Catalytic Asymmetric Iodocarbocyclization Reaction of 4-Alkenylmalonates and Its Application to Enantiotopic Group Selective Reaction

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The iodocarbocyclization reaction of 4-alkenylmalonate derivatives proceeded with excellent enantioselectivity (≥95% ee) in the presence of 10−40 mol % of Ti(TADDOLate)$_2$. The Ti(TADDOLate)$_2$-mediated catalytic asymmetric reaction was extended to the enantiotopic group selective reaction of bisalkenylated malonates, giving rise to trisubstituted cyclopentanoid compounds with both high diastereoselectivity (86−94% de) and excellent enantioselectivity (≥95% ee). An efficient synthesis of (+)-boschnialactone from the product of the present reaction was also achieved.

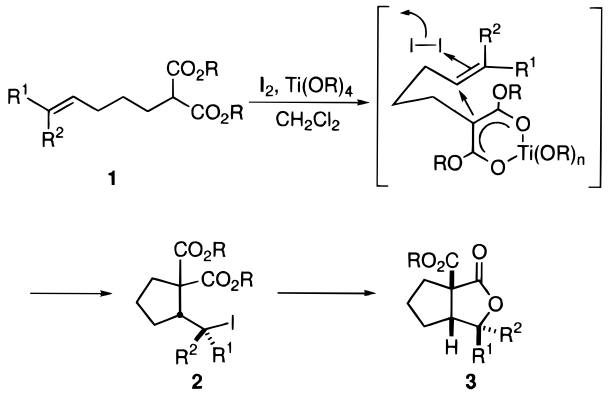
Introduction

The development of catalytic asymmetric reactions is one of the most challenging tasks in modern synthetic organic chemistry. In many reactions using a chiral catalyst, a high level of enantioselectivity has been achieved,[1] but success has not been reported for halocyclization reactions. Since a halocyclization reaction usually proceeds in the presence of an electrophilic halogenating reagent without any activating catalyst,[2] asymmetric catalysis of these reactions should be difficult to achieve.

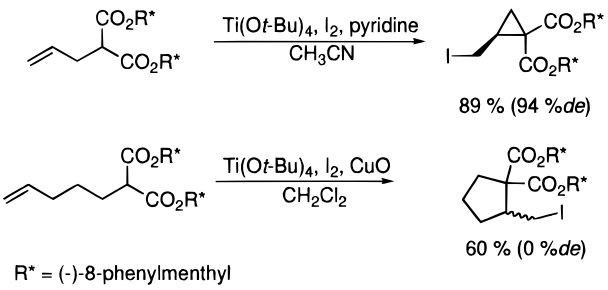
In 1992, we reported a titanium alkoxide-mediated "iodocarbocyclization reaction" of 4-pentenyl- or allylmalonate derivatives, which proceeds in a highly regio- and stereospecific manner to give cyclopentane or cyclopropane derivatives in good yields (Scheme 1).[3,4] In this reaction, the titanium alkoxide acts as a base and enhances the nucleophilicity of the malonate moiety through the formation of titanium enolate.

Furthermore, it was also found that the iodocarbocyclization reaction of allylmalonate using (−)-8-phenylmenthol as a chiral auxiliary proceeds with high diastereoselectivity (94% de, Scheme 2).[5] In contrast to the allylmalonate, the reaction of bis[(−)-8-phenylmenthyl]-4-pentenylmalonate proceeded without any chiral induction to give a 1:1 diastereomeric mixture of the cyclopentane derivative (Scheme 2). These results are possibly explained as follows. In the transition state of cyclopropanation, the olefinic moiety would be located close to the chiral ester, while in the 5-membered ring-forming reaction, it would be situated close to the Ti atom but not to the ester (Figure 1).

Scheme 1



Scheme 2



Therefore, we expected that an efficient enantiofacial selection of the olefinic group could be achieved through the formation of chiral titanium enolate by using a chiral titanium alkoxide. In addition, asymmetric catalysis of this reaction may be also possible because the present reaction does not proceed in the absence of titanium alkoxide.

In this paper, we report the result of catalytic asymmetric iodocarbocyclization which proceeds with excellent enantioselectivity (≥95% ee) in the presence of a catalytic amount of Ti(TADDOLate)$_2$.[6] The present catalytic reaction can be also applied to enantiotopic group selective reactions; in these cases, trisubstituted cyclopentane compounds, which are useful synthetic intermediates of cyclopentanoid natural products, are obtained with excel-

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(4) Examples of NaH-mediated iodocarbocyclization reaction of active methine or methylene compounds: (a) Cossy, J.; Thellend, A. *Tetrahedron Lett.* **1990**, *31*, 1427−1428. (b) Beckwith, A. L.; Zozer, M. J. *Tetrahedron Lett.* **1992**, *33*, 4975−4978.

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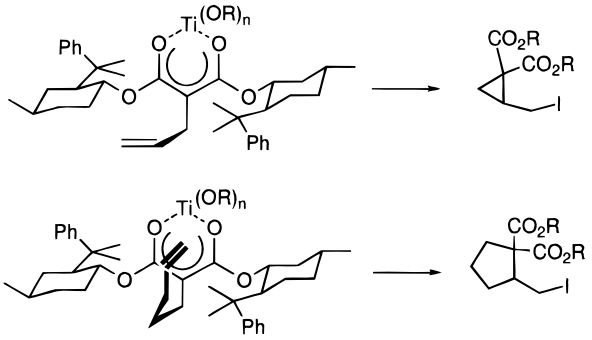
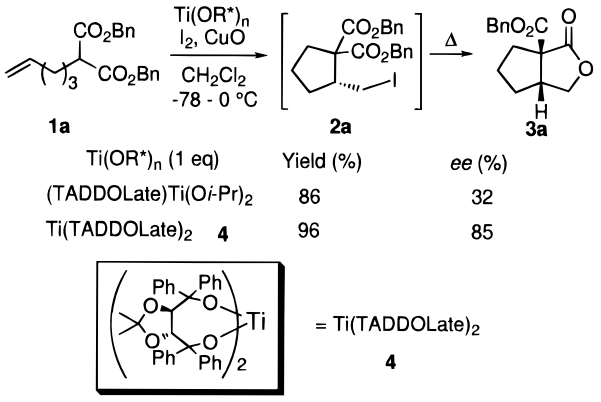


Figure 1. Transition state model in the reaction of allyl- or pentenylmalonate.

