ChemPubSoc Europe

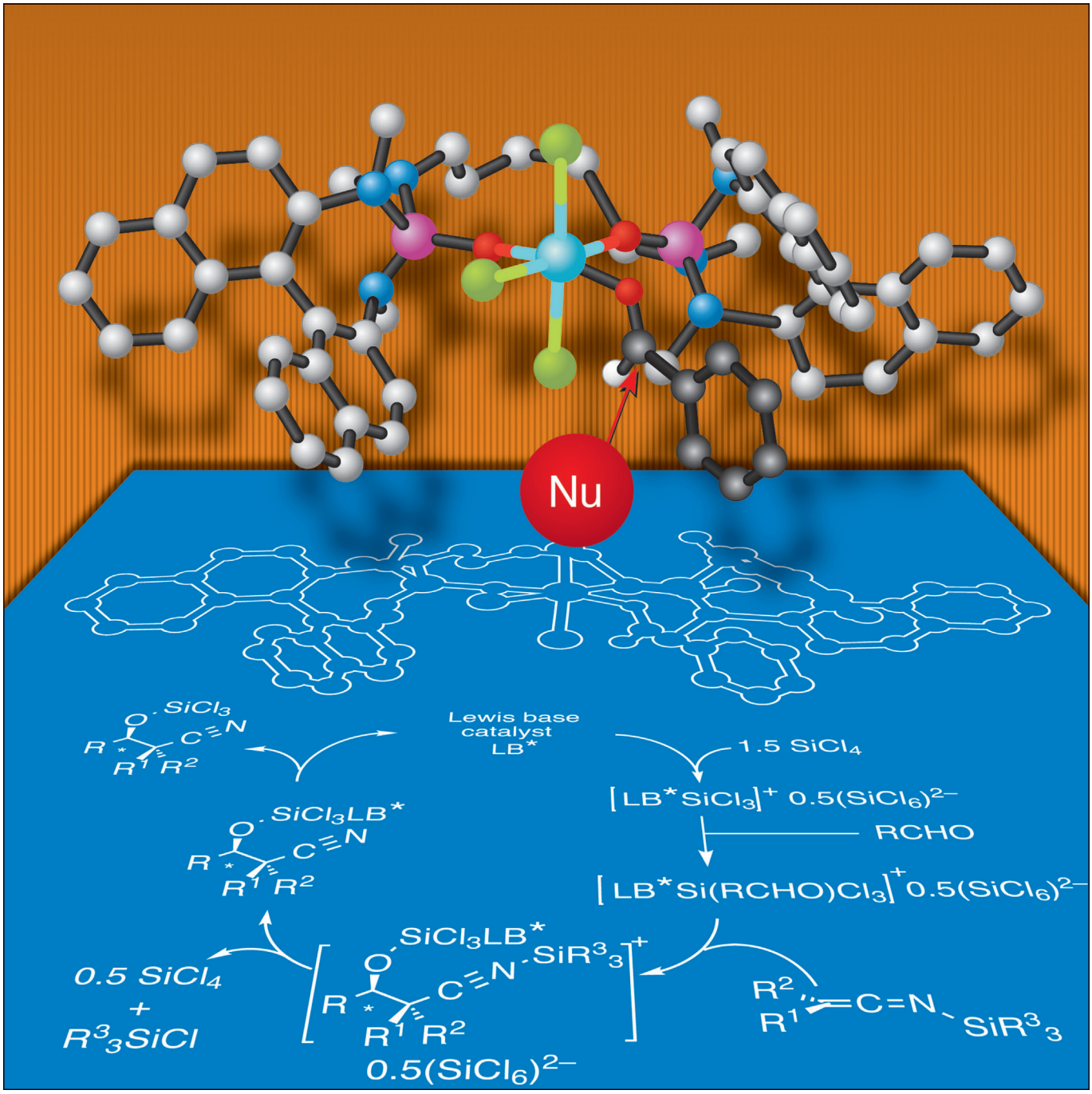
DOI: 10.1002/chem.201403342

CHEMISTRY
A European Journal
Full Paper

Asymmetric Synthesis

Enantioselective Construction of Quaternary Stereogenic Carbon Atoms by the Lewis Base Catalyzed Additions of Silyl Ketene Imines to Aldehydes

Scott E. Denmark,* Tyler W. Wilson, and Matthew T. Burk[a]



Abstract: Silyl ketene imines derived from a variety of α-branched nitriles have been developed as highly useful reagents for the construction of quaternary stereogenic centers via the aldol addition reaction. In the presence of $SiCl_4$ and the catalytic action of a chiral phosphoramide, silyl ketene imines undergo extremely rapid and high yielding addition to a wide variety of aromatic aldehydes with excellent diastereo- and enantioselectivity. Of particular note are the high yields and selectivities obtained from electron-rich, electron-poor, and hindered aldehydes. Linear aliphatic aldehydes did react with good diastereo- and enantioselectivity in the presence of $n Bu_4N^+I^-$, but branched aldehydes were much less reactive. Semiempirical calculations provided a rationalization of the observed diastereo- and enantioselectivity via open transitions states.

Introduction

The aldol reaction is one of the most well-studied, powerful, and reliable tools a synthetic chemist has for the stereoselective construction of carbon–carbon bonds. In the classic reaction an aldehyde or ketone is rendered nucleophilic at the α-carbon by pretreatment with a Brønsted or Lewis base. The resulting activated enolate species then undergoes addition to a second carbonyl compound giving rise to a β-hydroxy carbonyl product. A stereochemical analysis of this process reveals that when the reacting partners are both prochiral substrates, four possible stereoisomers can form (Figure 1).

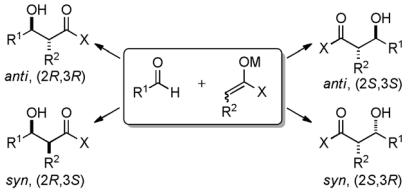
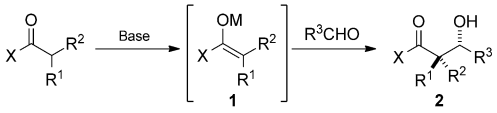


Figure 1. Stereochemical dyad resulting from aldol reaction of prochiral enolate and aldehyde.

Indeed, the primary focus over the past 30 years of research in aldol methodology has been on the development of catalytic, enantioselective methods for selectively obtaining single stereoisomers from this tetrad of compounds. Largely these challenges have been met by very inspired and elegant solutions and the aldol reaction has provided a useful testing ground for the development of modern asymmetric catalysis.[1] Despite these successes a remaining obstacle in aldol methodology is the synthesis of quaternary stereogenic centers.

The development of catalytic, enantioselective methods for the construction of quaternary stereogenic centers represents an ongoing challenge to organic chemists.[2] The difficulty in forming these centers arises from the high degree of steric repulsion that is encountered in the transition state during the key C–C bond-forming event. Furthermore, achieving high levels of enantiotopic face selectivity is difficult because of the relatively similar steric environments presented by the non-hydrogen substituents. Although a number of different catalytic, enantioselective reactions have been reported, very few exhibit generality over a wide range of architectures. Setting quaternary stereogenic centers in acyclic systems presents an even greater challenge, due to the additional degrees of freedom associated with these motifs.[3] The need for more general methods to prepare quaternary carbon atoms is underscored by the large number of biologically active natural products and pharmaceutical targets that possess quaternary stereogenic carbon atoms.[4]

The aldol addition of α,α-disubstituted enolates to aldehydes would provide a powerful method for generating quaternary centers; however, this approach is limited by the need for and inability to prepare geometrically defined α,α-disubstituted enolate (**1**) or enolate equivalents (Scheme 1). Therefore, to successfully utilize the aldol reaction for the asymmetric synthesis of quaternary centers, one must either address this deficiency or develop other nucleophile classes.



Scheme 1. Aldol reaction for the synthesis of quaternary carbon atoms.

Background

Stereoselective synthesis of E- and Z-substituted enolates

The ability to selectively control enolate geometry is paramount to the success of achieving stereocontrol in the aldol reaction. The additions proceed through either chair-like (Zimmerman–Traxler)[5] or open transition structures depending on the nature of the enolate and the reaction conditions employed (Figure 2). In both cases, the transition structures are well ordered and insufficient stereocontrol in the enolate geometry will be directly reflected in poor *anti/syn* diastereoselectivity in the product. For this reason, much work has been dedicated to developing reliable and robust methods for achieving highly selective enolizations. Pioneering studies by Ireland and co-workers showed that for monosubstituted ketones

[a] *Prof. Dr. S. E. Denmark, Dr. T. W. Wilson, Dr. M. T. Burk*
Department of Chemistry, University of Illinois
Urbana, Illinois 61801 (USA)
Fax: (+1) 217-333-3984
E-mail: sdenmark@illinois.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201403342.

