High efficiency and enantioselectivity in the Rh-catalyzed conjugate addition of arylboronic acids using monodentate phosphoramidites

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High efficiency and enantioselectivity in the Rh-catalyzed conjugate addition of arylboronic acids using monodentate phosphoramidites.

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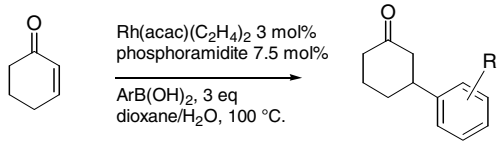
General procedure.

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. ^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectra were recorded at room temperature in $CDCl_3$ at 200 MHz or 300 MHz. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for proton atoms, δ = 77 ppm for carbon atoms; H_3PO_4, δ = 0 ppm for phosphorus atoms).

Standard reaction

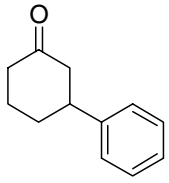


In a Schlenk tube flushed with nitrogen, 3.1 mg (12 μmol, 3 mol%) of Rh(acac)(eth)$_2$ and 12 mg (30 μmol, 7.5 mol%) of phosphoramidite **L4** were dissolved in 1 mL of dioxane. Water (0.1 mL) was added and the resulting solution was stirred 5 min at RT. 150 mg (1.2 mmol, 3 eq) of phenylboronic acid 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. $NaHCO_3$ 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).

For experiments at high temperature (110 – 140 °C) the reactions were performed in a sealed Schlenk tube.

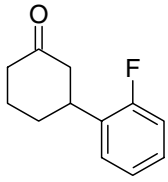
temperature	1/T	ee MonoPhos **L1**	ln ks/kr MonoPhos **L1**	ee **L4**	ln ks/kr **L4**
140	0.00242	82.2	2.32	94.2	3.51
130	0.00248			96.1	3.93
120	0.00254	82.6	2.35	98.4	4.81
110	0.00261			98.2	4.68
100	0.00268	83.9	2.43	98.3	4.71
80	0.00283	84.5	2.47	98.5	4.93
70	0.00291			98.8	5.17
60	0.003	85.8	2.57	98.7	5.04
45	0.00314			99.1	5.39
40	0.00319	86.7	2.63		

(S)-3-Phenylcyclohexanone (2a) [1]



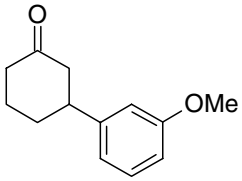
^{1}H-NMR (300 MHz, $CDCl_3$) δ : 1.73-1.89 (m, 2H), 2.07-2.13 (m, 2H), 2.34-2.59 (m, 4H), 2.95 (m, 1H), 7.26 (m, 5H).
^{13}C-NMR (75.4 MHz, $CDCl_3$) δ : 25.5, 32.7, 41.1, 44.7, 48.9, 126.5, 126.7, 128.6, 144.3, 211.0. HRMS calcd. for $C_{12}H_{14}O$ 174.104, found 174.103. Enantioseparation on chiral HPLC, DAICEL AD column, Hept/*i*-PrOH 99/1, rt 11.6 (Maj) 13.6.
$[\alpha]_D$ = - 21 °, ($CHCl_3$, c = 1.17).

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



^{1}H-NMR (300 MHz, $CDCl_3$) δ : 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, $CDCl_3$) δ : 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 $C_{12}H_{13}OF$: 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.

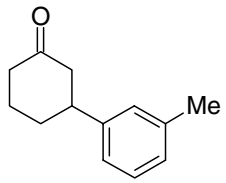
3-(3-Methoxyphenyl)cyclohexanone (2c) [1]



^{1}H-NMR (300 MHz, $CDCl_3$) δ : 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, $CDCl_3$) δ : 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.

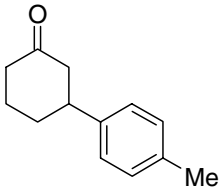
[1] Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5579-5581.

