Fluorophenols and (Trifluoromethyl)phenols as Substrates of Site-Selective Metalation Reactions: To Protect or not To Protect

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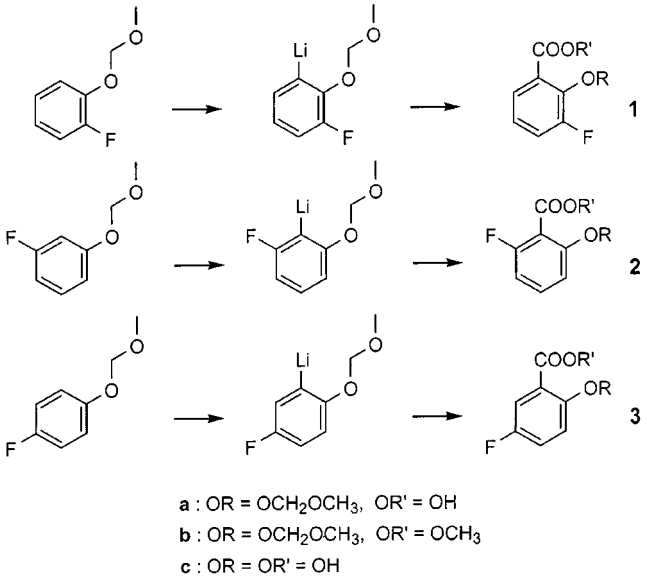
O-Methoxymethyl (MOM) protected fluorophenols can be cleanly metalated and subsequently be submitted to site-selective electrophilic substitution. The 2- and 4-isomers exhibit ambivalent reactivity: deprotonation occurs at the position adjacent to the oxygen when butyllithium is employed whereas the position adjacent to the fluorine is attacked by the superbasic mixture of butyllithium and potassium *tert*-butoxide (LIC-KOR). The MOM-protected (trifluoromethyl)-phenols react exclusively at oxygen-neighboring positions. The *meta* isomer provides another example of optional site selectivity, undergoing hydrogen/metal exchange at the 2-position with the LIC-KOR reagent and at the 6-position with *sec*-butyllithium. Unprotected (trifluoromethyl)phenols can also be *ortho*-metalated after *O*-deprotonation, although the products are formed in only moderate yields.

Introduction

The optionally site selective metalation of *ortho*- and *para*-fluoroanisole next to the halogen or next to the oxygen was the first example of a perfect and alternative discrimination against one or the other of two neighboring group-activated aromatic positions.[1] We consider this a landmark result because it corroborates our concepts of how to achieve regiocontrol in hydrogen/metal exchange processes through mechanism-based matching of substituents and reagents.[2−3] From a practical point of view, it would, of course, be much more useful to metalate fluorophenols than fluoroanisoles, as the former could subsequently be converted into any required ether or ester derivatives. However, phenolates react only reluctantly even with superbasic metalating reagents.[4−5] Therefore, we had to protect the phenolic hydroxy function as a methoxymethoxy group. As this group is known to outperform simple alkoxy groups as an *ortho*-directing substituent,[6−10] we had to worry whether fluorine could still compete with it. Fortunately this turned out to be the case.

Results

The metalation of all three fluoro(methoxymethoxy)-benzenes with butyllithium has been reported. As the hydrogen/metal exchange occurs preferentially or exclusively at the aromatic position adjacent to the oxygen, the yield of the main component was taken as the sole yardstick to measure the success: 59%, 79% and 77% in the case of the *ortho*,[11] *meta*[12] and *para*[13] isomers, respectively. In order not to overlook by-products, we first established a protocol for rigorous gas chromatographic analysis of the reaction mixtures. Improvements made on this basis allowed us to raise the yields of 2-fluoro-3-(methoxymethoxy)benzoic acid (**1a**), 2-fluoro-6-(methoxymethoxy)benzoic acid (**2a**) and 2-fluoro-5-(methoxymethoxy)benzoic acid (**3a**) to 79, 93 and 69%. Most importantly, all these products were found to be completely regioisomerically pure. The acetal acids **1a**, **2a** and **3a** were further converted into the methyl esters **1b**, **2b** and **3b** and into the hydroxy acids **1c**, **2c** and **3c** (Scheme 1).



