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N,N-Dimethyl-*S*-difluoromethyl-*S*-phenylsulfoximinium tetrafluoroborate: A versatile electrophilic difluoromethylating reagent

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ABSTRACT

Over the past decade, sulfur-based fluoromethyl containing compounds have been exhaustively investigated as versatile fluoroalkylating reagents by our research laboratory as well as many others. Lately, we have designed a novel electrophilic difluoromethylating protocol employing *in situ* prepared *N,N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfoximinium salt. The present reagent provides excellent reactivity toward a broad spectrum of nucleophilic species (*N*-, *P*-, *S*-, and *O*-nucleophiles) to yield the corresponding difluoromethylated products with high efficacy under mild conditions. Additional studies have been performed to elucidate the mechanistic fundamentals of the reactions.

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1. Introduction

Fluoroorganics have been found to possess unique physicochemical and biological properties [1]. Among fluoromethyl functionalities, the difluoromethyl moiety is of particular interest due to its isostericity and isopolarity to an ethereal oxygen, and has been utilized to replace specific oxygen atoms in various bioactive species to increase their metabolic stability and bioavailability [2]. Over the past decade, sulfur-based fluoromethyl containing compounds have been extensively investigated as versatile fluoroalkylating reagents by Prakash and Hu, as well as many others [3]. Particularly, *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate was first synthesized and exploited in our laboratory as an efficient electrophilic difluoromethylating reagent toward a series of nucleophilic species to provide the corresponding difluoromethylated products [4a,b]. Despite its feasible synthetic applications under many chemical régimes, the drawback of this reagent was found to be its slow decomposition over time even under low temperatures.

Sulfoximines have been widely employed in synthetic chemistry as versatile reagents and valuable ligands [5]. Johnson et al. treated *N,N*-dimethyl-*S*-methyl-*S*-phenylsulfoximinium tetrafluoroborate (the Johnson reagent) with bases to afford the corresponding sulfur ylide, which is capable of transferring the methylene group to various substrates [6]. The preparation of fluorinated sulfoximines has been pioneered by Shreeve and coworkers, who have investigated the properties of a series of bis(perfluoromethyl)sulfoximines [7]. In 1988, Finch reported α-fluoromethyl-*N*-methyl-phenylsulfoximine as a fluoromethylenation reagent for ketones and aldehydes [8]. Lately, Shibata and coworkers demonstrated the synthetic utility of the trifluoromethylated and the monofluoromethylated Johnson reagents in the electrophilic fluoromethylation of various nucleophilic species [4d,e]. It is worth mentioning that Hu et al. have exploited *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine as a difluorocarbene precursor, which readily reacts with a variety of *S*-, *N*-, and *C*-nucleophiles [4c]. However, to the best of our knowledge, the difluoromethylated Johnson reagent remains unexplored. Herein, we would like to disclose the development of *N,N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfoximinium tetrafluoroborate salt (**1**) as a robust *electrophilic* difluoromethylating reagent. Generated *in situ* from shelf-stable *N*-methyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**3**), the present reagent has exhibited good reactivity toward a broad scope of nucleophiles (*N*-, *P*-, *S*-, and *O*-nucleophiles).

2. Results and discussion

The preparation of **2** was initially conducted by treating difluoromethyl phenyl sulfoxide ($PhSOCF_2H$) with sodium azide (NaN_3) in 25% fuming H_2SO_4 as the reaction medium [4d,9], which unfortunately led to a minor explosion (Scheme 1). In contrast, $PhSOCF_2H$ was intact when subjected to NaN_3 and 98% H_2SO_4 in chloroform [8]. After several attempts, we were able to obtain the desired product **2** in quantitative yield by using a combination of NaN_3/oleum/CH_2Cl_2 as the oxidative imination system [10]. The

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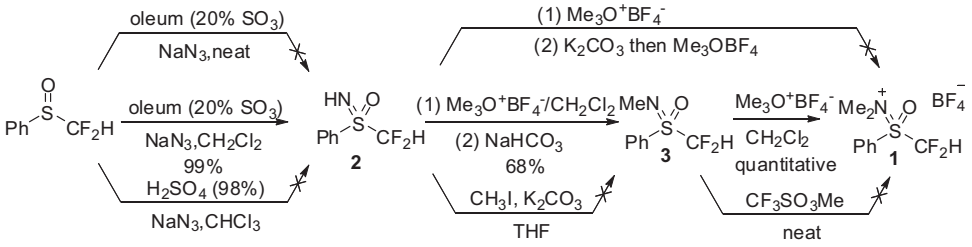


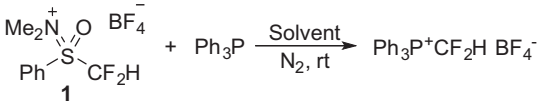
Scheme 1. Preparation of *N,N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfoximinium tetrafluoroborate (**1**).

subsequent methylation of **2** was first performed under the one-pot procedure described by Johnson [11], which resulted in the rapid decomposition of the parent sulfoximine. Further attempts to transform **2** via an established methylation protocol [4d], however, only gave the title products with unsatisfactory yields. Eventually, the methylation of **2** was achieved through a stepwise route utilizing trimethyloxonium tetrafluoroborate as the methylating reagent (Scheme 1). Obtained in high yields, salt **1** is a white solid possessing reasonable stability that allows its storage for several hours at room temperature [12]. Interestingly, in contrast to its trifluoromethylated analogue that was inert in MeOH [4d], a rapid reaction between **1** and CD_3OD has been observed via ^1H and ^{19}F NMR spectroscopy implying its remarkable reactivity [13]. Noticeably, despite the slight lability of sulfoximinium **1**, its precursor **3** has exhibited sufficient stability under ambient conditions permitting a facile access to **1**.

