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Asymmetric Catalysis

Lewis Base Catalysis of the Mukaiyama Directed Aldol Reaction: 40 Years of Inspiration and Advances

*Gregory L. Beutner and Scott E. Denmark**

aldol reaction · diastereoselectivity · enantioselectivity · Lewis bases · silanes

Dedicated to Professor Teruaki Mukaiyama

Since the landmark publications of the first directed aldol addition reaction in 1973, the site, diastereo-, and enantioselective aldol reaction has been elevated to the rarefied status of being both a named and a strategy-level reaction (the Mukaiyama directed aldol reaction). The importance of this reaction in the stereoselective synthesis of untold numbers of organic compounds, both natural and unnatural, cannot be overstated. However, its impact on the field extends beyond the impressive applications in synthesis. The directed aldol reaction has served as a fertile proving ground for new concepts and new methods for stereocontrol and catalysis. This Minireview provides a case history of how the challenges of merging site selectivity, diastereoselectivity, enantioselectivity, and catalysis into a unified reaction manifold stimulated the development of Lewis base catalyzed aldol addition reactions. The evolution of this process is chronicled from the authors' laboratories as well as in those of Professor Teruaki Mukaiyama.

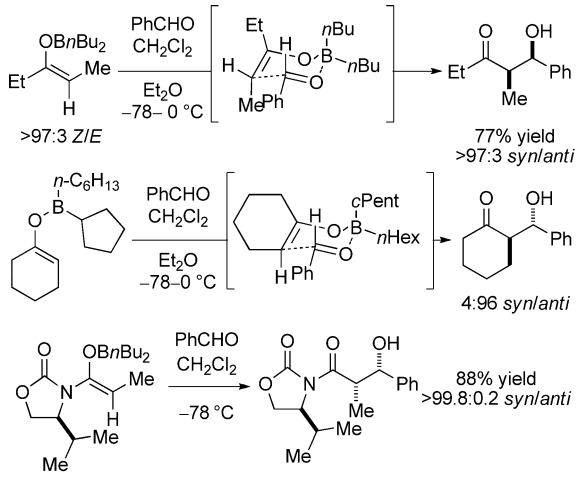
1. Introduction

The aldol reaction, an iconic carbon–carbon bond-forming process that is ubiquitous in nature and one of the oldest in the lexicon of organic chemistry, continues to serve as a platform for the demonstration of conceptual advances in the field.[1] The primary reason that the aldol reaction maintains such prominence is rooted in the numerous selectivity challenges that it poses in the forms of site, chemo-, enantio-, and diastereoselectivity. Because all four of these selectivity challenges can be present in a single pair of reactants, controlling them can be highly substrate dependent and universally applicable solutions are rare. For this reason, new methods or concepts that can broadly impact the ability to control these selectivity attributes represent remarkable accomplishments.

[*] Dr. G. L. Beutner
Bristol-Myers Squibb, Process Research & Development
New Brunswick, NJ 08903 (USA)
Prof. Dr. S. E. Denmark
Department of Chemistry, University of Illinois at Urbana-Champaign
Urbana, IL 61801 (USA)
E-mail: sdenmark@illinois.edu
Homepage: http://www.scs.illinois.edu/denmark

In this context, Professor Teruaki Mukaiyama's discovery of the directed aldol reaction of latent enolate equivalents is a major milestone whose 40th anniversary is being celebrated this year. His pioneering studies employed stable and isolable enol ethers such as enoxyborinates[2] and enoxysilanes,[3] whose structures can be readily controlled and manipulated. These enolate equivalents address the issues of site and chemoselectivity by allowing an unambiguous identification of which carbonyl compound plays the role of the nucleophile or electrophile in the bond-forming event.[4] Furthermore, the unique reactivity of these two classes of compounds provides highly effective options for control of diastereo- and enantioselectivity. In the case of enoxyborinates, the binding of the aldehyde to the Lewis acidic boron atom is required for electrophilic activation and high diastereoselectivity is observed as a consequence of highly-ordered, chairlike transition structures (Scheme 1).[5] Control over enantioselectivity in the reactions of enoxyborinates requires auxiliary based methods and has achieved strategy-level status.[6] However, at present no catalytic, enantioselective variant exists for this transformation.[7]

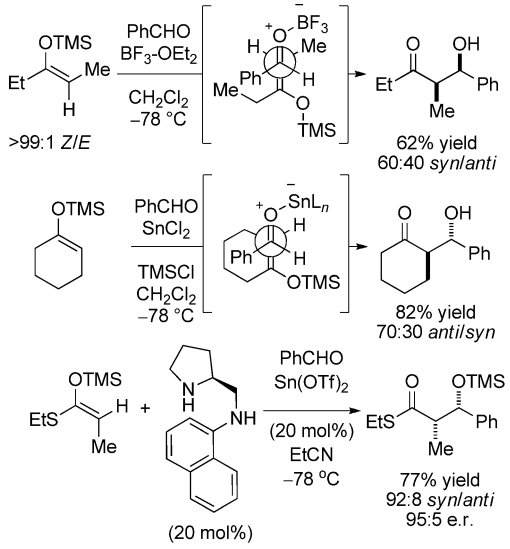
In the case of enoxysilanes, the central silicon atom is not sufficiently Lewis acidic to bind and activate the aldehyde, and serve as an organizational center for a six-membered transition structure (Scheme 2).[8] Although there are some



Scheme 1. Aldol reactions with enoxyborinates.

exceptions to this rule,[9] in general these reactions require activation by an exogenous Lewis acid and proceed via open transition structures.[10] In some cases, high levels of diastereoselectivity can be attained, but not in a general or predictable fashion. Although the open transition structure inherent to the aldol reaction of enoxysilanes presents challenges in terms of controlling diastereoselectivity, it does afford a unique opportunity for control over enantioselectivity. Thus, the use of chiral Lewis acid catalysts with enoxysilanes has been an immensely successful method for the development of enantioselective aldol reactions,[11] as illustrated by Mukaiyama's work with tin(II)/diamine complexes.[12]

