

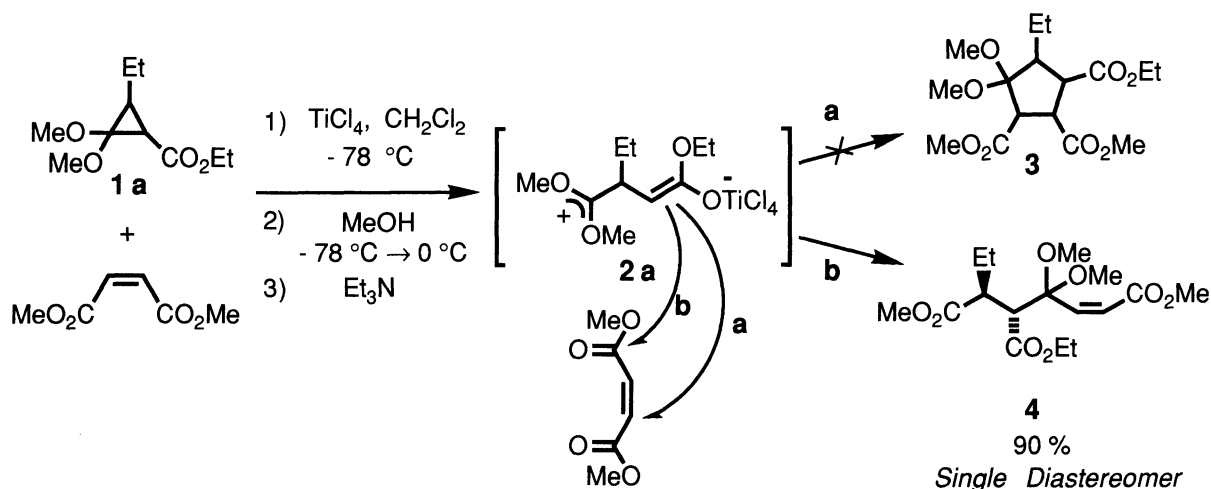
Diastereoselective Claisen Condensation-Type Reactions of Alkyl 2,2-Dialkoxycyclopropanecarboxylates  
with Esters and Acid Chlorides Promoted by Titanium(IV) Chloride

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In the presence of titanium(IV) chloride, alkyl 2,2-dialkoxycyclopropanecarboxylates reacted with esters and acid chlorides to give Claisen condensation-type products. The reaction essentially proceeded with extremely high diastereoselectivity.

Vicinally donor-acceptor-substituted cyclopropanes are valuable as synthetic building blocks in organic syntheses.<sup>1)</sup> We recently reported highly diastereoselective syntheses of  $\gamma$ -lactones<sup>2)</sup> and  $\gamma$ -lactams<sup>3)</sup> by the reactions of 2,2-dialkoxycyclopropanecarboxylic esters **1** with carbonyl compounds and with *N*-tosyl aldimines, respectively. We also reported that **1** reacted with carbon nucleophiles such as ketene silyl acetals to give cyclopentenones.<sup>4)</sup> These reactions probably involved the formation of (*E*)-1,3-zwitterion **2**. In the course of our study to find further application of **1** as a synthetic building block, we examined the reaction of **1** with olefinic electrophiles. For the reaction of **1** with an olefinic electrophile, we expected that a Michael-type reaction would occur and subsequent ring-closure would give a cyclopentane derivative. But, when **1a** was allowed to react with dimethyl maleate, a Claisen condensation-type reaction (Scheme 1, path b) occurred instead of a Michael-type reaction (Scheme 1, path a). Here we report diastereoselective, Lewis acid-mediated Claisen condensation-type reactions<sup>5)</sup> of **1** with esters and acid chlorides.



Scheme 1.

At first, we examined the reaction of ethyl 3-ethyl-2,2-dimethoxycyclopropanecarboxylate (**1a**)<sup>6)</sup> with dimethyl maleate. Under various reaction conditions, no Michael-type adduct like **3** was obtained. But, when the reaction was carried out in the presence of titanium(IV) chloride at -78 °C and then the reaction mixture was quenched by adding anhydrous methanol followed by triethylamine, single product was isolated. To our surprise, the structure of the product assigned on the basis of <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and IR spectra was of a Claisen condensation-type reaction as **4**, which was formed by the reaction of the enolate part of **2a** with dimethyl maleate at the ester carbonyl carbon instead of the olefinic carbon. Furthermore, **4** was found to be obtained as a single diastereomer.<sup>7)</sup> In order to examine the generality of this reaction, we next performed the reaction of **1** with various esters. The results are shown in Table 1. In some cases, acetals **5** were unstable, and during the work-up and/or the purification by silica gel column chromatography or silica gel preparative TLC, the products were partly converted into keto-form **6**. In all cases, **5** were obtained as a single diastereomer<sup>7)</sup> and **6** were obtained as a mixture of diastereomers. Esters with higher electrophilicity gave **5** in good yields (entries 1-3), and normal esters gave **5** and **6** in moderate yields (entries 4-6).

