m, 4 H, cat), 7.16-7.21 (ov m, 2 H, Ph), 7.27-7.32 (ov m, 2 H, Ph). ^{13}C NMR: 17.0 (CH_3), 25.6 (br, B-CH), 113.1 (CH), 113.3 (CH), 115.5 (d, J_{CF} = 21 Hz, CH), 123.4 (CH), 124.5 (CH), 130.7 (d, J_{CF} = 8 Hz, CH), 147.3 (d, J_{CF} = 3 Hz, C), 149.2 (C), 164.0 (d, J_{CF} = 244 Hz, C). $^{11}B\{^1H\}$ NMR: 35.2 (br).

Catalytic Hydroboration of 15e: Synthesis of 17e. ^1H NMR: δ 1.70 (d, J = 8 Hz, 3 H, CH_3), 3.13 (q, J = 8 Hz, 1 H, CH), 6.96-7.02 (ov m, 2 H, cat), 7.16-7.21 (ov m, 2 H, cat), 7.34-7.40 (ov m, 2 H, Ph), 7.48-7.51 (ov m, 1 H, Ph), 7.78 (br m, 4 H, Ph). ^{13}C NMR: 17.1 (CH_3), 26.0 (br, B-CH), 113.0 (CH), 123.3 (CH), 125.8 (CH), 126.5 (CH), 126.6 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.8 (CH), 133.1 (C), 134.9 (C), 142.1 (C), 149.4 (C). $^{11}B\{^1H\}$ NMR: 35.5 (br).

Catalytic Hydroboration of 18: Synthesis of 20. ^1H NMR: δ 0.96 (t, J = 7 Hz, 3 H, CH_3), 1.92, 2.15 (m, J = 7 Hz, 1 H, CH_2), 2.74 (d d, J = 7 Hz, 1 H, CH), 6.98-7.27 (ov m, 9 H, Ph and cat). ^{13}C NMR: 14.1 (CH_3), 26.2 (CH_2), 34.8 (br, B-CH), 112.9 (CH), 123.2 (CH), 126.3 (CH), 129.1 (CH), 129.3 (CH), 142.6 (C), 149.1 (C). $^{11}B\{^1H\}$ NMR: 34.6 (br).

Catalytic Hydroboration of 21: Synthesis of 23. ^1H NMR: δ 2.39 (d d, J = 8 Hz, 2 H, CH_2), 3.02 (ov m, J = 8 Hz, 2 H, CH_2), 3.23 (dd, J = 8 Hz, 1 H, CH), 6.99-7.15 (ov m, 4 H, cat), 7.18-7.21 (ov m, 3 H, Ph), 7.39-7.42 (m, 1 H, Ph). ^{13}C NMR: 28.9 (CH_2), 30.8 (br, B-CH), 33.8 (CH_2), 113.0 (CH), 123.3 (CH), 125.0 (CH), 125.3 (CH), 128.7 (CH), 128.9 (CH), 144.4 (C), 144.6 (C), 149.3 (C). $^{11}B\{^1H\}$ NMR: 34.8 (br).

Catalytic Hydroboration of 24: (a) Synthesis of 25. ^1H NMR: δ 1.22 (d, J = 8 Hz, 3 H, CH_3), 1.65 (ov m, J = 8 Hz, 2 H), 3.26 (sext, J = 8 Hz, 1 H), 6.97-7.30 (ov m, 9 H). ^{13}C NMR: 21.7 (br, B-CH_2), 25.3 (CH_3), 36.6 (CH), 113.0 (CH), 123.4 (CH), 126.8 (CH), 127.3 (CH), 129.3 (CH), 149.4 (C), 149.7 (C). $^{11}B\{^1H\}$ NMR: 35.0 (br).

(b) Synthesis of 26. ^1H NMR: δ 1.58 (s, 6 H, CH_3), 6.98-7.44 (ov m, 9 H, Ph and cat). ^{13}C NMR: 22 (br, B-C), 26.2 (CH_3), 113.1 (CH), 123.4 (CH), 126.3 (CH), 127.2 (CH), 129.1 (CH), 148.0 (C), 149.3 (C). $^{11}B\{^1H\}$ NMR: 35.4 (br).

Catalytic Hydroboration of 27: Synthesis of 28. ^1H NMR: δ 1.26, 2.69 (t, J = 8 Hz, 2 H, CH_2), 1.94 (m, J = 8 Hz, 2 H, CH_2), 6.95-7.28 (ov m, 9 H, Ph and cat). ^{13}C NMR: 10 (br, B-CH_2), 25.6 (CH_2), 38.0 (CH_2), 112.0 (CH), 122.2 (CH), 125.5 (CH), 128.2 (CH), 128.4 (CH), 142.0 (C), 148.4 (C). $^{11}B\{^1H\}$ NMR: 34.4 (br).

Catalytic Hydroboration of 29a: Synthesis of 30a. ^1H NMR: δ 0.91 (m, 3 H, CH_3), 1.37 (ov m, 12 H, CH_2), 1.69 (m, 2 H, CH_2), 7.02 (m, 2 H, cat), 7.21 (m, 2 H, cat). ^{13}C NMR: 11.4 (br, B-CH_2), 14.5 (CH_3), 23.6 (CH_2), 24.7 (CH_2), 30.2 (CH_2), 30.4 (CH_2), 32.9 (CH_2), 33.2 (CH_2), 112.8 (CH), 123.1 (CH), 149.5 (C). $^{11}B\{^1H\}$ NMR: 35.1 (br).

Catalytic Hydroboration of 29b: Synthesis of 30b. ^1H NMR: δ 0.81 (s, 9 H, CH_3), 1.20 (m, J = 8 Hz, 2 H, CH_2), 1.54 (m, J = 8 Hz, 2 H, CH_2), 6.87 (m, 2 H, cat), 7.01 (m, 2 H, cat). ^{13}C NMR: 5.2 (br, B-CH_2), 29.4 (CH_3), 31.2 (C), 38.3 (CH_2), 112.8 (CH), 123.3 (CH), 149.1 (C). $^{11}B\{^1H\}$ NMR: 35.5 (br).

Catalytic Hydroboration of 29c: Synthesis of 30c. ^1H NMR: δ 0.03 (s, 9 H, CH_3), 0.81 (m, J = 8 Hz, 2 H, CH_2), 1.23 (m, J = 8 Hz, 2 H, CH_2), 6.88 (m, 2 H, cat), 7.04 (m, 2 H, cat). ^{13}C NMR: -1.9 (CH_3), 4.1 (br, B-CH_2), 9.9 (CH_2), 112.9 (CH), 122.8 (CH), 149.4 (C). $^{11}B\{^1H\}$ NMR: 35.5 (br).

Catalytic Hydroboration of 31: Synthesis of 32. ^1H NMR: δ 0.92 (d, J = 7 Hz, 6 H, CH_3), 1.12 (s, 6 H, CH_3), 1.77 (m, J = 7 Hz, 1 H, CH), 7.02 (m, 2 H, cat), 7.19 (m, 2 H, cat). ^{13}C NMR: 28 (v br, B-C), 19.1 (CH_3), 22.5 (CH_3), 36.4 (CH), 112.3 (CH), 122.9 (CH), 149.3 (C). $^{11}B\{^1H\}$ NMR: 35.5 (br).

Acknowledgment. We thank Nancy J. Herling, John E. Feaster, Elwood A. Conaway, Yi Meng, Fred Davidson, John Nguyen, and Keith D. Raffell for expert technical assistance and Dr. Mark J. Burk (DuPont) for many valuable discussions. We also thank the referees for several helpful comments. T.B.M. acknowledges support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Natural Sciences and Engineering Research Council of Canada.

Supplementary Material Available: ^1H NMR, ^{11}B NMR, and ^{13}C NMR spectra at 25 °C in THF-d_8 of **17a** using **1**, **20** using **9**, and **32** using **12** (t = 40 h) (13 pages). Ordering information is given on any current masthead page.

Asymmetric [2 + 2] Cycloaddition Reaction Catalyzed by a Chiral Titanium Reagent

Koichi Narasaka,* Yujiro Hayashi, Hideshi Shimadzu, and Shigeo Niihata

Contribution from the Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan. *Received March 3, 1992*

Abstract: In the presence of certain Lewis acids, alkenes containing an alkylthio group (for example, ketene dithioacetals, alkenyl sulfides, alkynyl sulfides, and allenyl sulfides) react with electron deficient olefins to give the corresponding cyclobutane, cyclobutene, or methylene cyclobutane derivatives. By employing a chiral titanium catalyst generated in situ from dichlorodiisopropoxytitanium and a tartrate-derived chiral diol, the [2 + 2] cycloaddition reaction proceeds with high enantioselectivity.

The development of asymmetric reactions has been one of the main themes of modern synthetic organic chemistry, and currently much effort is being directed toward the development of catalytic asymmetric reactions.[1] Cyclopropane and cyclohexane frameworks have been constructed enantioselectively by the catalytic asymmetric cyclopropanation[2] and Diels-Alder reactions,[3] respectively. On the other hand, there exists no practical catalytic method for the synthesis of optically active cyclobutanes,[4] which hitherto have been prepared conventionally by diastereoselective reactions using chiral starting materials[5] or by optical resolution.[5a,6]

(1) Kagan, H. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: Orlando, FL, 1985; Vol. 5, p 1. Brunner, H. *Synthesis* **1988**, 645. Noyori, R.; Kitamura, M. In *Modern Synthetic Methods*; Springer: Berlin, 1989; Vol. 5, p 115. Narasaka, K. *Synthesis* **1991**, 1.

(2) Review: Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 542.

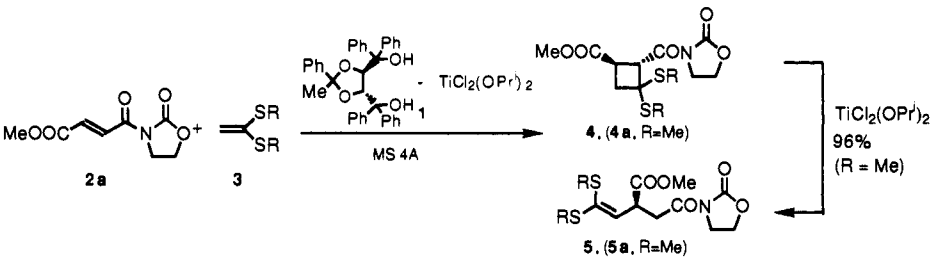
(3) (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340. (b) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947. (c) Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387. (d) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (e) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481. (f) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794 and references cited therein.

(4) (a) Recently Engler et al. reported the asymmetric [2 + 2] cycloaddition reaction between styrenes and 1,4-benzoquinones catalyzed by an equimolar amount of a chiral titanium reagent having **1** as a chiral auxiliary. Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068. (b) Asymmetric [2 + 2] cycloaddition for the preparation of β-lactone using quinidine as a catalyst, see: Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.

(5) Recent papers, see: (a) Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797. (b) Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306. (c) Fráter, G.; Müller, U.; Guenther, W. *Helv. Chim. Acta* **1986**, *69*, 1858. (d) Mori, K.; Miyake, M. *Tetrahedron* **1987**, *43*, 2229. (e) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752. (f) Redlich, H.; Lenfers, J. B.; Kopf, J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 777. (g) Hiroi, K.; Ogata, T. *Chem. Lett.* **1990**, 527. (h) Chen, L.; Ghosez, L. *Tetrahedron Lett.* **1990**, *31*, 4467. (i) Hegedus, L. S.; Bates, R. W.; Söderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923. (j) Ahmad, S. *Tetrahedron Lett.* **1991**, *32*, 6997. (k) Pan, J.; Hanna, I.; Lallemand, J.-Y. *Tetrahedron Lett.* **1991**, *32*, 7543.

0002-7863/92/1514-8869$03.00/0

Table I. Asymmetric [2 + 2] Cycloaddition between **2a** and Ketene Dithioacetals **3**[a]



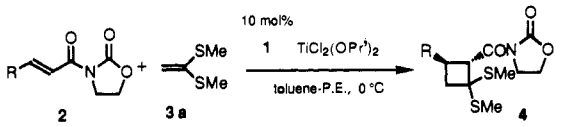
entry	R	R	amount of Ti/equiv	solvent	yield/% 4	yield/% 5	opt purity/% ee 4	opt purity/% ee 5
1	Me	Me (**3a**)	1.1	mesitylene	89	8	93	*b*
2			1.1	toluene–P.E.	78	11	98	*b*
3			0.1	toluene–P.E.	96	2	98	*b*
4			1.1[c]	toluene–P.E.	0	100		
5	Et	Et (**3b**)[d]	0.1	toluene–P.E.	82	12	88	97
6	$-(CH_2)_2-$ (**3c**)		1.1	mesitylene	18	82	*b*	59
7	$-(CH_2)_3-$ (**3d**)		1.1	toluene–P.E.	66	31	62	89

[a] Reaction was performed at 0 °C for 30 min, unless otherwise noted. [b] Optical purity was not determined. [c] $TiCl_2(OPr^i)_2$ was used instead of the chiral titanium reagent. [d] Reaction time was 3 h.

We have reported the preparation and properties of a chiral titanium reagent generated in situ by mixing dichlorodiisopropoxytitanium ($TiCl_2(OPr^i)_2$) and the tartrate-derived chiral 1,4-diol **1**.[7] This reagent promotes the Diels–Alder reaction,[3a-c] the hydrocyanation of aldehydes,[8] and the intramolecular ene reaction[9] with high enantioselectivity. While exploiting various asymmetric reactions using this chiral titanium reagent, it was found that this reagent catalyzes the [2 + 2] cycloaddition reaction between vinyl sulfides and electron deficient olefins, giving various cyclobutane derivatives of high optical purity.

As for the construction of the cyclobutane skeleton, the photochemical [2 + 2] cycloaddition and the [2 + 2] cycloaddition of ketenes have been widely employed. Besides these methods, a thermal [2 + 2] cycloaddition reaction is known to proceed between highly electrophilic and nucleophilic olefins.[5a,10] Although alkynyl[11] or allenyl carboxylates[12] have been employed in the Lewis acid-catalyzed [2 + 2] cycloaddition reaction, cyclobutane formation from α,β-unsaturated esters or α,β-enones has been known only from rather exceptional examples.[4a,5j,13] In this paper we report a full account of the Lewis acid-catalyzed [2 + 2] cycloaddition reaction including a chiral titanium-catalyzed asymmetric reaction and also its scope and limitations, particularly when vinyl sulfides are employed.[14]

Table II. Asymmetric [2 + 2] Cycloaddition between **2** and **3a**



entry	R	time/h	yield/%	opt purity/% ee
1	CO_2Me (**2a**)	0.5	96	98 (**4a**)
2	H (**2b**)	0.5	74	88 (**4b**)
3	Me (**2c**)	109	64	80 (**4c**)

Results and Discussion

We initially investigated the asymmetric Michael reaction of enamines with methyl (*E*)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate (**2a**), which is a suitable dienophile in the titanium-catalyzed asymmetric Diels–Alder reaction.[3a,c] When the chiral titanium reagent prepared in situ by mixing $TiCl_2(OPr^i)_2$ and (2*R*,3*R*)-1,1,4,4-tetraphenyl-2,3-((1-phenylethylidene)dioxy)-1,4-butanediol (**1**) was used, the asymmetric Michael reaction between enamines and **2a** proceeded to give the optically active Michael adducts in moderate optical purity.[15] When various

(6) (a) Mori, K. *Tetrahedron* **1978**, *34*, 915. (b) Jones, J. B.; Finch, M. A. W.; Jakovac, I. J. *Can. J. Chem.* **1982**, *60*, 2007. (c) Webster, F. X.; Silverstein, R. M. *J. Org. Chem.* **1986**, *51*, 5226.

(7) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581.

(8) Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379.

(9) Narasaka, K.; Hayashi, Y.; Shimada, S.; Yamada, J. *Isr. J. Chem.* **1991**, *31*, 261.

(10) Reviews, see: (a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis through Pericyclic Reactions*; ACS Monograph 180; American Chemical Society: Washington, DC, 1983; p 33. (b) Scheeren, J. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 71. (c) Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 117. (d) Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 199. (e) Baldwin, J. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5, p 63. Recent papers, see: (f) Brücker, R.; Huisgen, R. *Tetrahedron Lett.* **1990**, *31*, 2561. (g) Getty, S. J.; Borden, W. T. *J. Am. Chem. Soc.* **1991**, *113*, 4334. (h) Faron, K. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 6419 and references cited therein.

(11) (a) Snider, B. B.; Rodini, D. J.; Conn, R. S. E.; Sealfon, S. *J. Am. Chem. Soc.* **1979**, *101*, 5283. (b) Fienemann, H.; Hoffmann, H. M. R. *J. Org. Chem.* **1979**, *44*, 2802. (c) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248, 253. (d) Snider, B. B.; Roush, D. M.; Rodini, D. J.; Gonzalez, D.; Spindell, D. *J. Org. Chem.* **1980**, *45*, 2773. (e) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 2735. (f) Quendo, A.; Rousseau, G. *Tetrahedron Lett.* **1988**, *29*, 6443. (g) Ali, S. M.; Tanimoto, S. *J. Org. Chem.* **1989**, *54*, 2247.

(12) (a) Snider, B. B.; Spindell, D. K. *J. Org. Chem.* **1980**, *45*, 5017. (b) Hoffmann, H. M. R.; Ismail, Z. M.; Weber, A. *Tetrahedron Lett.* **1981**, *22*, 1953. (c) Snider, B. B.; Ron, E. *J. Org. Chem.* **1986**, *51*, 3643.

(13) (a) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872. (b) Takeda, T.; Fujii, T.; Morita, K.; Fujiwara, T. *Chem. Lett.* **1986**, 1311. (c) Engler, T. A.; Ali, M. H.; Velde, D. V. *Tetrahedron Lett.* **1989**, *30*, 1761. (d) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931. (e) Quendo, A.; Rousseau, G. *Synth. Commun.* **1989**, 1551. (f) Scheeren, H. W.; Frissen, A. E. *Synthesis* **1983**, 794. (g) Majetich, G.; Defauw, J.; Ringold, C. *J. Org. Chem.* **1988**, *53*, 50. (h) Hosomi, A.; Kobayashi, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 955. (i) Pardo, R.; Zahra, J. P.; Santelli, M. *Tetrahedron Lett.* **1979**, 4557. (j) House, H. O.; Gaa, P. C.; Vanderveer, D. *J. Org. Chem.* **1983**, *48*, 1661. (k) Majetich, G.; Khetani, V. *Tetrahedron Lett.* **1990**, *31*, 2243. (l) Gassman, P. G.; Lottes, A. C. *Tetrahedron Lett.* **1992**, *33*, 157.

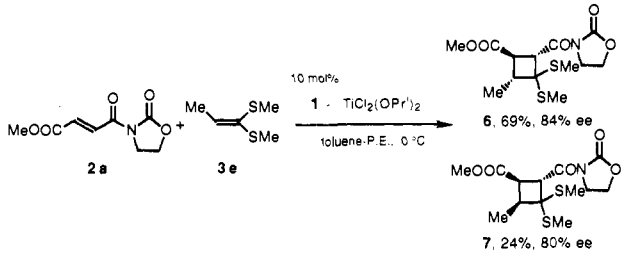
(14) For the preliminary communications of the asymmetric [2 + 2] cycloaddition, see: (a) Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1989**, 793. (b) Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1990**, 1295. (c) Hayashi, Y.; Niihata, S.; Narasaka, K. *Chem. Lett.* **1990**, 2091. (d) Errata of 10b, Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1992**, 189.

Michael donors were screened, vinyl ethers, silyl enol ethers, and ketene alkylsilyl acetals were found not to react with **2a**. But, to our surprise, the reaction of a ketene dithioacetal and **2a** afforded a cyclobutane derivative along with a small amount of a Michael-type product. That is, the treatment of **2a** and 1,1-bis(methylthio)ethylene (**3a**) with an equimolar amount of the chiral titanium reagent at 0 °C in mesitylene in the presence of molecular sieves 4A (MS 4A) afforded the cyclobutane derivative **4a** in 89% (93% ee) and the Michael-type adduct **5a** in 8% yield. The product selectivity toward the cyclobutane **4** and the enantioselectivity were greatly affected by the reaction solvent, the amount of the catalyst, and the alkylthio group of the ketene dithioacetal (Table I). In the reaction of cyclic ketene dithioacetals (**3c** and **3d**), a substantial amount of the Michael-type product **5** was obtained with moderate enantioselectivity (entries 6 and 7). When the reaction was performed employing the ketene dimethyl dithioacetal **3a** in a mixture of toluene and petroleum ether (P.E.) in the presence of MS 4A, the [2 + 2] cycloaddition reaction proceeded almost exclusively to afford **4a** in nearly optically pure form (98% ee) even when only 10 mol % of the chiral titanium reagent was employed (entry 3). However, the reaction of ketene diethyl thioacetal required a longer reaction time and resulted in lower enantioselectivity (88% ee) along with an increase in the Michael-type product **5** (entry 5), showing that the present [2 + 2] cycloaddition is particularly influenced by steric effects.

The ratio of the [2 + 2] cycloadduct **4a** to the Michael-type product **5a** is strongly dependent on the Lewis acidity of the promoter used. The use of a stronger Lewis acid such as $TiCl_2(OPr^i)_2$[7] afforded only the Michael-type product **5a**, which resulted from ring opening of the cycloadduct **4a** (Table I, entry 4). The instability of **4a** under the reaction conditions was proved by the smooth ring cleavage of **4a** with $TiCl_2(OPr^i)_2$ in CH_2Cl_2, giving the Michael-type product **5a**.[16] Accordingly, use of a relatively weak Lewis acid such as the chiral titanium reagent is essential for selective formation of the acid-sensitive cyclobutane derivative **4a**.

The ketene dimethyl dithioacetal **3a** also reacted with 3-acryloyl or 3-crotonoyl oxazolidinone **2b** or **2c**, giving the cyclobutane derivatives **4b** and **4c** in 88 and 80% ee, respectively (Table II).

The reaction of **2a** and a trisubstituted ketene dithioacetal, 1,1-bis(methylthio)propene (**3e**), proceeded with a catalytic

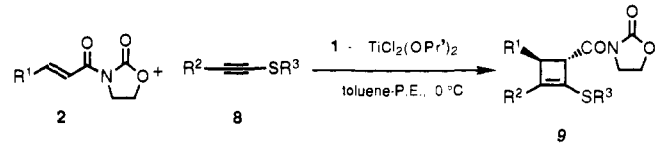


amount of the chiral reagent to afford the two diastereomers **6** and **7** in 69 (84% ee) and 24% (80% ee), respectively. But a tetrasubstituted ketene dithioacetal, 1,1-bis(methylthio)-2-methyl-1-propene, did not react with **2a** even when an equimolar amount of the titanium reagent was employed.

Asymmetric [2 + 2] Cycloaddition between 2 and Alkynyl Sulfides 8 and Alkenyl Sulfides 10 and 14. Since dithioacetals exhibited particularly high reactivity compared to the corresponding oxygen derivatives (ketene acetals and ketene alkylsilyl acetals), the reaction of **2** with unsaturated sulfides was investigated. First, the reaction between **2** and alkynyl sulfides **8** was performed in the presence of the chiral titanium reagent, and these results are summarized in Table III.

