

Copper-Mediated Difluoromethylation of Aryl and Vinyl Iodides at Room Temperature

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Experimental details, characterization data of all products, and copies of NMR spectra.

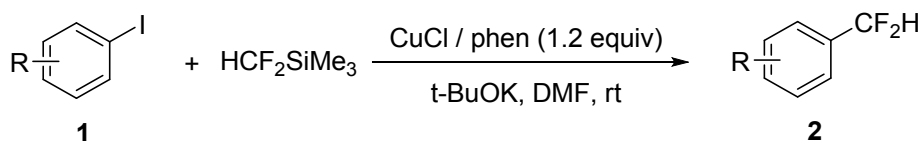
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General Information:

^1H NMR (TMS as the internal standard) and ^{19}F NMR spectra (CFCl_3 as the outside standard and low field is positive) were recorded on a Bruker AM300 or Bruker AM400 spectrometer. ^{13}C NMR was recorded on a Bruker AM400 spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Substrates were purchased from commercial sources (Aldrich, Alfa and Chemical Reagent Companies of China) and used as received. Reactions were performed under an atmosphere of nitrogen using glassware that was flame-dried under vacuum. Isopropyl 4-iodobenzenesulfonate (**1f**)¹ was prepared according to literature procedures. Compounds **2a**², **2c**², **2e**², **4b**³, **4c**³, **6a**³ and **6b**³ have been published previously.

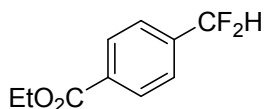
General Procedure for Copper-Mediated Difluoromethylation of Aryl and Vinyl Iodides at Room Temperature:



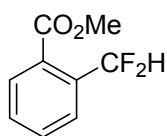
To a Shchlenk tube equipped with a magnetic stir bar were added CuCl (1.2 mmol) and $t\text{-BuOK}$ (2.4 mmol) were added under N_2 atmosphere. DMF (3.0 mL) was added to the tube. After stirring for 5 minutes, $\text{HCF}_2\text{SiMe}_3$ (2.4 mmol) was added to the mixture. The resulting mixture was stirred for 15 minutes and then phen (1.2 mmol) dissolved in DMF (2.0 mL) was added. After stirring for another 10 minutes, aryl iodides (1.0 mmol) was added to the mixture under N_2 atmosphere. The reaction mixture was kept at rt for 4 hours and then diluted with diethyl ether, washed with water and brine, dried over sodium sulfate, and concentrated. The crude products were purified by column chromatography on silica gel to give the corresponding products.

References

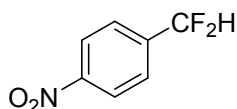
1. Kunst, E.; Gallier, F.; Dujardin, G.; Yusubov, M. S.; Kirschning, A. *Org. Lett.* **2007**, *9*, 5199.
2. Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560.
3. Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 12090.



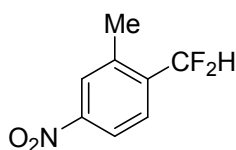
Ethyl 4-(difluoromethyl)benzoate (2a): Colorless liquid; yield 80%. ^1H NMR (300 MHz, CDCl_3) δ ppm 8.13 (d, $J = 8.4$ Hz, 2H), 7.59 (d, $J = 8.0$ Hz, 2H), 6.70 (t, $J = 56.4$ Hz, 1H), 4.41 (q, $J = 7.6$ Hz, 2H), 1.41 (t, $J = 7.2$ Hz, 3H). ^{19}F NMR (282 MHz, CDCl_3) δ ppm -112.2 (d, $J = 55.6$ Hz, 2F). ^{13}C NMR (100 MHz, CDCl_3) δ ppm 165.8, 138.4 (t, $J = 22.4$ Hz), 132.8, 123.0, 125.7 (t, $J = 5.3$ Hz), 114.1 (t, $J = 238.3$ Hz), 61.4, 14.3. IR (thin film) ν 3069, 1721, 1278, 1107, 1074 cm^{-1} . MS (EI): m/z 200 (M^+). HRMS Calculated for $\text{C}_{10}\text{H}_{10}\text{F}_2\text{O}_2$: 200.0649; Found: 200.0648.



