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THE HIGHLY *SYN*-SELECTIVE MICHAEL REACTION OF ENAMINES WITH 2-(1-ALKENYL)-1,3-DIOXOLAN-2-YLIUM CATIONS GENERATED FROM 2,2-DIMETHOXYETHYL 2-ALKENOATES *IN SITU*

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Abstract: 2,2-Dimethoxyethyl 2-alkenoates are easily transformed into 2-(1-alkenyl)-1,3-dioxolan-2-ylium cations *in situ* on the action of titanium tetrachloride, which react with enamines to predominantly give *syn* Michael adducts in good yields. This is the first example of such a high *syn*-selectivity for the Michael reaction of α,β-unsaturated ester derivatives with ketone enolate equivalents.

There are many kinds of anionic species such as organometallic reagents, ylides, and carbanions stabilized by a carbonyl, cyano, nitro, and/or sulfonyl group; these have been widely used in organic syntheses.[1] Moreover, the application of anionic species in stereoselective C-C bond-forming reactions has been extensively investigated.[2] In contrast, although such organocationic reagents as the Meerwein and Vilsmeier reagents as well as the Eschenmoser salt have been used in simple C-C bond-forming reactions, there have been only a few studies on stereoselective C-C bond formation using organocationic species.[3] As an exceptional example, the reaction of carbenium ions stabilized by the coordination of a transition metal, such as a π-allyl metal complex, is known; the carbenium ions react with nucleophiles stereoselectively.[4] However, a stereoselective C-C bond-forming reaction using cationic species is still considered to be a challenging field in organic synthesis.

The Michael reaction is one of the most important C-C bond-forming reactions, and stereoselective variants have been extensively investigated in recent years.[5-9] Generally, however, since the Michael reaction of α,β-unsaturated ester derivatives with ketone enolate equivalents is thermodynamically disfavored, it is difficult to control the stereoselectivity of the Michael reaction. This means that the strong activation of a Michael donor and/or acceptor is required in order to achieve a highly stereoselective Michael reaction. Concerning the activation of a Michael donor, Enders and co-workers used lithiated hydrazones in a reaction with α,β-unsaturated esters to obtain *anti* Michael adducts in high selectivities.[6] With regard to the activation of a Michael acceptor, Mukaiyama and co-workers have reported Lewis acid catalyzed reactions of thioesters,[7] orthoesters,[8] or 2-(1-alkenyl)-1,3-dithiolan-2-ylium cations[9] with silyl enol ethers under mild conditions. All of these reactions also gave an *anti* Michael adduct predominantly. In contrast, one of us found that though the Michael reaction of 2-(1-alkenyl)-1,3-dithiolan-2-ylium cations with enamines gave mainly *syn* Michael adducts, the stereoselectivity was rather low.[10] Namely, there has been no report concerning a highly *syn*-selective Michael reaction between α,β-unsaturated ester derivatives and ketone enolate equivalents, although it is important for organic synthesis in order to develop methods for the individual preparation of diastereomers. Accordingly, on the base of cationic chemistry, we have been aiming at developing new types of Michael acceptors, which are capable of reacting with ketone enolate equivalents in high *syn*-selectivities.

Concerning the cationic species, it is well-known in the field of carbohydrate chemistry that stereoselective glycosylation proceeds *via* 1,3-dioxolan-2-ylium cation, which can be easily formed from 2-*O*-acylated glycosyl

donor, owing to the neighboring effect of the acyloxy group toward its anomeric position.[11] Moreover, it was also reported that 1,3-dioxolan-2-ylium cations react with enamines to give Claisen-type condensates due to the high reactivity of the cationic species.[12] These facts indicate that carbenium ions, stabilized by two oxygen substituents, can be generated from highly designed esters and that stereoselective C-C bond-forming reactions can be developed by using this type of carbenium ion. Allyl-cationic species of α,β-unsaturated ester equivalents, generated by the action of a Lewis acid and stabilized by neighboring participation, should be a strongly activated Michael acceptor due to the electron-withdrawing character of the cationic moiety; further, the Michael reaction with a ketone enolate equivalent is expected to proceed kinetically to give a stereocontrolled product. According to this idea, we chose 2-(1-alkenyl)-1,3-dioxolan-2-ylium and 2-(1-alkenyl)-1,3-dioxan-2-ylium cations as the allyl cations. Since these types of cations are generally considered to be moisture-sensitive and to have low crystallinity, we tried to generate cationic species *in situ*.

In this paper we report on a new *syn*-selective Michael reaction of modified α,β-unsaturated esters with enamines, which was developed on the basis of cationic species chemistry.[13]

Results and Discussion

In order to generate cationic species from α,β-unsaturated ester derivatives, we designed three ester groups (Fig. 1) on the basis of the following considerations: In the presence of a Lewis acid, 2,2-dimethoxyethyl ester **1** and glycidyl ester **2** may easily transform to the corresponding dioxolanylium cations because of the neighboring participation of ester carbonyl toward the cation produced by extraction of the methoxide, or by the

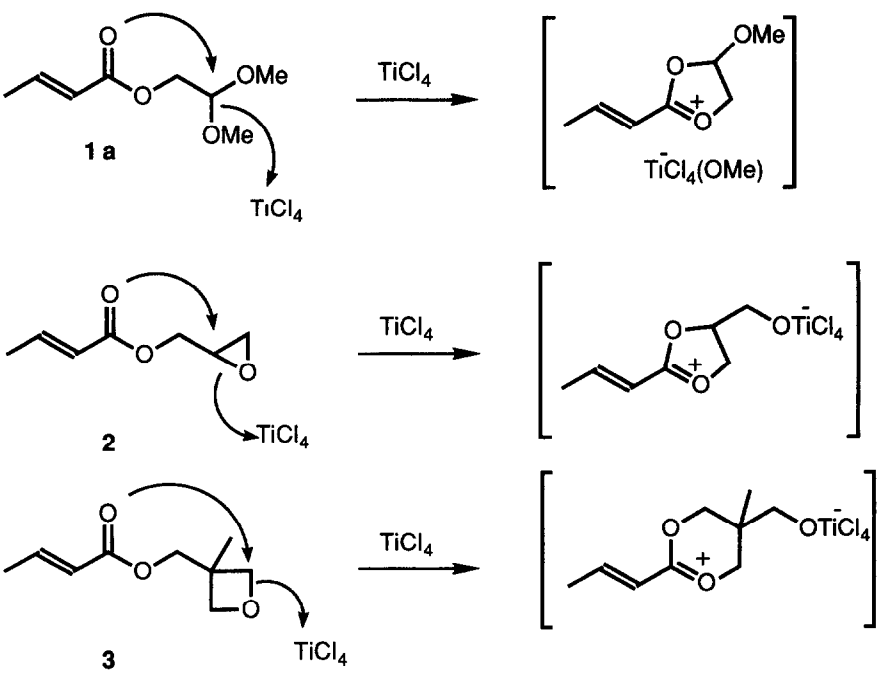


Fig. 1.

