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# C-H Electrophilic (Phenylsulfonyl)difluoromethylation of (Hetero)Arenes with a Newly Designed Reagent

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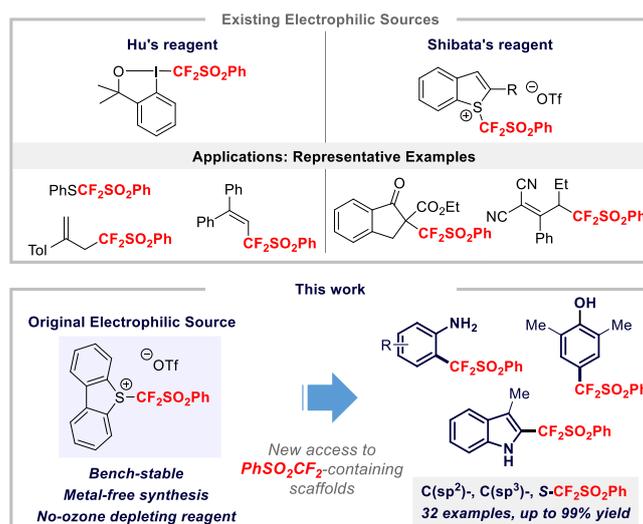
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**Abstract:** The synthesis of an original electrophilic difluoromethylating reagent was successfully achieved upon a straightforward protocol (3 steps). Like a Swiss army knife, this bench-stable reagent allowed the functionalization of various classes of compounds under mild and transition metal-free conditions. Hence, an efficient and operationally simple tool for the construction of C(sp<sup>2</sup>)-, C(sp<sup>3</sup>)- and S-CF<sub>2</sub>SO<sub>2</sub>Ph bonds was provided, expanding the chemical space of PhSO<sub>2</sub>CF<sub>2</sub>-containing molecules. Late-stage functionalization of bioactive molecules and the synthesis of PhSO<sub>2</sub>CF<sub>2</sub>- and HCF<sub>2</sub>-analogs of Lidocaine were also successfully achieved.

## Introduction

Organofluorine chemistry is a research area of paramount importance as fluorinated molecules are prevalent derivatives in material science, agrochemical and pharmaceutical industries.<sup>1</sup> More than 40% of pharmaceuticals approved by the FDA in 2019 contain at least one fluorine atom,<sup>2</sup> which could be explained since the incorporation of a fluorine atom or a fluorinated moiety drastically impact the properties of the corresponding molecules.<sup>3</sup> Therefore, over the year, the field of organofluorine chemistry has been revolutionized by impressive advances including original and efficient transformations along with the discovery and design of potent fluorinated groups, which have opened wider the chemical space of fluorinated compounds.<sup>4</sup> Whilst special attention was paid to the HCF<sub>2</sub> group,<sup>5</sup> the design of FGCF<sub>2</sub> moiety has emerged as an interesting lead to be followed. Among them, the PhSO<sub>2</sub>CF<sub>2</sub> residue proved to be of high importance and had aroused the interest of the scientific community.<sup>6</sup> Found in the analog of Fluconazole with antifungal activities,<sup>7</sup> this fluorinated group is a real synthetic handle. Indeed, it is easily converted into other valuable difluorinated moieties such as the difluoromethyl (HCF<sub>2</sub>), the difluoromethylene (-CF<sub>2</sub>-), and the difluoromethylidene (=CF<sub>2</sub>) groups. These later were found in drugs such as Eflornithine<sup>8</sup> and Seletracetam,<sup>9</sup> for instance. Main synthetic pathways to build up a C-CF<sub>2</sub>SO<sub>2</sub>Ph bond relied on the use of nucleophilic sources of (phenylsulfonyl)difluoromethyl residue or *via* a radical process.<sup>6</sup> In sharp contrast, methodologies involving electrophilic reagents are restricted to two major contributions from key players in the field, namely the groups of Hu<sup>10</sup> and Shibata.<sup>11</sup> They designed two electrophilic sources based on an hypervalent iodine and a sulfonium salt, respectively (Scheme 1). While the group of Hu showcased that its source was very efficient for the functionalization of thiols as well as for the copper-catalyzed allylic and vinylic (phenylsulfonyl)difluoro-methylation reaction, Shibata and co-workers successfully applied their reagent for the functionalization of C(sp<sup>3</sup>) centers with β-ketoesters, β-diketones and dicyanoalkylidenes. Although those reagents served as a proof-of-concept, we wondered whether it would be possible to synthesize a new electrophilic reagent, which will 1) be easily accessible on a large scale, 2) not require ozone depleting reagents for its synthesis and 3) react with a large panel of nucleophiles. Such reagent will definitely facilitate the access to difluoromethylated compounds.