The yield of Claisen condensation-type products were sufficiently improved when acid chlorides were used as electrophiles in the place of esters. The 1,3-zwitterion, derived from **1a** on the action of titanium(IV) chloride, smoothly reacted even with aliphatic acid chlorides to give mixtures of the corresponding Claisen condensation-type products **5** and **6** in good yields (Table 1, entries 7 and 8). Moreover, each acetal **5** also consisted of a single diastereomer.<sup>7)</sup>

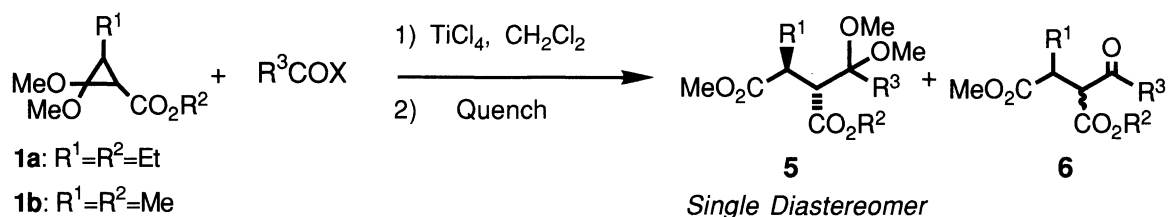


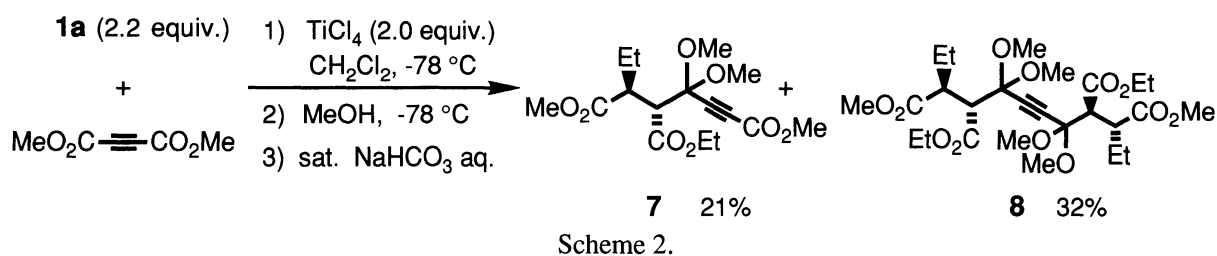
Table 1. The Reaction of **1** with Esters and Acid Chlorides

Entry	<b>1</b>	R <sup>3</sup>	X	Temp / °C	Quench <sup>a)</sup>	<b>5</b> / %	<b>6</b> / %
1	<b>1a</b>	(Z)-MeO <sub>2</sub> CCH=CH	OMe	-78	A	90	0
2	<b>1b</b>	(Z)-MeO <sub>2</sub> CCH=CH		-78	A	72	0
3	<b>1a</b>	(E)-MeO <sub>2</sub> CCH=CH		-78	A	89	0
4	<b>1a</b>	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>		-78	B	32	4
5	<b>1a</b>	C <sub>6</sub> H <sub>5</sub>		-45	B	37	8
6	<b>1a</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>		-45	B	15	15
7	<b>1a</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	Cl	-45	B	45	20
8	<b>1a</b>	CH <sub>3</sub>		-45	B	52	23

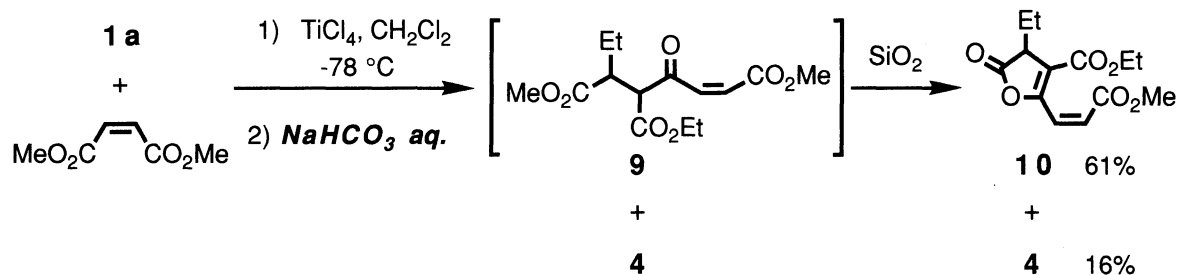
a) A: MeOH, -78 °C to 0 °C, then Et<sub>3</sub>N. B: MeOH, -78 °C or -45 °C, then sat. NaHCO<sub>3</sub> solution.

