

# Synthesis and Reactivity of $\alpha$ -Cumyl bromodifluoromethanesulfenate: Application to the Radiosynthesis of [ $^{18}\text{F}$ ]arylSCF<sub>3</sub>

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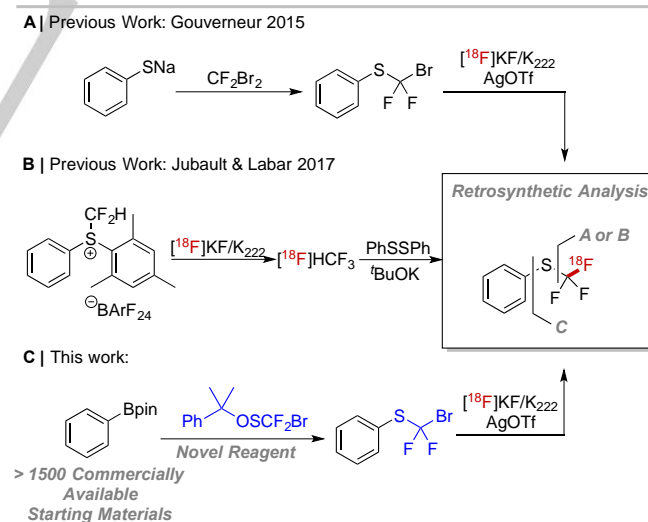
**Abstract:** A novel highly reactive electrophilic bromodifluoromethylthiolating reagent,  $\alpha$ -cumyl bromodifluoromethanesulfenate **1**, was prepared to allow for direct bromodifluoromethylthiolation of aryl boron reagents. This coupling reaction takes place under copper catalysis, and affords a large range of bromodifluoromethylthiolated arenes. These compounds are amenable to various transformations including halogen exchange with [ $^{18}\text{F}$ ]KF/K<sub>222</sub>, a process giving access to [ $^{18}\text{F}$ ]arylSCF<sub>3</sub> from the corresponding aryl boronic pinacol esters.

Positron Emission Tomography (PET) is a leading noninvasive imaging modality enabling the study of physiological processes *in vivo*. The technique has found a wide range of applications in the clinic, and serves as an aid to drug discovery by providing valuable information on the pharmacokinetic and pharmacodynamic properties of lead compounds.<sup>[1]</sup> Among the commonly used positron-emitting isotopes for PET, fluorine-18 is advantageous in part because of its relatively long half-life ( $t_{1/2}$  = 109.7 min).<sup>[2]</sup> As a consequence, considerable efforts have been devoted to the development of efficient methods for the preparation of  $^{18}\text{F}$ -labeled PET radiotracers.<sup>[3]</sup> The majority of  $^{18}\text{F}$ -labeling methods reported to date have focused on the direct [ $^{18}\text{F}$ ]fluorination of pre-functionalized arenes and alkanes,<sup>[4]</sup> while radiosynthetic routes towards  $^{18}\text{F}$ -labeled molecules with functional groups such as [ $^{18}\text{F}$ ]CF<sub>3</sub>,<sup>[5]</sup> [ $^{18}\text{F}$ ]CF<sub>2</sub>H,<sup>[6]</sup> [ $^{18}\text{F}$ ]SCF<sub>3</sub>,<sup>[7,8]</sup> [ $^{18}\text{F}$ ]OCF<sub>2</sub>H<sup>[8b]</sup> and [ $^{18}\text{F}$ ]OCF<sub>3</sub><sup>[8b]</sup> have appeared only more recently. Within this series, the trifluoromethylthiol group (-SCF<sub>3</sub>) has gained much attention in the context of medicinal chemistry due to its beneficial effects on pharmacokinetic and physicochemical properties including metabolic stability and lipophilicity.<sup>[9]</sup>

