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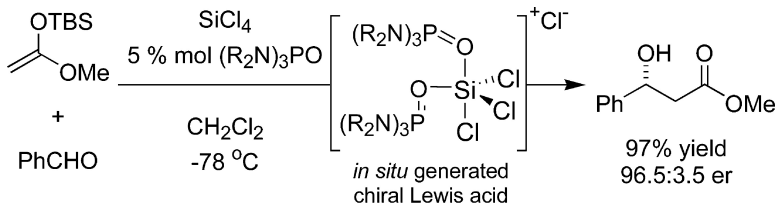

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Lewis Base Activation of Lewis Acids: Catalytic, Enantioselective Addition of Silyl Ketene Acetals to Aldehydes

Scott E. Denmark,* Gregory L. Beutner, Thomas Wynn, and Martin D. Eastgate

Contribution from the Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received May 6, 2004; E-mail: denmark@scs.uiuc.edu

Abstract: The concept of Lewis base activation of Lewis acids has been reduced to practice for catalysis of the aldol reaction of silyl ketene acetals and silyl dienol ethers with aldehydes. The weakly acidic species, silicon tetrachloride ($SiCl_4$), can be activated by binding of a strongly Lewis basic chiral phosphoramide, leading to in situ formation of a chiral Lewis acid. This species has proven to be a competent catalyst for the aldol addition of acetate-, propanoate-, and isobutyrate-derived silyl ketene acetals to conjugated and nonconjugated aldehydes. Furthermore, vinylogous aldol reactions of silyl dienol ethers are also demonstrated. The high levels of regio-, anti diastereo-, and enantioselectivity observed in these reactions can be rationalized through consideration of an open transition structure where steric interactions between the silyl cation complex and the approaching nucleophile are dominant.

Introduction

The appeal of Lewis acid catalysis as a platform for the development of asymmetric transformations can be attributed to the fact that the electron-deficient metal center retains its electrophilicity regardless of the identity or structure of its ligands.[1] The exchange of simple halide or alkoxide ligands for enantiopure alcohols or amines provides easy access to well-defined metal species with reduced electrophilicity and increased steric demands when compared to the parent metal complexes.

The fundamental mechanism by which a Lewis acid promotes reaction at an organic functional group is through electrophilic activation.[2] The binding of an electron-deficient metal complex to the nonbonding lone pair of some functional group polarizes the adjacent bonds, activating them toward nucleophilic attack (Figure 1). In this context, Lewis acid activation has been applied to the reactions of a number of functional groups, including carbonyl compounds, imines, and epoxides.[3] Save for cases of Lewis acid-catalyzed pericyclic reactions, the coordination complex is transformed into a covalent complex upon formation of the new bond.

This change in the nature of the bond between the catalyst and substrate along the reaction coordinate introduces the major challenge facing Lewis acid-catalyzed processes, namely, catalyst turnover. Because the strength of the metal−substrate bond increases upon changing from the substrate to the product complex, release of the catalyst must be assisted by a subsequent bond formation (Figure 1). In most successful cases, the reagent

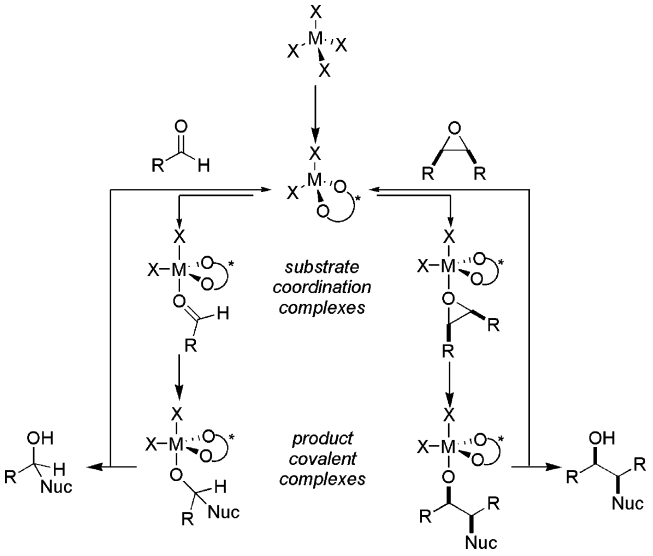

Figure 1. General picture of Lewis acid-catalyzed processes.

required for this step in the catalytic cycle is present either as part of the solvent or as part of the nucleophile, as in the case of latent silylated nucleophiles. Performing Lewis acid-catalyzed reactions in either highly polar or protic solvents is a simple method for promoting catalyst turnover. Protonation of the product complex, as demonstrated in the hydrolytic kinetic resolution of epoxides, is effective for release of the cobalt−(salen) complex from the ring-opened product.[4] Similarly, the

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(2) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996.
(3) Otera, J. *Modern Carbonyl Chemistry*; Wiley-VCH: Weinheim, Germany, 2000.
(4) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

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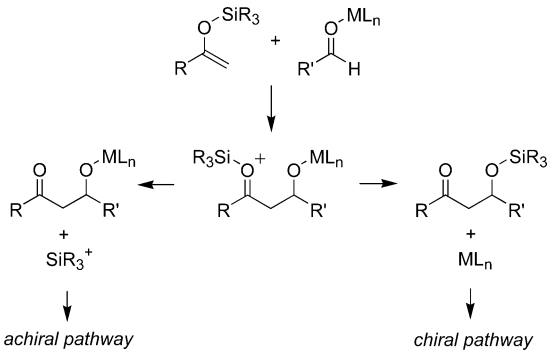
use of propionitrile increases the rate of catalyst turnover in the boryl complex-catalyzed aldol reaction of silyl ketene acetals.[5]

In the case of silylated nucleophiles, such as the silyl ketene acetals mentioned above, it is silylation of the product aldolate that actually completes the turnover event in the catalytic cycle. Several studies highlight the importance of this step, especially when considering the development of asymmetric methods. If release of the catalyst by silylation is slow compared to intervention of a silyl cation-catalyzed process, the overall mechanism of the reaction shifts from being one that is chiral metal complex-catalyzed to one that is chiral metal complex-initiated (Scheme 1). The titanium(IV) Schiff base complex developed by Carreira incorporates an achiral salicylate ligand since it can act as a silyl shuttle in the catalyst turnover step.[6] Alternatively, the use of additives can minimize catalyst inhibition or the involvement of a competitive, achiral silyl cation promoted pathway, such as in the use of trimethylsilyl triflate in the silyl ketene acetal aldol reactions developed by Evans and co-workers.[7]

Scheme 1



The aldol addition of ester-, ketone-, and aldehyde-derived enolates is a major focus in asymmetric catalysis, due to the potential to evaluate mechanisms for control of diastereo- and enantioselectivity in this single carbon−carbon bond-forming reaction.[8] Advances in the aldol reaction have always been tied to conceptual advances, the most recent and widespread being the arrival of Lewis acid catalysis. This report details a unique method of catalysis that capitalizes on the generality of Lewis acid catalysis, yet avoids the problems of that strategy, namely, the requirement for preformation of the chiral Lewis acid complex and a mechanism for catalyst turnover. The application of this new method to the aldol addition of silyl ketene acetals to aldehydes will be disclosed in full.

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Background

1. Lewis Base Activation of Lewis Acids. The need for preformation of a chiral Lewis acidic catalyst is linked to the inherent Lewis acidity of electron-deficient metal centers. Changes in the ligands can have a strong, but often unpredictable effect on the electrophilicity of the metal center. Therefore, care must be taken to ensure that the parent metal species is removed from the prepared catalyst complex to avoid reaction catalyzed by this species. Development of a Lewis acid-catalyzed aldolization that eliminates this concern could take a number of forms: (1) preformation and purification of the chiral metal−ligand complex, (2) highly favorable equilibrium formation of the metal−ligand complex, or (3) binding of the ligand in such a way as to significantly enhance the reactivity of the metal center. In the latter case, the contribution of the nascent Lewis acidic precursor to the overall reaction rate could be minimized. In the case of chiral ligands, this latter strategy would increase the observed rate of reaction through the chiral metal complex relative to the achiral one and presents an attractive possibility for the design of a novel catalytic method.

In the binding of a Lewis basic ligand to a Lewis acid, there is a net flow of electron density from the donor to the acceptor moiety. Therefore, the reactivity of the electrophilic acceptor moiety decreases, and this should preclude any kind of ligand-accelerated catalysis.[9] However, only considering the changes in the overall electron density upon adduct formation is a simplification of the true affects of a Lewis acid−base interaction, as pointed out by Gutmann.[10] Although the overall electron density on the acceptor may increase, this electron density is not distributed evenly among its constituent atoms. Gutmann has shown by careful examination of the X-ray crystal structures of antimony pentachloride, $SbCl_5$ (**1**), and its complex with tetrachloroethylene carbonate (**2**) that significant changes in bond lengths occur upon complexation (Figure 2).[10a] Gutmann proposed that the alternating pattern of these bond changes is indicative of changes in electron density throughout the complex that compensate for changes at the donor and acceptor atoms. The build-up of electron density in the acceptor fragment leads to a lengthening of the peripheral ligand−metal bonds that renders the metal center of the complex more electropositive.

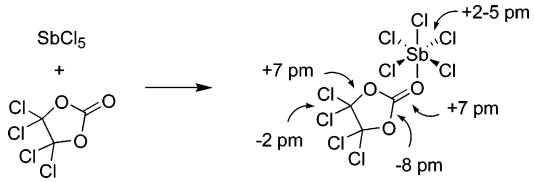

Figure 2. Effects of Lewis acid−base interactions on bond lengths and electron density.

Support for this conclusion can be derived from calculations performed with relevant Lewis acid−base adducts of silicon tetrachloride (Scheme 2). Gordon and co-workers have studied the binding of chloride ion to $SiCl_4$ (**3**) to form penta- and hexacoordinate silicates (**4** and **5**) at the 6-311^{++}G(d,p) level of theory and observed changes in bond lengths and electron densities consistent with the Gutmann analysis.[11] Binding of

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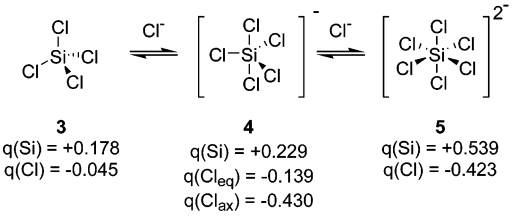
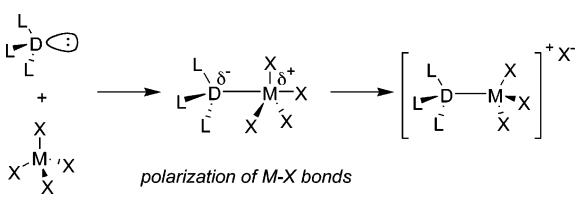
the first chloride ion is exothermic by 40.8 kcal/mol, but more interestingly leads to an increase in the partial positive charge at silicon by +0.051. A corresponding increase in the partial negative charge at the chlorine atoms accompanies this change. A greater degree of the negative charge accumulates at the axial chlorine atoms when compared to the equatorial chlorine atoms due to their involvement in a hypervalent three-center/four-electron bond. Binding of the second chloride ion, although now an endothermic process by 48.3 kcal/mol, further accentuates this polarization as the partial positive charge at silicon increases by another +0.310. Similar trends have been observed by Sakurai and co-workers in their computational studies of allyltrifluorosilanes and the corresponding fluorosilicates.[12] If enhanced electrophilicity at the metal center can be achieved upon simple coordination of a Lewis acid with a Lewis base, is this change kinetically significant? Only a few examples exist where simple coordination of a neutral donor to a metal species leads to enhanced reactivity.[13]

Scheme 2



Taken to the extreme, polarization of the adjacent bonds in the metal fragment of the adduct leads to ionization of one of the X ligands and generation of a cationic metal center (Scheme 3). A poorly Lewis acidic species, incapable of promoting a given reaction by itself, could be ionized upon binding of a chiral Lewis base, thus generating a cationic metal species with enhanced activity. This process would represent a unique direction in the development of Lewis acid catalysts because it not only addresses the problem of catalyst preformation but also holds potential for solving the problem of catalyst turnover. The use of a chiral ligand that is not covalently bound to the electrophilic metal species shifts the requirements of the turnover event from cleavage of the strong metal−oxygen bond in the product to dissociation of the ligand from the metal center. Another important difference compared to traditional Lewis acid catalysis is that the stoichiometry of the reaction changes from being catalytic in Lewis acid to stoichiometric in Lewis acid. Following this scheme, in each catalyst cycle, the Lewis acidic fragment would become incorporated into the product. Therefore, such a reaction would be Lewis base-catalyzed and Lewis acid-mediated.

