Chemistry of Enoxysilacyclobutanes. 3. Uncatalyzed, Syn-Selective, Asymmetric Aldol Additions

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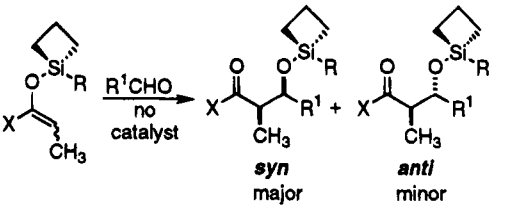
Summary: Asymmetrically modified *S,O*-(alkoxysilacyclobutyl) ketene acetals derived from methanethiol esters reacted with aromatic aldehydes at low temperature to afford, after desilylation, the corresponding β-hydroxy thiol ester aldolates in high enantiomeric excess (91–94% ee).

Previous reports from these laboratories have demonstrated that enoxysilacyclobutanes derived from esters and thiol esters engage in uncatalyzed, highly *syn*-selective aldol additions with a range of aldehydes at ambient temperature, Scheme 1.[1] Careful examination revealed the importance of various structural factors on rate and selectivity of the uncatalyzed additions of *O,O*-(silacyclobutyl) ketene acetals to aldehydes.[1b] The effects of the key structural features are summarized as follows: (1) (*E*)-ketene acetals react faster and are more syn-selective than the corresponding (*Z*)-ketene acetals, (2) the larger the group X the slower the reaction rate (methoxy ≫ *tert*-butoxy), and (3) the larger the spectator group R on silicon the slower the reaction rate (CH_3 > *tert*-butoxy ≫ *tert*-butyl). Furthermore, double-label crossover experiments show that these reactions proceed via direct *intramolecular* silicon group transfer, most likely via five-coordinate trigonal bipyramidal (tbp) intermediates. Thus, the high syn selectivity from (*E*)-ketene acetals necessarily implicates boatlike transition structures. Computational modeling reveals that a boat transition structure is slightly preferred over the chair, due to nonbonded interactions with the spectator R group.

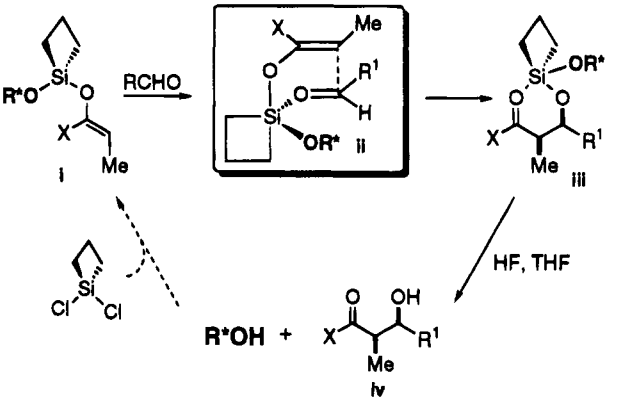
In continuation of our studies on the special opportunities provided by the silacyclobutane, we have investigated the potential for asymmetric induction. The pentacoordinate tbp and corresponding transition structures[1b] clearly implicate an important role for the spectator ligand on silicon on both the rate and stereoselectivity of the addition reaction. Since this group is intimately associated with the carbon–carbon bond-forming event, it represents the logical locus for asymmetric modification. Thus, we chose to assay the influence of the asymmetric environment provided by R on the enantioselectivity of the aldol addition.[2–4]

To realize an efficient and selective asymmetric addition, several design criteria for the ketene acetal had to be considered. First, given the importance of ketene acetal geometry on rate, an (*E*)-enolate system was required. Second, the chiral auxiliary needed to be relatively small, readily available in enantiomerically pure form, easily recoverable, and capable of strong dissymmetric influence. In view of the facility of addition

Scheme 1



Scheme 2



of *tert*-butoxysilacyclobutane derivatives, we chose to survey a series of secondary alcohols as the auxiliaries. Scheme 2 summarizes the proposed asymmetric variant of the aldol addition reaction. The auxiliary would be incorporated by formation of a chiral alkoxysilacyclobutyl chloride which would be used to form the chiral ketene acetal **i** by standard enolate trapping methods from selectively generated (*E*)-enolates.[1] Combination of **i** with an aldehyde to give the β-(silyloxy) aldolate **iii** (via the associative transition state **ii**) followed by removal and recovery of the chiral auxiliary by desilylation would give β-hydroxy ester **iv**.

