SUPPLEMENTARY INFORMATION

Synthesis of Aryl α,α-Difluoroethyl Thioethers a new Structure Motif in Organic Chemistry, extending to Aryl α,α-Difluoro Oxyethers

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General Experimental Procedures

All commercially available reagents were purchased from Alfa Aesar, Fisher Scientific, Fluorochem and Sigma Aldrich, and used without further purification. 1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TMS-EBX) was prepared in accordance with the literature procedures. CH₂Cl₂ and toluene were obtained from the MBraun SPS-800 Solvent Purification System, by passing the solvent through two drying columns under an argon atmosphere. Reactions involving the use of HF·Py were carried out in Teflon round-bottom flasks.

Thin layer chromatography (TLC) was performed on Merck TLC silica gel 60 F₂₅₄ supported on aluminum seat. Column chromatography was performed on Merck Geduran silica gel 40-63 micron.

NMR spectra were acquired on Bruker Avance II 400 spectrometer (¹H at 400 MHz, ¹³C at 100 MHz, ¹⁹F at 376 MHz) or Bruker Avance 500 spectrometer (¹H at 500 MHz, ¹³C at 126 MHz, ¹⁹F at 471 MHz). Chemical shift data are reported as δ in units of parts per million relative to residual solvent.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected.

Preparation of ethynyl(aryl)sulfanes

Ethynyl(phenyl)sulfane 1b: A solution of 1,3,5-Triazabicyclo[4.4.0]dec-5-ene (TBD) (0.696 g, 5.00 mmol) and benzenethiol 4b (0.51 mL, 4.95 mmol) in THF (60 mL) was stirred at room temperature for a few minutes. TMS-EBX (1.90 g, 5.51 mmol) was added and the solution was stirred at room temperature for 5 min. Then, TBAF·3H₂O (0.317 g, 1.00 mmol) and MeOH (20 mL) were added to the reaction mixture and stirred at room temperature for 1 h. After that, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether) to afford the title compound 1b (0.574 g, 4.28 mmol, 86% yield) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.46 (m, 2H), 7.35 (m, 2H), 7.25 (t, J_H-H = 7.2 Hz, 1H), 3.26 (s, 1H). The data were in good agreement with the literature values.

(4-Bromophenyl)(ethynyl)sulfane 1e: According to the procedure described for 1b, TBD (2.17 g, 15.6 mmol), and 4-bromobenzenthiol 4e (2.95 g, 15.6 mmol) in THF (200 mL) were stirred at room temperature. After few minutes TMS-EBX (5.92 g, 17.2 mmol) was added. Purification using silica gel column chromatography (petroleum ether) gave a colorless solid, to which THF (24 mL), MeOH (8 mL) and TBAF·3H₂O (0.500 g, 1.58 mmol) were added. The residue was purified by silica gel column chromatography (petroleum ether) to afford the title compound 1e (3.12 g, 14.6 mmol, 94% yield) as a white solid; M.p. = 35–36 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.47 (d, J_H-H = 8.8 Hz, 2H), 7.35 (m, 2H), 7.25 (t, J_H-H = 7.2 Hz, 1H), 3.26 (s, 1H).
(2-Bromophenyl)(ethynyl)sulfane 1f: According to the procedure described for 1b, TMS-EBX (1.89 g, 5.50 mmol) was added to a solution of TBD (0.697 g, 5.00 mmol), and 2-bromobenzenethiol (0.978 g, 5.17 mmol) THF (60 mL). Purification using silica gel column chromatography (petroleum ether) gave (((2-bromophenyl)thio)ethynyl)trimethylsilane as a colorless oil (1.46 g, 5.11 mmol, 99% yield).

1H NMR (400 MHz, CDCl₃, rt): δ 7.68 (dd, J_H-H = 8.0, 1.6 Hz, 1H), 7.49 (dd, J_H-H = 8.0, 1.2 Hz, 1H), 7.37 (m, 1H), 7.09 (m, 1H), 0.27 (s, 9H). Analysis conform to the literature.[3]

TBAF·3H₂O (0.129 g, 0.408 mmol) was added to a solution (((2-bromophenyl)thio)ethynyl)trimethylsilane (1.17 g, 4.10 mmol), THF (6 mL), MeOH (2 mL). Purification by silica gel column chromatography (petroleum ether) afforded the title compound 1f (0.796 g, 3.74 mmol, 91% yield) as colorless oil.

1H NMR (400 MHz, CDCl₃, rt): δ 7.73 (dd, J_H-H = 8.0, 1.2 Hz, 1H), 7.51 (dd, J_H-H = 8.0, 1.2 Hz, 1H), 7.37 (ddd, J_H-H = 8.0, 8.0, 1.2 Hz, 1H), 7.11 (ddd, J_H-H = 8.0, 7.6, 1.2 Hz, 1H), 3.39 (s, 1H).

13C NMR (126 MHz, CDCl₃, rt): δ 133.5, 132.9, 128.4, 127.8, 127.3, 119.9, 89.0, 70.6. HRMS (ESI), calculated for C₈H₅BrS [M+H]⁺ 212.9375; found 212.9379.

Ethynyl(4-methoxyphenyl)sulfane 1g: According to the procedure described for 1b, TMS-EBX (1.90 g, 5.51 mmol) was added to a solution of TBD (0.696 g, 5.00 mmol), and 4-methoxybenzenethiol (0.62 mL, 5.0 mmol), in THF (60 mL). Purification using silica gel column chromatography (petroleum ether/Et₂O = 19/1) gave a colorless oil which was reacted with TBAF·3H₂O (0.115 g, 0.363 mmol) in THF (6 mL), MeOH (2 mL). Purification using silica gel column chromatography (petroleum ether/Et₂O = 29/1→19/1) afforded the title compound 1g (0.591 g, 3.60 mmol, 72% yield) as a pale yellow oil.

1H NMR (400 MHz, CDCl₃, rt): δ 7.40 (d, J_H-H = 8.8 Hz, 2H), 6.90 (d, J_H-H = 8.8 Hz, 2H), 3.80 (s, 3H), 3.13 (s, 1H).

13C NMR (101 MHz, CDCl₃, rt): δ 159.4, 129.7, 121.7, 115.2, 85.2, 72.8, 55.5. HRMS (EI), calculated for C₉H₈OS [M]+ 164.0296; 164.0295.

