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Synthesis of 4,6-Dichloro- and 4,6-Difluorophthalides: a Systematic Study on the Lithiation of 3,5-Dihalo-*N*,*N*-diisopropylbenzamides

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By taking advantage of the *N*,*N*-diisopropylcarbamoyl moiety as a versatile *ortho*-directing lithiation group, the preparation of 4,6-dichloro- and 4,6-difluorophthalides, starting from the corresponding 3,5-dihalo-*N*,*N*-diisopropylbenzamides, is described here. The role of the lithiating agent, the formation of kinetically and thermodynamically favored products, and the marked difference between the dichloro and difluoro derivatives are discussed in detail.

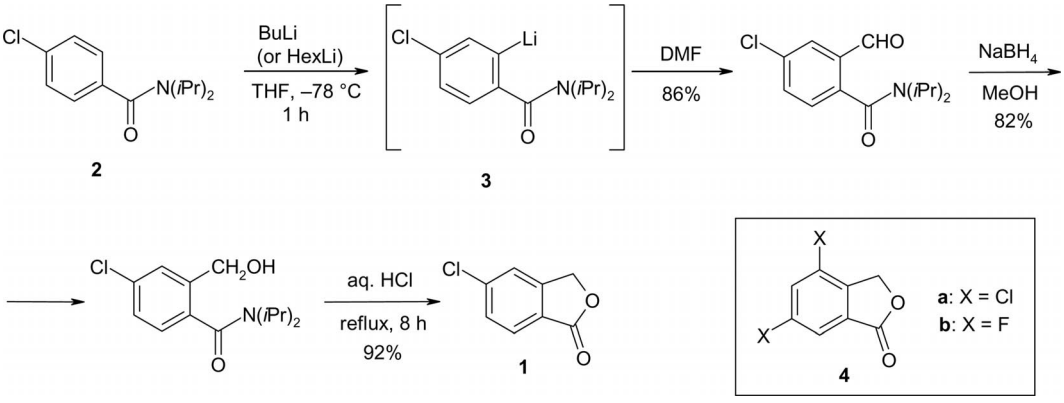
Introduction

The phthalide [2-benzofuran-1(3*H*)-one] skeleton is a common motif in biologically active substances, as demonstrated by two marketed drugs, the immunosuppressant mycophenolate mofetil[1,2] and the antiarthritic agent talniflumate.[3–5] Furthermore, 5-substituted phthalide intermediates are used in the manufacturing process of the antidepressant drug citalopram[6,7] and its optically active form escitalopram.[8]

Recently, we reported the manufacturing synthesis of 5-chlorophthalide (**1**, Scheme 1). The key step of the procedure is the selective *ortho*-lithiation of 4-chloro-*N*,*N*-diisopropylbenzamide (**2**) to produce lithio derivative **3**, followed by formylation with *N*,*N*-dimethylformamide (DMF).[9] The advantage of the *N*,*N*-diisopropylcarbamoyl group as an *ortho*-directing lithiation group over the more widely used *N*,*N*-diethylcarbamoyl analogue[10–12] is that butyllithium (BuLi) or hexyllithium (HexLi) can be applied as the lithiating agents instead of *sec*-butyllithium (*s*BuLi), thus opening the door to a less hazardous industrial implementation of the reaction.

As a part of our ongoing research project we aimed at extending the route shown in Scheme 1 for the synthesis of 4,6-dichloro- and 4,6-difluorophthalides (**4**, Scheme 1), starting with *ortho*-directing lithiation of 3,5-dichloro- and 3,5-difluoro-*N*,*N*-diisopropylbenzamide.[13]

Our literature search revealed that several examples have been published for the lithiation of benzene derivatives exhibiting both a directing metalation group (DMG) and also the two fluorine or two chlorine atoms in the *meta* positions. Of course, the halogen atoms can also act as DMGs. Lithiation of 3,5-difluoroanisole (**5a**, Scheme 2) with BuLi (1 equiv., –78 °C, 45 min) in tetrahydrofuran (THF) occurred at the 4-position to give **6a**, which was trapped with



Scheme 1.

carbon dioxide to give 2,6-difluoro-4-methoxybenzoic acid (**7a**) in 81%[14,15] and 86%[16] yield.

However, lithiation of 1,3-difluoro-5-(methoxymethoxy)-benzene (**5b**) with BuLi (1 equiv., –75 °C, 6 h) in diethyl

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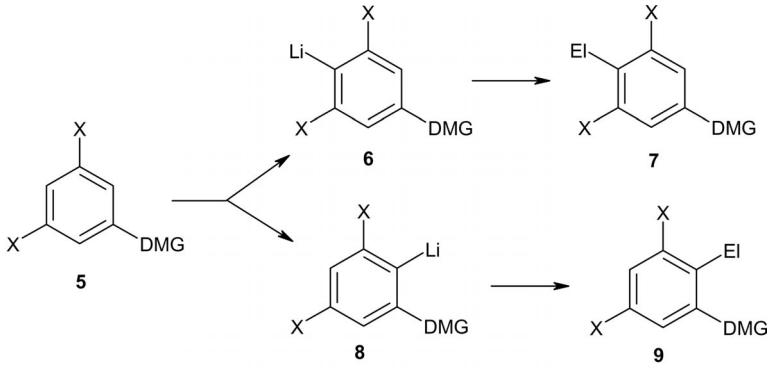


5, 6, 8	DMG	X
a	OMe	F
b	OCH_2OMe	F
c	$OCON(iPr)SiMe_3$	F
d	$OCON(iPr)SiMe_3$	Cl
e	OMe	Cl
f	OTBDMS	Cl
g	OMe	Br

	DMG	X	El
7a	OMe	F	COOH
7b	OH	F	COOH
7c	OMe	Cl	COOMe
7d	OMe	Br	TMS
9a	OH	F	COOH
9b	OH	F	CHO
9c	OH	Cl	CHO
9d	OMe	Cl	COOMe
9e	OMe	Br	TMS

Scheme 2.

ether occurred predominantly at the site adjacent to the methoxymethoxy group to give **8b**, as shown by the isolation of benzoic acid **9a** in 61% yield (Scheme 2). The formation of the isomeric product **7b** was also detected (ca. 2%). Compound **7b** was prepared in 83% yield by metalation of **5b** with the superbasic mixture LICKOR (1 equiv. BuLi and 1 equiv. potassium *tert*-butoxide) at –75 °C in THF for 2 h, followed by carboxylation and removal of the protecting group in the course of workup.[17]

