The Chemistry of Trichlorosilyl Enolates. 6. Mechanistic Duality in the Lewis Base-Catalyzed Aldol Addition Reaction

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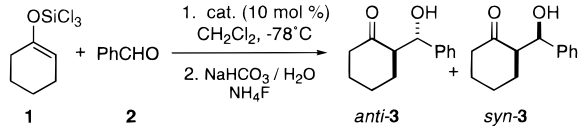
Received August 20, 1998

Recent disclosures from these laboratories have demonstrated the concept of Lewis base catalysis in asymmetric aldol additions[1] as illustrated in the reaction of trichlorosilyl enolates and aldehydes in the presence of a catalytic amount of chiral phosphoramides.[2] For example, trichlorosilyl enolate **1** reacts with benzaldehyde in very high enantio- and diastereoselectivity with 10 mol % of phosphoramide (*S*,*S*)-**4**, Scheme 1. On the basis of the geometry-dependent diastereoselectivity observed, these reactions are proposed to proceed via closed, chairlike transition structures organized about a hexacoordinate siliconate.[2b] We now report evidence in support of a mechanistic hypothesis that *a hexacoordinate, cationic silicon species with two chiral phosphoramide molecules is on the pathway from E-enolates to anti aldol products*.

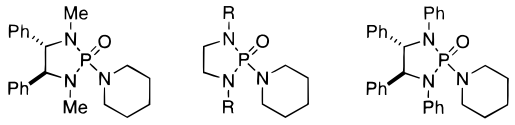
Scheme 1



Phosphoramide (*S*,*S*)-**4** dramatically accelerated the reaction in Scheme 1. In the absence of the catalyst the reaction between **1** and **2** was very slow; after 8 min at −78 °C only 2.3% conversion to the aldol product was detected by NMR (2% isolated). On the other hand, with 10 mol % of (*S*,*S*)-**4** the reaction proceeded to 100% conversion in 8 min at −78 °C (95% isolated).

To evaluate the effects of catalyst structure on rate and selectivity, we surveyed the series of achiral phosphoramides **5a**−**d** (Chart 1) with regard to their ability to promote the aldol process in Scheme 1. The results, Table 1, showed that increasing the bulk of the substituent had a dramatic effect on the diastereoselectivity of the reaction.

Chart 1



This intriguing switch of diastereoselectivity provided an important mechanistic insight when we discovered that it was also highly dependent on the catalyst loading. The syn/anti selectivity of the reaction between **1** and **2** catalyzed by **5c** decreased dramatically with increased loading of **5c**, Figure 1. The influence of the catalyst loading on selectivity is difficult to understand unless the reaction is viewed as proceeding by competitive pathways to the two diastereomers which respond differently to catalyst concentration. Since the anti diastereomer is prevalent with the less hindered catalysts (**4** and **5a**) as well as with **5c** at higher loadings, we postulated that this isomer arises from a pathway that involves *two* phosphoramide molecules. This pathway apparently proceeds through a chairlike transition structure on the basis of the $E \rightarrow$ anti correlation. If the syn diastereomer arises from an independent pathway that involves only one phosphoramide (consistent with its preferential formation from hindered catalysts and at low catalyst concentration), then the diastereomeric ratio could be loading dependent.[3]

To substantiate this proposition, we made use of nonlinear effects to identify a higher order molecularity of the catalyst in the pathway to the anti diastereomer.[4] The results with 10 mol % of **4**, shown in Figure 2 (●), clearly demonstrated a positive nonlinear effect and thus support the hypothesis of a transition structure with more than one phosphoramide molecule. These data fit very well with Kagan's two-ligand model,[4b] and assuming a

Table 1. Diastereoselectivity Dependence on Bulk of the N-Substituent in **5**[a]

phosphoramide	time, h	syn/anti[b]	yield,[c] %
5a	1.5	1/2.8	99
5b	6.0	27/1	93
5c	1.5	31/1	96
5d	1.5	40/1	95

[a] Reaction with 10 mol % **5** at −75 °C. [b] Determined by ^{1}H NMR analysis. [c] Isolated, purified product.

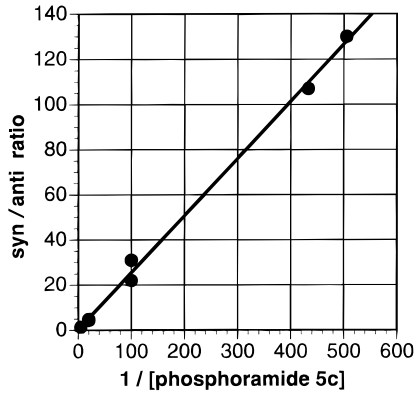


Figure 1. Loading dependence of selectivity.

