Atropisomeric Biarylbisphosphines Derived from 2,2-Difluoro-1,3-benzodioxole

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Abstract: Starting from the inexpensive 2,2-difluoro-1,3-benzodioxole or its 5-bromo derivative, two new atropisomeric bisphosphines have been prepared which, after racemate resolution, exhibit attractive features as ligands for enantioselective catalysts. The key step in their synthesis is a low temperature Ullmann reaction. An improved protocol secures coupling yields of 70–80%.

Key words: atropisomers, 2,2-difluoro-1,3-benzodioxole, bromo/lithium permutation, metalation, biarylbisphosphines

The singular electronic structure[1] of 2,2-difluoro-1,3-benzodioxole confers a distinctive reactivity profile to this compound and its congeners as well.[2–4] In particular, the 4- and 7-positions are strongly acidified and can be readily deprotonated. Thus, consecutive treatment of the commercial 5-bromo-2,2-difluoro-1,3-benzodioxole with lithium diisopropylamide and oxirane or carbon dioxide afforded, 2-(5-bromo-2,2-difluoro-1,3-benzodioxol-4-yl)ethanol (76%)[2] or 5-bromo-2,2-difluoro-1,3-benzodioxole-4-carboxylic acid (88%),[2] respectively, whereas 5-bromo-2,2-difluoro-4-iodo-1,3-benzodioxole (**1**) was isolated in 86% yield when the organometallic intermediate was trapped with elemental iodine. Employing an improved version[5] of the low temperature modification[6–10] of the Ullmann coupling,[11,12] the biaryl **2** was obtained in 72% yield. This was transformed to the bisphosphine **3** (67%) by halogen/metal permutation followed by condensation with two equivalents of chlorodiphenylphosphine (Scheme 1).

Bisphosphine **3** was independently accessed starting from 6-bromo-4-triethylsilyl-2,2-difluoro-1,3-benzodioxole. The same series of reactions as described above gave the iodo derivative **4** (73%), the silyl-protected dibromobiaryl **5** (84%) and the silyl-protected bisphosphine **6** (69%). The removal of the triethylsilyl groups was accomplished with tetrabutylammonium fluoride hydrate.

In contrast, we failed to introduce the bromine atoms at a later stage, i. e. after the aryl-aryl coupling. The reductive dimerization of 2,2-difluoro-4-iodo-7-triethylsilyl-1,3-benzodioxole (**7**; prepared in the usual way from 2,2-difluoro-4-triethylsilyl-1,3-benzodioxole[4] in 94% yield) occurred smoothly to provide the bissilylated biaryl **8** (77%). However, numerous attempts to dimetalate it and subsequently to convert it into the dibromo derivative **5**, the bisphosphine **6** or the dicarboxylic acid **9** proved unsuccessful.

The atropisomeric bisphosphine **3** is a tetrafluoro analog of SEGPHOS,[13,14] one of the best performing ligands for asymmetric synthesis.[15–17] Its racemate resolution can be easily accomplished by the fractional crystallization of the diastereomeric dibenzoyltartaric acid complexes of the corresponding bis(phosphine oxide),[18] as described for the popular BINAP-ligand.[19] The bis(phosphine oxide) can be made in virtually quantitative yield by the oxidation of the bisphosphine **3** with hydrogen peroxide. A shorter route leading to the same product in 35% overall yield consists of the consecutive treatment of 5-bromo-2,2-difluoro-1,3-benzodioxole with magnesium, chlorodiphenylphosphine and hydrogen peroxide and the subsequent reaction of the resulting 5-diphenylphosphoryl-2,2-difluoro-1,3-benzodioxole with lithium diisopropylamide and ferric chloride. After silane-promoted deoxygenation of the bisoxides the (+)- or (–)-bisphosphine **3** was coordinated with ruthenium salts and applied as an amazingly enantioselective catalyst for the asymmetric hydrogenation of a series of model substrates.[20]

Details concerning standard operations and abbreviations are specified in previous publications[21–23] from this laboratory. ^{1}H, (^{1}H-decoupled) ^{13}C and ^{31}P NMR spectra were recorded at 400 MHz, 101 MHz and 162 MHz, respectively. The samples were dissolved in $CDCl_3$ with TMS (for ^{1}H and ^{13}C NMR) or 85% aqueous H_3PO_4 (for ^{31}P NMR) being used as the internal or external reference (δ = 0 ppm). Although the rules of nomenclature would oblige us to classify compounds **4**–**8** as silanes, e.g. **4** as triethyl(5-bromo-2,2-difluoro-1,3-benzodioxol-4-yl)silane, we have preferred to call them benzodioxoles in order to preserve the same parent structure in all cases.

