

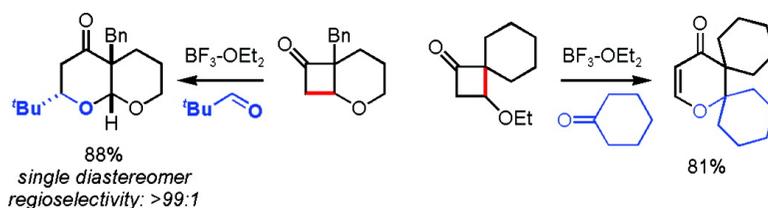
Communication

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Lewis Acid-Catalyzed Intermolecular [4 + 2] Cycloaddition of 3-Alkoxy-cyclobutanones to Aldehydes and Ketones

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Cyclobutanones are valuable compounds in organic synthesis: ring-expansion, ring-contraction, and ring-cleavage of the strained cyclobutane ring provide various synthetically useful reactions including C–C or C-heteroatom bond formations.¹ In the course of natural product synthesis, we tried to prepare eight-membered cyclic enone **3** by Lewis acid-catalyzed ring opening of bicyclic cyclobutanone **1a**, expecting formation of zwitterionic species **2** as an intermediate (Scheme 1, route a) since electrophilic activation of 2-substituted cyclobutanones has been reported to cleave the C2–C3 bond to form an intermediate having the more substituted enol or enolate moiety.² However, the desired compound **3** was not obtained at all, whereas tetracyclic compound **5** and acyclic compound **6** were obtained in 58% and 8% yields, respectively, when compound **1a** was treated with 1.3 equiv of trimethylsilyl triflate in dichloromethane at room temperature. These results suggested that ring-opening of cyclobutanone **1a** proceeded regioselectively to generate zwitterionic species **4** in route b.³ The results also suggested that compound **5** was formed by intermolecular cycloaddition of **4** to its starting ketone **1a**. Because the observed cycloaddition of cyclobutanones to carbonyl compounds has not been reported to date,⁴ we investigated this reaction further. We describe here a new cycloaddition reaction including regioselectivity in ring-opening of cyclobutanones and stereochemistry in the addition of carbonyl compounds and also one-pot synthesis of highly substituted dihydro- γ -pyrones from 3-ethoxycyclobutanones.

Tetrahydropyran-fused cyclobutanone **1b** bearing a benzyl group at the bridge-head position was activated by Lewis acid in the presence of benzaldehyde in order to investigate cross-cycloaddition reaction. After screening various Lewis acids, **1b** was found to react with benzaldehyde to give the desired cycloadduct **7** most efficiently by the employment of 1.2 equiv of boron trifluoride etherate at room temperature (Table 1, entries 1 and 2). The reaction was completed within 2.5 h in dichloromethane (method A), whereas the reaction proceeded more cleanly when diisopropyl ether was used as a solvent (method B). It was noted that **7** was obtained as a single diastereomer of four possible diastereomers by this cycloaddition.⁵

Pivalaldehyde, a sterically hindered aliphatic aldehyde, and ketones such as acetophenone and cyclohexanone also reacted with **1b** to afford the corresponding cycloadducts **8–10** (entries 3–7). The cycloaddition of acetophenone to **1b** in dichloromethane gave two diastereomers in the ratio of **9:9'** = 54:31, while the ratio changed to **9:9'** = 80:1 in the case of employing diisopropyl ether as a solvent. In all cases described above, aldehydes or ketones were inserted into the less substituted C2–C3 bond of the cyclobutanone ring of **1a,b**.

Next, monocyclic 3-ethoxycyclobutanone **11a** was employed with benzaldehyde. It was found that **11a** reacted at $-45\text{ }^{\circ}\text{C}$ to afford cycloadduct **12** in 93% yield (cis/trans = 76/24)⁶ along with regioisomer **13** (2%) and dihydro- γ -pyrone derivative **14** (<1%) under the conditions of using boron trifluoride etherate in dichloro-

Scheme 1. Activation of **1a** with Lewis Acid (LA = Trimethylsilyl Triflate) To Form Self-Cycloadduct **5** and Ring-Opened Compound **6**

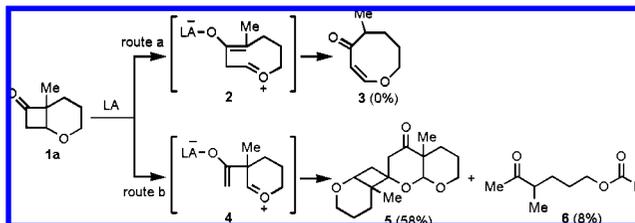
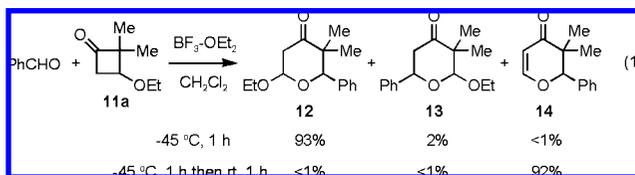


Table 1. Cycloaddition of Tetrahydropyran-Fused Cyclobutanone **1b** to Aldehydes and Ketones

entry	R ¹	R ²	method ^a	time (h)	product (% yield) ^b
1	Ph	H	A	2.5	7 (73)
2			B	22	7 (85)
3	<i>t</i> -Bu	H	A	3.5	8 (82)
4			B	23	8 (88)
5	Ph	Me	A	5	9 (54) + 9' (31)
6			B	48	9 (80) + 9' (1)
7	-(CH ₂) ₅ -		A	3.5	10 (84)

^a Method A: carbonyl compound (1.0 equiv), **1b** (1.5 equiv), and BF₃·OEt₂ (1.2 equiv) were employed in dichloromethane. Method B: carbonyl compound (1.0 equiv), **1b** (1.2 equiv), and BF₃·OEt₂ (1.2 equiv) were employed in diisopropyl ether. ^b Isolated yield.

methane (eq 1).⁷ When the reaction was performed at room temperature, cycloaddition of **11a** to benzaldehyde and subsequent elimination of ethanol proceeded in a one-pot manner to give **14** directly in 92% yield. In contrast to the above-mentioned regioselectivity for the cycloaddition of **1a,b**, benzaldehyde was inserted into the more substituted C2–C3 bond of **11a** with high regioselectivities.