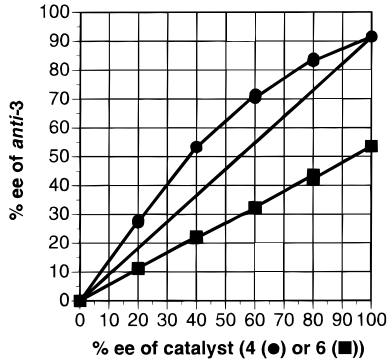


Figure 2. Ee dependence of catalysts **4** and **6**.

(1) For recent reviews see: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357 and referenced cited therein. (b) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. For recent advances, see: (c) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (d) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319.

(2) (a) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (b) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Org. Chem.* **1998**, *63*, 918. (c) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *Tetrahedron* **1998**, *54*, 10389.

(3) Given these divergent pathways and assuming one pathway is highly syn diastereoselective, we expect a linear relationship of syn/anti ratio with $[\mathbf{6}]^{-1}$ as seen in Figure 1, see Supporting Information for details.

10.1021/ja982993v CCC: $15.00
Published on Web 12/01/1998

Table 2. Conversion Dependence of Enantiomeric Purity[a]

entry	**2**, equiv	**4**,[b] equiv	time, s	conversion, %	yield,[c] %	*anti*-**3**, ee,[d] %
1	1.0	0.1	480	100	95	53.3
2	1.0	0.1	30	63	61	53.7
3	1.0	0.1	10	55	52	53.2
4	0.1	0.1	480	100	96	53.2
5	1.0	1.0	480	100	99	53.9

[a] Reaction of **1** and **2**, Scheme 1. [b] 40% ee catalyst used. [c] Isolated, purified product. [d] Determined by chiral stationary phase, supercritical fluid (CO_2) chromatographic analysis.

statistical distribution of the enantiomeric ligands, the calculated reaction rate of a homochiral catalyst assembly is about 3.6 times that of a meso catalyst assembly.

For this phenomenon to be responsible for the loading-dependent diastereoselectivity, the pathway to the syn diastereomer must have a different molecularity in catalyst. If the syn-selective pathway (for the *E*-enolate) proceeds through an intermediate with only one phosphoramide binding to silicon, then a linear relationship should exist between the ee of the syn aldol product and the ee of the catalyst. For this purpose we devised the hindered, phosphoramide **6** (Chart 1), and gratifyingly found that it was indeed a syn-diastereoselective catalyst, Scheme 1, albeit with still modest enantioselectivity.[5] Nevertheless, we could still make use of this compound for mechanistic purposes, and as clearly illustrated in Figure 2 (■), a linear relationship was in fact observed with an excellent correlation coefficient.

It is necessary to consider other factors that can give rise to a nonlinear dependence, such as the reservoir effect[4e] and interaction of the catalytic species with the forming product. We feel it is unlikely that phosphoramides are tightly aggregated in the ground state, but even if this were so, such an effect cannot explain the change of diastereoselectivity on the catalyst loading. In addition, if a reservoir effect were responsible for the observed nonlinear effect, then its magnitude should be catalyst concentration dependent. Comparison of entries 1 and 5 in Table 2 clearly shows that with **4** of 40% ee, the ee of *anti*-**3** is independent of catalyst concentration over a 10-fold range.

To rule out the possibility that the reaction product may be involved in the stereochemical determining step or in the nonlinear effect, we have examined the enantiomeric composition of the product as a function of conversion, Table 2. With the catalyst **4** of 40% ee, the conversion of the reaction after 10 s was 55% and the ee was essentially the same as at 100% conversion (entries 1 and 3). The reaction with 10 mol % **2** was employed to mimic the reaction at 10 mol % conversion and gave product *anti*-**3** with similar enantiomeric excess (entry 4). With 1 equiv of **4**, the possibility that one of the enantiomers of the phosphoramide may be selectively bound to the product to give rise to the nonlinear effects should be minimized and again essentially the same enantioselectivity was obtained. Taken together, these control experiments rule out other interpretations and support the hypothesis that two phosphoramide molecules in the transition structure are responsible for the nonlinear effects observed.

In our original formulation for the mechanism of this reaction we postulated pentacoordinate and hexacoordinate silicon intermediates for the unpromoted and promoted reactions, respectively.[2] This view must be modified for several reasons: (1) the simple change in coordination number or geometry at silicon cannot easily account for the dramatic rate acceleration the phosphoramide provides and (2) there must be a way to incorporate two phosphoramide molecules in the transition structure leading from **1** to the anti diastereomers. Both of the deficiencies with the earlier model can be accommodated if we posit the intermediacy of cationic silicon species, Figure 3.[6] Phosphoramide-promoted ionization of chloride to produce such a cationic silicon intermediate[7] would both explain the activation and allow for singly- (pentacoordinate, TBP) and doubly-(hexacoordinate, octahedral) complexed species.