Having the difluoromethylated Johnson reagent **1** on hand, we were able to systematically investigate its difluoromethyl-transfer ability to an arsenal of nucleophilic species. An examination of various reaction media revealed that anhydrous dichloromethane is the optimal solvent for the difluoromethylation of triphenylphosphine (Table 1). Other solvents such as tetrahydrofuran (THF) and dimethylformaldehyde (DMF) were found to promote the decomposition of the reagent presumably due to their slight nucleophilicity. After a careful modification of the reaction parameters such as the addition sequences of the reagents and the proportions of substrates, the optimized yields were achieved by the treatment of **1** with 1.5 equiv. of various nucleophiles in dichloromethane at room temperature.

We subsequently explored the scope of current protocol with a wide range of phosphorus nucleophiles. As depicted in Table 2, the difluoromethylation reaction underwent smoothly with both aromatic and aliphatic phosphines to afford the corresponding difluoromethyl phosphonium salts in moderate to good yields (Entries 1–6 and 8, Table 2). Intriguingly, the steric characters of phosphorus nucleophiles seem to be crucial to the outcome of the reaction (Entry 7, Table 2). Although the *meta*- and the *para*-substituted aryl phosphines exhibited satisfactory reactivity toward sulfoximinium **1**, the presence of *ortho* substituents on the aromatic rings dramatically inhibits the reactivity of the phosphines.

Table 1
Optimization of the reaction conditions.

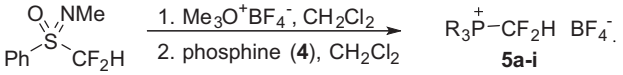


	CH_3CN	THF	DMF	CH_2Cl_2
Conv. (%)[a]	100	100	100	100
Yield (%)[a]	0	0	0	90

[a] Monitored by ^{19}F NMR using $PhCF_3$ as internal standard.

Intriguingly, the electrophilic difluoromethylating reagent **1** was also found to act as an ambident species capable of oxidizing phosphorous nucleophiles. Because the transformation from **3** to **1** was performed under heterogeneous conditions, control experiments have been performed to exclude the possible involvement of $Me_3O^+BF_4^-$ residue that can account for the observed side reaction. As depicted in Fig. 1B, the reaction between **3** and $Me_3O^+BF_4^-$, in a

Table 2
Difluoromethylation of phosphines using **1**.



Entry	Phosphine (**4**)	Product (**5**)	Yield (%)[a]
1	Ph_3P **4a**	$Ph_3P^+-CF_2H\ BF_4^-$ **5a**	90/57
2	$(n\text{-}Bu)_3P$ **4b**	$(n\text{-}Bu)_3P^+-CF_2H\ BF_4^-$ **5b**	64/53
3	Me, P–Ph, Me **4c**	Me, Ph–P+–CF2H BF4-, Me **5c**	84/49
4	P(3) **4d**	P+–CF2H BF4- (3) **5d**	87/49
5	P(3) **4e**	P+–CF2H BF4- (3) **5e**	65/43
6	P(3) **4f**	P+–CF2H BF4- (3) **5f**	80/56
7	P(3) **4g**	P+–CF2H BF4- (3) **5g**	0/0
8	MeO P(3) **4h**	MeO P+–CF2H BF4- (3) **5h**	50/35

[a] ^{19}F NMR yields/isolated yields based on **1**. The NMR yields were determined by ^{19}F NMR using $PhCF_3$ as the internal standard. The isolated yields were based on pure phosphonium salts, as the isolated products were found to be mixtures of phosphonium salts and the corresponding phosphine oxides in ca. 3:1 ratios, respectively.

