

Difluorocarbene-Derived Trifluoromethylthiolation and [¹⁸F]Trifluoromethylthiolation of Aliphatic Electrophiles

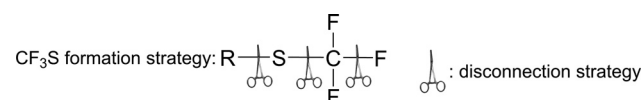
Jian Zheng, Lu Wang, Jin-Hong Lin, Ji-Chang Xiao,* and Steven H. Liang*

Abstract: The first trifluoromethylthiolation and [¹⁸F]trifluoromethylthiolation of alkyl electrophiles with in situ generated difluorocarbene in the presence of elemental sulfur and external (radioactive) fluoride ion is described. This transition-metal-free approach is high yielding, compatible with a variety of functional groups, and operated under mild reaction conditions. The conceptual advantage of this exogenous-fluoride-mediated transformation enables unprecedented syntheses of [¹⁸F]CF₃S-labeled molecules from most commonly used [¹⁸F]fluoride ions. The rapid radiochemical reaction time (≤ 1 min) and high functional-group tolerance allow access to a variety of aliphatic [¹⁸F]CF₃S compounds in high yields.

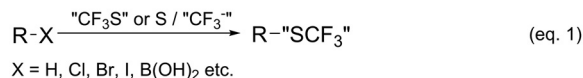
The most advanced technology currently available for studying in vivo molecular interactions, in terms of distribution, pharmacokinetics, and pharmacodynamics, positron emission tomography (PET), is a non-invasive quantitative imaging technology that is capable of detecting specific biological and pharmacological changes at the molecular level in humans and animals.^[1] Of the positron emitting isotopes, fluorine-18 (¹⁸F) is the most commonly used radionuclide because of its relatively long half-life of 109.7 minutes, high-yielding production and high specific activity, importance as fluorine substitution as isotopologue in drug discovery, and the extensive clinical use of [¹⁸F]FDG (2-[¹⁸F]fluoro-2-deoxy-D-glucose).^[2] Therefore, significant efforts have been devoted to the exploration of novel and efficient methodologies for ¹⁸F incorporation into small or biological molecules.^[3] However, approaches in ¹⁸F radiochemistry have so far been mostly limited to [¹⁸F]fluorination^[4] and [¹⁸F]trifluoromethylation.^[5] Despite the fact that the trifluoromethylthio group (CF₃S) is a valuable pharmacophore in medicinal chemistry and drug discovery,^[6] the formation of

the [¹⁸F]CF₃S moiety has never been realized and thus represents a significant challenge in the field.

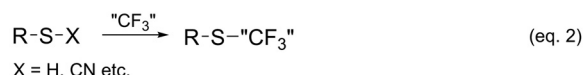
Recently, outstanding accomplishments have been made for the incorporation of the CF₃S group by nonradioactive methods.^[7] Two general strategies have been well established, including direct trifluoromethylthiolation by constructing a C–SCF₃ bond^[8] or sequential construction of S–CF₃ and C–SCF₃ bonds^[8c,9] (Scheme 1 a), and trifluoromethylation of



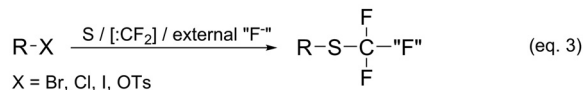
- Previous strategy I: direct trifluoromethylthiolation



- Previous strategy II: trifluoromethylation



- This work: difluorocarbene-derived trifluoromethylthiolation



Scheme 1. Bond-formation strategies for the trifluoromethylthio (CF₃S) group. Ts = 4-toluenesulfonyl.

sulfur-containing compounds to form a RS–CF₃ bond^[10] (Scheme 1 b). In both strategies, the CF₃S scaffold is derived from either CF₃S- or CF₃-containing reagents without the involvement of external fluoride, thus making it not applicable or difficult for translation into ¹⁸F radiolabeling. In particular, [¹⁸F]trifluoromethylthiolation, which involves the use of most readily available [¹⁸F]fluorides for the formation of the [¹⁸F]CF₃S group, is a promising strategy, but to date no convenient trifluoromethylthiolation reaction employs external fluoride to construct the CF₃S moiety. It is an urgent and unmet need to explore efficient methods for fast trifluoromethylthiolation in which exogenous fluoride is involved, and thus make [¹⁸F]trifluoromethylthiolation possible.

