Creating Structural Manifolds from a Common Precursor: Basicity Gradient-Driven Isomerization of Halopyridines

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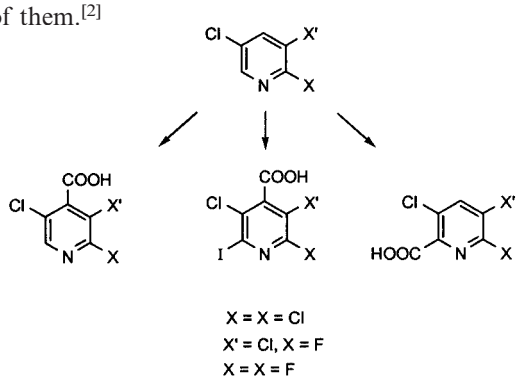
5-Chloro-2,3-difluoropyridine, an intermediate in the manufacturing process of an industrial pesticide, can be hydrolyzed to 5-chloro-3-fluoro-2*H*-pyridinone and the latter converted into 2,5-dichloro-3-fluoropyridine (**1a**), 2-bromo-5-chloro-3-fluoropyridine (**1b**), 5-chloro-3-fluoro-2-iodopyridine (**1c**) and 3-chloro-5-fluoropyridine (**1d**). Consecutive treatment of these four substrates with lithium diisopropylamide and carbon dioxide or lithium diisopropylamide and iodine affords the corresponding 4-pyridinecarboxylic acids **2** and 4-iodopyridines **3**, respectively. Amide-promoted deprotonation of such 4-iodopyridines **3** triggers an isomerization in which lithium and iodine change places. The resulting species can be trapped with carbon dioxide to give the acids **5a–c** or neutralized to give the halopyridines **4a–c**. The iodopyridines **4a** and **4b** can be converted into the acids **6a** and **6b**, the latter product leading also to the congeners **6c** and **6d**. The diiodopyridine **4c** provides an entry to the halopyridine **4d**, which at the same time may act as the precursor to the acid **5d**, the acid **7** or the bisacid **8**. Finally, the acid **9** is accessible from either one of the 5-chloro-3-fluoro-2-halopyridines **1b** and **1c**.

The spontaneous isomerization of lithiated bromo- or iodoarenes and bromo- or iodopyridines to less basic species is a powerful, though not widely known, tool for rational structural modification.[1] To demonstrate the practical utility of this method, we have recently reported the site-controlled conversion of 2,3,5-trichloropyridine, 3,5-dichloro-2-fluoropyridine and 5-chloro-2,3-difluoropyridine into each time three carboxylic acids, two of which were isomeric and the third one was an iodinated derivative of one of them.[2]



2,3,5-Trichloropyridine is a fairly inexpensive commercial product and at the same time it can serve as the precursor to prepare 3,5-dichloro-2-fluoropyridine. The third substrate, 5-chloro-2,3-difluoropyridine, is the key intermediate for the industrial manufacture of a herbicide. The availability of this material incited us to extend the scope of our investigations. To this end, 5-chloro-2,3-difluoropyridine was hydrolyzed in an alkaline medium to the 5-chloro-3-fluoro-2*H*-pyridinone (91%) which was then treated with phosphoryl trichloride or phosphoryl tribromide to afford 2,5-dichloro-3-fluoropyridine (**1a**) or 2-bromo-5-chloro-3-fluoropyridine (**1b**), respectively, in almost quantitative yield (91 and 97%). In contrast, the reaction between the pyridinone and iodine in the presence of red phosphorus proceeded sluggishly and only small amounts (1−5%) of 5-chloro-3-fluoro-2-iodopyridine (**1c**) could be isolated. Therefore, this compound was prepared in a satisfactory yield (59%) from the bromo analog **1b** by halogen/metal interconversion with isopropylmagnesium chloride and subsequent addition of elemental iodine. Reductive removal of the heaviest halogen in the halopyridine **1b** with zinc gave 3-chloro-5-fluoropyridine (**1d**; 92%).

Treatment of the four substrates **1** with lithium diisopropylamide (LIDA) or another strong base (e.g. butyllithium with starting materials **1a** and **1d**) followed by carboxylation and neutralization gave the 4-pyridinecarboxylic acids **2a** (82%), **2b** (74%), **2c** (84%) and **2d** (85%). The iodo compounds **3a** (80%), **3b** (76%), **3c** (86%) and **3d** (89%) were obtained when carbon dioxide was replaced by iodine as the electrophile.