5-Bromo-2,2-difluoro-4-iodo-1,3-benzodioxole (1)

At –75 °C, 2,2,6,6-tetramethylpiperidine (17 mL, 14 g, 0.10 mol) and 5-bromo-2,2-difluorobenzodioxole (14 mL, 24 g, 0.10 mol) were added consecutively to a solution of BuLi (0.10 mol) in THF (0.20 L) and hexanes (65 mL) The mixture was kept in dry ice–MeOH bath for 2 h before being treated with iodine (25 g, 0.10 mol) in THF (0.10 L). The solvents were evaporated and the residue was dissolved in Et_2O (0.10 L). After washing with a 10% aq solution of sodium thiosulfate (50 mL), the organic layer was dried and evaporated. After crystallization from EtOH, colorless cubes were obtained; yield: 31.2 g (86%); mp 65–67 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.3 Hz, 1 H), 6.93 (d, *J* = 8.3 Hz, 1 H).

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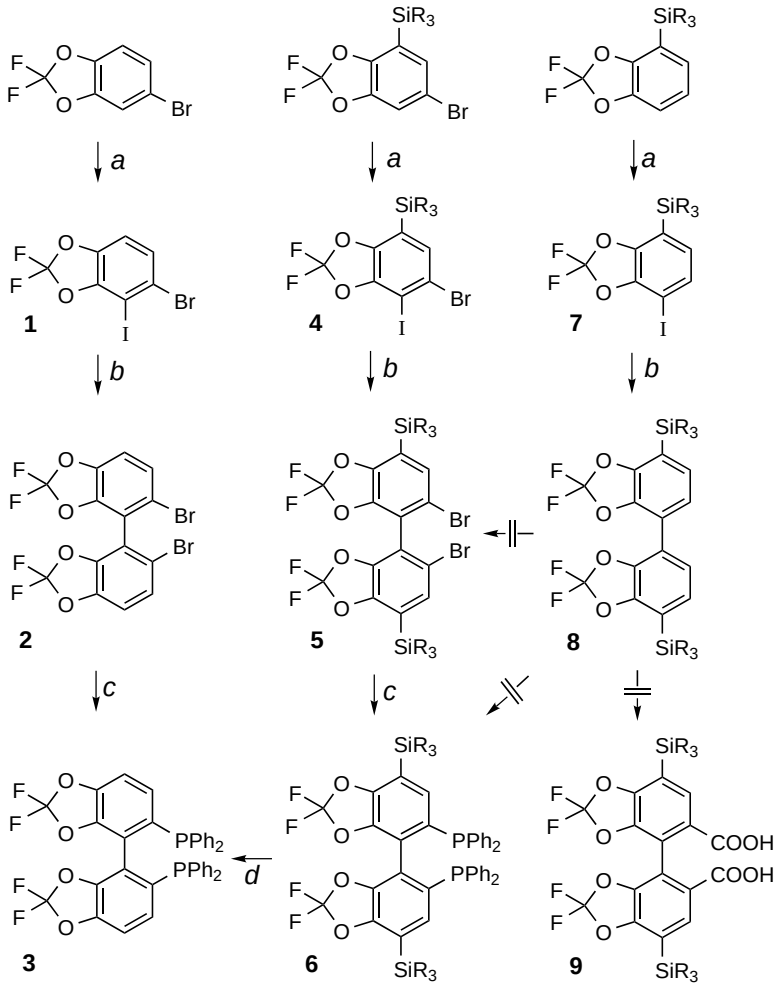

Scheme 1 R = Et. a) (1) Lithium 2,2,6,6-tetramethylpiperidide in THF, 2 h at –75 °C; (2) Iodine in THF at –75 °C. b) (1) BuLi in Et_2O, 5 min at –75 °C; (2) Cupric bromide, 45 min at –75 °C; (3) Nitrobenzene, –75 °C → +25 °C. c) (1) BuLi in Et_2O, 5 min at –75 °C; (2) Chlorodiphenylphosphine. d) Tetrabutylammonium hydrate in THF, 12 h at +75 °C (reflux).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.1 (s), 140.9 (s), 130.6 (t, *J* = 258.9 Hz), 127.0 (s), 123.5 (s), 110.2 (s).

