

Deprotonation-Triggered Heavy-Halogen Migrations as a Key to the Structural Elaboration of 2,2-Difluoro-1,3-benzodioxole

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Although proton abstraction from the 4-position of 2,2-difluoro-1,3-benzodioxole occurs with exceptional ease, lithiation of the more-remote 5-position can only be brought about if no oxygen-adjacent site remains unoccupied. Thus, unlike 4-bromo-2,2-difluoro-1,3-benzodioxole (**1**), (7-bromo-2,2-difluoro-1,3-benzodioxol-4-yl)triethylsilane (**5b**) does react with lithium diisopropylamide to generate an intermediate that isomerizes instantaneously by heavy-halogen migration. Upon neutralization and carboxylation, 5-bromo-

2,2-difluoro-1,3-benzodioxole (**8**) and 5-bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (**3**) are formed nearly quantitatively. A similar basicity gradient-driven heavy-halogen migration can be accomplished starting from 2,2-difluoro-4,7-diiodo-1,3-benzodioxole (**11**). These results procure a deeper insight in the acidifying effects of fluoroalkoxy groups and their distance dependence.

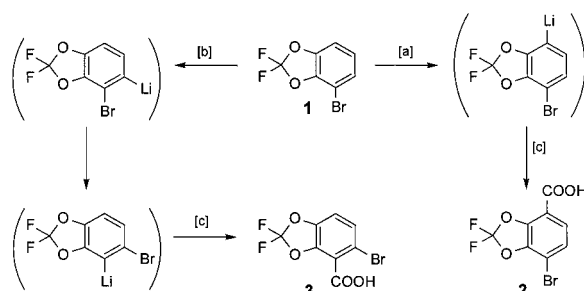
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Introduction

Having discovered the first clean and, hence, synthetically useful deprotonation-promoted heavy-halogen migration in the arene series,^[1,2] we embarked on a systematic exploration^[3,4] of the scope and the limitations of this kind of process. 2,2-Difluoro-1,3-benzodioxole, the key intermediate for the manufacture of an important herbicide,^[5,6] provided us with a prototypical model substrate because its exceptionally strong inherent acidity makes lithiation at the 4-position,^[5–7] and the subsequent introduction of a wide range of electrophiles at this site, extremely facile.^[8] The main objective of the present work was to probe the proton mobility at the heteroatom-remote 5-position relative to the 4-position.

We chose 4-bromo-2,2-difluoro-1,3-benzodioxole (**1**)^[8] to serve as the test compound. If it behaves as an ordinary 1-bromo-2,3-dialkoxyarene, deprotonation by a lithium dialkylamide should occur simultaneously at the halogen- and oxygen-adjacent positions because bromine or chlorine atoms and alkoxy or aryloxy substituents belong to the least-acidifying neighboring groups.^[2] Lithiation at the position next to the bromine atom would generate an intermediate doomed to undergo basicity gradient-driven halogen migration. Upon carboxylation, the isomerized species would provide 5-bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (**3**). Alternatively, the organo-

lithium compound resulting from deprotonation at the oxygen-activated 7-position would afford 7-bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (**2**). In fact, only the latter product **2** (96%) was obtained when 4-bromo-2,2-difluoro-1,3-benzodioxole was treated consecutively with lithium diisopropylamide (LIDA) and dry ice before the mixture was neutralized.



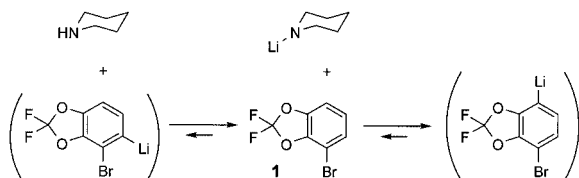
[a] Lithium diisopropylamide (LIDA) in tetrahydrofuran (THF) at -100 °C. [b] Lithium piperide (LIPiP) in tetrahydrofuran (THF) at -75 °C. [c] (1) CO₂, (2) HCl.

Obviously LIDA is basic enough to make the deprotonation of 4-bromo-2,2-difluoro-1,3-benzodioxole (**1**) at the 7-position virtually irreversible. When we employed a weaker base, lithium piperide, proton abstraction occurred concomitantly also at the 5-position, thus triggering the intended heavy-halogen migration. 5-Bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (**3**), however, was formed in only small amounts (8%) along with the isomeric 7-bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (**2**) and numerous by-products. Since bromobenzene is totally inert towards any lithium dialkylamide in the presence or absence of potassium *tert*-butoxide, the present

