Supporting Information

***N*-Tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine: A New Difluoromethylation Reagent for *S*-, *N*-, and *C*-Nucleophiles**

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General Methods:

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. The solvent CH₃CN and DMF were distilled from CaH₂, and the solvent THF was distilled from sodium. ¹H, ¹³C and ¹⁹F NMR spectra were recorded on a 400 MHz or 300 MHz NMR spectrometer. ¹H NMR chemical shifts were determined relative to internal (CH₃)₄Si (TMS) at δ 0.0 or to the signal of a residual protonated solvent: CDCl₃ δ 7.26. ¹³C NMR chemical shifts were determined relative to internal TMS at δ 0.0. ¹⁹F NMR chemical shifts were determined relative to CFCl₃ at δ 0.0. Mass spectra were obtained on a mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI, ESI or MALDI mode.

Preparation of *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**2**):

Under N₂ atmosphere, difluoromethyl phenyl sulfoxide (**3**) (2.0 g, 11.4 mmol, 1.0 equiv.) was added to a solution of Cu(TfO)₂ (0.41 g, 1.14 mmol, 10 %mol) in CH₃CN (45 ml) at rt. PhI=NTs (**4**) (5.33 g, 14.3 mmol, 1.3 equiv.) was then dropped in one batch. The mixture was heated to 50 °C for 24h. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:5, v/v) as eluent to give product **2** (2.34 g, 6.78 mmol, yield: 60%). Mp. 96–98 °C. IR (film): 3037, 1600, 1450, 1325, 1241, 1155, 1054, 661, 539 cm⁻¹. ¹H NMR: δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 55.2 Hz, 1H), 2.41 (s, 3H). ¹⁹F NMR: δ -114.7 (dd, ²*J*_{F-F} = 247.0 Hz, ³*J*_{H-F} = 53.6 Hz, 1F). δ -120.8 (dd, ²*J*_{F-F} = 247.9 Hz, ³*J*_{H-F} = 55.0 Hz, 1F). ¹³C NMR: δ 143.8, 139.5, 136.2, 130.8, 129.8, 129.6, 128.0, 126.9, 115.5 (t, *J* = 289.5 Hz), 21.6. MS (ESI): *m/z* 368 (M+Na⁺). Anal. Calcd. for C₁₄H₁₃F₂NO₃S₂: C, 48.68; H, 3.79; N, 4.06; Found: C, 48.62; H, 3.99; N, 3.90.

ORTEP Drawing of Compound 2:

Typical procedure for electrophilic difluoromethylation of S-nucleophiles with reagent 2 (Table 1, entries 1-9):

Under N₂ atmosphere, NaH (60%, wt.%, 11 mg, 1.1 equiv.) was added to a solution of 4-nitrobenzenethiol (**5b**) (40 mg, 1.0 equiv.) in DMF (4 ml) at rt. After stirring for 30 min, compound **2** (107 mg, 1.2 equiv.) was added, the mixture was heated to 60°C for 14 h. Then, the reaction was quenched by adding excess amount of H₂O, followed by extraction with Et₂O. The organic phase was washed successively with NaOH (5%) and brine, and then dried over anhydrous MgSO₄. After the solution was filtered and

the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **6b** (40 mg, yield: 76%) as a yellow liquid. ^1H NMR: δ 8.24 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 6.95 (t, J = 55.8 Hz, 1H). ^{19}F NMR: δ -91.2 (d, J = 55.3 Hz, 2F). MS (EI, m/z , %): 205 (M^+ , 100.00). The characterization data was consistent with the previous report.¹

Characterization data for the isolated compounds:

(difluoromethyl)(2,5-dimethoxyphenyl)sulfane (**6c**): Pink liquid. IR (film): 2838, 1494, 1274, 1224, 1044, 797, 735 cm^{-1} . ^1H NMR: δ 7.09 (d, J = 3.0 Hz, 1H), 6.96 (t, J = 58.2 Hz, 1H), 6.86–6.95 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H). ^{19}F NMR: δ -92.5 (d, J = 57.2 Hz, 2F). ^{13}C NMR: δ 153.7, 129.0, 127.6, 121.4, 120.6 (t, J = 271.8 Hz), 116.6, 112.5, 56.6, 55.8. MS (EI, m/z , %): 220 (M^+ , 7.50), 123 (100.00). HRMS (EI): calcd. for $\text{C}_9\text{H}_{10}\text{F}_2\text{O}_2\text{S}$: 220.0370; Found: 220.0367.