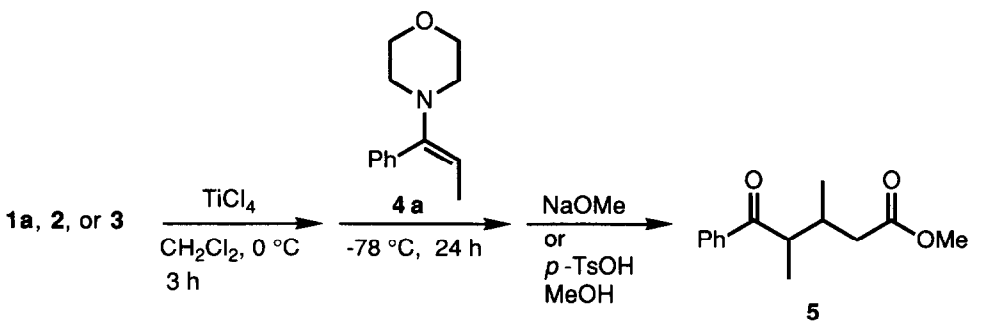
ring-opening of the oxirane on the action of the Lewis acid. In a similar manner, the corresponding dioxanylium cation may be obtained from oxetanylmethyl ester **3**.

At first, we compared esters **1a**, **2**, and **3** in view of the chemical yield and diastereoselectivity of the Michael adduct. The esters were treated with titanium tetrachloride (1.1 equiv.) in dichloromethane at 0 °C for 3 h in order to generate the corresponding cationic intermediates *in situ*, followed by a reaction with (*E*)-1-morpholino-1-phenylpropene **4a** (1.2 equiv.) at -78 °C for 24 h. The adducts were isolated as methyl ester **5** after transesterification of the corresponding products, which were obtained by quenching with excess saturated aqueous sodium hydrogencarbonate (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, both the yield and diastereoselectivity for the reaction of **1a** were better than those for the reaction of the other esters. Intermediate cations, derived from esters **2** and **3**, had rather low solubility in dichloromethane, and an oily precipitate appeared during the progress of cation generation. On account of this fact, the yield of the Michael adduct for the reaction of **2** or **3** is considered to become low in comparison with that of **1a**.

The reaction of methyl crotonate with enamine **4a** did not proceed at all under the same conditions, and the starting materials were recovered. On the basis of these results, it can be said that cationic species, generated from **1a**, **2**, and **3**, are strongly activated Michael acceptors and that the 2,2-dimethoxyethyl ester group is the best precursor for the formation of a cationic intermediate.

The above-mentioned observation indicates that the 2,2-dimethoxyethyl ester can be a potent synthetic intermediate. We then reinvestigated synthetic methods for 2,2-dimethoxyethanol and 2,2-dimethoxyethyl esters. As a result, 2,2-dimethoxyethanol was easily synthesized from ethyl vinyl ether by oxidation with

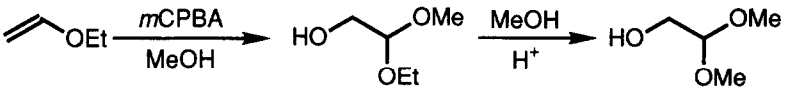


Scheme 1.

Table 1. The Michael Reaction of Cationic Species, Generated from Esters **1a**, **2**, and **3**, with Enamine **4a**

ester	yield of **5** (%)	*syn* : *anti* a)
1a	77	88 : 12
2	21	83 : 17
3	40	60 : 40

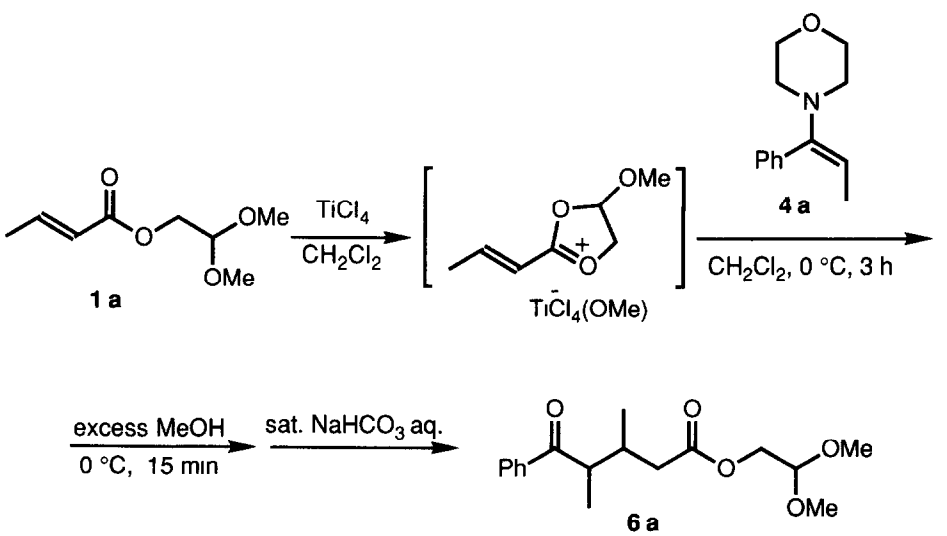
a) Determined by GC.



Scheme 2.

m-chloroperbenzoic acid (*m*CPBA),[14] followed by ring-opening with methanol and transacetalization (Scheme 2). Other peracids, namely peroxyacetimidic acid derived from acetonitrile and hydrogen peroxide[15] and monoperoxyphthalic acid magnesium salt hexahydrate (MMPP),[16] could be used instead of *m*CPBA. This synthetic method is superior to the reported one[17] from the viewpoints of both yield and simplicity. The usual 2,2-dimethoxyethyl esters were easily prepared by the reaction of 2,2-dimethoxyethanol with the corresponding acid chloride in the presence of pyridine. It is noted that since 2,2-dimethoxyethyl esters are somewhat thermally unstable, purification by distillation results in a low yield. In the case of esters having a more complicated or reactive structure, dehydration between 2,2-dimethoxyethanol and the corresponding carboxylic acid using 2-chloro-1-methylpyridinium iodide[18] or diethyl azodicarboxylate (DEAD) / triphenylphosphine[19,20] was more effective. Thus, sorbate **1d** was prepared in a good yield by using DEAD / triphenylphosphine as a condensing agent.

