Development of Catalytic Methods for the Synthesis of Oxa- and Thiazolines and Asymmetric Diels–Alder Catalysis Using Chiral Bis(oxazoline) Ligands

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Nagoya, 2009

Contents

Chapter 1

Introduction and General Summary

Oxazoline and thiazoline are five-membered heterocycles that contain both oxygen/sulfur and nitrogen. Oxazolines and thiazolines are numbered around the ring starting at the oxygen/sulfur atoms (Figure 1.1). They are key structures in numerous bioactive natural products and pharmaceuticals.[1] In addition, oxazolines have various uses in modern organic synthesis. In particular, chiral bis(oxazoline)s are important fragments of chiral ligands for asymmetric catalysis.[2]

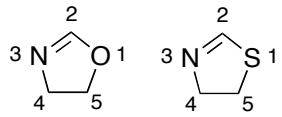


Figure 1.1. Structures of oxazoline and thiazoline.

The biosynthesis of oxazolines and thiazolines appears to involve the dehydrative cyclization of serine, threonine, and cysteine residues in peptides.[3] Although several chemical methods for the preparation of oxazolines and thiazolines have been developed,[4] some disadvantages still exist in current organic synthesis. To achieve a truly efficient chemical synthesis, the author tried to develop new catalysts for the biomimetic dehydrative cyclization of serine, threonine and cysteine derivatives to oxazolines and thiazolines.

The author also designed a new type of chiral bis(oxazoline) ligand with a secondary coordinating site to a metal cation and demonstrated the effectiveness of new bis(oxazoline)-copper(II) complexes for enantioselective Diels–Alder catalysis.

1.1. Oxazoline and Thiazolines in Bioactive Natural Products and Organic Synthesis

Oxazolines and thiazolines are widely present in bioactive natural products[1] (Figure 1.2). The oxidation of oxazolines and thiazolines generates heteroaromatic oxazole and thiazole rings.

They have a wide range of antitumor, antiviral, and antibiotic activities, as well as the ability to bind to proteins, DNA and RNA. These heterocycles and oligomers thereof are key structural features in bioactive natural products. For example, vibriobactin, an iron-chelating siderophore, has two oxazoline rings. Bis(oxazole) heteroaromatic rings are the key structures of hennoxazole A, which was isolated from the marine sponge *Polyfibrospongia* and exhibits antiviral activity against herpes simplex type 1, as well as peripheral analgesic activity. The thiazoline moiety of the antibiotic bacitracin is vital for biological activity. Myxothiazole, which contains the bis(thiazole) structure, inhibits mitochondrial respiration.

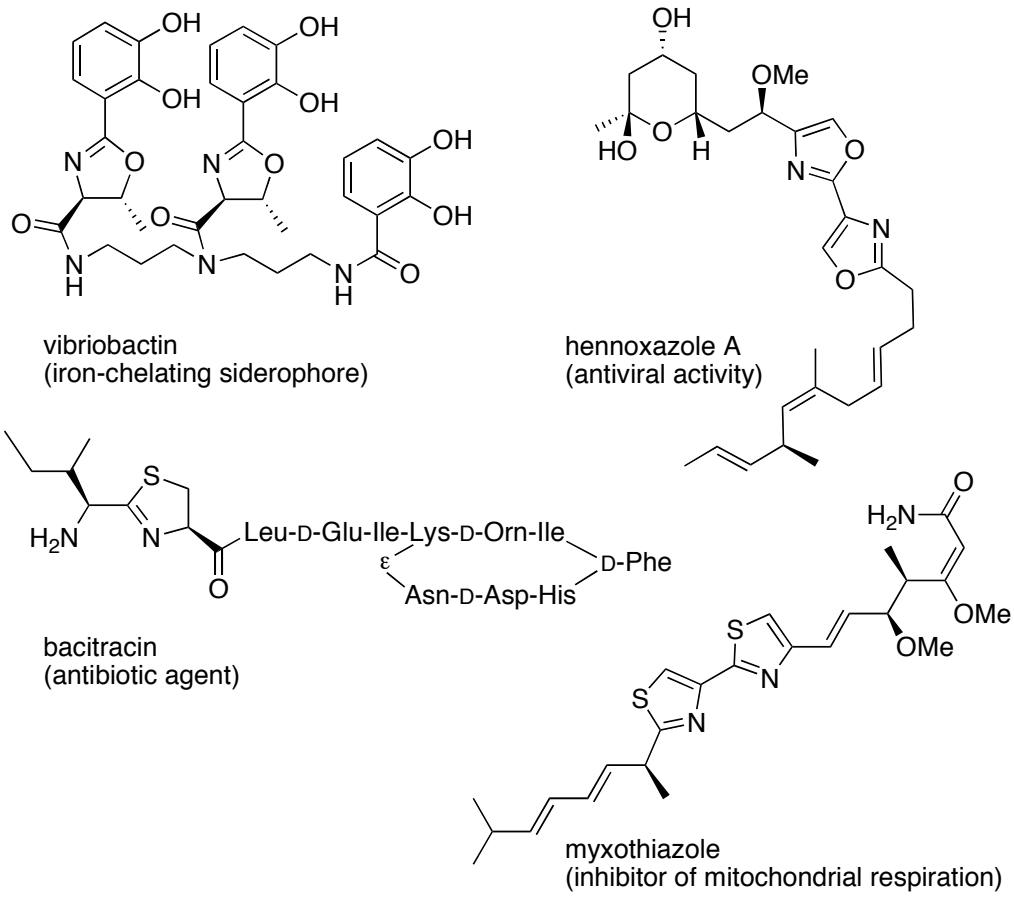


Figure 1.2. Oxazolines, oxazoles, thiazolines and thiazoles in bioactive natural products.

Oxazolines are also important structures in organic synthesis.[4] They are used as (1) chiral auxiliaries or ligands for asymmetric catalysis, such as bis(oxazoline)s or phosphinooxazolines, (2) efficient directors for *ortho*-methalation, nucleophilic substitution, or addition to aromatic systems and (3) protecting groups for carboxylic acids to resist nucleophiles, bases, and radicals.

In particular, C_2-symmetric bis(oxazoline)s are some of the most popular classes of chiral ligands, and have received a great deal of attention in asymmetric catalysis.[3] In 1991, Evans et al. reported the application of a chiral *t*-Bu-bis(oxazoline) complex of Cu(II) as a catalyst in the asymmetric cyclopropanation of alkenes (Figure 1.3).[5] In addition, Corey et al. reported enantioselective Diels–Alder reactions using a Ph-bis(oxazoline) complex of Fe(III) as a catalyst.[6] Davies[7] and Ghosh et al.[8] each used a bis(oxazoline) template derived from aminoindanol. The use of a hydrated nickel(II) complex of dibenzofurandiyl-bis(oxazoline) as a chiral catalyst for cycloadditions was reported by Kanemasa et al.[9] Nishiyama et al. reported the application of a bis(oxazolinyl)pyridine-rhodium(III) complex to the catalytic enantioselective hydrosilylation of ketones in 1989.[10] As shown here, bis(oxazoline) is one of the most successful structures as a chiral ligand for asymmetric reactions.

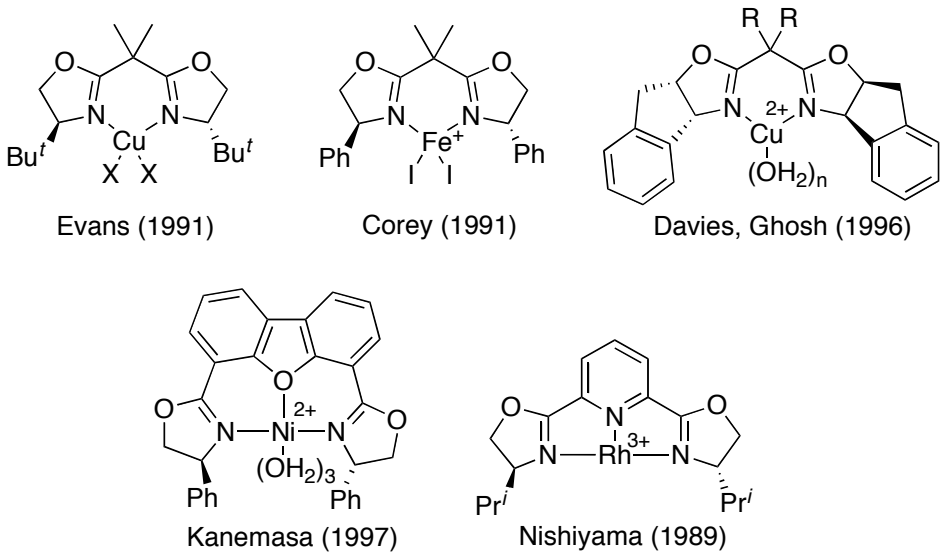
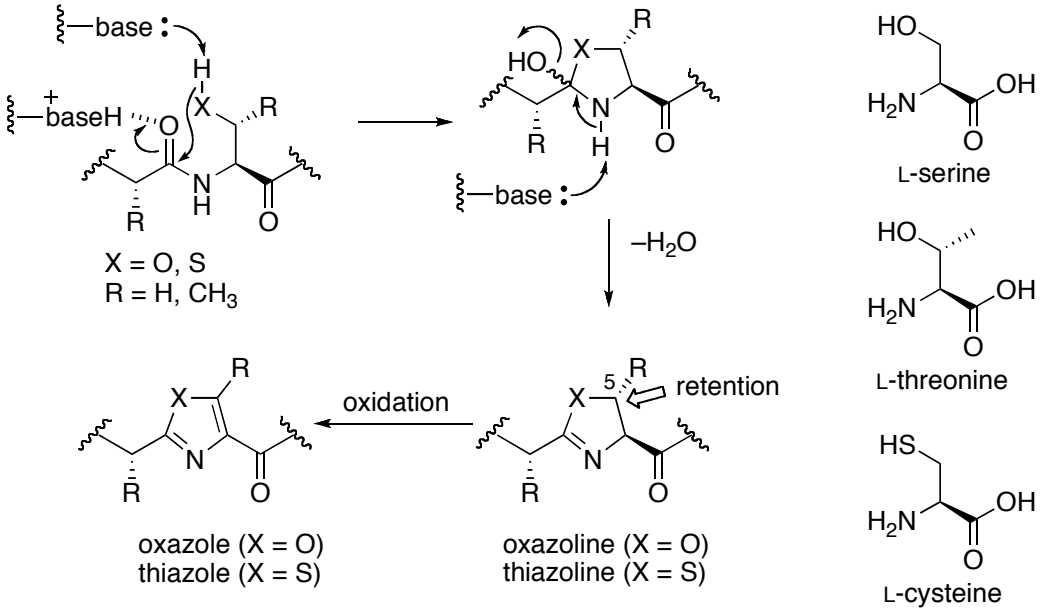


Figure 1.3. Bis(oxazoline)-metal complexes for asymmetric reactions.

1.2. Biosynthesis and Chemical Synthesis of Oxazolines and Thiazolines

Naturally occurring oxazolines and thiazolines are derived from enzymatic post-translational modifications of peptide-based precursors. The oxygen/sulfur functionality on the side chain of *N*-acylated serine, threonine or cysteine is capable of undergoing heterocyclization onto the preceding carbonyl group to create a five-membered saturated heterocycle (Scheme 1.1).[2] After dehydration, these compounds result in oxazoline and thiazoline. A two-electron oxidation generates the heteroaromatic oxazole and thiazole systems. As shown here, oxazolines and thiazolines are biosynthesized by dehydrative cyclization under mild conditions using enzymes with a retention of configuration at the 5-position.

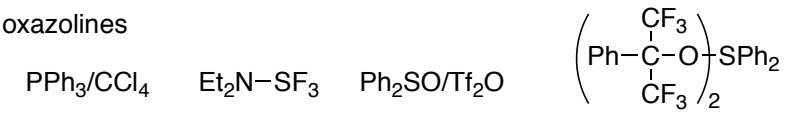
Scheme 1.1. Biosynthesis of Oxazolines, Thiazolines, Oxazoles and Thiazoles



On the other hand, a wide range of methods have been devised for the chemical synthesis of oxazolines, thiazolines, oxazoles and thiazoles.[4] Among the reported methodologies, biomimetic dehydrative cyclization is thought to be the most efficient and is commonly used in peptide substrates. Indeed, many reagents and catalysts for dehydrative cyclization to oxazolines and thiazolines have been developed.

Several stoichiometric dehydrating reagents to effect the transformation of *N*-(β-hydroxyethyl)amides or *N*-(β-hydroxyethyl)thioamides to oxazolines or thiazolines have been reported previously. For example, oxazolines were formed by dehydrative cyclization with PPh_3–CCl_4,[11] DAST,[12] Ph_2SO–Tf_2O,[13] Martin's sulfurane,[14] Burgess reagent,[15] and Mitsunobu reagent (Figure 1.4).[16] Thiazolines were synthesized with Burgess reagent,[17a] Mitsunobu reagent[15] and Ph_3PO–Tf_2O.[18]

· for oxazolines



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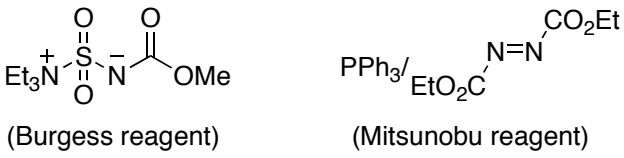


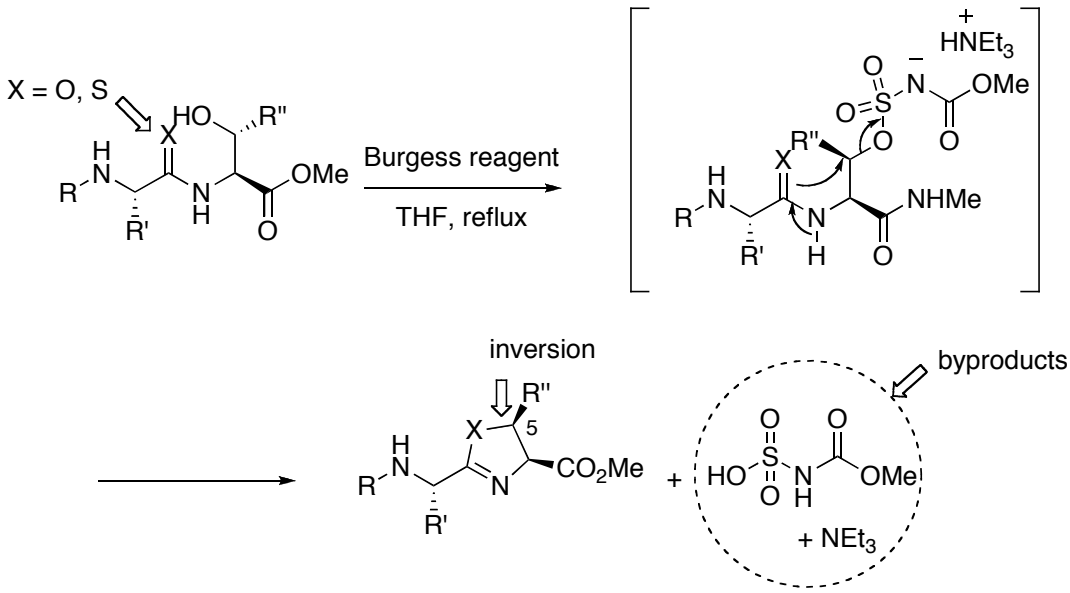
· for thiazolines

Ph_3PO/Tf_2O

Figure 1.4. Stoichiometric dehydrating reagents for the synthesis of oxazolines and thiazolines.

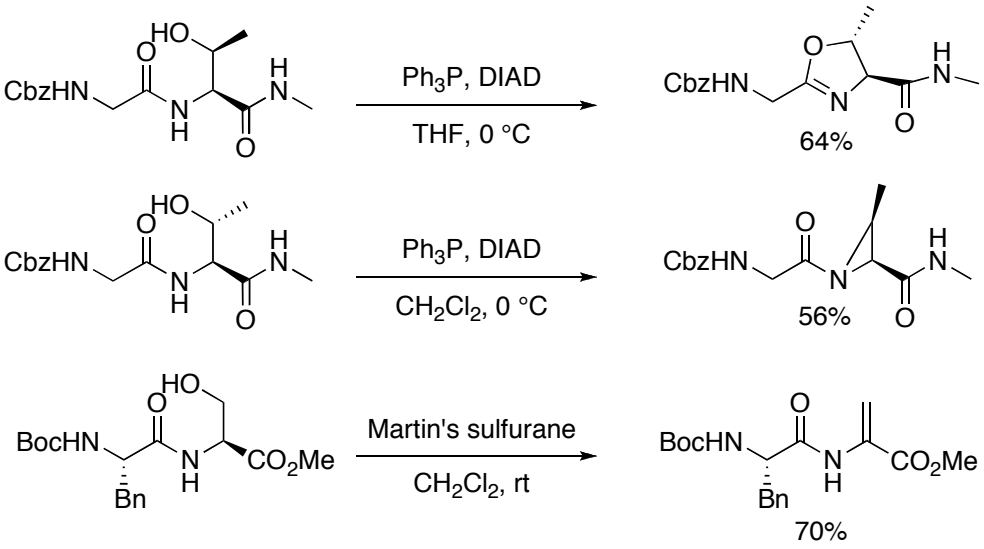
Wipf et al. reported the transformation to oxazolines[13] and thiazolines[17a] using Burgess reagent in 1992 and 1994, respectively (Scheme 1.2). This methodology provided the desired oxazoline or thiazoline as the sole product and proved to be effective with peptide substrates. However, it has three major disadvantages. (1) Stoichiometric amounts of byproducts are produced along with the desired product. It is not efficient with regard to atom economy or the cost of purification. (2) In contrast to biosynthesis, thiazolines are not synthesized from cysteine derivatives, but rather from *N*-(β-hydroxyethyl)thioamides, which should be prepared in advance. Finally, (3) invertive cyclization occurs at the 5-position, which is opposite the retentive cyclization in biosynthesis. Therefore, an expensive unnatural amino acid, L-*allo*-threonine, must be used for the synthesis of oxazolines derived from natural L-threonine. The latter two problems are due to the reaction mechanism. First, Burgess reagent activates a hydroxyl group, as shown in Scheme 1.2. Next, amide/thioamide attacks the carbon next to the activated hydroxy group to generate oxazoline/thiazoline ring. That is why invertive cyclization occurs and thioamide compounds must be used.

Scheme 1.2. Burgess Reagent for the Synthesis of Oxazolines and Thiazolines



In addition, issues regarding chemoselectivity arise with some stoichiometric dehydrating reagents. For example, the Mitsunobu-type cyclization of Cbz-glycyl-L-*allo*-threonine *N*-methyl amide with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) provided the desired oxazoline in 64% yield at 0 °C (Scheme 1.3). However, the analogous reaction with Cbz-glycyl-L-threonine *N*-methyl amide led to the formation of aziridine.[15] In another case, only dehydroamino acid derivative was isolated in the reaction with Martin's sulfurane from Boc-L-Phe-L-Ser-OMe in 70% yield.[14]

Scheme 1.3. Chemoselectivity of Stoichiometric Dehydrating Reagents



Although several stoichiometric reagents are known to be effective for dehydrative cyclization to oxazolines and thiazolines, only a few examples of dehydrating catalysts have been reported: 3-nitrophenylboronic acid (0.1 equiv.),[19] a lanthanide chloride (0.05–0.2 equiv.),[20] a zeolite (0.16 g/mmol),[21] *p*-TsOH (0.1 equiv.)[22] for oxazolines and $TiCl_4$ (3 equiv.)[23] for thiazolines (Figure 1.5).

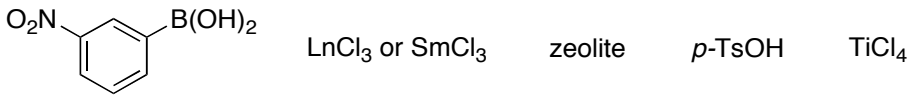
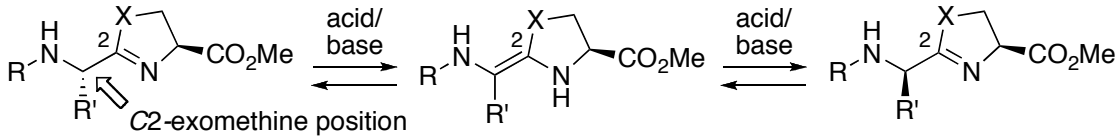


Figure 1.5. Dehydrating acid catalysts for the synthesis of oxazolines and thiazolines.

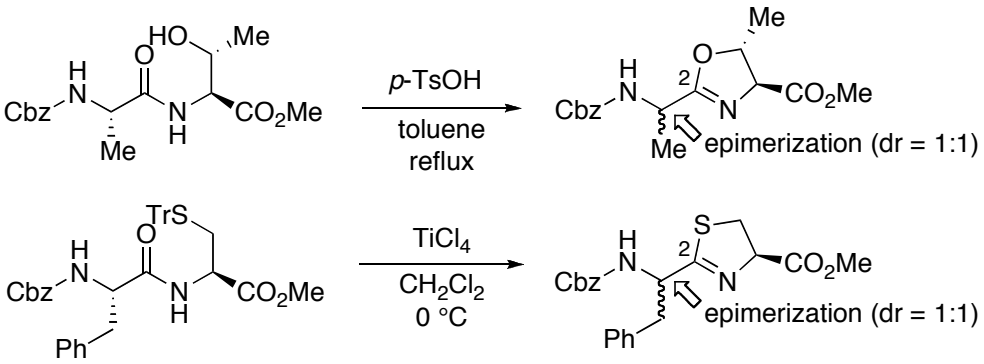
However, these catalytic methods are limited to simple acid-tolerant substrates due to the acidity of the catalysts themselves. In addition, the *C*2-exomethine position of oxazolines and especially thiazolines in peptides is readily epimerized by either acid or base (Scheme 1.4).[17]

Scheme 1.4. Epimerization of the *C*2-Exomethine Position by Acid or Base (X = O, S)



In fact, we found that epimerization occurred with the Cbz-L-Ala-L-Thr-OMe dipeptide substrate in *p*-TsOH-catalyzed oxazoline synthesis to give a 1:1 diastereomeric mixture of product (Scheme 1.5). Kelly et al. also reported the epimerization in peptide substrates by the $TiCl_4$-mediated thiazoline synthesis of trityl-protected cysteine *N*-amides.[23] To the best of the author's knowledge, there is no efficient dehydrating catalyst for the synthesis of oxazolines or thiazolines within a peptide without a significant loss of stereochemistry at the *C*2-exomethine position.

Scheme 1.5. Epimerization of the *C*2-Exomethine Position by Acid Catalysts



A mild, highly efficient, stereoretentive and environmentally friendly procedure for the synthesis of oxazolines and thiazolines would be very desirable. The author envisioned that the development of a new conjugate acid-base catalyst, in which the acidic and basic elements are

stereoelectronically connected to each other, would be the key to overcome the limitations associated with current methods.[24] Thus, acidic elements activate the amide bond and basic elements activate the hydroxy or mercapto group by deprotonation (Figure 1.6). The author expected that the catalyst would work similar to enzymes in biosynthesis. Next, the author focused on metal oxo compounds as conjugate acid-base catalysts. Lewis acidic metal and a Brønsted basic oxo part would cooperatively activate the dehydrative cyclization to oxazolines and thiazolines. On the other hand, dehydrating acid catalysts such as *p*-TsOH or $TiCl_4$ activate only an amide group so that epimerization and an undesired side reaction occur. Dehydrating reagents only activate a hydroxy group so that invertive cyclization occurs at the 5-position of oxazolines, and thioamide compounds must be used.

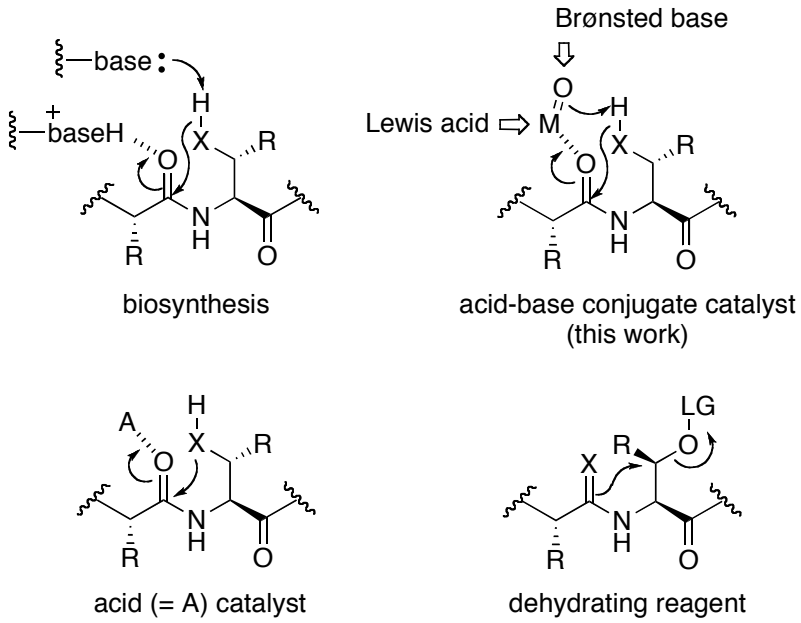
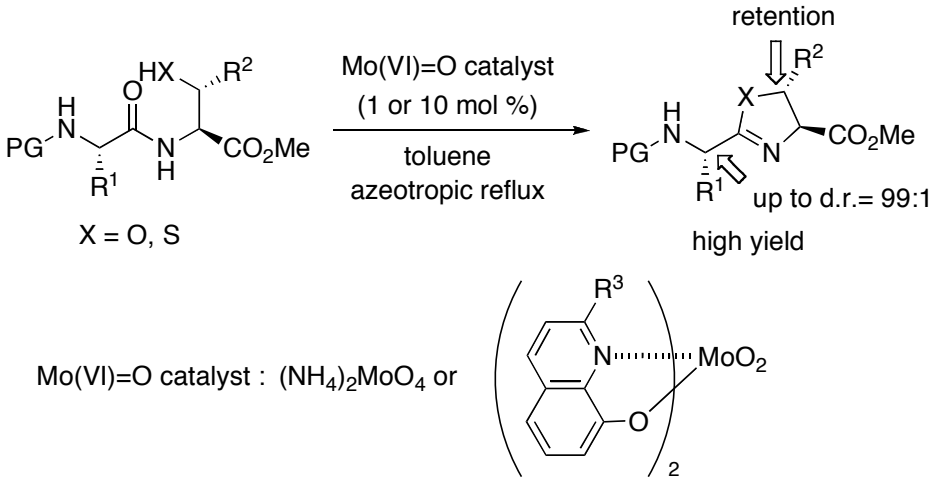


Figure 1.6. Metal oxo compounds as acid-base conjugate catalysts (X = O, S).

In the course of screening various metal oxo compounds as conjugate acid-base catalysts for the dehydrative cyclization to oxazolines and thiazolines, we found that molybdenum(VI) oxo compounds were effective catalysts. The ammonium salts $(NH_4)_2MoO_4$ have excellent catalytic

activity for dehydrative cyclization of serine and threonine derivatives to oxazolines,[25] and bis(quinolinolato)dioxomolybdenum(VI) complexes have remarkable catalytic activity for the dehydrative cyclization of cysteine derivatives to thiazolines (Scheme 1.6).[26] The author's catalysts were highly efficient, especially for peptide substrates, and could overcome the problems with previous methods.

Scheme 1.6. Efficient Synthesis of Oxazolines and Thiazolines Using Mo(VI)=O Catalysts



1.3. Chiral Bis(oxazoline) Ligands for Asymmetric Reactions

While great strides have been made in asymmetric catalysis, the development of new chiral ligands to accelerate and direct Lewis acid-catalyzed reactions continues to be an area of intense scrutiny. The author's group has been interested in the design of new ligands with a secondary coordinating site to the metal, which is a catalytic center, for use in a variety of asymmetric transformations. This secondary ligand-metal coordination would create a more conformationally rigid asymmetric environment around the catalytic center and also improve the reactivity by kicking

out a counter anion from an active Lewis acid catalyst.

In 2006, the author's group developed a new ligand design using non-covalent bonding interaction as secondary coordination with copper(II) cation and the π-electrons of 3-(2-naphthyl)-L-alanine amide for asymmetric [4+2] and [2+2] cycloadditions (Figure 1.7).[27] Following our recent disclosure of an intramolecular cation–π interaction, a non-covalent bonding interaction with cation and *n*-electrons of substituents at the 4-position of bis(oxazoline) ligand became the focal point of the author's interest. The author focused on a bis(oxazoline) structure to examine this idea. In general, a large group such as phenyl or *tert*-butyl at the 4-position of the oxazolines blocks one side through steric hindrance of itself. The author was intrigued by the question of whether Lewis basic substituents at the 4-position of bis(oxazoline) work for non-covalent bonding interaction with a metal cation and create a superior chiral environment. In addition, the author expected that the catalysts become more active with cation-π or cation-*n* interactions by kicking out counter anions.

