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Chiral Phosphoramide-Catalyzed Aldol Additions of Ketone Enolates. Preparative Aspects

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Abstract: Trichlorosilyl enolates of ketones (enoxytrichlorosilanes) were demonstrated to be highly reactive aldol addition reagents. Trichlorosilyl enolates of cyclohexanone (*E*-enolate) and propiophenone (*Z*-enolate) reacted readily at room temperature with a wide variety of aldehydes to afford aldol addition products in high yield and diastereoselectivity ($E \rightarrow$ syn, $Z \rightarrow$ anti). These reactions were shown to be highly susceptible to acceleration by catalytic quantities of chiral phosphoramides. In particular, a phosphoramide derived from (*S,S*)-stilbenediamine was remarkably effective not only in accelerating the reaction but also in modulating the diastereoselectivity and in providing the aldol addition products in good to excellent enantioselectivity. The diastereoselectivity of the unpromoted process has been interpreted as a consequence of reaction via a pentacoordinate, trigonal bipyramidal (tbp) silicon complex through a boatlike transition structure. The phosphoramide-catalyzed reactions are more complicated and are believed to proceed via hexacoordinate, octahedral complexes through chairlike transition structures. A systematic examination of the influence of solvent, concentration, addition rate, and catalyst loading on rate and stereoselectivity is also described.

Introduction

The aldol addition reaction has achieved the venerable status of a "strategy-level reaction" in organic synthesis.[1] The generality, versatility, and selectivity associated with this construction has been the subject of countless reviews and authoritative summaries.[2] In addition, the historians of chemistry will no doubt recognize that the revolution in organic synthesis that ushered in the era of reagent-controlled strategies for total synthesis can be associated with the development of stereoselective aldol addition reactions.[3]

Our interest in the aldol addition has focused on an understanding of the origins of stereochemical control in the most common variants of the reaction involving both metal enolates[4] and stable enoxysilane species.[5] After a detailed examination of the methods currently available for enantioselective aldolizations, it was apparent that there was still an opportunity for a fundamental conceptual advance that could satisfy the long sought goal of high stereoselectivity from readily available precursors under asymmetric catalysis. Our objective was to develop a new type of aldol addition that embodied the most advantageous features of existing approaches and also obviated their limitations. Detailed herein is a full account of our studies on the invention of an aldol addition reaction that provides high diastereo- and enantioselectivity from easily prepared[6] (or in situ prepared)[7d,f] trichlorosilyl enolates (enoxytrichlorosilanes) in the presence of catalytic quantities of chiral phosphoramides (Lewis bases).[7] This paper is concerned primarily with the preparative aspects of the reaction and its current scope and limitations. The attendant studies on the mechanism and origin of selectivity will be addressed in a subsequent disclosure.

To provide the conceptual framework for the invention of the process described herein, we will first outline briefly the status of the existing methods with particular attention to the advantages and disadvantages which the new advance was designed to address.

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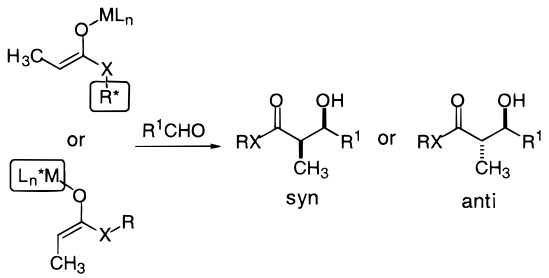
Background

Some of the earliest examples of asymmetric aldol addition reactions involved lithium enolates of chiral carbonyl compounds that reacted with aldehydes, presumably through organized transition structures to give good diastereoselectivities.[8] Because the enolates were chiral, these translated to enantiomerically enriched products once the auxiliaries were destroyed or removed. Although high selectivities were obtained, these reactions were not ideal from a practical point of view because they required a stoichiometric amount of covalently bound auxiliaries. Moreover, the highly reactive lithium enolates employed do not necessarily require the pre-assembly of aldehyde and enolate in the reactive intermediates or transition structures[4] which attenuates the stereochemical information transfer from the covalently bound auxiliary.

One of the greatest advances in aldol technology was the use of less reactive metalloenolates (boron or titanium) which do facilitate the association of aldehyde, enolate, and auxiliary in the closed transition structure, Scheme 1.

Scheme 1

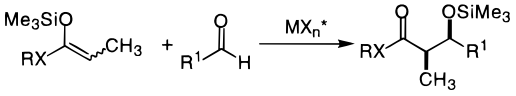


Some of the most powerful reagents for asymmetric aldol addition employ auxiliary modified enolates in which the chiral appendage is attached through an acyl linkage or directly around the metal of the enolate. Reactions of the geometrically defined enolates with aldehydes give, with extremely high stereochemical felicity, the syn- or anti-diastereomers with high enantiomeric excess after cleavage of the controlling group. Some of these powerful reagents are the acyl oxazolidinone boron enolates,[2a] the diazaborolidine derived enolates,[9] titanium enolates derived from diacetone glucose,[10] the diisiopinylcamphenyl boron enolates for ketone aldolizations[2m] and proline-derived silanes for *N*,*O*-ketene acetals.[11]

The key features common to these agents are: (1) the metal serves as an organizational center, (2) the electrophile, nucleophile, and asymmetric modifier are held in close proximity around the coordination sphere of the metal, ensuring high stereochemical information transfer, (3) the geometry of the enolate translates with high stereochemical responsiveness to diastereoselectivity in the aldol product. Despite these powerful advantages one of the most significant disadvantages is that these reactions have never been rendered catalytic, and in fact it is the high degree of metal affinity between aldehyde, enolate, and chiral auxiliary that interferes with the turnover.

Catalytic processes have, however, been developed for the aldol addition reaction, Scheme 2[12]. These reactions take advantage of the well-known Mukaiyama directed-aldol addition reaction of enoxysilane derivatives of ketones, esters, thioesters, and amides in combination with aldehydes activated by chiral Lewis acids.[2d,2k] Some of the more commonly used and selective chiral Lewis acids are: diamine complexes of tin(II) triflate,[13] borane complexes of a monoester of tartaric acid (CAB catalysts),[14] sulfonamido amino acid borane complexes,[15] titanium binaphthol[16] and binaphthylimine complexes,[17] ferrocenylphosphine−gold[18a] and BINAP−silver[18b] complexes, and most recently, copper(II) bis-oxazoline complexes.[19]

Scheme 2



These variants of the aldol reaction have a number of key features in common: (1) the additions have been demonstrated for aldehydes and enol metal derivatives with catalytic loading of the chiral Lewis acid, (2) the diastereo- and enantioselectivity is variable although can be high in certain cases, and (3) these reactions are not responsive to prostereogenic features, i.e., when the configuration of the enolsilane nucleophile changes, the diastereoselectivity of the product does not change.[20]

A very recently developed class of aldol addition involves the use of chirally modified metalloids in a catalytic process.[18b,21] In these reactions, a metal/phosphine complex is proposed to undergo transmetalation with TMS enol ethers or tributylstannyl ketones to provide chiral metalloid enolates in situ. Aldol addition then proceeds, with turnover of the metalloid species to another latent enol donor. Other approaches have used chiral fluoride sources for Nakamura/Kuwajima/Noyori[22] aldol addi-