Listed in Chart 1 are the ketene acetals employed in this study. The acetals were synthesized by trapping of the preformed ester enolates with the appropriate alkoxysilyl chlorides.[1b,5] There were inherent problems associated with the synthesis of the acetals **1a–6a** from

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(1) (a) Denmark, S. E.; Griedel, B. D.; Coe, D. M. *J. Org. Chem.* **1993**, *58*, 988. (b) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.*, in press.

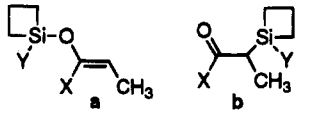
(2) In an earlier account, Myers reported the aldol addition of *O*-silacyclobutyl-*N,O*-ketene acetals derived from (*S*)-prolinol propanamide with aldehydes which afforded nine-membered ring, silicon bridged *anti* aldol products with high diastereoselectivity. Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922.

(3) For recent reviews of enantioselective aldol additions see: (a) 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. (b) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; Vol. 5B, p 177. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2. (d) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis, Vol. 2, Additions to C–X π Bonds, Part 2*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; pp 239–275. (e) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (f) 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. (g) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1791. (h) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417.

(4) (a) For a previous example of asymmetric Mukaiyama aldol addition with a chiral enol silane see: Jung, M. E.; Hogan, K. T. *Tetrahedron Lett.* **1988**, *29*, 6199. (b) For a review of chiral organosilicon reagents see: Chan, T. H.; Wang, D. *Chem. Rev.* **1992**, *92*, 995.

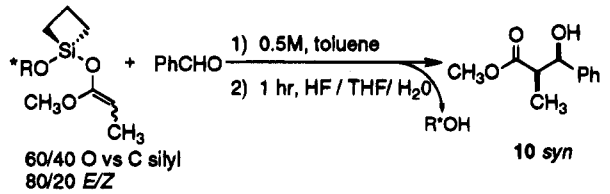
0022-3263/94/1959-5136$04.50/0

Chart 1



1a,b: X= OCH_3, Y= (-)-menthol
2a,b: X= OCH_3, Y= (+)-2,2-diphenylcyclopentanol
3a,b: X= OCH_3, Y= (+)-*endo*-borneol
4a,b: X= OCH_3, Y= (+)-*trans*-2-phenylcyclohexanol
5a,b: X= OCH_3, Y= (-)-8-phenylmenthol
6a,b: X= OCH_3, Y= (-)-*trans*-2-cumylcyclohexanol
7a,b: X= S*t*-Bu, Y= (-)-menthol
8a,b: X= SCH_3, Y= (-)-menthol
9a,b: X= SCH_3, Y= (+)-*trans*-2-cumylcyclohexanol

Table 1. Uncatalyzed Aldol Additions of Chiral Enoxysilacyclobutanes 1–6



60/40 O vs C silyl
80/20 *E/Z*

10 *syn*

entry	ketene acetal	temp, °C	syn/anti[a]	ee,[a] %
1	**1**	20	9/1	48
2	**1**	0	9/1	51
3	**1**	−20	19/1	58
4	**1**	−60	>99/1	74
5	**2**	−60	>99/1	7
6	**3**	−60	>99/1	11
7	**4**	−60	>99/1	63
8	**5**	−60	>99/1	95
9	**6**	−60	>99/1	97

[a] Ratios for the desilylated aldol product, determined by chiral phase gas chromatography.

methyl propanoate. First, we found that the sterically unencumbered alkoxysilyl chlorides reacted competitively with both the enolate and the diisopropylamine (from LDA) in the enolization step. This could be overcome by the use of lithium tetramethylpiperidide (LiTMP) for the deprotonation of the ester (80/20, *E/Z*). However, there still existed a problem of O- vs C-silylation (typically 60/40, O- vs C-silylation; **a/b**). All attempts to suppress the C-silylation were unsuccessful, and unfortunately, these ester-derived ketene acetals were also prone to thermal rearrangement to their corresponding *C*-silyl isomers during distillation. Despite the problems in the synthesis and isolation of **1a–6a**, they could be used in crude form for orienting experiments.

