A Homologous Series of *O*- and *N*-Functionalized 2,2-Difluoro-1,3-benzodioxoles: an Exercise in Organometallic Methodology

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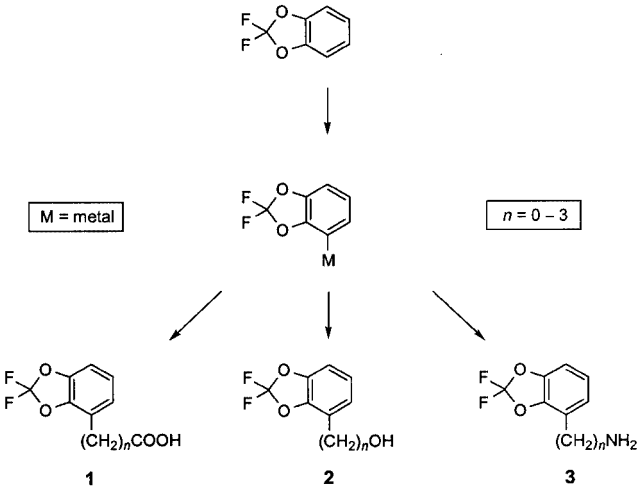
Keywords: Lithiation / Alcohols / Aldehydes / Acids / Amines

The conversion of 2,2-difluoro-1,3-benzodioxole, an exceptionally acidic arene, via a 4-lithiated intermediate into more than three dozen new derivatives was conceived as a case study. The lithiated species was trapped by C_0-electrophiles (4-toluenesulfonyl azide, fluorodimethoxyborane, iodine), C_1-electrophiles (carbon dioxide, *N*,*N*-dimethylformamide, formaldehyde, dimethyl sulfate), C_2-electrophiles (oxalic acid diesters, oxirane), C_3-electrophiles (oxetane), and higher alkyl iodides. The resulting carboxylic acid **1a** may be treated with organolithium compounds to afford ketones (e.g. **10**) and the aldehyde **9** can be condensed with nitromethane or acetic anhydride under basic conditions. If not oxidized with chromium trioxide to the corresponding carboxylic acids, the alcohols **2b**, **2c**, and **2d** can be transformed into the corresponding bromides (**12**) or sulfonates (**13**). Their condensation with nitrogen-containing C_0-nucleophiles (hydroxylamine, sodium azide, potassium phthalimide), C_1-nucleophiles (potassium cyanide), and C_2-nucleophiles (acetonitrile) opens a convenient access to the amines **3**. Other reactions gave, despite a proven track record in other areas, only moderate yields.

Introduction

In the literal sense, "methodology" means the *knowledge* of methods and, by extension, also their critical evaluation. Organometallic reactions have become favorite tools of modern organic synthesis, and therefore we deemed it appropriate to embark on a systematic investigation of how efficiently metal-bearing intermediates can be functionalized and chain-lengthened. In other words, rather than scrutinize various possibilities for the generation of organometallic species,[1] we wanted this time to put electrophiles, in particular carboelectrophiles, to the test.

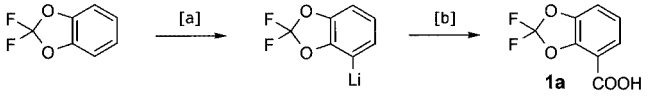
2,2-Difluoro-1,3-benzodioxole, a technical bulk product, was selected as the substrate for structural elaboration, as it undergoes metalation at the 4-position with extraordinary ease.[2] We set ourselves the task to explore, in a comparative study, the various ways for converting it into the carboxylic acids **1**, the phenolic or alcoholic hydroxy derivatives **2** and the aromatic or aliphatic amines **3**.



Results

Carboxylic Acids

The carboxylation of (2,2-difluoro-1,3-benzodioxol-4-yl)-lithium has already been reported to afford the acid **1a** in 81% yield.[3] As this reaction is of unmatched simplicity, we did not attempt to find a second route to product **1a**.



[a] LiCH(CH3)C2H5 in tetrahydrofuran (THF) at –75 °C. [b] (1.) CO_2, (2.) Ethereal HCl.

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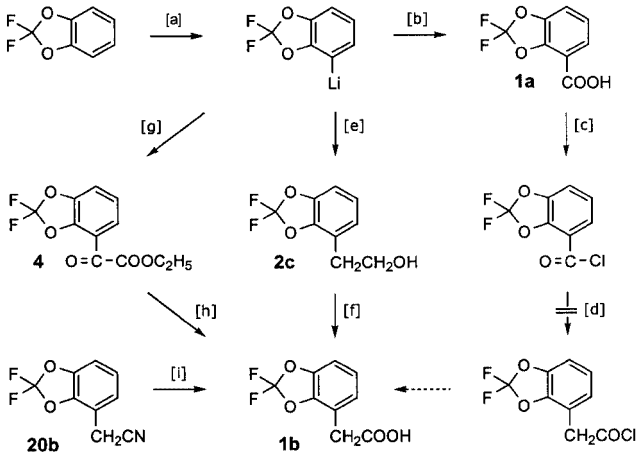
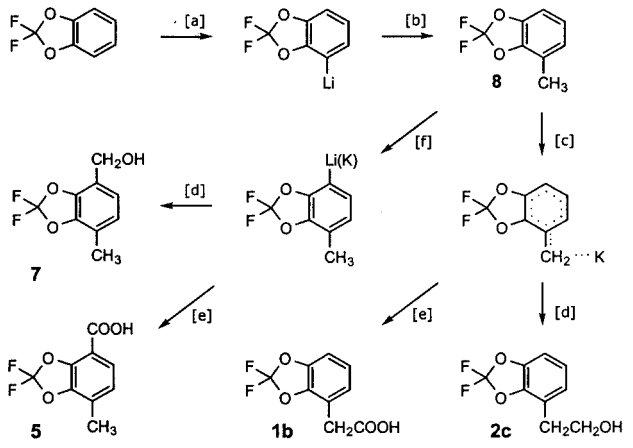
An expedient transformation was achieved when the 4-lithiated 2,2-difluoro-1,3-benzodioxole was trapped with diethyl oxalate and the resulting α-oxo ester **4** (83%) subsequently submitted to a Wolff−Kishner−Huang reduction and concomitant saponification to (2,2-difluoro-1,3-benzodioxol-4-yl)acetic acid (**1b**; 82%). The latter compound could also be prepared in a most straightforward manner by Jones oxidation of 2-(2,2-difluoro-1,3-benzodioxol-4-yl)ethanol (**2c**)[3] or by hydrolysis of (2,2-difluoro-1,3-benzodioxol-4-yl)acetonitrile (**20b**; see below). In contrast, the attempted conversion of the aromatic acid **1a** into its rearranged homolog **1b** by means of the Arndt−Eistert sequence failed completely.



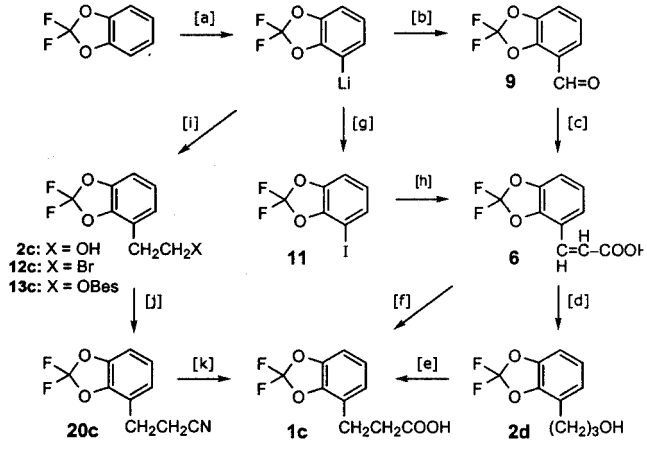
[a] LiCH(CH$_3$)C$_2$H$_5$ in THF at −75 °C. [b] (1.) CO_2, (2.) HCl. [c] $SOCl_2$. [d] CH_2N_2 (2 equiv.) in diethyl ether (DEE). [e] (1.) CuI; (2.) oxirane. [f] Chromium trioxide. [g] Diethyl oxalate. [h] Hydrazine hydrate and KOH in diethylene glycol. [i] Aqueous KOH.

The acid **1b** and the alcohol **2c** could be finally accessed via 2,2-difluoro-4-methyl-1,3-benzodioxole (**8**), readily obtained by condensation of the lithiated intermediate with dimethyl sulfate in 71% yield. Deprotonation with lithium diisopropylamide (LIDA) in the presence of potassium *tert*-butoxide (KOR),[4−8] followed by carboxylation or by addition to formaldehyde, gave the products **1b** (71%) and **2c** (35%), respectively. However, substrate **8** offered another impressive example of "optional site selectivity".[9−11] When LIDA/KOR was replaced by either *sec*-butyllithium or lithium 2,2,6,6-tetramethylpiperidide (LITMP) in the presence of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA) and potassium *tert*-butoxide as the base, proton abstraction occurred exclusively at the aromatic 7-position. Consequently, the acid **5** (93%) and the benzyl alcohol **7** (64%) were formed with carbon dioxide and formaldehyde, respectively.

Alcohol **2c** was also the starting point for an expedient preparation of the next higher acid homologue **1c**. The corresponding bromide **12c** and benzenesulfonate **13c** (Bes = $SO_2C_6H_5$) underwent nucleophilic substitution with potassium cyanide to give the nitrile **20c** (87% and 88%, respectively), the alkaline hydrolysis of which produced the acid **1c** (82%). The same compound was obtained by submitting the aldehyde **9** to a Perkin condensation. The resulting α,β-unsaturated acid **6** (88%), also accessible by a Heck−Morizawa reaction between 2,2-difluoro-4-iodo-1,3-benzodioxole (**11**) and acrylic acid in 96% yield, was either completely reduced to the arylpropanol **2d** (84%), which then had to be reoxidized to the acid **1c** (92%), or the latter was obtained in 99% yield by partial hydrogenation of the unsaturated acid **6**. Finally, acid **1c** was isolated in 48% yield after the bromo compound **12c** was subjected to a substitution[12,13] reaction with disodium tetracarbonylferrate followed by oxidation with air.

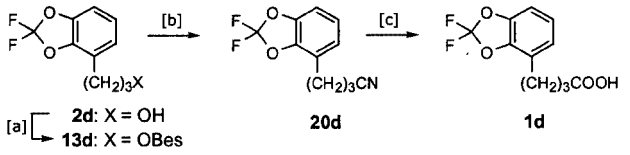


[a] LiCH(CH$_3$)C$_2$H$_5$ in THF at −75 °C. [b] Dimethyl sulfate. [c] Lithium diisopropylamide in the presence of potassium *tert*-butoxide (LIDA-KOR) in THF at −75 °C. [d] Paraformaldehyde. [e] (1.) CO_2, (2.) HCl. [f] *sec*-Butyllithium or lithium 2,2,6,6-tetramethylpiperidide (LITMP) in the presence of *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PMDTA) and potassium *tert*-butoxide (KOR).



[a] LiCH(CH$_3$)C$_2$H$_5$ in THF at −75 °C. [b] (1.) O=CHN(CH$_3$)$_2$, (2.) H_2O. [c] $(H_3CCO)_2O$ and $H_3CCOONa$ at 250 °C. [d] $LiAlH_4$ in DEE at 40 °C. [e] $K_2Cr_2O_7$ in aqu. H_2SO_4 at 0 °C. [f] H_2 {Pd} in $HOCH_3$ at 25 °C. [g] I_2 in THF at −75 °C. [h] H_2C=CH−COOH and N(C$_2$H$_5$)$_3$ in the presence of {Pd(OOCCH$_3$)$_2$} in H_3CCN at 80 °C. [i] (1.) Oxirane, (2.) $(H_5C_6)_3PBr_2$ or (1.) oxirane, (2.) $ClSO_2C_6H_5$ in DEE and aqueous KOH. [j] KCN in C_2H_5OH. [k] KOH in aqueous ethanol under reflux.

