The Structural Proliferation of 2,6-Difluoropyridine through Organometallic Intermediates

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Contrary to a literature claim, 2,6-difluoropyridine-3-carboxaldehyde can be readily prepared by consecutive treatment of 2,6-difluoropyridine with lithium diisopropylamide and *N*,*N*-dimethylformamide. Regioselective displacements of fluorine from the aldehyde by nucleophiles were carried out. To demonstrate the versatility of the organometallic approach, some two dozens of further 2,6-difluoropyridine derivatives were prepared applying a combination of modern organometallic methods such as site selective hydrogen/metal and halogen/metal permutations and deprotonation-triggered heavy halogen migrations.

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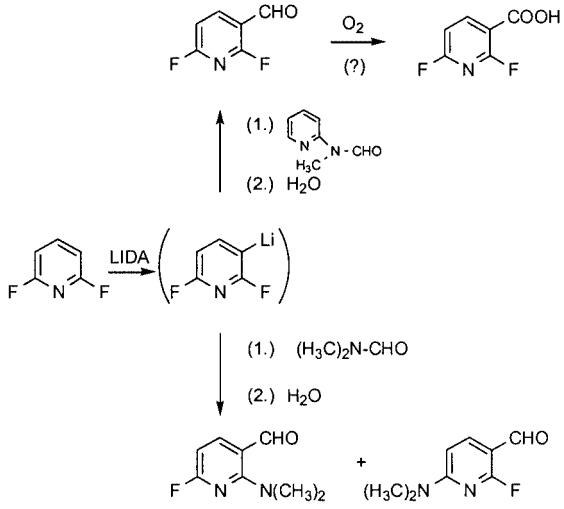
Introduction

Although all 16 dichloropyridinecarboxylic acids are known,[1,2] only a single difluoro analog has been reported so far. After treating the commercially available 2,6-difluoropyridine in tetrahydrofuran with lithium diisopropylamide (LIDA) in the same way as this had been previously been performed with 2-fluoropyridine[3,4] and trapping the organometallic intermediate with *N*-methyl-*N*-(pyridin-2-yl)formamide, G. M. Shutske et al.[5] isolated a crude product mixture which contained the allegedly air-sensitive 2,6-difluoropyridine-3-carboxaldehyde. Subsequent oxidation provided the 2,6-difluoropyridine-3-carboxylic acid in poor yield. When the lithiated 2,6-difluoropyridine was treated with *N*,*N*-dimethylformamide, the only identified compounds were a 2:3 mixture (66%) of 2-dimethylamino-6-fluoropyridine-3-carbaldehyde and 6-dimethylamino-2-fluoropyridine-3-carbaldehyde. The problems encountered by the authors of that work raised our curiosity and encouraged us to embark on the systematic study described below.



Results

The first step was to convert 2,6-difluoropyridine through the 3-lithiated species into a variety of 3-hetero- and 3-carbosubstituted derivatives. Thus the reaction with iodine afforded 2,6-difluoro-3-iodopyridine (**1**; 96%), with 1,2-dibromo-1,1,2,2-tetrafluoroethane 3-bromo-2,6-difluoropyridine (**2**; 72%), with 1,1,2-trichloro-1,2,2-trifluoroethane 3-chloro-2,6-difluoropyridine (**3**; 76%), with fluorodimethoxyborane[6,7] and ensuing treatment with alkaline hydrogen peroxide 2,6-difluoropyridin-3-ol (**4**; 80%), with chlorotrimethylsilane (2,6-difluoropyridin-3-yl)trimethylsilane (**5**; 95%), with acetone 2,6-difluoro-α,α-dimethyl-3-pyri-

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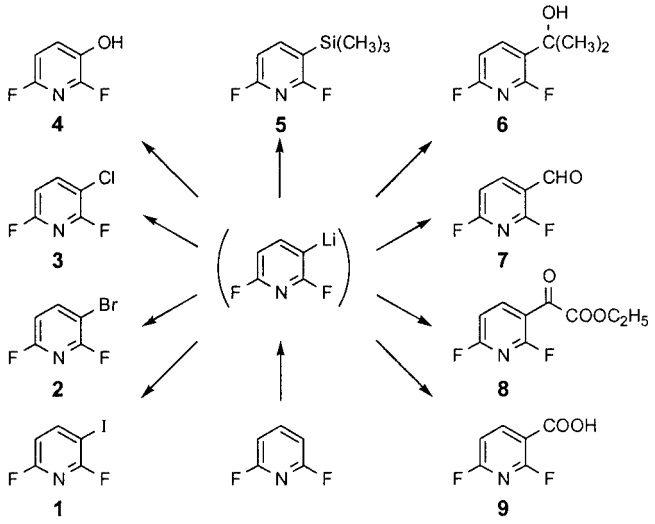
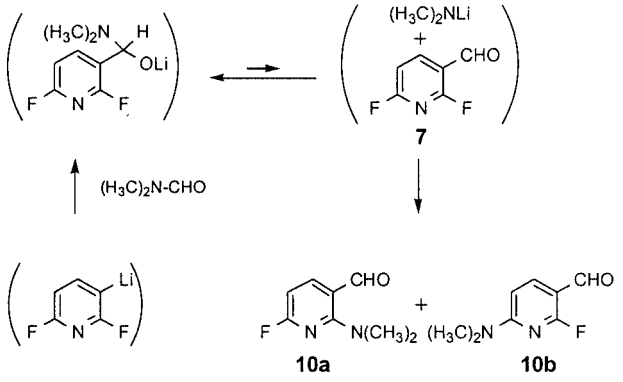
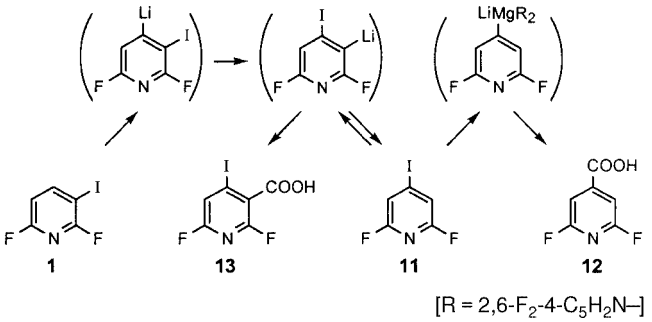
dinemethanol (**6**; 97%), with *N*,*N*-dimethylformamide 2,6-difluoropyridine-3-carbaldehyde (**7**; 72%), with diethyl oxalate ethyl 2-(2,6-difluoropyridin-3-yl)-2-oxoacetate (**8**; 58%), and with dry ice 2,6-difluoropyridine-3-carboxylic acid (**9**; 94%).



