DOI: 10.1002/adsc.200700068

Catalytic Synthesis of Peptide-Derived Thiazolines and Oxazolines using Bis(quinolinolato)dioxomolybdenum(VI) Complexes

Akira Sakakura,[a] Rei Kondo,[a] Shuhei Umemura,[a] and Kazuaki Ishihara[a,*]

[a] Graduate School of Engineering, Nagoya University, Chikusa, Nagoya, 464-8603 Japan
Fax: (+81)-52-789-3222; e-mail: ishihara@cc.nagoya-u.ac.jp

Received: January 26, 2007

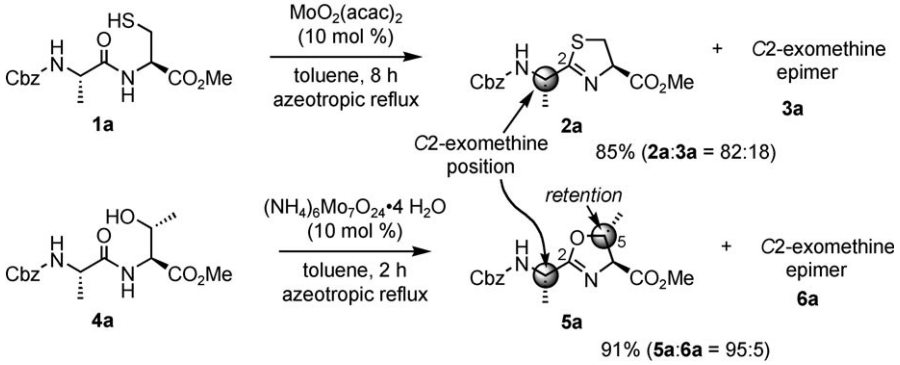
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Bis(2-ethyl-8-quinolinolato)dioxomolybdenum(VI) (**9**) (1 mol%) shows remarkable catalytic activity for the dehydrative cyclization of cysteine-containing dipeptides **1** to give the corresponding thiazolines **2** with less than 6% epimerization at the *C*2-exomethine position. For the dehydrative cyclization of threonine-containing dipeptides **4**, 1 mol% of bis(2-phenyl-8-quinolinolato)dioxomolybdenum(VI) (**10**) gives the corresponding oxazolines **5** with retention of configuration at the 5-position.

Keywords: catalysis; dehydrative cyclization; molybdenum; oxazolines; quinolinolato species; thiazolines

Thiazolines and oxazolines have been found in many biologically active natural products of peptide origin. Their wide range of antitumor, antiviral and antibiotic activities has fueled numerous synthetic investigations.[1] Thiazolines and oxazolines are thought to be biosynthesized *via* the dehydrative cyclization of cysteine, threonine and serine residues.[1c] Most chemical syntheses of thiazolines start from *N*-(β-hydroxyethyl)thioamides using stoichiometric amounts of dehydrating reagents,[2] while a few methods have been reported for the biomimetic synthesis of thiazolines from cysteine derivatives.[2a,3] For the chemical synthesis of L-threonine-derived oxazolines using stoichiometric amounts of dehydrating reagents, L-*allo*-threonine, which is much more expensive than L-threonine, is needed,[4,5] since the reaction proceeds with an inversion of configuration at the 5-position.[6]

Recently, we reported molybdenum oxides (10 mol%) as effective acid-base monoconjugate catalysts[7] for the biomimetic dehydrative cyclization of *N*-acylcysteines, *N*-acylthreonines and *N*-acylserines (Scheme 1).[8] $MoO_2(acac)_2$ has good catalytic activity for the dehydrative cyclization of cysteine-containing dipeptide **1a** to thiazoline **2a**. For the synthesis of oxazoline **5a** from dipeptide **4a** that includes a threonine residue, the ammonium salts $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and $(NH_4)_2MoO_4$ show good catalytic activities. Since the molybdenum oxide-catalyzed dehydrative cyclization of L-threonine derivatives proceeds with a retention of configuration at the 5-position, the molybdenum oxide-catalyzed method is very useful for the synthesis of naturally occurring oxazolines derived from L-threonine. This method is the first successful

