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Lewis Base Catalyzed Aldol Additions of Chiral Trichlorosilyl Enolates and Silyl Enol Ethers

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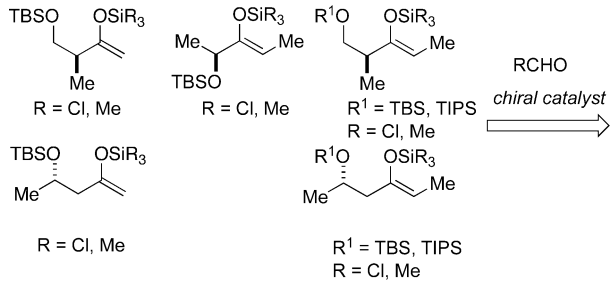

The consequences of double diastereodifferentiation in chiral Lewis base catalyzed aldol additions using chiral enoxysilanes derived from lactate, 3-hydroxyisobutyrate, and 3-hydroxybutyrate have been investigated. Trichlorosilyl enolates derived from the chiral methyl and ethyl ketones were subjected to aldolization in the presence of phosphoramides, and the intrinsic selectivity of these enolates and the external stereoinduction from chiral catalyst were studied. In the reactions with the lactate derived enolate, the strong internal stereoinduction dominated the stereochemical outcome of the aldol addition. For the 3-hydroxyisobutyrate- and 3-hydroxybutyrate derived enolates, the catalyst-controlled diastereoselectivities were observed, and the resident stereogenic centers exerted marginal influence. The corresponding trimethylsilyl enol ethers were employed in $SiCl_4$/bisphosphoramide catalyzed aldol additions, and the effect of double diastereodifferentiation was also investigated. The overall diastereoselection of the process was again controlled by the strong external influence of the catalyst.

Introduction

Enantioselective aldol additions are among the most useful synthetic transformations in organic synthesis. The development of highly diastereo- and enantioselective variants has been amply documented in numerous recent reviews.[1] High stereoselectivities can be achieved using chiral auxiliaries[2] and chiral catalysts.[3] When these methods are used in conjunction with a chiral substrate, these reactions are called double diastereodifferentiating aldol additions. In these cases, two different modes of stereoinduction are operating in the aldolization process: induction from catalyst or auxiliary and from chiral substrate. The concept of double diastereodifferentiation has been studied in detail, and several authoritative reviews have appeared.[4] The presence of stereogenic centers in substrates can complicate the stereoselective processes in the construction of complex molecules because the selectivity of the reaction is affected not only by the catalyst or auxiliary but also by the stereogenic center(s) in the substrate. A careful analysis of the matching/mismatching interaction between the two modes of stereoinduction is required for installation of

(1) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry;* Eliel, E. L., Wilen, S. H., Eds.; Wiley-Interscience: New York, 1982; Vol. 13; pp 1−115. (b) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; Vol. 5B, pp 177−237. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203−331. (d) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24−37. (e) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1−103. (f) Norcross, R.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114. (g) Carreira, E. M. In *Modern Carbonyl Chemistry;* Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 8. (h) Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 9. (i) Carreira, E. M. In *Comprehensive Asymmetric Catalysis, Vols. I−III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999. Chapter 29. (j) Carreira, E. M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 8B2. (k) Braun, M. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, ed. E21; Helmchen, G., Hoffman, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3; pp 1603−1735. (l) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2.

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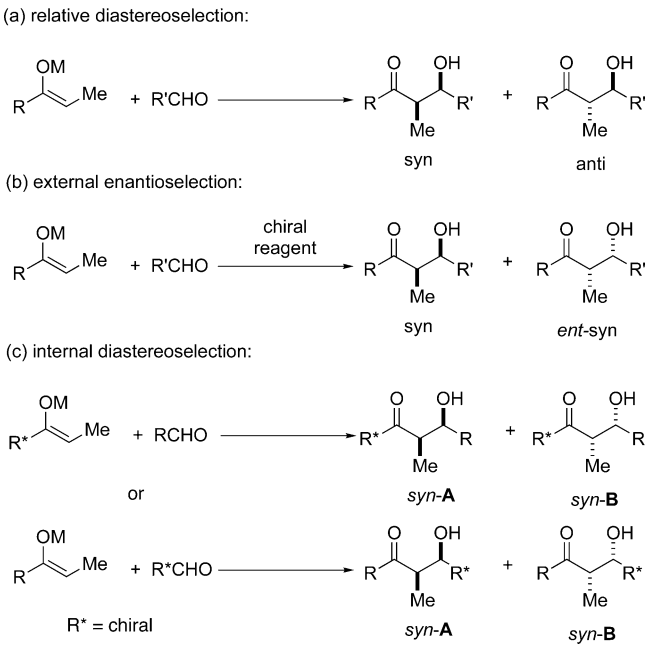
new stereogenic centers in a predictable and controlled manner.

When discussing double diastereo-differentiating aldol additions, the following nomenclature allows the different kinds of stereoinduction to be clearly distinguished.[5] There are three types of stereoselection processes associated with typical aldol additions (Scheme 1). The first is the *relative diastereoselection*, which corresponds to the relative topicity (*like* or *unlike*)[6] of the two reacting faces (enolate and carbonyl group). In highly organized aldol additions, this is often interpreted in terms of the chair/boat selectivity in the transition structure. The relative diastereoselection only pertains to α-substituted enolates since the term refers to the relative configuration of the two substituents (*like* or *unlike*) at the newly created stereogenic centers. The other is the absolute stereoselection (*external stereoselection*) determined by a chiral reagent. This term is used to describe the enantiofacial outcome at the newly created stereogenic centers. In the addition of chiral enolates or the addition to chiral aldehydes, there is a third stereoselection process that is controlled by resident stereogenic centers. The diastereoselection resulting from the influence of the stereogenic centers in either of the reactants is referred as *internal diastereoselection*. For example, when a chiral catalyst is used in conjunction with a chiral enolate, there is a possibility of double diastereodifferentiation. In a matched case wherein the sense of external stereoinduction coincides with the internal stereoinduction, the diastereoselectivity of the reaction can be considerably enhanced.

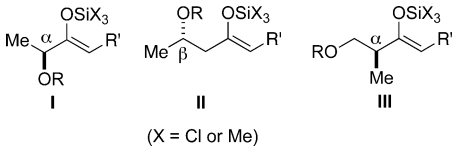
SCHEME 1



Over the past 10 years, catalytic enantioselective aldol additions using chiral Lewis bases have been developed in these laboratories.[7] In the presence of a chiral phosphoramide, trichlorosilyl enolates derived from various carbonyl compounds undergo stereoselective aldol additions. More recently, it was found that aldol additions of trialkylsilyl enol ethers and ketene acetals are also catalyzed by chiral phosphoramides in the presence of silicon tetrachloride. The scope of nucleophile in these reactions has been expanded to include chiral silyl enol ethers.

In this report, our investigations on the use of chiral nucleophiles for asymmetric aldol additions is fully described.[8] The primary objective of this study was to evaluate the effect of a stereogenic center on the stereochemical outcome of the aldol addition, including the effect of double diastereodifferentiation using chiral phosphoramides. Initial studies would involve the aldol additions of these chiral enol ethers to benzaldehyde to establish the reaction conditions, and then the substrate scope with respect to aldehyde would be investigated. Three classes of chiral silyl enol ethers were chosen to investigate the effect of the resident stereogenic center in the context of Lewis base catalyzed aldol addition (Chart 1). Two of these enolates bear heteroatom-based stereogenic centers either at the α- or β-carbons on the spectator side (I and II), and one bears a carbon-based stereogenic center on the spectator side (III). These types of nucleophiles were chosen because the aldol products derived from these enolates and enol ethers resemble the 1,2,4- and 1,3,5-triol structural motifs that are commonly found in natural products.

CHART 1



Background

As mentioned in the introduction, two types of Lewis base catalyzed aldol reactions have been developed that differ by the nucleophilic addition partner. The first of these methods employs trichlorosilyl enolates. These

(2) For example: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.

(3) For examples: (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2. (b) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC: Boca Raton, 1996. (c) Kobayashi, S.; Uchiro, H.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761−1772. (d) Nelson, S. G. *Tetrahedron Asymmetry* **1998**, *9*, 357−389. (e) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455−1458. (f) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860. (g) Kobayashi, S.; Horibe, M.; Hachiya, I. *Tetrahedron Lett.* **1995**, *36*, 3173−3176. (h) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292−3302. (i) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873. (j) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. (k) Shibasaki, M.; Matsunaga, S.; Kumagai, N. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2. Chapter 6.

(4) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−76. (b) Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953−6018.

(5) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10.

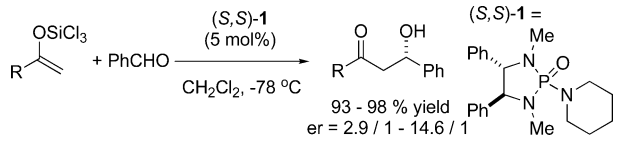
(6) Seebach, D.; Prelog, V. *Angew. Chem.* **1982**, *21*, 654−660.

(7) (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432−440. (b) Denmark, S. E.; Fujimori, S. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2. Chapter 7.

(8) For preliminary communications, see: (a) Denmark, S. E.; Fujimori, S. *Synlett* **2000**, 1024−1029. (b) Denmark, S. E.; Pham, S. M. *Org. Lett.* **2001**, *3*, 2201−2204. (c) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3477−3480. (d) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3473−3476.

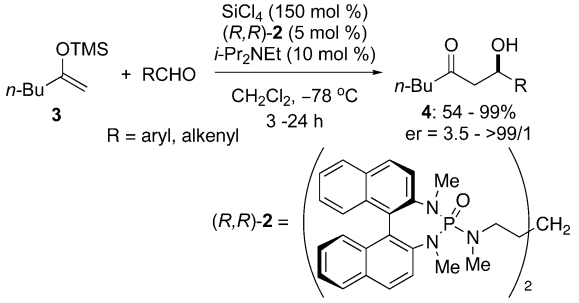
species undergo highly stereoselective aldol additions in the presence of a chiral phosphoramide such as (*S*,*S*)-**1** (Scheme 2).[9] Trichlorosilyl enolates derived from acetates,[10] methyl ketones,[9] ethyl ketones,[11] cyclic ketones,[12] and aldehydes[13] are competent and selective nucleophiles in this aldolization process.

SCHEME 2



The second type of Lewis base catalysis involves activation of weak Lewis acids for Mukaiyama-type aldol additions of trialkylsilyl enol ethers and ketene acetals.[14] These nucleophiles undergo highly stereoselective aldol addition to aromatic and conjugated aldehydes in the presence of $SiCl_4$ and chiral bisphosphoramide **2** as the catalyst (Scheme 3). The aldol addition of propanoate derived ketene acetals shows excellent *anti* (relative) diastereoselectivity and enantioselectivity.[14d] This catalyst system remains as one of the very few *anti*-selective catalytic, enantioselective aldol additions.[15]

SCHEME 3



In the context of double diastereodifferentiation, the lactate derived trichlorosilyl enolates were among the first to be examined (Scheme 4).[16] The aldol addition of **5** is efficiently catalyzed by phosphoramides (*R*,*R*)- and (*S*,*S*)-**1**, and in both cases the 1,4-*syn* diastereomer is obtained as the major product. The observed selectivity is significantly higher when (*R*,*R*)-**1** is used as the catalyst compared to (*S*,*S*)-**1**. This observation indicates that there is matched and mismatched relationship[4] between the stereoinduction by the catalyst and the resident stereogenic center. In the matched case, there is a strong enhancement of the *syn* selectivity because the sense of stereoinduction by the catalyst and that of the chiral enolate are the same. On the other hand, the use of (*S*,*S*)-**1** gives rise to an eroded *syn* selectivity because the stereoselection caused by the catalyst is opposite to the effect of resident stereogenic center. The resulting *syn* selectivity in this case is largely controlled by the strong stereoinduction from the α-silyloxy stereogenic center in the chiral enolate.

SCHEME 4

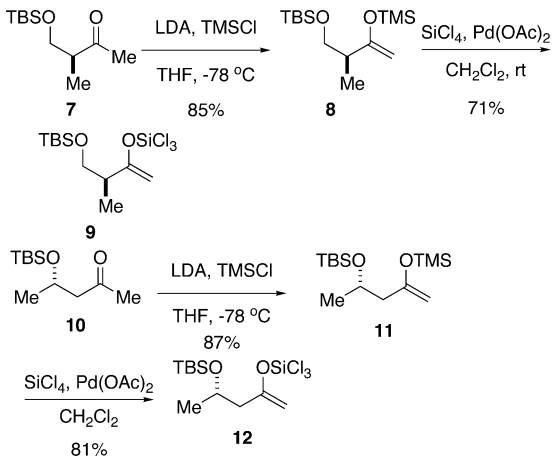
catalyst	yield	syn/anti
(*R*,*R*)-**1**	85%	73/1
(*S*,*S*)-**1**	85%	1.5/1

In the following sections, the aldol additions of chiral nucleophiles catalyzed by chiral Lewis bases are described. The results are organized as follows: (1) preparations of these chiral silyl nucleophiles, (2) the aldol additions of the methyl ketone derived nucleophiles, and (3) the aldol additions of the ethyl ketone derived nucleophiles. In the description of aldol additions, the reactions of trichlorosilyl enolates are presented first, and then the additions of trimethylsilyl enol ethers are described.

Results

1. Preparation of Chiral Silyl Enol Ethers. The chiral methyl ketones **7** and **10** were prepared from methyl (*S*)-3-hydroxyisobutyrate and from methyl (*S*)-3-hydroxybutyrate, respectively.[8] The TBS ether was chosen as the protective group for the hydroxyl group on the basis of previous studies.[16] The site-selective enolizations of the methyl ketones were accomplished by deprotonation with lithium diisopropylamide followed by the reaction with TMSCl (Scheme 5). The corresponding TMS enol ethers **8** and **11** were obtained in excellent yields. The conversion of the TMS enol ethers to the trichlorosi-

SCHEME 5



(9) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837−8847.

(10) (a) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404−7405. (b) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233−4235.

(11) Denmark, S. E.; Pham, S. M. *J. Org. Chem.* **2003**, *68*, 5045−5055.

(12) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *Tetrahedron* **1998**, *54*, 10389−10402.

(13) (a) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4759−4762. (b) Denmark, S. E.; Bui, T. *Proc. Nat. Acad. Sci*. **2004**, *101*, 5439−5444.

(14) (a) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405−13407. (b) Denmark, S. E.; Heemstra, J. R., Jr. *Org. Lett.* **2003**, *5*, 2303−2306. (c) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800−7801. (d) Denmark, S. E.; Beutner, G. B.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774−3789.

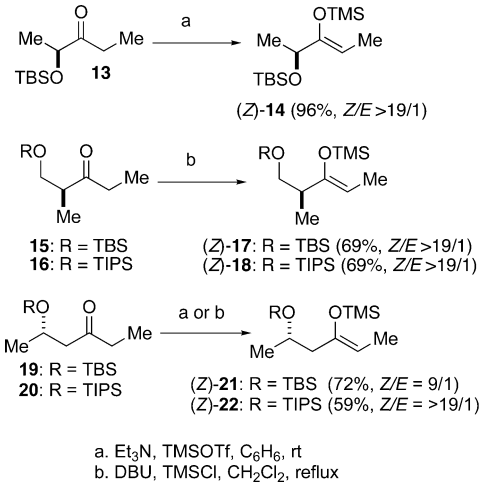
(15) For examples of *anti*-selective catalytic aldol additions, see: (a) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860. (b) Kobayashi, S.; Horibe, M.; Hachiya, I. *Tetrahedron Lett.* **1995**, *36*, 3173−3176. (c) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292−3302.

