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Dehydrative cyclization of serine, threonine, and cysteine residues catalyzed by molybdenum(VI) oxo compounds

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

[a] EcoTopia Science Institute, Nagoya University, Chikusa, Nagoya 464-8603, Japan
[b] Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

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ABSTRACT

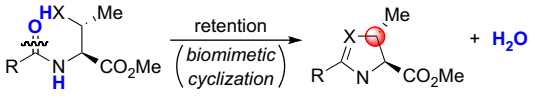
Commercially available molybdenum(VI) oxides such as $(NH_4)_2MoO_4$, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, $MoO_2(acac)_2$, and $MoO_2(TMHD)_2$ are highly effective dehydrative cyclization catalysts for the synthesis of a variety of oxazolines. The reaction proceeds with a complete retention of configuration at the β-position. For the dehydrative cyclization of cysteine derivatives, bis(2-ethyl-8-quinolinolato)dioxomolybdenum(VI) shows remarkable catalytic activity and gives thiazolines without a significant loss of stereochemical integrity at the *C*2-exomethine positions.

1. Introduction

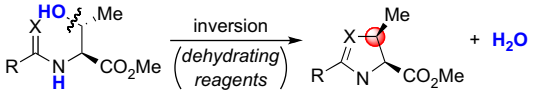
Oxazolines, oxazoles, thiazolines, and thiazoles are important constituents of numerous bioactive natural products of peptide origin.[1] Their wide range of antitumor, antiviral, and antibiotic activities has fueled numerous synthetic investigations. The biosynthesis of many naturally occurring oxazolines and thiazolines appears to involve the dehydrative cyclization of serine, threonine, and cysteine residues (Scheme 1).[1c] Oxazoles and thiazoles are synthesized by the oxidation of oxazolines and thiazolines, respectively.

Although several methods have been reported for the synthesis of oxazolines and thiazolines using stoichiometric dehydrating reagents,[2] few dehydrating catalysts are known to be effective for the dehydrative cyclization of *N*-(β-hydroxyethyl)amides or *N*-(β-mercaptoethyl)amides to oxazolines or thiazolines: 3-nitrophenylboric acid,[3] a tetranuclear zinc cluster,[4] a lanthanide chloride,[5] a zeolite,[6] $TiCl_4$,[7] TsOH,[8] etc. However, these catalytic methods are limited to simple substrates derived from an amino alcohol or a monopeptide (amino acid). Since oxazolines and thiazolines readily epimerize at the *C*2-exomethine position under both acidic and basic conditions,[7a,9] the synthesis of oxazolines and thiazolines must be conducted under mild and weakly acidic or basic conditions.

There are two known methodologies for the chemical synthesis of oxazolines and thiazolines: retentive cyclization at the β-position (biomimetic cyclization) (Eq. 1), and its invertive cyclization (Eq. 2). For the chemical synthesis of naturally occurring oxazolines and thiazolines, biomimetic retentive cyclization is more desirable. However, most reactions that use stoichiometric dehydrating reagents proceed with an inversion of configuration at the β-position. Therefore the conventional synthesis using stoichiometric dehydrating reagents requires expensive L-*allo*-threonine for the synthesis of L-threonine-derived oxazolines.[10,11] In addition, for the synthesis of thiazolines, the use of *N*-(β-hydroxyethyl)thioamides is required.[2a,d,f]



(1)



(X = O, S)

(2)

For the synthesis of oxazoline- and/or thiazoline-containing bioactive natural compounds, a more effective catalytic method for the dehydrative cyclization of serine, threonine, and cysteine residues that proceeds with a retention of configuration at the β-position is needed. In this report, we describe a detailed investigation of molybdenum(VI) oxo compounds as highly effective catalysts for the dehydrative cyclization of serine, threonine, and cysteine residues.[12,13] To the best of our knowledge, this is the first successful example of the catalytic dehydrative cyclization of dipeptide substrates for the biomimetic synthesis of oxazolines and thiazolines. The present method is highly useful for the synthesis of common

* Corresponding author. Tel.: +81 52 789 3331; fax: +81 52 789 3222.
E-mail address: ishihara@cc.nagoya-u.ac.jp (K. Ishihara).

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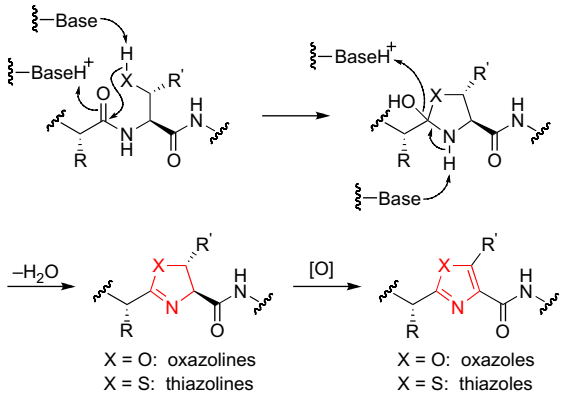


Scheme 1. Proposed biosynthesis of oxazolines, thiazolines, oxazoles, and thiazoles.

building blocks for various bioactive natural products[14,15] and chiral oxazoline ligands for asymmetric synthesis.[16]

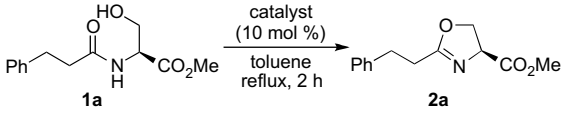
2. Results and discussion

2.1. Catalytic dehydrative cyclization of serine and threonine derivatives

Our initial studies focused on the catalytic activities of various metal compounds (10 mol %) for the dehydrative cyclization of *N*-(3-phenylpropionyl)-L-serine methyl ester (**1a**) in toluene under reflux conditions for 2 h (Table 1). Commercially available molybdenum oxides such as $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, MoO_2, and MoO_3 showed high catalytic activities (51–68% yield, entries 1–3). Perrhenic acid ($HOReO_3$) and trimethylsilylperrhenate ($TMSOReO_3$) also gave good results (49% yields, entries 6 and 7). In contrast, the catalytic activities of other metal compounds such as Na_2MoO_4 and ReO_2 were very low (entries 4, 5, 8–14). When the MoO_3-catalyzed dehydrative cyclization was conducted in polar solvents such as nitroethane, propionitrile, and 1,4-dioxane, the yields of **2a** significantly decreased (<3% yields).

