

Fluorine-Flanked Congested Sites: Minimal, Though Perceptible Buttressing Effects on the Proton Mobility of Arenes

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(2,6-Difluorophenyl)trimethylsilane, -triethylsilane and -triisopropylsilane undergo *sec*-butyllithium-mediated metalation at the 3- and 4-position (*ortho* and *meta* relative to the halogen) in ratios of 99.6:0.4, 98:2 and 95:5, respectively. The steric pressure transmitted by the fluorine atoms can be increased if the trialkylsilyl group is locked up on the other side by a relatively voluminous substituent. Whereas (2,6-di-

fluorophenyl)triethylsilane is attacked by lithium 2,2,6,6-tetramethylpiperidide under deprotonation of the 4- and 5-position in a ratio of 99.4:0.6, the proportion of "*ortho*" / "*meta*" metalation changes to 84:16 when (2-bromo-6-fluorophenyl)-triethylsilane acts as the substrate.

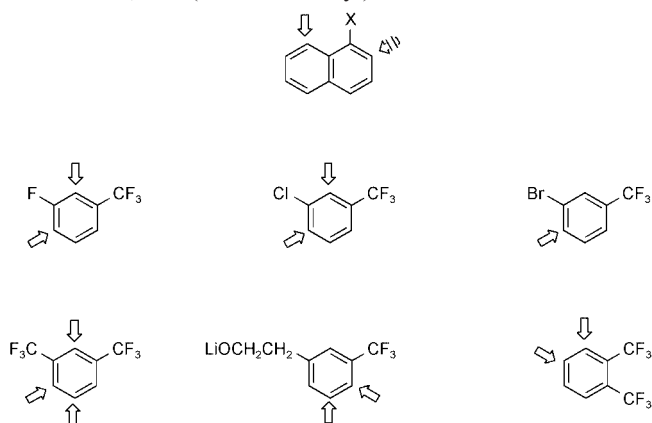
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Introduction

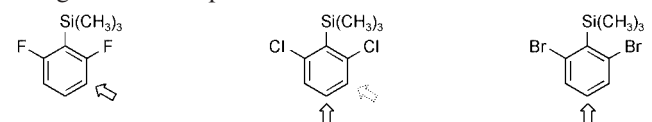
Halobenzenes, anisoles and other electronegatively substituted arenes or heterocycles are known to react with alkylolithium reagents under permutational hydrogen/metal interconversion at a position adjacent to the heteroatom or hetero group.^[1] The "directed *ortho* metalation" (a somewhat distorted translation of G. Wittig's "gezielte *ortho*-Metallierung") has become a most popular and even irreplaceable tool for synthetically oriented work in the field of aromatic chemistry.

Exceptions to the *ortho* rule have so far passed almost unnoticed. Naphthalenes carrying strongly coordinating, but poorly electron-withdrawing substituents such as lithiooxy,^[2] dialkylamino^[3,4] or dialkylaminomethyl^[5] at the α -position are deprotonated preferentially or even exclusively at the *peri*- rather than the β -position. Depending on the base employed, 3-fluorobenzotrifluoride^[6] and 3-chlorobenzotrifluoride^[7] are attacked either at the doubly activated 2-position or at the sterically uncongested 4-position whereas 3-bromobenzotrifluoride^[7] reacts solely at the latter site when treated with a lithium dialkylamide. 1,3-Bis-(trifluoromethyl)benzene displays a unique acidity profile as it is metalated by the superbasic mixture of butyllithium and potassium *tert*-butoxide (LIC + KOR = LIC-KOR)^[8] or, better, lithium 2,2,6,6-tetramethylpiperidide (LITMP) in the presence of potassium *tert*-butoxide^[9] at the 2-position, by *sec*-butyllithium in the presence of *N,N,N',N'',N'''*-

pentamethylethylenediamine (PMDTA)^[8] or, better, LITMP alone,^[9] at the 4-position and by *tert*-butyllithium^[8] in tetrahydropyran (rather than in the standard solvent tetrahydrofuran) concomitantly at the 4-position and – *sic!* – 5-position. Simultaneous proton abstraction from the 4- and 5-position was also observed with lithium 2-(3-trifluoromethylphenyl)ethoxide^[10] and from the 3- and 4-position with 1,2-bis(trifluoromethyl)benzene.^[9]



We came recently across a novel and totally unexpected deviation from the ordinary regioselectivity of metalation. Unlike (2,6-difluorophenyl)trimethylsilane, which was smoothly metalated at the 3-position,^[11] the chloro and bromo analogs were mainly or exclusively substituted at the halogen-remote 4-position.^[12]



At the moment we suspect a special "buttressing effect"^[13,14] to operate. Hypotheses about its origin, nature

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and implications are still tentative.^[15,16] To gain more insight, one first has to explore the scope of the phenomenon.

