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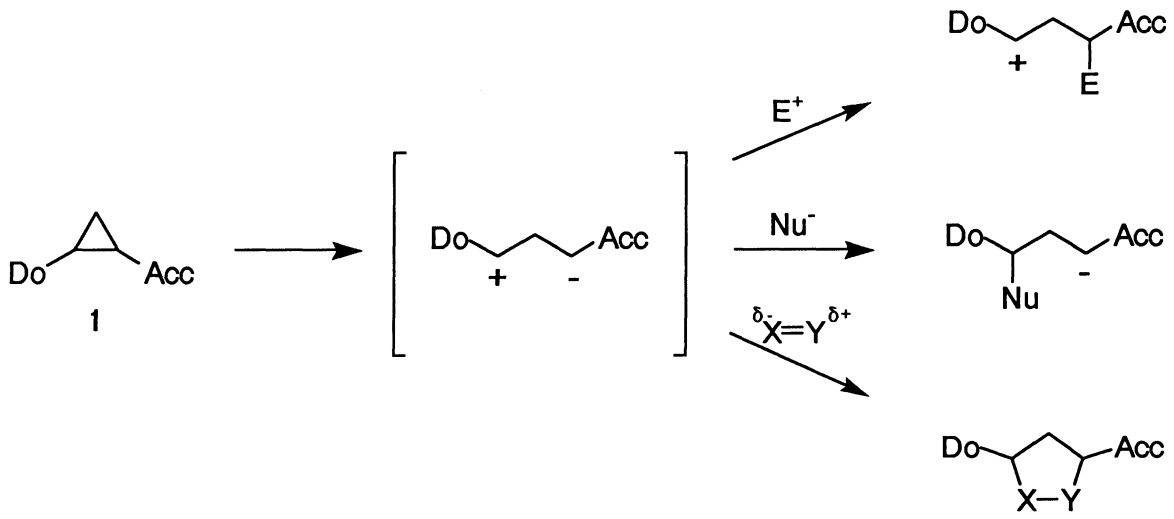
Diastereoselective Synthesis of γ-Lactones by the Aldol-Type Reaction of Ethyl 2,2-Dialkoxycyclopropanecarboxylates with Aldehydes

Kazuhiko SAIGO,* Shigeru SHIMADA, Yukihiko HASHIMOTO, and Masaki HASEGAWA
Department of Synthetic Chemistry, Faculty of Engineering,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

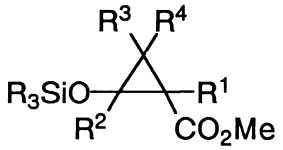
Ethyl 2,2-dialkoxycyclopropanecarboxylates, considered as three carbon 1,3-dipole equivalents, reacted smoothly with aldehydes in the presence of titanium(IV) bromide to give γ-lactones in good yields with high diastereoselectivity.

Vicinally donor-acceptor-substituted cyclopropane **1** has recently attracted much attention as a useful synthetic building block.[1] The heterolytic ring opening reaction of **1** would proceed smoothly to give a 1,3-dipole intermediate because the ring strain is released and the separated charges can be stabilized by the neighboring substituents. Therefore, **1** is recognized as a good reactant for electrophiles and nucleophiles. Moreover, in the reaction with polarized unsaturated compounds, the products are expected to have a five membered ring system through a [3+2] type addition reaction.



Recently, Reissig *et al.* have reported the reaction of methyl 2-(trialkylsiloxy)cyclopropanecarboxylates **2** with various substrates.[1,2] These cyclopropane derivatives **2** have an electron-donating trialkylsiloxy group and an electlon-accepting ester group. By contrast, we were interested in the reaction of ethyl 2,2-dialkoxycyclopropanecarboxylates **3**, readily prepared from ketene acetals and ethyl diazoacetate.[3] Since they have two alkoxy groups as donors and

an ester group as an acceptor, an easy heterolytic C-C bond cleavage would result. As the reactions of 3, only two solvolytic ring opening reactions have been reported, namely hydrolysis and alcoholysis.[3,4] To our knowledge, there is no publication concerning the C-C bond forming reactions of 3. In this paper, we wish to report our first result on the C-C bond forming reactions by use of 3 as a systhetic building block, giving γ-lactones with high diastereoselectivity.



