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The site-selective functionalization of halogen-bearing phenols: an exercise in diversity-oriented organometallic synthesis

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Abstract—The organometallic approach to diversity-oriented organic synthesis was subjected to a further test, this time in the phenol series. The model compounds selected were 2,3,6-trifluorophenol, the three isomers of (trifluoromethoxy)phenol and the three isomers of chlorophenol. A combination of optionally site selective metalations and protective group-controlled metalations enabled the selective generation of several isomeric intermediates in each case and their subsequent conversion into functionalized derivatives, in particular hydroxybenzoic acids.

1. Introduction

Phenols as a class of compounds do presently not attract much attention. This happened to be different at the dawn of organic chemistry. In these days they played a prominent role as both targets and intermediates of structural elaboration. In fact, they rapidly became one of the cornerstones supporting the progress in a frenetically developing area. The names of the researchers involved in this process reads like an almanac of chemical nobility: Baeyer, Bucherer, Claisen, Fries, Kolbe, Pechmann, Reimer, Schmitt, Simonis, Tiemann, Ullmann and Vilsmeier.

Some of the classical phenol reactions give rise to mainly *ortho*-substituted derivatives as they benefit from neighboring group assistance provided by the neutral or deprotonated hydroxyl group or proceed in a concerted fashion, in particular as a [3.3]-sigmatropic rearrangement. Others favor, for steric and electronic reasons, the *para* isomers. By and large, however, electrophilic substitutions of phenols tend to give mixtures of *ortho* and *para* isomers, *meta* isomers being formed only in trace amounts, if at all.

The only rigorous way to secure regiochemical predictability and fidelity in phenol reactions is to transit organometallic species wherein the nucleophilically active center is unequivocally defined. To realize this idea in a most simple fashion, one needs only to select the appropriate bromophenol, treat it with two equivalents of an organometallic agent such as butyllithium or *tert*-butyllithium and trap the generated (lithiooxy)phenyllithium with a suitable electrophile. Such sequences have been successfully carried out in several cases indeed.[1] The yields, in general moderate to good, can still be improved if the phenolic hydroxyl group is protected as a methoxymethoxy or 2-tetrahydropyranyloxy unit prior to the crucial halogen/metal permutation step.[1]

This scheme nevertheless suffers from a serious drawback. Only the most simple bromophenols are commercially available and even those are rarely inexpensive. Thus, the access to the required starting material will often constitute a major obstacle. It would be more straightforward and economic to start from a bromine-free (or iodine-free) phenol and to subject it to a permutational hydrogen/metal rather than halogen/metal interconversion. Unfortunately, the direct 'metalation' of halogen-devoid phenols has only been accomplished with phenol itself[2] and with 2-naphthol[3,4] as the substrates (at the 2- and 3-position, respectively). 1-Naphthol was found to be attacked concomitantly at the 2- and 8-position.[4] Alkoxy- and aroxy-substituted phenols[5–7] also tend to produce regioisomeric mixtures despite poor yields, unless they dispose of no more than one vacant position.[8]

We wondered whether halogen-substituents would not considerably facilitate the metalation of phenol-derived acetals and, moreover, comprise an option on more regioflexibility. This was anticipated on the basis of

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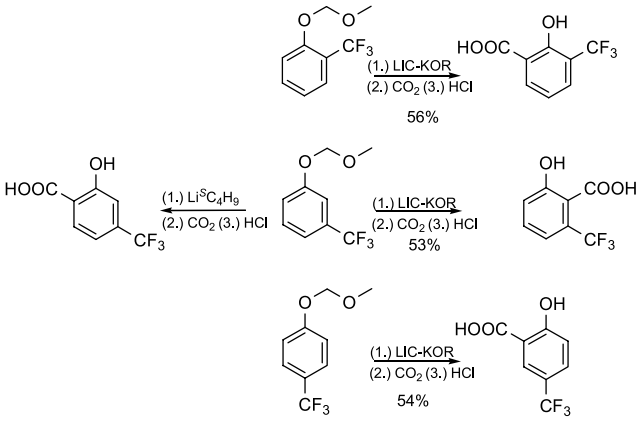
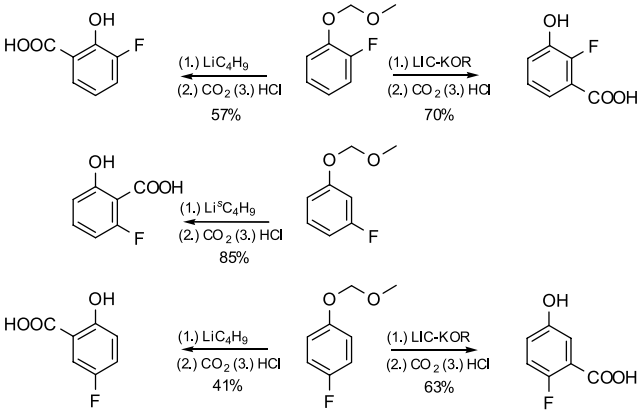
optionally site selective metalations we had previously carried out with a variety of halogenated substrates, in particular fluorotoluenes,[9,10] fluoroanisoles,[11] fluoroanilines,[12] chlorofluorobenzenes,[13] bromofluorobenzenes,[13] (trifluoromethyl)toluenes,[9] (trifluoromethyl)anilines,[12] fluorobenzotrifluorides,[14] chlorobenzotrifluorides,[14] bromobenzotrifluorides[14] and bis- or tris(trifluoromethyl)benzenes.[15,16] Our first endeavors in this direction proved to be quite encouraging.

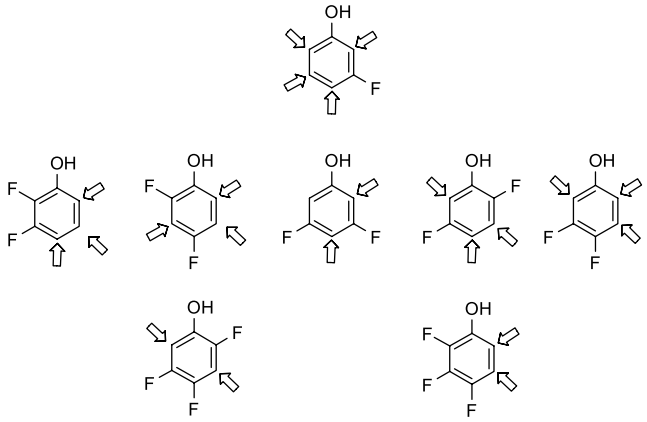
The *O*-methoxymethyl protected 2- and 4-(trifluoromethyl)-phenols reacted with the mixture of butyllithium and potassium *tert*-butoxide ('LIC-KOR' superbase) under proton abstraction from the oxygen-adjacent positions to provide the corresponding hydroxybenzoic acids in 56 and 54% yield.[17] The *meta* isomer featured another example of optional site selectivity by undergoing metalation with LIC-KOR at the 2-position flanked by both substituents and at the coordinatively assisted 6-position with *sec*-butyllithium, affording the corresponding hydroxybenzoic acids in 53 and 93% yield, respectively.[17]



The metalation of the three fluoro(methoxymethoxy)benzenes with butyllithium or *sec*-butyllithium at the position next to the oxygen substituent having already been reported, we were still able to improve the yields of the isolated fluorohydroxybenzoic acids (to 69–93%).[17] At the same time we installed optional site selectivity in the metalation of the *ortho* and *para* isomers, which were deprotonated and subsequently carboxylated (84 and 80% of the acids) at the fluorine-adjacent positions when LIC-KOR was employed as the base.[17]