Scheme 1

The crucial question now was whether or not the positions adjacent to the halogens of the *ortho* and *para* isomers could also be selectively deprotonated. This turned out to be the case if the superbasic mixture of butyllithium and potassium *tert*-butoxide was employed in tetrahydrofuran at −75 °C. Subsequent carboxylation and neutralization converted the intermediates generated from 2- and 4-me-

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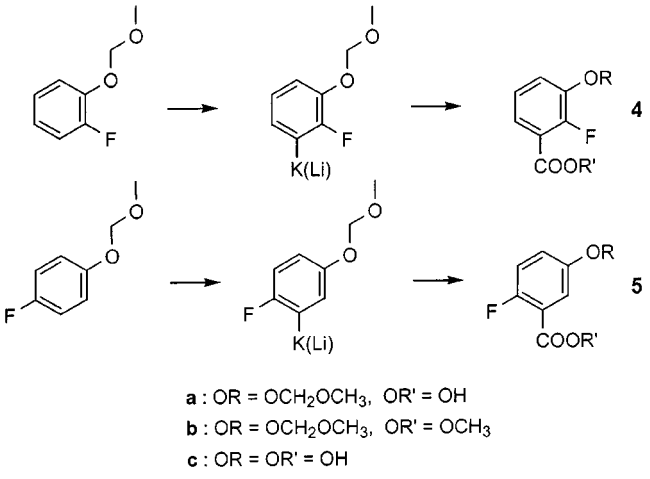
thoxymethoxy-1-fluorobenzene into the acids **4a** and **5a**, respectively. The gas chromatographic analysis of the corresponding methyl esters **4b** and **5b** revealed yields of 83 and 82%. Acidic hydrolysis afforded the fluorohydroxybenzoic acids **4c** (84%) and **5c** (80%) (Scheme 2).

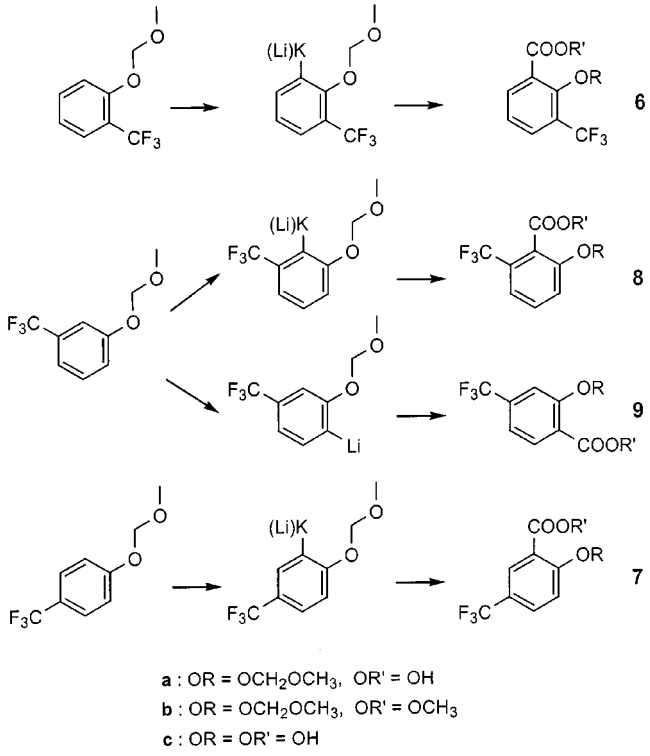


Scheme 2

For comparison, we extended our investigation to methoxymethyl-protected trifluoromethylphenols. The trifluoromethyl substituent not only acidifies the nearby *ortho* positions but also the more distant *meta* and *para* positions, and almost to the same extent. This "altruistic" behavior[14] in conjunction with the relative bulkiness of the CF_3 group should discriminate against a metalation in its immediate vicinity in favor of a more remote attack. Indeed, the methoxymethoxy-protected 2- and 4-isomers afforded the carboxylic acids **6a** and **7a** in 56 and 54% yield, respectively, after consecutive treatment with butyllithium in the presence of potassium *tert*-butoxide, dry ice and acid. In other words, they had reacted exclusively at a position adjacent to the oxygen. The same proved to be true for the 3-isomer, which nevertheless gave rise to another example of "optional site selectivity".[3] Notoriously insensitive to steric hindrance, the superbasic mixture of butyllithium and potassium *tert*-butoxide abstracted a proton exclusively from the doubly activated 2-position whereas *sec*-butyllithium did not attack any other site than the O-adjacent, but CF_3-distant 6-position. The corresponding acids **8a** and **9a** (Scheme 3) were collected in 53% and 93% yield.

The acetal acids **6a**−**9a** can be converted quantitatively into the more volatile methyl esters **6b**−**9b** by treatment with ethereal diazomethane, and into the hydroxy acids **6c**−**9c** by treatment with methanol and a catalytic amount of boron trifluoride−diethyl ether. One obtains superior overall yields of 90, 92, 64 and 94%, respectively, if the sensitive acetal acids are not isolated as intermediates but deprotonated immediately by hydrolysis.

