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Selective Functionalization of 2-Fluoropyridine, 2,3-Difluoropyridine, and 2,5-Difluoropyridine at Each Vacant Position

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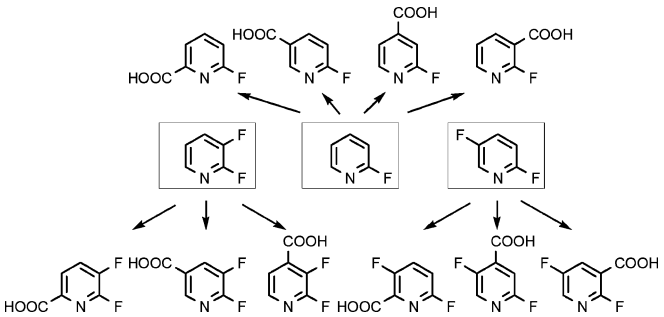

The concept of "regioexhaustive substitution" has been successfully applied to 2-fluoro-, 2,3-difluoro-, and 2,5-difluoropyridine. All vacant positions were amenable to regioselective metalation and subsequent carboxylation by employing either chlorine as a neighboring site activating protective group or trimethylsilyl as a neighboring site screening protective group. In this way, approximately half a dozen fluorinated pyridinecarboxylic acids were derived from each starting material.

Introduction

There are conjectures such as the four-shades-suffice map coloring theorem[1] which resist all efforts to present a logical and mathematically rigorous proof. This holds also for the principle of regioexhaustive functionalization of arenes and heterocycles. Let us consider an arene bearing two different heteroelements at 1- and 2-positions or 1- and 3-positions. Is it really possible to introduce further substituents optionally at any of the vacant positions by merely relying on a handful of advanced organometallic methods,[2] as asserted recently?[3] The only way to make this claim credible is to subject it to scrutiny by a variety of "tough" model cases. To this end, we have examined as substrates 3-fluorophenol,[4] several difluorophenols[5] and trifluorophenols,[5,6] 4-, 5-, 6-, and 7-fluoroindole,[7] 4-bromo-6- and -7-fluoro-2-(trifluoromethyl)quinoline,[8] *N*-methyl- and *N*-phenyl-5-(trifluoromethyl)pyrazole,[9] various bromo-, chloro-, and iodo(trifluoromethyl)pyridines,[10] 3-fluoropyridine,[4] and 2,4-difluoropyridine.[11]

The present investigation of further fluorinated pyridines complements the previous examples and adds new facets. All three substrates are of moderate acidity as there is no position flanked by two fluorine atoms (as, e.g., in 2,4-difluoropyridine). Moreover, all of them carry a fluorine atom at the 2-position, which makes them very prone to nucleophilic aromatic substitution.[12]

(1) Appel, K.; Haken, W. *Sci. Am.* **1977**, *237*, 108.
(2) Schlosser, M. *Angew. Chem.* **2005**, *117*, 380; *Angew. Chem., Int. Ed.* **2005**, *44*, 376.
(3) Schlosser, M. In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; ACS Symposium Series; American Chemical Society: Washington, DC, 2005.
(4) Marzi, E.; Bobbio, C.; Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, in press.
(5) Marzi, E.; Gorecka, J.; Schlosser, M. *Synthesis* **2004**, 1609.
(6) Marzi, E.; Schlosser, M. *Tetrahedron* **2005**, *61*, 3393−3401.
(7) Schlosser, M.; Ginanneschi, A. Unpublished. Ginanneschi, A. Ph.D. Thesis, Ecole Polytechnique Fédérale de Lausanne, November 2004.
(8) Marull, M.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 1008.
(9) Schlosser, M.; Volle, J.-N.; Leroux, F.; Schenk, K. *Eur. J. Org. Chem.* **2002**, 2913.
(10) (a) Cottet, F.; Marull, M.; Lefebvre O.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 1559. (b) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 3793. (c) Cottet, F.; Marull, M.; Mongin, F.; Espinoza, D.; Schlosser, M. *Synthesis* **2004**, 1619. (d) Cottet, F.; Schlosser, M. *Tetrahedron* **2004**, *60*, 11869.
(11) Schlosser, M.; Bobbio, C.; Rausis, T. *J. Org. Chem.* **2005**, *70*, 2494.
(12) (a) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137. (b) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151; *Chem. Abstr.* **1993**, *119*, 95281e.

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Results and Discussion

2-Fluoropyridine as the Substrate. 2-Fluoropyridine is known to undergo deprotonation at the 3-position when treated with lithium diisopropylamide.[12,13] Subsequent carboxylation and neutralization afforded the 2-fluoropyridine-3-carboxylic acid (**1**) in 84% yield. To make the isomeric acids (**5**, **7** and **11**), the most acidic 3-position had to be protected. Reaction of the 3-lithiated species with 1,1,2-trichloro-1,2,2-trifluoroethane provided 3-chloro-2-fluoropyridine (**2**; 85%) which reacted smoothly with butyllithium to give the 3-chloro-2-fluoropyridine-4-carboxylic acid (**6**; 75%), 3,4-dichloro-2-fluoropyridine (**3**; 80%), and 3-chloro-2-fluoro-4-(trimethylsilyl)pyridine (**8**; 90%) after trapping with dry ice, 1,1,2-trichloro-1,2,2-trifluoroethane, and chlorotrimethylsilane, respectively. Lithium diisopropylamide cleanly abstracted a proton from the 5-position of 3,4-dichloro-2-fluoropyridine (**3**) to give the 4,5-dichloro-6-fluoropyridine-3-carboxylic acid (**4**; 80%) upon carboxylation and the 6-fluoropyridine-3-carboxylic acid (**5**; 71%) after catalytic transfer hydrogenation. In the same way, the chlorinated acid **6** was reduced to the 2-fluoropyridine-4-carboxylic acid (**7**; 83%). The silane **8** was metalated with an excess of butyllithium and lithium 2-(dimethylamino)ethoxide ("Caubère's base"[14]) at the 6-position to furnish the 5-chloro-6-fluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (**9**; 37%), which was converted into the 5-chloro-6-fluoropyridine-2-carboxylic acid (**10**; 84%) by protodesilylation with tetrabutylammonium fluoride hydrate and into the 6-fluoropyridine-2-carboxylic acid (**11**; 71%) by catalytic hydrogenation.

