On the Mechanism of Catalytic, Enantioselective Allylation of Aldehydes with Chlorosilanes and Chiral Lewis Bases

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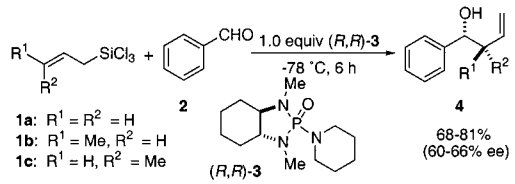
The enantioselective addition of allylmetal reagents to aldehydes is now well established as a powerful and general method for stereoselective carbon−carbon bond formation.[1] One of the more useful variants to emerge in recent years is the Lewis-base promoted addition of allyl- and crotyltrihalosilanes.[2,3] In 1994, the first example of enantioselective addition of allylic trichlorosilanes by the use of chiral phosphoramides was disclosed from these laboratories, Scheme 1.[4] Since then, a number of groups

Scheme 1



have reported enantioselective additions promoted by chiral phosphoramides,[5a,b] formamides,[5c,d] and *N*-oxides,[5e] ureas,[5f] and diamines.[5g] Despite significant efforts at improving the enantioselectivity by empirical modification of the promoter structure, a clear mechanistic picture for the origin of rate acceleration and stereoselection is still lacking. Our ongoing investigations on the related reactions of trichlorosilyl enolates have revealed divergent pathways involving both first- and second-order dependence on catalyst and the intermediacy of cationic chlorosiliconate species.[6] We now provide kinetic, stereochemical, and structural evidence in support of a similar pathway operating in the allylation process.

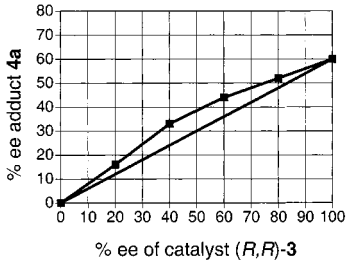


Figure 1. Plot of ee dependence of allylation as a function of ee catalyst.

In our preliminary disclosure[4] we noted that at reduced catalyst loadings the enantioselectivity eroded despite the lack of a competitive, uncatalyzed component under the reaction conditions.[7] This suggested the possibility that a the reaction could proceed by a pathway involving two phosphoramides bound to the chlorosilane along with a less selective pathway involving only one catalyst molecule. To gain support for this hypothesis, we made use of the powerful method, pioneered by Kagan, of asymmetric amplification by nonlinear effects.[8] The results of this study, graphically depicted in Figure 1, clearly demonstrate a modest ($g = 0.46$), but real, positive nonlinear effect.[9] The observed asymmetric amplification is interpreted as arising from the presence of two molecules of (*R*,*R*)-**3** in the stereochemically determining transition structure.[10]

To establish if the both phosphoramide molecules were also present in the rate-determining step, we determined the overall rate expression and order in each component. Toward that end the kinetic parameters of the allylation were determined by in situ monitoring of the consumption of benzaldehyde by the use of a ReactIR 1000 instrument.[11] Order in benzaldehyde was established by using a large excess of **1a** (10 equiv) and 1 equiv of (*R*,*R*)-**3**. Plotting −ln[benzaldehyde] versus time gave a straight line ($R^2 = 0.9984$), thus establishing first-order dependence in aldehyde.[12a] Order in **1a** was established indirectly by determining the overall reaction order at equimolar concentration. For this experiment, a plot of [benzaldehyde]$^{-1}$ versus time gave a straight line ($R^2 = 0.9986$), indicating that the reaction is overall second order[12b] and therefore first order in **1a**.

The reaction order in phosphoramide was established by determining the kinetic rate constants at various promoter concentrations (at −78 °C). For these experiments equimolar amounts of **1a** and benzaldehyde were used at catalyst loadings of 50−400 mol %. A ln/ln plot of the second-order rate constants (ln(k_{obs})) versus the catalyst concentration (ln[(*R*,*R*)-**3**]) gave a straight line ($R^2 = 0.9987$) with a slope of 1.77.[13] Clearly the reaction displays a higher-order dependence on catalyst. The reason that the order

(1) For recent reviews of allylmetal additions see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J.; Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10. (b) Roush, W. R.; Chemler, C. R. In *Modern Carbonyl Chemistry*; Otera, J.; Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11. (c) *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*; Edition E21; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3; pp 1357−1602. (d) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(2) (a) Sakurai, H. *Synlett* **1989**, 1. (b) Sakurai, H. In *Proceedings of the 5th International Kyoto Conference on New Aspects of Organic Chemistry*; Yoshida, Z.-I., Ohshiro, Y., Eds.; Kodansha Press, 1992; pp 129−157 and references cited therein. (c) Kira, M.; Zhang, L.; Kabuto, C.; Sakurai, H. *Organometallics* **1996**, *15*, 5335.