(16) Denmark, S. E.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 9524−9527.

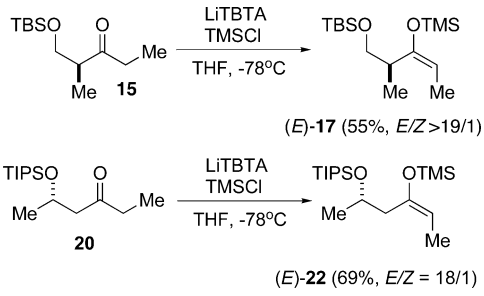
lyl enolates has been studied in detail.[17] Either Hg(II) or Pd(II) acetate efficiently catalyzed the transsilylation of **8** and **11** with $SiCl_4$ to afford the trichlorosilyl enolates **9** and **12** in good yields.

Geometrically defined TMS enol ethers from the chiral ethyl ketones were prepared under the following conditions. The *Z* TMS enol ethers were generated by a combination of TMSOTf/Et_3N[18] or TMSCl/DBU[19] (Scheme 6), whereas the *E* TMS enol ethers were formed by the use of lithium *tert*-butyltritylamine (LiTBTA),[20] affording (*E*)-**17** and (*E*)-**22** (Scheme 7).

SCHEME 6

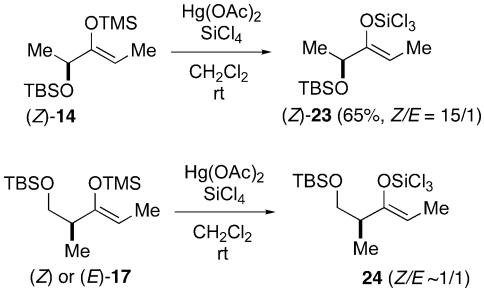


SCHEME 7



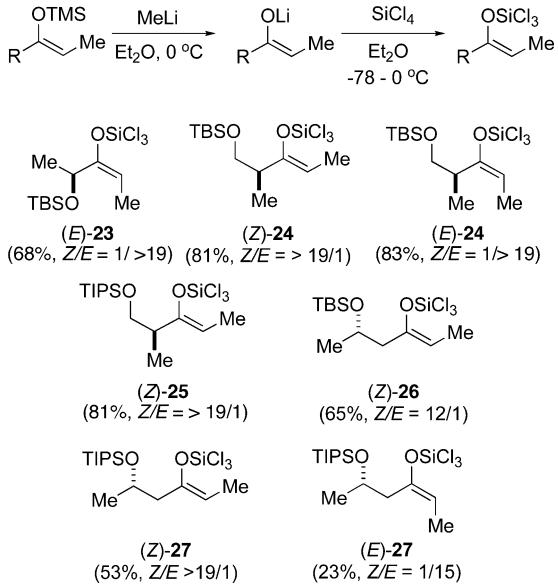
The preparation of geometrically defined trichlorosilyl enolates from *achiral* ethyl ketones has been studied.[11] It has been shown that (*Z*)-trichlorosilyl enolates can be prepared selectively using the Hg(II)- or Pd(II)-catalyzed transsilylation. However, the *E*/*Z*-selectivity of the transsilylation is dependent on the size of the spectator group: larger spectator groups show higher *Z*-selectivity. The Hg(II)-catalyzed transsilylations gave variable results for the chiral ethyl ketone enolates (Scheme 8). The lactate derived TMS enol ether **14** provided enolate (*Z*)-**23** with high selectivity. However, the transsilylation of either (*Z*)- or (*E*)-**17** under similar conditions resulted in formation of 1/1 mixture of **24**.

SCHEME 8



Geometrically defined trichlorosilyl enolates are prepared more reliably by an alternative two-step procedure that involves lithium enolate formation followed by silylation with silicon tetrachloride (Scheme 9).[13] By the use of this method, both (*E*)- and (*Z*)-trichlorosilyl enolates can be prepared without erosion of the *E*/*Z* ratio of the starting TMS enol ether. The resulting enolates were purified by bulb-to-bulb distillation; however, variable amounts of bisenoxydichlorosilane species were observed in the isolated trichlorosilyl enolates.

SCHEME 9



2. Aldol Additions of Methyl Ketone Derived Chiral Trichlorosilyl Enolates. 2.1. Addition of Trichlorosilyl Enolate 9. Optimization of the aldol addition of **9** with benzaldehyde involved a survey of the reaction concentration, catalyst structure, and loading (Table 1). The chiral phosphoramide (*R*,*R*)-**1** effectively promoted the aldol addition at 5 mol % loading and a 0.5 M reaction concentration to afford *syn*-**28a** as the major isomer.[21] The increasing the catalyst loading

(17) Denmark, S. E.; Stavenger, R. A.; Winter, S. B. D.; Wong, K.-T.; Barsanti, P. A. *J. Org. Chem.* **1998**, *63*, 9517−9523.

(18) (a) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982−3984. (b) Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234−1235. (c) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455−3458.

(19) Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3229−3232.

(20) Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **2000**, *41*, 2515−2518.

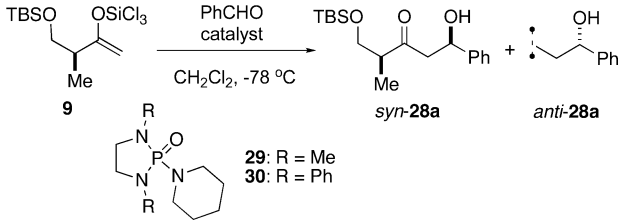
(21) The configurational assignment of the major diastereomer as *syn*-**28a** was confirmed by single-crystal X-ray analysis of the diol **31** obtained by deprotection of TBS ether with PPTS in ethanol. (a) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965−6968. Recrystallization of the crude diol provided a crystal suitable for X-ray analysis. (b) The crystallographic coordinates of **31** have been deposited with the Cambridge Crystallographic Data Centre, deposition no. CCDC 270359. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

showed no influence on the diastereoselectivity (entries 2−4). The enantiomeric catalyst (*S*,*S*)-**1** was equally effective in promoting the aldol addition (5 mol % loading at 0.5 M) to afford *anti*-**28a** as the major product (entry 8). Lower reaction concentration can be used if the catalyst concentration is increased.

In the presence of an achiral phosphoramide, intrinsic, internal diastereoselectivity in the catalyzed reaction was investigated. The *N*,*N*-dimethyl phosphoramide **29** provided the *syn*-**28a** as the major product with modest diastereoselectivity. The reaction using *N*,*N*-diphenyl phosphoramide **30** was significantly slower and only 31% yield of **28a** was obtained after 12 h.

Thus, it was found that (*R*,*R*)-**1** yielded *syn*-**28a** selectively (*syn*/*anti*, 10/1), whereas (*S*,*S*)-**1** afforded *anti*-**28a** with attenuated selectivity (*syn*/*anti*, 1/6). In the presence of achiral phosphoramide **29**, the reaction weakly favored the *syn* product, indicating that there is a mild inherent selectivity toward the *syn* product by the resident stereogenic center (Table 1, entry 10). However, the stereoselection in this aldol reaction was dominated by the catalyst configuration since there was a switch in the sense of asymmetric induction.

TABLE 1. Optimization of the Aldol Addition of 9 with Phosphoramides 1, 29, and 30



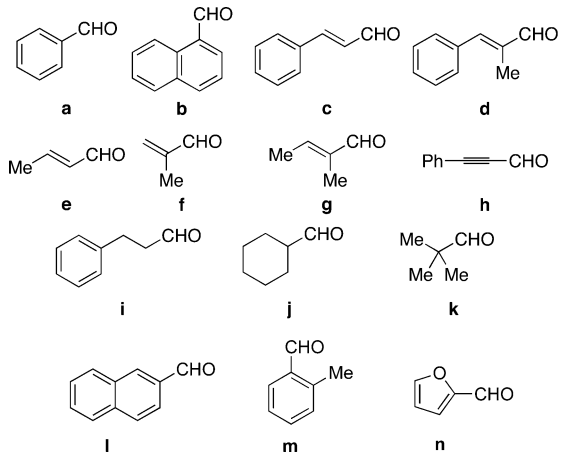
entry	catalyst	concn, M	cat., mol %	time, h	yield, %[a]	*syn*/*anti*[b]
1	(*R*,*R*)-**1**	0.1	5	2	43[c]	14/1
2	(*R*,*R*)-**1**	0.5	5	2	79	10/1
3	(*R*,*R*)-**1**	0.5	10	1	73	10/1
4	(*R*,*R*)-**1**	0.5	15	1	71	10/1
5	(*S*,*S*)-**1**	0.1	15	3	57[c]	1/9
6	(*S*,*S*)-**1**	0.2	10	2	81	1/6
7	(*S*,*S*)-**1**	0.2	15	2	72[c]	1/6
8	(*S*,*S*)-**1**	0.5	5	2	76[c]	1/6
9	**29**	0.1	5	5	51[c]	5/1
10	**30**	0.1	15	12	31[c]	2/1

[a] Yield of chromatographically homogeneous material. [b] Determined by CSP-SFC (OD; 175 bar, 2.5 mL/min, 1.7% MeOH). [c] Incomplete reaction.

Next, the generality of this aldol addition with other aldehydes was investigated. For this study, the in situ generation of **9** was employed to further demonstrate the practicality of this aldol addition. For their transsilylation 1 mol % of $Hg(OAc)_2$ was employed for the in situ formation of trichlorosilyl ether **9**. The standard conditions for surveying aldehydes employed 10 mol % of the catalyst at 0.5 M overall reaction concentration (Table 2). The aldehydes surveyed include aromatic, olefinic, acetylenic and aliphatic with various substitution patterns (Chart 2).

The in situ method gave superior results compared to those obtained with isolated **9** (Table 2, entry 1). The overall yields of the aldol products from the TMS enol ether were significantly improved, and the diastereoselectivities of the aldol additions were also noticeably

CHART 2



improved. In general, the aldol addition of in situ generated **9** was efficiently catalyzed by phosphoramide **1** affording **28a** in good yields except for aliphatic aldehydes (entries 9 and 10).

The effect of the resident stereogenic center was again examined using achiral phosphoramide **29** for the in situ generated trichlorosilyl enolate **9**. The addition showed a slight preference to the *syn* isomer consistent with the previous experiment (Table 2, entry 12).

The diastereoselectivities were dependent on aldehyde structure, but the selectivities were always higher when (*R*,*R*)-**1** was used as the catalyst.[22] The selectivity seemed to depend on the substitution pattern of the aldehyde such that aldehydes containing α-branching generally gave higher diastereoselectivity. For example, the additions to pivaldehyde and tiglic aldehyde afforded the highest 1,4-*syn* selectivity when (*R*,*R*)-**1** was used (Table 2, entries 7 and 11). The lowest *syn* selectivity was obtained with the acetylenic aldehyde (entry 8) presumably due to the absence of sterically demanding groups leading to less steric differentiation of the π-faces. The yields for the aliphatic aldehydes were significantly lower because these reactions did not go completion, though the

(22) The absolute configuration of the aldol products was assigned by analogy to the benzaldehyde aldol product. However, to ensure the consistency of stereoinduction from the catalyst system across the various aldehyde structures, the configuration of the β-hydroxy ketone obtained from pivaldehyde (*syn*-**28k**) was assigned by chemical correlation to the known acid **34** The site-selective Baeyer−Villiger oxidation of the ketone was accomplished using conditions developed by Shibasaki et al. to provide the ester **33** (Gottlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971−973). The ester was hydrolyzed to the corresponding acid in good yield, the optical rotation of which compared well to the literature value of *S*-**34**. (Devant, R.; Braun, M. *Chem. Ber.* **1986**, *119*, 2191−2207). Thus, the sense of stereoinduction with (*R*,*R*)-**1** was consistent between aldol additions to benzaldehyde and to pivaldehyde.

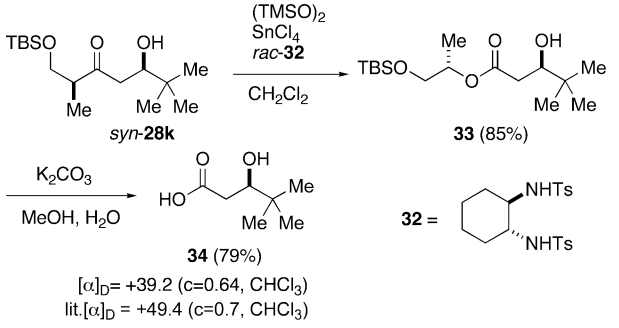
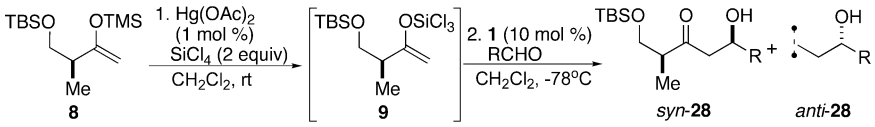


TABLE 2. Aldol Addition of in Situ Generated Trichlorosilyl Enolate 9 to Aldehydes



				(*R*,*R*)-**1**		(*S*,*S*)-**1**	
entry	aldehyde R	product	time, h	yield, %[a]	dr (*syn*/*anti*)[b]	yield, %[a]	dr (*syn*/*anti*)[a]
1	phenyl	**1a**	2.5	80	19.0/1	75	1/7.33
2	1-naphthyl	**1b**	2	85	15.7/1	83	1/8.09
3	(*E*)-cinnamyl	**1c**	7	81	8.00/1	82	1/4.26
4	(*E*)-2-Me-cinnamyl	**1d**	4	84	10.1/1	80	1/6.69
5	(*E*)-crotyl	**1e**	4	85	4.88/1[c]	83	1/2.87[c]
6	CH_2=CMe	**1f**	2	81	15.7/1[c]	84	1/8.09[c]
7	MeCH=CMe	**1g**	4	78	24.0/1[c]	75	1/4.56[c]
8	PhC≡C–	**1h**	5	83	3.35/1	82	1/1.32
9	$PhCH_2CH_2$	**1i**	10[d]	34	10.1/1	22	1/2.45
10	cyclohexyl	**1j**	10[d]	47	15.7/1[c]	31	1/4.00[c]
11	*t*-butyl	**1k**	4	73	27.9/1[e]	78	1/6.51[e]
12[f]	phenyl	**1a**	2.5	83	4.88/1		

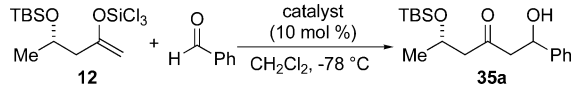
[a] Yield of analytically pure material. [b] Determined by CSP-SFC. [c] Determined by CSP-SFC on the corresponding benzoate. [d] Incomplete reaction. [e] Determined by ^{1}H NMR analysis in d_6-benzene. [f] 10 mol % of **29** was used as catalyst.

selectivities were good for the matched cases (entries 9 and 10). The low conversion in these cases was believed to arise from the formation of an unreactive α-chloro silyl ether under these reaction conditions.[7]

2.2. Addition of Trichlorosilyl Enolate 12. In the previous section, the effect of an α-stereogenic center bearing carbon substituents on the stereochemical course of the aldol addition of trichlorosilyl enolate was studied. The effect of a remote stereogenic center on diastereoselection of the aldol addition is also worthy of investigation because the resulting aldol product resembles the 1,3-polyol fragment present in numerous natural products.[23] In the aldol addition of boron enolates, it has been demonstrated that a β-oxygen bearing stereogenic center can strongly influence the stereochemical course of the reaction.[23]

The aldol addition of the methyl ketone enolate **12** to benzaldehyde was examined under catalysis by the chiral and achiral phosphoramides **1** and **29** (Scheme 10). The use of 10 mol % of the catalyst effectively promoted the addition at 0.5 M reaction concentration. The intrinsic (substrate-induced) selectivity determined using **29** was almost negligible, indicating that the β-stereogenic center does not exert significant stereoinduction under phosphoramide catalysis. Unfortunately, with either enantiomer of the chiral catalyst, only marginal diastereoselectivities were obtained. These results are perplexing considering that the phosphoramide **1** shows high selectivities in the aldol additions with other methyl ketone enolates.[9]

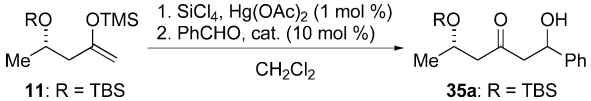
SCHEME 10



(*R*,*R*)-**1**: 72%, dr (*syn*/*anti*) = 1/2.5
(*S*,*S*)-**1**: 72%, dr (*syn*/*anti*) = 1.3/1
29: 55%, dr (*syn*/*anti*) = 1/1.4

The addition of the methyl ketone enolates can be performed using the in situ generated enolate for operational simplicity (Table 3). This method not only avoided handling of sensitive trichlorosilyl enolates but also provided improved selectivities for the additions of **11** as compared to those of isolated **12** (Table 3, entries 1 and 2). The stereochemical course of the reaction seems to be controlled only by the catalyst because similar selectivities for both diastereomers were obtained using either enantiomer of **1**. The addition of **36** provided good yields of the aldol products; however, the selectivity was significantly attenuated compared to the aldol additions of **9** (Table 3, entries 3 and 4).

