The Chemistry of Enoxysilacyclobutanes: Highly Selective, Uncatalyzed Aldol Additions

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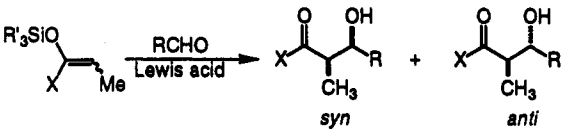
Received December 16, 1992

Summary: *O*-(Silacyclobutyl) ketene acetals derived from esters, thiol esters, and amides reacted with a variety of aldehydes at room temperature without the need for catalysts. The *O,O*-ketene acetal of *E*-configuration reacted rapidly to afford the syn aldol products with high diastereoselectivity (93/7–99/1).

In the 18 years since Mukaiyama's landmark report,[1] the directed aldol addition reaction of trialkylsilyl enol ethers with aldehydes has developed into a powerful and selective carbon–carbon bond forming reaction,[2] Scheme I. The reaction accommodates enoxysilanes derived from ketones, acids, esters, thiol esters, amides, and thiol amides, and normally requires stoichiometric or catalytic activation by Lewis acids. Indeed, the demonstration that a wide range of Lewis acidic species promotes this reaction has stimulated the advances in catalytic asymmetric aldol technology by the use of chiral Lewis acids.[3] In addition, the reaction can also be promoted by fluoride ion,[4] high pressure,[5] water,[6] and elevated temperatures.[7] Although by no means definitively established, the current dogma for the transition-state structure favors an acyclic arrangement in which the silyl group is not associated with the aldehyde.[8]

We were intrigued by the possibility of developing an aldol reaction that used the silicon atom as an organizational node.[8a,9] Since this implicates a pentacoordinate silicon, we chose to assay the potential of "strain release

Scheme I



Lewis acidity"[10] to promote reaction via this pathway. The demonstration of retentive nucleophilic substitution at silicon in four-membered rings[11] suggested that *enoxysilacyclobutanes* could react with aldehydes by silicon group transfer via trigonal bipyramidal (tbp) intermediates.[12] We describe below the mild and stereoselective uncatalyzed aldol reactions of enoxysilacyclobutanes.

To examine the role of the silicon substituent, the 1-methyl- (**1a**),[13a] 1-*tert*-butyl- (**1b**),[13b] and 1-phenyl-1-chlorosilacyclobutanes (**1c**)[13c] were prepared, Chart I. The enoxysilane derivatives **2–6** were prepared by standard enolization/silylation protocols for those functional groups.[14,15] In addition, the corresponding dimethylsilyl analogs derived from **1d–1f** were prepared and examined as controls.[16] Orienting experiments with enoxysilanes **2a** and **3a** and benzaldehyde were disappointingly slow. For example, **2a** required heating for prolonged periods (1 M, C_6D_6, 100 °C, $t_{1/2}$ 800 min; syn/anti 85/15). Nevertheless, the control **2d** showed no sign of reaction under similar conditions after 66 hours.

More satisfying results were obtained with silyl ketene acetal **4**, Table I. The *tert*-butyl derivatives (*E*)-**4b** and (*Z*)-**4b** were employed since the methyl analogs **4a** were contaminated by C-silylated esters. The reactions of (*E*)-**4b** with representative aldehydes proceeded smoothly at room temperature in 1 M solution to afford, predominantly, the syn aldol products.[17] The fact that an 89/11 *E*/*Z* mixture of **4b** afforded a >95/5 syn/anti mixture of

(1) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am Chem. Soc.* **1974**, *96*, 7503.

(2) (a) Gennari, C. In *Comprehensive Organic Synthesis, Vol. 2, Additions to C-X π Bonds, Part 2*; Heathcock, C. H., Ed.; Pergamon Press: Oxford; 1991; pp 629–660. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley Interscience: New York, 1983; Vol. 13, p 1. (c) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; Vol. 5B, p 177. (d) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2. (e) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(3) (a) Narasaka, K. *Synthesis* **1991**, 1. (b) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. (c) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (d) Kiyooka, S.; Kaneo, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276. (d) Parmee, E. R.; Tempkin, O.; Masamune, S.; Akibo, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365.

