

Asymmetric [2+2] Cycloaddition Reaction between  $\alpha,\beta$ -Unsaturated Acid Derivatives and Alkynyl or Alkenyl Sulfides Catalyzed by a Chiral Titanium Reagent

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Asymmetric [2+2] cycloaddition reaction between 3-(acryloyl)-1,3-oxazolidin-2-one derivatives and alkynyl or alkenyl sulfides proceeds by the use of a chiral titanium reagent to give the corresponding cyclobutene or cyclobutane derivatives in high enantioselectivity.

[2+2] Cycloaddition reaction is one of the most fundamental methods for the construction of cyclobutane derivatives, which are important intermediates in organic synthesis.<sup>1)</sup> As for the asymmetric [2+2] cycloaddition reactions, methodologies based on stoichiometric asymmetric induction have been commonly employed by the use of substrates having chiral auxiliaries.<sup>2)</sup> And it is a rare precedent for [2+2] cycloaddition between prochiral substrates to proceed enantioselectively.<sup>3)</sup> We have reported that asymmetric [2+2] cycloaddition between  $\alpha,\beta$ -unsaturated carboxylic acid derivatives **1** and a ketene dithioacetal proceeds with a catalytic amount of a chiral titanium reagent<sup>4)</sup> to afford the cyclobutane derivatives in high optical purity.<sup>5a)</sup> In this paper is reported further applications of this catalytic process for preparing various optically active cyclobutenes and cyclobutanes.

The exceptional reactivity of a ketene dithioacetal as compared with its oxygen analogue in the previous reaction<sup>5a)</sup> indicated that unsaturated compounds having an alkylthio group would be suitable for the electron rich olefins in the asymmetric [2+2] cycloaddition reaction. The reaction of alkynyl sulfides **2** with acrylic acid derivatives **1** was, therefore, examined for the preparation of optically active cyclobutenes. That is, the chiral titanium reagent was generated *in situ* by mixing dichlorodiisopropoxytitanium and the tartrate-derived chiral 1,4-diol **3** in toluene.<sup>4)</sup> In the presence of an equimolar amount of this chiral titanium reagent, the reaction of 3-acryloyl-1,3-oxazolidin-2-one (**1a**) and 1-hexynyl methyl sulfide (**2a**) was carried out at 0 °C in a toluene-petroleum ether (P.E., 1:1) solvent to afford the corresponding cyclobutene **4a** in 86% yield as a nearly optically pure form (>98 %ee, entry 1). A catalytic use of the chiral titanium reagent (10 mol%) was also effective in this reaction to give **4a** with little loss of the optical yield (98 %ee, entry 2).

By the use of the chiral titanium, acrylic and fumaric acid derivatives **1a,b** smoothly reacted with some alkynyl sulfides **2a-d**, yielding cyclobutenes **4** in quite high optical purity as shown in Table 1. In the synthesis of trisubstituted cyclobutenes, the reaction proceeded in good yield and

in high enantioselectivity with only a catalytic amount of the chiral titanium reagent (entries 2 and 7). For the preparation of tetrasubstituted cyclobutenes, on the other hand, an equimolar amount of the chiral titanium was required for the completion of the reaction. The reaction of the crotonoyl oxazolidinone **1c**, however, did not proceed even by employing an equimolar amount of the chiral titanium reagent (entry 8).