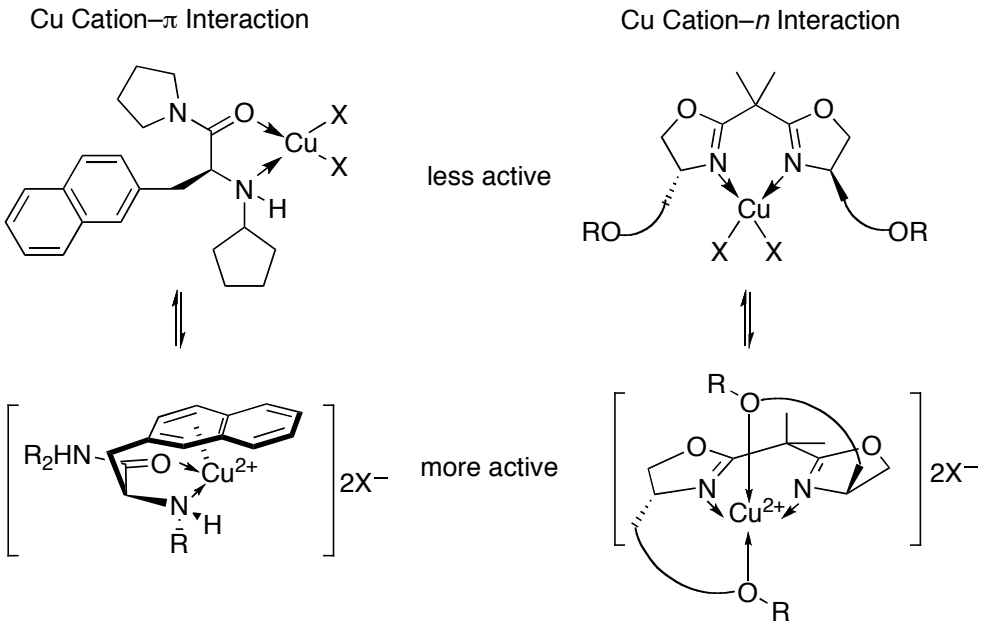


Figure 1.7. Non-covalent bonding interactions of Cu^{2+} with ligands.

Although there are many kinds of chiral bis(oxazoline) compounds, only a few successful asymmetric catalysts with a bis(oxazoline) ligand bearing Lewis basic substituents at the 4-position of the oxazoline have been reported (Figure 1.8). Reiser et al. designed bis(oxazoline)s with hydroxymethyl and amide substituents at the 4-position of oxazolines for enantioselective 1,4-addition[28] and cyclopropanation,[29] respectively. These substituents at 4-position interact with carbonyl groups of substrates. However, to the best of the author's knowledge, there has been no report on enantioselective reactions using non-covalent bonding interaction of substituents at the 4-position of bis(oxazoline) to a metal cation for an effective chiral environment.

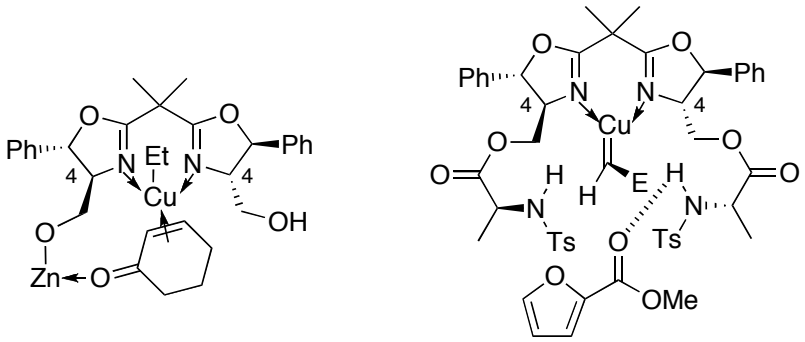


Figure 1.8. Bis(oxazoline) ligands including heteroatoms at the 4-position as reported by Reiser.

The Diels–Alder reaction is arguably the most powerful construction process in organic synthesis, and for this reason there has been much research on the development of enantioselective versions. Evans' bis(oxazoline)-Cu(II) catalyst is one of the most important advances in the enantioselective Diels–Alder reaction[5,30] (Figure 1.9). Corey et al. described the use of an aluminum(III)–stilbenediamine complex.[31] Narasaka et al. reported an effective titanium(IV) complex of chiral tartrate-derived 1,4-diol.[32] Kobayashi[33a] and Nakagawa[33b] et al. independently reported chiral BINOL-Yb(III) catalysts. More recently, Sibi et al. developed a chiral ligand with a fluxional group[34] and Ellman et al. used bis(sulfinyl)imidoamidine ligands for the

copper(II)-catalyzed Diels–Alder reaction.[35]

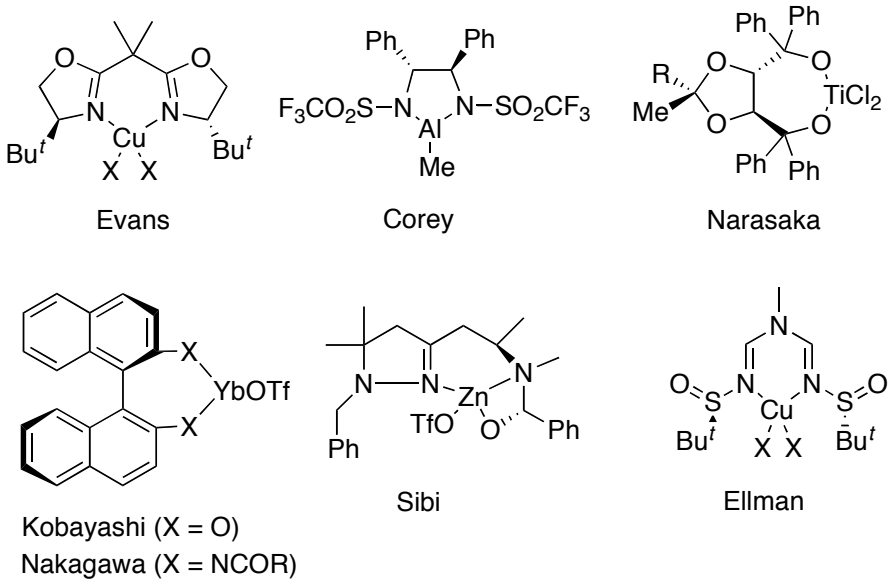
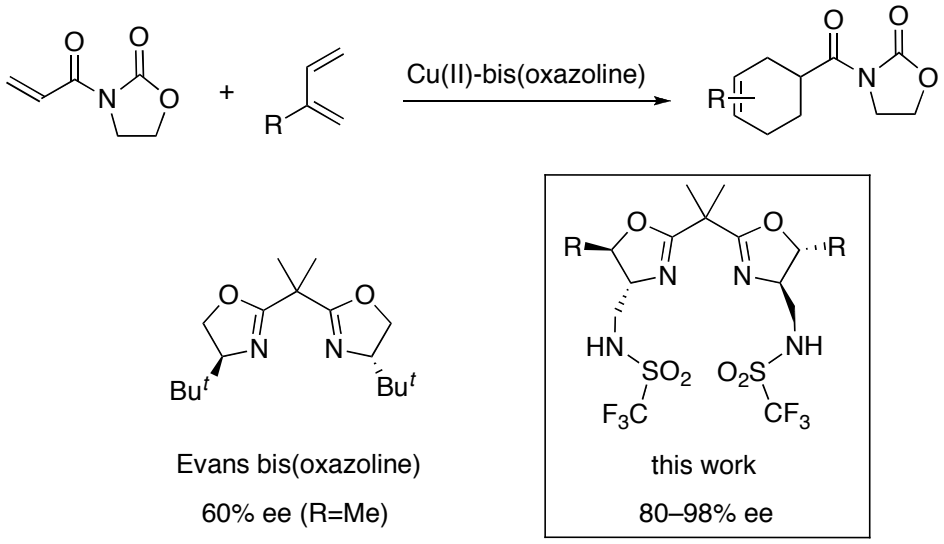


Figure 1.9. Catalyst systems for the asymmetric Diels–Alder reaction.

However, there are still challenges with regard to reactivity and selectivity. Thus, the author tried to design a new bis(oxazoline) using the non-covalent bonding interaction of *n*-electrons to copper cation for the enantioselective Diels–Alder reaction. As a result, the author found that complexes of Cu(II) and bis(oxazoline) bearing a sulfonamide group at the 4-position of oxazolines catalyzed the enantioselective Diels–Alder reaction with a variety of substrates. It is worth noting that 2-substituted-1,3-butadienes with 3-propenoyl-2-oxazolidinone react to afford the Diels–Alder product with excellent enantioselectivity, while Evans' catalyst is much less selective[36] (Scheme 1.7).

Scheme 1.7. Highly Enantioselective Diels–Alder Reaction Using Cu(II)-bis(oxazoline) Catalyst with Cation-*n* Interaction



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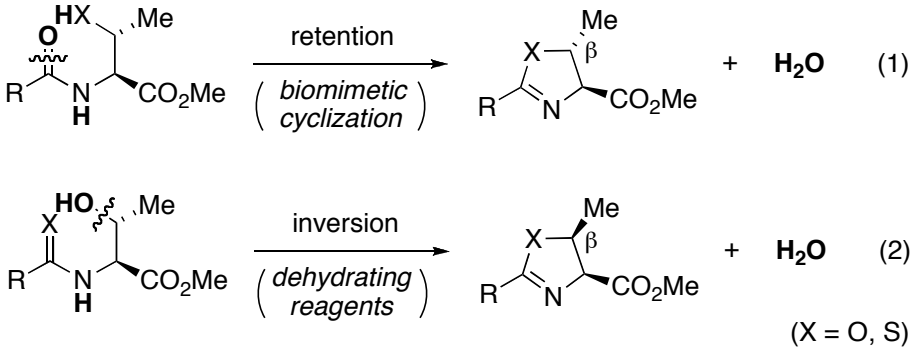
Chapter 2

Development of Catalysts for the Synthesis of Oxazolines and Thiazolines by Dehydrative Cyclization Using Molybdenum(VI) Oxo Compounds

Abstract: Commercially available molybdenum(VI) oxides such as $(NH_4)_2MoO_4$, $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$, and $MoO_2(acac)_2$ 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.

Oxazolines, oxazoles, thiazolines and thiazoles are important constituents of numerous bioactive natural products of peptide origin. 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.



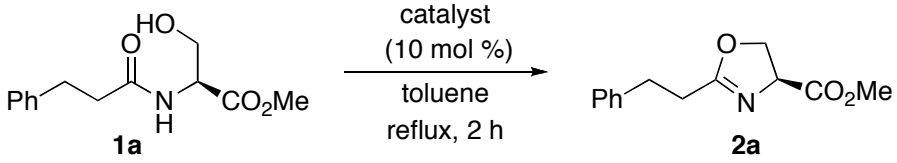
For the synthesis of oxazoline- and/or thiazoline-containing bioactive natural compounds, a more effective catalytic method for the dehydrative cyclization of serine, threonine and cysteine residues that proceeds with a retention of configuration at the β-position is needed. In this chapter, the author describes a biomimetic and green synthesis of oxazolines and thiazolines catalyzed by molybdenum(VI) oxides. 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 useful for the synthesis of common building blocks for various bioactive natural products[1,2] and chiral bis(oxazoline) ligands for asymmetric synthesis.[3]

2.1. Initial Screening of Metal Compounds for the Synthesis of Oxazolines

The author's 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 2.1). Commercially available molybdenum oxides such as $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$, 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).[4] In contrast, the catalytic activities of other metal compounds such as Na_2MoO_4 and ReO_2 were very low (entries 4, 5 and 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).

Table 2.1. Initial Screening for Catalytic Activities of Metal Compounds for the Deydrative Cyclization of **1a**[a,b]



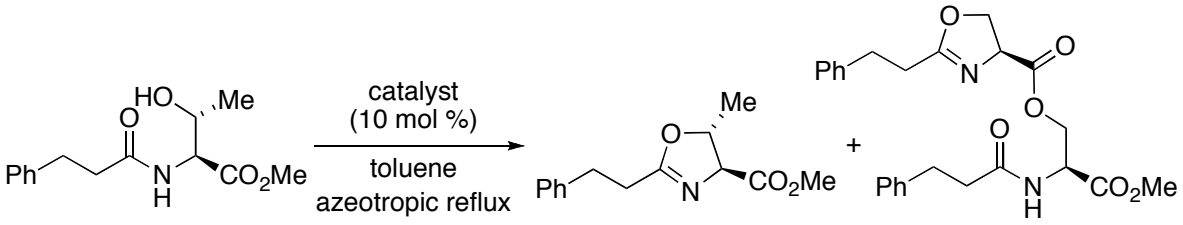
entry	catalyst	yield (%)[c]	entry	catalyst	yield (%)[c]
1	$(NH_4)_6Mo_7O_{24}\bullet 4H_2O$	68	8	ReO_2	0
2	MoO_2	53	9	V_2O_4	14
3	MoO_3	51	10	VCl_3	4
4	MoO_2Cl_2	30	11	WO_3	0
5	Na_2MoO_4	13	12	$TiCl_4$	22
6	$HOReO_3$	49	13	TiO_2	0
7	$TMSOReO_3$	49	14	SnO_2	0

[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.

2.2. Catalytic Synthesis of Oxazolines Using Molybdenum(VI) Oxo Compounds

Next, the author 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 2.2). 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 $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$, $(NH_4)_2MoO_4$ 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 $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$, $(NH_4)_2MoO_4$ and $MoO_2(acac)_2$ (entries 6 and 7). 3-Nitrophenylboronic acid [3-$(NO_2)C_6H_4B(OH)_2$][5] was almost inert for the present reaction (entry 8).

Table 2.2. Catalytic Activities of Molybdenum Oxo Compounds for the Deydrative Cyclization of **1**[a]



1a: R = H
1b: R = Me

2a: R = H
2b: R = Me

3a: R = H
3b: R = Me

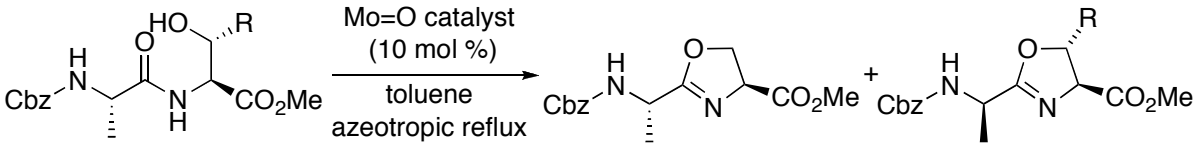
		1a → 2a		**1b → 2b**	
entry	catalyst	time (h)	yield (%)[b,c]	time (h)	yield (%)[b,c]
1	MoO_2	8	86 (10)	8	97 (0)
2	MoO_3	8	78 (5)	8	99 (0)
3	$(NH_4)_6Mo_7O_{24}•4H_2O$	4	87 (11)	2	97 (0)
4	$(NH_4)_2MoO_4$	4	87 (11)	2	95 (0)
5	$MoO_2(acac)_2$	1	87 (7)	1	90 (0)
6	$CoMoO_4$		–	4	96 (0)
7	$FeMoO_4$		–	4	96 (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.

Then, the author 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 2.3). The ammonium salts of molybdenum(VI) oxides, $(NH_4)_6Mo_7O_{24}•4H_2O$ 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 *p*-TsOH[6] gave a 1:1 mixture of **5b** and **6b**, probably due to the strong acidity of *p*-TsOH.

Table 2.3. Synthesis of Oxazoline **5**[a]



4a: R = H
4b: R = Me

5a: R = H
5b: R = Me

6a: R = H
6b: R = Me

entry	Mo=O 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.

2.3. Synthesis of a Key Synthetic Intermediate of Hennoxazole A

Hennoxazole A (Figure 2.1), 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.[7] The author synthesized a key synthetic intermediate **15**

of hennoxazole A,[8] which includes the bis(oxazole) structure, using the present Mo(VI)=O-catalyzed dehydrative cyclization as a key step (Scheme 2.1). The author 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 elimination product **9** as a major product (47%) and the desired product **8** was not obtained.[9] 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.

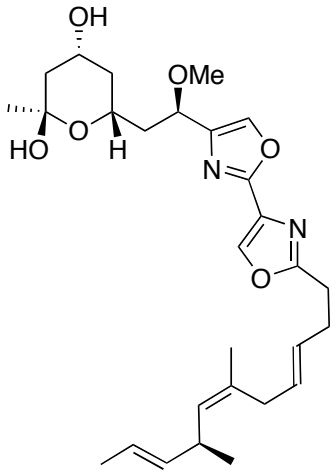
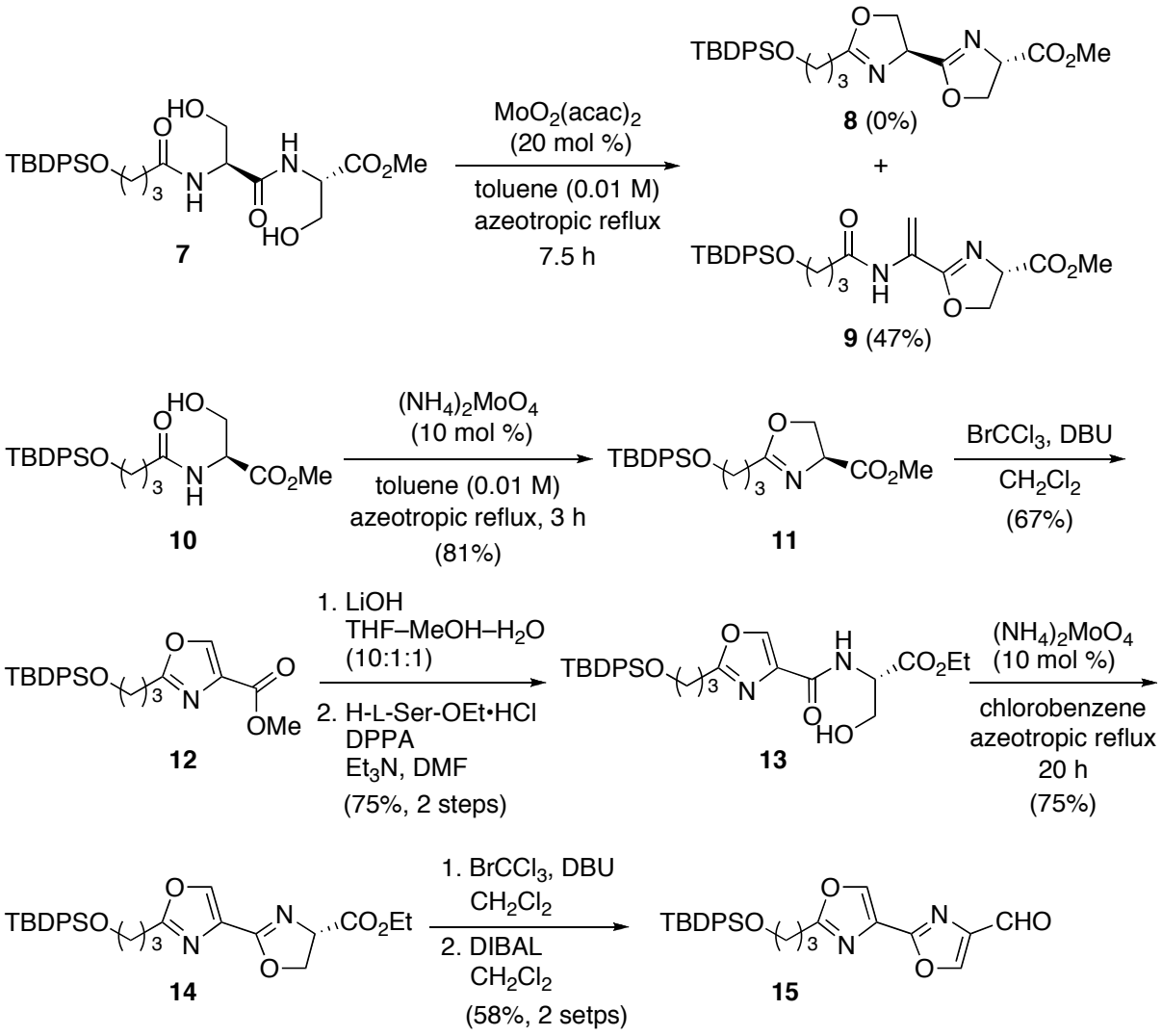


Figure 2.1. Hennoxazole A.

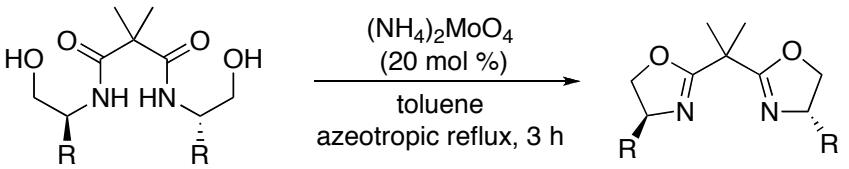
The author next tried to construct two oxazole rings in a stepwise manner. Dehydrative cyclization of **10** using $(NH_4)_2MoO_4$ (10 mol %) gave oxazoline **11** in 81% yield. Oxidation of oxazoline **11** to oxazole **12** (67%),[2a] hydrolysis of methyl ester, and condensation with L-serine ethyl ester gave **13** (75% in 2 steps). Since **13** was less reactive in the Mo(VI)=O-catalyzed dehydrative cyclization, the reaction of **13** was conducted in chlorobenzene (bp. 132 °C) and gave oxazoline **14** (75%) along with recovered **13** (8%). Oxidation of the oxazoline ring[2a] and reduction of the ethyl ester of **14** gave **15** in 58% yield.

Scheme 2.1. Synthesis of **15**, a Key Synthetic Intermediate of Hennoxazole A



Bis(oxazoline)s are a very useful class of chiral ligands for asymmetric catalysis[10] and are generally synthesized from the corresponding bis(amide)s via sulfonylation or chlorination of the two hydroxyl groups. Bis(oxazoline)s **17** could be easily synthesized by the molybdenum(VI) oxide-catalyzed dehydrative double-cyclization of bis(amide)s **16** (Scheme 2.2). Bis(amide)s **16a** and **16b** 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 **17a** and **17b** were obtained in respective yields of 84% and 83%.

Scheme 2.2. Synthesis of Chiral Bis(oxazoline)s **17**

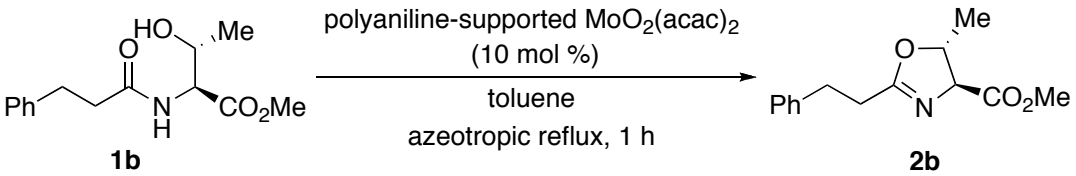


16a: R = *i*-Pr
16b: R = Ph

17a: R = *i*-Pr
17b: R = Ph

Next, we examined polymer-supported molybdenum(VI) oxides as recyclable catalysts. Polyaniline-supported $MoO_2(acac)_2$[11] also catalyzed efficiently the dehydrative cyclization of **1b**. The immobilized catalyst was recovered by filtration and reused more than five times for the dehydrative cyclization of **1b** (Scheme 2.3).

Scheme 2.3. Dehydrative Cyclization Using Polyaniline-Supported $MoO_2(acac)_2$ as a Recyclable Catalyst



1b **2b**

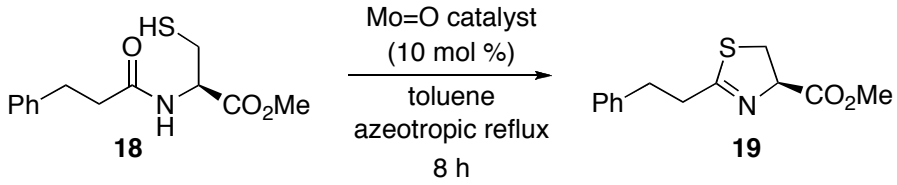
run	1	2	3	4	5
yiled (%)	99	95	91	92	87

2.4 Catalytic Synthesis of Thiazolines Using Molybdenum(VI) Oxo Compounds

The author first examined the dehydrative cyclization of *N*-(3-phenylpropionyl)-L-cysteine methyl ester (**18**) using molybdenum oxo compounds as catalysts (Table 2.4). As a result,

$(NH_4)_6Mo_7O_{24}•4H_2O$, $(NH_4)_2MoO_4$ 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 2.4. Dehydrative Cyclization of *N*-(3-phenylpropionyl)-L-cysteine methyl ester (**18**)[a]

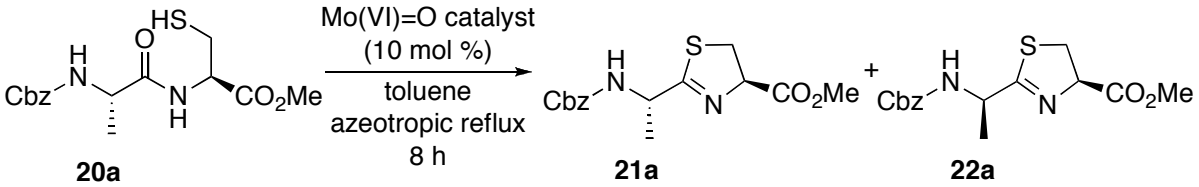


entry	Mo=O catalyst	yield (%)[b]
1	MoO_2	29
2	MoO_3	18
3	$(NH_4)_6Mo_7O_{24}•4H_2O$	96
4	$(NH_4)_2MoO_4$	99
5	$MoO_2(acac)_2$	81
6	No catalyst	9

[a] The reaction of **18** (0.5 mmol) was conducted in the presence of catalyst (10 mol %) in toluene (50 mL) under azeotropic reflux conditions for 8 h.
[b] Estimated by HPLC analysis.

The reactivity of a more complex dipeptide substrate, Cbz-L-Ala-L-Cys-OMe (**20a**), was much lower than that of **18**, and MoO_3, $(NH_4)_6Mo_7O_{24}•4H_2O$ and $(NH_4)_2MoO_4$ gave poor results (Table 2.5, 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 **21a** and the epimer **22a** (entry 4). The dehydrative cyclization of **20a** was conducted under high-dilution conditions (0.01 M of **20a**) because the yield of thiazoline **21a** was decreased (62%) at a higher substrate concentration (0.05 M).

Table 2.5. Dehydrative Cyclization of Cbz-L-Ala-L-Cys-OMe (**20a**)[a]



20a **21a** **22a**

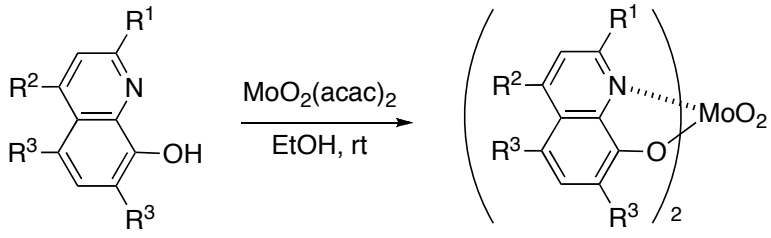
entry	Mo(VI)=O catalyst	yield (%)[b]	dr (**21a**:**22a**)[c]
1	MoO_3	9	ND
2	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	16	ND
3	$(NH_4)_2MoO_4$	26	ND
4	$MoO_2(acac)_2$	85	82:18
5	No catalyst	0	ND

[a] The reaction of **20a** (0.1 mmol) was conducted with Mo(VI)=O catalyst (10 mol %) in toluene (10 mL) under azeotropic reflux with the removal of water. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis.

It is conceivable that the generation of epimer **22a** could be attributed to the relatively high acidity of $MoO_2(acac)_2$. Thiazolines are generally more susceptible to epimerization than oxazolines under both acidic and basic conditions.[12,13] The author 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. 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 %). Through the intensive examination of molybdenum complexes as dehydrative cyclization catalysts, we found that molybdenum(VI) complexes with 8-quinolinols showed good catalytic activities.[14]

Bis(quinolinolato)dioxomolybdenum(VI) complexes **30a–30f** were easily prepared from $MoO_2(acac)_2$ and known 8-quinolinols (2 equiv) in EtOH in yields of 69–99% (Scheme 2.4). The structures of **30a–30f** were confirmed by ^{1}H NMR, IR, HRMS, and X-ray crystallographic analyses. The X-ray single-crystal structures of **30c** and **30d** are shown in Figure 2-2. These hexacoordinated complexes may have a total of three arrangements: (a) the two quinolinolato nitrogen atoms 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*).[15] X-ray crystallographic analyses revealed that both **30c** and **30d** had *N-trans* configurations (Figure 2.2).[16] The X-ray single-crystal structure of **30d** is more distorted than that of **30c** (O1–Mo–O2 bond angle of **30c** = 163.69° and that of **30d** = 147.96°). ^{1}H NMR spectra indicated that **30c** 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 **30d**, 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*.