Over the past 30 years, Mukaiyama and others have undertaken extensive investigations on the reactivity of enoxyborinates and enoxysilanes, thus forging them into the predictable and versatile reagents they are today. Mukaiyama's determination to demonstrate that novel reagents can yield solutions to synthetic challenges is an inspiration. His continued explorations have greatly expanded the scope of Lewis acid catalysis to many synthetic transformations. But he has also touched upon the Lewis base catalyzed aldol reaction, an area independently investigated in these laboratories. This review will describe the development of reagents for n–σ* Lewis base catalyzed aldol reactions and illustrate how gaining an understanding of these new reagents can lead to unexpected advances.[13]

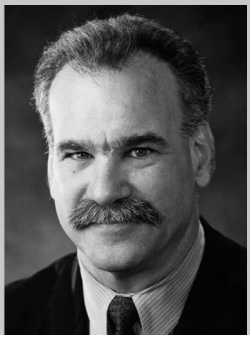


Scheme 2. Aldol reactions with enoxysilanes. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

2. Conceptual Framework

The overarching motivation for our investigations of the aldol reaction was to amalgamate the properties of enoxyborinates and enoxysilanes into a single species and thereby capitalize on the benefits of both. Could a latent enolate equivalent be identified, one that would be susceptible to asymmetric catalysis (and thus control enantioselectivity) as in the case of enoxysilanes, yet also react through a closed transition structure (and thus control diastereoselectivity) as in the case of enoxyborinates? To this end, we envisioned that applying the concept of Lewis base catalysis[14] to the activation of an enoxysilane could be a successful tactic. The general formulation envisions an enoxysilane (**A**) bearing a weakly Lewis acidic silicon moiety incapable of electrophilic activation of the aldehyde partner (Figure 1). Binding of a strong, neutral Lewis base to the silicon atom through an n–σ* type interaction generates the hypercoordinate silicate **B**. Gutmann's insightful analysis of Lewis acid/Lewis base complexes[15] suggests that binding of the Lewis base to the central silicon atom leads to a polarization of the Si–X bonds.

Gregory L. Beutner obtained a B.S. from Tufts University and a Ph.D. from UIUC under the direction of Prof. S. E. Denmark in 2004. After completion a post-doctoral study with Prof. R. H. Grubbs in 2006, he began work at Merck and Co., Inc. in Rahway, New Jersey. Currently, he is a member of Late Phase Chemical Development at Bristol-Myers Squibb and Co. in New Brunswick, New Jersey.



Scott E. Denmark obtained an S.B. degree from MIT in 1975 and his D.Sc.Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich in 1980. That same year he began his career at the University of Illinois and since 1991 he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry, and the origin of stereocontrol in fundamental carbon–carbon bond-forming processes.

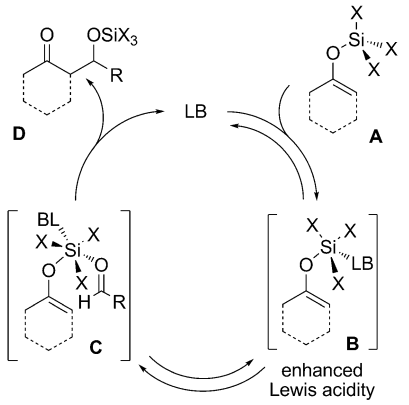


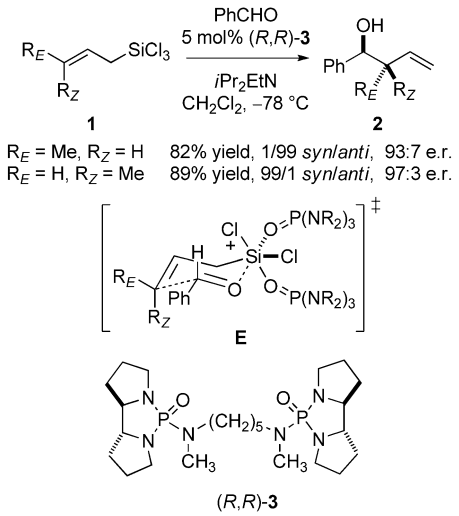
Figure 1. A general view of Lewis base catalysis with enoxysilanes.

This redistribution of the electron density in the Si–X bonds decreases the electron density at the central silicon atom and increases electron density at the peripheral X groups. As this polarization increases, the silicon atom is rendered sufficiently Lewis acidic to be capable of activating the aldehyde through a closed transition structure (**C**) and aldolization would proceed only in the presence of the Lewis base! In addition to the diastereoselectivity inherent to aldolization through a closed transition structure, the potential for control of enantioselectivity is introduced by the use of a chiral Lewis base.

3. Development of Aldol Reactions of Enoxytrichlorosilanes

In view of the negligible Lewis acidity of trialkylsilyl enol ethers,[16] a different class of enoxysilanes is required for n–σ* activation by a neutral Lewis base. Although some studies have shown that a wide variety of dipolar, aprotic compounds can promote aldol reactions of trialkylsilyl enol ethers,[17] asymmetric variants have not been disclosed. Inspiration for the class of enoxysilanes needed to satisfy this criterion came from related studies on the Lewis base catalyzed allylation of aldehydes with polyhalo allylic silanes. Following upon early reports from Sakurai and co-workers on the use of allyltrifluorosilane,[18] our laboratories and those of Kobayashi independently initiated investigations of closely related allyltrichlorosilanes (**1**; Scheme 3).[19] These trihaloallylsilanes, which are extremely poor π nucleophiles,[20] can be rendered highly reactive in the presence of strong, neutral Lewis bases such as formamides and phosphoramides. In the case of the chiral phosphoramide (*R*,*R*)-**3**, high levels of diastereo- and enantioselectivity can be obtained (Scheme 3).[21] Diastereoselectivity is rationalized through consideration of a closed, chairlike transition structure (**E**).

