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Lewis Base Activation of Lewis Acids: Catalytic, Enantioselective Vinylogous Aldol Addition Reactions

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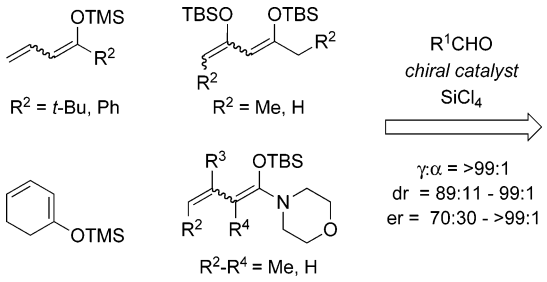

The generality of Lewis base catalyzed, Lewis acid mediated, enantioselective vinylogous aldol addition reactions has been investigated. The combination of silicon tetrachloride and chiral phosphoramides is a competent catalyst for highly selective additions of a variety of α,β-unsaturated ketone-, 1,3-diketone-, and α,β-unsaturated amide-derived dienolates to aldehydes. These reactions provided high levels of γ-site selectivity for a variety of substitution patterns on the dienyl unit. Both ketone- and morpholine amide-derived dienol ethers afforded high enantio- and diastereoselectivity in the addition to conjugated aldehydes. Although α,β-unsaturated ketone-derived dienolate did not react with aliphatic aldehydes, α,β-unsaturated amide-derived dienolates underwent addition at reasonable rates affording high yields of vinylogous aldol product. The enantioselectivities achieved with the morpholine derived-dienolate in the addition to aliphatic aldehydes was the highest afforded to date with the silicon tetrachloride−chiral phosphoramide system. Furthermore, the ability to cleanly convert the morpholine amide to a methyl ketone was demonstrated.

Introduction and Background

The polyketides form a family of structurally diverse natural products that have interesting biological activity.[1] Many of these compounds are of great commercial interest as potential leads for the development of promising pharmaceutical agents and have provided attractive targets for total synthesis. The main structural characteristic shared by these compounds is the complex polyol subunits with 1,3-diol relationships residing within their core. Thus, a wide variety of highly selective transformations have been developed for the construction of these linear acyclic polyol structures, such as crotylations,[2] alkylations of 4-cyano-1,3-dioxanes,[3] nucleophilic epoxide-opening reactions of epoxy alkynols,[4] nitrile dipolar cycloadditions,[5] and epoxidation of α,β-unsaturated morpholinyl amides.[6] Furthermore, biomimetically inspired iterative aldol reactions have been applied extensively for the synthesis of 1,3-polyol arrays, and the selectivity, generality, and predictability obtainable with current aldol technology have allowed this reaction to emerge as a strategy-level reaction in natural product synthesis.[7]

Along with being ideally suited for efficient access to the targeted polyol structures, the polar nature of the enolate precursor in the aldol addition reaction allows for a vinylogous extension of this reaction.[8] Defined as the transmission of electronic effects through a conjugated π-system, the principle of vinylogy allows for the extension of the nucleophilic or electrophilic character of a function group through the π-system of a carbon−carbon double bond. This vinylogous modification of the aldol reaction is possible when γ-enolizable α,β-unsaturated carbonyl substrates are employed as "extended

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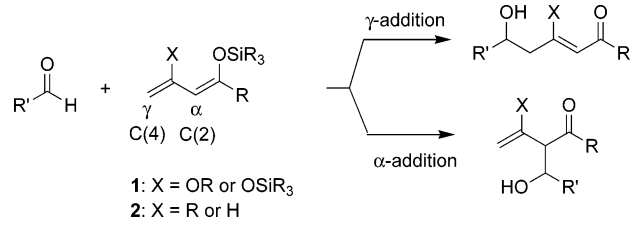
dienolates." This process leads to the formation of δ-hydroxy-β-keto esters or δ-hydroxy-α,β-unsaturated carbonyl compounds in which up to two stereocenters and one double bond can be created simultaneously.[9] These functional arrays are common structural motifs and important intermediates in the synthesis of polyketide natural products. Moreover, the newly created hydroxyl stereocenter is adjacent to a double bond or carbonyl group and allows these versatile intermediates to be further elaborated using several highly selective substrate-directable reactions.[10]

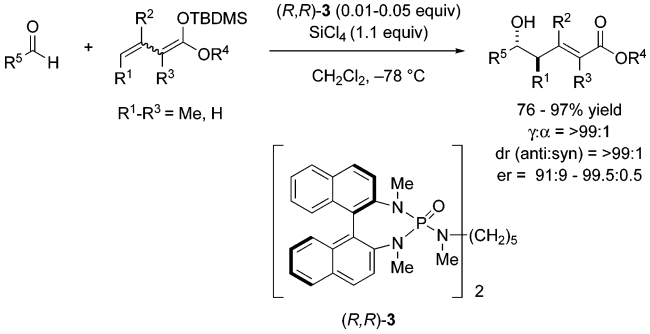
For all of its advantages, the vinylogous aldol reaction is still a challenging transformation because it overlays the problem of site selectivity on top of the issues of diastereo- and enantioselectivity already present in simple aldol reactions. Addition of a dienolate to an aldehyde has the possibility of generating a mixture of both the α- and γ-addition products (Scheme 1). A strategy that allows for γ-site selectivity is the use of silyl dienolates as nucleophiles in Lewis acid promoted, vinylogous, Mukaiyama aldol additions.[9] Furthermore, silyl dienol ether **1** is a synthetic equivalent of a keto ester dianion that reacts with exclusive γ-site selectivity owing to the high nucleophilicity at C(4). However, silyl dienol ethers derived from α,β-unsaturated carbonyl compounds (**2**) are not as electronically biased, and steric effects from both the dienolate and catalyst structure are needed to achieve high site selectivity. Indeed, both α- and γ-addition products have been observed in vinylogous aldol reactions employing ester-derived dienol ethers.[9]

SCHEME 1



The inherent γ-selectivity of silyl dienol ethers in Lewis acid promoted vinylogous Mukaiyama aldol additions has provided an ideal platform for the development of several catalytic, enantioselective variants and several highly selective systems employing lactone-, dioxanone-, and simple ester-derived silyl dienol ethers have been reported.[9] A recent disclosure from these laboratories further expanded the scope of the vinylogous aldol reaction of ester-derived dienol ethers by demonstrating that the combination of the chiral bisphosphoramide (*R*,*R*)-**3** and silicon tetrachloride ($SiCl_4$) is able to promote the addition of simple, ester-derived silyl dienol ethers to aldehydes with almost exclusive γ-site selectivity for a variety of substitution patterns on the ketene acetal while maintaining high enantio- and diastereoselectivity (Scheme 2).[11] The extremely high selectivity for the γ-position attests to the strong differentiation provided by the catalyst during the addition reaction.

SCHEME 2



Although the catalytic, enantioselective, vinylogous aldol addition of α,β-unsaturated ester-derived dienol ethers has been successfully developed, extension of the nucleophile scope to other acyclic α,β-unsaturated carbonyl compounds has not been reported. Application of these reactions in total syntheses highlights the need for the development methods that employ nucleophiles other than ester-derived reagents. Notably, the ester is rarely the desired functional group in the final product and is frequently converted to an aldehyde or a ketone.[9,11] In view of the high selectivities and broad substrate scope in the vinylogous aldol reactions of simple ester-derived silyl dienol ethers promoted by the chiral phosphoramide/$SiCl_4$ catalyst system, we were encouraged to pursue the reactions of *ketone*-derived silyl dienol ethers, which could provide a more direct access to chiral building blocks used in the preparation of many natural products. Furthermore, the use of *amide*-derived dienolates was envisioned owing to the versatility of these compounds.[12] The ability to transform the amide function into either ketones or aldehydes would provide indirect access to aldol products derived from these α,β-unsaturated carbonyl compounds. This report details our full investigations on the scope and limitations of the Lewis base catalyzed, $SiCl_4$-mediated vinylogous aldol additions of ketone- and amide-derived silyl dienol ethers to various aldehydes.[13]

Results

1. Lewis Base Catalyzed Vinylogous Aldol Reactions of α,β-Unsaturated Ketone-Derived Dienol Ethers. Silyl dienol ethers derived from α,β-unsaturated carbonyl compounds favor

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(13) Portions of this work have been communicated: (a) Denmark, S. E.; Heemstra, J. R., Jr. *Synlett* **2004**, 2411−2416. (b) Denmark, S. E.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 1038−1039.

reaction at the γ-position owing to the larger HOMO coefficients and electronic susceptibilities at C(4) than at C(2) (Figure 1).[14] However, the difference between the two reactive centers is not large, and both α- and γ-addition products have been observed in aldol reactions employing ester-derived dienol ethers.[9] Comparison of the HOMO orbital coefficients (O.C.) and electrophilic susceptibility (E.S.) of the trimethylsilyl ketene acetal of methyl crotonate (*E*)-**4** and the trimethylsilyl enol ether of methyl 2-propenyl ketone (*E*)-**5** reveals an even smaller difference between the values at C(2) and C(4) in the ketone-derived silyl enol ether and suggests that its selectivity may be attenuated compared to silyl ketene acetals.[9] Therefore, along with expanding the scope of the vinylogous aldol reaction, the study of α,β-unsaturated, ketone-derived silyl dienol ethers would provide a more stringent test of the ability of the phosphoramide/$SiCl_4$ catalyst system to provide high γ-site selectivity in the addition to aldehydes.

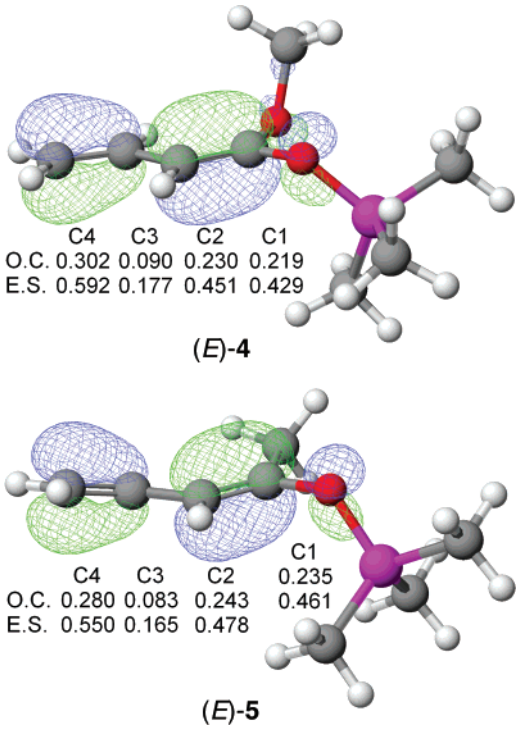
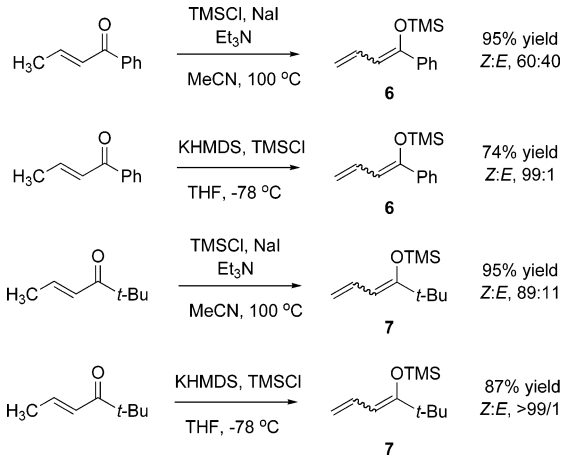


FIGURE 1. Electronic structures of the silyl ketene acetal (*E*)-**4** and silyl enol ether (*E*)-**5**.

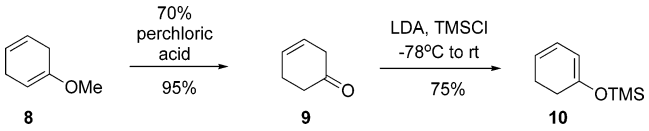
1.1. Preparation of Silyl Dienol Ethers Derived from α,β-Unsaturated Ketones. Although the formation of cross-conjugated dienolates is overwhelmingly favored under conditions of kinetically controlled enolization, the extended, conjugated dienolates of α,β-unsaturated ketones are difficult to obtain when protons are present on the α′-carbon, and mixtures of the cross and extended conjugated dienolates are typically isolated.[15] To simplify the analysis of the product mixture, α,β-unsaturated ketones lacking protons on the α′-carbon were initially examined in this study to ensure exclusive formation of fully conjugated dienolates. Trimethylsilyl dienol ethers **6** and **7** were accessed following the procedure reported by Fleming and co-workers[16] by heating the corresponding ketones in the presence of Et_3N, TMSCl, and NaI at 100 °C (Scheme 3). The dienol ethers were formed as mixtures of geometrical isomers in which the major isomer in both dienolates contains a (1*Z*)-double bond as determined by analysis of their ^{1}H NOE NMR spectra. In addition, a protocol that provides geometrically pure (1*Z*)-dienol ethers was developed that involves the deprotonation of the α,β-unsaturated ketone with 1.1 equiv of potassium hexamethyldisilazide (KHMDS) at −72 °C followed by trapping of the resulting potassium dienolate with TMSCl (Scheme 3).

SCHEME 3



A less direct route allowed for the synthesis cyclohexenone-derived silyl dienol ether **10** (Scheme 4). Following a reaction sequence developed by Fleming and co-workers,[17] 1,4-cyclohexadienyl vinyl ether **8** was hydrolyzed under acidic conditions to afford γ,β-unsaturated ketone **9**. Deprotonation with LDA followed by trapping of the lithium dienolate yielded dienolate **10** exclusively as the extended-conjugated isomer.

SCHEME 4



1.2. Vinylogous Aldol Reactions of Simple α,β-Unsaturated Ketone-Derived Silyl Dienol Ethers. Orienting experiments were conducted with dienol ether **6** and benzaldehyde under the reaction conditions developed in these laboratories for the addition of TMS enol ethers of methyl ketones to aldehydes.[18] Thus, dienol ether **6** (1.2 equiv) was combined with benzaldehyde, $SiCl_4$ (1.5 equiv), and *i*-Pr_2NEt (0.1 equiv) at 0.5 M in CH_2Cl_2 in the presence of 0.05 equiv of (*R*,*R*)-**3** at −78 °C for 4 h. ^{1}H NMR analysis of the crude reaction mixture (obtained by quenching the reaction with a 1:1 mixture of satd aq KF/satd aq $NaHCO_3$ solutions) showed that only unreacted starting material and proteodesilylated α,β-unsaturated ketone were present. By executing the reaction at an elevated temper-

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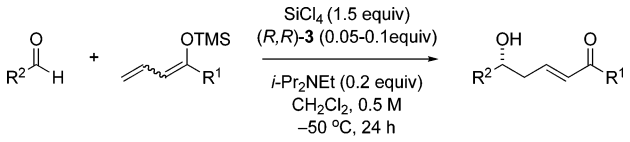
(18) Denmark, S. E.; Heemstra, J. R., Jr. *Org. Lett.* **2003**, *5*, 2303−2306.

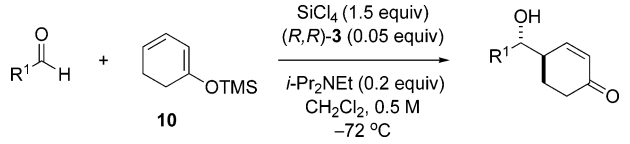
TABLE 1. Vinylogous Aldol Reactions of Ketone-Derived Dienolates with Aldehydes



entry	dienolate	R^1	R^2	product	yield,[a] %	γ:α[b]	er[c]
1	**6**	Ph	Ph	**11**	80	>99:1	99.0:1.0
2	**7**	*t*-Bu	Ph	**12**	94	>99:1	99.5:0.5
3	**7**	*t*-Bu	1-naphthyl	**13**	85	>99:1	99.0:1.0
4	**7**	*t*-Bu	2-furyl	**14**	90	>99:1	96.0:4.0
5[d]	**7**	*t*-Bu	2-thienyl	**15**	50[e]	>99:1	94.0:6.0
6	**7**	*t*-Bu	(*E*)-PhCH=CH	**16**	82	>99:1	>99.5:0.5
7	**7**	*t*-Bu	(*E*)-PhCH=C(CH_3)	**17**	24[e]	>99:1	64.5:35.5
8[d]	**7**	*t*-Bu	PhC≡C	**18**	40[e]	>99:1	84.0:16.0
9	**7**	*t*-Bu	$PhCH_2CH_2$	**19**	0	nd	nd

[a] Yields of analytically pure material. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP-SFC. [d] Reaction employed 0.10 equiv of (*R*,*R*)-**3**. [e] Yield after chromatography.