The Michael reaction of 2,2-dimethoxyethyl ester **1a** with enamine **4a** involves two steps: 1) generation of a cationic intermediate on the action of the Lewis acid and 2) a Michael addition of the enamine to the cationic intermediate. We then evaluated the temperature dependence for cation generation on the basis of the yield of the Michael adduct, which was obtained by a reaction with enamine **4a** (1.2 equiv.) at 0 °C for 3 h. The Michael adduct was isolated as the corresponding 2,2-dimethoxyethyl ester **6a** upon quenching with methanol at 0 °C, followed by a treatment with saturated aqueous sodium hydrogencarbonate (excess) (Scheme 3). The results are



Scheme 3.

Table 2. Temperature Effect on the Cation Generation in the Reaction of Ester **1a** with Enamine **4a**

temperature for cation generation (°C)	yield of **6a** (%)
-78	51
-45	80
-23	62
0	43

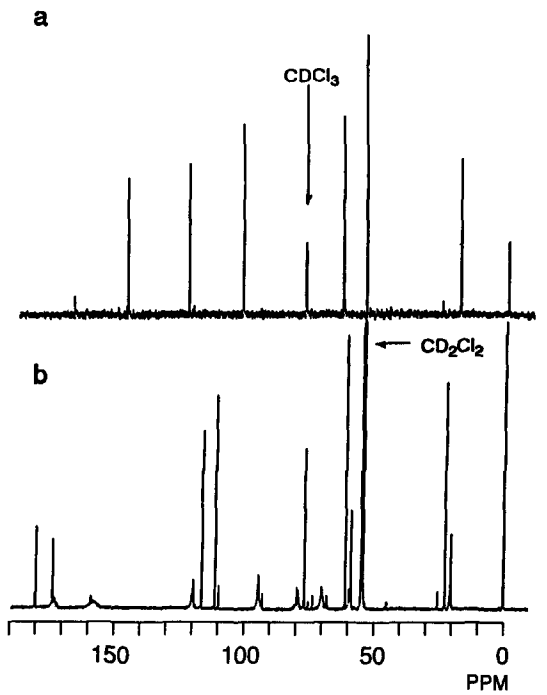


Fig. 2 ^{13}C-NMR spectra of a) ester **1a** (in $CDCl_3$, r.t.) and b) the cation generated at -45 °C on the action of $TiCl_4$ (in CD_2Cl_2, -70 °C).

summarized in Table 2. At -78 °C, the cation generation was not sufficient, and a large amount of the starting ester **1a** was recovered. This means that the temperature was too low for the Lewis acid to extract a methoxy group. In contrast, although a temperature of 0 °C was sufficient for the generation of the cationic intermediate, the intermediate decomposed at that temperature to yield a mixture of many unknown products. Among the temperature examined, -45 °C was found to be the most suitable for cation generation. Cationic intermediate formation at -45 °C was further confirmed by ^{13}C-NMR recorded at a low temperature (Fig. 2). Upon cation formation, the signals of the ester **1a** disappeared completely, and the peaks corresponding to the cationic species appeared at 180 (cation center) and 173 (C2 of 1-propenyl) ppm.[21]

Table 3. Temperature Effect on the Michael Addition of Enamine **4a** to the Cationic Intermediate Derived from Ester **1a**

temperature (°C)	reaction time (h)	yield of **6a** (%)	*syn* : *anti* a)
-78	24	82	93 : 7
-45	14	73	88 : 12
-23	14	47	85 : 15
0	1	72	55 : 45

a) Determined by HPLC.

In the next stage, the reaction conditions for Michael addition, namely the effects of temperature, solvent, and Lewis acid, were optimized by using the reaction of ester **1a** with enamine **4a** as a model reaction.

It is known that the Michael reaction proceeds stereoselectively under kinetic conditions, and that it is indispensable for kinetic control to maintain the reaction at low temperature. Accordingly, we investigated the temperature effect on the Michael addition in dichloromethane (Table 3). Below -23 °C, the Michael reaction proceeded stereoselectively to give *syn* adduct **6a** predominantly. In contrast, at 0 °C the stereoselectivity almost disappeared owing to the thermodynamic *syn-anti* equilibrium. The rather low chemical yield of the Michael adduct for a reaction above -23 °C would be due to an unknown side reaction and/or a decomposition of the cationic intermediate.

The solvent effect was examined on the basis of the chemical yield and stereoselectivity for the reaction (Table 4). In acetonitrile or diethyl ether, the Michael addition did not proceed at all. In these solvents, a methoxy group of the ester may not be extracted due to a depression of the Lewis acidity of titanium tetrachloride by the coordination of the solvent; it is also possible that the generated cationic intermediate may be too stabilized to react with the enamine by solvation with a polar solvent, resulting in no reaction. Among the solvents examined, dichloromethane was found to be the most favorable solvent in this type reaction because of its appropriate polarity and solubility of the cationic species.

Table 4. Solvent Effect on the Yield and Diastereoselectivity of Michael Adduct **6a**

solvent	yield of **6a** (%)	*syn* : *anti* a)
dichloromethane	82	93 : 7
toluene	28	83 : 17
acetonitrile	0	—
diethyl ether	0	—

a) Determined by HPLC.

In addition, Lewis acidity influenced the formation of a cationic intermediate from the 2,2-dimethoxyethyl ester. Among the Lewis acids examined, titanium tetrachloride with an appropriate Lewis acidity was found to be specifically effective (Table 5). In the presence of a rather weak Lewis acid, no Michael adduct was obtained, probably because its Lewis acidity is too weak to extract a methoxy group in the ester. In the case of a stronger Lewis acid, further reactions occurred and a mixture of unknown products was obtained.

The reactivity of an enamine and the interaction between a cationic intermediate and the enamine may depend

Table 5. Effect of Lewis Acids on the Yield of Michael Adduct **6a**

Lewis acid	temperature for cation generation (°C)	time for cation generation (h)	yield of **6a** (%)	*syn* : *anti* a)
$SbCl_5$	-45	3	0	—
$TiCl_4$	-45	3	82	93 : 7
Me_3SiOTf	-45	3	31	90 : 10
$SnCl_4$	-45	3	31	90 : 10
$EtAlCl_2$	0	3	19	94 : 6 b)
$AlCl_3$	-45	6	0	—
$BF_3{\cdot}OEt_2$	0	1	0	—

a) Determined by HPLC unless otherwise stated. b) Determined by GC.

on the basicity of the amino part of the enamine. Taking into account this consideration, we prepared several kinds of enamines derived from propiophenone, and then compared the chemical yield and stereoselectivity in the reactions of **1a** with the enamines under the optimized conditions.

