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# Asymmetric Catalysis of Aldol Reactions with Chiral Lewis Bases

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**ABSTRACT**

In an extension of studies both on the stereochemical course of the aldol addition and on Lewis-base-catalyzed allylation reactions, we have invented a new Lewis-base-catalyzed asymmetric aldol addition. This Account outlines the conceptual development, the identification of design criteria, and the underlying principles for such a process. The reduction of these elements to practice in the demonstration of enantioselective aldol additions of trichlorosilyl enolates catalyzed by chiral phosphoramides is also presented. From a combination of stereochemical, kinetic, and structural studies, an intriguing mechanistic hypothesis is forwarded that explains the origin of catalysis and diastereoselectivity.

> "*...with complete generality we may say that a basic substance is one which has a lone pair of electrons which may be used to complete the stable group of an other atom, and that an acid substance is one which can employ a lone pair from another molecule in completing the stable group of one of its own atoms...*" — Gilbert N. Lewis (1923)[1]

## Introduction

The invention and development of catalytic enantioselective reactions is among the most challenging and intensively studied frontiers in organic synthesis. The chronicles of this enterprise have been compiled in a recent and comprehensive treatise.[2] The achievement of highly selective, catalytic, asymmetric processes represents the pinnacle of methodological engineering and synthetic efficiency. Central to the success of this endeavor is the design and optimization of the catalyst. Nearly all nonenzymatic catalysts for asymmetric organic synthesis can be assigned to one of two categories: (1) those involving transition metals and their associated ligands and (2) those involving "purely" organic or organoelement structures. By far the majority of the second group can be classified under the rubric of chiral Lewis acid catalysts. This class of reagents has dominated the field of non-transition metal asymmetric catalysis for several decades.[3] Some of the reasons are obvious: Lewis acids display a powerful and reasonably well-understood activating function for a wide range of organic reactions, and, if properly designed, can lead to exquisite selectivity. A corollary to this is the ability of many common organic functional groups to interact with Lewis acidic species; this interaction can result in activation of the substrate to nucleophilic attack by electron-rich species. Stated differently, Lewis acid activation is pervasive because most organic reactions occur on unsaturated functions which are inherently electron rich and can therefore productively associate with electrophilic agents.

Why, then, have Lewis bases not enjoyed the same widespread utility that Lewis acids have as reagents or catalysts in modern asymmetric synthesis? One certain reason is that, as stated above, typical organic compounds possess few functions that can productively interact with Lewis bases.[4] However, some organic systems, especially certain organoelement assemblies, are well suited for activation by Lewis bases.[5] One such class of compounds, organosilanes, are known to access hypercoordinate states in the presence of nucleophiles, and these hypercoordinate species often exhibit enhanced reactivity.[6] Intrigued by the underexploited potential of this phenomenon, we formulated a program to manifest the unique advantages of Lewis base activation in the invention of a new catalytic, enantioselective aldolization process.

## Why a New Aldolization Process?

At the inception of this project we could identify two basic families of asymmetric aldol addition reactions.[7] The first (and most synthetically useful) employs auxiliary-modified enolates in which the chiral appendage is attached through an acyl linkage or directly around the metal of the enolate.[8] Despite the widespread use of these general and selective reagents, they do suffer from the disadvantage that they must be used in stoichiometric quantities. The second family is based on the well-known Mukaiyama directed-aldol addition reaction of enoxysilanes in combination with aldehydes activated by chiral Lewis acids.[9] These variants of the aldol reaction can proceed with a substoichiometric loading of the chiral Lewis acid, but the diastereoselectivity and enantioselectivity are variable and dependent on the structure of the reactants. Importantly, the stereochemical course is independent of the configuration of the enolsilane nucleophile.

To address the deficiencies in these two families, we envisioned the invention of a conceptually new aldol addition which embodied both the selectivity and the versatility of the stoichiometric reactions combined with the efficiency of the catalytic methods. We felt that Lewis

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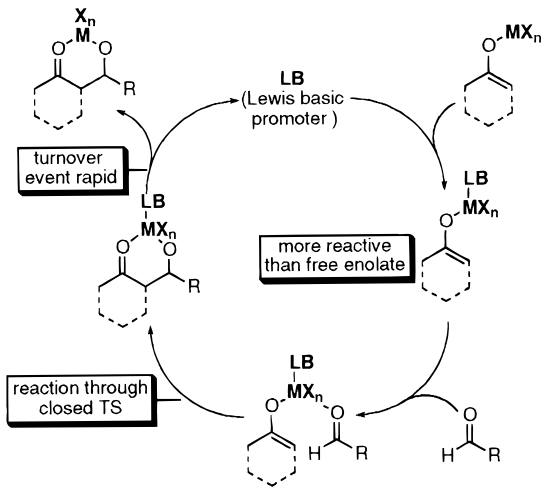
base activation could potentially provide the opportunity to devise this new class of aldol reactions which would be a valuable addition to the above methods. In this Account we describe our efforts in the formulation, development, and understanding of this new process.

