The Chemistry of Trichlorosilyl Enolates. Aldol Addition Reactions of Methyl Ketones

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Abstract: Investigations on the aldol addition chemistry of trichlorosilyl enolates derived from methyl ketones are presented in full. These trichlorosilyl enolates are competent aldol reagents in the absence of additives, reacting with aldehydes at ambient temperature to provide high yields of aldol adducts. When either enol or aldehyde partner bears a stereogenic center, low diastereoselectivity is observed in this uncatalyzed aldol process. The aldol additions are dramatically accelerated by the addition of catalytic quantities of chiral phosphoramides, particularly one derived from *N*,*N*′-dimethylstilbene-1,2-diamine. In this catalyzed mode, good to high enantioselectivities are obtained with a variety of achiral trichlorosilyl enolates and aldehydes. When either partner bears a stereogenic center, high diastereoselectivities are obtained with one enantiomer of the catalyst (matched case), while the other enantiomer provides low diastereoselectivity (mismatched case). The reaction scope, optimization of conditions, and stereoselection events are also discussed.

Introduction

In recent years we have been engaged in a broadly based program to explore the synthetic potential and mechanistic underpinnings of asymmetric catalysis with chiral Lewis bases.[1] The centerpiece of this program has involved the invention of a new class of aldol reactions based on novel silicon reagents (enoxytrichlorosilanes) which undergo spontaneous addition to aldehydes at or below ambient temperature. More importantly, the action of these reagents has been shown to be highly responsive to catalysis by (chiral) phosphoramides.[2,3] The preparative aspects of both catalyzed and uncatalyzed reactions of trichlorosilyl enolates derived from α-substituted (cyclic and acyclic) ketones has recently appeared.[4] Contemporaneously, a relatively clear mechanistic view is emerging from studies of the trichlorosilyl enolate derived from cyclohexanone.[5]

A significant component of our mission in developing this new type of aldol process is to establish its scope with the ultimate objective of creating a general synthetic method. This mandates the investigation of the reactivity of a broad range of trichlorosilyl enolates and aldehyde partners. Some of the more useful members of the aldol reagent family are enolates derived from methyl ketones. The utility of reagents capable of delivering an $RC(O)CH_2$ unit enantioselectively is self-evident, yet such transformations have traditionally been among the most challenging to accomplish.[3i,6] While the reasons for the difficulty are still in debate, one consensus view is the greater accessibility of competing, diastereomeric transition structures resulting from the reduced steric demand of the nucleophile. In view of our discovery that the catalyzed reactions of trichlorosilyl enolates derived from cyclic ketones proceed through closed, six-membered transition structures and that the arrangement of reactants is strongly influenced by the structure of the phosphoramide catalyst, we were encouraged to pursue this recalcitrant class of aldol components. This report details our full investigations of the trichlorosilyl enolates derived from achiral and chiral methyl ketones, in both uncatalyzed and catalyzed reaction with chiral and achiral aldehyde acceptors.[7]

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(4) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982−4991.

(5) (a) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990−12991. (b) Denmark, S. E.; Pham, S. M. *Helv. Chim. Acta* **2000**, *83*, 1846−1853.

(6) For examples of other catalytic asymmetric aldol additions of methyl ketones, see: (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−6910. (b) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483−3491. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039−7040. (d) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649−3650. (e) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. *Synlett* **1997**, 463−466. (f) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507−1510. (g) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873.

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Results

A. Synthesis of Enolates. The preparation of several classes of trichlorosilyl enolates has been described in detail.[8] The methyl ketone enolates used in this study are shown in Chart 1. All of the enoxytrichlorosilanes (except for **1** which was prepared by the method of Benkeser[8b]) were prepared via the corresponding trimethylsilyl enol ethers by use of the mercury(II)-catalyzed trans-silylation reaction (with $SiCl_4$) developed in these laboratories.[7a,8a] It should be noted that although these species are hydrolytically sensitive, they are otherwise stable and can be stored for many weeks under an inert atmosphere without noticeable degradation (as determined by spectroscopic analysis and chemical reactivity).

Chart 1

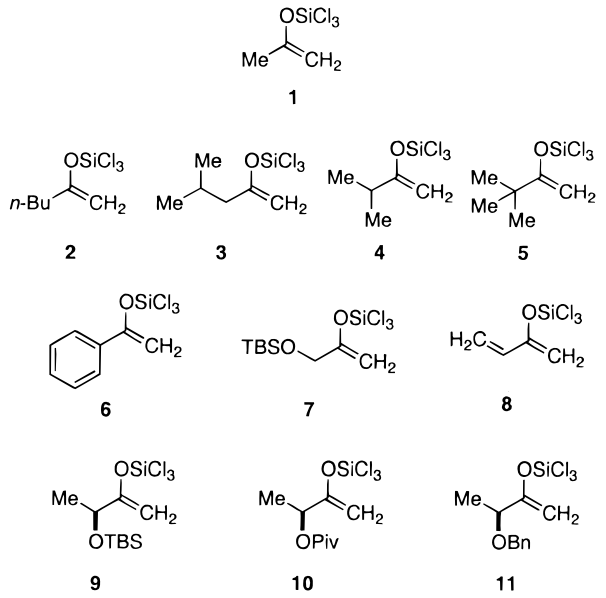
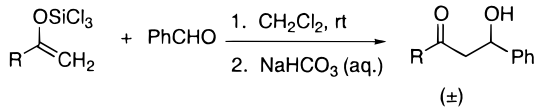


Table 1. Uncatalyzed Aldol Additions of Trichlorosilyl Enolates to Benzaldehyde[a]



entry	enolate	time, h	product	yield,[b] %
1	**1**	4	(±)-**12**	92
2	**2**	4	(±)-**13**	95
3	**3**	4	(±)-**14**	94
4	**4**	5	(±)-**15**	93
5	**6**	4	(±)-**17**	91
6	**7**	6	(±)-**18**	93
7	**8**	6	(±)-**19**	97[c]

[a] Reactions performed at 0.5 M. [b] Analytically pure material. [c] Chromatographically homogeneous material, decomposed after initial purification.

B. Reactions of Achiral Enolates and Achiral Aldehydes. 1. Uncatalyzed Reactions. Initial experiments were carried out to determine the inherent reactivity of these trichlorosilyl enolates with respect to aldehydes. The results, summarized in Table 1, clearly show that the trichlorosilyl enolates **1**−**8** all reacted rapidly with benzaldehyde at ambient temperature in CH_2Cl_2 solution. Standard aqueous workup and purification provided the racemic β-hydroxy ketones in excellent yields as analytically pure compounds. The adduct (±)-**19** derived from methyl vinyl ketone polymerized upon purification. The instability of this product precluded the further use of enolate **8** for subsequent studies.

To examine the scope of the reaction with respect to the aldehyde component, a representative enolate, **2**, was then combined with a variety of acceptors (Chart 2). A marked effect of the aldehyde structure on the rate of the addition was noted (Table 2) in that aliphatic and hindered aldehydes were less reactive. In the extreme, almost no reaction took place with trimethylacetaldehyde (**i**) and after a period of days only the Claisen-Schmidt product was isolated. With the knowledge that these additions could be accelerated by Lewis bases, the reaction was repeated using 10 mol % of HMPA as catalyst, Table 2, entry 7. Now the reaction with **i** proceeded rapidly (1 h) and the aldol adduct (±)-**26** could be isolated in good yield.

Chart 2

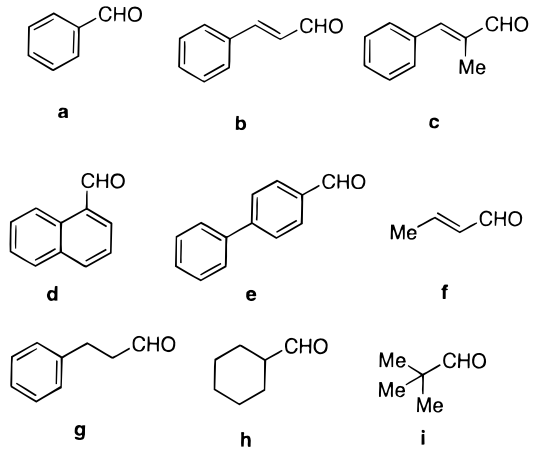
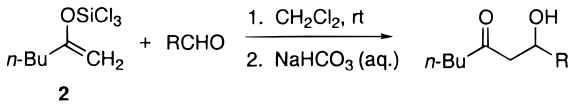


Table 2. Uncatalyzed Aldol Additions of **2**[a]



entry	RCHO	time, h	product	yield,[b] %
1	**b**	7	(±)-**20**	91
2	**c**	14	(±)-**21**	92
3	**d**	4	(±)-**22**	92
4	**e**	4	(±)-**23**	91
5	**g**	12	(±)-**24**	84
6	**h**	9	(±)-**25**	93
7[c]	**i**	1	(±)-**26**	86

[a] Reactions performed at 0.5 M. [b] Analytically pure material. [c] 10 mol % HMPA added.

