Supporting Information

Molybdenum Oxides as Highly Effective Dehydrative Cyclization Catalysts Directed toward the Green Synthesis of Oxazolines and Thiazolines

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General Method.

IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^1H spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (CDCl_3 at 77.0 ppm). Analytical HPLC was performed on a Shimadzu Model LC-6A instrument using a column of Nomura Chemical Develosil 30-5 (4.6 $\times$ 250 mm) or Daicel CHIRALPAK OD-H (4.6 $\times$ 250 mm). All experiments were carried out under an atmosphere of dry nitrogen. For TLC analysis, Merck precoated TLC plates (silica gel 60 F₂₅₄ 0.25 mm) were used. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University.

Dry toluene was purchased from Wako as the “anhydrous” and stored under nitrogen. Dichloromethane and triethylamine were freshly distilled from calcium hydride. MoO_2 (Wako Pure Chemical Industries, Ltd.), MoO_3 (Aldrich), $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ (Nacalai tesque), $(\text{NH}_4)_2\text{MoO}_4$ (Aldrich), $\text{MoO}_2(\text{acac})_2$ (Wako Pure Chemical Industries, Ltd.) and other materials were obtained from commercial supplies and used without further purification. Compounds **2a**,¹ **4a**,² **4b**,³ **5a**,^{1,4} **7b**,⁵ **8a**,⁶ **8b**,^{4,7} **9b**,⁸ **10a**,⁹ **10b**,¹⁰ **11–13**,¹¹ and **16**¹¹ were reported previously.

N-(3-Phenylpropionyl)-L-serine methyl ester (1a). To a solution of L-serine methyl ester hydrochloride (5.0 g, 32 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (8.9 mL, 64 mmol) and a solution of 3-phenylpropionyl chloride (4.5 mL, 30 mmol) in CH_2Cl_2 (15 mL) dropwise at $-5\text{ }^\circ\text{C}$. After being stirred at $-5\text{ }^\circ\text{C}$ for 1 h and at ambient temperature for 1 h, the reaction mixture was diluted with EtOAc and washed successively with a saturated aqueous solution of NaHCO_3 and brine. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was

purified by column chromatography on silica gel using a 1:2 mixture of hexane–EtOAc, to give **1a** (6.12 g, 76% yield): IR (KBr) 3432, 1741, 1727, 1643, 1617, 1550 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.11 (br s, 1H), 2.54 (dt, $J = 14.4, 8.1$ Hz, 1H), 2.62 (dt, $J = 14.4, 7.2$ Hz, 1H), 2.99 (dd, $J = 7.2, 8.1$ Hz, 2H), 3.70–3.92 (m, 2H), 3.77 (s, 3H), 6.27 (br d, $J = 7.2$ Hz, 1H), 7.19–7.33 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 31.4, 38.0, 52.6, 54.5, 63.0, 126.2, 128.3 (2C), 128.5 (2C), 140.4, 170.9, 172.6; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4\text{N}$ $[\text{M}+\text{H}]^+$ 252.1236, found 252.1234.

***N*-(3-Phenylpropionyl)-L-threonine methyl ester (1b).** Experimental procedure was followed as described for **1a**. **1b:** IR (KBr) 3483, 1719, 1645, 1543 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.10 (d, $J = 6.3$ Hz, 1H), 1.93 (br s, 1H), 2.60 (m, 2H), 3.00 (t, $J = 7.8$ Hz, 2H), 3.76 (s, 3H), 4.29 (m, 1H), 4.60 (dd, $J = 2.7, 9.0$ Hz, 1H), 6.12 (br d, $J = 9.0$ Hz, 1H), 7.16–7.32 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.8, 31.5, 38.2, 52.6, 56.9, 68.0, 126.3, 128.4, 128.5, 140.5, 171.5, 172.5; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4\text{N}$ $[\text{M}+\text{H}]^+$ 266.1392, found 266.1397.

