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Ring Cleavage and Successive Aldol Reaction of 3-[(Trialkylsilyl)methyl]cyclobutanones

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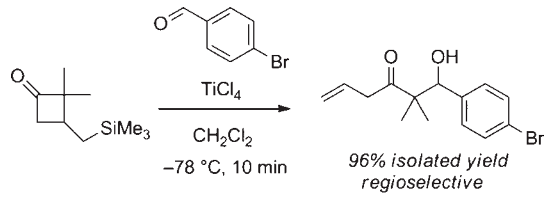
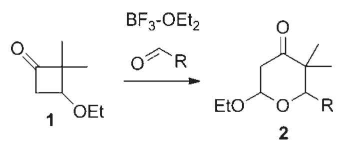
ABSTRACT



3-[(Trialkylsilyl)methyl]cyclobutanones reacted with aldehydes by activation with titanium(IV) chloride to give acyclic β,γ-unsaturated β'-hydroxyketones.

Cyclobutanones are interesting building blocks for organic synthesis,[1] and we have reported on the synthetic utility of 3-ethoxycyclobutanones for formal [4 + 2] cycloaddition reactions with aldehydes,[2] ketones,[2] *N*-Ts imines,[3] allylsilanes,[4] and silyl enol ethers[5] to give the corresponding six-membered ring compounds.[6−8] For example, 3-ethoxycyclobutanone **1** reacted with benzaldehyde to give tetrahydropyrone **2** under the catalysis of Lewis acid (eq 1).[2] In the course of these studies, it was also found that substitution with a (trialkylsilyl)methyl group at the 2-position of cyclobutanone facilitated ring cleavage of the cyclobutanone ring.[9] We then tried to investigate the effect of the (trialkylsilyl)methyl group at the 3-position of the cyclobutanone and found that a reaction between 3-[(trimethylsilyl)methyl]cyclobutanone **3** and an aldehyde gave an acyclic aldol product **4** bearing a β,γ-unsaturated group, which would be difficult to prepare by the regioselective aldol reaction of β,γ-unsaturated ketone **5** (Scheme 1).[10] We would like to describe here this unique ring cleavage and aldol reaction of 3-[(trialkylsilyl)methyl]cyclobutanones.



(1)

The 3-[(trialkylsilyl)methyl]cyclobutanones **7a**−**h** employed in this study were prepared by a [2 + 2] cycloaddition reaction between allylsilane and a keteneiminium salt

(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.

(2) Matsuo, J.; Sasaki, S.; Tanaka, H.; Ishibashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 11600.

(3) Matsuo, J.; Okado, R.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 3266.

(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.

(6) Matsuo, J.; Sasaki, S.; Hoshikawa, T.; Ishibashi, H. *Chem. Commun.* **2010**, *46*, 934.

(7) Reaction of donor−acceptor cyclobutanes: (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. (c) Moustafa, M. M. A.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4732. (d) Moustafa, M. M. A.; Stevens, A. C.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4736. (e) Stevens, A. C.; Palmer, C.; Pagenkopf, B. L. *Org. Lett.* **2011**, *13*, 1528.

(8) Related reaction: Shan, G.; Liu, P. F.; Rao, Y. *Org. Lett.* **2011**, *13*, 1746.

(9) Matsuo, J.; Kawano, M.; Okuno, R.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 3960.

(10) (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (b) Mahrwald, R. *Modern Aldol Reaction*; Wiley-VCH: Weinheim, 2004. (c) Trost, B. M.; Fleming, I.; Semmelhack, M. F. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.4−1.9. (d) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