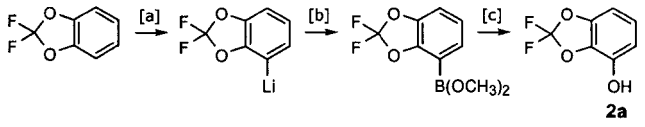
The 3-aryl-1-propanol **2d** was converted via the corresponding benzenesulfonate **13d** (OBes = $OSO_2C_6H_5$) into the nitrile **20d** (82%) in the same way as described above for the lower homolog **20c**. Alkaline hydrolysis of nitrile **20d** afforded the acid **1d** (87%).



[a] $ClSO_2C_6H_5$ in DEE and aqueous KOH. [b] KCN in ethanol. [c] KOH in aqueous ethanol under reflux.

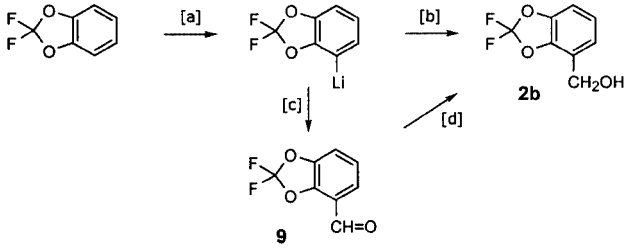
Phenols and Alcohols

The phenol **2a** was readily prepared by consecutive lithiation, borylation (using fluorodimethoxyborane[14,15]), and oxidation. Product **2a** was isolated in high yield (92%) and purity.



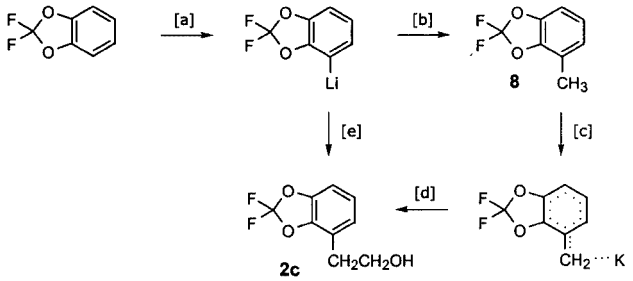
[a] $LiCH(CH_3)C_2H_5$ in THF at −75 °C. [b] $FB(OCH_3)_2$ diethyl etherate. [c] H_2O_2 (30% aqueous) and NaOH.

The benzyl alcohol **2b** was formed in only moderate yield (27%) when the lithiated species was treated with paraformaldehyde. It proved preferable to formylate the intermediate with *N*,*N*-dimethylformamide to obtain, after hydrolysis, the aldehyde **9** (88%), which then was reduced with sodium borohydride in methanol to the alcohol **2b** (95%).



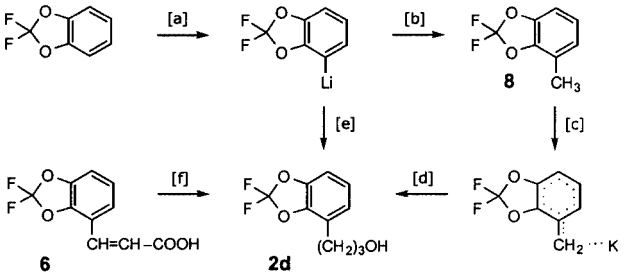
[a] $LiCH(CH_3)C_2H_5$ in THF at −75 °C. [b] (1.) Paraformaldehyde, (2.) H_2O. [c] (1.) $O{=}CH{-}N(CH_3)_2$, (2.) HCl. [d] $NaBH_4$ in methanol.

Alcohol **2c** has previously been prepared by the reaction with oxirane in only 54% yield.[3] Apparently, the organolithium intermediate acts as both a nucleophile and as a base, thus causing deprotonation of the electrophile and ring-opening to the acetaldehyde enolate. The supernucleophilic, but only marginally basic, cuprates avoid this kind of problem. Readily prepared by treatment of the lithium species with cuprous iodide, the resulting copper reagent afforded the alcohol **2c** in almost quantitative yield (85% being isolated). Alternatively, alcohol **2c** was found to be accessible in 35% yield by deprotonation of the methyl derivative **8** at the benzylic position (see above), followed by the addition of paraformaldehyde.



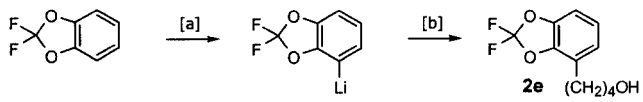
[a] $LiCH(CH_3)C_2H_5$ in THF at −75 °C. [b] Dimethyl sulfate. [c] LIDA-KOR in THF at −75 °C. [d] (1.) Paraformaldehyde, (2.) H_2O. [e] (2.) Oxirane, (2.) HCl.

The homologous 3-(2,2-difluoro-1,3-benzodioxol-4-yl)-propanol (**2d**; 72%) was prepared similarly by benzylic deprotonation of 2,2-difluoro-4-methyl-1,3-benzodioxole (**8**) followed by addition to oxirane. Alternatively, alcohol **2d** could be prepared by the reaction of (2,2-difluoro-1,3-benzodioxol-4-yl)lithium with oxetane in 41% yield. Finally, the Perkin condensation product **6** was cleanly reduced with lithium aluminum hydride to the alcohol **2d** (84%).



[a] $LiCH(CH_3)C_2H_5$ in THF at −75 °C. [b] (1.) Dimethyl sulfate. [c] LIDA-KOR in THF at −75 °C. [d] (1.) Oxirane, (2.) HCl. [e] (1.) Oxetane, (2.) HCl. [f] $LiAlH_4$ in refluxing DEE.

A chain length of three methylene units does not set limits for the accessibility of ω-(2,2-difluoro-1,3-benzodioxol-4-yl)alkanols. To prepare higher homologs one has simply to replace oxirane or oxetane by suitably acetal-protected ω-haloalkanols.[16] Thus, 1-iodo-4-(methoxymethoxy)butane was smoothly condensed with the 4-lithiated 2,2-difluoro-1,3-benzodioxole to afford, after deprotonation with acid, the alcohol **2e** in 18% yield.

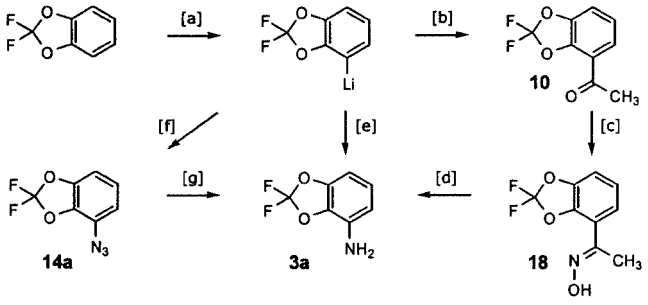


[a] $LiCH(CH_3)C_2H_5$ in THF at −75 °C. [b] (1.) $I(CH_2)_4OCH_2OCH_3$, (2.) Ethereal HCl.

The poor yield suggests the occurrence of β-eliminations and other side reactions. Improved results could presumably be achieved by first attaching an (ω−1)-alkenyl side chain[17] and its subsequent hydroboration and oxidation.

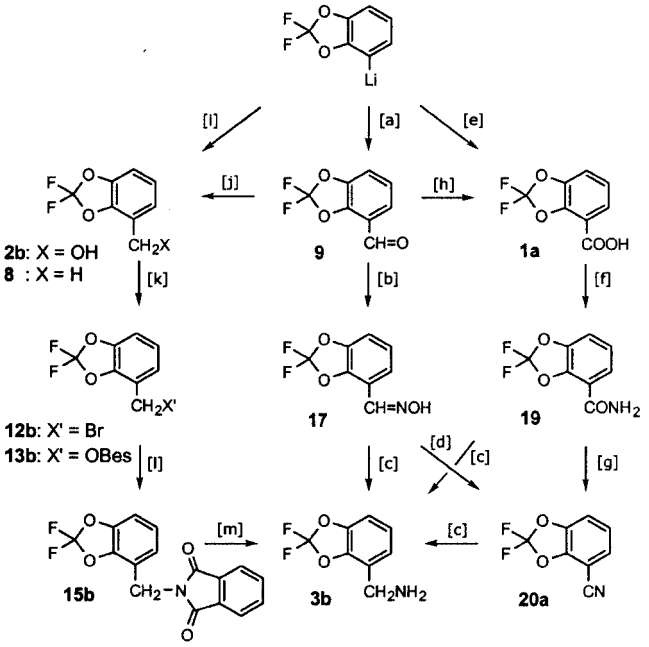
Aromatic and Aliphatic Amines

Using lithium methoxyamide,[18−20] (2,2-difluoro-1,3-benzodioxol-4-yl)lithium could be directly converted into the aniline **3a** although only in moderate yield (40%). The more lengthy route through the ketone **10** (68% from the carboxylic acid **1a**), condensation with hydroxylamine and Beckmann rearrangement of the resulting oxime **18** (84%) proved to be more expedient (83% of **3a** in the last step). Superior still was the reaction of the organolithium intermediate with *p*-toluenesulfonyl azide followed by the reduction of the azido derivative **14a** (94%) to the amine **3a** (80%).



[a] LiCH(CH$_3$)C$_2$H$_5$ in THF at −75 °C. [b] (1.) CO_2, (2.) LiCH$_3$, (3.) H_2O. [c] H_2NOH. [d] (1.) PCl_5 in refluxing benzene, (2.) HCl in refluxing C_2H_5OH. [e] LiNHOCH$_3$ in THF. [f] 4-H$_3$CC$_6$H$_4$SO$_2$N$_3$. [g] H_2 and {Pd} in methanol at 25 °C.

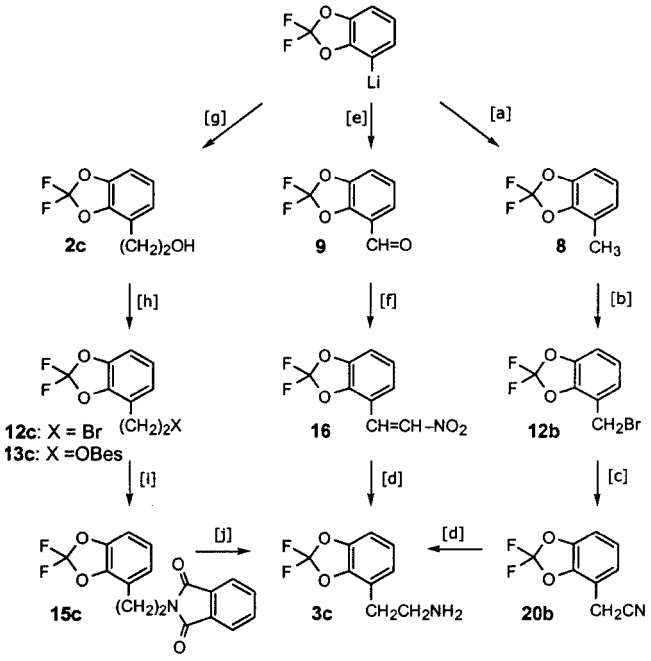
The most straightforward route to the benzylamine **3b** proceeds via the aldehyde **9** and the oxime **17** (96%). The latter compound was reduced to **3b** either with lithium aluminum hydride (89%) or by catalytic hydrogenation (93%). The detour via the nitrile **20a** (91% by dehydration with cyanuric chloride in the presence of pyridine) did not offer any practical advantage. Nevertheless, nitrile **20a**, readily accessible (in 91% yield) by dehydration of the carboxamide **19** (from the carboxylic acid **1a** through the acyl chloride and concentrated aqueous ammonia in 92% yield), could be smoothly reduced with lithium aluminum hydride to give the amine **3b** (86%). Direct reduction of carboxamide **19** with lithium aluminum hydride afforded the amine **3b** in 80% yield. Attempts to subject the carboxamide **19** to a Hofmann rearrangement failed completely. Finally, amine **3b** could also be obtained by means of the Gabriel method. Starting from the benzyl alcohol **2b** or 2,2-difluoro-4-methyl-1,3-benzodioxole (**8**), the benzyl bromide **12b** (86%) or sulfonate **13b** (89%) and the *N*-alkylphthalimide **15b** (75%) were the intermediates.