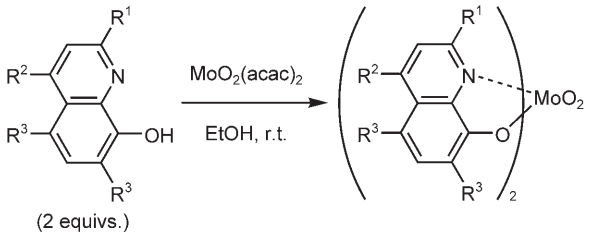


Scheme 1. Molybdenum oxide-catalyzed dehydrative cyclization of peptides (our previous work[8]).

example of the catalytic dehydrative cyclization of dipeptides that include cysteine, threonine and serine residues. Thiazolines and oxazolines such as **2a** and **5a** are useful building blocks for the synthesis of various bioactive natural products.[4–9]

Although the $MoO_2(acac)_2$-catalyzed dehydrative cyclization of Cbz-L-Ala-L-Cys-OMe (**1a**) proceeds well, epimerization product **3a** is also obtained in significant yield (**2a**:**3a** = 82:18) probably because of the acidity of $MoO_2(acac)_2$. Thiazolines are generally more susceptible to epimerization than oxazolines under both acidic and basic conditions.[2d,10] We considered that it was important to control the Lewis acidities and Brønsted basicities of molybdenum catalysts by more suitable ligands for the efficient design of dehydration catalysts.[7] Furthermore, homogeneous monomeric molybdenum complexes were expected to exhibit higher catalytic activities even under lower catalyst-loading conditions, while $MoO_2(acac)_2$, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and $(NH_4)_2MoO_4$ are heterogeneous oligomeric species and require rather higher catalyst loading (10 mol%).[8] Through the intensive examination of molybdenum complexes as dehydrative cyclization catalysts, we found that molybdenum (VI) complexes with 8-quinolinols showed good catalytic activities.[11,12] We report here bis(quinolinolato)-dioxomolybdenum(VI) complexes as efficient catalysts for the dehydrative cyclization of dipeptides including a cysteine or threonine residue to thiazolines and oxazolines.

Bis(quinolinolato)dioxomolybdenum(VI) complexes **7**–**12** were easily prepared from $MoO_2(acac)_2$ and known 8-quinolinols (2 equivs.) in EtOH in yields of 69–99% (Scheme 2). The structures of the bis(quinolinolato)dioxomolybdenum(VI) complexes were confirmed by ^{1}H NMR, IR, HR-MS, and X-ray crystallographic analyses. The X-ray single-crystal structures of **9** and **10** are shown in Figure 1. These hexacoordinated complexes may have a total of three arrangements: a) the two quinolinolato nitrogen atoms



	R^1	R^2	R^3		R^1	R^2	R^3
7	H	H	H	**10**	Ph	H	H
8	Me	H	H	**11**	Me	Me	H
9	Et	H	H	**12**	Me	Me	Br

Scheme 2. Preparation of bis(quinolinolato)dioxomolybdenum(VI) complexes.

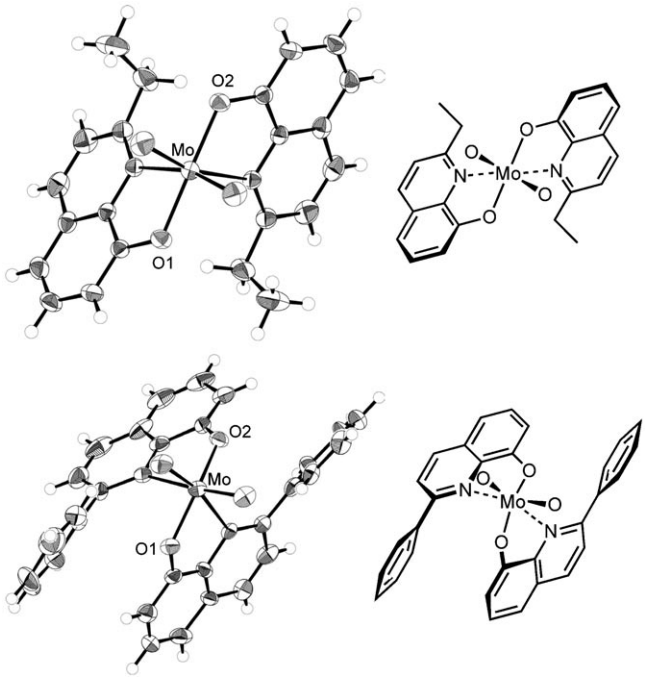
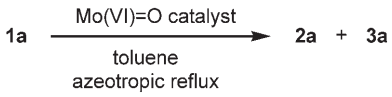