Scheme 2.4. Preparation of Bis(quinolinolato)dioxomolybdenum(VI) Complexes



30

	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

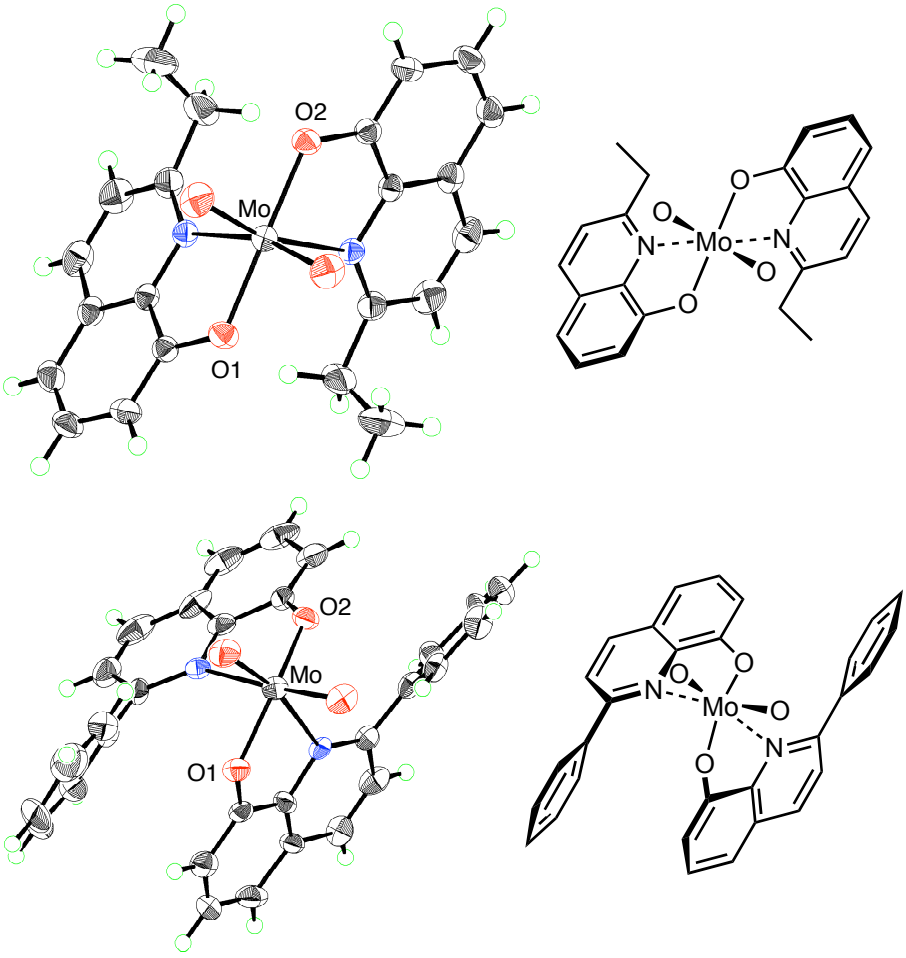
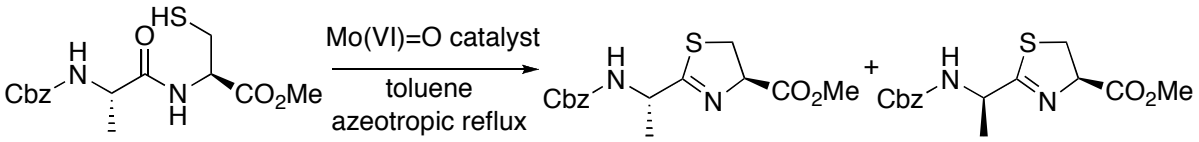


Figure 2.2. X-ray single-crystal structures of **30c** (top) and **30d** (bottom).

With the bis(quinolinolato)dioxomolybdenum(VI) complexes **30a**–**30f** in hand, we examined their catalytic activities for the dehydrative cyclization of **20a** to thiazoline **21a** (Table 2.6). 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 **30a**–**30f** 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 **30a** (10 mol %) showed good catalytic activity (80% yield), and the generation of epimer **22a** was effectively reduced, as expected (**21a**:**22a** = 96:4) (entry 1). The author then tried to

reduce the catalyst loading, but unfortunately the use of 1 mol % of **30a** decreased the reactivity (entry 2). Interestingly, we found that the introduction of an alkyl group to the 2-position of 8-quinolinol significantly increased the catalytic activities of the quinolinolato complexes (entries 3–6). In particular, 2-ethyl-8-quinolinolato complex **30c** and 2,4-dimethyl-8-quinolinol complex **30e** exhibited remarkably higher catalytic activities than $MoO_2(acac)_2$, to give **21a** in 96% yield despite the lower catalyst loading (1 mol %) (entries 4,6). Furthermore, the use of complexes **30c** and **30e** 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 **30f** showed good catalytic activity, epimerization increased to 86:14 dr (entry 7). It is conceivable that the stronger 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.

Table 2.6. Catalytic Activities of Bis(quinolinolato)dioxomolybdenum(VI) Complexes for the Dehydrative Cyclization of **20a**



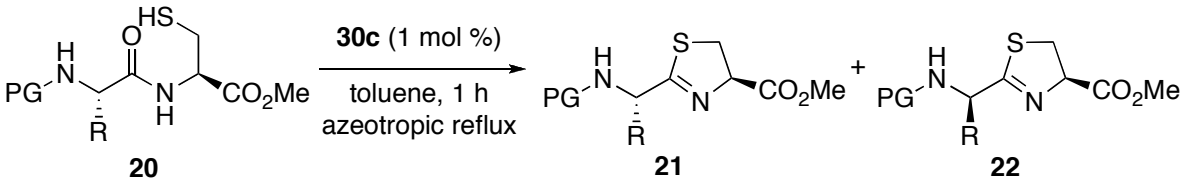
20a **21a** **22a**

entry	Mo(VI)=O catalyst, mol %	time (h)	yield (%)[b]	dr (**21a**:**22a**)[c]
1	**30a**, 10	5	80	96:4
2	**30a**, 1	5	40	89:11
3	**30b**, 1	5	93	95:5
4	**30c**, 1	2	96	97:3
5	**30d**, 1	5	80	85:15
6	**30e,** 1	5	96	96:4
7	**30f**, 1	2	94	86:14

[a] The reaction of **20a** (0.1 mmol) was conducted with Mo(VI)=O catalyst (1–10 mol %) in toluene (10 mL) under azeotropic reflux with the removal of water. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis.

The author then examined the dehydrative cyclization of other cysteine-containing dipeptides Cbz-L-Phe-L-Cys-OMe (**20b**), Boc-L-Ala-L-Cys-OMe (**20c**) and Fmoc-L-Ala-L-Cys-OMe (**20d**) (Table 2.7). Dipeptides **20b–d** could be converted to the corresponding thiazolines **21b–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%.

Table 2.7. Dehydrative Cyclization of Dipeptide **20** to Thiazoline **21** Catalyzed by **30c**[a]



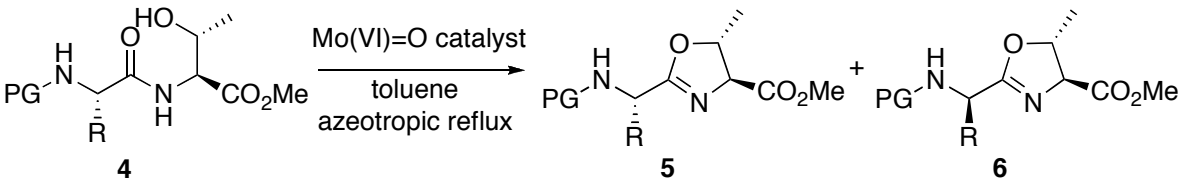
20 **21** **22**

entry	dipeptide **20** [PG, R]	yield (%)[b]	dr (**21**:**22**)[c]
1	**20b** [Cbz, Bn]	85	98:2
2	**20c** [Boc, Me]	82	94:6
3	**20d** [Fmoc, Me]	91	96:4

[a] The reaction of **20** (0.1 mmol) was conducted with **30c** (1 mol %) in toluene (10 mL) under azeotropic reflux conditions for 1 h.
[b] Isolated yields of **21** and **22**. [c] Determined by HPLC analysis.

The author previously discussed the dehydrative cyclization of **4b** to oxazoline **5b** in good yields using $(NH_4)_6Mo_7O_{24}•4H_2O$ and $(NH_4)_2MoO_4$ as catalysts (Table 2.3, entries 3 and 4). 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 (**4b**), Cbz-L-Phe-L-Thr-OMe (**4c**), Boc-L-Ala-L-Thr-OMe (**4d**) and Fmoc-L-Ala-L-Thr-OMe (**4e**) to the corresponding oxazolines **5b–e** (Table 2.8). Although **30a** and **30b** showed moderate catalytic activities (entries 1 and 2), 2-phenyl-8-quinolinolato complex **30d** gave excellent results (entries 3–6). The catalytic activity of the homogeneous complex **30d** was higher than those of heterogeneous $(NH_4)_2MoO_4$ and $(NH_4)_6Mo_7O_{24}•4H_2O$, and the amount of **30d** could be reduced to 1 mol %. Furthermore, the yield of epimers **6b–e** was less than 6%. The present reactions also showed a complete retention of configuration at the 5-position.

Table 2.8. Dehydrative Cyclization of Dipeptides **4** to Oxazolines **5** Catalyzed by Bis(quinolinolato)dioxomolybdenum(VI) Complexes[a]



entry	Mo(VI)=O, mol %	dipeptide **4** [PG, R]	time (h)	yield (%)[b]	dr (**5**:**6**)[c]
1	**30a**, 10	**4b** [Cbz, Me]	5	70[d]	81:19
2	**30b**, 10	**4b** [Cbz, Me]	5	51[d]	98:2
3	**30d**, 1	**4b** [Cbz, Me]	1	85	94:6
4	**30d**, 1	**4c** [Cbz, Bn]	1	92	96:4
5	**30d**, 1	**4d** [Boc, Me]	2	89	98:2
6	**30d**, 1	**4e** [Fmoc, Me]	1	88	95:5
7	**30f**, 10	**4b** [Cbz, Me]	6	42	ND

[a] The reaction of **4** (0.1 mmol) was conducted with Mo(VI)=O catalyst (1–10 mol %) in toluene (10 mL) under azeotropic reflux with the removal of water.
[b] Isolated yileds. [c] Determined by HPLC analysis. [d] Determined by ^{1}H NMR analysis.

In summary, the author has 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.

References and Notes

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9. In general, $(NH_4)_2MoO_4$ is slightly more active than $MoO_2(acac)_2$ for the dehydrative cyclization of serine residue, as shown in Table 2.3. However, $MoO_2(acac)_2$ showed slightly higher catalytic activity than $(NH_4)_2MoO_4$ for the dehydrative cyclization of **7**. For example, when the reaction of **7** was conducted with $(NH_4)_2MoO_4$, **9** was obtained in 28% yield.

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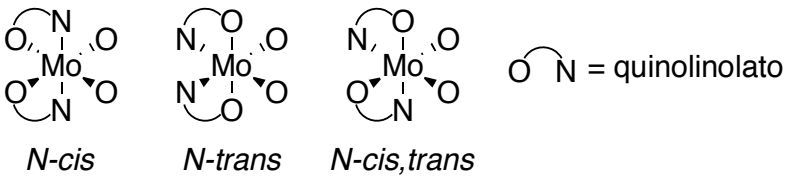


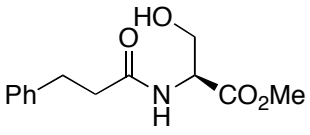
16. The X-ray single-crystal structure of **30a** has been reported. The crystal structure of **30a** also shows an *N-trans* configuration. Fun, H.-K.; Sivakumar, K.; Niu, J.-Y.; Wang, J.-P.; You, X.-Z. *Acta Crystallogr.* **1996**, *C52*, 1150.

Experimental Section

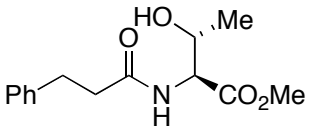
General Methods. IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the δ scale, multiplicity (s = singlet; 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 × 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 Chemical Instrument Facility, Nagoya University. X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å) and the structure was solved by direct methods and expanded using Fourier techniques (Sir97 and SHELXL-97[1]).

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), $(NH_4)_6Mo_7O_{24}•4H_2O$ (Nacalai tesque), $(NH_4)_2MoO_4$ (Aldrich), $MoO_2(acac)_2$ (Wako Pure Chemical Industries, Ltd.), 8-quinolinol (Wako Pure Chemical Industries, Ltd.), 2-methyl-8-quinolinol (TCI) and other materials were obtained from commercial supplies and used without further purification. Compounds **2a**,[2] **4a**,[3] **4b**,[4] **5a**,[2,5] **10**–**12**,[6] **15**,[6] **16b**,[7] **17a**,[8] **17b**,[9] **19**,[10] **20a**,[11] **21a**,[5,12] 2-Ethyl-8-quinolinol,[13] 2-phenyl-8-quinolinol,[14] 2,4-dimethyl-8-quinolinol,[15] 5,7-dibromo-2,4-dimethyl-8-quinolinol,[16] *cis*-bis(8-quinolinolato-*N,O*)dioxomolybdenum(VI) (**30a**),[17]

cis-bis(2-methyl-8-quinolinolato-*N,O*)dioxomolybdenum(VI) (**30b**),[18] and thiazoline **21b**[19] were reported previously.

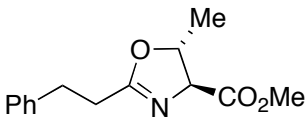


***N*-(3-Phenylpropionyl)-L-serine methyl ester (1a).** To a solution of L-serine methyl ester hydrochloride (5.0 g, 32 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (8.9 mL, 64 mmol) and a solution of 3-phenylpropionyl chloride (4.5 mL, 30 mmol) in CH_2Cl_2 (15 mL) dropwise at –5 °C. After being stirred at –5 °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 $C_{13}H_{18}O_4N$ $[M+H]^+$ 252.1236, found 252.1234.

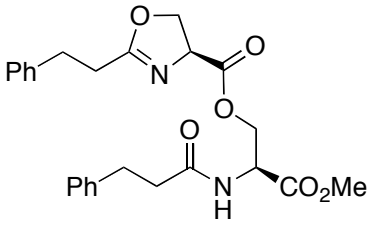


***N*-(3-Phenylpropionyl)-L-threonine methyl ester (1b).** Experimental procedure was followed as described for **1a**. **1b:** IR (KBr) 3483, 1719, 1645, 1543 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.3 Hz, 1H), 1.93 (br s, 1H), 2.60 (m, 2H), 3.00 (t, *J* = 7.8 Hz, 2H), 3.76 (s, 3H), 4.29 (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 $C_{14}H_{20}O_4N$ $[M+H]^+$ 266.1392, found 266.1397.

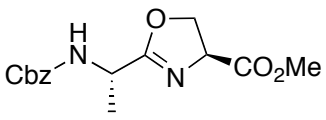
General Procedure for the Dehydrative Cyclization of Serine, Threonine Derivatives 1 and 4. A solution of substrate (0.50 mmol) and molybdenum oxide catalyst (0.050 mmol) in toluene (10 mL for threonine derivatives, 50 mL for serine derivatives) was heated at azeotropic reflux with the removal of water 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 ^{1}H NMR analysis.



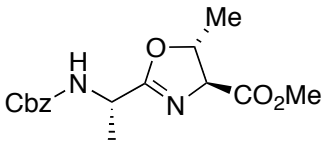
(4*S*,5*R*)-Methyl 5-methyl-2-phenethyl-4,5-dihydrooxazole-4-carboxylate (2b): IR (neat) 3028, 2977, 2952, 1741, 1659, 1204, 1179, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, J = 6.3 Hz, 3H), 2.63 (t, J = 8.1 Hz, 2H), 2.98 (t, J = 8.1 Hz, 2H), 3.78 (s, 3H), 4.23 (d, J = 7.5 Hz, 1H), 4.80 (dq, 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 $C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1287, found 248.1281.



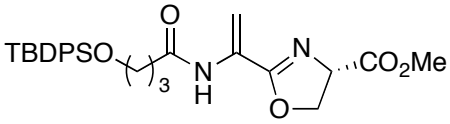
Dimer 3a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45–2.67 (m, 4 H), 2.83–3.08 (m, 4 H), 3.74 (s, 3 H), 4.25–4.56 (m, 4 H), 4.64 (d, J = 6.9, 7.2 Hz, 1 H), 4.90 (m, 1 H), 6.64 (d, J = 6.9 Hz, 1 H), 7.08–7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.6, 31.2, 31.9, 37.8, 51.4, 52.9, 64.7, 67.8, 69.2, 126.2, 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 2. The product included the diastereomer **6a**, and the diastereomeric 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.

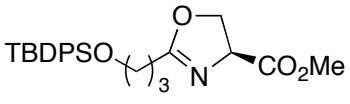


Oxazoline 5b: IR (KBr) 3326, 1724, 1661, 1531, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, J = 7.2 Hz, 3H), 1.44 (d, J = 7.2 Hz, 3H), 3.79 (s, 3H), 4.27 (d, J = 7.5 Hz, 1H), 4.52 (dq, J = 7.5, 7.2 Hz, 1H), 4.86 (dq, J = 7.5, 7.2 Hz, 1H), 5.08 (d, J = 12.3 Hz, 1H), 5.13 (d, J = 12.3 Hz, 1H), 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 $C_{16}H_{21}O_5N_2$ $[M+H]^+$ 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.

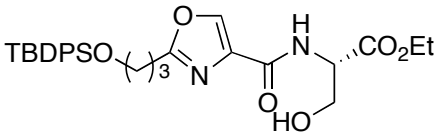


Oxazoline 9. The reaction of **7** (0.6 mmol) was conducted with $MoO_2(acac)_2$ (20 mol %) in toluene (60 mL) according to the procedure shown in Section 4.2 to give dehydrative elimination product **9** (47% yield). IR (neat) 3390, 1746, 1698, 1608, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (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, 9 H); ^{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.

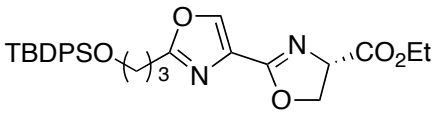


Oxazoline 11. Experimental procedure was followed as described for dehydrative cyclization of **1**. The resultant crude product was purified by column chromatography on silica gel to give oxazoline **11** (81% yield).

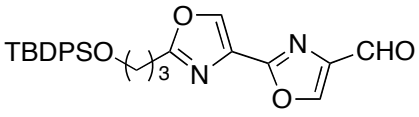


Amide 13. To a solution of **12** (297 mg, 0.70 mmol) in THF–MeOH (10:1, 4 mL) was added a 2 M aqueous solution of LiOH (0.40 mL, 0.77 mmol) and the mixture was stirred at ambient temperature for 8 h. The reaction mixture was acidified (pH 3) with 1 M aqueous HCl. Sodium chloride was added to the mixture 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 mL, 1.54 mmol) at 0 °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 → 1:1) to give amide **13** (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 $C_{28}H_{37}O_6N_2Si$ $[M+H]^+$ 525.2421, found 525.2419.

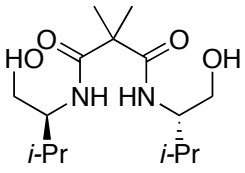


Oxazoline 14. A solution of amide **13** (125 mg, 0.24 mmol) and $(NH_4)_2MoO_4$ (4.7 mg, 0.024 mmol) in chlorobenzene (24 mL) was heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. After 20 h, the reaction mixture was cooled to ambient temperature, and then the organic solvent was removed. The resultant crude product was purified by column chromatography on silica gel using $CHCl_3$–Et_2O (50:1 → 30:1 → 10:1) to give oxazoline **14** (90 mg, 75% yield) along with amide **13** (10 mg, 8% yield): IR (neat) 1738, 1679, 1586, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{28}H_{35}O_5N_2Si$ $[M+H]^+$ 507.2315, found 507.2311.



Aldehyde 15. To a solution of **14** (59 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) was added DBU (34.5 mL, 0.23 mmol) at 0 °C and the mixture was stirred for 5 min. $BrCCl_3$ (12.5 mL, 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 NH_4Cl (5 mL), dried (Na_2SO_4), 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 CH_2Cl_2 (0.5 mL) was added a 0.95 M hexane solution of DIBAL (166 mL, 0.16 mmol) dropwise at –78 °C and stirred for 15 min.

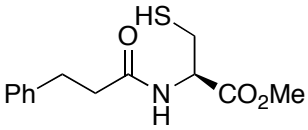
Anhydrous acetone (0.6 mL) was added to the reaction mixture and stirred at –78 °C for 10 min, then warmed to ambient temperature. A 20% aqueous sodium potassium tartrate (0.6 mL) was added to the mixture and stirred vigorously until the two layers rapidly separated (2 h). The mixture was extracted with Et_2O (10 mL × 2). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resultant crude product was purified by column chromatography on silica gel using hexane–EtOAc (2:1 → 1:1) to give aldehyde **15** (26 mg, 71% yield).



Bis(amide) 16a. 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 → 2:3) to give bis(amide) **16a** (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 $C_{15}H_{31}O_4N_2$ $[M+H]^+$ 303.2284, found 303.2285.

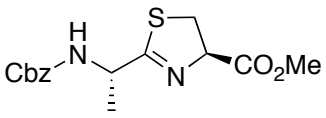
Procedure for the Dehydrative Cyclization of Bis(amide)s 16. A solution of bis(amide) **16a**, **b** (1.0 mmol) and molybdenum oxide catalyst (0.20 mmol) in toluene (10 mL) was heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. After 3 hours, the reaction mixture was 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 → 4:1) to give bis(oxazoline) **17a** (84% yield), **17b** (83% yield).



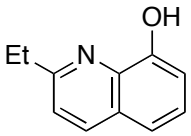
***N*-(3-Phenylpropionyl)-L-cysteine methyl ester (18).** Experimental procedure was followed as described for **1a**. **18:** IR (KBr) 3328, 1731, 1641, 1540, 1263 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, *J* = 9.0 Hz, 1H), 2.54 (dt, *J* = 14.7, 8.1 Hz, 1H), 2.63 (ddd, *J* = 6.6, 7.5, 14.7 Hz, 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 $C_{13}H_{18}O_3NS$ $[M+H]^+$ 268.1007, found 268.1010.

General Procedure for the Dehydrative Cyclization of Cysteine Derivatives 18 and 20a (Table 2.4 and 2.5). A solution of substrate (0.50 mmol) and molybdenum oxide catalyst (0.050 mmol) in toluene (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.

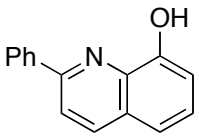


Thiazoline 21a. Spectral data of thiazoline **21a** were identical with those in ref 5. The data did not provide any evidence of the presence of the diastereomer **22a**. The detailed analysis by HPLC on Develosil 30-5 showed that the product included the diastereomer **22a**, and the diastereo ratio was 4.7:1. **21a:** t_R = 32.2 min, **22a:** t_R = 34.3 min (hexane–EtOAc–MeOH = 64:16:1). Authentic sample of **22a** was prepared from Cbz-D-Ala-L-Cys-OCH_3.

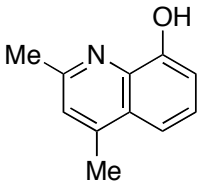
Preparation of Bis(quinolinolato)dioxomolybdenum(VI) Complexes



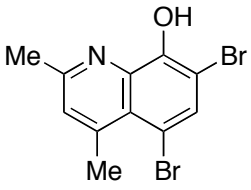
2-Ethyl-8-quinolinol. 2-Ethyl-8-quinolinol was prepared according to the reported procedure.[13] 40% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.5 Hz, 3H), 3.00 (q, *J* = 7.5 Hz, 2H), 7.15 (dd, J = 1.2, 7.5 Hz, 1H), 7.29 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 7.5, 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H).



2-Phenyl-8-quinolinol. 2-Phenyl-8-quinolinol was prepared according to the reported procedure.[14] 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 1.5, 7.4 Hz, 1H), 7.32 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.43 (dd, *J* = 7.4, 8.2 Hz, 1H), 7.49–7.60 (m, 3H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.12–8.19 (m, 2H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.25–8.50 (s, 1H).

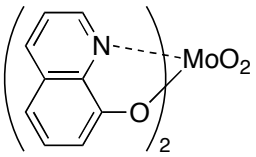


2,4-Dimethyl-8-quinolinol. 2,4-Dimethyl-8-quinolinol was prepared according to the reported procedure.[15] 45% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (d, *J* = 0.9 Hz, 3H), 2.67 (s, 3H), 7.13 (dd, *J* = 2.7, 6.0 Hz, 1H), 7.14 (s, 1H), 7.39 (d, *J* = 6.0 Hz, 1H), 7.40 (d, *J* = 2.7 Hz, 1H).

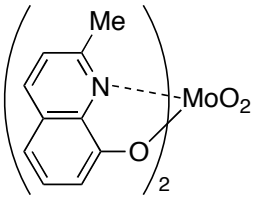


5,7-Dibromo-2,4-dimethyl-8-quinolinol. 5,7-Dibromo-2,4-methyl-8-quinolinol was prepared according to the reported procedure.[16] 92%

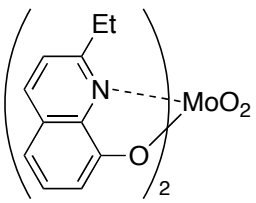
yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 1H), 2.66 (s, 3H), 3.05 (s, 3H), 7.19 (s, 1H), 7.87 (s, 1H).



***cis*-Bis(8-quinolinolato-*N,O*)dioxomolybdenum(VI) (30a).** **30a** was prepared according to the reported procedure.[17] 98% yield; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42 (dd, J = 1.2, 7.5 Hz, 1H), 7.53 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.55 (dd, *J* = 5.4, 7.8 Hz, 1H), 7.69 (dd, *J* = 7.5, 8.4 Hz, 1H), 8.52 (d, *J* = 7.8 Hz, 1H), 8.53 (d, *J* = 5.4 Hz, 1H).

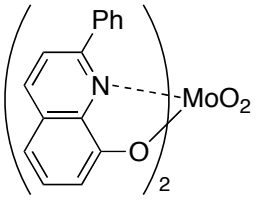


***cis*-Bis(2-methyl-8-quinolinolato-*N,O*)dioxomolybdenum(VI) (30b).** **30b** was prepared according to the reported procedure.[18] 99% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 0.75H), 2.73 (s, 0.75H), 2.95 (s, 3H), 3.41 (s, 1.5H), 5.30 (d, *J* = 7.5 Hz, 0.25H), 5.76 (d, *J* = 7.5 Hz, 0.25H), 6.20 (dd, *J* = 2.4, 6.3 Hz, 0.25H), 6.49 (m, 0.5H), 6.67 (t, *J* = 8.4 Hz, 0.25H), 7.01 (m, 1H), 7.15 (m, 0.5H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.21 (m, 0.5H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.30 (m, 0.5H), 7.38 (t, *J* = 7.8 Hz, 0.25H), 7.42–7.55 (m, 0.75H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 0.25H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 0.25H), 8.12 (d, *J* = 8.7 Hz, 0.25H), 8.25 (d, *J* = 8.4 Hz, 0.25H). **8** was a ca. 2:1:1 isomeric mixture in $CDCl_3$.



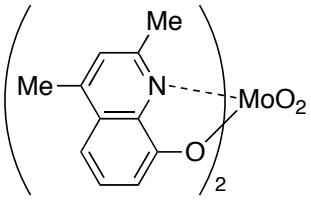
***cis*-Bis(2-ethyl-8-quinolinolato-*N,O*)dioxomolybdenum(VI) (30c).** To a

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, **30c** was obtained by filtration (58 mg, 91%). Single crystals suitable for X-ray analysis were obtained from CH_2Cl_2. IR (KBr) 908 (Mo=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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; **30c** was a ca. 3:2 isomeric mixture in $CDCl_3$; HRMS (FAB) calcd for $C_{22}H_{21}MoN_2O_4$ $[M+H]^+$ 475.0555, found 475.0563.

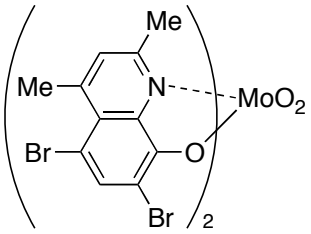


***cis*-Bis(2-phenyl-8-quinolinolato-*N,O*)-dioxomolybdenum(VI) (30d).** To a solution of $MoO_2(acac)_2$ (65.2 mg, 0.20 mmol) in EtOH (0.50 mL) was added a solution of 2-phenyl-8-quinolinol (88.5 mg, 0.40 mmol) in EtOH (1.0 mL). After being stirred at ambient temperature for 15 min, **30d** was obtained by filtration (91 mg, 80%). Single crystals suitable for X-ray analysis were obtained from EtOH. IR (KBr) 900 (Mo=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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; **30d** was a ca. 9:1 isomeric mixture in $CDCl_3$; HRMS (FAB) calcd for $C_{30}H_{21}MoN_2O_4$ $[M+H]^+$ 571.0555, found 571.0542.



***cis*-Bis(2,4-dimethyl-8-quinolinolato-*N,O*)-dioxomolybdenum(VI) (30e).** To a solution of $MoO_2(acac)_2$ (32.6 mg, 0.10 mmol) in EtOH (0.50 mL) was added 2,4-dimethyl-8-quinolinol (34.6 mg, 0.20 mmol). After being stirred at ambient temperature for 12 h, **30e** was obtained by filtration (41 mg, 87%). IR (KBr) 903 (Mo=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 0.3H), 2.53 (s, 5.3H), 2.64 (s, 0.3H), 2.67 (s, 0.4H), 2.89 (s, 5.3H), 3.34 (s, 0.4H), 6.97 (s, 2H), 7.18 (dd, J = 1.2, 7.5 Hz, 2H), 7.32 (dd, J = 1.2, 8.4 Hz, 2H), 7.46 (dd, J = 7.5, 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 23.3, 114.4, 114.5, 125.7, 127.4, 127.7, 140.2, 147.5, 159.3, 160.3; **30e** was ca. 88:7:5 isomeric mixture in $CDCl_3$; HRMS (FAB) calcd for $C_{22}H_{21}MoN_2O_4$ $[M+H]^+$ 475.0555, found 475.0550.