## Phosphoramide-Catalyzed Aldol Additions of Chlorosilyl Enolates

**Reaction Design.** The challenges that face the development of Lewis basic catalysis of the aldol addition are outlined in Scheme 1. Our design postulated activation of the enoxymetal derivative by preassociation with a chiral Lewis basic group (LB) bearing a nonbonding pair of electrons. The resulting ate complex must be more reactive than the free enolate for the ligand-accelerated catalysis to be observed.[10] Next, association of this (still Lewis acidic) ate complex with the Lewis basic carbonyl oxygen of the aldehyde produces a hyper-reactive complex in which the metal has expanded its valence by two. It is expected that this association complex between enolate, aldehyde, and the chiral Lewis basic group reacts through a closed-type transition structure to produce the metal aldolate product. For turnover to be achieved, the aldolate must undergo the expulsion of the LB group with the formation of the chelated metal aldolate product. *Thus, Lewis base catalysis involves simultaneous activation of the nucleophile and the electrophile within the coordination sphere of the metal. The reaction must take place in a closed array and be capable of releasing the activating group by chelation or change in the Lewis acidity.*

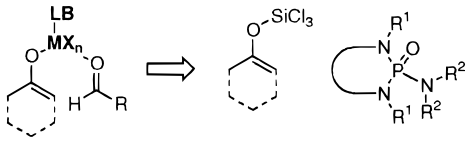
**Scheme 1**




To invent such a process, one must carefully select the appropriate enoxymetal and activator moieties. For the metal, the $MX_n$ subunit must be able to expand its valence by two and balance the nucleophilicity of the enolate with electrophilicity to coordinate both the Lewis basic aldehyde and the chiral LB group. To impart sufficient Lewis acidity to that metal group and accommodate the valence expansion such that two Lewis basic atoms may associate, the ligands (X) should be small and strongly electron withdrawing. The chiral Lewis basic group LB must be able to activate the addition without cleaving the $O-MX_n$ linkage and provide an effective asymmetric environment. Candidates for the Lewis basic group would include species with high donicity properties as reflected in solvent basicity scales.[11]

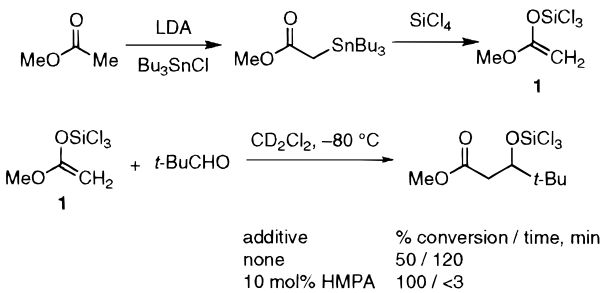
Thus, to reduce the plan to practice, we envisioned the use of a new class of aldol reagents, trichlorosilyl enolates, in conjunction with one of the most Lewis basic neutral functional groups, the phosphoramides (Scheme 2). Trichlorosilyl enolates of esters and ketones had been reported in the literature[12] and (due to the electron-withdrawing chloride ligands on silicon) were expected to be highly electrophilic, and thus able to stabilize the hypervalent silicon species[6] necessary in such a process. The phosphoramides can be seen as chiral analogues of hexamethylphosphoric triamide (HMPA), the Lewis basicity of which is well documented,[13] especially toward silicon-based Lewis acids.[14]

**Scheme 2**



**Reaction Discovery: Ester Enolates.** The trichlorosilyl enolate of methyl acetate had been reported by Baukov (from a transmetalation of the α-stannyl ester with $SiCl_4$ (Scheme 3)) and thus provided a logical starting point for our investigations.[12b] Given the very low nucleophilicity of allyltrichlorosilane compared to allyltrimethylsilane,[15] we expected this enolate to be relatively unreactive toward aldehydes, thus possessing high potential for acceleration and catalysis. We quickly became calibrated on the reactivity of these species when we discovered that the reaction of **1** with benzaldehyde is complete within minutes at −80 °C in the absence of external promoters.[16] More useful and exciting information came from low-temperature NMR studies with pivalaldehyde, which is a slower reacting substrate in this uncatalyzed aldol process. A series of low-temperature NMR experiments demonstrated that HMPA dramatically and catalytically accelerated the addition of the trichlorosilyl ketene acetal to pivalaldehyde (Scheme 3).

