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Cost-efficient, Multigram Scalable Synthesis of Shelf-Stable Electrophilic (Phenylsulfonyl)difluoromethylating Reagents

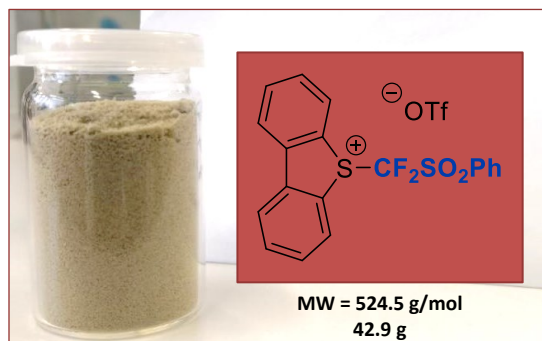
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ABSTRACT

An easy-to-handle protocol for the synthesis of an efficient electrophilic (phenylsulfonyl)difluoromethylating reagent, namely the *S*-([phenylsulfonyl]difluoromethyl)-dibenzothiophenium salt **I**, is depicted. The latter was synthesized on approximately 40 g scale in a three-steps/one-purification sequence from commercially available or easy-to-synthesize starting materials with an estimated global prize of about 10.6 €/g. The bench-stable reagent **I** was found to be air-and moisture-tolerant. By changing the counter-anion, a small library of electrophilic sources (reagents **I-III**) is now available for the (phenylsulfonyl)difluoromethylation reaction. Differential scanning calorimetry (DSC) measurements have been also carried out on the different salts (**I-III**) along with a key intermediate to ensure a safe process.

Electrophilic reagents; Fluorine; Synthetic methods; Difluoromethylation; Library of *S*-([phenylsulfonyl]difluoromethyl)dibenzothiophenium salts

INTRODUCTION

Organofluorine chemistry is a well-established research area in organic synthesis. Indeed, due to its remarkable properties, the incorporation of a fluorine atom or a fluorinated moiety onto a molecule will modulate its physico-chemical properties (lipophilicity, metabolic stability, among others) and may have a deep impact on its bioactivity.¹ Since the middle of the 20th century, fluorinated molecules have found widespread applications in pharmaceutical and agrochemical industries along with materials science.² In particular, the number of fluorine-containing drugs steadily increased over the years.³ In this context, the development of efficient and original transformations for the selective incorporation of a fluorine atom and a fluorinated residue is nowadays highly demanded and still represents a challenging synthetic task.⁴ Recently, whereas a particular attention has been paid to the design of methodologies for the difluoromethylation of a variety of compounds considering the unique properties of the HCF₂ residue, the FGCF₂ groups remains underexplored.⁵ Among them, the PhSO₂CF₂ group, which can be found in the structure of an analog of Fluconazole,⁶ has emerged as an interesting fluorinated residue as it can be readily converted into the difluoromethyl (HCF₂), the difluoromethylene (–CF₂–) and the difluoromethylidene (=CF₂) moieties.⁷ Among the different approaches to synthesize PhSO₂CF₂-containing molecules, transformations involving the use of nucleophilic sources or radical processes have been generally developed.⁷ In contrast, electrophilic sources used to be restricted to the reagents of Hu^{8a-c} and Shibata.^{8d} Indeed, an hypervalent iodine reagent was synthesized by the group of Hu and successfully applied for the functionalization of thiol derivatives and in copper-catalyzed allylic and vinylic (phenylsulfonyl)difluoromethylation reactions.^{8a-c} Moreover, thanks to the sulfonium-based phenylsulfonyldifluoromethyl electrophilic source designed by the group of Shibata, the functionalization of β -ketoesters, β -diketones and dicyanoalkylidenes was

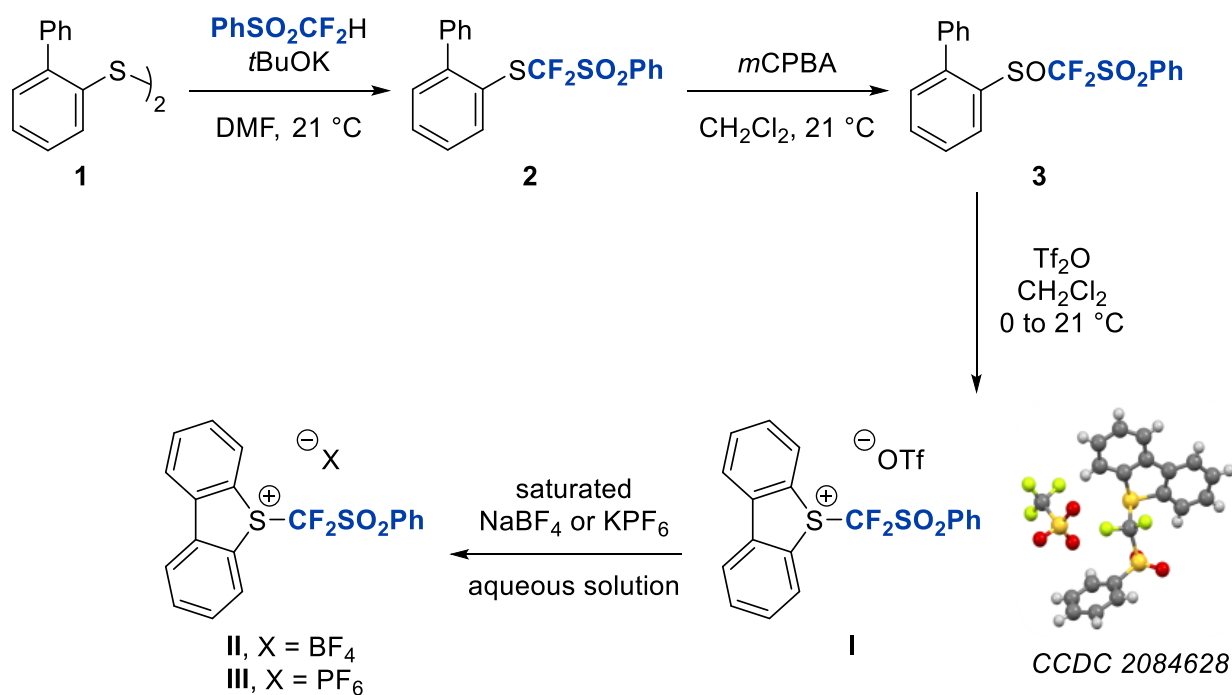
achieved. Aiming at developing a versatile tool towards the synthesis of PhSO₂CF₂-containing molecules, our group reported in 2021 a new bench-stable, air- and moisture-tolerant electrophilic source of PhSO₂CF₂ group.⁹ Worth mentioning that the synthesis of the *S*-([phenylsulfonyl]difluoromethyl)dibenzothiophenium **I** was achieved thanks to a metal-free protocol, which did not require ozone-depleting reagents. Its application as an electrophilic source considerably broadens the toolbox to access PhSO₂CF₂-containing derivatives including the construction of either C(sp²)- or C(sp³)-CF₂SO₂Ph bond. Moreover, anilines, phenols, (hetero)arenes, β-ketoesters and a dicyanoalkylidene were also used as nucleophiles and in case of thiophenols, the synthesis of highly valuable PhSO₂CF₂S-containing compounds was possible.⁹ Considering that the reagent **I** could be used to provide original PhSO₂CF₂-containing active pharmaceutical ingredients and various molecules of interest for agrochemicals and materials science, the process for its scale-up synthesis (more than 40 gram-scale) was studied and will be depicted. Moreover, the synthesis of two analogs of the reagent **I** (namely, sources **II** and **III**), will be reported along with differential scanning calorimetry (DSC) measurements to show the stability of these synthesized reagents and one key intermediate. Finally, the total cost for the multigram synthesis of the reagent **I** will be discussed.