Although these reactions were found to be sluggish at room temperature, it was nonetheless imperative to determine the extent of uncatalyzed reaction that took place under standard conditions for the catalyzed process. This would provide crucial information for the optimization of the enantioselective, catalyzed reaction by minimizing the competitive (achiral) pathway. Accordingly, enolate **2** was allowed to react with biphenyl carboxaldehyde (**e**) at −78 °C for 2 h (standard conditions for the catalyzed reactions, vide infra), Scheme 1. After isolation and purification, the aldol adduct (±)-**23** was isolated in 4% yield, along with a 95% recovery of the starting aldehyde. Thus, the background reaction is of little concern in this system.

2. Catalyzed Reactions. 2.1. Reaction Optimization. Having established that the methyl ketone trichlorosilyl enolates were viable aldolization reagents in uncatalyzed reactions, we turned

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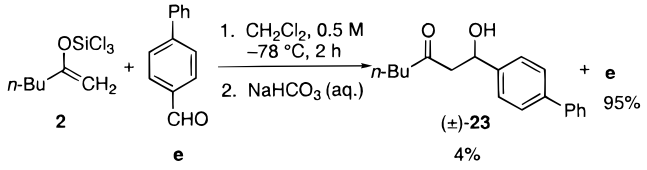
Scheme 1



our attention to additions under the influence of chiral catalysts. On the basis of our previous experience with other trichlorosilyl enolates we surveyed a collection of phosphoramide-based catalysts (Chart 3),[9] in the aldol addition of the acetone-derived trichlorosilyl enolate **1** to benzaldehyde under the standard conditions (10 mol % phosphoramide, 0.1 M in CH_2Cl_2, −78 °C), Table 3. We were pleased to observe that these reactions were highly susceptible to catalysis by the chiral Lewis bases. The results in Table 3 clearly show that the stilbenediamine-derived phosphoramide (*S*,*S*)-**27** was both the most selective catalyst and the most effective in promoting the reaction.[10]

Chart 3

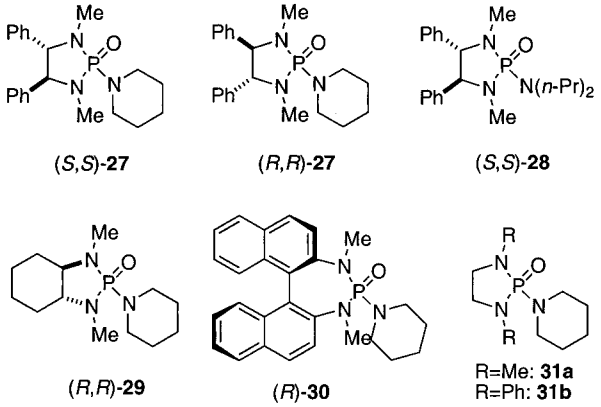
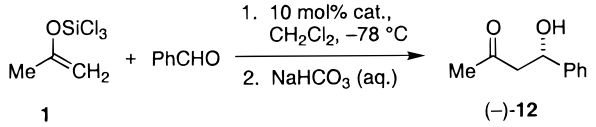


Table 3. Survey of Phosphoramide Catalysts with Enolate **1**[a]

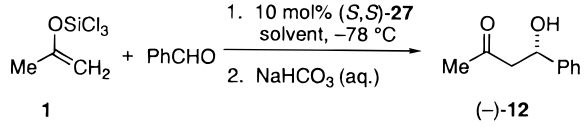


entry	catalyst	er[b]	yield,[c]%
1	(*S*,*S*)-**27**	12.5/1	92
2	(*R*,*R*)-**29**	1/3.31	76
3	(*R*)-**30**	4.29/1	71
4	(*S*,*S*)-**28**	1.70/1	79

[a] Reactions performed at 0.1 M for 2 h. [b] Ratio of the *S*/*R* isomer; determined by CSP HPLC analysis of the dinitrophenyl carbamates. [c] Chromatographically homogeneous material.

The optimization of the aldol addition continued with an investigation of solvent and stoichiometry effects on the same transformation using catalyst (*S*,*S*)-**27**. The solvents selected for study (Table 4) represented a wide spectrum of polarities and donicites, but were obviously limited by the compatibility with the trichlorosilyl enolates.[11] Several trends were apparent from the yields and er values of (−)-**12** in Table 4. First, CH_2Cl_2 was clearly the solvent of choice for this transformation affording both the highest yield and er of all solvents tested. Moving to either more polar or less polar solvent dramatically decreased the enantioselectivity of the process. However, the use of propionitrile did provide the aldol adduct in good, albeit reduced, enantioselectivity relative to CH_2Cl_2. The rate of the reaction (as judged by isolated yield of the aldol adduct) was also attenuated in Et_2O, THF, and toluene, while the use of trichloroethylene and propionitrile still provided good yields of purified aldol adducts.

Table 4. Solvent Effects in Addition of Enolate **1** Catalyzed by (*S*,*S*)-**27**[a]

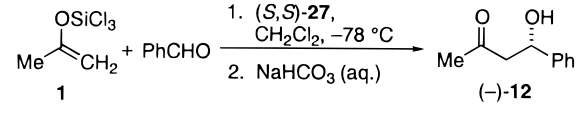


entry	solvent	er[b]	yield,[c] %
1	CH_2Cl_2	12.5/1	92
2	trichloroethylene	4.03/1	88
3	Et_2O	2.25/1	37
4	toluene	1.85/1	48
5	THF	3.37/1	59
6[d]	CH_3CH_2CN	1/8.71	88

[a] Reactions performed at 0.1 M/2 h. [b] Ratio of the *S*/*R* isomer; determined by CSP HPLC analysis of the dinitrophenyl carbamates. [c] Chromatographically homogeneous material. [d] Performed with 10 mol % (*R*,*R*)-**27**.

The influence of both lower temperatures and different catalyst loadings was investigated to improve enantioselectivity (Table 5). Comparison of entries 1−3 in Table 5 reveals that performing the reaction at −90 °C had no beneficial effects, and though there was an increase in selectivity when 20 mol % of the catalyst was used, the difference was not substantial. At the other end, initial experimentation at 1 mol % catalyst loading led to low yields. Increasing the reaction concentration to 0.5 M reduced reaction times to 2 h for consumption of the aldehyde (Table 5, entries 4−8). Whereas the use of 5 mol % catalyst did not alter the selectivity, dropping the loading to 3 mol % and below afforded the adduct with significantly lower enantioselectivity.

Table 5. Effect of Catalyst Loading on Aldol Additions with Enolate **1**[a]



entry	mol % (*S*,*S*)-**27**	concn, M	er[b]	yield,[c] %
1	10	0.1	11.3/1	90
2	10[d]	0.1	9.99/1	89
3	20	0.1	12.3/1	82
4	10[e]	0.5	1/11.7	87
5	5	0.5	11.5/1	88
6	3	0.5	8.60/1	86
7	2	0.5	7.77/1	88
8	1	0.5	5.10/1	92

[a] Reaction time, 2 h. [b] Ratio of the *S*/*R* isomer; determined by CSP HPLC analysis of the dinitrophenyl carbamates. [c] Chromatographically homogeneous material. [d] Reaction performed at −90 °C. [e] Performed with 10 mol % (*R*,*R*)-**27**.

2.2. Survey of Substrates. With optimized conditions in hand, we investigated the effect of substitution on the ketone donor in the catalyzed aldol addition (Table 6).[10] The size and electronic character of the spectator substituent had little role

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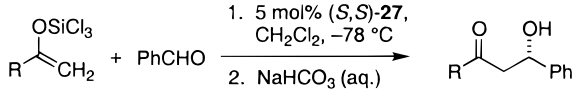
(10) The absolute configuration of adducts **12**−**22**, **24**−**26**, and **43** were assigned by analogy to (−)-**23**, see below.

(11) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988.

in the chemical efficiency of the process; all of the enolates provided high yields of aldol adducts with benzaldehyde. The enantioselectivity of the process, however, was very sensitive to the enolate structure, with larger groups providing lower enantioselectivities, as illustrated by the trend from R = methyl through R = *t*-Bu, (entries 1−5). In addition, a phenyl substituent also led to low enantioselectivity, entry 6. The success of the functionalized enolate (**7**) underscored the important feature that the silyloxy group had no deleterious effect on either the yield or enantioselectivity of the process.

