JOC Article

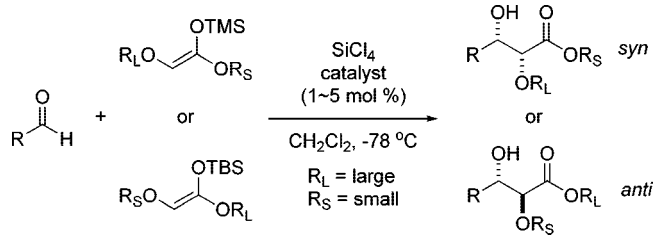
Lewis Base Activation of Lewis Acids: Catalytic, Enantioselective Addition of Glycolate-Derived Silyl Ketene Acetals to Aldehydes

Scott E. Denmark* and Won-jin Chung

Department of Chemistry, Roger Adams Laboratory, University of Illinois, Urbana, Illinois 61801

denmark@scs.uiuc.edu

Received March 22, 2008

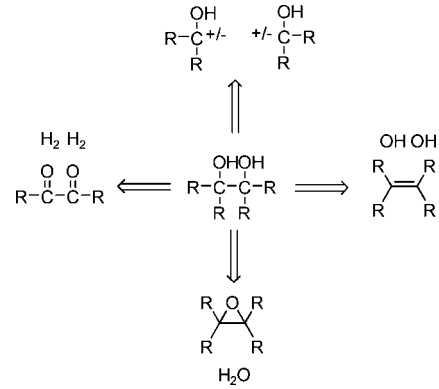


A catalytic system involving silicon tetrachloride and a chiral, Lewis basic bisphosphoramide catalyst is effective for the addition of glycolate-derived silyl ketene acetals to aldehydes. It was found that the sense of *diastereoselectivity* could be modulated by changing the size of the substituents on the silyl ketene acetals. In general, the trimethylsilyl ketene acetals derived from methyl glycolates with a large protecting group on the α-oxygen provide enantiomerically enriched α,*β*-dihydroxy esters with high *syn*-diastereoselectivity, whereas the *tert*-butyldimethylsilyl ketene acetals derived from bulky esters of α-methoxyacetic acid provide enantiomerically enriched α,*β*-dihydroxy esters with high *anti*-diastereoselecitvity.

Introduction

Stereodefined 1,2-diol units are found in a number of natural products such as macrolides and carbohydrates as well as in many important organic compounds such as chiral ligands in asymmetric catalysis. 1,2-Diols are also very versatile precursors that can be easily transformed to a variety of useful structures. There are several different approaches that can be envisioned for the preparation of 1,2-diols (Scheme 1): (1) sequential reduction of 1,2-diketones, (2) oxidation of alkenes via either direct dihydroxylations or epoxidation and opening, and (3) carbon−carbon bond-forming reaction between the two oxygen bearing carbons. Among these approaches, OsO_4-catalyzed enantioselective dihydroxylation of olefins developed by Sharpless et al. is widely recognized as one of the most practical methods for syntheses of enantiomerically pure 1,2-diols.[1] Although *syn*-1,2-diol can be prepared with high enantioselectivities by this method, the synthesis of enantiomerically pure *anti*-1,2-diols suffers from low stereoselectivity. Moreover, the resulting two hydroxyl groups are not differentiated. More efficient synthesis of *anti*-1,2-diols can be achieved by asymmetric epoxidation and ring opening.[2] To achieve high selectivities, it is necessary to control the geometry of the starting olefins prior to the asymmetric dihydroxylations or epoxidation since these methods are highly stereospecific.

SCHEME 1



Background

The aldol reaction of glycolate esters with aldehydes represents a third alternative to the preparation of stereodefined 1,2-

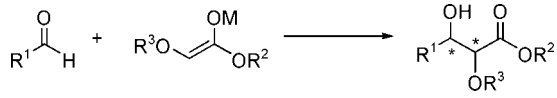
(1) (a) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568–7570. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(2) (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496. (b) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497–505. (c) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603–1662.

10.1021/jo8006539 CCC: $40.75
Published on Web 05/28/2008

diol units (Scheme 2). In this approach, a number of well-developed platforms of the aldol reaction allow for the selective formation of both *syn*- and *anti*-diastereomers.[3] Although the level of diastereoselectivity is often limited by the geometrical purity of enolate, the highly *syn*-selective enolization of glycolate esters alleviates this problem. Also, in the case of Mukaiyama-type aldol reactions,[4] it is often observed that both *E* and *Z* isomers of enol ethers afford the same diastereomers (diastereoconvergent) so that the requirement of the selective formation of geometrically homogeneous enol ethers is unnecessary. In addition, the two hydroxyl groups of the glycolate aldol product are intrinsically differentiated.

SCHEME 2



1. Auxiliary-Based Stereoselective Glycolate Aldol Reaction. Chiral auxiliary-based reactions with preformed enolates are most commonly used for the stereoselective glycolate aldol reaction.[5,6] In most cases, *syn*-stereoselectivity is observed using boron enolates of chiral oxazolidinone derivatives of glycolate esters. However, systematic studies that examine a range of aldehydes for the chiral auxiliary-based method are rare.[6] Recently, Andrus and co-workers reported a number of *syn*- and *anti*-selective auxiliary-based glycolate aldol reactions that took advantage of highly selective enolizations of acyclic and cyclic glycolate esters and the high specificity of boron-mediated aldol reactions.[7] Although both diastereomers could be prepared with high selectivity, an excess of boron triflate and amine bases were necessary. Moreover, additional steps were required for the removal and recovery of the auxiliary.

2. Catalytic, Enantioselective Glycolate Aldol Reactions. In contrast to the successful glycolate aldol additions using chiral auxiliaries, only a few studies of catalytic, enantioselective glycolate aldol reactions have been reported. Kobayashi and co-workers have developed a catalytic system that involves a tin-based Lewis acid and chiral amines for the asymmetric glycolate aldol reaction.[8] Both diastereomers can be obtained in high diastereoselectivity and enantioselectivity by changing both the geometry of ketene acetals and the structure of chiral amines. However, this method has some disadvantages that limit its practicality: (1) an excess of tin reagents is employed and a stoichiometric amount of the chiral amine is required in some cases, (2) tin reagents had to be added slowly for several hours via syringe pump, and (3) aliphatic aldehydes are problematic substrates. Therefore, the development of a new catalytic system that requires only a substoichiometric amount of a chiral source and that is applicable to a wide range of aldehydes is highly desirable.

3. Lewis Base Activation of Lewis Acids. The generation of chiral Lewis acid catalysts usually involves the complexation of chiral ligand to a strong metal-based Lewis acid.[9] In general, the donor properties of the ligand result in the attenuation of electrophilicity of the metal center.[10] Therefore, the chiral catalyst should be preformed or else a high association constant is necessary to avoid the achiral background reaction from the uncomplexed Lewis acid.[11]

However, donor−acceptor interactions do not always reduce electrophilicity of the metal center. Although electron density is transferred from the donor to the acceptor in the coordination interaction, it is not equally distributed since the electron density is polarized in the complexed species toward the peripheral ligands of the Lewis acid acceptor. Therefore, the coordination of a polyatomic donor to a polyatomic acceptor causes an increase of electron density on the central atom of the donor and a decrease of electron density on the central atom of the acceptor (Scheme 3).[12] This polarization can result in the ionization of one of the ligands from the acceptor atom and the formation of a strongly Lewis acidic cation.[13] Thus, it becomes possible to employ stoichiometric amounts of a weak, achiral Lewis acid and substoichiometric amounts of a chiral Lewis base for asymmetric catalysis. Since the most reactive catalytic species will be chiral, the chiral catalyst can be generated in

(3) (a) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 2.4. (b) Cameron, J. C.; Paterson, I. *Org. React.* **1997**, *51*, 1. (c) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, Chapter 29.1. (d) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (e) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389. (f) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374.

(4) (a) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymmetry* **1991**, *2*, 635–638. (b) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, *19*, 1455–1458.

(5) (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526. (b) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157–1159. (c) Ku, T. W.; Kondrad, K. H.; Gleason, J. G. *J. Org. Chem.* **1989**, *54*, 3487–3491. (d) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031. (e) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S *J. Org. Chem.* **1992**, *57*, 1961–1963. (f) Saika, H.; Fruh, T.; Iwasaki, G.; Koizumi, S.; Mori, I.; Hayakawa, K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2129–2134. (g) Andrus, M. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10420–10421. (h) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111–12112. (i) Rudge, A. J.; Collins, I.; Holmes, A. B.; Baker, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2320–2322. (j) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Limberakis, C.; Hartmann, M. *Tetrahedron* **1996**, *52*, 3229–3246. (k) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548–7549. (l) Nakamura, Y.; Hirata, M.; Kuwano, E.; Taniguchi, E. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1550–1554. (m) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660. (n) Haight, D.; Birrell, H. C.; Cantello, B. C. C.; Eggleston, D. S.; Haltiwanger, R. C.; Hindley, R. M.; Ramaswany, A.; Stevens, N. C. *Tetrahedron: Asymmetry* **1999**, *10*, 1353–1367. (o) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473–5476. (p) Crimmins, M. T.; King, B. W.; Zuercher, W. J.; Choy, A. L. *J. Org. Chem.* **2000**, *65*, 8499–8509. (q) Zhang, W.; Carter, R. G.; Yokochi, A. F. T. *J. Org. Chem.* **2004**, *69*, 2569–2572.

(6) (a) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., III *J. Am. Chem. Soc.* **2000**, *122*, 386–387. (b) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591–594. (c) Hoover, T. R.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3233–3241.

(7) (a) Andrus, M. B.; Sekhar, B. B. V. S.; Turner, T. M.; Meredith, E. L. *Tetrahedron Lett.* **2001**, *42*, 7197–7201. (b) Andrus, M. B.; Sekhar, B. B. V. S.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035–3037. (c) Andrus, M. B.; Mendenhall, K. G.; Meredith, E. L.; Sekhar, B. B. V. S. *Tetrahedron Lett.* **2002**, *43*, 1789–1792.

(8) (a) Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, *12*, 911–913. (b) Kobayashi, S.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 3329–3332. (c) Kobayashi, S.; Horibe, M *J. Am. Chem. Soc.* **1994**, *116*, 9805–9806. (d) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098–1099. (e) Kobayashi, S.; Horibe, M.; Matsumura, M. *Synlett* **1995**, *6*, 675–676. (f) Kobayashi, S.; Horibe, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2565–2569. (g) Kobayashi, S.; Horibe, M.; Hachiya, I. *Tetrahedron Lett.* **1995**, *36*, 3173–3176. (h) Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472–1481.

(9) Yamamoto, H. *Lewis Acids in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001.

(10) (a) Suzuki, I.; Yamamoto, Y. *J. Org. Chem.* **1993**, *58*, 4783–4784. (b) Santelli, M.; Pos, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996.

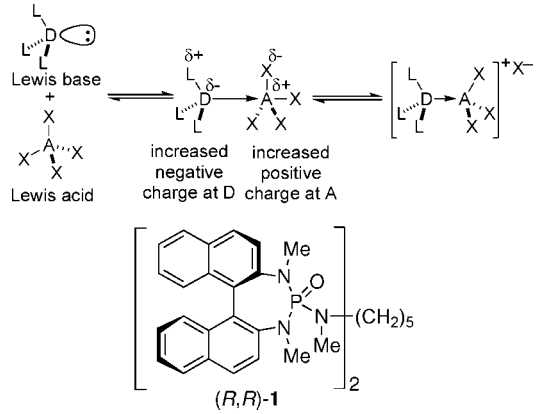
(11) Gauthier, D. R., Jr.; Carreira, E. M *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363–2365.