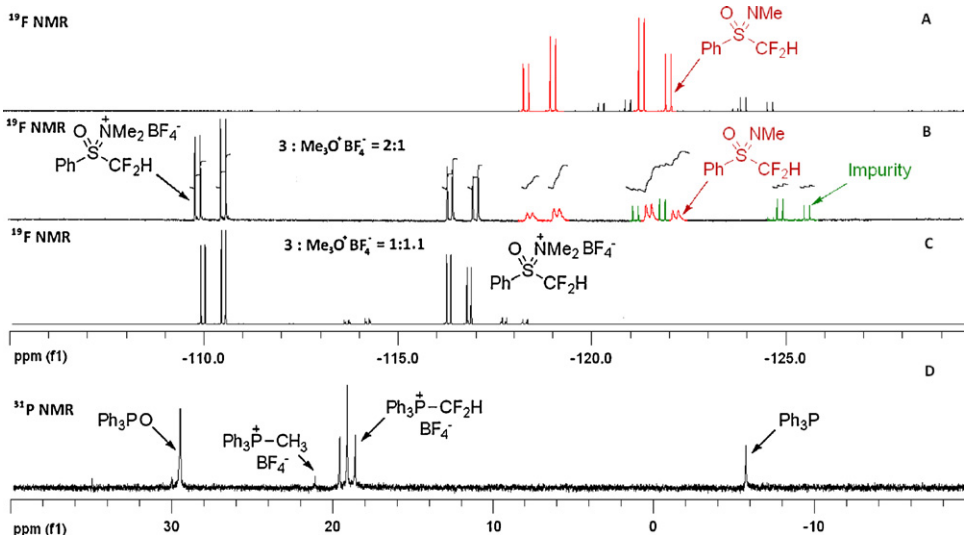
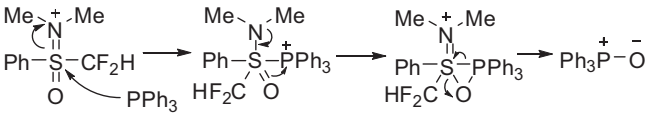


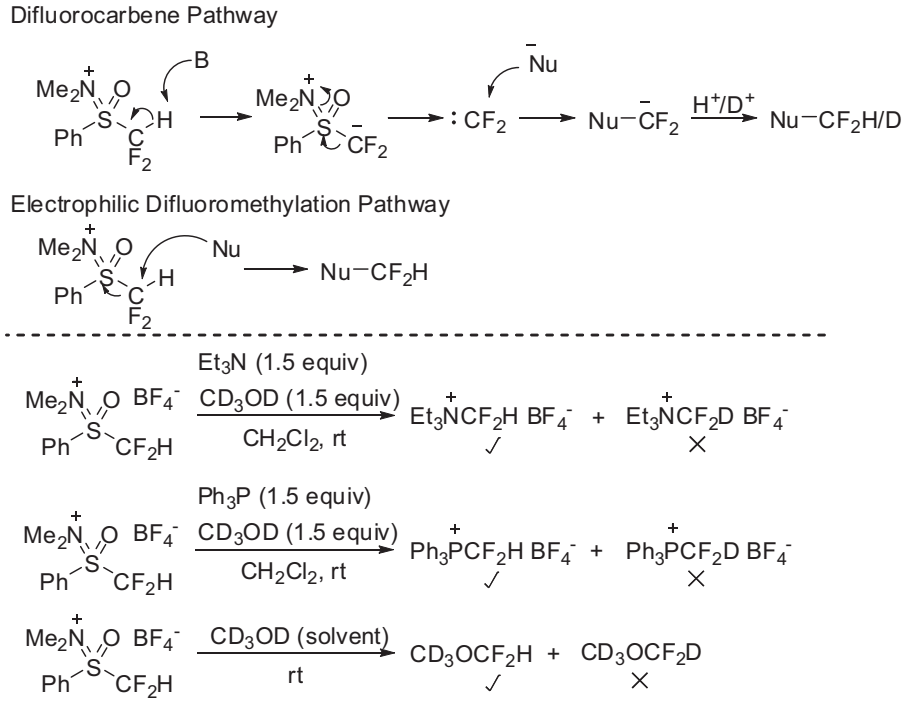
Fig. 1. Investigation of the difluoromethylation and oxidation ability of **1** with Ph_3P. (A) ^{19}F NMR spectrum of **3**; (B) ^{19}F NMR spectrum of the reaction mixture of **3** and $Me_3O^+BF_4^-$ in 2:1 ratio; (C) ^{19}F NMR spectrum of the reaction mixture of **3** and $Me_3O^+BF_4^-$ in 1:1 ratio; (D) ^{31}P NMR spectrum of the reaction mixture **B** and Ph_3P. All the spectra were taken in CD_3CN.



Scheme 2. Plausible mechanism of the oxidation of Ph_3P.

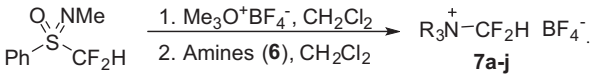
molar ratio of 2:1, gave a mixture of **3**, **1**, and a small amount of impurities in 4.1:2.7:0.7 ratio according to the ^{19}F NMR spectrum, which provides compelling evidence for the complete consumption of $Me_3O^+BF_4^-$ under the present reaction conditions. Further treatment of the same mixture with a stoichiometric amount of Ph_3P afforded the difluoromethyl phosphonium salt and the corresponding phosphine oxide in a ratio of approximately 3:1, which was similar to the observation in the reaction employing a slightly excess amount of $Me_3O^+BF_4^-$. This striking observation was found to resemble the previously described oxidation of phosphines with sulfoxides in the presence of Lewis acids, and a similar mechanism has been proposed (Scheme 2) [14].

