The Chemistry of Trichlorosilyl Enolates. 2. Highly-Selective Asymmetric Aldol Additions of Ketone Enolates

Scott E. Denmark,* Ken-Tsung Wong, and Robert A. Stavenger

Roger Adams Laboratory, Department of Chemistry University of Illinois, Urbana, Illinois 61801

Received October 23, 1996

Asymmetric catalysis of the aldol addition reaction has been an area of intense activity in recent years.[1−4] Despite considerable success to date, these efforts have identified the same solution to the problem, namely, the invention/discovery of a suitable chiral Lewis acid catalyst to effect the reaction between an enoxysilane derivative and an aldehyde, Scheme 1 (X = Me).

In a recent Communication we have described a conceptually distinct approach which employs chiral Lewis bases (phosphoramides) in combination with trichlorosilyl enolates, Scheme 1 (X = Cl).[5] These reactions were designed to proceed via highly-organized, hexacoordinate siliconate assemblies of enolate, aldehyde, and Lewis base and are thus distinguished from the classic Mukaiyama aldol reactions which are believed to proceed via open transition structures.[6] Consequently, we expected to observe a stereochemical dependence of enolate geometry reflected in the product in contradistinction to the geometry-independent, syn diastereoselectivity observed in Lewis acid catalyzed reactions of silyl enolates.[3,6,7] *We report herein the highly diastereo- and enantioselective aldol additions of geometrically defined trichlorosilyl enolates of ketones.*

The two trichlorosilyl enolates employed in this study, **1**[5] and **2**,[8] were prepared by $SiCl_4$ metathesis of the stannyl ketones which arise from treatment of enol acetates with *n*-Bu_3SnOCH_3,[9]

Scheme 1

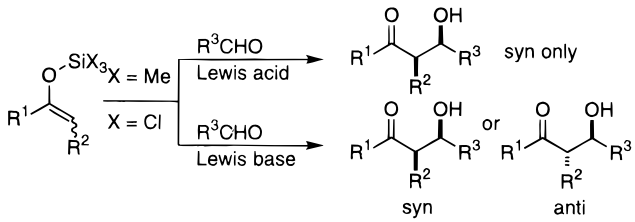


Chart 1

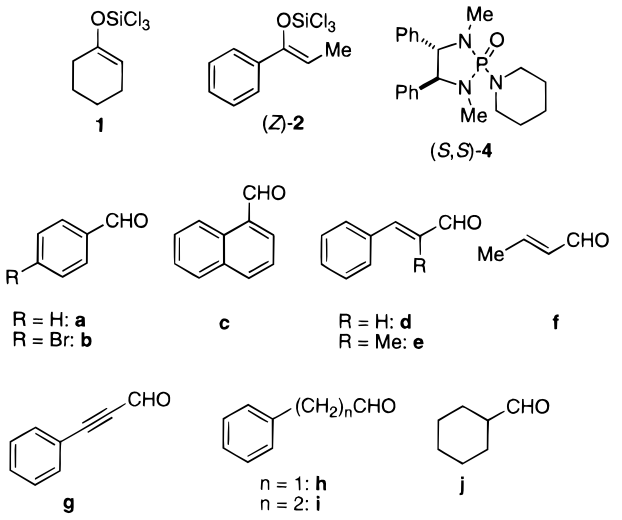


Chart 1. An assortment of aromatic, olefinic, and aliphatic aldehydes was surveyed to assay generality and structural effects on rate and selectivity in all the subsequent reactions, Chart 1.

Both **1** and **2** were highly effective aldolization reagents albeit much less reactive than the trichlorosilyl enolates of esters. Thus, **1** cleanly combined with eight different aldehydes at 0 °C in the absence of external promoters to afford the aldol adducts **3**[8] in 78−92% yield, Table 1. The conjugated aldehydes gave good to excellent diastereoselectivity favoring the syn isomer.[10] The production of a syn stereoisomer from an *E*-enolate through a closed transition structure necessarily implicates a boat-like arrangement (**i**, Chart 2). We have previously demonstrated that the *E*-enolate to syn adduct correlation is characteristic of uncatalyzed aldol reactions of enoxysilacyclobutanes. The putative pentacoordinate siliconate transition structures were shown computationally to prefer boat-like arrangements in this array.[11]

To examine the consequences of promoting the reaction with chiral Lewis bases, we surveyed a variety of chiral phosphoramides, of which (*S*,*S*)-**4** (Chart 1) proved to be the most effective, Table 2. First, we noted a significant rate acceleration; with only 10 mol % of (*S*,*S*)-**4** the aldol additions proceeded in high yield within 2 h at −78 °C.[12] Second, we were surprised to discover the dramatic reversal in diastereoselectivity; in the presence of (*S*,*S*)-**4**, the anti diastereomer now predominated in all cases, often exclusively (compare entries 1−5, Tables 1 and 2). Finally, we were delighted to find that the major, anti diastereomer in all of these cases was produced with good to

(1) For reviews containing catalytic enantioselective aldol additions, see: (a) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417. (b) Franklin, A. S.; Paterson, I. *Contemporary Org. Syn.* **1994**, *1*, 317−416. (c) Braun, M.; Sacha, H. *J. Prakt. Chem.* **1993**, *335*, 653−668. (d) Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 367−388. (e) Yamamoto, H.; Maruoka, K.; Ishihara, K. *J. Synth. Org. Jpn.* **1994**, *52*, 912.