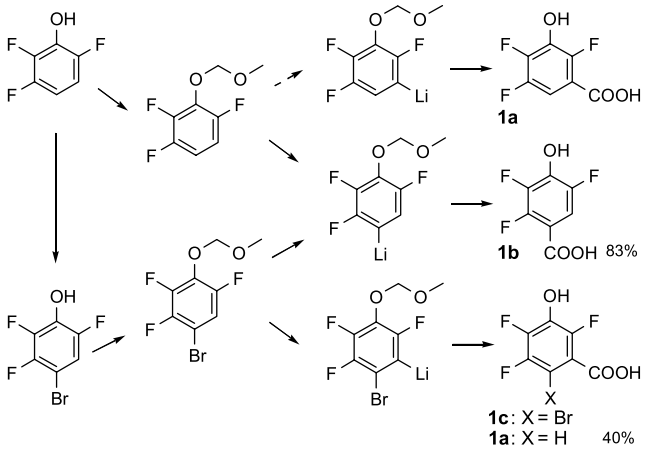


Work of this kind contributes to the prospects of diversity-oriented synthesis.[18] Meanwhile the toolbox approach[19,20] has been conceived to extend and perfect such opportunities. By virtue of sophisticated organometallic protocols any vacant position in an aromatic or heterocyclic substrate can be selectively metalated and subsequently functionalized. To demonstrate the validity of the concept, several model substrates were converted into all possible isomeric derivatives by carrying out regioisomerically exhaustive metalations and functionalizations. Mono-, di- and trifluorophenols belong to the noteworthy examples in this respect.[21,22]



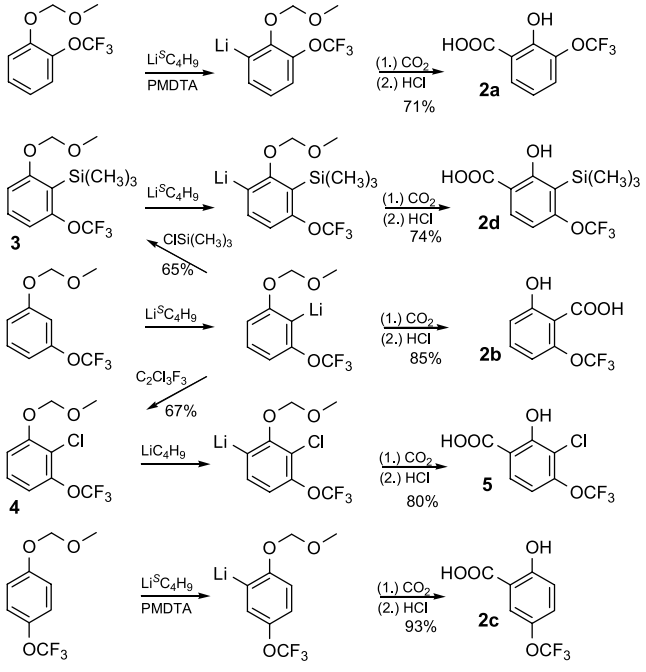
2. Results and discussion

We wanted to complement our study of trifluorophenols by including the 2,3,6-trifluoro isomer into the investigations. This model compound represents a challenge. Although there are only two vacant positions left, both of them are activated in an almost identical manner each having a fluorine atom as a direct neighbor. Actually, the metalation of either the *O*-methoxymethyl or *O*-triisopropylsilyl protected 2,3,6-trifluorophenol gave more or less random mixtures of organolithium species, the latter being eventually trapped as the hydroxybenzoic acid **1a** and **1b**. The highest regioselectivity of 5:95 was achieved when the acetal was treated with lithium diisopropylamide (LIDA) in tetrahydrofuran. The problem could be easily circumvented by bromination of the phenol at the *para* position. Halogen/metal permutation accomplished with butyllithium in tetrahydrofuran afforded the acid **1b** in 83% yield. The isomeric acid **1a** (40%) was prepared in a one-pot procedure by consecutive deprotonation of the acetal with lithium diisopropylamide, reaction with dry ice and debromination of the intermediate with zinc powder in alkaline medium.

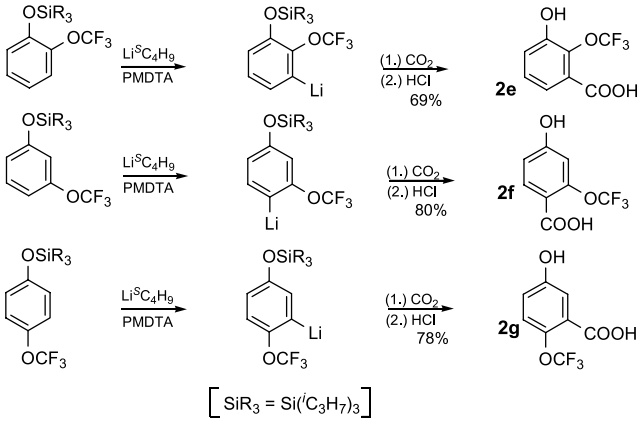


The (trifluoromethoxy)phenols, the next selection of model substrates, are quite expensive starting materials. Therefore, we contented ourselves to make only seven rather than all ten of the corresponding carboxylic acids. Optional site selectivity was this time not achieved by reagent matching[18] but rather by an appropriate choice of the *O*-protecting entity.

1-Methoxymethoxy-2- and -4-(trifluoromethoxy)benzene reacted smoothly at the acetal-adjacent sites thus leading to the acids **2a** (71%) and **2c** (93%). The *meta* isomer underwent metalation at the doubly activated position flanked by the two substituents thus providing the acid **2b** (85%) after carboxylation and neutralization. When, instead of the carboxy function, a trimethylsilyl group or a chlorine atom was introduced in the lithiated 2-position (to give the silane **3** or the chloroarene **4**), the next metalation took place at the methoxymethoxy-neighboring 6-position. This opened an entry to the acids **2d** (74%; after protodesilylation using tetrabutylammonium fluoride hydrate ['TBAF']) and **5** (80%).

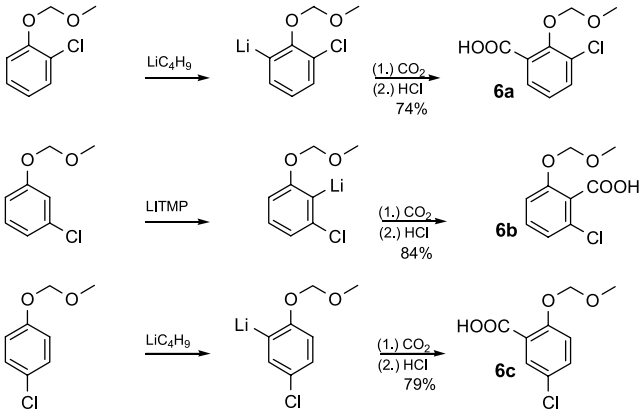


On the other hand, the bulky triisopropylsilyl group sterically shields its immediate vicinity. Therefore, metalation with *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine ('PMDTA') was deflected to the remote OCF_3-adjacent position. Carboxylation and deprotection afforded the hydroxy(trifluoromethoxy)-benzoic acids **2e**–**2g** (in 69, 80 and 78% yield).



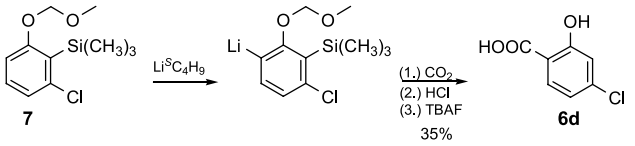
Trifluoromethoxy groups resemble chloro substituents in several respects[23] even if the latter are a bit less effective in activating *ortho*-position toward metalation.[24] For sake of comparison, the three chlorophenols were protected as methoxymethyl and triisopropylsilyl ethers before being metalated with butyllithium and *sec*-butyllithium, respectively.

