Exploring Structural Opportunities: The Regioflexible Substitution of 1,3-Difluorobenzene

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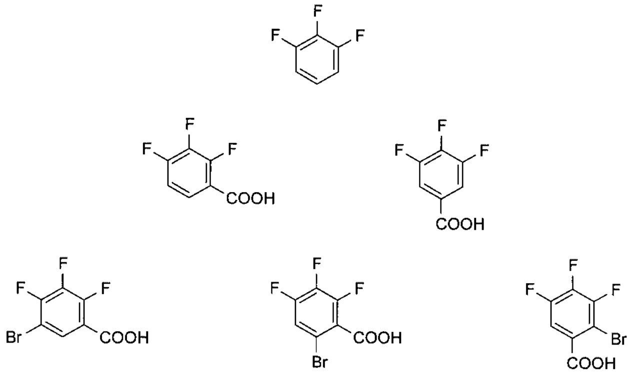
To demonstrate the superiority of modern organometallic methods, the inexpensive starting material 1,3-difluorobenzene has been selectively converted into the three benzoic acids and all seven bromobenzoic acids containing the two fluorine atoms in homovicinal positions. The 2,6-difluorobenzoic acid (**1**) was prepared in a one-pot reaction consisting of direct metallation and carboxylation. The key step on the route to the bromobenzoic acid **4** was a deprotonation-triggered bromine migration from the 2- to the 4-position. All other products were attained through (2,6-difluorophenyl)triethylsilane (**11**). Consecutive deprotonation of the sites adjacent to the fluorine atoms, followed by appropriate electrophilic substitution, provided not only the acid **7** but also the dibromo and iodobromo derivatives **13** and **23**. These in turn gave the isomers **14** and **24** upon base-mediated migration of the heaviest halogen, which made the acids **8** and **10** directly accessible. The regiocontrolled monodebromination of intermediate **14** afforded (4-bromo-2,6-difluoro)triethylsilane (**15**), which opened the route to the acids **3** and **5** (by carboxylation and protodesilylation) and to acid **9** (by carboxylation and bromodesilylation).

Introduction

In a recent publication[1] we have shown how 1,2,3-trifluorobenzene can be converted into the two corresponding trifluorobenzoic acids and the three corresponding bromotrifluorobenzoic acids. All reactions were straightforward and expeditious. The precursors to the acids having invariably been lithium species, any functional entity besides the carboxy group could have been introduced into the aromatic nucleus in the same way.

1,3-Difluorobenzene, a particularly inexpensive starting material (approx. 30 Euro/mol retail price), can give rise to a great variety of derivatives. This time, three benzoic acids and seven bromobenzoic acids containing two fluorine atoms in homovicinal positions were targeted. The bromo compounds may be used as components in Suzuki coupling reactions.[1]

Starting from 1,3-difluorobenzene, we have made all these ten compounds, most of them yet unknown. To secure the required regioflexibility, we again relied on the same toolbox of organometallic methods that had already proven successful in previous model studies.[1–3] Besides the familiar direct hydrogen/metal and halogen/metal permutations,[4] modern modifications were applied individually or in any suitable combination:



- metallation of the next reactive site after blocking of the most acidic position by the introduction of bromine,
- metallation of the next reactive site after protection of the most acidic position with a trialkylsilyl group (to be removed later by hydrolysis or halogenolysis),
- deprotonation-triggered and basicity gradient-driven halogen migration,
- element-specific halogen/metal permutation, an iodobromoarene being the substrate, and
- site-specific halogen/metal permutation, a dibromoarene being the substrate.

The chart below offers a survey of all the reactions carried out in the course of this investigation. Details of preparation are described thereafter.

