2-, 3-, and 4-(Trifluoromethoxy)phenyllithiums: Versatile Intermediates Offering Access to a Variety of New Organofluorine Compounds

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Consecutive treatment of (trifluoromethoxy)benzene with *sec*-butyllithium and electrophilic reagents affords previously inaccessible *ortho*-substituted derivatives in generally excellent yields. 2-(Trifluoromethoxy)phenyllithium acts as the key intermediate. The 3- and 4-isomers can readily be generated from the corresponding 3- and 4-bromo precursors by halogen-metal interconversion with butyllithium or *tert*-butyllithium. Upon trapping of the 2-, 3- and 4-(trifluoromethoxy)phenyllithiums with 11 different electrophiles the expected products were formed in generally high yields. Only the attempted nucleophilic addition of 2-(trifluoromethoxy)phenyllithium to oxirane did not succeed. This failure is tentatively attributed to a lowering of the nucleophilicity by fluorine-lithium interactions. Conformationally restricted analogs — i.e., 2,2-difluoro-1,3-benzodioxol-4-phenyllithium and its 5-fluoro- and 5-bromo-substituted congeners — did indeed react smoothly with oxirane, affording the adducts in ordinary yields.

Introduction

Although both methoxy and trifluoromethyl substituents act as neighboring groups promoting *ortho*-metalation, they exhibit totally different electronic characteristics. Alkoxy groups display a relatively weak inductive electron-withdrawing effect. They accelerate metalation reactions mainly by coordinating the organolithium reagent at the ground state and, more importantly, at the transition state.[1−3] Their charge-stabilizing effect levels off rapidly with distance — it is small at the *meta* position and negligible (if not inverse) at the *para* position.[4] In contrast, the trifluoromethyl group is a powerful inductive electron attractor, which operates by simultaneous σ-bond and π-cloud polarization.[4−6] Its acidifying effect weakens only slightly when the substituent is moved from the *ortho* to the *meta* and eventually the *para* position. Thus, butyllithium in diethyl ether attacks the 2- and 3-position of trifluoromethylbenzene concomitantly in a 6:1 ratio[7−8] and *sec*-butyllithium metalates 1,3-bis(trifluoromethyl)benzene exclusively at the 4-position.[1] Only superbasic mixed-metal reagents, notoriously insensitive towards steric hindrance, perform clean proton abstractions from sites adjacent to CF₃.[1,9]

We were intrigued by the idea of gaining insight into the electronic profile of the trifluoromethoxy group, a structural hybrid between the two aforementioned substituents. As described in this article, (trifluoromethoxy)benzene readily undergoes a hydrogen/metal exchange at the *ortho* position when treated with *sec*-butyllithium in tetrahydrofuran. The resulting 2-(trifluoromethoxy)phenyllithium is perfectly stable at −50 °C, as are its 3- and 4-isomers. We are presently attempting to quantify the effect of the OCF₃ substituent on the rate of metalation and the stability of the resulting organometallic intermediates. These results will be reported in due course.

Whereas several *meta*- and *para*-substituted (trifluoromethoxy)benzenes can be purchased from suppliers of speciality chemicals, only a single *ortho* derivative, 2-(trifluoromethoxy)aniline, is commercially available. Thus, our first objective was to provide a new and convenient means of access to this class of compounds. It indeed proved possible, by using *sec*-butyllithium in the presence of N,N,N′,N′-tetramethylethylenediamine (2 h at −75 °C in *tetrahydrofuran*), to convert the inexpensive (trifluoromethoxy)benzene into the *ortho*-lithiated intermediate **1a** and to intercept the latter with a variety of electrophiles (see Scheme 1 and Table 1).
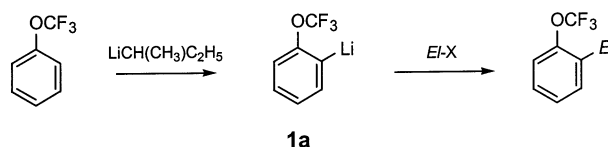
Scheme 1

Yields were excellent in most cases. The poor results encountered with the cyano group transfer (series **l**: no effective reagent known up to now) and with the maloylation (series **j**: both precursors and product harboring a strongly acidic methylene group) were predictable. What does remain to be explained, however, is why the attempted β-hydroxyalkylation of 2-(trifluoromethoxy)phenyllithium failed completely, while the same reaction performed with the 3- and 4-isomers caused no trouble at all. A speculative explanation might be based on the assumption that in the *ortho* isomer **1a** the lithium atom is intramolecularly coordinated to two fluorine atoms[11] (structure **1b**), and thus unable to participate fully in the highly concerted, *anti*-periplanar push-pull mechanism[12] of organometallic oxirane ring-opening. Thus, proton abstraction, producing the lithium

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Table 1. Reaction between 2-, 3- and 4-(trifluoromethoxy)phenyllithiums and electrophiles: yields of isolated products