Figure 1. X-ray single-crystal structures of **9** (top) and **10** (bottom).

are *cis* to both oxo groups (*N-cis*); b) each nitrogen atom is *trans* to one oxo group (*N-trans*) and c) one nitrogen atom is *cis* to the oxo groups and the other is *trans* to one oxo group (*N-cis,trans*).[13] X-ray crystallographic analyses revealed that both **9** and **10** had *N-trans* configurations (Figure 1).[14] The X-ray single crystal structure of **10** is more distorted than that of **9** (O1–Mo–O2 bond angle of **9** = 163.69° and that of **10** = 147.96°). ^{1}H NMR spectra indicated that **9** was a 44:56 isomeric mixture in toluene-d_8 at ambient temperature. When the solution was heated at 100 °C, the ratio changed to 100:0. For **10**, the ratio of the isomers in toluene-d_8 was 77:23 at ambient temperature and 100:0 at 60 °C. The major isomers at high temperature are thought to be *N-trans*, and the minor isomers are *N-cis,trans*.

With the bis(quinolinolato)dioxomolybdenum(VI) complexes **7**–**12** in hand, we examined their catalytic activities for the dehydrative cyclization of **1a** to thiazoline **2a** (Table 1). The reaction was conducted in the presence of a bis(quinolinolato)dioxomolybdenum (VI) complex in toluene under azeotropic reflux conditions with the removal of water. Molybdenum(VI) complexes **7**–**12** could be dissolved in toluene and appeared to be stable under these reaction conditions. After removal of the solvent, the resulting crude product was analyzed by HPLC. 8-Quinolinolato complex **7** (10 mol%) showed good catalytic activity (80% yield), and the generation of epimer **3a** was effectively reduced, as expected (**2a**:**3a** = 96:4) (entry 1). We then tried to reduce the catalyst loading, but un-

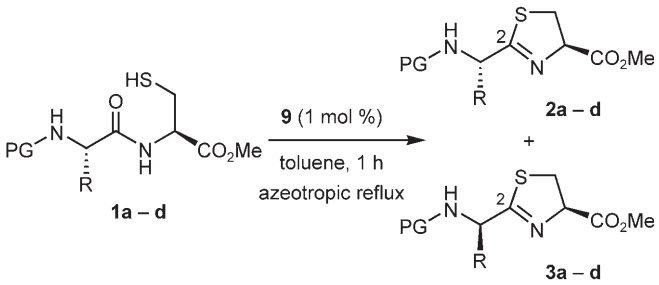
Table 1. Catalytic activities of bis(quinolinolato)dioxomolybdenum(VI) complexes for the dehydrative cyclization of **1a.**[a]



Entry	Mo(VI)=O [mol%]	Time [h]	Yield[b] [%]	*dr*[c] (**2a**:**3a**)
1	**7** [10]	5	80	96:4
2	**7** [1]	5	40	89:11
3	**8** [1]	5	93	95:5
4	**9** [1]	2	96	97:3
5	**10** [1]	5	80	85:15
6	**11** [1]	5	96	96:4
7	**12** [1]	2	94	86:14
8	$MoO_2(acac)_2$ [10]	8	85	82:18

[a] The reaction of **1a** (0.10 mmol) was conducted in the presence of an Mo(VI)=O catalyst in toluene (10 mL) under azeotropic reflux conditions.
[b] Yieds of **2a** and **3a** were determined by ^{1}H NMR analysis.
[c] Determined by HPLC analysis.

Table 2. Dehydrative cyclization of dipeptides **1** to thiazolines **2** catalyzed by **9**.[a]



Entry	Dipeptide **1** PG	R		Yield[b] [%]	*dr*[c] (**2**:**3**)
1	Cbz	Me	**1a**	83	99:1
2	Cbz	Bn	**1b**	85	98:2
3	Boc	Me	**1c**	82	94:6
4	Fmoc	Me	**1d**	91	96:4

[a] The reaction of dipeptides **1** (0.10 mmol) was conducted in the presence of **9** (1 mol%) in toluene (10 mL) under azeotropic reflux conditions for 1 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.

