JOC Article

Catalytic (2 + 2)-Cycloaddition Reactions of Silyl Enol Ethers. A Convenient and Stereoselective Method for Cyclobutane Ring Formation

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An efficient catalytic (2 + 2)-cycloaddition reaction leading to the formation of cyclobutane rings has been devised. The process transforms silyl enol ethers and α,β-unsaturated esters into polysubstituted cyclobutanes with a high degree of *trans*-stereoselectivity. Both the rate and stereoselectivity of the process can be controlled by the choice of the ester group and silyl substituents. The results of stereochemical studies show that the cycloaddition step in this reaction proceeds in a nonstereospecific manner and, thus, by a pathway involving sequential nucleophilic additions via a short-lived zwitterionic intermediate.

Introduction

The facile and stereoselective synthesis of mono- and polycyclic compounds from simple starting materials has remained as one of the main goals in synthetic organic chemistry.[1] Much attention has been devoted to the construction of cyclopropane, cyclopentane, and cyclohexane rings by cycloaddition and stepwise-annulation reactions. As a result, a number of efficient and/or stereoselective strategies have been devised. On the other hand, only a limited number of practical methods have been developed to form cyclobutane ring systems from simple substrates. This represents a deficiency in the area of synthetic organic chemistry since cyclobutanes abound in nature as biologically active substances[2] and are used as important synthetic intermediates in routes targeted at medicinally useful substances.[3] Photochemical (2 + 2)-cycloaddtions of alkenes and enones[4] and thermal (2 + 2)-cycloadditions of ketenes and alkenes[5] are the usual methods used to prepare cyclobutanes, but controlling reactivity and selectivity in these processes often is a difficult task.

We have developed a strategy for cyclobutane ring construction involving stepwise nucleophilic addition reactions of silyl enol ether. It is well-known that conjugate addition reactions of enolates (or their equivalents) with α,β-unsaturated carbonyl compounds afford 1,5-dicarbonyl products. In this process, the in situ formed δ-keto-enolate is quenched by an external electrophile, such as a proton (Scheme 1, path a). However, the carbonyl group in the initially formed Michael adduct, which originates from the enolate component, can act as an internal electrophile in an intramolecular addition process leading to formation of a cyclobutanol product (Scheme 1, path b). The cyclobutanol forming reaction can be described as a Michael-aldol-like (2 + 2)-cycloaddition. Vinyl sulfides or selenides have been employed in similar stepwise reactions.[6] In contrast, cyclobutane formation from silyl enol ethers, which are one of the most easily prepared ketone-equivalents, has not been achieved except in a limited number of cases.[7,8] A significant problem with some of the reported reactions

* Corresponding author.

(1) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002.

(2) For examples, see: (a) Kepler, J. A.; Wall, M. E.; Mason, J. E.; Basset, C.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1967**, *89*, 1260−1261. (b) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *220*, 77−78. (c) Schenk, H.; Driessen, R. A. J.; de Gelder, R.; Goubits, K.; Nieboer, H.; Brüggemann-Rotgans, I. E. M.; Diepenhorst, P. *Croat. Chem. Acta* **1999**, *72*, 593−606. (d) Cremin, P.; Guiry, P. J.; Wolfender, J.-L.; Hostettmann, K.; Donnely, D. M. X. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2325−2329.

(3) For examples, see: (a) Lange, G. L.; Lee, M. *Synthesis* **1986**, 117−120. (b) Haque, A.; Ghatak, A.; Ghosh, S.; Ghoshal, N. *J. Org. Chem.* **1997**, *62*, 5211−5214. (c) Crimmins, M. T.; Wang, Z.; McKerlie, L. A. *J. Am. Chem. Soc.* **1998**, *120*, 1747−1756. (d) Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425−7426. (e) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485−1537.

(4) (a) Crimmins, M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 123−149. (b) Bach, T.; Bergmann, H. *J. Am. Chem. Soc.* **2000**, *122*, 11525−11526. (c) Chen, C.; Chang, V.; Cai, X.; Duesler, E.; Mariano, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 6433−6434.

(5) (a) Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*; Academic Press: London, 1967. (b) Ahmad, S. *Tetrahedron Lett.* **1991**, *32*, 6997−7000.

(6) (a) Yamazaki, S.; Kumagai, H.; Yamabe, S.; Yamamoto, K. *J. Org. Chem.* **1998**, *63*, 3371−3378. (b) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869−8885.

