Electronic Supplementary Information

Direct Catalytic Asymmetric Aldol Reaction of β-Keto Esters with Formaldehyde Promoted by a Dinuclear Ni2-Schiff Base Complex

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Experimental Section

General:
Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-LA500, ECX500, or ECA500 spectrometers, operating at 500 MHz for 1H NMR and 125.65 MHz for 13C NMR. Chemical shifts in CDCl3 were reported in the scale relative to tetramethylsilane (0 ppm) for 1H NMR. For 13C NMR, chemical shifts were reported in the scale relative to CHCl3 (77.0 ppm) as an internal reference. Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Waters micromass ZQ (for LRMS) and FAB mass spectra (for HRMS) were measured on a JEOL JMS-700 spectrometer. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-2080 plus; detector, UV-2075 plus, measured at 280 nm; column, DAICEL CHIRALPAK AS-H or AD-H; mobile phase, hexane-2-propanol. Diisopropylether (iPr2O) was distilled from sodium benzophenone ketyl. Other reagents were purified by the usual methods. Formaldehyde solution (37% w/w in H2O) and paraformaldehyde were purchased from Aldich. β-Keto esters[S1, S2] were prepared by following the same procedures as described in literatures.

References
Preparation of Ni₂-Schiff Base 1 Complex:

To a solution of (R,R)-Schiff base ligand 1 (400 mg, 0.76 mmol) in EtOH (7.6 mL), was added Ni(OAc)₂•4H₂O (378 mg, 1.52 mmol), and the mixture was stirred for 12 h under reflux. After cooling down to room temperature, H₂O (1.0 mL) was added to the mixture. The precipitate (Ni₂/Schiff base 1 complex) was collected by filtration. Then, the solid was washed with hexane and EtOH. The solid was dried under reduced pressure at 50 °C to afford the Ni₂-Schiff base 1 complex (417 mg) as a dark yellow solid. The complex was used for the asymmetric reaction without further purification, and was stored under Ar at room temperature. Catalytic activity did not change for 5 months.

General Procedure for Catalytic Asymmetric Hydroxymethylation of β-Keto Esters Using a Ni₂-Schiff Base 1 Catalyst:

To a stirred solution of the Ni₂/Schiff base 1 catalyst (0.096 mg, 0.15 µmol) in iPr₂O (7.5 mL) was added β-keto ester 2a (26.2 mg, 0.15 mmol). To the mixture at 40 °C was added 37% aqueous formaldehyde solution (21.7 mg, 0.165 mmol), and the resulting suspension was stirred for 1 h. The mixture was diluted with diethyl ether, and the precipitate was removed by filtration through a pad of Celite. After the filtrate was concentrated under reduced pressure, the residue was purified by silica gel flash column chromatography (hexane/ethyl acetate = 3/1) to give the desired product 3a (30.2 mg, 94% yield) as a colorless oil.

(S)-tert-butyl 1-(hydroxymethyl)-2-oxocyclopentanecarboxylate (3a)

colorless oil; IR (neat) ν 3460, 2973, 1748, 1721 cm⁻¹; ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 1.93-2.11 (m, 2H), 2.14-2.20 (m, 1H), 2.25-2.36 (m, 2H), 2.42-2.50 (m, 1H), 2.74 (dd, J = 4.6, 9.0, 1H), 3.75 (dd, J = 9.0, 12.0, 1H), 3.85 (dd, J = 4.6, 12.0, 1H); ¹³C NMR (CDCl₃) δ 19.7, 27.9, 31.3, 38.4, 62.2, 63.8, 82.6, 170.8, 215.4; LRMS(ESI): m/z 237 [M+Na]⁺; HRMS (FAB): m/z calculated for C₁₁H₁₈O₄Cs⁺ [M+Cs]⁺: 347.0260, found: 347.0272, [α]D⁻¹₆.₀ +6.3 (c 1.00, CHCl₃); HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol
= 95/5, flow 0.5 mL/min, detection at 280 nm) \( t_R \) 20.4 min (major) and 25.2 min (minor).

**(S)-**tert-butyl 1-(hydroxymethyl)-2-oxocyclohexanecarboxylate (3b)
colorless oil; IR (neat) 3463, 2978, 1709 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.49 (s, 9H), 1.49-1.63 (m, 3H), 1.78-1.82 (m, 1H), 2.02-2.08 (m, 1H), 2.27-2.32 (m, 1H), 2.41-2.47 (m, 1H), 2.60-2.68 (m, 1H), 2.85 (dd, \( J = 5.3, 9.7 \) Hz, 1H), 3.68 (dd, \( J = 9.7, 11.5 \) Hz, 1H), 3.78 (dd, \( J = 5.3, 11.5 \) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 22.0, 26.9, 27.9, 32.9, 41.0, 63.1, 66.7, 82.7, 170.3, 211.3; LRMS(ESI): \( m/z \) 251 [M+Na]\(^+\); HRMS (FAB): \( m/z \) calculated for C\(_{12}\)H\(_{20}\)O\(_4\)Cs\(^+\) [M+Cs]\(^+\): 361.0416, found: 361.0406; \([\alpha]_D^{190} +5.2 \) (c 1.04, CHCl\(_3\)); HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol = 95/5, flow 0.5 mL/min, detection at 280 nm) \( t_R \) 14.3 min (major) and 17.2 min (minor).

