Organometallic Control over the Regiospecificity of Functionalization Reactions: 1,2,3-Trifluorobenzene and Bromo Derivatives thereof as Substrates

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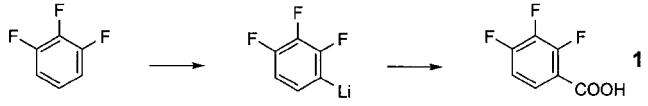
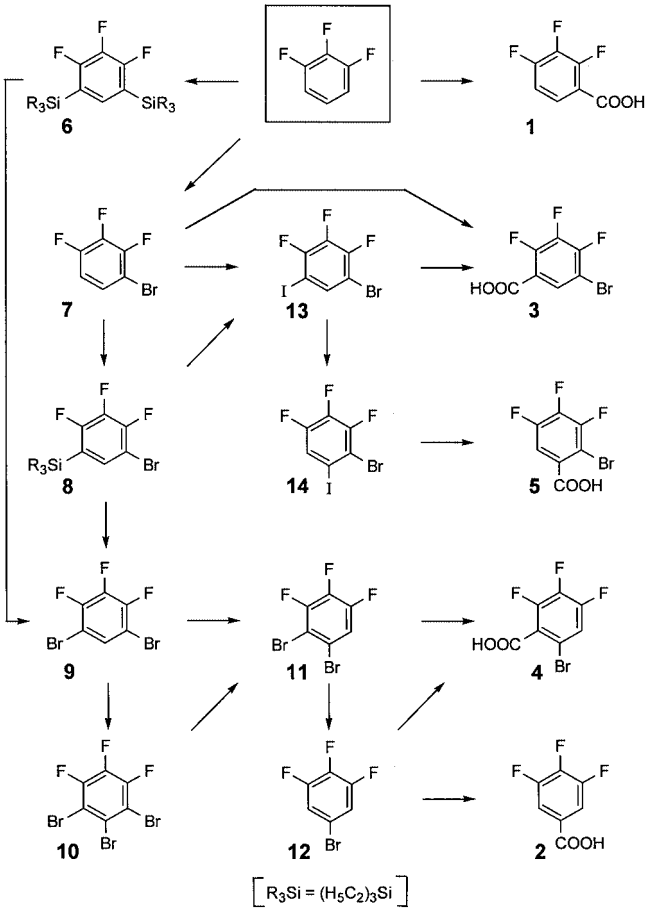
In a case study, 1,2,3-trifluorobenzene was functionalized at each of the two vacant positions (producing the benzoic acids **1** and **2**) and, in addition, bromine was introduced into all available positions (producing the benzoic acids **3**–**5**). The required regioflexibility was achieved by applying novel organometallic recipes such as deprotonation-triggered halogen migrations and site-discriminating competitive halogen–metal permutations.

At first glance, 1,2,3-trifluorobenzene hardly qualifies as a good example for demonstrating the merits of the organometallic approach to the creation of molecular diversity.[1] Having just two regiochemically distinct sites unoccupied, any deprotonation/functionalization sequence can give rise to not more than two isomers. To make our exercise in regioflexibility more demanding, we have therefore allowed for the presence of an additional substituent by targeting both the two trifluorobenzoic acids **1** and **2** and also the three bromo derivatives **3**−**5**. The chart shown below summarizes the transformations involving the bromo-, iodo-, or triethylsilyl-substituted trifluorobenzenes **6**−**14**. Details will be specified in the subsequent sections.

The *ortho*-lithiation of 1,2,3-trifluorobenzene with *sec*-butyllithium in tetrahydrofuran at −75 °C has already been reported.[2] Subsequent carboxylation and neutralization afforded 2,3,4-trifluorobenzoic acid (**1**) in 94% yield.



In contrast, a multi-step procedure was required to prepare 3,4,5-trifluorobenzoic acid (**2**). Treatment of the metalated species with elemental bromine gave 1-bromo-2,3,4-trifluorobenzene (**7**; 95%), which was converted into (5-bromo-2,3,4-trifluorophenyl)triethylsilane (**8**; 92%) upon subsequent reaction with lithium diisopropylamide (LIDA) and chlorotriethylsilane. Heating silane **8** with bromine for 36 h in refluxing tetrachloromethane produced 1,5-dibromo-2,3,4-trifluorobenzene (**9**; 93%). The dibromo compound **9** (95%) was also formed when the bis(silane) **6**, resulting in 91% yield from the twofold repetitive reaction



