Convergent Total Syntheses of Oxazoline-Containing Natural Products and the Development of "Pyroc" as a Removable Directing Group for Catalytic Asymmetric Acylation

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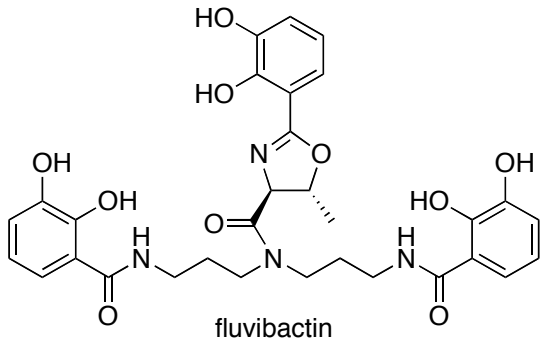
Chapter 1

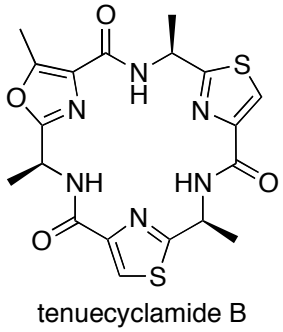
Introduction

Natural products such as nonribosomal peptides and polyketides have a broad range of biological activities and pharmacological properties, such as antibiotic, anti-tumor, and immunosuppressant activity.[1]

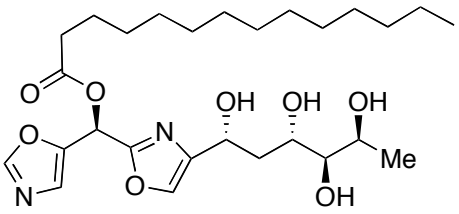
Nonribosomal peptides include various non-proteinogenic amino acids such as D-amino acids, *N*-methyl and *N*-formyl derivatives. In addition, nonribosomal peptides have a variety of structures. For example, serine, threonine and cysteine residues, which have a hydroxy or mercapto group at the β-position, sometimes cyclize to give five-membered heterocycles, oxazolines and thiazolines, and the oxidation of these heterocycles generates oxazoles and thiazoles. These heterocycle-containing natural products have attracted much attention with regard to their biological activities.[2] For example, catechol oxazoline-containing fluvibactin[3] and oxazole- and thiazole-containing tenucyclamide B[4] are nonribosomal peptides (Figure 1.1). They can chelate metal ion and exhibit fascinating biological activities. On the other hand, polyketides consist of carbon-chains that are biosynthesized through the stepwise decarboxylative condensation of malonyl CoA, and often have hydroxylated chiral carbons. Bengazole A,[5] which contains five hydroxylated chiral carbons, and geldanamycin,[6] which contains four hydroxylated chiral carbons, are polyketides (Figure 1.1). These bioactive natural products are important potent pharmaceutical agents or lead compounds. Therefore, many synthetic studies of nonribosomal peptides and polyketides have been reported. Further progress in the highly convergent syntheses of these natural products is still in strong demand.

Nonribosomal peptide





Polyketide



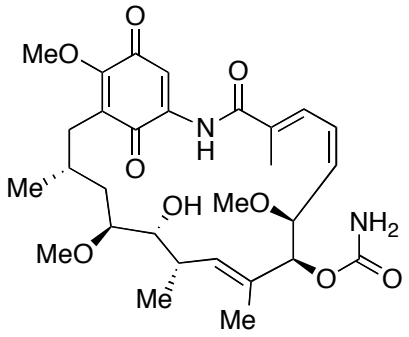
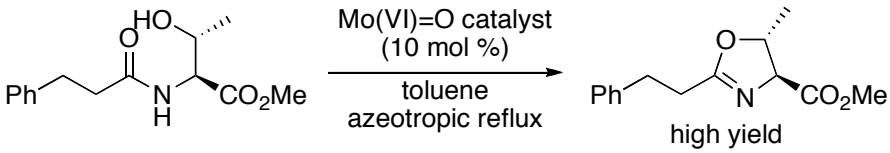
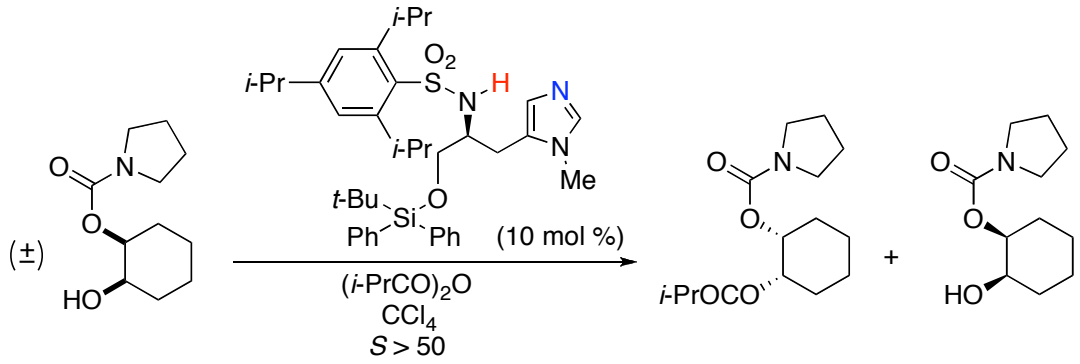


Figure 1.1. Nonribosomal Peptide and Polyketide as Natural Products

Recently, our group established two efficient organic synthetic reactions. The first is a biomimetic oxazoline synthesis through the molybdenum(VI) oxide-catalyzed dehydrative cyclization of serine and threonine residues (Scheme 1.1).[7] The dehydrative cyclization of *N*-(β-hydroxyethyl)amides proceeds in the presence of a catalytic amount of molybdenum(VI) oxides under azeotropic reflux conditions in toluene. The other reaction is the kinetic resolution of racemic alcohols induced by an artificial acylase, *tert*-butyldiphenylsilyl ether of *N*-(2,4,6-triisopropylbenzensulfonyl)-π(Me)-L-histidinol (Scheme 1.2).[8] The reaction shows high selectivities with an *S* value of more than 50, and is an effective method for obtaining optically active alcohols.



Scheme 1.1. Efficient Biomimetic Synthesis of Oxazolines Using Mo(VI)=O Catalysts



Scheme 1.2. Efficient Kinetic Resolution Using L-Histidine-Derived Organocatalyst

For the efficient synthesis of natural products via catalytic reactions, the author developed two themes: (1) Convergent total synthesis of oxazoline-containing nonribosomal peptides via molybdenum(VI) oxide-catalyzed dehydrative cyclization as a key step, and (2) Synthesis of hydroxylated chiral building blocks via asymmetric acylation using the L-histidine-derived catalyst for the synthesis of polyketides. In particular, these themes can be applied to enantioselective- and enantiodefined catalytic reactions.

1-1 Oxazoline-Containing Bioactive Natural Products

Oxazolines, as nonribosomal peptides, are important constituents of numerous secondary metabolites.[9] Since the 1980s, many oxazoline-containing natural products have been isolated from marine organisms. For example, BE-70016 (**1**),[10] which was isolated from the sponge *Actinoplanes*, is an antitumor agent that contains two 2-(*o*-hydroxyphenyl)oxazolines (Figure 1.2). This compound appears to be useful in the control of human and mouse tumors. Vibriobactin (**2**)[11], which contains two catecholate-oxazolines, was isolated from *Vibrio cholerae* in 1984. **1** and **2** are siderophores, which are defined as low-molecular-weight Fe(III)-specific transport agents that are metabolized from a microorganism. These compounds have received much attention due to their unique structures and biological activities.

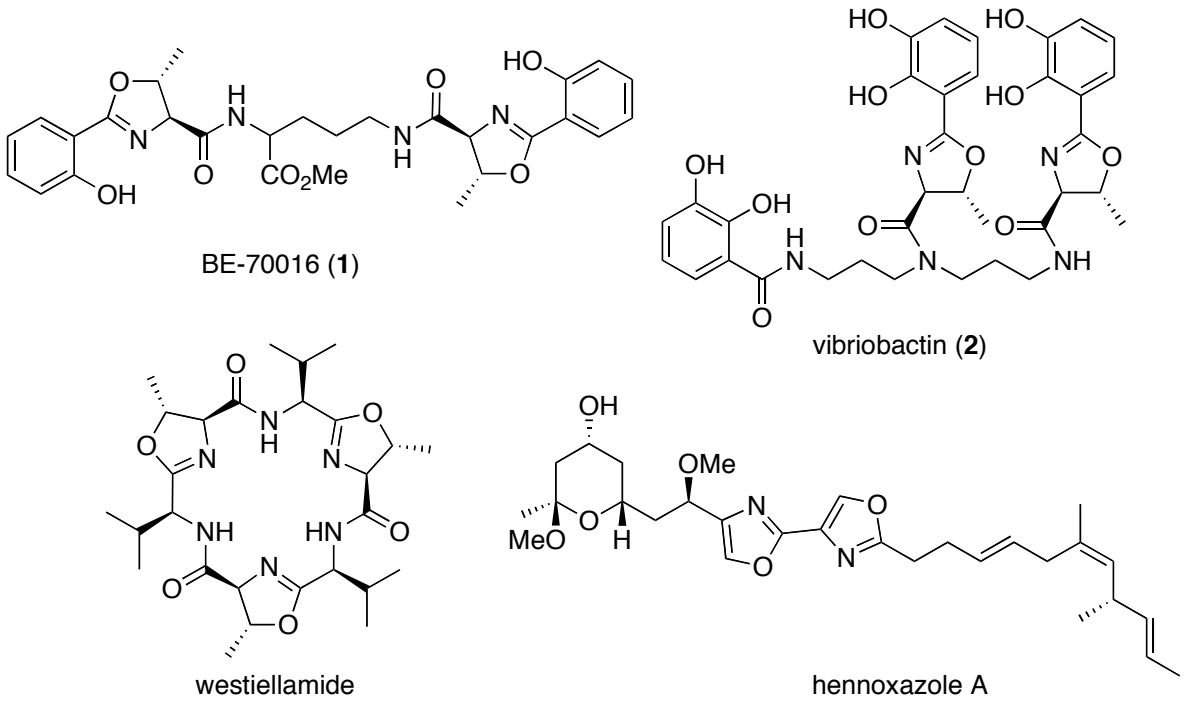
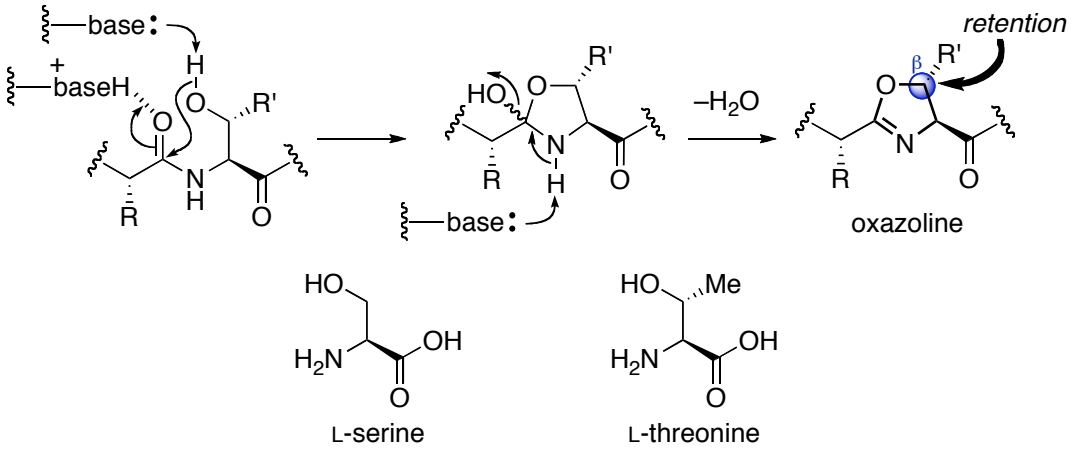


Figure 1.2. Oxazoline- or oxazole-containing bioactive natural products.

Westiellamide was isolated from the cyanobacterium *Westiellopsis prolifica*.[12] This compound has a macrocyclic structure, and contains three oxazolines derived from valine-threonine peptides. The antiviral agent hennoxazole A,[13] isolated from the sponge *Polyfibrospongia*, has a fascinating structure of bisoxazole, which is a highly effective chelating core. In biosynthesis, oxazoles are produced by the two-electron oxidation of oxazolines.[14]

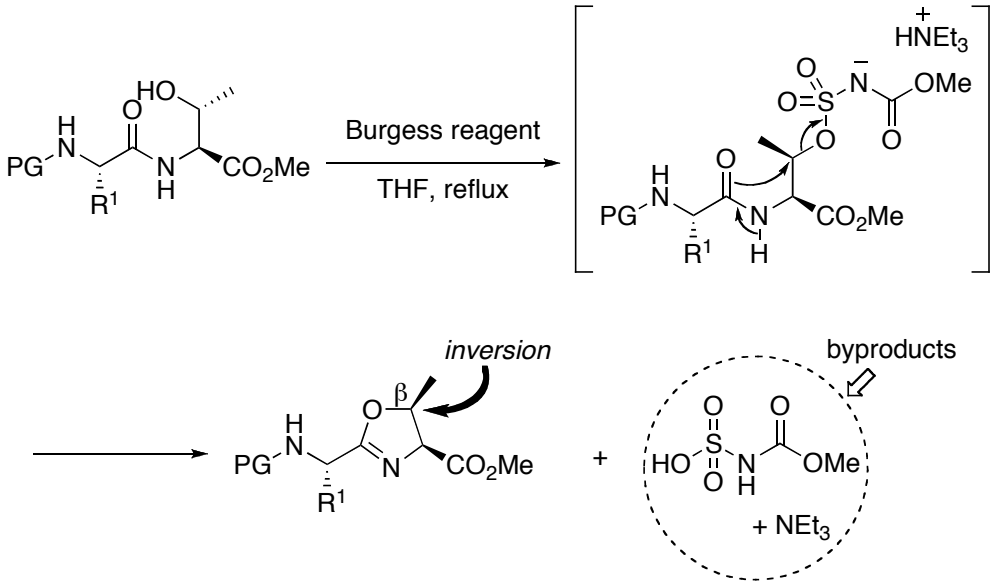
Naturally occurring oxazolines are derived from enzymatic post-translational modifications of peptide-based precursors.[2] The oxygen functionality on the side chain of serine and threonine residues can undergo dehydrative cyclization on the preceding carbonyl group to create a five-membered saturated heterocycle, oxazoline (Scheme 1.3). As shown in Scheme 1.3, the enzymatic dehydrative cyclization of serine and threonine residues proceeds with a *retention* of configuration at the β-position.



Scheme 1.3. Biosynthesis of Oxazolines

On the other hand, a wide range of methods have been devised for the chemical synthesis of oxazolines. Several stoichiometric dehydrating reagents have been reported to effect the dehydrative cyclization of *N*-(β-hydroxyethyl)amides to oxazolines. For example,

Burgess reagent, Mitsunobu reagent, Martin's sulfrane, DAST, Ph_2SO–Tf_2O, and PPh_3–CCl_4 have all been used for the synthesis of oxazolines (Scheme 1.4).[15]

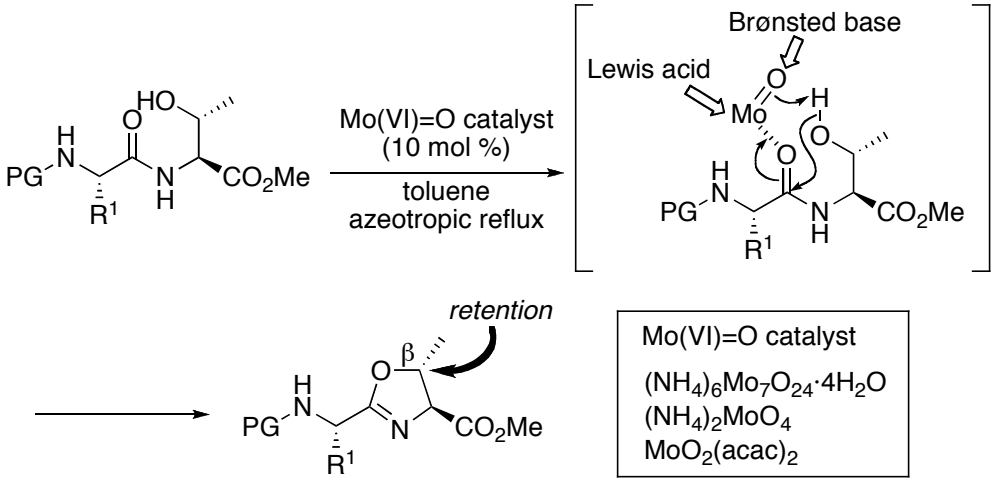


Scheme 1.4. Burgess Reagent for the Synthesis of Oxazolines

However, these stoichiometric dehydrating reagents have some drawbacks. Stoichiometric amounts of byproducts derived from the reagents are obtained along with the desired product. This is disadvantageous in terms of both atom economy and the expense of purification. In addition, *invertive* cyclization occurs at the β-position, in contrast to retentive cyclization in biosynthesis. Therefore, stoichiometric dehydrating reagents require the use of an expensive unnatural L-*allo*-threonine for the synthesis of oxazolines derived from natural L-threonine.

Recently, our group reported molybdenum(VI) oxides as efficient dehydrating catalysts for the synthesis of oxazolines (Scheme 1.5).[7] Commercially available molybdenum(VI) oxides efficiently catalyze the dehydrative cyclization of a variety of serine

and threonine derivatives to give oxazolines in good yields. The reaction proceeds under mild conditions with a *retention* of configuration at the β-position, as in the biosynthesis. Since the reaction generates water as the sole byproduct, the present method is an environmentally friendly procedure for the synthesis of oxazolines.

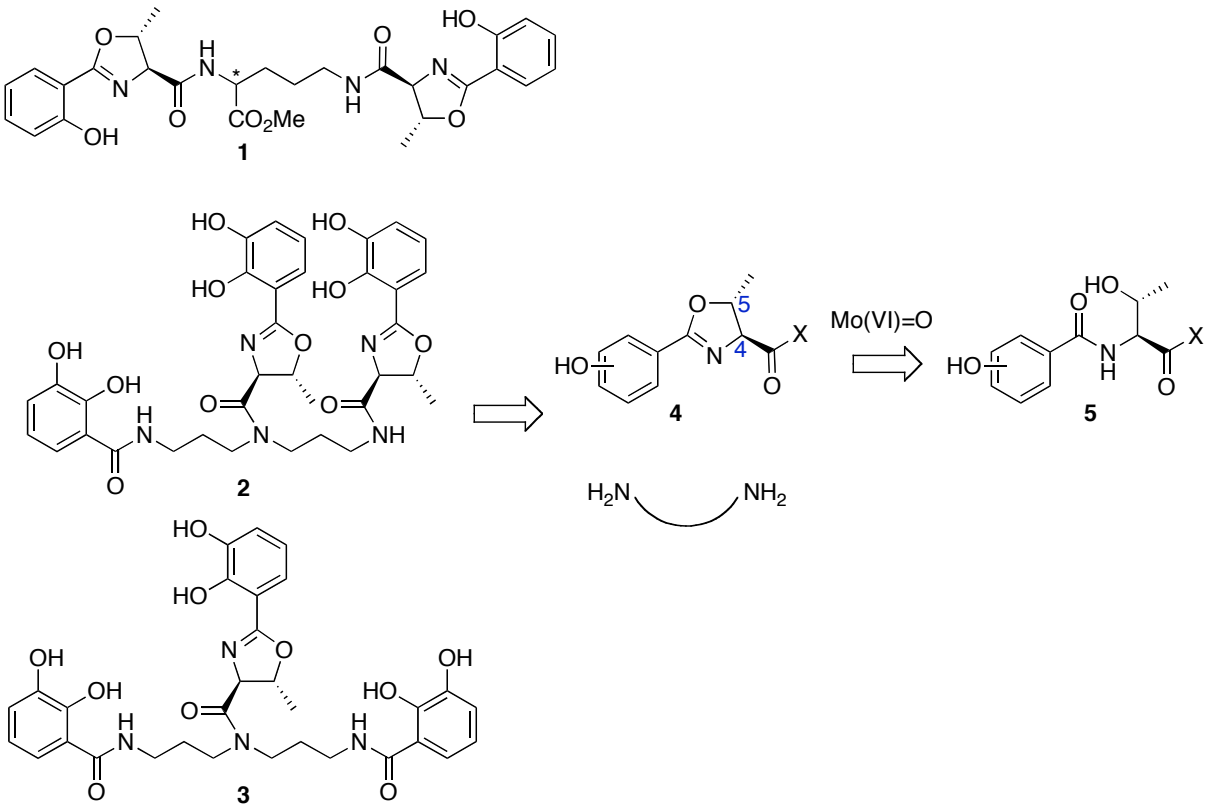


Scheme 1.5. Efficient Synthesis of Oxazolines Using Mo(VI)=O Catalysts

Molybdenum(VI) oxide is a conjugate acid-base catalyst, whose acidic and basic elements are stereoelectronically connected to each other. Thus, the Lewis acidic molybdenum(VI) activates the amide bond, and the Brønsted basic oxo part activates the hydroxy group through deprotonation. These cooperative activations successfully promote dehydrative cyclization to oxazolines. To the best of my knowledge, this is the first successful example of the catalytic dehydrative cyclization of dipeptide substrates for the biomimetic synthesis of oxazolines.

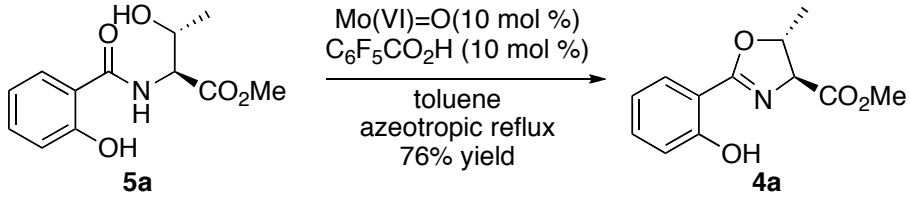
1-2 Convergent Synthesis of Siderophores Containing Oxazolines Using Molybdenum(VI) Oxide-Catalyzed Dehydrative Cyclization as a Key Step

In nature, there are many oxazoline-containing siderophores. BE-70016[9] (**1**) is a siderophore that contains two 2-(*o*-hydroxyphenyl)oxazoline moieties, and was isolated from the sponge *Actinoplanes*. It strongly suppresses of a mouse and human cancer cell growth. Vibriobactin (**2**)[11] and fluvibactin (**3**),[3] which are catecholate siderophores bearing 2-(*o,m*-dihydroxyphenyl)oxazoline structures, have been isolated from low-iron cultures of *Vibrio cholerae* and *Vibrio fluvialis*, respectively. The oxazolines in these siderophores are derived from L-threonine residues and have 4,5-*trans*-stereochemistry. Therefore, the molybdenum(VI) oxide-catalyzed method would be preferable for the synthesis of these oxazolines, since 4,5-*trans*-oxazolines can be synthesized from L-threonine derivatives. A plan for the convergent synthesis of oxazoline-containing siderophores is illustrated in Scheme 1.6. The dehydrative cyclization of hydroxylated benzoyl-L-threonines **5** using molybdenum(VI) oxide catalysts, followed by condensation of the resultant oxazolines **4** with polyamines, will convergently give the natural siderophores.



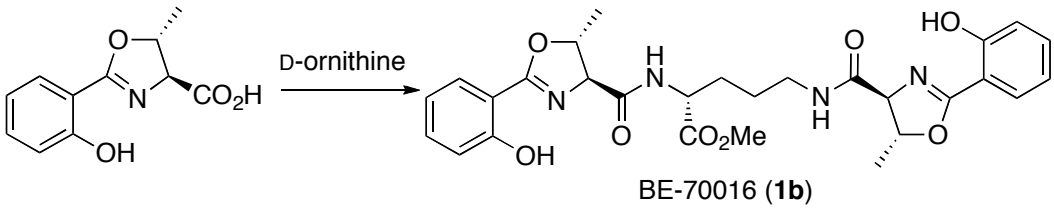
Scheme 1.6. Retrosyntheses of Oxazoline-Containing Siderophores

For the total synthesis of BE-70016 (**1**), the author initially examined the catalytic dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-L-threonine methyl ester (**5a**) by commercially available molybdenum(VI) oxides. Unfortunately, the catalytic activities of $(NH_4)_2MoO_4$ and $MoO_2(acac)_2$ were very low. Further investigation revealed that some benzoic acids bearing electron-withdrawing substituents efficiently promoted the molybdenum(VI) oxide-catalyzed dehydrative cyclization without any protection of the phenolic hydroxyl group (Scheme 1.7). In particular, pentafluorobenzoic acid gave good results.[16] This simple hydroxyphenyloxazoline derivative is also a bacterial siderophore.[17]



Scheme 1.7. Mo(VI)=O Catalyzed Dehydrative Cyclization of *N*-(*o*-Hydroxybenzoyl)-L-threonine

Amide condensation between 4-oxazolinecarboxylic acid and both enantiomers of ornithine methyl esters gave two diastereomers of **1** (Scheme 1.8). Based on a comparison of IR, ^{1}H and ^{13}C NMR, HRMS and specific rotation ($[\alpha]_D$), the product derived from non-proteinogenic D-ornithine was found to be identical to natural BE-70016. The author elucidated the stereochemical structure of **1b**, which was composed of salicylic acid, L-threonine and non-proteinogenic D-ornithine. Thus, the first total synthesis of BE-70016 was achieved by using retentive cyclization of the L-threonine derivative as a key reaction.

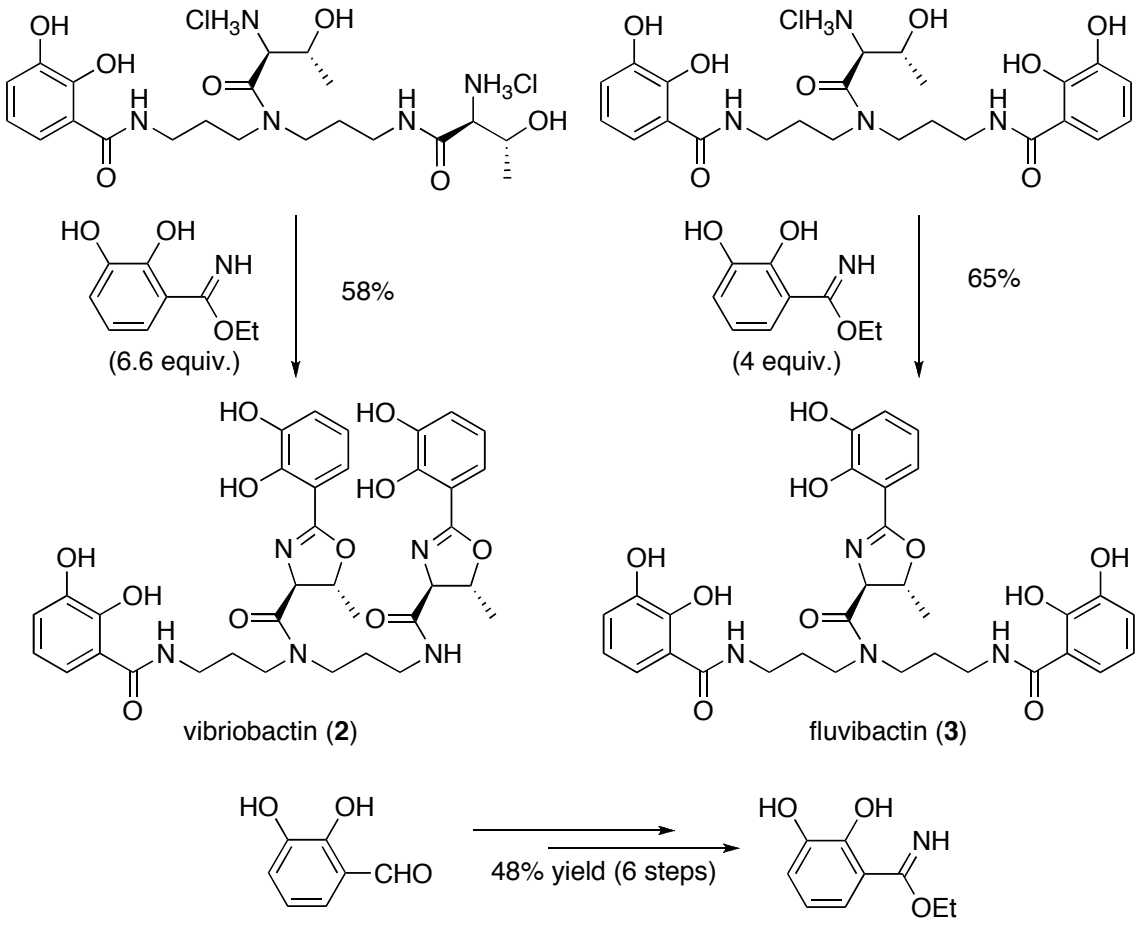


Scheme 1.8. Total Synthesis of BE-70016 from a Useful Oxazoline Building Block

The first total syntheses of vibriobactin (**2**) and fluvibactin (**3**) were reported by Bergeron et al. (Scheme 1.9).[18,19] According to their reports, the synthesis of the 2-(*o,m*-dihydroxyphenyl)oxazoline structure is one of the most problematic steps. They

synthesized the 2-(*o,m*-dihydroxyphenyl)oxazoline moieties by reacting L-threonine amides with 2,3-dihydroxybenzimidate at the last stage of the total synthesis. However, the yields of the products were moderate (65 and 58%), despite the use of large amounts (4 and 6.6 equivalents) of 2,3-dihydroxybenzimidate. It is conceivable that steric hindrance due to the L-threonine amides decreased the yields of **2** and **3**. Moreover, the synthesis of 2,3-dihydroxybenzimidate requires 6 steps (48% overall yield).

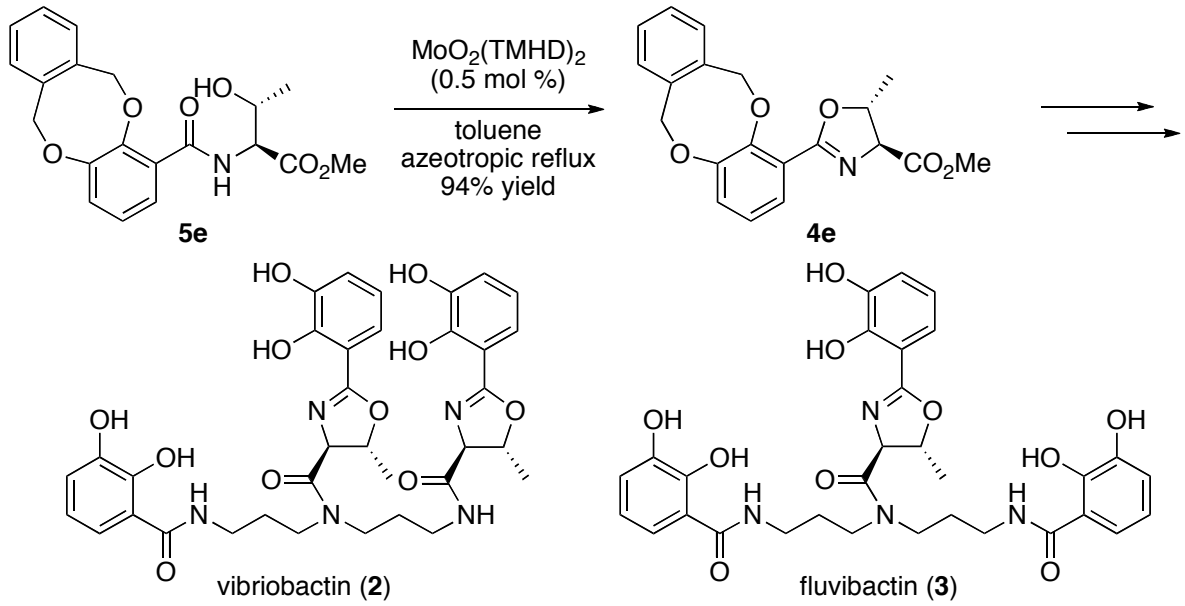
For more efficient total syntheses of **2** and **3**, construction of the 2-(*o,m*-dihydroxyphenyl)oxazoline (**4b**) moiety at an early stage, if possible, would be more desirable. The author planned to synthesize 2-(*o,m*-dialkoxyphenyl)oxazoline from *N*-(*o,m*-dialkoxybenzoyl)-L-threonine using the molybdenum(VI) oxide catalyst. Assembly of the oxazoline, 2,3-dialkoxybenzoate and norspermidine would then convergently give compounds **2** and **3**.[20]



Scheme 1.9. First Syntheses of Vibriobactin (**2**) and Fluvibactin (**3**) by Bergeron

For the syntheses of **2** and **3**, the author first investigated the catalytic dehydrative cyclization of *N*-(*o*,*m*-dihydroxybenzoyl)-L-threonine methyl ester (**5b**) using commercially available molybdenum(VI) oxides. However, the reaction did not proceed with the combination of $(NH_4)_2MoO_4$ and pentafluorobenzoic acid, and this was believed to be due to rapid oxidation of the unprotected catechol. Therefore, the cyclization of *N*-(*o*,*m*-dimethoxybenzoyl)-L-threonine methyl ester (**5c**), in which the catechol moiety is protected by a methyl group, by molybdenum(VI) oxide in the absence of pentafluorobenzoic acid gave the corresponding oxazoline in good yields. Furthermore, the author found that a cyclic *o*-xylylene group[21] was very effective for protection of the catechol moiety (Scheme

1.10). This compact protecting group helped the dehydrative cyclization of L-threonine derivative **5e** to proceed rapidly. In addition, the *o*-xylylene group could be easily removed by conventional hydrogenolysis. Chemoselective Sb(III)-catalyzed ester-amide transformation against norspermidine, as the triamine backbone, under solvent-free conditions was successful.[22] These convergent syntheses should be useful in further studies on synthesis and bioactivity of siderophores. The author describes the convergent syntheses of siderophores in details (Chapter 2).



Scheme 1.10. Total Syntheses of Vibriobactin (**2**) and Fluvibactin (**3**) Using Mo(VI)=O Catalyzed Dehydrative Cyclization as a Key Step

1-3 Catalytic Asymmetric Acylation of Racemic or *Meso* Compounds using a Pyroc Group: A Removable Directing Group

The bengazoles are a family of polyketides isolated from a *Jaspis* sponge that display potent antifungal and anthelmintic activities; they have five hydroxylated chiral carbons (Figure 1.3).[5] Geldanamycin,[6] which was isolated from *Streptomyces hygroscopicus*, is a macrocyclic polyketide bearing four hydroxylated chiral carbons. Geldanamycin interferes with the action of Heat shock protein 90 (Hsp 90). Geldanamycin also has antitumor properties. Many natural products that contain hydroxylated chiral carbons have a variety of biological activities. For the syntheses of these polyketides, efficient methods for obtaining chiral building blocks that contain hydroxylated chiral carbons are needed.

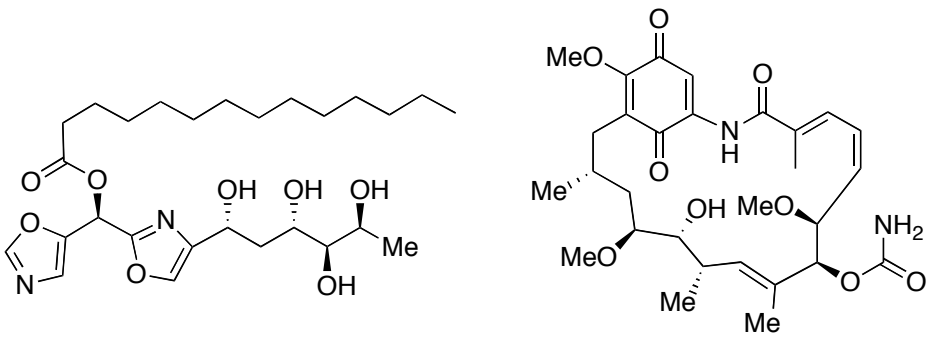
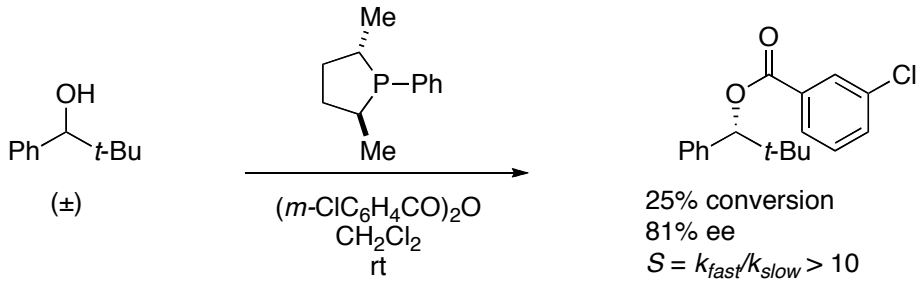


Figure 1.3. Hydroxylated Chiral Carbons Containing Natural Products

The kinetic resolution of racemic alcohols and carboxylic acids through catalytic asymmetric acylation is a convenient and powerful method for obtaining optically active compounds, which are chiral building blocks for the synthesis of polyketides. The first example of the kinetic resolution of racemic alcohols under nonenzymatic acylation catalysts (with $S > 10$) was reported by Vedejs et al. in 1996(Scheme 1.11).[23] Since then, numerous

kinetic resolutions of racemic alcohols have been developed using chiral nucleophilic catalysts. For example, chiral phosphines,[24] chiral DMAP derivatives,[25] chiral amidines,[26] and *N*-alkylimidazole derivatives[27] have been shown to be effective asymmetric acylation catalysts. In particular, Miller's biomimetic approach[27] to the identification of artificial acylases was based on β-turn peptide fragments with defined secondary structures that contain *N*-alkylimidazole residues (Figure 1.4).



Scheme 1.11. Kinetic Resolution Using Chiral Phosphine by Vedejs

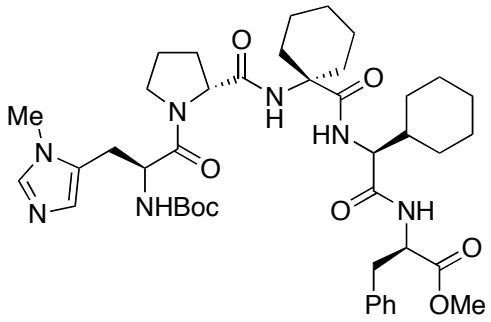
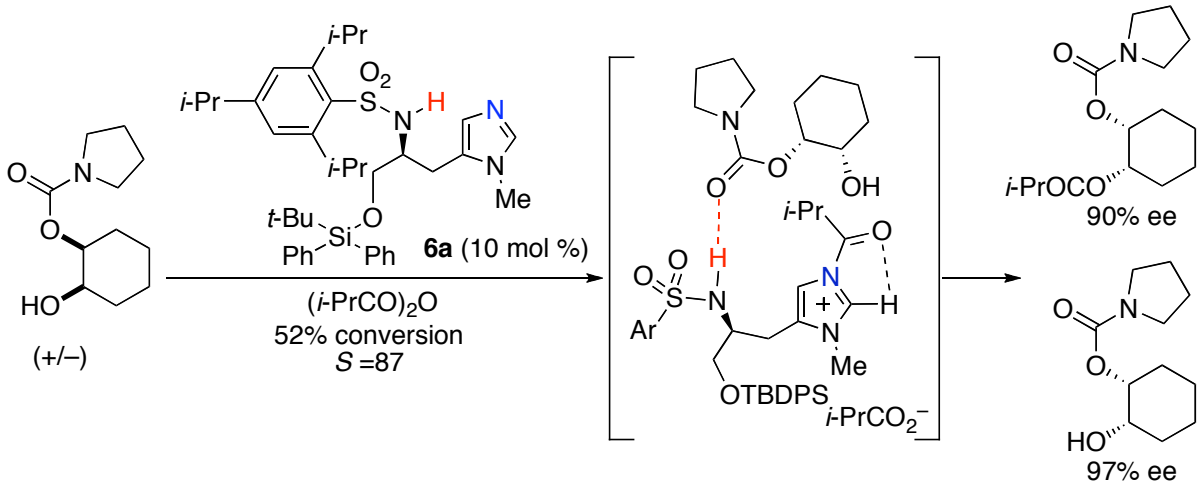


Figure 1.4. Artificial Acylase described by Miller

Recently, our laboratory reported the rational design of L-histidine-derived artificial acylases (**6**) bearing only one chiral carbon center that were derived from natural L-histidine (Scheme 1.12).[8] Catalyst **6** contains an *N*-methylimidazole moiety as a nucleophilic base and a sulfonamidyl proton as a Brønsted acid. The high-level kinetic resolution of

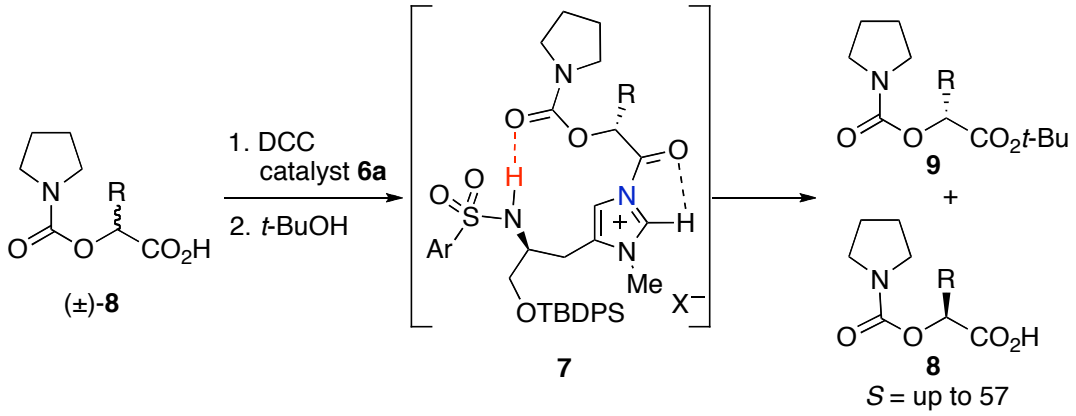
(±)-alcohols can be achieved through hydrogen bonding between the sulfonamidyl proton of **6** and a Brønsted base site of the substrate. Therefore, the introduction of an appropriate Brønsted basic site, such as a carbamoyl oxygen, into the substrate is essential for the effective kinetic resolution catalyzed by **6**. When kinetic resolution of the *cis*-1,2-dihydroxycyclohexane derivative was conducted with isobutyric anhydride, the ester was obtained in 52% conversion with 90% ee (S = 87).



Scheme 1.12. Kinetic Resolution of Racemic 1,2-Diols Using L-Histidine-Derived Organocatalysts

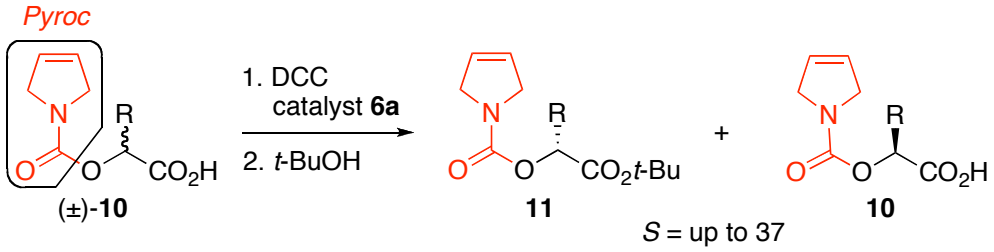
The synthesis of optically active carboxylic acid and ester is also important for the syntheses of natural products such as polyketides. Recently, Shiina et al. reported the kinetic resolution of racemic carboxylic acids using benzotetramisole derivatives as catalysts.[28] Our laboratory has also reported the kinetic resolution of racemic carboxylic acids bearing a pyrrolidine-1-carbonyl group by L-histidine-derived organocatalysts.[29] This report is the first successful example of the direct kinetic resolution of racemic carboxylic acids (±)-**8**. A plausible mechanism of the kinetic control in our method is shown in Scheme 1.13. When a

carboxylic acid is activated with DCC *in situ*, subsequent kinetic resolution of the carboxylic acid (±)-**8** may occur at the generation of acylammonium salt with or without an enantioselective hydrogen bonding interaction between the substrate and catalyst **6**. The reaction of the acylammonium intermediate **7** with *tert*-butyl alcohol gave the corresponding ester **9** with high enantioselectivity.



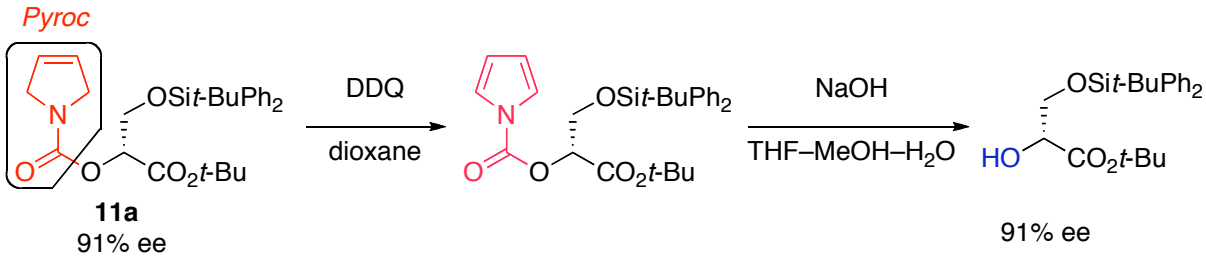
Scheme 1.13. Kinetic Resolution of Racemic Carboxylic Acids Using L-Histidine-Derived Organocatalysts

One major drawback of the present method is that the pyrrolidine-1-carbonyl group in the products is too robust to be removed chemoselectively without epimerization. Therefore, an alternative protecting group, which protects yet can be removed under mild conditions, is urgently needed for the practical application of the present kinetic resolution. The author reports here the 3-pyrroline-1-carbonyl (Pyroc) group and 3-pyrrolinamide as useful protecting groups for the kinetic resolution of racemic α-hydroxycarboxylic acids, β-hydroxycarboxylic acids, 1,2-dicarboxylic acids and 1,2-diols by **6**-induced asymmetric acylation (Scheme 1.14).[30] Pyroc was found to be highly useful for obtaining high selectivity in kinetic resolutions due to the appropriate basicity. The use of Pyroc gave almost the same selectivity as in kinetic resolution using substrates bearing a pyrrolidine-1-carbonyl group.



Scheme 1.14. Kinetic Resolution of Racemic Carboxylic Acids (±)-**10** Bearing a Pyroc Group

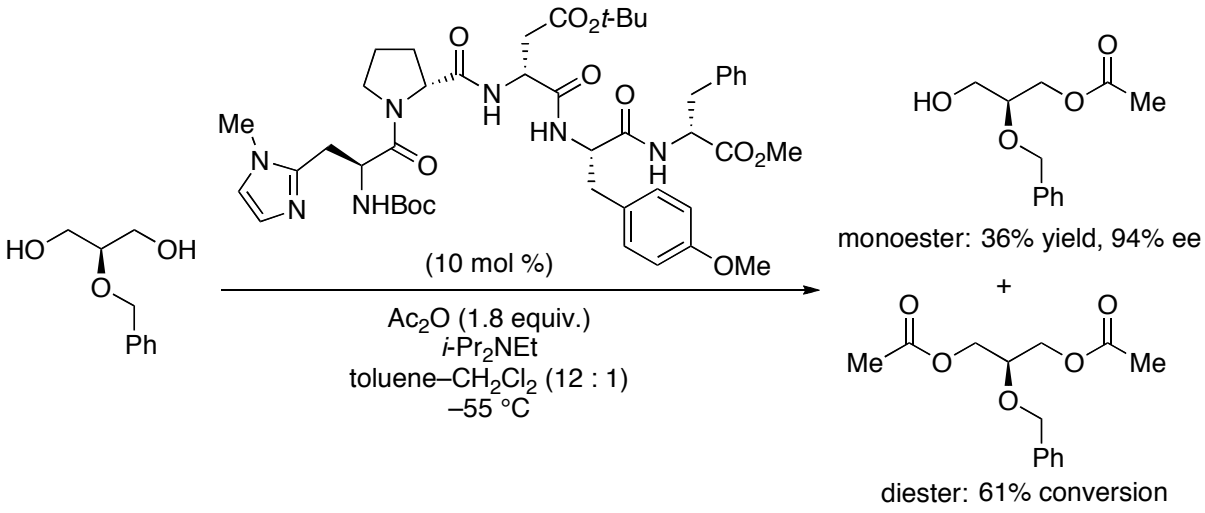
Selective cleavage of the Pyroc group in ester **11a** could be achieved through oxidation using DDQ followed by hydrolysis with NaOH to give α-hydroxyester without epimerization (Scheme 1.15). The resulting chiral esters and carboxylic acids can be used for the synthesis of natural products.



