Catalytic Asymmetric Transfer Hydrogenation of α -Ketoesters with Hantzsch Esters

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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).

Typical procedure for the preparation of Hantzsch ester [4b]:¹

A round-bottomed flask was charged with a mixture of neopentyl 3-oxobutanoate (14.00 g, 81.29 mmol), ammonium acetate (3.16 g, 40.65 mmol), hexamethylenetetramine (5.70 g, 40.65 mmol). The reaction mixture was heated to $100\text{ }^\circ\text{C}$ with stirring for 20 min, and then cooled to room temperature. The reaction mixture was quenched with H_2O and extracted with dichloromethane. The combined organic layer were dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel

(1) Torchy1, S.; Cordonnier1, G.; Barbry1, D.; Eynde, J. J. V. *Molecules* **2002**, 7, 528-533.

(10% ethyl acetate in hexane) to give Hantzsch ester **4b** (8.91 g, 65% yield) as pale yellowish solid.

^1H NMR (300 MHz, CDCl_3) δ 5.23 (brs, 1H), 3.70 (s, 4H), 3.31(s, 2H), 2.14 (s, 6H), 0.89 (s, 18H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 168.3, 145.4, 100.0, 73.6, 31.7, 26.9, 25.3, 19.3; HRMS (ESI) calcd for MNa^+ 360.21453, found 360.21448.

Typical procedure for the preparation of aliphatic substituted α -ketoester [*t*-butyl *t*-butylglyoxylate]:²

Trimethylpyruvic acid (5.00 g, 38.42 mmol)³ was dissolved in a mixture of THF (50 mL), *t*-BuOH (5.70 g, 76.84 mmol) and pyridine (7.60 g, 0.978 mmol). The mixture was cooled with stirring to -5 °C. MeSO_2Cl (5.28 g, 46.10 mmol) was added dropwise over 5 min. Precipitation of pyridinium salt began immediately. The suspension was stirred at room temperature overnight. The reaction mixture was quenched with H_2O and extracted with diethyl ether. The combined organic layer were dried over MgSO_4 , filtered and concentrated *in vacuo*. The residual oil was distilled under vacuum to afford corresponding product as colorless oil in 72% yield (5.14 g).

Typical procedure for the preparation of aromatic substituted α -ketoester [*t*-butyl 2-naphthoyl formate]:⁴

The *t*-butyl α -oxo-1*H*-imidazole-1-acetate (4.90 g, 24.97 mmol) was dissolved in THF (100 mL) under argon and cooled to -78 °C in a dry ice/acetone bath. The 2-naphthylmagnesium bromide solution (0.5 M in THF, 24.97 mmol) was added by dropping

(2) Hegarty, A. F.; O'Neill, P. *Synthesis* **1993**, 606-610.

(3) Koch, C.-J.; Šimonyiová, S.; Pabel, J.; Kärtner, A.; Polborn, K.; Wanner, K. T. *Eur. J. Org. Chem.* **2003**, 1244-1263.

(4) Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, 46, 211-213.

funnel over 15 min with stirring, and then the reaction mixture was warmed to room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with diethyl ether. The combined organic layer were dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexane) to give 2.88 g (45% yield) of corresponding product.

^1H NMR (300 MHz, CDCl_3) δ 7.90 (d, J = 8.1 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 6.6 Hz, 2H), 1.60 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 187.2, 164.1, 135.0, 132.9, 130.2, 129.2, 85.1, 28.4; HRMS (CI, isobutane) calcd for MH^+ 207.10157, found 207.10166.

^1H NMR (300 MHz, CDCl_3) δ 8.28 (d, J = 8.9 Hz, 2H), 8.11 (d, J = 8.9 Hz, 2H), 1.57 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 185.1, 162.5, 151.4, 137.5, 131.4, 124.3, 86.2, 28.4; HRMS (CI, isobutane) calcd for MH^+ 252.08695, found 252.08719.