**(S)-**tert-butyl 1-(hydroxymethyl)-2-oxocycloheptanecarboxylate (3c)
colorless oil; IR (neat) 3535, 2976, 2932, 2862, 1701 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) 1.48 (s, 9H), 1.58-1.64 (m, 4H), 1.74-1.84 (m, 3H), 1.91-1.96 (m, 1H), 2.49-2.54 (m, 1H), 2.71-2.76 (m, 1H), 3.04 (dd, \( J = 4.9, 9.7 \) Hz, 1H), 3.68 (dd, \( J = 9.7, 11.4 \) Hz, 1H), 3.94 (dd, \( J = 4.9, 11.4 \) Hz 1H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 25.2, 25.6, 27.9, 30.1, 30.9, 43.0, 64.4, 67.3, 82.6, 171.3, 212.6; ESI-MS \( m/z \) 265 [M+Na]\(^+\); HRMS calcd. for C\(_{13}\)H\(_{22}\)O\(_4\)Cs [M+Cs]\(^+\): 375.0573, found 375.0561; \([\alpha]_D^{180} +4.6 \) (c 1.23, CHCl\(_3\)); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 0.5 mL/min, detection at 280 nm) \( t_R \) 13.1 min (major) and 16.1 min (minor).

**(S)-**tert-butyl 2-(hydroxymethyl)-2-methyl-3-oxobutanoate (3d)
colorless oil; IR (neat) 3419, 2979, 1735, 1715 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.35 (s, 3H), 1.48 (s, 9H), 2.23 (s, 3H), 2.73 (dd, \( J = 6.9, 8.0 \) Hz), 3.76 (dd, \( J = 8.0, 11.5 \) Hz), 3.85 (dd, \( J = 6.9, 11.5 \)); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 17.2, 27.0, 27.9, 61.7, 66.6, 82.6, 171.5, 207.0; ESI-MS \( m/z \) 225 [M+Na]\(^+\); HRMS calcd. for C\(_{10}\)H\(_{16}\)O\(_4\)Cs [M+Cs]\(^+\): 335.0260, found 335.0250; \([\alpha]_D^{190} +4.6 \) (c 1.03, CHCl\(_3\)); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 90/10, flow 0.5 mL/min, detection at 280 nm) \( t_R \) 13.2 min (major) and 15.1 min (minor).
(S)-tert-butyl 2-ethyl-2-(hydroxymethyl)-3-oxobutanoate (3e)
colorless oil; $^1$H NMR (CDCl$_3$) $\delta$ 0.90 (t, $J = 8.0$ Hz, 3H), 1.49 (s, 9H), 1.81-1.89 (m, 1H), 2.23 (s, 3H), 2.47 (dd, $J = 6.0$, 8.0 Hz, 1H), 3.85 (dd, $J = 8.0$, 12.0 Hz, 1H), 3.96 (dd, $J = 6.0$, 12.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$) $\delta$ 8.8, 24.3, 27.5, 27.9, 63.9, 65.9, 82.5, 171.1, 206.8; ESI-MS $m/z$ 239 [M+Na]$^+$; HRMS calcd. for C$_{11}$H$_{20}$O$_4$Cs [M+Cs]$^+$: 349.0416, found 349.0408; [$$]_D^{26.0}$ +5.3 (c 1.11, CHCl$_3$); HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol = 90/10, flow 0.5 mL/min, detection at 280 nm) $t_R$ 12.3 min (major) and 13.1 min (minor).

(S)-tert-butyl 2-benzyl-2-(hydroxymethyl)-3-oxobutanoate (3f)
colorless oil; IR (neat) $\nu$ 3463, 2978, 2938, 1709 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.46 (s, 9H), 2.24 (dd, $J = 5.5$, 7.5, 1H), 2.27 (s, 3H), 3.18 (d, $J = 14.0$ Hz, 1H), 3.25 (d, $J = 14.0$, 1H), 3.79 (dd, $J = 7.5$, 12.0 Hz, 1H), 3.93 (dd, $J = 5.5$, 12.0 Hz, 1H), 7.18-7.29 (m, 5H); $^{13}$C NMR (CDCl$_3$) $\delta$ 27.87, 27.92, 36.5, 63.7, 66.7, 82.9, 127.0, 128.3, 130.1, 135.9, 170.2, 205.6; ESI-MS $m/z$ 301 [M+Na]$^+$; HRMS calcd. for C$_{16}$H$_{22}$O$_4$Cs [M+Cs]$^+$: 411.0573, found 411.0580; [$$]_D^{26.0}$ +2.6 (c 1.23, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 9/1, flow 0.5 mL/min, detection at 254 nm) $t_R$ 15.0 min (major) and 18.6 min (minor).

(S)-tert-butyl 2-benzyl-2-(hydroxymethyl)-3-oxo-3-phenylpropanoate (3g)
colorless solid; mp 66-70 °C; IR (neat) $\nu$ 3487, 2976, 2932, 1718, 1679 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.32 (s, 9H), 1.58 (s, 3H), 2.79 (dd, $J = 6.9$, 11.5 Hz, 1H), 4.01 (dd, $J = 6.9$, 11.5 Hz, 1H), 7.42-7.46 (m, 2H), 7.53-7.57 (m, 1H), 7.86-7.89 (m, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 18.6, 27.6, 59.6, 68.0, 82.6, 128.4, 128.8, 133.0, 135.4, 171.8, 199.3; ESI-MS $m/z$ 287 [M+Na]$^+$; HRMS calcd. for C$_{15}$H$_{29}$O$_4$Cs [M+Cs]$^+$: 397.0416, found 397.0414; [$$]_D^{13.0}$ +2.6 (c 1.00, CHCl$_3$); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol = 9/1, flow 0.5 mL/min, detection at 254 nm) $t_R$ 13.9 min (major) and 15.3 min (minor).
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