Converting Core Compounds into Building Blocks: The Concept of Regiochemically Exhaustive Functionalization

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In a model study, 3-fluorophenol and 3-fluoropyridine were converted into the each time four possible carboxylic acids by passing through the corresponding organometallic intermediates. As an attempt to generalize the findings reveals, a restricted set of principles and methods suffices to cope with all standard scenarios. The most valuable and versatile tools for the regiochemically exhaustive functionalization of a great variety of substrate patterns are the optionally site-selective metalation (either by reagent/substrate matching or by peripheral coordination control), the use of activating or congesting protective groups and the basicity gradient-driven heavy halogen migration (followed by halogen/metal permutation).

Introduction

Economy in chemistry may mean all sorts of things. In the present context it stands for the faculty to convert a simple starting material into any possible regioisomer belonging to a family of functionalized derivatives. In this way, structural opportunities are optimally exploited and building blocks displaying new substituent patterns are made accessible for life science oriented research work. To implement the projected regioflexibility, we rely on a set ("toolbox") of modified and adapted organometallic methods.[1] Carboxylation, the standard transformation applied throughout this work, has to be conceived as representative of the introduction of whatever functional group. Two examples, one taken from the aromatic, the other from the heterocyclic area, have been selected to illustrate both the concept and the principal options for its realization.

Results

Although *3-fluorophenol* is an inexpensive compound (approx. 100 EUR/mol retail price), very few derivatives are known. We set ourselves the goal to attach a carboxy group at any of the four vacant positions. This objective was achieved in a most straightforward manner in the case of the 6-fluoro-2-hydroxybenzoic acid (**1**). Consecutive treatment of the *O*-methoxymethyl-protected phenol[2] with *sec*-butyllithium, dry ice and a mineral acid afforded the product in 93% yield (see Scheme 1). The same key operations, metalation and carboxylation, were employed to access the three other isomers **2**, **3** and **4**. The only problem was to direct the deprotonating base to the targeted position by blocking all more acidic ones with protective groups. To this end, the acetal was lithiated again to be trapped this time with 1,1,2-trichloro-1,2,2-trifluoroethane. The resulting 2-chloro-1-fluoro-3-(methoxymethoxy)benzene (**5**; 83%) exhibited another example of reagent-matched optional site selectivity.[3–5a] Metalation and subsequent carboxylation occurred at the oxygen-adjacent 4-position when butyllithium and at the fluorine-adjacent 6-position when lithium 2,2,6,6-tetramethylpiperidide (LITMP) was employed as the base. The 3-chloro-4-fluoro-2-hydroxybenzoic acid (**6**; 69%) and the 3-chloro-2-fluoro-4-hydroxybenzoic acid (**7**; 73%) thus obtained were reduced by catalytic hydrogenation to the 4-fluoro-2-hydroxybenzoic acid (**2**) and the 2-fluoro-4-hydroxybenzoic acid (**3**).

The preparation of the last remaining product, the 3-fluoro-5-hydroxybenzoic acid (**4**), required a multi-step sequence. First, the most acidic 2-position in the 1-fluoro-3-(methoxymethoxy)benzene starting material was "switched off" by trimethylsilylation. When treated with the superbasic mixture of butyllithium and potassium *tert*-butoxide ("LIC-KOR"),[6–10] the silane **8** underwent smooth metalation at the fluorine-adjacent position. Carboxylation followed by acid-promoted desilylation of the intermediate **9** (not isolated) opened a second entry to the acid **3** (83%). The [3-chloro-2-fluoro-6-(methoxymethoxy)phenyl]trimethylsilane (**10**) formed by deprotonation and subsequent chlorination of the silane **8** was allowed to react consecutively with lithium 2,2,6,6-tetramethylpiperidide (LITMP) and carbon dioxide to give the 2-chloro-3-fluoro-4-methoxymethoxy-3-(trimethylsilyl)benzoic acid (**11**; 70%) after acidification. The deprotection had to be accomplished

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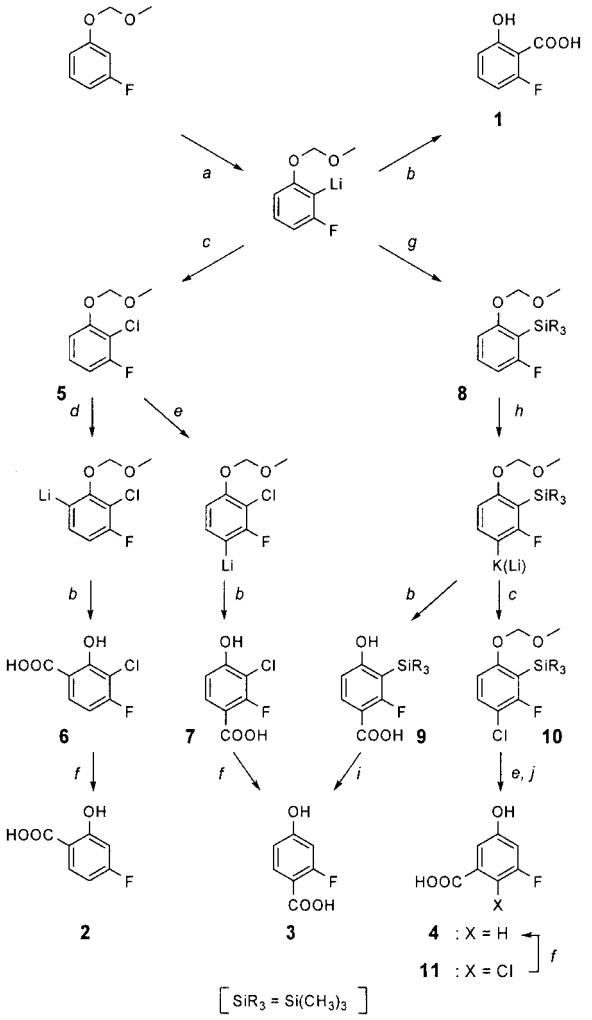
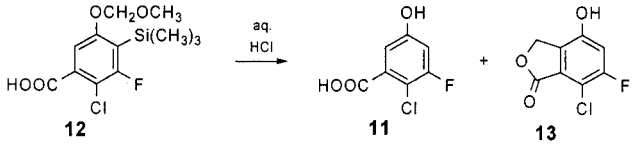
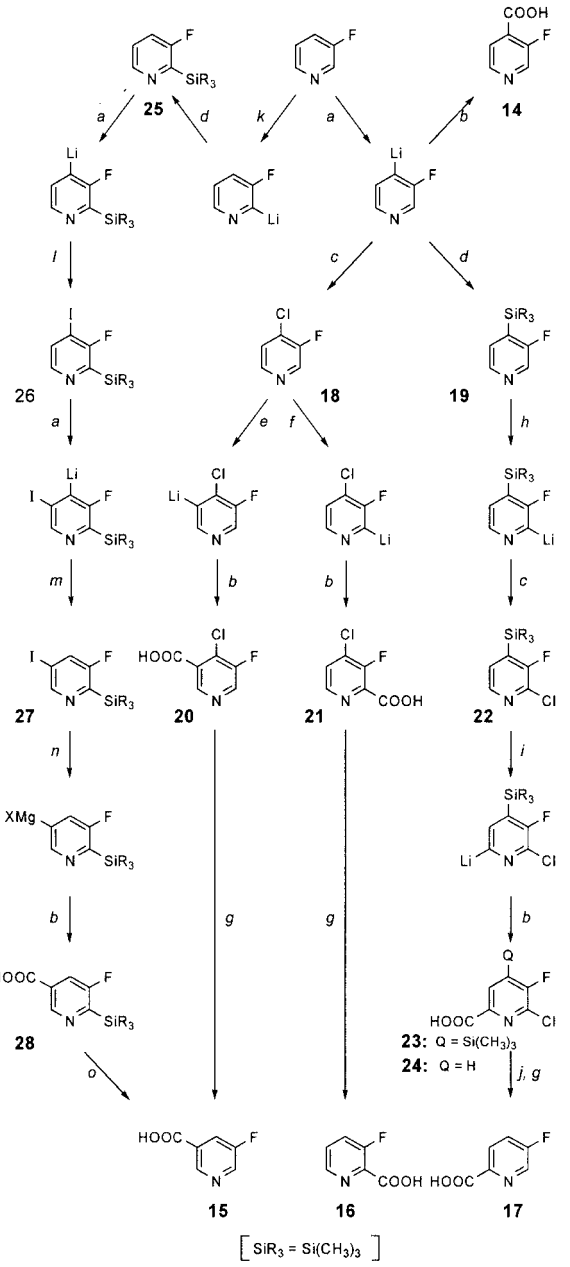