Scheme 3



The potential for development of a chiral Lewis base-catalyzed/Lewis acid-mediated process was first demonstrated in the phosphoramide-catalyzed/$SiCl_4$-mediated asymmetric ring opening of *meso*-epoxides reported from this laboratory in 1998.[14] In the presence of 10 mol % of the chiral phosphoramide and a stoichiometric amount of $SiCl_4$, high yields and moderate enantioselectivities were obtained for the formation of vicinal chlorohydrins.

Although the desymmetrization of *meso*-epoxides is an important synthetic process,[15] the main objective was the extension of this in situ-generated, chiral Lewis acid concept to the addition of main group organometallic nucleophiles to carbonyl compounds in analogy to earlier studies with trichlorosilyl nucleophiles.[16] Initial studies focused on the addition of tri-*n*-butylallylstannane to aldehydes.[17] High yields and selectivities are observed under the influence of the chiral, dimeric phosphoramide.[18]

The extension of this phosphoramide-catalyzed/$SiCl_4$-mediated system to other nucleophiles was the next logical step. Considering the nucleophilicity scales developed by Mayr and co-workers,[19] it was believed that more reactive trialkylsilyl enol ethers derived from esters could probe the limits of the asymmetric environment imposed by the catalyst. Issues of both diastereo- and enantioselectivity could be assessed in the reactions of acetate-, propanoate-, and isobutyrate-derived silyl ketene acetals. Earlier studies from these laboratories had shown that *trichloro*silyl ketene acetals gave the aldol adducts derived from aldehydes in low enantioselectivities, most likely because of the hyper-reactivity of these species.[20]

2. Catalytic Asymmetric Aldol Reactions. Despite the intense interest and notable successes in catalytic asymmetric aldol reactions of silyl ketene acetals, several limitations are still apparent: (1) a lack of anti diastereoselective methods for α-substituted silyl ketene acetals, (2) a low degree of stereoconvergence with respect to silyl ketene acetal geometry, and (3) poor substrate scope in vinylogous aldol reactions of silyl dienol ethers.

Most Lewis acid-catalyzed aldol reactions of silyl ketene acetals are highly syn diastereoselective.[21] This syn diastereoselectivity has been a commonly observed theme throughout the development of these methods, beginning with the early

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studies by Mukaiyama[22] and continuing into the studies of the highly selective catalysts developed by Masamune.[23] These studies show that the levels of diastereo- and enantioselectivity observed in the reactions of *E*- and *Z*-isomers of the silyl ketene acetals are often not comparable. Furthermore, only a few isolated examples of anti diastereoselectivity have been reported.[24,25]

Another interesting class of silyl ketene acetals that have received only limited attention are silyl dienol ethers.[26] The vinylogous aldol reaction is important because it provides rapid access to larger fragments useful for the synthesis of polypropionate-derived natural products. This type of aldol reaction introduces the added challenge of site selectivity along with the issues of diastereo- and enantioselectivity. In contrast to the vinylogous aldol reaction of metallodienolates, the reactions of silyl dienol ethers occur preferentially at the γ-carbon because these reactions typically operate under frontier molecular orbital control (Figure 3).[27] Most asymmetric methods provide high regio- and enantioselectivities only for a limited group of lactone- and dioxanone-derived silyl dienol ethers.[28] The reactions of simple ester-derived silyl dienol ethers are limited, and products are only obtained with moderate enantioselectivity.[29]

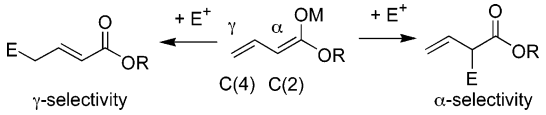
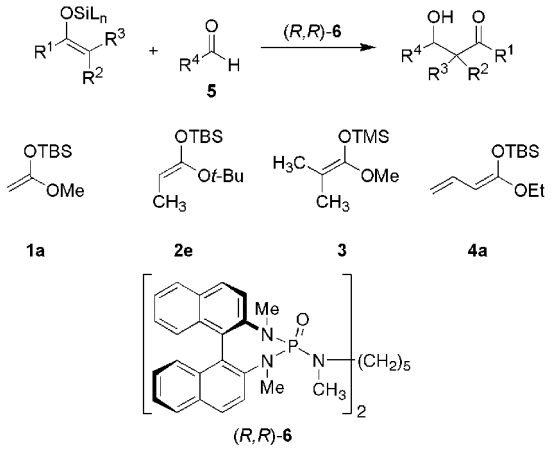


Figure 3. Site selectivity of vinylogous aldol reactions.

Thus, despite the enormous number of asymmetric aldol reactions of silyl ketene acetals on record, we felt that a comparison of the phosphoramide/$SiCl_4$ catalyst system with existing methods would provide an interesting test for the concept and may also address some of the remaining synthetic challenges in this field. The primary objective of this study was to assay the catalyst system in the reactions of three classes of ester-derived silyl ketene acetals (Scheme 4). Initial studies would focus on the reactions of acetate-derived silyl ketene acetals to establish proof of principle and to elucidate the reactivity and enantioselectivity of this catalyst system. The survey would then be expanded to include propanoate-derived silyl ketene acetals and silyl dienol ethers to investigate additional levels of site and stereochemical complexity. Finally,

Scheme 4



an investigation of the reaction with respect to aldehyde structure will be undertaken to illustrate substrate scope and functional group compatibility.[30]

Results

1. Acetate-Derived Silyl Ketene Acetal Additions. The promising results from the addition of the weakly nucleophilic tri-*n*-butylallylstannane ($N = 5.82$)[19] to aldehydes promoted by the phosphoramide/$SiCl_4$ catalyst system suggested that the more nucleophilic silyl ketene acetals would also prove to be viable substrates ($N = 9.49$ for **3**).[19] However, the high reactivity of these species raised immediate concerns about the possibilities of (1) competitive background reaction, (2) silyl metathesis to trichlorosilyl enol ethers, and (3) very early transition structures, all of which would lead to reduced levels of selectivity. Initial experiments with the commercially available silyl ketene acetal, 1-methoxy-1-*tert*-butyldimethylsilyloxyethene (**1a**), were conducted using the optimal conditions developed previously for the allylation reaction.[17] The bulky *tert*-butyldimethylsilyl ketene

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acetal provided ready availability and ease of handling compared to the more commonly used trimethylsilyl analogue. In the addition of **1a** to benzaldehyde (**5a**) promoted by 5 mol % of the dimeric phosphoramide (*R,R*)-**6**, an extremely rapid reaction was observed at −78 °C (<30 s), consistent with the high reactivity expected for this species. Despite our initial concerns, the desired product was obtained in high yield and enantioselectivity (Table 1, entry 1). Determination of the absolute configuration of the aldol adduct **7aa** by comparison of its optical rotation to literature values revealed that the 3*R*-isomer had been formed.[31] The sense of selectivity observed in this reaction was the same as that observed in the allylation reaction, clearly indicating that the catalyst complex enforced the same sense of facial differentiation at the aldehyde. Throughout these studies, the use of a slight excess of the silyl ketene acetal (1.2 equiv) and $SiCl_4$ (1.1 equiv) aided the reproducibility of the reaction, as was the case in earlier studies of the allylation. The requirement for an excess of these reagents is likely related to a small amount of unproductive trans-silylation that occurs upon addition of the silyl ketene acetal to the reaction mixture (vide infra).

Table 1. Aldol Reaction with 1-(*tert*-Butyldimethylsilyloxy)-1-methoxyethene (**1a**)[a]

5a-k **1a** **7aa-7ak**

entry	R	product	yield, %[b]	er[c]
1	C_6H_5 (**5a**)	**7aa**	97[e,f]	96.3:3.7
2	1-naphthyl (**5b**)	**7ab**	98	90.2:9.8
3	2-naphthyl (**5c**)	**7ac**	98	96.8:3.2
4	4-$CH_3C_6H_4$ (**5d**)	**7ad**	97	97.2:2.8
5	4-$CH_3OC_6H_4$ (**5e**)	**7ae**	97	98.7:1.3
6	4-$CF_3C_6H_4$ (**5f**)	**7af**	97	95.7:4.3
7	(*E*)-$C_6H_5CH{=}CH$ (**5g**)	**7ag**	95[e]	96.9:3.1
8	(*E*)-$C_6H_5CH{=}C(CH_3)$ (**5h**)	**7ah**	98	72.7:27.3
9	2-furyl (**5i**)	**7ai**	94	93.4:6.6
10	cyclohexyl (**5j**)[d]	**7aj**	86[e]	94.2:5.8
11	$PhCH_2CH_2$ (**5k**)[d]	**7ak**	72[e]	90.7:9.3

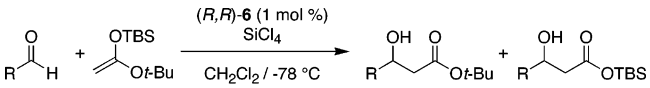
[a] All reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **1a**, and 0.05 equiv of (*R,R*)-**6** at 0.2 M in CH_2Cl_2 at −78 °C for 15 min. [b] Yields of analytically pure material. [c] Determined by CSP−SFC. [d] Reaction time of 6 h. [e] Chromatographically homogeneous material. [f] (3*R*)-**7aa** absolute configuration.

In the subsequent survey of aldehyde structure, the reactivity of aliphatic aldehydes was of particular interest. Traditionally, aliphatic aldehydes have demonstrated poor reactivity and only moderate levels of selectivity in the Lewis base-catalyzed reactions of trichlorosilyl nucleophiles.[16] Only the highly reactive methyl acetate-derived trichlorosilyl ketene acetal was able to participate in a productive reaction with these substrates under Lewis base catalysis.

The aldol reaction of **1a** with a wide range of aldehydes provided consistently high yields and enantioselectivities. In a series of aromatic aldehydes, 2-naphthaldehyde (**5c**) and 4-tolualdehyde (**5d**) gave yields and selectivities comparable to those of benzaldehyde (entries 2 and 4). However, the isomeric 1-naphthaldehyde (**5b**) showed a considerable drop in selectivity (entry 3). The electronic nature of the aldehyde seemed to have little effect on reactivity or selectivity. The electron-rich nature of aromatic aldehydes, such as 4-methoxybenzaldehyde (**5e**) and 2-furaldehyde (**5i**), preserved the high selectivity of the reaction (entries 5 and 9). Substrates at the opposite end of the electronic spectrum, such as 4-trifluoromethylbenzaldehyde (**5f**), also afforded high yield and selectivity (entry 6). Gratifyingly, olefinic aldehydes gave high yields although subtle effects on selectivity became apparent when comparing cinnamaldehyde (**5g**) and α-methylcinnamaldehyde (**5h**) (entries 7 and 8). Much to our delight, the two aliphatic aldehydes investigated in the initial survey, hydrocinnamaldehyde (**5k**) and cyclohexanecarboxaldehyde (**5j**), gave the *β*-hydroxy ester products in high yields and enantioselectivities (entries 10 and 11). Unfortunately, their rate of reaction was greatly attenuated when compared to that of either benzaldehyde or cinnamaldehyde. ReactIR monitoring of the reaction with benzaldehyde revealed that it required less than 30 s to go to completion, whereas the reaction of aliphatic aldehydes required close to 3 h.

Other acetate-derived silyl ketene acetals were briefly investigated to assay the effect of the steric demands of the alkoxy group on enantioselectivity (Table 2). As expected from a systematic study conducted with propanoate-derived silyl ketene acetals (vide infra), the *tert*-butyl acetate-derived *tert*-butyldimethylsilyl ketene acetal (**1b**) provided the corresponding *β*-hydroxy ester products with higher levels of enantioselectivity when compared to **1a**. For each of the problematic aldehydes examined in the initial survey (Table 1), 1-naphthaldehyde (**1b**), α-methylcinnamaldehyde (**5h**), and hydrocinnamaldehyde (**5k**), there were considerable improvements. Although these reactions clearly proceeded to completion based on consumption of the aldehyde, the isolated yields of the products were found to be consistently lower than those observed in the additions of **1a**. Careful analysis of the crude reaction mixtures revealed that varying amounts of the *tert*-butyldimethylsilyl ester **8** had been formed. The ratio of the esters was quite sensitive to the structure of the aldehyde. Cleavage of this silyl ester during the typical KF/KH_2PO_4 workup led to loss of the corresponding carboxylic acid in the aqueous phase, accounting for the lower yield. Attempts to modify the reaction and workup conditions were unable to suppress this undesired side reaction, suggesting it occurred during the reaction. The use of a mild, sodium bicarbonate workup allowed for isolation of a mixture of both the *tert*-butyl and *tert*-butyldimethylsilyl esters in a high overall conversion.

