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SUPPORTING INFORMATION

Title: Asymmetric Hydrogenation of Pyridines: Enantioselective Synthesis of Nipecotic Acid Derivatives
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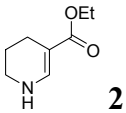
Ref. No.: O200600558

Experimental Section

General Procedures: All reactions were carried out in an inert atmosphere using standard Schlenk techniques unless otherwise stated. All chemicals were purchased from commercial sources (Aldrich) and used without further purification**.** THF and toluene were dried and distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride was dried over CaH_2 and flushed with nitrogen. Methanol and isopropanol were distilled from Mg under nitrogen. 1,2-dichloroethane were purchased from commercial sources (Aldrich) and used without further purification**.** Column chromatography was performed on EM silica gel 60 (200-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury 300 MHz, Bruker DPX-300, DRX-400 and AMX-360 spectrometers. Mass spectra were recorded on Varian GC-MS 3900-2100T and a KRATOS mass spectrometer MS 9/50 for LR-ESI and a Perseptive Mariner mass spectrometer for HR-APCI. GC analysis was carried out on Varian GC 2000 and a Helwett-Packard 6890 gas chromatograph using chiral capillary columns. HPLC analysis was carried out on a Waters^{TM} 600 chromatograph. Ru-Tunephos, Ru-Binapine and Rh-TangPhos catalysts were prepared according to the procedures reported previously.

General Procedure for Pd-C Catalyzed Partial Hydrogenation

A solution of ethyl nicotinate (15.1 g, 0.1 mol) in 50 mL of 95% ethanol solution was hydrogenated with 500 mg 5% Pd-C catalyst. The reaction was performed at room temperature under 100 psi hydrogen pressures for 36 hrs, when uptake has ceased. The solution was filtered and the solvent evaporated to give pale yellow oil**.** This was dissolved in ether and extracted with several small portions of **2%** hydrochloric acid to remove any of the basic impurities present. The ether solution was then dried with sodium carbonate and concentrated to a yellow oil which was subject to flash column chromatography. There was obtained 13.9 g (90%) colorless, pleasant-smelling oil, which set on standing to a pale yellow solid.

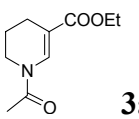


2

^{1}H NMR (300MHz, $CDCl_3$) δ 7.42 (d, *J* = 6.2 Hz, 1H), 4.54 (s, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.15 (m, 2H), 2.27 (t, *J* = 6.4 Hz, 2H), 1.75 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 169.0, 143.0, 95.5, 59.0, 40.9, 21.1, 20.8, 14.8

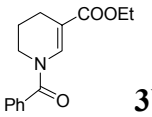
General Procedure for Preparation of *N*-Carbomate and *N*-Acyl Vinylogous Amides:

To a solution of 3-substituted tetrahydropyridine (1 mmol) in methylene chloride (3.0 mL) in Schlenk tube was added methyl chloroformate (198 mg, 2 mmol) and pyridine (154 mg, 2 mmol). The reaction mixture was allowed to stir at room temperature for 1hr. After the reaction complete, the solvent was removed under reduced pressure. The resulting residue was directly subject to silica gel column for flash chromatography.



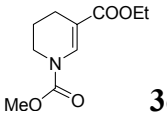
3a

^{1}H NMR (360MHz, $CDCl_3$) δ 7.78 (s, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.63 (t, *J* = 5.6 Hz, 2H), 2.31 (t, *J* = 6.1 Hz, 2H), 2.26 (s, 3H), 1.79 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (90MHz, $CDCl_3$) δ 169.5, 167.4, 135.5, 109.9, 60.5, 40.6, 21.6, 21.5, 20.6, 14.6



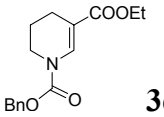
3b

^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.50-7.24 (m, 5H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 2H), 2.36 (dt, *J* = 1.2, 6.2 Hz, 2H), 1.92 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.5, 167.4, 134.0, 131.3, 128.8, 128.6, 60.4, 21.7, 21.0, 14.5; MS (APCI) m/z: [M^++1], 260.1; HRMS (APCI), Cacld for $C_{15}H_{18}NO_3$[M+1]: 260.1281, found: 260.1284