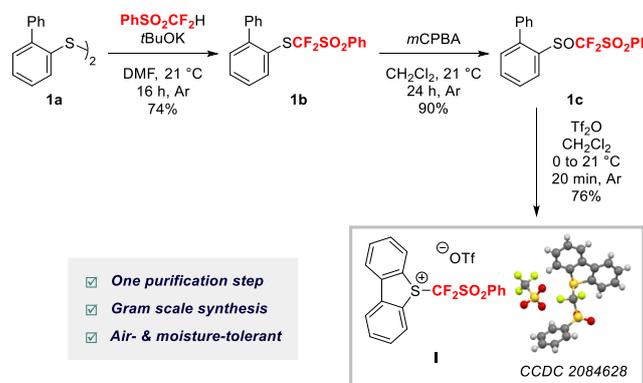


**Scheme 1.** State of the art.

By analogy with the Umemoto's reagent and its analogs,<sup>12</sup> we anticipated that the backbone of the reagent will be important to reach a good reactivity. Therefore, we imagine to synthesize a *S*-([phenylsulfonyl]difluoromethyl)dibenzothiophenium salt. Herein, we disclosed a simple and straightforward synthesis of an electrophilic source of PhSO<sub>2</sub>CF<sub>2</sub> group and its broad applications in various transformations.

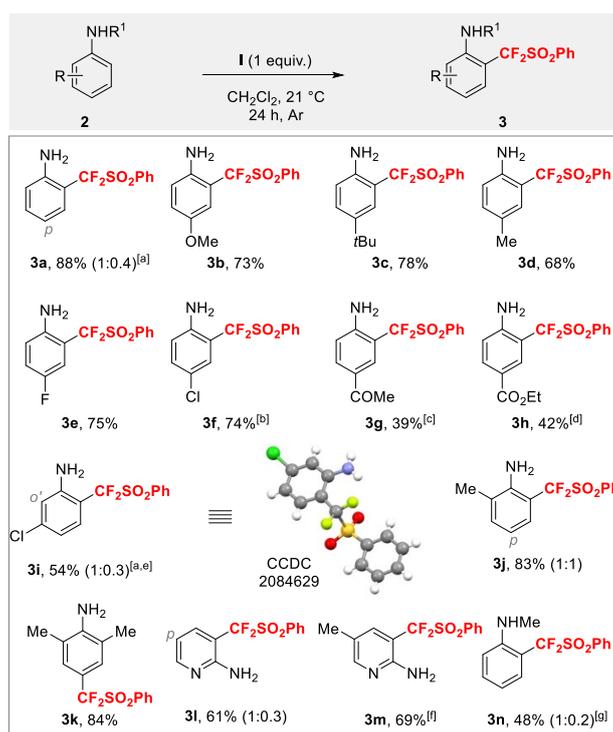
## Results and Discussion

With these considerations in mind, we embarked on the preparation of the reagent **I**. This newly designed reagent was synthesized in a three steps/one purification sequence in 51% overall yield starting from the commercially available or easy-to-synthesize biaryl disulfide **1a**<sup>13</sup> and the (difluoromethyl)sulfonylbenzene.<sup>14,15</sup> First, the (phenylsulfonyl)difluoromethylation of the disulfide **1a** under basic conditions provided **1b** in 74% yield. The selective oxidation of the sulfane with *m*CPBA furnished **1c** in 90% yield, without any purification. Finally, upon treatment with triflic anhydride, the sulfoxide **1c** was converted into the corresponding dibenzothiophenium salt **I** in 76% yield. The structure of **I** was further ascertained by a X-ray analysis.<sup>15</sup> The reagent turned out to be air- and moisture-tolerant, bench-stable and was kept for more than three months at room temperature under air with no alteration of its reactivity. Remarkably, its transition metal-free synthesis did not require any ozone depleting fluorinated reagents and was conveniently scalable as the reagent **I** was obtained in 46% overall yield on 48 mmol scale.