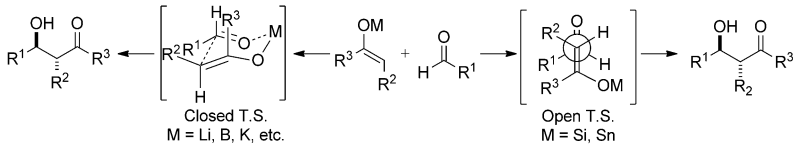
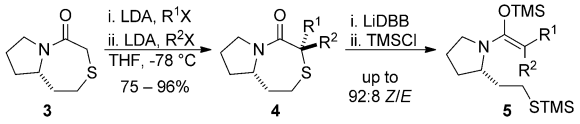


Figure 2. Transition structures for aldol addition reactions with various enolates.

and esters, the *E*/*Z* selectivity can be dramatically influenced by the choice of base, temperature, solvent, and additives, such as HMPA.[6] Subsequently, these observations led to the development of protocols for achieving either *E*- or *Z*-monosubstituted enolates by judicious choice of reaction conditions.[7] Despite this important body of work, very few methods have been realized for achieving control with trisubstituted enolates.

Stereoselective synthesis of trisubstituted enolates and their application in diastereoselective aldol reactions

Gleason and Manthorpe reported an innovative method for the synthesis of both *E*- and *Z*-trisubstituted amide enolates by the reduction of bicyclic thioglycolate lactams.[8] The design relies on the rigidity present in the bicyclic lactams, such that the sulfur atom is constrained to reside on only one face of the carbonyl plane. Upon two-electron reduction of the disubstituted thioglycolate lactam (**4**) with lithium di-*tert*-butylbiphenylide (LiDBB), the carbon–sulfur bond is cleaved and an enolate dianion is formed. Trapping of this intermediate with two equivalents of trimethylsilyl chloride (TMSCl) gave the silyl ketene aminals (**5**) in good yield and high diastereoselectivity (Scheme 2). Importantly, either *E*- or *Z*-enolates can be made using this method by simply changing the order in which the R groups are introduced onto the thioglycolate lactam (**3**).

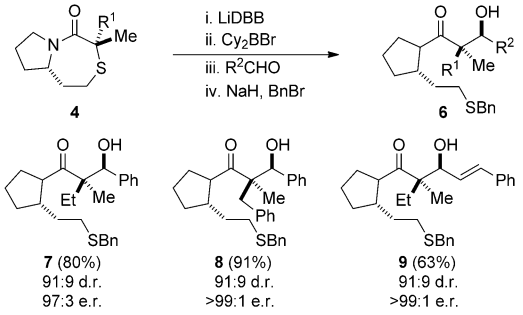


Scheme 2. Stereodefined trisubstituted enolates from bicyclic thioglycolate lactams.

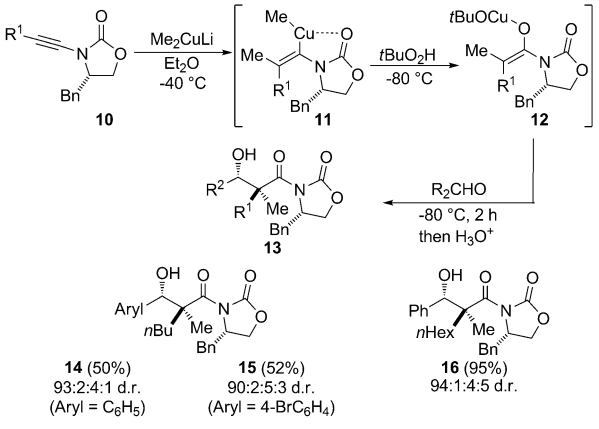
With the ability to selectively access trisubstituted amide enolates, Gleason then developed a diastereoselective aldol reaction for the synthesis of quaternary stereogenic centers.[9] The success of this reaction relies on the ability to convert the lithium enolate to a boron enolate using dicyclohexylboron bromide. The in situ formed boron enolate then undergoes diastereoselective *syn* aldol additions with aromatic and olefinic aldehydes in good yield and excellent stereoselectivities (Scheme 3). Gleason and co-workers have also reported an enantioselective Mannich-type addition with benzenesulfonylimines.[10]

Traditionally, methods for enolate formation have relied on the deprotonation of preexisting carbon skeletons. Recently, Marek and co-workers have developed alternative strategies for the synthesis of trisubstituted enolates that involve *syn*-carbometalation of oxazolidinone-modified ynamides (**10**) with organocuprates followed by either homologation with a zinc-carbenoid,[11] or stereoselective oxidation with *tert*-butyl hydroperoxide.[12] The latter method provides a facile route to stereodefined trisubstituted copper enolates (**12**), which can subsequently participate in diastereoselective quaternary aldol reactions (Scheme 4). The key to success in this methodology is the stereoselective oxidation of the vinyl copper species (**11**), which was confirmed by trapping experiments with TMSCl and characterization of the resulting silyl enol ether. Importantly this methodology has also proved effective in Mannich addition reactions with *N*-sulfonyl imines.

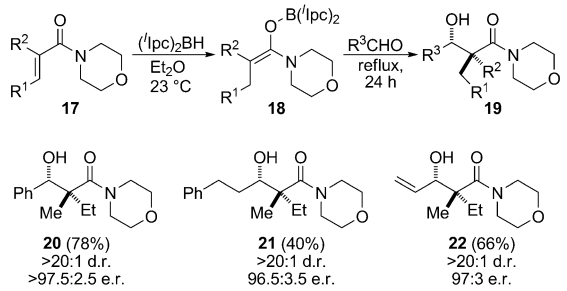
A simple and effective method for controlling enolate geometry in tetrasubstituted enol borinates was recently described by Roush and co-workers (Scheme 5).[13] The enol borinates (**18**) are generated in situ by the 1,4-hydroboration of α,β-unsaturated morpholine carboxamides (**17**) with (diisopinocampheyl)borane ($(^{l}Ipc)_2BH$). Subsequent aldol addition reactions of



Scheme 3. Aldol reaction of chiral, non-racemic bicyclic thiolactams for the preparation of quaternary stereogenic centers.



Scheme 4. Preparation of stereodefined trisubstituted copper enolates and their application to diastereoselective aldol reactions.



Scheme 5. Aldol reaction of tetrasubstituted enol borinates derived from the 1,4-hydroboration of acrylamides with (diisopinocampheyl)borane ($(^{l}Ipc)_2BH$).

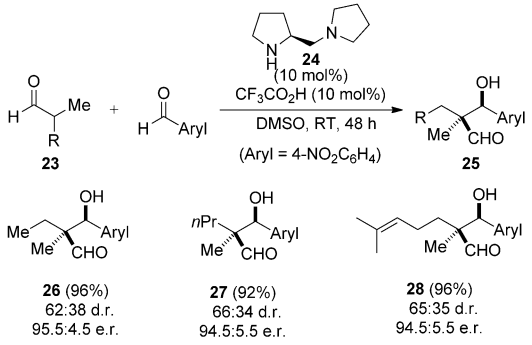
the enol borinates with a panel of aldehydes provided β-hydroxy amides (**19**) containing a stereogenic, α-quaternary center in excellent diastereo- and enantioselectivity.

Other methods for controlling tetrasubstituted enolate geometry based on the use of either chiral auxiliaries or stoichiometric chiral bases have also been reported. Myers described the use pseudoephedrine- and pseudoephenamine-derived amides for selective enolizations with LDA and subsequent diastereoselective enolate alkylation.[14] A chiral non-racemic lithium amide was utilized by Zakarian to prepare geometrically defined α,α-disubstituted silyl ketene acetals, which participate in highly selective Ireland–Claisen rearrangements.[15]

Catalytic, enantioselective aldol reactions for the synthesis of quaternary stereogenic centers

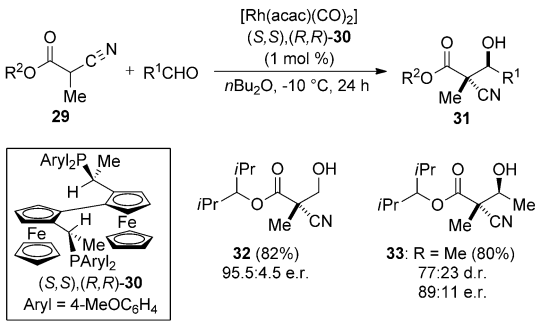
Each of the previous methods relies on the use of a chiral auxiliary as the stereocontrolling unit. Two initial investigations on catalytic, enantioselective aldol reactions for setting quaternary centers have been reported that employ distinct modes of catalysis.