Scheme 1.15. Selective Cleavage of the Pyroc Group in Ester **11a**

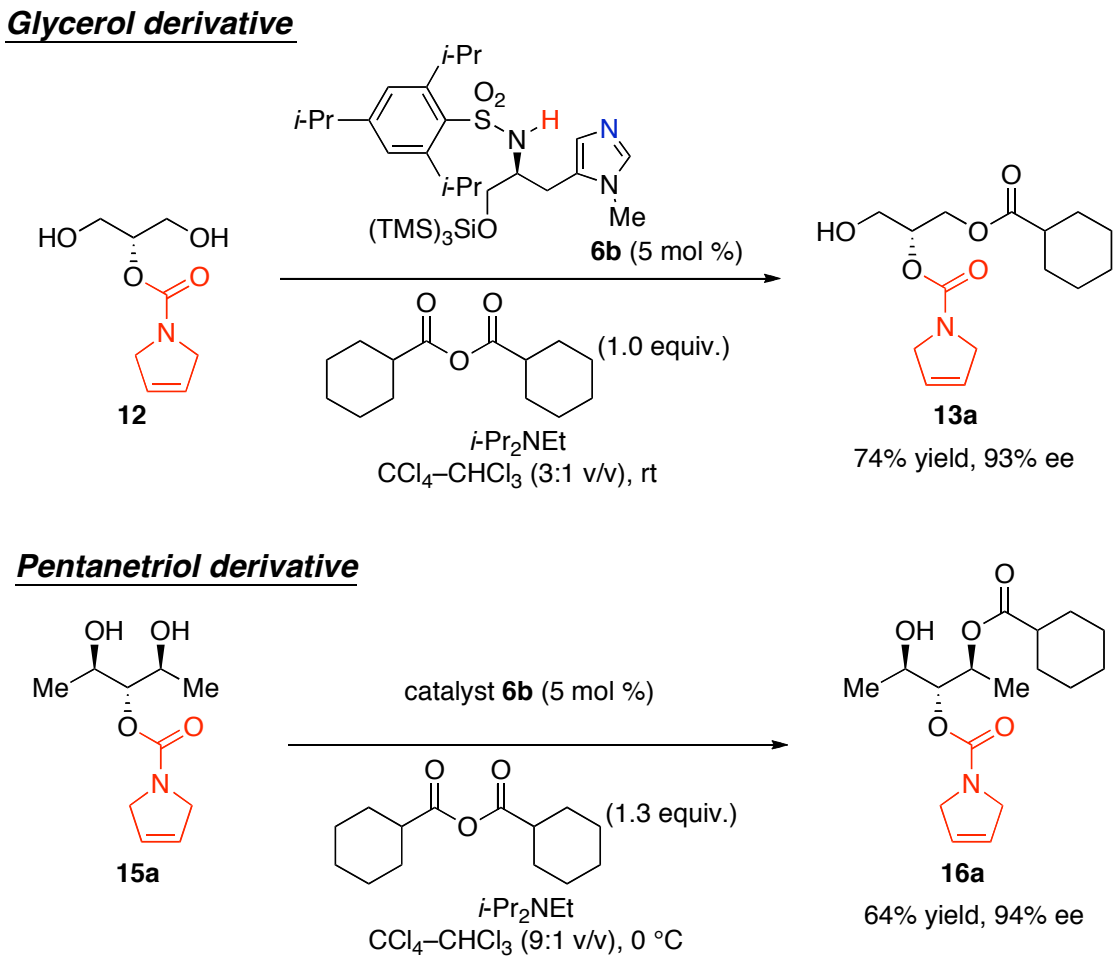
The nonenzymatic desymmetrization of several symmetrical polyols is a challenging issue in organic chemistry.[31,32] The enantioselective desymmetrization of glycerol derivatives is a form of asymmetric synthesis for constructing hydroxylated chiral carbons. A few examples of the nonenzymatic desymmetrization of glycerol derivatives have been described.[31] The only example of desymmetrization using an organocatalyst is the method using pentapeptides reported by Miller (Scheme 1.16).[32] Although the reaction showed high

enantioselectivity (>90% ee), the desired monoester was obtained in low yield. Unfortunately, the undesired diester was obtained with 61% conversion.



Scheme 1.16. Desymmetrization of Glycerol Derivatives by Miller

The author examined the **6**-induced desymmetrization of *meso*-*O*-Pyroc triols (Scheme 1.17). The asymmetric acylation of 2-*O*-Pyroc glycerol **12** with cyclohexane carboxylic anhydride in the presence of **6** and *i*-Pr_2NEt gave the desired monoester **13a** in good yield with high enantioselectivity (74% yield, 93% ee, Scheme 1.17). Moreover, the asymmetric acylation of pentanetriol derivative **15a** also proceeds in moderate yield with high enantioselectivity (64% yield, 94% ee). The author describes here the desymmetrization of *meso*-*O*-Pyroc triols in detail (Chapter 3).



Scheme 1.17. Desymmetrization of Glycerol Derivatives Based on Asymmetric Acylation

References and Notes

1. (a) Walsh, C. T. *Science* **2004**, *303*, 1805. (b) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249.
2. Bergeron, R. J. *Trends Biochem. Sci.* **1986**, *11*, 133.
3. Yamamoto, S.; Okujo, N.; Fujita, Y.; Saito, M.; Yoshida, T.; Shinoda, S. *J. Biochem.* **1993**, *113*, 538.
4. Banker, R.; Carmeli, S. *J. Nat. Prod.* **1998,** *61,* 1248.
5. Adamczeski, M.; Quinoa, E.; Crews, P.; *J. Am. Chem. Soc.* **1988**, *110*, 1598. (b) Searle, P. A.; Richter, R. K.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 4073. (c) Rodriguez, J.; Nieto, R. M.; Crews, P. *J. Nat. Prod.* **1993**, *56*, 2034. (d) Rudi, A.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *J. Nat. Prod.* **1994**, *57*, 829.
6. DeBoer, C.; Meulman, P. A.; Wunk, R. J.; Peterson, D. H. *J. Antibiot.* **1970**, *23*, 442.
7. (a) Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971. (b) Sakakura, A.; Kondo, R.; Umemura, S.; Ishihara, K. *Adv. Synth. Catal.* **2007**, *349*, 1641. (c) Sakakura, A.; Kondo, R.; Umemura, S.; Ishihara, K. *Tetrahedron* **2009**, *65*, 2102.
8. (a) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (b) Kosugi, Y.; Akakura, M.; Ishihara, K. *Tetrahedron* **2007**, *63*, 6191.
9. (a) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464, and references cited therein. (b) Lewis, J. R. *Nat. Prod. Rep.* **2002**, *19*, 223, and references cited therein.
10. Shitakawa, H.; Nakajima, S.; Hirayama, M.; Kondo, H.; Kojiri, K. (Banyu Pharmaceutical Co., Ltd.), *Jpn Kokai Tokkyo*, JP 2000–53660 [*Chem. Abstr.* **2000**, *132*, 150670].
11. Griffiths, G. L.; Sigel, S. P.; Payne, S. M.; Neilands, J. B. *J. Biol.Chem.* **1984**, *259*, 383.
12. Prinsep, M. R.; Moore, R. E.; Levine, I. A.; Patterson, G. M. L. *J. Nat. Prod.* **1992**, *55*, 140.

13. Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc*. **1991**, *113*, 3173.
14. Jin, Z. *Nat. Prod. Rep.* **1999**, *16*, 249.
15. (a) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471. (b) Meyers, A. I.; Denton, H. *Tetrahedron Lett.* **1985**, *26*, 4687. (c) Burrell, G.; Evans, J. M.; Jones,G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649. (d) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (e) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807. (f) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267. (g) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975. (h) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358. (i) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826. (j) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett.* **1992**, 153. (k) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (l) Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 8679.
16. Sakakura, A.; Umemura, S.; Kondo, R.; Ishihara, K. *Adv. Synth. Catal.* **2007**, *349*, 551.
17. Sasaki, T.; Otani, T.; Yoshida, K.; Unemi, N. *J. Antibiot*. **1997**, *50*, 881.
18. Bergeron, R. J.; Garlich, J. R.; McManis, J. S. *Tetrahedron* **1985**, *41*, 507.
19. Bergeron, R. J.; Xin, M. G.; Weimar, W. R.; Smith, R. E.; Wiegand, J. *J. Med. Chem.* **2001**, *44*, 2469.
20. Sakakura, A.; Umemura, S.; Ishihara, K. *Chem. Commun.* **2008**, 3561.
21. For using sugar; Balbuena, P; Rubio, E. R.; Ortiz Mellet, C.; García Fernández, J. M. *Chem. Commun.* **2006**, 2610.
22. (a) Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 1569. (b) Kuroki, Y.; Ishihara, K.; Hanaki, N.; Ohara, S.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1221.
23. Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809.
24. Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166.

25. (a) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542, and references therein. (b) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. (c) Spivey, A. C.; Fekner, T.; Spay, S. E. *J. Org. Chem.* **2000**, *65*, 3154. (d) Kawabata, T.; Yamamoto, K.; Homose, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Commun.* **2001**, 2700. (e) Kawabata, T.; Stragies, R.; Fukaya, T.; Fuji, K. *Chirality* **2003**, *15*, 71. (f) Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Schedel, H. *J. Am. Chem. Soc.* **2007**, *129*, 12890.

26. (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (c) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (d) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (e) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859. (f) Hu, B.; Meng, M.; Wang, Z.; Du, W. Fossey, J. S.; Hu, X.; Deng, W.-P. *J.Am. Chem. Soc.* **2010**, *132*, 17041.

27. (a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (b) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2824. (c) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.

28. (a) Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887. (b) Shiina, I.; Nakata, K.; Ono, K.; Onda, Y.; Itagaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11629.

29. Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191.

30. Sakakura, A.; Umemura, S.; Ishihara, K. *Synlett* **2009**, 1647.

31. (a) Jung, B.; Hong, M. S.; Kang, S. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2616. (b) Hong, M. S.; Kim, T. W.; Jung, B.; Kang. S. H. *Chem. Eur. J.* **2008**, *14*, 3290. (c) Mitsuda, M.; Tanaka, T.; Tanaka, T.; Demizu, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 8073. (d) Honjo, T.; Nakao, M.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y.; Nagao, Y. *Org. Lett.* **2007**, *9*, 509. (e) Sano, S.; Tsumura, T.; Tanimoto, N.; Honjo, T.; Nakao, M.; Nagao, Y. *Synlett* **2010**, 256.

32. (a) Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021. (b) Fiori, K. W.; Puchlopek, A. L. A.; Miller, S. J. *Nat. Chem.* **2009**, *1*, 630.

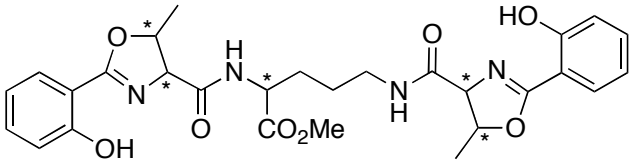
Chapter 2

Convergent Total Syntheses of Oxazoline-Containing Natural Products

2-1 Dehydrative Cyclization Catalyzed by the Combination of Molybdenum(VI) Oxides and Benzoic Acids: First Synthesis of the Antitumor Substance BE-70016

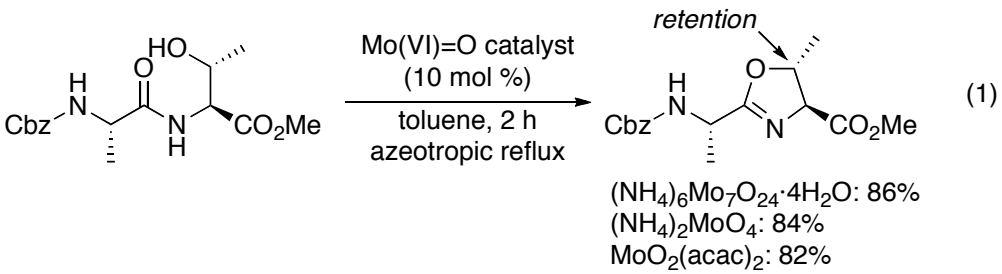
Abstract: The dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivative **5a** is efficiently promoted by the combined use of molybdenum(VI) oxides and benzoic acids bearing electron-withdrawing substituents. In the presence of $(NH_4)_2MoO_4$ (10 mol %) and $C_6F_5CO_2H$ (10 mol %), dehydrative cyclization of **5a** was conducted in toluene under azeotropic reflux conditions to give 2-(*o*-hydroxyphenyl)oxazoline **4a** in 76% yield. Furthermore, the first total synthesis of the antitumor substance BE-70016 was achieved using the catalytic dehydrative cyclization of **5a** 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 tumours. 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.



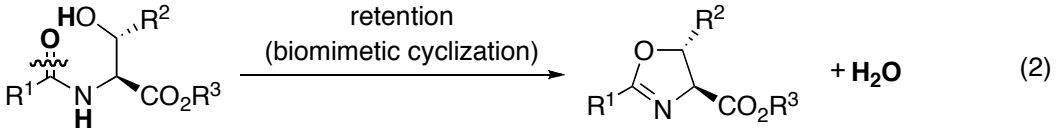
BE-70016

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]

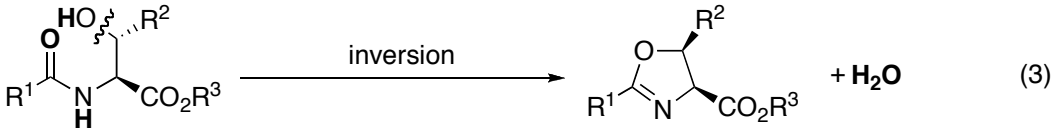


(1)

There are two known methodologies for the chmical 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.



(2)

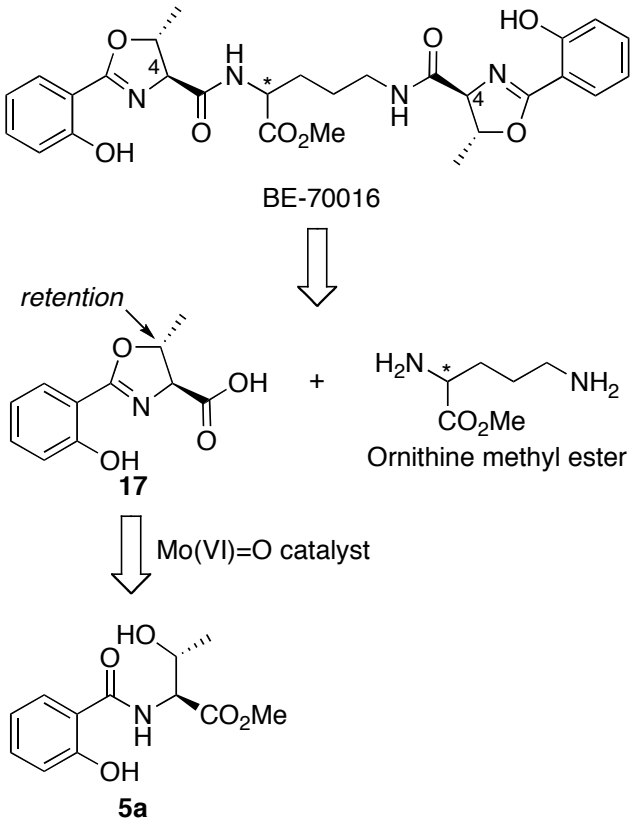


(3)

We report here the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivative **5a** 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 2.1 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 **17** 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 **13** could be prepared from L-threonine by molybdenum oxide-catalyzed dehydrative cyclization with a retention of configuration at the β-position.

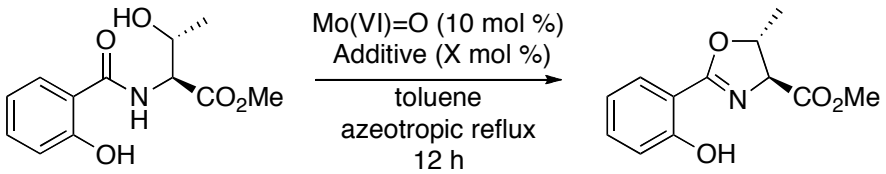


Scheme 2.1. Retrosynthesis of BE-70016

We initially investigated the dehydrative cyclization of **5a** to **4a** using molybdenum(VI) oxides as catalysts (Table 2.1). Compound **4a** 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 **5a** 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 (TsOH) did not promote the reaction of **5a** (entry 3). The catalytic activity of TsOH itself was also very low (entry 12), although it

shows good catalytic activity for the dehydrative cyclization of *N*-(*p*-methoxybenzoyl)-L-threonine methyl ester.[5g] Very interestingly, some benzoic acids bearing electron-withdrawing substituents efficiently promoted the molybdenum(VI) oxide-catalyzed dehydrative cyclization of **5a**. 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 **5a** 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 **4a** 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 **4a**. Actually, the reaction of *N*-(*o*-methoxybenzoyl)-L-threonine methyl ester (**5f**) proceeded well even in the absence of benzoic acids to give oxazoline **4f** 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 **4a** was decreased without an aqueous workup also supported the formation of stable complexes of the molybdenum(VI) oxide with **4a**.

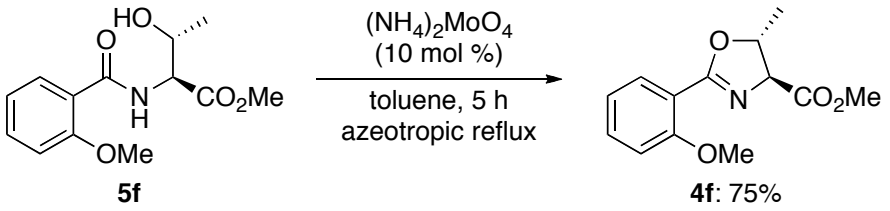
Table 2.1. Dehydrative Cyclization of *N*-(*o*-Hydroxybenzoyl)threonine Methyl Ester (**5a**)[a]



5a **4a**

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	$(NH_4)_2MoO_4$	$3,5\text{-}(CF_3)_2C_6H_3CO_2H$	10	76
9	$(NH_4)_2MoO_4$	$4\text{-}(NO_2)C_6H_4CO_2H$	10	67
10	$MoO_2(acac)_2$	$C_6F_5CO_2H$	10	76[c]
11	$MoO_2(acac)_2$	$3,5\text{-}(CF_3)_2C_6H_3CO_2H$	10	79
12	—	TsOH	10	19
13	—	$C_6F_5CO_2H$	10	1
14	—	$3,5\text{-}(CF_3)_2C_6H_3CO_2H$	10	0

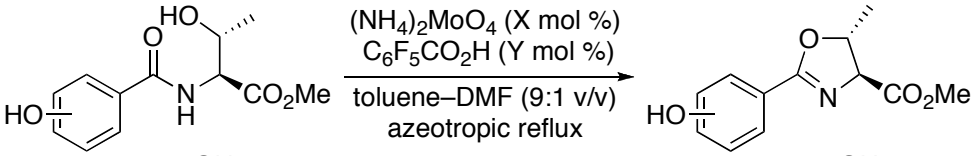
[a] The reaction of **5a** (1 mmol) was conducted in toluene (10 mL) under azeotropic reflux conditions. [b] Evaluated by ^{1}H NMR analysis. [c] The reaction was conducted for 10 h. [d] The reaction was conducted for 11 h.



(4)

Next, we examined the dehydrative cyclization of *m*- and *p*-hydroxy derivatives **5g** and **5h** (Table 2.2). Since **5g** and **5h** did not dissolve in toluene, the reaction was conducted in toluene–DMF (9:1 v/v). When the reaction of **5h** was conducted in the presence of $(NH_4)_2MoO_4$ (10 mol %) and $C_6F_5CO_2H$ (10 mol %), the corresponding oxazoline **4h** was obtained in 88% yield (entry 1). Interestingly, in contrast to the reaction of **5a**, the reactions of **5h** and **5g** proceeded smoothly in the absence of pentafluorobenzoic acid, to give **4h** and **4g** in respective yields of 87 and 91% (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 **4a** and **4h** to molybdenum(VI) oxides should be stronger than that of **4g** due to the resonance effect of the hydroxyl group at *o*- and *p*-positions. The higher reactivity of **5g** compared to those of **5a** and **5h** can be explained by the faster release of **4g** from the catalyst compared to **4a** and **4h**. Since **4a** was obtained in 18% yield when the reaction of **5a** 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 **5a**, which was soluble in toluene.[6]

Table 2.2. Dehydrative Cyclization of *m*- and *p*-Hydroxy Derivatives **5g** and **5h**[a]



5a: *o*-OH
5g: *m*-OH
5h: *p*-OH

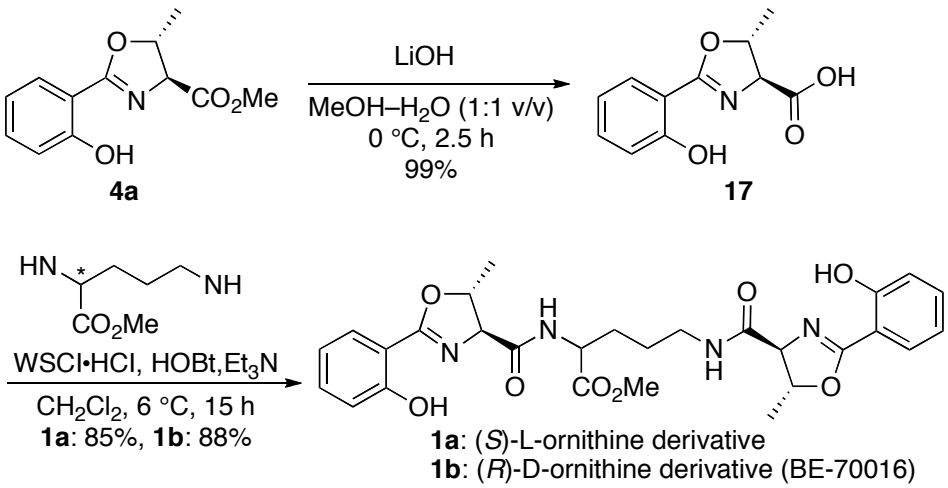
4a: *o*-OH
4g: *m*-OH
4h: *p*-OH

entry	substrate	$(NH_4)_2MoO_4$ (mol %)	$C_6F_5CO_2H$ (mol %)	time (h)	yield (%)[b]
1	**5h**	10	10	2	88
2	**5h**	2	0	4	87
3	**5g**	2	0	1	91
4	**5a**	10	10	10	18

[a] The reaction of **5g** or **5h** (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 (**4a**) for the synthesis of BE-70016 in hand, we investigated the synthesis of BE-70016 (Scheme 2.2). Hydrolysis of **4a** with lithium hydroxide gave carboxylic acid **17** in quantitative yield. The condensation of ornithine methyl esters was conducted with **17** (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 **1a** and (*R*)-D-ornithine derivative **1b** in respective yields of 85 and 88%. As shown in Table 2.3, some signals in the ^{1}H NMR spectra of **1a** were obviously different from those of natural BE-70016 and **1b**. Based on a comparison of IR, ^{1}H and ^{13}C NMR, HRMS and specific rotation ($[\alpha]_D$), **1b** was found to be identical to natural BE-70016. Thus, we have elucidated the stereochemical structure of BE-70016 as depicted in formula **1b**, 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 **5a** as a key reaction.



Scheme 2.2. Synthesis of BE-70016

Table 2.3. Selected Spectral Data of Natural BE70016, and Synthetic Products **13** and **1**

	natural BE-70016	**1a**	**1b**	
^{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

1. (a) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464 and references cited therein. (b) Lewis, J. R. *Nat. Prod. Rep.* **2002**, *19*, 223 and references cited therein. (c) Roy, R. S.; Gehring,A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249.
2. Shitakawa, H.; Nakajima, S.; Hirayama, M.; Kondo, H.; Kojiri, K. (Banyu Pharmaceutical Co., Ltd.), *Jpn Kokai Tokkyo*, JP 2000–53660 [*Chem. Abstr.* **2000**, *132*, 150670].
3. Bergeron, R. J. *Trends Biochem. Sci.* **1986**, *11*, 133.
4. (a) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471. (b) Meyers, A. I.; Denton, H. *Tetrahedron Lett.* **1985**, *26*, 4687. (c) Burrell, G.; Evans, J. M.; Jones,G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649. (d) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (e) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807. (f) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267. (g) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett.* **1992**, 153. (h) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (i) Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 8679.
5. (a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem*. **1992**, *57*, 5566. (b) Zhou, P.; Blubaum, J. E.; Burns, C. T.; Natale, N. R. *Tetrahedron Lett.* **1997**, *38*, 7019. (c) Kuriyama, N.; Akaji, K.; Kiso, Y. *Tetrahedron* **1997**, *53*, 8323. (d) Raman, P.; Razavi, H.; Kelly, J. K. *Org. Lett.* **2000**, *2*, 3289. (e) Wipf, P.; Wang, X.; *J. Comb. Chem.* **2002**, *4*, 656. (f) Cwik, A.; Hell, Z.; Hegedüs, A.; Finta, Z.; Horváth, Z. *Tetrahedron Lett.* **2002**, *43*, 3985. (g) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230.
6. Sakakura,; A. Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971.
7. Boden, C. D. J.; Pattenden, G. *Tetrahedron Lett.* **1995**, *36*, 6153. (b) Boden, C. D. J.;

Norley, M. C.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 9111. (c) Norley, M. C.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 3087. (d) Boden, C. D. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 875. (e) Boden, C. D. J.; Norley, M. C.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 883. (f) Yokokawa, F.; Sameshima, H.; Shioiri, T. *Synlett* **2001**, 986. (g) Kutsumura, N.; Sata, N. U.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 847.

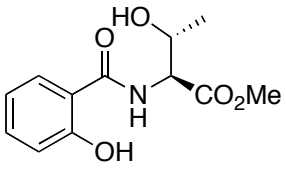
8. Wipf reported the conversion of *cis*-oxazolines, which were prepared from L-threonine derivatives with Burgess reagent, to *trans*-oxazolines by sequential treatment with 0.3 M HCl, K_2CO_3, and Burgess reagent. (a) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975. (b) Wipf, P.;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

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. (b) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2002**, *4*, 3399.

Experimental Section

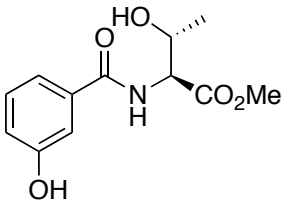
General Methods.

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; q = quartet; 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 Center, Nagoya University. Dry toluene was purchased from Wako as the "anhydrous" and stored under nitrogen. Dichloromethane and triethylamine were freshly distilled from calcium hydride. $(NH_4)_2MoO_4$ (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.

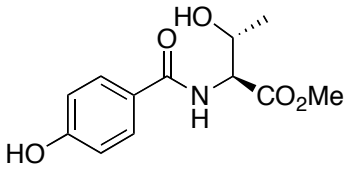


***N*-(*o*-Hydroxybenzoyl)-L-threonine methyl ester (5a).** To a solution of L-threonine methylester (1.70 g, 10 mmol), salicylic acid (1.38 g, 10 mmol), HOBt (135 mg, 1.0 mmol) and Et_3N (1.39 mL, 10 mmol) in CH_2Cl_2 (30 mL) was added a solution of WSCI•HCl (2.11 g, 11 mmol) in CH_2Cl_2 (30 mL) at 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 ×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 **5a** (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.

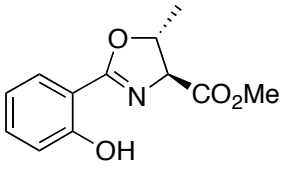


***N*-(*m*-Hydroxybenzoyl)-L-threonine methyl ester (5g):** colorless oil; IR (neat) 3366, 1739, 1644, 1585, 1530, 1486, 1439, 1316, 1217, 1158, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.6 Hz, 3H), 3.77 (s, 3H), 4.38 (dq, *J* = 3.3, 6.6 Hz, 1H), 4.66 (d, *J* = 3.3 Hz, 1H), 6.97 (td, *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.

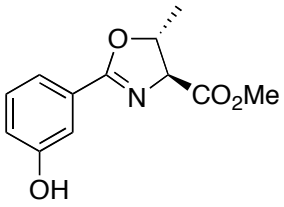


***N*-(*p*-Hydroxybenzoyl)-L-threonine methyl ester (5h):** colorless oil; IR (neat) 3358, 1740, 1640, 1609, 1588, 1541, 1507, 1439, 1281, 1239, 1177, 1111, 1084,

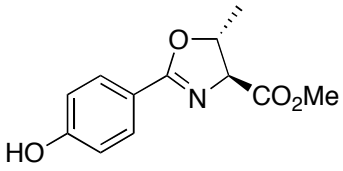
1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J = 6.6 Hz, 3H), 3.75 (s, 3H), 4.37 (dq, J = 3.3, 6.6 Hz, 1H), 4.66 (d, J = 3.3 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 52.9, 59.7, 68.6, 116.2, 125.6, 130.5, 162.4, 170.2, 172.8; HRMS (FAB) calcd for $C_{12}H_{16}NO_5$ $[M+H]^+$ 254.1028, found 254.1018.



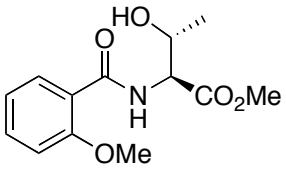
Preparation of Methyl (4*S*,5*R*)-2-(*o*-Hydroxyphenyl)-5-methyl-4-oxazolinecarboxylate (4a). A solution of **5a** (253 mg, 1 mmol), $(NH_4)_2MoO_4$ (20 mg, 0.10 mmol) and $C_6F_5CO_2H$ (21 mg, 0.10 mmol) in toluene (10 mL) was heated at azeotropic reflux with the removal of water using a Dean-Stark 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 **4a**: 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 (4g): 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.

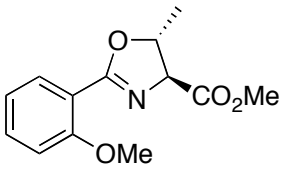


Methyl (4*S*,5*R*)-2-(*p*-hydroxyphenyl)-5-methyl-4-oxazolinecarboxylate (4h): colorless crystal (cryst. from EtOAc); mp 156–157 °C; IR (KBr) 1730, 1601, 1514, 1446, 1372, 1349, 1245, 1165, 1089, 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.3 Hz, 3H), 3.78 (s, 3H), 4.44 (d, *J* = 6.9 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.

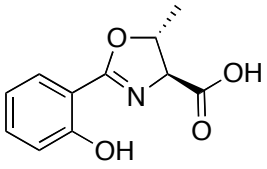


***N*-(*o*-Methoxybenzoyl)-L-threonine methyl ester (5f):** colorless oil; IR (neat) 3381, 1739, 1642, 1601, 1531, 1484, 1299, 1242, 1211, 1162, 1047, 1020 cm^{-1}; ^1H

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.

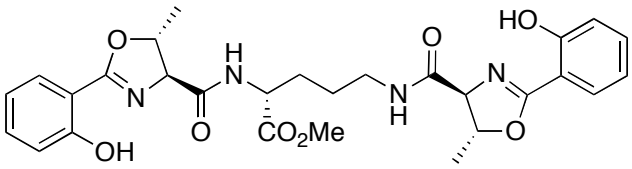


Methyl (4*S*,5*R*)-2-(*o*-methoxyphenyl)-5-methyl-4-oxazolinecarboxylate (4f): colorless oil; IR (KBr) 1739, 1631, 1601, 1493, 1468, 1437, 1344, 1271, 1212, 1126, 1084, 1043, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, J = 6.3 Hz, 3H), 3.80 (s, 3H), 3.91 (s, 3H), 4.51 (d, J = 7.5 Hz, 1H), 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.



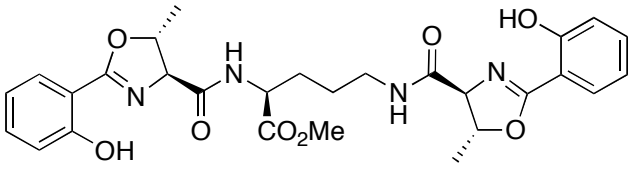
Preparation of (4*S*,5*R*)-2-(*o*-Hydroxyphenyl)-5-methyl-4-oxazolinecarboxylic acid (17). To a solution of **5a** (588 mg, 2.5 mmol) in methanol (10 mL) was added a 1.0 M aqueous solution of LiOH (10 mL, 10 mmol) at ambient temperature, and the mixture was stirred for 2.5 h. The reaction mixture was 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 **17** (550 mg, 99%): colorless amorphous powder, IR (KBr) 1732, 1637, 1491, 1446,

1372, 1308, 1259, 1158, 1133, 1073, 1037 cm^{-1}; ^1H 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 (1b). To a solution of **17** (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 **1** (340 mg, 88%): colorless amorphous powder; $[\alpha]^{23}_D$ +10.6 (MeOH, *c* 0.25); IR (KBr) 3352, 1743, 1668, 1637, 1613, 1523, 1490, 1445, 1372, 1350, 1310, 1258, 1227, 1157, 1134, 1074, 1039 cm^{-1}; ^1H 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.



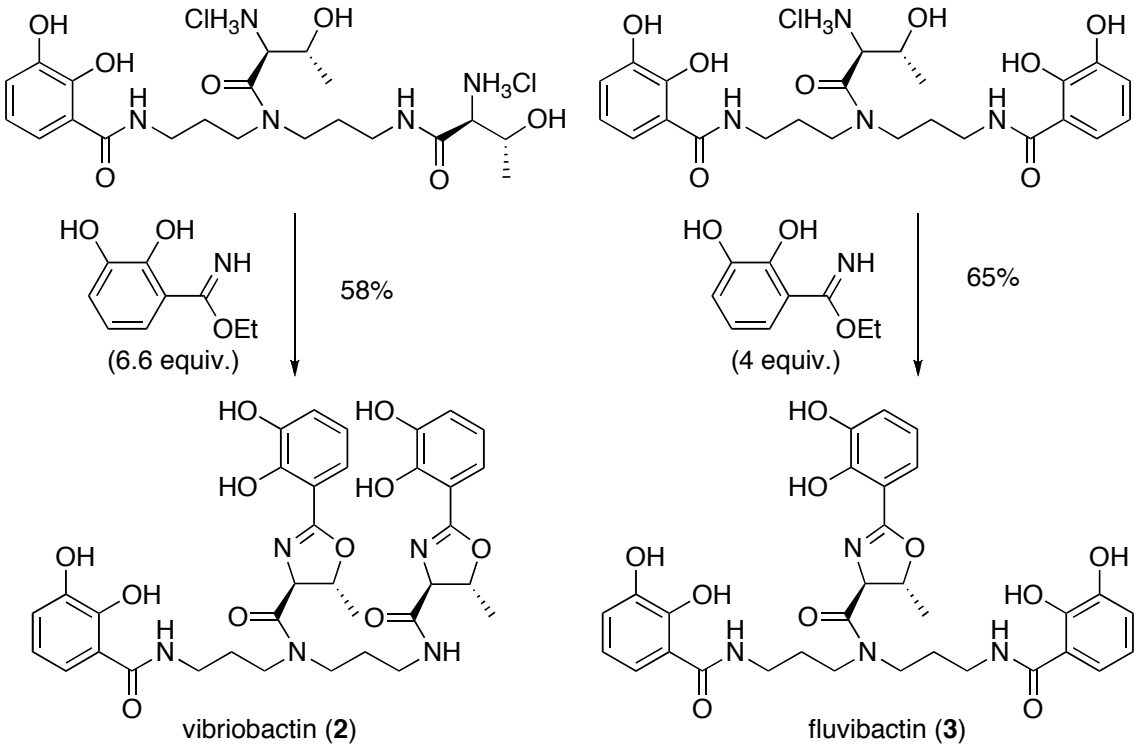
(*S*)-Ornithine derivative (1b). 1b was prepared according to the same manner with **1a** using (*S*)-L-ornithine methylester instead of (*R*)-D-ornithine methyl ester: 85% yield; colorless amorphous powder; $[a]^{23}_D$ +1.6 (CH_3OH, *c* 0.25); IR (KBr) 1740, 1655, 1610, 1534, 1490, 1444, 1374, 1354, 1309, 1260, 1228, 1212, 1158, 1134, 1072, 1046 cm^{-1}; ^{1}H 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.

2-2 Convergent Total Syntheses of Fluvibactin and Vibriobactin Using Molybdenum(VI) Oxide-Catalyzed Dehydrative Cyclization as a Key Step

Abstract: Convergent total syntheses of vibriobactin (**2**) and fluvibactin (**3**) are described. Cyclic *o*-xylyl protection allows the $MoO_2(TMHD)_2$-catalyzed dehydrative cyclization of **4e** to proceed rapidly, to give oxazoline **5e** in 94% yield. Assembly of **5e**, *o*-xylyl-protected 2,3-dihydroxybenzoate and norspermidine gives **2** and **3** in good overall yields.

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] Vibriobactin (**2**)[2] and fluvibactin (**3**)[3] are representative catecholate siderophores that have been isolated from low-iron cultures of *Vibrio cholerae* and *Vibrio fluvialis*, respectively. These compounds consist of a norspermidine backbone with 2-(*o,m*-dihydroxyphenyl)oxazoline-4-carboxylate and 2,3-dihydroxybenzoate moieties. They serve as Fe(III) ion-specific chelators and facilitate Fe(III) ion uptake.[4] These siderophores have been attracting much attention from researchers, and several reports concerning their chemical syntheses, biosyntheses and biological activities have been published.[5]

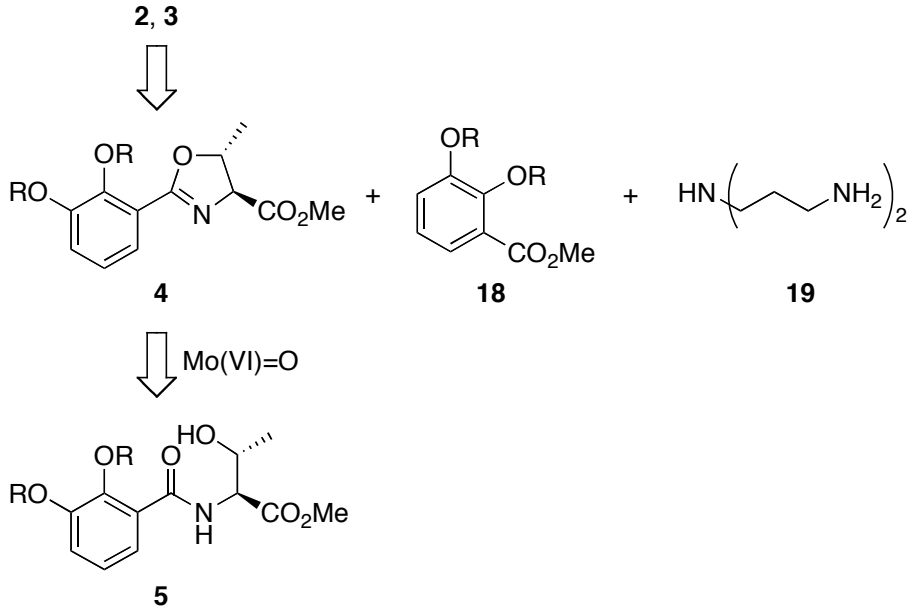
The first total syntheses of **2**[6] and **3**[7] were reported by Bergeron et al.[8] According to their reports, synthesis of the 2-(*o,m*-dihydroxyphenyl)oxazoline structure is one of the most problematic steps. They synthesized the 2-(*o,m*-dihydroxyphenyl)oxazoline moieties by reacting L-threonine amides with 2,3-dihydroxybenzimidate at the last stage of the total synthesis (Scheme 2.3). However, the yields of the products were moderate (58 and 65%), despite the use of large amounts (6.6 and 4 equivalents) of 2,3-dihydroxybenzimidate. It is conceivable that steric hindrance of the L-threonine amides decreased the yields of **2** and **3**. Moreover, the synthesis of 2,3-dihydroxybenzimidate requires 6 steps (48% overall yield).[8b, 9] For more efficient total syntheses of **2** and **3**, construction of the 2-(*o,m*-dihydroxyphenyl)oxazoline moiety at an early stage, if possible, would be more desirable.



Scheme 2.3. Bergeron's First Total Syntheses of Vibriobactin (**2**) and Fluvibactin (**3**)

Recently, we reported that molybdenum(VI) oxides were highly effective dehydrative cyclization catalysts for the synthesis of oxazolines and thiazolines.[10] As in biosynthesis, the molybdenum(VI) oxide-catalyzed dehydrative cyclization of L-threonine derivatives proceeds with retention of configuration at the β-position of the threonine residue. Therefore, this catalytic method is quite useful for the synthesis of naturally occurring oxazolines derived from an L-threonine residue. This Mo(VI)=O-catalyzed method was effective for the synthesis of (*o*-hydroxyphenyl)oxazolines, and we achieved the first synthesis of BE-70016, an antitumor substance, using the Mo(VI)=O-catalyzed method as a key step.[11] Since the Mo(VI)=O-catalyzed method was expected to work for the synthesis of 2-(*o,m*-dihydroxyphenyl)oxazoline structures, we investigated the total syntheses of **2** and **3** using Mo(VI)=O-catalyzed dehydrative cyclization as a key step.

Our plan for the convergent synthesis of vibriobactin (**2**) and fluvibactin (**3**) is illustrated in Scheme 2.4. We planned to synthesize 2-(*o,m*-dialkoxyphenyl)oxazoline **4** at an early stage from *N*-(*o,m*-dialkoxybenzoyl)-L-threonine **5** *via* the Mo(VI)=O-catalyzed method. Compounds **2** and **3** would be synthesized by the assembly of **4**, 2,3-dialkoxybenzoate **18** and norspermidine (**19**).



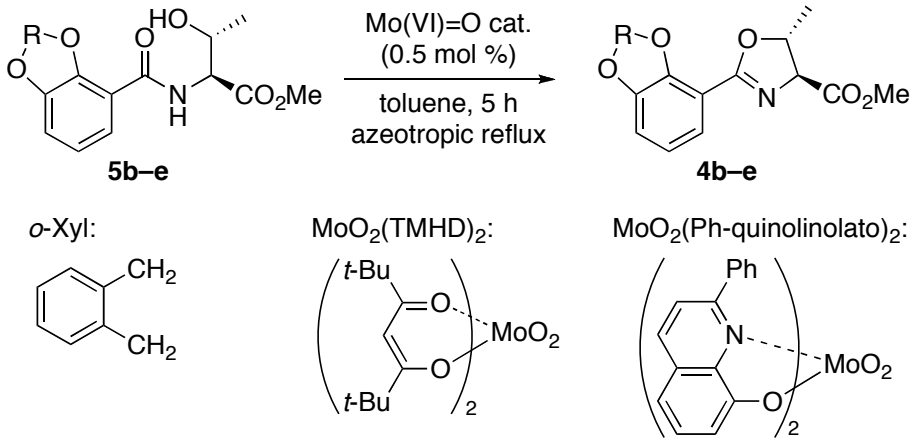
Scheme 2.4. Plan for the Synthesis of **2** and **3**

First, we investigated the molybdenum(VI) oxide-catalyzed dehydrative cyclization of **5** (Table 2.4). Recently, we reported that the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-L-threonine methyl ester could proceed using the combination of $(NH_4)_2MoO_4$ and pentafluorobenzoic acid ($C_6F_5CO_2H$), even without protection of the *o*-hydroxyl group, to give the corresponding oxazoline in good yield.[11] However, the combination of $(NH_4)_2MoO_4$ and $C_6F_5CO_2H$ did not work for the dehydrative cyclization of *N*-(*o,m*-dihydroxybenzoyl)-L-threonine methyl ester (**5b**) (entries 1 and 2), probably due to rapid oxidation of the unprotected catechol moiety of **5b**. The present Mo(VI)=O-catalyzed

reaction required protection of the catechol moiety. In fact, *N*-(*o,m*-dimethoxybenzoyl)threonine methyl ester (**5c**) showed good reactivity for $(NH_4)_2MoO_4$-catalyzed dehydrative cyclization under azeotropic reflux conditions in toluene, to give the corresponding oxazoline **5c** in 88% yield (entry 3). Methyl protection of the hydroxyl groups completely suppressed decomposition of the catechol moiety. Unfortunately, such methyl protection was difficult to remove at the last stage of our synthesis of **2** and **3**. Therefore, we investigated other protecting groups that could be more easily removed at the last step. Benzyl-protected substrate **5d** showed lower reactivity than **5c**, giving oxazoline **4d** in 46% yield (entry 4). The bulkiness of the benzyl group might decrease the reactivity of **5d**. In contrast to methyl protection, the benzyl groups in **4d** could be easily removed by conventional hydrogenolysis (H_2, Pd/C). Therefore, we examined other Mo(VI)=O catalysts for the dehydrative cyclization of **5d**. As a result, commercially available $MoO_2(acac)_2$ and $MoO_2(TMHD)_2$ were found to have good catalytic activities, and gave **4d** in respective yields of 77 and 91% (entries 5 and 6). Corey *et al.* reported the dehydrative cyclization of *p*-methoxybenzoyl-L-threonine methyl ester using TsOH (10 mol %) as a catalyst.[12] However, the catalytic activity of TsOH was lower than that of $MoO_2(TMHD)_2$ for the reaction of **5d** (entry 7).

Further investigation of the protecting groups for the hydroxyl groups of the catechol moiety revealed that compound **5e** protected by a cyclic *o*-xylylene group (*o*-Xyl)[13] showed excellent reactivity. When the reaction of **5e** was conducted with 10 mol % of $(NH_4)_2MoO_4$, oxazoline **4e** was obtained in 96% yield (entry 8). Very interestingly, only 0.5 mol % of $MoO_2(TMHD)_2$ efficiently promoted the reaction of **5e** to give **4e** in 94% yield (entry 9). The high reactivity of **5e** might be attributed to the lower steric hindrance of the *o*-xylylene group. Furthermore, the *o*-xylylene group in **4e** could be easily removed by conventional hydrogenolysis (H_2, Pd/C).