Next, we examined the catalytic activities of commercially available molybdenum oxides for the dehydrative cyclization of **1a** and *N*-(3-phenylpropionyl)-L-threonine methyl ester (**1b**) (Table 2).

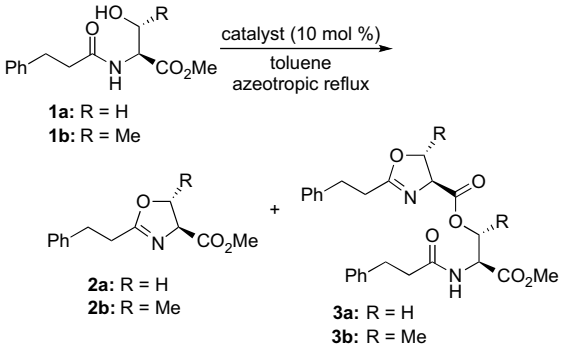
Table 1
Initial screening for catalytic activities of metal compounds for the dehydrative cyclization of **1a**[a,b]



Entry	Catalyst	Yield[c] (%)
1	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	68
2	MoO_2	53
3	MoO_3	51
4	MoO_2Cl_2	30
5	Na_2MoO_4	13
6	$HOReO_3$	49
7	$TMSOReO_3$	49
8	ReO_2	0
9	V_2O_4	14
10	VCl_3	4
11	WO_3	0
12	$TiCl_4$	22
13	TiO_2	0
14	SnO_2	0

[a] The reaction of **1a** (0.05 mmol) was conducted in the presence of catalyst (10 mol %) in toluene (2.5 mL) under reflux conditions for 2 h.
[b] The amounts of catalysts were calculated based on the metal.
[c] Estimated by HPLC analysis.

Table 2
Catalytic activities of molybdenum oxo compounds for the dehydrative cyclization of **1**[a]



Entry	Catalyst	1a→2a		1b→2b	
		Time (h)	Yield[b,c] (%)	Time (h)	Yield[b,c] (%)
1	MoO_2	8	86 (10)	8	97 (0)
2	MoO_3	8	78 (5)	8	99 (0)
3	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	4	87 (11)	2	97 (0)
4	$(NH_4)_2MoO_4$	4	89 (11)	2	95 (0)
5	$MoO_2(acac)_2$	1	87 (7)	1	90 (0)
6	$CoMoO_4$		—	4	96 (0)
7	$FeMoO_4$		—	4	96 (0)
8	$3\text{-}(NO_2)C_6H_4B(OH)_2$	8	3 (0)	8	4 (0)
9	No catalyst	8	0 (0)	8	0 (0)

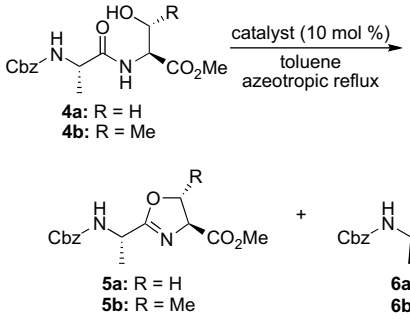
[a] The reaction of **1** (0.5 mmol) was conducted in the presence of catalyst (10 mol %) in toluene (50 mL for **1a** and 10 mL for **1b**) under azeotropic reflux with the removal of water.
[b] Determined by HPLC analysis.
[c] Yield of **3a** or **3b** in parentheses.

The reaction was conducted in toluene under azeotropic reflux conditions with the removal of water. As a result, the ammonium salts and acetylacetonate complex of molybdenum(VI) oxide such as $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, $(NH_4)_2MoO_4$, and $MoO_2(acac)_2$ were found to have good catalytic activities (entries 3–5). The reaction of **1a** was conducted under high-dilution conditions (0.01 M), since a small amount of dimer **3a** was obtained as a byproduct. When the reaction of **1a** was carried out using $(NH_4)_2MoO_4$ at a higher concentration (0.05 M), the yield of **3a** increased to 27% and the yield of **2a** decreased to 53%. In contrast, the reaction of **1b** did not produce dimer **3b** even at a higher concentration (0.05 M). Interestingly, the reaction of **1b** proceeded with a retention of configuration at the β-position of the threonine residue (biomimetic mechanism). $CoMoO_4$ and $FeMoO_4$ also effectively promoted the reaction of **1b**, but the catalytic activities were slightly lower than those of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, $(NH_4)_2MoO_4$ and $MoO_2(acac)_2$ (entries 6 and 7). 3-Nitrophenylboronic acid [$3\text{-}(NO_2)C_6H_4B(OH)_2$][3] was almost inert for the present reaction (entry 8).

We then examined the dehydrative cyclization of more complex dipeptide substrates Cbz-L-Ala-L-Ser-OMe (**4a**) and Cbz-L-Ala-L-Thr-OMe (**4b**) (Table 3). The ammonium salts of molybdenum(VI) oxides, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and $(NH_4)_2MoO_4$, showed excellent catalytic activities, and gave the corresponding oxazolines **5a** and **5b** in a short reaction time, along with small amounts of **6a** and **6b**, which are epimers at the *C*2-exomethine position of the alanine residue (entries 3 and 4). In contrast to molybdenum(VI) oxides, the dehydrative cyclization of **4b** catalyzed by TsOH[8] gave a 1:1 mixture of **5b** and **6b**, probably due to the strong acidity of TsOH.