(3) (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453. (b) Kobayashi, S.; Nishio, K. *Synthesis* **1994**, 457. (c) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620. For additions to hydrazones, see: (d) Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942. For propargylation, see: (e) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *118*, 6392.

(4) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.

(5) (a) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett.* **1996**, *37*, 5149. (b) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513. (c) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767. (d) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977. (e) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (f) Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 3633. (g) Angell, R. M.; Barrett, A. G. M.; Braddock, D. C.; Swallows, S.; Vickery. B. D. *J. Chem. Soc., Chem. Commun.* **1997**, 919.

(6) (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (b) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982. (c) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990. (d) Denmark, S. E.; Pham, S. M. *Helv. Chim. Acta* **2000**, *83*, 1846.

(7) With 10 mol % of (*R*,*R*)-**3**, only 53% ee was obtained.

(8) (a) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430. (b) Fenwick, D.; Kagan, H. B. *Top. Stereochem.* **1999**, *22*, 257. (c) Girard, G. L.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (d) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997. (e) Kitamura, N.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (f) Kitamura, N.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800.

(9) To support the operation of the "two-ligand model", we had to rule out the possibility that the nonlinear dependence was not arising from a reservoir effect[8e,f] or by interaction of the catalyst with the forming product. Both of these alternative interpretations could be eliminated experimentally. See Supporting Information for details.

(10) Iseki et al. have also demonstrated a nonlinear effect in allylation with **1a** and a chiral formamide.[5d] However, these experiments were done in the presence of 2 equiv of HMPA, and the alternative interpretations were not ruled out. Curiously, these workers nevertheless propose a transition structure with only one chiral promoter bound to silicon.

(11) ReactIR 1000 fitted with a 5/8" DiComp Probe, running software version 2.1a. ASI Applied Systems, Inc., 8223 Cloverleaf Drive, Suite 120, Millersville, MD 21108.

(12) (a) A second-order plot was clearly not linear. (b) A third-order plot was clearly not linear.

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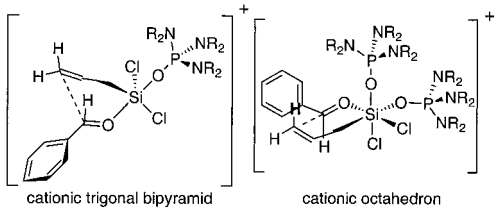
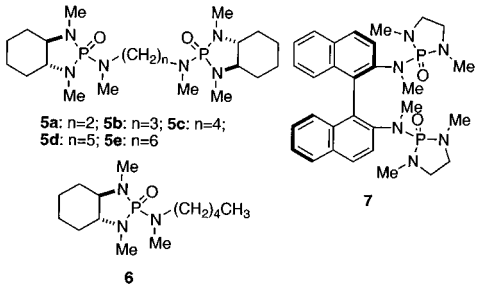


Figure 2. Penta- and hexacoordinate cationic silicon assemblies.

Chart 1



is less than 2.0 may very well be due to the intervention of competing pathways involving both one and two phosphoramides.

The demonstration of a nonlinear effect and higher-order dependence on phosphoramide requires that the trichlorosilane undergo ionization of a chloride to accommodate all of the components in a hexacoordinate array. Such ionization has been demonstrated in the analogous aldolizations[6c] and has been proposed for allylation and epoxide opening.[5e,14] The simultaneous operation of both mono- and diphosphoramide pathways provided a unique explanation for the less than spectacular enantioselectivities obtained in Lewis base-catalyzed allylations. Generalized, hypothetical transition structures for both pathways (Figure 2) clearly show how the monophosphoramide pathway, if operative through a trigonal bipyramidal pentacoordinate siliconate, would be less enantioselective than a diphosphoramide pathway involving an octahedral hexacoordinate siliconate due to the diminished influence of the singular chiral promoter in the former.[15]

The implications of the dual pathway hypothesis for the rate and selectivity in asymmetric catalysis are significant. First, since the reaction is second order in catalyst, the rate of reaction falls off as the square of catalyst concentration. Second, at lower catalyst loadings, a competing, less selective pathway can compromise overall reaction selectivity. We envisioned the utilization of bisphosphoramides of the general structure **5** (Chart 1) to address these problems by increasing the effective concentration of the second catalyst molecule through approximation. Although prior studies in these laboratories, provided a good notion of the geometric requirements to accommodate cis coordination by phosphoramides[15] it was difficult to predict a priori, the ideal type and length of linker to best connect to two participating functions. Accordingly, a family of bisphosphoramide catalysts of varying tether length was prepared and evaluated for their ability to promote enantioselective allylation of benzaldehyde. Monophosphoramide **6** was also prepared to mimic the behavior of compounds **5** if they bound in only a monodentate fashion.