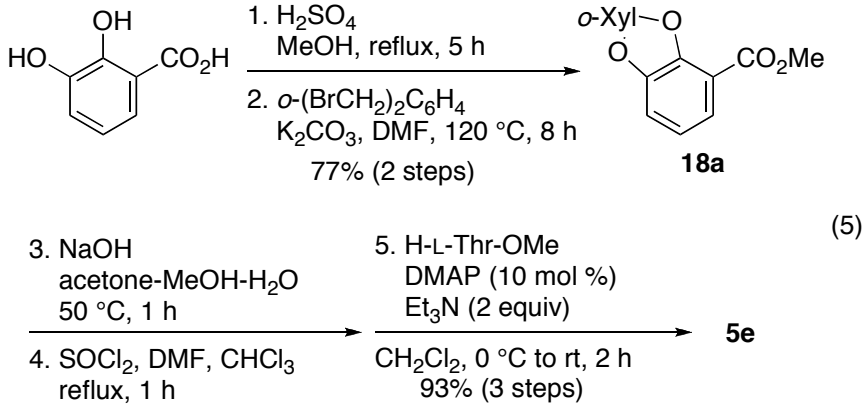
Table 2.4. Mo(VI)=O-Catalyzed Dehydrative Cyclization of **5b-e** [a]



entry	R (**5**)	Mo(VI)=O cat. (mol %)[b]	yield (%)[c]
1	H, H (**5b**)	$(NH_4)_2MoO_2$, 10	0
2[d]	H, H (**5b**)	$(NH_4)_2MoO_2$, 10	10
3	Me, Me (**5c**)	$(NH_4)_2MoO_2$, 10	88
4	Bn, Bn (**5d**)	$(NH_4)_2MoO_2$, 10	46
5	Bn, Bn (**5d**)	$MoO_2(acac)_2$, 10	77
6	Bn, Bn (**5d**)	$MoO_2(TMHD)_2$, 10	91
7[e]	Bn, Bn (**5d**)	TsOH, 10	44
8	*o*-Xyl (**5e**)	$(NH_4)_2MoO_2$, 10	96
9	*o*-Xyl (**5e**)	$MoO_2(TMHD)_2$, 0.5	94 [90][f]
10	*o*-Xyl (**5e**)	MoO_2(Ph-quinolinolato)$_2$, 1	83

[a] The reaction of **6** (1 mmol) was conducted with molybdenum(VI) oxide (10 mol %) in toluene (100 mL) under azeotropic reflux conditions for 5 h. [b] The amount of catalyst was calculated based on the metal. [c] Determined by ^{1}H NMR analysis. [d] The reaction was conducted in the presence of $C_6F_5CO_2H$ (10 mol %) in mesitylene–DMF (9:1 v/v) for 12 h. [e] The reaction was conducted in toluene (3 mL). [f] The reaction was conducted for 3 h.

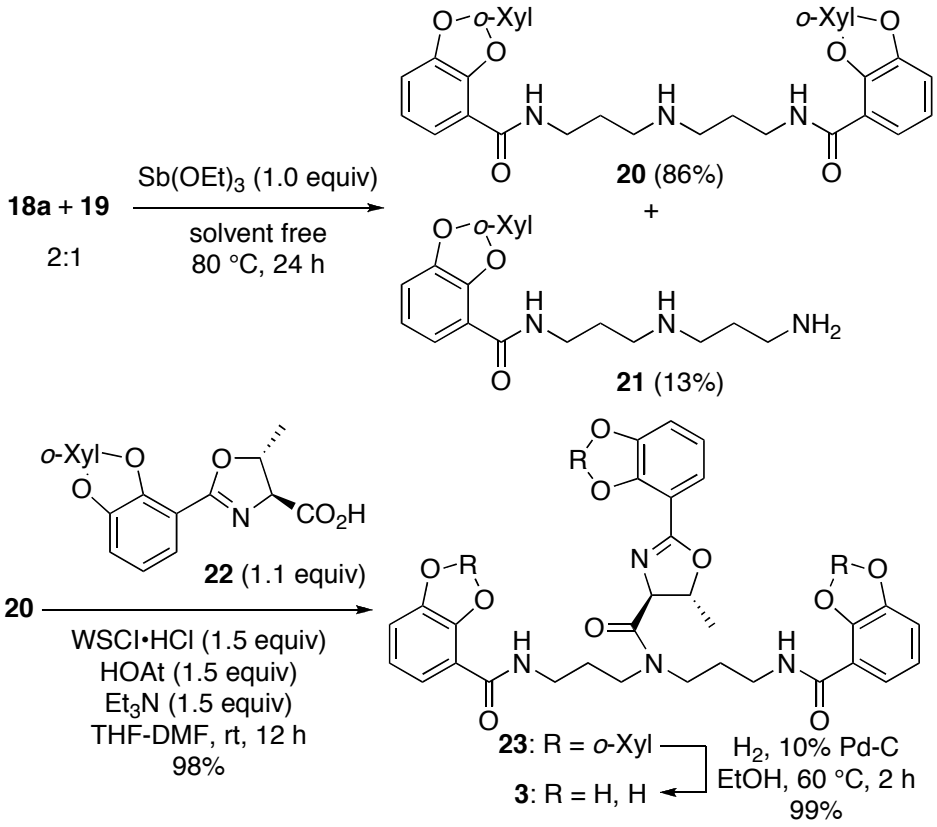
Recently, we reported that *cis*-bis(2-phenyl-8-quinolinolato-*N,O*)-dioxomolybdenum(VI) [MoO_2(Ph-quinolinolato)$_2$] showed good catalytic activity for the dehydrative cyclization of *N*-acyl-L-threonines to oxazolines.[10b] However, the activity of MoO_2(Ph-quinolinolato)$_2$ was lower than that of MoO_2(TMHD)$_2$ for the dehydrative cyclization of **5e** (entry 10). Compound **5e** could be easily prepared from commercially available 2,3-dihydroxybenzoic acid by a five-step transformation *via* compound **18a** (72% overall yield) (eq 5).



(5)

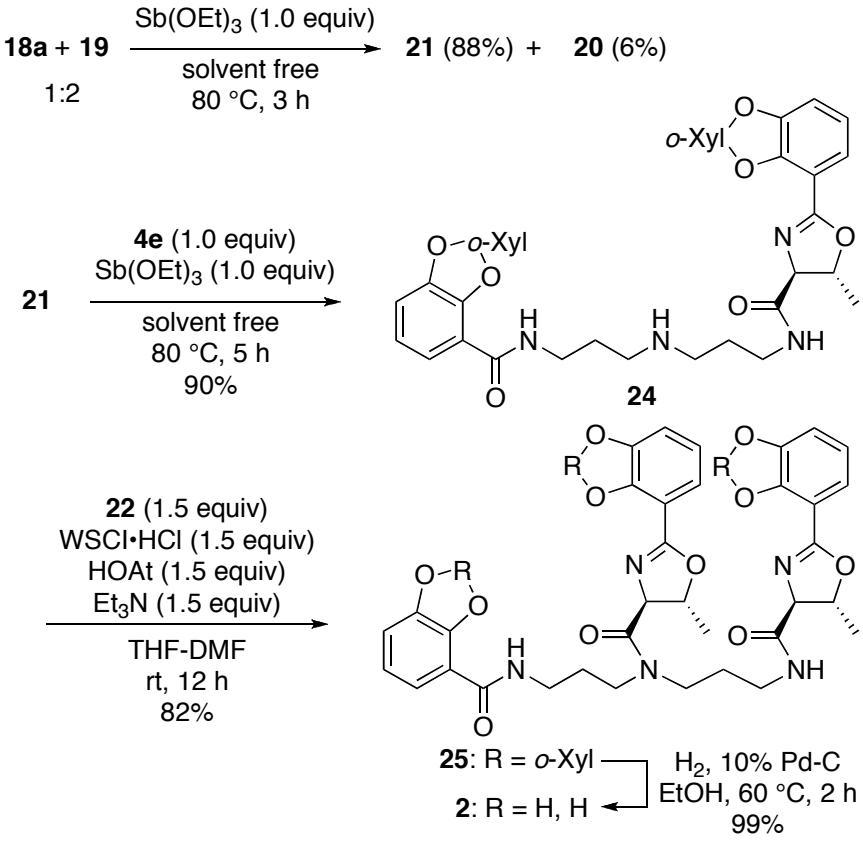
Next, we investigated the synthesis of fluvibactin (**3**) using **4e** as a key building block (Scheme 2.5). Sb(III) alkoxide-catalyzed ester–amide transformation[14] worked well for the selective synthesis of diamide **20**, although the reaction required an equimolar amount of Sb(III) alkoxide. When the reaction of a 2:1 mixture of **18a** and norspermidine (**19**) was conducted in the presence of Sb(OEt)$_3$ (1.0 equiv) under solvent-free conditions at 80 °C, the desired diamide **20** was selectively obtained in 86% yield along with monoamide **21** (13%). Interestingly, the present ester–amide transformation gave the best results under solvent-free conditions, although Sb(III)-templated macrolactamization was conducted in benzene or toluene under azeotropic reflux conditions.[14] The ester–amide transformation between **18a** and **19** in toluene under azeotropic reflux conditions resulted in 6% yield.[15]

With the key synthetic intermediate **20** in hand, the stage was set for amide formation at the secondary amine in **20**. In contrast to primary amines, the amide formation at the secondary amine in **20** was extremely difficult to promote. In fact, attempts with Sb(III)-catalyzed ester–amide transformation between **4e** and **9** failed under several reaction conditions, and resulted in decomposition of the oxazoline moiety of **4e** to give a mixture of byproducts.[16] Therefore, we investigated the dehydrative condensation of **20** with carboxylic acid **22** which was prepared from **4e** in 97% yield [CsOH (2 equiv), acetone-MeOH-H_2O (2:1:1 v/v/v), 0 °C, 1 h]. Through the intensive examination of dehydrative condensation of **20** with **22**, we found that WSCI•HCl and HOAt (1.5 equiv) showed high activity for the condensation of **20** with **22** (1.1 equiv) and gave the desired triamide **23** in 98% yield. Finally, the three *o*-xylylene groups in **23** were easily removed by hydrogenolysis using 10% Pd/C to give **3** in 99% yield. Synthetic **3** showed ^{1}H and ^{13}C NMR spectra and HRMS data[17] that were identical to those reported for natural fluvibactin.[3] The longest linear sequence required 9 steps from 2,3-dihydroxybenzoic acid, with an overall yield of 65%.



Scheme 2.5. Synthesis of fluvibactin (**3**)

Vibriobactin (**2**) could be synthesized from **18a**, **21** and **22** *via* a strategy similar to that for fluvibactin (**3**) (Scheme 2.6). Selective monoamide formation between **18a** and **19** could also be performed using $Sb(OEt)_3$. When the reaction of a 1:2 mixture of **18a** and **19** was conducted in the presence of $Sb(OEt)_3$ (1.0 equiv) under solvent-free conditions at 80 °C, monoamide **21** was obtained in 88% yield along with diamide **20** (6%). Monoamide **21** was then subjected to the second ester–amide transformation with an equimolar amount of **4e** using $Sb(OEt)_3$ (1.0 equiv), and gave diamide **24** in 90% yield. As in the case of fluvibactin, condensation of **24** with **22** (1.5 equiv) using WSCI•HCl and HOAt (1.5 equiv) successfully gave triamide **25** in 82% yield.[17] The final removal of *o*-xylylene groups in **25** gave **2** in 99% yield. The longest linear sequence required 9 steps from 2,3-dihydroxybenzoic acid, with an overall yield of 50%.



Scheme 2.6. Synthesis of vibriobactin (**2**)

In conclusion, we have convergently synthesized vibriobactin (**2**) and fluvibactin (**3**) in respective overall yields of 50 and 65%. Our $MoO_2(TMHD)_2$-catalyzed dehydrative cyclization was found to be a powerful protocol for constructing the 2-(*o,m*-dihydroxyphenyl)oxazoline core at an early stage in the total synthesis. A cyclic *o*-xylylene group was very effective for protecting the catechol moieties. This compact protecting group helped the dehydrative cyclization of **5e** to proceed rapidly. Sb(III)-catalyzed ester–amide transformation of the primary amines was conducted under solvent-free conditions, and diamide and monoamide could be selectively synthesized just by appropriately setting the ratio of **18a** and **19**. Furthermore, WSCI•HCl and HOAt successfully promoted amide formation at the secondary amines in **20** and **24** with carboxylic acid **22**. These successes significantly increased the overall yields of **2** and **3**.

References and Notes

1. (a) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (b) Lewis, J. R. *Nat. Prod. Rep.* **2002**, *19*, 223. (c) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249.
2. Griffiths, G. L.; Sigel, S. P.; Payne, S. M.; Neilands, J. B. *J. Biol.Chem.* **1984**, *259*, 383.
3. Yamamoto, S.; Okujo, N.; Fujita, Y.; Saito, M.; Yoshida, T.; Shinoda, S. *J. Biochem.* **1993**, *113*, 538.
4. (a) Drechsel, H.; Jung, G. *J. Pept. Sci.* **1998**, *4*, 147. (b) Wandersman, C.; Delepelaire, P. *Annu. Rev. Microbiol.* **2004**, *58*, 611.
5. For selected recent studies, see: (a) Haynes, S. W.; Challis, G. L. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 203. (b) Bergeron, R. J.; Bharti, N.; Singh, S. *Synthesis* **2007**, 1033. (c) Wyckoff, E. E.; Mey, A. R.; Payne, S. M. *BioMetals* **2007**, *20*, 405. (d) Zhou, Z.; Lai, J. R.; Walsh, C. T. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 11621. (e) Balibar, C. J.; Walsh, C. T. *ChemBioChem* **2008**, *9*, 42.
6. Bergeron, R. J.; Garlich, J. R.; McManis, J. S. *Tetrahedron* **1985**, *41*, 507.
7. Bergeron, R. J.; Xin, M. G.; Weimar, W. R.; Smith, R. E.; Wiegand, J. *J. Med. Chem.* **2001**, *44*, 2469.
8. (a) Bergeron, R. J.; Kline, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 4489. (b) Bergeron, R. J.; McManis, J. S.; Dionis, J. B.; Garlich, J. R. *J. Org. Chem.* **1985**, *50*, 2780.
9. Rastetter, W. H.; Erickson, T. J.; Venuti, M. C. *J. Org. Chem.* **1981**, *46*, 3579.
10. (a) Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971. (b) Sakakura, A.; Kondo, R.; Umemura, S.; Ishihara, K. *Adv. Synth. Catal.* **2007**, *349*, 1641. (c) Sakakura, A.; Kondo, R.; Umemura, S.; Ishihara, K. *Tetrahedron* **2009**, *65*, 2102.
11. Sakakura, A.; Umemura, S.; Kondo, R.; Ishihara, K. *Adv. Synth. Catal.* **2007**, *349*, 551.
12. Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230.

13. (a) Poss, A. J.; Smyth, M. S. *Synth. Commun.* **1989**, *19*, 3363. (b) Balbuena, P; Rubio, E. R.; Ortiz Mellet, C.; García Fernández, J. M. *Chem. Commun.* **2006**, 2610. (c) García-Moreno, M. I.; Aguilar, M.; Ortiz Mellet, C.; García Fernández, J. M. *Org. Lett.* **2006**, *8*, 297.
14. (a) Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 1569. (b) Kuroki, Y.; Ishihara, K.; Hanaki, N.; Ohara, S.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1221.
15. Compound **18a** was recovered in 50% yield. Monoamide **21** was obtained in 14% yield.
16. The structures of the byproducts were not determined.
17. Attempts at triamide formation between **24** and **4e** using $Sb(OEt)_3$ failed, and led to decomposition of the oxazoline moiety of **4e**.

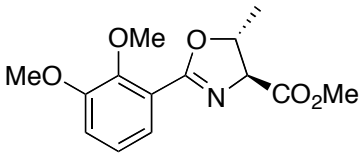
Experimental Section

General Method.

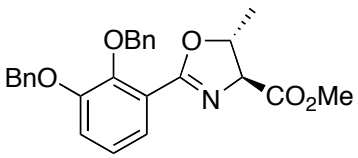
IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; 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 temparature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm, CD_3OD at 49.0 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 or NH_2 F_{254S} 0.25 mm) were used. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) or Fuji Silysia Chemical Ltd. Cromatorex(R) NH-DM1020 were used. High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. Dry toluene and tetrahydrofran (THF) 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 Pure Chemical Industries, Ltd.), $MoO_2(TMHD)_2$ (Strem), $C_6F_5CO_2H$ (TCI), $Sb(OEt)_3$ (Aldrich), Norspermidine (Wako) and other materials were obtained from commercial supplies and used without further purification.

General Procedure of Dehydrative Cyclization of 5: The reaction was carried out in a flask fitted with a pressure-equalized addition funnel (containing a cotton plug and ca. 4 g of molecular sieves 4Å, and functioning as a Soxhlet extractor) surmounted by a reflux condenser. A solution of **5e** (371 mg, 1.0 mmol), $MoO_2(TMHD)_2$ (2.5 mg, 0.0050 mmol) in toluene (100 mL) was heated at azeotropic reflux with the removal of water. After 5 h, the

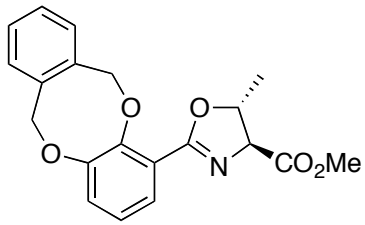
reaction mixture was cooled to ambient temperature, and concentrated to give a crude product. Yields were determined by 1H NMR analysis. The crude product was purified by column chromatography on silica gel using a mixture of hexane–EtOAc (3:1 → 2:1 → 3:2) as an eluent to give **4e**.



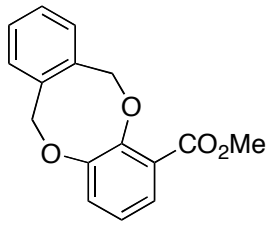
Methyl (4*S*,5*R*)-2-(*o,m*-dimethoxyphenyl)-5-methyl-4-oxazolinecarboxylate (4c): IR (neat) 1742, 1644, 1578, 1481, 1319, 1264, 1048, 1004 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 1.53 (d, *J* = 6.3 Hz, 3H), 3.80 (s, 3H), 3.87 (s, 6H), 4.48 (d, *J* = 7.2 Hz, 1H), 4.98 (dq, *J* = 7.2, 6.3 Hz, 1H), 7.03 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.08 (dd, *J* = 7.8, 7.5 Hz, 1H), 7.37 (dd, *J* = 7.5, 2.1 Hz, 1H), 11.8 (s, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 20.5, 52.0, 55.6, 60.9, 74.5, 78.3, 115.0, 122.0, 122.1, 123.4, 148.5, 153.0, 164.3, 171.2; HRMS (FAB) calcd for $C_{14}H_{18}NO_5$ $[M+H]^+$ 280.1185, found 280.1207.



Methyl (4*S*,5*R*)-2-(*o,m*-dibenzyloxyphenyl)-5-methyl-4-oxazolinecarboxylate (4d): IR (neat) 1741, 1641, 1577, 1476, 1454, 1319, 1265, 1218, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.3 Hz, 3H), 3.78 (s, 3H), 4.43 (d, *J* = 7.8 Hz, 1H), 4.93 (dq, *J* = 7.8, 6.3 Hz, 1H), 5.09 (d, *J* = 4.8 Hz, 1H), 5.13 (s, 2H), 7.03-7.16 (m, 2H), 7.27-7.47 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 51.5, 70.1, 74.1, 74.6, 77.8, 116.5, 122.2, 122.3, 123.3, 126.7 (2C), 127.0, 127.1, 127.3 (2C), 127.6 (2C), 127.8 (2C), 135.9, 136.9, 147.2, 151.9, 163.8, 170.6; HRMS (FAB) calcd for $C_{26}H_{26}NO_5$ $[M+H]^+$ 432.1811, found 432.1806.

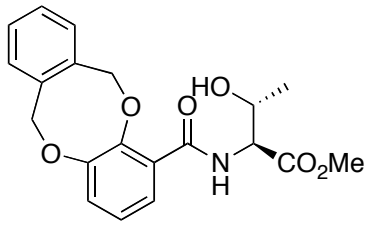


***o*-Xylylene-protected oxazolinecarboxylic acid methyl ester 4e:** IR (neat) 1741, 1638, 1579, 1466, 1376, 1280, 1259, 1207, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, *J* = 6.3 Hz, 3H), 3.82 (s, 3H), 4.51 (d, *J* = 6.9 Hz, 1H), 4.97 (dq, *J* = 6.9, 6.3 Hz, 1H), 5.39 (d, *J* = 12.6 Hz, 1H), 5.42 (d, *J* = 13.8 Hz, 1H), 5.48 (d, *J* = 13.8 Hz, 1H), 5.49 (d, *J* = 12.6 Hz, 1H), 6.95 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.10 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.11-7.32 (m, 4H), 7.42 (dd, *J* = 7.8, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 52.5, 74.6, 75.1, 75.8, 78.4, 121.8, 123.3, 124.6, 124.9, 128.3, 128.3, 128.5, 129.3, 135.1, 135.9, 149.2, 151.2, 164.2, 171.6; HRMS (FAB) calcd for $C_{20}H_{20}NO_5$ $[M+H]^+$ 354.1341, found 354.1370.



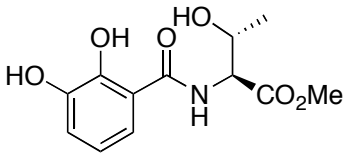
***o*-Xylylene-protected 2,3-dihydroxybenzoic acid methyl ester (18a):** To a solution of 2,3-dihydroxybenzoic acid (5.0 g, 32.4 mmol) in MeOH (50 mL) was added H_2SO_4 (3.0 mL) and the mixture was heated to reflux for 5 h. The reaction mixture was cooled to ambient temparature. After MeOH was removed *in vacuo*, the crude product was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL) and brine (50 mL). The combined extracts were dried over Na_2SO_4 and concentrated following was added a solution of α,α'-dibromo-*o*-xylene (8.18 g, 31 mmol), K_2CO_3 (12.4 g, 90 mmol) in DMF (100 mL). The mixture was heated at 120 °C. After 8 h, the reaction mixture was cooled to ambient

temparature, poured into ice-cold water (200 mL) following was passed through cotton to remove K_2CO_3. The aqueous layer was extracted with EtOAc (200 mL, 2 × 50 mL). The organic layers ware washed with ice-cold 1 M HCl (100 mL), water (80 mL) and brine (80 mL). The crude product was purified by column chromatography on silica gel using a mixture of hexane–EtOAc (15:1 → 10:1 → 7:1) as an eluent to give **18a** (6.7 g, 77%); IR (neat) 1728, 1585, 1467, 1434, 1375, 1281, 1193, 1141, 1077, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 5.42 (s, 2H), 5.48 (s, 2H), 6.95 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.15 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.17-7.31 (m, 4H), 7.41 (dd, *J* = 7.8, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2, 74.0, 75.1, 122.4, 124.3, 124.7, 124.8, 127.8, 127.9, 127.9, 128.4, 134.7, 135.1, 149.1, 150.7, 165.4; HRMS (FAB) calcd for $C_{16}H_{15}O_4$ $[M+H]^+$ 271.0970, found 271.0978.

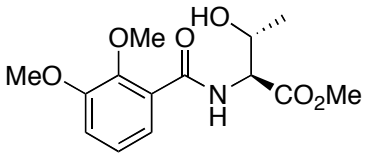


***o*-Xylylene-protected *N*-(2,3-dihydroxybenzoyl)-L-threonine methyl ester (5e):** To a solution of **18a** (3.43 g, 13 mmol) in acetone (50 mL) and MeOH (50 mL) was added a 1.0 M aqueous solution of NaOH (50 mL, 50 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min and then at 50 °C for 1 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 × 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. To a solution of the residue in $CHCl_3$ (35 mL) was added thionyl chlroride (2 mL) and DMF (5 drops) at ambient temperature, and the mixture was heated to reflux for 1 h. The reaction mixture was concentrated, and then added CH_2Cl_2 (35 mL). The resulting solution was cooled to 0 °C. The solution was added H-L-Thr-OMe·HCl (2.15g, 13 mmol), Et_3N (3.5 mL, 25 mmol) and DMAP (155 mg, 1.3

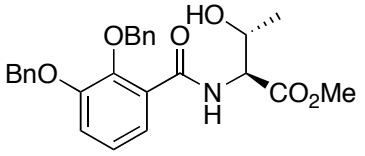
mmol) at 0 °C. After stirring at rt for 2 h, CH_2Cl_2 was removed *in vacuo* and dissolved in EtOAc (80 mL). The resulting solution was washed with 1 M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using a mixture of hexane–EtOAc (3:2 → 1:1) as a eluent to give **5e** (4.38 g, 93%); IR (KBr) 3369, 3330, 1743, 1642, 1579, 1527, 1460, 1281, 1259, 1081, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.6 Hz, 3H), 2.19 (d, *J* = 5.1 Hz, 1H), 3.83 (s, 3H), 4.45 (qdd, *J* = 6.6, 5.1, 2.4 Hz, 1H), 4.86 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.35 (d, *J* = 14.1 Hz, 1H), 5.43 (d, *J* = 14.1 Hz, 1H), 5.61 (d, *J* = 12.6 Hz, 1H), 5.67 (d, *J* = 12.6 Hz, 1H), 7.02 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.12–7.25 (m, 5H), 7.82 (dd, *J* = 8.1, 2.1 Hz, 1H), 8.90 (br d, *J* = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 52.4, 57.7, 68.1, 75.0, 76.2, 122.9, 124.8, 126.0, 126.6, 127.8, 128.6, 129.0, 130.1, 133.7, 136.3, 149.3, 150.0, 165.4, 171.7; HRMS (FAB) calcd for $C_{20}H_{22}NO_6$ $[M+H]^+$ 372.1447, found 372.1430.



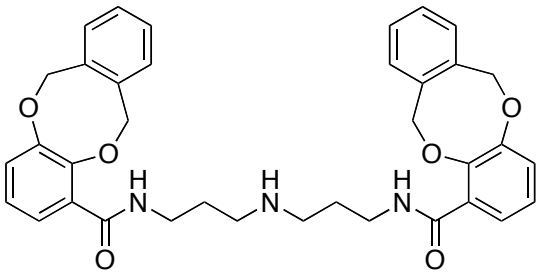
***N*-(*o,m*-Dihydroxybenzoyl)-L-threonine methyl ester (5b)**: IR (KBr) 3419, 1739, 1644, 1588, 1540, 1458, 1337, 1271, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.3 Hz, 3H), 1.80-3.20 (br, 1H), 3.80 (s, 3H), 4.50 (qd, *J* = 6.3, 2.4 Hz, 1H), 4.79 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.20–6.50 (br, 1H), 6.78 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.06 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.08 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 12.3 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 52.9, 57.1, 67.9, 113.6, 116.8, 118.7, 118.8, 145.6, 148.9, 170.4, 171.3; HRMS (FAB) calcd for $C_{12}H_{16}NO_6$ $[M+H]^+$ 270.0978, found 270.0996.



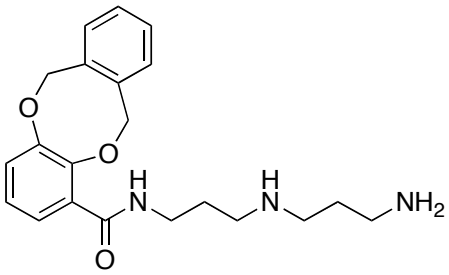
***N*-(*o,m*-Dimethoxybenzoyl)-L-threonine methyl ester (5c)**: IR (KBr) 3354, 1738, 1647, 1578, 1538, 1477, 1264, 1119, 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.6 Hz, 3H), 2.44 (br, 1H), 3.79 (s, 3H), 3.91 (s, 3H), 3.99 (s, 3H), 4.44 (qd, *J* = 6.6, 2.4 Hz, 1H), 4.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.08 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.16 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.71 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.93 (br d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 52.1, 55.9, 57.7, 67.6, 115.6, 122.5, 124.1, 125.6, 147.8, 152.5, 165.5, 171.4; HRMS (FAB) calcd for $C_{14}H_{20}NO_6$ $[M+H]^+$ 298.1291, found 298.1293.



***N*-(*o,m*-Dibenzyloxybenzoyl)-L-threonine methyl ester (5d)**: IR (KBr) 3342, 1754, 1647, 1575, 1540, 1457, 1348, 1260, 1206, 1131, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.6 Hz, 3H), 1.86 (d, *J* = 5.7 Hz, 1H), 3.73 (s, 3H), 4.31 (qdd, *J* = 6.6, 5.7, 2.7 Hz, 1H), 4.76 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 5.15 (s, 2H), 5.23 (d, *J* = 10.2 Hz, 1H), 7.16-7.48 (m, 12H), 7.75 (dd, *J* = 6.0, 3.6 Hz, 1H), 8.78 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 51.8, 57.8, 67.2, 70.7, 75.6, 116.8, 122.6, 122.7, 124.0, 126.3, 127.5 (2C), 127.8 (3C), 128.2 (2C), 128.6 (2C), 135.8, 135.9, 146.5, 151.4, 165.5, 170.9; HRMS (FAB) calcd for $C_{26}H_{26}NO_5$ $[M+H]^+$ 450.1917, found 450.1917.

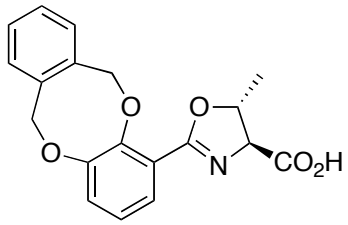


Diamide 20: A mixture of **18a** (620 mg, 2.3 mmol), **19** (150 mg, 160 μL, 1.1 mmol) was charged with $Sb(OEt)_3$ (293 mg, 190 μL, 1.1 mmol) at ambient temparature in N_2 atmosphere. The mixture was heated at 80 °C for 24 h. After cooling to ambient temparature, the mixture was quenched with MeOH (3 mL) and then filtered through pad of celite using $CHCl_3$–MeOH–*i*-$PrNH_2$, evaporated. The residue was purified by column chromatography on Cromatorex(R) NH-DM1020 using a mixture of $CHCl_3$–MeOH (1:0 → 300:1 → 100:1) as an eluent to give **20** (523 mg, 86%) along with **21** (54 mg, 13%): IR (neat) 3395, 1653, 1540, 1521, 1457, 1280 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (tt, *J* = 6.6, 6.6 Hz, 4H), 2.73 (t, *J* = 6.6 Hz, 4H), 3.53 (td, *J* = 6.6, 6.0 Hz, 4H), 5.35 (s, 4H), 5.48 (s, 4H), 6.99 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.12–7.32 (m, 10H) 7.75 (dd, *J* = 7.8, 1.5 Hz, 1H) 8.05 (br t, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.4, 37.4, 47.1, 74.9, 75.6, 122.6, 124.7, 125.6, 125.9, 127.7, 128.2, 128.6, 129.0, 133.6, 135.8, 148.5, 150.0, 164.7; HRMS (FAB) calcd for $C_{36}H_{38}N_3O_6$ $[M+H]^+$ 608.2761, found 608.2742.



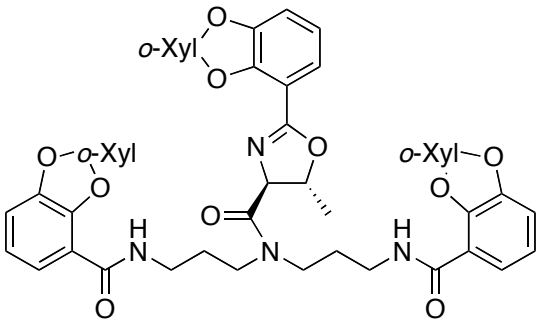
Monoamide 21: A mixture of **18a** (280 mg, 1.0 mmol), **19** (270 mg, 280 μL, 2.0 mmol) was charged with $Sb(OEt)_3$ (260 mg, 170 μL, 2.0 mmol) at ambient temparature in N_2 atmosphere.

The mixture was heated at 80 °C for 3 h. After cooling to ambient temparature, the mixture was quenched with MeOH (3 mL) and then filtered through pad of celite using $CHCl_3$–MeOH–*i*-$PrNH_2$, evaporated. The residue was purified by column chromatography on Cromatorex(R) NH-DM1020 using a mixture of hexane–$CHCl_3$–*i*-$PrNH_2$ (12:8:1 → 10:10:1 → 4:16:1) as an eluent to give **21** (330 mg, 88%) along with **20** (35 mg, 6%): IR (neat) 3386, 1648, 1578, 1530, 1464, 1442, 1375, 1280, 1260, 1074, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (tt, *J* = 6.9, 6.9 Hz, 2H), 1.80 (tt, *J* = 6.9, 6.9 Hz, 2H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.72 (t, *J* = 6.9 Hz, 2H), 3.54 (td, *J* = 6.9, 6.0 Hz, 2H), 5.36 (s, 2H), 5.50 (s, 2H), 7.00 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.12–7.35 (m, 5H) 7.76 (dd, *J* = 7.5, 2.1 Hz, 1H) 8.07 (br t, *J* = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8, 33.7, 37.9, 40.4, 47.6, 47.8, 75.4, 76.0, 123.0, 125.0, 126.0, 126.1, 128.0, 128.4, 129.0, 129.3, 134.0, 136.1, 148.9, 150.4, 165.0; HRMS (FAB) calcd for $C_{21}H_{28}N_3O_3$ $[M+H]^+$ 370.2131, found 370.2131.



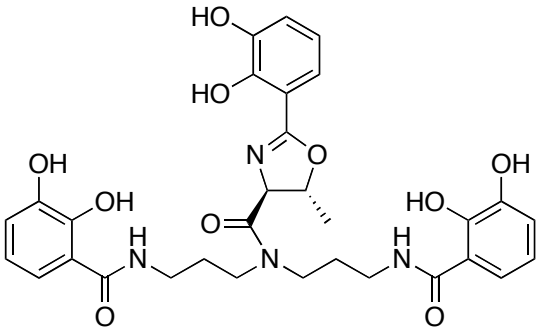
***o*-Xylylene-protected oxazolinecarboxylic acid 22:** To a solution of **4e** (300 mg, 0.85 mmol) in acetone (3.5 mL), MeOH (1.7 mL) and H_2O (1.7 mL) was added CsOH•H_2O (77 μL, 1.7 mmol) at 0 °C, and the mixture was stirred for 1 h. After MeOH was removed *in vacuo*, the resulting aqueous layer was acidified with conc. aqueous HCl, then white solid precipitated. The solid was collected by filtration, washed with 1 M aqueous HCl, and dried *in vacuo*, to give **22** (277 mg, 96%): IR (KBr) 3369 (br), 1742, 1627, 1487, 1420, 1381, 1287, 1260, 1034, 934 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.69 (d, *J* = 6.5 Hz, 3H), 5.04 (d, *J* = 6.5 Hz, 1H), 5.41 (s, 2H), 5.78 (qd, *J* = 6.5, 6.5 Hz, 1H), 6.23 (d, *J* = 11.0 Hz, 1H), 6.27 (d, *J* = 11.0 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 7.05 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.28 (dd, *J* = 7.5, 7.5 Hz, 1H),

7.32 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.55 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.64 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.82 (d *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 65.8, 73.9, 77.9, 83.9, 110.5, 122.4, 126.6, 128.0, 129.2, 129.6, 132.3, 133.4, 133.6, 136.0, 148.5, 153.8, 166.9, 167.3; HRMS (FAB) calcd for $C_{19}H_{18}NO_5$ $[M+H]^+$ 340.1185, found 340.1194.



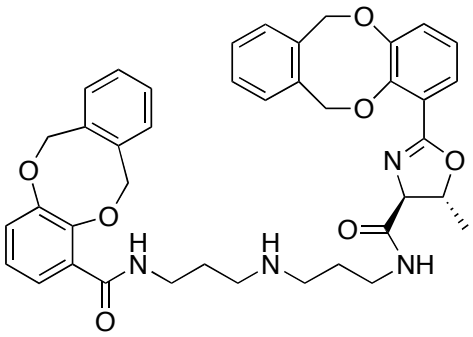
Triamide 23: To a solution of **20** (61 mg, 0.10 mmol), **22** (37 mg, 0.11 mmol), HOAt (20 mg, 0.15 mmol) and Et_3N (21 μL, 0.15 mmol) in THF (2.5 mL) and DMF (0.1 mL) was added WSCI•HCl (29 mg, 0.15 mmol) at 0 °C. After the mixture was stirred at ambient temperature for 12 h, solvent was removed *in vacuo* and dissolved in EtOAc (20 mL). The resulting solution was washed with 1 M HCl (2 × 15 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL) and brine (15 mL), and combined organic phase was combined and dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on Cromatorex(R) NH-DM1020 using a mixture of hexane–EtOAc–MeOH (10:20:1) as an eluent to give **23** (91 mg, 98%): $[\alpha]^{21}_D$ +112.8 (*c* 1.0, $CHCl_3$); IR (neat) 3388, 1647, 1523, 1460, 1377, 1281, 1072, 1010 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, *J* = 6.5 Hz, 3H), 1.87 (tdd, *J* = 6.0, 6.0, 6.0 Hz, 2H), 2.00–2.10 (m, 1H), 2.12–2.23 (m, 1H), 3.34 (m, 1H), 3.43–3.51 (m, 2H), 3.54 (m, 1H), 3.64 (m, 1H), 3.66–3.75 (m, 2H), 3.91 (ddd, *J* = 14.5, 9.0, 5.5 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 5.23–5.38 (m, 8H), 5.40–5.46 (m, 1H), 5.43 (s, 2H), 5.67 (d, *J* = 12.5 Hz, 1H), 5.73 (d, *J* = 12.5 Hz, 1H), 6.87 (t, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 7.00 (br d, *J* = 7.5 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.07–7.16 (m, 6H), 7.18 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.19 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.21–7.28 (m, 4H), 7.28 (dd, *J* = 8.0, 2.0 Hz,

1H), 7.33 (br d, J = 7.5 Hz, 1H), 7.64 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 6.0 Hz, 1H), 8.21 (t, J = 5.5 Hz, 1H), 8.71 (t, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 27.5, 29.0, 36.3, 37.1, 42.5, 44.9, 73.7, 74.5, 74.8, 75.6, 75.8, 76.4, 77.7, 121.9, 122.4, 123.1, 123.2, 124.5, 124.8, 125.0, 125.4, 125.4, 125.6, 126.3, 126.5, 126.5, 127.4, 128.1, 128.3, 128.4, 128.5, 128.5, 128.8, 128.9, 129.0, 129.2, 130.2, 134.1, 134.2, 135.1, 135.6, 136.0, 136.4, 148.9, 149.2, 149.5, 150.0, 150.5, 151.1, 163.1, 165.0, 165.5, 170.0; HRMS (FAB) calcd for $C_{55}H_{52}N_4O_{10}Na[M+Na]^+$ 951.3581, found 951.3594.

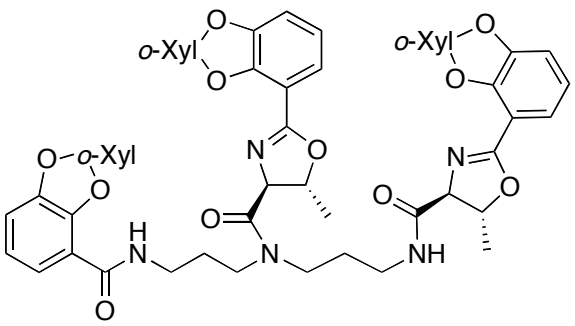


Fluvibactin (3): A mixture of triamide **23** (30 mg, 0.032 mmol) and 10% Pd/C (3.0 mg) in EtOH (4 mL) was stirred under a hydrogen atmosphere at 60 °C for 2 h. The mixture was filtered through a pad on Celite, and the residue was washed with EtOH. The filtrate and washings were combined and concentrated. The residue was purified by column chromatography on Sephadex® G-25 using EtOH as an eluent to give **3** (20 mg, 99%): $[\alpha]^{22}_D$ +59.9 (*c* 0.92, CH_3OH); IR (neat) 3363, 1636, 1592, 1541, 1458, 1324, 1264, 1170, 741 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.39 (d, J = 6.0 Hz, 3H), 1.80–1.93 (m, 2H), 1.98–2.14 (m, 2H), 3.28–3.71 (m, 6H), 3.78–3.88 (m, 2H), 4.80 (d, J = 6.0 Hz, 1H), 5.24 (qd, J = 6.0, 6.0 Hz, 1H), 6.62 (dd, J = 8.0, 7.0 Hz, 1H), 6.68 (dd, J = 8.0, 8.0 Hz, 1H), 6.72 (dd, J = 8.0, 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.14–7.23 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 20.2, 28.4, 30.3, 37.9, 45.0, 46.7, 72.9, 79.7, 111.8, 116.7, 118.6, 118.6, 119.6, 119.9, 120.2, 146.7,

147.4, 149.4, 150.4, 167.8, 171.4, 171.5, 171.8; HRMS (FAB) calcd for $C_{31}H_{35}N_4O_{10}$ $[M+H]^+$ 623.2353, found 623.2352.

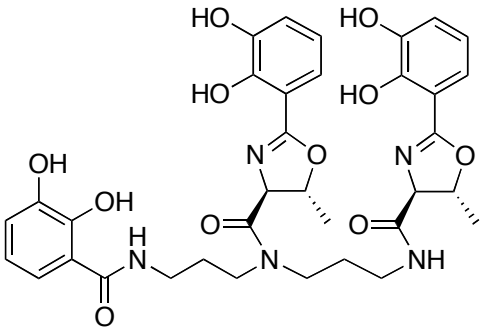


Diamide 24: A mixture of **21** (183 mg, 0.5 mmol), **4e** (178 mg, 0.5 mmol) was charged with $Sb(OEt)_3$ (128 mg, 85 μL, 0.5 mmol) at ambient temparature in N_2 atmosphere. The mixture was heated at 80 °C for 5 h. After cooling to ambient temparature, the mixture was quenched with MeOH (1 mL) and then filtered through pad of celite using $CHCl_3$, evaporated. The residue was purified by column chromatography on Chromatorex(R) NH-DM1020 using a mixture of hexane–$CHCl_3$ (1:2 → 1:3 → 1:5) as an eluent to give **24** (311 mg, 90%): IR (KBr) 3387, 2931, 1648, 1578, 1526, 1465, 1376, 1280, 1075, 1009 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (d, *J* = 6.3 Hz, 3H), 1.66 (tt, *J* = 6.6, 6.6 Hz, 2H), 1.72 (tt, *J* = 6.6, 6.6 Hz, 2H), 2.65 (t, *J* = 6.6 Hz, 4H), 3.22-3,42 (m, 2H), 3.48 (td, *J* = 6.6, 6.6 Hz, 2H), 4.32 (d, *J* = 7.2 Hz, 1H), 4.87 (dq, *J* = 7.2, 6.3 Hz, 1H), 5.35 (s, 2H), 5.39 (s, 1H), 5.40 (s, 1H), 5.44 (s, 2H), 5.47 (s, 2H), 6.95 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.99 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.05–7.36 (m, 10H), 7.38 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.75 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.01 (br t, *J* = 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 29.2, 29.4, 37.2, 37.5, 47.1, 47.3, 74.8 75.1, 75.2, 75.5, 75.6, 79.2, 121.4, 122.7, 122.9, 124.5, 124.6, 124.7, 125.6, 126.1, 127.8, 127.8, 128.2, 128.2, 128.3, 128.6, 128.7, 129.0, 129.0, 133.8, 135.1, 135.2, 135.8, 148.5, 149.2, 150.1, 150.9, 163.5, 164.8, 171.2; HRMS (FAB) calcd for $C_{40}H_{43}N_4O_7$ $[M+H]^+$ 691.3132, found 691.3154.



Triamide 25: To a solution of **24** (69 mg, 0.10 mmol), **22** (51 mg, 0.15 mmol), HOAt (20 mg, 0.15 mmol) and Et_3N (21 μL, 0.15 mmol) in THF (1.8 mL) and DMF (0.20 mL) was added WSCI•HCl (29 mg, 0.15 mmol) at 0 °C. After the mixture was stirred at ambient temperature for 12 h, solvent was removed *in vacuo* and dissolved in EtOAc (20 mL). The resulting solution was washed with 1 M HCl (2 × 15 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL) and brine (15 mL), and dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on Cromatorex(R) NH-DM1020 using a mixture of hexane–EtOAc–MeOH (10:20:1) as an eluent to give **25** (83 mg, 82%): $[\alpha]^{22}_D$ +102.5 (*c* 1.0, $CHCl_3$); IR (KBr) 3398, 1645, 1524, 1465, 1377, 1281, 1259, 1076, 1009 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.5 Hz, 1.2H), 1.42 (d, *J* = 6.5 Hz, 1.8H), 1.50 (d, *J* = 6.5 Hz, 1.8H), 1.58 (d, *J* = 6.5 Hz, 1.2H), 1.75–1.87 (m, 2.4H), 1.87–2.18 (m, 1.6H), 3.15 (m, 0.4H), 3.30 (m, 0.6H), 3.34–3.46 (m, 3H), 3.48–3.75 (m, 3H), 3.78–3.87 (m, 1H), 4.25 (d, *J* = 7.0 Hz, 0.6H), 4.37 (d, *J* = 7.5 Hz, 0.4H), 4.57 (d, *J* = 7.0 Hz, 0.4H), 4.59 (d, *J* = 6.0 Hz, 0.6H), 4.85 (dq, *J* = 7.0, 6.0 Hz, 0.4H), 4.86 (dq, *J* = 7.0, 6.5 Hz, 0.6H), 5.22–5.48 (m, 11.4H), 5.50 (d, *J* = 13.5 Hz, 0.4H), 5.67 (d, *J* = 12.0 Hz, 0.6H), 5.73 (d, *J* = 12.0 Hz, 0.4H), 6.82 (dd, *J* = 8.0, 8.0 Hz, 0.4H), 6.89 (dd, *J* = 8.0, 8.0 Hz, 0.6H), 6.90 (dd, *J* = 8.0, 8.0 Hz, 0.6H), 6.92 (dd, *J* = 8.0, 8.0 Hz, 0.4H), 6.93 (dd, *J* = 8.0, 8.0 Hz, 0.4H), 6.97 (dd, *J* = 8.0, 8.0 Hz, 0.6H), 7.01 (dd, *J* = 8.0, 1.5 Hz, 0.4H), 7.03 (br dd, *J* = 7.5, 7.5 Hz, 1H), 7.06 (dd, *J* = 8.0, 2.0 Hz, 0.6H), 7.07–7.30 (m, 16H), 7.32 (br d, *J* = 7.0 Hz, 0.8H), 7.33 (dd, *J* = 7.5, 1.5 Hz, 0.6H), 7.35 (dd, *J* = 7.5, 2.0 Hz, 0.6H), 7.42 (br t, *J* = 6.0 Hz, 0.4H), 7.53 (dd, *J* = 8.0, 2.0 Hz, 0.4H), 7.59 (dd, *J* = 8.0, 2.0 Hz, 0.4H), 7.84 (dd, *J* = 8.0, 1.5 Hz, 0.6H), 8.19 (br d, *J* = 5.5 Hz, 0.4H), 8.69 (br d,

J = 6.0 Hz, 0.6H), (a 3:2 mixture of rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 20.3, 20.4, 20.7, 21.7, 22.0, 24.3, 27.5, 28.9, 36.0, 36.2, 36.5, 37.0, 42.5, 42.7, 44.7, 45.1, 58.8, 72.7, 73.9, 74.0, 74.5, 74.7, 74.8, 75.0, 75.1, 75.2, 75.5, 75.6, 75.7, 75.8, 75.9, 76.0, 76.5, 77.6, 77.8, 79.3, 79.5, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 134.2, 134.6, 135.2, 135.4, 135.5, 135.5, 135.7, 135.8, 136.0, 136.4, 147.4, 148.8, 149.2, 149.3, 149.5, 149.6, 149.7, 150.1, 150.5, 150.8, 151.1, 151.2, 151.2, 151.3, 157.3, 163.0, 163.2, 163.9, 164.0, 164.4, 165.0, 169.6, 170.3, 171.8; HRMS (FAB) calcd for $C_{40}H_{43}N_4O_7Na$ $[M+Na]^+$ 1034.3952, found 1034.3933.



