Supporting Information

Catalytic Enantioselective Synthesis of α-Aminooxy and α-Hydroxy Ketone Using Nitrosobenzene

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Experimental Section.

General. All reactions were carried out under an atmosphere of standard grade argon gas (oxygen <10 ppm) in flame-dried glassware with magnetic stirring. THF was distilled over sodium and benzophenone under argon atmosphere. Nitrosobenzene was purchased from Tokyo Chemical Industry. AgOTf was used as purchased from Aldrich. $AgClO_4$ was used as purchased from Wako Pure Chemical. (*R*)-BINAP was used as purchased from Kanto Chemical. (*R*)-TolBINAP was used as purchased from Azmax. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (E. Merck 230-400 mesh), silica gel 60 silanized (E. Merck) and Florisil® (Wako Pure Chemical 60-100 mesh). Analytical thin layer chromatography (TLC) was performed on E. Merck precoated (0.25 mm) silica gel 60-F_{254} plates. Visualization was accomplished with UV light and phosphomolybdic acid solution in ethanol by heating.

Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer or Nicolet 20 SXB FTIR. ^{1}H-NMR spectra were recorded on a Varian Gemini-300 (300 MHz) spectrometer or Bruker DRX-500 (500 MHz), 400 (400 MHz) at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δscale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constant (Hz) and assignment. ^{13}C-NMR were recorded on a Varian Gemini-300 (75 MHz) spectrometers or Bruker DRX-500 (125 MHz), 400 (100 MHz) at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δscale, with solvent resonance employed as internal standard (deuterochloroform at 77.0 ppm). High-performance liquid chromatography (HPLC) was performed on a Shimadzu 10A or Varian ProStar Series equipped with a variable wavelength detector using a Chiralcel AD, AD-H or OD-H column (0.46 cm x 25 cm) from Daicel. Optical rotations were measured on a JASCO DIP-1000 polarimeter and reported as follows: $[\alpha]_{\lambda}^{T°C}$(c=g/100 ml, solvent). Mass spectra were obtained on QSTAR (Applied SCIEX Biochemistry/MDS) spectrometers and JMS700 (JEOL) spectrometers in Chemical Instrument Center of Nagoya University and Graduate school of Engineering, Nagoya University or Kratos MS-30 of department of Chemistry, University of Chicago. Elemental analysis was measured in Graduate school of Agriculture, Nagoya University.

General procedure for the preparation of vinyl acetates. A mixture of isopropenyl acetate (2 equiv), corresponding ketone (1 equiv) and $TsOH \cdot H_2O$ was stirred for 9 h at 90 °C. The acetone formed was continuously distilled off. The reaction mixture was cooled to room temperature and diluted with pentane and water. The organic layer was washed with $NaHCO_3$ aq. The aqueous layer was extracted with pentane. The combined organic layer was dried over Na_2SO_4 and evaporated. Distillation of residual oil gave the desired vinyl acetate.

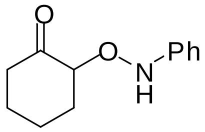
General procedure for the preparation of trichloro vinyl acetates. A mixture of trichloro acetic anhydride (6 equiv), corresponding ketone (1 equiv) and $TsOH \cdot H_2O$ was stirred for 9 h at 135 °C. The reaction mixture was cooled to room temperature and diluted with Et_2O. The organic layer was washed with $NaHCO_3$ aq and water. The aqueous layer was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4 and evaporated. Distillation of residual oil gave the desired trichloro vinyl acetate.

General procedure for the preparation of tirbutyltin enolate. A mixture of vinyl acetate (1 equiv) and Bu_3SnOMe (1 equiv) was stirred at 0 °C to room temperature for 6 h. The methyl acetate formed was removed with vacuum pump and distilled under reduced pressure to give the desired tin enolate.

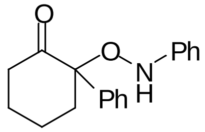
General procedure for the preparation of tin enolate *in situ*. A mixture of trichloro vinyl acetate (1 equiv) and tin methoxyde (1.2 equiv) was stirred in THF at –20 or 0 °C for 3 h.