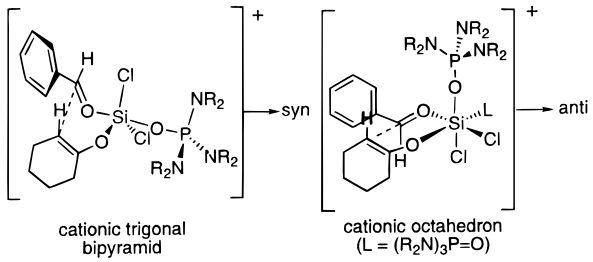


Figure 3. Penta- and hexacoordinate cationic silicon assemblies.

Thus, to probe the possibility of chloride ionization, we investigated the influence of various salts on the rate of the promoted aldol reaction. Catalyst **6** gave 44% conversion of **1** and **2** to the product *syn*-**3** with 53% ee after 8 min at −78 °C. In the presence of 1.2 equiv of $Bu_4N^+Cl^-$, the aldol addition was inhibited (8% conversion (26% ee)), while in the presence of an equivalent amount of $Bu_4N^+OTf^-$ the reaction was accelerated (92% conversion (55% ee)). These results are fully consistent with the hypothesis of prior ionization of the enolate **1** by the action of phosphoramides. The resulting cationic silicon species should have much higher Lewis acidity than **1** itself to activate the aldehyde for nucleophilic attack. Accordingly, $Bu_4N^+Cl^-$ inhibited the ionization of **1** through the common ion effect,[8] whereas the triflate facilitated the ionization by increasing the ionic strength of the medium.[9]

In summary, we have demonstrated that the origin of the rate acceleration in the aldol addition reactions between trichlorosilyl enolates and aldehydes stems from the ionization of the enolate promoted by the phosphoramides. Sterically demanding phosphoramides bind to the enolate in a 1/1 fashion and the resulting pentacoordinate cationic siliconate favors a boatlike arrangement. Sterically less demanding phosphoramides can bind in a 2/1 fashion, and the resulting hexacoordinate cationic siliconate favors a chairlike arrangement. Further development of highly enantioselective catalysts and studies of the reaction kinetics are underway.

Acknowledgment. We are grateful to the National Science Foundation for generous financial support (CHE 9500397 and 9803124). Y.N. thanks the Ministry of Science and Education of Japan for a postdoctoral fellowship. We thank Mr. R. A. Stavenger for stimulating discussions.

Supporting Information Available: Procedures for the preparation and full characterization of **5a**−**d** and **6** and representative procedures for aldol addition reactions and nonlinear effect studies and kinetic analysis of nonlinear effects and loading effects (17 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(4) Nonlinear effect: (a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353. (b) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430. (c) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997. (d) Kagan, H. B.; Fenwick, D. *Top. Stereochem.* **1999**, in press. Reservoir effect: (e) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800.

(5) The absolute configuraion of (−)-*syn*-**3a** was determined to be (2*S*,1′*S*) by X-ray crystal structure analysis of the 4-bromobenzoate ester.

(6) Cationic silicon species have been proposed as intermediates in other Lewis base-promoted reactions, see: (a) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428. (b) Chojnowski, J.; Cypryk, M.; Michalski, J.; Wozniak, L. *J. Organomet. Chem.* **1985**, *288*, 275. (c) Corriu, R. J. P.; Dabosi, G.; Martineau, M. *J. Organomet. Chem.* **1980**, *186*, 25. (d) Bassindale, A. R.; Lau, J. C.-Y.; Taylor, P. G. *J. Organomet. Chem.* **1995**, *490*, 75. (e) Bassindale, A. R.; Lau, J. C.-Y.; Taylor, P. G. *J. Organomet. Chem.* **1995**, *499*, 137.

(7) Berrisford and co-workers have recently postulated that Lewis bases promote the ionization of allyltrichlorosilanes. Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351. See also: Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6419.

(8) (a) Bateman, L. C.; Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1940**, 974, 1017. (b) Streitwieser, A. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962. (c) Thornton, E. *Solvolysis Mechanisms*; Ronald Press: New York, 1964.

(9) This result is in contrast to the observations made by Berrisford et al. in the allylation reactions.[7a] We cannot rule out the inhibition of reaction by chloride ion serving as a competitive ligand for the trichlorosilyl enolate.