The Superbase Approach to Flurbiprofen: An Exercise in Optionally Site-Selective Metalation

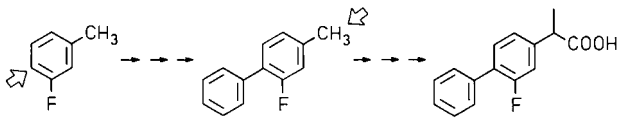
Manfred Schlosser* and Hervé Geneste

Abstract: A superior route to the analgesic flurbiprofen has been devised. Key steps are the selective deprotonation of 3-fluorotoluene with *tert*-butyllithium in the presence of potassium *tert*-butoxide (LIT-KOR) at the 4-position and the selective deprotonation of the 4-methyl-2-fluorobiphenyl with lithium diisopropylamide in the presence of potassium *tert*-butoxide (LIDA-KOR) at the benzylic position. Depending on the reagent and the substituent pattern, the 3- and 5-positions of 2-fluorobiphenyls can also be specifically attacked.

Keywords: antiinflammatories · metalations · site selectivity · substituent effects · superbases · Suzuki coupling

Introduction

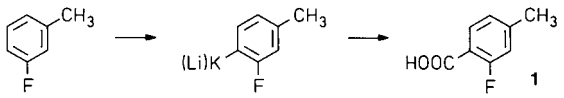
Flurbiprofen is commercially available as an antiinflammatory and analgesic drug under the brand names Froben and Cebutid. Its chemical structure, which is 2-(2-fluorobiphenylyl)propionic acid, makes it an attractive target for the illustration of some principles of regiocontrolled aromatic substitution through organometallic intermediates generated with optional site selectivity.[1–3] Numerous ways of synthesizing flurbiprofen have been disclosed in patent literature.[4–10] Most of them construct the biphenyl unit by means of a Bamberger–Kühling–Gomberg reaction;[11] in a few other cases an Ullmann reaction[12] is employed. All elements of the synthetic blueprint described below are unprecedented in the flurbiprofen area. As the starting material we selected 3-fluorotoluene, a simple and inexpensive building block. Its elaboration into the final product involves two hydrogen/metal exchange (metalation) reactions, specifically involving the aromatic 4-position and, in a later step, the benzylic α-position; between these two lies a Suzuki coupling[13–15] to build the biphenyl core (Scheme 1).



Scheme 1.

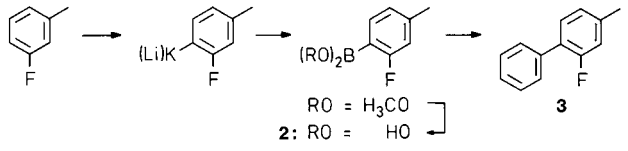
Results and Discussion

The metalation of 3-fluorotoluene with the superbasic (LIC-KOR) mixture of butyllithium and potassium *tert*-butoxide was reported[16] to occur exclusively at the 4-position, the sterically least congested site adjacent to the fluorine. As a reinvestigation has revealed, concomitant attack at the 2-position nevertheless takes place, if only to a small extent (<10%). The selectivity improved significantly when a combination of *tert*-butyllithium and potassium *tert*-butoxide was used as the mixed-metal reagent. After an exposure time of 3 h at −75 °C in tetrahydrofuran, carboxylation gave pure 2-fluoro-4-methylbenzoic acid (**1**) in 84% yield (Scheme 2). No further regioisomeric contamination was detected by gas chromatography or NMR spectroscopy.



Scheme 2.

Trapping of the arylpotassium(lithium) intermediate with fluorodimethoxyboron afforded the dimethyl boronate, which was immediately hydrolyzed to give the boronic acid **2** in 78% yield (Scheme 3). When sodium carbonate and a catalytic



Scheme 3.

[*] Prof. Dr. M. Schlosser, Dipl.-Chem. H. Geneste
Institut de Chimie organique de l'Université
Bâtiment de Chimie (BCh)
CH-1015 Lausanne-Dorigny (Switzerland)
Fax: (+41) 21-692-39-65

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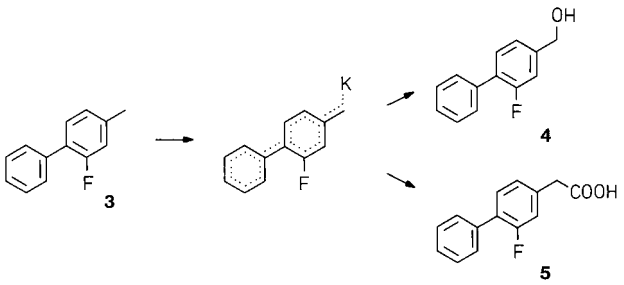
amount (0.6%) of tetrakis(triphenylphosphine)palladium were added to a solution of compound **2** and bromobenzene in ethylene glycol dimethyl ether and the mixture was refluxed for 6 h, 2-fluoro-4-methylbiphenyl (**3**) was formed in 84% yield. The four-step sequence consisting of metalation, borylation, hydrolysis, and arylation may be contracted to a one-pot procedure to produce biphenyl **3** with an overall yield of 79% (Scheme 3).

