The Basicity Gradient-Driven Migration of Iodine: Conferring Regioflexibility on the Substitution of Fluoroarenes

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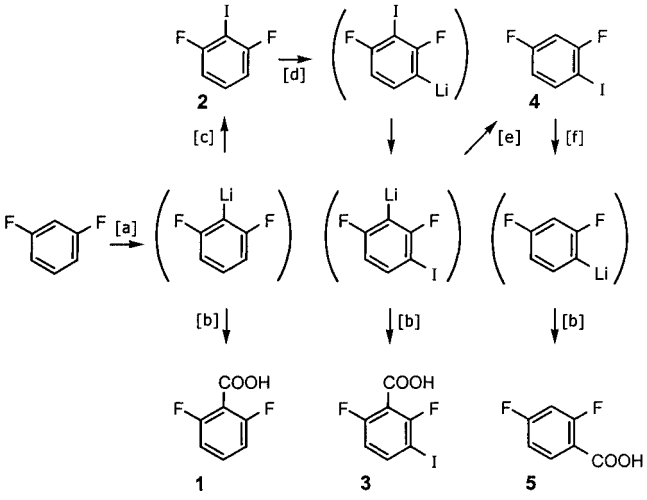
Six different fluoroarenes were submitted to the same transformations. Direct deprotonation with alkyllithium or lithium dialkylamide as reagents and subsequent carboxylation afforded the acids **1**, **6**, **11**, **16**, **18**, and **23**. If the aryllithium intermediate was trapped with iodine rather than with dry ice, an iodofluoroarene (**2**, **7**, **12**, **17**, **19**, and **24**) was formed. This, upon treatment with lithium diisopropylamide, underwent deprotonation and iodine migration. The resulting new aryllithium species was intercepted either by carboxylation, to give the acids **3**, **8**, **13**, **20**, and **25**, or by neutralization, to produce the iodofluoroarenes **4**, **9**, **14**, **21**, and **26**. The latter family of compounds was converted into another set of acids **5**, **10**, **15**, **22**, and **27** by subsequent treatment with butyllithium or isopropylmagnesium chloride and carbon dioxide.

A carbon-bound metal participating in a synthetic reaction sequence is equivalent to a joker in a card game, being replaceable by virtually anything. Under such circumstances, the principal skill required is to steer the metal to the targeted position. This task is trivial if this position happens to be the most acidic site, which can generally be efficaciously submitted to a hydrogen/metal permutation reaction with an alkyllithium or a lithium dialkylamide. However, depending on the substrate structure, it may prove quite challenging to attack any other position selectively. Among the strategies[1−2] developed to circumvent this obstacle, the basicity gradient-driven relocation of a heavy halogen and its subsequent replacement by a metal is a particularly attractive option. Its scope and limitations have been explored in the systematic investigation described below.

When treated with *sec*-butyllithium in tetrahydrofuran (THF) at −75 °C, 1,3-difluorobenzene was deprotonated exclusively at the doubly activated position flanked by the two halogens.[3] Carboxylation of the resulting organometallic intermediate produced 2,6-difluorobenzoic acid (**1**; 78%),[3] while iodolysis afforded 1,3-difluoro-2-iodobenzene (**2**; 98%). When the latter compound was exposed to lithium diisopropylamide (LIDA) in tetrahydrofuran, it underwent lithiation at a fluorine-adjacent site. The thus generated intermediate, however, could not be trapped as such. It instantaneously isomerized into a less basic species, which gave the 2,6-difluoro-3-iodobenzoic acid (**3;** 47% after purification by acid-catalyzed esterification with methanol, fractional distillation, and hydrolysis) upon carboxylation and 2,4-difluoro-1-iodobenzene (**4**; 48% after selective destruction of some unconsumed precursor **2** by addition of a small amount of butyllithium) upon hydrolysis, the latter compound being readily convertible into the 2,4-difluorobenzoic acid **5** (92%) by consecutive halogen/metal permutation and carboxylation. The poor yields observed are suggestive of extensive side reactions. These have been found to take place in related cases.[4]



[a] $LiCH(CH_3)C_2H_5$ in tetrahydrofuran (THF) at −75 °C. [b] (1.) CO_2, (2.) HCl. [c] I_2. [d] Lithium diisopropylamide (LIDA) in THF at −75 °C. [e] H_2O. [f] LiC_4H_9 in THF at −75 °C.

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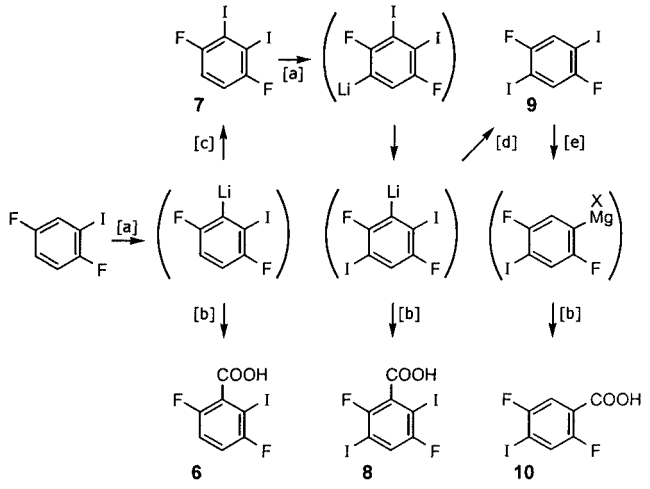
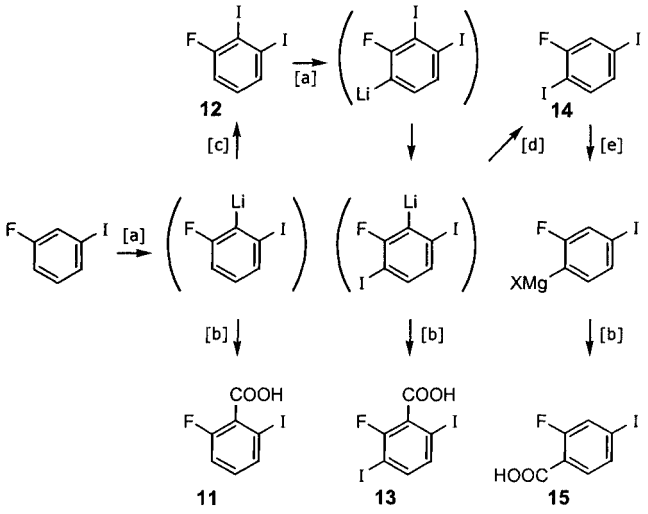
As pointed out previously,[5−8] the halogen migration mechanism does not involve short-lived *vic*-dehydrobenzenes ("arynes") but is rather mediated by incidentally formed small amounts of a halogen-richer species (1,3-difluoro-2,4-diiodobenzene in the given case), which act as a self-restoring turntable, promoting an incessant halogen/metal permutation. The results here provide additional evidence in favor of this plausible assumption, as the two sites involved in the exchange process are not neighboring, but remote from each other.

An analogous reaction sequence, although even less clean than the previous one, was accomplished when starting with 1,4-difluoro-2-iodobenzene. Deprotonation of this compound with lithium diisopropylamide and subsequent carboxylation or iodination afforded 3,6-difluoro-2-iodobenzoic acid (**6**; 38%) and 1,4-difluoro-2,3-diiodobenzene (**7**; 66%), respectively. The LIDA-promoted lithiation of the latter compound triggered the targeted iodine migration. The intermediate thus generated was carboxylated to give the 2,5-difluoro-3,6-diiodobenzoic acid **8** (31%); again after purification through the methyl ester followed by hydrolysis). The 1,4-difluoro-2,5-diiodobenzene (**9**; 45%) resulting from the hydrolytic quenching could easily be isolated as a pure compound. It was converted into the 2,5-difluoro-4-iodobenzoic acid **10** (83%) and into the acid **8** (80%) by halogen/metal permutation and by LIDA-mediated deprotonation, respectively, each followed by carboxylation.