(12) (a) Gutman, V. *The Donor-Acceptor Approach to Molecular Interactions*; Plenum Press: New York, 1978. (b) Jensen W. B. *The Lewis Acid-Base Concepts*; Wiley-Interscience: New York, 1980; Chapter 4.

(13) Bassindale, A. R.; Glynn, S. J.; Tayor, P. G. In *The Chemistry of Organosilicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, 1998; Vol. 2; pp 495−511.

situ without concern for an achiral background reaction promoted by the achiral Lewis acid.

SCHEME 3

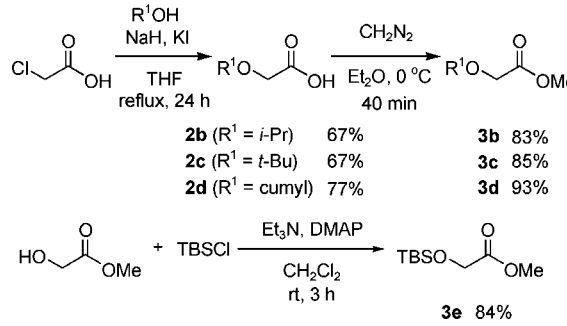


Studies from these laboratories have demonstrated the utility of this conceptually novel, Lewis base catalyzed, Lewis acid mediated process in the addition of various nucleophiles including silyl enol ethers, silyl dienol ethers, silyl ketene acetals, *N*,*O*-silyl ketene acetals, and isocyanides to a wide range of aldehydes utilizing the weakly Lewis acidic $SiCl_4$ and Lewis basic bisphosphoramide catalyst (*R*,*R*)-**1**.[14] The primary objective of this study is to extend the scope of nucleophile to the glycolate-derived silyl ketene acetals and thereby develop a catalytic, stereoselective glycolate aldol reaction. From the previous studies on other aldol processes it was known that all of the substituents on the double bond of α-substituted silyl ketene acetals played important roles in controlling stereoselectivity.[14d,i] Thus, one of the major challenges was to elucidate the influence of various structural features of the α-alkoxy silyl ketene acetal including the protecting group of the α-hydroxyl function, the alkyl group of the ester, and the silyl group of the ketene acetal on the stereoselectivity.[15]

Results

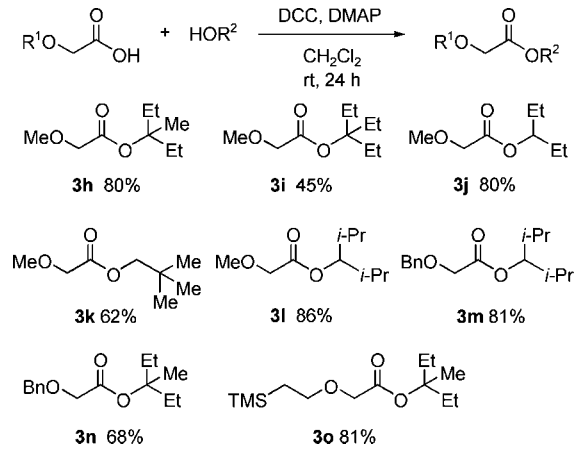
1. Preparation of Glycolate-Derived Silyl Ketene Acetals. A number of silyl ketene acetals were prepared from various alkyl α-alkoxyacetates with either trimethylsilyl or *tert*-butyldimethylsilyl groups. Methyl glycolates with a range of α-alkoxy groups were prepared from chloroacetic acid (Scheme 4). The ethers were formed by the reaction of chloroacetic acid with various sodium alkoxides in refluxing THF to afford the α-protected glycolic acids **2b**−**d** in good yields. Then, the corresponding methyl esters **3b**−**d** were obtained by the methylation of carboxylic acids with diazomethane in high yields. *tert*-Butyldimethylsilyl-protected methyl glycolate **3e** was prepared by silylation of commercially available methyl glycolate.

SCHEME 4



Other glycolate esters were synthesized by DCC−DMAP coupling of commercially available α-methoxyacetic acid or α-benzyloxyacetic acid with the corresponding alcohols (Scheme 5). The reactions generally proceeded smoothly and in high yields. The coupling with 3-ethyl-3-pentanol was the only sluggish reaction and provided the ester **3i** in moderate yield.

SCHEME 5



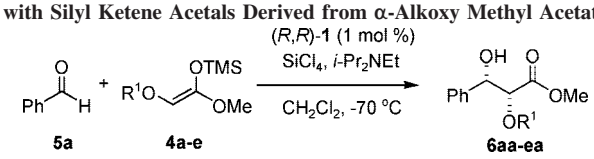
Although the enolization of glycolates is typically effected with lithium amide bases such as LDA or LHMDS,[16] it was found that commercially available KHMDS serves as an excellent base for the enolization (Scheme 6). Thus, various glycolates were enolized with KHMDS and the enolates were trapped with trimethylsilyl chloride to afford trimethylsilyl ketene acetals **4b**−**f** in high yields. The products could be purified by distillation and stored for a few months at −15 °C without significant decomposition. The methyl α-methoxyacetate-derived trimethylsilyl ketene acetal **4a** had to be sacrificially distilled to remove HMDS byproduct because the boiling points of **4a** and HMDS were very similar. All of the trimethylsilyl ketene acetals were obtained with very high

(14) (a) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428–2429. (b) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199–6200. (c) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235. (d) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405–13407. (e) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825–7827. (f) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800–7801. (g) Denmark, S. E.; Heemstra, J. R., Jr *Org. Lett.* **2003**, *5*, 2303–2306. (h) Denmark, S. E.; Heemstra, J. R., Jr. *Synlett* **2004**, *13*, 2411–2416. (i) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774–3789. (j) Denmark, S. E.; Fan, Y. *J. Org. Chem.* **2005**, *70*, 9667–9676. (k) Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10190–10193. (l) Denmark, S. E.; Heemstra, J. R., Jr *J. Am. Chem. Soc.* **2006**, *128*, 1038–1039. (m) Denmark, S. E.; Heemstra, J. R., Jr *J. Org. Chem.* **2007**, *72*, 56685688. (n) Denmark, S. E.; Fujimori S. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 7.

(15) For a preliminary communication, see: Denmark, S. E.; Chung, W.-j. *Angew. Chem., Int. Ed.* **2008**, *47*, 1890–1892.

(16) (a) Barrish, J. C.; Lee, H. L.; Baggiolini, E. G.; Uskokvic; M, R. *J. Org. Chem.* **1987**, *52*, 1372–1375. (b) Gould, T. J.; Balestra, M.; Wittmann, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889–3901. (c) Sato, T.; Tsunekawa, H.; Kohama, H.; Fujisawa, T. *Chem. Lett.* **1986**, *15*, 1553–1556. (d) Fujisawa, T.; Tajima, K.; Sato, T. *Chem. Lett.* **1984**, *13*, 1669–1672. (e) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221–5228. (f) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177–5180. (g) Annunziata, R.; Cinquini, M.; Cozzi, F.; Borgia, A. L. *J. Org. Chem.* **1992**, *57*, 6339–6342. (h) Mukaiyama, T.; Uchiro, H.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1990**, *19*, 1019–1022.

TABLE 1. Glycolate Aldol Reactions with Silyl Ketene Acetals Derived from α-Alkoxy Methyl Acetates[a]



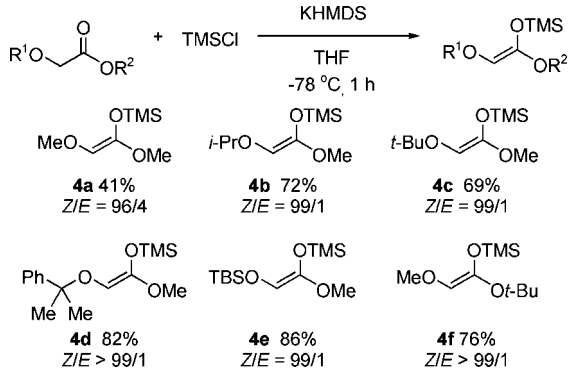
5a 4a-e 6aa-ea

entry	R^1	time,[b] min	product	yield,[c] %	*syn*/*anti*[d]	er (*syn*)[e]	er (*anti*)[e]
1	Me (**4a**)	0.5	**6aa**	98	57:43	73.6:26.4	81.5:18.5
2	*i*-Pr (**4b**)	0.5	**6ba**	95	86:14	79.8:20.2	77.0:23.0
3	*t*-Bu (**4c**)	1.5	**6ca**	93	99:1	93.4:6.6	ND
4	$PhMe_2C$ (**4d**)	10.0	**6da**	98	99:1	96.4:3.6[f]	ND
5	TBS (**4e**)	0.5	**6ea**	95	98:2	95.3:4.7[f]	ND

[a] All reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.2 M concentration. [b] Monitored in situ by ReactIR. [c] Yields of chromatographically homogeneous material. [d] Determined by ^1H NMR analysis of HC(2) or HC(3). [e] Determined by chiral stationary phase, supercritical fluid chromatography (CSP-SFC). [f] (2*R*,3*S*) absolute configuration.[20]

geometrical purities. The major geometrical isomers were assigned to the *Z* configuration by NOESY1D experiments.

SCHEME 6

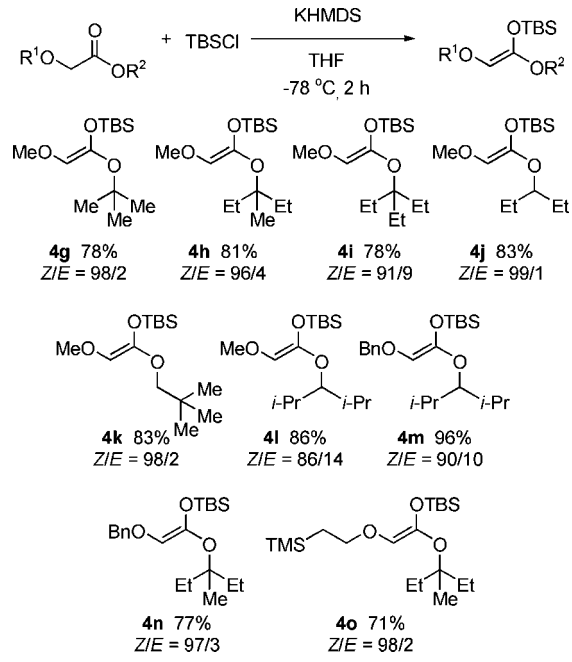


tert-Butyldimethylsilyl ketene acetals **4g**−**m** were also obtained in very good yields with high *Z*-selectivities by a similar protocol, although the geometrical purities were occasionally diminished (Scheme 7). In the case of high molecular weight ketene acetals such as **4m**−**o**, prolonged distillation at high temperature resulted in significant reduction of yield and purity most likely because of a retro-ene side reaction.[17] Thus, the ketene acetal **4m** had to be purified by bulb-to-bulb distillation within a short period of time. Unfortunately, it was not possible to obtain **4n** and **4o** with high purity. With the current protocol, a clear advantage of KHMDS over lithium amide bases was observed. For the *tert*-butyldimethylsilyl protection of lithiated esters, it is necessary to use additives such as HMPA or DMPU for rapid silylation. However, *tert*-butyldimethylsilyl ketene acetals could be synthesized without such additives by employing KHMDS presumably because the potassium salt is more reactive.