Kauch and Hoppe elaborated an efficient method for the *ortho*-specific derivatization of *N*-isopropyl-*N*-(trimethylsilyl)carbamates **5c** and **5d** of phenols. Lithiation with BuLi (2.0–2.2 equiv.) and *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA, 2.0–2.2 equiv.) at –78 °C for 1 h,[18,19] followed by treatment with DMF and hydrolysis of the carbamate moiety gave salicylaldehydes **9b** (81%) and **9c** (86%), respectively.[18]

Deprotonation of 3,5-dichloroanisole (**5e**) with BuLi (1.4 equiv.) and TMEDA (1.4 equiv.) at –78 °C in THF for 1.5 h and subsequent carboxylation yielded a mixture of benzoic acids, which were separated after esterification to give methyl esters **7c** (16%) and **9d** (14%).[20] Lithiation of the same substrate **5e** with *s*BuLi (1.05 equiv.) at –95 °C in THF for 1 h occurred regioselectively between the methoxy and chloro groups producing **8e**. In contrast, the *tert*-butyldimethylsilyl (TBDMS) ether of 3,5-dichlorophenol (**5f**) underwent lithiation under the same conditions (1.05 equiv. *s*BuLi, –95 °C, THF, 1 h) exclusively at the position between the two chlorine atoms to produce **6f**. This was due to the steric hindrance of the TBDMS protecting group.[21]

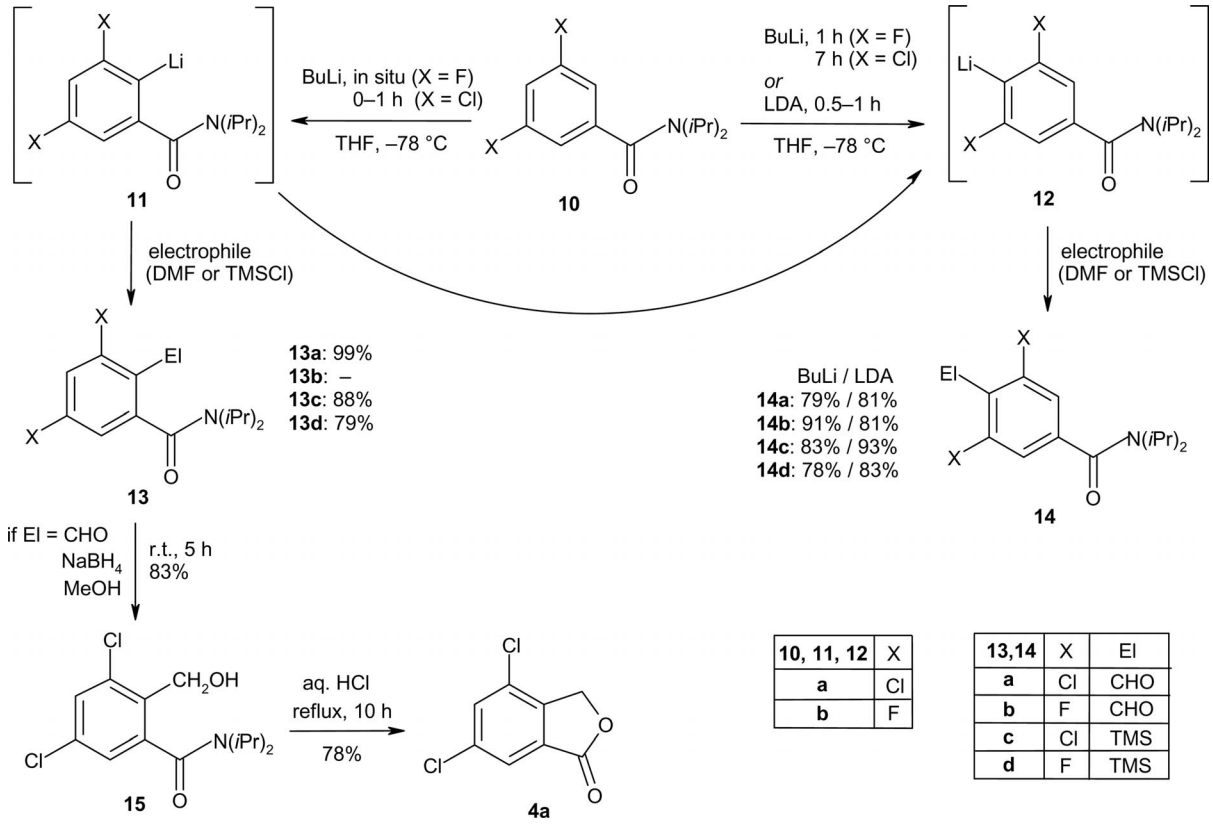
The results of the lithiation reactions shown above do not give a consistent view and eventually differ from the expectations based on the electron-withdrawing and coordinating properties of the substituents, the nature of the metalating agents, and the choice of the solvents. The role of kinetic and thermodynamic control in the product distribution was not studied in these papers. It is not clear whether the isolated products reflect a final distribution or just a snapshot of the lithio intermediates at the time of quenching.

Dabrowski et al. described a more detailed investigation of the lithiation reaction of 3,5-dibromoanisole (**5g**) with lithium diisopropylamide (LDA) at –85 °C in THF.[22] By trapping in situ with chlorotrimethylsilane (TMSCl), the prepared product **9e** indicated the primary formation of 2,4-dibromo-6-methoxyphenyllithium (**8g**). However, when the lithiation was carried out prior to the quench with an electrophile (ca. –85 °C, 2 h), the formation of the isomeric product **7d** derived from lithio derivative **6g** was also observed. The amount of the latter compound **7d** increased after longer lithiation times. It was suggested that lithiation at the 2-position was kinetically favored. However, the resultant aryllithium compound **8g** isomerized to form the thermodynamically more stable 2,6-dibromo-4-methoxyphenyllithium (**6g**).[22]

Schlosser mentioned several other examples in his review for lithiations of various substrates, where the initially formed metalated intermediate isomerized to the more stable lithio species (basicity-lowering isomerization).[13c]

Results and Discussion

We aimed at applying the manufacturing route leading to 5-chlorophthalide (**1**, Scheme 1) for the analogous preparation of 4,6-dichloro- and 4,6-difluorophthalides (**4a** and



10, 11, 12	X
a	Cl
b	F

13,14	X	El
a	Cl	CHO
b	F	CHO
c	Cl	TMS
d	F	TMS

Scheme 3.