[a] *sec*-Butyllithium in tetrahydrofuran (THF) at –75 °C for 2 h. [b] (1.) Dry ice; (2.) Hydrochloric acid. [c] 1,1,2-Trichloro-1,2,2-trifluoroethane at –75 °C for 45 min. [d] Butyllithium in THF at –75 °C for 6 h. [e] Lithium 2,2,6,6-tetramethylpiperidide (LITMP) at –75 °C for 2 h. [f] Ammonium formate in methanol in the presence of palladium on charcoal at +25 °C for 2–20 h. [g] Chlorotrimethylsilane at –75 °C for 45 min. [h] Butyllithium and potassium *tert*-butoxide in THF at –75 °C for 2 h. [i] Concentrated hydrochloric acid at +25 °C for 6 h. [j] (1.)Carbon dioxide, (2.)1.0 M aqueous solution of citric acid, (3.) tetrabutylammonium fluoride hydrate (TBAF), (4.) 6.0 M hydrochloric acid at +50 °C for 6 h.

Scheme 1. Regioexhaustive carboxylation of 3-fluorophenol.





[a] Lithium diisopropylamide (LIDA) in THF at –75 °C for 2 h. [b] (1.) Dry ice; (2.) Hydrochloric acid. [c] 1,1,2-Trichloro-1,2,2-trifluoroethane at –75 °C for 45 min. [d] Chlorotrimethylsilane at –75 °C for 45 min. [e] LIDA in THF at –75 °C for 20 h. [f] LITMP in diethyl ether (DEE) at –75 °C for 2 h. [g] Ammonium formate in methanol in the presence of palladium on charcoal at +50 °C for 6 h. [h] LITMP in THF at –75 °C for 2 h. [i] Excess of butyllithium and lithium 2-(dimethylamino)ethoxide in hexanes at –75 °C for 45 min. [j] Tetrabutylammonium fluoride trihydrate (TBAF) in THF at 25 °C for 20 h. [k] Butyllithium and 1,4-diazabicyclo[2.2.2]octane (DABCO) in DEE at -60 °C for 1 h. [l] Molecular iodine. [m] Water. [n] Isopropylmagnesium chloride in THF at –75 °C for 5 min. [o] 2.0 M aqueous solution of sodium hydroxide and ethanol as a 5:1 (v/v) mixture, 5 min heating under reflux.

Scheme 2. Regioexhaustive carboxylation of 3-fluoropyridine.

stepwise. The trimethylsilyl group was eliminated with tetrabutylammonium fluoride hydrate, the methoxymethoxy group with hydrochloric acid and the chlorine atom by catalytic hydrogenation. When the precursor **12** to the hydroxybenzoic acid **11** was directly treated with hydrochloric acid, the lactone **13** (19%) was formed along with 2-chloro-3-fluoro-5-hydroxybenzoic acid **11** (41%).

3-Fluoropyridine (150 EUR/mol retail price) also harbors four unoccupied positions. Even if several fluoropyridinecarboxylic acids have been reported in the literature,[11–13] the documented procedures of preparation are quite laborious or unattractive for other reasons. As usual, the organometallic approach to the functionalization problem provides one derivative effortless, in the present case the acid **14** (84%), whereas the isomers **15**–**17** demand more work (see Scheme 2). To make acid **14**, it sufficed to expose 3-fluoropyridine briefly to lithium diisopropylamide (LIDA) before pouring the reaction mixture onto dry ice. When the latter electrophile was replaced by 1,1,2-trichloro-1,2,2-trifluoroethane and chlorotrimethylsilane, 4-chloro-3-fluoropyridine (**18**; 57%) and 3-fluoro-4-(trimethylsilyl)pyridine (**19**; not isolated) were produced. It was gratifying to identify 4-chloro-3-fluoropyridine (**18**) as another substrate prone to optionally site selective metalation. Depending on the choice of the reagent, either LIDA in tetrahydrofuran for 20 h at –75 °C or LITMP in diethyl ether for 10 min at –75 °C, the 4-chloro-5-fluoropyridine-3-carboxylic acid (**20**; 87%) or the 4-chloro-3-fluoropyridine-2-carboxylic acid (**21**; 71%) were obtained after the reaction with dry ice. Removal of the heavier halogen by catalytic hydrogenation furnished, respectively, 5-fluoropyridine-3-carboxylic acid (**15**, 88%) and 3-fluoropyridine-2-carboxylic acid (**16**, 89%). Passing through the intermediates **22** (75%) and **23** (62%), the silane **19** led eventually to the missing 5-fluoropyridine-2-carboxylic acid (**17**; 67%).

