The Regioexhaustive Functionalization of Difluorophenols and Trifluorophenols Through Organometallic Intermediates

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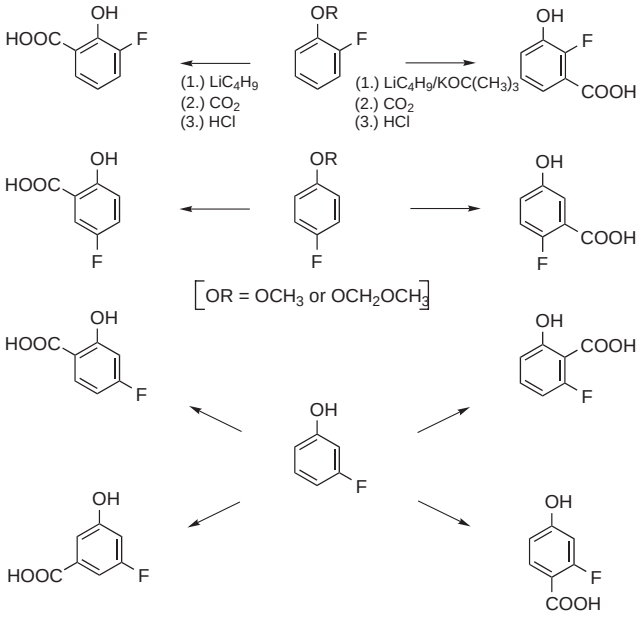
Abstract: 2,4-Difluorophenol, 2,5-difluorophenol, 2,3-difluorophenol, 3,5-difluorophenol, 3,4-difluorophenol, 2,4,5-trifluorophenol and 2,3,4-trifluorophenol were converted into all 18 possible di- or trifluorinated hydroxybenzoic acids (**1a**–**c**, **4a**–**c**, **9a**–**c**, **12a**,**b**, **14a**–**c**, **17a**,**b**, **18a**,**b**), all of them new compounds. The phenolic hydrogen atom was replaced by a methoxymethyl or, less frequently, by a triisopropylsilyl group, which exerted an *ortho* activating or *ortho* shielding effect, respectively. Sites flanked by two electronegative substituents (fluorine, alkoxy) were deprotonated with particular ease. They had to be silenced by the reversible attachment of a metalation-blocking trimethylsilyl group or of a metalation-deflecting chlorine atom if the metal was to be introduced elsewhere. In all cases but one, the stage was thus set for an intramolecular competition between metalation at an oxygen-adjacent or a fluorine-adjacent site. It proved indeed possible to secure the desired regioflexibility in either way by relying on an appropriate substrate-reagent matching. This demonstrates once more the potential of the organometallic approach to diversity-oriented synthesis.

Key words: alkyllithiums, carboxylation, (de-)chlorination, (de-)silylation, fluorophenols, organometallic reactions, protective groups, regioselectivity, superbases

The three fluorophenols represent milestones in the development of the organometallic approach to diversity-oriented synthesis.[1,2] The *ortho* and *para* isomers, after protection of the free phenols as anisoles[3] or methoxymethyl ethers[4] were found to undergo perfectly site-controlled metalation (and subsequent carboxylation) at either the oxygen- or halogen-adjacent position depending on the mechanism-matched choice of the reagent. The *meta* isomer acted as one of the first substrates to illustrate the concept of regioexhaustive functionalization by its transformation into each of the four possible fluorohydroxybenzoic acids (Scheme 1).[2]

Under these circumstances it deemed us worthwhile to extend our studies to difluorophenols and trifluorophenols. Most of such compounds are commercial if often expensive. On the other hand, many of them can be efficaciously prepared from cheap starting materials such as 1,2-difluorobenzene, 1,4-difluorobenzene, 1-bromo-3,5-difluorobenzene and 1-bromo-2,4,5-trifluorobenzene by hydrogen/metal or halogen/metal permutation followed by dimethoxyborylation[5,6] and oxidation.



Scheme 1

As demonstrated below, it proved possible to introduce a metal atom into any vacant position of five difluorophenols and two trifluorophenols selected as model compounds. The organometallic intermediates thus generated were always intercepted by carbon dioxide and only occasionally also by other electrophiles (in particular, chlorinating and silylating reagents). It is nevertheless tacitly understood that in the same way as the 18 fluorinated hydroxybenzoic acids described below were accessed, aldehydes, alcohols, amines, sulfonic acids, phosphonic acids and countless other functionalized products could be made.[7]

Derivatives of 2,4-Difluorophenol

The *O*-methoxymethyl protected 2,4-difluorophenol was smoothly deprotonated with *sec*-butyllithium at the position flanked by the two halogen atoms. The organometallic species was trapped with dry ice and with 1,1,2-trichloro-1,2,2-trifluoroethane to afford 2,6-difluoro-3-hydroxybenzoic acid (**1a**, 82%) and 2-chloro-1,3-difluoro-4-(methoxymethoxy)benzene (**2**, 82%). The latter compound reacted with butyllithium at the oxygen-adjacent, but with lithium 2,2,6,6-tetramethylpiperidide

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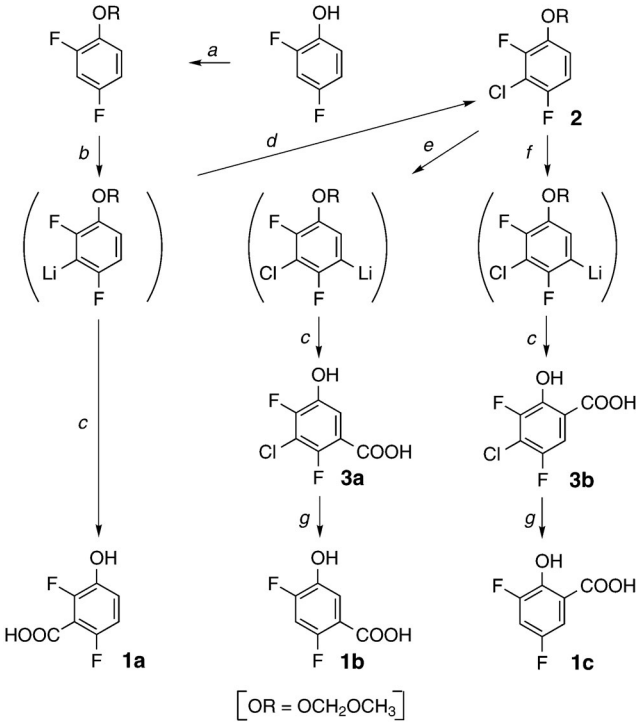
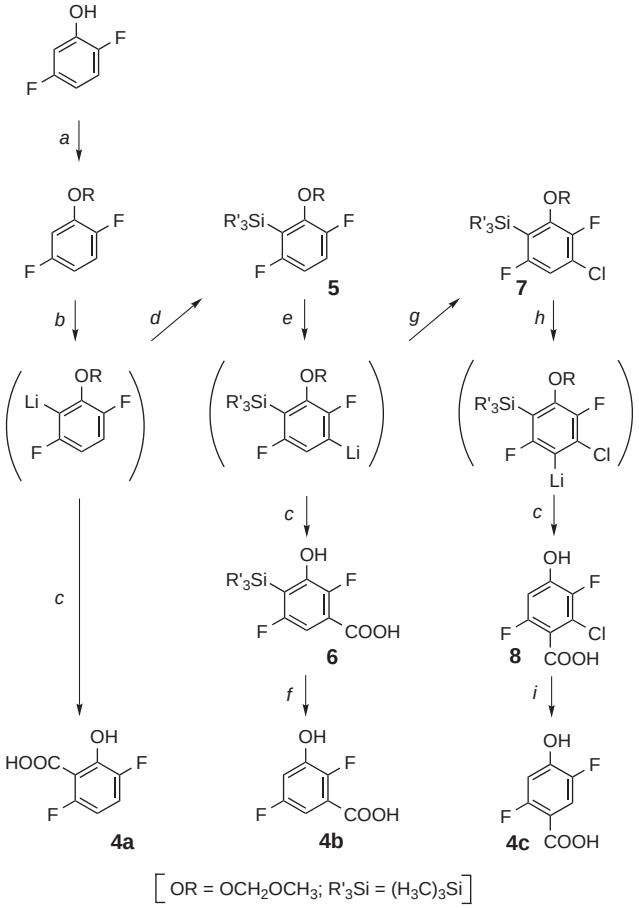
(LITMP) at the fluorine-adjacent position to give after carboxylation and acidification 3-chloro-2,4-difluoro-5-hydroxybenzoic acid (**3a**, 75%) and the 4-chloro-3,5-difluoro-2-hydroxybenzoic acid (**3b**, 61%) or, after catalytic hydrogenation, 2,4-difluoro-5-hydroxybenzoic acid (**1b**, 86%) and 3,5-difluoro-2-hydroxybenzoic acid (**1c**, 94%), respectively (Scheme 2).



Scheme 2 *a*) chloromethyl methyl ether and ethyldiisopropylamine in CH_2Cl_2 at 25 °C for 2 h; *b*) *sec*-BuLi in THF at –75 °C for 2 h; *c*) 1. excess dry ice, 2. HCl; *d*) 1,1,2-trichloro-1,2,2-trifluoroethane; *e*) LITMP in THF at –75 °C for 2 h; *f*) BuLi in Et_2O at –75 °C for 6 h; *g*) ammonium formate in MeOH in the presence of Pd/C at 25 °C for 20 h.

