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Formal [4+2] cycloaddition between 3-ethoxycyclobutanones and silyl enol ethers

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ABSTRACT

3-Ethoxycyclobutanones reacted with silyl enol ethers to give formal [4+2] cycloadducts, 3-ethoxy-5-trimethylsiloxycyclohexanone derivatives, by using ethylaluminum dichloride as a Lewis acid. Highly oxygenated cyclohexanone derivatives were stereoselectively prepared by this method.

[4+2] Cycloaddition reaction[1] is an effective method for the construction of a six-membered ring, and the Diels–Alder reaction[2] is frequently employed for this purpose. Silyl enol ethers are readily-available and versatile building blocks in organic synthesis.[3] Though siloxy dienes are employed as C4 units in Diels–Alder reaction,[4] the use of silyl enol ethers as C2 units is very rare.[5] For preparing six-membered carbocycles bearing an oxygen substituent, it is meaningful to establish [4+2] cycloaddition using silyl enol ethers as a C2 component.[6]

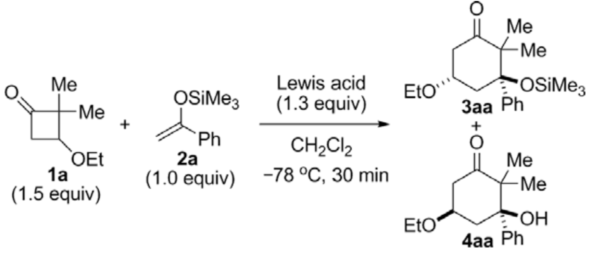
Recently, we found that dihydro-γ-pyrone derivatives were efficiently synthesized in a one-pot manner by boron trifluoride etherate-catalyzed formal [4+2] cycloaddition between 3-alkoxycyclobutanones and carbonyl compounds such as aldehydes and ketones.[7] Because the C–O bond of aldehydes and ketones was effectively inserted into a cyclobutanone ring,[8] we then planned the insertion of a C–C double bond of silyl enol ethers. We report herein formal [4+2] cycloaddition between 3-ethoxycyclobutanones and silyl enol ethers to afford cyclohexanone derivatives.

First, we tried to find a suitable Lewis acid which catalyzed [4+2] cycloaddition between 2,2-dimethyl-3-ethoxycyclobutanone (**1a**) and 1-phenyl-1-trimethylsilyloxyethene (**2a**) (Table 1). Boron trifluoride etherate, titanium(IV) chloride, and trimethylsilyl triflate did not catalyze the desired [4+2] cycloaddition reaction, whereas the Lewis acids shown in Table 1 catalyzed the desired cycloaddition reaction and cycloadducts (**3aa** and **4aa**)[9] were obtained in 22–70% yields. Ethylaluminum dichloride catalyzed the desired reaction most efficiently to afford a trimethylsilylated cycloadduct **3aa** in 70% yield along with a trace amount of a desilylated diastereomer **4aa** (entry 1). It should be noted that other products such as desilylated **3aa** and trimethylsilylated **4aa** were not obtained. Other Lewis acids such as antimony(V) chloride, tin(IV) chloride, scandium(III) triflate, and gallium(III) chloride also gave **3aa** as the major product but less efficiently (entries 2–5).

Typical experimental procedure is as follows: 1.3 equiv of ethylaluminum dichloride was added to a solution of 1.5 equiv of 3-ethoxycyclobutanone **1a** and 1.0 equiv of silyl enol ether **2a** in dichloromethane at −78 °C. After the reaction mixture was stirred at −78 °C for 30 min, the usual workup procedure gave **3aa**.[10]

Next, some silyl enol ethers of acetophenone derivatives **2b–e** were employed in the reaction with cyclobutanone **1a** (Table 2). When a methoxy or methyl group was substituted at the *para*-position (X) of the phenyl group, the yields of cycloadducts were low (entries 1 and 2). On the other hand, substitution with a chloro group gave a result comparable to that obtained by using silyl enol ether **2a** (X = H) (entries 3 and 4). Silyl enol ether **2e** having a nitro group reacted less stereoselectively to afford **3ae** in 44% yield along with **5ae** in 6% yield and two desilylated diastereomers (**4ae** and **6ae**) in 29% yield (entry 5).

Table 1
Effect of Lewis acids on formal [4+2] cycloaddition between cyclobutanone **1a** and silyl enol ether **2a**



Entry	Lewis acid	**3aa**[a] (yield %)	**4aa**[a] (yield %)
1	$EtAlCl_2$	70	Trace
2	$SbCl_5$	41	8
3	$SnCl_4$	35	1
4	$Sc(OTf)_3$	26	2
5	$GaCl_3$	22	0

[a] Isolated yield.

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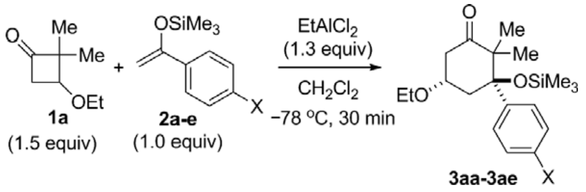
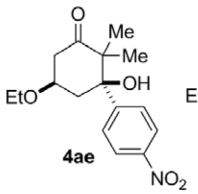
Table 2
Formal [4+2] cycloaddition with silyl enol ethers of acetophenone derivatives



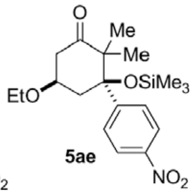
Entry	Silyl enol ether (X)	Product	Yield[a] (%)
1	**2b** (OMe)	**3ab**	37
2	**2c** (Me)	**3ac**	48
3	**2a** (H)	**3aa**	70
4	**2d** (Cl)	**3ad**	69
5	**2e** (NO_2)	**3ae**	44[b]

[a] Isolated yield.