Table 6. Aldol Additions of Trichlorosilyl Enolates to Benzaldehyde Catalyzed by (*S*,*S*)-**27**[a]

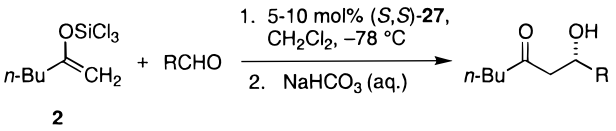


entry	enolate	R	product	er[b]	yield,[c] %
1	**1**	Me	(−)-**12**	14.6/1[d]	98
2	**2**	*n*-Bu	(−)-**13**	12.0/1	98
3	**3**	*i*-Bu	(−)-**14**	10.1/1	95
4	**4**	*i*-Pr	(−)-**15**	9.75/1	97
5	**5**	*t*-Bu	(−)-**16**	3.17/1	95
6	**6**	Ph	(−)-**17**	2.92/1	93
7	**7**	$TBSOCH_2$	(−)-**18**	13.5/1	94

[a] Reactions performed at 0.5 M for 2 h. [b] Ratio of the *S*/*R* isomer; determined by CSP HPLC analysis. [c] Analytically pure material. [d] Determined by CSP HPLC analysis of the dinitrophenyl carbamate.

The generality of the catalyzed reaction was evaluated by combination of the trichlorosilyl enolate of 2-hexanone (**2**) with a variety of aldehydes in the presence of 5−10 mol % of (*S*,*S*)-**27** (Table 7).[10,12] Unsaturated aldehydes reacted quickly and cleanly to provide the corresponding adducts in high enantioselectivity. Initial rates with the branched aldehydes **h** and **i** were disappointing, though further experimentation showed that using 10 mol % of the catalyst and increasing the reaction time to 6 h consistently led to acceptable yields and high enantioselectivities. Unfortunately, unbranched aliphatic aldehydes (such as hydrocinnamaldehyde (**g**)) did not afford aldol products in the catalyzed additions.

Table 7. Aldol Additions of Enolate **2** Catalyzed by (*S*,*S*)-**27**[a]



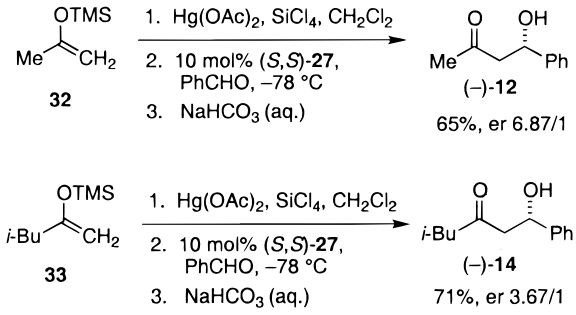
2

entry	RCHO	mol % (*S*,*S*)-**27**	time, h	product	er[b]	yield,[c] %
1	**b**	5	2	(−)-**20**	11.5/1	94
2	**c**	5	2	(−)-**21**	21.7/1	95
3	**d**	5	2	(−)-**22**	13.1/1	92
4	**e**	5	2	(−)-**23**	12.7/1	95
5	**h**	10	6	(−)-**25**	17.5/1[d]	79
6	**i**	10	6	(−)-**26**	24.0/1[d]	81

[a] Reactions performed at 0.5 M. [b] Ratio of the *S*/*R* isomer; determined by CSP HPLC analysis. [c] Analytically pure material. [d] Determined by CSP HPLC analysis of the dinitrophenyl carbamate.

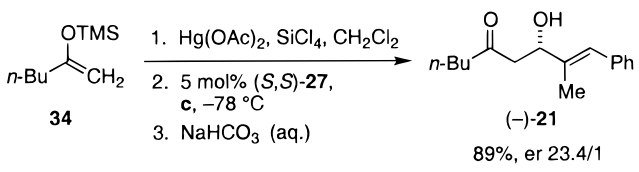
2.3. Development of Conditions for in Situ Generation and Reaction of Trichlorosilyl Enolates. The high chemical yields and enantioselectivities associated with the catalyzed reactions of trichlorosilyl enolates provided the motivation to develop a more practical protocol for the preparation and handling of these reactive species. The mercury(II)-catalyzed trans-silylation of the trimethylsilyl enol ethers with $SiCl_4$ provided an ideal opportunity to engineer a "one-pot" method for the generation and reaction of the enolates. For this process to be successful we had to determine if the mercury(II) salts and excess $SiCl_4$ would interfere with the subsequent aldolization. These questions were first addressed by the use of a minimal loading (1 mol %) of $Hg(OAc)_2$ and only 1 equiv of $SiCl_4$ (sub-optimal for formation of the desired mono(enoxy)trichlorosilanes[8a]). Treatment of the TMS enol ether of acetone (**32**) under these conditions (to form enolate **1**) followed by cooling and addition of the catalyst and benzaldehyde provided a 65% yield of the adduct with moderate enantioselectivity (er 6.87/1, compared to 14.6/1), Scheme 2. A similar protocol starting with the TMS enol ether of methyl isobutyl ketone (**33**) provided higher yield (71%) though even further reduction in enantioselectivity relative to the case with preformed enolate (er 3.67/1, compared to 9.75/1).

Scheme 2



The overall process was measurably improved if an additional step, namely removal of the volatiles (presumably only CH_2Cl_2, $SiCl_4$, and TMSCl), was incorporated into the reaction protocol. Initial experiments employing the standard stoichiometry (1.1 equiv of TMS enol ether **34**, 2.2 equiv of $SiCl_4$, 1.0 equiv of α-methylcinnamaldehyde (**c**), and 5 mol % of (*S*,*S*)-**27**) provided the adduct (−)-**21** in 75% yield with high enantioselectivity. As the low yield was probably due to the formation of unreactive bis(enoxy)dichlorosilane, excess TMS enol ether was employed in a subsequent experiment, Scheme 3. When 1.3 equiv of **34** were used, 89% yield of the adduct (−)-**21** was obtained, with excellent enantioselectivity (er 23.4/1, compared to 21.7/1) thus demonstrating that such in situ reactions can indeed be carried out without problem if the enol ether can be used in slight excess.

Scheme 3

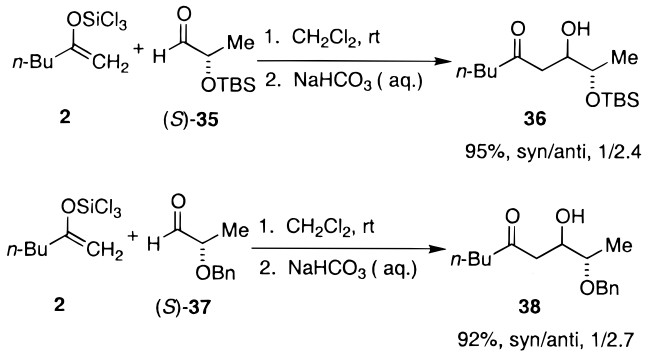


C. Reactions of Achiral Enolates and Chiral Aldehydes. 1. Uncatalyzed Reactions. To extend this technology to more synthetically interesting (and challenging) substrates, we pursued the reactions of simple trichlorosilyl enolates of methyl ketones with the chiral aldehydes (*S*)-**35**[13] and (*S*)-**37**,[14] Scheme 4.[15] In orienting experiments, uncatalyzed reactions with the TBS-

(12) The absolute configuration of (−)-**23** was determined by single-crystal X-ray analysis of the corresponding 4-bromobenzoate. The crystal structure data have been deposited in the Cambridge Crystallographic Data Center as supporting publication 111714. All other adducts were assigned by analogy.

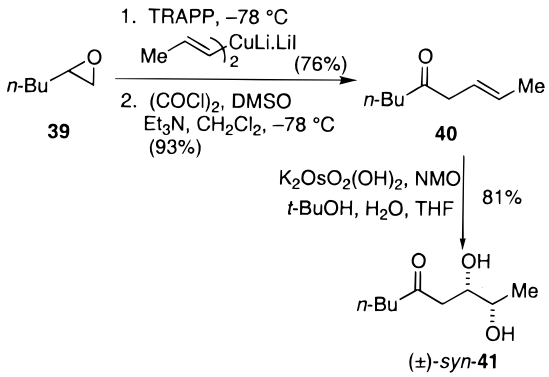
protected aldehyde (*S*)-**35** and enolate **2** in various solvents at 0.5 M afforded only modest yield and stereoselectivity (for determination of relative configuration, see below).[16] Side reactions, particularly elimination, over the long reaction times required for the aldolization, appeared to be a major contributor to the low yields of these reactions. Performing the reaction at higher concentration (1 M) alleviated these problems by shortening reaction times (5 h) and thus providing an excellent yield of the aldol adducts **36** as a mixture of diastereomers (syn/anti, 1/2.4), Scheme 4. The benzyloxy aldehyde (*S*)-**37** responded similarly under these conditions, affording a high yield and low (syn/anti, 1/2.7) diastereoselectivity.