Pure acid **8a** can only be obtained when the metalation is performed in neat tetrahydrofuran at 0.1 M dilution. An increase of the concentration to 0.5 M causes some regioisomeric leakage (the **8a/9a** ratio approaching 94:6) and



Scheme 3

if, in addition, the reaction medium contains about 30% of hexanes, the regioselectivity is lost entirely (**8a/9a** ≈ 1:1).

Organometallic reagents convert phenols instantaneously into phenolates, but the latter undergo *ortho*-metalation only sluggishly, as already mentioned.[4−5] However, phenolates carrying a trifluoromethyl substituent benefit from the powerful electron-withdrawing effect of the latter and *do* undergo metalation quite efficaciously even if not quantitatively. The carboxylic acids **6c**, **7c** and **8c** were derived from the 2-, 3- and 4-isomers in 58%, 65% and 65% yield, respectively.

Experimental Section

Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.[15−16] ^{1}H NMR spectra were recorded of samples dissolved in deuterochloroform at 400 MHz, ^{13}C NMR spectra at 101 MHz, unless stated otherwise. Starting materials were supplied by Fluka−Aldrich, 9471 Buchs (Switzerland), or by Apollo-Scientific, Whaley Bridge, SK23 7LY, UK, unless literature sources or details of the preparation are given.

Starting Materials

1-Fluoro-2-(methoxymethoxy)benzene: Chloromethyl methyl ether[17] (4.6 mL, 4.8 g, 60 mmol) was added dropwise, during 15 min., to a stirred, ice-cooled solution of 2-fluorophenol (4.6 mL, 5.6 g, 50 mmol) and *N*-ethyldiisopropylamine (17 mL, 13 g, 0.10 mol) in dichloromethane (40 mL). The mixture was kept for 2 h at +25 °C before being filtered and the solvents evaporated. Distillation gave a colorless liquid; b.p. 30−31 °C/1 Torr (ref.[11] b.p. 100 °C/20 Torr); n_D^{20} = 1.4836; d_4^{20} = 1.219; 6.5 g (83%). − ^{1}H NMR:

δ = 7.19 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.1 (m, 2 H), 6.94 (symm. m, 1 H), 5.20 (s, 2 H), 3.61 (s, 3 H). − ^{13}C NMR: δ = 153.3 (d, *J* = 245.7 Hz), 145.1 (d, *J* = 10.4 Hz), 124.4 (d, *J* = 3.2 Hz), 122.7 (d, *J* = 7.2 Hz), 118.2 (s), 116.4 (d, *J* = 18.5 Hz), 95.7 (s), 56.3 (s). − MS (CI): *m*/*z* (%) = 174 (97) [M$^+$ + NH$_4$], 156 (19) [M$^+$], 126 (100).

1-Fluoro-3-(methoxymethoxy)benzene: Prepared as above from 3-fluorophenol (4.5 mL, 5.6 g, 50 mmol); b.p. 25−26 °C/0.6 Torr); n_D^{20} = 1.4790; d_4^{20} = 1.117; 5.0 g (64%). − ^{1}H NMR: δ = 7.20 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1 H), 6.8 (m, 2 H), 6.68 (tdd, *J* = 8.7, 3.2, 0.8 Hz, 1 H), 5.13 (s, 2 H), 3.44 (s, 3 H). − ^{13}C NMR: δ = 163.6 (d, *J* = 244.9 Hz), 158.6 (d, *J* = 10.5 Hz), 130.3 (d, *J* = 9.7 Hz), 111.9 (s), 108.7 (d, *J* = 20.8 Hz), 104.0 (d, *J* = 24.1), 94.5 (s), 56.0 (s). − MS: *m*/*z* (%) = 156 (6) [M$^+$], 114 (100), 97 (52). − $C_8H_9FO_2$ (156.16): calcd. C 61.53, H 5.81; found C 61.95, H 6.07.

1-Fluoro-4-(methoxymethoxy)benzene: Prepared as above from 4-fluorophenol (5.6 g, 50 mmol); b.p. 26−27 °C/0.4 Torr); n_D^{20} = 1.4776; d_4^{20} = 1.114; 4.3 g (55%). − ^{1}H NMR: δ = 7.0 (m, 4 H), 5.08 (s, 2 H), 3.43 (s, 3 H). − ^{13}C NMR: δ = 158.0 (d, *J* = 239.3 Hz), 153.4 (s), 117.6 (d, *J* = 7.2 Hz, 2 C), 115.8 (d, *J* = 22.4 Hz, 2 C), 95.0 (s), 55.8 (s). − MS: *m*/*z* (%) = 156 (11) [M$^+$], 115 (39), 114 (100). − $C_8H_9FO_2$ (156.16): calcd. C 61.53, H 5.81; found C 61.84, H 6.14.