An amine-catalyzed, direct aldol addition of α,α-dialkyl aldehydes donors with aromatic aldehyde acceptors was identified by Barbas and co-workers.[16] The authors found that with 10 mol% each of chiral diamine **24** and trifluoroacetic acid, quaternary carbon containing aldol products (**25**) could be obtained in good yield and enantioselectivity (Scheme 6). The products are isolated with poor diastereomeric ratios, suggesting that the amine catalyst is unable to discriminate between the two possible enamine intermediates. Similar work has also been described by the Barbas group for the enantioselective Mannich reactions of protected α-imino ethyl glycolates, catalyzed by L-proline.[17]



Scheme 6. Lewis base catalyzed asymmetric direct aldol reaction for the synthesis of quaternary carbon atoms.

A mechanistically distinct, direct aldol reaction for the asymmetric synthesis of quaternary carbon atoms using catalytic amounts of an organo–transition-metal complex has been described by Ito and co-workers.[18] The aldol addition between ethyl 2-cyanopropionate and acetaldehyde is catalyzed by substoichiometric amounts of a rhodium complex generated in situ, to afford the corresponding α-cyano-β-hydroxy carboxylates (**31**) in good yield, but low diastereoselectivity (Scheme 7). On the basis of this preliminary result, the authors next evaluated chiral non-racemic phosphine ligands in an attempt to develop a catalytic, enantioselective process. The highest levels of enantioselectivity are achieved with a *trans*-chelating biferrocene ligand **30** and a bulky diisopropylmethyl-substituted ester group. Under these reaction conditions nitrile products containing a α-stereogenic quaternary centers could be prepared in good yield and with moderate to good diastereo- and enantioselectivities.



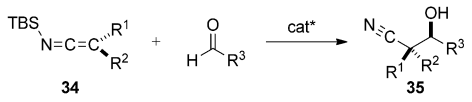
Scheme 7. Rhodium-catalyzed asymmetric direct aldol reaction for the synthesis of quaternary carbon atoms.

Despite these promising initial results for enantioselective aldol reactions for synthesizing quaternary carbon atoms, the generality of these systems remains limited. An analysis of the results from the previous researchers reveals two central challenges that continue to impede the development of this reaction: 1) controlling the enolate geometry of α,α-disubstituted enolates and 2) achieving high enough reactivity in the enolate to overcome the intrinsic steric repulsions encountered in the formation of quaternary carbon atoms. The development of a successful method for the synthesis of quaternary carbon atoms using the aldol addition must address these two challenges.

Research objectives

Silyl ketene imines (**34**) are a class of α,α-disubstituted nucleophiles that avoid the issues associated with enolate geometry. The key structural feature in these species is the pair of orthogonal substituent planes, which imparts an axis of chirality

when R^1 and R^2 are dissimilar. This unique geometry also places a significant portion of the steric bulk in a plane perpendicular to and distal from the nucleophilic carbon atom, which should alleviate some of the steric interactions encountered in the transition state for quaternary carbon formation. Aldol-type reactions of these nucleophiles generate synthetically useful β-hydroxy nitriles (**35**) containing a α-quaternary stereogenic center (Scheme 8).



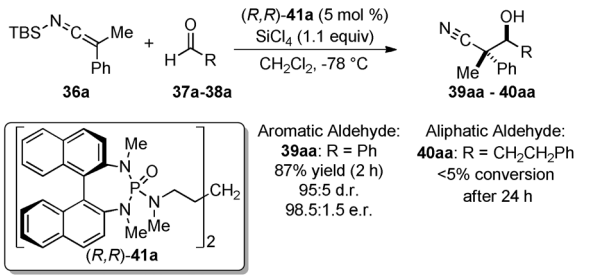
Scheme 8. Synthesis of quaternary carbon atoms by aldol addition of silyl ketene imines.

Although the preparation and characterization of silyl ketene imines (SKIs) are well known, only a few reports have documented their use as nucleophiles in catalytic asymmetric reactions.[19] Early work by Frainnett and co-workers establish that silyl ketene imines will undergo exothermic additions to aldehydes; however, at the onset of this work only a single study by Fu and co-workers had documented the use of SKIs in a catalytic, enantioselective acylation reaction.[19a] Previous studies in these laboratories on the Lewis base catalyzed, silicon tetrachloride mediated additions of silyl ketene acetals have attested to the sensitivity of this catalyst system to minor changes in nucleophile structure.[20] These studies suggested that the asymmetric environment provided by this catalyst system would be well suited for discriminating the two carbon substituents of a silyl ketene imine. Despite these promising attributes very little was known about the stability and reactivity of silyl ketene imines toward the $SiCl_4$/Lewis base catalyst system. Therefore the first goal of this study was to test the compatibility and background reactions of silyl ketene imines with simple aromatic aldehydes. The long-term goals of the study were to develop general, and highly selective carbonyl addition reactions for setting quaternary stereogenic centers.[19b–d]

Results

Proof of principle studies on the addition of silyl ketene imines to aldehydes

The initial investigations tested the compatibility and reactivity of silyl ketene imines under the standard reaction conditions previously developed for the additions of silyl ketene acetals to aldehydes. Reaction of silyl ketene imine **36a** with both an aromatic and an aliphatic aldehyde were examined (Scheme 9). For the addition to benzaldehyde, the results were very promising, showing not only that the silyl ketene imine was stable under the reaction conditions, but also that the addition product was isolated in high yield. Moreover, the β-hydroxy nitrile product (**39aa**) was isolated with high diastereo- and enantioselectivity. Although good reactivity and stereoselectivity was



Scheme 9. Proof of principle experiments for the Lewis base catalyzed, $SiCl_4$-mediated, aldol addition of silyl ketene imines with aromatic and aliphatic aldehydes.

observed for the addition of silyl ketene imine **36a** to benzaldehyde, the addition to aliphatic aldehyde proved more challenging and would require more detailed optimization studies. Encouraged by the proof of principle experiment with benzaldehyde further studies were undertaken to establish the rates of both the background and catalyzed reaction.

In situ IR monitoring of the background and catalyzed reaction rates

The reaction rate was determined by monitoring the loss of the aldehyde absorption by in situ IR kinetic analysis for the addition of silyl ketene imine **36a** to 1-naphthaldehyde in the presence of 5 mol% of (*R,R*)-**41a** and 1.1 equivalents of $SiCl_4$ at −65 °C. A slower-reacting, more-hindered aromatic aldehyde was chosen for this study to allow for the maximum spectral resolution. The plot of the aldehyde absorbance at 1700 cm^{-1} versus reaction time for the catalyzed reaction (red line) is shown in Figure 3, and indicates that the reaction is complete within 3 min of the addition of the SKI. Furthermore, upon quenching the reaction into a saturated aqueous solution of $KF/NaHCO_3$, and following aqueous workup and purification by column chromatography, the nitrile product **39ab** was isolated

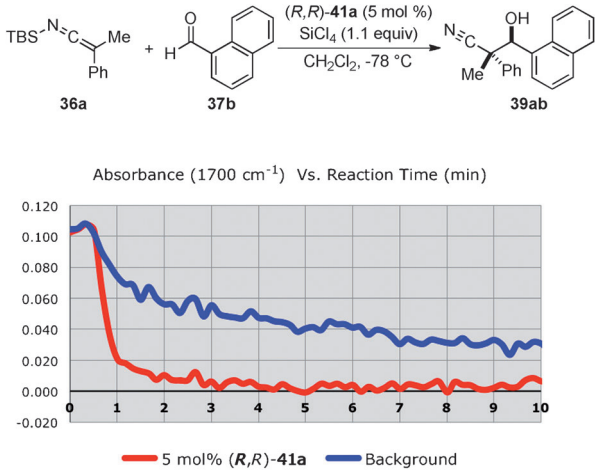


Figure 3. In situ IR kinetic data for catalyzed and background reactions of SKI **36a** addition to 1-naphthaldehyde.

in 70% yield and with excellent diastereo- and enantioselectivity.

Having established the reaction rate for the catalyzed process, the achiral background reaction was next examined. To monitor this rate the same experimental procedure was followed, except the Lewis base catalyst (*R,R*)-**41a** was not added. Surprisingly, a significant background reaction was observed showing about 70% conversion of the aldehyde in only 10 min (blue line, Figure 3). Nevertheless, the achiral reaction does not interfere with the catalyzed process since the nitrile product is obtained with excellent asymmetric induction.