O,O-Silacyclobutyl ketene acetal **1** was combined with benzaldehyde in toluene (0.5 M), and after 40 min, the reaction mixture was subjected to desilylative workup conditions (dilute HF in THF) to afford the *syn* β-hydroxy ester **10** (Table 1). The enantioselectivity of the aldol addition was first evaluated as a function of temperature (entries 1–4). As the temperature was lowered from +20 to −60 °C, there was a concomitant increase in the enantiomeric excess of **10**. Below −60 °C, no further increase in enantioselectivity was observed. Interestingly, the syn/anti ratio for **10** also increased as the temperature was lowered. From NMR studies, we have found that this reflects a kinetic resolution, since the (*Z*)-isomer of the ketene acetal does not react. The rates of these reactions were remarkable; for example, (*E*)-**1a** was consumed within 40 min at −60 °C! This represents a significant acceleration compared to the reactions with previous substrates.[1]

The survey of the various candidates for the chiral auxiliary was then carried out at the optimum reaction temperature. The ketene acetals **2–6** were combined with benzaldehyde (entries 5–9), and the aldol products **10** were analyzed after desilylation. As shown in Table 1, the highest selectivities (95–97% ee) were obtained with (−)-8-phenylmenthol-derived ketene acetal **5**[6] and the ketene acetal **6** derived from the less expensive (−)-trans-2-cumylcyclohexanol (TCC).[7]

Although the diastereo- and enantioselectivity in the addition were high, the yields of the products were unacceptably low due to the large component of *C*-silyl esters and (*Z*)-ketene acetal isomers. Thus, we examined other carbonyl substrates and returned to thiol esters on the basis of our initial reactivity survey. The silacyclobutyl *S,O*-ketene acetals **7a–9a** were synthesized in good yield (78–80%) via deprotonation of the corresponding methanethiol ester with LiTMP at −78 °C, followed by trapping of the enolates with the appropriate alkoxysilacyclobutyl chloride. This procedure afforded the *Z*-isomer[8] (92–98% *Z*) with <2% of the *C*-silyl analogs **7b–9b**.

To assess the reactivity of the ketene acetals **7a–8a**, reactions were conducted with benzaldehyde in toluene to afford **11** after desilylation. The yield and stereoselectivity were measured as a function of time and temperature. Ketene acetal **7a** reacted slowly ($t_{1/2}$ = 6 h), which was not unexpected because of the *tert*-butyl group on the sulfur. The less sterically encumbered ketene acetal **8a** reacted much faster than **7a** at room temperature (entry 2); however, the reaction was complicated by the formation of byproducts presumably due to addition of **8a** to **11**. A brief optimization of rate, yield, and enantioselectivity with **8a** and benzaldehyde as a function of temperature and concentration was carried out. The highest enantioselectivity (70% ee, cf. 74% ee for **1** at −60 °C) was obtained at −35 °C; lowering the temperature served only to lower the yield. The undesirable side reactions could be suppressed at lower temperatures, but the concentration had to be increased (2.0 M) to maintain acceptable rate and yields. Finally, **8a** was combined with aliphatic aldehydes and was found to give little or no reaction at −35 °C.