Ethynyl(4-nitrophenyl)sulfane 1j: According to the procedure described for 1b, TMS-EBX (1.90 g, 5.51 mmol) was reacted with 4-nitrobenzenthiol (0.778 g, 5.01 mmol), TBD (0.694 g, 4.98 mmol) in THF (60 mL). Purification by silica gel column chromatography (petroleum ether/Et₂O = 19/1) gave white solid which was treated with TBAF·3H₂O (66 mg, 0.21 mmol) in THF (3 mL), MeOH (1 mL). Purification using silica gel column chromatography (petroleum ether/Et₂O = 19/1) gave the title compound 1j (0.210 g, 1.17 mmol, 23% yield) as a white solid; M.p. = 78–79 °C. 1H NMR (400 MHz, CDCl₃, rt): δ 8.21 (d, J_H-H = 7.2 Hz, 2H), 7.58 (d, J_H-H = 7.2 Hz, 2H), 3.44 (s, 1H).

13C NMR (126 MHz, CDCl₃, rt): δ 146.6, 141.5, 126.1, 124.4, 90.0, 68.4. HRMS (ESI), calculated for C₈H₅NO₂S [M]+ 179.0039; 179.0037.

Ethynyl(naphthalen-2-yl)sulfane 1h: According to the procedure described for 1b, TMS-EBX (1.90 g, 5.51 mmol) was added to TBD (0.694 g, 4.98 mmol), and naphthalene-2-thiol (0.802 g, 5.00 mmol) in THF (60 mL). TBAF·3H₂O (0.330 g, 1.05 mmol) and MeOH (20 mL) were added to the reaction mixture. Purification using silica gel column chromatography (petroleum ether) afforded the title compound 1h (0.476 g, 2.58 mmol, 52% yield) as a white solid.

1H NMR (400 MHz, CDCl₃, rt): δ 7.92 (d, J_H-H = 1.6 Hz, 1H), 7.83–7.77 (m, 3H), 7.53–7.45 (m,
7-(Ethynylthio)-4-methyl-2H-chromen-2-one 1i: According to the procedure described for 1b, TMS-EBX (1.89 g, 5.50 mmol) was added to a solution of TBD (0.694 g, 4.98 mmol), and 7-mercapto-4-methylcoumarin 4i (0.961 g, 5.00 mmol) in THF (60 mL). Purification using silica gel column chromatography (petroleum ether/Et₂O = 3/1→1/1) gave white solid that was treated with TBAF·3H₂O (0.153 g, 0.486 mmol) in THF (7.5 mL), MeOH (2.5 mL). Purification using silica gel column chromatography (petroleum ether/EtOAc = 4/1→3/1) afforded the title compound 1i (0.931 g, 4.31 mmol, 86% yield) as a white solid. M.p. = 140–141 °C (decomposition); ¹H NMR (400 MHz, CDCl₃, rt): δ 7.55 (d, J₄-H = 8.4 Hz, 1H), 7.46 (d, J₅-H = 1.6 Hz, 1H), 7.30 (dd, J₆-H = 8.4, 2.0 Hz, 1H), 6.27 (q, J₇-H = 1.2 Hz, 1H), 3.42 (s, 1H), 2.43 (d, J₈-H = 1.2 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃, rt): δ 160.4, 154.0, 152.0, 137.4, 125.2, 121.6, 118.6, 114.9, 114.1, 89.5, 68.9, 18.8. HRMS (ESI), calculated for C₁₂H₉O₂S [M+H]+ 217.0323; found 217.0326.

Ethynyl (4-N-tert-butoxycarbonylaminophenyl)sulfane 1h: The title compound was prepared following the procedure described for 1b, using 4-(N-Boc-amino)benzenethiol 4h (1.31 g, 5.83 mmol), TMS-EBX (2.2 g, 6.40 mmol) and tetramethylene guanidine (0.86 mL, 6.97 mmol) in dry THF (20 mL). The crude product was passed through pad of silica gel (petroleum ether:dichloromethane 7:3) to provide a white solid, which was dissolved in THF:MeOH (15:5 mL). A 1M TBAF solution in THF (5.81 mL, 5.83 mmol) was added and the mixture was stirred at room temperature for 30 min. The mixture was poured brine and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layer was dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether: dichloromethane 7:3) to afford the title compound 1h (0.83 g, 95% yield) as a white solid. M.p. = 106 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.37 (br s, 4H), 6.49 (br s, H), 3.18 (s, 1H), 1.51 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 152.5, 137.8, 128.3, 124.5, 119.4, 85.9, 80.9, 71.9, 28.3. HRMS (ESI), calculated for C₁₃H₁₄O₂NS [M-H]⁻ 249.0828; found 248.0743.

Hydrofluorination of ethynyl(aryl)sulfanes

70% HF-Py
CH₂Cl₂
0 °C to RT

(1,1-Difluoroethyl)(phenyl)sulfane 3b: A 10 mL Teflon round-bottom flask was charged with ethynyl(phenyl)sulfane 1b (0.136 g, 1.02 mmol) and magnetic bar. The flask was capped with a rubber septum, evacuated, and then flushed three times with argon. Dry CH₂Cl₂ (4 mL), was added and the mixture was cooled to 0 °C. Then 70% HF-Py (104 μL, 4.0 mmol) was added and the mixture stirred at room temperature for overnight. Then, additional 70% HF-Py (104 μL, 4.0 mmol) was added to the reaction mixture at 0 °C, and the mixture was stirred at room temperature for 16 h. The reaction was quenched by slow addition of sat. NaHCO₃, and the resulting mixture was extracted with CH₂Cl₂ (20 mL x 3). The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pentane) to afford the title compound 3b (0.100 g, 0.576 mmol, 57% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.63–7.60 (m, 2H), 7.45–7.36 (m, 3H), 1.92 (t, J₆₇-H = 16.8 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃, rt): δ –66.55 (q, J₆₇-H = 16.5 Hz,
2% of monofluorinated product) as a colorless oil. 1H NMR (400 MHz, CDCl3, rt): δ 7.52 (d, JH-H = 8.8 Hz, 2H), 7.46 (d, JH-H = 8.8 Hz, 2H), 1.93 (t, JHF = 16.8 Hz, 3H). 19F NMR (376 MHz, CDCl3, rt): δ −66.46 (q, JHF = 16.5 Hz, 2F). 13C NMR (126 MHz, CDCl3, rt): δ 137.6, 132.4, 128.1 (q, JCF = 277 Hz), 126.5, 124.8, 26.2 (q, JCF = 25.8 Hz). HRMS (CI): calculated for C8H7BrF2S [M]+ 253.9395, required 253.9399.