In situ IR rate comparison of silyl ketene imines and silyl ketene acetals

The extremely facile reaction rates observed in both the catalyzed and uncatalyzed addition of SKI **36a** to 1-naphthaldehyde was unexpected and prompted further study. To elucidate how the unique geometry of the SKI may be affecting the observed reaction rates, a comparative rate study between silyl ketene imines and analogously substituted ketene acetals was conducted. Silyl ketene acetals (SKAs) were chosen for this study because they are the ester analogues of ketene imines and have the same oxidation state at the α and β carbon atoms. Structurally though, ketene acetals differ from ketene imines because they lack an orthogonal substituent plane, and a majority of the steric bulk resides in the same plane as the reacting carbon. Additionally, monosubstituted SKAs have been extensively studied within this catalyst system and are known to be excellent substrates for the addition to aromatic aldehydes.

To test the rate difference, SKA **42a** was prepared as a mixture of *E/Z* isomers (by lithiation of methyl 2-phenylpropionate followed by trapping with TBSCl) and its reactivity was assayed by in situ IR monitoring in the addition to 1-naphthaldehyde using the same experimental conditions as described for SKI **36a**. The IR data for each nucleophile is plotted in Figure 4 and the observed difference in reaction rates is dramatic. Under identical reaction conditions, SKA **42a** was nearly unreactive, whereas SKI **36a** reacted to completion in less than 3 min.

Survey of aldehyde structure in the addition of a silyl ketene imine

Motivated by the promising results obtained from the in situ IR rate studies, a more thorough study of the scope of this process with respect to the aldehyde structure was conducted. A wide range of aromatic aldehydes, including electron-neutral, electron-rich, electron-deficient, and heteroaromatic, were surveyed in the addition of SKI **36a** and overall consistently high selectivities and yields were observed (Table 1). Electron-neutral aromatic aldehydes: benzaldehyde, 1-naphthaldehyde, and 2-naphthaldehyde all reacted with comparable rates and selectivities. Furthermore, only a slight drop in the enantioselectivity was observed for addition to the more sterically encumbered aldehyde, 1-naphthaldehyde (Table 1, entry 2). Electron-poor

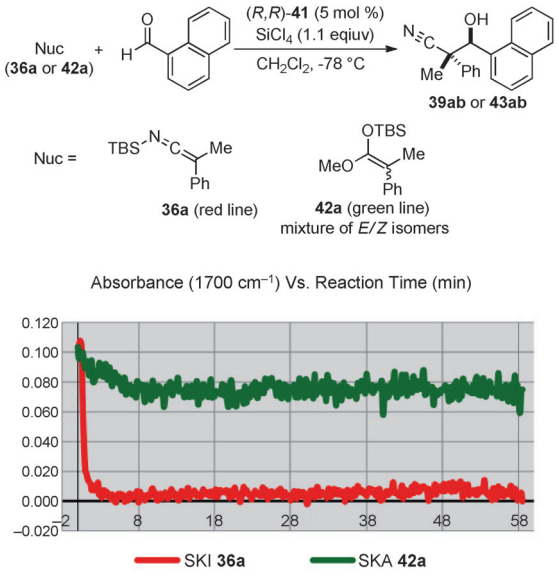
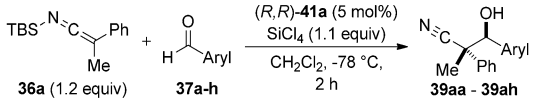


Figure 4. In situ IR study comparing reaction rate of silyl ketene acetal (**42a**) and silyl ketene imine (**36a**) in the addition to 1-naphthaldehyde.

and electron-rich aromatic aldehydes reacted with similar rates and selectivities to benzaldehyde (Table 1, entries 3–5). Finally, only a slight decrease in the enantioselectivity was observed for reaction with the electron-rich heteroaromatic aldehyde, 2-furaldehyde (Table 1, entry 8).

Table 1. Lewis base catalyzed aldol addition of α-phenylpropionitrile-derived silyl ketene imine **36a** with aromatic aldehydes.



Entry	Aryl	Product	Yield [%][b]	d.r.[c]	e.r.[c]
1	C_6H_5 (**37a**)	**39aa**	87	95:5	98.5:1.5
2	1-naphthyl (**37b**)	**39ab**	76	>99:1	98.4:1.6
3	4-$CF_3C_6H_4$ (**37c**)	**39ac**	88	>99:1[d]	99.3:0.7
4	4-BrC_6H_4 (**37d**)	**39ad**	93	99:1	98.9:1.1
5	4-$CH_3CO_2C_6H_4$ (**37e**)	**39ae**	93	>99:1	98.6:1.4
6	4-$CH_3OC_6H_4$ (**37f**)	**39af**	78	96:4	96.6:3.4
7	2-$CH_3C_6H_4$ (**37g**)	**39ag**	84	>99:1	99.2:0.8
8	2-furyl (**37h**)	**39ah**	92	99:1	94.9:5.1

[a] Reactions employed 1.1 equivalents of $SiCl_4$, 1.2 equiv of silyl ketene imine, 0.05 equivalents of (*R,R*)-**41a** at 0.25 M in CH_2Cl_2 at −78 °C for 2 h. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [d] Determined by ^1H NMR analysis.

Synthesis and survey of silyl ketene imine additions to aromatic aldehydes

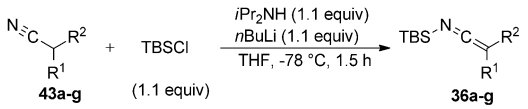
To further probe the scope of the Lewis base catalyzed aldol additions of SKIs, a thorough survey of the ketene imine structure was conducted. In formulating the parameters to evaluate in such a survey, a number of issues were considered: 1) what degree of steric differentiation in the alkyl groups of the

ketene imine is required to retain high levels of diastereoselectivity in the aldol addition and 2) how will the reactivity and stability of aryl- versus dialkyl-substituted ketene imines compare under the current reaction conditions? The latter question is especially relevant, since very few dialkyl silyl ketene imines have been reported. To address these questions, a number of different silyl ketene imines were prepared from the corresponding α,α-disubstituted nitriles.

The preparation of silyl ketene imines is straightforward and although modified protocols have been developed all basically follow the same general procedure first reported by Watt and co-workers[21] and subsequently modified by Fu.[19a] The modified procedure involves lithiation and trapping of the nitrile (**43**) with TBSCl, and following evaporation of the reaction solvent under vacuum, the LiCl byproduct was removed by precipitation with pentanes and anhydrous filtration. The product ketene imines (**36a–g**) were then obtained in high yield and purity by simply concentrating the pentane solution under reduced pressure. Following this general protocol, a number of silyl ketene imines (**36a–g**) were prepared from their respective nitrile precursors (Table 2). Both α-phenyl (Table 2, entries 1–5) and α-alkyl (Table 2, entries 6 and 7) nitriles reacted similarly, producing silyl ketene imines in high yields and greater than 98% purity as judged by ^{1}H NMR analysis of the crude reaction mixtures. Whereas some of these nucleophiles are stable to distillation (Table 2, entry 1), others have a tendency to isomerize to the C-silyl nitrile with prolonged heating. Importantly, no significant differences in the yield or selectivity of the aldol addition reactions have been observed when crude silyl ketene imines are employed. In addition, Fu and co-worker's have demonstrated the ability of disubstituted *C*-silyl nitriles to participate in enantioselective acylation reactions catalyzed by Lewis bases.[19a] Preliminary experiments using the conditions described in Table 1 have shown that *C*-silyl nitriles are unreactive in this catalyst system.

To test what role the nucleophile structure plays on the selectivity of the reaction, the additions of silyl ketene imines

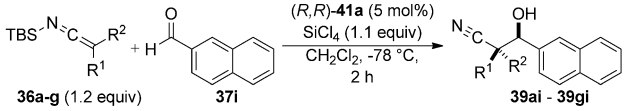
Table 2. Synthesis of *tert*-butyldimethylsilyl ketene imines from α,α-disubstituted nitriles.



Entry	R^1	R^2	Product	Yield [%][b]
1	Ph	Me	**36a**	95 (73[c])
2	Ph	Et	**36b**	96
3	Ph	*i*Pr	**36c**	98
4	Ph	*i*Bu	**36d**	98
5	Ph	allyl	**36e**	96
6	$-(CH_2)_5-$		**36f**	90
7	Me	*i*Pr	**35g**	92

[a] All reactions employed 1.0 equivalents of diisopropyl amine, 1.0 equivalents of *n*BuLi and 1.2 equivalents of TBSCl. [b] Yield of crude material, purity judged to be >95% by ^{1}H NMR (500 MHz) analysis of the crude reaction mixture. [c] Yield reported after short-path distillation under reduced pressure.