1-Methoxymethoxy-2-(trifluoromethyl)benzene: Prepared as above from 2-(trifluoromethyl)phenol (4.1 g, 25 mmol); b.p. 73−74 °C/8 Torr; n_D^{20} = 1.4459; 3.8 g (74%). − ^{1}H NMR: δ = 7.72 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.61 (t, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.6 Hz, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 5.37 (s, 2 H), 3.57 (s, 3 H). − ^{13}C NMR: δ = 155.0 (s), 133.2 (s), 127.1 (q, *J* = 4.8 Hz), 123.7 (q, *J* = 273.1 Hz), 121.1 (s), 119.6 (q, *J* = 30.5 Hz), 115.2 (s), 94.2 (s), 56.3 (s). − MS: *m*/*z* (%) = 206 (22) [M$^+$], 72 (90), 57 (100). − $C_9H_9F_3O_2$ (206.17): calcd. C 52.43, H 4.40; found C 52.76, H 4.38.

1-Methoxymethoxy-3-(trifluoromethyl)benzene: Prepared as above from 3-(trifluoromethyl)phenol (3.1 mL, 4.1 g, 25 mmol); b.p. 71−72 °C/8 Torr; n_D^{20} = 1.4394; 3.9 g (76%). − ^{1}H NMR: δ = 7.52 (t, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 1.4 Hz, 1 H), 7.39 (dd, *J* = 7.5, 0.9 Hz, 1 H), 7.34 (dd, *J* = 8.4, 2.3 Hz, 1 H), 5.29 (s, 2 H), 3.54 (s, 3 H). − ^{13}C NMR: δ = 157.5 (s), 132.0 (q, *J* = 32.2 Hz), 130.1 (s), 124.0 (q, *J* = 273.0 Hz), 119.6 (s), 118.6 (q, *J* = 4.0 Hz), 113.3 (q, *J* = 3.2 Hz), 94.5 (s), 56.2. − MS: *m*/*z* (%) = 206 (12) [M$^+$], 169 (12), 97 (34), 83 (59), 57 (100). − $C_9H_9F_3O_2$ (206.17): calcd. C 54.43, H 4.40; found C 52.78, H 4.10.

1-Methoxymethoxy-4-(trifluoromethyl)benzene: Prepared as above from 4-(trifluoromethyl)phenol (4.1 g, 25 mmol); m.p. −12 to −8 °C; b.p. 75−76 °C/8 Torr; n_D^{20} = 1.4416; 3.3 g (65%). − ^{1}H NMR: δ = 7.68 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.7 Hz, 2 H), 5.31 (s, 2 H), 3.54 (s, 3 H). − ^{13}C NMR: δ = 159.7 (s), 126.9, (q, *J* = 4.0 Hz, 2 C), 124.4 (q, *J* = 271.5 Hz), 124.0 (q, *J* = 33.0 Hz), 116.1 (s, 2 C), 94.2 (s), 56.2 (s). − MS: *m*/*z* (%) = 207 (23) [M$^+$ + 1], 206 (94), [M$^+$], 145 (100). − $C_9H_9F_3O_2$ (206.17): calcd. C 52.43, H 4.40; found C 52.82, H 4.05.

Reactions with Fluoro(methoxymethoxy)benzenes

3-Fluoro-2-(methoxymethoxy)benzoic Acid (1a): A solution containing 1-fluoro-2-(methoxymethoxy)benzene[7] (3.2 mL, 3.9 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) was kept for 6 h at −75 °C before being poured onto an excess of freshly crushed dry ice. After evaporation of most of the solvent, the residue was partitioned between diethyl ether (15 mL) and 1.0 M aqueous sodium hydroxide (25 mL). The aqueous phase was washed with diethyl ether (2 × 5 mL), acidified to pH 5 with citric acid (about 10 g) and extracted with dichloromethane (3 × 15 mL). One tenth of the combined organic layers was withdrawn and a known amount of benzoic acid (approx. 2 mg, 1 mmol) was added as an internal reference compound. After the solution had been treated with ethereal diazomethane until persistence of the yellow color, it was analyzed by gas chromatography (2 m, 5% SE-30, 140 °C; 2 m, 5% C-20M, 200 °C). The amount of methyl 3-fluoro-2-methoxymethoxy)benzoate (**1b**) formed was determined by comparison of its peak area with that of the "internal standard" (methyl benzoate) after response correction using calibration factors obtained by the evaluation of controls made with authentic mixtures. The yield thus found was 81%. The remainder (90%) of the dichloromethane solution was evaporated to dryness and the residue crystallized from a 1:9 (v/v) mixture of ethyl acetate and hexanes in the form of colorless needles; m.p. 71−73 °C; 3.6 g (79%). − ^{1}H NMR: δ = 7.50 (d, *J* = 8.1 Hz, 1 H), 7.33 (ddd, *J* = 8.1, 6.5, 1.8 Hz, 1 H), 7.22 (td, *J* = 5.2, 3.0 Hz, 1 H), 5.36 (s, 2 H), 3.61 (s, 3 H). − $C_9H_9FO_4$ (200.17): calcd. C 54.00, H 4.53; found C 54.02, H 4.55.