(7) (a) Kuehne, M. E.; Foley, L. *J. Org. Chem.* **1965**, *30*, 4280−4284. (b) Baar, M. R.; Ballesteros, P.; Roberts, B. W. *Tetrahedron Lett.* **1986**, *27*, 2083−2086. (c) Quendo, A.; Rousseau, G. *Tetrahedron Lett.* **1988**, *29*, 6443−6446. (d) Kniep, C. S.; Padias, A. B.; Hall, H. K., Jr. *Tetrahedron* **2000**, *56*, 4279−4288. (e) Loughlin, W. L.; McCleary, M. A. *Org. Biomol. Chem.* **2003**, *1*, 1347−1353.

(8) To our knowledge, only two *stoichiometric* reactions of silyl enolates with simple enoates have been reported. (a) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 253−255. (b) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578−579. (c) Magnus, P.; Rigollier, P.; Lacour, J.; Tobler, H. *J. Am. Chem. Soc.* **1992**, *114*, 3993−3995.

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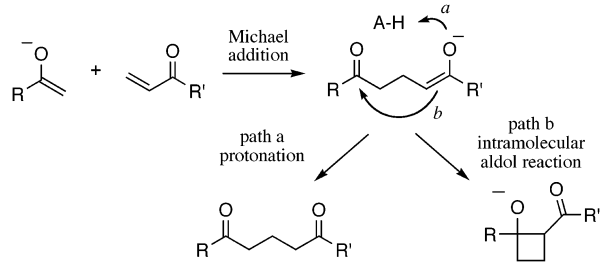
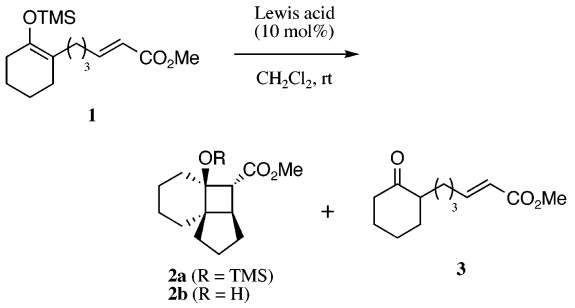
SCHEME 1



SCHEME 2



is that simple α,*β*-unsaturated esters have reactivity lower than that of esters of alkynyl and allenyl carboxylates and other highly electron-deficient olefines.[7]

In an earlier effort, we developed a new method to prepare polycyclic cyclobutanes starting with α,*β*-unsaturated esters having appended keto-carbonyl or silyl enol ether moieties. This process, termed the intramolecular Michael-aldol reaction, is mediated by stoichiometric amounts of R_3SiX-amine coreagents.[9] However, the reaction has several limitations, including the need for excess amounts (ca. 3 eq*uiv*) of the reagents. In addition, we found that the conditions used for the intramolecular reaction do not promote related intermolecular reactions owing to the poor reactivity of both substrates. Our continuing studies in this area have led to the development of a new catalytic intermolecular Michael-aldol-like (2 + 2)-cycloaddition reactions of silyl enol ethers with α,*β*-unsaturated esters. The results of this effort are described below.

Results and Discussions

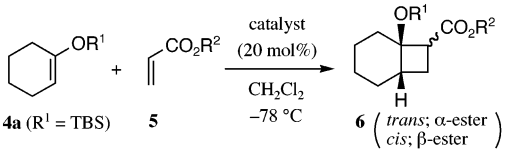
Catalytic Intramolecular (2 + 2)-Reaction. Our initial studies focused on an exploration of catalytic systems that promote intramolecular (2 + 2)-cycloadditions with the hope that it would provide information about catalysts for the intermolecular process. The reaction of silyl enol ether **1**, possessing an α,*β*-enoate moiety, in CH_2Cl_2 at 25 °C with 10 mol % BF_3·OEt_2 affords the tricyclo[5.4.0.$0^{3,7}$]undecane **2a** in 17% yield along with 32% of the desilylated substrate **3** (Scheme 2, Table 1, run 1). The use of Bu_2BOTf or $AlMe_3$ led to increased yields of the cyclobutane product **2a**, but production of the desilylated alcohol **2b** was also observed with these catalysts (runs 2 and 3). Broad screening of a number of Lewis acids showed that $EtAlCl_2$ and $TiCl_4$ were the optimal catalysts, both serving to promote formation of cycloadduct **2a** in 60−76% yields (runs 4 and 5). Diastereoselective formation of **2a** occurred in these reactions, as was seen in the stoichiometric reactions reported earlier.[9b] Several Lewis acids, including Et_2AlCl, $Sn(OTf)_2$, $SnCl_4$, TMSI, and $InCl_3$, were found to catalyze formation of **2a** and/or **2b**, but in low yields (run 6, other data not shown). On the contrary, no cyclobutane product is produced in reactions catalyzed by lanthanide Lewis acids and transition metal Lewis acids; starting enol ether **1** or desilylated ketone **2** were recovered in these cases.[10]