Difluorocarbene has served as a powerful reaction intermediate in organic synthesis.^[11] On the basis of our previous studies showing difluorocarbene can be readily trapped by fluoride to generate the trifluoromethyl anion (CF₃[−]),^[12] and the recent studies that the trifluoromethyl anion can react with elemental sulfur (S₈) to produce the

[*] J. Zheng,^[†] J.-H. Lin, Prof. Dr. J.-C. Xiao
Key Laboratory of Organofluorine Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
E-mail: jchxiao@sioc.ac.cn

L. Wang,^[†] Prof. Dr. S. H. Liang
Division of Nuclear Medicine and Molecular Imaging
Massachusetts General Hospital & Department of Radiology
Harvard Medical School, 55 Fruit St., White 427
Boston, MA (USA)
E-mail: liang.steven@mgh.harvard.edu

[†] These authors contributed equally to this work.

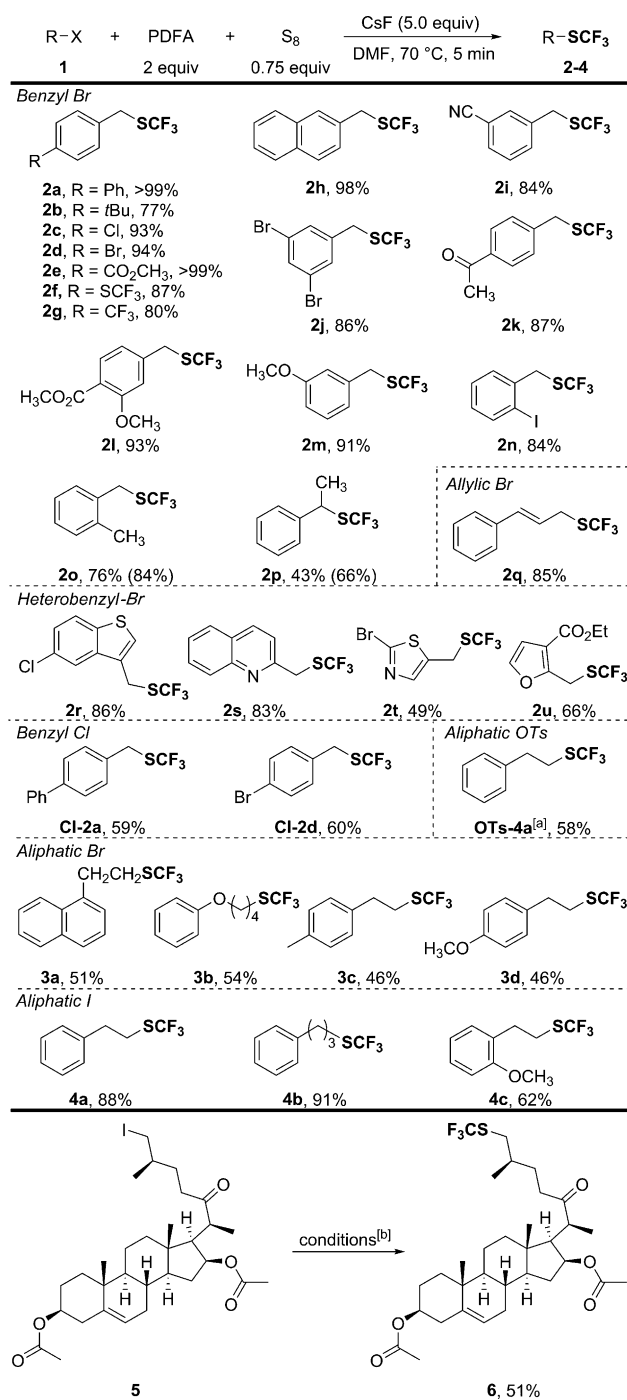
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201505446>.

