Catalytic Asymmetric Three-Component Acyl-Strecker Reaction

Subhas Chandra Pan and Benjamin List*

Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim an der Ruhr, Germany,

list@mpi-muelheim.mpg.de

Supporting Information

General: Reactions were monitored by thin layer chromatography using 0.25 mm E. Merck silica gel coated glass plates (60F-254) using UV light to visualize the course of reaction. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040–0.063 mm). Chemical yields refer to pure isolated substances. ^1H and ^{13}C NMR spectra were obtained using either a Bruker DPX-300 or AV-400 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet).

Preparation of Catalyst

Catalyst **5** was prepared according to the procedure reported by Jacobsen *et al.*¹

General experimental procedure for the catalytic asymmetric three-component acyl-Strecker reaction

Aldehyde **2** (0.5 mmol), amine **3** (0.5 mmol), and MS 5Å (150 mg) were placed into a dry Schlenk flask. Dry dichloromethane (2 ml) was added and the mixture was stirred for 2 h at rt. Then catalyst **5** (5 mol%) was added and the flask was cooled to -40 °C and the mixture was stirred for 10 min. Acylcyanide **1** (0.75 mmol, 1.5 equiv) was added and the mixture was stirred for 36-50 h at -40 °C. The mixture was directly subjected to silica gel column chromatography to give pure product **4**.

1. Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012-10014.

(**4a**): Compound **4a** was isolated in 94% yield after silica gel column chromatography (30% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.44-7.38 (m, 5H), 7.31-7.24 (m, 3H), 7.14-7.07 (m, 3H), 4.58 (d, $J = 17.6$ Hz, 1H), 4.49 (d, $J = 12.9$ Hz, 1H), 2.14 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 135.3, 131.9, 129.1, 128.8, 128.4, 127.4, 125.9, 116.1, 49.2, 48.3, 21.7; HRMS (EI) calcd for MH^+ 264.126062, found 264.126260; The enantiomeric ratio was determined to be 97.5:2.5 by chiral HPLC (ChiralPak AS-H column, 20% *i*-PrOH/heptane, 0.7 mL/min, 220 nm, t_R (major 23.3 min), t_R (minor 37.2 min)).

(**4b**): Compound **4b** was isolated in 88% yield after silica gel column chromatography (30% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.27-7.13 (m, 5H), 6.97 (d, $J = 7.3$ Hz, 3H), 6.80-6.76 (m, 1H), 4.45 (d, $J = 17.6$ Hz, 1H), 4.36 (d, $J = 17.4$ Hz, 2H), 3.71 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 160.0, 135.4, 128.9, 128.4, 127.3, 125.9, 123.8, 116.4, 114.2, 55.0, 49.0, 47.7, 21.7; HRMS (EI) calcd for MH^+ 294.137040, found 294.136826; The enantiomeric ratio was determined to be 96.5:3.5 by chiral HPLC (ChiralPak AS-H column, 30% *i*-PrOH/heptane, 0.7 mL/min, 220 nm, t_R (major 24.4 min), t_R (minor 35.6 min)).

(**4c**): Compound **4c** was isolated in 78% yield after silica gel column chromatography (25% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.27-7.14 (m, 7H), 7.00-6.95 (m, 3H), 7.20-7.11 (m, 4H), 7.03 (d, $J = 4.1$ Hz, 1H), 4.47 (d, $J = 17.5$ Hz, 1H), 4.40 (d, $J = 17.3$ Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 135.1, 134.9, 130.6, 128.9, 128.7, 128.5, 127.5, 125.9, 115.7, 49.4, 47.8, 21.6; HRMS (EI) calcd for MH^+ 298.087328, found 298.087290; The enantiomeric ratio was determined to be 96:4 by chiral HPLC (ChiralPak OJ-H column, 20% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (minor 24.9 min), t_R (major 28.8 min)).

