Synthesis of 5,5'-Disubstituted 2,2'-Bipyridines for Modular Chemistry

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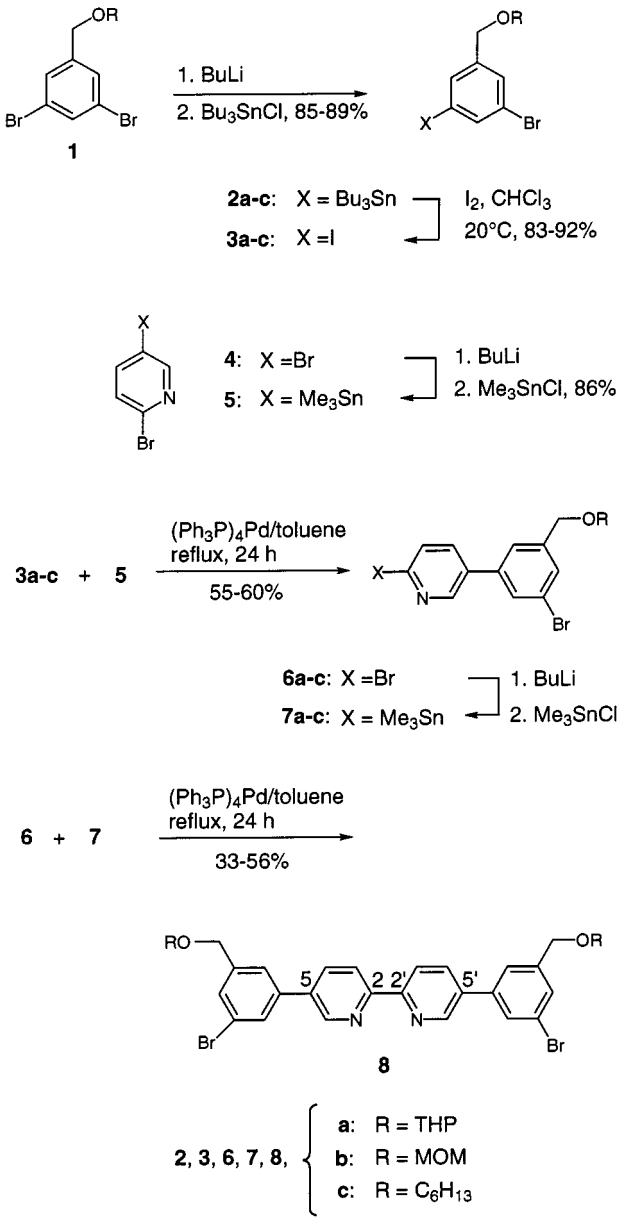
Abstract: A 0.5–11 g scale synthesis of the 5,5'-disubstituted 2,2'-bipyridines **8** is described. The pyridine units are connected to one another by Pd-catalyzed cross-coupling reactions. This method allows one to introduce bromo functions and flexible chains at the terminal phenyls which optimizes this class of bidentate ligands for supra- and macromolecular applications.

Key Words: Stille cross-coupling, bipyridines, supramolecular chemistry, modular chemistry

We have recently reported on repetitive syntheses of oligophenylene rods and hexagons using a construction kit of orthogonally protected building blocks.[1,2] These building blocks can be variably connected to one another by transition-metal mediated cross-coupling chemistry and allow to prepare a variety of monodisperse products with a reasonable quantity/effort ratio. We are presently developing a related methodology for the synthesis of shape-persistent macrocycles with integral 2,2':2:6"-terpyridine donor moieties for the subsequent transition-metal complexation and supramolecular assembly.[3] The goal of the present contribution is to expand this project to bipyridines. It describes a multigram scale synthesis of symmetrical bipyridines **8** in which pyridines, already containing all the substituents later required for achieving compatibility with the existing modules, are connected in the last step to bipyridines by the Stille reaction.

Bipyridines are one of the the most important ligands in supramolecular chemistry[4] and many syntheses have been reported.[5] One synthetic way to 5,5'-disubstituted bipyridines uses 5,5'-dibromobipyridines as starting material.[6] In a recent elegant example this compound was used to introduce acetylene units at these positions via transion metal-catalyzed coupling reactions.[7] The route most often used to 5,5'-dibromobipyridines involves direct bromination of bipyridines under harsh conditions.[7] With commonly available pressure equipments this reaction only gives a few grams of pure product. Additionally, workup is somewhat inconvenient. Some 2,2'-bipyridines[8,9] including the parent compound[10] have also been prepared by connecting two pyridine precursors at C-2 with the help of transition metal complexes.