2-Fluoro-6-(methoxymethoxy)benzoic Acid (2a): Prepared as above from 1-fluoro-3-(methoxymethoxy)benzene (1.4 mL, 1.6 g, 10 mmol), although the metalation was accomplished in 2 h at −75 °C with *sec*-butyllithium (10 mmol) in the presence of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (2.1 mL, 1.7 g, 10 mmol); colorless needles; m.p. 42−44 °C; 1.68 g (93%). − ^{1}H NMR: δ = 7.38 (td, *J* = 8.2, 6.0 Hz, 1 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.83 (t, *J* = 8.2 Hz, 1 H), 5.27 (s, 2 H), 3.52 (s, 3 H). − $C_9H_9FO_4$ (200.17): calcd. 54.00, H 4.53; found C 54.01, H 4.58. − Ester **2b**: 93% (by gas chromatography).

5-Fluoro-2-(methoxymethoxy)benzoic Acid (3a): Prepared as above from 1-fluoro-4-(methoxymethoxy)benzene (1.4 mL, 1.6 g, 10 mmol), the metalation conditions being the same as for the preparation of acid **1a** (butyllithium, 6 h at −75 °C); colorless needles; m.p. 56−58 °C; 1.28 g (71%). − ^{1}H NMR: δ = 7.87 (dd, *J* = 8.5, 3.0 Hz, 1 H), 7.3 (m, 2 H), 5.40 (s, 2 H, 3.57 (s, 3 H). − $C_9H_9FO_4$ (200.17): calcd. 54.00, H 4.53; found C 53.78, H 4.62. − Ester **3b**: 69% (by gas chromatography).

2-Fluoro-3-(methoxymethoxy)benzoic Acid (4a): At −75 °C, potassium *tert*-butoxide (1.1 g, 10 mmol) and 1-fluoro-2-(methoxymethoxy)benzene (1.3 mL, 1.6 g, 10 mmol) were added to a solution of butyllithium (10 mmol) in tetrahydrofuran (14 mL) and hexanes (6 mL). The mixture was stirred until homogeneous and then kept for 2 h at −75 °C. It was worked up as described for the acid **1a** and the ester **1b**. The acid **4a** was isolated in the form of white colorless needles; m.p. 104−105 °C; 1.51 g (84%). − ^{1}H NMR: δ = 7.65 (ddd, *J* = 8.0, 6.2, 1.9 Hz), 7.44 (td, *J* = 8.0, 1.9 Hz, 1 H), 7.15 (td, *J* = 8.0, 1.9 Hz), 5.25 (s, 2 H), 3.54 (s, 3 H). − $C_9H_9FO_4$ (200.17): calcd. 54.00, H 4.53; found C 54.09, H 4.61. − Ester **4b**: 83% (by gas chromatography).

2-Fluoro-5-(methoxymethoxy)benzoic Acid (5a): Prepared as above from 1-fluoro-4-(methoxymethoxy)benzene (1.4 mL, 1.6 g, 10 mmol; colorless prisms; m.p. 87−89 °C; 2.16 g (80%). − ^{1}H NMR: δ = 7.66 (dd, *J* = 6.0, 3.0 Hz, 1 H), 7.2 (m, 1 H), 7.10 (t, *J* = 10.0 Hz, 1 H), 5.17 (s, 2 H), 3.49 (s, 3 H). − $C_9H_9FO_4$ (200.17): calcd. 54.00, H 4.53; found C 53.93, H 4.49. − Ester **5b**: 82% (by gas chromatography).

3-Fluoro-2-hydroxybenzoic Acid (1c): The acetal acid **1a** (4.5 g, 25 mmol) was dissolved in anhydrous methanol (25 mL) to which a few drops of boron trifluoride−diethyl ether were added. After having stood overnight (15 h) at +25 °C, the solution was evaporated to dryness and the residue recrystallized from toluene; color-

less needles; m.p. 142.5−143.5 °C (ref.[18] m.p. 144−145 °C); 2.8 g (72%). − ^{1}H NMR: δ = 7.68 (d, *J* = 7.8 Hz, 1 H), 7.3 (m, 1 H), 6.80 (td, *J* = 7.8, 4.7 Hz, 1 H). − ^{13}C NMR: δ = 172.3 (s), 151.7 (d, *J* = 196.7 Hz), 150.4 (d, *J* = 35.3 Hz), 125.6 (d, *J* = 4.0 Hz), 121.1 (d, *J* = 16.9 Hz), 118.1 (d, *J* = 7.2 Hz), 115.2 (d, *J* = 3.2 Hz). − MS (CI): *m*/*z* (%) = 174 (100) [$M^+ + NH_4$], 156 (19) [M^+], 155 (21) [$M^+ - 1$], 138 (43) [$M^+ + H_2O$], 110 (44).