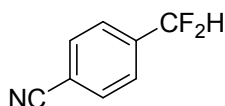
Methyl 2-(difluoromethyl)benzoate (2b): Colorless liquid; yield 77%. ^1H NMR (300 MHz, CDCl_3) δ ppm 8.04 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.40-7.68 (m, 3H), 3.94 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3) δ ppm -113.8 (d, $J = 54.9$ Hz, 2F). ^{13}C NMR (100 MHz, CDCl_3) δ ppm 166.5, 135.4 (t, $J = 22.0$ Hz), 132.8, 131.0, 130.5 (t, $J = 2.1$ Hz), 128.8 (t, $J = 5.0$ Hz), 126.0 (t, $J = 8.0$ Hz), 112.1 (t, $J = 236.7$ Hz), 52.6. IR (thin film) ν 2957, 1726, 1437, 1270, 1143, 1052 cm^{-1} . MS (EI): m/z 200 (M^+). HRMS Calculated for $\text{C}_9\text{H}_8\text{F}_2\text{O}_2$: 186.0492; Found: 186.0489.



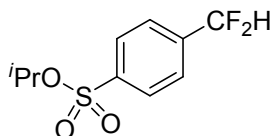
1-(Difluoromethyl)-4-nitrobenzene (2c): Yellow liquid; yield 78%. ^1H NMR (300 MHz, CDCl_3) δ ppm 8.33 (d, $J = 8.4$ Hz, 2H), 7.72 (d, $J = 8.4$ Hz, 2H), 6.75 (t, $J = 55.8$ Hz, 1H). ^{19}F NMR (282 MHz, CDCl_3) δ ppm -113.0 (d, $J = 55.6$ Hz, 2F). ^{13}C NMR (100 MHz, CDCl_3) δ ppm 149.5, 140.3 (t, $J = 23.5$ Hz), 126.9 (t, $J = 5.6$ Hz), 124.0, 113.3 (t, $J = 238.6$ Hz). IR (thin film) ν 3087, 1529, 1349, 1216, 1077 cm^{-1} . MS (EI): m/z 173 (M^+). HRMS Calculated for $\text{C}_7\text{H}_5\text{F}_2\text{NO}_2$: 173.0288; Found: 173.0286.



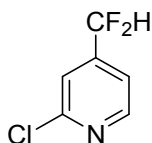
1-(Difluoromethyl)-2-methyl-4-nitrobenzene (2d): Yellow liquid; yield 83%. ^1H NMR (300 MHz, CDCl_3) δ ppm 8.11-8.14 (m, 2H), 7.71 (d, $J = 8.1$ Hz, 1H), 6.82 (t, $J = 55.8$ Hz, 1H). 2.55 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3) δ ppm -115.3 (d, $J = 54.4$ Hz, 2F). ^{13}C NMR (100 MHz, CDCl_3) δ ppm 149.1, 138.6 (t, $J = 4.5$ Hz), 138.2 (t, $J = 21.1$ Hz), 127.0 (t, $J = 7.5$ Hz), 125.8, 121.1, 112.9 (t, $J = 238.0$ Hz), 18.5. IR (thin film) ν 3081, 1530, 1348, 1186, 1045 cm^{-1} . MS (EI): m/z 187 (M^+). HRMS Calculated for $\text{C}_8\text{H}_7\text{F}_2\text{NO}_2$: 187.0443; Found: 187.0445.



4-(Difluoromethyl)benzonitrile (2e): Colorless liquid; yield 82%. ^1H NMR (300 MHz, CDCl_3) δ ppm 7.78 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.4$ Hz, 2H), 6.70 (t, $J = 55.6$ Hz, 1H). ^{19}F NMR (282 MHz, CDCl_3) δ ppm -113.2 (d, $J = 59.6$ Hz, 2F). ^{13}C NMR (100 MHz, CDCl_3) δ ppm 138.6 (t, $J = 23.2$ Hz), 132.6, 126.4 (t, $J = 6.9$ Hz), 114.8 (t, $J = 2.2$ Hz), 118.0, 113.4 (t, $J = 238.9$ Hz). IR (thin film) ν 3069, 2234, 1379, 1219, 1078 cm^{-1} . MS (EI): m/z 153 (M^+). HRMS Calculated for $\text{C}_8\text{H}_5\text{F}_2\text{N}$: 153.0390; Found: 153.0388.