TABLE 3. Aldol Addition of In Situ Generated Trichlorosilyl Enolates to Benzaldehyde



entry	TMS enol ether	catalyst	yield, %[a]	dr (*syn*/*anti*)[b]
1	**11**	(*R*,*R*)-**1**	61	1/5.5
2	**11**	(*S*,*S*)-**1**	58	4.4/1
3	**36**	(*R*,*R*)-**1**	89	1/1.8
4	**36**	(*S*,*S*)-**1**	86	2.3/1

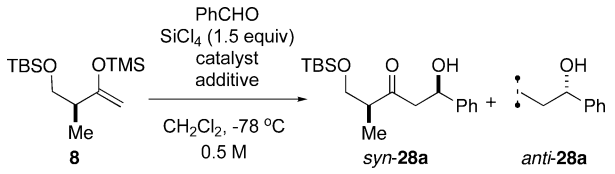
[a] Yield of chromatographically homogeneous material. [b] Determined by CSP-SFC.

3. Aldol Additions of Methyl Ketone Derived Chiral TMS Enol Ethers. 3.1. Aldol Addition of 8. To examine the effect of the resident stereogenic center on the stereochemical course of the reaction, the aldol addition of chiral TMS enol ether **8** was investigated using chiral bisphosphoramide **2** as the catalyst. The initial optimization surveyed the catalyst structure, effect of additives and reaction concentration (Table 4).

With (*R*,*R*)-**2**, the addition of **8** to benzaldehyde provided *syn*-**28a** in excellent yield and diastereoselectivity. On the other hand, when (*S*,*S*)-**2** was used as catalyst, *anti*-**28a** was obtained exclusively. The monomeric phosphoramide (*R*,*R*)-**1** was not as catalytically active as

(23) (a) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588. (b) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187−1191. (c) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581−8584. (d) Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem.* **1997**, *62*, 788−789. (e) Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893−10898.

TABLE 4. Aldol Addition of 8 to Benzaldehyde

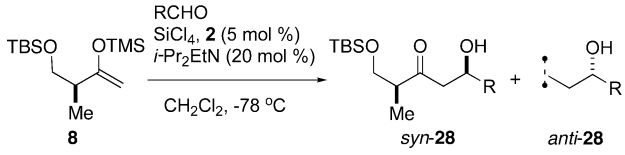


entry	catalyst	additive	yield, %	dr, *syn/anti*[b]
1	5 mol % (*R*,*R*)-**2**	none	88	24/1
2	5 mol % (*S*,*S*)-**2**	none	90	1/>99
3	10 mol % (*R*,*R*)-**1**	none	58	1/3
4	5 mol % (*R*,*R*)-**2**	tri-*tert*-butylpyridine (20 mol %)	92	29/1
5	5 mol % (*R*,*R*)-**2**	*i*-Pr_2EtN (20 mol %)	90	23/1
6[c]	5 mol % (*R*,*R*)-**2**	none	89	25/1

[a] Yield of chromatographically homogeneous material. [b] Determined by CSP-SFC. [c] Reaction was run at 1.0 M concentration.

bisphosphoramide, providing the aldol product in modest yield and selectivity. The introduction of additives such as tertiary amines and tetraalkylammonium salts has shown beneficial effects in the related studies. The addition of amines to scavenge adventitious acids helped to increase the yields for the additions of achiral TMS enol ethers. Indeed, in the additions of **8**, the yield and selectivities were increased slightly by the addition of 20 mol % of the amines (entries 4 and 5). Tri-*tert*-butylpyridine provided optimal results; however, diisopropylethylamine was chosen as an additive because of its lower cost. Interestingly, the reaction at higher concentration did not improve the yield or the selectivity (entry 6).

TABLE 5. Aldol Addition of 8 to Various Aldehydes Catalyzed by Bisphosphoramide 2



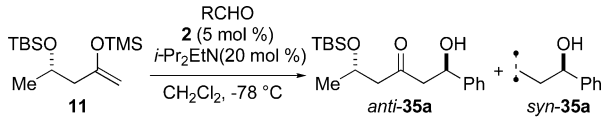
entry	aldehyde, R	product	catalyst	time, h	yield, %[a]	*syn/anti*[b]
1	phenyl	**28a**	(*R*,*R*)-**2**	4	91	24/1
2	phenyl	**28a**	(*S*,*S*)-**2**	4	94	1/49
3	1-naphthyl	**28b**	(*R*,*R*)-**2**	24	85	19/1
4	1-naphthyl	**28b**	(*S*,*S*)-**2**	24	83	1/43
5	2-naphthyl	**28l**	(*R*,*R*)-**2**	3	77	99/1
6	(*E*)-cinnamyl	**28c**	(*R*,*R*)-**2**	5	85	32/1
7	(*E*)-cinnamyl	**28c**	(*S*,*S*)-**2**	5	83	1/34
8	PhC≡C-	**28h**	(*R*,*R*)-**2**	6	74	1/1.5
9	PhC≡C-	**28h**	(*S*,*S*)-**2**	6	72	1/4
10	(*E*)-crotyl	**28e**	(*R*,*R*)-**2**	4	23	12/1
11	(*E*)-crotyl	**28e**	(*S*,*S*)-**2**	4	27	1/>19
12	(*E*)-2-Me-cinnamyl	**28d**	(*R*,*R*)-**2**	24	22	4/1
13	$PhCH_2CH_2$	**28i**	(*R*,*R*)-**2**	24	nr	
14	2-tolyl	**28m**	(*R*,*R*)-**2**	4	nr	

[a] Yield of chromatographically homogeneous material. [b] Determined by CSP-SFC.

The high yields and selectivities obtained in the addition of **8** to benzaldehyde prompted a study of the scope of aldehyde structure in this reaction (Table 5). The reaction with 1-naphthaldehyde showed a significant decrease in the reaction rate; however, the reaction proceeded to completion with increased reaction time (entries 3 and 4). On the other hand, addition to 2-naphthaldehyde (entry 5) and cinnamaldehyde (entries 6 and 7) proceeded smoothly to provide the aldol products in high yield and good diastereoselectivity. The addition to 3-phenylpropargyl aldehyde showed a significant decrease in the selectivity, although the yield was good (entries 8 and 9). Unfortunately, the aldol addition to crotonaldehyde was found to be problematic due to the formation of side products. The desired aldol products could only be obtained in low yield (albeit high selectivity) after chromatographic purification. The addition to aliphatic and α-substituted olefinic and α-substituted aromatic aldehydes (entries 12−14) provided little or no product.

3.2. Aldol Addition of 11. The initial study was carried out using benzaldehyde as the substrate (Scheme 11). In contrast to the results from aldol addition of trichlorosilyl enolate **12**, the aldol addition of **11** provided aldol product **35a** in good yield in the presence of **2** and $SiCl_4$. In addition, the selectivity observed was significantly higher than the selectivity obtained from addition of **12**. The aldol addition of **11** to benzaldehyde catalyzed by (*R*,*R*)-**2** provided 1,5-*anti* **35a** almost exclusively.[24] The 1,5-*syn* diastereomer of **35a** was obtained as the major product when enantiomeric catalyst (*S*,*S*)-**2** was used.

SCHEME 11



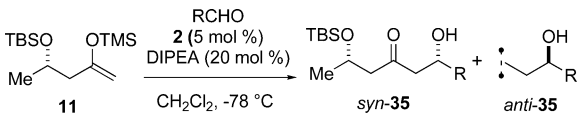
catalyst	yield, %	*syn/anti*
(*R*,*R*)-**2**	92	1/36
(*S*,*S*)-**2**	94	37/1

Because the diastereoselectivities were similar for both (*R*,*R*)-**2** and (*S*,*S*)-**2** catalyzed reactions, the inherent selectivity is almost nonexistent and the diastereoselectivity is primarily controlled by the catalyst configuration. This result is consistent with previous findings.[8b]

The high yields and selectivities observed for the addition of **11** to benzaldehyde prompted a survey of the aldehyde scope for this aldol addition (Table 6). Aromatic and conjugated aldehydes afforded high yields of aldol products with modest to excellent diastereoselectivities (entries 3−6). In most cases, (*S*,*S*)-**2** provided the 1,5-*syn* aldol products, whereas 1,5-*anti* aldol products were obtained using (*R*,*R*)-**2** as the catalyst. For cinnamaldehyde and naphthaldehyde, 1,5-*anti* selectivity with (*S*,*S*)-**2** was higher than that with the 1,5-*syn* stereoinduction with (*R*,*R*)-**2**. The addition to naphthaldehyde was very slow, but aldol products were obtained in good yields and high diastereoselectivities. The reaction with 3-phenylpropargyl aldehyde was completely unselective in both cases, providing a nearly 1/1 mixture of diastereomers

(24) The configuration of the aldol product was confirmed by single-crystal X-ray analysis of the corresponding diol *anti*-**38**. The TBS group was removed from *anti*-**35a** under acidic conditions to give diol *anti*-**38**, which provided a crystal suitable for X-ray analysis from refluxing acetone/hexanes. The crystallographic coordinates of *anti*-**38** have been deposited with the Cambridge Crystallographic Data Centre, deposition no. CCDC 270165. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

TABLE 6. Aldol Addition of 11 to Various Aldehydes



entry	aldehyde, R	product	catalyst	time, h	yield, %[a]	*syn/anti*[b]
1	phenyl	**35a**	(*R*,*R*)-**2**	5	92	1/36
2	phenyl	**35a**	(*S*,*S*)-**2**	5	94	37/1
3	1-naphthyl	**35b**	(*R*,*R*)-**2**	12	74	1/21
4	1-naphthyl	**35b**	(*S*,*S*)-**2**	12	79	61/1
5	(*E*)-cinnamyl	**35c**	(*R*,*R*)-**2**	7	88	1/30
6	(*E*)-cinnamyl	**35c**	(*S*,*S*)-**2**	7	90	>99/1
7	PhC≡C	**35h**	(*R*,*R*)-**2**	24	74	1.3/1
8	PhC≡C	**35h**	(*S*,*S*)-**2**	24	85	1.2/1
9	(*E*)-2-Me-cinnamyl	**35d**	(*R*,*R*)-**2**	24	nr	
10	(*E*)-crotyl	**35e**	(*S*,*S*)-**2**	12	tr	

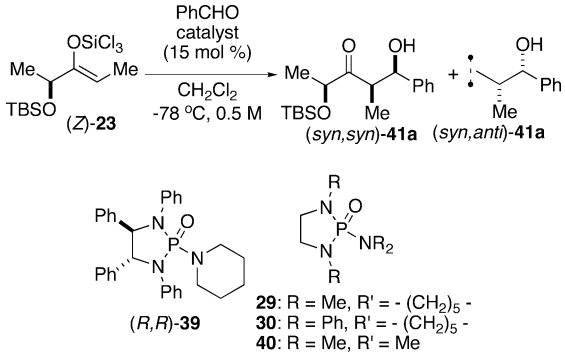
[a] Yield of chromatographically homogeneous material. [b] Determined by CSP−SFC.

(entries 7 and 8). The additions to 2-methylcinnamaldehyde and to crotonaldehyde failed to provide the aldol product under these conditions (entries 9 and 10).

4. Aldol Additions of Ethyl Ketone Derived Trichlorosilyl Enolates. 4.1. Aldol Addition of Trichlorosilyl Enolate 23. The next stage of the investigation involved the study of geometrically defined *ethyl* ketone chiral enolates. With methods in hand to prepare geometrically enriched enolates and enol ethers, we began with a survey of catalysts using lactate derived enolate (*Z*)-**23** as the test substrate (Table 7). In addition to catalyst (*R*,*R*)- and (*S*,*S*)-**1**, other structures surveyed include the diazaphospholidines shown in Table 7. A reaction concentration of 0.5 M was found to be optimal allowing the aldol reaction to reach completion within 2 h using (*R*,*R*)-**1** (Table 7, entry 1). Isolation of the crude product followed by purification afforded (*syn*,*syn*)-**41a** in 87% yield with greater than 50/1 internal diastereoselectivity for the (*syn*,*syn*)-adduct vs the (*syn*,*anti*)-adduct (*relative*, *internal*). The relative diastereoselectivity for the two new stereogenic centers formed during the aldol reaction correlated appropriately with the starting trichlorosilyl enolate geometry to give a 16/1 *syn*/*anti* ratio.[25]

A survey of various chiral and achiral phosphoramides showed a remarkable influence of the resident stereogenic center on the stereochemical course of the reaction when using enolate (*Z*)-**23** (Table 7, entries 3−7). Interestingly, the configuration of the catalyst employed in the aldol reaction had little effect on the stereochemical outcome (entry 2). The use of (*S*,*S*)-**1** led to only a minor attenuation in internal diastereoselectivity from 50/1 to 30/1 for (*R*,*R*)-**1** and (*S*,*S*)-**1**, respectively. Perhaps the most profound demonstration of the directing influence of the resident stereogenic center was seen with the achiral *N*,*N*′-dimethylphospholidine catalysts, **29** and **40** (entries 4 and 5). In both cases, the internal diastereoselectivity was greater than 30/1. Remarkably, even the use of hexamethylphosphoric triamide (HMPA) afforded **41a** with an internal diastereoselectivity of 30/1 (entry 7). Among the catalysts employed only those bearing *N*-phenyl substituents on the 1,3,2-diazaphospholidine ring afforded attenuated internal selectivities (entries 3 and 6).