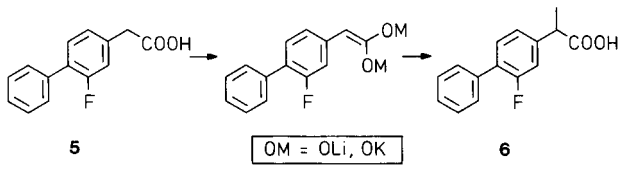
As expected,[16] the deprotonation of the benzylic methyl group could be smoothly achieved with lithium diisopropylamide in the presence of two equivalents of potassium *tert*-butoxide (LIDA-KOR 1:2). After 4 h at $-50\,^{\circ}C$ in tetrahydrofuran, the orange-red intermediate was intercepted with fluorodimethoxyborane (and subsequently oxidized with an alkaline solution of hydrogen peroxide), or with dry ice. The products, (2-fluorobiphenylyl)methanol (**4**) and (2-fluorobiphenylyl)acetic acid (**5**) were obtained in 72 and 84% yield, respectively (Scheme 4).



Scheme 4.

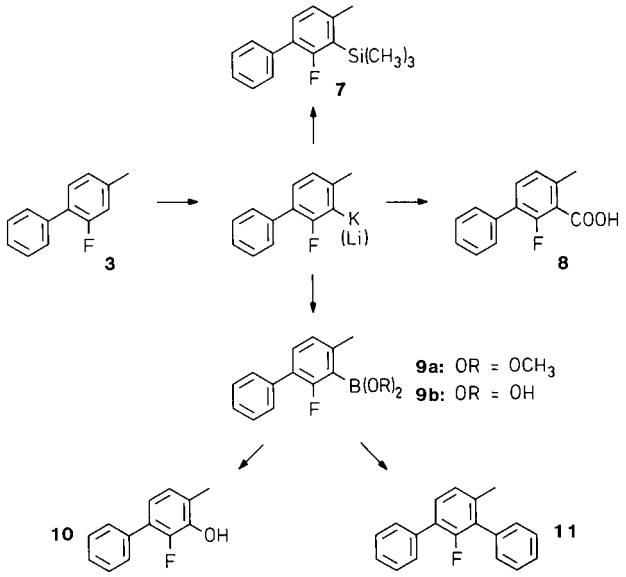
The introduction of the α-methyl group into the side chain was accomplished as described in our synthesis of ibuprofen.[17] Consecutive treatment of the acid **5** with two equivalents of LIDA-KOR (1:1 mixture) and methyl iodide gave flurbiprofen (**6**) in 92% yield (Scheme 5).

Congeners of acids **5** and **6** can be readily prepared by site-selective manipulation of the aromatic ring which bears the fluorine. Metalation of 2-fluoro-4-methylbiphenyl (**3**) with LIC-KOR for 2 h at $-75\,^{\circ}C$ in tetrahydrofuran followed by



Scheme 5.

trapping with various electrophiles opened a pathway to the silane **7** (69%), the carboxylic acid **8** (86%), and the boronate **9a**. The latter was not isolated but converted into the phenol **10** (82%) by oxidation with hydrogen peroxide and into the *m*-terphenyl **11** (65%) by palladium-catalyzed coupling of the boronic acid **9b** with bromobenzene (Scheme 6).



Scheme 6.

The terphenyl **11** was deprotonated at the benzylic position by means of two equivalents of LIDA-KOR in tetrahydrofuran at $-50\,^{\circ}C$ before it was submitted to the borylation/oxidation procedure. The resulting benzyl alcohol **12** (74%) reacted with three equivalents of *tert*-butyllithium in diethyl ether at $25\,^{\circ}C$ under *ortho*-lithiation. Quenching with *N*,*N*-dimethylformamide or *N*,*N*-diethylcarbamoyl chloride produced the lactol **13** (67%) and the amide **14** (68%) (Scheme 7).