Cpd. label	El[a]	2 OCF$_3$ El	3 OCF$_3$ El	4 OCF$_3$ El
b	B(OH)$_2$	89%	72%	84%
c	OH	88%	[b]	[b]
d	Br	71%	[b]	[b]
e	I	81%	74%	86%
f	CH$_3$	52%	77%	73%
g	CH$_2$CH$_2$OH	<5%	78%	70%
h	CHO	93%	90%	95%
i	COCOOC$_2$H$_5$	87%	63%	61%
j	COCH$_2$COOC$_2$H$_5$	52%	32%	26%
k	COOH	80%	85%	95%
l	CN	49%	[b]	21%

[a] Electrophiles (E-X) used for the preparation of compounds 1−3: **b**: FB(CH$_3$)$_2$ followed by treatment with water; **c**: FB(OCH$_3$)$_2$ followed by treatment with alkaline hydrogen peroxide; **d**: elemental bromine; **e**: elemental iodine; **f**: methyl iodide or dimethyl sulfate; **g**: oxirane; **h**: N,N'-dimethylformamide; **i**: dimethyl oxalate; **j**: ethyl 3-chloro-3-oxopropionate (ethyl malonyl chloride); **k**: carbon dioxide; **l**: 1-naphthyl cyanate. − [b] Reaction not attempted-

enolate of acetaldehyde, is faster than the projected nucleophilic addition. To test this hypothesis, we prepared conformationally restricted analogs of **1a/1b** by metalation of 2,2-difluoro-1,3-benzodioxole,[13] together with its 5-fluoro and 5-bromo analogs. As a matter of fact, the organolithium species **5a**, **6a**, and **7a** were found to combine readily with oxirane, affording the corresponding 2-(2,2-difluoro-1,3-benzodioxol-4-yl)ethanols **5g** (54%), **6g** (86%), and **7g** (76%) in satisfactory yields. The **5a**-isomeric organolithium intermediate generated from 5-bromo-2,2-difluoro-1,3-benzodioxole also reacted smoothly with oxirane to afford the expected adduct in 79% yield (Scheme 2).

5a : X = H
6a : X = F
7a : X = Br

5g : X = H
6g : X = F
7g : X = Br
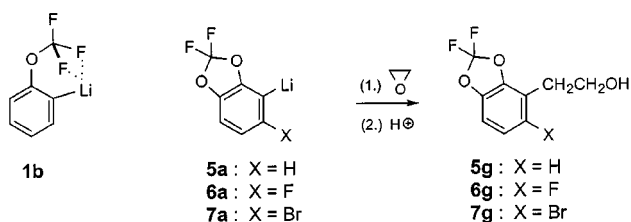
Scheme 2

The (trifluoromethoxy)phenyllithiums were perfectly stable at −50 °C in tetrahydrofuran, but underwent rapid and nonuniform decomposition above this threshold temperature. Upon addition of potassium tert-butoxide to a solution of 2-(trifluoromethoxy)phenyllithium, the mixture immediately turned black even at −75 °C, and afterwards no more trace of a trapping product could be observed, but only a whole spectrum of unidentified degradation products was found.

Experimental Section

General Remarks: Details concerning standard operations and abbreviations can be found in previous publications from this laboratory.[14−16] ^{1}H NMR spectra were recorded of samples dissolved in deuterochloroform at 400 MHz unless stated otherwise. Starting materials were supplied by Fluka-Aldrich, CH 9471-Buchs, or by Apollo-Scientific Whaley Bridge, UK-SK23 7LY, unless literature sources or details of the preparation are given.

Products Derived from (Trifluoromethoxy)benzene: sec-Butyllithium (25 mmol) in cyclohexane (16 mL) was added to a solution of (trifluoromethoxy)benzene (3.3 mL, 4.1 g, 25 mmol) and N,N,N',N'-tetramethylethylenediamine (TMEDA, 3.7 mL, 2.9 g, 25 mmol) in tetrahydrofuran (50 mL) at −75 °C. The metalation step required 2 h at −75 °C to reach completion.

2-(Trifluoromethoxy)phenylboronic Acid (2b): The reaction mixture was treated consecutively with fluorodimethoxyborane diethyl ether[17] (4.7 mL, 4.1 g, 25 mmol) and water (50 mL). After 30 min., it was extracted with diethyl ether (3 × 40 mL), washed with brine (2 × 50 mL), dried, and evaporated. The residue was crystallized from dichloromethane (10 mL) in the form of needles; m.p. 112−113 °C; yield 4.6 g (89%). − ^{1}H NMR: δ = 8.08 (dd, J = 7.7, 1.8 Hz, 1 H), 7.63 (ddd, J = 9.4, 7.6, 1.8 Hz, 1 H), 7.47 (td, J = 7.5, 0.9 Hz, 1 H), 7.37 (d, J = 8.4 Hz, 1 H). − C$_7$H$_6$BF$_3$O$_3$ (205.93): calcd. C 40.83, H 2.94; found C 40.73, H 2.81.