***cis*-Bis(5,7-dibromo-2,4-dimethyl-8-quinolinolato-*N,O*)-dioxomolybdenum(VI) (30f).** To a solution of $MoO_2(acac)_2$ (32.6 mg, 0.10 mmol) in EtOH (0.50 mL) was added a solution of 5,7-dibromo-2,4-dimethyl-8-quinolinol (66.2 mg, 0.20 mmol) in EtOH (1.0 mL) and acetone (1.5 mL). After being stirred at reflux for 2 h, **30f** was obtained by filtration (54.0 mg, 69%). IR (KBr) 1071, 803 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (s, 5.1H), 2.95 (s,

5.1H), 3.05 (s, 0.45H), 3.07 (s, 0.45H), 3.29 (s, 0.45H), 3.33 (s, 0.45H), 7.05 (s, 1.7H), 7.29 (s, 0.15H), 7.44 (s, 0.15H), 7.75 (s, 0.15H), 7.87 (s, 0.15H), 7.97 (s, 1.7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 24.8 107.9, 109.0,125.6, 129.2, 136.5, 141.7, 149.4, 156.0, 161.7. **30f** was ca. 85:15 isomeric mixture in $CDCl_3$; HRMS (FAB) calcd for $C_{22}H_{17}Br_4MoN_2O_4$ $[M+H]^+$ 786.6976, found 786.6948.

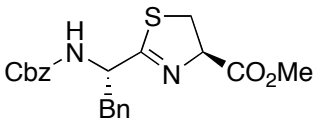
X-ray Crystallographic Analysis

Crystal data for 30c. Formula $C_{22}H_{20}MoN_2O_4$, colorless, crystal dimensions 0.40 × 0.40 × 0.30 mm^3, orthorhombic, space group $P2_12_12_1$(#19), a = 9.4211(19) Å, b = 9.4286(18) Å, c = 22.334(4) Å, V = 1983.9(7) Å^3, Z = 4, and D_{calc} = 1.581 g cm^{-3}, F(000) = 960, μ = 0.693 mm^{-1}, T = 223(2) K. 14851 reflections collected, 5243 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 29.14°), and 264 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0197 and *wR2* = 0.0528, GOF = 1.143. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk). Supplementary publication No. CCDC-630883.

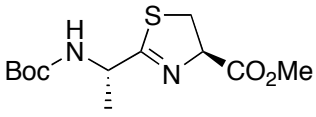
Crystal data for 30d. Formula $C_{30}H_{20}MoN_2O_4$, colorless, crystal dimensions 0.50 × 0.40 × 0.40 mm^3, monoclinic, space group *Cc*(#7), a = 27.814(5) Å, b = 12.760(2) Å, c = 15.796(3) Å, β = 119.415(3)°, V = 4883.3(14) Å^3, Z = 8, and D_{calc} = 1.546 g cm^{-3}, F(000) = 2304, μ = 0.578 mm^{-1}, T = 223(2) K. 17873 reflections collected, 11153 independent reflections with $I > 2\sigma(I)$ ($2\theta_{max}$ = 29.11°), and 667 parameters were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. R_1 = 0.0236 and *wR2* = 0.0630, GOF = 1.018. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre.

Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk). Supplementary publication No. CCDC-630884.

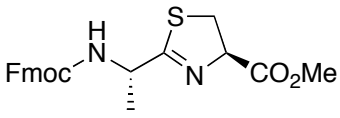
General Procedure for the Dehydrative Cyclization of Dipeptides 20 or 4 (Table 2.6, 2.7 and 2.8). A solution of a dipeptide **20** or **4** (0.10 mmol) and a molybdenum(VI) complex **30** (1 mol %) in toluene (10 mL) was heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. After several hours, the reaction mixture was cooled to ambient temperature, and the organic solvent was then removed to give a crude product. The obtained crude product was purified by column chromatography on silica gel using hexane–EtOAc, to give a corresponding thiazoline **21** or oxazoline **5**.



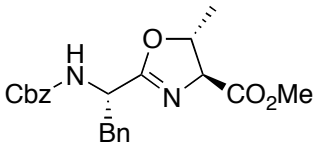
Thiazoline 21b. Spectral data of thiazoline **21b** were identical with those in ref 19. The diastereo ratio was determined by HPLC analysis on Develosil 30-5. **21b:** t_R = 16.1 min, **3b:** t_R = 17.6 min (hexane–EtOAc–MeOH = 32:8:1).



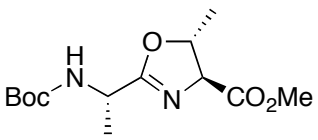
Thiazoline 21c. IR (neat) 3360, 1715, 1621, 1581, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.45(m, 3H), 3.53 (dd, J = 11.4, 9.6 Hz, 1H), 3.61 (dd, J = 11.4, 9.0 Hz, 1H), 3.82 (s, 3H), 4.52-4.65 (m, 1H), 5.11 (t, J = 9.6 Hz, 1H), 5.29 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 28.3, 35.4, 49.2, 52.7, 77.8, 79.8, 154.8, 171.0, 177.2; HRMS (FAB) calcd for $C_{12}H_{21}O_4N_2S$ $[M+H]^+$ 289.1222, found 289.1213. The diastereo ratio was determined by HPLC analysis on AD-H. **21c:** t_R = 64.4 min, **22c:** t_R = 58.8 min (hexane–*i*PrOH = 50:1).



Thiazoline 21d. IR (neat) 3311, 1716, 1522, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.9 Hz, 3H), 3.51-3.65 (m, 2H), 3.82 (s, 3H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.33-4.47 (m, 2H), 4.66 (dq, *J* = 7.5, 6.9 Hz, 1H), 5.11 (t, *J* = 9.0 Hz, 1H), 5.62 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.58–7.63 (m, 2H), 7.76 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 35.6, 47.1, 49.7, 52.8, 66.9, 77.7, 119.9, 125.0, 125.1, 127.0, 127.6, 141.2, 143.7, 143.9, 155.4, 171.0, 176.7; HRMS (FAB) calcd for $C_{22}H_{23}O_4N_2S$ $[M+H]^+$ 411.1379, found 411.1359. The diastereo ratio was determined by HPLC analysis on Develosil 30-5. **21d:** t_R = 25.9 min, **22d:** t_R = 27.1 min (hexane–EtOAc–MeOH = 32:8:1).

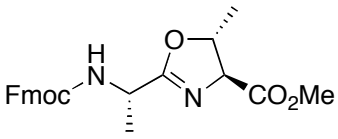


Oxazoline 5c. IR (neat) 3328, 1731, 1660, 1507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, *J* = 6.3 Hz, 3H), 3.06 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.14 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.72 (s, 3H), 4.22 (d, *J* = 6.0 Hz, 1H), 4.74-4.80 (m, 1H), 4.91 (dq, *J* = 6.3, 6.0 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.41 (d, *J* = 8.7 Hz, 1H), 7.08-7.11 (m, *2*H), 7.21–7.38 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 38.6, 50.1, 52.5, 66.8, 74.2, 79.6, 126.9, 127.9, 128.0, 128.3, 128.4, 129.6, 135.4, 136.3, 155.4, 167.9, 170.8; HRMS (FAB) calcd for $C_{22}H_{25}O_5N_2$ $[M+H]^+$ 397.1763, found 397.1776. The diastereo ratio was determined by HPLC analysis on Develosil 30-5. **5c:** t_R = 18.0 min, **6c:** t_R = 20.8 min (hexane–EtOAc–MeOH = 32:8:1).



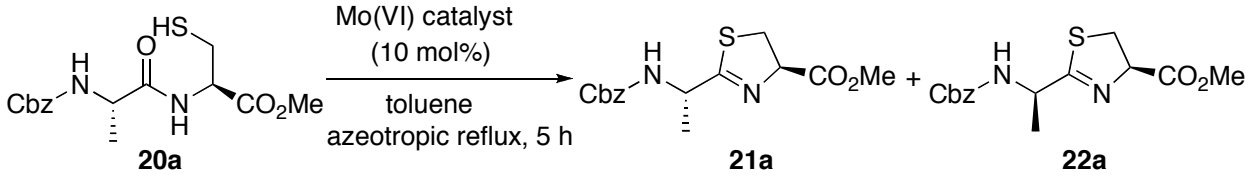
Oxazoline 5d. IR (KBr) 3370, 1715, 1661, 1506, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 1.45 (d, *J* = 6.3 Hz, 3H), 3.79 (s, 3H), 4.27 (d, *J* = 7.5 Hz, 1H), 4.45 (br q, *J* = 6.9 Hz, 1H), 4.86 (dq, *J* = 7.5, 6.3 Hz, 1H), 5.29 (br s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.8, 28.2, 44.8, 52.5, 52.6, 74.1, 79.7, 154.8, 170.2, 171; HRMS (FAB) calcd for $C_{13}H_{23}O_5N_2$ $[M+H]^+$ 287.1607, found 287.1617. The diastereo ratio was determined by HPLC analysis on AD-H. **5d:** t_R = 63.6 min, **6d:** t_R = 59.5 min (hexane–*i*PrOH= 50:1).



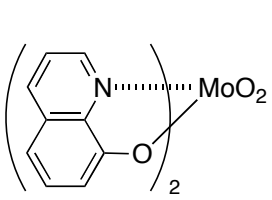
Oxazoline 5e. IR (KBr) 3425, 1618 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, *J* = 6.6 Hz, 6H), 3.80 (s, 3H), 4.22 (t, *J* = 6.9 Hz, 1H), 4.29 (d, *J* = 7.5 Hz, 1H), 4.39 (d, *J* = 6.9 Hz, 2H), 4.53 (dq, *J* = 7.5, 6.6 Hz, 1H), 4.87 (dq, *J* = 7.5, 6.6 Hz, 1H), 5.61 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.58–7.63 (m, 2H), 7.77 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 20.8, 45.3, 47.1, 52.7, 66.9, 74.1, 79.9, 119.9, 125.1, 127.0, 127.6, 141.2, 143.7, 143.9, 155.5, 169.9, 171.1; HRMS (FAB) calcd for $C_{23}H_{25}O_5N_2$ $[M+H]^+$ 409.1763, found 409.1777. The diastereo ratio was determined by HPLC analysis on Develosil 30-5. **5e:** t_R = 23.2 min, **6e:** t_R = 29.0 min (hexane–EtOAc–MeOH = 32:8:1).

Investigation of Catalytic Activities of Various Molybdenum(VI) Complexes.



20a **21a** **22a**

Mo(VI)=O catalyst
yield (%)
dr (**21a**:**22a**)



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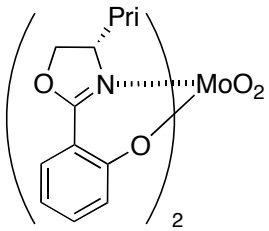

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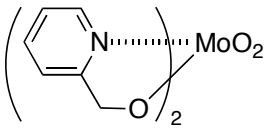

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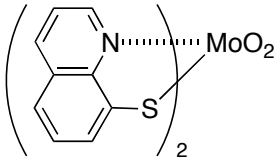

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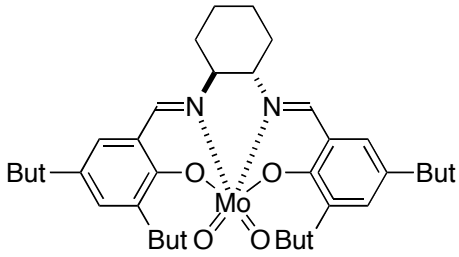

15
93:7

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Chapter 3

Asymmetric Diels–Alder Catalysis Using Copper(II) Cation with Chiral Bis(oxazoline) Ligands

Abstract: Complexes of copper(II) trifluoromethanesulfonimide [$Cu(NTf_2)_2$] and bis(oxazoline)s **1** with trifluoromethansulfonamide groups as the 4-substituents were highly efficient catalysts for the asymmetric Diels–Alder reaction of various dienes with bidentate dienophiles **2**. "Cation–*n* interaction" between copper(II) cation and *n* electrons of a bis(oxazoline) should play a key role not only in the construction of an effective chiral environment but also in increasing catalytic activity.

The asymmetric Diels–Alder reaction is one of the best methods for building six-membered carbocycles with control of up to four chiral centers, and has been widely used as a key step for the synthesis of natural products. Remarkable progress has been made in the development of chiral Lewis acid catalysts for the asymmetric Diels–Alder reaction.[1] However, there are still some challenges with regard to the substrate scope, and only a handful of reacting partners are accessible. To take full advantage of this powerful transformation, a more active and highly enantioselective catalyst is needed to provide greater flexibility with regard to both the nature of the dienes and the substitution pattern on the dienophiles.

Ligand design and synthesis is a central challenge in the development of an efficient chiral Lewis acid catalyst. The author's group has been interested in the design of new ligands with a secondary coordinating site to a metal cation for the construction of an effective chiral environment around the metal center. After our recent development of copper(II)-catalyzed asymmetric [4+2] and [2+2] cycloadditions using intramolecular "cation–π interaction" between copper cation and π electrons of 3-(2-naphthyl)-L-alanine amide ligand,[2] the author was attracted by the idea of "cation–*n* interaction" with *n* electrons (= lone pair) of a ligand. The author tried to develop a new catalyst system using "cation–*n* interaction" with copper(II) and bis(oxazoline)s, which is one of the most popular classes of chiral ligands, for the asymmetric Diels–Alder reaction. "Cation–*n* interaction" should work not only to build an efficient chiral environment but also to increase the reactivity by kicking out counter anions from the catalytic center (Figure 3.1).

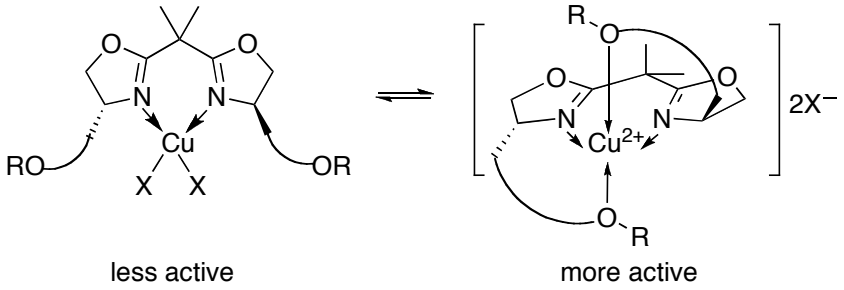


Figure 3.1. "Cation-*n* interaction" in the copper(II)-bis(oxazoline) system.

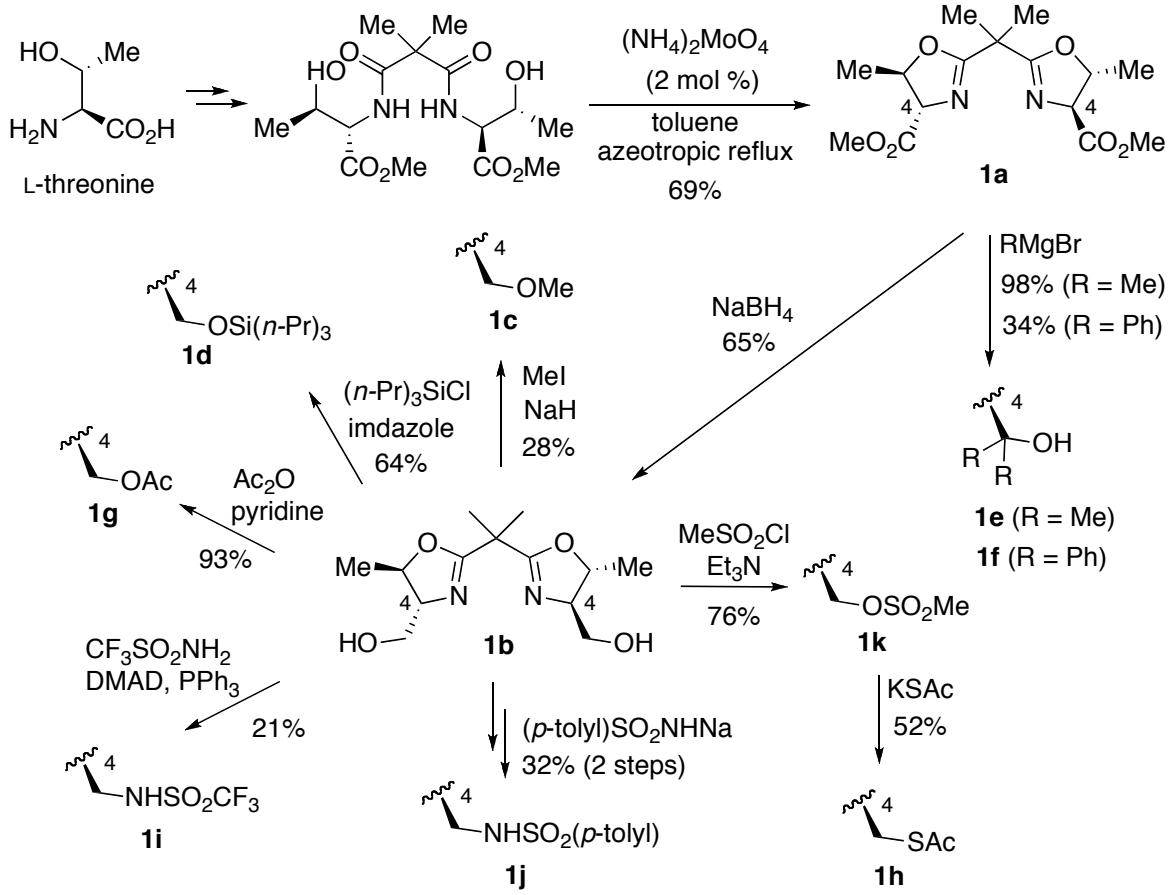
This chapter describes the design of a new catalyst system of copper(II)-bis(oxazoline)s with "cation–*n* interaction" and the development of catalysts toward a truly efficient asymmetric Diels–Alder reaction.

3.1. Syntheses of Bis(oxazoline) Ligands that Include Heteroatoms in the 4-Substituents

Although some reports have described syntheses of bis(oxazoline)s that include heteroatoms in the 4-substituents,[3] the author established a new synthetic route to the desired bis(oxazoline)s (Scheme 3.1). Bis(oxazoline) **1a** with a methoxy carbonyl group at the 4-position was synthesized from L-threonine via the ammonium salt of oxomolybdenum(VI) [$(NH_4)_2MoO_4$]-catalyzed dehydrative cyclization of the corresponding amide compounds in toluene under reflux conditions with the azeotropic removal of water for 12 h in good yield (68%).[4] The parent compound **1a** was transformed into hydroxymethyl bis(oxazoline) **1b** by reduction using sodium borohydride ($NaBH_4$) in 65% yield, or into *tert*-alcohols **1e** and **1f** using Grignard reagents [98% yield with methylmagnesium bromide (MeMgBr), 34% yield with phenylmagnesium bromide (PhMgBr)]. Compound **1b** was further transformed into various bis(oxazoline)s with functional groups such as methyl ether **1c** (28%), silyl ether **1d** (64%), acetyl ester **1g** (93%), sulfonamide **1i** (21%) and **1j**

(32%, 2 steps), and methanesulfonyl ester **1k** (76%). In addition, compound **1k** was transformed into bis(oxazoline) **1h** (52%) with acetyl thioester.

Scheme 3.1. Syntheses of Various Bis(oxazoline)s that Include Heteroatoms in the 4-Substituents

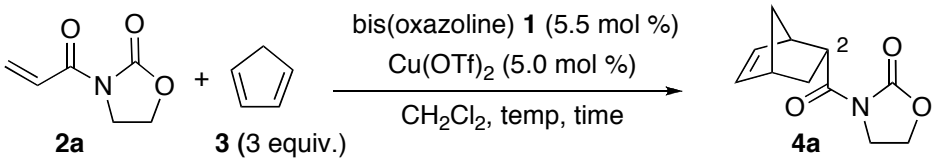


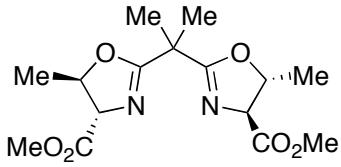
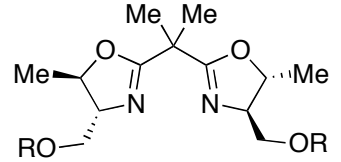
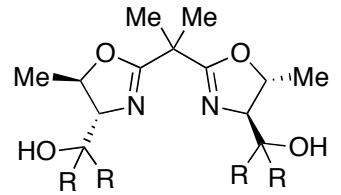
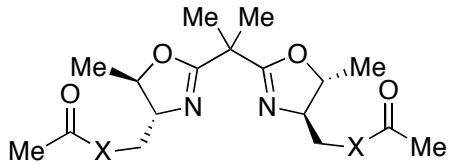
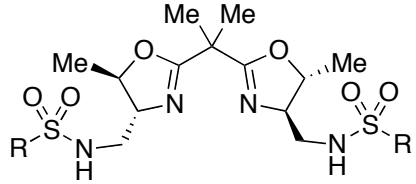
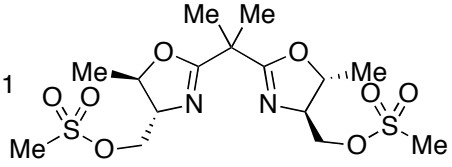
3.2. Effect of the 4-Substituents in Bis(oxazoline)s on the Copper(II)-Catalyzed Asymmetric Diels–Alder Reaction

With bis(oxazoline) ligands **1a–k** that include heteroatoms in the 4-substituents in hand, the author evaluated their effectiveness in the asymmetric Diels–Alder reaction between

3-acryloyl-1,3-oxazolidin-2-one (**2a**) as a bidentate dienophile, and cyclopentadiene (**3**) as a prototypical diene component (Table 3.1). The reaction was carried out using bis(oxazoline) **1** (5.5 mol%) and copper(II) triflate [$Cu(OTf)_2$, 5.0 mol %] in dichloromethane (CH_2Cl_2). Although the reaction with $Cu(OTf)_2$•**1a** proceeded at 0 °C to yield the desired adduct **4a** in moderate enantioselectivity (38% ee, entry 1), the use of **1b** gave good results and the reaction proceeded at –40 °C to yield **4a** as almost a sole product (98:2 mixture of *endo*/*exo* isomers) in 78% conversion with 71% ee (2*R* isomer, entry 2) despite the small C4-substituent. When bis(oxazoline)s **1c** and **1d** were used, however, a lower reactivity and enantioselectivities were observed than with the use of **1b** (8% ee and 54% ee, entries 3 and 4). Thus, the hydroxy group of **1b** would play a key role in the construction of an efficient chiral environment by coordination to a copper cation either directly or through a triflate anion. On the other hand, bis(oxazoline)s **1e** and **1f** with *tert*-alcohols were ineffective regardless of their bulky C4-substituents (*rac.* and 44% ee, entries 5 and 6). It is possible that the *tert*-hydroxy groups were too large to coordinate with ions. Bis(oxazoline)s with ester **1g** and thioester **1h** also resulted in moderate ee (24% ee and 60% ee, entries 7 and 8). The author found that the use of bis(oxazoline)s with trifluoromethansulfonamide **1i** and methanesulfonate **1k** showed higher reactivity and higher enantioselectivity than **1b**. The reaction with these ligands proceeded at –72 °C to afford **4a** with 80% ee and 83% ee, respectively (entries 9 and 11). In the sulfonamide series, the substituents affected both the reactivity and enantioselectivity (entries 9 and 10), and a trifluoromethyl group (**1i**) was superior to tolyl groups (**1j**). These results suggested that the electron-donating ability of sulfonyl oxygens in the 4-substituents plays a key role in both reactivity and enantioselectivity.

Table 3.1. Copper(II)-Catalyzed Diels–Alder Reaction with Bis(oxazoline) Ligands that Include Heteroatoms in the 4-Substituents

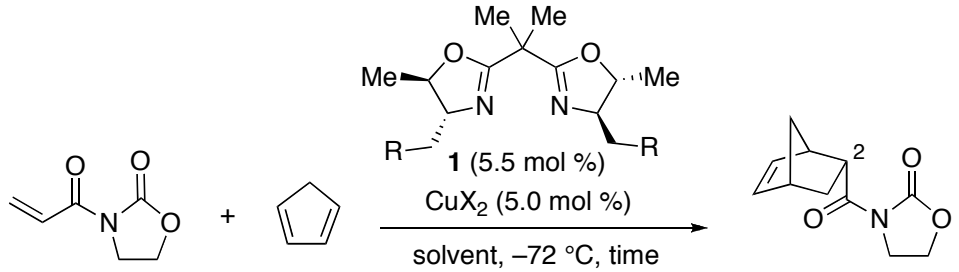


entry	bis(oxazoline) **1**	temp, time (°C) (h)	conv.[a] (%)	*endo*/*exo*[a]	ee[b] (%)
1	 **1a**	0, 3.5	64	88:12	38 (2*S*)
2	 **1b** R = H	–40, 16	78	98:2	71 (2*R*)
3	**1c** R = Me	–20, 12	63	90:10	8 (2*R*)
4	**1d** R = Si(*n*-Pr)$_3$	–20, 8	99	91:9	54 (2*R*)
5	 **1e** R = Me	0, 2.5	68	90:10	*rac.*
6	**1f** R = Ph	–40, 5	10	90:10	44 (2*R*)
7	 **1g** X = O	–40, 23	99	98:2	24 (2*R*)
8	**1h** X = S	–40, 24	82	95:5	60 (2*R*)
9	 **1i** R = CF_3	–72, 8.5	99	98:2	80 (2*R*)
10	**1j** R = *p*-tolyl	–40, 16	74	94:6	54 (2*R*)
11	 **1k**	–72, 20	18	98:2	83 (2*R*)

[a] Determined by ^{1}H NMR. [b] The ee of *endo* adduct was determined by chiral HPLC.

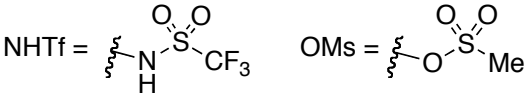
After evaluating the C4-substituents of bis(oxazoline)s, the author investigated the effects of the counter anion and solvent in the reaction between dienophile **2a** and cyclopentadiene (**3)** using bis(oxazoline) **1i** (Table 3.2). When $Cu(OTf)_2$, copper(II) trifluoromethanesulfonimide [$Cu(NTf_2)_2$], and copper(II) hexafluoroantimonate [$Cu(SbF_6)_2$] were tested as Lewis acids in CH_2Cl_2, the reaction using $Cu(NTf_2)_2$ showed the highest ee (95% ee, entries1–3) among the three. Meanwhile, nitroethane ($EtNO_2$) provided a significantly shorter reaction time than CH_2Cl_2 with $Cu(NTf_2)_2$ catalyst (entry 5). Under the optimized conditions using $Cu(NTf_2)_2$ in $EtNO_2$, the reaction with **1i** (entry 5) showed higher reactivity and ee than **1k** (entry 7). These results suggested that an efficient chiral environment was constructed with the use of a Lewis acidic copper(II)-**1i** catalyst in a polar solvent.

Table 3.2. Effects of Counter Anion and Solvent with Bis(oxazoline) **1i**



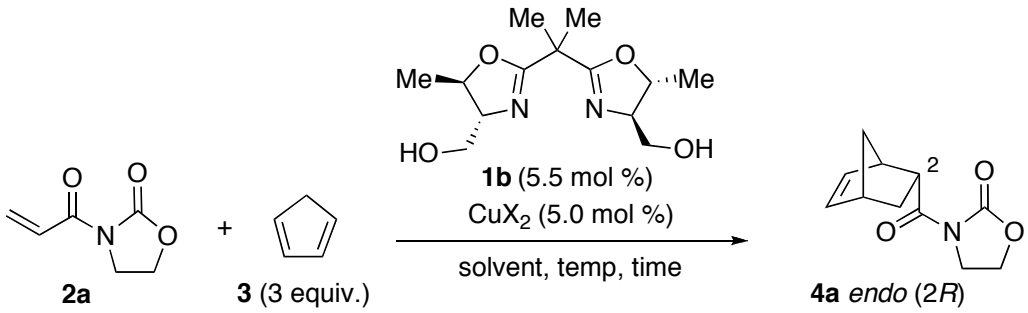
entry	**1** [R]	X	solvent	time (h)	conv. (%)[a]	*endo*/*exo*[a]	ee (%)[b]
1	**1i** [NHTf]	OTf	CH_2Cl_2	8.5	99	98:2	80
2	**1i** [NHTf]	NTf_2	CH_2Cl_2	8.5	50	92:8	95
3	**1i** [NHTf]	SbF_6	CH_2Cl_2	8.5	96	98:2	92
4	**1i** [NHTf]	OTf	$EtNO_2$	8.5	70	98:2	79
5	**1i** [NHTf]	NTf_2	$EtNO_2$	1.5	97	98:2	96
6	**1i** [NHTf]	SbF_6	$EtNO_2$	20	73	99:1	96
7	**1k** [OMs]	NTf_2	$EtNO_2$	11	98	99:1	87

[a] Determined by ^1H NMR. [b] The ee of *endo* adduct was determined by chiral HPLC.



Furthermore, the author also examined the effect of the counter anion and solvent with **1b** (Table 3.3). As in the case of bis(oxazoline) **1i**, the use of $Cu(NTf_2)_2$ in $EtNO_2$ provided the best result and 83% ee was achieved despite the small C4-substituent (entry 5). However, in contrast to the use of **1i**, the ee dropped with $Cu(SbF_6)_2$ instead of $Cu(NTf_2)_2$ (3% ee in CH_2Cl_2 and 66% ee in $EtNO_2$, entries 3 and 6). These experimental results support the proposed interaction (Table 3.2) between hydroxyl group and counter anions for the construction of an efficient chiral environment.

