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Lewis Base Activation of Lewis Acids. Addition of Silyl Ketene Acetals to Aldehydes

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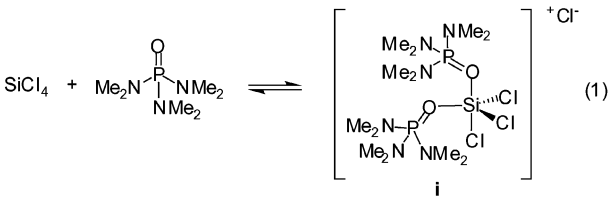
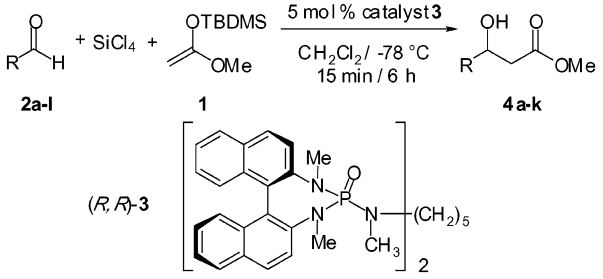
Chiral Lewis acids are widely used in asymmetric catalysis for the selective activation of electrophilic functional groups, in particular, carbonyls.[1] The vast array of reactions that are susceptible to chiral Lewis acid catalysis[2] are guided by a common design principle: an achiral metal species is transformed by ligand substitution with a chiral adjuvant into a chiral metal complex. A consequence of ligand binding, however, is a decrease in the inherent electrophilicity of the metal atom, thus requiring either a high association constant or preformation of the complex to avoid competition from an achiral background reaction.[3] Interestingly, not all Lewis acid−base interactions lead to diminished electrophilicity.[4] In a recent communication, we described the activation of the weak Lewis acid $SiCl_4$ by a strongly Lewis basic phosphoramide.[5] Binding of the phosphoramide polarizes the silicon−chlorine bonds, leading to ionization of a chloride and formation of a catalytically active, pentacoordinate trichlorosilyl cation **i** (eq 1).[6]



In the Lewis-base-catalyzed reactions of trichlorosilyl enolates and allyltrichlorosilanes,[7] the nucleophilic fragment is attached to the electrophilic silicon atom. Association of the electrophile and the chiral activator generates a single species which contains all of the reaction partners organized about the silicon center for a selective reaction via a closed transition structure. However, the scope of the process is limited by the ability to synthesize a given trichlorosilyl nucleophile. The use of $SiCl_4$ as an exogenous Lewis acid releases this synthetic constraint and allows for the conscription of many structurally diverse, main group organometallic nucleophiles.[5] To expand the scope of this Lewis-base-activated, $SiCl_4$-mediated process, we have begun to explore the reactivity and selectivity of other main group nucleophiles. Guided by the nucleophilicity scales developed by Mayr and co-workers,[8] we were particularly intrigued by the high reactivity of silyl ketene acetals. Herein, we report our initial studies into the highly enantio- and diastereoselective addition of acetate and propanoate derived silyl ketene acetals to a variety of aromatic, olefinic, propargylic, and *aliphatic* aldehydes.

Initial investigations focused on the simple, but highly reactive, ketene acetal **1**. The addition to benzaldehyde (**2a**) in the presence of 5 mol % of the dimeric phosphoramide (*R,R*)-**3** at −78 °C provided **4a** in good yield and selectivity (Table 1, entry 1). ReactIR studies revealed that complete consumption of the aldehyde occurred in under 5 min. In contrast, the reaction of allyltributylstannane under similar conditions required almost 1 h. Furthermore, it was determined that the absolute configuration of the newly formed stereocenter is *R*,[9] in agreement with the sense of asymmetric induction observed in the allylation reaction.

