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Titanium(IV) Chloride-Mediated Carbon−Carbon Bond-Forming Reaction between 3,3-Dialkylcyclobutanones and Aldehydes

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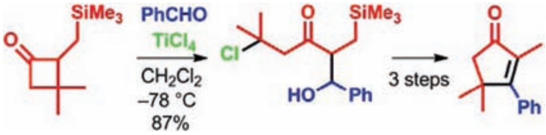
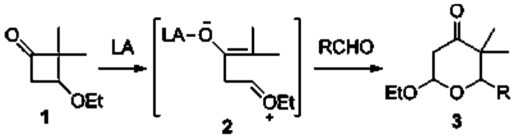
ABSTRACT

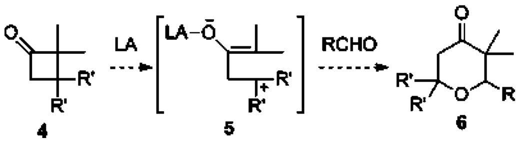


Treatment of 3,3-dialkylcyclobutanones with titanium(IV) chloride in the presence of aldehyde gave β'-chloro-β-hydroxy ketones in high yields. It was speculated that ring cleavage of the cyclobutanone ring with titanium(IV) chloride gave trichlorotitanium enolate having a tertiary alkyl chloride moiety and then aldol reaction of the titanium enolate proceeded. A trialkylsilylmethyl group at the 2-position of cyclobutanone facilitated the ring cleavage. Synthesis of substituted cyclopentenone from an obtained product is also described.

Cyclobutanones have often been employed as versatile building blocks in organic synthesis.[1] Synthetic utility of 3-alkoxycyclobutanones for preparing six-membered cyclic compounds was recently reported by our group. Thus, a zwitterionic intermediate **2**, generated by activation of 3-alkoxycyclobutanone **1** with Lewis acid (LA), reacts with aldehydes,[2] ketones,[2] imines,[3] allylsilanes,[4] and silyl enol ethers[5] to afford the corresponding six-membered cyclic compounds (eq 1).[6,7] The presence of the alkoxy group at the 3-position of the cyclobutanone ring of **1** makes ring cleavage easy. It was then thought that dialkyl groups at the 3-position of cyclobutanone **4** also promoted formation of zwitterionic intermediate **5** since the tertiary carbocationic part of **5** was stabilized by the dialkyl groups.[8] The zwitterionic species **5** was considered to react with aldehyde to give tetrahydro-γ-pyrone **6** as in the case of intermediate **2** (eq 2). However, reaction of 3,3-dialkylcyclobutanone **4** with aldehyde by activation of titanium(IV) chloride did not give the expected product **6** but afforded β-hydroxy ketone (aldol product) bearing a chloride group. We report here this unique aldol reaction from cyclobutanone **4** and also report synthesis of a substituted cyclopentenone from the aldol product.



(1)



(2)

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(1) (a) Conia, J. M.; Robson, M. J. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 473. (b) Belluš, D.; Ernst, B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797. (c) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (d) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.

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(4) Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Org. Lett.* **2009**, *11*, 3822.

(5) Matsuo, J.; Negishi, S.; Ishibashi, H. *Tetrahedron Lett.* **2009**, *50*, 5831.

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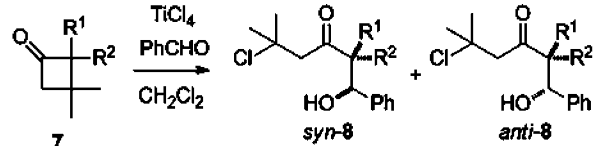
10.1021/ol101653b

Reaction of 2,2,3,3-tetramethylcyclobutanone **7a** and benzaldehyde was investigated first by employing various Lewis acids. Neither boron trifluoride diethyl etherate nor tin(IV) chloride promoted ring cleavage of cyclobutanone **7a**, whereas activation with titanium(IV) chloride smoothly cleaved the cyclobutanone ring of **7a** in the presence of benzaldehyde to afford an aldol product **8** bearing a tertiary alkyl chloride group in 80% yield (Table 1, entry 1). Tetrahydro-γ-pyrone **6** ($R' = \mathrm{Me}$, $R = \mathrm{Ph}$) was not obtained at all. A new carbon−carbon bond was formed regioselectively at the more substituted α-position of the carbonyl group of **7a**. Reaction of 3,3-dimethyl-2-ethylcyclobutanone **7b** with benzaldehyde also proceeded smoothly to afford aldol adduct **8b** in 80% yield as a mixture of diastereomers (syn/anti = 76:24) (entry 2). This result suggested that 3,3-dialkylcyclobutanone bearing a monoalkyl group at the 2-position was also an effective substrate for the present reaction. 3,3-Dialkyl groups on the cyclobutanone ring were found to be necessary for this reaction since ring-opening of 2,3-dipropylcyclobutanone with titanium(IV) chloride did not take place. Interestingly, reaction of cyclobutanone **7c**[9] bearing a 2-(trimethylsilyl)methyl group took place at a lower temperature (−78 °C) than that of 2,2-dialkyl and 2-alkyl cyclobutanones **7a** and **7b**, and the reaction afforded the corresponding product **8c** in 87% yield (syn/anti = 86:14) (entry 4). Reaction of **7b** at −78 °C gave only a trace amount of product **8b** (entry 3).