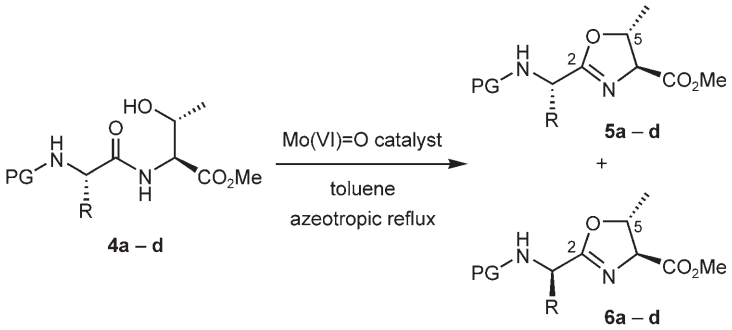
fortunately the use of 1 mol% of **7** decreased the reactivity (entry 2). Interestingly, we found that the introduction of an alkyl group to the 2-position of the 8-quinolinol significantly increased the catalytic activities of the quinolinolato complexes (entries 3–6). In particular, 2-ethyl-8-quinolinolato complex **9** and 2,4-dimethyl-8-quinolinol complex **11** exhibited remarkably higher catalytic activities than $MoO_2(acac)_2$, to give **2a** in 96% yield despite the lower catalyst loading (1 mol%) (entries 4 and 5 *versus* entry 8). Furthermore, the use of complexes **9** and **11** suppressed epimerization at the *C*2-exomethine position of the product to less than 4%. Although 2,4-dimethyl-5,7-dibromo-8-quinolinol complex **12** showed good catalytic activity, epimerization increased to 86:14 *dr* (entry 7). It is conceivable that the stronger acidity of complex **12** due to two electronegative bromine atoms promoted epimerization of the *C*2-exomethine position. In contrast, the introduction of an alkyl group to the 2-position increased the basicity of the quinolinolato-nitrogen to suppress epimerization.

We then examined the dehydrative cyclization of other cysteine-containing dipeptides, Cbz-L-Phe-L-Cys-OMe (**1b**), Boc-L-Ala-L-Cys-OMe (**1c**) and Fmoc-L-Ala-L-Cys-OMe (**1d**) (Table 2). Dipeptides **1a–d** could be converted to the corresponding thiazolines **2a–d** in good isolated yields (82–91%). *tert*-Butoxycarbonyl (Boc) and 9-fluorenylmethoxycarbonyl (Fmoc) groups, which are useful protecting groups for the synthesis of peptides and peptide-containing natural products, were also compatible with the reaction conditions (entries 3 and 4). In all cases, epimerization of the *C*2-exomethine position was suppressed to less than 6%.

We previously reported the dehydrative cyclization of **4a** to oxazoline **5a** in good yields using $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and $(NH_4)_2MoO_4$ as catalysts.[8] This reaction was accompanied by epimerization at the *C*2-exomethine position (95:5 *dr*) (Table 3, entry 8). We then compared the catalytic activities of bis(quinolinolato)dioxomolybdenum complexes for the dehydrative cyclization of threonine-containing dipeptides Cbz-L-Ala-L-Thr-OMe (**4a**), Cbz-L-Phe-L-Thr-OMe (**4b**), Boc-L-Ala-L-Thr-OMe (**4c**) and Fmoc-L-Ala-L-Thr-OMe (**4d**) to the corresponding oxazolines **5a–d** (Table 3). Although **7** and **8** showed moderate catalytic activities (entries 1 and 2), 2-phenyl-8-quinolinolato complex **10** gave excellent results (entries 3–6). The catalytic activity of the homogeneous complex **10** was higher than those of heterogeneous $(NH_4)_2MoO_4$ and $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, and the amount of **10** could be reduced to 1 mol%. Furthermore, the yield of epimers **6a–d** was less than 6%. The present reactions also showed a complete retention of configuration at the 5-position.