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



entry	R	product	yield, %[b]	er[c]
1	C_6H_5 (**2a**)	**4a**[d]	97[e]	96.5:3.5
2	1-naphthyl (**2b**)	**4b**	98	90:10
3	2-naphthyl (**2c**)	**4c**	98	97:3
4	4-$CH_3C_6H_4$ (**2d**)	**4d**	97	97:3
5	4-$CH_3OC_6H_4$ (**2e**)	**4e**	97	98.5:1.5
6	4-$CF_3C_6H_4$ (**2f**)	**4f**	97	95.5:4.5
7	(*E*)-PhCH=CH (**2g**)	**4g**	95[e]	97:3
8	(*E*)-PhCH=C(CH_3) (**2h**)	**4h**	98	72.5:27.5
9	2-furyl (**2i**)	**4i**	94[e]	93.5:6.5
10	cyclohexyl (**2j**)[f]	**4j**	86[e]	94:6
11	$PhCH_2CH_2$ (**2k**)[f]	**4k**	72[e]	90.5:9.5

[a] All reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **1**, and 0.05 equiv of (*R,R*)-**3** at 0.2 M in CH_2Cl_2 at −78 °C for 15 min. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [d] *R* absolute configuration.[9] [e] Chromatographically homogeneous material. [f] Reaction time 6 h.

Table 1 contains the results of an aldehyde survey for this reaction. In almost all cases, equally high reactivity and, more importantly, selectivity are maintained. Both electron-rich and electron-poor aromatic aldehydes react rapidly (entries 4−6), yielding products with comparable selectivity to benzaldehyde. Different aromatic structures, such as naphthyl and furyl, also provide products in good yields and high selectivities (entries 2, 3, 9). Olefinic aldehydes show high selectivity, although the presence of an α substituent did lead to an erosion in selectivity (entries 7, 8). Most importantly, aliphatic aldehydes reacted, albeit at a slightly slower rate, producing the aldol adducts in good yields and selectivities (entries 10, 11). These results are particularly noteworthy because aliphatic aldehydes have typically failed as useful substrates in the reactions with other trichlorosilyl-based nucleophiles.[7,10]

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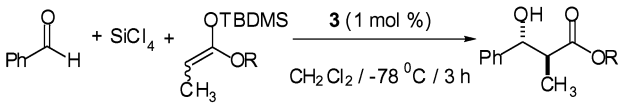
Table 2. Aldol Reaction with Propanoate-Derived *tert*-Butyldimethylsilyl Ketene Acetals[a]



2a **5a-d** **6a-d**

entry	R	*E*:*Z*[b]	product	yield, %[c]	er[d]	dr[b]
1	Me (**5a**)	82:18	**6a**	98	86:14	99:1
2	Et (**5b**)	95:5	**6b**[e]	78	88:12	98:2
3	Ph (**5c**)	94:6	**6c**	98	94:6	94:6
4	*t*-Bu (**5d**)	95:5	**6d**[e]	93[f]	>99:1	99:1
5	*t*-Bu (**5d**)	12:88	**6d**[e]	73	>99:1	99:1

[a] All reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of **5a**−**d**, and 0.01 equiv of (*R*,*R*)-**3** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [b] Determined by ^1H NMR analysis. [c] Chromatographically homogeneous material. [d] Determined by CSP-SFC. [e] *2S*,3*R* absolute configuration.[11] [f] Analytically pure material.

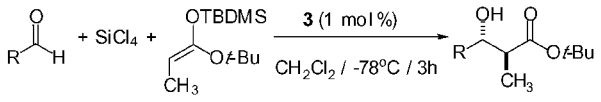
In light of the initial success of the addition reactions of the acetate-derived ketene acetal, the reactions of propanoate-derived ketene acetals were investigated to assess both enantio- and diastereoselectivity. Addition of the (*E*)-*tert*-butyldimethylsilyl ketene acetal (*E*)-**5b** derived from ethyl propanoate to benzaldehyde in the presence of 1 mol % of the catalyst (*R*,*R*)-**3** provided *anti*-**6b** with high enantio- and diastereoselectivity. The configuration of the product was determined to be (2*S*,3*R*)-**6b**,[11] the same absolute configuration observed in the acetate addition reactions.

A survey of ketene acetal structure revealed that the alkoxy substituent had little effect on the diastereoselectivity, although it did have a major influence on enantioselectivity, such that er increased with the steric bulk of the alkoxy substituent in the order of Me < Et < Ph ≪ *t*-Bu (Table 2). In the case of the (*E*)-*tert*-butyldimethylsilyl ketene acetal (*E*)-**5d** derived from *tert*-butyl propanoate, nearly complete selectivity is observed in the addition to benzaldehyde (entry 4). Surprisingly, it is also observed that enantio- and diastereoselectivity are not affected by the geometrical integrity of the nucleophile. The addition of (*Z*)-*tert*-butyldimethylsilyl ketene acetal (*Z*)-**5d** derived from *tert*-butyl propanoate also yielded the anti adduct with similar yield and selectivity (entry 5). The observation of a stereoconvergent, anti-selective aldol process strongly supports reaction through an open transition structure.[12] NMR investigations on the stability of the ketene acetals to the combination of $SiCl_4$ and HMPA revealed that little or no isomerization or metathesis is occurring. This rules out a cyclic, Zimmerman−Traxler type transition structure.[13] This result is particularly intriguing because there are few examples of stereoconvergent anti aldol processes.[14] Most ketene acetal aldol processes afford syn selectivities, and, in general, the (*Z*)-ketene acetal is unreactive and/or yields products with poor selectivities.