Derivatives of 2,5-Difluorophenol

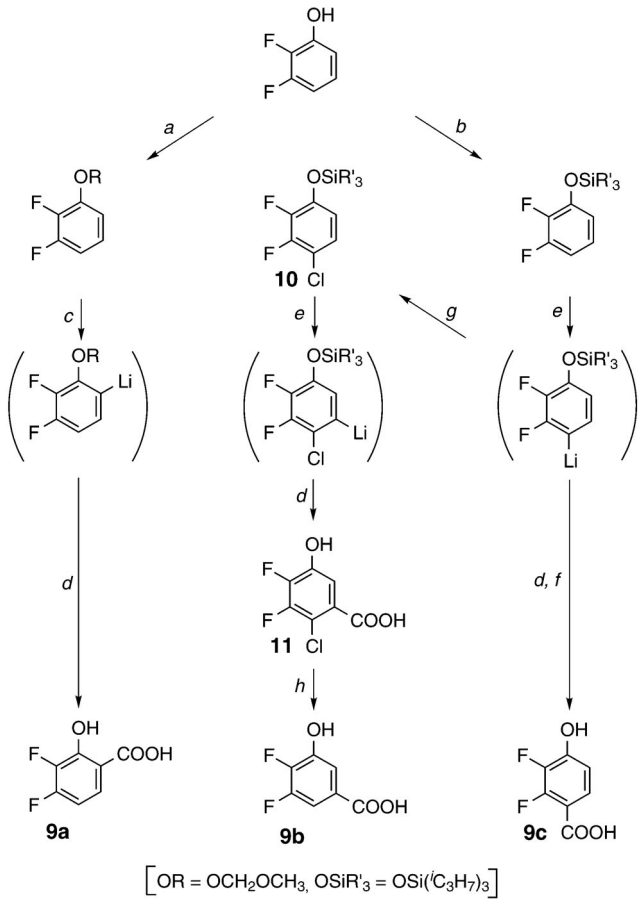
As expected, 1,4-difluoro-2-(methoxymethoxy)benzene (Scheme 3) was lithiated at the doubly activated 3-position to provide, after carboxylation and neutralization, 3,6-difluoro-2-hydroxybenzoic acid (**4a**, 92%) or, after reaction with chlorotrimethylsilane, [3,6-difluoro-2-(methoxymethoxy)phenyl]trimethylsilane (**5**, 84%). This compound underwent metalation with amazing selectivity at the 4-position to produce the silylated acid **6** (78%) and after deprotection 2,5-difluoro-3-hydroxybenzoic acid (**4b**, 93%). When the lithiated intermediate was trapped with 1,1,2-trichloro-1,2,2-trifluoroethane instead, [4-chloro-3,6-difluoro-2-(methoxymethoxy)phenyl]trimethylsilane (**7**, 64%) was obtained which was converted by deprotonation and carboxylation into 2-chloro-3,6-difluoro-4-hydroxybenzoic acid (**8**, 65%) and by subsequent catalytic hydrogenation into 2,5-difluoro-4-hydroxybenzoic acid (**4c**, 75%).



Scheme 3 *a*) chloromethyl methyl ether and ethyldiisopropylamine in CH_2Cl_2 at 25 °C for 2 h; *b*) BuLi in THF at –75 °C for 2 h; *c*) 1. excess dry ice, 2. HCl; *d*) Me_3SiCl; *e*) *sec*-BuLi in the presence of *N*,*N*′,*N*″,*N*‴-pentamethyldiethylenetriamine (PMDTA) in THF at –75 °C for 2 h; *f*) tetrabutylammonium fluoride trihydrate (TBAF) in THF at 25 °C for 2 h; *g*) 1,1,2-trichloro-1,2,2-trifluoroethane; *h*) LITMP in THF at –75 °C for 2 h; *i*) ammonium formate in MeOH and in the presence of Pd/C at 25 °C for 20 h.

Derivatives of 2,3-Difluorophenol

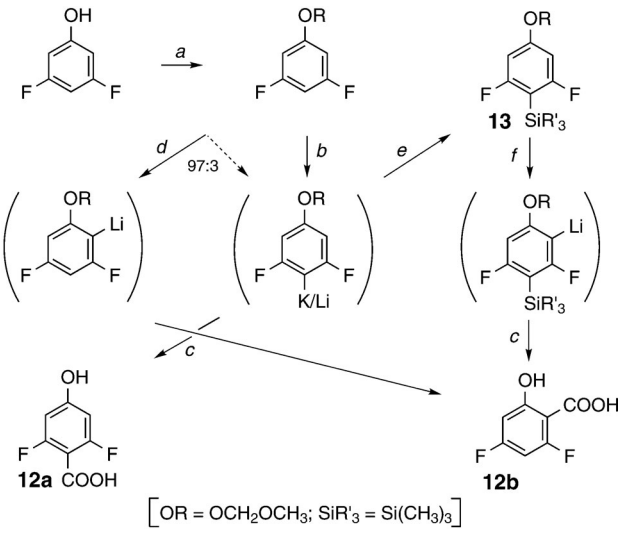
Butyllithium abstracted a proton from the *O*-methoxymethyl protected 2,3-difluorophenol exclusively from the oxygen-neighboring position (Scheme 4). 3,4-Difluoro-2-hydroxybenzoic acid (**9a**) was isolated in 87% yield after carboxylation and neutralization. In contrast, the *O*-triisopropylsilyl protected 2,3-difluorophenol was attacked by LITMP selectively at the halogen-adjacent position, affording 2,3-difluoro-4-hydroxybenzoic acid (**9c**, 89%) after carboxylation and acidification or (4-chloro-2,3-difluorophenoxy)triisopropylsilane (**10**, 77%) after chlorination. When treated consecutively with LITMP, carbon dioxide and acid, compound **10** gave 2-chloro-3,4-difluoro-4-hydroxybenzoic acid (**11**, 82%) and, after catalytic hydrogenolysis, 3,4-difluoro-5-hydroxybenzoic acid (**9b**, 98%).



Scheme 4 *a*) chloromethyl methyl ether and ethyldiisopropylamine in CH_2Cl_2 at 25 °C for 2 h; b) chlorotriisopropylsilane and imidazole in DMF at 25 °C for 20 h; *c*) BuLi in THF at –75 °C for 6 h; *d*) 1. excess dry ice, 2. HCl; *e*) LITMP in THF at –75 °C for 2 h; *f*) TBAF in THF at 25 °C for 2 h; *g*) 1,1,2-trichloro-1,2,2-trifluoroethane; *h*) H_2 (gas) in MeOH and in the presence of Pd/C at 25 °C for 20 h.

Derivatives of 3,5-Difluorophenol

3,5-Difluorophenol disposes of only two different vacant sites. The corresponding 2,6-difluoro-4-hydroxybenzoic acid (**12a**, 83%) and 2,4-difluoro-6-hydroxybenzoic acid (**12b**, 61%) were obtained from the same precursor by employing, prior to carboxylation, the superbasic mixture ('LIC-KOR') of butyllithium and potassium *tert*-butoxide in tetrahydrofuran and butyllithium in diethyl ether, respectively (Scheme 5). However, in the latter case the product **12b** contained trace amounts (about 2.4%) of the regioisomeric acid **12a**. Perfect regioselectivity was achieved when the intermediate resulting from the LIC-KOR metalation of 1,3-difluoro-5-(methoxymethoxy)-benzene was trapped with chlorotrimethylsilane and the [2,6-difluoro-4-(methoxymethoxy)phenyl]trimethylsilane (**13**, 78%) thus formed was consecutively lithiated (with *sec*-butyllithium), carboxylated and deprotected (89% of **12b**).



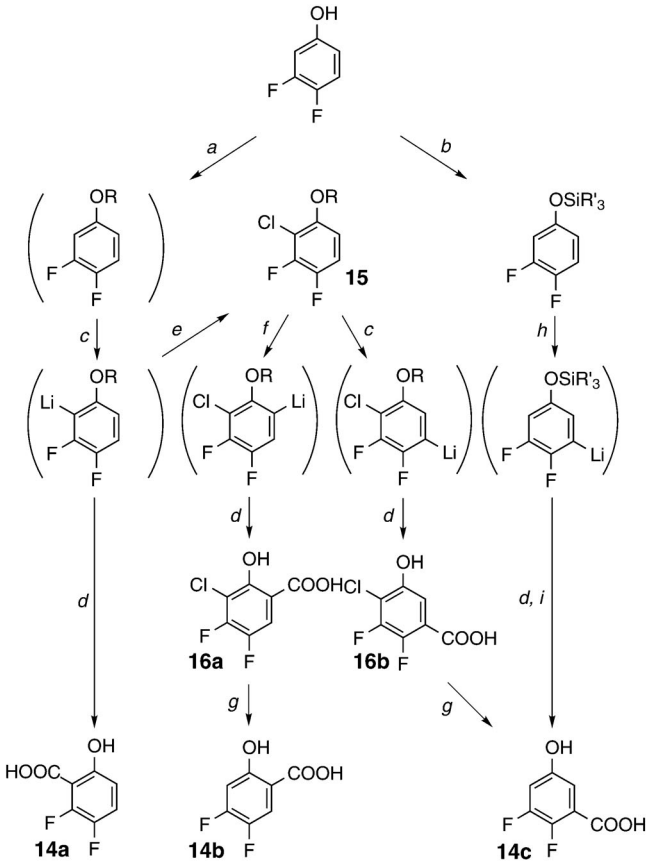
Scheme 5 *a*) chloromethyl methyl ether and ethyldiisopropylamine in CH_2Cl_2 at 25 °C for 2 h; *b*) BuLi and *t*-BuOK in THF at –75 °C for 2 h; *c*) 1. excess dry ice, 2. HCl; *d*) BuLi in Et_2O at –75 °C for 6 h; *e*) Me_3SiCl; *f*) *sec*-BuLi in THF at –75 °C for 2 h.