Table 3. Lewis base catalyzed aldol addition reaction of α,α-disubstituted silyl ketene imines with 2-naphthaldehyde.[a]



Entry	SKI	R^1	R^2	Product	Yield [%][b]	d.r.[c]	e.r.[d]
1	**36a**	Me	Ph	**39ai**	90	98:2	98.7:1.3
2	**36b**	Et	Ph	**39bi**	78	97:3	92.7:7.3
3	**36c**	*i*Bu	Ph	**39ai**	90	99:1	99.6:0.4
4	**36d**	*i*Pr	Ph	**39di**	73[c]	61:39	78.9:21.1[e]
5	**36e**	allyl	Ph	**39ei**	79	94:6	97.5:2.5
6	**36f**	$-(CH_2)_5-$		**39fi**	85	N/A	91.2:8.8
7	**36g**	Me	*i*Pr	**39gi**	92	60:40	92.1:7.9[f]

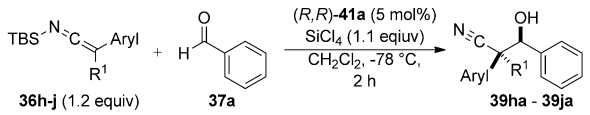
[a] Reactions employed 1.1 equivalents of $SiCl_4$, 1.2 equivalents of silyl ketene imine, 0.05 equivalents of (*R,R*)-**41a** at 0.25 M in DCM at −78 °C for 2 h. [b] Yield of analytically pure material. [c] Yield of chromatographically homogenous material. [d] Determined by CSP-SFC. [e] Enantiomeric ratio of the minor diastereomer was 71.4:28.6. [f] Enantiomeric ratio of the minor diastereomer was 96.6:3.4.

36a–g to 2-naphthaldehyde (**37i**) were surveyed in the presence of 5 mol% of (*R,R*)-**41a** and 1.1 equiv of $SiCl_4$ (Table 3). First, α-alkylbenzylnitrile-derived ketene imines **36a–e** were tested in the aldol addition. The results show that although steric bulk can be well tolerated at this position, the presence of an α-branched substituent leads to a drop in both the diastereomeric and enantiomeric purity of the product (Table 3, compare entries 1–3 to entry 4). The synthetically useful allyl-substituted silyl ketene imine **36e** was well tolerated in the reaction providing a nitrile product in good yield and high selectivity (Table 3, entry 5). To further expand the nucleophile scope, two dialkyl-substituted SKIs that do not contain an aryl ring were prepared and tested in the addition to 2-naphthaldehyde. The cyclohexane-derived ketene imine **36f** provided an aldol product with a non-stereogenic quaternary carbon in good yield and enantioselectivity (Table 3, entry 6). Silyl ketene imine **36g**, containing disparate alkyl groups, reacted to give a 60:40 mixture of enantiomerically enriched diastereomers in good yield (Table 3, entry 7). The high enantiomeric ratio observed within each diastereomer suggests that source of low d.r. was insufficient steric differentiation in the alkyl substituents of the ketene imine.

Next, a survey of silyl ketene imines with electron-rich, electron-poor, and sterically encumbered aryl substituents was conducted using benzaldehyde as the electrophile under the same conditions as the previous series (Table 4).

All members of this series reacted at indistinguishably rapid rates, and provided the products in good yields. Electron-withdrawing (Table 4, entry 1) and electron-donating (Table 4, entry 2) substituents in the *para*-position had no significant effects on the stereoselectivity of the reactions, while adding steric encumbrance at the *ortho*-position (Table 4, entry 3) resulted in a small reduction in enantioselectivity and a moderate reduction in diastereoselectivity.

Table 4. Scope of Lewis base catalyzed aldol reaction with aryl-substituted silyl ketene imines.

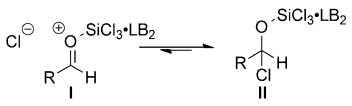


Entry	Aryl	R	SKI	Product	Yield [%][a]	d.r.[b]	e.r.[b]
1	4-$CF_3C_6H_4$	Et	**36h**	**39ha**	73	97:3[c]	99.5:0.5
2	4-$CH_3OC_6H_4$	Me	**36i**	**39ia**	90	98.7:1.3	99.1:0.9
3	2-$CH_3C_6H_4$	Me	**36j**	**39ja**	74	87:13[c]	94.2:5.8[d]

[a] Reactions employed 1.1 equivalents of $SiCl_4$, 1.2 equivalents of silyl ketene imine, 0.05 equivalents of (*R*,*R*)-41a at 0.25 M in DCM at −78 °C for 2 h. [b] Yield of analytically pure material. [c] Determined by CSP-SFC. [c] Determined by ^{1}H NMR analysis. [d] Determined by CSP-HPLC after derivatization with 3,5-dinitrobenzoyl chloride.

Addition of silyl ketene imines to aliphatic aldehydes

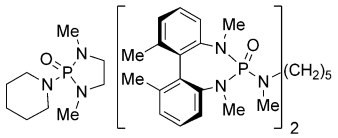
The reactions of aliphatic aldehydes with enoxysilane nucleophiles under Lewis base/silicon tetrachloride activation poses a challenge due to the formation of a parasitic trichlorosilyl chlorohydrin species **II** (Scheme 10). This difficulty can be overcome with a sufficiently reactive nucleophile. It was hypothesized that the high reactivity of silyl ketene imines could be applied to address the problem of addition to aliphatic aldehydes.



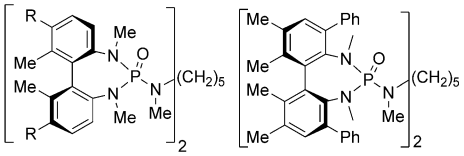
Scheme 10. Chloride trapping of activated aldehydes results in chlorohydrin formation.

A survey of reaction conditions was undertaken to optimize the addition of silyl ketene imines to an aliphatic aldehyde (Table 5). Monitoring of the course of the reaction was conveniently accomplished by in situ FT-IR monitoring, observing the very strong silyl ketene imine stretch (2030 cm^{-1}). Cooling to 0 °C or below was required to control side reactions (Table 5, entries 1–3), and −20 °C provided optimal selectivity (Table 5, entry 5). *n*Bu_4NI, which had previously been applied to the addition of silyl ketene acetals,[20a] proved superior to other halides, whereas *n*Bu_4NOTf did not affect the rate (Table 5, entry 8) and *n*Bu_4NCl (Table 5, entry 6) induced rapid desilylation of the ketene imine. The use of TIPS-protected ketene imine **36k** at 0 °C in place of **36a** (Table 5, entry 9) improved selectivity to a level comparable to that obtained with **36a** at −20 °C (Table 5, entry 5), with a rate similar to that observed at −10 °C (Table 5, entry 4). Further increases in the size of the silyl group reduced enantioselectivity and yield (Table 5, entry 10). The omission of *n*Bu_4NI led to lower enantio- and diastereoselectivity as well as decreased rate, which suggested that an increased loading of this reagent might be beneficial (Table 5, entry 11). Gratifyingly, a small increase in enantioselectivity was observed when a full equivalent of *n*Bu_4NI was used (Table 5, entry 12). Interestingly, there was no corresponding increase in rate or yield. Finally, by combining previous positive results, a set of optimal conditions was estimated (Table 5, entry 13). Under these conditions, high yield as well as enantio- and diastereoselectivities were achieved.

Several additional phosphoramide catalysts (**41c–e**) were prepared to explore the suitability of dimethylbiphenyldiamine as an alternative to 1,1′-binapthyl-2,2′-diamine, as well as the effects of substitution at the 3,3′- and 4,4′-positions. Substantially lower enantioselectivity was observed with biphenyl catalyst (*S*,*S*)-**41c** compared to (*R*,*R*)-**41a** (Table 5, entry 14) however the diastereoselectivity was unchanged. The 5,5′-substituted catalyst (*R*,*R*)-**41d** provided the same selectivity as (*S*,*S*)-**41c**, albeit in opposite absolute configuration (Table 5, entry 15). Disappointingly, catalyst (*S*,*S*)-**41e**, which is substituted at the 3,3′-position, (Table 5, entry 16) produced only racemic product with low diastereoselectivity.