In conclusion, bis(2-ethyl-8-quinolinolato)dioxomolybdenum(VI) (**9**) promoted the catalytic dehydrative cyclization of cysteine-containing dipeptides **1** to thiazolines **2** in high yield without a significant loss of stereochemical integrity at the *C*2-exomethine positions. For the synthesis of threonine-derived oxazolines **5**, bis(2-phenyl-8-quinolinolato)dioxomolybdenum(VI) (**10**) showed excellent catalytic activity, and the reaction proceeded with a retention at the 5-position. In

Table 3. Dehydrative cyclization of dipeptides **4** to oxazolines **5** catalyzed by bis(quinolinolato)dioxomolybdenum(VI) complexes.[a]



Entry	Mo(VI)=O [mol%]	Dipeptide **4**			Time [h]	Yield[b] [%]	*dr*[c] (**5**:**6**)
		PG	R				
1	**7** [10]	Cbz	Me	**4a**	5	70[d]	81:19
2	**8** [10]	Cbz	Me	**4a**	5	51[d]	98:2
3	**10** [1]	Cbz	Me	**4a**	1	85	94:6
4	**10** [1]	Cbz	Bn	**4b**	1	92	96:4
5	**10** [1]	Boc	Me	**4c**	2	89	98:2
6	**10** [1]	Fmoc	Me	**4d**	1	88	95:5
7	**12** [10]	Cbz	Me	**4a**	6	42[d]	nd
8	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ [10]	Cbz	Me	**4a**	2	91[d]	95:5

[a] The reaction of dipeptides **4** (0.10 mmol) was conducted in the presence of an Mo(VI)=O catalyst in toluene (10 mL) under azeotropic reflux conditions.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Determined by ^{1}H NMR analysis.

both reactions, catalyst loadings of 1 mol% were sufficient to give thiazolines and oxazolines in good yields. In addition to the total synthesis of thiazoline- and/or oxazoline-containing natural products, the present method should also be applicable to the synthesis of thiazole- and/or oxazole-containing natural products,[15] since thiazoles and oxazoles could be prepared from thiazolines and oxazolines by oxidation.[16]

Experimental Section

Preparation of *cis*-Bis(2-ethyl-8-quinolinolato-*N,O*)dioxomolybdenum(VI) (9)

To a solution of $MoO_2(acac)_2$ (44.2 mg, 0.135 mmol) in EtOH (0.50 mL) was added a solution of 2-ethyl-8-quinolinol (47.0 mg, 0.27 mmol) in EtOH (1.0 mL). After being stirred at ambient temperature for 12 h, **9** was obtained by filtration; yield: 58 mg (91%). Single crystals suitable for X-ray analysis were obtained from CH_2Cl_2. IR (KBr): $\nu = 908$ cm^{-1} (Mo=O); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.14$ (t, $J =$ 7.5 Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 1.7H), 1.32 (t, $J = 7.5$ Hz, 1.3H), 2.62 (m, 0.8H), 3.14 (m, 1.2H), 3.49 (m, 1.2H), 4.08 (m, 0.8H), 5.18 (d, $J = 7.5$ Hz, 0.4H), 5.74 (d, $J = 7.5$ Hz, 0.4H), 6.21 (dd, $J = 2.4$, 6.3 Hz, 0.4H), 6.46 (m, 0.8H), 6.62 (t, $J = 7.5$ Hz, 0.4H), 6.95–7.05 (m, 2.4H), 7.20–7.30 (m, 1.2H), 7.48 (t, $J = 8.1$ Hz, 1.2H), 7.53 (d, $J = 8.1$ Hz, 0.4H), 7.58 (d, $J = 8.1$ Hz, 0.4H), 7.91 (d, $J = 8.1$ Hz, 0.4H), 8.06 (d, $J = 8.1$ Hz, 0.6H), 8.15 (d, $J = 8.1$ Hz, 0.4H), 8.29 (d, $J =$ 8.7 Hz, 0.6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.0$, 14.0, 14.8, 27.4, 29.1, 29.2, 111.7, 113.4, 114.7, 115.9, 116.0, 118.2, 122.2, 123.0, 123.3, 124.7, 126.4, 127.0, 127.7, 127.8, 130.2, 132.8, 136.8, 138.1, 138.5, 140.1, 144.6, 150.3, 156.5, 159.0, 166.4; **9** was a *ca.* 3:2 isomeric mixture in $CDCl_3$; HR-MS (FAB): $m/z = 475.0563$, calcd. for $C_{22}H_{21}MoN_2O_4$ $[M+H]^+$: 475.0555.