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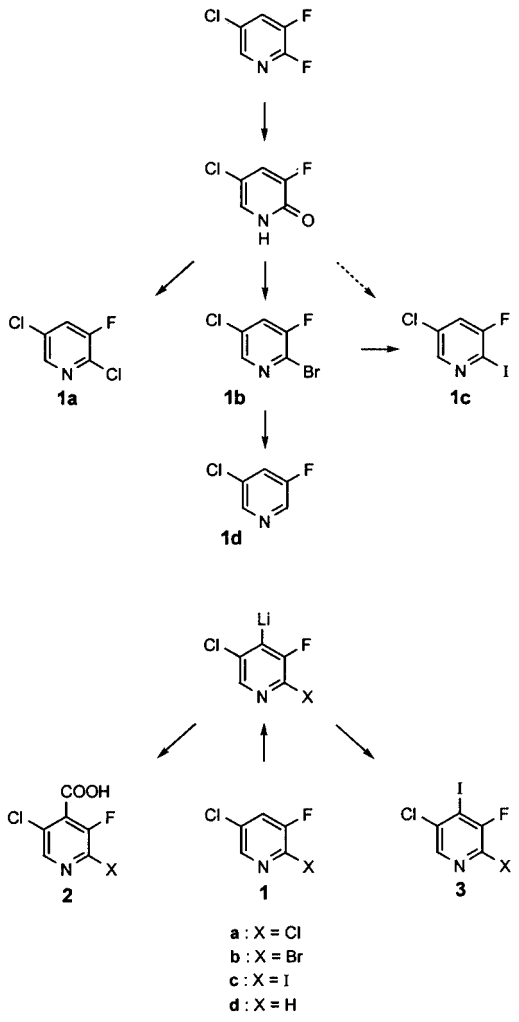
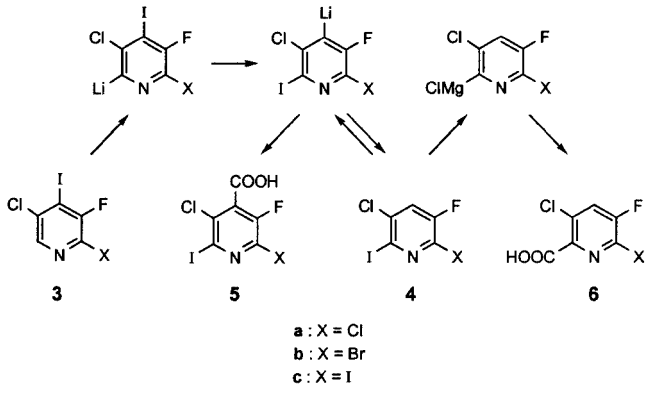
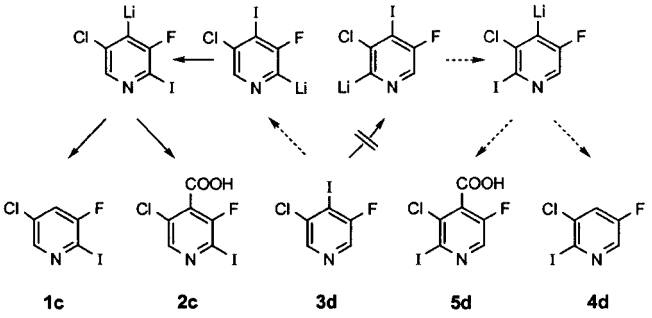


When the iodo compounds **3a**−**3c** were incubated with a solution of lithium 2,2,6,6-tetramethylpiperidide (LITMP) in tetrahydrofuran, deprotonation obviously had to occur at the 6-position. However, the species thus generated could not be trapped as it isomerized instantaneously by iodine/metal permutation presumably involving small amounts of the corresponding diiodopyridine as a turntable.[3] After the mixture had been quenched with water, the trihaloiodopyridines **4a**, **4b** and **4c** were found by gas chromatography to be present in 51%, 66% and 30% yield. However, due to their contamination by reduction products, they were isolated in only 46%, 57% and 23% yield, respectively. Exposure of compounds **4a**−**4c** to LIDA followed by carboxylation afforded the acids **5a** (89%), **5b** (88%) and **5c** (82%) whereas the acids **6a** (80%) and **6b** (79%) were formed when the deprotonation step was replaced by a halogen/metal permutation performed with isopropylmagnesium chloride.

The reaction takes a different course when the halogen at the 2-position is missing. The base then attacks the fluorine-adjacent rather than the chlorine-adjacent position. Thus, none of the intermediates is generated that could lead to the compounds **4d** and **5d** and from there ultimately also

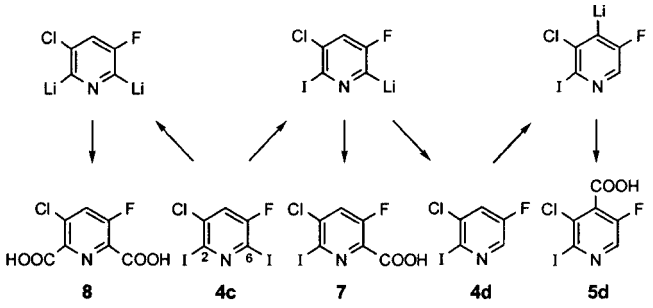


to **6d** (X = H). Instead concomitant reductive deiodination[4] (I → Li) and 2-lithiation triggering a basicity gradient driven iodine migration [3,5] took place. Depending on the choice of the trapping reagent, 3:2 mixtures of 3-chloro-5-fluoropyridine (**1d**) and 5-chloro-3-fluoro-2-iodopyridine (**1c**) or 3-chloro-5-fluoro-4-pyridinecarboxylic acid (**2d**) and 5-chloro-3-fluoro-2-iodo-4-pyridinecarboxylic acid (**2c**) were produced.

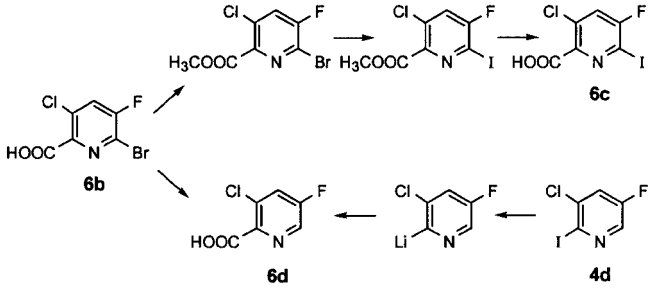


All what remained to be done was to prepare the still missing target compounds **4d**, **5d**, **6c** and **6d**. The regiochemical preference for deprotonation at the position next to fluorine is readily explained by the superior *ortho*-directing effect of this element when compared with chlorine.[6] For this reason, 3-chloro-5-fluoro-2,6-diiodopyridine (**4c**) underwent with butyllithium a halogen/metal permutation almost exclusively at the 6- and only marginally at the 2-position. Reaction of the 2-pyridyllithium intermediate with dry ice provided the 5-chloro-3-fluoro-6-iodo-2-pyridinecarboxylic acid (**7**; 35%), whereas hydrolysis gave the halopyridine **4d** (60%) which was submitted to consecutive deprotonation and carboxylation to afford the acid **5d** (85%). Treatment of 3-chloro-5-fluoro-2,6-diiodopyridine (**4c**) with 2 equiv. of butyllithium generated a dilithio species as evidenced by the trapping product 3-chloro-5-fluoro-2,6-dicarboxylic acid (**8**; 39%).