trifluoromethylthio anion (CF_3S^-),^[8c] we speculated that the reaction of difluorocarbene with fluoride in the presence of elemental sulfur may give the trifluoromethylthio anion, which is a key intermediate for a trifluoromethylthiolation reaction. This trifluoromethylthiolation protocol would sequentially construct $\text{F}-\text{CF}_2$, $\text{S}-\text{CF}_3$, and $\text{C}-\text{SCF}_3$ bonds, and involve the use of external fluoride for the formation of the CF_3S functionality. Even with the time constraint of PET radiochemistry, if the reaction occurs fast enough, this trifluoromethylthiolation strategy may be applicable in ^{18}F -labeled trifluoromethylthiolation. Herein we describe the first trifluoromethylthiolation and [^{18}F]trifluoromethylthiolation of alkyl electrophiles with in situ generated difluorocarbene in the presence of elemental sulfur and an external fluoride ion under transition-metal-free conditions (Scheme 1c).

We have previously shown that difluoromethylene phosphobetaine ($\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$; PDFA) is an efficient difluorocarbene reagent.^[12b,13] It can produce difluorocarbene in situ after decarboxylation of the phosphonium ylide $\text{Ph}_3\text{P}^+\text{CF}_2^-$ ^[14] under neutral conditions without the addition of any other additive or base. Given the operational simplicity and mild reaction conditions for the generation of difluorocarbene, PDFA was used to verify our trifluoromethylthiolation strategy. After screening various reaction conditions for trifluoromethylthiolation (see Table S1 in the Supporting Information), we found that the reactions employing CsF as the fluoride source occurred rapidly and quantitatively at 70°C, and is very attractive for the transition into radiolabeling with short-lived isotopes, such as fluorine-18. Notably no transition metal is necessary for these transformations.

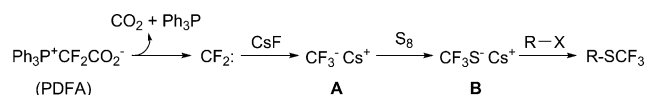
As shown in Scheme 2, the current method shows a wide substrate scope and high level of functional-group tolerance. An array of benzyl bromides were converted smoothly into the desired products in moderate to excellent yields (43–99% yields; **2a–p**). Electron-donating or electron-withdrawing substituents on the arene had no effect on reaction yields (**2a–o**). In addition to primary benzyl bromides, a secondary bromide was also found to be reactive under these reaction conditions (**2p**). It is worthy of note that low yields of the isolated **2o** and **2p** were mainly due to their high volatility. The transformation is applicable to allylic (**2q**) and several functionalized heterocycles (**2r–t**) with good to excellent yields (49–86%). Benzyl chlorides (**2a_{Cl}** and **2d_{Cl}**) were also successfully converted into the desired SCF_3 products, albeit in lower yields (59% and 60%, respectively) compared to those obtained with benzyl bromides, and it is partially attributed to the inferior leaving-group ability. Moderate yields (46–58%) were obtained for the transformation of aliphatic bromides and tosylate (**3a–d**, **4a_{TsO}**) although these substrates are less reactive than their benzyl counterparts. In the cases of aliphatic iodides, the desired products were obtained in 62–91% yields (**4a–c**). Trifluoromethylthiolation of the steroid **5** proceeded smoothly to provide the corresponding product **6** in 51% yield with no evidence of epimerization.

Based on the previous reports, it seems that this reaction may proceed through the following process (Scheme 3). Decarboxylation of PDFA releases triphenylphosphine and generates difluorocarbene in situ.^[13a] Difluorocarbene is read-