Anal. Calcd for $C_7H_2BrF_2IO_2$ (362.89): C, 23.17; H, 0.56. Found: C, 23.19; H, 0.54.

5,5′-Dibromo-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole (2)

At –75 °C and under vigorous stirring, BuLi (0.50 mmol) in hexanes (33 mL) was added to a solution of 5-bromo-2,2-difluoro-4-iodo-1,3-benzodioxole (**1**; 18 g, 50 mmol) in Et_2O (0.25 L) followed 5 min later by copper(II) bromide (11 g, 50 mmol) and 45 min later by nitrobenzene (5.1 mL, 6.2 g, 50 mmol). The reaction mixture was allowed to reach 25 °C slowly in the course of 12 h. The suspension was poured into a 12% aq solution of NH_3 (0.10 L). The organic phase was separated and the aq layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (over Na_2SO_4) before being evaporated. The residue was purified by chromatography on silica gel (0.50 L, 0.25 kg) using hexanes as the eluent. After crystallization from EtOH, colorless needles were collected; yield: 8.49 g (72%); mp 89–91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.5 Hz, 2 H), 7.07 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.0 (s), 142.7 (s), 138.7 (s), 131.6 (t, *J* = 258.5 Hz), 127.5(s), 117.5 (s), 111.3 (s).

Ana. Calcd for $C_{14}H_4Br_2F_4O_4$ (471.98): C, 35.63; H, 0.85. Found: C, 35.92; H, 0.94.

5,5′-Bis(diphenylphosphanyl)-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole (3)

At –75 °C, BuLi (30 mmol) in hexanes (19 mL) was added to a solution of 5,5′-dibromo-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole (**2**; 7.1 g, 15 mmol) in Et_2O (75 mL) followed 45 min later by chlorodiphenylphosphine (5.4 mL, 6.6 g, 30 mmol) in Et_2O (50 mL). The mixture was treated at 25 °C with a sat. aq solution of NH_4Cl (60 mL) before being extracted with EtOAc (3 × 30 mL). Evaporation of the solvents and crystallization from EtOAc–hexanes afforded colorless needles; yield: 6.85 g (67%); mp 218–220 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.3 (m, 12 H), 7.2 (m, 8 H), 7.01 (d, *J* = 8.1 Hz, 2 H), 6.87 (d, *J* = 8.3 Hz, 2 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = –12.3 (s).

Anal. Calcd for $C_{38}H_{24}F_4O_4P_2$ (682.55): C, 66.87; H, 3.54. Found: C, 66.70; H, 3.57.

Bisphosphine **3** was also formed when a solution of the silylated bisphosphine **6** (2.7 g, 3.0 mmol) and tetrabutylammonium fluoride tetrahydrate (4.0 g, 12 mmol) in THF (10 mL) was heated for 12 h under reflux; yield: 0.98 g (48%).

5-Bromo-2,2-difluoro-4-iodo-7-triethylsilanyl-1,3-benzodioxole (4)

Starting from 6-bromo-2,2-difluoro-4-triethylsilyl-1,3-benzodioxole[4] (23 g, 65 mmol) compound **4** was obtained analogously as described above for the preparation of compound **1**. After crystallization from MeOH, colorless cubes were obtained; yield: 22.6 g (73%); mp 34.0–35.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (s, 1 H), 1.0 (m, 9 H), 0.9 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.0 (s), 145.3 (s), 131.9 (s), 130.3 (t, *J* = 257.5 Hz), 123.7(s), 121.1 (s), 80.6 (s), 7.1 (s), 2.9 (s).

Anal. Calcd for for $C_{13}H_{16}BrF_2IO_2Si$ (477.16): C, 32.72; H, 3.38. Found: C, 32.84; H, 3.41.

