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Intramolecular formal [4 + 2] cycloaddition of 3-ethoxycyclobutanones and alkenes†‡

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Intramolecular formal [4 + 2] cycloaddition between 3ethoxycyclobutanones and a carbon-carbon double bond to the corresponding bicyclo[4.n.0]alkan-2-one derivatives proceeded 10 effectively by using ethylaluminum dichloride.

Intramolecular cycloaddition is a powerful tool for efficient and stereoselective construction of complex molecules. 1 Especially, [4 + 2] cycloaddition reactions such as intramolecular Diels-Alder (IMDA) reaction have been 15 successfully employed for the synthesis of biologically active compounds and natural products under the condition of a well-designed combination between diene and dienophile.² The utility of intramolecular [4 + 2] cycloaddition is expected to be enhanced by discovering a more potent and readily 20 available C4 unit.

We have recently reported that intermolecular [4 + 2]cycloaddition between 3-alkoxycyclobutanone and aldehyde or ketone proceeds to afford tetrahydro- or dihydro-γ-pyrone derivatives by catalysis with boron trifluoride etherate.³ In 25 the course of our study on this cycloaddition, we examined a reaction between 2,2-diallyl-3-ethoxycyclobutanone (1a) and benzaldehyde (Scheme 1). It was found that catalysis with boron trifluoride etherate gave expected adducts 2 and 3 in 67% and 13% yields, respectively, whereas the employment 30 of ethylaluminum dichloride gave intramolecular cycloadduct 4a as the major product (66% yield). The finding of unprecedented intramolecular cycloaddition of an allyl group into the C2-C3 bond of a cyclobutanone ring⁴⁻⁶ as well as the observed interesting chemoselectivity prompted us 35 investigate this intramolecular cycloaddition further. report herein formal [4 + 2] cycloaddition between a cyclobutanone skeleton and carbon-carbon double bond of the alkenyl group at the 2-position of 3-ethoxycyclobutanones.

Scheme 1 Lewis acid (LA)-controlled chemoselectivity: intermolecular formal [4 + 2] cycloaddition between 1a and benzaldehyde to 2 and 3 and intramolecular formal [4 + 2] cycloaddition of 1a to 4a

45 **Table 1** Intramolecular formal [4 + 2] cycloaddition of 2-allyl-3ethoxycyclobutanones 1 to 4^a

entry	1 (R)	cis trans ^b	product (%yield ^c)	cis/trans ^b
1	1a (allyl)	_	4a (92)	84:16
2^d	1a (allyl)	_	4a (89), 5 (3)	27:73
3	1b (H)	30:70	4b (0), 6 (41)	_
4	1c (Me)	56:44	4c (72)	89:11
5	1d (Bn)	34:66	4d (81)	85:15
6	1e (<i>i</i> -Pr)	28:72	4e (88)	82:18
7	1f (Ph)	100:0	4f (0), 7 (70)	_
8	1f (Ph)	0:100	4f (0), 7 (74)	_

^a EtAlCl₂ (1.2 equiv) was employed. ^b The ratios were determined by ¹H NMR analysis. For determination of relative stereochemistry, see 50 supporting information. ^c Isolated yield unless otherwise noted. Conditions: Tin(IV) chloride (1.2 equiv), allyltriisopropylsilane (1.5 equiv), -45 to 0 °C, 80 min. Yield of 4a was determined by ¹H NMR.

Among Lewis acids we tested,7 ethylaluminum dichloride most efficiently promoted intramolecular cycloaddition of 1a to give cis- and trans-4a in 92% combined yield (cis/trans = 84:16, Table 1, entry 1).8 Neither regioisomeric cycloaddition 60 nor elimination of ethanol from 4a were observed. It is notable that the activation of 1a with tin(IV) chloride in the presence of allyltriisopropylsilane inverted the ratio of cisand trans-4a (cis/trans = 27:73), and intermolecular cycloadduct 5⁹ was obtained in 3% yield (entry 2). 65 Cycloaddition 2-alkyl-2-allyl-3of several ethoxycyclobutanones 1b-e was next performed in order to investigate stereospecificity as well as generality of the intramolecular reaction (entries 3-6). Treatment of a mixture of diastereomers (cis/trans = 30:70) of 2-allyl-3-70 ethoxycyclobutanone 1b with ethylaluminum dichloride did not give a cycloadduct 4b, but a self-cycloadduct 6 was obtained in 41% yield (entry 3).³ 2-Allylcyclobutanones **1c-e** gave the desired products 4c-e in 72-88% yields, and the

