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Catalytic Asymmetric Direct Mannich Reactions of Carbonyl Compounds with a-Imino Esters**

Karsten Juhl, Nicholas Gathergood, and Karl Anker Jørgensen*

Experimental Section

General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm down field to TMS (δ=0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.3) for ^{13}C NMR. Solvents were dried according to standard procedures. Purification of reactions products was carried out by flash chromatography (FC) using Merck silica gel 60 (230-400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products were determined by HPLC using a Daicel Chiralpak AD column.

Materials.

2,2'-isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline], methylenebis[(4R,5S)-4,5-diphenyl-2-oxazoline], 2,2'-isopropylidenebis[(4R)-4-phenyl-2-oxazoline], $Cu(OTf)_2$,

2-oxo-butyric acid, ethyl pyruvate **1a**, ethyl 2-oxo-4-phenylbutyrate **1c**, di-*tert*-butyldicarbonate, *N*,*N*-dimethyl-4-aminopyridine and Mg-powder were purchased from Aldrich and used as recieved. Ethyl bromopyruvate **1d** was purchased from Acros in 80% pure form and used as recieved. (*R*)-Tol-BINAP was purchased from Lancaster and used as recieved. N-tosyl-α-ester **2**[1] and $CuPF_6$[2] were preparred by litterature procedures. Ethyl 2-oxo-butyrate **1b** was preparred by refuxing 2-oxo-butyric acid in ethanol in the precense of a catalytic amount of HCl followed by destillation.

General Procedure for Catalytic Asymmetric Mannich-type reaction: In an oven dried Schlenk tube equipped with a magnetic stirrer bar, $Cu(OTf)_2$ (9 mg, 0.025 mmol) and 2,2-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline] (9 mg, 0.027 mmol) were added. The mixture was stirred under vacuum for 2h and filled with Ar. Dry CH_2Cl_2 (1 mL) was added and the solution was stirred for 2h. 1.5 mL of a 0.25 M CH_2Cl_2 solution of the imine (0.375 mmol) were added followed by the addition of 0.25 mmol of the ethyl pyruvate derivative. After 40h the reaction mixture was filtered through a plug of silica using 30% EtOAc in CH_2Cl_2 as the eluent. Evaporation of the solvents *in-vacuo* afforded the crude product, which was purified by FC to give the diethyl-*N*-tosyl-4-oxo-glutamic acid ester.

Compound 3a: $[\alpha]^{rt}_D$=-29.6° (*c*=0.01 g/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2, 2H, ArH), 7.29 (d, *J* = 8.2 Hz, 2H, ArH), 5.53 (d, *J* = 7.4 Hz, 1H, NH), 4.42 (dt, *J* = 7.4, 4.8 Hz, 1H, CH), 4.31 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.04 (q, *J* = 7.1, 2H, OCH_2), 3.43 (d, *J* = 4.8 Hz, 2H, CH_2), 2.41 (s, 3H), 1.36 (t, *J* = 7.1, 3H, CH_3), 1.11 (t, *J* = 7.1, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 169.8, 159.9, 144.1, 136.6, 130.0, 127.5, 63.2, 62.7, 51.4, 43.2, 21.8, 14.2, 14.0; HRMS $C_{16}H_{21}NO_7S$ $[M+Na]^+$ calculated 394.0936; found 394.0940.

Compound 3b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0, 2H, ArH), 7.30 (d, *J* = 8.0 Hz, 2H, ArH), 5.55 (d, *J* = 8.8 Hz, 1H, NH), 4.60 (dd, *J* = 8.8, 5.6 Hz, 1H, CHN), 4.36 (dq, *J* = 7.2, 2.0 Hz, 2H, OCH_2), 4.00 (dq, *J* = 7.2, 2.0, 2H, OCH_2), 3.69 (dq, *J* = 6.4, 5.6, 1H, CHMe), 2.42 (s, 3H), 1.40 (t, *J* = 7.2, 3H, CH_3), 1.14 (d, *J* = 6.4, 3H, CH_3), 1.09 (t, *J* = 7.2, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 169.8, 160.3, 144.1, 136.5, 130.4, 128.0, 63.0, 62.7, 56.5, 45.4, 21.8, 14.2, 14.1, 11.1; HRMS $C_{17}H_{23}NO_7S$ $[M+Na]^+$ calculated 408.1093; found 408.1094.