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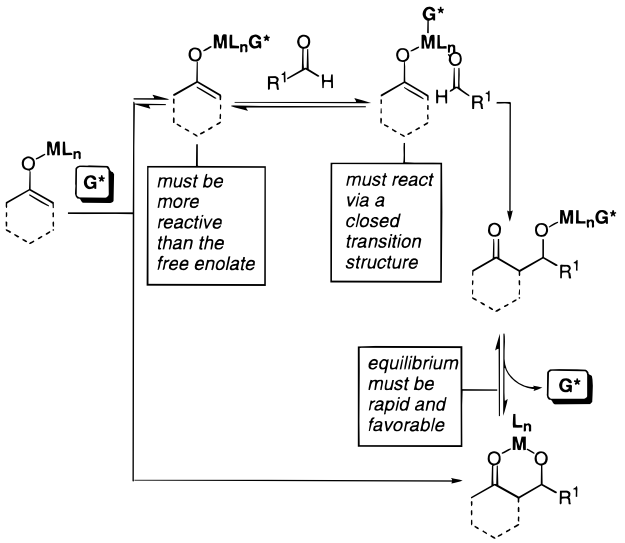
Scheme 3



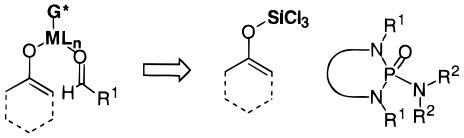
tions of ammonium enolates[23] and heterobimetallic catalysts which, through dual Lewis acid and Brønsted base activation, promote the addition of unmodified ketones to aldehydes.[24]

We envisioned the possibility of devising a new aldol addition reaction that uses Lewis base catalysis for activation of the nucleophile. The challenges that face the development of nucleophilic catalysis of the aldol addition are outlined in Scheme 3. In this case it is the enoxymetal derivative which is activated by preassociation with a chiral Lewis basic group (G*) bearing a nonbonding pair of electrons. The -ate complex must be more reactive than the free enolate for the ligand-accelerated catalysis to be observed. Next, association of this -ate complex with the Lewis basic carbonyl oxygen of the aldehyde produces a hyper-reactive complex in which the metal has expanded its valence by two. It is expected that this association complex between enolate, aldehyde, and the chiral Lewis basic group reacts through a closed-type transition structure with a high degree of information transfer to produce the metal aldolate product. This represents a single reaction event, and for turnover to be observed, the aldolate must undergo the expulsion of the Lewis basic G* group with the formation of the chelated metal aldolate product. Thus, Lewis base-catalysis involves simultaneous activation of the nucleophile and the electrophile within the coordination sphere of the metal. The reaction must take place in a closed array and be capable of releasing the activating group by chelation or change in the Lewis acidity.

To invent such a process one must consider the design criteria for the enoxy metal and the G* group. For the metal, the ML_n subunit must be able expand its valence by two and balance nucleophilicity of the enolate with electrophilicity to coordinate both the Lewis basic aldehyde and the chiral G* group. Such metals that would satisfy these criteria are those which can expand their valence such as silicon, tin, titanium, zirconium, and aluminum. To accommodate the valence expansion and impart sufficient Lewis acidity to that metal group such that two Lewis basic atoms may associate, the ligands (L) should be small and strongly electron-withdrawing such as halogen or carboxyl groups. The criteria necessary for the chiral Lewis basic group G* are that it must be able to activate the addition without cleaving the O-ML_n linkage and provide an effective asymmetric environment with single-point attachment. Candidates for the G* Lewis basic group would include phosphine oxides and derivatives such as phosphoramides or phosphonates, *N*-oxides, and sulfoxides but not negatively charged alkoxides or amides and carboxylates. It is viewed that these later groups would be too nucleophilic and effect the cleavage of the O−ML_n bond.[5d]

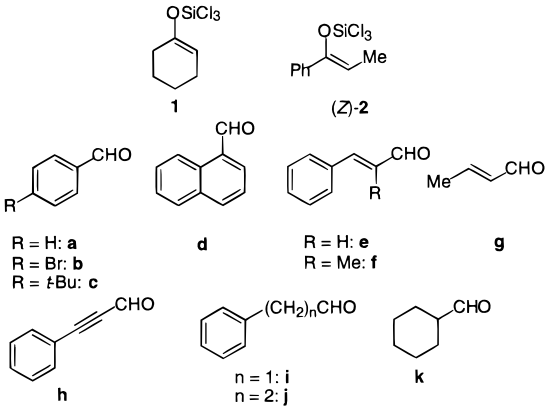
Thus, to reduce this to practice we envisioned the use of a new class of aldol reagents, trichlorosilyl enolates, in conjunction with perhaps the most Lewis basic of all of the groups considered, the phosphoramides, Scheme 4. These can be seen as chiral analogues of HMPA, the Lewis basicity of which is well documented.[25] To test the feasibility of this proposal we needed a ready and efficient access to this unusual class of enoxysilane derivatives, trichlorosilyl enol ethers.

Scheme 4



A variety of methods for the synthesis of chlorosilyl enolates **1**−**2** (Chart 1) from stannyl ketones, TMS enol ethers, and directly from cyclohexanone have been recently discussed in detail.[6] Thus, the current presentation will focus on the aldolization of these reagents, the experimental aspects of yield and selectivity optimization (catalyst structure and loading, solvent, addition rate), and the scope of the reaction.

Chart 1



Results

1. Uncatalyzed Reactions. 1.1. Cyclohexanone-Derived Enolate. With the knowledge that appropriately electrophilic silyl enolates can be reactive toward aldehydes in the absence of external promoters[5d,e,12,26] we attempted similar "unpromoted" aldol additions with this new class of ketone-derived silyl

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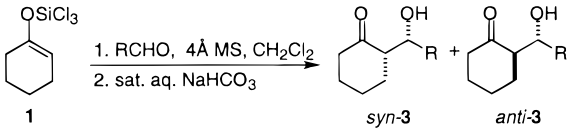
enolates. The preliminary examination of reactivity employed the cyclohexanone-derived trichlorosilyl enolate **1** (as a prototypical *E*-configured enolate) and benzaldehyde (**a**). These reactants cleanly provided the aldol adduct **3a** in high yield and with high diastereoselectivity, favoring the syn isomer, Table 1.[27] The transformation of such an *E*-configured enolate to a syn aldol product suggested that a closed, boatlike transition structures may be operative, as have previously been proposed for the reaction of Lewis-acidic silicon enolates.[5d,e,12]

To explore the generality of this aldolization, a representative selection of aldehyde acceptors (Chart 1) were combined with **1** under similar conditions, Table 1. All aldehyde classes examined reacted cleanly, and the adducts could be isolated in good to high yield. All of the reactions, save that with cyclohexanecarboxaldehyde (**k**) (entry 7), were syn-diastereoselective, to varying degrees. Hindered, conjugated aldehydes (entry 4) and aliphatic aldehydes (entries 6 and 7) provided modest selectivity, while benzaldehyde, cinnamaldehyde, and the propargyl aldehyde **h** provided excellent levels of diastereoselectivity (entry 5). Sterically congested aromatic aldehydes and aliphatic aldehydes tended to react more slowly than smaller, conjugated aldehydes. In the case of cinnamaldehyde (**e**), α-methyl cinnamaldehyde (**f**), and phenyl propargyl aldehyde (**h**), exclusive 1,2-addition was observed; the corresponding 1,4-addition product was not detected.

Table 1. Uncatalyzed Aldol Reactions of **1**[a]



entry	aldehyde	time, h	product	syn/anti[b]	yield, %
1	**a**	6	**3a**	49/1	92[c]
2	**d**	8	**3d**	16/1	90[d]
3	**e**	1	**3e**	49/1	83[c]
4	**f**	11	**3f**	5.7/1	86[d]
5	**h**	2	**3h**	36/1	91[c]
6	**i**	12	**3i**	7.3/1	78[c]
7	**j**	12	**3j**	5.3/1	82[d]
8	**k**	36	**3k**	1/1	92[d]

[a] 0.5 M/0 °C. [b] Determined by ^{1}H NMR analysis. [c] Analytically pure material. [d] Chromatographically homogeneous material.