Intrigued by this work and given our experience with Suzuki and Stille cross-coupling reactions[3,11] a route to the symmetrical target bipyridines **8** was devised based on the coupling of properly substituted pyridines (Scheme). Pyridine **7** was selected as the key compound, because it contains the Stille functionalities, a trimethyltin (TMSn) group at C-2, an aryl bromide substituent for further growth reactions once the bipyridines is formed, and finally, a flexible substituent which not only increases the solubility but is also designed as a protected anchor group for manifold purposes. An important prerequisite for the feasibility of this strategy was the high selectivity of the Stille coupling between **6** and **7** towards coupling at pyridine C-2.[12]



Scheme

The reactions depicted in the Scheme were carried out with three different R substituents [R = tetrahydropyranyl (THP), methoxymethyl (MOM), and hexyl]. Compounds **1** were prepared from the readily available corresponding benzyl alcohol.[13] Lithiation of **1** and subsequent stannylation allowed the selective incorporation of one tributylstannyl (TBSn) group to give **2** which was quantitively converted into the iodo analog **3**. The use of TBSn as place holder in this iodination reaction is superior to the more commonly used alternative trimethylsilyl because of its lower, in fact, practically lack of interference with THP.[14] The commercially available pyridine **4** was selectively stannylated at C-3 to give **5**[8,15] and then coupled with compounds **3** to give the key pyridines **6** on the 2 g (R = THP), 32 g (MOM), and 25 g scale (R = C_6H_{13}) and in 55–60% yields. The coupling between **3** and **5** proceeds in fact regioselectively as shown in the Scheme. Compound **5** does not undergo homopolymerization under the applied conditions. The conversion of **6** into **7** was carried out by the standard sequence of lithiation/stannylation. Pyridine **7** was used as the crude material because it decomposes rapidly on silica gel during chromatography and in a Kugelrohr apparatus on attempted distillation. The components **6** and **7** were subjected to a Stille coupling using the standard conditions[16] using 3 mol % of $Pd[(PPh_3)_4]$ as a catalyst. This coupling afforded the desired bipyridines **8** on a 400 mg (R = THP), 7 g (R = MOM) and 11 g scale (R = C_6H_{13}). The most convincing structural proof for **8** is its ^{13}C NMR spectrum which shows exactly the 11 expected aromatic signals.

All chemicals were purchased from Aldrich and Acros Chimica and used without further purification. Solvents: anhyd Et_2O, THF and toluene were distilled from sodium/benzophenone. The mass spectra were recorded in the electron impact (EI) mode.

2-(3,5-Dibromobenzyloxy)tetrahydropyran (1a)
To a stirred solution of 3,5-dibromobenzyl alcohol (5.0 g, 18.8 mmol) and dihydropyran (4.0 g, 47.6 mmol) in CH_2Cl_2 (40 mL) was added $TsOH \cdot H_2O$ at 20 °C. After stirring for 12 h, an aq 20% $NaHCO_3$ solution (20 mL) was added, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic phases were washed with H_2O (50 mL). The organic phase was dried ($MgSO_4$), the solvent removed and the resulting oil chromatographed on silica gel (EtOAc/hexane, 1:6) to give **1a** as a colorless oil; yield: 6.04 g (92%); R_f 0.54 (EtOAc/hexane, 1:6).

Anal. calcd for $C_{12}H_{14}Br_2O_2$ (350.0): C, 41.18; H, 4.03. Found C, 40.81; H, 3.82.

^1H NMR ($CDCl_3$/TMS, 250 MHz): δ = 1.45–1.95 (m, 6 H, THP), 3.49–3.61 (m, 1 H, THP), 3.80–3.94 (m, 1 H, THP), 4.41 (d, 1 H, *J* = 13 Hz, benzyl-H), 4.64–4.72 (m, 2 H, benzyl-H, THP), 7.44 (s, 2 H, phenyl-H), 7.59 (s, 1 H, phenyl-H).