**Scheme 3**

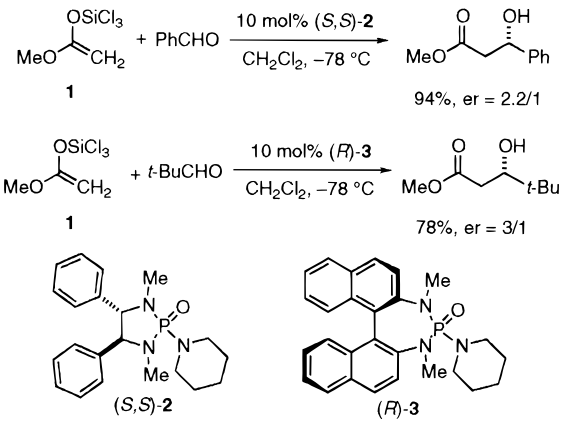



| additive | % conversion / time, min |
|---|---|
| none | 50 / 120 |
| 10 mol% HMPA | 100 / <3 |

Delighted that aldol addition with **1** was susceptible to Lewis base catalysis, we quickly turned our attention to a survey of chiral phosphoramide structures as potential

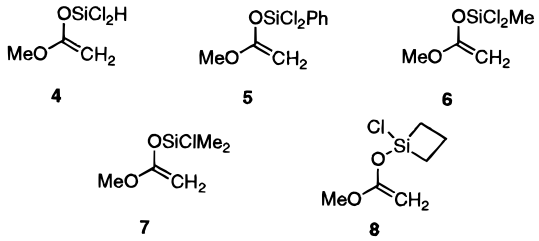
asymmetric catalysts. Many chiral phosphoramides can be prepared from chiral diamines such as, inter alia, stilbene-1,2-diamine, cyclohexane-1,2-diamine, 1,1′-binaphthyl-2,2′-diamine, and 2-(aminomethyl)pyrrolidine.[17] Under optimized conditions for catalysis, the most selective agents **2** and **3** afforded only moderate enantioselectivity (2.2/1−3/1 er, Scheme 4), even for the slow-acting aldehydes. A full equivalent of the phosphoramide promoter did provide slightly higher selectivity, hinting at a competitive background reaction.

**Scheme 4**




Several other acetate−enolates (Chart 1) adorned with various substituents on the silicon were synthesized[12a] to investigate the influence of the spectator groups on the ratio of catalyzed and uncatalyzed pathways.[18] Reactions of enolates **4**, **5**, and **6** are all accelerated by HMPA, whereas those of enolates **7** and **8** are not. Thus, we learned that at least three electronegative groups on silicon (including the enoxy substituent) are required for catalysis to take place. This seemed reasonable, as it is known that for silicon species to attain a hexacoordinate state (as required by our mechanistic postulate) several electronegative groups are required.[19]

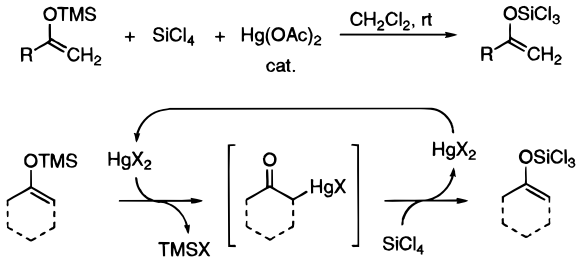
**Chart 1**




In addition, though the ratio of rates of promoted compared to unpromoted processes was now clearly very large in some cases, enantioselectivities with many chiral phosphoramides were still modest at best, none, in fact, surpassing the results obtained with the trichlorosilyl ketene acetal **1** originally investigated. We feared that perhaps the intrinsic facial selectivity of such a process with only single-point binding of the phosphoramide simply would not be high. Fortunately, ongoing parallel studies with ketone-derived enolates would prove that facial selectivity in this reaction could be very high. These substrates also provided a window to study the origin of catalysis and stereoselectivity.

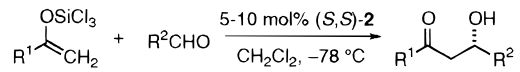
**Reaction Development: Ketone Enolates.** Though we were pleased that the investigations with the ester enolates provided a proof of principle, the general and selective reactions we had originally hoped for had thus far eluded us. We therefore began to examine ketone-derived trichlorosilyl enolates starting with the simpler methyl ketone substrates. The initial preparation of these enolates mirrored the useful though cumbersome procedure used previously, via the α-stannyl carbonyl compounds. A more efficient and general method of enolate synthesis was developed which employed a mercury(II)-catalyzed transsilylation[12a] of readily available trimethylsilyl enol ethers into the desired trichlorosilyl enolates (Scheme 5). An added feature of this method is the ability to generate the enolates in situ and obviate the isolation and handling of these reactive intermediates.

**Scheme 5**




The trichlorosilyl enolates of simple methyl ketones were first to be evaluated.[20] Control studies indicated that these enolates were significantly less reactive than their ester analogues, with essentially no reaction taking place at −78 °C. Even at room temperature, several hours were required to provide full conversion with no external promotion. To our delight, these reactions displayed dramatic rate enhancements in the presence of chiral phosphoramides; complete conversion could be obtained in only 2 h at −78 °C with a few percent of the catalyst. The stilbenediamine-derived phosphoramide **2** again proved to be the most stereoselective catalyst, and, in contrast to earlier studies, these reactions proceeded with satisfying enantioselectivity, up to 24/1 er (Table 1). In addition, the reaction proved rather general, though enolates derived from bulky or aromatic ketones provided only moderate levels of enantioinduction.