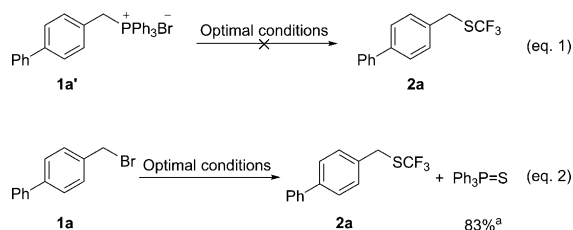
Scheme 2. Trifluoromethylthiolation of benzyl and alkyl electrophiles. Reaction conditions: **1** (0.2 mmol), PDFA (0.4 mmol), S_8 (0.15 mmol), CsF (1.0 mmol), DMF (1.5 mL), 70°C, 5 min. Yields are those of the isolated products. The yields within parentheses were determined by ^{19}F NMR spectroscopy with the use of trifluoromethylbenzene as an internal standard. [a] Reaction conditions: $\text{PhCH}_2\text{CH}_2\text{OTs}$ (0.2 mmol), PDFA (0.4 mmol), S_8 (0.15 mmol), CsF (1.0 mmol), $t\text{Bu}_4\text{NI}$ (0.1 mmol), DMF (1.5 mL), 70°C, 20 min. [b] Reaction conditions: **5** (0.025 mmol), PDFA (0.05 mmol), S_8 (0.02 mmol), CsF (0.125 mmol), DMF (1.0 mL), 70°C, 5 min. DMF = *N,N*-dimethylformamide.

ily trapped by cesium fluoride to produce the trifluoromethyl anion **A**, followed by the formation of the trifluoromethylthio anion **B** in the presence of elemental sulfur. The nucleophilic



Scheme 3. Proposed reaction mechanism.

substitution between **B** and an alkyl electrophile furnishes the final product. The final step for the reaction between **B** and the electrophile should proceed by direct nucleophilic substitution without the occurrence of quarternization of triphenylphosphine, since the phosphonium **1a'** was unreactive under the optimal reaction conditions (Scheme 4a). As a side reaction, triphenylphosphine and elemental sulfur undergo redox reaction to give triphenylphosphine sulfide in 83 % yield for the trifluoromethylthiolation of substrate **1a** (Scheme 4b).



Scheme 4. The attempts at trifluoromethylthiolation of benzyl phosphonium bromide. [a] Yield of isolated product based on PDFA.

The conceptual advantage of CF_3S formation by exogenous fluoride ion makes this methodology potentially useful in the direct radiolabeling of $[\text{F}^{18}]$ trifluoromethylthio groups. Our initial radiochemical studies commenced with the replacement of CsF with azeotropically dried $[\text{F}^{18}]\text{KF}/\text{K}_{222}$ under optimal nonradioactive reaction conditions (Table 1 and see Table S2 in the Supporting Information). We utilized 4-phenylbenzyl bromide as a model substrate and found that the desired product $[\text{F}^{18}]\text{2a}$ was formed in 55 % radiochemical

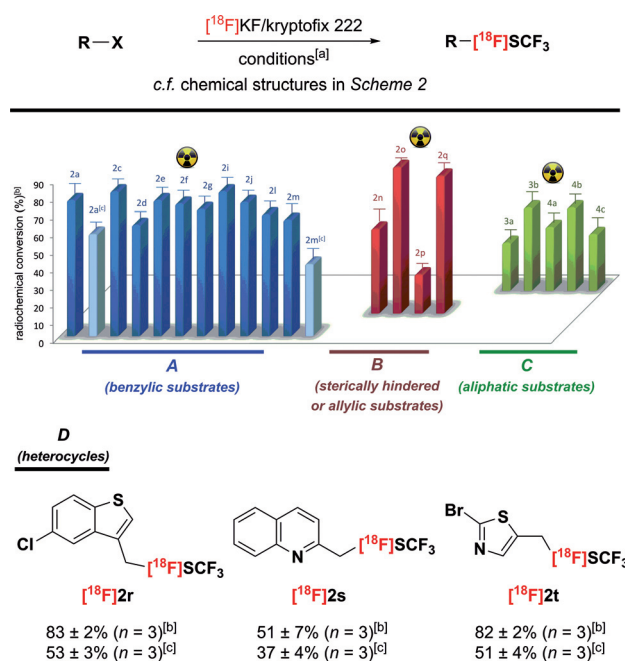
Table 1: Optimization of the $[\text{F}^{18}]$ trifluoromethylthiolation reaction conditions.