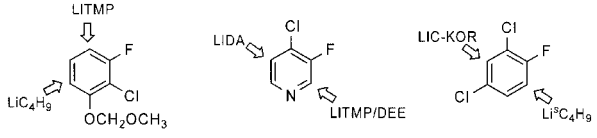
The 5-fluoropyridine-3-carboxylic acid (**15**) can be alternatively reached on another, lengthier, though still convenient route. 3-Fluoropyridine itself represents a substrate that can be induced to exhibit optional site selectivity in metalation reactions. Unlike all current reagents, butyllithium in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) abstracts a proton from the 2-position rather than the 4-position.[14] The 3-fluoro-2-(trimethylsilyl)pyridine (**25**) thus made available, was smoothly lithiated at the 4-position with LIDA and iodinated to give the 4-iodo compound **26** (78%) which was isomerized to 3-fluoro-5-iodo-2-(trimethylsilyl)pyridine (**27**; 85%) by a basicity driven heavy halogen migration.[5b] The latter compound was subjected to a permutational halogen/metal interconversion using isopropylmagnesium chloride as the reagent. Carboxylation afforded the acid **28** which, without isolation, was directly converted into the 5-fluoropyridine-3-carboxylic acid (**15**; 83%) by desilylation in alkaline medium.

Discussion and Conclusions

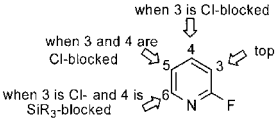
Regiochemically exhaustive substitution means to make all possible isomers available and thus not to miss any structural opportunity. The concept has been exemplified above by two archetypical substrates, an aromatic and a heterocyclic one. It has the potential of becoming a benchmark in parallel synthesis. There is of course no guarantee that a specific toolbox method or a combination of such methods offers the most comfortable and economic access to a given target compound. The organometallic approach to structure proliferation has nevertheless two distinct virtues: product flexibility and rapidity. Although carbon dioxide was used as the standard trapping reagent throughout this work, it might have been replaced by any of dozens if not hundreds of other electrophiles and thus have opened the entry to alcohols, aldehydes, nitriles, azides, amines, boronic acids and numerous other functional derivatives.[15] Moreover, the reaction sequences are either very short from the beginning or, if composed of several steps, may often be contracted to a one-flask protocol.[16] Therefore, the regioexhaustive elaboration of a readily available core compound offers an attractive option on the preparation and screening of complete families of congeners in order to identify the most promising substituent patterns for further development.

The crucial issue to be addressed in this context is whether the adequate toolbox methods have to be selected in a given case on a trial-and-error basis or can be identified in advance following rational guidelines. In other words, one has to worry about how representative the two model compounds investigated are as a test. The question is to what extent the experience gathered in the study summarized above can be applied to similar substrates. We shall deal with this question in two steps, first by comparing 3-fluorophenol and 3-fluoropyridine with each other and next by juxtaposing them with other halogenated phenols and pyridines.

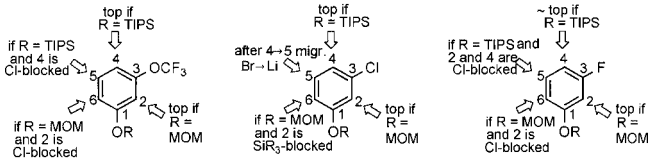
The case histories of 3-fluorophenol and 3-fluoropyridine resemble each other closely. The regiochemically exhaustive functionalization of both substrates, ultimately providing the carboxylic acids **2**–**4** and **15**–**17,** relied on optionally site selective metalation as the key tool. It was preceded by the blocking of the top reactive positions by introducing a chlorine atom there. The exploited reagent-modulated selectivity originated once more from the antagonism between an inductively electron-withdrawing substituent (actually fluorine or chlorine atoms) and a coordinatively competent centre (in the present study a methoxymethoxy group or the nitrogen incorporated in the heterocyclic ring). The competition between chlorine and fluorine as metalation-facilitating neighbors is a relatively rare event even if a first example, the alternative metalation of 2,4-dichloro-1-fluorobenzene at the 3- and 6-position was discovered already several years ago.[17,18]



Reagent-controlled optional site selectivity cannot be realized with all metalations. For example, *2-fluoropyridine*[19] requires LIDA[20,21] or a similar amide-type base for the clean deprotonation of the most acidic 3-position. In contrast, it reacts with butyllithium alone and, unlike 2-chloropyridine,[22] also with butyllithium in the presence of lithium 2-(dimethylamino)ethoxide ("Caubère's base[23]"), preferentially under nucleophilic displacement of the halogen. Therefore, we had to selectively block the 3-position alone or the 3- and 4-position simultaneously with chlorine atoms in order to metalate the 4- and 5-position, respectively. Clean proton abstraction from the 6-position was achieved after the 3-position had been protected by a chlorine and the 4-position by a trimethylsilyl substituent. Presumably the same would have happened if one had treated 2-fluoro-3-(trimethylsilyl)pyridine with Caubère's base.



Two phenols carrying heterosubstituents at the 3-position were successfully subjected to a regioexhaustive functionalization by taking advantage of optionally site selective metalation which was implemented by varying the hydroxy-protecting group rather than the metalating reagent.[24] When an *O*-methoxymethoxy (MOM) derivative of *3-(trifluoromethoxy)phenol* and *3-chlorophenol* were employed, the 2-position exhibited top reactivity. As soon as this site was silenced by the introduction of a chlorine atom or a trialkylsilyl group, the next metalation occurred at the 6-position. On the other hand, the 4-position was deprotonated when the *O*-triisopropylsilyl (TIPS) protected phenols served as the substrates. Chlorination of this site would then divert the attack of the reagent to the now activated 5-position. This approach worked well indeed with 3-(trifluoromethoxy)phenol but was obviously unsuitable with 3-chlorophenol as any additionally introduced chlorine atom could not have been selectively removed at a later stage. This gave a chance to bromine which was entered at the 4-position to be moved to the 5-position by deprotonation-triggered heavy halogen migration[5b,25,26] and eventually replaced with lithium by permutational halogen/metal interconversion. Finally, we also attempted to extend the OR-controlled optionally site selective metalation to 3-fluorophenol, although its regioexhaustive functionalization had already been accomplished as described above. However, the outcome was less perfect than observed with the two other phenols. Whereas the MOM-derivative did undergo metalation exclusively at the 2-position, the TIPS-derivative reacted with *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA) only preferentially at the 4-position but to some extent also at the 2-position. The two regioisomers were formed in moderate yield (56%) and in a 91:9 ratio.



In conclusion, a handful of well selected methods suffices to secure the goal of rational and regioexhaustive structure proliferation. The identification of the most suitable tool is straightforward in any given case. The most efficient way to create structural diversity is to play the two most reactive sites off against each other. Such kind of competition represents the standard situation whenever unequal substituents are present in the substrate. Under such circumstances optionally site selective metalation can be realized in two ways. One can match the reagent with either the more powerfully electron-withdrawing or with the better metal coordinating substituent ("*reagent-modulated selectivity*"). Alternatively, one can protect an already existing functional group such as hydroxy (see above, or carboxy,[1] amino[1] and phosphines[1]) by a slim and coordinatively competent or by merely a bulky substituent ("*peripherally controlled selectivity*").