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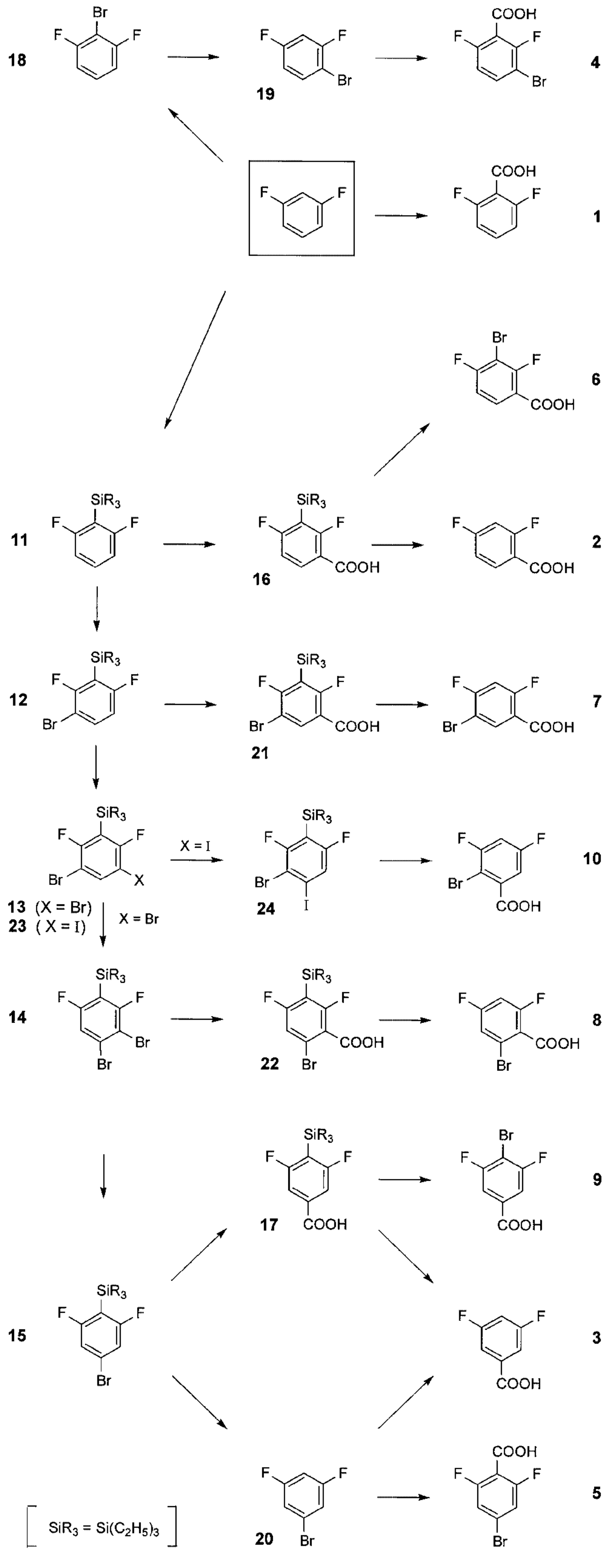
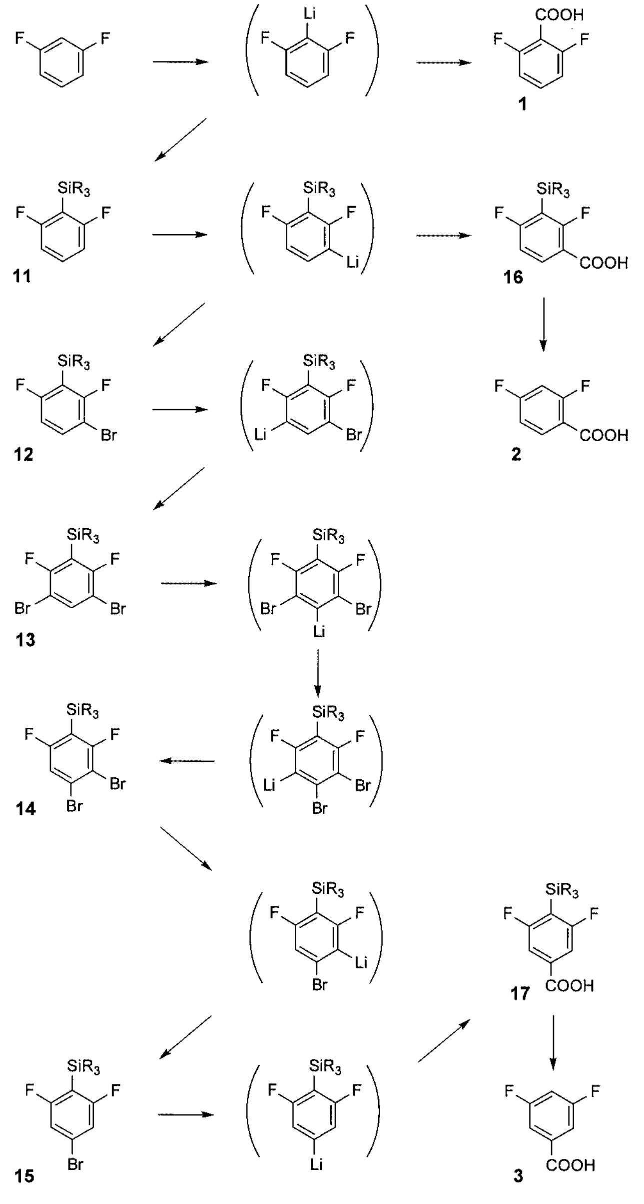
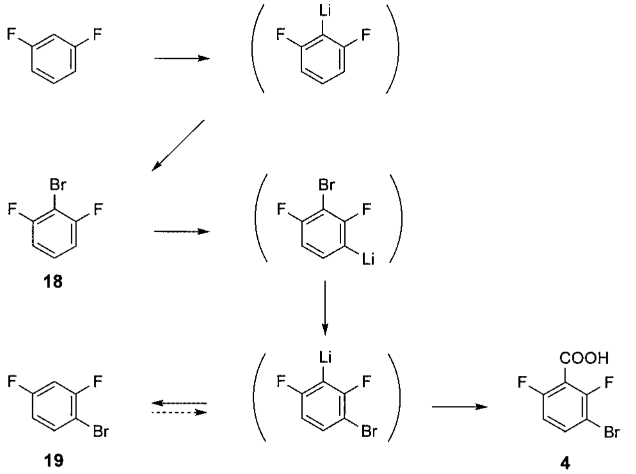
2,6-Difluorobenzoic acid (**1**; 90% after crystallization) was obtained after lithiation (with butyllithium in tetrahydrofuran at −75 °C for 45 min), carboxylation (dry ice), and neutralization in almost quantitative yield.[5] If the organolithium intermediate was instead intercepted with chlorotriethylsilane, (2,6-difluorophenyl)triethylsilane (**11**; 89%) was formed, again in high yield. Consecutive treatment of this compound with *sec*-butyllithium and carbon dioxide gave the acid **16** (89%), which was desilylated with potassium hydroxide in ethanol to afford the 2,4-difluorobenzoic acid (**2**; 98%). Alternatively, the silane **11** was subjected to a sequence of lithiation and bromination and thus converted into the bromo derivative **12** (92%). When this compound was deprotonated with lithium diisopropylamide (LIDA) and halogenated with 1,2-dibromotetrafluoroethane, the dibromo compound **13** (82%) was obtained first. LIDA-promoted heavy halogen migration[3] produced the vicinal dibromo isomer **14** (86%; though still contaminated with small amounts of its precursor **13**). Butyllithium selectively attacked the doubly activated bromine flanked by the other bromine and one of the fluorine atoms. Quenching of the resulting organolithium species with methanol afforded



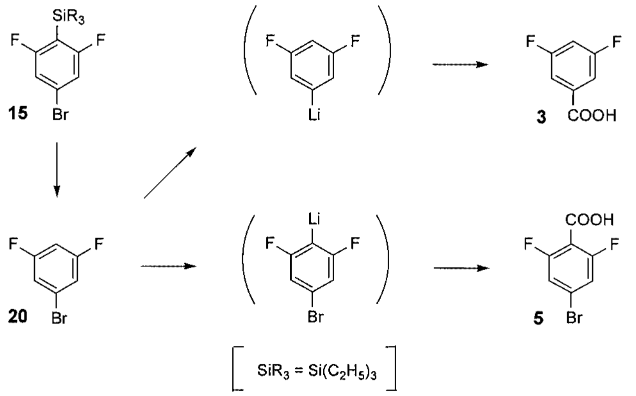


the 4-bromo-2,6-difluorosilane **15** (59%), which upon consecutive halogen/metal permutation and carboxylation gave the silylated acid **17** (93%) and, after treatment of the latter with potassium hydroxide, the 3,5-difluorobenzoic acid (**3**; 97%).

