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Asymmetric Cyclization of ω-Formyl-1,3-dienes Catalyzed by a Zerovalent Nickel Complex in the Presence of Silanes

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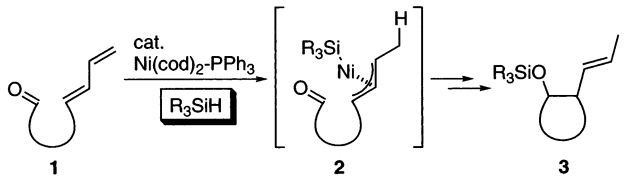
A nickel(0)-catalyzed asymmetric cyclization of ω-formyl-1,3-diene in the presence of silanes in which five- or six-membered carbocycles or pyrrolidine derivatives were afforded up to 86% ee by the use of (2*R*,5*R*)-2,5-dimethyl-1-phenylphospholane as a monodentate chiral ligand was investigated. The reaction course of this asymmetric cyclization can be explained for by two possible mechanisms: one in which the cyclization proceeds via a π-allylnickel intermediate to produce a cyclized product having an internal olefin in the side chain, and one in which the cyclization proceeds via a σ bond metathesis of silane and the nickel−oxygen bond of oxanickelacycle to produce a cyclized compound having a terminal olefin and/or an internal olefin in the side chain. It was speculated that both of these mechanisms operate in this asymmetric cyclization depending upon the nature of silanes and the reaction conditions.

Introduction

The development of methods for synthesizing cyclic compounds (i.e., carbocycles or heterocycles) as optically active forms is very important in modern synthetic organic chemistry since there are many biologically active compounds that have complicated cyclic structures. Transition metal-catalyzed cyclization of prochiral substrates by using chiral ligands is one of the most useful and promising strategies for the construction of chiral carbon centers, which are attached to the ring or contained in the ring framework, in cyclic compounds.[1,2] On the other hand, we have recently reported a nickel-catalyzed cyclization of 1,3-dienes and tethered carbonyl groups for producing five- to seven-membered ring carbocycles,[3a−c] heterocycles,[3e] and bicyclic heterocycles (pyrrolizidine and indolizidine)[3d,e] in a stereoselective manner (Scheme 1). The utility of this cyclization

SCHEME 1



prompted us to expand it to an asymmetric cyclization. We describe herein our results of nickel(0)-catalyzed asymmetric cyclization of ω-formyl-1,3-diene in the presence of silanes.[4]

Results and Discussion

Construction of Five-Membered Carbocycles via Ni(0)-Catalyzed Asymmetric Cyclization of ω-Formyl-1,3-dienes. To examine the feasibility of expanding this cyclization to an asymmetric cyclization, we attempted to cyclize a prochiral substrate **6** using various ligands in the presence of Et_3SiH. The substrate **6** was easily synthesized from malonate **4**[5] and 5-bromo-1,3-pentadiene[6] as shown in Scheme 2. First, treatment of **6** with $Ni(cod)_2$ (20 mol %) and PPh_3 (40 mol %) in the presence

(1) For reviews, see: (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635 and references therein. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49 and references therein. (c) Trost, B. M. *Science* **1991**, *254*, 1471 and references therein. (d) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259 and references therein. (e) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1 and references therein. (f) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (g) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(2) For recent key examples, see: (a) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662. (b) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. (c) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371 and references therein. (d) Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1997**, 425. (e) Murakami, M.; Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 2950. (f) Yamaura, Y.; Hyakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615. (g) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720. (h) Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. (i) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (j) Mandel, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457. (k) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225. (l) For asymmetric cyclopropanations, see **1f** and **1g**.

(3) (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 887. (c) Sato, Y.; Takimoto, M.; Mori, M. *Synlett* **1997**, 734. (d) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron Lett.* **1997**, *38*, 3931. (e) Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153. (f) Sato, Y.; Takanashi, T.; Hoshiba, M.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 5579. (g) Sato, Y.; Takanashi, T.; Mori, M. *Organometallics* **1999**, *18*, 4891. (h) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 1624. (i) Sato, Y.; Takimoto, M.; Mori, M. *Chem. Pharm. Bull.* **2000**, *48*, 1753−1760. (j) Sato, Y.; Takimoto, M.; Mori, M. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 576.

(4) Portions of this work have previously been communicated: Sato, Y.; Saito, N.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 2371.

(5) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.

(6) Mori, K. *Tetrahedron* **1974**, *30*, 3087.

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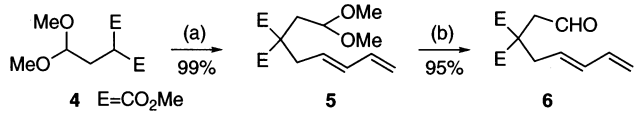
SCHEME 2[a]



[a] Reagents and conditions: (a) 5-bromo-1,3-pentadiene, NaH, THF, rt; (b) $FeCl_3.SiO_2$, acetone.

SCHEME 3

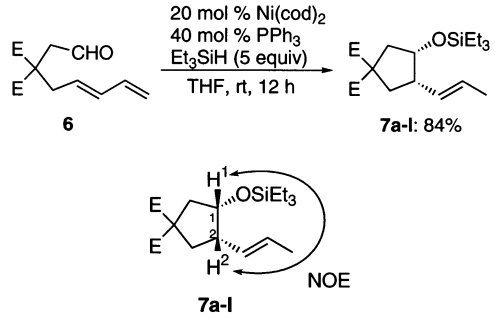
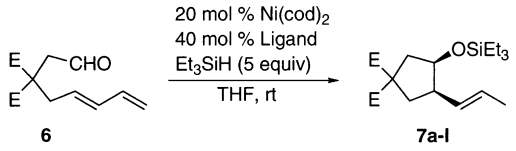


FIGURE 1.

of Et_3SiH (5 equiv) in degassed THF at room temperature for 12 h afforded the cyclized product **7a-I** in 84% yield as a sole product (Scheme 3). To determine the stereochemistry of **7a-I**, a NOESY experiment was carried out, and a cross-peak on NOE between H^1 and H^2 was observed as shown in Figure 1. On the basis of this result, the stereochemistry of two substituents at C1 and C2 on the cyclopentane ring in **7a-I** was determined to be a syn orientation. Next, we tried asymmetric cyclization of **6** with $Ni(cod)_2$ (20 mol %) and various chiral ligands[7] (20 mol % (bidentate ligand) or 40 mol % (monodentate ligand)) in the presence of Et_3SiH (5 equiv) in THF (Table 1). Unfortunately, the use of various chiral ligands gave only a low conversion and an enantiomeric excess of **7a-I**, which was determined by HPLC analysis of **9-I** (DAICEL CHIRALPAK AD, hexane/2-propanol 9/1) after conversion of **7a-I** into **9-I** as shown in Scheme 4. In these asymmetric cyclizations, (1*R*,2*R*)-**7a-I** was produced as the major enantiomer, and the details for determination of the absolute configuration of the cyclized product will be described in the following part.