In 2015, Gouverneur and co-workers reported the first radiosynthetic route towards [ $^{18}\text{F}$ ]arylSCF<sub>3</sub> via halogen exchange (halex) of ArSCF<sub>2</sub>Br with cyclotron-produced  $^{18}\text{F}$ -fluoride (Figure 1A).<sup>[8b]</sup> Two years later, Labar, Jubault and their co-workers described an elegant variant of this approach by reacting various aromatic disulfides with [ $^{18}\text{F}$ ]fluoroform, a reagent generated

from the bench-stable (difluoromethyl)(mesityl)(phenyl) sulfonium salt (Figure 1B).<sup>[10]</sup> These radiosynthetic protocols require either an aryl thiol or diaryl disulfide to enable arylS-CF<sub>3</sub> bond construction. In the present study, our aim was to explore a complementary strategy relying instead on aryl-SCF<sub>3</sub> bond formation (Figure 1C). We opted for a transformation using aryl boron reagents as these commercially or readily available reagents have proved highly valuable for synthesis and more recently for  $^{18}\text{F}$ -radiochemistry as exemplified with late stage  $^{18}\text{F}$ -fluorination or  $^{18}\text{F}$ -trifluoromethylation.<sup>[11]</sup> Herein, we demonstrate that aryl boronic esters can be converted to [ $^{18}\text{F}$ ]SCF<sub>3</sub>-arenes via direct aryl-SCF<sub>2</sub>Br bond construction followed by halex nucleophilic  $^{18}\text{F}$ -fluorination. This new methodology required the design and synthesis of a bespoke bromodifluoromethylthiolation reagent suitable for cross-coupling chemistry. Inspired by studies carried out in the Shen's laboratory on the development of the electrophilic trifluoromethylthiolation reagent  $\alpha$ -cumyltrifluoromethanesulfenate,<sup>[12]</sup> we envisaged that the structurally related bromodifluoromethylthiolation reagent **1** would be a good candidate for coupling with aryl boronic esters. The resulting bromodifluoromethylated arenes would subsequently undergo halogen exchange with [ $^{18}\text{F}$ ]KF,<sup>[8b]</sup> thereby affording [ $^{18}\text{F}$ ]arylSCF<sub>3</sub> from an aryl boron precursor.

**Figure 1.** Strategies for the preparation of [ $^{18}\text{F}$ ]SCF<sub>3</sub>-arenes



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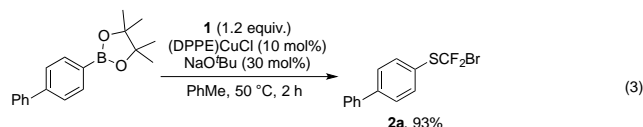
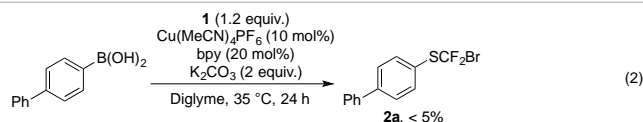
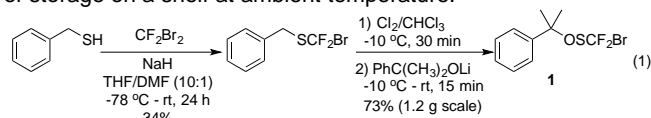
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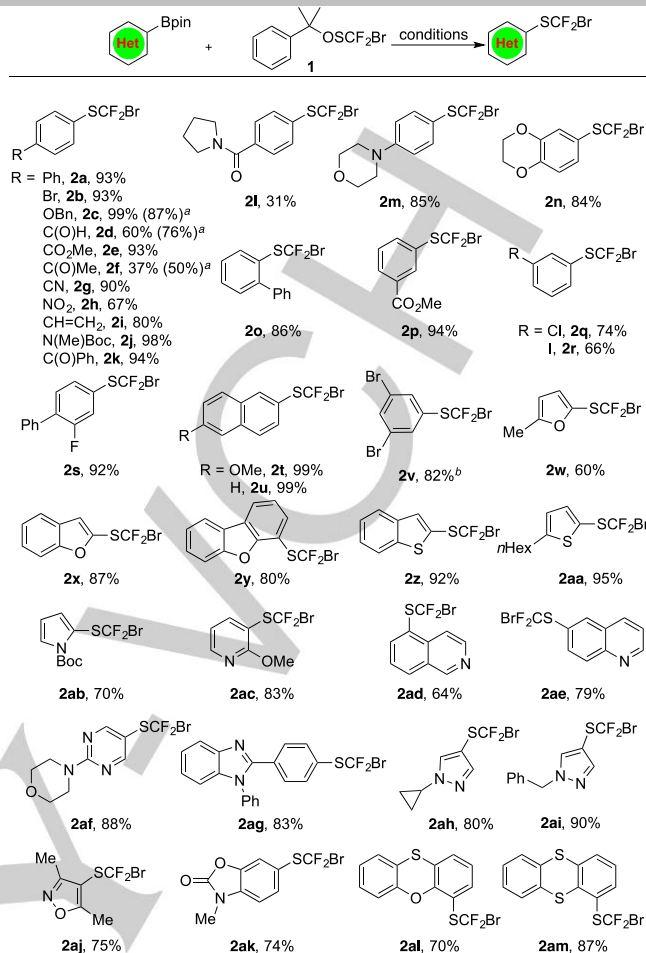
$\alpha$ -Cumyl bromodifluoromethanesulfenate **1** was synthesized via a three-step two-pot process from commercially available starting materials. The reaction of sodium benzylthiolate with CF<sub>2</sub>Br<sub>2</sub> in a mixed solvent THF/DMF (v/v = 10:1) at -78 °C for 24 h afforded benzyl bromodifluoromethylthioether in 34% yield. Benzyl bromodifluoromethylthioether was then treated with a saturated solution of chlorine in CHCl<sub>3</sub> at -10 °C for 30 min, followed by nucleophilic substitution of the *in situ* generated BrCF<sub>2</sub>SCl with lithium 2-phenylpropan-2-olate at room

