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Catalytic Enantioselective Addition of Nitro Compounds to Imines - A Simple Approach for the Synthesis of Optically Active b-Nitro-a-Amino Esters

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General: All reactions except for one (Table 1, entry 13) were carried out under N_2 using anhydrous solvents and flame-dried glassware. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Purification of the products was performed by flash column chromatography (FC) using Merck silica gel 60 (230-400 mesh). TLC was carried out using Merck silica gel 60 F_{254} plates and visualised with UV irradiation. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as the solvent, and are reported in ppm downfield from TMS (δ = 0) for ^{1}H NMR and relative to central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR. NMR conversions (Table 1) were calculated based on the integral value of $Cl_2CHCHCl_2$ as the internal standard. The enantiomeric excess (ee) of the products was determined by HPLC using Daicel Chiralcel OD and AS

columns. Diastereomeric ratio (dr) was also determined by HPLC, and this value was confirmed to be same with that calculated from NMR.

Materials: All ligands, metals and nitroalkanes, except for some compounds shown below, were obtained from commercial sources. $Cu(SbF_6)_2$ was prepared from $CuBr_2$ and $AgSbF_6$ in CH_2Cl_2, and the solution was used for the reaction after filtration through celite.

***N*-(*p*-Methoxyphenyl)-a-imino ester 1** was quantitatively synthesized by mixing ethyl glyoxylate (6.6 g, 65 mmol) and *p*-methoxyaniline (7.9 g, 65 mmol) in CH_2Cl_2 (20 mL) in the presence of molecular sieves 4 Å at room temperature (rt) for 1 day. After filtration, the solution was concentrated to afford almost pure **1**. Further purification was achieved by FC on silica gel using CH_2Cl_2 as the eluent.

2-Phenyl-1-nitroethane 2e was obtained by reduction of β-nitrostyrene (2.09 g, 14 mmol) with $NaBH_4$ (1.56 g, 42 mmol) in a mixed solvent ($CHCl_3$/*i*-PrOH = 4/1, 200 mL) in the presence of silica gel (20 g) at rt for 1 day. After filtration of insoluble materials, the filtrate was concentrated to afford almost pure **2e** in 92% yield. It was used for reaction without further purification.

a-Nitrotoluene 2f was prepared by the reaction of BnBr

(1.2 mL, 10 mmol) with $AgNO_2$(1.54 g, 10 mmol). A solution of these reagents in Et_2O (30 mL) was stirred at rt for 1 day. After filtration of insoluble materials, the filtrate was concentrated to afford crude **2f** in a quantitative yield. Further purification was performed by FC on silica gel using pentane as the eluent.

Typical Procedure for the Reaction under N_2: In a flame dried Schlenk tube $Cu(OTf)_2$ (14.4 mg, 0.04 mmol) and Ph-BOX (*R*)-**6** (14.7 mg, 0.044 mmol) were dried under reduced pressure for 0.5 h. The mixture was dissolved in CH_2Cl_2 (2 mL), and the solution was stirred at rt for 1 h. To the solution, were added imine **1** (38 μL, 0.2 mmol), NEt_3 (5.6 μL, 0.04 mmol) and nitropropane (27 μL, 0.3 mmol). The resultant solution was stirred at rt for 1 day and then the reaction was quenched with EtOH (0.5 mL). The catalyst was removed by filtration through silica gel, and the reaction mixture was concentrated. The residue was subjected to FC on silica gel using pentane/CH_2Cl_2 (1/1) as the eluent to give the β-nitro-α-amino ester **3a**. The diastereo- and enantioselectivity were determined by HPLC using OD column (hexane/*i*-PrOH (97/3), 0.5 mL/min). Reactions using other nitroalkanes were conducted similarly.

Ethyl 2-(4-Methoxyphenyl)amino-3-nitropentanoate 3a: ^1H NMR (400 MHz, $CDCl_3$, TMS) Diastereomer A δ 0.97 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.20 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.3-

1.9 (br, 1H), 1.93 (ddq, *J* = 14.8, 7.2, 4.0 Hz, 1H), 2.16 (ddq, *J* = 14.8, 10.0 , 7.2 Hz, 1H), 3.68 (s, 3H), 4.13 (dq, *J* = 11.2, 7.2 Hz, 1H), 4.18 (dq, *J* = 11.2, 7.2 Hz, 1H), 4.41 (d, *J* = 5.6 Hz, 1H), 4.65 (ddd, *J* = 10.0, 5.6, 4.0 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H); Diastereomer B δ 1.04 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.24 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.4 –1.7 (br, 1H), 1.87 (ddq, *J* = 14.8, 7.2, 4.8 Hz, 1H), 2.15 (ddq, *J* = 14.8, 9.6, 7.2 Hz, 1H), 3.74 (s, 3H), 4.17 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.22 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.40 (d, *J* = 6.4, 1H), 4.73 (ddd, *J* = 9.6, 6.4, 4.8 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) Diastereomer A δ 170.0, 153.7, 139.6, 116.2, 114.9, 90.3, 62.4, 60.7, 55.6, 23.1, 14.0, 10.6; MS (TOF ES$^+$): m/z 319 $(M+Na)^+$; HRMS calcd. for $C_{14}H_{20}N_2O_5Na$ 319.1270, found 319.1263.