Table 3.3. Effect of Counter Anion and Solvent with Bis(oxazoline) **1b**



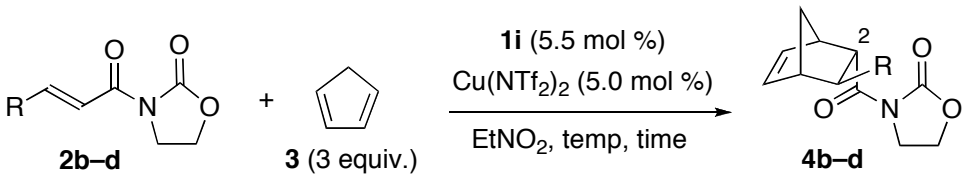
entry	X	solvent	temp, time (°C) (h)	conv.[a] (%)	*endo*/*exo*[a]	ee[b] (%)
1	OTf	CH_2Cl_2	–40, 16	78	98:2	71
2	NTf_2	CH_2Cl_2	–72, 8	18	93:7	75
3	SbF_6	CH_2Cl_2	–20, 24	18	92:8	3
4	OTf	$EtNO_2$	–40, 16	97	98:2	75
5	NTf_2	$EtNO_2$	–72, 8	63	98:2	83
6	SbF_6	$EtNO_2$	–40, 24	26	96:4	66

[a] Determined by ^1H NMR. [b] The ee of *endo* adduct was determined by chiral HPLC.

3.3. Substrate Scope in Asymmetric Diels-Alder Catalysis

The substrate scope of the present Diels–Alder reaction was investigated under the optimized conditions (Table 3.4). First, the author examined β-substituted dienophiles using $Cu(NTf_2)_2$•**1i** catalyst in $EtNO_2$. High enantioselectivities were observed in the reaction with dienophiles derived from crotonic acid (**2b**, R = Me, 95% ee, entry 1), cinnamic acid (**2c**, R = Ph, 82% ee, entry 2) and fumaric acid (**2d**, R = CO_2Et, 94% ee, entry 3), even at the higher temperatures required for less-reactive substrates.

Table 3.4 Diels–Alder Reaction with β-Substituted Dienophiles



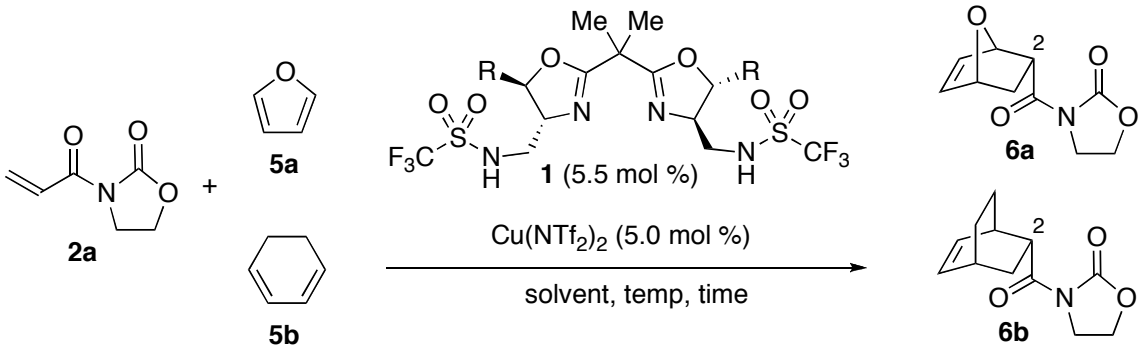
entry	**2** [R]	temp, time (°C) (h)	yield. (%)[a]	*endo*/*exo*[a]	ee (%)[b]
1	**2b** [Me]	–20, 7	58[c]	93:7	95 (2*R*)
2	**2c** [Ph]	0, 50	23[c]	87:13	82 (2*S*)
3	**2d** [CO_2Et]	–72, 19	99	95:5	94 (2*S*)

[a] Isolated yield. [b] The ee of *endo* adduct was determined by chiral HPLC.
[c] Conversion determined by ^1H NMR.

Next, the author examined the reaction of cyclic dienes other than cyclopentadiene with **2a** (Table 3.5). When the reaction of furan (**5a**) was performed under the optimized conditions [$Cu(NTf_2)_2$•**1i** in $EtNO_2$] at –72 °C for 3 days, the adduct **6a** was obtained as a 76:24 mixture of *endo*/*exo* isomers, while the *endo* isomer was formed in 98% ee along with the *exo* isomer in 12% ee (entry 1). With the high catalytic activity of $Cu(NTf_2)_2$•**1i**, attention was directed to less-reactive dienes, such as cyclohexadiene (**9b**). It reacted with **2a** at –20 °C to afford **6b** with 86% ee (entry 2). Fortunately, the author found that enantioselectivity was increased when the 5-substituents of

bis(oxazolines)s was changed from a methyl to a phenyl group and 93% ee was achieved with the use of $Cu(NTf_2)_2$•**1l** in $MeNO_2$ (entry 3).

Table 3.5. Diels–Alder Reaction of Cyclic Dienes



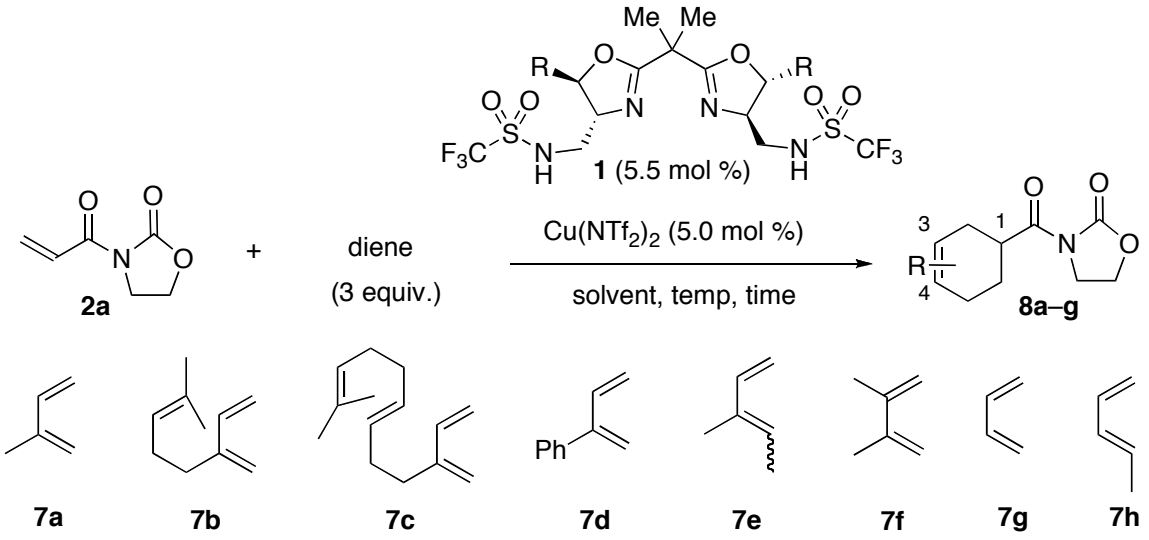
entry	**1** [R]	diene[d]	product	solvent	temp, time (°C) (h)	yield (%)[a]	*endo*/*exo*[b]	ee (%)[c]
1	**1i** [Me]	**5a**	**6a**	$EtNO_2$	–72, 72	92[f]	76:24	98 [2*R*]
2	**1i** [Me]	**5b**	**6b**	$EtNO_2$	–20, 25	57[f]	99:1	86 [2*R*]
3	**1l** [Ph][e]	**5b**	**6b**	$MeNO_2$	–20, 24	73	99.5:0.5	93 [2*S*]

[a] Isolated yield. [b] Determined by ^1H NMR. [c] The ee of *endo* adduct was determined by chiral HPLC. [d] 10 equiv, for **5a** and 3 equiv. for **5b**. [e] Absolute stereochemistry is opposite to **1i.** [f] Conversions determied by ^1H NMR.

The high reactivity and enantioselectivity in the reactions of cyclic dienes allowed for the use of acyclic dienes (Table 3.6). The reaction of isoprene (**7a**) with **2a** using $Cu(NTf_2)_2$•**1i** at –20 °C gave **8a** with 96% ee (entry 1). With diene **7a**, the use of Evans' *t*-Bu-bis(oxazoline) led to a decrease in both reactivity and selectivity (at 25 °C, 60% ee).[5a] Other 2-substituted acyclic dienes such as myrcene (**7b**), farnesene (**7c**), and 2-phenyl butadiene (**7d**) were also examined. The reactions proceeded at –20 °C and the desired adducts were obtained with 94% ee (**8b**), 98% ee (**8c**) and 80% ee (**8d**), respectively, in good yields (67%, 76% and 90%, entries 2–4). The reaction with 3-methyl-1,3-pentadiene (**7e**) gave **8e** with 95% ee at –20 °C (entry 5), which showed higher

reactivity and enantioselectivity than in the result reported by Sibi et al. using fluxional ligands (rt, 82% ee).[5b] The author then tried the reaction of 2,3-dimethyl butadiene (**7f**). The reaction between **2a** and **7f** proceeded at –20 °C and afforded **8f** with 85% ee (entry 6). When the catalyst was changed into $Cu(NTf_2)_2$•**1l**, the enantioselectivity was increased to 89% ee and **8f** was obtained in 84% yield (entry 7). 1,3-Butadiene (**7g**) and 1,3-pentadiene (**7h)** had a lower reactivity and the reaction was carried out at 0 °C to give **8g** and **8h** in 74% ee and 77% ee, respectively (entries 8 and 9). These results showed that the $Cu(NTf_2)_2$•**1**-catalyzed reaction of 2-substituted acyclic dienes resulted in higher reactivities and higher enantioselectivities than that of acyclic dienes without substituents at the 2-position.

Table 3.6. Diels–Alder Reaction of Acyclic Dienes



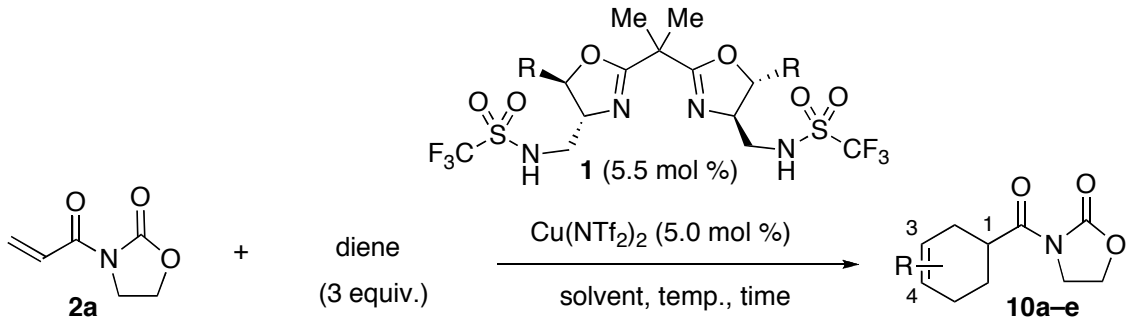
entry	**1** [R]	diene	product	solvent	temp, time (°C) (h)	yield (%)[a]	dr[b]	ee (%)[c]
1	**1i** [Me]	**7a**	**8a**	$EtNO_2$	–20, 48	49[g]	>99:1	96 [*R*]
2	**1i** [Me]	**7b**[e]	**8b**	$EtNO_2$	–20, 24	67	>99:1	94
3	**1i** [Me]	**7c**[e]	**8c**	$MeNO_2$	–20, 24	76	>99:1	98
4	**1i** [Me]	**7d**	**8d**	$EtNO_2$	–20, 6	90	>99:1	80
5	**1i** [Me]	**7e**	**8e**	$EtNO_2$	–20, 24	44	–[h]	95
6	**1i** [Me]	**7f**	**8f**	$MeNO_2$	–20, 24	75[g]	–	85 [*R*]
7	**1l** [Ph][d]	**7f**	**8f**	$MeNO_2$	–20, 24	84	–	89 [*S*]
8	**1i** [Me]	**7g**[f]	**8g**	$EtNO_2$	0, 24	57[g]	–	74 [*S*]
9	**1i** [Me]	**7h**	**8h**	$EtNO_2$	0, 24	54	89:13	77 [1*R*, 2*S*]

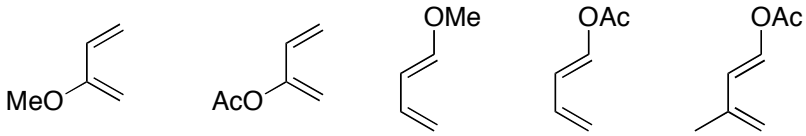
[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] The ee of major isomer was determined by chiral HPLC.
[d] Absolute stereochemistry is opposite to **1i.** [e] 1.5 equiv. [f] Excess.
[g] Conversions determied by ^{1}H NMR. [h] 65:23:7:5 mixtures of isomers.

The success of acyclic dienes encouraged the author to investigate acyclic dienes that include heteroatoms (Table 3.7). The reaction of 2-methoxy-1,3-butadiene (**9a**) catalyzed by $Cu(NTf_2)_2$•**1** proceeded under –72 °C to yield adduct **10a** with good enantioselectivities (83–96% ee, entries 1–3). The reactivity of **9a** was higher than that of isoprene (**7a**, Table 3.6, entry 1) due to electron-donation

by the 2-methoxy group. Unfortunately, the isolated yield of **10a** was inadequate even though most of dienophile **2a** was consumed under the reaction conditions. The enantioselectivity depended on the 5-substituents of the bis(oxazoline) ligand. When the reaction was performed with $Cu(NTf_2)_2$•**1m** (R = H) or $Cu(NTf_2)_2$•**1i** (R = Me), the adduct **10a** was obtained with 83% ee and 87% ee, respectively (entries 1 and 2). The best result was obtained with the use of $Cu(NTf_2)_2$•**1l** (R = Ph), and the reaction afforded **10a** in 55% yield with 96% ee (entry 3). Bis(oxazoline) ligands with larger 5-substituents showed higher reactivities and higher enantioselectivities. 2-Acetoxy-1,3-butadiene (**9b**) had low reactivity because of the electron-withdrawing nature of the acetoxy group, and only a trace amount of the product **10b** was obtained at 0 °C (entry 4). The reaction of 1-methoxy-1,3-butadiene (**9c**) catalyzed by $Cu(NTf_2)_2$•**1** also proceeded at –72 °C due to the effect of the electron-donating 2-methoxy group to give the adduct **10c** with 70–89% ee (entries 5–7)**.** Interestingly, **9c** preferred a ligand with smaller 5-substituents, which was opposite the trend with 2-methoxy-2,3-butadiene (**9a**). Indeed, the best reactivity and enantioselectivity were achieved with bis(oxazoline) ligand **1m** (R = H), and **10c** was obtained with 89% ee. 1-Acetoxy-1,3-butadiene (**9d**) was much less reactive than **9c** due to the electron-drawing acetoxy group**,** however, the reaction proceeded at 0 °C to give adduct **10d** in 95% yield with 79% ee (entry 8). A slight decrease in enantioselectivity occurred with the reaction of 1-heteroatom-substituted 1,3-dienes, as with 1,3-hexadiene (**7e**) (Table 3.6). In the case of 1-acetoxy-3-methyl-1,3-butadiene (**9e**), the reaction provided the product **10e** as a 52:48 mixture of *cis*/*trans* isomers, which were formed in 99% ee and 91% ee, respectively (entry 9). These excellent enantioselectivities were considered to result from the effect of a 3-methyl group.

Table 3.7. Diels–Alder Reaction of Heteroatom-Substituted Acyclic Dienes





9a **9b** **9c** **9d** **9e**

entry	**1** [R]	diene	product	solvent	temp, time (°C) (h)	yield (%)[a]	*cis*/*trans*[b]	ee (%)[c]
1	**1m** [H][d]	**9a**	**10a**	$EtNO_2$	–72, 24	32[e]	>99:1[f]	83
2	**1i** [Me]	**9a**	**10a**	$EtNO_2$	–72, 24	50[e]	>99:1[f]	87
3	**1l** [Ph][d]	**9a**	**10a**	$EtNO_2$	–72, 24	55 (84)[e]	>99:1[f]	96
4	**1i** [Me]	**9b**	**10b**	$EtNO_2$	0, 24	trace	–	–
5	**1m** [H][d]	**9c**	**10c**	$EtNO_2$	–72, 24	28 (59)[e]	96:4	89
6	**1i** [Me]	**9c**	**10c**	$EtNO_2$	–72, 24	35[e]	ND	76
7	**1l** [Ph][d]	**9c**	**10c**	$EtNO_2$	–72, 24	25[e]	ND	70
8	**1i** [Me]	**9d**	**10d**	$EtNO_2$	0, 22	95	75:25	79 [*cis*]
9	**1i** [Me]	**9e**	**10e**	$EtNO_2$	–20, 12	96	52:48	99 [1*R*, 2S] 91 [1*R*, 2*R*]

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.

[d] Absolute stereochemistry is opposite to **1i.** [e] Conversions determied by ^{1}H NMR. [f] Single isomer.

3.4. Proposed Transition State

The author proposed the transition state shown in Figure 3.2. Two-point catalyst–dienophile binding and reaction out of the *s-cis* dienophile conformation with a six-coordinate octahedral Cu(II) geometry, which including two cation–*n* interactions, occur in the catalyzed processes. These geometric constraints correlated the ligand chirality with the stereochemistry of the observed Diels–Alder adducts; for example, 2*R* isomer of **4a** was obtained with (4*R*,4*R*)-bis(oxazoline) ligand **1i** (Table 3.1, entry 9). The efficient chiral environment around the metal center was constructed by "cation–*n* interaction" between the sulfonyl oxygen and copper cation providing secondary coordination along with the primary coordination of oxazoline-nitrogen. In addition, trifluoromethansulfonimide anion (¯NHTf) might be removed from the metal center and may interact with the ligand by hydrogen bonding.

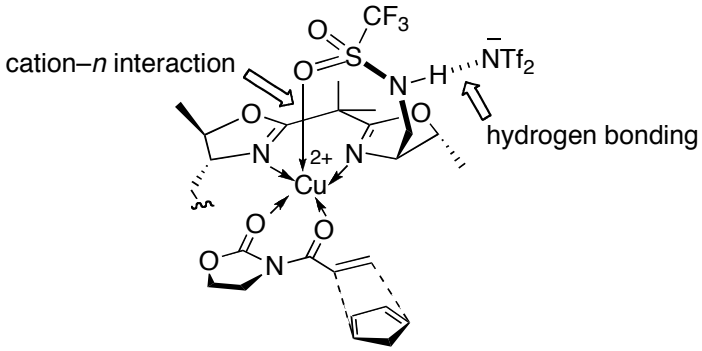


Figure 3.2. Proposed transition state with $Cu(NTf_2)_2$•**1i**.

To ascertain the possibility of intramolecular cation–*n* interaction and hydrogen bonding of $Cu(NTf_2)_2$•**1i**, theoretical calculations for a 1:1:1 chelate complex of copper(II) cation, bis(oxazoline) **1i**, and 3-acryloyl-1,3-oxazolidin-2-one were performed using the Gaussian03[6] programs (Figure 3.3). The geometries of the complex were optimized using gradienet-corrected density functional theory (DFT) calculations with Becke's three-parameter exchange with the Lee, Yang and Parr

correlation functional (B3LYP).[7] We chose the basis set as follows: for Cu, Wachter's primitive set (14s9p5d),[8] supplemented with three f polarization function[9] (Wachters+f), with a final basis set of (14s9p5d3f)/[8s6p4d1f]; for C, N, O, F, S and H, the standard 6-31G(d) basis set was used. The result suggests that the enantioselective Diels–Alder reaction might proceed via the transition state shown in Figure 3.2, as determined by theoretical calculations.

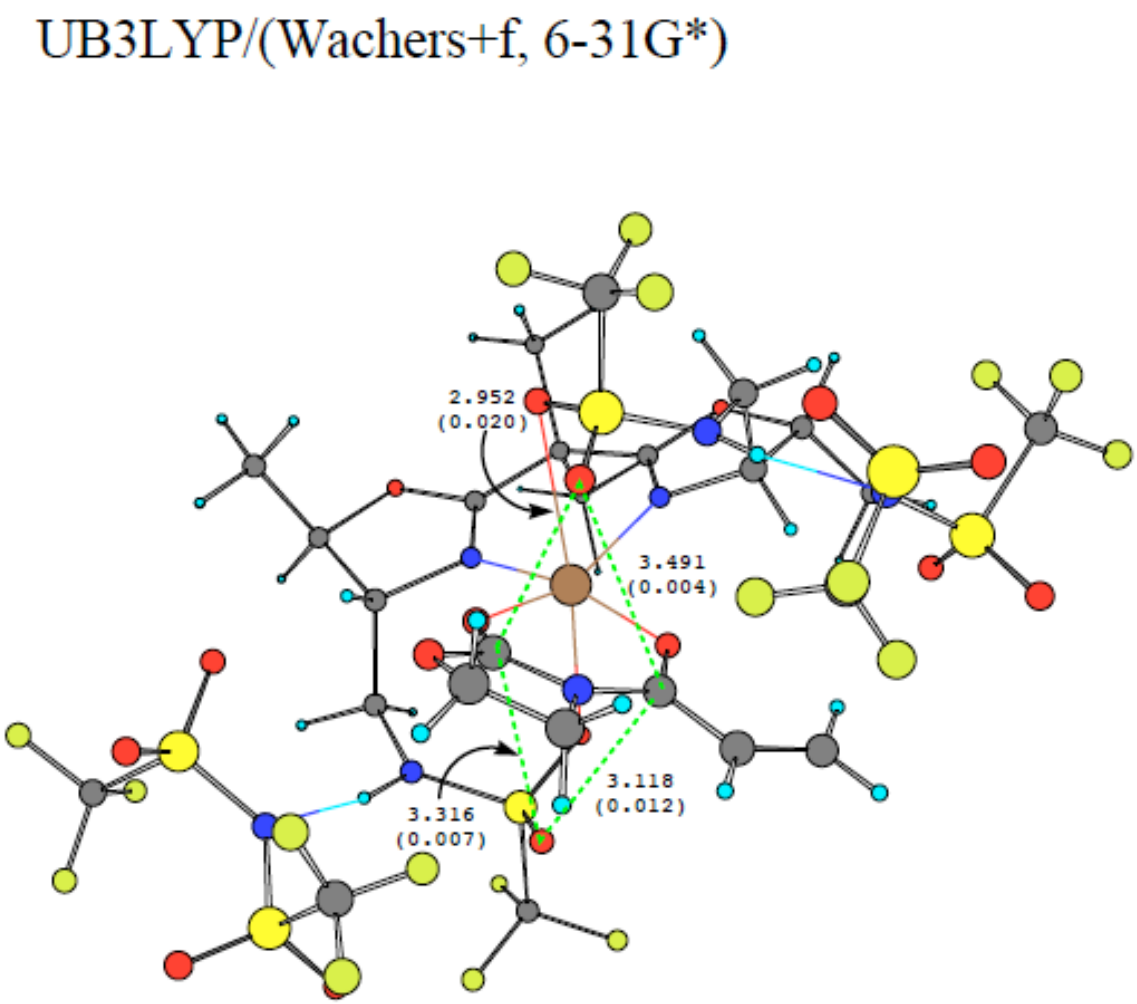
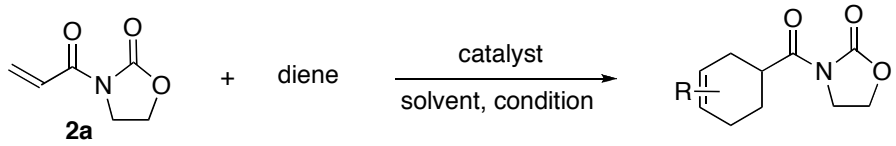
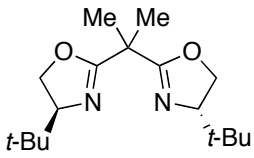
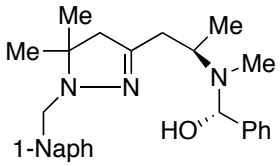
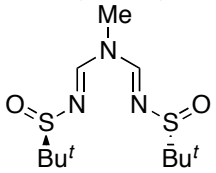
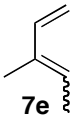
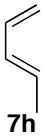


Figure 3.3. Theoretical calculations using the Gaussian03[6] programs.

In conclusion, the author designed a new class of bis(oxazoline) ligand that include heteroatoms in the 5-substituents for the copper-catalyzed highly enantioselective Diels–Alder reaction. The catalyst system promoted the reaction with a variety of substrates, and was especially successful with 2-substituted-1,3-butadiene (Table 3.8).[5] "Cation-*n* interaction" should be useful in these reaction systems.

Table 3.8. Comparison with Evans, Sibi and Ellman's chiral catalysts



	(the author)	(Evans)	(Sibi)	(Ellman)
catalyst:	**1i** or **1m**			
	$Cu(NTf_2)_2$	$Cu(SbF_6)_2$	$Zn(OTf)_2$	$Cu(SbF_6)_2$
solvent:	$MeNO_2$ or $EtNO_2$	CH_2Cl_2	CH_2Cl_2	CH_2Cl_2
 **3**	97[a], 96 (–78 °C, 1.5 h)	100[a], >98 (–78 °C, 4 h)	83, 96 (0 °C)	96, 98 (–78 °C, 0.1 h)
 **7a**	49[a], 96 (–20 °C, 48 h)	81, 59 (25 °C, 12 h)	69,95 (0 °C)	83, 93 (rt, 16 h)
 **7d**	90, 80 (–20°C, 6 h)	–	–	87, 45 (rt, 2 h)
 **7e**	44, 95 (–20 °C, 24 h)	–	27, 82 (0 °C)	–
 **7f**	84, 89 (–20 °C, 24 h)	78, 65 (25 °C, 12 h)	67, 90 (0 °C)	96, 92 (0 °C,16 h)
 **7h**	54, 77 (0 °C, 24 h)	89, 94 (25 °C, 12 h)	–	18, 41 (rt, 18 h)

[a] Conversions.

[yield (%), ee (%) (condition)]

References and Notes

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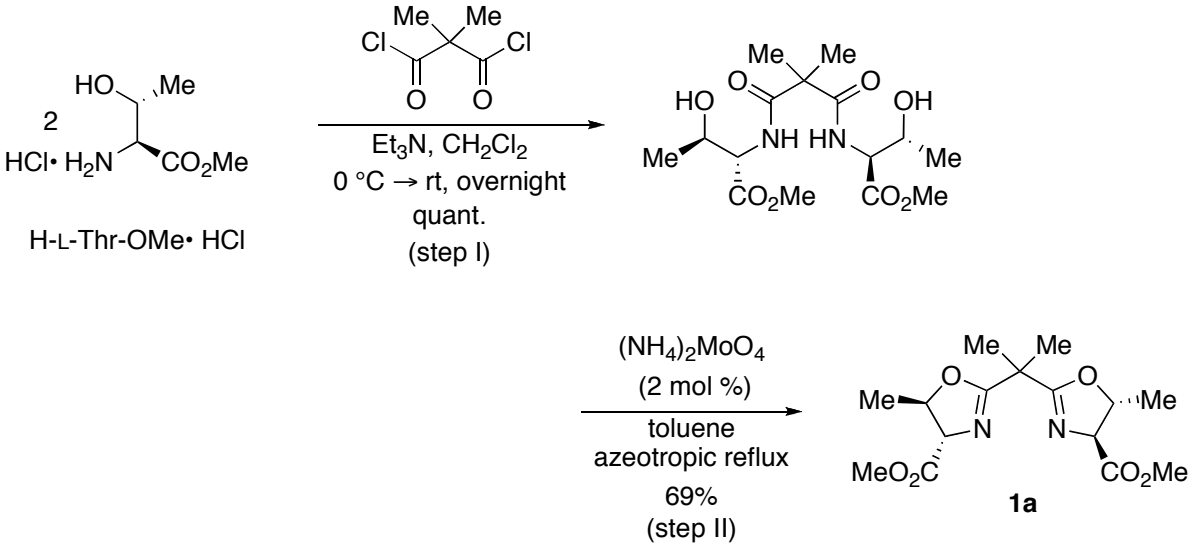
Experimental Section

General Methods. 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 ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane 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), a VXR 500 (125 MHz), or a JEOL ECS-400 (100 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-10AD instrument coupled diode array-detector SPD-MA-10A-VP using a column of Daicel CHIRALCEL OD-H (4.6 × 250 mm), Daicel CHIRALPAK AD-H (4.6 × 250 mm) or Daicel CHIRALCEL OJ-H (4.6 × 250 mm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. 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 Chemical Instrument Facility, Nagoya University.

Dry tetrahydrofuran was purchased from Kanto as the "anhydrous" and stored under nitrogen. Dichloromethane, nitroethane and triethylamine were freshly distilled from calcium hydride. Copper(II) triflate [$Cu(OTf)_2$] (Aldrich), **7b**, **7c**, **7e**, **7g**, **7h**, **9c**, **9d**, **9e** and other materials were obtained from commercial supplies and used without further purification. Copper(II) trifluoromethanesulfonimide[1] [$Cu(NTf_2)_2$] and **2a**–**d**[2] were reported previously.

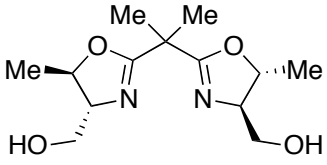
Preparation of (4*S*,4'*S*,5*R*,5'*R*)-dimethyl-2,2'-(propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4-carboxylate) (1a).