4b, respectively) using the regioselective *ortho*-lithiation of 4,6-dichloro- and 4,6-difluoro-*N*,*N*-diisopropylbenzamide (**10a** and **10b**, respectively, Scheme 3). Our experiments revealed that **4a** could be obtained under similar conditions, but the preparation of **4b** necessitated the elaboration of a modified synthetic approach. The results are described below in detail.

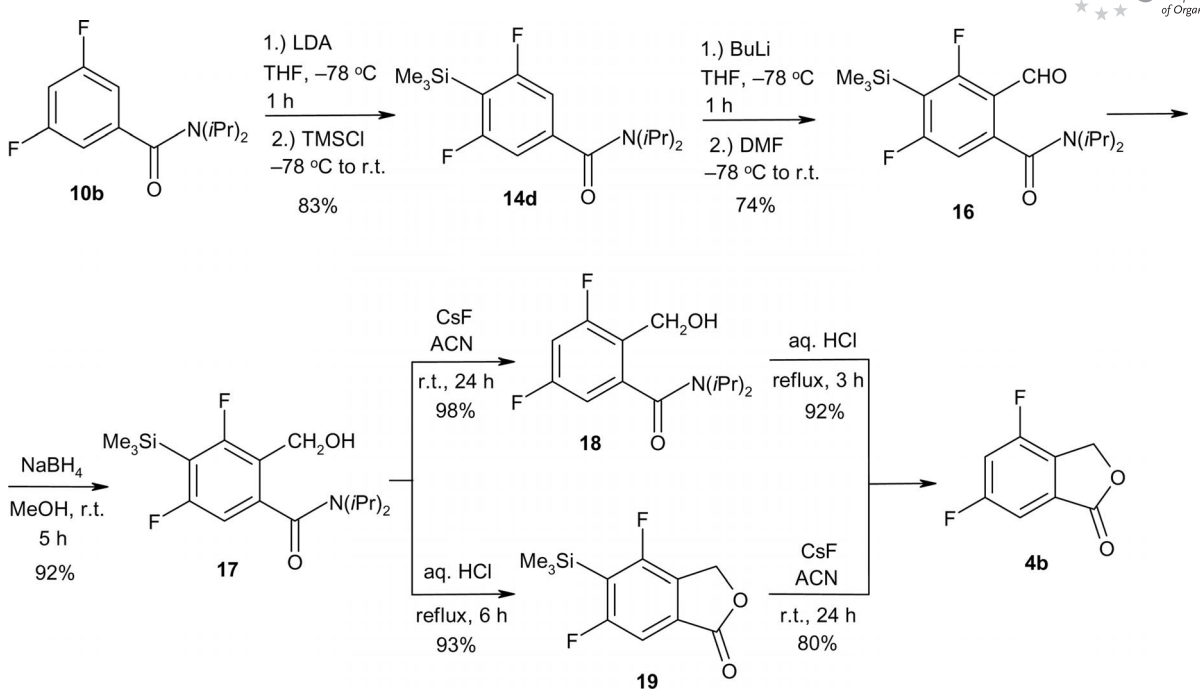
Lithiation of 3,5-dichloro-*N*,*N*-diisopropylbenzamide (**10a**) with BuLi in THF at –78 °C for 1 h (Scheme 3) and subsequent treatment with DMF afforded formyl derivative **13a** in 99% yield, demonstrating that lithiation occurred at the 2-position to give **11a**. Aldehyde **13a** was transformed to hydroxymethyl derivative **15** and then to the required phthalide **4a** by conventional methods.

However, when the 3,5-difluoro analogue **10b** was treated under the same conditions (BuLi, THF, –78 °C, 1 h), lithiation occurred at the 4-position flanked by two fluoro substituents giving **12b**, as indicated by the formation of aldehyde **14b** in 91% yield. This aldehyde is obviously unsuitable for the synthesis of the required 4,6-difluorophthalide **4b**. To find a solution for our synthetic problem, we decided to scrutinize the lithiation reactions of 3,5-dichloro- and 3,5-difluoro-*N*,*N*-diisopropylbenzamides **10**.

On the basis of all this, we decided to investigate first whether lithio derivative **12b** was a kinetic or thermodynamic product. In situ trapping with TMSCl of the lithio species, formed when difluoro derivative **10b** is treated with BuLi (THF, –78 °C), afforded trimethylsilyl derivative **13d**, demonstrating the initial preference for the formation of the 2-lithio species **11b** under these conditions. However, in accordance with the formation of aldehyde **14b**, quenching of the lithiation reaction (BuLi, THF, –78 °C) with TMSCl after 1 h gave trimethylsilyl derivative **14d**, showing that the initially formed lithio intermediate **11b** isomerized to the thermodynamically more stable (less basic) species **12b**. The regioselectivities observed in both cases were practically perfect. The ratios of **13d**/**14d** in the crude products were 100:1 and 1:64, respectively, as shown by GC measurements.

The isomerization of 3,5-dichloro-2-lithio derivative **11a** to the 4-lithio species **12a** proceeded similarly to that of the corresponding difluoro analogue, but much slower. In situ quenching of the metalation mixture (BuLi, THF, –78 °C) with TMSCl afforded **13c** in 88% yield, the **13c**/**14c** ratio, shown by GC measurements, being 65:1 in the crude product. However, when trapping was performed after 7 h of reaction time (BuLi, THF, –78 °C), the **13c**/**14c** ratio, as shown by GC measurements, was 1:100 in the crude product, and isomer **14c** was obtained in 83% yield. As expected,[23] LDA (THF, –78 °C) abstracted the proton from the most acidic site of compounds **10a** and **10b**, resulting after a short reaction time (1 h) in the formation of the thermodynamically more stable lithio isomers in both cases, as demonstrated by the isolation of compounds **14**.

Due to the very fast displacement of the metal atom in the initially formed lithio derivative **11b** to the 4-position in lithio derivative **12b**, the required aldehyde **13b** could not be obtained without substantial amounts of isomeric impu-



Scheme 4.

rity **14b**. Therefore, we decided to synthesize the required phthalide **4b** starting from compound **14d** using the trimethylsilyl moiety as a protecting group in the 4-position (Scheme 4). Lithiation of compound **14d** followed by formylation afforded aldehyde **16** in high yield, which was reduced to hydroxymethyl derivative **17**. The removal of the protecting group with CsF[24,25] could be carried out either before or after the cyclization of the furan ring (see **18** and **19**) to produce phthalide **4b** in high overall yield.