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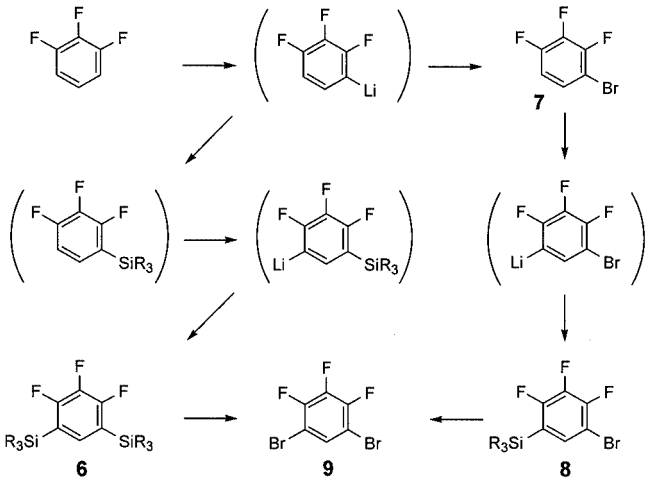
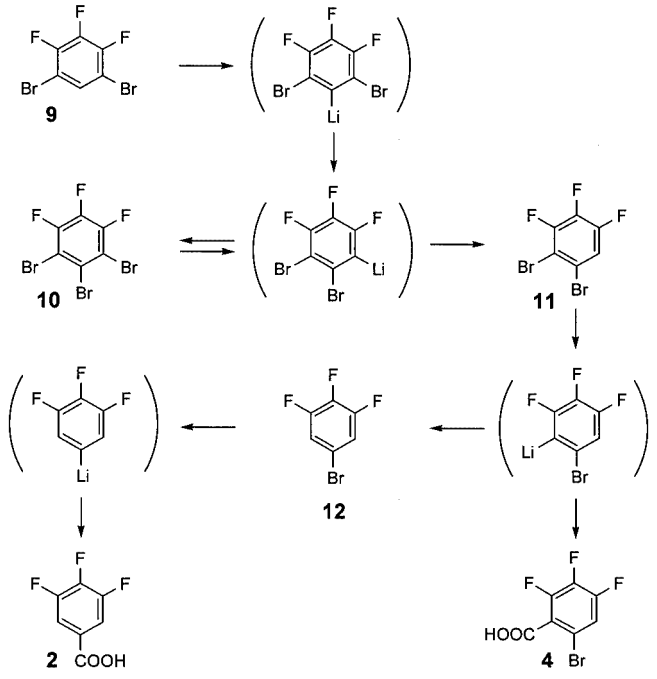
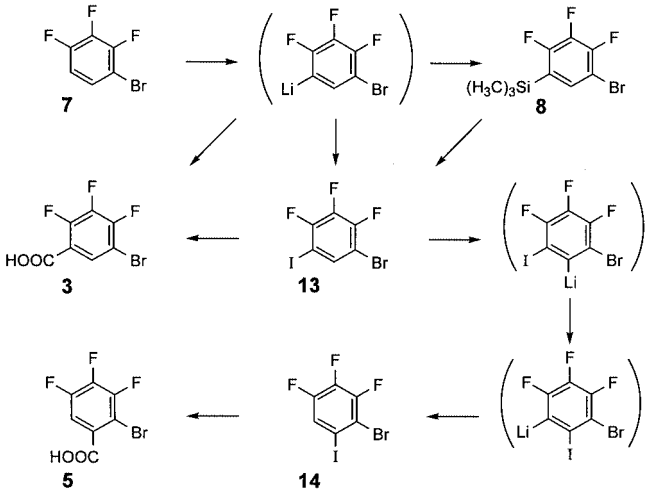
of 1,2,3-trifluorobenzene with, each time, 1 equiv. of *sec*-butyllithium and chlorotriethylsilane, was treated with an excess of bromine.



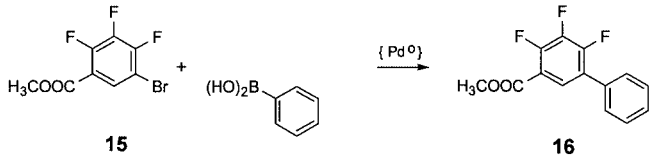
Upon addition of LIDA, 1,5-dibromo-2,3,4-trifluorobenzene (**9**) underwent a deprotonation-triggered migration[3−5] of the heavy halogen to afford, after neutralization, 1,2-dibromo-3,4,5-trifluorobenzene (**11**; 62%). This isomerization could be accomplished more cleanly and expediently (62% overall) if the lithiated intermediate was first intercepted with tetrabromomethane to produce 1,2,3-tribromo-4,5,6-trifluorobenzene (**10**; 67%) from which 2,3-dibromo-4,5,6-trifluorophenyllithium was then regenerated with lithium tributylmagnesiate[6−8] at −75 °C. 1,2-Dibromo-3,4,5-trifluorobenzene (**11**) was subjected to a site-selective halogen−metal permutation with butyllithium. Upon carboxylation or hydrolysis of the resulting 6-bromo-2,3,4-trifluorophenyllithium intermediate, 6-bromo-2,3,4-trifluorobenzoic acid (**4**; 80%) and 5-bromo-1,2,3-trifluorobenzene (**12**; 89%) were formed, respectively. 3,4,5-Trifluorobenzoic acid (**2**; 93%) was obtained from compound **12** by consecutive halogen−metal permutation, carboxylation, and neutralization.