The silane **7** also reacted with LIDA-KOR (in tetrahydrofuran for 6 h at $-75\,^{\circ}C$) to generate the benzylmetal species. The benzyl alcohol **15** (74%), obtained after borylation and oxidation, underwent a Brook metallotropy[18] when exposed to the action of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine-(TMEDA)-activated butyllithium in hexanes at $25\,^{\circ}C$. The resulting *ortho*-lithiated intermediate afforded lactol **16** (67%) upon interception by *N*,*N*-dimethylformamide (Scheme 8). Carboxylation of the benzylmetal species gave the carboxylic acid **17** (86%), which was converted into the methyl-branched homologue **18** (83%) by consecutive treatment with LIDA-KOR and methyl iodide. Iodolysis of this trimethylsilyl-substituted analogue of flurbiprofen afforded

Abstract in German: *Flurbiprofen ist ein entzündungshemmendes Schmerzmittel, das häufig zur Linderung rheumatischer Erkrankungen eingesetzt wird. Ein verbesserter Zugang zu diesem Propionsäure-Derivat wurde jetzt erschlossen. Die Schlüsselschritte sind die selektive Deprotonierung von 3-Fluortoluol in der 4-Position mit tert-Butyllithium in Gegenwart von Kalium-tert-butylalkoholat (LIT-KOR-Mischung) und die selektive Deprotonierung des erhaltenen 4-Methyl-2-fluorbiphenyls in der Benzylposition mit Lithiumdiisopropylamid in Gegenwart von Kalium-tert-butylalkoholat (LIDA-KOR-Mischung). Je nach vorliegendem Substitutionsmuster und dazu passend gewähltem Reagens, lassen sich auch die 3- und die 5-Positionen von 2-Fluorbiphenylenen selektiv angreifen. Die Fülle der durchgeführten Reaktionen soll veranschaulichen, welche praktischen Vorteile wahlweise positionsselektive Metallierungen bieten.*

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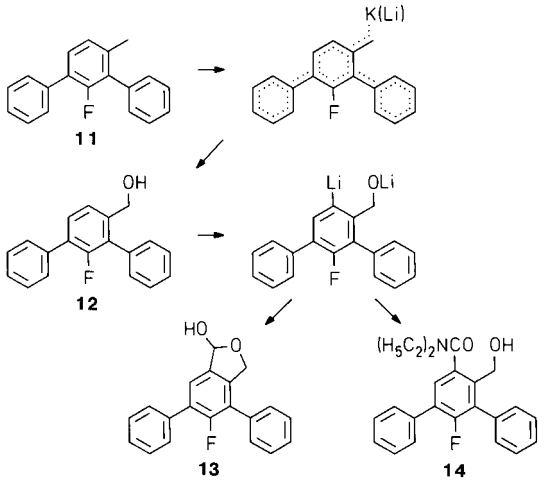
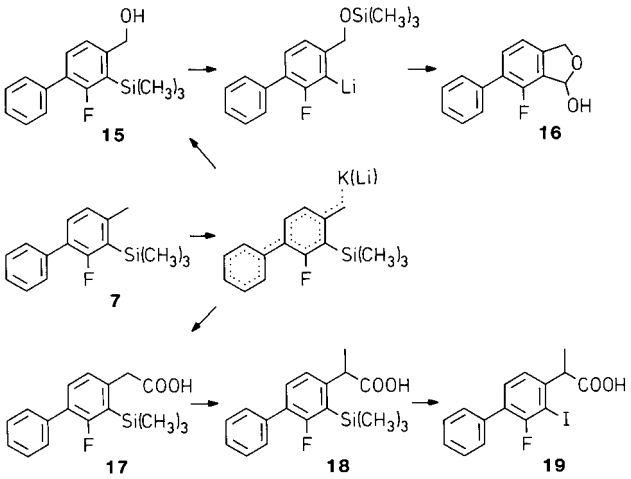


Scheme 7.

compound **19** (96%), which bears the lightest and the heaviest halogen in the same aromatic ring (Scheme 8).



Scheme 8.

Flurbiprofen belongs to the most efficacious nonsteroidal antiinflammatories, requiring only relatively moderate daily doses.[19] However, like all benzoic, acetic, and propanoic acid derivatives, it does not sufficiently discriminate as an inhibitor between the cyclooxygenase (COX) subtypes 1 and 2 and is hence expected to be replaced in the near future by "better aspirins".[20, 21] The purpose of the present study was not to develop new drugs but to demonstrate characteristic reactivity patterns.

Experimental Section

General: For standard working practice and abbreviations, see recent publications from this laboratory (for example ref. [22]). ^{1}H NMR spectra were recorded in perdeuteromethanol at 400 MHz unless stated otherwise.