temperature for 15 min. This protocol gave  $\alpha$ -cumyl bromodifluoromethanesulfonate **1** isolated in 73% yield (Eq. 1). Compound **1** is neither air nor moisture sensitive since no detectable decomposition was observed after more than a week of storage on a shelf at ambient temperature.



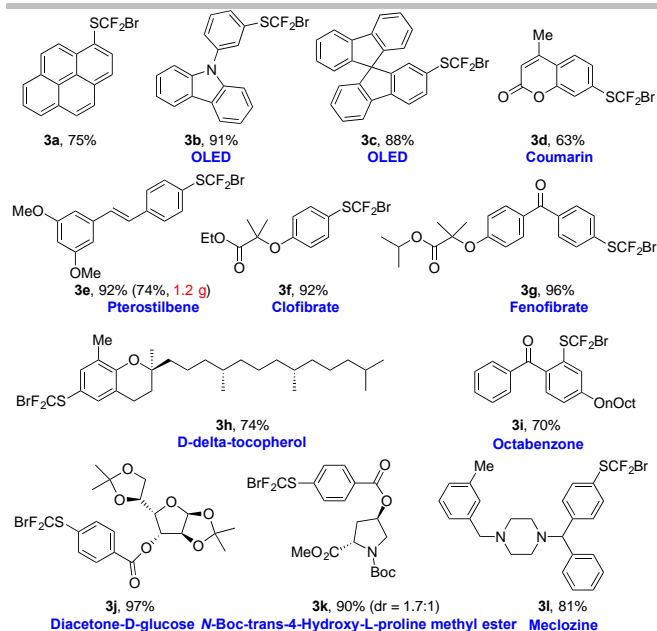
With reagent **1** in hand, we explored its reactivity by examining the bromodifluoromethylthiolation of the model substrate 4-biphenylboronic acid. When applying the reaction conditions previously described for the trifluoromethylthiolation of aryl boronic acids with  $\alpha$ -cumyltrifluoromethanesulfonate (10 mol% Cu(MeCN)<sub>4</sub>PF<sub>6</sub>, 20 mol% bpy, 2.0 equiv. of K<sub>2</sub>CO<sub>3</sub> in diglyme at 35 °C for 24 h),<sup>[13]</sup> the desired bromodifluoromethylated product **2a** was observed but obtained in less than 5% yield (Eq. 2). Attempts to improve the yield of **2a** by varying the copper source and using variously substituted bipyridine ligands were not successful. However, the replacement of the boronic acid with a boronic pinacol ester combined with the use of copper complexes derived from phosphine-based ligands (e.g. Xantphos, DPPE or DPPBz) instead of nitrogen-based ligands led to **2a** in high yield. Specifically, the reaction of pinacol-derived 4-biphenylboronic acid with reagent **1** in the presence of 10 mol% (DPPE)CuCl and 30 mol% NaOtBu in toluene occurred with full conversion after 2 h at 50 °C, and gave **2a** isolated in 93% yield (Eq. 3).<sup>[14]</sup>