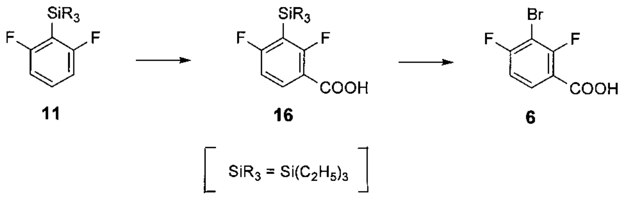
Another basicity gradient-driven halogen migration made the first of the five bromodifluorobenzoic acids accessible. 2-Bromo-1,3-difluorobenzene (**18**; 94%), prepared from 1,3-difluorobenzene by consecutive treatment with butyllithium and bromine, underwent a 1,3-bromine shift when treated with LIDA. However, the oil collected upon distillation after neutralization consisted of a 3:2 ratio of the expected product **19** (35% crude) and starting material **18** (23%). The latter isomer was selectively destroyed by treatment with the stoichiometrically required amount of butyllithium, followed by carboxylation and distillation (without prior neutralization). The pure 1-bromo-2,4-difluorobenzene (**19**; 20% overall) was eventually converted into the 3-bromo-2,6-difluorobenzoic acid (**4**) by deprotonation with lithium 2,2,6,6-tetramethylpiperidide (LITMP), followed by carboxylation.



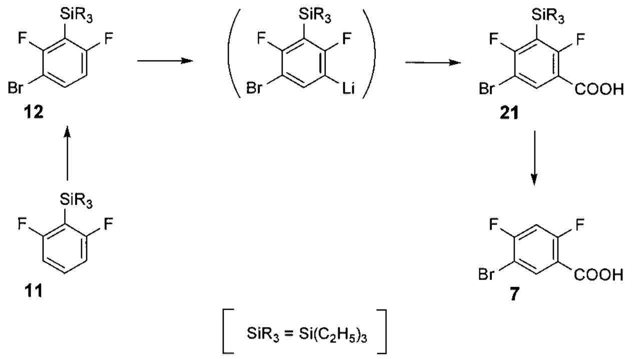
Fluoride-mediated protodesilylation of silane **15** afforded 1-bromo-3,5-difluorobenzene (**20**; 93%), which opened an alternative route to the 3,5-difluorobenzoic acid (**3**; 91%) by consecutive reaction with butyllithium and dry ice. If LITMP was employed as the base instead, the 4-bromo-2,6-difluorobenzoic acid[6] (**5**; 96%) was formed upon carboxylation.



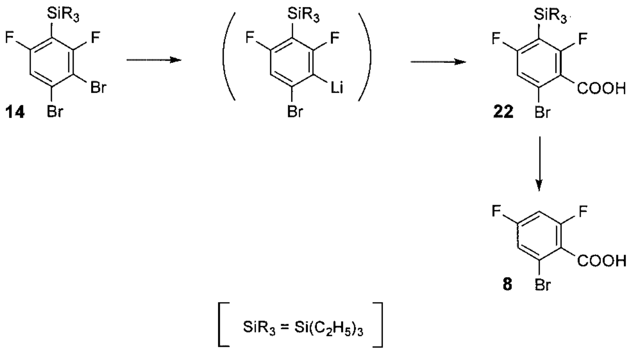
The route to the 3-bromo-2,4-difluorobenzoic acid (**6**; 84%) passed through the silylated acid **16** (see above). The heavy halogen substituent was introduced by the powerful and versatile method of bromodesilylation.



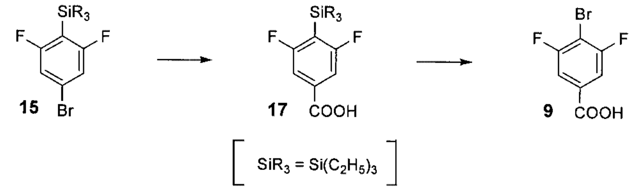
Protodesilylation was the last step in a reaction sequence providing the 5-bromo-2,4-difluorobenzoic acid (**7**; 95%). The preceding silylated acid **21** (70%) was obtained by treatment of the bromodifluorosilane **12** consecutively with LIDA and carbon dioxide.



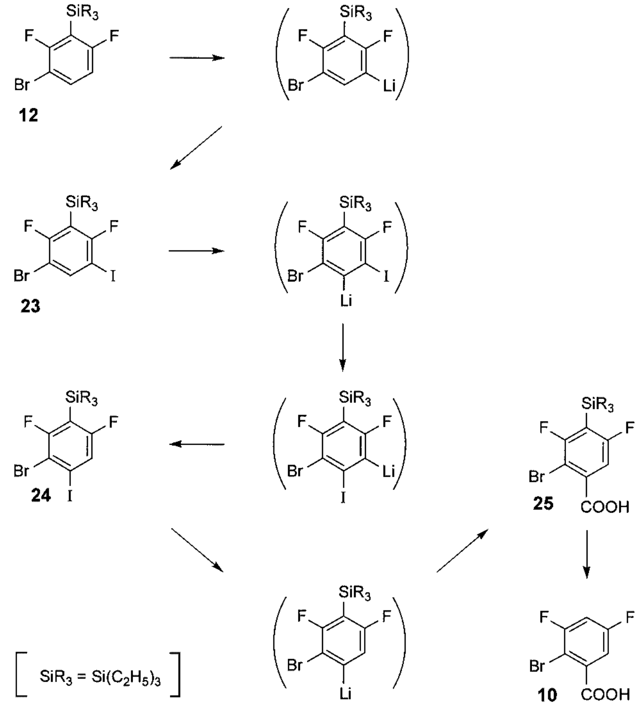
Analogously, the 2-bromo-4,6-difluorobenzoic acid (**8**; 94%) was produced from the silylated derivative **22** by protodesilylation. The latter intermediate was prepared from the *vic*-dibromodifluorosilane **14** by site-selective halogen/metal permutation followed by carboxylation, in 98% yield.