The results of the allylation with bisphosphoramides are collected in Table 1. Because compounds **5** are bisphosphoramides,

Table 1. Allylation with **1a** Promoted by Bisphosphoramides[a]

entry	promoter	tether, *n*	equiv	ee, %	yield, %	entry	promoter	tether, *n*	equiv	ee, %	yield, %
1	**5a**	2	0.5	0	60	8	**6**	-	1.0	51	73
2	**5b**	3	0.5	35	72	9	(*R*,*R*)-**3**	-	1.0	60	81
3	**5c**	4	0.5	17	82	10[b]	(*R*,*R*)-**3**	-	0.1	53	40
4	**5c**	4	0.1	10	52	11	**7**	-	0.1	80	49
5	**5d**	5	0.5	65	78	12[c]	**7**	-	0.1	80	67
6	**5d**	5	0.1	72	54	13[c]	**7**	-	0.5	80	76
7	**5e**	6	0.5	46	75	14[c]	**7**	-	0.05	79	43

[a] Reaction done at 1.0 M concentration at −78 °C for 6 h using 100% ee catalysts. [b] Reaction time, 24 h. [c] 5.0 equiv of *i*-Pr_2EtN was added to assist in reaction turnover.

0.5 equiv was used for comparison to (*R*,*R*)-**3**. The dependence of the product ee on the linker length was striking. A dramatic increase in ee was seen in the change from **5c**, where the ee of the product was only 17%, to **5d**, wherein the ee was 65%. The ee decreased again to 46% when **5e** was used. This behavior implies a cooperativity of binding with bisphosphoramides, since if there were no chelation with silicon, the ee of **5** would be chain-length independent and similar to that obtained with **6**. The lower selectivity obtained with promoter **5c** may have its origin in the detailed geometric consequences of binding. It is likely that **5c** is able to chelate with silicon; however, the phosphoramide groups may be constrained into an unfavorable arrangement due to the dictates of tether length and flexibility.[15b]

In the allylation promoted by the bisphosphoramides **5a**−**e**, there are three possible competing pathways: (a) only one phosphoramide coordinated to silicon in the transition structure, (b) two phosphoramides (nonchelated) bound in the transition structure, and (c) one molecule of phosphoramide intramolecularly chelated to silicon. The reaction rate of the pathway (b) is second order in phosphoramide concentration, while the rates of pathways (a) and (c) are first order in phosphoramide concentration. Since the enantioselectivity of these three pathways may be different, the product ee would be concentration-dependent. Accordingly, the dependence of the product ee on the promoter loading (concentration) was studied with **5c** and **5d** because these promoters gave the lowest and highest ee, respectively. Entries 3−6 in Table 1 show that when the loading of **5c** was decreased to 0.1 equiv, the ee of the product obtained also decreased from 17 to 10%. On the other hand, a similar lowering of the loading of **5d** brought about an increase in the ee of the product from 65 to 72%. The result with **5d** as the promoter was opposite to the reaction promoted by monophosphoramide (*R*,*R*)-**3** in which the ee decreased using a lower loading of the promoter. From these observations we conclude that both **5c** and **5d** are able to chelate to silicon, but with very different consequences.[16]

With the knowledge that a four- or five-unit tether is required for a bisphosphoramide to chelate with silicon, we prepared binaphthyldiamine-derived promoter **7**. We were pleased to find that allylation promoted by **7** afforded to 80% ee with only 10 mol % of **7** and that the ee was independent of the promoter concentration (Table 1, entries 11−14). This provides additional support for our hypothesis that **7** is able to chelate to silicon.

In summary, the mechanism of nucleophilic catalysis in asymmetric allylations with chiral phosphoramides has been clarified. Since the reactions most likely to proceed through closed transition structures involving hexacoordinate, cationic siliconates, modification of promoter structure to improve selectivity can be rationally based.

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Supporting Information Available: Preparation and full characterization of **5a**−**e**, **6**, and **7,** all homoallylic alcohols, a representative allylation procedure and all kinetic data are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A plot of k_{obs} versus [(*R*,*R*)-**3**]^2 gave a straight line (R^2 = 0.9987). See Supporting Information for plots.

(14) (a) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351. (b) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428.

(15) (a) The proposal of a cis-configured octahedron is supported by our crystallographic and solution NMR studies on complexation of $SnCl_4$ with phosphoramides. Denmark, S. E.; Su, X. *Tetrahedron* **1999**, *55*, 8727. (b) ^{31}P and ^{119}Sn NMR studies on complexation of **5c** with $SnCl_4$ support the contention that, for this Lewis acid, a chelated complex is highly favored, e.g,. $^{1}J_{Sn-P}$ = 141 Hz.

(16) Spectroscopic and X-ray crystallographic studies on complexation of these phosphoramides $SnCl_4$ support the conclusion that chelation is occurring.