Rhodium-Catalyzed Asymmetric Conjugate Additions of Boronic Acids Using Monodentate Phosphoramidite Ligands

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Published in: ChemInform

DOI: 10.1002/chin.200329031

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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):

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Rhodium-catalyzed asymmetric conjugate additions of boronic acids using monodentate phosphoramidite ligands

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Supporting information

**Standard reaction**

![Chemical structure](image)

In a Schlenck tube flushed with nitrogen, 3.1 mg (12 µmol, 3 mol%) of Rh(acac)(eth)$_2$ and (30 µmol, 7.5 mol%) of phosphoramidite were dissolved in 1 mL of dioxane. Water (0.1 mL) was added and the resulting solution was stirred 5 min at RT. 0.8 mmol (2 eq) of aryloboronic acid was added to the solution. The mixture was heated to 100 °C and 0.4 mmol of unsaturated ketone was added. The resulting solution was stirred for 5 hours at 100 °C after which the solution was cooled to room temperature, quenched with sat. NaHCO$_3$ and extracted with diethyl ether. The organic phase was dried on sodium sulfate and filtered over a patch of silica (1cm). The crude mixture was subjected to analysis (chiral GC or HPLC).

**3-Phenylcyclohexanone (1a)**

![NMR spectra](image)

$^1$H NMR : 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 : 25.51, 32.74, 41.14, 44.72, 48.92, 126.54, 126.65, 128.64, 144.31, 211.02. HRMS calcd. for C$_{12}$H$_{14}$O 174.104, found 174.103. Enantioseparation on chiral GC, α-TA-column, 130 C, rt. 36.10, 37.21 (Maj).

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1 We observed that the catalyst of choice was Rh(acac)(C$_2$H$_4$)$_2$. No reaction was observed with Rh(acac)CO$_2$ whereas [RhCl(C$_2$H$_4$)$_2$]$_2$ gave 83 % ee but with 77 % conversion. Rh(COD)$_2$BF$_4$ and [Rh(COD)Cl]$_2$ gave lower results probably due to the difficulty to replace the COD under these conditions.

3-(2-Methylphenyl)cyclohexanone (1b)

\[ \text{H NMR: } 1.71 (m, 2H), 1.97 (m, 1H), 2.13 (m, 1H), 2.28 (s, 3H), 2.40 (m, 4H), 3.15 (m, 1H), 7.16 (m, 5H). \]

\[ \text{13C NMR: } 19.23, 25.75, 31.96, 40.25, 41.25, 48.29, 125.02, 126.3, 126.39, 130.60, 135.05, 142.24, 211.81. \]

HRMS calcd. for C\textsubscript{13}H\textsubscript{16}O: 188.120, found 188.120.

Enantioseparation on chiral HPLC, DAICEL AD column, Hept/i-PrOH 99/1, rt 9.3(Maj), 11.7.

3-m-Tolyl-cyclohexanone (1c)

\[ \text{H NMR: } 1.68-1.85 (m, 2H), 1.99-2.13 (m, 2H), 2.29 (s, 3H), 2.29-2.55 (m, 4H), 2.92 (m, 1H), 6.98 (m, 3H), 7.17 (t, J = 7.6 Hz, 1H). \]

\[ \text{13C NMR: } 21.46, 25.58, 32.81, 41.21, 44.74, 48.98, 123.54, 127.38, 127.38, 128.56, 138.27, 144.34, 211.12. \]

MS, m/z (%): 188 (M+, 100), 173 (6.0), 145 (50.1), 131 (85.6); HRMS calcd for C\textsubscript{13}H\textsubscript{16}O: 188.1201, found 188.1199.

Enantioseparation on chiral HPLC, OD column, Hept/i-PrOH 99/1 grad 90/10, rt. 11.60(Maj), 13.83.