TABLE 1. Lewis Acid Catalyzed Intramolecular (2 + 2)-Cycloaddition of 1[a]

			yield (%)		
run	catalyst	reaction time (h)	**2a**	**2b**	**3**
1	BF_3·OEt_2	9.5	17	0	32
2	Bu_2BOTf	1.5	35	21	19
3	$AlCl_3$	8	31	11	50
4	$EtAlCl_2$	2	76	0	11
5	$TiCl_4$	0.17	61	0	20
6	$Sn(OTf)_2$	2	28	12	47

[a] Reactions were performed using 10 mol % catalyst and 1.0 equivof **1** in CH_2Cl_2 at room temperature until the starting material was fully consumed.

SCHEME 3



Catalytic Intermolecular (2 + 2)-Cycloaddition. The intermolecular version of the cycloaddition reaction was examined next by using silyl enol ethers **4** and α,*β*-esters unsaturated **5** (Scheme 3). To a solution of **4** (1.0 equiv) and **5** (2.0 equiv) in CH_2Cl_2 (0.2 M) was slowly added a solution of $EtAlCl_2$ (20 mol %) in hexane, at −78 °C. After standing at −78 °C, the mixtures were subjected to a standard workup procedure and chromatographic separation to afford the cyclobutane products **6**, which are stable under ambient conditions. Although these reactions are almost completed within 10 min, all were carried out for 4 h, at which time the enol ethers are completely consumed. It was observed that reactions performed at higher temperatures result in increased amounts of acrylate oligomers as byproducts.

The effects of changing the alkoxy group of the acrylate **5** on the yields of reactions with the TBS enol ether **4a** are summarized in Table 2. Methyl acrylate (**5a**) reacts to afford the diastereomeric cyclobutanes *trans*-**6a** and *cis*-**6a** in 60% and 19% yields, respectively (Table 2, run 1). The relative stereochemistry of these products was assigned by use of chemical methods. Both *trans*- and *cis*-**6a** are transformed into the corresponding diols **7** by reduction and desilylation. As expected, *trans*-**7** did not

(9) (a) Ihara, M.; Ohnishi, M.; Takano, M.; Makita, K.; Taniguchi, N.; Fukumoto, K. *J. Am. Chem. Soc.* **1992**, *114*, 4408−4410. (b) Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1993**, *115*, 8107−8115. (c) Takasu, K.; Misawa, K.; Yamada, M.; Furuta, Y.; Taniguchi, T.; Ihara, M. *Chem. Commun.* **2000**, 1739−1740. (d) Takasu, K.; Ueno, M.; Ihara. M. *J. Org. Chem.* **2001**, *66*, 4667−4672. (e) Takasu, K.; Misawa. K.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 8489−8491.

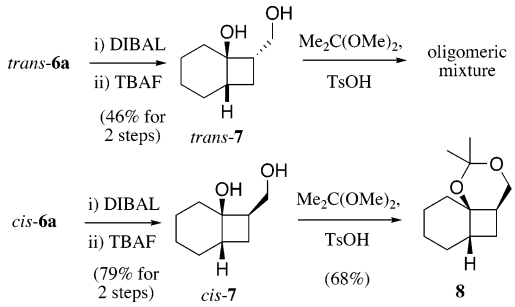
(10) The following Lewis acids were tested: $Mg(ClO_4)_2$, $Sc(OTf)_3$, $CuCl_2$, $Cu(OTf)_2$, $Zn(OTf)_2$, YCl_3, $Y(OTf)_3$, $ZrCl_4$, $Sn(OTf)_2$, $La(OTf)_3$, $Eu(OTf)_3$, and $Yb(OTf)_3$.

