Highly Enantioselective Asymmetric Hydrogenation of α -Phthalimide Ketone---An Efficient Entry to Enantiomerically Pure Aminoalcohol

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General Methods. All reactions were carried out in an inert atmosphere using standard Schlenk techniques. Column chromatography was performed on EM silica gel 60 (200-400 mesh). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-300, DRX-400 and AMX-360 spectrophotometers. Anhydrous solvents were purchased from commercial sources (Aldrich) and used without further purification. Ru-Tunephos catalysts were prepared according to the procedures reported previously.¹

General procedure for the syntheses of phthalimide ketones:

In a dried flask, to a solution of α -bromide or (chloride)-ketone (10 mmol) in DMF (10 mL) was added 110 mol% potassium phthalimide with stirring (the reaction can be carried out in the air without special handling; potassium phthalimide was not completely dissolved in the DMF). The reaction was run at room temperature and monitor by TLC. After the reaction was complete, the reaction mixture was poured into water (250 mL).

The desired products yield can be collected via filtration which normally is good enough for asymmetric hydrogenation as substrates. Further purification can be obtained via recrystallization from ethanol or isopropanol.

^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, J = 8.0 Hz, 2H), 7.86-7.83 (m, 2H), 7.72-7.69 (m, 2H), 7.61-7.56 (m, 1H), 7.47 (t, J = 7.8 Hz, 2H), 5.10 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.39, 168.28, 134.78, 134.54, 134.44, 132.61, 129.29, 128.54, 123.92, 44.60; MS (APCI) m/z : $[\text{M}^+ + 1]$, 266.1; HRMS (APCI), Calcd for $\text{C}_{16}\text{H}_{12}\text{NO}_3$ $[\text{M} + 1]$: 266.0812, found: 266.0819.

^1H NMR (400 MHz, CDCl_3) δ 7.99-7.87 (m, 4H), 7.75-7.40 (m, 2H), 7.47 (d, J = 8.0 Hz, 2H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.35, 168.22, 141.01, 134.61, 133.11, 132.56, 129.94, 129.67, 124.01, 44.48; MS (APCI) m/z : $[\text{M}^+ + 1]$, 300.0; HRMS (APCI), Calcd for $\text{C}_{16}\text{H}_{11}\text{NClO}_3$ $[\text{M} + 1]$: 300.0422, found: 300.0433

^1H NMR (300 MHz, CDCl_3) δ 7.89-7.86 (m, 2H), 7.74-7.71 (m, 2H), 7.57 (d, J = 7.6 Hz, 1H), 7.48 (s, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.15 (dd, J = 2.6, 8.3 Hz, 1H), 5.09 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 191.27, 168.28, 160.36, 136.08, 134.54, 132.62, 130.30, 123.95, 121.03, 120.98, 112.75, 55.89, 44.70; MS (APCI) m/z : $[\text{M}^+ + 1]$, 296.1; HRMS (APCI), Calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_4$ $[\text{M} + \text{H}]$: 296.0917, found: 296.0916

^1H NMR (300 MHz, CDCl_3) δ 7.93-7.85 (m, 3H), 7.72-7.70 (m, 2H), 7.52 (dt, $J = 1.8$, 7.4 Hz, 1H), 7.00 (d, $J = 7.4$ Hz, 2H), 5.06 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 192.22, 168.57, 160.16, 135.57, 134.38, 132.73, 131.77, 124.74, 123.83, 121.38, 111.99, 56.02, 49.06; MS (APCI) m/z : $[\text{M}^+ + 1]$, 296.1; HRMS (APCI), Calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_4$ $[\text{M} + \text{H}]$: 296.0917, found: 296.0918

^1H NMR (300 MHz, CDCl_3) δ 7.89-7.84 (m, 4H), 7.75-7.72 (m, 2H), 7.66-7.63 (m, 2H), 5.06 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.53, 168.21, 134.61, 133.51, 132.68, 132.56, 129.99, 129.77, 124.02, 44.45; MS (APCI) m/z : $[\text{M}^+ + 1]$, 344.0; HRMS (APCI), Calcd for $\text{C}_{16}\text{H}_{11}\text{NBrO}_3$ $[\text{M} + 1]$: 343.9917, found: 343.9920

^1H NMR (300 MHz, CDCl_3) δ 7.94 (d, $J = 8.9$ Hz, 2H), 7.85-7.80 (m, 2H), 7.72-7.67 (m, 2H), 6.92 (d, $J = 8.9$ Hz, 2H), 5.05 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 189.76, 168.36, 164.54, 134.48, 132.63, 130.84, 127.79, 123.87, 114.46, 55.94, 44.27; MS (APCI) m/z : $[\text{M}^+ + 1]$, 296.1; HRMS (APCI), Calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_4$ $[\text{M} + 1]$: 296.0917, found: 296.0920