(**4d**): Compound **4d** was isolated in 92% yield after silica gel column chromatography (20% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.88 (s, 1H), 7.75-7.73 (m, 3H), 7.45-7.43 (m, 2H), 7.32 (s, 1H), 7.19-7.10 (m, 4H), 6.98 (d, $J = 7.1$ Hz, 2H), 4.46 (d, $J = 17.6$ Hz, 1H), 4.36 (d, $J = 17.4$ Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 135.3, 133.0, 132.5, 129.2, 127.1, 126.7, 125.9, 124.2, 116.2, 49.2, 48.4, 21.7; HRMS (EI) calcd for MH^+

314.142044, found 314.141915; The enantiomeric ratio was determined to be 97:3 by chiral HPLC (ChiralPak OJ-H column, 30% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (minor 29.7 min), t_R (major 35.4 min).

(4e): Compound **4e** was isolated in 82% yield after silica gel column chromatography (35% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.28-7.11 (m, 10H), 6.77 (dd, $J = 1.5, 15.9$ Hz, 1H), 6.37 (d, $J = 4.6$ Hz, 1H), 5.84 (dd, $J = 5.4, 15.9$ Hz, 1H), 4.62 (d, $J = 17.4$ Hz, 1H), 4.49 (d, $J = 17.5$ Hz, 1H) 2.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.9, 135.8, 135.6, 134.5, 128.7, 128.5, 127.9, 127.5, 126.0, 119.4, 115.7, 49.2, 47.1, 21.5; HRMS (EI) calcd for MH^+ 290.141900, found 290.142060; The enantiomeric ratio was determined to be 96.5:3.5 by chiral HPLC (ChiralPak OJ-H column, 30% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (minor 26.3 min), t_R (major 34.2 min).

(4f): Compound **4f** was isolated in 92% yield after silica gel column chromatography (50% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.18 (m, 5H), 5.09 (d, $J = 9.7$ Hz, 1H), 4.65 (d, $J = 17.4$ Hz, 1H), 4.50 (d, $J = 17.4$ Hz, 1H), 2.16-2.05 (m, 1H), 2.00 (s, 3H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 135.6, 128.7, 127.6, 125.9, 117.0, 52.6, 50.6, 30.4, 21.8, 18.9, 18.5; HRMS (ESI) calcd for MNa^+ 253.130979, found 253.131132; The enantiomeric ratio was determined to be 96:4 by chiral HPLC (ChiralPak OJ-H column, 3% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (minor 36.5 min), t_R (major 38.8 min).

(4g): Compound **4g** was isolated in 46% yield after silica gel column chromatography (25% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.14 (m, 5H), 5.68 (br s, 1H), 4.77 (d, $J = 17.7$ Hz, 1H), 4.59 (d, $J = 17.7$ Hz, 1H), 1.89 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.0, 136.3, 128.7, 127.3, 125.3, 116.7, 55.0, 51.5, 37.4, 26.5, 22.1; HRMS (ESI) calcd for MNa^+ 267.146628, found 267.146781; The enantiomeric ratio was determined to be 97:3 by chiral HPLC (ChiralPak OJ-H column, 5% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 13.1 min), t_R (minor 16.0 min).

(4h): Compound **4h** was isolated in 75% yield after silica gel column chromatography (30% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ

7.33-7.17 (m, 5H), 5.42 (t, $J = 7.0$ Hz, 1H), 4.67 (d, $J = 17.5$ Hz, 1H), 4.52 (d, $J = 17.5$ Hz, 1H), 2.03 (s, 3H), 1.71-1.56 (m, 2H), 1.36-1.19 (m, 4H), 0.79 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.9, 135.8, 128.7, 127.6, 125.8, 117.6, 49.8, 46.1, 31.2, 27.5, 21.6, 21.5, 13.3; HRMS (ESI) calcd for MNa^+ 267.146579, found 267.146785; The enantiomeric ratio was determined to be 94:6 by chiral HPLC (ChiralPak OJ-H column, 3% *i*-PrOH/heptane, 0.7 mL/min, 220 nm, t_R (minor 42.7 min), t_R (major 45.5 min)).