Entry	Reagents (equiv)		DMF (mL)	<i>t</i> [min]	RCC [%] ^[a]
	Subst. (mg)	PDFA S ₈			
1	2	2	0.75	0.4	55 ± 3 (<i>n</i> = 3)
2	2	0.5	1.0	0.4	61 ± 4 (<i>n</i> = 3)
3	2	0.5	1.25	0.4	64 ± 2 (<i>n</i> = 3)
4	2	0.5	1.5	0.4	72 ± 7 (<i>n</i> = 3)
5	2	0.5	1.5	0.4	77 ± 6 (<i>n</i> = 3)
6	2	0.5	1.5	0.4	72 ± 5 (<i>n</i> = 3)
7	2	0.5	1.5	0.4	71 ± 1 (<i>n</i> = 3)
8	2	0.5	1.5	0.4 ^[b]	25 ± 1 (<i>n</i> = 3)
9	2	0.5	1.5	0.4 ^[c]	7 ± 3 (<i>n</i> = 3)
10	2	0.5	1.5	0.4 ^[d]	4 ± 1 (<i>n</i> = 3)

[a] Incorporation yield and product identity were determined by radioTLC and radioHPLC, respectively. [b] 1 % water in reaction mixture. [c] 3 % water in reaction mixture. [d] 5 % water in reaction mixture.

conversion (entry 1). Further optimization of the stoichiometries of the precursor, PDFA, and elemental sulfur increased the incorporation yield to 72 % (entries 2–4). The formation of the aliphatic $[\text{F}^{18}]\text{SCF}_3$ was very rapid and was completed in 77 % yield within 1 minute (entries 5–7), which is ideal for short-lived fluorine-18. $[\text{F}^{18}]\text{Tetraethylammonium fluoride}$ and $[\text{F}^{18}]\text{CsF}$ provided inferior yields of 29–53 % compared with that of $[\text{F}^{18}]\text{KF}/\text{K}_{222}$, and an increased amount of $\text{K}_2\text{CO}_3/\text{K}_{222}$ during ^{18}F drying gave the expected product but in low yield (32–65 %; see Table S2). The addition of 1–5 % water led to a dramatic reduction in conversion yields (as low as 4 %, entries 8–10). After thorough optimization of the radioactive reaction conditions, we identified that the combination of substrate, PDFA, and S_8 (molar ratio of 1:0.5:1.5) and $[\text{F}^{18}]\text{KF}/\text{K}_{222}$ in DMF at 70 °C provided the optimal outcome (entry 5).

As illustrated in Scheme 5, this new protocol allowed direct incorporation of $[\text{F}^{18}]\text{CF}_3\text{S}$ into a broad range of aliphatic moieties and the transformation was tolerated with a variety of functional groups, including ester, cyano, aryl halide, ether, and thioether moieties. Analogous to reaction outcomes in nonradioactive conditions, electron-rich and electron-deficient substituents on aromatic rings did not influence the radiochemical yield (Scheme 5a). While *ortho*-substituted arenes had little or no effect on the radiochemical incorporations, secondary halides were found to be less reactive than their primary counterparts (Scheme 5b). The $[\text{F}^{18}]$ trifluoromethylthiolation was also suitable for the transformation of aliphatic and allylic halides (Scheme 5c). For



Scheme 5. Difluorocarbene-mediated $[\text{F}^{18}]$ trifluoromethylthiolation of aliphatic halides. [a] Reaction conditions: Precursor (0.008 mmol), PDFA (1.5 mg), S_8 (3.0 mg), DMF (0.4 mL), 70 °C, 1 min. [b] Incorporation yield and product identity were determined by radioTLC and radioHPLC, respectively. [c] Radiochemical yield of the isolated product was reported as decay noncorrected with radiochemical purity of > 95 %. The isolation was performed by solid-phase extraction.