3-Fluorotoluene as the substrate: substitution at the 4-position:

2-Fluoro-4-methylbenzoic acid (**1**): A solution of 3-fluorotoluene (2.8 mL, 2.8 g, 25 mmol), *tert*-butyllithium (25 mmol) and potassium *tert*-butoxide (2.8 g, 25 mmol) in tetrahydrofuran (50 mL) and pentanes (15 mL) was kept for 3 h at $-75\,^\circ$C. The mixture was poured onto an excess of freshly crushed dry ice, and water (0.10 L) was added. The aqueous layer was washed with diethyl ether (2×20 mL), acidified with 20% hydrochloric acid to pH 2, and extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine (2×15 mL), dried, and evaporated. The residue was crystallized from cyclohexane. Yield: 3.2 g (84%); m.p. 182–183 °C.[16]

(2-Fluoro-4-methylphenyl)boronic acid (**2**): An analogously prepared organometallic solution was treated at $-75\,^\circ$C with fluorodimethoxyborane diethyl etherate[23] (4.7 mL, 4.2 g, 25 mmol). The mixture was acidified with 1M hydrochloric acid (approx. 35 mL) to pH 2, and extracted with dichloromethane (3×50 mL). The combined organic layers were dried and evaporated. Recrystallization of the residue from hexanes afforded a colorless solid. Yield: 3.0 g (78%); m.p. 188–192 °C (decomp); ^{1}H NMR ($CDCl_3$; 250 MHz): $\delta=7.72$ (t, $J=7.4$ Hz, 1H), 7.04 (d, $J=7.6$ Hz, 1H), 6.89 (d, $J=11.7$, 1H), 5.22 (d, $J=6.3$, 2H), 2.39 (s, 3H); MS: $m/z=154$ (30%, $[M^+]$), 135 (18%), 109 (100%); anal. calcd for $C_7H_8BFO_2$ (153.95): C 54.61, H 5.27; found C 54.76, H 5.42%.

2-Fluoro-4-methylbiphenyl (**3**): A solution of (2-fluoro-4-methylphenyl)-boronic acid (**2**; 4.3 g, 28 mmol; prepared as described in the preceding paragraph) in ethanol (40 mL) and a 2M aqueous solution (18 mL) of sodium carbonate (55 mmol) were consecutively added to a solution of bromobenzene (2.6 mL, 3.9 g, 25 mmol) and tetrakis(triphenylphosphine)-palladium[24] in (mono)ethylene glycol dimethyl ether (0.25 L). The mixture was refluxed for 6 h, absorbed on silica gel (25 mL), and evaporated to dryness. Elution with pentanes from a column filled with more silica gel (0.10 L) gave a colorless liquid. Yield: 4.3 g (91%); m.p. 1–3 °C; b.p. 90–92 °C/1 mmHg (ref. [25]: b.p. 120 °C/6 mmHg); $n_D^{20}=1.5801$; ^{1}H NMR: $\delta=7.49$ (dm, $J=7.3$ Hz, 2H), 7.39 (tm, $J=7.3$ Hz, 2H), 7.3 (m, 2H), 7.03 (d, $J=7.8$ Hz, 1H), 6.98 (d, $J=12.1$ Hz, 1H), 2.36 (s, 3H); MS: $m/z=186$ (100%, $[M^+]$), 165 (16%).

When the reaction sequence starting with 3-fluorotoluene was repeated without isolating the boronic acid intermediate, the coupling product **3** was obtained in 79% overall yield.

2-Fluoro-4-methylbiphenyl as the substrate: substitution at the benzylic position:

(2-Fluoro-4-biphenylyl)methanol (**4**): At $-75\,^\circ$C, butyllithium (50 mmol) in hexanes (35 mL) was added to a solution of diisopropylamine (7.1 mL, 5.1 g, 50 mmol), potassium *tert*-butoxide (5.6 g, 50 mmol) and 2-fluoro-4-methylbiphenyl (**3**; 4.6 g, 25 mmol) in tetrahydrofuran (50 mL). After 4 h at $-50\,^\circ$C, fluorodimethoxyborane diethyl etherate[23] (6.5 mL, 5.8 g, 35 mmol) and, at 25 °C, 35% aqueous hydrogen peroxide (17 mL, 19 g, 0.17 mol) were added. The mixture was stirred at 25 °C for 1 h and then poured into water (50 mL) and extracted with diethyl ether (3×50 mL). The organic material was absorbed on silica gel and chromatographed (diethyl ether/pentanes 1:1 (*v*/*v*)) to give a slightly ochre-colored solid. Yield: 3.6 g (72%); m.p. 60–62 °C (from pentanes); ^{1}H NMR ($CDCl_3$): $\delta=7.51$ (dm, $J=7.9$ Hz, 2H), 7.4 (m, 3H), 7.34 (tt, $J=7.3$, 1.4 Hz, 1H), 7.21 (d, $J=7.9$ Hz, 1H), 7.18 (d, $J=11.6$ Hz, 1H), 4.64 (br s, 2H); MS: $m/z=221$ (10%; $[M^+{+}19]$), 203 (100%, $[M^+{+}1]$); anal. calcd for $C_{13}H_{11}FO$ (202.23): C 77.21, H 5.48; found C 76.84, H 5.43%.