Table 2. Aldol Reaction with 1-(*tert*-Butyldimethylsilyloxy)-1-*tert*-butyloxyethene (**1b**)[a]



5a-k **1b** **7ba-7bk** **8a-k**

entry	R	**7**:**8**[b]	yield, %[c]	er[d]
1	C_6H_5 (**5a**)	4.4:1	68	97.9:2.1
2	1-naphthyl (**5b**)	6:1	79	96.9:3.1
3	(*E*)-$C_6H_5CH{=}C(CH_3)$ (**5h**)	2.2:1	58	85.5:14.5
4	$PhCH_2CH_2$ (**5k**)[e]	ND	46	96.9:3.1

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **1b**, and 0.01 equiv of (*R,R*)-**6** at 0.2 M in CH_2Cl_2 at −78 °C for 1 h. [b] Determined by ^1H NMR analysis. [c] Yields of analytically pure material. [d] Determined by CSP−SFC.

2. Propanoate-Derived Silyl Ketene Acetal Additions. 2.1. Survey of Propanoate Structure. The results of the aldol addition of the acetate-derived silyl ketene acetal **1a** demon-

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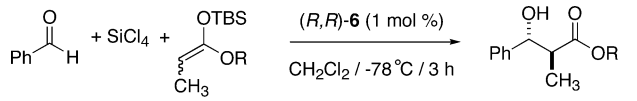
strated that the catalyst could exert a high degree of control over the approach of a nucleophile to one face of the activated aldehyde. In the next stage of this study, a series of propanoate-derived silyl ketene acetals (**2**) reacted with benzaldehyde **5a** under the standard conditions mentioned above to afford high yields of the desired products. Furthermore, high levels of anti diastereoselectivity were consistently obtained (Table 3). It should be noted that these high levels of anti diastereoselectivity were not dependent on the specific catalyst structure. Similar results were obtained from reactions run to obtain the racemates required for CSP−SFC analysis with HMPA. The structure of the alkoxy group seemed to have little effect on diastereoselectivity, although its influence on enantioselectivity was significant. Enantioselectivity increased with the size of the alkoxy group in the order of Me < Et < *i*-Pr < Ph ≪ *t*-Bu. In the reaction of the (*E*)-*tert*-butyldimethylsilyl ketene acetal **2e** with benzaldehyde, nearly complete selectivity for (2*S*,3*R*)-**9ea** was observed in the presence of only 1 mol % of the catalyst (*R*,*R*)-**6**. The product configuration was established by cleavage of the ester group and by comparison of the ^{1}H NMR spectrum and optical rotation of the carboxylic acid to the data reported in the literature.[32] This result indicates that *Re* face attack on the aldehyde had occurred, as was the case in the acetate-derived silyl ketene acetal additions described above.

Table 3. Aldol Reaction with Propanoate-Derived *tert*-Butyldimethylsilyl Ketene Acetals (**2**)[a]



5a **2a-e** **9aa-9ea**

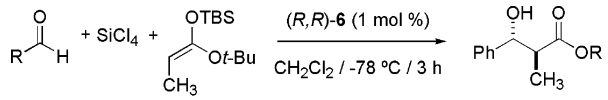
entry	R	*E*:*Z*[b]	product	yield, %	dr[b]	S/N[c]	er[d]
1	Me (**2a**)	82:18	**9aa**	98[e]	99:1	981	85.4:14.6
2	Et (**2b**)	95:5	**9ba**	78[e,f]	98:2		88.8:11.2
3	Et (**2b**)	7:93	**9ba**	76[e]	85:15		86.7:12.4
4	*i*-Pr (**2c**)	71:29	**9ca**	80[e]	98:2	264	91.1:8.9
5	Ph (**2d**)	94:6	**9da**	98[e]	94:6	92	93.9:6.1
6	*t*-Bu (**2e**)	95:5	**9ea**	93[f,g]	99:1	311	>99.9:0.1
7	*t*-Bu (**2e**)	12:88	**9ea**	73[e,g]	99:1	162	99.5:0.5

[a] All reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of silyl ketene acetal, and 0.01 equiv of (*R*,*R*)-**6** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis of HC(3). [d] Determined by CSP−SFC. [e] Chromatographically homogeneous material. [f] Analytically pure material. [g] (2*S*,3*R*) absolute configuration.

Although the size of the alkoxy substituent was crucial for obtaining high enantioselectivity, the geometry of the silyl ketene acetal was unimportant. Nearly identical levels of diastereo- and enantioselectivity were observed regardless of the geometry of the silyl ketene acetal. In the case of (*Z*)-**2b**, high, but not complete, anti diastereoconvergence was obtained when compared to the reaction of (*E*)-**2b** (Table 3, entries 2 and 3).[33] Examination of both the *Z*- and *E*-isomers of the *tert*-butyl propanoate-derived silyl ketene acetals demonstrated high anti diastereoconvergence (entries 6 and 7).[34] The major product (**9ea**) isolated from the reaction of (*Z*)-**2e** was found to have the same absolute and relative configuration as the product derived from the reaction of (*E*)-**2e**.

2.2. Scope of Aldehyde Structure in the Additions of the Silyl Ketene Acetal (*E*)-2e. Encouraged by the high levels of enantioselectivity and the anti diastereoconvergence observed in the reactions of (*E*)-**2e**, we investigated the scope of the reaction with a wide range of aldehydes. In all cases, the reactions were slower than the corresponding acetate additions, but high yields, anti diastereo-, and enantioselectivities were generally observed (Table 4). A variety of aromatic aldehydes, ranging from electron-rich substrates, such as 4-methoxybenzaldehyde (**5e**) and 2-furaldehyde (**5i**), to electron-poor aromatic aldehydes, such as 4-trifluoromethylbenzaldehyde (**5f**), reacted with consistently high selectivities (entries 4−6). Other aromatic aldehydes, such as 1- and 2-naphthaldehyde (**5c**) and thiophene-2-carboxaldehyde (**5l**), gave comparable yields and selectivities (entries 2, 3, 6, and 7).[35] Olefinic aldehydes, such as cinnamaldehyde (**5g**) and α-methylcinnamaldehyde (**5h**), also performed well under the standard reaction conditions (entries 8 and 9). However, the reactivity patterns of all conjugated aldehydes were not similar. Variable yields and selectivities were obtained with crotonaldehyde (**5m**) and 3-phenylpropargylaldehyde (**5n**) (entries 10 and 11). Comparison of these selectivities with those observed for the reactions of acetate-derived silyl ketene acetal **1a** showed that a drop in selectivity is not observed with aldehydes such as 1-naphthaldehyde and α-methylcinnamaldehyde.

Table 4. Aldol Reaction with (*E*)-1-(*tert*-Butyloxypropenyloxy)-*tert*-butyldimethylsilane (**2e**)[a]



5a-n **2e** **9ea-9en**

entry	R	product	yield, %[b]	dr[c]	S/N[d]	er[e]
1	C_6H_5 (**5a**)	**9ea**	93[f]	99:1	311	>99.9:0.1
2	1-naphthyl (**5b**)	**9eb**	98	>99:1	669	97.2:2.8
3	2-naphthyl (**5c**)	**9ec**	95	>99:1	711	99.6:0.4
4	4-$CH_3OC_6H_4$ (**5e**)	**9ee**	88	>99:1	209	99.2:0.8
5	4-$CF_3C_6H_4$ (**5f**)	**9ef**	93	>99:1	889	96.0:4.0
6	2-furyl (**5i**)	**9ei**	96	98:2		96.9:3.1
7	2-thiophenyl (**5l**)	**9el**	90	95:5		94.3:5.7
8	(*E*)-PhCH═CH (**5g**)	**9eg**	98	>99:1	98	>99.9:0.1
9	(*E*)-PhCH═C(CH_3)(**5h**)	**9eh**	90	>99:1		96.1:3.9
10	(*E*)-CH_3CH═CH (**5m**)	**9em**	55	>99:1		98.2:1.8
11	phenyl propargyl (**5n**)	**9en**	92	96:4		84.5:15.5

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **2e**, and 0.01 equiv of (*R*,*R*)-**6** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [b] Yields of analytically pure material. [c] Determined by ^{1}H NMR analysis. [d] Determined by ^{1}H NMR analysis of HC(3). [e] Determined by CSP−SFC. [f] (2*S*,3*R*) absolute configuration.

When the reaction of aliphatic aldehydes was investigated with the silyl ketene acetal (*E*)-**2e**, virtually no product was observed, even after extended reaction times (∼24 h). Although the reason was unclear at the time, aliphatic aldehydes did prove to be reactive with the less sterically encumbered silyl ketene

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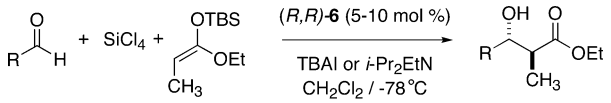
(33) Davies, S. G.; Edwards, A. J.; Evans, G. B.; Mortlock, A. A. *Tetrahedron* **1994**, *50*, 6621−6642.
(34) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakehi, A. *J. Org. Chem.* **1999**, *64*, 6353−6360.
(35) The diastereoselectivity reported in this work for the aldol product derived from 1-naphthaldehyde **5b** and **2e** (**9eb**) is higher than that reported in the previous communication. The species originally assigned as the syn diastereomer of **9eb** was, in fact, the aldol product derived from 2-naphthaldehyde (**9ec**). Commercially available 1-naphthaldehyde is contaminated with 2−4% 2-naphthaldehyde (Aldrich). This isomer could not be removed by simple distillation. The observed enantioselectivity is unaffected as the peaks for **9eb** and **9ec** were well separated in the CSP−SFC analysis.

Table 5. Aldol Reaction of (*E*)-1-(Ethoxypropenyloxy)-*tert*-butyldimethylsilane (**2b**) with Aliphatic Aldehydes



5k-r **2b** **9bk-9br**

entry	R	product	yield, %[a]	dr[b]	S/N[c]	er[d]
1	$PhCH_2CH_2$ (**5k**)[e]	**9bk**	71	91:9	234	94.9:5.1
2	$(CH_3)_2CHCH_2$ (**5o**)[e]	**9bo**	65[f]	89:11	105	93.0:7.0
3	$(CH_3)_2CHCH_2$ (**5o**)[g]	**9bo**	76	91:9	72	89.7:10.3
4	$TBSO(CH_2)_5$ (**5p**)[g]	**9bp**	51	96:4		96.7:3.3
5	$BnO(CH_2)_5$ (**5q**)[g]	**9bq**	70	95:5		96.7:3.3
6	$BzO(CH_2)_5$ (**5r**)[g]	**9br**	60	95:5		95.4:4.5
7	cyclohexyl (**5j**) [h]	**9bj**	40	89:11	430	67.8:32.2

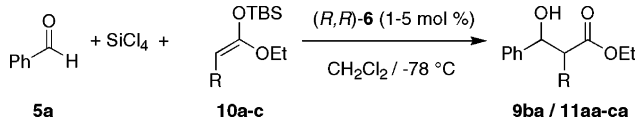
[a] Yields of analytically pure material. [b] Determined by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis of HC(3). [d] Determined by CSP−SFC. [e] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **2b**, 0.05 equiv of (*R,R*)-**6**, and 0.1 equiv of TBAI at 0.4 M in CH_2Cl_2 at −78 °C for 24 h. [f] Chromatographically homogeneous material. [g] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **2b**, 0.05 equiv of (*R,R*)-**6**, and 0.05 equiv of DIPEA at 0.4 M in CH_2Cl_2 at −78 °C for 24 h. [h] Reaction employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **2b**, 0.1 equiv of (*R,R*)-**6**, and 0.1 equiv of TBAI at 0.8 M in CH_2Cl_2 at −40 °C for 24 h.

acetal (*E*)-**2b** (Table 5). Further optimization showed that the combination of longer reaction times, higher catalyst loadings, and the addition of either tetrabutylammonium iodide (TBAI) or diisopropylethylamine (*i*-Pr_2EtN) to the solution could give synthetically useful yields of the aldol adducts (compare entries 2 and 3). In the case of the unbranched hydrocinnamaldehyde (**5k**) and the *β*-branched isovaleraldehyde (**5o**), moderate yields could be obtained under optimized conditions (entries 1−3). The levels of selectivity observed in these reactions, although high, fell short of the levels attained in the aldol reactions of conjugated aldehydes, such as benzaldehyde (**5a**) and cinnamaldehyde (**5g**). Disappointingly, the reaction with the α-branched cyclohexanecarboxaldehyde (**5j**) remained sluggish. Even with 10 mol % of the dimeric phosphoramide catalyst (*R,R*)-**6** at −40 °C, only moderate yields and selectivities were obtained (entry 7).

