SUPPLEMENTARY INFORMATION

Enantioselective Synthesis of 2-Aryl-4-piperidones via Rhodium/Phosphoramidite Catalyzed Conjugate Addition of Arylboroxines

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Experimental Procedures

S2 General Remarks
Synthesis of the Starting Material
Conjugate Addition Reactions
  General Procedure for Table 2
S3 Conjugate Addition Reactions
  Table 2, Entry 1, Compound 2a
  Table 2, Entry 2, Compound 2b
  Table 2, Entry 3, Compound 2c
  Table 2, Entry 4, Compound 2d
S4 Conjugate Addition Reactions
  Table 2, Entry 5, Compound 2e
  Table 2, Entry 6, Compound 2f
  Table 2, Entry 6, Compound 2g
  Table 2, Entry 6, Compound 2h
S5 Conjugate Addition Reactions
  Procedure for the synthesis of (S)-2a on 2.2 mmol scale
General remarks:

All air- and moisture-sensitive manipulations were carried out under a dry nitrogen atmosphere using standard Schlenk techniques. 1,4-Dioxane was distilled from sodium before use. $^1$H-NMR, and $^{13}$C-NMR spectra were recorded on a Varian 300 (300 and 75 MHz) in CDCl$_3$. Mass spectra (HRMS) were recorded on an AEI MS-902. Optical rotations were measured on a Schmidt and Haensch Polartronic MH8. Rh(acac)(C$_2$H$_4$)$_2$ was purchased from Strem and used without further purification. All other chemicals were purchased from Acros and used as received. Flash chromatography was performed using silica gel 60 Å (Merck, 230-400 mesh).

Synthesis of starting materials

Substrate 1 was synthesized from 4-piperidone monohydrate hydrochloride and benzyl chloroformate, following the literature procedure for ethyl 3,4-dihydro-4-oxo-1-(2H)-pyridinecarboxylate, and was obtained as a white solid in 64% yield. $^1$ Spectral data were in accordance with literature. $^2$ All arylboroxines were prepared from the corresponding arylboronic acids by heating at 300 °C in vacuo. $^3$ Phosphoramidite ligands (S)-L and (R)-L were prepared from the corresponding H$_8$-Bis-β-naphthol, PCl$_3$, and diethylamine according to a previously reported procedure. $^4$

Conjugate Addition Reactions:

General Procedure for Table 2

In a flame dried Schlenk tube flushed with nitrogen, 1.55 mg (6.0 µmol, 3 mol%) of Rh(acac)(C$_2$H$_4$)$_2$ and 5.93 mg (15.0 µmol, 7.5 mol%) of one of the enantiomers of phosphoramidite L were dissolved in 0.5 mL of 1,4-dioxane. After stirring for 15 min at room temperature, 46.2 mg (0.2 mmol) of substrate 1 and 0.6 mmol of the arylboroxine were added and the resulting mixture was stirred at reflux conditions with slow addition of a 20 vol% solution of water in 1,4-dioxane by syringe pump (0.1 ml/h). After 2 h the reaction mixture was cooled to RT, diluted with 2 mL of ether, and passed through a pad of silica gel. The solvent was removed in vacuo. Reactions were performed in duplo, using both enantiomers of the ligand. Enantioselectivity did not differ more than 1% between duplos.
Table 2, Entry 1, compound 2a

The crude product was purified by flash column chromatography (pentane: Et₂O = 1:2) to give (R)-2a as a white solid in 86% isolated yield. The ee was determined on a Chiralcel OD-H column with pentane : isopropanol = 90 : 10, flow = 0.5 mL/ min. Retention times: 27.3 min [(S)-enantiomer], 29.8 min [(R)-enantiomer]. 99% ee. Physical and spectral properties were in full agreement with the literature.²

Table 2, Entry 2, compound 2b

The crude product was purified by flash chromatography (pentane: Et₂O = 1:2) to give (R)-2b, in the case of the (R)-L ligand, as a clear oil in 82% isolated yield. The ee was determined on a Chiralcel OJ column with pentane : isopropanol = 90 : 10, flow = 1.0 mL/ min. Retention times: 14.7 min [(S)-enantiomer], 23.5 min [(R)-enantiomer]. 24% ee. Physical and spectral properties were in full agreement with the literature.²