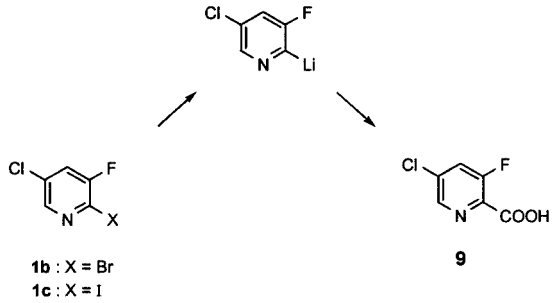
Both acids **6c** (46%) and **6d** (67%) could be selectively prepared from 6-bromo-3-chloro-5-fluoro-2-pyridinecarboxylic acid (**6b**) by esterification and silyl-mediated bro-



mine/iodine displacement [7] followed by hydrolysis and by reduction, respectively. The 3-chloro-5-fluoro-2-pyridinecarboxylic acid **6d** was also obtained from 3-chloro-5-fluoro-2-iodopyridine (**4d**) by consecutive treatment with butyllithium and dry ice in a 79% yield.



Finally, the 5-chloro-3-fluoro-2-pyridinecarboxylic acid (**9**) was prepared in a straight-forward manner by halogen/metal permutation and carboxylation. Depending on the starting material, 2-bromo-5-chloro-3-fluoropyridine or 5-chloro-3-fluoro-2-iodopyridine, the yield attained was 71% and 94%, respectively.



Experimental Section

Generalities: For the working practice and abbreviations, consult previous articles from this laboratory .[2,8,9] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, for samples dissolved in deuteriochloroform unless stated otherwise, chemical shifts being given relative to the signal of tetramethylsilane used as an internal standard.

1. Starting Materials

5-Chloro-3-fluoro-2(1*H*)-pyridinone: 5-Chloro-2,3-difluoropyridine (0.30 kg, 2.0 mol) in an aqueous solution (1.5 L) of sodium hydroxide (0.30 kg) was heated to 75 °C for 20 h. At 25 °C, precipitated salts were removed. The filtrate was diluted with water (3.0 L), acidified with hydrochloric acid to pH = 1 and heated under reflux until the solution had become homogeneous. At 25 °C, the product crystallized as colorless needles; m.p. 149−151 °C (from chloroform); 268 g (91%). ^{1}H NMR (D_3CCOCD_3): δ = 7.47 (dd, *J* = 3.8, 1.4 Hz, 1 H), 7.42 (dd, *J* = 10.1, 3.7 Hz, 1 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 155.6 (d, *J* = 25 Hz), 152.5 (d, *J* = 254 Hz), 130.2 (d, *J* = 6 Hz), 123.9 (d, *J* = 20 Hz), 111.1 (d, *J* = 7 Hz) ppm. C_5H_3ClFNO (147.54): calcd. C 40.70, H 2.05; found C 40.90, H 2.20.

2,5-Dichloro-3-fluoropyridine (1a): *N*,*N*-Dimethylformamide (4.0 mL, 3.6 g, 50 mmol), phosphoryl trichloride (47 mL, 77 g, 0.50 mol) and 5-chloro-3-fluoro-2(1*H*)-pyridinone (74 g, 0.50 mol) were heated to 130 °C for 2 h, before being submitted to a steam distillation. Extraction of the condensate with diethyl ether (3 × 50 mL), drying with sodium sulfate, filtration, evaporation of the solvent and crystallization from hexanes afforded colorless platelets; m.p. 34−35 °C; b.p. 55−56 °C/2 Torr; yield: 76 g (91%). ^{1}H NMR: δ = 8.22 (d, *J* = 2.0 Hz, 1 H), 7.54 (ddd, *J* = 7.5, 2.1, 0.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 154.2 (d, *J* = 267 Hz), 143.6 (d, *J* = 5 Hz), 137.4 (d, *J* = 19 Hz), 131.1 (s), 124.9 (d, *J* = 21 Hz) ppm. $C_5H_2Cl_2FN$ (165.98): calcd. C 36.18, H 1.21; found C 36.18; H 1.21.

2-Bromo-5-chloro-3-fluoropyridine (1b): Analogously from 5-chloro-3-fluoro-2(1*H*)-pyridinone (74 g, 0.50 mol) and phosphoryl tribromide (0.14 kg, 0.50 mol); colorless platelets; m.p. 28−30 °C (from hexanes); b.p. 77−78 °C/7 Torr; yield: 102 g (97%). ^{1}H NMR: δ = 8.23 (d, *J* = 2.2 Hz, 1 H), 7.48 (dd, *J* = 7.0, 2.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 155.6 (d, *J* = 265 Hz), 144.3 (d, *J* = 5 Hz), 131.6 (s), 127.7 (d, *J* = 23 Hz), 124.3 (d, *J* = 22 Hz) ppm. $C_5H_2BrClFN$ (210.44): calcd. C 28.54, H 0.96; found C 28.52, H 0.95.

5-Chloro-3-fluoro-2-iodopyridine (1c): 2-Bromo-5-chloro-3-fluoropyridine (**1b**; 21 g, 0.10 mol) in tetrahydrofuran (50 mL) was added in the course of 15 min to a 2.0 M solution of isopropylmagnesium chloride (0.10 mol) in tetrahydrofuran (50 mL), kept in an ice bath. After 2 h at 0 °C, the mixture was poured into a precooled solution of iodine (25 g, 0.10 mol) in tetrahydrofuran (0.10 L) and kept at −75 °C for 1 h with continuous stirring, before being partitioned between brine (0.10 L) and diethyl ether (70 mL). The organic phase was washed with a saturated aqueous solution of sodium thiosulfate (50 mL), dried with sodium sulfate, filtered and the solvents evaporated. Upon distillation under reduced pressure a yellowish liquid was collected that slowly crystallized; colorless needles; m.p. 39−40 °C (from methanol); b.p. 91−92 °C/6 Torr; yield: 15 g (59%). ^{1}H NMR: δ = 8.26 (d, *J* = 2.1 Hz, 1 H), 7.36 (dd, *J* = 6.8, 2.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 158.6 (d, *J* = 263 Hz), 145.5 (d, *J* = 4 Hz), 132.2 (d, *J* = 2 Hz), 122.8 (d, *J* = 23 Hz), 103.6 (d, *J* = 29 Hz) ppm. C_5H_2ClFIN (257.43): calcd. C 23.33, H 0.78; found C 23.30, H 0.83.