In view of the anticipated oxophilicity of the putative silyl cation intermediate, a brief investigation of the stability and influence of commonly used silyl-, ester-, and ether-protecting groups was undertaken. The reactions of 6-(*tert*-butyldimethylsilyloxy)-, 6-benzyloxy-, and 6-benzoyloxyhexanal (**5p**−**r**) revealed that comparable yields could be obtained under the modified conditions developed for simple aliphatic aldehydes. In the presence of Lewis basic functional groups, such as ethers and esters, similar levels of diastereo- or enantioselectivity were obtained when compared to simple, unfunctionalized aliphatic aldehydes (entries 4−6).

2.3. Scope of Silyl Ketene Acetal Structure in the Addition to Benzaldehyde. Although the steric demands of the alkoxy substituent in the silyl ketene acetal have a strong effect on the enantioselectivity of the aldol reaction, the influence of the structure of the ester-derived portion had not been investigated. Thus, a series of ethyl ester-derived silyl ketene acetals were prepared bearing methyl (**2b**), ethyl (**10a**), isopropyl (**10b**), and isobutyl (**10c**) substituents and were then subjected to the optimized reaction conditions with benzaldehyde. In this series, yields and selectivities were generally high and comparable to those obtained with (*E*)-**2b** (Table 6, entry 1). The isovalerate-derived silyl ketene acetal **10b**, bearing an α-branched substituent, did show a marked decrease in diastereoselectivity. However, in the presence of a larger substituent, such as the isobutyl group of the isocaproate-derived silyl ketene acetal **10c**, comparable levels of diastereo- and enantioselectivity were restored when compared to **2a** and **10a**.

Table 6. Aldol Reaction with α-Substituted *tert*-Butyldimethylsilyl Ketene Acetals

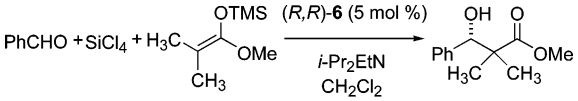


5a **10a-c** **9ba / 11aa-ca**

entry	R	product	yield,%[a]	dr[b]	S/N[c]	er[d]
1	Me (**2b**)[e]	**9ba**	78[f]	98:2	981	88.8:11.2
2	Et (**10a**)[e]	**11aa**	75	92:8		83.6:16.4
3	*i*-Pr (**10b**)[e]	**11ba**	82	85:15	339	85.8:14.2
4	*i*-Bu (**10c**)[e]	**11ca**	88	97:3		86.3:13.7

[a] Yields of analytically pure material. [b] Determined by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis of HC(3). [d] Determined by CSP−SFC. [e] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of the silyl ketene acetal, and 0.01 equiv of (*R,R*)-**6** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [f] Chromatographically homogeneous material.

Scheme 5



5a **3** **12**
91.1:8.9 er

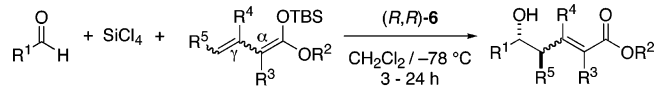
An α,α-disubstituted methyl ester-derived silyl ketene acetal **3** was also prepared to investigate the effect of α-disubstitution. Silyl ketene acetal **3** exhibited severely attenuated reactivity (Scheme 5). Synthetically useful yields for the addition of the isobutyrate-derived silyl ketene acetal **3** to benzaldehyde **5a** could be obtained by increasing the reaction times, increasing the catalyst loading of (*R,R*)-**6** to 5 mol %, and using 5 mol % of *i*-Pr_2EtN as an additive. Under these conditions, moderate yields and enantioselectivities were obtained for the *β*-hydroxy ester product **12**. The absolute configuration of this adduct was determined to be 3*S*[36] by optical rotation, which despite a priority change in assigning this center, still represents a *Re* face attack, as observed in the case of the propanoate addition product **9ea** and the acetate addition product **7aa**.

3. Vinylogous Aldol Reactions of Silyl Dienol Ethers. The low reactivity of the isobutyrate-derived silyl ketene acetal **3**, when compared to that of the other, less sterically demanding silyl ketene acetals examined in this survey, suggests that the degree of substitution at the nucleophilic carbon center has a significant effect on the rate of the aldol reactions. This sensitivity of the chiral phosphoramide/$SiCl_4$ catalyst system to steric factors might be used to augment the inherent *γ*-regioselectivity of vinylogous aldol reactions of silyl dienol ethers. If high regioselectivity could be achieved without affecting the high diastereo- and enantioselectivity observed in the reactions of simple ketene acetals, a general and highly selective vinylogous aldol process could be obtained.

3.1. Synthesis of the Silyl Dienol Ethers. Although the silyl dienol ethers for the studies of the Lewis base-catalyzed vinylogous aldol reaction are not thoroughly described in the

(36) Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, *57*, 861−866.

Table 7. Vinylogous Aldol Reactions of Simple, Ester-Derived Silyl Dienol Ethers **4a**−**d** with Aldehydes **5a**−**k**



entry	dienolate	R^1	R^2	R^3	R^4	R^5	product	yield, %[a]	γ/α[b]	dr[b]	er[c]
1	**4a**[d]	Ph (**5a**)	Et	H	H	H	**14aa**	89[e]	>99:1		98.8:1.2
2	**4a**[d]	PhCH=CH (**5g**)	Et	H	H	H	**14ag**	84[e]	>99:1		98.3:1.7
3	**4a**[f]	$PhCH_2CH_2$ (**5k**)	Et	H	H	H	**14ak**	68[g]	>99:1		95.3:4.7
4	**4b**[d]	Ph (**5a**)	Me	Me	H	H	**14ba**	93[e]	>99:1		99.5:0.5
5	**4b**[d]	PhCH=CH (**5g**)	Me	Me	H	H	**14bg**	88	>99:1		99.6:0.4
6	**4b**[f]	$PhCH_2CH_2$ (**5k**)	Me	Me	H	H	**14bk**		ND		ND
7	**4c**[d]	Ph (**5a**)	Et	H	Me	H	**14ca**	91[e]	>99:1	-	96.1:3.9
8	**4c**[d]	PhCH=CH (**5g**)	Et	H	Me	H	**14cg**	97	>99:1		94.0:6.0
9	**4c**[f]	$PhCH_2CH_2$ (**5k**)	Et	H	Me	H	**14ck**	73	>99:1		97.5:2.5
10	**4d**[d]	Ph (**5a**)	*t*-Bu	H	H	Me	**14da**	92[h]	99:1	>99:1	94.5:5.5
11	**4d**[d]	PhCH=CH (**5g**)	*t*-Bu	H	H	Me	**14dg**	71	99:1	>99:1	91.2:8.8
12	**4d**[f]	$PhCH_2CH_2$ (**5k**)	*t*-Bu	H	H	Me	**14dk**		ND	ND	ND

[a] Yields of analytically pure material. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP−SFC. [d] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of dienolate, and 0.01 equiv of (*R*,*R*)-**6** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [e] (*R*) absolute configuration. [f] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of dienolate, 0.05 equiv of (*R*,*R*)-**6**, and 0.05 equiv of *i*-Pr_2EtN at 0.2 M in CH_2Cl_2 at −78 °C for 24 h. [g] (*S*) absolute configuration. [h] (2*S*,3*R*) absolute configuration.

literature, the use of established synthetic methods allows for easy access to these compounds. The enolization procedure developed by Schlessinger and co-workers proved to be a versatile and reliable method.[37] In this procedure, the addition of 1 equiv of HMPA to the solution of LDA prior to addition of the unsaturated carbonyl compound is required to suppress competing conjugate addition of the amide base.

The modified protocol allowed for the synthesis of several *tert*-butyldimethylsilyl dienol ethers in good yields. The products could be purified by distillation and stored for 1−2 weeks at −15 °C without significant decomposition. In most cases, the products were not obtained as single geometrical isomers. The only case that did provide high selectivity was the ethyl senecioate-derived silyl dienol ether **4c** (Figure 4). In some cases, the configuration of the major isomer of the silyl dienol ethers could be determined by measuring their ^{1}H nOe NMR spectra. The major isomers obtained from ethyl crotonate and *tert*-butyl pentenoate are (1*Z*)-**4a** and (1*Z*)-**4d**, respectively. The preparation of the *tert*-butyldimethylsilyl analogue of Grunwell's diene[38] was also achieved under these conditions, providing **13** in good yield. In **4d**, the major isomer was assigned by inspection of the ^{1}H NMR coupling constants. The major isomer of the *tert*-butyl pentenoate-derived silyl dienol ether **4d**, bearing a methyl substituent at C(4), was determined to be the 1*Z*,3*Z*-isomer.[39]

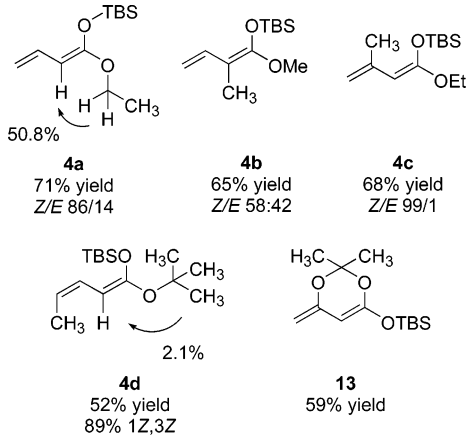


Figure 4. Silyl dienol ethers used in the vinylogous aldol reactions.

3.2. Vinylogous Aldol Reactions of Simple Ester-Derived Silyl Dienol Ethers. The reaction of the ethyl crotonate-derived silyl dienol ether **4a** with benzaldehyde was chosen to address the fundamental question of site selectivity with these nucleophiles. Without a substituent that might provide a steric bias for reactivity at the terminal γ-position, only the inherent site selectivity provided by orbital control would be operative. In the presence of only 1 mol % of the chiral dimeric phosphoramide (*R*,*R*)-**6**, the γ-addition product **14aa** was obtained exclusively in high yield and enantioselectivity (Table 7, entry 1). Similar results were obtained in the addition of **4a** to cinnamaldehyde as well as the aliphatic aldehyde, hydrocinnamaldehyde (**5k**) (entries 2 and 3). These results demonstrate that the catalyst complex provides sufficient differentiation, even between mono- and unsubstituted positions, giving nearly exclusive γ-site selectivity.

A survey of silyl dienol ethers bearing methyl substituents at different sites was then undertaken. In the case of the methyl tiglate-derived silyl dienol ether **4b**, with a competition between di- and unsubstituted reactive centers, high regio- and enantioselectivities were observed in the additions to benzaldehyde and cinnamaldehyde (entries 4 and 5). However, this more highly substituted substrate did not react with the aliphatic aldehyde **5k**. The β-methyl-substituted silyl dienol ether **4c** derived from ethyl senecioate showed more general reactivity, providing the γ-adduct in good yield, regio-, and enantioselectivity for all three aldehydes in the survey (entries 7 and 9). It is interesting to note that despite poor geometrical selectivity in the formation of the silyl dienol ethers, the *E*-isomer of the product was consistently obtained as a single isomer. Only in the reactions of the ethyl senecioate-derived silyl ketene acetal **4c** could any of the corresponding *Z*-isomer be detected by ^{1}H NMR analysis (*E*/*Z* 97:3).

Clearly, the high levels of enantioselectivity observed in the additions of simple silyl ketene acetals to aldehydes translated

(37) Herrman, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2433−2436.
(38) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91−95.
(39) The other *isomers* present could not be unambiguously identified by ^{1}H NMR analysis.