1.2. In Situ Generated Enolates. To avoid the isolation and handling of the sensitive trichlorosilyl enolates, we investigated the possibility of performing these useful reactions by in situ generation of **1**. Following the analogy of boron-based[2m] (R_2BOTf/amine base) and tin(II)-based[2l] ($Sn(OTf)_2$/amine base) enolate generation systems, we examined the use of the trichlorosilyl triflate[28] (Cl_3SiOTf)/amine base system for the direct enolsilylation of cyclohexanone. Enolization (Cl_3SiOTf/*i*-Pr_2NEt/0 °C) in CH_2Cl_2, followed by addition of benzaldehyde led to a disappointing 13/1 syn/anti ratio in modest yield. We surmised that the CH_2Cl_2-soluble ammonium salts were interfering in the reaction and therefore surveyed the effect of other solvents in the overall reaction. Although the yields were all low, the diastereoselectivities were dependent on solvent, with the highest syn-selectivity being obtained in solvents in which the ammonium salts had precipitated from solution (Et_2O and pentane).

(27) The presence of 4 Å molecular sieves in the reaction mixture has no apparent effect on the selectivity of the process, although they may prevent elimination of the trichlorosilyl aldolate.

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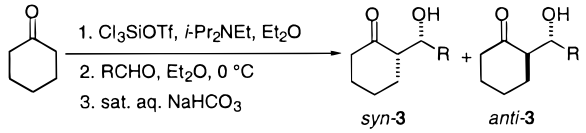
Table 2. Uncatalyzed Aldol Additions of in-Situ Generated **1**[a]



entry	aldehyde	product	syn/anti[b]	yield,[c] %
1	**a**	**4a**	>50/1	66
2	**e**	**4e**	38/1	59
3	**f**	**4f**	16/1	64
4	**d**	**4d**	1.8/1	52

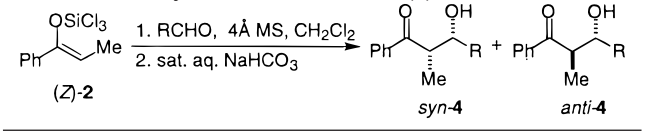
[a] (1) 1.5 equiv cyclohexanone/1.6 equiv Cl_3SiOTf/1.1 equiv *i*-Pr_2NEt/0.5 M/20 min. (2) 1.0 equiv RCHO/0.5 M/16 h. [b] Determined by ^{1}H NMR analysis. [c] Chromatographically homogeneous material.

The preliminary observation that Et_2O provided significantly higher diastereoselectivity than the other solvents prompted a brief optimization of the in situ aldolization in this medium. Gratifyingly, when the reaction concentration was raised to 0.5 M and reaction time extended to 16 h, respectable yields of the aldol adducts could be obtained, again with high diastereoselectivity, Table 2, entry 1. That the yields were still only moderate may reflect destruction of the enolate under the reaction conditions or the participation of competitive pathways. Analysis of the reaction mixture by ^{1}H NMR before addition of aldehyde indicated that clean, essentially quantitative conversion to **1** had occurred.

With a more useful protocol in hand, a representative subset of aldehydes (Chart 1) was surveyed, Table 2. Unfortunately, aliphatic (hydrocinnamaldehyde (**j**)) and hindered (trimethylacetaldehyde) aldehydes did not react under these conditions. However, both unsaturated aldehydes **e** and **f** provided high diastereoselectivity, while 1-naphthaldehyde (**d**) was nearly unselective. The trend in Table 2, entries 3 and 4 should be contrasted to that found in Table 1, entries 1 and 3.

1.3. Propiophenone-Derived Enolate. To determine the effect that enolate geometry would have on the unpromoted aldol process, the *Z*-configured trichlorosilyl enolate derived from propiophenone ((*Z*)-**2**)[6] was combined with a variety of aldehydes (Chart 1) under the standard conditions, Table 3. As was previously observed with enolate **1**, the reactions proceeded in high yield, except with hindered, conjugated aldehydes, Table 4, entry 5. Not unexpectedly,[5d] reactions with (*Z*)-**2** were weakly anti-selective as was observed previously with other *Z*-configured silyl enolates, again suggestive of a boatlike transition structure. As before, only 1,2-addition was observed for α,*β*-unsaturated aldehydes.

Table 3. Uncatalyzed Aldol Reactions of (*Z*)-**2**[a]



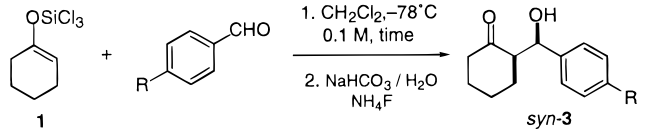
entry	aldehyde	time, h	product	syn/anti[b]	yield, %
1	**a**	10	**4a**	1/2.3	97[c]
2	**b**	10	**4b**	1/2.9	93[d]
3	**d**	16	**4d**	1/1.3	95[c]
4	**e**	10	**4e**	1/1.9	95[c]
5	**f**	12	**4f**	1/2.2	64[d]
6	**g**	16	**4g**	1/1.9	89[c]
7	**h**	11	**4h**	1/2.2	89[d]

[a] 0.5 M/0 °C. [b] Determined by ^{1}H NMR analysis. [c] Chromatographically homogeneous material. [d] Analytically pure material.

2. Catalyzed Aldol Additions. 2.1. Cyclohexanone-Derived Enolate. 2.1.1. Background Reaction. To assess the efficiency

of chiral phosphoramides in promoting the addition of **1** to benzaldehyde (**a**), a control experiment without phosphoramides was required. Two data points were collected at 8 min and at 2 h for the reaction of **1** with **a** at −78 °C (0.1 M CH_2Cl_2); by ^1H NMR analysis of the crude reaction mixtures, only 2 and 19% conversions, respectively, were observed (Table 4). With the less volatile 4-*tert*-butylbenzaldehyde (**c**), after 8 min at −78 °C, 2% of the syn aldol product **3c** was isolated along with 96% recovery of the starting aldehyde **c**. After 2 h at −78 °C, the isolated yield of *syn*-**3c** and recovered **c** were 19 and 78%, respectively. Although appreciable background reaction was observed with **a** and **c**, the reaction between **1** and 1-naphthylaldehyde (**d**) gave negligible background; after 2 h at −78 °C, 96% of the aldehyde **d** was recovered.

Table 4. Background Control Experiments

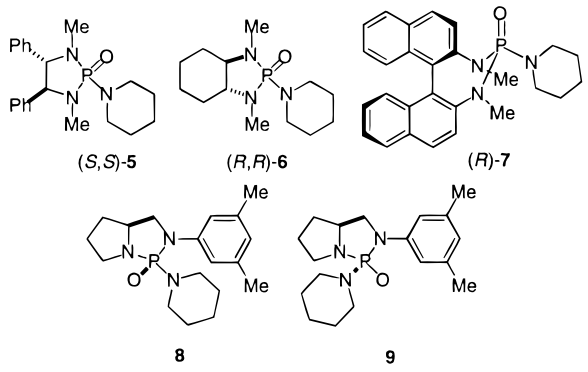


1 *syn*-3

aldehyde	time, min	conv., %[a]	yield **3**, %[b]	recovery aldehyde, %[b]
a	8	2	nd[c]	nd
a	120	19	nd	nd
c	8	nd	2	96
c	120	nd	19	78
d	120	nd	nd	96

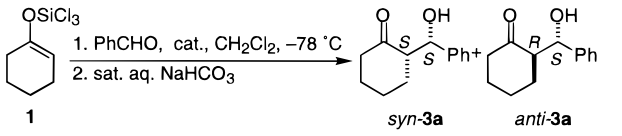
[a] Determined by ^1H NMR analysis. [b] Chromatographically homogeneous material. [c] Not determined.