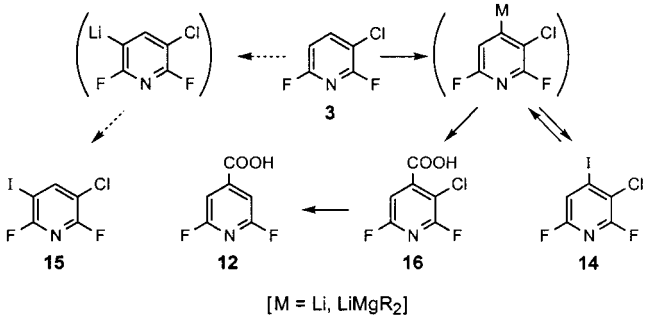
To obtain the aldehyde **7** in high yield, the adduct formed with *N*,*N*-dimethylformamide had to be neutralized at −75 °C. At higher temperatures, the lithium (α-dimethylamino)alkoxide intermediate (*O*-lithiated hemiaminal) was found to dissociate reversibly to the aldehyde **7** and lithium dimethylamide. These two components entered into a nucleophilic heteroaromatic substitution process giving eventually rise to the regioisomeric mixture of (dimethylamino)fluoropyridine-3-carbaldehydes **10a** and **10b** mentioned above in a 1:10 ratio.



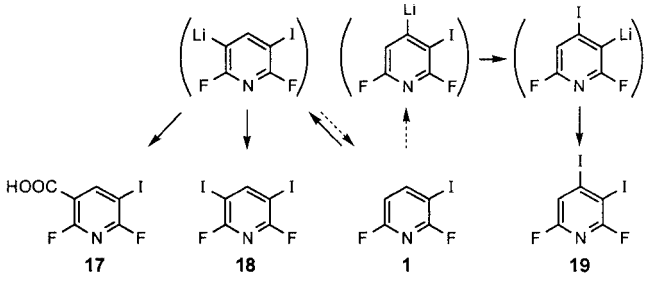
The iodo compound **1** was isomerized by LIDA-promoted heavy halogen migration[8,9] to 2,6-difluoro-4-iodopyridine (**11**; 81%) which was purified by crystallization thus removing unaltered starting material (**1**; 16%). Product **11** was transformed to the 2,6-difluoropyridine-4-carboxylic acid (**12**; 87%) by consecutive halogen/metal permutation and carboxylation. To obtain the 2,6-difluoro-4-iodopyridine-3-carboxylic acid (**13**; 91%), 2,6-difluro-4-iodopyridine (**11**) was treated first with LIDA and subsequently with dry ice.



Another facile access to the acid **12** involved the LIDA-mediated deprotonation of the chloro derivative **3**. It occurred with poor regioselectivity leading to a mixture of 3-chloro-2,6-difluoro-4-iodopyridine (**14**; 77%) and 3-chloro-2,6-difluoro-5-iodopyridine (**15**; 15%) after iodination. Obviously the intrinsically higher acidity[10,11] of the pyridine 4-position and the stronger neighboring group assistance[12] provided by a fluorine compared with a chlorine atom compensate each other to quite some extent. The main component **14** was again purified by crystallization. Carboxylation of the magnesium species generated from it by halogen/metal permutation afforded the 3-chloro-2,6-difluoropyridine-4-carboxylic acid (**16**; 90%). Transfer hydrogenation gave the 2,6-difluoropyridine-4-carboxylic acid (**12**; 94%).



Iodine being the least acidifying of all halogens, proton abstraction from 2,6-difluoro-3-iodopyridine (**1**) occurred initially, i.e. upon 5−15 min of exposure to LIDA, almost exclusively at the 5- rather than the 4-position. Trapping with dry ice or iodine provided the 2,6-difluoro-5-iodopyridine-3-carboxylic acid (**17**; 72%) or the 2,6-difluoro-3,5-diiodopyridine (**18**; 81%) respectively. However, when the reaction time with LIDA was prolonged to 30 h, reversible return to the starting material **1** set the stage for a sporadic deprotonation at the 4-position. This unleashed instan-



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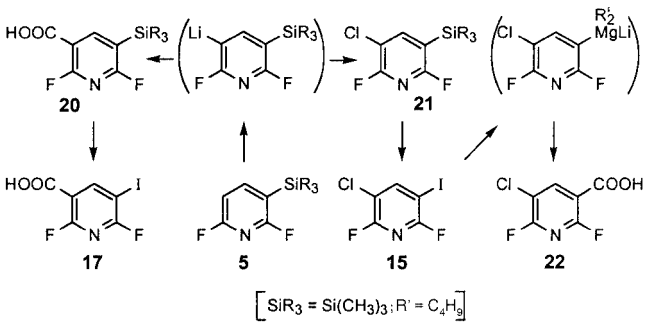
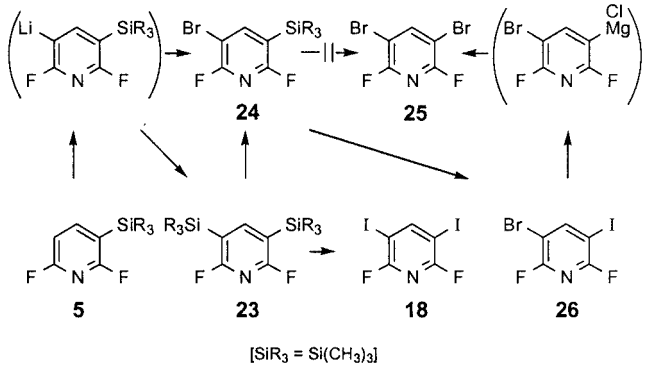
taneously a basicity gradient-driven heavy halogenmigration[9] producing the isomeric 2,6-difluoro-3,4-diiodopyridine (**19**; 80%) after iodination.