Conclusions

Although numerous papers discuss the lithiation reactions of 1,3,5-trisubstituted benzene derivatives **5** with two identical halogen substituents and an *ortho*-directing metalation group, very few systematic studies have investigated the role of kinetic and thermodynamic control of the lithiation reactions with this family of compounds. The systematic lithiation study of 3,5-dihalo-*N*,*N*-diisopropylbenzamides described here revealed that in the case of the 3,5-dichloro derivative, the rearrangement of the primarily formed 2-lithio intermediate was fairly slow; thus, derivatives substituted adjacent to the benzamide moiety could be prepared. By benefiting from this highly selective key reaction step, title compound 4,6-dichlorophthalide was prepared in high overall yield.

On the contrary, when lithiating the 3,5-difluoro congener, very fast isomerization of the initially formed 2-lithio intermediate to the thermodynamically more stable 4-lithio species was observed. In general, longer reaction times with BuLi or the use of LDA led to the 4-lithio intermediate by starting from either 3,5-dichloro- or 3,5-difluoro-*N*,*N*-diisopropylbenzamide.

The synthesis of 4,6-difluorophthalide via the 2-lithiobenzamide intermediate has been carried out with the temporary protection of the 4-position.

Experimental Section

General: All melting points were measured with a Büchi B-540 capillary melting point apparatus. Infrared (IR) spectra were recorded with a Bruker IFS-113v FT spectrometer in KBr pellets or neat. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Unity Inova 500 (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively), with a Bruker Avance III (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or with a Varian Gemini 200 (200 and 50 MHz for ^{1}H and ^{13}C NMR spectra, respectively) spectrometer. Deuterated dimethyl sulfoxide ([D$_6$]DMSO) or $CDCl_3$ was used as the solvent, and tetramethylsilane was used as the internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. Elemental analyses were performed with a Vario EL III analyzer. GC measurements were recorded with an Agilent 6890N chromatograph (column = DB-5.625, 30 m × 0.25 mm × 0.25 μm; temperature program = 80 °C for 2 min, 20 °C/min to 300 °C, 300 °C for 20 min; injector temperature = 250 °C; detector temperature = 300 °C; split = 50:1; flow rate = 1 mL/min; helium). The reactions were followed by analytical thin layer chromatography on silica gel 60 F_{254}. All reagents were purchased from commercial sources. Analytical samples of new compounds were obtained by recrystallization from the solvents given below. Procedures where the lithiation step used BuLi are referred to as Method A and those using LDA are referred to as Method B.

3,5-Dichloro-*N*,*N*-diisopropylbenzamide (10a): A mixture of diisopropylamine (40 mL, 28.9 g, 285 mmol) and triethylamine (40 mL, 29.0 g, 287 mmol) was added to a solution of 3,5-dichlorobenzoyl chloride (45.0 g, 215 mmol) in toluene (370 mL). After stirring at ambient temperature for 24 h, water (150 mL) was added. The organic layer was separated, washed with an aqueous solution of hy-

drochloric acid (10%, 150 mL) and brine (100 mL), and then dried with $MgSO_4$. The solvents were evaporated and, the residue was triturated with hexane (70 mL). The crystalline product was collected by filtration to give **10a** (48.7 g, 84%) as off-white crystals. M.p. 132–133 °C (hexane, colorless crystals); ref.[26] m.p. 127–129 °C. IR (KBr): $\tilde{\nu}$ = 1634 cm^{-1}. ^1H NMR (500 MHz, [D_6]-DMSO): δ = 7.62 (t, J = 1.6 Hz, 1 H), 7.36 (d, J = 1.6 Hz, 2 H), 3.59 (m, 2 H), 1.45 (m, 6 H), 1.14 (m, 6 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 166.6, 142.1, 134.5, 128.3, 124.2, 50.9, 45.2, 20.3 ppm.

3,5-Difluoro-*N*,*N*-diisopropylbenzamide (10b): A mixture of diisopropylamine (27.8 mL, 20.07 g, 198.3 mmol) and triethylamine (27.8 mL 20.18 g, 199.5 mmol) was added to a solution of 3,5-difluorobenzoyl chloride (25.0 g, 141.6 mmol) in toluene (208 mL). After stirring at ambient temperature for 24 h, water (200 mL) was added. The organic layer was separated, washed with an aqueous solution of hydrochloric acid (10%, 200 mL) and brine (150 mL), and then dried with charcoal and $MgSO_4$. The solvents were evaporated, and the residue was triturated with cold pentane (approximately –20 °C, 40 mL). The crystalline product was collected by filtration to give **10b** (25.6 g, 75%) as colorless crystals. M.p. 103–104 °C (hexane). IR (KBr): $\tilde{\nu}$ = 1632 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.83 (m, 2 H), 6.81 (m, 1 H), 3.65 (m, 2 H), 1.44 (m, 6 H), 1.26 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9 (t, J = 2.5 Hz), 162.9 (dd, J = 250.9, 12.4 Hz), 141.7 (t, J = 8.3 Hz), 114.0 (t, J = 25.4 Hz), 108.8 (dd, J = 20.0, 6.4 Hz), 50.9, 46.1, 20.5 ppm. $C_{13}H_{17}F_2NO$ (241.28): calcd. C 64.71, H 7.10, N 5.81; found C 64.38, H 7.22, N 5.71.

3,5-Dichloro-2-formyl-*N*,*N*-diisopropylbenzamide (13a): A solution of BuLi (2.5 M in hexane, 40.5 mL, 101 mmol) was added to a solution of **10a** (23.0 g, 83.9 mmol) in THF (200 mL) at –78 °C. After stirring at –78 °C for 1 h, DMF (8.4 mL, 7.93 g, 108.5 mmol) was added while the temperature of the mixture rose to –50 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (170 mL) and extracted with ethyl acetate (170 mL and 2 × 70 mL). The organic layer was washed with brine (120 mL) and dried with $MgSO_4$. The solvents were evaporated, and the resulting residue was triturated with hexane (70 mL). The crystalline product was collected by filtration to give **13a** (25.0 g, 99%) as colorless crystals. M.p. 116–117 °C (hexane/ethyl acetate). IR (KBr): $\tilde{\nu}$ = 1702, 1630 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.41 (s, 1 H), 7.45 (d, J = 1.8 Hz, 1 H), 7.10 (d, J = 1.8 Hz, 1 H), 3.53 (m, 1 H), 3.47 (m, 1 H), 1.58 (m, 6 H), 1.13 (d, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.3, 166.5, 142.4, 140.4, 138.9, 130.0, 127.4, 125.4, 51.3, 46.0, 20.52, 20.2 ppm. $C_{14}H_{17}Cl_2NO_2$ (302.20): calcd. C 55.64, H 5.67, Cl 23.26, N 4.63; found C 55.44, H 5.76, Cl 23.55, N 4.60.