Table 1. Reaction between 3,3-Dimethylcyclobutanones **7a**−**e** and Benzaldehyde by Activation with TiCl$_4$[a]



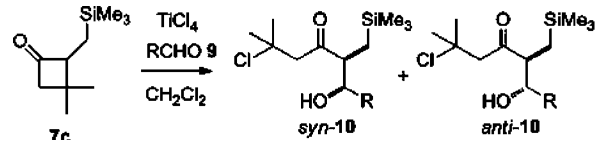
entry	**7**	R^1	R^2	conditions	**8**^{b}	dr^c
1	**7a**	Me	Me	−78 to 0 °C, 1 h	80	
2	**7b**	Et	H	−78 to −18 °C, 1.5 h	80	76:24
3	**7b**	Et	H	−78 °C, 0.5 h	trace	
4	**7c**	TMSCH$_2$	H	−78 °C, 0.5 h	87	86:14
5	**7d**	TBSCH$_2$	H	−78 °C, 0.5 h	85	71:29
6	**7e**	TIPSCH$_2$	H	−78 °C, 0.5 h	88	83:17

[a] Cyclobutanone **7** (1.5 equiv), TiCl$_4$ (1.5 equiv), and PhCHO (1.0 equiv) were employed. [b] Isolated yield (%). [c] Syn/anti ratio determined by ^{1}H NMR of a mixture of diasetereomers.

Titanium(IV) chloride-mediated ring-opening of **7a** and **7b** required raised reaction temperatures from −78 °C to −18−0 °C, while that of **7c** took place immediately at −78 °C. These results suggested that the silylmethyl group at the 2-position promoted cleavage of the cyclobutanone ring with titanium(IV) chloride. The *tert*-butyldimethylsilyl group and triisopropylsilyl group also accelerated the ring cleavage, and aldol products **8d** and **8e** were obtained in 85% and 88% yields, respectively (entries 5 and 6).[10,11]

Reaction of cyclobutanone **7c** with various aldehydes **9** was investigated (Table 2). 4-Chloro- and 4-bromobenzaldehyde **9a** and **9b** reacted smoothly at −78 °C, and the corresponding aldol products **10a** and **10b** were obtained in high yields with high *syn*-selectivities (entries 1 and 2). 1-Naphthyl aldehyde **9c** reacted at −45 °C, and aldol product **10c** was obtained in 72% yield with moderate *syn*-selectivity (syn/anti = 89:11, entry 3). Aldol reaction with aliphatic aldehydes such as 3-phenylpropanal **9d** and 2-methylpropanal **9e** also proceeded efficiently to afford the corresponding aldol products **10d** and **10e** in 87% and 76% yields, respectively (entries 4 and 5). However, reaction with ketones such as acetophenone did not proceed.

Table 2. Aldol Reaction between Cyclobutanone **7c** with Various Aldehydes **9a**−**f**[a]



entry	**9** (R)	*t* (°C)	time (min)	**10**^{b}	dr^c
1	**9a** (4-ClC$_6$H$_4$)	−78	40	84	95:5
2	**9b** (4-BrC$_6$H$_4$)	−78	45	95	97:3
3	**9c** (1-naphthyl)	−78 to −45	60	72	89:11
4	**9d** (PhCH$_2$CH$_2$)	−78 to −45	90	87	85:15
5	**9e** (*i*-Pr)	−78 to −45	90	76	85:15

[a] For conditions, see Table 1. [b] Isolated yield (%). [c] Syn/anti ratio determined by ^{1}H NMR.

Some 3,3-dialkyl-2-[(trimethylsilyl)methyl]cyclobutanones **11a**−**c**[9] were employed in this reaction with benzaldehyde. 3,3-Diethylcyclobutanone **11a** and spirocyclobutanones **11b** and **11c** also reacted with benzaldehyde to afford the corresponding aldol product bearing a tertiary alkyl chloride group in high yields with moderate to good *syn*-selectivities (Table 3).