In analogy with the behaviour of the corresponding (trifluoromethoxy)phenol derivatives, proton abstraction from the chloro(methoxymethoxy)benzenes occurred exclusively from oxygen-adjacent positions. The hydroxybenzoic acids **6a**, **6b** and **6c** were isolated in 74, 84 and 79% yield. The metalation of 1-chloro-2-(methoxymethoxy)benzene has been reported previously.[25]

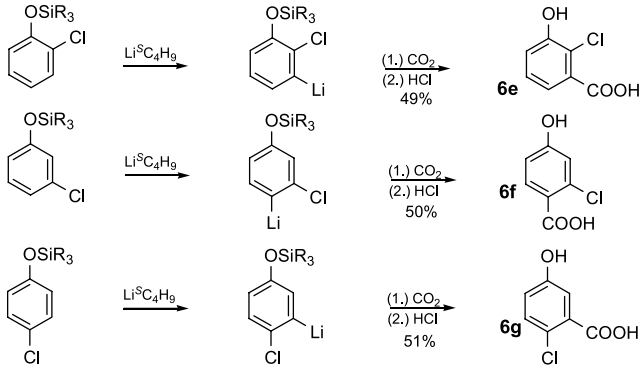


The weaker base[26] lithium 2,2,6,6-tetramethylpiperidide (LITMP) had to be employed with the *meta*-substituted substrate as both butyllithium and *sec*-butyllithium provided a mixture of the acid **6b** and its isomer **6d**. The latter compound was selectively prepared in 35% yield by treating the silane **7**, obtained after mixing 1-chloro-3-

(methoxymethoxy)benzene with LITMP and chlorotrimethylsilane, consecutively with *sec*-butyllithium, dry ice, hydrochloric acid and TBAF.



The *O*-triisopropylsilyl protected chlorophenols also followed the previously encountered pattern. *sec*-Butyllithium attacked solely the chlorine-adjacent positions remote from the silyloxy entity. After trapping with dry ice the hydroxybenzoic acids **6e**, **6f** and **6g** were obtained in 49, 50 and 51% yield.



Carboxylation is presumably the most common way to characterize an organometallic intermediate by derivatization. Despite its popularity, carbon dioxide remains just one out of dozens if not hundreds of eligible electrophiles. The metalation reactions disclosed above thus do not simply open a route leading to rare benzoic acids but may be used to access numerous classes of otherwise functionalized compounds.

3. Experimental

3.1. Generalities

Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.[27–29] ^{1}H and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, samples having been dissolved in $CDCl_3$ or, if marked by an asterisk (*), in acetone-d_6. Mass spectra were obtained by the chemical ionization technique (c.i.) in an ammonia atmosphere at 100 °C source temperature. To avoid redundancy, only the [^{35}Cl] and [^{79}Br] fragments, and not the [^{37}Cl] or [^{81}Br] isotopomers, are listed in all cases. Whenever possible and appropriate, yields and purities 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 stationary phases employed are encoded as DB-23 (silicone type) and DB-WAX (polyethylene glycol type).

3.2. Derivatives of 2,3,6-trifluorophenol

3.2.1. 4-Bromo-2,3,6-trifluorophenol. A solution containing 2,3,6-trifluorophenol (15 g, 0.10 mol) and *N*-bromosuccinimide (18 g, 0.10 mol) in chloroform (0.20 L) was kept 2 h at 0 °C. After the addition of a saturated aqueous solution (0.10 L) of sodium thiosulfate, the reaction mixture was extracted with dichloromethane (3×0.10 L). The organic layer was evaporated and the residue crystallized from hexanes as colorless platelets; mp 44–45 °C; yield: 19.8 g (87%). ^{1}H NMR: δ=7.16 (ddd, J=9.7, 5.8, 2.6 Hz, 1H), 5.38 (broad s, 1H) ppm; ^{13}C NMR: δ=148.0 (td, J=243, 4 Hz), 145.9 (ddd, J=245, 12, 4 Hz), 141.7 (ddd, J=248, 17, 6 Hz), 134.1 (ddd, J=15, 13, 2 Hz), 114.3 (dd, J=23, 4 Hz), 98.8 (dd, J=20, 11 Hz) ppm; MS (c.i.): m/z (%)=244 (0) [M^++NH_4], 229 (39) [M^++3], 228 (99) [M^++2], 227 (28) [M^++1], 226 (61) [M^+], 99 (100).

3.2.2. 1-Bromo-2,3,5-trifluoro-4-(methoxymethoxy)benzene. Prepared at 0 °C, a solution of 4-bromo-2,3,6-trifluorophenol (17 g, 75 mmol), chloromethyl methyl ether[30] (9.1 mL, 9.7 g, 90 mmol) and *N*-ethyldiisopropylamine (14 mL, 12 g, 90 mmol) in dichloromethane (75 mL) was kept at 25 °C for 2 h. The mixture was poured into a 3.0 M aqueous solution (0.15 L) of sodium hydroxide, extracted with dichloromethane (2×75 mL) and distilled; colorless liquid; bp 59–61 °C/3 mmHg; n_D^{20}=1.4902; yield: 17.9 g (88%). ^{1}H NMR: δ=7.16 (ddd, J=9.9, 6.1, 2.9 Hz, 1H), 5.20 (s, 2H), 3.61 (s, 3H) ppm; ^{13}C NMR: δ=152.2 (td, J=248, 4 Hz), 146.0 (ddd, J=254, 15, 6 Hz), 145.9 (ddd, J=249, 13, 4 Hz), 133.9 (ddd, J=16, 12, 2 Hz), 114.6 (dd, J=24, 4 Hz), 103.2 (ddd, J=29, 11, 2 Hz), 99.0 (t, J=4 Hz), 57.6 ppm; MS (c.i.): m/z (%)=288 (0) [M^++NH_4], 272 (2) [M^++2], 270 (3) [M^+], 228 (62), 99 (100); $C_8H_6BrF_3O_2$ (271.03): calcd C 35.45, H 2.23; found C 35.61, H 2.41.

3.2.3. 2,4,5-Trifluoro-3-hydroxybenzoic acid (1a). 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol), potassium *tert*-butoxide (2.8 g, 25 mmol), *N*,*N*,*N*′,*N*″,*N*″-pentamethylethylenediamine (5.2 mL, 4.3 g, 25 mmol) and 1-bromo-2,3,5-trifluoro-4-(methoxymethoxy)benzene (6.8 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (32 mL) and hexanes (16 mL) kept at −125 °C. After 45 min, the reaction mixture was poured onto freshly crushed dry ice and evaporated. The residue was partitioned between water (25 mL) and diethyl ether (50 mL). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3×50 mL). After evaporation of the solvents, the residue was dissolved in a 3.0 M aqueous solution (25 mL) of sodium hydroxide and stirred with zinc powder (4.9 g, 75 mmol) for 2 h at 25 °C. The reaction mixture was acidified to pH 1 with concentrated hydrochloric acid and extracted with diethyl ether (3×25 mL). After evaporation of the solvents, the residue was crystallized from chloroform; colorless needles; mp 143–144 °C; yield: 1.92 g (40%). ^{1}H NMR*: δ=7.35 (ddd, J=10.6, 8.3, 5.8 Hz, 1H) ppm; ^{13}C NMR*: δ=163.5 (m), 149.3 (ddd, J=254, 5, 3 Hz), 147.0 (ddd, J=242, 11, 3 Hz), 141.1 (ddd, J=251, 16, 5 Hz), 136.7 (ddd, J=18, 12, 3 Hz), 114.7 (ddd, J=17, 7, 4 Hz), 108.1 (d, J=21 Hz) ppm; MS (c.i.): m/z

(%)=210 (0) [$M^+ + NH_4$], 194 (8) [$M^+ + 2$], 193 (55) [$M^+ + 1$], 192 (76) [M^+], 175 (100); $C_7H_3F_3O_3$ (192.09): calcd C 43.77, H 1.57; found C 43.94, H 1.54.