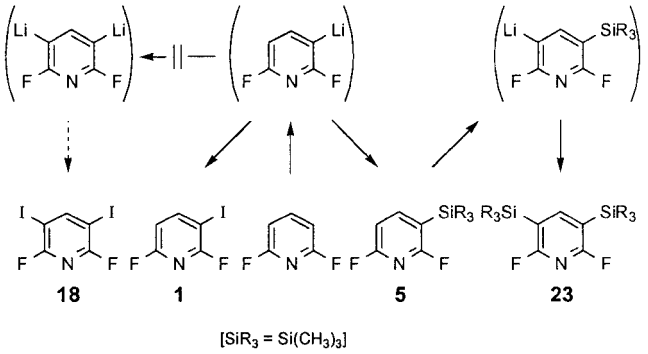
The LIDA-promoted deprotonation of (2,6-difluoropyridin-3-yl)trimethylsilane (**5**) also took place at the 5-position. The intermediate was trapped with dry ice or 1,1,2-trichloro-1,2,2-trifluoroethane to give 2,6-difluoro-5-(trimethylsilyl)pyridine-3-carboxylic acid (**20**; 98%) or (5-chloro-2,6-difluoropyridin-3-yl)trimethylsilane (**21**; 97%) respectively. Using iodine chloride, the acid **20** was iododesilylated to the 2,6-difluoro-5-iodopyridine-3-carboxylic acid (**17**; 96%). Under the same conditions, the chlorosilane **21** gave 3-chloro-2,6-difluoro-5-iodopyridine (**15**; 93%). The latter compound was converted into the 5-chloro-2,6-difluoropyridine-3-carboxylic acid (**22**; 91%), by halogen/metal permutation followed by carboxylation.



Condensation of the 5-lithiated (2,6-difluoropyridin-3-yl) trimethylsilane (**5**) with chlorotrimethylsilane provided the (2,6-difluoropyridin-3,5-diyl)bis(trimethylsilane) (**23**; 94%) which reacted with iodine chloride smoothly under double iododesilylation to afford the 2,6-difluoro-3,5-diiodopyridine (**18**; 93%) whereas the bromodesilylation effected with elemental bromine rigorously stopped after a unilateral displacement producing (5-bromo-2,6-difluoropyridin-3-yl)trimethylsilane (**24**; 95%). 3,5-Dibromo-2,6-difluoropyridine (**25**; 90%) was found to be accessible only indirectly by subjecting 3-bromo-2,6-difluoro-5-iodopyridylsilane (**26**) to element-specific halogen/metal permutation and subsequent bromination. The latter precursor **26** was readily prepared by iododesilylation of the bromopyridylsilane **24** in 91% yield.



The bis(silane) **23** was also obtained in 92% yield when 2,6-difluoropyridine was exposed to the simultaneous action of LIDA and chlorotrimethylsilane, both in twofold excess. This result does by no means imply the intermediacy of 3,5-dilithiated species. When 2,6-difluoropyridine was consecutively treated with each time two equivalents of LIDA and molecular iodine, only the monoiodopyridine **1** and not even trace amounts of the diiodo compound **18** were formed. Chlorotrimethylsilane is known to react with bulky reagents such as lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidide and *tert*-butyllithium much more slowly than with aryllithiums.[13–16] Consequently, organometallic intermediates such as 2,6-difluoropyridin-3-yllithium and 2,6-difluoro-5-(trimethylsilyl)pyridine-3-yllithium can be generated in situ, in other words in the presence of the trapping reagent chlorotrimethylsilane.



Experimental Section

Details regarding standard operations and abbreviations were explained in previous publications from this laboratory.[11,17,18] ^{1}H and ^{13}C NMR spectra were recorded of samples dissolved in deuterochloroform or, if marked by an asterisk, in perdeuteroacetone. Chemical shifts are listed relative to tetramethylsilane as an internal standard.

2,6-Difluoro-3-iodopyridine (1): Diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and 2,6-difluoropyridine (4.5 mL, 5.8 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (0.10 L) and hexanes (30 mL), cooled in a methanol/dry ice bath. After 45 min at −75 °C, the mixture was treated with a solution of iodine (13 g, 50 mmol) in tetrahydrofuran (50 mL) before being washed with a 10% aqueous solution (25 mL) of sodium sulfite. The organic phase was dried and the volatiles evaporated. Crystallization of the residue from hexanes afforded colorless platelets; m.p. 40−42 °C; yield: 11.6 g (96%). ^{1}H NMR: δ = 8.20 (td, *J* = 8.1, 7.3 Hz, 1 H), 6.70 (dd, *J* = 8.3, 3.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.9 (dd, *J* = 248, 13 Hz), 160.1 (dd, *J* = 242, 14 Hz), 153.5 (dd, *J* = 7, 2 Hz), 108.2 (dd, *J* = 35, 6 Hz), 69.1 (dd, *J* = 41, 6 Hz) ppm. $C_5H_2F_2IN$ (240.98): calcd. C 24.92, H 0.84; found C 24.97, H 1.00. When lithium diisopropylamide was replaced by butyllithium (25 mmol) under otherwise identical conditions, 2,6-difluoro-4-iodopyridine (**11**; see below) was identified by gas chromatography (30 m, DB-1, 100 °C; 30 m, DB-WAX, 100 °C; calibrated internal standard: tridecane) as a by-product (7%) along with 2,6-difluoro-3-iodopyridine (**1**) as the main component (86%).

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3-Bromo-2,6-difluoropyridine (2): Analogously as described in the preceding paragraph with 1,2-dibromo-1,1,2,2-tetrafluoroethane (13.0 g, 50 mmol) instead of iodine. Upon distillation, the product was collected as a colorless liquid; b.p. 48−50 °C/12 Torr (ref.[19] 169.5 °C); n_D^{20} = 1.5137 (ref.[19] n_D^{25} = 1.5047); yield: 6.98 g (72%). ^{1}H NMR: δ = 8.04 (td, *J* = 8.3, 6.9 Hz, 1 H), 6.79 (dd, *J* = 8.3, 3.2 Hz, 1 H) ppm.