***N*-(3-Phenylpropionyl)-L-cysteine methyl ester (7a).** Experimental procedure was followed as described for **1a**. **7a:** IR (KBr) 3328, 1731, 1641, 1540, 1263 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.08 (t, $J = 9.0$ Hz, 1H), 2.54 (dt, $J = 14.7, 8.1$ Hz, 1H), 2.63 (ddd, $J = 6.6, 7.5, 14.7$ Hz, 1H), 2.89–3.02 (m, 4H), 3.77 (s, 3H), 4.87 (dt, $J = 7.5, 3.9$ Hz, 1H), 6.23 (br d, $J = 7.5$ Hz, 1H), 7.19–7.33 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 26.8, 31.5, 38.1, 52.8, 53.4, 126.4, 128.4, 128.6, 140.4, 170.5, 171.7; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{NS}$ $[\text{M}+\text{H}]^+$ 268.1007, found 268.1010.

General Procedure for the Dehydrative Cyclization of Serine, Threonine Derivatives 1 and 4, and Cysteine Derivatives 7. A solution of substrate (0.50 mmol) and molybdenum oxide catalyst (0.050 mmol) in toluene (10 mL for threonine derivatives, 50 mL for serine and cysteine derivatives) was heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. After several hours, the reaction mixture was cooled to ambient temperature, and the organic solvent was then removed to give a crude product. Yields were determined by HPLC analysis or ^1H NMR analysis.

Oxazoline 2b: IR (neat) 3028, 2977, 2952, 1741, 1659, 1204, 1179, 1030 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.40 (d, $J = 6.3$ Hz, 3H), 2.63 (t, $J = 8.1$ Hz, 2H), 2.98 (t, $J = 8.1$ Hz, 2H), 3.78 (s, 3H), 4.23 (d, $J = 7.5$ Hz, 1H), 4.80 (dq, $J = 7.5, 6.3$ Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.7, 29.8, 31.8, 52.3, 74.4, 78.3, 126.1, 128.1, 128.3, 140.1, 169.0, 171.4; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{N}$ $[\text{M}+\text{H}]^+$ 248.1287, found 248.1281.

Dimer 3a: ^1H NMR (300 MHz, CDCl_3) δ 2.45–2.67 (m, 4 H), 2.83–3.08 (m, 4 H), 3.74 (s, 3 H), 4.25–4.56 (m, 4 H), 4.64 (d, $J = 6.9, 7.2$ Hz, 1 H), 4.90 (m, 1 H), 6.64 (d, $J = 6.9$ Hz, 1 H), 7.08–7.40 (m, 10 H); ^{13}C NMR (75 MHz, CDCl_3) δ 29.6, 31.2, 31.9, 37.8, 51.4, 52.9, 64.7, 67.8, 69.2, 126.2, 126.3, 128.1, 128.2, 128.4, 128.5, 140.2, 140.4, 169.6, 170.2, 170.8, 171.9.

Oxazoline 5a: Spectral data of oxazoline **5a** were identical with those in ref 1. The product included the diastereomer **6a**, and the diastereo ratio was determined by HPLC analysis on Develosil 30-5. **5a:** $T_R = 11.3$ min, **6a:** $T_R = 12.9$ min (hexane–EtOAc–MeOH = 16:8:1). Authentic sample of **6a** was prepared from Cbz-D-Ala-L-Ser- OCH_3 .

Oxazoline 5b: IR (KBr) 3326, 1724, 1661, 1531, 1454 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.44 (d, $J = 7.2$ Hz, 3H), 1.44 (d, $J = 7.2$ Hz, 3H), 3.79 (s, 3H), 4.27 (d, $J = 7.5$ Hz, 1H), 4.52 (dq, $J = 7.5, 7.2$ Hz, 1H), 4.86 (dq, $J = 7.5, 7.2$ Hz, 1H), 5.08 (d, $J = 12.3$ Hz, 1H), 5.13 (d, $J = 12.3$ Hz, 1H), 5.53 (br d, $J = 7.5$ Hz, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.3, 20.6, 45.2, 52.5, 66.6, 74.0, 79.7, 127.9, 127.9, 128.3, 136.2, 155.3, 169.7, 171.0; HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_5\text{N}_2$ $[\text{M}+\text{H}]^+$ 321.1450, found 321.1439. The product included the diastereomer **6b**, and the diastereo ratio was determined by HPLC analysis on Develosil 30-5. **5b:** $T_R = 9.7$ min, **6b:** $T_R = 10.9$ min (hexane–EtOAc–MeOH = 16:8:1). Authentic sample of **6b** was prepared from Cbz-D-Ala-L-Thr- OCH_3 .