^1H NMR (400 MHz, CDCl_3) δ 7.88-7.83 (m, 4H), 7.73-7.69 (m, 2H), 7.27 (d, $J = 7.9$ Hz, 2H), 5.08 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.92, 168.33, 145.41, 134.50, 132.65, 132.33, 130.05, 129.88, 128.60, 123.91, 44.50, 22.17;

^1H NMR (400 MHz, CDCl_3) δ 7.83-7.77 (m, 2H), 7.70-7.66 (m, 2H), 4.46 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.14, 168.01, 134.57, 132.41, 123.89, 47.48, 27.39; MS (APCI) m/z : $[\text{M}^++1]$, 204.1; HRMS (APCI), Calcd for $\text{C}_{11}\text{H}_{10}\text{NO}_3$ $[\text{M}+1]$: 204.0655, found: 204.0670.

^1H NMR (400 MHz, CDCl_3) δ 8.02-7.99 (m, 2H), 7.87-7.85 (m, 2H), 7.73-7.71 (m, 2H), 7.15 (t, $J = 8.5$ Hz, 2H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.89, 168.23, 134.58, 132.56, 131.24, 123.96, 116.73, 116.52, 116.35, 44.43; MS (APCI) m/z : $[\text{M}^++1]$, 284.1; HRMS (APCI), Calcd for $\text{C}_{16}\text{H}_{11}\text{NFO}_3$ $[\text{M}+\text{NH}_4]$: 284.0718, found: 284.0707

General procedure for asymmetric hydrogenation of the phthalimide ketones:

To a solution of phthalimide ketone substrate (0.2 mmol) in ethanol (3.0 mL) in a glovebox was added $[\text{NMe}_2\text{H}_2][\{\text{RuCl}((S)\text{-C3-TunePhos})\}_2(\mu\text{-Cl})_3]$ (0.004 mmol). The hydrogenation was performed at 80 °C under 100 bar of hydrogen pressure for 72 h. After the hydrogen was released, the reaction mixture was passed through a short silica gel

column to remove the catalyst. Enantiomeric excesses were determined by HPLC by using chiralcel OJ-H column (1 mL / min, Hexane: ¹PrOH = 80:20).

[α]_D²⁵ = +40.5 C=1.0 in CHCl₃ (from (*S*)-C₃-Tunephos)

¹H NMR (300 MHz, CDCl₃) δ 7.82-7.79 (m, 2H), 7.70-7.67 (m, 2H), 7.33 (dd, *J* = 1.5, 7.4 Hz, 1H), 7.24 (dt, *J* = 1.6, 8.0 Hz, 1H), 6.93-6.86 (m, 2H), 5.13-5.11 (m, 1H), 4.15 (dd, *J* = 8.3, 14.0 Hz, 1H), 3.97 (dd, *J* = 4.1, 14.0 Hz, 1H), 3.88 (s, 3H), 3.36 (br, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 166.97, 155.02, 132.17, 130.23, 127.29, 126.85, 125.78, 121.50, 119.04, 108.79, 68.66, 53.57, 42.07; MS (APCI) *m/z*: [M-OH], 280.1; HRMS (APCI), Calcd for C₁₇H₁₄NO₃[M-OH]: 280.0968, found: 280.0969.

[α]_D²⁵ = -18.8 C=1.0 in CHCl₃ (from (*R*)-C₃-Tunephos)

¹H NMR (300 MHz, CDCl₃) δ 8.08-7.99 (m, 2H), 7.82-7.80 (m, 2H), 7.30-7.28 (m, 2H), 6.86-6.83 (m, 2H), 4.66-4.62 (m, 1H), 3.99 (dd, *J* = 8.6, 14.0 Hz, 1H), 3.77 (s, 3H), 3.73 (dd, *J* = 5.5, 14.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 168.58, 159.89, 134.25, 132.44, 131.82, 128.58, 123.65, 114.28, 64.64, 55.63, 44.44; MS (APCI) *m/z*: [M⁺-OH], 280.1; HRMS (APCI), Calcd for C₁₇H₁₄NO₃[M-OH]: 280.0968, found: 280.0965

[α]_D²⁵ = +18.3 C=1.0 in CHCl₃ (from (*S*)-C₃-Tunephos)