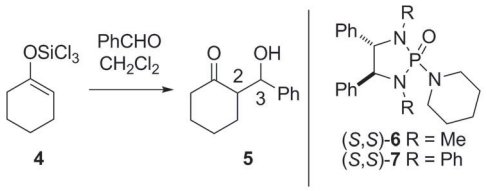
On the basis of these results, an extremely rare family of reagents, enoxytrichlorosilanes, was conceived. By analogy, these reagents were also expected to be poor nucleophiles owing to the strongly electron-withdrawing trichlorosilyl group, but had the important property of possessing a relatively Lewis-acidic silicon atom.[22] Could a Lewis base



Scheme 3. Asymmetric Lewis base catalyzed allylations.

activate these species and allow a novel, directed aldol process in analogy with the results of the Lewis base catalyzed allylation? The answers to these questions were quickly ascertained from early investigations on the reactivity of the trichlorosilyl enol ether **4** derived from cyclohexanone (Table 1).[23] In the absence of a Lewis base, aldolization does

Table 1: Lewis base catalyzed aldol reaction of trichlorosilyl enol ethers.



Catalyst loading	*T* [°C]	Yield [%]	d.r. *syn/anti*	e.r.[a]
–	0	92	98:2	n.d.
6 (10%)	−78	95	<1:99	96.5:3.5 (2*R*,3*S*)
7 (10%)	−78	94	99:1	76.5:23.5 (2*R*,3*R*)

[a] The configuration of C2 and C3 are given within parentheses.

proceed, thus providing the aldol product in high yield. High levels of *syn* diastereoselectivity are observed, as one would predict from a closed, boatlike transition structure. Despite the presence of this modest background reaction, addition of 10 mol% of the chiral phosphoramide (*S*,*S*)-**6** allowed a significantly faster catalytic process to dominate. The aldolization product is formed in high levels of diastereo- and enantioselectivity. Remarkably, the diastereoselectivity of the reaction can be controlled by the appropriate choice of the phosphoramide catalyst, (*S*,*S*)-**6** or (*S*,*S*)-**7**. Thus, either the *syn* or *anti* diastereomer may arise through aldolization via boat- or chairlike transition structures, respectively. The change in configuration at the C3 center reveals a switch in topicity at the aldehyde carbonyl group.

These initial results provided clear evidence that the hypothesis about the potential of n–σ* Lewis base catalysis

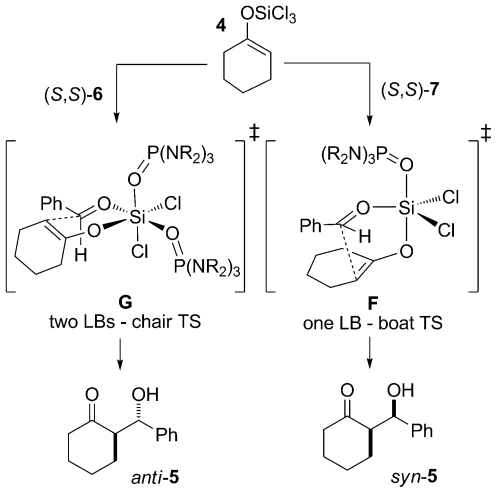
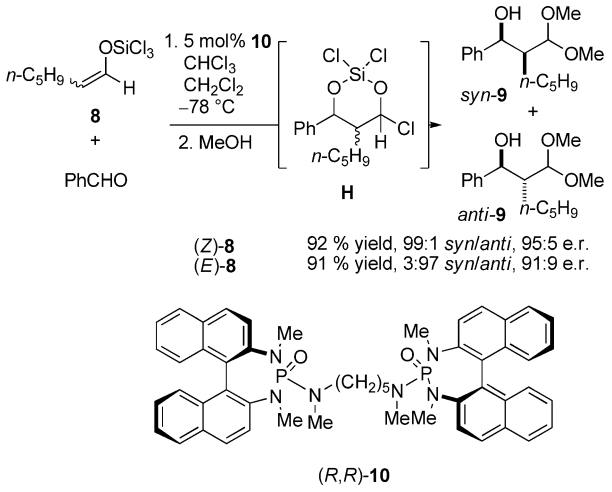


Figure 2. Rationale for diastereoselectivity with trichlorosilyl enol ethers. TS = transition structure.

was valid. Further mechanistic studies revealed details on how the phosphoramide catalyst exerts control over diastereo- and enantioselectivity in this process (Figure 2).[24] When the bulky phosphoramide catalyst (*S*,*S*)-**7** is employed, a single phosphoramide is bound to the trichlorosilyl moiety (first order in catalyst). After ionization of a chloride ion, this leads to formation of the pentacoordinate species **F** which binds to the aldehyde and proceeds to product through a boatlike transition structure. When the less bulky catalyst (*S*,*S*)-**6** is employed, two phosphoramide molecules bind to the trichlorosilyl fragment to generate the cationic trigonal bipyramidal species **G**. Subsequent binding of the aldehyde is then followed by carbon–carbon bond formation through a chairlike transition structure involving a cationic octahedral silicon complex.

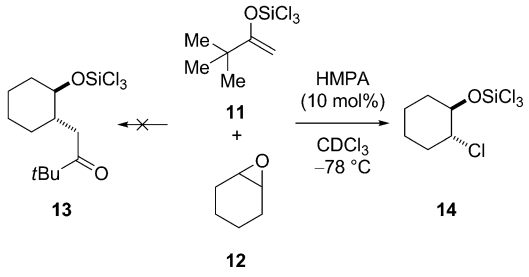
Similar levels of predictable diastereoselectivity are observed in the catalytic enantioselective Lewis base catalyzed aldol reactions of aldehyde-derived trichlorosilyl enol ethers (**8**; Scheme 4).[25] This class of aldol reaction, which is typically hampered by oligomerization processes, is possible and highly productive here owing to the in situ protection of the initially formed product aldehydes as the unreactive α-chloro silyl ether **H**. As expected, high levels of diastereoselectivity, consistent with reaction through a closed, chairlike transition structure, are obtained in the presence of the dimeric phosphoramide catalyst (*R*,*R*)-**10**.