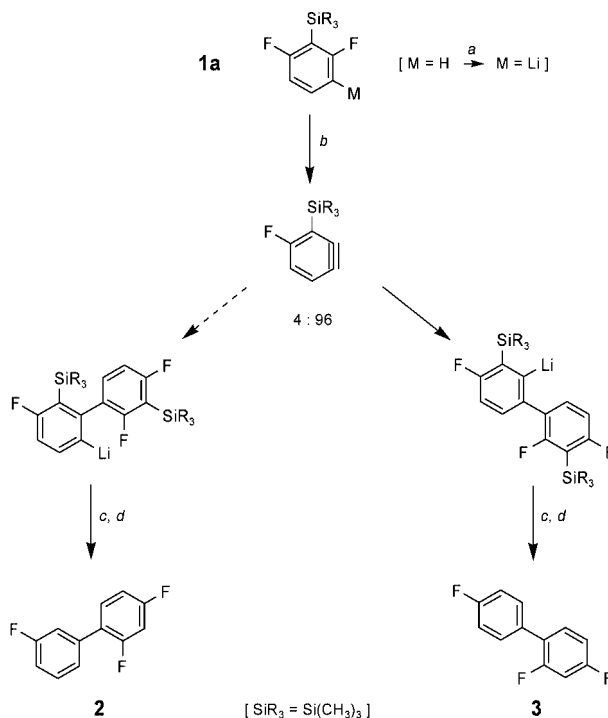
As previously reported,^[11] the consecutive treatment of (2,6-difluorophenyl)trimethylsilane with *sec*-butyllithium and standard electrophiles afforded 3-substituted products in approximate yields of 90%. The deprotonation of the fluorine-adjacent position (“*ortho* metalation”) caused no surprise as the smallest halogen should be inefficient as a transmitter of steric pressure. We nevertheless decided to revisit this reaction and extend our investigations in two directions. We wanted to vary the emitter of the buttressing effect by including also (2,6-difluorophenyl)triethylsilane and (2,6-difluorophenyl)triisopropylsilane into our study and to use high-performance gas chromatography to search for 4-substituted products (emanating from “*meta* metalation”) possibly formed in minor or even just trace amounts.

Results

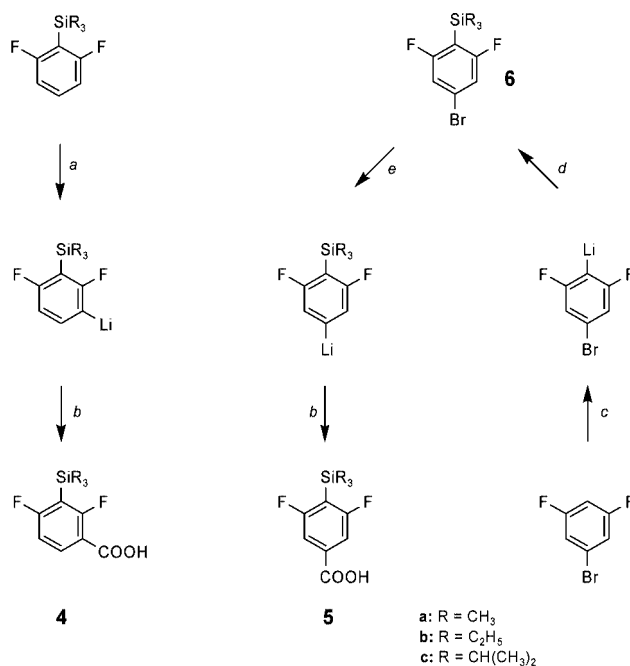
In view of the thermal lability of *ortho*-lithiated (2,6-dichlorophenyl)trimethylsilane,^[17] we first tested the temperature sensitivity of lithiated (2,6-difluorophenyl)trimethylsilane (**1a**), (2,6-difluorophenyl)triethylsilane (**1b**) and (2,6-difluorophenyl)triisopropylsilane (**1c**). All three proved to be perfectly stable at -75°C , whereas slow decomposition started at -50°C and became fast above -25°C . On one hand, the organometallic intermediate abstracted protons from the solvent and, on the other hand, it eliminated lithium fluoride. The aryne thus set free was immediately intercepted by the lithiated species which had served as its precursor. In this way, silane **1a** gave, after metalation with *sec*-butyllithium at -75°C and temperature raise to -50°C followed by neutralization, a 4:96 mixture of two regioisomeric adducts which were converted into 2,3',4'- and 2,4,4'-trifluorobiphenyl (**2** and **3**; isolated in a combined yield of 50%) by protodesilylation. The structure assignment is based on a comparison of retention times and spectroscopic data with authentic samples independently and unambiguously prepared by Suzuki–Miyaura coupling (see the Exp. Sect.).

