Extensive Halogen Scrambling and Buttressing Effects Encountered upon Treatment of Oligobromoarenes with Bases

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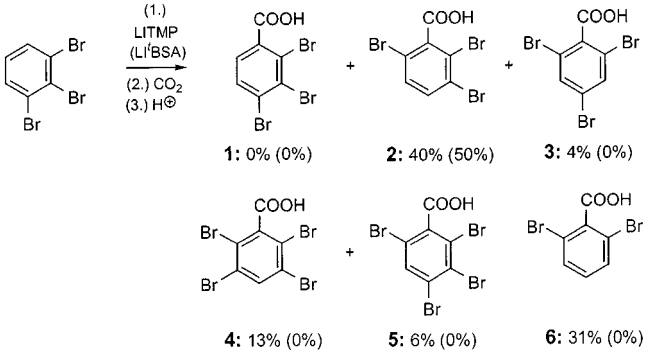
As a rule, tri-, tetra- and pentahaloarenes readily undergo *ortho*-lithiation when treated with amide-type bases. However, halogen migration occurs whenever the substrate contains three or more contiguous halogen atoms, provided that at least one of them is bromine or iodine. Dismutation and reduction processes often take place concomitantly. In this manner, a variety of organometallic intermediates may be formed, the driving force always being a decrease in basicity. When no such energy gain can be achieved, a sterically crowded substrate may just turn out to be inert; this was found to be the case with 1,5-dibromo-3-fluoro-2-(trimethylsilyl)benzene, 1,5-dibromo-3-fluoro-2,4-bis(trimethylsilyl)-benzene, and 1,5-dibromo-3-fluoro-2,4-diiodobenzene. Buttressing effects are apparently strong enough to prevent expedient deprotonation of those substrates.

Introduction

Benzene derivatives bearing one, two, three, four, or five fluoro[1] or chloro[2] substituents undergo smooth hydrogen/metal exchange (“metalation”) with *sec*-butyllithium, lithium diisopropylamide, or lithium 2,2,6,6-tetramethylpiperidide (LITMP) even at low temperatures (≤ −75 °C). In contrast, only one clean deprotonation reaction of a brominated arene, 1,3,5-tribromobenzene, has so far been reported.[3] Whereas 1-bromo-4-chlorobenzene and 1,4-dibromobenzene can be efficaciously metalated with LITMP in tetrahydrofuran at −75 °C, the 1,2-analogs afford 2-bromo-6-chlorophenyllithium and 2,6-dibromophenyllithium, respectively, under the same conditions.[3,4] To prevent this isomerization by halogen migration,[5,6] it is necessary to work at −100 °C. At this temperature the deprotonation proceeds only sluggishly (as evidenced by a meager 10−20% yield of trapping products).[3,4]

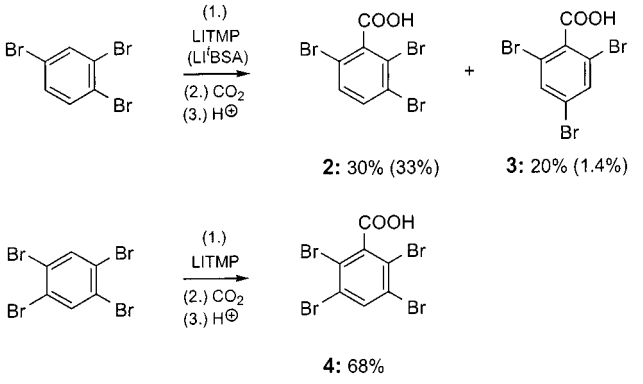
Results

Three contiguous bromo substituents intensify the complications encountered with 1,2-dibromobenzene. When 1,2,3-tribromobenzene was treated with LITMP and the intermediate subsequently quenched with dry ice, no trace of the direct metalation derivative 2,3,4-tribromobenzoic acid (**1**) was isolated. A mixture composed of 2,3,6-tribromobenzoic acid and 2,4,6-tribromobenzoic acid (**2** and **3**), 2,3,5,6-tetrabromobenzoic acid and 2,3,4,6-tetrabromobenzoic acid (**4** and **5**), and 2,6-dibromobenzoic acid (**6**) was obtained instead. When LITMP was replaced by the less basic lithium *tert*-butyl(*tert*-butyldimethylsilyl)amide [7] (LI^{t}BSA), the yield dropped from nearly quantitative to 50%, but this time the acid **2** was formed as the sole product (Scheme 1).



Scheme 1

2,3,6-Tribromophenyllithium was also directly generated from 1,2,4-tribromobenzene. When Li^{t}BSA was used as the base, the “autochthonous” acid **2** obtained after carboxylation was contaminated only with trace amounts of its isomer **3**, whereas with LITMP a 3:2 mixture of products **2** and **3** was produced. Under the same conditions, 1,2,4,5-tetrabromobenzene was found to form 2,3,5,6-tetrabromobenzoic acid (**4**) exclusively (Scheme 2).