2. Lewis Base Catalyzed Glycolate Aldol Reactions. 2.1. Aromatic Aldehydes. 2.1.1. Effect of the Size of α-Alkoxy Substituents on the Stereoselectivities. The silyl ketene acetals derived from methyl α-alkoxyacetates were employed in the aldol reactions with benzaldehyde (**5a**) to investigate the effect of the size of α-alkoxy substituents on the stereoselectivities (Table 1). Initially, the reaction with methyl α-methoxyacetate-derived trimethylsilyl ketene acetal **4a** was conducted under the conditions previously developed for the aldol reactions with simple silyl ketene actals.[14d,i] Reaction progress was monitored

(17) *tert*-Butyldimethylsilyl α-benzyloxyacetate was formed as a side product after distillation.

SCHEME 7



by in situ IR spectroscopic analysis. The reactivity of **4a** was comparable to the reactivity of simple acetate- or propanoate-derived silyl ketene acetals.[14d,i] The aldol addition of **4a** to **5a** in the presence of 1 mol % of the chiral bisphosphoramide catalyst (*R*,*R*)-**1** at −70 °C was complete in 30 s (entry 1).[18] However, whereas very high *anti*-diastereoselectivity and enantioselectivity were observed from the *E*- or *Z*-propanoate-derived silyl ketene acetal,[14d,i] **4a** afforded a nearly 1:1 mixture of diastereomers of **6aa** with only moderate enantioselectivity for each diastereomer. Interestingly, the stereoselectivities could be improved dramatically by increasing the size of the α-alkoxy substituent. The methyl α-isopropoxyacetate-derived trimethylsilyl ketene acetal **4b**, which was as reactive as **4a**, provided moderate but improved diastereoselectivity (entry 2). Surprisingly, the configuration of major diastereomer of **6ba** was assigned as *syn* (see section 2.1.3), which is opposite to the previously observed *anti*-selectivity from propanoate aldol reaction under similar reaction conditions. Furthermore, the aldol addition of methyl α-*tert*-butoxyacetate-derived trimethylsilyl ketene acetal **4c** resulted in very high *syn*-selectivity as well as improved enantioselectivity for the *syn*-diastereomer of **6ca** with

(18) For a discussion of the role of Hünig base, see ref 14g.

only slightly reduced reaction rate (entry 3). The enantioselectivity could be optimized further by introduction of even bulkier groups such as the cumyl or *tert*-butyldimethylsilyl group on the α-oxygen substituent. The reactivity of the methyl α-cumyloxyacetate-derived trimethylsilyl ketene acetal **4d** was substantially lower than other silyl ketene acetals. Nevertheless, the aldol addition of **4d** was complete in only 10 min. Moreover, the best diastereoselectivity and enantioselectivity within the series could be achieved (entry 4). The methyl α-*tert*-butyldimethylsiloxyacetate-derived trimethylsilyl ketene acetal **4e** also provided high diastereoselectivity and enantioselectivity without attenuation of reactivity (entry 5).[19] The reactivity of **4e** was comparable to that of **4a** and **4b**. The absolute configuration of the aldol product **6ea** was assigned to be (2*R*,3*S*) by comparison to the optical rotation of **6ea** to a literature value.[20]

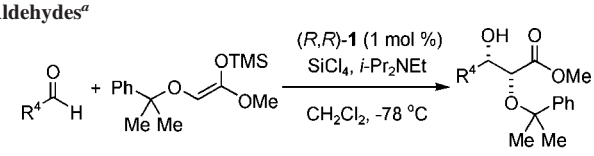
A number of aromatic aldehydes with diverse structural and electronic properties were surveyed with the most selective silyl ketene acetal **4d** (Table 2). The electronic nature of the aldehyde had little effect on reactivity and selectivity. Electron-rich aldehydes such as 4-tolualdehyde (**5b**) and 4-methoxybenzaldehyde (**5c**) provided high chemical yields as well as high diastereoselectivities and enantioselectivities although the reactivity of **5c** was slightly lower (entries 2 and 3). Similarly, electron-poor aldehydes such as 4-chlorobenzaldehyde (**5d**) and 4-trifluoromethylbenzaldehyde (**5e**) also gave high stereoselectivities and high chemical yields within 0.5 h (entries 4 and 5). However, the steric encumbrance in the aromatic aldehyde had a significant impact on the reactivity. The aldol reaction with the sterically hindered 2-tolualdehyde (**5f**) was very slow compared to the other aromatic aldehydes (entry 6). The reaction required 9 h for completion. Gratifyingly, the stereoselectivities remained high in spite of the steric hindrance. 2-Naphthaldehyde (**5g**) and 1-naphthaldehyde (**5 h**) also behaved well and afforded high yields and stereoselectivities (entries 7 and 8). Unfortunately, 2-benzofuraldehyde (**5i**) was not a suitable substrate for this reaction. Despite the high yield and diastereoselectivity, the enantioselectivity was only moderate (entry 9).

2.1.2. Effect of the Size of the Ester on Stereoselectivity. To evaluate the effect of the size of the ester residue, the silyl ketene acetals derived from alkyl α-methoxyacetates were also employed in the aldol reactions with benzaldehyde (**5a**) (Table 3). Again, a remarkable influence on the diastereoselectivity was observed by increasing the size of the ester. Simply by switching from the methyl ester-derived silyl ketene acetals to *tert*-butyl ester-derived silyl ketene acetal **4f**, the stereochemical course *reversed* to give high *anti*-diastereoselectivity (entry 1)! Interestingly, the size of the silyl group also had a noticeable effect on the stereoselectivities. By employing a *tert*-butyldimethylsilyl group instead of trimethylsilyl group, the *anti*-diastereoselectivity and the enantioselectivity of *anti*-diastereomer were enhanced (entry 2). A further improvement of enantioselectivity was achieved by the use of the 3-methyl-3-pentyl α-methoxyacetate-derived *tert*-butyldimethylsilyl ketene acetal **4h** (entry 3). The enantioselectivity turned out to be quite sensitive to small changes in the ester group. If the group was too bulky such as 3-ethyl-3-pentyl ester, the enantioselectivity decreased slightly (entry 4). Also, the 3-pentyl α-methoxyacetate-derived

(19) The reaction is highly exothermic. Later, it was found that the stereoselectivities could be improved by slow addition of silyl ketene acetal as a solution, thereby avoiding the increase of internal temperature. When the silyl ketene acetal **4e** was added as 0.24 M solution for 15 min, the aldol product **6ea** was obtained in 97% yield, 99/1 dr (*syn*/*anti*), and 96.5/3.5 er (*syn*).

(20) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677–683.

TABLE 2. *Syn*-Selective Glycolate Aldol Reactions with Aromatic Aldehydes[a]



5a-i **4d** **6da-di**

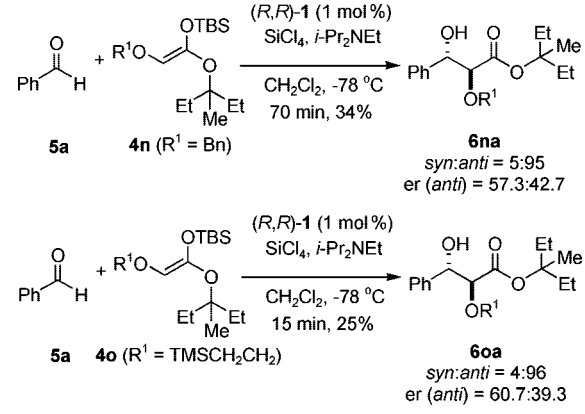
entry	R^4	time, h	product	yield,[b] %	dr[c]	er[d]
1	Ph (**5a**)	0.5	**6da**	87	99:1	96.6:3.4[e]
2	4-Me-C_6H_4 (**5b**)	0.5	**6db**	97	>99:1	97.5:2.5
3	4-MeO-C_6H_4 (**5c**)	1.5	**6dc**	98	99:1	97.7:2.3
4	4-Cl-C_6H_4 (**5d**)	0.5	**6dd**	93	>99:1	97.2:2.8
5	4-CF_3-C_6H_4 (**5e**)	0.5	**6de**	99	99:1	98.0:2.0
6	2-Me-C_6H_4 (**5f**)	9.0	**6df**	93	98:2	96.8:3.2
7	2-naphthyl (**5g**)	0.5	**6dg**	94	>99:1	98.5:1.5
8	1-naphthyl (**5h**)	1.5	**6dh**	93	99:1	96.1:3.9
9	2-benzofuryl (**5i**)	0.5	**6di**	95	98:2	72.2:27.8

[a] All reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.1 M concentration. The silyl ketene acetal was added as a 0.24 M solution over 15 min. [b] Yields of analytically pure material. [c] Determined by ^1H NMR analysis of HC(2) or HC(3). [d] Determined by CSP-SFC. [e] (2*R*,3*S*) absolute configuration.

tert-butyldimethylsilyl ketene acetal **4j**, which has one fewer methyl groups than **4h**, afforded significantly diminished diastereoselectivity and enantioselectivity (entry 5). Finally, the neopentyl α-methoxyacetate-derived *tert*-butyldimethylsilyl ketene acetal **4k** was tested. Although **4k** showed much higher reactivity compared to other bulky ester-derived silyl ketene acetals, the resulting diastereoselectivity and enantioselectivity were moderate, presumably because of the attenuation of steric bulk which seemed necessary to achieve the high stereoselectivities (entry 6).

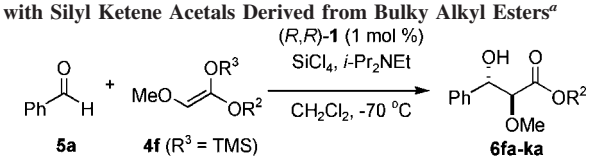
Although satisfactory yields and stereoselectivities were achieved for *anti*-diastereoselective glycolate aldol reactions with **4h**, the methyl group on the α-oxygen is not a desirable group. Therefore, **4h** was modified with more readily removable groups such as benzyl (**4n**) or trimethylsilylethyl (**4o**) groups. However, the aldol reactions with the modified silyl ketene acetals **4n** and **4o** resulted in significant reduction of enantioselectivity (Scheme 8).

SCHEME 8



Having identified an optimal silyl ketene acetal for the *anti*-selective glycolate aldol reaction (**4h**), a series of structurally and electronically diverse aromatic aldehydes were tested. The reactivity and selectivity profiles were very similar to the case of *syn*-selective glycolate aldol reactions. From the reactions with both electron-rich substrates, such as 4-tolualdehyde (**5b**)

TABLE 3. Glycolate Aldol Reactions with Silyl Ketene Acetals Derived from Bulky Alkyl Esters[a]

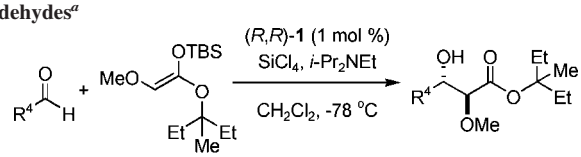


5a **4f** (R^3 = TMS) **4g-k** (R^3 = TBS) **6fa-ka**

entry	R^2	time,[b] min	product	yield,[c] %	*syn*:*anti*[d]	er (*syn*)[e]	er (*anti*)[e]
1	*t*-Bu (**4f**)	3.5	**6fa**	93	4:96	90.4:9.6	81.3:18.7
2	*t*-Bu (**4g**)	6.0	**6fa**	92	1:99	ND	92.1:7.9
3	Et_2MeC (**4h**)	6.0	**6ha**	92[f]	1:99	ND	94.0:6.0
4	Et_3C(**4i**)	6.0	**6ia**	93	2:98	ND	92.8:7.2
5	Et_2CH (**4j**)	0.5	**6ja**	97	8:92	37.8:62.2	82.9:17.1
6	*neo*-pentyl (**4k**)	0.5	**6ka**	98	17:83	15.3:84.7	79.7:20.3

[a] All reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.1 M concentration. [b] Monitored in situ by ReactIR. [c] Yields of chromatographically homogeneous material. [d] Determined by ^1H NMR analysis of HC(2) or HC(3). [e] Determined by CSP-SFC. [f] (2*S*,3*S*) absolute configuration.