General procedure for the reaction of tin enolate with nitrosobenzene catalyzed by chiral silver complex. An oven-dried schlenk tube equipped with direct light excluded was charged with (*R*)-BINAP or (*R*)-TolBINAP (10 mol%, 0.05 mmol) and silver salt (10 mol%, 0.05 mmol). THF (2 mL) was added by syringe and the resulting mixture was stirred at room temperature for 20 min. After cooling to –78 °C, nitrosobenzene (1 equiv, 53.6 mg, 0.5 mmol) in THF (1 ml) and tin enolate (1 equiv) was added in this order. The mixture was stirred at –78 °C for 2 h. The reaction mixture was quenched by cooled brine (20 mL) and the aqueous layer was extracted with ether (20 mLx2). The combined organic extracts were washed with brine, dried over Na_2SO_4 with cooling and concentrated under reduced pressure after filtration. The residual crude product in THF was chromatographed with cooling on a two-layered column filled with Florisil® (upper layer) and silica gel (lower layer) using a mixture of ethyl acetate and hexane as the eluant to give the product.

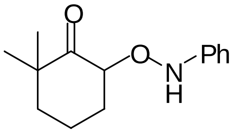
General procedure for the synthesis of α-hydroxy ketone. An oven-dried schlenk tube equipped with direct light excluded was charged with (*R*)-BINAP or (*R*)-TolBINAP (10 mol%, 0.05 mmol) and silver salt (10 mol%, 0.05 mmol). THF (2 mL) was added by syringe and the resulting mixture was stirred at room temperature for 20 min. After cooling to –78 °C, nitrosobenzene (1 equiv, 53.6 mg, 0.5 mmol) in THF (1 ml) and tin enolate (1 equiv) were added in this order. The mixture was stirred at –78 °C for 2 h. And then, $CuSO_4$ (0.3 eq) and MeOH (3 mL) were added at this temperature and stirred at 0°C for 12 h. The reaction mixture was quenched by cooled brine (20 mL) and the aqueous layer was extracted with ether (20 mLx2). The combined organic extracts were washed with brine, dried over Na_2SO_4 with cooling and concentrated under reduced pressure after filtration. The residual crude product was chromatographed on a silica gel using a mixture of ethyl acetate and hexane as the eluant to give the product.



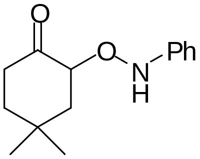
2-(*N*-Phenyl aminooxy) cyclohexanone(3a). Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish powder. TLC R_f = 0.30 (3:1 hexane: ethyl acetate); $[\alpha]_D^{23}$-53.0° (c = 0.62, $CHCl_3$); IR ($CHCl_3$) 3021, 2951, 2872, 1722, 1603, 1495, 1132, 1100, 1073, 1028, 928 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ7.82 (s, 1H, N*H*), 7.25 (t, 2H, *J* = 8.4 Hz, Ar-*H*), 6.94 (t, 3H, *J* = 8.1 Hz, Ar-*H*), 4.35 (q, 1H, *J* = 6.0 Hz, C*H*), 2.34 – 2.48 (m, 2H, CH_2), 2.00 – 2.02 (m, 2H, CH_2), 1.71 – 1.79 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ209.9, 148.0, 128.8 (2C), 122.0, 114.3 (2C), 86.2, 40.8, 32.5, 27.2, 23.7; Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.22; H, 7.42; N, 6.91. Enantiomeric excess was determined by HPLC with a Chiralcel AD column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 28.1 min, minor enantiomer t_r = 34.3 min.



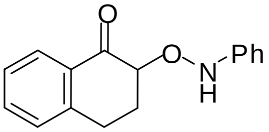
2-Phenyl-2-(*N*-Phenyl aminooxy) cyclohexanone (3b). Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish powder. TLC R_f = 0.28 (5:1 hexane: ethyl acetate); $[\alpha]_D^{22}$-98.5° (c = 0.32, $CHCl_3$); IR ($CHCl_3$) 3014, 2951, 2867, 1716, 1602, 1465, 1237, 1120, 1062, 1028, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.51 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.42 (s, 1H, N*H*), 7.40 (t, 3H, *J* = 8.0 Hz, Ar-*H*), 7.18 (t, 3H, *J* = 7.5 Hz, Ar-*H*), 6.86 (t, 3H, *J* = 8.0 Hz, Ar-*H*), 2.74 – 2.77 (m, 2H, CH_2), 2.52 – 2.58 (m, 2H, CH_2), 1.95 – 1.98 (m, 2H, CH_2), 1.76 – 1.83 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ209.7, 148.5, 136.2, 128.9, 128.8 (2C), 128.6 (2C), 127.7 (2C), 121.6, 114.4 (2C), 90.0, 40.9, 34.0, 27.0, 22.9; MS (CI) Exact Mass Calcd for $C_{18}H_{19}NO_2$ $(M+H)^+$: 282.1. Found: 282.1. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 33.6 min, minor enantiomer t_r = 39.2 min.