TABLE 2. Catalytic Intermolecular (2 + 2)-Cycloaddition between Silyl Enol Ether 4a and Acrylates 5[a]

run	acrylate (R^2)	catalyst	product (R^1 = TBS)	yield (%)	ratio *trans*:*cis*
1	**5a** (Me)	$EtAlCl_2$	**6a**	79	76:24[e]
2	**5b** (^{t}Bu)	$EtAlCl_2$	**6b**	trace	
3	**5c** (Ph)	$EtAlCl_2$	**6c**	trace	
4	**5d** (PFP)[d]	$EtAlCl_2$	**6d**	89	94:6[f]
5	**5e** (PCP)[d]	$EtAlCl_2$	**6e**	75	95:5[f]
6	**5f** (HFIP)[d]	$EtAlCl_2$	**6f**	93	93:7[f]
7[b]	**5f**	$EtAlCl_2$	**6f**	81	79:21[f]
8[c]	**5f**	$EtAlCl_2$	**6f**	91	90:10[f]
9	**5f**	Et_2AlCl	**6f**	77	81:19[f]

[a] Reactions were performed using 20 mol % catalyst and 2.0 equiv of **5**, and 1.0 equiv of **4a** in CH_2Cl_2 at −78 °C for 4 h. [b] Reaction was carried out using 10 mol % $EtAlCl_2$. [c] Reaction was carried out in toluene. [d] PFP = pentafluorophenyl, PCP = pentachlorophenyl, and HFIP = 1,1,1,3,3,3-hexafluoroisopropyl. [e] *trans*/*cis* ratio was based on isolated yield. [f] *trans*/*cis* ratio was determined by ^{1}H NMR.

SCHEME 4



produce an acetonide upon treatment with 2,2-dimethoxypropane, whereas *cis*-**6** reacted smoothly under these conditions to form the tricyclic acetonide **8** (Scheme 4). In contrast, reactions of acrylates **5b** and **5c** with **4a** led to formation of only trace quantities of the corresponding cyclobutanes (Table 2, runs 2 and 3). Further exploration demonstrated that incorporation of fluorine or chlorine in the alkoxy moiety led to enhanced yields for formation of the cyclobutane products and increased *trans*-selectivities. For example, Lewis acid catalyzed cyclobutane formation starting with the perfluorophenyl (PFP), perchlorophenyl (PCP), and hexafluoroisopropyl (HFIP) acrylates **5d**−**f** were both high yielding and diastereoselectivity (runs 4−6).[11] Interestingly, we unexpectedly observed that the diastereoselectivity of this process is dependent on the amount of catalyst used. For example, 10 mol % $EtAlCl_2$ led to decrease in *trans*-selectivity, although **6f** was obtained in good yield (run 7). Furthermore, reaction of **5f** with Et_2AlCl as catalyst provided **6f** with low stereoselectivity (run 9). Other Lewis acids failed to catalyze the cyclobutane forming reaction under the above conditions.[12]

We also examined the effects of silyl substituents (R^1) in the enol ether **4** on the efficiency of the (2 + 2)-cycloaddition of **5f** (Table 3). The TMS enol ether **4b** decomposes under the reaction conditions to form cyclohexanone (run 1), indicating that metal exchange to transform the silyl enol ether to an aluminum enolate might be rapid. In contrast, both the yield and the *trans*-selectivity of the cycloaddition reaction are dramatically enhanced when more sterically bulky and more stable silyl enol ethers are employed as substrates (Table 3, runs 2 and 3 vs Table 2, run 6). It is noteworthy that only the *trans*-isomer **6i** is produced in reaction of the TIPS enol ether **4d** (Table 3, run 3). Methyl enol ether **4e** also undergoes the cyclobutane-forming reaction with high stereoselectivity (run 4), although the desired reaction does not occur with enol acetate **4f** (run 5).

TABLE 3. Catalytic Intermolecular (2 + 2)-Cycloaddition between Enol Ethers 4 and Acrylate 5f[a]

run	enolate (R^1)	product (R^2 = HFIP)	yield (%)	ratio *trans*:*cis*[b]
1	**4b** (TMS)	**6g**	0	
2	**4c** (TES)	**6h**	39	89:11
3	**4d** (TIPS)	**6i**	80	>99:<1
4	**4e** (Me)	**6j**	84	92:8
5	**4f** (Ac)	**6k**	0	

[a] Reactions were performed using 20 mol % catalyst and 2.0 equiv of **5f**, and 1.0 equiv of **4** in CH_2Cl_2 at −78 °C for 4 h. [b] *trans*/*cis* ratio was determined by ^{1}H NMR.

