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Polymer-immobilized α,α-bis[bis-3,5-(trifluoromethyl)phenyl]prolinol silyl ether: synthesis and application in the asymmetric α-amination of aldehydes

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General Remarks

All reagents were purchased from commercial suppliers and used without further purification. Silica gel 40-60 mesh and TLC-plates was purchased from Macherey-Nagel Gmbh & Co.KG. All solvents were purified by distillation according to standard procedures.

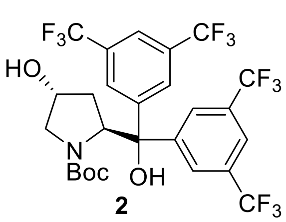
NMR spectra were recorded on a 400 MHz spectrometer (400.0, 100.6 and 376.3 MHz for ^{1}H, ^{13}C and ^{19}F, respectively) at room temperature; chemical shifts δ were measured with reference to the solvent for ^{1}H ($CDCl_3$, $\delta = 7.24$ ppm) and ^{13}C ($CDCl_3$, $\delta = 77.13$ ppm) and to $CFCl_3$ as external standard for ^{19}F. Mass spectra MALDI-TOF were recorded on Bruker Autoflex-II spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. Infrared (IR) spectra were recorded on a Thermo Nicolet FTIR-200 in KBr pellets.

The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (Daicel Co. CHIRALCEL OD-H, AD-H and AS-H; eluent: hexane / 2-propanol), by comparing the samples with the corresponding racemic samples.

Optical rotations were measured on an EPO-1A ‘‘VNIEKIPRODMASH” polarimetr.

I Catalyst preparation

tert-butyl (2*S*,4*R*)-2-{bis[3,5-bis(trifluoromethyl)phenyl](hydroxy)methyl}-4-hydroxypyrrolidine-1-carboxylate (2)



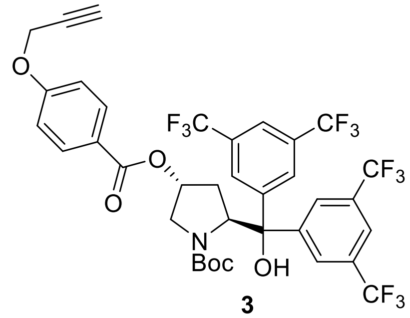
2

The solution of freshly prepared 3,5-bis(trifluoromethyl)magnesium bromide (50 mmol, 1M in THF) was added by dropwise to the solution of compound **1**[1] (2.45 g, 10 mmol) in THF (35 ml) at -78 ºC. The reaction was stirred for 12 h, quenched by addition of saturated NH_4Cl solution and diluted with DCM (50 ml). After decantation the precipitate was washed with DCM (150 ml). Organic layer was collected and washed with water, saturated

NaCl solution, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel using petrol ether – ethyl acetate mixture (5:1). Yield: 5.89 g (92%) as pale yellow oil. R_f = 0.3 (light petroleum – ethyl acetate, 5:1). $[\alpha]_D^{20}$ = +5.63 (c = 0.667, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.90 (bs, 2H), 7.88 (bs, 1H), 7.83 (bs, 1H), 7.80 (bs, 2H), 7.31 (bs, 1H), 4.97 (t, 1H ^3J = 8.6 Hz), 4.13-4.07 (m, 1H), 3.61 (d, 1H, ^2J = 12.5 Hz), 2.95 (dd, 1H, ^2J = 12.5 Hz, ^3J = 3.8 Hz), 1.91 (dd, 2H, ^3J = 8.6 Hz, ^3J = 8.4 Hz), 1.63 (bs, 1H), 1.32 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 157.61, 146.29, 144.90, 131.9 (q, 2C, $^2J_{CF}$ = 33.7 Hz), 131.6 (q, 2C, $^2J_{CF}$ = 33.7 Hz), 127.64, 127.43, 122.05, 121.85, 82.23, 80.33, 68.90, 66.25, 56.71, 39.80, 27.93 ($\underline{C}F_3$ were not unambiguously assigned). ^{19}F NMR (376.3 MHz, $CDCl_3$), δ: -62.86 (s, 6F), - 62.90 (s, 6F). MS (MALDI-TOF): *m/z* Found: 664.1327 $[M+Na]^+$. $C_{26}H_{23}F_{12}NO_4$. Calculated: $[C_{26}H_{23}F_{12}NO_4 + Na]$ 664.1333