Hennoxazole A (Fig. 1), which displays potency against herpes simplex virus type 1 and peripheral analgesic activity comparable to that of indomethacin, has a bisoxazole structure, in which two oxazole rings are directly connected.[17] We synthesized a key synthetic intermediate **14** of hennoxazole A,[18] which includes the

Table 3
Synthesis of oxazolines **5**[a]



Entry	Catalyst	4a→5a		4b→5b	
		Time (h)	Yield[b,c] (%)	Time (h)	Yield[b,c] (%)
1	MoO_2	8	80 (4)	2.5	80 (5)
2	MoO_3	8	83 (2)	3	82 (6)
3	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	2.5	90 (0)	2	86 (5)
4	$(NH_4)_2MoO_4$	1	93 (0)	1.5	84 (8)
5	$MoO_2(acac)_2$	1	68 (0)	1	82 (11)

[a] The reaction of **4** (0.5 mmol) was conducted in the presence of catalyst (10 mol %) in toluene (50 mL for **4a** and 10 mL for **4b**) under azeotropic reflux with the removal of water.
[b] Determined by HPLC analysis.
[c] Yield of **6a** or **6b** in parentheses.

bis(oxazole) structure, using the present Mo(VI)=O-catalyzed dehydrative cyclization as a key step (Scheme 2). We first tried to construct the bis(oxazoline) structure via the dehydrative double-cyclization of dipeptide **7**. Unfortunately, however, the $MoO_2(acac)_2$-catalyzed dehydrative cyclization of **7** gave the dehydrative

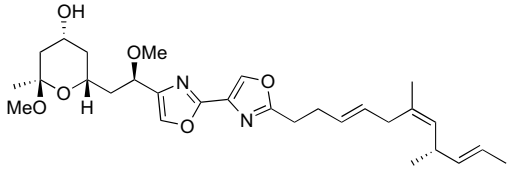
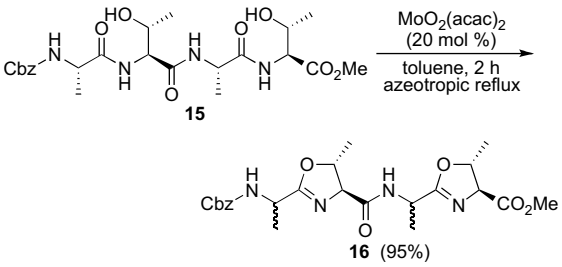


Figure 1. Hennoxazole A.

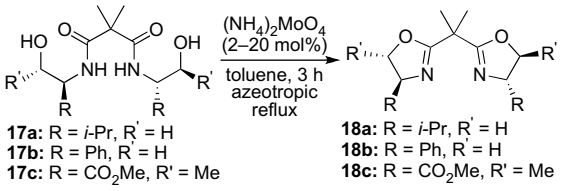


Scheme 3. Dehydrative cyclization of tetrapeptide **15**.

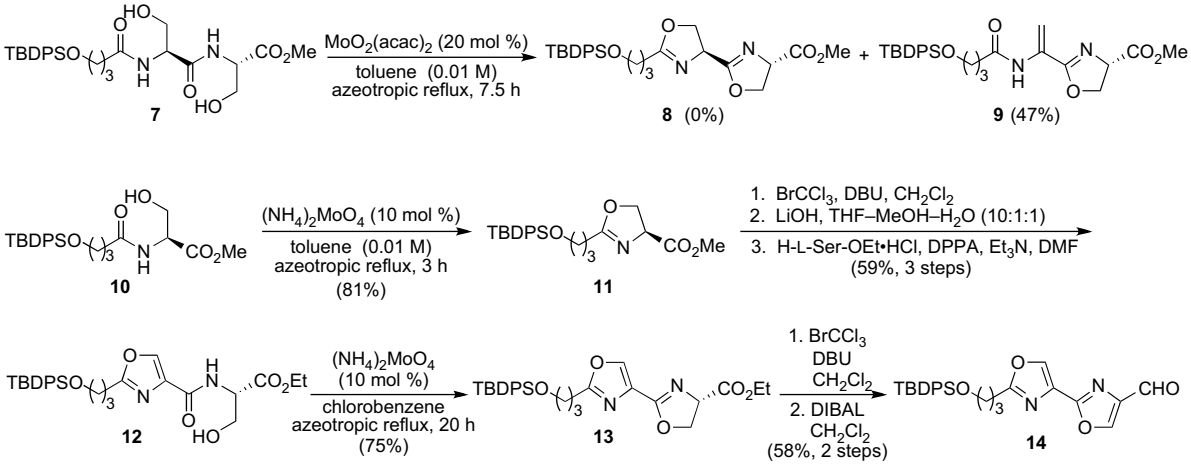
elimination product **9** as a major product (47%) and the desired product **8** was not obtained.[19] It is conceivable that the dehydrative double-cyclization of *N*-serylserine derivatives was very difficult. In fact, the reaction of **7** conducted with Burgess reagent (2.4 equiv) also gave **9** as a major product. In contrast, the dehydrative double-cyclization of tetrapeptide **15**, in which two threonine residues were separated by a alanine residue, proceeded rapidly to give the corresponding bis(oxazoline) **16** in 95% yield, although **16** was obtained as a diastereomeric mixture (Scheme 3).[20]

We next tried to construct two oxazole rings in a stepwise manner. Dehydrative cyclization of **10** using $(NH_4)_2MoO_4$ (10 mol %) gave oxazoline **11** in 81% yield. Oxidation of oxazoline **11** to oxazole,[15a] hydrolysis of methyl ester, and condensation with L-serine ethyl ester gave **12** in 59% overall yield. Since **12** was less reactive in the Mo(VI)=O-catalyzed dehydrative cyclization, the reaction of **12** was conducted in chlorobenzene (bp 132 °C) and gave oxazoline **13** (75%) along with recovered **12** (8%). Oxidation of the oxazoline ring[15a] and reduction of the ethyl ester of **13** gave **14** in 58% yield.