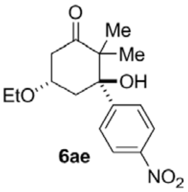
[b] A diastereomer was obtained in 6% yield along with two desilylated cycloadducts (29%).



4ae



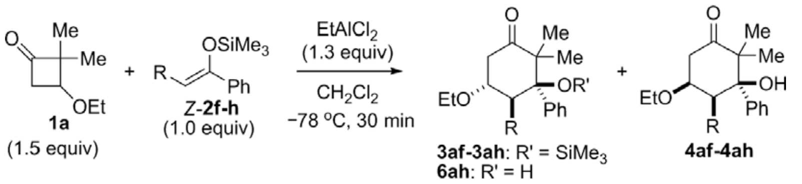
5ae



6ae

Table 3 shows the results of cycloaddition between cyclobutanone **1a** and trisubstituted silyl enol ethers. When *Z*-trimethylsilyl enol ether **2f** prepared from propiophenone was employed, only two diastereomers, **3af** and **4af**, were obtained in 52% and 19% yields, respectively (entry 1). Cycloaddition with *Z*-silyl enol ether **2g** prepared from butyrophenone also proceeded similarly, while the reaction with **2h** bearing an isopropyl group as R proceeded sluggishly to afford cyloadducts **3ah**, **4ah**, and **6ah** in low yields (entries 2 and 3). These results suggest that the present cycloaddition is strongly

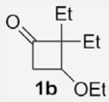
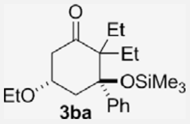
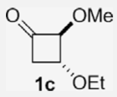
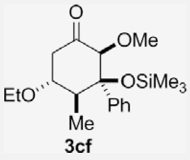
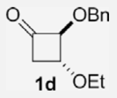
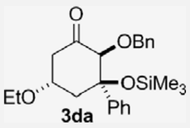
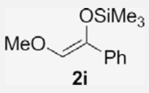
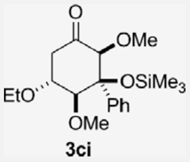
Table 3
Formal [4+2] cycloaddition between cyclobutanone **1a** and *Z*-silyl enol ethers **2f–h**



Entry	**2** (R)	**3**[a] (yield %)	**4**[a] (yield %)	**6**[a] (yield %)
1	**2f** (Me)	**3af** (52)	**4af** (19)	0
2	**2g** (Et)	**3ag** (52)	**4ag** (18)	0
3	**2h** (*i*-Pr)	**3ah** (14)	**4ah** (9)	**6ah** (11)

[a] Isolated yield.

Table 4
Formal [4+2] cycloaddition between cyclobutanones **10a–c** and silyl enol ethers

Entry	Cyclobutanone	Silyl enol ether	Product	Yield[a] (%)
1	 **1b**	**2a**	 **3ba**	51
2[b]	 **1c**	**2f**	 **3cf**	52[c]
3[b]	 **1d**	**2a**	 **3da**	48
4[b]	**1c**	 **2i**	 **3ci**	34

[a] Isolated yield.

[b] Two equivalents of cyclobutanone were employed.

[c] A diastereomer was obtained in 14% yield.

influenced by steric factors. It is interesting that the cis-relationship between R and OR′ (**3af–3ah**) or R and OH (**4af–4ah**) reflects the *Z*-configuration of silyl enol ethers **2f–h** employed.

Cycloaddition of various cyclobutanones **1b–d** with silyl enol ethers **2a**, **f**, and **i** was performed (Table 4). When 2,2-diethyl-3-ethoxycyclobutanone **1b** was employed for the cycloaddition with **2a**, the desired cycloadduct **3ba** was obtained in 51% yield (entry 1). Cycloaddition of *trans*-2-methoxy- or 2-benzyloxy-3-ethoxycyclobutanones **1c, d** gave the corresponding cycloadducts in 66% and 48% yields, respectively (entries 2 and 3).[9] A polyoxygenated cyclohexanone derivative **3ci** was obtained stereoselectively by cycloaddition between **1c** and **2i**.

Thus, [4+2] cycloaddition between 3-ethoxycyclobutanones and silyl enol ethers proceeded by the catalysis with ethylaluminum dichloride, and 3-ethoxy-5-trimethylsiloxycyclohexanone derivatives were obtained stereoselectively. The present cycloaddition will be useful for the stereoselective preparation of highly oxygenated cyclohexanone derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.013.

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9. Stereochemistry was determined by NOE experiments. See Supplementary data.
10. Various reaction conditions were surveyed, but cycloadducts were obtained up to 70% yield probably because 3-ethoxycyclobutanone **1a** and silyl enol ether **2a** were unstable in the presence of ethylaluminum dichloride.