2-(Trifluoromethoxy)phenol (2c): The mixture was treated as described above with fluorodimethoxyborane diethyl ether[17] (4.7 mL, 4.1 g, 25 mmol). A 3.0 M aqueous solution of sodium hydroxide (9.0 mL) and 30% aqueous hydrogen peroxide (2.5 mL, 0.85 g, 25 mmol) were then added. The reaction mixture was neutralized at 25 °C with 1 M hydrochloric acid (50 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried and evaporated. Upon distillation of the residue, a colorless liquid was collected; b.p. 69−71 °C/60 Torr. − n_D^{20} = 1.4366 (ref.:[18] b.p. 137 °C, n_D^{20} = 1.4362). − d_4^{20} = 1.332; yield 3.9 g (88%). − ^{1}H NMR: δ = 7.21 (dt, J = 8.3, 1.5 Hz, 1 H), 7.16 (td, J = 8.1, 1.5 Hz, 1 H), 6.99 (dd, J = 8.2, 1.5 Hz, 1 H), 6.87 (td, J = 7.8, 1.6 Hz, 1 H).

1-Bromo-2-(trifluoromethoxy)benzene (2d): The mixture was treated with bromine (1.3 mL, 4.0 g, 25 mmol). Distillation gave a colorless liquid, b.p. 72−73 °C/45 Torr. − n_D^{20} = 1.4615 (ref.:[19] b.p. 80−81 °C/50 Torr; n_D^{20} = 1.4620). − d_4^{20} = 1.632; yield 4.3 g (71%). − ^{1}H NMR: δ = 7.64 (dd, J = 8.5, 1.1 Hz, 1 H), 7.3 (m, 2 H), 7.15 (ddd, J = 8.9, 8.2, 2.2 Hz, 1 H).

1-Iodo-2-(trifluoromethoxy)benzene (2e): Trapping with a solution of iodine (6.4 g, 25 mmol) in tetrahydrofuran (15 mL) and immediate distillation afforded a colorless liquid; b.p. 64−65 °C/12 Torr. − n_D^{20} = 1.5050. − d_4^{20} = 1.916; yield 5.8 g (81%). − ^{1}H NMR: δ = 7.84 (d, J = 8.1 Hz, 1 H), 7.34 (t, J = 7.9 Hz, 1 H), 7.25 (d, J = 7.9 Hz, 1 H), 6.90 (t, J = 7.6 Hz, 1 H). − C$_7$H$_4$F$_3$IO (288.01): calcd. C 29.19, H 1.40; found C 29.26, H 1.41.

2-(Trifluoromethoxy)toluene (2f): In an analogous reaction employing methyl iodide (1.55 mL, 3.5 g, 25 mmol), the very volatile product **2f** was obtained and collected by immediate fractional distillation, b.p. 58−60 °C/100 Torr. − n_D^{20} = 1.4255 (ref.[20] b.p. 104 °C, n_D^{20} = 1.4268). − d_4^{20} = 1.177; yield 85% (by gas chromatography); isolated material 2.3 g (52%). − ^{1}H NMR: δ = 7.2 (m, 4 H), 2.34 (s, 3 H).

2-[2-(Trifluoromethoxy)phenyl]ethanol (2g): When the reaction mixture was treated with oxirane (1.3 mL, 1.1 g, 25 mmol), the organic

layer after aqueous workup contained only a small amount of material. The only indication for the formation of product **2g** in trace amounts was two characteristic ^{1}H NMR signals at δ = 3.86 (t, J = 6.7 Hz) and δ = 2.97 (t, J = 6.6 Hz).

2-(Trifluoromethoxy)benzaldehyde (2h): A reaction carried out with N,N-dimethylformamide (1.6 mL, 1.5 g, 25 mmol) as the trapping reagent gave, after washing with water (25 mL) and brine (2 × 25 mL), and distillation, a colorless liquid; b.p. 75−76 °C/20 Torr. − n_D^{20} = 1.4571. − d_4^{20} = 1.329; yield 4.4 g (93%). − ^{1}H NMR: δ = 10.40 (s, 1 H), 7.99 (dd, J = 7.9, 1.7 Hz, 1 H), 7.65 (ddd, J = 9.4, 7.6, 1.9 Hz, 1 H), 7.43 (t, J = 7.7 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 1 H). − $C_8H_5F_3O_2$ (190.12): calcd. C 50.54, H 2.65; found C 50.55, H 2.72.

Ethyl 2-Oxo-2-[2-(trifluoromethoxy)phenyl]acetate (2i): The mixture was treated with ethyl oxalyl chloride (2.8 mL, 3.4 g, 25 mmol). A colorless liquid was collected upon distillation; b.p. 109−110 °C/ 5 Torr. − n_D^{20} = 1.4646. − d_4^{20} = 1.398; yield 5.1 g (87%). − ^{1}H NMR: δ = 7.93 (dd, J = 7.8, 1.7 Hz, 1 H), 7.68 (td, J = 7.9, 1.9 Hz, 1 H), 7.46 (td, J = 7.7, 0.9 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 4.40 (q, J = 7.1 Hz, 2 H), 1.39 (t, J = 7.1 Hz, 3 H). − $C_{11}H_9F_3O_4$ (235.61): calcd. C 50.39, H 3.46; found C 50.32, H 3.91.