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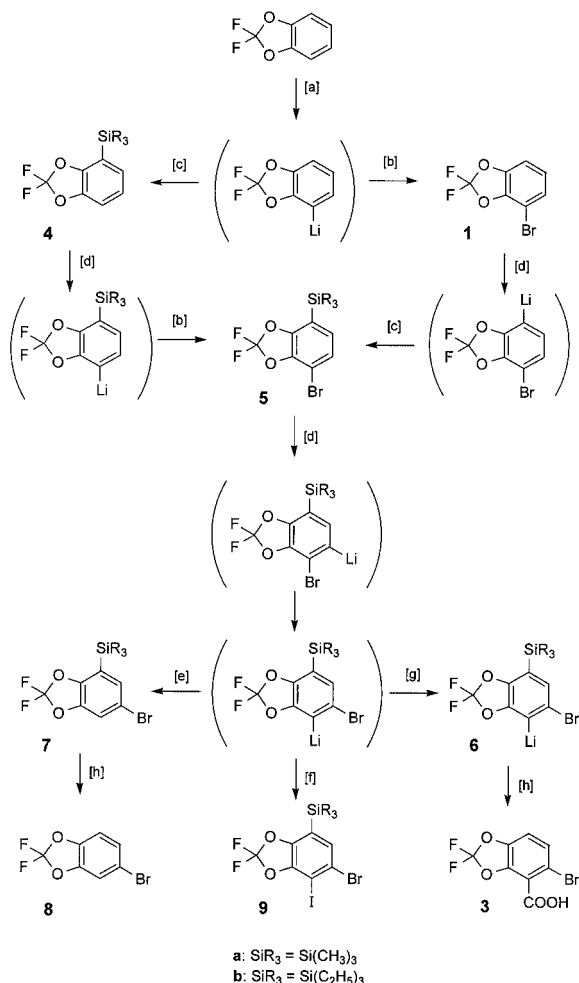
findings reveal an acidifying effect of the fluoroalkoxy unit, which is, of course, strongest at the 4- and 7-positions, but extends also to the 5- and 6-positions.



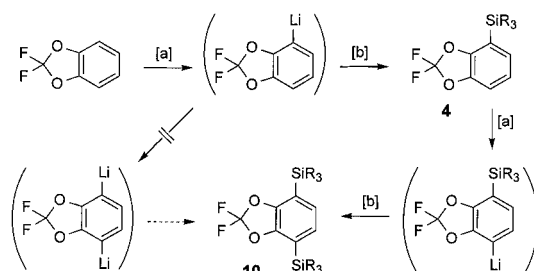
The heavy-halogen migration did take place smoothly once the 7-position was blocked by a trialkylsilyl group. This transformation was first attempted by treating the bromo compound **1** consecutively with LIDA and the chlorotrialkylsilane ClSiR_3 ($\text{R} = \text{CH}_3, \text{C}_2\text{H}_5$), but the yields of bromosilanes **5a** (12%) and **5b** (50%) were poor. Satisfactory results (**5a**: 83%; **5b**: 95%) were achieved when trialkyl(2,2-difluoro-1,3-benzodioxolan-4-yl)silane **4** (**a**: $\text{R} = \text{CH}_3$; **b**: $\text{R} = \text{C}_2\text{H}_5$) was allowed to react consecutively with LIDA and molecular bromine. The resulting bromosilanes **5** (**5a**: 83%, **5b**: 95%) underwent clean proton abstraction from the

bromine-adjacent position. The organolithium intermediate thus generated isomerized instantaneously through heavy-halogen migration. Carboxylation, neutralization, and iodination of the resulting species gave the 5-bromo-2,2-difluoro-7-trialkylsilyl-1,3-benzodioxole-4-carboxylic acids **6** (both **6a** and **6b**: 82%), the bromosilanes **7** (**7a**: 86%, **7b**: 85%), and the iodobromosilane **9b** (73%), respectively. Protodesilylation of the acids **6** and the bromosilanes **7** afforded 5-bromo-2,2-difluoro-1,3-benzodioxole (**8**; 79%) and 5-bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (**3**; 91%), respectively.

This bis(silanes) **10** (**10a**: 85%; **10b**: 83%) were obtained each time upon simultaneous exposure of 2,2-difluoro-1,3-benzodioxole to two equivalents of LIDA and chlorotrialkylsilane ClSiR_3 ($\text{R} = \text{CH}_3$ or C_2H_5). The reaction proceeds stepwise under such in situ trapping conditions.^[9] The attempted double metalation of 2,2-difluoro-1,3-benzodioxole using LIDA, butyllithium, or *N,N,N',N',N'*-pentamethyldiethylenetriamine-activated *sec*-butyllithium failed, as evidenced by the absence of any 2,2-difluoro-4,7-diiodo-1,3-benzodioxole (**13**; see below) after the addition of the reaction mixture to a solution of molecular iodine.