Bis(oxazoline)s are a very useful class of chiral ligands for asymmetric catalysis[21] and are generally synthesized from the corresponding bis(amide)s via sulfonylation or chlorination of the two hydroxyl groups. Bis(oxazoline)s **18** could be easily synthesized

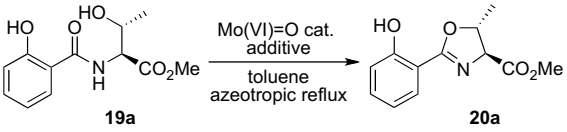


Scheme 4. Synthesis of bis(oxazoline)s **18**, chiral ligands for asymmetric catalysis.



Scheme 2. Synthesis of **14**, a key synthetic intermediate of hennoxazole A.

Table 4
Synthesis of oxazolines **20a**[a]



19a **20a**

Entry	Mo(VI)=O cat.	Additive, mol %	Yield[b] (%)
1	$(NH_4)_2MoO_4$	—	17
2	$MoO_2(acac)_2$	—	5
3	$(NH_4)_2MoO_4$	TsOH, 10	19
4	$(NH_4)_2MoO_4$	$C_6H_5CO_2H$, 10	57
5	$(NH_4)_2MoO_4$	$C_6F_5CO_2H$, 10	76
6	$(NH_4)_2MoO_4$	$C_6F_5CO_2H$, 2	47
7	$(NH_4)_2MoO_4$	$C_6F_5CO_2H$, 20	76
8	$(NH_4)_2MoO_4$	3,5-$(CF_3)_2C_6H_3CO_2H$, 10	76
9	$(NH_4)_2MoO_4$	4-$(NO_2)C_6H_4CO_2H$, 10	67
10	$MoO_2(acac)_2$	$C_6F_5CO_2H$, 10	76
11	$MoO_2(acac)_2$	3,5-$(CF_3)_2C_6H_3CO_2H$, 10	79
12	—	TsOH, 10	19
13	—	$C_6F_5CO_2H$, 10	1
14	—	3,5-$(CF_3)_2C_6H_3CO_2H$, 10	0

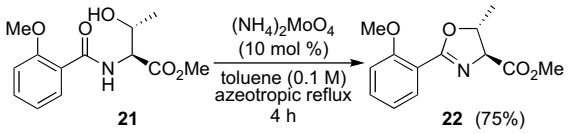
[a] The reaction of **19a** (1 mmol) was conducted with Mo(VI)=O (10 mol %) in toluene (10 mL) under azeotropic reflux conditions for 10–12 h.
[b] Determined by ^{1}H NMR analysis.

by the molybdenum(VI) oxide-catalyzed dehydrative double-cyclization of bis(amide)s **17** (Scheme 4). Bis(amide)s **17a** and **17b** were reacted with $(NH_4)_2MoO_4$ (20 mol %) under azeotropic reflux with the removal of water for 3 h. After purification by silica gel chromatography, bis(oxazoline)s **18a** and **18b** were obtained in respective yields of 84 and 83%. Furthermore, bis(oxazoline) **18c** was synthesized in the presence of $(NH_4)_2MoO_4$ (2 mol %) in 69% yield with a retention of configuration at the β-position.

2.2. Dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-L-threonine derivatives and *N*-(*o*,*m*-dihydroxybenzoyl)-L-threonine derivatives

Among oxazoline-containing natural compounds, 2-(*o*-hydroxyphenyl)oxazoline structures and 2-(*o*,*m*-dihydroxyphenyl)oxazoline structures are common. The biosynthesis of these natural products appears to involve the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-L-threonines or *N*-(*o*,*m*-dihydroxybenzoyl)-L-threonines with a retention of configuration at the β-position. For the chemical synthesis of these bioactive compounds, oxazolines **20** and **24** are useful building blocks.[22] Therefore, we investigated the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-L-threonines and *N*-(*o*,*m*-dihydroxybenzoyl)-L-threonines using molybdenum(VI) oxide catalysts.

We initially examined the catalytic activities of molybdenum(VI) oxides for the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-L-threonine methyl ester (**19a**) to oxazoline **20a** (Table 4).[12b] Unfortunately, the catalytic activities of $(NH_4)_2MoO_4$ and $MoO_2(acac)_2$ were very low (entries 1 and 2). One of the reasons for the low activities of these molybdenum(VI) oxides is their tight complexation with **20a**. Actually, the reaction of *N*-(*o*-methoxybenzoyl)-L-threonine methyl ester **21** proceeded well to give oxazoline **22** in 75% yield (Scheme 5). To increase the reactivity of **19a**, we examined several Brønsted acids as additives. *p*-Toluenesulfonic acid (TsOH) did not promote the reaction of **19a** at all (entry 3). The catalytic activity of TsOH itself was also very low (entry 12), although it shows good catalytic activity for the dehydrative cyclization of *N*-(*p*-methoxybenzoyl)-L-threonine methyl ester.[8] Very interestingly, some benzoic acids bearing electron-withdrawing substituents efficiently promoted the molybdenum(VI) oxide-catalyzed dehydrative cyclization of **19a**. In particular, pentafluorobenzoic acid ($C_6F_5CO_2H$), 3,5-bis(trifluoromethyl)benzoic acid [3,5-$(CF_3)_2C_6H_3CO_2H$], and 4-nitrobenzoic acid [4-$(NO_2)C_6H_4CO_2H$] gave good results (entries 5, 8–11). The optimal amount of $C_6F_5CO_2H$ was 1 mol equiv per molybdenum(VI) oxide (entries 5–7). Since these benzoic acids themselves showed no catalytic activities (entries 13 and 14), they primarily promoted the activities of molybdenum(VI) oxides. These benzoic acids might promote decomposition of the stable and inactivated complexes of molybdenum(VI) oxide and **20a** to regenerate the active catalyst. The experimental finding that the isolated yield of **20a** was decreased without an aqueous work-up also supported the formation of a stable complex of molybdenum(VI) oxides with **20a**.