(4i): Compound **4i** was isolated in 97% yield after silica gel column chromatography (30% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.18 (m, 5H), 5.35 (d, $J = 5.8$ Hz, 1H), 4.64 (d, $J = 17.4$ Hz, 1H), 4.51 (d, $J = 17.4$ Hz, 1H), 2.00 (s, 3H), 1.83 (dd, $J = 9.6, 13.9$ Hz, 1H), 1.43 (dd, $J = 4.0, 14.0$ Hz, 1H), 0.89 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.6, 135.7, 128.7, 127.6, 126.1, 118.8, 50.2, 45.5, 42.8, 29.9, 28.8, 21.7; HRMS (EI) calcd for MH^+ 258.173447, found 258.173211; The enantiomeric ratio was determined to be 96:4 by chiral HPLC (ChiralPak OJ-H column, 3% *i*-PrOH/heptane, 0.7 mL/min, 220 nm, t_R (major 28.2 min), t_R (minor 32.9 min)).

(4j): Compound **4j** was isolated in 95% yield after silica gel column chromatography (30% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.28 (m, 5H), 6.99 (s, 1H), 6.88 (d, $J = 8.0$ Hz, 2H), 6.73-6.69 (m, 2H), 4.42 (d, $J = 17.2$ Hz, 1H), 4.31 (d, $J = 17.0$ Hz, 1H), 3.68 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 158.8, 132.0, 129.0, 128.8, 128.5, 127.3, 127.1, 116.2, 113.8, 54.9, 48.8, 48.2, 21.7; HRMS (ESI) calcd for MNa^+ 317.125793, found 317.126045; The enantiomeric ratio was determined to be 97:3 by chiral HPLC (ChiralPak AS-H column, 20% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 24.6 min), t_R (minor 44.9 min)).

(4k): Compound **4k** was isolated in 93% yield after silica gel column chromatography (35% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.41-7.36 (m, 5H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.14 (s, 1H), 6.98 (d, $J = 8.1$ Hz, 2H), 4.55 (d, $J = 17.6$ Hz, 1H), 4.45 (d, $J = 17.4$ Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.0, 133.8, 133.2, 131.7, 129.2, 129.0, 128.6, 127.3, 116.0, 48.6, 48.2, 21.6; HRMS (ESI) calcd for MNa^+ 321.076391, found 321.076513; The enantiomeric ratio was determined to be 97.5:2.5 by chiral HPLC

(ChiralPak AS-H column, 20% *i*-PrOH/heptane, 0.7 mL/min, 220 nm, t_R (major 23.3 min), t_R (minor 39.3 min).

(4l): Compound **4l** was isolated in 92% yield after silica gel column chromatography (30% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.90-7.87 (m, 1H), 7.78 (d, $J = 8.2$ Hz, 2H), 7.56-7.51 (m, 2H), 7.47 (br s, 2H), 7.42 (t, $J = 7.5$ Hz, 1H), 7.36-7.34 (m, 3H), 7.28-7.23 (m, 2H), 5.10 (d, $J = 18.2$ Hz, 1H), 4.98 (d, $J = 18.0$ Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.6, 133.3, 131.9, 129.8, 129.0, 128.8, 128.7, 128.0, 127.3, 126.2, 125.7, 124.9, 122.8, 121.4, 116.0, 48.4, 46.9, 21.2; HRMS (ESI) calcd for MNa^+ 337.131117, found 337.131132; The enantiomeric ratio was determined to be 97:3 by chiral HPLC (ChiralPak AS-H column, 20% *i*-PrOH/heptane, 0.7 mL/min, 220 nm, t_R (major 35.5 min), t_R (minor 42.9 min).

(4m): Compound **4m** was isolated in 83% yield after silica gel column chromatography (40% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.27 (m, 5H), 7.21 (t, $J = 0.7$ Hz, 1H), 6.93 (s, 1H), 6.13 (d, $J = 2.5$ Hz, 1H), 5.87 (s, 1H), 4.40 (d, $J = 17.2$ Hz, 1H), 4.22 (d, $J = 17.1$ Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.9, 142.2, 131.5, 130.2, 128.9, 128.7, 127.9, 127.1, 110.2, 108.8, 47.5, 42.1, 21.3; HRMS (ESI) calcd for MNa^+ 277.095302, found 277.095314; The enantiomeric ratio was determined to be 90:10 by chiral HPLC (ChiralPak AS-H column, 20% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 16.4 min), t_R (minor 31.0 min).