Ethyl 3-Oxo-3-[2-(trifluoromethoxy)phenyl]propanoate (2j): The mixture was treated with cuprous bromide/dimethyl sulfide adduct (2.6 g, 13 mmol) and stirred at −75 °C until, after some 5 min, it became homogeneous. It was then added dropwise, by siphoning through a capillary tube under slight pressure, to a solution of ethyl malonyl chloride (3.1 mL, 3.8 g, 25 mmol) in tetrahydrofuran (10 mL) maintained at −75 °C. After 2 h at −75 °C, it was washed with a 7.0 M aqueous solution of ammonia (2 × 30 mL) and with 1.0 M hydrochloric acid (2 × 30 mL) before being dried and evaporated. The residue was distilled to give a colorless liquid; b.p. 121−123 °C/5 Torr. − n_D^{20} = 1.4702. − d_4^{20} = 1.486; yield 3.6 g (52%). − ^{1}H NMR: δ = 7.85 (dd, J = 7.9, 1.7 Hz, 1 H), 7.77 (dd, J = 7.8, 1.7 Hz, 0.7 H), 7.59 (td, J = 7.9, 1.7 Hz, 1 H), 7.47 (td, J = 7.9, 1.8 Hz, 0.7 H),), 7.40 (td, J = 7.6, 0.8 Hz, 1 H), 7.36 (td, J = 7.6, 0.9 Hz, 0.7 H), 5.65 (s, 0.7 H), 4.27 (q, J = 7.2 Hz, 1.4 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.00 (s, 2 H), 1.32 (t, J = 7.2 Hz, 2.1 H), 1.23 (t, J = 7.2 Hz, 3 H). − $C_{12}H_{11}F_3O_4$ (276.21): calcd. C 52.18, H 4.01; found C 51.69, H 4.33.

2-(Trifluoromethoxy)benzoic Acid (2k): Another reaction was terminated by pouring the mixture onto an excess of freshly crushed solid CO_2. Extraction into the alkaline aqueous phase and, following acidification, reextraction with diethyl ether followed by evaporation and crystallization from hexanes (10 mL) gave colorless platelets; m.p. 78−79 °C (ref.[21] m.p. 79−80 °C); yield 4.0 g (78%). − ^{1}H NMR: δ = 8.26 (dd, J = 8.1, 1.8 Hz, 1 H), 7.78 (td, J = 8.0, 1.8 Hz, 1 H), 7.57 (td, J = 7.8, 0.9 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1 H).

2-(Trifluoromethoxy)benzonitrile (2l): Interception with 1-naphthyl cyanate[22−23] (4.3 g, 25 mmol) and immediate distillation afforded a colorless liquid; b.p. 61−62 °C/8 Torr. − n_D^{20} = 1.4496. − d_4^{20} = 1.245; yield 2.3 g (49%). − ^{1}H NMR: δ = 7.73 (dd, J = 8.0, 1.8 Hz, 1 H), 7.68 (td, J = 8.1, 1.8 Hz, 1 H), 7.4 (m, 2 H). − $C_8H_4F_3NO$ (187.12): calcd. C 51.35, H 2.15; found C 51.42, H 2.22.

Products Derived from 1-Bromo-3-(trifluoromethoxy)benzene: A precooled solution of 1-bromo-3-(trifluoromethoxy)benzene (3.7 mL, 0.6 g, 25 mmol) in diethyl ether (50 mL) was added to butyllithium (25 mmol) in hexanes (15 mL) at −75 °C. The mixture was kept for 45 min. at this temperature and then treated with the electrophilic trapping reagent (25 mmol), after which the product was isolated.

3-(Trifluoromethoxy)phenylboronic Acid (3b): The mixture was treated with fluorodimethoxyborane diethyl ether[17] (4.7 mL, 4.1 g, 25 mmol) and, 15 min later, with water (20 mL). The aqueous phase was slightly acidified (to pH 3) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine (2 × 15 mL), dried, and evaporated. The residue crystallized from a 1:1 (v/v) mixture of dichloromethane and hexanes (7 mL) in the form of fans. M.p. 84−85 °C; yield 3.7 g (72%). − ^{1}H NMR: δ = 8.16 (d, J = 7.4 Hz, 1 H), 8.02 (s, 1 H), 7.55 (t, J = 7.8 Hz, 1 H), 7.45 (d, J = 8.1 Hz, 1 H). − $C_7H_6BF_3O_3$ (205.93): calcd. C 40.83, H 2.94; found C 41.02, H 3.21.