Reactions at Ambient Conditions: Glassware and CH_2Cl_2 were used without drying. A mixture of $Cu(OTf)_2$ and the chiral BOX ligand (*R*)-**6a** was used without precautions. The remaining procedure was as above.

Ethyl 2-(4-Methoxyphenyl)amino-3-nitropropanoate 3b: According to the generel procedure, imine **1** was subjected to reaction with $MeNO_2$ and **3b** was isolated by FC on silica gel using pentane/CH_2Cl_2 (1/3) as a yellow solid. The ee was determined by HPLC using OD column (hexane/*i*-PrOH (80/20), flow rate 0.7 mL/min). ^{1}H NMR

(400 MHz, $CDCl_3$, TMS) δ 1.29 (dd, *J* = 7.2, 7.2 Hz, 3H), 3.75 (s, 3H), 4.26 (dq, *J* = 7.2, 3.6 Hz, 1H), 4.29 (dq, *J* = 7.2, 3.6 Hz, 1H), 4.77 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.83 (dd, *J* = 13.6, 4.8 Hz, 1H), 4.96 (dd, *J* = 13.6, 4.8 Hz, 1H), 6.67 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 153.9, 139.4, 116.2, 115.2, 76.1, 62.8, 56.6, 55.9, 14.3; MS (TOF ES^+): m/z 291 $(M+Na)^+$; HRMS calc. for $C_{12}H_{16}N_2O_5$ 291.0957, found 291.0957.

Ethyl 2-(4-Methoxyphenyl)amino-3-nitrobutanoate 3c: According to the generel procedure, imine **1** was subjected to reaction with $EtNO_2$, and **3c** was isolated by FC on silica gel using pentane/CH_2Cl_2 (1/1) as a yellow oil. The ee was determined by HPLC using OD column (hexane/*i*-PrOH (97/3), flow rate 0.5 mL/min). ^1H NMR (400 MHz, $CDCl_3$, TMS) Diastereomer A δ 1.27 (dd, *J* = 7.2, 7.2 Hz, 3H), 1.61 (d, *J* = 7.2 Hz, 3H), 3.73 (s, 3H), 4.0-4.15 (bs, 1H), 4.21 (dq, *J* = 11.2, 7.2 Hz, 1H), 4.23 (dq, *J* = 11.2, 7.2 Hz, 1H), 4.66 (d, *J* = 4.4 Hz, 1H), 4.91 (dq, *J* = 7.2, 4.4 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (a mixture of diastereomers) δ 170.1, 170.0, 153.8, 153.5, 139.8, 139.7, 116.8, 115.9, 114.9, 114.8, 82.8, 82.7, 62.4, 62.3, 62.0, 61.5, 55.6, 55.6, 14.8, 14.1, 14.0 (one signal completely overlapped); MS (TOF ES^+): m/z 305 $(M+Na)^+$; HRMS calc. for $C_{13}H_{18}N_2O_5Na$ 305.1113, found 305.1114.

Ethyl 2-(4-Methoxyphenyl)amino-3-nitrooctanoate 3d: According to the generel procedure, imine **1** was subjected to reaction with nitrohexane and **3d** was isolated by FC on silica gel using pentane/CH_2Cl_2 (1/1) as a yellow oil. The ee was determined by HPLC using an OD column (hexane/*i*-PrOH (97/3), flow rate 0.5 mL/min). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) Diastereomer A δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.15-1.4 (m, 9H), 1.90 (ddt, *J* = 14.8, 5.6, 4.0 Hz, 1H), 2.21 (ddt, *J* = 14.8, 10.0, 5.6 Hz, 1H), 3.74 (s, 3H), 4.06 (bs, 1H), 4.20 (dq, *J* = 11.2, 7.2 Hz, 1H), 4.24 (dq, *J* = 11.2, 7.2 Hz, 1H), 4.47 (d, *J* = 5.6 Hz, 1H), 4,78 (ddd, *J* = 10.0, 5.6, 4.0 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) Diastereomer A δ 170.0, 153.7, 139.6, 116.3, 114.9, 88.8, 62.3, 61.0, 55.6, 31.1, 29.4, 25.6, 22.2, 14.0, 13.9; MS (TOF ES$^+$): m/z 361 $(M+Na)^+$; HRMS calc. for $C_{17}H_{26}N_2O_5Na$ 361.1789, found 361.1743.