Bromodesilylation offered the most convenient access to 4-bromo-3,5-difluorobenzoic acid (**9**; 87%). The key intermediate was the already described (see above) silylated difluorobenzoic acid **17**.



The last bromodifluorobenzoic acid proved to be a challenge. Firstly, iodine had to be introduced into the 5-position of silane **12**, and the resulting intermediate **23** (86%) then had to be isomerized to the silane **24** (57%) by LIDA-triggered migration of the iodine (rather than the bromine) atom. Next, the iodine had to be replaced by lithium under carefully controlled conditions in order to prevent the competitive exchange of the doubly activated bromine atom next to the fluorine. The remaining steps were trivial. The organolithium species was carboxylated and the benzoic acid **25** (91%) was isolated and subsequently protodesilylated to afford the 2-bromo-3,5-difluorobenzoic acid **10** (97%).



It may not be immediately obvious why we have preferred to use the tri*ethyl*silyl rather than the more common tri*methyl*silyl substituent as a protective group. Although it is difficult to predict when such side reactions will really occur, (trimethylsilyl)alkenes[7] and (trimethylsilyl)arenes[8] are known to be readily metallated at the silicon-bound methyl groups. Therefore, it was merely an act of precaution to avoid such complications through the use of triethylsilyl homologues.

Experimental Section

Generalities: See related publications from this laboratory[1,9−10] for working routine and abbreviations. ^{1}H and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, of samples dissolved in deuteriochloroform. Stationary phases in gas chromatographic columns are coded as OV-17 (silicon rubber) and FFAP or C-20M (both of the polyethylene glycol type).

1. Difluorobenzoic and Bromodifluorobenzoic Acids

2,6-Difluorobenzoic Acid (1): A solution of 1,3-difluorobenzene (2.3 mL, 2.9 g, 25 mmol) and butyllithium (25 mmol) in hexanes (16 mL) and tetrahydrofuran (35 mL) was kept at −75 °C for 45 min before being poured on an excess of freshly crushed dry ice. The mixture was acidified with an ethereal solution (15 mL) of hydrogen chloride (30 mmol). The volatile components were evaporated, and the residue was extracted with boiling ethyl acetate (3 × 15 mL). Upon filtration and concentration of the combined organic layers, the product crystallized as tiny, colorless needles; m.p. 158−160 °C (from hexanes; ref.[11] m.p. 161−162 °C); yield: 3.55 g (90%). ^{1}H NMR: $\delta = 7.51$ (ddd, $J = 8.1, 6.5, 2.2$ Hz, 1 H), 7.03 (t, $J = 8.5$ Hz, 2 H) ppm.

2,4-Difluorobenzoic Acid (2): 2,4-Difluoro-3-(triethylsilyl)benzoic acid (**16**; 6.8 g, 25 mmol) in a 4:1 (v/v) mixture of ethanol and water (25 mL) and potassium hydroxide (2.5 g) were heated under reflux for 2 h. The solvents were evaporated and the residue acidified with aqueous hydrochloric acid (1.0 M, 10 mL). The acid was extracted with diethyl ether (3 × 20 mL). Crystallization from hexanes (20 mL) gave colorless needles; m.p. 186−189 °C (ref.[12] m.p. 182−184 °C); yield: 3.84 g (98%). ^{1}H NMR: $\delta = 8.08$ (td, $J = 8.5, 6.5$ Hz, 1 H), 6.99 (symm. m, 1 H), 6.93 (ddd, $J = 11.1, 8.6, 2.5$ Hz, 1 H) ppm.

3,5-Difluorobenzoic Acid (3): 3,5-Difluoro-4-(triethylsilyl)benzoic acid (**17**; 3.4 g, 15 mmol) was treated in the same way as described in the preceding paragraph; colorless needles; m.p. 120−122 °C (from chloroform; ref.[13] m.p. 120−122 °C); yield: 2.30 g (97%). ^{1}H NMR: $\delta = 7.63$ (symm. m, 2 H), 7.09 (tt, $J = 8.5, 2.5$ Hz, 1 H) ppm. When 1-bromo-3,5-difluorobenzene was added at −75 °C to a solution of butyllithium (15 mmol) in hexanes (10 mL) and diethyl ether (20 mL), the mixture being quenched after 15 min by carboxylation and worked up as described for acid **2**, the acid **3** was obtained in a 91% yield.

3-Bromo-2,6-difluorobenzoic Acid (4): 2,2,6,6-Tetramethylpiperidine (2.5 mL, 2.1 g, 15 mmol) and 1-bromo-2,4-difluorobenzene (**19**; 2.9 g, 15 mmol) were added consecutively at −75 °C to a solution of butyllithium (15 mmol) in hexanes (9.5 mL) and tetrahydrofuran (20 mL). After 2 h, freshly crushed dry ice was added. The reaction mixture was worked up as described for the acid **1**; colorless needles; m.p. 137−139 °C (from hexanes; ref.[14,15] m.p. 140−141 °C); yield: 3.26 g (92%). ^{1}H NMR: $\delta = 7.70$ (ddd, $J = 9.0, 7.4, 5.5$ Hz, 1 H), 6.95 (td, $J = 9.0, 1.6$ Hz, 1 H) ppm.