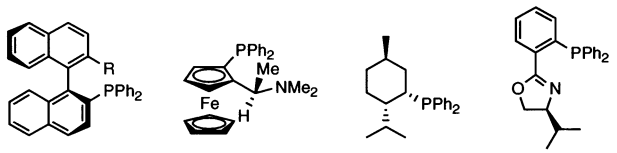
During the course of our investigation of asymmetric cyclization using various chiral ligands, we were surprised to find that the reaction of **6** using chiral phosphorane **10**[7f] (20 mol %) as a ligand smoothly proceeded at room temperature to afford cyclized products **7a-I** and an isomer **7a-T**, having a terminal olefin in the side chain, in 84% yield as an inseparable mixture (ratio of 4.3:1) (Scheme 5). An inseparable mixture of **7a-I** and **7a-T** was treated with HF and then subjected to hydrogenation to give the corresponding cyclopentanol derivative **11** as a sole product, whose spectral data were completely identical with those derived from a racemic **7a-I** obtained from the previous reaction using PPh_3 as

TABLE 1. Cyclization of 6 Using Various Ligands

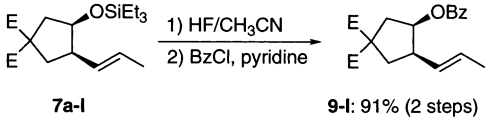


run	ligand	time (h)	yield (%)	ee (%)	SM recovery (%)
1	(*S*)-BINAP	62	2	0	40
2	(*R*)-H-MOP	40	2	16[a]	50
3	(*S*)-(*R*)-PPFA	76	3	10[a]	43
4	NMDPP	27	2	ND[b]	38
5	**8**	50	13	3[a]	32

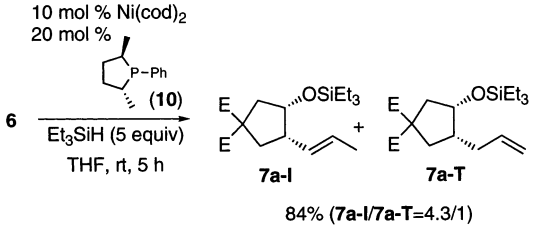
[a] In these cyclizations, (1*R*,2*R*)-**7a-I** was formed as a major enantiomer. [b] ND: not determined.



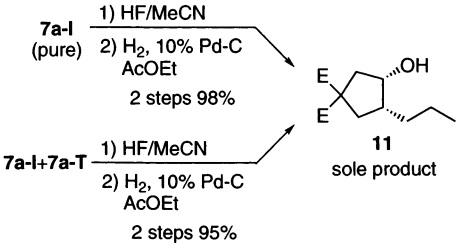
SCHEME 4



SCHEME 5



SCHEME 6



a ligand (Scheme 6). These results revealed that the two substituents at C1 and C2 positions on the cyclopentane ring in **7a-T** were also controlled to be a syn orientation. The determination of the enantiomeric excesses of **7a-I** and **7a-T** was difficult due to the inseparability of these products. However, this difficulty could be overcome by chemoselective Wacker oxidation as follows (Scheme 7): Treatment of a mixture of **9-I** and **9-T**, which was derived from a mixture of **7a-I** and **7a-T** by the same procedure as that shown in Scheme 4, with a catalytic amount of $PdCl_2$ and CuCl under an oxygen atmosphere in dioxane-H_2O gave methyl ketone **12** in 21% yield along with the recovery of **9-I** in 79% yield. This result indicates that

(7) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293. (c) Hayashi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, 4405. (d) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (e) Morrison, J. D.; Masler, W. F. *J. Org. Chem.* **1974**, *39*, 270. (f) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653.

SCHEME 7

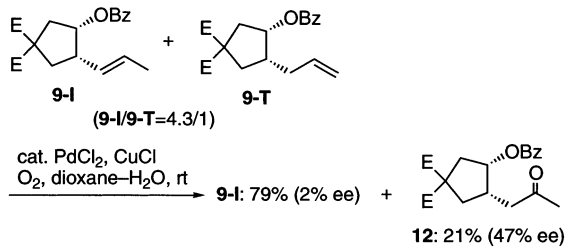
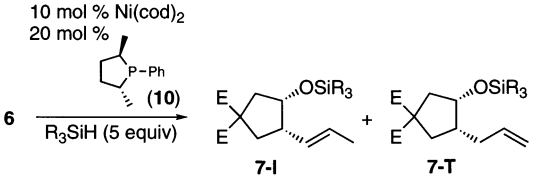


TABLE 2. Cyclization of 6 Using Ni(cod)$_2$ and 10 in the Presence of Various Silanes



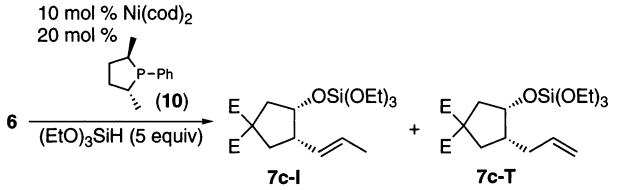
run	R_3SiH	time (h)	yield (%) (**7-I** + **7-T**)	ratio[a] (**7-I**/**7-T**)	ee (%)[b] (**7-I**/**7-T**)
1[c]	Et_3SiH (**a**)	5	84	4.3/1	2/47
2[c]	$^tBuMe_2SiH$ (**b**)	8	83	>50/1	16/–
3[d]	$(EtO)_3SiH$ (**c**)	5	60	12/1	46/33
4[d]	Ph_3SiH (**d**)	2	80	1.7/1	47/53
5[d]	Ph_2MeSiH (**e**)	2	83	1.2/1	27/78
6[d]	$PhMe_2SiH$ (**f**)	7	82	1.9/1	21/72

[a] The ratio was determined by ^1H NMR. [b] The enantiomeric excess was determined after conversion of the cyclized products **7b**–**f** into **9-I** and **12** in a similar manner to that shown in Scheme 4 and Scheme 7, respectively. [c] The reaction was carried out in THF at rt. [d] The reaction was carried out in THF at 0 °C.

only **9-T** in the inseparable mixture was converted into **12**, while **9-I** was intact under the Wacker oxidation conditions. The compounds **9-I** and **12** could be easily separated by silica gel column chromatography, and the enantiomeric excesses of **9-I** and **12** were determined by HPLC analysis with a chiral stationary phase column to be 2% ee (DAICEL CHIRALPAK AD, hexane/2-propanol 9/1) and 47% ee (DAICEL CHIRALPAK AD, hexane/2-propanol 9/1), respectively.

