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Difluorocarbene-derived Trifluoromethylthiolation and [^{18}F]Trifluoromethylthiolation of Aliphatic Electrophiles

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Abstract

The first trifluoromethylthiolation and [^{18}F]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 variety of functional groups and operated under mild conditions. The conceptual advantage of this exogenous fluoride mediated transformation enables unprecedented syntheses of [^{18}F]CF_3S-labeled molecules from most commonly used [^{18}F]fluoride ion. The rapid radiochemical reaction time (≤ 1 min) and highly functional group tolerance allow this method to access a variety of aliphatic [^{18}F]CF_3S compounds in high yields.

Keywords

trifluoromethylthiolation; difluorocarbene; fluorine-18; positron emission tomography; metal free

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As 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 (^{18}F) is the most commonly used radionuclide because of its relatively long half-life of 109.7 min, high-yielding production and high specific activity, importance of fluorine substitution as isotopologue in drug discovery, and extensive clinical use of [^{18}F]FDG (2-[^{18}F]fluoro-2-deoxy-*D*-glucose).[2] Therefore, significant efforts have been devoted to the exploration of novel and efficient methodologies for ^{18}F-incorporation into small or biological molecules.[3] However, approaches in ^{18}F-radiochemistry have so far been mostly limited to [^{18}F]fluorination[4] and [^{18}F]trifluoromethylation.[5] Despite the fact that trifluoromethylthio group (CF_3S) is a valuable pharmacophore in medicinal chemistry and drug discovery,[6] the formation of [^{18}F]CF_3S moiety has never been realized and thus represents a significant challenge in the field.

Recently, outstanding accomplishments have been made for the incorporation of CF_3S group via non-radioactive methods.[7] Two general strategies have been well established, including direct trifluoromethylthiolation by constructing C-SCF_3 bond[8] or squential constructing of S-CF_3 and C-SCF_3 bonds[8c, 9] (eq. 1, Scheme 1), and trifluoromethylation of sulfur-containing compounds to form RS-CF_3 bond[10] (eq. 2, Scheme 1). In both strategies, CF_3S scaffold are derived from CF_3S- or CF_3-containing reagents without the involvement of external fluoride, which makes it not applicable or difficult for translation into ^{18}F-radiolabeling. In particular, [^{18}F]trifluoromethylthiolation which involves the use of most readily available [^{18}F]fluoride for the formation of [^{18}F]CF_3S group is a promising strategy, but to date no convenient trifluoromethylthiolation reaction employs external fluoride to construct CF_3S moiety. It is an urgent and unmet need to explore efficient methods for fast trifluoromethylthiolation in which exogenous fluoride is involved and make the [^{18}F]trifluoromethylthiolation possible.

Difluorocarbene has served as a powerful reaction intermediate in organic synthesis.[11] On the basis of our previous studies that difluorocarbene can be readily trapped by fluoride to generate trifluoromethyl anion (CF_3^-)[12] and the recent studies that trifluoromethyl anion can react with elemental sulfur (S_8) to produce trifluoromethylthio anion (CF_3S^-),[8c] we speculated that the reaction of difluorocarbene with fluoride in the presence of elemental sulfur may give trifluoromethylthio anion, which is a key intermediate for trifluoromethylthiolation reaction. This trifluoromethylthiolation protocol would sequentially construct F-CF_2, S-CF_3 and C-SCF_3 bonds, and involve the use of external fluoride for the formation of CF_3S functionality. Due to the time constraint of PET radiochemistry, if the reaction occurs fast enough, this trifluoromethylthiolation strategy may be able to be applied 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 external fluoride ion under transition metal-free conditions (eq. 3, Scheme 1).