3.2.4. 2,3,5-Trifluoro-4-hydroxybenzoic acid (1b). 1-Bromo-2,3,5-trifluoro-4-(methoxymethoxy)-benzene (6.8 g, 25 mmol) was added to a solution of butyllithium (25 mmol) in hexanes (17 mL) and tetrahydrofuran (33 mL) kept in a dry ice/methanol bath. After 15 min at −75 °C, the reaction mixture was poured onto freshly crushed dry ice. After addition of water (25 mL) and washing with diethyl ether (2×25 mL), the aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3×50 mL). Evaporation of the solvents and crystallization from toluene afforded colorless needles; mp 154–156 °C; yield: 3.99 g (83%). ^{1}H NMR*: δ=7.53 (ddd, J=10.6, 6.7, 2.2 Hz, 1H) ppm; ^{13}C NMR*: δ=163.3 (m), 148.7 (ddd, J=258, 12, 4 Hz), 147.8 (dt, J=241, 4 Hz), 141.8 (ddd, J=243, 16, 6 Hz), 140.1 (ddd, J=17, 13, 5 Hz), 112.7 (symm. m), 109.8 (t, J=8 Hz) ppm; MS (c.i.): m/z (%)=210 (0) [$M^+ + NH_4$], 194 (5) [$M^+ + 2$], 193 (12) [$M^+ + 1$], 192 [M^+], 175 (100); $C_7H_3F_3O_3$ (192.09): calcd C 43.77, H 1.57; found C 43.58, H 1.49.

3.2.5. 1,2,4-Trifluoro-3-(methoxymethoxy)benzene. Prepared analogously as 1-bromo-2,3,5-trifluoro-4-(methoxymethoxy)benzene (see above) from 2,3,6-trifluorophenol (15 g, 0.10 mol), colorless liquid; bp 33–39 °C/3 mmHg; n_D^{20}=1.4429; yield: 16.7 g (87%).^{1}H NMR: δ=6.87 (m, 2H), 5.20 (s, 2H), 3.63 (s, 3H) ppm; ^{13}C NMR: δ=152.8 (td, J=244, 3 Hz), 148.1 (ddd, J=235, 11, 3 Hz), 145.6 (ddd, J=246, 15, 6 Hz), 134.8 (ddd, J=14, 12, 2 Hz), 111.2 (dd, J=20, 9 Hz), 110.7 (ddd, J=22, 8 Hz), 99.3 (t, J=4 Hz), 57.5 ppm; MS (c.i.): m/z (%)=200 (0) [$M^+ + NH_4$], 192 (100) [M^+], 141 (32), 82 (43); $C_8H_7F_3O_2$ (192.14): calcd C 50.01, H 3.67; found C 50.08, H 3.52. Upon reaction of the acetal with butyllithium or lithium diisopropylamide in tetrahydrofuran followed by carboxylation, a mixture of the acids **1a** and **1b** was obtained in the ratios of 40:60 (61%) and 5:95 (83%) respectively, as determined by gas chromatographic analysis of the crude product after esterification with ethereal diazomethane [30 m, DB-WAX, 150 °C; 30 m, DB-23, 150 °C].

3.2.6. Triisopropyl(2,3,6-trifluorophenoxy)silane. 2,3,6-Trifluorophenol (15 g, 0.10 mol), chlorotriisopropylsilane (22 mL, 20 g, 0.10 mol) and imidazole (6.8 g, 0.10 mol) were dissolved in *N*,*N*-dimethylformamide (50 mL). After 20 h at 25 °C, the mixture was poured into water (100 mL) and extracted with dichloromethane (3×50 mL). Distillation under reduced pressure gave a colorless liquid; bp 101–102 °C/3 mmHg; n_D^{20}=1.4695; yield: 25.0 g (82%). ^{1}H NMR: δ=6.76 (dddd, J=11.8, 9.6, 7.4, 2.2 Hz, 2H), 6.68 (symm. m, 1H), 1.30 (hept., J=7.4 Hz, 3H), 1.09 (d, J=7.4, 18 Hz) ppm; ^{13}C NMR: δ=151.4 (dt, J=241, 3 Hz), 148.2 (ddd, J=245, 12, 3 Hz), 144.2 (ddd, J=247, 15, 5 Hz), 135.2 (ddd, J=15, 12, 3 Hz), 110.0 (ddd, J=21, 8, 3 Hz), 107.5 (dd, J=20, 8 Hz), 18.0 (3 C), 13.2 (6 C) ppm; MS (c.i.): m/z (%)=322 (0) [$M^+ + NH_4$], 305 (4) [$M^+ + 1$], 304 (4) [M^+], 262 (100); $C_{15}H_{23}F_3OSi$ (304.42): calcd C 59.18, H 7.62; found C 59.16, H 7.79. Consecutive treatment of the silyl ether with lithium 2,2,6,6-tetramethylpiperidide in diethyl ether, dry ice and hydrochloric acid afforded a 10:90 mixture (80%) of the acids **1a** and **1b** as determined by gas chromatographic analysis of the crude product after esterification with ethereal diazomethane [30 m, DB-WAX, 150 °C; 30 m, DB-23, 150 °C].

3.3. Derivatives of (trifluoromethoxy)phenols

3.3.1. 1-(Methoxymethoxy)-2-(trifluoromethoxy)benzene. Prepared at 0 °C, a solution of 2-(trifluoromethoxy)-phenol (18 g, 0.10 mol), *N*-ethyldiisopropylamine (18 mL, 16 g, 0.12 mol) and chloromethyl methyl ether[30] (9 mL, 10 g, 0.12 mol) in dichloromethane (80 mL) was kept for 2 h at 25 °C, before being poured into a 3.0 M aqueous solution (0.20 L) of sodium hydroxide. Extraction with dichloromethane (2×0.10 L) and distillation gave a colorless liquid; bp 51–52 °C/6 mmHg; n_D^{20}=1.4320; yield: 16.2 g (73%). ^{1}H NMR: δ=7.22 (symm. m, 3H), 7.0 (m, 1H), 5.25 (s, 2H), 3.51 (s, 3H) ppm. ^{13}C NMR: δ=150.1, 139.2, 128.3, 123.5, 122.4, 121.1 (q, J=256 Hz), 117.3, 95.4, 56.5 ppm. MS (c.i.): m/z (%)=240 (0) [$M^+ + NH_4$], 222 (0) [M^+], 202 (86), 184 (51), 132 (26), 107 (100). $C_9H_9F_3O_3$ (222.16): calcd C 48.66, H 4.08; found C 48.73, H 4.11.

3.3.2. 1-(Methoxymethoxy)-3-(trifluoromethoxy)benzene. Prepared analogously from 3-(trifluoromethoxy)-phenol (18 g, 0.10 mol); colorless liquid, bp 42–43 °C/4 mmHg; n_D^{20}=1.4304; yield: 19.3 g (87%). ^{1}H NMR: δ=7.26 (t, J=8.3 Hz, 1H), 6.96 (ddd, J=8.3, 2.2, 0.6 Hz, 1H), 6.92 (broad s, 1H), 6.83 (dm, J=8.3 Hz, 1H), 5.14 (s, 2H), 3.45 (s, 3H) ppm. ^{13}C NMR: δ=158.7, 150.4 (q, J=2 Hz), 130.5, 120.9 (q, J=257 Hz), 114.8, 114.3, 109.9, 94.9, 56.4 ppm. MS (c.i.): m/z (%)=240 (0) [$M^+ + NH_4$], 223 (37) [$M^+ + 1$], 222 (100) [M^+], 191 (22), 161 (29). $C_9H_9F_3O_3$ (222.16): calcd C 48.66, H 4.08; found C 48.77, H 3.88.