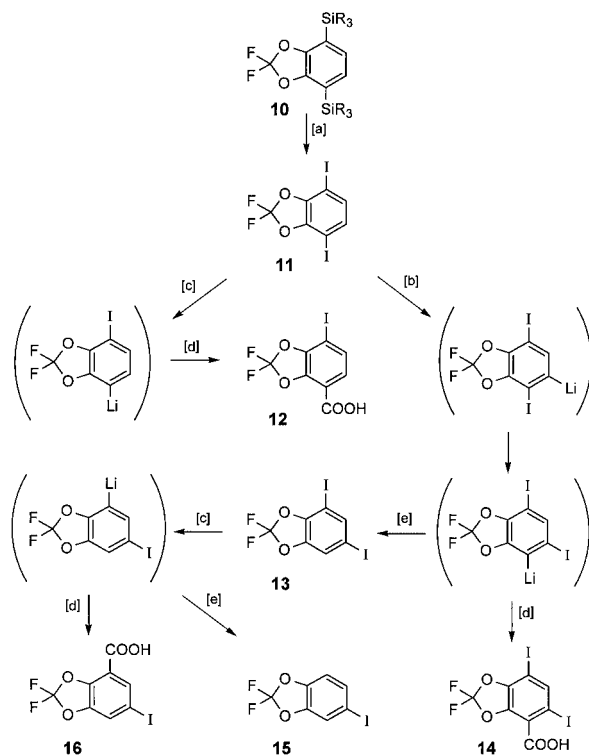


[a] $\text{LiCH}(\text{CH}_3)\text{C}_2\text{H}_5$ in THF at -75°C . [b] Br_2 . [c] ClSiR_3 . [d] Lithium diisopropylamide (LIDA) in THF at -75°C . [e] H_2COH . [f] I_2 in THF. [g] (1) CO_2 , (2) HCl . [h] Tetrabutylammonium fluoride hydrate (TBAF) in tetrahydrofuran at 25°C .



[a] $\text{LiCH}(\text{CH}_3)\text{C}_2\text{H}_5$ or lithium diisopropylamide (LIDA) in tetrahydrofuran (THF) at -75°C . [b] ClSiR_3 .

Iododesilylation of the bis(silanes) **10** produced 2,2-difluoro-4,7-diiodo-1,3-benzodioxole (**11**) in nearly quantitative yields (95 and 94% from **10a** and **10b**, respectively). Monolateral halogen/metal permutation followed by carboxylation gave 2,2-difluoro-7-iodo-1,3-benzodioxane-4-carboxylic acid (**12**; 64%). The same acid **12** was formed in 64% yield when the organolithium precursor was generated by incubating 2,2-difluoro-4-iodo-1,3-benzodioxole^[8] with LIDA in tetrahydrofuran for 2 h at -100°C . LIDA-promoted deprotonation of the diiodo compound **11** triggered a heavy-halogen migration. The isomerized aryllithium species afforded 2,2-difluoro-5,7-diiodo-1,3-benzodioxole-4-carboxylic acid (**14**; 91%) upon carboxylation and 2,2-difluoro-4,6-diiodo-1,3-benzodioxole (**13**; 86%) upon neutralization. When butyllithium was added to the latter compound, the metal replaced the oxygen-adjacent iodine atom exclusively. Subsequent neutralization or carboxylation afforded 2,2-difluoro-5-iodo-1,3-benzodioxole^[7] (**15**; 62%) and 2,2-difluoro-6-iodo-1,3-benzodioxole-4-carboxylic acid (**16**; 72%).



[a] 2.0 eq ICl in tetrachloromethane at reflux. [b] Lithium diisopropylamide (LIDA) in tetrahydrofuran (THF) at -75°C . [c] Butyllithium (LiC) in tetrahydrofuran at -75°C . [d] (1) CO_2 , (2) HCl. [e] H_3COH .

Being unleashed by the proton abstraction from the 5-position, the basicity gradient-driven isomerization of the diiodo compound **11** testifies again the far-reaching acidifying effect of the fluoroalkoxy unit. Iodine atoms hardly ever stabilize electron excess at adjacent *ortho* positions. For example, 1,3-diiodobenzene is inert toward both LIDA and lithium 2,2,6,6-tetramethylpiperide.^[10]

Even if this may sometimes be nothing more than an unwarranted precaution, we often prefer triethylsilyl to trimethylsilyl protective groups. Strong bases are known to be capable of deprotonating the latter, but not the former.^[11–13] Although in the present study the triethyl(2,2-difluoro-1,3-benzodioxolan-4-yl)silane (**4b**) gave excellent yields of the bromo derivative **5b** whatever the base, the trimethyl analog **4a** performed well only toward *sec*-butyllithium, whereas an inextricable mixture of compounds resulted, including protodesilylation products, when LIDA was employed. Moreover, the bulkiness of the triethylsilyl entity appears to facilitate the reaction of the bis(silane) **10b** ($\text{R} = \text{C}_2\text{H}_5$) with iodine monochloride. It is complete after 2 h. In contrast, the same iododesilylation of bisilane **10a** ($\text{R} = \text{CH}_3$) requires 20 h.

Experimental Section

Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.^[14,15] ^1H and (^1H -decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, with the samples having been dissolved in

deuteriochloroform (if not specified otherwise). Mass spectra were obtained at a 70-eV ionization potential while maintaining a source temperature of 200°C . Whenever no molecular peak was observed under such conditions, chemical ionization (“c.i.”) was applied in an ammonia atmosphere at source temperature of 100°C . To avoid redundancy, only the ^{79}Br fragments, and not the ^{81}Br isotopomers, are listed in all cases.

2,2-Difluoro-1,3-benzodioxole and 5-bromo-2,2-difluoro-1,3-benzodioxole are commercially available. The preparation of 4-bromo-2,2-difluoro-1,3-benzodioxole and 2,2-difluoro-4-iodo-1,3-benzodioxole are described in ref.^[8] (spec. on p. 460).