Scheme 3



lent enantioselectivity (≥95% ee) and high diastereoselectivity (86−94% de).

Results and Discussion

Catalytic Asymmetric Iodocarbocyclization Reaction. The iodocarbocyclization reaction of dibenzyl 4-pentenylmalonate (**1a**) with various chiral titanium(IV) alkoxides under the conditions [titanium(IV) alkoxide (1 equiv), I_2 (1.2 equiv), CuO (1.2 equiv), CH_2Cl_2] previously reported[3] was conducted to examine the enantioselectivity. In the presence of titanium(IV) alkoxide prepared from Ti(O*i*-Pr)$_4$ and L-(+)-diisopropyl tartrate, binaphthol, or (*R*,*R*)-1,2-diphenylethylene glycol, the reaction itself was retarded to give only a trace amount of the cyclized product **2a** or no chiral induction was observed. On the other hand, the iodocarbocyclization using the 1:1 complex of Ti(IV) and (*R*,*R*)-TADDOL[7] gave the cyclized product **3a** of 32% ee in good yield (86%, Scheme 3). Furthermore, the use of 1:2 complex [Ti(TADDOLate)$_2$] **4**[8] led to an increase in both enantioselectivity and chemical yield to give the product **3a** of 85% ee in 96% yield (Scheme 3). All the chiral titanium(IV) alkoxides used in these reactions were prepared *in situ* by ligand exchange of Ti(O*i*-Pr)$_4$ and chiral diols in toluene followed by complete azeotropic removal of propan-2-ol. In the reaction of **1a** using Ti(TADDOLate)$_2$ (**4**), the removal of propan-2-ol from the reaction mixture is essential to achieve high enantioselectivity; for example, the reaction in the presence of propan-2-ol resulted in a remarkable decrease in enantioselectivity (13% ee).

Table 1. Additive Effect in Catalytic Asymmetric Iodocarbocyclization

entry	additive	**4** (mol %)	yield (%)[b]	ee (%)[c]	config
1[d]	CuO	100	96	85	*R*,*R*
2[d]	CuO	50	85	50	*R*,*R*
3[d]	CuO	25	54	47	*R*,*R*
4	pyridine	30	trace		
5	2,6-lutidine	30	trace		
6	Et_3N	30	70	98	*R*,*R*
7	2,6-dimethoxypyridine	30	97	97	*R*,*R*

[a] Iodocarbocyclization: **1a** (0.5 mmol), **4** (see table), I_2 (2 mmol), additive (1 mmol), CH_2Cl_2 (5 mL), −78 to 0 °C. [b] Isolated yield. [c] The ee was determined by HPLC analysis using a Daicel CHIRALPACK AD column. [d] I_2 (0.6 mmol), CuO (0.6 mmol).

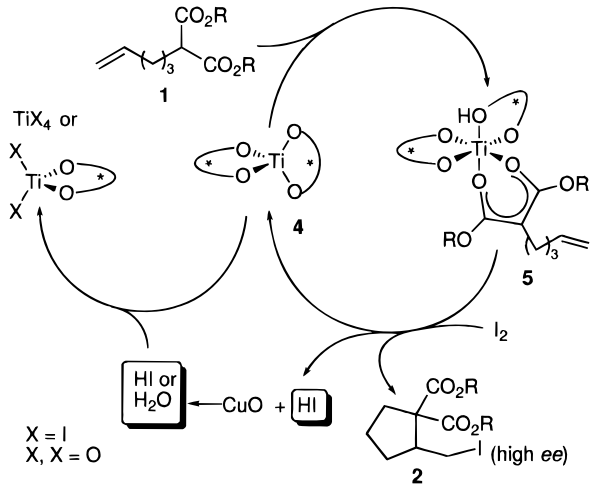


Figure 2. Possible mechanism of enantioselective iodocarbocyclization.

Asymmetric catalysis of the present reaction was further investigated (Table 1). Under conditions similar to our initial studies, the iodocarbocyclization of malonate **1a** using 50 mol % of **4** gave the cyclized product **3a** in good yield (85%) but with lower enantiomeric excess (50% ee) (entry 2). Further reduction to 25 mol % of **4** under the same conditions resulted in lowering of both the enantiomeric excess and the chemical yield (47% ee, 54%, entry 3). These results may be explained by the following proposed mechanism (Figure 2).

Ti(TADDOLate)$_2$ (**4**) promotes the deprotonation of malonate **1** to produce the chiral Ti(IV) enolate **5**. Intramolecular attack of **5** on a double bond activated by I_2 may give a cyclized product **2** in a highly enantioselective manner together with the reproduction of catalyst **4**. In the presence of CuO, however, **4** can be converted by HI or H_2O[9] to generate other Ti(IV) species such as (TADDOLate)TiX_2 or TiX_4[10] (X = I or X_2 = O), which results in the decrease in the enantioselectivity and the chemical yield.