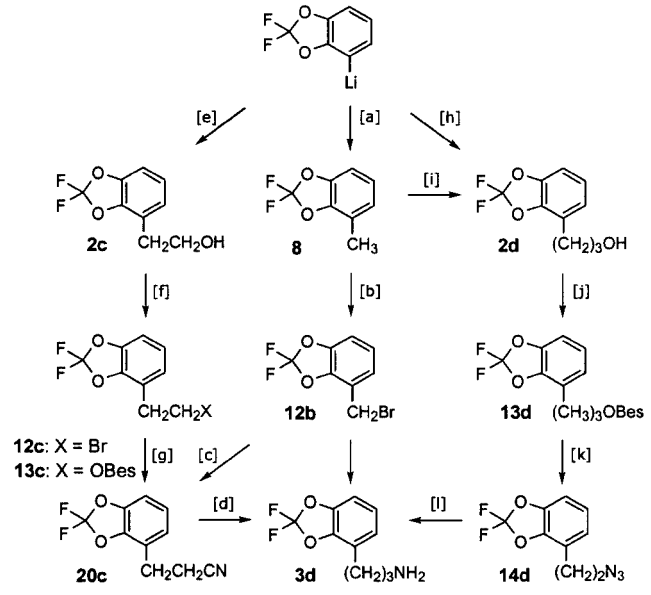
[a] (1.) O=CHN(CH$_3$)$_2$, (2.) H_2O. [b] H_2NOH. [c] $LiAlH_4$ in DEE at 40 °C. [d] Cyanuric chloride and pyridine in dichloromethane. [e] (1.) CO_2, (2.) HCl. [f] (1.) $SOCl_2$, (2.) aq. NH_3. [g] $SOCl_2$, 6 h at 80 °C. [h] $KMnO_4$ in H_3CCOOH. [i] (1.) Paraformaldehyde, (2.) H_2O (→ **2b**) or dimethyl sulfate (→ **8**). [j] $NaBH_4$ in methanol (→ **2b**). [k] **2b** + (H$_5$C$_6$)$_3$PBr$_2$ or **8** + Br_2 in tetrachloromethane (→ **12b**) or **2b** and H$_5$C$_6$SO$_2$Cl in DEE + aqueous KOH (→ **13b**). [l] Potassium phthalimide. [m] Hydrazine hydrate.

Similar principles were applied to prepare the homologous amine **3c**. This compound was obtained by reduction of the nitrile **20b** (86% from the benzyl bromide **12b**) and by hydrazinolysis of the phthalimide **15c** (86% from the alcohol **2c** via the bromide **12c** or sulfonate **13c**) in 89% and 77% yield, respectively. In addition, a Henry condensation was accomplished between the aldehyde **9** and nitromethane, and the nitro compound **16** (75%) thus formed was catalytically hydrogenated to the amine **3c** (89%).

The sequences aiming at the amine **3d** also featured a method not yet tested in the given context. Acetonitrile was deprotonated[21−23] particularly smoothly when the superbasic mixture of lithium diisopropylamide and potassium *tert*-butoxide (LIDA/KOR[4−8]) or of butyllithium and potassium *tert*-butoxide (LIC/KOR[24−26]) was applied and the metal keteneimide was alkylated[22,27] with the bromide **12b** (from **8** in 65% yield) to afford the nitrile **20c** in moderate yield (58%). This precursor to the amine **3d** (92% by reduction with lithium aluminum hydride) could also be efficaciously prepared by nucleophilic substitution of the sulfonate **13c** or the bromide **12c**, as already mentioned above. The final remaining option was the replacement of the hydroxy group in alcohol **2d** by the amino function. For sake of variation, the sulfonate **13d** was this time treated with sodium azide rather than with potassium phthalimide. The resulting azido compound **14d** (85%) was eventually transformed into amine **3d** (93%) by catalytic hydrogenation.

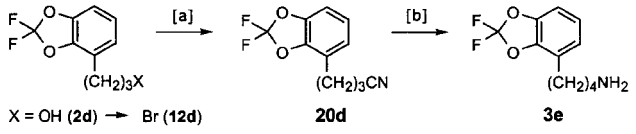


[a] Dimethyl sulfate. [b] Br_2 in tetrachloromethane [c] KCN in ethanol. [d] $LiAlH_4$ in refluxing DEE. [e] (1.) O=CH-N$(CH_3)_2$, (2.) H_2O. [f] (1.) CH_3NO_2 and NaOH in aqueous methanol, (2.) HCl. [g] (1.) CuI, (2.) oxirane. [h] $(H_5C_6)_3PBr_2$ in acetonitrile (→ **12c**) or $ClO_2C_6H_5$ in DEE and aqueous KOH (→ **13c**). [i] Potassium phthalimide. [j] Hydrazine hydrate.



[a] Dimethyl sulfate. [b] Br_2 in tetrachloromethane. [c] Acetonitrile after treatment with LIC-KOR in THF at −75 °C. [d] $LiAlH_4$ in refluxing DEE. [e] (1.) CuI, (2.) oxirane. [f] $(H_5C_6)_3PBr_2$ in acetonitrile (→ **12c**) or $H_5C_6SO_2Cl$ in DEE and aqueous NaOH (→ **13c**). [g] Potassium cyanide in ethanol. [h] (1.) Oxetane, (2.) HCl. [I] (1.) LIDA-KOR in THF at −75 °C, (2.) oxirane, (3.) HCl. [j] $ClSO_2C_6H_5$ in DEE and aqueous NaOH. [k] NaN_3 in aqueous ethanol. [l] H_2 and {Pd/c} in methanol at 25 °C.

The higher homolog **3e** was also found to be readily accessible. All it needed was again to convert the alcohol **2d**, via the corresponding bromide **12d** (88%), into the cyanide **20d** (91%) and to reduce the latter with lithium aluminum hydride to the desired amine **3e** (94%).



[a] KCN in ethanol. [b] $LiAlH_4$ in refluxing DEE.

As can be deduced from the reactions presented above, the cyano group is evidently the optimal precursor function to a primary amino group. It can be introduced quite readily by an S_N2 process using potassium cyanide or the anionized acetonitrile as a C_1- and C_2-nucleophile, respectively. The transition metal catalyzed addition of hydrogen cyanide to olefinic double bonds,[28−32] an economically most attractive option, should not remain unmentioned in this context.

Experimental Section

General: Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.[33−35] ^1H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, samples having been dissolved in deuterochloroform.

1. Carboxylic Acids and Esters

2,2-Difluoro-1,3-benzodioxole-4-carboxylic Acid (1a): The synthesis of **1a** has already been reported.[3] It was obtained by the consecutive reaction of 2,2-difluoro-1,3-benzodioxole with *sec*-butyllithium and dry ice in 81% yield.

Methyl 2,2-Difluoro-1,3-benzodioxole-4-carboxylate: A solution of 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid[3] (**1a**; 10 g, 50 mmol) and boron trifluoride−diethyl etherate (6.3 mL, 7.1 g, 50 mmol) was allowed to stand for 48 h at +25 °C. Distillation afforded a colorless liquid which solidified in an ice bath; needles; m.p. 14−15 °C; b.p. 100−102 °C/14 Torr; n_D^{20} = 1.4800; yield: 9.7 g (90%). ^1H NMR: δ = 7.69 (dd, *J* = 8.2, 1.4 Hz, 1 H), 7.25 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 3.97 (s, 3 H) ppm. ^{13}C NMR: δ = 163.5, 144.5, 143.5, 131.8 (t, *J* = 257 Hz), 125.1, 123.3, 114.2, 113.5, 52.5 ppm. $C_9H_6F_2O_4$ (216.14): calcd. C 50.01, H 2.80; found C 49.87, H 2.67. The methyl ester was formed directly in a yield of 81% when a solution of 2,2-difluoro-1,3-benzodioxole (2.9 mL, 4.0 g, 25 mmol) and *sec*-butyllithium (25 mmol) in tetrahydrofuran (30 mL) and cyclohexane (15 mL), after having been kept at −75 °C for 2 h, was transferred dropwise, in the course of 20 min, through a cannula into a solution of methyl chloroformate (5.0 mL, 6.1 g, 65 mmol) in tetrahydrofuran (20 mL), kept in a methanol/dry ice bath. Immediate distillation gave a colorless liquid; yield: 4.32 g (81%).

(2,2-Difluoro-1,3-benzodioxol-4-yl)acetic Acid (1b): 2-(2,2-Difluoro-1,3-benzodioxol-4-yl)ethanol[3] (**2c**; 2.0 g, 10 mmol) in acetone (50 mL) was added to potassium dichromate (5.9 g, 20 mmol) in 50% aqueous sulfuric acid (10 mL), cooled in an ice bath. After 1 h at 0 °C, the mixture was concentrated before being poured into water (0.10 L) and extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL), dried, and concentrated. The residue was crystallized from hexanes; colorless star-shaped crystals; m.p. 88−89 °C; b.p. 144−146 °C/6 Torr; yield: 1.79 g (82%). ^1H NMR: δ = 7.0 (m, 3 H), 3.73 (s, 2 H) ppm. ^{13}C NMR: δ = 176.1, 143.5, 142.5, 131.3 (t, *J* = 250 Hz),

125.1, 123.5, 115.7, 108.7, 34.1 ppm. $C_9H_6F_2O_4$ (216.14): calcd. C 50.01, H 2.80; found C 49.81, H 2.80. The same compound was prepared from the cyanide **20b** (see Section 6; 2.0 g, 10 mmol) and potassium hydroxide (1.7 g, 30 mmol) in 65% aqueous ethanol (30 mL) by heating under reflux for 3 h in 88% yield and subsequent reduction of ethyl (2,2-difluoro-1,3-benzodioxol-4-yl)oxoacetate (**4**; see below; 2.6 g, 10 mmol) with hydrazine hydrate (50 mL) in the presence of potassium hydroxide (14 g, 0.25 mol), dissolved in diethylene glycol (0.10 L), heated to 190 °C for 6 h, in 82% yield. Finally, the acid **1b** was obtained by the treatment of 2,2-difluoro-4-methyl-1,3-benzodioxole (**8**; see Section 4; 1.7 g, 10 mmol) with lithium diisopropylamide (10 mmol) and potassium *tert*-butoxide (1.1 g, 10 mmol) in tetrahydrofuran (20 mL) and hexanes (6.2 mL) for 2 h at −75 °C followed by carboxylation with dry ice in 71% yield.