3,5-Dichloro-*N*,*N*-diisopropyl-2-(trimethylsilyl)benzamide (13c): A solution of BuLi (2.5 M in hexane, 4.8 mL, 12 mmol) was added to a solution of **10a** (2.74 g, 10 mmol) and TMSCl (3.8 mL, 3.27 g, 30 mmol) in THF (24 mL) at –78 °C. After stirring at –78 °C for 1 h, the cooling bath was removed, and the temperature of the reaction mixture rose to –20 °C over a period of 1.5 h. After dilution with a saturated aqueous solution of ammonium chloride (40 mL), the reaction mixture was extracted with ethyl acetate (30 mL and 2 × 15 mL). The organic layer was washed with brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue (**13c**/**14c** = 65:1 by GC) was triturated with hexane (10 mL). The crystalline product was collected by filtration to give **13c** (3.06 g, 88%) as colorless crystals. M.p. 130–131 °C (hexane). IR (KBr): $\tilde{\nu}$ = 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 2.0 Hz, 1 H), 6.96 (d, J = 2.0 Hz, 1 H), 3.67 (m, 1 H), 3.50 (m, 1 H), 1.54 (d, J = 6.9 Hz, 3 H), 1.51 (d, J = 6.9 Hz, 3 H), 1.19 (d, J = 6.7 Hz, 3 H), 1.12 (d, J = 6.2 Hz, 3 H), 0.42 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 147.8, 143.0, 135.4, 133.7, 129.3, 124.3, 51.0, 46.0, 20.6, 20.2, 20.1, 20.0, 1.2 ppm. $C_{16}H_{25}Cl_2NOSi$ (346.38): calcd. C 55.48, H 7.28, Cl 20.47, N 4.04; found C 55.69, H 7.45, Cl 20.43, N 4.05.

3,5-Difluoro-*N*,*N*-diisopropyl-2-(trimethylsilyl)benzamide (13d): A solution of BuLi (2.5 M in hexane, 12.35 mL, 30.9 mmol) was added to a solution of **10b** (6.15 g, 25.5 mmol) and TMSCl (9.65 mL, 8.35 g, 76 mmol) in THF (63 mL) at –78 °C. After stirring at –78 °C for 1 h, the cooling bath was removed, and the temperature of the mixture rose to ambient temperature over a period of 1.5 h. After dilution with a saturated aqueous solution of ammonium chloride (50 mL), the reaction mixture was extracted with diethyl ether (50 mL and 2 × 30 mL). The organic layer was washed with brine (100 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue (8.35 g, **13d**/**14d** = 100:1 by GC) was triturated with cold pentane (approximately –20 °C, 25 mL) to give of **13d** (6.31 g, 79%) as colorless crystals. M.p. 126–127 °C (pentane). IR (KBr): $\tilde{\nu}$ = 2970, 1626 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.71 (td, J = 9.3, 2.2 Hz, 1 H), 6.65 (dd, J = 8.6, 2.4 Hz, 1 H), 3.71 (m, 1 H), 3.50 (m, 1 H), 1.52 (≈ t, J = 8.1 Hz, 6 H), 1.16 (≈ t, J = 6.9 Hz, 6 H), 0.34 (d, J = 1.8 Hz, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5 (t, J = 2.9 Hz), 168.4 (dd, J = 243.7, 11.2 Hz), 163.5 (dd, J = 252.5, 13.9 Hz), 147.3 (dd, J = 12.2, 7.3 Hz), 119.3 (dd, J = 30.8, 4.0 Hz), 109.0 (dd, J = 21.0, 3.4 Hz), 103.1 (dd, J = 31.7, 23.4 Hz), 50.8, 46.0, 20.6, 20.3, 20.0, 0.4 (d, J = 2.9 Hz) ppm. $C_{16}H_{25}F_2NOSi$ (313.47): calcd. C 61.31, H 8.04, N 4.47; found C 61.20, H 8.23, N 4.36.

3,5-Dichloro-4-formyl-*N*,*N*-diisopropylbenzamide (14a). By Method A: A solution of BuLi (2.5 M in hexane, 9.6 mL, 24 mmol) was added to a solution of **10a** (5.48 g, 20 mmol) in THF (48 mL) at –78 °C. After stirring at –78 °C for 7 h, DMF (3 mL, 2.85 g, 39 mmol) was added while the temperature of the mixture rose to –50 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (50 mL) and extracted with ethyl acetate (40 mL and 2 × 20 mL). The organic layer was washed with brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with hexane (15 mL). Filtration of the crystalline product gave **14a** (4.77 g, 79%) as colorless crystals. M.p. 95–96 °C (hexane/ethyl acetate). IR (KBr): $\tilde{\nu}$ = 1710, 1634 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 10.35 (s, 1 H), 7.55 (s, 2 H), 3.58 (m, 2 H), 1.43 (m, 6 H), 1.23 (m, 6 H) ppm. ^{13}C NMR (100 MHz, [D_6]-DMSO): δ = 189.1, 165.8, 144.21, 135.7, 130.2, 126.6, 51.0, 45.3, 20.2 ppm. $C_{14}H_{17}Cl_2NO_2$ (302.20): calcd. C 55.64, H 5.67, Cl 23.26, N 4.63; found C 55.76, H 5.73, Cl 23.51, N 4.55. **By Method B:** A solution of LDA (1.8 M in THF/heptane/ethylbenzene, 16.8 mL, 30 mmol) was added to a solution of 3,5-dichloro-*N*,*N*-diisopropylbenzamide (**10a**, 5.48 g, 20 mmol) in THF (48 mL) at –78 °C. After stirring at –78 °C for 1 h, DMF (3.0 mL, 2.85 g, 39 mmol) was added while the temperature of the mixture rose to –55 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (50 mL) and extracted with ethyl acetate (40 mL and 2 × 15 mL). The organic layer was washed with brine (80 mL) and dried with $MgSO_4$. The solvents were evaporated, and the resulting residue was triturated with hexane (20 mL). The crystalline product was collected by filtration to give of **14a** (4.90 g, 81%) as colorless crystals. M.p. 95–96 °C (hexane/ethyl acetate).

