

PegPhos: A Monodentate Phosphoramidite Ligand for Enantioselective Rhodium-Catalysed Hydrogenation in Water

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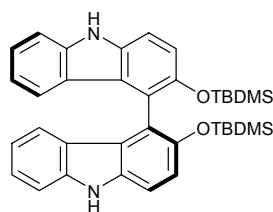
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SUPPORTING INFORMATION

General information. All reactions involving oxygen or moisture sensitive compounds were carried out under a dry nitrogen atmosphere. THF was distilled from sodium and CH₂Cl₂ was distilled from CaH₂. Column chromatography was performed using Acros silica gel (0.030-0.075 mm). Petroleum ether (PE, 60/80) used for chromatography was distilled prior to use. TLC analyses were performed on Merck F-254 silica gel plates. IR spectra were measured using a Bruker IFS 28 FT-spectrophotometer and wavenumbers (ν) are reported in cm⁻¹. ¹H NMR spectra were recorded on a Bruker ARX 400 (400 MHz) or Varian Inova (500 MHz) spectrometer. The latter machines were also used for ¹³C NMR spectra (50, 100 and 125 MHz, respectively). Unless otherwise indicated, CDCl₃ was used as the solvent. Chemical shifts are given in ppm (δ) relative to an internal standard of chloroform (7.26 ppm for ¹H-NMR and 77.0 for ¹³C-NMR).

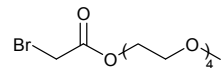
(S)-3,3'-Bis-(tert-butyl-dimethyl-silyloxy)-9H,9'H-[4,4']bicarbazolyl. A solution of BICOL¹ (0.50 g, 1.4 mmol), MeCN (14 cm³), imidazole (0.33 g, 4.8 mmol) and TBDMSCl (0.54 g, 3.6 mmol) in MeCN (15 cm³) was heated at 65 °C for 4 h. After cooling to room temperature the reaction mixture was quenched with water, EtOAc and NaHSO₄. The product was extracted with EtOAc and the water layer was extracted two times with EtOAc. The organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (PE/EtOAc = 60/40) afforded the product (0.69 g, 85%) as an off-white foam. *R*_f = 0.57. ¹H NMR (CDCl₃): δ -0.20 (s, 6 H), -0.01 (s, 6 H), 0.5 (s, 18 H), 6.69 (t, *J* = 7.2 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 7.18 (t, *J* = 7.2 Hz, 2 H), 7.26 (d, *J* = 7.2 Hz, 2 H), 7.37 (d, *J* = 8.8 Hz, 2 H), 7.93 (s, 2 H); ¹³C NMR (CDCl₃): δ 146.8, 140.2, 134.5, 124.9, 123.9, 123.5,



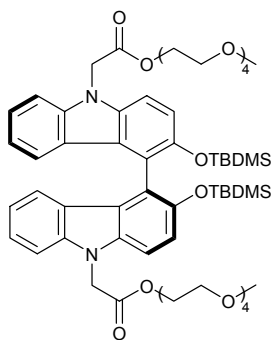
¹ P. N. M. Botman, M. Postma, J. Fraanje, K. Goubitz, H. Schenk, J. H. van Maarseveen, H. Hiemstra, *Eur. J. Org. Chem.*, 2002, 1952-1955; P. N. M. Botman, J. Fraanje, K. Goubitz, R. Peschar, J. W. Verhoeven, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Cat.*, 2004, **346**, 743-754.

122.3, 121.7, 118.4, 117.4, 109.6, 109.5, 25.0, 17.5, -4.7; IR (NaCl, cm^{-1}): 3422, 2954, 2929, 2886, 2856, 1507, 1478, 1435, 1287, 1265, 952, 832.