(2-Bromophenyl)(1,1-difluoroethyl)sulfane 3f: According to the procedure described for 3b, 70% HF-Py (104 μL, 4.0 mmol) was reacted with (2-bromophenyl)(ethynyl)sulfane 1f (0.216 g, 1.02 mmol) in dry CH2Cl2 (4 mL). Purification using silica gel column chromatography (petroleum ether) afforded the title compound 3f (0.170 g, 0.672 mmol, 66% yield) as a colorless oil. 1H NMR (400 MHz, CDCl3, rt): δ 7.77 (dd, JH-H = 8.0, 1.6 Hz, 1H), 7.69 (dd, JH-H = 8.0, 1.6 Hz, 1H), 7.33 (ddd, JH-H = 7.6, 7.6, 1.6 Hz, 1H), 7.25 (ddd, JH-H = 8.0, 7.6, 1.6 Hz, 1H), 1.97 (t, JHF = 16.8 Hz, 3H). 19F NMR (376 MHz, CDCl3, rt): δ −65.96 (q, JHF = 16.9 Hz, 2F). 13C NMR (126 MHz, CDCl3, rt): δ 138.7, 133.8, 131.2, 130.2, 129.4, 128.6 (q, JCF = 278 Hz), 128.0, 26.4 (q, JCF = 25.8 Hz). HRMS (ESI), calculated for C8H7NO2S [M]+ required 253.9399; found 253.9404.

(1,1-Difluoroethyl)(4-methoxyphenyl)sulfane 3g: According to the procedure described for 3b, 70% HF-Py (104 μL, 4.0 mmol) was reacted with ethynyl(4-methoxyphenyl)sulfane 1g (0.164 g, 1.00 mmol) in dry CH2Cl2 (4 mL). Purification using silica gel column chromatography (petroleum ether/Et2O = 100/0→49/1) afforded the title compound 3g (0.104 g, 0.509 mmol, 51% yield) as a colorless oil. 1H NMR (400 MHz, CDCl3, rt): δ 7.53 (d, JH-H = 8.8 Hz, 2H), 6.90 (d, JH-H = 8.8 Hz, 2H), 3.83 (s, 3H), 1.89 (t, JHF = 16.8 Hz, 3H). 19F NMR (376 MHz, CDCl3, rt): δ −67.52 (q, JHF = 16.5 Hz, 2F). 13C NMR (126 MHz, CDCl3, rt): δ 161.2, 138.2, 128.4 (t, JCF = 275 Hz), 118.1, 114.7, 55.5, 26.0 (t, JCF = 26.3 Hz). HRMS (CI): calculated for C8H11F2O5S [M+H]+ required 205.0499, found 205.0494.

(1,1-Difluoroethyl)(4-nitrophenyl)sulfane 3j: According to the procedure described for 3b, 70% HF-Py (416 μL, 16.0 mmol) was reacted with ethynyl(4-nitrophenyl)sulfane 1j (0.179 g, 0.997 mmol) in dry CH2Cl2 (4 mL) in dry CH2Cl2 (4 mL). Purification using silica gel column chromatography (petroleum ether/Et2O = 29/1) afforded the title compound 3j (0.185 g, 0.843 mmol, 85% yield) as a colorless oil. 1H NMR (400 MHz, CDCl3, rt): δ 8.22 (d, JH-H = 8.8 Hz, 2H), 7.76 (d, JH-H = 8.8 Hz, 2H), 2.00 (t, JHF = 16.4 Hz, 3H). 19F NMR (376 MHz, CDCl3, rt): δ −65.29 (q, JHF = 16.5 Hz, 2F). 13C NMR (126 MHz, CDCl3, rt): δ 148.4, 136.3, 135.3, 128.1 (t, JCF = 278 Hz), 124.0, 26.4 (t, JCF = 25.5 Hz). HRMS (EI), calculated for C8H7NO2F2S [M]+ 220.0246; found 220.0247.

(1,1-Difluoroethyl)(naphthalen-2-yl)sulfane 3h: According to the procedure described for 3b, 70% HF-Py (104 μL, 4.0 mmol) was reacted
with ethynyl(naphthalen-2-yl)sulfane 1h (0.185 g, 1.00 mmol) in dry CH₂Cl₂ (4 mL). Purification using silica gel column chromatography (petroleum ether) afforded the title compound 3h (0.109 g, 0.486 mmol, 49% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, rt): δ 8.14 (d, J_H-H = 0.8 Hz, 1H), 7.87–7.84 (m, 3H), 7.66 (dd, J_H-H = 8.4, 1.6 Hz, 1H), 7.57–7.51 (m, 2H), 1.96 (t, J_H-F = 16.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃, rt): δ 136.3, 133.6, 133.5, 132.3, 128.8, 128.7 (t, J_C-F = 276 Hz), 128.2, 127.9, 127.5, 126.8, 124.9, 26.4 (t, J_C-C = 26.3 Hz). HRMS (EI), calculated for C₁₂H₁₀F₂S [M]+ required 224.0476; found 224.0475.

7-((1,1-Difluoroethyl)thio)-4-methyl-2H-chromen-2-one 3i: According to the procedure described for 3b, 70% HF-Py (104 µL, 4.0 mmol) 7-(ethynylthio)-4-methyl-2H-chromen-2-one 1i (0.217 g, 1.00 mmol) in dry CH₂Cl₂ (4 mL) at 35 °C. Purification using silica gel column chromatography (petroleum ether/EtOAc = 5/1→4/1) to afford the title compound 3i (0.218 g, 0.849 mmol, 85% yield) as a white solid; M.p. = 96–97 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.60 (d, J_H-H = 6.0 Hz, 1H), 7.58 (s, 1H), 7.51 (dd, J_H-H = 8.4, 1.6 Hz, 1H), 6.34 (q, J_H-H = 1.2 Hz, 1H), 2.45 (d, J_H-H = 1.2 Hz, 3H), 1.98 (t, J_H-F = 16.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃, rt): δ 160.2, 153.2, 151.8, 132.0, 130.7, 128.2 (t, J_H-F = 278 Hz), 125.0, 123.4, 120.8, 116.2, 26.3 (t, J_H-F = 25.7 Hz), 18.8. HRMS (EI), calculated for C₁₂H₁₀F₂O₂S [M+H]+ required 257.0448; found 257.0450.