The rest are details. The metalating reagent can be selected following proven principles. To address specifically the most acidic position one has to use either a superbase (LIC-KOR, LIM-KOR, LIT-KOR) or butyllithium in the presence of PMDTA or a much weaker amide-type base (LIDA, LITMP, LIPIP). When coordination is sought, LITMP in diethyl ether (!) or butyllithium are the first choice. Activated but congested sites are most efficiently attacked by a superbase.

To deprotonate the less reactive positions, the privileged top sites have to be blocked. Chlorine, one of the two favorite protective units silences the site where it sits and activates simultaneously the adjacent position whereas a trialkylsilyl group, the other frequent choice, wipes out the reactivity also in its immediate vicinity due to steric screening. In case of special structural constraints one may resort to halogen/metal rather than hydrogen/metal permutation for the introduction of the metal. To this end, a heavy halogen may first be attached to a top site before being steered, by basicity gradient-driven, deprotonation-triggered migration, to the targeted position where it can be exchanged against a metal by treatment with butyllithium or lithium tributylmagnesate.

Experimental Section

1. Generalities: Details regarding standard operations and abbreviations were explained in previous publications from this laboratory.[27–29] The solvent for ^{1}H and (^{1}H-decoupled) ^{13}C spectra, recorded at 400 and 101 MHz, respectively, was deuteriochloroform or, if marked with an asterisk (*), perdeuterioacetone unless stated otherwise.

2. Functionalization of 3-Fluorophenol

2-Fluoro-6-hydroxybenzoic Acid (1): A mixture of 1-fluoro-3-(methoxymethoxy)benzene[2] (3.2 mL, 3.9 g, 25 mmol) and *sec*-butyllithium (25 mmol) in tetrahydrofuran (35 mL) and cyclohexane (15 mL) was kept at –75 °C for 2 h before being poured onto an excess of freshly crushed dry ice. After evaporation of the volatiles, the residue was treated with 2.0 M hydrochloric acid (25 mL) and extracted with diethyl ether (3 × 25 mL). Evaporation of the solvent and crystallization from toluene afforded 3.63 g (93%) of colorless platelets; m.p. 159–161 °C (ref.[2]: 159–161 °C). ^{1}H NMR ([D$_6$]-DMSO): δ = 7.36 (td, J = 8.5, 6.5 Hz, 1 H), 6.76 (d, J = 7.4 Hz, 1 H), 6.70 (dd, J = 10.3, 8.4 Hz, 1 H) ppm.

2-Chloro-1-fluoro-3-(methoxymethoxy)benzene (5): As described above, but running the reaction on a 0.10 mol scale and using 1,1,2-trichloro-1,2,2-trifluoroethane (12 mL, 19 g, 0.10 mol) as the reagent. Immediate distillation afforded a colorless liquid; b.p. 75–76 °C/2 Torr; n_D^{20} = 1.5042; d_4^{20} = 1.31; yield: 15.8 g (83%). ^{1}H NMR: δ = 7.1 (m, 1 H), 6.97 (d, J = 8.4 Hz, 1 H), 6.80 (t, J = 8.2 Hz, 1 H), 5.24 (s, 2 H), 3.49 (s, 3 H) ppm. ^{13}C NMR: δ = 159.1 (d, J = 248 Hz), 154.4 (d, J = 3 Hz), 127.4 (d, J = 10 Hz), 111.4 (d, J = 19 Hz), 111.3 (d, J = 3 Hz), 109.7 (d, J = 21 Hz), 95.3, 56.5 ppm. MS (c.i.): m/z (%) = 205 (35) [M$^+$ + 18], 192 (27) [M$^+$ + 1], 191 (24) [M$^+$], 190 (100) [M$^+$ – 1], 159 (78), 117 (76). $C_8H_8ClFO_2Si$ (190.60): calcd. C 50.41, H 4.23; found C 50.31, H 4.20.

[2-Fluoro-6-(methoxymethoxy)phenyl]trimethylsilane (8): Prepared and isolated analogously using chlorotrimethylsilane (13 mL, 11 g, 0.10 mol) as the reagent; colorless liquid; b.p. 63–64 °C/2 Torr (ref.[30]: no physical constants or analysis reported); n_D^{20} = 1.4854; d_4^{20} = 1.160; yield: 19.6 g (86%). ^{1}H NMR: δ = 7.23 (dt, J = 8.2, 6.4 Hz, 1 H), 6.83 (d, J = 8.2 Hz, 1 H), 6.63 (t, J = 8.3 Hz, 1 H), 5.14 (s, 2 H), 3.45 (s, 3 H) ppm. ^{13}C NMR: δ = 167.9 (d, J = 241 Hz), 163.3 (d, J = 15 Hz), 132.1 (d, J = 11 Hz), 114.7 (d, J = 32 Hz), 109.2 (d, J = 28 Hz), 109.0 (d, J = 3 Hz), 94.5, 56.5, 1.1 (d, J = 4 Hz) ppm. MS (c.i.): m/z (%) = 246 (1) [M$^+$ + 18], 229 (5) [M$^+$ + 1], 228 (16) [M$^+$], 183 (100), 168 (35), 153 (62). $C_{11}H_{17}FO_2Si$ (228.28): calcd. C 57.86, H 7.50; found C 57.86, H 7.20.

3-Chloro-4-fluoro-2-hydroxybenzoic Acid (6): 1-Chloro-2-fluoro-6-(methoxymethoxy)benzene (**5**; 4.8 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (34 mL) and hexanes (16 mL) were kept in a dry ice/methanol bath for 6 h before the mixture was poured on an excess of freshly crushed dry ice. The volatiles were allowed to evaporate and the residue was partitioned between diethyl ether (25 mL) and water (25 mL). The aqueous phase was acidified with concentrated hydrochloric acid to pH 1 and extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried, filtered and the solvents evaporated. The residue, a white powder, was recrystallized from a 1:9 (v/v) mixture of ethyl acetate and hexanes; colorless needles; m.p. 190–192 °C; yield: 3.29 g (69%). ^{1}H NMR*: δ = 7.94 (dd, J = 9.0, 6.4 Hz, 1 H), 6.93 (t, J = 8.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 171.5, 162.8 (d, J = 254 Hz), 160.3 (d, J = 5 Hz), 130.5 (d, J = 11 Hz), 110.5, 107.7 (d, J = 22 Hz), 107.6 (d, J = 23 Hz) ppm. MS (c.i.): m/z (%) = 209 (0) [M$^+$ + 18], 192 (9) [M$^+$ + 1], 190 (26) [M$^+$ – 1], 172 (100). $C_7H_4ClFO_3$ (190.56): calcd. C 44.12, H 2.12; found C 44.16, H 2.11.