3-p-Tolyl-cyclohexanone (1d)

\[ \text{H NMR: } 1.73-1.91 (m, 2H), 2.05-2.17 (m, 2H), 2.28-2.60 (m, 4H), 2.34 (s, 3H), 2.99 (m, 1H), 7.14 (m, 4H). \]

\[ \text{13C NMR: } 20.98, 25.56, 32.91, 41.21, 44.40, 49.09, 126.44, 129.35, 136.28, 141.43, 211.18. \]

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

3-(2-Methoxyphenyl)cyclohexanone (1e)

\[ \text{H NMR: } 1.68-2.10 (m, 4H), 2.10-2.58 (m, 4H), 3.72 (m, 1H), 3.76 (s, 3H), 6.84 (m, 2H), 7.21 (m, 2H). \]

\[ \text{13C NMR: } 25.50, 30.93, 37.87, 41.32, 47.50, 55.17, 110.25, 120.57, 126.44, 127.45, 132.42, 156.63, 211.62. \]

HRMS calcd. for C\textsubscript{13}H\textsubscript{16}O\textsubscript{2}: 204.115, found 204.115.

Enantioseparation on chiral HPLC, DAICEL OD column, Hept/i-PrOH 95/5, rt 8.76(Maj), 9.93.

3-(3-Methoxyphenyl)cyclohexanone (1f)

\[ \text{H NMR: } 1.73-1.91 (m, 2H), 2.05-2.17 (m, 2H), 2.28-2.60 (m, 4H), 2.96 (m, 1H), 3.80 (s, 3H), 6.75-6.83 (m, 3H), 7.24 (t, J = 8 Hz, 1H). \]

\[ \text{13C NMR: } 25.53, 30.93, 37.87, 41.19, 44.76, 48.93, 55.20, 111.65, 112.70, 118.90, 129.69, 146.04, 159.81, 210.99. \]

Enantioseparation on chiral HPLC, OD column, Hept/i-PrOH 99/1, rt. 27.47(Maj), 28.53.

3-(4-Methoxyphenyl)cyclohexanone (1g)

\[ \text{H NMR: } 1.71 (m, 2H), 2.01 (m, 2H), 2.2-2.5 (m, 4H), 2.91 (m, 1H), 3.73 (s, 3H), 6.79 (d, J = 9 Hz, 2H), 7.07 (d, J = 9 Hz, 2H). \]

\[ \text{13C NMR: } 25.42, 32.93, 41.11, 43.91, 49.17, 55.20, 113.95, 127.41, 136.51, 158.20, 211.15. \]

HRMS calcd. for C\textsubscript{13}H\textsubscript{16}O\textsubscript{2}: 204.115, found 204.116.

Enantioseparation on chiral HPLC, DAICEL OJ column, Hept/i-PrOH 90/10, rt 11.54(Maj), 13.22.

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3-(2-Fluoro-phenyl)-cyclohexanone (1h)

\(^1\)H NMR: 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: 25.37, 31.23, 38.09, 41.20, 47.22, 115.69 (d, J = 22 Hz), 124.34, 127.60, 130.96 (d, J = 13.6 Hz), 160.51 (d, J = 246 Hz), 177.52.

MS, m/z (%): 192 (M+, 100), 149 (97.3); HRMS calcld for C\(_{12}\)H\(_{13}\)OF: 192.0950, found 192.0954. Enantioseparation on chiral HPLC, OD column, Hept/Ii-PrOH 99.5/05, rt. 15.73(Maj), 18.50.

3-(3-Fluoro-phenyl)-cyclohexanone (1i)

\(^1\)H NMR: 1.77-1.87 (m, 2H), 2.07-2.17 (m, 2H), 2.31-2.60 (m, 4H), 3.01 (m, 1H), 6.90-7.00 (m, 3H), 7.26-7.30 (m, 1H).

\(^{13}\)C NMR: 25.37, 32.55, 41.10, 44.37, 48.68, 113.47 (d, J = 21 Hz), 113.56 (d, J = 20.6 Hz), 122.28 (d, J = 2.6 Hz), 130.15 (d, J = 8.2 Hz), 146.79 (d, J = 8 Hz), 163.01 (d, J = 241.9 Hz), 210.57.

MS, m/z (%): 192 (M+, 98.5), 149 (100); HRMS calcld for C\(_{12}\)H\(_{13}\)OF: 192.0950, found 192.0958. Enantioseparation on chiral HPLC, AD column, Hept/Ii-PrOH 99/1, rt. 13.30(Maj), 15.82.