4-((1,1-Difluoroethyl)thio)aniline 3j: A mixture of (1,1-difluoroethyl)(4-nitrophenyl)sulfane 3j (0.112 g, 0.509 mmol), EtOH (7 mL), concentrated HCl and SnCl₂ (0.756 g, 3.99 mmol) was stirred at 80 °C for 1 h. After cooling to room temperature, aqueous K₂CO₃ solution was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford the title compound 3k (0.156 g, 20% yield) as a white solid. ¹H NMR (126 MHz, CDCl₃, rt): δ 148.4, 138.1, 128.6 (t, J_H-C = 275 Hz), 115.4, 114.8, 25.9 (t, J_H-F = 26.5 Hz). HRMS (EI), calculated for C₈H₉F₂NS [M+H]+ required 190.0497; found 190.0496.

6-(1,1-Difluoroethoxy)-2-benzothiazolamine 16b: According to the procedure described for 3b, 70% HF-Py (1.32 mL, 51.4 mmol) Ethynyl (4-N-tert-butoxycarbonylaminothiophenyl)sulfane 1k (1.6 g, 6.42 mmol) in dry CH₂Cl₂ (10 mL) at 0 °C for 3 hrs. The crude product was passed through pad of silica gel (CH₂Cl₂/EtOAc 7:3) to give 4-[(1,1-difluoroethyl)thio]aniline 3k (0.945 g) as a brown oil which was used for next step. 4-[(1,1-Difluoroethoxy)thio]aniline 3k (0.47 g of the crude) and potassium thiocyanate (1.23 g, 12.70 mmol) in dry CH₂Cl₂ (10 mL) at 0 °C for 24 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL), made alkaline with 35% aqueous NH₄OH and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH₂Cl₂/EtOAc 8:2 to 7:3) to afford the title compound 16b (0.156 g, 20% yield) as a white solid; M.p. = 152 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.83 (d, J_H-H = 1.7
Palladium-catalyzed cross-coupling reactions of (4-Bromophenyl)(1,1-difluoroethyl)sulfane (1,1-Difluoroethyl)(4-((4-propylphenyl)ethynyl)phenyl)sulfane 9: A 25 mL round-bottom flask was charged with CuI (9.7 mg, 51 μmol), PdCl₂(PPh₃)₂ (35.1 mg, 50 μmol), NEt₃ (2 mL) and DMF (2 mL). The flask was degassed under reduced pressure and flushed with Ar for three times. (4-Bromophenyl)(1,1-difluoroethyl)sulfane 3e (0.254 g, 1.01 mmol) and 1-ethynyl-4-propylbenzene (0.176 g, 1.22 mmol) were added and the mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with Et₂O and washed with sat. NH₄Cl (20 mL x 3). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether) to afford the title compound 9 (0.206 g, 0.650 mmol, 65% yield) as a colorless solid; M.p. 69–70 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.57 (d, J_H-H = 8.4 Hz, 2H), 7.51 (d, J_H-H = 8.4 Hz, 2H), 7.45 (d, J_H-H = 8.4 Hz, 2H), 7.17 (d, J_H-H = 8.4 Hz, 2H), 2.60 (t, J_H-H = 7.6 Hz, 2H), 1.93 (t, J_H-F = 16.6 Hz, 3H), 1.65 (m, 2H), 0.94 (t, J_H-H = 7.4 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃, rt): δ –66.24 (q, J_F-H = 16.5 Hz, 2F). ¹³C NMR (126 MHz, CDCl₃, rt): δ 143.7, 135.9, 132.1, 131.7, 128.7, 128.4 (q, J_C-F = 276 Hz), 127.4, 125.3, 120.1, 91.8, 88.0, 38.1, 26.3 (q, J_C-F = 26.0 Hz), 24.5, 13.9. HRMS (EI), calculated for C₁₅H₁₄F₂O₂S [M]⁺ required 280.0733; found 280.0735.

(1,1-Difluoroethyl)(4'-methoxy-[1,1'-biphenyl]-4-yl)sulfane 10: A 50 mL round-bottom flask was degassed under reduced pressure and refilled with Ar. The flask was charged with H₂O (degassed by Ar bubbling, 1 mL), K₂CO₃ (0.416 g, 3.01 mmol), (4-methoxyphenyl)boronic acid (0.183 g, 1.20 mmol), toluene (purified, 4 mL), (4-bromophenyl)(1,1-difluoroethyl)sulfane 3e (0.255 g, 1.01 mmol) and Pd(PPh₃)₄ (58.7 mg, 51 μmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with Et₂O and washed with brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/Et₂O = 49/1) to afford the title compound 10 (0.258 g, 0.919 mmol, 91% yield) as a white solid. M.p. 99–100 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.64 (d, J_H-H = 8.4 Hz, 2H), 7.57–7.53 (m, 4H), 6.99 (d, J_H-H = 8.8 Hz, 2H), 3.86 (s, 3H), 1.95 (t, J_H-F = 16.8 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃, rt): δ –66.56 (q, J_F-H = 16.5 Hz, 2F). ¹³C NMR (126 MHz, CDCl₃, rt): δ 143.7, 135.9, 132.1, 131.7, 128.7, 128.4 (q, J_C-F = 276 Hz), 127.4, 125.3, 120.1, 91.8, 88.0, 38.1, 26.3 (q, J_C-F = 26.0 Hz), 24.5, 13.9. HRMS (EI), calculated for C₁₉H₁₈F₂OS [M]⁺ required 316.1097; found 316.1097.

4-(1,1-Difluoroethylthio)phenylmorpholine 8: An oven-dried flask equipped with a magnetic stirring bar was charged with Pd(dba)₃ (5 mol%, 0.0363 g, 0.0397 mmol), BINAP (0.075 g, 0.119 mmol), 18-crown-6 (0.315 g, 1.19 mmol and NaOBu-t (1.5 eq.,...
0.115 g, 1.20 mmol). The flask was capped with a rubber septum, evacuated, and then flushed three times with argon. 1-bromo-4-(1,1-difluoroethylthio)benzene 3e (0.170 g, 0.672 mmol) and degassed DMSO (5 mL) were then successively added by syringe. The reaction mixture was then heated at 100 °C until the starting material had been completely consumed as judged by TLC (24 h). The mixture was cooled to room temperature, poured into water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic phase was dried with MgSO₄, filtered and solvent was removed under reduced pressure. The product was purified by column chromatography (pentane/dichloromethane 8:2) to afford the title compound 7 (0.089 g, 49%) as colourless oil. 1H NMR (400 MHz, CDCl₃, rt): δ 7.48 (d, J_H-H = 9.0 Hz, 2H, H-3,5), 6.87 (d, J_H-H = 9.0 Hz, 2H, H-2,6), 3.86 (t, J_H-F = 4.9 Hz, 2H), 3.21 (t, J_H-F = 4.9 Hz, 2H), 1.88 (t, J_H-F = 16.6 Hz, 3H). 19F NMR (476.5 MHz, CDCl₃): δ –67.6. 13C NMR (100 MHz, CDCl₃): δ 152.3, 137.7, 128.4 (t, J_C-F = 275.0 Hz), 116.1, 115.2, 66.7, 48.3, 25.9 (t, J_C-F = 26.3 Hz). HMRS-ESI (C₁₄H₁₂F₂OS- [M + 1]+) required 266.0577; found: 266.0577.