3-Chloro-2,6-difluoropyridine (3): Analogously as described for the preparation of product **1** using 1,1,2-trichloro-1,2,2-trifluoroethane (6.0 mL, 9.4 g, 50 mmol); colorless liquid; m.p. −8 to −10 °C; b.p. 43−45 °C/20 Torr (ref.[20] 151 °C); n_D^{20} = 1.4744 (ref.[19] n_D^{24} = 1.4739); yield: 5.68 g (76%). ^{1}H NMR: δ = 7.90 (td, *J* = 8.6, 6.7 Hz, 1 H), 6.85 (dd, *J* = 8.3, 3.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 159.3 (dd, *J* = 248, 13 Hz), 156.4 (dd, *J* = 246, 15 Hz), 144.5 (d, *J* = 8 Hz), 113.0 (dd, *J* = 31, 7 Hz), 107.3 (dd, *J* = 37, 7 Hz) ppm.

2,6-Difluoropyridin-3-ol (4): The mixture obtained by the reaction of butyllithium with diisopropylamine and 2,6-difluoropyridine was treated with fluorodimethoxyborane-diethyl ether complex[6,7] (9.4 mL, 8.2 g, 50 mmol). After evaporation of the volatiles and following the addition of a 30% aqueous hydrogen peroxide (5.2 mL, 5.7 g, 50 mmol) and a 3.0 M aqueous solution (50 mL) of sodium hydroxide (0.15 mol), the mixture was stirred for 45 min before being acidified with concentrated hydrochloric acid to pH 2 and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried and the solvents evaporated. Crystallization of the residue from ethyl acetate afforded colorless platelets; m.p. 124−126 °C; yield: 5.24 g (80%). ^{1}H NMR: δ = 7.44 (ddd, *J* = 9.9, 8.3, 6.7 Hz, 1 H), 6.67 (dd, *J* = 8.3, 3.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 152.9 (dd, *J* = 239, 11 Hz), 149.4 (dd, *J* = 241, 14 Hz), 136.9 (dd, *J* = 25, 6 Hz), 131.2 (t, *J* = 6 Hz), 106.0 (dd, *J* = 37, 6 Hz) ppm. $C_5H_3F_2NO$ (131.08): calcd. C 45.81, H 2.31; found C 45.74, H 2.18.

(2,6-Difluoropyridin-3-yl)trimethylsilane (5): Analogously as described for the preparation of product **1**, this compound was obtained from 2,6-difluoropyridine except that 1,2-dibromo-1,1,2,2-tetrafluoroethane was replaced by using chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol); colorless liquid; m.p. 25−27 °C; b.p. 75−77 °C/20 Torr; yield: 8.89 g (95%). ^{1}H NMR: δ = 7.91 (q, *J* = 8.1 Hz, 1 H), 6.81 (ddd, *J* = 7.8, 2.4, 1.9 Hz, 1 H), 0.33 (d, *J* = 1.1 Hz, 9 H) ppm. ^{13}C NMR: δ = 165.2 (dd, *J* = 243, 13 Hz), 163.0 (dd, *J* = 247, 13 Hz), 150.6 (dd, *J* = 10, 7 Hz), 116.6 (dd, *J* = 42, 5 Hz), 105.7 (dd, *J* = 32, 5 Hz), −1.57 (s, 3 C) ppm. $C_8H_{11}F_2NSi$ (187.26): calcd. C 51.31, H 5.92; found C 51.25, H 6.02.

2,6-Difluoro-α,α-dimethyl-3-pyridinemethanol (6): Analogously as described for the preparation of product **1**, using acetone (3.7 mL, 2.9 g, 50 mmol). After 45 min, 5.0 M hydrochloric acid (25 mL) were added. The organic phase was dried and upon distillation, the product was collected as a colorless liquid; b.p. 102−104 °C/20 Torr; n_D^{20} = 1.4770; d_4^{20} = 1.236; yield: 8.40 g (97%). ^{1}H NMR: δ = 8.18 (dt, *J* = 9.9, 8.1 Hz, 1 H), 6.82 (dd, *J* = 8.3, 3.0 Hz, 1 H), 2.40 (s, 1 H), 1.64 (d, *J* = 1.1 Hz, 6 H) ppm. ^{13}C NMR: δ = 160.0 (dd, *J* = 246, 14 Hz), 157.2 (dd, *J* = 246, 14 Hz), 142.4 (t, *J* = 6 Hz), 127.2 (dd, *J* = 25, 6 Hz), 105.7 (dd, *J* = 34, 5 Hz), 70.5 (d, *J* = 6 Hz), 29.8 (d, *J* = 3 Hz, 2 C) ppm. $C_8H_9F_2NO$ (173.16): calcd. C 55.49, H 5.24; found C 55.23, H 5.28.

2,6-Difluoropyridine-3-carbaldehyde (7): Analogously as described for the preparation of product **1**, using *N,N*-dimethylformamide (7.7 mL, 7.3 g, 0.10 mol). After 45 min, 2.0 M ethereal hydrogen chloride (75 mL, 0.15 mol) were added still at −75 °C. All volatiles were evaporated and upon distillation, the product was collected as a colorless liquid; m.p. 19−20 °C; b.p. 64−66 °C/15 Torr; n_D^{20} = 1.4918; d_4^{20} = 1.378; yield: 10.3 g (72%). ^{1}H NMR: δ = 10.27 (s, 1 H), 8.47 (ddd, *J* = 9.0, 8.3, 7.7 Hz, 1 H), 7.05 (dd, *J* = 8.3, 2.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 184.4 (s), 164.2 (dd, *J* = 256, 15 Hz), 162.7 (dd, *J* = 257, 16 Hz), 144.2 (dd, *J* = 10, 3 Hz), 116.1 (dd, *J* = 20, 5 Hz), 107.8 (dd, *J* = 35, 6 Hz) ppm. $C_6H_3F_2NO$ (143.09): calcd. C 50.36, H 2.11; found C 50.38, H 2.07. The aldehyde **7** was left in the open air for several days without undergoing any noticeable oxidation.