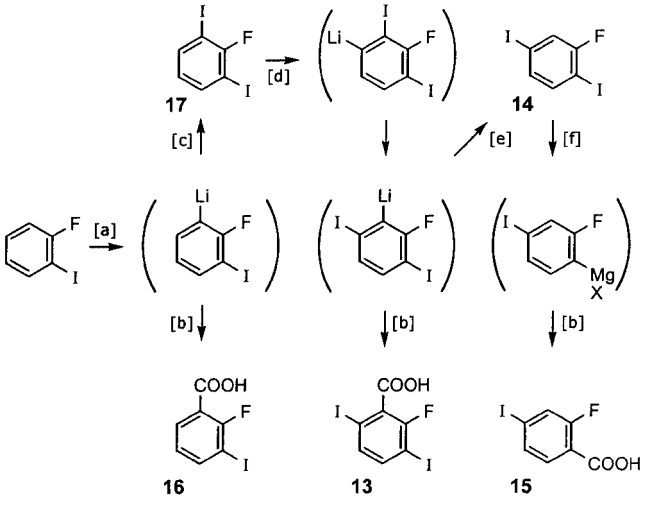
[a] LIDA in THF at −75 °C. [b] (1.) CO_2, (2.) HCl. [c] I_2. [d] H_2O. [e] $ClMgCH(CH_3)_2$ in THF at 0 °C [X = Cl or I].

1-Fluoro-3-iodobenzene was the starting point for a like series of transformations. The expected products − 2-fluoro-6-iodobenzoic acid (**11**; 95%), 1-fluoro-2,3-diiodobenzene (**12**; 92%), 2-fluoro-3,6-diiodobenzoic acid (**13**; 94%), 2-fluoro-1,4-diiodobenzene (**14**; 97%), and 2-fluoro-4-iodobenzoic acid (**15**; 96%) − were obtained in high yields. As expected,[9] the halogen/metal permutation step took place in a site-discriminating manner, the fluorine-adjacent iodine atom being removed exclusively.



[a] LIDA in THF at −75 °C. [b] (1.) CO_2, (2.) HCl. [c] I_2. [d] H_2O. [e] $ClMgCH(CH_3)_2$ in THF at 0 °C [X = Cl or I].

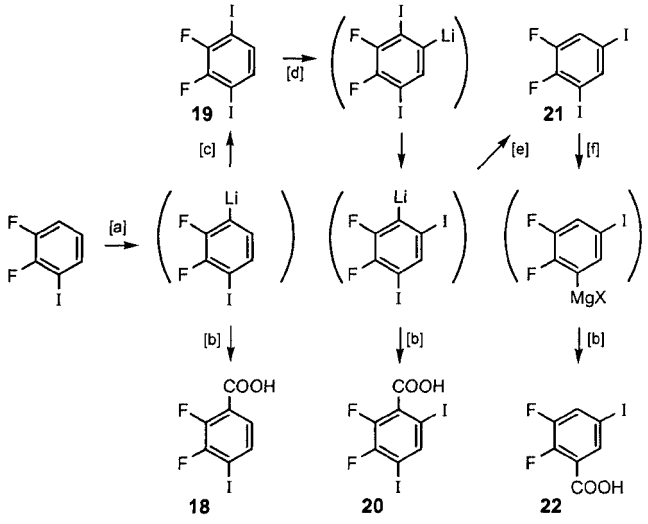
In all the examples presented so far, the halogen shuffling was unleashed by the lithiation of the substrate at a position *ortho* to a fluorine atom. Iodine being arguably the least acidifying electronegative substituent, deprotonation in its immediate vicinity should occur much more slowly than next to the smallest halogen. Consequently and in perfect agreement with the behaviour of 1-chloro-2-fluorobenzene[10] and 1-bromo-2-fluorobenzene,[10] 1-fluoro-2-iodobenzene exclusively gave 2-fluoro-3-iodobenzoic acid (**16**; 68%) when treated successively with LIDA and dry ice. 2-Fluoro-1,3-diiodobenzene (**17**; 83%), accessible through the same intermediate, reacted only sluggishly with LIDA, but reacted smoothly when lithium 2,2,6,6-tetramethylpiperidide (LITMP) was used. Carboxylation of the isomerized lithiated species afforded the 2-fluoro-3,6-diiodobenzoic acid (**13**; 67%), and hydrolysis 2-fluoro-1,4-diiodobenzene (**14**; 65%). Halobenzene **14** was also found to be accessible from 2-fluoro-1,3-diiodobenzene by



[a] LIDA in THF at −75 °C. [b] (1.) CO_2, (2.) HCl. [c] I_2. [d] Lithium 2,2,6,6-tetramethylpiperidide (LITMP) in THF at −75 °C. [e] H_2O. [f] $ClMgCH(CH_3)_2$ in THF at 0 °C [X = Cl or I].

LIDA-triggered heavy halogen migration in 65% yield and from (2-fluoro-4-iodophenyl)trimethylsilane (see Exp. Sect. 7) by iododesilylation in 95% yield. When subjected to consecutive halogen/metal permutation and carboxylation, it produced the 2-fluoro-4-iodobenzoic acid (**15**; 96%). The last three compounds mentioned (**13**, **14**, and **15**) had already been obtained from the preceding reaction series. In other words, the iodine migrations starting from 1-fluoro-2,3-diiodobenzene and from 2-fluoro-1,3-diiodobenzene are product-convergent.

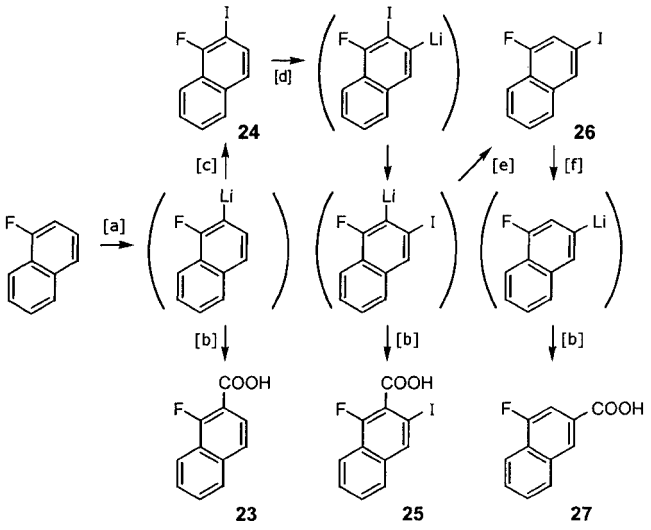
Application of the same reaction steps to 1,2-difluoro-3-iodobenzene opened an entry to the 2,3-difluoro-4-iodobenzoic acid (**18**; 76%) and 2,3-difluoro-1,4-diiodobenzene (**19**; 87%). The organolithium species generated from compound **19** with LITMP gave 2,3-difluoro-4,6-diiodobenzoic acid (**20**; 72%) after carboxylation and 1,2-difluoro-3,5-diiodobenzene (**21**; 77%) after neutralization. The 2,3-difluoro-5-iodobenzoic acid (**22**; 89%) was made from the latter compound in the usual way.



[a] LIDA in THF at −75 °C. [b] (1.) CO_2, (2.) HCl. [c] I_2. [d] LITMP in THF at −75 °C. [e] H_2O. [f] $ClMgCH(CH_3)_2$ in THF at 0 °C [X = Cl or I].