Chart 2



2.1.2. Optimization of Aldol Addition. 2.1.2.1. Promoter Structure. Clearly, the primary factor in effecting fast enantioselective aldol additions is the selection of an appropriate catalyst. Thus, the initial optimization focused on a broad survey of phosphoramide catalyst structure. A selection of phosphoramides derived from chiral, enantiopure amines is shown in Chart 2.[29] We chose the reaction of **1** with **a** at −78 °C (0.1 M CH_2Cl_2) as the test system. All of the phosphoramides **5**−**9** proved to be effective in catalyzing the addition (Table 5). In the presence of 10 mol % of the phosphoramides, high yields of the aldol addition products were obtained. The phosphoramide (*S*,*S*)-**5** gave the best results as gauged by both diastereomeric and enantiomeric ratios of the products. Phosphoramide (*R*,*R*)-**6** gave low diastereoselectivity and moderate enantioselectivity of the anti diastereomer. The binaphthyldiamine-derived phosphoramide (*R*)-**7** was the only syn-selective phosphoramide, but the enantioselectivity in both the syn and anti manifolds was moderate. Proline derived phosphoramides **8** and **9** were slightly anti-selective, but the enantioselectivities were very low.

Table 5. Chiral Phosphoramide Catalyzed Addition of **1** to Benzaldehyde[a]



1 *syn*-**3a** *anti*-**3a**

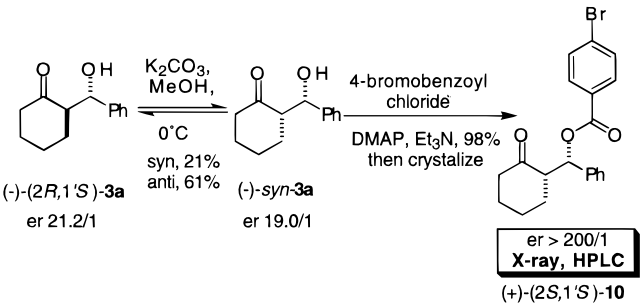
entry	catalyst	syn/anti[b]	er,[c] syn[d]	er,[c] anti[e]	yield,[f] %
1	(*S*,*S*)-**5**	1/50	nd	27.6/1	94
2	(*R*,*R*)-**6**	1/2.0	1.00/1	1/3.00	91
3	(*R*)-**7**	3.2/1	1/3.00	3.55/1	87
4	**8**	1/1.1	1.08/1	1/1.22	94
5	**9**	1/3.1	1.06/1	1/1.15	96

[a] 10 mol % cat./2 h. [b] Determined by ^1H NMR analysis. [c] Determined by CSP HPLC analysis. [d] Ratio (2*S*,1′*S*)/(2*R*,1′*R*) isomer. [e] Ratio (2*R*,1′*S*)/(2*S*,1′*R*) isomer. [f] Chromatographically homogeneous material.

2.1.2.2. Configuration of Aldol Products. The absolute configuration of *anti*-**3a** derived from the reaction using (*S*,*S*)-**5** was established to be (2*R*,1′*S*) (as drawn) by single-crystal X-ray analysis of the corresponding 4-bromobenzoate.[30]

To establish the absolute configuration of the major enantiomer of *syn*-**3a**, a highly enantiomerically enriched sample of *syn*-**3a** was prepared by epimerization of *anti*-**3a**. Thus, enantioenriched (−)-*anti*-**3a** was epimerized in methanolic potassium carbonate at 0 °C for 1.5 h, Scheme 5. Chromatographic isolation provided (−)-*syn*-**3a** in 21% yield and 19.0/1 enantiomeric ratio along with 61% of the anti-diastereomer. Extended reaction times resulted in further dehydration and decomposition of **3a**. Acylation of the levorotatory *syn*-**3a** with 4-bromobenzoyl chloride in the presence of excess of DMAP and triethylamine gave the crystalline dextrorotatory 4-bromobenzoate **10** in 98% yield, which was recrystallized to enantiomeric purity. Single crystals suitable for X-ray analysis established that the dextrorotatory ester has (2*S*,1′*S*) configuration.[30] Thus, the major enantiomer in the syn manifold formed with catalyst (*S*,*S*)-**5** is (2*S*,1′*S*)-**3a** by correlation of elution order on CSP HPLC.

Scheme 5



2.1.2.3. Reaction Conditions. After performing the initial survey of catalyst structure, we briefly examined the effect of different solvents and on both the diastereo- and enantioselectivity of the aldol additions catalyzed by (*S*,*S*)-**5**. This reaction, though efficient and always highly selective, suffered from variable diastereoselectivity. Although the dr of the product was always >20/1 anti/syn, the exact ratio seemed to vary with the batch of catalyst, enolate, and aldehyde. Some of the reasons

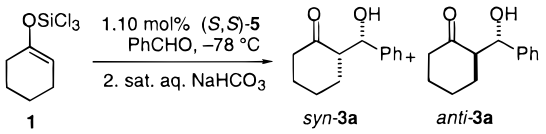
(29) Denmark, S. E.; Su, X.; Nishigaichi, Y. M.; Coe, D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J.-Y. *J. Org. Chem.* **1999**, *64*, 1958.

(30) All X-ray crystal structure data has been deposited in the Cambridge Crystallographic Data Center as supplementary publication Nos. CCDC-111716 ((+)-*anti*-**10**), CCDC-111826 ((+)-*syn*-**10**)), CCDC-111715 ((+)-*syn*-**4b**)). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

for this variability have since been identified and will be presented in a mechanistic analysis of the reaction.[10] Consequently, in each of these optimization studies the benchmark reaction (**1**, **a**, and 10 mol % (*S*,*S*)-**5**) was performed side-by-side with the other experiments in that particular study. Thus, in the following tables several examples of this specific reaction will be shown, each with slightly different results. This slight variability does not undermine the conclusions presented in each study, nor is it currently relevant due to improvements in reaction protocol (vide infra).

In the first series of experiments, benzaldehyde was added quickly to a cold (−78 °C) solution of phosphoramide (*S*,*S*)-**5** and **1** in various solvents, Table 6. The benchmark reaction proceeded well, with high (35/1) anti/syn selectivity and high er in the anti manifold. The use of the less polar solvents toluene and pentane provided significantly diminished dr and er, entries 3 and 4. The relatively low yield of the reaction in pentane most likely represents the limited solubility of the phosphoramide in this solvent at low temperature. When Et_2O was used, the diastereoselectivity of the process increased (entry 2), similar to the response of the unpromoted reaction (although in the opposite sense). However, the enantioselectivity of the anti process decreased appreciably, relative to that obtained in CH_2Cl_2.

Table 6. Solvent Effects in Catalyzed Aldol Additions of **1**[a]

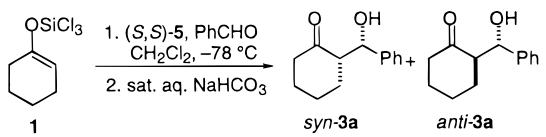


entry	solvent	syn/anti[b]	er,[c] syn[d]	er,[c] anti[e]	yield,[f] %
1	CH_2Cl_2	1/35	nd	25.3/1	85
2	Et_2O	1/>50	nd	8.52/1	82
3	toluene	1/6.2	1.43/1	5.02/1	84
4	pentane	1/2	1.56/1	1.88/1	70

[a] 0.1 M/2 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP HPLC analysis. [d] Ratio (2*S*,1′*S*)/(2*R*,1′*R*) isomer. [e] Ratio (2*R*,1′*S*)/(2*S*,1′*R*) isomer. [f] Chromatographically homogeneous material.