Scheme 2

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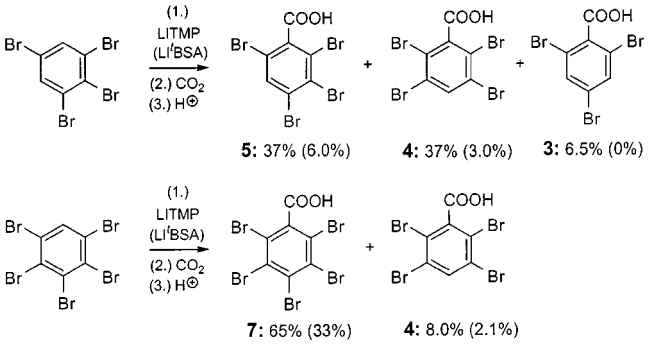
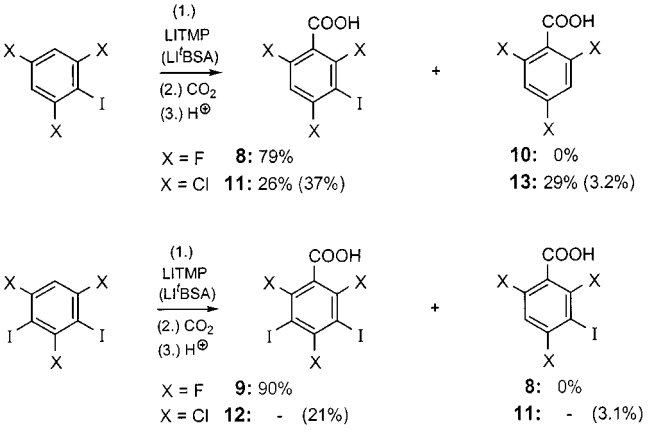
In contrast, considerable "leakage" to isomeric or partially dehalogenated products was found when 1,2,3,5-tetrabromobenzene was the substrate. With LITMP it gave a 1:1 mixture of 2,3,4,6-tetrabromobenzoic acid and 2,3,5,6-tetrabromobenzoic acid (**5** and **4**, respectively), along with some 2,4,6-tribromobenzoic acid (**3**). On the other hand, the main product obtained from pentabromobenzene was pentabromobenzoic acid (**7**), accompanied by only small amounts of 2,3,5,6-tetrabromobenzoic acid (**4**) (Scheme 3).



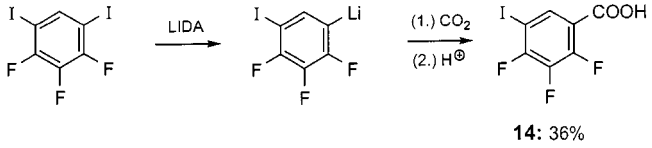
Scheme 3

Halogen loss may also occur when chlorine and iodine occupy vicinal positions. When treated with LITMP or LIᵗBSA, both 1,3,5-tri*fluoro*-2-iodobenzene and 1,3,5-tri*fluoro*-2,4-diiodobenzene readily undergo hydrogen/metal exchange to produce the acids **8** and **9** exclusively (no trace of by-products **10** and **8**, respectively; Scheme 4). However, 1,3,5-tri*chloro*-2-iodobenzene and 1,3,5-tri*chloro*-2,4-diiodobenzene do also give the partially deiodinated acids **13** and **11**, respectively, along with the expected acids **11** and **12**.



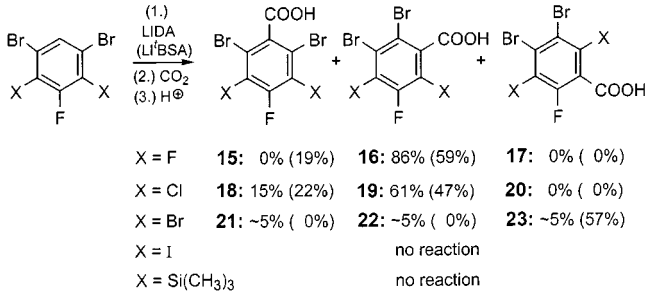
Scheme 4

2,3,4-Trifluoro-5-iodobenzoic acid (**14**) was the only product identified after consecutive treatment of 2,3,4-trifluoro-2,5-diiodobenzene with LIDA and dry ice. An amide-promoted conversion of an iodoarene into an aryllithium intermediate is without precedent. (Scheme 5).



Scheme 5

The reaction with the closely related 1,5-dibromo-2,3,4-trifluorobenzene took another course. Depending on the choice of the amide base (LIDA or LIᵗBSA), the "autochthonous" acid **15** was formed either only in small amounts or not at all (as was isomer **17**). The main product was isomer **16**. 1,5-Dibromo-2,4-dichloro-3-fluorobenzene gave both types of products (acids **18** and **19**, but no **20**) simultaneously. The next heavier member of this family, 1,2,4,5-tetrabromo-3-fluorobenzene, mushroomed into an inextricable spectrum of derivatives (including small amounts of acids **21**−**23**) in the presence of LIDA, while acid **23** was detected as the sole product in the presence of LIᵗBSA (Scheme 6).



Scheme 6

1,5-Dibromo-3-fluoro-2,4-diiodobenzene was recovered unchanged, whatever the base employed. While this lack of reactivity may be attributable to the poor solubility of the starting material, the same argument cannot be invoked in the case of 1,5-dibromo-3-fluoro-2,4-bis(trimethylsilyl)benzene. This substrate, however, also resists all attempts at deprotonation. We attribute this inertness to "buttressing effects"[8−15] preventing the two bromine atoms from moving out of the way of the approaching base and thus helping to accommodate a fairly crowded, four-center type transition state.[16,17]

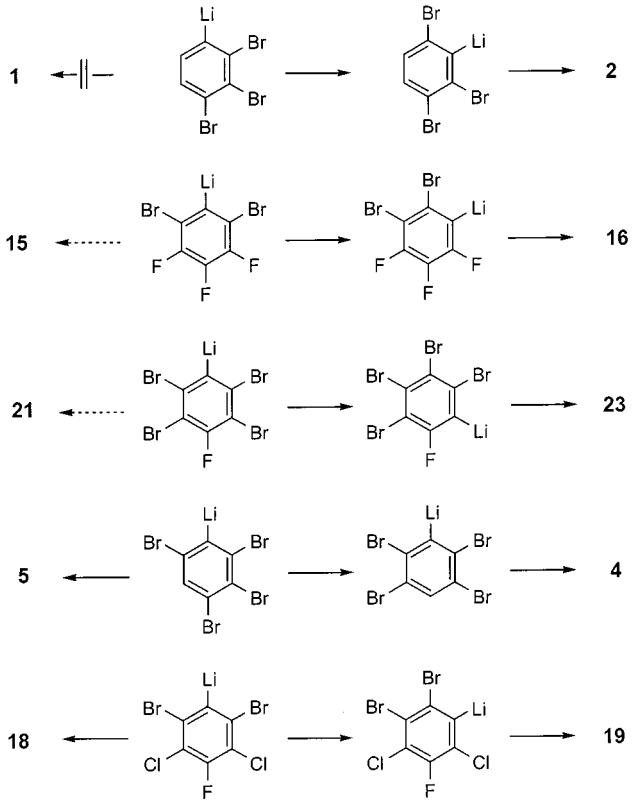
The buttressing effect of silyl groups is particularly strangulating. Although 1,3,5-tribromobenzene was smoothly deprotonated by LITMP,[3] one additional trimethylsilyl substituent sufficed to suppress all reactivity, no trace of acid **24** being formed from 1,3,5-tribromo-2-(trimethylsilyl)-benzene (Scheme 7).