As is observed in the reaction of ketene dithioacetals, the reactivity of alkynyl sulfides is also dependent on the substituent

Table III. Reaction of **2** with Alkynyl Sulfide **8**[a]



2 8 9

entry	R^1	R^2	R^3	Ti/ equiv	yield/ %	opt purity/ % ee
1	CO_2Me (**2a**)	Bu	Me (**8a**)	1.1	92	>98 (**9a**)
2				0.3	55	90
3		Me	Me (**8b**)	1.1	90	>98 (**9b**)
4		cyclohexyl	Me (**8c**)	1.1	84	>98 (**9c**)
5		H	Me (**8d**)	0.1	83	>98 (**9d**)
6	H (**2b**)	Bu	Me (**8a**)	1.1	86	>98 (**9e**)
7				0.1	80	98
8		cyclohexyl	Me (**8c**)	0.3	65	>98 (**9f**)
9	Me (**2c**)	Bu	Me (**8a**)	1.1	0	
10	CO_2Me (**2a**)	Bu	Ph	1.1	0	

[a] Reaction was performed at 0 °C for 12–18 h.

on sulfur. A phenyl sulfide, 1-(phenylthio)-1-hexyne, did not react with **2a** (entry 10), but methyl sulfides **8a–d** reacted smoothly with fumaric and acrylic acid derivatives **2a,b**, yielding cyclobutenes **9**. Trisubstituted cyclobutenes were prepared in good yields and in almost optically pure form with only a catalytic amount of the chiral titanium reagent (entries 5 and 7). For the preparation of tetrasubstituted cyclobutenes, however, an equimolar amount of the chiral titanium was required for the reaction to go to completion. Compared with ketene dimethyl thioacetal **3a**, alkynyl methyl sulfides are less reactive, and crotonoyloxazolidinone **2c** did not react with **8** even in the presence of an equimolar amount of the catalyst (entry 9).

There have been some examples in which cyclobutenes were prepared by thermal [2 + 2] cycloaddition reactions between electron rich alkenes and electron deficient alkynes,[11] but the present method realizes the alternative combination of substrates, i.e., electron rich alkynes and electron deficient alkenes.[17]

The generality of this asymmetric [2 + 2] cycloaddition was investigated further by employing vinyl sulfides which, in the presence of $AlCl_3$, are known to react with labile electron deficient olefins, such as methyl vinyl ketone, forming cyclobutanes.[13b] The reaction of 2-(ethylthio)-1-propene (**10a**) and **2a** in the presence of a catalytic amount of the chiral titanium reagent proceeded smoothly, affording a mixture of diastereomeric [2 + 2] cycloaddition products, **11a** and **12a**, in chemical and optical yields of 51 (>98% ee) and 19% (79% ee), respectively. In this reaction, however, the ene product **13a** was also obtained as a side product in 16% yield.

The reaction of **2a** with an allylsilane-type sulfide, 3-(trimethylsilyl)-2-(methylthio)-1-propene (**10b**), also afforded the cyclobutanes **11b** and **12b** in 54 (>98% ee) and 17% yield, respectively, without any formation of the possible allylation and ene products. The diastereoselectivity of these reactions using 2-(alkylthio)propene derivatives **10a,b** was not as high as desired, but the major isomers **11a,b** were obtained in nearly optically pure forms.

We found that the reaction course of [2 + 2] and ene reactions can be controlled by the substituent on the sulfur. That is, the use of a vinyl sulfide containing a bulkier alkylthio group increases the yield of the ene product, and, especially in the case of aryl vinyl sulfides, the ene reaction was found to predominate.[18] For example, the reaction between **2a** and 2-(phenylthio)propene (**10d**) in the presence of an equimolar amount of the chiral titanium

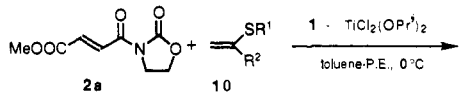
(15) Hayashi, Y.; Otaka, K.; Saito, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2122.

(16) When the optically pure **4a** was subjected to $TiCl_2(OPr^i)_2$, the optical purity of the Michael type product **5a** was 90%. This is because of the retro [2 + 2] cycloaddition reaction accompanied with the ring opening reaction.

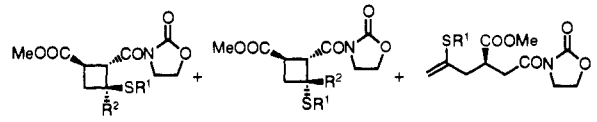
(17) [2 + 2] Cycloaddition using ynamines, see: (a) Eisch, J. J.; Galle, J. E.; Hallenbeck, L. E. *J. Org. Chem.* **1982**, *47*, 1608. (b) Ficini, J.; Krief, A. *Tetrahedron Lett.* **1970**, 1397.

(18) Carbonyl ene reaction using alkenyl sulfides, see: (a) Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967. (b) Tanino, K.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 2165. (c) Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386.

Table IV. Reaction of Acyclic Vinyl Sulfides 10 with 2a[a]



2a 10

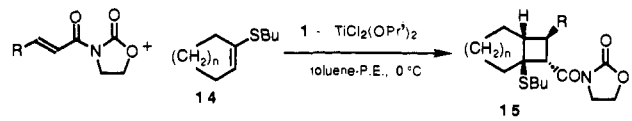


11 12 13 (R² = Me)

R¹	R²	yield/% 11	12	13	opt purity/% ee 11	12
Et	Me (10a)[b]	51 (11a)	19 (12a)	16 (13a)	>98	79
Me	CH_2SiMe_3 (10b)[b]	54 (11b)	17 (12b)		>98	d
Bu'	Me (10c)[c]	13	11	46	d	d
Ph	Me (10d)[c]	0	16 (12d)	83 (13d)[e]		d
p-Tolyl	Me (10e)[c]	0	14	79		d
p-$MeOC_6H_4$	Me (10f)[c]	0	14	72		d

[a] Reaction was performed at 0 °C for 12–18 h. [b] 10 mol % of the chiral titanium reagent was used. [c] An equimolar amount of the chiral titanium reagent was used. [d] Optical purity was not determined. [e] Optical purity of 13d is above 98%.

Table V. Reaction of 2a,b with Cyclic Alkenyl Sulfides 14[a]



14 15

+ the other isomer 16

entry	R	n	Ti/equiv	yield (15+16)/%	15:16	opt purity of 15/% ee
1	CO_2Me (2a)	2 (14a)	1.1	96	>99:1	>98 (15a)
2			0.15	92	>99:1	>98
3		3 (14b)	1.1	97	92:8	>98 (15b)
4		4 (14c)	1.1	89	91:9	>98 (15c)
5	H (2b)	2 (14a)	0.25	74	82:18	>98 (15d)

[a] Reaction was performed at 0 °C for 12–18 h.

reagent afforded the nearly optically pure ene product[19] 13d in 83% yield, together with the [2 + 2] cycloadduct 12d in 16% yield. Since treatment of the [2 + 2] cycloadduct 12d with the chiral titanium reagent under the same reaction conditions resulted in complete recovery of 12d, the ene product 13d is not derived by ring opening of the corresponding cyclobutane 12d. The reaction course ([2 + 2] or ene reaction) is presumably determined mainly not by any electronic factor but rather by the bulkiness of the substituent on the sulfur, because the reactions with various aryl sulfides 10d–f gave the [2 + 2] cycloadducts and the ene products in almost the same ratios (Table IV).

The Lewis acid-catalyzed cycloaddition using cycloalkenyl sulfides exhibited typical behavior, forming bicyclo[n.2.0] compounds with almost complete enantioselectivity. The results of the reactions of fumaric and acrylic acid derivatives 2a,b with cycloalkenyl butyl sulfides 14 are summarized in Table V. The reactivity of 14 is not high as compared with the reaction of acyclic alkenyl sulfides, so that, in some cases, the use of an equimolar amount of the chiral titanium reagent was required to attain a good chemical yield (entries 3 and 4), but diastereoselectivities were generally excellent and no ene product was detected.

Stereochemical Course of the [2 + 2] Cycloaddition of Alkenyl Sulfides. The stereospecificity of the [2 + 2] cycloaddition of alkenyl sulfides was investigated using the reaction of the *E* and *Z* stereoisomers of 2-(methylthio)-1-phenylpropene (17). Both stereoisomers of alkenyl sulfide 17 reacted with 2a in the presence of $TiCl_2(OPr^i)_2$. From the reaction of 2a with (*E*)-17, the cyclobutane derivative 18, in which the initial geometry of the olefinic moiety had been retained, was obtained stereospecifically in 80% yield. On the other hand, when 2a was treated with 1.5 molar equiv of the (*Z*)-alkenyl sulfide ((*Z*)-17:(*E*)-17=95:5) in the presence of $TiCl_2(OPr^i)_2$, three cycloadducts, 18, 19, and 20, were obtained in 13, 31, and 37% yields, respectively, with 19% recovery of the starting material 2a. During this reaction isomerization

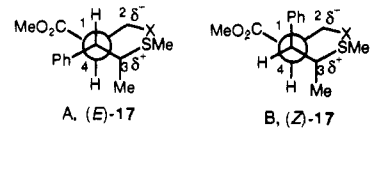
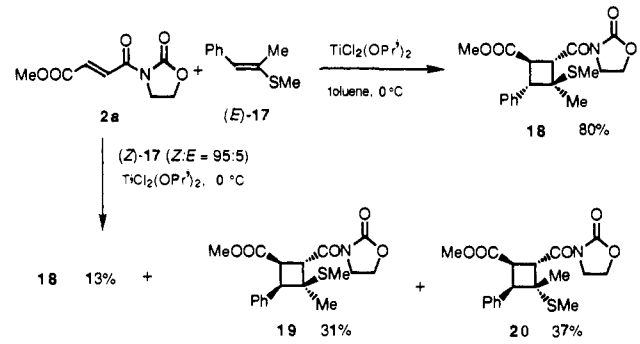


Figure 1.



of the (*Z*)-alkenyl sulfide occurred gradually, and the *Z*:*E* ratio of the recovered alkenyl sulfide 17 was 89:11. Since no reaction took place on treatment of the cycloadduct 19 with $TiCl_2(OPr^i)_2$ under the same reaction conditions, all the products 18, 19, and 20 are kinetic products and no equilibrium exists between these cyclobutane derivatives. The adduct 18 is thought to be formed from the contaminating (*E*)-17. The other two cyclobutanes 19 and 20, consequently, were produced from the (*Z*)-alkenyl sulfide.

Although the reaction of (*E*)-17 proceeded with retention of the configuration of (*E*)-17, the nonstereospecificity in the reaction of (*Z*)-17 indicates a stepwise mechanism for the present cyclobutane-forming reaction.

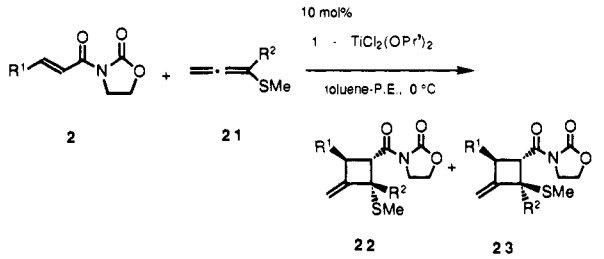
Two reaction pathways have been proposed for the mechanism of the thermal [2 + 2] cycloaddition reaction, one of which involves a zwitterion intermediate and the other a biradical intermediate. A biradical intermediate has been postulated in the [2 + 2] cycloadditions of fluorinated alkenes;[10g] in this case the radical intermediate is particularly stabilized by the fluoro group. For the present Lewis acid-catalyzed [2 + 2] cycloaddition reaction, a zwitterion intermediate, as proposed in the reaction between electron rich and deficient olefins (for example, alkenyl ethers with TCNE),[10c,d] is, by analogy, considered to be the most probable pathway.

Interesting stereoselectivity is observed in the above reaction of 17; namely, the retention of configuration with (*E*)-17 and nonstereoselectivity with (*Z*)-17. This difference is explained by Seebach's *topological rule*.[20] The approach of the donor 17 and the acceptor 2a occurs through the endo-gauche transition state and forms an intermediate A or B after the initial bond formation between C(1) and C(4) as shown in Figure 1. In the reaction of (*E*)-17, the phenyl group at C(4) moves away from the bulky methoxycarbonyl substituent at C(1) at the stage of formation of the C(2)–C(3) bond, making cyclization smooth and stereospecific. On the other hand, in the case of (*Z*)-17, the phenyl and methoxycarbonyl groups are forced to be eclipsed with each other during the cyclization. This steric repulsion prevents smooth cyclization, allowing rotation around the C(3)–C(4) bond.

(19) Asymmetric ene reactions by the use of a chiral catalyst, see refs 9 and 18a and (a) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 2203. (b) Mikani, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

(20) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

Table VI. Asymmetric [2 + 2] Cycloaddition Reaction of **2** and Allenyl Sulfide **21**[a]



entry	R^1	R^2	yield/% 22	yield/% 23	opt purity/% ee 22	opt purity/% ee 23
1	CO_2Me (**2a**)	$SiMe_3$ (**21a**)	quant[b] (**22a**)		>98	
2		$SnMe_3$ (**21b**)	93[b] (**22b**)		96	
3		$SnBu_3$	0	0		
4		CH_2Ph (**21c**)	30 (**22c**)	57	94	>98
5	H (**2b**)	$SiMe_3$ (**21a**)	41 (**22d**)	21	>98	*c*

[a] Reaction was performed at 0 °C for 12–18 h. [b] Other isomer was not detected by ^1H NMR. [c] Optical purity was not determined.

Asymmetric [2 + 2] Cycloaddition between 2 and Allenyl Sulfides 21. [2 + 2] cycloaddition reactions between allenes and ethylene derivatives have frequently been employed for the preparation of methylene cyclobutane derivatives. Most of the addition reactions proceed with photochemical activation,[21] and thermal reactions,[22] including Lewis acid-promoted reactions,[12,23] are restricted to a rather limited number of examples. By introducing an alkylthio group, it was expected that allene compounds could be utilized effectively in the [2 + 2] cycloaddition reaction, and to test this the reactions of allenyl sulfides **21** with **2a,b** were examined in the presence of a catalytic amount of the chiral titanium reagent (Table VI). Allenyl methyl sulfides having an α-trimethylsilyl, a trimethylstannyl, or a benzyl substituent (**21a–c**) reacted with **2a,b** to give the corresponding methylenecyclobutane derivatives **22** and **23** in good chemical yields in nearly optically pure form. The diastereoselectivities are high in the reactions of **2a** with the α-trimethylsilyl or trimethylstannyl allenes **21a,b**, in which these bulky substituents and the oxazolidinylcarbonyl group have the trans geometry in the product[24] (entries 1 and 2). While the α-trimethylstannyl allene **21b** reacted in high yield, the corresponding tributylstannyl analogue did not react with **2a**, presumably because of steric hindrance (entry 3).

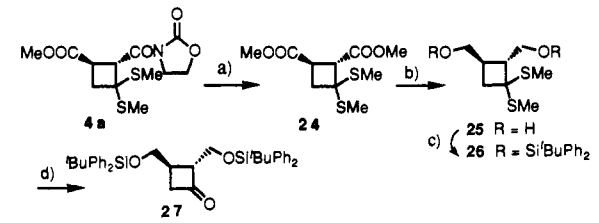
Comparison of the Reactivity of Alkenyl Sulfides, Alkenyl Ethers, and Alkenyl Selenide. Various unsaturated compounds having alkoxy, alkylthio, or alkylseleno groups were tested in the reaction in order to compare their reactivity. None of the vinyl ethers tried (1,1-diethoxyethylene, 2-methoxypropene, and 1-methoxy-1-(trimethylsilyl)-1,2-propadiene) reacted with **2a** in the presence of the chiral titanium reagent. On the other hand, vinyl sulfides, such as ketene dithioacetal **3**, alkynyl sulfide **8**, alkenyl sulfides **10** and **14**, and allenyl sulfide **21**, readily react to afford the [2 + 2] cycloaddition products in good yields. Though 1-(methylthio)-1-hexyne reacted with **2a** in high yield (92%, Table III, entry 1), under the same reaction conditions the corresponding seleno derivative, 1-(methylseleno)-1-hexyne, afforded the cycloadduct in only 35% yield.

Thus, the reactivity of the unsaturated compounds having group VI substituents increases in the order of O ≪ Se < S. The reactivity of the alkenyl sulfides is as follows: ketene dithioacetal > allenyl sulfide > alkenyl sulfide, alkynyl sulfide.[25]

A similar high reactivity of alkenyl sulfides compared to the alkenyl ethers has been observed in the thermal [2 + 2] cycloaddition reactions of TCNE[25a] and 2,2-bis(trifluoromethyl)-ethylene-1,1-dicarbonitrile[10f] in the intramolecular ene reaction[18c] and the intramolecular [4 + 2] cycloaddition of nitrosoalkenes.[26] In order to obtain some insight into the reactivity of alkenyl sulfides and ethers, the FMO energy levels of some model olefins were studied by using the PM3 Hamiltonian in MOPAC Ver. 6.01,[27] and these results are summarized in Table VII. The following features are noteworthy: (1) Alkenyl sulfides have higher HOMO and lower LUMO energies than the corresponding alkenyl ethers. The higher reactivity of alkenyl sulfides as compared with vinyl ethers is attributable to their higher HOMO energies. (2) Comparing the charge populations, it can be seen that for the alkenyl ether, C_β is negative but C_α is positive, whereas both C_α and C_β are negative in sulfides.

Contrary to the rapid reaction of **2** and 1,1-bis(methylthio)-ethylene (**3a**), (*E*)- and (*Z*)-1,2-bis(methylthio)ethylenes and (methylthio)ethylene failed to react with **2**. The low reactivity of these alkenyl sulfides without an α-substituent in spite of their appropriate HOMO and LUMO energies (entries 5, 6, and 7)

Scheme I[a]



[a] (a) $Mg(OMe)_2$, (b) $LiAlH_4$, (c) $^tBuPh_2SiCl$, imidazole, and catalytic DMAP, and (d) $AgNO_3$, NCS.

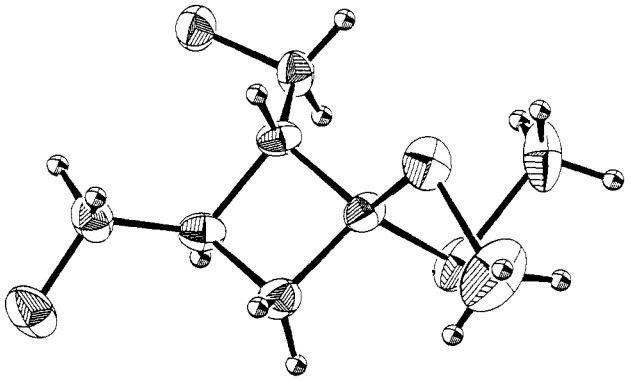


Figure 2. ORTEP drawing of **25** (30% probability level).

(21) (a) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570. (b) Eaton, P. E. *Tetrahedron Lett.* **1964**, 3695. (c) Farwaha, R.; de Mayo, P.; Schauble, J. H.; Toong, Y. C. *J. Org. Chem.* **1985**, *50*, 245. (d) Stensen, W.; Svendsen, J. S.; Hofer, O.; Sydnes, L. K. *Acta Chem. Scan.* **1988**, *B42*, 259 and references cited therein.

(22) Fluorinated allenes with alkenes: (a) Dolbier, W. R., Jr.; Weaver, S. L. *J. Org. Chem.* **1990**, *55*, 711. (b) Dolbier, W. R., Jr.; Burkholder, C. R.; Wicks, G. E.; Palenik, G. J.; Gawron, M. *J. Am. Chem. Soc.* **1985**, *107*, 7183. Reactions with allenes and electron deficient alkenes: (c) Cripps, H. N.; Williams, J. K.; Sharkey, W. H. *J. Am. Chem. Soc.* **1959**, *81*, 2723. (d) Kiefer, E. F.; Okamura, M. Y.; *J. Am. Chem. Soc.* **1968**, *90*, 4187. (e) Baldwin, J. E.; Roy, U. V. *Chem. Commun.* **1969**, 1225. (f) Pasto, D. J.; Yang, S.-H. *J. Am. Chem. Soc.* **1984**, *106*, 152. (g) Pasto, D. J.; Kong, W. *J. Org. Chem.* **1988**, *53*, 4807. Intramolecular reaction of allenyl ethers: (h) Hayakawa, K.; Aso, K.; Shiro, M.; Kanematsu, K. *J. Am. Chem. Soc.* **1989**, *111*, 5312. Intramolecular reaction of allenyl esters: (i) Yoshida, M.; Hidaka, Y.; Nawata, Y.; Rudinski, J. M.; Osawa, E.; Kanematsu, K. *J. Am. Chem. Soc.* **1988**, *110*, 1232.

(23) (a) Lukas, J. H.; Kouwenhoven, A. P.; Baardman, F. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 709. (b) Komiya, Z.; Nishida, S. *J. Org. Chem.* **1983**, *48*, 1500.

(24) The relative stereochemistry of **22a** was determined by X-ray crystallographic analysis.

(25) The reactivities of ketene dithioacetals and alkenyl sulfides in the [2 + 2] cycloaddition reaction of TCNE or (2,2-bis(trifluoromethyl)-ethylene)-1,1-dicarbonitrile have been reported. See ref 10f and (a) Okuyama, T.; Nakada, M.; Toyoshima, K.; Fueno, T. *J. Org. Chem.* **1978**, *43*, 4546. (b) Graf, H.; Huisgen, R. *J. Org. Chem.* **1979**, *44*, 2594.

(26) Denmark, S. E.; Sternberg, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 8277.

(27) MOPAC Ver. 6: Stewart, J. J. P. *QCPE Bull.* **1989**, *10*, 9. Revised as Ver. 6.01 by Tsuneo Hirano, University of Tokyo, for HITAC and UNIX machines, *JCPE Newsletter* **1989**, *10*, 1.

Table VII. MNDO-PM3 Calculation of Unsaturated Compounds Having Group VI Substituents

entry	compound	charge C_α	charge C_β	HOMO/eV	LUMO/eV
1	1,1-bis(methylthio)ethylene (**3a**)	−0.29	−0.18	−8.82	−0.42
2	1-(methylthio)-1-(trimethylsilyl)allene (**21a**)	−0.29	−0.14	−8.35	0.20
3	2-(methylthio)propene	−0.19	−0.20	−8.74	0.28
4	(methylthio)acethylene (**8d**)	−0.35	−0.11	−8.81	0.06
5	(methylthio)ethylene	−0.24	−0.17	−8.77	0.32
6	(*E*)-1,2-bis(methylthio)ethylene	−0.24	−0.24	−8.23	0.12
7	(*Z*)-1,2-bis(methylthio)ethylene	−0.25	−0.25	−8.25	0.11
8	1,1-dimethoxyethylene	0.20	−0.39	−9.26	1.33
9	2-methoxypropene	0.06	−0.31	−9.40	1.20
10	1-methoxy-1-(trimethylsilyl)allene	−0.04	−0.28	−8.86	0.64

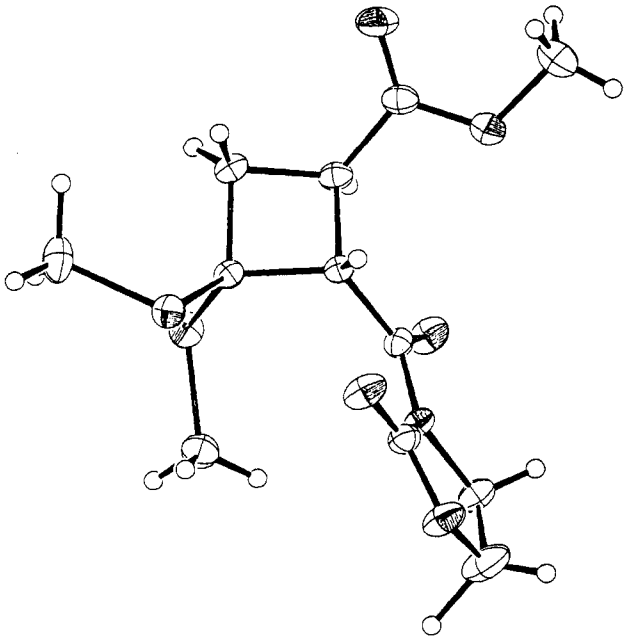


Figure 3. ORTEP drawing of **4a** (30% probability level).

is one piece of evidence for a zwitterionic intermediate; that is, an additional substituent is required for stabilization of the developing cationic center in the zwitterionic intermediate.