Derivatives of 3,4-Difluorophenol

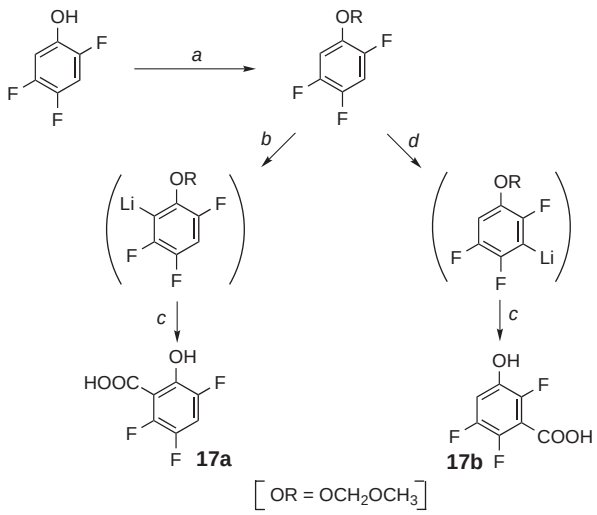
Using LITMP in tetrahydrofuran as the base, clean deprotonation occurred at the doubly activated 2-position affording 2,3-difluoro-6-hydroxybenzoic acid (**14a**, 92%) after carboxylation followed by acidification and 2-chloro-3,4-fluoro-1-(methoxymethoxy)benzene (**15**, 78%) after chlorination (Scheme 6). This intermediate was attacked by butyllithium in diethyl ether at the oxygen-adjacent and by LITMP in tetrahydrofuran at the fluorine-adjacent position. After carboxylation, 3-chloro-4,5-difluoro-2-hydroxybenzoic acid (**16a**, 87%) and 4-chloro-2,3-difluoro-5-hydroxybenzoic acid (**16b**, 83%) and, after catalytic hydrogenation, 4,5-difluoro-2-hydroxybenzoic acid (**14b**, 95%) and 2,3-difluoro-5-hydroxybenzoic acid (**14c**, 92%) were isolated. The latter product **14c** (74%) was also obtained in a more straightforward manner by treating the *O*-triisopropylsilyl protected 3,4-difluorophenol consecutively with *sec*-butyllithium in the presence of PMDTA, carbon dioxide and tetrabutylammonium fluoride trihydrate (Scheme 6).

Derivatives of 2,4,5-Trifluorophenol

Only two unoccupied positions being available, the same precursor proved adequate to access the prospective products 2,3,5-trifluoro-6-hydroxybenzoic acid (**17a**, 89%) and 2,3,6-trifluoro-5-hydroxybenzoic acid (**17b**, 93%). By virtue of reagent-controlled optional site selectivity,[1,2] 1,2,4-trifluoro-5-(methoxymethoxy)benzene was metalated and subsequently carboxylated when butyllithium in diethyl ether or butyllithium/potassium *tert*-butoxide were employed as the base (Scheme 7).



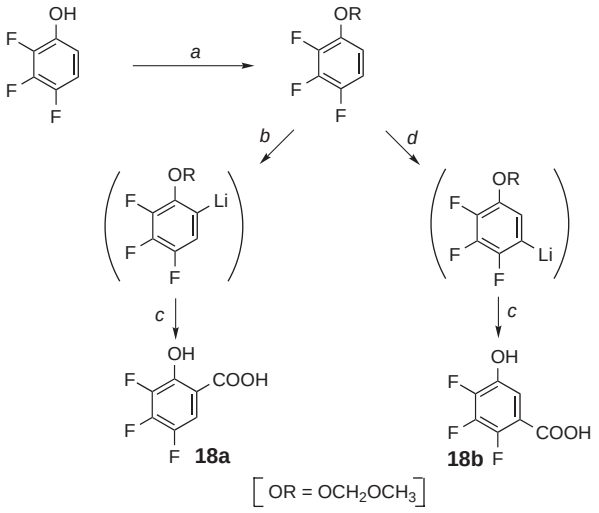
Scheme 6 *a*) chloromethyl methyl ether and ethyldiisopropylamine in CH_2Cl_2 at 25 °C for 2 h; *b*) chlorotriisopropylsilane and imidazole in DMF at 25 °C for 20 h; *c*) LITMP in THF at –75 °C for 2 h; *d*) 1. excess dry ice, 2. HCl; *e*) 1,1,2-trichloro-1,2,2-trifluoroethane; *f*) BuLi in Et_2O at –75 °C for 6 h; *g*) H_2 (gas) in MeOH and in the presence of Pd/C at 25 °C for 20 h; *h*) *sec*-BuLi in the presence of PMDTA in THF at –75 °C for 2 h; *i*) TBAF in THF at 25 °C for 2 h.



Scheme 7 *a*) chloromethyl methyl ether and ethyldiisopropylamine in CH_2Cl_2 at 25 °C for 2 h; *b*) BuLi in Et_2O at –75 °C for 6 h; *c*) 1. excess dry ice, 2. HCl; *d*) BuLi and *t*-BuOK (LIC-KOR) in THF at –75 °C for 2 h.

Derivatives of 2,3,4-Trifluorophenol

It was just as easy to discriminate between the two deprotonation sites in 1,2,3-trifluoro-4-methoxybenzene. 3,4,5-Trifluoro-2-hydroxybenzoic acid (**18a**, 61%) and 2,3,4-trifluoro-5-hydroxybenzoic acid (**18b**, 97%) were obtained free of reciprocal contamination after treatment of the acetal by butyllithium in diethyl ether and LIDA in tetrahydrofuran, respectively, followed by carboxylation and acidification (Scheme 8).



Scheme 8 *a*) chloromethyl methyl ether and ethyldiisopropylamine in CH_2Cl_2 at 25 °C for 2 h; *b*) BuLi in Et_2O at –75 °C for 6 h; *c*) 1. excess dry ice, 2. HCl; *d*) LIDA in THF at –75 °C for 2 h.

In summary, the objectives have been attained. All selected difluorophenols and trifluorophenols have been successfully subjected to regioexhaustive functionalization. The targeted acids **1a**–**c**, **4a**–**c**, **9a**–**c**, **12a**,**b**, **14a**–**c**, **17a**,**b** and **18a**,**b** have been prepared with minimal effort and absolute selectivity. The regiodiscrimination relied on well-established first-order principles. Remarkably, not more than two categories of our 2 × 3 toolkit[2] were needed to solve all problems. On one hand, the course of numerous metalation reactions was effectively controlled by *protective groups* such as the sterically screening trimethylsilyl group, the triisopropylsilyl group, still bulky even if located peripherally[2] at the phenol oxygen atom and the attack-deviating[2] chlorine substituent. On the other hand, there were many opportunities to take advantage of reagent-dominated *optional site selectivity*. Whereas butyllithium, especially when dissolved in diethyl ether rather than in the more polar tetrahydrofuran seeks neighboring group assistance by a coordinating donor substituent before accomplishing its deprotonation task, coordinatively saturated bases, such as the butyllithium complexes with potassium *tert*-butoxide or PMDTA, invariably abstract the proton from the most acidic site thus maximizing the partial neutralization.[3] Relatively weak bases such as LIDA and LITMP act in the same way for lack of an alternative as they cannot afford to generate high energy species[8] or because continuous reprotonation by the free

amine (diisopropylamine or 2,2,6,6-tetramethylpiperidine) catalyzes the equilibration[2] between a more basic and a less basic organometallic intermediate.

Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.[9,10] ^{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 at 70 eV ionization potential while a source temperature of 200 °C was maintained. Whenever no molecular peak was observed under such conditions, chemical ionization (c.i.) in an ammonia atmosphere at 100 °C source temperature was applied. To avoid redundancy, only the [^{35}Cl] fragments, and not the [^{37}Cl] isotopomers, are listed in all cases.

Starting Materials

1,3-Difluoro-4-(methoxymethoxy)benzene (19); Typical Procedure

Chloromethyl methyl ether[11] (9.1 mL, 9.7 g, 0.12 mol) was added to a solution of 2,4-difluorophenol (13 g, 0.10 mol) and *N*-ethyldiisopropylamine (18 mL, 16 g, 0.12 mol) in CH_2Cl_2 (80 mL) kept at 0 °C. After standing for 2 h at 25 °C, the mixture was poured into a 3.0 M aq solution of NaOH (0.20 L). Extraction with Et_2O (2 × 100 mL) and distillation gave a colorless liquid; bp 68–70 °C/4 Torr; n_D^{20} 1.4594; yield: 14.4 g (83%).

^{1}H NMR: δ = 7.14 (td, *J* = 9.1, 5.5 Hz, 1 H), 6.86 (td, *J* = 11.2, 1.6 Hz, 1 H), 6.78 (tm, *J* = 9.1 Hz, 1 H), 5.15 (s, 2 H), 3.52 (s, 3 H).

^{13}C NMR: δ = 157.9 (dd, *J* = 242, 10 Hz), 153.6 (dd, *J* = 256, 22 Hz), 141.8 (dd, *J* = 11, 4 Hz), 119.6 (dd, *J* = 9, 3 Hz), 110.0 (dd, *J* = 22, 4 Hz), 105.2 (dd, *J* = 27, 22 Hz), 95.8 (s), 56.7 (s).

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 174 (67, [M^+]), 143 (100), 129 (76).

1,4-Difluoro-2-(methoxymethoxy)benzene (20)

Prepared, analogously as compound **19**, from 2,5-difluorophenol (13 g, 0.10 mol); colorless liquid; bp 46–47 °C/3 Torr; n_D^{20} 1.4649; yield: 15.8 g (91%).

^{1}H NMR: δ = 7.05 (ddd, *J* = 10.5, 9.1, 5.3 Hz, 1 H), 6.96 (ddd, *J* = 12.1, 8.4, 5.4 Hz, 1 H), 6.7 (m, 1 H), 5.19 (s, 2 H), 3.51 (s, 3 H).

^{13}C NMR: δ = 158.6 (dd, *J* = 242, 2 Hz), 149.4 (dd, *J* = 241, 3 Hz), 145.6 (dd, *J* = 12, 4 Hz), 116.4 (dd, *J* = 21, 10 Hz), 108.2 (dd, *J* = 23, 6 Hz), 105.6 (d, *J* = 27 Hz), 95.6 (s), 56.4 (s).

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 174 (65, [M^+]), 144 (27), 143 (33), 84 (100).

1,2-Difluoro-3-(methoxymethoxy)benzene (21)

Prepared, analogously as compound **19**, from 2,3-difluorophenol (13 g, 0.10 mol); colorless liquid; bp 68–70 °C/9 Torr; n_D^{20} 1.4669; yield: 14.3 g (82%).

^{1}H NMR: δ = 7.0 (m, 2 H), 6.8 (m, 1 H), 5.22 (s, 2 H), 3.53 (s, 3 H).

^{13}C NMR: δ = 151.5 (dd, *J* = 247, 11 Hz), 146.7 (dd, *J* = 8, 3 Hz), 142.1 (dd, *J* = 248, 14 Hz), 123.3 (dd, *J* = 8, 5 Hz), 112.8 (d, *J* = 3 Hz), 110.4 (d, *J* = 17.5 Hz), 95.9, 56.5.