Thiazoline 8b: Spectral data of thiazoline **8b** were identical with those in ref 4. The data did not provide any evidence of the presence of the diastereomer **8c**. The detailed analysis by HPLC on Develosil 30-5 showed that the product included the diastereomer **8c**, and the diastereo ratio was 4.7:1. **8b:** $T_R = 32.2$ min, **8c:** $T_R = 34.3$ min (hexane–EtOAc–MeOH = 64:16:1). Authentic sample of **8c** was prepared from Cbz-D-Ala-L-Cys- OCH_3 .

Bis(amide) 9a. To a solution of (*S*)-valinol (1.03 g, 10 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (2.8 mL, 20 mmol). The mixture was cooled to 0 °C and solution of dimethylmalonyl chloride (0.66 mL, 5.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After being stirred at 0 °C for 1 h and at ambient temperature for 1 h, the reaction mixture was diluted with EtOAc, and washed with a saturated aqueous solution of NaHCO_3 and brine successively. The solution was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel using hexane-acetone (2:1 $\rightarrow$ 2:3) to give bis(amide) **9a** (1.4 g, 91% yield): IR (KBr) 3327, 1642, 1544, 1072, 1024 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.92 (d, $J = 6.9$ Hz, 6H), 0.95 (d, $J = 6.9$ Hz, 6H), 1.50 (s, 6H), 1.81 (d sept, $J = 6.9, 6.9$ Hz, 2H), 3.09 (br s, 2H), 3.52 (m, 2H), 3.73–3.80 (m, 4H),

6.38 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 18.8, 19.6, 23.7, 29.1, 50.2, 57.1, 63.3, 174.4; HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{31}\text{O}_4\text{N}_2$ $[\text{M}+\text{H}]^+$ 303.2284, found 303.2285.

Procedure for the Dehydrative Cyclization of Bis(amide)s 9. A solution of bis(amide) **9a, b** (1.0 mmol) and molybdenum oxide catalyst (0.20 mmol) in toluene (10 mL) was heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. After 3 hours, the reaction mixture was cooled to ambient temperature, and then the organic solvent was removed. The resultant crude product was purified by column chromatography on silica gel using hexane-acetone (6:1 $\rightarrow$ 4:1) to give bis(oxazoline) **10a** (84% yield), **10b** (83% yield).

Oxazoline 12. Experimental procedure was followed as described for dehydrative cyclization of **1**. The resultant crude product was purified by column chromatography on silica gel to give oxazoline **12** (81% yield).

Amide 14. To a solution of **13** (297 mg, 0.70 mmol) in THF-MeOH (10:1, 4 mL) was added a 2 M aqueous solution of LiOH (0.40 mL, 0.77 mmol) and the mixture was stirred at ambient temperature for 8 h. The reaction mixture was acidified (pH 3) with 1 M aqueous HCl. Sodium chloride was added to the mixture and the aqueous layer was extracted with Et_2O (10 mL). The organic extract was dried (Na_2SO_4) and concentrated to give a crude carboxylic acid. To a solution of the crude carboxylic acid and L-serine ethyl ester hydrochloride (131 mg, 0.77 mmol) in DMF (7 mL) was added DPPA (212 mg, 0.77 mmol) and Et_3N (215 μL , 1.54 mmol) at 0 $^\circ\text{C}$, and the mixture was stirred at ambient temperature for 10 h. After the removal of the solvent, the resultant residue was dissolved to EtOAc (10 mL) and washed with a saturated aqueous solution of NaHCO_3 and brine successively. The organic solution was dried (Na_2SO_4) and concentrated. The resultant crude product was purified by column chromatography on silica gel using hexane-EtOAc (2:1 $\rightarrow$ 1:1) to give amide **14** (280 mg, 76% yield): IR (neat) 3407, 1741, 1661, 1601, 1513, 1111 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.05 (s, 9H), 1.31 (t, $J = 7.2$ Hz, 3H), 2.03 (tt, $J = 6.0, 7.5$ Hz, 2H), 2.82 (t, $J = 6.0$ Hz, 1H), 2.92 (t, $J = 7.5$ Hz, 2H), 3.73 (t, $J = 6.0$ Hz, 2H), 4.01–4.07 (m, 2H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.79 (ddd, $J = 3.6, 3.9, 7.5$ Hz, 2H), 7.35–7.46 (m, 6H), 7.65 (m, 4H), 7.73 (d, $J = 7.5$ Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.1, 19.2, 24.6, 26.8, 29.4, 54.6, 62.0, 62.4, 63.6, 127.7, 129.6, 133.5, 135.3, 135.5, 141.1, 161.1, 164.9, 170.0; HRMS (FAB) calcd for $\text{C}_{28}\text{H}_{37}\text{O}_6\text{N}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 525.2421, found 525.2419.