Table 2, Entry 3, compound 2c

The crude product was purified by flash chromatography (pentane: Et₂O = 1:2) to give (R)-2c, in the case of the (R)-L ligand, as a clear oil in 92% isolated yield. The ee was determined on a Chiralcel OD-H column with pentane : isopropanol = 90 : 10, flow = 0.5 mL/ min. Retention times: 25.1 min [(S)-enantiomer], 29.0 min [(R)-enantiomer]. 98% ee. ¹H NMR δ = 7.02-7.39 (m, 5H), 7.14-7.21 (m, 1H), 6.95-7.03 (m, 3H), 5.75 (bs, 1H), 5.21 (d, J = 12.5 Hz, 1H), 5.14 (d, J = 12.5 Hz, 1H), 4.23 (m, 1H), 3.15 (m, 1H), 2.94 (d, J = 15.4 Hz, 1H), 2.79 (dd, J = 15.4, 7.0 Hz, 1H), 2.49 (m, 1H), 2.32 (m, 1H), 2.26 (s, 3H); ¹³C NMR δ = 207.3, 155.4, 139.6, 138.5, 136.2, 128.6, 128.4, 128.2, 127.9, 127.3, 123.6, 67.7, 54.5, 44.1, 40.5, 38.9, 29.6, 21.4; HRMS calculated for C₂₀H₂₁NO₃ 323.1521 found 323.1517; [α]D = +90.9° (c = 0.52, CHCl₃). The absolute configuration was assigned by analogy.²

Table 2, Entry 4, compound 2d

The crude product was purified by flash chromatography (pentane: Et₂O = 1:2) to give (R)-2d, in the case of the (R)-L ligand, as a clear oil in 86% isolated yield. The ee was determined on a Chiralcel OJ column with pentane : isopropanol = 90 : 10, flow = 1.0 mL/ min. Retention times: 27.3 min [(S)-enantiomer], 30.8 min [(R)-enantiomer]. 95% ee. ¹H NMR δ = 7.28-7.42 (m, 5H), 7.07-7.20 (m, 4H), 5.82 (bs, 1H), 5.26 (d, J = 12.2 Hz, 1H), 5.19 (d, J = 12.2 Hz, 1H), 4.25 (m, 1H), 3.18 (m, 1H), 2.98 (dd, J = 15.6, 3.2, 1.22 Hz, 1H), 2.83 (dd, J = 15.4, 6.6 Hz, 1H), 2.51 (m, 2H), 2.33 (s, 3H); ¹³C NMR δ = 207.3, 155.4, 137.4, 136.5, 136.2, 129.4, 128.5, 128.2, 127.9, 126.6, 67.7, 54.3, 44.1, 40.5, 38.8, 20.9; HRMS calculated for C₂₀H₂₁NO₃ 323.1521
found 323.1515; [α]D = +81.3° (c = 0.64, CHCl3). The absolute configuration was assigned by analogy.²

Table 2, Entry 5, compound 2e

The crude product was purified by flash chromatography (pentane: Et2O = 1:2) to give (R)-2e, using the (R)-L ligand, as a clear oil in 85% isolated yield. The ee was determined on a Chiralcel OD-H column with pentane : isopropanol = 90 : 10, flow = 0.5 mL/min. Retention times: 35.8 min [(S)-enantiomer], 39.9 min [(R)-enantiomer]. 96% ee. Spectral properties were in full agreement with the literature.²