3c

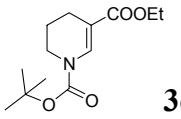
^{1}H NMR (300MHz, $CDCl_3$) δ 7.99 (br, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.56 (t, *J* = 5.6 Hz, 2H), 2.27 (t, *J* = 6.2 Hz, 2H), 2.26 (s, 3H),1.80 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 167.8, 135.5, 109.1, 60.4, 54.0, 42.7, 21.3, 21.0, 14.8; MS (APCI) m/z: [M^++1], 214.1; HRMS (APCI), Cacld for $C_{10}H_{16}NO_4$[M+1]: 214.1074, found: 214.1083



3d

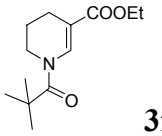
^{1}H NMR (400MHz, $CDCl_3$) δ 8.06 (br, 1H), 7.40-7.30 (m, 5H), 5.21 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.60 (t, *J* = 5.6 Hz, 2H), 2.28 (t, *J* = 6.1 Hz, 2H), 1.80 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 167.6, 153.5, 135.8, 135.1, 128.7, 128.6,

128.3, 108.9, 60.2, 42.5, 20.8, 14.5; MS (APCI) m/z: [M^++1], 290.1; HRMS (APCI), Cacld for $C_{16}H_{20}NO_4$[M+1]: 290.1387, found: 290.1388



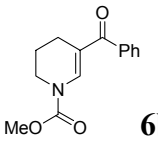
3e

^{1}H NMR (360MHz, $CDCl_3$) δ 7.97 (s, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.52 (m, 2H), 2.27 (t, *J* = 6.1 Hz, 2H), 1.80 (m, 2H), 1.49 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (90MHz, $CDCl_3$) δ 167.9, 60.1, 28.4, 21.1, 14.6; MS (APCI) m/z: [M^++1], 256.2; HRMS (APCI), Cacld for $C_{13}H_{22}NO_4$[M+1]: 256.1543, found: 256.1541



3f

^{1}H NMR (400MHz, $CDCl_3$) δ 8.21 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.60 (m, 2H), 2.29 (dt, *J* = 1.3, 6.1 Hz, 2H), 1.80 (m, 2H), 1.32 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 177.0, 167.7, 136.9, 108.3, 60.3, 42.5, 39.9, 28.7, 21.5, 21.1, 14.6; MS (APCI) m/z: [M^++1], 240.2



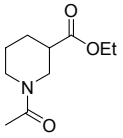
6b

^{1}H NMR (300MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.57-7.53 (m, 2H), 7.49-7.37 (m, 3H), 3.76 (s, 3H), 3.66 (t, *J* = 5.8 Hz, 2H), 2.49 (t, *J* = 6.1, 2H), 1.90 (m, 2H); MS (APCI) m/z: [M^++1], 246.1; HRMS (APCI), Cacld for $C_{14}H_{16}NO_3$[M+1]: 246.1125, found: 246.1116

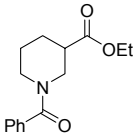
General Procedure for Asymmetric Hydrogenation of Vinylogous Amides

To a solution of vinylogous amide substrate (0.2 mmol) in methylene chloride (3.0 mL) in a glovebox was added [Rh((*S,S,R,R*)-TangPhos)NBD][SbF_6] (0.004 mmol). The

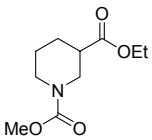
hydrogenation was performed at 80 °C under 1500 psi of hydrogen pressure for 72 h in autoclave. After the hydrogen was released, the reaction mixture was passed through a short silica gel column to remove the catalyst. The *R* configuration was assigned by comparing with (*S*)-nipecotic acid ethyl ester. Enantiomeric excesses were determined by HPLC by using Chiralcel AD and OJ-H columns (1 mL/min, Hexane: *i*PrOH = 95:5).



GC: Chiral select 1000, 140 °C, 2.0 mL/min, t_1=12.43, t_2=12.90 min

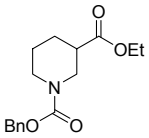


^{1}H NMR (360MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 4.70-4.20 (br, 1H), 4.07 (br, 2H), 3.90-3.50 (br, 1H), 3.40-3.05 (br, 1H), 3.00 (dt, *J* = 3.0, 13.4 Hz, 1H), 2.65-2.30 (br, 1H), 2.06 (m, 1H), 1.72-1.64 (m, 2H), 1.60-1.35 (br, 1H), 1.30-1.10 (br, 3H); ^{13}C NMR (90MHz, $CDCl_3$) δ 173.1, 170.7, 136.1, 129.7, 128.6, 127.0, 60.8, 48.1, 44.1, 41.6, 27.6, 24.9, 14.2; MS (APCI) m/z: [M^++1], 262.1; HRMS (APCI), Cacld for $C_{15}H_{20}NO_3$[M+1]: 262.1438, found: 262.1446; HPLC: Chiralcel AD, t_1=24.0, t_2=27.4 min (1 mL/min, Hexane: *i*PrOH = 95:5).