3-Chloro-5-fluoropyridine (1d): 2-Bromo-5-chloro-3-fluoropyridine (**1b**; 63 g, 0.30 mol) was stirred in an aqueous solution of sodium hydroxide (0.24 L, 0.60 mol) in the presence of zinc powder (29 g, 0.45 mol) for 6 h at 25 °C. The mixture was diluted with water and steam-distilled. Drying with sodium sulfate and distillation under reduced pressure afforded a colorless liquid that crystallized spontaneously; m.p. 26−27 °C; b.p. 132−134 °C; yield: 36.3 g (92%). ^{1}H NMR: δ = 8.43 (s, broad, 1 H), 8.40 (d, *J* = 2.5 Hz, 1 H), 7.47

(dt, J = 8.1, 2.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 158.6 (d, J = 262 Hz), 144.6 (d, J = 4 Hz), 136.0 (d, J = 23 Hz), 131.8 (d, J = 4 Hz), 123.1 (d, J = 21 Hz) ppm. C_5H_3ClFN (131.54): calcd. C 45.65, H 2.30; found C 45.69, H 2.22.

2. Di- and Trihalo-4-pyridinecarboxylic Acids

2,5-Dichloro-3-fluoro-4-pyridinecarboxylic Acid (2a): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,5-dichloro-3-fluoropyridine (**1a**; 4.1 g, 25 mmol) were consecutively added to a solution of 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 on an excess of freshly crushed solid 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). After evaporation of the solvent, the product was purified by crystallization; m.p. 151−152 °C (from chloroform); yield: 4.3 g (82%). ^{1}H NMR (D_3CCOCD_3): δ = 8.45 (s) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 161.5 (s), 151.5 (d, J = 266 Hz), 145.6 (d, J = 6 Hz), 138.3 (d, J = 19 Hz), 132.1 (d, J = 19 Hz), 128.4 (s) ppm. $C_6H_2Cl_2FNO_2$ (209.99): calcd. C 34.32, H 0.96; found C 34.24, H 0.98.

2-Bromo-5-chloro-3-fluoro-4-pyridinecarboxylic Acid (2b): Analogously from 2-bromo-5-chloro-3-fluoropyridine (**1b**; 5.3 g, 25 mmol); colorless prisms; m.p. 192−194 °C (from ethyl acetate); yield: 4.7 g (74%). ^{1}H NMR (D_3CCOCD_3): δ = 8.48 (s) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 161.4 (s), 152.8 (d, J = 265 Hz), 146.3 (d, J = 6 Hz), 131.4 (d, J = 21 Hz), 128.8 (d, J = 24 Hz), 128.7 (s) ppm. $C_6H_2BrClFNO_2$ (254.45): calcd. C 28.32, H 0.79; found C 28.38, H 0.86.

5-Chloro-3-fluoro-2-iodo-4-pyridinecarboxylic Acid (2c): Analogously from 5-chloro-3-fluoro-2-iodopyridine (**1c**; 6.4 g, 25 mmol); colorless prisms; m.p. 217 °C (decomp.; from methanol); yield: 6.3 g (84%). ^{1}H NMR (D_3CCOCD_3): δ = 8.49 (s) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 161.4 (s), 155.6 (d, J = 262 Hz), 147.4 (d, J = 5 Hz), 129.7 (d, J = 21 Hz), 129.0 (s), 105.2 (d, J = 29 Hz) ppm. $C_6H_2ClFINO_2$ (301.44): calcd. C 23.91, H 0.67; found C 23.85, H 0.65.

3-Chloro-5-fluoro-4-pyridinecarboxylic Acid (2d): A solution of 3-chloro-5-fluoropyridine (**1d**; 3.3 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) was kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured on an excess of freshly crushed solid carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (50 mL) and washed with diethyl ether (2 × 15 mL). When the aqueous phase was acidified to pH = 1, a precipitate formed which was collected by filtration; colorless needles; m.p. 207−208 °C (dec.; from methanol); yield: 3.7 g (85%). ^{1}H NMR (D_3CCOCD_3): δ = 8.65 (s, 1 H), 8.62 (s, broad, 1 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 162.2 (s), 155.9 (d, J = 263 Hz), 146.7 (d, J = 5 Hz), 138.0 (d, J = 23 Hz), 130.4 (d, J = 19 Hz), 128.7 (s) ppm. $C_6H_3ClFNO_2$ (175.55): calcd. C 41.05, H 1.72; found C 41.23, H 1.87.

3. 4-Iodo-Substituted Di- and Trihalopyridines

2,5-Dichloro-3-fluoro-4-iodopyridine (3a): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,5-dichloro-3-fluoropyridine (**1a**; 4.1 g, 25 mmol) were consecutively added to a solution of butyllithium (25 mmol) in tetrahydrofuran (35 mL) and hexanes (15 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, iodine (6.3 g, 25 mmol) in tetrahydrofuran (20 mL) was added. After 1 h at −75 °C, the mixture was warmed up to 25 °C and water (30 mL) and diethyl ether (10 mL) were added. The organic phase was decanted, washed with a saturated aqueous solution (20 mL) of sodium thiosulfate, dried and the solvents evaporated; colorless cubes; m.p. 114−116 °C (from chloroform); yield: 5.8 g (80%). ^{1}H NMR: δ = 8.18 (s) ppm. ^{13}C NMR: δ = 155.4 (d, J = 262 Hz), 142.5 (s), 136.8 (s), 136.0 (d, J = 23 Hz), 99.5 (d, J = 26 Hz) ppm. C_5HCl_2FIN (291.87): calcd. C 20.58, H 0.35; found C 20.61, H 0.29.