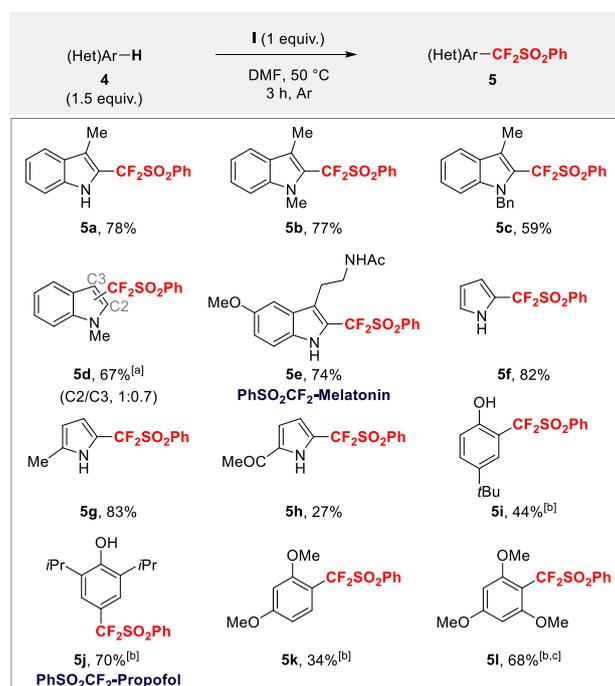
**Scheme 2.** Synthesis of the reagent **I**. Reaction performed on 5 mmol scale. See the Supporting Information for more details.

Having this reagent in hand, we first explored its reactivity towards the (phenylsulfonyl)difluoromethylation of aniline derivatives with a complete selectivity towards the formation of a C(sp<sup>2</sup>)-CF<sub>2</sub>SO<sub>2</sub>Ph bond (Scheme 3). When aniline **2a** was reacted with the reagent **I**, the compound **3a** was obtained in a high yield as an easy-to-separate mixture of *ortho* and *para* regioisomers, the *ortho* isomer being the major one.<sup>15,16</sup> As these fluorinated molecules might be of high interest for medicinal chemistry and drug discovery, the access to both regioisomers in one transformation might constitute a substantial advantage. Then, a panel of original and diversely *para*-substituted (phenylsulfonyl)difluoromethylated anilines was synthesized. Both anilines substituted with electron-donating groups (**2b-2d**), halogens (**2e-2f**) and electron-withdrawing groups (**2g-2h**) were suitable substrates, the transformation being more efficient with electron-rich compounds. The reaction was tolerant to various functional groups such as ketone (**3g**) and ester (**3h**). When the 3-chloroaniline **2i** reacted with the reagent **I**, the functionalization occurred on both *ortho* positions, the major isomer, resulting from the (phenylsulfonyl)difluoromethylation at the less sterically hindered position, was preferentially obtained as ascertained by NMR experiments and a X-ray analysis (CCDC 2084629).<sup>15</sup> In case of the 2-methylaniline, a 1:1 mixture of both *ortho*- and *para*-substituted products (**3j**) was obtained in 83% yield as confirmed by 2D-NMR experiments. Interestingly, the 2,6-xylylidine **2k**, a key scaffold found in several anesthetic such as Lidocaine, Bupicaine, Mepivacaine and Etidocaine, was smoothly functionalized in 84% yield. It is worth mentioning that heteroaryl amines (**2l** and **2m**) were also functionalized in good yields.<sup>15</sup> The methodology was not restricted to the functionalization of primary aniline as the *N*-methylaniline was reacted and **3n** was isolated in 48% for the *ortho* isomer.