5-Bromo-2,3,4-trifluorobenzoic acid (**3**) proved to be directly accessible from 1-bromo-2,3,4-trifluorobenzene (**7**) by carboxylation after prior deprotonation with lithium 2,2,6,6-tetramethylpiperidide (LITMP) in 91% yield and also from 1-bromo-2,3,4-trifluoro-5-iodobenzene (**13**) after prior halogen−metal permutation with butyllithium, in 90% yield. The bromoiodo derivative **13** was obtained after consecutive treatment of 1-bromo-2,3,4-trifluorobenzene (**7**) with LIDA and elemental iodine in 91% yield and also by iododesilylation of silane **8** in 89% yield. Incubation with a solution of LIDA in tetrahydrofuran at −75 °C caused a deprotonation-triggered iodine migration. After neutralization, 2-bromo-3,4,5-trifluoro-1-iodobenzene (**14**; 62%) was isolated. 2-Bromo-3,4,5-trifluorobenzoic acid (**5**; 90%) was formed upon consecutive treatment of the latter compound with butyllithium and carbon dioxide.



The bromotrifluorobenzoic acids **3**−**5** may be employed as versatile components in transition element mediated coupling reactions. For example, a smooth Suzuki−Miyaura condensation[9−11] was accomplished between the ester **15**, derived from acid **3**, and phenylboronic acid in the presence of catalytic amounts of tetrakis(triphenylphosphane)palladium(0) to afford methyl 4,5,6-trifluoro-3-biphenylcarboxylate (**16**) in 87% yield.



Experimental Section

General: Starting materials, if commercial, were purchased from Aldrich−Fluka (9479 Buchs, Switzerland), Acros Organics (2440 Geel, Belgium) or Apollo (SK6 2QR Stockport, United Kingdom) and used as such provided that adequate checks (melting ranges, n_D^{20}, gas chromatography) had confirmed the claimed purity. Solutions of butyllithium, *sec*-butyllithium and *tert*-butyllithium in pentanes, hexanes, or cyclohexane were supplied by Chemetall (60487 Frankfurt, Germany) and potassium *tert*-butoxide by Callery (Pittsburgh, PA 15230, USA). When known compounds had to be prepared according to literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in Schlenk tubes or Schlenk burettes. They were protected by, and handled under, 99.995% pure nitrogen, using appropriate glassware (Glasgerätebau Pfeifer, 98711 Frauenfeld, Germany). Paraffinic or aromatic hydrocarbons (hexanes, toluene) were subjected to azeotropic distillation. Diethyl ether and tetrahydrofuran were dried by distillation from sodium wire after the characteristic blue color of in situ generated sodium diphenyl ketyl (benzophenone−sodium "radical anion") had been found to persist.[12−13] Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. Prior to distillation, a spatula tip of hydroquinone or potassium carbonate was added to compounds prone to radical polymerization or sensitive to acids. If no reduced pressure is specified, boiling ranges (b.p.) refer to ordinary atmospheric conditions (725±25 Torr). Melting ranges (m.p.) given were found to be reproducible after resolidification, unless stated otherwise ("decomp."), and were corrected using a calibration curve established with authentic standards. If melting points are missing, it means all attempts to crystallise the liquid at temperatures down to −75 °C failed. The temperature of dry ice/methanol baths is consistently indicated as −75 °C and "room temperature" (22−26 °C) as 25 °C. Silica gel (Merck Kieselgel 60) of 70−230 mesh (0.06−0.20 mm) particle size was used for column chromatography. The solid support was suspended in hexanes and, when all air bubbles had escaped, was washed into the column. When the level of the liquid was still 3−5 cm above the support layer, the dry powder, obtained by adsorption of the crude mixture to some 25−50 mL of silica and subsequent evaporation of the solvent, was poured on top of the column. Whenever possible and appropriate, yields of products were determined, prior to isolation, by gas chromatographic comparison of their peak areas with that of a known amount of a reference substance ("internal standard") and correction of the ratios thus obtained by means of separately established calibration factors. The purity of distilled compounds was checked on at least two columns loaded with stationary phases of contrasting polarity. Chromosorb G-AW of 80−100 and 60−80 mesh particle sizes were used as the support for packed columns for the analytical and preparative scale (2 or 3 m long, 2 mm inner diameter and 3 or 6 m long, 1 cm inner diameter, respectively). Packed columns were made of glass, while quartz was the material selected for capillary columns (> 10 m long). In the case of programmed temperature increases, a constant rate of 10 °C/min was applied. The stationary phases employed are encoded as DB-1, OV-17 or SE-30 (of the silicone type), DEGS or DBS (both of the polyester type), AP-L (Apiezon-L hydrocarbon) and C-20M, DB-WAX or DB-FFAP (all belonging to the polyethylene glycol family). ^{1}H and ^{13}C NMR spectra were recorded of samples dissolved in deuterochloroform at 400 and 101 MHz, respectively. Chemical shifts δ refer to the signal of tetramethylsilane (δ = 0.00 ppm) and coupling constants *J* are given in Hz. Coupling patterns are, for example, abbreviated as s (singlet), d (doublet), t (triplet), qr (quadruplet), qn (quintuplet), hx (hextuplet), hp (heptuplet), oct (octuplet), non (nonuplet), td (triplet of doublets), and m (multiplet). Elemental analyses were executed by the laboratory of I. Beetz (96301 Kronach, Germany). The expected percentages were calculated by using the atomic masses listed in the 1999 IUPAC recommendations. Further hints concerning working routine, spectra, and abbreviations can be found in recent publications from this laboratory.[14−16]