7-Bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic Acid (2): Diisopropylamine (1.4 mL, 1.0 g, 10 mmol) and 4-bromo-2,2-difluoro-1,3-benzodioxole (**1**; 2.4 g, 10 mmol) were added consecutively to butyllithium (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5.0 mL) at -100°C . After 2 h at -100°C the mixture was poured onto an excess of freshly crushed carbon dioxide. Extraction with dichloromethane (20 mL) and, after acidification to pH 1, with diethyl ether (3×10 mL) followed by evaporation and crystallization from pentanes gave colorless prisms; m.p. $208\text{--}210^{\circ}\text{C}$; yield 2.73 g (96%). ^1H NMR: $\delta = 7.64$ (d, $J = 8.8$ Hz, 1 H), 7.34 (d, $J = 8.8$ Hz, 1 H) ppm. ^{13}C NMR: $\delta = 167.8, 144.0, 143.2, 131.3$ (t, $J = 258$ Hz), 127.1, 126.2, 112.2, 107.8 ppm. MS (c.i.): m/z (%) = 298 (35) [$\text{M}^+ + \text{NH}_4$], 280 (100) [M^+], 220 (38), 199 (24), 197 (25). $\text{C}_8\text{H}_3\text{BrF}_2\text{O}_4$ (281.01): calcd. C 34.19, H 1.08; found C 34.26, H 1.10.

5-Bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic Acid (3): 5-Bromo-2,2-difluoro-7-triethylsilyl-1,3-benzodioxole-4-carboxylic acid (**6b**; 3.9 g, 10 mmol) and tetrabutylammonium fluoride trihydrate (TBAF, 3.2 g, 10 mmol) in tetrahydrofuran (20 mL) were kept for 30 min at 25°C . After evaporation of the solvent, the residue was dissolved in water (15 mL), and extracted with diethyl ether (2×10 mL); colorless stars (cryst. from pentanes); m.p. $159\text{--}160^{\circ}\text{C}$ (ref.^[7] m.p. $148\text{--}149^{\circ}\text{C}$); yield 2.52 g (91%). ^1H NMR: $\delta = 7.45$ (d, $J = 8.5$ Hz, 1 H), 7.09 (d, $J = 8.0$ Hz, 1 H) ppm. ^{13}C NMR: $\delta = 167.4, 144.2, 143.4, 131.7$ (t, $J = 258$ Hz), 129.1, 115.4, 115.3, 113.4 ppm. The same compound was formed in a small amount (8%) when piperidine (1.0 mL, 0.85 g, 10 mmol) and 4-bromo-2,2-difluoro-1,3-benzodioxole (**1**; 2.4 g, 10 mmol) were added consecutively to butyllithium (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5.0 mL) at -75°C . The product was identified by gas chromatography [30 m, DB-Wax, 75°C (20 min); 30 m, DB-23, 75°C (20 min)] upon comparison with the authentic compound.

(2,2-Difluoro-1,3-benzodioxol-4-yl)trimethylsilane (4a): *sec*-Butyllithium (0.10 mol) in cyclohexanes (75 mL) and 2,2-difluoro-1,3-benzodioxole (16 g, 0.10 mol) in tetrahydrofuran (0.12 L) were mixed at -75°C . After 2 h in a dry ice/methanol bath, chlorotrimethylsilane (13 mL, 11 g, 0.10 mol) was added. Distillation under reduced pressure afforded the product as a colorless liquid; b.p. $64\text{--}66^{\circ}\text{C}/9$ Torr; $n_D^{20} = 1.4587$; yield 19.3 g (83%). ^1H NMR: $\delta = 7.09$ (dd, $J = 6.7, 2.2$ Hz, 1 H), 7.0 (m, 2 H), 0.34 (s, 9 H) ppm. ^{13}C NMR: $\delta = 148.2, 142.6, 131.3$ (t, $J = 253$ Hz), 128.3, 123.3, 121.8, 110.0, -1.4 (3 C) ppm. MS (c.i.): m/z (%) = 232 (21) [$\text{M}^+ + 2$], 231 (10) [$\text{M}^+ + 1$], 230 (51) [M^+], 215 (27), 149 (100), 130 (21). $\text{C}_{10}\text{H}_{12}\text{F}_2\text{O}_2\text{Si}$ (230.28): calcd. C 52.16, H 5.25; found C 52.25, H 5.38.

(2,2-Difluoro-1,3-benzodioxol-4-yl)triethylsilane (4b): Formed analogously to the procedure above using chlorotriethylsilane (17 mL, 15 g, 0.10 mol); colorless liquid; b.p. $107\text{--}109^{\circ}\text{C}/14$ Torr; $n_D^{20} = 1.4737$; yield 25.3 g (92%). ^1H NMR: $\delta = 7.0$ (m, 3 H), 1.0 (m, 9

H), 0.9 (m, 6 H) ppm. ^{13}C NMR: δ = 148.5, 142.7, 131.2 (t, J = 253 Hz), 129.2, 123.3, 119.2, 110.0, 7.2 (3 C), 3.2 (3 C) ppm. MS (CI): m/z (%) = 273 (19) [$\text{M}^+ + 1$], 272 (57) [M^+], 260 (100), 232 (14). $\text{C}_{13}\text{H}_{18}\text{F}_2\text{O}_4\text{Si}$ (272.36): calcd. C 57.33, H 6.66; found C 57.26, H 6.61.