3-(4-Fluoro-phenyl)-cyclohexanone (1j)

\(^1\)H NMR: 1.68-1.78 (m, 2H), 1.98-2.11 (m, 2H), 2.27-2.53 (m, 4H), 2.93 (m, 1H), 6.95 (t, J = 8.4 Hz, 2H), 7.12 (dd, J = 5.7, 8.1 Hz, 2H).

\(^{13}\)C NMR: 25.39, 32.87, 41.10, 43.98, 49.06, 115.42 (d, J = 21.2 Hz), 127.97 (d, J = 7.5 Hz), 139.98, 161.52 (d, J = 240.2 Hz), 210.81.

MS, m/z (%): 192 (M+, 98.5), 149 (100); HRMS calcld for C\(_{12}\)H\(_{13}\)OF: 192.0950, found 192.0950. Enantioseparation on chiral HPLC, AD column, Hept/Ii-PrOH 99/1, rt. 12.36(Maj), 16.54.

3-Phenylcyclopentanone (2a)

\(^1\)H NMR: 1.90 (m, 1H), 2.24-2.51 (m, 4H), 2.60 (d, J = 9 Hz, 2H), 3.35 (m, 1H), 6.95 (t, J = 8.4 Hz, 2H), 7.12 (dd, J = 5.7, 8.1 Hz, 2H).

\(^{13}\)C NMR: 28.70, 36.37, 39.72, 43.30, 124.22, 126.16, 140.53, 208.63. HRMS calcld for C\(_{11}\)H\(_{12}\)O: 160.089, found 160.090. Enantioseparation on chiral GC, \(\alpha\)-TA-column, 140 C, rt. 20.36(Maj), 22.59.

3-Phenylcycloheptanone (3a)

\(^1\)H NMR: 1.39 (m, 1H), 1.68 (m, 2H), 1.94 (m, 3H), 2.55 (m, 3H), 2.85 (m, 2H), 7.12 (m, 5H).

\(^{13}\)C NMR: 24.15, 29.23, 39.18, 42.72, 43.92, 51.24, 126.33, 126.39, 128.63, 146.33, 213.45. HRMS calcld for C\(_{13}\)H\(_{16}\)O: 188.120, found 188.120. Enantioseparation on chiral HPLC, DAICEL OD column, Hept/Ii-PrOH 95/5, rt 7.45(Maj), 8.21.
4-Phenyl-dihydro-furan-2-one (4a)

\[ \text{H NMR} \quad 2.61 (dd, J = 17.4 Hz, J = 9 Hz, 1H), 2.84 (dd, J = 17.7 Hz, J = 8.4 Hz, 1H), 3.76 (q, J = 8.5 Hz, 1H), 4.19 (t, J = 8.5 Hz, 1H), 4.64 (t, J = 8.5 Hz, 1H), 7.08 (m, 5H). \]

\[ \text{C NMR} \quad 35.72, 41.13, 74.05, 126.72, 127.75, 129.18, 139.47, 176.45. \]

HRMS calcd. for C10H10O2 162.068, found 162.068. Enantioseparation on chiral GC, G-TA column, 160°C, rt. 34.63(Maj), 35.64.

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

\[ \text{H NMR} \quad 1.99-2.21 (m, 2H), 2.53 (dd, J = 18 Hz, J = 9 Hz, 1H), 2.89 (ddd, J = 18 Hz, J = 6 Hz, J = 2 Hz, 1H), 3.17 (m, 1H), 4.36 (m, 2H), 7.19 (m, 5H). \]

\[ \text{C NMR} \quad 30.23, 37.37, 37.43, 68.59, 126.39, 127.17, 128.92, 142.71, 170.65. \]

HRMS calcd. for C11H12O2 176.084, found 176.083. Enantioseparation on chiral GC, G-TA column, 100°C to 160°C(5°C/min), rt 36.93(Maj), 38.25.

2-Phenyl-2-(4-methylphenyl)-nitroethane (6a)

\[ \text{H NMR} \quad 2.27 (s, 3H), 4.83 (t, J = 2Hz, 1H), 4.93 (d, J = 2Hz, 2H), 7.08 (s, 4H), 7.34 (m, 5H). \]

\[ \text{C NMR} \quad 20.99, 48.58, 79.32, 127.48, 127.58, 128.97, 129.66, 131.22, 136.15, 137.29, 139.39. \]

HRMS calcd. for C15H15NO2 241.110, found 241.111. Enantioseparation on chiral HPLC, DAICEL OJ column, Hept/PrOH 90/10 rt 26(Maj), 36.