1. Halobenzoic Acids 1−5

2,3,4-Trifluorobenzoic Acid (1): A solution of 1,2,3-trifluorobenzene (2.6 mL, 3.3 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (16 mL) was kept for 45 min at −75 °C, before being poured onto an excess of freshly crushed dry ice. The mixture was briefly stirred before a diethyl ether solution (15 mL) of hydrogen chloride (30 mmol) was added with shaking. The volatiles 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. 143−145 °C (from hexanes); yield: 4.1 g (94%). ^{1}H NMR: δ = 7.83 (m, 1 H), 7.08 (dddd, *J* = 9.0, 6.7, 2.4, 2.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 162.5 (s), 153.7 (dd, *J* = 257, 12 Hz), 151.8 (dd, *J* = 261, 12 Hz), 140.3 (dt, *J* = 250, 13 Hz), 126.9 (dd, *J* = 10, 3 Hz), 116.9 (m), 112.0 (dd, *J* = 12, 3 Hz) ppm. $C_7H_3F_3O_2$ (176.09): calcd. C 47.75, H 1.72; found C 47.74, H 1.67.

3,4,5-Trifluorobenzoic Acid (2): 5-Bromo-1,2,3-trifluorobenzene (**12**; see Section 2; 1.2 mL, 2.1 g, 10 mmol) was added to a solution of butyllithium (10 mmol) in hexanes (6.5 mL) and diethyl ether (14 mL) cooled in a dry ice/methanol bath. After 15 min at −75 °C, the mixture was carboxylated and worked up as described in the preceding paragraph; colorless needles; m.p. 91−93 °C (from hexanes); yield: 1.6 g (93%). ^{1}H NMR: δ = 7.76 (td, *J* = 6.5, 1.8 Hz, 2 H) ppm. ^{13}C NMR: δ = 165.9 (s), 152.5 (dd, *J* = 251, 12 Hz), 144.4 (dt, *J* = 258, 16 Hz), 128.8 (m), 115.9 (symm. m) ppm. $C_7H_3F_3O_2$ (176.09): calcd. C 47.75, H 1.72; found C 47.96, H 1.71.

5-Bromo-2,3,4-trifluorobenzoic Acid (3): 2,2,6,6-Tetramethylpiperidine (4.1 mL, 3.5 g, 25 mmol) and 1-bromo-2,3,4-trifluorobenzene (**7**; see below; 3.0 mL, 5.3 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (16 mL) and tetrahydrofuran (35 mL) kept in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide and worked up as described above giving colorless needles; m.p. 132−134 °C (from hexanes); yield: 2.3 g (91%). ^{1}H NMR: δ = 8.07 (td, *J* = 7.0, 2.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 160.1 (s), 152.5 (dd, *J* = 258, 12 Hz), 151.9 (dd, *J* = 269, 13 Hz), 141.1 (dt, *J* = 258, 15 Hz), 129.8 (d, *J* = 4 Hz), 115.8 (m), 105.0 (dd, *J* = 20, 5 Hz) ppm. $C_7H_2BrF_3O_2$ (254.92): calcd. C 32.97, H 0.79; found C 33.00, H 0.87. When 1-bromo-2,3,4-trifluoro-5-iodobenzene (**13**; see Section 2; 3.4 mL, 8.4 g, 25 mmol) was treated with butyllithium (25 mmol) in diethyl ether (35 mL) and hexanes (16 mL) for 15 min at −75 °C and carboxylated before being worked up as described above, the acid **3** was obtained; yield: 5.7 g (90%).

