*, 2661–2665.
- [3] a) G. Landelle, A. Panossian, F. R. Leroux, *Curr. Top. Med. Chem.* **2014**, *14*, 941–951; b) V. N. Boiko, *Beilstein J. Org. Chem.* **2010**, *6*, 880–921; c) F. R. Leroux, B. Manteau, J.-P. Vors, S. Pazenok, *Beilstein J. Org. Chem.* **2008**, *4*, 13.
- [4] a) H. J. M. van Kan, G. J. Groeneveld, S. Kalmijn, M. Spieksma, L. H. van den Berg, H. J. Guchelaar, *Br. J. Clin. Pharmacol.* **2005**, *59*, 310–313; b) S. J. Mathew, J. M. Amiel, J. D. Coplan, H. A. Fitterling, H. A. Sackeim, J. M. Gorman, *Am. J. Psychol.* **2005**, *162*, 2379–2381.

- [5] a) T. Silverstone, J. Fincham, J. Plumley, *Br. J. Clin. Pharmacol.* **1979**, *7*, 353–356; b) J. F. Giudicelli, C. Richer, A. Berdeaux, *Br. J. Clin. Pharmacol.* **1976**, *3*, 113–121.
- [6] Halex ^{18}F -fluorination under thermal activation: a) G. Angelini, M. Speranza, C.-Y. Shiue, A. P. Wolf, *J. Chem. Soc. Chem. Commun.* **1986**, 924–925; b) M. Suehiro, G. Yang, G. Torchon, E. Ackerstaff, J. Humma, J. Koutcher, O. Ouerfelli, *Bioorg. Med. Chem.* **2011**, *19*, 2287–2297; c) M. R. Kilbourn, M. R. Pavia, V. E. Gregor, *Appl. Radiat. Isot.* **1990**, *41*, 823–828; d) P. Johnström, S. Stone-Elander, *J. Labelled Compd. Radiopharm.* **1995**, *36*, 537–547; e) A. Hammadi, C. Crouzel, *J. Labelled Compd. Radiopharm.* **1993**, *33*, 703–710; f) J. Prabhakaran, M. D. Underwood, R. V. Parsey, V. Arango, V. J. Mayo, N. R. Simpson, R. Van Heertum, J. J. Man, J. S. D. Kumar, *Bioorg. Med. Chem.* **2007**, *15*, 1802–1807; g) T. Ido, T. Irie, Y. Kasida, *J. Labelled Compd. Radiopharm.* **1979**, *16*, 153–154; h) M. K. Das, J. Mukherjee, *Appl. Radiat. Isot.* **1993**, *44*, 835–842; i) G. Angelini, M. Speranza, A. P. Wolf, C.-Y. Shiue, *J. Labelled Compd. Radiopharm.* **1990**, *28*, 1441–1448.
- [7] a) H. Martinez, A. Rebeyrol, T. B. Nelms, W. R. Dolbier, Jr., *J. Fluorine Chem.* **2012**, *135*, 167–175; b) J. Guidotti, V. Schanen, M. Tordeux, C. Wakselman, *J. Fluorine Chem.* **2005**, *126*, 443–447.
- [8] For key references, see: a) B. H. Lipshutz, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 2793–2795; b) M. Naodovic, H. Yamamoto, *Chem. Rev.* **2008**, *108*, 3132–3148; c) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174–3198; d) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.* **2008**, *108*, 3149–3173; e) A. S. K. Hashmi, *Silver in Organic Chemistry* (Ed. M. Harmata), Wiley, Hoboken, **2010**, Chap. 12.
- [9] H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra, V. Gouverneur, *Angew. Chem. Int. Ed.* **2010**, *49*, 6821–6824; *Angew. Chem.* **2010**, *122*, 6973–6976.
- [10] I. S. R. Stenhagen, A. K. Kirjavainen, S. J. Forsback, C. G. Jørgensen, E. G. Robins, S. K. Luthra, O. Solin, V. Gouverneur, *Chem. Commun.* **2013**, *49*, 1386–1388.
- [11] S. Mizuta, I. S. R. Stenhagen, M. O'Duill, J. Wolstenhulme, A. Kirjavainen, S. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. Luthra, J. Passchier, O. Solin, V. Gouverneur, *Org. Lett.* **2013**, *15*, 2648–2651.
- [12] For an isolated example of Ag^{I} -mediated ^{18}F -fluorination, see: D. O. Kiesewetter, E. M. Jagoda, J. E. Starrett, Jr., V. K. Gribkoff, P. Hewawasam, N. Srinivas, D. Salazar, W. C. Eckelman, *Nucl. Med. Biol.* **2002**, *29*, 55–59.
- [13] For selected examples, see: a) C. Pooput, M. Medebielle, W. R. Dolbier, *Org. Lett.* **2004**, *6*, 301–303; b) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem. Int. Ed.* **2009**, *48*, 8551–8555; *Angew. Chem.* **2009**, *121*, 8703–8707; c) Y. Yang, X. Jiang, F.-L. Qing, *J. Org. Chem.* **2012**, *77*, 7538–7547; d) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 7312–7314; *Angew. Chem.* **2011**, *123*, 7450–7452; e) C. P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183–185; f) C. Chen, Y. Xie, L. Chu, R. W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem. Int. Ed.* **2012**, *51*, 2492–2495; *Angew. Chem.* **2012**, *124*, 2542–2545; g) C. Chen, L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454–12457; h) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457–3460; *Angew. Chem.* **2013**, *125*, 3541–3544.
