

Table 2. Oxidative cleavage of cyclic silanes.^[a]

| Entry | Silane | R | R' | 12 | Yield [%] ^[b] |
|-------|---------|---|-----|---------|--------------------------|
| 1 | (-)-11a | | H | (-)-12a | 78 |
| 2 | (+)-11b | | H | (-)-12b | 76 |
| 3 | (+)-11c | | H | (-)-12c | 79 |
| 4 | (-)-11f | | H | (-)-12d | 70 |
| 5 | (-)-11h | | MOM | (-)-12e | 74 |

[a] For detailed experimental procedures and compound characterization, see Supporting Information. [b] Refers to the yield of spectroscopically pure product isolated after silica gel chromatography.

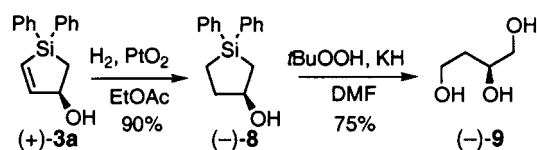
scaffold can be efficiently accomplished according to the Woerpel procedure employing the use of basic *t*BuOOH in DMF.^[16] Several representative tetraols **12** were prepared in good yields with complete overall diastereoselectivity illustrating the generality of this strategy (Table 2). The occurrence of a polyol motif **12** in a number of bioactive natural products is noteworthy. Representative examples include the side chain portion of bacteriohopanoid.^[17a] and the central macrolide segment of herbarumin I, a highly potent phytotoxic agent.^[17b]

In summary, we have demonstrated a highly enantioselective catalytic isomerization of silacyclopentene oxide, a pivotal point in our strategy for the stereoselective assembly of acyclic polyols. Development of an arsenal of new asymmetric processes utilizing cyclic silanes is currently in progress.

Received: September 6, 2001 [Z17864]

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The First Catalytic, Diastereoselective, and Enantioselective Crossed-Aldol Reactions of Aldehydes**

Scott E. Denmark* and Sunil K. Ghosh

The apotheosis of the aldol addition reaction is one of the most well-documented chapters of modern organic synthesis; the generality, versatility, and selectivity associated with this process have been the subject of countless reviews and authoritative summaries. Stimulated by the challenge posed by nature, a generation of synthetic organic chemists has constructed an impressive edifice of knowledge which constitutes insightful, elegant, and practical solutions to the structural and stereochemical problems presented by polypropionate-derived natural products. Yet, at this advanced vantage, it is remarkable that the most basic of aldol

[*] Prof. Dr. S. E. Denmark, Dr. S. K. Ghosh
Department of Chemistry, University of Illinois
Urbana, IL 61801 (USA)
Fax: (+1)217-333-3984
E-mail: denmark@scs.uiuc.edu

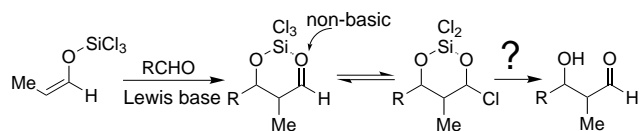
[**] We are grateful to the National Science Foundation for generous financial support (NSF CHE 9803124).

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constructions, namely the controlled, stereoselective self-condensation of aldehydes, has found no general solution.^[1]

Even within the realm of modern enolate chemistry,^[2] the problems inherent in this construction are readily apparent: 1) poly-aldolization that results from secondary additions to the aldehyde products, 2) dehydration of the product, which enables Michael-type additions, 3) Tishchenko-type processes, and 4) oligomerization of the product. Superimposed upon these issues is the relatively small size of aldehyde enolates, which renders stereoselection challenging. Nevertheless, a number of notable advances are on record which both overcome and illustrate these problems. Early studies by Heathcock et al. on the *E* and *Z* lithium enolates of propanal demonstrated the low selectivity and stereochemical convergence in the formation of the (metastable) *syn* and *anti* aldol products.^[3] In 1997, Mahrwald et al. reported the crossed addition of aldehydes promoted by TiCl₄.^[4] Good *syn* selectivity can be obtained with appropriate choice of aldehyde and the products can be isomerized to the more stable *anti* products with Ti(OiPr)₄^[3b] (also with concomitant Tishchenko reduction^[3c]). Aldol addition of trichlorotitanium enolates generated by both reduction and conjugate addition has also been studied by Oshima and co-workers.^[5] Stereoselectivity is variable, but highly *syn*-selective processes have been noted. More recently, this group has described the aldol additions of stereodefined *E* and *Z* (tributoxytitanium) enolates of aldehydes.^[6] Whereas good yields of aldol products were obtained (also with ketones) the diastereoselectivity was low and weakly dependent on enolate geometry.