2-Bromo-5-chloro-3-fluoro-4-iodopyridine (3b): Analogously from 2-bromo-5-chloro-3-fluoropyridine (**1b**; 5.3 g, 25 mmol); colorless prisms; m.p. 111−114 °C (from ethyl acetate); yield: 6.4 g (76%). ^{1}H NMR: δ = 8.20 (s) ppm. ^{13}C NMR: δ = 156.6 (d, J = 261 Hz), 143.3 (d, J = 6 Hz), 137.4 (s), 126.2 (d, J = 27 Hz), 99.0 (d, J = 26 Hz) ppm. $C_5HBrClFIN$ (336.33): calcd. C 17.86, H 0.30; found C 17.93, H 0.50.

5-Chloro-3-fluoro-2,4-diiodopyridine (3c): Analogously from 5-chloro-3-fluoro-2-iodopyridine (**1c**; 6.4 g, 25 mmol); colorless needles; m.p. 120−121 °C (from methanol); yield: 8.2 g (86%). ^{1}H NMR: δ = 8.18 (s) ppm. ^{13}C NMR: δ = 159.1 (d, J = 258 Hz), 144.5 (d, J = 5 Hz), 137.8 (s), 101.6 (d, J = 33 Hz), 97.3 (d, J = 28 Hz) ppm. C_5HClFI_2N (383.33): calcd. C 15.67, H 0.26; found C 15.78, H 0.38.

3-Chloro-5-fluoro-4-iodopyridine (3d): As described for compound **2d** starting from 3-chloro-5-fluoropyridine (**1d**; 3.3 g, 25 mmol) but adding, after 2 h at −75 °C, a solution of iodine (6.3 g, 25 mmol) in tetrahydrofuran (20 mL). At 25 °C, water (30 mL) and diethyl ether (10 mL) were added. The organic phase was decanted, washed with a saturated aqueous solution (20 mL) of sodium thiosulfate, dried with sodium sulfate, filtered and the solvents evaporated; colorless needles; m.p. 113−115 °C (from methanol); yield: 5.7 g (89%). ^{1}H NMR: δ = 8.37 (s, 1 H), 8.19 (s, broad, 1 H) ppm. ^{13}C NMR: δ = 159.9 (d, J = 259 Hz), 144.3 (d, J = 4 Hz), 137.7 (s), 134.8 (d, J = 27 Hz), 98.6 (d, J = 24 Hz) ppm. C_5H_2ClFIN (257.43): calcd. C 23.33, H 0.78; found C 23.26, H 0.77.

4. 6-Iodo-Substituted Di- and Trihalopyridines

2,5-Dichloro-3-fluoro-6-iodopyridine (4a): At −100 °C, 2,2,6,6-tetramethylpiperidine (8.5 mL, 7.1 g, 50 mmol) and 2,5-dichloro-3-fluoro-4-iodopyridine (**3a**; 7.3 g, 25 mmol) were consecutively added to a solution of butyllithium (50 mmol) in neat tetrahydrofuran (50 mL). After 15 min at −75 °C, the mixture was treated with methanol before being poured into water (30 mL) and diethyl ether (10 mL). The organic phases were washed with brine (3 × 50 mL). According to gas chromatography (30 m, DB-WAX, 120 °C; 30 m, DB-23, 120 °C; "internal standard": nonadecane), it contained 22% of 2,5-dichloro-3-fluoropyridine (**1a**) and 51% of the iodo compound **4a**. The latter was isolated upon distillation as an oily liquid which rapidly solidified; colorless needles; m.p. 52−54 °C (from ethanol); b.p. 91−92 °C/4 Torr; yield: 3.4 g (46%). ^{1}H NMR: δ = 7.54 (d, J = 7.3 Hz) ppm. ^{13}C NMR: δ = 154.2 (d, J = 267 Hz), 137.8 (s), 136.2 (d, J = 20 Hz), 124.9 (d, J = 22 Hz), 111.6 (d, J = 3 Hz) ppm. C_5HCl_2FIN (291.87): calcd.C 20.58, H 0.35; found C 20.59, H 0.70.

2-Bromo-5-chloro-3-fluoro-6-iodopyridine (4b): Analogously from 2-bromo-5-chloro-3-fluoro-4-iodopyridine (**3b**; 8.4 g, 25 mmol). According to gas chromatography (30 m, DB-WAX, 100 °C → 200 °C; 30 m, DB-23, 100 °C → 200 °C; heating rate 25 °C/min; "internal standard": nonadecane), the crude product contained 18%

of 2-bromo-5-chloro-3-fluoropyridine (**1b**) and 66% of the iodo derivative **4b**. Upon distillation a viscous liquid was collected that slowly crystallized; colorless needles; m.p. 60−62 °C (from ethanol); b.p. 110−112 °C/2 Torr; yield: 4.8 g (57%). ^{1}H NMR: δ = 7.47 (d, *J* = 6.7 Hz) ppm. ^{13}C NMR: δ = 155.7 (d, *J* = 266 Hz), 138.3 (s), 126.5 (d, *J* = 24 Hz), 124.3 (d, *J* = 23 Hz), 112.2 (d, *J* = 4 Hz) ppm. $C_5HBrClFIN$ (336.33): calcd. C 17.86, H 0.30; found C 18.04, H 0.33.

3-Chloro-5-fluoro-2,6-diiodopyridine (4c): Analogously from 5-chloro-3-fluoro-2,4-diiodopyridine (**3c**; 9.6 g, 25 mmol). According to gas chromatography (30 m, DB-WAX, 140 °C → 200 °C; 30 m, DB-23, 140 °C → 200 °C; heating rate 25 °C/min; "internal standard": nonadecane), the crude product contained 39% of 5-chloro-3-fluoro-2-iodopyridine (**1c**) and 30% of iodo derivative **4c**. The latter compound was isolated by trituration of the crude product with hexanes; colorless prisms; m.p. 105−106 °C (from hexanes); yield: 2.2 g (23%). ^{1}H NMR: δ = 7.34 (d, *J* = 6.3 Hz) ppm. ^{13}C NMR: δ = 158.8 (d, *J* = 264 Hz), 138.7 (d, *J* = 3 Hz), 122.8 (d, *J* = 24 Hz), 113.4 (d, *J* = 3 Hz), 102.2 (d, *J* = 29 Hz) ppm. C_5HClFI_2N (383.33): calcd. C 15.67, H 0.26; found C 16.04, H 0.38.