(2-Fluoro-4-biphenylyl)acetic acid (**5**): 2-Fluoro-4-methylbiphenyl (4.6 g, 25 mmol) was treated with lithium diisopropylamide and potassium *tert*-butoxide as described in the preceding paragraph. The reaction mixture was poured onto an excess of freshly crushed dry ice. The product was dissolved in water (50 mL), washed with diethyl ether (3×25 mL), acidified with concentrated hydrochloric acid to pH 2, and then extracted with dichloromethane (3×50 mL). After evaporation of the solvent, the residue was crystallized from hexanes to afford a colorless solid. Yield: 4.9 g (84%); m.p. 140–142 °C (ref. [26]: m.p. 143–144.5 °C); ^{1}H NMR: $\delta=7.52$ (dm, $J=7.8$ Hz, 2H), 7.4 (m, 3H), 7.34 (tt, $J=7.3$, 1.4 Hz, 1H), 7.17 (dd, $J=8.9$, 1.6 Hz, 1H), 7.13 (dd, $J=12.8$, 1.6 Hz, 1H), 3.66 (s, 2H); MS: $m/z=230$ (84%, $[M^+]$), 185 (100%).

2-(2-Fluoro-4-biphenylyl)propanoic acid (**6**): At $-75\,^\circ$C, diisopropylamine (7.1 mL, 5.1 g, 50 mmol), potassium *tert*-butoxide (5.6 g, 59 mmol), and (2-fluoro-4-biphenylyl)acetic acid (**5**; 5.9 g, 25 mmol) were consecutively added to a solution of butyllithium (50 mL) in tetrahydrofuran (50 mL) and hexanes (35 mL). After stirring for 2 h at $-25\,^\circ$C, the reaction mixture was treated with methyl iodide (1.9 mL, 4.3 g, 30 mmol). The product was isolated as described in the preceding paragraph for acid **5** and crystallized from hexanes. Yield: 5.6 g (92%); m.p. 110–111 °C (ref. [26]: 110–111 °C);

^{1}H NMR: $\delta = 7.51$ (dm, $J = 7.8$ Hz, 2H), 7.4 (m, 3H), 7.35 (tt, $J = 7.3$, 1.4 Hz, 1H), 7.20 (dd, $J = 7.9$, 1.8 Hz, 1H), 7.15 (dd, $J = 11.9$, 1.8 Hz, 1H), 3.77 (q, $J = 7.1$ Hz, 1H), 1.49 (d, $J = 7.1$ Hz, 3H); MS: $m/z = 244$ (100%, $[M^+]$), 199 (61%), 185 (25%).

(2-Fluoro-4-methyl)biphenyl as the substrate: substitution at the 3-position:

2-Fluoro-4-methyl-3-(trimethylsilyl)biphenyl (**7**): At $-75\,^\circ$C, potassium *tert*-butoxide was added to a solution of 2-fluoro-4-methylbiphenyl (**3**; 5.2 mL, 4.7 g, 25 mmol) and butyllithium (25 mmol) in tetrahydrofuran (50 mL) and hexanes (15 mL). The mixture was stirred until it became homogeneous, then kept for 2 h at $-75\,^\circ$C, and was then treated with chlorotrimethylsilane (3.5 mL, 3.0 g, 28 mmol). When the temperature reached 25 °C, the mixture was poured into water (50 mL) and extracted with diethyl ether (3×50 mL). The combined organic layers were washed with water (2×25 mL) and brine (25 mL). Upon distillation, a viscous oil was collected which slowly crystallized. Yield: 4.5 (69%); m.p. 41–43 °C (from methanol); b.p. 135–137 °C/2 mmHg; ^{1}H NMR: $\delta = 7.45$ (dm, $J =$ 7.7 Hz, 2H), 7.39 (tm, $J = 7.3$ Hz, 2H), 7.32 (dt, $J = 7.4$, 1.4 Hz, 1H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.02 (d, $J = 7.7$ Hz, 1H), 2.46 (s, 3H), 0.39 (d, $J = 2.3$ Hz, 9H); MS: $m/z = 258$ (100%, $[M^+]$), 223 (48%), 179 (47%); anal. calcd for $C_{16}H_{19}FSi$ (258.41): C 74.37, H 7.41; found C 74.26, H 7.47%.