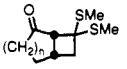
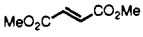
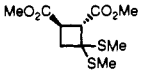
Recent ab initio calculations indicate that in the vapor phase an alkylthio substituent can stabilize an α-cation to the same extent as an alkoxy substituent.[28] Consequently, an alkylthio group increases the HOMO energy and acts as a good electron releasing group, making the whole olefinic moiety negatively charged, and also stabilizes the α-cationic center of the intermediate.

Determination of the Absolute Configurations of the Cycloadducts and Their X-ray Crystallographic Analyses. The structure of the cyclobutane **4a** was assigned chemically by the transformation shown in Scheme I. The IR (1782 cm^{-1}) and ^{13}C-NMR (208.8 ppm) spectra of **27** are in good agreement with the cyclobutanone structure.

An X-ray crystallographic analysis of a single crystal of the diol **25** revealed the absolute configuration to be (1*R*,2*R*), as depicted in Figure 2.[29] The regiochemistry of **4a** was determined by X-ray analysis of racemic **4a**, which gave a crystal more appropriate than the optically pure one (Figure 3).

As reported previously,[30] the cycloadduct between **2b** and ketene dithioacetal prepared with $TiCl_2(OPr^i)_2$ and the (2*S*,3*S*)-diol was transformed to (+)-grandisol. Hence the absolute configuration of the cycloadduct **4b** prepared by employing the (2*R*,3*R*)-diol **1** as an auxiliary was determined to be 1*R*.

Table VIII. Reaction between Electron Deficient Olefins and Ketene Dithioacetal **3a**

entry	electron deficient olefin	product	conditions[a]	time/h	yield/%
					
1	*n* = 1	**28**	A	0.3	25
2	*n* = 2	**29**	A	0.3	65
3	*n* = 3	**30**	A	3	71
4	*n* = 4	**31**	A	0.5	83
5		 **24**	B	1	68
6		 **32**	B	1	78
7		 **33**	B	0.5	69
8		 **34**	B	0.5	88

[a] A, $BF_3{\cdot}OEt_2$ was used in Et_2O; B, $EtAlCl_2$ was used in CH_2Cl_2.

The cyclobutene **9d** derived from **2a** and 1-(methylthio)-acetylene was converted to the cyclobutanone **27** by using the following reagents: (1) $Mg(OMe)_2$, (2) $LiAlH_4$, (3) $^tBuPh_2SiCl$, imidazole, and catalytic DMAP, and (4) $CuCl_2$–CuO.[31] The cyclobutanone thus prepared showed the same optical rotation as that derived from **4a**, indicating that **9d** has the (1*R*,4*R*) configuration.

In the above examples of the [2 + 2] cycloadditions, and also in the asymmetric Diels–Alder[3a–c] and intramolecular ene reactions[9] in which the same chiral titanium reagent and 2-alkenoyl oxazolidin-2-one derivatives **2a–c** are employed, the following generalization concerning the sense of enantioselection can be made. Without exception, the *re* face of the α-carbon in the acrylic acid derivatives **2** is attacked when the (*R*,*R*)-1,4-diol is employed as a chiral auxiliary. Therefore, the same sense of enantioselection is to be expected for all [2 + 2] cycloadducts.

[2 + 2] Cycloaddition Using Achiral Lewis Acid. The scope of the Lewis acid-catalyzed [2 + 2] cycloaddition was further investigated by employing some electron deficient olefins in place of oxazolidinone derivatives **2**. The reaction between 2-cyclohexen-1-one and 1,1-bis(methylthio)ethylene (**3a**), however, was not promoted by the chiral titanium reagent. The choice of a suitable Lewis acid and solvent is essential in order to carry out the reaction efficiently. For example, the reaction with $TiCl_2(OPr^i)_2$, $EtAlCl_2$, $TiCl_4$, $ZrCl_4$, $ZnBr_2$, or trimethylsilyl tri-

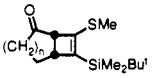
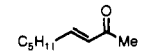
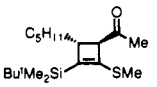
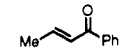
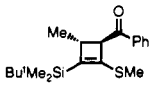
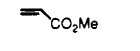
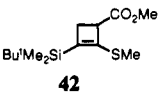
(28) Ösapay, K.; Delhalle, J.; Nsunda, K. M.; Rolli, E.; Houriet, R.; Hevesi, L. *J. Am. Chem. Soc.* **1989**, *111*, 5028.

(29) The absolute configuration was determined by the *R*-factor ratio test. Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.

(30) Narasaka, K.; Kusama, H.; Hayashi, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1471.

(31) Narasaka, K.; Sakashita, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3724.

Table IX. Reaction between Electron Deficient Olefins and Alkenyl Sulfide **35**

entry	electron deficient olefin	product	conditions[a]	time	yield/%
					
1	$n = 1$	**36**	A	16h	47
2	$n = 2$	**37**	B	30 min	83
3	$n = 3$	**38**	B	15 min	74
4	$n = 4$	**39**	B	15 min	64
5		 **40**	C	15 min	71
6		 **41**	C	15 min	68
7		 **42**	D	12 h	80

[a] A, $BF_3{\cdot}OEt_2$ at room temperature; B, $TiCl_4$ at −78 °C; C, $TiCl_4$ at 0 °C; D, $EtAlCl_2$ at room temperature.

fluoromethanesulfonate in CH_2Cl_2 afforded the ring-opened product and/or many unidentified products with only a small amount of the desired [2 + 2] cycloadduct **29**, whereas the use of $BF_3{\cdot}OEt_2$ in Et_2O was found to afford 8,8-bis(methylthio)bicyclo[4.2.0]octan-2-one (**29**) in 65% yield as a single regioisomer.

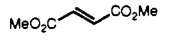
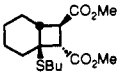
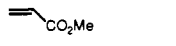
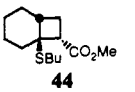
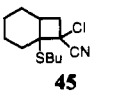
Various cyclic and acyclic enones reacted with ketene dithioacetal **3a**, and these results are summarized in Table VIII. Cyclic enones except for 2-cyclopenten-1-one reacted with **3a** to afford cyclobutanes in good yields by the use of $BF_3{\cdot}OEt_2$ in ether (entries 1–4). On the other hand, $EtAlCl_2$ was found to be a suitable Lewis acid for the reaction of acyclic electron deficient olefins (entries 5–8). A characteristic feature of the Lewis acid-catalyzed [2 + 2] cycloaddition reaction appears to be its regioselectivity. The sense of regioselectivity observed is opposite that of the photochemical reaction in which 1,1-dimethoxyethylene reacts with 2-cyclohexen-1-one to afford 7,7-dimethoxybicyclo[4.2.0]octan-2-one.[21a]

Alkynyl sulfides also react with a variety of electron deficient olefins to give cyclobutenes, but substituents of alkynes have a crucial influence on the product yield. That is, cyclobutenes were obtained in rather low yields in the reaction with (methylthio)-acetylene or 1-(methylthio)-2-(trimethylsilyl)acetylene because these alkynes are unstable under acidic conditions and also readily add to the carbonyl group of the [2 + 2] cycloadducts. On the other hand, 1-(*tert*-butyldimethylsilyl)-2-(methylthio)acetylene (**35**) containing a bulkier substituent reacted with electron deficient olefins in good yields in the presence of $TiCl_4$. Various cyclic and acyclic enones can be employed (Table IX), and even 2-cyclopenten-1-one, which reacted with ketene dimethyl dithioacetal (**3a**) in low yield (Table VIII, entry 1), afforded a synthetically useful bicyclo[3.2.0]heptanone derivative[32] (**36**) in acceptable yield (Table IX, entry 1). Although methyl acrylate gave the addition product in good yield (entry 7), the addition reaction with dimethyl fumarate did not occur because of the steric repulsion between the bulky silyl substituent and the methoxycarbonyl group.

In the reaction of acyclic vinyl sulfides and enones, both ene and [2 + 2] cycloaddition reactions proceeded to give complex mixtures. On the other hand, use of cyclohexenyl sulfide **14a** gave the [2 + 2] cycloaddition products in good yields in the reactions with relatively reactive electrophilic olefins such as dimethyl fumarate, methyl acrylate, and 2-chloroacrylonitrile in the presence of $EtAlCl_2$ in CH_2Cl_2 (Table X). Ring opening of the cycloadduct

(32) Ali, S. M.; Lee, T. V.; Roberts, S. M. *Synthesis* **1977**, 155.

Table X. Reaction between Various Electron Deficient Olefins and Cyclohexenyl Sulfide **14a**

entry	electron deficient olefin	product	yield/% (diastereomer ratio)
1		 **43**	76 (>98:2)
2		 **44**	75 (81:19)
3		 **45**	87 (>98:2)[a]

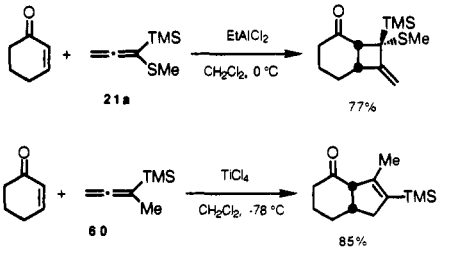
[a] Stereochemistry was not determined.

occurred in the reaction with acyclic α,β-unsaturated ketones such as 3-nonen-2-one and 1-phenyl-2-buten-1-one,[33] and 2-cyclohexen-1-one afforded a complex mixture.

Contrary to the limited success with vinyl sulfides, the [2 + 2] cycloadditions of the allenyl sulfide 1-(methylthio)-1-(trimethylsilyl)-1,2-propadiene (**21a**) showed wide generality. A rather broad range of electron deficient olefins, either cyclic or acyclic, having ketone, ester, or nitrile functionalities, can be employed for the preparation of methylene cyclobutanes (Table XI). But there are still some limitations. For instance, vinyl sulfoxides, nitro olefins, and trisubstituted α,β-enones such as 4-methyl-3-penten-2-one failed to react with **21a**. In the chiral titanium-catalyzed reaction, the α-benzyl-substituted allenyl sulfide **21c** also reacted with **2a**, giving the methylenecyclobutane derivatives in good yield. However, the reaction of **21c** with 2-cyclohexen-1-one resulted in the formation of a complex mixture.

The reaction of the allenyl sulfide **21a** is characterized by the following stereo- and regioselectivity. (1) Generally, high diastereoselectivities are attained. (2) Only the C_α–C_β double bond of the allenyl sulfide **21a** participates in the reaction, and in all cases the other regioisomer is not formed. (3) The photochemical reaction of cyclohexenone and allene gives an 8-methylene derivative as the major product,[21a] but the 7-methylene derivative was selectively obtained by the present reaction between cyclohexenone and **21a**.

α-Methylthioallenyl silane **21a**, which decomposes with the existence of $TiCl_4$, reacts with 2-cyclohexen-1-one in the presence of $EtAlCl_2$ at 0 °C to give only the [2 + 2] cycloadduct. On the other hand, Danheiser reported that the allenyl silane **60** reacts with electron deficient olefins in the presence of a Lewis acid ($TiCl_4$) at −78 °C to afford the [3 + 2] annulation products with migration of the TMS group.[34] [3 + 2] Cycloaddition product



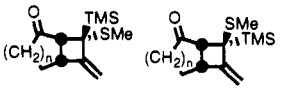
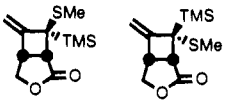
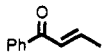
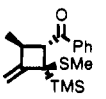
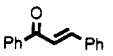
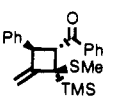
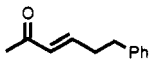
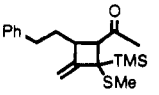
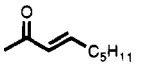
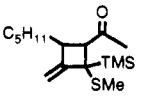
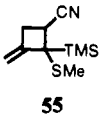
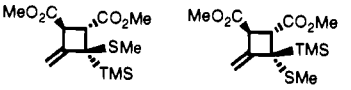
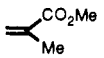
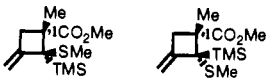
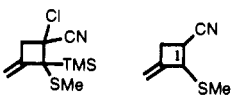
was also obtained by the use of $EtAlCl_2$, though in low yield (yield 9%, 0 °C for 12 h, and then room temperature for 24 h). Accordingly, the reaction course is determined not by the Lewis acid but by the substituent on allene.

Semiempirical MO calculations (PM3)[27] were performed on allene derivatives[35] such as 3-(methylthio)-1,2-butadiene (**61**),

(33) The reaction of 3-nonen-2-one and 1-phenyl-2-buten-1-one with **14a** afforded 4-(2-(butylthio)-1-cyclohexenyl)nonan-2-one and 3-(2-(butylthio)-1-cyclohexenyl)butyrophenone in 58 and 76% yield, respectively.

(34) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935.

Table XI. [2 + 2] Cycloaddition Reaction of **21a** with Electron Deficient Olefins[a]

entry	olefin	time/h	product	yield/%[b]
				
1	$n = 1$	3	**46**	56 (>98:2)
2	$n = 2$	1.8	**47**	77 (>98:2)
3	$n = 3$	5	**48**	70 (81:19)
4	$n = 4$	0.5	**49**	75 (83:17)
5		72	 **50**	54 (91:9)
6		1.75	 **51**	81[c]
7		1.75	 **52**	92[c]
8		16	 **53**	68 (67:33)
9		16	 **54**	80 (69:31)
10		1.75	 **55**	75 (55:45)
11		1.75	 **56**	84 (92:8)
12		1.5	 **57**	91 (85:15)
13		1.75	 **58** **59**	34, 51

[a] Reaction was performed in CH_2Cl_2 using an equimolar amount of $EtAlCl_2$. [b] Figures in parentheses are the diastereomer ratios of the cyclobutanes. [c] Other isomer was not detected.

1-(methylthio)-1-(trimethylsilyl)-1,2-propadiene (**21a**), and 3-(trimethylsilyl)-1,2-butadiene (**60**). The energies of the two highest occupied (HO) MOs and two lowest unoccupied (LU) MOs and their respective coefficients are summarized in Figure 4. The electron populations at each carbon of the allene derivatives are shown in Table XII. From a comparison of these quantites for the allenyl sulfide **61** and the allenyl silane **60**, we can quantitatively explain the effect of alkylthio and silyl substituents. (1) A methylthio-substituted allene (**61**) has a larger electron population on C_β rather than on C_γ, whereas a silyl substituent increases the electron population on C_γ. (2) For the allenyl sulfide **61**, the MO coefficient at C_β of the HOMO is much larger than that at C_γ. However, in the allenyl silane **60**, the energy gap of the HOMO and the next HOMO (NHOMO) is quite small by comparison to **61** and the NHOMO coefficient at C_γ is large. This suggests that both C_β and C_γ exhibit almost the same reactivity. The combination of the relative charge populations and the values of the HOMO or NHOMO coefficients together with the steric effect of the substituents at C_α leads to the conclusion that the reactivity of C_β is higher than that of C_γ in the allenyl sulfide **61**, while C_γ is supposed to be more reactive in the allenyl silane **60**.

Table XII. Electron Population at C_α, C_β, and C_γ of the Allene Derivatives

allene	electron population		
	C_α	C_β	C_γ
61	−0.13	−0.22	−0.05
21a	−0.29	−0.14	−0.11
60	−0.22	−0.12	−0.14

For the allene derivative **21a** having both methylthio and trimethylsilyl substituents, the effect of the alkylthio group apparently

(35) MNDO calculations on some of the allenes have been reported: see ref 22i and (a) Yasuda, M.; Harano, K.; Kanematsu, K. *J. Org. Chem.* **1980**, *45*, 659. (b) Conrads, M.; Mattay, J. *Chem. Ber.* **1991**, *124*, 867.

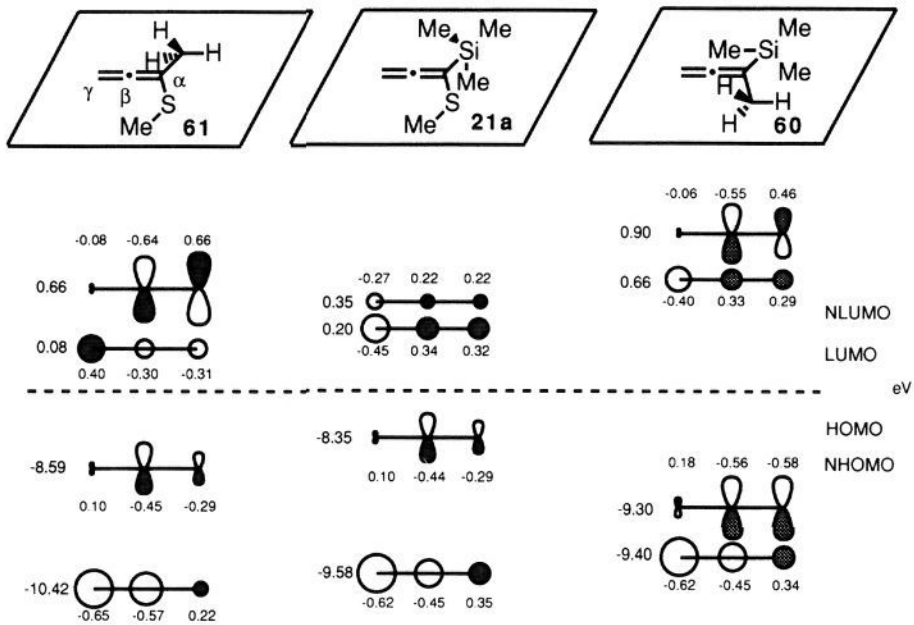


Figure 4. Energy levels and coefficients of the frontier orbitals.

predominates over that of the silyl group. Namely, the electron population at C_β is larger than that at C_γ, and the coefficient of the HOMO at C_β is much larger than that at C_γ. The reactivity at C_β is, consequently, much higher than that at C_γ, resulting in the exclusive formation of [2 + 2] cycloadducts.

Conclusion

The general Lewis acid-catalyzed [2 + 2] cycloaddition reaction, which has hitherto remained an unexplored area, can be achieved by employing various alkenyl sulfides. The current study also realized an asymmetric [2 + 2] cycloaddition reaction catalyzed by a chiral titanium reagent, which provides an efficient synthetic method for the preparation of a variety of cyclobutane derivatives in high optical purity.[36]

Experimental Section

General. NMR spectra were recorded on a Hitachi R24B (60 MHz) or Bruker AM500 (500 MHz) spectrometer. $CDCl_3$ was used as solvent unless otherwise noted. IR spectra were recorded on a Horiba FT-300S spectrometer. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-D300 mass spectrometer operating at 70 eV. The optical rotations were recorded on a JASCO DIP-370 polarimeter. Melting points and boiling points are uncorrected.

Column chromatography was conducted on silica gel (E. Merck, 7734, 70–230 mesh), and preparative thin-layer chromatography (TLC) was carried out on silica gel (Wakogel B-5F).

Dichloromethane was distilled from P_2O_5 and then from CaH_2 and dried over MS 4A. Toluene and petroleum ether were distilled and dried over MS 4A. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium diphenylketyl. (2*R*,3*R*)-1,1,4,4-Tetraphenyl-2,3-((1-phenylethylidene)dioxy)-1,4-butanediol (**1**) was prepared according to a published procedure.[3a] Methyl (*E*)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate (**2a**),[3a] 3-acryloyl-1,3-oxazolidin-2-one (**2b**),[30] and 3-crotonoyl-1,3-oxazolidin-2-one (**2c**)[3a] were prepared according to the literature procedures.

Syntheses of Alkenyl Sulfides 3, 8, 10, 14, 17, 21, and 35. According to the literature, 1,1-bis(methylthio)ethylene (**3a**),[37] 2-methylene-1,3-dithiolane (**3c**),[38] 2-methylene-1,3-dithiane (**3d**),[38] (methylthio)acetylene (**8d**),[39] 2-(phenylthio)propene (**10d**),[40] 1-(butylthio)-1-cyclohexene (**14a**),[41] 1-(butylthio)-1-cycloheptene (**14b**),[41] and 1-(butylthio)-1-cyclooctene (**14c**)[41] were prepared. (*E*)-2-(Methylthio)-1-phenyl-1-propene ((*E*)-**17**) and (*Z*)-2-(methylthio)-1-phenyl-1-propene ((*Z*)-**17**) were prepared according to the literature procedure[42] and purified by TLC before use. 1,1-Bis(ethylthio)ethylene (**3b**) and 1,1-bis(methylthio)-1-propene (**3e**) were prepared by the same procedure as that for **3a**.[37] 2-(Ethylthio)-1-propene (**10a**), 2-(*tert*-butylthio)propene (**10c**), 2-(tolylthio)propene (**10e**), and 2-(*p*-methoxyphenyl)propene (**10f**) were prepared by the same procedure as that for **10d**.[40]

1-(Methylthio)-1-hexyne (8a). To a THF solution (120 mL) of 1-hexyne (13.34 g, 0.162 mol) was added a hexane solution of *n*-BuLi (1.57 M, 103 mL, 0.162 mol) at 0 °C. After the reaction mixture was stirred for 2 h at 0 °C, a THF solution (25 mL) of dimethyl disulfide (15.33 g, 0.163 mol) was added, and the reaction mixture was stirred for 2 h. The reaction was quenched with water, and the organic materials were extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude materials were purified by distillation to give the title compound **8a** (17.16 g): yield 83%; bp 83 °C/29 mmHg; IR (neat) 1465, 1432, 1313, 977 cm^{-1}; ^1H NMR (500 MHz) δ = 0.86 (3 H, t, J = 7.3 Hz), 1.32–1.40 (2 H, m), 1.42–1.48 (2 H, m), 2.24 (2 H, t, J = 7.1 Hz), 2.30 (3 H, s); ^{13}C NMR (125 MHz) δ = 13.5, 19.2, 19.9, 21.8, 30.8, 69.7, 93.1; HRMS calcd for $C_7H_{12}S$ 128.0660, found 128.0653.

1-(Methylthio)-2-cyclohexylacetylene (8c). **8c** was prepared by the same method from cyclohexylacetylene as was **8a**, 20 mmol scale: yield 28%; bp 110 °C/15 mmHg; IR (neat) 1448, 978 cm^{-1}; ^1H NMR (500 MHz) δ = 1.21–1.30 (2 H, m), 1.36–1.52 (3 H, m), 1.62–1.69 (2 H, m), 1.73–1.79 (2 H, m), 2.32 (3 H, s), 2.39–2.47 (1 H, m), 2.62 (1 H, d, J = 9.3 Hz); ^{13}C NMR (125 MHz) δ = 19.5, 24.8, 25.8, 30.3, 32.9, 69.8, 97.2; HRMS calcd for $C_9H_{14}S$ 154.0817, found 154.0803.

