The Direct Amino Acid-Catalyzed Asymmetric Incorporation of Molecular Oxygen to Organic Compounds

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Supporting Information

General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25%), $\text{Ce}(\text{SO}_4)_2 \cdot \text{H}_2\text{O}$ (10%), conc. H_2SO_4 (60%), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35%), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), ^1H NMR and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in Hz. The spectra were recorded in CDCl_3 as solvent at room temperature, TMS served as internal standard ($\delta = 0$ ppm) for ^1H NMR, and CDCl_3 was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. GC was carried out using a Varian 3800 gas chromatograph. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter ($\lambda = 589$ nm, 1 dm cell). High

resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

Typical experimental procedure for the direct catalytic α -oxidation of 3-phenyl propanal with singlet oxygen. In a typical experiment, the aldehyde (1 mmol) was added to a vial containing solvent (4 mL), amino acid (20 mol%) and tetraphenylporphine (TPP) (5 mol%). A continuous flow of O₂ or air was bubbled through the vial and the reaction exposed to visible light by a 250W high-pressure sodium lamp at ambient temperature or 0 °C. After 1-2.5 hours the light was turned off, methanol was added (2 mL) and the corresponding α -hydroperoxide intermediate was reduced *in situ* with NaBH₄ (10 mmol) at 0 °C for 5 min. The reaction mixture was poured to a mixture of 1N HCl and EtOAc and vigorously stirred at 0 °C. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with MgSO₄, which was subsequently removed by filtration. The solvent was removed under reduced pressure following purification of the crude product mixture by silica-gel column chromatography (EtOAc:pentane-1:2) to afford the corresponding optically active (2*R*)-3-phenylpropane-1,2-diol **1**. The ee of the diol **1** was determined by chiral-phase HPLC analyses.

(2*R*)-3-Phenylpropane-1,2-diol 1: Derived by L-proline-catalysis. ¹H NMR (CDCl₃): δ = 1.85 (bs, , 2H, OH), 2.78 (m, 2H, PhCH₂CH), 3.54 (m, 1H, CH₂OH), 3.70 (m, 1H, CH₂OH), 3.95 (m, 1H, CHOH), 7.24 (m, 3H, ArH), 7.33 (m, 2H, ArH); ¹³C NMR: 40.0, 66.3, 73.3, 126.9, 128.9, 129.6, 137.9; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 98:2, flow rate 0.5 mL/min, λ = 242 nm): major isomer: *t*_R = 47.61 min; minor isomer: *t*_R = 53.08 min; $[\alpha]_D$ = +11.1 (c = 1.2, CHCl₃).

Results from the reactions in DMF at 0 °C. The ee is presented in parenthesis.

Direct organocatalytic α -oxidation of heptanal with singlet oxygen.

In a typical experiment, heptanal (1 mmol) was added to a vial containing DMF (1 mL), organic catalyst (20 mol%) and tetraphenylporphine (TPP) (5 mol%). A continuous flow of O_2 or air was bubbled through the vial and the reaction exposed to visible light by a 250W high-pressure sodium lamp at ambient temperature or 0 °C. After 2.5 hours the light was turned off, methanol was added (2 mL) and the corresponding α -hydroperoxide intermediate was reduced *in situ* with $NaBH_4$ (10 mmol) at 0 °C for 5 min. The reaction mixture was poured to a mixture of 1N HCl and EtOAc and vigorously stirred at 0 °C. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. The solvent was removed under reduced pressure following purification of the crude product mixture by silica-gel column chromatography (EtOAc:pentane-1:2) to afford the corresponding optically active *R*-heptane-1,2-diol **4**. The ee of the diol **4** was determined by chiral-phase GC analyses of the corresponding diacetylated product.