Scheme 4



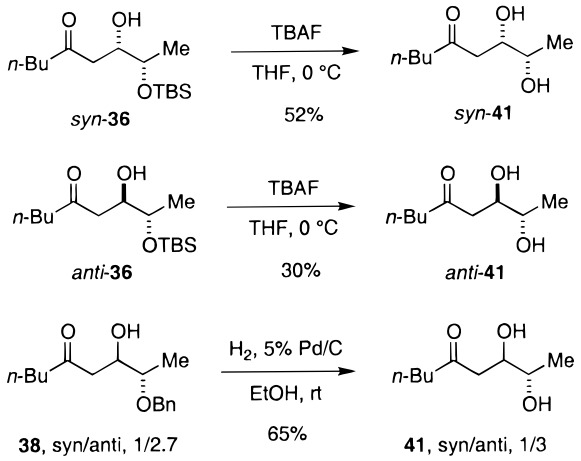
1.1. Determination of Relative Configuration. The relative configuration of adducts **36** and **38** was assigned by correlation to (±)-*syn*-**41**, synthesized unambiguously by the OsO_4-catalyzed dihydroxylation of the corresponding alkene (*E*)-**40**, Scheme 5. Addition of a cuprate derived from (*E*)-1-propenyllithium[17] to 1-hexene oxide (**39**)[18] led to the desired alcohol in 76% yield. Swern oxidation,[19] followed by dihydroxylation, provided authentic (±)-*syn*-**41**, which could be compared to the (deprotected) products from the aldol additions, vide infra.

Scheme 5



Deprotection of diastereomerically pure[20] adducts **36** (to compare with the authentic (±)-*syn*-**41**) was hampered by the sensitivity of the substrates: acidic media led to retro-aldolization, while basic media led to elimination. However, the use of 1 equiv of TBAF in THF at 0 °C, in combination with careful monitoring of the reaction, led to modest yields of the diastereomerically pure diols *syn*-**41** and *anti*-**41**, Scheme 6. Deprotection of the benzyloxy adduct **38** (as a 1/2.7 mixture of diastereomers) by hydrogenolysis then provided a mixture of diols **41** (syn/anti, 1/3), as correlated to the above materials.

Scheme 6



2. Catalyzed Reaction. 2.1. Catalyst Survey. Although aldehydes (*S*)-**35** and (*S*)-**37** have been used extensively in double diastereoselective aldol additions,[15] the lack of precedent in these new aldol processes prompted us to survey catalyst structure broadly to establish if the phosphoramide could control the facial selectivity of addition, regardless of the inherent bias in the aldehyde. The results of an initial study with enolate **2** and the silyloxy aldehyde (*S*)-**35** are collected in Table 8. The yields of these catalyzed reactions were modest. However, while HMPA and (*R*)-**30** were rather unselective, a number of the reactions proceeded with high anti-diastereoselectivity. Interestingly, the achiral phosphoramide **31b** provided moderate levels of stereoselection, suggesting that the intrinsic selectivity due to the aldehyde was not insignificant. Once again, the stilbenediamine-derived phosphoramide **27** provided the most interesting results. Whereas (*S*,*S*)-**27** provided only a weak syn-preference, the use of (*R*,*R*)-**27** provided very high (>15/1) levels of anti-selectivity, though still in modest yield. Changing the solvent (entries 7−9) did not improve the yield or selectivity.

Attempts to optimize the yield of this highly diastereoselective aldol addition focused on those variations which were beneficial in related additions of trichlorosilyl enolates. These included slow addition of aldehyde (known to suppress unfavorable monophosphoramide-catalyzed pathways[2d,4]), inclusion of 1.2 equiv of tetrabutylammonium triflate (known to increase the rate of the catalyzed reaction[5a]), higher temperature, excess enolate, and higher (25 mol %) catalyst loading. All attempts provided only modest yield (35−45%), accompanied by roughly

(13) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180−5182.

(14) Solladié-Cavallo, A.; Bonne, F. *Tetrahedron: Asymmetry* **1996**, *7*, 171−180.

(15) For previous studies on the diastereoselective addition of simple achiral methyl ketone enolates to chiral α-oxygenated aldehydes see: (a) Gennari, C. In *Comprehensive Organic Synthesis, Vol. 2, Additions to C−X π Bonds, Part 2*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; pp 639−647. (b) Braun, M. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, E21 ed.; Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3, pp 1713−1722. (c) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 693−700. (d) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027−3037. (e) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361.

(16) Selected results: Et_2O, 59% yield, syn/anti 1/2; toluene, 66% yield, syn/anti 1/2; hexane, 31% yield, syn/anti 1/2.

(17) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839−4842.

(18) Tang, P. W.; Williams, J. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1199−1203.

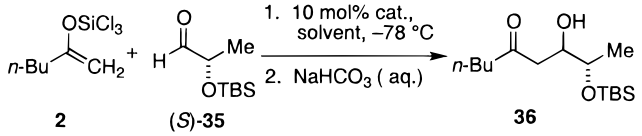
(19) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572.

(20) Though inseparable by simple column chromatography, pure samples of *syn*-**36** and *anti*-**36** were available from repeated preparative HPLC, see Supporting Information for details.

30% of recovered aldehyde; the balance of the material could not be identified. Although enolization is perhaps the most likely explanation, in one experiment, the recovered aldehyde was still enantiomerically enriched suggesting that aldehyde enolization may not be the only problem.

The benzyloxy aldehyde (*S*)-**37** was examined as well in a more limited survey. As was the case with (*S*)-**35**, the yields obtained were modest and the selectivity trends closely mirrored the results with the silyloxy aldehyde. Although the selectivity provided by (*S*,*S*)-**27** (mismatched case) was higher than that with the silyloxy aldehyde (*S*)-**35** above (syn/anti 4/1 vs 2/1), the matched case catalyzed by (*R*,*R*)-**27** was not as selective as that previously observed with the TBS derivative (syn/anti, 1/6 vs 1/15.6).

Table 8. Catalyzed Aldol Additions with Aldehyde (*S*)-**35**[a]



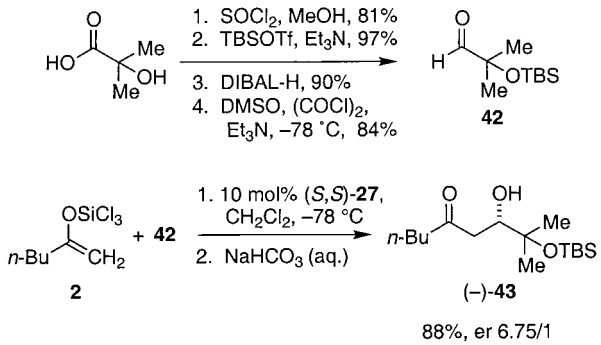
2 (*S*)-**35** **36**

entry	catalyst	solvent	syn/anti[b]	yield,[c] %
1	HMPA	CH_2Cl_2	1/1.3	41
2	**31b**	CH_2Cl_2	1/6.7	37
3	(*R*,*R*)-**29**	CH_2Cl_2	1/10.1	51
4	(*R*)-**30**	CH_2Cl_2	1/1.8	54
5	(*S*,*S*)-**27**	CH_2Cl_2	2.7/1	47
6	(*R*,*R*)-**27**	CH_2Cl_2	1/15.6	50
7	(*R*,*R*)-**27**	Et_2O	1/9.0	45
8	(*R*,*R*)-**27**	toluene	1/6.7	40
9	(*R*,*R*)-**27**	CH_3CH_2CN	1/11.5	43

[a] Reactions performed at 0.5 M for 6 h. [b] Determined by GC analysis. [c] Chromatographically homogeneous material.

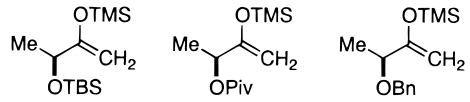
2.2. Test of α-Oxygen. To gain insight into the cause of the moderate yields for catalyzed additions to (*S*)-**35** and (*S*)-**37**, a test substrate was designed to determine if the oxygen substituent on the aldehyde acceptor was inherently problematic, or if the α-hydrogen was the culprit. To this end, the tertiary silyloxy aldehyde **42** was synthesized in four steps from 2-hydroxy-2-methylpropanoic acid, Scheme 7. This material proved to be a very capable substrate in the aldol addition of enolate **2** catalyzed by 10 mol % of (*S*,*S*)-**27**, and provided the corresponding aldol adduct (−)-**43**,[10] in 88% yield with a good enantiomeric ratio (6.75/1), Scheme 7. Clearly, the presence of oxygen functionality on the acceptor is not detrimental to the operation of the phosphoramide-catalyzed aldol addition, though selectivity was attenuated relative to the all carbon analogue (er 6.75/1 compared to 24.0/1, Table 7, entry 6).