3-Chloro-5-fluoro-2-iodopyridine (4d): Butyllithium (17 mmol) in hexanes (10 mL) was added to a solution of 3-chloro-5-fluoro-2,6-diiodopyridine (**4c**; 5.7 g, 15 mmol) in toluene (20 mL) cooled in a dry ice/methanol bath. After 15 min at −75 °C, the mixture was treated with methanol before being poured into water (20 mL). The organic layer was washed with water (15 mL), dried and the solvents were evaporated. The product was purified by crystallization from hexanes; colorless prisms; m.p. 82−84 °C; yield: 2.3 g (60%). ^{1}H NMR: δ = 8.24 (dd, *J* = 2.7, 0.5 Hz, 1 H), 7.49 (dd, *J* = 7.9, 2.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 158.7 (d, *J* = 264 Hz), 138.5 (d, *J* = 3 Hz), 136.7 (d, *J* = 23 Hz), 124.1 (d, *J* = 21 Hz), 114.3 (s) ppm. C_5H_2ClFIN (257.43): calcd. C 23.33, H 0.78; found C 23.30, H 0.76.

5. Di- and Trihalo-6-iodo-4-pyridinecarboxylic Acids

2,5-Dichloro-3-fluoro-6-iodo-4-pyridinecarboxylic Acid (5a): Diisopropylamine (2.1 mL, 1.5 g, 15 mmol) and 2,5-dichloro-3-fluoro-6-iodopyridine (**4a**; 4.4 g, 15 mmol) were consecutively 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 on an excess of freshly crushed solid carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (75 mL), washed with diethyl ether (3 × 15 mL), acidified with hydrochloric acid to pH = 1 and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried and the solvents evaporated. The product was purified by crystallization from ethyl acetate and hexanes; colorless prisms; m.p. 224−226 °C (decomp.); yield: 4.5 g (89%). ^{13}C NMR (D_3CCOCD_3): δ = 160.2 (s), 150.6 (d, *J* = 266 Hz), 136.1 (d, *J* = 20 Hz), 133.6 (s), 131.3 (d, *J* = 20 Hz), 113.1 (d, *J* = 4 Hz) ppm. $C_6HCl_2FINO_2$ (335.89): calcd. C 21.45, H 0.30; found C 21.31, H 0.36.

2-Bromo-5-chloro-3-fluoro-6-iodo-4-pyridinecarboxylic Acid (5b): Analogously from 2-bromo-5-chloro-3-fluoro-6-iodopyridine (**4b**; 5.0 g, 15 mmol); colorless needles; m.p. 233−236 °C (decomp.; from ethyl acetate and hexanes.); yield: 5.0 g (88%). ^{13}C NMR (D_3CCOCD_3): δ = 161.0 (s), 152.9 (d, *J* = 265 Hz), 134.9 (s), 131.6 (d, *J* = 21 Hz), 127.5 (d, *J* = 24 Hz), 114.7 (d, *J* = 3 Hz) ppm. $C_6HBrClFINO_2$ (380.34): calcd. C 18.95, H 0.26; found C 19.10, H 0.18.

3-Chloro-5-fluoro-2,6-diiodo-4-pyridinecarboxylic Acid (5c): Analogously from 3-chloro-5-fluoro-2,6-diiodopyridine (**4c**; 5.7 g, 15 mmol); colorless prisms; m.p. 238 °C (dec.; from ethyl acetate and hexanes); yield: 3.1 g (49%), which improved to 5.3 g (82%) when the reaction time was extended from 2 h to 6 h. ^{13}C NMR (D_3CCOCD_3): δ = 161.0 (s), 155.9 (d, *J* = 262 Hz), 134.9 (s), 130.0 (d, *J* = 23 Hz), 115.7 (s), 104.3 (d, *J* = 30 Hz) ppm. $C_6HClFI_2NO_2$ (427.34): calcd. C 16.86, H 0.24; found C 16.93, H 0.32.

3-Chloro-5-fluoro-2-iodo-4-pyridinecarboxylic Acid (5d): Diisopropylamine (1.4 mL, 1.0 g, 10 mmol) and 3-chloro-5-fluoro-2-iodopyridine (**4d**; 2.6 g, 10 mmol) were consecutively added to a solution of butyllithium (10 mmol) in tetrahydrofuran (13 mL) and hexanes (7 mL) kept in a dry ice/methanol bath. After 2 h at −75 °C, the mixture was poured on an excess of freshly crushed solid carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (50 mL), washed with diethyl ether (3 × 10 mL), acidified to pH = 1 and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried and the solvents evaporated. The product was purified by crystallization from ethyl acetate; colorless needles; m.p. 225−228 °C (dec.); yield: 2.6 g (85%). ^{1}H NMR (D_3CCOCD_3): δ = 8.54 (s) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 161.8 (s), 155.8 (d, *J* = 264 Hz), 138.5 (d, *J* = 24 Hz), 134.5 (s), 131.4 (d, *J* = 19 Hz), 116.3 (d, *J* = 3 Hz) ppm. $C_6H_2ClFINO_2$ (301.44): calcd. C 23.91, H 0.67; found C 24.04, H 0.62.

6. Di- and Trihalo-Substituted 2-Pyridinecarboxylic Acids

3,6-Dichloro-5-fluoro-2-pyridinecarboxylic Acid (6a): Isopropylmagnesium chloride (15 mmol) in tetrahydrofuran (7.5 mL) was added to 2,5-dichloro-3-fluoro-6-iodopyridine (**4a**; 4.4 g, 15 mmol) in tetrahydrofuran (10 mL) cooled in a dry ice/methanol bath. After 1 h at −75 °C, the mixture was poured on an excess of freshly crushed solid carbon dioxide and worked up as described above (see acid **5a**) to give colorless prisms; m.p. 146−149 °C (from ethyl acetate and hexanes); yield 2.5 g (80%). ^{1}H NMR (D_3CCOCD_3): δ = 8.18 (d, *J* = 7.8 Hz) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 163.6 (s), 156.0 (d, *J* = 268 Hz), 144.1 (d, *J* = 6 Hz), 136.9 (d, *J* = 20 Hz), 131.3 (d, *J* = 3 Hz), 122.8 (d, *J* = 22 Hz) ppm. $C_6H_2Cl_2FNO_2$ (209.99): calcd. C 34.32, H 0.96; found C 34.24, H 0.98.