41b **41c**



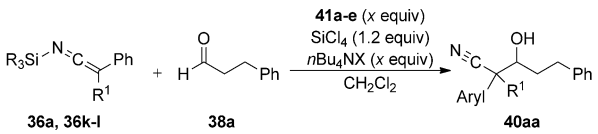
41d (R = 3,5-$(CH_3)_2C_6H_3$) **41e**

Next, a survey of simple aliphatic aldehydes was undertaken to explore the scope of this reaction. Five aliphatic aldehydes were selected to evaluate the effects of substitution patterns on reactivity and selectivity (Table 6). The reactions of silyl ketene imine **36k** with **38b**, which bears an *n*-pentyl chain, (Table 6, entry 1) and benzyloxy-functionalized aldehyde **38c** (Table 6, entry 2) proceeded in good yields although the enantioselectivities were somewhat lower than was observed with **38a**. The reaction with β-branched aldehyde **38d** also proceeded in good yield; however, the enantioselectivity was still lower. The silyl ketene imine addition was found to be completely intolerant of α-branching at the aldehyde (Table 6, entry 4), which lead to no reaction, as well as α-aryl substitution (Table 6, entry 5), which lead to a complex mixture. The latter is likely due to the increased acidity of the aldehyde and consequent increased self-condensation.

Determination of relative and absolute configurations of the aldol products

The β-hydroxy nitrile products prepared in this study had not been previously reported and consequently the absolute con-

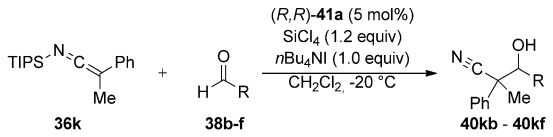
Table 5. Optimization of silyl ketene imine addition to aliphatic aldehydes.



Entry	catalyst (equiv)	SiR_3	nBu_4NX (equiv)	T [°C]	t [h]	Yield[a] [%]	e.r.[b]	d.r.[c]
1	**41b** (0.2)	TBS	nBu_4NI (0.5)	23	17	0	–	–
2	**41b** (0.2)	TBS	nBu_4NI (0.5)	0–14	17	33	–	–
3	**41a** (0.05)	TBS	nBu_4NI (0.5)	0	24	66	88:12	90:10
4	**41a** (0.05)	TBS	nBu_4NI (0.5)	−10	18	74	90:10	90:10
5	**41a** (0.05)	TBS	nBu_4NI (0.5)	−20	17	66	93:7	91:9
6	**41a** (0.05)	TBS	nBu_4NCl (0.5)	0	1	trace	—	–
7	**41a** (0.05)	TBS	nBu_4NBr (0.5)	0	17	56	87:13	82:18
8	**41a** (0.05)	TBS	nBu_4NOTf (0.5)	0	17	trace	–	–
9	**41a** (0.05)	TIPS (**36k**)	nBu_4NI (0.5)	0	17	63	92:8	93:7
10	**41a** (0.05)	TBDPS (**36l**)	nBu_4NI (0.5)	0	17	20	78:22	93:7
11	**41a** (0.05)	TBS	–	0	17	34	71:29	80:20
12	**41a** (0.05)	TBS	nBu_4NI (1.0)	0	17	67	90:10	90:10
13	**41a** (0.05)	TIPS (**36k**)	nBu_4NI (1.0)	−20	22	84	94.5:5.5	98.5:1.5
14	**41c** (0.05)	TIPS (**36k**)	nBu_4NI (1.0)	−20	24	95	24:76	98.5:1.5
15	**41d** (0.05)	TIPS (**36k**)	nBu_4NI (1.0)	−20	24	69	76:24	98.8:1.2
16	**41e** (0.05)	TIPS (**36k**)	nBu_4NI (1.0)	−20	24	84	50:50	75:25

[a] Yield after chromatography. [b] Determined by CSP-SFC. [c] Determined by ^{1}H NMR analysis.

Table 6. Substrate scope in the addition of a SKI 36k to aliphatic aldehydes.



Entry	Product	R	Yield[a] [%]	e.r.[b]	d.r.[c]
1	**40ab**	$CH_3(CH_2)_4$	94	~91:9[d]	98:2
2	**40ac**	$BnO(CH_2)_5$	83	90:10	98.5:1.5
3	**40ad**	*i*Bu	85	<85:15[d]	>95:5
4	**40ae**	*i*Pr	0	–	–
5	**40af**	$PhCH_2$	0	–	–

[a] Yield after chromatography [b] Determined by CSP-SFC [c] Determined by ^{1}H NMR analysis [d] Incomplete separation of stereoisomers.

figurations could not be determined by comparison of the optical rotations to known compounds. Furthermore, given the current challenges for preparing aldol-type products containing a quaternary stereogenic center it became difficult to even find suitable literature compounds that could be arrived at by functional group manipulation of the nitrile. Therefore, the absolute and relative configurations of the products were established by single-crystal X-ray crystallography on nitrile product **39ad.**[22] The *S* configuration at the alcohol center (C3) confirms that the nucleophile adds to the *Re*-face of the aldehyde and is in agreement with the sense of asymmetric induction observed in other reaction manifolds reported for this catalyst system.

Discussion

Trends in reactivity with respect to silyl ketene imine structure

The extremely facile addition rate exhibited by silyl ketene imines under the $SiCl_4$/bisphosphoramide catalyst system is truly remarkable and has allowed for the synthesis of quaternary carbon containing aldol products in high yields and stereoselectivities for the first time. To probe how the structure of silyl ketene imines could be accounting for the observed reaction rates a comparative study of silyl ketene acetals and silyl ketene imines was conducted. The results of these experiments showed that silyl ketene imines were significantly more reactive than silyl ketene acetals in this catalyst system. This large disparity in observed reactivity between silyl ketene imines and ketene acetals most likely results from both steric and electronic differences that exist between these two nucleophile classes. However, the steric component may play a more dominant role in these reactions due to the congestion associated with the formation of a quaternary center. This is especially apparent when comparing the open transition-state models, which have been proposed to explain the stereochemical outcome for addition of silyl ketene acetals to aldehydes with the (*R,R*)-**41a**/$SiCl_4$ catalyst system (Figure 5). Previous mechanistic and computational studies have suggested that the active catalytic species in these reactions is a phosphoramide-bound trichlorosilyl cation.[20a,23] This highly electrophilic chiral Lewis acid activates the aldehyde through coordination to the lone pair of the carbonyl and then controls the relative and absolute topicity for the combination of two prochiral reactants. The high diastereoselectivity observed for these additions can

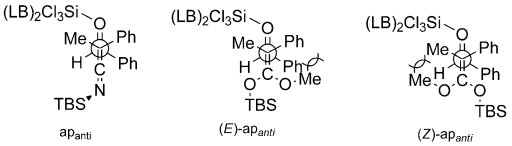


Figure 5. Open transition structures comparing silyl ketene imines and acetals.

then be rationalized by minimizing steric interactions between the approaching nucleophile and the sizable trichlorosilyl cation. Comparing the antiperiplanar open transition structures leading to the *anti*-aldol product for the addition of disubstituted silyl ketene acetals and silyl ketene imines show dramatic differences. For example, the transition structure for the addition of either *E* or *Z* silyl ketene acetal **42a** to benzaldehyde both suffer from unfavorable steric interactions with the alkoxy substituents (Figure 5). This space is completely open in the transition state proposed for the addition of silyl ketene imine **36a** to benzaldehyde. Furthermore, the bulky TBS substituent of the silyl ketene imine can occupy a position in space perpendicular to the plane of the aldehyde and away from the congestion of the newly forming quaternary center.

Reactivity trends with respect to aldehyde structure

Excellent selectivities were observed in the additions of silyl ketene imines to aromatic aldehydes. This outcome can be attributed largely to the extensive catalyst optimization studies that had previously been performed on Lewis base catalyzed, $SiCl_4$-promoted aldol and allylation reactions, culminating in the development of phosphoramide catalyst **41a**.[24]

Silyl ketene imine additions to aliphatic aldehydes were achieved at temperatures higher than those required for aromatic aldehydes. The levels of enantioselectivity observed in these reactions were more variable than those observed in additions to aromatic aldehydes, ranging from 94.5:5.5 to $<$85:15. Some of this reduction in selectivity may be the result of the reaction temperature. Aliphatic aldehydes are more conformationally flexible and structurally diverse than aromatic aldehydes, either of which may contribute to increased variability in substrate catalyst interactions.