We next investigated the scope of the optimized bromodifluoromethylthiolation with a range of (hetero)aryl boronic pinacol esters (Scheme 1). Electron-rich and electron-poor aryl boron reagents reacted with **1** to give the corresponding bromodifluoromethylthiolated arenes in high yields (Scheme 1, **2a-v**). Products with substituents at *ortho*- (**2o**), *meta*- (**2p-s**) or *para*- (**2a-m**) position were also accessible in high yields. Heteroarenes are important structural motifs in pharmaceuticals and agrochemicals, and medicinal chemists have long-standing interest in the preparation of fluoroalkylated heteroarenes. Gratifyingly, our protocol was successfully applied to heteroaryl boron reagents affording the desired bromodifluoromethylthiolated heteroarenes in high yields; this series include furan (**2w**), benzofuran (**2x**), dibenzo[*b,d*]furan (**2y**), benzothiophene (**2z**), thiophene (**2aa**), pyrrole (**2ab**), pyridine (**2ac**), isoquinoline (**2ad**), quinoline (**2ae**), pyrimidine (**2af**), benzo[*d*]imidazole (**2ag**), pyrazole (**2ah-ai**), isoxazole (**2aj**), benzo[*d*]oxazol-2(3*H*)-one (**2ak**), phenoxathiine (**2al**) and thianthrene (**2am**). Furthermore, many functional groups were well tolerated including halogens, aldehyde, enolizable ketone, ester, amide, alkene, *N*-Boc-protected amine, cyano and nitro groups.



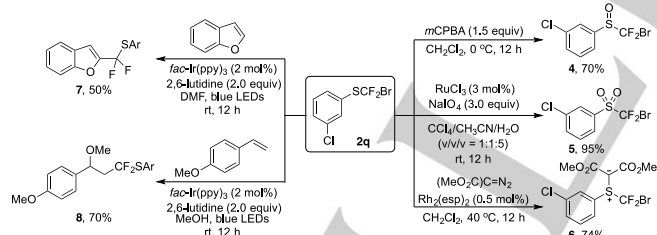
**Scheme 1.** Scope of copper-catalyzed bromodifluoromethylthiolation of (hetero)aryl boronic acid pinacol esters. Reaction conditions: (hetero)aryl boronic pinacol ester (0.50 mmol), bromodifluoromethylthiolation reagent **1** (0.60 mmol), (DPPE)CuCl (10 mol%) and NaOtBu (30 mol%) in 2.5 mL of toluene at 50 °C for 2.0 h under an argon atmosphere. Isolated yields. [a] Aryl boronic acid neopentyl ester was used. [b] The compound was prepared via a one-pot Ir-catalyzed C-H borylation/Cu-catalyzed bromodifluoromethylthiolation process. DPPE = 1,2-Bis(diphenylphosphino)ethane.

To further illustrate the value of this bromodifluoromethylthiolation protocol, we consider target molecules that are relevant for material sciences or the pharmaceutical industry (Scheme 2). Bromodifluoromethylthiolated derivatives of compounds that have found applications in OLED such as pyrene (**3a**), 9-phenyl-9*H*-carbazole (**3b**), and 9,9'-spirobi[fluorene] (**3c**) were generated in high yields. Similarly, BrCF<sub>2</sub>S-substituted natural products and drug molecules including coumarin (**3d**), pterostilbene (**3e**), clofibrate (**3f**), fenofibrate (**3g**), D-delta-tocopherol (**3h**), octabenzene (**3i**), diacetone-*D*-glucose derivative (**3j**), *N*-Boc-*trans*-4-hydroxy-*L*-proline methyl ester (**3k**) and meclozine (**3l**) were isolated in yields up to 97%. The method was amenable to scaling up and provided more than one gram of bromodifluoromethylthiolated pterostilben (**3e**). These results illustrate the broad applicability of the bromodifluoromethylthiolation protocol using reagent **1** to access products that may not be easily prepared applying previously reported methodologies.<sup>[8b]</sup>



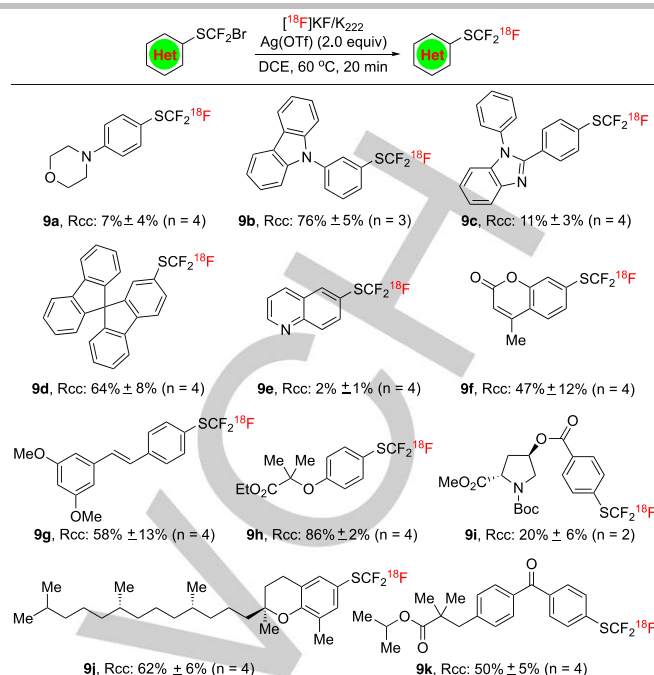
**Scheme 2.** Synthesis of bromodifluoromethylthiolated materials and drug molecules. Isolated yields.