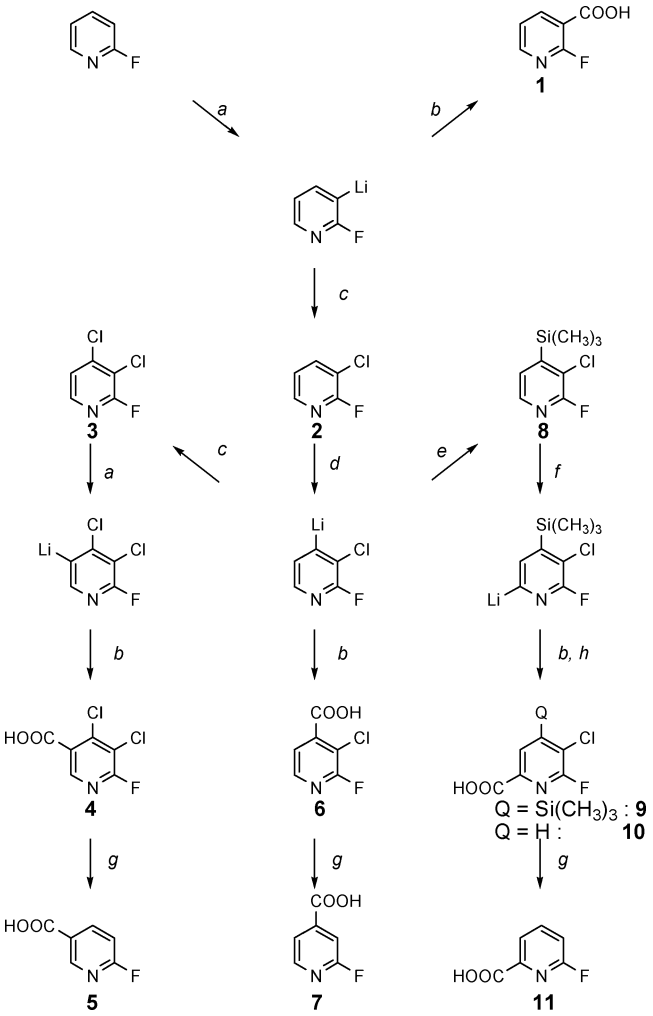
2,3-Difluoropyridine as the Substrate. 2,3-Difluoropyridine[15] was cleanly lithiated at the 4-position when lithium diisopropylamide was used as the base. After reaction with dry ice, 1,1,2-trichloro-1,2,2-trifluoroethane, elemental iodine, and chlorotrimethylsilane, respectively, the 2,3-difluoropyridine-4-carboxylic acid (**12**; 78%), 4-chloro-2,3-difluoropyridine (**13**; 59%), 2,3-difluoro-4-iodopyridine (**16**; 80%), and 2,3-difluoro-4-(trimethylsilyl)-pyridine (**18a**; 85%) were isolated in satisfactory or even high yields.

Amide-promoted lithiation of the chloro compound **13** occurred obviously at the 5-position to produce the 4-chloro-5,6-difluoro-3-carboxylic acid (**14**; 78%) upon carboxylation and the 5,6-difluoropyridine-3-carboxylic acid (**15**; 87%) upon catalytic hydrogenation. The latter acid (**15**) was also formed in 79% yield when 2,3-difluoro-4-iodopyridine (**16**) was isomerized by basicity gradient-driven heavy halogen migration[16] to 2,3-difluoro-5-iodopyridine (**17**; 48%) and the latter intermediate subjected to consecutive halogen/metal permutation (accomplished with butyllithium) and carboxylation.

The silane **18a** was selectively metalated at the 6-position using again Caubère's base. The 5,6-difluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (**19a**; 46%) thus obtained was converted into the 5,6-difluoropyridine-2-carboxylic acid (**20**; 75%) by protodesilylation. Somewhat better yields were achieved when the reaction sequence was repeated starting from 2,3-difluoro-4-(triethylsilyl)-pyridine (**18b**; 85%) and the acid **20** (77%) was accessed through the 5,6-difluoro-4-(triethylsilyl)pyridine-2-carboxylic acid (**19b**; 59%).

2,5-Difluoropyridine as the Substrate. The 4-position being the intrinsically most acidic site in pyridine,[17] the lithium diisopropylamide-promoted deprotonation of 2,5-difluoropyridine generated cleanly 2,5-difluoro-4-pyridyllithium. Upon treatment with dry ice, 1,1,2-trichloro-1,2,2-trifluoroethane, and chlorotrimethylsilane, this species afforded the 2,5-difluoropyridine-4-carboxylic acid (**21**; 76%), 4-chloro-2,5-difluoropyridine (**22**; 45%), and

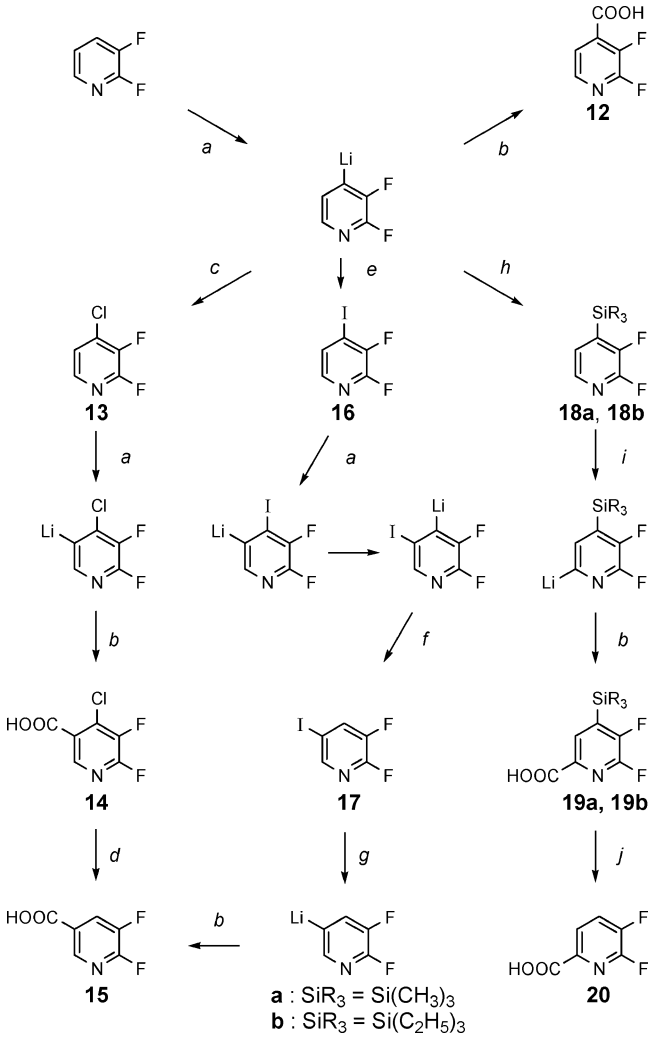
SCHEME 1. Functionalization of 2-Fluoropyridine[a]



[a] Reagents and conditions: (a) $LiN(^iC_3H_7)_2$ in tetrahydrofuran (THF) at −75 °C for 2 h. (b) (1) CO_2, (2) aq HCl. (c) $Cl_2CFCClF_2$. (d) LiC_4H_9 in THF at −75 °C for 2 h. (e) $ClSi(CH_3)_3$. (f) LiC_4H_9 + $LiOCH_2CH_2N(CH_3)_2$ in hexanes at −75 °C for 2 h. (g) $HCOONH_4$ + Pd/C (cat.) in ethanol at 25 °C for 2 h. (h) $(H_9C_4)_4NF$ hydrate in THF at 25 °C for 2 h.