3-(4-Methoxy-phenyl)-3-phenyl-propionic acid ethyl ester (7a)

\[ \text{H NMR} \quad 1.06 (t, J = 7Hz, 3H), 2.95 (d, J = 8 Hz, 2H), 3.71 (s, 3H), 3.97 (q, J = 7Hz, 2H), 4.41 (t, J = 8Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 7.08 (d, J = 9 Hz, 2H), 7.20 (m, 5 H). \]

\[ \text{C NMR} \quad 14.06, 41.03, 46.25, 55.17, 60.38, 113.85, 126.39, 127.37, 127.55, 128.61, 135.62, 143.84, 150.99, 171.85. \]

HRMS calcd. for C18H20O3 284.141, found 284.142. Enantioseparation on chiral HPLC, DAICEL OD column, Hept/PrOH 90/10, rt 6.0(Maj), 6.8.

5-Methyl-5-phenyl-2-heptanone (8a)

\[ \text{H NMR} \quad 0.66 (d, J = 7 Hz, 3H), 0.85 (d, J = 7 Hz, 3H), 1.76 (m, 1H), 1.89 (s, 3H), 2.73 (m, 2H), 2.86 (m, 1H), 7.08 (m, 3H), 7.18 (t, J = 7Hz, 2H). \]

\[ \text{C NMR} \quad 20.19, 20.60, 30.44, 33.16, 47.49, 47.92, 126.12, 128.03, 128.11, 128.37, 143.13, 208.15. \]

HRMS calcd. for C13H18O 190.136, found 190.137. Enantioseparation on chiral GC, G-TA column, 100 C, rt. 46.38, 47.22(Maj).

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**Synthesis of phosphoramidites.**

**Dimethylphosphoramidites** (L₆, L₈, L₉) were prepared shown below.

**General procedure**

(S)-1,1'2',1'';2'',1'''-quaterphenyl-3',5''-diol was prepared according to T. Harada; T. Mai; T. Tuyet; and A. Oku *Org. Lett.* 2000, 2, 1319-1322.

Racemic 6,6'-dimethoxy-2,2'-biphenyldiol was prepared according to G. Delegu, D.; Fabbri *Tetrahedron: Asymmetry.* 1997, 8, 759-763. (S)- and (R)-6,6'-dimethoxy-2,2'-biphenyldiol were obtained with ee > 99.9 % using preparative chiral HPLC Chiralpack AD, Hept/i-PrOH 75/25, rt.: 9.6 min and 14.75 min.

(S)-1,1'2',1'';2'',1'''-quaterphenyl-3',5''-diol 100 mg (0.29 mmol, 1 eq), was dissolved in 1 mL of benzene. One crystal of ammonium chloride was added, followed by 81 µL (0.44 mmol, 1.5 eq) of hexamethylphosphorous triamide. The resulting solution was heated under reflux for 16 hours. The solvent was removed and the resulting oil was chromatographed over silica gel (eluent Hept/AcOEt 4/1) to give 90 mg of L₈, y = 75% of a white foam.

Same procedure for L₉, starting from 44 mg (0.178 mmol) of (S)-6,6'-dimethoxy-2,2'-biphenyldiol. L₉ was obtained as a white foam (51 mg, y = 85%).

**(S)-(1,11-Diphenyl-5,7-dioxa-6-phospha-dibenzo[a,c]cyclohepten-6-yl)-dimethyl-amine** (L₈)

\[
\text{Ph} \quad \text{Ph} \quad \text{O} \quad \text{P} \quad \text{N}
\]

\[\text{1H NMR } 2.61 \text{ (d, } J = 9.0 \text{ Hz, 6H), 6.43 \text{ (dd, } J = 8.1, 19.5 \text{ Hz, 4H), 6.98-6.89 (m, 6H), 7.12-7.06 (m, 4H), 7.36-7.25 (m, 4H).}\]

\[\text{13C NMR } 35.88 \text{ (d, } J = 20.2 \text{ Hz), 120.39 (d, } J = 6.75 \text{ Hz), 126.11 (d, } J = 5.2 \text{ Hz), 126.31 (d, } J = 66 \text{ Hz), 127.48 (d, } J = 3 \text{ Hz), 128.98, 129.02 (d, } J = 6 \text{ Hz), 140.28, 143.31 (d, } J = 20.8 \text{ Hz), 152.05.}\]

\[\text{31P NMR } 142.52; \text{ MS, } m/z (\%) : 411 (M+, 100), 368 (50.7); \text{ HRMS calcd for } C_{26}H_{22}O_{2}NP: 411.1388, \text{ found 411.1398.}\]