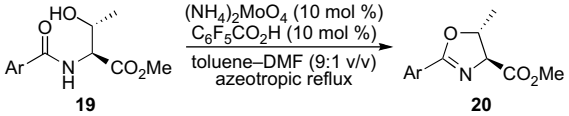
21 **22** (75%)

Scheme 5. Dehydrative cyclization of *N*-(*o*-methoxybenzoyl)-L-threonine methyl ester **21**.

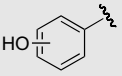
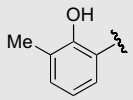
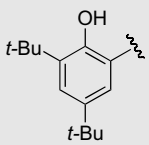
In contrast to the dehydrative cyclization of **19a**, the reaction of *m*- and *p*-hydroxy derivatives **19b** and **19c** proceeded smoothly even in the absence of $C_6F_5CO_2H$ to give **20b** and **20c** in respective yields of 91 and 87% (Table 5, entries 2 and 3). The reaction was conducted in toluene–DMF (9:1, v/v), since **19b** and **19c** did not dissolve in toluene. Since **20a** was obtained in only 18% yield when the reaction of **19a** catalyzed by $(NH_4)_2MoO_4$ and $C_6F_5CO_2H$ was conducted in toluene–DMF (9:1, v/v) (entry 1), DMF did not promote the reaction of **19b** and **19c**. The dehydrative cyclization of **19d** and **19e**, bearing *m*-alkyl substituents, showed very low reactivity even in the presence of $C_6F_5CO_2H$ (59 and 3%, entries 4 and 5). These poor results might be attributed to the greater stabilities of complexes of molybdenum(VI) oxide with **20d** and **20e**.

Next, we investigated the dehydrative cyclization of *N*-(*o*,*m*-dihydroxybenzoyl)-L-threonine methyl ester (**23a**) (Table 6).[12d] However, the combination of $(NH_4)_2MoO_4$ and $C_6F_5CO_2H$ did not work for the reaction of **23a** (entries 1 and 2). These poor results

Table 5
Synthesis of oxazolines **20**[a]

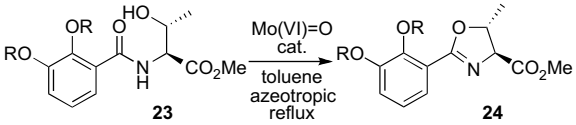


19 **20**

Entry	Ar		Time (h)	Yield[b] (%)
1		**19a**: *o*-OH	10	18
2[c]		**19b**: *m*-OH	1	91
3[c]		**19c**: *p*-OH	4	87
4[d]		**19d**	12	59
5[d]		**19e**	12	3

[a] The reaction of **19** (1 mmol) was conducted in toluene–DMF (9:1 v/v, 10 mL) under azeotropic reflux conditions.
[b] Determined by ^{1}H NMR analysis.
[c] The reaction was conducted with $(NH_4)_2MoO_4$ (2 mol %) in the absence of $C_6F_5CO_2H$.
[d] The reaction was conducted in toluene (10 mL).

Table 6
Synthesis of oxazolines **24**[a]



Entry	**23** [R, R]	Mo(VI)=O cat., mol %	Time (h)	Yield[b] (%)
1[c]	**23a** [H, H]	$(NH_4)_2MoO_4$, 10	12	0
2[d]	**23a** [H, H]	$(NH_4)_2MoO_4$, 10	12	10
3[c]	**23b** [Me, Me]	$(NH_4)_2MoO_4$, 10	8	72
4	**23b** [Me, Me]	$(NH_4)_2MoO_4$, 10	10	96
5	**23c** [Bn, Bn]	$(NH_4)_2MoO_4$, 10	5	46
6	**23c** [Bn, Bn]	$MoO_2(acac)_2$, 10	5	77
7	**23c** [Bn, Bn]	$MoO_2(TMHD)_2$, 10	5	91
8	**23d** [*o*-xylylene]	$(NH_4)_2MoO_4$, 10	5	96
9	**23d** [*o*-xylylene]	$MoO_2(TMHD)_2$, 0.5	5	94 [90][e]

[a] The reaction of **23** (1 mmol) was conducted with Mo(VI)=O cat. in toluene (100 mL) under azeotropic reflux conditions.
[b] Determined by ^1H NMR analysis.
[c] The reaction was conducted in toluene (10 mL).
[d] The reaction was conducted in mesitylene–DMF (9:1 v/v, 10 mL).
[e] The reaction was conducted for 3 h.