(2-Fluoro-4-methyl-3-biphenylyl)carboxylic acid (**8**): An analogously prepared reaction mixture was poured onto an excess of freshly crushed dry ice rather than treated with chlorotrimethylsilane. The product was isolated by extraction (see preparation of acid **5**, above), then converted into the methyl ester and purified by chromatography (silica gel, diethyl ether/pentanes 1:9 (*v*/*v*)). Yield: 4.8 g (78%); b.p. 81–82 °C/1 mmHg; $n_D^{20} =$ 1.5712; ^{1}H NMR: $\delta = 7.49$ (brd, $J = 7.8$ Hz, 2H), 7.43 (m, symm., 3H), 7.36 (brt, $J = 7.2$ Hz, 1H), 7.14 (brd, $J = 7.9$ Hz, 1H), 3.93 (brs, 3H), 2.37 (brs, 3H); MS: $m/z = 244$ (100%, $[M^+]$), 213 (34%), 184 (12%).

2-Fluoro-4-methyl-3-biphenylol (**10**): An analogous reaction mixture (see preparation of product **7**) was treated consecutively at $-75\,^\circ$C with fluorodimethoxyboron diethyl etherate[23] (4.7 mL, 4.2 g, 25 mmol) and, at 25 °C (stirred for 1 h), with 35% aqueous hydrogen peroxide (7.7 mL, 8.5 g, 75 mmol). The mixture was absorbed on silica gel and chromatographed (diethyl ether/pentanes 1:9 (*v*/*v*)) to give a colorless solid which was crystallized from pentanes. Yield: 4.1 g (82%); m.p. 58–60 °C (decomp); ^{1}H NMR: $\delta = 7.49$ (dm, $J = 7.9$ Hz, 2H), 7.39 (tm, $J = 7.4$ Hz, 2H), 7.31 (tt, $J = 7.4$, 1.3 Hz, 1H), 6.92 (d, $J = 7.9$ Hz, 1H), 6.77 (t, $J = 7.6$ Hz, 1H), 2.25 (3H, s); MS: $m/z = 202$ (100%, $[M^+]$), 169 (58%); anal. calcd for $C_{13}H_{11}FO$ (202.23): C 77.21, H 5.48; found C 77.40, H 5.47%.

2′-Fluoro-4′-methyl-*m*-terphenyl (**11**): The reaction was initiated as described in the preceding paragraph. After the addition of fluorodimethoxyboron diethyl etherate,[23] the mixture was evaporated to dryness. The residue was taken up in ethanol (40 mL) and added, together with a solution of bromobenzene (2.6 mL, 3.9 g, 25 mmol) and tetrakis(triphenylphosphine)palladium[24] (0.88 g, 0.75 mmol) in (mono)ethylene glycol dimethyl ether (0.25 L), to 2 M aqueous sodium carbonate (28 mL, 55 mmol). The mixture was refluxed for 6 h and then absorbed on silica gel and chromatographed (hexanes) to afford a viscous, colorless oil. M.p. -10 to $-8\,^\circ$C/0.6 mmHg; $n_D^{20} = 1.6124$; ^{1}H NMR: $\delta = 7.50$ (2H, dm, $J =$ 7.4 Hz,), 7.45 (tt, $J = 7.2$, 1.4 Hz, 2H), 7.4 (m, 3H), 7.33 (t, $J = 7.9$ Hz, 1H), 7.31 (tt, $J = 7.3$, 1.3 Hz, 1H), 7.27 (dm, $J = 7.4$ Hz, 2H), 7.16 (d, $J = 7.7$ Hz, 1H), 2.15 (s, 3H); MS: $m/z = 263$ (18%, $[M^+ + 1]$), 262 (59%, $[M^+]$), 239 (11%), 183 (34%), 165 (19%), 77 (100%); anal. calcd for $C_{19}H_{15}F$ (262.33): C 86.99, H 5.76; found C 87.10, H 5.82.