RESULTS AND DISCUSSION

The preparation of the reagent **I** started with the synthesis of the sulfane **2** (Scheme 1). This latter was obtained after the (phenylsulfonyl)difluoromethylation of the disulfide **1** with PhSO₂CF₂H under basic conditions. Then, the compound **2** was selectively oxidized by *m*CPBA to afford the sulfoxide **3**, which was directly treated without any purification with triflic anhydride to provide the desired dibenzothiophenium salt **I**. Two analogs of the electrophilic reagent **I** were then easily

obtained by changing the counter anion from ^-OTf (**I**) to $^-BF_4$ (reagent **II**) and $^-PF_6$ (reagent **III**). Each step of the synthesis will be carefully described.

Scheme 1. Preparation of the reagent **I** and its analogs **II** and **III**



Synthesis of the ((difluoromethyl)sulfanyl)benzene 2. Both **1** and $PhSO_2CF_2H$ being rather expensive chemicals ($> 2500\text{ €/g}$ for **1**),¹⁰ we decided to perform their synthesis following a four-steps procedure for **1** and a two-steps sequence for $PhSO_2CF_2H$ to minimize the global cost of the large-scale synthesis of **I** (see Supporting Information for more details). These two starting materials have been easily obtained on a multigram scale and have been used without any purification step. The disulfide **1** and $PhSO_2CF_2H$ were simply mixed together (Scheme 2) in anhydrous DMF at room temperature ($21\text{ }^\circ C$). Then, a solution of $tBuOK$ in anhydrous DMF was

added to furnish the desired sulfane **2**. This latter was smoothly synthesized from 1.4 g to 33.8 g (Table 1), although the yield decreased by increasing the scale of the reaction. When the reaction was carried out on 80 g of **1** (Table 1, entry 3), the reaction was followed by ^{19}F NMR and it appeared that after 2 hours, no remaining starting material was detected. The desired product **2** had to be purified from an unknown by-product, which had a deleterious impact on the next oxidation step. Note that this purification step was the only one needed for the whole synthesis of **1**. Moreover, whatever the scale of the reaction, the reaction mixture remained homogenous and mechanical stirring was not required.

Scheme 2. Synthesis of **2**

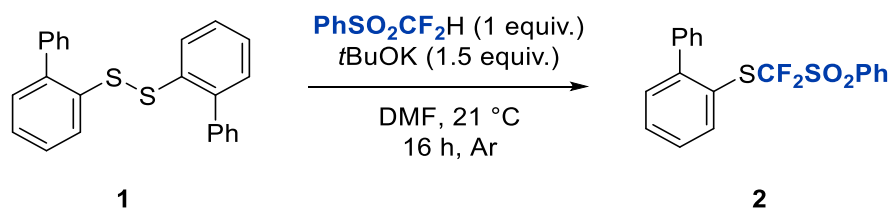


Table 1. Multigram Synthesis of **2**

Entry	1	$\text{PhSO}_2\text{CF}_2\text{H}$	$t\text{BuOK}$	DMF	2	Isolated yield
1	1.85 g	0.99 g	0.84 g	10 mL	1.40 g	74%
2	18.00 g	9.34 g	8.20 g	150 mL	9.81 g	54%
3 ^a	80.03 g	41.51 g	36.36 g	500 mL	33.84 g	42%

^a 2 h instead of 16 h.

Synthesis of 2-((phenylsulfonyl)difluoromethyl)sulfinyl-1,1'-biphenyl (sulfoxide 3). The selective oxidation of **2** with *m*CPBA afforded the sulfoxide **3** at 21 °C (Scheme 3). After a careful addition of the oxidant into a solution of **2** in dichloromethane at 0 °C, the reaction mixture was stirred at 21 °C for 24 h allowing full conversion of **2** into the product **3** (Scheme 3). Pleasingly,

the synthesis of **3** has been smoothly scaled up from 1 g (90% yield) to more than 35 g (quantitative yield, Table 2), showcasing the robustness of the transformation. Moreover, the practicability of the reaction was further demonstrated since the reaction mixture remained homogenous during the reaction (even on 35 gram scale) and no mechanical stirring was required. To get a better overview of this oxidation step, which would be of high interest for potential industrial applications, a monitoring of the conversion of **2** was achieved. Interestingly, upon these reaction conditions, **2** was selectively converted into the compound **3** as a single product in an efficient manner (Figure 1) and reached 94% conversion after 8.5 h and 99% after 23 h (Table 3). It is noteworthy to mention that the desired compound **3** was directly engaged in the next step without any further purification even after 8.5 h of reaction as only traces of **2** remained (about 6%). Considering the large scale of which this oxidation step was conducted, the stability of the sulfoxide **3** was evaluated by differential scanning calorimetry (DSC). The DSC studies showed a melting point for **3** around 69 °C. The DSC profile of **3** offered a high decomposition energy (846.7 J/g) with a peak very distant from the melting point. The decomposition temperature is about 163 °C (Figure 2), which is far from the reaction temperature used in the oxidation step.

Scheme 3. Synthesis of **3**

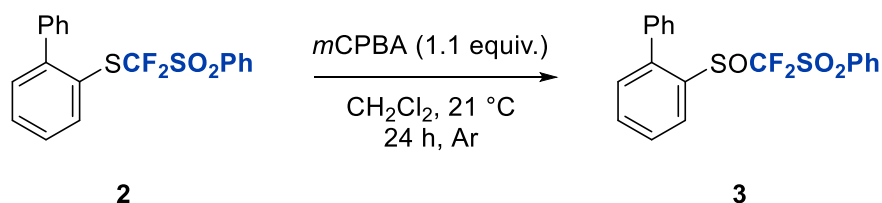


Table 2. Multigram Synthesis of **3**

Entry	2	<i>m</i> CPBA	CH ₂ Cl ₂	3	Isolated yield
1 ^a	1.09 g	0.77 g	20 mL	1.03 g	90%
2 ^b	9.81 g	6.93 g	100 mL	10.24 g	99%
3 ^b	33.84 g	23.90 g	300 mL	35.28 g	99%

^a*m*CPBA 72% purity was used. ^b*m*CPBA 74% purity was used.