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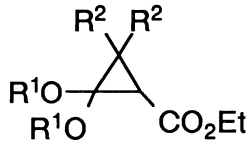
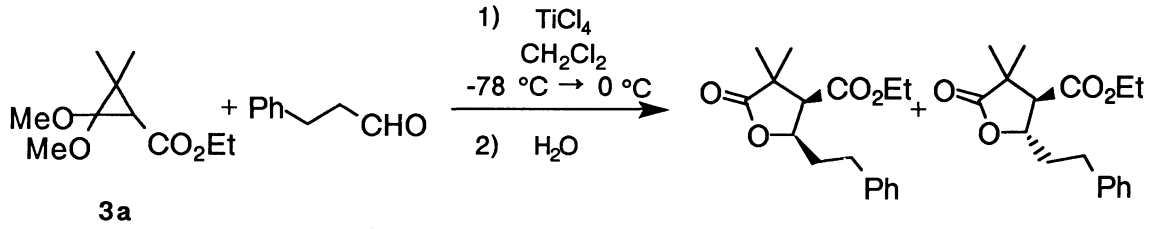


3a $R^1=R^2=Me$

3b $R^1=Et$, $R^2=H$

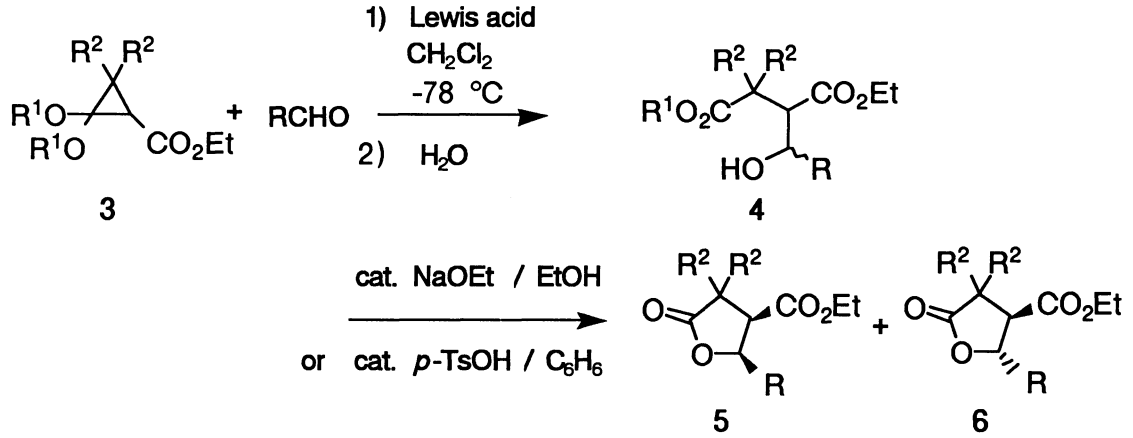
At first, the reaction of geminal dimethyl derivative 3a with 3-phenylpropanal was tried by using titanium(IV) chloride as an activator at -78 to 0 °C. After usual work-up with water, 3-ethoxycarbonyl-2,2-dimethyl-6-phenyl-4-hexanolide was obtained in 88% yield, and *cis*-isomer was found to be mainly formed (*cis* : *trans* = 78:22).[5]



3a

To improve the diastereoselectivity of this reaction, we examined the reaction conditions such as solvent, Lewis acid, reaction temperature, and reaction time. Among these conditions, the nature of Lewis acid influenced considerably on the diastereoselectivity. For example, in the presence of zinc bromide, the reaction of 3a with 3-phenylpropanal gave mainly the *trans* γ-lactone (*cis* : *trans* = 37:63), which is opposite to the result obtained from the reaction by using titanium(IV) chloride. Finally, titanium(IV) bromide was found to be an efficient promotor for the diastereoselective reaction of 3 (Table 1, Entry 1), and the reaction proceeded sufficiently even at -78 °C. Although the isolated product was a mixture of γ-lactones and open chain hydroxy diesters 4 after quenching with water at -78 °C, the crude product was completely converted to the γ-lactones by treatment with a catalytic amount of sodium ethoxide in ethanol or *p*-toluenesulfonic acid in benzene.