Rationalization of diastereoselectivity in silyl ketene imine additions

The diastereoselectivity of silyl ketene imine additions to aldehydes poses several interesting questions. The assumption of an open transition structure is justified by the difficulty of coordinating a nucleophile to an already hexacoordinate silicon complex. This assumption leads to two enantiomeric sets of six possible transition structures (**46a–f**), of which three (**46a–c**) are consistent with the observed diastereoselectivity (Figure 6a). Which of these dominates depends on several issues that cannot be answered from a simple diagram. First, by analogy to the chemistry of silyl ketene acetals, an electronic preference may operate in the *anti* transition-state structures.

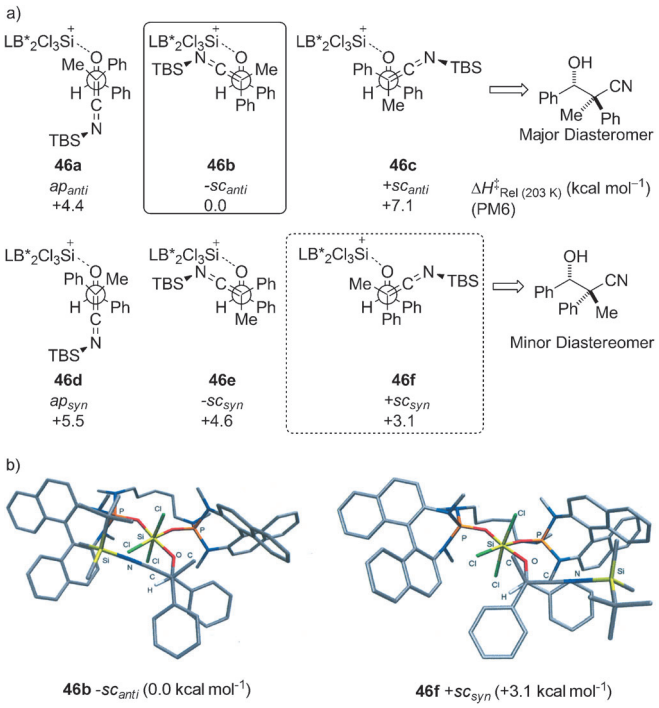


Figure 6. a) Calculated transition structure energies for addition of **36a** to benzaldehyde. b) Calculated transition structures for $-sc_{anti}$ and $+sc_{syn}$ addition of **36a** to benzaldehyde.

Second, the magnitude of steric interactions of the silyl group will depend on the degree of rehybridization occurring in the transition state. Although the silyl groups in Figure 6a are drawn as pointing out of the page, away from major interactions with anything, this is merely one set of limiting, ground-state like structures. Later in the reaction coordinate, the Si-N-C angles should approach 180° as the nitrogen of ketene imine **36a** becomes sp-hybridized, potentially bringing the silyl group into close interaction with sections of the transition structure some distance away from the forming bond.

In order to better understand the factors effecting diastereoselectivity in silyl ketene imine additions, semiempirical calculations (PM6, MOPAC2007 and MOPAC 2009)[25] were performed to locate transition structures of the reaction of **36a**, $SiCl_4$, catalyst (*R,R*)-**41a**, and benzaldehyde (Figure 6b). The lowest energy transition structure (**46b** $-sc_{anti}$) corresponds to the major diastereomer obtained experimentally.

Several aspects of these transition structures are of particular interest. Most notably, the two lowest energy transition structures are open synclinal (**46b** $-sc_{anti}$ and **46f** $+sc_{syn}$, Figure 6b). The unfavorable dipole–dipole interactions, which disfavor open synclinal transition states in aldol reactions of non-chelating alkali metal enolates and naked enolates,[26] are only modestly strong in the more closely analogous Mukaiyama type aldol reactions[27] and may be outweighed by steric factors in the case of silyl ketene imine additions.

In the lowest energy structure, **46b** $-sc_{anti}$, the ketene imine axis faces the bulky silicon Lewis acid, indicating that the ketene imine is effectively the smallest substituent, despite the

possibility of steric interactions with the TBS group (Figure 6b). The next smallest substituent, the methyl group, is positioned to the right as drawn, in a pocket formed by one of the naphthyl groups of the catalyst. This interaction may be how the catalyst reinforces the inherent diastereoselectivity of the reaction, as the far wall of the pocket is positioned to encounter the TBS group. This interaction may be seen in structure **46f** $+sc_{syn}$, in which the O-C-C-C dihedral angle of the forming bond is distorted to 92°, compared to the ideal 60°, to avoid this interaction (Figure 6b). The largest substituent, the phenyl group, points downward, a direction which appears essentially open. No attempt was made to locate the six additional transition structures that are isomeric at the ketene imine chiral axis, however, the C=N–Si angles in the six evaluated transition structures are 172–174°, which suggests that this omission is of little or no consequence, since the chiral axis has essentially been lost in the transition state. Furthermore, it is likely that silyl ketene imines undergo rapid stereoinversion under the reaction conditions, as no splitting of diastereotopic signals can be observed by ^{1}H NMR spectroscopy even at −60 °C. Previous studies have found low inversion barriers in analogous alkyl and aryl ketene imine systems.[28]

Rationale for the observed enantioselectivity with aromatic aldehydes

The structure of the Lewis base activated complex between (*R,R*)-**41a** and $SiCl_4$ has been of much interest, and kinetic studies have suggested that the catalytically active species involves a hexacoordinate silicate bound by two phosphoramide moieties.[23b] Direct evidence for the hexacoordinate silicon complex through X-ray crystallography has been elusive due to the transient nature of the phosphoramide–silicon bond. However, hexacoordinate complexes of $SiCl_4$ with hexamethylphosphoramide[23a] and $SnCl_4$ with bisphosphoramides[29] have been observed and characterized by X-ray crystallography in these laboratories. These results have aided in the development of a working computational model of the trichlorosilyl cation, in which both the chiral bisphosphoramide and a substrate aldehyde are bound to the silicon center (Figure 7).[20a] In the minimized structure, the aldehyde binds *trans* to one of the phosphoramides, owing to the nature of the hypervalent bonds in the ligand field around silicon. This geometry places the aldehyde close to one of the binaphthyl rings of the Lewis base catalyst, possibly stabilized by an edge-to-face π–π interaction.

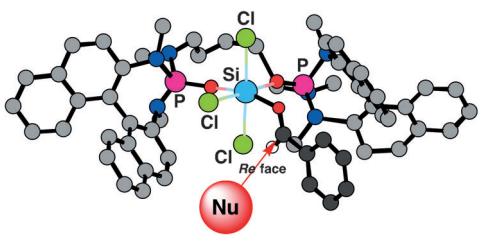


Figure 7. Calculated model of the benzaldehyde–silyl cation complex optimized with PM3 basis set using GAMESS(UC) QC package and visualized using Chem3D®.

The *N*-methyl group on the binaphthyl ring of the catalyst protrudes far into the binding pocket, effectively shielding the *Si*-face of the aldehyde and leaving the *Re*-face exposed for nucleophilic attack.

The absolute configuration for the nitrile products derived from silyl ketene imine additions to aromatic aldehydes catalyzed by (*R,R*)-**41a** are also consistent with this stereochemical model. The *S* configuration of the alcohol center confirmed that SKI underwent addition to the *Re*-face of the aldehyde and open transition-state models based on minimizing interactions between the silyl cation and phenyl substituents of the SKI are consistent with the observed relative configuration. These findings provide further support for the current stereochemical model.

Conclusion

The addition of silyl ketene imines to aromatic aldehydes is an efficient process for the enantioselective construction of quaternary stereocenters. The addition can accommodate a variety of substituents on both the aldehyde and the ketene imine, and products are generally isolated in high yields, as well as excellent diastereomeric and enantiomeric ratios. In situ IR monitoring for the Lewis base catalyzed addition of silyl ketene imines to aromatic aldehydes reveal an extremely facile reaction rate. Directly comparing silyl ketene imines to silyl ketene acetals in this reaction system suggests that the unique structure of the SKI accounts for the dramatic rate difference observed between these two nucleophile classes.

The *S*-absolute configuration for the nitrile product as determined by single-crystal x-ray crystallography is consistent with *Re*-face addition of the nucleophile to the aldehyde. Computational modeling was utilized to further examine the relative topicity for the approach of the ketene imine to the activated aldehyde/Lewis acid complex. On the basis of these studies, the major stereoisomer for the addition of silyl ketene imines is seen to arise from a synclinal transition structure in which the *Re*-face of the aldehyde is the most accessible.