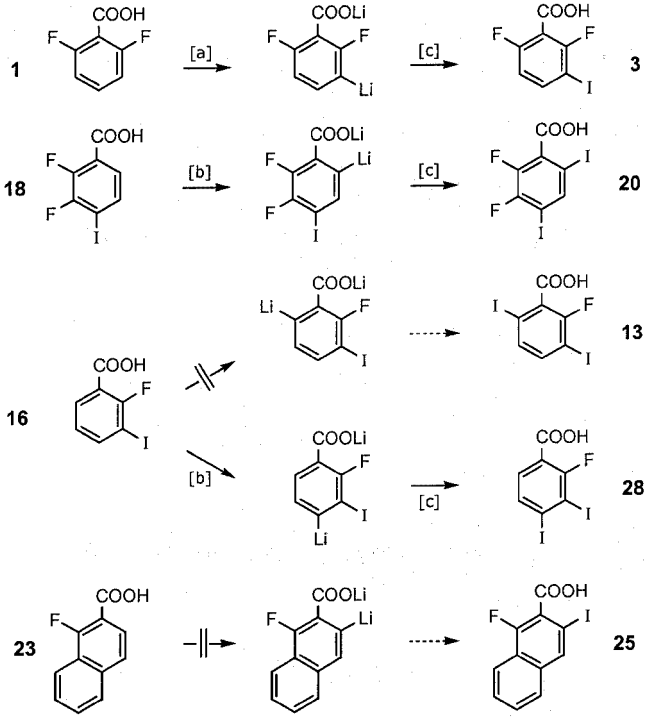
The last substrate was the only one to harbor just one halogen substituent. When treated with *sec*-butyllithium, 1-fluoronaphthalene underwent almost quantitative lithiation at the 2-position to afford 1-fluoro-2-naphthoic acid (**23**; 94%) or 1-fluoro-2-iodonaphthalene (**24**; 92%) depending on the choice of the electrophilic trapping reagent. Deprotonation with LITMP produced an organometallic reagent, which afforded the 1-fluoro-3-iodo-2-naphthoic acid **25** (93%) and 1-fluoro-3-iodonaphthalene **26** (78%), and from there also the 1-fluoro-3-naphthoic acid **27** (97%).

As reflected in the preceding schemes, three different carboxylic acids can be derived from each haloarene starting material. The formation of the acids **1**, **6**, **11**, **16**, **18**, and **23** was initiated by the deprotonation of the most acidic vacant position, whereas the isomeric acids **5**, **10**, **15**, **22**, and **27** bear the functional group at the second most acidic site of the original substrate. Finally, the acids **3**, **8**, **13**, **20**, and **25** have the same structure as the members of the first



[a] $LiCH(CH_3)C_2H_5$ in THF at −75 °C. [b] (1.) CO_2, (2.) HCl. [c] I_2. [d] LITMP in THF at −75 °C. [e] H_2O. [f] LiC_4H_9 in THF at −75 °C.

series except for the presence of an extra iodine atom located either next to a fluorine substituent or next to the carboxy group. Metalation and subsequent electrophilic substitution of benzoic acids at a carboxy-remote, but heteroatom-adjacent position has only sporadically been reported.[11−12] In contrast, the deprotonation of benzoic acids at the *ortho* position has been systematically investigated, in particular by J. Mortier et al.[13−17] We wondered whether the acids of type **3** might not be obtained in a straightforward manner by the deprotonation of the corres-



[a] LITMP/$KOC(CH_3)_3$ (2.0 equiv.) in THF at 75 °C. [b] LIDA in THF at −75 °C. [c] I_2 in THF at −75 °C.

ponding acid of type **1** at a fluorine- or carboxylate-neighboring position and subsequent iodination. This was found to be possible in only two out of four examined cases, and even then the yields of iodinated products were only moderate (**1** → **3**: 31%; **18** → **20**: 49%). 2-Fluoro-3-iodobenzoic acid (**16**) did not provide the expected derivative **13** but rather the regioisomer **28** (34%), which had to be purified through its methyl ester. Lithium 1-fluoro-2-naphthoate (**23**: COOLi instead of COOH) did not react at all with LITMP in the presence or absence of potassium *tert*-butoxide.

Experimental Section

Generalities: For working routine and abbreviations, see related publications from this laboratory.[18−20] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively. Samples were dissolved in deuteriochloroform unless stated otherwise.

1. Direct Carboxylation of the Starting Materials

2,6-Difluorobenzoic Acid (1): A solution containing 1,3-difluorobenzene (10 mL, 11 g, 0.10 mol) and *sec*-butyllithium (0.10 mol) in tetrahydrofuran (0.20 L) and cyclohexane (60 mL) was kept for 2 h at −75 °C before being poured onto an excess of freshly crushed dry ice. At +25 °C, 2.0 M ethereal hydrogen chloride (0.12 mol) was added, the volatiles were evaporated, and the residue was dissolved in hot water and, after concentration, cooled to crystallize; colorless needles; m.p. 155−157 °C (after sublimation; ref.[21]: m.p. 155−156 °C); yield: 12.3 g (78%). ^{1}H NMR: δ = 7.39 (ddd, *J* = 14.8, 8.6, 6.2 Hz, 1 H), 6.94 (t, *J* = 8.2 Hz, 2 H) ppm.

1-Fluoro-2-naphthoic Acid (23): This compound was produced analogously, from 1-fluoronaphthalene (15 g, 0.10 mol); colorless needles; m.p. 194−196 °C (from ethyl acetate; ref.[22]: m.p. 193−194 °C); yield: 17.8 g (94%). ^{1}H NMR: δ = 8.23 (d, *J* = 8.3 Hz, 1 H), 7.95 (dd, *J* = 8.6, 7.3 Hz, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.6 (m, 3 H) ppm.

3,6-Difluoro-2-iodobenzoic Acid (6): Diisopropylamine (14 mL, 10 g, 0.10 mol) and 1,4-difluoro-2-iodobenzene[23] (24 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.20 L) and hexanes (65 mL), cooled in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed pieces of solid carbon dioxide. After carboxylation and evaporation of all solvents, the residue was dissolved in methanol (50 mL), to which a small amount (1−2 mL) of boron trifluoride−diethyl ether had been added, and the solution was kept for 20 h at +25 °C. After esterification and before distillation, the crude product mixture contained methyl 2,5-difluorobenzoate (31%), methyl 3,6-difluoro-2-iodobenzoate (39%) and 1,4-difluoro-2,3-diiodobenzene (26%) as determined by gas chromatography (30 m, DB-1, 50 °C [5 min]→100 °C [15 min] →175 °C [10 min]; heating rate 30 °C/min; 30 m, DB-WAX, identical temperature program; internal standard: tridecane). Upon distillation, the main component, methyl 3,6-difluoro-2-iodobenzoate (14.6 g), was collected as the second fraction. − **Methyl Ester:** Colorless liquid; b.p. 91−93 °C/4 Torr; n_D^{20} = 1.5494; 14.6 g (39%). ^{1}H NMR: δ = 7.12 (d, *J* = 6.5 Hz, 1 H), 7.11 (d, *J* = 7.0 Hz, 1 H), 3.99 (s, 3 H) ppm. ^{13}C NMR: δ = 164.4 (s), 158.1 (d, *J* = 243 Hz), 154.9 (d, *J* = 252 Hz), 129.3 (d, *J* = 22 Hz), 117.2 (t, *J* = 7 Hz), 116.9 (t, *J* = 9 Hz), 80.9 (dd, *J* = 30, 4 Hz), 53.2 (s) ppm. $C_8H_5F_2IO_2$ (298.03): calcd. C 32.24, H 1.69; found C 32.38, H 1.76. − Hydrolysis to the free acid **6**: Potassium *tert*-butoxide (11 g, 0.10 mol), water (1.0 mL, 1.0 g, 56 mmol), and the methyl ester (7.5 g, 25 mmol) were consecutively added at 0 °C to diethyl ether (0.10 L) and kept for 2 h at +25 °C. The mixture was acidified with concentrated hydrochloric acid before being extracted with diethyl ether (3 × 25 mL). Evaporation of the volatiles under reduced pressure and crystallization (from ethyl acetate) afforded the pure acid; colorless platelets; m.p. 127−129 °C; yield: 7.0 g (98%). ^{1}H NMR: δ = 7.17 (t, *J* = 5.9 Hz, 2 H) ppm. ^{13}C NMR: δ = 169.6 (s), 158.3 (dd, *J* = 244, 2 Hz), 155.4 (dd, *J* = 253, 2 Hz), 127.8 (d, *J* = 19 Hz), 117.9 (dd, *J* = 28, 9 Hz), 117.5 (dd, *J* = 24, 8 Hz), 81.2 (dd, *J* = 31, 3 Hz) ppm. $C_7H_3F_2IO_2$ (284.00): calcd. C 29.60, H 1.06; found C 29.69, H 1.09.

