CHEMISTRY LETTERS, pp. 1093-1096, 1990.

Lewis Acid-Mediated Reaction of 2,2-Dialkoxycyclopropanecarboxylic Esters with Ketene Silyl Acetals. Synthesis of Cyclopentenones

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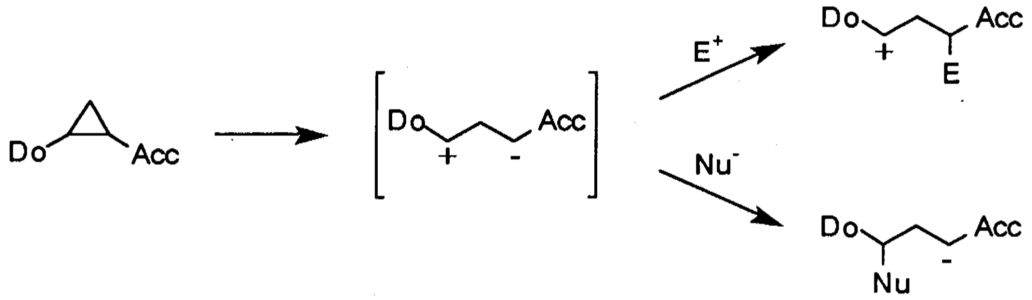
A novel [3+2] type reaction of 2,2-dialkoxycyclopropanecarboxylic esters with ketene silyl acetals, mediated by titanium(IV) chloride, afforded 3-alkoxy-2- (or -3-) cyclopentenone derivatives.

Cyclopropanes with donor and acceptor substituents at vicinal positions on the cyclopropane ring have been shown to be very versatile building blocks in organic synthesis, especially for polyfunctionalized compounds.1) These cyclopropanes should be susceptible to a heterolytic ring cleavage because of substituent effect to form a zwitterionic intermediate. Therefore, these cyclopropanes are expected to react with electrophiles and nucleophiles (Scheme 1). A number of reactions of these types of cyclopropanes with various electrophiles were reported, while the reaction with carbon nucleophiles is rare.1) Ring-opening addition reaction of cyclopropanes with carbon nucleophiles such as organocopper reagents (the homologous Michael reaction) usually requires two electron-withdrawing groups on the ring at geminal position.2) In the case of cyclopropanes with one electron-withdrawing group, 1,2-addition usually predominates.3,4) But, when cyclopropane ring is incorporated in a highly strained polycyclic system, 1,5-addition readily occurs.5) To our knowledge, for vicinally donor-acceptor-substituted cyclopropanes, only one example was reported on the ring-opening addition reaction with a carbon nucleophile, i.e., the reaction of highly strained tricyclic systems with lithium dimethylcuprate mediated by boron trifluoride etherate.6)



Scheme 1.

We recently reported highly diastereoselective synthesis of γ-lactones and γ-lactams by the Lewis acid-mediated reactions of ethyl 2,2-dialkoxycyclopropanecarboxylates 1 with aldehydes and aldimines as carbon electrophiles.7) On the basis of these results, we expected that 1 was transformed into a zwitterionic intermediate by the action of a Lewis acid and that the intermediate reacted with carbon nucleophiles. Here we report our first result on the Lewis acid-mediated reaction of **1** with carbon nucleophiles, ketene silyl acetals.

At first, we examined the reaction of ethyl 3-ethyl-2,2-dimethoxycyclopropanecarboxylate (**1a**) with ketene tert-butyldimethylsilyl methyl acetal (**2a**). In the presence of titanium(IV) chloride, **1a** smoothly reacted with **2a** in dichloromethane at -78 °C, and cyclopentenone **3** (R^1=R^3=Et, R^2=R^5=H, R^4=Me)[8] was obtained in 78% yield. The reaction of **1a** with methylketene methyl trimethylsilyl acetal (**2b**) under the same conditions, however, gave cyclopentenone **3** (R^1=R^3=Et, R^2=H, R^4=R^5=Me)[8] only in a low yield. Therefore, for the reaction of **1a** with **2b**, we examined, in detail, reaction conditions such as kind of Lewis acid, reaction temperature, and molar ratio. Lewis acids such as tin(IV) chloride, zinc bromide, and trimethylsilyl trifluoromethanesulfonate did not give the desired cyclopentenone, and titanium(IV) bromide was less effective than titanium(IV) chloride. The yield was improved when the reaction mixture was allowed to warm to room temperature just after the addition of titanium(IV) chloride and when **2b** was used in excess (3 equiv.). On the basis of these results, the reaction of cyclopropanes **1** with ketene silyl acetals **2** was carried out in the presence of titanium(IV) chloride using **1** and **2** in the ratio of 1.0/3.0 or 1.2-1.3/1.0 (for highly reactive combinations; **1a**/**2a** and **1b**/**2a**). The results are shown in Table 1.