^{13}C NMR ($CDCl_3$,/TMS, 63 MHz): δ = 18.96, 25.15, 30.15, 61.74, 66.87, 97.63, 122.60, 128.83, 132.62, 142.23.

MS (EI, 60 eV): *m/z* (%) = 348 (0.2), 350 (0.5), 352 (0.3).

1,3-Dibromo-5-(methoxymethoxymethyl)benzene (1b)
To a vigorously stirred suspension of P_2O_5 (120 g) in CCl_4 (300 mL) was added a solution of 3,5-dibromobenzyl alcohol (40.0 g, 150.4 mmol) in dimethoxymethane (480 g, 6.4 mol). After 10 h this mixture was added carefully to a 20% K_2CO_3 solution (1 L) at 0 °C and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (200 mL) and the combined organic phases were washed with H_2O (300 mL). The organic phase was dried ($MgSO_4$), the solvent removed and the resulting oil chromatographed on silica gel (EtOAc/hexane, 1:6) to give **1b** as a colorless oil; yield: 45.2 g (97%); R_f 0.53 (EtOAc/hexane, 1:6).

Anal. calcd for $C_9H_{10}Br_2O_2$ (310.0): C, 34.87; H, 3.25. Found C, 34.69; H, 3.16.

^1H NMR ($CDCl_3$/TMS, 250 MHz): δ = 3.40 (s, 3 H, CH_3), 4.50 (s, 2 H, CH_2), 4.69 (s, 2 H, CH_2), 7.42 (s, 2 H, phenyl-H), 7.58 (s, 1 H, phenyl-H).

^{13}C NMR ($CDCl_3$/TMS): δ = 55.41, 67.39, 95.77, 122.81, 129.05, 132.99, 141.92.

MS (EI, 70 eV): *m/z* (%) = 308 (1.0), 310 (2.0), 312 (1.0), 250 (100).

1,3-Dibromo-5-hexyloxymethylbenzene (1c)
To a stirred solution of NaH (4.3 g, 180.0 mmol) in THF (250 mL) under N_2 was added dropwise a solution of 3,5-dibromobenzyl alcohol (40 g, 150.0 mmol) in THF (50 mL). After stirring for 1 h, hexyl bromide (39.6 g, 240 mmol) was added and the mixture refluxed for 24 h. After cooling to 20 °C, H_2O was added until all salts had dissolved and the mixture diluted with Et_2O (100 mL). The phases were separated, the aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organic phases were washed with brine (100 mL). The organic phase was dried ($MgSO_4$), the solvent removed, and the resulting oil was distilled to afford **1c** as a colorless oil; yield: 44.1 g (84%); bp 127 °C/0.02 mbar; R_f 0.81 (EtOAc/hexane, 1:6).

Anal. calcd for $C_{13}H_{18}Br_2O$ (350.1): C, 44.60; H, 5.18. Found C, 44.63; H, 4.98.

^1H NMR ($CDCl_3$/TMS, 250 MHz): δ = 0.90 (t, 3 H, *J* = 7 Hz, CH_3), 1.21–1.43 (m, 6 H, γ-, δ-, ε-CH_2), 1.53–1.67 (m, 2 H, β-CH_2), 3.47 (t, 2 H, *J* = 7 Hz, α-CH_2), 4.42 (s, 2 H, benzyl-CH_2), 7.42 (s, 2 H, phenyl-H), 7.56 (s, 1 H, phenyl-H).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 14.03, 22.59, 25.79, 29.60, 31.62, 70.98, 71.20, 122.86, 128.96, 132.90, 142.84.

MS (EI, 80 eV): *m/z* (%) = 348 (0.9), 350 (1.7), 352 (0.8), 250 (100).

Tributyltin Derivatives 2; General Procedure
To a stirred suspension of the respective **1** (14.1 mmol) in Et_2O (50 mL) at –78 °C was added dropwise a solution of 1.6 M of BuLi in hexane (9.7 mL, 15.5 mmol). After 2 h, Bu_3SnCl (5.53 g, 17.0 mmol) was added and the mixture was allowed to warm to 20°C. Then H_2O (30 mL) was added, the phases were separated, the aqueous phase extracted with Et_2O (2 × 50 mL) and the combined organic phases were washed with H_2O (100 mL). The organic phase was dried ($MgSO_4$), the solvent removed and the resulting oil chromatographed on silica gel (EtOAc/hexane, 1:10) to give **2** as a colorless oil.