TABLE 7. Stereoselective Aldol Additions of (*Z*)-23 to Benzaldehyde Using Various Phosphoramides



entry	catalyst	time, h	yield, %[a]	internal dr[b] *syn/anti*	relative dr[c] *syn/anti*
1	(*R*,*R*)-**1**	2	87	>50/1	16/1
2	(*S*,*S*)-**1**	2	80	30/1	15/1
3	(*R*,*R*)-**39**	8	65	3/1	15/1
4	**40**	7	76	34/1	15/1
5	**29**	7	82	37/1	15/1
6	**30**	5	67	3/1	15/1
7	HMPA	7	79	30/1	15/1

[a] Yield of chromatographically homogeneous material. [b] Determined by CSP-SFC analysis. [c] Determined by ^{1}H NMR analysis.

To establish the generality of the reaction of (*Z*)-**23**, a survey of aldol additions to various aldehydes using either (*R*,*R*)-**1** or HMPA as catalysts was undertaken (Table 8). To further optimize the reaction protocol, the aldol additions were performed using in situ generated trichlorosilyl enolate (*Z*)-**23**. This obviates the need for handling of a sensitive compound, improving the overall yield of aldol product with respect to the TMS enol ether. Finally, to demonstrate the efficiency of the chiral phosphoramides, aldol reactions were done using 5 mol % of (*R*,*R*)-**1**, while still using 15 mol % of HMPA.

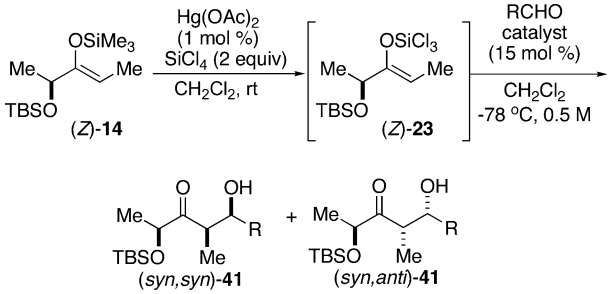
In the general in situ procedure, TMS enol ether (*Z*)-**14** was added dropwise to a solution of $SiCl_4$ (2 equiv) and 1 mol % $Hg(OAc)_2$ in CH_2Cl_2, and the reaction was monitored by ^{1}H NMR spectroscopy. Following complete conversion of the TMS enol ether, the contents of the reaction vessel were placed under vacuum to remove the volatile byproducts and solvent. A solution of phosphoramide in dry CH_2Cl_2 was then added via syringe. The reaction vessel was cooled to −78 °C at which point freshly distilled aldehyde was added dropwise via syringe.

Aromatic, heteroaromatic, olefinic and propargylic aldehydes react under these conditions to provide the (*syn*,*syn*)-aldol products in modest to good yields and high diastereoselectivities. When HMPA was used as the catalyst, the yields and selectivities were slightly attenuated. The highest selectivity was observed with 1-naphthaldehyde affording the *syn*,*syn*-adduct exclusively.

To probe the generality of the Lewis base catalyzed addition of **23** to aldehydes, addition of (*E*)-**23** to benzaldehyde was studied to establish the difference, if any, in rates between the chiral enolate geometrical isomers (Scheme 12). Initial reactions at 5 mol % catalyst loadings

(25) The diastereoselectivities were assigned on the basis of chemical correlation to the known methyl ester.

TABLE 8. Aldol Addition of in Situ Generated Trichlorosilyl Enolate (*Z*)-23 to Aldehydes

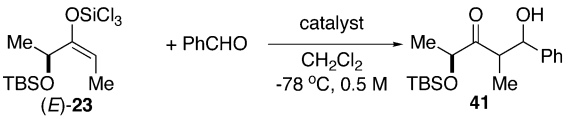


aldehyde R	catalyst	loading mol %	product	yield, %[a]	dr[b] (syn,syn)/ minors
phenyl	(*R*,*R*)-**1**	5	**41a**	88	95/5
	HMPA	15	**41a**	87	94/2/2/2
1-naphthyl	(*R*,*R*)-**1**	5	**41b**	72	98/1/1
	HMPA	15	**41b**	62	83/12/3/1
(*E*)-cinnamyl	(*R*,*R*)-**1**	5	**41c**	81	93/5/2
	HMPA	15	**41c**	79	91/6/3
(*E*)-crotyl	(*R*,*R*)-**1**	5	**41e**	85	93/4/3
	HMPA	15	**41e**	83	84/15/1
PhC≡C-	(*R*,*R*)-**1**	5	**41h**	79	95/3/2
	HMPA	15	**41h**	82	89/5/4/3
2-naphthyl	(*R*,*R*)-**1**	5	**41l**	71	94/3/3
	HMPA	15	**41l**	59	89/6/4/1
2-furyl	(*R*,*R*)-**1**	5	**41n**	82	94/6
	HMPA	15	**41n**	76	93/5/1

[a] Yield of chromatographically homogeneous material. [b] Determined by CSP-SFC analysis.

were atypically slow considering that benzaldehyde is often a superlative acceptor. Furthermore, analysis of the product revealed poor relative *anti*/*syn* stereoselectivity. To improve the results for the (*E*)-enolate, the reactions were repeated using a catalyst loading of 15 mol %. Although a marginal improvement in reaction rates was observed, the stereoselectivity remained modest relative to that observed from (*Z*)-**23**.

SCHEME 12

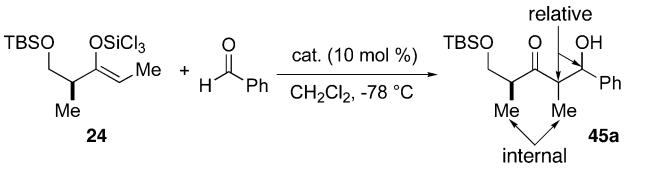


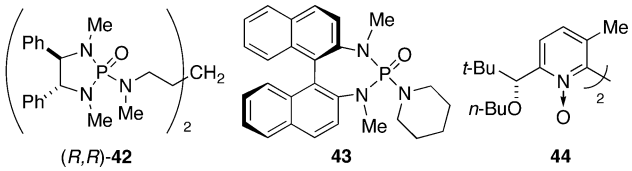
HMPA (15 mol %): 72%, rel. dr (*syn*/*anti*) = 3/1, int. dr (*syn*/*anti*) = 1/1
(*R*,*R*)-**1** (5 mol %): 81%, rel. dr (*syn*/*anti*) = 1/3, int. dr (*syn*/*anti*) = 1/4
(*S*,*S*)-**1** (5 mol %): 83%, rel. dr (*syn*/*anti*) = 1/2, int. dr (*syn*/*anti*) = 2/1

A brief survey of aldehyde acceptors was conducted to assess the stereochemical outcome of the addition of (*E*)-**23**. To allow for a direct comparison to the (*Z*)-analogue, reactions were conducted using 5 mol % (*R*,*R*)-**1** and allowed to proceed for 10−12 h. Unlike the broad substrate generality illustrated with the (*Z*)-enolate, aldol additions with (*E*)-**23** afforded very modest selectivities. Among the aldehydes surveyed, only benzaldehyde and *trans*-cinnamaldehyde afforded the desired *anti* (relative) products. Both 1-naphthaldehyde and 2-furaldehyde provided the undesired *syn* (relative) isomer. In all cases, internal diastereoselection was poor with the exception of 1-naphthaldehyde which afforded a 6/1 mixture of internal diastereomers.

4.2. Aldol Addition of Trichlorosilyl Enolates 24 and 25. Initial optimization studies for the addition of (*Z*)-**24** to benzaldehyde were performed using several different types of catalyst structures, and the results are summarized in Table 9. The aldol addition catalyzed by **1** provided the *syn* (relative) aldol product in good yield with good *syn* (internal) selectivity, although the *E*/*Z* ratio of the enolate did not exactly reflect to the (relative) diastereomeric ratio of the aldol product (entries 1 and 2). The survey of other catalysts also indicated the *syn* (relative) diastereoselectivity was attenuated significantly ranging from 4/1 to 11/1. Dimeric phosphoramide **42**, which exhibited improved diastereoselectivities for aldol addition of achiral ethyl ketone derived trichlorosilyl enolates,[11] showed the highest selectivity compared to the monomer **1** (entry 6). The use of achiral catalysts **29** and **30** showed lower catalytic activity compared to the chiral catalysts and also the relative diastereoselectivity was decreased (entries 3 and 4). Phosphoramide **43** was also relatively unselective (entry 5). Dimeric *N*-oxide **44**, which was the most selective catalyst for the addition of trichlorosilyl ketene acetal to ketones, showed low catalytic activity and selectivity (entry 7).

TABLE 9. Aldol Addition of to Benzaldehyde Catalyzed by Phosphoramides





entry	catalyst	loading, mol %	yield, %[a]	rel dr (*syn*/*anti*)[b]	int dr (*syn*/*anti*)[c]
1	(*R*,*R*)-**1**	10	72	90/10	10/1
2	(*S*,*S*)-**1**	10	82	92/8	1/7.4
3	**29**	10	46	81/19	2.7/1
4	**30**	10	50	91/9	1.4/1
5	(*R*)-**43**	10	58	86/14	1/1.6
6	(*R*,*R*)-**42**	5	88	92/8	12/1
7	*P*-(*R*,*R*)-**44**	5	12	82/18	5.3/1

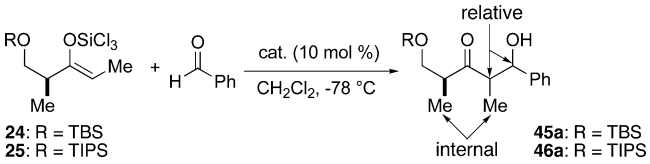
[a] Yield of chromatographically homogeneous material. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP-SFC.

With the chiral catalysts (*R*,*R*)-**1**, (*S*,*S*)-**1** and dimeric phosphoramide (*R*,*R*)-**42**, the aldol additions of (*Z*)-**24**, (*Z*)-**25** and (*E*)-**24** to benzaldehyde were studied (Table 10). Significantly higher relative and internal diastereoselectivities were achieved using TIPS-protected trichlorosilyl enolate **25**. The rate of the aldol addition for **25** was slower compared to the reactions with **24**; however, full conversion could be achieved within 8 h. The internal diastereoselection for **25** was also determined using **29**, which indicated that a small 1,4-*syn* stereoinduction results from the a-stereogenic center on the enolate. The reversal of internal diastereoselection was again observed by switching the catalyst configuration of **1**. The matched case was found to be the reaction with (*R*,*R*)-**1** providing the *syn*,*syn*-**46a** in excellent diastereoselectivity.

On the other hand, the addition of the (*E*)-enolate was not selective in either relative or internal sense. Despite

the high E/Z ratio of (*E*)-**24**, the reaction was only slightly *anti* (relative) selective (Table 10, entries 4−6). Also, the internal selectivities were poor, and the switch in internal diastereoselection was not observed in these cases. The use of dimeric catalyst **42** did not improve the relative diastereoselectivity.

TABLE 10. Aldol Addition of (*Z*)-24, (*E*)-24, and (*Z*)-25 to Benzaldehyde



entry	enolate	catalyst	yield, %[a]	rel dr (*syn*/*anti*)[b]	int dr (*syn*/*anti*)[c]
1	(*Z*)-**24**	(*R*,*R*)-**1**	72	9/1	10/1
2	(*Z*)-**24**	(*S*,*S*)-**1**	82	12/1	1/7
3	(*Z*)-**24**	(*R*,*R*)-**42**	88	12/1	12/1
4	(*Z*)-**25**	(*R*,*R*)-**1**	84	>19/1	24/1
5	(*Z*)-**25**	(*S*,*S*)-**1**	82	>19/1	1/8
6	(*Z*)-**25**	29	81	>19/1	5/1
7	(*E*)-**24**	(*R*,*R*)-**1**	72	1/4	6/1
8	(*E*)-**24**	(*S*,*S*)-**1**	72	1/2	2/1
9	(*E*)-**24**	(*R*,*R*)-**42**	80	1/2	9/1

[a] Yield of chromatographically homogeneous material. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP-SFC.

Because the selectivities observed for the addition of (*Z*)-**25** to benzaldehyde were sufficiently high, this enolate was chosen to examine the additions to other aromatic and olefinic aldehydes (Table 11). Surprisingly, the additions to these aldehydes under the previously established conditions were too slow to achieve significant conversion in a suitable time period. From previous studies, it was found that an addition of various ammonium salts can accelerate the aldol addition of trichlorosilyl enolates, presumably by increasing the ionic strength of the reaction medium. Therefore, 20 mol % of tetrabutylammonium iodide (TBAI) was added to the reaction mixture and the yields of the aldol products were improved without diminishing the diastereoselectivities.

The *syn* (relative) selectivities were maintained in all cases. The degree of relative diastereoselection varied depending on aldehyde structure. By comparing **a** and **b**, as well as **e** and **g**, the steric bulk of the aldehyde substituent seems to have detrimental effect on the relative diastereoselection (Table 11, entries 1−4 and 7−10). This phenomenon is contrary to the beneficial effect of large aldehyde substituents in the addition of methyl ketone enolates.[8a] A switch in the internal diastereoselection was also observed in all cases, with (*R*,*R*)-**1** affording the higher internal diastereomeric ratio. The internal diastereoselectivities were found to be significantly higher for aromatic aldehydes when compared to olefinic aldehydes (Table 11, entries 1 and 3). The olefinic aldehydes showed similar internal diastereoselectivities ranging from 13/1 to 15/1 for the matched cases (Table 11, entries 5, 7, and 9). Additions to aliphatic aldehydes, such as cyclohexanecarboxaldehyde and pivaldehyde produced only trace amounts of aldol products under these conditions. These aliphatic aldehydes form chlorohydrin species under these reaction conditions, and the chlorohydrins are unreactive toward aldol additions with trichlorosilyl enolates.[7c]

The absolute configuration of the aldol adduct **46c** was confirmed by comparing the physical data to the reported synthetic intermediate in the literature.[26] The configurations of other aldol products were assigned by analogy with the relative elution orders of diastereomers, using CSP-SFC.

4.3. Aldol Addition of Trichlorosilyl Enolate 26 and 27. The optimization of reaction conditions for the aldol addition of **26** and **27** was performed using benzaldehyde as the substrate (Table 12). A 10 mol % loading of phosphoramide **1** efficiently catalyzed the addition to provide the aldol products in moderate to good yields. The aldol reaction of (*Z*)-enolates showed good *syn* (relative) diastereoselectivities, indicating that the addition proceeds through chairlike transition structure. The beneficial effect of the TIPS protecting group was again observed in this case as it increased the diastereoselectivity in both relative and internal senses. The addition of (*E*)-**27** was surprisingly *syn* (relative) selective. The intrinsic selectivity of the chiral enolate (*Z*)-**27** was again determined using the achiral phosphoramide **29** (Table 12, entry 6).