TABLE 2. Vinylogous Aldol Reactions of Ketone-Derived Dienolate 10 with Aldehydes



entry	R^1	product	time, h	yield,[a] %	γ:α[b]	dr (anti:syn)[c]	er anti[c]	er syn[c]
1	Ph	**20**	2	90[d]	>99:1	97.5:2.5	97.5:2.5	nd
2[f]	1-naphthyl	**21**	10	80[d]	>99:1	89.0:11.0	95.0:5.0	>99.5:0.5
3	(*E*)-PhCH=CH_2	**22**	2	74	>99:1	98.0:2.0	84.5:15.5	nd
4	2-furyl	**23**	2	94	>99:1	95.5:4.5	81.5:18.5	nd
5	$PhCH_2CH_2$	**24**	24	0	nd	nd	nd	nd

[a] Yields of analytically pure material. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP-SFC. [d] Yield after chromatography.

ature (−50 °C) for 24 h, the γ-addition product could be obtained in high yield (80%), enantioselectivity (99.0:1.0 er) and exclusively of *E* configuration (Table 1, entry 1). The α-addition product could not be found by inspection of the ^{1}H NMR spectrum of the crude reaction mixture. Under these conditions, dienol ether **7** also reacted with benzaldehyde, and again, the γ-addition product was obtained exclusively in high yield (94%) and enantioselectivity (99.5:0.5 er). It is interesting to note that despite the fact that dienol ethers **6** and **7** were employed as mixtures of geometrical isomers, high selectivity for the (*E*)-α,β-unsaturated ketone product is observed.

To examine the scope of this process, a number of aldehydes were surveyed in reaction with dienolate **7**. Different aromatic subunits such as the more hindered 1-naphthaldehyde also reacted with excellent selectivity and yield (Table 1, entry 3). Heteroaromatic aldehydes are competent acceptors and showed only a minor decrease in selectivity (entries 4 and 5). As was seen in the addition of simple methyl ketone-derived enolates, branching at the α-position of olefinic aldehydes has dramatic effects both on rates and selectivities. Whereas cinnamaldehyde reacted with the highest enantioselectivity of all the aldehydes surveyed (entry 6), 2-methylcinnamaldehyde afforded the addition product in low yield and enantioselectivity (entry 7). 3-Phenylpropynal, a problematic aldehyde in many addition reactions,[19] displayed only a slightly lower selectivity (entry 8). Despite several attempts, aliphatic aldehydes were found to be completely unreactive with dienolate **7** (entry 9). Even warming of the reaction to 0 °C did not allow for the formation of a vinylogous aldol product. Only the γ-addition product could be observed by ^{1}H NMR analysis of the crude reaction mixture in all of the aldehydes that reacted.

In view of the high levels of selectivity observed in the addition of γ-unsubstituted enones to aldehydes, cyclic dienolate **10**[17] was investigated to evaluate the issue of diastereoselectivity as well as enantio- and regioselectivity. Initial studies showed that when **10** (1.2 equiv) was combined with benzaldehyde, $SiCl_4$ (1.5 equiv), *i*-Pr_2NEt (0.1 equiv) at 0.5 M in CH_2Cl_2 in the presence of 0.05 equiv of (*R*,*R*)-**3** at −78 °C for 2 h, the γ-addition product could be obtained exclusively with excellent anti diastereoselectivity (97.5:2.5) and enantioselectivity for the anti isomer (97.5:2.5) (Table 2, entry 1). Exclusive γ-regioselectivity was also observed in the addition of dienolate **10** to 1-naphthaldehyde; however, increasing the reaction time to 10 h was required to obtain high yields (entry 2). Although the diastereoselectivity was attenuated (89.0:11.0), both the anti and syn diastereomers were formed with high enantioselectivity (95.0:5.0 and >99.5:0.5, respectively). Reactions with cinnamaldehyde and 2-furaldehyde provided the γ-addition products in high yield with excellent anti diastereoselectivity and good enantioselectivity (entries 3 and 4). Despite several attempts, dienol ether **10** did not react with aliphatic aldehydes (entry 5).

1.3. Determination of the Absolute Configuration of the Ketone-Derived Vinylogous Aldol Products. The absolute

(19) For a notable exception, see: Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360−12361.

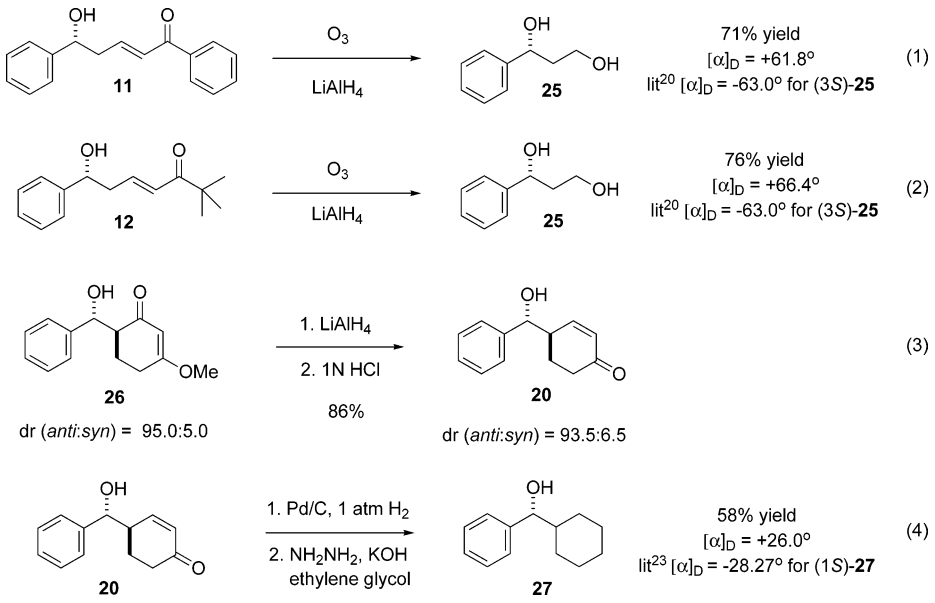


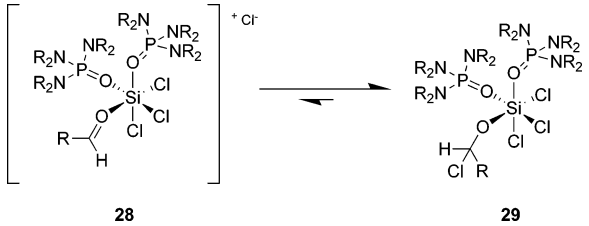
FIGURE 2. Correlation of the configuration of the ketone vinylogous aldol products to known compounds.

configuration of the vinylogous aldol products could not be determined by direct correlation to known examples in the literature and required their chemical degradation to a set of compounds for which the absolute configuration had been unambiguously assigned. To determine the absolute configuration of the acyclic vinylogous aldol adducts, a synthetic route involving cleavage of the C(2)−C(3) double bond and formation of a 1,3-diol afforded a compound of which the absolute configuration had been established by Masamune and others.[20] Thus, compounds **11** and **12** were subjected to ozonolysis followed by reduction of the ozonide with a solution of lithium aluminum hydride in tetrahydrofuran, which afforded the desired diols (**25**) in good yields (Figure 2, eqs 1 and 2). Comparison of their optical rotations with those reported in the literature showed that in both cases the aldol adduct derived from *Re* face attack on the aldehyde was the major enantiomer.

The racemic synthesis of cyclic vinylogous aldol adduct **20** had previously been reported in the literature by Yamamoto and co-workers;[21] however, the absolute configuration of the major diastereomer had not been determined. Therefore, an independent synthesis of cyclohexanone **20** was undertaken to unambiguously establish the configuration of the major diastereomer. Thus, a diastereomerically enriched (anti:syn, 95:5) sample of the 3-methoxy-1′-hydroxy ketone **26**[22] was prepared. Reduction ($LiAlH_4$) of **26** followed by acidic hydrolysis afforded 2-cyclohexenone **20** as a 93.5:6.5 mixture of diastereomers (Figure 1, eq 3). Comparison of their ^{1}H NMR spectra allowed the assignment of the major diastereomer from the reaction of **20** as anti. The absolute configuration of aldol adduct **20** could then be assigned by correlation to the known 1-cyclohexyl-1-phenylmethanol (**27**),[23] which was prepared by hydrogenation of the double bond in **20** followed by Wolff−Kishner reduction (eq 4). Comparison of the optical rotation of **27** to that in the literature shows that the C(1) center is of *R* configuration. Thus, the anti relationship between the two stereocenters in adduct **20** allows for assignment of the absolute configuration of the major enantiomer as (4*R*,7*R*)-**20**. In all three cases, the sense of asymmetric induction is consistent with that observed in all other reported cases employing chiral bisphosphoramide (*R*,*R*)-**3** and $SiCl_4$.

2. Lewis Base Catalyzed Vinylogous Aldol Reactions of 1,3-Diketone-Derived Dienol Ethers. Although excellent yields and selectivities had been achieved in the addition of the α,β-unsaturated ketone-derived silyl dienol ethers to conjugated aldehydes, aliphatic aldehydes remained unreactive. The low reactivity with aliphatic aldehydes under the chiral phosphoramide/$SiCl_4$ catalyst system is proposed to be the result of the rapid transformation of the aldehyde to an unreactive α-trichlorosilyl species (**29**) (Scheme 5).[11] As a consequence, only a low equilibrium concentration of the activated aldehyde complex **28** is available for aldolization. Although dienolates **6**, **7**, and **10** are capable of reacting with the activated aldehyde, they do not undergo addition at a rate that provides a synthetically useful process. Thus, a more reactive nucleophile must be employed to combine with the low concentration of **28** present in solution. To address the issue of nucleophile reactivity, the use of bis(silyloxy)-1,3-dienes derived from 1,3-diketones was explored, as the additional silyloxy group will enhance the nucleophilicity of the dienolate.[24]

SCHEME 5



(20) (a) Masamune, S.; Sato, T.; Kim, B.; Wollman, T. A. *J. Am. Chem. Soc*. **1986**, *108*, 8279−8281. (b) Nunez, M. T.; Martin, V. S. *J. Org. Chem*. **1990**, *55*, 1928−1932.

(21) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc*. **1998**, *120*, 813−814.

(22) Torii, S.; Inokuchi, T.; Ogawa, H. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1233−1234.

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2.1. Preparation of Bissilyl Dienol Ethers Derived from 1,3-Diketones. Although the use of 1,3-bis(silyloxy)-1,3-dienes in catalytic vinylogous aldol reactions has not been reported, their synthesis has been studied.[25] The procedure described by Simchen and co-workers proved to be a reliable and expedient method to access these nucleophiles. Treatment of a β-dicarbonyl compound with 2.2 equiv of Et_3N followed by the slow addition of a trialkylsilyl triflate (2.2 equiv) at 0 °C afforded several different bis(trialkyloxy)-1,3-dienes derived from acetylacetone (**30**) and 3,5-heptanedione (**31**) in high yields (Figure 3). The acetylacetone-derived dienolates (**32a**−**d**) were formed as 55:45 mixtures of geometrical isomers in all cases. However, high geometrical selectivity was obtained in the synthesis of the 3,5-heptanedione-derived dienolates (**33a**−**c**), which was determined to be the 3*Z*,5*Z* isomer as determined by analysis of the ^{1}H NOE NMR of **33b**.

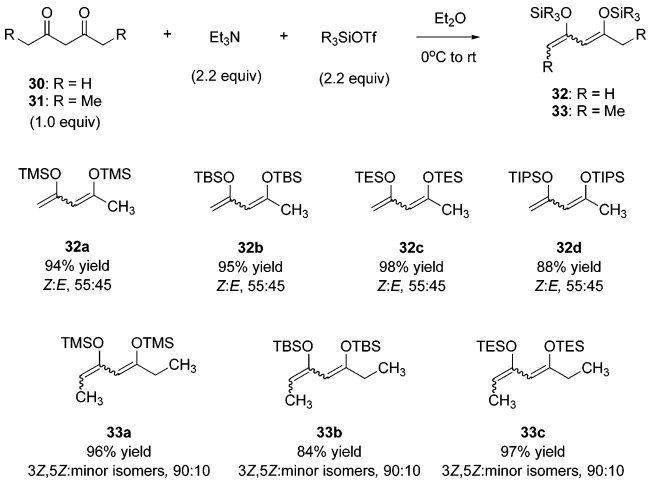
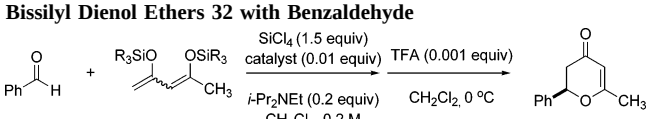


FIGURE 3. Bissilyl dienol ethers used in the vinylogous aldol reactions.

2.2. Vinylogous Aldol Reactions of 1,3-Diketone-Derived Bissilyl Dienol Ethers. To gauge the reactivity of the dienolates, the addition of bis(trimethylsilyl) dienol ether **32a** to benzaldehyde was initially studied. In the presence of 0.01 equiv of dimeric bisphosphoramide (*R*,*R*)-**3** and 1.5 equiv of $SiCl_4$ at −78 °C, the addition of dienolate **32a** to benzaldehyde was found to be complete in <2 min and afforded the product as a mixture of keto and enol tautomers in excellent yield (Table 3, entry 1). Determination of the enantiomeric composition of the adduct directly was not possible, so the δ-hydroxy-1,3-diketone was cyclized to pyranone **34** in the presence of trifluoroacetic acid. The pyranone was then easily analyzed by CSP-SFC, and this protocol was followed in the subsequent reactions of the catalyzed aldol reactions of the bissilyl dienol ethers. Unfortunately, the adduct was found to be of low enantiomeric purity, and control studies found racemization was not occurring in the TFA cyclization step. Two modifications were attempted to improve the selectivity: (1) changing the identity of the silyl group and (2) changing the catalyst structure. In the addition of simple ketone-derived dienol ethers, the silyl group had shown a large effect in the rate of the reaction so larger silyl groups were investigated. The use of the more sterically demanding *tert*-butyldimethylsilyl (TBS) group provided a moderated improvement in enantioselectivity (entry 2); however, when the addition of **32b** to benzaldehyde was executed at −90 °C, the product could be obtained in good enantioselectivity (entry 3). The bis(triethylsilyl) (TES) (**32c**) and bis(triisopropyl) (TIPS) (**32d**) dienolates were found to be less selective than **32b** at −90 °C (entries 4 and 5). Determination of the absolute configuration of the pyranone by comparison of its optical rotation to literature values revealed that the 3*R*-isomer had been formed.[26] This result indicates that *Re* face attack on the aldehyde had occurred, as was the case in the α,β-unsaturated ketone-derived silyl dienol ether additions described above.

TABLE 3. Vinylogous Aldol Reactions of Acetylacetone-Derived Bissilyl Dienol Ethers 32 with Benzaldehyde

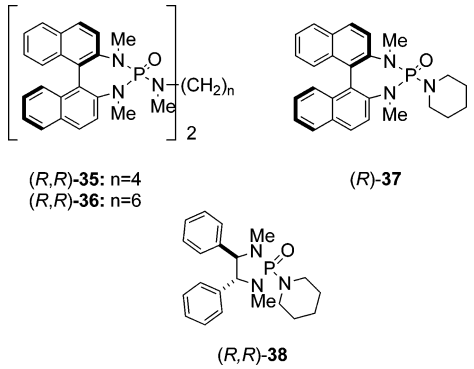


entry	SiR_3	catalyst	*T*, °C	yield,[a] %	γ:α[b]	er[c]
1	TMS	(*R*,*R*)-**3**	−78	95	>99:1	62.0:38.0
2	TBS	(*R*,*R*)-**3**	−78	89	>99:1	75.0:25.0
3	TBS	(*R*,*R*)-**3**	−90	89	>99:1	86.5:13.5
4	TES	(*R*,*R*)-**3**	−90	77	>99:1	61.0:39.0
5	TIPS	(*R*,*R*)-**3**	−90	83	>99:1	71.0:29.0
6	TBS	(*R*,*R*)-**35**	−90	76	>99:1	87.5:12.5
7	TBS	(*R*,*R*)-**36**	−90	80	>99:1	85.0:17.0
8	TBS	(*R*)-**37**	−90	57	>99:1	83.0:17.0
9	TBS	(*R*,*R*)-**38**	−90	98	>99:1	60.0:40.0

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

In these studies, bisphosphoramide (*R*,*R*)-**3** was chosen because of the high selectivity afforded by this catalyst in the addition to simple methyl ketone-derived enolates.[18] However, given the uncharacteristically low selectivity in the addition of the bissilyl dienol ethers, several other catalysts were surveyed (Chart 1). Changing the linker length in the dimeric 1,1′-binaphthyl-2,2′-diamine-derived phosphoramide catalyst was found to have only a small effect on the selectivity. Catalyst (*R*,*R*)-**35**, bearing a four-carbon linker, afforded slightly higher selectivity (Table 3, entry 6), whereas catalyst (*R*,*R*)-**36**, bearing

CHART 1



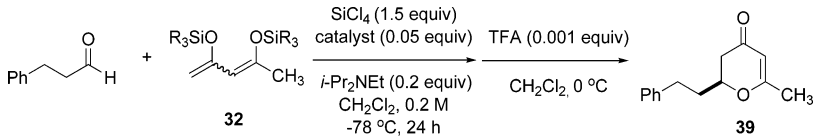
a six-carbon linker, effected a small decrease in selectivity (entry 7). The level of selectivity observed with these dimeric catalysts was nearly identical to that observed with the monomeric catalyst (*R*)-**37** (entry 8). Changing the backbone in the phosphoramide catalyst to the *N*,*N*′-dimethylcyclohexane-1,2-

(24) (a) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem Res*. **2003**, *36*, 66−77. (b) Burfeindt, J.; Patz, M.; Muller, M.; Mayr, H. *J. Am. Chem. Soc*. **1998**, *120*, 3629−3634.