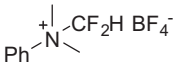
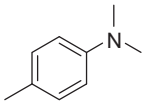
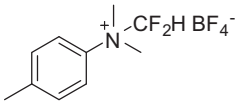
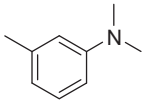
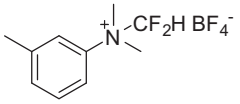
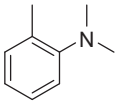
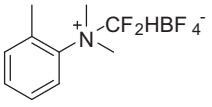
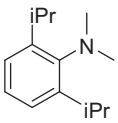
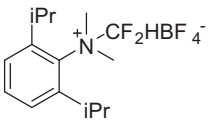
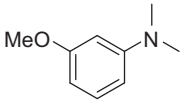
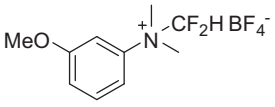
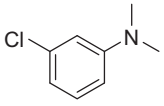
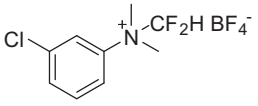
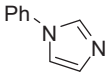
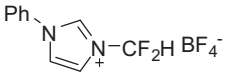
In addition to the phosphorus nucleophiles, a series of amines and several nitrogen-containing heterocyclic compounds were subjected to the reaction expecting the formation of difluoromethyl ammonium salts. Gratifyingly, tertiary amines were also found to readily react with **1** under the optimized reaction conditions. As shown in Table 3, the difluoromethylation of the tertiary amines generally gave the corresponding ammonium salts



Scheme 3. Mechanistic studies based on isotope-labeling experiments.

Table 3
Difluoromethylation of nitrogen nucleophiles using **1**.

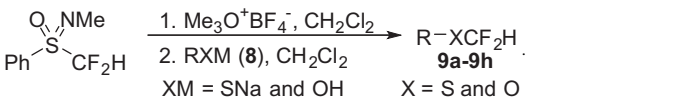


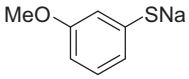
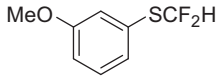
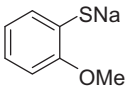
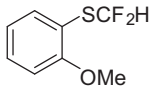
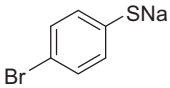
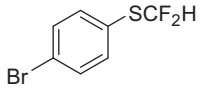
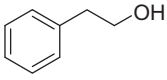
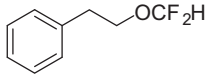
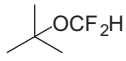
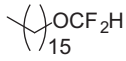
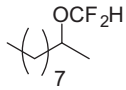
Entry	Substrate	Product	Yield (%)[a,b]
1	Et_3N **6a**	$Et_3N^+-CF_2H\ BF_4^-$ **7a**	99/69
2	 **6b**	 **7b**	76/71
3	 **6c**	 **7c**	72/70
4	 **6d**	 **7d**	90/83
5	 **6e**	 **7e**	20/–[c]
6	 **6f**	 **7f**	0/0
7	 **6g**	 **7g**	74/53
8	 **6h**	 **7h**	50/47
9	 **6i**	 **6i**	87/68

[a] The conversions of all the entries were monitored by ^{19}F NMR, and found to be 100%.
[b] ^{19}F NMR yields/isolated yields based on **1**, the NMR yields were determined by ^{19}F NMR using $PhCF_3$ as the internal standard.
[c] Not isolated.

in moderate to good yields as monitored by ^{19}F NMR spectroscopy (Entries 1–4 and 7–10, Table 3). Similar to the difluoromethylation of the phosphines, the reactivity of the amines toward **1** was also affected by the steric demand of the *ortho*-substituents. In particular, when highly bulky 2,2-diisopropyl aniline was subjected to the reaction, **1** was found to be intact. Noticeably, although 1-phenyl-1H-imidazole reacted with sulfoximinium **1** smoothly, the similar difluoromethylation of 1H-imidazole and pyridine was found to be rather sluggish. This observation,

Table 4
Difluoromethylation of sulfur and oxygen nucleophiles using **1**.



Entry	Substrate	Product	Yield (%)[a]
1	Ph–SNa **8a**	Ph–SCF_2H **9a**	78
2	 **8b**	 **9b**	45 (42)[b]
3	 **8c**	 **9c**	19
4	 **8d**	 **9d**	25
5	 **8e**	 **9e**	48 (32)[b,c]
6	 **8f**	 **9f**	45
7	 **8g**	 **9g**	25
8	 **8h**	 **9h**	37

[a] Yields were determined by ^{19}F NMR using $PhCF_3$ as the internal standard.
[b] The numbers in parentheses are isolated yields based on **1**.
[c] 2-Phenylethyl ether was found to be an inseparable impurity with the title product.

however, has not been rationalized yet. In particular, substantially differing from the reaction between **1** and phosphorous nucleophiles, oxidation of amines was not observed under the current reaction conditions.

We further investigated the reaction of reagent **1** with various oxygen and sulfur nucleophiles. Derived from the corresponding aryl thiols and NaH, sodium aryl thiolates displayed low to moderate reactivity toward sulfoximinium **1** (Entries 1–4, Table 4). In contrast, it has been observed that the treatment of **1** with sodium alkoxides and phenolates led to the rapid decomposition of the reagent instead of affording the corresponding difluoromethyl ethers. Surprisingly, the desired difluoromethyl ethers were achieved, when sulfoximinium **1** was reacted with a large excess amount of aliphatic alcohols (10 equiv.) under neutral conditions (Entries 5–8, Table 4). As depicted in Table 4, the current synthetic approach was applicable not only for the difluoromethylation of primary alcohols, but also for secondary and tertiary alcohols. It is worth noting that, in addition to (2-difluoromethoxyethyl)benzene, 2-phenylethyl ether was also isolated as the side product when 2-phenylethanol was employed as the substrate. Such an

outcome evidently indicates that the coupling reaction of nucleophiles toward the formation of the corresponding ethers is one of the significant competing reactions of the difluoromethylation process, which may account for the low yields observed in the reaction of **1** with alcohols. In particular, phenols were found to be inert under the present reaction conditions.