TABLE 4. *Anti*-Selective Glycolate Aldol Reactions with Aromatic Aldehydes[a]



5a-i **4h** **6ha-6hi**

entry	R^4	time, h	product	yield,[b] %	dr[c]	er[d]
1	Ph (**5a**)	0.5	**6ha**	91[e]	>99:1	95.1:4.9
2	4-Me-C_6H_4 (**5b**)	0.5	**6hb**	92	99:1	96.1:3.9
3	4-MeO-C_6H_4 (**5c**)	3.0	**6hc**	93	>99:1	98.3:1.7
4	4-Cl-C_6H_4 (**5d**)	0.5	**6hd**	92	99:1	95.1:4.9
5	4-CF_3-C_6H_4 (**5e**)	0.5	**6he**	96	>99:1	98.3:1.7
6	2-Me-C_6H_4 (**5f**)	18.0	**6hf**	91	98:2	93.1:6.9
7	2-naphthyl (**5g**)	0.5	**6hg**	93	>99:1	97.4:2.6
8	1-naphthyl (**5h**)	5.0	**6hh**	94	>99:1	78.2:21.8
9	2-benzofuryl (**5i**)	0.5	**6hi**	97	99:1	94.9:5.1

[a] All reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.1 M concentration. The silyl ketene acetal was added as a 0.24 M solution over 15 min. [b] Yields of analytically pure material. [c] Determined by ^1H NMR analysis of HC(2) or HC(3). [d] Determined by CSP-SFC. [e] (2*S*,3*S*) Absolute configuration.

and 4-methoxybenzaldehyde (**5c**), and electron-poor substrates, such as 4-chlorobenzaldehyde (**5d**) and 4-trifluoromethylbenzaldehyde (**5e**), consistently high yields, diastereoselectivities, and enantioselectivities were obtained (Table 4, entries 2−5). Again, a significantly decreased reaction rate was observed from 2-tolualdehyde (**5f**) while the stereoselectivities remained satisfying (entry 6). Whereas 2-naphthaldehyde (**5g**) provided high yield and stereoselectivities (entry 7), 1-naphthaldehyde (**5h**) exhibited relatively poor reactivity and resulted in low enantioselectivity (entry 8). In contrast to the *syn*-selective glycolate aldol reaction, 2-benzofuraldehyde (**5i**) served as a good substrate in the *anti*-selective manifold giving high yield as well as high stereoselectivities (entry 9).

2.1.3. Assignment of Relative and Absolute Configurations of Glycolate Aldol Products of Benzaldehyde. For unambiguous determination of the relative configurations, the glycolate aldol products from the optimization studies were reduced to the corresponding diols **7** with lithium aluminum hydride and then were converted to 6-membered cyclic acetals **8** (Scheme 9). The vicinal coupling constants between HC(1) and HC(2) of the major diastereomers of **8ba** and **8ca** were 2.2 and 2.4 Hz, respectively. Thus, the major aldol products of **6ba** and **6ca** were assigned to be the *syn*-configuration. On the other hand, the coupling constant between HC(1) and HC(2) of the major diastereomer of **8fa** was 9.3 Hz. Subsequently, the major diastereomer of **8fa** was assigned to be the *anti*-configuration. The aldol products **6ia**, **6ja**, and **6ka** were also reduced to the corresponding diols. The major diastereomers of those diols were identical to the major diastereomer of **8fa** by ^1H NMR analysis. Therefore, the configurations of the major diastereomers of **6ia**, **6ja**, and **6ka** were also confirmed to be *anti*-configuration.

The determination of absolute configuration required a few synthetic manipulations of representative glycolate aldol products (Scheme 10). The cumyl group of *syn*-glycolate aldol product **6da** was easily removed with in situ generated anhydrous HCl to give the known diol **9**.[21] Comparison of its optical rotation with the data reported for this compound revealed that the absolute configuration of **9** is (2*R*,3*S*). However, the selective removal of the methyl group of **6ha** without altering the sensitive benzylic hydroxyl group was challenging. After an extensive survey of demethylation conditions, the methyl group of **6da** was successfully removed by $AlCl_3$ in *n*-BuSH.[22] Although the tertiary alkyl group of the ester was also removed under the reaction conditions, the benzylic hydroxyl group remained intact. Because of the difficulty in the purification of the dihydroxy carboxylic acid, the crude material was directly treated with CH_2N_2. The resulting dihydroxy ester **10** was easily purified, and its absolute configuration was subsequently assigned as (2*S*,3*S*) by comparison of its optical rotation with the reported data.[23] The 3*S* configuration of both **9** and **10** imply a *Re* face attack of the nucleophile on the aldehyde. This sense of asymmetric induction is consistent with previously reported results from the related studies with the same catalytic system.[14]

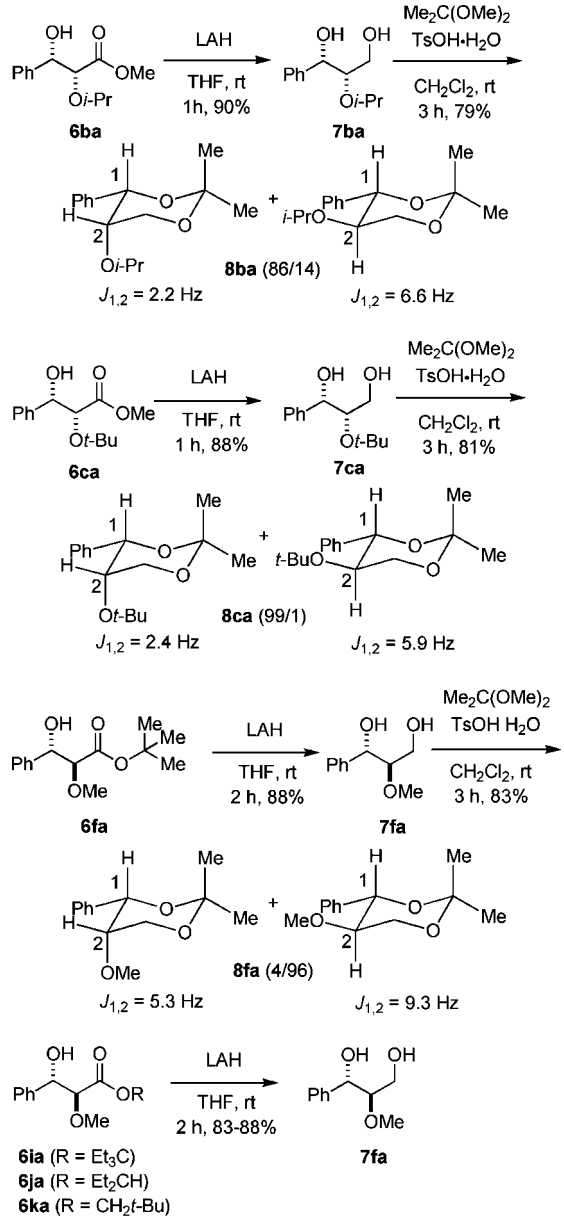
2.2. Aliphatic Aldehydes. 2.2.1. *Syn*-Selective Glycolate Aldol Reactions with Aliphatic Aldehydes. The attenuated reactivity of aliphatic aldehydes has been consistently observed in the previous studies of Lewis base catalyzed, $SiCl_4$-promoted carbonyl addition reactions.[14] It was demonstrated by ^1H and ^{13}C NMR analysis that cyclohexanecarboxyaldehyde (**5o**) is instantaneously converted to α-chloro trichlorosilyl ether **11** in the presence of HMPA and $SiCl_4$ (Scheme 11).[14i] The α-chloro trichlorosilyl ether is unreactive toward nucleophiles and thus

(21) (a) Choudary, B. M.; Chowdari, N. S.; Madhi, S.; Kantam, M. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 4620–4623. (b) Wang, Z.-H.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104–5105.

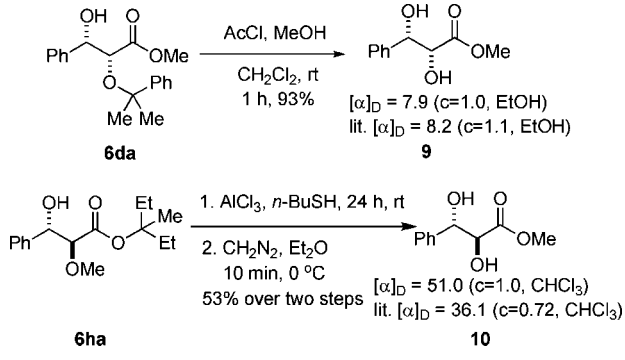
(22) Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, *8*, 97–98.

(23) (a) Matthews, B. R.; Jackson, W. R.; Jacobs, H. A.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 1195–1214. (b) Fujita, M.; Laine, D.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, *12*, 1647–1656.

SCHEME 9

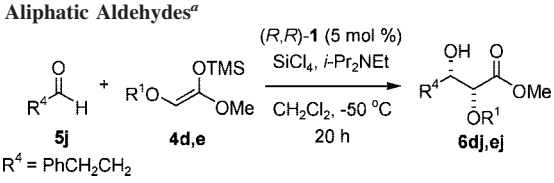


SCHEME 10



responsible for the low reactivity of aliphatic aldehydes. Moreover, because the equilibrium of this reaction lies on the α-chloro trichlorosilyl ether, the concentration of aldehyde is very low. Nevertheless, highly reactive nucleophiles still could react with these substrates at reasonable reaction rate.

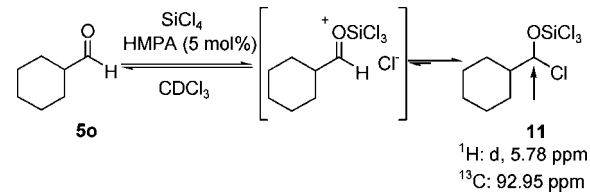
TABLE 5. Optimization of *syn*-Selective Glycolate Aldol Reactions with Aliphatic Aldehydes[a]



entry	R^1	product	yield,[b] %	dr[c]	er[d]
1	$PhMe_2C$ (**4d**)	**6dj**	trace	ND	ND
2	TBS (**4e**)	**6ej**	49	90:10	12.7:87.3[e]

[a] All reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of i-Pr_2NEt at 0.4 M concentration. [b] Yields of chromatographically homogeneous material. [c] Determined by ^1H NMR analysis of HC(2) or HC(3). [d] Determined by CSP-SFC. [e] (2*R*,3*S*) absolute configuration.