**Table 1. Catalytic Enantioselective Aldol Additions of Methyl Ketone Enolates**

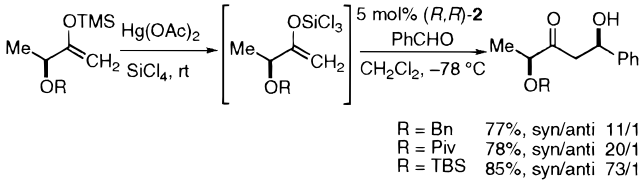



| $R^1$ | enolate | $R^2$ | mol % (*S*,*S*)-**2** | er | yield, % |
|---|---|---|---|---|---|
| Me | **9** | Ph | 5 | 14.6/1 | 98 |
| *t*-Bu | **10** | Ph | 5 | 3.2/1 | 95 |
| Ph | **11** | Ph | 5 | 2.9/1 | 93 |
| *n*-Bu | **12** | (*E*)-CH=CHPh | 5 | 11.5/1 | 94 |
| *n*-Bu | **12** | *c*-$C_6H_{11}$ | 10 | 17.5/1 | 79 |
| *n*-Bu | **12** | *t*-Bu | 10 | 24.0/1 | 81 |

An important practical feature of this transformation is that common protecting groups are fully compatible,

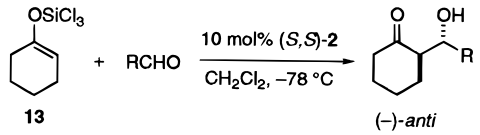
owing to the mildness of $SiCl_4$ and the reaction conditions overall. In addition, isolation and purification of the trichlorosilyl enolates can be avoided by generating and using them in the same reaction flask. Both of these useful characteristics were demonstrated in the diastereoselective additions of lactate-derived methyl ketone TMS enol ethers.[21] We found that with the (*R*,*R*)-enantiomer of phosphoramide **2**, very high 1,4-syn diastereoselectivity can be obtained in a "matched" double-stereodifferentiation manifold (Scheme 6).

**Scheme 6**




Encouraged by our success with methyl ketone enolates, we were able to test one of our original hypotheses: that these reactions proceed through closed transition structures, leading to predictable control over the relative diastereoselection event. Initial studies were conducted with geometrically defined trichlorosilyl enolates derived from cyclohexanone and propiophenone.[22] The cyclohexanone derivative **13** was much more reactive than the corresponding methyl ketone-derived enolates, providing up to 19% conversion with benzaldehyde after 2 h at −78 °C compared with 4% for enolate **12** under similar conditions. Gratifyingly, (*S*,*S*)-**2** catalyzed the reaction with benzaldehyde to provide aldol adducts in excellent yield (93%) and diastereoselectivity favoring the anti isomer (49/1); the anti diastereomer was formed in 24/1 er. The examples in Table 2 show that, with this catalyst, most aldehyde structures reacted with exceptionally high anti selectivity and that the anti products were obtained in high enantioselectivity. Unfortunately, aliphatic aldehydes proved incompatible with this system, presumably due to competitive enolization.

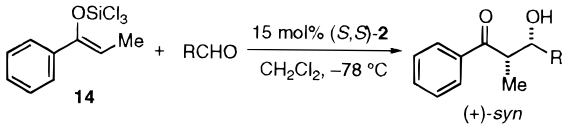
**Table 2. Catalytic Enantioselective Aldol Additions of Cyclohexanone Enolate**




| R | syn/anti | er, anti | yield, % |
|---|---|---|---|
| Ph | 1/49 | 27.6/1 | 95 |
| 1-Naphthyl | 1/99 | 65.7/1 | 94 |
| (*E*)-CH=CHPh | 1/99 | 15.7/1 | 94 |

The formation of anti aldols from an *E*-configured enolate is indicative of a chairlike transition structure, as we had initially expected. This supposition was confirmed by analogous reactions with the propiophenone-derived enolate (**14**, *Z*-configured) with 15 mol % of (*S*,*S*)-**2** as the catalyst. As predicted, these additions exhibited syn diastereoselectivity, wherein the syn adducts were formed with very high enantioselectivity (Table 3). These studies support the contention that the reaction takes place though a closed, chairlike transition structure and affords excellent diastereo- and enantioselectivities with single-point binding of the chiral catalyst.

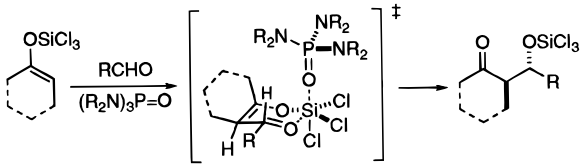
**Table 3. Catalytic Enantioselective Aldol Additions of Propiophenone Enolate**




| R | syn/anti | er, syn | yield, % |
|---|---|---|---|
| Ph | 18/1 | 39/1 | 95 |
| 1-Naphthyl | 3/1 | 11.5/1 | 96 |
| (*E*)-CH=CHPh | 9.4/1 | 24.0/1 | 97 |

On the surface, the new invention was behaving as anticipated. We had documented the viability of Lewis base catalysis and believed that the rate acceleration was due to the dual activation of the enol and aldehyde in close proximity. The relative stereoinduction could be viewed in terms of a ternary assembly wherein aldehyde, Lewis base, and enolate are arranged in a hexacoordinate constellation about the silicon atom (Scheme 7).[23] We were content that various precedents from the silicon literature provided enough support for this proposal, though the degree of acceleration seemed dramatic. Furthermore, we still had little understanding how such simple single-point binding could provide the highly dissymmetric environment which induced such high facial selectivities.