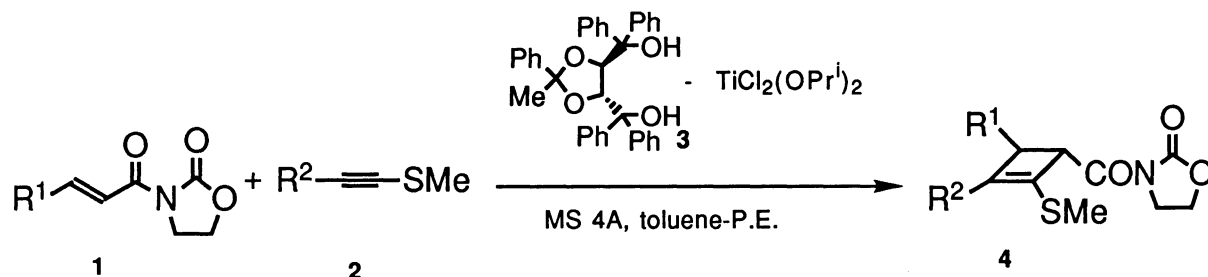


Table 1. The reaction of **1** with alkynyl sulfide **2**

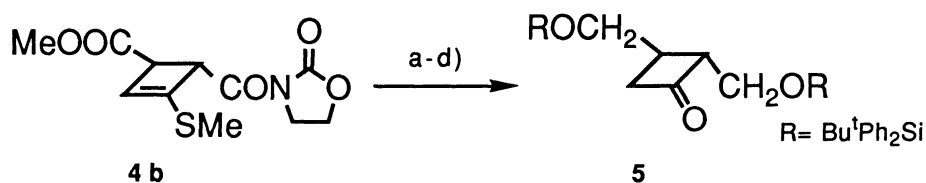
Entry	R <sup>1</sup>	R <sup>2</sup>	Amount of Ti/equiv.	Yield/%	Opt.yield/%ee <sup>a)</sup>
1	H ( <b>1a</b> )	Bu ( <b>2a</b> )	1.1	86	>98 ( <b>4a</b> )
2			0.1	80	98 <sup>b)</sup>
3	COOMe ( <b>1b</b> )	Bu ( <b>2a</b> )	1.1	92	>98
4			0.3	55	90 <sup>c)</sup>
5		Me ( <b>2b</b> )	1.1	90	>98
6		cyclohexyl ( <b>2c</b> )	1.1	84	>98
7		H ( <b>2d</b> )	0.1	83	>98 ( <b>4b</b> )
8	Me ( <b>1c</b> )	Bu ( <b>2a</b> )	1.1	0	

a) Optical yield was determined by the method in Ref. 6 except entries 2 and 4.

b) Optical yield was determined by the comparison of  $[\alpha]_D$  with the value of entry 1.

c) Optical yield was determined by the comparison of  $[\alpha]_D$  with the value of entry 3.

The absolute configuration of the cyclobutene **4b** derived from **1b** and **2d** was determined as 3S, 4R by the transformation to the cyclobutanone **5**, of which the absolute stereochemistry has been known.<sup>5)</sup> Similarly to the previous [2+2] cycloaddition of ketene dithioacetal<sup>5a)</sup> and the inter- and intramolecular Diels-Alder reactions,<sup>7)</sup> the *re*-face of the  $\alpha$ -carbon in the acrylic acid derivatives is attacked when the (R,R)-1,4-diol **3** is employed as a chiral auxiliary. So the same sense of the enantioselection would be anticipated in the other cyclobutene derivatives **4**.



a) Mg(OMe)<sub>2</sub> b) LiAlH<sub>4</sub> c) Bu<sup>t</sup>Ph<sub>2</sub>SiCl, imidazole, cat.DMAP d) CuO, CuCl<sub>2</sub>.<sup>8)</sup>

Takeda has reported the Lewis acid ( $\text{AlCl}_3$ ) promoted [2+2] cycloaddition reaction in which vinyl sulfides reacted with labile electron deficient olefins such as methyl vinyl ketone.<sup>9)</sup> By applying the chiral titanium, vinyl sulfides were also found to react with the fumaric acid derivative **1b**. The following equation exhibits the reactions of 2-ethylthio-1-propene (**6a**) and 3-trimethylsilyl-2-methylthio-1-propene (**6b**) with **1b**. The diastereoselectivity of the resulting cyclobutanes **7, 8** was not sufficiently high,<sup>10)</sup> but the major isomers **7a, b** were obtained in nearly optical pure form.