(13) Estel, L.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.
(14) Gros, P.; Fort, Y.; Caubère, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1685.
(15) Bobbio, C.; Rausis, T.; Schlosser, M. *Chem. Eur. J.* **2005**, *11*, 1903.
(16) Schlosser, M. *Organometallics in Synthesis*: *A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, UK, 2002; pp 1−352, spec. 262−265.
(17) (a) Tupitsyn, I. F.; Zatsepina, N. N.; Kirova, A. V.; Kaminskii, Y. L.; Ivanenko, A. G. *Reakts. Sposobn. Org. Soedin.* **1973**, *10*, 143; *Chem. Abstr.* **1973**, *79*, 114928v. (b) Reutov, E. A.; Beletskaya, I. P.; Butin, K. P. *CH−Acids*; Pergamon Press: Oxford, UK, 1978; pp 111−114. (c) Schlosser, M.; Marull, M. *Eur. J. Org. Chem.* **2003**, 1569.

SCHEME 2. Functionalization of 2,3-Difluoropyridine[a]

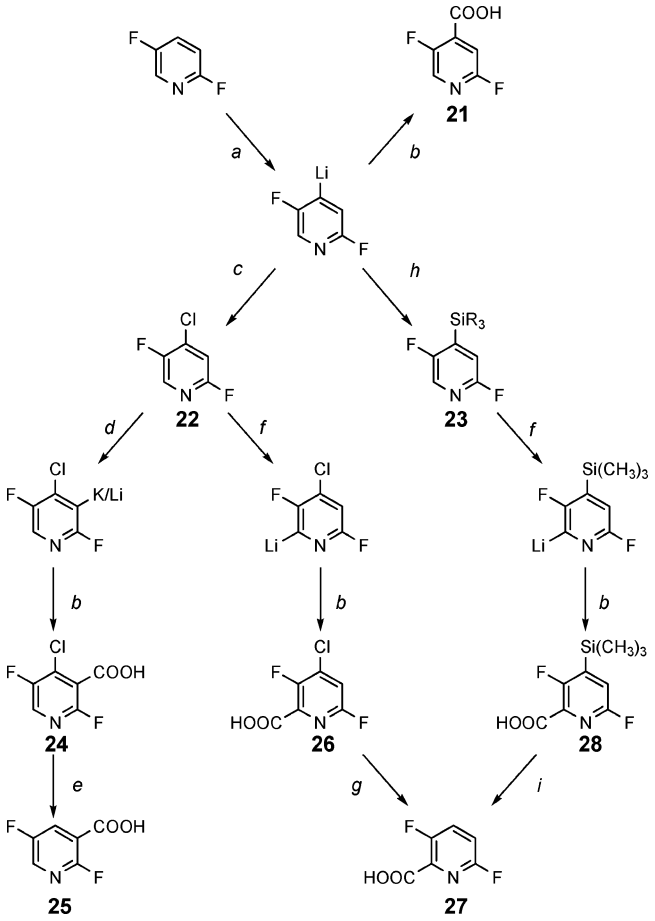


[a] Reagents and conditions: (a) $LiN(^iC_3H_7)_2$. (b) (1) CO_2, (2) aq HCl. (c) $Cl_2CFCClF_2$. (d) $HCOONH_4$ + Pd/C (cat.) in ethanol. (e) I_2 in THF. (f) $HOCH_3$. (g) LiC_4H_9 in toluene. (h) $ClSi(CH_3)_3$ or $ClSi(C_2H_5)_3$. (i) LiC_4H_9 + $LiOCH_2CH_2N(CH_3)_2$ in THF. (j) $(H_9C_4)_4NF$ hydrate.

2,5-difluoro-4-(trimethylsilyl)pyridine (**23**; 82%), respectively. The chlorinated derivative **22** exhibited a quite remarkable new case of "optional site selective metalation".[18] Lithium diisopropylamide, when simultaneously activated by potassium *tert*-butoxide and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine ("PMDTA"), abstracted a proton exclusively from the 3-position, thus giving rise to the 4-chloro-2,5-difluoropyridine-3-carboxylic acid (**24**; 53%), which was reduced with zinc powder in concentrated aqueous ammonia to the 2,5-difluoropyridine-3-carboxylic acid (**25**; 84%). In contrast, when lithium 2,2,6,6-tetramethylpiperidide in diethyl ether was employed as the base, 6- and 3-lithiated species were generated in a 95:5 ratio. After carboxylation, neutralization, and crystallization, the pure 4-chloro-3,6-difluoropyridine-2-carboxylic acid (**26**) was isolated in 36% yield. Its dechlorination by catalytic hydrogenation provided

(18) (a) Mongin, F.; Maggi, R.; Schlosser, M. *Chimia* **1996**, *50*, 650. (b) Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3975.

SCHEME 3. Functionalization of 2,5-Difluoropyridine[a]



[a] Reagents and conditions: (a) $LiN(^iC_3H_7)_2$. (b) (1) CO_2, (2) aq HCl. (c) $Cl_2CFCClF_2$. (d) $LiN(^iC_3H_7)_2$ + $H_3CN[CH_2CH_2N(CH_3)_2]_2$ + $KOC(CH_3)_3$ in THF. (e) Zn in aq NH_3. (f) $LiNC_5H_6(CH_3)_4$ (lithium 2,2,6,6-tetramethylpiperidide) in diethyl ether. (g) $HCOONH_4$ + Pd/C (cat.) in ethanol. (h) $ClSi(CH_3)_3$. (i) $(H_9C_4)_4NF$ hydrate in THF.

the 3,6-difluoropyridine-2-carboxylic acid (**27**; 79%), which could also be prepared by metalation of the silane **23** with lithium 2,2,6,6-tetramethylpiperidide in diethyl ether followed by carboxylation and by subsequent protodesilylation (in 94% yield) of the resulting 3,6-difluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (**28**; 74%).

Conclusions

In conclusion, the three mono- and difluorinated pyridines were selectively transformed into the 10 targeted pyridinecarboxylic acids. Furthermore, eight chloro- or silyl-substituted precursors have been prepared which equally may qualify as new and attractive building blocks for pharmaceuticals and agrochemicals.

From a more fundamental point of view, new insight was gained in the behavior of pyridines toward organometallic reagents. The role of the nitrogen atom proved to be ambivalent. It facilitates metalation processes by both inductive electron withdrawal and metal complexation. For example, 2,3-difluoropyridine undergoes proton abstraction (at the 4-position) far more rapidly than 1,2-difluorobenzene does (at the 3-position). On the other hand, coordination-seeking reagents such as Caubère's

base or lithium 2,2,6,6-tetramethylpiperidide in diethyl ether (as opposed to tetrahydrofuran) are specifically guided to the nitrogen-adjacent 2- or 6-positions.

The role of the heterocyclic nitrogen atom is modulated and often even surpassed by substituent effect. Electron-withdrawing atoms such as fluorine or chlorine activate strongly the adjacent sites and, though to a lesser extent, also more remote positions. Trialkylsilyl groups or other bulky substituents screen sterically the neighboring position against the attack of any metalation reagent. The judicious combination of such effects allows one to selectively switch on and off reactive sites. This concept is the basis of the "toolbox methods"[2] which enable the regiochemically exhaustive functionalization of aromatic and heterocyclic core compounds.