3-Chloro-2-fluoro-4-hydroxybenzoic Acid (7): 2,2,6,6-Tetramethylpiperidide (4.2 mL, 3.5 g, 25 mmol) and 1-chloro-2-fluoro-6-(methoxymethoxy)benzene (**5**; 4.8 g, 25 mmol) were added consecutively to butyllithium (25 mmol) in tetrahydrofuran (34 mL) and hexanes (16 mL) cooled in dry ice/methanol bath. After 2 h at –75 °C, the reaction mixture was treated and worked up as described in the preceding paragraph; colorless needles; m.p. 192–194 °C; yield: 3.48 g (73%). ^{1}H NMR*: δ = 7.81 (dd, J = 8.8, 8.4 Hz, 1 H), 6.96 (dd, J = 8.9, 1.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.6 (d, J = 4 Hz), 160.9 (d, J = 260 Hz), 159.7 (d, J = 3 Hz), 131.9 (d, J = 4 Hz), 112.1 (d, J = 10 Hz), 110.1 (d, J = 20 Hz) ppm. MS (c.i.): m/z (%) = 209 (1) [M$^+$ + 18], 192 (8) [M$^+$ + 1], 191 (3) [M$^+$], 190 (22) [M$^+$ – 1], 173 (100). $C_7H_4ClO_3$ (190.56): calcd. C 44.12, H 2.12; found C 44.40, H 2.02.

4-Fluoro-2-hydroxybenzoic Acid (2): Palladium (10% on charcoal, 0.53 g) was added to a solution of 3-chloro-4-fluoro-2-hydroxybenzoic acid (**6**; 1.9 g, 10 mmol) and ammonium formate (3.8 g, 60 mmol) in methanol (10 mL). The slurry was stirred for 20 h at 25 °C. After filtration and evaporation, the residue was dissolved in 1.0 M hydrochloric acid (20 mL) and extracted with diethyl ether (3 × 20 mL). Evaporation of the combined organic layers and crystallization from a 1:4 (v/v) mixture of ethyl acetate and hexanes mixture gave colorless platelets; m.p. 188–189 °C; (ref.[31]: m.p. 186 °C); yield: 1.48 g (95%). ^{1}H NMR*: δ = 7.96 (dd, J = 8.6, 6.6 Hz, 1 H), 6.7 (m, 2 H) ppm. ^{13}C NMR*: δ = 171.6, 167.6 (d, J = 252 Hz), 164.7 (d, J = 14 Hz), 133.3 (d, J = 12 Hz), 109.7 (d, J = 3 Hz), 107.4 (d, J = 13 Hz), 104.2 (d, J = 24 Hz) ppm. MS (c.i.): m/z (%) = 174 (1) [M$^+$ + 18], 157 (11) [M$^+$ + 1], 156 (65) [M$^+$], 155 (9) [M$^+$ – 1], 138 (100).

2-Fluoro-4-hydroxybenzoic Acid (3): [2-Fluoro-6-(methoxymethoxy)-phenyl]trimethylsilane (**8**; 5.7 g, 25 mmol) was added to a solution of butyllithium (25 mmol) and potassium *tert*-butoxide (2.8 g, 25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 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. The volatiles were allowed to evaporate and the solid left behind was partitioned between diethyl ether (25 mL) and water (25 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. The residue was recrystallised from methanol; colorless stars; m.p. 202–204 °C (ref.[32]: m.p. 204–205.5 °C); yield: 3.24 g (83%). ^{1}H NMR*: δ = 7.85 (t, J = 8.6 Hz, 1 H), 6.78 (dd, J = 8.5, 2.2 Hz, 1 H), 6.64 (dd, J = 12.3, 2.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.5 (d, J = 4 Hz), 164.5 (d, J = 258 Hz), 164.2 (d, J = 12 Hz), 134.8 (d, J = 2 Hz), 112.5 (d, J = 2 Hz), 110.7 (d, J = 10 Hz), 104.4 (d, J = 25 Hz) ppm. MS (c.i.): m/z (%) = 174 (0) [M$^+$ + 18], 157 (10) [M$^+$ + 1], 156 (45) [M$^+$], 139 (100). Compound **3** was also prepared starting from 3-chloro-2-fluoro-4-hydroxybenzoic acid (**7**) and using the same reaction conditions described for chlorine-free acid **2**; yield: 1.39 g (89%).

[3-Chloro-2-fluoro-6-(methoxymethoxy)phenyl]trimethylsilane (10): [2-Fluoro-6-(methoxymethoxy)phenyl]trimethylsilane (**8**; 17 g, 75 mmol) was added to a solution of butyllithium (75 mmol) and potassium *tert*-butoxide (8.4 g, 75 mmol) in hexanes (50 mL) and tetrahydrofuran (90 mL) cooled in a dry ice/methanol bath. After 2 h at –75 °C, the mixture was treated with 1,1,2-trifluoro-1,2,2-trichloroethane (8.9 mL, 14 g, 75 mmol). After further 45 min, the slurry was poured into brine (0.10 L) and extracted with diethyl ether (3 × 75 mL). The combined organic layers were dried, filtered and the solvents evaporated. Upon distillation under reduced pressure, a colorless liquid was collected; b.p. 110–112 °C/3 Torr; n_D^{20} = 1.5061; yield: 8.67 g (44%). ^{1}H NMR: δ = 7.29 (t, J = 8.7 Hz, 1 H), 6.84 (d, J = 8.7 Hz, 1 H), 5.16 (s, 2 H), 3.48 (s, 3 H), 0.36 (d, J = 1.9 Hz, 9 H) ppm. ^{13}C NMR: δ = 161.5 (d, J = 241 Hz), 161.0 (d, J = 14 Hz), 131.6 (d, J = 1 Hz), 116.1 (d, J = 32 Hz), 113.7 (d, J = 23 Hz), 109.6 (d, J = 4 Hz), 94.2, 56.0, 0.5 (d, J = 4 Hz) ppm. MS (c.i.): m/z (%) = 281 (0) [M$^+$ + 18], 264 (3) [M$^+$ + 1], 263 (4) [M$^+$], 262 (42) [M$^+$ – 1], 217 (100), 158 (78). $C_{11}H_{16}ClFO_2Si$ (262.78): calcd. C 50.28, H 6.14; found C 50.58, H 6.01.

2-Chloro-3-fluoro-4-hydroxybenzoic Acid (11): At –75 °C, 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and [3-chloro-2-fluoro-6-(methoxymethoxy)phenyl]trimethylsilane (**10**; 6.6 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) kept in dry ice/methanol bath. After 2 h at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice. The residue left behind after the evaporation of the volatiles was taken up in water (25 mL) and washed with diethyl ether (2×15 mL). Then the aqueous phase was acidified with a 1.0 M aqueous solution of citric acid and extracted with diethyl ether (3×25 mL). The combined organic layers were concentrated to roughly on third of the volume before tetrabutylammonium fluoride trihydrate (7.9 g, 25 mmol) was added. After 1 h at 25 °C, the reaction mixture was treated with 6.0 M hydrochloric acid (20 mL) and heated at 50 °C for 6 h. After extraction with diethyl ether (3×20 mL) and evaporation of the volatiles, the residue was crystallized from methanol; colorless needles; m.p. 164–165 °C; yield: 3.33 g (70%). ^{1}H NMR*: δ = 7.23 (dd, J = 2.9, 1.6 Hz, 1 H), 6.96 (dd, J = 10.6, 2.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.9 (d, J = 4 Hz), 159.8 (d, J = 245 Hz), 157.8 (d, J = 3 Hz), 114.6 (d, J = 3 Hz), 113.5 (d, J = 3 Hz), 111.0 (d, J = 20 Hz), 107.7 (d, J = 25 Hz) ppm. MS (c.i.): m/z (%) = 209 (1) [M$^+$ + 18], 192 (31) [M$^+$ + 1], 191 (11) [M$^+$], 190 (91) [M$^+$ – 1], 173 (100). $C_7H_4ClO_3$ (190.56): calcd. C 44.12, H 2.12; found C 44.14, H 2.18.