Scheme 7

Discussion

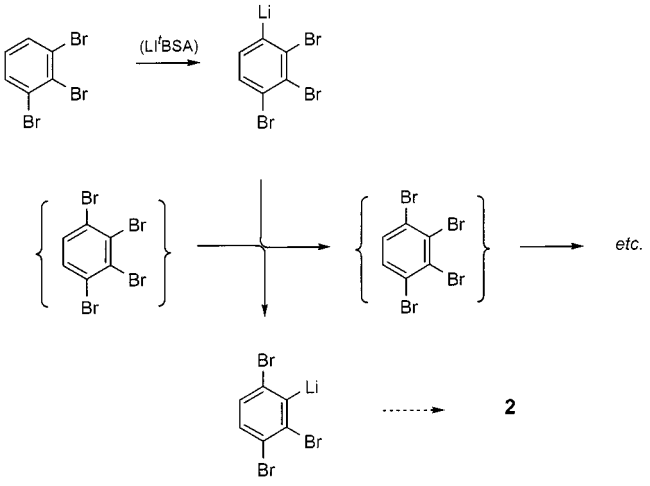
As documented in a forthcoming review,[18] the spontaneous isomerization of bromo- and iodoaryllithium compounds offers some synthetically attractive possibilities. In contrast, this article draws attention to the negative aspects of this isomerization mode. For example, although 2,3,4-tribromophenyllithium can readily be generated from 1,2,3-tribromobenzene using a suitable amide-type base, it is not subsequently possible to intercept it with an electrophilic trapping reagent, since it undergoes instantaneous metamorphosis to 2,3,6-tribromophenyllithium, and possibly to further isomerization and dismutation products, depending on the reaction conditions.

The model substrates studied in this work were selected in order to map out the scope of such base-promoted halogen migrations. As a quick survey reveals, it inevitably follows the basicity gradient in the descending direction. The obtainment of acids **2**, **16**, and **23** (rather than **1**, **15**, and **21**, respectively) merely underscores the fact that 2,6-dibromoaryllithium compounds are thermodynamically more stable (i.e., less basic) than 2,3-dibromoaryllithium compounds,[3,4] but more basic than 2-bromo-6-fluoroaryllithium compounds.[19] The driving force for the conversion of 2,3,4,6-tetrabromophenyllithium into 2,3,5,6-tetrabromophenyllithium (affording acids **5** and **4**, respectively) and of 2,6-dibromo-3,5-dichloro-4-fluorophenyllithium into 2,3-dibromo-4,6-dichloro-5-fluorophenyllithium (affording acids **18** and **19**, respectively) is much weaker. In the former case, one bromine atom slightly enhances its acidifying effect by switching from the *para* to a *meta* position (with respect to the metal center) and, at the same time, attenuates the intramolecular steric repulsion. In the latter case, formally a bromine and a chlorine atom (initially located at, respectively, an *ortho* and *meta* position relative to the metal-bearing center) and a chlorine and a fluorine atom (initially at *meta* and *para* positions, respectively) formally swap places as a consequence of the isomerization. The resulting difference in basicity can only be small, 0.5 kcal/mol at best (Scheme 8).



Scheme 8

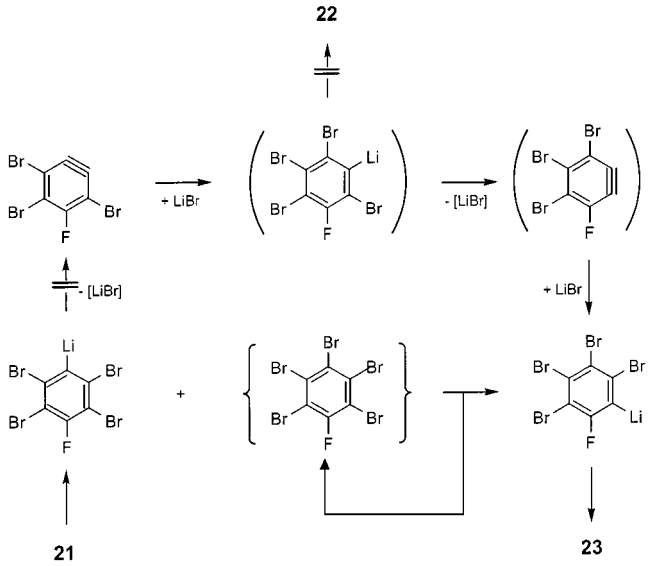
The isomerization mechanism has been established previously.[5,6,20–22] "Halogen scrambling" implies a bromine(iodine)/lithium permutation as the crucial step, catalytic quantities of a halogen-richer derivative (such as 1,2,3,4-tetrabromobenzene during the isomerization of 2,3,4-tribromophenyllithium) acting as a self-reproducing template. If the halogen migration occurs sluggishly it can be speeded up by artificial addition of this "turntable compound", which is otherwise formed in accidental side reactions (Scheme 9).