Experimental Section

Working practices and abbreviations are specified in previous articles from this laboratory.[19−21] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, relative to the internal standard tetramethylsilane (chemical shift δ = 0.00 ppm). The samples were dissolved in deuteriochloroform, if nothing specified, or hexadeuterioacetone, if marked with an asterisk. 2-Fluoropyridine is commercially available and the preparation of 2,3-difluoropyridine and 2,5-difluoropyridine has already been described.[15]

2-Fluoropyridine as the Starting Material. 2-Fluoropyridine-3-carboxylic acid (1): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2-fluoropyridine (2.4 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (15 mL) and tetrahydrofuran (35 mL) cooled in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto freshly crushed carbon dioxide. At 25 °C, water (40 mL) was added. After evaporation of the volatiles, the residue was triturated with hydrochloric acid (0.10 L) and the solid material collected by filtration and dried; mp 163−165 °C (lit.[22] mp 164−165 °C); yield 2.95 g (84%). ^{1}H NMR* δ 8.5 (m, 2 H), 7.50 (ddd, J = 7.4, 5.1, 1.9 Hz, 1 H) ppm.

3-Chloro-2-fluoropyridine (2): Prepared analogously as described above, but working on a 0.20 mol scale and replacing carbon dioxide by 1,1,2-trichloro-1,2,2-trifluoroethane (48 mL, 75 g, 0.40 mol). After 45 min at −75 °C, the mixture was poured into water (0.15 L). The organic phase was washed with a 5% aqueous solution (4 × 50 mL) of hydrochloric acid and dried. Upon distillation, a colorless liquid was collected; bp 68−70 °C/32 mmHg (lit.[23] mp 94−95 °C/100 mmHg); yield 22.4 g (85%). ^{1}H NMR δ 8.12 (dd, J = 4.8, 1.4 Hz, 1 H), 7.82 (ddd, J = 8.2, 7.6, 1.5 Hz, 1 H), 7.17 (ddd, J = 7.9, 4.8, 1.4 Hz, 1 H) ppm.

3-Chloro-2-fluoropyridine-4-carboxylic acid (6): 3-Chloro-2-fluoropyridine (**2**; 3.3 g, 25 mmol) was added to a solution of butyllithium (25 mmol) in hexanes (15 mL) and tetrahydrofuran (35 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto freshly crushed carbon dioxide, before being partitioned between water (40 mL) and diethyl ether (20 mL). The aqueous phase was acidified with an aqueous solution of hydrochloric acid and extracted with diethyl ether (3 × 20 mL). Evaporation of the solvent and crystallization from a 4:1 (v/v) mixture of ethyl acetate and hexanes afforded 3.29 g (75%) of colorless prisms; mp 154 °C dec. ^{1}H NMR* δ 8.31 (dd, J = 5.2, 1.4 Hz, 1 H), 7.74 (d, J = 5.2 Hz, 1 H) ppm. ^{13}C NMR* δ 164.5 (d, J = 4 Hz), 160.1 (d, J = 235 Hz), 146.4 (d, J = 14 Hz), 143.7 (d, J = 2 Hz), 123.5 (d, J = 5 Hz), 116.2 (d, J = 36 Hz) ppm. $C_6H_3ClFNO_2$ (175.55) Calcd: C 41.05, H 1.72. Found: C 41.22, H 1.75.

3,4-Dichloro-2-fluoropyridine (3): Prepared as described above but working on a 0.20 mol scale and with 1,1,2-trichloro-1,2,2-trifluoroethane (48 mL, 75 g, 0.40 mol) instead of carbon dioxide. Upon distillation, a colorless liquid was collected; mp 17−19 °C; bp 62−63 °C/10 mmHg; yield 26.6 g (80%). ^{1}H NMR δ 8.03 (dd, J = 5.5, 0.9 Hz, 1 H), 7.32 (d, J = 5.5 Hz, 1 H) ppm. ^{13}C NMR δ 159.7 (d, J = 239 Hz), 145.7 (d, J = 3 Hz), 144.5 (d, J = 24 Hz), 123.4 (d, J = 5 Hz), 117.0 (d, J = 36 Hz) ppm. $C_5H_2Cl_2FN$ (165.98) Calcd: C 36.18, H 1.21. Found: C 36.54, H 0.93.

3-Chloro-2-fluoro-4-(trimethylsilyl)pyridine (8): Prepared as described above with chlorotrimethylsilane (25 mL, 22 g, 0.20 mol); colorless liquid; bp 99−101 °C/12 mmHg; n_D^{20}1.4998; yield 37.7 g (90%). ^{1}H NMR δ 8.06 (dd, J = 4.7, 1.0 Hz, 1 H), 7.22 (dd, J = 4.7, 1.4 Hz, 1 H), 0.41 (s, 9 H) ppm. ^{13}C NMR δ 158.7 (d, J = 240 Hz), 154.8, 144.2 (d, J = 12 Hz), 127.2 (d, J = 5 Hz), 122.7 (d, J = 31 Hz), −1.0 ppm. $C_8H_{11}ClFNSi$ (203.72) Calcd: C 47.17, H 5.44. Found: C 47.07, H 5.27.

4,5-Dichloro-6-fluoropyridine-3-carboxylic acid (4): At −100 °C, diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 3,4-dichloro-2-fluoropyridine (**3**; 4.2 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in hexanes (15 mL) and tetrahydrofuran (35 mL). After 2 h at −100 °C, the mixture was poured onto freshly crushed carbon dioxide, before being partitioned between water (40 mL) and diethyl ether (20 mL). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3 × 30 mL). Evaporation of the solvent and crystallization from chloroform afforded 4.20 g (80%) of colorless prisms; mp 119−122 °C dec. ^{1}H NMR* δ 8.70 (d, J = 0.7 Hz, 1 H) ppm. ^{13}C NMR* δ = 163.8, 161.2 (d, J = 240 Hz), 148.3 (d, J = 17 Hz), 146.1 (d, J = 4 Hz), 127.4 (d, J 5 Hz), 118.7 (d, J = 37 Hz) ppm. $C_6H_2Cl_2FNO_2$ (209.99) Calcd: C 34.32, H 0.96. Found: C 33.97, H 0.91.

5-Chloro-6-fluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (9): 2-(Dimethylamino)ethanol (20 mL, 18 g, 0.20 mol) and 3-chloro-2-fluoro-4-(trimethylsilyl)pyridine (**8**; 20 g, 0.10 mol) in hexanes (50 mL) were added consecutively to a solution of butyllithium (0.40 mol) in hexanes (0.25 L) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide and later into water (0.10 L). The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid and extracted with diethyl ether (3 × 50 mL). Evaporation of the solvent, drying under vacuum, and subsequent trituration with pentanes afforded a white powder that was collected by filtration; colorless needles (from toluene); mp 159−161 °C dec; yield 9.26 g (37%). ^{1}H NMR δ 8.15 (d, J = 2.1 Hz, 1 H), 0.46 (s, 9 H) ppm. ^{13}C NMR δ 164.8, 157.8, 157.5 (d, J = 249 Hz), 140.8 (d, J = 9 Hz), 128.6 (d, J = 30 Hz), 128.1 (d, J = 4 Hz), −1.6 ppm. $C_9H_{11}ClFNO_2Si$ (247.73) Calcd: C 43.64, H 4.48. Found: C 43.76, H 4.34.