Compound 3c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0, 2H, ArH), 7.20 (m, 5H, ArH), 7.08 (d, *J* = 8.0, 2H, ArH), 5.40 (d, *J* = 7.9 Hz, 1H, NH), 4.27 (dd, *J* = 7.9, 5.2 Hz, 1H, CH), 4.18 (m, 2H, CH_2), 4.00 (m, 1H, CH), 3.88 (m, 2H, CH_2), 3.08 (dd, *J* = 14.0, 8.2 Hz, 1H, BnCH), 2.85

(dd, *J* = 14.0, 6.9 Hz, 1H, BnCH), 2.32 (s, 3H), 1.24 (dt, *J* = 7.1, 0.9, 3H, CH_3), 1.03 (dt, *J* = 7.1, 0.9, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 169.7, 160.1, 144.1, 137.6, 136.1, 129.9, 129.5, 128.8, 127.6, 127.0, 63.0, 62.8, 55.7, 53.1, 21.8, 14.1, 14.0; HRMS $C_{23}H_{27}NO_7S$ $[M+Na]^+$ calculated 484.1406; found 484.1404.

Compound 3d: HRMS $C_{16}H_{20}BrNO_7S$ $[M+Na]^+$ calculated 472.0042; found 472.0042. The enantiomeric excess of **3b** was determined by reduction of the compound to **3a**. Comnpound **3a** was formed by reaction of **3d** with MgI_2, followed by reduction with $NaHSO_3$.

Representative Procedure for Enantio- and Diastereoselective Formation of *N*-tosyl-4-amino-5-oxo-tetrahydro-furan-2-carboxylic acid ethyl esters: In an oven dried Schlenk tube equipped with a magnetic stirrer bar, $Cu(OTf)_2$ (41 mg, 0.1125 mmol) and 2,2-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline] (40 mg, 0.118 mmol) were added. The mixture was stirred under vacuum for 2h and filled with Ar. Dry CH_2Cl_2 (4 mL) was added and the solution was stirred for 2h. 430 mg of the imine (1.68 mmol) was added followed by the addition of 143 mL (1.125 mmol) of ethyl 2-oxo-butanoic acid ester. After 40h the reaction mixture was filtered through a plug of silica using 30% EtOAc in CH_2Cl_2 as the eluent. Evaporation of the solvents *in-vacuo* afforded the crude product. The crude product from the Mannich reaction was

added to a Schlenk tube equipped with a magnetic stirrer bar. The Schlenk tube was evacuated and filled with Ar. Dry THF (5 mL) was added, and the solution was cooled to –78°C. 1.3 mL of a 1 M THF solution of L-Selectride was added, and the solution was stirred for 90 minutes. The reaction mixture was then poured into 20 mL of 1 N HCl and extracted with CH_2Cl_2. Evaporation of the solvents *in-vacuo* afforded the crude alcohol, which after treatment with PTSA (cat) in toluene at 70°C for 4h gave the lactone, which was purified by FC.

Compound 8b: $[\alpha]^{rt}_D$=-19.9° (*c*=0.01 g/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4, 2H, ArH), d = 7.33 (d, *J* = 8.4, 2H, ArH),5.08 (d, *J* = 7.3 Hz, 1H, NH), 4.38 (d, *J* = 9.5 Hz, 1H, CHCOOEt), 4.28 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.75 (dd, *J* = 7.3, 10.5 Hz, 1H, CHN), 2.45 (m, 1H, CHMe), 2.43 (s, 3H, CH_3), 1.40 (d, *J* = 6.6, 3H, CH_3), 1.31 (t, *J* = 7.1, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 168.3, 144.2, 137.1, 130.0, 127.5, 79.1, 62.6, 58.9, 42.4, 21.8, 15.0, 14.3.HRMS $C_{15}H_{19}NO_6S[M+Na]^+$ calculated 364.0831; found 364.0895.