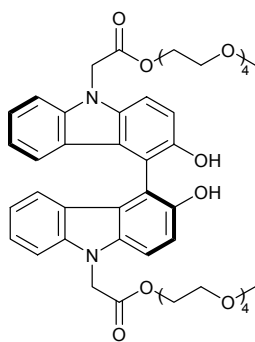
Bromo- acetic acid 2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester. To a stirred solution of bromoacetic acid (2.58 g, 18.5 mmol) and thionyl chloride (1.90 cm^3 , 22.2 mmol) in dichloromethane (185 cm^3), tetraethylene glycol monomethylether (5.00 g, 24.0 mmol) was added dropwise and the resulting reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the product was purified using column chromatography (PE/EtOAc = 25/75) yielding a slightly yellow liquid (4.98 g, 15.6 mmol, 82 %). R_f -value: 0.15 (PE/EtOAc, 50/50); ^1H NMR (CDCl_3): δ 4.31 (t, $J = 4.7$ Hz, 2H), 3.85 (s, 2H), 3.71 (t, $J = 4.8$ Hz, 2H), 3.64 (m, 10H), 3.53 (t, $J = 4.9$ Hz, 2H), 3.36 (s, 3H); ^{13}C NMR (CDCl_3): δ 166.95, 71.64, 70.35, 70.32, 70.31, 70.28, 70.21, 68.45, 65.03, 58.72, 25.62; IR (NaCl, cm^{-1}): 1736.5.



(S)-N-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester-3,3'-Bis-(tert-butyl-dimethylsilyloxy)-9H,9'H-[4,4']Bicarbazole. To a solution of the starting bicarbazole (722 mg, 1.22 mmol) in THF (12.2 cm^3) and DMF (12.2 cm^3), KHMDS (6.0 cm^3 of a 0.5 M solution in toluene, 3.0 mmol) was added dropwise at 0 °C and the solution was stirred at room temperature for 1 h. After this time the bromoalkyl ester (1.90 g, 4.88 mmol) was added dropwise and the resulting reaction mixture was stirred at room temperature for 4 h. After this time a two-phase separation was carried out using EtOAc, water, brine and NH_4Cl . The organic phase was washed four times with water and brine, dried over MgSO_4 and evaporated under reduced pressure. The product was further purified using column chromatography on silica gel (gradient PE/EtOAc = 4/1 to EtOAc/MeOH = 95/5) yielding a brown oil (260 mg, 20 %). R_f -value: 0.24 (EtOAc); ^1H NMR (CDCl_3): δ 7.26 (d, $J = 4.0$ Hz, 2H), 7.13 (d, $J = 3.6$ Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 2H), 6.80 (d, $J = 8.0$ Hz, 2H), 6.64 (m, 2H), 5.01 (s, 4H), 4.24 (m, 4H), 3.58 (m, 24H), 3.47 (m, 4H), 3.29 (d, $J = 6.8$ Hz, 6H), 0.38 (s, 18H), -0.11 (s, 6H), -0.31 (s, 6H); ^{13}C NMR (CDCl_3): δ 168.63, 147.16, 141.10, 135.70, 125.20, 123.64, 123.24, 122.52, 121.90, 118.76, 117.41, 107.47, 107.43, 71.89, 70.62, 70.58, 70.54, 70.49, 68.82, 68.71, 64.43, 58.98, 44.75, 25.06, 17.56, -4.60; IR (NaCl, cm^{-1}): 1754; $[\alpha]_D^{20} = -77$ (c = 0.55, CHCl_3).

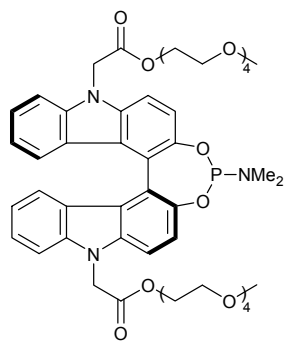


(S)-N-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester- 9H,9'H-[4,4']Bicarbazole-3,3'-diol. To a solution of the TBDMS-protected bicarbazole (260 mg, 0.23 mmol) in THF (5.0 cm^3), TBAF (0.483 cm^3 of a 1 M solution in THF, 0.47 mmol) was added and the resulting reaction mixture was stirred at room temperature for 10 minutes. After this time a two-phase separation was carried out using EtOAc, water, brine and NaHSO_3 (0.5 M). The organic phase was washed one time with water and brine, dried over MgSO_4 and evaporated under reduced pressure. The product was further purified using column chromatography (PE/EtOAc = 0/1) yielding a light brown oil (169 mg, 85%). R_f -value: 0.06 (PE:EtOAc, 0:1); ^1H NMR (CDCl_3): δ = 7.40 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 8.7$ Hz, 2H), 7.20 (m, 4H), 6.76 (d, $J = 7.8$ Hz, 2H), 6.71 (m, 2H), 5.03 (s, 4H), 4.27 (m, 4H), 3.57 (m, 18H), 3.47 (m, 10H), 3.29 (s, 6H); ^{13}C NMR (CDCl_3): δ 168.47, 148.32, 141.00, 135.50, 125.61, 122.48, 121.92,