Ethyl 2-(2,6-Difluoropyridin-3-yl)-2-oxoacetate (8): Analogously as described for the preparation of product **1**, using a solution of diethyl oxalate (6.8 mL, 7.3 g, 50 mmol) in tetrahydrofuran (50 mL). Distillation gave a colorless liquid; b.p. 78−80 °C/10 Torr; n_D^{20} = 1.4791; d_4^{20} = 1.316; yield: 6.24 g (58%). ^{1}H NMR: δ = 8.52 (ddd, *J* = 8.9, 8.3, 7.5 Hz, 1 H), 7.04 (dd, *J* = 8.3, 2.7 Hz, 1 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR: δ = 181.4 (d, *J* = 6 Hz), 164.4 (dd, *J* = 257, 15 Hz), 162.7(s), 160.8 (dd, *J* = 255, 16 Hz), 146.7 (d, *J* = 10 Hz), 114.0 (dd, *J* = 23, 6 Hz), 107.9 (dd, *J* = 35, 6 Hz), 63.0 (s), 13.7 (s) ppm. $C_9H_7F_2NO_3$ (215.15): calcd. C 50.24, H 3.28; found C 50.20, H 3.20.

2,6-Difluoropyridine-3-carboxylic Acid (9): The mixture obtained by the reaction of butyllithium, diisopropylamine, and 2,6-difluoropyridine (see above) was poured on an excess of freshly crushed dry ice. At 25 °C, 2.0 M ethereal hydrogen chloride (75 mmol) was added. Evaporation of the volatiles, extraction with hot ethyl acetate, filtration, concentration, and crystallization afforded the product as colorless needles; m.p. 165−167 °C (ref.[5] 164−165 °C); yield: 7.48 g (94%). ^{1}H NMR: δ = 8.54 (dt, *J* = 9.1, 8.1 Hz, 1 H), 6.94 (dd, *J* = 8.3, 3.0 Hz, 1 H) ppm.

2-Fluoro-6-dimethylamino-3-carbaldehyde (10b): When the same protocol as applied to the preparation of aldehyde **7** was repeated but ethereal hydrogen chloride was replaced by water (25 mL), 6-fluoro-2-dimethylamino-3-carboxaldehyde (**10a**), and 2-fluoro-6-dimethylamino-3-carboxaldehyde (**10b**) were formed in a ratio of 1:10 (by gas chromatography: 30 m, DB-1, 150 °C; 30 m, DB-WAX, 150 °C). The organic phase was dried and the solvents evaporated; crude yield: 7.31 g (87%). The main component was isolated by crystallization from ethyl acetate; colorless needles; m.p. 101−103 °C (ref.[5] 98−100 °C). ^{1}H NMR: δ = 7.99 (t, *J* = 9.1 Hz, 1 H), 6.39 (dd, *J* = 8.9, 2.2 Hz, 1 H), 3.19 (s, 6 H) ppm. ^{13}C NMR: δ = 184.8 (s), 164.7 (d, *J* = 247 Hz), 160.8 (d, *J* = 19 Hz), 139.2 (d, *J* = 3 Hz), 106.3 (d, *J* = 22 Hz), 103.2 (d, *J* = 3 Hz), 38.3 (s, 2 C) ppm. The mother liquor was absorbed on silica and eluted with a 3:7 mixture of ethyl acetate and hexanes. The minor component had the shorter retention time.

6-Fluoro-2-dimethylamino-3-carbaldehyde (10a): M.p. 61−62 °C (ref.[5] 61−63 °C). ^{1}H NMR: δ = 8.05 (t, *J* = 8.3 Hz, 1 H), 6.31 (dd, *J* = 8.3, 3.2 Hz, 1 H), 3.15 (s, 6 H) ppm.

2,6-Difluoro-4-iodopyridine (11): Diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and 2,6-difluoro-3-iodopyridine (**1**; 12 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (0.10 L) and hexanes (30 mL) kept in a methanol/dry ice bath. After 30 h at −75 °C, the mixture was treated with water (25 mL). Gas chromatography (30 m, DB-1, 50 °C [5 min] → 100 °C [15 min]; heating rate 30 °C/min; 30 m, DB-WAX, identical temperature program; internal standard: tridecane) revealed the presence of 2,6-difluoropyridine (3%), 2,6-difluoro-3-iodopyridine (**1**; 16%), and 2,6-difluoro-4-iodopyridine (**11**; 81%). The organic phase was dried and the solvents evaporated. Crystallization from hexanes afforded the main product as colorless prisms; m.p. 80−82 °C; yield: 9.16 g (76%). ^{1}H NMR: δ = 7.24 (t, *J* = 1.2 Hz, 2 H)

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ppm. ^{13}C NMR: δ = 161.1 (dd, *J* = 252, 16 Hz, 2 C), 115.6 (symm. m, 2 C), 110.0 (t, *J* = 7 Hz) ppm. $C_5H_2F_2IN$ (240.98): calcd. C 24.92, H 0.84; found C 24.88, H 0.84.

2,6-Difluoropyridine-4-carboxylic Acid (12): The solutions of butylmagnesium chloride (8.0 mmol) in tetrahydrofuran (4 mL) and of butyllithium (17 mmol) in hexanes (11 mL), were mixed in an ice bath. After 15 min at 0 °C, a solution of 2,6-difluoro-4-iodopyridine (**11**; 6.0 g, 25 mmol) in toluene (50 mL) was added. After 45 min at 0 °C, the mixture was poured on an excess of freshly crushed dry ice and neutralized with 5.0 M hydrochloric acid (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic layers were dried. Evaporation of the volatiles and crystallization of the residue from ethyl acetate afforded colorless platelets; m.p. 147−149 °C; yield: 3.47 g (87%). ^{1}H NMR*: δ = 7.48 (s, 2 H) ppm. ^{13}C NMR*: δ = 164.7 (s), 163.6 (dd, *J* = 245, 15 Hz, 2 C), 150.1 (t, *J* = 7 Hz), 108.2 (symm. m, 2 C) ppm. $C_6H_3F_2NO_2$ (159.09): calcd. C 45.30, H 1.90; found C 45.35, H 1.81. The same acid **12** was obtained when 10% palladium on charcoal (2.5 g, 2.4 mmol) was suspended in a solution of 3-chloro-2,6-difluoropyridine-4-carboxylic acid (**16**; see below; 4.9 g, 25 mmol) and ammonium formate (7.9 g, 0.13 mmol) in methanol (25 mL) and the slurry was stirred for 6 h at 25 °C; yield: 3.74 g (94%).