4-Bromo-2,6-difluorobenzoic Acid (5): 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and 1-bromo-3,5-difluorobenzene (4.8 g, 25 mmol) were added to a solution of butyllithium (25 mmol) in hexanes (16 mL) and tetrahydrofuran (35 mL) kept at −75 °C. After 2 h, freshly crushed dry ice was added and the reaction mixture was worked up as described above; colorless needles; m.p. 196−198 °C (from hexanes; ref.[6] m.p. 195−197 °C); yield: 5.67 g (96%). ^{1}H NMR: $\delta = 7.21$ (d, $J = 8.3$ Hz, 2 H) ppm.

3-Bromo-2,4-difluorobenzoic Acid (6): 2,4-Difluoro-3-(triethylsilyl)benzoic acid (**16**; 6.8 g, 25 mmol) in carbon tetrachloride (25 mL) and bromine (2.6 mL, 8.0 g, 50 mmol) were heated under reflux for 12 h. Evaporation of the solvent and the bromine gave the acid **6**; colorless needles; m.p. 132−134 °C (from hexanes); yield: 4.98 g

(84%). ^{1}H NMR: δ = 8.05 (ddd, J = 9.0, 7.9, 6.2 Hz, 1 H), 7.06 (ddd, J = 9.0, 7.2, 1.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 163.0 (s), 162.4 (dd, J = 255, 4 Hz), 159.7 (dd, J = 263, 5 Hz), 132.7 (d, J = 11 Hz), 116.7 (d, J = 12 Hz), 112.3 (dd, J = 21, 3 Hz), 99.0 (t, J = 25 Hz) ppm. $C_7H_3BrF_2O_2$ (237.00): calcd. C 35.48, H 1.28; found C 35.49, H 1.31.

3-Bromo-4,6-difluorobenzoic Acid (7): 3-Bromo-4,6-difluoro-5-(triethylsilyl)benzoic acid (**21**; 8.8 g, 25 mmol) in a mixture of ethanol and water (4:1 v/v, 50 mL) and potassium hydroxide (2.8 g, 50 mmol) were heated at reflux for 2 h. The reaction mixture was worked up as described for acid **2**; colorless needles; m.p. 148−150 °C; yield: 5.59 g (95%). ^{1}H NMR: δ = 8.31 (t, J = 8.0 Hz, 1 H), 7.03 (dd, J = 10.1, 8.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.2 (s), 163.4 (dd, J = 261, 11 Hz), 163.2 (dd, J = 255, 12 Hz), 138.2 (s), 118.6 (dd, J = 11, 3 Hz), 108.2 (t, J = 28 Hz), 105.1 (dd, J = 20, 4 Hz) ppm. $C_7H_3BrF_2O_2$ (237.00): calcd. C 35.48, H 1.28; found C 35.46, H 1.33.

2-Bromo-4,6-difluorobenzoic Acid (8): 2-Bromo-4,6-difluoro-5-(triethylsilyl)benzoic acid (**22**; 8.8 g, 25 mmol) was protodesilylated in the same way as described in the preceding paragraph; colorless needles; m.p. 91−93 °C (from pentanes); yield: 5.56 g (94%). ^{1}H NMR: δ = 7.24 (dm, J = 7.9 Hz, 1 H), 6.91 (symm. m, J = 8.5, 2.1 Hz) ppm. ^{13}C NMR: δ = 168.2 (s), 163.5 (dd, J = 258, 12 Hz), 160.8 (dd, J = 259, 13 Hz), 121.7 (dd, J = 12, 3 Hz), 119.5 (dd, J = 18, 2 Hz), 117.2 (dd, J = 25, 3 Hz), 104.2 (t, J = 25 Hz) ppm. $C_7H_3BrF_2O_2$ (237.00): calcd. C 35.48, H 1.28; found C 35.66, H 1.07.

4-Bromo-3,5-difluorobenzoic Acid (9): 3,5-Difluoro-4-(triethylsilyl)benzoic acid (**17**; 4.1 g, 15 mmol) was treated with elemental bromine (3.1 mL, 9.6 g, 60 mmol) in carbon tetrachloride (15 mL) at reflux for 12 h. Upon evaporation, the acid **9** was left behind; colorless needles; m.p. 177−178 °C (from hexanes); yield: 2.50 g (87%). ^{1}H NMR: δ = 7.70 (d, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR: δ = 165.7 (s), 161.3 (d, J = 247 Hz), 134.2 (t, J = 9 Hz), 114.6 (d, J = 34 Hz), 104.4 (t, J = 27 Hz) ppm. $C_7H_3BrF_2O_2$ (237.00): calcd. C 35.48, H 1.28; found C 35.59, H 1.21.

2-Bromo-3,5-difluorobenzoic Acid (10): 2-Bromo-3,5-difluoro-4-(triethylsilyl)benzoic acid (**25**; 5.3 g, 15 mmol) was protodesilylated by a method analogous to that described above (see the acid **2**); colorless needles; m.p. 140−142 °C (from hexanes); yield: 3.43 (97%). ^{1}H NMR: δ = 7.55 (dm, J = 8.2 Hz, 1 H), 7.11 (td, J = 8.1, 3.0 Hz) ppm. ^{13}C NMR: δ = 166.4 (s), 163.5 (dd, J = 250, 11 Hz), 161.1 (dd, J = 249, 12 Hz), 137.8 (d, J = 9 Hz), 115.5 (dd, J = 25, 3 Hz), 109.1 (t, J = 26 Hz), 105.2 (dd, J = 22, 3 Hz) ppm. $C_7H_3BrF_2O_2$ (237.00): calcd. C 35.48, H 1.28; found C 35.63, H 1.40.