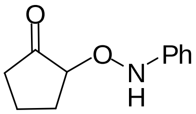
2,2-Dimethyl-6-(*N*-Phenyl aminooxy) cyclohexanone (3c). Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish oil. TLC $R_f = 0.40$ (5:1 hexane: ethyl acetate); $[\alpha]_D^{22}$+94.9° (c = 0.53, $CHCl_3$); IR ($CHCl_3$) 3028, 2967, 2309, 1716, 1600, 1494, 1470, 1200, 1077, 1017, 984, 916, 884 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.83 (s, 1H, N*H*), 7.24 (d, 2H, *J* = 6.5 Hz, Ar-*H*), 6.93 (t, 3H, *J* = 8.5 Hz, Ar-*H*), 4.67 (q, 1H, *J* = 7.8 Hz, C*H*), 1.78 – 1.83 (m, 2H, CH_2), 1.75 – 1.78 (m, 2H, CH_2), 1.57 – 1.74 (m, 2H, CH_2), 1.21 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ229.7, 149.8, 136.2, 128.8 (2C), 122.8, 114.3 (2C), 83.5, 40.9, 32.7 (2C), 24.9, 19.8 (2C); MS (CI) Exact Mass Calcd for $C_{14}H_{19}NO_2$ $(M+H)^+$: 234.1. Found: 234.1. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 38.8 min, minor enantiomer t_r = 31.6 min.



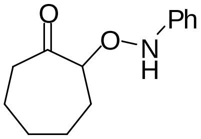
4,4-Dimethyl-2-(*N*-Phenyl aminooxy) cyclohexanone (3d). Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish powder. TLC R_f = 0.30 (5:1 hexane: ethyl acetate); $[\alpha]_D^{22}$-87.2° (c = 0.34, $CHCl_3$); IR ($CHCl_3$) 3037, 2956, 2928, 2309, 1718, 1602, 1495, 1471, 1390, 1305, 1230, 1078, 1029, 982, 894, 880 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.87 (s, 1H, N*H*), 7.26 (t, 2H, *J* = 5.5 Hz, Ar-*H*), 6.94 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 6.92 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 4.51 (q, 1H, *J* = 6.5 Hz, C*H*), 2.49 – 2.56 (m, 1H, CH_2), 2.35 – 2.38 (m, 1H, CH_2), 2.11 – 2.13 (m, 1H, CH_2), 1.66 – 1.79 (m, 3H, CH_2), 1.25 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ210.5, 148.1, 128.9 (2C), 122.0, 114.3 (2C), 83.3, 44.5, 39.5, 37.1 (2C), 31.4, 24.9; MS (CI) Exact Mass Calcd for $C_{14}H_{19}NO_2$ $(M+H)^+$: 234.1. Found: 234.1. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 15.9 min, minor enantiomer t_r = 12.2 min.



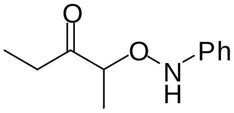
2-(*N*-Phenyl aminooxy) tetralone (3e). Purification by flash column chromatography with elution by hexane:ethyl acetate (15:1) provided as yellowish oil. TLC R_f = 0.28 (3:1 hexane: ethyl acetate); $[\alpha]_D^{22}$+64.2° (*c* = 0.47, $CHCl_3$); IR ($CHCl_3$) 3017, 2923, 2871, 2849, 2360, 2339, 1691, 1601, 1494, 1456, 1399, 1306, 1271, 1227, 1126, 1000, 982, 894 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ8.07 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 8.04 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.51 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.48 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.35 (t, 1H, *J* = 8.0 Hz, Ar-*H*), 7.33 (s, 1H, N*H*), 7.26 (d, 2H, *J* = 7.8 Hz, Ar-*H*), 6.70 (d, 1H, *J* = 7.5 Hz, Ar-*H*), 6.96 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 4.63 (q, 1H, *J* = 5.5 Hz, C*H*), 3.13 – 3.18 (m, 2H, CH_2), 2.54 – 2.58 (m, 1H, CH_2), 2.34 – 2.40 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ190.0, 143.1, 133.9, 128.9 (2C), 128.7, 127.6, 126.9, 122.8, 114.5 (2C), 29.7, 39.5, 28.1; MS (CI) Exact Mass Calcd for $C_{14}H_{19}NO_2$ $(M+H)^+$: 254.1. Found: 254.1. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 37.5 min, minor enantiomer t_r = 46.3 min.