(4n): Compound **4n** was isolated in 88% yield after silica gel column chromatography (30% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.32 (m, 5H), 6.98 (s, 1H), 5.57-7.47 (m, 1H), 5.05 (dd, $J = 11.4$ Hz, 13.3 Hz, 2H), 3.87-3.73 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 132.0, 131.9, 129.0, 128.8, 127.2, 117.7, 116.3, 48.0, 47.6, 21.2; HRMS (ESI) calcd for MNa^+ 237.099802, found 237.099833; The enantiomeric ratio was determined to be 94:6 by chiral HPLC (ChiralPak AS-H column, 20% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 11.3 min), t_R (minor 22.9 min).

(4o): Compound **4o** was isolated in 76% yield after silica gel column chromatography (25% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.32 (m, 5H), 6.95 (s, 1H), 3.22-3.14 (m, 1H), 3.11-3.03 (m, 1H), 2.15 (s, 3H), 1.58-1.54 (m, 1H), 1.18-1.03 (m, 5H), 0.74 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.3, 132.3, 128.9, 128.7, 127.0, 116.6, 47.3, 46.0, 28.6, 28.5, 21.6, 20.8, 13.4; HRMS (ESI) calcd for MNa^+ 357.193652, found 357.193728; The enantiomeric ratio was determined to be 87:13 by chiral HPLC (ChiralPak AS-H column, 20% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 8.3 min), t_R (minor 15.3 min).

(4p): Compound **4p** was isolated in 84% yield after silica gel column chromatography (10% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.31 (m, 2H), 7.29-7.26 (m, 3H), 7.21-7.13 (m, 3H), 7.06 (brs, 1H), 6.97 (d, $J = 6.9$ Hz, 2H), 4.49 (d, $J = 17.4$ Hz, 1H), 4.38 (d, $J = 17.4$ Hz, 1H), 2.22 (t, $J = 7.2$ Hz, 2H), 1.58-1.53 (m, 2H), 1.21-1.11 (m, 6H), 0.78 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 135.5, 132.1, 128.9, 128.8, 128.4, 127.3, 125.9, 116.2, 48.6, 48.4, 33.2, 31.1, 28.5, 24.6, 22.0, 13.6; The enantiomeric ratio was determined to be 94:6 by chiral HPLC (ChiralPak AS-H column, 10% *i*-PrOH/heptane, 0.7 mL/min, 220 nm, t_R (major 14.1 min), t_R (minor 20.1 min).

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	24.349	49.846
2	38.826	50.154
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	23.892	97.387
2	38.194	2.613
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	26.615	49.907
2	37.246	50.093
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	27.651	96.631
2	38.950	3.369
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	26.466	49.786
2	30.830	50.214
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	26.682	4.556
2	30.847	95.444
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	28.693	49.565
2	35.242	50.435
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	30.079	2.817
2	36.491	97.183
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	23.667	0.167
2	25.151	49.117
3	33.372	50.716
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	26.254	3.726
2	34.208	96.274
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	36.249	49.302
2	39.180	50.698
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	36.933	4.734
2	38.711	95.266
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	15.187	49.484
2	17.434	50.516
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	15.447	97.100
2	17.866	2.900
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	39.264	50.056
2	41.742	49.944
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	43.240	6.664
2	46.064	93.336
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	26.586	49.192
2	31.060	50.808
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	28.155	95.830
2	32.919	4.170
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	24.134	49.943
2	43.256	50.057
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	24.594	96.390
2	44.979	3.610
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	23.100	51.680
2	38.987	48.320
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	23.289	97.433
2	39.311	2.567
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	35.735	49.937
2	42.654	50.063
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	35.507	97.068
2	42.888	2.932
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	16.533	50.480
2	31.063	49.520
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	16.420	89.711
2	31.012	10.289
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	11.455	49.934
2	23.346	50.066
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	11.281	93.430
2	22.949	6.570
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	8.369	49.792
2	15.321	50.208
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	8.357	86.661
2	15.294	13.339
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	14.112	50.139
2	20.074	49.861
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	14.081	93.238
2	20.074	6.762
Total		100.000

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