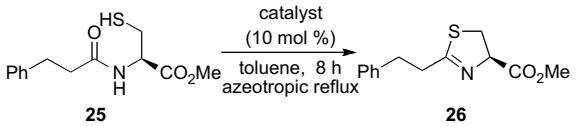
were probably attributed to rapid oxidation of the unprotected catechol moiety of **23a**. Therefore, the dehydrative cyclization of **23** required protection of the catechol moiety. Actually, the reaction of *N*-(*o*,*m*-dimethoxybenzoyl)-L-threonine methyl ester (**23b**) gave the corresponding oxazoline **24b** in 72% yield even in the absence of $C_6F_5CO_2H$ (entry 3). Methyl protection of the hydroxyl groups completely suppressed decomposition of the catechol moiety and the complexation of molybdenum(VI) oxide with **23b**. Furthermore, when the reaction of **23b** was conducted under high-dilution conditions (0.01 M of **23b**), the yield of **24b** significantly increased (entry 4). Since it was difficult to remove the methyl protection without decomposition of the oxazoline moiety, we next examined the benzyl group, which could be easily removed under conventional hydrogenolysis (H_2, 10% Pd/C, rt, EtOH), for protection of the catechol moiety. However, benzyl-protected substrate **23c** showed lower reactivity than **23b** (46% yield, entry 5). The bulkiness of the benzyl group might decrease the reactivity of **23c**. By screening the catalytic activities of several molybdenum(VI) oxides, we found that commercially available $MoO_2(acac)_2$ and $MoO_2(TMHD)_2$ showed good catalytic activities and gave **24c** in respective yields of 77 and 91% (entries 6 and 7).

Further investigation of the protecting groups for the catechol moiety revealed that compound **23d** protected by a cyclic *o*-xylylene [*o*-$C_6H_4(CH_2)_2$][23] showed excellent reactivity. Very interestingly, only 0.5 mol % of $MoO_2(TMHD)_2$ efficiently catalyzed the reaction of **23d** to give **24d** in 94% yield (entry 9). The high reactivity of **23d** might be attributed to the lower steric hindrance of the *o*-xylylene group. Since the *o*-xylylene group in **24d** could be easily removed by conventional hydrogenolysis (H_2, 10% Pd/C, rt, EtOH) without any decomposition of the oxazoline moiety, the *o*-xylylene is suitable for protection of the catechol moiety.

2.3. Dehydrative cyclization of cysteine derivatives

We first examined the dehydrative cyclization of *N*-(3-phenylpropionyl)-L-cysteine methyl ester (**25**) using molybdenum oxides as catalysts (Table 7). As a result, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, $(NH_4)_2MoO_4$, and $MoO_2(acac)_2$ showed good catalytic activities (respective yields of 96, 99, and 81%, entries 3–5), whereas the catalytic activities of MoO_2 and MoO_3 were very low (entries 1 and 2).

Table 7
Dehydrative cyclization of *N*-(3-phenylpropionyl)-L-cysteine methyl ester (**25**)[a]



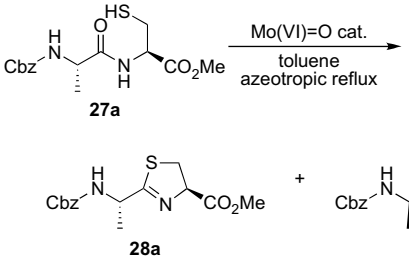
Entry	Catalyst	Yield[b] (%)
1	MoO_2	29
2	MoO_3	18
3	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	96
4	$(NH_4)_2MoO_4$	99
5	$MoO_2(acac)_2$	81
6	No catalyst	9

[a] The reaction of **25** (0.5 mmol) was conducted with catalyst (10 mol %) in toluene (50 mL) under azeotropic reflux conditions for 8 h.
[b] Determined by ^1H NMR analysis.

The reactivity of a more complex dipeptide substrate, Cbz-L-Ala-L-Cys-OMe (**27a**), was much lower than that of **25**, and MoO_3, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, and $(NH_4)_2MoO_4$ gave poor results (Table 8, entries 1–3). In contrast, $MoO_2(acac)_2$ showed good catalytic activity to give the corresponding thiazoline in 85% yield, although the obtained product was a 82:18 mixture of the desired thiazoline **28a** and epimer **29a** (entry 4). The dehydrative cyclization of **27a** was conducted under high-dilution conditions (0.01 M of **27a**). When the reaction of **27a** was conducted at a higher substrate concentration (0.05 M), the yield of thiazoline **28a** was decreased (62%).

It is conceivable that the generation of epimer **29a** could be attributed to the relatively high acidity of $MoO_2(acac)_2$. In general, thiazolines are more susceptible to epimerization than oxazolines under both acidic and basic conditions.[7a,9] To decrease the epimerization of thiazolines, it might be important to control the Lewis acidities and Brønsted basicities of molybdenum catalysts by more suitable ligands. Furthermore, homogeneous monomeric

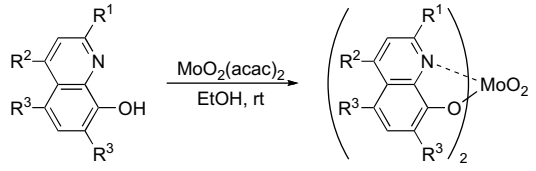
Table 8
Catalytic activities of molybdenum(VI) oxides for the dehydrative cyclization of dipeptide **27a**[a]



Entry	Mo(VI)=O cat., mol %	Time (h)	Yield[b] (%)	dr[c] (**28a**/**29a**)
1	MoO_3, 10	8	9	ND
2	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 10	8	16	ND
3	$(NH_4)_2MoO_4$, 10	8	26	ND
4	$MoO_2(acac)_2$, 10	8	85	82:18
5	**30a**, 10	5	80	96:4
6	**30a**, 1	5	40	89:11
7	**30b**, 1	5	93	95:5
8	**30c**, 1	2	96	97:3
9	**30d**, 1	5	80	85:15
10	**30e**, 1	5	96	96:4
11	**30f**, 1	2	94	86:14
12	No catalyst	8	0	ND

[a] The reaction of **27a** (0.1 mmol) was conducted with Mo(VI)=O cat. (1–10 mol %) in toluene (10 mL) under azeotropic reflux conditions.
[b] Determined by ^1H NMR analysis.
[c] Determined by HPLC analysis.