Next we made authentic samples of the acids **4** and **5** carrying the functional group at a fluorine-adjacent or fluorine-remote position. The “*ortho* isomers” **4** were simply isolated by crystallization after direct metalation of the silanes **1** and subsequent carboxylation. The “*meta* isomers” **5** were independently prepared starting from 1-bromo-3,5-difluorobenzene which was selectively^[18] lithiated and converted into the silanes **6** before being subjected to a heavy halogen/metal permutation and carboxylation.

Thus, the stage was set for systematically probing the regioselectivity of the deprotonation of silanes **1**. A variety of bases were examined (see Table 1). The acids, which formed in high yields (typically 85–95%), were converted into the more volatile methyl esters by treatment with diazomethane before the **4/5** (“*ortho*”/“*meta*”) ratios were assessed gas chromatographically. As the juxtaposition (see Table 1) re-



a: *sec*-Butyllithium in tetrahydrofuran (THF) at -75°C . *b*: Temperature raise to -50°C . *c*: Water. *d*: Tetrabutylammonium fluoride (TBAF) hydrate in *N,N*-dimethylformamide (DMF) at 100°C for 24 h.



a: *sec*-Butyllithium in THF at -75°C . *b*: (1.) Carbon dioxide; (2.) hydrochloric acid. *c*: Lithium diisopropylamide (LIDA) in THF at -75°C . *d*: Chlorotrimethylsilane, chlorotriethylsilane or chlorotriisopropylsilane. *e*: Butyllithium in diethyl ether (DEE) at -75°C .

veals, very little (1–2%) attack occurred at the halogen-remote 5-position when *sec*-butyllithium or lithium 2,2,6,6-tetramethylpiperidide (LITMP) was employed to accomplish the deprotonation of the (2,6-difluorophenyl)trimethylsilane (**1a**) or the triethyl analog **1b**. The proportions of the acid **5** in the product mixture increased noticeably when the triisopropylsilane **1c** acted as the substrate but remained nevertheless small (approx. 5%). Other reagents produced rather minor variations of the **4/5** ratios. This holds true even for potassium-containing reagents such as the LIC-KOR superbase (butyllithium in the presence of potassium *tert*-butoxide) which had exhibited a marked preference for proton abstraction from the halogen-remote position in the trialkyl(2,6-dichlorophenyl)silane series.^[17]

Table 1. Consecutive reaction of trialkyl(2,6-difluorophenyl)silanes **1a–1c** with various bases and dry ice: Ratio of benzoic acids **4/5** resulting from the attack on a halogen-adjacent or halogen-remote position.

Base	a: R = CH ₃	b: R = C ₂ H ₅	c: R = <i>i</i> C ₃ H ₇
LiC ₄ H ₉	–	98.6:1.4	–
LiCH(CH ₃)C ₂ H ₅	99.6:0.4	98.0:2.0	95.1:4.9
LiC(CH ₃) ₃	–	95.6:4.4	–
LIC-KOR	–	96.1:3.9	–
LITMP	99.7:0.3	98.4:1.6	96.3:3.7
LITMP + PMDTA ^[a]	–	97.7:2.3	–
Faigl mix ^[b]	–	97.9:2.1	–

[a] LITMP + PMDTA = lithium 2,2,6,6-tetramethylpiperidide and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine. [b] Faigl mix = LITMP + PMDTA + KOR (potassium *tert*-butoxide).

Two options exist to further foster the chances of “*meta* metalation”. One could subject the most congested silane **1c** to the action of a particularly bulky reagent such as *tert*-

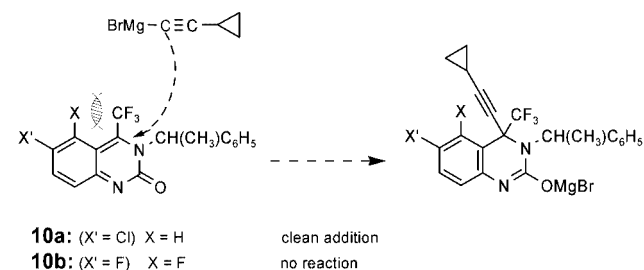
butyllithium or mesityllithium. Alternatively, one could indirectly increase the size of the silyl group by replacing one of the fluorine atoms with a more voluminous (but less acidifying) substituent and in this way lock up the silyl entity. We have explored the latter possibility. When (2-bromo-6-fluorophenyl)triethylsilane (**7**) was consecutively lithiated (using LITMP), carboxylated and protodesilylated, 4-bromo-2-fluorobenzoic acid (**8**) and 3-bromo-5-fluorobenzoic acid (**9**) were obtained in an 84:16 ratio and a 90% combined yield.

Conclusions

As the present study has revealed, buttressing effects manifest themselves only marginally, although perceptively, when fluorine operates as the transmitter of steric pressure. Depending on the specific trialkyl(2,6-difluorophenyl)silane employed as the substrate and on the bulkiness of the metalating agent the fluorine-adjacent (“*ortho*”) and fluorine-remote (“*meta*”) position are attacked in ratios ranging from 99.5:0.5 to 95:5.