2-(*N*-Phenyl aminooxy) cyclopentanone (3f). Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish powder. TLC R_f = 0.31 (3:1 hexane: ethyl acetate); $[\alpha]_D^{27}$+22.0° (*c* = 2.3, $CHCl_3$); IR ($CHCl_3$) 3021, 2979, 2890, 2402, 1752, 1603, 1520, 1472, 1232, 1215, 1101, 1046, 1026, 930, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ7.56 (s, 1H, N*H*), 7.26 (t, 2H, *J* = 8.4 Hz, Ar-*H*), 6.96 (t, 1H, *J* = 8.4 Hz, Ar-*H*), 6.94 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 4.33 (t, 1H, *J* = 9.6 Hz, C*H*), 2.13 – 2.38 (m, 2H, CH_2), 2.02 – 2.18 (m, 2H, CH_2), 1.72 – 1.85 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ216.3, 148.0, 128.9 (2C), 122.3, 114.7 (2C), 84.5, 35.7, 27.3, 17.2; Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.09; H, 6.87; N, 7.36 Enantiomeric excess was determined by HPLC with a Chiralcel AD column (100:1 hexane:2-propanol), 0.5 mL/min; major enantiomer t_r = 109.3 min, minor enantiomer t_r = 119.2 min.



2-(*N*-Phenyl aminooxy) cycloheptanone (3g). Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish powder. TLC R_f = 0.25 (5:1 hexane: ethyl acetate); $[\alpha]_D^{22}$-74.9° (*c* = 1.3, $CHCl_3$); IR ($CHCl_3$) 3021, 2979, 2890, 2402, 1752, 1603, 1520, 1472, 1132, 1215, 1101, 1046, 1026, 930, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ7.58 (s, 1H, N*H*), 7.25 (t, 2H, *J* = 8.6 Hz, Ar-*H*), 6.94 (t, 1H, *J* = 8.7 Hz, Ar-*H*), 6.93 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 4.64 (q, 1H, *J* = 3.9 Hz, C*H*), 2.41 – 2.62 (m, 2H, CH_2), 2.08 – 2.13 (m, 1H, CH_2), 1.68 – 1.92 (m, 6H, CH_2), 1.31 – 1.48 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ211.8, 147.9, 128.9 (2C), 122.1, 114.3 (2C), 88.2, 41.1, 30.0, 28.6, 26.6, 23.0; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.11; H, 6.56; N, 7.97 Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 28.4 min, minor enantiomer t_r = 40.8 min.



2-(*N*-Phenyl aminooxy) pentanone (3h). Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish oil. TLC R_f= 0.32 (5:1 hexane: ethyl acetate); $[\alpha]_D^{24}$-12.8° (*c* = 0.3, $CHCl_3$); IR ($CHCl_3$) 3052, 2979, 2936, 2361, 2336, 1718, 1602, 1494, 1454, 1376, 1240, 1172, 1100, 1073, 1027, 971, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.32 (s, 1H, N*H*), 7.27 (t, 2H, *J* = 6.0 Hz, Ar-*H*), 6.95 (t, 3H, *J* = 8.4 Hz, Ar-*H*), 4.48 (q, 1H, *J* = 7.1 Hz, C*H*), 2.55 (q, 2H, CH_2), 1.43 (d, 3H, CH_3), 1.72 – 1.11 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ211.7, 147.9, 131.1 (2C), 122.8, 114.5 (2C), 84.1, 31.5, 15.9, 7.3; MS (CI) Exact Mass Calcd for $C_{11}H_{15}NO_2$ $(M+H)^+$: 194.1. Found: 194.1. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer t_r = 19.6 min, minor enantiomer t_r = 18.3 min.