3-(2,2-Difluoro-1,3-benzodioxol-4-yl)propanoic Acid (1c): Under nitrogen, palladium (0.27 g, 0.25 mmol; 10 wt.-% on charcoal) was added to a solution of (*E*)-3-(2,2-difluoro-1,3-benzodioxol-4-yl)-2-propenoic acid (**6**; see below; 1.1 g, 5.0 mmol) in methanol (20 mL). Hydrogen gas was bubbled into the stirred reaction mixture until, after 6 h, the uptake ceased. The catalyst was removed by filtration, the solvent evaporated and the residue crystallized from pentanes; colorless platelets; m.p. 65−67 °C; yield: 1.10 g (99%). ^{1}H NMR: δ = 7.0 (m, 1 H), 6.9 (m, 1 H), 3.01 (t, *J* = 7.7 Hz, 2 H), 2.75 (t, *J* = 7.8 Hz, 2 H) ppm. ^{13}C NMR: δ = 177.4, 143.6, 142.1, 131.4 (t, *J* = 256 Hz), 124.2, 123.6, 122.6, 107.8, 33.2, 24.2 ppm. $C_{10}H_8F_2O_4$ (230.16): calcd. C 52.18, H 3.50; found C 52.01, H 3.33. The acid **1c** was independently obtained when a suspension of the disodium tetracarbonylferrate−dioxane (2:3) adduct (8.7 g, 25 mmol) in tetrahydrofuran (50 mL) was vigorously stirred at +25 °C for 2 h after the addition of 4-(2-bromoethyl)-2,2-difluoro-1,3-benzodioxole (6.6 g, 25 mmol), for a further 2 h while air was bubbled in and for a further 6 h after water (0.10 L) had been added. The product was purified by extraction with diethyl ether (3 × 25 mL) and crystallization from pentanes; yield: 2.75 g (48%). The acid **1c** was also prepared from 3-(2,2-difluoro-1,3-benzodioxol-4-yl)propanenitrile (**20c**; see Section 6) by hydrolysis in alkaline medium (for reaction conditions, see above: **20b** → **1b**) in 82% yield and from the alcohol **2d** by oxidation with potassium dichromate (for reaction conditions, see above: **2c** → **1b**) in 92% yield.

4-(2,2-Difluoro-1,3-benzodioxol-4-yl)butanoic Acid (1d): Potassium hydroxide (1.7 g, 30 mmol) in water (10 mL) was added to a solution of 4-(2,2-difluoro-1,3-benzodioxol-4-yl)butanenitrile (2.2 g, 10 mmol) in ethanol (20 mL). The mixture was refluxed for 4 h. Ethanol was then distilled off and the residue was dissolved in water (20 mL), washed with diethyl ether, and filtered. The water phase was acidified to pH = 1 with an aqueous solution of hydrochloric acid and then extracted with diethyl ether (2 × 10 mL). The ethereal phase was dried with sodium sulfate and the solvents were evaporated. The product was crystallized from hexanes as colorless prisms; m.p. 56−57 °C; yield: 2.08 g (87%). ^{1}H NMR: δ = 7.00 (t, *J* = 7.9 Hz, 1 H), 6.9 (m, 2 H), 2.73 (t, *J* = 7.6 Hz, 2 H), 2.41 (t, *J* = 7.4 Hz, 2 H), 2.00 (quint, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR: δ = 179.8, 143.5, 142.2, 131.5 (t, *J* = 252 Hz), 124.4, 123.7, 123.5, 107.5, 33.3, 28.3, 24.2 ppm. $C_{11}H_{10}F_2O_4$ (244.19): calcd. C 54.10, H 4.13; found C 54.24, H 4.20.

Ethyl (2,2-Difluoro-1,3-benzodioxol-4-yl)oxoacetate (4): A solution of 2,2-difluoro-1,3-benzodioxole (2.9 mL, 3.9 g, 25 mmol) and *sec*-butyllithium (25 mmol) in tetrahydrofuran (50 mL) and cyclohexane (20 mL) was kept for 2 h at −75 °C before being transferred through a cannula slowly, in the course of 5 min, into a flask containing diethyl oxalate (6.8 mL, 7.3 g, 50 mmol) in tetrahydrofuran (50 mL), cooled in a methanol/dry ice bath. After 1 h at −75 °C, the product **6** was isolated by distillation as a colorless liquid; b.p. 132−134 °C/6 Torr; n_D^{20} = 1.4829; yield: 5.29 g (83%). ^{1}H NMR: δ = 7.67 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.34 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.23 (t, *J* = 8.1 Hz, 1 H), 4.47 (q, *J* = 7.2 Hz, 3 H), 1.43 (t, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR: δ = 182.1, 162.9, 144.6, 143.8, 131.8 (t, *J* = 258 Hz), 124.2, 124.0, 116.8, 115.2, 63.0, 13.9 ppm. $C_{11}H_8F_2O_5$ (258.17): calcd. C 51.18, H 3.12; found C 50.85, H 3.17.

2,2-Difluoro-7-methyl-1,3-benzodioxole-4-carboxylic Acid (5): Potassium *tert*-butoxide (1.7 g, 15 mmol) and 2,2-difluoro-4-methyl-1,3-benzodioxole (**8**; 2.6 g, 15 mmol) were added consecutively to a solution of butyllithium (15 mL) in tetrahydrofuran (30 mL) and hexanes (10 mL), kept in a dry ice/methanol bath. After 30 min of vigorous stirring and a further 90 min of storing at −75 °C, the mixture was poured onto an excess of freshly crushed pieces of solid carbon dioxide. After evaporation of the solvent, a 1.0 M aqueous solution (30 mL) of sodium hydroxide was added and the organic material extracted with diethyl ether (3 × 15 mL). After drying, the solvent was removed and the residue crystallized; colorless prisms; m.p. 201−202 °C (ref.[36] m.p. 200 °C); yield: 2.8 g (85%). ^{1}H NMR: δ = 7.63 (d, *J* = 8.3 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 2.39 (s, 3 H) ppm. ^{13}C NMR: δ = 163.7, 143.0, 142.8, 131.6 (t, *J* = 254 Hz), 125.2, 125.0 (2 C), 111.9, 14.3 ppm. $C_9H_6F_2O_4$ (216.14): calcd. C 50.01, H 2.80; found C 49.99, H 2.73. The yield was raised to 93% (3.0 g) when 2,2,6,6-tetramethylpiperidine (2.6 mL, 2.1 g, 15 mmol) and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (3.0 mL, 2.6 g, 15 mmol) were added together with compound **8** and potassium *tert*-butoxide (15 mmol) to the solution of butyllithium (15 mmol).

(*E*)-3-(2,2-Difluoro-1,3-benzodioxol-4-yl)-2-propenoic Acid (6): A mixture of 2,2-difluoro-4-iodo-1,3-benzodioxole (**11**; see Section 4; 14 g, 50 mmol), acrylic acid (4.1 mL, 4.3 g, 60 mmol), palladium(II) acetate (0.11 g, 0.49 mmol), and triethylamine (17 mL, 12 g, 0.12 mol) in acetonitrile (20 mL) was heated at 80 °C for 4 h before being poured into 10% hydrochloric acid (0.25 L). The white precipitate formed was collected by filtration, thoroughly washed with water (0.2 L) and dried; colorless needles; m.p. 192−194 °C (from chloroform); yield: 10.9 g (96%). ^{1}H NMR: δ = 7.72 (d, *J* = 16.1 Hz, 1 H), 7.20 (dd, *J* = 6.9, 2.5 Hz, 1 H), 7.1 (m, 2 H), 6.67 (d, *J* = 16.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 170.7, 144.1, 142.2, 139.2, 131.6 (t, *J* = 256 Hz), 124.5, 123.9, 122.0, 118.0, 111.1 ppm. $C_{10}H_6F_2O_4$ (228.15): calcd. C 52.65, H 2.65; found C 52.46, H 2.61. When 2,2-difluoro-4-bromo-1,3-benzodioxole (**12a**; see below) was used instead of the iodo compound **11** under otherwise identical conditions, acid **6** was formed only in trace amounts. When 2,2-difluoro-4-iodo-1,3-benzodioxole (50 mmol) was allowed to react with *tert*-butyl acrylate (7.3 mL, 6.4 g, 50 mmol) under otherwise identical conditions, ***tert*-butyl (*E*)-3-(2,2-difluoro-1,3-benzodioxol-4-yl)-1-propenate** was obtained in 81% yield {11.5 g; colorless prisms; m.p. 90−91 °C (from pentanes); ^{1}H NMR: δ = 7.51 (d, *J* = 16.2 Hz, 1 H), 7.15 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.09 (t, *J* = 7.8 Hz, 1 H), 7.05 (dd, *J* = 7.9, 1.8 Hz, 1 H), 6.58 (d, *J* = 16.2 Hz, 1 H), 1.55 (s, 9 H) ppm; ^{13}C NMR: δ = 165.8 (s), 144.1 (s), 141.9 (s), 135.8 (s), 131.5 (t, *J* = 258 Hz), 125.1 (s), 124.3 (s), 123.8 (s), 118.6 (s), 110.3 (s), 81.0 (s), 28.2 (s, 3 C) ppm; MS: *m*/*z* (%) = 302 (91) [M^+ + NH_4], 284 (47) [M^+], 224 (100), 223 (99), 171 (32); $C_{14}H_{14}F_2O_4$ (284.26): calcd. C 59.15, H 4.96; found C 59.25, H 5.01}. The ester was converted into the α,β-unsaturated acid **6** (approx. 100%) by heating to 100 °C in the presence of one drop of formic acid for 2 h, until the gas evolution had ceased, and into ***tert*-butyl 3-(2,2-difluoro-1,3-benzodioxol-4-yl)propanoate** by palladium-catalyzed hydrogenation in methanol in 99% yield [colorless

oil; b.p. 107−109 °C/10 Torr; n_D^{20} = 1.4604; ^{1}H NMR: δ = 6.99 (t, *J* = 7.8 Hz, 1 H), 6.9 (m, 2 H), 2.96 (t, *J* = 7.7 Hz, 2 H), 2.60 (t, *J* = 7.7 Hz, 2 H), 1.42 (s, 9 H) ppm; ^{13}C NMR: δ = 171.5 (s), 143.4 (s), 142.0 (s), 131.4 (t, *J* = 253 Hz), 124.2 (s), 123.3 (s), 123.3 (s), 107.4 (s), 80.6 (s), 34.7 (s), 27.9 (s, 3 C), 24.6 (s) ppm; $C_{14}H_{16}F_2O_4$ (286.27): calcd. C 58.74, H 5.63; found C 59.09, H 5.32]. The latter compound was subsequently heated in the presence of formic acid (see above) to afford the free acid **1c** (98%) and reduced with lithium aluminum hydride in diethyl ether to the alcohol **2d** (91%). Acid **6** was also obtained by the condensation of 2,2-difluoro-1,3-benzodioxole-4-carbaldehyde (**9**; see Section 4; 4.6 g, 25 mmol) with acetic anhydride (4.7 mL, 5.1 g, 50 mmol) in the presence of sodium acetate (2.05 g, 25 mmol). After 4 h of heating at 250 °C, the yield reached 88%.

2. Phenols and Alcohols

2,2-Difluoro-1,3-benzodioxol-4-ol (2a): A solution containing 2,2-difluoro-1,3-benzodioxole (5.7 mL, 7.9 g, 50 mmol) and *sec*-butyllithium (50 mmol) in tetrahydrofuran (65 mL) and cyclohexane (35 mL) was kept for 2 h at −75 °C before fluorodimethoxyborane−diethyl ether[14,15] (9.4 mL, 8.2 g, 50 mmol) and, at +25 °C, sodium hydroxide (2.0 g, 50 mmol) and a 30% aqueous solution (10 mL) of hydrogen peroxide (3.4 g, 0.10 mol), were added. After 2 h of vigorous stirring, the mixture was acidified with hydrochloric acid to pH = 3 and extracted with diethyl ether (3 × 20 mL). Distillation afforded a colorless liquid; m.p. 29−30 °C (from hexanes at −25 °C); b.p. 68−70 °C/14 Torr; yield: 8.0 g (92%). ^{1}H NMR: δ = 6.95 (t, *J* = 8.3 Hz, 1 H), 6.69 (d, *J* = 8.5 Hz, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 5.43 (s, 1 H) ppm. ^{13}C NMR: δ = 144.8, 139.1, 131.5 (t, *J* = 256 Hz), 131.2, 124.0, 112.7, 102.2 ppm. $C_7H_4F_2O_3$ (174.10): calcd. C 48.29, H 2.32; found C 48.20, H 2.21.