2,6-Difluoro-4-iodopyridine-3-carboxylic Acid (13): Diisopropylamine (3.5 mL, 2.5 g, 25 mmol) and 2,6-difluoro-4-iodopyridine (**11**; 6.1 g, 25 mmol) were added consecutively to a solution of butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (15 mL) cooled in a methanol/dry ice bath. After 45 min at −75 °C, the mixture was poured onto an excess of carbon dioxide and worked up as described for the preparation of acid **9**; colorless platelets (from chloroform); m.p. 126−128 °C; yield: 6.48 g (91%). ^{1}H NMR*: δ = 7.74 (d, *J* = 2.6 Hz, 1 H) ppm. ^{13}C NMR*: δ = 164.5 (d, *J* = 5 Hz), 161.6 (dd, *J* = 251, 15 Hz), 157.7 (dd, *J* = 249, 16 Hz), 121.5 (dd, *J* = 32, 6 Hz), 118.7 (dd, *J* = 37, 6 Hz), 111.7 (dd, *J* = 8, 2 Hz) ppm. $C_6H_2F_2INO_2$ (284.99): calcd. C 25.29, H 0.71; found C 25.30, H 0.77.

3-Chloro-2,6-difluoro-4-iodopyridine (14): Diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and 3-chloro-2,6-difluoropyridine (**3**; 7.5 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in tetrahydrofuran (0.10 L) and hexanes (30 mL), cooled in a methanol/dry ice bath. After 45 min at −75 °C, the mixture was treated with a solution of iodine (13 g, 50 mmol) in tetrahydrofuran (50 mL) before being washed with a 10% aqueous solution (25 mL) of sodium sulfite. According to gas chromatography (30 m, DB-1, 100 °C; 30 m, DB-WAX, 100 °C; internal standard: tridecane), it contained 3-chloro-2,6-difluoro-4-iodopyridine (**14**; 77%) and 3-chloro-2,6-difluoro-5-iodopyridine (**15**; 15%; see below). After evaporation of the volatiles, the residue was crystallized from hexanes; colorless prisms; m.p. 90.5−92.5 °C; yield: 9.78 g (71%). ^{1}H NMR: δ = 7.37 (d, *J* = 3.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 158.9 (dd, *J* = 251, 14 Hz), 155.3 (dd, *J* = 249, 16 Hz), 119.2 (dd, *J* = 32, 7 Hz), 117.7 (dd, *J* = 38, 6 Hz), 115.5 (d, *J* = 8 Hz) ppm. C_5HClF_2IN (275.42): calcd. C 21.80, H 0.37; found C 21.69, H 0.50.

3-Chloro-2,6-difluoro-5-iodopyridine (15): A solution of (5-chloro-2,6-difluoropyridin-3-yl)trimethylsilane (**21**; see below; 22 g, 0.10 mol) and iodine monochloride (32 g, 0.20 mol) in tetrachloromethane (0.10 L) were heated under reflux for 20 h. The mixture was washed with a saturated aqueous solution (75 mL) of sodium sulfite, dried and the solvents evaporated. Crystallization from hexanes gave colorless needles; m.p. 58−60 °C; yield: 25.6 g (93%). ^{1}H NMR: δ = 8.23 (dd, *J* = 8.3, 7.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 158.3 (dd, *J* = 243, 12 Hz), 156.9 (dd, *J* = 248, 13 Hz), 152.3 (dd, *J* = 3, 2 Hz), 114.2 (dd, *J* = 32, 7 Hz), 69.7 (dd, *J* = 43, 6 Hz) ppm. C_5HClF_2IN (275.42): calcd. C 21.80, H 0.37; found C 21.94, H 0.30.

3-Chloro-2,6-difluoropyridine-4-carboxylic Acid (16): The solutions of butylmagnesium chloride (8.0 mmol) in tetrahydrofuran (4 mL) and of butyllithium (17 mmol) in hexanes (11 mL) were mixed in an ice bath. After 15 min at 0 °C, a solution of 3-chloro-2,6-difluoro-4-iodopyridine (**14**; 6.9 g, 25 mmol) in toluene (50 mL) was added. After 45 min at 0 °C, the mixture was poured on an excess of freshly crushed dry ice and neutralized with 5.0 M hydrochloric acid (25 mL). The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic layers were dried. Evaporation of the volatiles and crystallization of the residue from chloroform afforded colorless needles; m.p. 106−108 °C; yield: 4.35 g (90%). ^{1}H NMR: δ = 7.38 (d, *J* = 3.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 167.3 (t, *J* = 3 Hz), 159.1 (dd, *J* = 249, 13 Hz), 157.8 (dd, *J* = 247, 15 Hz), 143.6 (d, *J* = 7 Hz), 113.7 (dd, *J* = 33, 8 Hz), 108.6 (dd, *J* = 38, 6 Hz) ppm. $C_6H_2ClF_2NO_2$ (193.54): calcd. C 37.24, H 1.04; found C 37.13, H 1.08.