2. (Difluorophenyl)-, (Bromodifluorophenyl)-, and (Dibromodifluorophenyl)silanes

(2,6-Difluorophenyl)triethylsilane (11): Butyllithium (0.20 mol) in hexanes (0.12 L) was added at −75 °C to 1,3-difluorobenzene (20 mL, 23 g, 0.20 mol) in tetrahydrofuran (0.40 L). After the mixture had been kept for 45 min at −75 °C, chlorotriethylsilane (34 mL, 30 g, 0.20 mol) was added. After a further 45 min, the reaction solvents were evaporated and the residue was distilled to afford a colorless oil; b.p. 53−55 °C/5 Torr; n_D^{20} = 1.4844; d_4^{20} = 0.983; yield: 40.6 g (89%). ^{1}H NMR: δ = 7.3 (m, 1 H), 6.83 (t, J = 7.8 Hz, 2 H), 1.00 (m, 15 H) ppm. ^{13}C NMR: δ = 167.5 (dd, J = 228, 15 Hz), 132.0 (t, J = 10 Hz), 111.5 (m), 111.0 (d, J = 30 Hz), 7.6 (s), 4.5 (s) ppm. $C_{12}H_{18}F_2Si$ (228.36): calcd. C 63.12, H 7.95; found C 63.01, H 8.12.

(3-Bromo-2,6-difluorophenyl)triethylsilane (12): A solution of *sec*-butyllithium (0.15 mol) in cyclohexane (0.10 L) was added to the silane **11** (26 mL, 26 g, 0.15 mol) in tetrahydrofuran (0.20 L). After 45 min, bromine (7.7 mL, 24 g, 0.15 mol) was added. After evaporation of the volatile components, direct distillation afforded a colorless oil; b.p. 71−73 °C/0.6 Torr; n_D^{20} = 1.5018; d_4^{20} = 1.243; yield: 42.4 g (92%). ^{1}H NMR: δ = 7.50 (ddd, J = 8.7, 7.0, 6.0 Hz, 1 H), 6.73 (ddd, J = 9.9, 8.7, 7.0 Hz, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 166.4 (dd, J = 242, 12 Hz), 162.7 (dd, J = 245, 17 Hz), 135.0 (dd, J = 8, 2 Hz), 113.1 (t, J = 39 Hz), 112.3 (dd, J = 28, 4 Hz), 103.9 (dd, J = 27, 5 Hz), 7.0 (s), 4.1 (s) ppm. $C_{12}H_{17}BrF_2Si$ (307.25): calcd. C 46.91, H 5.58; found C 46.90, H 5.19.

(3,5-Dibromo-2,6-difluorophenyl)triethylsilane (13): Diisopropylamine (14 mL, 10 g, 0.10 mol) and (3-bromo-2,6-difluorophenyl)triethylsilane (**12**; 24 mL, 30 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in hexanes (60 mL) and tetrahydrofuran (0.14 L), cooled in a methanol/dry ice bath. After 2 h, 1,2-dibromotetrafluoroethane (14 mL, 31 g, 0.12 mol) was added. After 45 min at −75 °C, the reaction mixture was washed with hydrochloric acid (10%, 50 mL) and extracted with hexanes (3 × 50 mL). Upon distillation a colorless oil was obtained; b.p. 91−93 °C/0.15 Torr; n_D^{20} = 1.5421; d_4^{20} = 1.662; yield: 31.6 g (82%). ^{1}H NMR: δ = 7.76 (t, J = 7.4 Hz, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 162.1 (dd, J = 248, 16 Hz), 137.6 (s), 114.6 (t, J = 39 Hz), 105.1 (m), 7.6 (s), 4.4 (s) ppm. $C_{12}H_{16}Br_2F_2Si$ (386.15): calcd. C 37.33, H 4.18; found C 37.52, H 3.98.

(3,4-Dibromo-2,6-difluorophenyl)triethylsilane (14): Diisopropylamine (11 mL, 7.6 g, 75 mmol) and the silane **13** (28.9 g, 75 mmol) were added consecutively to a solution of butyllithium (75 mmol) in hexanes (50 mL) and tetrahydrofuran (0.10 L). After 2 h at −75 °C, the reaction mixture was treated with methanol (3.2 mL, 2.9 g, 90 mmol), washed with hydrochloric acid (10%, 50 mL), and extracted with hexanes (3 × 50 mL). Upon distillation a colorless oil was collected; b.p. 92−94 °C/0.2 Torr; yield: 37.2 g (86%). The colorless oil was a 5:1 mixture of isomer **14** and its precursor **13**, as shown by gas chromatography (2 m, 2% FFAP, 180 °C; 2 m, 2% OV-17, 220 °C; internal standard: tridecane). The main component was purified by preparative gas chromatography (2 m, 10% C-20M, 230 °C); n_D^{20} = 1.5411; d_4^{20} = 1.663. ^{1}H NMR: δ = 7.16 (dd, J = 7.9, 1.7 Hz, 1 H), 1.0 (m, 9 H), 0.9 (m, 6 H) ppm. ^{13}C NMR: δ = 165.7 (dd, J = 252, 18 Hz), 163.3 (dd, J = 249, 18 Hz), 127.3 (d, J = 12 Hz), 116.5 (dd, J = 32, 3 Hz), 111.9 (t, J = 38 Hz), 108.5 (dd, J = 32, 3 Hz), 7.2 (s), 4.1 (s) ppm. $C_{12}H_{16}Br_2F_2Si$ (386.15): calcd. C 37.33, H 4.18; found C 37.55, H 4.00.

(4-Bromo-2,6-difluorophenyl)triethylsilane (15): The 5:1 mixture of the two dibromodifluorophenylsilanes **13** and **14** (19 g, 50 mmol) was added to a solution of butyllithium (45 mmol) in hexanes (35 mL) and diethyl ether (0.17 L) kept at −100 °C. After 15 min, the reaction mixture was treated with methanol (2.1 mL, 1.9 g, 60 mmol) and the solvents were evaporated. The residue was distilled to afford a colorless oil; b.p. 72−74 °C/0.8 Torr; ${n^{20}}_D$ = 1.4789; d_4^{20} = 1.386; yield: 9.1 g (59%). ^{1}H NMR: δ = 7.00 (d, J = 6.9 Hz, 2 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 167.5 (dd, J = 260, 17 Hz), 124.0 (t, J = 12 Hz), 114.9 (m), 110.5 (t, J = 35 Hz), 7.2 (s), 4.0 (s) ppm. $C_{12}H_{17}BrF_2Si$ (307.25): calcd. C 46.91, H 5.58; found C 46.82, H 5.50.