The obtained β'-chloro-β-hydroxy ketones were precursors for multisubstituted cyclopentenones. Thus, a mixture of diastereomers (syn/anti = 86:14) of adduct **8c** was mesylated by using mesyl chloride and triethylamine, and treatment of the resulting mesylate with DBU at 45 °C gave dienone **13** in 79% yield in two steps. Nazarov cyclization[12] of **13** with

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(7) Formation of zwitterionic intermediates from cyclobutane derivatives: (a) Allart, E. A.; Christie, S. D. R.; Pritchard, G. J.; Elsegood, M. R. J. *Chem. Commun.* **2009**, 7339. (b) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 14202.

(8) (a) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Tetrahedron Lett.* **1983**, *24*, 4817. (b) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 439.

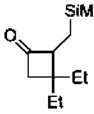
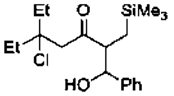
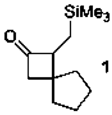
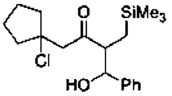
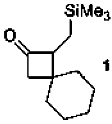
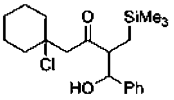
(9) Compounds **7c**−**e** and **11a**−**c** were prepared by [2+2] cycloaddition by using carboxylic acid chloride and (3,3-dialky-2-propenyl)trialkylsilane in the presence of triethylamine. For details, see the Supporting Information.

(10) Stereochemistry of *anti*-**8d** was determined by X-ray crystallography. Stereochemistry of other products **8b**−**e** and **12a**−**c** was deduced by ^{1}H NMR spectra of *syn*- and *anti*-**8d**. For details, see the Supporting Information.

(11) Ring expansion of silylmethylcyclobutanes: Knölker, H.-J.; Baum, G.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1612.

(12) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1.

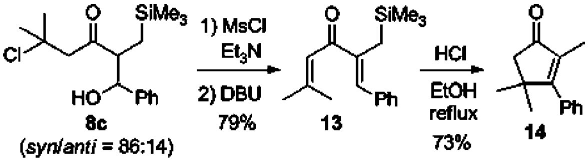
Table 3. Aldol Reaction between Various 3,3-Dialkyl-2-[(trimethylsilyl)methyl]cyclobutanones **11a**−**c** and Benzaldehyde[a]

entry	11	product 12	yield (%)[b]	dr[c]
1	 **11a**	 **12a**	91	94:6
2	 **11b**	 **12b**	84	91:9
3	 **11c**	 **12c**	88	79:21

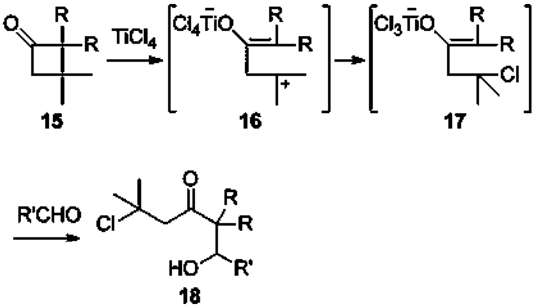
[a] For conditions, see Table 1. Reactions were carried out at -78 to -45 °C for 1−1.5 h. [b] Isolated yield (%). [c] Syn/anti ratio determined by ^{1}H NMR.

hydrochloric acid in refluxing ethanol gave cyclopentenone **14** in 73% yield (Scheme 1). The trimethylsilyl group was removed during this cyclization.

Scheme 1. Nazarov Cyclization to Tetrasubstituted Cyclopentenone **14**



Scheme 2. Proposed Mechanism



Our proposed mechanism for the present reaction between cyclobutanone **15** and aldehyde is shown in Scheme 2. Activation of 3,3-dialkylcyclobutanone **15** with titanium(IV) chloride gives zwitterionic intermediate **16** by cleaving the carbon−carbon bond between the more substituted C2 and C3. Chloride ion attacks the tertiary carbocationic center of **16** to form trichlorotitanium enolate **17**, which reacts with aldehydes to afford product **18**. Observed moderate to good *syn*-selectivity of product **18** is consistent with aldol reaction of trichlorotitanium enolate.[13] It was assumed that the trialkylsilylmethyl group at the 2-position of the cyclobutanone ring would stabilize bicyclobutonium ion[14] during the formation of zwitterionic intermediate **16**.

In conclusion, β'-chloro-β-hydroxy ketones were synthesized by the titanium(IV) chloride-mediated reaction between 3,3-dialkylcyclobutanones and aldehydes. Aldol reaction of in situ formed trichlorotitanium enolate, which was formed from 3,3-dialkylcyclobutanones and titanium(IV) chloride, was proposed. Trialkylsilylmethyl substituent at the 2-position of cyclobutanone accelerated this reaction, and products were useful precursors for substituted cyclopentenones.

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Supporting Information Available: Detailed experimental procedures and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343.

(14) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69.