proof of concept, several CF₃S-bearing heterocycles, including quinolone, benzothiophene, and thiazole were radiolabeled and isolated in 37–53% yields with greater than 95% radiochemical purity (Scheme 5 d). The specific activity of the quinoline **2s** was determined to be about 21 mCi μmol⁻¹ at the end of synthesis (see the Supporting Information for details), which is comparable with the recently reported aryl-[¹⁸F]CF₃^[5a] and aryl-[¹⁸F]SCF₃ labeling.^[15]

In summary, we have successfully developed an efficient, fast, and transition-metal-free trifluoromethylthiolation method with a wide substrate scope and applicability. This strategy has been successfully applied to [¹⁸F]trifluoromethylthiolation of alkyl electrophiles, and is the first example of [¹⁸F]CF₃S labeling. Rapid reaction time (≤1 min), operational simplicity, and exogenous addition of [¹⁸F]fluoride for the formation of [¹⁸F]CF₃S make this method suitable for a wide range of complex and heterocyclic functionalities with high radiochemical yields, as well as useful for radiolabeling of CF₃S-bearing pharmaceuticals.

Acknowledgements

This work was financially supported by the National Natural Science Foundation (21032006, 21172240, 21421002, 21472222, 21502214), National Basic Research Program of China (2015CB931900, 2012CBA01200), and the Chinese Academy of Sciences (XDA02020105, XDA02020106). We thank Professor Jinbo Hu for helpful discussion. S.H.L. is a recipient of an NIH career development award.

Keywords: carbenes · fluorine · isotopic labeling · positron emission tomography · sulfur

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 13236–13240
Angew. Chem. **2015**, *127*, 13434–13438