2-Bromo-4,5,6-trifluorobenzoic Acid (4): Both isomers **9** and **11** (see Section 2; 5.8 g, 20 mmol) in diethyl ether (5 mL) were added to a solution of butyllithium (17 mmol) in hexanes (8 mL) and diethyl ether (20 mL) at −100 °C. After 15 min, freshly crushed dry ice was added; work up as described above; tiny needles; m.p. 137−139 °C (from hexanes); yield: 4.1 g (80%). ^{1}H NMR: δ = 7.35 (td, *J* = 7.0, 2.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.0 (s), 153.1 (ddd, *J* = 255, 11, 3 Hz), 150.3 (ddd, *J* = 255, 11, 3 Hz), 141.0 (dt, *J* = 253,

17 Hz), 124.9 (dd, J = 17, 4 Hz) ppm. $C_7H_2BrF_3O_2$ (254.92): calcd. C 32.97, H 0.79; found C 33.19, H 0.86.

2-Bromo-3,4,5-trifluorobenzoic Acid (5): An analogous reaction was carried out with 2-bromo-3,4,5-trifluoro-1-iodobenzene (**14**; see Section 2; 3.4 g, 10 mmol); colorless needles; m.p. 101−103 °C (from hexanes); yield: 2.3 g (90%). ^{1}H NMR: δ = 7.78 (ddd, J = 10.0, 7.8, 2.6 Hz, H) ppm. ^{13}C NMR: δ = 165.5 (s), 151.3 (dd, J = 251, 10 Hz), 150.7 (dd, J = 248, 11 Hz), 143.5 (dt, J = 258, 17 Hz), 131.6 (s), 116.5 (dd, J = 19, 3 Hz), 107.0 (dd, J = 20, 3 Hz) ppm. $C_7H_2BrF_3O_2$ (254.92): calcd. C 32.97, H 0.79; found C 32.96, H 0.80.

2. Haloarenes without Functional Groups (6−14)

2,3,4-Trifluoro-1,5-phenylenebis(triethylsilane) (6): A solution of 1,2,3-trifluorobenzene (7.7 mL, 9.9 g, 75 mmol) and *sec*-butyllithium (75 mmol) in cyclohexanes (52 mL) and tetrahydrofuran (0.15 L) was kept for 45 min at −75 °C. Always at −75 °C, chlorotriethylsilane (13 mL, 11 g, 75 mmol) and, at 45 min intervals, more *sec*-butyllithium (75 mmol) in cyclohexane (52 mL) and chlorotriethylsilane (13 mL, 11 g, 75 mmol) were added. The product was isolated by immediate distillation as a colorless oil; b.p. 103−105 °C/0.5 Torr; n_D^{20} = 1.4656; d_4^{20} = 1.101; yield: 24.6 g (91%). ^{1}H NMR: δ = 7.03 (td, J = 7.0, 2.5 Hz, 1 H), 0.96 (t, J = 7.4 Hz, 18 H), 0.83 (q, J = 7.4 Hz, 12 H) ppm. ^{13}C NMR: δ = 156.4 (ddd, J = 247, 8, 3 Hz), 139.5 (dt, J = 256, 18 Hz), 135.2 (ddd, J = 17, 11, 2 Hz), 120.6 (symm. m), 7.1 (s), 3.6 (s) ppm. $C_{18}H_{31}F_3Si_2$ (360.60): calcd. C 59.95, H 8.66; found C 56.96, H 8.68.

Bromo-2,3,4-trifluorobenzene (7): A solution of *sec*-butyllithium (20 mmol) in cyclohexane (15 mL) was added dropwise to a solution of 1,2,3-trifluorobenzene (2.0 mL, 2.6 g, 20 mmol) in THF (40 mL) at −75 °C. After 45 min at −75 °C, bromine (1.1 mL, 3.2 g, 20 mmol) was added. Immediate distillation under reduced pressure afforded a colorless oil; b.p. 58−60 °C/30 Torr; n_D^{20} = 1.4863; d_4^{20} = 1.709; yield: 4.0 g (95%); ^{1}H NMR: δ = 7.30 (ddd, J = 7.9, 5.2, 2.5 Hz, 1 H), 6.93 (dddd, J = 9.5, 8.1, 2.2, 2.1 Hz, 1 H) ppm.

(5-Bromo-2,3,4-trifluorophenyl)triethylsilane (8): Diisopropylamine (21 mL, 15 g, 0.15 mol) and 1-bromo-2,3,4-trifluorobenzene (21 mL, 32 g, 0.15 mol) were added consecutively to a solution of butyllithium (0.15 mol) in hexanes (0.10 L) and tetrahydrofuran (0.25 L) cooled in a methanol/dry ice bath. After 2 h at −75 °C, chlorotriethylsilane (25 mL, 23 g, 0.15 mol) was added. Immediate distillation afforded a colorless oil; b.p. 71−73 °C/2 Torr; n_D^{20} = 1.4967; d_4^{20} = 1.289; yield: 45 g (92%). ^{1}H NMR: δ = 7.23 (ddd, J = 7.5, 4.9, 2.6 Hz, 1 H), 0.95 (t, J = 7.1 Hz, 9 H), 0.83 (q, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR: δ = 154.7 (dd, J = 243, 8 Hz), 149.6 (ddd, J = 254, 11, 3 Hz), 140.4 (dt, J = 260, 18 Hz), 132.1 (dd, J = 12, 3 Hz), 122.8 (d, J = 30 Hz), 105.2 (d, J = 17 Hz), 7.3 (s), 3.6 (s) ppm. $C_{12}H_{16}BrF_3Si$ (325.24): calcd. C 44.31, H 4.96; found C 44.29, H 4.90.