Consideration of the shortcomings outlined above suggested that a potential solution might accrue from the application of our recently developed aldol chemistry of trichlorosilyl enolates^[7] of esters,^[7b] substituted ketones,^[7c] and methyl ketones.^[7d] Our mechanistic understanding of this process^[8] identifies the crucial role of the Lewis basic oxygen atom of the carbonyl group to associate with the chiral, cationic trichlorosilyl enolate (Scheme 1). Because the aldolate exists

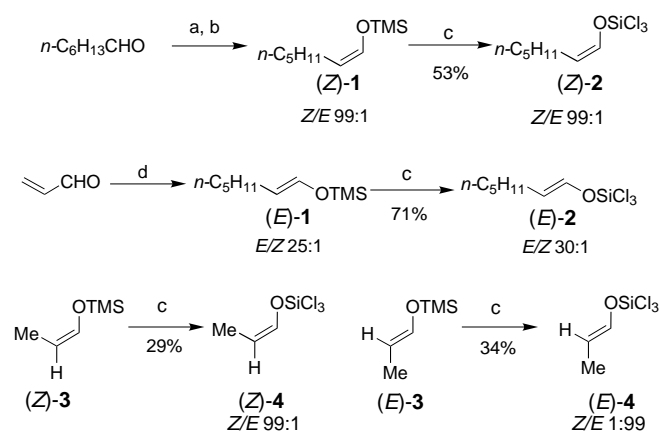


Scheme 1. Formulation of Lewis base catalyzed crossed-aldol reaction of aldehydes.

as a chelated complex, the basicity of the carbonyl group of the product is attenuated. Moreover, we expected that the immediate product might exist as a chlorohydrin by analogy with hemiacetal adducts noted by Oshima et al. Finally, in view of the dramatic rate enhancements seen for Lewis base catalysis of these processes, we anticipated that reactions would take place at low temperatures under the influence of chiral phosphoramides. We report herein the successful implementation of this plan which provides the first method of catalytic enantioselective crossed-aldol reactions of aldehydes.

To test the feasibility of this concept first required the generation of stereodefined trichlorosilyl enolates of aldehydes.

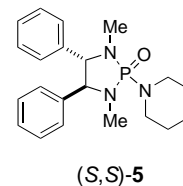
Although a number of different methods have been described from these laboratories, none were capable of delivering the enoxytrichlorosilanes with high geometrical purity.^[9] A new method was therefore devised that has its origins in the Stork–House generation of lithium enolates.^[10] Thus, the stereodefined trimethylsilyl enol ethers of heptanal ((*E*)- and (*Z*)-**1**) were prepared by either direct enolization (*Z/E* 87:13)^[11] followed by chromatographic enrichment or copper-catalyzed conjugate addition of *n*-butylmagnesium chloride to acrolein and trapping with TMSCl^[12] (Scheme 2). Cleavage of the TMS enol ethers with MeLi is known to lead to retention of the geometry of the double bond; moreover, after quenching with excess SiCl₄ the derived trichlorosilyl enolates (**2**) were found to be highly geometrically enriched. The corresponding trichlorosilyl enolates of propanal ((*E*)-**4** and (*Z*)-**4**) could also be obtained in high geometrical purity by a similar process.^[13]