A typical procedure is as follows: To a stirred solution of **1a** (120 mg, 0.594 mmol) and dimethyl maleate (70.6 mg, 0.490 mmol) in dry dichloromethane (3 ml) was added drop by drop a solution of titanium(IV) chloride (0.53 mmol) in dichloromethane (0.5 ml) at  $-78^{\circ}\text{C}$  under an argon atmosphere. The reaction mixture immediately became deep brown. After the addition was completed (4 min), the mixture was stirred for 5 h at the same temperature. During this period, fading of the color of the solution was observed and finally the solution became orange. Anhydrous methanol (0.6 ml) was added to the reaction mixture at  $-78^{\circ}\text{C}$ , and the stirring was continued for 15 min. Then, the mixture was warmed to  $0^{\circ}\text{C}$  (the reaction mixture almost became colorless) and triethylamine (0.22 g, 2.2 mmol) in dichloromethane (1.2 ml) was added. The stirring was continued for 10 min, and water (3 ml) was added. The mixture was allowed to warm to room temperature. Additional water (10 ml) was introduced, and the mixture was extracted with dichloromethane ( $4 \times 10$  ml). The combined organic layers were dried over sodium sulfate. After filtration and evaporation, the crude product was purified by column chromatography (eluent: hexane/EtOAc = 8:1) to give **4** (152 mg, 90% yield based on dimethyl maleate) as a colorless oil.

The reaction of **1a** with dimethyl acetylenedicarboxylate was also tried by using 2.2 equivalents of **1a**. As shown in Scheme 2, in addition to 1:1 adduct **7**, 2:1 adduct **8** was obtained.<sup>8)</sup> Only **8** was a crystalline product that we obtained in this study, and the structure was confirmed by X-ray structure analysis.<sup>9)</sup> On the basis of this result, we assumed that the relative stereochemistry of other acetal products **4**, **5**, and **7** were the same as that of **8** as shown in schemes.<sup>10, 11)</sup>



Furthermore, we also examined the effect of a quenching agent. As shown in Scheme 3, when the reaction of **1a** with dimethyl maleate was quenched by the addition of a saturated  $\text{NaHCO}_3$  solution instead of methanol, butenolide **10**, of potential value for natural product synthesis, was obtained as a main product (61% yield) after purification by silica gel column chromatography. From the  $^1\text{H}$ -NMR and IR analyses of crude products, it became clear that keto-type product **9** was initially formed, and then upon treatment with silica gel, **9** was transformed into butenolide **10**.<sup>11)</sup>

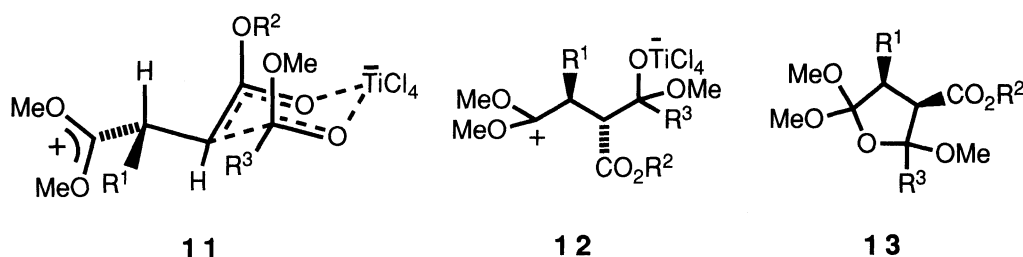


It is noted that the Lewis acid-mediated Claisen condensation-type reaction is very unusual,<sup>5)</sup> especially when a competitive Michael addition reaction is possible to occur. Moreover, the Claisen condensation-type products were exclusively obtained with high stereoselectivity in the present method, which can be attributable to the nature of the intermediate 1,3-zwitterion. Further applications using these multifunctional, diastereo-homogeneous products are now under investigation in this laboratory.

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- 7) The other diastereomer was not detected by 400 MHz  $^1\text{H}$ -NMR.
- 8) When the reaction of **1a** with dimethyl acetylenedicarboxylate was performed by using 1.2 equiv. of **1a**, 2:1 adduct **8** was also obtained in 23% yield. On the other hand, in the cases of dimethyl maleate and dimethyl fumalate, 2:1 adducts were not obtained at all (in these cases, 1.2 equiv. of **1a** was used).
- 9) The crystal data:  $\text{C}_{26}\text{H}_{42}\text{O}_{12}$ , MW=546.61, space group  $\text{P}\bar{1}$ ,  $a=8.530(1)$  Å,  $b=10.625(4)$  Å,  $c=8.381(1)$  Å,  $\alpha=91.78(2)^\circ$ ,  $\beta=102.98(1)^\circ$ ,  $\gamma=78.43(2)^\circ$ ,  $V=725.1(3)$  Å<sup>3</sup>,  $Z=1$ ,  $D_{\text{calc}}=1.25$  g/cm<sup>3</sup>,  $R=0.072$ .
- 10) The coupling constants between two hydrogens of vicinal asymmetric centers are 8-11 Hz for all acetal-type products **4**, **5**, **7**, and **8**.
- 11) The diastereoselectivity of this reaction is consistent with that of the reaction of **1** with ketones.<sup>2b)</sup> Although the reaction mechanism is not clear, we assumed that **1** reacted with esters through a transition state like **11**.<sup>2b)</sup> Then, the resultant intermediate like **12** or its cyclized form **13** was transformed into acetal- or keto-type product **5** or **6** by treatment with a quenching agent. Butenolide **10** would be formed through enolization and lactonization of **9** by treatment with acidic silica gel.



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