1-(Methylthio)-1-propyne was prepared by the isomerization of 3-(methylthio)-1-propyne by the modified method of the literature.[43]

3-(Methylthio)-1-propyne. To 3-chloro-1-propyne (79.7 g) were added an aqueous solution of MeSNa (15%, 500 mL) and a few drops of trioctylmethylammonium chloride, and the mixture was stirred for 3 h vigorously. The organic materials were extracted with pentane (1 L), and the organic phase was washed with brine and dried over Na_2SO_4. After distillation of the solvent, the title compound was purified by distillation, giving 60.3 g: yield 65%; bp 66–69 °C/170 mmHg (lit.[44] bp 67 °C/165 mmHg); ^1H NMR (60 MHz, CCl_4) δ = 2.1 (1 H, t, J = 2.4 Hz), 2.2 (3 H, s), 3.1 (2 H, d, J = 2.4 Hz).

(36) Synthetic applications of the asymmetric [2 + 2] cycloaddition reaction, see: (a) Carbocyclic oxetanocin-A and -G: Ichikawa, Y.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1919. (b) (+)-Grandisol, see ref 30.

(37) Kaya, R.; Beller, N. R. *J. Org. Chem.* **1981**, *46*, 196.

(38) Okuyama, T. *Tetrahedron Lett.* **1982**, *23*, 2665.

(39) Brandsma, L.; Wijers, H. E.; Jonker, M. C. *Recl. Trav. Chim.* **1964**, *83*, 208.

(40) Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967.

(41) Labiad, B.; Villemin, D. *Synthesis* **1989**, 143.

(42) Takai, K.; Sato, M.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 108.

(43) Bos, H. J. T.; Boleij, J. *Recl. Trav. Chim.* **1969**, *88*, 465.

(44) Mantione, R.; Alves, A.; Montijn, P. P.; Wildschut, G. A.; Bos, H. J. T.; Brandsma, L. *Recl. Trav. Chim.* **1970**, *89*, 97.

1-(Methylthio)-1-propyne (8b). To an ether solution (150 mL) of 3-(methylthio)-1-propyne (60.3 g) was added *t*-BuOK (4.7 g) at 0 °C, and the mixture was stirred at 0 °C for 3 h. The reaction was quenched with pH 7 phosphate buffer, and the organic materials were extracted with pentane and dried over Na_2SO_4. After distillation of the solvent, **8b** was isolated by distillation (51.2 g): yield 85%; bp 41 °C/49 mmHg (lit.[43] bp 40 °C/35 mmHg); ^1H NMR (60 MHz, CCl_4) δ = 1.9 (3 H, s), 2.1 (3 H, s).

2-(Methylthio)-3-(trimethylsilyl)-1-propene (10b). To a THF–HMPA (80 mL and 5 mL) solution of (methylthio)ethylene (2.22 g, 30 mmol) was added dropwise a hexane solution (19.9 mL) of *t*-BuLi (1.6 M, 30 mmol) at −78 °C, and the reaction mixture was stirred for 1 h at that temperature. To a THF suspension (40 mL) of NaI (6.7 g) was added a THF solution (40 mL) of Me_3SiCH_2Cl (3.50 g, 29 mmol) at room temperature, and the mixture was stirred for 4 h and then cooled to −78 °C. The prepared solution of 1-(methylthio)vinyllithium was added dropwise to the silylating reagent. The temperature of the reaction mixture was raised gradually to 0 °C over 6 h, and the reaction was quenched with pH 7 phosphate buffer. The organic materials were extracted with Et_2O two times, and the combined Et_2O extracts were washed with brine three times and dried over K_2CO_3. After distillation of the solvent, the title compound was purified by distillation (2.36 g): yield 49%; bp 170–174 °C; IR (neat) 1589, 1421, 1250 cm^{-1}; ^1H NMR (500 MHz) δ = 0.04 (9 H, s), 1.73 (2 H, s), 2.20 (3 H, s), 4.43 (1 H, s), 4.75 (1 H, s); ^{13}C NMR (125 MHz) δ = −1.5, 15.1, 28.2, 101.1, 144.4; HRMS calcd for $C_7H_{16}SiS$ 160.0743, found 160.0742.

1-(Methylthio)-1-(trimethylsilyl)-1,2-propadiene (21a). **21a** was prepared by the same method as that used for the preparation of 1-(phenylthio)-1-(trimethylsilyl)-1,2-propadiene.[45] To a THF solution (20 mL) of diisopropylamine (1.23 g, 12.2 mmol) was added *n*-BuLi (12.2 mmol, 1 M hexane solution) dropwise at 0 °C, and the mixture was stirred for 10 min. To this reaction mixture was added a THF solution (5 mL) of 1-(methylthio)-1-propyne (1.0 g, 11.6 mmol) at −78 °C, and after the mixture was stirred for 30 min, a THF solution (5 mL) of chlorotrimethylsilane (1.38 g, 12.7 mmol) was added. After the mixture was stirred at −78 °C for 1 h and then at 0 °C for 1 h, the reaction was quenched with pH 7 phosphate buffer. The organic materials were extracted with Et_2O, and the extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude materials were purified by distillation: yield 81%; bp 80 °C/35 mmHg; IR (neat) 1922 cm^{-1}; ^1H NMR (500 MHz) δ = 0.16 (9 H, s), 2.15 (3 H, s), 4.69 (2 H, s); ^{13}C NMR (125 MHz) δ = −1.7, 15.1, 75.6, 95.1, 203.7; HRMS calcd for $C_7H_{14}SiS$ 158.0586, found 158.0588.

1-(Methylthio)-1-(trimethylstannyl)-1,2-propadiene (21b). **21b** was prepared by the same method as that used for **21a**: yield 72%; bp 150 °C/27 mmHg (bulb to bulb distillation); IR (neat) 1916 cm^{-1}; ^1H NMR (500 MHz) δ = 0.26 (9 H, s), 2.19 (3 H, s), 4.57 (2 H, s); ^{13}C NMR (125 MHz) δ = −8.8, 15.7, 72.9, 89.9, 201.0; HRMS calcd for $C_7H_{14}SSn$ 245.9839, found 245.9791.

3-(Methylthio)-4-phenyl-1,2-butadiene (21c). **21c** was prepared by the same method as that used for **21a**: yield 88%; bp 130 °C/0.5 mmHg (bulb to bulb distillation); IR (neat) 1944 cm^{-1}; ^1H NMR (500 MHz) δ = 2.17 (3 H, s), 3.55 (2 H, s), 5.03 (2 H, s), 7.25–7.38 (5 H, m); HRMS calcd for $C_{11}H_{12}S$ 176.0661, found 176.0654.

1-(*tert*-Butyldimethylsilyl)-2-(methylthio)acetylene (35). To a THF solution (60 mL) of *tert*-butylethynyldimethylsilane (6.90 g, 49.2 mmol) was added an equimolar amount of *n*-BuLi at −78 °C. The mixture was stirred at that temperature for 30 min, and methyl thiocyanate (3.7 mL, 54.0 mmol) was added dropwise. After the mixture was stirred at −78 °C for 5 h, the reaction was quenched with pH 7 phosphate buffer. The organic materials were extracted with Et_2O, and the organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, **35** was purified by distillation (7.42 g): yield 81%; bp 99 °C/29 mmHg; IR (neat) 2094 cm^{-1}; ^1H NMR (500 MHz) δ = 0.07 (6 H, s), 0.90 (9 H, s), 2.37 (3 H, s); ^{13}C NMR (125 MHz) δ = −4.3, 16.7, 19.4, 25.1, 96.6, 97.8; HRMS calcd for $C_9H_{18}SSi$ 186.0899, found 186.0886.

1-(Methylseleno)-1-hexyne. To a THF solution (30 mL) of 1-hexyne (3.28 g, 40.0 mmol) was added a hexane solution of *n*-BuLi (1.60 M, 25 mL) at 0 °C. After the reaction mixture was stirred for 2 h at 0 °C, a THF solution (30 mL) of dimethyl diselenide (7.52 g, 40.0 mmol) was added to the reaction mixture, which then was stirred for 4 h. The reaction was quenched with water, and the organic materials were extracted with ether. The organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude materials were purified by distillation to give the title compound (5.88 g): yield 84%; bp 100 °C/42 mmHg; IR (neat) 2179, 1460, 1425, 1269, 914 cm^{-1}; ^1H NMR (500 MHz) δ = 0.87 (3 H, t, J = 7.4 Hz), 1.33–1.41 (2 H, m), 1.43–1.50 (2 H, m), 2.20 (3 H, s), 2.28 (2 H, t, J = 6.9 Hz); ^{13}C NMR (125 MHz) δ = 9.0, 13.4, 19.6, 21.7, 30.8, 59.1, 99.0; HRMS calcd for $C_7H_{12}Se$ 176.0105, found 176.0094.

Asymmetric [2 + 2] Cycloaddition between 2 and the Ketene Dithioacetal 3a (Table II, entry 1). The chiral titanium reagent was prepared by mixing $TiCl_2(OPr^i)_2$ (125 mg, 0.53 mmol) and the chiral diol **1** (305 mg, 0.58 mmol) in toluene (5 mL) at room temperature for 30 min with stirring. To the reaction vessel containing MS 4A (powder, 100 mg) were added successively a part of the solution of the above chiral titanium reagent (0.5 mL, 0.053 mmol), toluene, (1.5 mL) and petroleum ether (2.0 mL). The mixture was cooled to 0 °C, at which point (*E*)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate (**2a**, 107 mg, 0.54 mmol) and a petroleum ether solution (1.5 mL) of 1,1-bis(methylthio)ethylene (**3a**) (115 mg, 0.96 mmol) were added. After the mixture was stirred for 30 min at 0 °C (vigorous stirring is essential), the reaction was quenched with pH 7 phosphate buffer and inorganic materials were removed by filtration. The organic materials were extracted with ethyl acetate, and the extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by TLC (hexane:ethyl acetate = 1:1) to afford the mixture of **4a** and **5a** (164.5 mg, 98%, **4a**:**5a** = 98:2). The ratio of **4a**:**5a** was determined by 500-MHz ^1H NMR.

The optical purities of all the [2 + 2] cycloadducts were determined by analyzing the 500-MHz ^1H NMR of the (+)-MTPA [MTPA = α-methoxy-trifluoromethylphenylacetyl] ester[46] prepared from the [2 + 2] cycloadduct isolated by chromatography, unless otherwise noted. The [2 + 2] cycloadducts were converted to the (+)-MTPA esters by the following procedure: (1) $Mg(OMe)_2$, (2) $LiAlH_4$, and (3) (+)-MTPA-Cl, pyridine, catalytic DMAP. See the experimental procedure for the preparation of **25** from **4a** as a general procedure of the first and second steps (vide infra). The experimental procedure of the third step is as follows: To a pyridine solution (2 mL) of the diol **25** (5.0 mg) were added 3 drops of (+)-MTPA-Cl and a catalytic amount of 4-(dimethylamino)pyridine at room temperature. After the mixture was stirred for 12 h, the reaction was quenched with saturated NH_4Cl solution and the organic materials were extracted with Et_2O. The organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by TLC (hexane:ethyl acetate = 10:1) to afford the bis-MTPA ester quantitatively.

Spectral data, physical properties, and the determined optical purities of the cycloadducts **4a**,**b**,**c** are as follows.

Methyl (1*R*,2*R*)-3,3-Bis(methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)-carbonyl)cyclobutanecarboxylate (4a). **4a** was obtained as a mixture of **4a** and **5a** (**4a**:**5a**=98:2).

Determination of the Optical Purity of 4a. **4a** was converted to the bis-(+)-MTPA ester of **25**. Two sets of two singlet signals of the methylthio groups were observed in the NMR spectrum of the bis-(+)-MTPA ester derived from the racemic sample (1.85, 1.85, 1.91, and 1.97 ppm). A pair of very small signals (1.85, 1.91 ppm) (1%) was observed in the bis-(+)-MTPA ester of the reaction product **4a** prepared by the chiral catalyst.

Chemically and enantiomerically pure **4a** was obtained by recrystallization from benzene–hexane: mp 66.0–67.5 °C; IR (KBr, disk) 1780, 1730, 1690 cm^{-1}; ^1H NMR (500 MHz) δ = 2.01 (3 H, s), 2.10 (3 H, s), 2.54 (1 H, dd, J = 9.9, 12.3 Hz), 2.70 (1 H, dd, J = 7.9, 12.3 Hz), 3.86 (1 H, ddd, J = 7.9, 7.9, 9.9 Hz), 3.71 (3 H, s), 4.02 (1 H, ddd, J = 6.4, 8.9, 11.0 Hz), 4.12 (1 H, ddd, J = 7.6, 9.3, 11.0 Hz), 4.39–4.47 (2 H, m), 5.01 (1 H, d, J = 7.9 Hz); ^{13}C NMR (125 MHz) δ = 12.8, 12.8, 34.0, 36.5, 42.6, 51.5, 52.0, 58.8, 62.1, 153.0, 166.4, 173.0; $[\alpha]^{23}_D$ +11.1° (*c* 0.99, CH_2Cl_2), >98% ee. Anal. Calcd for $C_{12}H_{17}NO_5S_2$: C, 45.13; H, 5.36; N, 4.38; S, 20.07. Found: C, 44.99; H, 5.31; N, 4.37; S, 19.99.

(*R*)-3-(2,2-Bis(methylthio)-1-cyclobutanecarbonyl)-1,3-oxazolidin-2-one (4b). **4b** was obtained as a mixture of **4b** and 3-[5,5-bis(methylthio)-4-pentenoyl]-1,3-oxazolidin-2-one (**5b**) (**4b**, 80%; **4b**:**5b**=90:10).

Determination of the Optical Purity of 4b. Signals of the two methylthio groups were observed at 1.89, 1.92, 1.92, and 1.95 ppm in the spectrum of the (+)-MTPA ester prepared from the racemic sample, and the ratio of the integration of the signals at 1.89 and 1.95 ppm in the spectrum of the (+)-MTPA ester prepared from the optically active product **4b** is 94:6.

Chemically and enantiomerically pure **4b** was obtained by recrystallization from benzene–hexane: mp 90.5–92.0 °C; IR (KBr, disk) 1780, 1690 cm^{-1}; ^1H NMR (500 MHz) δ = 2.00 (3 H, s), 2.12 (3 H, s), 2.25–2.31 (1 H, m), 2.32–2.38 (1 H, m), 2.42–2.47 (1 H, m), 2.53–2.60 (1 H, m), 3.98–4.09 (2 H, m), 4.41 (2 H, t, J = 8.1 Hz), 4.61–4.65 (1 H, m); ^{13}C NMR (125 MHz) δ = 12.4, 12.7, 18.8, 33.6, 42.6, 49.5, 61.6,

(45) (a) Pearson, W. H.; Lin, K.-C.; Poon, Y.-F. *J. Org. Chem.* **1989**, *54*, 5814. (b) Tanaka, J.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 51.

(46) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

62.0, 153.0, 170.5; $[\alpha]^{26}_D$ +59.4° (*c* 1.17, CH_2Cl_2), >98% ee. Anal. Calcd for $C_{10}H_{15}NO_3S_2$: C, 46.00; H, 5.78; N, 5.36; S, 24.53. Found: C, 45.88; H, 5.69; N, 5.36; S, 24.92.

(1*R*,4*R*)-3-(2,2-Bis(methylthio)-4-methyl-1-cyclobutanecarbonyl)-1,3-oxazolidin-2-one (4c). Determination of the Optical Purity of 4c. Signals of the methoxy group appeared at 3.54 (d, *J* = 0.9 Hz) and 3.56 (d, *J* = 1.1 Hz) ppm in the spectrum of the (+)-MTPA ester derived from the racemic sample. The ratio of the integration of these signals in the spectrum of the (+)-MTPA ester derived from the optically active product **4c** is 90:10.

4c: IR (neat) 1775, 1690 cm^{-1}; ^1H NMR (500 MHz) δ = 1.18 (3 H, d, *J* = 6.8 Hz), 1.99 (3 H, s), 2.07 (3 H, s), 2.08 (1 H, dd, *J* = 8.7, 11.9 Hz), 2.41 (1 H, dd, *J* = 8.9, 11.9 Hz), 3.01–3.13 (1 H, m), 4.00 (1 H, ddd, *J* = 6.3, 8.9, 11.1 Hz), 4.09 (1 H, ddd, *J* = 7.8, 9.4, 11.1 Hz), 4.37–4.45 (2 H, m), 4.48 (1 H, d, *J* = 8.4 Hz); ^{13}C NMR (125 MHz) δ = 12.8, 12.9, 20.1, 28.7, 40.8, 42.8, 55.0, 58.6, 61.9, 153.2, 169.7; $[\alpha]^{24}_D$ +15.1° (*c* 1.07, CH_2Cl_2), 80% ee; HRMS calcd for $C_{11}H_{17}NO_3S$ 275.0651, found 275.0613.

Methyl (1*R*,2*R*,4*S*)-3,3-Bis(methylthio)-4-methyl-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)cyclobutanecarboxylate (6) and Methyl (1*R*,2*R*,4*R*)-3,3-Bis(methylthio)-4-methyl-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)cyclobutanecarboxylate (7). Determination of the Optical Purities of 6 and 7. Signals of the bis(methylthio) groups appeared in the spectrum prepared from the racemic sample for **6** at 1.043, 1.057 ppm and 1.048, 1.062 ppm and for **7** at 1.077, 1.092 ppm and 1.092, 1.106 ppm. The ratios of the integration of these signals in the spectrum of the bis-(+)-MTPA esters derived from the optically active products **6** and **7** are 92:8 and 10:90, respectively.

6 and **7** were obtained as a mixture (**6**:**7** = 74:26): IR (neat) 1776, 1733, 1693, 1438, 1213 cm^{-1}; ^1H NMR (500 MHz) δ = 1.25 (3 H × 0.26, d, *J* = 7.2 Hz), 1.28 (3 H × 0.76, d, *J* = 6.9 Hz), 1.96 (3 H × 0.26, s), 1.99 (3 H × 0.76, s), 2.00 (3 H × 0.26, s), 2.12 (3 H × 0.76, s), 2.73–2.80 (1 H × 0.26, m), 3.00 (1 H × 0.76, dq, J_d = 9.8 Hz, J_q = 6.9 Hz), 3.46 (1 H × 0.76, t, *J* = 9.8 Hz), 3.48 (1 H × 0.26, s), 3.94–4.00 (1 H, m), 4.07–4.13 (1 H, m), 4.37–4.46 (2 H, m), 4.96 (1 H × 0.76, d, *J* = 9.8 Hz), 5.04 (1 H × 0.26, dd, *J* = 0.7, 8.8 Hz); ^{13}C NMR (125 MHz) **6** δ = 12.3, 12.6, 15.8, 41.4, 42.8, 45.3, 49.1, 51.9, 62.0, 63.8, 153.0, 166.2, 172.8; **7** δ = 12.5, 13.2, 13.3, 39.4, 42.7, 43.1, 47.8, 51.7, 61.9, 85.1, 152.9, 166.9, 171.3. Anal. Calcd for $C_{13}H_{19}NO_5S_2$: C, 46.82; H, 5.74; N, 4.20; S, 19.23. Found: C, 46.43; H, 5.68; N, 4.16; S, 19.12. Stereochemistry was determined by NOESY; see supplementary material.

Ring-Opening Reaction of 4a. To a CH_2Cl_2 solution (2 mL) of $TiCl_2(OPr^i)_2$ (77 mg) was added a CH_2Cl_2 solution (2 mL) of the optically pure **4a** (53 mg, 0.16 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. The reaction was quenched with pH 7 phosphate buffer, and the inorganic materials were filtered off. The organic materials were extracted with CH_2Cl_2, and the extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed in vacuo, the crude materials were purified by TLC (hexane:ethyl acetate = 1:1) to afford **5a** in 96% yield. The optical purity of **5a** was 90% ee, which was determined by analyzing the 500-MHz ^1H NMR of the corresponding bis-(+)-MTPA ester; vinyl protons appeared at 5.45 (d, *J* = 9.4 Hz) and 5.48 (d, *J* = 9.4 Hz) ppm in the bis-(+)-MTPA ester prepared from the racemic sample, and the ratio of the integration of these signals in the spectrum of the bis-(+)-MTPA ester prepared from the optically active product is 5:95. **5a**: IR (neat) 1790, 1740, 1705 cm^{-1}; ^1H NMR (500 MHz) δ = 2.24 (3 H, s), 2.30 (3 H, s), 3.08 (1 H, dd, *J* = 5.5, 18.1 Hz), 3.45 (1 H, dd, *J* = 8.8, 18.1 Hz), 3.67 (3 H, s), 3.97 (2 H, t, *J* = 8.5 Hz), 4.33 (1 H, ddd, *J* = 5.5, 8.8, 9.6 Hz), 4.38 (2 H, t, *J* = 8.5 Hz), 5.67 (1 H, d, *J* = 9.6 Hz); ^{13}C NMR (125 MHz) δ = 16.5, 17.1, 37.7, 42.1, 42.3, 52.3, 62.2, 126.3, 138.0, 153.5, 170.6, 173.1; $[\alpha]^{21}_D$ +102.5° (*c* 1.00, CH_2Cl_2), 90% ee; HRMS calcd for $C_{12}H_{17}NO_5S_2$ 319.0549, found 319.0465.

Asymmetric [2 + 2] Cycloaddition between 2 and Alkynyl Sulfide 8 (Table III). The experimental procedure using a catalytic amount of the chiral titanium reagent was same as that of the reaction between **2** and the ketene dithioacetal **3a** (Table II). Following is the procedure in the case of an equimolar amount of the chiral titanium reagent (Table III, entry 1).

To a toluene solution (2 mL) of the chiral titanium reagent, which was prepared from $TiCl_2(OPr^i)_2$ (97 mg, 0.41 mmol) and the chiral diol **1** (244 mg, 0.46 mmol) at room temperature for 30 min, were added MS 4A (powder, 100 mg), **2a** (73.3 mg, 0.368 mmol), and petroleum ether (3 mL) at 0 °C. A petroleum ether solution (1.5 mL) of **8a** (108.4 mg, 0.85 mmol) was then added, and the mixture was stirred for 15 h at 0 °C. The reaction was quenched by pH 7 phosphate buffer, and inorganic materials were removed by filtration. The organic materials were extracted with ethyl acetate, and the extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by TLC (hexane:ethyl acetate = 1:1) to afford **9a** (110 mg, 92%).

Spectral data and physical properties of the cycloadducts **9** are as follows. Following are also listed the chemical shifts of the (+)-MTPA ester, which were used for the determination of the optical purity.

Methyl (1*S*,4*R*)-2-Butyl-3-(methylthio)-4-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-2-cyclobutenecarboxylate (9a). Separated Signal of the Bis-(+)-MTPA Ester. Signals of the methylthio group of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 2.06 and 2.08 ppm, and only a signal at 2.06 ppm was observed in the spectrum of the compound prepared from chromatographically isolated **9a**.

9a: IR (neat) 1781, 1727, 1691, 1681 cm^{-1}; ^1H NMR (500 MHz) δ = 0.90 (3 H, t, *J* = 7.3 Hz), 1.24–1.49 (4 H, m), 2.12–2.30 (2 H, m), 2.28 (3 H, s), 3.61 (1 H, d, *J* = 1.5 Hz), 3.72 (3 H, s), 4.05 (2 H, t, *J* = 8.2 Hz), 4.45 (2 H, t, *J* = 8.2 Hz), 4.84 (1 H, d, *J* = 1.5 Hz); ^{13}C NMR (125 MHz) δ = 13.6, 15.2, 22.3, 27.7, 28.5, 42.5, 47.6, 47.7, 51.9, 62.3, 133.2, 147.3, 153.2, 170.6, 171.4; $[\alpha]^{27}_D$ −127.0° (*c* 0.77, CH_2Cl_2), >98% ee; HRMS calcd for $C_{15}H_{21}NO_5S$ 327.1141, found 327.1136.