SCHEME 11

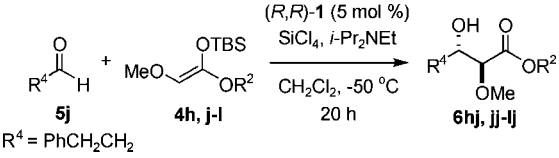


To extend the substrate scope to aliphatic aldehydes, the aldol reaction between the trimethylsilyl ketene acetal **4d** and hydrocinnamaldehyde (**5j**) was attempted (Table 5, entry 1). Because of the low reactivity of aliphatic aldehydes, more forcing reaction conditions such as elevated temperature, higher concentration, and higher catalyst loading were employed for this class of aldehydes. Disappointingly, only traces of aldol product were observed after 20 h in the presence of 5 mol % of (*R*,*R*)-**1** even at −50 °C and 0.4 M concentration. Although the silyl ketene acetal **4d** was the most selective silyl ketene acetal for the *syn*-selective aldol reactions with aromatic aldehydes, it was also the least reactive silyl ketene acetal. Thus, the reactivity problem could be solved simply by employing a more reactive silyl ketene acetal. During the survey of silyl ketene acetals for the aldol reaction with benzaldehyde, the methyl α-*tert*-butyldimethylsiloxyacetate-derived trimethylsilyl ketene acetal **4e** was identified as a highly reactive and stereoselective silyl ketene acetal. Therefore, the silyl ketene acetal **4e** was tested for the aldol reaction with **5j** (entry 2). Consequently, the chemical yield was dramatically improved although it is still moderate. Moreover, reasonable enantioselectivity and diastereoselectivity were observed. To improve the yield and selectivity further, the silyl group at α-hydroxy function of **4e** was modified to other silyl groups including triethylsilyl, triisopropylsilyl, *tert*-hexyldimethylsilyl, and dimethylphenylsilyl groups. In addition, the corresponding triethylsilyl and *tert*-butyldimethylsilyl ketene acetal analogues of **4e** were tested. However, these attempts were not successful. None of the modified silyl ketene acetals gave better results than the parent methyl α-*tert*-butyldimethylsiloxyacetate-derived trimethylsilyl ketene acetal **4e**.

2.2.2. *Anti*-Selective Glycolate Aldol Reactions with Aliphatic Aldehydes. An approach similar to that described above was employed for the *anti*-selective glycolate aldol reaction with **5j**. Poor reactivity was encountered again as only trace amounts of product were observed from the reaction of 3-methyl-3-pentyl α-methoxyacetate-derived *tert*-butyldimethylsilyl ketene acetal **4h** after 20 h in the presence of 5 mol % of (*R*,*R*)-**1** at −50 °C

and 0.4 M concentration (Table 6, entry 1). Thus, more reactive silyl ketene acetals were sought. During the survey of silyl ketene acetals for the aldol reaction with benzaldehyde, neopentyl α-methoxyacetate-derived *tert*-butyldimethylsilyl ketene acetal **4k** and 3-pentyl α-methoxyacetate-derived *tert*-butyldimethylsilyl ketene acetal **4j** showed very high reactivity. Even though the previously observed selectivities from these two silyl ketene acetals were moderate, the silyl ketene acetals **4k** and **4j** were tested for the glycolate aldol reaction with **5j**. Gratifyingly, the silyl ketene acetal **4k** afforded the aldol product **6kj** in good yield with high diastereoselectivity and enantioselectivity (entry 2). Moreover, even better results were realized from **4j** (entry 3). For further improvement of the stereoselectivities, the silyl ketene acetal **4j** was modified to more bulky silyl ketene acetal **4l** because the studies for the aromatic aldehydes suggested that increased steric bulk on the ester alkyl group would be beneficial for the high *anti*-selectivity. Consequently, the silyl ketene acetal **4l** afforded the aldol product **6lj** with exclusive diastereoselectivity and excellent enantioselectivity (entry 4).

TABLE 6. Optimization of *Anti*-Selective Glycolate Aldol Reactions with Aliphatic Aldehydes[a]

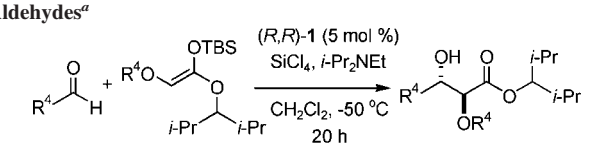


entry	R^2	product	yield,[b] %	dr[c]	er[d]
1	Et_2MeC (**4h**)	**6hj**	trace	ND	ND
2	*neo*-pentyl (**4k**)	**6kj**	81	91:9	94.7:5.3
3	Et_2CH (**4j**)	**6jj**	86	97:3	96.3:3.7
4	*i*-Pr_2CH (**4l**)	**6lj**	88	>99:1	97.0:3.0

[a] All reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.4 M concentration. [b] Yields of chromatographically homogeneous material. [c] Determined by ^1H NMR analysis of HC(2) or HC(3). [d] Determined by CSP-SFC.

In contrast to the *anti*-selective glycolate aldol reactions with aromatic aldehydes, the undesired α-methoxy group could be replaced by the more synthetically useful benzyloxy group in reactions with aliphatic aldehydes. The resulting silyl ketene acetal **4m** reacted with **5j** to afford *anti*-aldol product **6mj** without significant loss of chemical yield and stereoselectivities (Table 7, entry 1). Another primary aliphatic aldehyde, 6-benzyloxyhexanal (**5k**), which has an ether function at the remote position was an excellent substrate. The corresponding aldol product **6mk** was obtained with very high yield and selectivities (entry 2). However, the reactivity of the aldehyde decreased when the ether function was closer to the carbonyl group. In the case of 3-benzyloxypropanal (**5l**), an excess of the silyl ketene acetal was necessary for high chemical yield (entry 3). This reactivity trend was dramatically illustrated when only trace amounts of product were observed from the reaction with 2-benzyloxyacetaldehyde (**5m**) (entry 4). The branched aliphatic aldehydes were also surveyed. The result from β-branched isovaleraldehyde (**5n**) was comparable to the results from unbranched aldehydes (entry 5). On the contrary, the yield and enantioselectivity drops significantly when α-branched cyclohexanal (**5o**) was employed (entry 6). The yield and enantioselectivity could be improved by employing the silyl ketene acetal

TABLE 7. *Anti*-Selective Glycolate Aldol Reactions with Aliphatic Aldehydes[a]



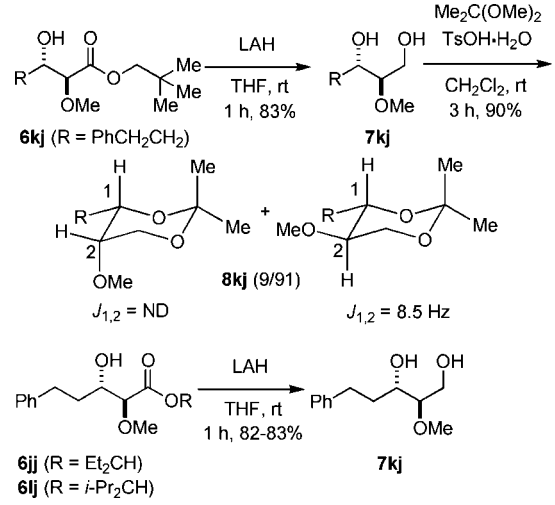
entry	R^1	R^4	product	yield,[b] %	dr[c]	er[d]
1	Bn (**4m**)	$PhCH_2CH_2$ (**5j**)	**6mj**	82	98:2	96.4:3.6[e]
2	Bn (**4m**)	$BnO(CH_2)_5$ (**5k**)	**6mk**	89	98:2	98.5:1.5
3	Bn (**4m**)	$BnOCH_2CH_2$ (**5l**)	**6mL**	59 (80)[f]	99:1	92.5:7.5
4	Bn (**4m**)	$BnOCH_2$ (**5m**)	**6mm**	trace	ND	ND
5	Bn (**4m**)	Me_2CHCH_2 (**5n**)	**6mn**	83	>99:1	95.3:4.7
6	Bn (**4m**)	*c*-C_6H_{11} (**5o**)	**6mo**	9[g]	98:2	68:0:32.0
7	Me (**4l**)	*c*-C_6H_{11} (**5o**)	**6lo**	46[g]	>99:1	87.7:12.3

[a] Reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.4 M concentration. [b] Yields of analytically pure material. [c] Determined by ^1H NMR analysis of HC(2) or HC(3). [d] Determined by CSP-SFC. [e] (2*S*,3*S*) absolute configuration. [f] Reaction employed 2.0 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.4 M concentration. [g] Yield of chromatographically homogeneous material.

4l instead of **4m**. The aldol reaction of **4l** with **5o** provided moderate yield and enantioselectivity (entry 7).

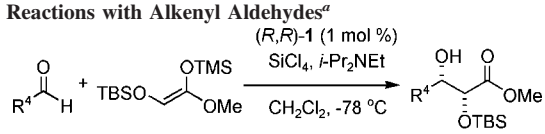
2.2.3. Assignment of Relative and Absolute Configurations of Glycolate Aldol Products of Hydrocinnamaldehyde. The relative configurations of the glycolate aldol products from the optimization study for the *anti*-aldol reaction with aliphatic aldehydes was unambiguously determined as before. Thus, the aldol product **6kj** was reduced to the corresponding diols **7kj** with lithium aluminum hydride and then was transformed to 6-membered cyclic acetal **8kj** (Scheme 12). The vicinal coupling constant between HC(1) and HC(2) of the major diastereomer of **8kj** was 8.5 Hz. Thus, the major diastereomer of **8kj** possessed the *anti*-configuration. The aldol products **6jj** and **6lj** were also reduced to the corresponding diols. The major diastereomers of those diols were identical to the major diastereomer of **7kj**. Consequently, the *anti*-configurations of **6jj** and **6lj** were confirmed.

SCHEME 12



A few synthetic transformations were needed to determine the absolute configurations of glycolate aldol products **6ej** and **6mj** (Scheme 13). The aldol product **6ej** was indirectly correlated with another aldol product **6ep** which was assigned

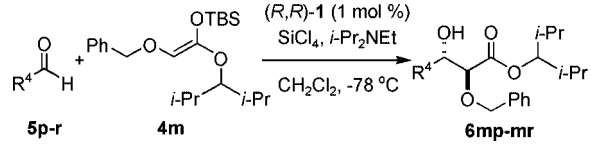
TABLE 8. ***Syn*-Selective Glycolate Aldol Reactions with Alkenyl Aldehydes**[a]



entry	R^4	time, h	product	yield,[b] %	1,2:1,4[c]	*syn*:*anti*[d]	er (*syn*)[e]
1	PhCH=CH (**5p**)	0.5	**6ep**	90	94:6	99:1	97.4:2.6[f]
2	PhCH=CMe (**5q**)	1.0	**6eq**	78[g] (16)[h]	99:1	83:17	75.3:24.7[i]
3	Me_2C=CH (**5r**)	0.5	**6er**	82	92:8	>99:1	95.3:4.7[j]

[a] All reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.1 M concentration. The silyl ketene acetal was added as a 0.24 M solution in CH_2Cl_2 over 15 min. [b] Yields of analytically pure material of 1,2-adduct. [c] Determined by ^1H NMR analysis. [d] Determined by ^1H NMR analysis of HC(2) or HC(3). [e] Determined by CSP-SFC. [f] (2*R*,3*S*) Absolute configuration. [g] Yield of *syn*-diastereomer. [h] Yield of *anti*-diastereomer. [i] er of *anti*-diastereomer was 96.4:3.6. [j] er was determined after 2,4-dinitrobenzoylation of the hydroxyl group.