As shown in Table 6, the yield and stereoselectivity were strongly influenced by the basicity of the amino part. The yield of the Michael adduct for the reaction of *N*-methylpiperazino enamine was rather low in comparison with that of morpholino enamine. This would be due to a very strong interaction between the nitrogen at the 4 position of the amino part and the cationic intermediate, resulting in a depression of the reactivity of the cationic species. The stereoselectivity for the reaction of **1a** with piperidino enamine was slightly low in comparison with that for the reaction with morpholino enamine. This means that the interaction between the piperidino part and the cationic intermediate is weaker than that of the morpholino part; the interaction plays an important role in the fixation of the conformation of the transition state, which influences the stereoselectivity. The yield for the reaction of **1a** with pyrrolidino enamine was rather low because of the instability of the enamine.

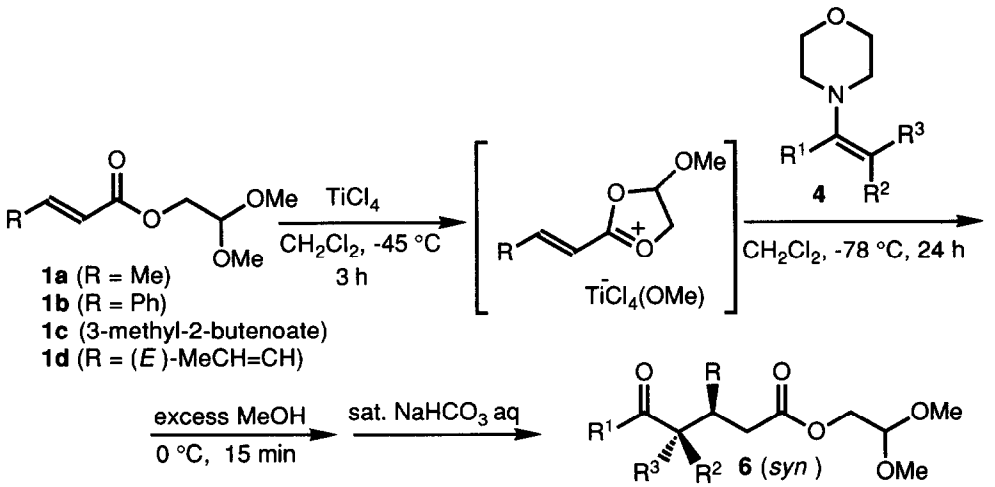
Table 6. The Michael Reaction of Ester **1a** with Enamines Derived from Propiophenone

enamine	yield of **6a** (%)	*syn* : *anti* a)
morpholino	82	93 : 7
N-methylpiperazino	18	80 : 20
pyrrolidino	43	68 : 32
piperidino	74	86 : 14

a) Determined by GC.

By considering these results concerning the reaction conditions, Michael reactions of 2,2-dimethoxyethyl 2-alkenoates **1** with various morpholino enamines **4** were carried out (Scheme 4, Table 7).

Crotonate **1a** smoothly reacted with a variety of enamines to give Michael adducts in good yields with high *syn*-selectivities, except for the enamine derived from phenylacetaldehyde **4f**. The quite low stereoselectivity for the reaction with **4f** was due to thermodynamic *syn-anti* isomerization, which occurred rapidly, even under



Scheme 4.

Table 7 The Michael Reaction of Esters **1** with Morpholino Enamines **4**

run	ester	R^1	R^2	R^3	enamine	adduct	yield of adduct (%)	*syn* : *anti*
1	**1a**	Ph	Me	H	**4a**	**6a**	82	93 : 7 a)
2		Et	Me	H	**4b**	**6b**	83	91 : 9 a)
3			$(CH_2)_4$	H	**4c**	**6c**	81	96 : 4 a)
4			$(CH_2)_3$	H	**4d**	**6d**	61	88 : 12 b)
5		H	Me	H	**4e**	**6e**	92	91 : 9 a)
6		H	Ph	H	**4f**	**6f**	68	3 : 1 c)
								3 : 2 d)
7		H	Me	Me	**4g**	**6g**	33	—
						7	33	—
8	**1b**	Ph	Me	H	**4a**	**6h**	95	64 : 36 e)
9		Et	Me	H	**4b**	**6i**	79	81 : 19 e)
10			$(CH_2)_4$	H	**4c**	**6j**	56	77 : 23 e)
11	**1c**	Ph	Me	H	**4a**	—	0	—
12	**1d**	Ph	Me	H	**4a**	**6k**	71	88 : 12 e,f)

a) Determined by GC.

b) Determined by ^{1}H-NMR.

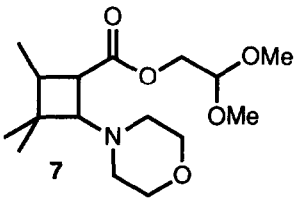
c) Determined by ^{1}H-NMR of the crude reaction mixture.

d) Determined by ^{1}H-NMR after purification.

e) Determined by HPLC.

f) 1,6-Adduct was not detectable.

quenching conditions. As shown in Run 7, the Michael addition of the 2,2-disubstituted enamine, derived from isobutyraldehyde **4g**, to **1a** proceeded smoothly. However, [2+2] cycloaddition occurred as observed in the general Michael reaction of α,β-unsaturated carbonyl compounds with 2,2-disubstituted enamines,[22] and a mixture of Michael adduct **6g** and cyclobutane derivative **7** was obtained. 2,2-Dimethoxyethyl 3-methyl-2-butenoate **1c** did not react at all with enamine **4a**; this may be due to the bulkiness of two methyl groups at the β position. It was noteworthy that sorbate **1d** gave 1,4-adduct **6k** with satisfactory *syn*-selectivity and that the corresponding 1,6-adduct was not detected.



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The stereoselectivity of these reactions can be explained by taking into account the effect of the amino part of an enamine: The lone pair of nitrogen atom in the enamine interacts with the cationic center of the Michael acceptor; this reaction proceeds *via* a six-membered chair-like cyclic transition state (Fig. 3) to give a *syn* adduct, as proposed by Seebach et al. for an explanation of the high *syn* selectivities in the Michael reaction between nitroalkene and enamines.[23]

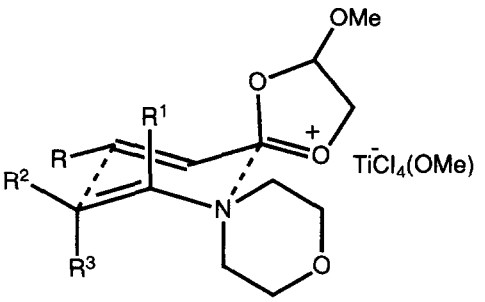


Fig. 3.