Methyl (1*S*,4*R*)-2-Methyl-3-(methylthio)-4-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-2-cyclobutenecarboxylate (9b). Separated Signal of the Bis-(+)-MTPA Ester. Signals of the methylthio group of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 2.11 and 2.13 ppm, and only a signal at 2.11 ppm was observed in the spectrum of the compound prepared from chromatographically isolated **9b**.

9b: IR (neat) 1792, 1774, 1736 cm^{-1}; ^1H NMR (500 MHz) δ = 1.83 (3 H, dd, *J* = 1.7, 1.7 Hz), 2.30 (3 H, s), 3.63 (1 H, br s), 3.73 (3 H, s), 4.05 (2 H, t, *J* = 7.7 Hz), 4.45 (2 H, t, *J* = 7.7 Hz), 4.88 (1 H, dq, J_d = 1.7 Hz, J_q = 1.7 Hz); ^{13}C NMR (125 MHz) δ = 13.5, 15.2, 42.5, 48.2, 48.9, 52.0, 62.3, 133.7, 143.5, 153.3, 170.7, 171.2; $[\alpha]^{24}_D$ −143.1° (*c* 1.03, CH_2Cl_2), >98% ee; HRMS calcd for $C_{12}H_{15}NO_5S$ 285.0672, found 285.0676.

Methyl (1*S*,4*R*)-2-Cyclohexyl-3-(methylthio)-4-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-2-cyclobutenecarboxylate (9c). The optical purity of **9c** was determined by analyzing the 125-MHz ^{13}C NMR of the corresponding bis-(+)-MTPA ester. Signals of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 149.7 and 149.9 ppm, and only a signal at 149.7 ppm was observed in the spectrum of the compound prepared from the reaction product **9c**.

9c: IR (neat) 1781, 1733, 1691 cm^{-1}; ^1H NMR (500 MHz) δ = 1.05–1.35 (5 H, m), 1.54–1.73 (5 H, m), 2.19 (3 H, s), 2.18–2.25 (1 H, m), 3.46 (1 H, br s), 3.66 (3 H, s), 3.97 (2 H, t, *J* = 8.1 Hz), 4.38 (2 H, t, *J* = 8.1 Hz), 4.67 (1 H, dd, *J* = 1.5, 1.5 Hz); ^{13}C NMR (125 MHz) δ = 15.1, 25.6, 25.8, 29.7, 29.8, 29.9, 38.2, 42.5, 47.0, 47.1, 52.0, 62.4, 131.4, 150.1, 153.3, 170.7, 172.0; $[\alpha]^{24}_D$ −63.0° (*c* 1.26, CH_2Cl_2), >95% ee; HRMS calcd for $C_{17}H_{23}NO_5S$ 353.1298, found 353.1322.

Methyl (1*S*,4*R*)-3-(Methylthio)-4-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-2-cyclobutenecarboxylate (9d). Separated Signal of the Bis-(+)-MTPA Ester. Signals of the methylthio group and the vinyl proton of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 2.17, 2.18 ppm and 5.65, 5.68 ppm, respectively, and only signals at 2.17 and 5.65 ppm were observed in the spectrum of the compound from chromatographically isolated **9d**.

9d: IR (neat) 1779, 1731, 1693 cm^{-1}; ^1H NMR (500 MHz) δ = 2.28 (3 H, s), 3.72 (3 H, s), 3.88 (1 H, dd, *J* = 1.6, 1.6 Hz), 4.05 (2 H, t, *J* = 5.6 Hz), 4.47 (2 H, t, *J* = 5.6 Hz), 4.88 (1 H, d, *J* = 1.6 Hz), 5.92 (1 H, d, *J* = 1.6 Hz); ^{13}C NMR (125 MHz) δ = 13.6, 42.3, 45.7, 50.6, 52.0, 62.5, 123.9, 144.1, 153.2, 169.4, 171.7; $[\alpha]^{24}_D$ −192.6° (*c* 1.02, CH_2Cl_2), >98% ee; HRMS calcd for $C_{11}H_{13}NO_5S$ 271.0515, found 271.0491.

(*R*)-3-(3-Butyl-2-(methylthio)cyclobut-2-enecarbonyl)-1,3-oxazolidin-2-one (9e). Separated Signal of the (+)-MTPA Ester. Signals of the methylthio group of the (+)-MTPA ester prepared from the racemic sample appeared at 2.13 and 2.15 ppm, and only a signal at 2.13 ppm was observed in the spectrum of the compound prepared from chromatographically isolated **9e**.

9e: IR (neat) 1780, 1690 cm^{-1}; ^1H NMR (500 MHz) δ = 0.91 (3 H, t, *J* = 7.3 Hz), 1.31–1.48 (4 H, m), 2.17–2.20 (2 H, m), 2.23 (3 H, s), 2.50 (1 H, dd, *J* = 1.6, 12.7 Hz), 2.76 (1 H, dd, *J* = 4.9, 12.7 Hz), 4.05 (2 H, t, *J* = 8.0 Hz), 4.44 (2 H, t, *J* = 8.0 Hz), 4.71–4.74 (1 H, m); ^{13}C NMR (125 MHz) δ = 13.7, 15.5, 22.3, 28.4, 28.7, 33.5, 42.5, 44.5, 62.2, 128.9, 150.9, 153.4, 172.7; $[\alpha]^{24}_D$ +78.6° (*c* 1.03, CH_2Cl_2), >98% ee; HRMS calcd for $C_{13}H_{19}NO_3S$ 269.1087, found 269.1094.

(*R*)-3-(3-Cyclohexyl-2-(methylthio)cyclobut-3-enecarbonyl)-1,3-oxazolidin-2-one (9f). Separated signals of the (+)-MTPA ester prepared from the racemic sample appeared at 2.45 (1 H, dd, *J* = 4.5, 13.7 Hz) and 2.48 (1 H, dd, *J* = 4.5, 12.9 Hz) ppm, and only a signal at 2.48 ppm was observed in the spectrum of the compound prepared from chromatographically isolated **9f**.

9f: IR (neat) 1787, 1683 cm^{-1}; ^1H NMR (500 MHz) δ = 1.10–1.30 (5 H, m), 1.36–1.75 (5 H, m), 2.18 (3 H, s), 2.21–2.30 (1 H, m), 2.42

(1 H, dd, J = 1.6, 13.5 Hz), 2.71 (1 H, dd, J = 4.8, 13.5 Hz), 4.01 (2 H, t, J = 8.0 Hz), 4.40 (2 H, t, J = 8.0 Hz), 4.64 (1 H, ddd, J = 1.6, 1.6, 4.8 Hz); ^{13}C NMR (125 MHz) δ = 15.7, 25.6, 25.7, 25.9, 30.2, 30.3, 31.6, 38.0, 42.6, 43.9, 62.2, 126.7, 153.4, 154.4, 172.9; $[\alpha]^{23}_{D}$ +90.6° (c 0.65, CH_2Cl_2), >98% ee; HRMS calcd for $C_{15}H_{21}NO_3S$ 295.1243, found 295.1209.

Asymmetric [2 + 2] Cycloaddition and Ene Reactions between 2a and Acyclic Alkenyl Sulfide 10 (Table IV). The reaction procedure of **10a** and **10b** was the same as that shown in Table II, in which 10 mol % of the chiral titanium reagent was used. The reaction procedure of **10c–f** was the same as that of Table III, in which an equimolar amount of the chiral titanium reagent was used. Spectral data and physical properties of the cycloadducts **11a**, **12a**, **11b**, **12d**, and **13d** are as follows. Following are also listed the chemical shifts of the (+)-MTPA ester, which were used for the determination of the optical purity.

Methyl (1*R*,2*R*,3*S*)-3-(Ethylthio)-3-methyl-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)cyclobutanecarboxylate (11a) and Methyl (1*R*,2*R*,3*R*)-3-(Ethylthio)-3-methyl-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)cyclobutanecarboxylate (12a). Separated singlet methyl signals of the bis-(+)-MTPA esters prepared from the racemic samples appeared at 1.325 and 1.359 ppm (**11a**) and 1.267 and 1.320 ppm (**12a**), respectively.

11a and **12a** were obtained as a mixture (**11a**:**12a**=72:28): IR (neat) 1782, 1732, 1691, 1479 cm^{-1}; ^{1}H NMR (500 MHz) δ = 1.19 (3 H × 0.28, t, J = 7.4 Hz), 1.25 (3 H × 0.72, t, J = 7.4 Hz), 1.33 (3 H × 0.72, s), 1.69 (3 H × 0.28, s), 2.17 (1 H × 0.72, dd, J = 1.0, 9.3 Hz), 2.33 (1 H × 0.28, dd, J = 3.8, 8.3 Hz), 2.45–2.85 (3 H, m), 3.62 (1 H × 0.72, ddd, J = 9.3, 9.3, 9.3 Hz), 3.66 (3 H, s), 3.89 (1 H × 0.28, dt, J_d = 10.2 Hz, J_t = 8.3 Hz), 3.95–4.12 (2 H, m), 4.37–4.46 (2 H, m), 4.60 (1 H × 0.28, d, J = 8.3 Hz), 5.00 (1 H × 0.72, d, J = 9.3 Hz); ^{13}C NMR (125 MHz) **11a** δ = 13.9, 22.8, 23.3, 32.7, 36.0, 42.6, 47.5, 47.6, 51.9, 61.8, 153.0, 169.6, 173.3, **12a** δ = 14.4, 22.8, 29.6, 32.7, 36.6, 42.6, 48.6, 51.7, 51.9, 62.2, 153.2, 169.4, 174.1; HRMS calcd for $C_{13}H_{19}NO_5S$ 301.0985, found 301.0956. Stereochemistry was determined by NOESY; see supplementary material.

Methyl (1*R*,2*R*,3*S*)-3-(Methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-3-(trimethylsilylmethyl)cyclobutanecarboxylate (11b). Separated Signal of the Bis-(+)-MTPA Ester. Separated signals of the methylthio and the trimethylsilyl groups of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 1.63, 1.75 ppm, and –0.02, 0.03 ppm, respectively.

11b: IR (neat) 1780, 1730, 1685 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.04 (9 H, s), 0.73 (1 H, dd, J = 1.4, 14.7 Hz), 1.34 (1 H, d, J = 14.7 Hz), 2.19 (3 H, s), 2.22 (1 H, ddd, J = 0.6, 9.9, 12.0 Hz), 2.51 (1 H, ddd, J = 1.3, 8.7, 12.0 Hz), 3.53 (1 H, ddd, J = 8.3, 8.7, 9.9 Hz), 3.65 (3 H, s), 3.95 (1 H, ddd, J = 6.2, 8.3, 11.0 Hz), 4.01–4.07 (1 H, m), 4.36–4.40 (2 H, m), 5.02 (1 H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz) δ = 0.6, 12.0, 24.6, 32.6, 34.3, 42.8, 49.2, 51.7, 52.0, 61.7, 153.2, 170.3, 173.7; $[\alpha]^{16}_{D}$ +22.8° (c 0.78, CH_2Cl_2), >98% ee; HRMS calcd for $C_{15}H_{25}NO_5SiS$ 359.1223, found 359.1203. Stereochemistry was determined by NOESY; see supplementary material.

Methyl (1*R*,2*R*,3*R*)-3-methyl-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-3-(phenylthio)cyclobutanecarboxylate (12d): IR (neat) 1782, 1732, 1691, 1438, 1332 cm^{-1}; ^{1}H NMR (500 MHz) δ = 1.71 (3 H, s), 2.20 (H, dd, J = 9.1, 12.0 Hz), 2.41 (H, dd, J = 9.9, 12.0 Hz), 3.65 (3 H, s), 3.87–4.01 (3 H, m), 4.23 (1 H, ddd, J = 7.8, 9.1, 9.1 Hz), 4.34 (1 H, ddd, J = 6.0, 9.1, 9.1 Hz), 4.60 (H, d, J = 10.0 Hz), 7.26–7.33 (3 H, m), 7.43–7.46 (2 H, m); ^{13}C NMR (125 MHz) δ = 31.2, 33.1, 36.8, 42.5, 51.4, 51.6, 52.0, 62.1, 128.6, 128.7, 131.5, 136.1, 153.1, 169.0, 174.0; HRMS calcd for $C_{17}H_{19}NO_5S$ 349.0985, found 349.1006. Stereochemistry was determined by NOESY; see supplementary material.

(3*R*)-3-(3-(Metboxycarbonyl)-5-(phenylthio)-5-hexenoyl)-1,3-oxazolidin-2-one (13d). Determination of the Optical Purity of 13d. Vinyl protons of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 4.84, 4.86, 4.95, and 5.00 ppm as singlets, and only signals at 4.84 and 5.00 ppm were observed in the spectrum of the bis-(+)-MTPA ester prepared from the optically active product **13d**.

13d: IR (neat) 1780, 1734, 1697, 1390 cm^{-1}; ^{1}H NMR (500 MHz) δ = 2.40 (1 H, dd, J = 8.5, 14.3 Hz), 2.62 (1 H, dd, J = 6.1, 14.3 Hz), 3.06 (1 H, dd, J = 3.5, 17.9 Hz), 3.21–3.28 (1 H, m), 3.32 (1 H, dd, J = 9.7, 17.9 Hz), 3.63 (3 H, s), 3.92–3.98 (2 H, m), 4.36 (2 H, t, J = 8.1 Hz), 4.92 (1 H, s), 5.16 (1 H, s), 7.26–7.32 (3 H, m), 7.38–7.41 (2 H, m); ^{13}C NMR (125 MHz) δ = 36.0, 38.0, 39.4, 42.2, 51.8, 62.1, 115.6, 128.0, 129.2, 132.1, 133.3, 142.4, 153.4, 171.4, 174.6; $[\alpha]^{23}_{D}$ +25.2° (c 0.76, CH_2Cl_2), >98% ee; HRMS calcd for $C_{17}H_{19}NO_5S$ 349.0985, found 349.0985.

Asymmetric [2 + 2] Cycloaddition between 2 and Cyclic Alkenyl Sulfide 14 (Table V). The reaction procedure was the same as that of Table II. Spectral data, physical properties, and the determination of the optical purities of the cycloadducts **15** and **16** are as follows.

Methyl (1*S*,6*R*,7*R*,8*R*)-1-(Butylthio)-8-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)bicyclo[4.2.0]octane-7-carboxylate (15a). Determination of the Optical Purity of 15a. Signals of the methylene protons (CH_2OMTPA) of bis-(+)-MTPA ester prepared from the racemic sample appeared at 4.03 (1 H, dd, J = 8.8, 11.5 Hz), 4.17–4.24 (3 H, m), 4.23–4.27 (2 H, m), 4.32 (1 H, dd, J = 6.4, 11.5 Hz), and 4.35 (1 H, dd, J = 6.4, 11.7 Hz) ppm. Only signals at 4.03, 4.23–4.27, and 4.32 ppm were observed in the spectrum of the bis-(+)-MTPA ester prepared from the optically active product **15a**.

15a: IR (neat) 1783, 1733, 1689 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.87 (3 H, t, J = 2.9 Hz), 1.30–1.62 (11 H, m), 1.91–1.98 (1 H, m), 2.47 (1 H, ddd, J = 6.1, 8.4, 11.2 Hz), 2.66 (1 H, dd, J = 4.9, 10.0 Hz), 2.72 (1 H, ddd, J = 6.4, 8.4, 11.2 Hz), 3.34 (1 H, dd, J = 10.0, 10.0 Hz), 3.62 (3 H, s), 3.88 (1 H, ddd, J = 5.0, 9.0, 11.0 Hz), 4.00 (1 H, ddd, J = 9.0, 9.0, 9.0 Hz), 4.12–4.40 (2 H, m), 4.77 (1 H, d, J = 10.0 Hz); ^{13}C NMR (125 MHz) δ = 13.5, 20.9, 21.0, 22.1, 22.5, 27.7, 29.0, 31.0, 36.6, 39.5, 42.7, 45.6, 51.2, 51.7, 61.8, 153.0, 169.7, 173.0; $[\alpha]^{25}_{D}$ +77.2° (c 1.13, CH_2Cl_2), >98% ee; HRMS calcd for $C_{18}H_{27}NO_5S$ 369.1611, found 369.1629. Stereochemistry was determined by NOESY; see supplementary material.

Methyl (1*S*,7*R*,8*R*,9*R*)-1-(Butylthio)-9-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)bicyclo[5.2.0]nonane-8-carboxylate (15b). 15b was obtained as a mixture of **15b** and the other isomer **16b** (**15b**:**16b** = 92:8).

Determination of the Optical Purity of 15b. Signals of one of the methylene protons (CH_2OMTPA) of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 4.33 (1 H, dd, J = 6.5, 10.9 Hz) and 4.40 (1 H, dd, J = 7.3, 10.9 Hz) ppm. Only the signal at 4.33 ppm was observed in the spectrum of the bis-(+)-MTPA ester prepared from the optically active product **15b**.

The recrystallization from benzene–hexane afforded the diastereomerically pure **15b**: mp 92.0–93.0 °C; IR (KBr disk) 1776, 1733, 1693, 1394 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.93 (3 H, t, J = 7.3 Hz), 1.20–1.75 (10 H, m), 1.80–1.96 (2 H, m), 2.00–2.15 (2 H, m), 2.58–2.62 (1 H, m), 2.67–2.75 (2 H, m), 3.22 (1 H, t, J = 8.5 Hz), 3.68 (3 H, s), 3.95–4.00 (1 H, m), 4.05–4.10 (1 H, m), 4.16–4.45 (2 H, m), 4.99 (1 H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz) δ = 13.8, 22.4, 24.7, 25.7, 28.0, 30.7, 31.4, 31.6, 33.7, 39.9, 42.9, 46.1, 46.8, 51.9, 56.3, 61.6, 153.0, 170.6, 173.6; $[\alpha]^{29}_{D}$ +36.0° (c 1.12, CH_2Cl_2), >98% ee. Anal. Calcd for $C_{19}H_{29}NO_5S$: C, 59.51; H, 7.62; N, 3.65; S, 8.35. Found: C, 59.15; H, 7.52; N, 3.92; S, 8.84.

Methyl (1*S*,8*R*,9*R*,10*R*)-1-(Butylthio)-10-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)bicyclo[6.2.0]decane-9-carboxylate (15c). 15c was obtained as a mixture of **15c** and the other isomer **16c** (**15c**:**16c** = 91:9).

Determination of the Optical Purity of 15c. Signals of the methylene protons (CH_2OMTPA) of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 3.90 (1 H, dd, J = 5.1, 12.5 Hz), 4.14–4.21 (2 H, m), 4.42 (1 H, dd, J = 9.4, 11.3 Hz), 4.30 (1 H, dd, J = 6.2, 11.3 Hz), 4.34 (1 H, dd, J = 7.0, 10.5 Hz), 4.38 (1 H, dd, J = 6.2, 14.8 Hz), 4.46 (1 H, dd, J = 6.2, 10.5 Hz) ppm. Only signals at 4.14–4.21 (2 H), 4.34 (1 H), 4.38 (1 H) were observed in the spectrum of the bis-(+)-MTPA ester prepared from the optically active product **15c**.

15c: IR (neat) 1782, 1731, 1689, 1386 cm^{-1}; ^{1}H NMR of **15c** (500 MHz) δ = 0.93 (3 H, t, J = 7.4 Hz), 1.15–1.93 (15 H, m), 2.05–2.13 (1 H, m), 2.51 (1 H, ddd, J = 2.6, 8.6, 11.3 Hz), 2.66 (1 H, dt, J_d = 11.0 Hz, J_t = 7.3 Hz), 2.77 (1 H, dt, J_d = 11.0 Hz, J_t = 7.3 Hz), 3.12 (1 H, dd, J = 8.6, 8.6 Hz), 3.69 (3 H, s), 3.97 (1 H, ddd, J = 5.6, 8.8, 11.0 Hz), 4.05–4.15 (1 H, m), 4.35–4.45 (2 H, m), 5.07 (1 H, d, J = 8.6 Hz); ^{13}C NMR (125 MHz) **15c** δ = 13.6, 22.2, 24.5, 25.0, 25.1, 25.3, 26.7, 27.7, 29.0, 30.8, 39.3, 42.8, 46.2, 47.0, 51.8, 55.4, 61.7, 152.9, 170.6, 173.4, **16c** δ = 13.5, 22.3, 24.9, 25.3, 25.5, 25.8, 28.0, 30.5, 31.0, 31.2, 39.8, 46.2, 46.6, 47.4, 51.5, 57.6, 61.8, 153.2, 169.7, 172.0. Anal. Calcd for $C_{20}H_{31}NO_5S$: C, 60.43; H, 7.86; N, 3.52; S, 8.07. Found: C, 60.13; H, 7.73; N, 3.68; S, 7.88. Stereochemistry was determined by NOESY; see supplementary material.

(1*S*,6*R*,8*R*)-3-(1-(Butylthio)bicyclo[4.2.0]octane-8-carbonyl)-1,3-oxazolidin-2-one (15d). 15d was obtained as a mixture of **15d** and the other isomer **16d** (**15d**:**16d** = 87:13).

Determination of the Optical Purity of 15d. Signals of the methoxy group of the (+)-MTPA ester prepared from the racemic sample appeared at 3.54 (3 H, d, J = 0.9 Hz) and 3.56 (3 H, d, J = 0.9 Hz) ppm, and only a signal at 3.54 ppm was observed in the spectrum of the bis-(+)-MTPA ester prepared from the optically active product **15d**.

15d: IR (neat) 1782, 1691, 1384 cm^{-1}; ^{1}H NMR of **15d** (500 MHz) δ = 0.92 (3 H, t, J = 7.3 Hz), 1.30–1.62 (11 H, m), 1.92 (1 H, ddd, J = 8.1, 8.1, 9.8 Hz), 2.09–2.18 (1 H, m), 2.28 (1 H, ddd, J = 9.8, 10.3, 10.3 Hz), 2.50–2.56 (2 H, m), 2.70 (1 H, ddd, J = 6.6, 8.3, 11.4 Hz), 3.92–4.05 (2 H, m), 4.35–4.43 (2 H, m), 4.48 (1 H, dd, J = 8.1, 10.3 Hz); distinguishable peaks of **16d** δ = 0.82 (3 H, t, J = 7.1 Hz), 1.97 (1 H, ddd, J = 7.9, 11.7, 11.7 Hz), 2.28–2.32 (1 H, m), 2.37 (1 H, ddd, J = 4.4, 9.0, 9.0 Hz), 4.02 (1 H, ddd, J = 1.6, 7.8, 7.8 Hz), 4.11 (1 H, dd,

J = 2.3, 7.9 Hz); ^{13}C NMR (125 MHz) **15d** δ = 13.7, 21.1, 21.2, 22.1, 22.3, 23.4, 27.8, 28.8, 31.5, 35.6, 42.8, 43.9, 53.9, 61.8, 153.3, 171.5, **16d** δ = 13.6, 20.8, 21.1, 21.8, 22.0, 24.3, 28.2, 31.7, 34.7, 37.6, 42.6, 50.0, 52.4, 61.9, 153.5, 172.5; HRMS calcd for $C_{16}H_{25}NO_3S$ 311.1556, found 311.1517. Stereochemistry was determined by NOESY; see supplementary material.

Reaction between 2a and (*E*)-17. The reaction vessel was wrapped in aluminum foil in order to shade it from light. To a toluene solution (2 mL) of $TiCl_2(OPr^i)_2$ (63.4 mg, 0.268 mmol) were added **2a** (49.7 mg, 0.25 mmol) and a toluene solution (1.5 mL) of (*E*)-**17** (60.0 mg, 0.365 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 24 h. The reaction was quenched with aqueous $NaHCO_3$, and inorganic materials were filtered off. The organic materials were extracted with ethyl acetate. The combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo, and the crude materials were purified by TLC (hexane:ethyl acetate = 1:1) to afford **18** (72.4 mg, 80%), and the starting material **2a** was recovered in 20% yield.