(7-Bromo-2,2-difluoro-1,3-benzodioxol-4-yl)trimethylsilane (5a): (2,2-Difluoro-1,3-benzodioxol-4-yl)trimethylsilane (**4a**; 11.5 g, 50 mmol) was added to *sec*-butyllithium (50 mmol) in tetrahydrofuran (60 mL) and cyclohexanes (40 mL) kept in a dry ice/methanol bath. After 2 h at -75°C the reaction mixture was treated with bromine (2.6 mL, 8.0 g, 50 mmol). Upon distillation, the product was isolated as a colorless liquid; b.p. $94\text{--}96^\circ\text{C}/7\text{ Torr}$; n_{D}^{20} = 1.4914; yield 12.8 g (83%). ^1H NMR: δ = 7.18 (d, J = 8.2 Hz, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 0.34 (s, 9 H) ppm. ^{13}C NMR: δ = 148.2, 141.2, 130.8 (t, J = 256 Hz), 129.3, 128.0, 126.8, 102.3, -1.5 (3 C) ppm. MS (c.i.): m/z (%) = 308 (34) [M^+], 302 (81), 286 (100), 227 (28). $\text{C}_{10}\text{H}_{11}\text{BrF}_2\text{O}_2\text{Si}$ (309.18): calcd. C 38.85, H 3.59; found C 39.18, H 3.48.

(7-Bromo-2,2-difluoro-1,3-benzodioxol-4-yl)triethylsilane (5b): Prepared analogously using the procedure above, starting from (2,2-difluoro-1,3-benzodioxol-4-yl)triethylsilane (**4b**; 13.6 g, 50 mmol); colorless liquid; b.p. $138\text{--}140^\circ\text{C}/16\text{ Torr}$; n_{D}^{20} = 1.5084; yield 16.6 g (95%). ^1H NMR: δ = 7.19 (d, J = 8.2 Hz, 1 H), 6.96 (d, J = 8.4 Hz, 1 H), 1.0 (m, 9 H), 0.9 (m, 6 H) ppm. ^{13}C NMR: δ = 148.5, 141.3, 130.7 (t, J = 256 Hz), 130.1, 126.9, 118.0, 102.3, 7.2 (3 C), 3.1 (3 C) ppm. MS (c.i.): m/z (%) = 350 (10) [M^+], 341 (56), 338 (55), 250 (27). $\text{C}_{13}\text{H}_{17}\text{BrF}_2\text{O}_2\text{Si}$ (351.26): calcd. C 44.45, H 4.88; found C 44.93, H 4.84.

5-Bromo-2,2-difluoro-7-trimethylsilyl-1,3-benzodioxole-4-carboxylic Acid (6a): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and (7-bromo-2,2-difluoro-1,3-benzodioxol-4-yl)trimethylsilane (**5a**; 7.7 g, 25 mmol) were added consecutively to butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (13 mL). After 2 h at -75°C , the mixture was poured onto an excess of freshly crushed carbon dioxide. Extraction with dichloromethane (50 mL) and, after acidification to pH 1, with diethyl ether ($3 \times 30\text{ mL}$) followed by evaporation and crystallization from hexanes gave colorless needles; m.p. $134\text{--}135^\circ\text{C}$; yield 7.21 g (82%). ^1H NMR: δ = 7.39 (s, 1 H), 0.37 (s, 9 H) ppm. ^{13}C NMR: δ = 167.5, 147.6, 142.8, 133.4, 131.4 (t, J = 253 Hz), 127.9, 115.3, 115.1, -1.7 (3 C) ppm. MS (c.i.): m/z (%) = 370 (31) [$\text{M}^+ + \text{NH}_4$], 352 (100) [M^+], 337 (67), 271 (58). $\text{C}_{11}\text{H}_{11}\text{BrF}_2\text{O}_4\text{Si}$ (353.19): calcd. C 37.41, H 3.14; found C 37.65, H 2.82.

5-Bromo-2,2-difluoro-7-triethylsilyl-1,3-benzodioxole-4-carboxylic Acid (6b): Prepared analogously using the procedure above, starting from (7-bromo-2,2-difluoro-1,3-benzodioxol-4-yl)triethylsilane (**5b**; 8.8 g, 25 mmol); colorless prisms (from pentanes); m.p. $142\text{--}144^\circ\text{C}$; yield 8.12 g (82%). ^1H NMR: δ = 7.37 (s, 1 H), 1.0 (m, 9 H), 0.9 (m, 6 H) ppm. ^{13}C NMR: δ = 167.4, 147.8, 142.8, 134.1, 131.3 (t, J = 258 Hz), 125.7, 115.3, 115.1, 7.1 (3 C), 2.9 (3 C) ppm. $\text{C}_{14}\text{H}_{17}\text{BrF}_2\text{O}_4\text{Si}$ (395.27): calcd. C 42.54, H 4.33; found C 42.83, H 4.19.