Encouraged by the fact that cyclopentanol derivatives were obtained as optically active forms in the reaction of **6** using a chiral phosphorane **10** as a ligand, the effects of silane on the ratio and enantiomeric excess of the cyclized products were carefully examined, and the results are summarized in Table 2. The cyclization of **6** using $^tBuMe_2SiH$ exclusively produced **7b-I** in 83% yield, and the ee increased to 16% (run 2). The use of $(EtO)_3SiH$ improved the enantiomeric excess of **7c-I**, having an internal olefin in the side chain, up to 46% ee, while the ratio of **7c-I** to **7c-T** was still relatively high (run 3). It was interesting that the reaction using Ph_2MeSiH afforded **7e-T**, having a terminal olefin in the side chain, with good enantioselectivity (78% ee), although the ratio of **7e-I** to **7e-T** was low (run 5). On the basis of these results, we focused on the solvent effects in the reaction using $(EtO)_3SiH$ and Ph_2MeSiH. In the reaction using $(EtO)_3SiH$, it was found that the use of a polar solvent (e.g., DMF, CH_3CN) gave a high ratio and enantioselectivity of **7c-I** to **7c-T** (Table 3). The reactions of **6** in DMF (run 4) and CH_3CN (run 5) at −30 °C exclusively afforded **7c-I** in 73% ee (60% yield) and 73% ee (83% yield), respectively.

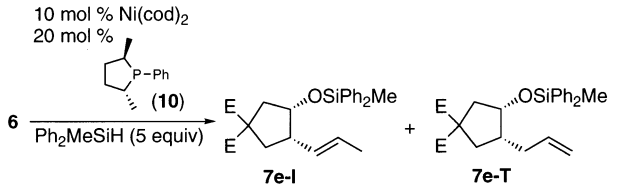
TABLE 3. Cyclization of 6 Using Ni(cod)$_2$ and 10 in the Presence of $(EtO)_3SiH$ under Various Conditions



run	solvent	temp (°C)	time (h)	yield (%) (**7c-I** + **7c-T**)	ratio[a] **I/T**	ee (%) (**7c-I**/**7c-T**)
1	toluene	0	7	69	5.7/1	35/24
2	DMF	0	3	74	12/1	58/41
3	CH_3CN	0	2	79	>50/1	61/–
4	DMF	−30	7	60	>50/1	73/–
5	CH_3CN	−30	8	83	>50/1	73/–

[a] The ratio was determined by ^1H NMR.

TABLE 4. Cyclization of 6 Using Ni(cod)$_2$ and 10 in the Presence of Ph_2MeSiH under Various Conditions



run	solvent	temp (°C)	time (h)	yield (%) (**7e-I** + **7e-T**)	ratio[a] **I/T**	ee (%) (**7e-I**/**7e-T**)
1	toluene	0	3	88	1.7/1	17/77
2	DMF	0	3	87	1.1/1	39/81
3	DMF	−20	28	73	1/1.2	44/86
4	CH_3CN	−20	24	83	1/1	40/85

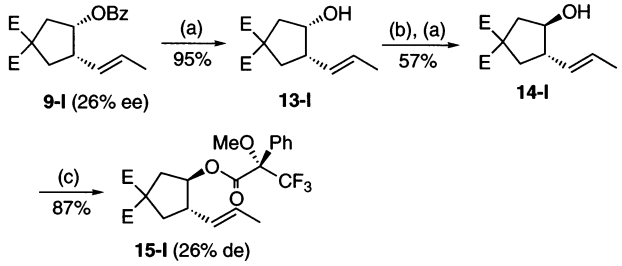
[a] The ratio was determined by ^1H NMR.

The same tendency was observed in the cyclization of **6** using Ph_2MeSiH as a silane, and the use of a polar solvent (e.g., DMF, CH_3CN) increased the formation of **7e-T** and improved the enantiomeric excesses of cyclized products (Table 4). Namely, in the reaction in DMF at 0 °C, the ratio of **7e-T** to **7e-I** was 1.1/1 and the enantiomeric excess of **7e-T** increased to 81%. The reaction of **6** in DMF at a lower temperature (−20 °C) gave **7e-T** in slight preference to **7e-I**, and the enantiomeric excess of **7e-T** reached up to 86%. The use of CH_3CN showed the same tendency, and the reaction of **6** in CH_3CN at −20 °C produced **7e-I** and **7e-T** in 40% ee and 85% ee at a ratio of 1 to 1, respectively.

The absolute configuration of **7-I** was determined by using the improved Mosher's method (Scheme 8 and Figure 2).[8] That is, after conversion of **7-I** into **9-I** via the above-mentioned Wacker oxidation, hydrolysis of **9-I** (26% ee) with K_2CO_3 in MeOH followed by treatment with CH_2N_2 gave alcohol **13-I**. Attempts to convert **13-I** into the corresponding MTPA ester were not successful due to the steric repulsion between the hydroxyl group and the neighboring *syn*-1′-propenyl group. Thus, **13-I** was transformed into *anti*-alcohol **14-I** using the Mitsunobu reaction, and this was successfully converted into

(8) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (b) Kusumi, T. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 462.

SCHEME 8[a]



[a] Reagents: (a) K_2CO_3, MeOH, then CH_2N_2, Et_2O; (b) DEAD, PPh_3, $PhCO_2H$, THF; (c) (*S*)-MTPA, DCC, DMAP, CH_2Cl_2.