Scheme 7



D. Reactions of Chiral Enolates and Achiral Aldehydes. To further explore the synthetic utility of methyl-ketone derived trichlorosilyl enolates, the aldol addition of chiral enolates to achiral aldehydes was investigated.[21] Whereas orienting studies with these enolates were conducted with isolated, distilled compounds **9**−**11** (Chart 1), all of the preparative experiments described below were performed with enolates that were prepared and used in situ starting from the corresponding TMS enol ethers **44**−**46**, Chart 4. As mentioned previously, the formation of bis(enoxy)dichlorosilanes in the mercury-catalyzed trans-silylation reaction leads to low yield of the aldol adduct unless excess TMS enol ether is employed. However, in the cases at hand, the enol donor should be considered precious and therefore used as the limiting reagent. Hence, all of the in situ reactions with chiral ketone enolates were performed with equivalent amounts of TMS enol ether and aldehyde.

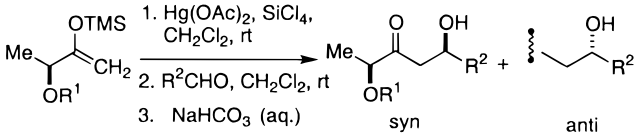
Chart 4



44 **45** **46**

1. Uncatalyzed Reactions. The addition of the oxygenated enolates to benzaldehyde proceeded in good yield with weak anti-selectivity (for determination of relative configuration, see below), Table 9. A modest dependence of selectivity on the O-protecting group was noted; the smaller group on the enolate (Bn > Piv > TBS) provided higher anti-selectivity in combination with benzaldehyde (entries 1−3). When other aldehyde acceptors were investigated (entries 4−6) the yields were generally lower, especially for the reaction with hydrocinnamaldehyde, where elimination under the reaction conditions again seemed to be problematic. In addition, only slight diastereoselectivity was observed though perhaps this is not surprising given the very low diastereoselectivity observed with the TBS substrate **44** and benzaldehyde. Interestingly, crotonaldehyde (**f**) provided slight syn-selectivity in this reaction, unlike other substrates investigated.

Table 9. Uncatalyzed Aldol Additions of Trichlorosilyl Enolates Generated in Situ[a]



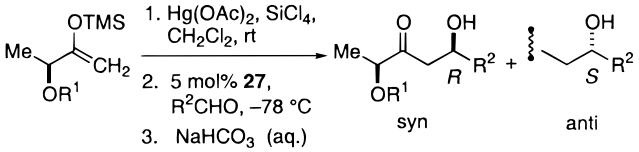
entry	R^1	enol	R^2CHO	products	syn/anti[b]	yield,[c] %
1	TBS	**44**	PhCHO	**47**	1/1.2[d]	82
2	Piv	**45**	PhCHO	**48**	1/2.4	71
3	Bn	**46**	PhCHO	**49**	1/3.4	75
4	TBS	**44**	**g**	**50**	1/1	35
5	TBS	**44**	**h**	**51**	1/3	55
6	TBS	**44**	**f**	**52**	2.3/1[e]	66

[a] Conditions: (1) 1 mol % of $Hg(OAc)_2$/2 equiv of $SiCl_4$/1 M/1 h. (2) Reactions performed at 1 M. [b] Determined by ^1H NMR analysis. [c] Analytically pure material. [d] Determined by CSP SFC analysis. [e] Determined by CSP SFC analysis of the benzoates.

2. Catalyzed Reactions. The rate and diastereoselectivity of the additions in the presence of phosphoramides **31a**, (*S*,*S*)-**27**, and (*R*,*R*)-**27** were investigated next, Table 10. Achiral catalyst **31a** served to establish the internal[22] diastereofacial selectivity in the catalyzed process. This reaction proceeded smoothly with 5 mol % of **31a** to provide **47** with a modest syn preference (1.2/1) and in good yield. With 5 mol % of catalyst (*S*,*S*)-**27**

the reactions were rapid and provided good yields of adducts but the diastereoselectivity of the process was low, marginally favoring the syn diastereomer. Because catalyst (*S*,*S*)-**27** typically provides aldol adducts with the *S*-configuration at the hydroxyl-bearing center (opposite to that found in the major syn-diastereomer) it was not surprising that the selectivity was attenuated compared to that obtained from **31a**. Moreover, it was reasonable to suspect that use of (*R*,*R*)-**27** as catalyst would provide higher syn-selectivities in an overall matched case of double diastereoselection. This was indeed found to be the case (entries 5−8); good to excellent syn-diastereoselectivity was observed. The TBS-protected enol ether **44** provided the adducts in the highest yield (85%) and selectivity (73/1 syn/anti).

Table 10. Catalyzed Additions of Trichlorosilyl Enolates Generated in Situ Using (*S*,*S*)-**27**[a]

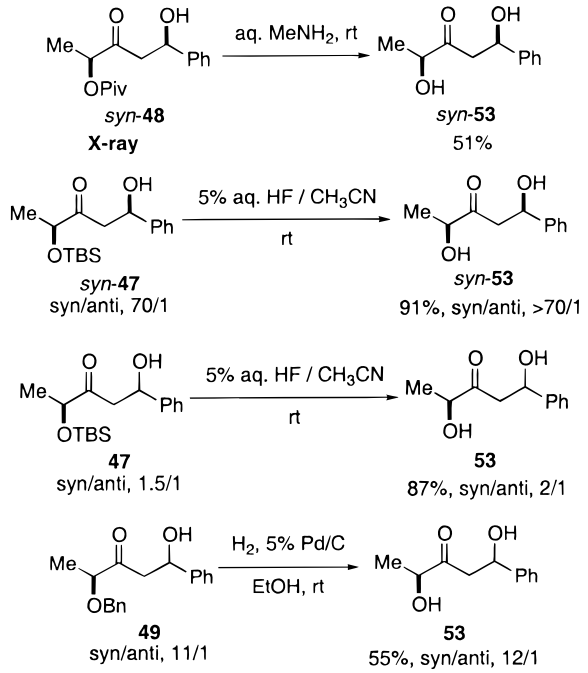


entry	R^1	enol	aldehyde	catalyst	products	syn/anti[b]	yield,[c] %
1	TBS	**44**	PhCHO	**31a**[d]	**47**	1.2/1	81
2	TBS	**44**	PhCHO	(*S*,*S*)-**27**	**47**	1.5/1[e]	85
3	Piv	**45**	PhCHO	(*S*,*S*)-**27**	**48**	3.4/1	78
4	Bn	**46**	PhCHO	(*S*,*S*)-**27**	**49**	1/1.1	78
5	TBS	**44**	**f**	(*S*,*S*)-**27**	**52**	1.3/1[f]	80
6	TBS	**44**	PhCHO	(*R*,*R*)-**27**	**47**	73/1[e]	85
7	Piv	**45**	PhCHO	(*R*,*R*)-**27**	**48**	20/1	78
8	Bn	**46**	PhCHO	(*R*,*R*)-**27**	**49**	11/1	77
9	TBS	**44**	**f**	(*R*,*R*)-**27**	**52**	6.2/1[f]	81

[a] Conditions: (1) 1 mol % of $Hg(OAc)_2$/2 equiv of $SiCl_4$/1 M/1 h. (2) Reactions performed at 0.5 M for 2 h. [b] Determined by ^1H NMR analysis. [c] Chromatographically homogeneous material. [d] 5 mol % of catalyst employed at 0.1 M for 4.5 h. [e] Determined by CSP SFC analysis. [f] Determined by CSP SFC analysis of the benzoates.

3. Determination of Relative Configuration. The relative configuration of the pivaloate **48** was established by crystallizing a sample (obtained from the reaction catalyzed by (*R*,*R*)-**27**, initial dr 20/1) to diastereomeric purity, followed by single-crystal X-ray analysis.[23] Diastereomerically pure *syn*-**48** was then deprotected with aqueous methylamine in methanol to provide pure *syn*-**53** in modest yield, Scheme 8. The major diastereomer (dr 70/1) from the reaction of **44** with benzaldehyde in the presence of the (*R*,*R*)-**27** catalyst was then deprotected with aqueous HF in acetonitrile to also give *syn*-**53** (as compared to the above material by TLC and ^1H NMR analysis) in high yield as essentially one diastereomer. In addition, a 1.5/1 mixture of diastereomers **47** (obtained from the reaction catalyzed by (*S*,*S*)-**27**) was similarly deprotected to give a 2/1 mixture of syn- and anti-diols **53**. Finally, the relative configurations of the benzyloxy adducts **49** were determined by hydrogenolytic deprotection of an 11/1 mixture

Scheme 8



of diastereomers (from the reaction catalyzed by (*R*,*R*)-**27**) which provided a 12/1 mixture of diols *syn*- and *anti*-**53** in moderate yield.