(6-Bromo-2,2-difluoro-1,3-benzodioxol-4-yl)trimethylsilane (7a): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and (7-bromo-2,2-difluoro-1,3-benzodioxol-4-yl)trimethylsilane (**5a**; 7.7 g, 25 mmol) were added consecutively to butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (13 mL). After 2 h at -75°C , the mixture was treated with methanol (5.0 mL). Direct distillation gave a colorless liquid; b.p. $86\text{--}88^\circ\text{C}/7\text{ Torr}$; n_{D}^{20} = 1.4916; yield 6.62 g (86%). ^1H NMR: δ = 7.18 (symm. m, presumably $2 \times \text{d}$, J = 2.0 Hz, 2 H), 0.34 (s, 9 H) ppm. ^{13}C NMR: δ = 147.2, 143.2, 131.4 (t, J =

256 Hz), 130.8, 128.0, 115.7, 113.5, -1.5 (3 C) ppm. MS (c.i.): m/z (%) = 308 (27) [M^+], 293 (26), 227 (100), 107 (40). $\text{C}_{10}\text{H}_{11}\text{BrF}_2\text{O}_2\text{Si}$ (309.18): calcd. C 38.85, H 3.59; found C 38.77, H 3.35.

(6-Bromo-2,2-difluoro-1,3-benzodioxol-4-yl)triethylsilane (7b): Prepared analogously using the procedure above, starting from (7-bromo-2,2-difluoro-1,3-benzodioxol-4-yl)triethylsilane (**5b**; 8.8 g, 25 mmol); colorless liquid; b.p. $135\text{--}137^\circ\text{C}/11\text{ Torr}$; n_{D}^{20} = 1.5002; yield 7.48 g (85%). ^1H NMR: δ = 7.18 (symm. m, presumably $2 \times \text{d}$, J = 1.8 Hz, 2 H), 1.0 (m, 9 H), 0.9 (m, 6 H) ppm. ^{13}C NMR: δ = 147.5, 143.2, 131.5, 131.3 (t, J = 255 Hz), 121.6, 115.8, 113.5, 7.1 (3 C), 3.1 (3 C) ppm. MS (c.i.): m/z (%) = 350 (55) [M^+], 321 (100), 293 (36), 227 (46), 199 (62). $\text{C}_{13}\text{H}_{17}\text{BrF}_2\text{O}_2\text{Si}$ (351.26): calcd. C 44.45, H 4.88; found C 44.96, H 4.73.

5-Bromo-2,2-difluoro-1,3-benzodioxole (8): (6-Bromo-2,2-difluoro-1,3-benzodioxol-4-yl)triethylsilane (**7b**; 3.5 g, 10 mmol) and TBAF (3.2 g, 10 mmol) in tetrahydrofuran (20 mL) were kept for 30 min at 25°C . After evaporation of the solvent, the residue was dissolved in water (15 mL), and extracted with diethyl ether ($2 \times 10\text{ mL}$). Upon distillation under reduced pressure, a colorless liquid was collected; b.p. $58\text{--}60^\circ\text{C}/10\text{ Torr}$; n_{D}^{20} = 1.4718 (ref.^[16] b.p. $78\text{--}79^\circ\text{C}/20\text{ Torr}$; n_{D}^{20} = 1.4722); yield 1.86 g (79%).

(6-Bromo-2,2-difluoro-7-iodo-1,3-benzodioxol-4-yl)triethylsilane (9b): Diisopropylamine (9.1 mL, 6.6 g, 65 mmol) and (6-bromo-2,2-difluoro-1,3-benzodioxol-4-yl)triethylsilane (**5b**; 23 g, 65 mmol) were added consecutively to a solution of butyllithium (65 mmol) in tetrahydrofuran (0.12 L) and hexanes (45 mL) kept in a dry ice/methanol bath. After 2 h at -75°C , a solution of iodine (16 g, 65 mmol) in tetrahydrofuran (40 mL) was added. The solvents were evaporated and the residue was dissolved in diethyl ether (0.10 L). After washing with 10% aqueous sodium thiosulfate (50 mL), the organic layer was dried before being evaporated to dryness. Colorless cubes were obtained upon crystallization from methanol; m.p. $34\text{--}35.5^\circ\text{C}$; yield 22.6 g (73%). ^1H NMR: δ = 7.35 (s, 1 H), 1.0 (m, 9 H), 0.9 (m, 6 H) ppm. ^{13}C NMR: δ = 146.0, 145.3, 131.9, 130.3 (t, J = 257 Hz), 123.7, 121.1, 80.6, 7.1 (3 C), 2.9 (3 C) ppm. $\text{C}_{13}\text{H}_{16}\text{BrF}_2\text{IO}_2\text{Si}$ (477.16): calcd. C 32.72, H 3.38; found C 32.84, H 3.41.