Figure 1. Conversion of **2** into the compound **3**.

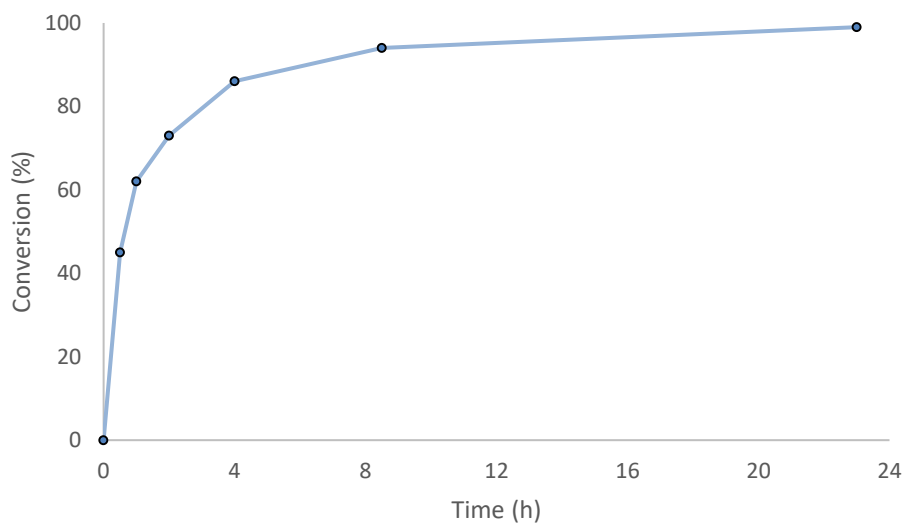
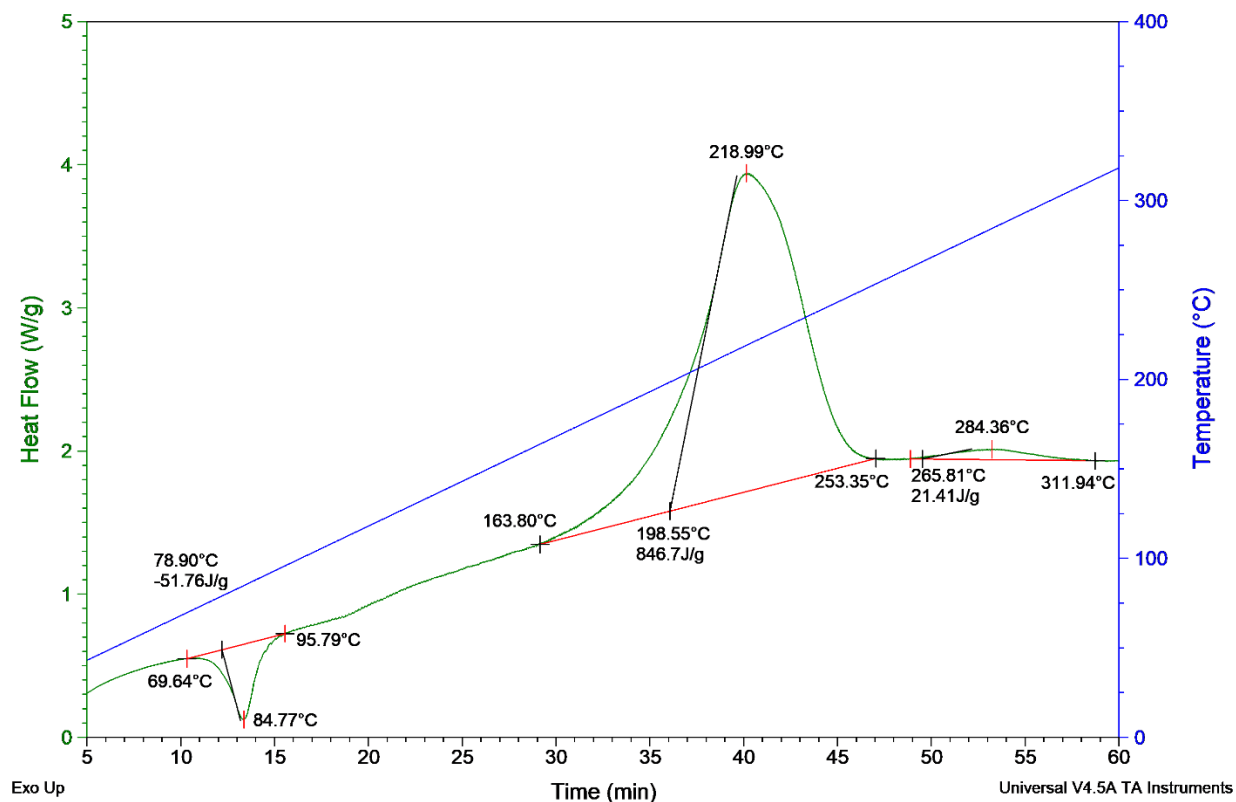


Table 3. Conversion of **2** vs time.^a

Entry	Time	Conversion	Entry	Time	Conversion
1	30 min	45%	4	4 h	86%
2	1 h	62%	5	8.5 h	94%
3	2 h	73%	6	23 h	99%

^a Reaction performed on 1.33 mmol scale. Conversions determined by ¹⁹F NMR.

Figure 2. DSC analysis of the product **3**.



Synthesis of the *S*-([phenylsulfonyl]difluoromethyl)dibenzothiophenium salt **I.** The last step was the formation of the targeted dibenzothiophenium salt **I** (Scheme 4). Addition of triflic anhydride (Tf₂O) to a solution of the crude sulfoxide **3** in dichloromethane at 0 °C led to the formation of a dark brown reaction mixture, which was allowed to warm up to 21 °C. The solution was magnetically stirred for only 20 minutes and the solvent was then completely removed to obtain a brown oil (Figure 3a). The later was dissolved in a minimum of dichloromethane and diethyl ether was carefully added until all the oil turned out to an off-white solid (Figure 3b). The solvent was removed with a syringe (Figure 3c) and the resulting product was dried under vacuum to afford **I** as a pale-yellow powder without any further purification step (Figure 3d). The

preparation of the compound **I** has been scaled up from 1 g (76% yield, Table 4, entry 1) to about 43 g (91% yield, Table 4, entry 3).