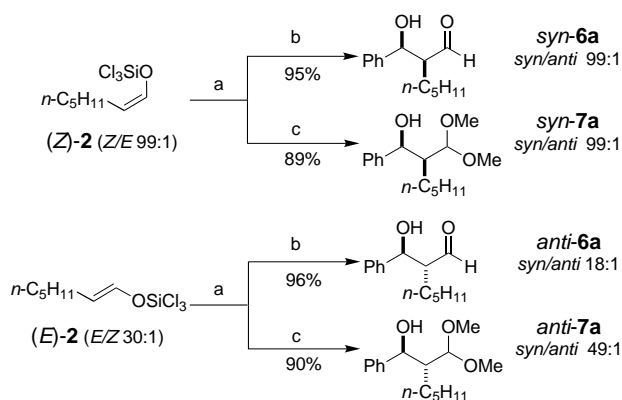


Scheme 2. a) TMSOTf, Et₃N, Et₂O, 56%; b) separate; c) 1. MeLi, Et₂O, 2. SiCl₄; d) 1. *n*BuMgCl, CuBr·Me₂S, 2. TMSCl, 41%. TMS = Me₃Si; Tf = CF₃SO₂.

Orienting experiments employed geometrically pure samples of (*Z*)- and (*E*)-**2** in the reaction with benzaldehyde and catalyst (*S,S*)-**5**. We were delighted to find that, by using just 5 mol % of catalyst, the aldehyde was consumed at -78°C within a few hours!^[14] Quenching the reactions under mildly basic conditions (THF/Et₃N/H₂O 18:1:1) afforded the hydroxy aldehydes **6a** in excellent yield and with extremely high diastereoselectivity (Scheme 3). However, these products were unstable and rapidly formed oligomers on standing.^[2, 15] Alternatively, quenching the reactions with dry methanol produced the stable dimethyl acetals **7a** in excellent yield and with similarly high diastereoselectivity. Although the enantioselectivities were poor (see below), the high yields and rigorous relative stereoselection encouraged us to optimize experimental variables and explore the scope of the reaction.

Optimization experiments employed a 78:22 mixture of (*E*)-**2** and (*Z*)-**2** with benzaldehyde and catalyst (*S,S*)-**5**. A brief examination of solvent and temperature revealed that a 4:1 blend of CHCl₃ and CH₂Cl₂ at -78°C gave faster and





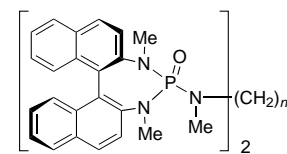
Scheme 3. a) PhCHO, (*S,S*)-**5** (0.05 equiv), CH₂Cl₂, –78 °C; b) THF, Et₃N, H₂O; c) MeOH.

cleaner reactions than CH₂Cl₂ alone. Surprisingly, the reaction rate, yield, and selectivity showed little sensitivity to concentration (0.1 to 1.0 M range) and catalyst loading (0.05 to 1.0 equiv). Accordingly, for the survey of catalyst structure, we employed the most convenient conditions of 0.25 M and only 0.05 equiv of catalyst.

From the wide range of chiral phosphoramides at our disposal^[16] several structural motifs were examined and although reactions were effectively catalyzed with excellent diastereoselectivity, the enantiomeric ratios were poor. In view of our recent demonstration that this aldolization process displays a second-order dependence on the phosphoramidate^[8] we investigated the use of alkyl linked bis-phosphoramides as promoters.^[17] Employment of dimeric versions of stilbene-1,2-diamine- and cyclohexyl-1,2-diamine derived cat-

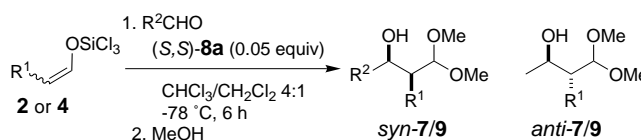
alysts were largely ineffective here. However, we were delighted to find that one structure, namely the dimeric 1,1'-binaphthyl-2,2'-diamine-derived phosphoramides **8a** uniquely gave excellent diastereomeric and enantiomeric selectivity. The homologous dimer **8b** was significantly less selective, which further illustrates the sensitivity of this reaction to catalyst structure.^[18]