Amounts of **1** used and yields for **2**: **1a**: 4.95 g, product **2a**: 6.75 g (85%); R_f 0.55 (EtOAc/hexane, 1:10). **1b**: 4.40 g, product **2b**: 6.45 g (87%); R_f 0.60 (EtOAc/hexane, 1:10). **1c**: 4.74 g, product **2c**: 6.77 g (89%); R_f 0.56 (EtOAc/hexane, 1:20).

2-(3-Bromo-5-tributylstannylbenzyloxy)tetrahydropyran (2a)
Anal. calcd for $C_{24}H_{41}BrO_2Sn$ (560.2): C, 51.46; H, 7.38. Found C, 51.28; H, 7.11.

^1H NMR ($CDCl_3$/TMS, 250 MHz): δ = 0.81–0.92 (m, 9 H, CH_3), 1.01–1.10 (m, 6 H, CH_2), 1.25–1.40 (m, 6 H, CH_2), 1.45–1.96 (m, 12 H, CH_2, THP), 3.49–3.61 (m, 1 H, THP), 3.82–3.96 (m, 1 H, THP), 4.44 (d, 1 H, benzyl-H, ^2J = 13 Hz), 4.66–4,78 (m, 2 H, benzyl-H, THP), 7.32 (s, 1 H, phenyl-H), 7.47 (s, 2 H, phenyl-H).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 9.69, 13.60, 19.24, 25.41, 27.27, 28.94, 30.46, 62.03, 68.05, 97.72, 123.12, 130.17, 133.79, 137.60, 139.84, 145.03.

MS (EI, 60 eV): *m/z* (%) = 557 (0.4), 559 (0.7), 661 (0.4), 503 (100).

1-Bromo-5-tributylstannyl-3-(methoxymethoxymethyl)benzene (2b)
Anal. calcd for $C_{21}H_{37}BrO_2Sn$ (520.1): C, 48.50; H, 7.17. Found C, 48.36; H, 6.88.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 0.85–0.95 (m, 9 H, CH_3), 1.02–1.11 (m, 6 H, CH_2), 1.26–1.41 (m, 6 H, CH_2) 1.48–1.61 (m, 6 H, CH_2), 3.44 (s, 3 H, CH_3), 4.58 (s, 2 H, CH_2), 4.71 (s, 2 H, CH_2), 7.33 (s, 1 H, phenyl-H), 7.46 (s, 1 H, phenyl-H), 7.49 (s, 1 H, phenyl-H).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 9.69, 13.59, 27.26, 28.93, 55.32, 68.45, 95.71, 123.15, 130.26, 133.85, 137.80, 139.41, 145.20.

MS (EI, 70 eV): *m/z* (%) = 519 (0.6), 461 (36.7), 463 (52.8), 465 (33.8).

1-Bromo-3-hexyloxymethyl-5-tributylstannylbenzene (2c)
Anal. calcd for $C_{25}H_{45}BrOSn$ (560.2): C, 53.60; H, 8.10. Found C, 53.69; H, 7.81.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 0.79–0.96 (m, 12 H, CH_3), 1.03–1.12 (m, 6 H, butyl-CH_2), 1.24–1.48 (m, 12 H, CH_2), 1.48–1.69 (m, 8 H, CH_2), 3.48 (t, 2 H, *J* = 7 Hz, α-CH_2), 4.47 (s, 2 H, *J* = 7 Hz, benzyl-CH_2), 7.33 (s, 1 H, phenyl-H), 7.42 (s, 1 H, phenyl-H), 7.49 (s, 1 H, phenyl-H).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 9.69, 13.60, 14.00, 22.60, 25.86, 27.28, 28.96, 29.70, 31.67, 70.62, 72.15, 123.13, 130.05, 133.58, 137.57, 140.27, 145.00.

MS (EI, 70 eV): *m/z* (%)= 559 (1.8), 501 (79.5), 503 (100), 505 (73.2).