(difluoromethyl)(2-methoxyphenyl)sulfane (**6f**): Colorless liquid. IR (film): 2943, 1587, 1481, 1277, 1250, 1077, 1025, 753 cm^{-1} . ^1H NMR: δ 7.52 (d, J = 7.5 Hz, 1H), 7.36–7.42 (m, 1H), 6.93–6.98 (m, 2H), 6.94 (t, J = 54.4 Hz, 1H), 3.89 (s, 3H). ^{19}F NMR: δ -92.5 (d, J = 57.8 Hz, 2F). ^{13}C NMR: δ 159.5, 136.6, 131.5, 121.3, 120.6 (t, J = 271.5 Hz), 115.0, 111.5, 56.0. MS (EI, m/z , %): 190 (M^+ , 0.82), 248 (100.00). HRMS (EI): calcd. for $\text{C}_8\text{H}_8\text{F}_2\text{OS}$: 190.0264; Found: 190.0271.

3-(difluoromethyl)benzo[d]thiazole-2(3H)-thione (**6ha**): White solid. ^1H NMR: δ 8.08 (t, J = 57.6 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.18–7.39 (m, 3H). ^{19}F NMR: δ -106.0 (d, J = 56.7 Hz, 2F). The characterization data was consistent with the previous report.²

2-(difluoromethylthio)benzo[d]thiazole (**6hb**): Yellow liquid. ^1H NMR: δ 7.91 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 55.8 Hz, 1H), 7.17–7.43 (m, 2H).

^{19}F NMR: δ -93.1 (d, J = 55.8 Hz, 2F). MS (EI, m/z , %): 217 (M^+ , 35.77), 167 (100.00). The characterization data was consistent with the previous report.²

1-(difluoromethyl)-4-phenyl-1H-tetrazole-5(4H)-thione (6i): White solid. ^1H NMR: δ 7.82 (d, J = 7.8 Hz, 2H), 7.46–7.55 (m, 3H), 7.55 (t, J = 57.0 Hz, 1H). ^{19}F NMR: δ -102.9 (d, J = 56.7 Hz, 2F). MS (EI, m/z , %): 228 (M^+ , 3.64), 123 (100.00). The characterization data was consistent with the previous report.³

Difluoromethylation of sodium 4, 6-dimethylpyrimidine-2-thiolate (5j) With Reagent 2 (Table 1, entry 10):

Under N_2 atmosphere, compound **2** (102 mg, 1.2 equiv) was added to the solution of sodium 4, 6-dimethylpyrimidine-2-thiolate (**5j**) (40 mg, 1 equiv) in DMF (4 ml). After stirring for 14 h at 60°C, the reaction was quenched by adding excess amount of H_2O , followed by extraction with Et_2O . The organic phase was washed with brine, and then dried over anhydrous MgSO_4 . After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **6j** (33 mg, 71%). Colorless solid. ^1H NMR: δ 7.85 (d, J = 55.8 Hz, 1H), 6.81 (s, 1H), 2.43 (s, 6H). ^{19}F NMR: δ -99.5 (d, J = 57.8 Hz, 2F). The characterization data was consistent with the previous report.⁴

Typical procedure for electrophilic difluoromethylation of N-nucleophiles with reagent 2 (Table 2, entries 1-9).

The *N*-difluoromethylated products were prepared by the same procedure for *S*-difluoromethylation with reagent **2** which is described above.