2,2-Difluoro-4,7-bis(trimethylsilyl)-1,3-benzodioxole (10a): Diisopropylamine (14 mL, 10 g, 0.10 mol), 2,2-difluoro-1,3-benzodioxole (7.9 g, 50 mmol), and chlorotrimethylsilane (13 mL, 11 g, 0.10 mol) were added consecutively to butyllithium (100 mmol) in hexanes (50 mL) and tetrahydrofuran (50 mL). After 2 h at -75°C , direct distillation under reduced pressure gave a colorless liquid that slowly crystallized upon standing; m.p. $35\text{--}36^\circ\text{C}$; b.p. $89\text{--}91^\circ\text{C}/10\text{ Torr}$; yield 12.8 g (85%). ^1H NMR: δ = 7.07 (s, 2 H), 0.33 (s, 18 H) ppm. ^{13}C NMR: δ = 147.1 (2 C), 131.0 (t, J = 253 Hz), 127.9 (2 C), 122.2 (2 C), -1.4 (6 C) ppm. MS (c.i.): m/z (%) = 303 (37) [$\text{M}^+ + 1$], 302 (100) [M^+], 301 (56) [$\text{M}^+ - 1$], 287 (54), 221 (35), 193 (66). $\text{C}_{13}\text{H}_{20}\text{F}_2\text{O}_2\text{Si}_2$ (302.46): calcd. C 51.62, H 6.66; found C 51.65, H 6.79.

2,2-Difluoro-4,7-bis(triethylsilyl)-1,3-benzodioxole (10b): Prepared analogously using the procedure described above, using chlorotriethylsilane (17 mL, 15 g, 0.10 mol); colorless liquid; b.p. $165\text{--}167^\circ\text{C}/9\text{ Torr}$; n_{D}^{20} = 1.4865; yield 16.0 g (83%). ^1H NMR: δ = 7.05 (s, 2 H), 1.0 (m, 18 H), 0.9 (m, 12 H) ppm. ^{13}C NMR: δ = 147.4 (2 C), 130.9 (t, J = 253 Hz), 128.8 (2 C), 119.6 (2 C), 7.3 (6 C), 3.2 (6 C) ppm. MS (c.i.): m/z (%) = 387 (25) [$\text{M}^+ + 1$], 386 (64) [M^+], 357 (100), 235 (38), 207 (58). $\text{C}_{19}\text{H}_{32}\text{F}_2\text{O}_2\text{Si}_2$ (386.62): calcd. C 59.02, H 8.34; found C 58.54, H 8.38.

2,2-Difluoro-4,7-diiodo-1,3-benzodioxole (11): A mixture of 2,2-difluoro-4,7-bis(trimethylsilyl)-1,3-benzodioxole (**10a**; 15 g, 50 mmol) and iodine monochloride (5.0 mL, 16 g, 0.10 mol) in tetrachloromethane (50 mL) was heated under reflux for 20 h. After washing with sodium thiosulfate solution (2 × 20 mL), the organic phase was dried and the solvents evaporated; colorless needles (from pentanes); m.p. 110–111 °C; yield 19.3 g (95%). ¹H NMR: δ = 7.15 (s, 2 H) ppm. ¹³C NMR: δ = 144.7 (2 C), 133.6 (2 C), 129.3 (t, *J* = 258 Hz), 70.8 (2 C) ppm. MS (c.i.): *m/z* (%) = 411 (8) [*M*⁺ + 1], 410 (100) [*M*⁺], 409 (90) [*M*⁺ − 1], 344 (5), 189 (10). C₇H₂F₂I₂O₂ (409.90): calcd. C 20.51, H 0.49; found C 20.49, H 0.59. The same product was obtained in 94% yield (18.9 g) after heating 2,2-difluoro-4,7-bis(triethylsilyl)-1,3-benzodioxole (**10b**; 19 g, 50 mmol) and iodine monochloride (5.0 mL, 16 g, 0.10 mol) in tetrachloromethane (50 mL) for 1 h under reflux.

2,2-Difluoro-7-iodo-1,3-benzodioxole-4-carboxylic Acid (12): 2,2-Difluoro-4,7-diiodo-1,3-benzodioxole (4.1 g, 10 mmol) was added to butyllithium (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5.0 mL) at −75 °C. Immediately afterwards, the reaction mixture was poured onto an excess of freshly crushed carbon dioxide. Extraction with dichloromethane (25 mL) and, after acidification of the aqueous phase to pH 1, with diethyl ether (3 × 15 mL), followed by evaporation and crystallization from chloroform, gave colorless needles; m.p. 201–202 °C; yield 2.52 g (77%). ¹H NMR (CD₃COCD₃): δ = 7.69 (d, *J* = 8.6 Hz, 1 H), 7.53 (d, *J* = 8.6 Hz, 1 H) ppm. ¹³C NMR (CD₃COCD₃): δ = 164.4, 148.2, 143.6, 134.4, 132.5 (t, *J* = 256 Hz), 128.4, 116.4, 78.6 ppm. MS (c.i.): *m/z* (%) = 329 (53) [*M*⁺ + 1], 328 (100) [*M*⁺], 311 (11), 262 (35), 245 (24), 79 (16). C₈H₃F₂IO₄ (328.01) calcd. C 29.29, H 0.92; found C 29.49, H 0.98. Acid **12** (2.10 g, 64%) was also obtained when 2,2-difluoro-4-iodo-1,3-benzodioxole^[8] (2.8 g, 10 mmol) was treated consecutively with lithium diisopropylamide (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5.0 mL), for 2 h at −100 °C, and dry ice.