Vibriobactin (2): A mixture of **25** (40 mg, 0.039 mmol) and 10% Pd/C (3.7 mg) in EtOH (4 mL) was stirred under a hydrogen atmosphere at 60 °C for 2 h. The mixture was filtered through a pad on Celite, and the residue was washed with EtOH. Thefiltrate and washings were combined and concentrated. The residue was purified by column chromatography on Sephadex® G-25 using EtOH as an eluent to give **2** (27 mg, 99%): $[\alpha]^{22}_D$ +32.6 (*c* 1.0, $CHCl_3$–DMSO 10:1); UV (EtOH) λmax 318 (ε 5970), 256 (ε 18500) nm; IR (neat) 3344, 1637, 1541, 1473, 1458, 1379, 1340, 1261, 1147, 1026, 741 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.34 (d, J = 6.5 Hz, 1.5H), 1.41 (d, J = 6.5 Hz, 1.5H), 1.42 (d, J = 6.5 Hz, 1.5H), 1.43 (d, J = 6.5 Hz, 1.5H), 1.61–1.71 (m, 1H), 1.71–1.79 (m, 1H), 1.81–2.02 (m, 2H), 3.00–3.56 (m, 6H), 3.61–3.74 (m, 2H), 4.41 (d, J = 7.5 Hz, 0.5H), 4.44 (d, J = 7.5 Hz, 0.5H), 4.84 (d, J = 6.5 Hz, 0.5H), 4.88 (d, J = 6.5 Hz, 0.5H), 4.80–4.90 (m, 1H), 5.17 (qd, J = 6.5, 6.5 Hz, 0.5H), 5.21 (qd, J = 6.5, 6.5 Hz, 0.5H), 6.63–4.90 (m, 3H), 6.89 (d, J = 8.0 Hz, 1H),

6.96 (d, J = 7.0 Hz, 2H), 7.05 (d, J = 8.5 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 0.5H), 7.29 (d, J = 8.0 Hz, 0.5H), 8.24 (t, J = 6.5 Hz, 1H), 8.39 (t, J = 6.5 Hz, 1H), 8.75 (t, J = 6.5 Hz, 1H), 8.86 (t, J = 6.5 Hz, 1H), 9.01–9.08 (m, 3H), 11.6–11.9 (m, 1H), 12.6–12.8 (m, 0.5H), (a 1:1 mixture of rotamer); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.7, 19.8, 20.6, 27.1, 27.2, 28.5, 28.8, 36.3, 36.4, 36.7, 43.1, 43.3, 44.9, 70.5, 73.7, 78.3, 78.4, 78.8, 110.2, 110.3, 114.9, 117.0, 117.2, 117.9, 118.6, 118.8, 119.4, 119.5, 145.7, 146.2, 148.2, 148.3, 149.6, 149.7, 165.4, 165.5, 165.7, 165.7, 168.3, 168.4, 169.4, 169.7, 170.0; HRMS (FAB) calcd for $C_{35}H_{40}N_5O_{11}$ $[M+H]^+$ 706.2724, found 706.2720.

Chapter 3

The Development of "Pyroc" as a Removable Directing Group for Catalytic Asymmetric Acylation

2-1 3-Pyrroline-1-carbonyl (Pyroc) Group: A Removable Protecting Group for the Kinetic Resolution of Racemic Carboxylic Acids and Alcohols through Catalytic Asymmetric Acylation

Abstract: The *O*-3-pyrroline-1-carbonyl (*O*-Pyroc) group and 3-pyrrolinamide are useful removable protecting groups for the kinetic resolution of racemic α-hydroxycarboxylic acids, β-hydroxycarboxylic acids, 1,2-dicarboxylic acids and 1,2-diols using the L-histidine-derived bifunctional catalysts **6**. The Pyroc group can be easily introduced from Pyroc chloride. Selective deprotection of the Pyroc group and 3-pyrrolinamide can be carried out via DDQ oxidation followed by hydrolysis using sodium hydroxide, without epimerization.

The kinetic resolution of racemic compounds through catalytic asymmetric acylation is a useful method for obtaining optically active compounds.[1] We recently reported the kinetic resolution of racemic carboxylic acids **8** bearing a pyrrolidine-1-carbonyl group as a Brønsted base site.[2–5] Compounds **6** are bifunctional acylation catalysts that contain an *N*-methylimidazole moiety as a nucleophilic base and a sulfonamidyl proton as a Brønsted acid (Figure 1). They induce the high-level kinetic resolution of (±)-**8** through hydrogen bonding between a sulfonamidyl proton of **6** and a carbonyl oxygen of **8** (Scheme 1). The strong basicity of the pyrrolidine-1-carbonyl group is essential for the effective induction of kinetic resolution. However, the pyrrolidine-1-carbonyl group in **9a** is too robust to be removed chemoselectively without epimerization.[6] Therefore, an alternative protecting group which is easily protective and removable is urgently required for the practical use of the present kinetic resolution. We report here the 3-pyrroline-1-carbonyl (Pyroc) group and 3-pyrrolinamide as useful protecting groups for the kinetic resolution of racemic α-hydroxycarboxylic acids, β-hydroxycarboxylic acids, 1,2-dicarboxylic acids and 1,2-diols by **6a**-induced asymmetric acylation.

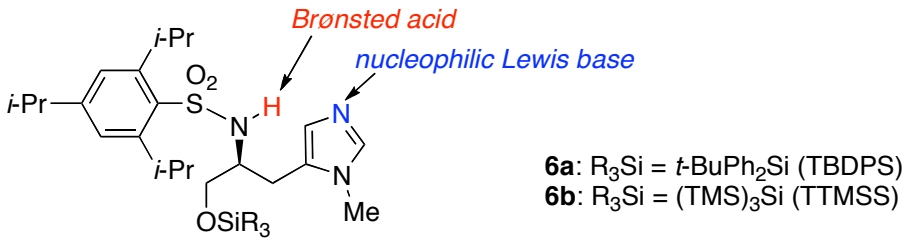
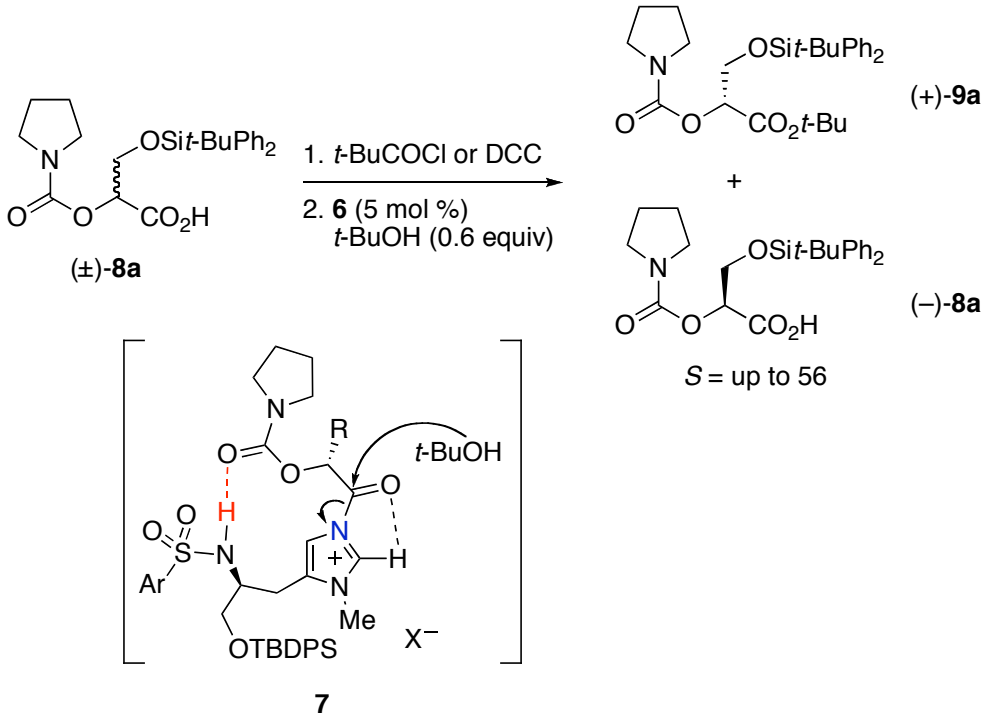
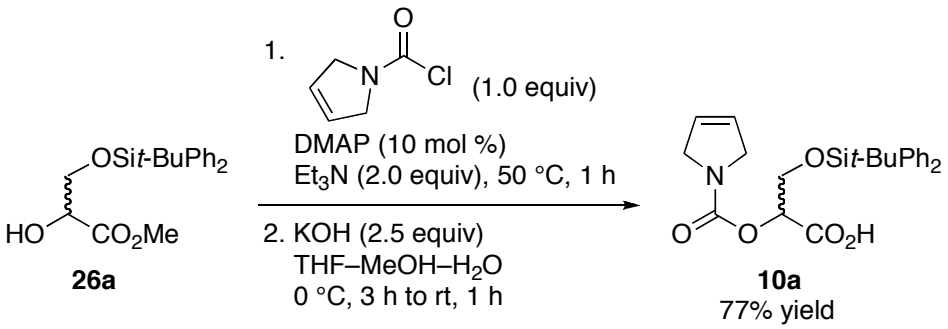


Figure 3.1. L-Histidine-derived Bifunctional Catalysts **6**



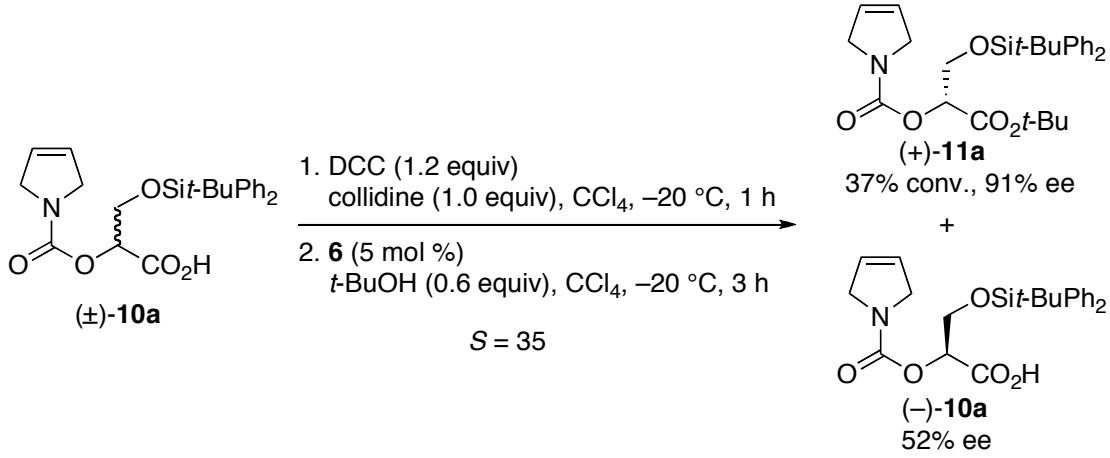
Scheme 3.1. Kinetic Resolution of (±)-**8a** Induced by **6**

Scheme 2 shows the preparation of *O*-Pyroc-protected α-hydroxycarboxylic acid **10a**. The α-hydroxy group of **26a** could be easily protected with Pyroc chloride[7,8] (1.0 equiv) in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP, 10 mol %) and triethylamine (2.0 equiv) under solvent-free conditions. Subsequent selective hydrolysis of methyl ester with KOH (2.5 equiv) in THF–MeOH–H_2O gave carboxylic acid **10a** in 77% overall yield.



Scheme 3.2. Protection of α-Hydroxycarboxylic Acid by a Pyroc Group

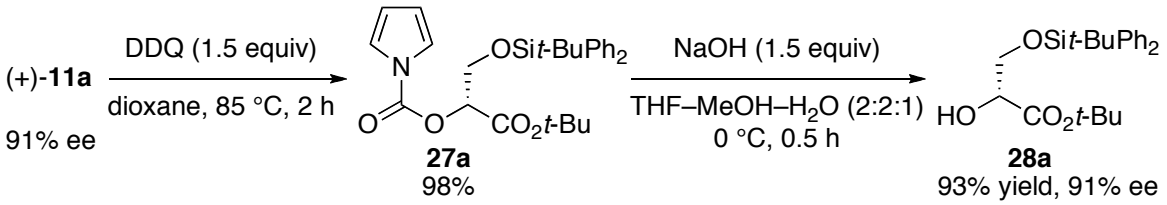
With *O*-Pyroc-protected α-hydroxycarboxylic acid (±)-**10a** in hand, we examined the kinetic resolution of (±)-**10a** with *N,N'*-dicyclohexylcarbodiimide (DCC) in the presence of **6a** (5 mol %) under the same conditions as reported previously (Scheme 3). As a result, the reaction gave (+)-**11a** in 37% yield with 91% ee. The selective factor (S = $k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}}$)[9] was 35, which is almost the same as that for the reaction of (±)-**8a** (S = 37) under the same reaction conditions. This result suggested that the Pyroc group in **10a** also acted as a Brønsted base to form a hydrogen bonding with the sulfonamidyl proton of **6a**.



Scheme 3.3. Kinetic Resolution of (±)-**10a** Induced by **6**

We next investigated selective removal of the Pyroc group in (+)-**11a** (Scheme 4). Oxidation of Pyroc to pyrrole-1-carbonyl was easily conducted using DDQ (1.5 equiv) in dioxane at 85 °C, and gave **27a** in 98% yield.[10] A relatively high reaction temperature (85 °C) was essential for promoting the reaction effectively. When the reaction was conducted at 70 °C, the yield of **27a** decreased to 50% (3 h) and a prolonged reaction time did not improve the yield of **27a**. The pyrrole-1-carbonyl group in **27a** could be rapidly and chemoselectively hydrolyzed under mild basic conditions [NaOH (1.5 equiv) in

THF–MeOH–H_2O (2:2:1), 0 °C, 0.5 h] and gave α-hydroxycarboxylic ester **28a** in 93% yield.[11] The enantiomeric excess of **28a** (91% ee) was completely retained during the deprotection sequences.



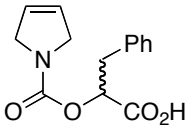
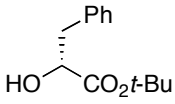
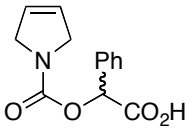
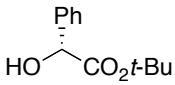
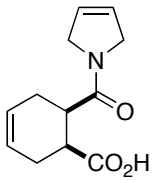
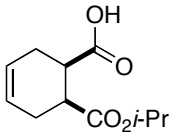
Scheme 3.4. Selective Removal of the 3-Pyrroline-1-carbonyl Group in (±)-**11a**

To explore the generality and scope of the **6a**-induced kinetic resolution of racemic carboxylic acids protected by a Pyroc group, we examined asymmetric acylation and selective removal of the Pyroc group (Table 1). The asymmetric acylation of *O*-protected 3-phenyllactic acid **10b** and mandelic acid **10c** also gave high *S* values (27 and 6.6, entries 1 and 2). Deprotection of the Pyroc group in esters (+)-**11b** and (+)-**11c** proceeded smoothly under the optimized conditions described in Scheme 4, and gave α-hydroxyesters **28b** and **28c** in respective yields of 90 and 95%. The enantiomeric excesses of **28b** and **28c** were completely retained (86 and 56% ees).

The present **6a**-induced asymmetric acylation was also effectively applied to racemic 1,2-dicarboxylic mono-3'-pyrrolinamides. (±)-*syn*-6-(Pyroc)cyclohex-3-enecarboxylic acid (**29**) was also a suitable substrate for **6a**-induced kinetic resolution (entry 3). As in the kinetic resolution of pyrrolidine derivative of **29**,[2] the use of *i*-PrOH as a nucleophile was essential for effective promotion of the reaction. Subsequent selective hydrolysis of the 3-pyrrolinamide group[12] of ester **30** could be carried out using DDQ [1.5 equiv, dioxane, 85 °C, 2 h] followed by NaOH [1.0 equiv, THF–*i*-PrOH–H_2O (2:2:1), 0 °C, 3 h] to give carboxylic acid **31** in 91% yield.

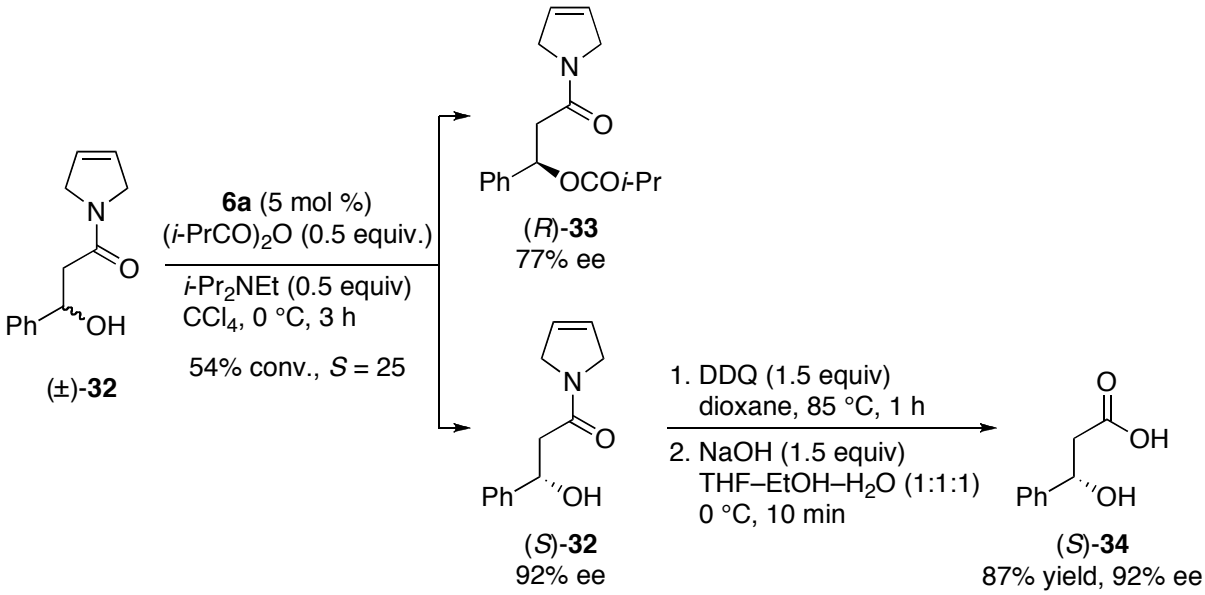
Table 3.1. **6a**-Induced Kinetic Resolution of Racemic Carboxylic Acids and Hydrolysis of Pyroc Group[a]

(±)-carboxylic acid —(1. DCC, collidine; 2. catalyst **6,** ROH)→ ester —(1. DDQ; 2. NaOH)→ product

entry	**6a**-induced kinetic resolution of racemic carboxylic acids						hydrolysis	
	(±)-carboxylic acid	ester	time (h)[b]	conv. (%)[c]	ee (%)[d] of ester, acid	*S*[e]	product	yield (%),[f] ee (%)[d]
1	 **10b**	**11b** (R = *t*-Bu)	6	44	86, 68	27 [29]	 **28b**	90, 86
2	 **10c**	**11c** (R = *t*-Bu)	12	52	56, 61	6.6 [8.9]	 **28c**	95,56
3	 **29**	**30** (R = *i*-Pr)	15	49	83, 79	25 [13[h]]	 **31**	91, 83

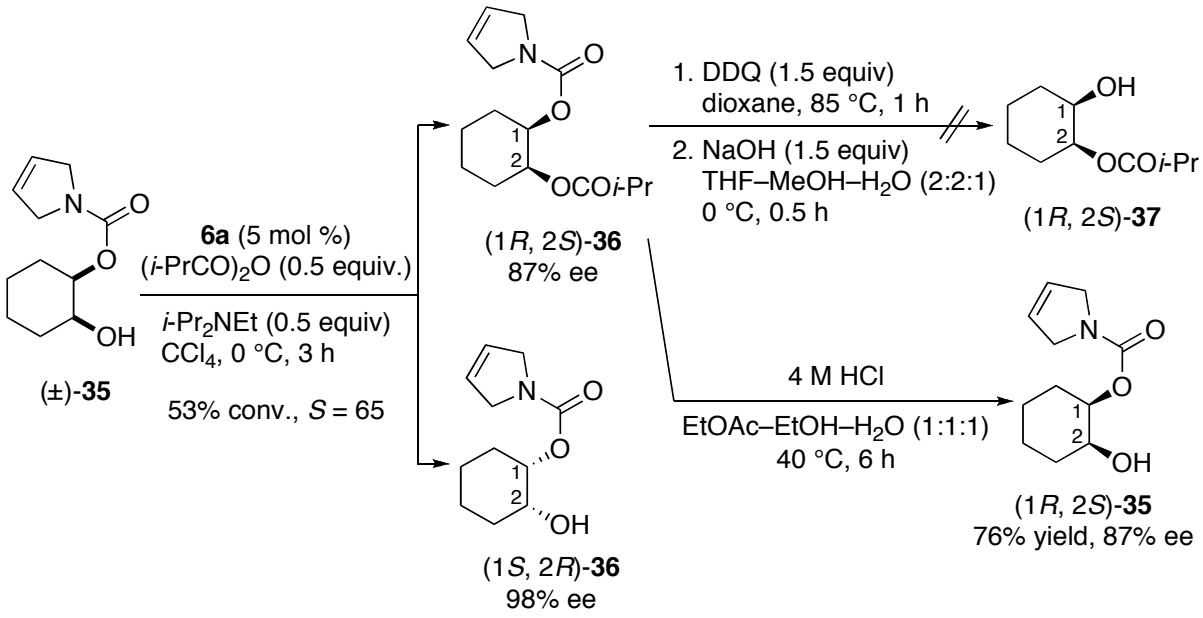
[a] The acylation reaction of (±)-carboxylic acid (0.25 mmol) was conducted in CCl_4 (1.5 mL) according to the reaction conditions shown in Scheme 3.3. [b] For step 2. [c] Conversion (%) = 100 × (ee of acid)/(ee of ester + ee of acid) [d] HPLC analysis. [e] The *S* value was calculated by using the ee of esters and acids; *S* for the kinetic resolution of the corresponding pyrrolidine-1-carbonyl derivative is shown in parantheses. See ref 9. [f] Isolated yield. [g] *i*-PrOH (0.6 equiv) was used at 0 °C. [h] *t*-BuCOCl was used.

We previously described the kinetic resolution of racemic secondary alcohols bearing a pyrrolidine-1-carbonyl group as a Brønsted base site.[5] Asymmetric acylation with isobutyric anhydride induced by bifunctional catalysts **6** gave optically active isobutyrates with an *S* value of up to 132. We examined the **6a**-induced kinetic resolution of racemic secondary alcohols and chemoselective deprotection. The asymmetric acylation of racemic 3-hydroxy-3-phenylpropanoic 3'-pyrrolinamide (**32**) with isobutyric anhydride (0.5 equiv) in the presence of **6a** (5 mol %) and *i*-Pr_2NEt (0.5 equiv) showed good selectivity (*S* = 25, Scheme 5). This selectivity was almost the same as that of the pyrrolidinamide derivative (*S* = 19).[5] As in the case of compounds **30**, selective cleavage of 3-pyrrolinamide in (*R*)-**32** could be achieved using DDQ followed by NaOH in THF–EtOH–H_2O (1:1:1) to give β-hydroxycarboxylic acid **34** in 87% yield without epimerization.



Scheme 3.5. Kinetic Resolution of Racemic β-Hydroxycarboxylic 3-Pyrrolinamide **32** and Selective Cleavage of 3-Pyrrolinamide

(±)-*cis*-1-(Pyroc-oxy)-2-cyclohexanol (**35**) was also a suitable substrate for **6a**-induced kinetic resolution (S = 65, Scheme 6). We then examined the selective deprotection of (1*R*,2*S*)-**36**. Although the corresponding pyrrole derivative was obtained from (1*R*,2*S*)-**36** in quantitative yield by DDQ oxidation, subsequent basic hydrolysis gave a complex mixture. The pyrrole-1-carbonyl group showed almost the same reactivity as the isobutyryl group under basic hydrolysis conditions. After intensive investigation of the chemoselective deprotection of (1*R*,2*S*)-**36**, we found that acidic hydrolysis [4 M HCl in EtOAc–EtOH–H_2O (1:1:1), 40 °C, 6 h] selectively removed the isobutyryl group and gave (1*R*,2*S*)-**35** in 76% yield without epimerization. For the practical use of chiral **35**, a Pyroc group could be removed after some modification of a 2-hydroxy group in **35**.



Scheme 3.6. Kinetic Resolution of Racemic Cyclohexane-1,2-diol Derivative **35** and Selective Deprotection of **36**

In conclusion, we reported a Pyroc group (for hydroxy group) and 3-pyrrolinamide (for carboxy group) as removable protecting groups that were suitable for the kinetic resolution induced by bifunctional catalysts **6**. These protecting groups played a key role in high-level asymmetric induction through hydrogen bonding with a sulfonamidyl proton of **6**. Furthermore, they could be selectively removed via DDQ oxidation followed by hydrolysis using NaOH without any loss of stereochemical integrity.

References and Notes

1. For recent reviews, see: (a) Connon, S. J.; *Lett. Org. Chem.* **2006**, *3*, 333. (b) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974. (c) Miller, S. J. *Acc. Chem. Soc.* **2004**, *37*, 601. (d) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (e) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.
2. Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191.
3. For recent reports of asymmetric derivatization of racemic alcohols, see: (a) Sánchez-Roselló, M.; Puchlopek, A. L. A.; Morgan, A. J.; Miller, S. J. *J. Org. Chem.* **2008**, *73*, 1774. (b) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454. (c) Lewis, C. A.; Miller, S. J. *Angew. Chem., Int. Ed*. **2006**, *45*, 5616. (d) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67. (e) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (f) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (g) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859. (h) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, 7, 3445. (i) Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021. (j) Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 13182. (k) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, 126, 12226. (l) Fierman, M. B.; O'Leary, D. J.; Steinmetz, W. E.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6967. (m) Griswold, K. S.; Miller, S. J. *Tetrahedron* **2003**, *59*, 8869. (n) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *Chem. Commun.* **2003**, 1781. (o) Kawabata, T.; Stragies, R.; Fukaya, T.; Fuji, K. *Chirality* **2003**, *15*, 71. (p) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, 68, 3844. (q) Pelotier, B.; Priem, G.; Campbell, I. B.; Macdonald, S. J. F.; Anson, M. S. *Synlett* **2003**, 679.

4. For kinetic resolution of racemic carboxylic acids, see: Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887.

5. (a) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (b) Ishihara, K.; Kosugi, Y.; Akakura, M. *Tetrahedron* **2007**, *63*, 6191. For an account article, see: (c) Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686.

6. Reduction with lithium aluminium hydride (4 equiv) gave the corresponding 1,2-diol in high yield without epimerization.[2]

7. Pyroc chloride was prepared as follows: Diallylaminocarbonyl chloride was reacted in the presence of Grubbs' 1st-generation catalyst (0.5 mol %) under heating conditions (CH_2Cl_2, reflux, 4 h). After the reaction mixture was concentrated, the residue was purified by column chromatography on silica gel to give Pyroc chloride in 95% yield. (a) Ferguson, M. L.; O'Leary, D. J.; Grubbs, R. H. *Org. Synth.* **2003**, *80*, 85. (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

8. For the synthesis of Pyroc chloride by ring-closing metathesis with the aid of microwave irradiation, see: Vo Thanh, G.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091.

9. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

10. (a) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105. (b) Ohri, R. V.; Radosevich, A. T.; Hrovat, K. J.; Musich, C.; Huang, D.; Holman, T. R.; Toste, F. D. *Org. Lett.* **2005**, *7*, 2501.

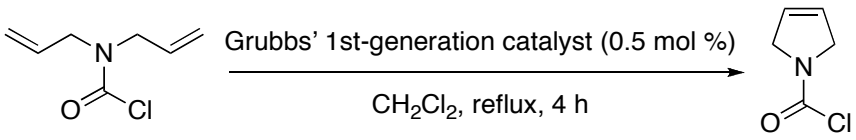
11. **Experimental Procedure for the Deprotection of Pyroc Group in 11a:** To a solution of **11a** (0.1 mmol) in dioxane (1 mL) was added DDQ (0.15 mmol) and the mixture was stirred at 85 °C for 2 h. After the reaction mixture was cooled to ambient temperature, dioxane was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give **27a** in 98% yield. **27a**: ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.49 (s, 9H), 4.02 (dd, *J* = 2.3, 11.0 Hz, 1H), 4.21 (dd, *J* = 4.1, 11.0 Hz, 1H),

5.22 (dd, J = 2.3, 4.1 Hz, 1H), 6.26 (dd, J = 1.8, 2.3 Hz, 2H), 7.29 (dd, J = 1.8, 2.3 Hz, 2H), 7.30–7.48 (m, 6H), 7.60–7.74 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.5, 28.0, 63.3, 76.0, 82.9, 112.6, 120.2, 127.8, 129.9, 132.7, 132.8, 135.4, 135.5, 149.9, 166.2. To a solution of **27a** (0.085 mmol) in THF (0.17 mL) and MeOH (0.17 mL) was added 1.5 M aq. NaOH (0.085 mL, 0.13 mmol) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. The reaction mixture was quenched with 1 M aq. HCl, and diluted with EtOAc. The organic layer was separated, washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give **28a** in 93% yield. **28a**: ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H), 1.51 (s, 9H), 3.88 (dd, J = 2.8, 10.6 Hz, 1H), 3.99 (dd, J = 2.3, 10.6 Hz, 1H), 4.10 (dd, J = 2.3, 2.8 Hz, 1H), 7.31–7.47 (m, 6H), 7.61–7.74 (m, 4H).

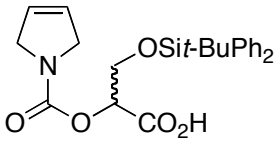
12. Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514.

Experimental Section

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm), Daicel CHIRALPAK AD-H (4.6 mm × 25 cm) or Daicel CHIRALCEL AS-H (4.6 mm × 25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. Melting points were determined using a Yanaco MP-J3. The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385 or Fuji Silysia Chemical Ltd. Cromatorex® NH-DM1020). Microanalyses were performed at the Graduate School of Agriculture, Nagoya University. High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer. In experiments that required dry solvent, ether, *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from TCI or Wako as the “anhydrous” and stored over MS 4Å. Benzene, hexane, toluene, and dichloromethane were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially.

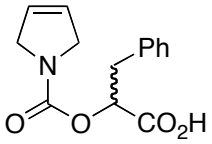


Preparation of PyrocCl:[1] Diallylaminocarbonyl chloride was reacted in the presence of Grubbs' 1st-generation catalyst (0.5 mol %) under heating conditions (CH_2Cl_2, reflux, 4 h). After the reaction mixture was concentrated, the residue was purified by column chromatography on silica gel to give Pyroc chloride in 95% yield. IR (neat) 2920, 2871, 1746, 1627, 1470, 1376, 1359, 1309, 1300, 1184, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25–4.31 (m, 2H), 4.35–4.41 (m, 2H), 5.80 (dddd, J = 1.8, 2.0, 2.3, 6.9 Hz, 1H), 5.86 (dddd, J = 1.8, 2.0, 2.3, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.7, 56.7, 124.8, 125.3, 146.5.

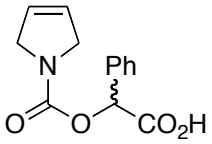


Preparation of *O*-Pyroc-protected α-Hydroxycarboxylic Acid 10a: A mixture of α-hydroxy ester **26a** (11.7 mmol), 3-pyrroline-1-carbonyl chloride (Pyroc chloride, 11.7 mmol, 1.0 equiv), 4-(*N,N*-dimethylamino)pyridine (DMAP, 1.17 mmol, 10 mol %) and triethylamine (23.4 mmol, 2.0 equiv) was stirred at 50 °C for 1 h. After the reaction mixture was concentrated, the residue was purified by column chromatography on silica gel to give α-Pyroc-oxy ester. To a solution of the obtained α-Pyroc-oxy ester in THF (10 mL) and MeOH (10 mL) was added slowly a solution of KOH (40 mmol) in water (10 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h, then at ambient temperature for 1 h. The reaction mixture was acidified by 1 M aqueous HCl and extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel to give **10a** in 77% yield. **10a**: IR (KBr) 2954, 2931, 2860, 1762, 1717, 1623, 1443, 1428, 1208, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ

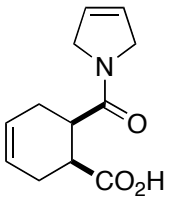
1.03 (s, 9H), 4.03 (dd, J = 3.0, 11.1 Hz, 1H), 4.08–4.37 (m, 4H), 4.15 (dd, J = 4.8, 11.1 Hz, 1H), 5.25 (dd, J = 3.0, 4.8 Hz, 1H), 5.80 (m, 2H), 7.30–7.48 (m, 6H), 7.59–7.73 (m, 4H), 8.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 26.4, 52.8, 53.2, 63.4, 73.9, 125.2, 125.4, 127.5, 129.6, 132.8, 135.28, 135.31, 153.9, 172.8.



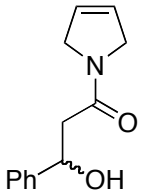
***O*-Pyroc-protected α-Hydroxycarboxylic Acid 10b:** IR (KBr) 2867, 1753, 1714, 1681, 1622, 1444, 1186, 1128 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (dd, J = 9.0, 14.1 Hz, 1H), 3.26 (dd, J = 3.9, 14.1 Hz, 1H), 3.97–4.33 (m, 4H), 5.19 (dd, J = 3.9, 9.0 Hz, 1H), 5.70–5.83 (m, 2H), 7.18–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 52.9, 53.2, 73.4, 125.3, 125.5, 126.8, 128.3, 129.3, 136.1, 153.9, 174.5.



***O*-Pyroc-protected α-Hydroxycarboxylic Acid 10c:** IR (KBr) 2868, 1752, 1715, 1622, 1439, 1208, 1181, 1128 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09–4.30 (m, 3H), 4.30–4.44 (m, 1H), 5.40 (br s, 1H), 5.77 (m, 2H), 5.94 (s, 1H), 7.32–7.45 (m, 3H), 7.45–7.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 53.4, 74.7, 125.4, 125.6, 127.5, 128.7, 129.1, 133.9, 153.7, 173.7.



***syn*-6-(Pyroc)cyclohex-3-enecarboxylic Acid (29):** IR (KBr) 2979, 2925, 2360, 2342, 1730, 1707, 1203, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.12–2.50 (m, 3H), 2.80–2.95 (m, 1H), 3.02–3.19 (m, 2H), 4.21–4.53 (m, 4H), 5.70 (m, 1H), 5.80 (m, 1H), 5.86 (m, 1H), 5.94 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 25.6, 28.9, 40.3, 40.5, 53.78, 53.84, 124.38, 124.41, 125.9, 127.0, 172.9, 175.1.

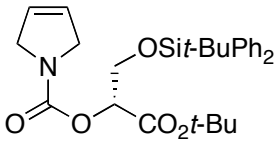


3-Hydroxy-3-phenylpropanoic 3'-Pyrrolinamide (32): IR (neat) 3338(3120–3600:br), 2861, 1638, 1614, 1454, 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (m, 2H), 4.13–4.25 (m, 2H), 4.25–4.37 (m, 2H), 4.81 (br s, 1H), 5.22 (dd, J = 3.2, 8.7 Hz, 1H), 5.77–5.87 (m, 1H), 5.87–5.97 (m, 1H), 7.25–7.50 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.6, 52.4, 53.0, 69.9, 124.5, 125.3, 127.0, 128.0, 143.0, 170.1. For analysis of (*S*)-**32**: HPLC (Daicel Chiralcel AD-H, hexane–2-propanol = 19:1, flow rate = 1 mL/min) t_R = 35.6 (major enantiomer), 44.0 (minor enantiomer) min.

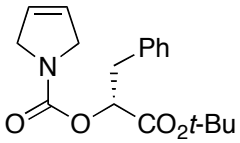
Kinetic Resolution of Racemic Carboxylic Acids and Secondary Alcohols by 1-induced Enantioselective Esterification Reaction.

Experimental procedure was followed as reported previously.[2] The ee value of the ester was determined by HPLC analysis of the crude products. The ee value of the recovered carboxylic acids was determined by HPLC analysis after conversion to the corresponding *N*-benzylamide by the treatment of the reaction mixture with benzylamine in place of a 0.1 *M*

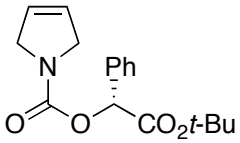
HCl aqueous solution. The conversion (c) was estimated by the isolation or the following equation: $c = ee_{\text{recovered carboxylic acid}}/(ee_{\text{recovered carboxylic acid}} + ee_{\text{ester}})$.[3] The S value was estimated by the following equation: $S = \ln[1-c(1+ee_{\text{ester}})]/\ln[1-c(1-ee_{\text{ester}})]$.[3]



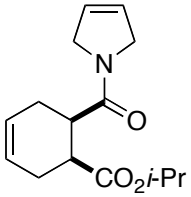
11a: HPLC (Daicel Chiralcel AD-H × 2, hexane–2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 21.3 (major enantiomer), 25.6 (minor enantiomer) min; IR (neat) 2932, 2859, 1749, 1716, 1625, 1419, 1255, 1147, 1022, 947 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.49 (s, 9H), 3.96 (dd, J = 2.8, 11.0 Hz, 1H), 4.08–4.39 (m, 4H), 4.15 (dd, J = 4.1, 11.0 Hz, 1H), 5.08 (dd, J = 2.8, 4.1 Hz, 1H), 5.79 (m, 2H), 7.32–7.46 (m, 6H), 7.63–7.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.6, 28.0, 53.0, 53.3, 63.8, 74.3, 81.9, 125.6, 125.7, 127.62, 127.64, 129.7, 133.0, 133.2, 125.4, 135.5, 153.8, 167.8.



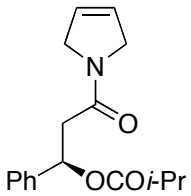
11b: HPLC (Daicel Chiralcel AD-H × 2, hexane–2-propanol = 19:1, flow rate = 0.5 mL/min) t_R = 38.6 (major enantiomer), 40.4 (minor enantiomer) min; IR (neat) 2978, 2864, 1747, 1715, 1423, 1368, 1157, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.09 (dd, J = 8.2, 14.2 Hz, 1H), 3.15 (dd, J = 4.6, 14.2 Hz, 1H), 4.00–4.32 (m, 4H), 5.08 (dd, J = 4.6, 8.2 Hz, 1H), 5.69–5.80 (m, 2H), 7.17–7.21 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 37.6, 52.9, 53.2, .73.7, 81.9, 125.6, 126.7, 128.2, 129.5, 136.5, 153.7, 169.5.



11c: HPLC (Daicel Chiralcel OD-H, hexane–2-propanol = 19:1, flow rate = 1 mL/min) t_R = 13.9 (major enantiomer), 14.8 (minor enantiomer) min; IR (neat) 2978, 2863, 1748, 1716, 1419, 1154, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 4.02–4.32 (m, 3H), 4.32–4.50 (m, 1H), 5.69–5.87 (m, 3H), 7.27–7.40 (m, 3H), 7.40–7.54 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 27.9, 53.1, 53.4, 75.1, 82.2, 125.6, 125.6, 127.3, 128.5, 128.6, 135.1, 153.6, 168.7.

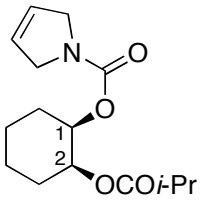


30: HPLC (Daicel Chiralcel OD-H, hexane–2-propanol = 19:1, flow rate = 1 mL/min) t_R = 20.7 (major enantiomer), 27.8 (minor enantiomer) min; IR (neat) 2930, 2854, 2118, 1731, 1654, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 6.4 Hz, 3H), 2.34–2.44 (m, 3H), 2.71–2.78 (m, 1H), 2.79–2.89 (m, 1H), 3.17 (ddd, J = 4.6, 5.5, 5.5 Hz, 1H), 4.07–4.34 (m, 3H), 4.35–4.47 (m, 1H), 5.01 (sept, J = 6.4 Hz, 1H), 5.62–5.71 (m, 1H), 5.76–5.84 (m, 2H), 5.84–5.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 21.8, 25.8, 26.0, 36.7, 39.7, 53.0,53.2, 67.6, 123.3, 124.7, 126.0, 126.5, 172.5, 173.4.



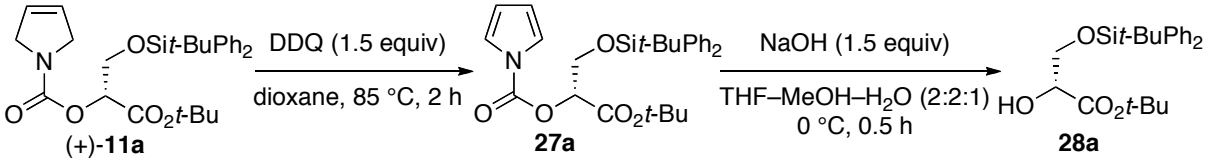
33: HPLC (Daicel Chiralcel AD-H, hexane–2-propanol = 19:1, flow rate = 1 mL/min) t_R = 43.8 (major enantiomer), 14.8 (minor enantiomer) min; IR (neat) 2941, 1747, 1472, 1350,

1308, 1181 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 2.55 (sept, *J* = 6.9 Hz, 1H), 2.69 (dd, *J* = 5.0, 15.1 Hz, 1H), 2.95 (dd, *J* = 8.7, 15.1 Hz, 1H), 4.06–4.36 (m, 4H), 5.76 (dddd, *J* = 1.8, 2.0, 2.3, 6.4 Hz, 1H), 5.86 (dddd, *J* = 1.8, 2.0, 2.3, 6.4 Hz, 1H), 6.24 (dd, *J* = 5.0, 8.7 Hz, 1H), 7.23–7.42 (m, 4H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 18.8, 34.0, 41.6, 52.9, 53.4, 72.5, 124.7, 126.2, 126.4, 128.0, 128.5, 140.4, 167.5, 175.5.



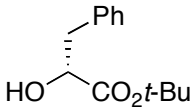
36: HPLC (Daicel Chiralcel AS-H, hexane–2-propanol = 19:1, flow rate = 1 mL/min) t_R = 13.0 (minor enantiomer), 15.1 (major enantiomer) min; IR (neat) 2974, 2863, 1736, 1712, 1420, 1330, 1196, 156, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, *J* = 7.3 Hz, 3H), 1.14 (d, *J* = 7.3 Hz, 3H), 1.39–1.55 (m, 2H), 1.55–1.78 (m, 4H), 1.78–1.93 (m, 2H), 2.58 (sept, *J* = 7.3 Hz, 2H), 4.10–4.18 (m, 2H), 4.18–4.24 (m, 2H), 4.96 (m, 1H), 5.09 (m, 1H), 5.72–5.80 (m, 2H), 5.80–5.88 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 18.9, 19.1, 21.4, 22.1, 27.9, 28.1, 34.2, 52.8, 53.2, 70.8, 71.9, 125.6, 125.8, 154.0, 176.1.

Experimental Procedure for the Deprotection of Pyroc Group in 11a:

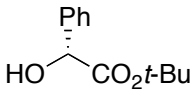


To a solution of **11a** (0.1 mmol) in dioxane (1 mL) was added DDQ (0.15 mmol) and the mixture was stirred at 85 °C for 2 h. After the reaction mixture was cooled to ambient temperature, dioxane was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give **27a** in 98% yield. **27a**: 1H NMR (400 MHz,

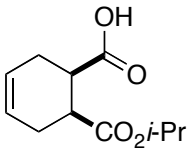
$CDCl_3$) δ 1.05 (s, 9H), 1.49 (s, 9H), 4.02 (dd, *J* = 2.3, 11.0 Hz, 1H), 4.21 (dd, *J* = 4.1, 11.0 Hz, 1H), 5.22 (dd, *J* = 2.3, 4.1 Hz, 1H), 6.26 (dd, *J* = 1.8, 2.3 Hz, 2H), 7.29 (dd, *J* = 1.8, 2.3 Hz, 2H), 7.30–7.48 (m, 6H), 7.60–7.74 (m, 4H); 13C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.5, 28.0, 63.3, 76.0, 82.9, 112.6, 120.2, 127.8, 129.9, 132.7, 132.8, 135.4, 135.5, 149.9, 166.2. To a solution of **27a** (0.085 mmol) in THF (0.17 mL) and MeOH (0.17 mL) was added 1.5 M aq. NaOH (0.085 mL, 0.13 mmol) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. The reaction mixture was quenched with 1 M aq. HCl, and diluted with EtOAc. The organic layer was separated, washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give **28a** in 93% yield. **28a**: HPLC (Daicel Chiralcel AD-H × 2, hexane–2-propanol = 19:1, flow rate = 0.5 mL/min) t_R = 19.4 (major enantiomer), 20.5 (minor enantiomer) min; IR (neat) 3523, 2961, 2932, 2858, 1734, 1428, 1369, 1254, 1163, 1114, 1019, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.51 (s, 9H), 3.88 (dd, *J* = 2.8, 10.6 Hz, 1H), 3.99 (dd, *J* = 2.3, 10.6 Hz, 1H), 4.10 (dd, *J* = 2.3, 2.8 Hz, 1H), 7.31–7.47 (m, 6H), 7.61–7.74 (m, 4H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 19.3, 26.7, 28.1, 65.9, 72.1, 82.4, 127.69, 127.71, 129.72, 129.75, 132.9, 133.3, 135.5, 135.6, 172.1.



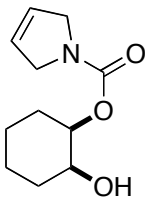
28b: HPLC (Daicel Chiralcel AD-H, hexane–2-propanol = 40:1, flow rate = 1 mL/min) t_R = 14.7 (major enantiomer), 16.6 (minor enantiomer) min; IR (neat) 2926, 1733, 1457, 1370, 1457, 1370, 1256, 1157, 1093 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.84 (br s, 1H), 2.94 (dd, *J* = 6.3, 14.0 Hz, 1H), 3.08 (dd, *J* = 4.9, 14.0 Hz, 1H), 4.32 (br s, 1H), 7.19–7.32 (m, 5H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 28.0, 40.5, 71.2, 82.6, 126.7, 128.2, 129.6, 136.7, 173.4.



28c: HPLC (Daicel Chiralcel OD-H, hexane–2-propanol = 39:1, flow rate = 1 mL/min) t_R = 7.8 (minor enantiomer), 17.8 (major enantiomer) min; IR (neat) 2864, 1748, 1716, 1419, 1154, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.51 (d, J = 5.5 Hz, 1H), 5.04 (d, J = 5.5 Hz, 1H), 7.28–7.38 (m, 3H), 7.38–7.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.8, 73.0, 83.1, 126.3, 128.1, 128.4, 138.9, 172.9.



31: IR (neat) 2978, 2925, 1731, 1708, 1374, 1203, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (d, J = 1.21 Hz, 3H), 1.22 (d, J = 1.21 Hz, 3H), 2.28–2.42 (m, 2H), 2.47–2.63 (m, 2H), 3.01–3.09 (m, 2H), 5.03 (sept, J = 6.5 Hz, 1H), 5.68 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 21.6, 25.5, 25.9, 39.5, 39.8, 68.2, 125.0, 125.2, 172.7, 178.5. Ee of **31** was measured after conversion to the methyl ester: HPLC (Daicel Chiralcel AS-H, hexane–2-propanol = 39:1, flow rate = 1 mL/min) t_R = 5.88 (major enantiomer), 6.32 (minor enantiomer) min.



35: HPLC (Daicel Chiralcel AS-H, hexane–2-propanol = 19:1, flow rate = 1 mL/min) t_R = 59.9 (major enantiomer), 64.7 (minor enantiomer) min; IR (neat) 3432, 2937, 2861, 1685, 1623, 1433, 1361, 1325, 1125, 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03–1.50 (m, 2H), 1.50–1.78 (m, 5H), 1.84–1.95 (m, 1H), 2.49 (br s, 1H), 3.85 (br s, 1H), 4.20 (s, 4H), 4.95 (m, 1H), 5.81

(m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 21.1, 21.7, 29.7, 52.6, 52.9, 69.5, 74.1, 125.3, 125.4, 154.4.

References

1. (a) Ferguson, M. L.; O'Leary, D. J.; Grubbs, R. H. *Org. Synth.* **2003**, *80*, 85. (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.
2. (a) Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191. (b) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (c) Ishihara, K.; Kosugi, Y.; Akakura, M. *Tetrahedron* **2007**, *63*, 6191.
3. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

3-2 Desymmetrization of *Meso* Glycerol Derivatives Induced by L-Histidine-Derived Acylation Catalysts

Abstract: The desymmetrization of *meso* glycerol derivatives bearing a "Pyroc" directing group is demonstrated through an enantioselective acylation reaction promoted by L-histidine-derived bifunctional catalysts. The desired monoacylated products are obtained in good yields (up to 74%) with high enantioselectivities (up to 99% ee).