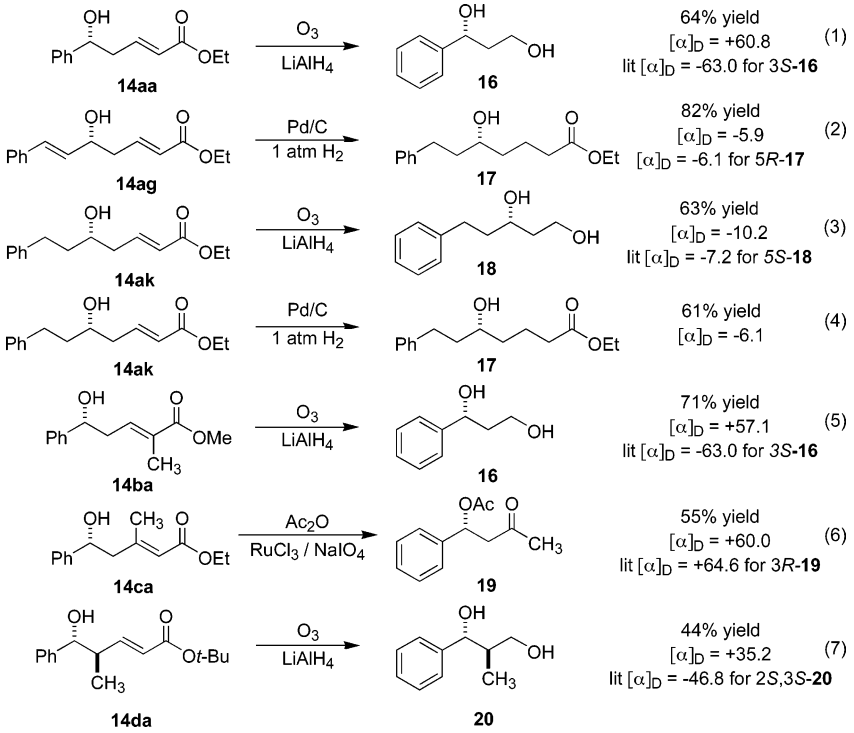
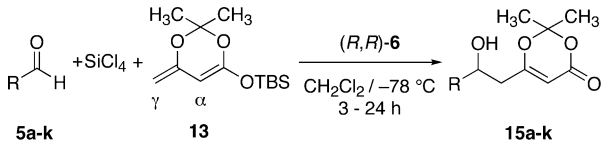


Figure 5. Correlation of the configuration of vinylogous aldol products to known compounds.

into high enantioselectivities for the additions of silyl dienol ethers. The use of a 2-pentenoate-derived silyl dienol ether, bearing a methyl group at the terminal γ-position, would address whether the high anti diastereoselectivity observed previously would also be maintained. Disappointingly, an ethyl 2-pentenoate-derived silyl dienol ether provided a statistical mixture of the two possible isomeric aldol adducts. However, increasing the size of the alkoxy substituent from ethyl to *tert*-butyl restored the high levels of regioselectivity observed in other cases (entries 10 and 11). The γ-addition product **14da** could be obtained in good yields as well as excellent anti diastereo- and enantioselectivities for aldol reactions with benzaldehyde and cinnamaldehyde. Despite several attempts, no reaction was observed with the aliphatic aldehyde **5k**. This behavior was similar to the reactivity pattern observed with the methyl tiglate-derived silyl dienol ether **4b**. The fact that these subtle changes in structure led to such dramatic changes in reactivity attests to the sensitivity of the catalyst complex to the steric demands of the nucleophile.

3.3. Vinylogous Aldol Reactions of a Dioxanone-Derived Silyl Dienol Ether. Simple ester-derived silyl dienol ethers, such as **4a**−**d**, comprise one class of commonly used nucleophiles in vinylogous aldol reactions. The other class, three-heteroatom-substituted silyl dienol ethers, such as Grunwell's diene,[38] were also investigated to provide a point of comparison with other catalytic asymmetric methods.[28] Reactions of the dioxanone-derived silyl dienol ether **13** gave uniformly high regioselectivities and yields (Table 8). However, the enantioselectivities of these reactions were extremely sensitive to the structure of the aldehyde. The selectivity obtained with the aliphatic aldehyde **5k** proved to be the highest in the series (er(**5k**) > er(**5g**) > er(**5a**)). This is particularly noteworthy because this trend is reversed to that usually observed in this series of aldehydes. Determination of the absolute configuration of these aldol products (vide infra) revealed that the product derived from *Re* face attack on the aldehyde had been produced, even though

Table 8. Table 8. Vinylogous Aldol Reactions of Dioxanone-Derived Silyl Dienol Ether **13** with Aldehydes **5a**−**k**



entry	R	product	yield, %[a]	γ/α[b]	er[c]
1	Ph (**5a**)[d]	**15a**	92[e]	>99:1	87.2:12.8
2	PhCH=CH (**5g**)[d]	**15g**	88[e]	>99:1	88.9:11.1
3	$PhCH_2CH_2$ (**5k**)[f]	**15k**	83[g]	>99:1	94.6:5.4

[a] Yields of chromatographically homogeneous material. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP−SFC. [d] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of dienolate, and 0.01 equiv of (*R*,*R*)-**6** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [e] (*R*) absolute configuration. [f] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of dienolate, 0.05 equiv of (*R*,*R*)-**6**, and 0.05 equiv of DIPEA at 0.2 M in CH_2Cl_2 at −78 °C for 24 h. [g] (*S*) absolute configuration.

in some cases the product possessed a 5*S* stereocenter due to Cahn−Ingold−Prelog priority changes.

4. Determination of the Absolute Configuration of the Products of the Vinylogous Aldol Reaction. Unlike the simple β-hydroxy esters produced in the reactions of acetate- and propanoate-derived silyl ketene acetals, the absolute configurations of many of these vinylogous aldol products could not be determined by direct correlation to known examples in the literature. Instead, a synthetic route needed to be devised to relate these structures to a set of compounds for which the absolute configurations had been unambiguously assigned. A straightforward chemical correlation involved cleavage of the C(2)−C(3) double bond and formation of a 1,3-diol, the absolute configuration of which has been established by Masamune and others,[23a,40] in analogy to the stereochemical model provided by the Sharpless asymmetric epoxidation.[41]

In the cases of the aldol adducts **14aa**, **14ak**, **14ba**, and **14da**, ozonolysis followed by reduction of the ozonide with a solution

of lithium aluminum hydride in tetrahydrofuran provided the desired diols in moderate yields (Figure 5, eqs 1, 3, 5, and 7). Comparison of their optical rotations with those reported in the literature revealed that in each case, the aldol adduct derived from *Re* face attack on the aldehyde had been produced, even though in some cases, the product possessed a 3*S* stereocenter due to priority changes. This sense of asymmetric induction is consistent with that observed in all other cases reported in this study.

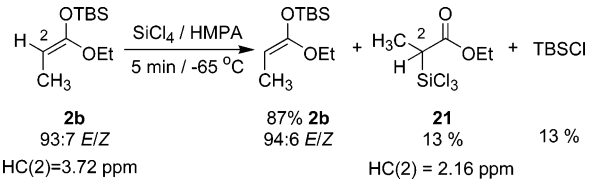
Two cases required different routes due to their substitution patterns. The aldol adduct **14ag** would not be amenable to this method because of concern about competitive ozonolysis of the C(6)−C(7) double bond. Therefore, an alternate route was employed that would not require differentiation of the two double bonds contained in the molecule. Both double bonds of **14ag** were hydrogenated, generating the alkanoate **17**. This compound was then compared to identical alkanoate prepared from the now known (5*R*)-**14ak** to establish absolute configuration, and the optical rotations were similar (compare eqs 2 and 4).

Finally, in the case of the ethyl senecioate-derived aldol adduct **14ca**, correlation to the known β-acetoxy methyl ketone was made by acetylation of **14ca** with acetic anhydride followed by cleavage of the C(2)−C(3) double bond with ruthenium tetraoxide (eq 5). Again, the product corresponding to the (3*R*) enantiomer was obtained.[42]

5. Spectroscopic Investigations of the Reaction Intermediates. To gain information regarding the identity of the active enolate equivalent as well as the cause of the reactivity problems associated with aliphatic aldehydes, several studies were undertaken using both ReactIR and ^{1}H NMR spectroscopy. To investigate the existence of the putative silyl cation intermediate, a series of low temperature ^{1}H and ^{29}Si NMR spectroscopic studies were undertaken. ^{1}H NMR investigations on the stability of the silyl ketene acetals in the presence of the phosphoramide and $SiCl_4$ could identify whether isomerization of the silyl ketene acetal or trans-silylation to the trichlorosilyl ketene acetal was occurring prior to aldolization. A clear understanding of the identity of the active enolate equivalent in these reactions is essential to the development of a rationale for the peculiar anti diastereoconvergence of this process. Because the chemical shift values for several *O*- and *C*-trichlorosilyl carbonyl compounds have been documented in the literature, ^{1}H NMR spectroscopy appeared to be the technique of choice for these studies.

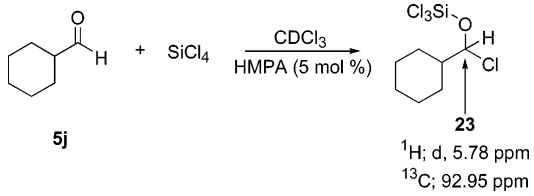
The stability of the ethyl propanoate-derived *O*-*tert*-butyldimethylsilyl ketene acetal **2b** was first studied. Upon mixing equimolar amounts of **2b** and $SiCl_4$ in $CDCl_3$ at 0.2 M at −65 °C in the presence of 10 mol % of HMPA, conditions similar to those used in the synthetic process but in the absence of the aldehyde, little change could be observed in the ^{1}H NMR spectrum of **2b** (Scheme 6). The silyl ketene acetal remained unchanged, with no noticeable erosion in the initial *E*/*Z* ratio, even after extended times. No evidence of signals corresponding to the *O*-trichlorosilyl ketene acetal could be observed. The only change was the appearance of a quartet signal at 2.16 ppm. Careful examination of the ^{1}H and ^{13}C NMR spectra of this reaction mixture revealed that only a small amount of this new species had been formed upon mixing. This new signal represented approximately 10% of the initial amount of silyl ketene acetal **2b**. Furthermore, the amount of this species initially formed did not change, even after 6 h. The formation of an equivalent amount of TBSCl was also observed, consistent with trans-silylation between $SiCl_4$ and the silyl ketene acetal **2b**. Analysis of these spectra and comparison to literature reports led to the conclusion that this new species was the α-trichlorosilyl ethyl propanoate **21**. Subsequent in situ ^{1}H NMR studies of the aldol reactions between **2b** and benzaldehyde or hydrocinnamaldehyde revealed that this newly formed species was completely unreactive and remained even after consumption of the aldehyde. The loss of a small amount of the silyl ketene acetal to this unproductive side reaction helps to understand the need for a slight excess of both the silyl ketene acetal and $SiCl_4$ in the optimal procedure.

Scheme 6



The attenuated reactivity of aliphatic aldehydes in the Lewis base-catalyzed reactions of trichlorosilyl enol ethers and allyltrichlorosilanes had long been an issue of concern.[16] Because the highly reactive acetate-derived silyl ketene acetal **1a** did react with aliphatic aldehydes, an examination of reactivity of this substrate was prompted. Monitoring the reaction of silyl ketene acetal **1a** with cyclohexanecarboxaldehyde (**5j**) in the presence of $SiCl_4$ and 5 mol % of (*R*,*R*)-**6** by ReactIR revealed the immediate disappearance of the aldehyde signal without a corresponding increase in the ester signal derived from the product. This reaction required approximately 1 h to reach completion, as indicated by monitoring the formation of the ester product **6aj**. This observation was surprising, considering that under similar conditions, the aldol reaction of **1a** and benzaldehyde required less than 30 s. To probe the unexplained disappearance of the aldehyde signal, further studies were performed. Upon mixing **5j** and $SiCl_4$ in $CDCl_3$ in the presence of 10 mol % of HMPA, examination of the ^{1}H NMR spectrum revealed that the aldehydic proton had completely disappeared only to be replaced by a new set of signals, assigned as the α-chloro trichlorosilyl ether **23** (Scheme 7). The structure of **23** was confirmed by comparison to similar species in the literature[43] and to a related compound that had previously been identified in these laboratories.[44] Similar ^{1}H NMR experiments performed with benzaldehyde showed little change in the ^{1}H NMR spectrum and no evidence for formation of an analogous α-chloro trichlorosilyl ether.