Scheme 9

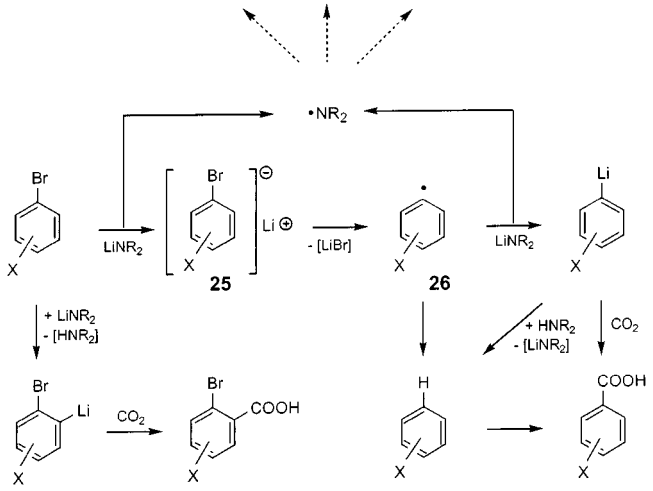
A lithium halide β-elimination/readdition mechanism has been ruled out, since all attempts to trap a transient dehydroarene ("aryne") failed. The present investigation provides additional evidence against the intermediacy of dehydroarenes. The LI'BSA-promoted deprotonation of 1,2,4,5-tetrabromo-3-fluorobenzene immediately generates 2,3,4,5-tetrabromo-6-fluorophenyllithium (producing the acid **23**), thus by-passing, at any reaction step, the isomeric 2,3,4,6-tetrabromo-5-fluorophenyllithium (the precursor to acid **22**), which would be an inevitable intermediate between two consecutive lithium halide β-elimination/readdition sequences (Scheme 10).

The choice of LI'BSA, LIDA, or LITMP, in the absence or presence of additional activators such as potassium *tert*-butoxide[23–25] and *N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine,[26] has to be made empirically rather than rationally. All of these amide bases are apparently strong enough to metalate a polyhalobenzene. Still, they display individuality not only as far as the rate of proton abstraction is



Scheme 10

concerned but also by the varying degrees of proneness to undergo side reactions, in particular towards dehalogenation. The LITMP-promoted transformation of 1,2,3-tribromobenzene may serve as an illustration (Scheme 1). Upon carboxylation, the acids **2**−**6** are isolated, resulting in part from isomerization ("halogen shuffling") and in part from dismutation. However, the combined yield of tetrabromobenzoic acids (**4** and **5**) is clearly inferior (19%) to that of the dibromobenzoic acid (**6**; 31%). Thus, the well-known dismutation process[5] must be accompanied by net reduction. As long as LIDA (or lithium diethylamide) is employed, one may invoke a hydride transfer mechanism as already postulated previously.[27−29] This argument, however, can be put forward neither for LITMP nor LI^{t}BSA, since both of these lack β-hydrogen atoms. Under such circumstances, single electron transfer (SET) from the base to the polyhalobenzene remains the sole plausible assumption. This has previously been suggested to explain the formation of the reductive dimerization product dilithium benzpinacolate upon treatment of benzophenone with LITMP.[30] The radical anion **25** thus generated will eliminate lithium bromide (or lithium iodide) to produce the aryl radical **26**. The latter may either abstract a hydrogen atom from the solvent or absorb another unpaired electron to give an aryllithium species to be quenched by the free amine or to survive until electrophilic trapping (see, for example, the acid **14**). The fate of the aminyl radical is a matter of speculation. Among the stabilization or decomposition modes worth consideration are its dimerization, its attacking the solvent and its cannibalizing hydrogen abstraction from a C−H bond of the free amine, which eventually breaks apart through ring scission (Scheme 11).



Scheme 11

Experimental Section

1. General: ^{1}H NMR spectra were recorded at 400 MHz, with all samples having been dissolved in deuterochloroform. For standard working practice, see recent publications (e.g., refs.[31,32]).

2. Starting Materials: 1,2-Difluorobenzene, 1,2,3-, 1,2,6- and 1,3,5-trifluorobenzene, 1,2,3,5- and 1,2,4,5-tetrafluorobenzene, pentafluorobenzene; 1,2-dichlorobenzene, 1,2,3-, 1,2,4- and 1,3,5-trichlorobenzene, 1,2,4,5-tetrachlorobenzene, pentachlorobenzene; 1,2,4-tribromobenzene and 1,2,4,5-tetrabromobenzene were purchased. All other substrates had to be prepared.

1,2,3-Tribromobenzene: A mixture of bromine (2.6 mL, 8.0 g, 50 mmol), (2,6-dibromophenyl)trimethylsilane (7.7 g, 25 mmol; see below), and carbon tetrachloride (25 mL) was heated at reflux for 4 d before being poured into a 1 M solution of sodium hydroxide (50 mL). After extraction with dichloromethane (3 × 20 mL), concentration, and sublimation, colorless crystals were obtained; m.p. 85−87 °C (ref.[33] m.p. 87.4 °C); 15.3 g (96%).

(2,6-Dibromophenyl)trimethylsilane: Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 1,3-dibromobenzene (3.0 mL, 5.9 g, 25 mmol) were consecutively added at −75 °C to a solution of butyllithium (25 mmol) in hexanes (17 mL) and tetrahydrofuran (50 mL). After 2 h at −75 °C, the mixture was treated with chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol). Addition of water (50 mL), extraction with dichloromethane (3 × 20 mL), and distillation gave a colorless liquid; b.p. 114−116 °C/3 Torr; n_D^{20} = 1.5817; d_4^{20} = 1.55 g/cm^3; 7.1 g (92%). − ^{1}H NMR: δ = 7.64 (d, J = 8.0 Hz, 2 H), 7.09 (t, J = 8.1 Hz, 1 H), 0.57 (s, 9 H). − $C_9H_{12}Br_2Si$ (308.10): calcd. C 35.09, H 3.93; found C 35.11, H 4.03.