Reaction between 2a and (*Z*)-17. The reaction vessel was wrapped in aluminum foil in order to shade it from light. To a toluene solution (2 mL) of $TiCl_2(OPr^i)_2$ (55.2 mg, 0.233 mmol) were added **2a** (42.5 mg, 0.21 mmol) and a toluene solution (1.5 mL) of **17** (*Z*:*E* = 95:5, 60.0 mg, 0.365 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 24 h. Quenching of the reaction was performed by the same procedure in the reaction of (*E*)-**17**, and the purification by TLC (benzene:ether = 1:1) afforded **19** (24.6 mg, 31%), a mixture of **18** and **20** (38.8 mg, 50%, **18**:**20** = 27:73), the starting material **2a** (8 mg, 19%), and alkenyl sulfide **17** (32.0 mg, *E*:*Z* = 89:11).

Spectral data and physical properties of the cycloadducts **18**, **19**, and **20** are as follows.

Methyl (1*R,2*R**,3*S**,4*S**)-3-methyl-3-(methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-4-phenylcyclobutanecarboxylate (18)**: IR (neat) 1780, 1731, 1689, 1385, 1263 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ = 1.10 (3 H, s), 2.35 (3 H, s), 2.95–3.05 (4 H, m), 3.31 (3 H, s), 4.21 (1 H, d, J = 10.5 Hz), 4.35 (1 H, dd, J = 9.8, 10.5 Hz), 5.55 (1 H, d, J = 9.8 Hz), 7.16–7.21 (3 H, m), 7.38–7.40 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 11.5, 18.6, 36.3, 42.8, 43.6, 46.5, 52.1, 52.7, 62.0, 127.0, 127.2, 128.2, 136.2, 153.2, 169.5, 172.7; HRMS calcd for $C_{18}H_{21}NO_5S$ 363.1141, found 363.1150. Stereochemistry was determined by NOESY; see supplementary material.

Methyl (1*R,2*R**,3*S**,4*R**)-3-methyl-3-(methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-4-phenylcyclobutanecarboxylate (19)**: IR (neat) 1780, 1730, 1687, 1384 cm^{-1}; ^{1}H NMR (500 MHz) δ = 1.50 (3 H, s), 1.63 (3 H, s), 3.36 (3 H, s), 3.62 (1 H, d, J = 10.8 Hz), 4.02 (1 H, ddd, J = 6.1, 8.8, 10.9 Hz), 4.10 (1 H, ddd, J = 7.8, 9.4, 10.9 Hz), 4.22 (1 H, dd, J = 10.0, 10.8 Hz), 4.40–4.49 (2 H, m), 5.29 (1 H, d, J = 10.0 Hz), 7.25–7.45 (5 H, m); ^{13}C NMR (125 MHz) δ = 11.3, 25.0, 39.1, 42.7, 46.6, 51.2, 51.6, 53.9, 61.9, 127.3, 127.7, 129.5, 137.0, 153.0, 170.2, 171.4; HRMS calcd for $C_{18}H_{21}NO_5S$ 363.1141, found 363.1168. Stereochemistry was determined by NOESY; see supplementary material.

Methyl (1*R,2*R**,3*R**,4*R**)-3-Methyl-3-(methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-4-phenylcyclobutanecarboxylate (20).** **20** was obtained as a mixture of **20** and **18** (**20**:**18** = 73:27): IR (neat) 1776, 1730, 1689, 1387 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ = 1.58 (3 H, s), 1.79 (3 H, s), 3.00–3.15 (2 H, m), 3.16 (3 H, s), 3.94 (1 H, d, J = 10.9 Hz), 4.86 (1 H, dd, J = 9.5, 10.9 Hz), 5.52 (1 H, d, J = 9.5 Hz), 7.00–7.28 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 11.7, 24.1, 39.3, 42.6, 49.3, 51.6, 52.2, 52.8, 62.2, 127.2, 128.0, 128.3, 137.0, 153.2, 169.6, 172.5; HRMS calcd for $C_{18}H_{21}NO_5S$ 363.1141, found 363.1143. Stereochemistry was determined by NOESY; see supplementary material.

Asymmetric [2 + 2] Cycloaddition between 2 and Allenyl Sulfide 21. The reaction procedure was the same as that of Table II. Spectral data and physical properties of the cycloadducts **22** and **23** are as follows.

Methyl (1*R*,2*R*,3*S*)-4-Methylene-3-(methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-3-(trimethylsilyl)cyclobutanecarboxylate (22a). Determination of the Optical Purity of 22a. Singlet signals of the methylthio group of the bis-(+)-MTPA ester prepared from the racemic sample appeared at 1.98 and 2.00 ppm, and only a signal at 2.00 ppm was observed in the spectrum of the bis-(+)-MTPA ester prepared from the optically active product **22a**.

22a: IR (neat) 1778, 1728, 1685, 1392, 1303 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.09 (9 H, s), 1.98 (3 H, s), 3.66 (3 H, s), 4.04 (2 H, t, J = 8.0 Hz), 4.39 (2 H, t, J = 8.0 Hz), 4.40–4.42 (1 H, m), 4.87 (1 H, d, J = 3.0 Hz), 5.03 (1 H, d, J = 7.0 Hz), 5.44 (1 H, d, J = 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = −3.3, 12.2, 42.8, 45.5, 45.6, 49.1, 52.0, 62.1, 112.3, 143.2, 153.0, 170.3, 171.5; $[\alpha]^{23}_D$ +33.1° (c 0.99, CH_2Cl_2), >98% ee; HRMS calcd for $C_{15}H_{23}NO_5SiS$ 357.1067, found 357.1088. Anal. Calcd for $C_{15}H_{23}NO_5SiS$: C, 50.40; H, 6.48; N, 3.92; S, 8.97. Found: C, 50.22; H, 6.44; N, 4.13; S, 9.21. Relative stereochemistry was determined by the X-ray crystallographic analysis, and details of the diffraction analysis along with tables of atomic coordinates and structural parameters have been submitted as supplementary material.

Methyl (1*R*,2*R*,3*S*)-4-Methylene-3-(methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)-3-(trimethylstannyl)cyclobutanecarboxylate (22b). Determination of the Optical Purity of 22b. **22b** reacted with $Mg(OMe)_2$ in THF to afford dimethyl 3-methyl-4-(methylthio)-3-cyclobutene-1,2-dicarboxylate with the isomerization of the double bond, which was the product of the reaction between **9b** and $Mg(OMe)_2$. The optical purity was determined by the same method as that of **9b**.

22b: IR (neat) 1780, 1734, 1689, 1654 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ = 0.52 (9 H, s), 2.03 (3 H, s), 3.00–3.11 (2 H, m), 3.18–3.23 (1 H, m), 3.29 (1 H, ddd, J = 6.7, 9.7, 9.7 Hz), 3.37 (3 H, s), 4.85 (1 H, ddd, J = 2.9, 2.9, 6.4 Hz), 4.97 (1 H, dd, J = 0.7, 2.9 Hz), 5.00 (1 H, d, J = 6.4 Hz), 5.43 (1 H, dd, J = 0.7, 2.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = −8.2, 11.4, 42.6, 45.4, 45.7, 48.6, 52.0, 62.3, 109.1, 146.2, 153.1, 170.9, 171.5; $[\alpha]^{23}_D$ +48.3° (c 1.05, CH_2Cl_2), >98% ee; HRMS calcd for $C_{15}H_{23}NO_5SSn$ 449.0320, found 449.0315. Anal. Calcd for $C_{15}H_{23}NO_5SSn$: C, 40.20; H, 5.17; N, 3.13; S, 7.16. Found: C, 40.25; H, 5.02; N, 3.27; S, 7.39. Stereochemistry was determined by NOESY; see supplementary material.

Methyl (1*R*,2*R*,3*S*)-3-Benzyl-4-methylene-3-(methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)cyclobutanecarboxylate (22c) and Methyl (1*R*,2*R*,3*R*)-3-Benzyl-4-methylene-3-(methylthio)-2-((2-oxo-1,3-oxazolidin-3-yl)carbonyl)cyclobutanecarboxylate (23c). Separated Signals of the Bis-(+)-MTPA Ester. Signals of the methylthio group of the bis-(+)-MTPA ester prepared from the racemic sample **22c** appeared at 2.01 and 2.04 ppm. Signals of vinyl protons of the bis-(+)-MTPA ester prepared from the racemic sample **23c** appeared at 4.90, 4.91, 4.95, and 4.96 ppm.

22c was obtained as a mixture of **22c** and the other isomer **23c** (**22c**:**23c** = 34:66): IR (neat) 1781, 1734, 1687, 1434 cm^{-1}; ^{1}H NMR (500 MHz) δ = 2.02 (3 H × 0.66, s), 2.10 (3 H × 0.34, s), 2.79 (1 H × 0.34, d, J = 14.1 Hz), 3.12 (1 H × 0.66, d, J = 13.4 Hz), 3.22 (1 H × 0.34, d, J = 14.1 Hz), 3.38 (1 H × 0.66, d, J = 13.4 Hz), 3.43 (3 H × 0.66, s), 3.74 (3 H × 0.34, s), 3.83 (1 H × 0.34, ddd, J = 5.3, 9.1, 11.9 Hz), 3.99 (1 H × 0.34, ddd, J = 9.3, 9.3, 10.8 Hz), 4.09 (2 H × 0.66, t, J = 8.0 Hz), 4.29 (1 H × 0.34, ddd, J = 8.7, 8.7, 8.7 Hz), 4.33–4.40 (1 H, m), 4.42–4.52 (1.66 H, m), 4.69 (1 H × 0.66, d, J = 6.7 Hz), 4.75 (1 H × 0.34, d, J = 3.3 Hz), 5.01 (1 H × 0.66, d, J = 3.0 Hz), 5.23 (1 H × 0.34, d, J = 8.7 Hz), 5.37 (1 H × 0.34, d, J = 2.7 Hz), 5.56 (1 H × 0.66, d, J = 2.8 Hz), 7.19–7.27 (3 H, m), 7.39–7.41 (2 H, m); $[\alpha]^{27}_D$ +87.1° (c 1.03, CH_2Cl_2); HRMS calcd for $C_{16}H_{25}NO_3S$ 311.1556, found 311.1517. **22c** and **23c** were separated by converting them to the corresponding diols by the following sequence: (1) $Mg(OMe)_2$, (2) $LiAlH_4$. The relative stereochemistry was determined by the NOESY spectrum of the diol of the minor isomer **22c**.

(1*R*,2*R*)-3-(3-Methylene-2-(methylthio)-2-(trimethylsilyl)-1-cyclobutanecarbonyl)-1,3-oxazolidin-2-one (22d) and (1*R*,2*S*)-3-(3-Methylene-2-(methylthio)-2-(trimethylsilyl)-1-cyclobutanecarbonyl)-1,3-oxazolidin-2-one (23d). Determination of the Optical Purity of 22d. Signals of the methylthio group of the (+)-MTPA ester prepared from the racemic sample appeared at 2.04 and 2.08 ppm, and only a signal at 2.08 ppm was observed in the spectrum of the (+)-MTPA ester prepared from the optically active product **22d**.

22d and **23d** were obtained as a mixture (**22d**:**23d** = 65:35): IR (neat) 1781, 1693, 1479, 1384 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.12 (9 H × 0.35, s), 0.13 (9 H × 0.65, s), 1.96 (3 H × 0.65, s), 2.04 (3 H × 0.35, s), 2.53 (1 H × 0.65, dddd, J = 2.6, 2.6, 8.5, 16.1 Hz), 2.65 (1 H × 0.35, dddd, J = 1.9, 1.9, 9.3, 14.7 Hz), 2.82 (1 H × 0.35, dddd, J = 2.8, 2.8, 9.3, 14.8 Hz), 3.18 (1 H × 0.65, dddd, J = 2.6, 2.6, 2.6, 16.1 Hz), 3.92–4.02 (2 H × 0.35, m), 4.05 (2 H × 0.65, t, J = 7.8 Hz), 4.31–4.42 (2 H, m), 4.55–4.61 (1 H, m), 4.62 (1 H × 0.65, t, J = 2.6 Hz), 4.77 (1 H × 0.35, t, J = 1.9 Hz), 5.00 (1 H × 0.35, t, J = 1.9 Hz), 5.08 (1 H × 0.65, t, J = 2.6 Hz); ^{13}C NMR (125 MHz) **22d** δ = −3.7, 11.3, 29.9, 42.3, 43.0, 50.5, 61.9, 108.6, 146.6, 153.2, 173.6; **23d** δ = −2.1, 9.7, 32.1, 40.3, 42.9, 52.9, 61.9, 105.7, 145.9, 153.1, 172.5; HRMS calcd for $C_{13}H_{21}NO_3SiS$ 299.1012, found 299.0955. Anal. Calcd for $C_{13}H_{21}NO_3SiS$: C, 52.14; H, 7.07; N, 4.68. Found: C, 51.95; H, 6.83; N, 4.65. **22d** and **23d** were separated by TLC after conversion to the corresponding methyl esters, and the relative stereochemistry was determined by a NOESY spectrum of the methyl ester of the major isomer, (1*R*,2*R*)-methyl 3-methylene-2-(methylthio)-2-(trimethylsilyl)cyclobutanecarboxylate; see supplementary material.

Dimethyl (1*R*,2*R*)-3,3-Bis(methylthio)cyclobutane-1,2-dicarboxylate (24). Dry methanol (4 mL) and a few drops of carbon tetrachloride were added to magnesium metal (86 mg, 3.53 mmol) at 0 °C to generate magnesium methoxide. When all the magnesium dissolved, a THF (5 mL) solution of the [2 + 2] adduct **4a** (329.2 mg, 1.03 mmol) was added. After the reaction mixture was stirred for 10 min at 0 °C, the reaction was quenched with saturated aqueous ammonium chloride solution, and

organic materials were extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to afford the dimethyl ester **24** (256.0 mg, 94% yield): IR (neat) 1735 cm^{-1}; ^1H NMR (500 MHz) δ = 2.01 (3 H, s), 2.12 (3 H, s), 2.47 (1 H, dd, J = 9.0, 12.2 Hz), 2.50 (1 H, dd, J = 9.4, 12.2 Hz), 3.69 (3 H, s), 3.72 (3 H, s), 3.63–3.75 (2 H, m); ^{13}C NMR (125 MHz) δ = 12.3, 12.8, 35.1, 36.3, 51.9, 52.0, 54.3, 57.4, 169.4, 173.1; $[\alpha]^{24}_D$ +20.4° (c 1.14, CH_2Cl_2), >98% ee; HRMS calcd for $C_{10}H_{16}O_4S_2$ 264.0491, found 264.0496.

(1*R*,2*R*)-(3,3-Bis(methylthio)-2-(hydroxymethyl)cyclobutyl)methanol (25). A THF solution (3 mL) of **24** (120.2 mg, 0.454 mmol) was added to a THF suspension (3 mL) of lithium aluminum hydride (35.0 mg, 0.922 mmol) at 0 °C, and the mixture was stirred for 10 min. Saturated aqueous sodium sulfate was then added dropwise until hydrogen evolution ceased. Inorganic materials were removed by filtration and washed with portions of hot isopropyl alcohol. The filtrate was concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane:ethyl acetate = 9:1) to give the title compound **25** (91.3 mg, 97%): mp 67.0–68.2 °C (CH_2Cl_2–hexane); IR (KBr disk) 3185, 1429, 1025 cm^{-1}; ^1H NMR (500 MHz) δ = 1.90 (1 H, dd, J = 9.0, 12.0 Hz), 1.92 (3 H, s), 1.94 (3 H, s), 2.15 (1 H, dd, J = 8.6, 12.0 Hz), 2.35–2.43 (1 H, m), 2.47–2.52 (1 H, m), 3.40 (1 H, dd, J = 9.5, 9.5 Hz), 3.55–3.61 (2 H, m), 3.67 (1 H, dd, J = 5.6, 10.4 Hz), 3.92–4.06 (2 H, br s); ^{13}C NMR (125 MHz) δ = 12.3, 12.3, 35.9, 37.3, 55.2, 57.7, 61.9, 65.1; $[\alpha]^{26}_D$ +28.8° (c 1.10, CH_2Cl_2), >98% ee. Anal. Calcd for $C_8H_{16}O_2S_2$: C, 46.12; H, 7.74; S, 30.78. Found: C, 45.78; H, 7.63; S, 31.06.

(2*R*,3*R*)-2,3-Bis((*tert*-butyldiphenylsiloxy)methyl)-1,1-bis(methylthio)cyclobutane (26). To a dimethylformamide (DMF) solution (1.5 mL) of **25** (82.3 mg, 0.395 mmol) was added imidazole (110.8 mg, 1.63 mmol). A DMF solution (2 mL) of *tert*-butylchlorodiphenylsilane (297.3 mg, 1.08 mmol) and a catalytic amount of 4-(dimethylamino)pyridine were then added.[47] After the mixture was stirred overnight at room temperature, the reaction was quenched with pH 7 phosphate buffer, and the organic materials were extracted with ethyl acetate. The extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by TLC (hexane:ethyl acetate = 10:1) to afford the di-TBDPS ether **26** (270.0 mg, quantitative): IR (neat) 1467, 1427, 1386, 1108 cm^{-1}; ^1H NMR (280 MHz) δ = 1.00 (9 H, s), 1.02 (9 H, s), 2.05 (3 H, s), 2.06 (3 H, s), 2.10–2.33 (3 H, m), 2.81 (1 H, dt, J_d = 5.7 Hz, J_t = 8.6 Hz), 3.54–3.68 (3 H, m), 3.90 (1 H, dd, J = 8.8, 10.6 Hz), 7.30–7.45 (12 H, m), 7.55–7.70 (8 H, m); ^{13}C NMR (125 MHz) δ = 12.3, 12.9, 19.1, 19.2, 26.8, 35.5, 38.4, 53.3, 59.1, 64.1, 66.1, 127.6, 129.5, 133.6, 135.5; $[\alpha]^{24}_D$ −14.3° (c 1.02, CH_2Cl_2), >98% ee. Anal. Calcd for $C_{40}H_{52}O_2Si_2S_2$: C, 70.12; H, 7.65; S, 9.36. Found: C, 70.00; H, 7.70; S, 9.17.

(2*R*,3*R*)-Bis((*tert*-butyldiphenylsiloxy)methyl)cyclobutanone (27). An acetonitrile solution (4 mL) of **26** (247.2 mg, 0.361 mmol) was added to a well-stirred solution of *N*-chlorosuccinimide (195.0 mg, 1.46 mmol) and silver nitrate (281.5 mg, 1.66 mmol) in aqueous 90% acetonitrile (6 mL) at 0 °C.[48] The mixture was stirred for 5 min and treated successively with saturated aqueous sodium sulfite, saturated aqueous sodium carbonate, and brine (4 mL each) at 1-min intervals. Inorganic materials were filtered off. The organic materials were extracted with ethyl acetate, and the organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by TLC (hexane:ethyl acetate = 10:1) to afford the title compound **27** (198.3 mg, 91% yield): IR (neat) 1782, 1467, 1427, 1108 cm^{-1}; ^1H NMR (280 MHz) δ = 1.02 (9 H, s), 1.04 (9 H, s), 2.74–3.05 (3 H, m), 3.25–3.33 (1 H, m), 3.68 (1 H, dd, J = 3.7, 10.6 Hz), 3.83 (1 H, dd, J = 4.8, 5.6 Hz), 3.88 (1 H, dd, J = 4.8, 5.6 Hz), 3.96 (1 H, dd, J = 4.0, 10.6 Hz), 7.35–7.50 (12 H, m), 7.60–7.70 (8 H, m); ^{13}C NMR (125 MHz) δ = 19.3, 26.8, 26.9, 29.4, 47.4, 60.7, 64.0, 65.5, 127.7, 127.8, 129.7, 129.8, 133.0, 133.3, 133.4, 133.4, 135.5, 135.6, 208.8; $[\alpha]^{24}_D$ −13.8° (c 0.94, CH_2Cl_2), >98% ee. Anal. Calcd for $C_{38}H_{46}O_3Si_2$: C, 75.20; H, 7.64. Found: C, 74.95; H, 7.63.

General Procedure for the Reaction between Cycloalkenones and 1,1-Bis(methylthio)ethylene (3a) (Table VIII, condition A, Entry 2). To an ether solution (2 mL) of 1,1-bis(methylthio)ethylene (**3a**) (1.0 mmol) and 2-cyclohexen-1-one (0.62 mmol) was added an ether solution of BF_3·OEt_2 (0.62 mmol) dropwise at −23 °C. The mixture was stirred at −23 °C for 20 min. The reaction was quenched with a few drops of NEt_3 and then with aqueous $NaHCO_3$. The organic materials were extracted with ether, and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by TLC (benzene:ethyl acetate = 10:1) to afford **29** in 65% yield.

Spectral data and physical properties of the cycloadducts **28–31** are as follows.

(1*S,5*R**)-7,7-Bis(methylthio)bicyclo[3.2.0]heptan-2-one (28)**: IR (neat) 1732 cm^{-1}; ^1H NMR (500 MHz) δ = 1.87 (1 H, dd, J = 9.5, 13.4 Hz), 1.95 (3 H, s), 1.95–2.02 (1 H, m), 2.00 (3 H, s), 2.15 (1 H, ddd, J = 0.8, 6.8, 14.0 Hz), 2.30–2.36 (1 H, m), 2.65 (1 H, ddd, J = 2.5, 9.0, 18.0 Hz), 2.72–2.83 (2 H, m), 3.15–3.21 (1 H, m); ^{13}C NMR (125 MHz) δ = 12.4, 12.5, 27.2, 31.7, 37.7, 40.5, 55.9, 56.9, 215.9; HRMS calcd for $C_9H_{14}OS_2$ 202.0487, found 202.0485.

(1*S,6*R**)-8,8-Bis(methylthio)bicyclo[4.2.0]octan-2-one (29)**: IR (neat) 1697 1429 cm^{-1}; ^1H NMR (500 MHz) δ = 1.70–1.86 (3 H, m), 1.98 (3 H, s), 2.07 (3 H, s), 2.09–2.26 (3 H, m), 2.51–2.57 (2 H, m), 3.06–3.16 (2 H, m); ^{13}C NMR (125 MHz) δ = 12.2, 13.0, 19.3, 27.0, 28.2, 39.7, 40.7, 56.2, 57.8, 208.6; HRMS calcd for $C_{10}H_{16}OS_2$ 216.0644, found 216.0650.

(1*S,7*R**)-9,9-Bis(methylthio)bicyclo[5.2.0]nonan-2-one (30)**: IR (neat) 1703 1442 cm^{-1}; ^1H NMR (500 MHz) δ = 1.35 (1 H, ddd, J = 9.5, 11.6, 23.2 Hz), 1.42–1.50 (1 H, m), 1.81–1.94 (3 H, m), 2.00–2.06 (2 H, m), 2.01 (3 H, s), 2.11 (3 H, s), 2.33–2.47 (3 H, m), 2.71–2.79 (1 H, m), 3.68 (1 H, d, J = 9.7 Hz); ^{13}C NMR (125 MHz) δ = 11.9, 13.4, 25.0, 28.9, 32.3, 34.9, 38.0, 44.0, 58.4, 83.2, 209.2; HRMS calcd for $C_{11}H_{18}OS_2$ 230.0800, found 230.0777.