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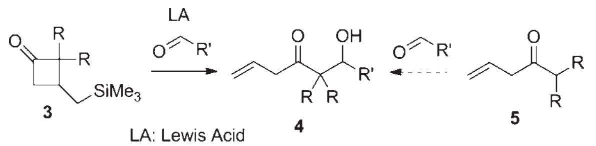
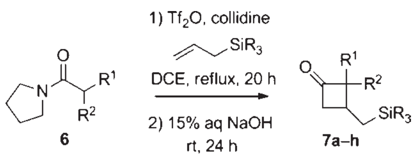
Scheme 1. Regioselective Formation of Aldol Adduct **4** from Cyclobutanone **3**



which was generated from the corresponding pyrrolidine amide **6** (Table 1).[11] 2,2-Dialkyl- and 2-monoalkyl-substituted 3-[(trimethylsilyl)methyl]cyclobutanones **7a**–**f** were prepared in good yields. Cyclobutanones having *tert*-butyldimethylsilyl and triisopropylsilyl groups **7g**,**h** were prepared by the same method. Attempted preparation of cyclobutanone **7i** which had no substituents at its 2-position gave an inseparable mixture of **7i** and byproducts by this procedure. Therefore, **7i** was prepared by another route: [2 + 2] cycloaddition between dichloroketene and allyltrimethylsilane followed by dechlorination afforded pure **7i** in good yield (Scheme 2).

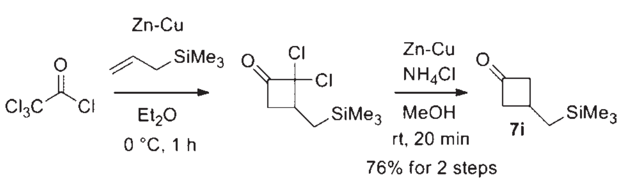
Table 1. Preparation of 3-[(Trialkylsilyl)mthyl]cyclobutanones **7a**–**h**



entry	7	R^1	R^2	SiR_3	yield (%)
1	**7a**	Me	Me	$SiMe_3$	77
2	**7b**	Et	Et	$SiMe_3$	75
3	**7c**	$-(CH_2)_4-$		$SiMe_3$	85
4	**7d**	$-(CH_2)_5-$		$SiMe_3$	88
5	**7e**	Me	H	$SiMe_3$	77[a]
6	**7f**	CH_2Ph	H	$SiMe_3$	64[a]
7	**7g**	Me	Me	$SiMe_2t$-Bu	85
8	**7h**	Me	Me	Si(*i*-Pr)$_3$	75

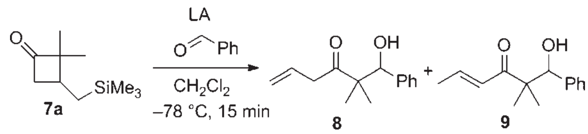
[a] Mixture of diastereomers: **7e** (84:16), **7f** (93:7).

Scheme 2. Preparation of Cyclobutanone **7i**



First, we screened Lewis acids which promoted the reaction between cyclobutanone **7a** and benzaldehyde (Table 2). It was found that the use of titanium(IV) chloride gave β,γ-unsaturated aldol product **8** in 93% yield, while the use of titanium(IV) bromide gave α,β-unsaturated **9** in 34% yield (entries 1 and 2).[12] It was assumed that enone **9** was formed by isomerization of the initially formed product **8**. Catalysis of tin(IV) chloride gave **8** in only 4% yield (entry 3). Even ring cleavage of **7a** was not observed in the case of other Lewis acids such as BF_3–OEt_2 and Sc(OTf)$_3$.

Table 2. Effect of Lewis Acid on Reaction between **7a** and Benzaldehyde



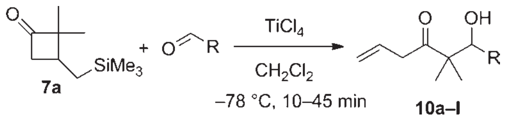
entry	Lewis acid	**8** (% yield)	**9** (% yield)
1	$TiCl_4$	93	–
2	$TiBr_4$	–	34
3	$SnCl_4$	4	–