Preparation of *cis*-Bis(2-phenyl-8-quinolinolato-*N,O*)-dioxomolybdenum(VI) (10)

To a solution of $MoO_2(acac)_2$ (65.2 mg, 0.20 mmol) in EtOH (0.50 mL) was added a solution of 2-phenyl-8-quinolinol (88.5 mg, 0.40 mmol) in EtOH (1.0 mL). After being stirred at ambient temperature for 15 min, **10** was obtained by filtration; yield: 91 mg (80%). Single crystals suitable for X-ray analysis were obtained from EtOH. IR (KBr): $\nu = 900$ cm^{-1} (Mo=O); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.50$ (d, $J =$ 7.5 Hz, 0.2H), 5.75 (d, $J = 5.1$ Hz, 0.1H), 5.76 (d, $J = 5.1$ Hz, 0.1H), 5.96 (dd, $J = 1.8$, 7.2 Hz, 0.9H), 6.24 (d, $J = 7.8$ Hz, 0.2H), 6.48 (s, 0.2H), 6.49 (d, $J = 2.1$ Hz, 0.2H), 6.76 (t, $J =$ 7.8 Hz, 0.2H), 6.97 (d, $J = 7.8$ Hz, 0.2H), 7.05 (t, $J = 6.6$ Hz, 0.6H), 7.13–7.25 (m, 4.2H), 7.35 (d, $J = 6.9$ Hz, 0.4H), 7.42–7.64 (m, 6.2H), 7.66–7.82 (m, 3.2H), 7.94 (d, $J = 8.7$ Hz, 0.2H), 8.00 (d, $J = 8.1$ Hz, 0.9H), 8.16 (m, 0.9H), 8.23 (m, 0.9H), 8.43 (d, $J = 8.4$ Hz, 0.2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 115.3$, 117.5, 124.8, 127.7, 128.0, 129.5, 130.5, 137.8, 138.0, 138.2, 139.9, 155.0, 158.2, 160.1; **10** was a *ca.* 9:1

isomeric mixture in $CDCl_3$; HRMS (FAB): $m/z = 571.0542$, calcd. for $C_{30}H_{21}MoN_2O_4$ $[M+H]^+$: 571.0555.

General Procedure for the Dehydrative Cyclization of Dipeptides 1 and 4

A 20-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 5-mL pressure-equalized addition funnel [containing a cotton plug and *ca.* 0.1 g of CaH_2] surmounted by a reflux condenser was charged with a dipeptide **1** or **4** (0.10 mmol) and a molybdenum(VI) complex (1 mol%) in toluene (10 mL). The mixture was heated for several hours under azeotropic reflux conditions with the removal of water. The reaction mixture was cooled to ambient temperature, washed with saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), and the organic solvent was then removed to give a crude product. The obtained crude product was purified by column chromatography on silica gel using toluene-acetone (for **2**) or hexane-EtOAc (for **5**), to give a corresponding thiazoline **2** or oxazoline **5**.

Acknowledgements

Financial support for this project was provided by JSPS KAKENHI (15205021 and 18750082), the 21st Century COE Program "Nature-Guided Materials Processing" of MEXT and The Japan Securities Scholarship Foundation.

References

[1] a) Z. Jin, *Nat. Prod. Rep.* **2006**, *23*, 464–496, and references cited therein; b) J. R. Lewis, *Nat. Prod. Rep.* **2002**, *19*, 223–258, and references cited therein; c) R. S. Roy, A. M. Gehring, J. C. Milne, P. J. Belshaw, C. T. Walsh, *Nat. Prod. Rep.* **1999**, *16*, 249–263.