1,5-Dibromo-2,3,4-trifluorobenzene (9): A solution of (5-bromo-2,3,4-trifluorophenyl)triethylsilane (**8**, 25 mL, 33 g, 0.10 mol) and bromine (10 mL, 32 g, 0.20 mol) in tetrachloromethane (0.10 L) was heated under reflux for 36 h. The product was immediately isolated by distillation as a colorless oil; b.p. 37−38 °C/3 Torr; n_D^{20} = 1.5320 (ref.[17] n_D^{20} = 1.5330); d_4^{20} = 2.275 (ref.[17] d_4^{20} = 2.27); yield 27 g (93%). ^{1}H NMR: δ = 7.59 (td, J = 7.0, 2.4 Hz, 1 H) ppm. The same compound was obtained when bis(silane) **6** (8.2 mL, 9.0, 25 mmol) was analogously treated with elemental bromine (2.6 mL, 8.0 g, 0.10 mol); yield: 6.9 g (95%).

1,2,3-Tribromo-4,5,6-trifluorobenzene (10): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 1,5-dibromo-2,3,4-trifluorobenzene (3.2 mL, 7.2 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (16 mL) and tetrahydrofuran (35 mL) cooled in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured into a precooled (−75 °C) solution of tetrabromomethane (10 g, 30 mmol) in tetrahydrofuran (30 mL). After rapidly turning dark and then black, the mixture was absorbed on basic alumina (15 mL) and eluted with hexanes (20 mL). After evaporation of the volatiles, the residue was crystallized from ethanol (10 mL) to give yellowish fine needles; m.p. 67−69 °C (ref.[18] m.p. 72 °C); yield 6.2 g (67%). ^{13}C NMR: δ = 148.4 (ddd, J = 251, 12, 5 Hz), 139.4 (td, J = 262, 18 Hz), 122.9 (d, J = 6 Hz), 109.7 (symm. m) ppm. $C_6Br_3F_3$ (368.74): calcd. C 19.54, H 0.00; found C 19.71, H 0.00.

1,2-Dibromo-3,4,5-trifluorobenzene (11): Diisopropylamine (7.0 mL, 5.1, 50 mmol) and 1,5-dibromo-2,3,4-trifluorobenzene (**9**, 6.4 mL, 14 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (70 mL) stored in a methanol/dry ice bath. After 2 h at −75 °C, methanol (5.0 mL, 4.0 g, 0.12 mol) was added. The volatiles were evaporated and the residue directly distilled; b.p. 37−39 °C/3 Torr. The colorless oil obtained was composed of isomer **11** and its precursor **9** in a 7:1 ratio as evidenced by gas chromatography: (2 m, 2% FFAP, 120 °C; 2 m, 2% OV-17, 150 °C); ^{1}H NMR of the major component: δ = 7.38 ppm (dd, J = 6.6, 2.1 Hz, 1 H). The dibromo compound **11** was obtained without regioisomeric contamination, when, at −75 °C, 1,2,3-tribromo-4,5,6-trifluorobenzene (10, 5.5 g, 15 mmol) was added to a solution of butylmagnesium chloride (5.0 mmol) and butyllithium (10 mmol) in tetrahydrofuran (3.5 mL), hexanes (6.5 mL), and toluene (30 mL) and the mixture, after having been kept for 45 min at 0 °C, was treated with methanol (0.7 mL, 0.6 g, 20 mmol). Direct distillation gave a colorless oil; b.p. 41−45 °C/3 Torr; n_D^{20} = 1.3320; d_4^{20} = 2.219; yield: 4.0 g (92%). ^{1}H NMR: δ = 7.38 (dd, J = 6.6, 2.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.3 (ddd, J = 255, 12, 3 Hz), 149.6 (ddd, J = 253, 15, 3 Hz), 139.5 (dt, J = 257, 16 Hz), 118.7 (dd, J = 9, 5 Hz), 116.7 (dd, J = 21, 2 Hz), 109.3 (dd, J = 20, 4 Hz) ppm. $C_6HBr_2F_3$ (289.88): calcd. C 24.86, H 0.35; found C 24.50, H 0.25.