2-Fluoro-6-iodobenzoic Acid (11): This compound was produced from 1-fluoro-3-iodobenzene (12 mL, 22 g, 0.10 mol) as described in the preceding paragraph (see acid **6**). After carboxylation and evaporation of all solvents, 2.0 M ethereal hydrogen chloride (0.25 mol) was added. Evaporation of the volatiles, extraction with hot chloroform, filtration, concentration, and crystallization afforded the product **11**; colorless needless; m.p. 124−125 °C; yield: 25.3 g (95%). ^{1}H NMR: δ = 7.7 (m, 1 H), 7.2 (m, 2 H) ppm. ^{13}C NMR: δ = 170.5 (s), 159.2 (d, *J* = 257 Hz), 135.5 (d, *J* = 3 Hz), 133.0 (d, *J* = 9 Hz), 126.9 (d, *J* = 18 Hz), 115.9 (d, *J* = 21 Hz), 92.5 (s) ppm. $C_7H_4FIO_2$ (266.01): calcd. C 31.61, H 1.52; found C 31.78, H 1.54.

2-Fluoro-3-iodobenzoic Acid (16): This compound was produced from 1-fluoro-2-iodobenzene (22 g, 0.10 mol) as described above (see the preparation of acid **6**). However, after carboxylation, neutralization, and evaporation of the volatiles, the residue was treated directly with hot ethyl acetate, and the extract after filtration was concentrated until crystallization set in; colorless platelets; m.p. 175−177 °C; yield: 18.2 g (68%). ^{1}H NMR: δ = 7.9 (m, 2 H), 6.97 (t, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.3 (d, *J* = 3 Hz), 160.6 (d, *J* = 258 Hz), 143.4 (s), 132.6 (s), 125.4 (d, *J* = 5 Hz), 120.3 (d, *J* = 13 Hz), 83.1 (d, *J* = 27 Hz) ppm. $C_7H_4FIO_2$ (266.01): calcd. C 31.61, H 1.52; found C 31.96, H 1.70.

2,3-Difluoro-4-iodobenzoic Acid (18): This compound was produced from 1,2-difluoro-3-iodobenzene (6.0 g, 25 mmol) exactly as described above (see preparation of acid **11**); colorless platelets; m.p. 195−197 °C (from ethyl acetate); yield: 5.4 g (76%). ^{1}H NMR: δ = 7.56 (ddd, *J* = 8.5, 5.1, 1.7 Hz, 1 H), 7.49 (ddd, *J* = 8.4, 6.3, 1.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.6 (s), 151.1 (dd, *J* = 247, 14 Hz), 149.6 (dd, *J* = 267, 16 Hz), 133.0 (d, *J* = 4 Hz), 127.7 (d, *J* = 4 Hz), 121.7 (d, *J* = 7 Hz), 87.7 (d, *J* = 23 Hz) ppm. $C_7H_3F_2IO_2$ (283.91): calcd. C 29.60, H 1.06; found C 29.73, H 1.09.

2. Iodination of the Starting Materials

1,3-Difluoro-2-iodobenzene (2): 1,3-Difluorobenzene (20 mL, 23 g, 0.20 mol) in tetrahydrofuran (0.40 L) and *sec*-butyllithium (0.20 mol) in cyclohexane (0.15 L) were mixed at dry ice temperature. After 2 h at −75 °C, a precooled solution of iodine (51 g, 0.20 mol) in tetrahydrofuran (0.20 L) and, when at +25 °C, some sodium thiosulfate (1.5 g) were added. The product **2** was isolated by steam distillation as a colorless liquid; m.p. 24.5−26.5 °C (ref.[24]: m.p. 22.5−25.5 °C); b.p. 55−56 °C/8 Torr (ref.[24]: b.p. 70.5−71 °C/14 Torr); yield: 46.0 g (98%). ^{1}H NMR: δ = 7.3 (m, 1 H), 6.89 (dd, *J* = 8.4, 6.6 Hz, 2 H) ppm.

1,4-Difluoro-2,3-diiodobenzene (7): Diisopropylamine (14 mL, 10 g, 0.10 mol) and 1,4-difluoro-2-iodobenzene[23] (24 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.20 L) and hexanes (65 mL), cooled in a meth-

anol/dry ice bath. After 2 h at −75 °C, the mixture was treated with a precooled solution of iodine (26 g, 0.10 mol) in tetrahydrofuran (0.10 L) and, when at +25 °C, some sodium thiosulfate (1.5 g) was added. Evaporation of the volatiles, extraction with hot hexanes, filtration, concentration, and crystallization afforded the product **7** as colorless needles; m.p. 72−74 °C; yield: 24.1 g (66%). ^{1}H NMR: δ = 7.10 (t, *J* = 5.6 Hz, 2 H) ppm. ^{13}C NMR: δ = 158.1 (dd, *J* = 245, 4 Hz, 2 C), 115.6 (symm. m, 2 C), 97.5 (symm. m, 2 C) ppm. $C_6H_2F_2I_2$ (365.89): calcd. C 19.70, H 0.55; found C 19.57, H 0.58.

1-Fluoro-2,3-diiodobenzene (12): This compound was produced from 1-fluoro-3-iodobenzene (12 mL, 22 g, 0.10 mol) as described in the preceding paragraph (see the preparation of compound **7**); colorless needles; m.p. 40.5−42.5 °C (from chloroform); yield: 32.0 g (92%). ^{1}H NMR: δ = 7.68 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.07 (td, *J* = 8.0, 5.6 Hz, 1 H), 7.01 (td, *J* = 8.0, 1.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.5 (d, *J* = 248 Hz), 134.9 (d, *J* = 3 Hz), 131.0 (d, *J* = 8 Hz), 114.5 (d, *J* = 25 Hz), 109.1 (s), 96.8 (d, *J* = 27 Hz) ppm. $C_6H_3FI_2$ (347.90): calcd. C 20.71, H 0.87; found C 20.60, H 0.97.

2-Fluoro-1,3-diiodobenzene (17): This compound was produced analogously, from 1-fluoro-2-iodobenzene (22 g, 0.10 mol); colorless needles; m.p. 67- 69 °C (from hexanes); yield: 28.9 g (83%). ^{1}H NMR: δ = 7.71 (dd, *J* = 7.8, 5.9 Hz, 2 H), 6.63 (t, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 160.1 (d, *J* = 243 Hz), 139.5 (s, 2 C), 127.3 (d, *J* = 4 Hz), 80.6 (d, *J* = 29 Hz, 2 C) ppm. $C_6H_3FI_2$ (347.90): calcd. C 20.71, H 0.87; found C 20.68, H 0.75.