(2) For recent advances with silyl ketene acetals, see: (a) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761. (b) Carriera, E. M. Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (d) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull. Jpn.* **1994**, *42*, 839. (e) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805. (f) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (g) Carreira, E. M. Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 12360. (h) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435. (i) Uotsu, K.; Sasai, H.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 71.

(3) For recent advances with silyl enol ethers, see: (a) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (b) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (c) Ishihara, K.; Maruyama, T.; Mouri, M.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483. (d) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490. (e) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (f) Barrett, A. G. M.; Kamimura, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1755. For an example with a methyl enol ether, see: (g) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

(4) For a recent summary of enzyme-catalyzed asymmetric aldol addition reactions see: Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994; Chapter 4.

(5) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404.

(6) (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043. (c) Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707.

(7) For a notable exception, see: Kobayashi, S.; Horibe, M.; Hachiya, I. *Tetrahedron Lett.* **1995**, *36*, 3173.

(8) All compounds described herein were fully characterized by spectroscopic and analytical methods. See Supporting Information.

(9) (a) Pereyre, M.; Bellegarde, B.; Mendelsohn, J.; Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97. (b) Yasuda, M.; Katoh, Y.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 4386.

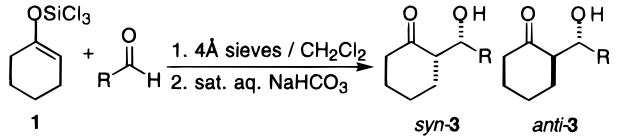
(10) The relative configuration of **3a** has been established in the literature. For all other compounds we made the assignment on the basis of the splitting pattern of the hydroxyl bearing methine. In the anti isomer, this proton typically appears as a doublet of doublets, $J_d = 7-8$ Hz; $J_d = 2-4$ Hz; while in the syn isomer it typically appears as a broad singlet or a doublet, $J = 3-4$ Hz. In addition, this proton in the anti isomers resonates 0.3−0.5 ppm upfield of the syn isomers.

(11) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026.

(12) Control experiments showed that no reaction took place under these conditions of time, temperature, and concentration without the promoter.

S0002-7863(96)03669-4 CCC: $14.00

Table 1. Unpromoted Aldol Reactions of **1**[a]



entry	aldehyde	time, h	product	syn/anti[b]	yield, %
1	**a**	6	**3a**	49:1	92[c]
2	**c**	8	**3c**	16:1	90[d]
3	**d**	1	**3d**	49:1	83[c]
4	**e**	11	**3e**	5.7:1	86[d]
5	**g**	2	**3g**	36:1	91[c]
6	**h**	12	**3h**	7.3:1	78[c]
7	**i**	12	**3i**	5.3:1	82[d]
8	**j**	36	**3j**	1:1	92[d]

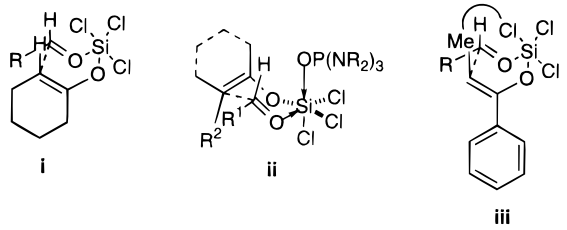
[a] All reactions performed at 0 °C/0.5 M in aldehyde. [b] Determined by ^{1}H NMR (400 MHz) analysis. [c] Analytically pure material. [d] Chromatographically homogeneous material.

Table 2. Aldol Reactions of **1**[a] Catalyzed by (*S*,*S*)-**4**

entry	aldehyde	product	syn/anti[b]	ee (anti),[c] %	yield,[d] %
1	**a**	**3a**	1:61	93	95
2	**c**	**3c**	<1:99	97	94
3	**d**	**3d**	<1:99	88	94
4	**e**	**3e**	<1:99	92	98
5	**g**	**3g**	1:5.3	82	90

[a] All reactions performed with 10 mol % of (*S*,*S*)-**4** at −78 °C/0.1 M in aldehyde for 2 h. [b] Determined by ^{1}H NMR (400 MHz) analysis. [c] Determined by chiral HPLC analysis. [d] Analytically pure material.