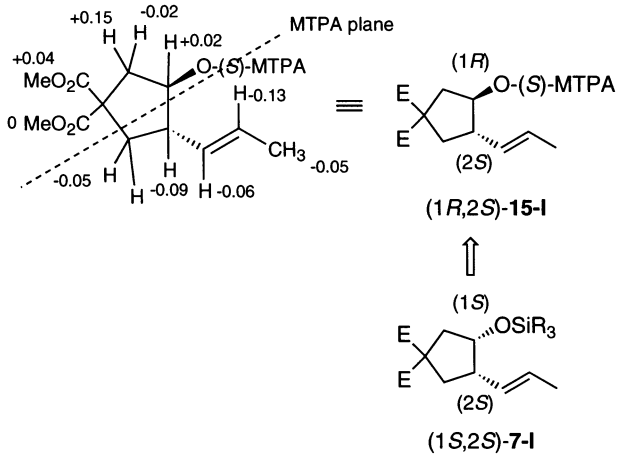
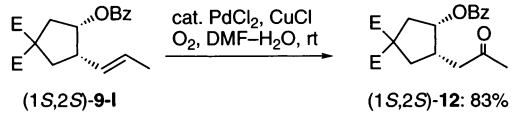


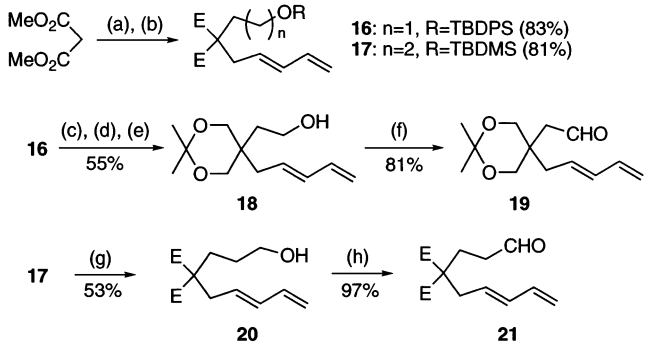
FIGURE 2.

SCHEME 9



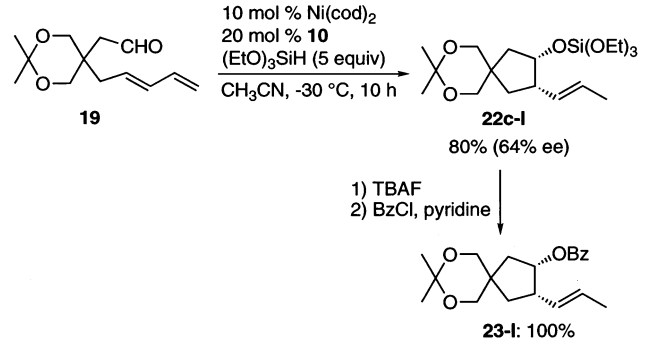
the corresponding (*S*)-MTPA ester **15-I**. The (*S*)-MTPA ester **15-I** was obtained as a mixture of two diastereomers (26% de), and the chemical shifts of each diastereomer were carefully assigned on the basis of 2D NMR. The values of $\Delta\delta = |\delta_{major}| - |\delta_{minor}|$ in the ^{1}H NMR spectrum of (*S*)-MTPA ester **15-I** were calculated and are shown in Figure 2. All assigned protons with positive and negative $\Delta\delta$ values are actually found on the right and left sides of the MTPA plane, respectively. On the basis of these results, the absolute configuration of the major diastereomer in **15-I** was determined to be *R* at the C1-position and *S* at the C2-position. These results indicate that the absolute configuration of the product **7-I** in the cyclization of **6** using chiral phosphorane **10** was 1*S* and 2*S*. On the other hand, the absolute configuration of **7-T** was determined by a combination of the chemical correlation and HPLC analysis with a chiral stationary phase column. It was found that **9-I** could be converted into the above-mentioned methyl ketone **12** via Wacker oxidation by changing the solvent from dioxane to DMF, and (1*S*,2*S*)-**12** was synthesized from (1*S*,2*S*)-**9-I** in 83% yield (Scheme 9). By comparison of the HPLC chart of the authentic (1*S*,2*S*)-**12** with that of **12** derived from a mixture of **9-I** and **9-T** by Wacker oxidation in dioxane (Scheme 7), the absolute configuration of the major

SCHEME 10[a]



[a] Reagents: (a) NaH, $Br(CH_2)_nOR$ (n = 2, R = TBDPS or n = 3, R = TBDMS); (b) 5-bromo-1,3-pentadiene, NaH, THF; (c) DIBAL-H, toluene; (d) $Me_2C(OMe)_2$, PPTS; (e) TBAF; (f) PCC, MS4A; (g) HF, CH_3CN; (h) Dess–Martin periodinane, CH_2Cl_2.

SCHEME 11

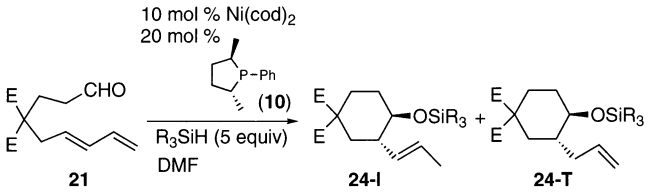


enantiomer in **9-T** was determined to be *S* at the C1-position and *R* at the C2-position. The results indicate that the absolute configuration of **7-T** produced in the asymmetric cyclization was also *S* at the C1-position and *R* at the C2-position. By using the above-described methods, the absolute configurations of all cyclized products in Tables 2 and 3 were determined. It was found that the cyclized product (1*S*,2*S*)-**7-I**, having an internal olefin in the side chain, or (1*S*,2*R*)-**7-T**, having a terminal olefin in the side chain, was produced as the major enantiomer in all cases.

The cyclization of **19**, which was prepared as shown in Scheme 10, with 10 mol % $Ni(cod)_2$ and ligand **10** in the presence of $(EtO)_3SiH$ in CH_3CN at −30 °C also afforded **22c-I**, having a terminal olefin in the side chain, in 80% yield as a sole product, whose enantiomeric excess was determined to be 64% ee by conversion of **22c-I** to **23-I** [HPLC analysis of **23-I** (DAICEL CHIRALCEL OJ-R, CH_3CN/H_2O 1/1)] (Scheme 11).

Construction of Six-Membered Carbocycles and Nitrogen-Containing Five-Membered Heterocycles via Ni(0)-Catalyzed Asymmetric Cyclization of ω-Formyl-1,3-dienes. Next, asymmetric cyclizations of various substrates were investigated. The cyclization of **21**, which was prepared as shown in Scheme 10, using $(EtO)_3SiH$ in DMF at −30 °C was carried out. An inseparable mixture of six-membered ring compounds **24c-I** and **24c-T** was obtained in a total yield of 51% at a ratio of 1 to 2.6 (Table 5, run 1). The cyclization of **21** using Ph_2MeSiH in DMF afforded **24e-I** in preference to **24e-T** at a ratio of 7.3 to 1 in a total yield of 61% (run 2).