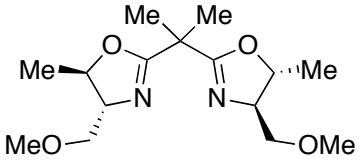
Step I. To a suspension of L-threonine methyl ester hydrochloride (4.0 g, 24 mmol) and triethylamine (7.3 mL, 52 mmol) in CH_2Cl_2 (40 mL) was added a solution of dimethylmalonyl chloride (1.6 mL, 12 mmol) in CH_2Cl_2 (10 mL) dropwise at 0 °C. After being stirred at 0 °C for 1 h and at ambient temperature for overnight, the solvent was evaporated and diluted with EtOAc. The mixture was filtered to remove the salt and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane-EtOAc-MeOH (4:4:1 → 2:2:1) to give bisamide (4.5 g, quant.) as a colorless oil.

Step II. 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 bisamide (11.9 mmol) and $(NH_4)_2MoO_4$ (2 mol %) in toluene (30 mL). The mixture was heated for 12 h 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-MeOH (30:30:1 → 10:10:1 → 5:5:1) to give bis(oxazoline) **1a** (69% yield) as a colorless oil along with monocyclized product (22% yield): R_f = 0.50 (hexane-EtOAc-MeOH = 5:5:1); IR (KBr) 1740, 1649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, J = 6.3 Hz, 6H), 1.55 (s, 6H), 3.77 (s, 6H), 4.29 (d, J = 6.6 Hz, 2H), 4.84 (dq, J = 6.3, 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 23.9, 38.7, 52.5, 74.3, 79.1, 170.9, 171.3; HRMS (FAB) calcd for $C_{15}H_{23}N_2O_6$ $[(M+H)^+]$ 327.1556. Found: 327.1566.

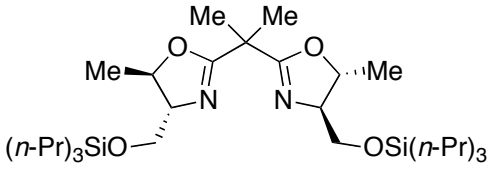


(4*R*,4'*R*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole- 4,2-diyl)dimethanol (1b).[3] To a solution of **1a** (5.2 g, 16 mmol) in EtOH (32 mL) was added sodium borohydride (1.2 g, 32 mmol) at 0 °C. After being stirred at 0 °C for 1 h and at ambient temperature for overnight, the reaction mixture was quenched with water (6 mL) and added 1 M HCl aqueous until pH = 7. The reaction mixture was filtered and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane-EtOAc-MeOH (5:5:1 → 2:2:1) to give **1b** (2.9 g, 66% yield).

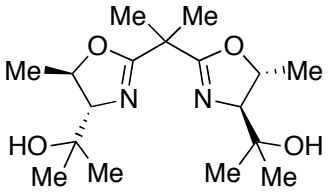


(4*R*,4'*R*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis(4-(methoxymethyl)-5-methy-4,5-dihydrooxazole) (1c). To a solution of **1b** (54 mg, 0.20 mmol) in THF (2.0 mL) was added sodium hydride (11 mg, 0.44 mmol) at ambient temperature. After being stirred at ambient temperature for 3 h, methyl iodide (27 μL, 0.44 mmol) was added to the reaction mixture and stirred for 14 h. The reaction mixture was diluted with EtOAc and washed successively with brine. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc-MeOH (10:10:1 → 5:5:1 → 2:2:1) to

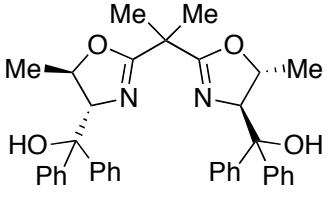
give **1c** (17 mg, 28% yield) as a colorless oil: R_f = 0.45 (hexane-EtOAc-MeOH = 2:2:1); $[\alpha]^{21}_D$ + 123.5 (c = 0.72, $CHCl_3$); IR (film) 3584, 2928, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1,28 (d, J = 6.4 Hz, 6H), 1,49 (s, 3H), 3.23 (dd, J = 7.8, 9.6 Hz, 2H), 3.36 (s, 6H), 3.55 (dd, J = 4.6, 9.6 Hz, 2H), 3.79 (ddd, J = 4.6, 6.4, 7.8 Hz, 2H), 4.49 (dq, J = 6.4, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 24.1, 38.5, 59.2, 72.0, 74.4, 79.7, 169.6; HRMS (FAB) calcd for $C_{15}H_{27}O_4N_2$ $[M+H]^+$ 299.1971, found 299.1969.



(4*R*,4'*R*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis[5-methyl-4-[(tri-*n*-propylsilyloxy)methyl]-4,5-dihydrooxazole] (1d). To a solution of **1b** (27 mg, 0.10 mmol) and imidazole (41 mg, 0.6 mmol) in THF (1.0 mL) was added tri(*n*-propyl)silyl chloride (87 μL, 0.40 mmol) at 0 °C. After being stirred at ambient temperature for 4 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc (5:1 → 4:1) to give **1d** (38 mg, 64% yield) as a colorless oil: R_f = 0.65 (hexane-EtOAc = 1:1); $[\alpha]^{22}_D$ +64.0 (c = 2.12, $CHCl_3$); IR (film) 2955, 2926, 2869, 1654, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (t, J = 8.5 Hz, 12H), 0.95 (t, J = 7.3 Hz, 18H), 1.28 (d, J = 6.4 Hz, 6H), 1.37 (tq, J = 8.5, 7.3 Hz, 12H), 1.48 (s, 6H), 3.40 (dd, J = 7.0, 10.1 Hz, 2H), 3.68 (ddd, J = 4.1, 6.0, 7.0 Hz, 2H), 3.80 (dd, J = 4.1, 10.1 Hz, 2H) 4.53 (dq, J = 6.0, 6.4 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 16.7, 18.3, 21.0, 24.1, 38.5, 64.4, 74.0, 79.6, 169.5; HRMS (FAB) calcd for $C_{31}H_{63}O_4N_2Si_2$ $[M+H]^+$ 583.4326, found 532.4338.

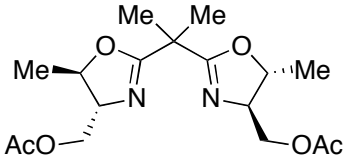


2,2'-(4*S*,4'*S*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4,2-diyl)dipropan-2-ol (1e). To a solution of **1a** (130 mg, 0.40 mmol) in THF (4.0 mL) was added methylmagnesium bromide (1.7 mL, 1.4 M solution in toluene-THF = 75:25, 2.4 mmol) at –78 °C. After being stirred at –78 °C for 1 h and at ambient temperature for 7 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (1 mL), washed with water and extracted with EtOAc. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc-MeOH (50:50:1 → 10:10:1 → 5:5:1) to give **1e** (137 mg, 98% yield) as an amorphous solid: R_f = 0.30 (hexane-EtOAc-MeOH = 5:5:1); $[\alpha]^{21}_D$ +132.8 (c = 0.76, $CHCl_3$); IR (film) 2978, 1656, 1468, 1379 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 6H), 1.25 (s, 6H), 1.30 (d, J = 6.4 Hz, 6H), 1.52 (s, 6H), 2.99 (br s, 2H), 3.52 (d, J = 5.0 Hz, 2H), 4.64 (dq, J = 5.0, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ21.6, 23.4, 24.9, 26.5, 39.2, 71.7, 77.8, 81.2, 170.2; HRMS (FAB) calcd for $C_{17}H_{31}O_4N_2$ $[M+H]^+$ 327.2284, found 327.2283.

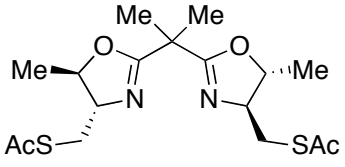


(4*S*,4'*S*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4,2-diyl)bis(diphenylmethanol) (1f). To a solution of **1a** (163 mg, 0.50 mmol) in THF (10 mL) was added phenylmagnesium bromide (4.5 mL, 1.07 M solution in THF, 4.5 mmol) at –78 °C. After being stirred at –78 °C for 2 h and at ambient temperature for overnight, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl, washed with water and extracted with EtOAc. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc (8:1 → 4:1 → 2:1) to give **1f** (98 mg, 34% yield) as an amorphous solid: R_f = 0.40 (hexane-EtOAc = 3:1); $[\alpha]^{22}_D$ –36.7 (c =

3.16, $CHCl_3$); IR (film) 3365, 1655, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.4 Hz, 6H), 1.37 (s, 6H), 3.59 (br s, 2H), 4.51 (dq, J = 5.5, 6.4 Hz, 2H), 4.81 (d, J = 5.5 Hz, 2H), 7.09–7.31 (m, 16H), 7.43 (d, J = 7.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 23.6, 39.4, 78.0, 78.4, 78.5, 125.9, 126.5, 126.7, 126.7, 127.9, 128.1, 143.9, 145.4, 171.6; HRMS (FAB) calcd for $C_{37}H_{39}O_4N_2$ $[M+H]^+$ 575.2910, found 575.2905.

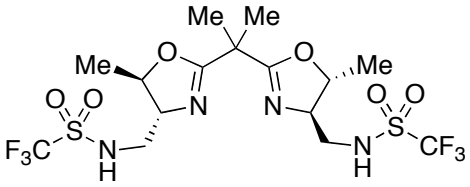


(4*R*,4'*R*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis(5-methyl-4,5-dihydroox azole-4,2-diyl)bis(methylene) diacetate (1g). To a solution of **1b** (27 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was added pyridine (36 μL, 0.44 mmol) and 4-dimethyamino pyridine (2.7 mg, 0.020 mmol) followed by acetyl anhydride (21 μL, 0.22 mmol) at 0 °C. After being stirred at ambient temperature for 1.5 h, the reaction mixture was washed with water and extracted with EtOAc. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using $CHCl_3$–acetone (5:1) to give **1g** (33 mg, 93% yield) as a colorless oil: R_f = 0.45 ($CHCl_3$–acetone = 2:1); $[\alpha]^{23}_D$ +186.7 (c = 1.45, $CHCl_3$); IR (film) 2979, 1743, 1655, 1241 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 6.3 Hz, 6H), 1.51 (s, 6H), 2.06 (s, 6H), 3.86 (ddd, J = 4.5, 6.0, 6.3 Hz, 2H), 4.06 (dd, J = 6.0, 11.1 Hz, 2H), 4.17 (dd, J = 4.5, 11.1 Hz, 2H), 4.46 (dq, J = 6.3, 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.7, 24.0, 38.6, 65.3, 71.1, 78.9, 169.9, 170.8; HRMS (FAB) calcd for $C_{17}H_{27}O_6N_2$ $[M+H]^+$ 355.1869, found 355.1882.



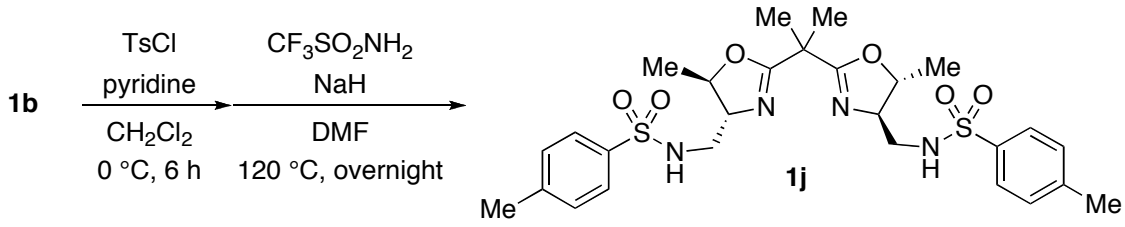
***S*,*S*'-(4*S*,4'*S*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4,2-diyl)bis(methylene) diethanethioate (1h).** To a solution of **1l** (427 mg, 1.0 mmol) in DMF (5.0 mL) was added potassium thioacetate (228 mg, 2.0 mmol) at ambient

temperature. After being stirred at 50 °C for 1 h, the reaction mixture was cooled to ambient temperature, diluted with EtOAc and washed with water. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc (2:1 → 1:1 → 1:2) to give **1h** (202 mg, 52% yield) as a yellowish oil: R_f = 0.20 (hexane-EtOAc = 1:1); $[\alpha]^{22}_D$ +64.8 (c = 5.56, $CHCl_3$); IR (film) 2979, 2929, 1693, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.4 Hz, 6H), 1.50 (s, 6H), 2.35 (s, 6H), 3.01 (dd, J = 6.4, 13.8 Hz, 2H), 3.16 (dd, J = 5.0, 13.8 Hz, 2H), 3.83 (ddd, J = 5.0, 6.0, 6.4 Hz, 2H), 4.30 (dq, J = 6.0, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 23.9, 30.5, 33.2, 38.5, 71.6, 80.1, 169.4, 195.2; HRMS (FAB) calcd for $C_{17}H_{27}O_4N_2S_2$ $[M+H]^+$387.1412, found 387.1412.



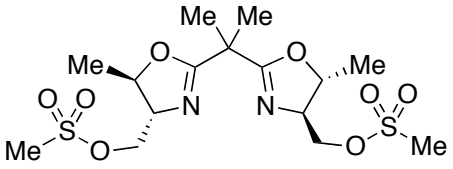
***N*,*N*'-(4*R*,4'*R*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis(5-methyl -4,5- dihydrooxazole-4,2-diyl)bis(methylene)bis(1,1,1-trifluoromethanesulfonamide) (1i).** To a solution of **1b** (208 mg, 0.77 mmol), trifluoromethanesulfonamide (230 mg, 1.54 mmol) and triphenylphosphine (404 mg, 1.54 mmol) in THF (8.0 mL) was added dimethyl azodicarboxylate (560 μL, 40% solution in toluene, 1.54 mmol) at 0 °C. . After being stirred at ambient temperature for 8 h, the reaction mixture was quenched with water, diluted with EtOAc and washed with 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 hexane–EtOAc (5:1 → 4:1 → 3:1). The obtained product was washed with toluene to remove impurities and applied to a short column chromatography on silica gel using hexane–EtOAc (4:1 → 7:3) to give **1i** (86 mg, 21% yield) as a white solid: R_f = 0.45 (hexane-EtOAc = 1:1); mp = 175 °C; $[\alpha]^{23}_D$ +40.0 (c = 1.0, $CHCl_3$); IR (KBr) 1649, 1377, 1231, 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, J = 6.6 Hz, 6H), 1.52 (s, 6H), 3.34 (br d, J = 13.2 Hz, 2H), 3.51 (dd, J = 3.0, 13.2 Hz, 2H), 3.86 (ddd , J = 2.1, 3.0, 6.0 Hz, 2H), 4.67 (dq, J = 6.0, 6.6 Hz, 2H), 7.70 (br s, 2H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 20.4, 23.2, 39.6, 46.6, 70.5, 79.1, 119.8 (q, J = 319.4 Hz, 1C), 172.2; HRMS (FAB) calcd for $C_{15}H_{23}O_6N_4S_2F_6$ $[M+H]^+$ 533.0963, found 533.0945.

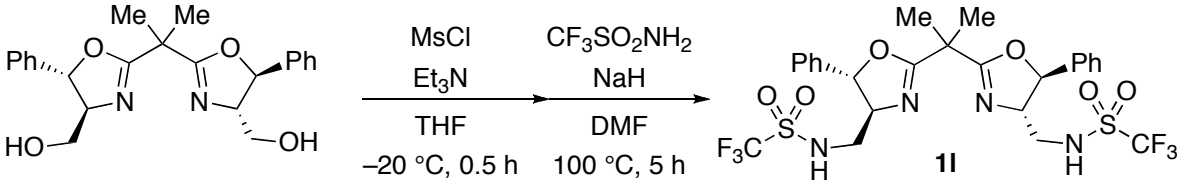


Preparation of *N*,*N*'-(4*R*,4'*R*,5*R*,5'*R*)-2,2'-(propane-2,2-diyl) bis(5-methyl-4,5-dihydrooxazole-4,2-diyl)bis(methylene)bis(4-methylbenzenesulfonamide) (1j). To a solution of **1b** (27 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) was added pyridine (40 μL, 0.50 mmol) followed by *p*-toluenesulfonyl chloride (48 mg, 0.25 mmol) in 3 portions at 0 °C. After being stirred at 0 °C for 6 h, the reaction mixture was quenched with water, diluted with EtOAc and washed with saturated aqueous solution of $NaHCO_3$ and brine. The organic solution was dried (Na_2SO_4) and concentrated to give the crude product as a yellow oil, which was used to the next step without purification. To a solution of *p*-toluenesulfonamide (68 mg, 0.40 mmol) in DMF (1.0 mL) was added sodium hydride (16 mg. abt. 60% oil suspension, 0.40 mmol) at 0 °C. After being stirred at 0 °C for 5 min, the mixture was added a solution of the crude product (1.0 mmol) in DMF (1.0 mL) dropwise at 0 °C. After being stirred at 120 °C for overnight, the reaction mixture was cooled to ambient temperature. The solvent was evaporated under reduced pressure, and the residue was diluted with EtOAc and filtrated to remove the solid. The organic solution was concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc (2:1 → 1:1) to give **1j** (18 mg, 32% yield) as a colorless oil: R_f = 0.35 (EtOAc); $[\alpha]^{21}_D$+108.7 (c = 0.95, $CHCl_3$); IR (film) 1654, 1330, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 6.4 Hz, 6H), 1.48 (s, 6H), 2.41 (s, 6H), 3.03 (ddd, J = 4.1, 8.7, 12.4 Hz, 2H), 3.11 (ddd, J = 3.7, 4.1, 12.4 Hz, 2H), 3.78 (ddd , J = 3.7, 6.0, 8.7 Hz, 2H), 4.54 (dq, J = 6.0, 6.4 Hz, 2H), 6.04 (t, J = 4.1 Hz, 2H), 7.25 (d, J = 8.4 Hz, 4H), 7.68 (d, J = 8.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4,

21.5, 23.3, 39.2, 45.9, 71.0, 79.1, 126.9, 129.6, 137.0, 143.1, 170.9; HRMS (FAB) calcd for $C_{27}H_{37}O_6N_4S_2$ $[M+H]^+$ 577.2155, found 577.2144.

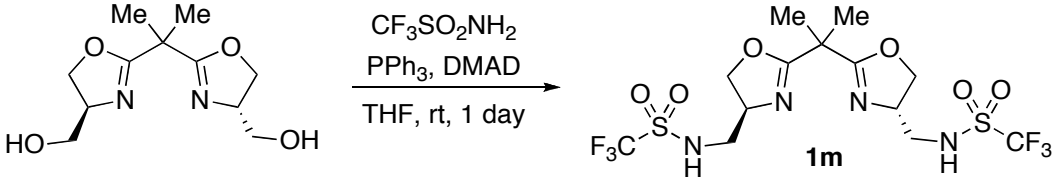


(4*R*,4'*R*,5*R*,5'*R*)-2,2'-(Propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4,2-diyl)bis(methylene) dimethanesulfonate (1k). To a solution of **1b** (54 mg, 0.20 mmol) in THF (1.0 mL) was added triethylamine (92 μL, 0.66 mmol) at ambient temperature. After being stirred at 50 °C for 1 h, the reaction mixture was cooled to ambient temperature, diluted with EtOAc and washed with water. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc-MeOH (5:5:1 → 2:2:1) to give **1k** (65 mg, 76% yield) as a white solid: R_f = 0.25 (hexane-EtOAc-MeOH = 2:2:1); $[\alpha]^{24}_D$ +129.4 (*c* = 2.34, $CHCl_3$); IR (KBr) 3434, 1658, 1348, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.3 Hz, 6H), 1.50 (s, 6H), 3.06 (s, 6H), 3.92 (ddd, *J* = 4.2, 5.7, 6.3 Hz, 2H), 4.17 (dd, *J* = 5.7, 10.2 Hz, 2H), 4.30 (dd , *J* = 4.2, 10.2 Hz, 2H), 4.59 (dq, *J* = 6.3, 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.9, 37.4, 38.7, 69.8, 71.1, 78.5, 170.6; HRMS (FAB) calcd for $C_{15}H_{27}O_8N_2S_2$ $[M+H]^+$ 427.1209, found 427.1201.



***N*,*N*'-(4*S*,4'*S*,5*S*,5'*S*)-2,2'-(Propane-2,2-diyl)bis(5-phenyl-4,5-dihydrooxazole-4,2-diyl)bis(methylene)bis(1,1,1-trifluoromethanesulfonamide) (1l).** To a solution of (4*S*,4'*S*,5*S*,5'*S*)-2,2'-(propane-2,2-diyl)bis(5-phenyl-4,5-dihydrooxazole-4,2-diyl)dimethanol[4] (145 mg, 0.41 mmol) in THF (2.0 mL) was added triethylamine (190 μL, 1.4 mmol) followed by methanesulfonyl chloride (96 μL, 1.2 mmol) at –20 °C. After being stirred at –20 °C for 0.5 h, the

reaction mixture was quenched with water (2 mL), diluted with EtOAc and washed with saturated aqueous solution of $NaHCO_3$ and brine. The organic solution was dried (Na_2SO_4) and concentrated to give the crude product, which was used to the next step without purification. To a solution of trifluoromethansulfonamide (135 mg, 0.91 mmol) in DMF (1.0 mL) was added sodium hydride (47 mg. abt. 60% oil suspension, 1.2 mmol) at 0 °C. After being stirred at 0 °C for 5 min, the mixture was added a solution of the crude product in DMF (2.0 mL) dropwise at 0 °C. After being stirred at 100 °C for 4.5 h, the reaction mixture was cooled to ambient temperature. The solvent was evaporated under reduced pressure, and the residue was diluted with EtOAc and filtrated to remove the solid. The organic solution was concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc (20:1 → 10:1 → 5:1) and recrystalized from hexane-EtOAc to give **1l** (31 mg, 11% yield in 2 steps) as a white needle solid: R_f = 0.55 (hexane-EtOAc = 1:1); mp = 212 °C; $[\alpha]^{22}_D$ –66.3 (*c* = 1.13, $CHCl_3$); IR (KBr) 3434, 1664, 1368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (s, 6H), 3.52 (dd, *J* = 7.3, 11.4 Hz, 2H), 3.67 (d, *J* = 11.4 Hz, 2H), 4.28 (ddd , *J* = 2.8, 3.2, 6.0 Hz, 2H), 5.48 (d, *J* = 6.0 Hz, 2H), 7.24–7.27 (m, 4H), 7.36–7.44 (m, 6H), 7.62 (br d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 39.9, 46.9, 72.4, 83.8, 119.8 (q, *J* = 319.4 Hz, 1C), 125.5, 129.1, 129.2, 138.8, 172.4; HRMS (FAB) calcd for $C_{25}H_{27}O_6N_4S_2F_6$ $[M+H]^+$ 657.1276, found 657.1298.



Preparation of *N*,*N*'-(4*S*,4'*S*)-2,2'-(propane-2,2-diyl)-bis(4,5-dihydrooxazole-4,2-diyl)bis(methylene)bis(1,1,1-trifluoromethanesulfonamide) (1m). To a solution of (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4,5-dihydrooxazole-4,2-diyl)dimethanol[5] (79 mg, 0.33 mmol), trifluoromethanesulfonamide (107 mg, 0.72 mmol) and triphenylphosphine (188 mg, 0.72 mmol) in THF (3.0 mL) was added dimethyl azodicarboxylate (260 μL, 40% solution in

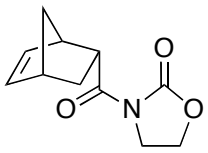
toluene, 0.72 mmol) at 0 °C. . After being stirred at ambient temperature for 1 day, the reaction mixture was quenched with water, diluted with EtOAc and washed with saturated aqueous solution of $NaHCO_3$ and brine. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc (10:1 → 5:1 → 2:1). The obtained product was washed with toluene to remove impurities and applied to a short column chromatography on silica gel using hexane–EtOAc (4:1 → 7:3) to give **1m** (39 mg, 23% yield) as a white solid: R_f = 0.35 (hexane-EtOAc = 1:1); $[\alpha]^{23}_D$ +7.5 (*c* = 0.80, $CHCl_3$); IR (KBr) 1648, 1374, 1231, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 6H), 3.34 (d, *J* = 13.8 Hz, 2H), 3.53 (d, *J* = 13.8 Hz, 2H), 4.38–4.43 (m, 6H), 7.88 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 39.7, 46.8, 64.1, 70.3, 119.8 (q, *J* = 319.3 Hz, 1C), 173.1; HRMS (FAB) calcd for $C_{13}H_{19}O_6N_4S_2F_6$ $[M+H]^+$ 505.0650, found 505.0651.

Cyclopentadiene (3). Cyclopentadiene dimer was cracked at 170 °C and stored over molecular sieves 4 Å at –80 °C.

General Procedure for the Catalyzed Diels-Alder Reaction of Cyclopentadiene (3) with 3-(2-Propenoyl)-2-oxazolidinone (2a) Using $Cu(OTf)_2$•1 or $Cu(NTf)_2$•1 (Table 3.1, 3.2, and 3.3). Copper(II) triflate (3.6 mg, 0.010 mmol) or copper(II) trifluoromethanesulfonimide (6.2 mg, 0.010 mmol) and ligand **1** (0.011 mmol) were combined in an inert atmosphere dry box. The sealed flask was then removed from the box and connected to a nitrogen balloon. Anhydrous CH_2Cl_2 or $EtNO_2$ (1.0 mL) was added, whereupon a blue solution was formed within 5 min. The solution was stirred for 1 h at ambient temperature. At the end of this time period the solution was checked visually for the presence of colorless, undissolved copper(II) triflate. If present, stirring was continued until all the triflate salt had dissolved, forming a homogeneous but slightly cloudy blue solution of the ligand complex. 3-(2-Propenoyl)-2-oxazolidinone (**2a**, 28 mg, 0.20 mmol) was added, which was then cooled to –78 °C. Cyclopentadiene (50 μL, 0.60 mmol) was added *via*

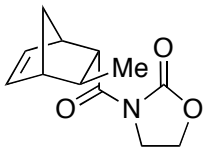
syringe. The resulting solution was stirred at the indicated temperature for the specified amount of time. The reaction mixture was quenched with triethylamine, diluted with EtOAc, and washed with saturated aqueous solution of $NaHCO_3$ and brine. The organic solution was dried (Na_2SO_4) and concentrated. The resultant residue was purified by column chromatography on silica gel using hexane–EtOAc (2:1) to give **4a**. The *endo*/*exo* ratio was determined by ^1H NMR analysis. The enantiomeric excess (ee) was determined through chiral HPLC analysis.

General Procedure for the Catalyzed Diels-Alder Reaction of Cyclopentadiene (3) with 3-(2-Propenoyl)-2-oxazolidinone (2a) Using $Cu(SbF_6)_2$•1 (Table 3.2, 3.3). Copper(II) bromide (2.2 mg, 0.010 mmol), $AgSbF_6$ (6.9 mg, 0.020 mol) and ligand **1** (0.011 mmol) were combined in an inert atmosphere dry box. The sealed flask was then removed from the box and connected to a nitrogen balloon. Anhydrous CH_2Cl_2 (1.0 mL) was added, and the flask was wrapped with alumina foil to protect the reaction mixture from light. The heterogeneous mixture was vigorously stirred for 6-12 h at ambient temperature. At the end of this period the mixture was filtered through a syringe filter. The solution of $Cu(SbF_6)_2$•1 was concentrated under reduced pressure at ambient temperature. To the residue were added anhydrous CH_2Cl_2 or $EtNO_2$ (1.0 mL) and 3-(2-Propenoyl)-2-oxazolidinone (**2a**, 28 mg, 0.20 mmol). The mixture was then cooled to –78 °C. Cyclopentadiene (50 μL, 0.60 mmol) was added *via* syringe. The resulting solution was stirred at the indicated temperature for the specified amount of time. The reaction mixture was quenched with triethylamine, diluted with EtOAc, and washed with 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 hexane–EtOAc (2:1) to give **4a**. The *endo*/*exo* ratio was determined by ^1H NMR analysis. The ee was determined through chiral HPLC analysis.



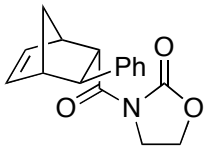
3-[(1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-enecarbonyl]oxazolidin-2-one (4a)[2]. The *endo*/*exo* ratio was determined by ^{1}H NMR analysis. The ee was determined through chiral HPLC analysis (Daicel OD-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 20:1; *endo* 2*R* t_R = 35.3 min, *endo* 2*S* t_R = 32.6 min, *exo* major t_R = 28.8 min, *exo* minor t_R = 30.2 min). Absolute configuration of the *endo* cycloadduct was assigned to be 2*R* by comparing the reported retention time.[2,7]

General Procedure for the Catalyzed Diels-Alder Reaction of Cyclopentadiene (3) with β–Substituted Dienophiles (2b–d) Using $Cu(NTf_2)_2$•1i (Table 3.4). $Cu(NTf_2)_2$ (6.2 mg, 0.010 mmol) and ligand **1i** (5.8 mg, 0.011 mmol) were combined in an inert atmosphere dry box. The sealed flask was then removed from the box and connected to a nitrogen balloon. Anhydrous $EtNO_2$ (1.0 mL) was added, whereupon a blue solution was formed within 5 min. The solution was stirred for 1 h at ambient temperature. β–Substituted Dienophiles **2b–d** (0.20 mmol) was added, which was then cooled to –78 °C. Cyclopentadiene (50 μL, 0.60 mmol) was added *via* syringe. The resulting solution was stirred at the indicated temperature for the specified amount of time. The reaction mixture was quenched with triethylamine, diluted with EtOAc, and washed with 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 hexane–EtOAc to give **4b–d**.