5-Chloro-6-fluoropyridine-2-carboxylic acid (10): 5-Chloro-6-fluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (**9**; 6.2 g, 25 mmol) and tetrabutylammonium fluoride trihydrate (7.9 g, 25 mmol) in tetrahydrofuran (25 mL) were kept for 2 h at 25 °C. After evaporation of the solvent, water (40 mL) and diethyl ether (20 mL) were added. The organic phase was extracted with water (3 × 20 mL) and the combined aqueous layers were acidified to pH 1 with concentrated hydrochloric acid. A white powder precipitated, which was collected by filtration and dried; mp 198−201 °C dec; yield 3.68 g (84%). ^{1}H NMR* δ 8.31 (dd, J = 8.9, 7.7 Hz, 1 H), 8.10 (dd, J = 7.9, 1.2 Hz, 1 H) ppm. ^{13}C NMR* δ 164.3, 158.4 (d, J = 238 Hz), 145.3 (d, J = 12 Hz), 143.4 (d, J = 2 Hz), 125.1 (d, J = 4 Hz), 121.9 (d, J = 34 Hz) ppm. $C_6H_3ClFNO_2$ (175.55) Calcd: C 41.05, H 1.72. Found: C 41.04, H 1.81.

(19) Bobbio, C.; Schlosser M. *Eur. J. Org. Chem*. **2003**, 4533.
(20) Heiss, C.; Schlosser M. *Eur. J. Org. Chem*. **2002**, 447.
(21) Schlosser, M.; Marull, M. *Eur. J. Org. Chem*. **2003**, 1569.
(22) Minor, J. T.; Hawkins, G. F.; VanderWerf, C. A.; Roe, A. *J. Am. Chem. Soc.* **1949**, *71*, 1125.
(23) Finger, G. C.; Starr, L. D.; Dickerson, D. R.; Gutowsky, H. S.; Hamer, J. *J. Chem. Soc*. **1963**, *28*, 1666.

2-Fluoropyridine-4-carboxylic acid (7): 3-Chloro-2-fluoropyridine-4-carboxylic acid (**6**; 1.8 g, 10 mmol), 10% palladium on charcoal (1.1 g, 1.0 mmol), and ammonium formate (1.3 g, 20 mmol) were mixed in ethanol (20 mL) and the solution was stirred for 2 h at 25 °C. After filtration and washing of the recovered palladium on charcoal with water (30 mL), the filtrate was concentrated and acidified with 2.0 M hydrochloric acid. The white precipitate formed was collected by filtration and dried; mp 194−196 °C dec (lit.[24] mp 195−197 °C); yield 1.17 g (83%). ^{1}H NMR* δ 8.45 (d, J = 5.4 Hz, 1 H), 7.86 (ddd, J = 5.1, 1.8, 1.3 Hz, 1 H), 7.6 (m, 1 H) ppm.

6-Fluoropyridine-3-carboxylic acid (5): Obtained analogously from 4,5-dichloro-6-fluoropyridine-3-carboxylic acid (**4**; 2.0 g, 10 mmol). After acidification of the aqueous layer, the latter was extracted with ethyl acetate (3 × 20 mL). Evaporation of the solvent afforded 1.01 g (71%) of a white powder; mp 144−146 °C dec (lit.[22] mp 146−147 °C). ^{1}H NMR* δ 8.84 (d, J = 2.2 Hz, 1 H), 8.52 (ddd, J = 8.2, 7.4, 2.4 Hz, 1 H), 7.25 (dd, J = 8.7, 2.9 Hz, 1 H) ppm.

6-Fluoropyridine-2-carboxylic acid (11): Obtained analogously from 5-chloro-6-fluoropyridine-2-carboxylic acid (**10**; 1.8 g, 10 mmol); colorless platelets (from chloroform); mp 135−137 °C (lit.[24] mp 135−137 °C dec); yield 1.21 g (86%). ^{1}H NMR* δ 8.25 (q, J = 7.0 Hz, 1 H), 8.11 (dd, J = 7.5, 2.3 Hz, 1 H), 7.42 (dd, J = 8.3, 2.9 Hz, 1 H) ppm.

2,3-Difluoropyridine as the Starting Material. 2,3-Difluoropyridine-4-carboxylic acid (12): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,3-difluoropyridine (2.9 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) kept in a dry ice/methanol bath. After 1 h at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (50 mL), washed with diethyl ether (2 × 15 mL), acidified to pH 1, and extracted with diethyl ether (3 × 25 mL). Evaporation of the solvent and crystallization from ethyl acetate afforded colorless prisms; mp 159−160 °C dec; yield 3.10 g (78%). ^{1}H NMR* δ 8.15 (ddd, J = 5.1, 2.1, 0.6 Hz, 1 H), 7.77 (dd, J = 5.1, 4.5 Hz, 1 H) ppm. ^{13}C NMR* δ 162.4, 153.1 (dd, J = 237, 15 Hz), 144.6 (dd, J = 272, 30 Hz), 141.9 (dd, J = 22, 8 Hz), 130.2 (d, J = 4 Hz), 123.5 ppm. $C_6H_3F_2NO_2$ (159.09) Calcd: C 45.30, H 1.90, N 8.80. Found: C 45.40, H 2.11, N 8.82.

4-Chloro-2,3-difluoropyridine (13): Prepared analogously with 1,1,2-trichloro-1,2,2-trifluoroethane (12 mL, 19 g, 0.10 mol) as the reagent. After 1 h at −75 °C, water (70 mL) was added and the organic phase was washed with water (2 × 70 mL), dried, and distilled; bp 141−142 °C; mp −25 to −23 °C; n_D^{20} 1.4726; yield 8.82 g (59%). ^{1}H NMR δ 7.91 (d, J = 5.4 Hz, 1 H), 7.34 (t, J = 4.9 Hz, 1 H). ^{13}C NMR δ 152.8 (dd, J = 240, 14 Hz), 143.0 (dd, J = 263, 31 Hz), 141.6 (dd, J = 15, 8 Hz), 133.6 (d, J = 13 Hz), 124.0 (t, J = 4 Hz). $C_5H_2ClF_2N$ (149.53) Calcd: C 40.16, H 1.35. Found: C 40.25, H 1.36.