6-Bromo-3-chloro-5-fluoro-2-pyridinecarboxylic Acid (6b): Analogously from 2-bromo-5-chloro-3-fluoro-6-iodopyridine (**4b**; 5.0 g, 15 mmol); colorless prisms; m.p. 156−158 °C (from ethyl acetate and hexanes); yield 3.0 g (79%). ^{1}H NMR (D_3CCOCD_3): δ = 8.11 (d, *J* = 7.4 Hz) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 163.5 (s), 157.5 (d, *J* = 267 Hz), 144.8 (d, *J* = 5 Hz), 131.8 (d, *J* = 4 Hz), 128.1 (d, *J* = 23 Hz), 127.4 (d, *J* = 24 Hz) ppm. $C_6H_2BrClFNO_2$ (254.45): calcd. C 28.32, H 0.79; found C 28.43, H 0.80.

3-Chloro-5-fluoro-6-iodo-2-pyridinecarboxylic Acid (6c): 6-Bromo-3-chloro-5-fluoro-2-pyridinecarboxylic acid (**6b**; 13 g, 50 mmol) was dissolved in methanol (50 mL) in the presence of sulfuric acid 96% (0.14 mL, 2.5 mmol) and heated under reflux for 15 h. After addition of a saturated aqueous solution of sodium bicarbonate (70 mL) and diethyl ether (0.10 L), the organic layer was separated and the solvents were evaporated. Crystallization from a 1:1 (v/v) mixture of diethyl ether and hexanes afforded *methyl 6-bromo-3-chloro-5-fluoro-2-pyridinecarboxylate* as colorless needles; m.p. 87−88 °C; yield: 9.9 g (74%). ^{1}H NMR: δ = 7.59 (d, *J* = 6.8 Hz, 1 H), 4.00 (s, 3 H) ppm. ^{13}C NMR: δ = 162.8 (s), 156.6 (d, *J* = 270 Hz), 143.1 (d, *J* = 5 Hz), 131.7 (d, *J* = 3 Hz), 127.4 (d, *J* = 24 Hz), 126.5 (d, *J* = 22 Hz), 53.3 (s) ppm. $C_7H_4BrClFNO_2$ (268.47): calcd. C 31.32, H 1.50; found C 31.52, H 1.62. Under

nitrogen, sodium iodide (7.5 g, 50 mmol) and chlorotrimethylsilane (5.4 g, 6.5 mL, 50 mmol) were consecutively added to a solution of this 6-bromo ester (6.7 g, 25 mmol) in acetonitrile (25 mL). After 6 h at reflux, water (30 mL) and diethyl ether (25 mL) were added and the organic phase was decanted, washed with a saturated aqueous solution of sodium thiosulfate (20 mL), dried with sodium sulfate and filtered. Concentration to dryness and crystallization from 1:1 (v/v) mixture of diethyl ether and hexanes gave *methyl 3-chloro-5-fluoro-6-iodo-2-pyridinecarboxylate* as colorless needles; m.p. 70−71 °C; yield: 5.4 g (69%). ^{1}H NMR: δ = 7.45 (d, *J* = 7.2 Hz, 1 H), 3.99 (s, 3 H) ppm. ^{13}C NMR: δ = 162.9 (s), 159.0 (d, *J* = 268 Hz), 144.5 (d, *J* = 5 Hz), 132.0 (d, *J* = 4 Hz), 124.7 (d, *J* = 24 Hz), 103.3 (d, *J* = 30 Hz), 53.3 (s) ppm. $C_7H_4ClFINO_2$ (315.47): calcd. C 26.65, H 1.28; found C 26.81, H 1.34. This 6-iodo ester (3.1 g, 10 mmol) and lithium hydroxide monohydrate (0.84 g, 20 mmol) were dissolved in 10 mL of a 3:1 (v/v) mixture of tetrahydrofuran and water. After 1 h at 25 °C, the mixture was diluted with water (10 mL) and acidified to pH = 1. Extraction with diethyl ether (3 × 15 mL), drying with sodium sulfate, filtration, evaporation of the solvents and crystallization from chloroform afforded compound **6c** as colorless needles; m.p. 127−129 °C; yield: 2.7 g (91%). ^{1}H NMR (D_3CCOCD_3): δ = 7.97 (d, *J* = 7.0 Hz, 1 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 163.6 (s), 160.5 (d, *J* = 265 Hz), 145.8 (d, *J* = 4 Hz), 132.1 (d, *J* = 4 Hz), 126.1 (d, *J* = 25 Hz), 103.8 (d, *J* = 30 Hz) ppm. $C_6H_2ClFINO_2$ (301.44): calcd. C 23.91, H 0.67; found C 24.16, H 0.76.