In an effort to gain the mechanistic insight into the protocol, isotope-labeling experiments have been performed to determine the pathway involved in the present reaction (Scheme 3). In theory, the difluoromethyl group is believed to undergo a deprotonation-protonation process in the difluorocarbene pathway. Hence, significant amounts of deuterated products (CF_2D) are anticipated in the presence of deuterated methanol under such mechanism. In contrast, such a proton–deuterium exchange is presumably unable to take place under the electrophilic difluoromethylation pathway due to the absence of the C–H cleavage. As demonstrated in Scheme 3, the results have ruled out difluorocarbene as a plausible intermediate under the current reaction conditions since no deuterated difluoromethyl group was detectable via ^{19}F NMR spectroscopy, which experimentally confirmed sulfoximinium **1** as a *de facto* electrophilic difluoromethylating reagent [15].

3. Conclusion

In conclusion, we have successfully prepared the unprecedented *N*,*N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfoximinium tetrafluoroborate as a versatile electrophilic difluoromethylating reagent. *In situ* generated from the shelf-stable *N*-methyl-*S*-difluoromethyl-*S*-phenylsulfoximine, difluoromethylated sulfoximinium salt has enabled a feasible synthetic approach toward a variety of difluoromethylated compounds. As a difluoromethylated analogue of the Johnson reagents, the compound has been found to transfer the difluoromethyl group via an electrophilic alkylation fashion instead of the commonly adopted difluorocarbene pathway.

4. Experimental

Unless otherwise mentioned, all chemicals were purchased from commercial sources. The NMR spectra were recorded on 400 MHz and 500 MHz superconducting NMR spectrometers, respectively. All the unknown compounds have been fully characterized by NMR spectroscopy and high resolution MS analysis, whereas structures of all known products were confirmed by comparison of their ^1H NMR and ^{19}F NMR spectra with reported data. ^1H NMR chemical shifts (δ) were determined relative to internal tetramethylsilane at δ 0.0 ppm or to the signal of a residual solvent in $CDCl_3$ (δ 7.26 ppm). ^{13}C NMR chemical shifts were determined relative to internal tetramethylsilane at δ 0.0 ppm or to the ^{13}C signal of $CDCl_3$ at δ 77.16 ppm. ^{19}F NMR chemical shifts were determined relative to internal $CFCl_3$ at δ 0.0 ppm. ^{31}P NMR chemical shifts were determined relative to internal H_3PO_4 (85%) at δ 0.0 ppm.

4.1. Typical procedure for the preparation of *S*-difluoromethyl-*S*-phenylsulfoximine (2)

$PhSOCF_2H$ (3.52 g, 20 mmol) was mixed with sodium azide (NaN_3, 2.6 g, 40 mmol) in dichloromethane (20 mL) under N_2. To the stirred reaction mixture, oleum (20%, 7.5 mL) was added dropwise within 15 min at −10 °C. The reaction was slowly warmed to room temperature and stirred over night. The resulting suspension was slowly poured into ice water (ca. 100 mL) and neutralized with NaOH (solid, 4.73 g, 120 mmol). $NaHCO_3$ was subsequently added in small portions until bubbling ceased. The mixture was then extracted with dichloromethane (50 × 3 mL). The combined organic phase was washed with water (20 mL) and dried over Na_2SO_4 before the removal of the solvent. The crude product was further purified by flash column chromatography (silicon gel) using hexane and ethyl acetate (4:1) as the eluent to afford an colorless oil (3.80 g, 99%). ^1H NMR ($CDCl_3$): δ 6.14 (t, J = 54.8 Hz, 1H), 7.57–7.66 (m, 2H), 7.73–7.77 (m, 1H), 8.06–8.08 (m, 2H). ^{19}F NMR ($CDCl_3$): δ −119.3 (dd, J = 258.5 Hz, J = 54.8 Hz, 1F), −122.4 (dd, J = 258.5, Hz J = 54.8 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 115.4 (t, J = 287.1 Hz), 129.5, 130.6, 133.3, 135.0. HRMS: calculated for $C_7H_8F_2NOS^+$ (MH^+) 192.0289, found: 192.0289.