The reaction of 3[6] with various aldehydes was carried out under the optimized conditions illustrated in Scheme 1, and the results are summarized in



Scheme 1.

Table 1. The Reaction of Ethyl 2,2-Dialkoxycyclopropanecarboxylates with Aldehydes

Entry	Carboxylate	Aldehyde	Lewis acid	Yield/%[a]	*cis* 5 : *trans* 6[b]
1	**3a**	$PhCH_2CH_2CHO$	$TiBr_4$	89	85 : 15
2			$SnBr_4$	50	99 : 1
3		PhCHO	$TiBr_4$	91	98 : 2
4		$(CH_3)_2CHCHO$	$TiBr_4$	87	95 : 5
5		$CH_3(CH_2)_6CHO$	$TiBr_4$	86	89 : 11
6	**3b**	$PhCH_2CH_2CHO$	$TiBr_4$	91	82 : 18
7		PhCHO	$TiBr_4$	93	80 : 20
8			$SnBr_4$	80	88 : 12
9		$(CH_3)_2CHCHO$	$TiBr_4$	70	71 : 29

a) Isolated yield. b) Determined by GLC.

Table 1.

A typical procedure is as follows: To a stirred solution of **3a** (128 mg, 0.63 mmol) and benzaldehyde (62 mg, 0.58 mmol) in dichloromethane (3 ml) was added dropwise a solution of titanium(IV) bromide (0.62 mmol) in dichloromethane (1 ml) at -78 °C under argon atmosphere. After being stirred for 2 h, the reaction was quenched at the same temperature by adding water (0.5 ml). The mixture was stirred vigorously for 15 min and allowed to warm to room temperature. The mixture was extracted with dichloromethane (10 ml × 3), and the combined extracts were washed with saturated aqueous sodium hydrogencarbonate (15 ml). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give crude product, which consisted mainly of hydroxy diester **4** (R^1=R^2=Me, R=Ph). An ethanolic sodium ethoxide solution (0.05 mol·l^{-1}, 0.06 ml) was added to a solution of the crude product in dry ethanol (1 ml). After being stirred for 30 min, saturated aqueous ammonium chloride (0.3 ml) was added. The mixture was extracted with dichloromethane (10 ml × 3), and the extracts were combined and dried over sodium sulfate. After evaporation, the crude product was

purified by TLC (eluent: CH_2Cl_2/hexane/EtOAc = 10/10/1) to give the corresponding γ-lactone (138 mg, 91% yield based on the aldehyde used, *cis* : *trans* = 98:2).

As shown in Table 1, γ-lactones were obtained generally in high yields with moderate to high *cis*-selectivity. It is noteworthy that when tin(IV) bromide was used instead of titanium(IV) bromide, the diastereoselectivity was much improved, while the yield was somewhat low (Entries 2 and 8).

γ-Lactones are important synthetic intermediates, and this new diastereoselective method would be very useful for their synthesis. The mechanistic aspect and further synthetic applications using these cyclopropane compounds are now under investigation in our laboratory.

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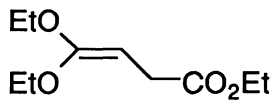
5) The stereochemistry of γ-lactones was determined by ^{1}H-NMR spectroscopy and GLC analysis. In the case of 2,2-dimethyl derivatives (Entries 1 to 5), the vicinal coupling constant between 3-H and 4-H was 10 Hz for *cis*-isomers and 5-6 Hz for *trans*-isomers. These values are consistent with literature data.[7] For 3-ethoxycarbonyl-4-phenyl-4-butanolide (Entries 7 and 8), its ^{1}H-NMR data was in well agreement with that of the corresponding methyl ester.[8] For other 2-unsubstituted derivatives (Entries 6 and 9), the stereochemistry was confirmed by comparison of ^{1}H-NMR data and GLC analysis (in all cases, the retention time of *trans*-isomers are shorter than that of the corresponding *cis*-isomers).
6) Cyclopropane **3b** is contaminated with a rearrangement product **7**. A mixture of **3b** and **7** (88:12) was used for the reaction without further purification.



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