(25) Konrad, K; Simchen, G. *Synthesis* **1981**, 30−32.

(26) Yang, W.; Shang, D.; Liu, Y.; Du, Y.; Feng, X. *J. Org. Chem*. **2005**, *70*, 8533−8537.

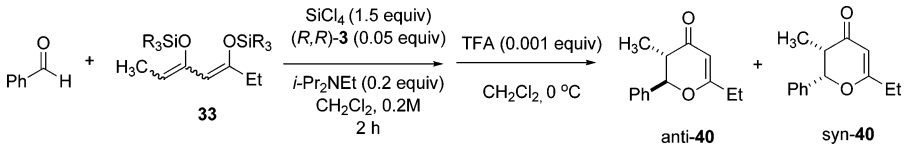
TABLE 4. Vinylogous Aldol Reactions of Acetylacetone-Derived Bissilyl Dienol Ethers 32 with Hydrocinnamaldehyde



entry	SiR_3	catalyst	yield,[b] %	γ:α[c]	er[d]
1	TBS	(*R*,*R*)-**3**	21	>99:1	70.0:30.0
2	TBS	(*R*,*R*)-**35**	21	>99:1	63.0:37.0
3	TBS	(*R*,*R*)-**36**	13	>99:1	54.0:46.0
4	TMS	(*R*,*R*)-**3**	31	>99:1	53.0:47.0
5	TES	(*R*,*R*)-**3**	19	>99:1	59.0:41.0
6	TIPS	(*R*,*R*)-**3**	9	>99:1	67.5:32.5

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

TABLE 5. Vinylogous Aldol Reactions of 3,5-Heptanedione-Derived Bissilyl Dienol Ethers 33 with Benzaldehyde



entry	SiR_3	*T*, °C	dr (anti:syn)[a]	yield anti,[b] %	er anti[c]	yield syn,[b] %	er syn[c]
1	TBS	−78	96:4	83	84.0:16.0	3	49.5:50.5
2	TBS	−90	95:5	66	84.5:15.5	1	47.0:53.0
3	TMS	−90	95:5	93	69.5:30.5	3	nd
4	TES	−90	95:5	81	72.5:27.5	3	nd

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

diamine ((*R*,*R*)-**38**) afforded extremely low levels of enantioselectivity (entry 9).

As mentioned above, the reactivity of aliphatic aldehydes with these bissilyl dienol ethers was of particular interest, as they had resisted addition to the silyl dienol ethers derived from α,β-unsaturated ketones. Initial experiments were conducted using the conditions developed for the vinylogous aldol reaction of aliphatic aldehydes with ester-derived silyl dienol ethers (Table 4). In the presence of 0.05 equiv of dimeric phosphoramide (*R*,*R*)-**3**, the addition of bissilyl dienol ether **32b** to hydrocinnamaldehyde afforded the product in disappointingly low yield and enantioselectivity (entry 1). All attempts at improving selectivity by changing the tether length in the dimeric catalyst (entries 2 and 3) and employing different silyl groups (entries 3−6) were unsuccessful.

To test if the high anti-diastereoselectivity observed in the addition of the α,β-unsaturated ketone-derived dienolate **10** to conjugated aldehydes would also be maintained in the addition of dienolates derived from β-diketones, dienolates derived from 3,5-heptanedione were surveyed in the addition to benzaldehyde. The addition of bissilyl dienol ether **33a** to benzaldehyde afforded the product in high yield and anti-diastereoselectivity (Table 5, entry 1). After separation of the two diastereomers by column chromatography, the anti-diastereomer was found to form with good enantioselectivity while the syn diastereomer was racemic. Unlike in the case of the acetylacetone-derived bissilyl dienol ethers, executing the reaction at −90 °C did not improve the enantioselectivity (entry 2). The bis(TMS) and TES dienol ethers also reacted with excellent anti-diastereoselectivity; however, they afforded considerably lower enantioselectivity than the bis(TBS) dienol ether.

3. Lewis Base Catalyzed Vinylogous Aldol Reactions of α,β-Unsaturated Amide-Derived Dienol Ethers. The use of amide-derived dienolates was initially conceived because of the ability to readily transform the amide function into either ketones or aldehydes, making them highly versatile adducts.[12] However, given the low reactivity of the ketone-derived silyl enol ethers with aliphatic aldehydes, the high reactivity of amide-derived, silyl enol ethers represented an equally desirable trait,[27] and the use of these nucleophiles was seen as a way to overcome some of the limitations of the ketone-derived dienolates.

3.1. Preparation of Silyl Dienol Ethers Derived from α,β-Unsaturated Amides. Previous studies with ester-derived dienolates demonstrated that the site-selectivity of the addition is largely influenced by the size of the alkoxy substituent.[11] Therefore, amides derived from various amine structures were chosen to probe their effect on site- (as well as stereo-) selectivity. Surprisingly, at the outset of these studies, a general procedure for the synthesis of conjugated *N*,*O*-silyl ketene acetals was absent in the literature.[28] Nevertheless, these dienolates are easily accessed by deprotonation of the corresponding α,β-unsaturated amide with 1.1 equiv of potassium hexamethyldisilazide (KHMDS) at −78 °C followed by trapping of the resulting potassium dienolate with TBSCl. This protocol allowed for the synthesis of *tert*-butyldimethylsilyl dienol ethers **41**−**45** in good to high yields (Figure 4). These dienolates are distillable oils with a wide range of stabilities. Whereas the pyrrolidine-derived dienolate **43** shows significant decomposition at −15 °C within hours of synthesis, morpholine-derived dienolate **45** could be stored indefinitely at this temperature without any noticeable signs of decomposition. In all cases, the

(27) Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc*. **1990**, *112*, 9672−9674.

(28) For a detailed study of the deprotonation of β,β-disubstituted α,β-unsaturated amides see: Green, J. R.; Majewski, M.; Snieckus, V. *Can. J. Chem.* **2006**, *84*, 1397−1410.

products were obtained as single geometrical isomers determined to be of the 1*Z* configuration by analysis of their ^{1}H NOE NMR spectra.

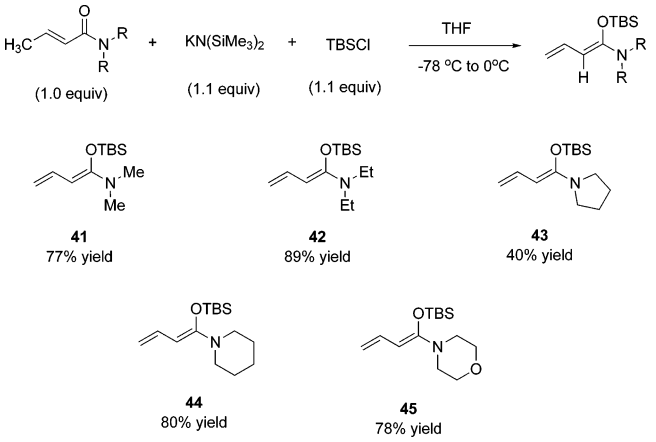
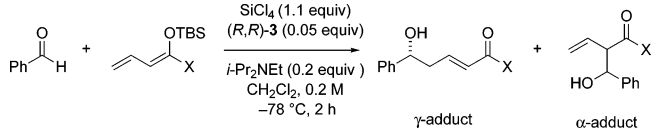


FIGURE 4. Amide-derived dienolate used in the vinylogous aldol reactions.

3.2. Vinylogous Aldol Addition Reactions of the Crotonamide-Derived Dienolates. 3.2.1. Orientating Studies on the Effect of the Nitrogen Substituent. With a reliable method to access the conjugated *N,O*-silyl ketene acetals in hand, the reactivity and selectivity of these dienolates in the addition to benzaldehyde could be evaluated (Table 6). Because high reactivity for these species was expected, the conditions developed for the reactions of the acetate-derived silyl ketene acetals were employed. Thus, 1.2 equiv of the dienolate was added neat to a solution containing 0.05 equiv of dimeric bisphosphoramide (*R*,*R*)-**3**, 1.1 equiv of $SiCl_4$, 1.0 equiv of benzaldehyde, and 0.1 equiv of *i*-PrNEt$_2$ in CH_2Cl_2 at −78 °C. After the reactions were quenched with a 1:1 mixture of satd aq KF/satd aq $NaHCO_3$ solutions, the corresponding aldol products were isolated in uniformly high yield, except for those derived from the pyrrolidine-derived dienolate (Table 6, entry 3), which was found to have very limited stability under the reaction conditions. As expected, the structure of the nitrogen substituent had a modest effect on the site-selectivity, with the morpholine-derived dienolate affording the highest selectivity. However, the strong influence of the nitrogen substituent on enantioselectivity was not anticipated. Whereas the pyrrolidine-derived dienolate afforded nearly racemic product, the morpholine-derived dienolate reacted with excellent enantioselectivity. Overall, the enantioselectivity was found to increase in the order of $N(CH_2)_4$ < NEt_2 < NMe_2 < $N(CH_2)_5$ < $N(CH_2CH_2)_2O$. This trend suggests the increase in selectivity is a result of a decrease in reactivity of the dienolates. In all cases, the resulting aldol product was exclusively of the *E* configuration.

The scope of aldehyde partner in the reaction of the morpholine-derived silyl dienol ether **45** was next studied with cinnamaldehyde. Unexpectedly, the reaction of dienolate **45** with cinnamaldehyde provided a mixture of three of the four possible constitutionally isomeric addition products, as determined by ^{1}H NMR analysis of the crude reaction mixture (Table 7, entry 1). After separation of the isomeric products by column

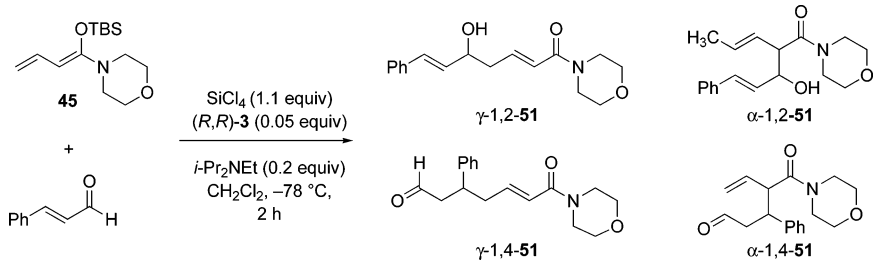
TABLE 6. Vinylogous Aldol Reactions of Amide-Derived Dienolates with Benzaldehyde: Effect of Nitrogen Substituent



entry	dienolate	X	product	yield,[a] %	γ:α[b]	er[c]
1	**41**	NMe_2	**46**	82	95:5	77.0:23.0
2	**42**	NEt_2	**47**	98	98.5:1.4	66.0:34.0
3	**43**	$N(CH_2)_4$	**48**	56	80:20	56.5:43.5
4	**44**	$N(CH_2)_5$	**49**	98	95:5	87.0:13.0
5	**45**	$N(CH_2CH_2)_2O$	**50**	69	>99:1	95.0:5.0

[a] Yields after chromatography. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP-SFC.

TABLE 7. Vinylogous Aldol Reactions of Dienolate 45 with Cinnamaldehyde



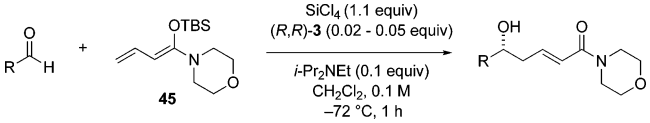
entry	(*R*,*R*)-**3**, equiv	final reaction conc, M	dienolate conc, M	γ-1,2:α-1,2:γ-1,4:α-1,4[a]	yield γ-1,2,[b] %	er γ-1,2[c]
1	0.05	0.2	neat	97:0:1:2	91	92.5:7.5
2	0.02	0.2	neat	97:0:1:2	97	94.5:5.5
3	0.02	0.1	neat	97:0:1:2	97	95.5:4.5
4	0.02	0.2	0.48	100:0:0:0	97	96.0:4.0
5	0.02	0.1	0.24	100:0:0:0	94	98.0:2.0

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yields after chromatography. [c] Determined by CSP-SFC.

chromatography, the γ-1,2-addition product was formed with high enantioselectivity. Optimization studies on this reaction showed that by decreasing both the catalyst loading and concentration of the reaction, the enantioselectivity could be increased (entry 2 and 3); however, small amounts of the 1,4-addition product were still obtained. During these optimization studies it was noticed that dienolate **45** was freezing on top of the reaction mixture before slowly dissolving into the solution. It was hypothesized that this biphasic mixture might be increasing the local concentration and temperature of the reaction at the surface of the frozen dienolate and reaction mixture. Therefore, adding the dienolate as a solution in CH_2Cl_2 may increase the selectivity. Indeed, after trying several different concentrations it was found that when the dienolate was added as a 0.24 M solution in CH_2Cl_2 to a 0.2 M reaction mixture (affording a final concentration of 0.1 M), the γ-1,2 addition product was formed exclusively in high yield and excellent enantioselectivity (entry 5).

3.2.2. Scope of Addition with Conjugated Aldehydes. With the newly optimized conditions in hand, the scope of the reaction of morpholine-derived dienolate **45** with other conjugate aldehydes was examined (Table 8). In all cases, only the *E*-α,β-unsaturated amide product was observed by ^{1}H NMR analysis of the crude reaction mixtures. As in the addition to cinnamaldehyde, the enantioselectivity increased in the addition to benzaldehyde when dienolate **45** was added as a solution (compare Table 8, entry 1, to Table 6, entry 5). Furthermore, both electron-rich and electron-poor aromatic aldehydes were found to react rapidly, providing vinylogous aldol adducts in high yields and selectivities (entries 2 and 3). Heteroaromatic aldehydes also performed well under the optimized conditions with only a minor decrease in enantioselectivity (entry 4). The same excellent yields, site-selectivity, and enantioselectivity achieved in the addition to cinnamaldehyde on a 0.25 mmol scale are maintained when the reaction is carried out on a 1 mmol scale (entry 5). Unfortunately, a continuing limitation of this catalyst system continues to be the lower enantioselectivity obtained with α-methyl branched, olefinic aldehydes (entry 6).

TABLE 8. Vinylogous Aldol Reactions of Morpholine-Derived Dienolate 45 with Conjugated Aldehydes



entry	R	product	yield,[a] %	γ:α[b]	er[c]
1[d]	C_6H_5	**50**	95	>99:1	97.2:2.8
2[d]	4-$CH_3OC_6H_4$	**52**	95	>99:1	99.0:1.0
3[d]	4-$CF_3C_6H_4$	**53**	93	>99:1	95.4:4.6
4[d]	2-furyl	**54**	94	>99:1	93.8:6.2
5[e]	(*E*)-PhCH=CH	**51**	94	>99:1	98.2:1.8
6[d]	(*E*)-PhCH=C(CH_3)	**55**	91	>99:1	75.5:24.5

[a] Yield of analytically pure material. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP-SFC. [d] Reactions employed 0.05 equiv of (*R*,*R*)-**3**. [e] Reactions employed 0.02 equiv of (*R*,*R*)-**3**.

The susceptibility of conjugated aldehydes to catalysis with such low loadings of chiral bisphosphoramide (*R*,*R*)-**3** is remarkable when considering control experiments found $SiCl_4$ alone effectively promotes the quantitative addition of **45** to benzaldehyde and cinnamaldehyde in under 1 h (Scheme 6). Furthermore, these results underscore the importance of the phosphoramide-bound catalyst complex in achieving the exclusive γ-site selectivity obtained in this Lewis base catalyzed vinylogous aldol reaction.

3.2.3. Addition to Aliphatic Aldehydes. Although high selectivity was observed in the addition to conjugated aldehydes, the true measure of the synthetic utility of these dienolates is their reactivity and selectivity with aliphatic aldehydes. Given the disparate behavior of aliphatic aldehydes compared to conjugated aldehydes in this phosphoramide/$SiCl_4$ catalyst system,[7] new optimization studies were needed for the addition to aliphatic aldehydes. Therefore, it was decided to assay all five amide-derived dienolates in the addition to hydrocinnamaldehyde, an aldehyde that had resisted addition to by ketone−dienolates. The corresponding aldol products were isolated in uniformly high yield under modified conditions that included longer reaction times (16 h) and the addition of tetrabutylammonium triflate (TBAOTf) to the reaction mixture (Table 9). Only the pyrrolidine-derived dienolate did not afford any product, again because of its instability under the reaction conditions. Although the same trend in enantioselectivity with respect the structure of the nitrogen substituent was observed, the enantioselectivities were dramatically higher than those achieved in the addition to benzaldehyde. This is particularly noteworthy as aliphatic aldehydes are typically the least selective substrates in this catalyst system. Moreover, the enantioselectivity obtained with morpholine-derived dienolate **45** was the highest among all nucleophiles surveyed in the addition to hydrocinnamaldehyde under the chiral phosphoramide/$SiCl_4$ catalyst system.