Conversion of 2 to Iodo Compounds 3; General Procedure
To a solution of the respective **2** (8.80 mmol) in $CHCl_3$ (50 mL) were added small portions of I_2 (2.20 g, 8.80 mmol) at 20 °C and the resulting mixture was stirred at this temperature for 30 min when an aq sat. solution of KF (20 mL) was added. Then aq 2 N Na_2CO_3 solution (25 mL) was added and the resulting mixture extracted with $CHCl_3$ (3 × 50 mL). The organic phase was washed with aq sat. $Na_2S_2O_5$ solution (50 mL), dried ($MgSO_4$), and the solvent removed. The resulting oil was chromatographed on silica gel (EtOAc/hexane, 1:20) to give **3** as a colorless oil.

Amounts of **2** used and yields for **3: 2a**: 4.90 g, product **3a**: 3.22 g (92%); R_f 0.40 (EtOAc/hexane, 1:20). **2b**: 3.50 g, product **3b**: 2.21 g (91%); R_f 0.36 (EtOAc/hexane, 1:20). **2c**: 3.36 g, product **3c**: 2.17 g (92%); R_f 0.67 (EtOAc/hexane, 1:20).

The conversions of **1** into **3** were also carried out at larger scales without isolating the intermediate **2**. **1b**: 38.5 g (124.2 mmol); yield of **3b**: 36.8 g (83%). **1c**: 37.0 g (105.7 mmol); yield of **3c**: 36.1 g (85%). In this larger scale, **3c** was isolated by distillation; bp 140 °C/0.008 mbar; without addition of KF solution.

2-(3-Bromo-5-iodobenzyloxy)tetrahydropyran (3a)
Anal. calcd for $C_{12}H_{14}BrIO_2$ (397.0): C, 36.30; H, 3.55. Found C, 36.26; H, 3.41.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 1.43–1.90 (m, 6 H, THP), 3.47–3.59 (m, 1 H, THP), 3.79–3.90 (m, 1 H, THP), 4.40 (d, 1 H, benzyl-H, ^2J = 13 Hz), 4.62–4.71 (m, 2 H, benzyl-H, THP), 7.46 (s, 1 H, phenyl-H), 7.61 (s, 1 H, phenyl-H), 7.72 (s, 1 H, phenyl-H).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 19.08, 25.24, 30.26, 61.94, 66.89, 94.29, 97.79, 122.76, 129.71, 134.88, 138.35, 142.37.

MS (EI, 60 eV): *m/z* (%) = 398 (1.3), 396 (1.2), 295 (100), 297 (91).

1-Bromo-3-iodo-5-(methoxymethoxymethyl)benzene (3b)
Anal. calcd for $C_9H_{10}BrIO_2$ (357.0): C, 30.28; H, 2.82. Found C, 30.21; H, 2.72.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 3.39 (s, 3 H, CH_3), 4.48 (s, 2 H, CH_2), 4.66 (s, 2 H, CH_2), 4.44 (s, 1 H, phenyl-H) 7.60 (s, 1 H, phenyl-H), 7.72 (s, 1 H, phenyl-H).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 55.35, 67.16, 94.33, 95.68, 122.76, 129.66, 134.84, 138.47, 141.91.

MS (EI, 70 eV): *m/z* (%) = 356 (9.3), 358 (9.0), 296 (47.0), 298 (45.5).

1-Bromo-3-hexyloxymethyl-5-iodobenzene (3c)
Anal. calcd for $C_{13}H_{18}BrIO$ (397.1): C, 39.32; H, 4.57. Found C, 39.53; H, 4.26.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 0.89 (t, 3 H, *J* = 7 Hz, CH_3), 1.21–1.45 (m, 6 H, γ-, δ-, ε-CH_2), 1.51–1.69 (m, 2 H, β-CH_2), 3.46 (t, 2 H, *J* = 7 Hz, α-CH_2), 4.40 (s, 2 H, benzyl-CH_2), 7.42 (s, 1 H, phenyl-H), 7.60 (s, 1 H, phenyl-H), 7.72 (s, 1 H, phenyl-H).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 14.07, 22.60, 25.79, 29.59, 31.62, 70.94, 71.02, 94.39, 122.90, 129.61, 134.78, 138.43, 142.89.

MS (EI, 70 eV): *m/z* (%) = 396 (4.8), 398 (4.7), 296 (100), 298 (98).