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 175 (57, [$M^+ + 1$]), 174 (79, [M^+]), 144 (71), 113 (35), 101 (100).

1,3-Difluoro-5-(methoxymethoxy)benzene (22)

Prepared, analogously as compound **19**, from 3,5-difluorophenol (13 g, 0.10 mol); colorless liquid; bp 40–42 °C/3 Torr; n_D^{20} 1.4684; yield: 14.1 g (81%).

^{1}H NMR: δ = 6.58 (dd, *J* = 8.9, 2.2 Hz, 2 H), 6.46 (tt, *J* = 9.0, 2.3 Hz, 1 H), 5.14 (s, 2 H), 3.47 (s, 3 H).

^{13}C NMR: δ = 163.5 (dd, *J* = 246, 16 Hz, 2 C), 159.1 (t, *J* = 14 Hz), 99.9 (d, *J* = 29 Hz), 97.3 (t, *J* = 26 Hz, 2 C), 94.5 (s), 56.1 (s).

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 175 (12, [$M^+ + 1$]), 174 (100, [M^+]), 143 (28), 113 (36).

1,2-Difluoro-4-(methoxymethoxy)benzene (23)

Prepared, analogously as compound **19**, from 3,4-difluorophenol (13 g, 0.10 mol); colorless liquid; bp 65–66 °C/10 Torr; n_D^{20} 1.4566; yield: 14.3 g (82%).

^{1}H NMR: δ = 7.06 (symm. m, 1 H), 6.89 (ddd, *J* = 11.8, 6.7, 3.0 Hz, 1 H), 6.7 (symm. m, 1 H), 5.12 (s, 2 H), 3.47 (s, 3 H).

^{13}C NMR: δ = 153.5 (dd, *J* = 8, 2 Hz), 150.3 (dd, *J* = 247, 14 Hz), 145.7 (dd, *J* = 241, 13 Hz), 117.1 (dd, *J* = 18, 2 Hz), 111.8 (dd, *J* = 6, 3.5 Hz), 106.0 (d, *J* = 20 Hz), 94.9, 55.9.

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 175 (70, [$M^+ + 1$]), 174 (100, [M^+]), 144 (28), 129 (14), 101 (20).

1,2,4-Trifluoro-5-(methoxymethoxy)benzene (24)

Prepared, analogously as compound **19**, from 2,4,5-trifluorophenol (7.4 g, 50 mmol); colorless liquid; bp 61–62 °C/8 Torr; n_D^{20} 1.4407; yield: 7.58 g (79%).

^{1}H NMR: δ = 7.09 (ddd, *J* = 11.3, 7.7, 7.7 Hz, 1 H), 6.98 (ddd, *J* = 10.2, 10.2, 7.4 Hz, 1 H), 5.15 (s, 2 H), 3.52 (s, 3 H).

^{13}C NMR: δ = 148.6 (ddd, *J* = 245, 9, 3 Hz), 146.3 (ddd, *J* = 244, 13, 4 Hz), 144.7 (ddd, *J* = 245, 14, 10 Hz), 141.2 (ddd, *J* = 12, 8, 4 Hz), 107.5 (dd, *J* = 22, 2 Hz), 106.0 (ddd, *J* = 24, 22, 2 Hz), 96.4, 56.5.

MS (c.i.): *m*/*z* (%) = 210 (0, [$M^+ + NH_4$]), 193 (25, [$M^+ + 1$]), 192 (45, [M^+]), 161 (52), 147 (34), 119 (100).

1,2,3-Trifluoro-4-(methoxymethoxy)benzene (25)

Prepared, analogously as compound **19**, from 2,3,4-trifluorophenol (14.8 g, 0.10 mol); mp 24 – 26 °C; yield: 15.5 g (81%).

^{1}H NMR: δ = 6.9 (m, 2 H), 5.18 (s, 2 H), 3.54 (s, 3 H).

^{13}C NMR: δ = 146.9 (ddm, *J* = 239, 10 Hz), 143.6 (ddd, *J* = 236, 11, 4 Hz), 142.9 (dd, *J* = 9, 4 Hz), 142.2 (ddd, *J* = 251, 16, 13 Hz), 112.2 (dd, *J* = 7, 4 Hz), 110.9 (dd, *J* = 18, 4 Hz), 96.8 (s), 56.8 (s).

MS (c.i.): *m*/*z* (%) = 210 (3, [$M^+ + NH_4$]), 192 (3, [M^+]), 154 (9), 130 (100).

(3,4-Difluorophenoxy)triisopropylsilane (26)

3,4-Difluorophenol (6.5 g, 50 mmol), chlorotriisopropylsilane (11 mL, 10 g, 50 mmol) and imidazole (3.4 g, 50 mmol) were dissolved in DMF (25 mL). After 20 h at 25 °C, the mixture was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). Distillaton under reduced pressure gave a colorless liquid; bp 186–188 °C/9 Torr; n_D^{20} 1.4759; yield: 11.2 g (78%).

^{1}H NMR: δ = 6.98 (q, *J* = 9.2 Hz, 1 H), 6.68 (ddd, *J* = 11.9, 6.7, 3.0 Hz, 1 H), 6.6 (symm. m, 1 H), 1.2 (m, 3 H), 1.09 (d, *J* = 7.2 Hz, 18 H).

^{13}C NMR: δ = 152.3 (dd, *J* = 9, 3 Hz), 150.2 (dd, *J* = 248, 14 Hz), 145.3 (dd, *J* = 240, 13 Hz), 116.9 (dd, *J* = 18, 2 Hz), 115.1 (dd, *J* = 6, 3 Hz), 109.1 (d, *J* = 18 Hz), 17.8 (6 C), 12.5 (3 C).

MS (c.i.): *m*/*z* (%) = 304 (0, [$M^+ + NH_4$]), 286 (21, [M^+]), 243 (86), 215 (22), 187 (100), 173 (62), 157 (53).

(2,3-Difluorophenoxy)triisopropylsilane (27)

Prepared, analogously as compound **26**, from 2,3-difluorophenol (6.5 g, 50 mmol); colorless liquid; bp 124–126 °C/8 Torr; n_D^{20} 1.4782; yield: 13.4 g (94%).

^{1}H NMR: δ = 6.9 (m, 1 H), 6.7 (m, 2 H), 1.3 (m, 3 H), 1.11 (d, *J* = 7.5 Hz, 18 H).

^{13}C NMR: δ = 151.9 (dd, *J* = 247, 11 Hz), 145.7 (dd, *J* = 9, 3 Hz), 143.1 (dd, *J* = 246, 13 Hz), 122.8 (dd, *J* = 9, 3.5 Hz), 116.9 (d, *J* = 3 Hz), 109.3 (d, *J* = 17.5 Hz), 17.7 (6 C), 12.7 (3 C).

MS (c.i.): *m*/*z* (%) = 304 (0, [M^+ + NH_4]), 286 (3, [M^+]), 261 (26), 244 (77), 173 (63), 77 (100).

Derivatives of 2,4-Difluorophenol

2,6-Difluoro-3-hydroxybenzoic Acid (1a)

1,3-Difluoro-4-(methoxymethoxy)benzene (**19**; 4.4 g, 25 mmol) was added to a solution of *sec*-BuLi (25 mmol) in THF (32 mL) and cyclohexane (18 mL) cooled in a dry ice/MeOH bath. After 2 h at –75 °C, the reaction mixture was poured onto freshly crushed dry ice. After addition of H_2O (25 mL) and washing the aqueous phase with Et_2O (2 × 15 mL), the aqueous phase was acidified to pH 1 with conc. HCl and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried and evaporated under reduced pressure. The residue was crystallized from toluene affording colorless prisms; mp 156–157 °C; yield: 3.57 g (82%).

^{1}H NMR*: δ = 7.15 (td, *J* = 9.2, 4.9 Hz, 1 H), 6.96 (td, *J* = 9.6, 1.4 Hz, 1 H).

^{13}C NMR*: δ = 162.6 (d, *J* = 4 Hz), 153.3 (dd, *J* = 244, 4 Hz,), 149.3 (dd, *J* = 250, 7 Hz), 146.6 (dd, *J* = 13, 4 Hz), 120.4 (dd, *J* = 9, 4 Hz), 113.2 (dd, *J* = 21, 19 Hz), 112.2 (dd, *J* = 24, 4 Hz).

MS (c.i.): *m*/*z* (%) = 192 (1, [M^+ + NH_4]), 175 (23, [M^+ + 1]), 174 (48, [M^+]), 157 (100).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.35; H, 2.32.

2-Chloro-1,3-difluoro-4-(methoxymethoxy)benzene (2)

Prepared, analogously as in the preceding paragraph, from 1,3-difluoro-4-(methoxymethoxy)benzene (**19**; 8.7 g, 50 mmol) but using 1,1,2-trichloro-1,2,2-trifluoroethane (5.9 mL, 9.4 g, 50 mmol) instead of CO_2. After having stored the reaction mixture for 1 h at –75 °C, direct distillation afforded a colorless liquid; bp 82–83 °C/3 Torr; n_D^{20} 1.4856; yield: 8.55 g (82%).

^{1}H NMR: δ = 7.09 (ddd, *J* = 9.3, 8.9, 5.1 Hz, 1 H), 6.89 (ddd, *J* = 9.3, 8.3, 2.3 Hz, 1 H), 5.16 (s, 2 H), 3.54 (s, 3 H).

^{13}C NMR: δ = 153.9 (dd, *J* = 245, 2 Hz), 150.2 (dd, *J* = 250, 4 Hz), 142.2 (dd, *J* = 11, 4 Hz), 116.3 (dd, *J* = 8, 2 Hz), 110.8 (dd, *J* = 22, 19 Hz), 110.6 (dd, *J* = 22, 4 Hz), 95.6 (s), 56.5 (s).

MS (c.i.): *m*/*z* (%) = 226 (15, [M^+ + NH_4]), 210 (42, [M^+ + 2]), 209 (16, [M^+ + 1]), 208 (100, [M^+]), 178 (51), 163 (45), 135 (78).