SCHEME 6

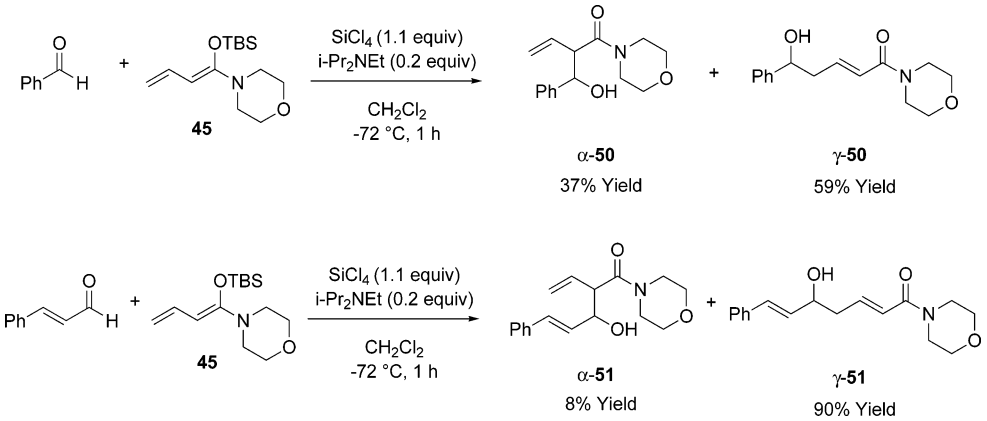
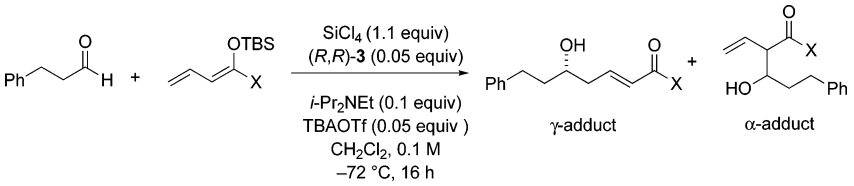


TABLE 9. Optimized Vinylogous Aldol Reactions of Amide-Derived Dienolates with Hydrocinnamaldehyde

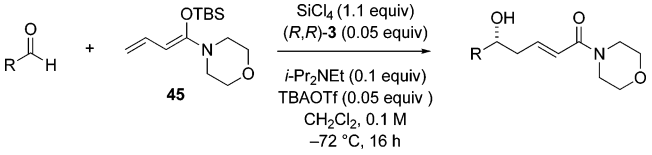


entry	dienolate	X	product	yield,[a] %	γ:α[b]	er[c]
1	**41**	NMe_2	**56**	69	92:8	91.0:9.0
2	**42**	NEt_2	**57**	78	95:5	84.8:15.2
3	**43**	$N(CH_2)_4$	**58**	trace	nd	nd
4	**44**	$N(CH_2)_5$	**59**	70	93:7	96.0:4.0
5	**45**	$N(CH_2CH_2)_2O$	**60**	80	>99:1	99.0:1.0

[a] Yields after chromatography. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP-SFC.

In view of the excellent selectivity in the addition of **45** to hydrocinnamaldehyde under the optimized reaction conditions, the reaction was surveyed with a variety of aliphatic aldehyde structures (Table 10). Reactions with the β-branched isovaleraldehyde and α-branched cyclohexanecarboxaldehyde proved to be even more selective than the reaction with hydrocinnamaldehyde to afford the γ-addition products exclusively in good to high yields and excellent enantioselectivities (entries 2 and 3). In the case of hexanal, the enantioselectivity was slightly attenuated, but the yield and site selectivity remained excellent (entry 4).

TABLE 10. Vinylogous Aldol Reactions of Morpholine-Derived Dienolate 226 with Aliphatic Aldehydes[a]

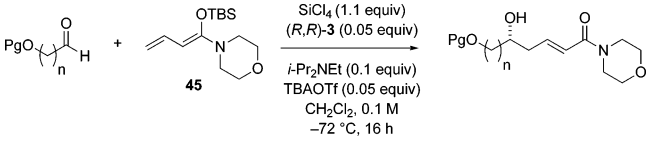


entry	R	product	yield,[a] %	γ:α[b]	er[c]
1	$PhCH_2CH_2$	**60**	80	>99:1	99.0:1.0
2	$(CH_3)_2CHCH_2$	**61**	84	>99:1	99.7:0.3
3	cyclohexyl	**62**	63	>99:1	99.4:0.6
4	$CH_3(CH_2)_4$	**63**	79	>99:1	94.3:5.7

[a] Yields after chromatography. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP-SFC.

Because of the excellent selectivity and reactivity of the morpholine-derived silyl dienolate **45** with a variety of simple, unfunctionalized aliphatic aldehydes, the scope of the reaction with several α- and β-oxygenated aliphatic aldehydes was investigated. Disappointingly, reactions with the TBS- and Bn-protected α-oxygenated aldehydes under the optimized conditions for aliphatic aldehydes did not afford any vinylogous aldol adduct (Table 11, entries 1 and 2). However, a survey of several β-oxygenated aldehydes with various silyl-, ester-, and ether-protecting groups revealed that product could be obtained but the yield was highly dependent on the identity of the protecting group. Whereas the reactions of 3-(*tert*-butyldimethylsilyloxy)- and 3-pivoyloxypropanal did not provide any vinylogous aldol adduct (entries 3 and 7), use of the 3-benzyloxy-, 3-allyloxy-, and 3-benzoyloxypropanol did allow for formation of the γ-addition product in low to moderate yields (entries 4−6). Unfortunately, the levels of enantioselectivity observed in these reactions fell short of the levels reached in the addition to simple, unfunctionalized aliphatic aldehydes.

TABLE 11. Vinylogous Aldol Reactions of Morpholine-Derived Dienolate 45 with Oxygenated Aliphatic Aldehydes



entry	Pg	n	product	yield,[a] %	γ:α[b]	er[c]
1	TBS	1	**64**	0	nd	nd
2	Bn	1	**65**	0	nd	nd
3	TBS	2	**66**	0	nd	nd
4	Bn	2	**67**	49	>99:1	84.5:15.5
5	Allyl	2	**68**	30	>99:1	83.7:14.3
6	Bz	2	**69**	41	>99:1	70.0:30.0
7	Piv	2	**70**	0	nd	nd
8	Bn	5	**71**	85	>99:1	92.5:7.5

[a] Yields after chromatography. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP-SFC.

Finally, 6-benzyloxyhexanal was examined to probe what effect the proximity of the oxygen substituent to the aldehydic carbonyl has on selectivity. This aldehyde afforded the same high yields and selectivities as that attained in the addition of hexanal to the morpholine-derived silyl dienol ether **45** (compare Table 4, entry 8, to Table 10, entry 4).

3.3. Preparation of Silyl Dienol Ethers Derived from α,β-Unsaturated Morpholine Amides. To probe the structural generality of this reaction, ketene acetal bearing methyl groups in the α-, β-, and γ-position of the dienyl unit were prepared employing the same reaction conditions as described above for the crotamide-derived dienolates (Figure 5). These morpholine-derived dienolates were also distillable oils which could be stored at −15 °C for several months without significant decomposition. However, unlike the crotonate-derived dienolates, the products were obtained as mixtures of geometrical isomers and the configuration of the major isomer could be determined by measuring their ^{1}H NOE NMR spectra.

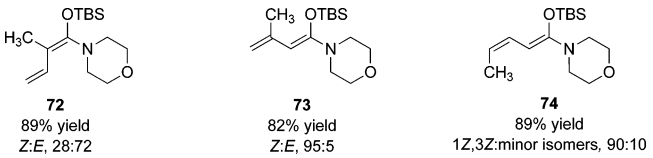
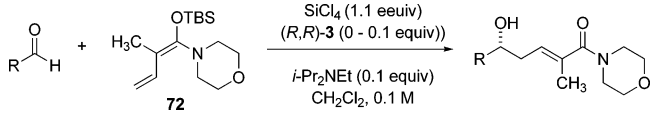


FIGURE 5. Morpholine amide-derived dienolates used in the vinylogous aldol reactions.

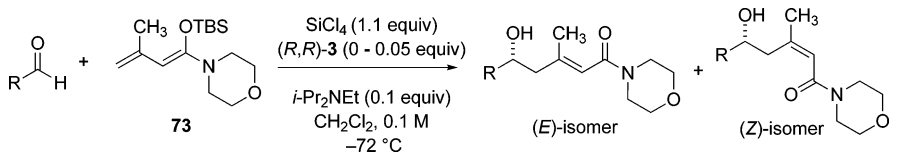
TABLE 12. Vinylogous Aldol Additions of Morpholine-Derived Dienolate 72 with Various Aldehydes



entry	R	product	(*R*,*R*)-**3**, equiv	*T*, °C	time, h	yield,[a] %	γ:$\alpha\alpha$[b]	er[c]
1[d]	$PhCH_2CH_2$	**75**	0.05	−72	16	32	>99:1	99.0:1.0
2[d]	$PhCH_2CH_2$	**75**	0.10	−50	16	68	>99:1	97.0:3.0
3	Ph	**76**	0.05	−72	1	98	>99:1	98.5:1.5
4	Ph	**76**	0	−72	1	35	>99:1	
5	PhCH═CH	**77**	0.05	−72	1	91	>99:1	99.2:0.8
6	PhCH═CH	**77**	0	−72	1	56	>99:1	

[a] Yield after chromatography. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP-SFC. [d] 0.05 equiv of n-$Bu_4N^+OTf^-$ was added.

TABLE 13. Vinylogous Aldol Additions of Morpholine Amide-Derived Dienolate 73 with Various Aldehydes



entry	R	product	(*R*,*R*)-**3**, equiv	time, h	γ:α[a]	*Z*:*E*[a]	*Z*-yield, %[b]	*Z*-er[c]	*E*-yield,[b] %	*E*-er[d]
1[d]	$PhCH_2CH_2$	**78**	0.05	16	>99:1	12:88	5	63.8:36.2	68	97.1:2.9
2	Ph	**79**	0.05	1	>99:1	12:88	10	57.2:42.8	89[e]	98.4:1.6
3	Ph	**79**	0	1	>99:1	52:48	51		49	
4	PhCH═CH	**80**	0.05	1	>99:1	11:89	8	59.6:40.4	90[e]	98.6:1.4
5	PhCH═CH	**80**	0	1	>99:1	80:20	77		20	

[a] Determined by ^{1}H NMR analysis of crude reaction mixture. [b] Yield after chromatography. [c] Determined by CSP-SFC. [d] 0.05 equiv of n-$Bu_4N^+OTf^-$ was added. [e] Yield of analytically pure material.

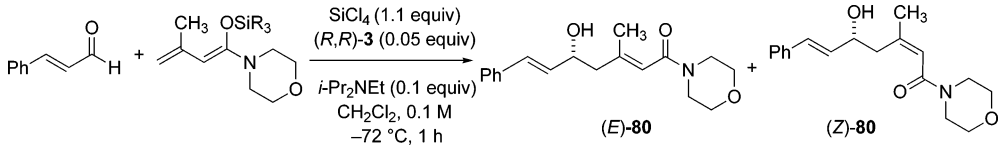
3.4. Vinylogous Aldol Reaction of Methyl-Substituted Conjugated *N*,*O*-Silyl Ketene Acetals. The reactivity of the α-methyl-substituted silyl dienol ether **72** with aliphatic aldehydes was of particular interest as the analogous α-methyl substituted ester-derived dienol ether does not undergo addition with hydrocinnamaldehyde under this chiral phosphoramide catalyst system.[11] Gratifyingly, the addition of dienolate **72** to hydrocinnamaldehyde under the optimized reaction conditions for aliphatic aldehydes afforded the product with exclusive γ-site selectivity and excellent enantioselectivity, albeit at an attenuated rate when compared to the crotamide-derived dienolate **45** (Table 12, entry 1). Optimization studies found that increasing the catalyst loading to 0.10 equiv and executing the reaction at an elevated temperature (−50 °C) for 16 h afforded vinylogous aldol adduct in good yields while maintaining exclusive γ-site selectivity and high enantioselectivity (entry 2). The addition of dienolate **72** to benzaldehyde and cinnamaldehyde under the optimized for conjugated aldehydes also proceeded with excellent site- and enantioselectivities affording product in high yields under the optimized reaction conditions for conjugated aldehydes (entries 3 and 5).

Despite the attenuated reactivity of dienolate **72** compared to crotamide-derived dienolate **45** under the chiral phosphoramide (*R*,*R*)-**3**/$SiCl_4$ catalyst system, this nucleophile still maintains the high reactivity need to undergo addition to benzaldehyde and cinnamaldehyde when promoted by $SiCl_4$ alone (entries 4 and 6). In contrast to the crotamide-derived dienolate **45**, the γ-addition product was formed exclusively in both cases with the mass balance isolated as unreacted started material.

The addition of β-methyl substituted dienolate **73** to hydrocinnamaldehyde under the optimized reaction conditions for aliphatic aldehydes provided the vinylogous aldol adduct with exclusive γ-site selectivity; however, for the first time the corresponding *Z*-isomer could also be detected by ^{1}H NMR analysis of the crude reaction mixture (*E*:*Z* 88:12) (Table 13, entry 1). Separation of the two isomeric products by column chromatography afforded the *E*-product in good yield and excellent enantioselectivity (97.1:2.9), whereas the *Z*-product was found to form in low enantioselectivity (63.0:36.2). Similar results were obtained in the addition to benzaldehyde and cinnamaldehyde, affording the γ-addition product in high yields with high geometrical selectivities and excellent enantioselectivity in *E*-adducts (entries 2 and 4). Remarkably, when the addition of dienolate **73** is promoted by $SiCl_4$ alone, the *Z*-product is favored in the addition to cinnamaldehyde and a statistical mixture of isomers is isolated in the addition to benzaldehyde (entries 3 and 5). These results clearly demonstrate that the phosphoramide-bound catalyst complex plays a dominant role in controlling the geometrical selectivities during aldolization. Whereas the geometrical selectivity is dependent on the presence of chiral phosphoramide (*R*,*R*)-**3**, the exclusive γ-site selectivity obtained with dienolate **73** in the addition to benzaldehyde and cinnamaldehyde is maintained in its absence.

A brief survey of silyl groups was performed to probe their effect on the geometrical selectivities in the addition of the β-methyl substituted dienolate **73** to cinnamaldehyde. The use of the less sterically demanding trimethylsilyl group resulted in a small decrease in the amount of *E*-product formed when compared to the TBS group, suggesting that the geometrical selectivity was sensitive to the size of the silyl group (Table 14, entry 2). However, the use of the larger triisopropylsilyl (TIPS) group did not show any improvement in the geometrical selectivity, although a slight increase in enantio-

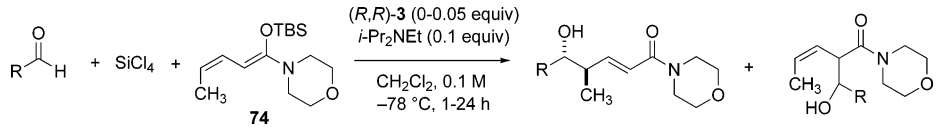
TABLE 14. Vinylogous Aldol Additions of β-Methyl-Substituted Morpholine-Derived Dienolates with Cinnamaldehyde



entry	SiR_3	γ:α[b]	Z:E[c]	(Z)-**80** yield,[c] %	(Z)-**80** er[d]	(E)-**80** yield,[c] %	(E)-**80** er[d]
1	TBS (**73**)	>99:1	11:89	8	59.6:40.4	90[e]	98.6:1.4
2	TMS (**81**)	>99:1	18:82	8	88.1:11.9	67	97.4:2.6
3	TIPS (**82**)	>99:1	13:87	7	86.6:13.4	75	99.5:0.5

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of dienolate. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Yield after chromatography. [d] Determined by CSP-SFC. [e] Yield of analytically pure material.

TABLE 15. Vinylogous Aldol Additions of Morpholine-Derived Dienolate 74 with Aldehydes[a]



entry	R	product	(R,R)-**3**, equiv	time, h	yield,[b] %	γ:α[c]	dr (anti:syn)[d]	er anti[d]
1	$PhCH_2CH_2$	**83**	0.05	24	0	nd	nd	nd
2	Ph	**84**	0.05	1	98	>99:1	97:3	88.2:11.8
3	Ph	**84**	0	1	87[e]	95:5	66:37	

[a] Reactions employed 1.1 equiv of $SiCl_4$, 1.2 equiv of dienolate. [b] Yield of analytically pure material. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by CSP-SFC. [e] Yield after chromatography.

selectivity of *E*-product was observed. The most dramatic effect the different silyl groups showed was in the improvement of the enantioselectivity obtained in the *Z*-product.