Scheme 7

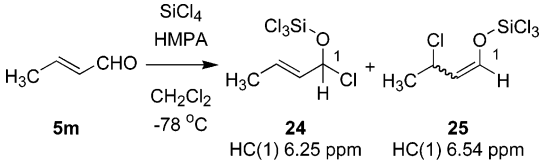


Crotonaldehyde (**5m**) also exhibited uncharacteristically low reactivity and provided low yields of the aldol product when

(40) Nuñez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928−1932.
(41) (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1−300. (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.
(42) Nair, M. S.; Joly, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2049−2052.

compared to the closely related substrate cinnamaldehyde. Upon mixing **5m** and $SiCl_4$ in the presence of 10 mol % of HMPA at −70 °C in $CDCl_3$, ^1H NMR analysis revealed a similar phenomenon to that observed with cyclohexanecarboxaldehyde (Scheme 8). The signal corresponding to the aldehydic proton decreased in intensity, coincident with the appearance of several new signals, assigned to the α-chlorosilyl ether **24** and the α-chloro trichlorosilyl ether **25**. After 15 min, these three species were found to exist in approximately a 2:1:1 ratio of **5m**:**24**:**25**.

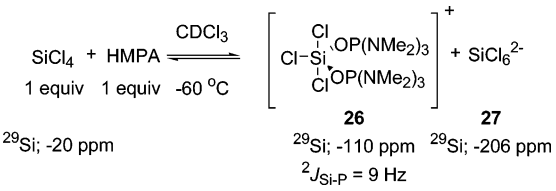
Scheme 8



Finally, the existence of the putative silyl cation intermediate could be addressed by NMR spectroscopy. This species is proposed to be the active Lewis acid that mediates these aldol processes. Preliminary kinetic studies show that the reaction is zero order in $SiCl_4$.[45] Thus, the equilibrium binding of the phosphoramide to $SiCl_4$ is quite strong, and at any time, the phosphoramide catalyst is saturated with $SiCl_4$ (or other chlorosilane species). If the catalyst resting state was indeed a silyl cation complex, it should be spectroscopically observable.

^{29}Si NMR experiments were performed under conditions that approximated those used in the synthetic protocol. Upon mixing $SiCl_4$ and HMPA in a 1:1 ratio in $CDCl_3$ at −60 °C, several signals could be observed (Scheme 9). The major signal corresponded to free $SiCl_4$ (−20 ppm), with new signals appearing at −110 and −206 ppm. The signal at −110 ppm, which lies in the region for a five-coordinate silicon species,[46] is split into a triplet with a coupling constant of $J = 9$ Hz. On the basis of these observations, this signal was tentatively assigned the structure $SiCl_3(HMPA)_2^+$ (**26**). The chemical shift value of the putative trichlorosilyl cation is consistent with values reported for other Lewis base adducts of heteroatom-substituted silyl cations.[47] The value is at lower field compared to the adduct between allyltrichlorosilane and DMF reported by Kobayashi and co-workers ($\delta = -170$ ppm). However, a chemical shift of −170 ppm more likely represents the neutral, hexacoordinate adduct rather than a pentacoordinate silyl cation.[48] A closer analogy is provided by the pentacoordinate trichlorosilyl amidinate complexes reported by Karsch and co-workers ($-89 < \delta < -99$ ppm).[49] The value of the $^2J_{Si-P}$ coupling, although small, is similar to those observed by Cremer and co-workers for HMPA-bound trimethylsilyl cations.[50] The second signal at −206 ppm is assigned as the hexachlorosilicate dianion (**27**) by consideration of its extremely low chemical shift (^{29}Si δ (SiF_6^{2-}) = −197 ppm).[51] Thus, the problem of poor anion solvation in CH_2Cl_2 ($\epsilon = 8.93$)[52] is partially alleviated.

Scheme 9



^{29}Si NMR spectroscopic experiments conducted with the dimeric phosphoramide catalyst (*R*,*R*)-**6** revealed the presence of similar species. However, it appears that the species are under rapid exchange under these conditions. The signal corresponding to the putative silyl cation is rather broad, obscuring the coupling, whereas the signal at −206 ppm could not be observed. Although these data are not as convincing as those obtained in the case of the HMPA-ligated silyl cation, it must be remembered that the dimeric phosphoramide (*R*,*R*)-**6** is a much weaker Lewis base than HMPA due to the electron-withdrawing effect of the naphthyl rings.[53] Regardless of these differences, observation of the ^{31}P NMR spectra of the samples prepared from $SiCl_4$ and either phosphoramide reveals a dramatic upfield shift of the phosphoramide signals from 27 to 19 ppm. This change in the chemical shift is suggestive of complexation to a metal center and is consistent with the upfield shifts in the ^{31}P NMR of related chiral phosphoramides induced upon binding to $SnCl_4$.[54]

Discussion

The chiral Lewis base-catalyzed/$SiCl_4$-mediated aldol additions of silyl ketene acetal nucleophiles are characterized by rapid rates and high levels of regio-, diastereo-, and enantioselectivity. To formulate a unified picture of this process, the trends derived from the structural changes in both the aldehyde and the silyl ketene acetal will first be highlighted. In particular, the significant influence of the steric demands of the nucleophiles will be considered. These trends will then be used as the basis for an open transition structure model to explain the high levels of anti diastereoselectivity observed in this reaction. With the aid of computational studies performed at the PM3 level of theory, this model will then be elaborated to include an analysis of the factors influencing enantioselectivity.

1. Reactivity Trends. The reactivity patterns observed with respect to silyl ketene acetal structure stand in contrast to the reactivity scales developed by Mayr and co-workers for main group organometallic nucleophiles.[20] In an extensive study of the reactivity of silyl enol ethers, Mayr found that an isobutyrate-

(43) (a) Lokensgard, J. P.; Fisher, J. W.; Bartz, W. J.; Meinwald, J. *J. Org. Chem.* **1985**, *50*, 5609−5611. (b) Gundersen, L.-L.; Benneche, T. *Acta Chem. Scand.* **1991**, *45*, 975−977.
(44) Chloro-1-trichlorosiloxyheptane: Ghosh, S. K. Unpublished results from these laboratories.
(45) Examination of the rate of reaction of 1-naphthaldehyde with the silyl ketene acetal **2e** in the presence of $SiCl_4$ (1−4 equiv) and 1 mol % of (*R*,*R*)-**6** by ReactIR revealed a zero-order dependence on the concentration of $SiCl_4$ ($m = 0.051 \pm 0.025$, $r^2 = 0.798$).
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(50) Arshadi, M.; Johnels, D.; Edlund, U.; Ottoson, C.-H.; Cremer, D. *J. Am. Chem. Soc.* **1996**, *118*, 5120−5131.
(51) Marsmann, H. In *NMR Basic Principles and Progress*, *Volume 17*; Diehl, P., Fluck, E., Kosfeld, R., Eds.; Springer-Verlag, Berlin, 1981; p 65.
(52) Reichardt, C. *Solvent and Solvent Effects in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 1988; p 407.
(53) ^{31}P and ^{119}Sn NMR studies have shown that the 1,1′-binaphthyl-2,2′-diamine-derived phosphoramide **6** can be displaced from $SnCl_4$ by a bispyrrolidine-derived phosphoramide: Schleusner, M. Unpublished results from these laboratories.
(54) (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2003**, *125*, 2208−2216. (b) Denmark, S. E.; Xu, S. *Tetrahedron* **1999**, *55*, 8727−8738.

derived silyl ketene acetal is more reactive than a related acetate-derived silyl ketene acetal ($N = 9.49$ versus 8.58).[19] Accordingly, one might have predicted that the α,α-disubstituted ketene acetal **3** would be more reactive than the unsubstituted **1a** in the aldol process. However, a reversed trend is observed wherein the unsubstituted acetate-derived silyl ketene acetal **1a** is far more reactive than the isobutyrate-derived silyl ketene acetal **3** (Figure 6). Furthermore, the presence or absence of an α-substituent plays a far greater role in determining reactivity than its size or structure. In a series of ethyl ester-derived silyl ketene acetals **10a**−**c**, bearing a variety of alkyl substituents, little reactivity difference could be discerned by ReactIR monitoring (Table 6). These reactions were typically complete in less than 30 min. Clearly, in this reaction, the use of a nucleophilicity scale based on electronic factors alone does not provide a good model for rationalizing reactivity. The observed trend suggests that steric factors have a dominant influence on the reactivity of silyl ketene acetals with aldehydes under catalysis by an in situ-generated, chiral phosphoramide-bound, trichlorosilyl cation.

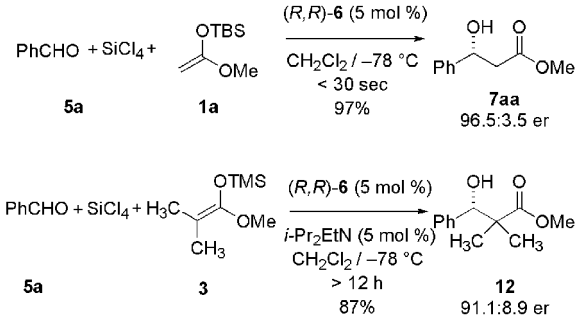


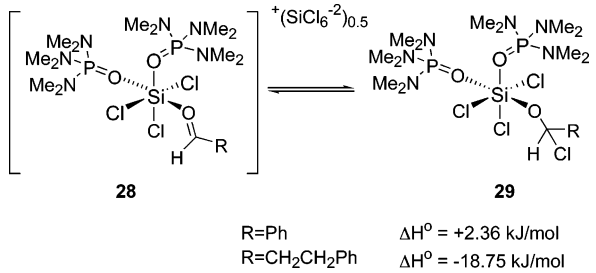
Figure 6. Comparison of reaction rates for substituted silyl ketene acetals.

The proximity of the α-substituents to the reactive center at C(2) of the silyl ketene acetal imparts the greatest significance to steric effects at this position. However, remote substituents still affect reactivity. In a series of propanoate-derived silyl ketene acetals **2a**−**e**, a slight, but noticeable, decrease in reaction rate was observed as the size of the alkoxy substituent was increased from methyl to a sterically more demanding *tert*-butyl ester. Although these reactivity differences were not as drastic as those observed in the case of varying the degree of α-substitution, the role of these substituents in determining selectivity proved more important (Table 3). Similar effects from remote substituents were observed in the vinylogous aldol reaction. For example, the presence or absence of a 2-methyl group, although remote from the reactive γ-position of the silyl dienol ether, greatly influenced the scope of the reaction (Table 7).

When considering reactivity trends with respect to the electrophilic partner in the reaction, steric effects are clearly not as important as they are for the nucleophilic partner. Instead, a different trend becomes apparent that is based on the structure of the electrophile. Conjugated aldehydes bearing aromatic and olefinic substituents show high reactivity in this aldol reaction. No differences were observed between the reactions of electron-rich and electron-poor conjugated aldehydes. However, aliphatic aldehydes proved to be unreactive. The low reactivity of this class of aldehydes had been reported in Lewis base-catalyzed reactions of trichlorosilyl enol ethers and allylic trichlorosilanes.[16,18] When viewed in the larger context of aldol reactions in general, this trend is puzzling because it stands in direct contrast to studies by Guthrie that have shown that aliphatic aldehydes are considerably more reactive than conjugated, aromatic aldehydes toward a wide variety of neutral and anionic nucleophiles.[55] Using Jencks' free energy relationship for carbonyl addition reactions (γ), acetaldehyde is shown to be at least 2 orders of magnitude more reactive than benzaldehyde.[56]

An alternative explanation for this trend can be formulated from the "in situ protection" of aliphatic aldehydes. ^{1}H NMR spectroscopic analysis revealed that both cyclohexanecarboxaldehyde and crotonaldehyde were rapidly transformed into α-chloro trichlorosilyl ethers. Presumably, this process occurs through attack of the ionized chloride on the silyl cation complex of the aldehyde **28** (Scheme 10). Therefore, to explain the poor reactivity of aliphatic aldehydes, we posit that an equilibrium exists between the aldehyde that is bound in the putative silyl cation **28** and an unreactive α-chloro trichlorosilyl ether **29**. Because of its low dielectric constant, dichloromethane ($\epsilon_r = 8.93$)[52] is poorly capable of supporting the ionic species **28**. Collapse of **28** to the α-chloro trichlorosilyl ether generates a more stable, neutral species. Consequently, a low equilibrium concentration of the activated aldehyde complex **28** is available for aldolization. To compensate for the apparent loss in reactivity of these substrates, a powerful nucleophile must be employed that can still react at an appreciable rate with the extremely low concentration of activated aldehyde present in solution at any time. Less nucleophilic species, although capable, cannot undergo reactions at rates that provide a synthetically useful process. The importance of steric factors in this reaction helps explain the higher reactivity of the ethyl propanoate-derived **2b** with aliphatic aldehydes when compared to that of the *tert*-butyl propanoate-derived **2e**. The fact that conjugated aldehydes are resistant to this side process may be due to the unfavorable loss of resonance stabilization in the extended conjugated system. This hypothesis can be confirmed through calculations performed on the addition of HCl to the two representative aldehydes, benzaldehyde and cyclohexanecarboxaldehyde, using the PC version of GAMESS(US) QC package employing the 6-31*(p,d) basis set.[57] In the case of benzaldehyde, formation of the chlorohydrin is an endothermic process ($\Delta H_o = +2.36$ kJ/mol), a result consistent with the resistance of this substrate to chlorohydrin formation under the reaction conditions. However, in the case of cyclohexanecarboxaldehyde, chlorohydrin formation is predicted to be highly exothermic ($\Delta H_o = -18.75$ kJ/mol), again consistent with experimental observations.[58]

Scheme 10



The poor reactivity observed for crotonaldehyde in the aldol reaction was surprising but can be explained using a similar rationale. Again, the reduced concentration of the activated aldehyde complex **28** translates into reduced reaction rate for the aldolization. However, the low yields associated with this

reaction are likely due to the formation of trichlorosilyl ether **25**. It is possible that side reactions involving the trichlorosilyl enol ether **25** can lead to undesired products, contributing to the reduced yield of the desired aldol product **9em**.

