A Metallocene-Pyrrolidinopyridine Nucleophilic Catalyst for Asymmetric Synthesis

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General considerations. Petroleum ether refers to that fraction boiling in the range 40-60 °C. THF was distilled from sodium benzophenone ketyl, and toluene from sodium wire. Silica gel 40-63 μm was used for chromatography. All reactions were performed under nitrogen. Butyllithium was used as a 2.5 M solution in hexanes, DIBAL as a 1.0 M solution in hexanes and ZnCl_2 as a 0.5 M solution in THF.

Synthesis of 4. To a solution of $(\eta^5\text{-iodocyclopentadienyl})(\eta^4\text{-tetraphenylcyclobutadiene})\text{cobalt(I)}$ ¹ (0.250 g, 0.41 mmol) in dry toluene (4 mL) at *ca.* -80 °C was added BuLi (0.18 mL, 0.45 mmol) and the resulting solution warmed to room temperature. After stirring for 20 min, a solution of ZnCl_2 (0.067 g, 0.49 mmol) in THF (2 mL) was added *via* cannular, and after stirring for a further 10 min, 3-bromo-4-pyrrolidinopyridine² (0.094 g, 0.41 mmol) was added to the resultant orange solution. In a separate flask a suspension of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.060 g, 0.09 mmol) in toluene (2 mL) at room temperature was treated with DIBAL (0.17 mL, 0.17 mmol) and stirring continued for a further 20 minutes. The resulting black solution was added *via* cannular to the other reaction vessel and the resultant mixture was heated at 100 °C for 18 hours. After cooling and removal of the solvent *in vacuo*, the resulting brown oil was column chromatographed (EtOAc to 1.5% $\text{NEt}_3/\text{EtOAc}$) to give **4** (0.065 g, 25%) as an orange crystalline solid: Mp 117-120 °C. IR (CH_2Cl_2) ν_{max} 1639, 1585 cm^{-1} . ^1H NMR (270 MHz, CDCl_3) 1.70 - 1.77 (4 H, m), 2.95 - 3.02 (4 H, m), 4.62 (2 H, t, *J* 2), 4.88 (2 H, t, *J* 2), 6.44 (1 H, d, *J* 6), 7.10 - 7.27 (12 H, m), 7.32 - 7.40 (8 H, m), 7.84 (1 H, s), 7.97 (1 H, d, *J* 6). $^{13}\text{C}\{^1\text{H}\}$ NMR (68 MHz, CDCl_3) 25.4, 50.5, 75.1, 83.5, 83.7, 99.3, 108.4, 117.0, 126.3, 127.6, 128.0, 128.8, 135.9, 147.1, 152.6, 154.4. High-resolution MS (*m/z*, FAB): found for MH^+ 627.2228. $\text{C}_{42}\text{H}_{36}\text{CoN}_2$ requires 627.2210.

Synthesis of 7. To a solution of 4-amino-3-bromopyridine (0.870 g, 5.03 mmol) in THF (30 mL) was added NaH (60% dispersion in mineral oil - 0.502 g, 12.6 mmol) and the resulting solution stirred at room temperature for 3 hours. Following the addition of a solution of (*S,S*)-2,5-bis(methylsulfonyloxy)hexane (0.689 g, 2.51 mmol – synthesised in 91% yield using the procedure previously reported³) in THF (25 mL), the resulting reaction mixture was heated at reflux for 20 hours. After cooling, quenching with water (10 mL) and extraction with CH₂Cl₂ (3 x 30 mL), the combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo*. Column chromatography (0.25% NEt₃/5% MeOH/CH₂Cl₂) gave **7** (0.307 g, 48% yield) as a yellow oil that was further purified by Kugelrohr distillation to give a pale yellow oil: $[\alpha]_D^{22} = +135$ (MeOH, *c* 1.0). IR (film) $\nu_{\max}$ 2910, 1575, 1480 cm⁻¹. ¹H NMR (270 MHz, CDCl₃) 0.97 (6 H, d, *J* 6), 1.53 - 1.65 (2 H, m), 2.16 - 2.22 (2 H, m), 4.33 - 4.46 (2 H, m), 6.64 (1 H, d, *J* 5), 8.15 (1 H, d, *J* 5), 8.41 (1 H, s). ¹³C{¹H} NMR (68 MHz, CDCl₃) 19.8, 20.7, 30.1, 32.4, 47.8, 55.0, 106.1, 111.9, 147.6, 151.7, 153.4. High-resolution MS (*m/z*, ES): found for MH⁺ 255.0492. C₁₁H₁₆⁷⁹BrN₂ requires 255.0491.