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We have previously shown that difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA) is an efficient difluorocarbene reagent.[12b, 13] It can *in situ* produce difluorocarbene after decarboxylation of phosphonium ylide $Ph_3P^+CF_2^-$[14] under neutral conditions without the addition of any other additive or base. Attributed to operational simplicity and and mild reaction conditions for the generation of difluorocarbene, PDFA was used to verify our trifluoromethylthiolation strategy. After screening various reaction conditions for trifluoromethylthiolation (Table S1 in the supporting information), we found that the reactions employing CsF as the fluoride source occurred rapidly and quantitatively at 70 °C, which is very attractive for 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 showed a wide substrate scope and high level of functional group tolerance. An array of benzyl bromides were converted smoothly into desired products in moderate to excellent yields (43%–99% yields, **2a–2p**). Electron-donating or -withdrawing substituents on the arene had no effect on reaction yields (**2a–2o**). In addition to primary benzyl bromides, a secondary bromide was also found to be reactive under these conditions (43%, **2p**). It was worthy of note that low isolated yields of **2o** and **2p** were mainly due to their high volatility. The transformation is applicable to allylic (85%, **2q**) and several well-functionalized heterocycles (**2r–2t**) with good to excellent yields (49–86%). Benzyl chlorides (**Cl-2a** and **Cl-2d**) were also successfully converted to desired SCF_3 products in lower yields (59% and 60%, respectively) compared with benzyl bromides, partially attributed to inferior leaving group ability. Moderate yields (46%–58%) were obtained for the transformation of aliphatic bromides and tosylate (**3a–3d, TsO-4a**) although these substrates are less reactive than their benzyl counterparts. In the cases of aliphatic iodides, desired products were obtained in 62%–91% yields (**4a–4c**). Trifluoromethylthiolation of 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 readily trapped by cesium fluoride to produce trifluoromethyl anion **A**, followed by the formation of trifluoromethylthio anion **B** in the presence of elemental sulfur. The nucleophilic substitution between anion **B** and alkyl electrophile furnishes the final product.

The final step for the reaction between intermediate **B** and alkyl electrophile should proceed via direct nucleophilic substitution without the occurrence of quarternization of triphenylphosphine since phosphonium **1a'** was unreactive under the optimal reaction conditions (eq. 1, Scheme 4). As a side reaction, triphenylphosphine and elemental sulfur underwent redox reaction to give triphenylphosphine sulfide in 83% yield for the trifluoromethylthiolation of substrate **1a** (eq. 2, Scheme 4).

The conceptual advantage of CF_3S formation via exogenous fluoride ion makes this methodology potentially useful in the direct radiolabeling of [^{18}F]trifluoromethylthio groups. Our initial radiochemical studies commenced with replacement of CsF with azeotropically dried [^{18}F]KF/K_{222} under optimal non-radioactive reaction conditions (Table

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1 and supplementary Table S2). We utilized 4-phenylbenzyl bromide as a model substrate and found the desired product **[^{18}F]2a** was formed in 55% radiochemical conversion (entry 1, Table 1). Further optimization of stoichiometry among precursor, PDFA and elemental sulfur increased incorporation yield to 72% (entries 2–4). The formation of aliphatic [^{18}F]SCF_3 was very rapid and can be completed in 77% yield within 1 min (entries 5–7), which is ideal for short-lived fluorine-18. [^{18}F]Tetraethylammonium fluoride and [^{18}F]CsF provided inferior yields of 29%–53% compared with [^{18}F]KF/K_{222}, and increased amount of K_2CO_3/K_{222} during ^{18}F drying gave the expected product yet in low yields (32%–65%, supplementary 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 the combination of substrate, PDFA and S_8 (molar ratio of 1: 0.5: 1.5) and [^{18}F]KF/K_{222} in DMF at 70 °C provided the optimal outcome (entry 5).