To expand the scope of this aldol addition, (*Z*)-**27** was chosen to survey other aromatic and olefinic aldehydes, and the results are summarized in Table 13. In all cases, high *syn* (relative) diastereoselectivities were maintained. Excellent *syn* (relative) diastereoselectivities were observed for all the aldehydes surveyed. The internal selectivity was variable depending on the aldehyde structure. Exceptionally high diastereoselectivity was observed for **48b** compared to that of **48a**. This trend may be related to the bulk of the aldehyde substituent, and a similar trend was observed for the addition of the ethyl ketone enolate bearing an α-methyl stereogenic center.[8c]

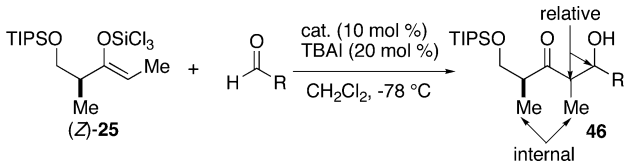
A switch in the internal diastereoselection was observed in all cases, depending on the catalyst configuration.[27] The internal selectivities were found to be significantly higher for aromatic aldehydes compared to those of other olefinic aldehydes (Table 13, entries 1 and 3). Interestingly, the disparity in the internal selectivity between (*R*,*R*)-**1** (*anti*) and (*S*,*S*)-**1** (*syn*) was larger in the aromatic aldehydes than in the olefinic aldehydes. The olefinic aldehydes showed modest internal diastereoselectivities ranging from 3/1 to 10/1 (Table 13, entries 5−10).

5. Aldol Additions of Ethyl Ketone Derived TMS Enol Ethers. 5.1. Aldol Addition of Chiral TMS Enol Ether 18. In the previous sections, the aldol additions of trichlorosilyl enolates derived from ethyl ketones were shown to selectively provide *syn* (relative) diastereomers; however, the corresponding *anti* diastereomers could not be obtained selectively. By analogy to the *anti*-selective addition of propanoate derived silyl ketene acetals,[14] it should be possible to develop an *anti* (relative) selective aldol addition of α-substituted trialkylsilyl enol ethers

(26) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2002**, *4*, 525−528.

(27) The absolute configuration of the aldol product *syn*,*anti*-**48a** was determined by chemical correlation. First, the aldol product was converted to the corresponding ester **49** by Baeyer−Villiger oxidation with buffered *m*-CPBA (Bernhard, W.; Fleming, I. *J. Organomet. Chem.* **1984**, *271*, 281−288). Next, **49** was hydrolyzed under basic conditions to provide diol **50** in good yield. The configuration was assigned as (1*S*,2*R*)-1-phenylpropane-1,2-diol by comparing the sign of the optical rotation to the literature value. (a) Kihumbum, D.; Stillger, T.; Hummel, W.; Liese, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1069−1072.

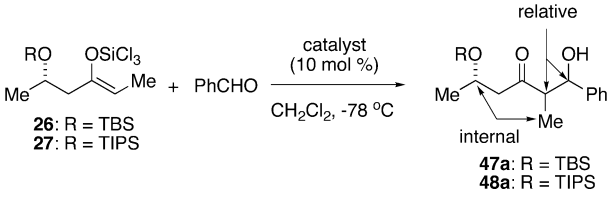
TABLE 11. Aldol Addition of (*Z*)-25 to Various Aldehydes[a]



entry	aldehyde R	product	catalyst	time, h	yield, %[b]	rel dr (*syn/anti*)[c]	int dr (*syn/anti*)[d]
1[e]	phenyl	**46a**	(*R,R*)-**1**	8	84	>19/1	24/1
2[e]	phenyl	**46a**	(*S,S*)-**1**	8	82	>19/1	1/8
3	1-naphthyl	**46b**	(*R,R*)-**1**	8	71	14/1	89/1
4	1-naphthyl	**46b**	(*S,S*)-**1**	8	79	14/1	1/17
5	(*E*)-cinnamyl	**46c**	(*R,R*)-**1**	10	88	9/1	14/1
6	(*E*)-cinnamyl	**46c**	(*S,S*)-**1**	10	75	15/1	1/6
7	(*E*)-crotyl	**46e**	(*R,R*)-**1**	6	90	>19/1	15/1
8	(*E*)-crotyl	**46e**	(*S,S*)-**1**	6	85	>19/1	1/5
9	MeCH=CMe	**46g**	(*R,R*)-**1**	7	85	13/1	13/1
10	MeCH=CMe	**46g**	(*S,S*)-**1**	7	80	19/1	1/5

[a] (*Z*)-**25** contained ~10% of bisenoxysilane. [b] Yield of chromatographically homogeneous material. [c] Determined by ^{1}H NMR analysis. [d] Determined by CSP−SFC. [e] No TBAI was added.

TABLE 12. Aldol Additions of 26 and 27 to Benzaldehyde



entry	enolate	*Z/E*	catalyst	yield, %[a]	rel dr (*syn/anti*)[b]	int dr (*syn/anti*)[c]
1	(*Z*)-**26**	12/1	(*R,R*)-**1**	59	6/1	1/14
2	(*Z*)-**26**	12/1	(*S,S*)-**1**	60	12/1	14/1
3	(*Z*)-**27**	16/1	(*R,R*)-**1**	84	>19/1	1/16
4	(*Z*)-**27**	16/1	(*S,S*)-**1**	86	>19/1	10/1
5	(*E*)-**27**	1/15	(*S,S*)-**1**	80	3/1	1/1
6	(*Z*)-**27**	>19/1	**29**	83	>19/1	1/1.4

[a] Yield of chromatographically homogeneous material. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP-SFC.

derived from ketones using the bisphosphoramide/$SiCl_4$ system. Therefore, the TMS enol ethers derived from the chiral ethyl ketones have been assayed in the bisphosphoramide-catalyzed Mukaiyama-type aldol additions.

The initial reaction optimization surveyed catalyst structure and the effect of tetraalkylammonium salts for the aldol addition of (*Z*)-**18** to benzaldehyde (Table 14). With 5 mol % of the dimeric catalyst **2**, the aldol product was obtained in modest yields although the reaction did not go to completion even after 24 h. The monomeric phosphoramide **1** was not catalytically active under these conditions (entries 3 and 4). When (*S,S*)-**2** was used, the internal diastereoselectivity was only 6/1 within the *anti* (relative) manifold (entry 2). With (*R,R*)-**2** as a catalyst, the *anti,anti* diastereomer was formed almost exclusively (entry 1).[28]

In aldol additions of the corresponding trichlorosilyl enolate, the addition of tetraalkylammonium salts was found to increase the yields of the reactions. Therefore, the effect of additives has been investigated in this aldol reaction. Addition of 20 mol % of tetrabutylammonium iodide indeed increased the yield. The effect was clear in the reaction catalyzed by monomeric catalyst **1** wherein the yield increased dramatically (entry 5). For the reaction catalyzed by dimeric phosphoramide **2**, the effect of the ammonium salt was relatively small; however, only a 10% increase in yield was observed without eroding the diastereoselectivity (entries 6 and 7).

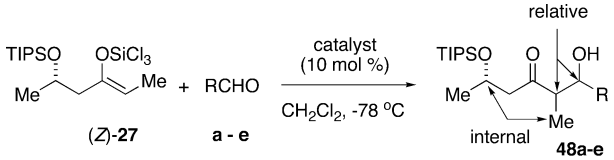
To increase the yield of the aldol addition, the reaction temperature for the aldol addition of **18** was varied (Table 15). An increase in yield was observed as the reaction temperature was raised to −50 °C; however, the reaction at −20 °C failed to afford the aldol product. Interestingly, as the temperature of the reaction increased, the relative diastereoselectivity dropped significantly, whereas the internal diastereoselectivity remained almost constant. Reaction at −60 °C was selected as the optimal reaction temperature because the diastereoselectivity was only slightly attenuated. The yield of the aldol product was further improved by using an excess (1.5 equiv) of the aldehyde. Because the enol ether now has become the limiting reagent, diisopropylethylamine was added as an acid scavenger to prevent the destruction of the nucleophile by adventitious acid that may occur during the reaction. Under the optimal conditions, up to an 81% yield of aldol product can be obtained.

The scope of aldehyde in this reaction was surveyed next. However, under the same conditions described above, the reaction of (*Z*)-**18** with cinnamaldehyde did not provide the addition product and the starting materials were recovered. Thus, the reaction conditions seem to be only applicable to the addition to benzaldehyde.

5.2. Aldol Addition of (*S*)-3-Hydroxybutyrate Derived TMS Enol Ethers 21 and 22. The aldol addition of TMS enol ether derived from an ethyl ketone bearing a β-silyloxy stereogenic center was also investigated using bisphosphoramide catalysis. Using the similar conditions established in the previous section, the aldol addition of (*Z*)-**21** to benzaldehyde was executed (Scheme 13). The aldol product was obtained in good yield under catalysis by (*R,R*)-**2**. However, it was surprising to find that the aldol addition provided the *syn* (relative) diastereomer as the major product. By the use of the monomeric phosphoramide **1**, the reaction was moderately *anti*-

(28) The assignments for the relative *anti* diastereomers were made by analogy to the assignment of aldol products from ref 7c.

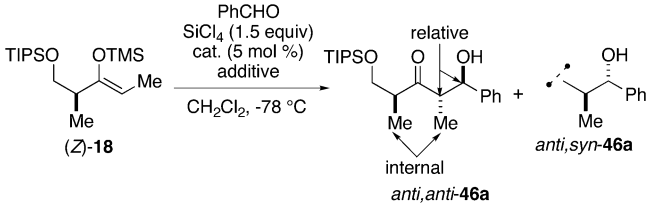
TABLE 13. Aldol Addition of (*Z*)-27 to Various Aldehydes[a]



entry	aldehyde R	product	catalyst	time, h	yield, %[b]	rel dr (*syn/anti*)[c]	int dr (*syn/anti*)[d]
1[e]	phenyl	**48a**	(*R,R*)-**1**	6	84	>19/1	1/16
2[e]	phenyl	**48a**	(*S,S*)-**1**	6	86	>19/1	10/1
3	1-naphthyl	**48b**	(*R,R*)-**1**	8	80	>19/1	1/30
4	1-naphthyl	**48b**	(*S,S*)-**1**	8	75	>19/1	10/1
5	(*E*)-cinnamyl	**48c**	(*R,R*)-**1**	12	83	>19/1	1/10
6	(*E*)-cinnamyl	**48c**	(*S,S*)-**1**	12	81	>19/1	8/1
7	(*E*)-2-Me-cinnamyl	**48d**	(*R,R*)-**1**	8	83	>19/1	1/3
8	(*E*)-2-Me-cinnamyl	**48d**	(*S,S*)-**1**	8	81	>19/1	3/1
9	(*E*)-crotyl	**48e**	(*R,R*)-**1**	8	79	>19/1	1/7
10	(*E*)-crotyl	**48e**	(*S,S*)-**1**	8	83	>19/1	6/1

[a] (*Z*)-**27** contained 10% of the bisenoxysilane, and the *Z*/*E* ratio was >19/1. [b] Yield of chromatographically homogeneous material. [c] Determined by ^{1}H NMR analysis. [d] Determined by CSP-SFC. [e] *Z*/*E* ratio was 16/1.

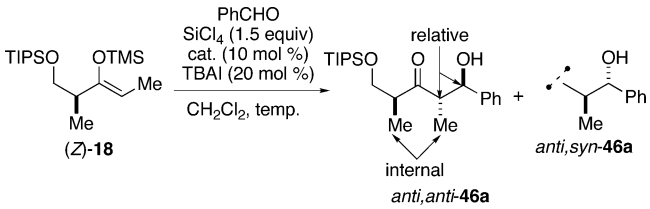
TABLE 14. Aldol Addition of (*Z*)-18 Catalyzed by Chiral Phosphoramides[a]



entry	catalyst	additive[b]	yield, %[c]	rel dr (*syn/anti*)[d]	int dr (*syn/anti*)[e]
1	(*R,R*)-**2**		40	1/>19	1/>50
2	(*S,S*)-**2**		46	1/>19	6/1
3	(*R,R*)-**1**		tr		
4	(*S,S*)-**1**		tr		
5	(*R,R*)-**1**	TBAI	55	1/>19	1/34
6	(*S,S*)-**2**	TBAI	50	1/>19	8/1
7[f]	(*R,R*)-**2**	TBAI	55	1/>19	1/>50

[a] *Z*/*E* ratio for **18** was >19/1. [b] 20 mol % added. [c] Yield of chromatographically homogeneous material. [d] Determined by ^{1}H NMR analysis. [e] Determined by CSP-SFC. [f] TBS-protected **17** was used as nucleophile.

TABLE 15. Aldol Addition of 18 at Higher Reaction Temperatures[a]



entry	catalyst	temp, °C	yield, %[b]	rel dr (*syn/anti*)[c]	int dr (*syn/anti*)[d]
1	(*R,R*)-**2**	−78	55	1/>19	1/34
2[e]	(*R,R*)-**2**	−60	62	1/>19	1/37
3	(*R,R*)-**2**	−50	75	1/17	1/35
4[f]	(*R,R*)-**2**	−60	81	1/>19	1/74
5[f]	(*S,S*)-**2**	−60	72	1/>19	5.6/1

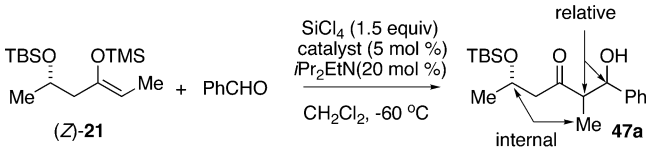
[a] *Z*/*E* ratio of **18** was >19/1. [b] Yield of chromatographically homogeneous material. [c] Determined by ^{1}H NMR analysis. [d] Determined by CSP-SFC. [e] 5 mol % of **2** was used. [f] Excess benzaldehyde (1.5 equiv) was used and 20 mol % of *i*-Pr$_2$EtN was added.

selective, though the yield of the aldol product was attenuated. Within the *anti* (relative) manifold, the internal diastereoselectivity was only modest.

Although the enolate geometry did not affect the diastereoselectivity of aldol addition in propanoate derived ketene acetals, the aldol addition of TIPS-protected (*E*)-**22** was attempted to examine the diastereoselectivity. Interestingly, the aldol addition catalyzed by (*S,S*)-**2** showed good relative *anti* selectivity (17/1); however, the yield of the aldol product was dramatically decreased. This observation is perplexing since there was no reactivity difference in the aldol addition of (*Z*)- and (*E*)-silyl ketene acetal derived from propanoate.[7c]

The aldol additions of chiral TMS enol ethers (*Z*)-**21** and (*E*)-**22** to benzaldehyde gave disappointing results. The addition of (*Z*)-**21** was not selective under these reaction conditions and provided a complex mixture of all four possible isomers. The addition of (*E*)-**22** was relative *anti*-selective but did not afford synthetically useful yields.

SCHEME 13



(*R,R*)-**2**: 87%, rel. dr (*syn*/*anti*) = 3/1, int dr (*anti*/*syn*) = 4/1
(*R,R*)-**1**: 53%, rel. dr (*syn*/*anti*) = 1/2, int dr (*anti*/*syn*) = 6/1

Discussion

1. Aldol Addition of Methyl Ketone Derived Trichlorosilyl Enolates 9 and 12. The aldol additions of **9** and **12** are efficiently catalyzed by phosphoramide **1**. Unlike the aldol addition of the lactate derived trichlorosilyl enolate,[9] the catalyst controlled diastereoselectivity was observed for both of these enolates. For **9**, there is a weak inherent (substrate-controlled) stereoinduction from the resident stereogenic center (entry 12, Table 2). This stereoinduction may be explained by the following two models (Figure 1). Transition structure **I** places the least sterically demanding group (hydrogen) facing toward the silicon to avoid the steric crowding at

the silicon center. This model predicts the approach of benzaldehyde from the face containing the methyl group rather than that containing the oxygenated substituent. The other model, **II**, proposes the coordination of the trichlorosilyl ether by the OTBS group. Although the TBS group is often considered as nonchelating protecting group, the nature of electrophilic silicon in this species is not well-known, and this proposal may be appropriate. Thus, the approach of the aldehyde is controlled by the difference between a hydrogen or a methyl group whereby approach from the hydrogen side is consistent with the observed selectivity.

