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Asymmetric Induction in Methyl Ketone Aldol Additions to α-Alkoxy and α,β-Bisalkoxy Aldehydes: A Model for Acyclic Stereocontrol

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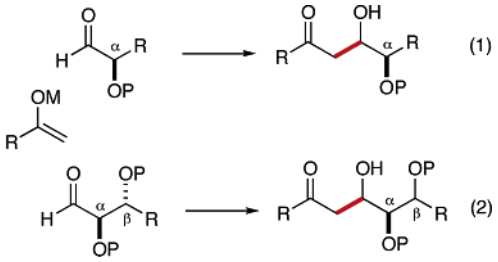
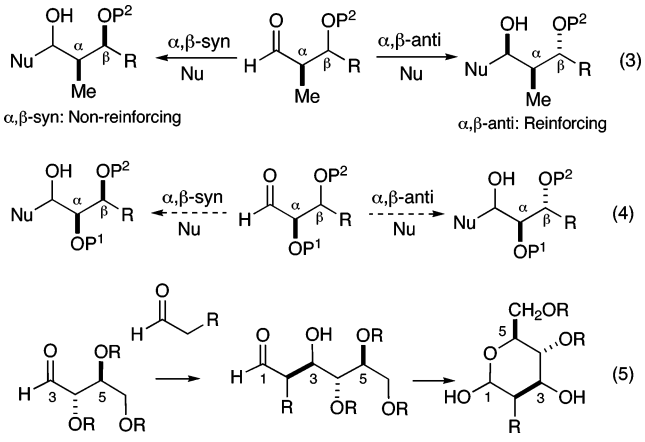
Abstract: A systematic study of methyl ketone aldol additions under nonchelating conditions with α-alkoxy and α,β-bisalkoxy aldehydes is described. Additions to aldehydes containing a single α-alkoxy stereocenter generally provide the product diastereomers in accord with the Cornforth/polar Felkin-Anh models for carbonyl addition. Vicinal asymmetric induction is sensitive to the aldehyde α-alkyl substituent, but is relatively insensitive to the nature of the alkoxy protecting group. Aldehyde π-facial selectivity in additions to substrates containing an additional β-alkoxy-substituted stereocenter exhibits a striking dependence on the relative configuration of the α- and β-stereocenters. Aldehydes with the α- and β-alkoxy substituents in an anti relationship in most cases exhibit good diastereoselectivity, while aldehydes with the α- and β-alkoxy substituents in a syn relationship unexpectedly give product mixtures. A stereochemical model based on Cornforth-like transition-state arrangements is proposed.

Introduction

Asymmetric induction in nucleophilic carbonyl addition reactions is a powerful control element for the selective construction of new stereocenters.[1] In this article, a systematic study of stereocontrol in aldol addition reactions of methyl ketone-derived enolates and aldehydes containing single and multiple alkoxy stereocenters is presented (eqs 1 and 2). The alkoxy protecting group, enolate type, and enolate steric hindrance are systematically varied to give a comprehensive picture of asymmetric induction in methyl ketone aldol additions to alkoxy-substituted aldehydes.



In previous studies we documented that both α-alkyl and β-alkoxy stereocenters play contributing roles in dictating aldehyde π-face selectivity in enol/enolate nucleophilic addition reactions (eq 3).[2] In these processes, the anti diastereomer exhibits uniformly high diastereoselection with unsubstituted enolates. For the *anti*-aldehyde diastereomers, both α- and β-stereocenters reinforce addition to the mutually preferred aldehyde π-face. In contrast, the corresponding *syn*-aldehyde diastereomers exhibit variable selectivity depending on enolate structure. In this instance, there is a nonreinforcing interplay between dipolar (β-OR) and steric effects (α-Me) where sterically demanding enolates respond to steric control and "smaller" enolates are controlled by dipolar effects.



The goal of this investigation is to determine whether similar correlations might exist in aldol additions with the corresponding *syn*- and *anti*-α,β-bisalkoxy aldehyde diastereomers (eq 4). Since these reactions reflect an emerging approach to the synthesis of extended polyol natural products such as carbohydrates (eq 5),[3] the documentation of trends in aldehyde face selectivity represents an important aspect of this assemblage strategy. In the following discussion, the numbering system that will be used

† This work is taken in part from the Ph.D. theses of V. J. Cee, Harvard University, 2003 and S. J. Siska, Harvard University, 2005.