1-Iodo-3-(trifluoromethoxy)benzene (3e): The mixture was treated with iodine (6.3 g, 25 mmol) dissolved in tetrahydrofuran (15 mL). The product was isolated by direct distillation, thus avoiding an aqueous workup; b.p. 70−71 °C/32 Torr. − n_D^{20} = 1.5002. − d_4^{20} = 1.917; yield 5.3 g (74%). − ^{1}H NMR: δ = 7.67 (d, J = 7.6 Hz, 1 H), 7.61 (s, 1 H), 7.23 (d, J = 8.4 Hz, 1 H), 7.15 (t, J = 8.1 Hz, 1 H). − $C_7H_4F_3IO$ (288.01): calcd. C 29.19, H 1.40; found C 29.22, H 1.20.

3-(Trifluoromethoxy)toluene (3f): The mixture was treated with methyl iodide (1.6 mL, 3.5 g, 25 mmol). Immediate distillation afforded a colorless liquid; b.p. 49−51 °C/44 Torr. − n_D^{20} = 1.4211 (ref.[20] b.p. 131 °C, n_D^{20} = 1.424). − d_4^{20} = 1.182; yield 3.4 g (77%). − ^{1}H NMR: δ = 7.22 (t, J = 7.8 Hz, 1 H), 7.05 (d, J = 7.7 Hz, 1 H), 7.0 (m, 2 H), 2.34 (s, 3 H).

2-[3-(Trifluoromethoxy)phenyl]ethanol (3g): The mixture was treated with oxirane (1.3 mL, 1.1 g, 25 mmol) and was then washed with water (25 mL) and brine (2 × 25 mL). Upon distillation a colorless liquid was collected; b.p. 86−87 °C/10 Torr. − n_D^{20} = 1.4558. − d_4^{20} = 1.343; yield 4.0 g (78%). − ^{1}H NMR: δ = 7.37 (dd, J = 8.8, 7.8 Hz, 1 H), 7.17 (d, J = 7.7 Hz, 1 H), 7.1 (m, 2 H), 3.90 (t, J = 6.5 Hz, 2 H), 2.91 (t, J = 6.5 Hz, 2 H). − $C_9H_9F_3O_2$ (206.16): calcd. C 52.43, H 4.41; found C 52.36, H 4.35.

3-(Trifluoromethoxy)benzaldehyde (3h): The mixture was treated with N,N-dimethylformamide (1.9 mL, 1.8 g, 25 mmol) and was worked up as described above to give a colorless liquid; b.p. 68−70 °C/12 Torr. − n_D^{20} = 1.4546 (ref.[24] b.p. 83−86 °C/24 Torr, n_D^{20} = 1.454). − d_4^{20} = 1.331; yield 4.3 g (90%). − ^{1}H NMR: δ = 10.01 (s, 1 H), 7.82 (d, J = 7.6 Hz, 1 H), 7.72 (s, 1 H), 7.59 (t, J = 7.9 Hz, 1 H), 7.46 (d, J = 7.9 Hz, 1 H).

Ethyl 2-Oxo-2-[3-(trifluoromethoxy)phenyl]acetate (3i): The mixture was treated with ethyl oxalyl chloride (2.8 mL, 3.4 g, 25 mmol). A colorless liquid was collected upon distillation; b.p. 108−110 °C/ 5 Torr. − n_D^{20} = 1.4607. − d_4^{20} = 1.515; yield 3.7 g (63%). − ^{1}H NMR: δ = 7.98 (dt, J = 7.6, 1.3 Hz, 1 H), 7.91 (s, 1 H), 7.58 (t, J = 7.8 Hz, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 4.47 (q, J = 7.1 Hz, 2 H), 1.44 (t, J = 7.1 Hz, 3 H). − $C_{11}H_9F_3O_4$ (235.61): calcd. C 50.39, H 3.46; found C 50.33, H 3.96.

Ethyl 3-Oxo-2-[3-(trifluoromethoxy)phenyl]propanoate (3j): The mixture was treated with cuprous bromide/dimethyl sulfide adduct (2.6 g, 13 mmol) and stirred until, after some 5 min, it became homogeneous. It was then added dropwise to a solution of ethyl malonyl chloride (3.1 mL, 3.8 g, 25 mmol) in diethyl ether (10 mL), maintained at −75 °C. After 2 h at −75 °C, it was washed with a 7.0 M aqueous solution of ammonia (2 × 30 mL) and with 1.0 M hydrochloric acid (2 × 30 mL) before being dried and evaporated. The residue was distilled to afford a colorless liquid; b.p. 125−127

°C/5 Torr. − n_D^{20} = 1.4759. − d_4^{20} = 1.619; yield 2.2 g (32%). − ^{1}H NMR: δ = 7.89 (dt, J = 7.8, 1.3 Hz, 1 H), 7.81 (s, 1 H), 7.72 (dt, J = 8.0, 1.3 Hz, 0.5 H), 7.65 (s, 0.5 H), 7.56 (t, J = 8.0 Hz, 1 H), 7.5 (m, 1.5 H), 7.34 (d, J = 7.9 Hz, 0.5 H), 5.68 (s, 0.5 H), 4.31 (q, J = 7.1 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 4.00 (s, 2 H), 1.36 (t, J = 7.0 Hz, 1.5 H), 1.26 (t, J = 7.0 Hz, 3 H). − $C_{12}H_{11}F_3O_4$ (276.21): calcd. C 52.18, H 4.01; found C 51.91, H 3.64.

