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Published in:
Journal of Organic Chemistry

DOI:
10.1021/jo035155e

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2003

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
High efficiency and enantioselectivity in the Rh-catalyzed conjugate addition of arylboronic acids using monodentate phosphoramidites.

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Supporting information

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S5 Synthesis and characterization of phosphoramidite L4.

General procedure.

All reactions were performed in a dry nitrogen atmosphere using standard Schlenk techniques. Cyclohexenone was distilled over calcium hydride and stored under nitrogen. Dioxane was distilled over Na and stored under nitrogen. Arylboronic acids were used as received. ¹H-NMR, ¹³C-NMR and ³¹P-NMR spectra were recorded at room temperature in CDCl₃ at 200 MHz or 300 MHz. Chemical shifts were determined relative to the residual solvent peaks (CHCl₃, δ = 7.26 ppm for proton atoms, δ = 77 ppm for carbon atoms; H₃PO₄, δ = 0 ppm for phosphorus atoms).

Standard reaction

\[
\text{Rh(acac)(C₂H₄)₂ (3 mol\%)} \quad \text{C₅H₅BH₂ (7.5 mol\%)} \\
\text{ArB(OH)₂ (3 eq)} \quad \text{C₂H₅OH/H₂O, 100 °C.}
\]

In a Schlenk tube flushed with nitrogen, 3.1 mg (12 µmol, 3 mol%) of Rh(acac)(eth)₂ and 12 mg (30 µmol, 7.5 mol%) of phosphoramidite L4 were dissolved in 1 mL of dioxane. Water (0.1 mL) was added and the resulting solution was stirred 5 min at RT. 150 mg (1.2 mmol, 3 eq) of phenylboronic acid was added to the solution. The mixture was heated to 100 °C and 40 µL (0.4 mmol) of cyclohexenone was added. The resulting solution was stirred for 20 min at 100 °C after which the solution was cooled to room temperature, quenched with sat. NaHCO₃ and extracted with diethyl ether. The organic phase was dried on sodium sulfate and filtered over a patch of silica (1 cm). The crude mixture was subjected to analysis (chiral GC or HPLC).
For experiments at high temperature (110 – 140 °C) the reactions were performed in a sealed Schlenk tube.

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<th>ln ks/kr MonoPhos L1</th>
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(S)-3-Phenylcyclohexanone (2a) \(^1\)

\[\text{O} \]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) : 1.73-1.89 (m, 2H), 2.07-2.13 (m, 2H), 2.34-2.59 (m, 4H), 2.95 (m, 1H), 7.26 (m, 5H).

\(^13\)C-NMR (75.4 MHz, CDCl\(_3\)) \(\delta\) : 25.5, 32.7, 41.1, 44.7, 48.9, 126.5, 126.7, 128.6, 144.3, 211.0. HRMS calcd. for C\(_{13}\)H\(_{14}\)O 174.104, found 174.103. Enantioseparation on chiral HPLC, DAICEL AD column, Hept/i-PrOH 99/1, rt 11.6 (Maj) 13.6.

\([\alpha]_D = -21^\circ\), (CHCl\(_3\), c = 1.17).

3-(2-Fluoro-phenyl)-cyclohexanone (2b)

\[\text{O} \]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) : 1.70-1.92 (m, 2H), 1.98-2.12 (m, 2H), 2.27-2.45 (m, 4H), 3.27 (m, 1H), 6.95-7.20 (m, 4H).

\(^13\)C-NMR (75.4 MHz, CDCl\(_3\)) \(\delta\) : 25.4, 31.2, 38.1, 41.2, 47.2, 115.7 (d, \(J = 22\) Hz), 124.3, 127.6, 128.2, 131.0 (d, \(J = 13.6\) Hz), 160.5 (d, \(J = 246\) Hz), 177.5.

MS, \(m/z\) (%): 192 (M+, 100), 149 (97.3); HRMS calcd for C\(_{13}\)H\(_{13}\)OF: 192.0950, found 192.0954. Enantioseparation on chiral HPLC, OD column, Hept/i-PrOH 99.5/05, rt. 14.65 min (Maj), 18.08 min.