Next, the influences of overall reaction concentration and catalyst loading were investigated again with a protocol involving fast addition of aldehyde. The results are compiled in Table 7. Increasing the concentration of the reaction solution from 0.1 to 0.5 M had a rather strong effect on diastereoselectivity (compare entries 1 and 4). Furthermore, on lowering the catalyst loading from 10 to 2 mol %, the diastereoselectivity dropped sharply, from 14/1 to 2.4/1 anti/syn. Importantly, the enantiomeric ratio of the products did not change significantly, either on changing the concentration or on lowering the loading of the phosphoramide.

Table 7. Phosphoramide Loading Effect in Aldol Addition with **1**

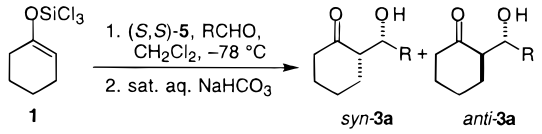


entry	loading	conc., M	syn/anti[a]	er,[b] syn[c]	er,[b] anti[d]	yield,[e] %
1	10%	0.5	1/14	1.46/1	16.9/1	94
2	5%	0.5	1/10	1.29/1	17.9/1	90
3	2%	0.5	1/2.4	1.31/1	14.9/1	84
4	10%	0.1	1/28	1.47/1	20.7/1	90

[a] Determined by ^{1}H NMR analysis. [b] Determined by CSP HPLC analysis. [c] Ratio (2*S*,1′*S*)/(2*R*,1′*R*) isomer. [d] Ratio (2*R*,1′*S*)/(2*S*,1′*R*) isomer. [e] Chromatographically homogeneous material.

2.1.3. Survey of Aldehyde. With a set of optimal conditions selected for the reaction, a survey of aldehyde structures in the reaction of **1** was undertaken, the results of which are summarized in Table 8. The phosphoramide (*S*,*S*)-**5** catalyzed all of the reactions admirably, adducts being formed in uniformly high yield. In all cases, save that with the sterically nondemanding propargylic aldehyde **h**, excellent anti-selectivity was observed. In addition, the enantioselectivity in the anti manifold was very high, e.g., the 1-naphthaldehyde-derived product being formed in 65.7/1 er. Unfortunately, the use of enolizable aldehydes did not afford the corresponding aldol adducts, probably due to competing deprotonation by the basic enolate/phosphoramide complex. Although in certain systems (specifically acetate[7a] and methyl ketone-derived[7d] trichlorosilyl enolates) the use of enolizable aldehydes is possible, in the present system (and with enolate (*Z*)-**2**) this remains a limitation.

Table 8. Aldol Additions of **1** Catalyzed by 10 mol % (*S*,*S*)-**5**[a]



entry	aldehyde	product	syn/anti[b]	er,[c] anti[d]	yield,[e] %
1	**a**	**3a**	1/61	27.6/1	95
2	**d**	**3d**	<1/99	65.7/1	94
3	**e**	**3e**	<1/99	15.7/1[f]	94
4	**f**	**3f**	<1/99	24.0/1	98
5	**h**	**3h**	1/5.3	10.1/1	90

[a] 10 mol % (*S*,*S*)-**5**/0.1 M/2 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP HPLC analysis. [d] Ratio (2*S*,1′*S*)/(2*R*,1′*R*) isomer. [e] Analytically pure material. [f] Ratio (2*R*,1′*R*)/(2*S*,1′*S*) isomer due to priority change.

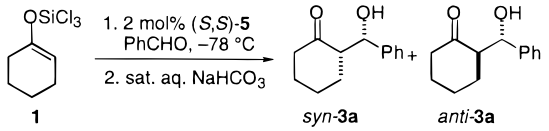
The absolute configurations of *syn*-**3a** and *anti*-**3a** have already been unambiguously assigned (Section 2.1.2.2.). The configurations of *syn*- and *anti*-**3d**−**h** were assigned by analogy.

2.1.4. Rate of Mixing. During the course of the optimization of related additions with cyclopentanone- and cycloheptanone-derived trichlorosilyl enolates, the rate of aldehyde addition to the reaction mixture was found to have dramatic consequences on diastereoselectivity.[7e] By dropwise addition of benzaldehyde to the reaction mixture (**1** and (*S*,*S*)-**5**) over 1 h such that the reaction is essentially complete upon addition of the aldehyde, the anti-selectivity not only increased, but became much more reproducible as well, consistently providing anti/syn ratios of >50/1. Notably, this reaction variable (like most others with catalyst (*S*,*S*)-**5**) had little effect on the enantioselectivity of the reaction. With this modified reaction protocol in hand, the effect of catalyst loading was reinvestigated. The same trend was apparent, with the anti-selectivity decreasing with decreasing catalyst loading. Also, the reaction was considerably slower at very low loading, providing only 53% yield at 0.5 mol %. This is due to poor conversion, and, if desired, the reaction conditions could probably be altered to provide a high yield in this case as well. Again, the er of *anti*-**3a** formed was unchanged over a 20-fold change in catalyst concentration, e.g., even 0.5 mol % of (*S*,*S*)-**5** provided *anti*-**3a** in 20.7/1 er albeit with a modest (5/1) anti/syn ratio. Indeed, with this new protocol, high (28/1) dr can now be routinely obtained with 2 mol % of (*S*,*S*)-**5**, while with the fast addition protocol, 10 mol % of (*S*,*S*)-**5** was required to obtain such selectivity.

With the advent of the slow addition/low catalyst loading protocol, the effect of solvent on the addition was reexamined, Table 9. The results of reactions in CH_2Cl_2, Et_2O, and toluene

were similar to those obtained previously (Table 6). However, the use of propionitrile as solvent provided slightly better diastereoselectivity (31/1 vs 28/1) and attenuated enantioselectivity (14.4/1 vs 22.8/1) compared to the use of CH_2Cl_2. The compatibility of such a Lewis basic solvent with a process catalyzed by Lewis bases demonstrates the dramatic accelerating effect the phosphoramide catalysts have on this reaction.

Table 9. Solvent Effects in Aldol Additions of **1** Catalyzed by 2 mol % (*S*,*S*)-**5**[a]



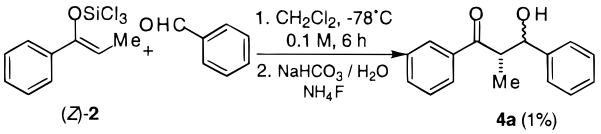
1 *syn*-**3a** *anti*-**3a**

entry	solvent	syn/anti[b]	er,[d] syn[d]	er,[c] anti[e]	yield,[f] %
1	CH_2Cl_2	1/28	1.03/1	22.8/1	91
2	Et_2O	1/49	1.46/1	7.00/1	59
3	toluene	1/5.2	1.06/1	4.56/1	51
4	CH_3CH_2CN	1/31	1.35/1	14.4/1	85

[a] 1 h addition/final concentration 0.1 M. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by CSP SFC analysis. [d] Ratio (2*S*,1′*S*)/(2*R*,1′*R*) isomer. [e] Ratio (2*R*,1′*S*)/(2*S*,1′*R*) isomer. [f] Chromatographically homogeneous material.

2.2. Propiophenone-Derived Enolates. To provide support for our hypothesis that the Lewis base-catalyzed aldol additions do indeed proceed via hypercoordinate siliconate transition structures, we examined the reaction of a *Z*-configured enolate, that derived from propiophenone, **2**. The addition of (*Z*)-**2** to benzaldehyde is much slower than the corresponding reaction of enolate **1** (Scheme 6). In the absence of an external promoter only 1% of the product **4a** was isolated after 6 h at −78 °C.