- [1] a) J. S. Fowler, A. P. Wolf, *Acc. Chem. Res.* **1997**, *30*, 181–188; b) M. E. Phelps, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9226–9233; c) *Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals* (Eds.: A. Tressaud, G. Haufe), Elsevier, Amsterdam, **2008**; d) T. J. Wadas, E. H. Wong, G. R. Weisman, C. J. Anderson, *Chem. Rev.* **2010**, *110*, 2858–2902; e) S. L. Pimlott, A. Sutherland, *Chem. Soc. Rev.* **2011**, *40*, 149–162; f) L. Zhu, K. Ploessl, H. F. Kung, *Chem. Soc. Rev.* **2014**, *43*, 6683–6691.
- [2] a) S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501–1516; b) L. Cai, S. Lu, V. W. Pike, *Eur. J. Org. Chem.* **2008**, 2853–2873; c) P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, *Angew. Chem. Int. Ed.* **2008**, *47*, 8998–9033; *Angew. Chem.* **2008**, *120*, 9136–9172.
- [3] a) M. Tredwell, V. Gouverneur, *Angew. Chem. Int. Ed.* **2012**, *51*, 11426–11437; *Angew. Chem.* **2012**, *124*, 11590–11602; b) R. Littich, P. J. H. Scott, *Angew. Chem. Int. Ed.* **2012**, *51*, 1106–1109; *Angew. Chem.* **2012**, *124*, 1132–1135; c) S. H. Liang, N. Vasdev, *Angew. Chem. Int. Ed.* **2014**, *53*, 11416–11418; *Angew. Chem.* **2014**, *126*, 11600–11602; d) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci.* **2014**, *5*, 4545–4553; e) M. G. Campbell, T. Ritter, *Chem. Rev.* **2015**, *115*, 612–633.
- [4] For recent reviews, see ref. [3]. For most recent work, see: a) B. H. Rotstein, N. A. Stephenson, N. Vasdev, S. H. Liang, *Nat. Commun.* **2014**, *5*, 4365; b) T. J. A. Graham, R. F. Lambert, K. Ploessl, H. F. Kung, A. G. Doyle, *J. Am. Chem. Soc.* **2014**, *136*, 5291–5294; c) 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; d) J. Cardinale, J. Ermert, S. Humpert, H. H. Coenen, *RSC Adv.* **2014**, *4*, 17293–17299; e) E. Emer, J. Twilton, M. Tredwell, S. Calderwood, T. L. Collier, B. Liégault, M. Taillefer, V. Gouverneur, *Org. Lett.* **2014**, *16*, 6004–6007; f) N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford, P. J. H. Scott, *Org. Lett.* **2014**, *16*, 3224–3227; g) N. A. Stephenson, J. P. Holland, A. Kassenbrock, D. L. Yokell, E. Livni, S. H. Liang, N. Vasdev, *J. Nucl. Med.* **2015**, *56*, 489–492; h) X. Huang, W. Liu, J. M. Hooker, J. T. Groves, *Angew. Chem. Int. Ed.* **2015**, *54*, 5241–5245; *Angew. Chem.* **2015**, *127*, 5330–5334; i) K. Sander, T. Gendron, E. Yiannaki, K. Cybulska, T. L. Kalber, M. F. Lythgoe, E. Arstad, *Sci. Rep.* **2015**, *5*, 9941; j) L. Wang, O. Jacobsen, D. Avdic, B. H. Rotstein, I. D. Weiss, L. Collier, X. Chen, N. Vasdev, S. H. Liang, *Angew. Chem. Int. Ed.* **2015**, *54*, DOI: 10.1002/anie.201505927.
- [5] a) M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur, J. Passchier, *Nat. Chem.* **2013**, *5*, 941–944; b) P. Ivashkin, G. Lemonnier, J. Cousin, V. Grégoire, D. Labar, P. Jubault, X. Pannecoucke, *Chem. Eur. J.* **2014**, *20*, 9514–9518; c) T. Rühl, W. Rafique, V. T. Lien, P. J. Riss, *Chem. Commun.* **2014**, *50*, 6056–6059; d) 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.
- [6] a) A. Leo, P. Y. C. Jow, C. Silipo, C. Hansch, *J. Med. Chem.* **1975**, *18*, 865–868; b) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
- [7] X. H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731–764.
- [8] For recent examples, see: a) C. Pooput, M. Medebielle, W. R. Dolbier, *Org. Lett.* **2004**, *6*, 301–303; b) C.-P. Zhang, D. A. Vivic, *J. Am. Chem. Soc.* **2012**, *134*, 183–185; c) F. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.* **2012**, *51*, 10382–10385; *Angew. Chem.* **2012**, *124*, 10528–10531; d) C. Chen, L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454–12457; e) Y. Yang, X. Jiang, F.-L. Qing, *J. Org. Chem.* **2012**, *77*, 7538–7547; f) S. Alazet, L. Zimmer, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 10814–10817; *Angew. Chem.* **2013**, *125*, 11014–11017; g) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 12856–12859; *Angew. Chem.* **2013**, *125*, 13093–13097; 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; i) A. Tlili, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 6818–6819; *Angew. Chem.* **2013**, *125*, 6952–6954; j) X. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 12860–12864; *Angew. Chem.* **2013**, *125*, 13098–13102; k) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548–1552; *Angew. Chem.* **2013**, *125*, 1588–1592; l) X. Shao, T. Liu, L. Lu, Q. Shen, *Org. Lett.* **2014**, *16*, 4738–4741; m) J. Xu, X. Mu, P. Chen, J. Ye, G. Liu, *Org. Lett.* **2014**, *16*, 3942–3945; n) K.-Y. Ye, X. Zhang, L.-X. Dai, S.-L. You, *J. Org. Chem.* **2014**, *79*, 12106–12110; o) S. Guo, X. Zhang, P. Tang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4065–4069; *Angew. Chem.* **2015**, *127*, 4137–4141; p) J. Lim, J. Pyun, K. Char, *Angew. Chem. Int. Ed.* **2015**, *54*, 3249–3258; *Angew. Chem.* **2015**, *127*, 3298–3308; q) J.-B. Liu, X.-H. Xu, Z.-H. Chen, F.-L. Qing, *Angew. Chem. Int. Ed.* **2015**, *54*, 897–900; *Angew. Chem.* **2015**, *127*, 911–914; r) H. Wu, Z. Xiao, J. Wu, Y. Guo, J.-C. Xiao, C. Liu, Q.-Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 4070–4074; *Angew. Chem.* **2015**, *127*, 4142–4146; s) G. Yin, I. Kalvet, U. Englert, F. Schoenebeck, *J. Am. Chem. Soc.* **2015**, *137*, 4164–4172; t) G. Yin, I. Kalvet, F. Schoenebeck, *Angew.*