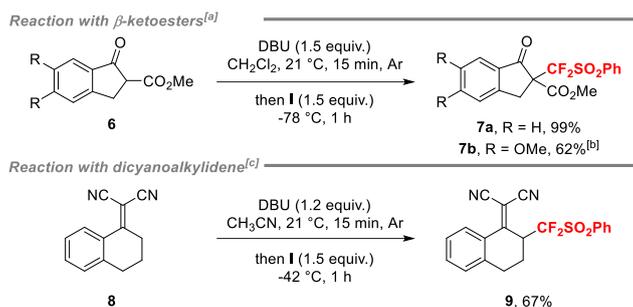


**Scheme 3.** (Phenylsulfonyl)difluoromethylation of anilines **2**. Reaction conditions: **2** (3 equiv.), **I** (0.3 mmol, 1 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (0.15 M), 21 °C, 24 h, argon. Isolated yields are given. In case of regioisomers, combined isolated yields were provided and the ratio of regioisomers, in parenthesis, was determined by <sup>19</sup>F NMR of the crude reaction mixture using the  $\alpha,\alpha,\alpha$ -trifluoro-acetophenone as an internal standard. <sup>a</sup> The minor isomer was isolated with an inseparable impurity. <sup>b</sup> 8 days. <sup>c</sup> 10 days. <sup>d</sup> 12 days. <sup>e</sup> 4 days. <sup>f</sup> The product was isolated with an inseparable impurity. <sup>g</sup> Only this isomer was isolated in 48% yield.

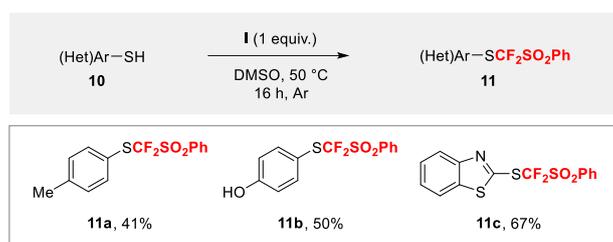
Encouraged by these results, we turned our attention to the electrophilic (phenylsulfonyl)difluoromethylation of electron-rich (hetero)arenes (Scheme 4). First indoles (**4a-4e**), a key scaffold for medicinal chemistry, were studied. Non-protected and *N*-protected 3-substituted indoles (**4a-4c**) were smoothly functionalized at the C2 position. When the *N*-methylindole **4d** was used as the substrate, the expected product **5d** was obtained as a mixture of regioisomers. Interestingly, the C2-functionalization of pyrroles was efficiently achieved, except in case of **5h**, which was isolated in a modest 27% yield. The (phenylsulfonyl)difluoromethylation of phenol and anisole derivatives (**4i-4l**) provided the corresponding products in decent to good yields. The late-stage functionalization of bioactive molecules such as Melatonin (**4e**), “the Sleep Hormone”, and Propofol (**4j**), a potent anesthetic, went smoothly. The expected products (**5e** and **5j**) were obtained with a complete regioselectivity in 74% and 70%, respectively. To further demonstrate the potential of the reagent **I**, the functionalization of C(sp<sup>3</sup>)-centered nucleophiles was studied (Scheme 5). Pleasingly, in the presence of DBU,  $\alpha$ -ketoesters **6** and dicyanoalkylidene **8** were efficiently functionalized at low temperature (-78 °C or -42 °C) and the corresponding (phenylsulfonyl)difluoromethylated products **7a-7b** and **9** were isolated in good to excellent yields with a complete selectivity for the *C*-functionalization: a valuable alternative to the pioneering work from Shibata.<sup>11</sup> Due to the recent interest to the (phenylsulfonyl)difluoromethyl sulfanyl group,<sup>10a,17</sup> we explored the possibility to access to PhSO<sub>2</sub>CF<sub>2</sub>S-containing derivatives by reacting *S*-nucleophiles with the reagent **I** (Scheme 6). The transformation proceeded smoothly with structurally diverse thiophenol derivatives (**10a-10c**) including the 2-benzothiazolethiol **10c** under mild reaction conditions (50 °C, no base). Interestingly, in case of the 4-mercaptophenol **10b**, a complete selectivity was observed for the formation of a *S*-CF<sub>2</sub>SO<sub>2</sub>Ph bond over a C(sp<sup>2</sup>)-CF<sub>2</sub>SO<sub>2</sub>Ph bond.



**Scheme 4.** Electrophilic (phenylsulfonyl)difluoromethylation of electron-rich (hetero)arenes. Reaction performed on 0.3 mmol scale. Isolated yields are given. <sup>a</sup> A combined isolated yield was provided and the ratio of regioisomers was determined by <sup>19</sup>F NMR of the crude reaction mixture using the  $\alpha,\alpha,\alpha$ -trifluoroacetophenone as an internal standard. The C3-regioisomer of **5d** was isolated with traces of the C4-regioisomer. <sup>b</sup> Reactions performed using 3 equivalents of **4** in DMSO, 50 °C, 16h, argon. <sup>c</sup> **5l** was isolated with 13% of remaining **4l**.