3-(Trifluoromethoxy)benzoic Acid (3k): The mixture was poured onto an excess of freshly crushed solid CO_2. Extraction of the product into the alkaline aqueous phase (50 mL), acidification, reextraction with diethyl ether (3 × 25 mL), washing with brine (2 × 25 mL), drying, evaporation, and crystallization from hexanes (10 mL) afforded colorless needles; m.p. 90−91 °C (ref.[25] m.p. 91−92 °C); yield 4.4 g (85%). − ^{1}H NMR: δ = 8.07 (td, J = 7.7, 1.3 Hz, 1 H), 7.97 (s, 1 H), 7.54 (t, J = 7.8 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H).

Products Derived from 1-Bromo-4-(trifluoromethoxy)benzene: Wholly in analogy to the methodology applied to 1-bromo-3-(trifluoromethoxy)benzene, the 1,4-isomer (3.7 mL, 6.0 g, 25 mmol), dissolved in precooled diethyl ether (50 mL), was added to butyllithium (25 mmol) in hexanes (15 mL) at −75 °C. The mixture was kept at this temperature for 45 min and then was treated with the electrophilic trapping reagent (25 mmol), after which the product was isolated.

4-(Trifluoromethoxy)phenylboronic Acid (4b): The mixture was treated with fluorodimethoxyborane diethyl ether (4.7 mL, 4.1 g, 25 mmol). The product was extracted (see **3b**) and crystallized; m.p. 114−115 °C; yield 4.3 g (84%). − ^{1}H NMR: δ = 8.25 (d, J = 8.6 Hz, 2 H), 7.34 (d, J = 7.9 Hz, 2 H). − $C_7H_6BF_3O_3$ (205.93): calcd. C 40.83, H 2.94; found C 40.88, H 2.71.

1-Iodo-4-(trifluoromethoxy)benzene (4e): The mixture was treated with iodine (6.3 g, 25 mmol) in tetrahydrofuran (15 mL). The product was purified by distillation; b.p. 96−97 °C/40 Torr. − n_D^{20} = 1.5031. − d_4^{20} = 1.909; yield 3.7 g (86%). − ^{1}H NMR: δ = 7.73 (d, J = 9.0 Hz, 2 H), 6.99 (dd, J = 8.9, 0.9 Hz, 2 H). − $C_7H_4F_3IO$ (288.01): calcd. C 29.19, H 1.40; found C 29.35, H 1.18.

4-(Trifluoromethoxy)toluene (4f): The mixture was treated with methyl iodide (1.3 mL, 2.8 g, 25 mmol) and immediately afterwards subjected to distillation; b.p. 76−77 °C/110 Torr. − n_D^{20} = 1.4159 (ref.[20,25]: b.p. 134−135 °C, n_D^{20} = 1.4160). − d_4^{20} = 1.181; yield. 3.2 g (73%). − ^{1}H NMR: δ = 7.29 (d, J = 8.5 Hz, 2 H), 7.21 (d, J = 8.3 Hz, 2 H), 2.38 (s, 3 H).

2-[4-(Trifluoromethoxy)phenyl]ethanol (4g): The mixture was treated with oxirane (1.3 mL, 1.1 g, 25 mmol) and worked up by extraction and distillation (see the preparation of compound **3g**); b.p. 83−86 °C/7 Torr. − n_D^{20} = 1.4523. − d_4^{20} = 1.344; yield 7.2 g (70%). − ^{1}H NMR: δ = 7.17 (d, J = 8.7 Hz, 2 H), 7.11 (d, J = 8.1 Hz, 2 H), 3.69 (t, J = 6.7 Hz, 2 H), 3.47 (s, 1 H), 2.75 (t, J = 6.7 Hz, 2 H). − $C_9H_9F_3O_2$ (206.16): calcd. C 52.43, H 4.41; found C 52.85, H 4.40.

4-(Trifluoromethoxy)benzaldehyde (4h): The mixture was treated with N,N-dimethylformamide (1.9 mL, 1.8 g, 25 mmol) and worked up by extraction and distillation (see **3h**); b.p. 73−75 °C/12 Torr. − n_D^{20} = 1.4566 (ref.[24] b.p. 93−97 °C/27 Torr; n_D^{20} = 1.4568). − d_4^{20} = 1.331; yield 4.5 g (95%). − ^{1}H NMR: δ = 9.99 (s, 1 H), 7.94 (d, J = 8.8 Hz, 2 H), 7.34 (d, J = 8.2 Hz, 2 H).