7-Chloro-6-fluoro-4-hydroxy-3*H*-isobenzofuran-1-one (13): When the same reaction sequence starting from [3-chloro-2-fluoro-6-(methoxymethoxy)phenyl]trimethylsilane (**10**; 6.6 g, 25 mmol) was performed but the treatment with tetrabutylammonium fluoride was omitted, a mixture containing 41% of 2-chloro-3-fluoro-5-hydroxybenzoic acid (**11**) and 19% of 7-chloro-6-fluoro-4-hydroxy-3*H*-isobenzofuran-1-one (**13**) was obtained. The latter compound was purified by trituration with chloroform followed by sublimation; m.p. 246–248 °C; yield: 0.76 g (15%). ^{1}H NMR*: δ = 7.10 (d, J = 10.6 Hz, 1 H), 5.26 (d, J = 1.4 Hz, 2 H) ppm. ^{13}C NMR*: δ = 164.6 (d, J = 4 Hz), 160.9 (d, J = 260 Hz), 159.7 (d, J = 3 Hz), 131.9 (d, J = 4 Hz), 112.1 (d, J = 10 Hz), 110.1 (d, J = 20 Hz) ppm. MS (c.i.): m/z (%) = 209 (1) [M$^+$ + 18], 192 (8) [M$^+$ + 1], 191 (3) [M$^+$], 190 (22) [M$^+$ – 1], 173 (100). $C_8H_4ClO_3$ (202.57): calcd. C 47.43, H 1.99; found C 47.32, H 2.08.

3-Fluoro-5-hydroxybenzoic Acid (4): Analogously as described for the conversion of the chlorine-containing acid **6** into the chlorine-free acid **2** (see above) but with a reaction time of 2 h; colorless prisms; m.p. 214–215 °C; yield: 1.31 g (84%). ^{1}H NMR*: δ = 7.25 (t, J = 1.9 Hz, 1 H), 7.21 (ddd, J = 9.3, 2.6, 1.3 Hz, 1 H), 6.83 (td, J = 10.2, 2.2 Hz, 1 H) ppm. ^{13}C NMR*: δ = 166.5 (d, J = 4 Hz), 164.2 (d, J = 243 Hz), 159.9 (d, J = 10 Hz), 134.2 (d, J = 3 Hz), 113.6 (d, J = 3 Hz), 108.1 (d, J = 24 Hz) ppm. MS (c.i.): m/z (%) = 157 (8) [M$^+$ + 1], 156 (64) [M$^+$], 139 (100). $C_7H_5FO_3$ (156.10): calcd. C 53.86, H 3.23; found C 54.07, H 3.10.

(3-Fluorophenyloxy)trisopropylsilane: 3-Fluorophenol (4.5 mL, 5.6 g, 50 mmol), chlorotriisopropylsilane (13 mL, 12 g, 60 mmol) and imidazole (8.8 g, 0.13 mol) were dissolved in *N*,*N*-dimethylformamide (25 mL). After 20 h at 25 °C, the mixture was poured into water and extracted with dichloromethane (3×50 mL). Distillation under reduced pressure gave a colorless liquid; b.p. 91–92 °C/4 Torr; n_D^{20} = 1.4854; yield: 11.2 g (83%). ^{1}H NMR: δ = 7.16 (dd, J = 15.2, 8.1 Hz, 1 H), 6.7 (m, 2 H), 6.6 (m, 1 H) 1.3 (m, 3 H), 1.09 (d, J = 7.3 Hz, 18 H) ppm. ^{13}C NMR: δ = 164.2 (d, J = 246 Hz), 158.1 (d, J = 12 Hz), 130.5 (d, J = 10 Hz), 116.3 (d, J = 3 Hz), 108.5 (d, J = 21 Hz), 108.2 (d, J = 22 Hz), 18.4, 13.5 ppm. MS (c.i.): m/z (%) = 286 (0) [M$^+$ + 18], 269 (11) [M$^+$ + 1], 268 (11) [M$^+$], 226 (64), 225 (100), 139 (38). $C_{15}H_{25}FOSi$ (268.44): calcd. C 67.11, H 9.39; found C 66.97, H 9.17. Consecutive treatment with PMDTA-activated *sec*-butyllithium in tetrahydrofuran at –75 °C for 2 h and dry ice followed by neutralization gave a mixture of 2-fluoro-4-hydroxybenzoic acid (**3**; 51%) and 2-fluoro-6-hydroxybenzoic acid (**1**; 5%). The latter compound became the sole isomer (isolated in 63% yield) when the same reaction was repeated in the presence of an equivalent amount of potassium *tert*-butoxide.

3. Functionalization of 3-Fluoropyridine

3-Fluoropyridine-4-carboxylic Acid (14): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 3-fluoropyridine (2.4 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol each) in tetrahydrofuran (35 mL) and hexanes (15 mL) cooled in an dry ice/methanol bath. After 2 h at –75 °C, the mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the volatiles, the residue was taken up in water (40 mL) and the aqueous phase was acidified with hydrochloric acid. Filtration of the white precipitate formed and drying under vacuum afforded 2.96 g (84%) of product; m.p. 254–256 °C (decomp., ref.[33]: 256–257 °C). ^{1}H NMR ([D$_6$]DMSO): δ = 8.75 (d, J = 2.3 Hz, 1 H), 8.59 (d, J = 4.7 Hz, 1 H), 7.80 (dd, J = 6.4, 4.7 Hz, 1 H) ppm.

4-Chloro-3-fluoropyridine (18): As described above, but running the reaction on a 0.20 mol scale and using 1,1,2-trichloro-2,2,1-trifluoroethane (48 mL, 75 g, 0.40 mol) as the reagent. Upon distillation a colorless liquid was collected; b.p. 142–143 °C; n_D^{20} = 1.5033; yield: 15.1 g (57%). ^{1}H NMR: δ = 8.51 (s, broad, 1 H), 8.34 (d, J = 5.3 Hz, 1 H), 7.39 (dd, J = 6.5, 5.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 155.8 (d, J = 259 Hz), 146.2 (d, J = 6 Hz), 139.1 (d, J = 23 Hz), 130.5 (d, J = 15 Hz), 125.5 ppm. C_5H_3ClFN (131.54): calcd. C 45.66, H 2.30; found C 45.74, H 2.23.