Although the acetate-derived silyl ketene acetal **1a** reacted at a reasonable rate with aliphatic aldehydes, the *tert*-butyl propanoate-derived silyl ketene acetal **2e** proved completely unreactive. By using the less sterically demanding ethyl propanoate-derived silyl ketene acetal **2b** and adding TBAI or *i*-Pr_2EtN in substoichiometric quantities, synthetically useful rates and yields could be obtained (Table 5, entries 1 and 2). The beneficial effect of the addition of tetrabutylammonium salts to the reactions of other trichlorosilyl nucleophiles has been investigated by Berrisford and co-workers.[59] It is believed that these additives enhance reactivity by increasing the ionic strength of the solution. An increase in ionic strength should shift the α-chloro trichlorosilyl ether equilibrium back toward the reactive, ionized species (Scheme 10). The specific role of *i*-Pr_2EtN in promoting the reactions of aliphatic aldehydes remains unclear at this time.[60]

The marginal reactivity of aliphatic aldehydes is further attenuated by the presence of α-substituents. Whereas linear and *β*-branched aldehydes, such as **5k** and **5o**, retain some reactivity under modified conditions, the α-branched substrate cyclohexanecarboxaldehyde (**5j**) remains relatively unreactive, most likely due to steric factors affecting approach of the nucleophile (Table 1, compare entries 1, 2, and 7).

2. Selectivity Trends. 2.1. Trends in Enantioselectivity. With regard to reactivity, steric effects play a dominant role in this chiral phosphoramide/$SiCl_4$ catalyst system. Examination of the corresponding trends in enantio-, diastereo-, and regioselectivity reveals a similar pattern. The most significant trend with respect to enantioselectivity was the consistent observation of aldol products derived from *Re* face attack on the aldehyde. The ability of the catalyst (*R*,*R*)-**6** to select for nucleophilic attack at this prochiral face of the aldehyde regardless of nucleophile structure even extends beyond the use of silyl ketene acetals to reactions of other nucleophiles, such as allylic stannanes,[17] silyl enol ethers,[61a] and isocyanides.[61b] This uniform facial selectivity suggests that it is the interaction between the catalyst-bound aldehyde and the incoming nucleophile that is the major contributor to the observed enantiofacial selectivity in this family of Lewis base-catalyzed reactions.

With respect to nucleophile structure, two important contributors to enantioselectivity are (1) the presence of α-substituents and (2) the size of the alkoxy substituent. The enantioselectivity for the methyl ester-derived silyl ketene acetals **1a**, **2a**, and **3** decreases in the following order: **1a** > **3** > **2a**, which clearly does not follow their reactivity (Figure 6). However, a clearer relationship between the size of the alkoxy substituent and enantioselectivity is apparent in the progressive improvement from methyl to *tert*-butyl esters (Table 3).

The dramatic reactivity differences observed between conjugated and aliphatic aldehydes are also evident with respect to diastereoselectivity. In almost all cases, the selectivity trend observed for a particular nucleophile shows that **5a** > **5g** ≫ **5k**. It is only in the case of the dioxanone-derived silyl enol ether **13** that a reversed trend is observed (Table 8).

2.2. Trends in Diastereoselectivity. The consistently high anti diastereoselectivity is at once a great advantage synthetically and also provides helpful insights into the overwhelming control features in relative topicity of attack in the aldol addition. Interestingly, it was observed that even the structure of the catalyst had little effect as both HMPA and (*R*,*R*)-**6** both gave high anti diastereoselectivity. A rationale for this behavior will be presented in detail in a subsequent section.

2.3. Trends in Regioselectivity. Although the reactivity of silyl dienol ethers favors reaction at the terminal *γ*-position, this selectivity is often variable, especially in the vinylogous aldol reaction of simple ester-derived silyl dienol ethers.[26] The high regioselectivity observed under the influence of the chiral phosphoramide/$SiCl_4$ catalyst system appears to be a consequence of the steric influence provided by the catalyst complex during the aldolization. In a direct comparison of differentially substituted methyl ester-derived silyl ketene acetals, there are large rate differences based on the degree of α-substitution (Figure 6). The reaction of a silyl dienol ether can then be considered as an intramolecular competition where, in this case, reaction generally occurs at the less substituted *γ*-position. This can be observed in the additions of the ethyl crotonate-derived silyl dienol ether **4a**, wherein the question of regioselectivity can be framed as an intramolecular competition between acetate-like (C(4)) and propanoate-like (C(2)) silyl ketene acetals (Table 7, entries 1−3). A more heavily biased system is seen in the case of the tiglate-derived silyl dienol ether **4b**, wherein the observed regioselectivity can be thought of as an intramolecular competition between acetate-like (C(4)) and isobutyrate-like (C(2)) silyl ketene acetals (Table 7, entries 4−6).

The problems encountered in the case of the 2-pentenoate-derived silyl dienol ethers further illustrate this trend and validate the hypothesis for the role of steric effects. Here, both the C(2) and C(4) reactive centers are monosubstituted, propanoate-like positions. In initial studies with the ethyl pentenoate-derived silyl dienol ether, a near equal distribution of products was observed. Only when a bulky *tert*-butyl ester substituent was introduced could high regioselectivity be recovered (Table 7, entries 10−12). The role of the alkoxy substituent at this point remains unclear, but consideration of the conformation of the silyl dienol ether provides some insight. From ^{1}H NMR nOe studies, the geometry of the major isomer of **4d** was determined to be 1*Z*,3*Z*. If the pinwheel effect is considered,[62] this would place the alkoxy substituent in an *s*-cis position, directed toward C(2), possibly accounting for the enhanced regioselectivity observed in this case (Figure 7). This analysis, if true, will have interesting consequences for regioselectivity in the vinylogous aldol reactions of ketone- and aldehyde-derived silyl dienol ethers.

(55) Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 962−973.
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(57) (a) Granovsky, A. A. (http://classic.chem.msu.su/gran/gamess/index.html). (b) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A., Jr. *J. Comput. Chem.* **1993**, *14*, 1347−1363.
(58) It is reasonable to assume that the aldol reaction occurs through the α-chloro trichlorosilyl ether because products derived from reactions with aliphatic aldehydes give similar levels of selectivity and the same sense of asymmetric induction as that observed with other substrates.
(59) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351−2354.
(60) Initially, *i*-Pr_2EtN was added to scavenge adventitious HCl in the reaction mixture over extended reaction times. Thus, small amounts of the ammonium chloride would be generated which could also alter the ionic strength of the solution. Moreover, *i*-Pr_2EtN may also facilitate catalyst turnover as was seen in the reactions of allyltrichlorosilanes (ref 18).
(61) (a) Denmark, S. E.; Heemstra, J. R., Jr. *Org. Lett.* **2003**, *5*, 2303−2306. (b) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825−7827.
(62) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451−1453.

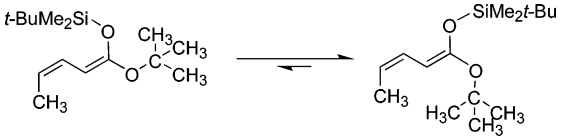

Figure 7. Conformation of *tert*-butyl pentenoate-derived silyl dienol ether **4d**.

2.4. Origin of Double Bond Geometries in the Products of the Vinylogous Aldol Reaction. Despite the fact that all of the silyl dienol ethers employed in these phosphoramide-catalyzed vinylogous aldol reactions were mixtures of geometrical isomers, high selectivity for the thermodynamically favored (*E*)-α,*β*-unsaturated ester product was observed throughout. Consideration of the silyl dienol ethers suggests that they most likely exist in and react through the *s*-trans conformation to avoid allylic strain in the *s*-cis conformation and to maximize conjugation.[63] This conformation should lead to the *E* product, regardless of the geometry of the silyl dienol ether.

3. Proposed Mechanism. The proposed catalytic cycle involves the intermediacy of a highly electrophilic, phosphoramide-bound silyl cation. As discussed in the Introduction, the active species in these reactions is a chiral Lewis acid. *However, these are not Lewis acid-catalyzed reactions*. ^{1}H NMR spectroscopic analysis of reaction mixtures revealed that the direct products of aldolization are trichlorosilyl ethers rather than the *tert*-butyldimethylsilyl ethers that would be formed by a process that would be catalytic in silicon tetrachloride. Examination of the catalytic cycle shown in Figure 8 reveals that each molecule of $SiCl_4$ that enters the catalytic cycle ends up incorporated into the product, while the Lewis basic phosphoramide catalyst is released to participate in subsequent turnovers. Therefore, these reactions are phosphoramide-catalyzed and $SiCl_4$-mediated.

The cycle is initiated by binding of the phosphoramide to the weakly Lewis acidic $SiCl_4$. This binding leads to polarization and eventual ionization of a chloride ion, generating a chiral, trichlorosilyl cation **i**. This species can then bind the aldehyde to form the complex **ii**. Depending on the nature of the bound aldehyde, this intermediate may be in equilibrium with the unreactive chlorohydrin species **iii**. Attack of the silyl ketene acetal on the activated aldehyde then generates a species, which after cleavage of the *tert*-butyldimethylsilyl group and dissociation of the catalyst, forms the product as the trichlorosilyl ether.

The key species in this cycle is the putative silyl cation. Because initial kinetics studies suggested that this species might be the catalyst resting state, low temperature ^{29}Si NMR investigations, as outlined in Scheme 9, provided direct evidence for the existence of this species. The spectroscopic detection of this species provides the first direct evidence for the intermediacy of a silyl cation in any Lewis base-catalyzed process and lends support to ideas about the dual roles of both the Lewis basic and Lewis acidic species in this catalytic asymmetric aldol reaction.

4. Mechanism of Stereoselection and Proposed Catalyst Structure. 4.1. Rationale for the Observed Diastereoselectivity. The high anti diastereoselectivity observed in these reactions stands in stark contrast to that of most other Lewis acid-catalyzed aldol reactions of silyl ketene acetals which produce the syn diastereomer with high selectivity.[8] Variable levels of stereoconvergence with respect to silyl ketene acetal geometry are observed with different catalyst systems. The trend toward syn diastereoselectivity is also apparent in simple, catalytic aldol reactions of silyl ketene acetals. Only two reports, one on the aldol reactions of *tert*-butyl thiopropanoate-derived silyl ketene acetals[64] and another on the use of trityl perchlorate as a catalyst for the additions of silyl enol ethers,[65] consistently provide the aldol adducts with synthetically useful levels of anti diastereoselectivity. The fact that this reaction is anti diastereoselective, as well as diastereoconvergent, is particularly noteworthy and deserves comment.[25]

The analysis of the diastereoselectivity of this reaction requires, first, knowledge of the structure of the active enolate equivalent. Because no trans-silylation to a reactive trichlorosilyl enol ether is observed with **2b** and because the direct products of the reaction are clearly trichlorosilyl ethers rather than *tert*-butyldimethylsilyl ethers, the reaction should proceed through an open transition structure. Furthermore, because the silyl ketene acetal does not lose its stereochemical integrity under the reaction conditions, this analysis must also explain the diastereoconvergence of both (*E*)- and (*Z*)-**2e**.