molybdenum complexes were expected to exhibit higher catalytic activities even under lower catalyst loading conditions. In an intensive examination of the catalytic activities of molybdenum complexes for the dehydrative cyclization of **27a**, we found that bis(quinolinolato)dioxomolybdenum(VI) complexes **30**, which were easily prepared from $MoO_2(acac)_2$ and known 8-quinolinols (Scheme 6), showed good catalytic activities.[12c] The reaction was conducted with a molybdenum(VI) complex **30** in toluene under azeotropic reflux conditions with the removal of water. Molybdenum(VI) complexes **30** dissolved well in toluene and appeared to be stable under the reaction conditions. 8-Quinolinolato complex **30a** (10 mol %) showed good catalytic activity (80% yield), and epimerization at the *C*2-exomethine position of **28a** was effectively suppressed, as expected (**28a**/**29a**=96:4) (entry 5). Unfortunately, however, the use of 1 mol % of **30a** decreased the reactivity (40% yield, entry 6). Further investigation of the design of 8-quinolinolato complexes **30** revealed that the introduction of an alkyl group to the 2-position of the 8-quinolinol significantly increased the catalytic activities of the quinolinolato complexes. In particular, 2-ethyl-8-quinolinolato complex **30c** and 2,4-dimethyl-8-quinolinolato complex **30e** exhibited remarkably higher catalytic activities than **30a** and $MoO_2(acac)_2$, to give **28a** in 96% yield despite the lower catalyst loading (1 mol %) (entries 8 and 10). The use of complexes **30c** and **30e** significantly suppressed the yield of **29a** to less than 4%. Although 2,4-dimethyl-5,7-dibromo-8-quinolinolato complex **30f** showed high catalytic activity (94% yield), epimerization increased to 86:14 dr (entry 11). It is conceivable that the stronger Lewis acidity of complex **30f** 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.

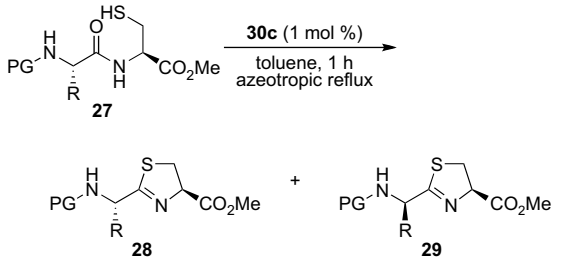


	R^1	R^2	R^3		R^1	R^2	R^3
30a	H	H	H	**30d**	Ph	H	H
30b	Me	H	H	**30e**	Me	Me	H
30c	Et	H	H	**30f**	Me	Me	Br

Scheme 6. Preparation of bis(quinolinolato)dioxomolybdenum(VI) complexes **30**.

We then examined the dehydrative cyclization of other cysteine-containing dipeptides Cbz-L-Phe-L-Cys-OMe (**27b**), Boc-L-Ala-L-Cys-OMe (**27c**), and Fmoc-L-Ala-L-Cys-OMe (**27d**) (Table 9). Dipeptides **27b**–**d** could be converted to the corresponding thiazolines **28b**–**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 2 and 3). In all cases, epimerization of the *C*2-exomethine position of the products was suppressed to less than 6%.[24]

Table 9
Synthesis of thiazoline **28**[a]



Entry	Dipeptide **27** [PG, R]	Yield[b] (%)	dr[c] (**28**:/**29**)
1	**27b** [Cbz, Bn]	85	98:2
2	**27c** [Boc, Me]	82	94:6
3	**27d** [Fmoc, Me]	91	96:4

[a] The reaction of dipeptide **27** (0.1 mmol) was conducted with **30c** (1 mol %) in toluene (10 mL) under azeotropic reflux conditions for 1 h.
[b] Isolated yields of **28** and **29**.
[c] Determined by HPLC analysis.

3. Conclusion

In summary, we have developed an efficient dehydrative cyclization of serine, threonine, and cysteine residues catalyzed by molybdenum(VI) oxo compounds. Commercially available molybdenum(VI) oxides efficiently catalyzed the dehydrative cyclization of a variety of serine and threonine derivatives to give oxazolines in good yields. For the dehydrative cyclization of cysteine derivatives, the use of bis(quinolinolato)dioxomolybdenum(VI) complexes significantly suppressed the loss of stereochemical integrity at the *C*2-exomethine position and gave thiazolines in excellent yields. The present reaction is useful for the synthesis of common intermediates for oxazoline- and/or thiazoline-containing bioactive natural products.

4. Experimental

4.1. General

IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) or a JEOL ESC400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in parts per million 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) or a JEOL ESC400 spectrometer (100 MHz). Chemical shifts were recorded in parts per million from the solvent resonance used 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 (4.6×250 mm) or Daicel CHIRALPAK OD-H (4.6×250 mm). All experiments were carried out under an atmosphere of dry nitrogen. For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 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 the Chemical Instrumentation Facility, Nagoya University. Oxazolines **2a**, **2b**, **5a**–**e**, **11**, **12**, **13**, **14**, **18a**, **18b**, **20a**–**c**, **22**, **24a**–**d**, thiazolines **26**, **28a**–**d**, and bis(quinolinolato)-dioxomolybdenum(VI) complexes **30a**–**f** were reported previously.[12]

4.2. General procedure for the dehydrative cyclization of dipeptides 4 and 27

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. 0.4 g of CaH_2]

surmounted by a reflux condenser was charged with a dipeptide **4** or **27** (0.50 mmol) and an oxomolybdenum(VI) catalyst (1–10 mol %) in toluene (50 mL for **1a** and **27**, 10 mL for **1b**). 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 $NaHCO_3$ and brine, 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 hexane–EtOAc (for **5**) or toluene–acetone (for **28**), to give the corresponding oxazoline **5** or thiazoline **28**.