It follows that trapping HI without generation of H_2O would be crucial to achieve the catalytic reaction. Several attempts were made by using various amine bases as the

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(7) (a) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109−1112. (b) Seebach, D.; Beck, A. K.; Imwinkelreid, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954−974. (c) Narasaka, K.; Iwasawa, N. *Organic Synthesis Theory and Applications*; Hudlicky, T., Ed.; JAI Press Inc.: London, 1993; p 93−112. (d) Dahinden, R.; Beck, A.; K. Seebach, D. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1994; Vol. 3, pp 2167−2170.

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(9) $2CuO + 4HI \rightarrow I_2 + 2CuI + 2H_2O$.

(10) In the presence of $TiCl_4$ having no activity as a base, the reaction gave only a complex mixture.

Table 2. Temperature Effect in Catalytic Asymmetric Iodocarbocyclization of 1a[a]

entry	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	−78 to 0	29	86	94
2	−35	15	96	77
3	rt	0.5	72	56
4	−78 (CH_2Cl_2:THF = 4:1)	1.5	87	98
5[d]	−78 (CH_2Cl_2:THF = 4:1)	3	98	98

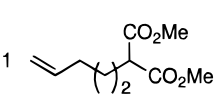
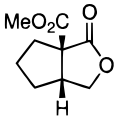
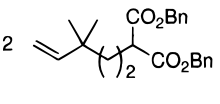
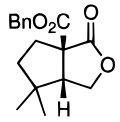
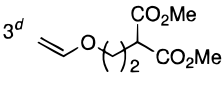
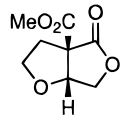
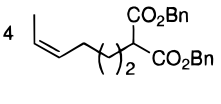
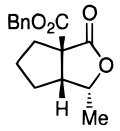
[a] Reaction conditions: **1** (0.5 mmol), **4** (0.1 mmol), I_2 (2 mmol), DMP (1 mmol), CH_2Cl_2 (5 mL), −78 °C and then, after workup, to complete lactonization, the reaction mixture of the iodocarbocyclization was briefly heated at 140 °C. [b] Isolated yield. [c] See footnote *c* of Table 1. [d] 10 mol % of **4** was used.

HI trapping agent. The use of pyridine or 2,6-lutidine was not effective; in these cases, the reaction hardly proceeded with a catalytic amount of Ti(TADDOLate)$_2$ (**4**) (Table 1, entries 4 and 5). In contrast, when 2,6-dimethoxypyridine (DMP) or Et_3N[11] was employed as an HI scavenger, the reaction smoothly proceeded in the presence of 30 mol % of **4** to give the cyclized product **3a** with higher enantiomeric excess than that obtained in the reaction using a stoichiometric amount of **4** and CuO (entries 6 and 7). In particular, the efficiency of DMP as an HI scavenger is noteworthy; that is, the reaction of **1a** with 30 mol % of **4**, DMP (2 equiv) and I_2 (4 equiv) gave the product **3a** in nearly quantitative yield (97%) with excellent enantioselectivity (97% ee).

Effects of reaction temperature and solvent in the catalytic asymmetric iodocarbocyclization of **1a** are summarized in Table 2. With 20 mol % of **4**, the product **3a** was obtained in slightly lower yield and ee (86%, 94% ee, Table 2, entry 1), while the reaction with 10 mol % of **4** resulted in considerable decrease in both yield (73%) and enantioselectivity (74% ee). On decreasing the catalyst **4**, prolonged time and slightly higher temperature were needed for completion of the reaction. Since the enantioselectivity of the present reaction was found to significantly depend on the reaction temperature (77% ee at −35 °C, 56% ee at rt, entries 2, 3), the decrease in enantioselectivity in the reaction using less than 20 mol % of **4** may be due to the requirement of slightly higher reaction temperature. After a survey of the reaction conditions, we found that the use of THF as a cosolvent is beneficial to both the reactivity and enantioselectivity; that is, the reaction with 20 mol % of **4** in CH_2Cl_2−THF (4:1) proceeded in good yield (87%) even at −78 °C to give **3a** of 98% ee (entry 4). Although a slightly longer reaction time was required, the reaction with 10 mol % of **4** also gave **3a** in excellent yield (98%) and ee (98% ee) by the addition of THF (entry 5).

The catalytic asymmetric iodocarbocyclization of various malonates **1b**−**e** was further examined under the improved conditions (Table 3). The ester moiety of pentenylmalonate showed no effect on the ee of the product; that is, similar to dibenzyl ester **1a**, the reaction of dimethyl ester **1b** also gave **3b** with excellent enantiomeric excess (99% ee, entry 1). The reaction of **1c** possessing a dimethyl group at the allylic position also gave the product **3c** with excellent enantioselectivity (98% ee) in CH_2Cl_2−THF. On the other hand, the reaction of **1c** in CH_2Cl_2 required higher temperature

Table 3. Catalytic Asymmetric Iodocarbocyclization of 4-Pentenylmalonate Derivatives[a]

Entry	Substrate **1**	**4** (mol%)	Product **3**	Yield (%)[b]	*ee* (%)[c]
1	 **1b**	20	 **3b**	87	99
2	 **1c**	20	 **3c**	76	98
3[d]	 **1d**	30	 **3d**	60	96
4	 **1e**	40	 **3e**	71	97

[a] Reaction conditions: **1** (0.5 mmol), **4** (see table 3), I_2 (2 mmol), DMP (1 mmol), CH_2Cl_2 (4 mL), THF (1 mL), −78 °C and then, after workup to complete lactonization, the reaction mixture of the iodocarbocyclization was briefly heated at 140 °C. [b] Isolated yield. [c] The ee was determined by HPLC analysis using a CHIRALPACK AD, AS, or OD column. [d] The reaction was performed at −95 °C in CH_2Cl_2.