With an optimized procedure in hand, we could evaluate the substrate generality of the crossed-aldol reaction with enolates **2** and **4** and a variety of aldehydes (Table 1). In all cases, the products were isolated and analyzed as the dimethyl acetals **7** and **9**. With the exception of aliphatic aldehydes as starting material, the aldol products were formed in near quantitative yields as analytically pure acetals. The diastereospecificity for all cases was a near perfect reflection of the geometrical composition of the trichlorosilyl enolate precursors.^[19] On the other hand, the enantioselectivity of the process was highly variable and dependent on both the enolate and the aldehyde structure.^[20, 21] For example, whereas the reaction of (*Z*)-**2** with benzaldehyde proceeded with very good enantioselectivity, (*E*)-**2** afforded *anti*-**7a** with somewhat attenuated *ee* (Table 1, entries 1 and 2). The effect of enolate structure was immediately apparent in the reactions of (*Z*)-**4** and (*E*)-**4** with benzaldehyde wherein the smaller size of the enolate lead to lower selectivities particularly for (*E*)-**4** (entries 3 and 4). The dependence of enantioselectivity on aldehyde structure was extensively investigated with aromatic, olefinic, acetylenic, and aliphatic aldehydes. In general, the enantioselectivity with



8a: *n* = 5, **8b**: *n* = 6

Table 1. Aldol reactions of **2** and **4**.^[a]



| Entry | Enolate | R ¹ | R ² | Product | Yield [%] ^[b] | <i>syn/anti</i> ^[c] | <i>ee</i> [%] ^[c] |
|-------|------------------------|----------------|--|-----------|--------------------------|--------------------------------|------------------------------|
| 1 | (<i>Z</i>)- 2 | <i>n</i> Pent | Ph | 7a | 92 | 99/1 | 90 |
| 2 | (<i>E</i>)- 2 | <i>n</i> Pent | Ph | 7a | 91 | 3/97 | 82 |
| 3 | (<i>Z</i>)- 4 | Me | Ph | 9a | 95 | 98/2 | 81 |
| 4 | (<i>E</i>)- 4 | Me | Ph | 9a | 97 | 1/99 | 59 |
| 5 | (<i>Z</i>)- 4 | Me | 2-naphthyl | 9b | 99 | 99/1 | 86 |
| 6 | (<i>E</i>)- 4 | Me | 2-naphthyl | 9b | 99 | 2/98 | 53 |
| 7 | (<i>Z</i>)- 4 | Me | 1-naphthyl | 9c | 97 | 98/2 | 54 |
| 8 | (<i>E</i>)- 4 | Me | 1-naphthyl | 9c | 97 | 2/98 | 70 |
| 9 | (<i>Z</i>)- 4 | Me | (<i>E</i>)-PhCH=CH | 9d | 86 | 99/1 | 42 |
| 10 | (<i>E</i>)- 4 | Me | (<i>E</i>)-PhCH=CH | 9d | 88 | 1/99 | 26 |
| 11 | (<i>Z</i>)- 4 | Me | (<i>E</i>)-PhCH=C(Me) | 9e | 91 | 97/3 | 68 |
| 12 | (<i>E</i>)- 4 | Me | (<i>E</i>)-PhCH=C(Me) | 9e | 89 | 1/99 | 90 |
| 13 | (<i>Z</i>)- 4 | Me | (<i>E</i>)-MeCH=CH | 9f | 85 | 99/1 ^[d] | 5 |
| 14 | (<i>E</i>)- 4 | Me | (<i>E</i>)-MeCH=CH | 9f | 91 | 2/98 ^[d] | 52 |
| 15 | (<i>Z</i>)- 4 | Me | PhC≡C | 9g | 98 | 98/2 | 7 |
| 16 | (<i>E</i>)- 4 | Me | PhC≡C | 9g | 99 | 2/98 | 76 |
| 17 | (<i>Z</i>)- 4 | Me | PhCH ₂ CH ₂ | 9h | 47 | 95/5 | 8 |
| 18 | (<i>E</i>)- 4 | Me | PhCH ₂ CH ₂ | 9h | 79 | 1/99 | 66 |
| 19 | (<i>Z</i>)- 4 | Me | <i>c</i> -C ₆ H ₁₁ | 9i | 42 | 97/3 ^[d] | 44 |
| 20 | (<i>E</i>)- 4 | Me | <i>c</i> -C ₆ H ₁₁ | 9i | 69 | 1/99 ^[d] | 19 |