Anal. Calcd for $C_8H_7ClF_2O_2$ (208.59): C, 46.06; H, 3.38. Found: C, 46.14; H, 3.29.

3-Chloro-2,4-difluoro-5-hydroxybenzoic Acid (3a)

2,2,6,6-Tetramethylpiperidine (2.5 mL, 2.1 g, 15 mmol) and 2-chloro-1,3-difluoro-4-(methoxymethoxy)benzene (**2**; 3.1 g, 15 mmol) were added consecutively to a solution of BuLi (15 mmol) in THF (20 mL) and hexanes (10 mL). After 2 h at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. After addition of H_2O (15 mL) and washing the aqueous layer with Et_2O (2 × 20 mL), the aqueous phase was acidified to pH 1 with conc. HCl and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried and evaporated under reduced pressure and the residue was crystallized from $CHCl_3$ to give colorless needles; mp 195–197 °C; yield: 2.35 g (75%).

^{1}H NMR*: δ = 7.55 (dd, *J* = 9.5, 6.7 Hz, 1 H).

^{13}C NMR*: δ = 163.9 (d, *J* = 4 Hz), 152.4 (dd, *J* = 255, 2 Hz,), 151.5 (dd, *J* = 253, 2 Hz), 142.6 (dd, *J* = 13, 4 Hz), 118.5 (dd, *J* = 4, 1 Hz), 116.1 (dd, *J* = 11, 4 Hz), 112.0 (dd, *J* = 23, 18 Hz).

MS (c.i.): *m*/*z* (%) = 226 (23, [M^+ + NH_4]), 209 (47, [M^+ + 1]), 208 (34, [M^+]), 191 (100).

Anal. Calcd for $C_7H_3ClF_2O_3$ (208.54): C, 40.32; H, 1.45. Found: C, 40.65; H, 1.42.

4-Chloro-3,5-difluoro-2-hydroxybenzoic Acid (3b)

2-Chloro-1,3-difluoro-4-(methoxymethoxy)benzene (**2**; 3.1 g, 15 mmol) was treated with BuLi (15 mmol) in CH_2Cl_2 (20 mL) and hexanes (10 mL) for 6 h at –75 °C. The reaction mixture was then poured onto an excess of dry ice and after workup as described in the preceding paragraph and crystallization from $CHCl_3$, colorless needles were obtained; mp 201–202 °C; yield: 1.90 g (61%).

^{1}H NMR*: δ = 7.61 (dd, *J* = 9.1, 2.3 Hz, 1 H).

^{13}C NMR*: δ = 170.9 (t, *J* = 4 Hz), 151.0 (dd, *J* = 241, 2 Hz,), 148.9 (dd, *J* = 249, 3 Hz), 148.6 (dd, *J* = 13, 3 Hz), 117.1 (dd, *J* = 22, 18 Hz), 113.0 (dd, *J* = 7, 4 Hz), 111.7 (dd, *J* = 23, 4 Hz).

MS (c.i.): *m*/*z* (%) = 226 (6, [M^+ + NH_4]), 209 (15, [M^+ + 1]), 208 (37, [M^+]), 207 (32), 192 (53), 190 (100).

Anal. Calcd for $C_7H_3ClF_2O_3$ (208.54): C, 40.31; H, 1.45. Found: C, 40.59; H, 1.34.

2,4-Difluoro-5-hydroxybenzoic Acid (1b)

A solution of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid (**3b**; 1.0 g, 5.0 mmol) and ammonium formate (1.9 g, 30 mmol) in MeOH (10 mL) was stirred in presence of 10% Pd/C (0.25 g) at 25 °C for 20 h. Filtration, evaporation of the solvent and crystallization from MeOH afforded colorless needles; mp 180–181 °C; yield: 0.77 g (86%).

^{1}H NMR*: δ = 7.59 (dd, *J* = 9.9, 7.0 Hz, 1 H), 7.15 (t, *J* = 10.6 Hz, 1 H).

^{13}C NMR*: δ = 164.2 (d, *J* = 4 Hz), 155.6 (dd, *J* = 253, 11 Hz,), 154.3 (dd, *J* = 252, 12 Hz), 141.6 (dd, *J* = 13, 4 Hz), 120.2 (dd, *J* = 5, 2 Hz), 115.2 (dd, *J* = 11, 4 Hz), 106.0 (dd, *J* = 28, 22 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0, [M^+ + NH_4]), 175 (7, [M^+ + 1), 174 (58, [M^+]), 157 (100).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.60; H, 2.42.

3,5-Difluoro-2-hydroxybenzoic Acid (1c)

Prepared, analogously as compound **1b**, from 4-chloro-3,5-difluoro-2-hydroxybenzoic acid (**3b**; 1.0 g, 5.0 mmol); colorless needles (from toluene); mp 188–189 °C [Lit.[12] mp 185–186 °C]; yield: 0.82 g (94%).

^{1}H NMR*: δ = 7.36 (ddd, *J* = 9.0, 3.2, 1.8 Hz, 1 H), 7.03 (ddd, *J* = 11.7, 8.6, 3.2 Hz, 1 H).

^{13}C NMR*: δ = 174.8 (t, *J* = 3 Hz,), 152.2 (dd, *J* = 234, 11 Hz), 151.2 (dd, *J* = 245, 12 Hz), 148.6 (dd, *J* = 12, 2 Hz), 122.6 (dd, *J* = 7, 4 Hz), 111.0 (dd, *J* = 22, 3 Hz), 107.4 (dd, *J* = 27, 22 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0, [M^+ + NH_4]), 175 (2, [M^+ + 1]), 174 (19, [M^+]), 157 (20), 156 (100), 128 (23).

Derivatives of 2,5-Difluorophenol

3,6-Difluoro-2-hydroxybenzoic Acid (4a)

1,4-Difluoro-2-(methoxymethoxy)benzene (**20**; 4.4 g, 25 mmol) was added to a solution of BuLi (25 mmol) in THF (35 mL) and hexanes (15 mL), cooled in a dry ice/MeOH bath. After 2 h at –75 °C, the reaction mixture was poured onto freshly crushed dry ice. After addition of H_2O (25 mmol), washing with Et_2O (2 × 15

mL), the aqueous phase was acidified to pH 1 and extracted with Et_2O (3 × 25 mL). After evaporation of the solvent, the residue was crystallized from toluene as colorless needles; mp 154–155 °C; yield: 3.99 g (92%).

^{1}H NMR*: δ = 7.44 (ddd, *J* = 10.2, 9.0, 4.8 Hz, 1 H), 6.73 (ddd, *J* = 10.6, 9.3, 3.8 Hz).

^{13}C NMR*: δ = 170.4 (t, *J* = 3 Hz), 158.3 (dd, *J* = 256, 3 Hz), 151.6 (dd, *J* = 15, 5 Hz), 148.0 (dd, *J* = 240, 4 Hz), 121.5 (dd, *J* = 20, 12 Hz), 105.9 (dd, *J* = 26, 7 Hz), 104.6 (dd, *J* = 15, 3 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 174 (15, [M^+]), 157 (20), 156 (100).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.38; H, 2.30.

[3,6-Difluoro-2-(methoxymethoxy)phenyl]trimethylsilane (5)

Prepared, analogously as compound **4a**, from 1,4-difluoro-2-(methoxymethoxy)benzene (**20**; 8.7 g, 50 mmol) but using Me_3SiCl (6.3 mL, 5.4 g, 50 mmol) instead of dry ice. After 45 min at –75 °C, MeOH (5 mL) was added. Direct distillation of the reaction mixture afforded a colorless liquid; bp 77–79 °C/4 Torr; n_D^{20} 1.4760; yield: 10.3 g (84%).

^{1}H NMR: δ = 7.03 (ddd, *J* = 10.9, 8.5, 5.1 Hz, 1 H), 6.67 (ddd, *J* = 8.6, 7.7, 3.2 Hz, 1 H), 5.19 (d, *J* = 1.9 Hz, 2 H), 3.57 (s, 3 H), 0.42 (d, *J* = 1.9 Hz, 9 H).

^{13}C NMR: δ = 163.0 (dd, *J* = 238, 2 Hz), 151.3 (dd, *J* = 243, 4 Hz), 148.7 (dd, *J* = 15, 11 Hz), 120.9 (d, *J* = 33 Hz), 118.8 (dd, *J* = 23, 11 Hz), 110.8 (dd, *J* = 30, 7 Hz), 99.2 (d, *J* = 9 Hz), 58.0 (s), 1.01 (d, *J* = 4 Hz).

MS (c.i.): *m*/*z* (%) = 264 (33, [$M^+ + NH_4$]), 247 (11, [$M^+ + 1$]), 246 (10, [M^+]), 201 (100).

Anal. Calcd for $C_{11}H_{16}F_2O_2Si$ (246.32): C, 53.64; H, 6.55. Found: C, 53.55; H, 6.37.

2,5-Difluoro-3-hydroxy-4-(trimethylsilyl)benzoic Acid (6)

[2,5-Difluoro-6-(methoxymethoxy)phenyl]trimethylsilane (**5**; 6.2 g, 25 mmol) was added to a solution of *sec*-BuLi (25 mmol) and *N*,*N*,*N*′,*N*″,*N*″-pentamethylethylenetriamine (5.2 mL, 4.3 g, 25 mmol) in THF (30 mL) and cyclohexane (20 mL), cooled in a dry ice/MeOH bath. After 2 h at –75 °C, the reaction mixture was poured onto freshly crushed dry ice. After addition of H_2O (25 mL) and washing the aqueous phase with Et_2O (2 × 15 mL), the aqueous phase was acidified to pH 1 and extracted with Et_2O (3 × 25 mL). Evaporation of the solvent and crystallization from CH_2Cl_2 gave colorless needles; mp 157–158 °C; yield: 4.79 g (78%).

^{1}H NMR*: δ = 6.76 (dd, *J* = 9.0, 4.5 Hz, 1 H), 0.14 (d, *J* = 1.9 Hz, 9 H).