2,3-Difluoro-1,4-diiodobenzene (19): This compound was produced analogously, from 1,2-difluoro-3-iodobenzene (24 g, 0.10 mol); colorless needles; m.p. 55−57 °C (from hexanes); yield: 31.8 g (87%). ^{1}H NMR: δ = 7.25 (symm. m, 2 H) ppm. ^{13}C NMR: δ = 150.0 (dd, *J* = 253, 18 Hz, 2 C), 134.9 (s, 2 C), 82.3 (symm. m, 2 C) ppm. $C_6H_2F_2I_2$ (365.89): calcd. C 19.70, H 0.55; found C 19.74, H 0.64.

1-Fluoro-2-iodonaphthalene (24): This compound was produced analogously, from 1-fluoronaphthalene (15 g, 0.10 mol); colorless liquid; m.p. 11−13 °C; b.p. 91−93 °C/2 Torr; n_D^{20} = 1.6789; yield: 25.0 g (92%). ^{1}H NMR: δ = 8.04 (symm. m, 1 H), 7.8 (m, 1 H), 7.67 (dd, *J* = 8.9, 6.2 Hz, 1 H), 7.53 (symm. m, 2 H), 7.37 (d, *J* = 8.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 158.0 (d, *J* = 250 Hz), 134.3 (d, *J* = 4 Hz), 134.1 (s), 127.4 (d, *J* = 2 Hz), 127.2 (s), 126.8 (s), 124.9 (d, *J* = 5 Hz), 123.5 (d, *J* = 18 Hz), 120.1 (d, *J* = 4 Hz), 75.5 (d, *J* = 26 Hz) ppm. $C_{10}H_6FI$ (272.06): calcd. C 44.15, H 2.22; found C 44.27, H 2.21.

3. Isomerization and Carboxylation of Iodination Products

2,6-Difluoro-3-iodobenzoic Acid (3): This compound was produced from 1,3-difluoro-2-iodobenzene[24] (**2**; 24 g, 0.10 mol) as described above (see Section 1, preparation of acid **6**). − **Methyl Ester:** colorless prisms; m.p. 53−55 °C (from ethyl acetate); b.p. 64−65 °C/1 Torr; 14.6 g (49%). ^{1}H NMR: δ = 7.82 (ddd, *J* = 8.9, 7.0, 6.2 Hz, 1 H), 6.81 (td, *J* = 8.9, 1.3 Hz, 1 H), 3.96 (s, 3 H) ppm. ^{13}C NMR: δ = 161.1 (s), 160.7 (dd, *J* = 258, 5 Hz), 159.6 (dd, *J* = 254, 6 Hz), 141.4 (dd, *J* = 10, 3 Hz), 113.9 (dd, *J* = 22, 4 Hz), 111.7 (t, *J* = 20 Hz), 75.6 (dd, *J* = 27, 4 Hz) 53.1 (s) ppm. $C_8H_5F_2IO_2$ (298.03): calcd. C 32.24, H 1.69; found C 32.47, H 1.47. − Hydrolysis of the ester to the free acid **3**: colorless platelets; m.p. 137−139 °C (from ethyl acetate; ref.[25]: m.p. 134−139 °C); yield: 6.9 g (97%). ^{1}H NMR: δ = 7.84 (dt, *J* = 8.9, 6.3 Hz, 1 H), 6.83 (td, *J* = 8.9, 1.1 Hz, 1 H).

Methyl 2,5-Difluoro-3,4,6-triiodobenzoate: Diisopropylamine (3.4 mL, 2.5 g, 25 mmol) and 1,4-difluoro-2,3-diiodobenzene (**7**; 9.1 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (15 mL), cooled in a methanol/dry ice-bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed pieces of solid carbon dioxide. The volatiles were evaporated and the residue was dissolved in a 1.0 M aqueous solution of sodium hydroxide (50 mL). After washing with diethyl ether (2 × 25 mL), the alkaline phase was acidified to pH 2 and extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (25 mL) and treated with an ethereal solution of diazomethane until the yellow color of the reagent persisted. According to gas chromatography (30 M, DB-1, 100 °C [15 min] → 175 °C [10 min]; heating rate: 30 °C/min; 30 m DB-WAX, identical temperature program; internal standard: tridecane), the ethereal solution contained 31% of the methyl ester of acid **8** along with 18% of the methyl ester of acid **3**. The bulk of the solution was evaporated to dryness and the residue was triturated with ethyl acetate before being crystallized from methanol: colorless needles; m.p. 153−155 °C; yield: 10.4 g (19%). ^{1}H NMR: δ = 3.99 (s, 3 H) ppm. ^{13}C NMR: δ = 163.6 (s), 157.5 (dd, ***J*** = 242, 3 Hz), 154.0 (dd, ***J*** = 251, 3 Hz), 128.7 (d, ***J*** = 25 Hz), 98.5 (d, ***J*** = 10 Hz), 98.2 (d, ***J*** = 14 Hz), 79.2 (dd, *J* = 35, 3 Hz), 53.5 (s) ppm. $C_8H_3F_2I_3O_2$ (549.82): calcd. C 17.48, H 0.55; found C 17.62, H 0.64.

2,5-Difluoro-3,6-diiodobenzoic Acid (8): Diisopropylamine (3.4 mL, 2.5 g, 25 mmol) and 1,4-difluoro-2,5-diiodobenzene (**9**; 9.1 g, 25 mol; see Section 4) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (15 mL), kept in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed pieces of solid carbon dioxide and worked up as described above (see acid **1**); tiny, colorless needles; m.p. 151−153 °C (decomp.; crystallized from ethyl acetate); yield: 8.2 g (80%). ^{1}H NMR: δ = 7.47 (dd, *J* = 6.4, 5.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.9 (s), 157.8 (dd, *J* = 247, 3 Hz), 154.1 (dd, *J* = 248, 3 Hz), 130.2 (d, *J* = 25 Hz), 125.2 (d, *J* = 29 Hz), 81.0 (dd, *J* = 29, 7 Hz), 80.5 (dd, *J* = 30, 3 Hz) ppm. $C_7H_2F_2I_2O_2$ (409.90): calcd. C 20.51, H 0.49; found C 20.71, H 0.59.

2-Fluoro-3,6-diiodobenzoic Acid (13): This compound was produced from 1-fluoro-2,3-diiodobenzene (**12**; 8.7 g, 25 mmol) as described in the preceding paragraph; colorless platelets; m.p. 163−165 °C (decomp.; cryst. from ethyl acetate); yield: 9.2 g (94%). ^{1}H NMR: δ = 7.46 (dd, *J* = 8.3, 6.2 Hz, 1 H), 7.37 (d, *J* = 8.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.9 (s), 157.5 (d, *J* = 252 Hz), 140.6 (s), 136.2 (d, *J* = 4 Hz), 130.0 (d, *J* = 23 Hz), 91.8 (s), 81.5 (d, *J* = 26 Hz) ppm. $C_7H_3FI_2O_2$ (391.90): calcd. C 21.45, H 0.77; found C 21.56, H 0.61. Acid **13** was also obtained when 2-fluoro-1,3-diiodobenzene (**17**; 35 g, 0.10 mol) was treated consecutively with lithium 2,2,6,6-tetramethylpiperidide and carbon dioxide (for details, see the following paragraph); yield: 26.3 g (67%).