Scheme 4. Lewis base catalyzed aldehyde–aldehyde aldol reaction.

4. A Paradigm Shift

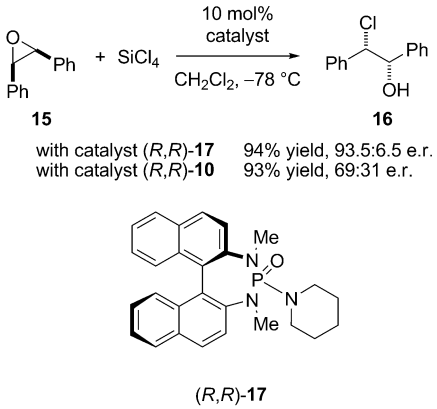
From the foregoing discussion it is clear how Mukaiyama's pioneering efforts to expand the scope of the aldol reaction through the development of new reagent classes served as inspiration for our work in the field of Lewis base catalysis. Furthermore, just as Mukaiyama's work on Lewis acid catalysis of the aldol reaction opened the door for the investigation of countless new Lewis acid catalyzed processes, our work on the Lewis base catalyzed aldol reaction of trichlorosilyl enol ethers served as an entrance into broader investigations of Lewis base catalysis in general. One example of this extension comes from investigations of the reactivity of enoxytrichlorosilanes with other electrophiles, specifically epoxides. Rather than obtaining the intended aldolization product **13**, the chlorohydrin **14** is formed (Scheme 5).[26]



Scheme 5. Unexpected reaction of a trichlorosilyl enol ether with an epoxide. HMPA = hexamethylphosphoramide.

Further investigations reveal that the parent chlorosilane, silicon tetrachloride ($SiCl_4$), is also capable of promoting the ring-opening reaction. When the chiral phosphoramide (*R*,*R*)-**17** and $SiCl_4$ are used in conjunction with *meso*-epoxides, a highly enantioselective process occurs (Scheme 6).[27]

The key lessons from this work, which were not fully comprehended for several years, are that binding of the phosphoramide to $SiCl_4$ is quantitative and that the catalyst resting state is in fact a chiral siliconium ion, similar in structure to **I** (Figure 3).[28] In effect, the ring-opening process is mediated by a Lewis acid which is generated in catalytic amounts in the presence of the chiral Lewis base. Although the active species is a Lewis acid, the reaction is not catalytic in this species because one molecule of $SiCl_4$ is consumed in each turnover. Release of the phosphoramide catalyst from the trichlorosilyl ether product **L** completes the catalytic cycle and shows that only the Lewis base is truly catalytic. Hence, this class of reaction is termed Lewis base catalyzed/Lewis acid activated.



Scheme 6. Lewis base catalyzed epoxide opening with $SiCl_4$.

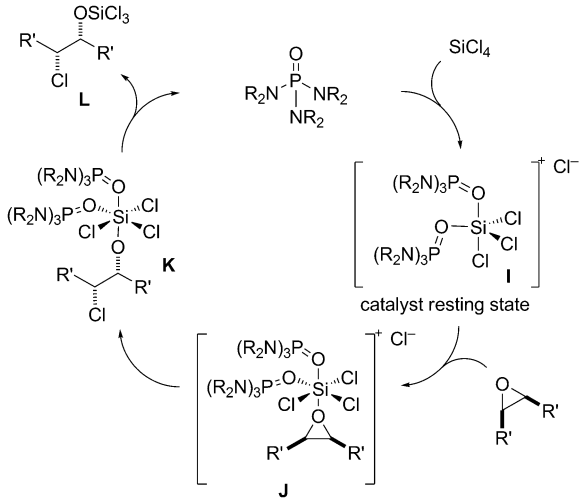
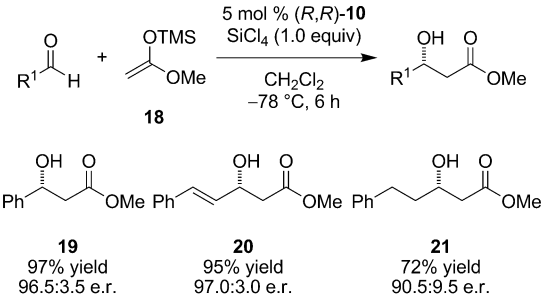


Figure 3. Catalytic cycle for Lewis base catalyzed epoxide openings.

Subsequent studies have shown that Lewis base activation of Lewis acids has much broader applications than the enantioselective opening of *meso*-epoxides. In fact, this application brings the story full circle as it employs the chemistry of the enoxytrialkylsilanes originally explored by Mukaiyama and co-workers.[3] Initial experiments combining this $SiCl_4$/phosphoramide catalyst system with the highly reactive acetate-derived silyl ketene acetal **18** afforded good yields and high levels of enantioselectivity for the desired aldol products (Scheme 7).[29] These results demonstrated that our in situ generated Lewis acid was capable of delivering high levels of enantioselectivity, despite the fact that we had presumably switched to an open transition structure more akin to the original Mukaiyama aldol reaction.