**Scheme 7**



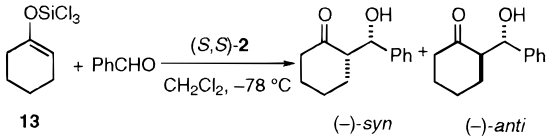

As is often the case in research, we began to accumulate a number of observations (as part of the synthetic optimization) which could not be explained through the simple model above. Several experiments performed at this point started us on a related journey, to understand the mechanism and origin of stereoselection in this aldolization process.

## Toward an Understanding of Mechanism and Stereocontrol

One of the first clues to the true molecular process at work was found during simple reaction optimization studies directed at lowering the catalyst loading in the benchmark reaction, i.e., of cyclohexanone-derived enolate **13** and benzaldehyde. Interestingly, under appropriate conditions, as the catalyst loading was reduced the process became more syn selective, though it still favored the anti isomers, even at 0.5 mol % (Table 4). The appearance of synisomers from *E*-configured enolates implied the intervention of boatlike transition structures.

The truly startling aspect of the trend was that although the diastereomeric ratio changed dramatically (suggesting

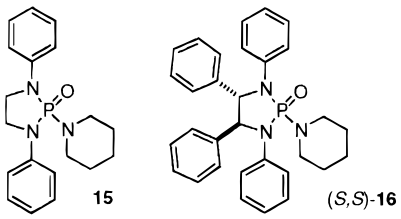
**Table 4. Catalyst Loading Effect with Slow Addition of Benzaldehyde**




| mol % (*S*,*S*)-**2** | syn/anti | er, syn | er, anti | yield, % |
|---|---|---|---|---|
| 10 | 1/>50 | 1.4/1 | 21.2/1 | 94 |
| 2 | 1/28 | 1.07/1 | 21.7/1 | 96 |
| 0.5 | 1/5 | 1.06/1 | 20.7/1 | 53 |

large changes in the gross transition structure arrangement), the enantiomeric ratio of the anti isomer remained virtually unchanged. This suggested to us that there could be two independent promoted pathways, one favoring the anti diastereomer (with high facial selectivity) and one favoring the syn isomer (with low facial selectivity). Aldolization studies with cyclopentanone- and cycloheptanone-derived enolates revealed similar behavior; the rate of aldehyde addition was critical to obtain high diastereoselectivity.[24] When the aldehyde was added slowly, high and reproducible anti selectivity was obtained, while fast addition provided lower and variable diastereoselectivity. In these cases as well, the enantiomeric ratio of the anti-configured products was effectively constant over a range of reaction conditions, suggesting the presence of two mechanistically distinct pathways.

**Chart 2**



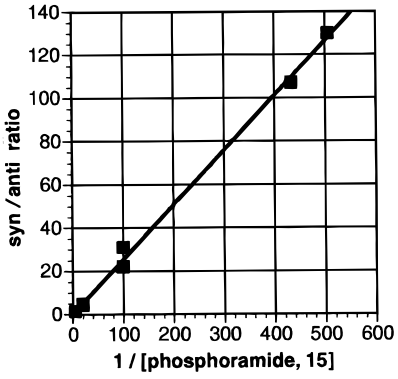
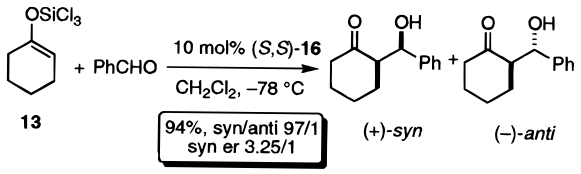




**FIGURE 1.** Loading dependence of selectivity with catalyst **15**.

Reactions promoted by the achiral phosphoramide **15** (Chart 2) also exhibited a dramatic dependence of diastereoselectivity on catalyst loading. First, it should be noted that, in contrast to **4**, this catalyst was generally syn selective for the reaction of **13** with benzaldehyde. Figure 1 graphically depicts the change in syn/anti ratio from 1.3/1 (at 200 mol % loading), up to 130/1 (at 2 mol % loading). The excellent correlation of diastereoselectivity with inverse phosphoramide concentration provided the first quantitative support for the dual-pathway hypothesis, namely, one phosphoramide leads to syn isomers and two phosphoramides lead to anti isomers.[25]

In view of the excellent syn selectivity obtained with **15**, we prepared a chiral analogue, **16**, with the hope of producing an enantioselective catalyst that favored the syn product. The phosphoramide (*S*,*S*)-**16** behaved as expected and afforded the syn aldol product in excellent diastereoselectivity (97/1), albeit with modest enantioselectivity (3.25/1 er) (Scheme 8).[25] Although disappointingly unselective, (*S*,*S*)-**16** would serve admirably to provide additional mechanistic insights on the nature of the reactive pre-aldol complexes.