3,5-Difluoro-4-formyl-*N*,*N*-diisopropylbenzamide (14b). By Method A: A solution of BuLi (2.5 M solution in hexane, 20.9 mL, 52 mmol)

was added to a solution of **10b** (11.0 g, 45.6 mmol) in THF (112 mL) at –78 °C. After stirring at –78 °C for 1 h, DMF (4.72 mL, 4.06 g, 61 mmol) was added while the temperature of the mixture rose to –55 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (100 mL) and extracted with ethyl acetate (100 mL and 2 × 50 mL). The organic layer was washed with brine (100 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with cold hexane (approximately –20 °C, 25 mL). The crystalline product was collected by filtration to give **14b** (11.2 g, 91%) as colorless crystals. M.p. 105–105.5 °C (hexane/ethyl acetate). IR (KBr): $\tilde{\nu}$ = 1705, 1631 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 10.34 (s, 1 H), 6.93 (m, 2 H), 3.61 (m, 2 H), 1.33 (m, 12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 183.7 (t, J = 4.2 Hz), 166.6 (t, J = 1.9 Hz), 163.1 (dd, J = 266.0, 5.7 Hz), 146.5 (t, J = 9.9 Hz), 114.1 (t, J = 11.1 Hz), 109.8 (dd, J = 23.2, 3.0 Hz), 50.9, 46.5, 20.5 ppm. $C_{14}H_{17}F_2NO_2$ (269.29): calcd. C 62.44, H 6.36, N 5.20; found C 62.11, H 6.22, N 5.13. **By Method B:** A solution of LDA (1.8 M in THF/heptane/ethylbenzene, 16.8 mL, 30 mmol) was added to a solution of **10b** (4.82 g, 20 mmol) in THF (48 mL) at –78 °C. After stirring at –78 °C for 1 h, DMF (3.0 mL, 2.83 g, 39 mmol) was added while the temperature of the mixture rose to –60 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (40 mL) and extracted with ethyl acetate (40 mL and 2 × 20 mL). The organic layer was washed with brine (90 mL) and dried with $MgSO_4$. The solvents were evaporated, and the resulting residue was triturated with cold hexane (approximately –20 °C, 15 mL). The crystalline product was collected by filtration to give **14b** (4.55 g, 81%) as an off-white solid. M.p. 105–105.5 °C (hexane/ethyl acetate).

3,5-Dichloro-*N*,*N*-diisopropyl-4-(trimethylsilyl)benzamide (14c). By Method A: A solution of BuLi (2.5 M in hexane, 4.8 mL, 12 mmol) was added to a solution of **10a** (2.74 g, 10 mmol) in THF (24 mL) at –78 °C. After stirring at –78 °C for 7 h, TMSCl (2.0 mL, 1.72 g, 15.8 mmol) was added while the temperature of the mixture rose to –65 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (50 mL) and extracted with ethyl acetate (25 mL and 2 × 10 mL). The organic layer was washed with brine (40 mL) and dried with $MgSO_4$. The solvents were evaporated, and the resulting residue (**14c/13c** = 100:1 by GC) was triturated with pentane (12 mL). The crystalline product was collected by filtration to give **14c** (2.87 g, 83%) as off-white crystals. M.p. 129–131 °C (hexane, colorless crystals). IR (KBr): $\tilde{\nu}$ = 1632 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.16 (s, 2 H), 3.73 (m, 1 H), 3.60 (m, 1 H), 1.43 (m, 6 H), 1.23 (m, 6 H), 0.51 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 142.0, 141.3, 137.3, 125.6, 51.1, 46.2, 20.6, 2.8 ppm. $C_{16}H_{25}Cl_2NOSi$ (346.38): calcd. C 55.48, H 7.28, Cl 20.47, N 4.04; found C 55.81, H 7.38, Cl 20.56, N 3.84. **By Method B:** A solution of LDA (1.8 M solution in THF/heptane/ethylbenzene, 16.8 mL, 30 mmol) was added to a solution of **10a** (5.48 g, 20 mmol) in THF (48 mL) at –78 °C. After stirring at –78 °C for 30 min, TMSCl (7.6 mL, 6.50 g, 60 mmol) was added while the temperature of the mixture rose to –60 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (80 mL) and extracted with ethyl acetate (60 mL and 2 × 20 mL). The organic layer was washed with brine (80 mL) and dried with $MgSO_4$. The solvents were evaporated, and the resulting residue was triturated with hexane (30 mL). The crystalline product was collected by filtration to give **14c** (6.43 g, 93%) as pale brown crystals. M.p. 129–131 °C (hexane, colorless crystals).

3,5-Difluoro-*N*,*N*-diisopropyl-4-(trimethylsilyl)benzamide (14d). By Method A: A solution of BuLi (2.5 M in hexane, 24.7 mL, 61 mmol) was added to a solution of **10b** (12.3 g, 51 mmol) in THF (126 mL) at –78 °C. After stirring at –78 °C for 1 h, TMSCl (19.3 mL, 16.7 g, 152 mmol) was added while the temperature of the mixture rose to –60 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (100 mL) and extracted with diethyl ether (70 mL and 2 × 50 mL). The organic layer was washed with brine (100 mL) and dried with $MgSO_4$. The solvents were evaporated, and the resulting residue (15.95 g, **14d/13d** = 64:1 by GC) was triturated with cold pentane (approximately –50 °C, 30 mL) to give **14d** (12.45 g, 78%) as colorless needles. M.p. 80–80.5 °C (pentane). IR (KBr): $\tilde{\nu}$ = 2975, 1632 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.74 (m, 2 H), 3.65 (m, 2 H), 1.34 (m, 12 H), 0.37 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.2 (t, J = 2.7 Hz), 166.9 (dd, J = 245.7, 16.5 Hz), 142.7 (t, J = 9.5 Hz), 119.2 (t, J = 5.3 Hz), 108.4 (dd, J = 30.2, 2.3 Hz), 50.7, 47.2, 20.6, 0.1 (t, J = 2.7 Hz) ppm. $C_{16}H_{25}F_2NOSi$ (313.47): calcd. C 61.31, H 8.04, N 4.47; found C 60.89, H 8.23, N 4.38. **By Method B:** A solution of LDA (1.8 M solution in THF/heptane/ethylbenzene, 16.8 mL, 30 mmol) was added to a solution of **10b** (4.82 g, 20 mmol) in THF (48 mL) at –78 °C. After stirring at –78 °C for 1 h, TMSCl (5 mL, 4.33 g, 39 mmol) was added while the temperature of the mixture rose to –60 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (40 mL) and extracted with ethyl acetate (40 mL and 2 × 20 mL). The organic layer was washed with brine (90 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with cold pentane (approximately –50 °C, 15 mL). The crystalline product was collected by filtration to give of **14d** (5.20 g, 83%) as an off-white solid. M.p. 80–80.5 °C (pentane).