(1) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223, and references therein.
(2) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

is based on the hexose open-chain product tautomer where the carbonyl moiety is designated as C_1. Accordingly, the carbonyl center in the aldehyde precursors is designated as C_3 (eq 5).

α-Alkoxy Aldehydes. It is well established that a carbonyl with an adjacent α-alkoxy substituent reacts with a characteristic stereochemical bias in the absence of chelate organization.[4,5] Under such conditions, most nucleophilic additions proceed with bias for the product diastereomer containing an anti configuration between the newly formed hydroxyl moiety and the vicinal oxygen heteroatom (Figure 1). Both the Cornforth[6] and polar Felkin-Anh[7] transition-state models account for the preferential formation of the 1,2-anti product diastereomer on the basis of *differing transition state control elements* (Figure 1). Recent experimental[8] and theoretical[9] evidence indicates that the Cornforth model more accurately describes asymmetric induction in enolborane additions to α-alkoxy aldehydes.

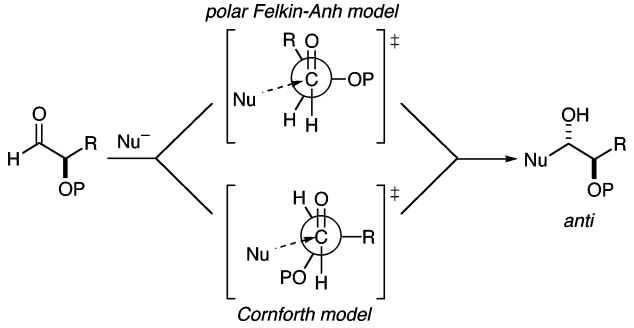
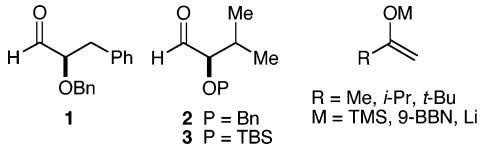


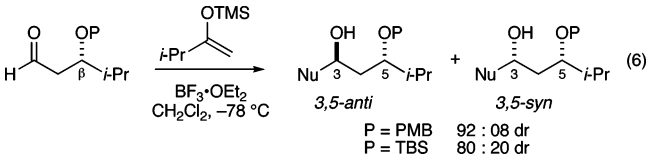
Figure 1. Nucleophilic addition models for α-alkoxy aldehydes.

Aldol additions between unsubstituted enolates and α-alkoxy aldehydes generally favor the formation of the anti product diastereomer, although significant variations in the magnitude of asymmetric induction have been reported.[10] To generate an internally consistent data set for this study, α-alkoxy aldehydes **1**−**3**[11] were studied in aldol addition reactions with methyl ketone-derived nucleophiles of three distinct types (Chart 1). Enolsilanes (M = TMS), enolboranes (M = 9-BBN), and lithium enolates (M = Li) derived from acetone, 3-methyl-2-butanone, and pinacolone were studied to evaluate the influence of both the type of enolate and the effects of nucleophile steric hindrance on diastereofacial selectivity.

Chart 1. α-Alkoxy Aldehyde and Enolate Structures



***β*-Alkoxy Aldehydes.** It is well established that nucleophilic additions to *β*-alkoxy aldehydes result in the preferential formation of the 3,5-anti product diastereomers (eq 6).[12] The



selectivity is dependent on the type of enolate nucleophile, with high levels of selectivity observed in Lewis acid-promoted additions, moderate levels of selectivity observed in lithium enolate additions, and little selectivity noted in enolborane addition reactions. A transition state model based on minimization of electrostatic and steric effects has been proposed to account for the observed sense of 1,3-asymmetric induction (Figure 2). The 3,5-anti product is proposed to arise from transition structure **C**, in which nucleophilic attack occurs anti to the α-carbon substituent, with the *β*-stereocenter oriented to minimize both destabilizing gauche interactions of the *β*-alkyl substituent and destabilizing electrostatic interactions between the *β*-C−O and C═O dipoles.[13] The most likely transition structures for the formation of the syn product contain either an unfavorable alignment of C−O and C═O dipoles (**D**), or an unfavorable gauche arrangement of the *β*-alkyl substituent with the reacting carbonyl (**E**).[14,15]

(3) (a) Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Synlett* **2002**, 1637−1640. (b) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1753−1755. (c) Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 3385−3400. (d) Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 348−359. (e) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B. Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343−1345. (f) Timmer, M. S. M.; Adibekian, A.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7605−7607.