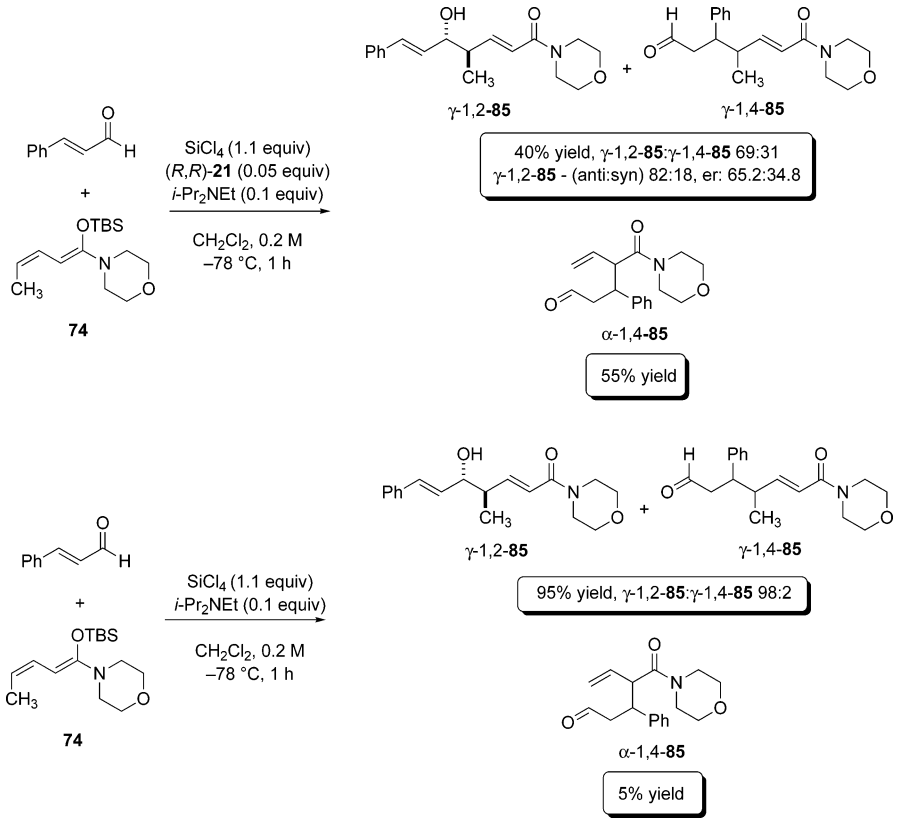
Although the use of amide-derived nucleophiles had allowed for dienolates bearing methyl groups in the α- and β-positions to react with aliphatic aldehydes under Lewis base catalysis, placement of a methyl group in the γ-position rendered the morpholine-derived dienolate (**74)** unreactive with hydrocinnamaldehyde (Table 15, entry 1). Executing the reaction at higher temperatures and employing higher catalyst loadings still did not allow for the formation of vinylogous aldol adduct. However, dienolate **74** did undergo a rapid reaction with benzaldehyde, affording the γ-addition product in excellent yield (entry 2). Although the enantioselectivity was attenuated compared to the crotamide-derived dienolate **45**, excellent γ-site selectivity and anti-diastereoselectivity was achieved and the product was exclusively of the *E* configuration. When the addition of **74** to benzaldehyde was carried out in the absence of phosphoramide (*R*,*R*)-**3**, both α- and γ-addition products were isolated and the γ-addition product was found to form with low anti-diastereoselectivity (entry 3).

As was observed in the initial studies with crotamide-derived dienolate **45**, the addition of dienolate **74** to cinnamaldehyde provided three of the four possible constitutionally isomeric addition products, as determined by ^1H NMR analysis of the crude reaction mixture (Scheme 6). However, instead of the 1,4-adducts being a minor component of the product mixture, these adducts were favored in a 69:31 over the 1,2-adducts. Column chromatography allowed for separation of α-1,4-adduct; however, the γ-1,2- and γ-1,4-adducts coeluted. The γ-1,2-addition product was formed with good anti-diastereoselectivity but only poor enantioselectivity. Interestingly, when the addition of dienolate **74** to cinnamaldehyde was promoted by $SiCl_4$ alone, the high 1,2 site selectivity was recovered and afforded the vinylogous aldol adduct in high yield (Scheme 7).

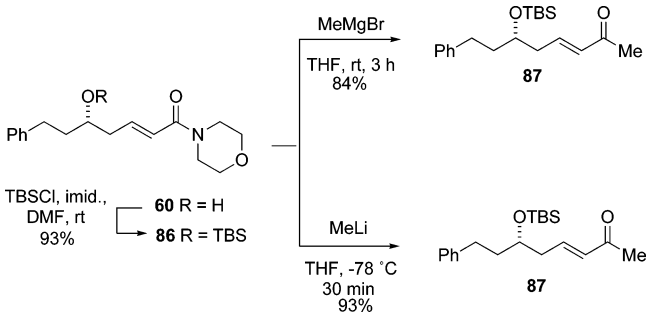
3.5. Conversion of Morpholine Amide 60 to Methyl Ketone 87. Coincidentally, of all the amides surveyed, the morpholine derivative is also the most effective at the acylation of organometallic nucleophiles to form ketones.[29] Although the conversion of α,β-unsaturated morpholine amides to ketones is known,[30] the generality of this process has not been demonstrated. Thus, after protection of **60** as a *tert*-butyldimethylsilyl (TBS) ether, both MeMgBr and MeLi cleanly converted morpholine amide **86** to methyl ketone **87** in high yield without any evidence for the formation of the tertiary alcohol arising from overaddition (Scheme 8).

3.6. Determination of the Absolute Configuration of the Amide-Derived Vinylogous Aldol Products. As in the case of the ketone-derived vinylogous aldol products, the absolute configuration of the amide-derived vinylogous aldol products could not be determined by direct correlation to known examples in the literature and required their chemical degradation to a set of compounds for which the absolute configuration had been unambiguously assigned. Following the same synthetic route used to establish the absolute configuration of the acyclic ketone-derived vinylogous aldol adducts, compounds **60**, **50**, **76**, and **84** were subjected to ozonolysis followed by reduction of the ozonide with a solution of lithium aluminum hydride in tetrahydrofuran, which afforded the expected diols in good yields (Figure 6, eqs 1, 4, 5, and 7). Comparison of their optical rotations with those reported in the literature[20] showed that in each case, the aldol adduct derived from *Re* face attack on the aldehyde was the major enantiomer. Furthermore, comparison

SCHEME 7



SCHEME 8



of the ^{1}H NMR data for diol **91** allowed for the anti configuration of the major diastereomer in **81** to be unambiguously assigned.

Vinylogous aldol adduct **51** required a different route to establish its absolute configuration because of concerns about competitive oxidative cleavage of the C(6)−C(7) double bond. Therefore, a route that had been developed previously in this group for the determination of the absolute configuration of the analogous ester vinylogous aldol adducts was employed.[11b] Hydrogenation of both of the double bonds in **51** produced amide **89**. This compound was then compared to identical amide prepared from hydrogenation of the now known (5*R*)-**89** to establish the absolute configuration, and the optical rotations were found to be similar (compare eqs 2 and 3).

Last, acetylation of vinylogous aldol adduct **79** with acetic anhydride followed by cleavage of the C(2)−C(3) double bound with ruthenium tetraoxide afforded the known β-acetoxy methyl ketone.[31] Comparison of optical rotations found the product derived from *Re* face attack on the aldehyde was the major enantiomer.

Discussion

The bisphosphoramide (*R*,*R*)-**3**/$SiCl_4$ catalyst system afforded highly site-, enantio-, and diastereoselective additions of ketone-, ester-, and amide-derived dienol ethers. To present a unified picture of this catalyst system in the vinylogous aldol reaction, trends in reactivity and selectivity will be analyzed for the three classes of carbonyl compounds to provide a clearer understanding of the generality of this method.

1. Reactivity Trends. 1.1. Trends in Reactivity with Respect to Ketone-Derived Silyl Dienol Ether Structure. The nucleophilicity scales developed by Mayr and co-workers for main group organometallic nucleophiles suggest there is a dramatic reactivity difference between structurally similar silyl enol ethers and silyl dienol ethers.[24] On this scale, 1-trimethylsiloxybutadiene ($N = 4.92$) possesses a higher nucleophilicity than trimethylsiloxyethene ($N = 3.81$). Therefore it was expected that the α,β-unsaturated ketone derived dienol ethers would show a comparable, if not higher, reactivity compared to the methyl ketone-derived silyl enol ethers. However, the overwhelming influence of remote steric effects on the nucleophile was evident in this study, as the acyclic α,β-unsaturated ketone-derived silyl dienol ethers were less reactive than the methyl ketone-derived enol ethers,[18] requiring the reaction to be executed at higher temperatures and longer reaction times.

(29) (a) Martin, R.; Romea, P.; Tey, C.; Urpi, R.; Vilarrasa, J. *Synlett* **1997**, 1414−1416. (b) Tosaki, S.; Horiuchi, Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Chem. Eur. J.* **2004**, *10*, 1527−1544.

(30) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447−2450.

(31) Nair, M. S.; Joly, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2049−2052.

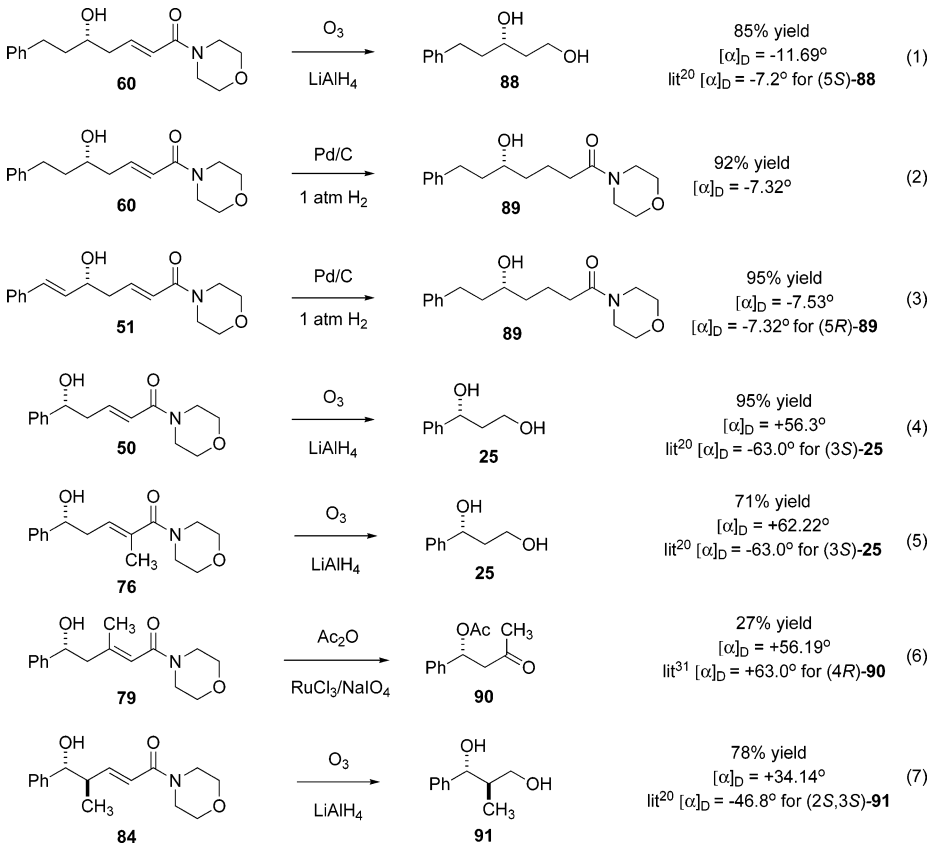


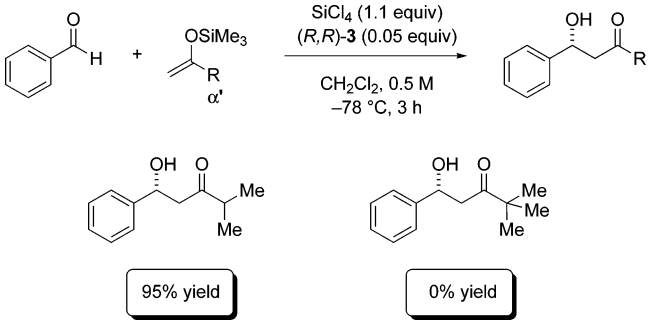
FIGURE 6. Correlation of the configuration of the amide vinylogous aldol products to known compounds.

The cyclic dienolate derived from cyclohexenone (**10**) was more reactive than the acyclic, γ-unsubstituted ketone-derived silyl dienol ethers **6** and **7**. This behavior stands in stark contrast to previous results obtained with this catalyst system in the addition of silyl ketene acetals to aldehydes. The presence of alkyl substituents on the reactive center at C(2) of simple ester-derived silyl ketene acetals decreases the rate of addition compared to its unsubstituted analogue.[11b] This same trend is seen in the addition of the α,β-unsaturated ester-derived dienolates as the introduction of a substituent at the C(4) position is detrimental to reactivity.[11] The fact that cyclic dienolate **10** is more reactive may be a result of its being constrained in the *s*-cis conformation, which should allow for a high degree of conjugation of the dienyl unit. The acyclic ketone-derived dienol ethers may not be able to achieve the same degree of conjugation for steric reasons and are therefore less nucleophilic at C(4) compared dienolate **10**.

As expected, the 1,3-diketone-derived bissilyl dienol ethers were considerably more reactive than the dienolates derived from α,β-unsaturated ketones. In fact, $SiCl_4$ alone effectively promoted the addition of **32a** to benzaldehyde and cinnamaldehyde quantitatively in under 1 h. Unfortunately, this higher nucleophilicity still did not allow these agents to undergo addition to hydrocinnamaldehyde at rate to provide a synthetically useful process.

1.2. Trends in Reactivity with Respect to Conjugated *N,O*-Silyl Ketene Acetal Structure. The amide-derived silyl ketene acetals showed superior reactivity to all of the ketone-derived dienolates surveyed in this study and in most cases afforded high yields in the addition to aliphatic aldehydes. However, the reactivity within this dienolate family varied widely, and the overwhelming influence of steric effects on the dienyl unit was evident throughout this study. The effect of substitution on the dienyl unit on rate was dramatically illustrated in the loss of reactivity with hydrocinnamaldehyde when a methyl group was introduced at the C(4) position (**74**). This loss in reactivity was not unexpected, as increasing the substitution at the reactive center has been shown to attenuate the reaction rate under catalysis by an in situ generated, chiral phosphoramide-bound silyl cation and was also observed in the addition of ester-derived dienolates.[11] Furthermore, substituents remote to the reactive center were also able to affect reactivity. Introduction of a methyl group at the C(2) position (**72**) afforded attenuated rates in the addition to hydrocinnamaldehyde. However, the influence of the substituent at this position was not as strong as that of a substituent at C(4), and modified conditions still allowed for good yields to be obtained (Table 12, entry 2). The reason for the attenuated reactivity of dienolate **72** can be rationalized when considering the reactivity trends observed in the addition of methyl ketone-derived silyl enol ethers under this catalyst system.[18] In a survey of various alkyl groups in the α'-position, a decrease in the reaction rate was observed as the size of the alkyl group increased (Scheme 9). The reduced rate arises from steric interactions between the alkyl substituent and the catalyst complex. The C(2) position on the dienyl unit of the conjugated *N,O*-silyl ketene acetal is the same distance from the reactive center as the α'-position of the methyl ketone-derived silyl enol ether and increasing the substitution at the (C2) position may have caused a similar steric interaction with the catalyst complex, affording a decrease in the reaction rate. Introduction of a methyl group at the C(3) position (**73**) did not bring about a noticeable change in the rate of addition to aliphatic aldehydes when compared to the unsubstituted, crotonamide-derived dienolate (**45**).

SCHEME 9



1.3. Trends in Reactivity with Respect to Aldehyde Structure. The reactivity trends with respect to the electrophilic partner in these vinylogous aldol reactions are consistent with the overall behavior that has been observed with this Lewis base catalyst system. In all cases, conjugated aldehydes bearing aromatic (both electron rich and electron poor) and olefinic substituents show high reactivity, whereas aliphatic aldehydes prove sluggish or unreactive. The poor reactivity of aliphatic aldehydes has recently been investigated and is proposed to result from an unproductive equilibrium between the aldehyde that is bound to the putative silyl cation and an unreactive α-chloro trichlorosilyl ether (Scheme 5).[11] Consequently, only a low equilibrium concentration of the activated aldehyde complex is available for aldolization. Therefore, a powerful nucleophile must be employed that can still react at an appreciable rate with the low concentration of activated aldehyde present in solution at any time. This phenomenon explains why α,β-unsaturated ketone-derived silyl enol ethers were unreactive, diketone-derived bissilyl dienol ether have low reactivity, and conjugated *N*,*O*-silyl ketene acetals react at a reasonable rate.

The low reactivity of aliphatic aldehydes can be further exacerbated through the introduction of alkoxy substituents in the α- and β-position. Although the β-oxygenated aldehydes retain some reactivity, the α-oxygenated substrates were unreactive, with the balance of material being aldehyde and proteodesilylated amide in all cases. It was anticipated that these aldehydes would show superior reactivity to the unfunctionalized, alkyl aliphatic aldehydes owing to the electron-withdrawing ability of the alkoxy group adjacent to the aldehydic carbonyl.[32] However, the increased electrophilicity of the aldehyde may further reduce the concentration of activated aldehyde present in solution by shifting the equilibrium farther toward the unreactive α-chloro trichlorosilyl ether. Moreover, this increased electrophilicity may raise the barrier to ionization of the α-chloro trichlorosilyl ether back to the activated aldehyde complex. Therefore, the number of carbon atoms separating the alkoxy group from the carbonyl group should have a large effect on the reactivity of the aldehyde under this catalyst system. Support for this hypothesis is seen by comparing the yields obtained with 2-benzyloxyacetaldehyde, 3-benzyloxypropanal, and 6-benzyloxyhexanal (Table 11, entries 2, 4, and 8). As predicted, when the reaction is performed under identical conditions, the yield of the aldol product increases as the distance of the alkoxy group from the carbonyl group is increased.