2,3-Difluoro-4,6-diiodobenzoic Acid (20): 2,2,6,6-Tetramethylpiperidine (17 mL, 14 g, 0.10 mol) and 2,3-difluoro-1,4-diiodobenzene (**19**; 37 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.20 L) and hexanes (65 mL), cooled in a methanol/dry ice bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed pieces of solid carbon dioxide and was worked up as described above (see acid **1**); colorless prisms; m.p. 180−182 °C (from ethyl acetate); yield: 29.6 g (72%). ^{1}H NMR: δ = 8.01 (dd, *J* = 5.1, 2.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 165.2 (s), 150.8 (dd, *J* = 249, 14 Hz), 146.3 (dd, *J* = 261, 17 Hz), 142.8 (d, *J* = 4 Hz), 131.4 (d, *J* = 18 Hz), 85.8 (d, *J* = 5 Hz), 84.6 (d, *J* = 23 Hz) ppm.

$C_7H_2F_2I_2O_2$ (409.90): calcd. C 20.51, H 0.49; found C 20.55, H 0.67.

1-Fluoro-3-iodo-2-naphthoic Acid (25): This compound was produced analogously, from 1-fluoro-2-iodonaphthalene (**24**; 14 g, 50 mmol), except that the reaction time at −75 °C was extended from 2 h to 20 h; colorless needles; m.p. 180−182 °C (decomp.; cryst. from methanol); yield: 14.7 g (93%). ^{1}H NMR: δ = 8.19 (s, 1 H), 8.1 (m, 1 H), 7.7 (m, 1 H), 7.59 (symm. m, 2 H) ppm. ^{13}C NMR: δ = 166.9 (s), 154.3 (d, *J* = 260 Hz), 135.4 (d, *J* = 6 Hz), 134.1 (d, *J* = 4 Hz), 128.4 (s), 127.2 (s), 126.1 (d, *J* = 2 Hz), 122.7 (d, *J* = 18 Hz), 122.4 (d, *J* = 18 Hz), 120.9 (d, *J* = 6 Hz), 86.7 (d, *J* = 4 Hz) ppm. $C_{11}H_6FIO_2$ (316.07): calcd. C 41.80, H 1.91; found C 41.86, H 1.86.

4. Isomerization and Reprotonation of Iodination Products

2,4-Difluoro-1-iodobenzene (4): Diisopropylamine (14 mL, 10 g, 0.10 mol) and 1,3-difluoro-2-iodobenzene (**2**; 24 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.20 L) and hexanes (65 mL), cooled in a methanol/dry ice bath. After 2 h at −75 °C, approx. 2.0 M ethereal hydrogen chloride (0.10 mol) was added. All volatiles were evaporated under reduced pressure. According to gas chromatography (30 m, DB-1, 50 °C [5 min]→100 °C [15 min]; heating rate: 30 °C/min; 30 m, DB-WAX, identical temperature program; internal standard: tridecane), the residue contained the product **4** (48%) along with starting material **2** (15%) in a ratio of 3:1. At −75 °C, diethyl ether (0.10 L), butyllithium (15 mmol) in hexanes (10 mL), and, 15 min later, methanol (5.0 mL) were added. The product was isolated by steam distillation as a colorless oil; b.p. 51−52 °C/11 Torr (ref.:[26] b.p. 75 °C/25 Torr); n_D^{20} = 1.5549 (ref.:[26] n_D^{20} = 1.5574); yield: 11.5 g (48%). ^{1}H NMR: δ = 7.70 (ddd, *J* = 8.7, 7.2, 6.2 Hz, 1 H), 6.85 (dt, *J* = 8.6, 2.7 Hz, 1 H), 6.72 (tdd, *J* = 8.7, 2.7, 1.0 Hz, 1 H).

1,4-Difluoro-2,5-diiodobenzene (9): In the same way as described in the preceding paragraph, 1,4-difluoro-2,3-diiodobenzene (**7**; 37 g, 0.10 mol) was treated with lithium diisopropylamide (0.10 mol) for 2 h at −75 °C. Ethereal hydrogen chloride (0.10 mol) was then added, the volatiles were evaporated, and the residue was eluted with hexanes from a column filled with silica (1.0 L). The collected organic material was dried and crystallized from hexanes; colorless small rods; m.p. 69−71 °C; yield: 16.4 g (45%). ^{1}H NMR: δ = 7.42 (t, *J* = 5.9 Hz, 2 H) ppm. ^{13}C NMR: δ = 158.1 (dd, *J* = 247, 4 Hz, 2 C), 125.1 (symm. m, 2 C), 80.5 (symm. m, 2 C) ppm. $C_6H_2F_2I_2$ (365.89): calcd. C 19.70, H 0.55; found C 19.72, H 0.63.

2-Fluoro-1,4-diiodobenzene (14): This compound was produced from 1-fluoro-2,3-diiodobenzene (**12**; 35 g, 0.10 mol) as described in the preceding paragraph; colorless platelets; m.p. 70−72 °C (from hexanes); yield: 33.7 g (97%). ^{1}H NMR: δ = 7.44 (dd, *J* = 8.3, 6.5 Hz, 1 H), 7.40 (dd, *J* = 7.3, 1.9 Hz, 1 H), 7.23 (dd, *J* = 8.3, 2.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.4 (d, *J* = 251 Hz), 140.4 (s), 135.0 (d, *J* = 4 Hz), 125.0 (d, *J* = 26 Hz), 93.1 (d, *J* = 7 Hz), 81.0 (d, *J* = 26 Hz) ppm. $C_6H_3FI_2$ (347.90): calcd. C 20.71, H 0.87; found C 20.82, H 0.91. Product **14** was also obtained when 2-fluoro-1,3-diiodobenzene (**17**; 35 g, 0.10 mol) was treated with lithium 2,2,6,6-tetramethylpiperidide (0.10 mol) and subsequently with methanol, or when (2-fluoro-4-iodophenyl)trimethylsilane (see Section 7; 15 g, 50 mmol) was treated with iodine chloride (8.1 g, 50 mmol) in refluxing tetrachloromethane for 15 h; yields: 22.6 g (65%) and 16.5 g (95%), respectively.

1,2-Difluoro-3,5-diiodobenzene (21): 2,2,6,6-Tetramethylpiperidine (17 mL, 14 g, 0.10 mol) and 2,3-difluoro-1,4-diiodobenzene (**19**; 37 g, 0.10 mol) were consecutively dissolved in tetrahydrofuran (0.20 L) and hexanes (60 mL) containing butyllithium (0.10 mol) and cooled in a methanol/dry ice bath. After 2 h at −75 °C, ethereal hydrogen chloride (0.10 mol) was added. The volatiles were evaporated and the residue was absorbed on silica gel (0.1 L). When dry, it was poured on top of a column filled with more silica (1.8 L) and eluted with hexanes. As revealed by thin layer chromatography, the isomerized product **21** had a shorter retention time than the starting material **19**, 16% (5.85 g) of which were recovered. The fractions collected first contained 77% (28.2 g) of 1,2-difluoro-3,5-diiodobenzene (**21**), which was isolated by distillation; colorless liquid; m.p. 15−17 °C; b.p. 74−76 °C/0.8 Torr; n_D^{20} = 1.6539; yield: 28.2 g (77%). ^{1}H NMR: δ = 7.83 (dt, *J* = 4.8, 1.9 Hz, 1 H), 7.47 (ddd, *J* = 8.9, 6.7, 1.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.7 (dd, *J* = 248, 14 Hz), 149.4 (dd, *J* = 259, 15 Hz), 141.7 (d, *J* = 4 Hz), 126.8 (d, *J* = 20 Hz), 86.5 (t, *J* = 6 Hz), 83.8 (d, *J* = 23 Hz) ppm. $C_6H_2F_2I_2$ (365.89): calcd. C 19.70, H 0.55; found C 19.69, H 0.57.