A typical procedure is as follows: To a stirred solution of **1a** (106 mg, 0.52 mmol) and **2c** (322 mg, 1.6 mmol) in dichloromethane (3 ml) was added drop by drop a solution of titanium(IV) chloride (0.56 mmol) in dichloromethane (0.5 ml) at -78 °C under an argon atmosphere. The reaction mixture immediately became deep wine-red. After the addition was completed (6 min), the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The stirring was continued for additional 2 h, and the color of the mixture changed from deep wine-red to deep orange. After the reaction mixture was quenched with anhydrous methanol (0.3 ml), water (10 ml) and dichloromethane (10 ml) were added. The organic layer was separated and then the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried with anhydrous sodium sulfate. After filtration and evaporation, the crude product was separated by PTLC (eluent: hexane/EtOAc = 1/1) to give cyclopentenones **3** (R^1=R^3=Et, R^2=H, R^4=R^5=Me; Rf = 0.5; 67 mg; 56% yield based on **1a**) and **4** (R^1=R^3=Et, R^2=H, R^5=Me; Rf = 0.65; 36 mg; 25% yield).

This reaction was influenced by steric hindrance. The combination of 3-monosubstituted cyclopropanes (**1a**, **1b**, and **1c**), and unsubstituted and monosubstituted ketene silyl acetals (**2a**, **2b**, and **2c**) gave a satisfactory result. But, the use of 3,3-disubstituted cyclopropane (**1d**) or disubstituted ketene silyl acetal (**2d**) gave cyclopentenone **3** or **5** only in a low yield. In some cases, 1:2 adduct **4**[8] was obtained other than 1:1 adduct **3**, probably because **2** was used in excess (3 equiv.) (entries 2, 3, and 6). When dimethylketene methyl trimethylsilyl acetal (**2d**) was employed, 3-cyclopentenone derivative **5**[8] was obtained (entry 4).

When cyclopropane **1d** was mixed with titanium(IV) chloride in $CDCl_3$ at room temperature, the mixture became deep wine-red and the ^1H-NMR signal of two methyl groups at 3-position of **1d** changed from two singlets into one singlet. These observations indicate the loss of chiral center and the formation of ring-opened, titanated ketene acetal-type intermediate[9] like **6**. Moreover, when 1:1 adduct **3** (R^1=R^3=Et, R^2=H, R^4=R^5=Me) was allowed to react with **2c** (1.3 equiv. of **2c**, 1 equiv. of $TiCl_4$, -78 °C → room temperature), the adduct was recovered almost quantitatively. On the basis of these results, the mechanism of this reaction can be explained as follows (Scheme 2). At the first step, cyclopropane **1** reacts with titanium(IV) chloride to afford ring-opened zwitterionic intermediate **6**. Then, ketene silyl acetal **2** attacks the cationic center, and the intramolecular Claisen condensation (the Dieckmann condensation) of the resulting intermediate **7** takes place to give cyclopentanone **8**. Finally, the elimination of alcohol from **8** affords cyclopentenone **3**. In the case of the