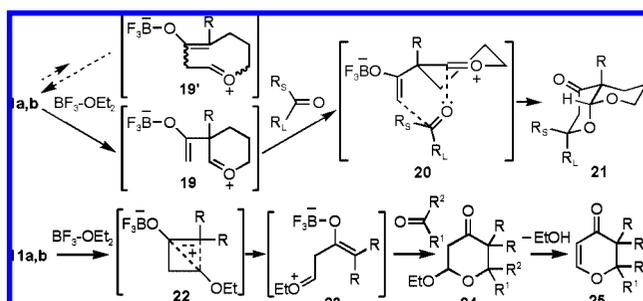
The scope of the present one-pot synthesis of dihydro- γ -pyrone derivatives was examined (Table 2). Acetophenone and cyclohexanone reacted with **11a** at $-45\text{ }^{\circ}\text{C}$, and one-pot elimination of ethanol took place readily at room temperature (entries 1 and 2). Spirocyclobutanone **11b** also reacted with benzaldehyde and cyclohexanone to give tri- and tetrasubstituted dihydro- γ -pyrones **17, 18** in 81% yields (entries 3 and 4).

Table 2. Cycloaddition of 3-Ethoxycyclobutanones **11a,b** to Aldehydes and Ketones^a

entry	aldehyde or ketone	cyclobutanone e	conditions	major product	yield (%) ^b
1			-45 °C, 3 h then rt, 1 h		83
2			-45 °C, 3 h then rt, 1 h		90
3			-45 °C, 2 h then rt, 2 h		81
4 ^c			-45 °C, 5 h then rt, 1 h		81

^a Carbonyl compound (1.0 equiv), **11a** (1.5 equiv) or **11b** (1.7 equiv), and boron trifluoride etherate (1.3 equiv) were employed in dichloromethane. ^b Isolated yield. ^c Compound **11b** (1.3 equiv) and boron trifluoride etherate (1.5 equiv) were employed.

Scheme 2. Proposed Mechanisms for Cycloaddition of 3-Alkoxy-cyclobutanones to Carbonyl Compounds Catalyzed with Boron Trifluoride Etherate



The regioselectivity of ring-opening of tetrahydropyran-fused cyclobutanones **1a,b** can be rationalized by considering that formation of an eight-membered ring bearing two double bonds within the main framework (**19'**, Scheme 2) is energetically unfavorable because of its ring strain. Therefore, the ring cleavage at the less substituted C2–C3 bond proceeds to form **19**. Lone pair electrons of oxygen of the carbonyl group which are anti to the larger substituent (R_L) interact with oxocarbenium ion along a pseudoaxial trajectory controlled by stereoelectronic effects⁸ (**20**), and the enolate part of the zwitterionic intermediate attacks the activated carbonyl group to afford cycloadduct **21**. The selectivity for the coordinating lone pair electrons depends on substrates and solvents employed. The solvent effect of diisopropyl ether can be explained by its complexation not only with boron trifluoride to suppress undesired activation of the cycloadduct but also with oxocarbenium ion to affect π -selectivity toward carbonyl compounds. On the other hand, in the case of 3-ethoxycyclobutanones **11a,b**, activation with boron trifluoride gives ring-opened zwitterionic species **23** by cleavage of the more substituted C2–C3 bond via bicyclobutonium ion **22**,⁹ and cycloadduct **24** is formed by the reaction of **23** with carbonyl compound. Elimination of ethanol from **24** to **25** then takes place by the catalysis of boron trifluoride etherate.

In summary, we have developed boron trifluoride etherate-catalyzed intermolecular cycloaddition of 3-alkoxycyclobutanones and aldehydes or ketones at the C2–C3 bond of cyclobutanone ring.¹⁰ Regioselectivity for insertion of these carbonyl compounds at the more or less substituted C2–C3 bond was different between 3-ethoxycyclobutanones **11a,b** and tetrahydropyran-fused bicyclobutanones **1a,b**. The selectivity for the latter case is rationalized by anomeric effect. The present reaction is especially useful for preparing various types of dihydro- γ -pyrones **14–18** having tri- or tetrasubstituents, which might be difficult to be prepared by hetero-Diels–Alder reaction between ketones and siloxydienes having a terminal gem-dialkyl moiety.¹¹ Thus, 3-alkoxycyclobutanones can be regarded as a highly versatile C4 component for [4 + 2] cycloaddition reaction, and there are many possibilities for their application to other valuable synthetic reactions.

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Supporting Information Available: Experimental procedures and characterization data of new compounds, crystallographic data of **8**, and ¹H and ¹³C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (6) A catalytic amount (30 mol%) of boron trifluoride etherate catalyzed this cycloaddition to afford **12** in 92% yield (–45 °C, 9 h).
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