3.3.3. 1-(Methoxymethoxy)-4-(trifluoromethoxy)benzene. Prepared analogously from 4-(trifluoromethoxy)-phenol (18 g, 0.10 mol); colorless liquid, bp 47–49 °C/5 mmHg; n_D^{20}=1.4295; yield: 14.2 g (64%). ^{1}H NMR: δ=7.18 (d, J=9.2 Hz, 2H), 7.07 (d, J=9.2 Hz, 2H), 5.18 (s, 2H), 3.50 (s, 3H) ppm. ^{13}C NMR: δ=156.2, 144.0 (q, J=2 Hz), 122.7 (2 C), 121.0 (q, J=257 Hz), 117.5 (2 C), 95.0, 56.2 ppm. MS (c.i.): m/z (%)=240 (0) [$M^+ + NH_4$], 223 (48) [$M^+ + 1$], 222 (63) [M^+], 192 (81), 137 (100). $C_9H_9F_3O_3$ (222.16): calcd C 48.66, H 4.08; found C 48.41, H 4.22.

3.3.4. Triisopropyl[2-(trifluoromethoxy)phenoxy]silane. 2-(Trifluoromethoxy)phenol (8.9 g, 50 mmol), chlorotriisopropylsilane (11 mL, 10 g, 50 mmol) and imidazole (3.4 g, 50 mmol) were dissolved in *N*,*N*-dimethylformamide (25 mL). After 20 h at 25 °C, the mixture was poured into water (50 mL) and extracted with dichloromethane (3×25 mL). Upon distillation under reduced pressure a colorless liquid was collected; bp 92–94 °C/7 mmHg; n_D^{20}=1.4582; yield: 12.9 g (77%). ^{1}H NMR: δ=7.24 (dm, J=8.0 Hz, 1H), 7.17 (ddd, J=8.9, 7.4, 1.6 Hz, 1H), 6.95 (dd, J=8.0, 1.6 Hz, 1H), 6.9 (m, 1H), 1.30 (sept, J=7.4 Hz, 3H), 1.13 (d, J=7.4 Hz, 18H) ppm. ^{13}C NMR: δ=149.0, 140.5, 127.9, 123.2, 121.4, 121.2 (q, J=257 Hz), 121.2, 18.1 (3 C), 13.2 (6 C) ppm. MS (c.i.): m/z (%)=352 (0) [$M^+ + NH_4$],

334 (5) [M^+], 291 (14), 139 (100). $C_{16}H_{25}F_3O_2Si$ (334.45): calcd C 57.46, H 7.53; found C 57.55, H 7.35.

3.3.5. Triisopropyl[3-(trifluoromethoxy)phenoxy]silane. Prepared analogously from 3-(trifluoromethoxy)phenol (8.9 g, 50 mmol); colorless liquid; bp 82–83 °C/4 mmHg; $n_D^{20}=1.4549$; yield: 15.0 g (90%). ^{1}H NMR: $\delta=7.24$ (t, $J=8.3$ Hz, 1H), 6.9 (m, 2H), 6.79 (broad s, 1H), 1.31 (sept, $J=7.4$ Hz, 3H), 1.14 (t, $J=7.4$ Hz, 18H) ppm. ^{13}C NMR: $\delta=157.6$, 150.4 (q, $J=2$ Hz), 130.3, 120.9 (q, $J=257$ Hz), 118.8, 113.7, 113.4, 18.2 (3 C), 13.0 (6 C) ppm. MS (c.i.): *m/z* (%)=352 (0) [$M^+ + NH_4$], 335 (8) [$M^+ + 1$], 334 (1) [M^+], 293 (18), 292 (100). $C_{16}H_{25}F_3O_2Si$ (334.45): calcd C 57.46, H 7.53; found C 57.47, H 7.54.

3.3.6. Triisopropyl[4-(trifluoromethoxy)phenoxy]silane. Prepared analogously from 4-(trifluoromethoxy)phenol (8.9 g, 50 mmol); colorless liquid; bp 126–127 °C/5 mmHg; $n_D^{20}=1.4551$; yield: 14.4 g (86%). ^{1}H NMR: $\delta=7.13$ (d, $J=8.6$ Hz, 2H), 6.91 (dd, $J=8.9$, 1.6 Hz, 2H), 1.30 (sept, $J=7.4$ Hz, 3H), 1.14 (d, $J=7.4$ Hz, 18H) ppm. ^{13}C NMR: $\delta=155.1$, 143.4 (q, $J=2$ Hz), 122.6 (2 C), 121.0 (q, $J=254$ Hz), 121.0 (2 C), 18.2 (3 C), 13.0 (6 C) ppm. MS (c.i.): *m/z* (%)=352 (0) [$M^+ + NH_4$], 336 (28) [$M^+ + 2$], 335 (47) [$M^+ + 1$], 334 (81) [M^+], 236 (100). $C_{16}H_{25}F_3O_2Si$ (334.45): calcd C 57.46, H 7.53; found C 57.50, H 7.58.

3.3.7. 2-Hydroxy-3-(trifluoromethoxy)benzoic acid (2a). 1-(Methoxymethoxy)-2-(trifluoromethoxy)benzene (5.6 g, 25 mmol) was added to a solution of *sec*-butyllithium and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (5.2 mL, 4.3 g, 25 mmol) in tetrahydrofuran (30 mL) and cyclohexane (20 mL), cooled in a dry ice/methanol bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the solvents, the residue was partitioned between water (25 mL) and diethyl ether (50 mL). The aqueous phase was acidified with concentrated hydrochloric acid to pH 1 and extracted with diethyl ether (3×25 mL). After evaporation of the combined organic layers, the residue was crystallized from hexanes; colorless needles; mp 132–133 °C; yield: 3.94 g (71%). ^{1}H NMR*: $\delta=7.94$ (dd, $J=8.1$, 1.5 Hz, 1H), 7.57 (dm, $J=8.1$ Hz, 1H), 7.06 (t, $J=8.0$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=172.0$, 155.8, 137.8 (q, $J=2$ Hz), 130.3, 129.9, 121.7 (q, $J=256$ Hz), 119.6, 115.6 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (4) [$M^+ + 1$], 222 (29) [M^+], 205 (13), 204 (100). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.27; found C 43.19, H 2.29.

3.3.8. 2-Hydroxy-5-(trifluoromethoxy)benzoic acid (2c). Prepared analogously from 1-(methoxymethoxy)-4-(trifluoromethoxy)benzene (5.6 g, 25 mmol); colorless stars (from toluene); mp 133–134 °C (lit.[31]: mp 128–129 °C); yield: 5.16 g (93%). ^{1}H NMR*: $\delta=7.80$ (dd, $J=2.9$, 1.0 Hz, 1H), 7.55 (ddd, $J=9.0$, 2.9, 0.6 Hz, 1H), 7.08 (d, $J=9.0$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=171.1$, 161.3, 140.9 (q, $J=2$ Hz), 129.7, 123.0, 121.0 (q, $J=254$ Hz), 119.4, 113.2 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (12) [$M^+ + 1$], 222 (16) [M^+], 205 (16), 204 (30), 107 (100).

3.3.9. 2-Hydroxy-6-(trifluoromethoxy)benzoic acid (2b). Prepared analogously from 1-(methoxymethoxy)-3-(trifluoromethoxy)benzene (5.6 g, 25 mmol) using *sec*-butyllithium alone; colorless needles (from chloroform); mp 119–120 °C yield: 4.72 g (85%). ^{1}H NMR*: $\delta=7.57$ (t, $J=8.6$ Hz, 1H), 7.06 (d, $J=8.6$ Hz, 1H), 6.92 (d, $J=7.4$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=170.5$, 163.7, 148.7 (q, $J=2$ Hz), 135.4, 121.1 (q, $J=256$ Hz), 117.3, 113.6, 108.2 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (25) [$M^+ + 1$], 222 (36) [M^+], 205 (53), 204 (88), 107 (100). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.27; found C 43.28, H 2.17.