2′-Fluoro-4′-methyl-*m*-terphenyl as the substrate: substitution at the benzylic position:

(2′-Fluoro-4′-terphenylyl)methanol (**12**): 2′-Fluoro-4′-methyl-*m*-terphenyl (**11**; 6.5 g, 25 mmol) was treated consecutively with lithium diisopropylamide in the presence of potassium *tert*-butoxide, fluorodimethoxyboron,[23] and 35% aqueous hydrogen peroxide, as described for the preparation of product **4** (see above). The hydroxylated derivative **12** was isolated by chromatography on silica (diethyl ether/pentanes 1:1 (*v*/*v*)). Yield: 4.9 g (74%); m.p. 81–83 °C (from pentanes); ^{1}H NMR: $\delta = 7.55$ (dm, $J = 7.6$ Hz, 2H,), 7.4 (m, 7H), 7.35 (tt, $J = 7.2$, 1.3 Hz, 1H), 7.31 (dm, $J = 7.6$ Hz, 2H), 4.39 (s, 2H); MS: $m/z = 278$ (100%, $[M^+]$), 260 (36%), 244 (16%); anal. calcd for $C_{19}H_{15}FO$ (278.32): C 81.99, H 5.43; found C 82.18, H 5.36%.

2′-Fluoro-4′-methyl-*m*-triphenylyl)methanol as the substrate: substitution at the 5-position:

5-Fluoro-1,3-dihydro-4,6-diphenylisobenzofuran-1-ol (**13**): At $-25\,^\circ$C, solutions of (2′-fluoro-4′-terphenylyl)methanol (**12**; 7.0 g, 25 mmol) in diethyl ether (0.15 L) and *tert*-butyllithium (75 mmol) in hexanes (50 mL) were mixed. After 6 h at 25 °C, *N*,*N*-dimethylformamide (5.8 mL, 5.5 g, 75 mmol) at $-25\,^\circ$C and, at $+25\,^\circ$C, a saturated aqueous solution (0.15 L) of ammonium chloride were added. The aqueous phase was extracted with diethyl ether (3×0.10 L). The combined organic layers were evaporated and the residue absorbed on silica gel and chromatographed (diethyl ether/pentanes 1:1 (*v*/*v*)) to give a colorless amorphous solid. Yield: 5.1 g (67%); m.p. (decomp) 51–56 °C; ^{1}H NMR: $\delta = 7.6$ (m, 2H), 7.4 (m, 9H), 6.57 (brs, 1H), 5.25 (dd, $J = 13.6$, 1.0 Hz, 1H), 4.88 (d, $J = 13.6$ Hz, 1H), 3.33 (brs, 1H); MS: $m/z = 324$ (13%, $[M^+ + 18]$), 306 (55%), 289 (100%), 259 (65%), 241 (25%); anal. calcd for $C_{20}H_{15}FO_2$ (306.33): C 78.42, H 4.94; found C 78.11, H 5.27%.

***N*,*N*-Diethyl-5′-(2′-fluoro-4′-hydroxymethyl-*m*-terphenyl)carboxamide** (**14**): In a reaction performed as described in the preceding paragraph, *N*,*N*-dimethylformamide was replaced by *N*,*N*-diethylcarbamoyl chloride (9.5 mL, 10.2 g, 75 mmol). The product was isolated by chromatography (diethyl ether/pentanes 3:7 (*v*/*v*)). Yield: 6.4 g (68%); m.p. 4–6 °C; b.p. 111–113 °C/0.5 mmHg; $n_D^{20} = 1.5676$; ^{1}H NMR: $\delta = 7.54$ (dm, $J = 7.4$ Hz, 2H), 7.4 (m, 9H), 4.93 (s, 2H), 3.26 (q, $J = 7.1$ Hz, 4H), 1.09 (t, $J = 7.1$ Hz, 6H); MS: $m/z = 377$ (18%, $[M^+]$), 261 (100%), 74 (54%); anal. calcd for $C_{24}H_{24}FNO_2$ (279.34): C 76.37, H 6.13; found C 76.10, H 6.40%.

2-Fluoro-4-methyl-3-(trimethylsilyl)biphenyl as the substrate:

2-Fluoro-3-trimethylsilyl-4-biphenylyl)methanol (**15**): 2-Fluoro-4-methyl-3-(trimethylsilyl)biphenyl (7.2 mL, 6.5 g, 25 mmol) was consecutively treated with lithium diisopropylamide in the presence of potassium *tert*-butoxide, fluorodimethoxyborane,[23] and 35% aqueous hydrogen peroxide as described above (see the preparation of alcohol **4**). Chromatography (silica gel, diethyl ether/pentanes 1:1 (*v*/*v*)) gave a slowly crystallizing, analytically pure oil. Yield: 4.0 g (58%); m.p. 56–58 °C, ^{1}H NMR: $\delta = 7.47$ (dm, $J = 7.6$, Hz, 2H), 7.4 (m, 3H), 7.3 (m, 2H), 4.69 (s, 2H), 0.42 (d, $J = 2.1$, Hz, 9H); MS: $m/z = 274$ (92%, $[M^+]$), 259 (93%), 185 (100%); anal. calcd for $C_{16}H_{19}FOSi$ (274.41): C 70.03, H 6.98; found C 70.14, H 7.12%.