Scheme 6

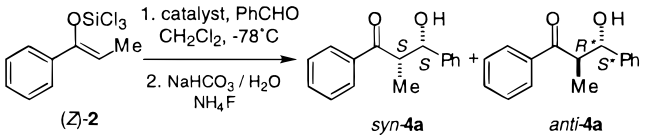


(*Z*)-**2** **4a** (1%)

Fortunately, this chlorosilyl enolate, like **1**, was susceptible to Lewis base catalysis. Phosphoramides **5**, **6**, and **7** catalyzed the addition of (*Z*)-**2** to benzaldehyde to give good yields of the aldol addition product **4a** (Table 10). The stilbenediamine derived phosphoramide (*S*,*S*)-**5** again gave the best results; a syn/anti ratio of 11.5/1 and the er in the syn manifold up to 32.3/1. Phosphoramides **6** and **7** were poorly selective catalysts in both diastereo- and enantioselective senses. The lower yields of the reactions may be a reflection of slower reaction with enolate **1**. Increasing the catalyst loading from 10 to 15 mol % increased the reaction yield to 95% and also improved the diastereoselectivity (as expected, cf. Table 11) but not the enantioselectivity.

The generality of the catalyzed reaction of enolate (*Z*)-**2** was surveyed with various aldehydes, Table 11. In the presence of 15 mol % of (*S*,*S*)-**5**, (*Z*)-**2** reacted with aromatic, olefinic and acetylenic aldehydes at −78 °C to give high yields of the aldol adducts **4.** The diastereoselectivity of the reactions varied from moderate to high depending on the structure of the aldehyde. The syn isomer is generally preferred except for the acetylenic aldehyde **h**. The enantioselectivity for the major syn diastereomer was very high except for aldehyde **h**. In contrast, the enantioselectivity for the minor anti diastereomer was uniformly low. The absolute configuration of *syn*-**4b** was unambiguously established by single X -ray analysis.[30] The absolute configurations of the other syn products were assigned by analogy.

Table 10. Chiral Phosphoramide Catalyzed Addition of (*Z*)-**2** to Benzaldehyde[a]

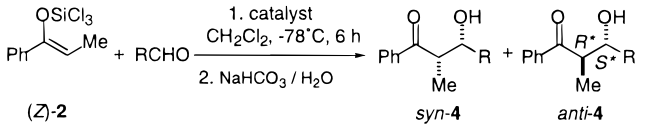


(*Z*)-**2** *syn*-**4a** *anti*-**4a**

entry	catalyst	syn/anti[c]	er,[d] syn[e]	er,[d] anti[f]	yield,[g] %
1	(*S*,*S*)-**5**	11.5/1	32.3/1	1.22/1	77
2[b]	(*S*,*S*)-**5**	18/1	39.0/1	1.23/1	95
3	(*R*,*R*)-**6**	1/2.7	1/1.38	1.08/1	72
4	(*R*)-**7**	1/1.5	1/2.23	1.13/1	61

[a] 10 mol % catalyst/0.1 M/6 h. [b] 15 mol % (*S*,*S*)-**5** used. [c] Determined by ^{1}H NMR analysis. [d] Determined by CSP HPLC analysis. [e] Ratio (2*S*,3*S*)/(2*R*,3*R*)-isomer. [f] Configuration of major enantiomer not assigned. [g] Chromatographically homogeneous material.

Table 11. Aldol Additions of (*Z*)-**2** Catalyzed by (*S*,*S*)-**5**[a]



(*Z*)-**2** *syn*-**4** *anti*-**4**

entry	aldehyde	product	syn/anti[b]	er,[c] syn[d]	er,[c] anti[e]	yield,[f] %
1	**a**	**4a**	18/1	39.0/1	1.23/1	95
2	**b**	**4b**	12/1	49.0/1	nd	89
3	**d**	**4d**	3.0/1	11.5/1	1.44/1	96
4	**e**	**4e**	9.4/1	24.0/1[g]	1.27/1	97
5	**g**	**4g**	7.0/1	21.2/1[g]	1.22/1	94
6	**h**	**4h**	1/3.5	3.76/1	1.22/1	92

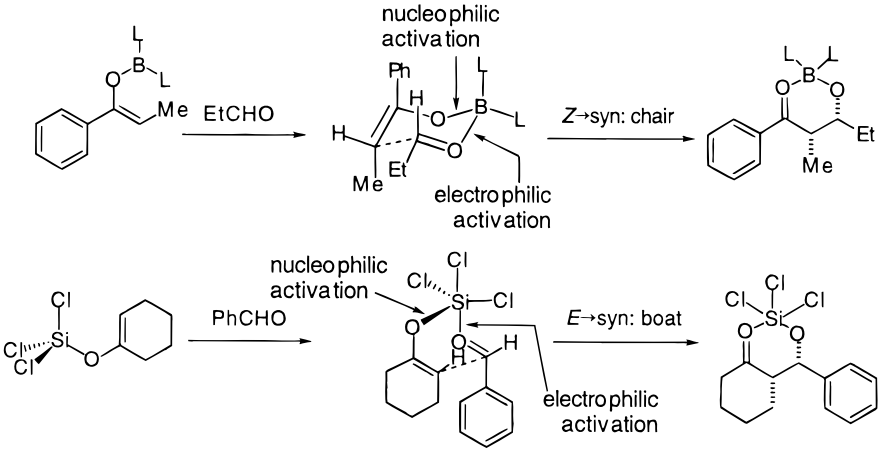
[a] 15 mol % (*S*,*S*)-**5**/0.1 M/6 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP HPLC analysis. [d] Ratio (2*S*,3*S*)/(2*R*,3*R*)-isomer. [e] Configuration of major enantiomer not assigned. [f] Analytically pure material. [g] Ratio (2*S*,3*R*)/(2*R*,3*S*) isomer due to priority change.

Discussion

1. Uncatalyzed Reactions. 1.1. Enolate Reactivity. Chlorosilyl enolates are unique in their ability to undergo both direct and catalyzed aldol additions under mild conditions. They are distinguished from common alkylsilyl enol ethers in their ability to react with aldehydes under mild thermal conditions.[31] It is important to realize, however, that this is not due to a higher nucleophilicity, as might be presumed in the context of "enolate chemistry". The term enolate is used throughout this work primarily to distinguish the remarkable and divergent reactivity of these *chloro*silyl enolic species form their *alkyl*silyl counterparts. In reality they are better considered as enol ethers, rather than true enolates which are typically highly charge-localized species associated with a cation (metal, ammonium, or sulfonium salt) and whose reactivity is usually governed by the nucleophilicity of the double bond. Rather, this reactivity is due to the highly electrophilic nature of the silicon atom, and in fact, the reagents themselves are non-nucleophilic (certainly less nucleophilic than the corresponding trimethylsilyl enol ethers) due to the inductive polarization of electron density from the enol system to the electropositive silicon center. The relatively high reactivity toward aldehydes is, therefore, most likely due to the activation accorded both partners when the aldehyde is coordinated to the Lewis acidic silicon center. The aldehyde is activated by virtue of the increased electrophilicity of the

(31) For reactions of alkylsilyl enol ethers under mild conditions, see: (a) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741. (b) RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083.

Scheme 7



carbonyl function upon coordination to the Lewis acidic silicon center. The enol species is concurrently activated by making the silyl enolate more electron rich overall and therefore more nucleophilic. This finds good analogy in the reaction of boron enolates[2m] with aldehydes and in reactions of strained-ring alkyl silyl enolates.[5d]

Thus, although trichlorosilyl enolates are reactive toward aldehydes, they are unreactive when combined with non-Lewis basic electrophiles, such as alkylating agents.[32] The reaction potential of these reagents is only enabled upon coordination with an aldehyde (or other suitable Lewis basic electrophile). As such, dual activation of substrates is needed and the reaction most likely takes place via a closed, six-membered transition structure as has been proposed for numerous other enol- and allylmetal species.[4] Such organizational control which is commonly thought of in the chemistry of boron, titanium, and other metal enolates, although not associated with the Lewis acid-promoted reactions of silyl enol ethers,[4,5d] can lead to high, geometry-divergent stereoselectivity in both a relative and (when a chiral auxiliary is part of the assembly) an absolute sense, Scheme 7.