Next, the scope and limitations of the reaction of 3-[(trialkylsilyl)methyl]cyclobutanones and aldehydes were studied using titanium(IV) chloride as a Lewis acid. Benzaldehyde derivatives with methyl, methoxy, or halogens at the para positions of the benzene ring were employed first. It was found that substitution with halogens gave high yields of the desired products **10a**–**c** (Table 3, entries 1–3) whereas reactions of methyl or methoxy-substituted benzaldehyde gave the desired compounds **10d**,**e** in 80 and 54% yields, respectively (entries 4 and 5). Therefore, the electrophilicity of the aldehydes affected the efficiency of this reaction. The reaction with 1-naphthyl aldehyde proceeded sluggishly to afford **10f** in 55% yield, but that of 2-naphthyl aldehyde gave the corresponding product **10g** in 88% yield (entries 6 and 7). Notable differences were observed in the reaction with 1- and 2-naphthyl aldehydes suggesting that this reaction was influenced easily by steric effects. Aliphatic aldehydes such as octanal and 3-phenylpropanal gave the desired products **10h**,**i** in high yields (entries 8 and 9), while increased steric hindrance in aldehydes such as isobutyl aldehyde, isopropyl aldehyde, and *tert*-butyl aldehyde caused decreased yields of the desired products **10j**–**l** (entries 10–12). When the reactions were carried out at higher reaction temperatures, the β,γ-unsaturated aldol products **10** isomerized to the corresponding α,β-unsaturated ones. The reaction with ketones such as acetophenone did not proceed.

(11) (a) Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Ghosez, L.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 2920. (b) Marko, I.; Ronsmans, B.; Hesbain-Frisque, A. M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192.

(12) Other regioisomers were not obtained.

Table 3. $TiCl_4$-Promoted Reaction between **7a** and Various Aldehydes[a]



entry	R	10	yield (%)
1	4-FC_6H_4	**10a**	86
2	4-ClC_6H_4	**10b**	93
3	4-BrC_6H_4	**10c**	96
4	4-MeC_6H_4	**10d**	80
5	4-$MeOC_6H_4$	**10e**	54
6[b]	1-Naph	**10f**	55
7	2-Naph	**10g**	88
8	$CH_3(CH_2)_6$	**10h**	93
9	$Ph(CH_2)_2$	**10i**	83
10	*i*-$PrCH_2$	**10j**	49
11	*i*-Pr	**10k**	17
12	*t*-Bu	**10l**	0

[a] Cyclobutanone **7a** (1.4 equiv), Aldehyde (1.0 equiv), and $TiCl_4$ (1.4 equiv) were employed. [b] Reaction temperature: −78 to −18 °C, 3 h.

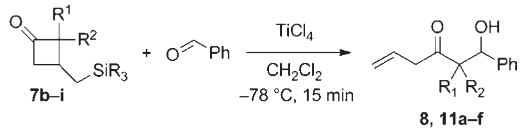
The reaction of other 2,2-dialkylcyclobutanones such as diethylcyclobutanone **7b** and spirocyclobutanones **7c**,**d** with benzaldehyde proceeded smoothly at −78 °C to afford β,γ-unsaturated aldol products **11a**−**c** in good to high yields (Table 4, entries 1−3). The reaction of 2-monoalkylcyclobutanones **7e**,**f** required a slightly elevated temperature (−45 °C), and that of 2-nonsubstituted cyclobutanone **7i** needed to be carried out at −20 °C for efficient conversion (entries 4−6). More substituted cyclobutanones reacted at lower temperatures. Moderate *syn* selectivities were observed in the products **11d**,**e** (entries 4 and 5). It was noted that cyclobutanones bearing other trialkylsily groups such as TBS and TIPS groups **7g**,**h** gave the aldol product **8** (entries 7 and 8). These results suggested that even sterically hindered trialkylsilyl groups reacted in this reaction.