3-m-Tolyl-cyclohexanone (2d)



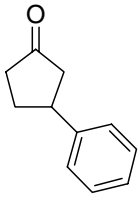
^{1}H-NMR (300 MHz, $CDCl_3$) δ : 1.68-1.85 (m, 2H), 1.99-2.13 (m, 2H), 2.29 (s, 3H), 2.29-2.55 (m, 4H), 2.92 (m, 1H), 6.98 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H).
^{13}C-NMR (75.4 MHz, $CDCl_3$) δ : 21.5, 25.6, 32.8, 41.2, 44.7, 49.0, 123.5, 127.4, 127.4, 128.6, 138.3, 144.3, 211.1. MS, *m/z* (%): 188 (M+, 100), 173 (6.0), 145 (50.1), 131 (85.6); HRMS calcd for $C_{13}H_{16}O$: 188.1201, found 188.1199.
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)[1]



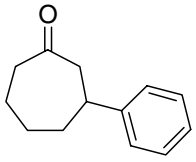
^{1}H-NMR (300 MHz, $CDCl_3$) δ : 1.73-1.91 (m, 2H), 2.05-2.17 (m, 2H), 2.28-2.60 (m, 4H), 2.34 (s, 3H), 2.99 (m, 1H), 7.14 (m, 4H).
^{13}C-NMR (75.4 MHz, $CDCl_3$) δ : 21.0, 25.6, 32.9, 41.2, 44.4, 49.1, 126.4, 129.4, 136.3, 141.4, 211.2.
Enantioseparation on chiral GC, α-TA-column, 130 ºC, rt. 60.67min, 62.39 min (Maj).

3-Phenylcyclopentanone (3a) [1]



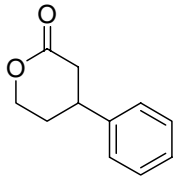
^{1}H-NMR (300 MHz, $CDCl_3$) δ : δ 1.90 (m, 1H), 2.24-2.51 (m, 4H), 2.60 (dd, *J* = 19 Hz, *J* = 8 Hz, 1H), 3.35 (m, 1H), 7.19 (m, 3H), 7.29 (m, 2H).
^{13}C-NMR (75.4 MHz, $CDCl_3$) δ : 28.7, 36.4, 39.7, 43.3, 124.2 (2C), 126.2, 140.5, 208.6. HRMS calcd. for $C_{11}H_{12}O$ 160.089, found 160.090. Enantioseparation on chiral GC, α-TA-column, 140°C, rt. 20.36 min (Maj), 22.59min.

3-Phenylcycloheptanone (4a) [1]



^{1}H-NMR (300 MHz, $CDCl_3$) δ : 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 (75.4 MHz, $CDCl_3$) δ : 24.2, 29.2, 39.2, 42.7, 43.9, 51.2, 126.3, 126.4, 128.6, 146.3, 213.5. HRMS calcd. 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 min (Maj), 8.21min.

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



^{1}H-NMR (300 MHz, $CDCl_3$) δ : 1.99-2.21 (m, 2H), 2.53 (dd, *J* = 18 Hz, *J* = 9 Hz, 1 H), 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).
^{13}C-NMR (75.4 MHz, $CDCl_3$) δ : 30.2, 37.4, 37.4, 68.6, 126.4, 127.2, 128.9, 142.7, 170.7.
HRMS calcd. for $C_{11}H_{12}O_2$ 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.

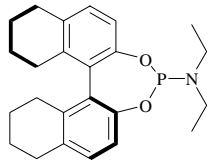
[2] Iguchi, Y.; Itooka, R.; Miyaura N. *Synlett*. **2003**, *7*, 1040.

Synthesis of phosphoramidite.

Ligand **L1** MonoPhos™ 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 PCl_3, and heated under reflux for 6 hours. Excess of PCl_3 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 %).



^{1}H-NMR (300 MHz, $CDCl_3$) δ : 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).
^{13}C-NMR (75.4 MHz, $CDCl_3$) δ : 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).
^{31}P-NMR (81 MHz, $CDCl_3$) : 143.1 ppm
MS, *m/z* (%) :395 (M+, 53.2 %), 380 (72.3 %), 323 (100 %). HRMS calcd for $C_{24}H_{30}O_2NP$: 395.2014, found 395.2024.
$[\alpha]_D$ = + 239 °, ($CHCl_3$, c = 0.66).

[3] Hulst, R. ; Devries, N. K., Feringa, B. L. *Tetrahedron :Asymmetry* **1994**, *5*, 699.
[4] Arnold, L. A. ; Imbos, R. ; Mandoli, A. ; de Vries, A. H. M. ; Naasz, R. ; feringa, B. L. *Tetrahedron* **2000**, *56*, 2865.