(2,2-Difluoro-1,3-benzodioxol-4-yl)methanol (2b): A solution containing 2,2-difluoro-1,3-benzodioxole (5.7 mL, 7.9 g, 50 mmol) and *sec*-butyllithium (50 mmol) in tetrahydrofuran (65 mL) and cyclohexane (35 mL) was kept for 2 h at −75 °C before dry paraformaldehyde (1.5 g, 50 mmol) was added and the suspension stirred for 1 h at −75 °C before the temperature was allowed to raise to +25 °C. After dilution with diethyl ether (0.10 L), the mixture was washed with brine (2 × 50 mL). Upon steam distillation a colorless liquid was collected, which solidified; colorless needles; m.p. 30−31 °C (from hexanes at −75 °C); b.p. 72−74 °C/3 Torr; yield: 2.6 g (27%). ^{1}H NMR: δ = 7.13 (d, *J* = 8.0 Hz, 1 H), 7.08 (t, *J* = 7.9 Hz, 1 H), 7.00 (dd, *J* = 7.8, 1.3 Hz, 1 H), 4.77 (s, 2 H), 1.91 (s, 1 H) ppm. ^{13}C NMR: δ = 143.6, 141.2, 131.6 (t, *J* = 253 Hz), 123.7, 123.4, 122.8, 108.8, 59.1 ppm. $C_8H_6F_2O_3$ (188.13): calcd. C 51.08, H 3.21; found C 51.06, H 3.16. The alcohol **2b** was obtained in 95% yield by reduction of the aldehyde **9** (9.6 g, 50 mmol) with sodium borohydride (1.9 g, 50 mmol) in methanol (50 mL) at 0 °C for 15 min. The mixture was neutralized with 2.0 M ethereal hydrogen chloride and distilled directly.

2-(2,2-Difluoro-1,3-benzodioxol-4-yl)ethanol (2c): A solution of 2,2-difluoro-1,3-benzodioxole (5.7 mL, 7.9 g, 50 mmol) and *sec*-butyllithium (50 mmol) in tetrahydrofuran (65 mL) and cyclohexane (35 mL) was stored 2 h at −75 °C before copper(I) iodide (4.8 g, 25 mmol) was added. The mixture was stirred at −75 °C until, after about 45 min, it became homogeneous. Oxirane was then added (2.5 mL, 2.2 g, 50 mmol) and the mixture was then allowed to attain slowly, in the course of 2 h, +25 °C. Neutralization with a small excess of ethereal hydrogen chloride and immediate distillation gave the product **2c** as a colorless liquid; b.p. 114−115 °C/6 Torr (ref.[3] b.p. 99−101 °C/4 Torr); n_D^{20} = 1.4962 (ref.[3] n_D^{20} = 1.4966); yield: 4.19 g (82%). Alcohol **2c** formed in a mere 54% yield when the same reaction was repeated in the absence of copper(I) iodide. Alcohol **2c** was isolated in 35% yield when a solution of butyllithium (20 mmol) and potassium *tert*-butoxide (20 mmol) in tetrahydrofuran (40 mL) and hexanes (15 mL) was consecutively treated with diisopropylamine (2.8 mL, 2.0 g, 20 mmol) and 2,2-difluoro-4-methyl-1,3-benzodioxole (**8**; 3.4 g, 20 mmol) while cooled in a methanol/dry ice bath. After 2 h at −75 °C, dry paraformaldehyde (0.6 g, 20 mmol) was added and the reaction was worked up as described for the lower homolog **2b** (see above).

3-(2,2-Difluoro-1,3-benzodioxol-4-yl)-1-propanol (2d): A solution of 2,2-difluoro-1,3-benzodioxole (2.8 mL, 3.9 g, 25 mmol) and *sec*-butyllithium (25 mmol) in tetrahydrofuran (50 mL) and cyclohexane (15 mL) was kept for 2 h at −75 °C before oxetane (1.7 mL, 1.5 g, 25 mmol) and boron trifluoride−diethyl ether (3.2 mL, 3.5 g, 25 mmol) were added consecutively. At +25 °C, the mixture was neutralized with a slight excess of ethereal hydrogen chloride and concentrated. Distillation afforded a colorless oil; b.p. 111−113 °C/5 Torr; n_D^{20} = 1.4801; yield: 2.2 g (41%). ^{1}H NMR: δ = 6.99 (t, *J* = 7.9 Hz, 1 H), 6.9 (m, 2 H), 3.67 (t, *J* = 6.3 Hz, 2 H), 2.76 (t, *J* = 7.6 Hz, 2 H), 2.91 (m, 2) ppm. ^{13}C NMR: δ = 143.4, 142.0, 131.4 (t, *J* = 254 Hz), 124.3, 124.2, 123.4, 107.2, 61.9, 32.1, 25.4 ppm. $C_{10}H_{10}F_2O_3$ (216.19): calcd. C 55.56, H 4.66; found C 55.52, H 4.67. Alcohol **2d** was isolated in 61% yield by deprotonation of 2,2-difluoro-4-methyl-1,3-benzodioxole (**8**; 3.4 g, 20 mmol) with lithium diisopropylamide (20 mmol) in the presence of potassium *tert*-butoxide (20 mmol) as described above (see the end of the preceding paragraph dealing with alcohol **2c**) followed by the addition of oxirane (20 mmol). The alcohol **2d** was finally obtained in 84% yield when a solution of (*E*)-3-(2,2-difluoro-1,3-benzodioxol-4-yl)-2-propenoic acid (**6**; see Section 1; 2.3 g, 10 mmol) and lithium aluminum hydride (0.76 g, 20 mmol) in diethyl ether (20 mL) was heated for 2 h under reflux and nitrogen before being poured onto ice, extracted with diethyl ether (3 × 10 mL) and distilled.

4-(2,2-Difluoro-1,3-dioxol-4-yl)-1-butanol (2e): From 2,2-difluoro-1,3-benzodioxole (2.9 mL, 4.0 g, 25 mmol) and, 2 h later, 1-iodo-4-(methoxymethoxy)butane (see below; 6.1 g, 25 mmol) in tetrahydrofuran (30 mL) and cyclohexane (15 mL) cooled in a methanol/dry ice bath. When, after 2 h, the mixture was allowed to attain +25 °C, it was neutralized with a slight excess of ethereal hydrogen chloride and distilled under reduced pressure; colorless liquid; b.p. 144−146 °C/19 Torr; n_D^{20} = 1.4879; yield: 1.02 g (18%). ^{1}H NMR: δ = 6.98 (t, *J* = 7.9 Hz, 1 H), 6.9 (m, 2 H), 3.67 (t, *J* = 6.5 Hz, 2 H), 2.69 (t, *J* = 7.6 Hz, 2 H), 1.90 (s, 1 H), 1.7 (m, 2 H), 1.6 (m, 2 H) ppm. ^{13}C NMR: δ = 143, 142.1, 131.5 (t, *J* = 253 Hz), 124.9, 124.4, 123.4, 107.1, 62.4, 32.1, 28.9, 25.7 ppm. MS (c.i.): *m/z* (%) = 248 (100) [$M^+ + NH_4$], 231 (25) [$M^+ + 1$], 230 (52) [M^+], 207 (52), 184 (60), 171 (30). $C_{11}H_{12}F_2O_3$ (230.21): calcd. C 57.39, H 5.25; found C 57.10, H 5.32.

1-Iodo-4-(methoxymethoxy)butane: At 0 °C, chloromethyl methyl ether (4.6 mL, 4.8 g, 60 mmol; "technical grade" quality) was added to a solution of 4-iodo-1-butanol[37] (10 g, 50 mmol) and *N*-ethyldiisopropylamine (13 mL, 9.7 g, 75 mmol) in anhydrous dichloromethane (25 mL). The mixture was immediately absorbed onto silica gel (25 mL) and the powder, once dry, poured on top of a column filled with more silica (0.20 L) from which the product was eluted with hexanes; colorless oil; n_D^{20} = 1.4876; yield: 9.6 g (79%). ^{1}H NMR: δ = 4.61 (s, 2 H), 3.55 (t, *J* = 6.3 Hz, 2 H), 3.36 (s, 3 H), 3.23 (t, *J* = 7.0 Hz, 2 H), 1.94 (symm. m, 2 H), 1.7 (m, 2 H) ppm. ^{13}C NMR: δ = 96.4, 66.4, 55.2, 30.6, 30.4, 6.6 ppm. $C_6H_{13}IO_2$ (244.07): calcd. C 29.53, H 5.37; found C 29.72, H 5.07.

(2,2-Difluoro-7-methyl-1,3-benzodioxol-4-yl)methanol (7): At −75 °C, *sec*-butyllithium (25 mmol) in cyclohexane (18 mL) was added

to a solution of 2,2-difluoro-4-methyl-1,3-benzodioxole (4.3 g, 25 mmol) in tetrahydrofuran (32 mL). After 2 h at −75 °C, paraformaldehyde (1.5 g, 50 mmol) was added to the reaction mixture and the mixture was then warmed up to 25 °C. After steam distillation, an oil was collected which was then distilled under reduced pressure as colorless liquid and crystallized from pentanes as colorless needles; m.p. 55−57 °C; b.p. 112−114 °C/15 Torr; yield: 3.23 g (64%). ^{1}H NMR: δ = 7.01 (d, *J* = 8.1 Hz, 1 H), 6.88 (d, *J* = 8.1 Hz, 1 H), 4.73 (s, 2 H), 2.31 (s, 3 H), 1.81 (s, 1 H) ppm. ^{13}C NMR: δ = 142.2, 140.9, 131.6 (t, *J* = 252 Hz), 125.3, 126.6, 120.5, 119.7, 59.1, 14.3 ppm. $C_9H_8F_2O_3$ (202.16): calcd. C 53.47, H 3.99; found C 53.40, H 3.93.

3. Amines

(2,2-Difluoro-1,3-benzodioxol-4-yl)amine (3a): Under nitrogen, palladium (1.33 g, 1.25 mmol; 10 wt.-% on charcoal) was added to a solution of 4-azido-2,2-difluoro-1,3-benzodioxole (**14a**; see Section 6; 5.0 g, 25 mmol) in methanol (50 mL). Hydrogen gas was bubbled into the stirred reaction mixture until, after 6 h, the uptake ceased. The catalyst was removed by filtration, the solvent evaporated and the residue distilled under reduced pressure as a colorless liquid; b.p. 78−80 °C/8 Torr; n_D^{20} = 1.4600; yield: 3.48 g (80%). ^{1}H NMR: δ = 6.86 (t, *J* = 8.2 Hz, 1 H), 6.5 (m, 2 H), 3.7 (s, 2 H) ppm. ^{13}C NMR: δ = 144.2, 131.4 (t, *J* = 256 Hz), 131.1, 130.2, 124.0, 111.7, 99.6 ppm. $C_7H_5F_2NO_2$ (173.12): calcd. C 48.57, H 2.91; found C 49.04, H 2.80. Amine **3a** was formed in 40% yield when 2,2-difluoro-1,3-benzodioxole (10 mmol), after lithiation with *sec*-butyllithium (10 mmol), was added to *O*-methylhydroxylamine (0.94 g, 20 mmol) which had beforehand been treated dropwise with a 1.7 M ethereal solution of methyllithium (20 mol); the mixture was kept for 2 h at −15 °C. Amine **3a** was obtained in 82% yield when a mixture containing (2,2-difluoro-1,3-benzodioxol-4-yl)ethanone oxime (**18**; see Section 6; 2.2 g, 10 mmol) and phosphorus pentachloride (6.2 g, 30 mmol) in benzene (50 mL) was heated under reflux for 15 min and, after addition of 32% hydrochloric acid (5.0 mL) and ethanol (0.10 L), heated again for 6 h. The solid residue left behind upon evaporation of the solvents was dissolved in water (10 mL) and basified with sodium hydroxide until pH = 12 was attained. The product **3a** was isolated by extraction with diethyl ether and distillation.