(4) (a) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932. (b) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181. (c) Chuit, C.; Corriu, R. J. P.; Reyé, C. *J. Organomet. Chem.* **1988**, *358*, 57. (d) Corriu, R. J. P.; Perz, R.; Reyé, C. *Tetrahedron* **1983**, *39*, 999.

(5) (a) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Am. Chem. Soc.* **1983**, *105*, 6963. (b) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *Tetrahedron Lett.* **1984**, *25*, 1075.

(6) Lubineau, A. *J. Org. Chem.* **1986**, *51*, 2142.

(7) (a) Creger, P. L. *Tetrahedron Lett.* **1972**, 79. (b) Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Kishino, H.; Ke, Y. Y.; Tamura, Y. *J. Org. Chem.* **1988**, *53*, 554.

(8) An important exception to this rule is the anti selective aldol condensation of chiral *N,O*-ketene acetals reported by Myers which apparently proceeds through pentacoordinate silicon. (a) Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672. (b) Myers, A. G.; Widdowson, K. L.; Kukkola, P. *J. Am. Chem. Soc.* **1992**, *114*, 2765.

(9) For reactions of allylsiliconates that react with aldehydes via closed-type transition states see: Sakurai, H. *Synlett* **1989**, *1*, 1.

(10) Denmark, S. E.; Jacobs, R. T.; Dai-Ho, G.; Wilson, S. *Organometallics* **1990**, *9*, 3015.

(11) (a) Corriu, R. J. P.; Guérin, C. *J. Organomet. Chem.* **1980**, *195*, 261. (b) Dubac, J.; Mazerolles, P.; Serres, B. *Tetrahedron* **1974**, *30*, 749. (c) McKinnie, B. G.; Bhacca, N. S.; Cartledge, F. K.; Fayssoux, J. *J. Am. Chem. Soc.* **1974**, *96*, 2637.

(12) While this manuscript was under review a paper describing a similar approach appeared: Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922.

(13) (a) Vdovin, V. M.; Nametkin, N. S.; Grinberg, P. L. *Dokl. Akad. Nauk. SSSR (Engl. Transl.)* **1963**, *150*, 449 (modified as per Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698). (b) Jutzi, P.; Langer, P. *J. Organomet. Chem.* **1977**, *132*, 45. (c) Auner, N.; Grobe, J. *J. Organomet. Chem.* **1980**, *188*, 25.

(14) (a) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650. (c) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.

(15) All new compounds were fully characterized. See supplementary material for spectroscopic and experimental details.

(16) We have found that all of these reactions, especially those of the enoxysilanes, are subject to adventitious catalysis. All reported experiments were performed in sealed tubes using analytically pure reagents and freshly distilled solvents.

(17) The assignment of configuration of the aldol products was made by ^{1}H NMR correlation with literature values. (a) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (b) Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1412. (c) Reference 14c.

0022-3263/93/1958-0988$04.00/0

Chart I

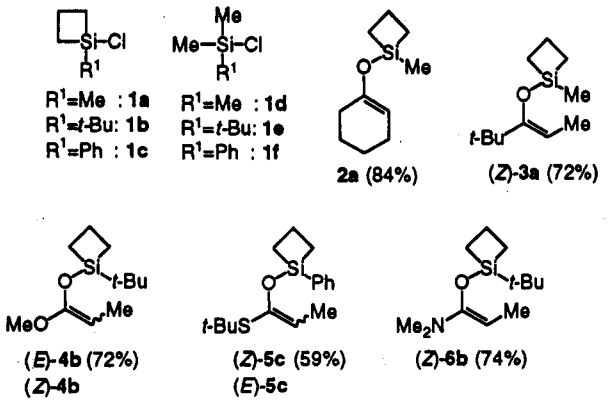
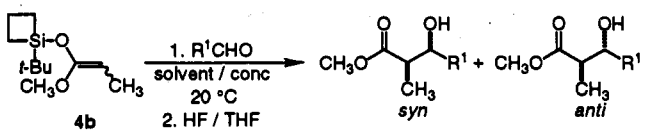


Table I. Aldol Reactions of 4b[a]