The bromodifluoromethylthio group can be easily converted to other functional groups as exemplified with **2q** (Scheme 3). Oxidation of **2q** with *m*CPBA (1.5 equiv) or  $\text{RuCl}_3/\text{NaIO}_4$  gave the bromodifluoromethylated sulfinate **4** or sulfone **5** in 70% and 95% yield, respectively. Compound **2q** also reacted with dimethyl diazomalonate in the presence of  $\text{Rh}_2(\text{esp})_2$  ( $\text{esp}$  = tetramethyl *m*-benzenedipropionate) to give sulfonium ylide **6** in 74% yield. This compound may serve itself as an electrophilic bromodifluoromethylating reagent.<sup>[15]</sup> Furthermore, under photoredox catalysis, the carbon-bromine bond of **2q** underwent homolytic cleavage to generate the radical  $\text{ArSCF}_2\cdot$ ,<sup>[16]</sup> which react with benzofuran or 1-methoxy-4-vinylbenzene to afford compounds **7** and **8** in 50% and 70% yield, respectively.



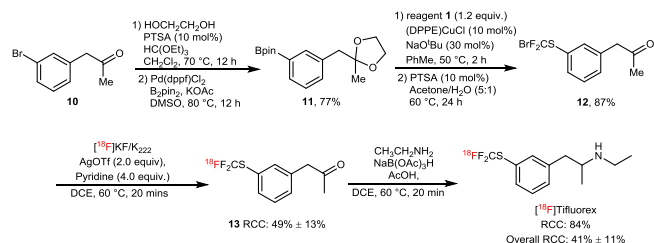
**Scheme 3.** Functional transformations of bromodifluoromethylthiolated compound **2q**.

Next, we subjected selected  $\text{BrCF}_2\text{S}$ -substituted (hetero)arenes to silver-mediated halex with  $^{18}\text{F}$ KF. Our previous study provided limited information on the scope of this process,<sup>[8b]</sup> so it was of interest to subject more structurally complex precursors to nucleophilic  $^{18}\text{F}$ -fluorination (Scheme 4). Selected bromodifluoromethylthiolated (hetero)arenes were treated with  $^{18}\text{F}$ KF/ $\text{K}_{222}$  in the presence of 2.0 equivalents of  $\text{AgOTf}$  in 1,2-dichloroethane at 60 °C for 20 minutes (Scheme 4).<sup>[8b]</sup> Precursors with electron-donating substituents reacted in higher radiochemical conversions (RCCs) than those with electron-withdrawing substituents. Heteroarenes such as **3b** and



**Scheme 4.** Scope of silver-mediated  $^{18}\text{F}$ -fluorination of bromodifluoromethylthiolated arenes/heteroarenes. Reaction condition: precursor (0.040 mmol),  $\text{AgOTf}$  (0.080 mmol),  $^{18}\text{F}$ KF/ $\text{K}_{222}$  (20–30 MBq), 1,2-dichloroethane (300  $\mu\text{L}$ ) at 60 °C for 20 min. RCC (radiochemical conversion) and product identity were determined by radioHPLC. RCC's were reported as non-decay corrected. See previous study for molar activity calculation (~0.1 GBq/ $\mu\text{mol}$ -1).<sup>[8b]</sup>

and **2ag** gave the corresponding  $^{18}\text{F}$ SCF<sub>3</sub>-heteroarenes **9b** and **9c** in 76% and 11% RCY, respectively. Not all heteroarenes underwent efficient halex  $^{18}\text{F}$ -fluorination. For example, **9e** was obtained in less than 5% RCC, a result possibly explained evoking sequestration of  $\text{AgOTf}$  as an inactive nitrogen-based complex.<sup>[17]</sup> Radiolabelled derivatives of natural compounds such as coumarin (**9f**), pterostilbene (**9g**), *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester (**9i**), and D- $\delta$ -tocopherol (**9j**) were all be obtained in RCCs up to 60%. Furthermore, clofibrate (**9h**) and fenofibrate (**9k**), two lipid-lowering agents used for controlling cholesterol and triacylglyceride level in the blood,<sup>[18]</sup> were also successfully radiolabelled in 86% and 50% RCCs, respectively, and greater than 95% radiochemical purity.