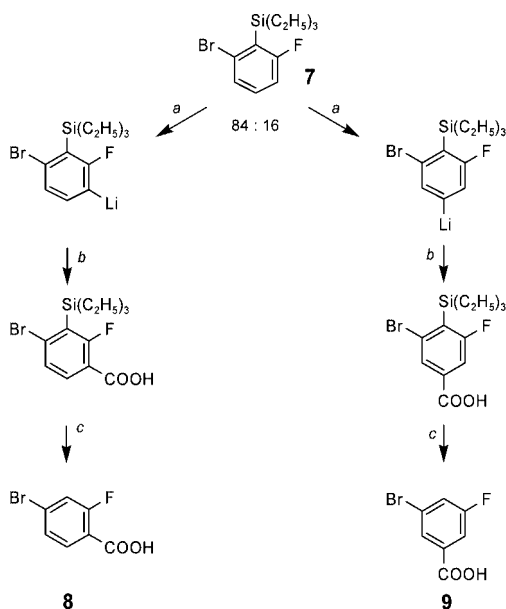
If the trialkylsilyl group is locked up on one side by a relatively large substituent, its buttressing potential is enhanced. Due to such a relay amplification of steric pressure, (2-bromo-6-fluorophenyl)triethylsilane undergoes LITMP-promoted lithiation at the 5- and 4-position (“*ortho*” vs. “*meta*” with respect to fluorine) in a 5:1 ratio, whereas the 2,6-difluoro analog shows a 60:1 ratio.

Buttressing effects on chemical reactivity may not be restricted to rates of deprotonation, the mode of reaction that has led to their discovery. It may be rewarding to look out for such effects also in different areas. For example, no rationale is yet available to explain why 4-trifluoromethyl-3-(1-phenylethyl)-3H-quinazolin-2-ones react smoothly with cyclopropylethynylmagnesium bromide when the 5-position is vacant (as in **10a**) and not at all when it is occupied by a fluorine substituent (as in **10b**).^[19]



Experimental Section

1. Generalities: Starting materials, if commercial, were purchased from Aldrich-Fluka (9479 Buchs, Switzerland), Acros Organics (2440 Geel, Belgium) and Apollo (Whaley Bridge, SK23 7LY, UK). They were 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 Calery (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 diphenylketyl (benzophenone/sodium "radical anion") had been found to persist.^[20,21] Ethereal or other organic extracts were dried by washing with brine and subsequent 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 that all attempts had failed to crystallize the liquid at temperatures down to -75 °C. 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 the 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 size was 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 case of programmed temperature increase, a constant rate of 10 °C/min was applied. The stationary phases employed are encoded as HP-5, DB-1, OV-17 or SE-30 (of the silicone type), DEGS or DBS (both of the polyester type), AP-L (Apiezon-L hydrocarbon), C-20M, DB-WAX or DB-FFAP (all belonging to the polyethylene glycol family) and PFO-XR75 (perfluoropolyethylene type). ¹H and ¹³C NMR spectra were recorded of samples, dissolved in deuteriochloroform, at 400 and 101 MHz, respectively. Chemical shifts δ refer to the signal of tetramethylsilane (δ = 0.00 ppm). Coupling constants *J* are given in Hz and coupling patterns are, for example, abbreviated as q (quadruplet), quint (quintuplet), sext (sextuplet), sept (septuplet), oct (octuplet), non (nonuplet), td (triplet of doublets) and m (multiplet). Elementary analyses were executed by the laboratory of I. Beetz (96301 Kronach, Germany) or by Solvias Analytik (4058 Basel, Switzerland). The expected percentages were calculated using the atomic weight numbers listed in the 1999 IUPAC recommendations.

1. Starting Materials and Compounds for Comparison

a) Silanes

(2,6-Difluorophenyl)trimethylsilane (**1a**) and (2,6-difluorophenyl)triethylsilane (**1b**) have been reported previously.^[11]

(2,6-Difluorophenyl)triisopropylsilane (1c): 1,3-Difluorobenzene (9.0 mL, 11 g, 0.10 mol) was added to a solution of *sec*-butyllithium (0.10 mol) in cyclohexane (60 mL) and tetrahydrofuran (0.14 L) cooled in a methanol/dry ice bath. After 45 min at -75 °C, chlorotriisopropylsilane (21 mL, 19 g, 0.10 mol) was added to the reaction mixture. Direct distillation afforded a colorless oil; b.p. 80–82 °C/3 Torr; n_D^{20} = 1.5832; d_4^{20} = 0.998; yield: 23.3 g (86%). ¹H NMR: δ = 7.3 (m, 1 H), 6.83 (t, *J* = 8.0 Hz, 2 H), 1.54 (sept, *J* = 8.0 Hz, 3 H), 1.08 (d, *J* = 8.0 Hz, 18 H) ppm. ¹³C NMR: δ = 167.6 (dd, *J* = 245, 18 Hz), 132.0 (t, *J* = 12 Hz), 111.1 (symm. m), 109.5 (t, *J* = 36 Hz), 18.8 (s, 6 C), 12.3 (t, *J* = 3 Hz, 3 C) ppm. C₁₅H₂₄F₂Si (270.44): calcd. C 66.62, H 8.95; found C 66.31, H 8.72.