**Scheme 8**




With enantioselective catalysts now available for both syn and anti pathways, an important link between the bulk and amount of catalyst and the resulting diastereoselectivity could be forged. Recalling the dual-pathway hypothesis of one (to syn) and two (to anti) catalyst molecules in the transition structures, we were able to formulate an indirect test by making use of nonlinear effects and asymmetric amplification, as has been elegantly pioneered by Kagan.[26] The dependence of enantiomeric excess (ee) of the aldol products on the enantiomeric composition of the catalysts is illustrated in Figure 2. The linear relationship between catalyst ee and syn adduct ee with phosphoramide (*S*,*S*)-**16** (Figure 2 (■)) suggested that this product arose from a transition structure involving only one chiral phosphoramide. In contrast, the obvious nonlinear relationship between catalyst ee and anti adduct ee with phosphoramide (*S*,*S*)-**2** (Figure 2 (●)) suggested the participation of two phosphoramide molecules in the transition structure for aldolization.[25]

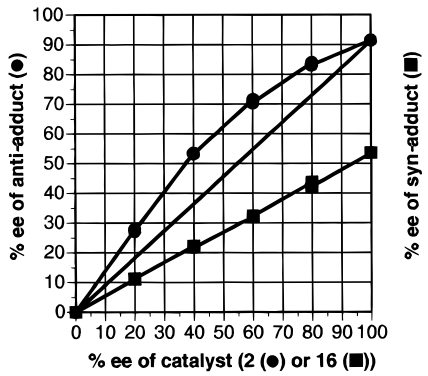



**FIGURE 2.** Correlation of product and catalyst ee for (*S*,*S*)-2 (●) and (*S*,*S*)-16 (■).

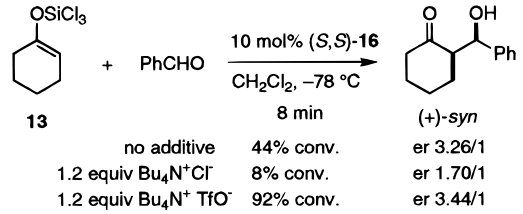
The most compelling direct evidence for the operation of dual pathways was provided by establishment of the reaction order in catalyst for (*S*,*S*)-**16** and (*S*,*S*)-**2**.[27] The

rate and sensitivity of these reactions required the use of in situ monitoring techniques such as ReactIR[28] for the former and a newly constructed rapid injection NMR (RINMR) apparatus for the latter.[29] The catalyzed aldol additions between **13** and benzaldehyde displayed first-order dependence on (*S*,*S*)-**16** (plot of $k_{obs}$ versus [catalyst], $R^2 = 1.000$) over typical catalyst loadings (1.0−5.0 mol %) at −35 °C. Importantly, the rate of reaction at very low catalyst loadings showed pronounced curvature, indicative of a change in mechanism between the promoted and unpromoted pathways. RINMR analysis for the reaction catalyzed by (*S*,*S*)-**2** at −80 °C revealed that aldol addition had a *second*-order dependence (plot of log($k_{obs}$) versus log([catalyst]), $m = 2.113$, $R^2 = 0.992$) on phosphoramide.

Now secure in the knowledge that two phosphoramide molecules can be bound to the enolate in the transition structure, we were faced with formulating a construct for this assembly. Given the reasonable postulate that aldehyde is also coordinated to silicon, two possibilities arise: (1) formation of a heptacoordinate silicon atom or (2) ionization of chloride, forming a cationic hexacoordinate silicon moiety.

Because the intermediacy of cationic silicon species finds better precedent than does heptavalency, we probed the effects of ionic additives on the rate and selectivity of the reaction.[6,25] For reactions with catalyst (*S*,*S*)-**16,** a clear trend emerges (Scheme 9). The addition of 1.2 equiv of tetrabutylammonium chloride caused a marked deceleration and diminution in enantioselectivity. Moreover, the addition of 1.2 equiv of tetrabutylammonium triflate caused a moderate acceleration, attended by a slight increase in the enantioselectivity of the overall process. The decrease in rate (and attendant loss in selectivity) is consistent with a common ion effect, wherein ionization of chloride precedes the rate-determining step. The corresponding increase in rate and selectivity with tetrabutylammonium triflate confirms the notion of ionization by increasing the ionic strength of the medium.