By using this new methodology, several cyclobutanes were synthesized, starting with the silyl enol ethers shown in Table 4.[13] Cyclic enol silyl ethers **9a**−**c** react smoothly with HFIP acrylate (**5f**) to give the corresponding bicylic-cyclobutanes **10a**−**c**. The diastereoselectivity of this process is significantly influenced by ring size (Table 4, runs 1−3 vs Table 2, run 6). Specifically, substrates with ring sizes greater than seven-membered react to form only *trans* products. Quarternary substituted enol ether **9d** is also a good substrate for the reaction, which yields *trans*-product **10d** or **10d′** exclusively (Table 4, runs 4 and 5). These products have substituents on both the ring-juncture positions. A fluorinated substituent enhances the chemical yield, although the *trans*/*cis*-stereoselectivity is almost identical. As noted above (see Table 3), HFIP ester **5f** has proven to be a more suitable substrate than the corresponding methyl ester. Acyclic substrate **9e** reacts to give monocyclic cyclobutane **10e** in 65% yield with moderate *trans*/*cis*-selectivity (run 6). On the other hand, the simple enol silyl ether **9f** does not react to produce cyclobutane **10f** under these conditions. Decomposition of enol ether to generate acetoaldehyde occurs instead (run 7). It is especially noteworthy that this reaction can be applied to the preparation of derivatives of medicinally useful substances, such as the estrone analogue **10g** (run 8). α- or β-Substituted enoates, possessing fluorinated alkoxy moieties, such as in PFP crotonate (**5g**) and HFIP methacrylate (**5h**), also participate in the (2 + 2)-cycloaddition to give the corresponding cyclobutanes **10i** and **10h** as a single isomers (runs 9 and 10). On the other hand, methyl crotonate and methyl methacrylate are unreactive under these conditions.

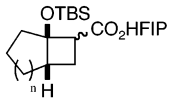
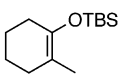
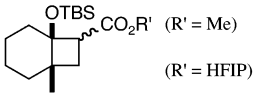
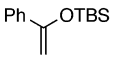
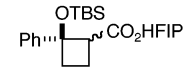
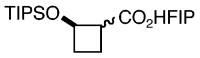
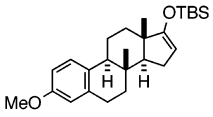
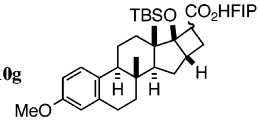
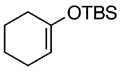
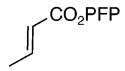
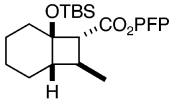
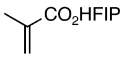
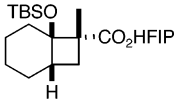
Proposed Reaction Mechanism. The cyclobutane-forming reaction, described above, contrasts with the

(11) Maruoka and co-workers reported that nonbonding Al−F interaction enhances the reactivity and stereoselectivity. (a) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754−5755. (b) Ooi, T.; Kagoshima, N.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 7105−7108.

(12) In addition to Al catalysts, only $TiCl_4$ (20 mol %) promotes the (2 + 2)-cycloaddition but only to give **6f** in 10% yield.

(13) Stereochemistry of cyclobutane adducts were assigned on the basis of 1D and 2D NMR experiments (see Supporting Information).

TABLE 4. $EtAlCl_2$-Catalyzed Synthesis of Cyclobutanes[a]

run	silyl enol ether[b]	enoate	product	% yield	ratio *trans* : *cis* [b]
1	**9a**  (n = 1)	**5f** (R = HFIP)	**10a** 	74	60 : 40
2	**9b** (n = 3)	**5f** (R = HFIP)	**10b**	82	100 : 0
3	**9c** (n = 4)	**5f** (R = HFIP)	**10c**	33	100 : 0
4	**9d** 	**5a** (R = Me)	**10d**  (R' = Me)	79	95 : 5
5	**9d**	**5f** (R = HFIP)	**10d'** (R' = HFIP)	90	96 : 4
6	**9e** 	**5f** (R = HFIP)	**10e** 	65	77 : 23
7	**9f** 	**5f** (R = HFIP)	**10f** 	0	–
8	**9g** 	**5f** (R = HFIP)	**10g** 	79	58 : 42
9	**4a** 	**5g** 	**10h** 	15	100 : 0
10	**4a**	**5h** 	**10i** 	69	100 : 0

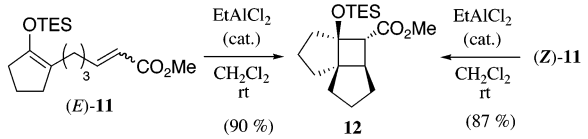
[a] Reactions were performed using 20 mol % catalyst and 2.0 equiv of **5**, and 1.0 equiv of silyl enolate in CH_2Cl_2 at −78 °C for 4 h. [b] *trans*/*cis* ratio was determined by ^1H NMR.