The large difference in yields depending on the protecting group employed on the β-oxygenated aldehydes is believed to be a result of steric factors. However, it is unclear if the more sterically encumbering *tert*-butyldimethylsilyl and pivoyl protecting groups are preventing the aldehyde from effectively binding to the phosphoramide-bound silyl cation or if binding is occurring but steric factors with the approaching nucleophile are preventing aldolization.

2. Trends in Enantioselectivity. Although several structurally and electronically diverse nucleophiles were examined in this study, the aldol products derived from *Re* face attack were consistently formed. The ability of the catalyst (*R*,*R*)-**3** to select for nucleophilic attack at this prochiral face of the aldehyde regardless of the dienolate structure extends not only to ester-derived dienolates but also to silyl enol ethers,[18] isocyanides,[33] and allylic stannanes.[34] This uniform facial selectivity implies the dominant contributor to the observed enantiofacial selectivity is the interaction between the catalyst complex bound aldehyde and the incoming nucleophile.[11b]

Although enantioselectivities were generally high, the bissilyl dienol ethers gave fairly low selectivity. Modification of the catalyst structure, the silyl group, temperature, and addition rate did not substantially improve the selectivity. We believe that the low selectivity arises from a significant background reaction given the high reactivity of these nucleophiles. Reactions were complete in <2 min at −78 °C with only 0.01 equiv of catalyst.

The enantioselectivity of additions of *N*,*O*-silyl ketene acetals was strongly influenced by the nature of the nitrogen substituent. This was unexpected as the identity of the alkoxy substituent on the α,β-unsaturated ester-derived dienolates[11] and the alkyl group at the α′-position of the ketone-derived dienolates had no apparent consequences for enantioselectivity. This outcome suggested that the effect was most likely not due to steric interactions with the catalyst complex but was instead electronic in origin. Indeed, a clear relationship between nucleophilicty of the dienolate and enantioselectivity is apparent when comparing the ^{13}C NMR chemical shifts of the C(4) carbons of the dienolate with the enantioselectivities obtained in the addition to benzaldehyde (Table 16). The ^{13}C NMR chemical shift of the dienyl unit is primarily controlled by the π- and σ-electron density located on each carbon and shows a downfield shift when the π-electron density decreases.[35] Table 16 shows higher enantioselectivity was achieved as the dienolate became less nucleophilic, as indicated by a downfield shift of C(4), suggesting the possibility of a competing achiral background reaction promoted by $SiCl_4$ alone or a very early transition structure, both of which would lead to reduced selectivity. The fact that $SiCl_4$ alone promoted the quantitative addition of the least nucleophilic dienolate surveyed (**45**) to benzaldehyde and cinnamaldehyde in less than 1 h implies the intervention of an achiral background reaction is a strong possibility.

With respect to structure of the dienyl unit, substitution of a methyl group at the α and β atoms had very little effect on enantioselectivity and excellent selectivity was achieved in all cases. However, α,β-unsaturated ester-, ketone-, and morpholine amide-derived dienolates bearing methyl groups in the γ-position afforded attenuated enantioselectivities compared to their unsubstituted analogues. Whereas this decrease was modest in the

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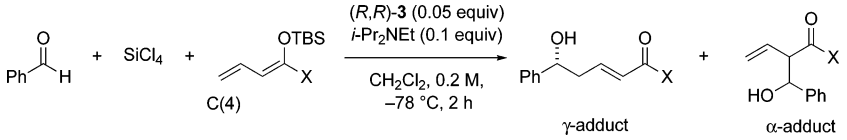
(33) (a) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825−7827. (b) Denmark, S. E.; Fan, Y. *J. Org. Chem.* **2005**, *70*, 9667−9676.

(34) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199−6200.

(35) (a) Strothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972. For the use of carbon-13 NMR spectroscopy in measuring enamine reactivity, see: (a) Cook, A. G., Ed. *Enamines: Synthesis, Structure and Reactions*, 2nd ed.; Dekker: New York, 1988.

TABLE 16. Comparison of the Trends in Enantioselectivity with the Nucleophilicity of the Amide-Derived Dienolate



entry	dienolate	X	yield, %	γ:α	er	^{13}C C(4), ppm
1	**43**	$N(CH_2)_4$	56	80:20	56.5:43.5	102.43
2	**42**	NEt_2	98	98.5:1.4	66.0:34.0	104.83
3	**41**	NMe_2	82	95:5	77.0:23.0	105.59
4	**44**	$N(CH_2)_5$	98	95:5	87.0:13.0	106.70
5	**45**	$N(CH_2CH_2)_2O$	69	>99:1	95.0:5.0	107.99

addition to aromatic aldehydes, cinnamaldehyde afforded considerably lower selectivity, especially with the morpholine amide-derived dienolate (**74**).

Although introduction of a methyl group at the β-atom of the dienyl unit had no apparent consequences on enantioselectivity, introduction of a silyloxy group at this position on the ketone-derived dienol ethers caused a substantial decrease in enantioselectivity. Given the excellent selectivity achieved with a variety of methyl ketone-derived silyl enol ethers in the addition to benzaldehyde,[18] the low selectivity afforded by this class of bis(silyloxy) dienolates remains difficult to rationalize. The large temperature dependence on enantioselectivity and high reactivity when promoted by $SiCl_4$ alone suggests that the higher nucleophilicity of these dienolates may be responsible for their low selectivity.

With regard to the electrophilic acceptor, the dramatic reactivity disparity between conjugated and aliphatic aldehydes did not translate into a significant difference in enantioselectivity. In fact, the enantioselectivities achieved in the addition of α,β-unsaturated ester- and morpholine amide-derived dienolates to simple, unfunctionalized aliphatic aldehyde are the highest reported to date (>95:5 in all cases) with this chiral phosphoramide/$SiCl_4$ catalyst system. The morpholine amide-derived dienolates are particularly selective, affording excellent selectivity with linear, α-, and β-branched aliphatic aldehydes.

Structural features of the aldehyde that influence enantioselectivity are (1) substituents in the α-position of olefinic aldehydes and (2) oxygen substituents at the β-position of aliphatic aldehydes. The enantioselectivity achieved with 2-methylcinnamaldehyde continues to be the lowest observed with this catalyst system.[11,33,34]

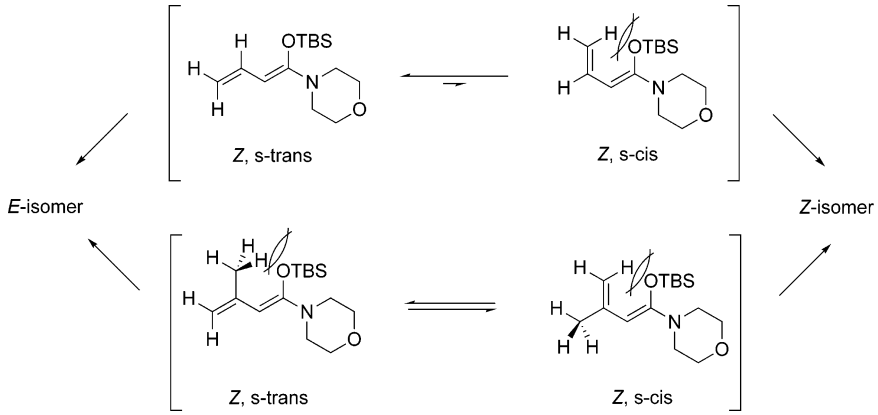
3. Trends in Diastereoselectivity. In contrast to the dramatic sensitivity of the reactivity and enantioselectivity to the structure of the nucleophile and electrophile, there appear to be few factors that affect the high anti diastereoselectivity observed with this catalyst system. Similarly high levels of anti diastereoselectivity were obtained in the addition of ketone-, 1,3-diketone-, and amide-derived dienolates to conjugated aldehydes under catalysis by an in situ generated, chiral phosphoramide-bound silyl cation. Although the bissilyl dienol ethers **33a**−**c** and conjugated *N*,*O*-silyl ketene acetal **74** were a mixture of isomers, high diastereoselectivity was maintained, showing that the reaction is stereoconvergent. Furthermore, the structure of the phosphoramide catalyst had little effect on the remarkable high levels of anti diastereoselectivity observed in these vinylogous aldol reactions. The use of achiral phosphoramides for the preparation of racemic samples still afforded high selectivity in the addition of dienolates **33a**−**c** and **74**. The only structural trend that was observed with respect to diastereoselectivity is the need for a phosphoramide catalyst in the reaction mixture. The addition of morpholine-derived silyl dienol ether **74** to benzaldehyde promoted by $SiCl_4$ alone, although still anti selective, provided the lowest observed diastereoselectivities in this work (Table 16).

4. Trends in Site Selectivity. Throughout this study, high γ site selectivity was observed under the influence of the chiral phosphoramide (*R*,*R*)-**3**/$SiCl_4$ catalyst system regardless of dienolate structure. The isolation of γ-addition products exclusively from the addition of bissilyl dienol ethers **32a**−**d** and **33a**−**c** to aldehydes was expected as they are synthetic equivalents of a diketone dianions that react with exclusive γ site selectivity owing to the higher nucleophilicity at C(4). However, silyl dienol ethers derived from α,β-unsaturated carbonyl compounds are not as electronically biased, and steric effects from both the catalyst and nucleophile are needed to achieve high site selectivity. Furthermore, calculations have shown a smaller difference between the electrophilic susceptibility and HOMO coefficients at C(2) and C(4) in the trimethylsilyl enol ether of methyl 2-propenyl ketone relative to the trimethylsilyl ketene acetal of methyl crotonate and suggested that the selectivity in ketone dienol ethers may be attenuated compared to silyl ketene acetals (Figure 1).[9c] Nevertheless, in all cases, the α,β-unsaturated ketone-derived dienol ethers reacted with exclusive γ site selectivity under the influence of the chiral phosphoramide/$SiCl_4$ catalyst system. Even when both the C(2) and C(4) reactive centers were equally substituted (**10**), which has been shown to attenuate the site selectivity in ester-derived silyl dienol ethers,[9] no evidence for any α-addition product was observed (Table 2).

The importance of the steric influence provided by the phosphoramide bound silyl cation in achieving high site-selectivity during aldolization was dramatically highlighted in the addition of the α,β-unsaturated amide-derived silyl dienol ethers. Owing to the high nucleophilicty of these dienolates, $SiCl_4$ alone promotes their addition to aldehydes and allowed for a measure of the inherent site selectivity of these nucleophiles when promoted by a less sterically encumbering Lewis acid. The addition of the morpholine-derived silyl dienol ether **45** to benzaldehyde promoted by $SiCl_4$ alone afforded a 3:2 mixture of constitutional isomers favoring the γ-addition product (Scheme 6). However, when 0.05 equiv of bisphosphoramide (*R*,*R*)-**3** was included in the reaction mixture, the γ-addition product was obtained exclusively (Table 8). This same trend was seen in the addition of **45** to cinnamaldehyde; however, in the presence of $SiCl_4$ alone this aldehyde afforded higher γ site selectivity than benzaldehyde suggesting that the structure of the aldehyde is also important in controlling site-selectivity.

In addition to structural features of the promoter and aldehyde,

SCHEME 10



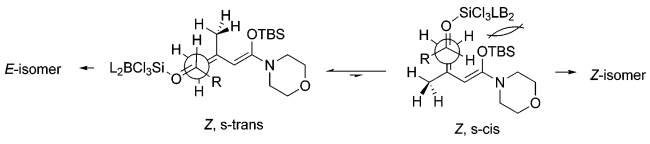
substitution on the dienyl unit also had a large effect on site selectivity in the addition of amide-derived dienolates. Introduction of methyl group at C(2) or C(3) allowed for exclusive γ-site selectivity in the addition to benzaldehyde and cinnamaldehyde promoted by $SiCl_4$ alone. In the case of the γ substituted silyl dienol ether **74**, where both the C(2) and C(4) reactive centers are mono substituted, α-addition product was again isolated in the addition to benzaldehyde when promoted by $SiCl_4$ in absence of phosphoramide. However, the phosphoramide (*R*,*R*)-**3**/$SiCl_4$ catalyst complex was able to provide the vinylogous aldol adduct with exclusive γ site selectivity in the addition to **74** to conjugated aldehydes and further validates the role the of the catalyst complex in achieving high site selectivity in the vinylogous aldol addition reactions.

Whereas introduction of a methyl group at the terminal γ-position had a small effect on the morpholine amide-derived dienolate site selectivity, it had a large effect on the aldehyde site selectivity (Scheme 7). In fact, increasing the substitution at the reactive γ-position caused the 1,4-addition pathway to become the favored reaction pathway in the addition to cinnamaldehyde under the phosphoramide (*R*,*R*)-**3**/$SiCl_4$ catalyst system. The 1,4-addition products may be result of the dramatic sensitivity of the phosphoramide-bound silyl cation to substituents on the reactive center of the dienolate. The increased steric interactions between the nucleophile and catalyst complex will raise the activation energy of the C−C bond forming, and could render the aldol addition pathway similar to or higher in energy than the conjugate addition pathway. This rationalization gains support from the fact that the 1,2-addition pathway was favored when the addition of dienolate **74** to cinnamaldehyde was promoted by $SiCl_4$ alone.

5. Origin of Double Bond Geometries. Despite the fact that most of the *acyclic* silyl dienolates employed in the phosphoramide-catalyzed, vinylogous aldol reactions were mixtures of geometrical isomers, the aldolate containing the *E*-double bond was formed in high selectivity for all of the aldehydes surveyed. Only in the case of the β-methyl substituted dienolate **73** was any of the isomeric *Z*-product isolated. Analysis of the conformation of the silyl dienolates with a hydrogen substituent in the β-position suggests that they most likely exist and react through the s-trans conformation to maximize conjugation and to avoid allylic strain in the s-cis conformation (Scheme 10).[12] Vinylogous aldol addition through this conformation will lead to the *E* product, regardless of the geometry of the silyl enol ether. However, when the β-substituent is a methyl group, allylic strain is encountered in both the s-cis and s-trans conformers rendering them similar in activation energy for aldolization.

However, in rationalizing geometrical selectivities, the influence of the phosphoramide-bound, silyl cation cannot be ignored. The addition of dienolate **73** to benzaldehyde, cinnamaldehyde, and hydrocinnamaldehyde promoted by $SiCl_4$ alone or with achiral phosphoramides afforded a near statistical distribution of double bond isomers (Table 13). However, when catalyst (*R*,*R*)-**3** was employed, high geometrical selectivities favoring the *E*-α,β-unsaturated amide product were observed. These reactions are believed to proceed through an open transition structure.[11] In this manifold the dienolate is proposed to approach the Lewis acid-bound aldehyde in an antiperiplaner orientation to avoid dipole interactions between the enolate and the activated carbonyl. If the dienolate adopts the *s*-cis conformation (which leads to the *Z*-double bond product) and reacts through the antiperiplanar transition structure, the silyloxy group of the dienolate will be in close proximity to the bound silyl cation. Given the large size of the silyl cation/(*R*,*R*)-**3** complex and the previous observations of the sensitivity of the catalyst system to the steric demands of the incoming nucleophile, this conformation should be sterically disfavored (Scheme 11). Instead, the reaction most likely proceeds through the s-trans conformation to minimize the steric interactions between the silyloxy group and the bound silyl cation, affording the *E*-configured product. This analysis also helps to rationalize the large effect the silyl group had on the enantioselectivity obtained in the *Z*-configured product (Table 14); however, it remains unclear why the TMS and TIPS groups should afford higher enantioselectivities than the TBS group in the addition to cinnamaldehyde.

SCHEME 11



6. Rationale for Observed Enantioselectivity. Despite numerous attempts at crystallization, a structural determination of the aldehyde-bound, catalyst complex is still lacking. However, ^{29}Si NMR studies combined with computer modeling have provided insight into the structural features that govern enantioselectivity and that are consistent with the observed trends. Calculations were performed in these laboratories on a complex of benzaldehyde and the dimeric phosphoramide (*R*,*R*)-**3** bound trichlorosilyl cation using the PC version of GAMESS(US) QC package where a PM3 basis set was

employed (Figure 7).[11b] Consideration of the nature of hypervalent bonds in the ligand field around silicon places the aldehyde trans to one of the phosphoramides. When bound in this configuration, the model shows the *Re* face of the aldehyde is exposed owing to its interaction with one of the *N*-methyl groups of the 1,1′-binaphthyl-2,2′-diamine backbone and one of the naphthyl rings. The *N*-methyl group extends into the pocket of the catalyst and effectively shields the *Si* face from attack of the nucleophile. Furthermore, the interaction with naphthyl ring suggests a possibility of a stabilizing, edge to face $\pi-\pi$ interaction for this conformation.

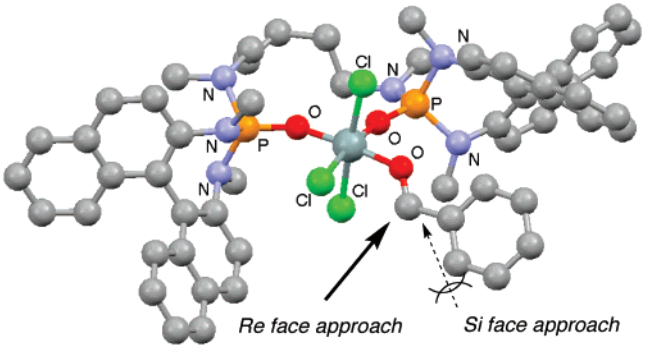


FIGURE 7. Calculated structure of the aldehyde−silyl cation complex optimized in GAMESS(US) QC package at the PM3 level and visualized using Chem3D, with selected hydrogens omitted for clarity.