As illustrated in Scheme 5, this new protocol allowed us for direct incorporation of [^{18}F]CF_3S 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. Analogous to reaction outcomes in non- radioactive conditions, electron-rich and deficient substituents on aromatic ring did not influence the radiochemical yield (Scheme 5A). While *ortho*-substituted arenes had little or no effect on the radiochemical incorporations, secondary halides was found to be less reactive than primary counterparts (Scheme 5B). The [^{18}F]trifluoromethylthiolation was also suitable for the transformation of aliphatic and allylic halides (Scheme 5C). For proof of concept, several CF_3S-bearing heterocycles, including quinolone, benzothiophene and thiazole were radiolabeled and isolated in 37–53% yields with greater than 95% radiochemical purity (Scheme 5D). The specific activity of quinoline **2s** was determined to be *ca.* 21 mCi/μmol at the end of synthesis (see supporting information for details), which is comparable with the recently reported Aryl-[^{18}F]CF_3[5a] and Aryl-[^{18}F]SCF_3 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 [^{18}F]trifluoromethylthiolation of alkyl electrophiles, which is the first example for [^{18}F]CF_3S labeling. Rapid reaction time (≤ 1 min), operational simplicity and exogenous addition of [^{18}F]fluoride for the formation of [^{18}F]CF_3S make this method suitable for a wide range of complex and heterocyclic functionalities with high radiochemical yields, as well as useful for radiolabeling of CF_3S-bearing pharmaceuticals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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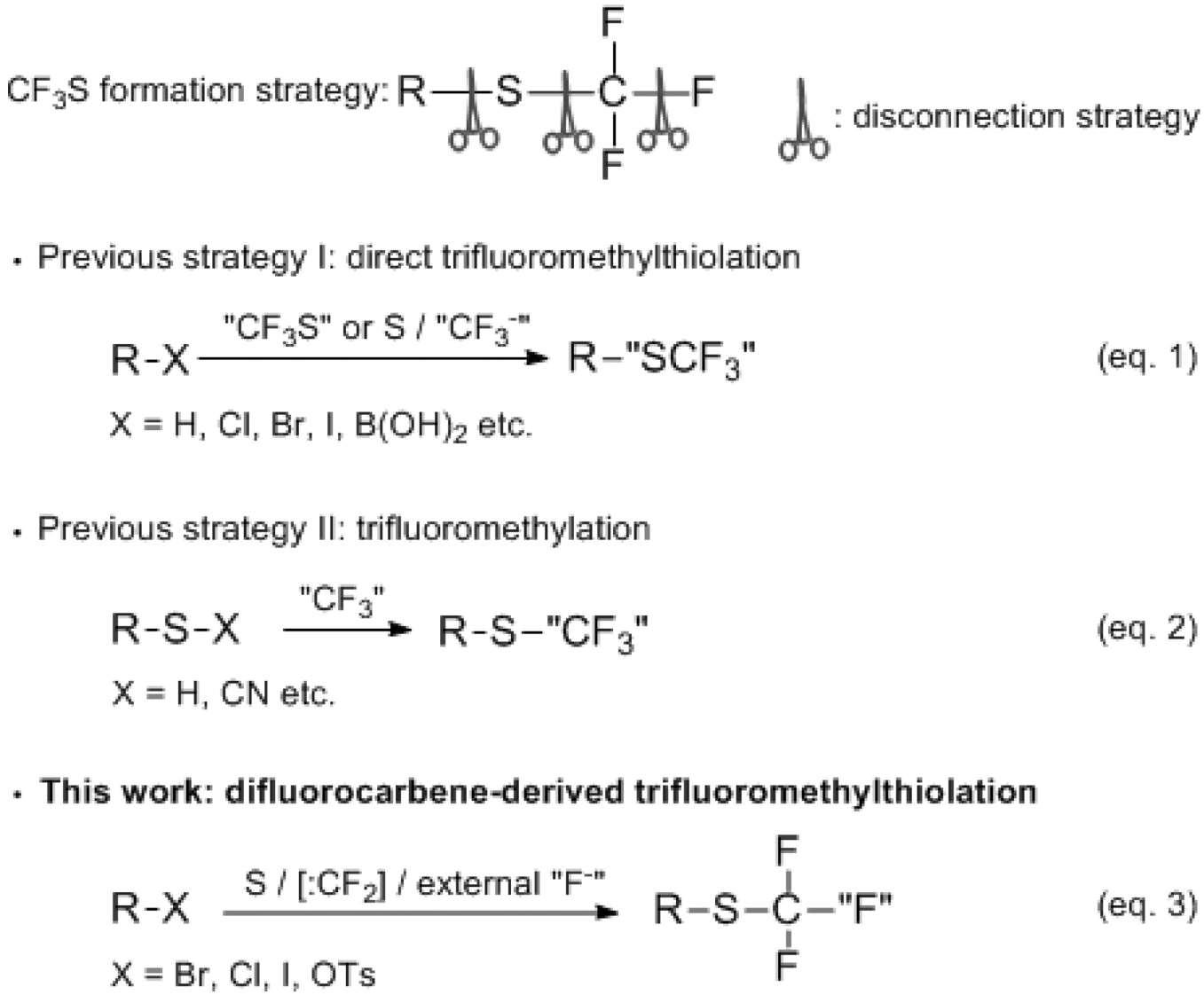

Scheme 1.
Bond formation strategies of trifluoromethylthio (CF_3S) group.