5,5′-Dibromo-2,2,2′,2′-tetrafluoro-7,7′-bis-(triethylsilanyl)-4,4′-bi-1,3-benzodioxole (5)

Starting from 5-bromo-2,2-difluoro-4-iodo-7-triethylsilanyl-1,3-benzodioxole (**4**; 15 g, 31 mmol) compound **5** was obtained analogously as described above for the preparation of biaryl **2**. After crystallization from EtOH colorless needles were isolated; yield: 9.12 g (84%); mp 99–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 2 H), 1.02 (t, *J* = 7.1 Hz, 18 H), 0.91 (q, *J* = 7.0 Hz, 12 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 147.4 (s), 141.4 (s), 132.4 (s), 131.2 (t, *J* = 256.8 Hz), 122.5(s), 118.0 (s), 117.6 (s), 7.1 (s), 3.0 (s).

Anal. Calcd for $C_{26}H_{32}Br_2F_4O_4Si_2$ (700.51): C, 44.58; H, 4.61. Found: C, 44.66; H, 4.73.

5,5′-Bis(diphenylphosphanyl)-2,2,2′,2′-tetrafluoro-7,7′-bis(triethylsilanyl)-4,4′-bi-1,3-benzodioxole (6)

Starting from the dibromo compound **5** (3.5 g, 5.0 mmol), compound **6** was obtained analogously as described above for the preparation of bisphosphine **3**. Upon crystallization from EtOH colorless needles were obtained; yield : 3.14 g (69%); mp 140–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.3 (m, 20 H), 6.81 (t, *J* = 1.6 Hz, 2 H), 0.82 (t, *J* = 7.4 Hz, 18 H), 0.66 (q, *J* = 7.4 Hz, 12 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = –11.5 (s).

Anal. Calcd for $C_{50}H_{52}F_4O_4P_2Si_2$ (911.07): C, 65.92; H, 5.75. Found: C, 66.17; H, 5.73.

2,2-Difluoro-4-iodo-7-triethylsilanyl-1,3-benzodioxole (7); Typical Procedure

A mixture of 2,2-difluoro-4-triethylsilanyl-1,3-benzodioxole[4] (41 g, 0.15 mol) and *sec*-BuLi (0.15 mol) in THF (0.18 L) and cyclohexane (0.12 L) was kept for 2 h at –75 °C before being treated with iodine (38 g, 0.15 mol) in THF (30 mL). At 25 °C, it was washed with a sat. aq solution of sodium thiosulfate (50 mL). Upon distillation, a colorless liquid was collected; yield: 56.1 g (94%); bp 150–152 °C/9 Torr; n_D^{20} = 1.5250.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.0 Hz, 1 H), 6.83 (d, *J* = 8.1 Hz, 1 H), 1.0 (m, 9 H), 0.9 (m, 6 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 147.2, 144.7, 132.2, 130.6, 130.1 (t, *J* = 255 Hz), 119.0, 72.0, 7.1 (3 C), 3.0 (3 C).

Anal. Calcd for $C_{13}H_{17}F_2IO_2Si$ (398.26): C, 39.21; H, 4.30. Found: C, 39.64; H, 4.83.

2,2,2′,2′-Tetrafluoro-7,7′-bis(triethylsilanyl)-4,4′-bi-1,3-benzodioxole (8)

Starting from 2,2-difluoro-4-iodo-7-triethylsilanyl-1,3-benzodioxole (**7**; 48 g, 0.12 mol) compound **8** was obtained analogously as described above for the preparation of biaryl **2**. After crystallization from MeOH colorless platelets were obtained; yield: 25.0 g (77%); mp 44.5–45.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 1.01 (t, *J* = 7.8 Hz, 18 H), 0.89 (q, *J* = 8.0 Hz, 12 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.9 (s), 139.7 (s), 131.1 (t, *J* = 253.9 Hz), 129.4 (s), 123.6 (s), 119.4 (s), 117.8 (s), 7.2 (s), 3.1 (s).

Anal. Calcd for $C_{26}H_{34}F_4O_4Si_2$ (542.72): C, 57.54; H, 6.31. Found: C, 57.32; H, 6.00.

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