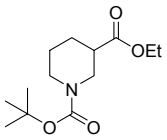


^{1}H NMR (360MHz, $CDCl_3$) δ 4.12 (dq, *J* = 1.8, 7.1 Hz, 2H), 3.93 (d, *J* = 11.4 Hz, 1H), 3.67 (s, 3H), 3.01 (s, 1H), 2.84 (t, *J* = 11.8 Hz, 1H), 2.42 (m, 1H), 2.03 (m, 1H), 1.90 (s, 1H), 1.71-1.55 (m, 2H), 1.47 (m, 1H), 1.23 (dt, *J* = 1.9, 7.1 Hz, 3H); ^{13}C NMR (90MHz, $CDCl_3$) δ 173.4, 156.0, 60.7, 52.8, 45.9, 44.3, 41.5, 27.4, 24.4, 14.3; MS (APCI) m/z:

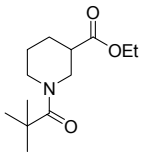
[M^++1], 216.1; HRMS (APCI), Cacld for $C_{10}H_{18}NO_4$[M+1]: 216.1230, found: 216.1228; HPLC: Chiralcel AD, t_1=7.2, t_2=8.3 min (1 mL/min, Hexane: *i*PrOH = 95:5).



^{1}H NMR (360MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H), 5.14 (s, 2H), 4.24 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.96 (d, *J* = 14.3 Hz, 1H), 3.10 (s, 1H), 2.95-2.87 (m, 1H), 2.46 (m, 1H), 2.05 (m, 1H), 1.74-1.58 (m, 2H), 1.50 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (90MHz, $CDCl_3$) δ 173.4, 155.4, 137.0, 128.7, 128.2, 128.0, 67.3, 60.7, 46.0, 44.4, 41.6, 27.4, 24.4, 14.3; MS (APCI) m/z: [M^++1], 292.2; HRMS (APCI), Cacld for $C_{16}H_{22}NO_4$[M+1]: 292.1543, found: 292.1535; HPLC: Chiralcel AD, t_1=10.3, t_2=11.0 min (1 mL/min, Hexane: *i*PrOH = 95:5).



^{1}H NMR (360MHz, $CDCl_3$) δ 4.11 (d, *J* = 7.1 Hz, 2H), 4.14-4.08 (m, 1H), 3.89 (d, *J* = 13.2 Hz, 1H), 2.95 (s, 1H), 2.82-2.74 (m, 1H), 2.44-2.36 (m, 1H), 2.01 (dd, *J* = 3.6, 13.0 Hz, 1H), 1.71-1.53 (m, 2H), 1.50-1.38 (m, 1H), 1.44 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (90MHz, $CDCl_3$) δ 173.6, 154.8, 79.8, 60.6, 45.9, 44.2, 41.6, 28.6, 27.5, 24.5, 14.3; MS (APCI) m/z: [M^++1], 258.2; HRMS (APCI), Cacld for $C_{13}H_{24}NO_4$[M+1]: 258.1700, found: 258.1717; HPLC: Chiralcel AD, t_1=4.7, t_2=5.3 min (1 mL/min, Hexane: *i*PrOH = 95:5).



^{1}H NMR (360MHz, $CDCl_3$) δ 4.49 (d, *J* = 13.4 Hz, 1H), 4.28 (d, *J* = 13.3 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 1H), 2.92 (dd, *J* = 11.1, 13.1 Hz, 1H), 2.80 (t, *J* = 12.6 Hz, 1H), 2.44-2.38 (m, 1H), 2.08 (d, *J* = 13.0 Hz, 1H), 1.78-1.62 (m, 2H), 1.52-1.38 (m, 1H), 1.26 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (90MHz, $CDCl_3$) δ 176.6, 173.4, 60.7, 47.2, 45.8, 42.0, 39.0, 28.5, 27.7, 27.3, 24.9, 14.3; MS (APCI) m/z: [M^++1], 242.2; HRMS (APCI), Cacld for $C_{13}H_{24}NO_3$[M+1]: 242.1751, found: 242.1768; HPLC: Chiralcel AD, t_1=6.8, t_2=7.9 min (1 mL/min, Hexane: *i*PrOH = 95:5).