With this in mind, several open transition structures were considered to rationalize the diastereoselectivity of this reaction. In each enantiomorphic series, six possible transition structures can be envisioned for each silyl ketene acetal isomer. Within those six structures, there are three ((+)-synclinal, antiperiplanar, (−)-synclinal) that lead to the anti product and three that lead to the syn product. These transition structures can be further refined if the conformation of the silyl ketene acetal is also con-

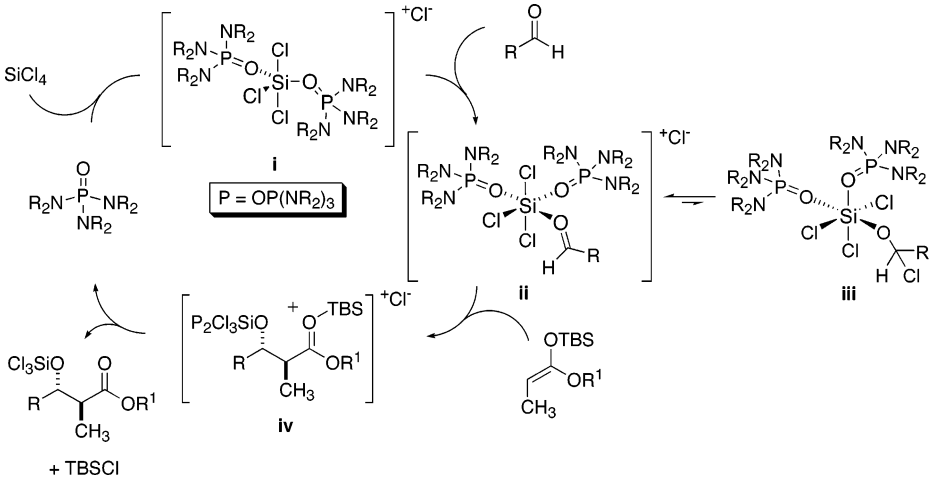

Figure 8. Proposed catalytic cycle.

sidered. According to Wilcox et al., the geometry of the double bond and the position of the α-substituent are the relevant factors in understanding the conformation of these molecules (Figure 9).[62]

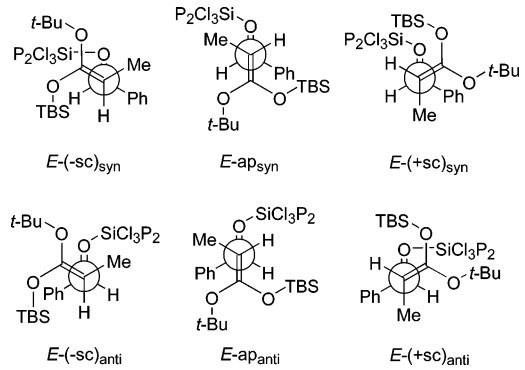

Figure 9. Possible open transition structures for the reaction of (*E*)-**2e**.

The next step in the analysis is to narrow down the number of possible transition structures that are consistent with the observations. The (+)-synclinal (+sc) and (−)-synclinal (−sc) transition structures were eliminated on the basis of unfavorable dipole−dipole interactions, as explained by Heathcock et al. for the diastereoselectivity in silyl enol ether aldol reactions.[66] This hypothesis is supported by stereochemical studies from these laboratories in which a rigid model shows a clear preference for the antiperiplanar (ap) transition structure in the presence of a wide variety of Lewis acid catalysts.[67] Although no cationic Lewis acids were considered in these studies, the validity of extending this analysis will be borne out by other observations based on steric rather than electronic considerations (vide infra). Therefore, two ap transition structures, one leading to the anti and another to the syn product, had to be considered for the reactions of (*E*)- and (*Z*)-silyl ketene acetals, respectively (Figure 10).

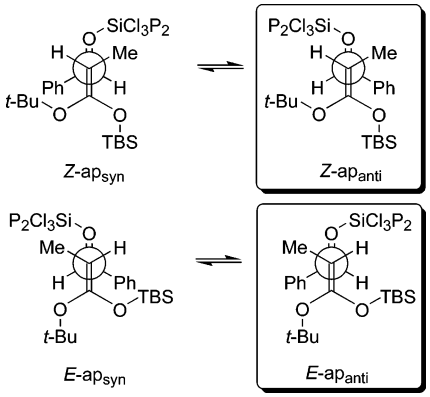

Figure 10. Stereochemical analysis of the aldol reaction of silyl ketene acetals.

The most obvious difference between the transition structures leading to the syn and those leading to anti is the position of the α-substituent. In the transition structures for the anti pathway from both (*Z*)- and (*E*)-silyl ketene acetals, the α-methyl substituent lies in the sector adjacent to the bound silyl cation ((*Z*)-ap$_{anti}$ and (*E*)-ap$_{anti}$). The reverse is true for the syn pathway ((*Z*)-ap$_{syn}$ and (*E*)-ap$_{syn}$). In his studies of the additions of silyl enol ethers to aldehydes catalyzed by trityl perchlorate, Mukaiyama et al. rationalized the high level of anti selectivity obtained for both the *E*- and *Z*-isomers of the *tert*-butyldimethylsilyl enol ether of 3-pentanone on the basis of interaction between the α-substituent and the bound trityl cation.[65] Molecular models of the silyl cation/phosphoramide catalyst complex (vide infra) attest to the size of the ligated silyl cation. Therefore, we propose that it is the interaction between the α-substituent and the bound silyl cation complex that is responsible for the high degree of anti diastereoconvergence observed in these aldol reactions.

This rationalization gains support from the precipitous loss in reactivity that occurs when an α,α-disubstituted silyl ketene acetal is employed (Figure 6). Under the assumption that the sector containing the silyl cation complex is the most sterically congested, there are only two transition structures that place the α-hydrogen substituent on the silyl ketene acetal in this position for the approach of (*E*)-**2e**, (*E*)-sc$_{syn}$, and (*E*)-ap$_{anti}$ (Figure 9). Exchange of this α-hydrogen for a methyl group, as would be the case upon changing from the propanoate-derived **2e** to the isobutyrate-derived **3**, forces a substituent into that region of space and accounts for the significant loss in reactivity. Examination of the influence of this additional methyl group on any of the other transition structures reveals that it would appear in a relatively uncongested sector and the loss in reactivity for **3** would be difficult to explain.

The antiperiplanar transition structure is also helpful in understanding the change in the degree of diastereoconvergence upon changing from an ethyl to a *tert*-butyl propanoate-derived silyl ketene acetal. Although the major difference between the ap$_{anti}$ and ap$_{syn}$ transition structures in either the *Z*- or *E*-series is the position of the α-substituent, a second difference is also apparent. This difference, based on careful consideration of the pinwheel conformation, was originally suggested by Gennari and co-workers in studies of the diastereoconvergent aldol reactions of thioketene acetals and appears applicable to this system.[64] In the *Z*-series, there is a gauche interaction between the alkoxy group and the aldehyde R group in (*Z*)-ap$_{syn}$ that is absent in (*Z*)-ap$_{anti}$ (Figure 10). A similar gauche interaction is also present the *E*-series, but now it is between the silyloxy substituent and the aldehyde R group in (*E*)-ap$_{syn}$. On the basis of this analysis, a decrease in the steric demands of the alkoxy substituent would have a greater affect on the degree of anti diastereoselectivity in the *Z*-series than in the *E*-series. This is consistent with the observed trends in diastereoselectivity, where a lesser degree of diastereoconvergence is observed with **2b** as compared to **2e**, lending further support to the conclusion that an ap$_{anti}$ transition structure is operative in this aldol addition (Table 3, entries 2 and 3).

The assumption that the phosphoramide-bound trichlorosilyl cation complex acts as an extremely large Lewis acid not only rationalizes the observed anti diastereoconvergence but also is consistent with earlier conclusions regarding the sensitivity of this catalyst system to the steric demands of the incoming nucleophile.

4.2. Rationale for the Observed Enantioselectivity. Although the diastereoselectivity in this reaction can be rationalized

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(65) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1535−1538.
(66) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027−3037.
(67) Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707−709.

through use of general models for the aldol transition structure, more information about the structure of the catalyst complex is required to rationalize the high enantioselectivity. Despite numerous attempts at crystallization, a structure determination for the catalyst complex is lacking. However, from ^{29}Si NMR studies aided by computer modeling, some predictions can be made that are consistent with the observed trends in enantioselectivity.

Calculations on a complex of benzaldehyde and the dimeric phosphoramide (*R*,*R*)-**6**-bound trichlorosilyl cation were performed using the PC version of GAMESS(US) QC package employing the PM3 basis set. The aldehyde is bound trans to one of the phosphoramides, consistent with a consideration of the nature of the hypervalent bonds in the ligand field around silicon.[68] This constellation places the aldehyde against one of the binaphthyl units. In this model, the exposure of the *Re* face of the aldehyde is determined by two factors: interaction with the *N*-methyl group of the 1,1′-binaphthyl-2,2′-diamine backbone and interactions with one of the naphthyl rings of the 1,1′-binaphthyl-2,2′-diamine. The *N*-methyl groups, previously thought to play little role in the reactivity or selectivity of the catalyst, protrude far into the binding pocket. This substituent effectively blocks the approach of the nucleophile from the *Si* face (Figure 11). The structure also suggests the possibility of a stabilizing, edge-to-face $\pi-\pi$ interaction for this conformation.[69] This interaction may help to rationalize the higher selectivity observed for conjugated compared to that for aliphatic aldehydes.[70]

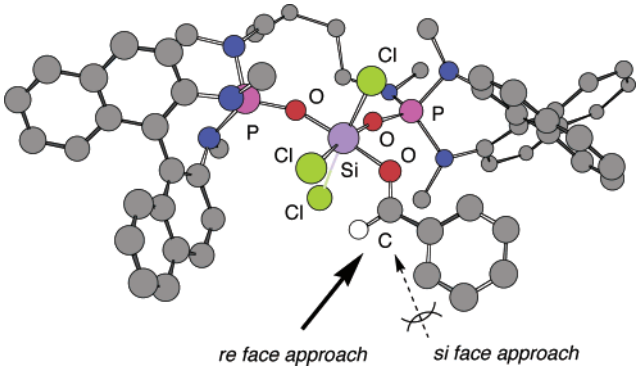

Figure 11. Calculated structure of the aldehyde−silyl cation complex optimized in GAMESS(US) QC package at the PM3 level and visualized using Chem3D, with selected hydrogens omitted for clarity.

The shape of the binding pocket also helps to explain the dramatic influence of branching α to the reactive center on the silyl ketene acetal or the aldehyde. In the case of larger, branched α-substituents on the nucleophile, interactions between such a substituent and the adjacent naphthyl ring may disfavor the anti approach through (*E*)-ap$_{anti}$. Smaller, unbranched α-substituents, such as the ethyl substituent in **10a** or the isobutyl substituent in **10c**, can be rotated into a gauche orientation that would direct them away from an unfavorable interaction with the catalyst. However, the isopropyl substituent in **10b** cannot be rotated into a conformation that avoids destabilizing approach through an (*E*)-ap$_{anti}$ transition structure.

In aldehydes bearing α-substituents, unfavorable interactions with the catalyst system may be responsible for reduced selectivity. For cyclohexanecarboxaldehyde, this unfavorable interaction is particularly clear. The preferred conformation of α-branched aldehydes has one of the alkyl substituents eclipsed with the carbon−oxygen double bond.[71] Therefore, the remainder of the ring system experiences steric interactions with the catalyst backbone which allow a lower energy, syn-selective pathway for nucleophilic attack.

Conclusion

The use of chiral Lewis acids generated by Lewis base catalysis has allowed for the development of a novel and general aldol reaction between a wide range of silyl ketene acetals and aldehydes. The putative, in situ-generated chiral silyl cation provides high levels of diastereo- and enantioselectivity. This process represents one of the few examples of an anti stereoconvergent aldol reaction of silyl ketene acetals. Furthermore, the extension of this method to silyl dienol ethers derived from esters shows exceptionally high levels of regioselectivity in addition to comparable diastereo- and enantioselectivities. Analysis of trends in reactivity and selectivity shows that the catalyst binding pocket is congested, and steric considerations are predominant influences on diastereo- and enantioselectivity. Conclusions drawn from computational studies of the aldehyde-bound catalyst complex support the hypothesis of steric control. Considering that this chiral phosphoramide/$SiCl_4$ catalyst system has also proven to be useful in a number of other carbonyl addition processes, it appears that the Lewis base-catalyzed reactions of main group organometallic nucleophiles represent a general method. Further studies are underway to optimize and structurally define the catalyst structure and to further expand the scope of Lewis base-catalyzed, carbon−carbon bond-forming processes.

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Supporting Information Available: Experimental details for the preparation and full spectroscopic and analytical characterization of all compounds reported along with coordinates for the catalyst−aldehyde complex in Figure 11. This material is available free of charge via the Internet at http://pubs.acs.org.

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