3. (Bromodifluoroiodophenyl)triethylsilanes

(3-Bromo-2,6-difluoro-5-iodophenyl)triethylsilane (23): Diisopropylamine (14 mL, 10 g, 0.10 mol) and the silane **12** (25 mL, 31 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in hexanes (60 mL) and tetrahydrofuran (0.14 L), cooled in a methanol/dry ice bath. After the mixture had been kept at −75 °C for 2 h, iodine (25 g, 0.10 mol) in tetrahydrofuran (0.10 L) was added. The reaction mixture was washed with hydrochloric acid (10%, 50 mL) and extracted with hexanes (3 × 0.10 L). Upon distillation a colorless oil was obtained; b.p. 102−104 °C/0.6 Torr; n_D^{20} = 1.5672; d_4^{20} = 1.780; yield: 37.2 g (86%). ^{1}H NMR: δ = 7.92 (t, *J* = 8.0 Hz, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 165.0 (dd, *J* = 244, 15 Hz), 162.5 (dd, *J* = 248, 15 Hz), 142.9 (s), 113.6 (t, *J* = 38 Hz), 104.8 (dd, *J* = 30, 4 Hz), 75.6 (dd, *J* = 32, 4 Hz), 7.0 (s), 3.8 (s) ppm. $C_{12}H_{16}BrF_2ISi$ (433.15): calcd. C 33.28, H 3.72; found C 33.78, H 3.87.

(3-Bromo-2,6-difluoro-4-iodophenyl)triethylsilane (24): Diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and the silane **23** (12 mL, 22 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (70 mL) cooled in a methanol/dry ice bath. After 2 h at −75 °C, the reaction mixture was treated with methanol (2.1 mL, 1.9 g, 60 mmol), washed with hydrochloric acid (10%, 20 mL), and extracted with hexanes (3 × 50 mL). The combined organic phases were concentrated, dried with sodium sulfate, and distilled. A colorless oil was obtained; yield: 17.8 g (82%). The colorless oil was composed of product **24** and its isomeric precursor **23** in a 3:2 ratio as shown by gas chromatography (2 m, 2% FFAP, 200 °C; 2 m, 2% OV-17, 250 °C; internal standard: pentadecane). Most of the material (17.3 g, 40 mmol) was added to a solution of butyllithium (14 mmol) in hexanes (26 mL) and diethyl ether (20 mL) cooled to −100 °C. After 15 min at this temperature, an excess of powdered dry ice was poured into the reaction mixture, which afterwards was immediately distilled to give a colorless oil; b.p. 110−112 °C/0.1 Torr; n_D^{20} = 1.4977; d_4^{20} = 1.772; yield: 9.8 g (57%). ^{1}H NMR: δ = 7.37 (dd, *J* = 7.6, 1.7 Hz, 1 H), 0.9 (m, 15 H) ppm. ^{13}C NMR: δ = 165.8 (dd, *J* = 250, 18 Hz), 162.0 (dd, *J* = 249, 18 Hz), 122.8 (dd, *J* = 32, 3 Hz), 113.0 (dd, *J* = 29, 4 Hz), 112.9 (t, *J* = 38 Hz), 103.0 (d, *J* = 10 Hz), 7.2 (s), 4.0 (s) ppm. $C_{12}H_{16}BrF_2ISi$ (433.15): calcd. C 33.28, H 3.72; found C 33.55, H 3.83.

4. Difluoro(triethylsilyl)benzoic Acids and Bromodifluoro(triethylsilyl)benzoic Acids

2,4-Difluoro-3-(triethylsilyl)benzoic Acid (16): (2,6-Difluorophenyl)triethylsilane (**11**; 12 mL, 11 g, 50 mmol) was added to a precooled solution of *sec*-butyllithium (50 mmol) in cyclohexane (40 mL) and tetrahydrofuran (60 mL). After 45 min, an excess of freshly powdered dry ice was poured into the reaction mixture. Workup was as described for acid **1**; colorless needles; m.p. 45−47 °C (from hexanes); yield: 12.1 g (89%). ^{1}H NMR: δ = 8.07 (dt, *J* = 7.8, 6.5 Hz, 1 H), 6.93 (t, *J* = 6.5 Hz, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 171.2 (dd, *J* = 252, 15 Hz), 169.5 (s), 168.0 (dd, *J* = 260, 18 Hz), 136.0 (d, *J* = 12 Hz), 113.9 (d, *J* = 15 Hz), 113.4 (t, *J* = 38 Hz), 112.0 (d, *J* = 31 Hz), 7.6 (s), 4.5 (s) ppm. $C_{13}H_{18}F_2O_2Si$ (272.37): calcd. C 57.33, H 6.66; found C 57.25, H 6.52.

3,5-Difluoro-4-(triethylsilyl)benzoic Acid (17): (4-Bromo-2,6-difluorophenyl)triethylsilane (**15**; 15.3 g, 50 mmol) was added to a solution of butyllithium (45 mmol) in hexanes (25 mL) and diethyl ether (80 mL), cooled in a methanol/dry ice bath. After the mixture had been kept at −75 °C for 15 min , freshly crushed dry ice was added and the reaction mixture was worked up as described for acid **1**; colorless needles; m.p. 101−103 °C (from hexanes); yield: 12.6 g (93%). ^{1}H NMR: δ = 7.52 (d, *J* = 7.1 Hz, 2 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 170.4 (s), 167.3 (dd, *J* = 245, 18 Hz), 133.1 (t, *J* = 12 Hz), 118.5 (t, *J* = 36 Hz), 112.6 (m), 7.1 (s), 4.0 (s) ppm. $C_{13}H_{18}F_2O_2Si$ (272.37): calcd. C 57.33, H 6.66; found C 57.29, H 6.72.