4.2. Typical procedure for the preparation of *N*-methyl-*S*-difluoromethyl-*S*-phenyl sulfoximine (3)

S-Difluoromethyl-*S*-phenylsulfoximine **2** (3.80 g, 19.9 mmol) was dissolved in anhydrous dichloromethane (20 mL) under N_2. Trimethyloxonium tetrafluoroborate (3.25 g, 22 mmol) was added into the stirred solution in small portions. The reaction was monitored by thin layer chromatography until the completion. The resulting mixture was then quenched with saturated $NaHCO_3$ aqueous solution and extracted with dichloromethane (50 × 3 mL). The combined organic layer was dried over Na_2SO_4 before evaporation of the solvent. The crude product was purified by column chromatography (silica gel) using hexane and ethyl acetate (5:1) as the eluent to accommodate **2** as a colorless oil (2.8 g, 68%). ^1H NMR ($CDCl_3$): δ 2.98 (s, 3H), 6.20 (t, J = 54.4 Hz, 1H), 7.55–7.65 (m, 2H), 7.68–7.78 (m, 1H), 7.95–8.05 (m, 2H). ^{19}F NMR ($CDCl_3$): δ −118.0 (dd, J = 259.8 Hz, J = 54.3 Hz, 1F), −120.5 (dd, J = 259.7 Hz, J = 54.5 Hz, 1F). ^{13}C NMR ($CDCl_3$): δ 29.3, 115.6 (t, J = 287.8 Hz), 129.6, 130.8, 132.3, 134.7. HRMS: calculated for $C_8H_{10}F_2NOS^+$ (MH^+) 206.0446, found: 206.0447.

4.3. Typical procedure for the preparation of *N*,*N*-dimethyl-*S*-difluoromethyl-*S*-phenyl sulfoximinium tetrafluoroborate (1)

To a stirred solution of *N*-methyl-*S*-difluoromethyl-*S*-phenylsulfoximine **2** (3.08 g, 15 mmol) in anhydrous dichloromethane (15 mL), trimethyloxonium tetrafluoroborate (2.43 g, 16.5 mmol) was added all at once under N_2. The reaction mixture was stirred for 30 min before the removal of volatile substances under vacuum. A white solid was obtained and subject to the difluoromethylations reaction without further purification (4.3 g, 99%). ^1H NMR (CD_3CN): δ 3.24 (s, 6H), 7.70 (t, J = 51.5 Hz, 1H), 7.94–8.00 (m, 2H), 8.14–8.21 (m, 3H). ^{19}F NMR (CD_3CN): δ −108.9 (dd, J = 249.4 Hz, J = 51.9 Hz, 1F), −115.3 (dd, J = 248.5 Hz, J = 51.1 Hz, 1F), −154.0 (b, 4F). ^{13}C NMR (CD_3CN): δ 40.3, 117.2 (t, J = 295.8 Hz), 121.2, 132.6, 133.0, 141.0. HRMS calculated for $C_9H_{12}F_2NOS^+$ (M^+) 220.0602, found: 220.0601.

4.4. Typical procedure for difluoromethylations of phosphorus nucleophiles

To the *in situ* generated **1** (0.2 mmol), a solution of phosphines (**4a**–**4i**) (0.3 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was quickly added under N_2 protection and the reaction mixture was stirred for 1 h. The reaction was monitored via ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard. The solvent was then evaporated under vacuum and the residue was purified by flash column chromatography or thin layer chromatography (silica gel) using CH_2Cl_2 and MeOH as the eluent.

P-(Difluoromethyl)triphenylphosphonium tetrafluoroborate (**5a**). Yield = 82%. ^1H NMR (DMSO-d_6): δ 7.85–7.93 (m, 12H), 8.04–8.06 (m, 3H), 8.40 (dt, J = 47.1 Hz, J = 29.3 Hz, 1H). ^{19}F NMR (DMSO-d_6): δ −125.7 (dd, J = 77.3 Hz, J = 47.1 Hz, 2F), −147.65 (s, 1F), −147.70 (s, 3F).

P-(Difluoromethyl)tri(*n*-butyl)phosphonium Tetrafluoroborate (**5b**). Yield = 53%. ^1H NMR (CD_3OD): δ 1.01 (t, J = 7.2 Hz, 9H), 1.54 (sextet, J = 7.1 Hz, 6H), 1.65 (quintet, J = 7.1 Hz, 6H), 2.50–2.57 (m,

6H), 7.16 (dt, J = 47.3 Hz, J = 26.8 Hz, 1H). ^{19}F NMR (CD_3OD): δ −129.30 (dd, J = 68.9 Hz, J = 47.4 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F). ^{31}P NMR (CD_3OD): δ 38.2 (t, J = 68.9 Hz). ^{13}C NMR (CD_3OD): δ 12.1 (d, J = 0.8 Hz), 15.0 (d, J = 41.9 Hz), 22.7 (d, J = 5.0 Hz), 23.6 (d, J = 16.2 Hz), 113.95 (dt, J = 265.4 Hz, J = 75.4 Hz). HRMS calculated for $C_{13}H_{28}F_2P^+$ (M^+) Expected: 253.1891. Found: 253.1894.