**Scheme 9**




## Unified Mechanistic Scheme

As originally conceived, the phosphoramide-catalyzed aldol addition was believed to involve the ternary association of enolate, aldehyde, and Lewis base. This mechanism was deemed sufficient for activation and stereoselection. From a combination of stereochemical evidence, kinetics measurements, and related experiments, we have formulated a revised picture of the mechanism of the catalyzed process which is much more complex (Figure 3). We now propose that upon binding the Lewis basic phosphoramide, the trichlorosilyl enolate undergoes ionization of chloride. Depending on the size and concentration of the phosphoramide, two scenarios can be operative.[30] With a bulky phosphoramide, or at the lower limit of catalyst loading, aldehyde coordination and aldolization through a boatlike transition structure (with low facial selectivity) provides the syn aldol product (bottom pathway). Alternatively, with smaller phosphoramides or at higher catalyst loading, a second molecule of catalyst can be bound to the cationic dichlorosilyl enolate to form a trigonal

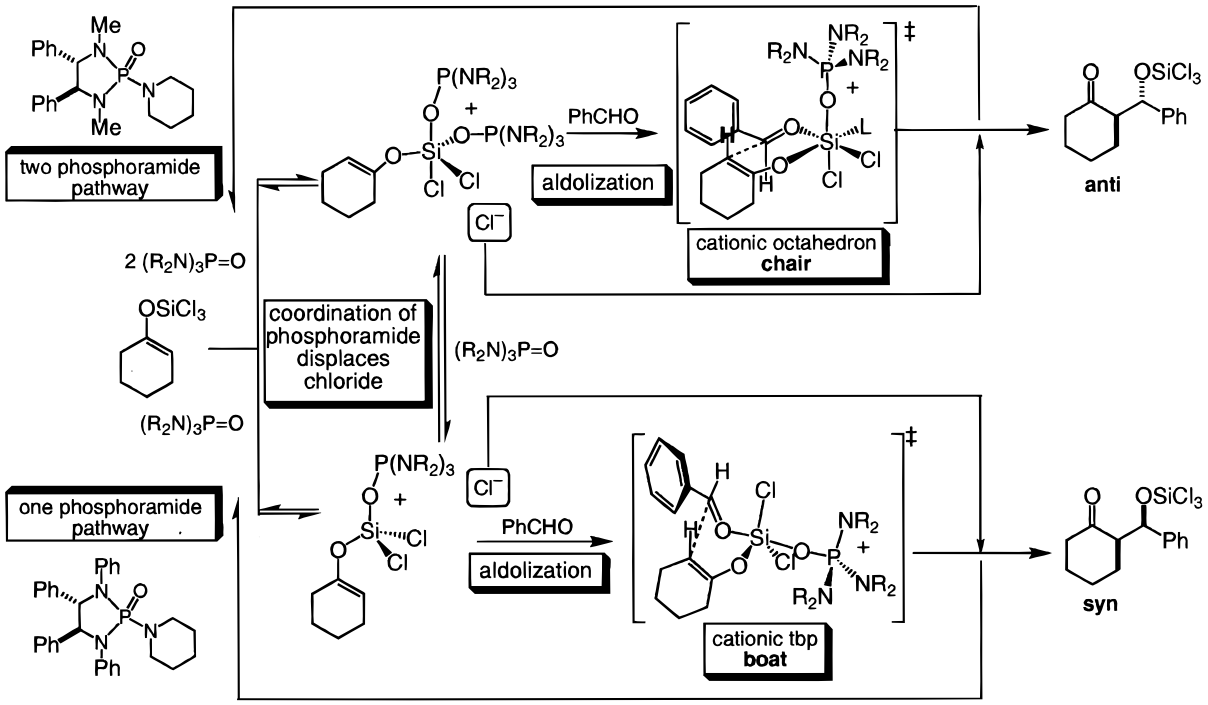



**FIGURE 3.** Unified mechanistic scheme for phosphoramide-promoted aldolizations.

bipyramidal silicon cation. Upon binding of the aldehyde, this intermediate undergoes aldolization through a chair-like transition structure organized around a hexacoordinate silicon atom (top pathway). This process takes place with a high level of facial selectivity, most likely because of the greater stereochemical influence of two chiral moieties in the assembly.

## Structural Insights

Although the revised mechanistic picture provides a better understanding of the remarkable change in diastereoselectivity with catalyst size and loading, the origin of enantioselectivity remained obscure. To secure a structural basis for analysis of the stereochemical consequences of catalyst binding, we examined the solution and solid-state structures of chiral phosphoramide complexes of tin(IV) Lewis acids.[31]

The unified mechanistic scheme posits the preference for 2/1 complexation with (*S*,*S*)-**2** and the preference for 1/1 complexation with (*S*,*S*)-**16**. Both scenarios are confirmed crystallographically. Single-crystal X-ray structural analysis of the 2/1 complex, ((*S*,*S*)-**2**)$_2$·$SnCl_4$, revealed interesting features (Figure 4): (1) 2/1 complexation is feasible, (2) a cis geometry of the complex is preferred, (3) the nitrogen in the piperidino group is planar and oriented orthogonal to the diazaphospholidine ring, and (4) the P−O−Sn angle is nonlinear such that the tin moiety is oriented over the phospholidine ring. $^{119}$Sn solution NMR studies corroborated the observation of 2/1 complexes favoring the cis configuration by analysis of the $^1J_{P-Sn}$ coupling constants.