*4.2.1. Dehydrative cyclization of dipeptide **7***

The reaction of **7** (0.6 mmol) was conducted with $MoO_2(acac)_2$ (20 mol %) in toluene (60 mL) according to the procedure shown in Section 4.2 to give dehydrative elimination product **9** (47% yield). IR (neat) 3390, 1746, 1698, 1608, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.65 (d, J=6.9 Hz, 4H), 7.54–7.34 (m, 6H), 6.52 (s, 1H), 5.61 (s, 1H), 4.83 (dd, J=7.8, 10.5 Hz, 1H), 4.65 (dd, J=7.8, 9.0 Hz, 1H), 4.56 (dd, J=9.0, 10.5 Hz, 1H), 3.80 (s, 3H), 3.70 (t, J=6.3 Hz, 2H), 2.46 (t, J=7.2, Hz, 2H), 1.92 (tt, J=6.3, 7.2 Hz, 2H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.8, 163.7, 135.5, 133.7, 129.6, 128.5, 127.6, 106.8, 70.5, 67.8, 62.8, 52.8, 34.0, 27.9, 26.8, 19.2; HRMS (FAB) calcd for $C_{27}H_{35}N_2O_5Si$ [(M+H)$^+$] 495.2315. Found: 495.2317.

*4.2.2. Dehydrative cyclization of tetrapeptide **15***

The reaction of **15** (0.1 mmol) was conducted with $MoO_2(acac)_2$ (20 mol %) in toluene (10 mL) according to the procedure shown in Section 4.2 to give bis(oxazoline) **16** (95% yield) as a diastereomeric mixture. IR (neat) 1718, 1657, 1522, 1453, 1260, 1216, 1058 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.41–7.18 (m, 5H), 5.20–5.05 (m, 2H), 4.98–4.78 (m, 1H), 4.78–4.69 (m, 1H), 4.69–4.56 (m, 1H), 4.47–4.35 (m, 1H), 4.36–4.25 (m, 1H), 4.23–4.14 (m, 1H), 3.75 (s, 2.1H), 3.73 (s, 0.9H), 1.52–1.30 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 18.4, 20.9, 21.4, 48.6, 48.8, 49.6, 67.6, 74.8, 75.6, 81.5, 82.0, 128.8, 129.0, 129.4, 138.2, 158.1, 171.7, 172.2, 172.5, 173.0.

*4.2.3. Dehydrative cyclization of **17c***

The reaction of **17c** (11.9 mmol) was conducted with $(NH_4)_2MoO_4$ (2 mol %) in toluene (30 mL) for 12 h according to the procedure shown in Section 4.2 to give bis(oxazoline) **18c** (69% yield) along with monocyclized product (22% yield). IR (KBr) 1740, 1649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (dq, J=6.3, 6.9 Hz, 2H), 4.29 (d, J=6.6 Hz, 2H), 3.77 (s, 6H), 1.55 (s, 6H), 1.38 (d, J=6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.9, 79.1, 74.3, 52.5, 38.7, 23.9, 20.8; HRMS (FAB) calcd for $C_{15}H_{23}N_2O_6$ [(M+H)$^+$] 327.1556. Found: 327.1566.

*4.2.4. Dehydrative cyclization of **19d** and **19e***

The reaction of **19d** or **19e** (1 mmol) was conducted with $(NH_4)_2MoO_4$ (10 mol %) and $C_6F_5CO_2H$ (10 mol %) in toluene (10 mL) according to the procedure shown in Section 4.2 to give oxazoline **20d** (59% yield) or **20e** (3% yield). Compound **20d**: IR (neat) 2953, 1744, 1633, 1437, 1303, 1261, 1205, 1146, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.0 (br s, 1H), 7.51 (d, J=7.8 Hz, 1H), 7.25 (d, J=7.4 Hz, 1H), 6.77 (dd, J=7.4, 7.8 Hz, 1H), 4.97 (qd, J=6.4, 6.8 Hz, 1H), 4.49 (d, J=6.8 Hz, 1H), 3.78 (s, 3H), 2.28 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 20.7, 52.6, 73.5, 78.3, 109.4, 118.1, 125.8, 125.9, 134.7, 158.3, 167.2, 170.9; HRMS (FAB) calcd for $C_{13}H_{16}NO_4$ [(M+H)$^+$] 250.1079. Found: 250.1096. Compound **20e**: IR (neat) 2957, 1744, 1631, 1439, 1362, 1278, 1254, 1218, 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.2 (s, 1H), 7.53 (d, J=2.3 Hz, 1H), 7.46 (d, J=2.7 Hz, 1H), 4.95 (qd, J=6.4, 7.3 1H), 4.49 (d, J=7.3 Hz, 1H), 3.80 (s, 3H), 1.54 (d, J=6.4 Hz, 3H), 1.43 (s, 9H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 29.4, 31.5, 34.3, 35.2, 52.7, 73.7, 78.2, 109.4, 122.4, 128.6, 136.6, 140.1, 157.1, 167.9, 171.1; HRMS (FAB) calcd for $C_{20}H_{30}NO_4$ [(M+H)$^+$] 348.2175. Found: 348.2183.

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24. 8-Quinolinolato complexes **30d** (1 mol %) showed excellent catalytic activity for the dehydrative cyclization of **4b**, Cbz-L-Phe-L-Thr-OMe (**4c**), Boc-L-Ala-L-Thr-OMe (**4d**), and Fmoc-L-Ala-L-Thr-OMe (**4e**) to give the corresponding oxazolines **5b**–**e** in 85–92% yields.[12c] The reaction also proceeded with a complete retention of configuration at the β-position.