Conclusions

The use of chiral Lewis acids generated by chiral Lewis base activation of Lewis acids has allowed for the development of a highly selective vinylogous aldol reaction between dienolates derived from a variety of α,β-unsaturated carbonyl compounds to aldehydes. These reactions are characterized by exceptionally high levels of γ-site selectivity for a variety of substitution patterns on the dienyl unit. Both ketone- and morpholine amide-derived dienol ethers provide excellent enantio- and diastereoselectivity in the addition to conjugated aldehydes. Although ketone-derived dienolate did not react with aliphatic aldehydes, amide-derived dienolates were found to undergo addition at reasonable rates affording high yields of vinylogous aldol product. Furthermore, the enantioselectivity achieved with the morpholine derived-dienolate in the addition to aliphatic aldehydes was the highest afforded to date with the bisphosphoramide (*R*,*R*)-**3**/$SiCl_4$ catalyst system. Along with the excellent selectivity achieved in the addition to a variety of aldehydes, the ability to cleanly convert the morpholine amide to a ketone or aldehyde make these vinylogous aldol adducts highly versatile and should bode well for their use in the synthesis of complex polyol-containing natural products.

Experimental Section

General Experimental Details. See the Supporting Information.[36]

Experimental Procedures. Representative Procedure 1. Enolization of α,β-Unsaturated Ketones To Form Silyl Dienol Ethers. Preparation of (*Z*)-1-(Phenylbuta-1,3-dienyloxy)trimethylsilane (6). To a flame-dried, 100-mL, three-necked, round-bottomed flask fitted with a magnetic stir bar, thermocouple, gas inlet tube, and septum was added 2.85 g (20.0 mmol, 1.0 equiv) of 1-phenyl-2-buten-1-one, 3.46 mL (24.8 mmol, 1.24 equiv) of Et_3N, and 3.15 mL (24.5 mmol, 1.24 equiv) of TMSCl. Then, a solution of 3.72 g (24.8 mmol, 1.24 equiv) of NaI in 25 mL of CH_3CN was added slowly dropwise over 5 min via cannula. The resulting solution was then placed in an oil bath at 80 °C and stirred for 6 h. The mixture was cooled to rt, and 50 mL of cold pentane was added. The organic layer was then separated, and the aqueous layer was washed with pentane (3 × 50 mL). The combined organic extracts were washed with H_2O (2 × 50 mL), $CuSO_4$ (satd aq) (2 × 50 mL), and brine (50 mL), dried over Na_2SO_4 (10 g), and filtered, and the filtrate was concentrated in vacuo. The resulting residue was purified by bulb-to-bulb distillation (60 °C ABT at 0.05 mmHg) to yield 4.135 g (95%, *Z*:*E* 60:40) of **6** as a clear, colorless oil.[16] ^{1}H NMR (500 MHz, $CDCl_3$): 7.53 (dt, J = 7.3, 1.7, 2 H, (*Z*)-HC(6)), 7.42 (dt, J = 7.1, 1.7, 2 H, (*E*)-HC(6)), 7.37−7.31 (m, 6 H, (*Z*)-HC(7) and (*E*)-HC(7,8), 7.28−7.25 (m, 1 H, (*Z*)-HC(8)), 6.74 (dt, J = 17.1, 10.5, 1 H, (*Z*)-HC(3)), 6.48 (dt, J = 16.7, 10.8, 1 H, (*E*)-HC(3)), 6.06 (d, J = 10.7, 1 H, (*Z*)-HC(2)), 5.78 (d, J = 11.0, 1 H, (*E*)-HC(2)), 5.22 (d, J = 17.1, 1 H, (*Z*)-HC(4)), 5.10 (d, J = 16.8, 1 H, (*E*)-HC(4)), 5.03 (d, J = 10.3, 1 H, (*Z*)-HC(4)), 4.85 (d, J = 11.3, 1 H, (*E*)-HC(4)), 0.19 (s, 9 H, (*E*)-H_3C(9)), 0.17 (s, 9 H, (*Z*)-H_3C(9)). NOE ^{1}H NMR (500 MHz, $CDCl_3$): irradiation at 6.06 ppm ((*Z*)-HC(2)) enhanced signal at 7.53 ppm ((Z)-HC(6)) and 5.22 ppm ((*Z*)-HC(4)). Irradiation at 6.48 ppm ((E)-HC(3)) enhanced signal at 7.42 ppm ((*E*)-HC(6)) and 4.85 ppm ((*E*)-HC(4)). ^{13}C NMR (126 MHz, $CDCl_3$): 152.9 ((*E*)-C(1)), 150.4 ((*Z*)-C(1)), 138.2 ((*Z*)-C(5)), 137.3 (*E*-C(5)), 133.6 ((*E*)-C(3)), 131.9 ((*Z*)-C(3)), 128.7 ((*E*)-C(6)), 128.3 ((*E*)-C(8)), 128.1 ((*Z*)-C(7)), 128.0 ((*Z*)-C(8)), 127.9 ((*E*)-C(7)), 125.5 ((*Z*)-C(6)), 114.5 ((*Z*)-C(4)), 113.4 ((*E*)-C(4)), 112.6 ((*Z*)-C(2)), 112.0 ((*Z*)-C(2)), 0.5 ((*Z*)-C(9)), 0.3 ((*E*)-C(9)). IR (neat): 3086 (w), 3059 (w), 3037 (w), 3012 (w), 2961 (m), 2900 (w), 2360 (w), 2342 (w), 1950 (w), 1890 (w), 1783 (w), 1689 (m), 1670 (w), 1628 (s), 1590 (w), 1573 (w), 1492 (m), 1447 (m), 1416 (m), 1330 (s), 1308 (m), 1284 (m), 1253 (s), 1210 (s), 1174 (m), 1115 (s), 1067 (s), 1028 (m), 996 (m), 948 (m), 922 (m), 888 (s), 845 (s), 791 (m), 759 (s), 732 (m), 697 (s), 666 (m), 651 (w), 629 (w). MS (EI, 70 eV): 219 (12), 218 (M^+, 51), 217 (35), 203 (30), 210 (13), 129 (68), 128 (27), 127 (11), 115 (14), 105 (23), 77 (25), 75 (43), 74 (12), 73 (100). HRMS: calcd for $C_{13}H_{18}OSi$ 218.1127, found 218.1126.

Representative Procedure 2. Enolization of 1,3-Diketones To Form Bissilyl Dienol Ethers. Preparation of 2,4-Bis(trimethylsilyloxy)-1,3-pentadiene (32a). To a flame-dried, 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser, septum, and 125 mL addition funnel was added 2.57 mL (25.0 mmol, 1.0 equiv) of acetylacetone (**30**), 7.14 mL (51.25 mmol, 2.05 equiv) of Et_3N, and 50 mL of Et_2O. The solution was cooled to 0 °C (bath temperature). The addition funnel was charged with 9.28 mL (51.25 mmol, 2.05 equiv) of TMSOTf and 10 mL of Et_2O, and the solution was added slowly dropwise over 15 min. The resulting biphasic solution was stirred for 1 h at 0 °C prior to addition of 50 mL of cold H_2O. The organic layer was separated and the aqueous layer washed with pentane (3 × 50 mL). The combined organic extracts were washed with $NaHCO_3$ (sat aq) (50 mL), H_2O (50 mL), and brine (75 mL), dried using K_2CO_3 (10 g), and filtered, and the filtrate was concentrated in vacuo. The residue was purified by bulb-to-bulb distillation (55 °C ABT at 0.2 mmHg) to afford 5.765 g (94%, *Z*:*E*, 55:45) of **32a** as a clear, colorless oil. The spectroscopic data for **32a** matched those in the literature.[25] ^{1}H NMR (500 MHz, $CDCl_3$): 5.20 (s, 0.45 H, (*E*)-HC(3)), 4.75 (s, 0.45 H, (*E*)-HC(1)), 4.73 (s, 0.55 H, (*Z*)-HC(3)), 4.32 (d, J = 1.2, 0.45 H, (*E*)-HC(1)), 4.14 (s, 0.55 H, (*Z*)-HC(1)), 4.10 (s, 0.55 H, (*Z*)-HC(1)), 2.01 (s, 1.75 H, (*E*)-H_3C(5)), 1.85 (s, 1.25 H, (*Z*)-H_3C(5)), 0.24 (s, 4.95 H, (*Z*)-H_3C(6)), 0.22 (s, 4.05 H, (*E*)-H_3C(6)), 0.21 (s, 4.05 H, (*E*)-H_3C(7)), 0.20 (s, 4.95 H, (*Z*)-H_3C(7)).

Representative Procedure 3. Enolization of α,β-Unsaturated Amides To Form Conjugated *N*,*O*-Silyl Ketene Acetals. Prepa-

(36) For the chemical shift assignments listed in the Experimental Section, see the structures in the Supporting Information.

ration of (*Z*)-[1-(*tert*-Butyldimethylsilanyloxy)-1,3-butadienyl]-dimethylamine (41). To a flame-dried, 200-mL, three-necked, round-bottomed flask fitted with a magnetic stir bar, thermocouple, gas inlet tube, and septum was added 1.13 g (10 mmol) of 2-butenoic acid dimethylamide and 50 mL of THF. The solution was cooled to −72 °C, and then a solution of 2.19 g (1.1 mmol, 1.1 equiv) of potassium hexamethyldisilazide in 20 mL of THF was added slowly dropwise over 5 min via syringe. The resulting yellow solution was stirred for 30 min at −72 °C prior to addition of a solution of 1.66 g (11 mmol, 1.1 equiv) of TBSCl in 10 of THF via syringe. The dry ice bath was then removed, and the solution was allowed to warm to 0 °C. The yellow solution was then concentrated in vacuo, and the resulting residue was taken up in 50 mL of pentane. The yellow precipitate was then filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by bulb-to-bulb distillation (60 °C ABT at 0.01 mmHg) to afford 1.738 g (77%) of **41** as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): 6.54 (dt, J = 17.1, 10.5, 1 H, HC(3)), 4.79 (dd, J = 17.1, 2.2, 1 H, HC(4)), 4.61 (d, J = 10.7, 1 H, HC(2)), 4.53 (dd, J = 10.5, 2.3, 1 H, HC(4)), 2.58 (s, 6 H, H_3C(5)), 1.00 (s, 9 H, H_3C(8)), 0.16 (s, 6 H, H_3C(6)). NOE ^{1}H NMR (500 MHz, $CDCl_3$): irradiation at 3.58 ppm (H_3C(5)) enhanced signal at 4.61 ppm (HC(2)). ^{13}C NMR (126 MHz, $CDCl_3$): 155.5 (C(1)), 133.4 (C(3)), 105.6 (C(4)), 89.2 (C(2)), 39.5 (C(5)), 25.7 (C(8)), 18.3 (C(7)), −4.7 (C(6)). IR (neat): 3083 (m), 3060 (m), 3013 (m), 2955 (s), 2932 (s), 2886 (m), 2859 (s), 2793 (m), 1631 (s), 1474 (s), 1461 (s), 1438 (m), 1419 (s), 1390 (m), 1346 (s), 1298 (m), 1281 (m), 1254 (s), 1195 (s), 1145 (s), 1125 (s), 1102 (m), 1055 (m), 1023 (s), 1005 (m), 996 (m), 944 (m), 881 (s), 839 (s), 825 (s), 810 (s), 782 (s), 739 (m), 679 (m), 655 (m), 642 (m). MS (EI, 70 eV): 228 (18), 227 (M^+, 85), 212 (51), 171 (32), 170 (71), 157 (15), 156 (100), 147 (12), 130 (14), 96 (19), 81 (13), 75 (13), 73 (52), 59 (12), 57 (19). HRMS: calcd for $C_{12}H_{25}NOSi$ 227.170543, found 227.1694.

Representative Procedure 4. Addition of Acyclic α,β-Unsaturated Ketone-Derived Silyl Dienol Ethers to Aldehydes. Preparation of (+)-(5*R*,2*E*)-5-Hydroxy-1,5-diphenyl-2-penten-1-one (11) (Table 1, Entry 1). Diisopropylethylamine (35 μL, 0.2 mmol, 0.2 equiv) was added via syringe to a flame-dried, 5-mL, Schlenk flask under Ar containing a solution of 42 mg (0.05 mmol, 0.05 equiv) of bisphosphoramide (*R*,*R*)-**3** CH_2Cl_2 (2 mL). To this solution was added 102 μL (1.0 mmol, 1.0 equiv) of benzaldehyde in one portion, and the reaction mixture was cooled to −50 °C over 15 min. To the resulting solution was added 172 μL (1.1 mmol, 1.1 equiv) of $SiCl_4$ in one portion. Then, 284 μL (1.2 mmol, 1.2 equiv) of **6** was added dropwise over 1 min via syringe. The resulting mixture was stirred at −50 °C for 24 h whereupon 3.0 mL of chilled CH_2Cl_2 was added before the cold reaction mixture was poured into a rapidly stirring solution of 1:1 satd aq $NaHCO_3$/satd aq KF (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 1 h before being filtered through Celite on a glass frit. The phases were then separated, and the aqueous layer was washed with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4 (5 g) and filtered, and the filtrate was concentrated in vacuo. The ratio of γ:α addition products was determined to be >99:1 by ^{1}H NMR (500 MHz) analysis of the crude reaction mixture. The residue was purified by column chromatography (SiO_2 (25 g), 3 cm diameter, hexanes/EtOAc, 4:1) to yield 201 mg (80%) of (+)-**11** as a thick, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (d, J = 7.1, 2 H, HC(11)), (dt, J = 7.5, 1.5, 1 H, HC(13)), 7.43 (t, J = 7.6 2 H, HC(12)), 7.39−7.35 (m, 4 H, HC(7,8)), 7.32−7.28 (m, 1 H, HC(9)), 7.06−7.00 (m, 1 H, HC(3)), 6.91 (dt, J = 15.4, 1.3, 1 H, HC(2)), 4.90 (dd, J = 7.7, 5.1, 1 H, HC(5)), 2.83−2.71 (m, 2 H, HC(4)), 2.31 (br s, 1 H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): 190.7 (C(1)), 145.0 (C(3)), 143.5 (C(6)), 137.6 (C(10)), 132.8 (C(13)), 128.6 (C(11)), 128.6 (C(8)), 128.6 (C(2) or C(12)), 128.5 (C(2) or C(12)), 127.9 (C(9)), 125.8 (C(7)), 73.2 (C(5)), 42.5 (C(4)). IR (neat): 4057 (w), 3430 (m), 3061 (w), 3030 (w), 2894 (w), 2360 (w), 2340 (w), 1964 (w), 1901 (w), 1817 (w), 1668 (m), 1652 (m), 1621 (m), 1598 (m), 1578 (w), 1494 (w), 1448 (m), 1418 (w), 1344 (m), 1285 (m), 1226 (m), 1180 (w), 1020 (m), 987 (m), 915 (w), 894 (w), 834 (w), 764 (m), 698 (m), 667 (m). MS (CI, CH_4): 253 (M^+ + H, 17), 236 (10), 235 (51), 175 (18), 148 (11), 147 (100), 146 (43), 145 (11), 107 (71), 105 (79), 79 (13). $[\alpha]^{24}_D$: +14.40 (c = 1.00, EtOH). TLC: R_f 0.30 (hexanes/EtOAc, 3:2) [UV (254 nm)]. SFC: (*R*)-**11**, t_R 3.04 min (99.0%); (*S*)-**11**, t_R 4.06 min (1.0%) (Chiralpak AD, 175 psi, 40 °C, 20.0% MeOH in CO_2, 3.0 mL/min, 220 nm). Anal. Calcd for $C_{17}H_{16}O_2$ (252.31): C, 80.93; H, 6.39. Found: C, 80.63; H, 6.33.

