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Palladium Catalyzed Enantioselective Conjugate Addition of Boronic Acids

Francesca Gini, Bart Hessen, Adriaan J. Minnaard*

Department of Organic Chemistry and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands
General Experimental.

1H NMR spectra were recorded at 300 or 400 MHz with CDCl₃ as solvent. 13C NMR spectra were obtained at 75.4 or 100.6 MHz in CDCl₃, (Varian VXR300 or AMX400 spectrometers). Chemical shifts were determined relative to the residual solvent peaks (δ = 7.26 ppm for hydrogen, δ = 77.0 for carbon). Data are reported as follows: chemical shifts, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) and coupling constants (Hz). Mass spectra were recorded on a AEI-MS-902 mass spectrometer. Enantioselectivities were determined by capillary GC analysis (Chiraldex G-TA column (30 m x 0.25 mm) or Chiraldex a-TA column (30 m x 0.25 mm)) using a flame ionization detector and compared with the racemic 1,4 addition products. HPLC analysis was carried out on a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. Conversion of the reaction was determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Thin-layer chromatography (TLC) was performed on silica gel, components were visualized by staining with KMnO₄ reagent. Flash chromatography was performed on silica gel. All reactions were carried out under nitrogen atmosphere using dried glassware. All solvents were dried and distilled before use according to standard procedures.

Ligand L*₁ was provided by Solvias, L*₂ was purchased from Fluka and L*₃, L*₄, L*₅ were purchased from Strem. All starting materials and products have been described in the literature.

Racemic 3k was prepared by reaction of 1d with phenylmagnesium bromide in dry THF at 0 °C in the presence of CuCl (3 mol %) and TMSCl (1.1 eq.). Both enantiomers of 3l were synthesized by the asymmetric rhodium/phosphoramidite catalyzed addition of phenylboronic acid to 1e according to reported procedure.¹

Racemic 3m was prepared by reaction of trans-4-phenyl-3-buten-2-one with n-butylmagnesium bromide in dry Et₂O at 0 °C in the presence of stoichiometric CuI.

The Heck coupling product 4 was synthesized by reaction of 1h with iodobenzene in NMP in the presence of Pd(OAc)₂ (0.05 mol %).²

Synthesis of racemic 3-Phenylhexanal (3n).³

A solution of Et₃N (5 mmol, 0.7 mL) in hexane (2.5 mL) was added dropwise to a solution of cinnamoyl chloride (4.5 mmol, 750 mg) and EtSH (4.5 mmol, 0.34 mL) in hexane (10 mL) at 0°C. The mixture was stirred overnight and allowed to reach room temperature. The precipitate was filtered off and washed with hexane/Et₂O (1:1). Purification of the crude by column chromatography (pentane/Et₂O = 50:1) afforded the (E)-3-phenyl-thioprop-2-ene-oic acid (S)-ethyl ester as colorless oil (563 mg, 2.9 mmol, 65%). The ethyl ester was dissolved in dry Et₂O (20 mL) in the presence of Cul (100 mol %, 2.9 mmol, 552 mg) and n-PrMgBr (3.09 M in Et₂O, 1.2 eq., 3.5 mmol, 1.2 mL) was added dropwise at 0 °C. After stirring for 30 min at rt, NH₄Cl aq. was added dropwise,
the organic layer concentrated and then the crude was purified by column chromatography (pentane/\text{Et}_2\text{O} = 50:1) to isolate the 1,4-addition product 3-phenylthiohexanoic acid (S)-ethyl ester (130 mg, 0.6 mmol, 20%). The product was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) and 10% Pd-C (5 mol %, 30 mg) was added at rt under nitrogen. After addition of Et\textsubscript{3}SiH (3 eq., 1.8 mmol, 0.3 mL) the mixture was stirred at rt overnight and then filtered over Celite and washed with CH\textsubscript{2}Cl\textsubscript{2}. Purification by column chromatography (pentane/\text{Et}_2\text{O} =100:1) afforded the racemic 3-phenylhexanal 3n as colorless oil (40 mg, 0.23 mmol, 41%).