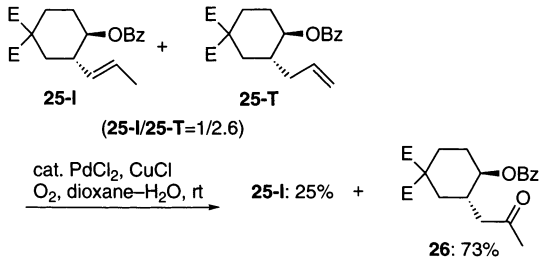
TABLE 5. Cyclization of 21 Using Ni(cod)$_2$ and 10



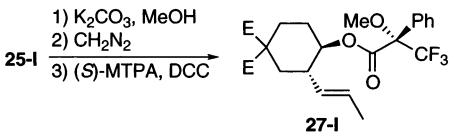
run[a]	R_3SiH	time (h)	yield (%) (**24-I** + **24-T**)	ratio[b] **24-I**/**24-T**	ee (%) (**24-I**/**24-T**)
1	$(EtO)_3SiH$ (**c**)	24	51	1/2.6	42/66
2	Ph_2MeSiH (**e**)	9	61	7.3/1	61/66

[a] The reaction was carried out at −30% °C (run 1) or 0 °C (run 2). [b] The ratio was determined by ^{1}H NMR.

SCHEME 12



SCHEME 13



The enantiomeric excesses of the cyclized products shown in Table 5 were determined using the above-mentioned chemoselective Wacker oxidation. That is, after conversion of an inseparable mixture of **24-I** and **24-T** (**24-I**/**24-T** 1/2.6, run 1, Table 5) into the corresponding benzoates **25-I** and **25-T**, the mixture of **25-I** and **25-T** was subjected to the Wacker oxidation in a manner similar to that in the case of the five-membered ring system (Scheme 12), and **25-I** and **26** were obtained in 25% yield and 73% yield, respectively. The compounds **25-I** and **26** could be easily separated by silica gel column chromatography, and their enantiomeric excesses were determined by HPLC analysis [**25-I**: DAICEL CHRALCEL OJ-R, CH_3CN/H_2O 99/1; **26**: DAICEL CHIRALCEL OJ, hexane/2-propanol 9/1]. Based on a comparison of HPLC charts, it was also found that the same enantiomers of **24-I** and **24-T** were produced as the major enantiomers in both reactions of runs 1 and 2 in Table 5.

The absolute configuration of **25-I** was determined to be *R* at the C1-position and *S* at the C2-position by the improved Mosher's method after conversion of **25-I** into **27-I** in a manner similar to that described above (Scheme 13 and Figure 3). This result indicates that (1*R*,2*S*)-**24-I** was produced as the major enantiomer in the asymmetric cyclization of **21**. On the other hand, the absolute configuration of **26** was determined as follows (Scheme 14): (1*R*,2*S*)-**25-I** was converted into (1*R*,2*S*)-**26** via Wacker oxidation in DMF, and then by the comparison of HPLC chart of authentic (1*R*,2*S*)-**26** with that of **26** derived from a mixture of **25-I** and **25-T** as shown in

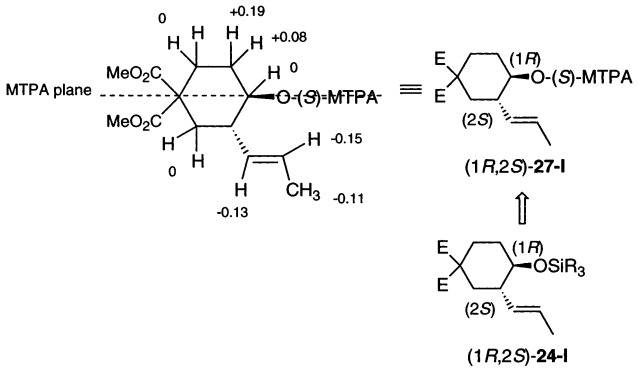


FIGURE 3.

SCHEME 14

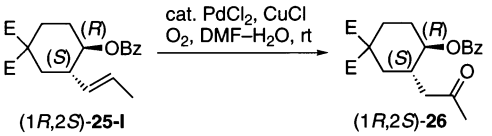
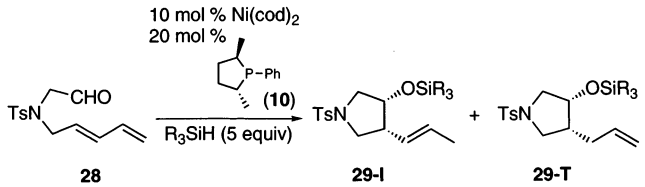


TABLE 6. Cyclization of 28 Using Ni(cod)$_2$ and 10



run[a]	R_3SiH	time (h)	yield (%) (**29-I** + **29-T**)	ratio[b] **29-I**/**29-T**	ee (%) (**29-I**/**29-T**)
1	$(EtO)_3SiH$ (**c**)	6	60	4.6/1	48/41
2	Ph_2MeSiH (**e**)	42	22	1/2.4	10/67

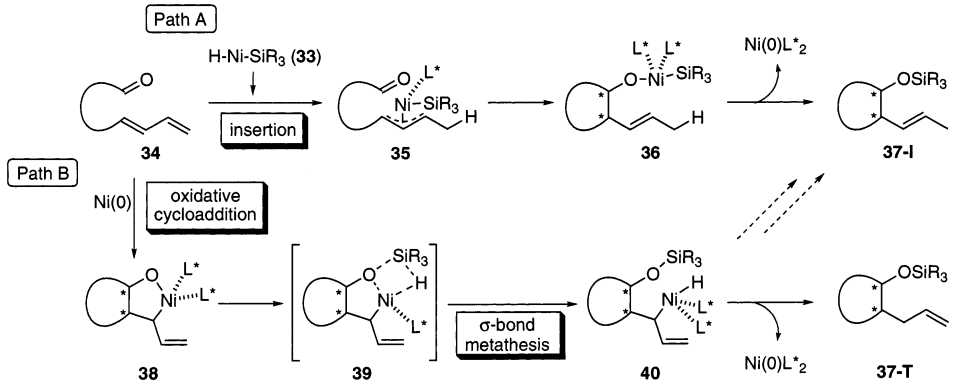
[a] The reaction was carried out in CH_3CN (run 1) or DMF (run 2) at 0 °C. [b] The ratio was determined by ^{1}H NMR.