^1H NMR (300 MHz, CDCl_3) δ 7.84 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 185.7, 163.4, 141.6, 131.5, 131.3, 129.9, 85.4, 28.4; HRMS (ESI) calcd for MNa^+ 263.04448, found 263.04454.

^1H NMR (300 MHz, CDCl_3) δ 7.86 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 186.5, 163.9, 145.9, 130.1, 130.0, 129.6, 84.5, 28.1, 21.9; HRMS (ESI) calcd for MNa^+ 243.09936, found 243.09916.

^1H NMR (300 MHz, CDCl_3) δ 7.86 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 3.80 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 185.8, 165.1, 164.4, 132.7, 125.9, 114.1, 84.8, 56.0, 28.4; HRMS (ESI) calcd for MNa^+ 259.09388, found 259.09407.

^1H NMR (300 MHz, CDCl_3) δ 8.41 (s, 1H), 7.95-7.78 (m, 4H), 7.58-7.45 (m, 2H), 1.59 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 187.2, 164.2, 136.6, 133.5, 132.7, 130.3, 130.2, 129.8, 129.3, 128.3, 127.5, 124.4, 85.2, 28.5; HRMS (ESI) calcd for MNa^+ 279.09919, found 279.09916.

^1H NMR (300 MHz, CDCl_3) δ 7.77-7.76 (m, 1H), 7.62-7.61 (m, 1H), 6.64-6.62 (m, 1H), 1.62 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 172.5, 160.6, 149.8, 149.2, 124.0, 112.9, 84.7, 27.9; HRMS (CI, isobutane) calcd for MH^+ 197.08125, found 197.08138.

^1H NMR (300 MHz, CDCl_3) δ 2.95 (brs, 1H), 1.90-1.70 (m, 5H), 1.55 (s, 9H), 1.37-1.23 (m, 5H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 198.5, 161.8, 83.8, 46.1, 27.9, 27.7, 25.5, 25.3; HRMS (CI, isobutane) calcd for MH^+ 213.14852, found 213.14881.

NMR spectra are in accordance with the literature.⁴

Table. Influence of the Hantzsch Ester

Reaction scheme: Ethyl phenylglyoxal (**1a**) reacts with Chiral Ligand **3f** (20 mol%), Cu(OTf)₂ (20 mol%), and Hantzsch Ester **4** (1.4 equiv) in CHCl₃ at room temperature to yield (S)-ethyl mandelate ((S)-**2a**).

entry	Hantzsch ester	R ₁	R ₂	R ₃	R ₄	time (h)	yield (%) ^a	<i>er</i> ^b
1	4a	Me	Me	CO ₂ Et	CO ₂ Et	7	90	91:9
2	4b	Me	Me	CO ₂ <i>i</i> Bu	CO ₂ <i>i</i> Bu	4	97	91:9
3	4c	Pr	Pr	CO ₂ Me	CO ₂ Me	4	90	90:10
4	4d	Me	Me	CO ₂ Me	CO ₂ <i>t</i> Bu	5	85	92:8
5	4e	Me	<i>i</i> Pr	CO ₂ Me	CO ₂ Me	48	<5	n.d

^aIsolated yield. ^bDetermined by chiral HPLC analysis on Chiralcel OD-H column.

General procedure for Cu(II)-Bisoxazoline-Catalyzed Asymmetric Transfer Hydrogenation of α -Ketoesters with Hantzsch Esters.