^{13}C NMR*: δ = 164.1 (t, *J* = 3 Hz), 162.0 (dd, *J* = 237, 3 Hz), 151.0 (t, *J* = 16 Hz), 147.5 (dd, *J* = 250, 3 Hz), 120.9 (t, *J* = 11 Hz), 120.1 (d, *J* = 35 Hz), 107.8 (d, *J* = 33 Hz), –0.1 (d, *J* = 4 Hz).

MS (c.i.): *m*/*z* (%) = 264 (100, [$M^+ + NH_4$]), 246 (3, [M^+]), 231 (4), 230 (7).

Anal. Calcd for $C_{10}H_{12}F_2O_3Si$ (246.28): C, 48.77; H, 4.91. Found: C, 48.79; H, 4.79.

2,5-Difluoro-3-hydroxybenzoic Acid (4b)

2,5-Difluoro-3-hydroxy-4-(trimethylsilyl)benzoic acid (**6**; 3.7 g, 15 mmol) and tetrabutylammonium fluoride trihydrate (4.7 g, 15 mmol) were dissolved in THF (15 mL). After 2 h at 25 °C, a 10% aq solution of HCl was added and the reaction mixture was extracted with Et_2O (3 × 15 mL). The product was crystallized from toluene affording colorless needles; mp 154–155 °C; yield: 2.42 g (93%).

^{1}H NMR*: δ = 6.96 (ddd, *J* = 9.0, 4.8, 3.5 Hz, 1 H), 6.64 (ddd, *J* = 9.3, 6.4, 3.2 Hz, 1 H).

^{13}C NMR*: δ = 164.0 (t, *J* = 3 Hz), 158.1 (dd, *J* = 242, 3 Hz), 148.3 (dd, *J* = 251, 3 Hz), 147.5 (dd, *J* = 15, 12 Hz), 120.6 (t, *J* = 9 Hz), 109.3 (dd, *J* = 27, 3 Hz), 107.6 (d, *J* = 27 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 175 (1, [$M^+ + 1$]), 174 (100, [M^+]), 144 (3), 101 (13).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.36; H, 2.05.

[4-Chloro-3,6-difluoro-2-(methoxymethoxy)phenyl]trimethylsilane (7)

Prepared as described above for compound **6**, from [2,5-difluoro-6-(methoxymethoxy)phenyl]trimethylsilane (**5**; 6.2 g, 25 mmol) but using 1,1,2-trichloro-1,2,2-trifluoroethane (3.0 mL, 4.7 g, 25 mmol) instead of dry ice. After distillation under reduced pressure a colorless liquid was obtained; bp 91–92 °C/5 Torr; n_D^{20} 1.4894; yield: 4.50 g (64%).

^{1}H NMR: δ = 6.79 (dd, *J* = 8.0, 4.8 Hz, 1 H), 5.16 (d, *J* = 1.6 Hz, 2 H), 3.56 (s, 3 H), 0.35 (d, *J* = 1.9 Hz, 9 H).

^{13}C NMR: δ = 162.0 (dd, *J* = 241, 3 Hz), 149.6 (dd, *J* = 16, 11 Hz), 148.1 (dd, *J* = 246, 4 Hz), 123.9 (dd, *J* = 19, 15 Hz), 119.6 (td, *J* = 26, 2 Hz), 112.4 (d, *J* = 34 Hz), 99.4 (d, *J* = 9 Hz), 58.1, 0,84 (d, *J* = 3 Hz).

MS (c.i.): *m*/*z* (%) = 298 (86, [$M^+ + NH_4$]), 282 (11, [$M^+ + 2$]), 281 (7, [$M^+ + 1$]), 280 (7, [M^+]), 90 (100).

Anal. Calcd for $C_{11}H_{15}ClF_2O_2Si$ (280.77): C, 47.06; H, 5.38. Found: C, 47.03; H, 5.27.

2-Chloro-3,6-difluoro-4-hydroxybenzoic Acid (8)

Prepared, analogously as compound **3a**, from [4-chloro-3,6-difluoro-2-(methoxymethoxy)phenyl]trimethylsilane (**7**; 4.2 g, 15 mmol). Crystallization from toluene gave small colorless needles; mp 163–164 °C; yield: 2.03 g (65%).

^{1}H NMR*: δ = 6.89 (dd, *J* = 10.6, 6.7 Hz, 1 H).

^{13}C NMR*: δ = 162.9 (d, *J* = 2 Hz), 156.0 (dd, *J* = 248, 4 Hz), 148.4 (t, *J* = 14 Hz), 145.2 (dd, *J* = 241, 4 Hz), 120.1 (dd, *J* = 18, 9 Hz), 174.3 (dd, *J* = 22, 2 Hz), 104.5 (dd, *J* = 17, 2 Hz).

MS (c.i.): *m*/*z* (%) = 226 (0, [$M^+ + NH_4$]), 209 (42, [$M^+ + 1$]), 208 (31, [M^+]), 192 (14), 191 (100).

Anal. Calcd for $C_7H_3ClF_2O_3$ (208.54): C, 40.32; H, 1.45. Found: C, 40.48; H,1.31.

2,5-Difluoro-4-hydroxybenzoic Acid (4c)

Prepared, analogously as compound **1c**, from 2-chloro-3,6-difluoro-4-hydroxybenzoic acid (**8**; 1.0 g, 5 mmol); tiny colorless needles (from toluene); mp 163–165 °C; yield: 0.65 g (75%).

^{1}H NMR*: δ = 7.66 (dd, *J* = 11.2, 6.7 Hz, 1 H), 6.86 (dd, *J* = 11.5, 7.0 Hz, 1 H).

^{13}C NMR*: δ = 164.0 (dd, *J* = 4, 2 Hz), 159.4 (dd, *J* = 255, 2 Hz,), 151.0 (dd, *J* = 15, 2 Hz), 147.7 (dd, *J* = 238, 3 Hz), 118.8 (dd, *J* = 22, 4 Hz), 109.6 (dd, *J* = 12, 6 Hz), 106.2 (dd, *J* = 27, 3 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 175 (15, [$M^+ + 1$]), 174 (69, [M^+]), 157 (100).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.04; H, 2.20.

Derivatives of 2,3-Difluorophenol

3,4-Difluoro-2-hydroxybenzoic Acid (9a)
Prepared, analogously as compound **4a**, from 1,2-difluoro-3-(methoxymethoxy)benzene (**21**; 1.7 g, 10 mmol) but extending the reaction time to 6 h. Crystallization from $CHCl_3$ gave colorless prisms; mp 171–172 °C; yield: 1.51 g (87%).

^{1}H NMR*: δ = 7.77 (ddd, *J* = 9.0, 5.9, 2.3 Hz, 1 H), 6.92 (ddd, *J* = 16.0, 9.1, 6.9 Hz, 1 H).

^{13}C NMR*: δ = 171.8 (d, *J* = 3 Hz), 155.4 (dd, *J* = 253, 10 Hz), 153.3 (dd, *J* = 10, 5 Hz), 140.6 (dd, *J* = 246, 14 Hz), 126.8 (dd, *J* = 10, 5 Hz), 111.7 (t, *J* = 2 Hz), 108.0 (d, *J* = 18 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0) [M^++NH_4], 174 (9) [M^+], 156 (92), 128 (100), 100 (9).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.36; H, 2.15.

2,3-Difluoro-4-hydroxybenzoic Acid (9c)
Prepared, analogously as compound **3a**, from (2,3-difluorophenoxy)triisopropylsilane (**27**; 7.2 g, 25 mmol); colorless prisms (from $CHCl_3$); mp 210–211 °C; yield: 3.87 g (89%).

^{1}H NMR*: δ = 7.66 (ddd, *J* = 9.0, 7.7, 2.2 Hz, 1 H), 6.92 (ddd, *J* = 9.0, 7.7, 1.9 Hz, 1 H).

^{13}C NMR*: δ = 164.6 (t, *J* = 3 Hz), 152.6 (dd, *J* = 259, 11 Hz), 151.6 (dd, *J* = 10, 3 Hz), 141.4 (dd, *J* = 242, 15 Hz), 127.8 (dd, *J* = 4, 2 Hz), 113.3 (dd, *J* = 3.5, 2 Hz), 112.1 (dd, *J* = 7, 1 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0, [M^+ + NH_4]), 175 (17, [M^+ + 1]), 174 (13, [M^+]), 158 (72), 157 (100), 102 (17).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.39; H, 2.15.

(4-Chloro-2,3-difluorophenoxy)triisopropylsilane (10)
Prepared, analogously as compound **3a**, from (2,3-difluorophenoxy)triisopropylsilane (**27**; 14.3 g, 50 mmol) but replacing CO_2 (dry ice) by 1,1,2-trichloro-1,2,2-trifluoroethane (6.0 mL, 9.4 g, 50 mmol). Distillation under reduced pressure gave a colorless liquid; bp 145–147 °C/7 Torr; n_D^{20} 1.4908; yield: 12.3 g (77%).

^{1}H NMR: δ = 6.98 (ddd, *J* = 9.1, 7.8, 2.4 Hz, 1 H), 6.67 (ddd, *J* = 9.1, 8.0, 2.2 Hz, 1 H), 1.3 (m, 3 H), 1.10 (d, *J* = 7.3 Hz, 18 H).

^{13}C NMR: δ = 148.4 (dd, *J* = 250, 13 Hz), 144.8 (dd, *J* = 9, 2 Hz), 144.1 (dd, *J* = 249, 13 Hz), 123.8 (d, *J* = 5 Hz), 116.7 (d, *J* = 3 Hz), 114.2 (d, *J* = 15 Hz), 18.0 (6 C), 13.0 (3 C).

MS (c.i.): *m*/*z* (%) = 339 (0.2, [M^+ + NH_4]), 321 (9, [M^+]), 295 (31), 207 (53), 174 (57), 77 (100).

Anal. Calcd for $C_{15}H_{23}ClF_2OSi$ (320.88): C, 56.15; H, 7.22. Found: C, 56.51; H, 7.02.

2-Chloro-3,4-difluoro-5-hydroxybenzoic Acid (11)
Prepared, analogously as compound **3a**, from (4-chloro-2,3-difluorophenoxy)triisopropylsilane (**10**, 8.0 g, 25 mmol). The triisopropylsilyl group was removed using tetrabutylammonium fluoride trihydrate (8.0 g, 25 mmol) according to the procedure described for compound **4b**. Crystallization from toluene afforded colorless platelets; mp 156–157 °C; yield: 4.26 g (82%).