4b, E/Z	R¹	solvent[b]	$t_{1/2}$,[b] h	yield,[c] %	syn/anti[d]
89/11	Ph	$CDCl_3$	2.8		98/2[e]
89/11	Ph	C_6D_6	0.7		98/2[e]
89/11	Ph	d_8-THF	1.1		97/3[e]
95/5	Ph	$CDCl_3$	2.2	94	95/5
0/100	Ph	$CDCl_3$	28.3	80	42/58
89/11	cinnamyl	$CDCl_3$	6.7	95	93/7
89/11	*n*-pentyl	$CDCl_3$	17.0	91	93/7
89/11	cyclohexyl	$CDCl_3$	38.3	85	>99/1

[a] All reactions run at rt. Solution reactions run at 1.0 M. [b] Reactions monitored by ^{1}H NMR. [c] Yield of isolated, desilylated product. [d] Ratio determined by ^{1}H NMR on purified, desilylated products. [e] After 8 h, the majority of the *Z*-isomer still remained.

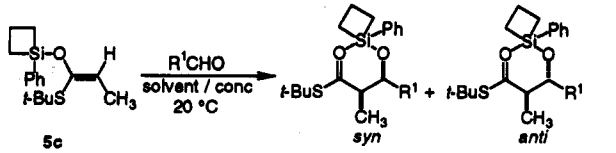
aldol products most likely arises from the more rapid reaction of the *E* isomer. Indeed, pure (*Z*)-**4b** reacted sluggishly and with modest anti selectivity. Several other observations are noteworthy: (1) control experiments with (*E*)-**4e** and benzaldehyde (1 M C_6D_6 or d_8-THF)[18] showed no reaction after 120 h, (2) the ketene acetals did not isomerize during the reaction, and (3) the more basic and less hindered aldehydes reacted faster.

The results from *O*-silyl *S,O*-ketene acetals (*E*)-**5c** and (*Z*)-**5c** are collected in Table II. Interestingly, in this series the *tert*-butyl derivative **5b** failed to react suggesting a substituent effect on reactivity at silicon (vide infra). Overall, the sulfur analog was slightly less reactive than its oxygen counterpart, though control experiments with (*E*)-**5f** and each aldehyde (both neat and in C_6D_6 solution) showed no trace of product after 24 h. The reactions of (*Z*)-**5c** afforded predominantly the syn isomer albeit less selectively than (*E*)-**4b**. Unlike *O,O*-ketene acetals, in this series changing ketene acetal geometry did not effect the stereochemical course, but only reduced the syn selectivity. As for **4b**, the conjugated aldehydes reacted faster, but there was an erosion of selectivity in THF.

The reactions of *O*-silyl *N,O*-ketene acetal (*Z*)-**6b** with various aldehydes were next examined, Table III. These aldolizations were rapid, antiselective, and very sensitive to solvent. The desilylated aldol product from benzaldehyde (C_6D_6) was isolated in 84% yield. The control experiments with (*Z*)-**6e** revealed a comparable reactivity

(18) In $CDCl_3$ 14% conversion was seen (120 h) presumably due to catalysis by trace HCl.

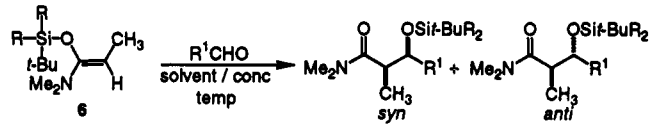
Table II. Aldol Reactions of 5c[a]



5c, E/Z	R¹	solvent[b]	time,[c] h	convn,[c] %	syn/anti[d]
4/96	Ph	$CDCl_3$	50.5	84	98/2
4/96	Ph	C_6D_6	50.5	97	97/3
4/96	Ph	d_8-THF	49.5	93	89/11
100/0	Ph	neat			85/15
4/96	cinnamyl	$CDCl_3$	51.0	91	70/30
4/96	*n*-pentyl	$CDCl_3$	50.5	42	90/10
4/96	*n*-pentyl	neat	24.0	68	90/10
4/96	cyclohexyl	$CDCl_3$	50.0	NR	
4/96	cyclohexyl	neat	29.0	46	80/20

[a] All reactions run at rt. [b] Solution reactions run at 0.5 M. [c] Reaction progress and selectivity monitored by ^{1}H NMR. [d] Ratio of silylated aldols.