Enantioselective transformations of C_2-symmetrical molecules are among the most useful reactions in asymmetric synthesis. In particular, optically active glycerol derivatives are valuable chiral building blocks for the synthesis of natural products and bioactive compounds. For the synthesis of these chiral building blocks, various methods have been developed for the desymmetrization of *meso* diols through enantioselective acylation.[1] Although some methods have been reported for the desymmetrization of acyclic *meso* 1,3-diols with good yields and enantioselectivities,[2–5] there are only a few examples of the desymmetrization of *meso* glycerol derivatives through enantioselective acylation.[2] In 2005, Miller and coworkers reported peptide-based acylation catalysts for the desymmetrization of glycerol derivatives.[2a] Although Miller's reaction was highly enantioselective (>90% ee), the desired monoesters were obtained in moderate yields along with significant amounts of undesired diesters. The non-enzymatic organocatalyzed desymmetrization of *meso* glycerol derivatives is still a challenging issue in organic chemistry.

We previously reported the kinetic resolution of racemic secondary alcohols and carboxylic acids through asymmetric acylation promoted by L-histidine-derived bifunctional catalysts **6** (Figure 3.2).[6] Catalysts **6** contain an *N*-methylimidazole moiety as a nucleophilic base and a sulfonamidyl proton as a Brønsted acid, and induce high-level kinetic resolution through hydrogen bonding between the sulfonamidyl proton and a Brønsted basic site of the substrates. The 3-pyrroline-1-carbonyl (Pyroc) group is a useful directing group of substrates in **6**-catalyzed kinetic resolutions.[6d] The strong Brønsted basicity of Pyroc plays a key role in high-level asymmetric induction through the formation of strong hydrogen bonding with the sulfonamidyl proton of **6**. In addition, Pyroc can be selectively removed via DDQ oxidation[7] followed by hydrolysis through the use of NaOH without any loss of stereochemical integrity. We report here the desymmetrization of *meso* glycerol derivatives bearing a Pyroc group by a **6**-catalyzed asymmetric acylation reaction.

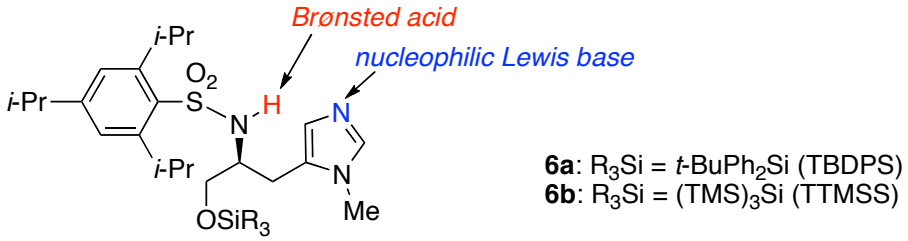


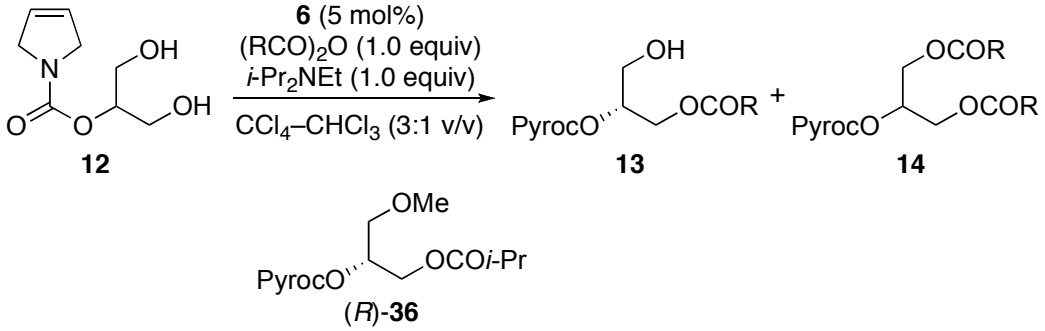
Figure 3.2. L-Histidine-derived Bifunctional Catalysts **6**

First, the desymmetrization of 2-*O*-Pyroc-glycerol **12** with a carboxylic anhydride (1.0 equiv) was examined in the presence of **6** (5 mol %) and *i*-Pr_2NEt (1.0 equiv) (Table 3.2). Although the use of a less polar solvent such as CCl_4 is the most suitable for obtaining high enantioselectivity, the reaction of **12** was carried out in CCl_4–$CHCl_3$ (3:1 v/v) due to the poor solubility of **12** in CCl_4. When the reaction with isobutyric anhydride (R = *i*-Pr) was conducted in the presence of **6a** at –20 °C, the corresponding monoester (*R*)-**13a** (R = *i*-Pr) was obtained in 37% yield with 98% ee along with diester **14** (16%) (entry 1). The Pyroc group successfully acted as a directing group in the **6a**-catalyzed desymmetrization of **12**. The **6a**-catalyzed kinetic resolution of racemic **13a** with $(i\text{-PrCO})_2O$ (0.5 equiv) gave (*R*)-**13a** in 53% yield with 82% ee along with 47% yield of **14a** [Selective factor: S $(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})^8 = 74$] (Scheme 3.7). These results indicated that (*S*)-**13a** was more reactive than (*R*)-**13a** in the **6a**-catalyzed acylation. The second acylation (acylation of generated **13a**) in the desymmetrization of **12** should increase the enantiomeric excess of monoacylated product **13a**.

Despite the high enantioselectivity of the **6a**-catalyzed desymmetrization of **12**, the yield of **13a** did not increase further even when the reaction time was prolonged. The catalysis of **6a** might be inhibited by the interaction of generated **13a**, since the reaction was significantly prevented by the addition of optically active (*R*)-**36** (0.7 equiv, 98% ee) (entry 3). To overcome this problem, the reaction conditions were investigated. We found that the use

of 3 equivalents of *i*-Pr_2NEt significantly improved the yield of **13a** to 55% and suppressed the generation of **14a** to 6% (entry 3). Alternatively, when the reaction was conducted at ambient temperature, the yield of **13a** increased to 61%, while the enantioselectivity decreased to 81% ee (entry 4). These reaction conditions might successfully prevent the interaction between **6a** and **13a**. The use of bulkier catalyst **6b** gave improved enantioselectivity without any loss of reactivity (61% yield, 91% ee, entry 6).

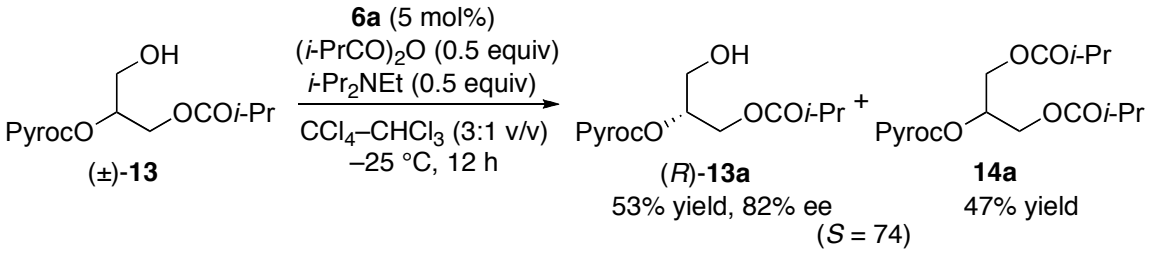
Table 3.2. Desymmetrization of 2-*O*-Pyroc-glycerol **12**



entry	**6**	R	T (°C), t (h)	yield of **13** (%)	ee of **13** (%)	yield of **14** (%)
1	**6a**	*i*-Pr	–20, 3	37	98	16
2[a]	**6a**	*i*-Pr	–20, 3	17	99	28
3[b]	**6a**	*i*-Pr	–20, 12	55	98	6
4	**6a**	*i*-Pr	rt, 3	61	81	13
5	**6b**	*i*-Pr	rt, 3	61	91	15
6	**6b**	Cy	rt, 15	74	93	13
7	**6b**	Et	rt, 2	63	94	12
8	**6b**	*t*-Bu	rt, 48	71	86	12

[a] The reaction was conducted in presence of (*R*)-**36** (0.7 equiv, 98% ee). [b] 3 equiv of *i*-Pr_2Net was used.

The reactivity and enantioselectivity of the **6**-catalyzed asymmetric acylations depended on the carboxylic anhydrides.[6] For the present **6b**-catalyzed desymmetrization of **12**, the use of cyclohexanecarboxylic anhydride (R = Cy) gave the best results (74% yield, 93% ee, **13b**/**14b** = 5.7, entry 7). Under the present reaction conditions, racemization of these monoesters through acyl migration was not observed. Although less bulky carboxylic anhydride (R = Et) gave the corresponding ester **13c** with high enantioselectivity, the corresponding monoester was too labile to racemize gradually through acyl migration (entry 8). More bulky pivalic anhydride (R = *t*-Bu) showed poor reactivity (entry 9).

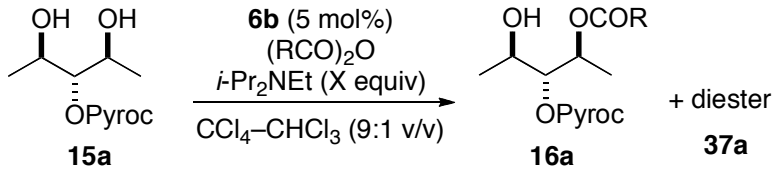


Scheme 3.7. Kinetic Resolution of Racemic **13**

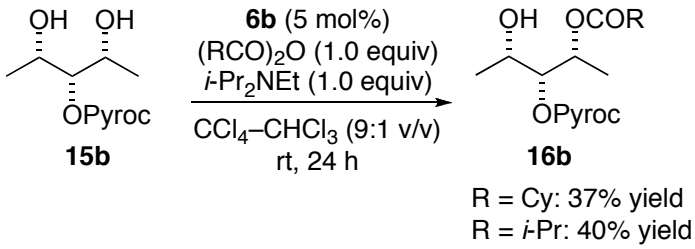
We next examined the desymmetrization of *meso* secondary 1,3-diol **15a** (Table 3.3). The solubility of **15a** in less polar solvent was good enough for the reaction to proceed in CCl_4–$CHCl_3$ (9:1 v/v). The reactivity of **15a** was lower than that of **12**, and the reaction required a prolonged reaction time to give the corresponding monoester **16a** in an appreciable yield. When the reaction of **15a** with $(CyCO)_2O$ (1.0 equiv) was conducted at ambient temperature for 24 h, **16a** was obtained in 59% yield with 89% ee (entry 1). The use of $(i\text{-PrCO})_2O$ significantly decreased the yield of **16a** and the ratio of **16a** to diester **37a**, although the enantioselectivity was high (entry 2). To improve the yield of **16a**, the reaction of **15a** was conducted with 1.3 equivalents of $(CyCO)_2O$ and 3 equivalents of $i\text{-Pr}_2NEt$. As a result, the reaction at ambient temperature increased the yield of **16a** (75%), and the enantioselectivity was slightly decreased (entry 3). When the reaction was conducted at

lower temperature (0–10 °C), the enantioselectivity was not improved (89–94% ee) with a slight decrease in the yield of **16a** (64–70 %) (entries 4 and 5). On the other hand, the desymmetrization of diastereomeric *meso* secondary 1,3-diol **15b** showed poor reactivity and enantioselectivity (Scheme 3.9).

Table 3.3. Desymmetrization of 3-*O*-Pyroc-2,3,4-pentanetriol **15a**



entry	R [equiv]	X	T (°C), t (h)	yield of **16a** (%)	ee of **16a** (%)	**16a**/**37a**
1	Cy [1.0]	2	rt, 24	59	98	3.1
2[a]	*i*-Pr [1.0]	2	rt, 12	34	99	1.5
3	Cy [1.3]	3	rt, 4	71	95	3.1
4	Cy [1.3]	3	10, 24	70	81	2.5
5	Cy [1.3]	3	0, 24	64	91	2.4



Scheme 3.9. Desymmetrization of **15b**

In the **6**-catalyzed kinetic resolution of racemic secondary alcohols, intermolecular hydrogen bonding between the sulfonamidyl proton in **6** and the carbamoyl oxygen of the

substrates has been proposed to promote the acylation by a proximity effect with high enantioselectivity.[6] Based on this intermolecular hydrogen bonding, plausible transition-state assemblies **38** and **39a** were proposed for the present desymmetrization of **12** and **15a** (Figure 3.3). In these transition-state assemblies, pro-(*R*) hydroxyl groups of **12** and **8a** would be placed close to the acyl ammonium moiety and acylated selectively. In addition, the pro-(S) hydroxyl proton might be interact with the sulfonyl oxygen to stabilize the conformation of the transition state. In contrast, for the desymmetrization of **15b**, steric repulsion between the methyl group (R^b) and the Pyroc group would direct the pro-(*R*) hydroxyl group outside in the transition-state assembly **39b**, which might cause poor reactivity and enantioselectivity.

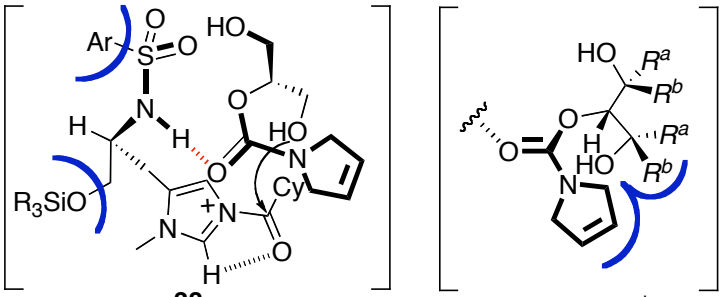
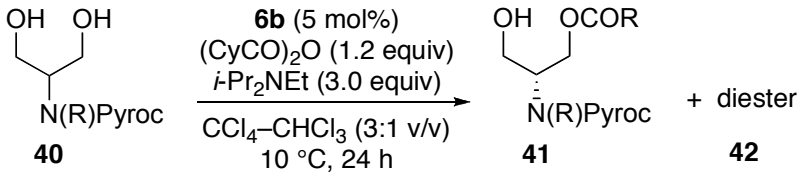


Figure 3.3. Plausible Transition-State Assemblies **38** and **39**

For further application of the present method, we investigated *meso* 2-amino-1,3-propanediols bearing a Pyroc group at the 2-position (Table 3.4). First, the desymmetrization of *N*-Pyroc-2-amino-1,3-propanediol **40a** (R = H)[4] was examined in $CHCl_3$ due to the poor solubility of **40a**. The reaction with $(CyCO)_2O$ (1.2 equiv) gave the corresponding monoester **41a** in 64% yield with 59% ee (entry 1). The moderate enantioselectivity was probably due to the high polarity of the reaction solvent. Therefore, we next examined the desymmetrization of *N*-methyl and *N*-benzyl derivatives **40b** and **40c**,

both of which could be dissolved in CCl_4–$CHCl_3$ (3:1 v/v). Disappointingly, the yield and enantioselectivity of **41** decreased with an increase in the steric bulkiness of the substituent on the nitrogen (entries 1–3). Furthermore, the desymmetrization of **40c** predominantly gave the corresponding diester **42c** (**41c**/**42c** = 0.45, entry 3). Steric hindrance of the substituents on the nitrogen, which would be directed to the catalyst in the transition-state, might prevent interaction with the catalyst.

Table 3.3. Desymmetrization of 3-*N*-Pyroc-1,3-propanediols **40**



entry	**40** [R]	yield of **41** (%)	ee of **41** (%)	**41**/**42**
1[a]	**40a** [H]	64	59	2.4
2	**40b** [Me]	60	55	2.7
3	**40c** [Bn]	15	11	0.45

[a] The reaction was conducted in $CHCl_3$

In conclusion, we have demonstrated the desymmetrization of acyclic *meso* 1,3-diols by asymmetric acylation induced by bifunctional catalyst **6b**. A Pyroc group successfully acted as a directing group through intermolecular hydrogen bonding for high-level asymmetric induction.

References and Notes

1. For reviews of the enzymatic desymmetrization of *meso* diols, see: (a) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313. (b) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557. (c) Chênevert, R.; Pelchat, N.; Jacques, F. *Curr. Org. Chem.* **2006**, *10*, 1067. (d) de María, P. D.; García-Burgos, C. A.; Bargeman, G.; van Gemert, R. W. *Synthesis* **2007**, 1439. (e) Hudlicky, T.; Reed, J. W. *Chem. Soc. Rev.* **2009**, *38*, 3117.
2. (a) Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021. (b) Trost, B. M.; Malhotra, S.; Mino, T.; Rajapaksa, N. S. *Chem. Eur. J.* **2008**, *14*, 7648.
3. (a) Oriyama, T.; Taguchi, H.; Terakado, D.; Sano, T. *Chem. Lett.* **2002**, *31*, 26. (b) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410. (c) Yamada, S.; Misono, T.; Masumizu, A.; Akiyama, Y. *J. Org. Chem.* **2006**, *71*, 6872. (d) Matsumoto, K.; Mitsuda, M.; Ushijima, N.; Demizu, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 8453. (e) Jung, B.; Hong, M. S.; Kang, S. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2616. (f) Fiori, K. W.; Puchlopek, A. L. A.; Miller, S. J. *Nature Chem.* **2009**, *1*, 630. (g) Sano, S.; Tsumura, T.; Tanimoto, N.; Honjo, T.; Nakao, M.; Nagao, Y. *Synlett* **2010**, 256.
4. (a) Honjo, T.; Nakao, M.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y.; Nagao, Y. *Org. Lett.* **2007**, *9*, 509. (b) Hong, M. S.; Kim, T. W.; Jung, B.; Kang, S. H. *Chem. Eur. J.* **2008**, *14*, 3290. (c) Mitsuda, M.; Tanaka, T.; Tanaka, T.; Demizu, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 8073.
5. For selected examples of the desymmetrization of acyclic *meso* 1,2-diols through asymmetric acylation, see: (a) Müller, C. E.; Zell, D.; Schreiner, P. R. *Chem. Eur. J.* **2009**, *15*, 9647. (b) Kündig, E. P.; Garcia, A. E.; Lomberget, T.; Garcia, P. P.; Romanens, P. *Chem. Commun.* **2008**, 3519. (c) Vedejs, E.; Daugulis, O.; Tuttle, N. *J.*

Org. Chem. **2004**, *69*, 1389. (d) Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379. (e) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem. Int. Ed.* **2003**, *42*, 3383. (f) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052.

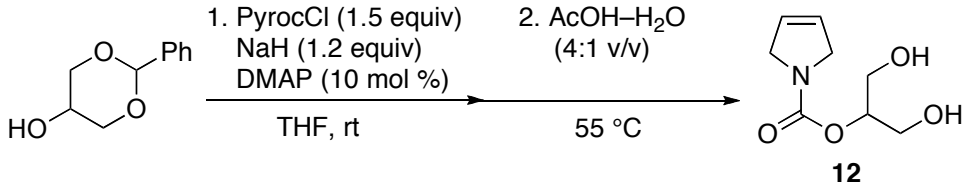
6. (a) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (b) Ishihara, K.; Kosugi, Y.; Akakura, M. *Tetrahedron* **2007**, *63*, 6191. (c) Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191. (d) Sakakura, A.; Umemura, S.; Ishihara, K. *Synlett* **2009**, 1647. (e) For an account article, see: Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686.
7. (a) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105. (b) Ohri, R. V.; Radosevich, A. T.; Hrovat, K. J.; Musich, C.; Huang, D.; Holman, T. R.; Toste, F. D. *Org. Lett.* **2005**, *7*, 2501.
8. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

Experimental Section

General Methods.

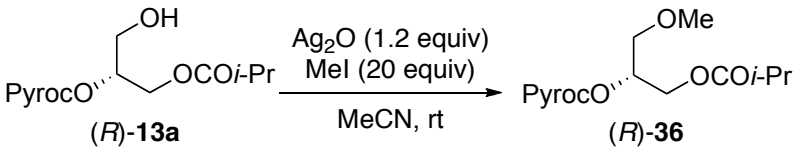
Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm), Daicel CHIRALPAK AD-H (4.6 mm × 25 cm) or Daicel CHIRALCEL AS-H (4.6 mm × 25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. Melting points were determined using a Yanaco MP-J3. The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385 or Fuji Silysia Chemical Ltd. Cromatorex® NH-DM1020). Microanalyses were performed at the Graduate School of Agriculture, Nagoya University. High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer. In experiments that required dry solvent, ether, *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from TCI or Wako as the “anhydrous” and stored over MS 4Å. Benzene, hexane, toluene, and dichloromethane were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially.

Preparation of 2-*O*-Pyroc-glycerol 12.



To a solution of 2-phenyl-1,3-dioxan-5-ol[1] (570 mg, 3.2 mmol) and PyrocCl (630 mg, 4.8 mmol, 1.5 equiv) in THF (10 mL) were added NaH (150 mg, 60% in oil, 3.8 mmol, 1.2 equiv) and DMAP (40 mg, 0.33 mmol, 10 mol %) at 0 °C. The mixture was stirred at ambient temperature for 1 h. After cooled to 0 °C, the reaction mixture was poured onto a 1 M aqueous HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc = 3:2 → 1:2) to give 2-phenyl-1,3-dioxan-5-yl 2,5-dihydro-1*H*-pyrrole-1-carboxylate in 85% yield (880 mg). The obtained 2-phenyl-1,3-dioxan-5-yl 2,5-dihydro-1*H*-pyrrole-1-carboxylate (880 mg) was dissolved in AcOH (8 mL) and H_2O (2 mL), and heated at 55 °C for 3 h. After the reaction mixture was concentrated, the residue was purified by column chromatography on silica gel (DIOL, hexane–EtOAc = 2:1 → 1:3) to give **12** in 90% yield (460 mg).

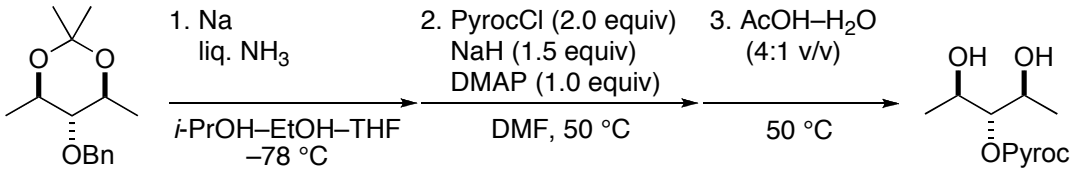
Preparation of (*R*)-6.



To a solution of (*R*)-**13a** (64 mg, 0.25 mmol) in MeCN (1 mL) were added MeI (310 mL, 710 mg, 5.0 mmol, 20 equiv) and Ag_2O (72 mg, 0.3 mmol, 1.2 equiv) at ambient temperature, and the mixture was stirred at the same temperature for 15 h, then heated at 60 °C for 7 h. After cooled to ambient temperature, the reaction mixture was filtered by Celite pad. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column

chromatography on silica gel (hexane–EtOAc = 7:1 → 3:1) to give (*R*)-**36** in 75% yield (51 mg).

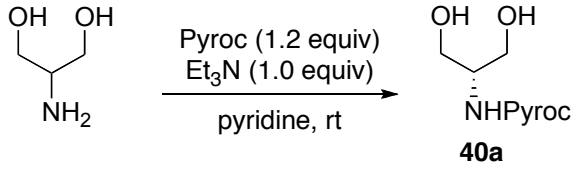
Preparation of 3-*O*-Pyroc-2,4-propanediol 8a.



15a

To a solution of (4*S*,5*s*,6*R*)-5-(benzyloxy)-2,2,4,6-tetramethyl-1,3-dioxane[2] (2.0 g, 8.2 mmol) in liq. NH_3 (30 mL), *i*-PrOH (6 mL), EtOH (6 mL) and THF (24 mL), was added Na (500 mg, 22 mmol, 2.7 equiv) at –78 °C, and the mixture was stirred at the same temperature for 2 h. workup. The crude product was purified by column chromatography on silica gel (hexane–EtOAc = 3:1) to give the corresponding alcohol. To a solution of the obtained alcohol and PyrocCl (1.3 g, 9.8 mmol, 1.2 equiv) in DMF (16 mL) were added NaH (490 mg, 60% in oil, 12.3 mmol, 1.5 equiv) and DMAP (1.0 g, 8.2 mmol, 1.0 equiv) at 0 °C, and the mixture was heated at 50 °C for 5 h. After cooled to ambient temperature, the reaction mixture was poured onto 1 M aqueous HCl and extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (hexane–Et_2O = 10:1 → 3:1). The obtained Pyroc-protected compound was dissolved in AcOH (12 mL) and H_2O (3 mL), and heated at 50 °C for 3 h. After the reaction mixture was concentrated under reduced pressure, the residue was purified by column chromatography on silica gel (DIOL, hexane–EtOAc = 2:1 → 1:1) to give **15a** in 77% yield (3 steps, 1.4 g).

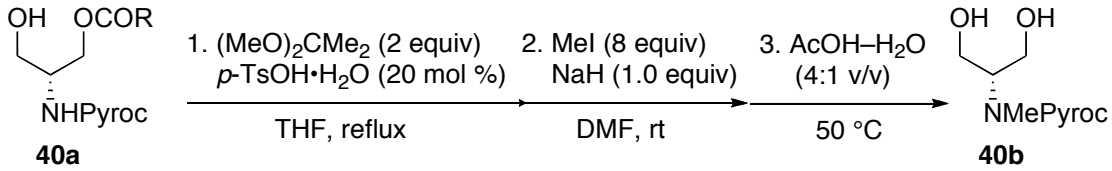
Preparation of *N*-Pyroc-2-amino-1,3-propanediol 40a.



40a

To a solution of 2-aminopropane-1,3-diol (1.2 g, 13 mmol) and PyrocCl (2.0 g, 16 mmol, 1.2 equiv) in pyridine (13 mL) were added Et_3N (1.8 mL, 13 mmol, 1.0 equiv) and DMAP (60 mg, 0.5 mmol, 3.7 mol%) at 0 °C, and the mixture was stirred at the same temperature for 3 h. After the reaction mixture was evaporated *in vacuo*, the residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH = 20:1 → 5:1) to give **40a** in 92% yield (2.2 g).

Preparation of *N*-methyl-*N*-Pyroc-2-amino-1,3-propanediol 40b.

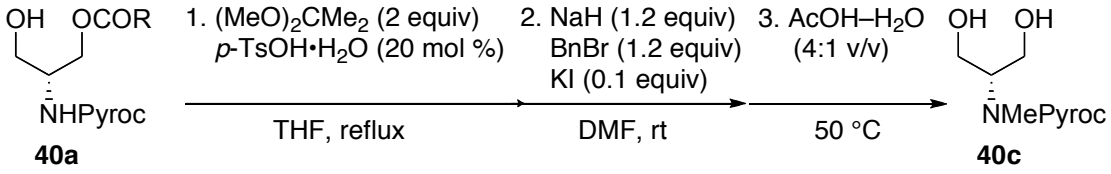


40a **40b**

To a solution of **40a** (560 mg, 3.0 mmol) and 2,2-dimethoxypropane (740 mL, 6.0 mmol, 2.0 equiv) in THF (30 mL) was added *p*-TsOH•H_2O (114 mg, 20 mol %), and the mixture was refluxed for 2 h. After cooled to ambient temperature, the reaction was quenched by the addition of Et_3N. The resultant mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc = 1:2 → EtOAc) to give the desired acetonide. To a solution of the obtained acetonide in DMF (30 mL) were added NaH (120 mg, 60% in oil, 3.0 mmol, 1.0 equiv) and MeI (1.5 ml, 24 mmol, 8 equiv), and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured onto ice-cold water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 3:1 → 1:5) the desired *N*-methylated product. The obtained *N*-methyl compound was dissolved in AcOH (10 mL)

and H_2O (2.5 mL) and heated at 50 °C for 3 h. After the reaction mixture was evaporated, the residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH = 25:1 → 9:1) to give **40b** in 61% yield (3 steps, 370 mg)

Preparation of *N*-benzyl-*N*-Pyroc-2-amino-1,3-propanediol 40c.



To a solution of **40a** (190 mg, 1.0 mmol) and 2,2-dimethoxypropane (250 mL, 2.0 mmol, 2.0 equiv) in THF (10 mL) was added *p*-TsOH•H_2O (38 mg, 20 mol %), and the mixture was refluxed for 2 h. After cooled to ambient temperature, the reaction was quenched by the addition of Et_3N. The resultant mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc = 1:2 → EtOAc) to give the dedired acetonide. To a solution of the obtained acetonide in DMF (10 mL) were added NaH (48 mg, 60% in oil, 1.2 mmol, 1.2 equiv), BnBr (120 mL, 1.2 mmol, 1.2 equiv) and KI (17 mg, 0.1 mmol, 10 mol %) at ambient temperature, and the mixture was stirred at the same temperature overnight. After cooled to 0 °C, the reaction mixture was poured onto water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc = 10:1 → 1:1) to give the desired *N*-benzylated product. The obtained *N*-benzylated product was dissolved in AcOH (4 mL) and H_2O (1 mL), and heated at 50 °C for 3 h. After the reaction mixture was evaporated, the residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH = 30:1 → 10:1) to give **40c** in 27% yield (3 steps, 74 mg).

Representative Procedure for the Desymmetrization of *Meso* 1,3-Diols by 6-induced

Enantioselective Esterification Reaction.

General procedure for the desymmetrization of 2-*O*-Pyroc-glycerol **12** with carboxylic anhydride.

To a solution of racemic alcohol (0.24 mmol) and catalyst **6** (0.012 mmol) in $CHCl_3$ (1.2 mL) and CCl_4 (3.6 mL) were added *i*-Pr_2NEt (41.8 mL, 0.24 mmol) and carboxylic anhydride (0.24 mmol) at ambient temperature or –20 °C (for each reaction temperature). After being stirred at ambient temperature or –20 °C, the reaction mixture was treated with 0.1 M HCl aqueous solution and extracted with EtOAc. The organic layer was washed with Bribe, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc = 2:1 → 1:2) to give the desired mono ester. The ee value was determined by HPLC analysis of the crude products. The *S* value was estimated by the following equation, $S = \ln[1-c(1+ee_{ester})]/\ln[1-c(1-ee_{ester})]$.[3]

References

(1) Jurij, S.; Gerhard, N.; Bernhaed, K.; Juergen, E.; Peter, H.; Frankfurt, W. *Angew. Chem. Int. Ed.* **1995**, *32*, 238

(2) (a) Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021. (b) Fiori, K. W.; Puchlopek, A. L. A.; Miller, S. J. *Nature Chem.* **2009**, *1*, 630.

(3) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

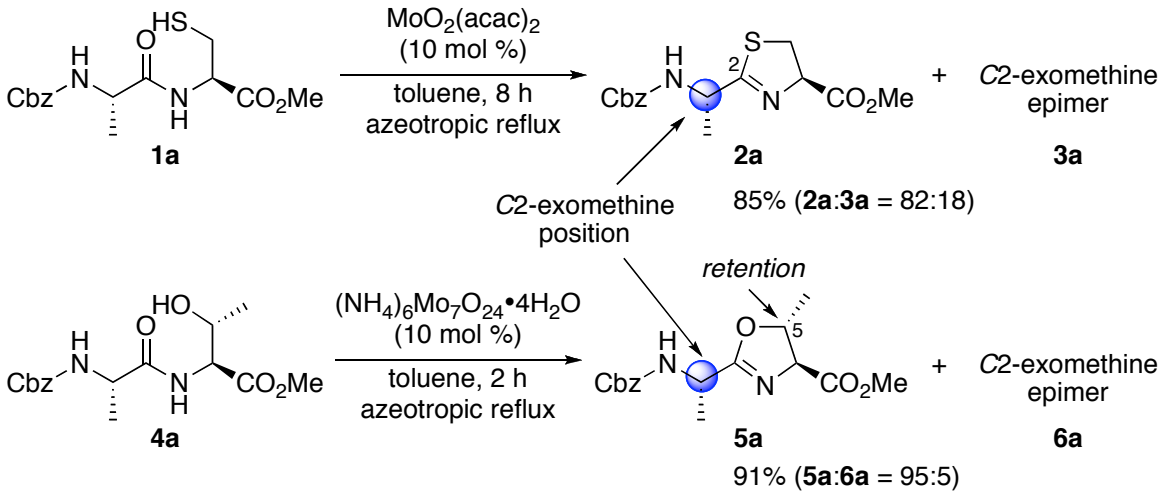
Appendix 1

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

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

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

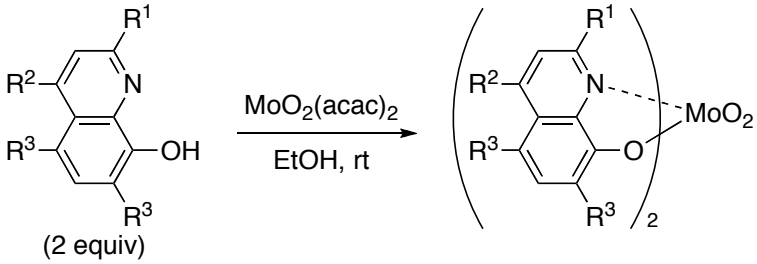
Recently, we reported molybdenum oxides (10 mol %) as effective acid-base monoconjugate catalysts[7] for the biomimetic dehydrative cyclization of *N*-acylcysteines, *N*-acylthreonines and *N*-acylserines (Scheme A1.1).[8] $MoO_2(acac)_2$ has good catalytic activity for the dehydrative cyclization of cysteine-containing dipeptide **1a** to thiazoline **2a**. For the synthesis of oxazoline **5a** from dipeptide **4a** that includes a threonine residue, the ammonium salts $(NH_4)_6Mo_7O_{24}•4H_2O$ and $(NH_4)_2MoO_4$ show good catalytic activities. Since the molybdenum(VI) oxide-catalyzed dehydrative cyclization of L-threonine derivatives proceeds with a retention of configuration at the 5-position, the molybdenum(VI) oxide-catalyzed method is very useful for the synthesis of naturally occurring oxazolines derived from L-threonine. This method is the first successful example of the catalytic dehydrative cyclization of dipeptides that include cysteine, threonine and serine residues. Thiazolines and oxazolines such as **2a** and **5a** are useful building blocks for the synthesis of various bioactive natural products.[4–9]



Scheme A1.1. Molybdenum(VI)oxide-Catalyzed Dehydrative Cyclization of Peptides[8]

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

Bis(quinolinolato)dioxomolybdenum(VI) complexes **7**–**12** were easily prepared from $MoO_2(acac)_2$ and known 8-quinolinols (2 equivs.) in EtOH in yields of 69–99% (Scheme A1.2). The structures of the bis(quinolinolato)dioxomolybdenum(VI) complexes were confirmed by ^{1}H NMR, IR, HR-MS, and X-ray crystallographic analyses. The X-ray single-crystal structures of **9** and **10** are shown in Figure 1. These hexacoordinated complexes may have a total of three arrangements: a) the two quinolinolato nitrogen atoms are *cis* to both oxo groups (*N-cis*); b) each nitrogen atom is *trans* to one oxo group (*N-trans*) and c) one nitrogen atom is *cis* to the oxo groups and the other is *trans* to one oxo group (*N-cis,trans*).[13] X-ray crystallographic analyses revealed that both **9** and **10** had *N-trans* configurations (Figure A1.1).[14] The X-ray single crystal structure of **10** is more distorted than that of **9** (O1–Mo–O2 bond angle of **9** = 163.69° and that of **10** = 147.96°). ^{1}H NMR spectra indicated that **9** was a 44:56 isomeric mixture in toluene-d_8 at ambient temperature. When the solution was heated at 100 °C, the ratio changed to 100:0. For **10**, the ratio of the isomers in toluene-d_8 was 77:23 at ambient temperature and 100:0 at 60 °C. The major isomers at high temperature are thought to be *N-trans*, and the minor isomers are *N-cis,trans*.



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

Scheme A1.2. Preparation of Bis(quinolinolato)dioxomolybdenum(VI) Complexes

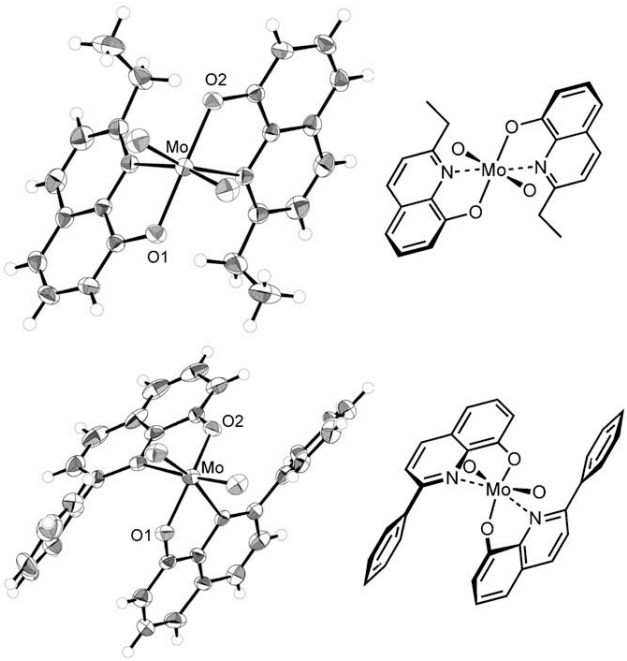
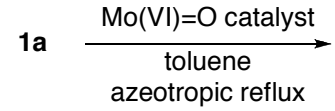


Figure A1.1. X-ray Single-Crystal Structures of **9** (top) and **10** (bottom)

With the bis(quinolinolato)dioxomolybdenum(VI) complexes **7**–**12** in hand, we examined their catalytic activities for the dehydrative cyclization of **1a** to thiazoline **2a** (Table A1.1). The reaction was conducted in the presence of a bis(quinolinolato)dioxomolybdenum(VI) complex in toluene under azeotropic reflux conditions with the removal of water. Molybdenum(VI) complexes 7–12 could be dissolved in toluene and appeared to be stable under these reaction conditions. After removal of the solvent, the resulting crude product was analyzed by HPLC. 8-Quinolinolato complex **7** (10 mol %) showed good catalytic activity (80% yield), and the generation of epimer **3a** was effectively reduced, as expected (**2a**:**3a** = 96:4) (entry 1). We then tried to reduce the catalyst loading, but unfortunately the use of 1 mol% of **7** decreased the reactivity (entry 2). Interestingly, we found that the introduction of an alkyl group to the 2-position of the 8-quinolinol significantly increased the catalytic activities of the quinolinolato complexes (entries 3–6). In particular, 2-ethyl-8-quinolinolato complex **9** and 2,4-dimethyl-8-quinolinol complex **11** exhibited remarkably higher catalytic activities than

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

Table A1.1. Catalytic Activities of Bis(quinolinolato)dioxomolybdenum(VI) Complexes for the Dehydrative Cyclization of **1a**[a]

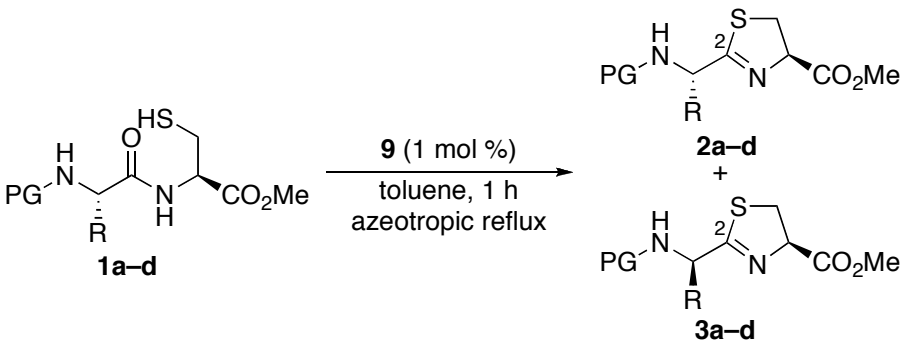


entry	Mo(VI)=O [mol %]	time (h)	yield[b] (%)	*dr*[c] (**2a**:**3a**)
1	**7**, [10]	5	80	96:4
2	**7**, [1]	5	40	89:11
3	**8**, [1]	5	93	95:5
4	**9**, [1]	2	96	97:3
5	**10**, [1]	5	80	85:15
6	**11**, [1]	5	96	96:4
7	**12**, [1]	2	94	86:14
8	$MoO_2(acac)_2$, [10]	8	85	82:18

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

We then examined the dehydrative cyclization of other cysteine-containing dipeptides, Cbz-L-Phe-L-Cys-OMe (**1b**), Boc-L-Ala-L-Cys-OMe (**1c**) and Fmoc-L-Ala-L-Cys-OMe (**1d**) (Table A1.2). Dipeptides **1a**–**d** could be converted to the corresponding thiazolines **2a**–**d** in good isolated yields (82–91%). *tert*-Butoxycarbonyl (Boc) and 9-fluorenylmethoxycarbonyl (Fmoc) groups, which are useful protecting groups for the synthesis of peptides and peptide-containing natural products, were also compatible with the reaction conditions (entries 3 and 4). In all cases, epimerization of the *C*2-exomethine position was suppressed to less than 6%.

Table A1.2. Dehydrative Cyclization of Dipeptide **1** to Thiazoline **2** Catalyzed by **9**[a]

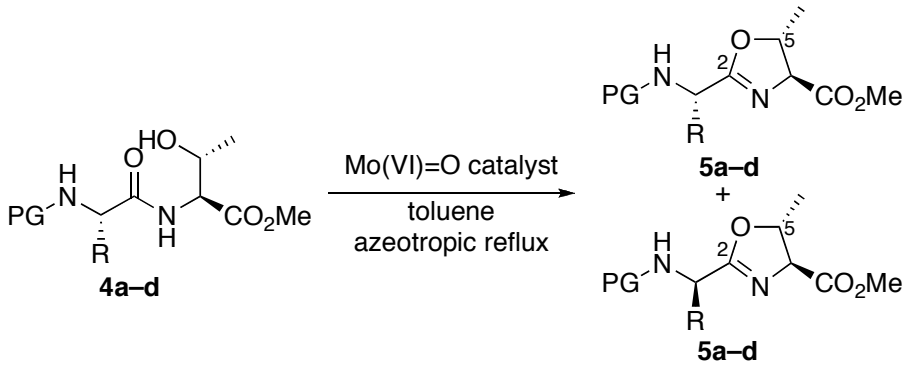


entry	dipeptide **1**			yield[b] (%)	*dr*[c] (**2a**:**3a**)
	PG	R			
1	Cbz	Me	**1a**	83	99:1
2	Cbz	Bn	**1b**	85	98:2
3	Boc	Me	**1c**	82	94:6
4	Fmoc	Me	**1d**	91	96:4

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

[c] Determined by HPLC analysis.

Table A1.3. 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*[c] (**2a**:**3a**)
1	**7**, [10]	Cbz	Me	**4a**	5	70[d]	81:19
2	**8**, [10]	Cbz	Me	**4a**	5	51[d]	98:2
3	**10**, [1]	Cbz	Me	**4a**	1	85	94:6
4	**10**, [1]	Cbz	Bn	**4b**	1	92	96:4
5	**10**, [1]	Boc	Me	**4c**	2	89	98:25
6	**10**, [1]	Fmoc	Me	**4d**	1	88	95:5
7	**12**, [1]	Cbz	Me	**4a**	6	42[d]	nd
8	$(NH_4)_6Mo_7O_{24}$•$4H_2O$, [10]	Cbz	Me	**4a**	2	91[d]	95:5

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

We previously reported the dehydrative cyclization of **4a** to oxazoline **5a** in good yields using $(NH_4)_6Mo_7O_{24}$•$4H_2O$ and $(NH_4)_2MoO_4$ as catalysts.[8] This reaction was accompanied by epimerization at the *C*2-exomethine position (95:5 *dr*) (Table A1.3, entry 8).

We then compared the catalytic activities of bis(quinolinolato)dioxomolybdenum complexes for the dehydrative cyclization of threonine-containing dipeptides Cbz-L-Ala-L-Thr-OMe (**4a**), Cbz-L-Phe-L-Thr-OMe (**4b**), Boc-L-Ala-L-Thr-OMe (**4c**) and Fmoc-L-Ala-L-Thr-OMe (**4d**) to the corresponding oxazolines **5a**–**d** (Table A1.3). Although **7** and **8** showed moderate catalytic activities (entries 1 and 2), 2-phenyl-8-quinolinolato complex **10** gave excellent results (entries 3–6). The catalytic activity of the homogeneous complex **10** was higher than those of heterogeneous $(NH_4)_2MoO_4$ and $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$, and the amount of **10** could be reduced to 1 mol%. Furthermore, the yield of epimers **6a**–**d** was less than 6%. The present reactions also showed a complete retention of configuration at the 5-position.

In conclusion, bis(2-ethyl-8-quinolinolato)dioxomolybdenum(VI) (**9**) promoted the catalytic dehydrative cyclization of cysteine-containing dipeptides **1** to thiazolines **2** in high yield without a significant loss of stereochemical integrity at the *C*2-exomethine positions. For the synthesis of threonine-derived oxazolines **5**, bis(2-phenyl-8-quinolinolato)dioxomolybdenum(VI)(**10**) showed excellent catalytic activity, and the reaction proceeded with a retention at the 5-position. In both reactions, catalyst loadings of 1 mol% were sufficient to give thiazolines and oxazolines in good yields. In addition to the total synthesis of thiazoline and/or oxazoline-containing natural products, the present method should also be applicable to the synthesis of thiazole- and/or oxazole-containing natural products,[15] since thiazoles and oxazoles could be prepared from thiazolines and oxazolines by oxidation.[16]

References and Notes

1. (a) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464–496, and references cited therein. (b) Lewis, J. R.; *Nat. Prod. Rep.* **2002**, *19*, 223–258, and references cited therein. (c) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T.; *Nat. Prod. Rep.* **1999**, *16*, 249–263.
2. (a) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 83–85. (b) Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 8679–8682. (c) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168. (d) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397–5400. (e) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907–910. (f) GalRotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807–2810. (g) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267–6270. (h) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 153–154. (i) Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649–3652. (j) Meyers, A. I.; Denton, H. *Tetrahedron Lett.* **1985**, *26*, 4687–4690. (k) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471–4474.
3. Kelly reported the synthesis of the thiazoline from Cbz-L-Phe-L-Cys(Tr)-OMe using $TiCl_4$ (300 mol %). However, complete epimerization at the *C*2-exomethine position occurred because of the strong acidity of $TiCl_4$: Raman, P.; Razavi, H.; Kelly, J. W. *Org. Lett.* **2000**, *2*, 3289–3292.
4. (a) You, S.-L.; Kelly, J. W. *Tetrahedron* **2005**, *61*, 241–249. (b) You, S.-L.; Kelly, J. W. *Chem. Eur. J.* **2004**, *10*, 71–75. (c) Yokokawa, F.; Sameshima, H.; In, Y.; Minoura, K.; Ishida, T.; Shioiri, T. *Tetrahedron* **2002**, *58*, 8127–8143. (d) Kutsumura, N.; Sata, N. U.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 847–850. (e) Yokokawa, F.; Sameshima, H.; Shioiri, T. *Synlett* **2001**, 986–988. (f) Wipf, P.; Miller, C. P.; Grant, C. M. *Tetrahedron* **2000**, *56*, 9143–9150. (g) Boden, C. D. J.; Norley, M. C.; Pattenden, G.

J. Chem. Soc., Perkin Trans. 1 **2000**, 883–888. (h) Boden, C. D. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 875–882. (i) Norley, M. C.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 3087–3090. (j) Boden, C. D. J.; Norley, M. C.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 9111–9114. (k) Boden, C. D. J.; Pattenden, G. *Tetrahedron Lett.* **1995**, *36*, 6153–6156.