^{1}H NMR*: δ = 7.46 (dd, *J* = 8.6, 2.2 Hz, 1 H).

^{13}C NMR*: δ = 165.1 (dd, *J* = 3, 1 Hz), 149.0 (dd, *J* = 245, 12 Hz), 145.7 (dd, *J* = 10, 3 Hz), 143.7 (dd, *J* = 252, 15 Hz), 127.0 (d, *J* = 3 Hz), 116.0 (t, *J* = 3 Hz), 113.2 (d, *J* = 17 Hz).

MS (c.i.): *m*/*z* (%) = 226 (0, [M^+ + NH_4]), 210 (26, [M^+ + 2]), 209 (20, [M^+ + 1]), 208 (69, [M^+]), 191 (100), 163 (27).

Anal. Calcd for $C_7H_3ClF_2O_3$ (208.55): C, 40.32; H, 1.45. Found: C, 40.22; H, 1.40.

3,4-Difluoro-5-hydroxybenzoic Acid (9b)
Under N_2, 10% Pd/C (0.53 g) was added to a solution of 2-chloro-3,4-difluoro-5-hydroxybenzoic acid (**11**; 1.0 g, 5.0 mmol) in MeOH (10 mL). H_2 gas was bubbled into the stirred reaction mixture until, after 20 h, the uptake ceased. The catalyst was removed by filtration and the solvent evaporated. The product was crystallized from hexanes–EtOAc (5:1) as colorless needles; mp 214–215 °C; yield: 0.85 g (98%).

^{1}H NMR*: δ = 7.53 (dt, *J* = 7.4, 1.9 Hz, 1 H), 7.40 (ddd, *J* = 10.5, 6.8, 2.0 Hz, 1 H).

^{13}C NMR*: δ = 166.8 (dd, *J* = 3, 2 Hz), 152.6 (dd, *J* = 245, 11 Hz), 148.3 (dd, *J* = 10, 3 Hz), 145.0 (dd, *J* = 250, 14 Hz), 128.2 (dd, *J* = 8, 4 Hz), 116.4 (t, *J* = 3 Hz), 110.7 (d, *J* = 19 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0, [M^+ + NH_4]), 175 (23, [M^+ + 1]), 174 (41, [M^+]), 137 (100), 129 (26).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.12; H, 2.04.

Derivatives of 3,5-Difluorophenol

2,6-Difluoro-4-hydroxybenzoic Acid (12a)
1,3-Difluoro-5-(methoxymethoxy)benzene (**22**; 4.3 g, 25 mmol) was added to a solution of BuLi (25 mmol) and *t*-BuOK (2.8 g, 25 mmol) in THF (35 mL) and hexanes (15 mL), kept in a dry ice/MeOH bath. After 2 h at –75 °C, the reaction mixture was poured onto freshly crushed dry ice. After neutralization and extraction with CH_2Cl_2, the product crystallized from toluene; colorless prisms; mp 175–176 °C; yield: 3.61 g (83%).

^{1}H NMR*: δ = 6.55 (d, *J* = 10.0 Hz, 2 H).

^{13}C NMR*: δ = 162.7 (dd, *J* = 255, 10 Hz, 2 C), 162.2 (t, *J* = 15 Hz, 2 C), 100.1 (dd, *J* = 26, 3 Hz, 3 C).

MS (c.i.): *m*/*z* (%) = 192 (0, [M^+ + NH_4]), 175 (4, [M^+ + 1]), 174 (18, [M^+]), 157 (100).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.57; H, 2.22.

[2,6-Difluoro-4-(methoxymethoxy)phenyl]trimethylsilane (13)
Prepared, analogously as described in the preceding paragraph, from 1,3-difluoro-5-(methoxymethoxy)benzene (**20**; 5.2 g, 30 mmol) but using Me_3SiCl (3.8 mL, 3.3 g, 30 mmol) instead of dry ice. After 45 min at –75 °C and addition of MeOH (5.0 mL), the solution was directly distilled affording a colorless liquid; bp 91–93 °C/6 Torr; n_D^{20} 1.4689; yield: 5.76 g (78%).

^{1}H NMR: δ = 6.50 (d, *J* = 9.0 Hz, 2 H), 5.13 (s, 2 H), 3.46 (s, 3 H), 0.31 (t, *J* = 1.6 Hz, 9 H).

^{13}C NMR: δ = 167.6 (dd, *J* = 242, 20 Hz, 2 C), 160.2 (t, *J* = 15 Hz), 106.0 (t, *J* = 35 Hz), 99.6 (dd, *J* = 32, 3 Hz, 2 C), 94.3 (s), 56.1 (s), 0.2 (s).

MS (c.i.): *m*/*z* (%) = 264 (0, [M^+ + NH_4]), 246 (8, [M^+]), 143 (13), 84 (100).

Anal. Calcd for $C_{11}H_{16}F_2O_2Si$ (246.32): C, 53.64; H, 6.55. Found: C, 53.77; H, 6.55.

4,6-Difluoro-2-hydroxybenzoic Acid (12b)
1,3-Difluoro-5-(methoxymethoxy)benzene (**22**; 4.3 g, 25 mmol) was added to a solution of BuLi (25 mmol) in Et_2O (15 mL) and hexanes (30 mL) kept in a dry ice/MeOH bath. After 6 h at –75 °C, the reaction mixture was poured onto freshly crushed dry ice. After addition of H_2O (25 mL) and washing the aqueous phase with Et_2O (2 × 15 mL), the aqueous phase was acidified to pH 1 and extracted

with Et_2O (3 × 25 mL). A sample was withdrawn and, after addition of the 'internal standard' tridecane treated with ethereal diazomethane until persistence of the yellow color. According to GC (20 m, DB-WAX, 150 °C; 20 m, DB-17, 150 °C), the crude material contained 79% of 4,6-difluoro-2-hydroxybenzoic acid (**12b**) along with 2% of 2,6-difluoro-4-hydroxybenzoic acid (**12a**). The rest of the ethereal solution was evaporated and the residue was crystallized from $CHCl_3$ affording colorless prisms; mp 182–183 °C; yield: 2.65 g (61%).

^{1}H NMR*: δ = 6.57 (ddd, *J* = 9.9, 2.6, 1.6 Hz, 1 H), 6.46 (ddd, *J* = 11.2, 9.0, 2.6 Hz, 1 H).

^{13}C NMR*: δ = 171.1 (t, *J* = 2 Hz), 167.5 (dd, *J* = 253, 17 Hz), 166.2 (t, *J* = 12 Hz), 164.7 (dd, *J* = 262, 17 Hz), 101.1 (symm. m, 2 C), 97.0 (t, *J* = 27 Hz).

MS (c.i.): *m*/*z* (%) = 192 (1, [$M^+ + NH_4$]), 174 (15, [M^+]), 157 (27), 156 (89), 128 (100).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.28; H, 2.32.

The same compound was prepared, analogously as compound **1a**, from [2,6-difluoro-4-(methoxymethoxy)phenyl]trimethylsilane (**13**; 4.9 g, 20 mmol). Crystallization from $CHCl_3$ gave colorless prisms; yield: 3.10 g (89%).

Derivatives of 3,4-Difluorophenol

2,3-Difluoro-6-hydroxybenzoic Acid (14a)
Prepared, analogously as compound **3a**, from 1,2-difluoro-4-(methoxymethoxy)benzene (**23**; 4.35 g, 25 mmol). Crystallization from hexanes gave colorless needles; mp 185–186 °C; yield: 4.00 g (92%).

^{1}H NMR: δ = 7.36 (symm. m, 1 H), 6.78 (ddd, *J* = 9.3, 3.7, 2.1 Hz, 1 H).

^{13}C NMR*: δ = 170.6 (t, *J* = 3 Hz), 159.5 (t, *J* = 2 Hz), 150.6 (dd, *J* = 261, 14 Hz), 144.6 (dd, *J* = 237, 14 Hz), 124.1 (dd, *J* = 19, 2 Hz), 113.4 (dd, *J* = 6, 4 Hz), 104.4 (d, *J* = 10 Hz).

MS (c.i.): *m*/*z* (%) = 192 (15, [$M^+ + NH_4$]), 174 (27, [M^+]), 173 (35, [$M^+ - 1$]), 156 (57), 128 (100).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.46; H, 2.20.

2-Chloro-3,4-difluoro-1-(methoxymethoxy)benzene (15)
Prepared, analogously as compound **3a**, from 1,2-difluoro-4-(methoxymethoxy)benzene (**23**; 8.7 g, 50 mmol) but using 1,1,2-trichloro-1,2,2-trifluoroethane (6.0 mL, 9.4 g, 50 mmol) instead of dry ice. Distillation under reduced pressure gave colorless liquid that spontaneously crystallized; mp 24–25 °C; bp 88–90 °C/9 Torr; yield: 8.12 g (78%).

^{1}H NMR: δ = 7.02 (symm. m, 1 H), 6.92 (ddd, *J* = 9.4, 4.3, 2.2 Hz, 1 H), 5.21 (s, 2 H), 3.52 (s, 3 H).

^{13}C NMR: δ = 150.1 (d, *J* = 2.5 Hz), 147.6 (dd, *J* = 250, 15 Hz), 146.3 (dd, *J* = 245, 13 Hz), 114.6 (dd, *J* = 18, 1.5 Hz), 110.6 (dd, *J* = 7, 4 Hz), 104.6 (d, *J* = 21 Hz), 95.8, 56.5.

MS (c.i.): *m*/*z* (%) = 226 (0, [$M^+ + NH_4$]), 209 (49, [$M^+ + 1$]), 208 (100, [M^+]), 178 (46), 163 (43), 135 (88).

Anal. Calcd for $C_8H_7ClF_2O_3$ (208.59): C, 46.07; H, 3.38. Found: C, 45.76; H, 3.15.