3-(3-Methoxyphenyl)cyclohexanone (2c) \(^1\)

\[\text{O} \]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) : 1.74-1.86 (m, 2H), 2.05-2.17 (m, 2H), 2.30-2.60 (m, 4H), 2.96 (m, 1H), 3.80 (s, 3H), 6.75-6.83 (m, 3H), 7.24 (t, \(J = 8\) Hz, 1H).

\(^13\)C-NMR (75.4 MHz, CDCl\(_3\)) \(\delta\) : 25.5, 32.6, 41.2, 44.8, 48.9, 55.2, 111.7, 112.7, 118.9, 129.7, 146.0, 159.8, 211.0. Enantioseparation on chiral HPLC, OD column, Hept/i-PrOH 99/1, rt. 39.5 min (Maj), 44.52 min.

3-m-Tolyl-cyclohexanone (2d)

\[
\begin{align*}
\text{1H-NMR (300 MHz, CDCl}_3 \text{) } \delta & : 1.68-1.85 (m, 2H), 1.99-2.13 (m, 2H), 2.29 (s, 3H), 2.29-2.55 (m, 4H), 2.92 (m, 1H), 6.98 (m, 3H), 7.17 (t, J = 7.6 Hz, 1H). \\
\text{13C-NMR (75.4 MHz, CDCl}_3 \text{) } \delta & : 21.5, 25.6, 41.2, 44.7, 49.0, 123.5, 127.4, 127.4, 128.6, 138.3, 144.3, 211.1. \text{ MS, } m/z \text{ (%): 188 (M+, 100), 173 (6.0), 145 (50.1), 131 (85.6); HRMS calcd for C}_{13}\text{H}_{16}\text{O: 188.1201, found 188.1199.}
\end{align*}
\]

Enantioseparation on chiral HPLC, OD column, Hept/i-PrOH 99/1 grad 90/10, rt. 11.20 min (Maj), 14.01 min.

3-p-Tolyl-cyclohexanone (2e)

\[
\begin{align*}
\text{1H-NMR (300 MHz, CDCl}_3 \text{) } \delta & : 1.73-1.91 (m, 2H), 2.05-2.17 (m, 2H), 2.28-2.60 (m, 4H), 2.34 (s, 3H), 2.99 (m, 1H), 7.14 (m, 4H). \\
\text{13C-NMR (75.4 MHz, CDCl}_3 \text{) } \delta & : 21.0, 25.6, 32.9, 41.2, 44.4, 49.1, 126.4, 129.4, 136.3, 141.4, 211.2.
\end{align*}
\]

Enantioseparation on chiral GC, α-TA-column, 130 °C, rt. 60.67min, 62.39 min (Maj).

3-Phenylcyclopentanone (3a)

\[
\begin{align*}
\text{1H-NMR (300 MHz, CDCl}_3 \text{) } \delta & : 1.90 (m, 1H), 2.24-2.51 (m, 4H), 2.60 (dd, J = 19 Hz, J = 8 Hz, 1H), 3.35 (m, 1H), 7.19 (m, 3H), 7.29 (m, 2H). \\
\text{13C-NMR (75.4 MHz, CDCl}_3 \text{) } \delta & : 28.7, 36.4, 39.7, 43.3, 124.2 (2C), 126.2, 140.5, 208.6. \text{ HRMS calcd for C}_{11}\text{H}_{12}\text{O: 160.089, found 160.090. Enantioseparation on chiral GC, α-TA-column, 140°C, rt. 20.36 min (Maj), 22.59min.}
\end{align*}
\]