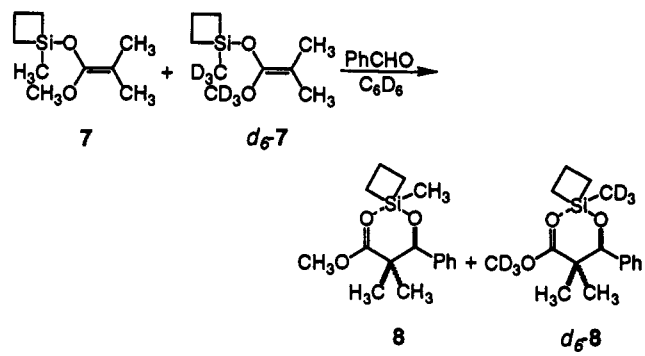
Table III. Aldol Reactions of 6b and 6e



N,O-acetal	R¹	solvent[a]	$t_{1/2}$,[b] h	syn/anti[b,c]
(*Z*)-**6b**	Ph[d]	$CDCl_3$	0.67	9/91
(*Z*)-**6b**	Ph[d]	C_6D_6	3.6	31/69[e]
(*Z*)-**6b**	Ph[d]	d_8-THF	3.8	33/67
(*Z*)-**6b**	*n*-pentyl[f]	C_6D_6	4.6	40/60
(*Z*)-**6b**	cyclohexyl[f]	C_6D_6	12.8	50/50
(*Z*)-**6e**	Ph[d]	$CDCl_3$	0.75	11/89
(*Z*)-**6e**	Ph[d]	C_6D_6	26.7	17/83
(*Z*)-**6e**	Ph[d]	d_8-THF	33.3	22/78
(*Z*)-**6e**	*n*-pentyl[f]	C_6D_6	46.7	23/77

[a] Reactions run at 0.5 M. [b] Reaction progress and selectivity monitored by ^{1}H NMR. [c] Ratio determined by ^{1}H NMR of silylated aldols. [d] Reactions run at rt. [e] Yield of isolated, purified aldol 84%. [f] Reactions run at 52 °C.

Scheme II



towards benzaldehyde in $CDCl_3$ solution, but were 8–10 times slower in other solvents or with other aldehydes.

Finally, we have unambiguously established that these reactions proceed by *direct silicon group transfer* by the double-label, crossover experiment shown in Scheme II. The ketene acetal **7**[15] reacted extremely rapidly (1 M, C_6D_6, 18 °C, $t_{1/2}$ 4.5 min) demonstrating a significant effect of the silicon substituent. Deuterium analysis of the product **8** from a 1:1 mixture of **7** and d_6-**7** (96.8% d_6) showed less than 1% crossover (0.54% d_3-**8**).

The enhanced reactivity of ketene acetals **4b** and **5c** over their counterparts **4e** and **5f** strongly suggests involvement of pentacoordinate silicon species. Moreover,

the dramatic differences in reactivity and selectivity for (*E*)- and (*Z*)-**4b** are also inconsistent with open transition structures. Indeed, the Lewis acid catalyzed reactions of ketene acetals (wherein open transition states are implicated) are generally anti selective aldol processes.[14a,c,17a] Thus, the high syn selectivity exhibited by (*E*)-**4b** and (*Z*)-**5c** may be interpreted as a preference for reaction via boatlike transition structures in tbp assemblies. We speculate that the small O–Si–O angle (90°) provides a significant distortion to the closed transition structure, thus favoring a boat. This rationale has been advanced by Evans to explain the high syn selectivity observed in aldolizations with zirconium enolates.[2b,19]

In summary, we have demonstrated that enoxysilacyclobutanes derived from esters and thiol esters engage in syn-selective uncatalyzed aldol condensations with a range of aldehydes at ambient temperature. Studies aimed at (1) clarifying the origin of diastereoselectivity, (2) defining the role of the spectator ligand on silicon, and (3) asymmetric catalysis are in progress.

Acknowledgment. We are grateful to the National Science Foundation (CHE-8818147 and CHE-9121631) for generous financial support. D.M.C. thanks the Fulbright Commission for a travel grant. Mr. Robert Harlan is thanked for the large-scale preparation of **1a**, **1b**, and 1,1-dichlorosilacyclobutane.

Supplementary Material Available: Procedures for the preparation of **2a**, (*Z*)-**3a**, (*E*)- and (*Z*)-**4b**, (*Z*)-**5c**, (*Z*)-**5f**, (*Z*)-**6b**, and **7** along with full spectroscopic and analytical data (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(19) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975.