Scheme 12, the absolute configuration of the major enantiomer in **25-T** was determined to be *R* at the C1-position and *S* at the C2-position. This result indicates that the absolute configuration of **24-T** obtained in the asymmetric cyclization of **21** was also *R* at the C1-position and *S* at the C2-position.

It is noteworthy that this asymmetric cyclization is applicable to the construction of a pyrrolidine ring (Table 6). The cyclization of **28**[3e] with 10 mol % Ni(cod)$_2$ and ligand **10** in the presence of $(EtO)_3SiH$ in CH_3CN gave **29c-I** (48% ee) and **29c-T** (41% ee) (ratio of 4.6 to 1) in a total yield of 60% (run 1).[9] On the other hand, the cyclization of **28** using Ph_2MeSiH produced **29e-T** (67% ee) in preference to **29e-I** (10% ee) in a ratio of 2.4 to 1 (run 2). In both cyclizations, (1*R*,2*R*)-**29-I** and (1*R*,2*R*)-**29-T** were produced as the major enantiomers.[9] It was found that the pyrrolidine system showed the same tendency as that of the five-membered carbocyclic system, in which the use of $(EtO)_3SiH$ increased the formation of **29-I** having an internal olefin in the side chain, while the reaction using Ph_2MeSiH reversed the ratio of **29-I** to **29-T**.

(9) The enantiomeric excesses and the absolute configurations of **29-I** and **29-T** were determined by procedures similar to those used for the above-mentioned five- and six-membered carbocyclic systems. See Supporting Information.

SCHEME 15



Mechanism of Ni(0)-Catalyzed Asymmetric Cyclization of ω-Formyl-1,3-dienes. A possible mechanism of the asymmetric cyclization of ω-formyl-1,3-diene in the presence of silanes is shown in Scheme 15. The formation of **37-I** having an internal olefin in the side chain can be explained by the mechanism via a π-allylnickel intermediate (Scheme 15, Path A).[3h] That is, nickel hydride complex **33** would be initially formed by oxidative addition of silane (R_3SiH) to a zerovalent nickel complex, and this complex would react with the 1,3-diene moiety of **34** to give π-allylnickel intermediate **35**. The reaction of the aldehyde in a tether of **35** with the π-allylnickel moiety would give **36**, and the cyclized product **37-I** having an internal olefin in the side chain would be produced through reductive elimination from **36**. On the other hand, the formation of **37-T** having a terminal olefin in the side chain cannot be explained by this mechanism, and it was speculated that **37-T** is produced via path B, which involves a σ bond metathesis of silanes and the nickel−oxygen bond of oxanickelacycle.[10] Namely, oxidative cycloaddition of both olefin and aldehyde moieties of **34** to a zerovalent nickel complex would occur to give oxanickelacycle **38**. σ bond metathesis of R_3SiH and the nickel−oxygen bond of **38** via **39** would produce nickel hydride intermediate **40**, which would afford **37-T**, having a terminal olefin in the side chain, directly by reductive elimination. The formation of **37-I**, having an internal olefin in the side chain, also might be explainable by path B through reductive elimination from **40** via a π-allylnickel intermediate. As described above, both the ratio and enantiomeric excess of the cyclized products, having an internal olefin or a terminal olefin in the side chain, varied depending upon the substrates and/or silanes. Thus, we speculate that both mechanisms of path A and path B operate in this asymmetric cyclization.

Conclusions

A nickel(0)-catalyzed asymmetric cyclization of ω-formyl-1,3-dienes in the presence of silanes was investigated, and it was found that five- or six-membered carbocycles or pyrrolidine derivatives were afforded in ee up to 86% by the use of phosphorane **10** as a chiral monodentate ligand. The reaction course of this asymmetric cyclization can be explained for by two possible mechanisms: one in which the cyclization proceeds via a π-allylnickel intermediate to produce a cyclized product having an internal olefin in the side chain, and one in which the cyclization proceeds via a σ bond metathesis of silane and the nickel−oxygen bond of oxanickelacycle to produce a cyclized compound having a terminal olefin and/or an internal olefin in the side chain. The present results should pave the way to the establishment of a novel strategy for construction of cyclic compounds as optically active forms.

Experimental Section

General. All manipulations were performed under an argon atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (Merck, 70−230 mesh), and flash chromatography was performed on silica gel 60 (Merck, 230−400 mesh).

General Procedure for Ni(0)-Catalyzed Cyclization in the Presence of Silane. To a solution of $Ni(cod)_2$ (10 or 20 mol % to the substrate) and ligand (20 or 40 mol % to the substrate) in degassed solvent (ca. 0.01 M) was added a silane (5 equiv of substrate) at 0 °C, and the mixture was stirred at the same temperature. To the solution was added a solution of substrate in degassed solvent (ca. 0.08 M) at the temperature indicated in the text, and the mixture was stirred at the same temperature. After removal of the solvent, the crude product was purified by silica gel column chromatography to give the cyclized product.

Typical Procedure for Asymmetric Cyclization of 6 Using Chiral Phosphorane 10 in the Presence of Et_3SiH (Scheme 5 and Table 2, run 1). According to the General Procedure for Cyclization, the crude product, which was prepared from $Ni(cod)_2$ (7.7 mg, 0.03 mmol), **10** (10.8 mg, 0.056 mmol), **6** (67 mg, 0.28 mmol), and Et_3SiH (0.23 mL, 1.4 mmol) in THF (5.6 mL) at room temperature for 5 h, was purified by column chromatography on silica gel (hexane/Et_2O 10/1) to give an inseparable mixture of **7a-I** and **7a-T** (84 mg, total yield 84%, ratio of 4.3:1).