Oxazoline 15. A solution of amide **14** (125 mg, 0.24 mmol) and $(\text{NH}_4)_2\text{MoO}_4$ (4.7 mg, 0.024 mmol) in chlorobenzene (24 mL) was heated at azeotropic reflux with the removal of water using a

Dean-Stark apparatus. After 20 h, the reaction mixture was cooled to ambient temperature, and then the organic solvent was removed. The resultant crude product was purified by column chromatography on silica gel using CHCl₃–Et₂O (50:1 □ 30:1 □ 10:1) to give oxazoline **15** (90 mg, 75% yield) along with amide **14** (10 mg, 8% yield): IR (neat) 1738, 1679, 1586, 1110 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) □ 1.04 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H), 2.05 (m, 2H), 2.95 (t, *J* = 8.1 Hz, 2H), 3.72 (t, *J* = 6.0 Hz, 2H), 4.25 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.26 (dq, *J* = 7.2, 7.2 Hz, 1H), 4.57 (dd, *J* = 8.7, 10.5 Hz, 1H), 4.67 (dd, *J* = 8.1, 8.7 Hz, 1H), 4.91 (dd, *J* = 8.1, 10.5 Hz, 1H), 7.37–7.40 (m, 6H), 7.64 (m, 4H), 8.06 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) □ 14.1, 19.1, 24.7, 26.8, 29.5, 61.8, 62.5, 68.5, 69.6, 127.6, 129.6, 129.8, 133.5, 135.5, 141.0, 160.0, 165.8, 170.8; HRMS (FAB) calcd for C₂₈H₃₅O₅N₂Si [M+H]⁺ 507.2315, found 507.2311.

Aldehyde 16. To a solution of **15** (59 mg, 0.12 mmol) in CH₂Cl₂ (1.2 mL) was added DBU (34.5 □L, 0.23 mmol) at 0 °C and the mixture was stirred for 5 min. BrCCl₃ (12.5 □L, 0.13 mmol) was added to the reaction mixture and stirred for 2 h. The reaction mixture was diluted with EtOAc (15 mL) and washed with a saturated aqueous solution of NH₄Cl (5 mL), dried (Na₂SO₄), and concentrated. The resultant crude product was purified by column chromatography on silica gel using hexane–EtOAc (3:1 □ 2:1) to give bis(oxazole) (40 mg, 69% yield). To a solution of the bis(oxazole) (40 mg, 0.080 mmol) in CH₂Cl₂ (0.5 mL) was added a 0.95 M hexane solution of DIBAL (166 □L, 0.16 mmol) dropwise at –78 °C and stirred for 15 min. Anhydrous acetone (0.6 mL) was added to the reaction mixture and stirred at –78 °C for 10 min, then warmed to ambient temperature. A 20% aqueous sodium potassium tartrate (0.6 mL) was added to the mixture and stirred vigorously until the two layers rapidly separated (2 h). The mixture was extracted with Et₂O (10 mL □ 2). The combined organic extracts were dried (Na₂SO₄) and concentrated. The resultant crude product was purified by column chromatography on silica gel using hexane–EtOAc (2:1 □ 1:1) to give aldehyde **16** (26 mg, 71% yield).

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115

3.739

7.268
7.262
7.260
7.247
7.202
7.179

4.460
4.447

2.962

ppm

1

2

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1.01
4.23
4.58
3.19
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4.33
1.00

1.053
1.282
1.305

1.329

4.283
4.260

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7.661
7.642
7.640
7.636
7.410
7.404
7.380
7.262

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3.05

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2.86

1.83

2.01

2.00

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