1,2,3,5-Tetrabromobenzene: This compound was prepared from (2,4,6-tribromophenyl)trimethylsilane as described for 1,2,3-tribromobenzene (see above); m.p. 96−98 °C (ref.[34] m.p. 98 °C); 17.9 g (91%).

(2,4,6-Tribromophenyl)trimethylsilane: This compound was prepared by consecutive treatment of 1,3,5-tribromobenzene with lithium diisopropylamide and chlorotrimethylsilane [as described for (2,6-dibromophenyl)trimethylsilane]; colorless liquid; b.p. 95−97 °C/0.2 Torr; n_D^{20} = 1.6077; d_4^{20} = 1.88 g/cm^3; 7.0 g (72%). − ^{1}H NMR: δ = 7.81 (s, 2 H), 0.55 (s, 9 H). − $C_9H_{11}Br_3Si$ (387.00): calcd. C 27.93, H 2.87; found C 28.01, H 3.03.

1,3,5-Trifluoro-2-iodobenzene: A solution of lithium 2,2,6,6-tetramethylpiperidide (25 mmol) was prepared from 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (20 mL). At −75 °C, 1,3,5-trifluorobenzene (2.6 mL, 3.3 g, 25 mmol) and, 2 h later, iodine

(6.3 g, 25 mmol) were added. Distillation afforded a colorless liquid; b.p. 165−167 °C (ref.[35] b.p. 165 °C); 4.2 g (65%).

1,3,5-Trifluoro-2,5-diiodobenzene: This compound was prepared analogously, from 1,3,5-trifluoro-2-iodobenzene (see the preceding paragraph); colorless needles; m.p. 88−91 °C (ref.[36] m.p. 91−92 °C); 7.6 g (79%).

1,3,5-Trichloro-2-iodobenzene: This compound was prepared analogously, from 1,3,5-trichlorobenzene; colorless needles; m.p. 52−54 °C (ref.[34] m.p. 54 °C); 7.0 g (91%).

1,3,5-Trichloro-2,4-diiodobenzene: A mixture of (2,4,6-trichloro-3-iodophenyl)trimethylsilane (9.5 g, 25 mmol; see below) and iodine chloride (8.1 g, 50 mmol) was heated at reflux for 7 d. The product was isolated by extraction and sublimation; colorless feathers; m.p. 113−115 °C; 9.4 g (90%). − ^{1}H NMR: δ = 7.62 (s, 1 H). − $C_6HCl_3I_2$ (433.24): calcd. C 16.63, H 0.23; found C 16.98, H 0.24.

Trimethyl(2,4,6-trichlorophenyl)silane: This compound was prepared from 1,3,5-trichlorobenzene as described for trimethyl(2,4,6-tribromophenyl)silane (see above); b.p. 75−77 °C/0.4 Torr; n_D^{20} = 1.5527; d_4^{20} = 1.31 g/cm^3; 4.6 g (72%). − ^{1}H NMR: δ = 7.38 (s, 2 H), 0.50 (s, 9 H). − $C_9H_{11}Cl_3Si$ (253.63): calcd. C 42.62, H 4.37; found C 42.65, H 4.30.

Trimethyl(2,4,6-trichloro-3-iodophenyl)silane: This compound was prepared from trimethyl(2,4,6-trichlorophenyl)silane, using lithium 2,2,6,6-tetramethylpiperidide as the base and iodine as the electrophile; b.p. 102−104 °C/0.1 Torr; n_D^{20} = 1.6182; d_4^{20} = 1.78 g/cm^3; 8.5 g (90%). − ^{1}H NMR: δ = 7.49 (s, 1 H), 0.50 (s, 9 H). − $C_9H_{10}Cl_3ISi$ (379.53): calcd. C 28.48, H 2.66; found C 28.34, H 2.84.

2,3,4-Trifluoro-1-iodobenzene: This compound was prepared from 1,2,3-trifluorobenzene, using butyllithium in tetrahydrofuran at −75 °C for 2 h as the base and iodine as the electrophile; b.p. 62−64 °C/12 Torr; n_D^{20} = 1.5363; d_4^{20} = 2.20 g/cm^3; 4.0 g (62%). − ^{1}H NMR: δ = 7.47 (dddd, *J* = 11.8, 8.4, 5.5, 2.7 Hz, 1 H), 6.8 (m, 1 H). − $C_6H_2F_3I$ (257.98): calcd. C 27.93, H 0.78; found C 28.00, H 0.69.

2,3,4-Trifluoro-1,5-diiodobenzene: This compound was prepared from 2,3,4-trifluoro-1-iodobenzene as described above (preparation of 1,3,5-trifluoro-2-iodobenzene); m.p. 26−27 °C; 8.4 g (88%). − ^{1}H NMR: δ = 8.05 (td, *J* = 6.3, 2.8 Hz, 1 H). − $C_6HF_3I_2$ (383.88): calcd. C 18.77, H 0.26; found C 18.69, H 0.27.

Trimethyl(2,3,4-trifluorophenyl)silane: This compound was prepared by consecutive treatment of 1,2,3-trifluorobenzene (cf. above); b.p. 62−64 °C/12 Torr; n_D^{20} = 1.4529; d_4^{20} = 1.29; 4.3 g (84%). − ^{1}H NMR: δ = 7.2 (m, 1 H), 7.1 (m, 1 H), 0.32 (s, 9 H). − $C_9H_{11}F_3Si$ (204.27): calcd. C 52.92, H 5.43; found C 53.22, H 5.16.