2-Fluoro-6-hydroxybenzoic Acid (2c): Prepared as above from the acetal acid **2a**; colorless platelets; m.p. 159−161 °C; 3.6 g (91%). − ^{1}H NMR (D_3CSOCD_3): δ = 7.36 (td, *J* = 8.5, 6.5 Hz, 1 H), 6.76 (d, *J* = 7.4 Hz, 1 H), 6.70 (dd, *J* = 10.3, 8.4 Hz, 1 H). − ^{13}C NMR (D_3CSOCD_3): δ = 168.4 (s), 161.1 (d, *J* = 249.8 Hz), 159.5 (s), 134.0 (d, *J* = 10.5 Hz), 113.0 (s), 107.5 (d, *J* = 16.1), 106.7 (d, *J* = 22.5). − MS (CI): *m*/*z* (%) = 174 (28) [$M^+ + NH_4$], 156 (25) [M^+], 155 (30) [$M^+ + 1$], 138 (39) [$M^+ + H_2O$], 110 (100). − $C_7H_5FO_3$ (156.11): calcd. 53.86, H 3.23; found C 53.87, H 3.31.

5-Fluoro-2-hydroxybenzoic Acid (3c): Prepared as above from the acetal acid **3a**; colorless platelets; m.p. 178−179 °C (ref.[19] m.p. 178.5−179.5 °C); 2.3 g (58%). − ^{1}H NMR (D_3CSOCD_3): δ = 7.50 (dd, *J* = 9.2, 3.1 Hz, 1 H), 7.39 (td, *J* = 8.9, 3.1 Hz, 1 H), 6.98 (dd, *J* = 9.1, 4.5 Hz, 1 H). − ^{13}C NMR (D_3CSOCD_3): δ = 171.3 (s), 157.8 (s), 154.9 (d, *J* = 236.1 Hz), 123.4 (d, *J* = 24.0 Hz), 119.2 (d, *J* = 6.4 Hz), 115.7 (d, *J* = 8.0 Hz). − MS: *m*/*z* (%) = 156 (29) [M^+], 138 (51) [$M^+ - H_2O$], 110 (100).

2-Fluoro-3-hydroxybenzoic Acid (4c): Prepared as above from the acetal acid **4a**; colorless needles; m.p. 185−187 °C; 3.2 g (83%). − ^{1}H NMR (D_3CSOCD_3): δ = 10.00 (s, 1 H), 7.21 (ddd, *J* = 7.8, 6.3, 1.9 Hz, 1 H), 7.13 (td, *J* = 8.1, 2.0 Hz, 1 H), 7.03 (td, *J* = 8.1, 1.1 Hz, 1 H), 3.29 (s, broad, 1 H). − ^{13}C NMR (D_3CSOCD_3): δ = 175.7 (s), 150.8 (d, *J* = 254.5 Hz), 146.3 (d, *J* = 12.9 Hz), 124.3 (d, *J* = 3.2 Hz), 121.9 (s), 121.3 (s), 120.9 (d, *J* = 8.0 Hz). − MS: *m*/*z* (%) = 157 (10) [$M^+ + 1$], 156 (97) [M^+], 139 (100). − $C_7H_5FO_3$ (156.11): calcd. C 53.86, H 3.23; found C 53.76, H 3.06.

2-Fluoro-5-hydroxybenzoic Acid (5c): Prepared as above from the acetal acid **5a**; colorless stars; m.p. 198.5−200.0 °C; 3.1 g (79%). − ^{1}H NMR (D_3CSOCD_3): δ = 9.69 (s, 1 H), 7.18 (dd, *J* = 5.9, 3.0 Hz, 1 H), 7.09 (dd, *J* = 10.7, 9.0 Hz, 1 H), 6.95 (td, *J* = 7.2, 3.5 Hz, 1 H), 3.34 (s, broad, 1 H). − ^{13}C NMR (D_3CSOCD_3): δ = 165.5 (d, *J* = 2.4 Hz), 154.9 (d, *J* = 247.4 Hz, 153.6 (s), 121.4 (d, *J* = 8.0 Hz), 119.8 (d, *J* = 12.0 Hz), 118.1 (d, *J* = 24.0 Hz), 117.3 (s). − MS: *m*/*z* (%) = 157 (20) [$M^+ + 1$], 156 (100) [M^+], 139 (98). − $C_7H_5FO_3$ (156.11): calcd. C 53.86, H 3.23; found C 53.76, H 3.36.