In the case of cinnamate **1b**, the superiority of the cyclic transition state over an acyclic type decreases due to a strong *gauche* interaction between the phenyl group and R^2 in the cyclic transition state, resulting in a rather low *syn*-selectivity, in comparison with that of crotonate **1a** (Fig. 3).

The regioselectivity of the Michael addition with sorbate **1d** can also be explained by considering a six-membered transition state. 1,4-Adduct is produced *via* such a six-membered transition state, whereas it is necessary to pass through an eight-membered transition state in order to form a 1,6-adduct. It is well-known that a six-membered transition state is more stable than an eight-membered type. Then, 1,4-adduct is exclusively obtained.

Generally, since the Michael reaction of enamines is carried out under relatively drastic conditions, stereochemical control of the reaction is rather difficult. Only one exception have been reported for the reaction of enamines with nitroalkene.[23] This method, however, cannot be applied to reactions with ordinary α,β-unsaturated carbonyl compounds. In contrast, the Michael reaction of the α,β-unsaturated esters with enamines,

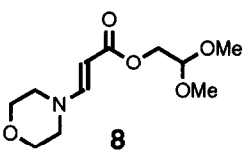
reported in this paper, proceeds under extremely mild conditions with high *syn*-selectivity. It is noteworthy that this reaction is the first example of a highly *syn*-selective Michael reaction of α,β-unsaturated esters with ketone enolate equivalents.

The 2,2-dimethoxyethyl ester is considered to be a new, potent function for the activation of ester carbonyl. In our laboratory, the Claisen-type condensation[24] and the Diels-Alder reactions[20] using the 2,2-dimethoxyethyl ester as a precursor of a cyclic cation have been already studied, and further applications of this ester are now being investigated.

Experimental Section

^{1}H-NMR spectra were recorded with a JEOL JNM-GX400 FT NMR or a JEOL JNM-PMX 60SI NMR instrument with tetramethylsilane as an internal standard. ^{13}C-NMR spectra were recorded with a JEOL JNM-GX400 FT NMR instrument. The chemical-shift values were recorded as parts per million. IR spectra were recorded with a JASCO IR-810 Infrared Spectrophotometer. HPLC analysis was performed on a Shimadzu LC-6A HPLC system with a Hibar LiChrosorb Si60 Merck (Cat. 50388) column. GC analysis was performed on a Shimadzu GC-14A GC system with a capillary column (CBP10-M25-025). Mass spectra were recorded with a JEOL JMS-AX505H instrument. The high-resolution mass spectra (HRMS) showed an M^+ peak in a few cases. Consequently, HRMS were measured for $(M-MeO)^+$ or $(M-MeOH)^+$ peak. In the case of **7**, we could not measure the high-resolution spectra for either the $(M-MeO)^+$ or $(M-MeOH)^+$ peak, since the cyclobutane ring

opened. We thus measured the HRMS of $\mathbf{8}^+$, $(\mathbf{8}-MeO)^+$ and $(\mathbf{8}-MeOH)^+$ peaks instead of the M^+ one. All reaction solvents were distilled from an appropriate dehydrating agent. Enamines were synthesized according to the general procedure.[25] (3-Methyl-3-oxetanyl)methanol was prepared according to the method in the literature.[26]



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Synthesis of 2,2-Dimethoxyethanol.

Method (A).

To a methanol solution (20 ml) of *m*-chloroperbenzoic acid (*m*CPBA, 4.26 g, 85 % purity, 21.0 mmol) was slowly added a methanol solution (6 ml) of ethyl vinyl ether (4 ml, 42 mmol) at 0 °C. The solution was stirred at this temperature for 1.5 h and was then allowed to stand overnight at room temperature. After excess ethyl vinyl ether was distilled off, 20 ml of methanol was added, followed by the addition of 0.4 ml of concd. sulfuric acid. The mixture was stirred for 1 h, and then 6 g (43 mmol) of potassium carbonate was added. After stirring for several hours, 400 ml of dichloromethane was added to the reaction mixture, and the resulting white precipitate was filtrated off through a Celite pad and washed with dichloromethane (50 ml). The distillates below 42 °C were removed, and then 20 ml of dichloromethane was added to the residue. The solution was treated with MS 4Å overnight, after which precipitate was filtrated off through a Celite pad and washed with dichloromethane (50 ml). The filtrate was concentrated and distilled from CaH_2 to give 1.46 g of 2,2-dimethoxyethanol (66 %). B.p. 47-48 °C (9 mmHg), lit.[17] 58-60 °C (12 mmHg).

^{1}H-NMR (60 MHz, $CDCl_3$): δ 4.4 (t, J = 5.5 Hz, 1H), 3.7 (d, J = 5.5 Hz, 2H), 3.4 (s, 6H), 2.1 (m, 1H); IR: (NaCl) 3445, 1450, 1365, 1195, 1135, 1080, 1050, 970 cm^{-1}.

Method (B).

To a methanol solution (1 l) of potassium hydrogencarbonate (16.7 g, 0.17 mol), acetonitrile (78 g, 1.9 mol), and ethyl vinyl ether (151 g, 2.1 mol) was slowly added 56.7 g of 60 % hydrogen peroxide (hydrogen peroxide 34 g, 1.0 mol) at 0 °C. The solution was stirred at the temperature for 1.5 h and allowed to stand for two days at room temperature, followed by refluxing for 12 h. The reaction mixture was dried overnight over MS 3Å. After excess ethyl vinyl ether was distilled off, the resulting precipitate was filtered off and washed with 300 ml of methanol; 15 ml of concd. sulfuric acid was then added to the filtrate. To the reaction mixture was added 100 ml of trimethyl orthoformate, and the mixture refluxed for 1 h. Potassium carbonate (100 g) and MS 3Å were added to the solution. After standing overnight, the precipitate was filtrated off through a Celite pad and washed with dichloromethane. After distillates below 73 °C were removed, 400 ml of water and 200 ml of chloroform were added to the residue. The white precipitate was filtered off through a Celite pad, and the filtrate was extracted repeatedly with dichloromethane (600 ml). After the organic layer was dried with MS 4Å overnight, the solvent was evaporated. The residue was dried again with MS 4Å overnight and distilled from MS 4Å to give 30 g of 2,2-dimethoxyethanol (28 %).