(−35 °C), which leads to a decrease in enantioselectivity (70% ee).[12] In the case of a reactive vinyl ether derivative **1d**, the reaction proceeded at lower temperature (−95 °C) even in CH_2Cl_2 without the addition of THF to give an optically active tetrahydrofuran derivative **3d** with high enantioselectivity (96% ee, entry 3), while the reaction of **1d** at −78 °C resulted in considerable decrease in enantioselectivity (78% ee). In the reaction of (*Z*)-4-hexenylmalonate derivative **1e**, although 40 mol % of **4** was required to achieve high diastereo- and enantioselectivity, the optically active form of the cyclopentanoid **3e** having three consecutive chiral centers was obtained in a highly stereospecific and enantioselective manner (99% de, 97% ee, entry 4). In the cases of **1a**−**d**, (iodoalkyl)cyclopentane derivatives **2a**−**d** formed by iodocarbocyclization were heated at 140 °C to convert them to stable lactone derivatives **3a**−**d**.[13]

The absolute configurations of **3a** and **3b** were determined on the basis of the optical rotation value after conversion to the known lactone **6a**,[14] while those of **3c**, **3d**, and **3e** were assigned on the basis of comparison of the CD spectra with **3a** (Scheme 4).

The absolute configurations of the cyclized products **3a**−**e** clearly indicate that the reactions of **1a**−**c** proceed in the same enantiofacial selective manner; that is, in all cases with Ti(TADDOLate)$_2$ (**4**) prepared from (*R*,*R*)-TADDOL, the enolate and I_2 attack in a *trans*-addition manner from the *Re* and *Si* faces of the olefin, respectively (Figure 3).

(11) As shown in Table 1, the use of Et_3N gave the product in lower yield (70%) than that of DMP (97%). This result may be due to the decrease in the basicity of amine and the electrophilicity of iodine on the basis of the formation of a strong charge transfer complex between iodine and Et_3N.

(12) In the present reaction, the use of THF as a solvent resulted in the decrease in both enantioselectivity and yield (85% ee, 34%).

(13) In the reaction of **1e**, complete lactonization to **3e** from **2e** was observed even at −78 °C.

(14) Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659−4665.

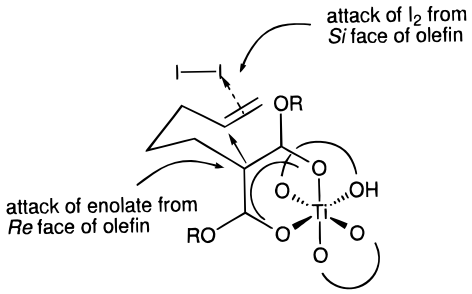
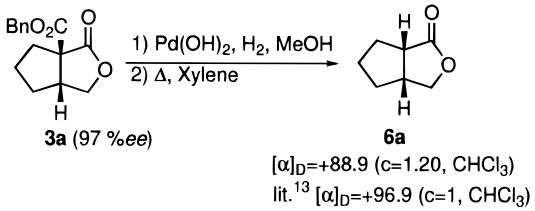


Figure 3. Transition state model in iodocarbocyclization with (*R,R*)-TADDOL ligand.

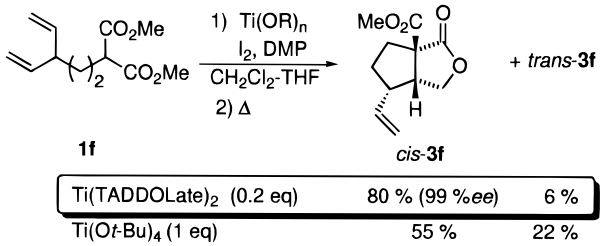
Scheme 4



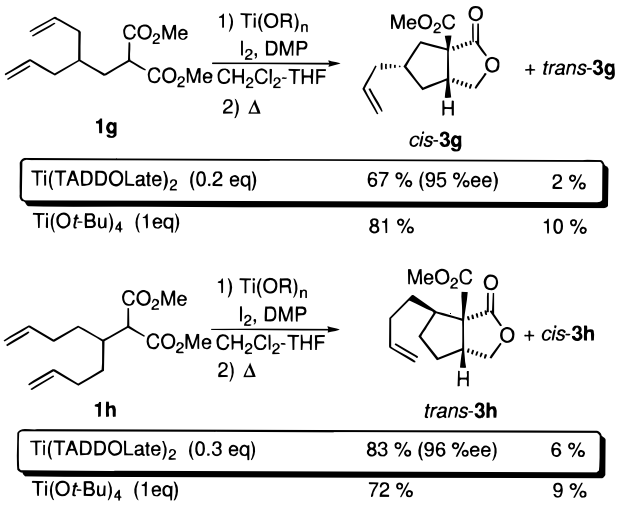
Enantiotopic Group Selective Iodocarbocyclization Using Ti(TADDOLate)$_2$ Catalyst (4). Catalytic asymmetric syntheses of cyclopentane derivatives have attracted much attention in the field of natural product synthesis because of the large number of cyclopentanoid natural products and their interesting biological activity.[15] In the above enantiofacial selective reaction, cyclopentanoid compounds having two chiral centers on the ring were obtained with excellent enantioselectivity (≥95% ee). For the synthesis of cyclopentanoid natural products utilizing the present reaction, however, the construction of more highly substituted cyclopentane skeletons is required. For this purpose, we attempted the application of the present catalytic asymmetric reaction to enantiotopic group selective reaction; that is, the enantiotopic group selective iodocarbocyclization of malonate derivatives with two prochiral olefinic groups should provide the optically active forms of the cyclopentane derivatives having three chiral centers.[16]