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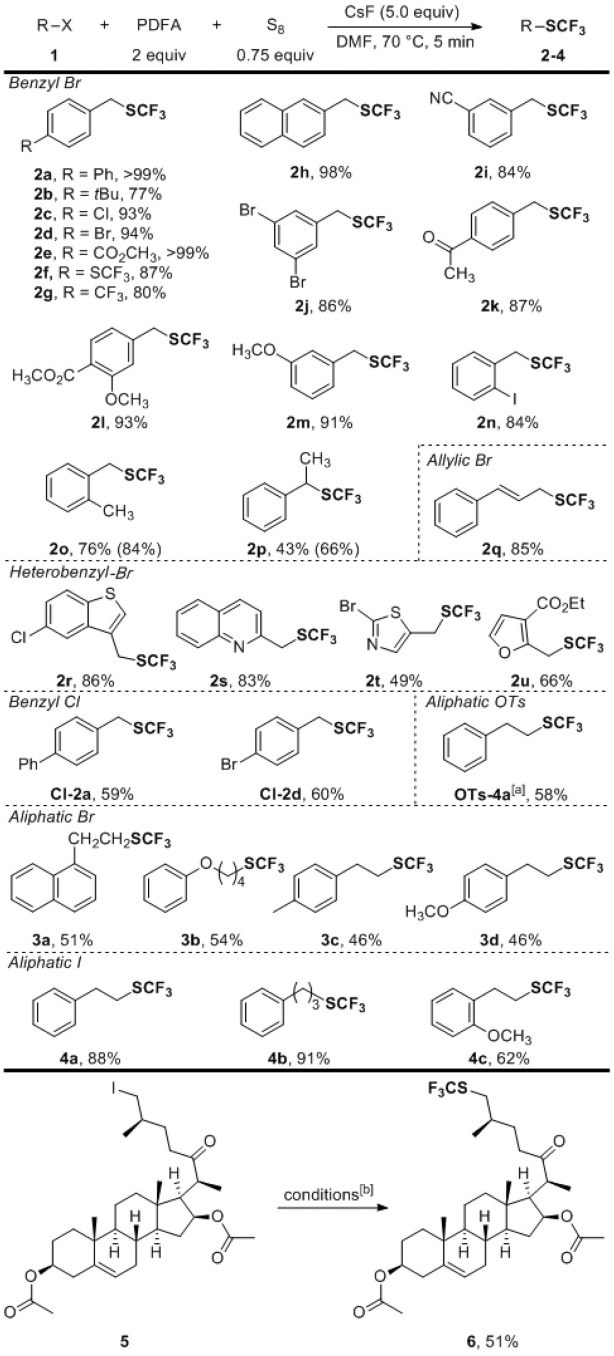

Scheme 2.

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, 5min. Yields were that of the isolated products. The yields in parentheses were determined by ^{19}F NMR with the use of trifluoromethylbenzene as an internal standard. [a] Reaction conditions: $PhCH_2CH_2OTs$ (0.2 mmol), PDFA (0.4 mmol), S_8 (0.15 mmol), CsF (1.0 mmol), $^tBu_4NI$ (0.1 mmol), DMF (1.5 mL), 70 °C, 20min. [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.

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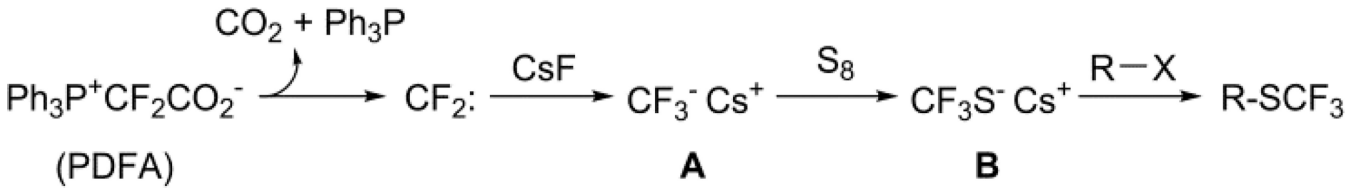

Scheme 3.
Proposed reaction mechanism.