**General procedure for the palladium catalyzed asymmetric conjugate addition of arylboronic acids.**

In a flame dried Schlenk tube equipped with septum and stirring bar, Pd(O\textsubscript{2}CCF\textsubscript{3})\textsubscript{2} (5 mol %, 5 µmol, 1.66 mg) and ligand L\textsubscript{3} (5.5 mol %, 5.5 µmol, 1.68 mg) were dissolved in dry THF (1.0 mL) and stirred under nitrogen at room temperature for 10 min. Arylboronic acid (3 eq., 0.30 mmol) was added, followed by the addition of enone 1 (0.1 mmol). After the addition of H\textsubscript{2}O (0.1 mL) the mixture was degassed by alternating vacuum-nitrogen cycles and then heated to 50 °C. When the reaction was complete according to TLC analysis, the mixture was cooled down to room temperature and aqueous NaHCO\textsubscript{3} sat. solution was added. The organic phase was separated and the resulting aqueous layer was extracted with Et\textsubscript{2}O. The combined organic phases were filtered over a plug of silica, dried on MgSO\textsubscript{4}, concentrated and purified by flash chromatography (Et\textsubscript{2}O/pentane) to yield the corresponding products 3. The composition and the conversion in the crude mixture were determined by NMR and GC-MS analysis.

(R)-3-Phenyl-cyclohexanone (3a)

Ketone 3a was obtained after purification by flash chromatography (eluent pentane/\text{Et}_2\text{O} 5:1) in 80% yield, 98% ee. \textsuperscript{1}H-NMR \(\delta\) 1.69-1.86 (2H, m), 2.02-2.14 (2H, m), 2.29-2.58 (4H, m), 2.93-2.99 (1H, m), 7.17-7.31 (5H, m); \textsuperscript{13}C-NMR \(\delta\) 211.5, 144.3, 128.7, 126.7, 126.6, 48.9, 44.7, 41.2, 32.8, 25.5. MS, \textit{m/z} (%): 174 (M+, 100), 131 (86.8), 117 (86.8). HRMS for C\textsubscript{12}H\textsubscript{14}O calcd 174.104, found 174.105. E.e. was determined by HPLC analysis, Chiralpak AD column, Heptane/i-PrOH 99:1, detection at 209 nm, retention times: 12.1 (Min) / 13.8 (Maj) min.

(+)-(R)-3-(2-Methoxyphenyl)-cyclohexanone (3b)

Ketone 3b was obtained after purification by flash chromatography (eluent pentane/\text{Et}_2\text{O} 5:1) in 80% yield, 99% ee. \textsuperscript{1}H-NMR \(\delta\) 1.75-2.14 (4H, m), 2.32-2.60 (4H, m), 3.37-3.48 (1H, m), 3.81 (3H, s), 6.85-6.95 (2H, m), 7.16-7.26 (2H, m). MS, \textit{m/z} (%): 204 (M+, 91.9), 131 (68.4), 117 (86.8). HRMS for C\textsubscript{13}H\textsubscript{16}O\textsubscript{2} calcd 204.115, found 204.116. E.e. was determined by chiral
HPLC analysis, Chiralcel OD column, Heptane/i-PrOH 95:5, detection at 210 nm, retention times: 8.1 (Min) / 9.0 (Maj) min.