Ethyl 2-(4-Methoxyphenyl)amino-3-nitro-4-phenylbutanoate 3e: According to the generel procedure, imine **1** was subjected to reaction with 2-phenyl-1-nitroethane **2e** and **3e** was isolated by FC on silica gel using pentane/CH_2Cl_2 (1/1) as a yellow oil. The ee was determined by HPLC using an AS column (hexane/*i*-PrOH (97/3), flow rate 0.5 mL/min). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) Diastereomer A δ 1.22 (t, *J* = 7.2 Hz, 3H), 3.30 (dd, *J* = 14.4, 6.4 Hz, 1H), 3.43 (dd, *J* = 14.4, 8.4 HZ, 1H), 3.73 (s, 3H), 4.14

(q, *J* = 7.2 Hz, 2H), 4.40 (bd, *J* = 4.8 Hz, 1H), 4.96 (ddd, *J* = 8.4, 6.4, 4.8 Hz, 2H), 6.42 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 7.2-7.3 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) Diastereomer A δ 169.6, 153.6, 139.2, 135.0, 129.2, 129.0, 127.7, 116.1, 114.9, 89.5, 62.5, 59.8, 55.6, 35.6, 14.1; MS (TOF ES$^+$): m/z 381 $(M+Na)^+$; HRMS calc. for $C_{19}H_{22}N_2O_5Na$ 381.1426, found 381.1426.

Ethyl 2-(4-Methoxyphenyl)amino-3-nitro-3-phenylpropanoate 3f: According to typical procedure, imine **1** was subjected to reaction with α-nitrotoluene **2f** and **3f** was isolated by FC on silica gel using pentane/CH_2Cl_2 (1/1) as a reddish yellow oil. The ee was determined by HPLC using an OD column (hexane/*i*-PrOH (95/5), flow rate 1.0 mL/min). Since adduct **3f** was obtained as a mixture of diastereomers, NMR analyses were performed with the mixture. The major diastereomer was called A. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.89 (dd, *J* = 7.2, 7.2 Hz, $3H_B$), 1.22 (dd, *J* = 7.2, 7.2 Hz, $3H_A$), 3.73 (s, $3H_B$), 3.74 (s, $3H_A$), 3.91 (dq, *J* = 7.2, 3.6 Hz, $1H_A$), 3.93 (dq, *J* = 7.2, 3.6 Hz, $1H_A$), 4.17 (dq, *J* = 7.2, 3.6 Hz, $1H_B$), 4.19 (dq, *J* = 7.2, 3.6 Hz, $1H_B$), 4.84 (d, *J* = 9.6 Hz, $1H_A$), 4.99 (d, *J* = 7.2 Hz, $1H_B$), 5.70 (d, *J* = 9.6 Hz, $1H_A$), 5.86 (d, *J* = 7.2 Hz, $1H_B$), 6.6-6.8 (m, $4H_A$+$4H_B$), 7.35-7.5 (m, $5H_A$+$5H_B$), 7.5-7.6 (m, $1H_A$+$1H_B$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.4, 154.4, 154.1, 139.8, 139.7, 131.1, 130.8, 130.8, 130.4, 129.2, 129.2, 129.0, 128.9, 117.6, 117.1, 115.0, 115.0, 92.5, 90.4, 63.5, 62.5, 62.1, 62.0, 55.8

(this signal was completely overlapped), 14.3, 13.9; MS (TOF ES$^+$): m/z 289; HRMS calc. for $C_{18}H_{20}N_2O_3Na$ 367.1270, found 367.1267.

Preparation of Ethyl (*2R*,*3R*)-3-Amino-2-(4-methoxyphenyl)aminopentanoate 8: Compound *erythro*-**3a** (74 mg, 0.25 mmol, 95% ee from (*R*)-**6a**) was dissolved in EtOH (3.6 mL) and Raney nickel (100 mg) was added. The reaction was treated with H_2 at 1 atm and left at rt for 48 h. The catalyst was filtered off and the crude was purified by FC in 20% EtOAc/CH_2Cl_2 to yield the title compound 53.0 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.97 (d, *J* = 4.4 Hz, 1H), 3.73 (s, 3H), 2.97 (ddd, *J* = 8.8, 4.4, 4.4 Hz, 1H), 1.62 (ddq, *J* = 14.0, 7.2, 4.4 Hz, 1H), 1.55-1.35 (br, 3H), 1.35 (ddq, *J* = 14.0, 8.8, 7.2 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.02 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.26, 152.95, 141.38, 115.63, 115.03, 62.62, 61.13, 55.90, 55.48, 28.08, 14.52, 11.18; MS (TOF ES$^+$): m/z 289; HRMS calc. for $C_{14}H_{22}N_2O_3Na$ 289.1528, found 289.1528.