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Novel [4+2]-Type Reaction of 2-(Dimethylamino)cyclobutanecarboxylic Esters with Carbonyl Compounds

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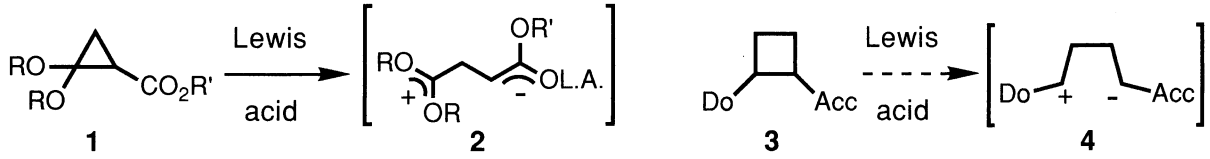
In the presence of titanium(IV) chloride, 2-(dimethylamino)cyclobutanecarboxylic esters, equivalents of 1,4-zwitterions, reacted with carbonyl compounds to give δ-lactols or dihydropyrans.

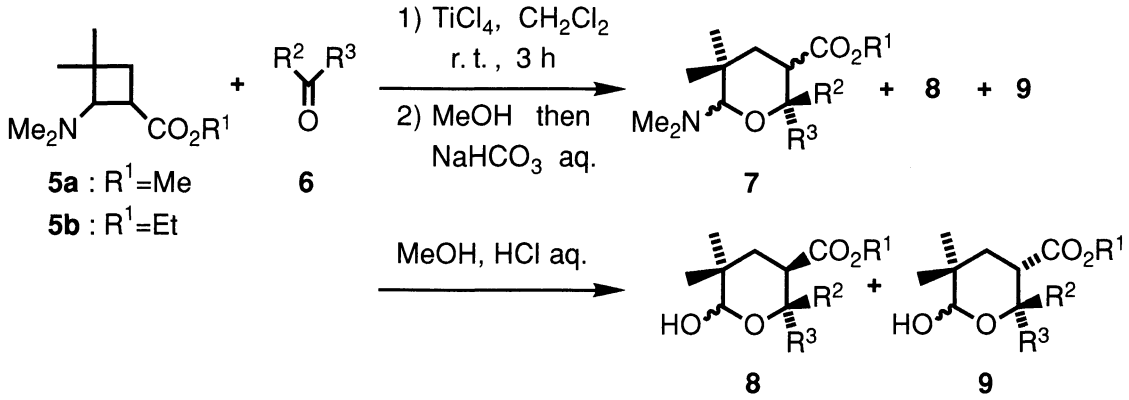
Small ring compounds have been widely used in organic syntheses.[1,2] Among these compounds, vicinally donor-acceptor-substituted cyclopropanes are versatile synthetic building blocks.[1e] These cyclopropane compounds are susceptible to heterolytic ring-cleavage because of substituents' effects and are recognized as equivalents of 1,3-zwitterionic species. We recently reported the Lewis acid-promoted reactions of 2,2-dialkoxycyclopropanecarboxylic esters **1** with aldehydes,[3a] ketones,[3b] *N*-tosylaldimines,[3c] esters,[3d] and ketene silyl acetals.[3e] In these reactions, upon the action of a Lewis acid a ring-opening reaction of **1** easily proceeded and 1,3-zwitterionic intermediates like **2** were probably formed. On the basis of these results, we expected that cyclobutane compounds with donor- and acceptor-substituents at the vicinal positions like **3** would also cause a Lewis acid-mediated ring-opening reaction to form 1,4-zwitterionic intermediates like **4** and that subsequent C-C bond forming reactions would take place with various electrophiles and nucleophiles. To our knowledge, vicinally donor- and acceptor-substituted cyclobutanes have been rarely used in the ring-opening C-C bond forming reactions except for rearrangement reactions.[2a, 4] Here we report a synthesis of δ-lactols and dihydropyrans by a novel ring-opening addition reaction of 2-(dimethylamino)cyclobutanecarboxylic esters **5** and **12** with carbonyl compounds.[5]



1 **2** **3** **4**

2-(Dimethylamino)cyclobutanecarboxylic esters **5** and **12** are readily available by a thermal [2+2] addition reaction of enamines with acrylic esters.[6] At first, the reaction of methyl 2-(dimethylamino)-3,3-dimethylcyclobutanecarboxylate **5a** with 3-phenylpropanal was examined. When the reaction was performed in the presence of titanium(IV) chloride in dichloromethane at -78 to 0 °C and was quenched with anhydrous methanol followed by a saturated $NaHCO_3$ solution, δ-lactols **8a** and **9a** (R^1=Me, R^2=$PhCH_2CH_2$, R^3=H) were obtained in 31% yield (the ratio of **8a** : **9a** = 1 : 2).[7] In order to improve the yield and diastereoselectivity of this reaction, various reaction conditions, such as reaction temperature, order of addition of the substrates, molar ratio of the substrates, Lewis acid, solvent, ester alkyl group, and amino alkyl group, were optimized.