TABLE 9. ***Anti*-Selective Glycolate Aldol Reactions with Alkenyl Aldehydes**[a]

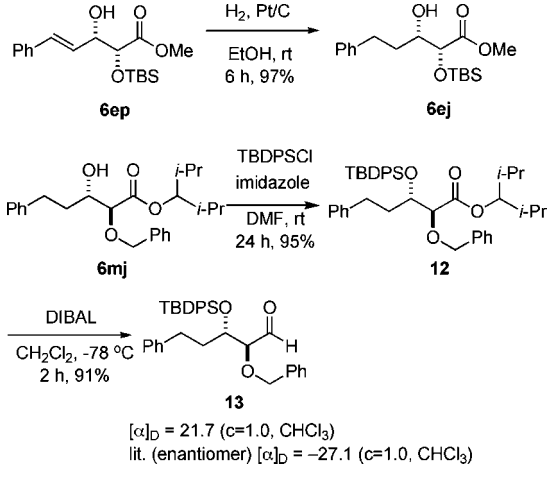


entry	R^4	time, h	product	yield,[b] %	1,2:1,4[c]	dr[d]	er[e]
1	PhCH=CH (**5p**)	0.5	**6mp**	90	95:5	99:1	98.0:2.0[f]
2	PhCH=CHMe (**5q**)	1.0	**6mq**	70	80:20	>99:1	89.1:10.9
3	Me_2C=CH_2 (**5r**)	1.0	**6mr**	79	91:9	78:22	96.1:3.9

[a] All reactions employed 1.2 equiv of silyl ketene acetal, 1.1 equiv of $SiCl_4$, and 0.1 equiv of *i*-Pr_2NEt at 0.1 M concentration. The silyl ketene acetal was added as a 0.24 M solution in CH_2Cl_2 over 15 min. [b] Yields of analytically pure material of 1,2-adduct. [c] Determined by ^1H NMR analysis. [d] Determined by ^1H NMR analysis of HC(2) or HC(3). [e] Determined by CSP-SFC. [f] (2*S*,3*S*) Absolute configuration.

to be (2*R*,3*S*) (see section 2.3.3). Hydrogenation of **6ep** afforded the product whose major stereoisomer was identical to the major stereoisomer of **6ej** by ^1H NMR and CSP-SFC analyses. Thus, the absolute configuration of **6ej** was also assigned to be (2*R*,3*S*). The aldol product **6mj** was transformed to the known aldehyde **13** through the sequence of *tert*-butyldiphenylsilyl protection and partial reduction to aldehyde by diisobutylaluminum hydride.[24] Comparison of its optical rotation with the reported data revealed that the absolute configuration of **13** is (2*S*,3*S*). Both **6ej** and **6mj** have a 3*S* configuration at the β-hydroxyl-bearing carbon center. The *Re* face attack of the nucleophile on the aldehyde was confirmed again.

SCHEME 13



2.3. Alkenyl Aldehydes. 2.3.1. *Syn*-Selective Glycolate Aldol Reactions with Alkenyl Aldehydes. The silyl ketene acetal that was optimal for aldol reaction of aliphatic aldehydes could be applied to the aldol reaction of alkenyl aldehydes. The reactions were carried out in the presence of 1 mol % of (*R*,*R*)-**1** at −78 °C and 0.1 M concentration due to the high reactivity of alkenyl aldehydes. Accordingly, the methyl α-*tert*-butyldimethylsiloxyacetate-derived trimethylsilyl ketene acetal **4e** reacted with *E*-cinnamaldehyde (**5p**) to afford *syn*-aldol product **6ep** in high yield with high diastereoselectivity and enantioselectivity (Table 8, entry 1). The reaction of the silyl ketene acetal **4e** and α-methylcinnamaldehyde (**5q**), which is a typically problematic substrate under Lewis base catalysis, proceeded with moderate diastereoselectivity (entry 2). Although the minor diastereomer of **6eq** was formed with high enantiopurity, the enantioselectivity of the major diastereomer was poor. Finally, 3-methyl-2-butenal (**5r**) gave the aldol product **6er** with excellent diastereoselectivity and enantioselectivity (entry 3). Along with major 1,2-adducts, small amounts of 1,4-adducts were observed in all cases.

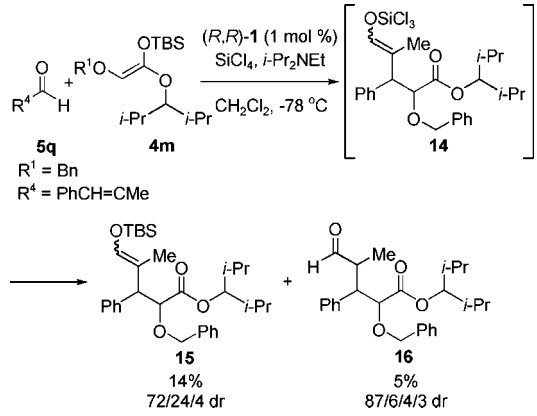
2.3.2. *Anti*-Selective Glycolate Aldol Reactions with Alkenyl Aldehydes. The 2,4-dimethyl-3-pentyl α-benzyloxyacetate-derived *tert*-butyldimethylsilyl ketene acetal **4m** was also suitable for the aldolizations with alkenyl aldehydes (Table 9). Under the reaction conditions, the silyl ketene acetal **4m** rapidly reacted with **5p** to produce the corresponding *anti*-diastereomer of aldol product **6mp** with high stereoselectivity (entry 1). Extremely high diastereoselectivity was also observed from the reaction of the silyl ketene acetal **4m** with **5q** (entry 2). However, the enantioselectivity was only moderate. On the other hand, the **5r** gave the aldol product **6mr** with low diastereoselectivity whereas the enantioselectivity was high (entry 3). The desired aldol products were again accompanied by small amounts of the 1,4-adduct.

The direct product of 1,2-addition is a trichlorosilyl ether, which is hydrolyzed upon aqueous workup to afford the

(24) Evans, D. A.; Glorius, F.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3331–3333.

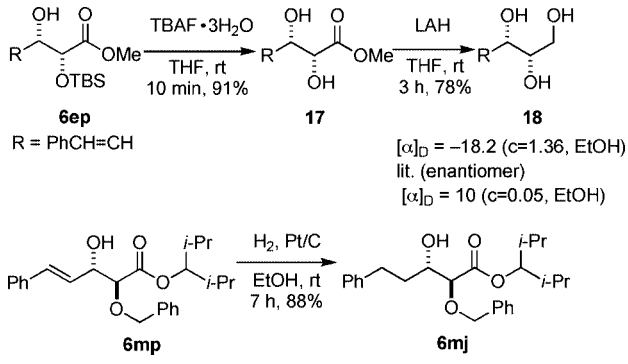
corresponding alcohol. Thus, the direct product of 1,4-addition is most likely a trichlorosilyl enol ether (Scheme 14). However, whereas no trans-silylation of the trichlorosilyl group with the trimethylsilyl or *tert*-butyldimethylsilyl groups of the ketene acetal has been observed in the case of 1,2-addition, the trans-silylated 1,4-adduct **15** was isolated as a mixture of diastereomers in 14% yield from the reaction of **5q** and **4m**.

SCHEME 14



2.3.3. Assignment of Relative and Absolute Configurations of Glycolate Aldol Products of *E*-Cinnamaldehyde. To assign the absolute configuration, **6ep** was transformed to the known triol **18** through the sequence of TBAF-promoted TBS deprotection and lithium aluminum hydride reduction (Scheme 15). Comparison of its optical rotation with the reported data revealed that the absolute configuration of **18** is (2*R*,3*S*).[25] The aldol product **6mp** was indirectly correlated with another aldol product **6mj** which was assigned to be (2*S*,3*S*) (see section 2.2.3). The hydrogenation of **6mp** afforded the product whose major stereoisomer was identical to that of **6mj** as confirmed by ^{1}H NMR and CSP-SCF analyses. Thus, the absolute configuration of **6mp** was also assigned to be (2*R*,3*S*). The 3*S* configuration at the β-hydroxyl-bearing carbon centers of **6ep** and **6mp** confirmed the *Re* face attack of the nucleophile.

SCHEME 15

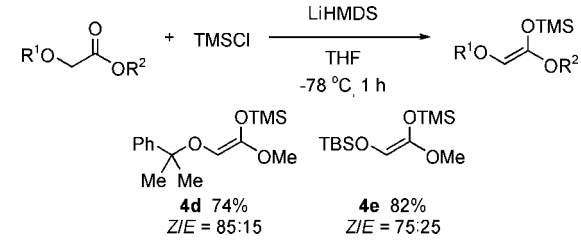


The most unique feature of Lewis base catalyzed glycolate aldol reactions is the accessibility of both diastereomers with the same catalytic system. Through an extensive and systematic examination of the structure of the silyl ketene acetal, it was possible to optimize the structure of the silyl ketene acetal for both *syn*- and *anti*-manifolds. The generality of these reactions were also demonstrated. Reactions of the structurally and electronically diverse aldehydes provided the glycolate aldol products with high diastereoselectivity and enantioselectivity. The relative and absolute configurations were unambiguously assigned. In every single case, the *Re*-face attack of the nucleophiles was confirmed.

Discussion

1. High *Z*-Selectivity of Formation of Glycolate-Derived Silyl Ketene Acetals. The enolization of simple propanoate esters can be controlled by changing base or solvent system.[26] Thus, it is possible to obtain both *Z*- and *E*-propanoate-derived silyl ketene acetals with good selectivity. On the contrary, the enolization of glycolate esters generally affords *Z*-enolates with high selectivity regardless of reaction conditions.[16] Only a few examples of *E*-selective enolization of glycolate esters with limited success have been reported.[27] The high *Z*-selectivity is generally attributed to the coordination of the α-oxygen to the countercation of the base which is typically lithium. Thus, the *Z*-selectivity is attenuated if the α-oxygen bears a bulky protecting group. Enolization of **3d** and **3e**, which bear bulky groups on the α-oxygens, with LHMDS affords the corresponding silyl ketene acetals **4d** and **4e** with 85:15 and 75:25 (*Z*/*E*) selectivities, respectively (Scheme 16). However, the enolization of **3d** and **3e** with KHMDS afforded the silyl ketene acetal **4d** and **4e** with almost exclusive *Z*-selectivity (Scheme 6) in spite of poor coordinating ability of potassium cation. These results can be explained by thermodynamic equilibration of enolate anion. It is known that the *Z*-selectivity of the enolization of glycolate esters could be further improved under thermodynamic conditions.[16] For example, the equilibration can be initiated by the addition of HMPA, which weakens the Li−O bond, to afford a more stable *Z*-enolate with improved selectivity. Similarly, potassium enolates can undergo equilibration even in the absence of additives because of the weak K−O bond. Therefore, higher *Z*-selectivity was obtained from the enolization with KHMDS than the enolization with LHMDS.

SCHEME 16



2. 1,4-Addition to Alkenyl Aldehydes. The formation of a 1,4-adduct from the addition of glycolate-derived silyl ketene acetals to alkenyl aldehydes (Table 8 and 9) was unexpected, as it had previously not been detected from the addition of acetate- or propanoate-derived silyl ketene acetal. The steric hindrance of reacting carbon of silyl ketene acetals in this study is probably responsible for the observation of 1,4-addition. The glycolate-derived silyl ketene acetal has a bulkier substituent at the reacting carbon compared to previously employed

(25) Evans, P.; Johnson, P.; Tayler, R. J. K. *Eur. J. Org. Chem.* **2006**, *7*, 1740–1754.

(26) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650–657.

(27) (a) Sparks, M. A.; Panek, J. S *J. Org. Chem.* **1991**, *56*, 3431–3438. (b) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 5301–5303. (c) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3099–3112.

nucleophiles such as acetate- or propanoate-derived silyl ketene acetal. As a result, the reaction with the carbonyl carbon of alkenyl aldehyde, which is located inside of the congested catalyst pocket (vide infra), becomes relatively difficult. Therefore, the minor reaction takes place at the more accessible β-carbon of alkenyl aldehyde.

3. Rationalization of the Observed Diastereoselectivity. To gain an understanding of the substituent dependence on diastereoselectivity, several possible transition structures were considered. The fact that both *syn*- and *anti*-diastereomers were obtained from the same *Z*-enolate rules out the possibility of a closed, chairlike transition structure.[3] Instead the aldol additions are likely proceeding through an open transition structure.[3] Six limiting, staggered, open transition structures for the addition of propanoate derived silyl ketene acetal to aldehydes have been carefully analyzed previously to explain the observed *anti*-diastereoselectivity.[14i] Following Heathcock and co-worker's analysis,[28] minimization of the unfavorable dipole−dipole interaction was considered as one of the major stabilizing factors. Consequently, the observed *anti*-diastereoselectivity for this propanoate aldol reaction was explained by the two antiperiplanar (ap) transition structures where the position of the α-substituent is the major stereochemistry-determining factor.