As substrates for the enantiotopic group selective reaction, three malonate derivatives, **1f**, **1g**, or **1h**, with enantiotopic vinyl, allyl, or homoallyl groups were chosen. The reaction of bis-vinyl derivative **1f** proceeded with high diastereoselectivity (*cis*/*trans* = 13) and excellent enantioselectivity under the above conditions [**4** (0.2 equiv), DMP (2 equiv), I_2 (4 equiv), CH_2Cl_2:THF (4:1)] to give *cis*-**3f**[17] of 99% ee as the major product (Scheme 5). Similar to **1a**−**c** and **1e**, the use of THF as the cosolvent was essential for achievement of excellent enantioselectivity, since the reaction of **1f** in CH_2Cl_2 required higher temperature to give *cis*-**3f** of lower ee (68% ee). It should be also noted that the use of Ti(TADDOLate)$_2$ (**4**) led to an increase in diastereoselectivity; for example, the reaction in the presence of Ti(O*t*-Bu)$_4$ instead of **4** gave **3f** in a ratio of *cis*/*trans* = 2.5.

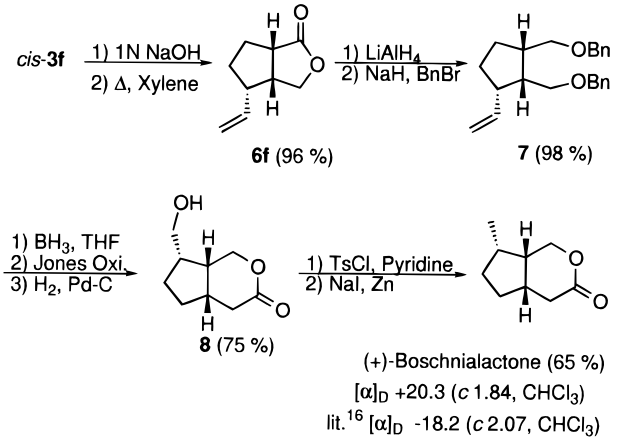
Scheme 5



Scheme 6



Scheme 7



The reaction of bis-allyl derivative **1g** also proceeded with excellent diastereo- and enantioselectivity to give *cis*-**3g**[17] (*cis*/*trans* = 30) of 95% ee as the major product (Scheme 6). Again, the increase of diastereoselectivity by the use of **4** compared to Ti(O*t*-Bu)$_4$ was observed in this reaction.

In contrast, opposite diastereoselectivity was observed in the reaction of bis-homoallyl derivative **1h** to afford *trans*-**3h**[17] (*cis*/*trans* = 1/13) as the major stereoisomer with excellent enantioselectivity (96% ee, Scheme 6). The good yield of **3h** required the use of 30 mol % of **4**, as 20 mol % of **4** provided **3h** in lower yield (44%) and slightly lower enantioselectivity (90% ee).

In order to apply the present approach to natural product synthesis and to aid the determination of the absolute configurations of **3f**−**h**, the synthesis of boschnialactone from **3f** was examined (Scheme 7). (−)-Boschnialactone,[18,19] isolated from *Boschniakia rossica hult*, possesses interesting biological properties such as cat-attracting and insecticidal activities. The cyclized product

(15) Examples of the catalytic asymmetric synthesis of cyclopentanoid compounds: (a) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593−2596. (b) Wu, X. M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 5927−5930. (c) Sato, Y.; Mori, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 757−766. (d) Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108−7116.

(16) (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (b) Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566−6568.

(17) The relative configurations of *cis*-**3f**, *cis*-**3g**, and *trans*-**3h** were determined on the basis of NOE experiments.

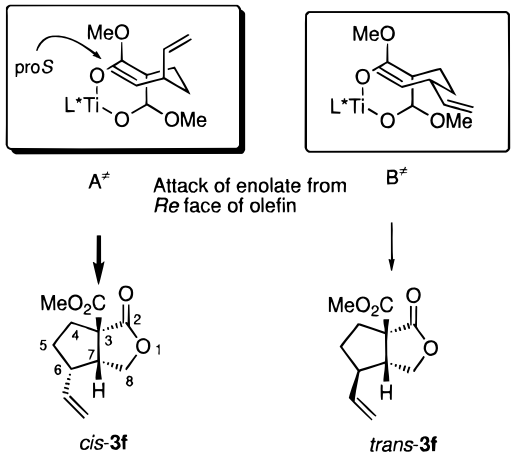


Figure 4. Transition state model in the reaction of **1f**.

cis-**3f** having three consecutive *cis*-substituents on the ring was viewed as a useful synthetic intermediate for boschnialactone.

The $LiAlH_4$ reduction of the lactone **6f** obtained by demethoxycarbonylation of *cis*-**3f**, followed by the benzylation of the hydroxyl groups gave bis-benzyl ether **7** in good yield (96% from *cis*-**3f**). Compound 7 was converted to bicyclic lactone **8** in a yield of 75% through hydroboration, Jones oxidation, and hydrogenolysis of benzyl ether. Tosylation of the hydroxyl group of **8** and subsequent treatment with Zn−NaI led to boschnialactone in 46% overall yield from *cis*-**3f**. Boschnialactone derived from *cis*-**3f** was confirmed to be the antipode of the natural form on the basis of the comparison of $[\alpha]_D$ value with that reported in the literature[18] {$[\alpha]_D$ +20.3 (*c* 1.84, $CHCl_3$), lit.[18] $[\alpha]_D$ −18.2 (*c* 2.07, $CHCl_3$)}. Thus, the stereochemistry of *cis*-**3f** which was obtained by the use of Ti(TADDOLate)$_2$ (**4**) from (*R*,*R*)-TADDOL was determined as 3*S*,6*S*,7*R*. The absolute configurations of *cis*-**3g** and *trans*-**3h** were assigned on the basis of comparison of the CD spectra with that of **3a**.