Discussion

A. Uncatalyzed Reactions. 1. Reactivity Trends. The reactivity of trichlorosilyl enolates and the mechanism of their direct aldolization is believed to involve initial coordination of the aldehyde to the Lewis acidic silicon center forming a trigonal bipyramidal (tbp) silicon species.[1a,2d,e,4] It has been suggested[24] (and demonstrated computationally[25]) that such associative aldol additions of enoxysilanes undergo carbon−carbon bond formation through a closed transition structure that resembles a boat. In the absence of obvious steric interactions in either the boat or chairlike arrangements, the underlying reasons for the preference for tbp silicon enolates to react preferentially through a boatlike structure are unclear. Although many factors (O−M−O bond angles, M−O bond lengths, overall coordination geometry around M, spectator ligands on M, and substitution pattern on enol donor)[26] have been implicated in the relative stability of chair- and boatlike transition structures involving metal enolates, there seem to be no clear-cut rules governing such predictions a priori. As the present additions involve α-unsubstituted enolates, there is no stereochemical reporter

(21) For previous studies on the diastereoselective addition of simple chiral methyl ketone enols to aldehydes, see: (a) Seebach, D.; Ehrig, V.; Teschner, M. *Liebigs Ann. Chem.* **1976**, 1357−1369. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111. (c) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290−2300. (d) Lagu, B. R.; Crane, H. M.; Liotta, D. C. *J. Org. Chem.* **1993**, *58*, 4191−4193. (e) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121−7124. (f) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982−3983. (g) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3447−3450.

(22) For a definition of these terms see: Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10.

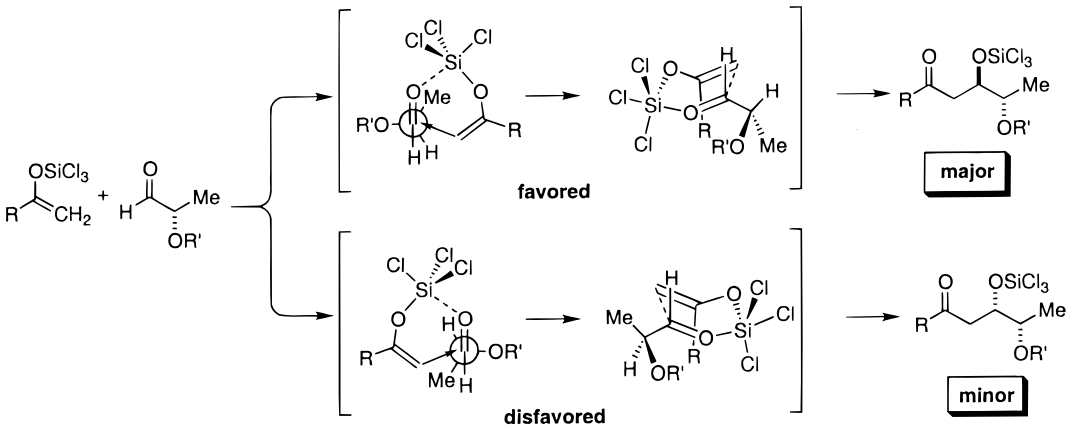
(23) The crystal structure of (+)-*syn*-**48** has been deposited in the Cambridge Crystallographic Data Center as supplemental publication CCDC 111712.

(24) See refs 1a, 2d, 2e, and 4. The reactions of enoxysilacyclobutanes are also thought to proceed through boatlike transition structures involving tbp silicon species, see: (a) Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922−7923. (b) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026−7043.

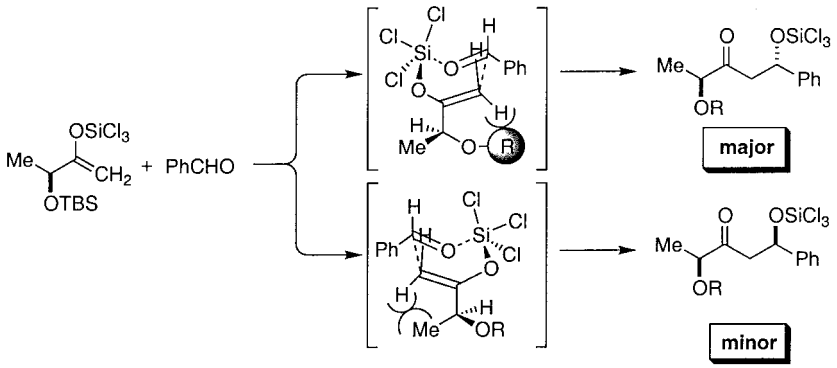
(25) Gung, B. W.; Zhu, Z.; Fouch, R. A. *J. Org. Chem.* **1995**, *60*, 2860−2864. See also ref 22b.

(26) (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975−3978. (b) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343−3346. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (d) Hoffmann, R. W.; Ditrich, K.; Froech, S. *Tetrahedron* **1985**, *41*, 5517−5524. (e) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471−3484. (f) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481−493.

Scheme 9



Scheme 10



group that can provide information about the relative topicity of bond formation. Thus, little direct speculation can be made about the nature of the transition structure. However given the ample precedent for boatlike structures in related systems it seems reasonable to consider such assemblies in these additions as well.

All of the achiral enolates reacted cleanly with a wide selection of aldehydes, though the reaction rate was retarded with increasing branching of the aldehyde partner. In addition, conjugated aldehydes (aromatic and olefinic) were generally more reactive than aliphatic aldehydes, presumably due both to their smaller size and higher Lewis basicity.[27] The 2-hexanone-derived enolate **2** also added cleanly to the α-oxygenated aldehydes (*S*)-**35** and (*S*)-**37** in uncatalyzed reactions, though the stereoselectivity of the process was low, favoring the anti-isomer. In addition, it was found that the aldol additions proceeded cleanly and without retardation when performed with enolates formed in situ from the corresponding TMS enol ether via the mercury-catalyzed trans-silylation reaction. Apparently the presence of the mercury(II) species has little if any effect on the uncatalyzed aldolization.

2. Stereoselection. In the uncatalyzed additions of achiral enolates to chiral, α-oxygenated aldehydes, a definitive analysis of the stereoselection process is difficult due to the small energy differences involved ($\Delta\Delta G^{\ddagger}$(298 K) = 0.5 kcal for 2.4−2.7/1, anti/syn). However, if boatlike transition structures are considered and if the aldehyde is assumed to exist in a conformation such that the oxygen is anti to the incoming nucleophile, as suggested by the Heathcock modification[15e] of the Felkin-Ahn model, then addition of the enolate to the sterically more accessible face would provide the observed anti-diastereomer, Scheme 9.[28]

It seems that the stereoelectronic preferences of the oxygen atom on the acceptor dominates the stereochemistry-determining event, as both silyloxy and benzyloxy substrates provided similar results, despite their vastly different steric profiles and coordinating abilities.[29] This result is in line with Heathcock's analysis for nonchelation controlled additions wherein electronic, rather than steric, interactions dominate the reactive conformation of simple α-oxygenated aldehydes.[15e]

Chiral methyl ketone enolates **9**−**11** were only weakly diastereoselective in uncatalyzed reactions. Note that in these additions the nature of the oxygen substituent did appear to play a small role in stereoselection, with OTBS being unselective, while OPiv and OBn were slightly anti-selective (Table 9). Such modest changes in selectivity should be interpreted with extreme caution. One simple explanation for this trend invokes a conformation wherein the oxygenated substituent eclipses the enol double bond to minimize dipoles.[30] In this conformation, the anti-diastereomer would be formed by attack of the less hindered face of the enolate on the aldehyde through a boatlike

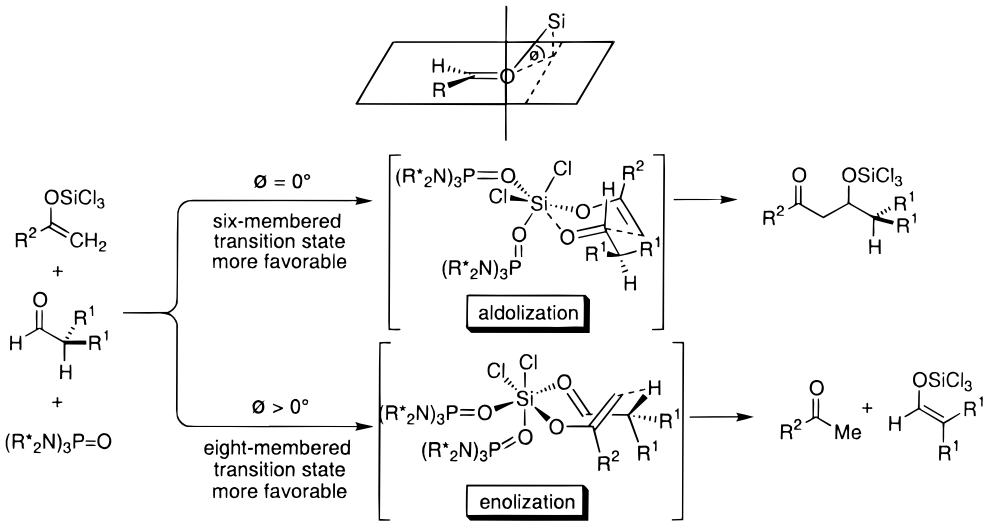
(27) Based on the enthalpy of formation of aldehyde−BF_3 complexes, see: Maria, P.-C.; Gal, J.-F. *J. Phys. Chem.* **1985**, *89*, 1296−1304.