Ethyl 2-Oxo-2-[4-(trifluoromethoxy)phenyl]acetate (4i): The mixture was treated with ethyl oxalyl chloride (2.8 mL, 3.4 g, 25 mmol). A colorless liquid was collected upon distillation; b.p. 110−112 °C/

5 Torr. − n_D^{20} = 1.4655. − d_4^{20} = 1.554; yield 3.6 g (61%). − ^{1}H NMR: δ = 8.11 (d, J = 9.1 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H), 4.45 (q, J = 7.1 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H). − $C_{11}H_9F_3O_4$ (235.61): calcd. C 50.39, H 3.46; found C 50.26, H 3.65.

Ethyl 3-Oxo-3-[4-trifluoromethoxy)phenyl]propanoate (4j): The mixture was treated with cuprous bromide/dimethyl sulfide adduct (2.6 g, 13 mmol) and stirred until, some 5 min later, it became homogeneous. It was then added dropwise to a solution of ethyl malonyl chloride (3.1 mL, 3.8 g, 25 mmol) in diethyl ether (10 mL), maintained at −75 °C. After 2 h at −75 °C, it was washed with a 7.0 M aqueous solution of ammonia (2 × 30 mL) and with 1.0 M hydrochloric acid (2 × 30 mL) before being dried, evaporated, and distilled; b.p. 129−130 °C/5 Torr. − n_D^{20} = 1.4731. − d_4^{20} = 1.631; yield 1.8 g (26%). − ^{1}H NMR: δ = 8.04 (d, J = 8.8 Hz, 2 H), 7.83 (d, J = 8.9 Hz, 0.8 H), 7.59 (d, J = 8.8 Hz, 0.8 H), 7.34 (d, J = 8.6 Hz, 2 H), 5.66 (s, 0.4 H), 4.30 (q, J = 7.1 Hz, 0.8 H), 4.24 (q, J = 7.0 Hz, 2 H), 4.00 (s, 2 H), 1.36 (t, J = 7.1 Hz, 1.2 H), 1.27 (t, J = 7.1 Hz, 3 H). − $C_{12}H_{11}F_3O_4$ (276.21): calcd. C 52.18, H 4.01; found C 51.99, H 3.48.

4-(Trifluoromethoxy)benzoic Acid (4k): m.p. 150−152 °C (from hexanes; ref.[25] m.p. 153 °C); yield 4.9 g (95%). − ^{1}H NMR: δ = 8.17 (dd, J = 9.0, 3.1 Hz, 2 H), 7.31 (d, J = 8.9 Hz, 2 H).

4-(Trifluoromethoxy)benzonitrile (4l): The mixture was treated with 1-naphthyl cyanate[22−23] (4.3 g, 25 mmol). After 1 h at 25 °C, it was evaporated and the residue distilled to give a colorless liquid; b.p. 41−43 °C/0.8 Torr. − n_D^{20} = 1.4528 (ref.[21] b.p. 192−193 °C, n_D^{20} = 1.452). − d_4^{20} = 1.284; yield 1.0 g (21%). − ^{1}H NMR: δ = 7.76 (d, J = 8.9 Hz, 2 H), 7.34 (d, J = 8.3 Hz, 2 H).

Products Derived from 2,2-Difluoro-1,3-benzodioxoles:
2-(2,2-Difluoro-1,3-benzodioxol-4-yl)ethanol (5g): 2,2-Difluoro-1,3-benzodioxole (3.9 g, 2.8 mL, 25 mmol) was added to a solution of sec-butyllithium (25 mmol) in tetrahydrofuran (50 mL) and cyclohexane (13 mL), kept in a dry ice bath. After 2 h at −75 °C, the mixture was treated with oxirane (1.3 mL, 1.1 g, 25 mmol) and allowed to reach +25 °C. It was diluted with diethyl ether (0.10 L), washed with water (5 × 25 mL) and brine (2 × 25 mL), dried, and concentrated. Upon distillation under reduced pressure, a colorless liquid was collected. This crystallized from hexanes (5 mL) at −75 °C; m.p. 40−41 °C. − b.p. 99−101 °C/4 Torr. − n_D^{20} = 1.4966; yield 2.7 g (54%). − ^{1}H NMR: δ = 6.9 (m, 3 H), 3.91 (t, J = 6.5 Hz, 2 H), 2.92 (t, J = 6.6 Hz, 2 H). − $C_9H_8F_2O_3$ (202.16): calcd. C 53.47, H 3.99; found C 53.45, H 3.93.