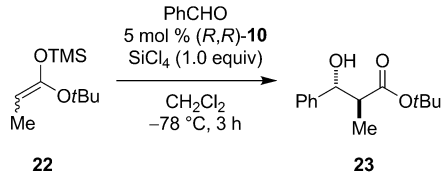
Further evidence for the involvement of an open transition structure in this class of Lewis base catalyzed aldol reactions was gained from the study of other silyl ketene acetals and the attempt to establish the direction and level of diastereoselectivity that this catalyst system could enforce. In the case of propanoate-derived silyl ketene acetals, high levels of *anti* diastereoselectivity and high enantioselectivity were



Scheme 7. Lewis base catalyzed aldol reaction of silyl ketene acetals.

observed with the use of the sterically demanding *tert*-butyl-ester-derived silyl ketene acetal **22** (Table 2). The reaction is diastereoconvergent, a hallmark of aldol reactions that proceed through open transition structures.[1f] Consideration of the six possible open transition structures leads to the

Table 2: Lewis base catalyzed aldol reaction of silyl ketene acetals.



E/*Z* (**22**)	Yield [%]	e.r. (**23**)	d.r. (**23**)
95:5	93	>99:1	99:1
12:88	73	>99:1	99:1

conclusion that the reaction proceeds through the antiperiplanar transition-structure **M**, in which steric interactions between the α-methyl group and the bound catalyst complex control the orientation of the approaching nucleophile to the aldehyde/catalyst complex (Figure 4).[30] Both *E*- and *Z*-silyl ketene acetals give high levels of *anti* diastereoselectivity because of the overwhelming steric influence of the catalyst on the position of the α-methyl group.

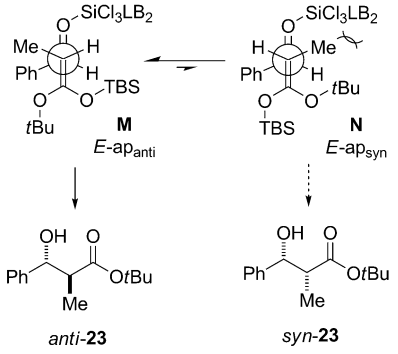
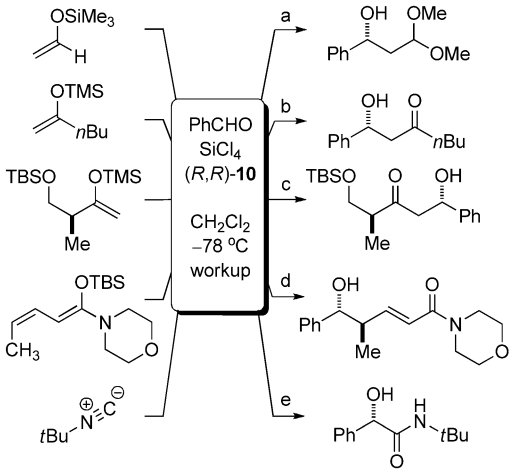


Figure 4. Stereochemical analysis of diastereoselectivity. TBS = *tert*-butyldimethylsilyl.

The high levels of enantio- and diastereoselectivity observed in these initial studies came at the beginning of a broad investigation of Lewis base catalyzed/Lewis acid activated aldol reactions with a wide variety of enoxysilanes derived from esters,[30] ketones,[31] aldehydes.[32] and α,β-unsaturated carbonyl compounds[33] with aldehydes which uniformly gave high levels of site, diastereo-, and enantioselectivity (Scheme 8). By considering the selectivity trends



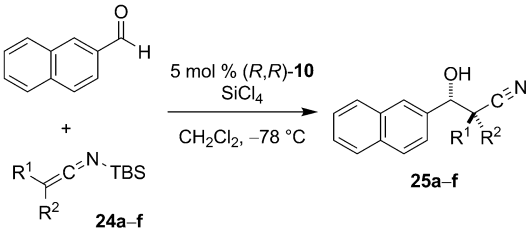
Scheme 8. Lewis acid mediated/Lewis base catalyzed reactions. a) 84% yield, 97:3 e.r.; b) 97% yield, 98:2 e.r.; c) 91% yield, 24:1 *anti*/*syn*; d) 98% yield, >99:1 γ/α, 97:3 e.r., 88:12 e.r.; e) 96% yield, >99:1 e.r..

observed within this diverse class of π nucleophiles, combined with mechanistic studies,[34] a unified mechanism emerged and helped rationalize the large body of data. In addition, this mechanistic understanding also provided confidence to extend this novel mode of catalysis to reactions outside of the typical scope of Lewis acid catalyzed processes, as is nicely illustrated in the case of the Lewis base catalyzed Passerini reaction of isonitriles.[35]

The highly diastereoconvergent *anti* selectivity of these processes, a quality which is rare among Mukaiyama aldol reactions,[1f,4] prompted the application of this unique reaction manifold to novel substrate classes and refractory selectivity challenges for the aldol reaction in general. Moreover, the possibility of introducing further control over diastereoselectivity to gain access to a *syn*-selective process appeared equally intriguing. The solutions to these challenges were revealed by more recent investigations into the chemistry of silyl ketene imines and glycolate-derived silyl ketene acetals.

The formation of quaternary stereocenters is a formidable challenge, particularly in the context of the Mukaiyama aldol reaction.[36] Extensive study of reactivity and diastereoselectivity with α,α-disubstituted silyl ketene acetals and this phosphoramide/$SiCl_4$ system led to disappointing results, mostly because of the poor reactivity of these sterically demanding nucleophiles. Nevertheless, if a sufficiently reactive α,α-disubstituted nucleophile could be found, this catalyst system could still provide high levels of diastereoselectivity and a pathway to selective formation of quaternary stereocenters. The answer presented itself in the form of silyl ketene imines, a little-investigated class of π nucleophiles.[37] Silyl ketene imines contain an sp-hybridized carbon atom adjacent to the reactive center and thus are sterically compact and obviate the *E*/*Z* selectivity issues which plague other ketene acetal derivatives. Orienting experiments with the silyl ketene imines **24a–f** provided surprisingly high levels of enantio- as well as diastereoselectivity (Table 3).[38] In line with the *anti* diastereoselectivity observed with α-substituted nucleophiles, the relative disposition of the hydroxy group and the larger substituent R^1 in the β-hydroxy nitrile product are *anti*.[30]

Table 3: Lewis base catalyzed reactions of silyl ketene imines.