(4-Bromo-2,6-difluorophenyl)trimethylsilane (6a): Diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and 1-bromo-3,5-difluorobenzene (9.6 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (70 mL) kept in a dry ice/methanol bath. After 2 h at -75 °C, the mixture was treated with chlorotrimethylsilane (6.4 mL, 5.4 g, 50 mmol). Immediate distillation gave a colorless oil; b.p. 57–58 °C/2 Torr; n_D^{20} = 1.4975; d_4^{20} = 1.413; yield: 12.3 g (93%). ¹H NMR: δ = 6.99 (d, *J* = 6.8 Hz, 2 H), 0.35 (t, *J* = 1.5 Hz, 9 H) ppm. ¹³C NMR: δ = 167.0 (dd, *J* = 248, 18 Hz), 123.9 (t, *J* = 13 Hz), 120.1 (dd, *J* = 31, 3 Hz), 112.9 (t, *J* = 35 Hz), 0.1 (t, *J* = 3 Hz, 3 C) ppm. C₉H₁₁BrF₂Si (265.17): calcd. C 40.77, H 4.18; found C 41.25, H 4.05.

(4-Bromo-2,6-difluorophenyl)triisopropylsilane (6c): Prepared analogously but using chlorotriisopropylsilane (11 mL, 9.6 g, 50 mmol) as the reagent. Upon direct distillation, a colorless oil was obtained; b.p. 96–99 °C/0.4 Torr; n_D^{20} = 1.4745; d_4^{20} = 1.302; yield: 15.0 g (86%). ¹H NMR: δ = 7.03 (d, *J* = 7.0 Hz, 2 H), 1.52 (sept, *J* = 7.2 Hz, 3 H), 1.08 (d, *J* = 7.8 Hz, 18 H) ppm. ¹³C NMR: δ = 167.4 (dd, *J* = 247, 18 Hz), 123.9 (t, *J* = 15 Hz), 115.2 (dd, *J* = 33, 4 Hz), 109.0 (t, *J* = 56 Hz), 18.6 (s, 6 C), 12.1 (t, *J* = 3 Hz, 3 C) ppm. C₁₅H₂₃BrF₂Si (349.33): calcd. C 51.57, 6.64; found C 51.51, H 6.34.

(2-Bromo-6-fluorophenyl)triethylsilane (7): Diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and 1-bromo-3-fluorobenzene (5.1 mL, 8.7 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 chlorotriethylsilane (8.5 mL, 7.5 g, 50 mmol) before, after 45 min at -75 °C, being evaporated and distilled under reduced pressure; b.p. 80–82 °C/1 Torr; n_D^{20} = 1.5282; d_4^{20} = 1.413; yield: 13.0 g (90%). ¹H NMR (CDCl₃, 300 MHz): δ = 7.35 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.16 (td, *J* = 8.1, 2.1 Hz, 1 H), 6.93 (td, *J* = 9.4, 1.1 Hz, 1 H), 1.0 (m, 15 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 168.0 (d, *J* = 246 Hz), 131.7 (d, *J* = 13 Hz), 130.6 (d, *J* = 3 Hz), 129.6 (s), 125.2 (d, *J* = 34 Hz), 114.3 (d, *J* = 29 Hz), 7.5 (s), 4.5 (s) ppm. C₁₂H₁₈BrFSi (289.24): calcd. C 49.83, H 6.27; found C 49.76, H 6.22.

b) Biphenyls

2,3',4'-Trifluorobiphenyl (2): 3-Fluorophenylboronic acid (1.4 g, 10 mmol), 2,4-difluoro-1-iodobenzene (1.3 mL, 2.4 g, 10 mmol), tetrakis(triphenylphosphane)palladium(0) (0.34 g, 0.30 mmol), benzene (10 mL) and a 2.0 M aqueous solution of sodium carbonate (10 mL, 20 mmol) were stirred vigorously at +25 °C for 12 h. Then a 33% aqueous solution of hydrogen peroxide (10 mL) was

added, and stirring continued at +25 °C for further 45 min. The organic layer was decanted and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried and the solvents evaporated. Crystallization from hexanes gave small colorless needles; m.p. 37–39 °C (ref.^[22] 40 °C); yield: 1.95 g (94%). ¹H NMR: δ = 7.4 (m, 3 H), 7.2 (m, 2 H), 7.07 (tm, *J* = 8.6 Hz, 1 H), 6.9 (m, 1 H) ppm.