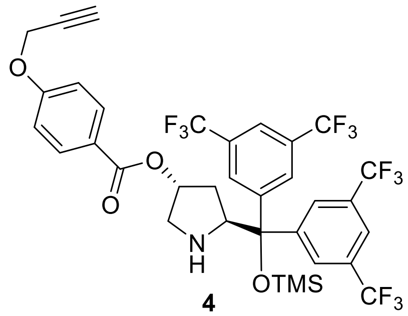
***tert*-butyl (2*S*,4*R*)-2-{bis[3,5-bis(trifluoromethyl)phenyl](hydroxy)methyl}-4-[4-(prop-2-yn-1-yloxy)benzoyloxy]pyrrolidine-1-carboxylate (3)**



3

The solution of DCC (2.09 g, 10.13 mmol) and DMAP (124 mg, 1.01 mmol) in DCM (8 ml) was cooled at 0 °C. To this mixture 4-propargyloxybenzoic acid[2] (1.78 g, 10.13 mmol) in DCM (6 ml) was added and mixture stirred for 10 min. Then the solution of compound **2** (4.33 g, 6.75 mmol) in DCM (6 ml) was added and reaction mixture was kept for 72 h at 4 °C. After competition of the reaction (control by TLC) the solution was filtered and washed with 1N HCl (30 ml), saturated $NaHCO_3$ and water. Organic layer was separated, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel using light petroleum – ethyl acetate mixture (5:1). Yield 5.19 g (95%) as pale-yellow oil. R_f = 0.4 (light petroleum – ethyl acetate, 5:1). $[\alpha]_D^{20}$ = -45.00 (c = 0.667, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.95 (bs, 2H), 7.94 -7.91 (m, 2H), 7.90 (bs, 1H), 7.86 (bs, 2H), 7.83 (s, 1H), 7.02-6.96 (m, 2H,), 5.08 (t, 1H, ^3J = 8.6 Hz), 4.75 (d, 2H ^4J = 2.4 Hz), 3.85 (d, 1H, ^3J = 13 Hz), 3.23-3.16 (m, 1H), 2.54 (t, 1H, ^4J = 2.4 Hz), 2.16 (dd, 2H, ^3J = 12.5 Hz, ^3J = 3.8 Hz), 1.63 (bs, 1H), 1.28 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 165.38, 161.62, 157.16, 145.99, 144.85, 131.9 (q, 2C, $^2J_{CF}$ = 32.8 Hz), 131.6 (q, 2C, $^2J_{CF}$ = 32.8 Hz), 114.64, 82.26, 80.49, 77.58, 76.19, 72.24, 65.65, 55.83, 54.25, 36.39, 27.85. ^{19}F NMR (376.3 MHz, $CDCl_3$), δ: -62.88 (s, 12F). MS (MALDI-TOF): *m/z* Found: 822.1701 $[M+Na]^+$. Calculated $[C_{36}H_{29}F_{12}NO_6+Na]$: 822.1718

(3*R*,5*S*)-5-{bis[3,5-bis(trifluoromethyl)phenyl](trimethylsilyloxy)methyl}pyrrolidin-3-yl 4-(prop-2-yn-1-yloxy)benzoate (4)

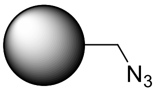


4

To the solution of compound **3** (1.14 g, 1.43 mmol) in DCM (30 ml) triethylamine (495 μl, 4.56 mmol) was added and cooled at 0 °C. To the resulted solution was added freshly prepared TMSOTf (1 ml, 5.6 mmol) and mixture stirred at room temperature for 12 h. After competition of the reaction (control by TLC) reaction mixture was washed with water, dryed over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel using light petroleum – ethyl acetate mixture (10:1). Yield: 1.05 g (95%) as light yellowish oil. R_f = 0.3 (light petroleum – ethyl acetate, 10:1). $[\alpha]_D^{20}$ = -14.46 (c = 0.622, CH_2Cl_2)