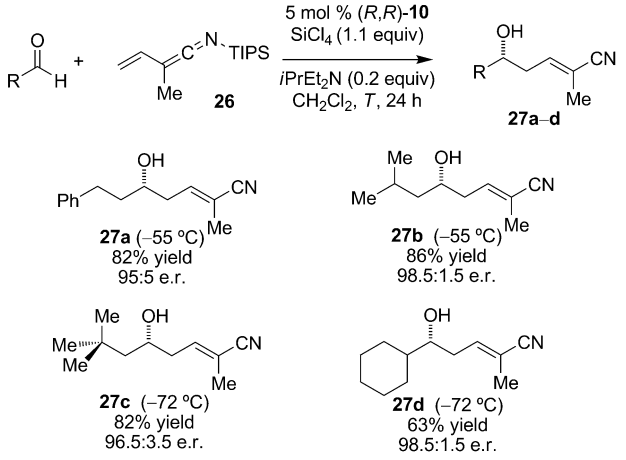
R^1	R^2	Yield [%]	d.r. *anti*/*syn*	e.r.
Ph	Me	87 (**25a**)	95:5	98.5:1.5
Ph	Et	78 (**25b**)	97:3	92.7:7.3
Ph	*i*Bu	90 (**25c**)	99:1	99.6:0.4
Ph	*i*Pr	73 (**25d**)	61:39	78.9:21.1
*i*Pr	Me	92 (**25e**)	60:40	92.1:7.9
$-(CH_2)_5-$		85 (**25f**)	n.a.[a]	91.2:8.8

[a] Not applicable.

The vinylogous extension of the addition of silyl ketene imines to aldehydes has been successfully developed. These interesting nucleophiles (**26**) display significantly enhanced reactivity (likely because of the greatly reduced steric hindrance at the γ-carbon atom). All additions gave the γ-addition product **27** exclusively with aliphatic, olefinic, and aromatic aldehydes. The results with selected aliphatic aldehydes are illustrated in Scheme 9.

The use of silyl ketene imines derived from cyanohydrins allows the construction of highly functionalized β-hydroxy cyanohydrins, whose diverse functional transformations can be employed for the synthesis of many classes of natural products (Scheme 10).[39]

The consistent preference for the formation of the *anti* diastereomer, regardless of the structure of the participating π nucleophile provides compelling support for the stereochemical model. It was of interest to determine if this overwhelming bias, which arises from the dominant influence of the catalyst, could be conscripted to afford either *syn* or *anti* diastereomers by manipulating the relative size of the substituents on the nucleophile. A new family of π nucleophiles, the glycolate-derived silyl ketene acetals provided the ideal opportunity to probe this question.[40]

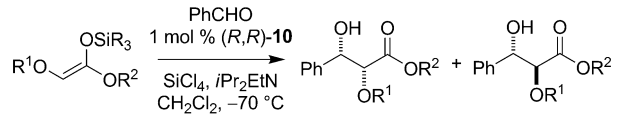


Scheme 9. Vinylogous aldol additions of *N*-silyl vinyl ketene imine. TIPS = triisopropylsilyl.

Scheme 10. Lewis base catalyzed reactions of N-silyl oxyketene imines. DIPEA = diisopropylethylamine.

By considering the disposition of the silyl group and the ester group, an orientation enforced by the geometry of the double bond,[41] a strategy can be envisioned for selecting combinations which will favor either the *syn* or the *anti* product. By modulating the steric demand of the α-alkoxy substituent together with the ester substituent, either diastereomer can be obtained with uniformly high levels of enantioselectivity (Table 4). As observed for **30a–c**, by increasing the size of the α substituent and employing a compact ester substituent, the *syn* diastereomer is obtained in high levels of selectivity. Contrariwise, the *anti* isomer can be obtained by increasing the bulk of the ester substituent as in **30d–f** while simultaneously employing a compact α-alkoxy substituent. These changes in selectivity can again be rationalized through consideration of open transition structures, similar to those shown above (see Figure 4). The *anti* diastereoselectivity observed with silyl ketene acetals such as **30f** is clearly understood through consideration of the antiperiplanar transition-structure **O** wherein the primary contribution to the observed selectivity is the minimization of steric repulsion between the α substituent and the bound catalyst complex in the upper right sector (Figure 5). The *syn*

Table 4: Lewis base catalyzed aldol reactions of glycolate silyl ketene acetals.



R^1	R^2	SiR_3	Yield [%]	*syn*/*anti*	e.r. (*syn*)	e.r. (*anti*)
Me (**30a**)	Me	TMS	98 (**31a**)	57:43	74:26	82:19
*t*Bu (**30b**)	Me	TMS	93 (**31b**)	99:1	93:7	n.d.[a]
$PhMe_2C$ (**30c**)	Me	TMS	98 (**31c**)	99:1	96:4	n.d.[a]
Me (**30d**)	*t*Bu	TMS	93 (**31d**)	4:96	90:10	81:19
Me (**30e**)	*t*Bu	TBS	92 (**31e**)	1:99	n.d.[a]	92:8
Me (**30f**)	Et_2MeC	TBS	92 (**31f**)	1:99	n.d.[a]	94:6

[a] Not determined.

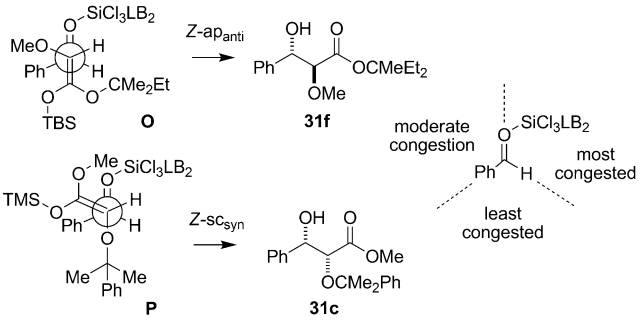


Figure 5. Stereochemical analysis of diastereoselectivity.