2,4,4'-Trifluorobiphenyl (3): As described in the preceding paragraph, but starting from 4-fluorophenylboronic acid (1.4 g, 10 mmol) and 2,4-difluoro-1-iodobenzene (2.4 g, 10 mmol); colorless needles; m.p. 81–83 °C (from methanol; ref.^[23–25] 83 °C); yield: 1.83 g (88%). ¹H NMR: δ = 7.5 (m, 2 H), 7.35 (dd, *J* = 8.9, 2.3 Hz, 1 H), 7.12 (tm, *J* = 8.5 Hz, 2 H), 6.9 (m, 2 H) ppm.

c) Carboxylic Acids

2,4-Difluoro-3-(triethylsilyl)benzoic acid (**4b**) and 3,5-difluoro-4-(triethylsilyl)benzoic acid (**5b**) have been described previously.^[11] All benzoic acids were converted into the more volatile methyl esters for gas chromatographic analysis by treatment with an excess of ethereal diazomethane.

2,4-Difluoro-3-(trimethylsilyl)benzoic Acid (4a): At dry ice temperature, (2,6-difluoro-phenyl)trimethylsilane (**1a**; 4.5 mL, 4.6 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (20 mL) and tetrahydrofuran (30 mL). After 45 min at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice before being acidified with 2.0 M hydrochloric acid (20 mL) and extracted with ethyl acetate (3 × 25 mL). One tenth of the organic solution was treated with an ethereal solution of diazomethane. According to gas chromatographic analysis (30 m, DB-WAX, 200 °C; 30 m, DB-1, 200 °C; internal calibrated standard: tridecane), the raw material contained the acids **4a** and **5a** in the ratio of 99.4: 0.6. The rest of the organic solution was concentrated and the solid residue thus obtained was crystallized from hexanes (10 mL); colorless needles; m.p. 124–126 °C; yield: 5.29 g (92%). ¹H NMR: δ = 8.04 (ddd, *J* = 8.6, 6.7, 1.9 Hz, 1 H), 6.89 (t, *J* = 8.6 Hz, 1 H), 0.40 (t, *J* = 1.6 Hz, 9 H) ppm. ¹³C NMR: δ = 171.0 (dd, *J* = 249, 16 Hz), 168.0 (dd, *J* = 256, 17 Hz), 166.1 (d, *J* = 4 Hz), 137.3 (dd, *J* = 11, 3 Hz), 117.1 (dd, *J* = 14, 4 Hz), 116.2 (t, *J* = 35 Hz), 113.1 (dd, 27, 4 Hz), 1.10 (t, *J* = 3 Hz, 3 C) ppm. C₁₀H₁₂F₂O₂Si (230.28): calcd. C 52.16, H 5.25; found C 51.87, H 5.20. When lithium 2,2,6,6-tetramethylpiperidide was used as the base under the same reaction conditions, the acids **4a** and **5a** were obtained in the ratio 99.7:0.3. Upon crystallization from hexanes (10 mL), the acid **4a** was obtained in a yield of 5.06 g (88%).

2,4-Difluoro-3-(triisopropylsilyl)benzoic Acid (4c): Prepared analogously from (2,6-difluorophenyl)triisopropylsilane (**1c**; 6.8 mL, 6.8 g, 25 mmol). As revealed by gas chromatography (30 m, DB-WAX, 220 °C; 30 m, DB-1, standard: tridecane), the reaction mixture contained the acids **4c** and **5c** in the ratio of 95.1:4.9. Crystallization from hexanes (10 mL) afforded colorless needles; m.p. 161–163 °C; yield: 6.91 g (88%). ¹H NMR: δ = 8.10 (dd, *J* = 8.9, 2.2 Hz, 1 H), 6.95 (t, *J* = 8.5 Hz, 1 H), 1.59 (sept, *J* = 7.5 Hz, 3 H), 1.12 (d, *J* = 7.5 Hz, 18 H) ppm. ¹³C NMR: δ = 170.9 (dd, *J* = 252, 18 Hz), 169.3 (d, *J* = 2 Hz), 167.8 (dd, *J* = 261, 18 Hz), 135.9 (dd, *J* = 29, 2 Hz), 113.9 (dd, *J* = 19, 3 Hz), 111.4 (d, *J* = 12 Hz), 18.7 (s, 6 C), 12.2 (t, *J* = 3 Hz, 3 C) ppm. C₁₆H₂₄F₂O₂Si (314.44): calcd. C 61.11, H 7.69; found C 61.05, H 7.47. When lithium 2,2,6,6-tetramethylpiperidide was used as the base under the same reaction conditions, the acids **2c** and **3c** were obtained in the ratio of 96.3:3.7. Crystallization from hexanes (10 mL) gave the acid **2c** in a yield of 6.52 g (83%).