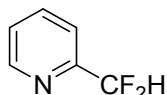


Isopropyl 4-(difluoromethyl)benzenesulfonate (2f): Colorless liquid; yield 80%. ^1H NMR (300 MHz, CDCl_3) δ ppm 8.02 (d, $J = 8.1$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H), 6.72 (t, $J = 55.8$ Hz, 1H), 4.79-4.84 (m, 1H), 1.31 (d, $J = 6.3$ Hz, 6H). ^{19}F NMR (282 MHz, CDCl_3) δ ppm -112.9 (d, $J = 57.3$ Hz, 2F). ^{13}C NMR (100 MHz, CDCl_3) δ ppm 139.9 (t, $J = 2.3$ Hz), 139.2 (t, $J = 23.8$ Hz), 128.1, 126.6 (t, $J = 6.6$ Hz), 113.5 (t, $J = 239.5$ Hz), 78.3, 22.8. IR (thin film) ν 3066, 1366, 1191, 1085 cm^{-1} . MS (EI): m/z 250 (M^+). HRMS Calculated for $\text{C}_{10}\text{H}_{12}\text{F}_2\text{O}_3\text{S}$: 250.0475; Found: 250.0478.

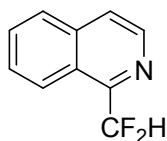


2-Chloro-4-(difluoromethyl)pyridine (4a): Colorless liquid; yield 83%. ^1H NMR (300 MHz,

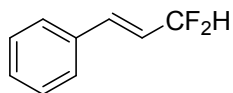
CDCl₃) δ ppm 8.53 (d, J = 5.1 Hz, 1H), 7.47 (s, 1H), 7.36 (d, J = 4.8 Hz, 1H), 6.63 (t, J = 55.5 Hz, 1H). ¹⁹F NMR (282 MHz, CDCl₃) δ ppm -116.2 (d, J = 55.0 Hz, 2F). ¹³C NMR (100 MHz, CDCl₃) δ ppm 152.4, 150.6, 145.2 (t, J = 24.6 Hz), 121.0 (t, J = 7.0 Hz), 118.8 (t, J = 5.4 Hz), 112.1 (t, J = 240.7 Hz). IR (thin film) ν 3069, 1602, 1561, 1367, 1131, 1088 cm⁻¹. MS (EI): m/z 163 (M⁺). HRMS Calculated for C₆H₄ClF₂N: 163.0000; Found: 163.9999.



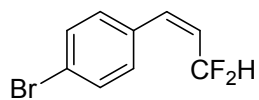
2-(Difluoromethyl)pyridine (4b): Yellow liquid; yield 70%. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.67 (d, J = 4.4 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 6.2 Hz, 1H), 6.65 (t, J = 54.8 Hz, 1H). ¹⁹F NMR (282 MHz, CDCl₃) δ ppm -115.8 (d, J = 53.8 Hz, 2F). ¹³C NMR (100 MHz, CDCl₃) δ ppm 152.8 (t, J = 25.2 Hz), 149.5, 137.2, 125.4 (t, J = 2.2 Hz), 120.1 (t, J = 2.4 Hz), 113.9 (t, J = 239.2 Hz).



1-(Difluoromethyl)isoquinoline (4c): Colorless liquid; yield 93%. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.46-8.51 (m, 2H), 7.64-7.89 (m, 4H), 6.98 (t, J = 54.3 Hz, 1H). ¹⁹F NMR (282 MHz, CDCl₃) δ ppm -110.0 (d, J = 54.4 Hz, 2F). ¹³C NMR (100 MHz, CDCl₃) δ ppm 151.1 (t, J = 26.2 Hz), 141.1, 136.9, 130.6, 128.2, 127.3, 125.1, 125.0 (t, J = 3.8 Hz), 123.5, 117.9 (t, J = 241.2 Hz). IR (thin film) ν 3060, 1586, 1370, 1111, 1033 cm⁻¹. MS (EI): m/z 179 (M⁺). HRMS Calculated for C₁₀H₇F₂N: 179.0547; Found: 179.0544.



(E)-(3,3-difluoroprop-1-enyl)benzene (6a): Colorless liquid; yield 51%. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.41-7.43 (m, 2H), 7.32-7.38 (m, 3H), 6.83-6.89 (m, 1H), 6.08-6.38 (m, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ ppm -109.6 – -109.8 (m, 2F). MS (EI): m/z 154 (M⁺).



(Z)-1-bromo-4-(3,3-difluoroprop-1-enyl)benzene (6b): Colorless liquid; yield 82%. ^1H NMR (300 MHz, CDCl_3) δ ppm 7.52 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 11.7$ Hz, 1H), 6.27 (td, $J = 55.2$ Hz, $J = 7.5$ Hz, 1H), 5.85-5.94 (m, 1H). ^{19}F NMR (282 MHz, CDCl_3) δ ppm -108.2 (dd, $J = 55.0$ Hz, $J = 8.2$ Hz, 2F). MS (EI): m/z 232 (M^+).