As mentioned in the enantiofacial selective reaction, the chiral titanium enolate from (*R*,*R*)-**4** preferentially attacks from the *Re* face of the olefinic group. The enantiotopic group selectivity in the reaction of **1f**−**h** would possibly be explained by considering this preferential *Re* face attack of the chiral titanium enolate. In the reaction of bis-vinyl derivative **1f**, the chair-like transition state models A≠ and B≠,[20] which give the two diastereoisomers of product **3f**, are shown in Figure 4. B≠, with an equatorial vinyl group, is disfavored relative to A≠ with an axial one due to destabilization of B≠ by overlap between the π-orbital of the double bond activated by I_2 and the lower lying σ^*-orbital of the C-vinyl bond in comparison with that of the C−H bond.[3c,d] Thus, the reaction of **1f** preferentially proceeds through transition state A≠ with an axial vinyl group leading to attack of the enolate on the *Re* face of the pro-*S* vinyl group to give **3f** having the (3*S*,6*S*,7*R*)-configuration as the major stereoisomer.

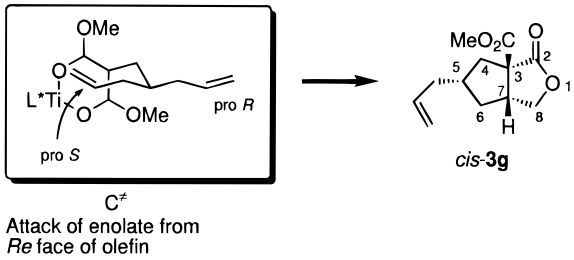


Figure 5. Transition state model in the reaction of **1g**.

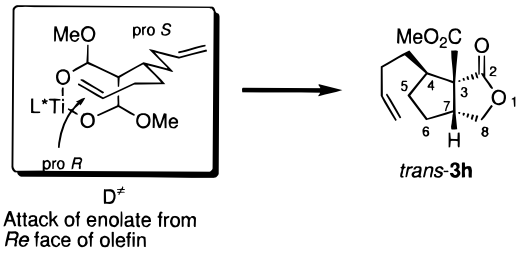


Figure 6. Transition state model in the reaction of **1h**.

Contrary to the case of **1f**, in the reactions of **1g** and **1h**, the transition states with equatorial allyl and homoallyl groups are more favorable than those with axial ones due to minimization of 1,3-diaxial repulsion (Figures 5 and 6). Thus, the reactions of **1g** and **1h** may give *cis*-**3g** and *trans*-**3h** as major diastereomers, respectively. In addition, the preferential *Re* face attack of the enolate on the olefin directs attack to the pro-*S* allyl group in **1g** and to the pro-*R* homoallyl group in **1h**. Thus, the reactions of **1h** and **1g** give **3g** having the (3*S*,5*S*,7*R*)-configuration and **3h** having the (3*S*,4*R*,7*R*)-configuration through transition states C≠ (Figure 5) and D≠ (Figure 6), respectively.

In conclusion, we have succeeded in the development of a catalytic asymmetric iodocarbocyclization reaction which proceeds with excellent enantioselectivity (≥95% ee) using a Ti(TADDOLate)$_2$ catalyst. In the application to enantiotopic group selective reaction, trisubstituted cyclopentanoid compounds were obtained with high diastereoselectivity and excellent enantioselectivity. As shown in the synthesis of boschnialactone, the present reaction should be widely applicable to the catalytic asymmetric synthesis of cyclopentanoid natural products.

Experimental Section

General. Melting points were determined on a micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on 400 or 300 MHz spectrometer. In ^{1}H- and ^{13}C-NMR, chemical shifts were expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm) as an internal standard, respectively. Medium-pressure liquid chromatography (MPLC) was performed on a 30 cm × 4 cm i.d. prepacked column (silica gel, 50 μm). Mass spectra were recorded by electron impact.

General Procedure for Catalytic Asymmetric Iodocarbocyclization. Under an argon atmosphere, to a toluene solution (3 mL) of (*R*,*R*)-TADDOL (93 mg, 0.2 mmol) was added 0.61 M toluene solution of Ti(O*i*-Pr)$_4$ (0.16 mL, 0.1 mmol) at room temperature. After the mixture was stirred for 30 min at this temperature, toluene and 2-propanol were removed under reduced pressure. To this solid residue was added CH_2Cl_2:THF solution (4 mL:1 mL) of malonate **1a** (176 mg, 0.5 mmol) and 2,6-dimethoxypyridine (0.13 mL, 1.0 mmol), and then the mixture was cooled to −78 °C. After stirring for 30 min at this temperature, I_2 (508 mg, 2.0 mmol) was added to the mixture and the mixture was then stirred for 1.5 h at −78 °C. The mixture was poured into 10% HCl (10 mL) and

(18) Sakan, T.; Murai, Y.; Hayashi, Y.; Honda, Y.; Shono, T.; Nakajima, M.; Kato, M. *Tetrahedron* **1967**, *23*, 4635−4652.

(19) Examples of asymmetric synthesis of boschnialactone; (a) Arai, Y.; Kawanami, S.; Koizumi, T. *Chem. Lett.* **1990**, 1585−1586. (b) Arai, Y.; Kawanami, S.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2969−2975. (c) Tanaka, D.; Yoshino, T.; Kouno, I.; Miyashita, M.; Irie, H. *Tetrahedron* **1993**, *49*, 10253−10262. (d) Nangia, A.; Prasuna, G.; Bheema Rao, P. *Tetrahedron Lett.* **1994**, *35*, 3755−3758.