(2,2-Difluoro-1,3-benzodioxol-4-yl)methanamine (3b): 2,2-Difluoro-1,3-benzodioxole-4-carbonitrile (**20a**; see Section 6; 1.8 g, 10 mol) and lithium aluminum hydride (0.76 g, 20 mmol) in diethyl ether (20 mL) were heated under reflux for 2 h before being poured onto crushed ice (25 g). The organic layer was decanted, dried and concentrated. Distillation gave product **3b** as a colorless liquid; b.p. 94−95 °C/6 Torr; n_D^{20} = 1.4860; yield: 1.58 g (86%). ^{1}H NMR: δ = 7.1 (m, 2 H), 7.0 (m, 1 H), 3.95 (s, 2 H), 1.68 (s, 2 H) ppm. ^{13}C NMR: δ = 143.6, 141.5, 131.6 (t, *J* = 251 Hz), 125.9, 123.7, 122.8, 108.1, 40.5 ppm. $C_8H_7F_2NO_2$ (187.15): calcd. C 51.34, H 3.77; found C 50.98, H 3.91. Amine **3b** was formed in 80% and 89% yield, respectively, when 2,2-difluoro-1,3-benzodioxole-4-carboxamide (**19**; see Section 6; 2.0 g, 10 mmol) and 2,2-difluoro-1,3-benzodioxole-4-carbaldehyde oxime (**17**; see Section 6; 4.0 g, 20 mmol) were submitted to the same lithium hydride reduction protocol.

(2,2-Difluoro-1,3-benzodioxol-4-yl)ethanamine (3c): Exactly as described in the preceding paragraph, (2,2-difluoro-1,3-benzodioxol-4-yl)acetonitrile (**20b**; see Section 6; 2.0 g, 10 mmol) was reduced with lithium aluminum hydride (20 mmol) to afford product **3c** as a colorless liquid; b.p. 80−82 °C/6 Torr; n_D^{20} = 1.4866; yield: 1.75 g (86%). ^{1}H NMR: δ = 7.0 (m, 1 H), 6.9 (m, 2 H), 3.02 (t, *J* = 7.0 Hz, 2 H), 2.81 (t, *J* = 6.9 Hz, 2 H) ppm. ^{13}C NMR: δ = 143.6, 142.4, 131.5 (t, *J* = 256 Hz), 124.8, 123.5, 122.6, 107.6, 41.8, 33.6 ppm. $C_9H_9F_2NO_2$ (201.17): calcd. C 53.74, H 4.51, N 6.96; found C 53.44, H 4.48, N 6.99. Amine **3c** was obtained in 89% yield when the same lithium aluminum reduction protocol was applied to (*E*)-2,2-difluoro-4-(2-nitroethenyl)-1,3-benzodioxole (**16**, see Section 6).

3-(2,2-Difluoro-1,3-benzodioxol-4-yl)-1-propanamine (3d): As above, from 3-(2,2-difluoro-1,3-benzodioxol-4-yl)propanenitrile (**20c**; see Section 6; 2.1 g, 10 mmol); colorless oil; b.p. 104−106 °C/12 Torr; n_D^{20} = 1.4806; yield: 1.97 g (92%). ^{1}H NMR: δ = 6.99 (t, *J* = 7.8 Hz, 1 H), 6.9 (m, 2 H), 2.7 (m, 4 H), 1.81 (quint, *J* = 7.4 Hz, 2 H), 1.4 (s, 2 H) ppm. ^{13}C NMR: δ = 143.3, 142.0, 131.3 (t, *J* = 258 Hz), 124.5, 124.2, 123.3, 107.0, 41.3, 33.1, 26.4 ppm. $C_{10}H_{11}F_2NO_2$ (215.20): calcd. C 55.81, H 5.15; found C 55.24, H 5.15.

4-(2,2-Difluoro-1,3-benzodioxol-4-yl)-1-butanamine (3e): As above, from 4-(2,2-difluoro-1,3-benzodioxol-4-yl)butanenitrile (**20d**; see Section 6; 2.3 g, 10 mmol); colorless oil; b.p. 110−111 °C/6 Torr; n_D^{20} = 1.4788; yield: 2.20 g (94%). ^{1}H NMR: δ = 7.0 (m, 1 H), 6.9 (m, 2 H), 2.74 (t, *J* = 7.0 Hz, 2 H), 2.67 (t, *J* = 7.6 Hz, 2 H), 1.7 (m, 2 H), 1.5 (m, 4 H) ppm. ^{13}C NMR: δ = 143.4, 142.0, 131.5 (t, *J* = 254 Hz), 125.0, 124.3, 123.4, 107.1, 41.9, 33.2, 29.0, 26.8 ppm. $C_{11}H_{13}F_2NO_2$ (229.23): calcd. C 57.64, H 5.72; found C 56.78, H 5.63.

4. Methyl Derivative, Aldehyde, Ketone, and Iodo Compound

2,2-Difluoro-4-methyl-1,3-benzodioxole (8): A solution of 2,2-difluoro-1,3-benzodioxole (11.4 mL, 15.8 g, 0.10 mol) and *sec*-butyllithium (0.10 mol) in tetrahydrofuran (0.15 L) and cyclohexane (60 mL) was kept at −75 °C before dimethyl sulfate (9.5 mL, 12.6 g, 0.10 mol) was added. Upon direct distillation, the product was collected as a colorless liquid; b.p. 79−81 °C/6 Torr; n_D^{20} = 1.4496; yield: 12.2 g (71%). ^{1}H NMR: δ = 6.91 (m, 3 H), 2.31 (s, 3 H) ppm. ^{13}C NMR: δ = 143.4, 142.5, 131.5 (t, *J* = 251 Hz), 125.3, 123.2, 120.4, 106.9, 14.3 ppm. $C_8H_6F_2O_2$ (172.13): calcd. C 55.82, H 3.51; found C 55.55, H 3.34.

2,2-Difluoro-1,3-benzodioxole-4-carbaldehyde (9): A solution of 2,2-difluoro-1,3-benzodioxole (5.7 mL, 7.9 g, 50 mol) and *sec*-butyllithium (50 mol) in tetrahydrofuran (70 mL) and cyclohexane (30 mL) was kept at −75 °C before *N*,*N*-dimethylformamide (3.9 mL, 3.7 g, 50 mmol) was added. The solvents were evaporated and the residue was treated with 2.0 M hydrochloric acid (50 mL) before being extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL), dried, and distilled; colorless liquid; b.p. 73−74 °C/6 Torr; n_D^{20} = 1.4988; yield: 8.2 g (88%). ^{1}H NMR: δ = 10.20 (s, 1 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.23 (t, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 186.0, 144.6, 144.2, 132.1 (t, *J* = 259 Hz), 123.9, 123.1, 119.8, 114.7 ppm. $C_8H_4F_2O_3$ (186.12): calcd. C 51.63, H 2.17; found C 51.52, H 2.27.

(2,2-Difluoro-1,3-benzodioxol-4-yl)ethanone (10): At −75 °C, an ethereal solution (75 mL) of methyllithium (0.11 mol) was added to 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (10 g, 50 mmol). The mixture was kept for 3 h at +25 °C before being neutralized with a slight excess of ethereal hydrogen chloride. Upon distillation, first of the solvents and eventually of the product, a viscous liquid was collected that solidified in the refrigerator; colorless star-shaped crystals; m.p. 32−33 °C (from pentanes at −75 °C); b.p. 87−89 °C/12 Torr; yield: 6.8 g (68%). ^{1}H NMR: δ = 7.65 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.26 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 2.67 (s, 3 H) ppm. ^{13}C NMR: δ = 193.5, 144.5, 143.2, 131.5 (t, *J* = 256 Hz), 123.6, 123.5, 120.9, 113.7, 30.3 ppm. $C_9H_6F_2O_3$ (200.14): calcd. C 54.01, H 3.02; found C 53.76, H 2.95.

2,2-Difluoro-4-iodo-1,3-benzodioxole (11): A solution of 2,2-difluoro-1,3-benzodioxole (5.7 mL, 7.9 g, 50 mmol) and *sec*-butyllithium (50 mol) in tetrahydrofuran (70 mL) and cyclohexane (30 mL) was kept for 2 h at −75 °C before a precooled solution of iodine (13 g, 50 mmol) was added. The solvents were evaporated and the residue was treated with water (0.10 L) and extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with a saturated aqueous solution (25 mL) of sodium thiosulfate and brine (25 mL) before being concentrated. Low temperature crystallization afforded the product **11** as colorless star-shaped crystals; m.p. 39−40 °C (from ethanol); yield: 13.8 g (97%). ^{1}H NMR: δ = 7.39 (d, *J* = 8.3 Hz, 1 H), 7.03 (d, *J* = 8.1 Hz, 1 H), 6.86 (t, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 145.8, 142.7, 132.5, 130.3 (t, *J* = 262 Hz), 125.1, 109.4, 70.9 ppm. $C_7H_3F_2IO_2$ (284.00): calcd. C 29.61, H 1.06; found C 29.55, H 1.19.

5. Bromo Compounds and Sulfonates

4-Bromo-2,2-difluoro-1,3-benzodioxole (12a): After 2 h at −75 °C, bromine (1.3 mL, 4.0 g, 25 mmol) was added to a solution initially containing 2,2-difluoro-1,3-benzodioxole (2.8 mL, 3.9 g, 25 mmol) and *sec*-butyllithium (25 mmol) in tetrahydrofuran (35 mL) and cyclohexane (15 mL). Immediate distillation gave a colorless oil; b.p. 75−77 °C/16 Torr; n_D^{20} = 1.4966; yield: 4.21 g (71%). ^{1}H NMR: δ = 7.22 (dd, *J* = 8.1, 1.6 Hz, 1 H), 6.9 (m, 2 H) ppm. ^{13}C NMR: δ = 143.7, 131.0 (t, *J* = 260 Hz), 127.1, 124.5, 108.5, 106.6, 101.4 ppm. $C_7H_3BrF_2O_2$ (237.01): calcd. C 35.47, H 1.28; found C 35.42, H 1.38.

4-(Bromomethyl)-2,2-difluoro-1,3-benzodioxole (12b): A solution of triphenylphosphane (6.6 g, 25 mmol) in acetonitrile (50 mL) was cooled in an ice bath and treated with bromine (1.3 mL, 4.0 g, 25 mmol) before 4-(2,2-difluoro-1,3-benzodioxol-4-yl)methanol (**2b**; see Section 6; 4.7 g, 25 mmol) was added. The solution was heated for 2 h at +50 °C. Immediate distillation afforded a colorless liquid; m.p. 24−25 °C (from hexanes at −75 °C); b.p. 86−88 °C/6 Torr; yield: 5.40 g (86%). ^{1}H NMR: δ = 7.10 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H), 7.00 (dd, *J* = 7.8, 1.7 Hz, 1 H), 4.48 (s, 2 H) ppm. ^{13}C NMR: δ = 143.7, 141.7, 131.5 (t, *J* = 256 Hz), 124.7, 123.9, 120.4, 109.6, 24.4 ppm. $C_8H_5BrF_2O_2$ (251.03): calcd. C 38.28, H 2.01; found C 37.99, H 2.26. The same compound **12b** was prepared in 65% yield from 2,2-difluoro-4-methyl-1,3-benzodioxole (**8**; see Section 4; 4.3 g, 25 mmol) and bromine (1.3 mL, 4.0 g, 25 mmol) in tetrachloromethane (50 mL).