(4) For a review of chelation-controlled nucleophilic additions, see: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468. For experimental evidence of chelates as reactive intermediates see: (c) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784.

(5) For a study of chelation-controlled enolate additions see: Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840−10852.

(6) (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112−127. The Cornforth model discussed here is modified from its original form to incorporate contemporary concepts of a staggered arrangement about the forming C−Nu bond and a >90° angle of attack for the incoming nucleophile. This is often referred to as the Dunitz-Bürgi angle: (b) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065−5067. (c) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563−1572.

(7) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199−2204. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2205−2208. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70. (d) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162.

(8) The relationship between enolborane geometry and diastereofacial selectivity in additions to α-alkoxy aldehydes has been interpreted as supporting a modified Cornforth model: (a) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761−1765. For an alternative explanation based on substituted allylborane additions to α-alkoxy aldehydes, see: (b) Roush, W. R. In *Houben-Weyl*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E. Eds.; Thieme: Stuttgart, 1995; Vol. E21, pp 1410−1486. For additional examples of substituted enolborane and allylborane additions to α-alkoxy aldehydes, see: (c) Hoffmann, R. W. *Chem. Scr.* **1985**, *25* (Special Issue), 53−60. (d) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422−3434. (e) Williams, D. R.; Moore, J. L.; Yamada, M. *J. Org. Chem.* **1986**, *51*, 3916−3918. (f) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881−887. (g) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1988**, *53*, 5023−5034. (h) Brinkmann, H.; Hoffmann, R. W. *Chem. Ber.* **1990**, *123*, 5−2401. (i) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1998**, *63*, 8843−8849.

(9) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920−2930.

(10) Lithium enolate addition: (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846−3856. (b) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361. (c) Mahler, U.; Devant, R. M.; Braun, M. *Chem. Ber.* **1988**, *121*, 2035−2044. (d) Dondoni, A.; Merino, P. *J. Org. Chem.* **1991**, *56*, 5294−5301. Mukaiyama aldol: (e) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027−3037. (f) Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Kishino, H.; Ke, Y. Y.; Tamura, Y. *J. Org. Chem.* **1988**, *53*, 554−561. (g) Gennari, C. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 640−647. Enolborane addition: (h) Gennari, C.; Bernardi, A.; Cardani, S.; Scolastico, C. *Tetrahedron* **1984**, *40*, 4059−4065.

(11) For experimental details concerning the construction of aldehydes **1**−**17**, and stereochemical proofs of the products, see the Supporting Information.

(12) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537−8540, and references therein.

(13) This assumption is supported by semiempirical calculations of ground-state aldehyde conformations. For aldehyde-BF_3 complexes (AM1), see ref 2. For uncomplexed aldehydes (AM1 and PM3), see: Bonini, C.; Esposito, V.; D'Auria, M.; Righi, G. *Tetrahedron* **1997**, *53*, 13419−13426.

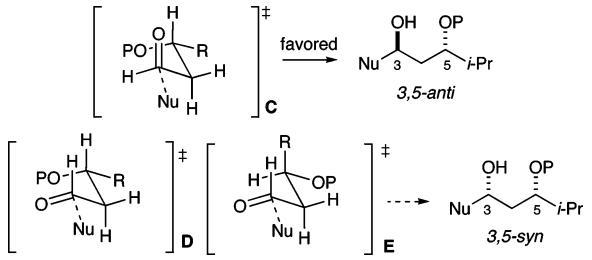
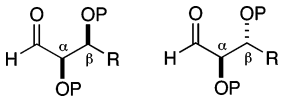


Figure 2. 1,3-Polar model for asymmetric induction in β-alkoxy aldehydes.

α,β-Bisalkoxy Aldehydes. There is no unified body of literature that might be used to predict the diastereoselectivities resulting from nucleophilic additions to the diastereomeric *syn*- and *anti*-aldehyde diastereomers depicted below.



The impact of multiple stereocenters on aldehyde diastereofacial selectivity might be analyzed in terms of the stereocontrol elements provided by the individual substituents. Such an approach has proven successful in describing trends in π-facial selectivity for nucleophilic addition reactions of α-methyl-β-alkoxy aldehydes (eq 3). Consideration of the individual observed face selectivities for additions to α- and β-alkoxy aldehydes leads to the conclusion that the two stereocenters in the *syn*-aldehyde diastereomer should be mutually reinforcing, since the α- and β-configurations promote nucleophilic addition to the same aldehyde π-face (Figure 3). Alternatively, the *anti*-aldehyde diastereomer appears to be nonreinforcing where the α- and β-configurations promote nucleophilic addition to opposite aldehyde π-faces. On the basis of this simple analysis, one would predict high levels of stereoselectivity for nucleophilic additions to the *syn*-aldehyde, and low levels for the *anti*-aldehyde.