Compound 8c: $[\alpha]^{rt}_D$=-48.7° (*c*=0.01 g/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0, 2H, ArH), 7.18-7.27 (m, 7H, ArH), 5.40 (d, *J* = 6.6 Hz, 1H, NH), 4.41 (d, *J* = 8.4 Hz, 1H, CHCOOEt), 4.04 (m, 1H, CHN), 3.92 (m, 2H, CH_2), 3.14 (m, 1H, CHBn), 2.84 (m, 2H, CH_2Ph), 2.34 (s, 3H), 1.12 (t, *J* = 7.1, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 172.2, 168.7, 144.3, 137.0, 135.8, 130.1, 130.0, 129.0, 127.6, 127.5, 77.2, 62.7, 55.8, 47.5, 34.6, 21.8, 14.1. HRMS $C_{21}H_{23}NO_6S[M+Na]^+$ calculated 440.1144; found 440.1149.

Boc-protection of lactone 8b. 50 mg (0.15 mmol) of lactone **8b** is placed in a flask which evacuated and filled with Ar. 5 mL HPLC-grade MeCN is added followed by 0.2 equiv DMAP and 1.5 equivalent di-*tert*-butyldicarbonate. The solution is stirred at room temperature over night. The solvent is removed *in-vacuo*. The crude is redissolved in ether and extracted twice with 0.2 M citric acid and once with saturated $NaHCO_3$. The crude is filtered through a plug of silica and transferred to a Schlenk flask after removal of the solvent *in-vacuo*. Lactone **9** is obtained as white crystals in 98% yield (63 mg) after FC.

Compound 9: $[\alpha]^{rt}_D$=-61.6° (*c*=0.01 g/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0, 2H, ArH), d = 7.27 (d, *J* = 8.0, 2H, ArH), 4.93 (d, *J* = 10.8 Hz, 1H, CHN), 4.41 (d, *J* = 9.6 Hz, 1H, CHCOOEt), 4.24 (q, *J* = 7.2 Hz, 2H, CH_2), 2.98 (m, 1H, CHMe) , 2.37 (s, 3H, CH_3), 1.41 (d, *J* = 6.4, 3H, CH_3), 1.26 (t, *J* = 7.2, 3H, CH_3), 1.24 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.0, 149.2, 145.0, 136.3, 130.2, 129.3, 128.6, 128.1, 86.8, 79.6, 79.0, 62.4, 38.8, 27.9, 21.3, 15.8, 14.4. HRMS $C_{20}H_{27}NO_8S[M+Na]^+$ calculated 464.1355; found 464.1367.

Detosylation of aminolactone 9. 90 mg (0.2 mmol) of lactone **9** is transferred to an oven dried Schlenk tube equipped with a magnetic stirrer bar. The Schlenk flask is evacuated and filled with Ar and then charged with 1.5 mL of dry MeOH followed by the addition of 5 equiv of Mg. The reaction mixture is sonicated for 45 min and then poured into 1M HCL and extracted with ether. The organic phase is washed with saturated $NaHCO_3$ and brine. The solvent is removed *in-vacuo* and 41 mg of **10** (71%) is obtained after FC.

Compound **10**: $[\alpha]^{rt}_D$=-9.1 (*c*=0.01 g/mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (d, *J* = 8.0, 1H, NH), 4.44 (d, *J* = 10.0, 1H, CHCOOEt), 4.21 (dd, *J* = 8.0, 10.8 Hz, 1H, CHN), 2.45 (m, 1H, CHMe), 3.81 (s, 3H, OCH_3), 1.34 (d, *J* = 6.8, 3H, CH_3), 1.43 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 168.9, 155.7, 81.0, 79.2, 56.9, 53.2, 42.7, 28.5, 15.4. HRMS $C_{12}H_{19}NO_6$ $[M+Na]^+$ calculated 296.1110; found 296.1115.

References.

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