Characterization data for the isolated compounds:

1-(difluoromethyl)-5,6-dimethyl-1H-benzo[d]imidazole (8a): White solid. mp. 131-132°C. IR (film): 1513, 1470, 1371, 1212, 1083, 1046, 867 cm^{-1} . ^1H NMR: δ 7.99 (s, 1H), 7.59 (s, 1H), 7.38 (s, 1H), 7.26 (t, J = 60.3 Hz, 1H), 2.39 (d, J = 4.8 Hz,

2H). ^{19}F NMR: δ -93.9 (d, J = 60.1 Hz, 2F). ^{13}C NMR: δ 142.5, 138.3, 134.2, 133.2, 120.8, 111.2, 109.0 (t, J = 247.5 Hz, 1H), 20.5, 20.1. MS (ESI): m/z 197 ($\text{M}+\text{H}^+$). HRMS ($\text{M}+\text{H}^+$): calcd. for $\text{C}_{10}\text{H}_{11}\text{F}_2\text{N}_2$: 197.08848; Found: 197.0873.

1-(difluoromethyl)-2-phenyl-1H-benzo[d]imidazole (8b): Colorless liquid. ^1H NMR: δ 7.71–7.86 (m, 4H), 7.55–7.59 (m, 3H), 7.38–7.43 (m, 2H), 7.28 (t, J = 58.8 Hz, 1H). ^{19}F NMR: δ -94.8 (d, J = 58.1 Hz, 2F). The characterization data was consistent with the previous report.⁵

1-(difluoromethyl)-6-nitro-1H-benzo[d]imidazole (8ca) and *1-(difluoromethyl)-5-nitro-1H-benzo[d]imidazole (8cb)*: White solid. IR (film): 3115, 1622, 1521, 1346, 1305, 1051, 810 cm^{-1} . ^1H NMR: δ 8.76 (d, J = 2.1 Hz, 1H), 8.60 (d, J = 1.8 Hz, 1H), 8.32–8.41 (m, 4H), 7.96 (d, J = 9.3 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.49 (t, J = 59.7 Hz, 1H), 7.46 (t, J = 60.0 Hz, 1H). ^{19}F NMR: δ -94.3 (d, J = 61.5 Hz, 2F), -94.5 (d, J = 58.4 Hz, 2F). ^{13}C NMR: δ 148.1, 145.1, 145.0, 143.6, 143.4, 142.2, 134.5, 129.9, 121.4, 120.4, 119.9, 117.5, 111.6, 108.8 (t, J = 251.7 Hz), 108.2. MS (EI, m/z , %): 213 (100.00). HRMS (EI): calcd. for $\text{C}_8\text{H}_5\text{F}_2\text{N}_3\text{O}_2$: 213.0340; Found: 213.0355.

1-(difluoromethyl)-2-phenyl-1H-imidazole (8d): White solid. ^1H NMR: δ 7.60–7.63 (m, 2H), 7.52–7.55 (m, 3H), 7.42 (s, 1H), 7.25 (s, 1H), 7.08 (d, J = 59.4 Hz, 1H). ^{19}F NMR: δ -90.9 (d, J = 59.8 Hz, 2F). The characterization data was consistent with the previous report.⁶

2-(difluoromethyl)-5-phenyl-2H-tetrazole (8ea): Colorless liquid. ^1H NMR: δ 8.21–8.24 (m, 2H), 7.68 (d, J = 57.3 Hz, 1H), 7.49–7.56 (m, 3H). ^{19}F NMR: δ -97.8 (d, J = 56.1 Hz, 2F). The characterization data was consistent with the previous report.⁶

1-(difluoromethyl)-5-phenyl-1H-tetrazole (8eb): Colorless liquid. ^1H NMR: δ 7.86 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 57.6 Hz, 1H), 7.57–7.66 (m, 3H). ^{19}F NMR: δ –94.8 (d, J = 57.2 Hz, 2F). The characterization data was consistent with the previous report.⁶

1-(difluoromethyl)-1H-benzo[d]imidazole (8f): White solid. ^1H NMR: δ 8.13 (s, 1H), 7.85–7.88 (m, 1H), 7.61–7.64 (m, 1H), 7.37–7.44 (m, 2H), 7.34 (d, J = 60.3 Hz, 1H). ^{19}F NMR: δ –94.1 (d, J = 60.9 Hz, 2F). The characterization data was consistent with the previous report.⁵