2,2-Difluoro-4,6-diiodo-1,3-benzodioxole (13): Diisopropylamine (1.4 mL, 1.0 g, 10 mmol) and 2,2-difluoro-4,7-diiodo-1,3-benzodioxole (**11**; 4.0 g, 10 mmol) were added consecutively to butyllithium (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5.1 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, methanol (5.0 mL, 0.10 mol) was injected. Upon steam distillation, a yellow liquid was collected that crystallized from pentanes; colorless prisms; m.p. 51–52 °C; yield 3.44 g (86%). ¹H NMR: δ = 7.74 (d, *J* = 1.5 Hz, 1 H), 7.34 (d, *J* = 1.5 Hz, 1 H) ppm. ¹³C NMR: δ = 146.0, 142.8, 140.0, 130.2 (t, *J* = 258 Hz), 118.4, 85.4, 72.2 ppm. MS (c.i.): *m/z* (%) = 411 (8) [*M*⁺ + 1], 410 (87) [*M*⁺], 206 (25), 189 (100), 188 (43). C₇H₂F₂I₂O₂ (409.90): calcd. C 20.51, H 0.49; found C 20.18, H 0.64.

2,2-Difluoro-5,7-diiodo-1,3-benzodioxole-4-carboxylic Acid (14): The reaction mixture obtained by consecutive addition of diisopropylamine (3.2 mL, 2.5 g, 25 mmol) and 2,2-difluoro-4,7-diiodo-1,3-benzodioxole (**11**; 10 g, 25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) was poured, after 2 h at −75 °C, onto an excess of freshly crushed dry ice. After evaporation of the volatiles, the residue was treated with 2.0 M hydrochloric acid (20 mL) and the solid material collected by filtration. Crystallization from chloroform gave colorless prisms; m.p. 224–226 °C; yield 10.0 g (91%). ¹H NMR: δ = 8.18 (s, 1 H) ppm. ¹³C NMR: δ = 163.7, 147.3, 143.8, 141.2, 131.2 (t, *J* = 258 Hz), 121.6, 87.0, 76.4 ppm. MS (c.i.): *m/z* (%) = 455 (15) [*M*⁺ + 1], 454 (100) [*M*⁺], 453 (86) [*M*⁺ − 1], 371 (11), 77 (13). C₈H₂F₂I₂O₄ (453.90): calcd. C 21.17, H 0.44; found C 21.23, H 0.97.

2,2-Difluoro-5-iodo-1,3-benzodioxole (15): 2,2-Difluoro-4,6-diiodo-1,3-benzodioxole (**13**; 4.0 g, 10 mmol) was added to butyllithium (10 mmol) in hexanes (5.1 mL) and tetrahydrofuran (15 mL) at −75 °C. After 45 min at −75 °C, methanol (5.0 mL, 0.12 mol) was injected. Distillation under reduced pressure afforded a colorless liquid; b.p. 70–71 °C/6 Torr; *n*_D²⁰ = 1.5416; yield 1.72 g (62%). ¹H NMR: δ = 7.42 (dd, *J* = 8.3, 1.6 Hz, 1 H), 7.40 (d, *J* = 1.6 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 1 H) ppm. ¹³C NMR: δ = 144.3, 143.7, 132.6, 131.3 (t, *J* = 258 Hz), 118.6, 111.3, 84.6 ppm. MS (c.i.): *m/z* (%) = 285 (14) [*M*⁺ + 1], 284 (100) [*M*⁺], 218 (15), 158 (7). C₇H₃F₂IO₂ (284.00): calcd. C 29.60, H 1.06; found C 29.71, H 1.14.

2,2-Difluoro-6-iodo-1,3-benzodioxole-4-carboxylic Acid (16): 2,2-Difluoro-4,6-diiodo-1,3-benzodioxole (**13**; 4.0 g, 10 mmol) was added to butyllithium (10 mmol) in tetrahydrofuran (15 mL) and hexanes (5.0 mL) at −75 °C. After 45 min at −75 °C, the reaction mixture was poured onto an excess of freshly crushed carbon dioxide. Extraction with dichloromethane (20 mL) and, after acidification of the aqueous phase to pH 1, with diethyl ether (3 × 10 mL), followed by evaporation and crystallization from chloroform, gave colorless prisms; m.p. 167–168 °C; yield 2.36 g (72%). ¹H NMR (CD₃COCD₃): δ = 7.85 (d, *J* = 8.5 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 1 H) ppm. ¹³C NMR (CD₃COCD₃): δ = 164.8, 145.6, 143.5, 137.6, 133.1 (t, *J* = 255 Hz), 124.2, 115.0, 86.5 ppm. MS (c.i.): *m/z* (%) = 329 (47) [*M*⁺ + 1], 328 (100) [*M*⁺], 245 (11). C₈H₃F₂IO₄ (328.01): calcd. C 29.29, H 0.92; found C 29.13, H 0.99.

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