Although the reactions bear striking mechanistic similarity to reactions involving boron enolates, the present aldolizations are slower. This is most likely due to the greater Lewis acidity of the enol boronates relative to the trichlorosilyl enolates. In addition, it is likely that aldehyde activation dominates the reactivity of the species, as silacyclobutyl ketene acetals (certainly more nucleophilic species) react with aldehydes more slowly than the trichlorosilyl enolates of ketones and much more slowly than with trichlorosilyl enolates derived from methyl acetate. In a computational study of the silicon-directed aldol addition of a trihydridosilyl enolate to acetaldehyde, Gung concluded the nucleophilicity of the enol double bond is more important in the bond-forming event than is aldehyde activation.[33] However, such a hydridosilyl species would be both more nucleophilic and less electrophilic than the trichlorosilyl enolates employed herein. Hence, we favor an explanation wherein aldehyde activation of primary importance in the reaction pathway.

1.2. Stereochemical Consequences and Transition Structure. The uncatalyzed reactions of enolate **1** (*E*-configured) are all highly syn-selective, while those of enolate **2** (*Z*-configured) are slightly anti-selective. Two limiting global arrangements of the reacting partners in the aldol addition are possible; closed, six-membered transition structures with aldehyde coordinated to the metal center and so-called "open-chain" transition structures often associated with Lewis acid-promoted aldol additions.[4] Open transition structures are characterized by variable, though often high syn-selectivity, which is effectively independent of starting enol geometry. Although the results with **1** (and the corresponding cyclopentanone- and cycloheptanone-derived enolates)[7e] could be rationalized in terms of an open-chain structure, the uniformly moderate-to-high syn-selectivity with enolate **1** and the uniformly low anti-selectivity with enolate **2** are better explained by invoking a closed transition structure in agreement with the dual activation proposal above. Given the stereochemical course of the reactions with **1**, ($E \rightarrow$ syn) a boatlike structure is predicted to be favored in such a model which could also explain the modest $Z \rightarrow$ anti selectivity observed with enolate **2**. Indeed, these stereochemical outcomes are in complete agreement with previous work on silacyclobutyl-derived ketene acetals, wherein intramolecular silyl group transfer (necessitating a closed transition structure) was demonstrated by a double label crossover study.[5d] In this case as well, the $E \rightarrow$ syn correlation was excellent whereas the $Z \rightarrow$ anti correlation was not.

The high syn-selectivity arising from boatlike transition structures with **1** (*E*-enolate) is reasonable since there are few unfavorable steric interactions in these assemblies; however, why then are *Z*-enolates relatively unselective in these processes. One reason that can be identified is that when the configuration around silicon is assumed to be trigonal bipyramidal (tbp), with aldehyde binding in the apical position, there are severe steric interactions between the enolic *Z*-substituent and a substituent in the basal plane of the trigonal bipyramidal silicon complex, Figure 1. In addition, the *Z*-substituent also eclipses the aldehydic H, an apparently unimportant interaction with *Z*-H enolates (**1**), though potentially relevant with increasing size of the *Z*-substituent (i.e., methyl in (*Z*)-**2**). Without a clearer picture of the exact conformations in the transition structure it is difficult to rationalize the selectivity differences when different aldehydes are used in the uncatalyzed reactions. In addition, the effect of solvents is challenging to understand. Considering the proposed closed nature of the assembly, less polar solvents would lead to higher selectivity, due to "solvent-driven compression"[34] of the transition structure. This was found not to be the case, however, and it is unclear what role solvation has on these

(32) Winter, S. D. W.; Stavenger, R. A., unpublished results from these laboratories.

(33) Gung, B. W.; Zhu, Z.; Fouch, R. *J. Org. Chem.* **1995**, *60*, 2860.

(34) (a) Dubois, J. E.; Dubois, M. *J. Chem. Soc., Chem. Commun.* **1968**, 1567. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

reactions, especially given the relatively polar nature of the hypervalent silicon intermediate.

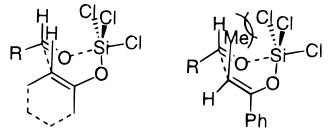


Figure 1. Possible boatlike transition structures.

2. Catalyzed Reactions. 2.1. Phosphoramide Catalysis and Global Transition Structure Picture. The concepts and practicality of Lewis base catalysis have recently been reviewed;[35] therefore, only salient points will be made here. The most distinguishing factor in Lewis base (compared to Lewis acid) catalysis of the aldol addition, is that substrate(s) may be activated in either electrophilic, nucleophilic, or synergistic manner in the former, whereas electrophilic activation is the rule for the later. Although Lewis-base-catalyzed aldol additions have been previously reported, in all cases they involve the use of strong, anionic Lewis bases (primarily fluoride) which cleave the enol/silicon bond to provide ammonium or tris(amino)-sulfonium ("free") enolates which then react via an open-chain transition structure. The distinguishing point of neutral Lewis base catalysis is the potential of reaction through an associative ("closed") transition structure with enol, aldehyde, and catalyst simultaneously organized around a metal center, thereby providing good, *stereodivergent* internal diastereoselection and control of absolute configuration. This concept is closely related to the fluoride-catalyzed additions of crotyltrifluorosilanes[36] and the formamide,[37,38c] phosphoramide,[38a,b,d] and *N*-oxide-catalyzed[39] additions of crotyltrichlorosilanes, all of which are believed to proceed through a closed transition structure organized around a hexacoordinate silicon center.

A detailed study and analysis of the mechanism of the phosphoramide-catalyzed aldol addition has been completed and will be elaborated in detail in a forthcoming paper. As an aid for further discussion, the current mechanistic hypothesis will be presented without the supporting documentation to allow analysis of the reaction features presented above. We currently believe that the reaction of **1** and benzaldehyde catalyzed by phosphoramide (*S*,*S*)-**5** proceeds through a chairlike transition structure, with aldehyde, enol, and two chiral phosphoramide molecules organized around a cationic, hexacoordinate silicon atom, Figure 2.[40] This hypothesis best explains all of the results at hand. In addition, there is a competing pathway, also involving a cationic silicon species, but with only one phosphoramide bound to the silicon, leading to a pentacoordinate, boatlike transition structure. Full discussion of rate acceleration (catalysis), effect of phosphoramide loading, and the effect of the rate of aldehyde addition will be deferred to a subsequent paper, with only practical, preparative aspects being considered here.

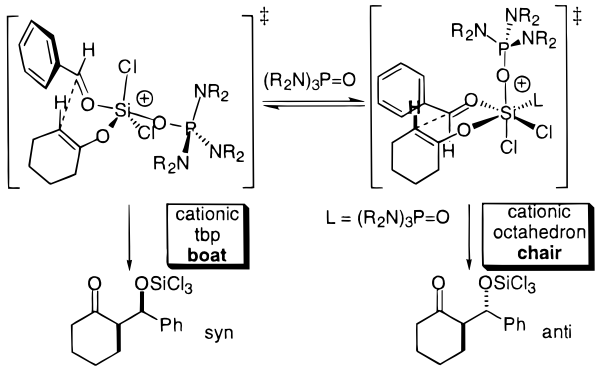


Figure 2. Unified mechanistic scheme.