Synthesis of 1. To a solution of (η⁵-iodocyclopentadienyl)(η⁴-tetraphenylcyclobutadiene)cobalt(I) (0.250 g, 0.41 mmol) in toluene (4 mL) at *ca.* -80 °C was added BuLi (0.18 mL, 0.45 mmol) and the resulting solution warmed to room temperature. After stirring for 30 min, the reaction was re-cooled to *ca.* -80 °C and a solution of ZnCl₂ in THF (0.95 mL, 0.48 mmol) was added *via* syringe. After warming to room temperature, addition of **7** (0.125 g, 0.49 mmol) was followed by addition of the catalyst prepared in a separate flask by suspending PdCl₂(PPh₃)₂ (0.014 g, 0.02 mmol) in toluene (4 mL) at room temperature, followed by addition of DIBAL (0.04 mL, 0.04 mmol) and stirring for a further 20 minutes. The resultant mixture was heated at 100 °C for 22 h, cooled, quenched with EtOAc (10 mL) and filtered through a short plug of SiO₂ prior to removal of the solvent *in*

vacuo. Column chromatography (0.25% NEt₃/5%MeOH/CH₂Cl₂) gave **1** (0.134 g, 50%) as an orange crystalline solid: Mp 120 - 125 °C. $[\alpha]_D^{22} = -340$ (MeOH, *c* 0.05). IR (nujol) $\nu_{\max}$ 3100, 1500 cm⁻¹. ¹H NMR (270 MHz, CDCl₃) 0.46 (3 H, br), 0.97 (3 H, br), 1.93 - 2.06 (4 H, m), 3.67 - 3.78 (2 H, m), 4.58 (1 H, s), 4.73 (1 H, s), 4.92 (1 H, s), 5.14 (1 H, s), 6.61 (1 H, d, *J* 5), 7.08 - 7.38 (20 H, m), 7.76 (1 H, s), 8.02 (1 H, d, *J* 5). ¹³C{¹H} NMR (100 MHz, CDCl₃ - pyrrolidine methyl and methylenes not observed) 74.4, 81.5, 82.1, 82.2, 82.9, 95.4, 113.8, 122.0, 125.2, 126.9, 127.7, 134.8, 145.4, 150.2, 151.3. High-resolution MS (*m/z*, ES): found for MH⁺ 655.2521. C₄₄H₄₀CoN₂ requires 655.2518.

General method of alcohol acetylation. 1-(1-Naphthyl)ethanol **8** (0.086 g, 0.5 mmol) was dissolved in CH₂Cl₂ (2 mL) and the reaction vessel cooled to -78 °C. To this was added the catalyst (0.005 mmol) dissolved in toluene (1 mL) followed by triethylamine (0.07 mL, 0.5 mmol) and acetic anhydride (0.12 mL, 1.3 mmol). The reaction mixture was stirred and maintained at -78 °C for 5 hours. After quenching with methanol, the solvent was removed *in vacuo* and ¹H NMR was used to determine the level of conversion (**8**: CH(CH₃)OH = 5.63 ppm, **9**: CH(CH₃)OAc = 6.65 ppm). The product **9** was isolated by column chromatography (5% ethyl acetate /petroleum ether to 25% ethyl acetate/petroleum ether to 2% MeOH/CH₂Cl₂), and the enantiomeric excess determined by gas chromatography (Chirasil-Dex CB 25m × 0.25mm), starting temperature 130 °C, initial time 1 min, rate 1 °C/min, final temperature 180 °C, final time 10 minutes. Retention time 45.76 min (*S*-**8**) and 47.74 min (*R*-**8**).

Synthesis of 10b. 2-(4-Methoxyphenyl)-4-methyloxazalone⁴ (1.00 g, 4.9 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. To this was added Et₃N (0.75 mL, 5.4 mmol) followed by 2,2,2-trichloro-1,1-dimethylethyl chloroformate (1.24 g, 5.2 mmol). The reaction

mixture was allowed to stir for 30 min at 0 °C and then poured into water and extracted with diethyl ether (25 mL). The combined organic layers were washed with 0.1M HCl, sat aqueous NaHCO₃ and brine (25 mL of each), dried with MgSO₄ and the solvent removed *in vacuo*. Column chromatography (1:1 diethyl ether/petroleum ether) gave **10b** (1.29g, 65% yield) as a colourless powder: Mp 97 - 101 °C. IR (nujol) $\nu_{\max}$ 1782, 1674, 1614 cm⁻¹. ¹H NMR (270 MHz, CDCl₃) 2.00 (6 H, s), 2.12 (3 H, s), 3.85 (3 H, s), 6.92 (2 H, d, *J* 8.6), 7.86 (2 H, d, *J* 8.6). ¹³C{¹H} NMR (68 MHz, CDCl₃) 10.4, 21.1, 55.4, 92.3, 104.6, 114.2, 119.9, 120.2, 127.6, 145.4, 148.5, 155.1, 161.4. High-resolution MS (*m/z*, ES) MH⁺ 408.0172. C₁₆H₁₇³⁵Cl₃NO₅ requires 408.0167.