Chart 2

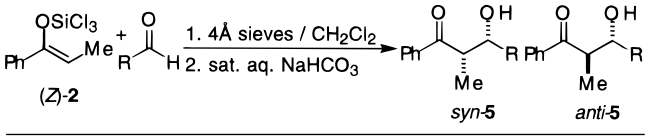


excellent ee. The absolute configuration of the major diastereomer was established to be (2*R*,1′*S*) by X-ray crystallographic analysis of the 4-bromobenzoate of *anti*-**3a**. The generation of an anti aldol product from an *E*-enolate suggests the change to a chair-like transition structure involving the putative hexacoordinate siliconate species (**ii**, Chart 2)

The unpromoted reactions of (*Z*)-**2** proceeded somewhat more slowly than for **1** but still in excellent yields,[8] Table 3. As expected for a boat-like, closed transition structure, the anti diastereomer was found to predominate, but the selectivity was poor. The decreased rate and diastereoselectivity associated with *Z*-configured trichlorosilyl enolates are presaged by the same observations in the case of *Z*-enoxysilacyclobutanes.[11] Here again, the intervention of boat-like structures in pentacoordinate siliconates (**iii**, Chart 2) leads to a nonbonded interaction between the pseudoaxially placed substituent on the enolate with a ligand on silicon.

In the presence of a catalytic amount (15 mol%) of (*S*,*S*)-**4** the reactions of (*Z*)-**2** were significantly faster but still slower compared to the promoted reactions of **1** (Table 4). Excellent yields of aldol adducts from conjugated aldehydes were obtained after 6−8 h at −78 °C. Aliphatic aldehydes did not react, presumably due to competitive enolization. The major diastereomer produced in the promoted reactions was syn as would

Table 3. Unpromoted Aldol Reactions of **2**[a]



entry	aldehyde	time, h	product	syn/anti[b]	yield,[c] %
1	**a**	10	**5a**	1:2.3	97
2	**b**	10	**5b**	1:2.9	93
3	**c**	16	**5c**	1:1.3	95
4	**d**	10	**5d**	1:1.9	95
5	**e**	12	**5e**	1:2.2	64
6	**f**	16	**5f**	1:1.9	89
7	**g**	11	**5g**	1:2.2	89

[a] All reactions performed at 0 °C/0.5 M in aldehyde. [b] Determined by ^{1}H NMR (400 MHz) analysis. [c] Chromatographically homogeneous material.

Table 4. Aldol Reactions of **2**[a] Catalyzed by (*S*,*S*)-**4**

aldehyde	time, h	product	syn/anti[b]	ee (syn),[c] %	yield,[d] %
a	6	**5a**	18:1	95	95
b	6	**5b**	12:1	96	89
c	8	**5c**	3:1	84	96
d	6	**5d**	9.4:1	92	97
f	8	**5f**	7:1	91	94
g	6	**5g**	1:3.5	58	92

[a] All reactions performed with 15 mol % of (*S*,*S*)-**4** at −78 °C/0.1 M in aldehyde. [b] Determined by ^{1}H NMR (400 MHz) analysis. [c] Determined by chiral HPLC anaylsis. [d] Analytically pure material.

be expected from a switch from boat- to chair-like transition structures. However, the diastereoselectivity was highly aldehyde dependent. Gratifyingly, the enantiomeric excess of the major (syn) diastereomer was very high except for **5g**. The absolute configuration of the major diastereomer was established to be (2*S*,3*S*) by X-ray crystallographic analysis of *syn*-**5b**.[13]

The high diastereo- and enantioselectivity of the aldolization process and the stereochemical response to the enolate geometry strongly support our current hypothesis of a highly-ordered, chair-like transition structure involving hexacoordinate siliconate species. The fact that (*S*,*S*)-**4** induced the same configuration at the hydroxyl-bearing methine in both *anti*-**3a** and *syn*-**5a** suggests that, even with single point binding, the phosphoramides are capable of creating a highly dissymmetric environment which maintains the same enantiofacial preference at the coordinated aldehyde with either enolate geometry. However, the lack of structural information about the coordination geometry at silicon makes the formulation of a sensible transition structure model tenuous at this stage. That notwithstanding, the catalytic, enantioselective generation of anti aldol products is noteworthy for practical applications.

Extension of this process to other enolate types and the elucidation of structure/selectivity correlations for the promoters will be reported in due course.

Acknowledgment. We are grateful to the National Science Foundation for generous financial support (CHE 9500397).

Supporting Information Available: Procedures for the preparation and full characterization of **1**; **2**; (±)-*syn*-**3a**, **c**, **d**, **e**, **g**, **h**, **i**, **j**; (±)-*anti*-**5a**−**g**; enantiomerically enriched-*anti*-**3a**, **c**, **d**, **e**, **g**; and enantiomerically enriched-*syn*-**5a**, **b**, **c**, **d**, **f**, **g**, (34 pages). See any current masthead page for ordering and Internet access instructions.

JA9636698

(13) Debromination of (2*S*,3*S*)-**5b** afforded the major enantiomer of *syn*-**5a** thus establishing its configuration as (2*S*,3*S*) as well. All others are assigned by analogy.