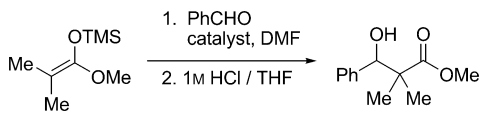
diastereoselectivity of the silyl ketene acetal **30c** cannot be explained through this analysis because it would require placing the bulky alkoxy group close to the bound catalyst complex, thus engendering an unfavorable steric interaction with the catalyst backbone. To avoid this unfavorable interaction, the nucleophile approach shifts to a (+)-synclinal pathway (**P**). Here, the bulky α substituent can reside in the open, lower sector while the masked ester group, bearing less sterically demanding TMS and methoxy groups is disposed away from the bound catalyst complex.

5. Aldol Reactions Catalyzed by Anionic Lewis Bases

The foregoing studies on the Lewis base catalyzed aldol reaction, while unique in exploiting the peculiar properties of trichlorosilyl derivatives, are not the sole examples of Lewis base catalyzed aldol reactions. In fact, they are not unique even when one considers n–σ* Lewis base catalyzed reactions of enoxysilanes. Early studies by Noyori and Kuwajima demonstrated that fluoride ions were capable of catalyzing the aldol reaction of trialkylsilyl enol ethers through the intermediacy of highly reactive ammonium or sulfonium enolates.[42] Subsequent work by Hosomi and co-workers shows that chloride and bromide ions can also promote this reaction in dipolar aprotic solvents, irrespective of their counterion.[43]

Mukaiyama has also made extensive contributions to this area. In a series of studies starting in 2002, it was shown that a diverse range of anionic Lewis bases are capable of catalyzing the aldolization of trialkylsilyl enol ethers (Ta-

Table 5: Directed aldol reactions with anionic Lewis bases.[a]



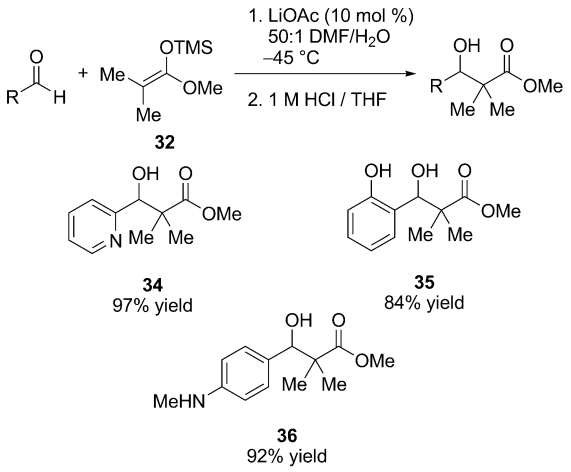
32 **33**

Catalyst (mol%)	pK_a	T [°C]	t [h]	Yield [%]
LiNPh$_2$ (20)	22.4	0	1	84
LiO*t*Bu (5)	19.2	−45	2	96
Li 2-pyrrolidinone (10)	ca. 15	−45	2	95
LiOPh (5)	10	−45	2	97
LiOAc (10)	4.8	−45	1	83
LiOBz (10)	4.2	−45	3	98

[a] DMF = *N*,*N*′-dimethylfromamide.

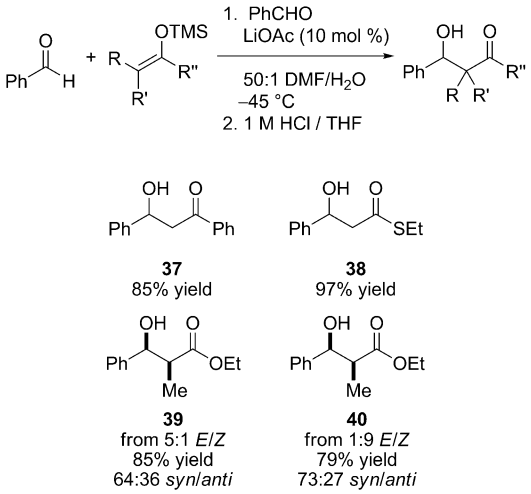
ble 5).[44] Whereas the initial studies focus on the use of strongly Brønsted basic species, such as lithium diphenylamide, subsequent work demonstrates that both nitrogen- and oxygen-based anions spanning a wide range of pK_a values are capable of promoting the reaction with similar facility.[45] Indeed, such weakly basic species as lithium acetate can afford high yields with short reaction times at sub-ambient temperatures in polar aprotic solvents such as DMF.[46]

The scope of the reaction with respect to the aldehyde is notable as aldehydes bearing Lewis basic or even protic functional groups (which could inhibit a Lewis acid catalyzed process) proceed smoothly (Scheme 11).[47] The scope with



Scheme 11. LiOAc catalyzed aldol reactions of silyl ketene acetals with aldehydes. THF = tetrahydrofuran.

respect to the trialkylsilyl enol ether is equally broad (Scheme 12). Ketone-, thioester-, and ester-derived enol silanes all react rapidly under surprisingly mild reaction conditions. These reactions presumably procceed through open transition structures, and therefore, it is not surprising that diastereoselectivity is only moderate. Some influence of enol silane geometry is observed, but selectivity uniformly favors the *syn* diastereomer.



Scheme 12. LiOAc catalyzed aldol reactions of silyl ketene acetals.