[2] a) Ph_3PO–Tf_2O: S.-L. You, H. Razavi, J. W. Kelly, *Angew. Chem. Int. Ed.* **2003**, *42*, 83–85; b) Martin's sulfrane: F. Yokokawa, T. Shioiri, *Tetrahedron Lett.* **2002**, *43*, 8679–8682; c) DAST: A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno, D. R. Williams, *Org. Lett.* **2000**, *2*, 1165–1168; d) Burgess reagent: P. Wipf, P. C. Fritch, *Tetrahedron Lett.* **1994**, *35*, 5397–5400; e) Burgess reagent: P. Wipf, C. P. Miller, *Tetrahedron Lett.* **1992**, *33*, 907–910; f) Mitsunobu reagent: N. Galéotti, C. Montagne, J. Poncet, P. Jouin, *Tetrahedron Lett.* **1992**, *33*, 2807–2810; g) Mitsunobu reagent: P. Wipf, C. P. Miller, *Tetrahedron Lett.* **1992**, *33*, 6267–6270; h) Ph_2SO–Tf_2O: F. Yokokawa, Y. Hamada, T. Shioiri, *Synlett* **1992**, 153–154; i) DAST: G. Burrell, J. M. Evans, G. E. Jones, G. Stemp, *Tetrahedron Lett.* **1990**, *31*, 3649–3652; j) PPh_3–CCl_4: A. I. Meyers, H. Denton, *Tetrahedron Lett.* **1985**, *26*, 4687–4690; k) PPh_3–CCl_4: H. Vorbrüggen, K. Krolikiewicz, *Tetrahedron Lett.* **1981**, *22*, 4471–4474.

[3] Kelly reported the synthesis of the thiazoline from Cbz-L-Phe-L-Cys(Tr)-OMe using $TiCl_4$ (300 mol%). However, complete epimerization at the *C*2-exomethine position occurred because of the strong acidity of $TiCl_4$: P. Raman, H. Razavi, J. W. Kelly, *Org. Lett.* **2000**, *2*, 3289–3292.

[4] a) S.-L. You, J. W. Kelly, *Tetrahedron* **2005**, *61*, 241–249; b) S.-L. You, J. W. Kelly, *Chem. Eur. J.* **2004**, *10*, 71–75; c) F. Yokokawa, H. Sameshima, Y. In, K. Minoura, T. Ishida, T. Shioiri, *Tetrahedron* **2002**, *58*, 8127–8143; d) N. Kutsumura, N. U. Sata, S. Nishiyama, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 847–850; e) F. Yokokawa, H. Sameshima, T. Shioiri, *Synlett* **2001**, 986–988; f) P. Wipf, C. P. Miller, C. M. Grant, *Tetrahedron* **2000**, *56*, 9143–9150; g) C. D. J. Boden, M. C. Norley, G. Pattenden, *J. Chem. Soc., Perkin Trans. 1* **2000**, 883–888; h) C. D. J. Boden, G. Pattenden, *J. Chem. Soc., Perkin Trans. 1* **2000**, 875–882; i) M. C. Norley, G. Pattenden, *Tetrahedron Lett.* **1998**, *39*, 3087–3090; j) C. D. J. Boden, M. C. Norley, G. Pattenden, *Tetrahedron Lett.* **1996**, *37*, 9111–9114; k) C. D. J. Boden, G. Pattenden, *Tetrahedron Lett.* **1995**, *36*, 6153–6156.

[5] Wipf reported the conversion of *cis*-oxazolines to *trans*-oxazolines; a) P. Wipf, C. P. Miller, *J. Am. Chem. Soc.* **1992**, *114*, 10975–10977; b) P. Wipf, C. P. Miller, *J. Org. Chem.* **1993**, *58*, 1575–1578; c) P. Wipf, P. C. Fritch, *J. Am. Chem. Soc.* **1996**, *118*, 12358–12367; d) S. V. Downing, E. Aguilar, A. I. Meyers, *J. Org. Chem.* **1999**, *64*, 826–831.

[6] Corey reported the dehydrative cyclization of a threonine derivative using TsOH (10 mol%) as a catalyst. The reaction proceeds with a retention of configuration at the 5-position: L. R. Reddy, P. Saravanan, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 6230–6231; in our experiment, dehydrative cyclization of **4a** using TsOH gave a 1:1 mixture of **5a** and **6a** due to its strong acidity.

[7] K. Ishihara, A. Sakakura, M. Hatano, *Synlett* **2007**, in press.

[8] a) A. Sakakura, R. Kondo, K. Ishihara, *Org. Lett.* **2005**, *7*, 1971–1974; b) A. Sakakura, S. Umemura, R. Kondo, K. Ishihara, *Adv. Synth. Catal.* **2007**, in press.