4-Phenoxy-4-[(1,1-difluoroethyl)sulfanyl]benzene 7: An oven-dried flask equipped with a magnetic stirring bar was charged with CuI (0.289 g, 1.36 mmol), K₃PO₄ (0.289 g, 1.36 mmol), picolinic acid (0.009 g, 0.068 mmol) and phenol (0.095, 1.02 mmol). The flask was capped with a rubber septum, evacuated, and then flushed three times with argon. 1-bromo-4-(1,1-difluoroethylthio)benzene 3e (0.170 g, 0.672 mmol) and degassed DMSO (5 mL) were then successively added by syringe. The reaction mixture was then heated at 100 °C until the starting material had been completely consumed as judged by TLC (24 h). The mixture was cooled to room temperature, poured into water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic phase was dried with MgSO₄, filtered and solvent was removed under reduced pressure. The crude product was purified by column chromatography (pentane/dichloromethane 8:2) to afford the title compound 4 (0.077 g, 43%) as colourless oil. 1H NMR (400 MHz, CDCl₃, rt): δ 7.48 (d, J_H-H = 9.0 Hz, 2H, H-3,5), 6.87 (d, J_H-H = 9.0 Hz, 2H, H-2,6), 4.26 (m, 1H), 1.95-2.02 (m, 2H), 1.88 (t, J_H-F = 16.6 Hz, 3H). 19F NMR (476.5 MHz, CDCl₃): δ –67.6. 13C NMR (100 MHz, CDCl₃): δ 159.5, 138.0, 128.3 (t, J_C-F = 275.2 Hz), 116.3, 75.5, 166.7, 31.7, 25.9 (t, J_C-F = 26.4 Hz), 25.6. HMRS-ESI (C₁₄H₁₂F₂OS) ([M]+)
Preparation of ethynyl(oxy)benzene 11b

A solution of (E)-1-(1,2-dichlorovinyl)oxybenzene (2.17 g, 11.5 mmol) in Et₂O (120 mL) was cooled to -78 °C and stirred for 30 min. nBuLi (18 mL, 46.00 mmol, 2.5 M) was added dropwise and stirred at -78 °C for 1 h. The mixture is left to reach -40 °C over the course of 1 h, and stirred at -40 °C for 2 h. The reaction mixture was quenched by addition of water (100 mL) at cold temperature. The organic phase was separated, and the aqueous phase extracted thrice with Et₂O (3 x 100 mL). The combined organic phases were washed successively with a saturated solution of ammonium chloride and brine, dried over MgSO₄ and evaporated under reduced pressure. No further purification was required. Ethynyl(oxy)benzene 11b was obtained as a brown oil (1.17 g, 9.90 mmol, 86 % yield).

Hydrofluorination of ethynyl(oxy)benzene 12b

Ethynyl(oxy)benzene (1 g, 8.47 mmol) was added into a 50 mL Teflon round-bottom flask and dissolved into CH₂Cl₂ (5 mL). The solution was cooled to -78 °C and stirred for 15 min. HF·py (6 mL, 67.8 mmol) was added to the flask and the reaction mixture was stirred for 18 h and left to reach room temperature. The reaction was quenched by slow addition of the solution into a saturated solution of NaHCO₃ (150 mL). The resulting mixture was extracted thrice with CH₂Cl₂ (3 x 200 mL). The combined organic layers were washed with brine, dried over MgSO₄ and evaporated under reduced pressure. The residue was further purified by washing with CuSO₄ (7%, 25 mL) and extracting with Et₂O (3 x 25 mL), which afforded the product 12b as a colourless oil. (75% yield).

1H NMR (500 MHz, CDCl₃, rt): δ 7.42 – 7.34 (m, 2H), 7.30 (dt, J = 7.9, 1.1 Hz, 2H), 7.22 – 7.12 (m, 1H), 2.09 (s, 1H). The data were in good agreement with the literature values.

19F NMR (471 MHz, CDCl₃, rt): δ -64.4 (q, J₃–F = 13.2 Hz, 2F)

13C NMR (126 MHz, CDCl₃, rt): δ 129.3, 125.4, 124.0 (t, J = 261.5 Hz), 121.8, 22.8 (t, J = 32 Hz).
4-(1,1-Difluoroethoxy)biphenyl 12c

4-(Ethynyloxy)-1,1'-biphenyl (1.5 g, 7.73 mmol) was placed in a 25 mL Teflon round-bottom flask which was evacuated and flushed with argon three times. Then dry CH$_2$Cl$_2$ (10 mL) was added and the mixture was cooled to 0 °C. 70% HF·Py (0.6 mL, 24 mmol) was added to the solution and stirred at rt for overnight. The mixture was poured into ice-cold sat. NaHCO$_3$, and the resulting mixture was extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether) to afford the title compound as a white solid (1.53 g, 85% yield). M.p. = 59 °C.

$^1$H NMR (400 MHz, CDCl$_3$, rt): δ 7.55-7.58 (m, 2H), 7.56 (d, $J_{H-H}$ = 8.7 Hz, 2H), 7.44 (tt, $J_{H-H}$ = 7.4, 1.4 Hz, 1H), 7.35 (d, $J_{H-H}$ = 7.4, 1.4 Hz, 2H), 7.25 (d, $J_{H-H}$ = 8.7 Hz, 2H), 1.97 (t, $J_{H-F}$ = 13.3 Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$, rt): δ –64.4 (q, $J_{F-H}$ = 13.3 Hz, 2F).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 150.2, 140.4, 138.5, 128.8, 128.0, 127.0, 127.1, 124.4 (t, $J_{C-F}$ = 263.3 Hz), 22.9 (t, $J_{C-F}$ = 32.6 Hz). HRMS (ESI), calculated for C$_{14}$H$_{12}$OF$_2$ [M]+ 234.0856; found 234.0853.