The scope of the reaction was again explored with a variety of aldehydes (Table 3). As was observed with the acetate-derived ketene acetal **1**, both electron-rich and electron-poor substrates react with high selectivities (entries 4, 5). For olefinic aldehydes, selectivities were also high (entries 6, 7). The propargylic aldehyde, which is the problematic case in many catalyst systems, has a slightly lower selectivity (entry 8). However, aliphatic aldehydes did not react with the sterically hindered ketene acetal **5d**!

To enhance the reactivity of the propanoate derived ketene acetals, less sterically demanding esters were tested with the aliphatic aldehyde substrates. Whereas (*E*)-**5d** yielded a trace of product after 24 h at −78 °C, a moderate yield could be obtained through the use of the less sterically demanding (*E*)-**5b** (Table 4).

Table 3. Aldol Reaction with (*E*)-1-(*tert*-Butoxy-propenyl)-*tert*-butyldimethylsilane (**5d**)[a]

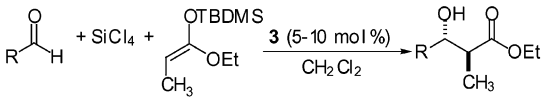


2a-l (*E*)-**5d** **6dx**

entry	R	product	yield, %[b]	dr[c]	er[d]
1	C_6H_5 (**2a**)	**6da**[e]	93	99:1	>99:1
2	1-naphthyl (**2b**)	**6db**	98	96:4	97:3
3	2-naphthyl (**2c**)	**6dc**	95	>99:1	>99:1
4	4-$CH_3OC_6H_4$ (**2e**)	**6de**	88	>99:1	99:1
5	4-$CF_3C_6H_4$ (**2f**)	**6df**	93	>99:1	96:4
6	(*E*)-PhCH═CH (**2g**)	**6dg**	98	>99:1	>99:1
7	(*E*)-PhCH═C(CH_3) (**2h**)	**6dh**	90	>99:1	96:4
8	phenyl propargyl (**2l**)	**6dl**	92	96:4	84:16

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of (*E*)-**5d**, and 0.01 equiv of (*R*,*R*)-**3** at 0.2 M in CH_2Cl_2 at −78 °C for 3 h. [b] Yields of analytically pure material. [c] Determined by ^1H NMR analysis. [d] Determined by CSP-SFC. [e] *2S*,3*R* absolute configuration.[9]

Table 4. Aldol Reaction of (*E*)-1-(Ethoxy-propenyl)-*tert*-butyldimethylsilane ((*E*)-**5b**) with Aliphatic Aldehydes



2j-k (*E*)-**5b** **6bx**

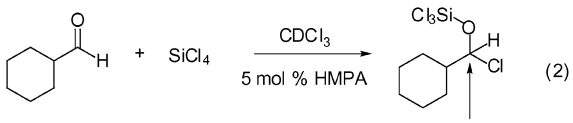
entry	R	product	yield, %	dr[a]	er[b]
1	$PhCH_2CH_2$ (**2k**)[c]	**6bk**	55[d]	93:7	94.5:5.5
2	$PhCH_2CH_2$ (**2k**)[e]	**6bk**	71[f]	91:9	94:6
3	cyclohexyl (**2j**)[e]	**6bj**	29[d]	92:8	ND
4	cyclohexyl (**2j**)[g]	**6bj**	49[f]	89:11	67.8:32.2

[a] Determined by ^1H NMR analysis. [b] Determined by CSP-SFC. [c] Reaction employed 1.1 equiv of $SiCl_4$, 1.2 equiv of (*E*)-**5b**, and 0.05 equiv of (*R*,*R*)-**3** at 0.4 M in CH_2Cl_2 at −78 °C for 24 h. [d] Chromatographically homogeneous material. [e] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of (*E*)-**5b**, 0.05 equiv of (*R*,*R*)-**3**, and 0.1 equiv of TBAI at 0.4 M in CH_2Cl_2 at −78 °C for 24 h. [f] Yield of analytically pure material. [g] Reaction employed 1.1 equiv of $SiCl_4$, 1.2 equiv of (*E*)-**5b**, 0.1 equiv of (*R*,*R*)-**3**, and 0.1 equiv of TBAI at 0.8 M in CH_2Cl_2 at −40 °C for 24 h.