Representative Procedure 5. Addition of Cyclic Ketone-Derived Silyl Dienol Ether 10 to Aldehydes. Preparation of (+)-(4*R*,7*R*)-4-(7-Hydroxy(phenyl)methyl)-2-cyclohexen-1-one (20) (Table 2, entry 1). Diisopropylethylamine (18 μL, 0.1 mmol, 0.1 equiv) was added via syringe to a flame-dried, 5-mL, Schlenk flask under N_2 containing a solution of 42 mg (0.05 mmol, 0.05 equiv) of bisphosphoramide (*R*,*R*)-**3** in CH_2Cl_2 (2 mL). To this solution was added 102 μL (1.0 mmol) of benzaldehyde in one portion. To the resulting solution was added 172 μL (1.5 mmol, 1.5 equiv) of $SiCl_4$ in one portion, and the reaction mixture was cooled to −72 °C over 15 min. Then, 224 μL (1.2 mmol, 1.2 equiv) of **10** was added dropwise over 1 min. The resulting mixture was stirred at −72 °C for 2 h, whereupon 3.0 mL of chilled CH_2Cl_2 was added before the cold reaction mixture was poured into a rapidly stirring solution of 1:1 satd aq $NaHCO_3$/satd aq KF (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 1 h before being filtered through Celite on a glass frit. The phases were then separated, and the aqueous layer was washed with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the filtrate was concentrated in vacuo. The ratio of γ:α addition products was determined to be >99:1 by ^{1}H NMR (500 MHz) analysis of the crude reaction mixture. The residue was purified by column chromatography (SiO_2 (25 g), 3 cm diameter, pentane/Et_2O, 1:1) to yield 182 mg (90%) of (+)-**20** as a thick, colorless oil that solidified upon standing. The diastereomeric ratio was determined to be anti:syn, 97.5:2.5 by SFC analysis. The spectroscopic data for **20** matched those in the literature.[21] ^{1}H NMR (500 MHz, $CDCl_3$): 7.43−7.32 (m, 5H, HC-(9,10,11)), 7.25 (dt, J = 10.3, 1.7, 1 H, HC(3)), 6.09 (dd, J = 10.3, 2.4, 1 H, HC(2)), 4.59 (dd, J = 7.8, 3.2, 1 H, HC(7)), 2.78−2.73 (m, 1 H, HC(4)), 2.49−2.21 (m, 1 H, HC(6)), 2.35−2.28 (m, 1 H, HC(6)), 2.03 (br s, 1H, OH), 1.75−1.68 (m, 2 H, H_2C(5)). ^{13}C NMR (125 MHz, $CDCl_3$): 200.0 (C(1)), 151.6 (C(3)), 142.2 (C(8)), 129.9 (C(2)), 128.6 (C(10)), 128.1 (C(11)), 126.2 (C(9)), 76.5 (C(7)), 43.6 (C(4)), 36.7 (C(6)), 25.8 (C(5)). $[\alpha]^{24}_D$ +114.38 (c = 1.00, EtOH). TLC: R_f 0.10 (pentane/Et_2O, 1:1) [UV (254 nm)]. SFC: (4*S*,7*S*)-**20**, t_R 6.52 min (2.5%); (4*R*,7*R*)-**20**, t_R 9.65 min (97.5%) (Chiralpak OJ, 150 psi, 40 °C, 6.0% MeOH in CO_2, 2.75 mL/min, 220 nm).

Representative Procedure 6. Addition of Bissilyl Dienol Ethers to Conjugated Aldehydes. Preparation of (−)-(2*R*)-2,3-Dihydro-6-methyl-2-phenylpyran-4-one (34) (Table 3, Entry 3). Diisopropylamine (18 μL, 0.1 mmol, 0.1 equiv) was added via syringe to a flame-dried, 20-mL, two-necked, round-bottomed flask fitted with a magnetic stir bar, thermocouple, gas inlet tube, and septum under N_2 containing a solution of 9 mg (0.01 mmol, 0.01 equiv) of bisphosphoramide (*R*,*R*)-**3** in CH_2Cl_2 (2 mL). To this solution was added 102 μL (1.0 mmol) of benzaldehyde in one portion. The resulting solution was cooled to −90 °C over 15 min, and to the reaction mixture was added 172 μL (1.5 mmol, 1.5 equiv) of $SiCl_4$ in one portion. Then, 394 mg (1.2 mmol, 1.2 equiv) of **32b** was added dropwise over 5 min. The resulting mixture was stirred at −90 °C for 2 h, whereupon 3.0 mL of chilled CH_2Cl_2 was added before the cold reaction mixture was poured into a rapidly stirring solution of 1:1 satd aq $NaHCO_3$/satd aq KF (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 3 h after which the aqueous layer was washed with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4

(5 g) and filtered through Celite on a glass frit, and the filtrate was concentrated in vacuo. The residue was dissolved in 10 mL of CH_2Cl_2 and cooled in an ice−water bath for 15 min, and to the reaction mixture was added 10 drops of TFA. The resulting mixture was stirred at rt for 16 h, whereupon 10 mL of satd aq $NaHCO_3$ added. This biphasic mixture was stirred for 10 min, after which the aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 (5 g) and filtered through Celite on a glass frit, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (30 g SiO_2, 2 cm column diameter, hexanes/EtOAc, 2:1). The product-containing fractions were combined, and the solvent was removed in vacuo to yield 165 mg (88%) of (−)-**34** as a clear oil. The spectroscopic data for **34** matched those in the literature.[26] ^{1}H NMR (500 MHz, $CDCl_3$): 7.44−7.36 (m, 5 H, HC(8,9,10)), 5.43 (s, 1 H, CH(5)), 5.38 (dd, J = 14.2, 3.2 HC(2)), 2.81 (dd, J = 16.7, 14.4, 1 H, HC(3)), 2.610 (dd, J = 16.8, 3.3, HC(3)), 2.09 (s, 3 H, H_3C(11)). ^{13}C NMR (125 MHz, $CDCl_3$): 192.1 (C(5)), 174.1 (C(6)), 138.1 (C(7)), 128.7 (C(8,9)), 126.1 (C(8)), 105.1 (C(5)), 80.7 (C(2)), 42.3 (C(3)), 21.0 (C(11)). $[\alpha]^{24}_D$: −48.00 (c = 1.15, CH_2Cl_2). TLC: R_f 0.28 (hexanes/EtOAc, 4:1) [UV (254 nm)]. SFC: (*S*)-**34**, t_R 1.86 min (19.9%); (*R*)-**34**, t_R 2.02 min (80.1%) (Chiralpak OD, 150 psi, 40 °C, 15.0% MeOH in CO_2, 3.0 mL/min, 220 nm).

Representative Procedure 7. Vinylogous Aldol Additions of Bissilyl Dienol Ethers 32a−c to Hydrocinnamaldehyde. Preparation of (2*S*)-2,3-Dihydro-6-methyl-2-phenylethylpyran-4-one (39) (Table 4, Entry 1). Diisopropylamine (18 μL, 0.1 mmol, 0.1 equiv) was added via syringe to a flame-dried, 20-mL, two-necked round-bottomed flask fitted with a magnetic stir bar, gas inlet tube, and septum under N_2 containing a solution of 21 mg (0.025 mmol, 0.05 equiv) of bisphosphoramide (*R*,*R*)-**3** in CH_2Cl_2 (2 mL). To this solution was added 66 μL (0.5 mmol) of hydrocinnamaldehyde in one portion. The resulting solution was cooled to −78 °C (bath temperature) over 15 min, and to the reaction mixture was added 86 μL (0.75 mmol, 1.5 equiv) of $SiCl_4$ in one portion. Then, 197 mg (0.6 mmol, 1.2 equiv) of **32b** was added dropwise over 5 min. The resulting mixture was stirred at −78 °C for 24 h, whereupon 3.0 mL of chilled CH_2Cl_2 was added before the cold reaction mixture was poured into a rapidly stirring solution of 1:1 satd aq $NaHCO_3$/satd aq KF (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 3 h after which the aqueous layer was washed with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 (5 g) and filtered through Celite on a glass frit, and the filtrate was concentrated in vacuo. The residue was dissolved in 10 mL of CH_2Cl_2 and cooled in an ice−water bath for 15 min, and to the reaction mixture was added 10 drops of TFA. The resulting mixture was stirred at rt for 16 h whereupon 10 mL of satd aq $NaHCO_3$ was added. This biphasic mixture was stirred for 10 min after which the aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 (5 g) and filtered through Celite on a glass frit, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (12 g SiO_2, 2 cm column diameter, pentane/Et_2O, 1:1). The product-containing fractions were combined, and the solvent was removed in vacuo to yield 23 mg (21%) of **39** as a clear, colorless oil. ^{1}H NMR (500 MHz, $CHCl_3$): 7.32−7.29 (m, 2 H, HC(11)), 7.23−7.19 (m, 3 H, HC(10,12)), 5.32 (s, 1 H, CH(5)), 4.38−4.32 (m, 1 H, HC(2), 2.86−2.73 (m, 2 H, H_2C(8)), 2.48−2.35 (m, 2 H, HC(3)), 2.22−2.12 (m, 1 H, HC(7)), 2.02 (s, 3 H, H_3C(13)), 1.99−1.92 (m, 2 H, HC(7)). TLC: R_f 0.28 (hexanes/EtOAc, 4:1) [UV (254 nm)]. SFC: (*R*)-**39**, t_R 2.67 min (30.0%); (*S*)-**39**, t_R 3.43 min (70.0%) (Chiralpak OD, 125 psi, 40 °C, 15.0% MeOH in CO_2, 3.0 mL/min, 220 nm).

Representative Procedure 8. Vinylogous Aldol Additions of Conjugated *N*,*O*-Silyl Ketene Acetals to Conjugated Aldehydes. Preparation of (+)-4-[(5*R*,2*E*)-1-Oxo-5-phenyl-5-hydroxy-2-pentenyl]morpholine (50) (Table 8, entry 1). Diisopropylethylamine (18 μL, 0.1 mmol, 0.1 equiv) was added via syringe to a flame-dried, 20-mL, Schlenk flask under Ar containing a solution of 42 mg (0.05 mmol, 0.05 equiv) of bisphosphoramide (*R*,*R*)-**3** in CH_2Cl_2 (5 mL). To this solution was added 102 μL (1.0 mmol) of benzaldehyde in one portion. To the resulting solution was added 126 μL (1.1 mmol, 1.1 equiv) of $SiCl_4$ in one portion, and the reaction mixture was cooled to −72 °C over 15 min. Then, a solution of 324 mg (1.2 mmol, 1.2 equiv) of **45** in 5 mL of CH_2Cl_2 was added dropwise over 5 min via syringe. The resulting mixture was stirred at −72 °C for 1 h whereupon 3.0 mL of chilled CH_2Cl_2 was added before the cold reaction mixture was poured into a rapidly stirring solution of 1:1 satd aq $NaHCO_3$/satd aq KF (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 3 h after which the organic layer was removed and aqueous layer was washed with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 (5 g) and filtered, and the filtrate was concentrated in vacuo. The ratio of γ:α-addition products was determined to be >99:1 by ^{1}H NMR (500 MHz) analysis of the crude reaction mixture. The residue was purified by column chromatography (SiO_2 (30 g), 3 cm diameter, EtOAc (200 mL) to EtOAc/MeOH, 19:1 (150 mL)) to yield a solid which was recrystallized by precipitation from hot EtOAc (5 mL) with minimal amounts of hexanes to yield 247 mg (95%) of (+)-**50** as white needles. Mp: 108−109 °C (EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): 7.38−7.27 (m, 5 H, HC(7,8,9)), 6.87 (dt, J = 15.1, 7.1, 1 H, HC(3)), 6.24 (dt, J = 15.1, 1.4, 1 H, HC(2)), 4.85 (dd, J = 7.5, 5.5, 1 H, HC(5)), 3.66−3.56 (m, 8 H, H_2C(10,11)), 2.72−2.63 (m, 2 H, H_2C(4)), 2.15 (br s, 1 H, OH). ^{13}C NMR (126 MHz, $CDCl_3$): 165.5 (C(1)), 143.9 (C(6)), 142.5 (C(3)), 128.2 (C(8)), 127.4 (C(9)), 125.7 (C(7)), 122.3 (C(2)), 72.7 (C(5)), 66.5 (C(11)), 45.9 (C(10)), 42.4 (C(4)), 42.0 (C(10)). IR ($CHCl_3$): 3674 (w), 3647 (w), 3600 (m), 3392 (s), 3058 (m), 3063 (s), 3010 (s), 2972 (s), 2924 (s), 2902 (s), 2861 (s), 2762 (m), 2714 (m), 2686 (m), 2581 (w), 2459 (m), 2402 (m), 2360 (m), 2334 (w), 2233 (w), 2016 (w), 1952 (w), 1881 (w), 1812 (w), 1759 (w), 1732 (w), 1657 (s), 1607 (s), 1493 (s), 1437 (s), 1389 (s), 1362 (s), 1302 (s), 1227 (s), 1217 (s), 1115 (s), 1068 (s), 1042 (s), 1008 (s), 977 (s), 917 (s), 893 (m), 855 (s), 756 (s), 701 (s), 667 (s), 628 (s). MS (CI, CH_4): 262 (M^+ + H, 29), 245 (20), 244 (100), 156 (14), 155 (31), 114 (11), 107 (27). $[\alpha]^{24}_D$: +10.42 (c = 0.90, EtOH). TLC: R_f 0.17 (EtOAc) [UV(254 nm)]. SFC: (*R*)-**50**, t_R 3.39 min (97.1%); (*S*)-**50**, t_R 4.11 min (2.9%) (Chiralpak OB, 125 psi, 40 °C, 10.0% MeOH in CO_2, 3.0 mL/min, 220 nm). Anal. Calcd for $C_{15}H_{19}NO_3$ (261.32) C, 68.94; H, 7.33; N, 5.36. Found: C, 68.92; H, 7.33; N, 5.36.

Representative Procedure 9. Addition of Conjugate *N*,*O*-Ketene Acetals to Aliphatic Aldehydes. Preparation of (−)-(2*E*,5*S*)-5-Hydroxy-7-phenyl-2-heptenoic Acid Dimethylamide (56) (Table 9, Entry 1). Diisopropylethylamine (18 μL, 0.1 mmol, 0.1 equiv) was added via syringe to a flame-dried, 20-mL, Schlenk flask under Ar containing a solution of 42 mg (0.05 mmol, 0.05 equiv) of bisphosphoramide (*R*,*R*)-**3** and 20 mg (0.05 mmol, 0.05 equiv) of tetrabutylammonium triflate in CH_2Cl_2 (5 mL). To this solution was added 132 μL (1.0 mmol, 1.0 equiv) of hydrocinnamaldehyde in one portion, and the reaction mixture was cooled to −72 °C over 15 min. To the resulting solution was added 126 μL (1.1 mmol, 1.1 equiv) of $SiCl_4$ in one portion. Then, a solution of 273 mg (1.2 mmol, 1.2 equiv) of **41** in 5 mL of CH_2Cl_2 was added dropwise over 5 min via syringe. The resulting mixture was stirred at −72 °C for 16 h whereupon 3.0 mL of chilled CH_2Cl_2 was added before the cold reaction mixture was poured into a rapidly stirring solution of 1:1 satd aq $NaHCO_3$/satd aq KF (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 3 h after which the organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 (5 g) and filtered, and the filtrate was concentrated in vacuo. The ratio of γ:α-addition products was determined to be >99:1 by ^{1}H NMR (500 MHz) analysis of the crude reaction mixture. The residue was purified by column chromatography (SiO_2 (30 g), 3 cm diameter, EtOAc (200 mL) to

EtOAc/MeOH, 19:1 (150 mL)) to yield 171 mg (69%) of (−)-**56** as a colorless oil. Bp: 140 °C (6.5×10^{-5} mmHg, ABT). ^{1}H NMR (500 MHz, $CDCl_3$): 7.28 (dt, J = 7.6, 2.0, 2 H, HC(10)), 7.21−7.17 (m, 3 H, HC(9,11)), 6.88 (dt, J = 15.0, 7.8, 1 H, HC(3)), 6.34 (dt, J = 15.0, 1.3, 1 H, HC(2)), 3.81−3.76 (m, 1 H, HC(5)), 3.04 (br s, 6 H, H_3C(12)), 2.82 (dt, J = 13.9, 7.6, 1 H, HC(7)), 2.69 (dt, J = 13.8, 8.1, 1 H, HC(7)), 2.47−2.33 (m, 2 H, H_2C(4)), 2.00 (br s, 1 H, OH), 1.84−1.79 (m, 2 H, H_2C(6)). ^{13}C NMR (100 MHz, $CDCl_3$): 166.6 (C(1)), 142.4 (C(3)), 142.0 (C(8)), 128.3 (C(9)), 128.2 (C(10)), 125.6 (C(11)), 122.6 (C(12)), 69.5 (C(2)), 40.7 (C(4)), 38.6 (C(6)), 37.2 (C(12)), 35.6 (C12)), 31.9 (C(7)). IR (neat): 3391 (m), 3085 (w), 3061 (w), 3026 (m), 2931 (m), 2863 (m), 2361 (w), 1951 (w), 1875 (w), 1810 (w), 1660 (s), 1605 (s), 1495 (s), 1455 (m), 1398 (s), 1261 (m), 1225 (w), 1152 (m), 1086 (m), 1053 (m), 1032 (m), 978 (m), 929 (w), 876 (w), 824 (w), 750 (m), 701 (s), 639 (m). MS (CI, CH_4): 249 (16), 248 ($M^+ + H$, 100), 230 (44), 113 (22), 98 (12), 91 (20), 72 (13), 59 (11). $[\alpha]^{24}_D$: −6.48 (c = 1.02, EtOH). TLC: R_f 0.11 (EtOAc) [UV (254 nm)]. SFC: (*S*)-**56**, t_R 5.89 min (90.9%); (*R*)-**56**, t_R 6.37 min (9.1%) (Chiralpak AD, 125 psi, 40 °C, 10.0% MeOH in CO_2, 2.5 mL/min, 220 nm). HRMS: calcd for $C_{15}H_{22}NO_2$ 248.1651, found 248.1649.

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Supporting Information Available: Full characterization of all dienol ethers and aldol products along with representative procedures for the addition reactions and configurational assignments as well as atomic coordinates for the calculated transition structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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