A similar argument can be applied for the glycolate aldol reaction. However, because of the additional dipole of the α-alkoxy substituent, none of the transition structures has substantially more favorable dipole−dipole interaction than the others (Figure 1). Although $-sc_{syn}$ and $+sc_{anti}$ transition structures (sc = synclinal) have most unfavorable dipole−dipole interactions between the carbonyl group of aldehyde and the alkoxy substituents of the silyl ketene acetal, the other four transition structures also possess unfavorable dipole−dipole interactions. Moreover, the silyl ketene acetals in this study have bulkier substituents than the propanoate-derived silyl ketene acetals in the previous studies. Consequently, steric interactions may determine the relative stability of the transition structures more than the dipole−dipole interactions. Therefore, it is necessary to carefully analyze the steric interactions of the silyl ketene acetal and the catalyst in all six limiting staggered open transition structures.

3.1. Transition-State Model for *Syn*-Selective Glycolate Aldol Reactions. First, the most stable conformation of the complex of (*R*,*R*)-**1**, $SiCl_3^+$, and benzaldehyde was obtained by examining the dihedral angle around the bond between the central silicon and the oxygen atom of aldehyde.[29] Then, the reaction coordinates of the glycolate aldol reaction was calculated by mapping the distance between the α-carbon of silyl ketene acetals and the carbonyl carbon of the aldehyde. The structure at the highest position of the reaction coordinates was refined and verified by the presence of a single negative vibration after vibrational transition calculations. The most stable conformation of the silyl ketene acetal in each transition structure was obtained by calculating the Gibbs free energy of each transition structure with four limiting conformations of silyl ketene acetals (Figure 2)[30] at 200 K. These calculations were performed by the PC version of CAChe 6.1 with the PM3 basis set. To minimize the total number of possible conformations, the structure of methyl α-*tert*-butoxyacetate-derived trimethylsilyl ketene acetal **4c** was employed instead of more complex structure of methyl α-cumyloxyacetate-derived trimethylsilyl ketene acetal **4d**.

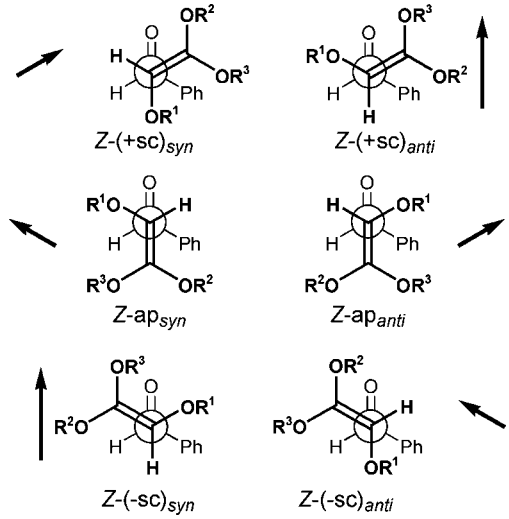


FIGURE 1. Overall dipoles of six limiting, staggered, open transition structures.

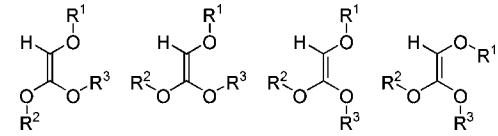


FIGURE 2. Four limiting conformations of silyl ketene acetals.

The computationally generated transition structures suggest that the major steric interactions come from two naphthyl rings of each binaphthyl group and the two chlorine atoms at the central silicon cation (Figure 3). While the ap_{syn}, $-sc_{syn}$, and $-sc_{anti}$ transition structures suffer from severe steric encumbrance between the chlorine atoms of the central silicon cation and one of the alkoxy substituents of the silyl ketene acetal, the $+sc_{anti}$ and ap_{anti} transition structures are destabilized by the steric interaction between one of the naphthyl ring of the catalyst and one of the bulky substituents of the silyl ketene acetal. The $+sc_{syn}$ transition structure possesses the least unfavorable steric interaction between the catalyst and the silyl ketene acetal because the bulky *tert*-butyl group and the trimethylsilyl group of the silyl ketene acetal are located away from the catalyst. Therefore, the observed *syn*-diastereoselectivity can be explained by $+sc_{syn}$ transition structure.

3.2. Transition-State Model for *Anti*-Selective Glycolate Aldol Reactions. A similar analysis can be made for the transition structures of glycolate aldol reactions of bulky tertiary ester-derived silyl ketene acetals (Figure 4). The stable conformation of the silyl ketene acetal in each transition structure was also obtained by calculating the Gibbs free energy of each transition state with all possible limiting conformations of silyl ketene acetals at 200 K as above. To minimize the total number of possible conformations, the structure of *tert*-butyl α-methoxyacetate-derived trimethylsilyl ketene acetal **4f** was used instead of the more complex structure of 3-methyl-3-pentyl α-methoxyacetate-derived *tert*-butyldimethylsilyl ketene acetal **4h**. Whereas the ap_{anti} transition structure has only small steric interaction between the catalyst and the methoxy substituent of the silyl ketene acetal, the other transition structures suffer from

(28) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027–3037.

(29) The calculated coordinates of the complex (*R*,*R*)-**1**·$SiCl_3$ were obtained from those previously published, see ref 14i.

(30) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451–1453.

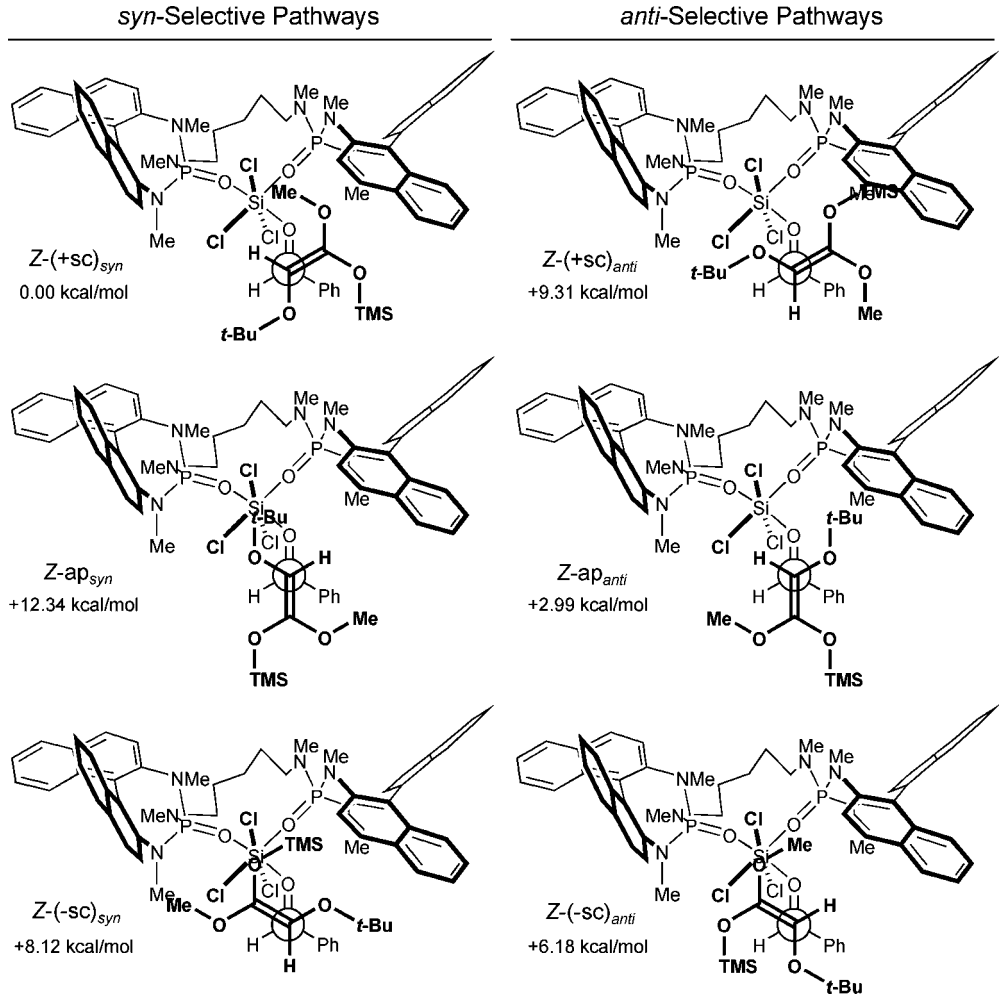


FIGURE 3. Six open transition structures for glycolate aldol reactions with a bulky α-alkoxy group.

severe steric encumbrance between the trichlorosilyl cation-bisphosphoramide complex and one of the alkoxy substituents of the silyl ketene acetal. Therefore, the observed *anti*-diastereoselectivity can be explained by ap$_{anti}$ transition structure. The ap$_{anti}$ transition structure also explains the necessity of the methyl group on the α-oxygen for the high diastereoselectivity. Because the α-alkoxy group and the catalyst are closely located in ap$_{anti}$ transition structure, bulky α-alkoxy group would destabilize the transition structure. Thus, the introduction of benzyl group or trimethylsilylethyl group on the α-oxygen resulted in low diastereoselectivity.

4. Reactivity Trends. 4.1. *Syn*-Selective Glycolate Aldol Reactions. The observed reactivity trend of silyl ketene acetal of *syn*-selective glycolate aldol reactions can be rationalized by the +sc$_{syn}$ transition structure (Figure 3). Because the α-alkoxy group is present in relatively vacant space of the +sc$_{syn}$ transition structure, the variation of the size of the α-alkoxy group would not have a significant influence on the reaction rate until the size of the α-alkoxy group becomes large enough to experience steric repulsion. Thus, the observed reaction rates of the silyl ketene acetals **4a**-**c** and **4e** are similar whereas the bulkiest silyl ketene acetal **4d** showed an attenuated reaction rate.

4.2. *Anti*-Selective Glycolate Aldol Reactions. On the basis of the ap$_{anti}$ transition structure (Figure 4), the observed reactivity trend of silyl ketene acetals can be rationalized. As the alkyl group of the ester is pointing toward the catalyst, the reaction rate would be inversely proportional to the size of the ester. Consequently, the primary or secondary ester-derived silyl ketene acetals such as **4j** and **4k** exhibited greater reactivity than those that were derived from tertiary esters. The ability of the *anti*-selective reagents to combine with aliphatic aldehydes most likely results from the reduced steric demand of the alkoxy substituent on the α-carbon.

5. Reactivity Trend of Aliphatic Aldehydes with Ether Functions. The reactivity of the aliphatic aldehyde dramatically decreased when the ether function is closer to the carbonyl group (Table 7, entries 2−4). This trend can be rationalized by the equilibrium between ionized aldehyde−$SiCl_4$ complex and α-chloro trichlorosilyl enol ether (Scheme 11). Because the electron-withdrawing ether function will destabilize the cationic complex, the equilibrium position will shift to the neutral α-chloro trichlorosilyl enol ether. Therefore, the concentration of active aldehyde decreases further when the ether function is located closer to the carbonyl group.