(1*S,8*R**)-10,10-Bis(methylthio)bicyclo[6.2.0]decan-2-one (31)**: IR (neat) 1697 1442 cm^{-1}; ^1H NMR (500 MHz) δ = 1.25–1.42 (3 H, m), 1.55–1.76 (4 H, m), 1.78 (1 H, dd, J = 9.7, 11.4 Hz), 1.80–1.87 (1 H, m), 1.95 (3 H, s), 2.10 (3 H, s), 2.15 (1 H, ddd, J = 4.4, 4.4, 12.2 Hz), 2.30 (1 H, dd, J = 8.1, 11.4 Hz), 2.80–2.89 (1 H, m), 2.91 (1 H, ddd, J = 5.7, 12.2, 12.2 Hz), 3.00 (1 H, d, J = 10.4 Hz); ^{13}C NMR (125 MHz) δ = 11.9, 13.1, 25.5, 25.6, 26.3, 35.1, 36.5, 39.0, 39.1, 59.5, 66.0, 211.8; HRMS calcd for $C_{12}H_{20}OS_2$ 244.0957, found 244.0952. Anal. Calcd for $C_{12}H_{20}OS_2$: C, 58.97; H, 8.25; S, 26.24. Found: C, 58.69; H, 8.14; S, 26.64.

General Procedure for the Reaction between Acyclic Electron Deficient Olefins and 1,1-Bis(methylthio)ethylene (3a) (Table VIII, condition B, Entry 6). To a CH_2Cl_2 solution (2 mL) of 1,1-bis(methylthio)ethylene (**3a**) (1.0 mmol) and methyl acrylate (0.58 mmol) was added $EtAlCl_2$ (0.58 mmol, 1.0 M hexane solution) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h, and the reaction was quenched with a few drops of NEt_3 and then with aqueous $NaHCO_3$. Inorganic materials were removed by filtration. The organic materials were extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by TLC (hexane:ethyl acetate = 10:1) to afford **32** in 78% yield.

Spectral data and physical properties of the cycloadducts are as follows.

Methyl 2,2-bis(methylthio)cyclobutane-1-carboxylate (32): IR (neat) 1736 cm^{-1}; ^1H NMR (500 MHz) δ = 2.01 (3 H, s), 2.10 (3 H, s), 2.21–2.34 (3 H, m), 2.51–2.56 (1 H, m), 3.38–3.42 (1 H, m), 3.73 (3 H, s); ^{13}C NMR (125 MHz) δ = 12.3, 12.7, 16.8, 33.4, 51.5, 51.7, 60.7, 171.1; HRMS calcd for $C_8H_{14}O_2S_2$ 206.0436, found 206.0431.

2,2-Bis(methylthio)cyclobutanecarbonitrile (33): IR (neat) 2237, 1423 cm^{-1}; ^1H NMR (500 MHz) δ = 2.00 (3 H, s), 2.08 (3 H, s), 2.20–2.25 (1 H, m), 2.34 (1 H, ddd, J = 8.8, 8.8, 12.2 Hz), 2.40–2.52 (2 H, m), 3.32 (1 H, t, J = 8.5 Hz); ^{13}C NMR (125 MHz) δ = 12.4, 12.5, 21.7, 34.4, 36.1, 59.6, 116.4; HRMS calcd for $C_7H_{11}NS_2$ 173.0334, found 173.0303.

2,2-Bis(methylthio)-1-chlorocyclobutanecarbonitrile (34): IR (neat) 2237, 1427 cm^{-1}; ^1H NMR (500 MHz) δ = 2.07 (3 H, s), 2.16 (3 H, s), 2.29 (1 H, ddd, J = 8.5, 8.5, 12.3 Hz), 2.41 (1 H, ddd, J = 4.9, 9.8, 12.3 Hz), 2.78 (1 H, ddd, J = 8.5, 9.8, 12.3 Hz), 2.99 (1 H, ddd, J = 4.9, 8.5, 12.3 Hz); ^{13}C NMR (125 MHz) δ = 12.6, 13.0, 31.6, 35.5, 60.7, 67.9, 117.1; HRMS calcd for $C_7H_{10}NClS_2$ 206.9945, found 206.9958.

[2 + 2] Cycloaddition Reaction between Electron Deficient Olefins and the Alkynyl Sulfide 35 (Table IX).

(1*R,5*R**)-6-(*tert*-Butyldimethylsilyl)-7-(methylthio)bicyclo[3.2.0]-hept-6-en-2-one (36)** (Table IX, condition A, Entry 1). To a CH_2Cl_2 solution (2.5 mL) of 2-cyclopenten-1-one (42.6 mg, 0.519 mmol) and 1-(*tert*-butyldimethylsilyl)-2-(methylthio)acetylene (**35**) (240.2 mg, 1.29 mmol) was added dropwise a CH_2Cl_2 solution (0.5 mL) of BF_3·OEt_2 (73.9 mg, 0.521 mmol) at room temperature. The mixture was stirred for 16 h at room temperature, and the reaction was quenched with a few drops of NEt_3 and then with aqueous $NaHCO_3$. The organic materials were extracted with CH_2Cl_2, and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by TLC (hexane:ethyl acetate = 5:1) to afford **36** in 47% yield: IR (neat) 1733, 1531 1469 cm^{-1}; ^1H NMR (500 MHz) δ = 0.07 (3 H, s), 0.09 (3 H, s), 0.89 (9 H, s), 1.88–1.93 (2 H, m), 2.08–2.15 (1 H, m), 2.28 (3 H, s), 2.83–2.91 (1 H, m), 3.29–3.32 (1 H, m), 3.53–3.54 (1 H, m); ^{13}C NMR (125 MHz) δ = −6.1, −6.0, 13.8, 17.6, 23.7, 28.7, 34.4, 42.9, 57.6, 149.1, 152.2, 215.9; HRMS calcd

(47) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975; **1977**, *55*, 562.

(48) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

for $C_{14}H_{24}OSiS$ 268.1318, found 268.1339.

General Procedure for the Reaction between Electron Deficient Olefins and the Alkynyl Sulfide 35 (Table IX, condition B, Entry 2). To a CH_2Cl_2 solution (2.5 mL) of 2-cyclohexen-1-one (46.0 mg, 0.687 mmol) and **35** (172.0 mg, 0.922 mmol) was added dropwise a CH_2Cl_2 solution (0.8 mL) of $TiCl_4$ (0.76 mmol) at −78 °C. The mixture was stirred for 30 min at −78 °C, and the reaction was quenched with a few drops of NEt_3 and then with aqueous $NaHCO_3$. Inorganic materials were removed by filtration, and the organic materials were extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by TLC (hexane:ethyl acetate = 5:1) to afford **37** in 83% yield.

Spectral data and physical properties of the cycloadducts are as follows.

(1*R,6*R**)-7-(*tert*-Butyldimethylsilyl)-8-(methylthio)bicyclo[4.2.0]-oct-7-en-2-one (37)**: IR (neat) 1699, 1535 cm^{-1}; ^1H NMR (500 MHz) δ = 0.05 (3 H, s), 0.11 (3 H, s), 0.89 (9 H, s), 1.56–1.72 (2 H, m), 1.85–1.97 (2 H, m), 2.12–2.20 (1 H, m), 2.29 (3 H, s), 2.54–2.59 (1 H, m), 3.26–3.30 (1 H, m), 3.78 (1 H, d, J = 4.3 Hz); ^{13}C NMR (125 MHz) δ = −5.6, −5.7, 14.3, 17.4, 18.0, 26.7, 26.8, 40.5, 42.8, 57.8, 149.7, 150.3, 210.9; HRMS calcd for $C_{15}H_{26}OSiS$ 282.1474, found 282.1469.

(1*R,7*R**)-8-(*tert*-Butyldimethylsilyl)-9-(methylthio)bicyclo[5.2.0]-non-8-en-2-one (38)**: IR (neat) 1697, 1531 cm^{-1}; ^1H NMR (500 MHz) δ = 0.02 (3 H, s), 0.09 (3 H, s), 0.86 (9 H, s), 1.18–1.27 (1 H, m), 1.36–1.53 (2 H, m), 1.69–1.79 (2 H, m), 1.88–1.95 (1 H, m), 2.19 (3 H, s), 2.37–2.47 (2 H, m), 3.04 (1 H, ddd, J = 3.5, 5.3, 11.5 Hz), 4.19 (1 H, d, J = 5.3 Hz); ^{13}C NMR (125 MHz) δ = −5.7, −5.5, 14.3, 17.7, 24.8, 26.3, 26.7, 31.5, 42.2, 44.7, 61.2, 144.9, 151.4, 209.5; HRMS calcd for $C_{16}H_{28}OSiS$ 296.1631, found 296.1628.

(1*R,8*R**)-9-(*tert*-Butyldimethylsilyl)-10-(methylthio)bicyclo-[6.2.0]dec-9-en-2-one (39)**: IR (neat) 1701, 1541 cm^{-1}; ^1H NMR (500 MHz) δ = 0.05 (3 H, s), 0.09 (3 H, s), 0.87 (9 H, s), 1.12 (1 H, ddd, J = 2.0, 11.8, 26.6 Hz), 1.18–1.33 (2 H, m), 1.64–1.89 (5 H, m), 2.06 (3 H, s), 2.19–2.27 (1 H, m), 2.47–2.55 (1 H, m), 3.06 (1 H, ddd, J = 1.8, 5.1, 11.8 Hz), 4.19 (1 H, d, J = 5.1 Hz); ^{13}C NMR (125 MHz) δ = −5.7, −5.1, 14.2, 17.6, 24.6, 26.8, 27.8, 29.6, 30.1, 46.5, 49.8, 58.5, 146.6, 150.2, 211.2; HRMS calcd for $C_{17}H_{30}OSiS$ 310.1788, found 310.1764.

(1*R,4*S**)-3-(*tert*-Butyldimethylsilyl)-2-(methylthio)-4-pentyl-1-cyclobut-2-enyl Methyl Ketone (40)** (Table IX, condition C, Entry 5). The reaction procedure of condition C is the same as that of condition B, except for the reaction temperature. The reaction temperature of condition C is 0 °C.

40: IR (neat) 1701, 1539 cm^{-1}; ^1H NMR (500 MHz) δ = 0.06 (3 H, s), 0.13 (3 H, s), 0.86 (3 H, t, J = 6.9 Hz), 0.90 (9 H, s), 1.20–1.39 (7 H, m), 1.66–1.74 (1 H, m), 2.12 (3 H, s), 2.18 (3 H, s), 2.61 (1 H, ddd, J = 1.5, 3.3, 11.0 Hz), 3.44 (1 H, d, J = 1.5 Hz); ^{13}C NMR (125 MHz) δ = −5.9, −5.3, 13.6, 14.0, 17.7, 22.5, 25.6, 26.7, 27.2, 31.6, 34.7, 47.1, 64.1, 150.2, 151.1, 208.5; HRMS calcd for $C_{18}H_{34}OSiS$ 326.2101, found 326.2088.

(1*R,4*S**)-3-(*tert*-Butyldimethylsilyl)-4-methyl-2-(methylthio)-1-cyclobut-2-enyl phenyl ketone (41)**: IR (neat) 1678, 1537 cm^{-1}; ^1H NMR (500 MHz) δ = 0.08 (3 H, s), 0.14 (3 H, s), 0.89 (3 H, d, J = 7.0 Hz), 0.91 (9 H, s), 2.13 (3 H, s), 3.37 (1 H, dq, J_d = 5.3 Hz, J_q = 7.0 Hz), 5.02 (1 H, d, J = 5.3 Hz), 7.42–7.49 (2 H, m), 7.52–7.57 (1 H, m), 7.89–7.94 (2 H, m); ^{13}C NMR (125 MHz) δ = −5.7, −5.4, 14.4, 16.3, 17.6, 26.8, 42.3, 56.0, 128.1, 128.7, 133.1, 136.9, 148.0, 150.4, 197.7; HRMS calcd for $C_{19}H_{28}OSiS$ 332.1631, found 332.1637.

Methyl 3-(*tert*-Butyldimethylsilyl)-2-(methylthio)cyclobut-2-ene-carboxylate (42) (Table IX, condition D, Entry 7). To a CH_2Cl_2 solution (1.5 mL) of methyl acrylate (56.6 mg, 0.657 mmol) and **35** (230.9 mg, 1.24 mmol) was added dropwise a hexane solution of $EtAlCl_2$ (1.07 M, 0.70 mL) at 0 °C. After the mixture was stirred for 1 h at 0 °C and then at room temperature for 12 h, the reaction was quenched with a few drops of NEt_3 and then with aqueous $NaHCO_3$. Inorganic materials were removed by filtration, and the organic materials were extracted with CH_2Cl_2 and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by TLC (hexane:ethyl acetate = 10:1) to afford **42** in 80% yield.

42: IR (neat) 1739, 1548 cm^{-1}; ^1H NMR (500 MHz) δ = 0.03 (3 H, s), 0.06 (3 H, s), 0.87 (9 H, s), 2.20 (3 H, s), 2.55 (1 H, dd, J = 2.5, 12.3 Hz), 2.61 (1 H, dd, J = 4.7, 12.3 Hz), 3.67 (3 H, s), 3.89 (1 H, dd, J = 2.5, 4.7 Hz); ^{13}C NMR (125 MHz) δ = −6.4, −6.4, 14.0, 17.5, 26.5, 33.5, 49.1, 51.8, 148.2, 149.3, 172.7; HRMS calcd for $C_{13}H_{24}O_2SiS$ 272.1267, found 272.1266.

General Procedure for the Reaction between Electron Deficient Olefins and the Alkenyl Sulfide 14a (Table X, Entry 1). To a CH_2Cl_2 solution (3.0 mL) of dimethyl fumarate (0.46 mmol) and 1-(butylthio)-1-cyclohexene (**14a**) (0.59 mmol) was added a hexane solution of $EtAlCl_2$ (0.46 mmol, 1.0 M) dropwise at 0 °C. The mixture was stirred at 0 °C for 12 h, and the reaction was quenched with a few drops of NEt_3 and then with aqueous $NaHCO_3$. Inorganic materials were removed by filtration, and the organic materials were extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by TLC (hexane:ethyl acetate = 10:1) to afford **43** in 76% yield.

Spectral data and physical properties of the cycloadducts **43–45** are as follows.

Dimethyl (1*S,6*R**,7*R**,8*R**)-1-(Butylthio)bicyclo[4.2.0]octane-7,8-dicarboxylate (43)**. One isomer: IR (neat) 1734, 1438 cm^{-1}; ^1H NMR (500 MHz) δ = 0.85 (3 H, t, J = 7.3 Hz), 1.27–1.40 (4 H, m), 1.42–1.62 (7 H, m), 1.68–1.72 (1 H, m), 2.45–2.50 (1 H, m), 2.51–2.60 (2 H, m), 3.15 (1 H, t, J = 10.2 Hz), 3.32 (1 H, d, J = 9.7 Hz), 3.62 (3 H, s), 3.63 (3 H, s); ^{13}C NMR (125 MHz) δ = 13.5, 20.6, 21.2, 22.1, 22.9, 27.9, 29.8, 31.6, 38.4, 40.9, 48.4, 50.4, 51.6, 51.8, 170.9, 173.2; HRMS calcd for $C_{16}H_{26}O_4S$ 314.1553, found 314.1548.

Methyl (1*S,6*R**,8*R**)-1-(Butylthio)bicyclo[4.2.0]octane-8-carboxylate (44)**. **44** was obtained with the other isomer (diastereomer ratio 81:19): IR (neat) 1734, 1438 cm^{-1}; ^1H NMR (500 MHz) for the major isomer δ = 0.85 (3 H, t, J = 7.3 Hz), 1.27–1.54 (10 H, m), 1.62–1.75 (2 H, m), 1.91 (1 H, dt, J_d = 10.7 Hz, J_t = 8.5 Hz), 2.11 (1 H, ddd, J = 10.7, 10.7, 10.7 Hz), 2.28–2.37 (1 H, m), 2.47–2.60 (2 H, m), 3.05 (1 H, dd, J = 8.0, 10.1 Hz), 3.60 (3 H, s); distinguishable peaks of the minor isomer δ = 0.82 (3 H, t, J = 7.3 Hz), 2.20–2.27 (1 H, m), 2.38–2.42 (1 H, m), 3.65 (3 H, s); ^{13}C NMR (125 MHz) for the major isomer δ = 13.6, 20.5, 21.1, 22.2, 22.9, 23.8, 27.9, 28.9, 31.8, 36.4, 48.6, 51.3, 51.4, 172.4; HRMS calcd for $C_{14}H_{24}O_2S$ 256.1498, found 256.1509.

1-(Butylthio)-8-chlorobicyclo[4.2.0]octane-8-carbonitrile (45). One isomer, and the stereochemistry is not determined: IR (neat) 2237, 1458 cm^{-1}; ^1H NMR (500 MHz) δ = 0.85 (3 H, t, J = 7.3 Hz), 1.28–1.68 (10 H, m), 1.94 (1 H, ddd, J = 3.0, 12.6, 12.6 Hz), 2.09 (1 H, d, J = 14.7 Hz), 2.31 (1 H, dd, J = 8.0, 11.8 Hz), 2.43–2.55 (2 H, m), 2.69–2.75 (1 H, m), 2.79 (1 H, dd, J = 11.4, 11.4 Hz); ^{13}C NMR (125 MHz) δ = 13.5, 20.7, 21.1, 21.9, 22.8, 28.2, 30.6, 31.5, 35.8, 37.3, 57.9, 60.6, 117.3; HRMS calcd for $C_{13}H_{20}NSCl$ 257.1007, found 257.1019.

General Procedure for the Reaction between Electron Deficient Olefins and 1-(Methylthio)-1-(trimethylsilyl)-1,2-propadiene (21a) (Table XI, entry 2). To a CH_2Cl_2 solution (4 mL) of **21a** (1.0 mmol) and 2-cyclohexen-1-one (0.73 mmol) was added dropwise a hexane solution of $EtAlCl_2$ (0.73 mmol, 1 M) at 0 °C. The mixture was stirred for 1.8 h at 0 °C, and the reaction was quenched with a few drops of NEt_3 and then with aqueous $NaHCO_3$. Inorganic materials were separated by filtration, and the organic materials were extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by TLC (hexane:ethyl acetate = 10:1) to afford **47** in 77% yield.

Spectral data and physical properties of the cycloadducts **46–59** are as follows.

(1*S,5*R**,7*S**)-6-Methylene-7-(methylthio)-7-(trimethylsilyl)bicyclo[3.2.0]heptan-2-one (46)**: IR (neat) 1733, 1658, 1446, 1249 cm^{-1}; ^1H NMR (500 MHz) δ = 0.11 (9 H, s), 1.92 (3 H, s), 1.90–1.98 (2 H, m), 2.20–2.28 (1 H, m), 2.52–2.62 (1 H, m), 2.72 (1 H, d, J = 6.4 Hz), 3.24–3.30 (1 H, m), 4.81 (1 H, d, J = 2.4 Hz), 5.04 (1 H, s); ^{13}C NMR (125 MHz) δ = −3.3, 12.1, 27.4, 38.5, 43.7, 48.0, 50.9, 107.1, 154.0, 216.2; HRMS calcd for $C_{12}H_{20}OSiS$ 240.1005, found 240.1008. Stereochemistry was determined by NOESY; see supplementary material.

(1*S,6*R**,8*S**)-7-Methylene-8-(methylthio)-8-(trimethylsilyl)bicyclo[4.2.0]octan-2-one (47)**: IR (neat) 1697, 1658, 1247 cm^{-1}; ^1H NMR (500 MHz) δ = 0.12 (9 H, s), 1.53–1.62 (1 H, m), 1.67–1.72 (1 H, m), 1.78–1.84 (1 H, m), 1.89 (3 H, s), 1.98–2.12 (2 H, m), 2.45–2.52 (1 H, m), 2.95 (1 H, d, J = 8.8 Hz), 3.11–3.15 (1 H, m), 4.82 (1 H, d, J = 2.3 Hz), 4.94 (1 H, dd, J = 0.7, 2.3 Hz); ^{13}C NMR (125 MHz) δ = −3.4, 12.7, 18.5, 25.4, 39.8, 40.8, 48.9, 49.5, 105.6, 153.5, 210.7; HRMS calcd for $C_{13}H_{22}OSiS$ 254.1162, found 254.1167. Stereochemistry was determined by NOESY; see supplementary material.

(1*S,7*R**,9*S**)-8-Methylene-9-(methylthio)-9-(trimethylsilyl)bicyclo[5.2.0]nonan-2-one (48a) and (1*S**,7*R**,9*R**)-8-Methylene-9-(methylthio)-9-(trimethylsilyl)bicyclo[5.2.0]nonan-2-one (48b)**. **48a** and **48b** were separated by TLC. **48a**: IR (neat) 1704, 1658, 1245 cm^{-1}; ^1H NMR (500 MHz) δ = 0.11 (9 H, s), 1.35–1.45 (2 H, m), 1.62 (1 H, q, J = 13.0 Hz), 1.78–1.86 (1 H, m), 1.91 (3 H, s), 2.00–2.09 (2 H, m), 2.27 (1 H, ddd, J = 2.4, 12.4, 14.9 Hz), 2.49 (1 H, dd, J = 5.8, 18.5 Hz), 2.56–2.62 (1 H, m), 3.19 (1 H, d, J = 10.2 Hz), 4.65 (1 H, d, J = 2.5 Hz), 4.97 (1 H, d, J = 2.5 Hz); ^{13}C NMR (125 MHz) δ = −1.9, 10.2, 23.8, 29.5, 32.2, 43.4, 46.1, 47.1, 56.7, 104.8, 149.5, 210.7; HRMS calcd for $C_{14}H_{24}OSiS$ 268.1318, found 268.1337. **48b**: IR (neat) 1706, 1652, 1247 cm^{-1}; ^1H NMR (500 MHz) δ = 0.11 (9 H, s), 1.39–1.82 (3 H, m), 1.70–1.90 (3 H, m), 2.01 (3 H, s), 2.39 (1 H, ddd, J = 3.0, 9.8, 12.5 Hz), 2.48 (1 H, ddd, J = 2.6, 9.0, 12.5 Hz), 2.96–3.04 (1 H, m), 3.34 (1 H, d, J = 9.5 Hz), 4.74 (1 H, d, J = 2.2 Hz), 4.95 (1 H, d, J = 2.2 Hz);

^{13}C NMR (125 MHz) δ = −3.5, 1.9, 14.4, 24.0, 27.0, 31.0, 43.2, 44.2, 52.9, 105.9, 151.8, 209.9; HRMS calcd for $C_{14}H_{24}OSiS$ 268.1318, found 268.1286.

(1S*,8R*,10S*)-9-Methylene-10-(methylthio)-10-(trimethylsilyl)bicyclo[6.2.0]decan-2-one and (1S*,8R*,10R*)-9-Methylene-10-(methylthio)-10-(trimethylsilyl)bicyclo[6.2.0]decan-2-one (49) (diastereomer ratio 83:17): IR (neat) 1700, 1660, 1245 cm^{-1}; ^{1}H NMR (500 MHz) for the major isomer δ = 0.09 (9 H, s), 1.30–1.46 (3 H, m), 1.55–1.65 (1 H, m), 1.70–1.79 (2 H, m), 1.80–1.86 (1 H, m), 1.91 (3 H, s), 1.95–2.01 (1 H, m), 2.28 (1 H, ddd, J = 3.7, 5.8, 9.5 Hz), 2.67–2.80 (2 H, m), 3.0 (1 H, d, J = 9.3 Hz), 4.64 (1 H, d, J = 2.6 Hz), 4.96 (1 H, d, J = 2.6 Hz); ^{13}C NMR (125 MHz) for the major isomer δ = −2.0, 10.3, 24.1, 25.2, 26.3, 31.6, 41.0, 47.2, 49.0, 57.0, 104.6, 150.2, 212.6. Distinguishable peaks of the minor isomer: ^{1}H NMR (500 MHz) δ = 0.10 (9 H, s), 1.94 (3 H, s), 4.77 (1 H, d, J = 2.9 Hz), 4.93 (1 H, d, J = 2.9 Hz); ^{13}C NMR (125 MHz) δ = −2.7, 14.4, 25.2, 25.9, 26.4, 31.3, 48.4, 52.5, 105.7, 151.3, 212.6. Anal. Calcd for $C_{15}H_{26}OSiS$: C, 60.43; H, 7.86; N, 3.52; S, 8.07. Found: C, 60.13; H, 7.73; N, 3.68; S, 7.88.