3,5-Difluoro-4-(trimethylsilyl)benzoic Acid (5a): (4-Bromo-2,6-difluorophenyl)trimethylsilane (**6a**; 4.7 mL, 6.6 g, 25 mmol) was

added to a solution of butyllithium (25 mmol) in hexanes (16 mL) and diethyl ether (35 mL) kept in a dry ice/methanol bath. After 15 min at –75 °C, the reaction mixture was poured onto freshly crushed dry ice before being acidified with an ethereal solution (15 mL) of hydrogen chloride. 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 acid **5a** was crystallized from hexanes (10 mL); colorless needles; m.p. 138–140 °C; yield: 5.35 g (94%). ¹H NMR: δ = 7.51 (d, *J* = 7.7 Hz, 2 H), 0.40 (t, *J* = 1.5 Hz, 9 H) ppm. ¹³C NMR: δ = 168.4 (dd, *J* = 243, 15 Hz), 166.4 (t, *J* = 10 Hz), 137.0 (t, *J* = 10 Hz), 120.4 (t, *J* = 30 Hz), 113.5 (symm. m), 0.89 (t, *J* = 3 Hz, 3 C) ppm. C₁₀H₁₂F₂O₂Si (230.28): calcd. C 52.16, H 5.25; found C 51.86, H 5.19.

3,5-Difluoro-4-(triisopropylsilyl)benzoic Acid (5c): Prepared analogously from (4-bromo-2,6-difluorophenyl)triisopropylsilane (**6c**; 6.7 mL, 8.7 g, 25 mmol); colorless needles; m.p. 169–171 °C (from hexanes); yield: 7.38 g (94%). ¹H NMR: δ = 7.53 (d, *J* = 8.3 Hz, 2 H), 1.56 (sept, *J* = 7.3 Hz, 3 H), 1.09 (d, *J* = 7.4 Hz, 18 H) ppm. ¹³C NMR: δ = 169.0 (dd, *J* = 244, 16 Hz), 166.0 (t, *J* = 3 Hz), 166.5 (t, *J* = 36 Hz), 137.2 (t, *J* = 10 Hz), 113.9 (dd, *J* = 31, 3 Hz), 19.8 (s, 6 C), 13.7 (t, *J* = 3 Hz, 3 C) ppm. C₁₆H₂₄F₂O₂Si (314.44): calcd. C 61.11, H 7.69; found C 61.04, H 7.44.

4-Bromo-2-fluorobenzoic Acid (8): A solution of butyllithium (10 mmol) in hexanes (6.0 mL) and a solution of 1,4-dibromo-5-fluorobenzene (3.8 g, 15 mmol) in tetrahydrofuran (5.0 mL) were added consecutively to a solution of butylmagnesium chloride (5.0 mmol) in tetrahydrofuran (25 mL) cooled in a dry ice/ethanol bath. After 45 min at 0 °C, the reaction mixture was poured onto freshly crushed dry ice. It was acidified with 2.0 M hydrochloric acid (10 mL) and extracted with diethyl ether (3 × 15 mL). After drying with sodium sulfate and concentration of the combined organic layers, the acid **2** crystallized as small colorless needles; m.p. 209–210 °C; yield: 2.95 g (90%). ¹H NMR (CDCl₃, 300 MHz): δ = 7.91 (t, *J* = 8.5 Hz, 1 H), 7.4 (m, 2 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 163.7 (d, *J* = 4 Hz), 162.1 (d, *J* = 263 Hz), 133.6 (d, *J* = 1 Hz), 127.6 (d, *J* = 4 Hz), 127.2 (d, *J* = 10 Hz), 120.4 (d, *J* = 26 Hz), 118.2 (d, *J* = 8 Hz) ppm. C₇H₄BrFO₂ (219.01): calcd. C 38.39, H 1.84; found C 38.19, H 1.81.

3-Bromo-5-fluorobenzoic Acid (9): Prepared analogously from 1,3-dibromo-5-fluorobenzene (3.8 g, 15 mmol); colorless needles; m.p. 141–143 °C (from hexanes); yield: 2.92 g (89%). ¹H NMR (CDCl₃, 300 MHz): δ = 8.06 (s, 1 H), 7.73 (ddd, *J* = 8.5, 2.3, 1.3 Hz, 1 H), 7.51 (td, *J* = 7.7, 1.9 Hz, 1 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 164.5 (d, *J* = 3 Hz), 161.8 (d, *J* = 250.9 Hz), 134.3 (d, *J* = 7 Hz), 128.5 (d, *J* = 3 Hz), 123.6 (d, *J* = 25 Hz), 122.3 (d, *J* = 10 Hz), 115.1 (d, *J* = 23 Hz) ppm. C₇H₄BrFO₂ (219.01): calcd. C 38.39, H 1.84; found C 38.25, H 1.90.