4-Chloro-5-fluoropyridine-3-carboxylic Acid (20): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 4-chloro-3-fluoropyridine (**18**; 3.3 g, 25 mmol) were added consecutively to butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) cooled in a dry ice/methanol bath. After 20 h at –75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide. The volatiles were allowed to evaporate and the residue was taken up in water (0.10 L). The aqueous solution was acidified with hydrochloric acid and extracted with ethyl acetate (4×20 mL) to afford 3.82 g (87%) of an orange solid; yellowish prisms (from acetone); m.p. 152 °C (decomp.). ^{1}H NMR*: δ = 8.91 (s, 1 H), 8.78 (d, J = 0.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.1, 156.9 (d, J = 257 Hz), 148.6 (d, J = 6 Hz), 142.0 (d, J = 24 Hz), 131.2 (d, J = 17 Hz), 128.2 (d, J = 3 Hz) ppm. $C_6H_3ClFNO_2$ (175.55): calcd. C 41.05, H 1.72; found C 41.42, H 1.47. The evolution of the reaction as a function of time has been followed by gas chromatography (30 m, DB-23, 100 °C; 30 m DB-WAX, 120 °C). To this end the acids were converted into the more volatile methyl esters using ethereal diazomethane. In this way, the 4-chloro-5-fluoropyridine-3-carboxylic acid (**20**) and its isomer **21** were found to be present in the rations of 12:88, 85:15, 96:4 and 100:0 and in combined yields of 78, 83, 91 and 91% after, respectively, 0.05, 2, 6 and 20 h of reaction time before quenching.

4-Chloro-3-fluoropyridine-2-carboxylic Acid (21): 2,2,6,6-Tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) and 4-chloro-3-fluoropyridine (**18**; 3.3 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) cooled in a dry ice/methanol bath. After 10 min at –75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide covered with tetrahydrofuran (25 mL). The residue left behind after the evaporation of the volatiles was treated with 2.0 M hydrochloric acid (50 mL). The white solid obtained was collected and dried under vacuum; colorless platelets (from water);

m.p. 122–123 °C (decomp.); yield: 3.1 g (71%). ^{1}H NMR ([D$_6$]-DMSO): δ = 8.48 (d, J = 5.1 Hz, 1 H), 7.96 (t, J = 5.3 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 163.4 (d, J = 6 Hz), 154.2 (d, J = 269 Hz), 145.8 (d, J = 7 Hz), 138.9 (d, J = 11 Hz), 131.3 (d, J = 16 Hz), 128.7 ppm. $C_6H_3ClFNO_2$ (175.55): calcd. C 41.05, H 1.72; found C 41.15, H 1.98.

3-Fluoropyridine-2-carboxylic Acid (16):[14] Palladium, 10% on charcoal (0.53 g), was added to a solution of 4-chloro-3-fluoropyridine-2-carboxylic acid (**21**; 1.8 g, 10 mmol) in ethanol (40 mL). After 6 h of stirring under hydrogen, the catalyst was removed by filtration and washed with ethanol (2 × 20 mL). Evaporation of the filtrate afforded 1.26 g (89%) of a slightly yellowish powder; m.p. 152–155 °C (decomp.). ^{1}H NMR ([D$_6$]DMSO): δ = 8.53 (d, J = 4.4 Hz, 1 H), 7.91 (dd, J = 9.7, 8.4 Hz, 1 H), 7.73 (dt, J = 8.5, 4.2 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 164.0 (d, J = 6 Hz), 158.2 (d, J = 266 Hz), 145.2 (d, J = 5 Hz), 137.6 (d, J = 11 Hz), 128.7 (d, J = 5 Hz), 125.9 (d, J = 20 Hz) ppm. $C_6H_4FNO_2$ (141.10): calcd. C 51.07, H 2.86; found C 50.91, H 2.80**.**

5-Fluoropyridine-3-carboxylic Acid (15):[34,35] Prepared analogously from 4-chloro-5-fluoropyridine-3-carboxylic acid (**20**; 1.8 g, 10 mmol); tiny colorless prisms (from aqueous ethanol); m.p. 196–198 °C (ref.[34]: 195–197 °C); yield 1.24 g (88%). ^{1}H NMR*: δ = 9.02 (s, broad, 1 H), 8.76 (d, J = 0.9 Hz, 1 H), 8.08 (ddd, J = 9.1, 3.0, 1.5 Hz, 1 H) ppm. Acid **15** was also made by dissolving 3-fluoro-5-iodo-2-(trimethylsilyl)pyridine (**27** [prepared from the iodo compound **26**, see below]; 4.9 mL, 7.4 g, 25 mmol) in an ice-cold solution of isopropylmagnesium chloride (25 mmol) in tetrahydrofuran (50 mL). After 5 min at 0 °C, carbon dioxide was bubbled into the reaction mixture for 20 min. The volatiles were evaporated. Ethanol (20 mL) and a 2.0 M aqueous solution (0.10 L) of sodium hydroxide were added to the residue. Upon heating under reflux for 5 min, acidification to pH 1 and cooling in an ice bath, a white solid was formed; yield: 2.91 g (83%).

3-Fluoro-4-iodo-2-(trimethylsilyl)pyridine (26): 3-Fluoro-2-(trimethylsilyl)pyridine (**25** [see below]; 8.6 mL, 8.5 g, 50 mmol) was treated with a solution prepared from diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and butyllithium (50 mmol) in tetrahydrofuran (70 mL) and hexanes (33 mL) cooled in a dry ice/methanol bath. After 2 h at –75, iodine (13 g, 50 mmol) dissolved in tetrahydrofuran (50 mL) was added all at once. The reaction mixture was diluted with diethyl ether (50 mL) and washed with a 2.0 M aqueous solution of sodium thiosulfate (20 mL), 2.0 M hydrochloric acid (2 × 30 mL) and brine (50 mL). Distillation afforded a slightly yellow oil; b.p. 83–85 °C/7 Torr; m.p. 15–17 °C; n_D^{20} = 1.5522; yield: 11.5 g (78%). ^{1}H NMR: δ = 8.17 (dd, J = 4.9, 1.9 Hz, 1 H), 7.65 (t, J = 5.1 Hz, 1 H), 0.38 (d, J = 1.3 Hz, 9 H) ppm. ^{13}C NMR: δ = 164.1 (d, J = 250 Hz), 155.4 (d, J = 34 Hz), 146.6 (d, J = 5 Hz), 133.8 (d, J = 5 Hz), 92.0 (d, J = 27 Hz), –1.7 (d, J = 2 Hz) ppm. $C_8H_{11}FINSi$ (295.17): calcd. C 32.55, H 3.76; found C 32.71, H 4.01.