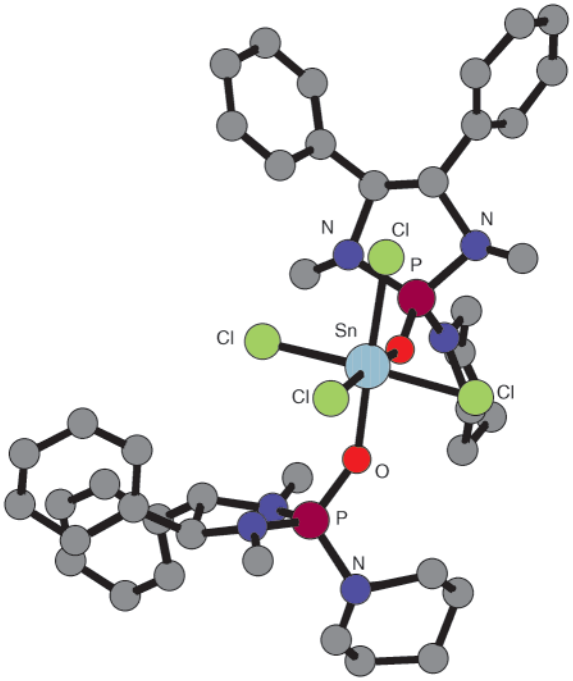



**FIGURE 4.** X-ray crystal structure ((*S*,*S*)-**2**)$_2$·$SnCl_4$.

Crystallization of (*S*,*S*)-**16** with $SnCl_4$ afforded a 1/1/1 complex of (*S*,*S*)-**16**·$SnCl_4$ with one molecule of water completing the tin octahedron. Cocrystallization of (*S*,*S*)-**16** with $SnCl_4$ and benzaldehyde afforded a ternary complex, PhCHO·(*S*,*S*)-**16**·$SnCl_4$ (Figure 5). Both of these complexes displayed the same basic features as are found in the 2/1 complex ((*S*,*S*)-**2**)$_2$·$SnCl_4$.

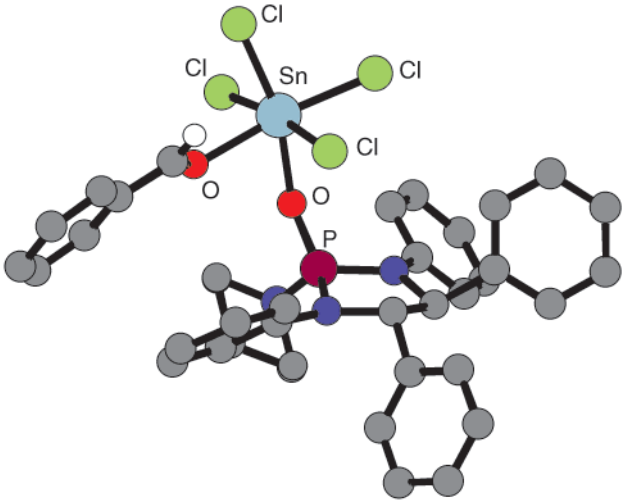



**FIGURE 5.** X-ray crystal structure of PhCHO·(*S*,*S*)-**16**·$SnCl_4$.

While these studies do, indeed, provide structural clues to the arrangement of groups around the central group 14 atom, there are still far too many degrees of freedom to allow a compelling depiction of the most favorable placement of reactive groups and alignment of combining faces to be composed. Nevertheless, the structural insights available from these studies have allowed important trends to emerge that facilitate the invention of new and better catalysts such as those that can enforce 2/1 binding by tethering and still accommodate the preferred arrangement of groups around the central atom.[32]

## Conclusion and Outlook

Over the past 5 years, we have been able to formulate the design criteria for the invention of a chiral Lewis base-promoted aldol reaction and document it experimentally. Enoxytrichlorosilanes represent a new class of aldolization reagents which are highly susceptible to catalysis by Lewis basic phosphoramides. The reactions are characterized by high yields, good functional group compatibility, excellent (and predictable) diastereoselectivity, and high enantioselectivity. The origins of rate enhancement and stereoselection represent new dimensions in catalysis of the aldol addition. Moreover, it should not be lost on the reader that the concepts developed in this enterprise are equally applicable (and have been applied) to other reactions such as allylation,[33] imine addition, Michael addition, and epoxide opening.[34] In addition, Lewis base catalysis should find use in activation of processes associated with other main group elements capable of structural changes similar to silicon.

The synergistic evolution of synthetic utility and mechanistic understanding outlined in this Account illustrates the fruitful interplay of synthesis, reactivity, and structure. We submit that these central activities constitute a chemi-

cal evergreen that will continue to provide the aficionado and craftsman with challenges and tools for many years to come.

*We are pleased to acknowledge the experimental and intellectual contributions of our co-workers in the aldol subgroup, Stephen Winter, Ken-Tsung Wong, Xiping Su, Yutaka Nishigaichi, Son Pham, Jiping Fu, and Yu Fan, whose efforts have helped forge ideas into realities. Funding for this research was provided by the National Science Foundation.*

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