3-Chloro-4,5-difluoro-2-hydroxybenzoic Acid (16a)
Prepared, analogously as compound **3b,** from 2-chloro-3,4-difluoro-1-(methoxymethoxy)benzene (**15**; 2.1 g, 10 mmol). Crystallization from toluene gave colorless prisms; mp 173–174 °C; yield: 1.82 g (87%).

^{1}H NMR*: δ = 7.82 (dd, *J* = 10.4, 8.8 Hz, 1 H).

^{13}C NMR*: δ = 171.2 (s), 156.8 (s), 152.4 (dd, *J* = 255, 16 Hz), 144.3 (dd, *J* = 242, 13 Hz), 116.6 (dd, *J* = 20, 2 Hz), 111.5 (dd, *J* = 16, 2 Hz), 109.2 (dd, *J* = 6, 3 Hz).

MS (c.i.): *m*/*z* (%) = 226 (0, [$M^+ + NH_4$]), 208 (5, [M^+]), 192 (32), 191 (26), 190 (100), 162 (46), 134 (69).

Anal. Calcd for $C_7H_3ClF_2O_3$ (208.55): C, 40.32; H, 1.45. Found: C, 40.51; H, 1.31.

4-Chloro-2,3-difluoro-5-hydroxybenzoic Acid (16b)
Prepared, analogously as compound **3a**, from 2-chloro-3,4-difluoro-1-(methoxymethoxy)benzene (**15**; 2.1 g, 10 mmol); colorless prisms (from toluene); mp 168–170 °C; yield: 1.73 g (83%).

^{1}H NMR*: δ = 7.40 (dd, *J* = 5.9, 2.3 Hz, 1 H).

^{13}C NMR*: δ = 163.9 (t, *J* = 3.5 Hz), 150.6 (dd, *J* = 3, 2 Hz), 149.0 (dd, *J* = 247, 16 Hz), 145.2 (dd, *J* = 254, 14 Hz), 119.4 (d, *J* = 8 Hz), 115.3 (d, *J* = 16 Hz), 112.9 (d, *J* = 3 Hz).

MS (c.i.): *m*/*z* (%) = 226 (0, [$M^+ + NH_4$]), 210 (34, [$M^+ + 2$]), 209 (17, [$M^+ + 1$]), 208 (100, [M^+]), 207 (25, [$M^+ - 1$]), 191 (94), 135 (32).

Anal. Calcd for $C_7H_3ClF_2O_3$ (208.55): C, 40.32; H, 1.45. Found: C, 40.53; H, 1.31.

4,5-Difluoro-2-hydroxybenzoic Acid (14b)
Prepared, analogously as compound **9b**, from 3-chloro-4,5-difluoro-2-hydroxybenzoic acid (**16a**; 1.0 g, 5.0 mmol). Crystallization from hexanes gave colorless needles; mp 151–152 °C; yield: 0.87 g (95%).

^{1}H NMR*: δ = 7.78 (dd, *J* = 10.8, 9.1 Hz, 1 H), 6.94 (dd, *J* = 11.9, 6.7 Hz, 1 H).

^{13}C NMR*: δ = 171.3 (d, *J* = 3 Hz), 160.5 (dd, *J* = 12, 2 Hz), 155.7 (dd, *J* = 255, 14 Hz), 144.1 (dd, *J* = 239, 13 Hz), 118.6 (dd, *J* = 19, 3 Hz), 109.2 (dd, *J* = 5, 3 Hz), 106.8 (d, *J* = 20 Hz).

MS (c.i.): *m*/*z* (%) = 192 (0, [$M^+ + NH_4$]), 176 (4, [$M^+ + 2$]), 175 (5) [M^++1], 174 (4) [M^+], 156 (100).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.66; H, 2.26.

2,3-Difluoro-5-hydroxybenzoic Acid (14c)
Prepared, analogously as compound **6**, from (3,4-difluorophenoxy)triisopropylsilane (**26**; 7.2 g, 25 mmol). Crystallization from $CHCl_3$ afforded colorless prisms; mp 191–192 °C; yield: 3.22 g (74%).

^{1}H NMR*: δ = 7.2 (symm. m, 1 H), 7.03 (ddd, *J* = 11.7, 6.2, 3.1 Hz, 1 H).

^{13}C NMR*: δ = 164.5 (t, *J* = 3.5 Hz), 153.9 (dd, *J* = 10, 3 Hz), 152.0 (dd, *J* = 245, 14 Hz), 144.8 (dd, *J* = 251, 14 Hz), 121.8 (dd, *J* = 8, 1 Hz), 113.4 (d, *J* = 3 Hz), 109.6 (d, *J* = 20 Hz).

MS (c.i.): *m*/*z* (%) = 192 (100, [$M^+ + NH_4$]), 174 (23, [M^+]), 157 (54).

Anal. Calcd for $C_7H_4F_2O_3$ (174.10): C, 48.29; H, 2.32. Found: C, 48.37; H, 2.26.

The same compound was prepared by hydrogenation of 4-chloro-2,3-difluoro-5-hydroxybenzoic acid (**16b**; 1.0 g, 5.0 mmol); yield: 0.84 g (92%).

Derivatives of 2,4,5-Trifluorophenol

2,3,5-Trifluoro-6-hydroxybenzoic Acid (17a)
Prepared, analogously as compound **16a**, from 1,2,4-trifluoro-5-(methoxymethoxy)benzene (**24**; 1.9 g, 10 mmol); colorless platelets (from toluene); mp 166–168 °C; yield: 1.71 g (89%).

^{1}H NMR*: δ = 7.66 (ddd, *J* = 10.5, 10.5, 7.4 Hz, 1 H).

^{13}C NMR*: δ = 170.9 (dd, *J* = 7, 4 Hz), 148.7 (dt, *J* = 14, 3 Hz), 148.0 (ddd, *J* = 244, 10, 4 Hz), 147.7 (ddd, *J* = 257, 14, 4 Hz), 143.8 (ddd, *J* = 240, 15, 10 Hz), 112.5 (td, *J* = 23, 2 Hz), 106.7 (dd, *J* = 12, 4 Hz).

MS (c.i.): *m*/*z* (%) = 210 (0, [$M^+ + NH_4$]), 192 (9, [M^+]), 175 (29), 174 (100), 146 (35), 118 (40), 99 (17).

Anal. Calcd for $C_7H_3F_3O_3$ (192.09): C, 43.77; H, 1.57. Found: C, 44.12; H, 1.47.

2,3,6-Trifluoro-5-hydroxybenzoic Acid (17b)
Prepared, analogously as compound **12a**, from 1,2,4-trifluoro-5-(methoxymethoxy)benzene (**24**; 1.9 g, 10 mmol). Crystallization from $CHCl_3$ gave tiny colorless needles; mp 136–137 °C; yield: 1.78 g (93%).

^{1}H NMR*: δ = 7.14 (ddd, *J* = 11.5, 7.9, 7.9 Hz, 1 H).

^{13}C NMR*: δ = 161.9 (d, *J* = 3 Hz), 147.4 (ddd, *J* = 243, 14, 3 Hz), 145.6 (ddd, *J* = 247, 5, 3 Hz), 142.8 (dd, *J* = 15, 13 Hz), 141.6 (ddd, *J* = 247, 16, 6 Hz), 114.3 (t, *J* = 18 Hz), 108.9 (dd, *J* = 22, 4 Hz).

MS (c.i.): *m*/*z* (%) = 210 (0, [$M^+ + NH_4$]), 192 (59, [M^+]), 175 (63), 148 (21), 119 (40), 99 (53), 75 (100).

Anal. Calcd for $C_7H_3F_3O_3$ (192.09): C, 43.77; H, 1.57. Found: C, 44.09; H, 1.52.

Derivatives of 2,3,4-Trifluorophenol

3,4,5-Trifluoro-2-hydroxybenzoic Acid (18a)
Prepared, analogously as compound **3b**, from 1,2,3-trifluoro-4-(methoxymethoxy)benzene (**25**; 4.8 g, 25 mmol); colorless needles (from toluene); mp 148–150 °C; yield: 2.93 g (61%).

^{1}H NMR*: δ = 7.67 (ddd, *J* = 10.9, 8.6, 2.6 Hz, 1 H).

^{13}C NMR*: δ = 170.5 (m), 149.1 (tdd, *J* = 10, 6, 3 Hz), 144.6 (ddd, *J* = 246, 17, 12 Hz), 143.5 (ddd, *J* = 247, 11, 2 Hz), 140.1 (ddd, *J* = 249, 12, 2 Hz), 113.5 (t, *J* = 3 Hz), 111.9 (ddd, *J* = 20, 4, 1 Hz).

MS (c.i.): *m*/*z* (%) = 210 (0, [$M^+ + NH_4$]), 192 (3, [M^+]), 175 (73), 174 (100), 146 (31).

Anal. Calcd for $C_7H_3F_2O_3$ (192.09): C, 43.77; H, 1.57. Found: C, 43.91; H, 1.45.

2,3,4-Trifluoro-5-hydroxybenzoic Acid (18b)
Prepared, analogously as compound **3a**, from 1,2,3-trifluoro-4-(methoxymethoxy)benzene (**25**; 4.8 g, 25 mmol) but replacing 2,2,6,6-tetramethylpiperidine by diisopropylamine (3.5 mL, 2.5 g, 25 mmol); colorless needles (from toluene); mp 165–167 °C; yield: 4.66 g (97%).

^{1}H NMR*: δ = 7.40 (ddd, *J* = 9.0, 6.4, 2.2 Hz, 1 H).

^{13}C NMR*: δ = 163.8 (m), 145.1 (ddd, *J* = 255, 11, 2 Hz), 144.0 (ddd, *J* = 253, 17, 2 Hz), 142.1 (ddd, *J* = 19, 4, 2 Hz), 141.3 (ddd, *J* = 248, 17, 13 Hz), 114.9 (dd, *J* = 8, 4 Hz), 113.5 (t, *J* = 3 Hz).

MS (c.i.): *m*/*z* (%) = 210 (1, [$M^+ + NH_4$]), 192 (42, [M^+]), 175 (100), 174 (31).

Anal. Calcd for $C_7H_3F_2O_3$ (192.09): C, 43.77; H, 1.57. Found: C, 44.01; H, 1.54.

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