**(S)-(1,11-Dimethoxy-5,7-dioxa-6-phospha-dibenzo[a,c]cyclohepten-6-yl)-dimethyl-amine** (L₉)

\[
\text{MeO} \quad \text{MeO} \quad \text{O} \quad \text{P} \quad \text{N}
\]

\[\text{1H NMR } 2.53 \text{ (d, } J = 8.1 \text{ Hz, 6H), 3.77 (d, } J = 6 \text{ Hz, 6H), 6.71 (t, } J = 7.8 \text{ Hz, 2H), 6.794 (dd, } J = 8.1, 17.1 \text{ Hz, 2H), 7.23 (dt, } J = 8.4, 20.5, 2H).\]

\[\text{13C NMR } 35.83 \text{ (d, } J = 21.1 \text{ Hz), 55.95 (d, } J = 3.7 \text{ Hz), 107.11 (d, } J = 72.1 \text{ Hz), 114.18 (d, } J = 6.1 \text{ Hz), 129.17 (d, } J = 11 \text{ Hz), 151.40 (d, } J = 59.6 \text{ Hz), 152.39, 158.02 (d, } J = 15.8 \text{ Hz).}\]

\[\text{31P NMR } 145.80; \text{ MS, } m/z (\%) : 319 (M+, 100), 276 (94.7); \text{ HRMS calcd for } C_{16}H_{18}O_{4}NP: 319.0973, \text{ found 319.0977.}\]
Bis-ßnaphthol based phosphoramidites

1.55 g (5.4 mmol) of -Bis-betanaphthol was dissolved in 5 mL of PCl₃, and heated under reflux for 8 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. (1.87 g, y = 99%). This solid was dissolved in 7 mL of toluene. 1.9 mL (1.4 mmol) of the previous solution were added to a suspension of N,O-dimethyl hydroxylamine hydrochloride in 2 ml of THF and 1 mL of triethylamine. The resulting suspension was stirred for 16 hours at room temperature. The suspension was diluted with diethyl ether and filtered over silica. The residual oil was chromatographed over silica gel (hept/AcOEt 4/1) giving L6 as a white foam (320 mg y =63 %).

(S)-N-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-O,N-dimethyl-hydroxylamine (L6)

\[
\text{\begin{align*}
\text{\textsuperscript{1}H NMR} & \quad 2.74 \text{ (d, } J = 9.3 \text{ Hz, 3H)}, 3.57 \text{ (s, 3H)}, 7.18-7.51 \text{ (m, 8H)}, 7.85-7.96 \text{ (m, 4H).} \\
\text{\textsuperscript{13}C NMR} & \quad 34.33 \text{ (d, } J = 2.6 \text{ Hz), 62.43, 120.49 \text{ (d, } J = 40.7 \text{ Hz), 121.82} \\
& \quad \text{ (d, } J = 9 \text{ Hz), 124.83 \text{ (d, } J = 16.75 \text{ Hz), 126.14 \text{ (d, } J = 9.8 \text{ Hz), 126.95 \text{ (d, } J = 6 \text{ Hz), 128.29 \text{ (d, } J = 5 \text{ Hz), 130.23 \text{ (d, } J = 25.9 \text{ Hz), 131.16 \text{ (d, } J = 35.5 \text{ Hz), 132.58 \text{ (d, } J = 17.9 \text{ Hz), 149.44 \text{ (d, } J = 82.4 \text{ Hz).} \\
\text{\textsuperscript{31}P NMR} & \quad 140.35; \text{ MS, } m/z (%) \text{: 375 (M+, 32.3), 315 (100), 268 (35.5); HRMS calcd for C_{22}H_{18}O_{3}NP: 375.1024, found 375.1017.}
\end{align*}}
\]