3,5-Dichloro-2-(hydroxymethyl)-*N*,*N*-diisopropylbenzamide (15): Sodium borohydride (1.0 g, 26.4 mmol) was added to a solution of **13a** (5.0 g, 16.5 mmol) in methanol (80 mL), and the reaction mixture was cooled in an ice/water bath. After stirring for 5 h, the solvent was evaporated, water (40 mL) was added to the residue, and the mixture was extracted with diethyl ether (3 × 30 mL). The ethereal layer was washed with brine (40 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with hexane (20 mL). The product was collected by filtration to give **15** (4.20 g, 83%) as colorless crystals. M.p. 141–142 °C (hexane). IR (KBr): $\tilde{\nu}$ = 3510, 3069, 1615 cm^{-1}. ^1H NMR (200 MHz, [D_6]DMSO): δ = 7.58 (d, J = 2.2 Hz, 1 H), 7.24 (d, J = 2.2 Hz, 1 H), 5.10 (dd, J = 5.5, 4.0 Hz, 1 H), 4.59 (dd, J = 11.7, 4.0 Hz, 1 H), 4.45 (dd, J = 11.7, 5.9 Hz, 1 H), 3.55 (m, 1 H), 3.53 (m, 1 H), 1.45 (d, J = 6.6 Hz, 6 H), 1.10 (d, J = 6.6 Hz, 3 H), 1.08 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 166.7, 142.2, 135.5, 133.9, 133.0, 128.6, 123.8, 57.8, 50.8, 45.0, 20.3, 20.1, 20.0, 19.7 ppm. $C_{14}H_{19}Cl_2NO_2$ (304.22): calcd. C 55.27, H 6.30, Cl 23.31, N 4.60; found C 55.35, H 6.39, Cl 23.34, N 4.54.

3,5-Difluoro-2-formyl-*N*,*N*-diisopropyl-4-(trimethylsilyl)benzamide (16): A solution of BuLi (2.5 M in hexane, 15 mL, 37.5 mmol) was added to a solution of **14d** (10.3 g, 32.9 mmol) in THF (72 mL) at –78 °C. After stirring at –78 °C for 1 h, DMF (3.4 mL, 3.21 g, 44 mmol) was added while the temperature of the mixture rose to –60 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (50 mL) and extracted with ethyl acetate (50 mL and 2 × 20 mL). The organic layer was washed with brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue (11.1 g) was triturated with cold pentane (approximately –50 °C, 35 mL) to give **16** (8.25 g, 74%) as colorless crystals. M.p. 87–88 °C

(pentane). IR (KBr): $\tilde{\nu}$ = 2976, 1638 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.27 (s, 1 H), 6.67 (d, J = 7.9 Hz, 1 H), 3.52 (m, 2 H), 1.59 (m, 6 H), 1.12 (d, J = 6.6 Hz, 6 H), 0.41 (t, J = 1.3 Hz, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.9 (d, J = 8.3 Hz), 170.1 (dd, J = 255.7, 17.6 Hz), 169.7 (dd, J = 257.2, 17.6 Hz), 166.6 (t, J = 1.0 Hz), 143.9 (dd, J = 10.2, 1.9 Hz), 117.3 (dd, J = 12.7, 3.0 Hz), 114.7 (t, J = 34.7 Hz), 109.9 (dd, J = 28.8, 2.9 Hz), 51.2, 46.0, 20.4, 20.0, 0.0 (t, J = 2.6 Hz) ppm. $C_{17}H_{25}F_2NO_2Si$ (341.48): calcd. C 59.80, H 7.38, N 4.10; found C 60.37, H 7.42, N 4.11.

3,5-Difluoro-2-(hydroxymethyl)-*N*,*N*-diisopropyl-4-(trimethylsilyl)-benzamide (17): Sodium borohydride (1.0 g, 26.4 mmol) was added to a solution of **16** (6.0 g, 17.6 mmol) in methanol (50 mL), and the reaction mixture was cooled with an ice/water bath. After stirring for 5 h, the solvent was evaporated, water (40 mL) was added to the residue, and the mixture was extracted with diethyl ether (3 × 40 mL). The ethereal layer was washed with brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with hexane (20 mL). The product was collected by filtration to give of **17** (5.54 g, 92%) as colorless crystals. M.p. 110–111 °C (hexane). IR (KBr): $\tilde{\nu}$ = 3283, 1621 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.62 (dd, J = 7.9, 0.9 Hz, 1 H), 4.67 (m, 1 H), 4.45 (m, 1 H), 3.82 (m, 1 H), 3.55 (m, 1 H), 3.17 (t, J = 6.7 Hz, 1 H), 1.55 (m, 6 H), 1.15 (m, 6 H), 0.38 (t, J = 1.5 Hz, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.6 (dd, J = 3.4, 2.7 Hz), 166.0 (dd, J = 246.5, 16.4 Hz), 165.4 (dd, J = 247.3, 16.4 Hz), 142.3 (dd, J = 8.8, 5.3 Hz), 121.1 (dd, J = 22.1, 3.8 Hz), 114.4 (dd, J = 36.2, 33.9 Hz), 107.6 (dd, J = 28.2, 4.2 Hz), 56.2 (d, J = 5.3 Hz), 51.3, 46.3, 20.8, 20.5, 20.5, 20.3, 0.1 (t, J = 3.1 Hz) ppm. $C_{17}H_{27}F_2NO_2Si$ (343.49): calcd. C 59.45, H 7.92, N 4.08; found C 59.14, H 8.09, N 3.95.