(20) (a) Labelle, M.; Morton, H. E.; Guindon, Y.; Springler, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533−4540. (b) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *11*, 2204−2210.

extracted with Et_2O. The ether extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over anhydrous $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane:Et_2O = 19:1) gave a mixture of 1,1-bis[(benzyloxy)carbonyl]-2-(iodomethyl)cyclopentane and 2,6-dimethoxypyridine. The mixture was heated for 10 min at 140 °C and then purified by column chromatography (hexane:AcOEt = 6:1) to give lactone **3a** (113 mg, 87%, 98% ee). The *ee* was determined by HPLC analysis using a Daicel CHIRALPAK AD column [25 cm × 0.46 cm i.d.; solvent, hexane:*i*-PrOH = 99:1 v/v; flow rate, 1.0 mL/min; t_R = 35.4 min (minor), t_R = 39.7 min (major)].

(3a*R*,6a*R*)-Tetrahydro-3-oxo-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylic Acid Phenylmethyl Ester (3a). **3a**: colorless oil; $[\alpha]^{28}_D$ +68.2 (*c* 1.11, $CHCl_3$); IR (neat) 2966, 2863, 1773, 1741 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.28−7.42 (5H, m), 5.24 (1H, d, *J* = 12.4 Hz), 5.16 (1H, d, *J* = 12.4 Hz), 4.52 (1H, dd, *J* = 7.5, 9.2 Hz), 4.06 (1H, dd, *J* = 2.4, 9.2 Hz), 3.06 (1H, m), 2.40 (1H, ddd, *J* = 7.0, 9.0, 13.4 Hz), 2.29 (1H, m), 2.05 (1H, m), 1.82 (1H, m), 1.56−1.71 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 176.2, 169.6, 135.1, 128.6, 128.3, 127.8, 72.9, 67.4, 61.6, 45.6, 34.8, 34.0, 25.8; MS *m*/*z* 260 (M^+), 232, 184. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.31; H, 6.21.

(3a*S*,6a*R*)-Tetrahydro-4-oxo-furo[3,4-*b*]furan-3a(4*H*)-carboxylic Acid Methyl Ester (3d). According to the general procedure, Ti(TADDOLate)$_2$ was prepared from Ti(O*i*-Pr)$_4$ (0.15 mmol) and (*R*,*R*)-TADDOL (140 mg, 0.3 mmol). To the solid residue of Ti(TADDOLate)$_2$ was added a CH_2Cl_2 solution (5 mL) of malonate **1d**[21] (101 mg, 0.5 mmol) and 2,6-dimethoxypyridine (0.13 mL, 1.0 mmol), and then the mixture was cooled to −95 °C. After stirring for 30 min at this temperature, I_2 (508 mg, 2 mmol) was added to the mixture and then the mixture was stirred for 3 h at −95 °C. The mixture was poured into 10% HCl (10 mL) and extracted with Et_2O. The ether extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over anhydrous $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane:Et_2O = 19:1) gave 3,3-bis(methoxycarbonyl)-2-(iodomethyl)tetrahydrofuran. This compound was heated for 6 h at 140 °C and then purified by column chromatography (hexane:AcOEt = 6:1) to give lactone **3d** (56 mg, 60%, 96% ee). The ee was determined by HPLC analysis using a Daicel CHIRALPAK AS column [25 × 0.46 cm i.d.; solvent, hexane:*i*-PrOH = 95:5 v/v; flow rate, 1.0 mL/min; t_R = 15.6 min (major), t_R = 20.1 min (minor)]. **3d**: colorless oil; $[\alpha]^{24}_D$ + 87.8 (*c* 0.51, $CHCl_3$); IR (neat) 2961, 2878, 1780, 1747 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.71 (1H, d, *J* = 4.3 Hz), 4.53 (1H, dd, *J* = 4.3, 10.7 Hz), 4.41 (1H, d, *J* = 10.7 Hz), 3.91−4.05 (2H, m), 3.81 (3H, s), 2.75 (1H, td, *J* = 7.7, 13.0 Hz), 2.50 (1H, ddd, *J* = 6.2, 6.6, 12.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 175.0, 168.1, 83.4, 73.5, 69.6, 62.5, 54.1, 34.7; MS *m*/*z* 187 (M^+ + H), 156 (M^+ − OMe), 143. Anal. Calcd for $C_8H_{10}O_5$: C, 51.61; H, 5.41. Found: C, 51.78; H, 5.45.

(3a*S*,6a*R*)-Tetrahydro-1*H*-cyclopenta[c]furan-3-one (6a). A solution of **3a** (130 mg, 0.5 mmol) in 1 N NaOH (10 mL) was stirred for 12 h at room temperature. The mixture was poured into 10% HCl and extracted with AcOEt. The AcOEt extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in xylene (15 mL) and refluxed for 12 h. After evaporation of xylene, purification of the residue by column chromatography (hexane:AcOEt = 5) gave **6a** (60 mg, 95%). **6a**: colorless oil; $[\alpha]^{28}_D$ +88.9 (*c* 1.20, $CHCl_3$); ^{1}H and ^{13}C-NMR data of **6a** coincided with those reported in the literature.[14]

(3a*S*,6*S*,6a*R*)-Hexahydro-6-vinyl-1*H*-cyclopenta[*c*]furan-3-one (6f). A solution of *cis*-**3f** (191 mg, 0.9 mmol) in 1 N NaOH (10 mL) was stirred for 12 h at room temperature. The mixture was poured into 10% HCl and extracted with AcOEt. The AcOEt extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in xylene (15 mL) and refluxed for 12 h. After evaporation of xylene, purification of the residue by column chromatography (hexane:AcOEt = 5:1) gave **6f** (132 mg, 96%). **6f**: colorless oil; $[\alpha]^{28}_D$ +110.9 (*c* 0.98, $CHCl_3$); IR (neat) 2959, 2878, 1768 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.80 (1H, ddd, *J* = 6.4, 10.6, 17.1 Hz), 5.15 (1H, td, *J* = 1.5, 10.6 Hz), 5.12 (1H, td, *J* = 1.6, 17.1 Hz), 4.26 (1H, dd, *J* = 8.5, 9.9 Hz), 4.13 (1H, dd, *J* = 4.4, 9.9 Hz), 3.01−3.12 (2H, m), 2.75 (1H, m), 2.16 (1H, dd, *J* = 7.0, 13.0 Hz), 1.80−2.04 (2H, m), 1.46 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 181.0, 136.3, 117.0, 68.6, 47.5, 44.2, 41.9, 30.2, 29.3; MS *m*/*z* 153 (M^+ + H$^+$), 124 (M^+ − CO). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.71; H, 7.79.