^1H NMR (300 MHz, CDCl_3) δ 7.84-7.81 (m, 2H), 7.72-7.69 (m, 2H), 7.42-7.37 (m, 2H), 7.06-6.98 (m, 2H), 5.05-5.02 (m, 1H), 4.10-3.86 (m, 2H), 2.99 (br, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.14, 137.19, 134.62, 132.17, 128.05, 127.94, 123.92, 116.02, 115.73, 72.44, 46.12; MS (APCI) m/z : [M-OH], 268.1; HRMS (APCI), Calcd for $\text{C}_{16}\text{H}_{11}\text{NFO}_2$ [M-OH]: 268.0768, found: 268.0749

$[\alpha]_D^{25} = -23.8$ $C=1.0$ in CHCl_3 (from (*R*)- C_3 -Tunephos)

^1H NMR (300 MHz, CDCl_3) δ 7.77-7.73 (m, 2H), 7.67-7.63 (m, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 7.8$ Hz, 2H), 4.97-4.93 (m, 1H), 4.04-3.71 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.15, 138.49, 138.22, 134.50, 132.29, 129.67, 126.22, 123.84, 72.81, 46.09, 21.55; MS (APCI) m/z : [M^+ -OH], 264.1; HRMS (APCI), Calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_2$ [M-OH]: 264.1019, found: 264.1039

$[\alpha]_D^{25} = -11.3$ $C=1.0$ in CHCl_3 (from (*R*)- C_3 -Tunephos)

^1H NMR (300 MHz, CDCl_3) δ 7.78-7.76 (m, 2H), 7.67-7.65 (m, 2H), 7.33-7.19 (m, 4H), 4.99-4.96 (m, 1H), 4.05-3.81 (m, 2H), 3.02 (br, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.14, 139.89, 134.65, 134.19, 132.14, 129.14, 127.67, 123.95, 72.46, 46.03; MS (APCI) m/z : [M^+ -OH], 284.0; HRMS (APCI), Calcd for $\text{C}_{16}\text{H}_{11}\text{NClO}_2$ [M-OH]: 284.0473, found: 284.0481

$[\alpha] = -20.3$ $C=1.0$ in CHCl_3 (from (*R*)- C_3 -Tunephos)

^1H NMR (300 MHz, CDCl_3) δ 7.78-7.75 (m, 2H), 7.66-7.63 (m, 2H), 7.39-7.18 (m, 4H), 5.02-4.96 (m, 1H), 4.07-3.83 (m, 2H), 2.87 (br, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.84, 141.15, 134.22, 131.96, 128.68, 128.19, 125.96, 123.54, 72.69, 45.83; MS (APCI) m/z : $[\text{M}^+ + \text{H} - \text{OH} - \text{Br}]$, 250.1; HRMS (APCI), Calcd for $\text{C}_{16}\text{H}_{12}\text{NO}_2[\text{M} + \text{H} - \text{OH} - \text{Br}]$: 250.0863, found: 250.0865

$[\alpha] = -25.6$ $C=1.0$ in CHCl_3 (from (*R*)- C_3 -Tunephos)

^1H NMR (300 MHz, CDCl_3) δ 7.72-7.69 (m, 2H), 7.58-7.57 (m, 2H), 7.32-7.11 (m, 5H), 4.94-4.90 (m, 1H), 3.91-3.77 (m, 2H), 2.76 (br, 1H);

$[\alpha] = -14.9$ $C=1.0$ in CHCl_3 (from (*R*)- C_3 -Tunephos)

^1H NMR (300 MHz, CDCl_3) δ 7.79-7.76 (m, 2H), 7.66-7.64 (m, 2H), 7.20-7.17 (m, 1H), 6.96-6.94 (m, 2H), 6.78-6.74 (m, 1H), 4.98-4.94 (m, 1H), 3.98-3.82 (m, 2H), 3.73 (s, 3H), 2.92 (br, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.16, 160.24, 143.12, 134.55, 132.27, 130.06, 123.87, 118.54, 114.29, 111.47, 72.97, 55.68, 46.10; MS (APCI) m/z : $[\text{M}^+ - 1]$, 280.1; HRMS (APCI), Calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_3[\text{M} - \text{OH}]$: 280.0968, found: 280.0968

$[\alpha]_D^{25} = +41.3$, 1.0 in CHCl_3 (from (*S*)- C_3 -Tunephos)

^1H NMR (300 MHz, CDCl_3) δ 7.89-7.79 (m, 2H), 7.71-7.67 (m, 2H), 4.50-4.40 (m, 1H),

3.89-3.66 (m, 2H), 2.45 (br, 1H), 1.23 (d, $J = 6.3$ Hz, 3H), ^{13}C NMR (75 MHz, CDCl_3)

δ 169.32, 134.51, 132.32, 123.82, 45.91, 21.48, 21.40;

Reference:

(1) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. lett.*, **2002**, 4, 4495.