3-(2-Bromoethyl)-2,2-difluoro-1,3-benzodioxole (12c): Prepared and worked-up as its lower homolog **12b** (see below; 5.0 g, 25 mmol); colorless liquid; b.p. 131−133 °C/12 Torr; n_D^{20} = 1.5029; yield: 5.83 g (89%). ^{1}H NMR: δ = 7.03 (t, *J* = 7.9 Hz, 1 H), 6.97 (dd, *J* = 8.2, 1.4 Hz, 1 H), 6.94 (d, *J* = 8.6 Hz, 1 H), 3.61 (t, *J* = 7.3 Hz, 2 H), 3.24 (t, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR: δ = 143.6, 141.3, 130.6 (t, *J* = 252 Hz), 124.7, 123.6, 121.4, 108.3, 32.8, 30.3 ppm. $C_9H_7BrF_2O_2$ (265.05): calcd. C 40.78, H 2.66; found C 40.71, H 2.62.

4-(3-Bromopropyl)-2,2-difluoro-1,3-benzodioxole (12d): As above, from alcohol **2d** (5.4 g, 25 mmol); colorless oil; b.p. 102−103 °C/6 Torr; n_D^{20} = 1.4988; yield: 6.12 g (88%). ^{1}H NMR: δ = 6.9 (m, 3 H), 3.42 (t, *J* = 6.5 Hz, 2 H), 2.84 (t, *J* = 7.4 Hz, 2 H), 2.2 (m, 2 H) ppm. ^{13}C NMR: δ = 143.6, 142.1, 131.4 (t, *J* = 251 Hz), 124.5, 123.6, 123.1, 107.6, 32.6, 32.0, 27.7 ppm. $C_{10}H_9BrF_2O_2$ (279.08): calcd. C 43.04, H 3.25; found C 42.79, H 3.42.

(2,2-Difluoro-1,3-benzodioxol-4-yl)methyl Benzenesulfonate (13b): A biphasic mixture of (2,2-difluoro-1,3-benzodioxol-4-yl)methanol (**2b**; Section 2; 4.7 g, 25 mmol) and benzenesulfonyl chloride (3.2 mL, 4.4 g, 25 mmol) in diethyl ether (50 mL) and potassium hydroxide (4.2 g, 75 mmol) in water (10 mL) was stirred for 15 h at +25 °C. The organic layer was washed with brine (2 × 25 mL), dried, and the solvents were evaporated. The oil left behind crystallized spontaneously when put in an ice bath; colorless star-shaped crystals; m.p. 34−35 °C; yield: 7.30 g (89%). ^{1}H NMR: δ = 7.9 (m, 2 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 7.52 (t, *J* = 7.8 Hz, 2 H), 7.0 (m, 3 H), 5.14 (s, 2 H) ppm. ^{13}C NMR: δ = 143.6, 141.9, 135.9, 134.0, 131.4 (t, *J* = 258 Hz), 129.3 (2 C), 127.9 (2 C), 124.3, 123.8, 116.0, 110.4, 65.3 ppm.

2-(2,2-Difluoro-1,3-benzodioxol-4-yl)ethyl Benzenesulfonate (13c): As above, from alcohol **2c** (see Section 2; 2.0 g, 10 mmol); colorless star-shaped crystals; m.p. 26−28 °C; yield: 2.61 g (77%). ^{1}H NMR: δ = 7.79 (dd, *J* = 8.4, 1.2 Hz, 2 H), 7.62 (tt, *J* = 7.5, 1.2 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 2 H), 6.98 (t, *J* = 7.9 Hz, 1 H), 6.92 (dd, *J* = 8.0, 1.4 Hz, 1 H), 6.87 (dm, *J* = 8.4 Hz, 1 H), 4.30 (t, *J* = 6.6 Hz, 2 H), 3.01 (t, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR: δ = 143.5, 142.1, 135.7, 133.8, 131.3 (t, *J* = 258 Hz), 129.2 (2 C), 127.7 (2 C), 125.0, 123.6, 118.9, 108.3, 68.4, 29.1 ppm.

3-(2,2-Difluoro-1,3-benzodioxol-4-yl)propyl Benzenesulfonate (13d): As above, from alcohol **2d** (see Section 2; 5.4 g, 25 mmol); colorless oil (after chromatography); n_D^{20} = 1.5214 yield: 7.21 g (81%). ^{1}H NMR: δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.67 (tt, *J* = 7.5, 1.3 Hz, 1 H), 7.56 (t, *J* = 7.4 Hz, 2 H), 6.95 (t, *J* = 7.8 Hz, 1 H), 6.89 (dd, *J* = 8.0, 1.3 Hz, 1 H), 6.79 (dm, *J* = 7.9 Hz, 1 H), 4.11 (t, *J* = 6.1 Hz, 2 H), 2.72 (t, *J* = 7.6 Hz, 2 H), 2.0 (m, 2 H) ppm. ^{13}C NMR: δ = 143.5, 142.0, 136.0, 133.9, 131.4 (t, *J* = 258 Hz), 129.3 (2 C), 127.9 (2 C), 124.4, 123.6, 122.9, 107.7, 69.5, 28.4, 25.3 ppm.

6. Azido Compounds, Phthalimides, Nitro Compounds, Carboxamides, and Nitriles

4-Azido-2,2-difluoro-1,3-benzodioxole (14a): A solution of 2,2-difluoro-1,3-benzodioxole (2.9 mL, 4.0 g, 25 mmol) and *sec*-butyllithium (25 mmol) in tetrahydrofuran (50 mL) and cyclohexane (20 mL) was kept for 2 h at −75 °C. After the addition of *p*-toluenesulfonyl[38] azide (4.9 g, 25 mmol), the mixture was allowed to stand at +25 °C for 2 h. Immediate distillation afforded the product **14a** as an orange-colored, solidifying oil; m.p. 20−22 °C (from pentanes); b.p. 80−82 °C/10 Torr; yield: 4.74 g (94%). ^{1}H NMR: δ = 7.06 (t, *J* = 8.2 Hz, 1 H), 6.84 (dd, *J* = 8.1, 1.0 Hz, 1 H), 6.80 (dd, *J* = 8.4, 1.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 144.9, 132.4, 131.6 (t, *J* = 258 Hz), 124.4, 123.8, 114.9, 105.9 ppm. $C_7H_3F_2N_3O_2$ (199.12): calcd. C 42.23, H 1.52; found C 42.40, H 1.68.

4-(3-Azidopropyl)-2,2-difluoro-1,3-benzodioxole (14d): A mixture of 3-(2,2-difluoro-1,3-benzodioxol-4-yl)propyl benzenesulfonate (3.6 g, 10 mmol) and sodium azide (0.65 g, 10 mmol) in ethanol (20 mL) was refluxed for 6 h. The reaction mixture was then cooled, the ethanol was evaporated, the residue dissolved in diethyl ether (20 mL) and washed with water (2 × 10 mL). After drying with sodium sulfate, the solvents were evaporated from the ethereal phase and the product was distilled under reduced pressure as a colorless liquid; b.p. 117−119 °C/12 Torr; n_D^{20} = 1.4877; yield: 2.07 g (85%). ^{1}H NMR: δ = 7.01 (t, *J* = 7.9 Hz, 1 H), 6.9 (m, 2 H), 3.33 (t, *J* = 6.7 Hz, 2 H), 2.76 (t, *J* = 7.7 Hz, 2 H), 1.9 (symm. m, 2 H) ppm. ^{13}C NMR: δ = 143.6, 142.1, 131.5 (t, *J* = 253 Hz), 124.4, 123.6, 123.5, 107.6, 50.6, 28.6, 26.4 ppm. $C_{10}H_9F_2N_3O_2$ (241.19): calcd. C 49.80, H 3.76; found C 50.35, H 3.74.

***N*-[(2,2-Difluoro-1,3-benzodioxol-4-yl)methyl]phthalimide {2-[(2,2-Difluoro-1,3-benzodioxol-4-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione; 15b}:** A mixture of (2,2-difluoro-1,3-benzodioxol-4-yl)methyl benzenesulfonate (**13b**; 8.2 g, 25 mmol), potassium phthalimide (18.5 g, 100 mmol) and 18-crown-6 (0.66 g, 2.5 mmol) in *N*,*N*-dimethylformamide (50 mL) was stirred under reflux for 3 h. Then, the

solvent was distilled under reduced pressure and the solid residue was dissolved in dichloromethane (40 mL) and washed with water (2 × 20 mL). The organic phase was separated, dried with sodium sulfate, and the solvents were evaporated. The product crystallized from pentanes as colorless needles; m.p. 118−119 °C; yield: 5.94 g (75%). ^{1}H NMR: δ = 7.87 (m, 2 H), 7.74 (m, 2 H), 7.05 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.01 (t, *J* = 8.0 Hz, 1 H), 6.96 (dd, *J* = 7.9, 1.3 Hz, 1 H), 4.93 (s, 2 H) ppm. ^{13}C NMR: δ = 167.6 (2 C), 143.6, 141.6, 134.2 (2 C), 131.9 (2 C), 131.4 (t, *J* = 258 Hz), 123.7, 123.55, 123.5 (2 C), 118.8, 108.8, 35.1 ppm. $C_{16}H_9F_2NO_4$ (317.25): calcd. C 60.58, H 2.86; found C 60.53, H 2.81.

***N*-[2-(2,2-Difluoro-1,3-benzodioxol-4-yl)ethyl]phthalimide {2-[(2,2-Difluoro-1,3-benzodioxol-4-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione; 15c}:** As above, from 2-(2,2-difluoro-1,3-benzodioxol-4-yl)ethyl benzenesulfonate (**13c**; 8.5 g, 25 mmol); colorless needles (hexanes/chloroform, 5:1); m.p. 116−118 °C; yield: 6.1 g (74%). ^{1}H NMR: δ = 7.8 (m, 2 H), 7.7 (m, 2 H), 7.00 (t, *J* = 7.8 Hz, 1 H), 6.9 (m, 2 H), 4.02 (t, *J* = 7.0 Hz, 2 H), 3.09 (t, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR: δ = 168.0 (2 C), 143.3, 142.4, 133.9 (2 C), 131.9 (2 C), 131.2 (t, *J* = 254 Hz), 124.7, 123.6, 123.2 (2 C), 120.8, 108.0, 37.3, 28.3 ppm. $C_{17}H_{11}F_2NO_4$ (331.28): calcd. C 61.64, H 3.35; found C 61.77, H 3.38.

***N*-[3-(2,2-Difluoro-1,3-benzodioxol-4-yl)propyl]phthalimide {2-[3-(2,2-Difluoro-1,3-benzodioxol-4-yl)propyl]-1*H*-isoindole-1,3(2*H*)-dione; 15d}:** As above, from 3-(2,2-difluoro-1,3-benzodioxol-4-yl)-propyl benzenesulfonate (**13d**; 8.9 g, 25 mmol); colorless prisms (from pentanes); m.p. 86−88 °C; yield: 6.12 g (71%). ^{1}H NMR: δ = 7.8 (m, 2 H), 7.7 (m, 2 H), 6.9 (m, 2 H), 6.86 (dd, *J* = 7.5, 1.7 Hz, 1 H), 3.77 (t, *J* = 7.1 Hz, 2 H), 2.74 (t, *J* = 7.8 Hz, 2 H), 2.09 (quint, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR: δ = 168.3 (2 C), 143.4, 142.0, 134.0 (2 C), 132.1 (2 C), 131.4 (t, *J* = 250 Hz), 124.1, 123.5 (2 C), 123.2 (2 C), 107.3, 37.5, 27.8, 26.6 ppm. MS: *m*/*z* (%) = 363 (51) [$M^+ + NH_4$], 346 (11) [$M^+ + 1$], 345 (11) [M^+], 327 (23), 326 (96), 324 (39), 323 (100). $C_{18}H_{13}F_2NO_4$ (345.30): calcd.C 62.61, H 3.79; found C 62.68, H 3.70.