3,5-Difluoro-2-(hydroxymethyl)-*N*,*N*-diisopropylbenzamide (18): A mixture of **17** (2.0 g, 5.8 mmol) and cesium fluoride (2.0 g, 13.2 mmol) in acetonitrile (20 mL) was stirred at ambient temperature for 16 h. The solvent was evaporated, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (20 mL and 2 × 15 mL). The organic layer was washed with brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with hexane (10 mL). The product was collected by filtration to give **18** (1.55 g, 98%) as colorless needles. M.p. 134–134.5 °C (hexane/ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3346, 1618 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.84 (app. td, J = 9.3, 2.0 Hz, 1 H), 6.71 (d, J = 7.5 Hz, 1 H), 4.69 (d, J = 11.5 Hz, 1 H), 4.46 (d, J = 11.5 Hz, 1 H), 3.79 (m, 1 H), 3.56 (m, 1 H), 3.15 (m, 1 H), 1.57 (d, J = 6.2 Hz, 3 H), 1.54 (d, J = 6.2 Hz, 3 H), 1.20 (d, J = 6.0 Hz, 3 H), 1.14 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4 (d, J = 3.0 Hz), 162.0 (dd, J = 251.0, 12.2 Hz), 161.6 (dd, J = 252.0, 11.7 Hz), 141.4 (dd, J = 12.2, 11.7 Hz), 121.8 (d, J = 17.5, 3.9 Hz), 108.1 (dd, J = 22.4, 3.9 Hz), 104.3 (dd, J = 26.4, 25.0 Hz), 55.8 (d, J = 4.9 Hz), 51.4, 46.3, 20.8, 20.5, 20.3 ppm. $C_{14}H_{19}F_2NO_2$ (271.31): calcd. C 61.98, H 7.06, N 5.16; found C 61.63, H 7.17, N 5.07.

4,6-Difluoro-5-(trimethylsilyl)-2-benzofuran-1(3*H*)-one (19): A mixture of **17** (4.0 g, 11.6 mmol) and aqueous hydrochloric acid (12%, 40 mL, 140 mmol) was heated to reflux for 6 h. After cooling to ambient temperature, the reaction mixture was extracted with dichloromethane (3 × 25 mL). The organic layers were combined, extracted with brine (50 mL), and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with cold hexane (approximately –20 °C, 8 mL). The product was collected by filtration to give **19** (2.64 g, 93%) as colorless crystals. M.p. 82–83 °C (hexane). IR (KBr): $\tilde{\nu}$ = 1766 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 6.8 Hz, 1 H), 5.32 (s, 2 H), 0.43 (t, J = 1.6 Hz, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7 (dd, J = 4.9, 2.9 Hz), 167.6 (dd, J = 246.6, 12.7 Hz), 160.4 (dd, J = 248.5, 16.1 Hz), 130.5 (dd, J = 11.2, 6.8 Hz), 128.1 (dd, J = 24.9, 2.9 Hz), 121.2 (dd, J = 36.6, 31.7 Hz), 107.8 (dd, J = 30.3, 4.9 Hz), 66.9 (d, J = 1.5 Hz), –0.14 (t, J = 3.4 Hz) ppm. $C_{11}H_{12}F_2O_2Si$ (242.30): calcd. C 54.53, H 4.99; found C 54.48, H 4.91.

4,6-Dichloro-2-benzofuran-1(3*H*)-one (4a): A mixture of **15** (40.0 g, 131.5 mmol) and aqueous hydrochloric acid (10%, 215 mL) was heated to reflux for 10 h. After cooling to ambient temperature, the reaction mixture was extracted with dichloromethane (3 × 100 mL). The organic layers were combined, extracted with brine (200 mL), and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with a mixture of hexane/ethyl acetate (10:1, 120 mL). The product was collected by filtration to give **4a** (20.9 g, 78%) as colorless crystals. M.p. 87–88 °C (hexane/ethyl actate). IR (KBr): $\tilde{\nu}$ = 1775 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.81 (d, J = 1.5 Hz, 1 H), 7.66 (d, J = 1.6 Hz, 1 H), 5.28 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.5, 142.8, 136.4, 133.8, 129.5, 129.1, 124.2, 68.4 ppm. $C_8H_4Cl_2O_2$ (203.03): calcd. C 47.33, H 1.99, Cl 34.92; found C 47.36, H 2.03, Cl 34.89.

4,6-Difluoro-2-benzofuran-1(3*H*)-one (4b). By Deprotection of 19: A mixture of **19** (0.80 g, 3.3 mmol) and cesium fluoride (0.94 g, 6.2 mmol) in acetonitrile (12 mL) was stirred at ambient temperature for 24 h. The solvent was evaporated, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (20 mL and 2 × 15 mL). The organic layer was washed with brine (50 mL) and dried with $MgSO_4$. The solvents were evaporated, the residue was triturated with hexane (10 mL), and the product was collected by filtration to give of **4b** (0.45 g, 80%) as colorless needles. M.p. 88–89 °C (hexane). IR (KBr): $\tilde{\nu}$ = 1761 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 (dd, J = 6.6, 2.0 Hz, 1 H), 7.15 (td, J = 8.6, 2.0 Hz, 1 H), 5.35 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4 (dd, J = 4.4, 2.5 Hz), 163.6 (dd, J = 252.4, 8.8 Hz), 156.7 (dd, J = 54.9, 12.2 Hz), 129.7 (dd, J = 10.3, 5.8 Hz), 128.4 (dd, J = 19.5, 2.9 Hz), 109.6 (dd, J = 27.4, 22.9 Hz), 108.5 (dd, J = 23.9, 4.4 Hz), 66.7 (d, J = 1.0 Hz) ppm. $C_8H_4F_2O_2$ (170.12): calcd. C 56.48, H 2.37; found C 56.31, H 2.36. **By Cyclization of 18:** A mixture of **18** (1.40 g, 5.16 mmol) and aqueous hydrochloric acid (18%, 12 mL, 60 mmol) was heated to reflux for 3 h. After cooling to ambient temperature, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The ethereal layers were combined, extracted with brine (15 mL), and dried with $MgSO_4$. The solvents were evaporated, and the residue was triturated with cold hexane (approximately –20 °C, 5 mL). The product was collected by filtration to give of **4b** (0.81 g, 92%) as colorless needles. M.p. 88–89 °C (hexane).

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