General method of asymmetric Steglich rearrangement. A stirred solution of substrates **10a** or **10b** (0.5 mmol) in the relevant solvent (5 mL) was cooled to 0 °C and to this was added a solution of the catalyst **1** (0.0033 g, 0.005 mmol) in the same solvent (2 mL), and the reaction mixture made up to 0.05M by addition of a further 3 mL of solvent. The reaction was then stirred at 0 °C and progress monitored by TLC (1:1 diethyl ether/petroleum ether). On completion, the catalyst was removed by filtering the reaction mixture through a 2 cm silica plug washing with CH₂Cl₂ followed by ethyl acetate. The solvent was removed *in vacuo* and subsequent column chromatography (1:1 diethyl ether/petroleum ether) gave either **11a**⁴ or **11b** as colourless oils. **11a**: [α]_D²⁵ = +40 (CHCl₃, *c* 0.95) (Lit.,⁴ [α]_D²⁰ = -55 (CHCl₃, *c* 0.95) for a sample of (*S*)-**11a** of 91% e.e.). **11b** (0.13 g, 64 % yield). HPLC (Chiralcel OD, 4.6mm × 25m, 90:10 hexane/isopropanol, 1 mL/min) T_R = 13.25 min (major), T_R = 15.56 min (minor), 76% e.e. [α]_D²² = +18 (CHCl₃, *c* 1.0). IR (film) $\nu_{\max}$ 1825, 1762, 1651, 1608 cm⁻¹. ¹H NMR (270 MHz, CDCl₃) 1.73 (3 H, s), 1.87 (3 H, s), 1.90 (3H, s), 3.87 (3H, s), 6.96 (2 H, d, *J* 8.7), 7.94 (2 H, d, *J* 8.7). ¹³C{¹H} NMR (68 MHz, CDCl₃) 19.4, 21.0, 21.2, 55.6, 73.6, 90.8, 105.8, 114.4, 117.4, 125.5, 129, 130.3, 163.8, 174.9.

Synthesis of 12a. To a solution of **11a** (0.100 g, 0.29 mmol) in CH₂Cl₂ (10 mL) was added MeOH (2 mL), NEt₃ (0.03 g, 0.3 mmol) and SiO₂ (1.5 g). The resulting mixture was stirred for 30 min, the solvent removed *in vacuo*, and the residual silica added to the top of a chromatography column followed by subsequent elution (CH₂Cl₂ to 2% MeOH/CH₂Cl₂) to give product **12a** (0.060 g, 55% yield) as a colourless oil. HPLC (Chiralcel OD, 4.6mm × 25m, 90:10 hexane/isopropanol, 1 mL/min) T_R = 28.02 min (minor), T_R = 30.48 min (major), 72% e.e. $[\alpha]_D^{22} = -16.7$ (CHCl₃, *c* 0.8). IR (film) $\nu_{\max}$ 3400, 1739, 1670 cm⁻¹. ¹H NMR (270 MHz, CDCl₃) 1.86 (3 H, s), 3.71 (3 H, s), 3.84 (3 H, s), 5.24 (2 H, s), 6.92 (2 H, d, *J* 8.4), 7.28 - 7.32 (5 H, m), 7.43 (1 H, brs), 7.76 (2 H, d, *J* 8.4). ¹³C{¹H} NMR (68 MHz, CDCl₃) 21.17, 53.50, 55.52, 63.25, 68.10, 113.9, 125.7, 128.1, 128.5, 128.6, 129.1, 135.1, 162.7, 165.6, 168.8. High-resolution MS (*m/z*, ES) MH⁺ 372.1439. C₂₀H₂₂NO₆ requires 372.1442.

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ORTEP representation of **4**.

^1H NMR spectrum of **4**.

^1H NMR spectrum of 7.

^1H NMR spectrum of **1**.

^1H NMR spectrum of

¹H NMR spectrum of

11b.

^1H NMR spectrum of

HPLC analysis of **11b**.

HPLC (Chiralcel OD, 4.6mm × 25m, 90:10 hexane/isopropanol, 1 mL/min) T_R = 13.25 min (major), T_R = 15.56 min (minor), 76% e.e.

HPLC analysis of **12a**.

HPLC (Chiralcel OD, 4.6mm × 25m, 90:10 hexane/isopropanol, 1 mL/min) T_R = 28.02 min (minor), T_R = 30.48 min (major), 75% e.e.

Shimadzu CLASS-VP V5.02 *Area % Report*

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