(28) A referee has suggested that chair-like structures should be considered as well. Although we cannot a priori exclude such structures because of the absence of a stereochemical marker, our previous studies on uncatalyzed reactions with *E*-configured enolates (ref 4) reveal an overwhelming (albeit not exclusive) preference for reaction via boatlike structures. Insofar as overriding steric interactions are unlikely to differentiate unsubstituted from *E*-enolates we feel confident in this assumption.

(29) For a thorough discussion of the effects of α-heteroatom substituents on the stereochemical course of addition to aldehydes see: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569. (b) Reetz, M. T. *Acc. Chem Res.* **1993**, *26*, 462−468. (c) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162.

(30) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200.

Scheme 11



transition structure, Scheme 10. By changing the nature of the oxygen substituent (size, hyperconjugative ability, chelating potential (see below)) the energetic cost of placing it in an eclipsing position may become higher, thus allowing an electronically less favorable reactive conformation, with the methyl group eclipsed, to compete, lowering the facial selectivity of attack on the enolate.

B. Catalyzed Reactions. 1. Reactivity Trends. The mechanism of the phosphoramide-catalyzed aldol additions of trichlorosilyl enolates is the subject of an extensive, ongoing investigation. For the purposes of the immediate discussion, we assume that the reaction pathway for the methyl ketones described herein is the same as for the substituted enolates that are the subject of the mechanistic studies.[1a,3d,4,5] At the current level of understanding, the dominant catalyzed pathway involves the intermediacy of a cationic, diphosphoramide silyl enolate complex, which, upon binding an aldehyde, reacts through a chairlike transition structure organized around a hexacoordinate silicon species. Furthermore, a second pathway, which is typically less facially selective, involves a cationic monophosphoramide species wherein the transition structure resembles a boat, organized around a cationic, pentacoordinate silicon center. This second pathway can contribute significantly in reactions catalyzed by bulky phosphoramides and/or at low catalyst loading. A more detailed analysis of the mechanism of this reaction (specifically with regard to cyclic ketone enolates) including the relative stability of chair- and boatlike transition structures for both tbp and octahedral siliconate arrangements will be the subject of an upcoming report.[31]

Although the selectivities of the reactions with chiral aldehydes were often high, the yields of the processes were low. This was the case regardless of the protecting group used and did not change over a range of reaction conditions. A control experiment with the TBS-protected, quaternary aldehyde **42** demonstrated that neither oxygenation nor silyl-protection in the α-position of the aldehyde acceptor was harmful to the overall efficiency of the catalyzed pathway, though the selectivity obtained was rather low. Because of this, and the previous problems with enolizable aldehydes,[4] it is reasonable to conclude that at least some of the problem is due to enolization and trichlorosilyl-group transfer. However, as the aldehyde that was recovered from one of the catalytic reactions was still enantiomerically enriched, stoichiometric enolization of the aldehyde can be ruled out. A more likely scenario is that enolization does take place and the resulting mixture inhibits the reaction either through catalyst destruction or by interfering with catalyst turnover.[32]

The successful catalyzed aldolization with cyclohexanecarboxaldehyde and the less than satisfactory results with chiral aldehydes (in addition to the wholly unsuccessful catalytic additions to hydrocinnamaldehyde) highlight the dramatic substrate dependence on the proposed enolization. This apparent inconsistency may be rationalized by proposing that enolization intercedes as a shunt from a structurally similar transition structure. We suggest that enolization, like aldolization, requires dual activation of the enolate and the aldehyde and that enolization can only occur via a closed, eight-membered transition structure, Scheme 11. Such a reactive conformation is unfavorable if purely σ-complexation ($\phi = 0°$) of the aldehyde (i.e. antiperiplanar to the aldehyde residue) to the silicon is assumed. However, if the complexation is allowed to be looser and the silicon slips to an anticlinal orientation relative to the aldehyde residue ($\phi > 0°$, e.g., 20−30°), such an eight-membered-ring transition structure is feasible and perhaps favorable. It hardly seems unreasonable that subtle differences in the structure of the aldehyde or enolate could lead to small changes in the conformation of the aldehyde/enolate complex such that the relative energy barriers for enolization or aldolization are altered.[32b]

2. Stereoselection. 2.1. Achiral Enolates and Achiral Aldehydes. The catalyzed reactions involving achiral substrates proceeded with moderate to high enantioselectivity when the stilbenediamine-derived phosphoramide (*S*,*S*)-**27** was used. Other phosphoramide structures were markedly less selective, as was also true in the related reactions of trichlorosilyl enolates of cyclic ketones where both diastereo- and enantioselectivity were low.[4] The opposite absolute configuration of adducts provided by cyclohexanediamine catalyst (*R*,*R*)-**29** was expected

(31) Denmark, S. E.; Su, X.; Wong, K.-T.; Nishigaichi, Y.; Stavenger, R. A.; Pham, S. M. Manuscript in preparation.

(32) (a) We have recently noticed that both aldehydes and ketones are converted to trichlorosilyl enolates in the presence of $SiCl_4$ and phosphoramides without the need for added base. This implies that the generation of HCl is thermodynamically favorable. If this also occurs with the chiral aldehydes, trichlorosilyl enolates, and phosphoramides at a rate competitive with aldolization, then only a small amount of HCl needs to be generated to inhibit the catalyst. (b) Preliminary experiments suggest that $SiCl_4$ can form adducts of aliphatic aldehydes in the presence of phosphoramides. This might also constitute a explanation for the failure of these substrates to react. T. Wynn, unpublished observations from these laboratories.

as this catalyst is enantiomorphic to both phosphoramides (*R*)-**30** and (*S*,*S*)-**27**.

Unfortunately, it is difficult to draw useful transition structures to explain the absolute stereoselection process for these catalyzed aldol additions. In addition to the obvious difficulties of drawing conclusions on the basis of a single stereochemical observable (enantioselectivity), the sheer size and complexity of the system makes a fundamental analysis challenging. Issues that must be addressed before proposing reasonable transition structures include (but are not limited to) the following: multiple configurations around a (chiral) octahedral silicon center; order and timing of Lewis base (phosphoramide *and* aldehyde) complexation to silicon; conformational freedom of rotation about the presumed phosphoryl oxygen−silicon bonds; and timing of C−C bond formation (i.e., determining the stereochemistry determining step). These considerations must be resolved before embarking on an analysis of the traditional aldol problems involving sets of boatlike and chairlike transition structures leading to the observed products. While we have made preliminary attempts to tackle these questions computationally, we quickly realized that the magnitude of the problem surpassed our current capabilities. Indeed, analysis of simple molecular models reveals the vast number of potential configurations and conformations of the proposed *quaternary* molecular assembly and the task becomes clear and daunting.

It should be noted that the apparent facial selectivities (er) of the methyl ketone enolate additions are slightly lower than the facial selectivities (er of the adduct arising from a di-phosphoramide (chairlike) transition structure) of the reactions of cyclic ketone enolates. This lower enantioselectivity observed with some of the substrates (particularly acetophenone) was somewhat surprising, especially given the excellent enantioselectivities obtained with the propiophenone-derived enolate.[4] However, it is important to recognize that changes in the relative diastereoselection processes (i.e. chairlike vs boatlike transition structures) can manifest themselves in the enantioselectivity of the reaction if the change in relative topicity is due to a change at the face of the aldehyde.[33] Although modest diastereoselectivity was obtained with the propiophenone enolate, the dr was highly dependent on catalyst loading. It is perhaps not surprising that lower enantioselectivity was observed with the acetophenone-derived enolate **6**, arising not from poor facial selectivity in the competing chairlike transition structures but from lesser differentiation of competing chair and boat structures. An explanation for the low selectivity observed with the pinacolone-derived enolate **5** is less clear and may be due either to a chair-boat selection problem, as above, or to inherently lower facial selectivity arising from the steric bulk of the enolate.

The observation that the product er decreases with decreasing catalyst loading is consistent with a change in relative rates of the two reaction pathways, and is not ascribable to intervention of an uncatalyzed, racemic pathway.[34] In the case of the cyclohexanone enolate, lowering catalyst loading decreases the diastereoselectivity, but not the enantiomeric composition of the diastereomers. The implication is clear; with less catalyst the same process that impacts the relative stereoselection process for the cyclohexanone enolate (chairlike versus boatlike transition structures) also causes the erosion of the enantioselectivity in the present case. As catalyst loading drops the rate of the di-phosphoramide pathway (chairlike) decreases as the square of the concentration, while the mono-phosphoramide pathway (boatlike) drops linearly. With methyl ketone enolates, these two pathways retain the same topicity at the enol faces, but change the face of the aldehyde being attacked. From the results in Table 5 it can be concluded that at loadings from 1 to 5 mol %, both mono- and di-phosphoramide pathways are operative, while at loadings above 5 mol %, only the di-phosphoramide pathway is operative and the constant er from 5 to 20 mol % represents the energy difference between competing hexacoordinate, chairlike transition structures.