(+)-(R)-3-(2-Methylphenyl)-cyclohexanone (3c)$^5$
Ketone 3c was obtained from the reaction of 1a with 2c in quantitative yield without further purification in 99% ee. $^1$H-NMR δ 1.75-1.82 (2H, m), 1.94-1.98 (1H, m), 2.11-2.15 (1H, m), 2.28 (3H, s), 2.35-2.48 (4H, m), 3.11-3.22 (1H, m), 7.11-7.21 (4H, m). MS, m/z (%): 188 (M+, 100), 145 (92.4), 131 (81.3). HRMS for C$_{13}$H$_{16}$O calcd 188.120, found 188.121. E.e. was determined by chiral HPLC analysis, Chiralpak AD column, Heptane/i-PrOH 99:1, detection at 209 nm, retention times: 9.3 (Min) / 11.63 (Maj) min.

(+)-3-(3-Methylphenyl)-cyclohexanone (3d)$^5$
Ketone 3d was obtained from the reaction of 1a with 2d in quantitative yield without further purification in 97% ee. $^1$H-NMR δ 1.68-1.83 (2H, m), 2.01-2.13 (2H, m), 2.30 (3H, s), 2.34-2.53 (4H, m), 2.89-2.92 (1H, m), 6.96-7.02 (3H, m), 7.15-7.21 (1H, m). MS, m/z (%): 188(M+, 100), 145 (52.6), 131 (85). HRMS for C$_{13}$H$_{16}$O calcd 188.120, found 188.121. E.e. was determined by chiral HPLC analysis, Chiralpak AD column, Heptane/i-PrOH 99:1 grad. 90/10, detection at 209 nm, retention times: 11.37 (Min) / 13.61 (Maj) min.

(+)-3-(2-Methoxyphenyl)-cyclohexanone (3e)$^5$
Ketone 3e was obtained after purification by flash chromatography (eluent pentane/Et$_2$O 5:1) in 98% yield, 98% ee. $^1$H-NMR δ 1.65-1.82 (2H, m), 2.01-2.13 (2H, m), 2.29-2.58 (4H, m), 2.89-2.97 (1H, m), 3.75 (3H, s), 6.71-6.78 (3H, m), 7.17-7.23 (1H, m). MS, m/z (%): 204 (M+, 100), 163 (29.3), 134 (51.0). HRMS for C$_{13}$H$_{16}$O$_2$ calcd 204.115, found 204.116. E.e. was determined by chiral HPLC analysis, Chiralcel OD column, Heptane/i-PrOH 99:1, detection at 210 nm, retention times: 33.7 (Min) / 38.3 (Maj) min.

3-p-Tolyl-cyclohexanone (3f)$^4$
Ketone 3f was obtained after purification by flash chromatography (eluent pentane/Et$_2$O 5:1) in 90% yield, 97% ee. $^1$H-NMR δ 1.70-1.81 (2H, m), 2.00-2.13 (2H, m), 2.29 (3H, s), 2.30-2.55 (4H, m), 2.89-2.96 (1H, m), 7.06-7.22 (4H, m). $^{13}$C-NMR δ 211.05, 141.4, 136.2, 129.3, 126.4, 49.1, 44.4, 41.2, 32.9, 25.6, 20.96. MS, m/z (%): 188 (M+, 51.9), 145 (25.5), 131 (100). HRMS for C$_{13}$H$_{16}$O calcd 188.120, found 188.121. E.e. was determined by chiral HPLC analysis, Chiralpak AD column, Heptane/i-PrOH 98:2, detection at 209 nm, retention times: 7.3 (Min) / 7.65 (Maj) min.
min or by chiral GC, Chiraldex G-TA column (30 m x 0.25 mm) 140 °C, retention times: 52.9 (Maj) / 54.6 (Min) min.

3-(3-Methylphenyl)-cyclohexanone (3h)

2-Cyclohexenone gave 60% of conversion in 3h that was obtained after purification by flash chromatography (eluent pentane/EtO 5:1) in 40% yield, 98% ee. 1H-NMR δ 1.66-1.96 (2H, m), 2.02-2.12 (2H, m), 2.27-2.56 (4H, m), 2.88-2.96 (1H, m), 7.01-7.14 (1H, m), 7.15-7.22 (3H, m); 13C-NMR δ 210.4, 146.3, 134.5, 129.9, 126.9, 126.8, 124.8, 48.6, 44.4, 41.1, 32.5, 25.4. E.e. was determined by chiral HPLC analysis, Chiralcel AD column, Heptane/i-PrOH 98:2, detection at 254 nm, retention times: 8.8 (Min) / 9.9 (Maj) min.