Reactions with *O*-Protected or Unprotected (Trifluoromethyl)phenols

2-Methoxymethoxy-3-(trifluoromethyl)benzoic Acid (6a): At −75 °C, potassium *tert*-butoxide was added to a solution of 1-methoxymethoxy-3-(trifluoromethyl)benzene (5.2 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL). The mixture was vigorously stirred until homogeneous and kept for 2 h at −75 °C before being poured onto an excess of freshly crushed dry ice. After evaporation of most of the solvent, the residue was partitioned between diethyl ether (15 mL) and 1.0 M aqueous sodium hydroxide (25 mL). The aqueous phase was washed with diethyl ether (2 × 5 mL), acidified to pH 5 with citric acid (about 10 g) and extracted with dichloromethane (3 × 15 mL). One tenth of the combined organic layers was withdrawn and, after addition of a known amount of benzoic acid (approx. 2 mg, 1 mmol) as an internal reference compound, treated with ethereal diazomethane until persistence of the yellow color, and analyzed by gas chromatography (2 m, 5% SE-30, 140 °C; 2 m, 5% C-20M, 200 °C). The amount of methyl 2-methoxymethoxy-3-(trifluoromethyl)benzoate (**6b**; 59%) formed was determined by comparison of its peak area with that of the "internal standard" (methyl benzoate) after response correction by means of calibration factors derived from authentic mixtures. The remainder (90%) of the dried dichloromethane solution was evaporated and the residue crystallized from a 1:9 mixture of ethyl acetate and hexanes in the form of colorless prisms; m.p. 82−84 °C; 3.5 g (56%). − ^{1}H NMR: δ = 8.16 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.86 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.33 (t, *J* = 7.9 Hz, 1 H), 5.19 (s, 2 H), 3.61 (s, 3 H). − $C_{10}H_9F_3O_4$ (250.17): calcd. C 48.01, H 3.63; found C 47.91, H 3.25. − Ester **6b**: 59% yield (by gas chromatography).

2-Methoxymethoxy-5-(trifluoromethyl)benzoic Acid (7a): Prepared as above from 1-methoxymethoxy-4-(trifluoromethyl)benzene (5.2 g, 25 mmol); colorless needles; m.p. 72−74 °C (from a 1:9 mixture of ethyl acetate and hexanes); 3.4 g (54%). − ^{1}H NMR: δ = 8.44 (d, *J* = 2.3 Hz, 1 H), 7.78 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.40 (d, *J* = 8.6 Hz, 1 H), 5.47 (s, 2 H), 3.58 (s, 3 H). − $C_{10}H_9F_3O_4$ (250.17): calcd. C 48.01, H 3.63; found C 47.88, H 3.25. − Ester **7b**: 60% yield (by gas chromatography).

2-Methoxymethoxy-6-(trifluoromethyl)benzoic Acid (8a): When the same metalation conditions as described above (see preparation of acid **6a**) were applied to 1-methoxymethoxy-3-(trifluoromethyl)-benzene (5.2 g, 25 mmol), a 1:1 mixture (82%) of acid **8a** and its isomer **9a** (see below) was obtained after the usual workup. When the commercial hydrocarbon solvent was stripped off the butyllithium and the reaction was conducted in neat tetrahydrofuran (50 mL), a 96:4 ratio of **8a** vs. **9a** was found (79% combined yield). Pure acid **8a** resulted when the reaction was carried out in neat tetrahydrofuran (0.25 mL) at a 0.1 M dilution; colorless platelets; m.p. 47−49 °C (from a 1:9 mixture of ethyl acetate and hexanes); 3.3 g (53%). − ^{1}H NMR: δ = 7.50 (t, *J* = 8.2 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 5.28 (s, 2 H), 3.51 (s, 3 H). − $C_{10}H_9F_3O_4$ (250.17): calcd. C 48.01, H 3.63; found C 47.96, H 3.27. − Ester **8b**: 56% yield (by gas chromatography).

2-Methoxymethoxy-4-(trifluoromethyl)benzoic Acid (9a): 1-Methoxymethoxy-4-(trifluoromethyl)benzene (5.2 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (3.8 mL, 2.9 g, 25 mmol) in tetrahydrofuran (35 mL) and cyclohexane (15 mL). The mixture was kept for 2 h at −75 °C before being carboxylated and worked up as specified above (see preparation of acid **6a**). The acid **9a** was isolated in the form of colorless needles; m.p. 91−93 °C (from a 1:9 mixture of ethyl acetate and hexanes); 5.8 g (93%). − ^{1}H NMR: δ = 8.22 (d, *J* = 8.3 Hz, 1 H), 7.54 (s, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 5.44 (s, 2 H), 3.58 (s, 3 H). − $C_{10}H_9F_3O_4$ (250.17): calcd. C 48.01, H 3.63; found C 47.88, H 3.30. − Ester **9b**: 94% yield (by gas chromatography).