1-Methoxy-4-(1,1-trifluoroethoxy)benzene 12d

70% HF·Py (3.9 mL, 15.4 mmol) was added to solution of 1-(ethynyloxy)-4-methoxybenzene (4.0 g, 3.0 mmol) in DCM (10 mL) in a Teflon flask at 0 °C and the reaction stirred for 16hrs. The mixture was poured into ice-cold sat. NaHCO$_3$, and the resulting mixture was extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. Purification silica gel column chromatography (petroleum ether: CH$_2$Cl$_2$ 10:0 to 8:2) to provide the title compound 12d (3.21 mg, 76% yield) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$, rt): δ 7.11 (d, $J_{H-H}$ = 9.0 Hz, 2H), 6.86 (d, $J_{H-H}$ = 9.0 Hz, 2H), 3.79 (s, 3H), 1.92 (t, $J_{H-F}$ = 13.3 Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$, rt): δ –64.6 (q, $J_{F-H}$ = 13.3 Hz, 2F).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 157.2, 143.9, 124.2 (t, $J_{C-F}$ = 263.1 Hz), 123.1, 114.3, 55.6, 22.7 (t, $J_{C-F}$ = 32.3 Hz). HRMS (ESI), calculated for C$_9$H$_{10}$O$_2$F$_2$ [M]+ 188.0649; found 188.0652.

E-1-(1,2-Dichloronyl)oxy-N-tert-butoxycarbonylaniline. A solution of 4-N-tert-butoxycarbonylaniline (4 g, 19.13 mmol) in dry DMF (5 mL) was added to a suspension of NaH (0.81 g, 20.25 mmol) in dry DMF (20 mL) under Ar and the resulting mixture was stirred at room temperature for 1 h. Afterwards 1,1,2-trichloroethylene (1.73 mL, 19.13 mmol) was slowly added and the resulting mixture was stirred 50 °C for 16h. After completion the mixture was poured into water and the organics were extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (100 mL x 4), dried over MgSO4 and concentrated under reduced pressure. The crude product was subjected to flash column chromatography (petroleum ether: CH$_2$Cl$_2$ 8:2) to give E-1-(1,2-dichloronyl)oxy-N-tert-butoxycarbonylaniline (4.3 g, 74%) as a white solid. M.p. = $^1$H NMR (400 MHz, CDCl$_3$, rt): δ 7.35 (d, $J_{H-H}$ = 9.0 Hz, 2H), 7.00 (d, $J_{H-H}$ = 9.0 Hz, 2H), 6.45 (bs, 1H), 5.90 (s, 1H), 1.51 (s, 9H). HRMS (ESI), calculated for C$_9$H$_{10}$O$_2$F$_2$ [M]+ 188.0649; found 188.0652.
(ESI), calculated for C_{9}H_{10}O_{2}F_{2} [M]^{+} 188.0649; found 188.0652.

development of compound 18 (2.0 g, 6.6 mmol) in anhydrous diethyl ether (30 mL) at -78 °C. The reaction mixture was then maintained at -78°C and -40°C for 1 h and 2 h respectively, ethanol (10 mL) was added dropwise. After 10 min, the reaction mixture was then diluted with ether (100 mL) and then washed with saturated solution of ammonium chloride (50 mL). The organic phase was later washed twice with water (100 mL) and then finally with brine (50 mL), dried over MgSO_{4}, filtered and concentrated to give brown solid. The solid was purified by column chromatography (petroleum ether: DCM 8:2) to give the title compound 19 (1.38 g, 90%) as a white solid. M.p. = 107 °C.

H NMR (400 MHz, CDCl_{3}, rt): δ 7.35 (d, J_{H-H} = 9.0 Hz, 2H), 7.21 (d, J_{H-H} = 9.0 Hz, 2H), 6.46 (bs, 1H), 2.06 (s, 1H), 1.52 (s, 9H).

C NMR (100 MHz, CDCl_{3}): δ 152.8, 151.1, 135.4, 119.9, 115.4, 84.8, 33.0, 28.3. HRMS (ESI), calculated for C_{9}H_{10}O_{2}F_{2} [M]^{+} 188.0649; found 188.0652.

6-(1,1-Difluoroethoxy)-2-benzothiazolamine 16a: According to the procedure described for 16b, 70% HF·Py (1.4 mL, 49 mmol) Ethynyl tert-Butyl N-(4-ethynyloxyphenyl)carbamate (2.45 g, 10.5 mmol) in dry CH_{2}Cl_{2} (10 mL) at 0 °C for 8 hrs. The crude product was passed through pad of silica gel (CH_{2}Cl_{2}/EtOAc 7:3) to give 4-(1,1-difluoroethoxy)aniline (0.945 g) a as a brown oil. 4-(1,1-Difluoroethoxy)aniline (0.22 g, 1.27) and potassium thiocyanate (0.49 g, 5.08 mmol) were placed in a flask and evacuated and flushed with Ar for three times. After addition of glacial acetic acid (5 mL) the mixture was stirred vigorously at room temperature for 15 minutes. Then a solution of bromine (0.065 mL, 1.27 mmol) in acetic acid (0.5 mL) was added and the mixture was stirred at 35 °C for 24 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL), made alkaline with 35% aqueous NH_{4}OH and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over MgSO_{4}, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_{2}Cl_{2}/EtOAc 8:2 to 7:3) to afford the title compound 16a (0.215 g, 38% yield over 2 steps) as a white solid; M.p. = 149 °C. H NMR (400 MHz, CDCl_{3}, rt): δ 7.47 (d, J_{H-H} = 8.7 Hz, 1H, H-5), 7.43 (d, J_{H-H} = 2.4 Hz, 1H, H-5), 7.12 (d, J_{H-H} = 8.7 Hz, 1H, H-5), 5.44 (br s, 2H), 1.91 (t, J_{H-F} = 13.3 Hz, 3H). F NMR (476.5 MHz, CDCl_{3}): δ –64.5. C NMR (100 MHz, CDCl_{3}): δ 165.9, 149.8, 145.5, 132.0, 124.4 (t, J_{C-F} = 262.1 Hz), 120.7, 119.3, 114.7, 22.7 (t, J_{C-F} = 32.1 Hz). HMRS-ESI (C_{9}H_{9}ON_{2}F_{2}S) ([M + 1]^{+}) 231.0398; found: 231.0398.
Measurement of lipophilicities (LogP) by reverse-phase HPLC

The evaluation of lipophilicity values was conducted using a Phenomenex Luna C\textsubscript{18} 100A (250 mm × 4.60 mm) 5μ column in a Shimadzu Prominence HPLC. A series of reference compounds were injected (5–10 μL of 0.5 mg/mL in AcCN) and their retention times (R\textsubscript{t}) plotted against their known LogP values to obtain a reference graph. The retention times of all compounds were measured using 60 : 40 AcCN : water as eluent, with a flow rate of 1 mL/min.