2,3-Difluoro-4-iodopyridine (16): Prepared analogously as acid **12** from 2,3-difluoropyridine (5.8 g, 50 mmol) with a solution of iodine (13 g, 50 mmol) in tetrahydrofuran (40 mL) as the reagent. After 1 h at −75 °C, water (0.10 L) and diethyl ether (50 mL) were added. The organic layer was washed with a saturated aqueous solution of sodium thiosulfate (50 mL) and brine (25 mL). The solvents were evaporated and the residue crystallized from methanol to give 9.64 g (80%) of slightly yellow prisms; mp 66−68 °C. ^{1}H NMR δ 7.68 (dd, J = 5.2, 0.9 Hz, 1 H), 7.57 (dd, J = 5.1, 3.5 Hz, 1 H) ppm. ^{13}C NMR δ 151.0 (dd, J = 243, 17 Hz), 146.6 (dd, J = 259, 29 Hz), 142.0 (dd, J = 14, 7 Hz), 132.0, 94.8 (d, J = 20 Hz) ppm. $C_5H_2F_2IN$ (240.98) Calcd: C 24.92, H 0.84, N 5.81. Found: C 24.95, H 0.89, N 5.85.

2,3-Difluoro-4-(trimethylsilyl)pyridine (18a): Prepared analogously as acid **12** from 2,3-difluoropyridine (5.8 g, 50 mmol) with chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol) as the reagent. Distillation under reduced pressure gave 7.96 g (85%) of a colorless liquid; bp 78−79 °C/15 mmHg; mp −2 to +1 °C; n_D^{20} 1.4621. ^{1}H NMR δ 7.92 (dd, J = 4.8, 1.5 Hz, 1 H), 7.15 (ddd, J = 4.5, 1.9, 1.0 Hz, 1 H), 0.36 (d, J = 0.7 Hz, 9 H) ppm. ^{13}C NMR δ 151.7 (dd, J = 242, 19 Hz), 149.2 (dd, J = 253, 26 Hz), 140.9 (dd, J = 12, 6 Hz), 140.9 (d, J = 25 Hz), 126.4 (t, J = 5 Hz), −1.6 ppm. $C_8H_{11}F_2NSi$ (187.26) Calcd: C 51.31, H 5.92. Found: C 51.35, H 5.94.

2,3-Difluoro-4-(triethylsilyl)pyridine (18b): Prepared analogously with chlorotriethylsilane (8.4 mL, 7.5 g, 50 mmol) as the reagent. Upon distillation 9.75 g (85%) of a colorless liquid was collected; bp 88−90 °C/1.5 mmHg; mp −59 to −58 °C; n_D^{20} 1.4776. ^{1}H NMR δ 7.93 (dt, J = 4.7, 0.7 Hz, 1 H), 7.1 (m, 1 H), 0.9 (m, 15 H) ppm. ^{13}C NMR δ 153.1 (dd, J = 241, 19 Hz), 150.7 (dd, J = 252, 26 Hz), 140.8 (dd, J = 11, 6 Hz), 138.5 (d, J = 26 Hz), 127.2 (t, J = 5 Hz), 7.0, 3.0 ppm. $C_{11}H_{17}F_2NSi$ (229.35) Calcd: C 57.61, H 7.47. Found: C 57.30, H 7.30.

4-Chloro-5,6-difluoropyridine-3-carboxylic acid (14): At −100 °C, diisopropylamine (3.0 g, 4.3 g, 30 mmol) and 4-chloro-2,3-difluoropyridine (**13**; 4.5 g, 30 mmol) in tetrahydrofuran (10 mL) were added consecutively to butyllithium (30 mmol) in tetrahydrofuran (30 mL) and hexanes (20 mL). After 2 h at −100 °C, the mixture was poured onto an excess of carbon dioxide. Water (40 mL) was added. The aqueous layer was washed with diethyl ether (2 × 15 mL), acidified to pH 1, and extracted with diethyl ether (3 × 20 mL). After evaporation of the solvent, the product was crystallized from chloroform and hexanes; colorless needles; mp 117−118 °C dec; yield 4.53 g (78%). ^{1}H NMR δ 8.73 (t, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR δ 167.3, 154.7 (dd, J = 248, 15 Hz), 145.4 (dd, J = 16, 8 Hz), 143.2 (d, J = 264, 29 Hz), 135.6 (dd, J = 14, 5 Hz), 123.7 (dd, J = 6, 4 Hz) ppm. $C_6H_2ClF_2NO_2$ (193.54) Calcd: C 37.24, H 1.04. Found: C 37.53, H 0.98.

5,6-Difluoropyridine-3-carboxylic acid (15): 4-Chloro-5,6-difluoropyridine-3-carboxylic acid (**14**; 2.9 g, 15 mmol) was dissolved in ethanol (15 mL) and stirred for 2 h at 25 °C in the presence of 10% palladium on charcoal (0.80 g, 0.75 mmol) and ammonium formate (1.9 g, 30 mmol). After filtration and washing of the solid with water (50 mL), the filtrate was concentrated, acidified with hydrochloric acid, and extracted with diethyl ether (3 × 15 mL). Evaporation of the solvent and crystallization from chloroform afforded 2.08 g (87%) of colorless prisms; mp 129−132 °C dec. ^{1}H NMR* δ 8.62 (t, J = 1.8 Hz, 1 H), 8.31 (td, J = 9.4, 2.1 Hz, 1 H) ppm. ^{13}C NMR* δ 165.0, 154.8 (dd, J = 241, 15 Hz), 145.8 (dd, J = 260, 29 Hz), 144.7 (dd, J = 15, 6 Hz), 128.8 (dd, J = 17, 5 Hz), 128.4 (dd, J = 5, 2 Hz) ppm. $C_6H_3F_2NO_2$ (159.09) Calcd: C 45.30, H 1.90. Found: C 45.44, H 1.97. The same pyridinecarboxylic acid **15** was obtained when 2,3-difluoro-5-iodopyridine (**17**; see below; 2.4 g, 10 mmol) in tetrahydrofuran (15 mL) was treated with butyllithium (10 mmol) in hexanes (7.0 mL) and when, after 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide. Extraction and crystallization from chloroform afforded 1.26 g (79%) of colorless prisms.

2,3-Difluoro-5-iodopyridine (17): At −75 °C, a solution of lithium diisopropylamide (prepared from diisopropylamine and butyllithium, 50 mmol each) in tetrahydrofuran (20 mL) and hexanes (35 mL) was added over 20 min to a solution of 2,3-difluoro-4-iodopyridine (**16**; 6.0 g, 25 mmol) in tetrahydrofuran (15 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was treated with methanol (3.0 mL) and water (20 mL). According to gas chromatography (30 m, DB-WAX; 30 m, DB-23, 50→100 °C; tridecane as an internal standard), the organic layer contained 74% of 2,3-difluoro-5-iodopyridine (**17**), 20% of 2,3-difluoropyridine, and 5% of 2,3-difluoro-4-iodopyridine (**16**). It was washed with water (2 × 20 mL) and dried. Upon distillation under reduced pressure a colorless liquid was collected, which was purified by crystallization; colorless prisms (from methanol); mp 34−35 °C; bp 69−71 °C/15 mmHg; yield 2.89 g (48%). ^{1}H NMR δ 8.20 (s, broad, 1 H), 7.87 (td, J = 8.4, 1.9 Hz, 1 H) ppm. ^{13}C NMR δ

(24) Roe, A.; Cheek, P. H.; Hawkins, G. F. *J. Am. Chem. Soc.* **1949**, *71*, 4152.