Table 2, Entry 6, compound 2f

The crude product was purified by flash chromatography (pentane: Et2O = 1:5) to give (R)-2f, using the (R)-L ligand, as a clear oil in 86% isolated yield. The ee was determined on a Chiralcel OD-H column with pentane : isopropanol = 80 : 20, flow = 0.5 mL/min. Retention times: 28.9 min [(S)-enantiomer], 31.8 min [(R)-enantiomer]. 98% ee. ¹H NMR δ = 7.21-7.38 (m, 5H), 6.61-6.78 (m, 3H), 5.77 (bs, 1H), 5.22 (dd, J = 12.1 Hz, 1H), 5.15 (d, 12.5 Hz, 1H), 4.21 (bs, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.06 (m, 1H), 2.91 (d, J = 14.3 Hz, 1H), 2.78 (dd, J = 15.6, 6.8 Hz, 1H), 2.46 (m, 1H), 2.30 (d, 15.4 Hz, 1H), 13C NMR δ = 207.4, 155.4, 149.2, 148.6, 136.3, 132.0, 128.6, 128.3, 128.0, 119.0, 110.85, 110.1, 67.7, 55.9, 55.7, 54.3, 44.1, 40.7, 38.7; HRMS calculated for C21H23NO5 369.1576 found 369.1566; [α]D = +100.5° (c = 1.26, CHCl3). The absolute configuration was assigned by analogy.²

Table 2, Entry 7, compound 2g

The crude product was purified by flash chromatography (pentane: Et2O = 1:2) to give 2g as a clear oil in 71% isolated yield. The ee was determined on a Chiralcel OD-H column with pentane : isopropanol = 90 : 10, flow = 0.5 mL/min. Retention times: 29.8 min [(S)-enantiomer], 30.6 min [(R)-enantiomer]. 94% ee. Spectral properties were in full agreement with the literature.²

Table 2, Entry 8, compound 2h

The crude product was purified by flash chromatography (pentane: Et2O = 1:2) to give 2h as a clear oil in 55% isolated yield. The ee was determined on a Chiralcel OD-H column with pentane : isopropanol = 90 : 10, flow = 0.5 mL/min. Retention times: 27.3 min [(S)-enantiomer], 29.8 min [(R)-enantiomer]. 96% ee. ¹H NMR δ = 7.22-7.36 (m, 7H) 7.08-7.16 (m, 2H), 5.73 (bs, 1H), 5.19 (d, J = 12.1 Hz, 1H), 5.13 (d, J = 12.1 Hz, 1H), 4.35 (m, 1H), 3.13 (m, 1H), 2.91 (dd, J = 15.6, 3.1 Hz, 1H), 2.80 (dd, J = 15.4, 6.6 Hz,
$^1$H), 2.47 (m, 1H), 2.30 (d, 16.1 Hz, 1H); $^{13}$C NMR $\delta = 206.8, 155.4, 138.3, 136.0, 133.7, 129.0, 128.6, 128.3, 128.0, 97.9, 67.9, 54.2, 44.1, 40.5, 39.0$; HRMS calculated for C$_{19}$H$_{18}$NO$_3$Cl 343.0975 found 343.0991; $[\alpha]_D = +74.2^\circ$ (c = 1.11, CHCl$_3$). The absolute configuration was assigned by analogy.$^2$

**Procedure for the synthesis of (S)-2a on 2.2 mmol scale**

In a flame dried Schlenk tube, flushed with nitrogen, 16.74 mg (64.8 µmol, 3 mol%) of Rh(acac)(C$_2$H$_4$)$_2$ and 69.97 mg (162.0 µmol, 7.5 mol%) of phosphoramidite (S)-L were dissolved in 5 mL of 1,4-dioxane. After stirring for 15 min at room temperature, 0.5 g (2.2 mmol) of substrate 1 and 2.1 g (6.6 mmol; 3 equiv) phenylboroxine were added and the resulting mixture was stirred at reflux conditions with slow addition of a 20 vol% solution of water in 1,4-dioxane by syringe pump (1.0 ml/h). After 2 h the reaction mixture was cooled to RT, diluted with 5 mL of ether, and quenched with a sat. NaHCO$_3$ (aq.) solution. After extraction with ether (3 x 15 mL), the combined organic layers were passed through a pad of silica gel with ether and the solvent was removed in vacuo. The crude product was purified by flash chromatography (pentane: Et$_2$O = 1:2) to give 585.2 mg (S)-2a as a white solid in 86% isolated yield. The ee was determined on a Chiralcel OD-H column with pentane : isopropanol = 90 : 10, flow = 0.5 mL/ min. Retention times: 27.3 min [(S)-enantiomer], 29.8 min [(R)-enantiomer]. 99% ee. Physical and spectral properties were in full agreement with the literature.$^2$