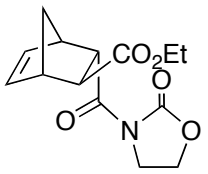


3-[(1*R*,2*R*,3*S*,4*S*)-3-Methylbicyclo[2.2.1]hept-5-enecarbonyl]oxazolidin-2-one (4b).[2] The *endo*/*exo* ratio was determined by ^{1}H NMR analysis. The ee was determined through

chiral HPLC analysis (two linear Daicel OD-H columns; flow rate = 0.50 mL/min; hexane-EtOH = 20:1; *endo* 2*R* t_R = 73.3 min, *endo* 2*S* t_R = 68.0 min, *exo* major t_R = 61.5 min, *exo* minor t_R = 62.8 min). $[\alpha]^{24}_D$ +167.0 (*c* = 0.70, $CHCl_3$), Absolute configuration of the *endo* cycloadduct was assigned to be 2*R* by comparing the reported retention time as well as from the sign of measured optical rotation.[6]



3-[(1*R*,2*S*,3*S*,4*S*)-3-Phenylbicyclo[2.2.1]hept-5-enecarbonyl]oxazolidin-2-one (4c).[2] The *endo*/*exo* ratio was determined by ^{1}H NMR analysis. The ee was determined through chiral HPLC analysis (Daicel AD-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 19:1; *endo* 2*S* t_R = 21.1 min, *endo* 2*R* t_R = 51.3 min, *exo* major t_R = 18.2 min, *exo* minor t_R = 30.5 min). Absolute configuration of the *endo* cycloadduct was assigned to be 2*R* by comparing the reported retention time.[7]



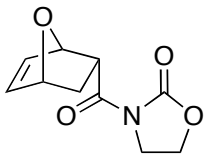
(1*S*,2*S*,3*S*,4*R*)-Ethyl 3-(2-oxooxazolidine-3-carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (4d).[2] The *endo*/*exo* ratio was determined by ^{1}H NMR analysis. The ee of *endo* was calculated from the known optical rotation of the iodolactone derived from **4d**. The cycloadduct **4d** (mixture of *endo* and *exo*) was converted to iodolactone using a procedure in the literature.[8] Yield of iodolactone is 83%. $[\alpha]^{23}_D$ –39.1 (*c* = 0.51, $CHCl_3$), 94% ee (2*R* isomer); Lit[9] 94% ee (2*S*-isomer), $[\alpha]^{23}_D$ –39.2 (*c* = 4.65, $CHCl_3$).

General Procedure for the Catalyzed Diels-Alder Reaction of Dienes with 2a Using $Cu(NTf_2)_2$•1 (Table 3.5–3.7). $Cu(NTf_2)_2$ (6.2 mg, 0.010 mmol) and ligand **1** (0.011 mmol) were

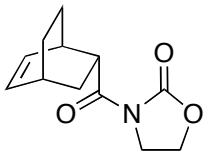
combined in an inert atmosphere dry box. The sealed flask was then removed from the box and connected to a nitrogen balloon. Anhydrous $EtNO_2$ (1.0 mL) was added, whereupon a blue solution was formed within 5 min. The solution was stirred for 1 h at ambient temperature. **2a** (28 mg, 0.20 mmol) was added, which was then cooled to –78 °C. Diene (0.60 mmol) was added *via* syringe. The resulting solution was stirred at the indicated temperature for the specified amount of time. The reaction mixture was quenched with triethylamine, diluted with EtOAc, and washed with 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.

Furan (5a). **5a** was distilled from potassium hydroxide.

Cyclohexadiene (5b). **5b** was distilled from sodium borohydride.



3-[(1*R*,2*R*,4*R*)-7-Oxabicyclo[2.2.1]hept-5-enecarbonyl]oxazolidin-2-one (6a).[10] The *endo*/*exo* ratio was determined by ^{1}H NMR analysis. The ee was determined through chiral HPLC analysis (Daicel OD-H column; flow rate = 0.65 mL/min; hexane-*i*-PrOH = 7:3; *endo* 2*R* t_R = 33.9 min, *endo* 2*S* t_R = 27.9 min, *exo* major t_R = 37.2 min, *exo* minor t_R = 54.4 min). Absolute configuration of the *endo* cycloadduct was assigned to be 2*R* by comparing the reported retention time.[10]



3-((1*R*,2*R*,4*R*)-Bicyclo[2.2.2]oct-5-enecarbonyl)oxazolidin-2-one (6b).[10] The *endo*/*exo* ratio was determined by ^{1}H NMR analysis. The ee was determined through chiral HPLC

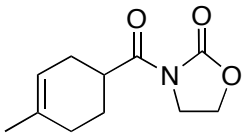
analysis (Daicel AD-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 20:1; *endo* 2*R* t_R = 22.6 min, *endo* 2*S* t_R = 25.0 min, *exo* major t_R = 18.4 min, *exo* minor t_R = 19.6 min). Absolute configuration of the *endo* cycloadduct was assigned by comparing the reported retention time.[7]

Isoprene (7a). **7a** was distilled from sodium borohydride.

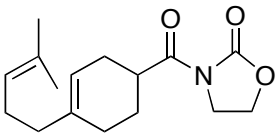
2-Phenylbutadiene (7d). **7d** was prepared according to the previously reported method.[11]

3-methylpentadiene (7e). **7e** was mixture of *cis* and *trans* (73:27). The ratio was determined by ^{1}H NMR analysis.

2,3-Dimethylbutadiene (7f). **7f** was distilled from sodium borohydride.

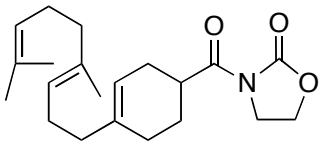


3-(4-Methylcyclohex-3-enecarbonyl)oxazolidin-2-one (8a).[10] The ee was determined through chiral HPLC analysis (Daicel OJ-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 20:1; major *R* t_R = 42.0 min, minor *S* t_R = 45.8 min). Absolute configuration was assigned to be *R* from the sign of measured optical rotation. $[\alpha]^{24}_D$ +20.3 (*c* = 1.50, $CHCl_3$), 96% ee (*R*-isomer); Lit[10] 60% ee (*S*-isomer), $[\alpha]_{589}$ –34.9 (*c* = 1.85, CH_2Cl_2).

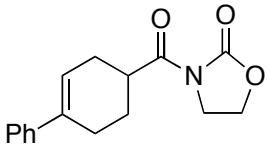


3-[4-(4-Methylpent-3-enyl)cyclohex-3-enecarbonyl]oxazolidin-2-one (8b): Amorphous solid; R_f = 0.45 (hexane-EtOAc = 1:1); $[\alpha]^{23}_D$ +28.4 (*c* = 2.0, $CHCl_3$) for 94% ee; IR (film) 1792, 1769, 1687, 1384 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.69 (s, 3H), 1.62–1.80 (m, 2H), 1.96–2.24 (m, 8H), 3.67 (m, 1H), 4.03 (t, *J* = 8.1 Hz, 2H), 4.42 (t, *J* = 8.1 Hz, 2H),

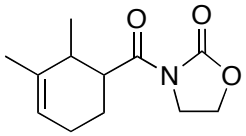
5.10 (t, J = 6.9 Hz, 1H), 5.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 25.7, 25.9, 26.3, 27.3, 27.9, 37.4, 38.3, 42.8, 61.9, 118.6, 124.2, 131.5, 137.3, 153.2, 176.7; HRMS (FAB) calcd for $C_{16}H_{24}O_3N$ $[M+H]^+$ 278.1756, found 278.1756. The ee was determined through chiral HPLC analysis (two linear Daicel AD-H column; flow rate = 0.60 mL/min; hexane-*i*-PrOH = 40:1; major t_R = 57.7 min, minor t_R = 61.0 min). The absolute configuration has not been determined.



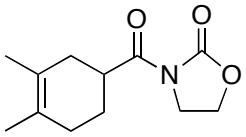
(*E*)-3-[4-(4,8-Dimethylnona-3,7-dienyl)cyclohex-3-enecarbonyl]oxazolidin-2-one (8c): White solid; R_f = 0.60 (hexane-EtOAc = 1:1); $[\alpha]^{22}_D$ (c = 4.68, $CHCl_3$) = 29.6 for 98% ee; IR (KBr) 1787, 1691, 1381 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.68 (s, 3H), 1.66 (m, 2H), 1.97–2.34 (m, 12H), 3.67 (m, 1H), 4.03 (t, J = 8.2 Hz, 2H), 4.41 (t, J = 8.2 Hz, 2H), 5.10 (t, J = 5.5 Hz, 1H), 5.11(t, J = 5.5 Hz, 1H), 5.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 17.6, 25.7, 25.9, 26.2, 26.7, 27.3, 27.9, 37.4, 38.3, 39.7, 42.8, 61.9, 118.6, 124.0, 124.3, 131.2, 135.1, 137.3, 153.1, 176.6; HRMS (FAB) calcd for $C_{21}H_{32}O_3N$ $[M+H]^+$ 346.2382, found 346.2362. The ee was determined through chiral HPLC analysis (three linear Daicel AD-H column; flow rate = 0.50 mL/min; hexane-*i*-PrOH = 9:1; major t_R = 43.8 min, minor t_R = 44.8 min). The absolute configuration has not been determined.



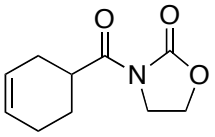
3-(4-Phenylcyclohex-3-enecarbonyl)oxazolidin-2-one (8d):[12] $[\alpha]^{25}_D$ +27.0 (c = 2.00, $CHCl_3$) for 80% ee. The ee was determined through chiral HPLC analysis (Daicel AD-H column; flow rate = 1.00 mL/min; hexane-EtOH = 9:1; major t_R = 53.7 min, minor t_R = 59.1 min). The absolute configuration has not been determined.



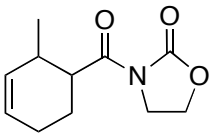
3-(2,3-Dimethylcyclohex-3-enecarbonyl)oxazolidin-2-one (8e).[7] The diastereomeric ratio (dr) was determined by ^{1}H NMR analysis. The ee was determined through chiral HPLC analysis (two linear Daicel OD-H column; flow rate = 0.60 mL/min; hexane-*i*-PrOH = 9:1; *endo* major t_R = 64.8 min, *endo* minor t_R = 62.0 min, another isomer 68.3 min). The absolute configuration has not been determined.



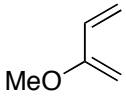
3-(3,4-Dimethylcyclohex-3-enecarbonyl)oxazolidin-2-one (8f).[10] The *endo*/*exo* ratio was determined by ^{1}H NMR analysis. The ee was determined through chiral HPLC analysis (Daicel OD-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 20:1; *R* t_R = 21.5 min, *S* t_R = 18.2 min). Absolute configuration was assigned from the sign of measured optical rotation. Lit[13] 60% ee (*S*-isomer), $[\alpha]_D$ –35.7 (*c* = 1.96, CH_2Cl_2).



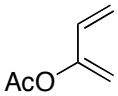
3-(Cyclohex-3-enecarbonyl)oxazolidin-2-one (8g).[13] The ee was determined through chiral HPLC analysis (Daicel OJ-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 20:1; *R* t_R = 35.8 min, *S* t_R = 33.7 min). Absolute configuration was assigned to be *S* from the sign of measured optical rotation. $[\alpha]^{25}_D$ +9.2 (*c* = 2.00, $CHCl_3$), 74% ee (*S* isomer); Lit[13] 89% ee (*R*-isomer), $[\alpha]^{23}_D$ –20.2 (*c* = 1.75, CH_2Cl_2).



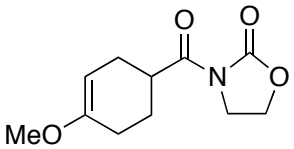
3-(2-Methylcyclohex-3-enecarbonyl)oxazolidin-2-one (8h).[10] The *cis*/*trans* mixture was recrystalized from hexane-diethyl ether to give a single diastereomer. The dr was determined by ^{1}H NMR analysis. The ee was determined through chiral HPLC analysis (two linear Daicel OD-H column; flow rate = 0.50 mL/min; hexane-EtOH = 9:1; major t_R = 57.1 min, minor t_R = 79.8 min). Absolute configuration was assigned to be *1R, 2S* from the sign of measured optical rotation. $[\alpha]^{25}_D$ +234.3 (*c* = 1.15, $CHCl_3$), 99% ee (1*R,* 2*S*-isomer); Lit[10] >99% ee (1*S,* 2*R*-isomer), $[\alpha]_D$ –230 (*c* = 0.40, CH_2Cl_2).



2-Methoxy-1,3-butadiene (9a).[14] **9a** was prepared according to the previously reported method.[14]

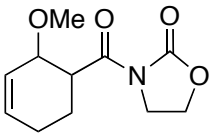


2-Acethoxy-1,3-butadiene (9b).[15] **9b** was prepared according to the previously reported method.[15]

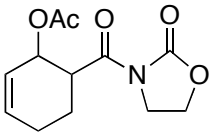


3-(4-Methoxycyclohex-3-enecarbonyl)oxazolidin-2-one (10a). Colorless oil; R_f = 0.50 (hexane-EtOAc = 1:1); $[\alpha]^{23}_D$ +5.6 (*c* = 1.00, $CHCl_3$) for 82% ee; IR (film) 2952, 1776, 1697, 1389 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (m, 1H), 2.09 (m, 1H), 2.14 (m, 1H), 2.26 (m,1H), 2.32 (dd, *J* = 3.3, 7.5 Hz, 2H), 3.51 (s, 3H), 3.68 (m, 1H), 4.03 (t, *J* = 8.1 Hz, 2H), 4.42 (t, *J* = 8.1 Hz, 2H), 4.61(t, *J* = 3.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 25.8, 27.0, 38.5, 42.8, 54.0, 61.9, 91.2, 153.1, 154.7, 176.2; HRMS (FAB) calcd for $C_{11}H_{16}O_4N$ $[M+H]^+$ 226.1079, found

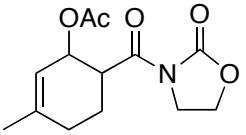
226.1081. The ee was determined through chiral HPLC analysis (AD-H column; flow rate = 0.50 mL/min; hexane-*i*-PrOH = 4:1; major t_R = 14.0 min, minor t_R = 18.8 min). The absolute configuration has not been determined.



3-(2-Methoxycyclohex-3-enecarbonyl)oxazolidin-2-one (10c): Colorless oil; R_f = 0.35 (hexane-EtOAc = 1:1); $[\alpha]^{22}_D$ –232.8 (*c* = 0.59, $CHCl_3$) for 89% ee; IR (film) 1775, 1706, 1385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76 (m, 1H), 2.04 (m, 1H), 2.22 (m, 1H), 3.31 (s, 3H), 3.77 (ddd, *J* = 3.2, 4.1, 11.9 Hz 1H), 4.07 (m, 2H), 4.18 (dd, *J* = 3.2, 4.1 Hz, 1H), 4.44 (t, *J* = 7.8 Hz, 2H), 5.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 24.8, 42.8, 44.2, 56.5, 62.2, 71.9, 124.4, 132.4, 153.5, 173.3; HRMS (FAB) calcd for $C_{11}H_{16}O_4N$ $[M+H]^+$ 226.1079, found 226.1081. The *cis*/*trans* ratio was determined by ^1H NMR analysis. The ee was determined through chiral HPLC analysis (Daicel AD-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 9:1; *cis* major t_R = 12.5 min, *cis* minor t_R = 15.5 min). The absolute configuration has not been determined.



6-(2-Oxooxazolidine-3-carbonyl)cyclohex-2-enyl acetate (10d).[10] The *cis*/*trans* ratio was determined by ^1H NMR analysis. The ee was determined through chiral HPLC analysis (Daicel OD-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 8:2; *cis* major t_R = 11.0 min, *cis* minor t_R = 16.6 min, *trans* major t_R = 20.4 min, *trans* minor t_R = 24.0 min).



3-Methyl-6-(2-oxooxazolidine-3-carbonyl)cyclohex-2-enyl acetate (10e).[10]

The *cis*/*trans* ratio was determined by ^{1}H NMR analysis. The ee was determined through chiral HPLC analysis (Daicel OD-H column; flow rate = 1.00 mL/min; hexane-*i*-PrOH = 9:1; *cis* major t_R = 16.2 min, *cis* minor t_R = 24.4 min, *trans* major t_R = 33.0 min, *trans* minor t_R = 39.8 min). Absolute configuration of the *cis* cycloadduct was assigned to be 1*R,* 2*R* by comparing the reported retention time of 1*S,* 2*S* -isomer.[10]

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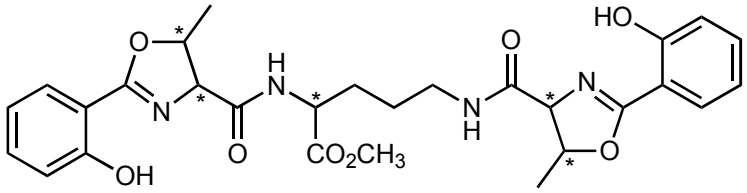
Appendix

Dehydrative Cyclization Catalyzed by the Combination of Molybdenum(VI) Oxides and Benzoic Acids: First Synthesis of the Antitumor Substance BE-70016

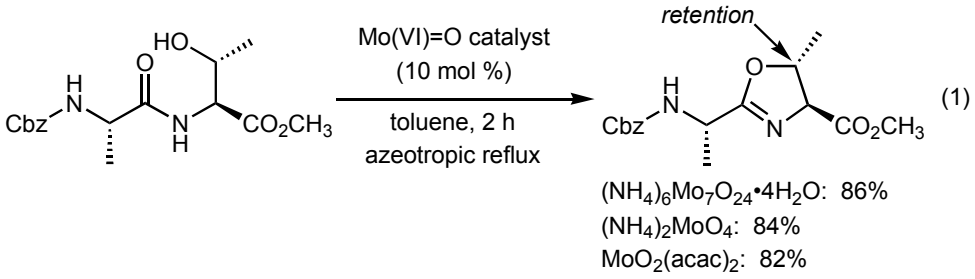
Abstract: The dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivative **1a** is efficiently promoted by the combined use of molybdenum(VI) oxides and benzoic acids bearing electron-withdrawing substituents. In the presence of $(NH_4)_2MoO_4$ (10 mol %) and $C_6F_5CO_2H$ (10 mol %), dehydrative cyclization of **1a** was conducted in toluene under azeotropic reflux conditions to give 2-(*o*-hydroxyphenyl)oxazoline **2a** in 76% yield. Furthermore, the first total synthesis of the antitumor substance BE-70016 was achieved using the catalytic dehydrative cyclization of **1a** as a key reaction.

Since the late 1980s, many oxazoline-containing natural products have been isolated from marine organisms.[1] The biosynthesis of these oxazolines appears to involve the dehydrative cyclization of serine and threonine residues.[1c] Among these oxazoline-containing natural compounds, 2-(*o*-hydroxyphenyl)oxazoline structures are often found. For example, BE-70016 is an antitumor substance that was isolated from *Actinoplanes sp.*[2] This compound appears to be useful in the control of human and mouse tumors. These 2-(*o*-hydroxyphenyl)oxazoline-containing natural products are generally considered to be siderophores,[3] which are defined as low-molecular-weight Fe(III)-specific transport agents. These compounds are thought to be derived from *N*-(*o*-hydroxybenzoyl)threonine.



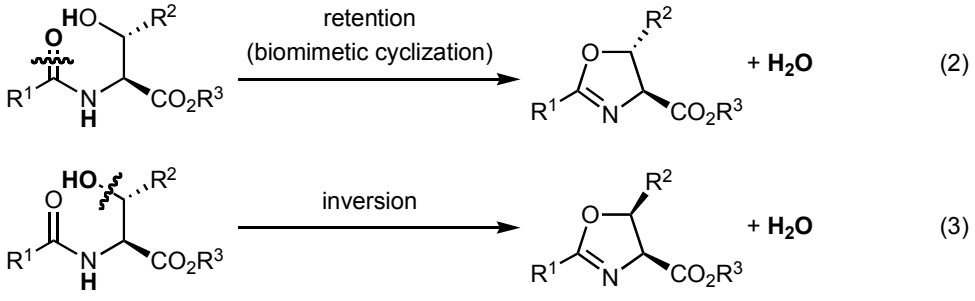
BE-70016

Although several stoichiometric reagents are known to be effective for the chemical dehydrative cyclization of serine and threonine residues,[4] few successful examples of dehydrating catalysts have been reported.[5] Recently, we reported molybdenum(VI) oxides as highly effective dehydrative cyclization catalysts for the synthesis of oxazolines and thiazolines (Eq. 1).[6]



(1)

There are two known methodologies for the chemical synthesis of oxazolines: the retentive cyclization of *N*-acylthreonine derivatives at the β-position (biomimetic cyclization) (Eq. 2), and its invertive cyclization (Eq. 3). As in the biosynthesis, the molybdenum oxide-catalyzed dehydrative cyclization of threonine derivatives proceeds with a retention of configuration at the β-position, while most reactions that use stoichiometric dehydrating reagents proceed with an inversion of configuration at the β-position.[4b–g, 4i, 4j] Therefore, the molybdenum oxide-catalyzed method (Eq. 1) is quite useful for the synthesis of naturally occurring oxazolines derived from an L-threonine residue. When we synthesize L-threonine-derived oxazolines using stoichiometric dehydrating reagents,[7, 8] L-*allo*-threonine, which is much more expensive than L-threonine, is needed.

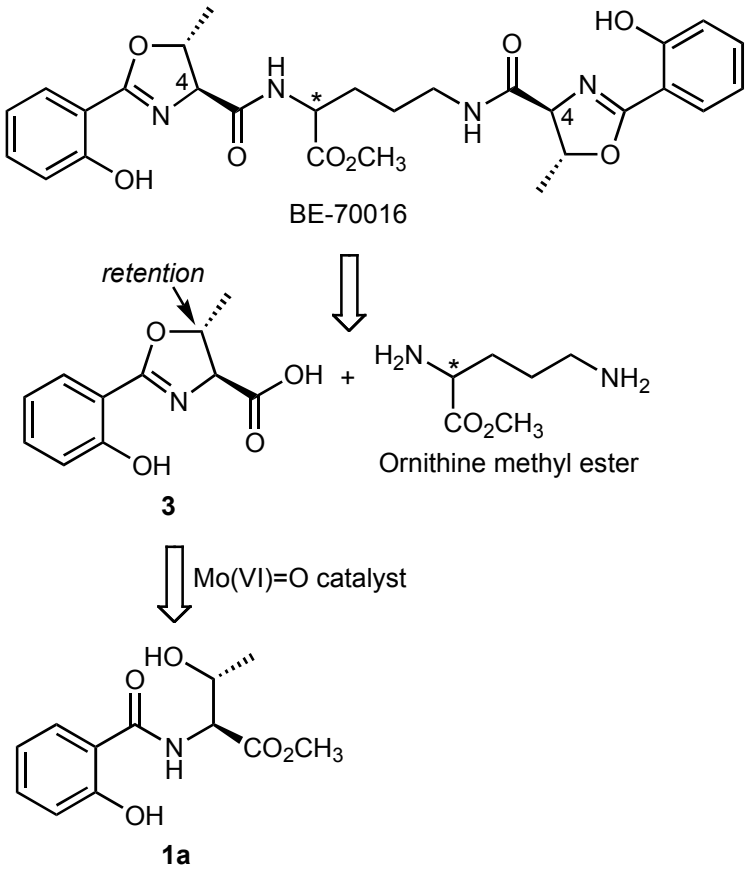


We report here the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivative **1a** catalyzed by the combination of molybdenum(VI) oxides and benzoic acids bearing electron-withdrawing substituents. Furthermore, we have achieved the first total synthesis of BE-70016 using the molybdenum oxide-catalyzed dehydrative cyclization as a key reaction.

Scheme 1 shows a retrosynthesis of BE-70016. This compound is composed of two molecules of salicylic acid, two molecules of threonine, and one molecule of ornithine. We planned to synthesize BE-70016 biomimetically by the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine methyl ester[9] followed by condensation with ornithine methyl ester. Although the relative and absolute stereochemistries of natural BE-70016 are not shown in the

original patent,[2] we considered that the relative stereochemistries of the two oxazoline rings were *trans* based on the coupling constants of protons at the 4-positions of the oxazoline rings [δ 4.39 (d, J = 7.6 Hz, 1H) and 4.43 (d, J = 7.6 Hz, 1H)].[5g] Amide condensation between 4-oxazolinecarboxylic acid **3** and both enantiomers of ornithine methyl esters would give two possible diastereomers of BE-70016. The absolute stereochemistry of BE-70016 would be determined based on a comparison of the sense of the optical rotation. It was expected that compound **3** could be prepared from L-threonine by molybdenum oxide-catalyzed dehydrative cyclization with a retention of configuration at the β-position.

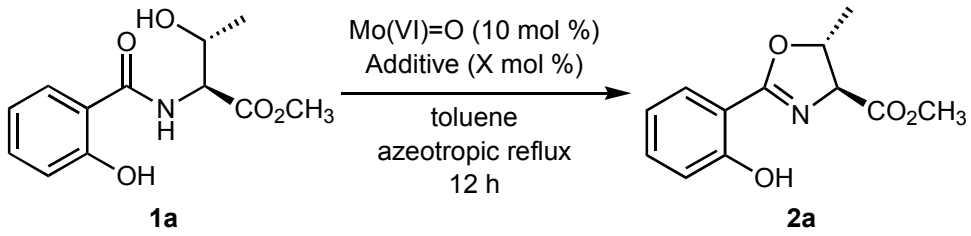
Scheme 1. Retrosynthesis of BE-70016



We initially investigated the dehydrative cyclization of **1a** to **2a** using molybdenum(VI)

oxides as catalysts (Table 1). Compound **2a** is one of the most important common intermediates for the synthesis of many oxazoline-containing bioactive natural products. The development of an efficient and practical method for the synthesis of this compound is strongly needed. Unfortunately, however, the catalytic activities of $(NH_4)_2MoO_4$ and $MoO_2(acac)_2$ for the dehydrative cyclization of **1a** were very low (entries 1 and 2), although they show excellent catalytic activities for the reaction of Cbz-L-Ala–L-Thr-OCH_3 (see Eq. 1).[6] To increase the reactivity, we examined several Brønsted acids as additives. *p*-Toluenesulfonic acid (*p*-TsOH) did not promote the reaction of **1a** (entry 3). The catalytic activity of *p*-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.[5g] Very interestingly, some benzoic acids bearing electron-withdrawing substituents efficiently promoted the molybdenum(VI) oxide-catalyzed dehydrative cyclization of **1a**. 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 excellent results (entries 4, 6 and 8–11). In the presence of $(NH_4)_2MoO_4$ (10 mol %) and $C_6F_5CO_2H$ (10 mol %), a solution of **1a** was heated under azeotropic reflux conditions with the removal of water for 12 h. After aqueous workup (washing with a 1 M aqueous solution of citric acid), oxazoline **2a** was obtained in 76% yield. Since these benzoic acids themselves showed very low catalytic activities (entries 13 and 14), they primarily promoted the activities of molybdenum(VI) oxides. The optimized amount of benzoic acid was 1 mol equiv per molybdenum(VI) oxide (entries 5−7). One of the reasons for the low catalytic activities of molybdenum(VI) oxides is the tight complexation of molybdenum(VI) oxide with **2a**. Actually, the reaction of *N*-(*o*-methoxybenzoyl)-L-threonine methyl ester (**3**) proceeded well even in the absence of benzoic acids to give oxazoline **4** in 75% yield (Eq. 4). Benzoic acids might promote decomposition of the stable and inactivated complexes to regenerate the active molybdenum(VI) oxide species. The experimental result that the isolated yield of **2a** was decreased without an aqueous workup also supported the formation of stable complexes of the molybdenum(VI) oxide with **2a**.

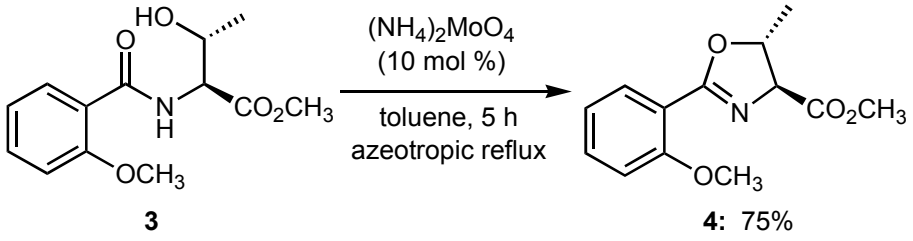
Table 1. Dehydrative Cyclization of *N*-(*o*-Hydroxybenzoyl)threonine Methyl Ester (**1a**)[a]



1a **2a**

entry	Mo(VI)=O	additive	X (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[c]
5	$(NH_4)_2MoO_4$	$C_6F_5CO_2H$	2	47[d]
6	$(NH_4)_2MoO_4$	$C_6F_5CO_2H$	10	76
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[c]
11	$MoO_2(acac)_2$	3,5-$(CF_3)_2C_6H_3CO_2H$	10	79
12	—	*p*-TsOH	10	19
13	—	$C_6F_5CO_2H$	10	1
14	—	3,5-$(CF_3)_2C_6H_3CO_2H$	10	0

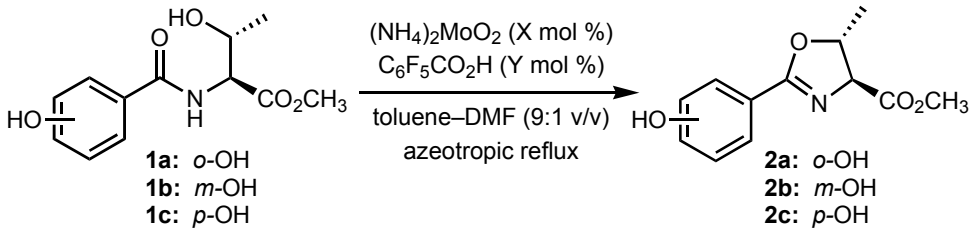
[a] The reaction of **1a** (1 mmol) was conducted in toluene (10 mL) under azeotropic reflux conditions. [b] Evaluated by ^{1}H NMR analysis. [c] The reaction was conducted for 10 h. [d] The reaction was conducted for 11 h.