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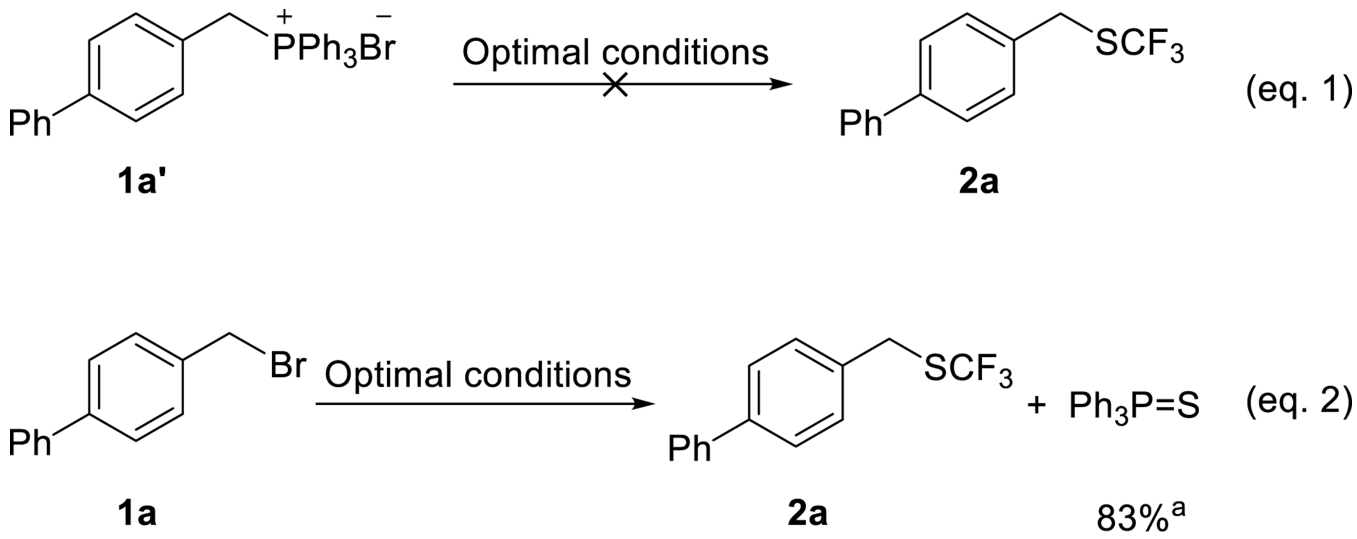

Scheme 4.

The attempts at trifluoromethylthiolation of benzyl phosphonium bromide. [a]Isolated yields based on PDFA.