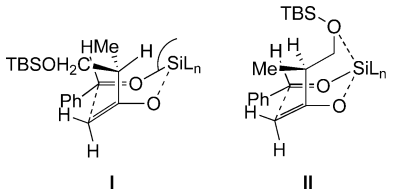


FIGURE 1. Transition state model for the aldol addition of **9**.

The α-stereogenic center exhibited a modest, intrinsic 1,4-*syn* stereoinduction, but the 1,4-*syn* selectivity could be increased dramatically by catalysis with (*R*,*R*)-**1**. The external stereoinduction from the catalyst dominated the stereochemical course of the aldol addition, allowing for selective preparation of either diastereomer by simply changing the catalyst configuration. The reaction was found to be general for various aldehydes including aromatic, olefinic, acetylenic and aliphatic aldehydes which are traditionally problematic substrates under these reaction conditions.

The aldol addition of **12** showed that the stereoinduction from β-stereogenic center is almost nonexistent (Scheme 10). This results contrasts to the recent reports on the aldol additions of boron enolates bearing a β-stereogenic center.[12] In these cases, a strong 1,5-*anti* stereoinduction is observed. However, these studies also revealed that the nature of the protecting group at the β-hydroxyl group significantly affects the substrate-controlled stereoinduction. The changing the substituent at the β-position from alkyl ethers (benzyl and 4-methoxybenzyl) to TBS ether lead to almost complete loss of the diastereoselectivity. Therefore, it is conceivable that, in the aldol addition of **12**, the substrate-controlled diastereoselectivity may be increased by changing to, for example, a benzyl ether.

The absence of internal stereoinduction allowed the catalyst-controlled diastereoselection for the aldol additions of **12**. Using chiral phosphoramide **1**, either diastereomer of **35a** could be obtained; however, the diastereoselectivities are unacceptably low. By changing the protecting group on β-hydroxyl from TBS to TIPS, the diastereoselectivity was decreased. Because the observed selectivities for benzaldehyde were not high, the scope of the aldehyde for the aldol addition of **12** was not investigated. However, these types of aldol products are obtained in high yields and selectivities using the TMS enol ether **11** as the nucleophile (Table 6).

2. Aldol Additions of Methyl Ketone Derived TMS Enol Ethers. The aldol addition of trialkylsilyl enol ethers is catalyzed by the Lewis acid generated by activating $SiCl_4$ with various chiral phosphoramides. This process is mechanistically distinct from the addition of trichlorosilyl enolates, and thus, the nature and extent of diastereoselection will be different. Indeed, the aldol addition of TMS enol ether **8** showed significantly higher diastereoselectivity than the aldol addition of the corresponding trichlorosilyl enolate **9** for benzaldehyde (Table 5). Interestingly, the *anti* diastereomer was obtained in the matched case using (*S*,*S*)-**2**. The internal diastereoselectivity was not measured directly using achiral phosphoramide; however, it is clear from the results that the stereoinduction from the resident stereogenic center is small. Thus, the catalyst-controlled diastereoselection dominated allowing for selective preparation of both diastereomers.

The stereoinduction of the β-stereogenic center is also absent in the addition of TMS enol ether **11** (Scheme 11). Unlike the corresponding to the addition of trichlorosilyl enolate **12**, the aldol adducts of benzaldehyde were obtained in excellent diastereoselectivities.

The observed facial selectivity of the aldehyde is consistent with the aldol additions of achiral nucleophiles using the same catalyst system. The calculated model predicts the complex shown in Figure 2 is one of the lowest energy species.[14d] In this model, (*R*,*R*)-**2** blocks the *Si* face of the aldehyde, and the nucleophile can preferentially attack from the *Re* face.

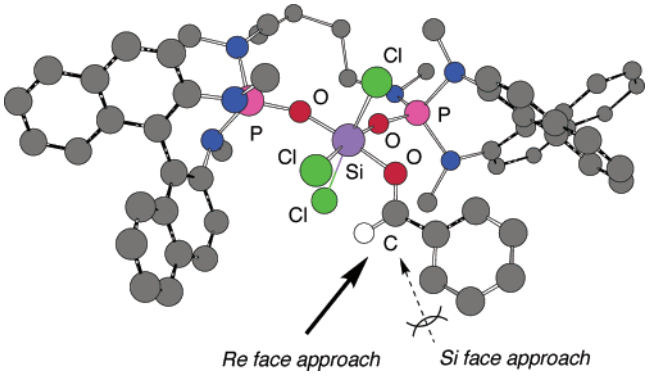


FIGURE 2. $SiCl_4$-(*R*,*R*)-**2**-PhCHO complex.

The aldehyde scope for the addition of TMS enol ethers is relatively limited compared to the corresponding aldol additions of trichlorosilyl enolates. The aromatic and cinnamaldehyde provided aldol products in high yields and excellent selectivities. However, the additions to simple olefinic aldehydes such as crotonaldehyde provided a complex mixture of products, and the desired aldol adducts can only be obtained in low yields. Interestingly, the presence of α-branching in the aldehyde led to significant decrease in the reactivity and selectivity. These results contrasts to the aldol additions of trichlorosilyl enolates where these aldehydes showed increased selectivities. Presumably, the added steric bulk around the carbonyl hinders the coordination of the aldehyde to the catalyst complex in these aldehydes.

For aliphatic aldehydes, the chlorosilyl ether formation inhibits the aldol addition.[14a] When stronger nucleophiles such as ketene acetals and isocyanides are used, the addition to aliphatic aldehydes was observed under similar conditions. Lack of reactivity for silyl enol ethers toward aliphatic aldehydes confirms the less nucleophilic nature of trialkylsilyl enol ethers.

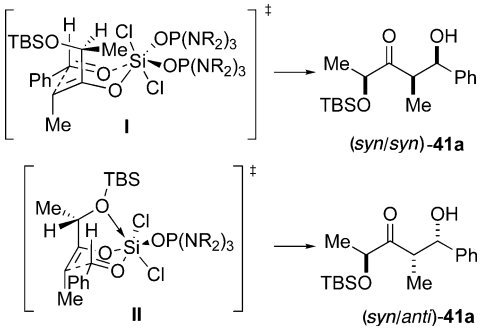
3. Aldol Additions of Ethyl Ketone Derived Trichlorosilyl Enolates. Earlier studies on the aldol additions of α-substituted trichlorosilyl enolates showed that the enolate geometry is strictly reflected in the relative diastereoselectivity, which is consistent with a Zimmerman−Traxler-type transition state model.[29] Therefore, the geometrically enriched (*Z*)-enolate should provide the *syn* (relative) diastereomer exclusively, whereas the cyclic enolates ((*E*)-enolates) provide the *anti* (relative) diastereomer as the major product when chiral phosphoramide **1** is used.

The aldol addition of lactate derived enolate (*Z*)-**23** under phosphoramide catalysis provides the *syn*,*syn*-aldol product in high selectivity (Table 8). A survey of chiral and achiral phosphoramide demonstrated the near perfect *syn*/*anti*-*Z*/*E* correlation indicating that the chairlike transition structure is maintained. Even the bulky phosphoramide **39**, which catalyzes the aldol addition preferentially through a boat transition structure, provided the *syn* product.

The internal stereoselectivities vary for different catalyst structure. For the stilbene-1,2-diamine derived catalyst, (*R*,*R*)-**1**, an excellent internal *syn* selectivity can be obtained. The use of the enantiomeric catalyst (*S*,*S*)-**1** is unable to reverse the sense of internal selectivity, and the aldol product is obtained with good internal *syn* selectivity. These observations indicate the strong influence of the resident stereogenic center, and the stereochemical course of the aldol addition is determined solely by this stereocenter. To support this explanation, the additions using various achiral phosphoramides including HMPA demonstrate that the internal *syn* aldol product is preferentially formed under catalyzed conditions regardless of the catalyst configuration. The bulky phosphoramides such as (*R*,*R*)-**39** show attenuated internal diastereoselectivity when compared to other phosphoramides.

The observed stereochemical outcome can be explained by the nonchelation model that places the OTBS substituent on the enolate in plane with the enolate double bond to minimize the dipole moment (Scheme 14).[16] The two enolate faces are differentiated by the size of the groups on the stereogenic center (H vs Me), and the aldehyde approaches from the less hindered *Si* face of the enolate. The chairlike arrangement of the aldehyde leads to the formation of the observed *syn*,*syn* diastereomer. The low selectivities observed for the bulky phosphoramides can be rationalized by the other transition structure **II**.[8b] These phosphoramides are known to favor boatlike transition structures via a mechanism that involves only one phosphoramide in the stereodetermining step.[30] In this pentacoordinate species, it is possible that the silyloxy group could coordinate the Lewis acidic silicon to form an octahedral, cationic silicon intermediate. This internal coordination may favor the chairlike arrangement over the usual boatlike transition structure for these phosphoramides. Although the coordinating ability of the TBS ether is modest at best,[31] the proximity of the silyloxy group to the cationic silicon is believed to enhance the possibility for this type of chelation.[32] In this model, the aldehyde now approaches from the *re* face of the enolate, leading to the *syn*,*anti* diastereomer.

SCHEME 14



The relative diastereoselectivity for the addition of (*Z*)-**24** did not strictly mirror the *Z*/*E* ratio of the enolate (Table 10). This result indicates that there are other competitive transition structures (possibly boat-shaped models) leading to *anti* (relative) diastereomers and resulting in erosion of relative diastereoselectivity. However, the relative diastereoselectivity is improved by changing the protecting group on β-hydroxyl group from TBS to TIPS group. With (*Z*)-**25**, the *syn* (relative) diastereomers are obtained exclusively.

The internal diastereoselection varied significantly with catalyst structure (Table 10). The 1,2-stilbenediamine derived catalyst **1** provided the best internal diastereoselection. Catalyst (*R*,*R*)-**1** showed 1,4-*syn* (internal) stereoinduction yielding the *syn*,*syn* diastereomer as the major product, whereas the catalyst (*S*,*S*)-**1** provided the *syn*,*anti* diastereomer selectively. The internal diastereoselection from the chiral enolate was determined using achiral catalyst **29**, and showed a very weak 1,4-*syn* stereoinduction. Thus, the reaction with (*R*,*R*)-**1** represents the matched case affording the *syn*,*syn* diastereomer with high selectivity. The external diastereoselection from the catalyst dominates in this reaction allowing for catalyst controlled preparation of either *syn* (relative) diastereomer.

As was the case for methyl ketone enolate **12**, the effect of the resident stereogenic center in the aldol addition of (*Z*)-**27** was negligible, inducing nearly 1/1 internal diastereoselection (Table 12). This outcome allowed diastereocontrolled aldol addition to produce either *syn* (relative) diastereomer by changing the configuration of **1**. The use of (*R*,*R*)-**1** produced the *syn*,*anti* diastereomer, while the *syn*,*syn* diastereomer was obtained using the (*S*,*S*)-**1**. Thus, the external stereoinduction from the catalyst determined the diastereoselection in these aldol additions. This catalyst-controlled aldol addition enhances the synthetic utility of trichlorosilyl enolates.

For the aldol additions of (*Z*)-trichlorosilyl enolates, the scope in the aldehyde was proven to be broad, and aromatic and conjugated aldehydes afforded the *syn*

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(30) (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.

(31) For a discussion of the coordinating abilities of various ether substituents, see: (a) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468. (b) Chen, X. N.; Hortellano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130−6131. (c) Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055−5056.

(32) For a discussion of chelation as a stereocontrol element in lactate derived stannous enolate, see: Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233−4236.

(relative) products selectively using the chiral phosphoramide **1**. The aldol addition of (*Z*)-**23** to various aldehydes revealed that the strong effect of the resident stereogenic center dominated the stereochemical outcome, and the reactions catalyzed by HMPA exhibited high selectivity for the *syn*,*syn* diastereomers. For (*Z*)-**25** and (*Z*)-**27**, the weak or almost negligible internal stereoinduction allowed the catalyst control to dominate the overall stereoinduction, which in turn provided access to both of the *syn* (relative) diastereomers selectively for various aldehydes. However, these nucleophiles failed to react with aliphatic aldehydes. This is presumably because the added steric bulk of α-substituent on the enolate decreases the reactivity.

On the other hand, reactions with the *E*-configured trichlorosilyl enolate demonstrated only modest stereoselectivity even with chiral phosphoramides. The lack of stereoinduction by either the resident stereogenic center or the chiral phosphoramide appears to be a common problem with (*E*)-trichlorosilyl enolates.[1k] Although it may typically be expected that the reaction of (*E*)-enolates would be more facile due to the orientation of the enolate substituent being placed in a pseudoequatorial position as observed in the aldol addition of cyclic trichlorosilyl enolates,[33] the results from the reactions of (*E*)-trichlorosilyl enolates derived from acyclic ketones would suggest otherwise. This appears counterintuitive since reactions of an (*E*)-enolate would obviate the axial orientation of the enolate substituent. Based upon experimental results, the position of the enolate substituent in an (*E*)-enolate has negative repercussions on the overall stereoselectivity of the aldol addition. Unlike typical conformational analyses of cyclohexanes, the transition structures for the aldol additions contain no severe 1,3-diaxial interactions for a (*Z*)-enolate substituent positioned axially in a chairlike arrangement. Conversely, an equatorial substituent from an (*E*)-enolate would provide 1,2-gauche interactions. To minimize these unfavorable steric interactions, the aldehyde substituent can be oriented axially to afford *syn* aldol products in the relative manifold. Since the axial orientation of the aldehyde substituent affords 1,3-diaxial interactions with the enolate spectator group, the overall effect is that both transition structures become similar in energy, resulting in the loss of stereoselectivity.[34] In addition, positioning of the enolate substituent in an *E*-conformation allows the metal center to rotate away from the bulky spectator substituents, minimizing steric encumbrances. This now allows the components to adopt alternative transition structures, altering the predicted stereochemical course of the reaction.[35] The poor stereoselectivities observed for the reactions of the (*E*)-enolates to aldehydes certainly suggest multiple transition structures are operative.

4. Aldol Additions of Ethyl Ketone Derived TMS Enol Ethers. In the aldol addition of (*Z*)-**18** to benzaldehyde catalyzed by bisphosphoramide **2**, the relative configuration of the major aldol product was predominantly *anti* (Table 15). Unlike the addition of the analogous trichlorosilyl enolates, the formation of *anti* (relative) product from the (*Z*)-enol ether indicates the involvement of an open transition structure. This observation is consistent with the previous studies that employed propanoate derived silyl ketene acetals, wherein the geometry of the ketene acetal did not influence the relative diastereoselectivity of the aldol addition.[14d]

The internal diastereoselectivity differed dramatically between the two enantiomeric catalysts (Table 15). Thus, the reaction catalyzed by (*R*,*R*)-**2** is apparently the matched case providing *anti*,*anti* diastereomer in high stereoselectivity, and it is clear that the internal stereoinduction from the α-stereogenic center showed strong 1,4-*syn* stereoinduction. However, the diastereoselection was switched between these two enantiomeric catalysts, indicating that the primary diastereoselection is provided by the external stereoinduction from the catalyst.