Scheme 4. Synthesis of **I**.

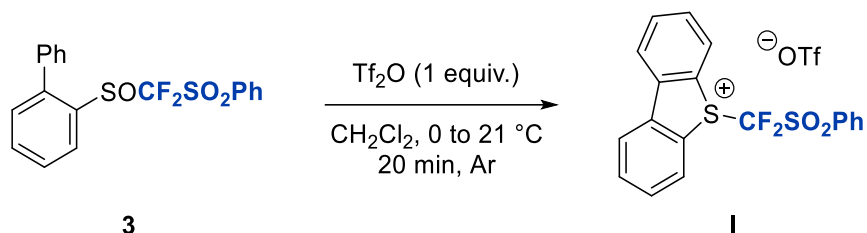


Figure 3. Work-up to obtain **I**. (a) Crude reaction mixture as a brown oil. (b) Precipitation of the compound **I**. (c) Removal of the solvent. (d) Dried compound **I**.

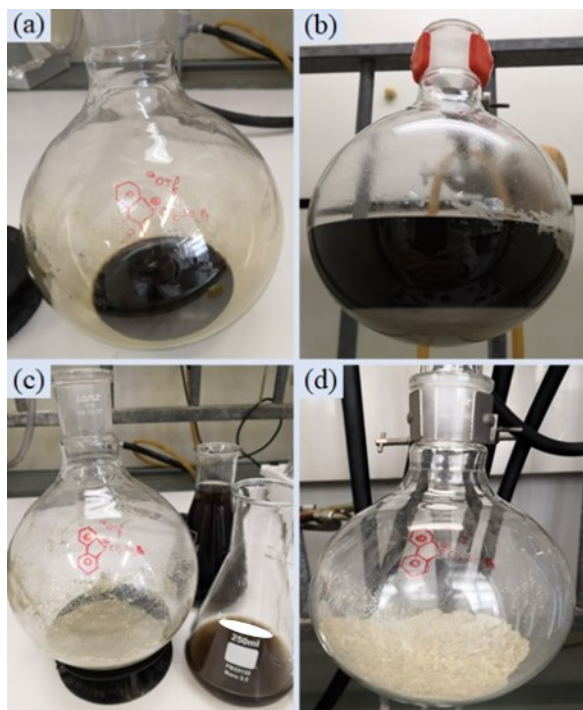
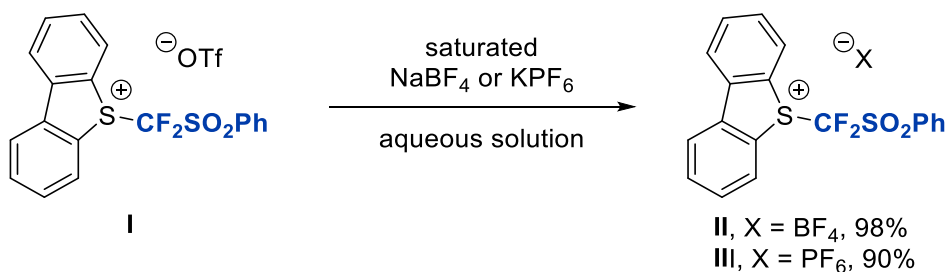


Table 4. Multigram Synthesis of **I**.

Entry	3	Tf₂O	CH₂Cl₂	I	Isolated yield
1	1.02 g	0.44 mL	20 mL	1.03 g	76%
2	10.20 g	4.40 mL	80 mL	11.96 g	87%
3	35.28 g	15.20 mL	200 mL	42.90 g	91%

Anion metathesis. Finally, from the reagent **I**, two new PhSO₂CF₂-containing sources (**II** and **III**) were easily obtained on a one-gram scale in excellent yields (98% and 90%, respectively) by switching the counter anion after washing **I** with either a saturated aqueous solution of sodium tetrafluoroborate or a saturated aqueous solution of sodium hexafluorophosphate (Scheme 5).

Scheme 5. Synthesis of **II** and **III**.



DSC Analysis.¹¹ As these electrophilic sources (**I**, **II** and **III**) are planned to be used on a large scale, their stability is a key parameter to be taken in consideration. Therefore, the thermal stability of these three final products was also analyzed by DSC analysis (Figures 4 to 6). The compounds **I**, **II** and **III** show an exothermic decomposition phenomenon close to the melting temperature, i.e. around 123 °C for **I**, 159 °C for **II** and 184 °C for **III**. In the case of **I**, there is clearly a succession of decomposition reactions (about 4) with a cumulative energy of 442.6 J/g (Figure 4). The thermal decomposition of **II** occurs in two stages: a first complex peak with an energy of 208 J/g and a second peak at 233 °C with an energy of 139.1 J/g (Figure 5). Finally, the decomposition of **III** is characterized by a single exothermic peak with an energy of 218.5 J/g (Figure 6). In all cases, these analyses show that the decomposition of this family of products occurs at temperatures well above those used for their synthesis and for the reactions for which these reagents have been developed.

Figure 4. DSC analysis of the product I.

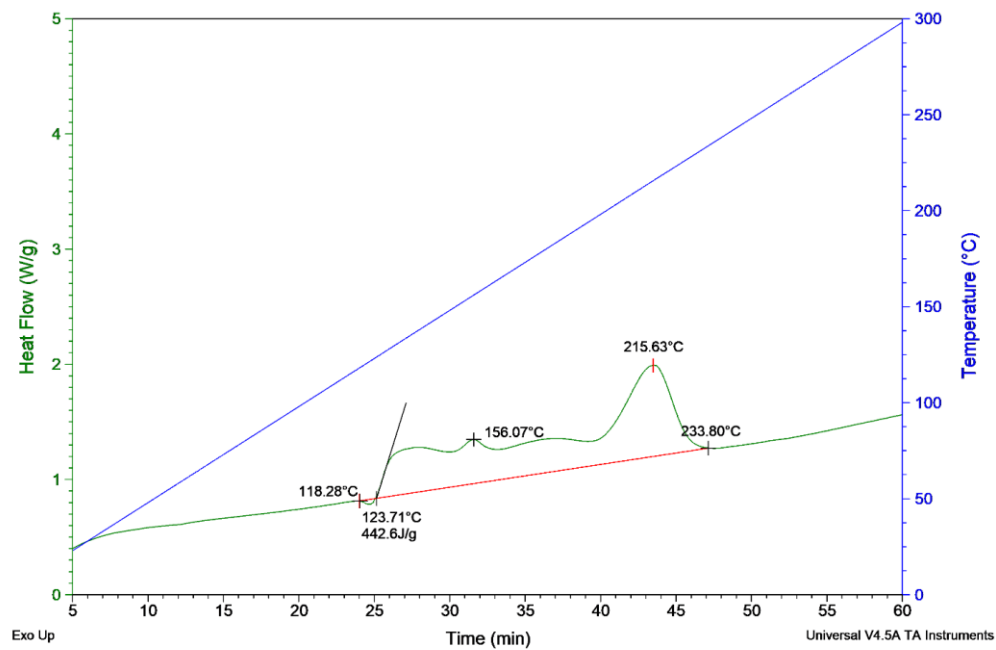


Figure 5. DSC analysis of the product II.