3 **4:** 75% (4)

Next, we examined the dehydrative cyclization of *m*- and *p*-hydroxy derivatives **1b** and **1c** (Table 2). Since **1b** and **1c** did not dissolve in toluene, the reaction was conducted in toluene–DMF (9:1 v/v). When the reaction of **1c** was conducted in the presence of $(NH_4)_2MoO_4$ (10 mol %) and $C_6F_5CO_2H$ (10 mol %), the corresponding oxazoline **2c** was obtained in 88% yield (entry 1). Interestingly, in contrast to the reaction of **1a**, the reactions of **1c** and **1b** proceeded smoothly in the absence of pentafluorobenzoic acid, to give **2c** and **2b** in respective yields of 91 and 87% (entries 2 and 3). Only 2 mol % of the catalyst was sufficient to obtain the products in good yields. The coordination of the oxazolyl nitrogen of **2a** and **2c** to molybdenum(VI) oxides should be stronger than that of **2b** due to the resonance effect of the hydroxyl group at *o*- and *p*-positions. The higher reactivity of **1b** compared to those of **1a** and **1c** can be explained by the faster release of **2b** from the catalyst compared to **2a** and **2c**. Since **2a** was obtained in 18% yield when the reaction of **1a** catalyzed by $(NH_4)_2MoO_4$ and $C_6F_5CO_2H$ was conducted in toluene–DMF (9:1 v/v) (entry 4), DMF did not promote the reaction. A highly polar solvent such as DMF was not suitable for **1a** which was soluble in toluene.[6]

Table 2. Dehydrative Cyclization of *m*- and *p*-Hydroxy Derivatives **1b** and **1c**[a]



entry	substrate	$(NH_4)_2MoO_4$ (mol %)	$C_6F_5CO_2H$ (mol %)	time (h)	yield (%)[b]
1	**1c**	10	10	2	88
2	**1c**	2	0	4	87
3	**1b**	2	0	1	91
4	**1a**	10	10	10	18

[a] The reaction of **1b** or **1c** (1 mmol) was conducted in toluene–DMF (9:1 v/v, 10 mL) under azeotropic reflux conditions. [b] Evaluated by ^{1}H NMR analysis.

With the key intermediate (**2a**) for the synthesis of BE-70016 in hand, we investigated the synthesis of BE-70016 (Scheme 2). Hydrolysis of **2a** with lithium hydroxide gave carboxylic acid **5** in quantitative yield. The condensation of ornithine methyl esters was conducted with **5** (3.0 mol equiv) using WSCI•HCl (3.0 mol equiv) and HOBt (2.0 mol equiv) in CH_2Cl_2, to give (*S*)-L-ornithine derivative **6** and (*R*)-D-ornithine derivative **7** in respective yields of 85 and 88%. As shown in Table 3, some signals in the ^{1}H NMR spectra of **6** were obviously different from those of natural BE-70016 and **7**. Based on a comparison of IR, ^{1}H and ^{13}C NMR, HRMS and specific rotation ($[\alpha]_D$), **7** was found to be identical to natural BE-70016. Thus, we have elucidated the stereochemical structure of BE-70016 as depicted in formula **7**, which was composed of salicylic acid, L-threonine and unnatural D-ornithine. Furthermore, we have achieved the first total synthesis of BE-70016 using the retentive cyclization of **1a** as a key reaction.

Scheme 2. Synthesis of BE-70016

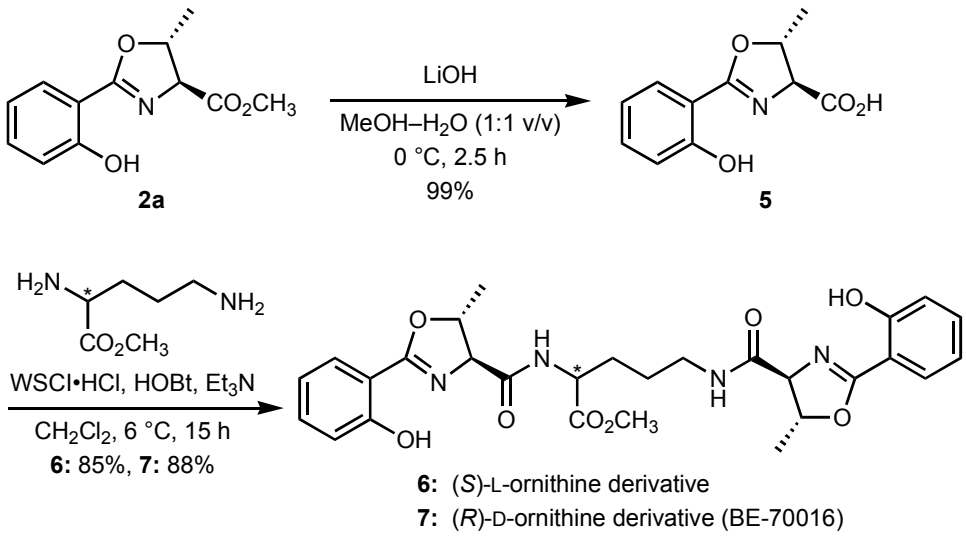


Table 3. Selected Spectral Data of Natural BE70016, and Synthetic Products **6** and **7**

	natural BE-70016	**6**	**7**	
^{1}H NMR (ppm)	1.76	1.72	1.76	m, 1H (β-position of ornithine)
	3.33	3.20	3.33	m, 1H (δ-position of ornithine)
	3.69	3.76	3.69	s, 3H (methyl ester)
$[\alpha]_D$	+10.3	+1.6	+10.6	

In conclusion, we have succeeded in the catalytic dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivatives without protecting the *o*-hydroxy group. The reaction was efficiently promoted by the combination of molybdenum(VI) oxides and benzoic acids bearing electron-withdrawing substituents, such as $C_6F_5CO_2H$. Furthermore, we have achieved the first

total synthesis of the antitumor substance BE-70016 via a biomimetic strategy using molybdenum(VI) oxide-catalyzed dehydrative cyclization as a key reaction. The present strategy may be suitable for the efficient and practical synthesis of several bioactive natural products containing 2-(*o*-hydroxyphenyl)oxazolines.

References and Notes

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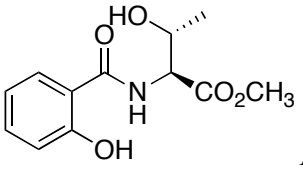
8. Wipf reported the conversion of *cis*-oxazolines, which were prepared from L-threonine derivatives with Burgess reagent, to *trans*-oxazolines by sequential treatment with 0.3 M HCl, K_2CO_3, and Burgess reagent. (a) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975–10977. (b) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358–12367. (c) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826–831.

9. No examples of the catalytic dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivatives have been reported previously. Some stoichiometric dehydrating reagents can promote the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivatives. However, these reactions proceed with an inversion of configuration at the β-position of threonine residues. (a) Scheurer, A.; Mosset, P.; Bauer, W.; Saalfrank, R. W. *Eur. J. Org. Chem.* **2001**, 3067–3074. (b) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2002**, *4*, 3399–3401.

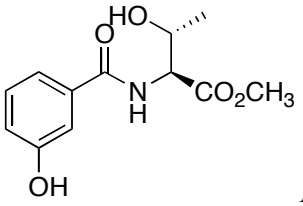
Experimental Section

General Methods: 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) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the d 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 INOVA spectrometer (125 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). 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 Chemical Instrument Facility, Nagoya University. Dry toluene was purchased from Wako as the "anhydrous" and stored under nitrogen. Dichloromethane and triethylamine were freshly distilled from calcium hydride. $(NH_4)_2MoO_4$ (Aldrich), $MoO_2(acac)_2$ (Wako), $(CF_3)_2C_6H_3CO_2H$ (TCI), 4-$(NO_2)C_6H_4CO_2H$ (Kishida) and other materials were obtained from commercial supplies and used without further purification.

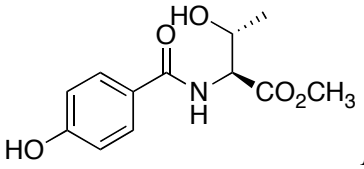


***N*-(*o*-Hydroxybenzoyl)-L-threonine methyl ester (1a).** To a solution of L-threonine methylester (1.70 g, 10 mmol), salicylic acid (1.38 g, 10 mmol), HOBt (135 mg, 1.0 mmol) and Et_3N (1.39 mL, 10 mmol) in CH_2Cl_2 (30 mL) was added a solution of WSCI•HCl (2.11 g, 11 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After stirring at 6 °C for 12 h, CH_2Cl_2 was removed in vacuo and dissolved in EtOAc (80 mL). The resulting solution was washed with 1 M HCl (80 mL), saturated aqueous $NaHCO_3$ (2 Å~ 80 mL) and brine (80 mL), dried over Na_2SO_4 and concentrated. The residue

was purified by column chromatography on silica gel using a mixture of hexane–EtOAc (2:1 → 3:2) as an eluent to give **1a** (2.25 g, 89%): colorless oil; IR (neat) 3373, 1745, 1644, 1600, 1538, 1493, 1439, 1361, 1308, 1217, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.3 Hz, 3H), 3.17 (br s, 1H), 3.78 (s, 3H), 4.48 (dq, *J* = 2.1, 6.3 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 0.5H), 4.81 (d, *J* = 2.4 Hz, 0.5H), 6.85 (ddd, *J* = 1.2, 7.2, 7.8 Hz, 1H), 6.97 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.39 (ddd, *J* = 1.5, 7.2, 8.4 Hz, 1H), 7.59 (dd, *J* = 1.5, 7.8 Hz, 1H), ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 52.7, 57.3, 67.7, 114.0, 117.9, 119.0, 126.7, 134.4, 160.5, 170.1, 171.4; HRMS (FAB) calcd for $C_{12}H_{16}NO_5$ $[M+H]^+$ 254.1028, found 254.1022.

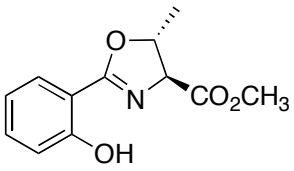


***N*-(*m*-Hydroxybenzoyl)-L-threonine methyl ester (1b):** colorless oil; IR (neat) 3366, 1739, 1644, 1585, 1530, 1486, 1439, 1316, 1217, 1158, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.6 Hz, 3H), 3.77 (s, 3H), 4.38 (dq, *J* = 3.3, 6.6 Hz, 1H), 4.66 (d, *J* = 3.3 Hz, 1H), 6.97 (td, *J* = 2.4, 6.9 Hz, 1H), 7.25–7.35 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 52.9, 59.8, 68.5, 115.3, 119.2, 120.0, 130.8, 136.4, 158.9, 170.6, 172.6; HRMS (FAB) calcd for $C_{12}H_{16}NO_5$ $[M+H]^+$ 254.1028, found 254.1022.

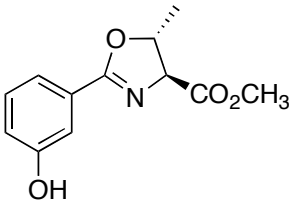


***N*-(*p*-Hydroxybenzoyl)-L-threonine methyl ester (1c):** colorless oil; IR (neat) 3358, 1740, 1640, 1609, 1588, 1541, 1507, 1439, 1281, 1239, 1177, 1111, 1084, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.6 Hz, 3H), 3.75 (s, 3H), 4.37 (dq, *J* = 3.3, 6.6 Hz, 1H), 4.66 (d, *J* = 3.3 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (125 MHz,

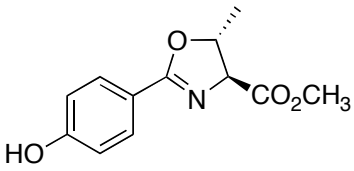
$CDCl_3$) δ 20.4, 52.9, 59.7, 68.6, 116.2, 125.6, 130.5, 162.4, 170.2, 172.8; HRMS (FAB) calcd for $C_{12}H_{16}NO_5$ $[M+H]^+$ 254.1028, found 254.1018.



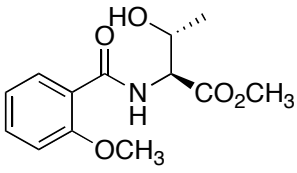
Preparation of Methyl (4*S*,5*R*)-2-(*o*-Hydroxyphenyl)-5-methyl-4-oxazolinecarboxylate (2a). A solution of **1a** (253 mg, 1 mmol), $(NH_4)_2MoO_4$ (20 mg, 0.10 mmol) and $C_6F_5CO_2H$ (21 mg, 0.10 mmol) in toluene (10 mL) was heated at azeotropic reflux with the removal of water using a Dean-Stark apparatus. After 12 hours, the reaction mixture was cooled to ambient temperature, diluted with EtOAc (10 mL) and washed with 1 M citric acid in saturated aqueous NaCl (15 mL), saturated aqueous $NaHCO_3$ and NaCl (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a crude product. Yields were determined by HPLC analysis or ^1H NMR analysis. The crude product was purified by column chromatography on silica gel using a mixture of hexane–EtOAc (15:1 → 13:1 → 10:1) as an eluent to give **2a**: colorless oil; IR (neat) 1743, 1638, 1614, 1491, 1438, 1355, 1310, 1259, 1229, 1207, 1157, 1134, 1072, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, J = 6.3 Hz, 3H), 3.80 (s, 3H), 4.50 (d, J = 6.9 Hz, 1H), 4.98 (qd, J = 6.3, 6.9 Hz, 1H), 6.87 (ddd, J = 0.9, 7.2, 7.8 Hz, 1H), 7.01 (dd, J = 0.9, 8.4 Hz, 1H), 7.39 (ddd, J = 1.5, 7.2, 8.4 Hz, 1H), 7.66 (dd, J = 1.5, 7.8 Hz, 1H), 11.8 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 52.8, 73.7, 78.5, 110.4, 117.0, 118.8, 128.4, 134.0, 160.1, 167.0, 171.0; HRMS (FAB) calcd for $C_{12}H_{14}NO_4$ $[M+H]^+$ 236.0923, found 236.0925.



Methyl (4*S*,5*R*)-2-(*m*-hydroxyphenyl)-5-methyl-4-oxazolinecarboxylate (2b): colorless oil; IR (neat) 1740, 1670, 1586, 1453, 1438, 1388, 1216, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.3 Hz, 3H), 3.78 (s, 3H), 4.48 (d, *J* = 7.2 Hz, 1H), 4.99 (qd, *J* = 6.3, 7.2 Hz, 1H), 6.97 (ddd, *J* = 1.2, 2.7, 8.1 Hz, 1H), 7.26 (dd, *J* = 7.8, 8.1 Hz, 1H), 7.34 (dd, *J* = 1.5, 2.7 Hz, 1H), 7.40 (ddd, *J* = 1.2, 1.5, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 53.0, 75.4, 80.7, 116.0, 120.4, 120.6, 129.2, 130.8, 158.8, 167.6, 172.8; HRMS (FAB) calcd for $C_{12}H_{14}NO_4$ $[M+H]^+$ 236.0923, found 236.0919.

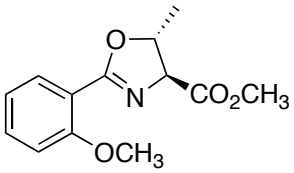


Methyl (4*S*,5*R*)-2-(*p*-hydroxyphenyl)-5-methyl-4-oxazolinecarboxylate (2c): colorless crystal (cryst. from EtOAc); mp 156–157 °C; IR (KBr) 1730, 1601, 1514, 1446, 1372, 1349, 1245, 1165, 1089, 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.3 Hz, 3H), 3.78 (s, 3H), 4.44 (d, *J* = 6.9 Hz, 1H), 4.96 (qd, *J* = 6.3, 6.9 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 53.0, 75.3, 80.4, 116.3, 118.9, 131.5, 162.7, 167.8, 173.0; HRMS (FAB) calcd for $C_{12}H_{14}NO_4$ $[M+H]^+$ 236.0923, found 236.0924.

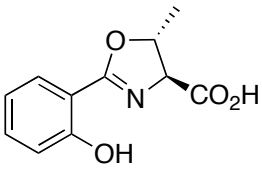


***N*-(*o*-Methoxybenzoyl)-L-threonine methyl ester (3):** colorless oil; IR (neat) 3381, 1739, 1642, 1601, 1531, 1484, 1299, 1242, 1211, 1162, 1047, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.3 Hz, 3H), 2.83 (br s, 1H), 3.79 (s, 3H), 4.00 (s, 3H), 4.41 (m, 1H),

4.82 (d, J = 2.7 Hz, 0.5H), 4.84 (d, J = 2.4 Hz, 0.5H), 7.00 (d, J = 8.1 Hz, 1H), 7.07 (dd, J = 6.9, 7.5 Hz, 1H), 7.47 (ddd, J = 1.8, 6.9, 8.4 Hz, 1H), 8.18 (dd, J = 1.8, 7.5 Hz, 1H), 8.74 (br d, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 52.4, 56.0, 58.1, 67.8, 114.4, 120.6, 121.1, 132.1, 133.2, 157.8, 165.8, 171.7.

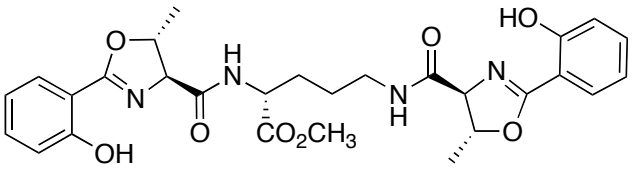


Methyl (4*S*,5*R*)-2-(*o*-methoxyphenyl)-5-methyl-4-oxazolinecarboxylate (4): colorless oil; IR (KBr) 1739, 1631, 1601, 1493, 1468, 1437, 1344, 1271, 1212, 1126, 1084, 1043, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, J = 6.3 Hz, 3H), 3.80 (s, 3H), 3.91 (s, 3H), 4.51 (d, J = 7.5 Hz, 1H), 4.94 (qd, J = 6.3, 7.5 Hz, 1H), 6.92–7.02 (m, 2H), 7.44 (ddd, J = 1.8, 7.5, 8.4 Hz, 1H), 7.79 (dd, J = 1.8, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 52.7, 56.2, 75.5, 78.2, 111.8, 116.6, 120.3, 131.7, 132.8, 158.7, 164.7, 171.9.

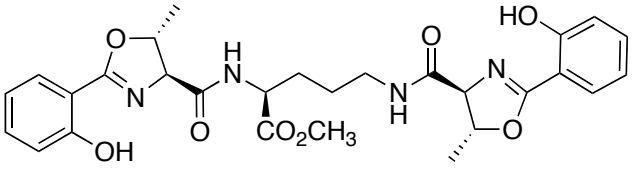


Preparation of (4*S*,5*R*)-2-(*o*-Hydroxyphenyl)-5-methyl-4-oxazolinecarboxylic acid (5). To a solution of **2a** (588 mg, 2.5 mmol) in methanol (10 mL) was added a 1.0 M aqueous solution of LiOH (10 mL, 10 mmol) at ambient temperature, and the mixture was stirred for 2.5 h. The reaction mixture was cooled to 0 °C and acidified (pH 2) with conc. aqueous HCl. After MeOH was removed *in vacuo*, the resulting aqueous layer was extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated, to give **5** (550 mg, 99%): colorless amorphous powder, IR (KBr) 1732, 1637, 1491, 1446, 1372, 1308, 1259, 1158, 1133, 1073, 1037 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, J = 6.3 Hz, 3H), 4.39 (d, J = 7.5 Hz, 1H), 4.93 (qd, J = 6.3, 7.5 Hz, 1H), 6.78 (dd, J = 7.8, 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.4, 8.4 Hz,

1H), 7.56 (d, J = 7.8 Hz, 1H), 11.8 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 73.5, 78.4, 110.3, 116.8, 118.4, 128.2, 133.6, 160.1, 166.6, 171.6; HRMS (FAB) calcd for $C_{11}H_{12}NO_4$ $[M+H]^+$ 222.0766, found 222.0772.



Preparation of BE-70016 (7). To a solution of **2a** (465 mg, 2.1 mmol), (*R*)-ornithine methyl ester•2HCl (153 mg, 0.70 mmol), HOBt (189 mg, 1.4 mmol) and Et_3N (195 μL, 1.4 mmol) in CH_2Cl_2 (10 mL) was added a solution of WSCI•HCl (403 mg, 2.1 mmol) and Et_3N (293 μL, 2.1 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After the mixture was stirred at 6 °C for 15 h and then at ambient temperature for 2 h, CH_2Cl_2 was removed *in vacuo* and dissolved in EtOAc (50 mL). The resulting solution was washed with 1 M HCl (40 mL), saturated aqueous $NaHCO_3$ (2 × 40 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using a mixture of hexane–acetone (3:1 → 2:1→ 1:1) as an eluent to give **7** (340 mg, 88%): colorless amorphous powder; $[\alpha]^{23}_D$ +10.6 (CH_3OH, *c* 0.25); IR (KBr) 3352, 1743, 1668, 1637, 1613, 1523, 1490, 1445, 1372, 1350, 1310, 1258, 1227, 1157, 1134, 1074, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (d, J = 6.5 Hz, 3H), 1.62 (d, J = 6.0 Hz, 3H), 1.6–1.7 (m, 2H), 1.76 (m, 1H), 1.93 (dddd, J = 5.5, 8.5, 9.0, 14.0 Hz, 1H), 3.33 (ddd, J = 6.5, 7.0, 13.5 Hz, 1H), 3.38 (ddd, J = 6.5, 7.0, 13.5 Hz, 1H), 3.69 (s, 3H), 4.39 (d, J = 7.5 Hz, 1H) 4.43 (d, J = 8.0 Hz, 1H), 4.58 (dt, J = 5.0, 7.5 Hz, 1H), 4.84–4.93 (m, 2H), 6.67 (br s, 1H), 6.90 (ddd, J = 1.0, 7.5, 8.0 Hz, 2H), 6.91 (ddd, J = 1.0, 7.5, 8.0 Hz, 2H), 7.02 (m, 2H), 7.08 (br d, J = 8.0 Hz, 1H), 7.41 (ddd, J = 1.0, 7.5, 8.5 Hz, 1H), 7.42 (ddd, J = 1.0, 7.5, 8.5 Hz, 1H), 7.69 (dd, J = 1.5, 8.0 Hz, 1H), 7.69 (dd, J = 1.5, 8.0 Hz, 1H), 11.5 (br s, 1H), 11.5 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 21.8, 25.8, 29.7, 38.7, 51.8, 52.7, 74.3, 74.3, 79.4, 79.7, 110.4, 117.0, 117.1, 119.1, 119.2, 128.7, 128.7, 134.3, 134.3, 159.9, 160.0, 167.2, 167.5 170.7, 170.8, 172.0; HRMS (FAB) calcd for $C_{28}H_{33}N_4O_8$ $[M+H]^+$ 553.2298, found 553.2294.



(*S*)-Ornithine derivative (6). 6 was prepared according to the same manner with **7** using (*S*)-L-ornithine methylester instead of (*R*)-D-ornithine methyl ester: 85% yield; colorless amorphous powder; $[\alpha]^{23}_{D}$ +1.6 (CH_3OH, *c* 0.25); IR (KBr) 1740, 1655, 1610, 1534, 1490, 1444, 1374, 1354, 1309, 1260, 1228, 1212, 1158, 1134, 1072, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.3 Hz, 3H), 1.60 (d, *J* = 6.3 Hz, 3H), 1.72 (m, 1H), 1.83–1.97 (m, 1H), 3.20 (m, 1H), 3.38 (m, 1H), 3.76 (s, 3H), 4.36 (d, *J* = 7.5 Hz, 1H), 4.43 (d, *J* = 7.8 Hz, 1H), 4.59 (ddd, *J* = 5.4, 7.8, 7.8 Hz, 1H), 4.88 (qd, *J* = 6.3, 7.5 Hz, 1H), 4.91 (qd, *J* = 6.3, 7.8 Hz, 1H), 6.75 (br t, *J* = 6.3 Hz, 1H), 6.90 (ddd, *J* = 1.2, 7.2, 7.8 Hz, 1H), 6.91 (ddd, *J* = 1.2, 7.2, 7.8 Hz, 1H), 7.02 (dd, *J* = 1.2, 8.1 Hz, 2H), 7.15 (br d, *J* = 7.8 Hz, 1H), 7.41 (ddd, *J* = 1.8, 7.2, 8.1 Hz, 1H), 7.43 (ddd, *J* = 1.8, 7.2, 8.1 Hz, 1H), 7.69 (dd, *J* = 1.8, 7.8 Hz, 2H), 11.49 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 21.8, 25.9, 29.5, 38.7, 52.1, 52.7, 74.3, 74.4, 79.4, 79.7 110.3, 110.3, 117.0, 117.1, 119.1, 119.2, 128.7, 128.7, 134.3, 134.3, 159.9, 160.0, 167.2, 167.2, 170.6, 170.8, 172.1; HRMS (FAB) calcd for $C_{28}H_{33}N_4O_8$ $[M+H]^+$ 553.2298, found 553.2316.

Publication List

1. "Molybdenum Oxides as Highly Effective Dehydrative Cyclization Catalysts for the Synthesis of Oxazolines and Thiazolines"
   Akira Sakakura, Rei Kondo and Kazuaki Ishihara
   Org. Lett. **2005**, *7*(10), 1971–1974.

2. "Dehydrative Cyclization Catalyzed by the Combination of Molybdenum(VI) Oxides and Benzoic Acids: First Synthesis of the Antitumor Substance BE-70016"
   Akira Sakakura, Shuhei Umemura, Rei Kondo and Kazuaki Ishihara
   Adv. Synth. Catal. **2007**, *349*(4–5), 551–555.

3. "Catalytic Synthesis of Peptide-derived Thiazolines and Oxazolines Using Dioxobis(quinolinolato)molybdenum(VI) Complexes"
   Akira Sakakura, Rei Kondo, Shuhei Umemura and Kazuaki Ishihara
   Adv. Synth. Catal. **2007**, *349*(10), 1641–1646.

4. "Dehydrative cyclization of serine, threonine and cysteine residues catalyzed by molybdenum(VI) oxo compounds"
   Akira Sakakura, Rei Kondo, Shuhei Umemura and Kazuaki Ishihara
   Tetrahedron **2009**, in press.

5. "Asymmetric Diels–Alder Catalysis of Acyclic Dienes Using Copper(II) Cation with Bis(oxazoline) Ligands "
   Akira Sakakura, Rei Kondo and Kazuaki Ishihara
   In preparation

6. “Catalytic Enantioselective [3+2] Nitrone Cycloaddition Reactions with Propiolamides and Acrylamides”

   Akira Sakakura, Masahiro Hori, Rei Kondo, Makoto Fushimi and Kazuaki Ishihara

   In preparation

Acknowledgement

I would like to express my grateful acknowledgment to my supervisors, Professor Kazuaki Ishihara and Associate Professor Akira Sakakura, whose encouragement and helpful suggestions have been indispensable in the completion of the present thesis. The excitement with which they approach synthesis and their dedication to the goal of producing good science is inspiring. Their teaching style in the laboratory and positive attitude for the research work motivated me to be engaged in chemistry. It has been a privilege to work under their tutelage.

I am indebted to Associate Professor Manabu Hatano and Assistant Professor Muhammet Uyanik for their practical and fruitful discussions. I am also very grateful to Associate Professor Matsujiro Akakura (Aichi University of Education) for collaborative research. It is pleasant to express my appreciation to the former and present colleagues in Ishihara's group, especially Drs. Aiko Hasegawa, Yoshiro Furuya, Yuji Kosugi, Takashi Miyamoto, Makoto Fushimi, Toshikatsu Maki, Kazuhiko Nakano, Mrs. Takafumi Asai, Mikimoto Katsukawa, Tokihiko Matsumura, Shuhei Umemura, Masahiro Hori and Miss Shoko Nakagawa.

I am grateful to Professor Dirk Trauner, who kindly gave me the opportunity to study at the University of California, Berkeley, USA, from June to August 2007. I am also grateful for the support of my colleagues in Professor Trauner's group.

I would like to thank Professors Takashi Yamane, Hiroyuki Asanuma and Toshio Nishikawa for serving on my discussion committee.

I am very grateful to the Fellowships from the Nature COE Program and the Japan Society for the Promotion of Science for Japanese Junior Scientist (JSPS).

Finally, I would like to thank my friends and my family, especially my mother Kayoko, my father Hideji, my sister Jun and my husband Yusuke for their true regard and unwavering support during my Ph.D. study. Thank you.

January 2009

Rei Kondo