3-Chloro-5-fluoro-2-pyridinecarboxylic Acid (6d): 3-Chloro-5-fluoro-2-iodopyridine (**4d**; 1.3 g, 5.0 mmol) was added to a solution of butyllithium (5 mmol) in toluene (7 mL) and hexanes (3 mL) kept in a dry ice/methanol bath. After 1 h at −75 °C, the reaction mixture was poured on an excess of freshly crushed solid carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (50 mL), washed with diethyl ether (2 × 10 mL), acidified to pH = 1 and extracted with diethyl ether (3 × 15 mL). Drying with sodium sulfate, filtration, evaporation of the solvent and crystallization from chloroform gave colorless needles; m.p. 142−144 °C (dec.); yield: 0.69 g (79%). ^{1}H NMR (D_3CCOCD_3): δ = 8.59 (d, *J* = 2.5 Hz, 1 H), 8.02 (dd, *J* = 8.4, 2.5 Hz, 1 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 164.4 (s), 160.5 (d, *J* = 264 Hz), 144.8 (s), 136.7 (d, *J* = 24 Hz), 132.0 (d, *J* = 5 Hz), 127.0 (d, *J* = 22 Hz) ppm. $C_6H_3ClFNO_2$ (175.55): calcd. C 41.05, H 1.72; found C 41.11, H 1.83. Compound **6d** has also been obtained from 6-bromo-3-chloro-5-fluoro-2-pyridinecarboxylic acid (**6b**; 6.4 g, 25 mmol) with zinc powder (2.4 g, 37 mmol) in an aqueous solution of sodium hydroxide (2.0 g, 20 mL, 50 mmol) stirring at 25 °C for 6 h. After filtration and washing with water (75 mL), the filtrate was acidified to pH = 1 with hydrochloric acid. Extraction with diethyl ether (6 × 20 mL), evaporation of the solvent and crystallization from chloroform afforded 2.9 g (67%) of colorless needles.

5-Chloro-3-fluoro-6-iodo-2-pyridinecarboxylic Acid (7): Butyllithium (15 mmol) in hexanes (10 mL) was added to a solution of 3-chloro-5-fluoro-2,6-diiodopyridine (**4c**; 5.7 g, 15 mmol) in toluene (20 mL) cooled in a dry ice/methanol bath. After 15 min at −75 °C, the mixture was poured on an excess of freshly crushed solid carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (50 mL) washed with diethyl ether (3 × 15 mL), acidified with hydrochloric acid to pH = 1 and extracted with ethyl acetate (3 × 20 mL). One twentieth of the solution was withdrawn and, after addition of a known amount (approx. 10 mg) of 2-biphenylcarboxylic acid as an internal reference compound, treated with ethereal diazomethane until the yellow color persisted, and analyzed by gas chromatography (30 m, DB-23, 170 °C; 30 m, DB-WAX, 180 °C). By comparison of the peak retention times with those of authentic samples and the peak areas relative to that of the reference compound after response correction by means of calibration factors derived from authentic mixtures, the crude product contained 65% of compound **7**, 7% of 3-chloro-5-fluoro-2,6-dicarboxylic acid (**8**; see below) and 5% of compound **6c**. The remainder of the dried organic solution was concentrated. By trituration of the solid obtained with chloroform (2 × 10 mL) and recrystallization from ethyl acetate, acid **7** was obtained as colorless prisms; m.p. 171−172 °C (decomp.); yield: 1.6 g (35%). ^{1}H NMR (D_3CCOCD_3): δ = 8.09 (d, *J* = 9.5 Hz) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 162.0 (d, *J* = 6 Hz), 159.7 (d, *J* = 275 Hz), 142.9 (d, *J* = 5 Hz), 136.7 (d, *J* = 10 Hz), 127.6 (d, *J* = 24 Hz), 114.0 (d, *J* = 3 Hz) ppm. $C_6H_2ClFINO_2$ (301.44): calcd. C 23.91, H 0.67; found C 23.80, H 0.69.

3-Chloro-5-fluoro-2,6-pyridinedicarboxylic Acid (8): Butyllithium (20 mmol) in hexanes (13 mL) was added to a solution of 3-chloro-5-fluoro-2,6-diiodopyridine (**4c**; 3.8 g, 10 mmol) in toluene (13 mL) kept in a dry ice/methanol bath. After 15 min at −75 °C, the mixture was poured on an excess of freshly crushed solid carbon dioxide. After addition of water (50 mL), acidification to pH = 1, extraction with ethyl acetate (3 × 10 mL), drying with sodium sulfate and evaporation of the solvent, the product was crystallized from a 5:1 (v/v) mixture of chloroform and ethyl acetate; colorless prisms; m.p. 128−129 °C (dec.); yield: 0.85 g (39%). ^{1}H NMR (D_3CCOCD_3): δ = 8.11 (d, *J* = 9.5 Hz) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 163.6 (s), 162.1 (d, *J* = 6 Hz), 160.2 (d, *J* = 278 Hz), 143.7 (d, *J* = 5 Hz), 137.7 (d, *J* = 6 Hz), 135.2 (d, *J* = 10 Hz), 129.9 (d, *J* = 23 Hz) ppm. $C_6H_2ClFINO_2$ (219.55): calcd. C 38.29, H 1.38; found C 38.01, H 1.32.

5-Chloro-3-fluoro-2-pyridinecarboxylic Acid (9): 5-Chloro-3-fluoro-2-iodopyridine (**1c**; 3.9 g, 15 mmol) was added to a solution of butyllithium (15 mmol) in toluene (20 mL) and hexanes (10 mL) kept in a dry ice/methanol bath. After 1 h at −75 °C, the reaction mixture was poured on an excess of freshly crushed solid carbon dioxide. After evaporation of the volatiles, the residue was taken up in water (50 mL), washed with diethyl ether (2 × 15 mL) and acidified to pH = 1. The precipitate formed was collected, dried and recrystallized from ethanol; colorless prisms; m.p. 172−174 °C; yield 2.5 g (94%). ^{1}H NMR (D_3CCOCD_3): δ = 8.57 (dd, *J* = 1.9, 0.9 Hz, 1 H), 8.05 (dd, *J* = 9.9, 1.9 Hz, 1 H) ppm. ^{13}C NMR (D_3CCOCD_3): δ = 162.8 (d, *J* = 6 Hz), 159.7 (d, *J* = 275 Hz), 144.8 (d, *J* = 5 Hz), 136.5 (d, *J* = 4 Hz), 136.0 (d, *J* = 9 Hz), 127.0 (d, *J* = 23 Hz) ppm. $C_6H_3ClFNO_2$ (175.55): calcd. C 41.05, H 1.72; found C 40.91, H 2.08. As described above but starting from 2-bromo-5-chloro-3-fluoropyridine (**1b**; 3.1 g, 15 mmol) compound **9** has been obtained in 71% yield.

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