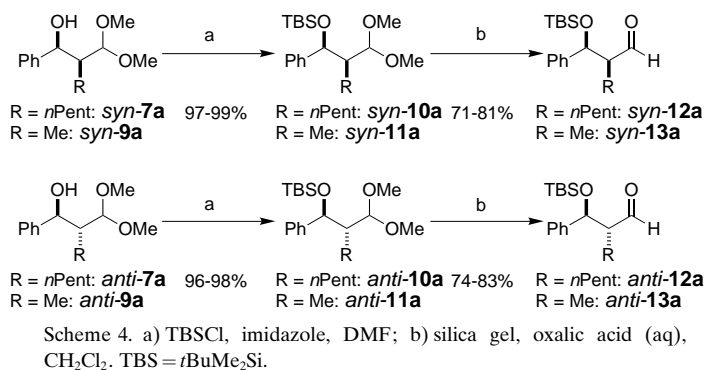
[a] All reactions run on 1.0 mmol scale. [b] Yield of analytically pure product. [c] Determined by CSP-SFC on Chiralpak columns. [d] Determined by CSP-SFC of the derived benzoates on Chiralpak columns.

aromatic aldehydes (entries 3–8) was good with the *syn* isomer giving slightly better results. In fact, *syn*-**9b** could be obtained in 66% yield and >99% *ee* after recrystallization. Curiously, 1-naphthaldehyde behaved differently in that the *anti* diastereomer was formed in higher *ee* than the *syn* isomer.

As a class, the unsaturated aldehydes gave overall disappointing enantioselectivities (with the significant exception of 2-methylcinnamaldehyde and (*E*)-**4**) and no trends were immediately apparent (entries 9–14). Here again, the enolate that exhibited the higher enantioselectivity was structure dependent and dramatically so in the case of (*E*)-2-butenal. This behavior was seen in the reaction of phenylpropynal as well. In this case, the *anti* isomer **9g** (from (*E*)-**4**) was formed with good enantioselectivity while *syn*-**9g** (from (*Z*)-**4**) was nearly racemic.

We were pleased to find that (*Z*)-**4** and (*E*)-**4** also reacted with enolizable aliphatic aldehydes although higher temperature (–25 °C) and longer reaction times (20 h) were required (entries 17–20). Hydrocinnamaldehyde reacted in moderate to good yield, but again, the divergence in behavior of the *Z* and *E* enolates is dramatic. Moreover, in the case of cyclohexanecarbaldehyde, (*Z*)-**4** afforded *syn*-**9i** with moderate selectivity whereas (*E*)-**4** now afforded *anti*-**9i** in poor enantioselectivity.

To demonstrate the synthetic utility of the acetals, we converted them to the TBS-protected aldehydes **12a** and **13a** in two high-yielding steps (Scheme 4). These products are stable, chromatographable, distillable liquids that could be obtained in analytically pure form without detectable epimerization.



In summary, we have documented the first catalytic enantioselective crossed-aldol reactions of aldehydes. Geometrically defined trichlorosilyl enolates of aldehydes undergo high yielding, diastereoselective additions to a wide range of aldehyde acceptors with good albeit highly variable enantioselectivity. The use of a dimeric chiral Lewis base as the catalyst was critical for achieving useful enantioselectivities. Extension of these studies to other aldehyde enolates and improvements in catalyst design are underway.

Received: August 15, 2001 [Z17734]

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- [19] The relative configuration of the products was assigned on the basis of the ³J_{HH} couplings in **7** and **9** which displayed the characteristic range of 1.7–3.4 Hz for the *syn* isomers and 6.8–8.8 Hz for the *anti* isomers (see Supporting Information).
- [20] The absolute configurations of *syn*-**9a** was assigned by conversion to methyl (–)-3-hydroxy-2-methyl-3-phenylpropanoate which has been unambiguously assigned as the (2*S*,3*S*)-isomer. a) T.-H. Yan, C.-W. Tan, H.-C. Lee, H.-C. Lo, T.-Y. Huang, *J. Am. Chem. Soc.* **1993**, *115*, 2613; b) C. H. Heathcock, C. T. White, J. J. Morrison, D. Van Derveer, *J. Org. Chem.* **1981**, *46*, 1296.
- [21] The absolute configuration of *anti*-**9a** was determined by conversion to (–)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-3-phenylpropanal which has been unambiguously assigned as the (2*R*,3*S*)-isomer. I. Paterson, D. J. Wallace, C. J. Cowden, *Synthesis* **1998**, 639. We thank Professor Paterson for providing detailed information.