^1H NMR (400 MHz, $CDCl_3$), δ: 8.07-7.95 (m, 4H), 7.86 (s, 2H), 7.77 (s, 2H), 7.01 (m, 2H), 5.14 (bs, 1H), 4.75 (d, ^4J = 2.4 Hz), 4.50 (bs, 1H), 3.11 (d, 1H, ^3J = 13 Hz), 2.63 (bs, 1H), 2.54 (t, 1H, ^4J = 2.4 Hz), 1.98 (bs, 1H), 1.75(bs, 1H), -0.07 (s, 9H). ^{13}C NMR ($CDCl_3$), δ: 165.69, 161.40, 147.87, 145.80, 131.97 (q, 2C $^2J_{CF}$ = 32.8 Hz), 131.63 (q, 2C, $^2J_{CF}$ = 32.8 Hz), 128.67, 127.95, 124.62 (d, J = 273.1 Hz), 124.48 (d, J = 273.3 Hz), 122.17 – 122.57 (m, 2C), 114.61, 82.09, 77.74, 76.10, 75.79, 63.53, 55.85 , 53.33, 34.97, 1.83.^{19}F NMR (376.3 MHz, $CDCl_3$): -62.76 (s, 3F), -62.83 (s, 3F). -62.84 (s, 3F), -62.88 (s, 3F). MS (MALDI-TOF): *m/z* Found: 772.1752 $[M+H]^+$. $C_{34}H_{29}F_{12}NO_4Si$. Calculated: 772.1734.

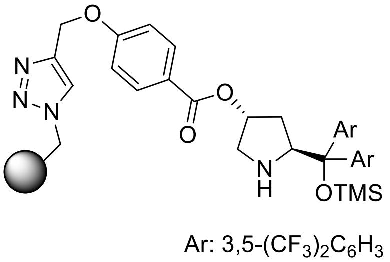
Azido-polystyrene



To the solution of sodium azide (8 g, 123 mmol) in DMF (40 ml) Merrifield resin (6 g, 1.6 mmol/g loading) was added and mixture stirred for 24 h at 60 °C. After cooling to the room temperature polymer was filtered and washed with water (400 ml), THF (200 ml), THF/MeOH=1/1 (200 ml), MeOH (200 ml) and THF (200 ml). Polymer was dried *in vacuo* (1 Torr) at 50 ºC. Yield: 98% as beige powder.

Elemental analysis: Calculated: C 86.24%, H 7.13%, N 6.63%. Found: C 86.00%, H 7.12%, N 6.92%. IR: 2090.46 cm^{-1} (N_3).

Immobilized catalyst 5



To the mixture of azido-polystyrene (2.5 g, 4 mmol), solution of compound **4** (4.60 g, 6 mmol) in mixture DMF/THF (1/1 v/v, 30 ml), CuI (76 mg, 0,4 mmol), TTTA (160 mg, 0,4 mmol) and diisopropylamine (1 ml). The mixture was gently stirred for 24 h at 50 °C. The polymer was filtered off and washed with THF (200 ml), THF/MeOH(1/1, v/v, 200 ml), MeOH (200 ml) and THF (200 ml). To remove trace amounts of copper the catalyst **5** was additionally stirred with 8-hydroxyquinoline solution (c 10g/l) until yellow color disappeared. Polymer was dried *in vacuo* (1 Torr) at 50 ºC. Yield: 99% as tile-red powder.

Elemetal analysis: Calculated: C 67.73%, H 6.36%, N 4.01%; found C 67.97%, H 6.10%, N 4.01%. IR: 1716.34 cm^{-1} (*C(O)*).

II General procedure for asymmetric α-amination of aldehydes

The mixture of catalyst **5** (0.1 mmol), appropriate azodicarboxylate (0.5 mmol) and aldehyde (2 mmol) are heated at 30 ºC in an microwave oven (1W, reactor Monowave 300, Anton Paar) under magnetic stirring for the specified reaction time. Then mixture was diluted with THF, filtered and polymer was additionally washed with EtOH. For the catalyst recycling it was dried *in vacuo* (1 Torr, rt) and used repetitive as is. For the product isolation NaBH$_4$ (0.75 mmol) was added to the mother liquor at 0ºC and the mixture was stirred for 3-5 h. The mixture was diluted with DCM and washed with water. Organic layer was collected, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel using light petroleum – ethyl acetate mixture (5:1) to afford compounds **6a-d**. Values *ee* of compounds **6a-d** were determined by HPLC, chiral phases: Chiralcel AS-H, or Chiralpak AD–H. NMR spectra and HPLC data for compound **6a-d** are available in the cited articles[3,4].

References

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IR-spectrum of azido-polystyrene (on top) and catalyst 5 (below)