1-Fluoro-3-iodonaphthalene (26): 2,2,6,6-Tetramethylpiperidine (34 mL, 28 g, 0.20 mol) and 1-fluoro-2-iodonaphthalene (**24**; 54 g, 0.20 mol) were consecutively dissolved in tetrahydrofuran (0.24 L) and hexanes (0.13 L) containing butyllithium (0.20 mol) and cooled in a methanol/dry ice bath. After 20 h at −75 °C, approx. 2.0 M ethereal hydrogen chloride (0.20 mol) was added. According to gas chromatography (30 m, DB-1, 50 °C [5 min]→100 °C [15 min]; heating rate: 30 °C/min; 30 m, DB-WAX, 50 °C [5 min]→100 °C [15 min] →175 °C [5 min]; internal standard: tridecane), the mixture contained the product **26** (78%) and its precursor **24** (15%) in a ratio of 5:1. All volatiles were evaporated under reduced pressure. At −75 °C, diethyl ether (0.10 L), butyllithium (33 mmol) in hexanes (20 mL), and, 5 min later, methanol (5.0 mL, 4.0 g, 0.12 mol) were added to the residue. Upon distillation, the product was collected as a colorless liquid; b.p. 90−92 °C/2 Torr; n_D^{20} = 1.6689; yield: 42.4 g (78%). ^{1}H NMR: δ = 8.0 (m, 2 H), 7.7 (m, 1 H), 7.52 (symm. m, 2 H), 7.40 (dd, *J* = 9.7, 1.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 157.8 (d, *J* = 258 Hz), 135.7 (d, *J* = 5 Hz), 132.5 (d, *J* = 5 Hz), 127.6 (s), 126.5 (s), 126.2 (d, *J* = 3 Hz), 122.6 (d, *J* = 16 Hz), 120.6 (d, *J* = 5 Hz), 118.3 (d, *J* = 22 Hz), 88.8 (d, *J* = 10 Hz) ppm. $C_{10}H_6FI$ (272.06): calcd. C 44.15, H 2.22; found C 44.47, H 2.10.

5. Isomerization Products Submitted to Halogen/Metal Permutation and Carboxylation

2,4-Difluorobenzoic Acid (5): Butyllithium (50 mmol) in hexanes (30 mL) was added at −75 °C to 2,4-difluoro-1-iodobenzene (**4**; 12 g, 50 mmol) in tetrahydrofuran (0.10 L). After 5 min, the mixture was poured onto an excess of freshly crushed dry ice and worked up as described above (see acid **1**); colorless needles; m.p. 180−182 °C (from methanol; ref.:[27] 182−184 °C); yield: 7.3 g (92%). ^{1}H NMR: δ = 8.01 (td, ***J*** = 8.7, 6.7 Hz, 1 H), 6.9 (m, 2 H).

1-Fluoro-3-naphthoic Acid (27): This compound was produced analogously, from 1-fluoro-3-iodonaphthalene (**26**; 14 g, 50 mmol); tiny, colorless needles; m.p. 186−188 °C (from methanol; ref.:[28] 186−189 °C); yield: 9.2 g (97%). ^{1}H NMR: δ = 8.43 (s, 1 H), 8.11 (d, *J* = 8.1 Hz, 1 H), 7.97 (d, *J* = 8.1 Hz, 1 H), 7.73 (dd, *J* = 11.0, 1.3 Hz, 1 H), 7.63 (dddd, *J* = 21.0, 8.3, 7.0, 1.3 Hz, 2 H).

2,5-Difluoro-4-iodobenzoic Acid (10): 1,4-Difluoro-2,5-diiodobenzene (**9**; 9.2 g, 25 mmol) was added to a solution of isopropylmagnesium chloride (25 mmol) in tetrahydrofuran (50 mL), cooled in an ice bath. After 2 h at 0 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide and worked up as described above (see acid **1**); colorless, tiny needles; m.p. 177−179 °C (from ethyl acetate); yield: 5.9 g (83%). ^{1}H NMR: δ = 7.62 (dd, *J* = 7.8, 5.9 Hz, 1 H), 7.56 (dd, *J* = 9.1, 4.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 164.5 (s), 157.7 (dd, *J* = 243, 3 Hz), 157.3 (dd, *J* =

260, 3 Hz), 127.4 (d, J = 27 Hz), 120.5 (dd, J = 12, 6 Hz), 117.5 (d, J = 27 Hz), 86.8 (dd, J = 29, 9 Hz) ppm. $C_7H_3F_2IO_2$ (284.00): calcd. C 29.60, H 1.06; found C 29.65, H 1.05.

2-Fluoro-4-iodobenzoic Acid (15): This compound was produced from 2-fluoro-1,4-diiodobenzene (**14**; 8.7 g, 25 mmol) as described in the preceding paragraph; colorless platelets; m.p. 210−212 °C (decomp.; cryst. from ethyl acetate); yield: 6.4 g (96%). ^{1}H NMR: δ = 7.67 (t, J = 8.0 Hz, 1 H), 7.5 (m, 2 H) ppm. ^{13}C NMR: δ = 165.6 (d, J = 4 Hz), 161.3 (d, J = 265 Hz), 133 (m, 2 C), 126.2 (d, J = 25 Hz), 118.8 (d, J = 10 Hz), 99.3 (d, J = 9 Hz) ppm. $C_7H_4FIO_2$ (266.01): calcd. C 31.61, H 1.52; found C 31.58, H 1.71.

2,3-Difluoro-5-iodobenzoic Acid (22): This compound was produced analogously, from 1,2-difluoro-3,5-diiodobenzene (**21**; 9.2 g, 25 mmol); colorless prisms; m.p. 147−149 °C (from ethyl acetate); yield: 6.3 g (89%). ^{1}H NMR: δ = 8.05 (dt, J = 5.6, 2.2 Hz, 1 H), 7.65 (ddd, J = 8.9, 6.7, 2.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 163.7 (s), 150.7 (dd, J = 255, 14 Hz), 150.4 (dd, J = 264, 14 Hz), 135.7 (d, J = 4 Hz), 129.8 (d, J = 20 Hz), 122.9 (d, J = 8 Hz), 84.5 (t, J = 6 Hz) ppm. $C_7H_3F_2IO_2$ (284.00): calcd. C 29.60, H 1.06; found C 29.76, H 1.03.

6. Deprotonation and Iodination of Lithium Benzoates

2,6-Difluoro-3-iodobenzoic Acid (3): 2,2,6,6-Tetramethylpiperidine (8.4 mL, 7.1 g, 50 mmol), potassium *tert*-butoxide (5.6 g, 50 mmol), and 2,6-difluorobenzoic acid (**1**; 4.0 g, 25 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (50 mL) and hexanes (30 mL), cooled in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was treated with iodine (6.4 g, 25 mmol) dissolved in precooled tetrahydrofuran (25 mL). At +25 °C, some disodium sulfite (1.5 g, 12 mmol) and 2.0 M ethereal hydrogen chloride (0.10 mol) were added, the volatiles were evaporated, and the residue was dissolved in methanol (25 mL) to which a small amount (1−2 mL) of boron trifluoride−diethyl ether had been added. The solution was kept for 20 h at +25 °C. According to gas chromatography (30 m, DB-1, 50 °C [5 min] → 100 °C [15 min] → 175 °C [10 min]; heating rate 30 °C/min; 30 m, DB-WAX, identical temperature program; calibrated internal standard: tridecane), the reaction mixture contained methyl 2,6-difluorobenzoate (65%) and methyl 2,6-difluoro-3-iodobenzoate (33%). Upon distillation, the latter component was collected as the second fraction (b.p., 64−65 °C/1 Torr). Potassium *tert*-butoxide (3.6 g, 32 mmol), water (0.30 mL, 0.30 g, 17 mmol), and the methyl ester (2.4 g, 8.1 mmol) were added consecutively to diethyl ether (32 mL) at 0 °C and kept for 2 h at +25 °C. The mixture was acidified with concentrated hydrochloric acid before being extracted with diethyl ether (3 × 15 mL). After evaporation of the volatiles and crystallization from ethyl acetate, the product had the same properties as specified in the first paragraph of Section 3; yield: 2.3 g (31%).