3-Fluoro-2-(trimethylsilyl)pyridine (25): A solution containing butyllithium (0.10 mol) and 1,4-diazabicyclo[2.2.2]octane ("DABCO", 11 g, 0.10 mol) in diethyl ether (0.50 L) and hexanes (65 mL) was kept 1 h at –20 °C before being cooled to –60 °C. 3-Fluoropyridine (8.6 mL, 9.7 g, 0.10 mol) was added, followed, after 1 h at –60 °C, by chlorotrimethylsilane (13 mL, 11 g, 0.10 mol). The reaction mixture was washed with 2.0 M hydrochloric acid (2 × 0.10 L), filtered through a pad of basic alumina (50 mL) and eluted with diethyl ether (0.10 L). Distillation afforded a colorless oil; b.p. 63–65 °C/15 Torr (ref.[36]: b.p. 72/15 Torr); n_D^{20} = 1.4754; yield: 19.4 g (57%). ^{1}H NMR: δ = 8.59 (ddd, J = 5.0, 2.6, 1.6 Hz, 1 H), 7.3–7.2 (m, 2 H), 0.38 (d, J = 1.0 Hz, 9 H) ppm. ^{13}C NMR: δ = 165.2 (d, J = 251 Hz), 155.2 (d, J = 30 Hz), 146.4 (d, J = 4 Hz), 124.1 (d, J = 5 Hz), 121.0 (d, J = 22 Hz), –1.7 (d, J = 2 Hz) ppm.

2-Chloro-3-fluoro-4-(trimethylsilyl)pyridine (22) via 3-Fluoro-4-(trimethylsilyl)pyridine (19; not isolated): 2,2,6,6-Tetramethylpiperidine (17 mL, 14 g, 0.10 mol) and 3-fluoropyridine (8.6 mL, 9.7 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.14) and hexanes (60 mL) cooled in dry ice/methanol bath. After 2 h at –75 °C, the mixture was treated with chlorotrimethylsilane (13 mL, 11 g, 0.10 mol) and, 10 min later, butyllithium (0.10 mol). After further 2 h at –75 °C, 1,1,2-trichloro-1,2,2-trifluoroethane (16 mL, 25 g, 0.15 mol) was added. Upon distillation a colorless oil was collected; b.p. 99–101 °C/16 Torr; m.p. 11–13 °C; n_D^{20} 1.4995; yield: 15.2 g (75%). ^{1}H NMR: δ = 8.16 (dd, J = 4.5, 1.3 Hz, 1 H), 7.24 (dd, J = 4.5, 3.5 Hz, 1 H), 0.37 (d, J = 0.6 Hz, 9 H) ppm. ^{13}C NMR: δ = 158.9 (d, J = 254 Hz), 144.5 (d, J = 5 Hz), 138.9 (d, J = 36 Hz), 138.6 (d, J = 29 Hz), 128.6 (d, J = 6 Hz), –1.2 (d, J = 2 Hz) ppm. $C_8H_{11}ClFNSi$ (203.72): calcd. C 47.17, H 5.44; found C 47.13, H 5.49.

6-Chloro-5-fluoro-4-(trimethylsilyl)pyridine-2-carboxylic Acid (23): At dry ice temperature, *N,N*-dimethylethanolamine (4.0 mL, 3.6 g, 40 mmol) dissolved in hexanes (50 mL) and 2-chloro-3-fluoro-4-(trimethylsilyl)pyridine (**22**; 1.8 mL, 2.0 g, 10 mmol) were added consecutively to butyllithium (80 mmol) in hexanes (0.10 mL). After 45 min at –75 °C, the reaction mixture was poured onto an excess of freshly crushed dry ice covered with diethyl ether (0.15 L). The reaction mixture was treated with 6.0 M hydrochloric acid (50 mL) and water (0.30 L). The suspension was subjected to a steam distillation and the product was isolated by extraction of the aqueous layer with diethyl ether (2 × 0.10 L). The residue obtained after evaporation of the solvent was crystallized from heptanes; colorless needles; m.p. 122–124 °C; yield: 1.53 g (62%). ^{1}H NMR: δ = 8.19 (d, J = 3.2 Hz, 1 H), 0.42 (s, 9 H) ppm. ^{13}C NMR: δ = 164.5, 161.3 (d, J = 261 Hz), 141.2 (d, J = 5 Hz), 140.6 (d, J = 31 Hz), 138.4 (d, J = 27 Hz), 130.2 (d, J = 9 Hz), –1.7 (d, J = 2 Hz) ppm. $C_9H_{11}ClFNO_2Si$ (247.73): calcd. C 43.64, H 4.48; found C 43.98, H 4.43.

6-Chloro-5-fluoropyridine-2-carboxylic Acid (24): 6-Chloro-5-fluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (**23**; 2.5 g, 10 mmol) and tetrabutylammonium fluoride trihydrate (3.1 g, 10 mmol) were dissolved in diethyl ether (25 mL) for 20 h at 25 °C. The organic solution was stirred with 2.0 M hydrochloric acid (20 mL) for 30 min, then decanted, dried and the solvents evaporated. The residue was sublimed; colorless needles (from heptanes); m.p. 193–195 °C; yield: 1.93 g (84%). ^{1}H NMR*: δ = 8.24 (dd, J = 8.3, 3.5 Hz, 1 H), 8.01 (t, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.1, 157.7 (d, J = 265 Hz), 144.7 (d, J = 5 Hz), 138.8 (d, J = 21 Hz), 127.4 (d, J = 5 Hz), 126.9 (d, J = 20 Hz) ppm. $C_6H_3ClFNO_2$ (175.55): calcd. C 41.05, H 1.72; found C 41.34, H 1.53.

5-Fluoropyridine-2-carboxylic Acid (17): A suspension containing 6-chloro-5-fluoropyridine-2-carboxylic acid (**24**; 2.6 g, 15 mmol), ammonium formate (1.9 g, 30 mmol) and 10% palladium on charcoal (0.80 g) in methanol (70 mL) was heated at 50 °C for 6 h. The reaction mixture was filtered and the solvents evaporated. The residue was partitioned between ethyl acetate (3 × 0.10 L) and 2.0 M hydrochloric acid (50 mL). The organic layer was dried and the volatiles evaporated. Crystallization of the residue from a 1:6 (v/v) mixture of ethyl acetate and hexanes afforded colorless platelets; m.p. 156–158 °C; yield: 1.41 g (67%). ^{1}H NMR*: δ = 8.63 (d, J = 2.9 Hz, 1 H), 8.27 (dd, J = 8.7, 4.7 Hz, 1 H), 7.88 (td, J = 8.6, 2.9 Hz, 1 H) ppm. ^{13}C NMR*: δ = 165.1, 162.7 (d, J = 260 Hz), 145.3 (d, J = 4 Hz), 138.6 (d, J = 25 Hz), 127.6 (d, J = 6 Hz), 125.3 (d, J =

19 Hz) ppm. $C_6H_3ClFNO_2$ (141.10): calcd. C 51.07, H 2.86; found C 51.24, H 2.92.

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