[9] a) B. Wagner, D. Schumann, U. Linne, U. Koert, M. A. Marahiel, *J. Am. Chem. Soc.* **2006**, *128*, 10513–10520; b) R. J. Boyce, G. C. Mulqueen, G. Pattenden, *Tetrahedron Lett.* **1994**, *35*, 5705–5708.

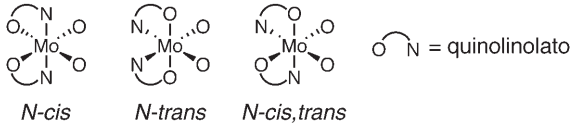
[10] K. Yonetani, Y. Hirotsu, T. Shiba, *Bull. Chem. Soc., Jpn.* **1975**, *48*, 3302–3305.

[11] See Supporting Information for catalytic activities of other molybdenum(VI) complexes.

[12] For recent studies of bis(quinolinolato)complex-catalyzed reactions, see: a) G. Xia, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 2554–2555; b) N. Takenaka, G. Xia, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 13198–13199.

[13] M. Gómez, S. Jansat, G. Muller, G. Noguera, H. Teruel, V. Moliner, E. Cerrada, M. Hursthouse, *Eur. J. Inorg. Chem.* **2001**, 1071–1076.

[14] The X-ray single-crystal structure of **8** has been reported. The crystal structure of **8** also shows an *N-trans* configuration: H.-K. Fun, K. Sivakumar, J.-Y. Niu, J.-P. Wang, X.-Z. You, *Acta Crystallogr.* **1996**, *C52*, 1150–1152.



[15] a) S. K. Chattopadhyay, S. Biswas, B. K. Pal, *Synthesis* **2006**, 1289–1294; b) Y. Nakamura, S. Takeuchi, *QSAR Comb. Sci.* **2006**, *25*, 703–708; c) K. C. Nicolaou, D. Y.-K. Chen, X. Huang, T. Ling, L. Bella, S. A. Snyder, *J. Am. Chem. Soc.* **2004**, *126*, 12888–12896; d) A. Plant, F. Stieber, J. Scherkenbeck, P. Lösel, H. Dyker, *Org. Lett.* **2001**, *3*, 3427–3430; e) Z. Xia, C. D. Smith, *J. Org. Chem.* **2001**, *66*, 3459–3466; f) L. Somogyi, G. Haberhauer, J. Rebek, Jr., *Tetrahedron* **2001**, *57*, 1699–1708; g) F. Yokokawa, T. Asano, T. Shioiri, *Org. Lett.* **2000**, *2*, 4169–4172; h) J. Kempson, G. Pattenden, *Synlett* **1999**, 533–536; i) J. C. Muir, G. Pattenden, R. M. Thomas, *Synthesis* **1998**, 613–618; j) P. M. Pihko, A. M. P. Koskinen, *J. Org. Chem.* **1998**, *63*, 92–98; k) R. J. Boyce, G. C. Mulqueen, G. Pattenden, *Tetrahedron* **1995**, *51*, 7321–7330; l) M. Nakamura, T. Shibata, K. Nakane, T. Nemoto, M. Ojika, K. Yamada, *Tetrahedron Lett.* **1995**, *36*, 5059–5062; m) E. Agullar, A. I. Meyers, *Tetrahedron Lett.* **1994**, *35*, 2477–2480; n) D. W. Knight, G. Pattenden, D. E. Rippon, *Synlett* **1990**, 36–37.

[16] a) D. R. Williams, P. D. Lowder, Y.-G. Gu, D. A. Brooks, *Tetrahedron Lett.* **1997**, *38*, 331–334; b) A. I. Meyers, F. X. Tavares, *J. Org. Chem.* **1996**, *61*, 8207–8215; c) F. Tavares, A. I. Meyers, *Tetrahedron Lett.* **1994**, *35*, 6803–8606; d) J. C. Barrish, J. Singh, S. H. Spergel, W.-C. Han, T. P. Kissick, D. R. Kronenthal, R. H. Mueller, *J. Org. Chem.* **1993**, *58*, 4494–4496; e) D. L. Evans, D. K. Minster, U. Jordis, S. M. Hecht, A. L. Mazzu, Jr., A. I. Meyers, *J. Org. Chem.* **1979**, *44*, 497–501.