(2,3,4-Trifluoro-1,5-phenylene)bis(trimethylsilane): This compound was prepared by consecutive treatment of trimethyl(2,3,4-trifluorophenyl)silane with butyllithium (in tetrahydrofuran for 2 h at −75 °C) and chlorotrimethylsilane; b.p. 71−73 °C/3 Torr; n_D^{20} = 1.4635; d_4^{20} = 1.09 g/cm^3; 5.9 g (86%). − ^{1}H NMR: δ = 7.17 (td, *J* = 6.1, 2.4 Hz, 1 H), 0.32 (s, 18 H). − $C_{12}H_{19}F_3Si_2$ (276.45): calcd. C 52.14, H 6.93; found C 52.04, H 7.07.

1,5-Dibromo-2,3,4-trifluorobenzene: This compound was prepared by heating a mixture of (2,3,4-trifluoro-1,5-phenylene)bis(trimethylsilane) and bromine in tetrachloromethane at reflux for 45 d; b.p. 28−30 °C/0.7 Torr; 71%; n_D^{20} = 1.5330; d_4^{20} = 2.27 g/cm^3; 5.1 g (71%). − ^{1}H NMR: δ = 7.71 (td, *J* = 6.7, 2.7 Hz, 1 H). − $C_6HBr_2F_3$ (289.89): calcd. C 24.86, H 0.35; found C 24.90, H 0.40.

(2,4-Dichloro-3-fluorophenyl)trimethylsilane: This compound was prepared from 1,3-dichloro-2-fluorobenzene in tetrahydrofuran at −75 °C by consecutive addition of 2,2,6,6-tetramethylpiperidine and chlorotrimethylsilane to butyllithium; b.p. 115−117 °C/11 Torr; n_D^{20} = 1.5204; d_4^{20} = 1.29 g/cm^3; 5.0 g (85%). − ^{1}H NMR: δ = 7.40 (dd, *J* = 5.5, 1.8 Hz, 1 H), 7.26 (dd, *J* = 8.2, 1.5 Hz, 1 H), 0.38 (s, 9 H). − $C_9H_{11}Cl_2FSi$ (237.18): calcd. C 45.58, H 4.67; found C 45.73, H 4.74.

(2,4-Dichloro-3-fluoro-1,5-phenylene)bis(trimethylsilane): This compound was prepared from (2,4-dichloro-3-fluorophenyl)trimethylsilane in tetrahydrofuran at −75 °C, by consecutive addition of 2,2,6,6-tetramethylpiperidine and chlorotrimethylsilane to butyllithium; b.p. 71−73 °C/0.2 Torr; n_D^{20} = 1.5152; d_4^{20} = 1.17 g/cm^3; 5.8 g (75%). − ^{1}H NMR: δ = 7.38 (d, *J* = 1.4 Hz, 1 H), 0.38 (s, 18 H). − $C_{12}H_{19}Cl_2FSi_2$ (309.36): calcd. C 46.59, H 6.19; found C 46.59, H 6.03.

1,5-Dibromo-2,4-dichloro-3-fluorobenzene: This compound was prepared by addition of (2,4-dichloro-3-fluoro-1,5-phenylene)bis(trimethylsilane) to a solution of bromine in tetrachloromethane and keeping the mixture at reflux for 27 d; colorless needles; m.p. 79−81 °C; 6.9 g (86%). − ^{1}H NMR: δ = 7.89 (d, *J* = 2.1 Hz, 1 H). − $C_6HBr_2Cl_2F$ (322.80): calcd. C 22.33, H 0.31; found C 22.34, H 0.25.

(2,4-Dibromo-6-fluorophenyl)trimethylsilane: This compound was prepared from 1,3-dibromo-5-fluorobenzene by consecutive treatment with lithium 2,2,6,6-tetramethylpiperidide (2 h at −75 °C) and chlorotrimethylsilane in tetrahydrofuran at −75 °C; b.p. 72−73 °C/0.4 Torr; n_D^{20} = 1.5565; 6.5 g (80%). − ^{1}H NMR: δ = 7.65 (dd, *J* = 1.5, 0.9 Hz, 1 H), 7.24 (dd, *J* = 9.0, 1.8 Hz, 1 H), 0.44 (d, *J* = 2.6 Hz, 9 H). − $C_9H_{11}Br_2FSi$ (326.09): calcd. C 33.15, H 3.40; found C 33.23, H 3.29.

(4,6-Dibromo-2-fluoro-1,3-phenylene)bis(trimethylsilane): This compound was prepared analogously from (2,4-dibromo-6-fluorophenyl)trimethylsilane; b.p. 74−75 °C/0.1 Torr; n_D^{20} = 1.5515; 8.5 g (85%). − ^{1}H NMR: δ = 7.70 (s, 1 H), 0.43 (d, *J* = 2.7 Hz, 18 H). − $C_{12}H_{19}Br_2FSi_2$ (398.27): calcd. C 36.19, H 4.81; found C 36.10, H 4.95.

1,2,4,5-Tetrabromo-3-fluorobenzene: This compound was prepared by heating a solution of (4,6-dibromo-2-fluoro-1,3-phenylene)bis(trimethylsilane) and bromine at reflux for 7 d. The product was isolated by extraction and sublimation; colorless tufts; m.p. 117−120 °C; 8.9 g (86%). − ^{1}H NMR: δ = 7.90 (d, *J* = 2.0 Hz, 1 H). − C_6HBr_4F (411.71): calcd. C 17.50, H 0.24; found C 17.63, H 0.24.

1,5-Dibromo-3-fluoro-2-iodobenzene: This compound was prepared from 1,3-dibromo-5-fluorobenzene by consecutive treatment with lithium 2,2,6,6-tetramethylpiperidide (2 h at −75 °C) and iodine in tetrahydrofuran; m.p. 44−46 °C; 8.6 g (91%). − ^{1}H NMR: δ = 7.76 (dd, *J* = 2.2, 1.6 Hz, 1 H), 7.29 (dd, *J* = 7.4, 2.0 Hz, 1 H). − $C_6H_2Br_2FI$ (379.81): calcd. C 18.97, H 0.53; found C 18.97, H 1.04.