5. Wipf reported the conversion of cis-oxazolines to transoxazolines; (a) Wipf, P.; Miller, C. P.; *J. Am. Chem. Soc.* **1992**, *114*, 10975–10977. (b) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575–1578. (c) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358–12367. (d) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826–831.
6. Corey reported the dehydrative cyclization of a threonine derivative using TsOH (10 mol %) as a catalyst. The reaction proceeds with a retention of configuration at the 5-position: Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230–6231. in our experiment, dehydrative cyclization of **4a** using TsOH gave a 1:1 mixture of **5a** and **6a** due to its strong acidity.
7. Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686.
8. (a) Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971–1974. (b) Sakakura, A.; Umemura, S.; Kondo, R.; Ishihara, K. *Adv. Synth. Catal.* **2007**, *349*, 551.
9. (a) Wagner, B.; Schumann, D.; Linne, U.; Koert, U.; Marahiel, M. A. *J. Am. Chem. Soc.* **2006**, *128*, 10513–10520. (b) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 5705–5708.
10. Yonetani, K.; Hirotsu, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3302–3305.
11. See Supporting Information for catalytic activities of other molybdenum(VI) complexes.
12. For recent studies of bis(quinolinolato)complex-catalyzed reactions, see: (a) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554–2555. (b) Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198–13199.

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

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

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

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

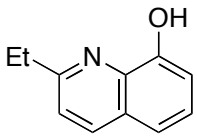
Experimental Section

General Method.

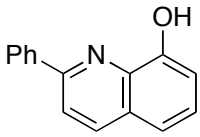
IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz) or Varian INOVA-500 spectrometer (125 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 a Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP instrument using a chiral column of Daicel CHIRALCEL AD-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 Center, 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. $MoO_2(acac)_2$ (Wako Pure Chemical Industries, Ltd.), $(NH_4)_6Mo_7O_{24}•4H_2O$ (Nacalai tesque), $(NH_4)_2MoO_4$ (Aldrich), 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. 2-Ethyl-8-quinolinol,[2] 2-phenyl-8-quinolinol,[3] 2,4-dimethyl-8-quinolinol,[4] 5,7-dibromo-2,4-dimethyl-8-quinolinol,[5] *cis*-bis(8-quinolinolato-*N,O*)dioxomolybdenum(VI) (**7**),[6]

cis-bis(2-methyl-8-quinolinolato-*N,O*)dioxomolybdenum(VI) (**8**),[7] thiazoline **2a**[8] and **2b**,[9] and oxazoline **5a**[8] were reported previously.

Preparation of dioxobis(quinolinolato)molybdenum(VI) Complexes

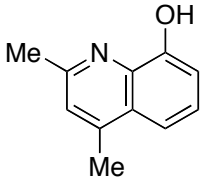


2-Ethyl-8-quinolinol.[2] A mixture of 0.26 M solution of EtLi in hexane–cyclohexane (9:1) (11.5 mL, 3.0 mmol) and 0.21 M solution of EtMgCl in THF (7.0 mL, 1.50 mmol) was stirred at –10 °C for 15 min under nitrogen atmosphere. To this solution was added a solution of 8-quinolinol (72.6 mg, 0.50 mmol) in THF (1 mL) at –78 °C. After being stirred at –10 °C for 5.5 h, the mixture was quenched by saturated aqueous NH_4Cl (5 mL), extracted with ether (15 mL), washed by brine (10 mL), dry over Na_2SO_4 and air was bubbled through the mixture for 2 h at rt. The combined organic layer was evaporated *in vacuo* and the residue was purified by column chromatography using a mixture of hexane–EtOAc (50/1 → 40/1 → 5/1) as an eluent to give the product as pale yellow solid (61.3 mg, 71%); ^{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).

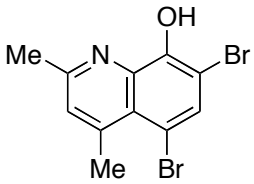


2-Phenyl-8-quinolinol. 2-Phenyl-8-quinolinol was prepared according to the reported procedure.[3] 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 1.5, 7.4 Hz, 1H), 7.32 (dd,

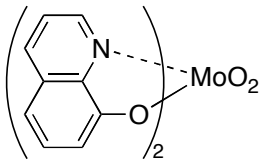
J = 1.5, 8.2 Hz, 1H), 7.43 (dd, *J* = 7.4, 8.2 Hz, 1H), 7.49–7.60 (m, 3H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.12–8.19 (m, 2H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.25–8.50 (s, 1H).



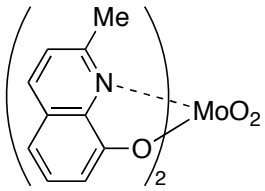
2,4-Dimethyl-8-quinolinol. 2,4-Dimethyl-8-quinolinol was prepared according to the reported procedure.[4] 45% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (d, *J* = 0.9 Hz, 3H), 2.67 (s, 3H), 7.13 (dd, *J* = 2.7, 6.0 Hz, 1H), 7.14 (s, 1H), 7.39 (d, *J* = 6.0 Hz, 1H), 7.40 (d, *J* = 2.7 Hz, 1H).



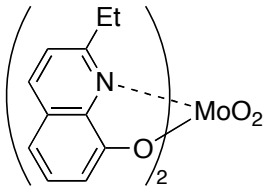
5,7-Dibromo-2,4-dimethyl-8-quinolinol. 5,7-Dibromo-2,4-methyl-8-quinolinol was prepared according to the reported procedure.[5] 92% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 1H), 2.66 (s, 3H), 3.05 (s, 3H), 7.19 (s, 1H), 7.87 (s, 1H)



***cis*-Bis(8-quinolinolato-*N,O*)dioxomolybdenum(VI) (7).** **7** was prepared according to the reported procedure.[6] 98% yield; 1H 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).

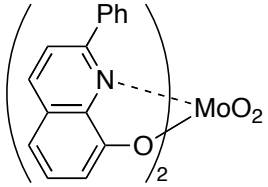


***cis*-Bis(2-methyl-8-quinolinolato-*N,O*)dioxomolybdenum(VI) (8).** **8** was prepared according to the reported procedure.[7] 99% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 0.75H), 2.73 (s, 0.75H), 2.95 (s, 3H), 3.41 (s, 1.5H), 5.30 (d, *J* = 7.5 Hz, 0.25H), 5.76 (d, *J* = 7.5 Hz, 0.25H), 6.20 (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 $CDCl_3$.

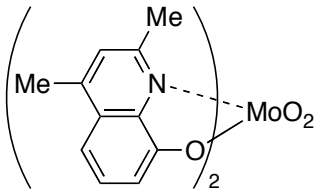


***cis*-Bis(2-ethyl-8-quinolinolato-*N,O*)dioxomolybdenum(VI) (9).** To a solution of $MoO_2(acac)_2$ (44.2 mg, 0.135 mmol) in EtOH (0.50 mL) was added a solution of 2-ethyl-8-quinolinol (47.0 mg, 0.27 mmol) in EtOH (1.0 mL). After being stirred at ambient temperature for 12 h, **9** was obtained by filtration (58 mg, 91%). Single crystals suitable for X-ray analysis were obtained from CH_2Cl_2. IR (KBr) 908 (Mo=O) cm^{-1}; ^{1}H 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),

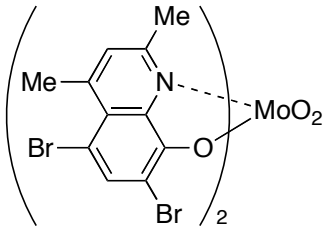
8.15 (d, J = 8.1 Hz, 0.4H), 8.29 (d, J = 8.7 Hz, 0.6H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0, 14.0, 14.8, 27.4, 29.1, 29.2, 111.7, 113.4, 114.7, 115.9, 116.0, 118.2, 122.2, 123.0, 123.3, 124.7, 126.4, 127.0, 127.7, 127.8, 130.2, 132.8, 136.8, 138.1, 138.5, 140.1, 144.6, 150.3, 156.5, 159.0, 166.4; **9** 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) (10).** To a solution of $MoO_2(acac)_2$ (65.2 mg, 0.20 mmol) in EtOH (0.50 mL) was added a solution of 2-phenyl-8-quinolinol (88.5 mg, 0.40 mmol) in EtOH (1.0 mL). After being stirred at ambient temperature for 15 min, **10** was obtained by filtration (91 mg, 80%). Single crystals suitable for X-ray analysis were obtained from EtOH. IR (KBr) 900 (Mo=O) cm^{-1}; ^{1}H 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; **10** 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) (11).** 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, **11** was obtained by filtration (41 mg, 87%). IR (KBr) 903 (Mo=O) cm^{-1}; ^1H 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; **11** 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) (12).** To a solution of MoO2(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, **12** was obtained by filtration (54.0 mg, 69%). IR (KBr) 1071, 803 cm^{-1}; ^1H 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. **12** 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.

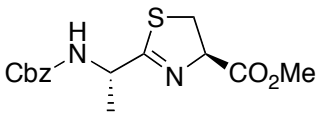
X-ray Crystallographic Analysis

Crystal data for 9. 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.

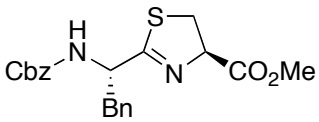
Crystal data for 10. Formula $C_{30}H_{20}MoN_2O_4$, colorless, crystal dimensions 0.50 × 0.40 × 0.40 mm^3, monoclinic, space group *Cc*(#7), a = 27.814(5) Å, b = 12.760(2) Å, c = 15.796(3) Å, β = 119.415(3)°, V = 4883.3(14) $Å^3$, Z = 8, and D_{calc} = 1.546 g cm^{-3}, F(000) = 2304, μ = 0.578 mm^{-1}, 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.

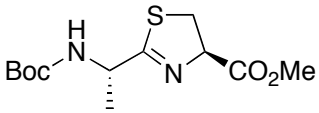
General Procedure for the Dehydrative Cyclization of Dipeptides 1 and 4. A 20-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 5-mL pressure-equalized addition funnel [containing a cotton plug and ca. 0.1 g of CaH_2] surmounted by a reflux condenser was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



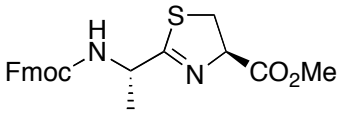
Thiazoline 2a. Spectral data of thiazoline **2a** were identical with those in ref 8. The data did not provide any evidence of the presence of the epimer **3a**. The diastereo ratio was determined by HPLC analysis on Develosil 30-5. **2a:** t_R = 32.2 min, **3a:** t_R = 34.3 min (hexane–EtOAc–MeOH = 64:16:1).



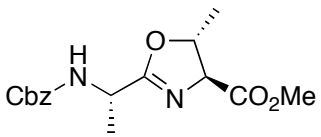
Thiazoline 2b. Spectral data of thiazoline **2b** were identical with those in ref 9. The diastereo ratio was determined by HPLC analysis on Develosil 30-5. **2b:** t_R = 16.1 min, **3b:** t_R = 17.6 min (hexane–EtOAc–MeOH = 32:8:1).



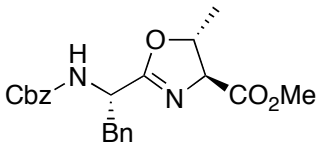
Thiazoline 2c. IR (neat) 3360, 1715, 1621, 1581, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.45(m, 3H), 3.53 (dd, *J* = 11.4, 9.6 Hz, 1H), 3.61 (dd, *J* = 11.4, 9.0 Hz, 1H), 3.82 (s, 3H), 4.52-4.65 (m, 1H), 5.11 (t, *J* = 9.6 Hz, 1H), 5.29 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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. **5b:** t_R = 64.4 min, **6b:** t_R = 58.8 min (hexane–*i*PrOH = 50:1).



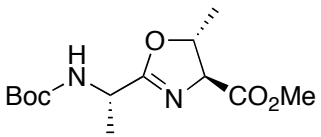
Thiazoline 2d. IR (neat) 3311, 1716, 1522, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.9 Hz, 3H), 3.51-3.65 (m, 2H), 3.82 (s, 3H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.33-4.47 (m, 2H), 4.66 (dq, *J* = 7.5, 6.9 Hz, 1H), 5.11 (t, *J* = 9.0 Hz, 1H), 5.62 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 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. **5b:** t_R = 25.9 min, **6b:** t_R = 27.1 min (hexane–EtOAc–MeOH = 32:8:1).



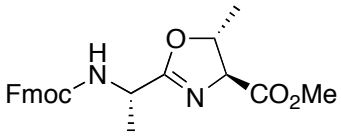
Oxazoline 5a.[8b] IR (KBr) 3326, 1724, 1661, 1531, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, *J* = 7.2 Hz, 3H), 1.44 (d, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 4.27 (d, *J* = 7.5 Hz, 1H), 4.52 (dq, *J* = 7.5, 7.2 Hz, 1H), 4.86 (dq, *J* = 7.5, 7.2 Hz, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 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 diastereo ratio was determined by HPLC analysis on Develosil 30-5. **5a:** t_R = 9.7 min, **6a:** t_R = 10.9 min (hexane–EtOAc–MeOH = 16:8:1).



Oxazoline 5b. 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. **5b:** t_R = 18.0 min, **6b:** t_R = 20.8 min (hexane–EtOAc–MeOH = 32:8:1).

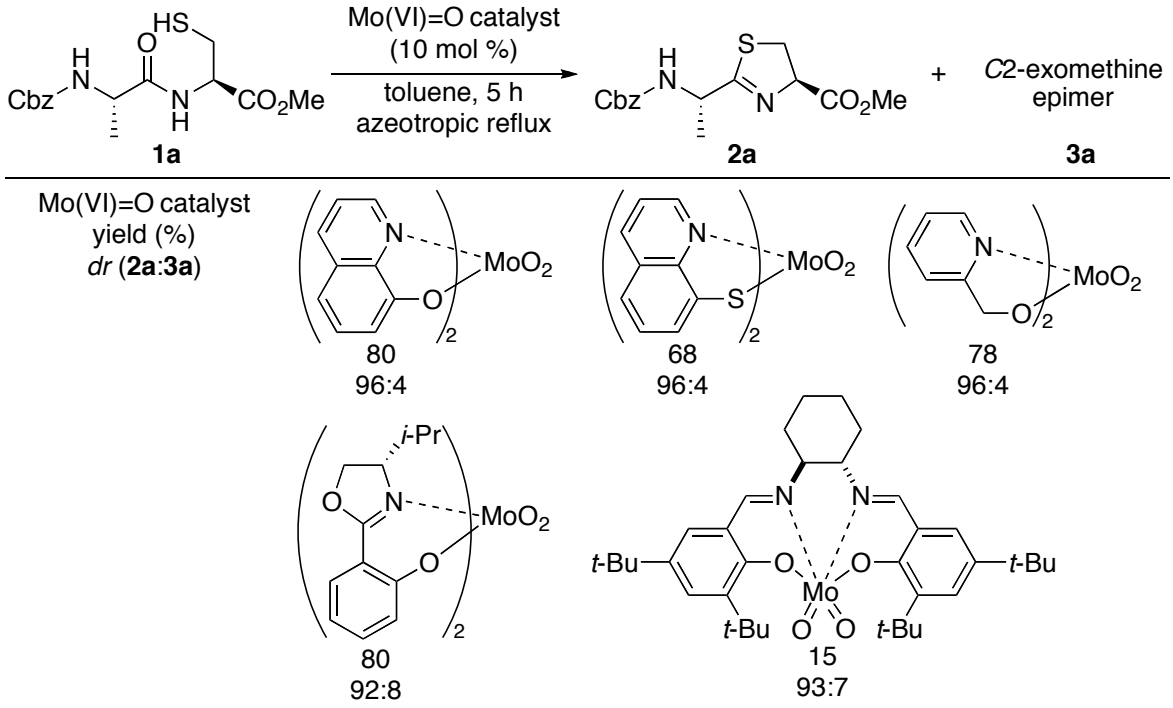


Oxazoline 5c. IR (KBr) 3370, 1715, 1661, 1506, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 1.45 (d, *J* = 6.3 Hz, 3H), 3.79 (s, 3H), 4.27 (d, *J* = 7.5 Hz, 1H), 4.45 (br q, *J* = 6.9 Hz, 1H), 4.86 (dq, *J* = 7.5, 6.3 Hz, 1H), 5.29 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{23}N_2O_5$ $[M+H]^+$ 287.1607, found 287.1617. The diastereo ratio was determined by HPLC analysis on AD-H. **5c:** t_R = 63.6 min, **6c:** t_R = 59.5 min (hexane–*i*PrOH= 50:1).



Oxazoline 5c. IR (KBr) 3425, 1618 cm^{-1}; ^1H 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 $C_{23}H_{25}N_2O_5$ $[M+H]^+$ 409.1763, found 409.1777. The diastereo ratio was determined by HPLC analysis on Develosil 30-5. **5c:** t_R = 23.2 min, **6c:** t_R = 29.0 min (hexane–EtOAc–MeOH = 32:8:1).

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



References

1. Sheldrick, G. M. SHELXL-97, *Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, 1997.
2. Kaneko, H.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1910.
3. Delapierre, G.; Brunel, J. M.; Constantieux, T.; Buono, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1345.
4. Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Synlett* **1997**, 445.
5. Phillips, J. P.; Elbinger, R. L.; Merritt, Jr., L. L. *J. Am. Chem. Soc.* **1949**, *71*, 3986.
6. (a) Dawoodi, Z.; Kelly, R. L. *Polyhedron* **1986**, *5*, 271. (b) Isbell, Jr., A. F.; Sawyer, D. T. *Inorg. Chem.* **1971**, *10*, 2449.
7. Fun, H.-K.; Sivakumar, K.; Niu, J.-Y.; Wang, J.-P.; You, X.-Z. *Acta Cryst.* **1996**, *C52*, 1150.

8. (a) Yonetani, K.; Hirotsu, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3302. (b) Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971.

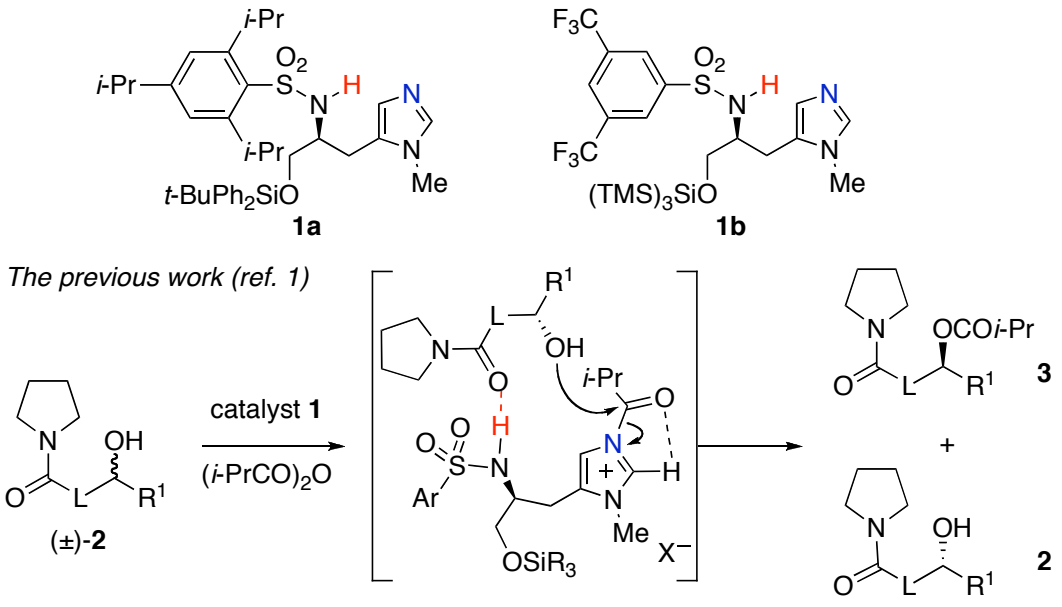
9. Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397.

Appendix 2

Kinetic Resolution of Racemic Carboxylic Acids by an L-Histidine-derived Sulfonamide-induced Enantioselective Esterification Reaction

Abstract: The direct and catalytic kinetic resolution of racemic carboxylic acids bearing a Brønsted base such as O-protected α-hydroxy carboxylic acids and N-protected α-amino acids has been accomplished through an L-histidine-derived sulfonamide-induced enantioselective esterification reaction with *tert*-butyl alcohol for the first time. Highly asymmetric induction [$S(k_{fast}/k_{slow})$ = up to 56] has been achieved under the equilibrium between a chiral catalyst and two diastereomeric acylammonium salts through an intramolecular hydrogen-bonding interaction.

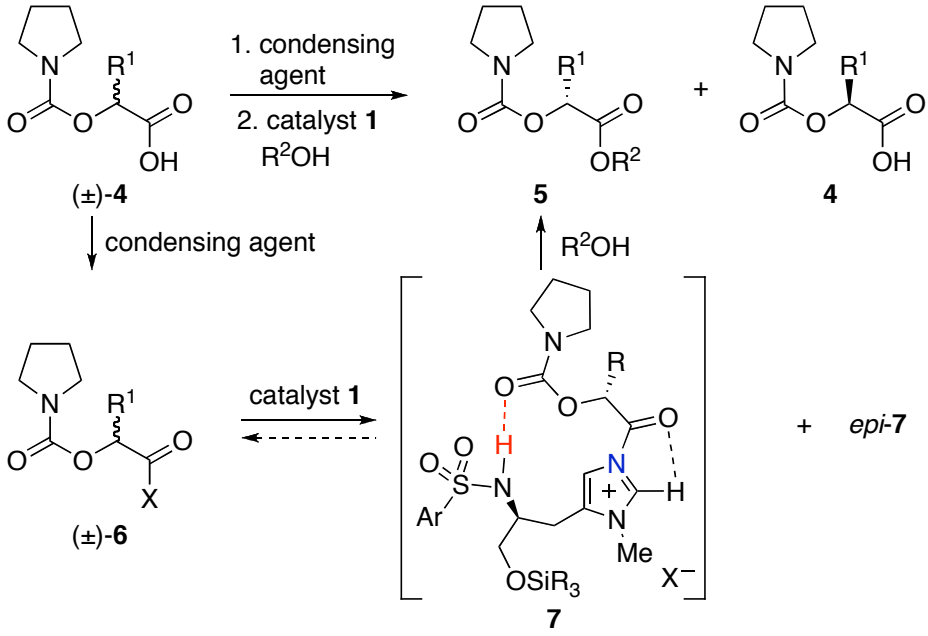
We recently described the kinetic resolution of racemic alcohols **2** bearing a Brønsted base site such as a carbamoyl oxygen by L-histidine-derived sulfonamide (**1**)-induced enantioselective acylation with isobutyric anhydride (Scheme A2.1).[1–3] Compounds **1** are small artificial acylases that contain an *N*-methylimidazole moiety as a nucleophilic base and a sulfonamidyl proton as a Brønsted acid and induce the highlevel kinetic resolution of (±)-**2** through hydrogen bonding between a sulfoamidyl proton of **1** and a carbonyl oxygen of **2**.



Scheme A2.1. Kinetic Resolution of (±)-**2**

We report here the kinetic resolution of racemic carboxylic acids **4** bearing a Brønsted base site as well as (±)-**2** by **1**-induced enantioselective esterification (Scheme A2.2). To the best of our knowledge, this is the first successful example of the *direct* kinetic resolution of racemic carboxylic acids induced by artificial enzymes. In contrast, there have been several reported examples of the enantioselective catalytic alcoholysis or thiolysis of racemic or prochiral 2-pyridinethiol esters,[4] oxazolidinethiones,[5] and cyclic carboxylic acid derivatives

or anhydrides.[6,7] However, such activated derivatives of racemic carboxylic acids must be used as isolated substrates for kinetic resolution.



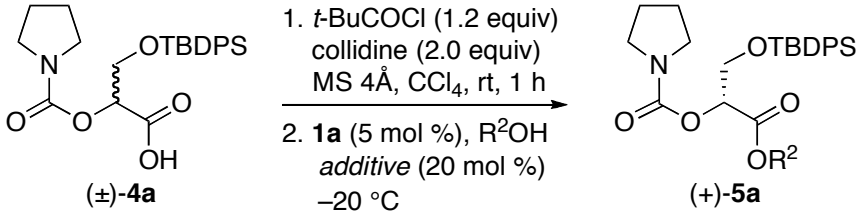
Scheme A2.2. Our Proposal for the Kinetic Resolution of (±)-**4**

Our proposal is shown in Scheme A2.2. If (±)-**4** can be activated as (±)-**6** with a suitable condensing agent in situ, the subsequent kinetic resolution of (±)-**6** may occur at the generation step of acylammonium salts **7** and *epi*-**7** with or without an enantioselective hydrogen bonding interaction between (±)-**6** and **1** regardless of alcohols (R^2OH) (*the first kinetic control*). However, if the conversion of (±)-**6** to **7** and/or *epi*-**7** is reversible, the enantioselectivity would be determined by the rate difference of the esterification of **7** and *epi*-**7** with R^2OH (*the second kinetic control*).

First, the esterification of (±)-**4a**, which was derived from (±)-glyceric acid with alcohols, was attempted in the presence of 5 mol % of **1a** in carbon tetrachloride at –20 °C (Table A2.1). **4a** was activated as a mixed anhydride **6a** (X = *t*-$BuCO_2$) with pivaloyl

chloride (1.2 equiv) in the presence of 2,4,6-collidine and MS 4Å in situ before the addition of **1a** (5 mol %) and alcohols (0.5~0.7 equiv).[8] Although the esterification of **6a** with benzyl alcohol proceeded even at –20 °C, kinetic resolution was observed at quite a low level (entry 1). The reactivity of benzyl alcohol is high enough to react with the mixed anhydride in the absence of **1a** (entry 1). This is one of the reasons why the esterification with benzyl alcohol showed poor enantioselectivity. The reaction with isopropyl alcohol in the presence of pivaloyl chloride (1.0 equiv) showed low reactivity and gave moderate enantioselectivity [Selective factor: $S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$[9]] = 1.8) (entry 3). The use of 1.2 equiv of pivaloyl chloride increased the reactivity without loss of enantioselectivity (entry 4). Interestingly, the addition of pivalic acid (20 mol %) improved the reactivity and enantioselectivity (S = 3.1, entry 5). Pivalic acid would probably serve as a Brønsted acid (ammonium proton) to activate **6a** or a nucleophilic base[10] or Brønsted base (pivalate anion) to assistthe equilibrium between **6a** and its acylammonium salt **7a** in the presence of collidine.[11] However, the enantioselectivity was still moderate. Surprisingly, the use of *tert*-butyl alcohol gave high enantioselectivity (S = 31, entry 8). Pivalic acid promoted the esterification with *tert*-butyl alcohol as well as that with isopropyl alcohol (entry 4 *versus* entry 5, entry 7 *versus* entry 8). The dramatic improvement in enantioselectivity upon switching from isopropyl alcohol to *tert*-butyl alcohol suggests that equilibrium between **4a** and **7a** may be important for attaining a high level of kinetic resolution.[12] These experimental results suggest that *the first kinetic resolution*at the generation step of **7a** would occur at a low level. However, when the esterification step was much slower than the generation step of **7a**, such as in entry 5, higher enantioselectivity was observed with *the second kinetic control*. In fact, higher asymmetric induction was observed with the dropwise addition of isopropyl alcohol (entry 5 *versus* entry 6). Catalyst **1b** was inferior to **1a** with regard to enantioselectivity (entry 9).

Table A2.1. Kinetic Resolution of (±)-**4** induced by **1a**[a]

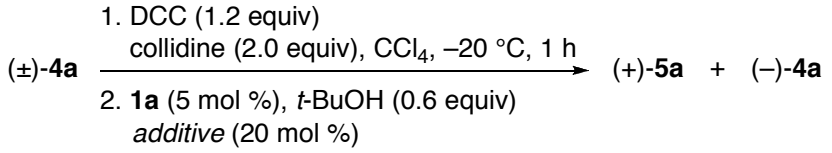


entry	R^2OH (equiv)	additive[b]	t (h)[b]	yield (%)[c] of **5a**	ee (%)[d] of **5a**, **4a**	S[e]
1[f]	BnOH, 0.5	—	6	14	—, —	—
2	BnOH, 0.5	—	6	31	6, 0	1
3[g]	*i*-PrOH, 0.7	—	24	34	23, —	1.8
4	*i*-PrOH, 0.7	—	22	55	27, —	2.3
5	*i*-PrOH, 0.7	*t*-$BuCO_2H$	19	69 [66]	28, 55	3.1 [2.9]
6[h]	*i*-PrOH, 0.5	*t*-$BuCO_2H$	25	50 [44]	69, 54	11 [9.3]
7	*t*-BuOH, 0.6	—	48	16	92, —	27
8	*t*-BuOH, 0.6	*t*-$BuCO_2H$	52	39	89, —	31
9[i]	*t*-BuOH, 0.6	*t*-$BuCO_2H$	24	29 [26]	73, 25	8.6 [8.3]

[a] Unless otherwise noted, (±)-**4a** (0.50 mmol) was used in CCl_4 (1.5 mL). TBDPS = Si*t*-$BuPh_2$. [b] For step 2. [c] Isolated yield. The conversion, which was calculated by using the ee's of **5a** and **4a**, is shown in brackets. [d] HPLC analysis. [e] The S was calculated by using the yield and ee of (+)-**5a**. The S, which was calculated by using the ee's of (+)-**5a** and (–)-**4a**, is shown in brackets. See ref 9. [f] The reaction was conducted in the absence of **1a**. [g] 1.0 equiv of *t*-BuCOCl was used. [h] After a solution of *i*-PrOH in CCl_4 (1.0 mL) was added dropwise to a solution of **6a** in CCl_4 (0.5 mL) for 24 h, the reaction mixture was stirred for 1 h. [i] **1b** was used instead of **1a**

Next, other condensing agents were examined for the above reaction. As shown in Table A2.2, the esterification of (±)-**4a** with *tert*-butyl alcohol proceeded more smoothly with the use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) instead of pivaloyl chloride at –20 °C under the same conditions as for entry 5 in Table A2.1 (entry 1). When DCC was used in the absence of pivalic acid and dried MS 4Å, the enantioselectivity and reactivity were further increased (entry 3). Thus, the esterification proceeded even at –40 °C with the use of DCC without the addition of pivalic acid to give (+)-**5a** in 38% yield with 94% ee (*S* = 56, entry 3).[13]

Table A2.2. Kinetic Resolution of (±)-**4** induced by **1a**[a]

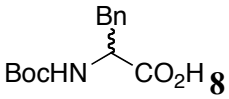
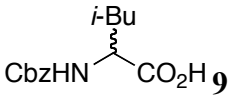
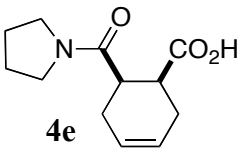


entry	additive	Temp (°C) t (h)[b]	yield (%)[c] of (+)-**5a**	ee (%)[d] of (+)-**5a**, (–)-**4a**	*S*[e]
1	*t*-$BuCO_2H$	–20, 17	41	89, —	28
2	—	–20, 3	[35]	92, 49	[37]
3[f]	—	–20, 38	38 [37]	94, 56	57 [56]

[a] Unless otherwise noted, (±)-**4a** (0.50 mmol) was used in CCl_4 (1.5 mL). [b] For step 2. [c] Isolated yield. The conversion, which was calculated by using the ee's of **5a** and **4a**, is shown in brackets. [d] HPLC analysis. [e] The *S* was calculated by using the yield and ee of (+)-**5a**. The *S*, which was calculated by using the ee's of (+)-**5a** and (–)-**4a**, is shown in brackets. See ref 9. [f] Toluene (1.0 mL) was used instead of CCl_4.

To explore the generality and scope of the above **1**-induced kinetic resolution, the esterification of several structurally diverse carboxylic acids was examined according to method A (conditions in entry 8 in Table A2.1) or method B (conditions in entry 2, Table A2.2) which were optimized for (±)-**4a** (Table 4.6). The esterification of not only **4a** but also other O-protected α-hydroxycarboxylic acids **4b-d** gave high *S* values (entries 1-6). (±)-*N*-Boc phenylalanine (**8**),[15] (±)-*N*-Cbz leucine (**9**), and (±)-*syn*-6-(pyrrolidine-1-carbonyl) cyclohex-3-enecarboxylic acid (**4e**) were also suitable substrates (entries 7-11). Although the reaction conditions were not optimized for each substrate, methods A and B were both effective for racemic carboxylic acids bearing a Brønsted base site.

Table A2.3. Generality and Scope of the **1**-Induced Kinetic Resolution of Racemic Carboxylic Acids (Method A or B)[a]

entry	(±)-carboxylic acid	***Method*** (catalyst **1**)	t (h)[b]	yield (%)[c]	ee (%)[d] of esters, acids	S[e]
1	**4b** [R^1 = Bn, L = O]	***A*** (**1a**)	48	34	86, —	21
2	**4b** [R^1 = Bn, L = O]	***B*** (**1a**)	6	39 [39]	88, 57	29 [29]
3	**4c** [R^1 = *i*-Pr, L = O]	***A*** (**1a**)	48	10	83, —	11
4	**4d** [R^1 = Ph, L = O]	***A*** (**1a**)	48	34	79(*R*), —	12
5	**4d** [R^1 = Ph, L = O]	***A*** (**1b**)	24	10	91(*R*), —	24
6	**4d** [R^1 = Ph, L = O]	***B*** (**1a**)	10	[52]	63(*R*), 68(*S*)	[8.9]
7	 **8**	***A*** (**1a**)	48	32	68(*R*), —	7.0
8	**8**	***B*** (**1a**)	20	[41]	39(*R*), 27(*S*)	[2.9]
9[f]	 **9**	***B*** (**1a**)	24	12	75, —	7.5
10	 **4e**	***A*** (**1a**)	25	0	—, —	—
11[g]	**4e**	***A*** (**1a**)	25	42	76, —	13

[a] Unless otherwise noted, (±)-carboxylic acid (0.25 mmol) was used in CCl_4[14] (1.5 mL) according to method A or method B. [b] For step 2. [c] Isolated yield of esters. The conversion, which was calculated by using the ee's of esters and acids, is shown in brackets. [d] HPLC analysis. [e] The *S* was calculated by using the yield and ee of esters. The *S*, which was calculated by using the ee's of esters and acids, is shown in brackets. See ref 9. [f] Toluene was used as solvent. [g] *i*-PrOH (0.6 equiv) was used at 0 °C.

Since the equilibrium between **1a**, (±)-**6d**, **7d**, and *epi*-**7d** is fast relative to esterification with *tert*-butyl alcohol to **5d**, the Curtin-Hammett principle applies, and the relative free energies of activation for the reaction of **7d** and *epi*-**7d** with *tert*-butyl alcohol will determine the enantioselectivity (*selectivity factor*). If intramolecular hydrogen bonding exists between the sulfonamidyl proton and the carbamoyl oxygen in **7d**, **7d** would be thermodynamically more stable than *epi*-**7d** because of the steric hindrance between R^b and the pyrrolidinyl group (Figure A2.1). Furthermore, when *tert*-butyl alcohol attacks the carbonyl carbon of **7d**, the carbonyl carbon changes hybridization to sp^3, and the interaction between R^b and the pyrrolidinyl group gets more severe, whereas less change occurs in the steric environment of R^a. Thus, the relative free energy of activation for the reaction of **7d** would be lower than that of *epi*-**7d** to give (*R*)-**5d** predominantly.

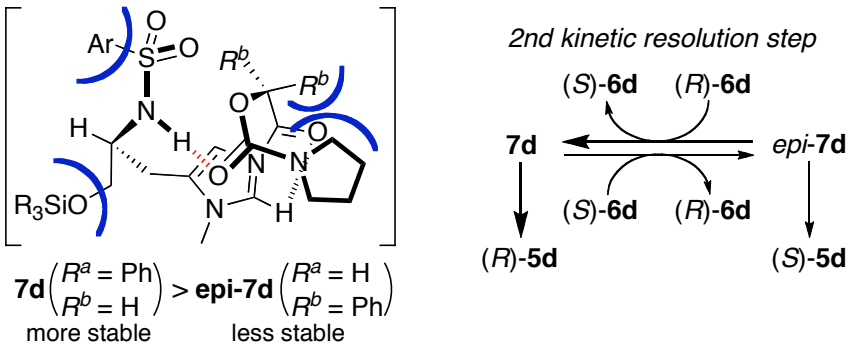
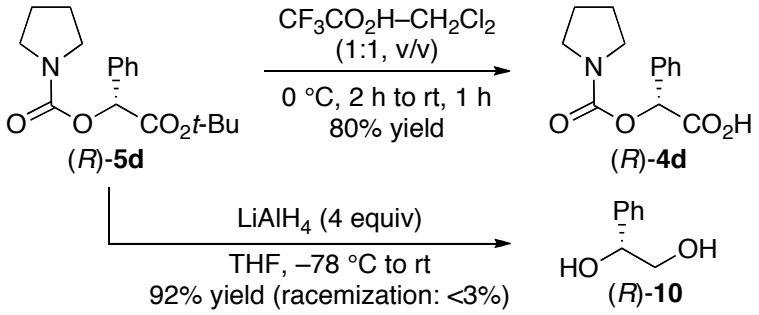


Figure 4.2. Predictable Diastereomeric Acylammonium Salts **7d** and *epi*-**7d** and the Second Kinetic Resolution Step.

(*R*)-*tert*-Butyl α-(carbamoyloxy)carboxylate **5d**, which was produced by the asymmetric esterification, was chemoselectively chemoselectively transformed to (*R*)-**4d** under acidic conditions without any epimerization (Scheme A2.3).[16] In contrast, it was difficult to hydrolyze the carbamoyloxy group of (*R*)-**5** or (*R*)-**4** without epimerization.

However, the reduction of (*R*)-**5d** with lithium aluminum hydride gave (*R*)-1,2-diol **11** in high yield without epimerization (Scheme A2.3).



Scheme A2.3. Deprotection of Optically Active (*R*)- **5d** without Epimerization

In summary, we achieved a catalytic and direct kinetic resolution of racemic carboxylic acids for the first time under the equilibrium between a chiral catalyst and two diastereomeric acylammonium salts through an intramolecular hydrogen-bonding interaction.

References and Notes

1. Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (b) Ishihara, K.; Kosugi, Y.; Akakura, M. *Tetrahedron* **2007**, *63*, 6191. For an account article, see: (c) Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686.
2. For recent reviews, see: (a) Connon, S. J. *Lett. Org. Chem.* **2006**, *3*, 686. (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (c) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.
3. For asymmetric alcohol derivatizations using chiral *N*-alkylimidazole catalysts, see: (a) Sánchez-Roselló, M.; Puchlopek, A. L. A.; Morgan, A. J.; Miller, S. J. *J. Org. Chem.* **2008**, *73*, 1774. (b) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454. (c) Lewis, C. A.; Miller, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5616. (d) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67. (e) Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021. (f) Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 13182. (g) Fierman, M. B.; O'Leary, D. J.; Steinmetz, W. E.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6967. (h) Griswold, K. S.; Miller, S. J. *Tetrahedron* **2003**, *59*, 8869. (i) Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125. (j) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. (k) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, Jr., P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (l) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.
4. Narasaka, K.; Kanai, F.; Okudo, M.; Miyoshi, N. *Chem. Lett.* **1989**, 1187.
5. (a) Notte, G. T.; Sammakia, T.; Steel, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13502. (b) Notte, G. T.; Sammakia, T. *J. Am. Chem. Soc.* **2006**, *128*, 4230.

6. (a) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539. (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Honjo, T.; Sano, S.; Shiro, M.; Nagao, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5838.
7. For the enantioselective dynamic kinetic resolution of azalactones, see: (a) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154. (b) Berkessel, A.; Mukherjee, S.; Mu¨ller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudörfl, J.-M.; Lex, J.-M. J. *Org. Biomol. Chem.* **2006**, *4*, 4319.
8. It was ascertained that a mixed anhydride **6** was quantitatively obtained from **4** and pivaloyl chloride under the conditions for step 1 shown in Table 4.1. Dried MS 4Å was effective at preventing the hydrolysis of pivaloyl chloride during the reaction of step 1.
9. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.
10. Pivalate anion might promote the conversion of **7a** to **6a**.
11. The results of entries 3 and 4 indicated that unreacted pivaloyl chloride did not inactivate **1a**.
12. (a) Spivey, A. C.; Arseniyadis, S. *Angew Chem. Int. Ed.* **2004**, *43*, 5436. (b) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglish, W.; Zipse, H. *Chem.-Eur. J.* **2005**, *11*, 4751.
13. A mixed anhydride of **4a** and *t*-BuCO_2H was formed in situ (entry 1). However, anhydride of **4a** was not formed as a major species under conditions of entries 2 and 3.
14. Carbon tetrachloride was more suitable than toluene to dissolve substrates.
15. The ureas derived from reacting (±)-α-amino acids with 1-pyrrolidine-1-carbonyl chloride were decomposed by treatment with condensing agents.
16. *tert*-Butyl group of **5a** (R^2 = *t*-Bu) was also chemoselectively cleaved under acidic conditions (CF_3CO_2H–CH_2Cl_2 (1:1(v/v)), 0 °C, 2 h) to give (+)-**4a** in >99% yield.

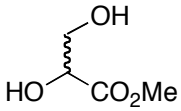
Experimental Section

General Methods.

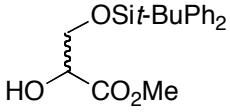
Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on Varian Gemini-2000 (300 MHz) and VXR 500 (500 MHz) spectrometers at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on Varian Gemini-2000 (75 MHz) and VXR 500 (125 MHz) spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (CD_3Cl at 77.00 ppm). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm) or Daicel CHIRALPAK AD-H (4.6 mm × 25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. GC analysis was performed with Shimadzu 17A instruments with a flame-ionization detector and a capillary column of PEG-HT Bonded (25 m × 0.25 mm) using nitrogen as carrier gas. Melting points were determined using a Yanaco MP-J3. The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385 or Fuji Silysia Chemical Ltd. Cromatorex® NH-DM1020). Microanalyses were performed at the Graduate School of Agriculture, Nagoya University. High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University on JEOL JMS-700 spectromemer. In experiments that required dry solvent, ether, *N*,*N*-dimethylformamide (DMF) and tetrahydorofuran (THF) were purchased from TCI or Wako as the “anhydrous” and stored over MS 4Å. Benzene, hexane, toluene, and dichloromethane were freshly

distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially.

Preparation of (±)-3-(*tert*-Butyldiphenylsilyloxy)-2-(pyrrolidine-1-carbonyloxy)propanoic acid (4a).

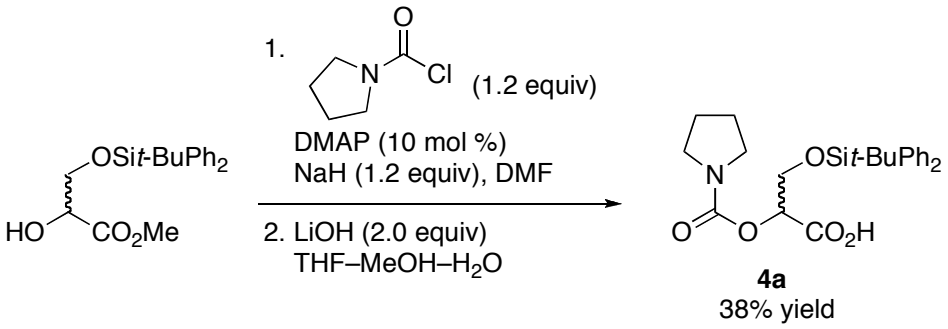


(±)-Methyl 2,3-dihydroxypropanoate.[2] A solution of (±)-glyceric acid (65% in water) (4.08 g, 25 mmol) and *p*-TsOH•H2O (237.5 mg, 2.5 mmol) in MeOH (10 mL) was heated under reflux conditions. After being stirred for 12 h, the resultant solution was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc–MeOH = 50:1 ~ 10:1) to give 3.00 g (99% yield) of product as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16–2.25 (m, 1H), 3.15–3.21 (m, 1H), 3.84 (s, 1H), 3.85 (ddd, *J* = 11.7, 5.4, 3.6 Hz, 1H), 3.92 (ddd, *J* = 11.7, 5.4, 3.3 Hz, 1H), 4.29 (q, *J* = 4.2 Hz, 1H). All spectral values is consistent with thosereported in the literature.[2]



(±)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-hydroxypropanoate.[3] To a solution of (±)-methyl 2,3-dihydroxypropanoate (2.88 g, 24 mmol) and imidazole (3.59 g, 52.8 mmol) in THF (80 mL) was added dropwise *t*-$BuPh_2SiCl$ (6.87 mL, 26.4 mmol) at 0 °C. The white solid precipitated. The reaction mixture was diluted with Et_2O, washed with brine and water. The organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc = 10:1 ~ 2:1) to give 7.73 g (90% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 3.16 (d, *J* = 7.8 Hz, 1H), 3.80 (s, 3H), 3.92 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.98 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.25 (dt, *J* = 5.1,

3.0, Hz, 1H), 7.35–7.48 (m, 6H), 7.60–7.68 (m, 4H). All spectral values is consistent with those reported in the literature.[3]

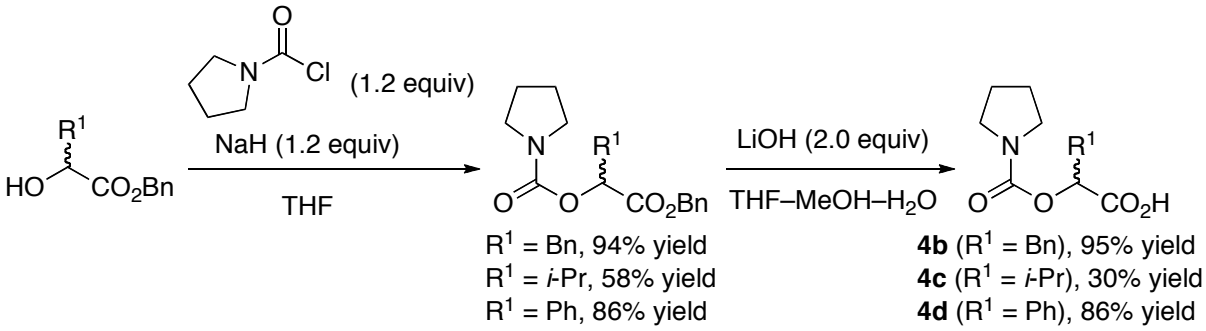


3-(*tert*-Butyldiphenylsilyloxy)-1-methoxy-1-oxopropan-2-yl pyrrolidine-1-carboxylate. To a solution of (±)-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-hydroxypropanoate (8.01 g, 22 mmol), DMAP (244 mg, 2 mmol) and 1-pyrrolidinecarbonyl chloride (2.96 mL, 26.8mmol) in DMF (50 mL) was added NaH (60% in oil, 1.07 g, 26.8 mmol) slowly at 0 °C. The reaction mixture was stirred at room temperature for overnight, cooled to 0 °C, poured onto 1 *M* HCl aqueous solution and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc = 10:1 ~ 1:1) to give 4.63 g (46% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.80–1.98 (s, 4H), 3.30–3.48 (m, 3H), 3.48–3.59 (m, 1H), 3.77 (s, 3H), 3.98 (dd, *J* = 11.1, 3.0 Hz, 1H), 4.11 (dd, *J* = 11.1, 5.1 Hz, 1H), 5.19 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.34–7.47 (m, 6H), 7.62–7.71 (m, 4H).