In contrast, the aldol addition of TMS enol ether (*Z*)-**21** was unselective. Only modest diastereoselectivities were observed for the reactions with chiral phosphoramides **1** and **2**. The relative diastereoselectivities could be improved by changing the double bond geometry of the enol ether; however, this change resulted in loss of reactivity. These results are unexpected considering the additions of the propanoate derived ketene acetals are insensitive to the double bond geometry both in terms of the diastereoselectivity and the reactivity.

Overall, the aldol addition of chiral TMS enol ethers **18** and **21** under bisphosphoramide catalysis provided the access to the *anti* (relative) diastereomers. The reaction was slow compared to the analogous TMS enol ether derived from methyl ketones, and the increased catalyst loading and temperature were required to achieve significant conversion. This is presumably due to the low reactivity of the TMS enol ether. For this process to be synthetically useful, the development of a more active catalyst and/or the use of a more reactive nucleophile need to be investigated.

5. Summary. These aldol additions using the different classes of chiral trichlorosilyl enolates and TMS enol ethers represent interesting cases of double diastereodifferentiating aldol additions. Given the number of permutations investigated in this study, a summary of the key findings is warranted:

(1) In the aldol addition of methyl ketone derived trichlorosilyl enolates **9** and **12**, the resident stereogenic centers exhibited modest and weak stereoinduction respectively, leading to dominant catalyst controlled selectivity. The scope of aldehyde structure was examined with **9**, and various aldehydes including aromatic, olefinic, acetylenic, and aliphatic aldehydes provided aldol products in modest to good diastereoselectivities.

(2) The additions of methyl ketone derived TMS enol ethers **8** and **11** catalyzed by bisphosphoramide **2** showed extremely high diastereoselectivities. In this family, the aldehyde scope is limited to aromatic aldehydes. In all cases, catalyst-controlled diastereoselection was achieved allowing for access to either the 1,5-*syn* or -*anti* diastereomer.

(3) In the aldol additions of ethyl ketone derived enolates **23**, **25** and **27**, the addition of the (*Z*)-enolates afforded predominantly the *syn* (relative) diastereomer. On the other hand, aldol addition of the corresponding

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(*E*)-enolates was not selective. The stereochemical course in the addition of (*Z*)-**23** was primarily controlled by the strong induction from the resident stereogenic center. The *syn*,*syn* diastereomer was obtained in high selectivity regardless of the catalyst configuration and structure. On the other hand, the aldol additions of (*Z*)-**25** and (*Z*)-**27** showed catalyst-controlled diastereoselection. With these enolates, aromatic and olefinic aldehydes react to provide the *syn* (relative) diastereomers in good diastereoselectivities.

The aldol additions of TMS enol ethers (*Z*)-**18** and (*Z*)-**21** were *anti* (relative) selective. However, the lack of reactivity under the $SiCl_4$/bisphosphoramide catalysis was apparent, and the search for a more active catalyst system and better reaction conditions is needed.

Conclusion

The aldol additions of chiral silyl enol ethers were investigated under Lewis base catalysis. The aldol additions of chiral trichlorosilyl enolates were efficiently catalyzed by chiral phosphoramide **1**, whereas the additions of chiral TMS enol ethers were catalyzed by dimeric phosphoramide **2**. In aldol additions of lactate derived trichlorosilyl enolates, the internal stereoinduction from α-silyloxy group dominated the overall diastereoselection. On the other hand, the effects of α-methyl and β-silyloxy groups were relatively small, allowing for catalyst-controlled diastereoselection. A wide variety of aldehydes including aromatic and alkenyl aldehydes reacted under phosphoramide catalysis, providing stereodyads and triads that resemble common structural motifs found in natural products. Further studies are currently underway to develop reagents capable of reacting with aliphatic aldehydes and to apply these methods in the synthesis of complex natural products.

Experimental Section

General Experimental. See Supporting Information.

Experimental Procedures. General Procedure I. MeLi-Mediated Transsilylation of 17: (2*Z*,4*S*)- 5-(*tert*-Butyldimethyl-silyloxy)-4-methyl-3-trichlorosilyloxy-2-pentene ((*Z*)-24). In a 25-mL two-neck flask was placed a solution of (*Z*)-**17** (908 mg, 3.00 mmol) in ether (6 mL) at 0 °C. To the solution was slowly added MeLi (3.00 mL, 4.50 mmol, 1.5 equiv, 1.5 M in ether). The reaction mixture was stirred for 4.5 h at room temperature, then cooled to −70 °C using an dry ice/2-propanol bath. The reaction mixture was transferred dropwise using a cannula to a 100-mL two-neck flask containing a cold (−70 °C) solution of silicon tetrachloride (3.45 mL, 30.0 mmol, 10 equiv) in ether (6 mL). The reaction mixture was stirred at −70 °C for 1 h and gradually warmed to room temperature. The precipitate settled at the bottom of the flask, and the supernatant was transferred to a 35-mL round-bottom flask. The volatiles were removed under vacuum (0.5 mmHg), and the residue was distilled using a Kugelrohr apparatus (150 °C ABT at 1.0 mmHg), to afford 901 mg (2.48 mmol, 83%) of (*Z*)-**24** as a clear colorless oil. ^{1}H NMR: ($CDCl_3$, 500 MHz) 4.53 (qd, J = 6.8, 0.5, 1 H, HC(2)); 3.69−3.43 (ABX, 2 H, $H_2C(5)$); 2.40 (sext, J = 6.3, 1 H, HC(4)); 1.60 (dd, J = 7.1, 0.7, 3 H, $H_3C(1)$); 1.07 (d, J = 7.1, 3 H, $H_3C(6)$); 0.88 (s, 9 H, $H_3C(9)$); 0.03 (s, 6 H, $H_3C(7)$) ^{13}C NMR: ($CDCl_3$, 126 MHz) 150.8 (C(3)); 106.4 (C(2)); 65.3 (C(5)); 42.1 (C(4)); 25.8 (C(9)); 18.2 (C(8)); 14.9 (C(7)); 11.0 (C(1)); −5.5, −5.4 (C(7)).

General Procedure II. Aldol Reaction of Isolated Trichlorosilyl Enolate: (2*S*,5*R*)-1-*tert*-Butyldimethylsililoxy-2-methyl-5-hydroxy-5-phenyl-3-pentanone (*syn*-28a). Trichlorosilyl enolate **9** (140 mg, 0.40 mmol, 1.2 equiv) was added to a solution of (*R*,*R*)-**1** (12.2 mg, 0.033 mmol, 0.10 equiv) in 0.66 mL of CH_2Cl_2. The reaction mixture was cooled using an acetone/CO_2 bath, and PhCHO (34 μL, 0.33 mmol, 1 equiv) was added using a syringe. The reaction was monitored by taking an aliquot from the reaction mixture and analyzing on TLC (hexane/EtOAc, 5/1). After 1 h of stirring (or when the aldehyde spot disappeared), the reaction mixture was quenched by pouring into a vigorously stirring 5 mL of cold saturated $NaHCO_3$ aq. The resulted slurry was stirred for 15 min and filtered through Celite. The layers were separated, and the aqueous layer was extracted with 10 mL of CH_2Cl_2. The organic phases were combined, washed with 2 mL of brine and dried over sodium sulfate. After filtration, the filtrate was concentrated. The crude product was purified by column chromatography (hexane/EtOAc, 5/1), and 78 mg (0.24 mmol, 73%) of **28a** was obtained as a clear viscous oil. ^{1}H NMR: (500 MHz, $CDCl_3$) *syn*-**28a** 7.37−7.26 (m, 5 H, aromatic); 5.17 (dt, J = 8.5, 3.2, 1 H, HC(5)); 3.75−3.65 (ABX, 2 H, $H_2C(1)$); 3.50 (d, J = 2.9, 1 H, HO); 2.98−2.84 (ABX, 2 H, $H_2C(4)$); 2.78 (sext, J = 7.1, 1 H, HC(2)); 1.03 (d, J = 7.1, 3 H, $H_3C(6)$); 0.87 (s, 9H, C(9)); 0.04 (d, J = 1.7, 6 H, C(7)); *anti*-**28a** 7.37−7.26 (m, 5 H, aromatic); 5.14 (dt, J = 9.3, 3.0, 1 H, HC(5)); 3.77−3.65 (ABX, 2 H, $H_2C(1)$); 3.54 (d, J = 3.0, 1 H, HO); 2.98−2.84 (ABX, 2 H, $H_2C(4)$); 2.79 (sext, J = 7.1, 1 H, HC(2)); 1.04 (d, J = 7.1, 3 H, $H_3C(6)$); 0.88 (s, 9H, C(9)); 0.04 (d, J = 1.7, 6 H). SFC: (OD column, 175 bar, 2.5 mL/min, 1.7% MeOH) t_R *syn*-**28a** 5.414 min (91.3%); t_R *anti*-**28a** 5.989 min (8.7%).

General Procedure III. Aldol Addition of in Situ Generated Trichlorosilyl Enolate Using 8: (1*S*,4*R*)-5-*tert*-Butyldimethylsililoxy-4-methyl-1-hydroxy-1-phenyl-3-pentanone (*syn*-28a). To a suspension of mercury(II) acetate (3.2 mg, 0.01 mmol, 0.01 equiv) in 1 mL of methylene chloride was added silicon tetrachloride (0.23 mL, 2.0 mmol, 2.0 equiv) and the trimethylsilyl enol ether **8** (288 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 30 min. The excess silicon tetrachloride and the solvent were removed under vacuum. To the residue was added solution of the chiral phosphoramide (*R*,*R*)-**1** (36.9 mg, 0.10 mmol, 0.10 equiv) in 2 mL of methylene chloride via a cannula. The reaction mixture was cooled to −78 °C before the addition of benzaldehyde (102 μL, 1.00 mmol, 1 equiv). The reaction mixture was stirred at −78 °C for 2.5 h and then was quenched by pouring into 5 mL of vigorously stirring cold saturated aqueous sodium bicarbonate. The resulting slurry was stirred for 1 h and was filtered through Celite. The layers were separated and the aqueous layer was extracted with 20 mL of methylene chloride. The combined organic extracts were washed with 5 mL of brine, dried over sodium sulfate and concentrated. The crude product was chromatographed (hexane/ether, 5/1, SiO_2) to give **28a** (268 mg, 0.83 mmol, 83%) as viscous colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) 7.23−7.47 (m, 5H, aromatic); 5.17 (dt, J = 8.8, 3.2, 1H, HC(1)); 3.65−3.76 (ABX, 2H, C(5)H_2); 3.49 (d, J = 2.9, 1H, OH); 2.86−2.96 (ABX, 2H, C(2)H_2); 2.78 (m,1H, C(4)-H); 1.03 (d, J = 6.9, 3H, C(6)H_3); 0.87 (s, 9H, (C(9)H_3)$_3$); 0.04 (d, J = 2, 6H, C(7)H_3). ^{13}C NMR: (125 MHz, $CDCl_3$) 214.7 (C(3));142.9, 128.5, 127.5, 125.6 (aromatic); 69.7 (C(1)); 65.6 (C(5)); 51.4 (C(2)); 49.0 (C(4)); 25.8 (C(9)); 18.2 (C(8)); 12.6 (C(6)); −5.6 (C(7)); IR: (neat) 3467 (m, br); 3064 (w); 3031 (w); 2954 (s); 2931 (s); 2885 (m); 2858 (m); 1708 (m); 1463 (m); 1388 (m); 1256 (m); 1100 (s); 838 (s). SFC: (Chiralpak OD column, 150 bar, 3.0 mL/min, 1.4% MeOH) t_R (2*S*,5*R*)-*syn*-**28a** 4.74 min (95%); (2*S*,5*S*)-*anti*-**28a** 5.21 min (5%). Anal. Calcd for $C_{18}H_{30}O_3Si$ (322.51) C 67.03; H 9.38. Found: C 66.94; H 9.42.

General Procedure IV. Aldol Addition of in Situ Generated Trichlorosilyl Enolate Using 11: (1*R*,5*S*)-5-*tert*-Butyldimethylsililoxy-1-hydroxy-1-phenyl-3-hexanone (*anti*-35a). To a suspension of mercury(II) acetate (3.2 mg, 0.01 mmol, 0.01 equiv) in 1 mL of methylene chloride was added silicon tetrachloride (0.23 mL, 2.0 mmol, 2.0 equiv) and the trimethylsilyl enol ether **11** (289 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 30 min.

The excess silicon tetrachloride and the solvent were removed under vacuum. To the residue was added a solution of the chiral phosphoramide (*R*,*R*)-**1** (36.9 mg, 0.10 mmol, 0.10 equiv) in 2 mL of methylene chloride via a cannula. The reaction mixture was cooled to −78 °C before the addition of benzaldehyde (102 μL, 1.00 mmol, 1 equiv). The reaction mixture was stirred at −78 °C for 4 h and then was quenched by pouring into 5 mL of vigorously stirring cold saturated aqueous sodium bicarbonate. The resulting slurry was stirred for 3 h and was filtered through Celite. The layers were separated and the aqueous layer was extracted with 20 mL of methylene chloride. The combined organic extracts were washed with 5 mL of brine, dried over sodium sulfate and concentrated. The crude product was chromatographed (pentane/ether, 3/1, SiO_2) to give **35a** (198 mg, 0.61 mmol, 61%) as viscous colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) 7.35−7.34 (m, 4 H, HC(8), HC(9)); 7.29−7.26 (m, 1 H, HC(10)); 5.15 (dt, J = 8.6, 3.5, 1H, HC(1)); 4.32 (sext, J = 6.1, 1 H, HC(5)); 3.36 (d, J = 3.2, 1 H, OH); 2.92−2.82 (ABX, 2H, H_2C(2)); 2.67−2.41 (ABX, 2H, H_2C(4)); 1.17 (d, J = 6.2, 3H, H_3C(6)); 0.86 (s, 9H, H_3C(13)); 0.05 (d, J = 12.4, 6H, H_3C(11)). ^{13}C NMR: (125 MHz, $CDCl_3$) 210.6 (C(3));142.7 (C(7)); 128.5 (C(9)); 127.6 (C(10)); 125.6 (C(8)); 69.6 (C(5)); 65.6 (C(1)); 53.3 (C(4)); 52.9 (C(2)); 25.7 (C(13)); 24.0 (C(6)); 17.9 (C(12)); −4.5, −5.0 (C(11)). IR: (neat) 3438 (m, br); 3064 (w); 3032 (w); 2956 (s); 2929 (s); 2895 (m); 2850 (m); 1711 (s); 1495 (w); 1462 (m); 1377 (m); 1255 (m); 1134 (m); 1090 (m); 1066 (s); 1041 (m); 1007 (m). SFC: t_R = 4.695 min (OD, 150 bar, 3 mL/min, 2% MeOH). Anal. Calcd for $C_{18}H_{30}O_3Si$ (322.51): C, 67.03; H, 9.38. Found: C, 66.94; H, 9.52%