2,3-Difluoro-4,6-diiodobenzoic Acid (20): This compound was produced by starting with 2,3-difluoro-4-iodobenzoic acid (**18**; 7.1 g, 25 mmol) and performing the reaction essentially as described in the preceding paragraph, except that the potassium *tert*-butoxide activated lithium 2,2,6,6-tetramethylpiperidide was replaced by lithium diisopropylamide (50 mmol). The properties of product **20** agreed with those of the same compound made as outlined in Section 3; yield: 5.0 g, (49%).

2-Fluoro-3,4-diiodobenzoic Acid (28): Diisopropylamine (28 mL, 20 g, 0.20 mol) and 2-fluoro-3-iodobenzoic acid (**16**; 27 g, 0.10 mol) were added consecutively at −75 °C to butyllithium (0.20 mol) in tetrahydrofuran (0.25 L) and hexanes (0.12 L). After 45 min of storing in a methanol/dry ice bath, a precooled solution of iodine (25 g, 0.10 mol) in tetrahydrofuran (0.10 L) was added. The volatiles were evaporated and the residue was dissolved in a 2.0 M aqueous solution (0.15 L) of sodium hydroxide that also contained some disodium sulfite (4.0 g). The aqueous phase was washed with diethyl ether (2 × 25 mL), acidified with hydrochloric acid to pH 2, and extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with brine (2 × 25 mL) and the solvents were evaporated. The residue was dissolved in methanol (0.10 L) to which some boron trifluoride−diethyl ether (2.0 mL, 2.3 g, 16 mmol) had been added. The mixture was allowed to stand for 20 h. According to gas chromatography (30 m, DB-1, 50 °C [5 min] → 100 °C [15 min] → 175 °C [10 min]; heating rate 30 °C/min; 30 m, DB-WAX, identical temperature program; tridecane as a calibrated internal standard), it contained methyl 2-fluoro-3-iodobenzoate (61%) and methyl 2-fluoro-3,4-diiodobenzoate (35%). The methyl ester of acid **16** was removed by distillation (b.p., 67−69 °C/2 Torr). The methyl 2-fluoro-3,4-diiodobenzoate left behind was purified by crystallization from methanol. **Methyl Ester:** colorless needles; m.p. 77−79 °C (from methanol); yield: 13.8 g (34%). ^{1}H NMR: δ = 7.78 (dd, J = 8.3, 1.1 Hz, 1 H), 7.64 (dd, J = 8.3, 7.0 Hz, 1 H), 3.93 (s, 3 H) ppm. ^{13}C NMR: δ = 163.6 (d, J = 6 Hz), 160.1 (d, J = 262 Hz), 134.7 (d, J = 4 Hz), 132.7 (s), 118.1 (d, J = 14 Hz), 111.3 (s), 99.1 (d, J = 28 Hz), 52.7 (s) ppm. $C_8H_5FI_2O_2$ (405.93): calcd. C 23.67, H 1.24; found C 23.63, H 1.14. Hydrolysis of the methyl ester to the free acid **28**: A proportion of the ester (10.1 g, 25 mmol) was converted into the free acid **28** as described above (see the preparation of acid **6**); colorless platelets; m.p. 211−213 °C (from ethyl acetate); yield: 9.1 g (93%). ^{1}H NMR (D_3CCOCD_3): δ = 7.96 (dd, J = 8.2, 1.0 Hz, 1 H), 7.74 (dd, J = 8.4, 7.4 Hz, 1 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 164.1 (d, J = 4 Hz), 161.0 (d, J = 260 Hz), 135.9 (d, J = 4 Hz), 133.9 (s), 119.4 (d, J = 14 Hz), 115.8 (s), 99.6 (d, J = 28 Hz) ppm. $C_7H_3FI_2O_2$ (391.90): calcd. C 21.45, H 0.77; found C 21.69, H 0.83.

7. Miscellaneous

(2-Fluoro-3-iodophenyl)trimethylsilane: *sec*-Butyllithium (0.10 mol) in cyclohexane (70 mL), followed 5 min later by chlorotrimethylsilane (13 mL, 11 g, 0.10 mol), followed a further 15 min later by more *sec*-butyllithium (0.10 mol) in cyclohexane (70 mL), and, finally, after another 5 min, a precooled solution of iodine (25 g, 0.10 mol) in tetrahydrofuran (0.10 L) were added at −75 °C to fluorobenzene (9.4 mL, 9.6 g, 0.10 mol) to produce a colorless liquid; b.p. 92−94 °C/8 Torr; n_D^{20} = 1.5527; yield: 26.8 g (91%). ^{1}H NMR: δ = 7.74 (ddd, J = 7.8, 6.7, 1.6 Hz, 1 H), 7.34 (ddd, ***J*** = 6.7, 4.8, 1.6 Hz, 1 H), 6.87 (t, J = 7.5 Hz, 1 H), 0.31 (d, J = 1.1 Hz, 9 H) ppm. ^{13}C NMR: δ = 166.6 (d, J = 240 Hz), 141.9 (s), 136.4 (d, J = 10 Hz), 128.7 (d, J = 33 Hz), 126.9 (d, J = 4 Hz), 82.9 (d, J = 30 Hz), 0.2 (s, 3 C) ppm. $C_9H_{12}FISi$ (294.18): calcd. C 36.74, H 4.11; found C 36.92, H 4.24.

(2-Fluoro-4-iodophenyl)trimethylsilane: 2,2,6,6-Tetramethylpiperidine (34 mL, 28 g, 0.20 mol) and (2-fluoro-3-iodophenyl)trimethylsilane (see above; 40 mL, 59 g, 0.20 mol) were added consecutively to a solution of butyllithium (0.20 mol) in tetrahydrofuran (0.25 L) and hexanes (0.12 L), kept in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured into water and was extracted with diethyl ether (3 × 0.10 L). As revealed by gas chromatography (30 m, DB-1, 50 °C [5 min]→100 °C [15 min] →175 °C [10 min]; heating rate 30 °C/min; 30 m, DB-WAX, identical temperature program; internal standard: tridecane), starting material and product were present in the ratio of 1:2. The ethereal solution was washed with brine (50 mL) and dried, before being treated with butyllithium (55 mmol) in hexanes (35 mL) for 5 min at −75 °C. After the addition of methanol (5.0 mL, 4.0 g, 0.12 mol), the product was

isolated by distillation under reduced pressure; colorless oil; b.p. 72−74 °C/2 Torr; n_D^{20} = 1.5481; yield: 35.9 g (61%). ^{1}H NMR: δ = 7.47 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.36 (dd, *J* = 7.8, 1.3 Hz, 1 H), 7.09 (dd, *J* = 7.8, 5.9 Hz, 1 H), 0.29 (d, *J* = 1.1 Hz, 9 H) ppm. ^{13}C NMR: δ = 168.2 (d, *J* = 246 Hz), 137.7 (d, *J* = 12 Hz), 134.5 (d, *J* = 3 Hz), 127.3 (d, *J* = 30 Hz), 125.5 (d, *J* = 29 Hz), 96.7 (d, *J* = 9 Hz), 0.27 (s, 3 C) ppm. $C_9H_{12}FISi$ (294.18): calcd. C 36.74, H 4.11; found C 37.03, H 4.19.

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