Typical Procedure for Separation of an Inseparable Mixture of 7-I and 7-T into 9-I and 12 via Chemoselective Wacker Oxidation (Scheme 7). To a mixture of **7a-I** and **7a-T** (84 mg, 0.23 mmol, ratio of 4.3:1) in CH_3CN (1.0 mL) was added 1.0 mL of HF−CH_3CN solution (prepared by mixing a concentrated HF aq solution with CH_3CN (ratio of 1:9)) and the mixture was stirred at room temperature for 20 min. To the mixture was added a saturated $NaHCO_3$ aq solution, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the mixture of the alcohols was treated

(10) Recently, σ bond metathesis of silanes and the nickel/oxygen bond of oxanickelacycle has also been proposed by Montgomery in a Ni(0)-catalyzed cyclization of ynals in the presence of silanes. See: Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098 and references cited therein.

with BzCl (0.26 mL, 2.2 mmol) and a catalytic amount of DMAP in pyridine (1.5 mL) at 50 °C for 18 h. After the usual workup, the residue was purified by column chromatography on silica gel (hexane/Et_2O 3/1) to give an inseparable mixture of **9-I** and **9-T** (77 mg, total yield 95%, ratio of 4.3:1). To a mixture of benzoate **9-I** and **9-T** (37 mg, 0.11 mmol, ratio of 4.3:1) in 1,4-dioxane−H_2O (10:1, 1.5 mL) were added $PdCl_2$ (1.9 mg, 0.01 mmol) and CuCl (1.4 mg, 0.01 mmol), and the mixture was stirred at room temperature for 1.5 h under an atmosphere of oxygen. The mixture was diluted with Et_2O, and 10% HCl aq solution was added to the mixture. The aqueous layer was extracted with Et_2O, and the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/EtOAc 5/1 to 2/1) to give **12** (8 mg, 21%), and unchanged **9-I** (29 mg, 79%) was recovered.

Spectral data for 9-I: IR (neat) 1736, 1720, 1654, 1602, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (dd, J = 6.3, 1.3 Hz, 3 H), 2.37 (dd, J = 13.6, 7.8 Hz, 1 H), 2.53 (dd, J = 13.6, 11.8 Hz, 1 H), 2.57 (dd, J = 15.2, 1.7 Hz, 1 H), 2.63 (dd, J = 15.2, 4.4 Hz, 1 H), 2.77 (m, 1 H), 3.56 (s, 3 H), 3.68 (s, 3 H), 5.34 (m, 1 H), 5.37 (ddq, J = 15.3, 7.3, 1.3 Hz, 1 H), 5.50 (dq, J = 15.3, 6.3 Hz, 1 H), 7.30−7.41 (m, 2 H), 7.48 (m, 1 H), 7.88−7.93 (m, 2 H); EI-LRMS m/z 346 (M^+), 315, 278, 241, 224, 164, 105, 77, 59; EI-HRMS calcd for $C_{19}H_{22}O_6$ 346.1417, found 346.1402; $[\alpha]^{23}_D$ +26.8 (c 1.66, $CHCl_3$, 73% ee) (for (1*S*,2*S*)-**9-I** derived from **7c-I** in Table 3, run 4)

Spectral data for 12: IR (neat) 1734, 1720, 1718, 1654, 1602, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3 H), 2.39 (dd, J = 13.6, 11.1 Hz, 1 H), 2.49−2.52 (m, 2 H), 2.63 (dd, J = 15.2, 1.2 Hz, 1 H), 2.67−2.78 (m, 3 H), 3.62 (s, 3 H), 3.75 (s, 3 H), 5.51 (m, 1 H), 7.42−7.49 (m, 2 H), 7.57 (m, 1 H), 7.94−7.99 (m, 2 H); EI-LRMS m/z 363 (M^+ + H), 362 (M^+), 331, 319, 305, 240, 198, 183, 105, 77; EI-HRMS calcd for $C_{19}H_{23}O_7$ (M^+ + H) 363.1444, found 363.1416; $[\alpha]^{24}_D$ −3.7 (c 1.36, $CHCl_3$, 86% ee) (for (1*S*,2*S*)-**12** derived from **7e-T** in Table 4, run 3)

The enantiomeric excess of **9-I** or **12** was determined by HPLC analysis [DAICEL CHIRALPAK AD (hexane/2-propanol 9/1) or DAICEL CHIRALPAK AD (hexane/2-propanol 9/1), respectively]. The enantiomeric excesses of other cyclized products in Tables 2−4 were determined by HPLC analysis after transformation to **9-I** and **12** by similar procedures as those for **7a-I** and **7a-T**.

Typical Procedure for Determination of Absolute Configurations of the Cyclized Products 7-I and 7-T (Schemes 8 and 9). (1*S*,2*S*)-4,4-Bismethoxycarbonyl-2-[(1*E*)-propenyl]cyclopentan-1-ol (13-I). To a solution of **9-I** (341 mg, 0.98 mmol, 26% ee) in CH_3OH (10 mL) was added K_2CO_3 (677 mg, 4.9 mmol), and the mixture was stirred at room temperature for 20 h. After the usual workup, the crude material was treated with an excess amount of CH_2N_2 in Et_2O, and the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 4/1) to give **13-I** as a colorless oil (225 mg, 95%). IR (neat) 3526, 1732, 1654, 1198, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (dd, J = 6.2, 1.3 Hz, 3 H), 1.82 (br d, J = 3.4 Hz, 1 H), 2.31−2.45 (m, 3 H), 2.49 (dd, J = 14.7, 1.7 Hz, 1 H), 2.61 (m, 1 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 4.15 (m, 1 H), 5.50 (dq, J = 15.5, 1.3 Hz, 1 H), 5.61 (dq, J = 15.5, 6.2 Hz, 1 H); EI-LRMS m/z 242 (M^+), 224, 174, 164, 145, 113, 105, 68, 59; EI-HRMS calcd for $C_{12}H_{18}O_5$ 242.1154, found 242.1176; $[\alpha]^{22}_D$ +7.27 (c 1.15, $CHCl_3$, 26% ee).

(1*R*,2*S*)-1-Benzoyloxy-4,4-bismethoxycarbonyl-2-[(1*E*)-propenyl]cyclopentane. To a solution of **13-I** (85 mg, 0.35 mmol, 26% ee) in THF (2 mL) were added PPh_3 (185 mg, 0.70 mmol), benzoic acid (102 mg, 0.46 mmol), and DEAD (136 mg, 0.78 mmol), and the mixture was stirred at room temperature for 4 h. To the mixture was added a saturated $NaHCO_3$ aq solution, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/Et_2O 5/1) to give the benzoate as a colorless oil (71 mg, 58%). IR (neat) 1736, 1722, 1654, 1602, 1270 $cm^{-}1$; ^1H NMR (270 MHz, $CDCl_3$) δ 1.65 (d, J = 6.3 Hz, 3 H), 2.02 (dd, J = 13.5, 9.0 Hz, 1 H), 2.44 (dd, J = 14.5, 5.1 Hz, 1 H), 2.76 (dd, J = 13.5, 7.9 Hz, 1 H), 2.86 (dd, J = 14.5, 6.8 Hz, 1 H), 2.88 (m, 1 H), 3.01 (s, 3 H), 3.75 (s, 3 H), 5.12 (m, 1 H), 5.43 (dd, J = 15.4, 7.3 Hz, 1 H), 5.58 (dq, J = 15.4, 6.3 Hz, 1 H), 7.43 (dd, J = 7.7, 7.7 Hz, 2 H), 7.55 (dd, J = 7.7, 7.7 Hz, 1 H), 8.00 (d, J = 7.7 Hz, 2 H); EI-LRMS m/z 346 (M^+), 315, 224, 164, 105, 77; EI-HRMS calcd for $C_{19}H_{22}O_6$ 346.1416, found 346.1438; $[\alpha]^{23}_D$ −8.60 (c 2.42, $CHCl_3$, 26% ee).