General Procedure V. Aldol Addition of Methyl Ketone Derived TMS Enol Ethers: (1*R*,4*S*)-5-*tert*-Butyldimethyl-sililoxy-4-methyl-1-hydroxy-1-phenyl-3-pentanone (*syn*-28a). In a 10-mL Schlenk flask was placed (*R*,*R*)-**2** (42 mg, 0.05 mmol, 0.05 equiv) in dichloromethane (1 mL). To the solution was added benzaldehyde (0.102 mL, 1.00 mmol), and the solution was cooled to −78 °C (bath temperature) using a dry ice/acetone bath. To the solution was added silicon tetrachloride (0.172 mL, 1.50 mmol, 1.5 equiv), and the solution was stirred for 5 min. To the solution was added dropwise **8** (346 mg, 1.20 mmol, 1.2 equiv), and the reaction mixture was stirred at −78 °C (bath temperature) for 4 h. The reaction mixture was quenched by pouring into a vigorously stirring cold (0 °C) saturated aqueous $NaHCO_3$ solution (15 mL), and the resulting emulsion was stirred for at least 2 h. The emulsion was filtered through a pad of Celite, and the filtrate was transferred into a 60-mL separatory funnel. The biphasic mixture was extracted with dichloromethane (2 × 20 mL), and the combined extracts were washed with brine (10 mL). The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was chromatographed (silica gel, pentane/ether, 3/1, 30 mm) to afford 294 mg (0.91 mmol, 91%) of **28a** as a clear colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) 7.23−7.47 (m, 5H, aromatic); 5.17 (dt, J = 8.8, 3.2, 1H, HC(1)); 3.65−3.76 (ABX, 2H, C(5)H_2); 3.49 (d, J = 2.9, 1H, OH); 2.86−2.96 (ABX, 2H, C(2)H_2); 2.78 (m,1H, C(4)H); 1.03 (d, J = 6.9, 3H, C(6)H_3); 0.87 (s, 9H, (C(9)-H_3)$_3$); 0.04 (d, J = 2, 6H, C(7)H_3). ^{13}C NMR: (125 MHz, $CDCl_3$) 214.7 (C(3));142.9, 128.5, 127.5, 125.6 (aromatic); 69.7 (C(1)); 65.6 (C(5)); 51.4 (C(2)); 49.0 (C(4)); 25.8 (C(9)); 18.2 (C(8)); 12.6 (C(6)); −5.6 (C(7)). SFC: (Chiralpak OD column, 125 bar, 3.0 mL/min, 2.0% MeOH) t_R (1*R*,4*S*)-*syn*-**28a** 4.797 min (95.9%); (1*S*,4*S*)-*anti*-**28a** 5.271 min (4.1%).

General Procedure VI: Aldol Addition of in Situ Generated Lactate Derived Enolate (*Z*)-23: (+)-(2*S*,4*R*,5*S*)-5-Hydroxy-4-methyl-5-phenyl-2-[((dimethyl)-(1,1-dimethylethyl)-silyl)oxy]-3-pentanone (41a). Silyl enol ether **14** (273 mg, 1.0 mmol) was added quickly to a stirred suspension of silicon tetrachloride (230 μL, 2.0 mmol, 2.0 equiv) and mercuric acetate (3.2 mg, 0.01 mmol, 0.01 equiv) in CH_2Cl_2 (1.0 mL) at room temperature. After addition, the mixture was stirred at room temperature for 18 h, and then the volatile components were removed under reduced pressure (0.1 mmHg) to give a cloudy oil. A solution of (*R*,*R*)-**1** (18 mg, 0.05 mmol, 0.05 equiv) in CH_2Cl_2 (2.0 mL) was then added via cannula and the mixture was cooled to −78 °C. Benzaldehyde (102 μL, 1.0 mmol) was then added dropwise via syringe and the reaction mixture was allowed to stir at −78 °C for 10 h. The reaction mixture was then poured into a rapidly stirring saturated aqueous $NaHCO_3$ solution (30 mL) submerged in an ice bath and was allowed to stir at room temperature for 6 h. The heterogeneous mixture was then filtered through Celite, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated to give a crude oil. Purification by column chromatography (SiO_2, pentane/Et_2O, 6/1) afforded 284 mg (88%) of **41a** as a clear, colorless oil. The diastereomeric ratio was determined to be (*syn*,*syn*)-**41a**/minor isomers, 95/5 by SFC analysis. ^{1}H NMR: ($CDCl_3$, 500 MHz) 7.38−7.20 (m, 5 H, 2 × H(C2″), 2 × HC(3″), HC(4″)); 5.06 (dd, J = 5.0, 2.8, 1 H, HC(5), *syn*,*syn*); 5.01 (dd, J = 5.0, 2.8, 1 H, HC(5), *anti*,*syn*); 4.77 (dd, J = 8.5, 4.2, 1 H, HC(5), *anti*-relative); 4.73 (dd, J = 8.5, 4.2, 1 H, HC(5), *anti*-relative); 4.19 (q, J = 6.9, 1 H, HC(2)); 3.37 (dq, J = 7.2, 5.0, 1 H, HC(4)); 3.25, (d, J = 2.8, 1 H, OH); 1.27 (d, J = 6.9, 3 H, H_3C(1)); 1.05 (d, J = 7.2, 3 H, H_3C(1′)); 0.90 (s, 9 H, H_3C-(3‴)); 0.08 (s, 3 H, H_3C(1‴)); 0.06 (s, 3 H, H_3C(1‴)). ^{13}C NMR: ($CDCl_3$, 125 MHz) 218.7 (C(3)); 141.7 (C(1″)); 128.2 (C(3″)); 127.2 (C(4″)); 126.0 (C(2″)); 75.7 (C(2)); 72.8 (C(5)); 46.9 (C(4)); 25.7 (C(3‴)); 21.1 (C(1)); 18.0 (C(8)); 10.4 (C(1′)); −4.7 (C(1‴)); −5.0 (C(1‴)). SFC: t_R (2*S*,4*R*,5*S*)-**41a**, 5.1 min (Daicel Chiralpak AD, 5% MeOH in CO_2, 150 bar, 40 °C, 3.0 mL min^{-1}).

General Procedure VII. Aldol Addition of (*Z*)-24: (1*R*,2*R*,4*S*)-5-*tert*-Butyldimethylsilyloxy-2,4-dimethyl-1-hydroxy-1-phenyl-3-pentanone (*syn*,*syn*-45a). In a 10-mL Schlenk flask was placed a solution of (*R*,*R*)-**1** (37 mg, 0.10 mmol, 0.10 equiv) in CH_2Cl_2 (1 mL). To the solution was added (*Z*)-**24** (364 mg, 1.00 mmol) and the solution was cooled to −70 °C using an acetone/CO_2 bath. To the solution was added dropwise PhCHO (102 μL, 1.00 mmol, 1 equiv) and the reaction mixture was stirred for 6 h at −70 °C. The reaction mixture was quenched by pouring into a vigorously stirring cold saturated aqueous $NaHCO_3$ solution (5 mL). The resulting slurry was stirred for 1 h and filtered through Celite. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, pentane/ether, 3/1, 30 mm) to afford 241 mg (0.72 mmol, 72%) of **45a** as a clear viscous oil. ^{1}H NMR: (500 MHz, $CDCl_3$) 7.34−7.32 (m, 4 H, HC(7), HC(8)); 7.25 (m, 1 H, HC(9)); 5.22 (t, J = 2.4, 1 H, HC(1)); 3.75−3.60 (ABX, 2 H, H_2C(5)); 3.45 (d, J = 2.4, 1 H, HO); 3.02 (sext, J = 5.4, 1 H, HC(4)); 2.97 (qd, J = 7.1, 2.7, 1 H, HC(2)); 1.02 (d, J = 6.8, 3 H, H_3C(11)); 1.01 (d, J = 7.3, 3 H, H_3C(10)); 0.89 (s, 9H, H_3C(14)); 0.06 (d, J = 3.2, 6 H, H_3C-(12)). ^{13}C NMR: (126 MHz, $CDCl_3$) 219.2 (C(3)); 141.7 (C(6)); 128.1 (C(8)); 127.1 (C(9)); 125.8 (C(7)); 71.9 (C(5)); 66.3 (C(1)); 52.8 (C(2)); 47.3 (C(4)); 25.9 (C(14)); 18.3 (C(13)); 13.2 (C(11)); 8.8 (C(10)); −5.6 (C(12)). IR: (neat) 3469 (br, w); 2954 (m); 2931 (m); 2858 (m); 1702 (m); 1462 (m); 1389 (w); 1255 (m); 1097 (m). SFC: t_R = 1.834 min (AD, 150 bar, 3 mL/min, 5% MeOH) Anal. Calcd for $C_{19}H_{32}O_3Si$ (336.54): C, 67.81; H, 9.58. Found: C, 67.74; H, 9.69.

General Procedure VIII. Aldol Additions of Trichlorosilyl enolate (*Z*)-26: (1*R*,2*R*,5*S*)-5-*tert*-Butyldimethylsilyloxy-2-methyl-1-hydroxy-1-phenyl-3-hexanone (*syn*,*anti*-47a). In a 10-mL Schlenk flask was placed a solution of (*R*,*R*)-**1** (37 mg, 0.10 mmol, 0.10 equiv) in CH_2Cl_2 (1 mL). To the solution was added (*Z*)-**26** (364 mg, 1.00 mmol) and the solution was cooled to −68 °C using *i*-PrOH/CO_2 bath. To the solution was added PhCHO (102 μL, 1.00 mmol, 1 equiv) and the reaction mixture was stirred for 6 h at −68 °C. The reaction mixture was quenched by pouring into a vigorously stirring cold saturated aqueous $NaHCO_3$ solution (15 mL). The result-

ing slurry was stirred for 3 h and filtered through Celite. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined extracts were washed with brine (5 mL), dried over sodium sulfate and concentrated. The crude oil was purified by column chromatography (silica gel, pentane/ether, 3/1, 30 mm) to afford 200 mg (0.59 mmol, 59%) of **47a** as a clear viscous oil. ^{1}H NMR: (500 MHz, $CDCl_3$) 7.36−7.30 (m, 4 H, HC(8), HC(9)); 7.25 (m, 1 H, HC(10)); 5.15 (t, J = 2.9, 1 H, HC(1)); 4.32 (sext, J = 6.6, 1 H, HC(5)); 3.16 (d, J = 2.6, 1 H, HO); 2.81 (qd, J = 7.3, 3.1, 1 H, HC(2)); 2.72−2.43 (ABX, 2 H, H_2C(4)); 1.16 (d, J = 6.1, 3 H, H_3C(6)); 1.04 (d, J = 7.3, 3 H, H_3C(11)); 0.87 (s, 9H, H_3C(14)); 0.06 (d, J = 11.2, 6 H, H_3C(12)). ^{13}C NMR: (126 MHz, $CDCl_3$) 214.7 (C(3)); 141.6 (C(7)); 128.2 (C(9)); 127.2 (C(10)); 125.8 (C(8)); 72.3 (C(5)); 65.4 (C(1)); 52.5 (C(2)); 51.3 (C(4)); 25.8 (C(14)); 23.9 (C(6)); 17.9 (C(13)); 9.2 (C(11)); −4.6, −4.9 (C(12)). IR: (neat) 3458 (br, m); 3064 (w); 3032 (w); 2956 (m); 2931 (m); 2895 (m); 2858 (m); 1707 (m); 1454 (m); 1375 (m); 1255 (m); 1134 (m); 1095 (m); 1005 (m). SFC: t_R = 2.441 min (OD, 150 bar, 3 mL/min, 5% MeOH). Anal. Calcd for $C_{19}H_{32}O_3Si$ (336.54): C, 67.81; H, 9.58. Found: C, 67.61; H, 9.59.

General Procedure IX. Aldol Addition of TMS Enol Ether 25: (1*R*,2*S*,4*S*)-1-Hydroxy-2,4-dimethyl-1-phenyl-5-triisopropylsilanyloxy-pentan-3-one (*anti*,*anti*-46a). In a 10-mL Schlenk flask were placed (*R*,*R*)-**2** (84 mg, 0.10 mmol, 0.10 equiv), tetrabutylammonium iodide (74 mg, 0.20 mmol, 0.2 equiv) in dichloromethane (2 mL). To the solution were added benzaldehyde (0.152 mL, 1.50 mmol, 1.5 equiv) and diisopropylethylamine (0.035 mL, 0.20 mmol, 0.2 equiv), and the solution was cooled to −72 °C (internal temperature) using a dry ice/2-propanol bath. To the solution was added silicon tetrachloride (0.172 mL, 1.50 mmol, 1.5 equiv), and the solution was stirred for 5 min. To the solution was added dropwise **25** (345 mg, 1.00 mmol), and the reaction mixture was stirred at −60 °C (internal temperature) for 24 h. The reaction mixture was quenched by pouring into a vigorously stirring cold (0 °C) saturated aqueous $NaHCO_3$ solution (15 mL), and the resulting emulsion was stirred for at least 3 h. The emulsion was filtered through a pad of Celite, and the filtrate was transferred into a 60-mL separatory funnel. The biphasic mixture was extracted with dichloromethane (2 × 20 mL), and the combined extracts were washed with brine (10 mL). The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was chromatographed (silica gel, pentane/ether, 4/1, 30 mm) to afford 307 mg (0.81 mmol, 81%) of **46a** as a clear colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) 7.36−7.26 (m, 5 H, 2 × HC(7), 2 × HC(8), HC(9)); 4.78 (dd, J = 8.0, 4.8, 1 H, HC(1)); 3.78 (ABX, 2 H, 2 × HC(5)); 3.09 (d, J = 4.6, 1 H, HO); 3.05 (pent, J = 7.6, 1 H, HC(2)); 2.89 (sextd, J = 5.1, 1.2, 1 H, HC(4)); 1.04 (m, 21 H, 3 × HC(12), 18 × HC(13)); 0.97 (d, J = 7.1, 3 H, 3 × HC(10)); 0.93 (d, J = 7.1, 3 H, 3 × HC(11)). ^{13}C NMR: (126 MHz, $CDCl_3$) 217.9 (C(3)); 142.3 (C(6)); 128.3 (2 × C(7)); 127.7 (C(9)); 126.5 (2 × C(8)); 76.5 (C(1)); 65.5 (C(5)); 53.1 (C(2)); 49.1 (C(4)); 17.88, 17.89 (6 × C(13)); 13.8 (C(10)); 12.8 (C(11)); 11.8 (3 × C(12)). IR: (neat) 3452 (br, m); 3064 (w); 3032 (w); 2943 (s); 2893 (m); 2868 (s); 1711 (m); 1495 (w); 1462 (m); 1383 (m); 1248 (m); 1101 (m); 1066 (m); 1011 (m). SFC: (Chiralcel-OD, 125 bar, 3 mL/min, 5.0% MeOH) (*anti*,*anti*)-**46a**, t_R = 4.194 min (96.5%); (*anti*,*syn*)-**46a**, t_R = 3.311 min (1.3%); (*syn*,*syn*)-**46a**, t_R = 3.712 min (1.4%); (*syn*,*anti*)-**46a**, t_R = 4.979 min (0.7%). Anal. Calcd for $C_{22}H_{38}O_3Si$ (378.62): C, 69.79; H, 10.12. Found: C, 69.86; H, 10.31.

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Supporting Information Available: Experimental details for the preparation and full spectroscopic and analytical characterization of all compounds reported, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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