(±)-4a. To a solution of (±)-3-(*tert*-butyldiphenylsilyloxy)-1-methoxy-1-oxopropan-2-yl pyrrolidine-1-carboxylate (2.53 g, 5.6 mmol) in THF (5 mL) and MeOH (5 mL) was added slowly the solution of LiOH (470 mg, 11 mmol) in water (5 mL) at 0 °C. After 3 h, the reaction mixture was diluted with Et_2O and brine, washed with Et_2O, acidified by 1 *M* HCl aqueous solution, extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was recrystallized from $CHCl_3$–hexane to give 2.05 g (83% yield) of product as white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H),

1.79–1.97 (m, 4H), 3.38–3.56 (m, 4H), 4.01 (dd, J = 11.1, 3.0 Hz, 1H), 4.13 (dd, J = 11.1, 5.1 Hz, 1H), 5.22 (dd, J = 5.4, 3.0 Hz, 1H), 7.32–7.46 (m, 6H), 7.62–7.72 (m, 4H), 8.58–9.02 (br, 1H); ^{13}C NMR (75 MHZ, $CDCl_3$) δ 19.4, 25.1, 25.9, 26.7 (3C), 46.1, 46.5, 63.6, 74.0, 127.9 (4C), 129.9 (4C), 133.1 (2C), 135.7, 154.4, 173.3; IR (KBr) 3650–3300 (br), 2959, 2931, 1660, 1447, 1209, 1114, 707 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{32}NO_5Si$ [$(M+H)^+$] 442.2050, found 442.2047.

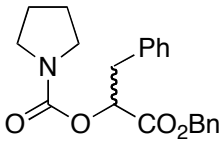
General Procedure for Preparing (±)-2-(Pyrrolidine-1-carbonyloxy)carboxylic Acids (4b–d).



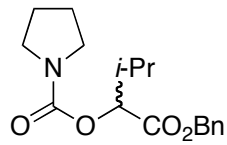
To a solution of (±)-benzyl 2-hydroxycarboxylate (5 mmol) and 1-pyrrolidinecarbonyl chloride (0.66 mL, 6 mmol) in THF (10 mL) was added NaH (240 mg, 60% in oil, 6 mmol) carefully at 0 °C. The reaction mixture was stirred at room temperature for 12 h, cooled to 0 °C, poured onto a 1 M HCl aqueous solution and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc = 40:1 ~ 2:1) to give (±)-benzyl 2-(pyrrolidine-1-carbonyloxy)carboxylate in good yield.

To a solution of (±)-benzyl 2-(pyrrolidine-1-carbonyloxy)carboxylate (4.3 mmol) in THF (5 mL) and MeOH (5 mL) was added slowly a solution of LiOH (240 mg, 10 mmol) in water (5 mL) at 0 °C. After 3 h, the reaction mixture was diluted with Et_2O and brine, washed with Et_2O, acidified by 1 M HCl aqueous solution, extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and extracted. The residue was

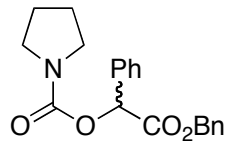
recrystallized from $CHCl_3$–hexane or purified by flash column chromatography on silica gel to give (±)-2-(pyrrolidine-1-carbonyloxy)carboxylic acid (**4b**–**d**). The corresponding physical and spectroscopic data for **4b**–**d** is as follows.



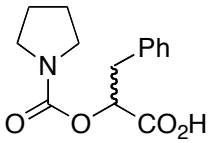
1-(Benzyloxy)-1-oxo-3-phenylpropan-2-yl pyrrolidine-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70–1.99 (m, 4H), 3.09 (dd, *J* = 14.1, 8.3 Hz, 1H), 3.17 (dd, *J* = 14.1, 5.0 Hz, 1H), 3.56 (m, 4H), 4.21 (d, *J* = 12.5 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.19 (t, *J* = 3.3 Hz, 1H), 7.15–7.45 (m, 10H).



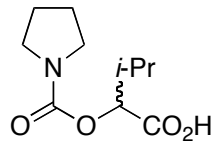
1-(Benzyloxy)-3-methyl-1-oxobutan-2-yl pyrrolidine-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J* = 5.1 Hz, 3H), 1.00 (d, *J* = 5.1 Hz, 3H), 1.78–1.96 (m, 4H), 2.24 (septet d, *J* = 6.9, 4.5 Hz, 1H), 3.30–3.58 (m, 4H), 4.13 (d, *J* = 12.3 Hz, 1H), 4.86 (d, *J* = 4.5 Hz, 1H), 5.24 (d, *J* = 12.3 Hz, 1H), 7.28–7.44 (m, 5H).



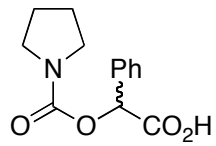
2-(Benzyloxy)-2-oxo-1-phenylethyl pyrrolidine-1-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$) δ1.78–1.98 (m, 4H), 3.32–3.52 (m, 3H), 3.52–3.65 (m, 1H), 5.16 (s, 2H), 5.98 (s, 1H), 7.17–7.25 (m, 2H), 7.25–7.42 (m, 6H), 7.44–7.52 (m, 2H).



(±)-3-Phenyl-2-(pyrrolidine-1-carbonyloxy)propanoic acid (4b): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75–1.93 (m, 4H), 3.11 (dd, *J* = 14.1, 9.0 Hz, 1H), 3.20–3.50 (m, 4H), 3.25 (dd, *J* = 14.1, 3.5, Hz, 1H), 5.15 (dd, *J* = 9.3, 3.9, Hz, 1H), 7.20–7.34 (m, 5H), 9.26–9.60 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.7, 37.5, 46.0, 73.7, 127.0, 128.5 (2C), 129.6 (2C), 136.4, 154.5, 174.7; IR(KBr) 3650–3350 (br), 2937, 2884, 1762, 1656, 1441, 1253, 1216, 1195, 1129, 760, 700 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{18}NO_4$ [$(M+H)^+$] 264.1236, found 264.1237.

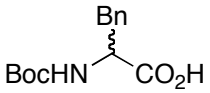


(±)-3-Methyl-2-(pyrrolidine-1-carbonyloxy)butanoic acid (4c): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 2.27 (septet d, *J* = 6.9, 3.9 Hz, 1H), 3.33–3.57 (m, 4H), 4.83 (d, *J* = 4.2 Hz, 1H), 6.70–7.43 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 19.2, 25.1, 25.8, 30.3, 45.9, 46.4, 77.1, 154.7, 175.0; IR (film) 2969, 2879, 1714, 1441, 1335, 1182, 1135, 1111, 768 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{18}NO_4$ [$(M+H)^+$] 216.1237, found 216.1235.

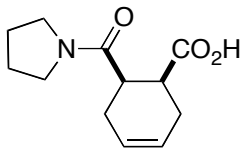


(±)-2-Phenyl-2-(pyrrolidine-1-carbonyloxy)acetic Acid (4d): White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78–2.00 (m, 3H), 3.52–3.64 (m, 1H), 5.92 (s, 1H), 7.34–7.42 (m, 3H),

7.45–7.55 (m, 2H), 8.64–9.04 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.8, 46.1, 46.5, 74.7, 127.7 (2C), 128.8, (2C), 129.2, 134.2, 154.2, 174.0; IR (KBr) 3650–3350 (br), 2964, 2896, 1757, 1661, 1437, 1207, 1168, 1135, 1114, 766, 727 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{16}NO_4$ [$(M+H)^+$] 250.1079, found 250.1080.



(±)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanoic acid (8): 8 was prepared according to the known method using $(Boc)_2O$.[4]



(1*SR*,6*RS*)-6-(Pyrrolidine-1-carbonyl)cyclohex-3-enecarboxylic acid (4e): To a solution of *cis*-Δ^4-tetrahydrophthalic anhydride (1.52 g, 10 mmol) in CH_2Cl_2 (100 mL) was added pyrrolidine (1.67 mL, 20 mmol) at room temperature. After 5 h, the solution was concentrated *in vacuo*. The residue was diluted with Et_2O, washed with 1 *M* HCl aqueous solution, and extracted with Et_2O. The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was recrystallized from $CHCl_3$–hexane to give 1.40 g (90% yield) of product as brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99–2.48 (m, 7H), 2.80–2.92 (m, 1H), 3.08–3.16 (m, 2H), 3.45–3.66 (m, 4H), 5.64–5.73 (m, 1H), 5.76–5.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 26.0, 26.2, 29.4, 409.6, 41.2, 476.0, 47.5, 124.7, 127.3, 173.0, 175.4; IR (film) 3600–3300 (br), 3025, 2981, 2888, 2333, 2256, 1935, 1713, 1563, 1514, 1457, 1377, 1339, 1287, 1256, 1217, 1054, 764 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{18}NO_3$ [$(M+H)^+$] 224.1287, found 224.1282.

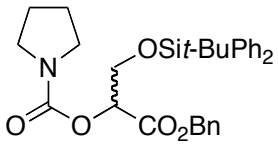
Representative Procedure for the Kinetic Resolution of Racemic Carboxylic Acids by 1-induced Enantioselective Esterification Reaction.

Method A: To a suspension of racemic carboxylic acid (0.50 mmol), 2,4,6-collidine (1.0 mmol) and anhydrous MS 4Å in CCl_4 (1.0 mL) was added pivaloyl chloride (74 μL, 0.60 mmol) at room temperature. After 1 h, the reaction mixture was cooled to –20 °C, and a solution of **1a** (17 mg, 0.025 mmol), pivalic acid (12 μL, 0.10 mmol) and *tert*-butyl alcohol (29 μL, 0.30 mmol) in CCl_4 (0.50 mL) was added. After being stirred for 48 h at –20 °C, the reaction mixture was treated with 0.1 *M* HCl aqueous solution, diluted with EtOAc, washed with 0.1 *M* HCl aqueous solution and brine. The aqueous layer was extracted with EtOAc. The extracted organic layer was washed with 0.1 *M* HCl aqueous solution and brine. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on Cromatorex® NH-DM1020 (eluent: hexane–EtOAc = 20:1 ~ 5:1) to give the corresponding *tert*-butyl ester. The ee value of the ester was determined by HPLC analysis of the crude products. The ee value of the recovered carboxylic acids was determined by HPLC analysis after conversion to the corresponding *N*-benzylamide by the treatment of the reaction mixture with benzylamine in place of a 0.1 *M* HCl aqueous solution. The conversion (*c*) was estimated by the isolation or the following equation: $c = ee_{\text{recovered carboxylic acid}}/(ee_{\text{recovered carboxylic acid}} + ee_{\text{ester}})$.[5] The *S* value was estimated by the following equation: $S = \ln[1-c(1+ee_{\text{ester}})]/\ln[1-c(1-ee_{\text{ester}})]$.[5]

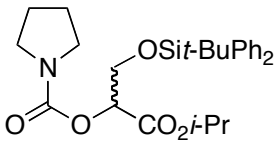
Method B: To a suspension of racemic carboxylic acid (0.25 mmol) and 2,4,6-collidine (0.5 mmol) in CCl_4 (1.0 mL) was added *N*,*N*-dicyclohexylcarbodiimide (DCC) (62 mg, 0.30 mmol) at –20 °C. After 1 h, a solution of **1a** (8.5 mg, 0.018 mmol) and *tert*-butanol (15 μL, 0.15 mmol) in CCl_4 (0.50 mL) was added at –20 °C. After being stirred for several hours at the same temperature, the reaction mixture was treated with 0.1 *M* HCl aqueous solution, diluted with EtOAc, washed with 0.1 *M* HCl aqueous solution and brine. The aqueous layer was extracted with EtOAc. The extracted organic layer was washed with 0.1 *M* HCl

aqueous solution and brine. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on Cromatorex® NH-DM1020 (eluent: hexane–EtOAc = 20:1 ~ 5:1) to give the corresponding *tert*-butyl ester. The ee value of the ester was determined by HPLC analysis of the crude products. The ee value of the recovered carboxylic acids was determined by HPLC analysis after conversion to the corresponding *N*-benzylamide by the treatment of the reaction mixture with benzylamine in place of a 0.1 *M* HCl aqueous solution. The conversion (*c*) was estimated by the isolation or the following equation: $c = ee_{\text{recovered carboxylic acid}}/(ee_{\text{recovered carboxylic acid}} + ee_{\text{ester}})$.[5] The *S* value was estimated by the following equation: $S = \ln[1-c(1+ee_{\text{ester}})]/\ln[1-c(1-ee_{\text{ester}})]$.[5]

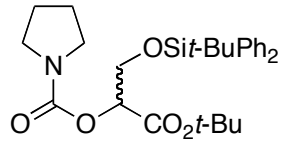
The corresponding physical and spectroscopic data for the esters as follows.



(+)-1-(Benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)-1-oxopropan-2-yl pyrrolidine-1-carboxylate (5a, R^2=Bn): TLC (hexane–EtOAc = 2:1) R_f = 0.32; $[\alpha]^{22}_D$ = 0.7 (*c* = 2.7, $CHCl_3$) for 6% ee; HPLC (Daicel Chiralcel OD-H, hexane–2-propanol = 20:1, flow rate = 1.0 mL/min) t_R = 11.6 ((–)-enantiomer, minor), 20.2 ((+)-enantiomer, major) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.80–1.94 (m, 4H), 3.28–3.48 (m, 3H), 3.48–3.59 (m, 1H), 4.07 (dd, *J* = 11.1, 2.7 Hz, 1H), 4.16 (dd, *J* = 11.1, 4.2 Hz, 1H), 7.25–7.47 (m, 11H), 7.57–7.72 (m, 4H), ^{13}C NMR (75MHz, $CDCl_3$) δ 19.4, 25.1, 25.9, 26.7 (3C), 46.0, 46.4, 63.8, 67.1, 74.1, 127.8, 128.3, 128.4, 128.6, 129.9, 133.0, 133.2, 135.6, 135.7, 154.2, 169.1; IR (KBr) 3650–3300 (br), 2952, 2879, 1763, 1714, 1421, 1196, 1117, 701 cm^{-1}; HRMS (FAB) calcd for $C_{31}H_{38}NO_5Si$ [$(M+H)^+$] 532.2519, found 532.2519.

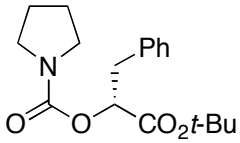


(+)-3-(*tert*-Butyldiphenylsilyloxy)-1-isopropoxy-1-oxopropan-2-yl pyrrolidine-1-carboxylate (5a, R^2 = *i*-Pr): TLC (hexane–EtOAc = 2:1) R_f = 0.32; $[\alpha]^{22}_D$ = 8.6 (*c* = 2.1, $CHCl_3$) for 69% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol = 20:1, flow rate = 1.0 mL/min) t_R = 13.5 ((+)-enantiomer, major), 16.3 ((–)-enantiomer, minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.82–1.94 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.28–3.50 (m, 3H), 3.96 (dd, *J* = 11.1, 3.0 Hz, 1H), 4.14 (dd, *J* = 11.1, 4.8 Hz, 1H), 5.10 (septet, *J* = 6.3 Hz, 1H), 5.12 (dd, *J* = 4.2, 3.0 Hz, 1H), 7.34–7.48 (m, 6H), 7.64–7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 22.0 (2C), 25.1, 25.9, 26.7 (3C), 46.0, 46.4, 63.9, 69.1, 74.2, 127.8 (2C), 129.9 (2C), 133.2, 133.4, 135.6 (2C), 135.7 (2C), 154.3, 168.7; IR (film) 2982, 2933, 2833, 1701, 1428, 1113, 704 cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{38}NO_5Si$ [$(M+H)^+$] 484.2519, found 484.2520.

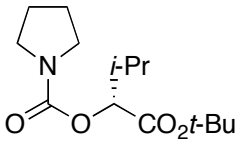


(+)-1-*tert*-Butoxy-3-(*tert*-butyldiphenylsilyloxy)-1-oxopropan-2-yl pyrrolidine-1-carboxylate (5a, R^2 = *t*-Bu): TLC (hexane–EtOAc = 2:1), R_f = 0.37; $[\alpha]^{22}_D$ = 9.4 (*c* = 1.1, $CHCl_3$) for 83% ee; HPLC (Daicelpak AD-H × 2, hexane–2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 22.1 ((+)-enantiomer, major), 24.4 ((–)-enantiomer, minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.49 (s, 9H), 1.79–1.96 (m, 4H), 3.28–3.30 (m, 3H), 5.06 (dd, *J* = 4.5, 2.7 Hz, 1H), 7.34–7.47 (m, 10H), 7.65–7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 25.1, 25.9, 26.7 (3C), 28.2 (3C), 46.0, 46.4, 64.1, 74.3, 82.0, 127.8 (2C), 129.8 (2C), 133.2, 133.5, 135.6 (2C), 135.8 (2C), 154.3, 168.2; IR (film) 2955, 2932, 2878, 1754, 1713, 1426, 1368, 1254, 1226, 1163, 1114, 823, 704 cm^{-1}; HRMS (FAB) calcd for

$C_{28}H_{40}NO_5Si$ [$(M+H)^+$] 498.2676, found 498.2676. The absolute configuration was not established.

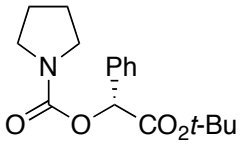


(+)-1-*tert*-Butoxy-1-oxo-3-phenylpropan-2-yl pyrrolidine-1-carboxylate (5b, R^2 = *t*-Bu): TLC (hexane–EtOAc = 2:1) R_f = 0.37; $[\alpha]^{22}_D$ = 0.9 (*c* = 1.1, $CHCl_3$) for 86% ee; HPLC (Daicel Chiralpak AD-H × 2, hexane:2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 52.0 ((–)-enantiomer, minor), 55.6 ((+)-enantiomer, major) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.74–1.94 (m, 4H), 3.07 (dd, *J* = 13.9, 8.0 Hz, 1H), 3.13 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.23–3.41 (m, 3H), 3.41–3.52 (m, 1H), 5.04 (dd, *J* = 8.0, 5.3 Hz, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.8, 28.0 (3C), 37.8, 45.9, 46.2, 73.6, 81.9, 126.8, 128.3 (2C), 129.6 (2C), 136.7, 154.1, 169.8; IR (film) 2981, 1742, 1702, 1429, 1370, 1209, 1156, 1348, 1217 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{26}NO_4$ [$(M+H)^+$] 320.1862, found 320.1862. The absolute configuration was not established.



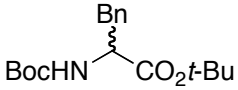
(–)-1-*tert*-Butoxy-3-methyl-1-oxobutan-2-yl pyrrolidine-1-carboxylate (5c, R^2 = *t*-Bu): TLC (hexane–EtOAc = 2:1) R_f = 0.41; $[\alpha]^{23}_D$ = –5.3 (*c* = 0.9, CHCl3) for 83% ee; HPLC (Daicel Chiralpak AD-H × 2, hexane–2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 40.1 ((–)-enantiomer, major), 42.8 ((+)-enantiomer, minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.47 (s, 9H), 1.80–1.95 (m, 4H), 2.21 (d, septet, *J* = 6.9, 4.2 Hz, 1H), 3.33–3.46 (m, 3H), 3.46–3.58 (m, 1H), 4.70 (d, *J* = 4.2 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 19.1, 25.1, 25.8, 28.2, 30.5, 45.9, 46.3, 77.2, 81.6, 154.6, 170.0; IR (film) 2973, 2933, 2878, 1739, 1697, 1431, 1370, 1162, 1348 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{26}NO_4$ [$(M+H)^+$] 272.1862, found 272.1867.



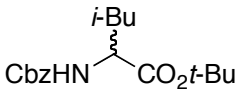
(*R*)-(–)-2-*tert*-Butoxy-2-oxo-1-phenylethyl pyrrolidine-1-carboxylate (5d, R^2 = *t*-Bu): TLC (hexane–EtOAc = 2:1) R_f = 0.37; $[\alpha]^{22}_D$ = –53.0 (*c* = 1.6, $CHCl_3$) for 61% ee; HPLC (Daicel Chiralpak AD-H × 2, hexane–2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 28.3 ((*R*)-(–)-enantiomer, major), 31.7 ((*S*)-(+)-enantiomer, minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3H), 177–1.99 (m, 4H), 3.33–3.53 (m, 3H), 3.53–3.68 (m, 1H), 5.81 (s, 1H), 7.30–7.42 (m, 3H), 7.44–7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.8, 28.0, 46.0, 46.3, 75.1, 82.1, 127.4 (2C), 128.6 (2C), 128.7, 135.3, 154.0, 169.0; IR (KBr) 3600–3300 (br), 2979, 2874, 1744, 1704, 1427, 1343, 1276, 1226, 1153, 1127, 1110 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{24}NO_4$ [$(M+H)^+$] 306.1705, found 306.1702.

The absolute configuration was determined by reduction with $LiAlH_4$ to the corresponding diol and comparison with commercially available (*R*)-2-phenyl-1,2-ethanediol by chiral-GC-analysis.

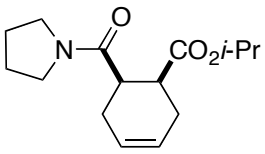


(*R*)-(–)-*tert*-Butyl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate: TLC (hexane–EtOAc = 2:1) R_f = 0.12; $[\alpha]^{21}_D$ = –24.3 (*c* = 0.9, $CHCl_3$) for 83% ee; HPLC (Daicel Chiralpak AD-H × 2, hexane–2-propanol = 9:1, flow rate = 1 mL/min) t_R = 10.3 ((*R*)-(–)-enantiomer, major), 16.3 ((*S*)-(+)-enantiomer, minor) min; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.40 (s, 9H), 1.42 (s, 9H), 3.05 (d, J = 6.0 Hz, 2H), 4.45 (dd, J = 14.3, 6.2 Hz, 1H), 5.00 (d, J = 8.4 Hz, 1H), 7.18–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1 (3C), 28.4 (3C), 38.7, 54.9, 79.8, 82.1, 126.9, 128.4 (2C), 130.0 (2C), 136.5, 155.2, 171.1. The absolute stereochemistry was determined by comparison with the optical rotation of this product with that reported in the literature [Lit:[6] *N*-Boc-L-Phe-O*t*-Bu $[\alpha]^{24}_D$ = 32.04 (c = 1.08, $CHCl_3$)].



(*R*)-*tert*-Butyl 2-(benzyloxycarbonylamino)-4-methylpentanoate:[7] $[\alpha]^{22}_D$ = 1.43 (c = 0.84, $CHCl_3$) for 75% ee; HPLC (Daicel Chiralcel OD-H, hexane–2-propanol = 20:1, flow rate = 1.0 mL/min) t_R = 9.6 ((+)-enantiomer, major), 10.4 ((–)-enantiomer, minor) min. All spectral values is consistent with those reported in the literature.[7]



***syn*-(+)-Isopropyl 6-(pyrrolidine-1-carbonyl)cyclohex-3-enecarboxylate (5e, R^2 = *i*-Pr):** $[\alpha]^{22}_D$ = 9.5 (c = 2.4, $CHCl_3$) for 58% ee; HPLC (Daicel Chiralcel OD-H, hexane–2-propanol = 20:1, flow rate = 1.0 mL/min) t_R = 20.5 ((+)-enantiomer, major), 24.3 ((–)-enantiomer, minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 3.3 Hz, 3H), 1.23 (d, J = 3.3 Hz, 3H), 1.78–2.20 (m, 4H), 2.32–2.46 (m, 3H), 2.50–2.89 (m, 2H), 3.12–3.20 (m, 1H), 3.37–3.62 (m, 4H), 5.01 (septet, J = 6.3 Hz, 1H), 5.62–5.73 (m, 1H), 5.73–5.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 21.9, 24.3, 26.0, 26.1, 26.4, 37.4, 39.7, 45.8, 46.6, 67.6, 123.7, 125.9, 172.7, 173.6; IR (film) 2981, 2877, 1722, 1627, 1447, 1374, 1344, 1293, 1249, 1184, 1108 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{24}NO_3$ $[(M+H)^+]$ 266.1756, found 266.1754.

Deprotection of *tert*-butyl ester of 5d: Deprotection of *tert*-butyl ester of (*R*)-**5d** (61 mg, 0.2 mmol) was conducted through a standard protocol[8] using CF_3CO_2H–CH_2Cl_2 (1:1 v/v, 4 mL), to give (*R*)-**4d** (40 mg, 80%).

Reduction of 5d: Reduction of (*R*)-**5d** (15 mg, 0.05 mmol) was conducted through a standard protocol8 using 1.0 M solution of $LiAlH_4$ in THF (7.6 mg, 0.2 mmol) in THF (0.5 mL) at –78 °C, to give diol (*R*)-**10** (6.4 mg, 92%).

References

1. (a) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212. (b) Ishihara, K.; Kosugi, Y.; Akakura, M. *Tetrahedron* **2007**, *63*, 6191.
2. (a) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659. (b) Sugiyama, S.; Ohigashi, S.; Sawa, R. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3202.
3. (a) Green, M. E.; Rech, Jason C.; Floreancig, P. E. *Org. Lett.* **2005**, *7*, 4117. (b) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh H.;Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.
4. Caplar, V.; Zinic, M.; Pozzo, J.-L.; Fages, F.; Mieden-Gundert, G.; Vögtle, F. *Eur. J. Org. Chem.* **2004**, 4048.
5. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.
6. Konda, Y.; Takahashi, Y.; Arima, S.; Sato, N.; Takeda, K.; Dobashi, K.; Baba, M.; Harigaya, Y. *Tetrahderon* **2001**, *57*, 4311.
7. Anderson, G. W.; Callahan, F. M. *J. Am. Chem. Soc.* **1960**, *82*, 3359.
8. Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis,* 4th ed.; John Wiley & Sons, Inc.: New Jersey, 2007.

Appendix 3

Convergent Synthesis of Stereodefined Exo-alkylidene-γ-Lactams from β-Halo Allylic Alcohols

Abstract: A convergent process for the assembly of stereodefined mono- and bicyclic exo-alkylidene γ-lactams is described that proceeds through the union of β-halo allylic alcohols, aromatic imines and CO. Overall, regio- and stereoselective Ti-mediated reductive cross-coupling, followed by Pd-catalyzed carbonylation can be performed in a one or two-pot procedure, defining a highly selective three-component coupling process for heterocycle synthesis.

Nitrogen-containing heterocycles are ubiquitous structural motifs in natural products and small molecules of biomedical relevance.[1] Among this class, stereodefined pyrrolidines and γ-lactams are abundant (Figure A3.1). A wealth of chemical pathways are indeed available for the synthesis of these functionalized heterocycles.[2] However, strategic considerations for the preparation of highly substituted and stereodefined systems often limit the utility of many available methods. In a program aimed at defining convergent coupling reactions for complex molecule synthesis, we have been investigating the potential of reductive cross-coupling processes between imines and alkynes, alkenes or allenes to serve as a general foundation for heterocycle synthesis.[3]

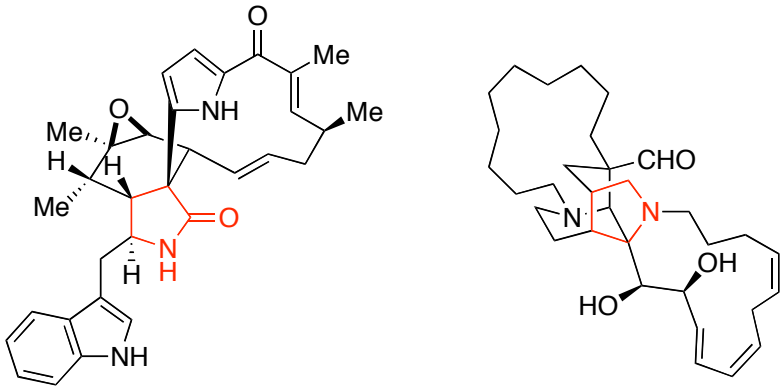


Figure A3.1. Examples of Natural Products Bearing a Substituted γ-Lactam Pyrrolidine

Recently, we set our sights on the development of a multicomponent coupling reaction suitable for the synthesis of exo-alkylidene γ-lactams (Figure A3.2A). These architectures, while representing interesting heterocycles in their own right, possess a rich reactivity profile suitable for diverse elaboration (Figure A3.2B). Herein, we report the realization of a stereoselective synthesis of exo-alkylidene γ-lactams from the convergent and stereoselective union of homoallylic alcohols, imines and carbon monoxide.

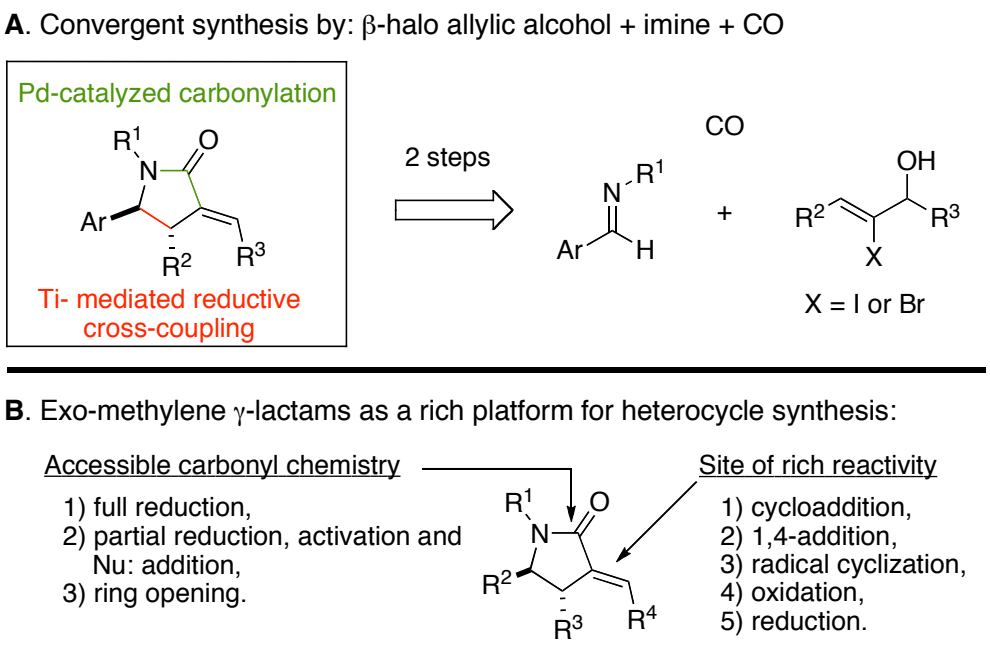


Figure A3.2. *exo*-Alkylidene-γ-lactams

Recently, we reported a stereoselective synthesis of homoallylic amines that proceeds by regioselective reductive cross-coupling of allylic alcohols with aromatic imines.[3d] Of particular interest to our goals here, coupling of 2-halo allylic alcohols to aromatic imines was found to provide stereoselective access to *anti*-homoallylic amines that contain a stereodefined vinyl halide (dr ≥ 20:1; *E:Z* ≥ 20:1; Figure A3.3). While the mechanistic details that result in these high levels of stereoselection remain undefined, an emperical model has emerged to explain the patterns of reactivity and selectivity observed. The proposed model, based on a sequence of directed carbometalation and *syn*-elimination (**A** → **B**; Figure A3.3), embraces a boat-like geometry in the transition state for C–C bond formation to reflect the presumed mechanistic requirement of preassociating the allylic alkoxide to the Ti-center of the azametallacyclopropane and the orbital requirements for carbometalation (coplanarity of the σ_{Ti-C} and the $\pi_{C=C}$). A key factor for stereocontrol then derives from the minimization

of A-1,2 strain in the boat like orientation **A** (minimize steric interaction between R^3 and X). As a consequence, high selectivity is observed for the formation of products containing a pendant *E*-alkene. Overall, the general reactivity pattern is consistent with formal metallo-[3,3] rearrangement by way of **C**.[4]

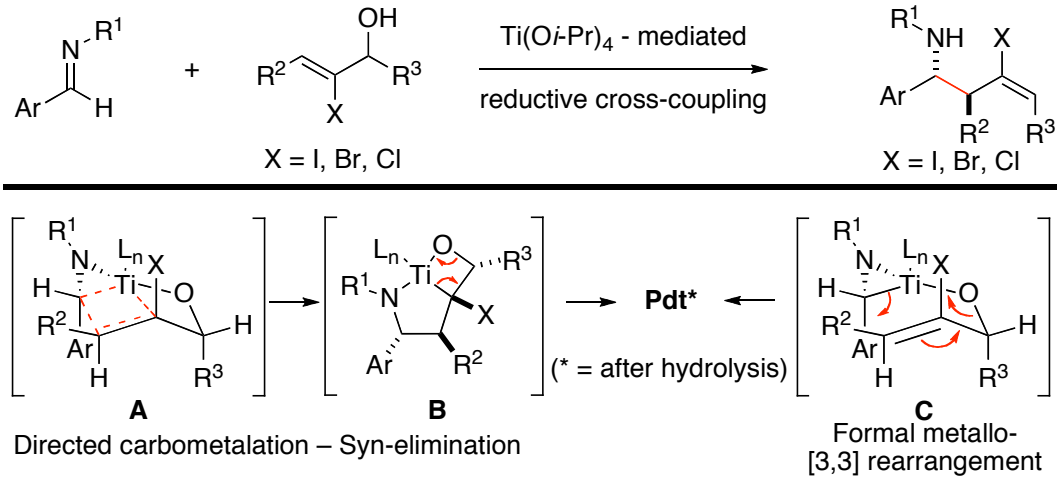
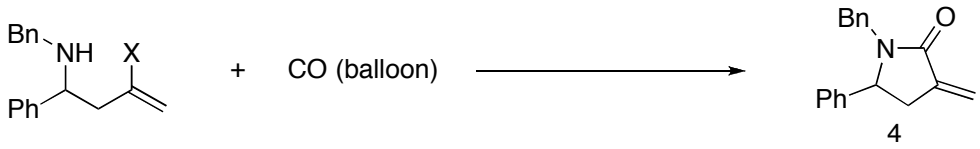


Figure A3.3. Imine–Allylic Alcohol Coupling Reaction

While having a stereoselective coupling reaction in place for the synthesis of highly functionalized homoallylic amines, we were aware of the potential of halogenated homoallylic amines to participate in Pd-catalyzed carbonylation chemistry.[5, 6] As depicted in Figure A3.4, this was indeed the case. Carbonylation of vinylbromide **1** and vinyliodide **2** resulted in the production of the *exo*-methylene γ-lactam **3** in ≥ 93% yield.



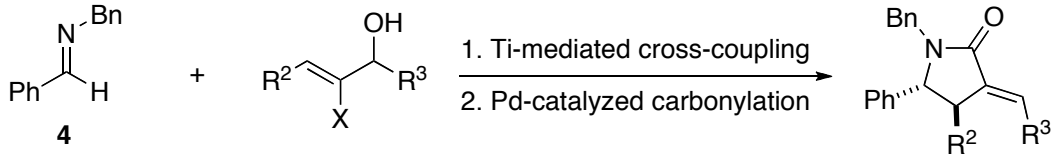
	reaction condition	yield [%]
1; X = Br	μ-Pd(P*t*-Bu$_3$)$_2$ (5 mol %), *n*-Bu$_3$N (2 equiv), DMF, 100°C	95
2; X = I	Cl$_2$Pd(PPh$_3$)$_2$ (5 mol %), Et$_3$N (2 equiv), toluene, 70°C	93

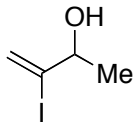
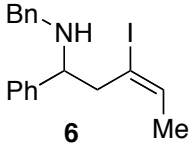
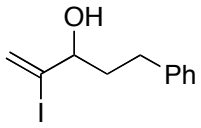
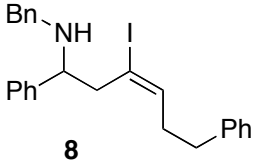
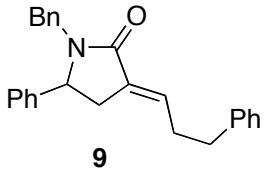
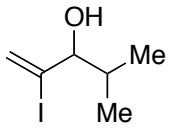
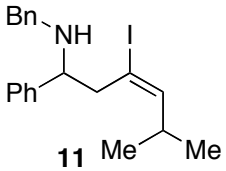
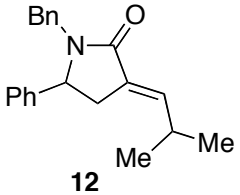
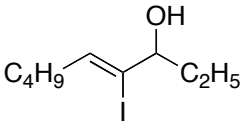
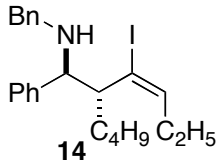
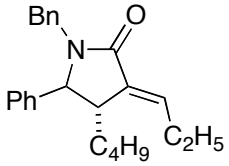
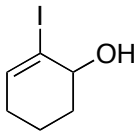
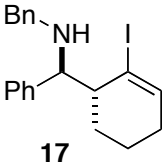
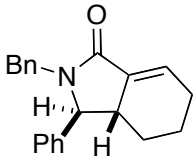
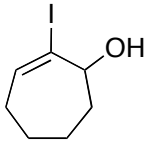
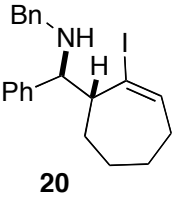
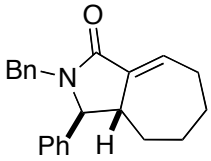
Figure A3.4. Pd-Catalyzed Carbonylative Cyclization

With the knowledge gleaned from these initial studies, we moved on to explore the compatibility of more complex substrates in this two-step reductive cross-coupling/carbonylation process as a means to access a variety of stereodefined γ-lactams (Table A3.1).[7] As depicted in entries 1–3, the size of the alkyl group at the allylic position plays an important role in stereoselection. While reductive cross coupling of allylic alcohol **5** with imine **4** proceeds in a fairly unselective manner (*E:Z* = 1.5:1), union of imine **4** with allylic alcohol **7** occurs with increased levels of stereoselection and produces the homoallylic amine **8** in 76% yield (E:Z ≥ 4:1). Subsequent carbonylation then delivers the stereodefined unsaturated γ-lactam **9** in 99% yield. As depicted in entry 3, branched alkyl substitution on the allylic alcohol leads to the highest levels of *E*-selectivity in this coupling reaction. Here, the homoallylic amine **11** is forged in 58% yield with greater than 20:1 selectivity for the formation of the stereodefined *E*-alkene. Palladium catalyzed carbonylation then furnishes γ-lactam **12** in 94% yield. Moving on to a more highly substituted allylic alcohol, the conversion of **13** to homoallylic amine **14** proceeds in 53% yield and delivers the stereodefined *anti*-product as essentially a single isomer. Similarly, carbonylation then provides the highly substituted exo-alkylidene γ-lactam **15** in 66% yield.

Finally, this two-step three-component heterocycle synthesis is useful for the synthesis of stereodefined bicyclic lactams. As illustrated in entries 5 and 6, reductive cross-coupling

Table A3.1. *exo*-Alkylidene-γ-lactams via Imine–Allylic Alcohol Reductive Cross-Coupling



entry	alcohol	% yield	homoallylic amine	% yield	γ-lactam
1	 5	81[a]	 **6** *E/Z* = 1.5 : 1	–	–
2	 7	76[a]	 **8** *E/Z* = 4 : 1	>99	 **9**
3	 10	58[b]	 **11** *E/Z* ≥ 20 : 1	94	 **12**
4	 13	53[a]	 **14** d.r. ≥ 20 : 1	66	 **15**
5	 18	67[b]	 **17** d.r. ≥ 20 : 1	87	 **18**
6	 23	53[b]	 **20** d.r. ≥ 13 : 1	92	 **21**

Ti-mediated cross-coupling: $ClTi(O\textit{i}\text{-}Pr)_3$ (1.25 equiv.), *c*-C_5H_9MgCl (2.5 equiv.), Et_2O or toluene (–70 to –40 °C), then the sodium alkoxide of the allylic alcohol was added as a solution in THF.[7] Pd-catalyzed carbonylation: $Cl_2Pd(PPh_3)_2$ (3-5 mol %), Et_3N, toluene or MeOH ,CO (balloon), 70 °C. [a]4 equiv. of imine were employed. [b]1.5 equiv. of alcohol were employed.

of cyclic allylic alcohols **16** and **17** with imine **4** can be accomplished in a highly stereoselective manner to deliver vinyliodides **17** and **20** (dr up to ≥ 20:1). These substrates are equally effective in the Pd-catalyzed carbonylative cyclization and deliver the bicyclo[4.3.0] and [5.3.0] systems **18** and **21** in 87% and 92% yield.

While this two-step procedure is effective for the stereoselective convergent synthesis of mono- and bicyclic γ-lactams, this multi-component coupling sequence can be streamlined. Specifically, we have defined a one-pot three-component coupling reaction that converts 2-halo allylic alcohols, imines and carbon monoxide directly to stereodefined exo-alkylidene γ-lactams. Aware of the compatibility of Pd-catalyzed coupling processes with water and base, we speculated that aqueous quenching of the titanium-mediated reductive cross-coupling reaction may directly furnish a suitable environment for Pd-catalyzed carbonylation. This expectation was indeed the case.

As depicted in Figure A3.5, this sequential multicomponent coupling process for the synthesis of substituted γ-lactams can be conducted in a single reaction vessel. Here, union of imine **4** with allylic alcohol **2** furnishes lactam **3** in 69% yield. Similarly, union of imine **4** with allylic alcohol **22** provides the stereodefined bicyclic lactam **18** in 73% yield.[7] Notably, avoiding the requirement for purification of the intermediate homoallylic amines substantially improves the overall yield for this γ-lactam forming annulation process.

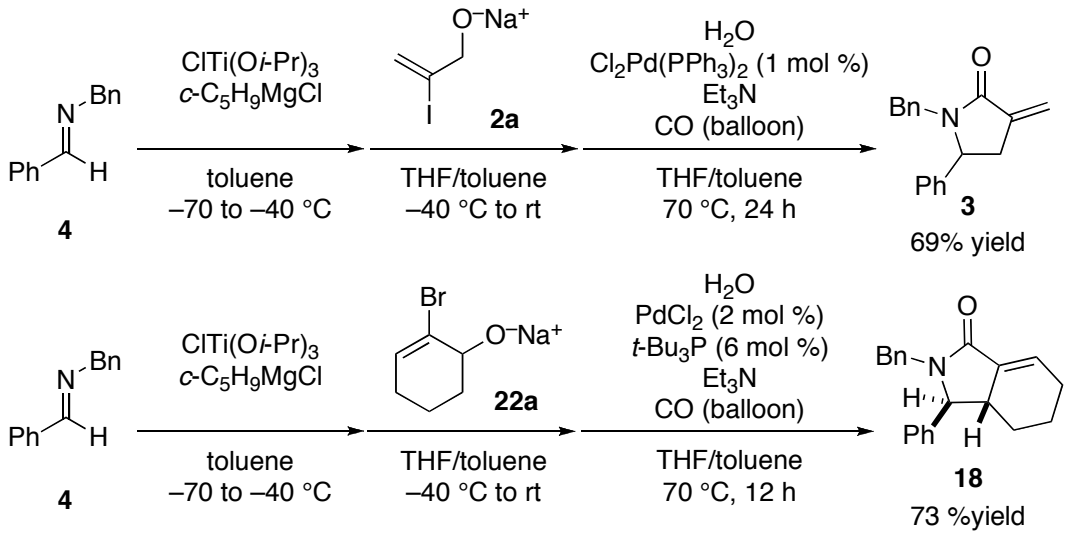


Figure A3.4. One-pot, Three-Component Coupling for Heterocycle Synthesis

Overall, we have described studies that have culminated in the elucidation of a multi-component coupling process for the synthesis of stereodefine exo alkylidene γ-lactams. In short, titanium-mediated regio- and stereoselective coupling of aromatic imines with 2-halo allylic alcohols furnishes intermediate homoallylic amines that are well-suited for palladium-catalyzed carbonylation. This two-step process has been demonstrated with a variety of allylic alcohols and has defined a convergent and stereoselective pathway to mono- and bicyclic γ-lactams. Finally, a one-pot procedure has been developed that enables direct preparation of stereodefined lactams from allylic alcohols and imines. Given the flexibility of the titanium-mediated coupling with respect to imine structure,[3d] and the ability to translate stereochemical information from the allylic alcohol to the homoallylic amine intermediates,[3d] we anticipate that this heterocycle-forming annulation will be of utility in medicinal chemistry and natural product synthesis.

References and Notes

1. Fischer, J.; Ganellin, C. R.; editors. *Analogue-based Drug Discovery.* Wiley-VCH; Weinheim: **2002**.
2. For reviews that cover the synthesis of nitrogen heterocycles, see: (a) Nakamura, I.; Yamamoto, Y.; *Chem. Rev.* **2004**, *104*, 2127. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004,** *104*, 2199. (c) Barluenga, J.; Santamaría, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004,** *104*, 2285. (e) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, 104, 2311. (f) Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Chem. Rev.* **2004**, *104*, 2353. (g) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004,** *104*, 2401. (h) Mitchinson, A.; Nadin, A. *J. Chem. Soc. Perkin. Trans. 1* **1999**, 2553. (i) Nadin, A. *J. Chem. Soc. Perkin. Trans. 1* **1998**, 3493. (j) Harrison, T. *Contemp. Org. Synth.* **1995**, *2*, 209.
3. For the coupling of homoallylic alcohols to imines, see: (a) Takahashi, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514. (b) Lysenko, I. L.; Lee, H. G.; Cha, J. K. *Org. Lett.* **2009**, *11*, 3132. For the coupling of homopropargylic alcohols to imines, see: (c) McLaughlin, M.; Takahashi, M.; Micalizio, G. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 3912. For the coupling of allenic alcohols to imines, see: (d) McLaughlin, M.; Shimp, H. L.; Navarro, R.; Micalizio, G. C. *Synlett* **2008**, 735. For the coupling of allylic alcohols to imines, see: (e) Takahashi, M.; McLaughlin, M.; Micalizio, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 3702.
4. For related reductive cross-coupling reactions that appear to proceed by formal metallo-[3,3] rearrangement, see: (a) Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112. (b) Shimp, H. L.; Hare, A.; McLaughlin, M.; Micalizio, G. C. *Tetrahedron* **2008**, *64*, 6831. (c) Belardi, J. K.; Micalizio, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 16870. (d) Lysenko, I.L.; Kim, K.; Lee, H. G.; Cha, J. K. *J. Am. Chem. Soc.* **2008**, *130*, 15997.

5. For a review of Pd-catalyzed carbonylation for the synthesis of lactams and lactones, see: Farina, V.; Magnus, E. *Handbook of Organopalladium Chemistry for Organic Synthesis.* Negishi, E-I.; Ed.; John Wiley & Sons, Inc; Hoboken, NJ: **2002**, pp. 2351.

6. For early examples of Pd-catalyzed carbonylation for lactam synthesis, see: (a) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43,* 1684. (b) Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, Y.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058. (c) Crisp, G. T.; Meyer, A. G. *Tetrahedron* **1995**, *51*, 5585.

7. General experimental procedure for the two-step γ-lactam synthesis described in Table 1: Synthesis of (*S**)-*N*-benzyl-1-((*R**)-2-iodocyclohex-2-enyl)-1-phenylmethanamine 17: To a solution of imine **4** (563 μL, 586 mg, 3.00 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 3.75 mmol) in diethyl ether (12 mL) at −70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 7.50 mmol) in a drop-wise manner with a syringe. The brown solution was slowly warmed to −40 °C over 30 minutes and stirred at −40 °C for a further 1.5 hours. A solution of the sodium alkoxide, generated from the deprotonation of alcohol **16** (1.01 g, 4.50 mmol) with NaH (60 % suspension, 225 mg, 5.63 mmol), in THF (15 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at −40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (5 mL) was added and the resulting biphasic mixture was stirred rapidly. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/40 → 1/30 EtOAc/Hexanes) to yield haloallylic amine **17** as a colorless oil, (811 mg, 67%, dr ≥ 20:1). Synthesis of (3*S**,3*S**)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one **18**: To a round bottom flask equipped with a reflux condenser was sequentially added amine **17** (169 mg,

0.420 mmol), toluene (4.2 mL), $Cl_2Pd(PPh_3)_2$ (14 mg, 0.021 mmol) and Et_3N (114 μ L, 83 mg, 0.820 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10 → 1/5 EtOAc/Hexanes) to yield γ-lactam **18** as a white solid, (111 mg, 87%).