(1*S*,2*R*,3*S*)-1,2-Bis[(phenylmethoxy)methyl]-3-vinyl-cyclopentane (7). To a solution of $LiAlH_4$ (98 mg, 2.57 mmol) in Et_2O (5 mL) at 0 °C was added a solution of **6f** (391 mg, 2.6 mmol) in Et_2O (5 mL). After being stirred for 30 min at this temperature, 1 N NaOH (5 mL) was added to the mixture and then the mixture was dried over $MgSO_4$. Insoluble materials were removed by filtration with a Celite pad, and the filtrate was evaporated under reduced pressure. To a suspension of NaH (320 mg, 7.8 mmol) in 1,4-dioxane (3 mL) was added a solution of the residue in 1,4-dioxane (3 mL) at 0 °C. After being stirred for 30 min, BnBr (0.8 mL, 17.8 mmol) was added and then the reaction mixture was refluxed for 1 h. The mixture was poured into 10% HCl and extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated to dryness. Purification of the residue by column chromatography (hexane:AcOEt = 30:1) gave **7** (853 mg, 98%). **7**: colorless oil; $[\alpha]^{28}_D$ +22.5 (*c* 1.03, $CHCl_3$); IR (neat) 3030, 2862 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.21−7.40 (10H, m), 5.86 (1H, ddd, *J* = 8.2, 10.2, 17.2 Hz), 4.92−5.06 (2H, m), 4.45 (2H, s), 4.38 (2H, s), 3.56 (1H, dd, *J* = 7.2, 9.1 Hz), 3.39−3.46 (3H, m), 2.72 (1H, quint, *J* = 7.7 Hz), 2.44 (1H, td, *J* = 7.4, 15.2 Hz), 2.30 (1H, ddd, *J* = 5.3, 7.1, 12.4 Hz), 1.50−1.91 (4H, m); ^{13}C-NMR ($CDCl_3$) δ 140.4, 138.7, 128.3, 128.2, 127.7, 127.5, 127.4, 127.3, 114.3, 73.1, 73.0, 71.9, 68.4, 46.9, 45.3, 42.2, 29.5, 27.8; MS *m*/*z* 337 (M^+ + H$^+$), 245 (M^+ − Bn). Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.09; H, 8.30.

Hydroxyboschnialactone (8). To a solution of **7** (168 mg, 0.5 mmol) in THF (1 mL) at 0 °C was added BH_3·THF (0.5 M THF solution, 2 mL, 1 mmol) under an argon atmosphere. After being stirred for overnight at this temperature, Jones reagent (5 mL) was added and then the reaction mixture was stirred for 1 h. The mixture was poured into 10% HCl and extracted with AcOEt. The AcOEt extracts were dried over $MgSO_4$ and evaporated to dryness. MeOH (1 mL) and 10% Pd−C was added to the residue and then the reaction mixture was stirred under a H_2 atmosphere for 2 h. Pd−C was removed by filtration and the filtrate was evaporated under reduced pressure. A solution of the residue in Et_2O (10 mL) was stirred with $MgSO_4$ for 12 h. After removal of $MgSO_4$ by filtration and evaporation of Et_2O, purification of the residue by column chromatography (hexane:AcOEt = 1:1) gave **8** (64 mg, 75%). **8**: white solid; mp 34 °C; $[\alpha]^{28}_D$ −13.3 (*c* 1.10, $CHCl_3$); IR (neat) 3424, 2942, 2873, 1741 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.33 (1H, dd, *J* = 5.2, 11.6 Hz), 4.26 (1H, *J* = 7.6, 11.6 Hz), 3.64−3.80 (2H, m), 2.56−2.71 (3H, m), 2.23−2.38 (2H, m), 1.94 (1H, m), 1.72 (1H, dtd, *J* = 2.5, 6.5, 12.1 Hz), 1.35−1.61 (3H, m); ^{13}C-NMR ($CDCl_3$) δ 173.6, 67.2, 62.8, 45.5, 38.1, 35.0, 34.7, 32.8, 27.9; MS *m*/*z* 170 (M^+). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.52; H, 8.47.

(+)-Boschnialactone. According to the procedure in the literature,[19b] (+)-boschnialactone was prepared from **8** (48 mg, 0.3 mmol). Purification by column chromatography (hexane:AcOEt = 2:1) gave boschnialactone (30 mg, 65%). (+)-Boschnialactone: $[\alpha]^{28}_D$ +20.3 (*c* 1.84, $CHCl_3$). [lit.[18] $[\alpha]^{28}_D$ −18.2 (*c* 2.07, $CHCl_3$).] ^{1}H and ^{13}C-NMR data of boschnialactone coincided with those reported in the literature.[18]

Supporting Information Available: Characterization data and experimental procedures of **3b**, **3c**, **3e**, *cis*-**3f**, *trans*-**3f**, *cis*-**3g**, and *trans*-**3h** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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