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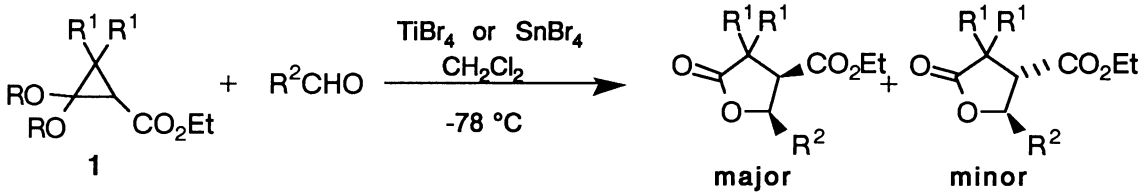
Highly Diastereoselective Synthesis of *cis*-3,4-Disubstituted γ-Lactams by the Reaction of Ethyl 2,2-Dialkoxycyclopropanecarboxylates with *N*-Tosyl Aldimines

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

In the presence of titanium(IV) chloride, ethyl 2,2-dialkoxycyclopropanecarboxylates reacted with imines to give γ-lactams. Especially, when *N*-tosyl aldimines were employed, *cis*-3,4-disubstituted γ-lactams were obtained in good yields with high diastereoselectivity.

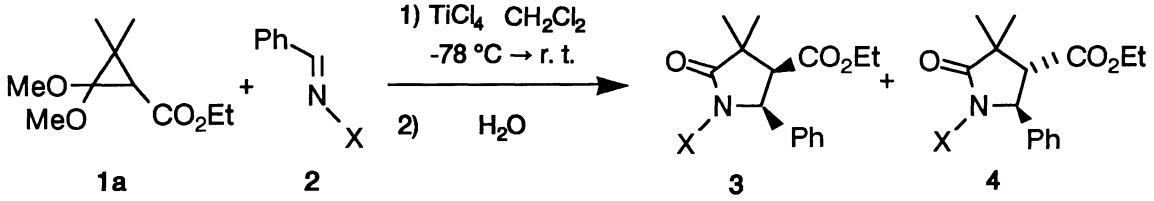
Cyclopropane derivatives with donor and/or acceptor substituent have been widely used in organic synthesis.[1] Among these cyclopropane derivatives, vicinally donor-acceptor-substituted cyclopropanes are expected to readily occur ring-opening addition reaction with various substrates because of substituents' effects.[2] But, relatively little has been studied about this ring-opening addition reaction except for the study performed by Reißig et al. on 2-trialkylsilyloxycyclopropanecarboxylic esters.[2] We recently reported highly diastereoselective synthesis of γ-lactones by the reaction of ethyl 2,2-dialkoxycyclopropanecarboxylates with aldehydes mediated by Lewis acid (Scheme 1).[3,4]



Scheme 1.

On the basis of this result, we expected that γ-lactam should be obtained as a product, if the same type of reaction occurs between **1** and imine. To our knowledge, only one example was reported concerning the ring-opening addition reaction of cyclopropane derivatives with imine, i.e., the reaction of methyl 2-tert-butyl-2-trimethylsilyloxycyclopropanecarboxylate with *N*-benzylideneaniline to afford secondary amine,[2] and no systematic study has been reported. Here we report highly diastereoselective synthesis of γ-lactams by the titanium(IV) chloride-mediated reaction of **1a** with *N*-tosyl aldimines.

At first, we tried the reaction of ethyl 2,2-dimethoxy-3,3-dimethylcyclopropanecarboxylate **1a**[5] with several benzaldimines **2** having a substituent on nitrogen (Scheme 2). In the presence of titanium(IV) chloride, **1a** did not react with **2** at -78 °C (at this temperature **1a** reacted smoothly with aldehydes). But, the reactions proceeded and γ-lactams, *N*-substituted 3-ethoxycarbonyl-2,2-dimethyl-4-phenyl-4-butanelactams, were



Scheme 2.

Table 1. The Reaction of **1a** with Benzaldimines **2**

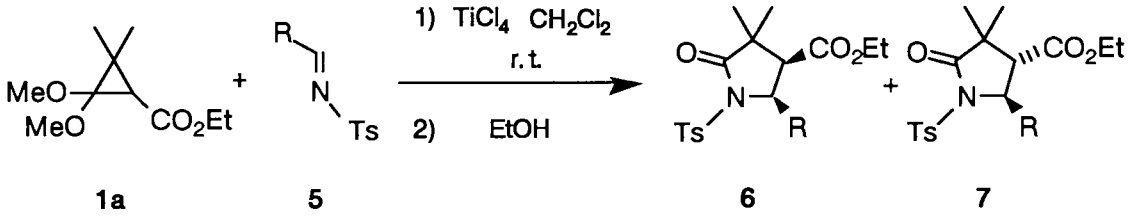
Entry	X	Yield / % a)	*cis*: *trans*
1	$PhCH_2$	42	56 : 44
2	Ph	37	52 : 48
3	*p*-$NO_2C_6H_4$	87	25 : 75
4	Me_3Si	0	—
5	*o*-$NO_2C_6H_4SO$	0	—
6	*p*-$MeC_6H_4SO_2$	72	96 : 4

a) Isolated yield.

obtained as a mixture of *cis*-isomer **3** and *trans*-isomer **4** when the reaction mixtures were warmed to 0 °C — room temperature. As shown in Table 1, some imines did not react with **1a** (entries 4 and 5), while imines with an electron-withdrawing substituent on nitrogen showed relatively high reactivity to **1a**, and γ-lactams were obtained in good yields (entries 3 and 6). Most noticeable is that the reaction of **1a** with *N*-tosyl aldimine[6] (entry 6) gave *cis*-3,4-disubstituted γ-lactam with high diastereoselectivity. Therefore, we next examined various reaction conditions for the reaction of **1a** with *N*-tosyl aldimines. Optimized conditions are shown in Scheme 3 and in the following typical procedure. The key point of this reaction is that imine and titanium(IV) chloride should be mixed in dichloromethane at room temperature and then **1a** is added at the same temperature. The results for the reaction with some *N*-tosyl aldimines are shown in Table 2. In all cases, *cis*-3,4-disubstituted γ-lactams were obtained in good yields with high diastereoselectivity.