The references compounds have been well-studied and consensus Log P values have been described.

The values used are those recommended by Hansch and Leo (1987, 1995) or Sangster (1989).\textsuperscript{8,9,10}

The characteristic retention times (R\textsubscript{t}) of each of the reference molecules was used to calculate their capacity factor (k), using the following equation:

$$\text{Capacity factor (k)} = \frac{\text{Retention Time - Dead Time of the column}}{\text{Dead Time of the column}}$$

Where the dead time of the column is the time that takes for an unretained molecule (such as the solvent) to pass through the column; in this study that time was 1.965 min.
Table S1, collates Log P values of the reference compounds⁸⁻¹⁰ (in red), along with the experimental retention times observed for each molecule, which were measured in triplicates to avoid and detect possible measuring errors. An average retention time was calculated using each of the three values obtained, and this average value was used to calculate the capacity factor for each reference (using the equation described above). Finally, the logarithm of k was calculated (displayed in green).

The logarithm of the capacity factor (Y axis) was represented against the Log P of the reference compounds (X axis), to obtain a regression line and its corresponding equation.

Using this equation, and by measuring the retention time of the studied compounds, the LogP values can be approximated.

The calculated log k (Y-axis) values were plotted against their reported LogP values (X-axis) to obtain a linear regression equation, as represented in Plot S1.

\[
\text{Log } k \text{ vs Log } P
\]

Plot S1. Regression line obtained for the reference compounds

<table>
<thead>
<tr>
<th>Reference</th>
<th>LogP</th>
<th>Rt 1</th>
<th>Rt 2</th>
<th>Rt 3</th>
<th>Average Rt</th>
<th>Capacity factor (k)</th>
<th>Logk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td>1.50</td>
<td>4.300</td>
<td>4.300</td>
<td>4.295</td>
<td>4.298</td>
<td>1.187</td>
<td>0.075</td>
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<tr>
<td>2-Fluorophenol</td>
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<td>4.201</td>
<td>4.208</td>
<td>4.495</td>
<td>4.301</td>
<td>1.189</td>
<td>0.075</td>
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<tr>
<td>Benzofuran</td>
<td>2.67</td>
<td>8.375</td>
<td>8.375</td>
<td>8.383</td>
<td>8.378</td>
<td>3.263</td>
<td>0.514</td>
</tr>
<tr>
<td>Toluene</td>
<td>2.73</td>
<td>10.256</td>
<td>10.274</td>
<td>10.253</td>
<td>10.261</td>
<td>4.222</td>
<td>0.626</td>
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<tr>
<td>Naphthalene</td>
<td>3.35</td>
<td>12.733</td>
<td>12.734</td>
<td>12.758</td>
<td>12.742</td>
<td>5.484</td>
<td>0.739</td>
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<tr>
<td>Cumene</td>
<td>3.66</td>
<td>17.059</td>
<td>17.066</td>
<td>17.167</td>
<td>17.097</td>
<td>7.701</td>
<td>0.887</td>
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<tr>
<td>t-butylbenzene</td>
<td>4.11</td>
<td>23.445</td>
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<td>23.372</td>
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<td>14.410</td>
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<td>Pyrene</td>
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<td>32.802</td>
<td>32.707</td>
<td>15.645</td>
<td>1.353</td>
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</table>
The equation obtained in Plot S1 was afterwards used to calculate the LogP values from a series of compounds by substitution of the logarithm of their capacity factor values in the equation above. All the retention times obtained experimentally, the calculated capacity factors and their logarithms are shown in Table S2, along with the LogP values (blue), estimated by substitution of the log k values in the regression line equation in Plot S1.

**Table S2.** Estimation of LogP (blue) by using the logarithm of the measured capacity factors (green)

<table>
<thead>
<tr>
<th>Compound</th>
<th>LogP</th>
<th>Rt 1</th>
<th>Rt 2</th>
<th>Rt 3</th>
<th>Average Rt</th>
<th>Capacity factor (k)</th>
<th>Logk</th>
</tr>
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<tr>
<td>PhSCF3</td>
<td>3.70</td>
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<td>17.675</td>
<td>17.680</td>
<td>17.676</td>
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<td>13.876</td>
<td>13.882</td>
<td>6.065</td>
<td>0.783</td>
</tr>
<tr>
<td>PhSCH2CF3</td>
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<tr>
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<td>9.609</td>
<td>9.618</td>
<td>9.613</td>
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<tr>
<td>PhOCF3</td>
<td>3.35</td>
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<td>13.497</td>
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<tr>
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<td>10.088</td>
<td>10.120</td>
<td>10.210</td>
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<td>0.623</td>
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<tr>
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<td>9.571</td>
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<tr>
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<td>9.479</td>
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<td>0.575</td>
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<tr>
<td>PhOCH2CF3</td>
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<td>7.573</td>
<td>2.854</td>
<td>0.455</td>
</tr>
</tbody>
</table>

**References**

Computational Details

Full geometry optimisations were performed in the gas phase in the given symmetry at the B3LYP\textsuperscript{1,2} /6-31+G(d,p) level, followed by computation of the harmonic vibrational frequencies at the same level (which were also used to evaluate corrections to free energies at standard temperature and pressure) and single-point energy calculations at the B3LYP-D3\textsuperscript{3}6-311+G(2d,p) level.

Chart S1

Compounds and rotamers studied computationally are sketched in Chart S1. For validation purposes, phenyl ethers \textbf{17} and \textbf{18} where included, because for the oxo-species it is known that methyl ethers prefer an in-plane conformation (\textbf{17b-ip}), whereas trifluoromethyl ethers are perpendicular (\textbf{18b}). This preference is nicely reproduced at the chosen level (e.g. \textbf{17b-ip} is more stable than \textbf{17b}, and \textbf{18b} is more stable than \textbf{18b-ip}, Table S1). Similar preferences are obtained for the analogous thio ethers \textbf{17a} and \textbf{18a}.