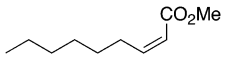
Mukaiyama−Michael reaction[14] in the conditions and substrates for both processes. Two possible reaction pathways to form the cyclobutane ring from enol silyl ether and α,β-unsaturated ester can be envisaged. One involves Lewis acid promoted, concerted (2 + 2)-cycloaddition, and the other a stepwise Michael-aldol like (2 + 2)-cycloaddition reaction.

In experiments designed to gain information about the mechanism of this process, we first attempted to detect reaction intermediates. However, a simple mono-Michael adduct could not be isolated from the $EtAlCl_2$-catalyzed reaction mixture. In addition, the transient formation of a zwitterionic intermediate could not be observed by using IR and NMR spectroscopic analysis of the reaction mixture even at temperatures lower than −78 °C. The results indicate that the zwitterionic intermediate formed by Michael addition is extremely short-lived.

Next, we examined the stereochemical course of the Michael-aldol-like (2 + 2)-cycloaddition. Interestingly, the stereochemistry of the cyclobutane adducts is not governed by the geometry of the unsaturated ester substrate. Accordingly, reaction of both (*E*)-**11** and (*Z*)-**11** under the above intramolecular conditions results in production of **12** as a sole diastereomer in respective 90% and 87% yields (Scheme 5). Rapid (*E*)/(*Z*) preequilibration of the substrates or epimerization of products might explain the stereochemical outcome of these reactions. However, these explanations can be ruled out on the basis of the following results. No transformation of (*Z*)-enoate **13** into the (*E*)-isomer is observed by the treatment with catalytic $EtAlCl_2$ at ambient temperature. Exposure of *trans*-**6a** with $EtAlCl_2$ at room temperature does not cause epimerization to form *cis*-**6a**, and epimerization of *cis*- to *trans*-**6a** also does not occur under these conditions. Thus, the results suggest that the catalytic reaction to afford cyclobutane adducts proceeds by way of a stepwise pathway, involving the intermediacy of a zwitterionic species.

SCHEME 5





(*Z*)-**13**

A plausible mechanism for the catalytic (2 + 2)-cycloaddition reaction is depicted in Figure 1. The Mukaiyama-type Michael addition of silyl enol ether to enoate catalyzed by $EtAlCl_2$ affords the corresponding silyl ketene acetal, and then it successively to the intramolecular silyl oxonium carbon to provide a cyclobutane ring. Stereoselectivity would be determined in the second aldol step, depending on chair- or boatlike transition state. The reason our reaction system produces further intramolecular aldol addition after the Mukaiyama−Michael reaction would be explained as follows.

(14) (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem Lett.* **1974**, 1223−1224. (b) Loh, T.-P.; Wei, L.-L. *Tetrahedron* **1998**, *54*, 7615−7624. (c) Evans, D. A.; Willis, M. H.; Uehling, D. E. *Org. Lett.* **1999**, *1*, 865−868 and references therein.

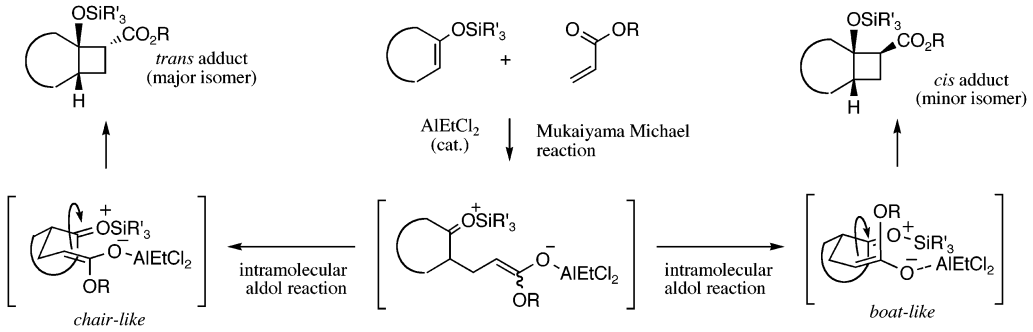


FIGURE 1. Hypothesized reaction mechanisms and postulated TS models of our system.