2,2-Dimethoxyethyl Crotonate (1a).

To a dichloromethane solution (20 ml) of crotonoyl chloride (7.8 g, 75 mmol) was added dropwise a dichloromethane solution (32 ml) of 2,2-dimethoxyethanol (5.3 g, 50 mmol) and pyridine (6.5 g, 82 mmol) at 0 °C. The solution was stirred at that temperature for 1 h and treated with a buffer solution (pH 6.8). Excess pyridine was extracted twice with saturated aqueous copper(II) sulfate (50 ml); the organic layer was then successively washed with water, twice with saturated aqueous sodium hydrogencarbonate (50 ml) and with water. After being dried with potassium carbonate, the solvent was removed and the residue purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 5) to give ester **1a** (2.2 g, 25 %). B.p. 97-97.5 °C (10 mmHg).

^{1}H-NMR (60 MHz, CCl_4): δ 7.1 (m, 1H), 5.8 (m, 1H), 4.5 (t, J = 5.5 Hz, 1H), 4.1 (d, J = 5.5 Hz, 2H), 3.3 (s, 6H), 1.9 (dd, J = 2, 7 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166, 145, 122, 101, 63, 54, 18; IR: (NaCl) 1725, 1660, 1445, 1380, 1185, 1140, 1080, 975 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_7H_{11}O_3$: m/z = 143.0709, found 143.0728.

According to a method using diethyl azodicarboxylate (DEAD) / triphenylphosphine as a dehydrating reagent, ester **1a** was obtained in 92 % yield.

2,2-Dimethoxyethyl Cinnamate (1b).

Ester **1b** was synthesized in a similar manner as in the preparation of **1a**, except for purification. **1b** was purified by distillation under reduced pressure (28 %). B.p. 149-154 °C (5 mmHg).

^{1}H-NMR (60 MHz, $CDCl_3$): δ 7.8 (d, J = 17 Hz, 1H), 7.4 (m, 5H), 6.5 (d, J = 17 Hz, 1H), 4.8 (t, J = 5.5 Hz, 1H), 4.3 (d, J = 5.5 Hz, 2H), 3.4 (s, 6H); IR: (NaCl) 1720, 1640, 1580, 1445, 1375, 1175, 1135, 1080, 990, 765, 710 cm^{-1}; MS: calcd for $C_{13}H_{16}O_4$: m/z = 236.1049, found 236.1024.

2,2-Dimethoxyethyl 3-Methyl-2-butenoate (1c).

Ester **1c** was synthesized in a similar manner as in the preparation of **1a**, except for purification. **1c** was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 11) (78 %).

^{1}H-NMR (60 MHz, CCl_4): δ 6.7 (m, 1H), 4.6 (t, *J* = 5.5 Hz, 1H), 4.1 (d, *J* = 5.5 Hz, 2H), 3.3 (s, 6H), 2.1 (s, 3H), 0.9 (s, 3H); IR: (NaCl) 1720, 1650, 1450, 1380, 1155, 1135, 1085, 990 cm^{-1}; MS: $(M\text{-}MeO)^+$ calcd for $C_8H_{13}O_3$: m/z = 157.0865, found 157.0860; $(M\text{–}MeOH)^+$ calcd for $C_8H_{12}O_3$: m/z = 156.0787, found 156.0771.

2,2-Dimethoxyethyl (2*E*,4*E*)-2,4-Hexadienoate (1d).

To a mixture of triphenylphosphine (6.9 g, 26 mmol), 2,2-dimethoxyethanol (2.2 g, 21 mmol), and hexadienoic acid (3.0 g, 26 mmol) in 30 ml of THF was added dropwise a THF solution (10 ml) of diethyl azodicarboxylate (DEAD, 4.5 g, 26 mmol) at -78 °C. The solution was then allowed to warm to room temperature and stirred for 9 h. Then, THF was evaporated and a 100 ml of 1:1 mixture of hexane and diethyl ether was added to the residue. The resulting precipitate was filtered off through a Celite pad, and the solvent was removed. The residue was purified twice by silica gel column chromatography (diethyl ether : hexane = 5 : 95 → 10 : 90, then ethyl acetate : hexane = 1 : 9) to give 3.4 g of ester **1d** (82 %).

^{1}H-NMR (60 MHz, CCl_4): δ 7.4 (m, 1H), 6.2 (m, 2H), 5.8 (d, *J* = 15 Hz, 1H), 4.5 (t, *J* = 5.5 Hz, 1H), 4.1 (d, *J* = 5.5 Hz, 2H), 3.3 (s, 6H), 1.8 (d, *J* = 5 Hz, 3H); IR: (NaCl) 1720, 1645, 1620, 1445, 1380, 1190, 1135, 1080, 1000 cm^{-1}; MS: calcd for $C_{10}H_{16}O_4$: m/z = 200.1048, found 200.1023.

2-Oxylanylmethyl Crotonate (2).

Ester **2** was synthesized in a similar manner as in the preparation of **1b** (17 %). B.p. 78-80 °C (6 mmHg), lit.[27] 71 °C (3 mmHg).

^{1}H-NMR (60 MHz, CCl_4): δ 7.1 (m, 1H), 5.8 (m, 1H), 4.5-3.8 (m, 2H), 3.2 (m, 1H), 2.9-2.5 (m, 2H), 1.9 (d, *J* = 7 Hz, 3H); IR: (NaCl) 1725, 1660, 1450, 1265, 1185, 1030, 970 cm^{-1}.

(3-Methyl-3-oxetanyl)methyl Crotonate (3).

Ester **3** was synthesized in a similar manner as in the preparation of **1b** (34 %). B.p. 69 °C (6 mmHg).

^{1}H-NMR (60 MHz, CCl_4): δ 7.1 (m, 1H), 5.8 (m, 1H), 4.6-4.1 (m, 6H), 2.0 (d, *J* = 7 Hz, 3H), 1.4 (s, 3H); IR: (NaCl) 1735, 1660, 1450, 1260, 1180, 1100, 1030, 980, 840 cm^{-1}.

Typical Procedure for the Michael Reaction of Ester 1 with Enamine 4.