- [14] a) E. A. Nodiff, S. Lipschutz, P. N. Craig, M. Gordon, *J. Org. Chem.* **1960**, *25*, 60–65; b) L. M. Yagupolskii, V. N. Boiko, *Zh. Obshch. Khim.* **1969**, *39*, 195–198; c) L. Z. Gandelsman, E. I. Mostoslavskaya, L. M. Yagupolskii, *Ukr. Khim. Zh. (Russ. Ed.)* **1975**, *41*, 61–66.
- [15] T. Umamoto, S. Ishihara, *J. Fluorine Chem.* **1998**, *92*, 181–187.
- [16] M. Suda, C. Hino, *Tetrahedron Lett.* **1981**, *22*, 1997–2000.
- [17] For details, see the Supporting Information.
- [18] RCY in this context is determined by radio-TLC (EtOAc/Hexane, 1:1) after quenching the reactions with EtOH/H₂O (9:1; 500 μL), taking in to account by radiochemical purity by radio-HPLC.
- [19] a) T. Shoeib, H. El Aribi, K. W. M. Siu, A. C. Hopkinson, *J. Phys. Chem. A* **2001**, *105*, 710–719; b) V. Romanov, C.-K. Siu, U. H. Velker, H. El Aribi, A. C. Hopkinson, K. W. M. Siu, *J. Phys. Chem. A* **2008**, *112*, 10912–10920; c) H. El Aribi, T. Shoeib, Y. Ling, C. F. Rodriguez, A. C. Hopkinson, K. W. M. Siu, *J. Phys. Chem. A* **2002**, *106*, 2908–2914.
- [20] a) L. M. Yagupolskii, *Dokl. Akad. Nauk SSSR* **1955**, *105*, 100–102; b) J. Salomé, C. Mauger, S. Brunet, V. Schanen, *J. Fluorine Chem.* **2004**, *125*, 1947–1950.
- [21] a) W. A. Sheppard, *J. Org. Chem.* **1964**, *29*, 1–11; b) F. Mathey, J. Bensoam, *Tetrahedron Lett.* **1973**, *14*, 2253–2256; c) M. Kuroboshi, K. Kanie, T. Hiyama, *Adv. Synth. Catal.* **2001**, *343*, 235–250; d) M. Kuroboshi, K. Suzuki, T. Hiyama, *Tetrahedron Lett.* **1992**, *33*, 4173–4176.
- [22] a) W. Entzian, S. Aronow, A. H. Soloway, W. H. Sweet, *J. Nucl. Med.* **1964**, *5*, 542–550; b) M. Jauregui-Osoro, K. Sunassee, A. J. Weeks, D. J. Berry, R. L. Paul, M. Cleij, J. P. Banga, M. J. O'Doherty, P. K. Marsden, S. E. M. Clarke, J. R. Ballinger, I. Szanda, S.-Y. Cheng, P. J. Blower, *Eur. J. Nucl. Med. Mol. Imaging* **2010**, *37*, 2108–2116.
- [23] K. Müller, *Chimia* **2014**, *68*, 356–362.
- [24] a) G. A. Olah, Q. Wang, G. Neyer, *Synthesis* **1994**, 276–278; b) V. Jagannadham, T. L. Amyes, J. P. Richard, *J. Am. Chem. Soc.* **1993**, *115*, 8465–8466.
- [25] a) A. Katsifis, K. Hamacher, J. Schnitter, G. Stöcklin, *Appl. Radiat. Isot.* **1993**, *44*, 1015–1020; b) K. Hamacher, W. Hamkens, *Appl. Radiat. Isot.* **1995**, *46*, 911–916; c) T. Bourdier, R. Shepherd, P. Berghofer, T. Jackson, C. J. R. Fookes, D. Denoyer, D. S. Dorow, I. Greguric, M.-C. Gregoire, R. J. Hicks, A. Katsifis, *J. Med. Chem.* **2011**, *54*, 1860–1870.
- [26] a) T. Irie, K. Fukushi, T. Ido, T. Nozaki, Y. Kasida, *Int. J. Appl. Radiat. Isot.* **1982**, *33*, 1449–1452; b) T. Irie, K. Fukushi, T. Ido, T. Nozaki, Y. Kasida, *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 517–520; c) W. Qu, Z. Zha, K. Ploessl, B. P. Lieberman, L. Zhu, D. R. Wise, C. B. Thompson, H. F. Kung, *J. Am. Chem. Soc.* **2011**, *133*, 1122–1133; d) N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford, P. J. Scott, *Org. Lett.* **2014**, *16*, 3224–3227.
- [27] S. E. Lapi, M. J. A. Welch, *Nucl. Med. Biol.* **2013**, *40*, 314–320.
- [28] M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur, J. Passchier, *Nat. Chem.* **2013**, *5*, 941–944; for an elegant follow-up study leading to improved specific activity ranging from 1 to 32 GBq μmol^{-1} , see Ref. [2e].
- [29] Control experiments demonstrate that the thioether precursor **1h** gave **2h** in the presence of AgOTf ($[\text{D}_2]\text{DCM}$, room temperature) and in the absence of an external source of fluoride. This Ag^{I} -mediated process could account for the SA measured for the ^{18}F -labeled products.^[17]
- [30] ICP-AES measurements were performed by PhosphonicS Limited.

Received: May 22, 2015

Published online: July 3, 2015