152.0 (dd, J = 241, 14 Hz), 147.7 (dd, J = 13, 6 Hz), 145.4 (dd, J = 268, 29 Hz), 134.8 (dd, J = 17, 3 Hz), 86.2 (d, J = 5 Hz) ppm. $C_5H_2F_2IN$ (240.98) Calcd: C 24.92, H 0.84. Found: C 24.89, H 0.93.

5,6-Difluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (19a): 2-(Dimethylamino)ethanol (7.5 mL, 6.7 g, 75 mmol) and 2,3-difluoro-4-(trimethylsilyl)pyridine (**18a**; 4.7 g, 25 mmol) were added consecutively to a solution of butyllithium (0.15 mol) in hexanes (0.12 L) kept in a dry ice/methanol bath. After 6 h at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide. The products were partitioned between water (50 mL) and diethyl ether (2 × 20 mL). The aqueous phase was acidified to pH 1 with hydrochloric acid and extracted with diethyl ether (3 × 20 mL). After evaporation of the solvent the residue was crystallized from hexanes and diethyl ether; colorless needles; mp 120−121 °C; yield 2.66 g (46%). ^{1}H NMR δ 8.16 (dd, J = 2.6, 0.8 Hz, 1 H), 0.45 (d, J = 0.9 Hz, 9 H) ppm. ^{13}C NMR δ 165.9, 152.3 (dd, J = 260, 24 Hz), 150.8 (dd, J = 249, 20 Hz), 143.3 (dd, J = 27, 2 Hz), 138.2 (dd, J = 8, 5 Hz), 129.2 (dd, J = 8, 4 Hz), −1.6 (d, J = 2 Hz) ppm. $C_9H_{11}F_2NO_2Si$ (231.27) Calcd: C 46.74, H 4.79. Found: C 46.90, H 4.78.

5,6-Difluoro-4-(triethylsilyl)pyridine-2-carboxylic acid (19b): Prepared analogously from 2,3-difluoro-4-(triethylsilyl)-pyridine (**18b**; 5.7 g, 25 mmol); colorless needles (from hexanes); yield 4.03 g (59%); mp 80−82 °C. ^{1}H NMR δ 8.12 (dd, J = 2.7, 0.8 Hz, 1 H), 1.0 (m, 15 H) ppm. ^{13}C NMR δ 164.5, 152.7 (dd, J = 260, 24 Hz), 150.7 (dd, J = 251, 21 Hz), 141.5 (d, J = 27 Hz), 138.0 (dd, J = 7, 4 Hz), 129.4 (dd, J = 11, 4 Hz), 7.1, 2.9 ppm. $C_{12}H_{17}F_2NO_2Si$ (273.35) Calcd: C 52.73, H 6.27. Found: C 52.84, H 6.31.

5,6-Difluoropyridine-2-carboxylic acid (20): 5,6-Difluoro-4-(triethylsilyl)pyridine-2-carboxylic acid (**19b**; 1.4 g, 5.0 mmol) was dissolved in a 0.50 M solution (10 mL) of tetrabutylammonium fluoride (5.0 mmol) in tetrahydrofuran. After 45 min at 25 °C, the solvent was evaporated and water (20 mL) was added. Acidification to pH 1 with hydrochloric acid, extraction with diethyl ether (3 × 10 mL), evaporation of the solvent, and crystallization from chloroform afforded 0.61 g (77%) of colorless needles; mp 161−162 °C. ^{1}H NMR* δ 8.17 (ddd, J = 8.3, 3.4, 0.8 Hz, 1 H), 8.08 (td, J = 9.1, 8.4 Hz, 1 H) ppm. ^{13}C NMR* δ 164.2, 151.7 (dd, J = 240, 15 Hz), 148.9 (dd, J = 264, 28 Hz), 141.6 (dd, J = 11, 6 Hz), 129.0 (dd, J = 17, 3 Hz), 126.1 (t, J = 4 Hz) ppm. $C_6H_3F_2NO_2$ (159.09) Calcd: C 45.30, H 1.90. Found: C 45.29, H 1.93. The same reaction performed with 5,6-difluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (**19a**) gave the acid **20** in 75% yield.

2,5-Difluoropyridine as the Starting Material. 2,5-Difluoropyridine-4-carboxylic acid (21): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,5-difluoropyridine (2.9 g, 25 mmol) were added consecutively to butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL), kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (50 mL), washed with diethyl ether (2 × 15 mL), acidified to pH 1, and extracted with diethyl ether (3 × 25 mL). Evaporation of the solvent and crystallization from chloroform afforded 3.0 g (76%) of colorless prisms; mp 155−157 °C. ^{1}H NMR* δ 8.34 (t, J = 3.5 Hz, 1 H), 7.53 (dd, J = 4.4, 3.2 Hz, 1 H) ppm. ^{13}C NMR* δ 162.8 (t, J = 3 Hz), 160.2 (dd, J = 235, 3 Hz), 156.3 (dd, J = 261, 5 Hz), 138.0 (dd, J = 30, 16 Hz), 132.3 (dd, J = 12, 8 Hz), 111.7 (d, J = 43 Hz) ppm. $C_6H_3F_2NO_2$ (159.09) Calcd: C 45.30, H 1.90. Found: C 45.56, H 1.84.

4-Chloro-2,5-difluoropyridine (22): Prepared analogously on a 0.10 mol scale with 1,1,2-trichloro-1,2,2-trifluoroethane (12 mL, 19 g, 0.10 mol) as the reagent. The product was isolated by distillation; bp 139−141 °C; n_D^{20} 1.4764; yield 6.73 g (45%). ^{1}H NMR δ 8.13 (s, broad, 1 H), 7.08 (t, J = 4.0 Hz, 1 H) ppm. ^{13}C NMR δ 159.0 (dd, J = 239, 3 Hz), 154.0 (dd, J = 254, 6 Hz), 135.1 (dd, J = 27, 18 Hz), 134.9 (dd, J = 18, 12 Hz), 111.5 (dd, J = 44, 1 Hz) ppm. $C_5H_2ClF_2N$ (149.53) Calcd: C 40.16, H 1.35. Found: C 40.26, H 1.30.

2,5-Difluoro-4-(trimethylsilyl)pyridine (23): Prepared analogously on a 50 mmol scale with chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol) as the reagent. Upon distillation under reduced pressure 7.68 g (82%) of a colorless liquid was collected; bp 41−42 °C/2.8 mmHg; mp 17−19 °C. ^{1}H NMR δ 7.93 (d, J = 1.6 Hz, 1 H), 6.91 (t, J = 3.1 Hz 1 H), 0.36 (d, J = 0.6 Hz, 9 H) ppm. ^{13}C NMR δ 161.4 (dd, J = 244, 4 Hz), 159.2 (d, J = 239 Hz), 142.9 (dd, J = 32, 5 Hz), 133.4 (dd, J = 33, 15 Hz), 114.3 (dd, J = 39, 9 Hz), −1.9 ppm. $C_8H_{11}F_2NSi$ (187.26) Calcd: C 51.31, H 5.92. Found: C 51.26, H 5.82.