To a dichloromethane solution (2 ml) of 2,2-dimethoxyethyl ester **1** (0.5 mmol) was added dropwise a dichloromethane solution (1 ml) of titanium tetrachloride (0.55 mmol) at -45 °C. The solution was stirred at that temperature for 3 h, and then cooled down to -78 °C. A dichloromethane solution (2 ml) of enamine **4** (0.6 mmol) was slowly added to the solution, and the mixture was stirred at -78 °C for 24 h. After the addition of dry methanol (1 ml), the solution was warmed up to 0 °C and stirred for 15 min. Then, saturated aqueous sodium hydrogencarbonate solution (10 ml) was added, and the mixture was stirred for an additional 30 min at room temperature. Insoluble solid mass was filtered off through a Celite pad, and the organic materials in the filtrate were extracted with dichloromethane (3 x 15 ml). After the organic layer was dried with anhydrous sodium sulfate and concentrated, the residue was purified by silica gel thin layer or column chromatography.

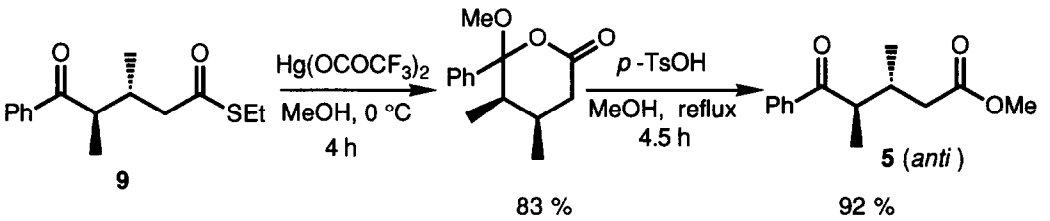
^{13}C-NMR Data of 4-Methoxy-2-(1-propenyl)-1,3-dioxolan-2-ylium Cation.

^{13}C-NMR (100 MHz, CD_2Cl_2): δ 180 (cation center), 173 (C2 of 1-propenyl), 116 (C1 of 1-propenyl), 112 (C4 of 1,3-dioxolan-2-ylium), 76 (C5 of 1,3-dioxolan-2-ylium), 61 (methoxy), 22 (C3 of 1-propenyl).

Determination of the Stereochemistry.

The stereochemistry of the Michael adducts was determined as follows: Methyl 3,4-dimethyl-5-oxo-5-phenylpentanoate **5** was easily obtained by transesterification of the corresponding 2,2-dimethoxyethyl ester **6a** on treatment with sodium methoxide (1.0 equiv.) in methanol. On the other hand, *anti* -rich methyl ester **5** could

be derived from the corresponding *S*-ethyl thioester, synthesized according to a method reported by Mukaiyama et al.[7] (Scheme 5). By means of a comparison of the ^1H and ^{13}C NMR and GC data, the main product, obtained by our method, was concluded to be *syn* adduct. We also compared the ^1H-NMR data with that of *anti* methyl 3,4-dimethyl-5-oxoheptanoate, which was provided by Prof. Enders. The major diastereomers of the other Michael adducts were determined as *syn* adducts on the basis of the same tendency in NMR and HPLC or GC analysis, compared with *syn* 2,2-dimethoxyethyl ester **6a**.



Scheme 5.

2,2-Dimethoxyethyl 3,4-Dimethyl-5-oxo-5-phenylpentanoate (6a).
^1H-NMR (400 MHz, $CDCl_3$): δ 7.95 (m, 2H), 7.55 (m, 3H), 4.55 (t, *J* = 5.5 Hz, 1H), 4.10 (d, *J* = 5.5 Hz, 2H), 3.60 (m, 1H), 3.35 (s, 6H), 2.50 (m, 1H), 2.35 (m, 2H), 1.13 (d, *J* = 7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); IR: (NaCl) 1740, 1680, 1600, 1450, 1375, 1180, 1135, 1080, 745, 700 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{16}H_{21}O_4$: m/z = 277.1440, found 277.1422; $(M-MeOH)^+$ calcd for $C_{16}H_{20}O_4$: m/z = 276.1361, found 276.1352.

2,2-Dimethoxyethyl 3,4-Dimethyl-5-oxoheptanoate (6b).
^1H-NMR (400 MHz, $CDCl_3$): δ 4.55 (t, *J* = 5.5 Hz, 1H), 4.10 (d, *J* = 5.5 Hz, 2H), 3.35 (s, 6H), 2.61-2.20 (m, 6H), 1.05 (t, *J* = 7.5 Hz, 3H), 1.01 (d, *J* = 7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H); IR: (NaCl) 1740, 1715, 1455, 1375, 1180, 1135, 1075 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{12}H_{21}O_4$: m/z = 229.1440, found 229.1432; $(M-MeOH)^+$ calcd for $C_{12}H_{20}O_4$: m/z = 228.1362, found 228.1372.

2,2-Dimethoxyethyl 3-(2-Oxocyclohexyl)butanoate (6c).
^1H-NMR (400 MHz, $CDCl_3$): δ 4.55 (t, *J* = 5.5 Hz, 1H), 4.10 (d, *J* = 5.5 Hz, 2H), 3.35 (s, 6H), 2.55 (m, 1H), 2.35 (m, 4H), 2.10 (m, 2H), 1.90 (m, 1H), 1.70 (m, 3H), 1.49 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 3H); IR: (NaCl) 1740, 1710, 1450, 1375, 1180, 1135, 1080 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{13}H_{21}O_4$: m/z = 241.1440, found 241.1444; $(M-MeOH)^+$ calcd for $C_{13}H_{20}O_4$: m/z = 240.1361, found 240.1351.

2,2-Dimethoxyethyl 3-(2-Oxocyclopentyl)butanoate (6d).
^1H-NMR (400 MHz, $CDCl_3$): δ 4.55 (t, *J* = 5.5 Hz, 1H), 4.10 (d, *J* = 5.5 Hz, 2H), 3.35 (s, 6H), 2.55 (m, 2H), 2.30 (m, 2H), 2.10 (m, 4H), 1.70 (m, 2H), 0.88 (d, *J* = 6.7 Hz, 3H); IR: (NaCl) 1740, 1455, 1375, 1180, 1135, 1080 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{12}H_{19}O_4$: m/z = 227.1284, found 227.1313; $(M-MeOH)^+$ calcd for $C_{12}H_{18}O_4$: m/z = 226.1205, found 226.1207.