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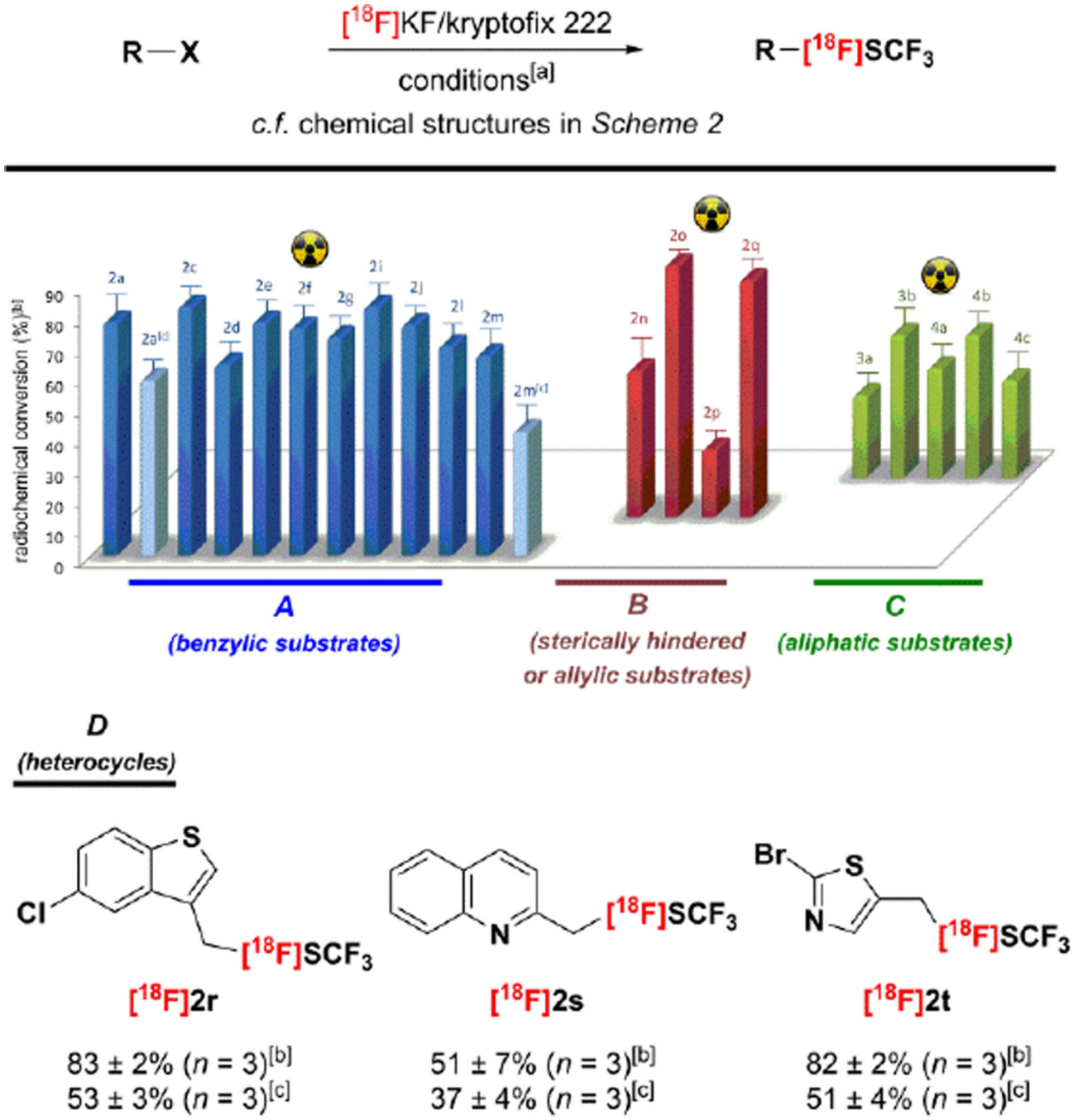

Scheme 5.

Difluorocarbene-mediated [^{18}F]trifluoromethylthiolation of aliphatic halides. Conditions: [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] Isolated radiochemical yield was reported as decay non-corrected with radiochemical purity > 95%. The isolation was performed by solid phase extraction.

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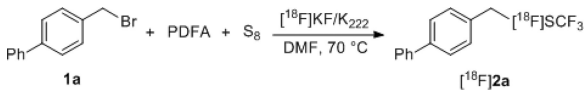
Table 1

Optimization of [^{18}F] trifluoromethylthiolation reaction conditions



1a [^{18}F]2a

Entry	Reagents [equiv]			DMF [mL]	*t* [min]	RCC [%][a]
	Substrate	PDFA	S_8			
1	2 mg	2	0.75	0.4	5	55 ± 3 (n = 3)
2	2 mg	0.5	1.0	0.4	5	61 ± 4 (n = 3)
3	2 mg	0.5	1.25	0.4	5	64 ± 2 (n = 3)
4	2 mg	0.5	1.5	0.4	5	72 ± 7 (n = 3)
5	**2 mg**	**0.5**	**1.5**	**0.4**	**1**	**77 ± 6 (n = 3)**
6	2 mg	0.5	1.5	0.4	3	72 ± 5 (n = 3)
7	2 mg	0.5	1.5	0.4	10	71 ± 1 (n = 3)
8	2 mg	0.5	1.5	0.4[b]	1	25 ± 1 (n = 3)
9	2 mg	0.5	1.5	0.4[c]	1	7 ± 3 (n = 3)
10	2 mg	0.5	1.5	0.4[d]	1	4 ± 1 (n = 3)

[a] Incorporation yield and product identity were determined by radioTLC and radioHPLC, respectively.

[b, c, d] Amount of water in the reaction mixture: 1% for b, 3% for c, and 5% for d.