Conclusion

A general and selective Lewis base catalyzed addition of glycolate-derived silyl ketene acetals to a wide range of aldehydes has been developed. Both *syn*- and *anti*-diastereomers were accessible without changing the catalyst or controlling the geometry of the silyl ketene acetal. Only relatively simple

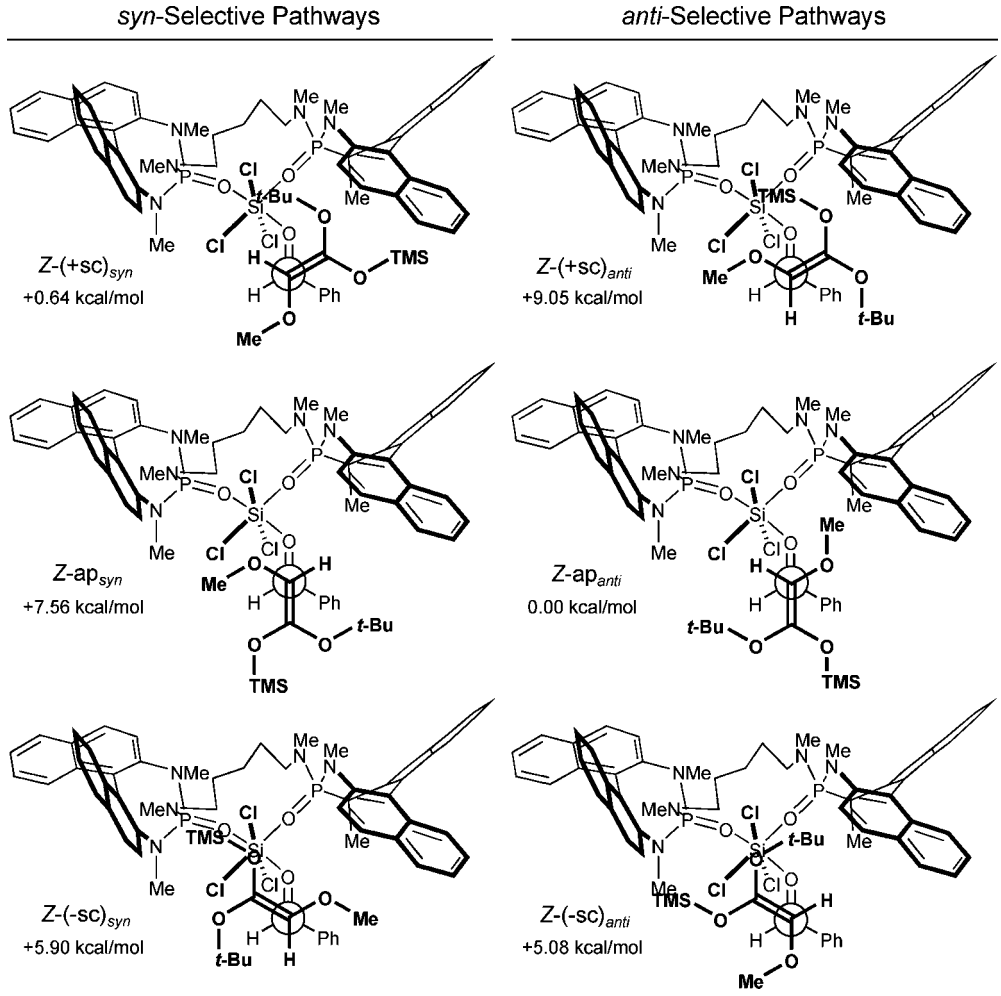


FIGURE 4. Six open transition structures for glycolate aldol reactions with a bulky ester.

modification of the size of the alkyl groups on the silyl ketene acetal was sufficient to reverse the stereochemical course. The Lewis base catalyzed glycolate aldol reaction should provide an attractive alternative for the synthesis of enantiomerically enriched *syn*- or *anti*-1,2-diol units. The observed diastereoselectivity and reactivity could be rationalized by the analysis of six open transition structures with the aid of computational analysis.

Experimental Section

Representative Procedure for *Syn*-Selective Glycolate Aldol. Preparation of (2*R*,3*S*)-3-Hydroxy-2-(1-methyl-1-phenylethoxy)-3-phenylpropanoic Acid Methyl Ester ((2*R*,3*S*)-6da) (Table 2, Entry 1). To a flame-dried, 10-mL Schlenk flask fitted with a magnetic stir bar, a thermocouple, a gas inlet tube, and a septum were added (*R*,*R*)-**1** (8.4 mg, 0.01 mmol, 0.01 equiv), CH_2Cl_2 (5 mL), and benzaldehyde (101.6 μL, 1.0 mmol). The solution was cooled to −78 °C (internal temperature) in a dry ice−acetone bath. After diisopropylethylamine (17.4 μL, 0.1 mmol, 0.1 equiv) and $SiCl_4$ (126 μL, 1.1 mmol, 1.1 equiv) were added to the flask via syringe, a solution of **4d** (336.5 mg, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (5 mL) was added dropwise via syringe over 15 min. The internal temperature was kept below −70 °C during the addition of **4d**. The reaction mixture was stirred for additional 15 min at −78 °C before a mixture of MeOH (1 mL), Et_3N (1 mL), and CH_2Cl_2 (5 mL) was added. The resulting solution was transferred into a 125-mL Erlenmeyer flask containing a satd aq $NaHCO_3$ solution (10 mL) and a satd aq KF solution (10 mL). The biphasic mixture was stirred vigorously for 2 h at room temperature. The mixture was filtered through a glass frit, and the filtrate was transferred to a 125-mL separatory funnel where the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4 (15 g), filtered, and concentrated in vacuo (23 °C, 30 mmHg). The residue was purified by column chromatography (18 mm diameter, hexane/EtOAc, 5/1 to 1/1) on silica gel (10 g) to give **6da** (275 mg, 87%) as a colorless oil. The *syn*/*anti* ratio was determined to be 99/1 by ^{1}H NMR (500 MHz) analysis of the crude reaction mixture. Data for (2*R*,3*S*)-**6da**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.33 (m, 2 H, HC(12)), 7.31−7.22 (m, 8 H, HC(5), HC(6), HC(7), HC(13), HC(14)), 4.79 (d, J = 6.1, 1 H, HC(3)), 3.86 (d, J = 6.1, 1 H, HC(2)), 3.40 (s, 3 H, HC(8)), 2.98 (bs, 1 H, OH), 1.53 (s, 3 H, HC(10)), 1.52 (s, 3 H, HC(10)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3 (C(1)), 143.8 (C(11)), 138.8 (C(4)), 128.1 (C(6) or C(13)), 128.03 (C(6) or C(13)), 127.99 (C(7)), 127.4 (C(14)), 126.5 (C(5)), 126.1 (C(12)), 78.8 (C(9)), 77.4 (C(2)), 75.0 (C(3)), 51.5 (C(8)), 27.9 (C(10)), 27.1 (C(10)); IR (neat) ν 3490 (br), 3062 (w), 3031 (w), 2981 (m), 2950 (w), 1745 (s), 1496 (m), 1451 (m), 1435 (m), 1385 (m), 1368 (m), 1264 (m), 1197 (m), 1170 (m), 1151 (m), 1086 (s), 1076 (s), 1059 (s), 1028 (m), 983 (m), 914 (m), 879 (m), 767 (s), 722 (m), 700 (s); MS (ESI) 119.1 (86), 120.1 (5), 136.1 (15), 179.1 (35), 214.1 (8), 332.2 (100), 337.1 (M^+ + Na, 58), 338.1 (6), 353.1 (23); HRMS calcd for $C_{19}H_{22}O_4Na$ 337.1416, found 337.1413; TLC R_f 0.27 (hexane/EtOAc, 4/1) [UV(254)/$KMnO_4$]; SFC (2*R*,3*S*)-**6da**, t_R 7.61 min (96.6%); (2*S*,3*R*)-

6da, t_R 8.95 min (3.4%) (Chiralpak AS, 125 bar, 40 °C, 1.6% MeOH in CO_2, 2.5 mL/min, 220 nm); $[\alpha]^{24}_D$ 42.2 (c = 1.0, EtOH). Anal. Calcd for $C_{19}H_{22}O_4$ (314.38): C, 72.59; H, 7.05. Found: C, 72.59; H, 7.08.

Representative Procedure for *Anti*-Selective Glycolate Aldol. Preparation of (2*S*,3*S*)-3-Hydroxy-2-methoxy-3-phenylpropanoic Acid 1-Ethyl-1-methylpropyl Ester ((2*S*,3*S*)-6ha) (Table 4, Entry 1). Following the representative procedure above, (*R*,*R*)-**1** (8.4 mg, 0.01 mmol, 0.01 equiv) was combined with diisopropylethylamine (17.4 μL, 0.1 mmol, 0.1 equiv), benzaldehyde (101.6 μL, 1.0 mmol), $SiCl_4$ (126 μL, 1.1 mmol, 1.1 equiv), and **4h** (346.2 mg, 1.2 mmol, 1.2 equiv) to yield, after column chromatography (30 mm diameter, hexane/EtOAc, 5/1) on silica gel (30 g), **6ha** (255 mg, 91%) as a colorless oil. The *syn*/*anti* ratio was determined to be >1/99 by ^{1}H NMR (500 MHz) analysis of the crude reaction mixture. Data for (2*S*,3*S*)-**6ha**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.40 (m, 2 H, HC(5)), 7.35−7.32 (m, 2 H, HC(6)), 7.29−7.26 (m, 1 H, HC(7)), 4.96 (d, J = 5.6, 1 H, HC(3)), 3.89 (d, J = 5.6, 1 H, HC(2)), 3.40 (s, 3 H, HC(12)), 2.96 (bs, 1 H, OH), 1.81−1.73 (m, 3 H, HC(9)), 1.60 (dq, J = 13.9, 7.5, 1 H, HC(9)), 1.30 (s, 3 H, HC(11)), 0.77 (dd, J = 7.5, 7.5, 3 H, HC(10)), 0.74 (dd, J = 7.5, 7.5, 3 H, HC(10)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4 (C(1)), 139.6 (C(4)), 128.2 (C(6)), 127.9 (C(7)), 126.8 (C(5)), 87.7 (C(8)), 84.6 (C(2)), 74.0 (C(3)), 58.8 (C(12)), 30.3 (C(9)), 30.2 (C(9)), 22.6 (C(11)), 7.9 (C(10)), 7.8 (C(10)) IR (neat) ν 3474 (br), 3064 (w), 3033 (w), 2976 (m), 2941 (m), 2884 (m), 2829 (w), 1734 (s), 1495 (w), 1456 (m), 1376 (m), 1266 (m), 1196 (s), 1151 (m), 1124 (s), 1065 (m), 980 (m), 846 (m), 752 (m), 700 (s), 613 (m); MS: (ESI) 179.1 (100), 180.1 (3), 197.1 (18), 298.2 (36), 303.2 (M^+ + Na, 7); HRMS calcd for $C_{16}H_{24}O_4Na$ 303.1572, found 303.1559; TLC R_f 0.27 (hexane/EtOAc, 5/1) [UV(254)/$KMnO_4$]; SFC (2*S*,3*S*)-**6ha**, t_R 10.81 min (95.1%); (2*R*,3*R*)-**6ha**, t_R 11.40 min (4.9%) (Chiralpak AD, 125 bar, 40 °C, 2.0% MeOH in CO_2, 2.0 mL/min, 220 nm); $[\alpha]^{24}_D$ −5.6 (c = 4.0, EtOH). Anal. Calcd for $C_{16}H_{24}O_4$ (280.36): C, 68.54; H, 8.63. Found: C, 68.35; H, 8.72.

Acknowledgment. We are grateful to the National Science Foundation for generous financial support (NSF CHE 0414440 and CHE 0717989).

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

JO8006539