2,2-Dimethoxyethyl 3,4-Dimethyl-5-oxopentanoate (6e).
^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 4.55 (t, *J* = 5.5 Hz, 1H), 4.10 (d, *J* = 5.5 Hz, 2H), 3.35 (s, 6H), 2.60 (m, 1H), 2.35 (m, 3H), 1.05 (d, *J* = 7.3 Hz, 3H), 0.92 (d, *J* = 7.3 Hz, 3H); IR: (NaCl) 1740, 1705, 1460, 1380, 1190, 1135, 1075 cm^{-1}; MS:$(M-MeO)^+$ calcd for $C_{10}H_{17}O_4$: m/z = 201.1127, found 201.1105; $(M-MeOH)^+$ calcd for $C_{10}H_{16}O_4$: m/z = 200.1049, found 200.1036.

2,2-Dimethoxyethyl 3-Methyl-5-oxo-4-phenylpentanoate (6f).
^{1}H-NMR (60 MHz, $CDCl_3$): δ 9.7 (s, 1H), 7.2 (m, 5H), 4.6 (t, *J* = 5.5 Hz, 1H), 4.1 (d, *J* = 5.5 Hz, 2H), 4.0-3.5 (m, 1H), 3.4 (s, 6H), 3.1-2.0 (m, 3H), 0.8 (d, *J* = 7 Hz, 3H); IR: (NaCl) 1730, 1700, 1600, 1460, 1380, 1175, 1135, 1080, 760, 705 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{15}H_{19}O_4$: m/z = 263.1283, found 263.1274; $(M-MeOH)^+$ calcd for $C_{15}H_{18}O_4$: m/z = 262.1205, found 262.1206.

2,2-Dimethoxyethyl 3,4,4-Trimethyl-5-oxopentanoate (6g).
^{1}H-NMR (60 MHz, CCl_4): δ 9.6 (s, 1H), 4.6 (t, *J* = 6 Hz, 1H), 4.1 (d, *J* = 6 Hz, 2H), 3.3 (s, 6H), 2.5-2.0 (m, 3H), 1.2 (d, *J* = 10 Hz, 3H), 1.05 (s, 6H); IR: (NaCl) 1740, 1710, 1460, 1380, 1180, 1140, 1080 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{11}H_{19}O_4$: m/z = 215.1284, found 215.1286; $(M-MeOH)^+$ calcd for $C_{11}H_{18}O_4$: m/z = 214.1205, found 214.1204.

2,2-Dimethoxyethyl 4-Methyl-5-oxo-3,5-diphenylpentanoate (6h).
^{1}H-NMR (60 MHz, CCl_4): δ 8.1 (m, 2H), 7.5 (m, 3H), 7.2 (s, 5H), 4.2 (t, *J* = 5.5 Hz, 1H), 3.8 (d, *J* = 5.5 Hz, 2H), 4.0-3.3 (m, 2H), 3.2 (s, 6H), 2.7 (m, 2H), 0.9 (d, *J* = 7 Hz, 3H); IR: (NaCl) 1740, 1680, 1600, 1450, 1380, 1170, 1140, 1075, 760, 705 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{21}H_{23}O_4$: m/z = 339.1597, found 339.1573; $(M-MeOH)^+$ calcd for $C_{21}H_{22}O_4$: m/z = 338.1518, found 338.1511.

2,2-Dimethoxyethyl 4-Methyl-5-oxo-3-phenylheptanoate (6i).
^{1}H-NMR (60 MHz, CCl_4): δ 7.2 (s, 5H), 4.3 (t, *J* = 5.5 Hz, 1H), 3.9 (d, *J* = 5.5 Hz, 2H), 3.2 (s, 6H), 2.8-2.2 (m, 6H), 1.05 (t, *J* = 7 Hz, 3H), 0.9 (d, *J* = 7 Hz, 3H); IR: (NaCl) 1740, 1715, 1600, 1455, 1380, 1175, 1135, 1080, 760, 700 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{17}H_{23}O_4$: m/z = 291.1596, found 291.1613; $(M-MeOH)^+$ calcd for $C_{17}H_{22}O_4$: m/z = 290.1518, found 290.1501.

2,2-Dimethoxyethyl 3-(2-Oxocyclohexyl)-3-phenylpropanoate (6j).
^{1}H-NMR (60 MHz, CCl_4): δ 7.3 (s, 5H), 4.4 (t, *J* = 5.5 Hz, 1H), 4.05 (d, *J* = 5.5 Hz, 2H), 3.3 (s, 6H), 2.9 (m, 2H), 2.9-1.2 (m, 10H); IR: (NaCl) 1740, 1710, 1600, 1455, 1375, 1170, 1135, 1080, 735, 705 cm^{-1}; MS: calcd for $C_{19}H_{26}O_5$: m/z = 334.1780, found 334.1828.

2,2-Dimethoxyethyl 4-Methyl-5-oxo-5-phenyl-3-[(*E*)-1-propenyl]pentanoate (6k).
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.95 (m, 2H), 7.55 (m, 3H), 5.45 (m, 1H), 5.30 (m, 1H), 4.60 (t, *J* = 5.5 Hz, 1H), 4.10 (d, *J* = 5.5 Hz, 2H), 3.60 (m, 1H), 3.35 (s, 6H), 3.00 (m, 1H), 2.45 (m, 2H), 1.65 (dd, *J* = 1.8, 6 Hz, 3H), 1.15 (d, *J* = 7.3 Hz, 3H); IR: (NaCl) 1740, 1680, 1600, 1450, 1375, 1175, 1135, 1080, 970, 750, 710 cm^{-1}; MS: $(M-MeO)^+$ calcd for $C_{18}H_{23}O_4$: m/z = 303.1596, found 303.1569; $(M-MeOH)^+$ calcd for $C_{18}H_{22}O_4$: m/z = 302.1518, found 302.1553.

2,2-Dimethoxyethyl 2,3,3-Trimethyl-4-morpholinocyclobutanecarboxylate (7).
^{1}H-NMR (60 MHz, CCl_4): δ 4.6 (t, *J* = 5.5 Hz, 1H), 4.1 (d, *J* = 5.5 Hz, 2H), 3.6 (m, 4H), 3.3 (s, 6H), 2.5 (m, 1H), 2.3 (m, 4H), 2.1-1.6 (m, 2H), 1.1 (d, *J* = 6 Hz, 3H), 0.9 (s, 6H); IR: (NaCl) 1740, 1455, 1375, 1335, 1200, 1140, 1080, 880 cm^{-1}; MS: $\mathbf{8}^+$ calcd for $C_{11}H_{19}O_5N$: m/z = 245.1263, found 245.1254; $(\mathbf{8}-MeO)^+$ calcd for $C_{10}H_{16}O_4N$: m/z = 214.1079, found 214.1102; $(\mathbf{8}-MeOH)^+$ calcd for $C_{10}H_{15}O_4N$: m/z = 213.1001, found 213.1006.

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