3.3.10. [2-Methoxymethoxy-6-(trifluoromethoxy)-phenyl]trimethylsilane (3). The metalation was carried out as described for the preparation of the acid **2b**, but the reactant dry ice was replaced by chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol). Upon distillation, a colorless liquid was collected; bp 75–76 °C/5 mmHg; $n_D^{20}=1.4514$; yield: 4.78 g (65%). ^{1}H NMR: $\delta=7.30$ (t, $J=8.3$ Hz, 1H), 7.01 (d, $J=8.3$ Hz, 1H), 6.89 (dm, $J=8.3$ Hz, 1H), 5.18 (s, 2H), 3.45 (s, 3H), 0.34 (s, 9H) ppm. ^{13}C NMR: $\delta=163.5$, 154.8 (q, $J=2$ Hz), 131.8, 121.1 (q, $J=257$ Hz), 121.0, 113.5, 111.6, 94.6, 56.4, 1.3 ppm. MS (c.i.): *m/z* (%)=314 (0) [$M^+ + NH_4$], 296 (15) [$M^+ + 2$], 295 (24) [$M^+ + 1$], 294 (61) [M^+], 279 (70), 105 (100). $C_{12}H_{17}F_3O_3Si$ (294.32): calcd C 48.67, H 5.82; found C 48.66, H 5.99.

3.3.11. 2-Hydroxy-4-(trifluoromethoxy)benzoic acid (2d). [1-(Methoxymethoxy)-6-(trifluoromethoxy)phenyl]-trimethylsilane (**3**, 2.9 g, 10 mmol) in tetrahydrofuran (14 mL) was treated with *sec*-butyllithium in cyclohexane (6 mL) at −75 °C for 6 h before being poured on dry ice. The residue was neutralized with ethereal hydrogen chloride and dissolved in diethyl ether (10 mL) containing tetrabutylammonium fluoride trihydrate (3.2 g, 10 mmol). After 2 h at 25 °C, a 10% aqueous solution (10 mL) of hydrochloric acid was added and the reaction mixture was extracted with diethyl ether (3×15 mL). The combined organic layers were dried and evaporated; colorless needles (from toluene); mp 122–123 °C; yield: 1.62 g (73%). ^{1}H NMR: $\delta=7.59$ (d, $J=8.6$ Hz, 1H), 6.5 (m, 1H), 6.40 (dm, $J=8.6$ Hz, 1H) ppm. ^{13}C NMR: $\delta=174.2$, 164.0, 155.8 (q, $J=2$ Hz), 133.2, 120.6 (q, $J=260$ Hz), 111.9, 109.9, 109.3 ppm. MS (c.i.): *m/z* (%)=240 (4) [$M^+ + NH_4$], 223 (5) [$M^+ + 1$], 222 (41) [M^+], 176 (100). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.27; found C 43.27, H 2.15. When *sec*-butyllithium was replaced by butyllithium as the metalating agent, the yield dropped to 47%.

3.3.12. 1-Chloro-2-(methoxymethoxy)-6-(trifluoromethoxy)benzene (4). Prepared analogously as the silane **3** but replacing the reactant chlorotrimethylsilane by 1,1,2-trichloro-1,2,2-trifluoroethane (3.1 mL, 4.8 g, 25 mmol). Direct distillation of the reaction mixture afforded a colorless liquid; bp 61–63 °C/4 mmHg; $n_D^{20}=1.4554$; yield: 4.29 g (67%). ^{1}H NMR: $\delta=7.20$ (t, $J=8.1$ Hz, 1H), 7.13 (dd, $J=8.1$, 1.8 Hz, 1H), 7.00 (dm, $J=8.2$ Hz, 1H), 5.26 (s, 2H), 3.49 (s, 3H) ppm. ^{13}C NMR: $\delta=154.9$, 146.7 (q, $J=2$ Hz), 127.6, 120.8 (q, $J=256$ Hz), 118.0, 115.7, 114.5, 95.7, 56.8 ppm. MS (c.i.): *m/z* (%)=274 (14) [$M^+ + NH_4$], 258 (20) [$M^+ + 2$], 257 (8) [$M^+ + 1$], 256 (100) [M^+]. $C_9H_8ClF_3O_3$ (256.61): calcd C 42.13, H 3.14; found C 42.25, H 3.11.

3.3.13. 3-Chloro-2-hydroxy-4-(trifluoromethoxy)benzoic acid (5). The chloroarene **4** (2.6 g, 10 mmol) in tetrahydrofuran (14 mL) was treated with butyllithium (10 mmol) in hexanes (6 mL) at −75 °C for 6 h before being poured onto an excess of freshly crushed dry ice. Acidification with concentrated hydrochloric acid, extraction with diethyl ether (3×15 mL) and crystallization from toluene afforded colorless tiny needles; mp 186–187 °C; yield: 2.05 g (80%). ^{1}H NMR*: δ=8.01 (d, J=8.9 Hz, 1H), 7.11 (dm, J=8.9 Hz, 1H), ppm. ^{13}C NMR*: δ=171.3, 160.9, 150.2 (q, J=2 Hz), 130.0, 120.7 (q, J=259 Hz), 115.1, 112.9, 112.1 (q, J=2 Hz) ppm. MS (c.i.): *m/z* (%)=274 (0) [$M^+ + NH_4$], 257 (3) [$M^+ + 1$], 256 (30) [M^+], 240 (31), 238 (100). $C_8H_4ClF_3O_4$ (256.56): calcd C 37.45, H 1.57; found C 37.23, H 1.43.

3.3.14. 3-Hydroxy-2-(trifluoromethoxy)benzoic acid (2e). Triisopropyl[2-(trifluoromethoxy)-phenoxy]silane (3.4 g, 10 mmol) was added to a solution of *sec*-butyllithium (10 mmol) and *N*,*N*,*N*′,*N*″,*N*‴-pentamethyldiethylenetriamine (2.1 mL, 1.7 g, 10 mmol) in tetrahydrofuran (12 mL) and cyclohexane (8 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. Acidification with a 1.0 M aqueous solution (10 mL) of citric acid, extraction with diethyl ether (3×15 mL) and evaporation of the solvents afforded a residue which was treated with tetrabutylammonium fluoride trihydrate (3.2 g, 10 mmol) in diethyl ether (10 mL). After 2 h at 25 °C, the mixture was evaporated to dryness. The residue crystallized from toluene as colorless platelets; mp 152–153 °C; yield: 1.53 g (69%). ^{1}H NMR*: δ=7.42 (dd, J=7.4, 1.9 Hz, 1H), 7.3 (m, 2H) ppm. ^{13}C NMR*: δ=165.5, 151.4, 135.3, 128.4, 122.3, 121.6 (2 C), 121.2 (q, J=257 Hz) ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (3) [$M^+ + 1$], 222 (62) [M^+], 202 (47), 136 (100). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.27; found C 43.52, H 2.19.

3.3.15. 4-Hydroxy-2-(trifluoromethoxy)benzoic acid (2f). Prepared analogously from triisopropyl[3-(trifluoromethoxy)phenoxy]silane (3.4 g, 10 mmol); colorless needles (from chloroform); mp 129–130 °C; yield: 1.73 g (78%). ^{1}H NMR*: δ=7.99 (d, J=8.6 Hz, 1H), 6.98 (dd, J=8.6, 2.2 Hz, 1H), 6.87 (symm. m, 2H) ppm. ^{13}C NMR*: δ=164.9, 162.7, 149.8, (q, J=2 Hz), 134.5, 120.8 (q, J=257 Hz), 116.3, 114.6, 110.2 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (77) [$M^+ + 1$], 222 (100) [M^+], 206 (66), 205 (90). $C_8H_5F_3O_4$ (222.12): calcd C 48.66, H 4.08; found C 48.77, H 3.88.