2.2. Stereochemical Consequences. The reactions of **1** catalyzed by (*S*,*S*)-**5** proceeded with varying levels of diastereoselectivity, all favoring the anti product. Conversely, (*Z*)-**2** provided the syn-configured adducts, albeit with generally lower diastereoselectivity. This stereodivergence is stronger than that associated with the uncatalyzed reaction and is not consistent with reaction through an open-chain transition structure. Rather, this stereochemical course strongly suggests that the reaction proceeds through a closed, chairlike transition structure, as presented above. The lower diastereoselectivity of the *Z*-enolate can again be explained by consideration of nonbonded interactions of the enolic *Z*-substituent with groups on the silicon, although inspection of molecular models suggests that these groups are more distant in a hexacoordinate silicon chair, thus leading to a reasonable degree of selectivity. The reason for the switch from boatlike to chairlike transition structures with configuration at silicon (pentacoordinate or hexacoordinate) is unclear at this time.

In simplistic terms the changes in diastereoselectivity with both catalyst loading and slow aldehyde addition is due to the 2/1, phosphoramide/enolate ratio present in the transition structure for the formation of *anti*-**3a**. The related cationic 1/1 complex, which would involve a pentacoordinate silicon species, is then considered to provide *syn*-**3a**. Thus, higher phosphoramide loading favors 2/1 coordination, leading to better $E \rightarrow$ anti correlation. Similarly, when aldehyde is added slowly to enolate and phosphoramide, a high catalyst loading (relative to aldehyde) protocol is mimicked. If the rate of the reaction is fast relative to the aldehyde addition rate, one would expect that the results obtained from slow addition of aldehyde would mimic the results obtained from high catalyst loading experiments, whatever that result (higher $E \rightarrow$ anti correlation) or its origin (2/1, phosphoramide/enolate ratio in the transition structure) may be.

The effect of solvent in the catalyzed reaction is more difficult to explain, due to the multiple transition structures potentially operable (i.e., pentacoordinate chairs and boats, hexacoordinate chairs and boats). It seems that very nonpolar solvents (toluene and pentane) lower the energy difference between competing pathways, both between chairs and boats (leading to reduced diastereoselection) and between the major, chairlike pathways (leading to reduced enantioselection). Relatively polar solvents (relative to CH_2Cl_2) lead to higher diastereoselectivity, with only small changes in enantioselectivity. Neither of these trends can be definitively explained at the present time, given our limited knowledge of the conformation of the proposed cationic transition structures and the generally poor understanding of solvation effects on the stereochemical course of such reactions.

Other chiral phosphoramide structures were uniformly less successful catalysts compared to the stilbenediamine-derived

(35) Stavenger, R. A.; Denmark, S. E. *Angew. Chem., Int. Ed.*, manuscript submitted.

(36) (a) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081. (b) Sato, K.; Kira, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 6429.

(37) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620.

(38) (a) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Greidel, B. G. *J. Org. Chem.* **1994**, *59*, 6161. (b) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513−3526. (c) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767. (d) For a related asymmetric allenylation, see: Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2889.

(39) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6419.

(40) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990.

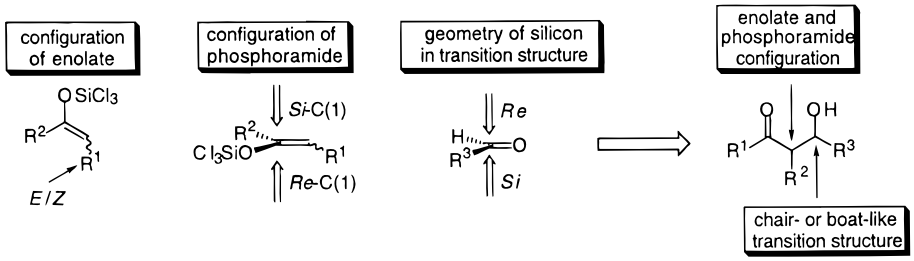


Figure 3. Factors leading to observed stereoselectivity.

(*S*,*S*)-**5**. The reasons for this are unclear, although phosphoramides **7**−**9** have vastly different structures. The poor performance of the cyclohexanediamine-derived phosphoramide **6** is more surprising since the local structure (piperidinodiazaphospholidine oxide) is similar to (*S*,*S*)-**5**, although the overall shape is fairly different due to the dihedral angles between the C(4) and C(5) substituents. Clearly, this change is enough to significantly alter both the overall composition of the transition structure (1 or 2 phosphoramides, leading to boat- or chairlike transition structures) and the more subtle differences between competing boat- or chairlike structures (leading to diminished enantioselectivity). Differences between the aldol reaction and the related allylation of aldehydes with allyltrichlorosilanes are exemplified by the lack of reactivity of catalyst **7** in the later reaction and the very successful use of **6**, **8**, and **9**. By comparison, these phosphoramides afforded only meager selectivities in the aldol reactions described herein.

The absolute stereochemical course of the reactions with (*S*,*S*)-**5** does offer clues about the overall arrangement of the components in the transition structure and the effects the phosphoramide catalysts have on the reaction, Figure 3. Given the absolute configurations of the major products, it can be concluded that the face of the enolate is preserved, whether an *E*- or *Z*-enolate is used. Also, the aldehyde face is preserved, with the change in the stereochemical course of the reaction being simply due to change in configuration of the starting enol double bond. This suggests that, whatever the mode of differentiation, in the hexacoordinate array, the *Si*−C(1)[41] face of the enolate is blocked, and the configuration of the products is then determined by (a) enol geometry, (b) the intrinsic preference of hexacoordinate silicon enols for a chairlike transition structure, and (c) the configuration of the chiral catalyst.[42] The use of (*S*,*S*)-**5** effectively blocks the *Si*−C(1) face of the enolate; placement of the aldehyde in a chairlike transition structure then correctly predicts both the predominant diastereomer formed and the observed absolute configuration of the major diastereomer, regardless of the geometry/conformation around the silicon atom and in the actual transition structure. Thus, cyclic enolates (*E*-configured) typically provide excellent anti-selectivity in reactions catalyzed by (*S*,*S*)-**5**, while *Z*-enolates provide moderate to high syn-selectivity in the analogous reactions. In both cases (and in the case of methyl ketone- and methyl acetate-derived trichlorosilyl enolates) the newly formed hydroxyl-bearing center is of the *S*-configuration if the aldehyde substituent has priority over the enol backbone.

(41) This notation is used to describe the faces of the enol double bond relative to the C(1) (oxygen-bearing) position, rather than the more typical C(2) position which is actually transformed into the resultant tetrahedral center.

(42) For a discussion of the solid stae structures of $[(S,S)\text{-}\mathbf{5}]_2 \cdot SnCl_4$ and related complexes, see: Denmark, S. E.; Su, X. *Tetrahedron* **1999**, in press.

Conclusions

The chemistry of a new class of aldol addition reagents, enoxytrichlorosilanes (trichlorosilyl enolates), has been investigated. These novel species are reactivity-inverted enolates in that their chemistry is dominated by the electrophilicity of the silicon unit. Trichlorosilyl enolates of cyclohexanone and propiophenone react spontaneously with a wide variety of aldehydes to afford the aldol addition products via a trigonal bipyramidal siliconate complex through predominantly boatlike transition structures. Most importantly, the aldol addition of trichlorosilyl enolates with aldehydes is highly susceptible to catalysis by chiral phosphoramides which function as Lewis-basic activators. In the presence of a stilbenediamine-derived phosphoramide, the aldol additions are highly diastereo- and enantioselective. The predominant products can be interpreted as arising from chairlike assemblies of phosphoramide, aldehyde, and enolate around a hexacoordinate siliconate complex. Both *E*- and *Z*-configured enolates react with high diastereoselectivity and enantioselectivity to the respective anti and syn aldol products with nonenolizable aldehydes. This represents a unique illustration of the dual activation afforded by Lewis base complexation of electrophilic species and augurs well for broader applications in the vast domain of organosilicon chemistry.

Experimental Section

See Supporting Information.

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Supporting Information Available: Full experimental details, general procedures for aldol addition reactions and full characterization data for all aldol products and derivatives described are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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