P-(Difluoromethyl)dimethylphenylphosphonium tetrafluoroborate (**5c**). Yield = 70%. ^{1}H NMR (CD_3OD): δ 2.54 (d, J = 14.7 Hz, 6H), 7.10 (dt, J = 48.5 Hz, J = 28.8 Hz, 1H), 7.78–7.83 (m, 2H), 7.94 (t, J = 7.8 Hz, 1H), 8.04 (dd, J = 13.3 Hz, J = 8.2 Hz, 1H). ^{19}F NMR (CD_3OD): δ −126.55 (dd, J = 77.7 Hz, J = 47.3 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F). ^{31}P NMR (CD_3OD): δ 28.0 (t, J = 77.9 Hz). ^{13}C NMR (CD_3OD): δ 2.54 (d, J = 52.2 Hz), 114.9 (dt, J = 265.3 Hz, J = 84.4 Hz), 123.3 (d, J = 87.5 Hz), 131.4 (d, J = 13.1 Hz), 134.0 (d, J = 10.4 Hz), 137.2 (d, J = 3.3 Hz). HRMS calculated for $C_9H_{12}F_2P^+$ (M^+) Expected: 189.0639. Found: 189.0639.

P-(Difluoromethyl)tricyclohexylphosphonium tetrafluoroborate (**5d**). Yield = 69%. ^{1}H NMR (CD_3OD): δ 2.59 3.00 (m, 30H), 2.93 (m, 3H), 7.32 (dt, J = 46.8 Hz, J = 26.3 Hz, 1H). ^{19}F NMR (CD_3OD): δ −126.9 (dd, J = 61.1 Hz, J = 47.0 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F).

P-(Difluoromethyl)tri(*p*-tolyl)phosphonium tetrafluoroborate (**5e**). Yield = 61%. ^{1}H NMR (CD_3OD): δ 2.54 (s, 9H), 7.34–7.71 (m, 12H), 7.95 (dt, J = 47.3 Hz, J = 29.6 Hz). ^{19}F NMR (CD_3OD): δ −126.72 (dd, J = 76.9 Hz, J = 47.4 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F). ^{31}P NMR (CD_3OD): δ 18.7 (t, J = 77.0 Hz). ^{13}C NMR (CD_3OD): δ 21.9, 110.2 (d, J = 88.8 Hz), 115.9 (dt, J = 268.3 Hz, J = 87.0 Hz), 132.8 (d, J = 13.6 Hz), 135.8 (d, J = 10.8 Hz), 150.1 (d, J = 3.2 Hz). HRMS calculated for $C_{22}H_{22}F_2P^+$ (M^+) Expected: 355.1422. Found: 355.1421.

P-(Difluoromethyl)tri(*m*-tolyl)phosphonium tetrafluoroborate (**5f**). Yield = 78%. ^{1}H NMR (CD_3OD): δ 2.47 (s, 9H), 7.58–7.65 (m, 6H), 7.70–7.74 (m, 3H), 7.84–7.85 (m, 3H), 7.96 (dt, J = 47.3 Hz, J = 29.6 Hz, 1H). ^{19}F NMR (CD_3OD): δ −126.24 (dd, J = 77.0 Hz, J = 47.3 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F). ^{31}P NMR (CD_3OD): δ 19.1 (t, J = 77.0 Hz). ^{13}C NMR (CD_3OD): δ 21.3, 113.6 (d, J = 85.0 Hz), 115.9 (dt, J = 272.0 Hz, J = 89.5 Hz), 132.0 (d, J = 14.1 Hz), 133.2 (d, J = 10.3 Hz), 135.7 (d, J = 10.3 Hz), 138.8 (d, J = 3.2 Hz), 143.0 (d, J = 13.3 Hz). HRMS calculated for $C_{22}H_{22}F_2P^+$ (M^+) Expected: 355.1422. Found: 355.1423.

P-(Difluoromethyl)tri(*p*-methoxyphenyl)phosphonium tetrafluoroborate (**5 h**). Yield = 48%. ^{1}H NMR (CD_3OD): δ 3.96 (s, 9H), 7.33–7.36 (m, 6H), 7.69–7.74 (m, 6H), 7.76 (dt, J = 47.7 Hz, J = 29.1 Hz, 1H). ^{19}F NMR (CD_3OD): δ −127.62 (dd, J = 76.5 Hz, J = 47.6 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F). ^{31}P NMR (CD_3OD): δ 17.7 (t, JP-F = 76.5 Hz). ^{13}C NMR (CD_3OD): δ 56.7, 103.8 (d, J = 95.3 Hz), 115.9 (dt, J = 266.8 Hz, J = 88.5 Hz), 117.8 (d, J = 14.3 Hz), 137.9 (d, J = 12.1 Hz), 167.7 (d, J = 3.1 Hz). HRMS calculated for $C_{22}H_{22}F_2O_3P^+$ (M^+) Expected: 403.1269. Found: 403.1268.

4.5. Typical procedure for difluoromethylations of nitrogen nucleophiles

To the *in situ* generated **1** (0.2 mmol), a solution of amines or nitrogen-containing heterocyclics (**6a–6j**) (0.3 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was quickly added under N_2 protection and the reaction mixture was stirred for 1 h. The reaction was monitored via ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard. The solvent was then evaporated under vacuum and the residue was purified by flash column chromatography or thin layer chromatography (silica gel) using CH_2Cl_2 and MeOH as the eluent.

N-(Difluoromethyl)triethylammonium tetrafluoroborate (**7a**). Yield: 69%. ^{1}H NMR (CD_3OD): δ 1.42 (q, J = 5 Hz, 9H), 3.67(t, J = 5 Hz, 6H), 7.14 (t, J = 55.0 Hz, 1H). ^{19}F NMR (CD_3OD): δ −112.97 (d, J = 56.0 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F).