(*E*)-2,2-Difluoro-4-(2-nitroethenyl)-1,3-benzodioxole (16): A 1.0 M aqueous solution (30 mL) of sodium hydroxide was added dropwise to a stirred solution of 2,2-difluoro-1,3-benzodioxole-4-carbaldehyde (**9**; see Section 4; 4.6 g, 25 mmol) and nitromethane (1.4 mL, 1.5 g, 25 mmol) in methanol (0.10 L), cooled in a ice/salt bath at such a rate that the temperature remained below +15 °C. After an additional 15 min of stirring at 0 °C, the mixture was added dropwise to 10% hydrochloric acid (15 mL, 50 mmol). The yellow precipitate formed was collected by filtration, washed with water (50 mL) and dried. Recrystallization from methanol gave yellow star-shaped crystals; m.p. 91−92 °C; yield: 4.25 g (75%). ^{1}H NMR: δ = 7.93 (d, *J* = 13.8 Hz, 1 H), 7.79 (d, *J* = 13.8 Hz, 1 H), 7.2 (m, 3 H) ppm. ^{13}C NMR: δ = 144.2, 142.3, 140.6, 131.7, 131.5 (t, *J* = 251 Hz), 125.9, 124.5, 114.0, 112.6 ppm. $C_9H_5F_2NO_4$ (229.14): calcd. C 47.18, H 2.20, N 6.11; found C 47.21, H 2.06, N 6.11.

2,2-Difluoro-1,3-benzodioxol-4-carbaldehyde Oxime (17): A solution of 2,2-difluoro-1,3-benzodioxol-4-carbaldehyde (**9**; see Section 4; 9.3 g, 50 mmol), hydroxylamine hydrochloride (5.2 g, 75 mmol), and sodium acetate trihydrate (10 g, 75 mmol) in methanol (0.10 L) was heated under reflux for 30 min. When the mixture was poured into water (0.12 L), a white mass precipitated. This was collected by filtration, washed with water, and dried; colorless needles; m.p. 120−121 °C (from methanol); yield: 9.7 g (96%). ^{1}H NMR: δ = 8.21 (s, 1 H), 7.29 (dd, *J* = 7.2, 1.8 Hz, 1 H), 7.1 (m, 2 H) ppm. ^{13}C NMR: δ = 144.4, 144.3, 141.2, 131.7 (t, *J* = 252 Hz), 123.9, 122.4, 115.7, 110.5 ppm. $C_8H_5F_2NO_3$ (201.13): calcd. C 47.78, H 2.51, N 6.96; found C 47.69, H 2.89, N 6.99.

(2,2-Difluoro-1,3-benzodioxol-4-yl)ethanone Oxime (18): In the same way as described in the preceding paragraph, (2,2-difluoro-1,3-benzodioxol-4-yl)ethanone (**10**; see Section 4; 2.0 g, 10 mmol) was condensed with hydroxylamine (15 mmol) to afford colorless needles; m.p. 110−111 °C (from methanol); yield: 1.80 g (84%). ^{1}H NMR: δ = 7.31 (dd, *J* = 7.4, 2.0 Hz, 1 H), 7.1 (m, 2 H), 2.35 (s, 3 H) ppm. ^{13}C NMR: δ = 152.1, 144.2, 141.4, 131.7 (t, *J* = 258 Hz), 123.7, 122.0, 120.2, 110.0, 12.7 ppm. $C_9H_7F_2NO_3$ (215.16): calcd. C 50.24, H 3.28; found C 50.47, H 3.19.

2,2-Difluoro-1,3-benzodioxole-4-carboxamide (19): A mixture of methyl 2,2-difluoro-1,3-benzodioxole-4-carboxylate (5.4 g, 25 mmol) and freshly distilled formamide (4.0 mL, 4.5 g, 100 mmol) in anhydrous *N*,*N*-dimethylformamide (30 mL) were heated to 100 °C and sodium methoxide solution (1.1 g, 20 mmol) was added slowly as small portions over 20 min to the reaction mixture. The mixture was then heated at 100 °C for 6 h, cooled and 2-propanol was added. The solvents were then distilled under reduced pressure and the product was obtained as a white powder that was recrystallized from a methanol/water (4:1) mixture giving colorless star-shaped crystals; m.p. 132−133 °C; yield: 2.81 g (56%). ^{1}H NMR: δ = 7.81 (dd, *J* = 7.5, 1.9 Hz, 1 H), 7.2 (m, 2 H), 6.5 (s, 1 H), 6.0 (s, 1 H) ppm. ^{13}C NMR: δ = 163.2, 143.7, 141.3, 131.2 (t, *J* = 251 Hz), 125.0, 124.0, 116.0, 113.1 ppm. $C_8H_5F_2NO_3$ (201.13): calcd. C 47.78, H 2.51, N 6.96; found C 47.65, H 2.88, N 6.99. The yield increased to 92% when 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (**1a**; 25 mmol) was first converted into the acyl chloride (employing an excess of thionyl chloride for 2 h at reflux temperature) before treating the latter with a concentrated aqueous solution of ammonia, collecting the precipitate formed and recrystallizing it.

2,2-Difluoro-1,3-benzodioxole-4-carbonitrile (20a): A solution of 2,2-difluoro-1,3-benzodioxole-4-carbaldehyde oxime (**17**; 4.0 g, 20 mmol), cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, 1.8 g, 10 mmol) and pyridine (1.6 mL, 1.6 g, 20 mmol) in dichloromethane (20 mL) was kept for 2 h at +25 °C before being poured into water (50 mL). The organic layer was decanted and the aqueous one extracted with diethyl ether (2 × 15 mL). The combined organic phases were dried and concentrated. Distillation gave the product as a solidifying liquid; colorless needles; m.p. 32−34 °C (from hexanes); b.p. 84−86/10 Torr; yield: 3.31 g (91%). ^{1}H NMR: δ = 7.35 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.32 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.20 (t, *J* = 8.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 145.2, 144.2, 131.4 (t, *J* = 261 Hz), 126.6, 124.5, 114.1, 112.7, 95.2 ppm. $C_8H_3F_2NO_2$ (183.11): calcd. C 52.48, H 1.65, N 7.65; found C 52.16, H 1.98, N 7.62. The same product **20a** was obtained when a solution of the aldehyde **9** (see Section 4; 4.7 g, 25 mmol) in tetrahydrofuran (25 mL) was simultaneously treated with iodine (6.3 g, 25 mmol) and 28% aqueous ammonia (0.10 L) for 2 h at +25 °C. The mixture was decolorized with sodium thiosulfate (2.5 g) and extracted with diethyl ether (3 × 15 mL). After washing with brine (2 × 10 mL), the combined organic layers were dried, and the volatiles evaporated. Upon distillation, nitrile **20a** was isolated in 68% yield. Finally, nitrile **20a** was formed in 91% yield when the carboxamide **19** (5.0 g, 25 mmol) and thionyl chloride (15 mL, 24 g, 0.20 mol) were heated under reflux for 6 h before the volatiles were evaporated and the residue was purified by crystallization.

(2,2-Difluoro-1,3-benzodioxol-4-yl)acetonitrile (20b): A mixture containing 4-(bromomethyl)-2,2-difluoro-1,3-benzodioxole (**12b**; see Section 5; 6.3 g, 25 mmol) and potassium cyanide (1.6 g, 25 mmol) in 80% aqueous ethanol (60 mL) was heated under reflux for 6 h before being concentrated to about one sixth of the volume. After the addition of water (20 mL), the organic product was ex-

tracted with diethyl ether (2 × 25 mL) and purified by distillation; b.p. 106−108 °C/13 Torr; crystallization from hexanes at −75 °C gave colorless star-shaped crystals; m.p. 31−32 °C; yield: 2.14 g (43%). ^{1}H NMR: δ = 7.1 (m, 2 H), 7.07 (dd, *J* = 7.3, 1.7 Hz, 1 H), 3.81 (s, 2 H) ppm. ^{13}C NMR: δ = 143.7, 141.6, 131.4 (t, *J* = 257 Hz), 124.3, 123.5, 115.8, 112.5, 109.6, 17.6 ppm. $C_9H_5F_2NO_2$ (197.14): calcd. C 54.83, H 2.56, N 7.10; found C 54.90, H 2.77, N 7.09. Alternatively, the benzenesulfonate **13b** (see Section 5; 3.3 g, 10 mmol), potassium cyanide (1.3 g, 20 mmol), 1,4,7,10,13,16-hexaoxacyclooctadecane ("18-crown-6", 0.26 g, 1.0 mmol), and acetonitrile (20 mL) were heated under reflux for 20 h. Nitrile **20b** was again isolated as colorless star-shaped crystals; m.p. 31−32 °C (from hexanes at −75 °C); yield: 1.4 g (71%).

3-(2,2-Difluoro-1,3-benzodioxol-4-yl)propanenitrile (20c): A solution of 3-(2-bromoethyl)-2,2-difluoro-1,3-benzodioxole (**12c**; see Section 5; 6.6 g; 25 mmol) and potassium cyanide (3,2 g, 50 mmol) in 75% aqueous ethanol (75 mL) was heated under reflux for 6 h. Upon distillation a colorless liquid was collected; b.p. 123−124 °C/12 Torr; n_D^{20} = 1.4810; yield: 4.58 g (87%). ^{1}H NMR: δ = 7.06 (t, *J* = 7.9 Hz, 1 H), 7.0 (m, 2 H), 3.04 (t, *J* = 7.4 Hz, 2 H), 2.72 (t, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR: δ = 143.6, 141.9, 131.4 (t, *J* = 256 Hz), 124.2, 124.0, 120.3, 118.4, 108.7, 25.3, 17.3 ppm. $C_{10}H_7F_2NO_2$ (211.17): calcd. C 56.88, H 3.34, N 6.63; found C 56.77, H 3.35, N 6.73. Under the same conditions as specified at the end of the preceding paragraph, benzenesulfonate **13c** (see Section 5; 3.4 g, 10 mmol) was converted into the nitrile **20c** in 88% yield. The nitrile **20c** was produced again when potassium *tert*-butoxide (2.8 g, 25 mmol) and acetonitrile (2.3 mL, 1.0 g, 25 mmol) were added consecutively to a vigorously stirred solution of butyllithium (25 mmol) in tetrahydrofuran (40 mL) and hexanes (15 mL) kept in a methanol/dry ice bath before, after 15 min at −75 °C, 4-(bromomethyl)-2,2-difluoro-1,3-benzodioxole (6.3 g, 25 mmol) was dissolved in the mixture which was warmed up to +25 °C and then distilled; b.p. 123−124 °C/12 Torr; yield: 3.1 g (59%). When not only the alkoxide and acetonitrile but, in between these two ingredients, also diisopropylamine (3.5 mL, 2.5 g, 25 mmol) was added to the butyllithium-containing reaction mixture, the yield of products **20c** remained unchanged (58%).

4-(2,2-Difluoro-1,3-benzodioxol-4-yl)butanenitrile (20d): Analogously as described above for the lower homologs **20b** and **20c**, nitrile **20d** was prepared from the bromo compound **12d** (25 mmol) and the benzenesulfonate **13d** (10 mmol) in 91% and 82% yield, respectively. It was purified by distillation: colorless oil; b.p. 134−136 °C/10 Torr; n_D^{20} = 1.4756; yield: 5.14 g (91%). ^{1}H NMR: δ = 7.03 (t, *J* = 7.9 Hz, 1 H), 6.95 (dd, *J* = 8.1, 1.3 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 2.84 (t, *J* = 7.6 Hz, 2 H), 2.38 (t, *J* = 7.1 Hz, 2 H), 2.04 (quint, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR: δ = 143.6, 142.1, 131.4 (t, *J* = 254 Hz), 124.4, 123.8, 122.3, 119.1, 108.0, 28.2, 25.0, 16.6 ppm. $C_{11}H_9F_2NO_2$ (225.19): calcd. C 58.67, H 4.03; found C 58.72, H 4.02.

Acknowledgments

This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grant 20-55′303-98) and the Bundesamt für Bildung und Wissenschaft, Bern (grant 97.0083 linked to the TMR project FMRXCT-970129).

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Received August 7, 2002
[O02461]