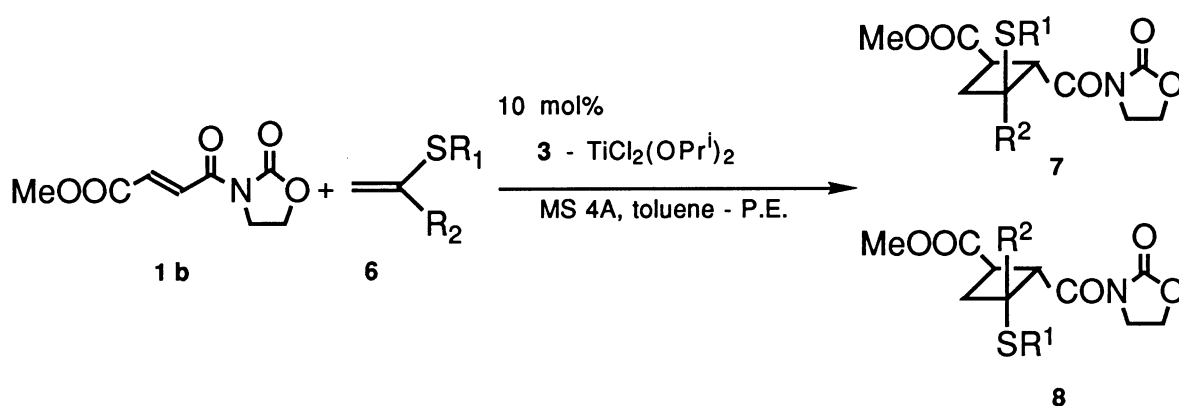


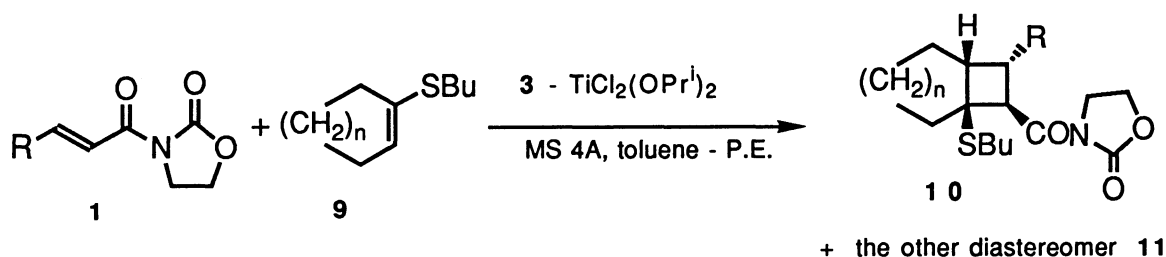
Table 2. The reaction of **1b** and vinyl sulfide **6**

R <sup>1</sup>	R <sup>2</sup>		Yield/%		Opt.yield/%ee	
			7	8	7	8
Et	Et	( <b>6a</b> )	51	19	99a)	79a)
Me	CH <sub>2</sub> SiMe <sub>3</sub>	( <b>6b</b> )	54	17	99b)	

a) Optical yield was determined by the method in Ref. 6 using a mixture of **7** and **8**.

b) Optical yield was determined by the method in Ref. 6 after separating **7** and **8**.

Then, for the preparation of synthetically useful bicyclo[n.2.0] compounds, this asymmetric cycloaddition was applied to cyclic vinyl sulfides. The reaction of 1-butylthio-1-cyclohexene (**9a**) and **1b** with an equimolar amount of the chiral titanium afforded the bicyclo[3.2.0]octane derivative **10** almost in diastereomerically<sup>10)</sup> and enantiomerically<sup>6)</sup> pure form. The results of the reactions of various cyclic vinyl sulfides **9** with **1a, b** are summarized in Table 3. Good to excellent diastereoselectivities were observed in the reaction of cyclic vinyl sulfides. Moreover, almost complete enantioselection was attained in the preparation of various bicyclo[n.2.0] derivatives **10**.

Table 3. The reaction of **1a,b** with cyclic vinyl sulfides **9**

R	n	Amount of Ti/equiv.	Yield( <b>10</b> + <b>11</b> )/%	<b>10</b> : <b>11</b> <sup>a)</sup>	Opt.yield of <b>10</b> / % <sup>cc</sup>
COOMe ( <b>1b</b> )	2 ( <b>9a</b> )	1.1	96	>99:1	>98 <sup>b)</sup>
		0.15	92	>99:1	>98 <sup>b)</sup>
	3 ( <b>9b</b> )	1.1	97	92:8	>98 <sup>c)</sup>
	4 ( <b>9c</b> )	1.1	89	91:9	>98 <sup>c)</sup>
H ( <b>1a</b> )	2 ( <b>9a</b> )	0.25	74	82:18	>98 <sup>c)</sup>

a) Diastereomer ratio was determined by 500 MHz <sup>1</sup>H-NMR.

b) Optical yield was determined by the method in Ref. 6.

c) Optical yield was determined by the method in Ref. 6 using a mixture of **10** and **11**.

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- 6) Optical purity was determined by measuring the 500 MHz <sup>1</sup>H-NMR spectrum of the (+)-MTPA ester,<sup>11)</sup> which was prepared by the following sequences: 1) Mg(OMe)<sub>2</sub>, 2) LiAlH<sub>4</sub>, 3) (+)-MTPA-Cl, pyridine, cat.DMAP.
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