The presence of a bulky silyl substituent might contribute to stabilization of the silyl oxonium cation generated by the first Michael process, and therefore an enolate could react with the oxonium carbon before the migration of the silyl group.

Conclusions

We have developed a general method for facile cyclobutane ring formation by catalytic (2 + 2)-cycloaddition reactions of silyl enol ethers and α,β-unsaturated esters. The process requires catalysis by hard Lewis acids, such as $EtAlCl_2$. In this process, stereochemistry can be controlled at three of the four cyclobutane stereogenic centers. We observed that reactions of fluorinated enoates are more efficient and proceed with higher *trans*-selectivities. Moreover, the process is sufficiently versatile to allow its use for the concise introduction of cyclobutane rings into structurally complex substrates.[15] The mechanistic investigations carried out thus far demonstrate that this Michael-aldol-like (2 + 2)-cycloaddition reaction takes place by a stepwise pathway via short-lived zwitterionic intermediates.

Experimental Section

General Procedure for Intramolecular Reaction. To a solution of silyl enol ether in CH_2Cl_2 (0.15 M solution) was added Lewis acid at room temperature, and the mixture was stirred until the substrate was completely consumed. The resulting mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O, and combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, giving a residue that was subjected to column chromatography on silica gel (Et_2O/hexane) to afford the cyclobutane adduct.

(15) Recently, the synthesis and biological evaluation of epothilone cyclobutyl analogues were reported. Nicolaou, K. C.; Namoto, K.; Ritzén, A.; Ulven, T.; Shoji, M.; Li, J.; D'Amico, G.; Liotta, D.; French, C. T.; Wartmann, M.; Altmann. K.-H.; Giannakakou, P. *J. Am. Chem. Soc.* **2001**, *123*, 9313−9323.

General Procedure for Intermolecular Reaction. To a solution of α,β-unsaturated ester (2.0 equiv) and silyl enol ether (1.0 equiv, 0.10 M solution) in CH_2Cl_2 at −78 °C was added $EtAlCl_2$ (0.9 M hexane solution, 20 mol %), and the mixture was stirred for 4 h at −78 °C. The resulting mixture was diluted with Et_2O and then washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O, and combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, giving a residue that was subjected to column chromatography on silica gel (Et_2O/hexane) to afford the cyclobutane product. *trans*-**6a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.90 (dd, J = 10.2, 8.5 Hz, 1 H), 2.24 (m, 1H), 1.80−1.20 (m, 10H), 0.88 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 76.3, 51.0, 49.8, 40.8, 31.6, 25.5, 23.4, 21.3, 20.5, 18.8, 17.8, −3.04; IR (neat) ν 2929, 2856, 1735, 1463, 1249, 1215, 1190, 1102, 836, 774 cm^{-1}; LRMS (EI) m/z 283 (M^+); HRMS calcd for $C_{15}H_{27}O_3Si$ 283.1729, found 283.1730. *cis*-**6a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.02 (ddd, J = 7.8, 5.0, 0.8 Hz, 1 H), 2.59 (m, 1H), 2.22 (ddd, J = 11.0, 9.1, 5.0 Hz, 1H), 1.85−1.65 (m, 3H), 1.58−1.24 (m, 6H), 0.84 (s, 9H), 0.10 (s, 6H), 0.082 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 77.1, 51.2, 48.8, 40.6, 36.8, 26.7, 25.5, 22.0, 21.7, 21.6, 17.9, −2.7, −2.8; IR (neat) ν 2933, 2856, 1738, 1463, 1434, 1359, 1250, 1198, 1155, 1085, 1070, 835, 773 cm^{-1}; LRMS (EI) m/z 283 ($M^+ - CH_3$); HRMS calcd for $C_{15}H_{27}O_3Si$ 283.1729, found 283.1735.

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Supporting Information Available: Experimental procedures for the synthesis of silyl enol ethers **1**, (*E*)-**11**, and (*Z*)-**11**; procedures for the conversion into **7** and **8**; and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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