5-Bromo-1,2,3-trifluorobenzenes (12): A precooled solution of the 1:7 mixture (see above; 12 g, 40 mmol) of 1,5-dibromo-2,3,4-trifluorobenzene (**9**) and 1,2-dibromo-3,4,5-trifluorobenzene (**11**) in diethyl ether (10 mL) was added to butyllithium (35 mmol) in hexanes (20 mL) and diethyl ether (70 mL) kept at −100 °C. After 15 min, methanol (5.0 mL, 4.0 g, 0.12 mol) was added. Evaporation of the volatiles and direct distillation of the residue gave a colorless oil; b.p. 41−43 °C/15 Torr; n_D^{20} = 1.3731; d_4^{20} = 1.711; yield 6.3 g (75%). ^{1}H NMR: δ = 7.18 (t, J = 6.5 Hz, 2 H) ppm. ^{13}C NMR: δ = 151.2 (ddd, J = 255, 11, 4 Hz), 139.4 (dt, J = 255, 15 Hz), 116.2 (symm. m), 114.8 (ddd, J = 10, 6, 4 Hz) ppm. $C_6H_2BrF_3$ (210.98): calcd. C 34.16, H 0.96; found C 34.25, H 1.00. When pure 1,2-dibromo-3,4,5-trifluorobenzene (**11**, 10 mmol) was consecutively treated with butyllithium (10 mmol) in diethyl ether (20 mL) and hexanes (5.0 mL) at −100 °C for 15 min, and afterwards with methanol (0.50 mL, 0.40 g, 12 mmol), the product **12** was formed in yield 1.1 g (89%).

1-Bromo-2,3,4-trifluoro-5-iodobenzene (13): Diisopropylamine (14 mL, 10 g, 0.10 mol) and 1-bromo-2,3,4-trifluorobenzene (**7**, 12 mL, 21 g, 0.10 mol) were consecutively introduced into a solution of butyllithium (0.10 mol) in hexanes (63 mL) and tetrahydrofuran (0.14 L) cooled in a methanol/dry ice bath. After 2 h at −75 °C, a precooled solution of iodine (25 g, 0.10 mol) in tetrahy-

drofuran (0.10 L) was added. The residue left behind after evaporation of the solvents was distilled under reduced pressure to give a colorless oil; b.p. 45−47 °C/1 Torr; n_D^{20} = 1.4638; d_4^{20} = 2.450; yield: 31 g (91%); ^{1}H NMR: δ = 7.74 (ddd, *J* = 6.7, 5.2, 1.7 Hz, H) ppm. ^{13}C NMR: δ = 150.5 (dd, *J* = 250, 11 Hz), 148.7 (dd, *J* = 252, 11 Hz), 139.6 (dt, *J* = 261, 17 Hz), 134.4 (d, *J* = 4 Hz), 105.8 (dd, *J* = 19, 4 Hz), 75.5 (dd, *J* = 24, 4 Hz) ppm. C_6HBrF_3I (336.82): calcd. C 21.39, H 0.30; found C 21.47, H 0.32. The same product **13** was obtained when (5-bromo-2,3,4-trifluorophenyl)triethylsilane (**8**, 16 g, 50 mmol) was treated with iodine monochloride (16 g, 0.10 mol) for 36 h in refluxing tetrachloromethane (0.10 L). The reaction mixture was washed with a saturated aqueous sodium sulfite solution, extracted with chloroform (3 × 30 mL) and distilled under reduced pressure; yield: 15 g (89%).

2-Bromo-3,4,5-trifluoro-1-iodobenzene (14): Diisopropylamine (5.6 mL, 4.0 g, 40 mmol) and 1-bromo-2,3,4-trifluoro-5-iodobenzene (**13**, 5.5 mL, 13 g, 40 mmol) were consecutively added to a solution of butyllithium (40 mmol) in hexanes (25 mL) and tetrahydrofuran (75 mL) kept in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was treated with methanol (5.0 mL, 4.0 g, 0.12 mol) before being immediately submitted to distillation; b.p. 55−57 °C/2 Torr; yield: 12 g (87%). The colorless oil collected consisted of isomer **14** and its precursor **13** in a 5:1 ratio according to gas chromatography: (2 m, FFAP 2%, 150 °C; 2 m, OV-17 2%, 180 °C). Most of the material (10 g, 30 mmol) was added to a solution of butyllithium (7.0 mmol) in hexanes (5.0 mL) and diethyl ether (20 mL) cooled to −100 °C. After 45 min at this temperature, an excess of freshly crushed dry ice was introduced into the reaction mixture which was distilled, without prior extraction, to give a colorless, slowly solidifying oil; m.p. 22−25 °C; b.p. 55−57 °C/2 Torr; yield: 6.1 g (62%); ^{1}H NMR: δ = 7.59 (ddd, *J* = 9.4, 7.0, 2.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.2 (ddd, *J* = 256, 12, 3 Hz), 148.4 (ddd, *J* = 255, 11, 3 Hz), 140.2 (td, *J* = 257, 17 Hz), 122.8 (dd, *J* = 20, 2 Hz), 114.0 (dd, *J* = 18, 3 Hz), 52.9 (t, *J* = 5 Hz) ppm. C_6HBrF_3I (336.82): calcd. C 21.39, H 0.30; found C 21.18, 0.25.