***R*-Heptane-1,2-diol 4:** $^1\text{H NMR}$ (CDCl_3): δ = 1.29 (t, J = 7.2 Hz, 3H, CH_3), 1.51-1.84 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.17 (bs, 2H, OH), 3.80 (m, 1H, CH_2OH), 4.06 (m, 2H, CH_2OH , CHOH); $^{13}\text{C NMR}$: 14.6, 22.0, 22.1, 23.3, 33.4, 67.4, 72.9; Chiral-phase GC (CP-Chirasil-Dex CB): T_{inj} = 250 °C, T_{det} 275 °C, flow = 1.8 mL/min t_{r} = 80 °C (9 min), 80 °C $\rightarrow$ 120 °C, rate = 20.0 °C/min, 120 °C (6 min), 120 °C $\rightarrow$ 200 °C, rate = 80.0 °C/min, 200 °C (5 min); retention times : t_{min} = 17.1, t_{maj} = 17.2.

Examples of amino acid derivatives that catalyzed the reaction between singlet molecular oxygen and heptanal. The ee is displayed in parenthesis.

R = *n*-Pent

Typical experimental procedure for the direct catalytic α -oxidation of aldehydes with singlet oxygen.

In a typical experiment, the aldehyde (1 mmol) was added to a vial containing DMF (1 mL), amino acid (15 mol%) and tetraphenylporphine (TPP) (5 mol%). A continuous flow of O₂ or air was bubbled through the vial and the reaction exposed to visible light by a 250W high-pressure sodium lamp at the temperature shown in Table 1. After 1-3.5 hours the light was turned off, methanol was added (2 mL) and the corresponding α -hydroperoxide intermediate was reduced *in situ* with NaBH₄ (10 mmol) at 0 °C for 5 min. The reaction mixture was poured to a mixture of 1N HCl and EtOAc and vigorously stirred at 0 °C. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with MgSO₄, which was subsequently removed by filtration. The solvent was removed under reduced pressure following purification of the crude product mixture by silica-gel column chromatography (EtOAc:pentane-1:2) to afford the corresponding optically active diols. The ee of the diols were determined by chiral-phase HPLC analyses or Chiral-phase HPLC analyses of the corresponding diacetates.

(2R)-3-Phenyl-propane-1,2-diol 1: ¹H NMR (CDCl₃): δ = 1.85 (bs, , 2H, OH), 2.78 (m, 2H, PhCH₂CH), 3.54 (m, 1H, CH₂OH), 3.70 (m, 1H, CH₂OH), 3.95 (m, 1H, CHOH), 7.24 (m, 3H, ArH), 7.33 (m, 2H, ArH); ¹³C NMR: 40.0, 66.3, 73.3, 126.9, 128.9, 129.6, 137.9; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 98:2, flow rate 0.5 mL/min, λ = 242 nm): major isomer: t_R = 47.61 min; minor isomer: t_R = 53.08 min; $[\alpha]_D^{25}$ = +11.1 (c = 1.2, CHCl₃).

(1R)-1-Phenyl-ethane-1,2-diol 2: ¹H NMR (CDCl₃): δ = 2.56 (s, 2H, OH), 3.67 (dd, *J* = 8.4, 11.6 Hz, 1H, CH₂OH), 3.77 (dd, *J* = 10.8 Hz, 1H, CH₂OH), 4.83 (dd, *J* = 3.6, 8.0 Hz,

1H, ArCHOH), 7.29-7.34 (m, 5H, ArH); ^{13}C NMR: 68.1, 74.4, 126.0, 128.0, 128.6, 140.5; $[\alpha]_{\text{D}} = -38.1$ ($c = 1.2$, CHCl_3); HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 95:5, flow rate 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_{\text{R}} = 30.2$ min; minor isomer: $t_{\text{R}} = 33.0$ min.