Table 2 EtAlCl₂-catalyzed intramolecular formal [4 + 2] cycloaddition of various 2-alkenyl-3-ethoxycyclobutanones 8^a

entry	cyclobutanone	major product (% yield ^b)	d.r.
1 2 3	8a (n = 1) 8b (n = 2) 8c (n = 3)	9a (18) 9b (86) 9c (0)	>99:1 >99:1 —
4	O Bn OEt 8df	Bn 9d (67)	two isomers
5	OEt 8e ^d	9e (89)	two isomers 95:5
6	O OEt 2	9f (87)	>99:1

^a Conditions: see Table 1. ^b Combined yield of diastereomers. ^c A mixture of diastereomers (53:47). ^d A mixture of four diastereomers was 5 treated at -45 to 0 °C.

reactions were found to proceed nonstereospecifically since cis/trans ratios of 1c-e did not correspond to the efficiency of the cycloaddition nor cis/trans ratios of 4c-e. 10 cyclobutanones bearing a bulky alkyl group tended to give the cycloadducts more efficiently (entries 4-6). On the other hand, both isolated diastereomers of 2-allyl-3-ethoxy-2phenylcyclobutanones 1f gave no [4 + 2] cycloadduct 4f but afforded 1-allyl-2-naphthol 7 (entries 7 and 8). These results 15 suggest that cyclization of the phenyl group 10 followed by aromatization to the 2-naphthol derivative 7 took place selectively rather than insertion of the allyl group.

Preparation of bicyclic or tricyclic compounds other than bicyclo[4.1.0]heptan-2-ones 4 was next investigated (Table 2). 20 Cyclobutanones **8a,b** having a 3-butenyl or 4-pentenyl group at the 2-position gave the corresponding cycloadducts 9a and 9b in 18% and 86% yields, respectively, as a single diastereomer (entries 1 and 2). Cyclobutanone 8c bearing a 5hexenyl group did not give a cycloadduct 9c (entry 3), 25 whereas the reaction of 2-(o-allylbenzyl)cyclobutanone 8d gave two products, 9d and its 4-epimer 9d' (9d : 9d' = 65:35) in 67% combined yield (entry 4). Restricted conformation of the o-allylbenzyl group might help the successful cycloaddition of 8d. Intramolecular cycloaddition of 30 spirocyclobutanones 8e,f proceeded smoothly to afford the corresponding tricyclic compounds 9e,f in good yields (entries 5 and 6), and stereochemical convergence was observed. That is, treatment of a mixture of four diastereomers of 8f with ethylaluminum dichloride gave **9f** as a single diastereomer. 11 A plausible mechanism for the present intramolecular cycloaddition is shown in Scheme 2. A zwitterionic intermediate 11 is regioselectively formed by EtAlCl₂-

catalyzed ring cleavage of cyclobutanone 10, and [4 + 2]cycloaddition of a terminal alkenyl group proceeds to give an

40 adduct 12.

Scheme 2. Plausible mechanism for EtAlCl₂-catalyzed [4 + 2] cycloaddition of 2-alkenyl-3-ethoxycyclobutanones 10 to 4-45 ethoxybicyclo[4.n.0]alkan-2-ones 12.

In summary, we have developed ethylaluminum dichloridepromoted intramolecular insertion of a carbon-carbon double bond into 3-ethoxycyclobutanones. This intramolecular [4 + cycloaddition shows high regioselectivity stereoselectivity. Studies on the nature of zwitterionic intermediates 3generated by activation ethoxycyclobutanones and the reaction mechanism for the present intramolecular cycloaddition is currently underway.

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† Electronic Supplementary Information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/b000000x/

‡CCDC 735720 for 9d, CCDC735721 for 9d', and CCDC 735722 for a derivative of 9f contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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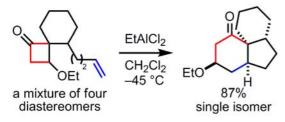
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Graphical contents entry



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Intramolecular [4+2] cycloaddition of 3-ethoxycyclobutanones and alkenes proceeded regioselectively and stereoselectively by using ethyl aluminumdichloride as a Lewis acid.