2,6-Difluoro-5-iodopyridine-3-carboxylic Acid (17): At −75 °C, diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and a solution of 2,6-difluoro-3-iodopyridine (**1**; 12.1 g, 50 mmol) in tetrahydrofuran (50 mL) were consecutively added to butyllithium (50 mmol) in tetrahydrofuran (60 mL) and hexanes (35 mL). After 15 min at −75 °C, the mixture was poured on an excess of freshly crushed dry ice. The volatiles were evaporated and the residue was dissolved in a 2.0 M aqueous solution (50 mL) of sodium hydroxide. The aqueous phase was washed with diethyl ether (2 × 25 mL), acidified with hydrochloric acid to pH 2 and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried and the solvents evaporated. According to gas chromatography (30 m, DB-1, 100 °C [15 min] → 175 °C [15 min]; heating rate 30 °C/min; 30 m, DB-WAX, same temperature program; internal standard: tridecane), the organic solution contained 2,6-difluoro-3-iodopyridine (**1**; 9%), 2,6-difluoro-3,5-diiodopyridine (**18**; 8%), and methyl 2,6-difluoro-5-iodopyridine-3-carboxylate (72%). Crystallization from ethyl acetate afforded the product as colorless platelets; m.p. 166−168 °C (decomp.); yield: 9.52 g (67%). ^{1}H NMR*: δ = 8.90 (t, *J* = 8.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 162.7 (dd, *J* = 244, 14 Hz), 162.1 (d, *J* = 7 Hz), 161.4 (dd, *J* = 258, 14 Hz), 157.3 (dd, *J* = 5, 2 Hz), 114.0 (dd, *J* = 23, 6 Hz), 70.5 (dd, *J* = 42, 6 Hz) ppm. $C_6H_2F_2INO_2$ (284.99): calcd. C 25.29, H 0.71; found C 25.45, H 1.18.

2,6-Difluoro-3,5-diiodopyridine (18): When the mixture resulting from the reaction between butyllithium, diisopropylamine and 2,6-difluoro-3-iodopyridine (**1**; see the preceding paragraph) was treated with a solution of iodine in tetrahydrofuran at −75 °C (rather than poured on dry ice), the residue contained, according to gas chromatography (30 m, DB-1, 100 °C [15 min] → 175 °C [15 min]; heating rate 30 °C/min; 30 m, DB-WAX, same temperature program; internal standard: tridecane), 2,6-difluoro-3-iodopyridine (**1**; 2%), 2,6-difluoro-3,4-diiodopyridine (**19**; 17%; see below), and 2,6-difluoro-3,5-diiodopyridine (**18**; 81%). Washing with an aqueous solution (50 mL) of sodium sulfite, evaporation and crystallization from hexanes gave colorless needles; m.p. 108−110 °C; yield: 13.8 g (75%). ^{1}H NMR: δ = 8.52 (t, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 160.6 (dd, *J* = 244, 14 Hz, 2 C), 160.5 (s), 70.8 (symm. m, 2 C) ppm. $C_5HF_2I_2N$ (366.87): calcd. C 16.37, H 0.27; found C 16.22, H 0.31. The same compound **18** was isolated in 93% yield (8.53 g) after a solution of (2,6-difluoropyridin-3,5-

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diyl)bis(trimethylsilane) (**23**; see below; 6.5 g, 25 mmol) and iodine monochloride (16 g, 0.10 mol) in tetrachloromethane (0.10 L) had been heated for 20 h under reflux.

2,6-Difluoro-3,4-diiodopyridine (19): A second reaction was undertaken exactly as described in the preceding paragraph, except that the reaction time at −75 °C was extended from 15 min to 30 h. According to gas chromatography, the mixture contained 2,6-difluoro-3-iodopyridine (**1**; 4%), 2,6-difluoro-3,5-diiodopyridine (**18**; 16%) and 2,6-difluoro-3,4-diiodopyridine (**19**; 80%) this time. The main component was purified by crystallization from hexanes; colorless platelets; m.p. 91−93 °C; yield: 13.6 g (74%). ^{1}H NMR: δ = 7.41 (d, *J* = 3.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 161.7 (dd, *J* = 251, 14 Hz), 159.9 (dd, *J* = 244, 15 Hz), 125.9 (d, *J* = 7 Hz), 117.4 (dd, *J* = 37, 6 Hz), 86.1 (dd, *J* = 41, 6 Hz) ppm. $C_5HF_2I_2N$ (366.87): calcd. C 16.37, H 0.27; found C 16.38, H 0.29.

2,6-Difluoro-5-(trimethylsilyl)pyridine-3-carboxylic Acid (20): Diisopropylamine (14 mL, 10 g, 0.10 mol) and (2,6-difluoropyridin-3-yl)trimethylsilane (**5**; 19 g, 0.10 mol) were added consecutively to a solution of butyllithium (0.10 mol) in tetrahydrofuran (0.20 L) and hexanes (60 mL) cooled in a methanol/dry ice bath. After 45 min at −75 °C, the mixture was poured on an excess of freshly crushed dry ice. At 25 °C, 2.0 M ethereal hydrogen chloride (0.15 mol) was added. Evaporation of the volatiles, extraction with hot chloroform, filtration, concentration, and crystallization afforded the product; colorless needles; m.p. 171−173 °C; yield: 22.7 g (98%). ^{1}H NMR: δ = 8.56 (dd, *J* = 9.9, 7.7 Hz, 1 H), 0.38 (s, 9 H) ppm. ^{13}C NMR: δ = 168.0 (d, *J* = 7 Hz), 167.6 (dd, *J* = 251, 14 Hz), 162.5 (dd, *J* = 261, 17 Hz), 154.1 (d, *J* = 13 Hz), 118.5 (dd, *J* = 44, 7 Hz), 109.5 (dd, *J* = 20, 5 Hz), −1.7 (s, 3 C) ppm. $C_9H_{11}F_2NO_2Si$ (231.27): calcd. C 46.74, H 4.79; found C 46.65, H 4.80.

(5-Chloro-2,6-difluoropyridin-3-yl)trimethylsilane (21): Analogously as described in the preceding paragraph using 1,1,2-trichloro-1,2,2-trifluoroethane (11.9 mL, 18.7 g, 0.10 mol) instead of carbon dioxide. The product was collected upon distillation as a colorless liquid; m.p. −8 to −6 °C; b.p. 87−89 °C/15 Torr; n_D^{20} = 1.4779; d_4^{20} = 1.179; yield: 21.5 g (97%). ^{1}H NMR: δ = 7.85 (dd, *J* = 9.6, 7.0 Hz, 1 H), 0.34 (s, 9 H) ppm. ^{13}C NMR: δ = 162.7 (dd, *J* = 243, 12 Hz), 157.5 (dd, *J* = 246, 16 Hz), 149.7 (dd, *J* = 11, 2 Hz), 119.3 (dd, *J* = 45, 7 Hz), 112.9 (dd, *J* = 29, 7 Hz), −1.8 (s, 3 C) ppm. $C_8H_{10}ClF_2NSi$ (221.71): calcd. C 43.34, H 4.55; found C 43.57, H 4.44.