3.3.16. 5-Hydroxy-2-(trifluoromethoxy)benzoic acid (2g). Prepared analogously as described above for the acid **2e** from triisopropyl[4-(trifluoromethoxy)phenoxy]silane (3.4 g, 10 mmol); colorless tiny needles (from dichloromethane); mp 201–202 °C; yield: 1.78 g (80%). ^{1}H NMR*: δ=7.45 (d, J=3.2 Hz, 1H), 7.28 (dm, J=9.0 Hz, 1H), 7.14 (dd, J=9.0, 3.2 Hz, 1H) ppm. ^{13}C NMR*: δ=165.0, 156.6, 140.4 (q, J=2 Hz), 126.9, 124.8, 121.0 (q, J=255 Hz), 120.4, 118.3 ppm. MS (c.i.): *m/z* (%)=240 (0) [$M^+ + NH_4$], 223 (22) [$M^+ + 1$], 222 (100) [M^+], 205 (18), 136 (31). $C_8H_5F_3O_4$ (222.12): calcd C 43.26, H 2.57; found C 43.52, H 1.99.

3.4. Derivatives of chlorophenols

3.4.1. 1-Chloro-3-(methoxymethoxy)benzene. Mixed at 0 °C, a solution of 2-chlorophenol (13 g, 10 mL, 0.10 mol), chloromethyl methyl ether[30] (9.1 mL, 9.7 g, 0.12 mol) and *N*-ethyldiisopropylamine (18 mL, 16 g, 0.12 mol) in dichloromethane (80 mL) was kept at 25 °C for 2 h. The mixture was then poured into a 3.0 M aqueous solution (0.20 L) of sodium hydroxide. Extraction with diethyl ether (2×100 mL) and distillation gave a colorless liquid; bp 59–61 °C/5 mmHg; n_D^{20}=1.5209; yield: 9.4 g (55%). ^{1}H NMR: δ=7.20 (t, J=8.3 Hz, 1H), 7.06 (tm, J=2.2 Hz, 1H), 6.99 (dm, J=8.0 Hz, 1H), 6.92 (dm, J=8.3 Hz, 1H), 5.16 (s, 2H), 3.53 (s, 3H) ppm. ^{13}C NMR: δ=158.4, 135.2, 130.6, 122.4, 117.2, 115.0, 94.8, 56.4 ppm. MS (c.i.): *m/z* (%)=190 (0) [$M^+ + NH_4$], 174 (3) [$M^+ + 2$], 173 (97) [$M^+ + 1$], 172 (100) [M^+]. $C_8H_9ClO_2$ (172.61): calcd C 55.67, H 5.26; found C 55.75, H 5.19.

3.4.2. (2-Chlorophenoxy)triisopropylsilane. 2-Chlorophenol (6.4 g, 5.1 mL, 50 mmol), chlorotriisopropylsilane (11 mL, 10 g, 50 mmol) and imidazole (3.4 g, 50 mmol) were dissolved in *N*,*N*-dimethylformamide (25 mL). After 20 h at 25 °C, the mixture was poured into water (50 mL) and extracted with dichloromethane (3×25 mL). Distillation under reduced pressure gave a colorless liquid; bp 108–109 °C/5 mmHg; n_D^{20}=1.5216; yield: 12.3 g (83%). ^{1}H NMR: δ=7.34 (dd, J=8.0, 1.3 Hz, 1H), 7.11 (td, J=8.0, 1.3 Hz, 1H), 6.93 (dd, J=8.0, 1.3 Hz, 1H), 6.86 (t, J=8.0 Hz, 1H), 1.33 (sept, J=7.4 Hz, 3H), 1.18 (d, J=7.4 Hz, 18H) ppm. ^{13}C NMR: δ=152.4, 130.7, 127.8, 125.7, 122.0, 120.5, 18.3 (3 C), 13.3 (6 C) ppm. MS (c.i.): *m/z* (%)=302 (0) [$M^+ + NH_4$], 287 (1) [$M^+ + 3$], 284 (0) [M^+], 241 (100). $C_{15}H_{25}ClOSi$ (284.90): calcd C 63.24, H 8.84; found C 63.18, H 8.94.

3.4.3. (3-Chlorophenoxy)triisopropylsilane. Prepared analogously from 3-chlorophenol (6.4 g, 5.1 mL, 50 mmol); colorless liquid; bp 110–112 °C/6 mmHg; n_D^{20}=1.4968; yield: 6.43 g (45%). ^{1}H NMR: δ=7.13 (t, J=8.0 Hz, 1H), 6.93 (ddd, J=8.0, 1.9, 0.6 Hz, 1H), 6.88 (t, J=2.2 Hz, 1H), 6.75 (ddd, J=8.0, 2.0, 0.6 Hz, 1H), 1.24 (sept, J=7.4 Hz, 3H), 1.08 (t, J=7.4 Hz, 18H) ppm. ^{13}C NMR: δ=157.3, 135.0, 130.4, 121.7, 120.8, 118.6, 18.3 (3 C), 13.1 (6 C) ppm. MS (c.i.): *m/z* (%)=302 (0) [$M^+ + NH_4$], 286 (25) [$M^+ + 2$], 285 (31) [$M^+ + 1$], 284 (15) [M^+], 157 (100). $C_{15}H_{25}ClOSi$ (284.90): calcd C 63.24, H 8.84; found C 63.43, H 8.62.

3.4.4. (4-Chlorophenoxy)triisopropylsilane. Prepared analogously from 4-chlorophenol (6.4 g, 4.9 mL, 50 mmol); colorless liquid; bp 91–93 °C/5 mmHg; n_D^{20}=1.5031; yield: 13.6 g (96%). ^{1}H NMR: δ=7.18 (t, J=8.9 Hz, 2H), 6.82 (d, J=8.9 Hz, 2H), 1.3 (m, 3H), 1.12 (d, J=7.4 Hz, 18H) ppm. ^{13}C NMR: δ=155.1, 129.7 (2 C), 126.3, 121.5 (2 C), 18.3 (3 C), 13.0 (6 C) ppm. MS (c.i.): *m/z* (%)=302 (0) [$M^+ + NH_4$], 286 (9) [$M^+ + 2$], 285 (17) [$M^+ + 1$], 284 (15) [M^+], 185 (100). $C_{15}H_{25}ClOSi$ (284.90): calcd C 63.24, H 8.84; found C 63.25, H 8.86.

3.4.5. 3-Chloro-2-hydroxybenzoic acid (6a). 1-Chloro-2-(methoxymethoxy)benzene[25,32] (4.3 g, 25 mmol) was added to a solution of butyllithium (25 mmol) in tetrahydrofuran

(35 mL) and hexanes (15 mL), cooled in a dry ice/methanol bath. After 6 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the solvents, the residue was taken up in water (25 mL) and washed with diethyl ether (2×15 mL). The aqueous phase was acidified to pH 1 and extracted with diethyl ether (3×25 mL). After evaporation of the combined and dried organic layers, the residue was crystallized from toluene; colorless needles; mp 176–178 °C (lit.[33]: mp 183–183.5 °C); yield: 3.19 g (74%). ^{1}H NMR: δ=7.89 (dd, J=8.0, 1.6 Hz, 1H), 7.67 (dd, J=8.0, 1.6 Hz, 1H), 6.96 (t, J=8.0 Hz, 1H) ppm. ^{13}C NMR: δ=172.0, 158.2, 136.2, 129.5, 121.9, 119.7, 114.2 ppm. MS (c.i.): m/z (%)=192 (0) [M^++NH_4], 174 (6) [M^++2], 173 (3) [M^++1], 172 (26) [M^+], 154 (100).

3.4.6. 5-Chloro-2-hydroxybenzoic acid (6c). Prepared analogously from 1-chloro-4-(methoxymethoxy)benzene[25,32] (4.3 g, 25 mmol); colorless needles (from toluene); mp 173–175 °C (lit.[34]: mp 172 °C); yield: 3.41 g (79%). ^{1}H NMR: δ=7.85 (d, J=2.9 Hz, 1H), 7.54 (dd, J=9.0, 2.9 Hz, 2H), 6.99 (d, J=9.0 Hz, 1H) ppm. ^{13}C NMR: δ=171.5, 161.7, 136.5, 130.3, 124.1, 120.1, 114.4 ppm. MS (c.i.): m/z (%)=190 (0) [M^++NH_4], 173 (13) [M^++1], 172 (0) [M^+], 154 (100).