Among these conditions, the order of addition of the substrates dramatically influenced the yield of δ-lactols. When cyclobutane **5a** (1.5 equiv.) was added to a mixture of 3-phenylpropanal (1 equiv.) and titanium(IV) chloride (1.5 equiv.) in dichloromethane at room temperature, **8a** and **9a** were obtained in 72% yield. Lewis acids other than titanium(IV) chloride resulted in rather lower yields (titanium(IV) bromide; 58%, tin(IV) chloride; 34%) or did not promote the reaction at all (boron trifluoride etherate, trimethylsilyl trifluoromethanesulfonate, etc.). In contrast to the yield, the diastereoselectivity of this reaction was not improved upon changing these reaction conditions, and the ratio of **8a** : **9a** varied from 1 : 3 to 2 : 1. The optimized reaction conditions are shown in Scheme 1 and in the following typical procedure. In some cases, the crude products contained unhydrolyzed dimethylamino-derivatives **7**, and acidic treatment was required in order to convert **7** into **8** and **9**. The results of the reaction of **5** with several aldehydes and 4-heptanone under the optimized conditions are shown in Table 1. In all cases, δ-lactols were obtained in moderate to good yields.



Scheme 1.

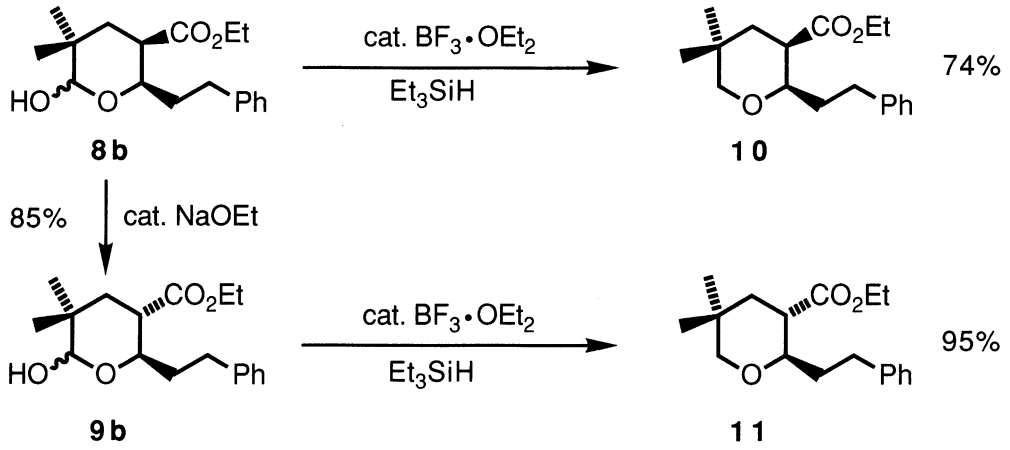
Table 1. The Reaction of Cyclobutanes **5** with Aldehydes and 4-Heptanone

Entry	5	R^2	R^3	Yield of **8** + **9** / %	**8** : **9**
1	**5a**	$PhCH_2CH_2$	H	72	1 : 2
2	**5b**	$CH_3(CH_2)_6$	H	62	1 : 4
3		$(CH_3)_2CH$	H	55	1 : 2
4		Ph	H	47	1 : 1
5	**5a**	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	65	-

A typical procedure is as follows: To a stirred solution of octanal (52.6 mg, 0.410 mmol) in dry dichloromethane (1.6 ml) was added drop by drop a solution of titanium(IV) chloride (0.62 mmol) in dry dichloromethane (0.6 ml) at room temperature, and the mixture was stirred for 10 min. A solution of cyclobutane **5b** (123 mg, 0.617 mmol) in dry dichloromethane (1.5 ml) was slowly added drop by drop (6 min) to the resulting yellow solution at room temperature. The reaction mixture was stirred for 3 h at room temperature and was quenched by adding anhydrous methanol (0.6 ml). To this mixture were successively added a saturated $NaHCO_3$ solution (3 ml), water (10 ml), and ethyl acetate (30 ml). The mixture was filtered