2. Thermal Decomposition of 3-Lithiated (2,6-Difluorophenyl)tri-methylsilane

(2,6-Difluorophenyl)trimethylsilane (**1a**, 9.0 mL, 9.3 g, 50 mmol) was added to a solution of *sec*-butyllithium (50 mmol) in cyclohexane (40 mL) and tetrahydrofuran (60 mL) cooled in a dry ice/methanol bath. After 45 min at –75 °C, the reaction mixture was kept at –50 °C for 12 h before methanol (2.1 mL, 1.9 g, 60 mmol) was added. According to gas chromatographic analysis (30 m, DB-1, 50 °C; 1 m, SE-30, 5%, 50 °C; nonane as the internal calibrated standard), the crude reaction mixture contained 46% of (2,6-difluorophenyl)trimethylsilane (**1a**). The solvents were evaporated and the residue was extracted with hexanes (3 × 50 mL). After evaporation of the solvents, a yellowish oil was collected (9.23 g). Distillation under reduced pressure gave 3.44 g (37%) of (2,6-difluoro-

rophenyl)trimethylsilane (**1a**) as a colorless liquid; b.p. 35–37 °C/6 Torr (ref.^[26] 75 °C/30 Torr) and as a second fraction, a slightly yellowish oil (4.75 g). According to gas chromatography (1 m, PFO-XR75, 130 °C; 1 m, C-20M, 180 °C; 2,2',6,6'-tetrabromobiphenyl as the internal calibrated standard), the latter was composed of two products in a 4:96 ratio (4.40 g). A major part of the second fraction (2.6 g, 7.5 mmol) was heated with an excess of tetrabutylammonium fluoride trihydrate (4.7 g, 15 mmol) in dimethylformamide (50 mL) at +100 °C for 24 h. Water (20 mL) was added and the reaction mixture was extracted with hexanes (3 × 50 mL). The two products obtained in a 4:96 ratio were identified as 2,3',4-trifluorobiphenyl (**5**) and 2,4,4'-trifluorobiphenyl (**6**) (2 m, PFO-XR75, 130 °C; 2 m, C-20M, 150 °C, standard: 2,2',6,6'-tetrabromobiphenyl). Distillation under reduced pressure afforded 1.56 g (30%) of the biphenyls **5** and **6**, again in the ratio of 4:96; b.p. 94–97 °C/0.8 Torr.

3. Isomers Formed upon Consecutive Metalation and Carboxylation of *ortho*-Fluorophenylsilanes

a) Trialkyl(2,6-difluorophenyl)silanes **1a–1c** as the Substrates

Trialkyl(2,6-difluorophenyl)silane (25 mmol) was added to a solution containing *sec*-butyllithium (25 mmol) or lithium 2,2,6,6-tetramethylpiperidide (prepared from butyllithium and 2,2,6,6-tetramethylpiperidine, each 25 mmol) in a paraffinic hydrocarbon (20 mL) and tetrahydrofuran (30 mL) cooled in a dry ice/methanol bath. After 45 min at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice and the residue, after evaporation of the volatiles, acidified with a 2.0 M hydrochloric acid (10 mL) before being extracted with ethyl acetate (3 × 25 mL). An aliquot was treated with an ethereal solution of diazomethane until the yellow color persisted. The esters formed were identified by gas chromatography (30 m, DB-1, 180 °C; 30 m, DB-WAX, 180 °C). The yields of the products formed were quantified by comparison of the peak areas with that of an internal standard (tridecane, 1 mmol) and corrected by means of independently determined calibration factors.

b) (2-Bromo-6-fluorophenyl)triethylsilane (**7**) as the Substrate

2,2,6,6-Tetramethylpiperidine (2.5 mL, 2.1 g, 15 mmol) and the silane **7** (3.0 mL, 4.3 g, 15 mmol) were added consecutively to a solution of butyllithium (15 mmol) in hexanes (10 mL) and tetrahydrofuran (20 mL) cooled in a dry ice/methanol bath. After 2 h at –75 °C, the reaction mixture was poured onto freshly crushed dry ice, concentrated, acidified with 2.0 M hydrochloric acid (10 mL) and extracted with ethyl acetate (3 × 15 mL). The yellowish oil obtained after the concentration of the combined organic layers (4.8 g) was treated with tetrabutylammonium fluoride hydrate (19 g, 60 mmol) in refluxing *N,N*-dimethylformamide (20 mL) for 12 h. The reaction mixture was diluted with 2.0 M hydrochloric acid (20 mL) and extracted with diethyl ether (3 × 20 mL). Evaporation of the volatiles gave a colorless solid; yield: 3.03 g (90%). According to gas chromatography (30 m, HP-5 methylsiloxane, 150 °C; tridecane as the internal calibrated standard), the raw material contained the acids **2** (76%) and **3** (14%). When the same reaction was conducted in the presence of potassium *tert*-butoxide (1.7 g, 15 mmol), the acids **2** (80%) and **3** (6.4%) were obtained in slightly different ratios.

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