N-(Difluoromethyl)-*N*,*N*-dimethylanilinium tetrafluoroborate (**7b**). Yield: 71%. ^{1}H NMR (DMSO-d_6): δ 3.77 (s, 6H), 7.56 (t, J = 58.6 Hz, 1H), 7.61–7.62 (m, 3H), 7.86–7.88 (m, 2H). ^{19}F NMR (DMSO-d_6): δ −115.04 (d, J = 61.0 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F).

N-(Difluoromethyl)-*N*,*N*-dimethyl-*p*-toluenedinium tetrafluoroborate (**7c**). Yield: 70%. ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H), 3.78 (s, 6H), 7.41–7.52 (m, 2H), 7.55 (t, J = 60.0 Hz, 1H), 7.81–7.87 (m, 2H). ^{19}F NMR (DMSO-d_6): δ −117.10 (d, 2F, J = 56 Hz), −153.95 (s, 1F), −154.00 (s, 3F).

N-(Difluoromethyl)-*N*,*N*-dimethyl-*m*-toluenedinium tetrafluoroborate (**7d**). Yield: 83%. ^{1}H NMR (DMSO-d_6): δ 3.02 (s, 3H), 4.25 (t, J = 1.5 Hz, 6H), 7.60 (t, J = 58.8 Hz, 1H), 8.06–8.09 (m, 1H), 8.11–8.16 (m, 1H), 8.20–8.23 (m, 1H). ^{19}F NMR (DMSO-d_6): δ −114.5 (dt, J = 58.8 Hz, J = 1.5, Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F). ^{13}C NMR (CD_3OD): δ 21.4, 49.1, 117.0 (t, J = 277.6 Hz), 120.2, 123.6, 131.7, 133.6, 141.4, 143.1. HRMS calculated for $C_{10}H_{14}F_2N^+$ (M^+) Expected: 186.1089. Found: 186.1089.

N-(Difluoromethyl)-*N*,*N*-dimethyl-*m*-aminoanisolium tetrafluoroborate (**7 g**). Yield: 53%. ^{1}H NMR (CD_3OD): δ 3.83 (s, 6H), 3.92 (s, 3H), 7.29 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 58.9 Hz, 1H, partially overlapping with aromatic signals), 7.43–7.50 (m, 2H), 7.63 (t, J = 8.4 Hz, 1H). ^{19}F NMR (CD_3OD): δ −112.16 (d, J = 58.7 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F). ^{13}C NMR (CD_3OD): δ 49.2 (partially overlapping with solvent signal), 56.7, 109.8, 114.8, 117.0 (t, J = 277.5 Hz, partially overlapping with aromatic signals), 142.4, 162.7. HRMS calculated for $C_{10}H_{14}F_2NO^+$ (M^+) Expected: 202.1038. Found: 202.1038.

N-(Difluoromethyl)-*N*,*N*-dimethyl-*m*-chloroanilinium tetrafluoroborate (**7h**). Yield: 47%. ^{1}H NMR (CD_3OD): δ 3.87 (t, J = 2.4 Hz, 6H), 7.45 (t, J = 58.6 Hz, 1H), 7.71–7.79 (m, 2H), 7.93 (d, J = 8.1 Hz, 1H), 8.11 (pseudo t, J = 2.1 Hz, 1H). ^{19}F NMR (CD_3OD): δ −111.2 (d, J = 58.6 Hz, 2F), −153.95 (s, 1F), −154.00 (s, 3F). ^{13}C NMR (CD_3OD): δ 49.2, 109.8, 114.8, 117.0 (t, J = 280.7 Hz), 118.1, 132.8, 142.4, 162.7. HRMS calculated for $C_9H_{11}ClF_2N^+$ (M^+) Expected: 206.0543. Found: 206.0543.

N-(Difluoromethyl)-3-phenylimidazolium tetrafluoroborate (**7i**). Yield: 68%. ^{1}H NMR (CD_3CN): 7.61 (t, J = 59.1 Hz, 1H), 7.66 (5H), 7.94 (s, 1H), 7.96 (s, 1H), 9.41 (s, 1H). ^{19}F NMR (CD_3CN): 95.5 (d, J = 59.0 Hz), −153.95 (s, 1F), −154.00 (s, 3F).

4.6. Typical procedure for difluoromethylations of sulfur nucleophiles

To a stirred solution of aryl thiols (**8a–8d**) (0.3 mmol) in anhydrous THF, NaH (0.3 mmol) was added in small portions under N_2. The solvent was evaporated under vacuum until the bubbling ceased. The residue was added to freshly prepared **1** (0.2 mmol) in one portion under N_2 and the reaction mixture was stirred for 1 h. The reaction was monitored via ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard, and the yields were calculated on the basis of substrate **1** used.

4.7. Typical procedure for difluoromethylations of oxygen nucleophiles

To the *in situ* generated **1** (0.2 mmol), a solution of alcohols (**8e–8h**) (2 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was quickly added under N_2 protection and the reaction mixture was stirred for 1 h. The reaction was monitored via ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard, and the yields were calculated on the basis of substrate **1** used.

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