(1S*,5S*,7S*)-6-Methylene-7-(methylthio)-3-oxo-7-(trimethylsilyl)-bicyclo[3.2.0]heptan-2-one and (1S*,5S*,7R*)-6-Methylene-7-(methylthio)-3-oxo-7-(trimethylsilyl)bicyclo[3.2.0]heptan-2-one (50). Diastereomer ratio 91:9: IR (neat) 1762, 1249 cm^{-1}; ^{1}H NMR (500 MHz) for the major isomer δ = 0.18 (9 H, s), 2.13 (3 H, s), 3.18 (1 H, d, J = 8.8 Hz), 3.65 (1 H, dddd, J = 1.6, 2.6, 8.8, 9.3 Hz), 4.32 (1 H, dd, J = 2.6, 9.3 Hz), 4.39 (1 H, dd, J = 9.3, 9.3 Hz), 5.00 (1 H, s), 5.14 (1 H, t, J = 1.6 Hz), and for the minor isomer δ = 0.13 (9 H, s), 2.00 (3 H, s), 3.05 (1 H, d, J = 7.2 Hz), 3.37–3.42 (1 H, m), 4.15–4.50 (2 H, m), 4.90 (1 H, s), 5.24 (1 H, s); ^{13}C NMR (125 MHz) δ = −2.4, 10.2, 16.6, 36.4, 52.5, 54.6, 104.3, 128.4, 129.2, 133.1, 136.7, 152.1, 199.1; HRMS calcd for $C_{11}H_{18}O_2SiS$ 242.0794, found 242.0819. Stereochemistry was determined by NOESY; see supplementary material.

(1R*,2S*,4R*)-2-Methyl-3-methylene-4-(methylthio)-4-(trimethylsilyl)-1-benzoylcyclobutane (51): IR (neat) 1672, 1560 cm^{-1}; ^{1}H NMR (500 MHz) δ = −0.09 (9 H, s), 1.07 (3 H, d, J = 6.7 Hz), 2.13 (3 H, s), 3.40–3.47 (1 H, m), 3.58 (1 H, d, J = 8.4 Hz), 4.78 (1 H, d, J = 2.9 Hz), 5.00 (1 H, d, J = 2.4 Hz), 7.45 (2 H, t, J = 7.8 Hz), 7.53 (1 H, t, J = 7.4 Hz), 8.10 (2 H, d, J = 7.8 Hz); ^{13}C NMR (125 MHz) δ = −2.4, 10.2, 16.6, 36.4, 52.5, 54.6, 104.3, 128.4, 129.2, 133.1, 136.7, 152.1, 199.1; HRMS calcd for $C_{17}H_{24}OSiS$ 304.1318, found 304.1289. Stereochemistry was determined by NOESY; see supplementary material.

(1R*,2R*,4R*)-3-Methylene-4-(methylthio)-1-phenyl-4-(trimethylsilyl)-1-benzoylcyclobutane (52): IR (neat) 1670, 1599, 879 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.02 (9 H, s), 2.31 (3 H, s), 4.12 (1 H, d, J = 9.0 Hz), 4.65 (1 H, dt, J = 9.0, 2.7 Hz), 5.00 (1 H, d, J = 2.7 Hz), 5.17 (1 H, d, J = 2.7 Hz), 7.20 (1 H, t, J = 7.2 Hz), 7.29 (2 H, t, J = 7.4 Hz), 7.33 (2 H, d, J = 7.1 Hz), 7.45 (2 H, t, J = 7.8 Hz), 7.55 (1 H, t, J = 7.4 Hz), 8.12 (2 H, d, J = 7.8 Hz); ^{13}C NMR (125 MHz) δ = −2.3, 10.4, 46.6, 52.1, 55.4, 107.1, 126.8, 127.9, 128.5, 128.6, 129.3, 133.3, 136.7, 140.6, 149.7, 198.2; HRMS calcd for $C_{22}H_{26}OSiS$ 366.1475, found 366.1471. Stereochemistry was determined by NOESY; see supplementary material.

3-Methylene-4-(methylthio)-2-(2-phenylethyl)-4-(trimethylsilyl)cyclobutyl Methyl Ketone (53). The product was isolated as a diastereomer mixture in the ratio of 67:33, and the stereochemistry was not determined: IR (neat) 1707, 1658, 1355, 1249 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.11 (9 H × 0.67, s), 0.20 (9 H × 0.33, s), 1.55–1.72 (1.33 H, m), 1.90–1.99 (0.67 H, m), 1.98 (3 H × 0.33, s), 2.02 (3 H × 0.67, s), 2.13 (3 H × 0.67, s), 2.14 (3 H × 0.33, s), 2.42–2.50 (1 H, m), 2.60–2.65 (1 H, m), 2.99 (1 H, d, J = 8.1 Hz), 3.12–3.17 (0.67 H, m), 3.49–3.54 (0.33 H, m), 4.76 (0.67 H, d, J = 2.5 Hz), 4.85 (0.33 H, d, J = 0.7 Hz), 5.06 (0.67 H, d, J = 2.5 Hz), 5.12 (0.33 H, d, J = 0.7 Hz), 7.15–7.18 (3 H, m), 7.25–7.28 (2 H, m); ^{13}C NMR (125 MHz) for the major isomer δ = −2.4, 10.0, 30.9, 33.3, 34.2, 41.2, 46.4, 56.7, 104.5, 125.8, 128.2, 128.3, 141.8, 150.5, 207.1, the minor isomer δ = −2.8, 12.3, 30.8, 33.7, 33.7, 42.7, 51.0, 56.3, 107.8, 125.8, 128.2, 128.3, 141.8, 151.8, 206.7; HRMS calcd for $C_{19}H_{28}OSiS$ 332.1631, found 332.1654.

3-Methylene-4-(methylthio)-2-pentyl-4-(trimethylsilyl)cyclobutyl Methyl Ketone (54). The product was isolated as a diastereomer mixture in the ratio of 69:31, and the stereochemistry was not determined: IR (neat) 1706, 1658, 1459, 1425 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.08 (9 H × 0.69, s), 0.17 (9 H × 0.31, s), 0.83 (3 H, t, J = 6.9 Hz), 1.10–1.31 (6 H, m), 1.50–1.61 (1 H, m), 1.94 (3 H × 0.31, s), 2.00 (3 H × 0.69, s), 2.16 (3 H × 0.69, s), 2.20 (3 H × 0.31, s), 2.95 (1 H × 0.69, d, J = 8.7 Hz), 2.96–3.05 (0.69 H, m), 3.02 (0.31 H, d, J = 7.6 Hz), 3.35–3.42 (0.31 H, m), 4.70 (0.69 H, d, J = 2.6 Hz), 4.80 (0.31 H, d, J = 3.1 Hz), 5.01 (0.69 H, d, J = 2.3 Hz), 5.08 (0.31 H, d, J = 2.7 Hz); ^{13}C NMR (125 MHz) for the major isomer δ = −2.4, 10.0, 14.0, 22.5, 26.6, 30.9, 31.8, 32.6, 41.5, 50.7, 57.0, 104.3, 150.9, 207.2, the minor isomer δ = −2.7, 12.4, 14.0, 22.5, 26.9, 30.8, 31.7, 32.0, 42.8, 46.3, 56.5, 107.6, 152.2, 206.8; HRMS calcd for $C_{16}H_{30}OSiS$ 298.1788, found 298.1811.

3-Methylene-2-(methylthio)-2-(trimethylsilyl)-1-cyclobutanecarbonitrile (55). The product was isolated as a diastereomer mixture in the ratio of 55:45, and the stereochemistry was not determined: IR (neat) 2235, 1666, 1251 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.10 (9 H × 0.55, s), 0.24 (9 H × 0.45, s), 1.95 (3 H × 0.45, s), 3.22 (3 H × 0.55, s), 2.72–2.93 (2 H, m), 2.23–3.27 (1 H, m), 4.77–4.78 (1 H, m), 5.01 (1 H × 0.45, s), 5.05 (1 H × 0.55, s); ^{13}C NMR (125 MHz) δ = −4.4, −3.4, 9.5, 11.7, 26.2, 28.9, 33.4, 33.6, 49.7, 51.4, 107.9, 109.1, 120.2, 120.3, 144.6, 145.1; HRMS calcd for $C_{10}H_{17}NSiS$ 211.0834, found 211.0852.

Dimethyl (1S*,2S*,3R*)-4-Methylene-3-(methylthio)-3-(trimethylsilyl)cyclobutane-1,2-dicarboxylate (56a) and Dimethyl (1S*,2S*,3S*)-4-Methylene-3-(methylthio)-3-(trimethylsilyl)cyclobutane-1,2-dicarboxylate (56b). 56a and **56b** were obtained as a mixture (**56a**:**56b** = 92:8): IR (neat) 1735, 1662, 1436, 1299 cm^{-1}; **56a** ^{1}H NMR (500 MHz) δ = 0.09 (9 H, s), 1.97 (3 H, s), 3.67 (3 H, s), 3.69 (3 H, s), 3.69 (1 H, dd, J = 2.0, 8.8 Hz), 3.81 (1 H, ddd, J = 2.8, 2.8, 8.8 Hz), 4.84 (1 H, dd, J = 1.0, 2.8 Hz), 5.24 (1 H, dd, J = 1.2, 2.8 Hz); ^{13}C NMR (125 MHz) δ = −2.9, 10.0, 43.6, 46.2, 49.7, 51.8, 52.1, 107.7, 143.9, 169.6, 172.0; **56b** ^{1}H NMR (500 MHz) δ = 0.12 (9 H, s), 2.06 (3 H, s), 3.70 (3 H, s), 3.73 (3 H, s), 3.68–3.77 (1 H, m), 4.22 (1 H, ddd, J = 3.0, 3.0, 7.7 Hz), 4.93 (1 H, dd, J = 1.0, 3.0 Hz), 5.38 (1 H, dd, J = 1.0, 3.0 Hz); ^{13}C NMR (125 MHz) δ = −3.6, 12.6, 45.5, 47.1, 48.1, 51.7, 52.1, 110.7, 144.3, 170.2, 171.6; HRMS calcd for $C_{13}H_{22}O_4SiS$ 302.1009, found 302.0979. Relative stereochemistry of the minor isomer **56b** was determined by the comparison of the NMR spectrum with that of the dimethyl ester derived from **22a** whose stereochemistry was determined by the X-ray crystallographic analysis.

Methyl (1R*,2S*)-1-Methyl-3-methylene-2-(methylthio)-2-(trimethylsilyl)cyclobutanecarboxylate (57a) and Methyl (1R*,2R*)-1-Methyl-3-methylene-2-(methylthio)-2-(trimethylsilyl)cyclobutanecarboxylate (57b). 57a and **57b** were obtained as a mixture of (**57a**:**57b** = 85:15) IR (neat) 1732, 1286 cm^{-1}; **57a** ^{1}H NMR (500 MHz) δ = 0.06 (9 H, s), 1.40 (3 H, s), 2.07 (3 H, s), 2.23 (1 H, dt, J_d = 15.4 Hz, J_t = 2.0 Hz), 3.04 (1 H, dt, J_d = 15.4 Hz, J_t = 2.6 Hz), 3.62 (3 H, s), 4.63 (1 H, t, J = 2.6 Hz), 5.00 (1 H, t, J = 2.0 Hz), **57b** δ = 0.19 (9 H, s), 1.45 (3 H, s), 1.98 (3 H, s), 2.30 (1 H, dt, J_d = 15.3 Hz, J_t = 2.2 Hz), 2.31 (1 H, dt, J_d = 15.3 Hz, J_t = 2.5 Hz), 3.66 (3 H, s), 4.69 (1 H, t, J = 2.5 Hz), 4.95 (1 H, t, J = 2.2 Hz); ^{13}C NMR (125 MHz) for **57a** δ = −2.0, 13.7, 23.2, 39.8, 48.7, 51.5, 54.3, 106.4, 145.1, 176.1; **57b** δ = −0.6, 13.5, 22.7, 39.8, 51.4, 52.0, 52.8, 107.4, 146.0, 175.0; HRMS calcd for $C_{12}H_{22}O_2SiS$ 258.1110, found 258.1099. Relative stereochemistry of **57a** was determined by the NOESY spectrum in which NOE between 1-Me and MeS was observed.

1-Chloro-3-methylene-2-(methylthio)-2-(trimethylsilyl)cyclobutanecarbonitrile (58). The product was obtained as a single isomer, and the stereochemistry was not determined: IR (neat) 2238, 1666, 1250 cm^{-1}; ^{1}H NMR (500 MHz) δ = 0.28 (9 H, s), 2.24 (3 H, s), 3.21 (1 H, ddd, J = 2.7, 2.7, 16.8 Hz), 3.48 (1 H, ddd, J = 2.1, 2.3, 16.8 Hz), 4.79 (1 H, br s), 5.17 (1 H, br s); HRMS calcd for $C_{10}H_{16}NSiSCl$ 245.0463, found 245.0436.

3-Methylene-2-(methylthio)-1-cyclobutenecarbonitrile (59): IR (neat) 2196, 1670, 1533, 1428 cm^{-1}; ^{1}H NMR (500 MHz) δ = 2.62 (3 H, s), 3.20 (2 H, s), 4.86 (1 H, s), 5.05 (1 H, s); ^{13}C NMR (125 MHz) δ = 12.9, 38.0, 106.0, 106.8, 115.9, 142.8, 155.9; HRMS calcd for C_7H_7NS 137.0300, found 137.0316.

Crystallographic data of the [2 + 2] cycloadduct 4a: $C_{12}H_{17}NO_5S_2$, MW = 319.39, triclinic, a = 9.552 (2), b = 10.452 (2), and c = 8.021 (1) Å, V = 729.1 (5) Å^3, space group $P\bar{1}$, Z = 2, D_c = 1.45 g cm^{-3}, μ(Mo Kα) = 3.76 cm^{-1}. Data collection: crystal size = 0.500 × 0.500 × 0.500 mm, T_c = 23 °C, Mo Kα radiation (graphite monochrometer), 4275 independent reflections (θ < 60°). The structure was finally refined anisotropically for S, C, O and N and isotropically for H to give R and R_w factors of 0.037 and 0.044 for 3439 independent reflections with $I > 3.0\sigma(I)$.

Crystallographic data of the diol 25: $C_8H_{16}O_2S_2$, MW = 208.33, monoclinic, a = 8.213 (3), b = 7.123 (4), and c = 9.897 (2) Å, β = 108.61 (2)°, V = 548.7 (4) Å^3, space group $P2_1$, Z = 2, D_c = 1.261 g cm^{-3}, μ(Cu Kα) = 40.53 cm^{-1}. Data collection: crystal size = 0.400 × 0.200 × 0.100 mm, T_c = 23 °C, Cu Kα radiation (graphite monochrometer), 897 independent reflections (θ < 60°). The structure was finally refined anisotropically for S, C, and O and isotropically for H to give R and R_w factors of 0.051 and 0.075 for 842 independent reflections with $I > 3.0\sigma(I)$.

Acknowledgment. We thank Drs. Hikaru Ichida and Akiko Kobayashi, The University of Tokyo, for the assistance with the X-ray crystallographic analyses. This work is supported by Grant-in-Aids for Scientific Research on Priority Areas (multiplex Organic Systems) from the Ministry of Education, Science, and Culture, Japan.

Supplementary Material Available: Tables of crystal data, atomic coordinates, bond lengths and angles, and anisotropic displacement parameters of **4a**, **22a**, and **25**; ^{1}H NMR spectra of the new compounds; final results of PM3 calculation; data of NOESY of the compounds **6**, **11a**, **11b**, **12d**, **15a**, **15c**, **15d**, **18**, **19**, **20**, **22b**, **46**, **47**, **50**, **51**, and **52** (155 pages); tables of observed and calculated structure factors (42 pages). Ordering information is given on any current masthead page.

Prediction of the Best Linear Precursor in the Synthesis of Cyclotetrapeptides by Molecular Mechanic Calculations

Florine Cavelier-Frontin,[†] Gérard Pèpe,*[,‡] Jean Verducci,[†] Didier Siri,[‡] and Robert Jacquier[†]

Contribution from the URA-CNRS 468 Amino acides et peptides, Université Montpellier II, Place Eugène Bataillon, 34095 Montpellier Cedex 05, France, and CRMC2[§]-CNRS Campus de Luminy Case 913, 13288 Marseille Cedex 09, France. *Received December 27, 1991*

Abstract: Small cyclopeptides of four to six residues are of great interest because of their biological properties (drugs, insecticides, etc.). Identification of a good precursor that is able to undergo cyclization is very important because of the lengthy synthesis of the linear precursors. Several factors are involved in the cyclization yield. In order to determine the relative influence of each factor in this reaction, molecular modeling calculations were performed using the GenMol program. The transition-state energy rather than the dimerization reaction is the determining factor in ring closure, as evidenced by calculations performed on 4-Ala-chlamydocin, HC-toxin analogues, cyclotetrapeptides of sarcosine with glycine, and 4-Ala-chlamydocin and Cyl 2 analogues.

Introduction

Small cyclopeptides of four to six residues are of great interest because of their specific properties:

(i) Cyclization of a peptide reduces the number of allowed conformations. It is of interest to determine the structure of the receptor sites of the resulting rigid molecules after identifying the active conformations.[1-3]

(ii) Cyclic peptides are more resistant "in vivo" because they are not recognized by the exoproteases. The absence of charged extremities facilitates the crossing of lipid membranes, leading to better bioavailability which can present some advantages in therapeutic applications. The cyclization of a linear biologically active peptide often leads to a derivative drug which is more specific and sometimes more efficient.[4,5]

(iii) Most natural cyclopeptides or cyclodepsipeptides present interesting biological properties. The following examples illustrate the diversity of their structures and of their biological activities: gramicidin S[6,7] is an antibiotic, dolastatin 3[8,9] is one of the most powerful antineoplastics known, peptides of the destruxin family[10,11] are very efficient insecticides, tentoxin[12-15] and HC-toxin[16-19] are phytotoxins whilst another phytotoxin, chlamydocin,[20-24] exhibits cytostatic and cancerostatic properties.

Cyclization is the limiting step in small cyclopeptide synthesis. The various techniques suggested in the literature[25,26] are often unsatisfactory. Competition between dimerization and cyclization can reduce the monocyclopeptide yields.

The rigidity of the linear precursor gives rise to the difficulty in cyclization. Peptide bonds possess strong π character and preferentially adopt a transoid conformation. The linear precursor is elongated with the terminal acid and amine functions in remote positions, this being unfavorable to intramolecular coupling.

Some structural features are observed in natural cyclopeptides. (i) The presence of N-substituted amino acids (imino acids) reestablishes the transoid–cisoid equilibrium. An experimental result concerning cyclization of tetraglycine[27] and tetrasarcosine[28] under the same conditions confirms this effect. The cyclomonomer yields are 5% and 43%, respectively. (ii) D and L amino acids in

* To whom correspondence should be addressed.
† URA-CNRS 468 Amino acides et peptides, Université Montpellier II.
‡ CRMC2[§]-CNRS Campus de Luminy Case 913.
§ Laboratorie associé aux Universités d'Aix-Marseille II et III.

(1) Kessler, H.; Kutscher, B. *Tetrahedron Lett.* **1985**, *26*, 177-180.
(2) Chippens, G. I.; Mutilis, F. K.; Myshlyakova, N. V.; Musina, F. R.; Vitolina, R. O.; Klusha, V. J.; Katayev, B. S. *Int. J. Pept. Protein Res.* **1985**, *26*, 460-468.
(3) Spear, K. L.; Brown, M. S.; Reinhard, E. J.; Mc Mahon, E. G. *J. Med. Chem.* **1990**, *33*, 1935-1940.
(4) Charpentier, B.; Dor, A.; Roy, P.; England, P. *J. Med. Chem.* **1989**, *32*, 1184-1190.
(5) Spanevello, R. A.; Hirschmann, R.; Raynor, K.; Reisine, T.; Nutt, R. F. *Tetrahedron Lett.* **1991**, *32*, 4675-4678.
(6) Ovchinnikov, V. A.; Ivanov, V. T. *Tetrahedron Lett.* **1975**, *31*, 2177-2209.
(7) Izumiyia, N.; Kato, T.; Waki, M. *Biopolymers* **1991**, *20*, 1785-1791.
(8) Schmidt, U.; Utz, R.; Lieberknecht, A.; Griesser, H.; Potzoli, B.; Bhar, J.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 233-236 and 236-241.
(9) Holzapfel, C. W.; Van Zyl, W. J. *Tetrahedron* **1990**, *46*, 649-660.
(10) Pais, M.; Das, B. C.; Ferron, P. *Phytochemistry* **1981**, *20*, 715-723.
(11) Morel, E.; Pais, M.; Turpin, M.; Guyot, M. *Biomed. Pharmacother.* **1983**, *37*, 184-185.
(12) Rich, D. H.; Mathiaparanam, P. *Tetrahedron Lett.* **1974**, *46*, 4037-4040.
(13) Rich, D. H.; Bathnagar, P. K.; Grant, J. A.; Tam, J. P. *J. Org. Chem.* **1978**, *43*, 296-302.
(14) Jacquier, R.; Verducci, J. *Tetrahedron Lett.* **1984**, *25*, 2775-2778.
(15) Heitz, F.; Jacquier, R.; Kaddari, F.; Verducci, J. *Biophys. Chem.* **1986**, *23*, 245-249.
(16) Kawai, M.; Rich, D. H.; Walton, J. D. *Biochem. Biophys. Res. Commun.* **1983**, *111*, 398-404.
(17) Kawai, M.; Rich, D. H. *Tetrahedron, Lett.* **1983**, *24*, 5309-5312.
(18) Jacquier, R.; Lazaro, R.; Ranirisehenо, H.; Viallefont, P. *Tetrahedron Lett.* **1986**, *27*, 4735.
(19) Jacquier, R.; Lazaro, R.; Ranirisehenо, H.; Viallefont, P. *Int. J. Pept. Protein Res.* **1987**, *30*, 22-32.
(20) Rich, D. H.; Gardner, J. *Tetrahedron Lett.* **1983**, *24*, 5305-5308.
(21) Schmidt, U.; Beutler, T.; Lieberknecht, A.; Griesser, H. *Tetrahedron Lett.* **1983**, *24*, 3573-3576.
(22) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Bartowiak, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 318-320.
(23) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Utz, R.; Beutler, T.; Bartowiak, F. *Synthesis* **1986**, 361-366.
(24) Kawai, M.; Gardner, J. H.; Rich, D. H. *Tetrahedron Lett.* **1986**, *27*, 1877-1880.
(25) Spatola, A. F.; Anwer, M. K.; Rockwell, A. L.; Gierash, L. M. *J. Am. Chem. Soc.* **1986**, *108*, 825-831.
(26) Rovero, P.; Quartara, L.; Fabbri, G. *Tetrahedron Lett.* **1991**, *32*, 2639-2642.

0002-7863/92/1514-8885$03.00/0