1,5-Dibromo-3-fluoro-2,4-diiodobenzene: This compound was prepared analogously, from 1,5-dibromo-3-fluoro-2-iodobenzene; m.p. 151−153 °C; 11.6 g (92%). − ^{1}H NMR: δ = 7.88 (d, *J* = 1.5 Hz, 1 H). − $C_6HBr_2FI_2$ (505.70): calcd. C 14.25, H 0.20; found C 14.13, H 0.18.

3. Products (Benzoic Acids)

Tri-, Tetra- and Pentabromoarenes: The deprotonations were carried out with lithium *N*-*tert*-butyl-*N*-(*tert*-butyldimethylsilyl)amide (LI^{t}BSA), lithium diisopropylamide (LIDA), or lithium 2,2,6,6-tetramethylpiperidide (LITMP), prepared by mixing the corresponding amine − *N*-*tert*-butyl-*N*-(*tert*-butyldimethylsilyl)amine,[37] diisopropylamine, or 2,2,6,6-tetramethylpiperidine − and butyllithium, in tetrahydrofuran at −75 °C. After treatment of the lithiated intermediate with dry ice, the acids were isolated by extraction and purified by preparative gas chromatography, crystallization, or sublimation.

2,3,6-Tribromobenzoic Acid (2): This compound was prepared from 1,2,3-tribromobenzene (7.9 g, 25 mmol), using LI^{t}BSA; m.p. 192−193 °C; 4.5 g (50%).

2,6-Dibromobenzoic Acid (6) and 2,4,6-Tribromobenzoic Acid (3): Compounds **6** (m.p. 141−144 °C; ref.[38] m.p. 146 °C; 6.2 g, 89%) and **3** (m.p. 188−190 °C; ref.[39] m.p. 194 °C; 7.0 g, 78%) were prepared by treatment with LIDA and subsequent carboxylation as described recently.[3]

2,3,5,6-Tetrabromobenzoic Acid (4):[40] This compound was prepared from 1,2,4,5-tetrabromobenzene (9.8 g, 25 mmol), using LITMP; m.p. 218−221 °C; 7.4 g (68%). − ^{1}H NMR: δ = 8.04 (s, 1 H). − ^{13}C NMR: δ = 142.3, 136.6, 125.2 (2 C), 120.7 (2 C).

2,3,4,6-Tetrabromobenzoic Acid (5):[41] This compound was prepared from 1,2,3,5-tetrabromobenzene (9.8 g, 25 mmol), using LI^{t}BSA; m.p. 231−233 °C (dec.; cryst. from toluene); 0.33 g (3%).

2,3,4,5,6-Pentabromobenzoic Acid (7): This compound was prepared from pentabromobenzene[42] (11.8 g, 25 mmol), using LIDA (rather than LITMP); m.p. 265−268 °C (cryst. from toluene; ref.[43] m.p. 273 °C); 9.8 g (76%).

Monoiodo- and Diiodo-Substituted 2,4,6-Trifluoro- and 2,4,6-Trichlorobenzoic Acids: The metalations and subsequent carboxylations of the corresponding arenes were carried out and the products isolated as described recently.[3] 2,4,6-Trifluorobenzoic acid[44] and 2,4,6-trichlorobenzoic acid[45] are known compounds.

2,4,6-Trifluoro-3-iodobenzoic Acid (8): This compound was prepared from 1,3,5-trifluoro-2-iodobenzene, using LI^{t}BSA; colorless needles; m.p. 176−179 °C; 4.8 g (79%). − $C_7H_2F_3IO_2$ (301.99): calcd. C 27.84, H 0.67; found C 28.27, H 0.99.

2,4,6-Trifluoro-3,5-diiodobenzoic Acid (9): This compound was prepared analogously, from 1,3,5-trifluoro-2,4-diiodobenzene; faintly yellowish triclinic microcrystals; m.p. 183−185 °C; 9.6 g (90%). − ^{13}C NMR: δ = 163.3 (dt, *J* = 248.2, 8.8 Hz), 162.6, 161.2 (dt, *J* = 249.0, 8.0 Hz, 2 C), 107.6 (td, *J* = 21.7, 4.8 Hz), 66.0 (td, *J* = 32.9, 4.0 Hz, 2 C). − $C_7HF_3I_2O_2$ (427.89): calcd. C 19.65, H 0.24; found C 19.85, H 0.26.

2,4,6-Trichloro-3-iodobenzoic Acid (11): This compound was prepared analogously, from 1,3,5-trichloro-2-iodobenzene; colorless needles; m.p. 198−201 °C (cryst. from toluene); 2.7 g (31%). − ^{1}H NMR: δ = 7.58 (s). − $C_7H_2Cl_3IO_2$ (351.36): calcd. C 23.93, H 0.57; found C 24.00, H 0.66.

2,4,6-Trichloro-3,5-diiodobenzoic Acid (12): This compound was prepared analogously, from 1,3,5-trichloro-2,4-diiodobenzene; cream-colored feathers; m.p. 224−227 °C (cryst. from toluene); 2.1 g (18%). − ^{13}C NMR: δ = 165.3, 145.7, 136.9 (2 C), 132.8, 101.7 (2 C). − $C_7HCl_3I_2O_2$ (477.25): calcd. C 17.62, H 0.21; found C 17.71, H 0.24.