The reduced reaction rate observed for addition of silyl ketene imines to aliphatic aldehydes could be overcome by increasing the reaction temperature and employing nBu$_4$NI as an additive. Under the optimized reaction conditions, the addition of silyl ketene imines to aliphatic aldehydes was achieved in high yield with un-hindered linear aliphatic aldehydes. The reaction rate of this process was strongly dependent on aldehyde structure, for which more hindered aliphatic aldehydes were unreactive. The enantioselectivity for the addition of silyl ketene imines to aliphatic aldehydes ranged from good to excellent. Efforts to identify a catalyst structure that would allow for increased reactivity with a broader class of aliphatic aldehydes and/or better enantioselectivity with linear aliphatic aldehydes were unsuccessful. The current binaphthylamine derived Lewis base, (*R,R*)-**41a**, appears to represent at least a local optimum as all accessible modifications produced less selective catalysts. Future directions will focus on applying silyl ketene imines to new classes of electrophiles.

Acknowledgements

Financial support was provided by the National Science Foundation (NSF CHE-0717989 and CHE-1012663). M.T.B. thanks the University of Illinois for a Seemon H. Pines Graduate Fellowship.

Keywords: aldol reaction · asymmetric synthesis · quaternary stereogenic center · semiempirical calculations · stereoselective catalysis

[1] a) D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, *13*, 1 – 116; b) C. H. Heathcock, in *Asymmetric Synthesis, Vol. 3* (Ed.: J. D. Morrison), Academic Press, New York, **1984**, pp. 111 – 212; c) I. Paterson, in *Comprehensive Organic Synthesis Part 2* (Ed.: C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 301 – 320; d) M. Braun, in *Stereoselective Synthesis Methods of Organic Chemisty, Vol. 3* (Eds.: G. Helmchen, R. Hoffman, J. Mulzer, E. Schaumann), Houben-Weyl, Stuttgart, **1996**, pp. 1603 – 1666; e) R. Mahrwald, *Modern Aldol Reactions, Vol. 1 and 2*, Wiley-VCH, Weinheim, Germany, **2004**; f) E. M. Carreira, A. Fettes, C. Marti, *Org. React.* **2006**, *67*, 1 – 216.

[2] a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 2092 – 2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 388 – 401; b) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725 – 4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591 – 4597; c) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105 – 10146; d) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363 – 5367; e) J. Christoffers, A. Baro, Wiley-VCH, Weinheim, Germany, **2005**; f) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369 – 396; g) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583 – 1614; h) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295 – 7306.

[3] a) I. Marek, G. Sklute, *Chem. Commun.* **2007**, 1683 – 1691; b) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593 – 4623; c) I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik, J. P. Das, *J. Am. Chem. Soc.* **2014**, *136*, 2682 – 2694.

[4] a) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943 – 11948; b) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745 – 2759.

[5] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920 – 1923.

[6] R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868 – 2877.

[7] a) Z. A. Fataftah, I. E. Kopka, M. W. Rathke, *J. Am. Chem. Soc.* **1980**, *102*, 3959 – 3960; b) E. J. Corey, A. W. Gross, *Tetrahedron Lett.* **1984**, *25*, 495 – 498; c) R. E. Ireland, P. Wipf, J. D. Armstrong, *J. Org. Chem.* **1991**, *56*, 650 – 657.

[8] J. M. Manthorpe, J. L. Gleason, *J. Am. Chem. Soc.* **2001**, *123*, 2091 – 2092.

[9] E. D. Burke, J. L. Gleason, *Org. Lett.* **2004**, *6*, 405 – 407.

[10] E. A. Tiong, J. L. Gleason, *Org. Lett.* **2009**, *11*, 1725 – 1728.

[11] J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128 – 132.

[12] Y. Minko, M. Pasco, L. Lercher, M. Botoshansky, I. Marek, *Nature* **2012**, *490*, 522 – 526.

[13] C. Allais, A. S. Tsai, P. Nuhant, W. R. Roush, *Angew. Chem.* **2013**, *125*, 13126 – 13129; *Angew. Chem. Int. Ed.* **2013**, *52*, 12888 – 12891.

[14] a) D. A. Kummer, W. J. Chain, M. R. Morales, O. Quiroga, A. G. Myers, *J. Am. Chem. Soc.* **2008**, *130*, 13231 – 13233; b) M. R. Morales, K. T. Mellem, A. G. Myers, *Angew. Chem.* **2012**, *124*, 4646 – 4649; *Angew. Chem. Int. Ed.* **2012**, *51*, 4568 – 4571.

[15] a) Y.-c. Qin, C. E. Stivala, A. Zakarian, *Angew. Chem.* **2007**, *119*, 7610 – 7613; *Angew. Chem. Int. Ed.* **2007**, *46*, 7466 – 7469; b) C. E. Stivala, A. Zakarian, *J. Am. Chem. Soc.* **2008**, *130*, 3774 – 3776.

[16] N. Mase, F. Tanaka, C. F. Barbas, III, *Angew. Chem.* **2004**, *116*, 2474 – 2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420 – 2423.

[17] N. S. Chowdari, J. T. Suri, C. F. Barbas, III, *Org. Lett.* **2004**, *6*, 2507 – 2510.

[18] R. Kuwano, H. Miyazaki, Y. Ito, *J. Organomet. Chem.* **2000**, *603*, 18 – 29.

[19] a) A. H. Mermerian, G. C. Fu, *Angew. Chem.* **2005**, *117*, 971 – 974; *Angew. Chem. Int. Ed.* **2005**, *44*, 949 – 952; b) S. E. Denmark, T. W. Wilson, M. T. Burk, J. R. Heemstra, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 14864 – 14865; c) S. E. Denmark, T. W. Wilson, *Synlett* **2010**, 1723 – 1728; d) S. E. Denmark, T. W. Wilson, *Nat. Chem.* **2010**, *2*, 937 – 943; e) G. T. Notte, V. J. M. Baxter, J. L. Leighton, *Org. Lett.* **2011**, *13*, 816 – 818; f) S. E. Denmark, T. W. Wilson, *Angew. Chem.* **2012**, *124*, 3290 – 3293; *Angew. Chem. Int. Ed.* **2012**, *51*, 3236 – 3239; g) S. E. Denmark, T. W. Wilson, *Angew. Chem.* **2012**, *124*, 10120 – 10132; *Angew. Chem. Int. Ed.* **2012**, *51*, 9980 – 9992; h) J. Guin, G. Varseev, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 2100 – 2103.

[20] a) S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774 – 3789; b) S. E. Denmark, W.-j. Chung, *J. Org. Chem.* **2008**, *73*, 4582 – 4595; c) S. E. Denmark, J. R. Heemstra, *J. Org. Chem.* **2007**, *72*, 5668 – 5688.

[21] D. S. Watt, *Synth. Commun.* **1974**, *4*, 127 – 131.

[22] CCDC-659734 (**39 ad**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] a) S. E. Denmark, B. M. Eklov, *Chem. Eur. J.* **2008**, *14*, 234 – 239; b) S. E. Denmark, B. M. Eklov, P. J. Yao, M. D. Eastgate, *J. Am. Chem. Soc.* **2009**, *131*, 11770 – 11787.

[24] S. E. Denmark, T. Wynn, *J. Am. Chem. Soc.* **2001**, *123*, 6199 – 6200.

[25] a) J. Stewart, *J. Mol. Model.* **2007**, *13*, 1173 – 1213; b) J. J. P. Stewart, MOPAC2007 ed., Stewart Computational Chemistry, Colorado Springs, CO, USA, http://OpenMOPAC.net, **2007**.

[26] a) C. H. Heathcock, S. K. Davidsen, K. T. Hug, L. A. Flippin, *J. Org. Chem.* **1986**, *51*, 3027 – 3037; b) S. E. Denmark, B. R. Henke, *J. Am. Chem. Soc.* **1989**, *111*, 8032 – 8034; c) S. E. Denmark, B. D. Griedel, D. M. Coe, *J. Org. Chem.* **1993**, *58*, 988 – 990; d) S. E. Denmark, B. R. Henke, *J. Am. Chem. Soc.* **1991**, *113*, 2177 – 2194.

[27] S. E. Denmark, W. Lee, *Chem. Asian J.* **2008**, *3*, 327 – 341.

[28] a) J. C. Jochims, J. Lambrecht, U. Burkert, L. Zsolnai, G. Huttner, *Tetrahedron* **1984**, *40*, 893 – 903; b) J. Lambrecht, B. Gambke, J. Vonseyerl, G. Huttner, G. K. Nell, S. Herzberger, J. C. Jochims, *Chem. Ber.* **1981**, *114*, 3751 – 3771.

[29] S. E. Denmark, X. P. Su, *Tetrahedron* **1999**, *55*, 8727 – 8738.

Received: April 30, 2014
Published online on July 7, 2014