1-(difluoromethyl)-1H-benzo[d][1,2,3]triazole (8g): White solid. ^1H NMR: δ 8.15 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 3.6 Hz, 1H), 7.83 (t, J = 62.1 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.50 (t, J = 8.1 Hz, 1H). ^{19}F NMR: δ –97.5 (d, J = 53.3 Hz, 2F). The characterization data was consistent with the previous report.⁵

3-(difluoromethoxy)-1-phenyl-4,5-dihydro-1H-pyrazole (8h): Colorless liquid. ^1H NMR: δ 7.26 (t, J = 7.8 Hz, 2H), 7.11 (d, J = 72.0 Hz, 1H), 6.95 (d, J = 7.5 Hz, 2H), 6.86 (t, J = 7.5 Hz, 1H), 3.83 (t, J = 9.6 Hz, 2H), 3.02 (t, J = 9.6 Hz, 2H). ^{19}F NMR: δ –87.4 (d, J = 72.0 Hz, 2F).

Typical procedure for electrophilic difluoromethylation of C-nucleophiles with reagent 2 (Table 3, entries 1-5):

Under N_2 atmosphere, butyllithium (1.6 M, 0.29ml, 1.0 equiv) was added to a solution of phenylacetylene (**9a**) (48 mg, 1.0 equiv) in THF (3 ml) at 0°C . After stirring for 0.5 h, reagent **2** (81 mg, 0.5 equiv) was added at -78°C , then the mixture was gradually warmed to room in 6h. The reaction was quenched by adding excess amount of H_2O , followed by extraction with Et_2O . The yield which was determined by ^{19}F NMR spectroscopy using PhCF_3 as internal standard is 87%. The organic phase was washed with brine, and then dried over anhydrous MgSO_4 . After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **10a** (11 mg, 30%). The isolated yield is low

due to the high volatility of the products **10a**). Colorless liquid. ^1H NMR: δ 7.53–7.51 (m, 2H), 7.39–7.36 (m, 3H), 6.52 (t, $J = 54.9$ Hz, 1H). ^{19}F NMR: δ –105.6 (d, $J = 54.9$ Hz, 2F). The characterization data was consistent with the previous report.⁸

1-(3,3-difluoroprop-1-ynyl)-4-methoxybenzene (10b): ^{19}F NMR: δ –104.5 (d, $J = 56.4$ Hz, 2F).

1-(3,3-difluoroprop-1-ynyl)-4-methylbenzene (10c): ^{19}F NMR: δ –107.2 (d, $J = 54.4$ Hz, 2F).

1-(3,3-difluoroprop-1-ynyl)-4-methoxy-2-methylbenzene (10d): ^{19}F NMR: δ –105.5 (d, $J = 55.0$ Hz, 2F).

2-(3,3-difluoroprop-1-ynyl)-6-methoxynaphthalene (10e): ^{19}F NMR: δ –106.1 (d, $J = 55.6$ Hz, 2F).

Difluoromethylation of Sodium Thiophenolate With Reagent 2 By Added 10 Equivalents of D₂O (Scheme 3, Eq 1):

Under N₂ atmosphere, compound **2** (73 mg, 1.3 equiv), and D₂O (33 μl , 10.0 equiv) was added to the sodium thiophenolate (**5a'**) (90% purity, 24 mg, 1.0 equiv) in DMF (4 ml). After stirring for 14 h at 60 °C, the reaction mixture was detected by ^{19}F NMR: PhSCF₂H (**6a**): –89.6 (d, $J = 56.1$ Hz), PhSCF₂D (**6a'**): –90.3 (t, $J = 7.6$ Hz). The overall yield of **6a** and **6a'** is 80%, and the ratio of **6a** : **6a'** is 1:6.

References:

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^1H , ^{19}F , and ^{13}C NMR spectra of all new products:

^{19}F NMR

^{13}C NMR