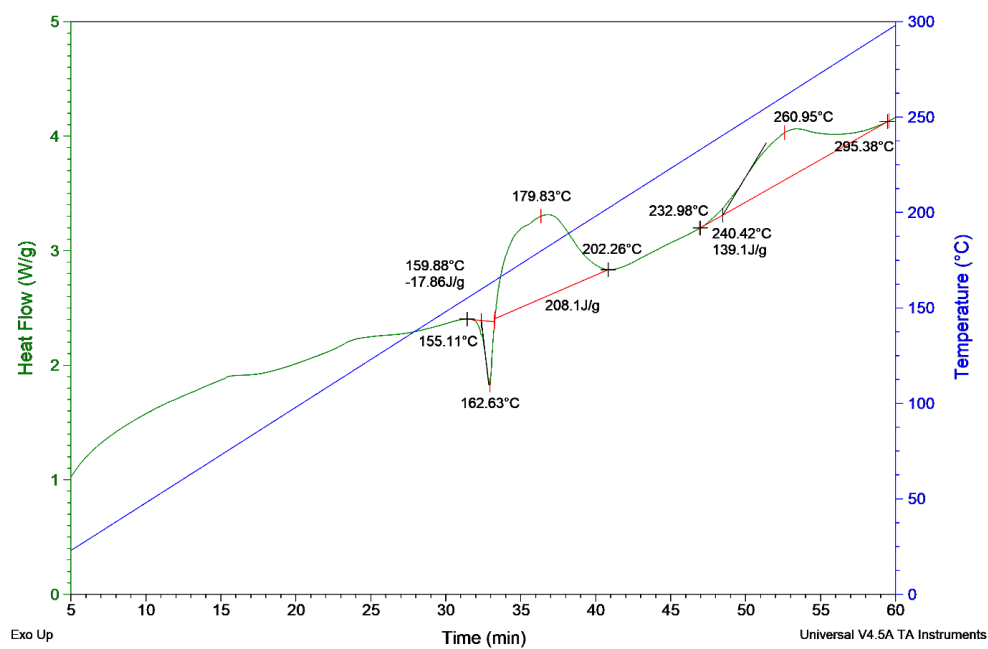
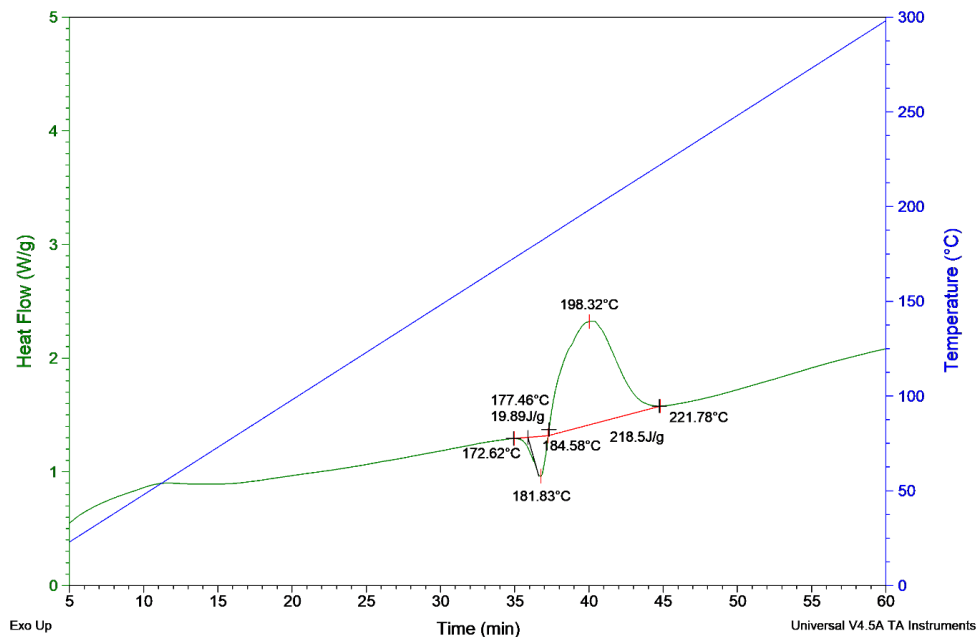


Figure 6. DSC analysis of the product **III**.



Financial Estimation for the Synthesis of I. The cost of production of 42.9 g of product **I** was finally estimated. To do so, due to the high commercial prices of **1** and $\text{PhSO}_2\text{CF}_2\text{H}$, we considered the cost of their synthesis in our laboratory. The solvents used for the reactions, the extractions or the purification step as well as silica have been considered (see details in Table 5). Note that the cost related to the manpower was not taken in consideration. Production of 1 g of **I** is fairly reasonable (only 10.63 €) and the synthesis of almost 43 grams of **I** cost about 456 €.

Table 5. Financial Estimation for the Synthesis of **I**.

Reagent	Chemicals Cost ^a	Quantity	Cost (€)
Disulfide 1^b	1.53 €/1 g	80.03 g	122.44
PhSO₂CF₂H^b	4.57 €/1 g	41.51 g	189.7
<i>t</i>BuOK	130.0 €/500 g	36.36 g	9.45
<i>m</i>CPBA	235.2 €/500 g	23.9 g	11.24
Tf₂O	106.14 €/250 g	26.0 g	11.04
DMF	57.93 €/1 L	500 mL	28.96
Et₂O			
Extraction	13.74 €/2.5 L	3.0 L	16.49
Purification		600 mL	3.29
Petroleum ether	10.25 €/5 L	11.4 L	23.37
CH₂Cl₂			
Reaction		500 mL	2.60
Purification	13.0 €/2.5 L	4.3 L	22.36
Extraction		1.8 L	9.36
Silica	12.02 €/1 kg	493 g	5.92
^a Prices negotiated with chemical suppliers.		Total per 42.9 g	456.22 €
^b See details in the Supporting Information.		Total per 1 g	10.63 €

CONCLUSION

The synthesis of **I** has been performed on a about 43 gram-scale in a three steps/one purification procedure with a 38% global yield, without the use of metal or ozone-depleting reagents and in a reasonable price. Note that the reagent **I** was obtained in 46% overall yield on a 48 mmol scale. The compound **I** was found to be air- and moisture tolerant. DSC analyses performed on each final products and the key intermediate sulfoxide **3** showed a good stability of the compounds, making us confident for their synthesis/use on a large scale. Due to the technical limitations of our laboratory, the synthesis of the source **I** has been carried out on 216 mmol scale but we do believe that the synthesis can be achieved on an even industrial scale. Thus, the easy and practical access

to these reagents will ensure their applications in a large variety of transformations and we hope that they will be of high interest for the scientific community.