3-Phenylcycloheptanone (4a)

\[
\begin{align*}
\text{1H-NMR (300 MHz, CDCl}_3 \text{) } \delta & : 1.39 (m, 1H), 1.68 (m, 2H), 1.94 (m, 3H), 2.55 (m, 3H), 2.85 (m, 2H), 7.12 (m, 5H). \\
\text{13C-NMR (75.4 MHz, CDCl}_3 \text{) } \delta & : 24.2, 29.2, 39.2, 42.7, 43.9, 51.2, 126.3, 126.4, 128.6, 146.3, 213.5. \text{ HRMS calcd for C}_{13}\text{H}_{16}\text{O: 188.120, found 188.120. Enantioseparation on chiral HPLC, DAICEL OD column, Hept/i-PrOH 95/5, rt 7.45 min (Maj), 8.21min.}
\end{align*}
\]

4-Phenyl-tetrahydro-2H-pyran-2-one (5a)

\[
\begin{align*}
\text{1H-NMR (300 MHz, CDCl}_3 \text{) } \delta & : 1.99-2.21 (m, 2H), 2.53 (dd, J = 18 Hz, J = 9 Hz, 1H), 2.89 (ddd, J = 18 Hz, J = 6 Hz, J = 2 Hz, 1H), 3.17 (m, 1H), 4.36 (m, 2H), 7.19 (m, 5H). \\
\text{13C-NMR (75.4 MHz, CDCl}_3 \text{) } \delta & : 30.2, 37.4, 37.4, 68.6, 126.4, 127.2, 128.9, 142.7, 170.7. \text{ HRMS calcd for C}_{11}\text{H}_{12}\text{O}_2: 176.084, found 176.083. Enantioseparation on chiral GC, G-TA column, 100°C to 160°C (5°C/min), rt 36.93min (Maj), 38.25min.}
\end{align*}
\]

Synthesis of phosphoramidite.

Ligand L1 MonoPhosTM and L3 were prepared from (S)-Bis-β-naphthol and HMPT.3 Ligand L2 was prepared according to known literature.4

Synthesis of phosphoramidite L4.

1.50 g (5.1 mmol) of (S)-H8-Bis-β-naphthol was dissolved in 4 mL of PCl3, and heated under reflux for 6 hours. Excess of PCl3 was removed by distillation. The residual solid was subjected to an azeotropic distillation with toluene (5 mL) and dried under vacuum until a white foam was obtained. This solid was dissolved in 4 mL of toluene and added to a solution of diethylamine (0.68 mL, 6.6 mmol) and triethylamine (3 mL, 21 mmol) in 5 mL of THF. The resulting suspension was stirred for 16 hours at room temperature. The suspension was diluted with diethyl ether and filtered over silica. After evaporation, the residual oil was chromatographed over silica gel (hept/AcOEt 4/1) giving L4 as a white foam (1.71 g y =85 %).

\[
\begin{align*}
\text{H-NMR (300 MHz, CDCl}_3) & \delta : 1.06 (t, J = 7.05, 6H); 1.55-1.63 (m, 2H); 1.77-1.85 (m, 6H); 2.26-2.39 (m, 2H); 2.62-3.05 (m, 10H); 6.98 (dd, J = 8.1, 66 1H); 7.03 (d, J = 8.4, 2H). \\
\text{C-NMR (75.4 MHz, CDCl}_3) & \delta : 14.7; 22.6 (d, J = 21 Hz); 22.7; 27.7 (d, J = 9 Hz); 29.1 (d, J = 9 Hz); 38.0 (d, J = 21 Hz); 118.5 (d, J = 27 Hz); 128.7 (d, J = 95 Hz); 129.1 (d, J = 18 Hz); 133.2 (d, J = 80 Hz); 137.6 (d, J = 36 Hz); 148.6 (d, J = 45 Hz). \\
\text{P-NMR (81 MHz, CDCl}_3) & \delta : 143.1 ppm \\
\text{MS, m/z (%):} 395 (M+, 53.2 %), 380 (72.3 %), 323 (100 %). \\
\text{HRMS calcd for C}_{24}H_{30}O_2NP: 395.2014, found 395.2024. \\
[\alpha]_D = +239^\circ, (\text{CHCl}_3, c = 0.66).
\end{align*}
\]