(+)-(R)-3-Phenyl-cyclopentanone (3i)

Ketone 3i was obtained following the general procedure at room temperature after purification by flash chromatography (eluent pentane/EtO 5:1) in 75% yield, 82% ee. 1H-NMR δ 1.89-1.97 (1H, m), 2.21-2.46 (4H, m), 2.63 (1H, dd, J = 6.96 and 17.96 Hz), 3.34-3.41 (1H, m), 7.19-7.32 (5H, m); 13C-NMR δ 218.5, 142.9, 128.6, 126.7, 45.7, 42.5, 38.8, 31.1. MS, m/z (%): 160 (M+, 82.8), 117 (37.6), 104 (100). HRMS for C11H12O calcd 160.0888, found 160.0896. E.e. was determined by chiral GC, Chiraldex α-TA column (30 m x 0.25 mm) 140°C, retention times: 16.8 (Min) / 18.6 (Maj) min.

(+)-(R)-3-Phenyl-cycloheptanone (3j)

Ketone 3j was obtained after purification by flash chromatography (eluent pentane/EtO 5:1) in 53% yield, 86% ee. 1H-NMR δ 1.43-1.47 (1H, m), 1.63-1.72 (2H, m), 1.93-2.06 (3H, m), 2.53-2.62 (3H, m), 2.85-2.92 (2H, m), 7.12-7.27 (5H, m); 13C-NMR δ 213.3, 146.9, 128.6, 126.4, 51.2, 43.9, 42.7, 39.2, 29.7, 24.2. MS, m/z (%): 188 (M+, 100), 130 (57.4), 104 (82.8). HRMS for C13H16O calcd 188.120, found 188.121. E.e. was determined by chiral HPLC analysis, Chiralcel OD column, Heptane/i-PrOH 95:5, detection at 210 nm, retention times: 6.7 (Min) / 7.2 (Maj) min.

(+)-(R)-N-Carbobenzyloxy-2-Phenyl-4-piperidone (3l)

Piperidone 3l was obtained according to the general procedure performing the reaction at 70 °C after purification by flash chromatography (eluent pentane/EtO 1:1) in 60% yield, > 99% ee. 1H-NMR δ 2.28-2.34 (1H, d, J = 16.11 Hz), 2.42-2.79 (1H, m), 2.80-2.84 (1H, dd, J = 3.66 and 6.59 Hz), 2.93 (1H, d, J = 15.38 Hz), 3.13 (1H, t, J = 11.35 Hz), 4.21 (1H, bs), 5.11-5.21 (2H, m), 5.78 (1H, bs), 7.19-7.33 (10H, m); 13C-NMR δ 207.2, 155.3, 139.6, 136.2, 128.8, 128.5, 128.2, 127.9, 126.7, 67.8, 54.6, 44.1, 40.5, 38.9.
MS, m/z (%): 309 (M+), 218 (43), 132, 91 (100). E.e. was determined by chiral HPLC analysis, Chiralcel OD-H column, Heptane/i-PrOH 90:10, detection at 210 nm, retention times: 26.6 (min, not visible) / 31.6 (Maj) min.

General procedure for the asymmetric conjugate addition of phenylboroxine.