EXPERIMENTAL SECTION

2-([(Phenylsulfonyl)difluoromethyl]sulfanyl)-1,1'-biphenyl 2. In an oven-dried 2 L round-bottom flask equipped with a magnetic stir bar and purged with argon was added bis([1,1'-biphenyl]-2-yl)disulfide **1** (80.03 g, 216 mmol, 1.0 equiv.), DMF (250 mL) and ((difluoromethyl)sulfonyl)benzene (41.51 g, 216 mmol, 1.0 equiv.). A solution of *t*BuOK (36.36 g, 324 mmol, 1.5 equiv.) in DMF (250 mL) was then added to the reaction mixture, which was stirred at 21 °C for 2 h. The resulting mixture was then quenched with ice-cold water (1 L) and extracted with Et₂O (3 × 1 L). The combined organic layers were washed with a saturated NH₄Cl aqueous solution (1 L), water (4 × 1 L), dried with MgSO₄ and filtered. The solvent was removed under reduced pressure to get a yellow solid. The residue was purified by silica gel flash column chromatography (height 24 cm, width 8 cm) by dry loading and eluting with petroleum ether/dichloromethane (from 100:0 to 30:70). **2** was obtained as a pale yellow amorphous solid (33.84 g, 42%).

mp: 78 – 80 °C. *R_f* (in petroleum ether/dichloromethane = 70:30): 0.35. **¹H NMR** (300.1 MHz, CDCl₃) δ 7.76 – 7.66 (m, 3H), 7.61 – 7.53 (m, 1H), 7.43 – 7.33 (m, 3H), 7.31 – 7.21 (m, 5H), 7.21 – 7.13 (m, 2H). **¹⁹F NMR** (282.4 MHz, CDCl₃) δ –78.3 (s). **¹³C NMR** (75.5 MHz, CDCl₃) δ 148.5, 140.1, 138.2, 135.3, 132.2, 131.2, 130.9, 130.7, 129.7, 129.2, 128.1 (t, *J* = 326.2 Hz), 128.1, 127.8, 127.4, 122.0 (t, *J* = 1.5 Hz). **IR** (neat, cm^{–1}) ν: 3059, 2962, 1446, 1347, 1345, 1260, 1170, 1090, 1068, 902, 750. HRMS (ESI⁺) calcd for C₁₉H₁₈NO₂F₂S₂ *m/z* 394.0747 [M+NH₄]⁺, Found 394.0743 (Δ = –1.0 ppm).

2-([(Phenylsulfonyl)difluoromethyl]sulfinyl)-1,1'-biphenyl 3. In an oven-dried 1 L round-bottom flask equipped with a magnetic stir bar and purged with argon was charged with 2-([(phenylsulfonyl)difluoromethyl]sulfonyl)-1,1'-biphenyl **2** (33.84 g, 89.9 mmol, 1.0 equiv.) and CH₂Cl₂ (300 mL). The resulting mixture was cooled to 0 °C and *m*CPBA (74% purity) (23.90 g, 102.5 mmol, 1.14 equiv.) was added portionwise. The suspension was allowed to warm up to 21 °C and was stirred for 24 h. A saturated Na₂SO₃ aqueous solution (600 mL) was added to quench the reaction and the resulting solution was then extracted with CH₂Cl₂ (3 × 600 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. The crude sulfoxide **3** (35.28 g, quant.) was used without purification for the next step.

mp: 92 – 94 °C. *R_f* (in petroleum ether/dichloromethane = 70:30): 0.19. **¹H NMR** (300.1 MHz, CDCl₃) δ 8.20 – 8.12 (m, 1H), 7.95 – 7.88 (m, 2H), 7.80 – 7.71 (m, 1H), 7.69 – 7.51 (m, 4H), 7.45 – 7.37 (m, 4H), 7.35 – 7.27 (m, 2H). **¹⁹F NMR** (282.4 MHz, CDCl₃) δ –97.5 (d, *J* = 203.3 Hz, 1F), –113.2 (d, *J* = 203.3 Hz, 1F). **¹³C NMR** (75.5 MHz, CDCl₃) δ 143.6, 143.5, 136.8, 136.0, 134.4, 133.2, 132.5, 130.9, 130.6, 129.5, 128.4, 128.4, 128.3, 127.0, 123.5 (dd, *J* = 354.8, 347.3 Hz). **IR** (neat, cm^{–1}) ν: 1452, 1354, 1120, 1088, 755, 699. **HRMS** (ESI⁺) calcd for C₁₉H₁₅O₃F₂S₂ *m/z* 393.0431 [M+H]⁺, Found 393.0435 (Δ = 1.0 ppm).

Dibenzo[*b,d*]-5-[(phenylsulfonyl)difluoromethyl]-5*H*-thiophen-5-ium triflate I. In an oven-dried 1L round-bottom flask equipped with a magnetic stir bar and purged with argon was charged with 2-([(phenylsulfonyl)difluoromethyl]sulfinyl)-1,1'-biphenyl **3** (35.28 g, 89.9 mmol, 1.0 equiv.) and CH₂Cl₂ (200 mL). The resulting mixture was cooled to 0 °C and Tf₂O (15.20 mL, 89.9 mmol, 1.0 equiv.) was added dropwise. The mixture was allowed to warm up to 21 °C and was stirred for 20 min. The solvent was removed under reduced pressure and the resulting brown oil was dissolved in a minimum of CH₂Cl₂ (ca. 100 mL). Then, Et₂O (ca. 400 mL) was carefully added until all the

brown oil has turned to an off-white solid. The solvent was removed with a syringe or by filtration through a sintered glass funnel and fresh cold Et₂O was added to wash the solid and removed using the same technique. The resulting product was dried under vacuum to afford **I** as a pale-yellow solid (42.90 g, 91%).

mp: 143 – 145 °C. ¹H NMR (300.1 MHz, CDCl₃) δ 8.39 (d, *J* = 8.1 Hz, 2H), 8.22 – 8.08 (m, 4H), 7.98 – 7.88 (m, 3H), 7.81 – 7.67 (m, 4H). ¹⁹F NMR (282.4 MHz, CDCl₃) δ –78.8 (s, 3F), –82.2 (s, 2F). ¹³C NMR (75.5 MHz, CDCl₃) δ 141.9, 138.3, 136.4, 131.6, 131.3, 131.3, 130.6, 129.3, 126.1 (t, *J* = 360.1 Hz), 124.9, 121.8, 120.5 (q, *J* = 320.9 Hz). IR (neat, cm^{–1}) ν: 3101, 1451, 1360, 1256, 1166, 1140, 1029, 765. HRMS (ESI⁺) calcd for C₁₉H₁₃O₂F₂S₂ *m/z* 375.0325 [M–OTf]⁺, Found 375.0319 (Δ = –1.6 ppm).