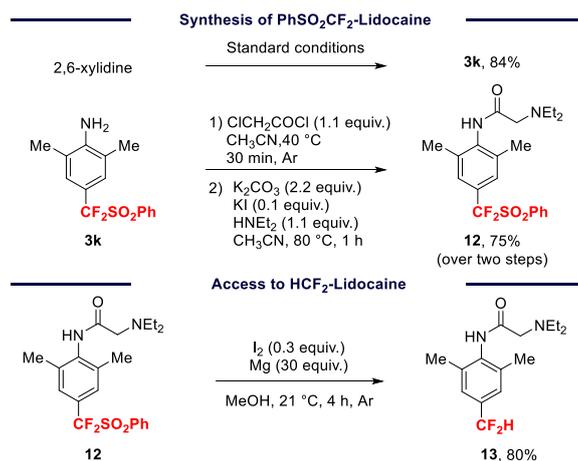


**Scheme 5.** Isolated yields were given. <sup>a</sup> Reaction performed on 0.1 mmol scale. <sup>b</sup> Reaction performed on 0.15 mmol scale for 30 min instead of 1 h. <sup>c</sup> Reaction performed on 0.2 mmol scale.



**Scheme 6.** Synthesis of (phenylsulfonyl)difluoromethylthio-containing molecules from thiol derivatives. Reaction conditions: **10** (3 equiv.), **I** (0.3 mmol, 1 equiv.), DMSO (0.15 M), 50 °C, 16 h, argon. Isolated yields were given.

To further showcase the synthetic utility of the reagent **I**, the straightforward synthesis of a PhSO<sub>2</sub>CF<sub>2</sub>-analog of Lidocaine **12**, an anesthetic, was achieved in 63% overall yield after the following sequence: (phenylsulfonyl)difluoromethylation of the commercially available 2,6-xylidine (**3k**, 84% yield), followed by an amidation with the chloroacetyl chloride and reaction with diethylamine under basic conditions in a one pot process (75% yield, Scheme 7). Pleasingly, this fluorinated group was then converted into the valuable HCF<sub>2</sub> moiety.<sup>5</sup> Indeed, in the presence of Mg and using a catalytic amount of I<sub>2</sub>, the difluoromethylated product **13** was obtained in 80% yield starting from **12**.



**Scheme 7.** Synthesis of the PhSO<sub>2</sub>CF<sub>2</sub>-Lidocaine and post-functionalization reaction.

## Conclusion

In summary, a straightforward synthesis of a bench-stable PhSO<sub>2</sub>CF<sub>2</sub> reagent **I** was developed. This transition metal-free protocol was convenient, efficiently scalable and did not require any use of ozone depleting fluorinated reagents. Pleasingly, access to unprecedented fluorinated

scaffolds was possible under simple and practical reaction conditions, as illustrated with the synthesis of PhSO<sub>2</sub>CF<sub>2</sub>-containing aniline derivatives and electron-rich (hetero)arenes in moderate to excellent yields. Moreover, the reagent **I** was also applied to the functionalization of C(sp<sup>3</sup>) centers and for the preparation of valuable PhSO<sub>2</sub>CF<sub>2</sub>S-containing derivatives. The PhSO<sub>2</sub>CF<sub>2</sub> residue was efficiently converted into the high-value added HCF<sub>2</sub> group, which highlighted the versatility of this fluorinated group. The late-stage functionalization of bioactive molecules into their corresponding PhSO<sub>2</sub>CF<sub>2</sub>-containing analogs further demonstrated the synthetic utility of the novel reagent, particularly appealing in the quest of interesting scaffolds for medicinal chemistry. This newly-designed electrophilic source is distinguished by its straightforward and practical synthesis and its wide scope, thus offering a new platform to introduce the PhSO<sub>2</sub>CF<sub>2</sub> motif on various skeletons. We believe that this original tool will enlarge the current toolbox of electrophilic reagents, will open new routes for functionalizing complex molecules and will be useful for the discovery of new bioactive molecules.

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