4-Chloro-2,5-difluoropyridine-3-carboxylic acid (24): At −75 °C, potassium *tert*-butoxide (2.2 g, 20 mmol), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (4.2 mL, 3.5 g, 20 mmol), and 4-chloro-2,5-difluoropyridine (**22**; 3.0 g, 20 mmol) were added consecutively to a solution of diisopropylamine (2.8 mL, 2.0 g, 20 mmol) and butyllithium (20 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide. The residue was dissolved in water (30 mL), washed with diethyl ether (2 × 15 mL), acidified to pH 1, and extracted with diethyl ether (3 × 20 mL). After evaporation of the solvent, the product was purified by crystallization; colorless needles (chloroform and hexanes); mp 98−100 °C; yield 2.05 g (53%). ^{1}H NMR δ 8.26 (d, J = 1.4 Hz, 1 H) ppm. ^{13}C NMR δ 164.9 (dd, J = 5, 2 Hz), 155.9 (dd, J = 245, 3 Hz), 154.0 (dd, J = 256, 5 Hz), 136.4 (dd, J = 27, 17 Hz), 134.5 (dd, J = 19, 6 Hz), 116.4 (dd, J = 37, 2 Hz) ppm. $C_6H_2ClF_2NO_2$ (193.54) Calcd: C 37.24, H 1.04. Found: C 37.47, H 0.95.

4-Chloro-3,6-difluoropyridine-2-carboxylic acid (26): 2,2,6,6-Tetramethylpiperidine (1.7 mL, 1.4 g, 10 mmol) and 4-chloro-2,5-difluoropyridine (**22**; 1.5 g, 10 mmol) were added to a solution of butyllithium (10 mmol) in diethyl ether (15 mL) and hexanes (7.0 mL) kept in a dry ice/methanol bath. After 6 h at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide. Water (20 mL) was added and the phases were separated. The aqueous phase was acidified with hydrochloric acid to pH 1 and extracted with diethyl ether (3 × 15 mL). An aliquot of the organic layer was withdrawn and treated with ethereal diazomethane until the yellow color persisted. According to gas chromatographic analysis (30 m, DB-23; 30 m, DB-WAX, 120 °C; tetradecane as internal standard), the raw material contained the 4-chloro-3,6-difluoropyridine-2-carboxylic acid (**26**) and the 4-chloro-2,5-difluoropyridine-3-carboxylic acid (**24**) in a ratio of 95:5 and in a total yield of 57%. The bulk of the organic solution was evaporated and the residue crystallized from chloroform affording 0.60 g (31%) of slightly pink needles; mp 105−107 °C. ^{1}H NMR δ 7.41 (t, J = 3.5 Hz, 1 H) ppm. ^{13}C NMR δ 162.5, 156.6 (dd, J = 246, 3 Hz), 154.6 (dd, J = 274, 5 Hz), 138.7 (dd, J = 19, 11 Hz), 131.8 (dd, J = 14, 12 Hz), 117.1 (d, J = 42 Hz) ppm. $C_6H_2ClF_2NO_2$ (193.54) Calcd: C 37.24, H 1.04. Found: C 37.35, H 0.91.

3,6-Difluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (28): 2,2,6,6-Tetramethylpiperidine (2.5 mL, 2.1 g, 15 mmol) and 2,3-difluoro-4-(trimethylsilyl)pyridine (**23**; 2.8 g, 15 mmol) were added to a solution of butyllithium (15 mmol) in tetrahydrofuran (20 mL) and hexanes (10 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (50 mL). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3 × 15 mL). Evaporation of the solvent and crystallization from hexanes gave 2.57 g (74%) of colorless cotton-like needles; mp 113−114 °C. ^{1}H NMR* δ 7.38 (dd, J = 3.8, 2.3 Hz, 1 H), 0.42 (d, J = 0.9 Hz, 9 H) ppm. ^{13}C NMR* δ 163.0 (d, J = 7, Hz), 161.5 (dd, J = 257, 3 Hz), 158.2 (d, J = 240 Hz), 147.8 (dd, J = 34, 5 Hz), 133.4 (dd, J = 19, 13 Hz), 120.5 (dd, J = 39, 10 Hz),

−1.7 (d, $J = 2$ Hz) ppm. $C_9H_{11}F_2NO_2Si$ (231.27) Calcd: C 46.74, H 4.79. Found: C 46.83, H 4.73.

2,5-Difluoropyridine-3-carboxylic acid (25): Zinc powder (0.65 g, 10 mmol) was added to a solution of 4-chloro-2,5-difluoropyridine-3-carboxylic acid (**24**; 0.97 g, 5.0 mmol) in 25% aqueous ammonia (5.0 mL). After the slurry had been stirred for 2 h at 25 °C, the mixture was filtered and the solid was washed with water (2 × 5.0 mL). The filtrate was acidified with hydrochloric acid to pH 1 and extracted with diethyl ether (3 × 15 mL). Evaporation of the solvent and crystallization from chloroform gave 0.67 g (84%) of acid **25**; colorless needles; mp 90−92 °C. ^{1}H NMR δ 8.34 (dd, $J = 3.4$, 1.6 Hz, 1 H), 8.20 (td, $J = 7.1$, 3.2 Hz, 1 H). ^{13}C NMR δ 167.0 (d, $J = 8$ Hz), 157.8 (dd, $J = 250$, 2 Hz), 156.8 (dd, $J = 255$, 5 Hz), 140.1 (dd, $J = 27$, 16 Hz), 130.4 (d, $J = 23$ Hz), 113.4 (dd, $J = 28$, 4 Hz). $C_6H_3F_2NO_2$ (159.09) Calcd: C 45.30, H 1.90. Found: C 45.26, H 1.98.

3,6-Difluoropyridine-2-carboxylic acid (27): At 25 °C, 3,6-difluoro-4-(trimethylsilyl)pyridine-2-carboxylic acid (**28**; 1.2 g, 5.0 mmol) and tetrabutylammonium fluoride trihydrate (1.6 g, 5.0 mmol) were mixed in tetrahydrofuran (10 mL). After 1 h, the solvent was evaporated, water (15 mL) was added, and the solution was acidified with concentrated hydrochloric acid. Extraction with diethyl ether (3 × 10 mL), evaporation of the solvent, and crystallization from chloroform gave 0.75 g (94%) of colorless needles; mp 139−141 °C. ^{1}H NMR* δ 8.03 (td, $J =$ 8.9, 5.8 Hz, 1 H), 7.47 (ddd, $J = 9.0$, 3.8, 2.8 Hz, 1 H). ^{13}C NMR* δ 162.7 (d, $J = 6$ Hz), 158.3 (dd, $J = 238$, 2 Hz), 158.2 (dd, $J = 264$, 5 Hz), 134.1 (t, $J = 14$ Hz), 133.0 (dd, $J = 24$, 8 Hz), 116.6 (dd, $J = 42$, 6 Hz). $C_6H_3F_2NO_2$ (159.09) Calcd: C 45.30, H 1.90. Found: C 45.60, H 1.84.

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