2-Bromo-5-trimethylstannylpyridine (5)
To a stirred suspension of **4** (25.0 g, 106 mmol) in Et_2O (700 mL) was added dropwise at –78 °C a solution 1.6 M of BuLi in hexane (70.0 mL, 112 mmol). After 4 h, Me_3SnCl (22,5 g, 112 mmol) was added to the resulting red solution and the mixture was allowed to warm to 20 °C. Then H_2O (300 mL) was added, the phases were separated, the aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organic phases were washed with H_2O (2 × 300 mL). The organic phase was dried ($MgSO_4$), the solvent removed and the resulting oil chromatographed over silica gel (EtOAc/hexane, 1:6) to give a colorless oil; yield: 29.1 g (86%); R_f 0.56 (EtOAc/hexane, 1:6); bp 86°C/0.03 mbar).

HRMS: *m/z* calcd for $C_8H_{12}BrNSn$ 320.91745, found 320.91738.

^{1}H NMR ($CDCl_3$/TMS, 270 MHz): δ = 0.31 [s, 9 H, $Sn(CH)_3$], 7.40 (d, 1 H, pyrid-H, ^3J = 8 Hz), 7.58 (dd, 1 H, pyrid-H, ^3J = 8 Hz, ^4J = 2 Hz), 8.31 (d, 1 H, pyrid-H, ^4J = 2 Hz).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = –9.6, 127.7, 135.8, 142.7, 145.4, 156.6.

MS (EI, 70 eV): *m/z* (%) = 319 (7.1), 321 (10.6), 323 (6.6), 304 (68.9), 306 (100), 308 (64.5), 276 (23.0).

Coupling of Iodides 3 with 2-Bromo-5-trimethylstannylpyridine (5); General Procedure
To a solution of the respective **3** (6.90 mmol) and **5** (7.60 mmol) in toluene (15 mL) was added $(Ph_3P)_4Pd$ (240 mg, 0.20 mmol) and the mixture refluxed for 24 h. After cooling to 20 °C, first an aq sat. KF solution (15 mL) and then aq 2 N Na_2CO_3 solution (25 mL) were added. After removal of the solids formed, the phases were separated, the aqueous phase was extracted with toluene, the combined organic phases were washed with H_2O (2 × 50 mL) and dried ($MgSO_4$). After removal of the solvent, the residual oil was chromatographed on silica gel (EtOAc/hexane, 1:10) to give **6** as a colorless oil which slowly crystallized.

Amounts of **3** and **5** used and yields for **6**: **3a**: 2.70 g (6.90 mmol), **5**: 2.40 g (7.60 mmol), product **6a**: 2.17 g (59%); mp 90 °C; R_f 0.16 (EtOAc/hexane, 1:10). **3b**: 54.70 g (153.2 mmol), **5**: 51.60 g (160.8 mmol), product **6b**: 32.70 g (55%); mp 67 °C; R_f 0.13 (EtOAc/hexane, 1:10). **3c**: 40.00 g (100.7 mmol), **5**: 35.54 g (110.7 mmol), product **6c**: 24.7 g (58%); mp 39 °C; R_f 0.28 (EtOAc/hexane, 1:20).

2-Bromo-5-[3-bromo-5-(tetrahydropyran-2-yloxymethyl)phenyl]pyridine (6a)

HRMS: *m/z* calcd for $C_{17}H_{17}Br_2NO_2$ 424.96260, found 424.96423.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 1.35–1.83 (m, 6 H, THP), 3.39–3.49 (m, 1 H, THP), 3.71–3.84 (m, 1 H, THP)**,** 4.39 (d, 1 H, benzyl-H, ^2J = 13 Hz), 4.62 (dd, 1 H, THP), 4.68 (d, 1 H, benzyl-H, ^2J = 13 Hz), 7.32 (s, 1 H, phenyl-H), 7.36–7.44 (m, 3 H, 2 phenyl-H, 1 pyrid-H), 7.56 (d, 1 H, pyrid-H, ^3J = 8 Hz, ^4J = 2 Hz), 8.39 (d, 1 H, pyrid-H, ^4J = 2 Hz).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 18.95, 25.00, 30.07, 61.78, 67.30, 97.66, 122.84, 124.26, 127.68, 128.38, 129.97, 133.93, 136.46, 137.92, 141.13, 141.33, 147.86.