\textbf{Table S1}: Relative energies $\Delta E$ (in kcal/mol, B3LYP-D3/6-311+G(2d,p) level) and free energies $\Delta G$ of conformers of compounds \textbf{17} and \textbf{18} (Chart S1, all in $C_s$ symmetry).\textsuperscript{b}

<table>
<thead>
<tr>
<th>Compd</th>
<th>NImag\textsuperscript{c}</th>
<th>$\Delta E$</th>
<th>$\Delta G$</th>
<th>Compd</th>
<th>NImag\textsuperscript{c}</th>
<th>$\Delta E$</th>
<th>$\Delta G$</th>
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<tbody>
<tr>
<td>\textbf{17a}</td>
<td>(1)</td>
<td>1.0</td>
<td>1.6</td>
<td>\textbf{17a-ip}</td>
<td>(0)</td>
<td>0.0</td>
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<tr>
<td>\textbf{18a}</td>
<td>(0)</td>
<td>0.0</td>
<td>0.0</td>
<td>\textbf{18a-ip}</td>
<td>(1)</td>
<td>2.6</td>
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<td>\textbf{17b}</td>
<td>(1)</td>
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<td>2.8</td>
<td>\textbf{17b-ip}</td>
<td>(0)</td>
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</tr>
<tr>
<td>\textbf{18b}</td>
<td>(0)</td>
<td>0.0</td>
<td>0.0</td>
<td>\textbf{18b-ip}</td>
<td>(0)</td>
<td>0.6</td>
<td>1.3</td>
</tr>
</tbody>
</table>

\textsuperscript{a}At 298K; thermodynamic corrections at B3LYP/6-31+G(d,p) level. \textsuperscript{b}Relative to the most stable conformer in each row. \textsuperscript{c}In parentheses: number of imaginary frequencies (0 and 1 denoting minimum and transition state, respectively).
For the target compound 3a and its oxygen analog 3i conformational analyses were performed in order to identify the most stable rotamers about the C-O and C-S single bonds. When one F atom in the trifluoromethyl ethers is replaced with a methyl group, the preference for a perpendicular orientation of the resulting difluoroethyl group decreases slightly, but is still very pronounced (compare, e.g. the relative energies of 3a-ip in Table S2 and 18a-ip in Table S1). In-plane conformations can only be obtained when the C-Me group is anti to the aryl-X bond (3a-ip and 3i-ip). The corresponding gauche rotamers (which cannot be fixed by imposing symmetry) optimise directly to the corresponding perpendicular gauche forms 3a" and 3i". The perpendicular forms with anti orientation of the C-Me group (3a' and 3i') are the most stable conformations, but the gauche rotamers are only around a kcal/mol or less higher, so that both variants should exist in an equilibrium. For instance for the thioether 3a, the computed difference in ΔG, 0.8 kcal/mol, translates into an equilibrium composition of 3a':3a" of ca. 64:36 at room temperature (from a Boltzmann distribution, taking the double degeneracy of chiral 3a" into account).

**Table S2:** Relative energies ΔE (in kcal/mol, B3LYP-D3/6-311+G(2d,p) level) and free energies ΔG of conformers of compounds 3a and 3i (Chart S1).^b^  

<table>
<thead>
<tr>
<th>Compd</th>
<th>Symm</th>
<th>ΔE</th>
<th>ΔG</th>
<th>Compd</th>
<th>Symm</th>
<th>ΔE</th>
<th>ΔG</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a'</td>
<td>Cs(0)</td>
<td>0.0</td>
<td>0.0</td>
<td>3i'</td>
<td>Cs(0)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>3a&quot;</td>
<td>C1(0)</td>
<td>0.1</td>
<td>0.8</td>
<td>3i&quot;</td>
<td>C1(0)</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>3a-ip</td>
<td>Cs(1)</td>
<td>2.1</td>
<td>3.9</td>
<td>3i-ip</td>
<td>Cs(0)</td>
<td>0.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

^aAt 298K; thermodynamic corrections at B3LYP/6-31+G(d,p) level. ^b^Relative to the most stable conformer in each column. ^c^Point group (in parentheses: number of imaginary frequencies, 0 and 1 denoting minimum and transition state, respectively).

Plots of the electrostatic potential of the lowest difluoroethylether minima, 3a' and 3i', are shown in Figure S1, which show the expected negative potential at the fluorine sites. The predicted dipole moments for 3a' and 3i' are 0.53 D and 1.03 D, respectively at the B3LYP/6-311+G(2d,p) level (3.48 D and 3.27 D for the gauche minima 3a" and 3i"), which might therefore become more favourable in a polar solvent).
Figure S1: Electrostatic potentials for 3a' (top) and 3i' (bottom) at the B3LYP/6-311+G(2d,p) level, plotted on a colour scale from -0.003 a.u. (red) to +0.003 a.u. (blue) and mapped onto an isodensity surface ($\rho = 4 \times 10^{-4}$ a.u.).

References


NMR Spectra of synthesised compounds

\[
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3) \]

\[\text{1e}\]
$^{13}$C NMR (126 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (126 MHz, CDCl$_3$)

![Chemical structure 1f]

$^1$H NMR (400 MHz, CDCl$_3$)

![Chemical structure 1g]
$^{13}$C NMR (101 MHz, CDCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (126 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (126 MHz, CDCl$_3$)

![Chemical Structure Image]
\(^1\)H NMR (400 MHz, CDCl\(_3\))

including 2% of

3e
\[ ^{19}\text{F NMR (376 MHz, CDCl}_3\text{)} \]

\[
\begin{align*}
\text{Br} & \quad \text{S} \quad \text{Me} \\
\text{Br} & \quad \text{S} \quad \text{F} \quad \text{F}
\end{align*}
\]

including 2% of

\[
\begin{align*}
\text{Br} & \quad \text{S} \quad \text{F} \\
\text{Br} & \quad \text{S} \quad \text{F}
\end{align*}
\]

\[ ^{13}\text{C NMR (126 MHz, CDCl}_3\text{)} \]

\[
\begin{align*}
\text{Br} & \quad \text{S} \quad \text{Me} \\
\text{Br} & \quad \text{S} \quad \text{F} \quad \text{F}
\end{align*}
\]

including 2% of

\[
\begin{align*}
\text{Br} & \quad \text{S} \quad \text{F} \\
\text{Br} & \quad \text{S} \quad \text{F}
\end{align*}
\]
$^1$H NMR (400 MHz, CDCl$_3$)

$^{19}$F NMR (376 MHz, CDCl$_3$)
$^{13}$C NMR (126 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{19}F$ NMR (376 MHz, CDCl$_3$)
$^{13}$C NMR (126 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{19}F$ NMR (376 MHz, CDCl$_3$)
$^{19}$F NMR (471 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{19}$F NMR (376 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{19}F$ NMR (376 MHz, CDCl$_3$)
$^{13}$C NMR (126 MHz, CDCl$_3$)