- Chem. Int. Ed.* **2015**, *54*, 6809–6813; *Angew. Chem.* **2015**, *127*, 6913–6917.
- [9] a) 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; b) Y. Huang, X. He, X. Lin, M. Rong, Z. Weng, *Org. Lett.* **2014**, *16*, 3284–3287.
- [10] a) T. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65–68; b) I. Kiehltsch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.* **2007**, *46*, 754–757; *Angew. Chem.* **2007**, *119*, 768–771.
- [11] For recent reviews, see: a) D. L. S. Brahm, W. P. Dailey, *Chem. Rev.* **1996**, *96*, 1585–1632; b) D. Burton, Z.-Y. Yang, W. Qiu, *Chem. Rev.* **1996**, *96*, 1641–1716; c) W. R. Dolbier, M. A. Battiste, *Chem. Rev.* **2003**, *103*, 1071–1098; d) C. Ni, J. Hu, *Synthesis* **2014**, 842–863; For recent examples, see: e) F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.* **2011**, *50*, 7153–7157; *Angew. Chem.* **2011**, *123*, 7291–7295; f) P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 2092–2095; *Angew. Chem.* **2013**, *125*, 2146–2149; g) V. V. Levin, A. A. Zemtsov, M. I. Struchkova, A. D. Dilman, *Org. Lett.* **2013**, *15*, 917–919; h) L. Li, F. Wang, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12390–12394; *Angew. Chem.* **2013**, *125*, 12616–12620; i) G. M. Lee, D. J. Harrison, I. Korobkov, R. T. Baker, *Chem. Commun.* **2014**, *50*, 1128–1130; j) G. K. S. Prakash, S. Krishnamoorthy, S. K. Ganesh, A. Kulkarni, R. Haiges, G. A. Olah, *Org. Lett.* **2014**, *16*, 54–57; k) V. V. Levin, A. A. Zemtsov, M. I. Struchkova, A. D. Dilman, *J. Fluorine Chem.* **2015**, *171*, 97–101; l) M. D. Kosobokov, V. V. Levin, M. I. Struchkova, A. D. Dilman, *Org. Lett.* **2015**, *17*, 760–763.
- [12] a) X. Deng, J. Lin, J. Zheng, J. Xiao, *Chin. J. Chem.* **2014**, *32*, 689–693; b) J. Zheng, J. H. Lin, X. Y. Deng, J. C. Xiao, *Org. Lett.* **2015**, *17*, 532–535.
- [13] a) J. Zheng, J.-H. Lin, J. Cai, J.-C. Xiao, *Chem. Eur. J.* **2013**, *19*, 15261–15266; b) X.-Y. Deng, J.-H. Lin, J. Zheng, J.-C. Xiao, *Chem. Commun.* **2015**, *51*, 8805–8808.
- [14] a) J. Zheng, J. Cai, J.-H. Lin, Y. Guo, J.-C. Xiao, *Chem. Commun.* **2013**, *49*, 7513–7515; b) Y. Qiao, T. Si, M.-H. Yang, R. A. Altman, *J. Org. Chem.* **2014**, *79*, 7122–7131; c) V. V. Levin, A. L. Trifonov, A. A. Zemtsov, M. I. Struchkova, D. E. Arkhipov, A. D. Dilman, *Org. Lett.* **2014**, *16*, 6256–6259.
- [15] While the manuscript was under review, an article entitled “¹⁸F-Labeling of Aryl-SCF₃, -OCF₃ and -OCHF₂ with [¹⁸F]Fluoride” was published in this journal: T. Khotavivattana, S. Verhoog, M. Tredwell, L. Pfeifer, S. Calderwood, K. Wheelhouse, T. Lee Collier, V. Gouverneur, *Angew. Chem. Int. Ed.* **2015**, *54*, 9991–9995; *Angew. Chem.* **2015**, *127*, 10129–10133.

Received: June 13, 2015

Revised: July 7, 2015

Published online: September 21, 2015