MS (EI, 60 eV): *m/z* (%) = 425 (1.3), 427 (2.3), 429 (1.2), 327 (100).

2-Bromo-5-[3-bromo-5-methoxymethoxymethyl)phenyl] pyridine (6b)

Anal. calcd for $C_{14}H_{13}Br_2NO_2$ (387.1): C, 43.44; H, 3.38; N, 3.61. Found C, 43.33; H, 3.33; N, 3.47.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 3.38 (s, 3 H, CH_3), 4.59 (s, 2 H, CH_2), 4.69 (s, 2 H, CH_2)**,** 7.40 (s, 1 H, phenyl-H), 7.46–7.54 (m, 3 H, 2 phenyl- H, 1 pyrid- H), 7.64 (dd, 1 H, pyrid-H, ^3J = 8 Hz, ^4J = 2 Hz), 8.49 (d, 1H, pyrid-H, ^4J= 2 Hz).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 55.36, 67.88, 95.79, 123.12, 124.52, 127.93, 128.85, 130.25, 134.20, 136.68, 138.34, 141.17, 141.42, 148.13.

MS (EI, 70 eV): *m/z* (%) = 385 (7.5), 387 (14.2), 389 (7.2), 327 (100).

2-Bromo-5-(3-bromo-5-hexyloxymethylphenyl)pyridine (6c)

Anal. calcd for $C_{18}H_{21}Br_2NO$ (427.2): C, 50.61; H, 4.96; N, 3.28. Found C, 50.52; H, 4.92; N, 3.16.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 0.89 (t, 3 H, J = 7 Hz, CH_3), 1.20–1.46 (m, 6 H, γ-, δ-, ε-CH_2), 1.53–1.70 (m, 2 H, β-CH_2)**,** 3.51 (t, 2 H, J = 7 Hz, α-CH_2), 4.52 (s, 2 H, benzyl-CH_2), 7.41 (s, 1 H, phenyl-H), 7.50– 7.56 (m, 3 H, 2 phenyl-H, 1 pyrid.-H), 7.68 (dd, 1 H, pyrid.-H, ^3J = 8 Hz, ^4J = 2 Hz), 8.52 (d, 1 H , pyrid. H, ^4J = 2 Hz).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 13.96, 22.52, 25.77, 29.57, 31.56, 71.01, 71.64, 123.21, 124.42, 128.01, 128.80, 130.21, 134.45, 136.78, 138.41, 141.48, 142.11, 148.26.

MS (EI, 70 eV): *m/z* = 425 (5.0), 427 (9.4), 429 (4.8), 327 (100).

Bipyridines 8; General Procedure

To a stirred solution of the respective **6** (1.80 mmol) in Et_2O (20 mL) was added at –78 °C a 1.6 N solution of BuLi in hexane (1.2 mL, 1.9 mmol). After 2 h, to the resulting red solution was added a solution of Me_3SnCl (5% excess based on BuLi) in Et_2O (10 mL). The mixture was allowed to reach 20 °C and the solvent removed. To the remaining brownish oil **7** was added a second portion of the same **6** dissolved in toluene (10 mL). After the addition of $(Ph_3P)_4Pd$ (3 mol %), the mixture was refluxed for 24 h and then cooled to 20 °C. Then, first an aq sat. KF solution (15 mL) was added followed by aq 2 N Na_2CO_3 solution (25 mL) before the organic material was extracted with toluene (50 mL). The organic phase was washed with H_2O (100 mL) and dried ($MgSO_4$). After removal of the solvent, the residual oil was chromatographed on silica gel (EtOAc/hexane, 1:3) to give a yellow oil which slowly crystallized.

Amounts of **6** used and yields for **8**: **6a** first portion: 780 mg (1.80 mmol), second portion: 770 mg (1.80 mmol), product **8a**: 420 mg (34%); mp 144 °C; R_f 0.19 (EtOAc/hexane, 1:3). **6b** first portion: 14.0 g (36.2 mmol), second portion: 14.0 g (36.2 mmol), product **8b**: 7.3 g (33%); mp 143 °C; R_f 0.10 (EtOAc/hexane, 1:3). **6c** first portion: 12.0 g (28.1 mmol), second portion: 12.0 g (28.1 mmol), product **8c**: 11.0 g (56%); mp 90 °C; R_f 0.19 (EtOAc/hexane, 1:6).