121.56, 119.14, 115.17, 113.46, 109.67, 107.87, 71.65, 70.31, 70.25, 70.23, 70.21, 70.19, 68.57, 64.63, 58.75, 44.59; IR (NaCl, cm^{-1}): 3333, 1750; $[\alpha]_{\text{D}}^{20} = -45$ ($c = 0.5$, CHCl_3).

(S)-N-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester- 9H,9'H-[4,4']Bicarbazole-3,3'-



O₂PNMe₂. To a solution of the diol (169 mg, 0.19 mmol) in MeCN (2 cm^3), HMPT (37 μl , 0.19 mmol) was added and the resulting reaction mixture was refluxed at 70 °C for 4 h. After this time the solvent was removed under reduced pressure to obtain a yellow oil (160 mg, 90%). R_f -value: 0.04 (PE:EtOAc, 0:1); ^{31}P -NMR (CDCl_3): δ 148.05; ^1H NMR (CDCl_3): δ 7.47 (d, $J = 1.6$ Hz, 2H), 7.40 (d, $J = 8.7$ Hz, 1H), 7.33 (d, $J = 8.7$ Hz, 1H), 7.24 (m, 4H), 6.85 (d, $J = 8.0$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.51 (m, 2H), 5.14 (m, 4H), 4.34 (m, 4H), 3.63 (m, 4H), 3.54 (m, 20H), 3.49 (m, 4H), 3.35 (d, $J = 1.2$ Hz, 12H), 2.55 (d, $J = 9$ Hz, 6H); ^{13}C NMR (CDCl_3): δ 168.22 (d, $J = 4$ Hz), 144.81 (d, $J = 12$ Hz),

140.97 (d, $J = 5$ Hz), 137.68, 137.13, 125.65, 122.56 (d, $J = 13$ Hz), 122.20, 122.42, 119.63, 118.78 (d, $J = 4$ Hz), 108.80 (d, $J = 10$ Hz), 107.60 (d, $J = 6$ Hz), 71.72, 70.39, 70.32, 70.29, 68.64, 68.61, 64.57, 64.48, 58.82, 44.60, 34.81 (d, $J = 21$ Hz); IR (NaCl, cm^{-1}): 1751; $[\alpha]_{\text{D}}^{20} = +297$ ($c = 0.1$, CH_3Cl).

Preparation of the catalyst:

The Rh complex was prepared *in situ* by dissolving $\text{Rh}(\text{COD})_2\text{BF}_4$ (33.7 mg, 0.083 mmol) and (S)-PEG-Phos (155 mg, 0.17 mmol) in CH_2Cl_2 (3.2 cm^3) and after evaporation of the solvent under reduced pressure a yellow powder was obtained that was used directly without further purification.

General procedure hydrogenations:

In a glass tube, 2 μmol of a preformed catalyst (0.81 mg (2 μmol) of $\text{Rh}(\text{COD})_2\text{BF}_4$, 4 μmol of ligand in case of *in situ* formation), 200 μmol of the substrate and 4 cm^3 of solvent, was added. This small glass tube was placed in a semi-automated autoclave with eight reactors (Endeavor™) that was purged 4 times with nitrogen and once with hydrogen. Then, the autoclave was pressurized with 10 bar of hydrogen. The reaction was stirred for 16 hours. A sample (1 cm^3) of the resulting mixture was evaporated and dissolved in MeOH. To this solution was added 0.7 cm^3 of a 2 M (trimethylsilyl)diazomethane solution in ether. The yellow solution was filtered over a short silica plug and subjected to conversion (^1H NMR) and e.e. determination (capillary GC). CP Chirasil-L-Val from Chrompack (30m x 0.25mm x 0.12 μm), 110 °C. Retention times: 3,4 minutes (R), 3.9 minutes (S).