2-Hydroxy-3-(trifluoromethyl)benzoic Acid (6c): The acetal acid **6a** (3.8 g, 15 mmol) was dissolved in anhydrous methanol (15 mL) to which a few drops of boron trifluoride−diethyl ether were added. The mixture was allowed to stand overnight (15 h) at 25 °C before being evaporated to dryness. Crystallization of the residue from hexanes afforded colorless needles; m.p. 161−163 °C; 2.8 g (90%). − ^{1}H NMR: δ = 8.26 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.12 (t, *J* = 8.0 Hz, 1 H). − ^{13}C NMR: δ = 173.1 (s), 160.2 (s), 134.6 (s), 133.6 (q, *J* = 4.8 Hz), 123.2 (q, *J* = 272.3 Hz), 118.9 (s), 118.5 (s), 113.2 (s). − MS: *m*/*z* (%) = 207 (23) [$M^+ + 1$], 206 (76) [M^+], 188 (100), 160 (87), 132 (98). − $C_8H_5F_3O_3$ (206.12): calcd. C 46.62, H 2.45; found C 46.69, H 2.49.

2-Hydroxy-5-(trifluoromethyl)benzoic Acid (7c): Prepared as above from the acetal acid **7a**: colorless needles; m.p. 150−152 °C (from

hexanes); 2.9 g (93%). − ^{1}H NMR: δ = 8.37 (d, *J* = 1.8 Hz, 1 H), 7.90 (dd, *J* = 8.9, 2.3 Hz, 1 H), 7.26 (d, *J* = 9.0 Hz, 1 H). − ^{13}C NMR: δ = 173.4 (s), 164.5 (s), 133.5 (s), 128.7 (q, *J* = 4.0 Hz), 123.6 (q, *J* = 271.5 Hz), 122.3 (q, *J* = 33.0 Hz), 118.1 (s), 111.1 (s). − MS: *m*/*z* (%) = 207 (22) [M$^+$ + 1], 206 (70) [M$^+$], 188 (99), 160 (100), 132 (71). − $C_8H_5F_3O_3$ (206.12): calcd. C 46.62, H 2.45; found C 46.86, H 2.39.

2-Hydroxy-6-(trifluoromethyl)benzoic Acid (8c): Prepared as above from the acetal acid **8a**: colorless prisms; m.p. 155−157 °C (ref.[20] m.p. 156−158 °C); 2.0 g (64%). − ^{1}H NMR: δ = 7.69 (td, *J* = 8.3, 0.7 Hz, 1 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 7.40 (s, broad, 1 H), 7.38 (s, 1 H), 5.30 (s, broad, 1 H). − ^{13}C NMR: δ = 171.2 (s), 162.4 (s), 133.5 (s), 130.6 (q, *J* = 31.4 Hz), 126.1 (q, *J* = 273.1 Hz), 122.2 (s), 118.6 (s), 113.8 (s). − MS: *m*/*z* (%) = 207 (5) [M$^+$ + 1], 206 (34) [M$^+$], 188 (93), 160 (69), 132 (100).

2-Hydroxy-4-(trifluoromethyl)benzoic Acid (9c): Prepared as above from the acetal acid **9a**: colorless needles; m.p. 176−178 °C (ref.[21] m.p. 178−178.5 °C); 2.9 g (94%). − ^{1}H NMR: δ = 8.15 (d, *J* = 8.4 Hz, 1 H), 7.37 (s, 1 H), 7.25 (d, *J* = 8.6 Hz, 1 H). − ^{13}C NMR: δ = 172.0 (s), 161.9 (s), 136.9 (q, *J* = 32.2 Hz), 131.5 (s), 123.2 (q, *J* = 273.9 Hz), 115.4 (q, *J* = 3.2 Hz), 115.3 (s), 114.8 (q, *J* = 4.0 Hz). − MS: *m*/*z* (%) = 207 (17) [M$^+$ + 1], 206 (59) [M$^+$], 188 (100), 160 (97), 132 (65).

The acids **6c**, **7c** and **8c** can be made directly from the corresponding (trifluoromethyl)phenols in 58%, 65% and 65% yield. The metalation was accomplished by adding the substrate (25 mmol), potassium *tert*-butoxide (25 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (50 mmol) to a solution of butyllithium (50 mmol) in hexanes (50 mL) and by stirring the mixture vigorously for 30 min. at +10 °C before pouring it onto dry ice.

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