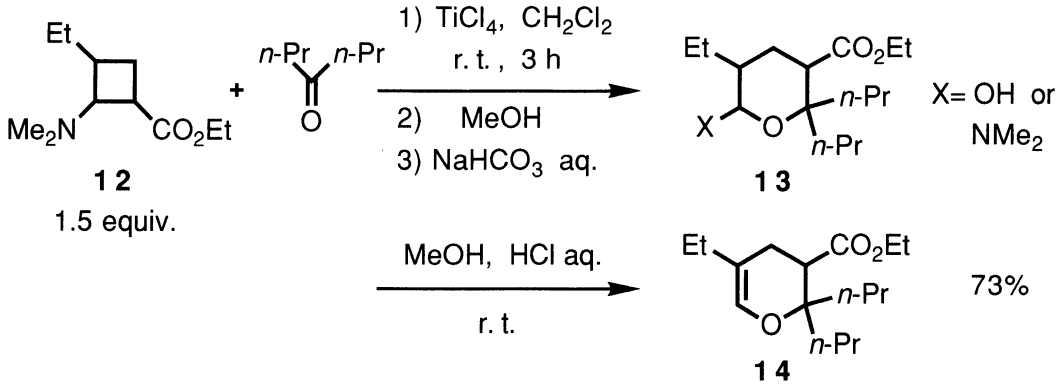
through Celite, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 10 ml), and the combined organic layers were dried over anhydrous sodium sulfate. Filtration and evaporation gave a crude product, which consisted of **7**, **8**, and **9** (R^1=Et, R^2=$CH_3(CH_2)_6$, R^3=H). The crude product was dissolved in a mixture of methanol (4 ml) and water (1 ml), and hydrochloric acid (1 mol dm^{-3}, 1 ml) was added to this solution. Stirring was continued for 6 h, and then the solvent was removed in vacuo. The residue was purified by column chromatography (eluent: hexane/EtOAc=20:1) to give the corresponding δ-lactols **8** (R^1=Et, R^2=$CH_3(CH_2)_6$, R^3=H, 61.2 mg, 50% yield based on octanal) and **9** (R^1=Et, R^2=$CH_3(CH_2)_6$, R^3=H, 15.1 mg, 12% yield).

In this reaction, no noticeable diastereoselectivity was observed. But, as shown in Scheme 2, *cis*-lactol **8b** was easily converted into *trans*-one **9b** in a good yield. Furthermore, by treatment with triethylsilane in the presence of a catalytic amount of boron trifluoride etherate,[8] lactols **8b** and **9b** were easily transformed into tetrahydropyrans **10** and **11**, respectively [7, 9]



Scheme 2.

We also performed the reaction of ethyl 2-(dimethylamino)-3-ethylcyclobutanecarboxylate **12**, which had a hydrogen at 3-position, with 4-heptanone. The crude product was the same as that of the reaction of **5**, a mixture of δ-lactols and their dimethylamino-derivatives (**13**, X=OH or NMe_2). But, in this case, the crude product was converted into dihydropyran **14** by acidic treatment (73% yield, based on 4-heptanone).



Scheme 3.

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4) An example of ring-opening C-C bond forming reaction; L. Weintraub, A. Wilson, D. L. Goldhamer, and D. P. Hollis, *J. Am. Chem. Soc.*, **86**, 4880 (1964).

5) The reaction of methyl 2,2-diethoxycyclobutanecarboxylate, a cyclobutane analogue of **1**, with 3-phenylpropanal was also examined. In this case, the corresponding ring-opening addition product was obtained only in 32% yield under optimized reaction conditions.

6) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29**, 801 (1964).

7) The reaction of **5** with aldehydes gave a mixture of four diastereomeric δ-lactols. In all cases, the mixture of δ-lactols was separated in two fractions, both of which contained two diastereomers, by preparative TLC or column chromatography. As mentioned in the text, δ-lactols, obtained from **5b** and 3-phenylpropanal, were converted into tetrahydropyrans. More polar and less polar fractions **8b** and **9b** gave **10** and **11**, respectively. From this result, we assigned more polar fraction was a mixture of 2,3-*cis*-lactols and less polar fraction was a mixture of 2,3-*trans*-lactols in all cases. The ^{1}H-NMR spectra of these fractions were consistent with this assignment.

8) G. A. Kraus, K. A. Frazier, B. D. Roth, M. J. Taschner, and K. Neuenschwander, *J. Org. Chem.*, **46**, 2417 (1981).

9) The structure of **10** and **11** was unambiguously assigned by ^{1}H-NMR analysis. The vicinal coupling constants between 2-H and 3-H were 5 Hz for **10** and 10 Hz for **11**, respectively.

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