Methyl 3-Bromo-4,5,6-trifluorobenzoate (15): 5-Bromo-2,3,4-trifluorobenzoic acid (**3**, 6.4 g, 25 mmol) and boron trifluoride−diethyl ether (1.0 mL, 1.1 g, 10 mmol) were dissolved in methanol (12 mL) and the mixture was stored for 12 h at 25 °C. After evaporation of the volatiles, tiny needles were obtained; m.p. 71−73 °C (from hexanes); yield: 6.2 g (93%). ^{1}H NMR: δ = 7.93 (td, *J* = 7.5, 2.5 Hz, 1 H), 3.96 (s, 3 H) ppm. ^{13}C NMR: δ = 162.0 (s), 151.2 (dd, *J* = 256, 12 Hz), 150.7 (dd, *J* = 267, 12 Hz), 140.7 (dt, *J* = 258, 18 Hz), 129.0 (s), 116.5 (dd, *J* = 7, 3 Hz), 104.3 (dd, *J* = 20, 4 Hz), 52.7 (s) ppm. $C_8H_4BrF_3O_2$ (268.94): calcd. C 35.73, H 1.49; found C 35.77, H 1.42.

Methyl 2,3,4-Trifluoro-5-phenylbenzoate (16): A solution of phenylboronic acid (1.3 g, 5 mmol) in ethanol (5 mL) was rapidly added to a vigorously stirred and refluxing two-phase mixture containing methyl 3-bromo-4,5,6-trifluorobenzoate (**15**, 2.7 g, 10 mmol), tetrakis(triphenylphosphane)palladium(0) (0.34 g, 0.30 mmol), benzene (20 mL), and a 2.0 M aqueous solution of sodium carbonate (10 mL, 20 mmol). After 12 h of heating, the organic phase was decanted and the aqueous one extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried and the solvents evaporated. Crystallization gave tiny needles; m.p. 81−83 °C (from ethanol); yield: 2.3 g (87%). ^{1}H NMR: δ = 7.86 (td, *J* = 7.6, 2.5 Hz, 1 H), 7.5 (m, 5 H), 3.97 (s, 3 H) ppm. ^{13}C NMR: δ = 163.2 (s), 151.7 (dd, *J* = 257, 10 Hz), 150.7 (ddd, *J* = 266, 12, 2 Hz), 140.7 (dt, *J* = 252, 18 Hz), 132.9 (s), 132.0 (s), 131.9 (s), 128.7 (s), 128.6 (s), 126.5 (s), 115.6 (dd, *J* = 7, 3 Hz), 52.9 (s) ppm. $C_{14}H_9F_3O_2$ (266.10): calcd. C 63.16, H 3.41; found C 63.11, H 3.43.

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[1] M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3975−3984.
[2] H. H. Büker, N. M. M. Nibbering, D. Espinosa, F. Mongin, M. Schlosser, *Tetrahedron Lett.* **1997**, 8519−8522.
[3] M. Schlosser, in: *Organometallics in Synthesis: A Manual* (Ed.: M. Schlosser), 2nd ed., Wiley, Chichester, **2002**, pp. 1−352, spec. 262−265.
[4] F. Mongin, A. Tognini, F. Cottet, M. Schlosser, *Tetrahedron Lett.* **1998**, *39*, 1749−1752.
[5] T. Rausis, M. Schlosser, *Eur. J. Org. Chem.*, **2002**, 3351−3358.
[6] T. Iida, T. Wada, K. Tomimoto, T. Mase, *Tetrahedron Lett.* **2001**, *42*, 4841−4844.
[7] A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333−4339.
[8] J. Kondo, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem.* **2001**, *113*, 2146−2148; *Angew. Chem. Int. Ed.* **2001**, *40*, 2085−2087.
[9] N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *17*, 513−519.
[10] A. Suzuki, *Pure Appl. Chem.* **1994**, *66*, 213−222.
[11] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457−2483.
[12] K. Ziegler, F. Crössmann, H. Kleinert, O. Schäfer, *Justus Liebigs Ann. Chem.* **1929**, *473*, 1−35, spec. 20.
[13] H. Metzger, E. Müller, in: *Houben-Weil: Methoden der organischen Chemie* (Ed.: E. Müller), Thieme, Stuttgart, **1959**, vol. *1/2*, pp. 321−384, spec. 337−338.
[14] M. Schlosser, J. Porwisiak, F. Mongin, *Tetrahedron* **1998**, *54*, 895−900.
[15] Q. Wang, H.-x. Wei, M. Schlosser, *Eur. J. Org. Chem.* **1999**, 3263−3268.
[16] C. Bobbio, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 4533−4536.
[17] F. Mongin, E. Marzi, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 2771−2777.
[18] M. Weidenbruch, G. Abrotat, K. John, *Chem. Ber.* **1971**, *104*, 2124−2133.

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