The typical procedure is as follows: To a stirred solution of *N*-tosyl benzaldimine **5** (R=Ph, 101 mg, 0.39 mmol) in dry dichloromethane (2 ml) was added drop by drop a solution of titanium(IV) chloride (0.48 mmol) in dichloromethane (0.3 ml) at room temperature. To the resulting yellow solution, cyclopropane **1a** (99 mg, 0.49 mmol) in dry dichloromethane (2 ml) was slowly added drop by drop (30 min) at room temperature. During the addition of **1a**, dramatic color change of the reaction mixture was observed, and finally the solution became pale red-brown. The reaction mixture was stirred for 5 h at room temperature and quenched by adding anhydrous ethanol (0.3 ml). To this mixture were added water (10 ml) and dichloromethane (15 ml), and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 5 ml). The combined organic layers were dried with anhydrous sodium sulfate. After filtration and evaporation, the crude product was purified by TLC (eluent: hexane/CH_2Cl_2/ EtOAc = 10/5/1) to give the corresponding γ-lactam **6** and **7** (132 mg, 81 % yield based on the imine, *cis*: *trans* = 98 : 2).

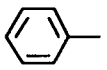
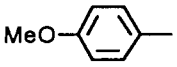
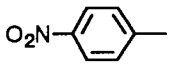
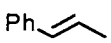
The stereochemistry of γ-lactams **6** and **7** was determined by ^{1}H-NMR spectroscopy and an isomerization reaction. The signals of methyl and methylene protons of the ester group in major isomers appeared at 0.1-0.4 ppm *higher* field compared to those of the corresponding minor isomers. In contrast to ester protons, the signal of 3-H of major isomers appeared at *lower* field than that of minor isomers by



1a 5 6 7

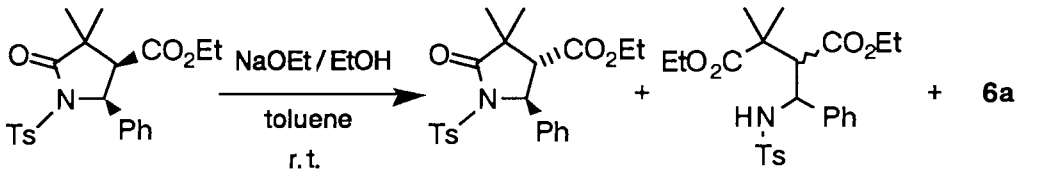
Scheme 3.

Table 2. The Reaction of **1a** with *N*-Tosyl Aldimines 5

Entry	R	Yield/% [a]	*cis* :	*trans* [b]
1		81	98 :	2
2		73	98 :	2
3		91	98 :	2
4		83	95 :	5
5		67	96 :	4

a) Isolated yield. b) Determined by HPLC.

0.20-0.45 ppm. Additionally, the difference in chemical shift between two 2-methyl groups was 0.05-0.06 ppm for all major isomers and 0.26-0.41 ppm for minor isomers. These characteristic chemical shifts are attributed to the effect of aromatic group at 4-C, indicating that in major isomers 3-ester and 4-aryl groups are located in *cis* configuration. This assignment is also supported by an isomerization experiment. Major isomer **6a** (R=Ph) was treated with sodium ethoxide in ethanol/toluene at room temperature for 1 week. TLC separation of the products gave isomerized product **7a** (74% yield), open chain product **8** (10% yield), and trace of starting material **6a** (Scheme 4). In this experiment, major *cis*-isomer must have isomerized to thermodynamically more stable *trans*-isomer.



6a 7a, 74% 8, 10% trace

Scheme 4.

This new synthetic method is useful for stereoselective synthesis of γ-lactams, which are important intermediates for the synthesis of natural products such as alkaloids. The mechanistic aspect[7] and further application of this reaction are now under investigation in our laboratory.

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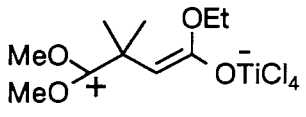
7) The mechanism of this reaction is not clear. But, when cyclopropane **1a** was mixed with titanium(IV) chloride in $CDCl_3$ at room temperature, the ^{1}H-NMR signal of two 2-methyl groups changed from two singlets into one singlet. Moreover, the color of the mixture of **1a** and titanium(IV) chloride became deep wine-red, which indicated the formation of titanated ketene acetal moiety.[8] High diastereoselectivity of this reaction may be explained by assuming that *E*-ketene acetal intermediate such as **9** or **10** is formed and that the reaction proceeds through an eight-membered ring transition state like **11**. This explanation is also consistent with that for the high diastereoselectivity of the reaction of **1** with aldehydes,[3] although in this case a six-membered ring transition state in a chair form may be involved.



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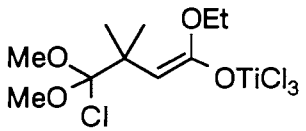

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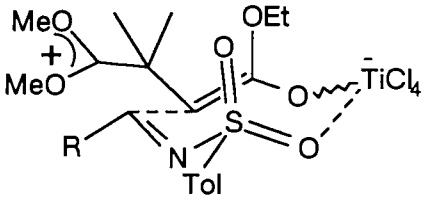

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