(2R)-3-Methyl-butane-1,2-diol 3: ^1H NMR (CDCl_3): $\delta = 0.91$ (d, $J = 6.5$ Hz, 3H), 0.98 (d, $J = 6.5$ Hz, 3H), 1.71 (m, 1H), 3.42 (m, 1H), 3.51 (dd, $J = 10.5, 8.0$ Hz, 1H), 3.71 (dd, $J = 10.5, 3.0$ Hz, 1H); ^{13}C NMR: 18.2, 18.7, 30.9, 64.9; Chiral-phase GC (CP-Chirasil-Dex CB): $T_{\text{inj}} = 250^\circ \text{C}$, $T_{\text{det}} = 275^\circ \text{C}$, flow = 1.8 mL/min $t_{\text{i}} = 110^\circ \text{C}$ (9 min) $t_{\text{f}} = 200^\circ \text{C}$ rate = 85°C/min ; retention times : $t_{\text{maj}} = 4.1$, $t_{\text{min}} = 4.3$.¹

R-Heptane-1,2-diol 4: ^1H NMR (CDCl_3): $\delta = 1.29$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.51-1.84 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.17 (bs, 2H, OH), 3.80 (m, 1H, CH_2OH), 4.06 (m, 2H, CH_2OH , CHOH); ^{13}C NMR: 14.6, 22.0, 22.1, 23.3, 33.4, 67.4, 72.9; Chiral-phase GC (CP-Chirasil-Dex CB): $T_{\text{inj}} = 250^\circ \text{C}$, $T_{\text{det}} = 275^\circ \text{C}$, flow = 1.8 mL/min $t_{\text{i}} = 80^\circ \text{C}$ (9 min), $80^\circ \text{C} \rightarrow 120^\circ \text{C}$, rate = 20.0°C/min , 120°C (6 min), $120^\circ \text{C} \rightarrow 200^\circ \text{C}$, rate = 80.0°C/min , 200°C (5 min); retention times : $t_{\text{min}} = 17.1$, $t_{\text{maj}} = 17.2$.

R-Hexane-1,2-diol 5: ^1H NMR (CDCl_3): $\delta = 1.29$ (t, $J = 7.2$ Hz, 3H, CH_3), 1.51-1.84 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.17 (bs, 2H, OH), 3.80 (m, 1H, CH_2OH), 4.06 (m, 2H, CH_2OH , CHOH); ^{13}C NMR: 14.6, 23.3, 33.4, 67.4, 72.9; Chiral-phase GC (CP-Chirasil-Dex CB): $T_{\text{inj}} = 250^\circ \text{C}$, $T_{\text{det}} = 275^\circ \text{C}$, flow = 1.8 mL/min $t_{\text{i}} = 110^\circ \text{C}$ (9 min) $t_{\text{f}} = 200^\circ \text{C}$ rate = 85°C/min ; retention times : $t_{\text{maj}} = 7.54$, $t_{\text{min}} = 7.42$.²

Typical experimental procedure for the direct catalytic α -oxidation of aldehydes with singlet oxygen in aqueous buffer.

In a typical experiment, the aldehyde (1 mmol) was added to a vial containing aqueous phosphate buffer (40mM NaH₂PO₄, pH = 7.1), amino acid (30 mol%) and protoporphine (5 mol%). A continuous flow of O₂ or air was bubbled through the vial and the reaction exposed to visible light by a 250W high-pressure sodium lamp at ambient temperature. After 1-3.5 hours the light was turned off, methanol was added (2 mL) and the corresponding α -hydroperoxide intermediate was reduced *in situ* with NaBH₄ (20 mmol) at 0 °C for 5 min. EtOAc was added and the aqueous phase separated. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with MgSO₄, which was subsequently removed by filtration. The solvent was removed under reduced pressure following purification of the crude product mixture by silica-gel column chromatography (EtOAc:pentane-1:2) to afford the corresponding optically active diols.

1. (a) B. T. Cho, Y. S. Chun, *J. Org. Chem.* **1998**, 63, 5280. (b) B. T. Cho, Y. S. Chun, *Tetrahedron:*

Asymmetry **1999**, 10, 1843.

2. J. Hasegawa, M. Ogura, S. Tsuda, S. Maemoto, H. Kutsuki, T. Ohashi, *Agric. Biol. Chem.* **1990**, 54, 1819.