**Scheme 5.** Preparation of  $^{18}\text{F}$ -labelled Tiflorex.

To further evaluate the applicability of the current protocol, we tried to synthesize  $^{18}\text{F}$ -labelled Tiflorex-a potent anorectic drug for the treatment of obesity.<sup>[19]</sup> As shown in Scheme 5, starting from easily available 3-bromophenylacetone, bromodifluoromethyl-thiolated compound **12** can be readily synthesized in 4 steps in high yields. Treatment of compound **12** with  $^{18}\text{F}$ KF/ $\text{K}_{222}$  in the presence of 2.0 equivalents of  $\text{AgOTf}$  and 4.0 equivalent of pyridine in 1,2-dichloroethane at 60 °C for



20 minutes afforded [ $^{18}\text{F}$ ]-labelled compound **13** in 49% RCC. Reductive amination at 60 °C for 20 min generated the radiolabelled Tiflorex in 41% RCC with 84% conversion. As a comparison, efforts to prepare [ $^{18}\text{F}$ ]Tiflorex by our previous reported methods was unsuccessful because of the difficulty in the synthesis of the corresponding aryl thiol. These results clearly demonstrate the advantage of the current strategy for the preparation of previously inaccessible radiolabeled [ $^{18}\text{F}$ ]Aryl-SCF<sub>3</sub>.

In summary, we have developed a novel highly reactive bromodifluoromethylthiolating reagent,  $\alpha$ -cumyl bromodifluoromethanesulfonate **1**, and have demonstrated its applicability for the conversion of (hetero)aryl boronic pinacol esters into bromodifluoromethylthiolated (hetero)arenes under copper catalysis. This protocol provides facile access to a large range of BrCF<sub>2</sub>S-substituted (hetero)arenes including molecules relevant to material science and drug discovery. This chemistry enabled the validation of a new retrosynthetic route to  $^{18}\text{F}$ -labeled arylSCF<sub>3</sub> featuring (hetero)aryl-SCF<sub>3</sub> instead of (hetero)arylS-CF<sub>3</sub> bond construction, an advance that expands the range of precursors available for trifluoromethylthiolation, and therefore also expands the radiochemical space available to radiochemists for PET imaging studies.

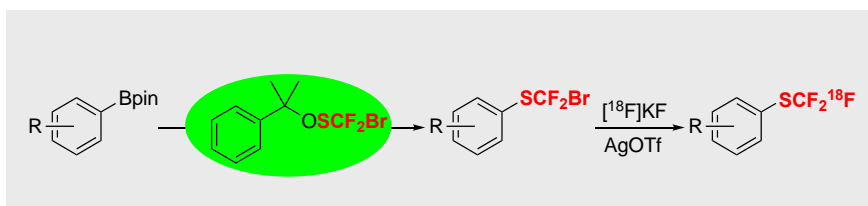
## Acknowledgements

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**Keywords:** PET • fluorine • bromodifluoromethylthiolation • trifluoromethylthiolation • radiolabeling

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## COMMUNICATION



A highly reactive electrophilic bromodifluoromethylthiolating reagent  $\alpha$ -cumyl bromodifluoromethanesulfonate **1** was invented. Reagent **1** coupled with a wide range of (hetero)aryl boronic pinacol esters under copper catalysis. The resulting bromodifluoromethylthiolated (hetero)arenes were amenable to various transformations including halox using  $[^{18}\text{F}]\text{KF}/\text{K}_{222}$ . As such, the first radiosynthetic route to  $[^{18}\text{F}]\text{arylsulfonates}$  via (hetero)aryl- $\text{SCF}_3$  bond construction is reported.

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Page No. – Page No.

**Synthesis and Reactivity of  $\alpha$ -Cumyl bromodifluoromethanesulfonate: Application to the Radiosynthesis of  $[^{18}\text{F}]\text{arylsulfonates}$**

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