Not surprisingly, in view of the cationic nature of the reactive silicon intermediates, the reaction medium had a dramatic effect on the selectivity of the overall process. Dichloromethane and propionitrile were the only solvents truly suited for the reaction.

The in situ formation and use of enolate **2** demonstrated that the presence of a small amount of mercury salts had no effect on the stereoselectivity of the aldolization catalyzed by (*S*,*S*)-**27** (compare Scheme 3 and Table 7, entry 2). In contrast, when the reaction was performed without intermediate removal of the $SiCl_4$ and TMSCl (with enol ethers **32** and **33**, Scheme 2) much lower yields and attenuated enantioselectivities were observed. Fortunately, the additional manipulation of reagent removal is neither time-consuming nor challenging when nonvolatile enolates are used.

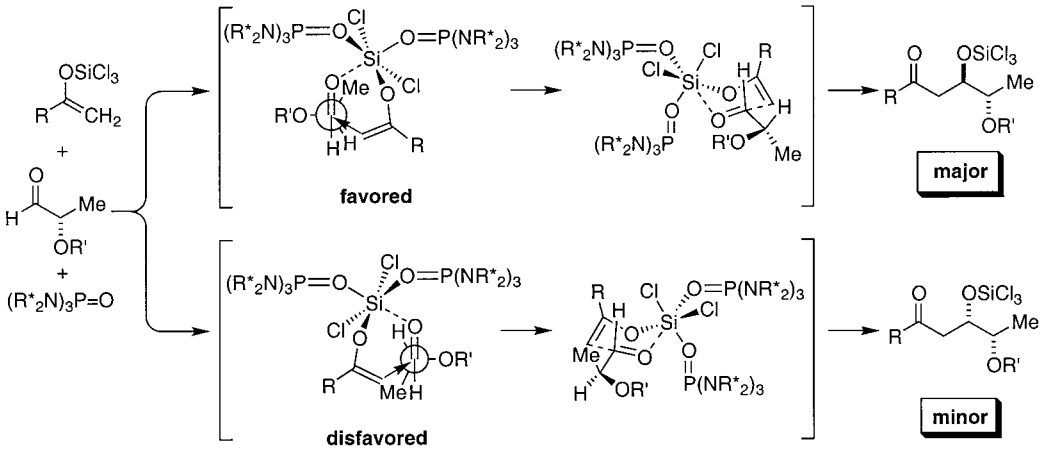
2.2. Achiral Enolates and Chiral Aldehydes. The yields of the catalyzed additions of enolate **2** to chiral aldehydes (*S*)-**35** and (*S*)-**37** were modest, though the selectivities obtained do show considerable promise. The catalyzed reactions were all (save that catalyzed by (*S*,*S*)-**27**) anti-selective. As previously observed in the achiral enolate/achiral aldehyde systems, solvents other than CH_2Cl_2 led to less selective reactions. Although the phosphoramide (*R*,*R*)-**27** proved to be the best catalyst, the cyclohexanediamine-derived catalyst (*R*,*R*)-**29** also performed well, providing up to 10/1 diastereoselectivity. This is in contrast to the very poor enantioselectivity observed in the additions with acetone enolate **1** and benzaldehyde (Table 3, entry 2). When the benzyloxy aldehyde (*S*)-**37** was used, less substrate control was observed and the configuration of catalyst **27** played a larger role in the stereochemical course of the reaction.

The stereochemical course of the catalyzed additions to chiral aldehydes (*S*)-**35** and (*S*)-**37** was predictable on the basis of the intrinsic facial selectivity of the aldehyde and the influence of the catalyst (*R*,*R*)-**27** on the external stereoselection process. First, if one applies the Felkin−Heathcock analysis to the (*S*)-configured aldehyde, approach to the *Re* face of the carbonyl group is preferred which leads to the anti-diastereomer. Second, if one assumes that the catalyst (*R*,*R*)-**27** has the same facial bias for the enolate **2** as it does for the cyclohexanone enolate then with the additional assumption of a chairlike transition structure, attack on the *Re* face of the aldehyde is again preferred which further reinforces the formation of the anti-adduct, Scheme 12. When (*S*,*S*)-**27** was used, syn-selectivity was obtained with aldehyde (*S*)-**35**; apparently the catalyst can override the intrinsic facial selectivity of the aldehyde in this mismatched case. Unfortunately, it is unclear at this time how the enolate face is shielded by the complex involving chiral phosphoramides. Given the unknown configuration around silicon, the conformational degrees of freedom, and number of third row elements, even computational modeling has little hope of providing compelling answers.

(33) The minor diastereomers in the aldol additions of substituted trichlorosilyl enolates are nearly racemic indicating that a topicity change at either enolate or aldehyde is equally feasible.

(34) The methyl ketone enolates are less reactive than the substituted enolates. In addition, control experiments showed that only 4% of the aldol product is formed in the absence of catalyst under the conditions of the catalyzed reactions.

Scheme 12

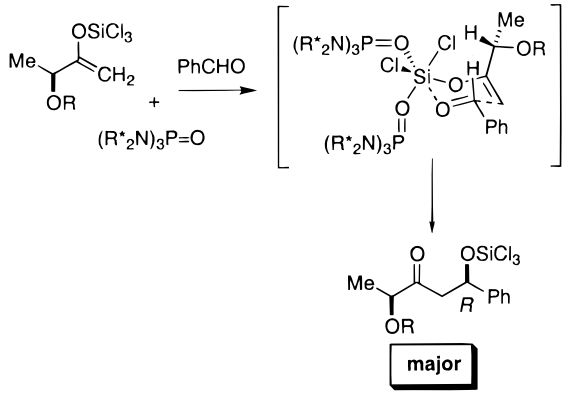


2.3. Chiral Enolates and Achiral Aldehydes. This series of additions also served to illustrate the utility of in situ generation and reaction of trichlorosilyl enolates. In a number of examples, both catalyzed and uncatalyzed additions were performed cleanly and selectively with the in situ protocol developed previously. In addition to the convenience the in situ procedure provides, these studies with chiral methyl ketones demonstrated the compatibility of the trichlorosilyl enolate/phosphoramide technology with several common protecting groups.

The additions of both pivaloyloxy- and silyloxy-enolates to benzaldehyde catalyzed by (*R*,*R*)-**27** demonstrated that this process can be extremely syn-diastereoselective. When the catalyst (*S*,*S*)-**27** was used in an overall mismatched case only low selectivity was observed, still favoring the syn-isomer. Thus, the internal selectivity of the chiral enolate (established from the weak syn selectivity observed with achiral catalyst **31a**) dominated the stereochemical course of addition. Apparently, in catalyzed aldol additions of trichlorosilyl enolates, the facial bias provided by stereogenic centers on the enolate is higher than the bias provided by stereogenic centers on the aldehyde portion.

The reactions catalyzed by (*R*,*R*)-**27** were highly syn-diastereoselective and correlated well with the size of the protecting group, The overall syn-selectivity can be rationalized by assuming an eclipsed conformation of the oxygen substituent to minimize dipoles,[30] similar to that described above for the uncatalyzed additions, Scheme 13. The observation that diastereoselectivity decreases in the order OTBS > OPiv > OBn suggests that a pathway involving chelation of the silicon cation may become possible with smaller and more basic oxygen functions.[35]

Scheme 13



Conclusion

A mild, general method for the synthesis of methyl ketone-derived trichlorosilyl enolates has been developed. This mercury(II)-catalyzed trimethylsilyl to trichlorosilyl metathesis was shown to be compatible with a variety of oxygen functions on the starting ketone, in addition to being amenable to in situ formation and use of the trichlorosilyl enolates, with no change in the selectivity of the ensuing reactions. It was shown that trichlorosilyl enolates of methyl ketones are unselective in uncatalyzed reactions when either donor or acceptor centered substrate control is possible. However, high diastereoselectivity could be obtained by the combination of either chiral enolates or chiral aldehydes with the appropriate chiral phosphoramide catalyst. In addition, the same chiral catalysts provide good to high absolute control (enantioselectivity) in the addition of achiral enolates to achiral (including one enolizable) aldehydes. Extension of these studies to include chiral ethyl ketones bearing oxygen substituents in the α'- and β'-positions along with further exploration of catalyst dependencies are currently under investigation. Kinetic analysis of the reactions of methyl ketone enolates is also of importance in substantiating the existence of the dual reaction pathways and will be reported in due course.

Experimental Section

See Supporting Information.

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

JA001023G

(35) The possibility of chelation of the silicon by the α-oxygen substituent becomes more plausible in the catalyzed reactions wherein the silicon is a more electrophilic cationic center. The intriguing possibility that the sense of internal diastereoselection might be tunable by the use of catalysts which prefer the mono- versus the diphosphoramide pathway is currently under investigation.