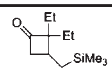
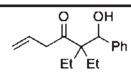
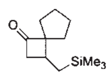
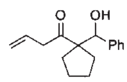
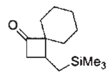
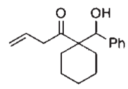
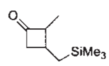
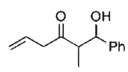
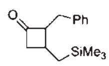
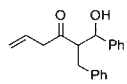
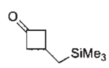
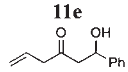
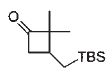
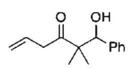
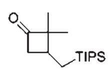
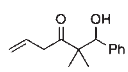
A plausible mechanism for the present ring cleavage and aldol reaction of 3-[(trialkylsilyl)methyl]cyclobutanones is shown in Scheme 3. Activation of cyclobutanone **12** with titanium(IV) chloride gave bicyclobutonium ion **13**,[13] and the chloride ion attacked the trialkylsilyl group to form a trichlorotitanium enolate **14**, whose formation was consistent with *syn* selectivity for the aldol reaction of a trichlorotitanium enolate.[14] The regioselectivity for the formation of **14** was controlled by formation of the more substituted bicyclobutonium ion **13**, and the regioselectivity was preserved during the reaction. The aldol reaction of **14** with aldehyde proceeded to give **15**.

The synthetic utility of the β,γ-unsaturated aldol adducts was exemplified by transformation of **8** to the

(13) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69.
(14) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett*. **1983**, *24*, 3343.

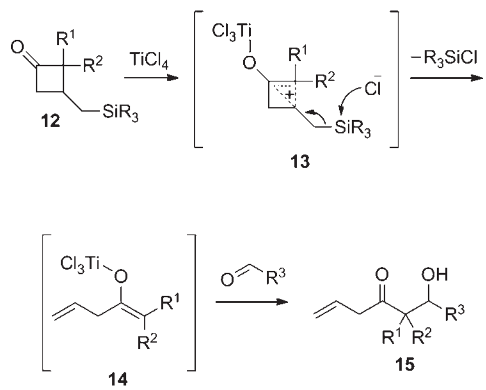
Table 4. $TiCl_4$-Promoted Reaction of Various 3-(Silylmethyl)cyclobutanones **7b**−**i** with Benzaldehyde[a]



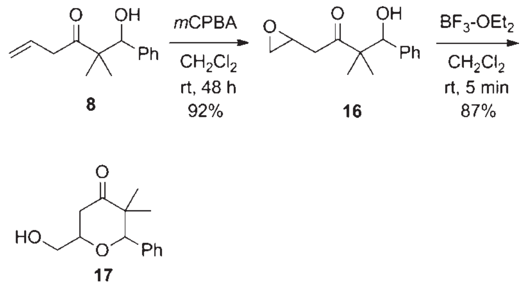
entry			conditions[a]	yield (%)
1	 **7b**	 **11a**	−78 °C, 30 min	59
2	 **7c**	 **11b**	−78 °C, 15 min	91
3	 **7d**	 **11c**	−78 °C, 30 min	92
4	 **7e**	 **11d**	−45 °C, 24 h	87[b]
5	 **7f**	 **11e**	−45 °C, 24 h	67[c]
6[d]	 **7i**	 **11f**	−20 °C, 30 min	82
7	 **7g**	 **8**	−78 °C, 15 min	86
8	 **7h**	 **8**	−78 °C, 30 min	88

[a] For reaction conditions, see Table 3 unless otherwise noted. [b] syn/anti = 80:20. [c] syn/anti = 70:30. [d] **7i** (1.4 equiv) and $TiCl_4$ (2.1 equiv) were employed.

Scheme 3. Plausible Reaction Mechanism



Scheme 4. An Example of Transformation of **8**



tetrahydropyrone **17** (Scheme 4). Epoxidation of β,γ-unsaturated aldol adduct **8** with *m*CPBA gave epoxide **16** in 92% yield. Treatment of epoxide **16** with boron trifluoride etherate gave tetrahydropyrone **17** in 87% yield.

In conclusion, 3-[(trialkylsilyl)methyl]cyclobutanones react with aldehydes upon activation with titanium(IV) chloride to afford β,γ-unsaturated aldol adducts. Regioselective formation of a β,γ-unsaturated trichlorotitanium enolate was proposed. The present method for generation of this unique enolate will likely be applicable to reactions with other electrophiles.

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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.