To a flame-dried Schlenk tube was added Cu(OTf)₂ (18.1 mg, 0.05 mmol) and [(*S,S*)-benzyl-box] **3f** (18.1 mg, 0.05 mmol). The mixture was dried under vacuum for 0.5 h and distilled anhydrous CHCl₃ (2.5 mL) was added. After stirring for 1 h, *t*-butyl benzoylformate **1d** (103.1 mg, 0.5 mmol) was added and the mixture was cooled to -25 °C. After addition of Hantzsch ester **4b** (216.6 mg, 0.7 mmol), the mixture was stirred under argon at the same temperature until disappearance of the starting material (48 h). After conclusion of the reaction, the mixture was washed using H₂O and the aqueous layer was extracted with CHCl₃. The organic layer was dried (MgSO₄), filtered, and concentrated *in vacuo* to yield the crude product as an off-white solid. Purification by column chromatography (15% EtOAc/hexanes) gave the pure product as a white solid (92.2 mg, 89%), identical in all respects to previously described *t*-butyl (*S*)-mandelate **2d**. [α]_D +90.7 (*c* 1.0, MeOH); [[α]_D +97.4 (*c* 1.0, MeOH), for >99:1 *e.r.*].⁵

^1H NMR (300 MHz, CDCl_3) δ 7.35-7.24 (m, 5H), 4.96 (d, $J = 5.9$ Hz, 1H), 3.49 (d, $J = 5.9$ Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.3, 139.3, 128.6, 128.5, 126.8, 83.4, 73.4, 28.2; HRMS (CI, isobutane) calcd for MH^+ 209.11777, found 209.11782; The enantiomeric ratio was determined to be 96:4 by chiral HPLC (Chiralcel OD-H column, 3% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 7.4 min), t_R (minor 18.0 min)).

^1H NMR (300 MHz, CDCl_3) δ 8.14 (d, $J = 8.7$ Hz, 2H), 7.56 (d, $J = 8.7$ Hz, 2H), 5.09 (d, $J = 5.1$ Hz, 1H), 3.69 (d, $J = 5.1$ Hz, 1H) 1.34 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 171.9, 148.1, 146.3, 127.6, 123.9, 84.6, 72.6, 28.1; HRMS (CI, isobutane) calcd for MH^+ 254.10290, found 254.10284; The enantiomeric ratio was determined to be 90:10 by chiral HPLC (Chiralcel OD-H column, 2% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 16.8 min), t_R (minor 18.4 min)).

^1H NMR (300 MHz, CDCl_3) δ 7.29-7.22 (m, 4H), 4.94 (d, $J = 5.0$ Hz, 1H), 3.51 (d, $J = 5.4$ Hz, 1H) 1.33 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 172.8, 137.8, 134.3, 128.9, 128.1, 83.8, 72.7, 28.2; HRMS (ESI) calcd for MNa^+ 265.06009, found 265.06019; The enantiomeric ratio was determined to be 94:6 by chiral HPLC (Chiralcel OD-H column, 3% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 13.1 min), t_R (minor 14.1 min)).

^1H NMR (300 MHz, CDCl_3) δ 7.20 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 8.0$ Hz, 2H), 4.92 (s, 1H), 3.35 (brs, 1H), 2.26 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.4, 138.1, 136.4, 129.5, 126.6, 83.3, 73.2, 28.2, 21.5; HRMS (ESI) calcd for MNa^+ 245.11482, found 245.11478; The enantiomeric ratio was determined to be 96:4 by chiral

HPLC (Chiralcel OD-H column, 3% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 6.8 min), t_R (minor 13.3 min).

^1H NMR (300 MHz, CDCl_3) δ 7.24 (d, $J = 8.7$ Hz, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 4.91 (d, $J = 4.8$ Hz, 1H), 3.73 (s, 3H), 3.36 (d, $J = 4.8$ Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.5, 159.8, 131.6, 128.0, 114.2, 83.3, 72.9, 55.6, 28.2; HRMS (ESI) calcd for MNa^+ 261.10973, found 261.10984; The enantiomeric ratio was determined to be 97:3 by chiral HPLC (Chiralcel OD-H column, 3% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 9.4 min), t_R (minor 22.9 min).