5-Chloro-2,6-difluoropyridine-3-carboxylic Acid (22): From 3-chloro-2,6-difluoro-5-iodopyridine (**15**; 6.9 g, 25 mmol) analogous as described for the preparation of compound **16**; colorless platelets (from ethyl acetate); m.p. 136−138 °C; yield: 4.40 g (91%). ^{1}H NMR*: δ = 8.66 (t, *J* = 8.3 Hz, 1 H) ppm. ^{13}C NMR*: δ = 162.3 (d, *J* = 8 Hz), 159.1 (dd, *J* = 257, 14 Hz), 158.8 (dd, *J* = 248, 15 Hz), 148.3 (t, *J* = 3 Hz), 114.0 (dd, *J* = 25, 6 Hz), 113.7 (dd, *J* = 17, 6 Hz) ppm. $C_6H_2ClF_2NO_2$ (193.54): calcd. C 37.24, H 1.04; found C 37.44, H 1.02.

(2,6-Difluoropyridin-3,5-diyl)bis(trimethylsilane) (23): Diisopropylamine (28.3 mL, 20.2 g, 0.20 mol) and (2,6-difluoropyridin-3-yl)trimethylsilane (**5**; 37.5 g, 0.20 mol) were added consecutively to a solution of butyllithium (0.20 mol) in tetrahydrofuran (0.35 L) and hexanes (0.12 L) cooled in a methanol/dry ice bath. After 45 min at −75 °C, the mixture was treated with chlorotrimethylsilane (25 mL, 22 g, 0.20 mol) and, again 45 min later, with water (0.10 L). Upon distillation, the product was collected as a colorless liquid; m.p. 23−25 °C; b.p. 60−62 °C/0.6 Torr; yield: 49.0 g (94%). ^{1}H NMR: δ = 7.89 (t, *J* = 9.1 Hz, 1 H), 0.33 (s, 18 H) ppm. ^{13}C NMR: δ = 166.9 (dd, *J* = 244, 14 Hz, 2 C), 156.2 (t, *J* = 10 Hz), 116.1 (symm. m, 2 C), −1.4 (s, 6 C) ppm. $C_{11}H_{19}F_2NSi_2$ (259.44): calcd. C 50.92, H 7.38; found C 50.74, H 7.41. The same bissilane **23** was isolated by distillation in 92% yield (5.97 g) 2 h after 2,6-difluoropyridine (2.3 mL, 2.9 g, 25 mmol) had been added at −75 °C to a solution containing chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol) and lithium diisopropylamide, generated from each time 50 mmol of diisopropylamine and butyllithium in tetrahydrofuran (70 mL) and hexanes (30 mL).

(5-Bromo-2,6-difluoropyridin-3-yl)trimethylsilane (24): A solution of (2,6-difluoropyridin-3,5-diyl)bis(trimethylsilane) (**23**; 13 g, 50 mmol) and bromine (5.2 mL, 16.0 g, 0.10 mol) in tetrachloromethane (50 mL) was heated for 20 h under reflux before it was washed with a saturated aqueous solution (50 mL) of sodium sulfite, dried, and the solvents evaporated. Distillation gave a colorless liquid; m.p. 0−2 °C; b.p. 84−86 °C/12 Torr; n_D^{20} = 1.4975; d_4^{20} = 1.399; yield: 12.7 g (95%). ^{1}H NMR: δ = 7.98 (dd, *J* = 9.4, 7.0 Hz, 1 H), 0.34 (s, 9 H) ppm. ^{13}C NMR: δ = 163.9 (dd, *J* = 244, 12 Hz), 158.7 (dd, *J* = 244, 15 Hz), 152.8 (d, *J* = 10 Hz), 119.9 (dd, *J* = 45, 6 Hz), 100.0 (dd, *J* = 34, 6 Hz), −1.6 (s, 3 C) ppm. $C_8H_{10}BrF_2NSi$ (266.16): calcd. C 36.10, H 3.79; found C 36.04, H 3.67.

3,5-Dibromo-2,6-difluoropyridine (25): At 0 °C, 3-bromo-2,6-difluoro-5-iodopyridine (**26**; see below; 8.0 g, 25 mmol) was added to a solution of isobutylmagnesium chloride (25 mmol) in tetrahydrofuran (50 mL). The mixture was kept in an ice bath for 2 h, before being treated with bromine (1.3 mL, 4.0 g, 25 mmol) and, 15 min later, a 10% aqueous solution (25 mL) of sodium sulfite. Evaporation of the volatiles and crystallization of the residue from hexanes afforded colorless platelets; m.p. 80−82 °C; yield: 6.14 g (90%). ^{1}H NMR: δ = 8.21 (t, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 156.5 (dd, *J* = 245, 13 Hz, 2 C), 149.4 (s), 100.6 (symm. m, 2 C) ppm. $C_5HBr_2F_2N$ (272.87): calcd. C 22.01, H 0.37; found C 21.92, H 0.34.

3-Bromo-2,6-difluoro-5-iodopyridine (26): A solution of (2,6-difluoropyridin-3,5-diyl)bis(trimethylsilane) (**23**; 13 g, 50 mmol) and bromine (5.2 mL, 16 g, 0.10 mol) in tetrachloromethane (50 mL) was heated under reflux for 20 h. After the addition of iodine monochloride (16 g, 0.10 mol), the heating under reflux was continued for further 20 h. The mixture was washed with a saturated aqueous solution (50 mL) of sodium sulfite, dried, and the solvents evaporated. Crystallization from hexanes afforded colorless needles; m.p. 85−87 °C; yield: 14.6 g (91%). ^{1}H NMR: δ = 8.36 (dd, *J* = 7.8, 7.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 159.2 (dd, *J* = 244, 13 Hz), 157.9 (dd, *J* = 246, 14 Hz), 155.0 (s), 100.9 (dd, *J* = 36, 6 Hz), 70.3 (dd, *J* = 43, 6 Hz) ppm. C_5HBrF_2IN (319.87): calcd. C 18.77, H 0.32; found C 18.97, H 0.49.

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