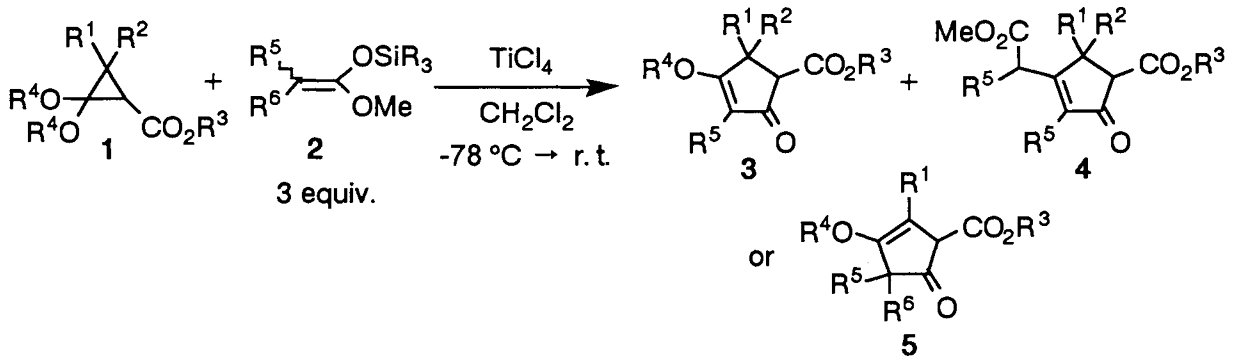
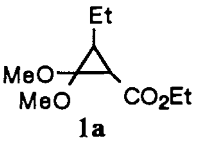
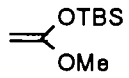
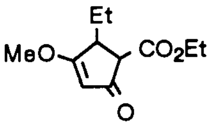
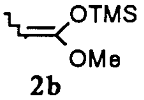
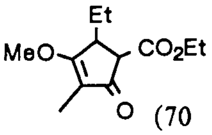
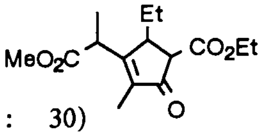
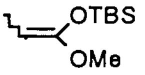
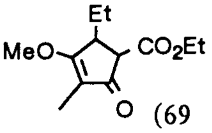
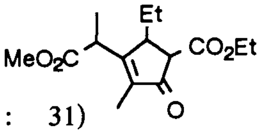
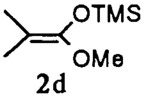
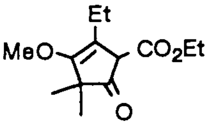
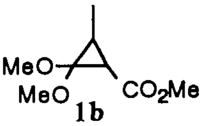
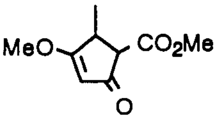
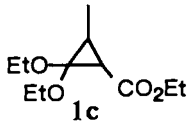
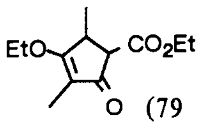
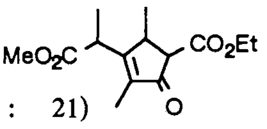
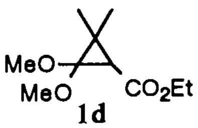
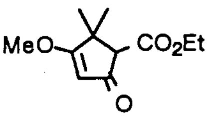
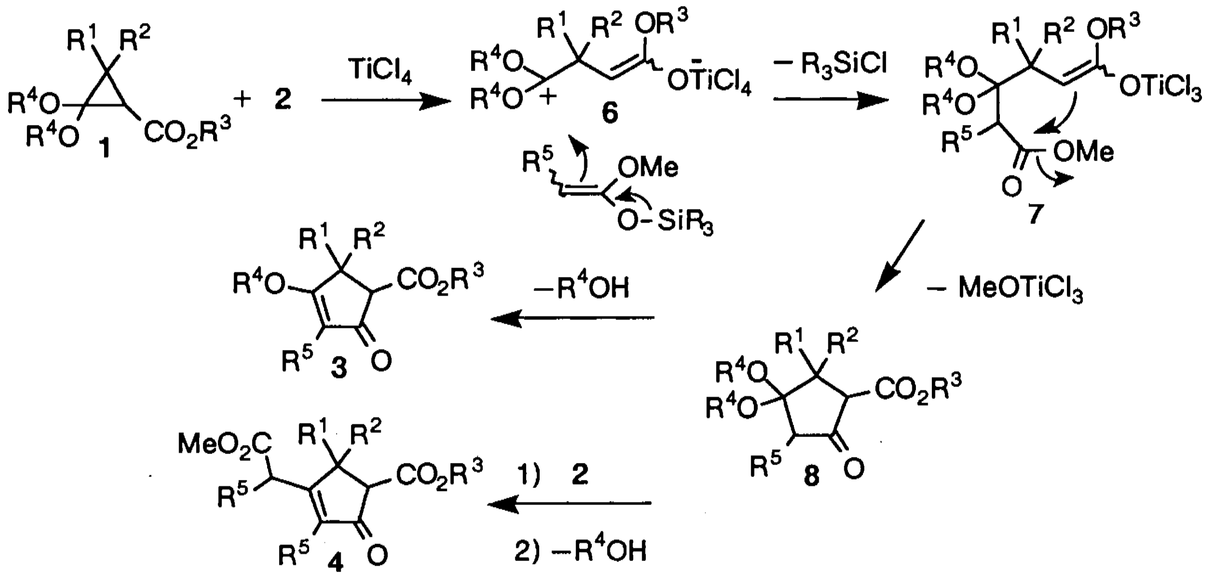


Table 1. The Reaction of Cyclopropanes 1 with Ketene Silyl Acetals 2

Entry	1	2$^{a)}$	Product (ratio)	Yield / %$^{b)}$
1	 1a	 2a		75 (78)$^{c)}$
2		 2b	  (70 : 30)	70
3		 2c	  (69 : 31)	81
4		 2d		31
5	 1b	2a		43 (81)$^{c)}$
6	 1c	2c	  (79 : 21)	67
7	 1d	2a		28

a) TBS = tert-butyldimethylsilyl, TMS = trimethylsilyl. b) Isolated yield based on 1. c) The value in parenthesis represents the yield of 3 (based on 2) when the reaction was performed under the following conditions; 1.2-1.3 equiv. of 1, 1 equiv. of 2, and 1.2 equiv. of TiCl$_4$, -78 °C.



Scheme 2.

reaction of **1a** with dimethylketene silyl acetal **2d**, the elimination of alcohol occurs to afford **5**. 1:2 adduct **4** is not produced by the reaction of **3** with ketene silyl acetal **2** used in excess but by the reaction of **8** with **2**, followed by the elimination of alcohol.

Further studies on the clarification of the mechanism and on the reactions of **1** with other carbon nucleophiles are currently in progress.

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(Received March 28, 1990)