5,5'-Bis-[3-bromo-5-(tetrahydropyran-2-yloxymethyl)phenyl]-2,2'-bipyridyl (8a)

Anal. calcd for $C_{34}H_{34}Br_2N_2O_2$ (694.5): C, 58.80; H, 4.94; N, 4.03. Found C, 58.81; H, 4.89 3.64.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 1.41–1.90 (m, 12 H, THP), 3.44–3.59 (m, 2 H, THP), 3.77–3.91 (m, 2 H, THP)**,** 4.46 (d, 2 H, benzyl-H, ^2J = 13 Hz), 4.68 (dd, 2 H, THP), 4.77 (d, 2 H, benzyl-H, ^2J = 13 Hz), 7.50 (s, 4 H, phenyl-H), 7.61 (s, 2 H, phenyl-H), 7.90 (dd, 2 H, pyrid-H, ^3J = 8 Hz, ^4J = 2 Hz), 8.43 (d, 2 H, pyrid-H, ^3J = 8 Hz), 8.80 (d, 2 H, pyrid-H, ^4J = 2 Hz).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 19.22, 25.31, 30.40, 62.12, 67.78, 97.98, 120.92, 123.12, 124.71, 128.91, 130.08, 134.93, 135.10, 139.50, 141.46, 147.50, 154.88.

MS (EI, 60 eV): *m/z* = 692 (10.3), 694 (20.2), 696 (11.8), 594 (100).

5,5'-Bis-[3-bromo-5-(methoxymethoxymethyl)phenyl]-2,2'-bipyridyl (8b)

Anal. calcd for $C_{28}H_{26}Br_2N_2O_4$ (614.3): C, 54.74; H, 4.27; N, 4.56. Found C, 54.85; H, 4.31; N, 4.40.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 3.44 (s, 6 H, CH_3), 4.65 (s, 4 H, CH_2), 4.75 (s, 4 H, CH_2)**,** 7.57 (s, 4 H, phenyl-H), 7.70 (s, 2 H, phenyl- H), 7.99 (dd, 2 H, pyrid-H, ^3J = 8 Hz, ^4J = 2 Hz), 8.50 (d, 2 H, pyrid-H, ^3J = 8 Hz), 8.89 (d, 2 H, pyrid-H, ^4J = 2 Hz).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 55.49, 68.15, 95.92, 121.00, 123.21, 124.78, 129.14, 130.15, 134.95, 135.19, 139.65, 141.08, 147.53, 154.94.

MS (EI, 70 eV): *m/z* = 612 (53.4), 614 (100), 616 (55.4).

5,5'-Bis-(3-bromo-5-hexyloxymethylphenyl)-2,2'-bipyridyl (8c):

Anal. calcd for $C_{36}H_{42}Br_2N_2O_2$ (694.5): C, 62.23; H, 6.10; N, 4.03. Found C, 62.22; H, 6.16; N, 3.88.

^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ = 0.89 (t, 6 H, J = 7 HZ, CH_3), 1.19–1.46 (m, 12 H, γ-, δ-, ε-CH_2), 1.55–1.70 (m, 4 H, β-CH_2), 3.54 (t, 4 H, J = 7 Hz, α-CH_2), 4.58 (s, 4 H, benzyl-CH_2), 7.53 (s, 4 H, phenyl-H), 7.68 (s, 2 H, phenyl-H), 7.99 (dd, 2 H, pyrid-H, ^3J = 8 Hz, ^4J = 2 Hz), 8.50 (d, 2 H , pyrid- H, ^3J = 8 Hz), 8.88 (d, 2 H, pyrid-H, ^4J = 2 Hz).

^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ = 13.98, 22.55, 25.81, 29.62, 31.60, 70.97, 71.78, 120.94, 123.15, 124.49, 128.88, 129.93, 134.95, 135.09, 139.53, 141.91, 147.50, 154.90.

MS (EI, 70 eV): *m/z* (%) = 692 (43.3) 694 (82.0), 696 (48.7).

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