6-Fluoro-1,3-dihydro-5-phenylisobenzofuran-1-ol (**16**): Butyllithium (50 mmol) in hexanes (35 mL) was added to a solution containing the benzylic alcohol **15** (6.9 g, 25 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine 87.5 mL, 5.8 g, 50 mmol). After 2 h at 25 °C, the mixture was treated at $-75\,^\circ$C with *N*,*N*-dimethylformamide (1.9 mL, 1.8 g, 25 mmol) and, at $+25\,^\circ$C, with a saturated aqueous solution (25 mL) of ammonium chloride. The aqueous phase was extracted with diethyl ether (3×25 mL). The combined organic layers were concentrated and absorbed on silica gel (15 mL). Elution from a column filled with more silica gel (85 mL) with diethyl ether/pentanes (1:1 (*v*/*v*)) afforded a colorless and crystalline product. Yield: 3.5 g (60%); m.p. 139–141 °C (decomp); ^{1}H NMR: $\delta = 7.53$ (dm, $J = 7.7$ Hz, 2H), 7.4 (m, 3H), 7.37 (tt, $J = 7.3$, 1.4 Hz, 1H), 7.17 (d, $J =$ 7.7 Hz, 1H), 6.75 (brs, 1H), 5.11 (brs, 2H); MS: $m/z = 230$ (100%, $[M^+]$), 213 (48%), 201 (32%); anal. calcd for $C_{14}H_{11}FO_2$ (230.24): C 73.04, H 4.82; found C 72.98, H 5.05.

(2-Fluoro-3-trimethylsilyl-4-biphenylyl)acetic acid (**17**): 2-Fluoro-4-methyl-3-(trimethylsilyl)biphenyl (7.2 mL, 6.5 g, 25 mmol) was consecutively treated with lithium diisopropylamide in the presence of potassium *tert*-butoxide and dry ice, as described above (see preparation of the acid **5**). The crude acid was extracted with dichloromethane (see above) and converted with diazomethane into the methyl ether, which was purified by chromatography (silica gel, diethyl ether/pentanes 1:9 (*v*/*v*)). Yield: 6.2 g (79%); m.p. 54–56 °C (from methanol); ^{1}H NMR: $\delta = 7.48$ (dm, $J = 7.8$ Hz, 2H), 7.39 (t, $J = 7.6$ Hz, 2H), 7.30 (sym m, 2H), 7.07 (d, $J = 7.8$ Hz, 1H), 3.67 (s, 2H), 0.40 (d, $J = 2.2$ Hz, 9H); methyl ester (after treatment with etheral diazomethane): anal. calcd for $C_{18}H_{21}FO_2Si$ (316.45): C 68.32, H 6.69; found C 68.26, H 6.70%.

2-(2-Fluoro-3-trimethylsilyl-4-biphenylyl)propanoic acid (**18**): The acetic acid derivative **17** (7.6 g, 25 mmol) was converted into the propanoic acid homologue **18** and isolated as described above (see the preparation of acid **6**). Yield: 6.6 g (83%); m.p. 171–175 °C (cryst. from hexanes); ^{1}H NMR: $\delta = 7.46$ (symm. m, 2H), 7.42 (t, $J = 7.4$ Hz, 2H), 7.3 (m, 3H), 3.97 (q, $J =$ 7.1 Hz, 1H), 1.41 (d, $J = 7.1$ Hz, 3H), 0.44 (d, $J = 2.4$ Hz, 9H); MS: $m/z =$ 316 (13%, $[M^+]$), 301 (100%), 272 (19%); anal. calcd for $C_{18}H_{21}FO_2Si$ (316.45): C 68.32, H 6.69; found C 68.73, H 6.73%.

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2-(2-Fluoro-3-iodo-4-biphenylyl)propanoic acid (**19**): Acid **18** (7.9 g, 25 mmol) was added to a solution of iodine (mono)chloride (4.1 g, 25 mmol) in tetrachloromethane (20 mL) and the suspension was refluxed for 1 h. Product **19** was isolated by filtration and crystallization from hexanes. M.p. 160–162 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.5$ (m, 5H), 7.42 (br t, $J = 7.2$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 1H), 4.06 (q, $J = 7.1$ Hz, 1H), 1.41 (d, $J = 7.1$ Hz, 3H); MS: $m/z = 388$ (78%, [M^++18]), 370 (46%, [M^+]), 326 (100%), 262 (58%), 244 (79%); anal. calcd for $C_{15}H_{12}FIO_2$ (370.16): C 48.67, H 3.27; found C 48.60, H 3.15%.

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