In a flame dried Schlenk tube equipped with septum and stirring bar, Pd(O2CCF3)2 (5 mol %, 5 µmol, 1.66 mg) and ligand L3 (5.5 mol %, 5.5 µmol, 1.68 mg) were dissolved in dry THF (1.0 mL) and stirred under nitrogen at room temperature for 10 min. Phenylboroxine (3 eq., 0.30 mmol, 94 mg) was added, followed by the addition of enone 1 (0.1 mmol). The resulting mixture was heated to 50 °C and 0.4 mL of a 20 vol % solution of water in THF was added slowly by syringe pump (0.1 mL/h). After the addition, stirring was continued overnight and then the reaction was cooled down to room temperature, diluted with Et2O and filtered over a plug of silica. The crude was dried, concentrated and purified by flash chromatography (Et2O/pentane) to yield the corresponding products 3. The composition and the conversion in the crude mixture were determined by NMR and GC-MS analysis.

(+)-(S)-4-Phenyl-tetrahydro-2H-pyran-2-one (3k)

Pyranone 3k was obtained after purification by flash chromatography (eluent pentane/Et2O 3:2) in 75% yield, 94% ee. 1H-NMR δ 1.97-2.02 (1H, m), 2.11-2.15 (1H, m), 2.59 (1H, dd, J = 10.6 and 17.6 Hz), 2.88 (1H, ddd, J = 1.8, 5.9 and 17.6 Hz), 3.18-3.21 (1H, m), 4.32-4.38 (1H, m), 4.43-4.48 (1H, m), 7.16-7.34 (5H, m). MS, m/z (%): 176 (M+, 100), 117 (85.8), 104 (82.4). HRMS for C11H12O2 calcd 176.084, found 176.085. E.e. was determined by chiral GC, Chiraldex G-TA column (30 m x 0.25 mm), 170 °C, retention times: 123.0 (Min) / 124.1 (Maj) min.

4-Phenyl-2-octanone (3m)

3-octen-2-one 1f gave 60% conversion in ketone 3m that was obtained after purification by flash chromatography (eluent pentane/Et2O 100:1) in 45% yield and 82% ee. 1H-NMR δ 0.78 (3H, t, J = 7.3), 1.04-1.26 (4H, m), 1.50-1.59 (2H, m), 1.96 (3H, s), 2.62-2.68 (2H, m), 3.03-3.08 (1H, m), 7.07-7.26 (5H, m); 13C-NMR δ 207.9, 144.5, 128.4, 127.4, 126.2, 50.9, 41.2, 36.1, 30.6, 29.5, 22.5, 13.9. MS, m/z (%): 204 (M+, 17.2), 147 (80.2), 91 (100). HRMS for C14H20O calcd 204.151, found 204.152. E.e. was determined by chiral HPLC analysis, Chiralcel OB-H column, Heptane/i-PrOH 99:1, detection at 210 nm, retention times: 13.6 (Maj) / 19.3 (Min) min.
3-Phenyl-hexanal (3n)$^6$

$^\text{trans}$-2-hexenal gave 42% conversion in aldehyde $3n$ that was obtained after purification by flash chromatography (eluent pentane/ Et$_2$O 100 : 1) in 30% yield and 50% ee. $^1$H-NMR $\delta$ 0.82 (3H, t, $J = 7.3$ Hz), 1.11-1.18 (2H, m), 1.55-1.61 (2H, m), 2.67 (2H, dd, $J = 1.83$ and 6.97 Hz), 3.12-3.16 (1H, m), 7.13-7.28 (5H, m), 9.62 (1H, t, $J = 2.2$ Hz); $^{13}$C-NMR $\delta$ 202.1, 143.9, 128.6, 127.4, 126.5, 50.5, 39.8, 38.8, 20.4, 13.9. MS, $m/z$ (%): 176 (M+, 8.1), 132 (57.9), 107 (79.9), 91 (100). HRMS for C$_{12}$H$_{16}$O calcd 176.120, found 176.123. E.e. was determined by chiral HPLC analysis, Chiralcel OD-H column, Heptane/i-PrOH 98:2, detection at 210 nm, retention times: 20.9 (Min) / 31 (Maj) min.

References.