2,2-Difluoro-1,3-benzodioxole-4-carboxylic Acid: A reaction mixture prepared as described above was poured onto an excess of freshly crushed solid CO_2. A 1 M aqueous solution (50 mL) of sodium hydroxide was added. The organic phase was decanted and the aqueous one washed with diethyl ether (3 × 10 mL) before being acidified to pH 1. The product was extracted with diethyl ether (3 × 30 mL). The residue left behind after evaporation of the dried organic layers was crystallized from hexanes (10 mL) to give colorless needles; m.p. 195−197 °C; yield 4.1 g (81%). − ^{1}H NMR: δ = 7.70 (dd, J = 8.2, 1.6 Hz, 1 H), 7.30 (dd, J = 8.0, 1.3 Hz, 1 H), 7.18 (t, J = 8.1 Hz, 1 H). − $C_8H_4F_2O_4$ (202.12): calcd. C 47.54, H 1.99; found C 47.73, H 2.17.

2-(2,2,5-Trifluoro-1,3-benzodioxol-4-yl)ethanol (6g): Obtained from 2,2,5-trifluoro-1,3-benzodioxole (4.4 g, 25 mmol) and isolated as described above (see the preparation of **5g**); b.p. 108−110 °C/5 Torr. − n_D^{20} = 1.4727; yield 4.7 g (86%). The colorless oil did not crystallize. − ^{1}H NMR: δ = 6.88 (dd, J = 8.7, 4.1 Hz, 1 H), 6.78 (dd, J = 10.0, 8.9 Hz, 1 H), 3.90 (t, J = 6.6 Hz, 2 H), 2.96 (t, J =

6.7 Hz, 2 H). − $C_9H_7F_3O_3$ (202.12): calcd. C 49.10, H 3.20; found C 49.62, H 3.32.

2,2,5-Trifluoro-1,3-benzodioxole-4-carboxylic Acid: Obtained from 2,2,5-trifluoro-1,3-benzodioxole (4.4 g, 25 mmol) and isolated as described above (see the preparation of 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid); colorless needles; m.p. 137−138 °C (from a 1:4 mixture of ethyl acetate and hexanes); yield 5.2 g (94%). − ^1H NMR: δ = 7.25 (dd, $J = 9.0, 4.8$ Hz, 1 H), 6.97 (dd, $J = 8.9$ Hz, 1 H). − $C_8H_3F_3O_4$ (220.11): calcd. C 43.66, H 1.37; found C 43.64, H 1.24.

2-(5-Bromo-2,2-difluoro-1,3-benzodioxol-4-yl)ethanol (7g): Butyllithium (25 mmol) in hexanes (16 mL) and 5-bromo-2,2-difluoro-1,3-benzodioxole (5.9 g, 25 mmol) were added consecutively to 2,2,6,6-tetramethylpiperidine (4.2 mL, 3.5 g, 25 mmol) in tetrahydrofuran (50 mL), cooled in a dry ice/acetone bath. After 2 h at −75 °C, the mixture was treated with oxirane (1.3 mL, 1.1 g, 25 mmol) and the colorless product isolated as described above (see preparation of **5g**); m.p. 59−60 °C (needles; from hexanes); b.p. 122−124 °C/2 Torr; yield 5.3 g (76%). − ^1H NMR: δ = 7.32 (d, $J = 8.5$ Hz, 1 H), 6.86 (d, $J = 8.6$ Hz, 1 H), 3.93 (t, $J = 6.7$ Hz, 2 H), 3.10 (t, $J = 6.7$ Hz, 2 H). − $C_9H_7BrF_2O_3$ (281.06): calcd. 38.46, H 2.51; found C 38.61, H 2.21.

5-Bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic Acid: A reaction mixture, prepared as described in the preceding paragraph, was poured onto an excess of freshly crushed solid CO_2 in place of the treatment with oxirane. The colorless product was isolated as before (see above); m.p. 148−149 °C (cubes; from toluene); yield 6.2 g (88%). − ^1H NMR: δ = 7.44 (d, J 8.5 Hz, 1 H), 7.09 (d, $J = 8.6$ Hz, 1 H). − $C_8H_3BrF_2O_4$ (281.02): calcd. C 34.19, H 1.08; found C 34.13, H 1.18.

2-(2,2-Difluoro-1,3-benzodioxol-5-yl)ethanol: A solution of *tert*-butyllithium (50 mmol) in pentanes (30 mL) was added at −75 °C to 5-bromo-2,2-difluoro-1,3-benzodioxole (5.9 g, 25 mmol) in tetrahydrofuran (50 mL), followed 15 min later by oxirane (1.3 mL, 1.1 g, 25 mmol). When the mixture had reached +25 °C, it was worked up as before (see preparation of **5g**) to obtain a colorless oil; b.p. 106−108 °C/3 Torr. − $n_D^{20} = 1.4836$; yield 3.7 g (73%). − ^1H NMR: δ = 6.98 (d, $J = 8.1$ Hz, 1 H), 6.97 (d, $J = 1.1$ Hz, 1 H), 6.91 (dd, $J = 8.2, 1.3$ Hz, 1 H), 3.83 (t, $J = 6.2$ Hz, 2 H), 2.84 (t, $J = 6.4$ Hz, 2 H). − $C_9H_8F_2O_3$ (202.16): calcd. C 53.47, H 3.99; found C 53.33, H 4.16.

Acknowledgments

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