2,3,4-Trifluoro-5-iodobenzoic Acid (14): This compound was prepared analogously, from 2,3,4-trifluoro-1,5-diiodobenzene using LIDA; colorless needles; m.p. 153−156 °C; 2.7 g (36%). − ^{1}H NMR: δ = 8.40 (td, *J* = 7.1, 2.5 Hz, 1 H). − ^{13}C NMR: δ = 167.0, 154.7 (dd, *J* = 253.4, 11.6 Hz), 152.3 (dd, *J* = 270.2, 12.5 Hz), 140.1 (dt, *J* = 257.0, 16.5 Hz), 135.5, 11.5 (dd, *J* = 7.2, 4.0 Hz), 75.3 (dd, *J* = 23.2, 4.0 Hz). − $C_7H_2F_3IO_2$ (301.99): calcd. C 27.84, H 0.67; found C 27.82, H 0.88.

Dibromotrifluorobenzoic Acids, Dibromodichlorofluorobenzoic Acids, and Tetrabromofluorobenzoic Acids: The deprotonations of the respective arenes were carried out with LIDA, unless stated otherwise, and, after carboxylation, the products were isolated as described above.

2,6-Dibromo-3,4,5-trifluorobenzoic Acid (15): This compound was prepared from 1,5-dibromo-2,3,4-trifluorobenzene, using LI^{t}BSA; colorless felt; m.p. 106−108 °C (after sublimation and repetitive fractional crystallization from hexanes); 1.3 g (16%). − ^{13}C NMR: δ = 165.7 (s), 148.1 (dd, *J* = 252.2, 11.2 Hz), 140.4 (dt, *J* = 260.3, 16.9 Hz, 2 C), 134.8 (d, *J* = 4.0 Hz, 2 C), 102.8 (symm. m). − $C_7HBr_2F_3O_2$ (333.90): calcd. C 25.18, H 0.30; found C 25.22, H 0.32.

2,3-Dibromo-4,5,6-trifluorobenzoic Acid (16): This compound was prepared from 1,5-dibromo-2,3,4-trifluorobenzene; colorless needles; m.p. 126−128 °C; 7.2 g (86%). − ^{13}C NMR: δ = 163.9 (s), 149.6 (ddd, *J* = 253.7, 11.2, 3.2 Hz), 147.6 (ddd, *J* = 257.1, 12.1, 4.8 Hz), 139.4 (dt, *J* = 257.8, 16.5 Hz), 123.8 (dd, *J* = 18.5, 3.0 Hz), 116.8 (t, *J* = 4.4 Hz), 110.6 (dd, *J* = 20.1, 4.0 Hz). − $C_7HBr_2F_3O_2$ (333.90): calcd. C 25.18, H 0.30; found C 25.36, H 0.28.

2,6-Dibromo-3,5-dichloro-4-fluorobenzoic Acid (18): This compound was present as the minor component in a reaction mixture formed upon consecutive treatment of 1,5-dibromo-2,4-dichloro-4-fluorobenzene with LIDA, dry ice and acid. It was separated by sublimation and repetitive fractional crystallization from hexanes; colorless prisms; m.p. 164−166 °C from hexanes); 1.4 g (15%). − ^{13}C NMR: δ = 166.5, 155.0 (d, *J* = 258.6 Hz), 135.8, 124.1 (d, *J* = 20.0 Hz, 2 C), 118.9 (2 C). − $C_7HBr_2Cl_2FO_2$ (366.81): calcd. C 22.92, H 0.27; found C 23.00, H 0.30.

2,3-Dibromo-4,6-dichloro-5-fluorobenzoic Acid (19): This compound was contained as the major component in the reaction mixture mentioned in the preceding paragraph. It was isolated by crystallization; colorless needles; m.p. 170−172 °C (cryst. from hexanes); 5.6 g (61%). − ^{13}C NMR: δ = 168.1 (s), 153.9 (d, *J* = 255.5 Hz), 135.2 (s), 126.7 (s), 126.5 (d, *J* = 19.3 Hz), 119.1 (d, *J* = 20.9 Hz), 117.5 (d, *J* = 4.8 Hz). − $C_7HBr_2Cl_2FO_2$ (366.81): calcd. C 22.92, H 0.27; found C 23.00, H 0.27.

2,3,4,5-Tetrabromo-6-fluorobenzoic Acid (23): This compound was prepared from 3-fluoro-1,2,4,5-tetrabromobenzene, using LITMP; colorless needles; m.p. 220−222 °C; 6.5 g (57%). − ^{13}C NMR: δ = 164.1 (s), 154.5 (d, *J* = 253.7 Hz), 130.1 (s), 127.1 (d, *J* = 24.1 Hz), 125.0 (d, *J* = 4.8 Hz), 121.7 (s), 113.8 (d, *J* = 22.5 Hz). − $C_7HBr_4FO_2$ (455.72): calcd. C 18.45, H 0.22; found C 18.48, H 0.22.

2,3,4,6-Tetrabromo-5-fluorobenzoic Acid (22) and 2,3,5,6-Tetrabromo-4-fluorobenzoic Acid (21): Authentic samples were required to identify compounds **22** (m.p. 196−198 °C) and **21** (m.p. 230−232 °C). These were prepared according to a literature procedure.[46] Consecutive treatment of 1,2,4,5-tetrabromo-3-fluorobenzene with LITMP and dry ice gave a complex product mixture.

The presence of the acids **21**, **22**, and **23**, though suspected, could not be rigorously established. The reaction mixture obtained after deprotonation of the substrate was therefore neutralized with diluted mineral acid and, in addition to starting material (10%), the isomerization or dehalogenation products, 1,3,4,5-tetrabromo-2-fluorobenzene (5%), 1,2,3,4-tetrabromo-5-fluorobenzene (30%), 1,2,3-tribromo-5-fluorobenzene (10%), 1,2,5-tribromo-3-fluorobenzene (35%) and 1,2,4-tribromo-5-fluorobenzene (10%) were identified by gas chromatography and NMR spectroscopy. With LI′BSA under the same conditions, 1,2,3,4-tetrabromo-5-fluorobenzene was formed as the sole product.

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