3.4.7. 6-Chloro-2-hydroxybenzoic acid (6b). 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and 1-chloro-3-(methoxymethoxy)benzene (4.3 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (34 mL) and hexanes (16 mL) kept in a dry ice/ methanol bath. After 2 h at −75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. After addition of water (25 mL) and washing with diethyl ether (2×30 mL), the aqueous phase was acidified to pH 1 with concentrated hydrochloric acid, extracted with dichloromethane (3×25 mL), dried and evaporated under reduced pressure, crystallization of the residue from toluene afforded colorless needles; mp 169–170 °C (lit.[35]: mp 171.5–172.5 °C); yield: 3.62 g (84%). ^{1}H NMR: δ=7.37 (d, J=8.0 Hz, 1H), 7.01 (dd, J=8.0, 1.0 Hz, 1H), 6.91 (dd, J=8.3, 1.3 Hz, 1H) ppm. ^{13}C NMR: δ=169.5, 161.1, 133.6 (2 C), 122.0, 116.2, 116.3 ppm. MS (c.i.): m/z (%)=192 (0) [M^++NH_4], 174 (7) [M^++2], 173 (7) [M^++1], 172 (24) [M^+], 154 (100). When butyllithium was used instead of lithium 2,2,6,6-tetramethylpiperidide in otherwise identical conditions, a mixture of 6-chloro-2-hydroxybenzoic acid and 4-chloro-2-hydroxybenzoic acid was obtained in the ratio 60:40 (89%) according to gas chromatographic analysis (30 m, DB-WAX, 150 °C; 30 m, DB-23, 150 °C).

3.4.8. [2-Chloro-6-(methoxymethoxy)phenyl]trimethylsilane (7). 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol), 1-chloro-3-(methoxymethoxy)benzene (4.3 g, 25 mmol) and chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) kept in a dry ice/methanol bath. Upon distillation, a colorless liquid was collected; bp 82–85 °C/4 mmHg; n_D^{20}=1.5062; yield: 4.03 g (66%). ^{1}H NMR: δ=7.26 (t, J=8.3 Hz, 1H), 7.05 (d, J=8.3 Hz, 2H), 5.21 (s, 2H), 3.54 (s, 3H), 0.50 (s, 9H) ppm. ^{13}C NMR: δ=163.4, 141.6, 131.5, 127.1, 124.1, 111.9, 94.6, 56.5, 2.6 ppm. MS (c.i.): m/z (%)=262 (22) [M^++NH_4], 246 (11) [M^++2], 245 (2) [M^++1], 244 (16) [M^+], 199 (100). $C_{11}H_{17}ClO_2Si$ (244.18): calcd C 53.97, H 7.00; found C 54.38, H 7.41.

3.4.9. 2-Hydroxy-4-chlorobenzoic acid (6d). [2-(Chloro)-6-(methoxymethoxy)phenyl]trimethylsilane (**7**, 2.4 g, 10 mmol) in tetrahydrofuran (15 mL) was treated with *sec*-butyllithium in cyclohexane (6 mL) at −75 °C for 6 h before being poured on dry ice. After evaporation of the solvents, the residue was partitioned between water (10 mL) and diethyl ether (50 mL). The aqueous phase was acidified with concentrated hydrochloric acid to pH 1 and extracted with diethyl ether (3×15 mL). After evaporation of the combined organic layers, the residue was dissolved in *N*,*N*-dimethylformamide (10 mL) containing tetrabutylammonium fluoride trihydrate (3.2 g, 10 mmol) and heated to 100 °C for 48 h. A 10% aqueous solution (20 mL) of hydrochloric acid was then added. The product was isolated by extraction with diethyl ether (3×15 mL); colorless stars (from dichloromethane); mp 206–208 °C (lit.[36]: mp 207 °C); yield: 0.60 g (35%). ^{1}H NMR*: δ=7.92 (d, J=8.6 Hz, 1H), 7.02 (d, J=1.9 Hz, 1H), 7.00 (dd, J=8.6, 1.9 Hz, 1H) ppm. ^{13}C NMR*: δ=171.6, 163.1, 141.2, 132.2, 120.0, 117.5, 111.7 ppm. MS (c.i.): m/z (%)=190 (0) [M^++NH_4], 174 (12) [M^++2], 173 (6) [M^++1], 172 (34) [M^+], 156 (34), 154 (100).

3.4.10. 2-Chloro-3-hydroxybenzoic acid (6e). (2-Chlorophenoxy)triisopropylsilane (2.8 g, 10 mmol) was added to a solution of *sec*-butyllithium in tetrahydrofuran (12 mL) and cyclohexane (8 mL) kept at −100 °C. After 6 h at this temperature, the reaction mixture was poured onto an excess of freshly crushed dry ice. After acidification with 1.0 M aqueous solution (10 mL) of citric acid and extraction with diethyl ether (3×15 mL), the combined organic layers were reduced to a volume of 10 mL and tetrabutylammonium fluoride trihydrate (3.2 g, 10 mmol) was added. After standing for 2 h at 25 °C, the solvents were evaporated and the product crystallized from toluene to give colorless platelets; mp 157–158 °C (lit.[37]: mp 157.5–158.5 °C); yield: 0.85 g (49%). ^{1}H NMR: δ=7.34 (dd, J=7.7, 1.9 Hz, 1H), 7.25 (t, J=8.0 Hz, 1H), 7.16 (dd, J=8.0, 1.6 Hz, 1H) ppm. ^{13}C NMR: δ=166.6, 154.2, 132.9, 127.8, 122.1, 119.5, 119.4 ppm. MS (c.i.): m/z (%)=190 (0) [M^++NH_4], 174 (41) [M^++2], 173 (16) [M^++1], 172 (98) [M^+], 155 (100).

3.4.11. 2-Chloro-4-hydroxybenzoic acid (6f). Prepared analogously from (3-chlorophenoxy)triisopropylsilane (2.8 g, 10 mmol); colorless tiny needles (from dichloromethane); mp 192–193 °C (lit.[38]: mp 159 °C); yield: 0.86 g (50%). ^{1}H NMR: δ=7.92 (d, J=8.6 Hz, 1H), 6.95 (d, J=2.6 Hz, 1H), 6.89 (dd, J=8.6, 2.6 Hz, 1H) ppm. ^{13}C NMR: δ=166.2, 162.0, 136.2, 134.8, 121.5, 118.6, 114.9 ppm. MS (c.i.): m/z (%)=192 (0) [M^++NH_4], 174 (18) [M^++2], 173 (11) [M^++1], 172 (66) [M^+], 155 (100).

3.4.12. 2-Chloro-5-hydroxybenzoic acid (6g). Prepared analogously from (4-chlorophenoxy)triisopropylsilane (2.8 g, 10 mmol); colorless needles (from toluene); mp 167–168 °C (lit.[37]: mp 168–169 °C); yield: 0.87 g (51%). ^{1}H NMR: δ=7.36 (d, J=3.2 Hz, 1H), 7.34 (d, J=8.6 Hz, 2H),

7.04 (dd, $J=8.6$, 2.9 Hz, 1H) ppm. ^{13}C NMR: $\delta=166.2$, 156.5, 132.1, 131.9, 120.1, 118.2, 118.1 ppm. MS (c.i.): *m/z* (%)=190 (0) [$M^+ + NH_4$], 174 (27) [$M^+ + 2$], 173 (16) [$M^+ + 1$], 172 (81) [M^+], 155 (100).

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