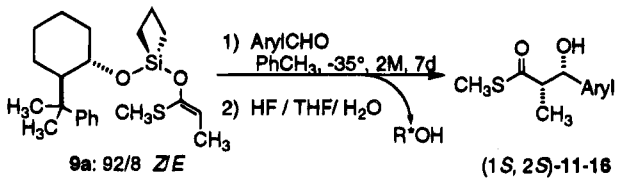
Thus, in the optimized protocol, the (+)-TCC-derived ketene acetal **9a** was combined with a variety of aromatic aldehydes (Table 2). The reactions were run at -35 °C in toluene (2.0 M) for 7 days in sealed tubes and then were quenched at −35 °C with dilute HF/THF to afford pure syn aldols **11–16** in fair yields and with high enantiomeric excess. The (+)-TCC could be recovered in 82–87% yield. The relative configurations of **11–16** were established by comparison to authentic samples prepared via addition of the corresponding lithium enolates to the aldehydes and chromatographic separation of the syn and anti isomers.

Finally, to establish the absolute configuration of the aldolates **11–16** and to demonstrate the synthetic utility of this process, **11** was converted to **10** via a trans

(5) All carbinols used to synthesize the alkoxysilacyclobutyl chlorides were of 98% ee or greater.

(6) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(7) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656.
(8) In thiol esters the priority changes such that in (*Z*)-**7–9** MeS and CH_3 are cis.

Table 2. Asymmetric Aldol Addition of *S,O*-Ketene Acetal 9a with Aromatic Aldehydes



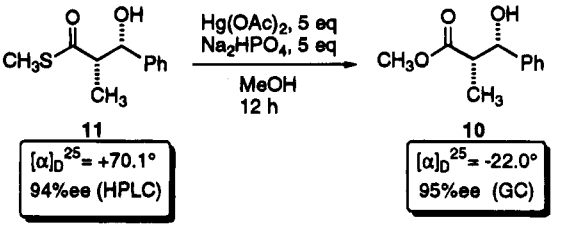
entry	ArylCHO[a]	product[a]	yield,[b] %	$[\alpha]^{25}_D$[c] (deg)	% ee[d]
1	benzaldehyde	**11**[e]	60	+70.1	94
2	cinnamaldehyde	**12**[f,g]	64	67.4	92
3	*p*-anisaldehyde	**13**	62	+71.1	94
4	furfural	**14**	68	+33.1	90
5	1-naphthaldehyde	**15**[h]	50	+51.5	94
6	α,α,α-trifluoro-*p*-tolualdehyde	**16**	45	+55.3	94

[a] 1.0 equiv. [b] Yields (of desilylated, chromatographed product) do not reflect the composition of **9a**. [c] $CHCl_3$, $c = 1.0$. [d] Determined by chiral phase HPLC. [e] (+)-TCC recovered in 85% yield. [f] (+)-TCC recovered in 87% yield. [g] (1*S*,2*R*) Configuration due to priority change. [h] (+)-TCC recovered in 87% yield.

esterification (Scheme 3). Thiol ester **11** was treated with mercuric acetate at room temperature in methanol with sodium phosphate buffer for 12 h to afford **10** in 90% yield.[9] The enantiomeric purity of **10** was confirmed by chiral phase gas chromatography, and the absolute configuration and rotation were compared to the literature values.[10]

In summary, we have demonstrated that chirally modified *S,O*-(alkoxysilacyclobutyl) ketene acetals derived from methanethiol esters react with aromatic aldehydes to afford, after desilylation, the corresponding

Scheme 3



β-hydroxy thiol esters in high enantiomeric excess (91–94% ee) and in reasonable yields. The thiol esters of high enantiomeric excess can be easily converted to the corresponding methyl esters with no loss of stereochemical integrity. Current efforts are focused on a catalytic asymmetric variant of the aldol addition.

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Supplementary Material Available: Procedures for the preparation of **7**–**9**, the corresponding alkoxysilacyclobutyl chlorides used to make them, experimental procedures for the preparation of **11**–**16**, and full spectroscopic and analytical data are provided (10 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.

(9) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.
(10) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. J. *J. Am. Chem. Soc.* **1990**, *112*, 2767. (c) Yan, T. H.; Tan, C. W.; Lee, H. C.; Lo, H. C.; Huang, T. Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613.