(1*R*,2*S*)-4,4-Bismethoxycarbonyl-2-[(1*E*)-propenyl]cyclopentan-1-ol (14-I). According to the procedure described above, **14-I** was prepared in 98% yield (48 mg) by the reaction of the above benzoate (71 mg, 0.21 mmol) and K_2CO_3 (142 mg, 1.0 mmol) in CH_3OH (3 mL) at room temperature for 36 h followed by treatment of CH_2N_2. IR (neat) 3432, 1734, 1640, 1168, 1076 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.68 (dd, J = 6.5, 1.2 Hz, 3 H), 1.05 (dd, J = 13.6, 10.1 Hz, 1 H), 2.01 (br d, J = 4.4 Hz, 1 H), 2.16 (dd, J = 14.0, 7.2 Hz, 1 H), 2.43 (m, 1 H), 2.57 (dd, J = 13.6, 7.7 Hz, 1 H), 2.63 (dd, J = 14.0, 7.2 Hz, 1 H), 3.73 (s, 3 H), 3.75 (s, 3 H), 3.89 (m, 1 H), 5.31 (ddq, J = 15.2, 7.8, 1.2 Hz, 1 H), 5.58 (ddq, J = 15.2, 1.0, 6.5 Hz, 1 H); EI-LRMS m/z 224 (M^+ − H_2O), 164, 105, 59; EI-HRMS calcd for $C_{12}H_{16}O_4$ 224.1048 (M^+ − H_2O), found 224.1051; $[\alpha]^{24}_D$ −3.23 (c 1.93, $CHCl_3$, 26% ee).

Conversion of 14-I into (*S*)-MTPA Ester 15-I. To a solution of **14-I** (28 mg, 0.11 mmol, 26% ee) in CH_2Cl_2 (1.5 mL) were added DCC (36 mg, 0.17 mmol), (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (40 mg, 0.17 mmol), and DMAP (22 mg, 0.18 mmol), and the mixture was stirred at room temperature for 15.5 h. The mixture was diluted with Et_2O, 10% HCl aq solution was added to the mixture, and the solution was stirred at room temperature for 1 h. The aqueous layer was extracted with Et_2O, and the organic layer was washed with a saturated $NaHCO_3$ aq solution and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/Et_2O 5/1 to 3/1) to give two diastereomers as an inseparable mixture (46 mg, 87%, 26% de). The NMR spectral data (including COSY spectrum) of the mixture were fully considered by application of the improved Mosher's method, and it indicates that (1*R*,2*S*)-**15-I** was a major diastereomer. (1*R*,2*S*)-**15-I**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.61 (d, J = 6.4 Hz, 3 H), 1.97 (dd, J = 13.6, 10.5 Hz, 1 H), 2.38 (dd, J = 14.4, 6.5 Hz, 1 H), 2.58 (dd, J = 13.6, 7.8 Hz, 1 H), 2.68 (m, 1 H), 2.83 (dd, J = 14.4, 7.4 Hz, 1 H), 3.53 (s, 3 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 5.14 (ddd, J = 7.4, 7.4, 6.5 Hz, 1 H), 5.30 (dd, J = 15.3, 8.1 Hz, 1 H), 5.43 (dq, J = 15.3, 6.4 Hz, 1 H), 7.36−7.43 (m, 3 H), 7.49−7.51 (m, 2 H). (1*S*,2*R*)-**15-I**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.66 (d, J = 6.3 Hz, 3 H), 1.95 (dd, J = 13.6, 11.7 Hz, 1 H), 2.23 (dd, J = 14.5, 6.4 Hz, 1 H), 2.63 (dd, J = 13.6, 7.9 Hz, 1 H), 2.77 (m, 1 H), 2.85 (dd, J = 14.5, 7.3 Hz, 1 H), 3.53 (s, 3 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 5.12 (ddd, J = 7.3, 7.3, 6.4 Hz, 1 H), 5.30 (dd, J = 15.1, 7.9 Hz, 1 H), 5.56 (dq, J = 15.1, 6.3 Hz, 1 H), 7.36−7.43 (m, 3 H), 7.49−7.51 (m, 2 H).

Other spectral data of a mixture of (1*R*,2*S*)-**15-I** and (1*S*,2*R*)-**15-I**: IR (neat) 1738, 1736, 1654, 1252 cm^{-1}; EI-LRMS m/z 427 (M^+ − OMe), 224, 189, 165, 105, 77, 59; EI-HRMS calcd for $C_{21}H_{22}F_3O_6$ (M^+ − OMe) 427.1368, found 427.1379.

Conversion of (1*S*,2*S*)-9-I into (1*S*,2*S*)-12. According to a procedure similar to that described above, the crude product, which was prepared from (1*S*,2*S*)-**9-I** (40 mg, 0.12 mmol, 46% ee), $PdCl_2$ (2.0 mg, 0.011 mmol), and CuCl (1.4 mg, 0.014 mmol) in DMF−H_2O (10:1, 1.5 mL) at room temperature for

45 h under an atmosphere of oxygen, was purified by column chromatography on silica gel (hexane/EtOAc 10/1) to give (1*S*,2*S*)-**12** as a colorless oil (35 mg, 83%, 46% ee), whose spectral data were identical with those described above.

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Supporting Information Available: Procedures for the synthesis of the substrates and its spectral data; procedures for determination of the enantiomeric excess and the absolute configuration of cyclized products **22c-I**, **24**, and **29**, and spectral data for the related compounds; ^{1}H NMR spectra for new compounds lacking elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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