8. General experimental procedure for the one-pot γ-lactam synthesis described in Figure 5: Synthesis of (3*S**,3*S**)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one **18**: To a solution of imine **4** (74 μL, 78 mg, 0.400 mmol) and $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in diethyl ether, 0.500 mmol) in toluene (1.6 mL) at −70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 1.00 mmol) in a drop-wise manner with a syringe. The orange-brown solution was slowly warmed to −40 °C over 30 minutes and stirred at −40 °C for a further 1.5 hours. A solution of the sodium alkoxide, generated from the deprotonation of allylic alcohol **22** (106 mg, 0.600 mmol) with NaH (60 % suspension, 30 mg, 0.750 mmol), in THF (1.6 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine-Ti complex at −40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. The following morning H_2O (36 μL, 36 mg, 2.00 mmol) was added and then rapidly stirred for 2 hours at ambient temperature. To the yellow solution of the reaction mixture was added $PdCl_2$ (1 mg, 0.008 mmol), *t*-Bu_3P (1.0 M toluene, 0.024 mmol) and Et_3N (223 μL, 161 mg, 1.60 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel

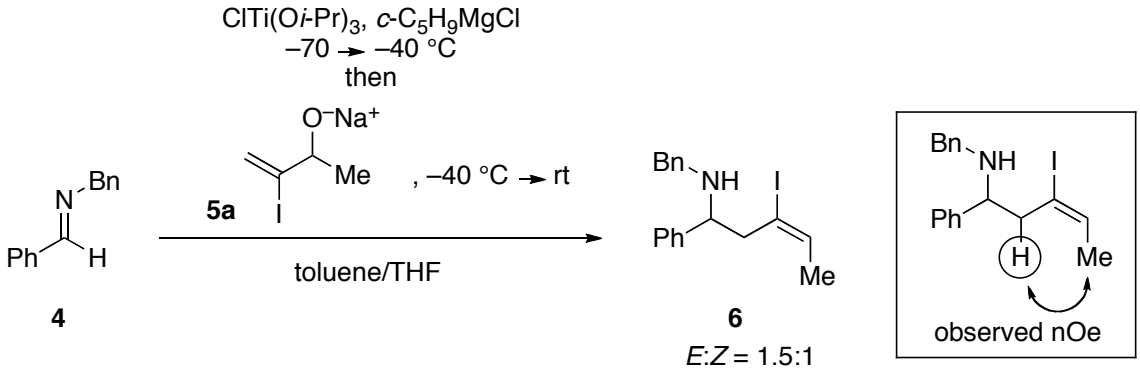
was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction vessel was then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (10 mL), the solids ware removed by filtration through celite. The filtrate was further diluted with EtOAc (75 mL) and washed with 1 M HCl aq. (75 mL), saturated aqueous $NaHCO_3$ (75 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10 → 1/5 EtOAc/Hexanes) to yield γ-lactam **18** as a white solid, (89 mg, 73%, dr ≥20:1).

Experimental Section

General Methods.

All reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents, unless otherwise noted. Dry diethyl ether, tetrahydrofuran, toluene and dichloromethane were obtained by passing inhibitor-free, HPLC grade solvents through activated alumina columns. Triethylamine, and chlorotrimethylsilane were distilled from CaH_2 before use. Chlorotriisopropoxytitanium(IV) was purchased from Sigma-Aldrich Co. as a 1.0 M solution in hexanes and used as received, with no bottle being used more than one month after opening. Cyclopentylmagnesium chloride was purchased as solution in Et_2O, and titrated on a monthly basis.[1] Carbon monoxide was purchased from Praxair in research purity (99.99%). Imine **4**,[2] and alcohols **1**,[3] **2**,[4] **5**,[5] **7**,[6] **13**,[7] and **22**[8] were prepared according to literature procedures. Alcohols **16** and **19** were prepared from iodination of the cyclic enone[9] followed by reduction.[10] Alcohol **10** was prepared by adapting the procedure from alcohol **7**.[6] All other commercially available reagents were used as received. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 250 μm E. Merck silica gel plates (60F-254) and visualized using UV light or appropriate stains, including ninhydrin, *p*-anisaldehyde, ceric ammonium nitrate, and potassium permanganate. Silica gel for flash column chromatography was purchased from Silicycle (P60, particle size 40-63 μm). ^{1}H NMR data were recorded at 400 or 500 MHz using a Bruker AM-400 or AM-500 instruments. ^{1}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm) or TMS (0.00 ppm). ^{13}C NMR data were recorded at 100 or 126 MHz using a Bruker AVANCE-400 or AM-500 instruments. ^{13}C NMR chemical shifts were reported relative to the central line of CDCl3 (77.23 ppm). Infrared spectra were recorded using a Perkin Elmer Spectrum One FT-IR spectrometer. Low-resolution mass spectrometry was performed on a Waters Micromass® ZQTM instrument using electrospray ionization.

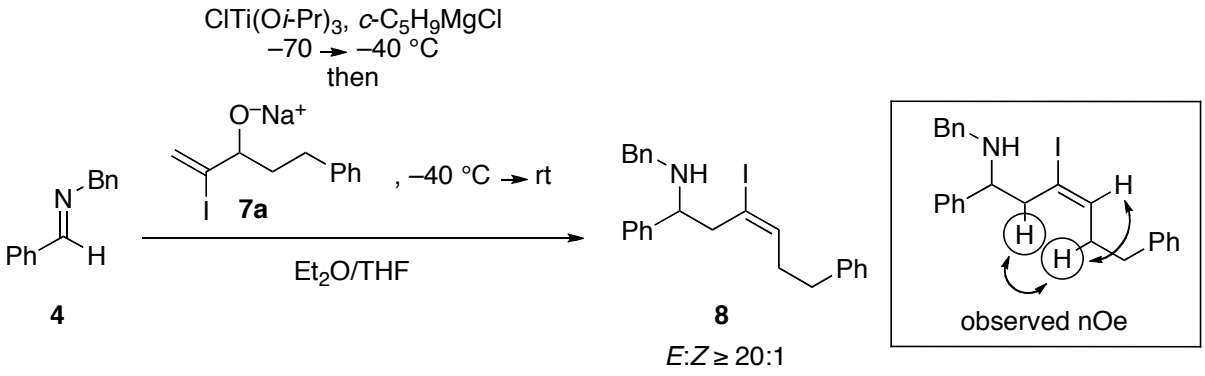
High resolution mass spectrometry was performed by the University of Florida Mass Spectrometry Services. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless indicated otherwise. Diastereoselectivity is reported from the ^{1}H NMR of the crude reaction mixture. Relative stereochemistry was defined using the *R**/*S** convention proposed by IUPAC.



Synthesis of (*E*)-*N*-benzyl-3-iodo-1-phenylpent-3-en-1-amine 6: To a solution of imine **4** (451 μL, 473 mg, 2.42 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 2.55 mmol) in toluene (10 ml) at –70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 5.09 mmol) in a drop-wise manner with a syringe. The orange-brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **5a**, generated from the deprotonation of the corresponding alcohol (120 mg, 0.606 mmol) with NaH (60 % suspension, 30 mg, 0.76 mmol), in THF (2.5 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (5 mL) was added and the resulting biphasic mixture was stirred rapidly for 15 minutes. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude

material was purified by column chromatography on silica gel (1/40→1/25 EtOAc/Hexanes) to yield haloallylic amine **6** as a colorless oil, (185 mg, 81%, *E*:*Z* = 1.5:1).

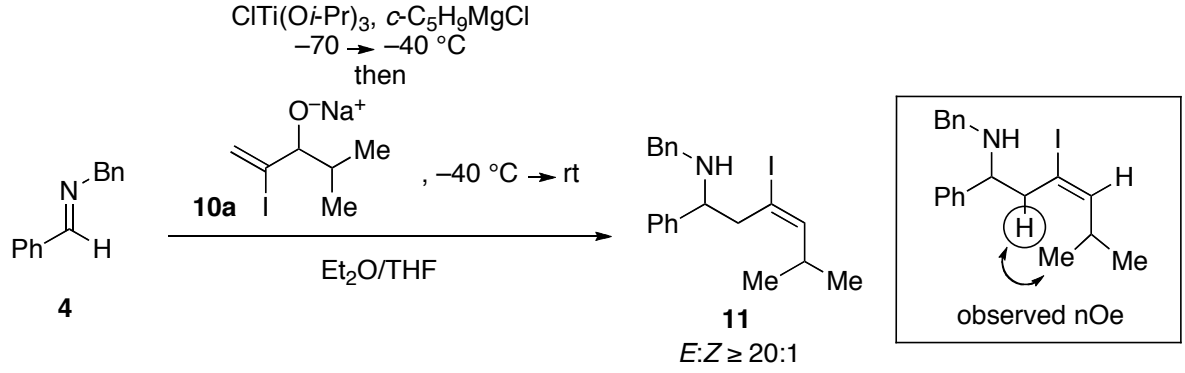
Data for *N*-benzyl-3-iodo-1-phenylpent-3-en-1-amine 6: ^{1}H NMR (400 MHz, $CDCl_3$) (*E*)-isomer: δ 7.47-7.19 (m, 10H), 6.30 (q, *J* = 7.1 Hz, 1H), 4.00 (dd, *J* = 7.6, 6.0 Hz, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.58 (d, *J* = 13.2 Hz, 1H), 2.78 (dd, *J* = 14.2, 7.6 Hz, 1H), 2.61 (dd, *J* = 14.2, 6.0 Hz, 1H), 1.45 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 142.8, 140.6, 138.7, 128.5, 128.4, 128.1, 127.5, 127.4, 126.9, 98.9, 77.4, 77.1, 76.8, 61.5, 51.7, 47.1, 16.6; IR (thin film, NaCl) 3027, 2917, 2848, 1602, 1494, 1455, 1114, 1027, 697 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{18}H_{21}IN$ $(M+H)^+$ 378.0713; found $(M+H)^+$ 378.0737.



Synthesis of (*E*)-N-benzyl-3-iodo-1,6-diphenylhex-3-en-1-amine 8: To a solution of imine **4** (216 μL, 227 mg, 1.16 mmol) and $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in diethyl ether, 1.22 mmol) in diethyl ether (4.5 mL) at –70 °C was added *c*-C_5H_9MgCl (1.94 M in diethyl ether, 2.44 mmol) in a drop-wise manner with a syringe. The orange-brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **7a**, generated from the deprotonation of the corresponding alcohol (83 mg, 0.290 mmol) with NaH (60 % suspension, 15 mg, 0.363 mmol), in THF (1.2 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight.

Next, saturated aqueous NH_4Cl (2.5 mL) was added and the resulting biphasic mixture was stirred rapidly for 15 minutes. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/50→1/30 EtOAc/Hexanes) to yield haloallylic amine **8** as a colorless oil, (103 mg, 76%, *E*:*Z* ≥4:1).

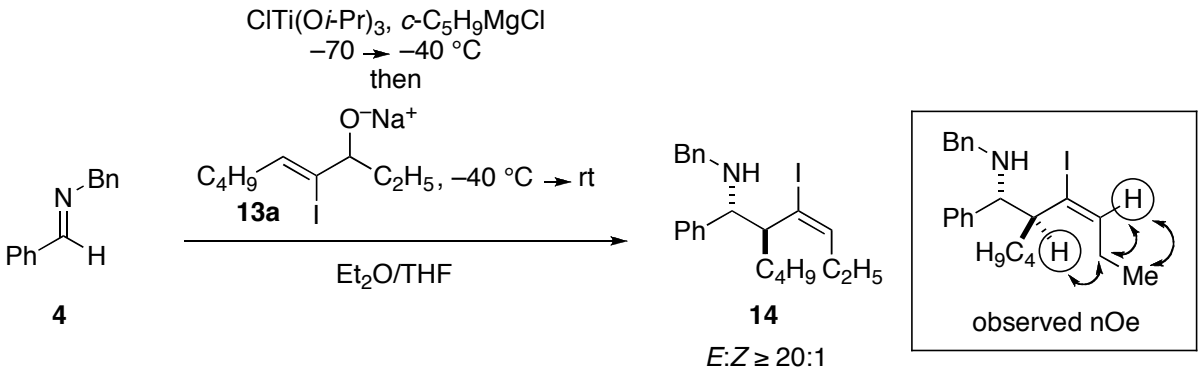
Data for (*E*)-N-benzyl-3-iodo-1,6-diphenylhex-3-en-1-amine 8: ^{1}H NMR (400 MHz, $CDCl_3$) (*E*)-isomer: δ 7.42-7.31 (m, 2H), 7.30-7.05 (m, 11H), 6.97 (d, *J* = 7.1 Hz, 1H), 6.17 (t, *J* = 7.4 Hz, 1H), 3.91 (t, *J* = 6.8 Hz, 1H), 3.59 (d, *J* = 13.2 Hz, 1H), 3.49 (d, *J* = 13.2 Hz, 1H), 2.64 (dd, *J* = 6.8, 14.2 Hz, 1H), 2.51 (dd, *J* = 6.8, 14.2 Hz, 1H), 2.43-2.23 (m, 2H), 2.21-1.98 (dd, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 143.5, 142.9, 141.1, 140.7, 128.7, 128.6, 128.5, 128.5, 128.3, 127.7, 127.6, 127.1, 126.2, 99.5, 61.6, 51.9, 47.7, 35.1, 33.0; IR (thin film, NaCl) 3026, 2947, 2857, 1603, 1494, 1454, 1028, 747, 698 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{25}H_{27}IN$ $(M+H)^+$ 468.1188; found $(M+H)^+$ 468.1188.



Synthesis of (*E*)-N-benzyl-3-iodo-5-methyl-1-phenylhex-3-en-1-amine 11: To a solution of imine **4** (93 μL, 98 mg, 0.500 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 0.625 mmol) in diethyl ether (2.5 mL) at –70 °C was added *c*-C_5H_9MgCl (1.94 M in diethyl ether, 1.25 mmol) in a drop-wise manner with a syringe. The brown solution was slowly warmed to –40 °C

over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **10a**, generated from the deprotonation of the corresponding alcohol (167 mg, 0.750 mmol) with NaH (60 % suspension, 38 mg, 0.94 mmol), in THF (2.5 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (2.5 mL) was added and the resulting biphasic mixture was stirred rapidly for 15 minutes. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/50→1/30 EtOAc/Hexanes) to yield haloallylic amine **11** as a colorless oil, (117 mg, 58%, *E*:*Z* ≥ 20:1).

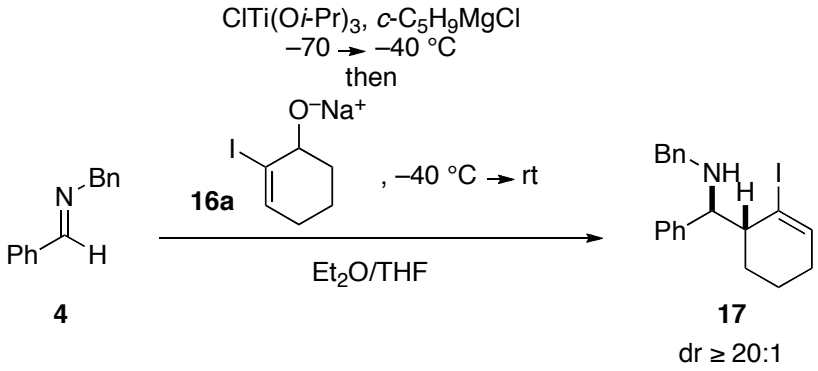
Data for (*E*)-N-benzyl-3-iodo-5-methyl-1-phenylhex-3-en-1-amine 11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (m, 2H), 7.30-7.13 (m, 8H), 5.98 (d, *J* = 10.0 Hz, 1H), 3.93 (dd, *J* = 7.6, 6.1 Hz, 1H), 2.67 (dd, *J* = 14.2, 7.6 Hz, 1H), 2.56 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.36 (dtt, *J* = 10.0, 6.6, 6.6 Hz, 1H), 0.82 (d, *J* = 6.6 Hz, 1H), 0.55 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 143.0, 140.7, 128.7, 128.6, 128.3, 127.7, 127.6, 127.1, 97.1, 61.7, 52.0, 47.8, 31.2, 22.7, 22.3; IR (thin film, NaCl) 3026, 2959, 2866, 1492, 1453, 1004, 759, 699 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{20}H_{25}IN$ $(M+H)^+$ 406.1026; found $(M+H)^+$ 406.1038.



Synthesis of (1*R, 2*S**, *E*)-*N*-benzyl-2-butyl-3-iodo-1-phenylhex-3-en-1-amine 14:** To a solution of imine **4** (250 μL, 260 mg, 1.34 mmol) in toluene (2.8 mL) at room temperature was added ClTi(O*i*-Pr)$_3$ (1.40 mmol, 1.0 M in hexanes). The reaction was then cooled to −70 °C and *c*-C_5H_9MgCl (2.28 M in ether, 2.80 mmol) was added in a drop-wise manner with a syringe. The mixture was warmed to −30 °C over 30 minutes and stirred for 2 hours at this temperature. Then freshly distilled TMSCl (160 μL, 137 mg, 1.27 mmol) was added and the reaction stirred at −30 °C for an additional 1hour. A solution of sodium alkoxide **13a**, prepared by the deprotonation of alcohol **13** (90 mg, 0.335 mmol) in THF (2.0 mL) at 0 °C with NaH (20 mg, 0.502 mmol, 60% dispersion in mineral oil) for 30 minutes, was added in a drop-wise manner to the brown solution of imine−Ti complex at −30 °C via Teflon cannula. An additional 3 mL of toluene was added to facilitate stirring. The mixture was allowed to warm to room temperature in the cooling bath and stir overnight. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (5.0 mL) followed by rapid stirring at room temperature for 15 minutes. The mixture was then diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (3→4% EtOAc/hexanes) to afford haloallylic amine **14** as a yellow oil (79 mg, 53%, dr ≥20:1). A portion of the product was purified a second time by column chromatography on silica gel (3% EtOAc/hexanes) to yield analytically pure **14**. See the transformation of **14→15**, and accompanying data for the assignment of relative stereochemistry.

Data for (1*R, 2*S**, *E*)-*N*-benzyl-2-butyl-3-iodo-1-phenylhex-3-en-1-amine 14:** ^{1}H NMR (500 MHz, $CDCl_3$) d 7.42-7.02 (m, 10H), 6.44 (t, *J* = 7.5 Hz, 1H), 3.46 (d, *J* = 13.4 Hz, 1H), 3.34 (d, *J* = 13.4 Hz, 1H), 3.27 (d, *J* = 9.3 Hz, 1H), 2.28-2.09 (m, 2H), 1.94-1.87 (m 1H), 1.77 (s (br), 1H), 1.14-0.90 (m, 7H), 0.83-0.59 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6,

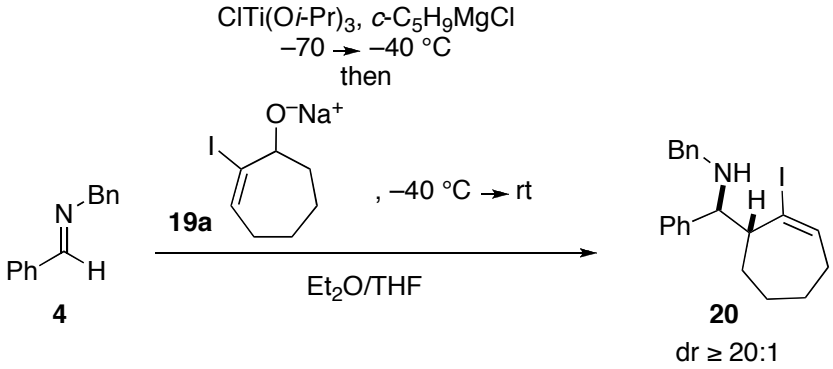
142.0, 140.9, 129.3, 128.5, 128.4, 128.4, 127.6, 126.9, 110.6, 66.4, 51.8, 50.2, 31.1, 29.2, 25.6, 22.6, 14.1, 14.0; IR (thin film, NaCl) 3026, 2958, 2932, 2871, 2858, 1455, 1132, 756, 700 cm^{-1}; LRMS (ESI, H) *m/z* calc'd for $C_{23}H_{31}IN$ $(M + H)^+$ 448.2; found $(M+H)^+$ 448.2.



Synthesis of (*S)-*N*-benzyl-1-((*R**)-2-iodocyclohex-2-enyl)-1-phenylmethanamine 17:** To a solution of imine **4** (563 μL, 586 mg, 3.00 mmol) and $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in diethyl ether, 3.75 mmol) in diethyl ether (12 mL) at –70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 7.50 mmol) in a drop-wise manner with a syringe. The brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **16a**, generated from the deprotonation of the corresponding alcohol (1.01 g, 4.50 mmol) with NaH (60 % suspension, 225 mg, 5.63 mmol), in THF (15 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (5 mL) was added and the resulting biphasic mixture was stirred rapidly. The resulting solution was further diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/40→1/30 EtOAc/Hexanes) to yield haloallylic amine **17** as a colorless oil, (811 mg, 67%, dr ≥ 20:1).

See the transformation of **17→18,** and accompanying data for the assignment of relative stereochemistry.

Data for (*S)-*N*-benzyl-1-((*R**)-2-iodocyclohex-2-enyl)-1-phenylmethanamine 17:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.37-7.22 (m, 8H), 6.48 (dt, *J* = 1.5, 4.1 Hz, 1H), 4.34 (d, *J* = 3.9 Hz, 1H), 3.77 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H), 2.70-2.63 (m, 1H), 1.92-1.77 (m, 2H), 1.75-1.58 (m, 2H), 1.29-1.20 (m, 1H), 0.74-0.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.9, 140.8, 128.6, 128.4, 128.3, 128.2, 128.1, 127.3, 127.1, 103.0, 64.5, 52.1, 50.6, 29.4, 25.2, 18.2; IR (thin film, NaCl) 3027, 2934, 2867, 1602, 1494, 1454, 1115, 1028, 958, 732 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{20}H_{23}IN$ $(M+H)^+$ 404.0870; found $(M+H)^+$ 404.0834.

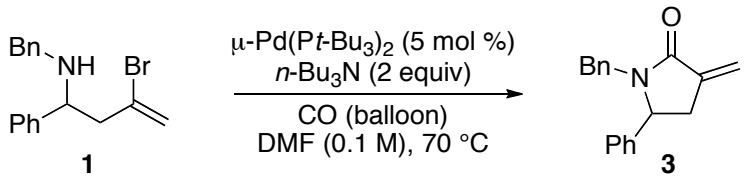


Synthesis of (*S)-*N*-benzyl-1-((*R**)-2-iodocyclohept-2-enyl)-1-phenylmethanamine 20:** To a solution of imine **4** (563 μL, 586 mg, 3.00 mmol) and $ClTi(O\textit{i}\text{-}Pr)_3$ (1.0 M in diethyl ether, 3.75 mmol) in diethyl ether (12 mL) at –70 °C was added *c*-C_5H_9MgCl (2.00 M in diethyl ether, 7.50 mmol) in a drop-wise manner with a syringe. The brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **19a**, generated from the deprotonation of the corresponding alcohol (1.07 g, 4.50 mmol) with NaH (60 % suspension, 225 mg, 5.63 mmol), in THF (12 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti

complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. Next, saturated aqueous NH_4Cl (5 mL) was added and the resulting biphasic mixture was rapidly stirred. The resulting red brown solution was further diluted with saturated aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/25→1/20 EtOAc/Hexanes) to yield amine **20** as a colorless oil, (665 mg, 53%, dr ≥13:1).

See the transformation of **20→21**, and accompanying data for the assignment of relative stereochemistry.

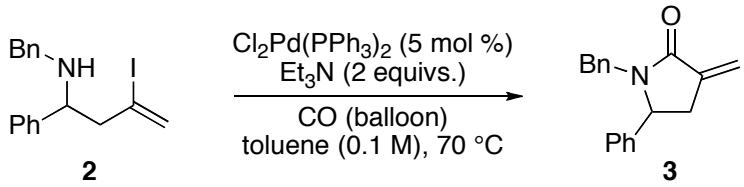
Data for (*S)-*N*-benzyl-1-((*R**)-2-iodocyclohept-2-enyl)-1-phenylmethanamine 20:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.18 (m, 10H), 6.67 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.95 (d, *J* = 10.0 Hz, 1H), 3.64 (d, *J* = 13.6 Hz, 1H), 3.48 (d, *J* = 13.6 Hz, 1H), 3.00 (ddd, *J* = 10.0, 7.2, 3.6 Hz, 1H), 2.10-1.76 (m, 3H, (NH)), 1.75-1.18 (m, 5), 1.14-1.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 142.0, 140.8, 128.5, 128.4, 128.4, 128.4, 127.5, 126.9, 104.8, 64.6, 57.6, 51.6, 30.6, 26.7, 15.7; IR (thin film, NaCl) 3026, 2924, 2847, 1602, 1494, 1453, 1114, 1027, 735 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{21}H_{25}IN$ $(M+H)^+$ 418.1026; found $(M+H)^+$ 418.0988.



Synthesis of 1-benzyl-3-methylene-5-phenyl-2-pyrrolidinone 3: To a round bottom flask equipped with a reflux condenser was sequentially added amine **1** (79 mg, 0.250 mmol), DMF (2.5 mL), μ-Pd(P*t*-Bu_3)$_2$ (6 mg, 0.012 mmol) and *n*-Bu_3N (119 μL, 92 mg, 0.500 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to

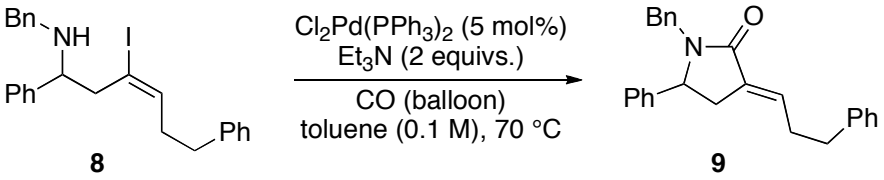
vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/7→1/5 EtOAc/Hexanes) to yield γ-lactam **3** as a white solid, (63 mg, 95%).

Data for 1-benzyl-3-methylene-5-phenyl-2-pyrrolidinone 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 6H), 7.17-7.08 (m, 4H), 6.15 (t, *J* = 2.4 Hz, 1H), 5.40 (t, *J* = 2.4 Hz, 1H), 5.19 (d, *J* = 14.8 Hz, 1H), 4.40 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.54 (d, *J* = 14.8 Hz, 1H), 3.14 (ddt, *J* = 17.2, 8.4, 2.4 Hz, 1H), 2.64 (ddt, *J* = 17.2, 4.0, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 140.9, 139.1, 136.3, 129.3, 129.2, 128.8, 128.7, 127.4, 127.8, 126.9, 116.4, 58.3, 44.9, 34.8; IR (thin film, NaCl) 3030, 2922, 2242, 1694, 1682, 1495, 1416, 922 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{18}H_{18}NO$ $(M+H)^+$ 264.1383; found $(M+H)^+$ 264.1382.



Synthesis of 1-benzyl-3-methylene-5-phenyl-2-pyrrolidinone 3: To a round bottom flask equipped with a reflux condenser was sequentially added amine **2** (230 mg, 0.630 mmol), toluene (6.3 mL), $Cl_2Pd(PPh_3)_2$ (22 mg, 0.031 mmol) and Et_3N (176 μL, 127 mg, 1.26 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton

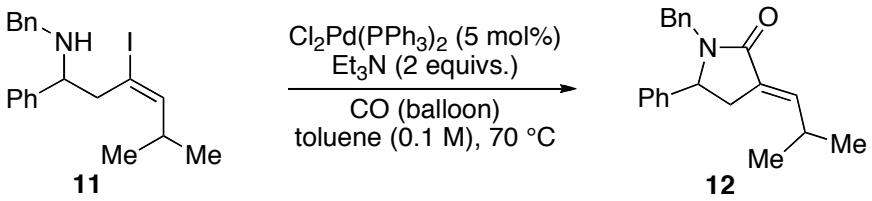
and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/7→1/5 EtOAc/Hexanes) to yield γ-lactam **3** as a white solid, (155 mg, 93%). NMR data was in accordance with that described for the transformation of **1→3**.



Synthesis of (*E*)-1-benzyl-5-phenyl-3-(3-phenylpropylidene)-2-pyrrolidinone 9: To a round bottom flask equipped with a reflux condenser was sequentially added amine **8** (54 mg, 0.115 mmol), toluene (1.2 mL), $Cl_2Pd(PPh_3)_2$ (4 mg, 5.75 μmol) and Et_3N (32 μL, 23 mg, 0.230 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/7 EtOAc/Hexanes) to yield γ-lactam **9** as a white solid, (42 mg, 99%).

Data for (*E*)-1-benzyl-5-phenyl-3-(3-phenylpropylidene)-2-pyrrolidinone 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 3H), 7.23-7.13 (m, 5H), 7.12-7.06 (m, 3H), 7.06-7.00 (m, 2 H), 7.00-6.95 (m, 2H), 6.62-6.54 (m, 1H), 5.09 (d, *J* = 14.6 Hz, 1H), 4.24 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.40 (d, *J* = 14.6 Hz, 1H), 2.86-2.74 (m, 1H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.50 (dt, *J* = 7.5, 7.5 Hz, 2H), 2.34-2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 141.3, 136.6, 132.7, 131.6, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 127.7, 126.9, 126.2, 58.4, 44.7, 34.9, 32.6, 31.5; IR (thin film, NaCl) 3028, 2923, 2856, 1694, 1682, 1603, 1494, 1455, 1435, 1246,

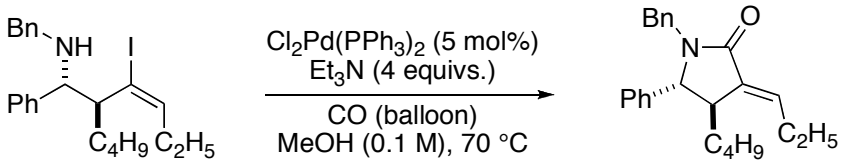
1029, 700 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{26}H_{26}NO$ $(M+H)^+$ 368.2009; found $(M+H)^+$ 368.2016.



Synthesis of (*E*)-1-benzyl-3-(2-methylpropylidene)-5-phenyl-2-pyrrolidinone 12: To a round bottom flask equipped with a reflux condenser was sequentially added amine **11** (54 mg, 0.160 mmol), toluene (1.6 mL), $Cl_2Pd(PPh_3)_2$ (6 mg, 0.008 mmol) and Et_3N (45 μL, 33 mg, 0.320 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/7 EtOAc/Hexanes) to yield γ-lactam **12** as a white solid, (42 mg, 99%).

Data for (*E*)-1-benzyl-3-(2-methylpropylidene)-5-phenyl-2-pyrrolidinone 12: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 3H), 7.23-7.13 (m, 5H), 7.12-7.06 (m, 3H), 7.06-7.00 (m, 2H), 7.00-6.95 (m, 2H), 6.62-6.54 (m, 1H), 5.09 (d, *J* = 14.6 Hz, 1H), 4.24 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.40 (d, *J* = 14.6 Hz, 1H), 2.86-2.74 (m, 1H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.50 (dt, *J* = 7.5, 7.5 Hz, 2H), 2.34-2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 141.3, 136.6, 132.7, 131.6, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 127.7, 126.9, 126.2, 58.4, 44.7, 34.9, 32.6, 31.5; IR (thin film, NaCl) 3028, 2923, 2856, 1694, 1682, 1603, 1494, 1455, 1435, 1246,

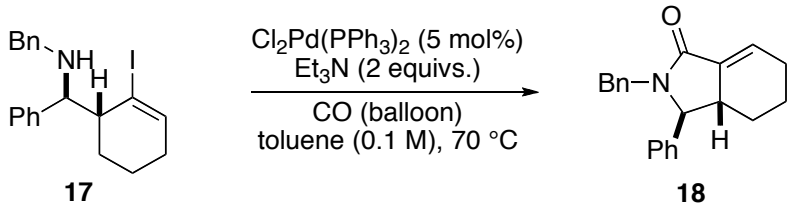
1029, 700 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{21}H_{24}NO$ $(M+H)^+$ 306.1852; found $(M+H)^+$ 306.1862.



14 **15**

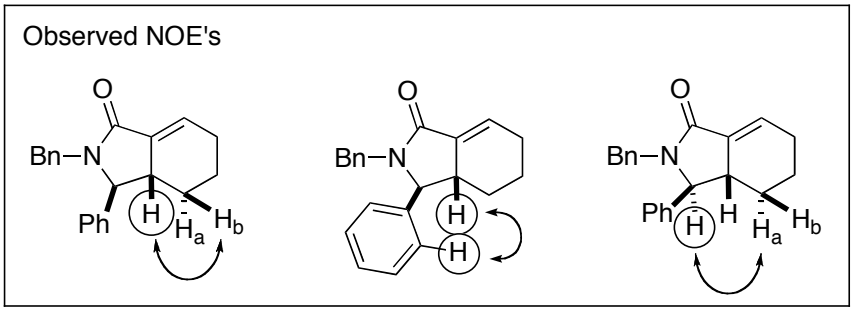
Synthesis of (4*S,5*S**,*E*)-1-benzyl-4-butyl-5-phenyl-3-propylidenepyrrolidin-2-one 15:** To a Schlenk tube was sequentially added amine **14** (80 mg, 0.178 mmol), MeOH (1.5 mL), $Cl_2Pd(PPh_3)_2$ (6 mg, 0.009 mmol), and triethylamine (100 μL, 72 mg, 0.712 mmol). The Schlenk tube was then cooled to −30 °C, evacuated (house-vac, 100 torr), and backfilled with 20 psig CO (evacuation and backfilling repeated three times) and placed in a preheated oil bath (70 °C) for 20 hours. The reaction was then diluted with H_2O, extracted with ether (3 × 50 mL), the combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/7 EtOAc/Hexanes) to yield lactam **15** as a colorless oil (41 mg, 66%).

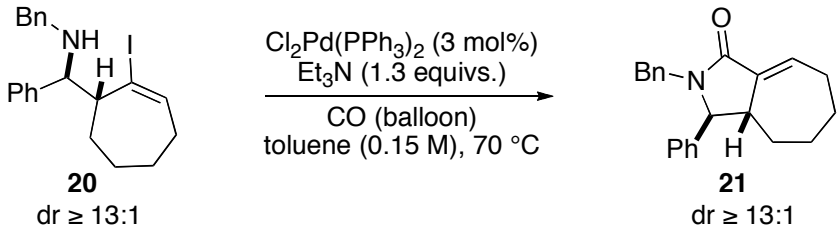
Data for (4*S,5*S**,*E*)-1-benzyl-4-butyl-5-phenyl-3-propylidenepyrrolidin-2-one 15:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.21 (m, 6H), 7.12-7.11 (m, 2H), 7.04-7.02 (m, 2H), 6.58 (td, *J* = 7.7, 1.9 Hz, 1H), 5.19 (d, *J* = 14.7 Hz, 1H), 3.96 (s, 1H), 3.43 (d, *J* = 14.7 Hz, 1H), 2.72-2.70 (m, 1H), 2.15-2.06 (m, 2H), 1.48-1.37 (m, 2H), 1.25-0.99 (m, 7H), 0.76 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 141.5, 136.7, 136.6, 134.5, 129.2, 128.8, 128.7, 128.1, 127.7, 126.5, 64.5, 44.7, 44.5, 35.1, 28.5, 22.8, 22.4, 14.0, 13.7; IR (thin film, NaCl) 3029, 2960, 2930, 2871, 2858, 1693, 1673, 1417, 1243, 739, 701 cm^{-1}; LRMS (EI, H) calcd for: $C_{24}H_{30}NO$ 348.2 *m/z* $(M + H)^+$; found $(M + H)^+$ 348.2 *m/z*.



Synthesis of (3*S,3*S**)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one 18:** To a round bottom flask equipped with a reflux condenser was sequentially added amine **17** (169 mg, 0.420 mmol), toluene (4.2 mL), $Cl_2Pd(PPh_3)_2$ (14 mg, 0.021 mmol) and Et_3N (114 μL, 83 mg, 0.820 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/5 EtOAc/Hexanes) to yield γ-lactam **18** as a white solid, (111 mg, 87%).

Data for (3*S,3*S**)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one 18:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 3H), 7.18-7.10 (m, 3H), 7.10-7.05 (m, 2H), 6.94-6.86 (m, 2H), 6.54 (dt, *J* = 3.3, 3.3 Hz, 1H), 5.04 (d, *J* = 14.4 Hz, 1H), 3.78 (d, *J* = 7.6 Hz, 1H), 3.50 (d, *J* = 14.4 Hz, 1H), 2.54-2.40 (m, 1H), 2.28-2.14 (m, 1H), 1.85-1.66 (m, 2H), 1.43-1.26 (m, 1H), 1.16-0.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 139.3, 136.5, 134.9, 129.0, 128.8, 128.5, 128.3, 127.6, 127.4, 66.7, 45.3, 44.4, 25.1, 24.8, 21.5; IR (thin film, NaCl) 3026, 2929, 2862, 1688, 1494, 1455, 1393, 1272, 736, 701 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{21}H_{22}NO$ $(M+H)^+$ 304.1696; found $(M+H)^+$ 304.1666.





Synthesis of (3*S,3*S**)-2-benzyl-3-phenyl3,3a,4,5,6,7-hexahydrocyclohepta-[*c*]-pyrrol-1(2*H*)-one 21:** To a round bottom flask equipped with a reflux condenser was sequentially added amine **20** (156 mg, 0.374 mmol), toluene (2.5 mL), $Cl_2Pd(PPh_3)_2$ (9 mg, 0.012 mmol) and Et_3N (70 μL, 50 mg, 0.500 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc, filtered through cotton and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/7→1/5 EtOAc/Hexanes) to yield γ-lactam **21** as a white solid, (109 mg, 92%, dr ≥13:1).

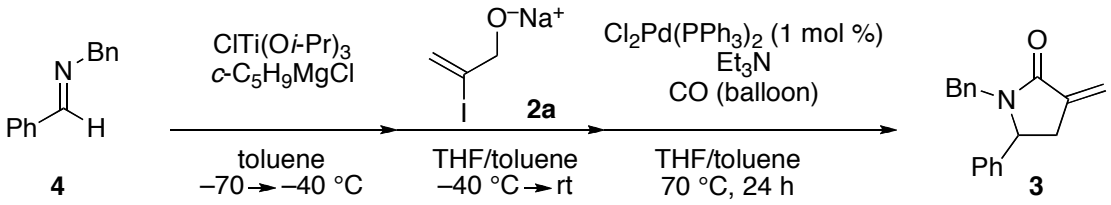
Data for

(3*S,3*S**)-2-benzyl-3-phenyl-3,3a,4,5,6,7-hexahydrocyclohepta-[*c*]-pyrrol-1(2*H*)-one 21:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.12 (m, 6H), 7.11-7.02 (m, 2H), 7.00-6.93 (m, 2H),

6.92-6.86 (m, 2H), 5.07 (d, J = 14.4 Hz, 1H), 3.75 (d, J = 5.6 Hz, 1H), 3.44 (d, J = 14.4 Hz, 1H), 2.70-2.60 (m, 1H), 2.43-2.32 (m, 1H), 2.16-2.02 (m, 1H), 1.93-1.83 (m, 1H), 1.79-1.67 (m, 2H), 1.38-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 140.3, 138.1, 136.5, 135.3, 129.1, 128.8, 128.7, 128.6, 128.4, 127.5, 127.5, 66.0, 48.6, 44.8, 31.7, 30.3, 29.3, 27.4; IR (thin film, NaCl) 3030, 2920, 1695, 1668, 1494, 1415, 1271, 912, 730 cm^{-1}; HRMS (ESI, TOF-MS) *m/z* calcd for: $C_{22}H_{24}NO$ $(M+H)^+$ 318.1864; found $(M+H)^+$ 318.1864.

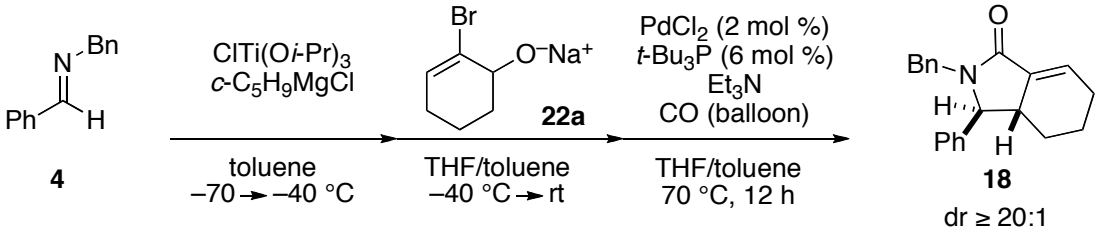
Relative stereochemistry for the major diastereomer was assigned in analogy to compound **18**.

One Pot γ-Lactam Synthesis:



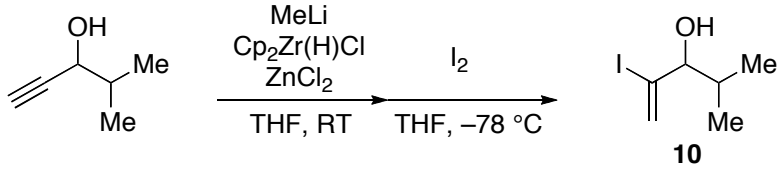
Synthesis of 1-benzyl-3-methylene-5-phenyl-2-pyrrolidinone 3: To a solution of imine **4** (372 μL, 0.391 g, 2.00 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 2.50 mmol) in toluene (8.0 mL) at –70 °C was added *c*--C_5H_9MgCl (2.00 M in diethyl ether, 5.00 mmol) in a drop-wise manner with a syringe. The orange brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 2 hours. A solution of sodium alkoxide **2a**, generated from the deprotonation of the corresponding alcohol (552 mg, 3.00 mmol) with NaH (60 % suspension, 150 mg, 3.75 mmol), in THF (8.0 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine–Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. The following morning H_2O (180 μL, 180 mg, 10.0 mmol) was added and the reaction was rapidly stirred for 2 hours. To the reaction mixture was then added $Cl_2Pd(PPh_3)_2$ (14 mg, 0.020 mmol) and Et_3N (1.11 mL, 808 mg, 8.00 mmol). The reaction was placed under an

atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 24 hours. The reaction mixture was then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (25 mL), the solids ware removed by filtration through CeliteTM. The filtrate was further diluted with EtOAc (75 mL) and washed with 1 M HCl aq. (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was then dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/5 EtOAc/Hexanes) to yield γ-lactam **3** as a white solid, (363 mg, 69%). NMR data was in accordance with that described for the transformation of **1→3**.



Synthesis of (3*S*,3a*S*)-2-benzyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1*H*-isoindol-1-one 18: To a solution of imine **4** (74 μL, 78 mg, 0.400 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in diethyl ether, 0.500 mmol) in toluene (1.6 mL) at –70 °C was added *c*-C$_5$H$_9$MgCl (2.00 M in diethyl ether, 1.00 mmol) in a drop-wise manner with a syringe. The orange-brown solution was slowly warmed to –40 °C over 30 minutes and stirred at –40 °C for a further 1.5 hours. A solution of sodium alkoxide **22a**, generated from the deprotonation of the corresponding alcohol (106 mg, 0.600 mmol) with NaH (60 % suspension, 30 mg, 0.750 mmol), in THF (1.6 mL) at 0 °C, was added in a drop-wise manner via Teflon cannula to the brown solution of imine-Ti complex at –40 °C. The reaction was allowed to warm to ambient temperature and stirred overnight. The following morning H_2O (36 μL, 36 mg, 2.00 mmol) was added and then

rapidly stirred for 2 hours at ambient temperature. To the yellow solution of the reaction mixture was added $PdCl_2$ (1 mg, 0.008 mmol), *t*-Bu_3P (1.0 M toluene, 0.024 mmol) and Et_3N (223 μL, 161 mg, 1.60 mmol). The reaction was placed under an atmosphere of CO by briefly exposing the reaction vessel to vacuum and backfilling with carbon monoxide from a balloon. The atmosphere of CO was maintained by a balloon for the remainder of the reaction. The reaction vessel was then submerged in a preheated oil bath (70 °C), and stirred for 12 hours. The reaction vessel was then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (10 mL), the solids ware removed by filtration through celite. The filtrate was further diluted with EtOAc (75 mL) and washed with 1 M HCl aq. (75 mL), saturated aqueous $NaHCO_3$ (75 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (1/10→1/5 EtOAc/Hexanes) to yield γ-lactam **18** as a white solid, (89 mg, 73%, dr ≥20:1). NMR data was in accordance with that described for the transformation of **17→18**.



10

Synthesis of 2-iodo-4-methyl-1-penten-3-ol 10. Alcohol **10** was prepared in accordance with the published procedure for directed hydrozirconation/iodination by Zhang, D.; Ready.[6] The crude material was purified by column chromatography on silica gel (1/7→1/4 EtOAc/Hexanes) to yield haloallylic alcohol **10** as a colorless oil.

Data for 2-iodo-4-methyl-1-penten-3-ol 10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 1.6, 0.8 Hz, 8H), 5.84 (d, *J* = 1.6 Hz, 1H), 3.08 (ddd, *J* = 7.2, 6.0, 0.8 Hz, 1H), 1.77 (d, *J* = 6.0 Hz, 1H), 1.75 (dqq, *J* = 7.2, 6.8, 6.4 Hz, 1H), 0.96 (d, *J* = 6.4 Hz, 1H), 0.78 (d, *J* = 6.8 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 126.4, 118.4, 83.6, 33.1, 19.4, 17.5; IR (thin film, NaCl) 3436 (br), 2921, 1729, 1463, 1260, 1021, 800, 735 cm^{-1}.

References

1. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
2. Simion, A.; Simion, C.; Kanada, T.; Nagashima, S.; Mitoma, Y.; Yamada, T.; Mimura,K.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2071.
3. Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014.
4. Kurosu, M.; Lin, M. H.; Kishi, Y. J. *J. Am. Chem. Soc.* **2001**, *123*, 12248.
5. Gras, J. L.; Chang, Y. Y.; Win, K.; Bertrand, M. *Tett. Lett.* **1982**, *23*, 3571.
6. Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 12088.
7. Takahashi, M.; McLaughlin, M.; Micalizio, G. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 3648.
8. Suffert, J.; Salem, B.; Klotz, P. *J. Am. Chem. Soc.* **2001**, *123*, 12107.
9. Krafft, M. E.; Cran, J. W. *Synlett* **2005**, *8*, 1263.
10. Sha, C.-K.; Huang, S.-J.; Zhan, Z.-P. *J. Org. Chem.* **2002**, *67*, 831.

論文リスト

1. Dehydrative Cyclization Catalyzed by the Combination of Molybdenum(VI) Oxides and Benzoic Acids: First Synthesis of the Antitumor Substance BE-70016
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   Adv. Synth. Catal. **2007**, *349*, 1641–1646.

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   Chem. Commun. **2008**, 3561–3563. Highlight in *Synfacts*.

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   Org. Lett. **2008**, *10*, 3191–3194.

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   Tetrahedron **2009**, *65*, 2102-2109.

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   Akira Sakakura; Shuhei Umemura; Kazuaki Ishihara
   Synlett **2009**, *10*, 1647–1650.

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   Shuhei Umemura; Martin McLaughlin; Glenn C. Micalizio
   Org. Lett. **2009**, *11*, 5402–5405.

8. Preparation of Stereodefined Homoallylic Amines from the Reductive Cross-Coupling of Allylic Alcohols with Imines

Ming Z. Chen; Martin McLaughlin; Masayuki Takahashi; Michael A. Tarselli; Dexi Yang; Shuhei Umemura; Glenn C. Micalizio

J. Org. Chem. **2010**, *75*, 8048-8059.

9. Desymmetrization of *Meso* Glycerol Derivatives Induced by an L-Histidine-Derived Acylation Catalysts

Akira Sakakura; Shuhei Umemura; Kazuaki Ishihara

Org. Lett. submitted.

10. Catalytic Asymmetric Acylation of Racemic or *Meso* Compounds Using Removable Directing Group; Pyroc

Shuhei Umemura; Akira Sakakura; Kazuaki Ishihara

In preparation.

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Shuhei Umemura