Dibenzo[*b,d*]-5-[(phenylsulfonyl)difluoromethyl]-5*H*-thiophen-5-ium tetrafluoroborate II. Dibenzo[*b,d*]-5-[(phenylsulfonyl)difluoromethyl]-5*H*-thiophen-5-ium triflate **I** (1.0 g, 1.9 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂ (50 mL). The resulting mixture was washed with a saturated NaBF₄ aqueous solution (5 × 50 mL). Then, the organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure to afford **II** as a yellow solid (861 mg, 98%).

mp: 171 – 173 °C. ¹H NMR (300.1 MHz, (CD₃)₂CO) δ 8.71 – 8.64 (m, 2H), 8.63 – 8.56 (m, 2H), 8.23 – 8.08 (m, 5H), 8.03 – 7.87 (m, 4H). ¹⁹F NMR (282.4 MHz, (CD₃)₂CO) δ –82.1 (s, 2F), –150.1 (s, 1F), –150.1 (s, 3F). ¹³C NMR (75.5 MHz, (CD₃)₂CO) δ 143.2, 139.6, 137.5, 132.9, 132.3, 132.2, 131.9, 130.5, 126.8 (t, *J* = 357.1 Hz), 126.1, 123.6. IR (neat, cm^{–1}) ν: 3095, 1449, 1361, 1190, 1137, 1060, 764, 717. HRMS (ESI⁺) calcd for C₁₉H₁₃O₂F₂S₂ *m/z* 375.0325 [M–BF₄]⁺, Found 375.0335 (Δ = 2.7 ppm).

Dibenzo[*b,d*]-5-[(phenylsulfonyl)difluoromethyl]-5*H*-thiophen-5-ium hexafluorophosphate **III.** Dibenzo[*b,d*]-5-[(phenylsulfonyl)difluoromethyl]-5*H*-thiophen-5-ium triflate **I** (1.0 g, 1.9 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂ (50 mL). The resulting mixture was washed with a saturated KPF₆ aqueous solution (3 × 50 mL). Then, the organic phase was dried over Na₂SO₄ and the solvent was removed under reduced pressure to afford **III** as a yellow solid (898 mg, 90%).

mp: 165 – 167 °C. ¹H NMR (300.1 MHz, (CD₃)₂CO) δ 8.71 – 8.64 (m, 2H), 8.62 – 8.55 (m, 2H), 8.24 – 8.08 (m, 5H), 8.04 – 7.88 (m, 4H). ¹⁹F NMR (282.4 MHz, (CD₃)₂CO) δ –70.2 (s, 3F), –72.7 (s, 3F), –82.1 (s, 2F). ¹³C NMR (75.5 MHz, (CD₃)₂CO) δ 143.3, 139.7, 137.6, 133.0, 132.3, 132.2, 132.0, 130.5, 126.9 (t, *J* = 358.6 Hz), 126.2, 123.7. IR (neat, cm^{–1}) ν: 1449, 1374, 1179, 1120, 762, 717. HRMS (ESI⁺) calcd for C₁₉H₁₃O₂F₂S₂ *m/z* 375.0325 [M–PF₆]⁺, Found 375.0322 (Δ = –0.8 ppm).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

¹H, ¹⁹F and ¹³C NMR spectra of each compound, synthesis, characterization and financial estimation for the compounds **1** and PhSO₂CF₂H and the crystallographic data of **I** (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* **2008**, 37, 308–319. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd ed; Wiley-VCH: Weinheim, 2013.

(2) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem Soc. Rev.* **2008**, *37*, 320–330. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. (c) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals To Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* **2014**, *57*, 2832–2842. (d) Müller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science*, **2007**, *317*, 1881–1886.

(3) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506. (b) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633–10640. (c) Britton, R.; Gouverneur, V.; Lin, J.-H.; Meanwell, M.; Ni, C.; Pupo, G.; Xiao, J.-C.; Hu, J. Contemporary synthetic strategies in organofluorine chemistry. *Nat Rev Methods Primers* **2021**, *1*, 47.

(4) For a selection of reviews, see: (a) Kirk, K. L. Fluorination in Medicinal Chemistry: Methods, Strategies, and Recent Developments. *Org. Process Res. Dev.* **2008**, *12*, 305–321. (b) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264. (c) Besset, T.; Poisson, T.; Pannecoucke, X. Recent Progress in Direct Introduction of Fluorinated Groups on Alkenes and Alkynes by means of C–H Bond Functionalization. *Chem. Eur. J.* **2014**, *20*, 16830–16845. (d) Landelle, G.; Panossian, A.; Leroux, F. R. Trifluoromethyl ethers and -thioethers as tools for medicinal chemistry and drug discovery. *Curr. Top. Med. Chem.* **2014**, *14*, 941–951. (e) Merino, E.; Nevado, C. Addition of CF₃ across unsaturated moieties: a powerful functionalization tool. *Chem. Soc. Rev.* **2014**, *43*, 6598–

6608. (f) Egami, H.; Sodeoka, M. Trifluoromethylation of Alkenes with Concomitant Introduction of Additional Functional Groups. *Angew. Chem. Int. Ed.* **2014**, *53*, 8294–8308. (g) Charpentier, J.; Früh, N.; Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem. Rev.* **2015**, *115*, 650–682. (h) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073–9174. (i) Liu, X.; Xu, C.; Wang, M.; Liu, Q. Trifluoromethyltrimethylsilane: Nucleophilic Trifluoromethylation and Beyond. *Chem. Rev.* **2015**, *115*, 683–730. (j) Ni C.; Hu, J. The unique fluorine effects in organic reactions: recent facts and insights into fluoroalkylations. *Chem. Soc. Rev.* **2016**, *45*, 5441–5454. (k) Song, H.-X.; Han, Q.-Y.; Zhao, C.-L.; Zhang, C.-P. Fluoroalkylation reactions in aqueous media: a review. *Green Chem.* **2018**, *20*, 1662–1731. (l) Pan, Y. The Dark Side of Fluorine. *ACS Med. Chem. Lett.* **2019**, *10*, 1016–1019. (m) Ruyet, L.; Besset, T. Copper-based fluorinated reagents for the synthesis of CF₂R-containing molecules (R ≠ F). *Beilstein J. Org. Chem.* **2020**, *16*, 1051–1065. (n) Tian, F.; Yan, G.; Yu, J. Recent advances in the synthesis and applications of α-(trifluoromethyl)styrenes in organic synthesis. *Chem. Commun.* **2019**, *55*, 13486–13505.