When a new mode of catalysis is identified and its usefulness demonstrated, the next stage of development is to establish if the discovery can be parlayed into a new catalytic, enantioselective method. The evolution of this n–σ* Lewis base catalyzed aldol reaction into an asymmetric method, a journey well known to Mukaiyama from his work on Lewis acid catalyzed aldol reactions, required careful consideration of the mechanism. Although these reactions can be termed Lewis base catalyzed processes, the identity of the Lewis base catalyst is uncertain (Figure 6). Because a wide variety of anionic Lewis bases promote the reaction, including the aldolate products, it is conceivable that the initially added catalyst may be only an initiator. In studies using the lithium aldolate product **S**, Mukaiyama showed that this species is in fact a competent catalyst.[44] Even though silylation of this intermediate aldolate is feasible and observed under these reaction conditions, the possibility that both reactions manifolds may be operative cannot be excluded. Therefore, to render this particular Lewis base catalyzed reaction asymmetric, the employment of a chiral, anionic Lewis base may be ill-advised.

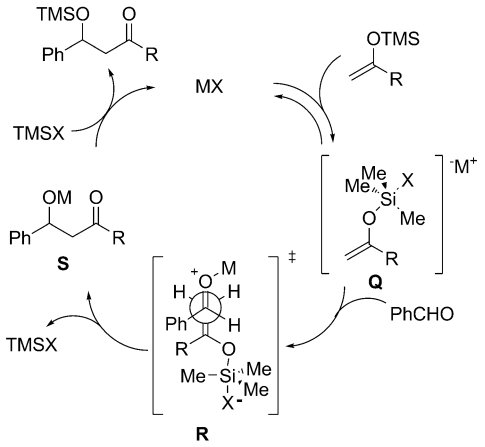
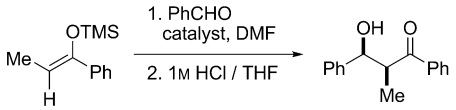


Figure 6. Mechanism of anionic Lewis base catalyzed aldol reactions.

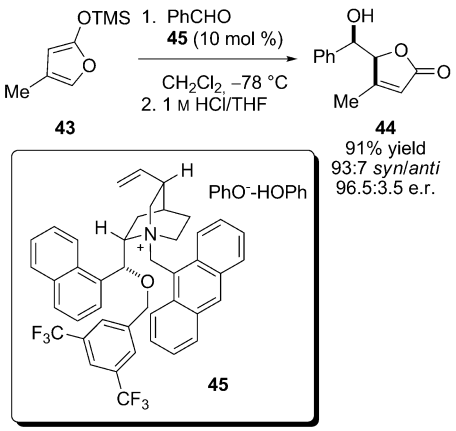
Consideration of these mechanistic insights reveals that, regardless of the identity of the chain-carrying species, one component of the reaction is truly catalytic and could provide a source for asymmetric induction. In each cycle, the cationic portion of the anionic Lewis base (M^+, Figure 6) is conserved. Recognizing this subtlety, Mukaiyama and co-workers chose to investigate the use of anionic Lewis bases bearing ammonium counterions (Table 6).[48] High levels of *syn* diastereoselectivity were observed in the formation of **42** with an ammonium phenoxide. In the case of ammonium phenoxides, the reactions are run in a less polar solvent, namely THF, presumably to allow better ion pairing between the chiral ammonium salt and the in situ generated enolate. Making the transition to the chiral ammonium phenoxide **45** renders these anionic Lewis base catalyzed reactions asymmetric, as can clearly be seen in the high levels of enantioselectivity obtained from the aldol reaction shown in Scheme 13.[49]

Table 6: Survey of anionic Lewis bases for catalytic aldol reactions.



41 **42**

Catalyst	Solvent	T [°C]	t [h]	Yield [%]	*syn*/*anti*
LiOAc	DMF	0–23	6	87	63:37
LiOPh	DMF	−45	5	98	75:25
$Bu_4N^+OPh^-$	THF	−78	3	79	94:6



Scheme 13. Aldol reaction with a chiral ammonium phenoxide.

In the same way that Mukaiyama's original disclosure of the Lewis acid catalyzed aldol reaction of enoxysilanes opened new possibilities in the area of Lewis acid catalysis, his work with anionic Lewis bases has also proven fruitful and finds applications in a variety of carbon–carbon bond-forming processes. For example, Mannich,[50] Michael,[51] Strecker,[52] and Diels–Alder[53] reactions as well as [2,3] Wittig rearrangements,[54] cyanomethylation,[55] dithiane additions,[56] and perfluoroalkylations,[57] among others, have all succumbed to n–σ* catalysis using Lewis bases.

8. Summary and Outlook

The evolution and development of catalytic enantioselective (and diastereoselective) aldol addition reactions represents the apotheosis of organic synthesis methodology. The generality, versatility, and selectivity associated with this process is among the most extensively investigated of all synthetic reactions. Stimulated by the challenges posed by nature, generations of synthetic organic chemists have constructed an impressive edifice of knowledge which constitutes insightful, elegant, and practical solutions to the structural and stereochemical problems presented by polypropionate-derived natural products. Beyond its obvious utility for the synthesis of natural and non-natural compounds bearing the signature β-hydroxy carbonyl subunit, the asymmetric aldol addition reaction has been both an engine and a proving ground for new methodological advances. For example, the study of the structure and reactivity of metal enolates, the design and development of chiral Lewis acids based on nearly every element in the periodic table, and the most recent frenzy of disclosures on direct aldolization by enamine catalysis amply illustrate this point.

If one views the genesis of these spectacular accomplishments through the lenses of history, it is easily seen that the confluence of the challenges posed by acyclic stereocontrol and the development of the directed aldol reaction in the early 1970s provided the inspiration and fuel for decades of fruitful investigation. In that context, the landmark papers of Professor Teruaki Mukaiyama are seen as truly transformative in a way that could not be appreciated at the time.

Whether the aldol reaction continues to provide inspiration for newer and better methods of bond construction and stereochemical control is impossible to know. However, the lesson of how the aldol reaction evolved to be a major component of the edifice of synthetic organic chemistry is its everlasting legacy.

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