1-Bromo-2,6-difluorobenzene (18): Solutions of butyllithium (0.10 mol) in hexanes (65 mL) and 1,3-difluorobenzene (10 mL, 11 g, 0.10 mmol) in tetrahydrofuran (0.14 L) were mixed at −75 °C. After the mixture had been kept for 45 min at this temperature, bromine (5.1 mL, 16 g, 0.10 mol) was added. Immediate distillation afforded a colorless oil; b.p. 135−137 °C/760 Torr; n_D^{20} = 1.5100; d_4^{20} = 1.769; yield: 18.1 g (94%). ^{1}H NMR: δ = 7.3 (m, 1 H), 0.95 (dd, *J* = 8.4, 2.1 Hz, 2 H) ppm.

1-Bromo-2,4-difluorobenzene (19): Diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and 1-bromo-2,6-difluorobenzene (**18**; 9.6 g, 50 mmol) were added consecutively at −75 °C to a solution of butyllithium (50 mmol) in hexanes (35 mL) and tetrahydrofuran (70 mL). After 2 h at −75 °C, the mixture was treated with methanol (2.0 mL, 1.9 g, 60 mmol) and the solvents were evaporated. Immediate distillation afforded a colorless oil; b.p. 130−134 °C/760 Torr; yield: 5.57 g (58%). According to gas chromatography (2 m, 2% FFAP, 100 °C; 2 m, 2% OV-17, 120 °C; internal standard: undecane) it was composed of the product **19** and its isomeric precursor **18** in a 3:2 ratio. Most of the material (4.8 g, 25 mmol) was added to a solution of butyllithium (10 mmol) in hexanes (6.5 mL) and diethyl ether (40 mL) cooled to −75 °C. After 15 min, freshly crushed dry ice was poured into the reaction mixture. Immediate distillation afforded a colorless oil; b.p. 145−147 °C (ref.[16] b.p. 147 °C); n_D^{20} = 1.5061 (ref.[16] n_D^{20} = 1.5059); yield: 2.71 g (57%).

Bromo-3,5-difluorobenzene (20): A biphasic mixture containing the silane **15** (15 g, 50 mmol), potassium fluoride (12 g, 0.20 mol), tetrahydrofuran (40 mL), and water (10 mL) was heated under reflux for 2 h. Evaporation, followed by distillation, afforded a colorless oil; b.p. 58−60 °C/30 Torr (ref.[3] b.p. 140 °C/760 Torr); n_D^{20} = 1.4988 (ref.[3] n_D^{20} = 1.4989); yield: 8.96 g (93%). ^{1}H NMR: δ = 7.06 (symm. m, 2 H), 6.78 (symm. m, 1 H) ppm.

3-Bromo-4,6-difluoro-5-(triethylsilyl)benzoic Acid (21): Diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and (3-bromo-2,6-difluorophenyl)triethylsilane (**12**; 12 mL, 15 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (70 mL), cooled in a methanol/dry ice bath. After the mixture had been kept for 2 h at −75 °C, an excess of freshly powdered dry ice was added. The reaction mixture was worked up as described for acid **1**; colorless needles; m.p. 67−69 °C (from hexanes); yield: 12.3 g (70%). ^{1}H NMR: δ = 8.26 (m, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 168.7 (s), 166.3 (dd, *J* = 261, 16 Hz), 166.0 (dd, *J* = 256, 17 Hz), 138.3 (s), 115.1 (m), 114.8 (m), 104.4 (d, *J* = 26 Hz), 7.2 (s), 4.0 (s) ppm. $C_{13}H_{17}BrF_2O_2Si$ (351.26): calcd. C 44.85, H 4.88; found C 44.46, H 4.85.

2-Bromo-4,6-difluoro-5-(triethylsilyl)benzoic Acid (22): A mixture of the two dibromodifluorosilanes **13** and **14** (5:1, 9.7 g, 25 mmol) was added at −100 °C to a solution of butyllithium (20 mmol) in hexanes (15 mL) and diethyl ether (90 mL). After 15 min at this temperature, the mixture was treated with an excess of powdered dry ice. The reaction mixture was worked up as described for acid **1**, yielding 8.60 g (98%) of a viscous oil. ^{1}H NMR: δ = 7.21 (d, *J* = 8.1 Hz, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: δ = 169.8 (s), 167.8 (dd, *J* = 252, 18 Hz), 164.5 (dd, *J* = 253, 18 Hz), 122.3 (dd, *J* = 6, 5 Hz), 119.5 (dd, *J* = 23, 3 Hz), 116.5 (dd, *J* = 32, 3 Hz), 111.7 (t, *J* = 38 Hz), 7.1 (s), 4.0 (s) ppm.

2-Bromo-3,5-difluoro-4-(triethylsilyl)benzoic Acid (25): The silane **24** (8.7 g, 20 mmol) in diethyl ether (10 mL) was added at −100 °C to a solution of butyllithium (20 mmol) in hexanes (15 mL) and diethyl ether (30 mL). After 15 min, powdered dry ice was added and the reaction mixture was worked up as described for acid **1**; colorless needles; m.p. 52−54 °C (from hexanes); yield: 6.40 g

(91%). ^{1}H NMR: $\delta = 7.43$ (dd, $J = 8.4$, 1.5 Hz, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR: $\delta = 170.4$ (s), 165.7 (dd, $J = 246$, 18 Hz), 163.4 (dd, $J = 245$, 18 Hz), 134.9 (d, $J = 10$ Hz), 117.6 (t, $J = 38$ Hz), 114.2 (d, $J = 32$ Hz), 104.7 (dd, $J = 30$, 4 Hz), 7.2 (s), 4.1 (s) ppm. $C_{13}H_{17}BrF_2O_2Si$ (351.26): calcd. C 44.85, H 4.88; found C 44.40, H 4.64.

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