(5) (a) Erickson, J. A.; McLoughlin, J. I. Hydrogen Bond Donor Properties of the Difluoromethyl Group. *J. Org. Chem.* **1995**, *60*, 1626–1631. (b) Banks, J. W.; Batsanov, A. S.; Howard, J. A. K.; O'Hagan, D.; Rzepa, H. S.; Martin-Santamaria, S. The preferred conformation of α-fluoroamides. *J. Chem. Soc. Perkin Trans. 2*, **1999**, *11*, 2409–2411. (c) Martínez, M. D.; Luna, L.; Tesio, A. Y.; Feresin, G. E.; Durán, F. J.; Burton, G. J. Antioxidant properties in a non-polar environment of difluoromethyl bioisosteres of methyl hydroxycinnamates. *Pharm. Pharmacol.* **2016**, *68*, 233–244. (d) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529–2591. (e) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg,

J. M.; Wang, F.; Lippard, S. J. CF₂H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **2017**, *139*, 9325–9332. (f) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept. *J. Med. Chem.* **2017**, *60*, 797–804. (g) Zafrani, Y.; Sod-Moriah, G.; Yeffet, D.; Berliner, A.; Amir, D.; Marciano, D.; Elias, S.; Katalan, S.; Ashkenazi, N.; Madmon, M.; Gershonov, E.; Saphier, S. CF₂H, a Functional Group-Dependent Hydrogen-Bond Donor: Is It a More or Less Lipophilic Bioisostere of OH, SH, and CH₃? *J. Med. Chem.* **2019**, *62*, 5628–5637. (h) Belhomme, M.-C.; Bayle, A.; Poisson, T.; Pannecoucke, X. Copper-Catalyzed Innate Ethoxycarbonyldifluoromethylation of Electron-Rich-Arenes. *Eur. J. Org. Chem.* **2015**, 1719–1726. (i) Ivanova, M. V.; Bayle, A.; Besset, T.; Pannecoucke, X.; Poisson, T. Copper-Mediated Introduction of the CF₂PO(OEt)₂ Motif: Scope and Limitations. *Chem. Eur. J.* **2017**, *23*, 17318–17338.

(6) Eto, H.; Kaneko, Y.; Takeda, S.; Tokizawa, M.; Sato, S.; Yoshida, K.; Namiki, S.; Ogawa, M.; Maebashi, K.; Ishida, K.; Matsumoto, M.; Asaoka, T. S. New Antifungal 1, 2, 4-Triazoles with Difluoro(substituted sulfonyl)methyl Moiety. *Chem. Pharm. Bull.* **2001**, *49*, 173–182.

(7) For a selection of reviews, see: (a) Prakash, G. K. S.; Hu, J. Selective fluoroalkylations with fluorinated sulfones, sulfoxides, and sulfides. *Acc. Chem. Res.* **2007**, *40*, 921–930. (b) Hu, J. Nucleophilic, radical, and electrophilic (phenylsulfonyl)difluoromethylations. *J. Fluorine Chem.* **2009**, *130*, 1130–1139. (c) Hu, J.; Zhang, W.; Wang, F. Selective difluoromethylation and monofluoromethylation reactions. *Chem. Commun.* **2009**, *48*, 7465–7478. (d) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. Recent advances in transition metal-catalyzed Csp²-monofluoro-, difluoro-, perfluoromethylation and trifluoromethylthiolation. *Beilstein J. Org. Chem.* **2013**, *9*, 2476–2536. (e) Sap, J. B. I.; Meyer, C. F.; Straathof, N. J. W.;

Iwumene, N.; am Ende, C. W.; Trabanco, A. A.; Gouverneur, V. Late-stage difluoromethylation: concepts, developments and perspective. *Chem. Soc. Rev.* **2021**, *50*, 8214–8247. (f) Jia, R.; Wang, X.; Hu, J. Recent advance in synthetic applications of difluoromethyl phenyl sulfone and its derivatives. *Tetrahedron Lett.* **2021**, *75*, 153182. For selected examples, see: (f) Su, Y.-M.; Hou, Y.; Yin, F.; Xu, Y.-M.; Li, Y.; Zheng, X.; Wang, X.-S. Visible Light-Mediated C–H Difluoromethylation of Electron-Rich Heteroarenes. *Org. Lett.* **2014**, *16*, 2958–2961. (g) Yin, G.; Zhu, M.; Fu, W. Visible-light mediated regioselective (phenylsulfonyl)difluoromethylation of fused imidazoles with iododifluoromethyl phenyl sulfone. *Heterocycl. Commun.* **2017**, *23*, 275–279. (h) Surapanich, N.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V. Palladium-Mediated Heck-Type Reactions of [(Bromodifluoromethyl)sulfonyl]benzene: Synthesis of α -Alkenyl- and α -Heteroaryl-Substituted α,α -Difluoromethyl Phenyl Sulfones. *Eur. J. Org. Chem.* **2012**, 5943–5946.

(8) (a) Zhang, W.; Zhu, J.; Hu, J. Electrophilic (phenylsulfonyl)difluoromethylation of thiols with a hypervalent iodine(III)–CF₂SO₂Ph reagent. *Tetrahedron Lett.* **2008**, *49*, 5006–5008. (b) He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. Copper-catalyzed di- and trifluoromethylation of α,β -unsaturated carboxylic acids: a protocol for vinylic fluoroalkylations. *Angew. Chem. Int. Ed.* **2012**, *51*, 3944–3947. (c) He, Z.; Hu, M.; Luo, T.; Li, L.; Hu, J. Copper-Catalyzed Difluoromethylation of β , γ -Unsaturated Carboxylic Acids: An Efficient Allylic Difluoromethylation. *Angew. Chem. Int. Ed.* **2012**, *51*, 11545–11547. (d) Wang, X.; Liu, G.; Xu, X.-H.; Shibata, N.; Tokunaga, E.; Shibata, N. S-((Phenylsulfonyl)difluoromethyl)thiophenium Salts: Carbon-Selective Electrophilic Difluoromethylation of β -Ketoesters, β -Diketones, and Dicyanoalkylidenes. *Angew. Chem. Int. Ed.* **2014**, *53*, 1827–1831.

(9) Nobile, E.; Castanheiro, T.; Besset, T. C–H Electrophilic (phenylsulfonyl)difluoromethylation of (hetero)arenes with a newly designed reagent. *Chem. Commun.* **2021**, 57, 12337–12340.

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(11) The difference between the Mp and DSC values is explained by a fast decomposition of the products during the DSC measurements.