To further increase the reaction rate, the use of tetrabutylammonium iodide (TBAI) as an additive was investigated. Earlier reports demonstrated that addition of ammonium salts increased the rate of chlorosilyl nucleophile additions by increasing the ionic strength of the medium.[15] It was thought that increasing the ionic strength of the solution could similarly favor the ionization of $SiCl_4$ to form species **i**. Hydrocinnamaldehyde **2k** reacted with good yield and selectivity after 24 h in the presence of 5 mol % of (*R*,*R*)-**3** and 10 mol % of TBAI at −78 °C. However, the α branched cyclohexanecarboxaldehyde **2j** could not be induced to react under these conditions. Use of a higher catalyst loading of 10 mol % and higher temperature could provide the product **6bj** in moderate yield and selectivity.

In an effort to better understand the decreased reactivity of aliphatic aldehydes under these reaction conditions, careful ReactIR and ^1H NMR investigations were undertaken. Upon mixing equimolar amounts of cyclohexanecarboxaldehyde **2j** and $SiCl_4$ in the presence of a catalytic amount of HMPA at −78 °C, the ^1H NMR signals corresponding to the aldehyde immediately disappeared! The disappearance of the signal corresponding to the aldehydic proton coincides with the appearance of a new signal at 5.78 ppm (eq 2). This signal was assigned as the α chloro silyl ether **7** by analogy to related compounds.[16] Similar experiments

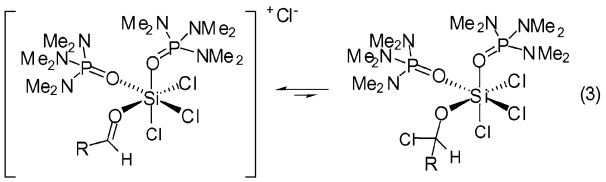
with benzaldehyde only reveal a slight broadening of the aldehydic proton without the appearance of any new signals. The resistance of such conjugated aldehydes to chloride addition may be due to the unfavorable loss of resonance stabilization in the extended, conjugated system.



2j **7**

^{1}H NMR: 5.78 ppm, d
^{13}C NMR: 92.95 ppm

With this new piece of information in hand, a working model for the catalytic cycle, including an unproductive equilibrium between the activated aldehyde **ii** and the α chloro silyl ether **iii**, can be formulated (eq 3). It can also be concluded that this equilibrium strongly favors the unreactive species **iii**. The nucleophile must intercept a small, equilibrium amount of the activated aldehyde **ii** for the reaction to proceed. Hence, more powerful nucleophiles are required to compensate for this effective loss in reactivity. This can explain why allylstannanes proved unreactive, propanoate-derived ketene acetals such as **5** have moderate reactivity, and acetate-derived ketene acetals **1** react at a reasonable rate.[8]



ii **iii**

In conclusion, we have developed a highly selective, Lewis-base-catalyzed reaction for the addition of ketene acetals to a variety of aldehydes. Catalyst loadings as low as 1 mol % can be employed without the requirement of long reaction times. In contrast to earlier methods involving trichlorosilyl enolates, aliphatic aldehydes react to provide products with good yields and high selectivities. Studies revealed that the lack of reactivity observed with aliphatic aldehydes may be due to unproductive formation of an α chloro silyl ether. The stereoconvergent, anti selective nature of the addition of propanoate-derived ketene acetals is particularly noteworthy. Not only is this a rare example of such a catalytic process, it attests to the powerful influence of the Lewis basic catalyst over the carbon−carbon bond forming transition structure. Further studies are currently underway to expand the scope of this reaction with respect to both the aldehyde and ketene acetal components.

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Supporting Information Available: Full characterization of the catalyst and all products along with representative procedures for the addition reactions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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