^1H NMR (300 MHz, CDCl_3) δ 7.82 (s, 1H), 7.82-7.74 (m, 3H), 7.45-7.39 (m, 3H), 5.13 (d, $J = 5.6$ Hz, 1H), 3.57 (d, $J = 5.7$ Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.2, 136.7, 133.6, 133.5, 128.6, 128.5, 128.0, 126.6, 126.5, 126.0, 124.5, 83.6, 73.5, 28.2; HRMS (ESI) calcd for MNa^+ 281.11481, found 281.11462; The enantiomeric ratio was determined to be 97:3 by chiral HPLC (Chiralcel OD-H column, 3% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 11.3 min), t_R (minor 13.9 min).

^1H NMR (300 MHz, CDCl_3) δ 7.39-7.38 (m, 1H), 6.36-6.32 (m, 2H), 5.05 (s, 1H), 3.38 (brs, 1H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 170.6, 151.6, 142.7, 110.4, 108.1, 83.5, 67.1, 27.8; HRMS (CI, isobutane) calcd for MH^+ 199.09696, found 199.09703; The enantiomeric ratio was determined to be 97:3 by chiral HPLC (Chiralcel OD-H column, 3% *i*-PrOH/heptane, 1.0 mL/min, 220 nm, t_R (major 9.0 min), t_R (minor 10.2 min).

^1H NMR (300 MHz, CDCl_3) δ 3.88 (d, $J = 2.3$ Hz, 1H), 2.62 (brs, 1H), 1.78-1.76 (m, 2H), 1.67-1.64 (m, 3H), 1.49 (s, 9H), 1.45-1.44 (m, 1H), 1.99-1.12 (m, 5H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 174.1, 82.3, 74.8, 42.0, 29.1, 28.1, 26.2, 26.1; HRMS (ESI) calcd for MNa^+ 237.14600, found 237.14611; The enantiomeric ratio was determined to be 90:10 by chiral GC analysis [diethyl *tert*-butyl β -cyclodex, 60 $^\circ\text{C}$ /1 min, 130 $^\circ\text{C}$ /20 min, 220 $^\circ\text{C}$ /10 min, and 320 $^\circ\text{C}$ /isothermal, 0.6 bar, t_{R} (major 63.4 min), t_{R} (minor 64.4 min)].

^1H NMR (300 MHz, CDCl_3) δ 3.67 (s, 1H), 2.84 (brs, 1H), 1.50 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 173.7, 82.5, 78.4, 35.3, 28.1, 25.9; HRMS (CI, isobutane) calcd for MH^+ 189.14911, found 189.14907; The enantiomeric ratio was determined to be 92:8 by chiral GC analysis [diethyl *tert*-butyl β -cyclodex, 60 $^\circ\text{C}$ /1 min, 86 $^\circ\text{C}$ /6 min, 220 $^\circ\text{C}$ /5 min, and 320 $^\circ\text{C}$ /isothermal, 0.6 bar, t_{R} (major 24.7 min), t_{R} (minor 25.0 min)].

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	18.009	49.859
2	39.197	50.141
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	18.046	89.632
2	39.408	10.368
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	7.411	50.034
2	18.019	49.966
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	7.233	95.963
2	16.097	4.037
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	16.892	49.877
2	18.421	50.123
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	16.712	89.898
2	18.473	10.102
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	13.094	49.945
2	14.087	50.055
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	13.074	94.449
2	14.078	5.551
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	6.872	50.221
2	13.397	49.779
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	6.880	95.538
2	13.477	4.462
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	9.459	50.050
2	22.932	49.950
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	9.470	96.350
2	23.009	3.650
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	11.340	50.021
2	13.919	49.979
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	11.346	97.432
2	13.947	2.568
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	9.033	50.276
2	10.296	49.724
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	9.011	97.463
2	10.282	2.537
Total		100.000

No.	min.	area-%
8	63.43	50.0
9	64.45	50.0

No.	min.	area-%
12	63.47	90.6
13	64.53	9.43

No.	min.	area-%
9	24.70	49.7
10	25.09	50.3

No.	min.	area-%
12	23.27	92.0
13	23.64	8.04