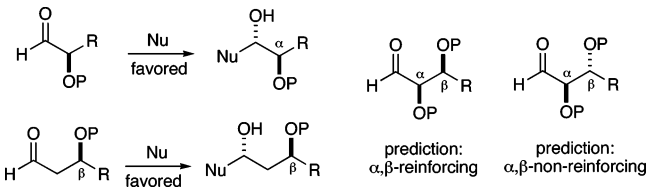
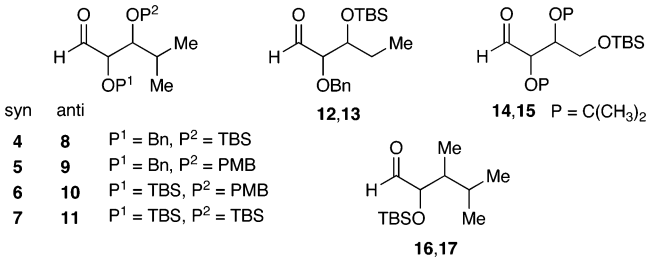


Figure 3. Predicted impact of α- and β-alkoxy stereocenters.

To investigate these qualitative projections, aldehydes **4**−**11** were selected for study in aldol addition reactions (Chart 2). The structural features of these aldehydes were chosen to correspond to the 1,2- and 1,3-asymmetric induction studies (vide supra). These aldehydes share a branched *iso*-propyl substituent at the β-position. Benzyl and silyl groups were selected to protect the α- and β-oxygen atoms due to their common use in synthesis design and their significant steric and electronic differences. The benzyl (Bn) and *tert*-butyldimethylsilyl (TBS) protecting groups were selected for the α-oxygen substituent in accord with the study of 1,2-asymmetric induction,

Chart 2. α,β-Alkoxy Aldehyde Structures Studied



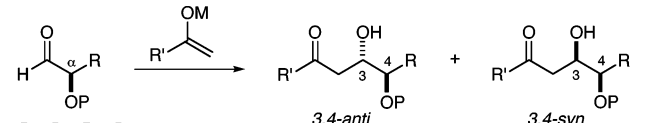
syn	anti	
4	**8**	P^1 = Bn, P^2 = TBS
5	**9**	P^1 = Bn, P^2 = PMB
6	**10**	P^1 = TBS, P^2 = PMB
7	**11**	P^1 = TBS, P^2 = TBS

whereas the *para*-methoxybenzyl (PMB) and TBS protecting groups were chosen for the β-oxygen substituent in accord with the study of 1,3-asymmetric induction. Three additional aldehyde structural types were selected to evaluate the effect of an unbranched β-alkyl group (**12**,**13**), a cyclic protecting group (**14**,**15**), and a methyl-substituted β-stereocenter (**16**,**17**).

Results and Discussion

α-Alkoxy Aldehydes. The π-facial selectivities exhibited by aldehydes **1**−**3** in aldol addition reactions with methyl ketone-derived enolates is presented in Table 1. In the majority of cases, the 3,4-anti product diastereomer predominates in accord with expectation. Since the 3,4-syn adduct may be rationalized through a chelate-controlled addition, it is noteworthy that the lithium enolates (THF, −78 °C) exhibit a neglible tendency to respond to this control element. The steric hindrance of the nucleophile appears to affect diastereofacial selectivity only in the Lewis acid-promoted enolsilane addition reactions (M = $TMS/BF_3{\cdot}OEt_2$). Comparison of the benzyl-substituted α-benzyloxy aldehyde **1** and the *iso*-propyl-substituted α-benzyloxy aldehyde **2** reveals that β-branching results in improved diastereofacial selectivity in the lithium enolate addition reactions. The corresponding *iso*-propyl-substituted α-silyloxy aldehyde **3** exhibits comparable results to **2**, with a slight improvement observed for enolborane additions. Lithium enolate additions afford an effective strategy for the construction of *anti*-β,γ-alkoxy carbonyl compounds in high diastereomeric purity, provided the α-alkyl substituent is branched.[16]

Table 1. Aldol Reactions of α-Alkoxy Aldehydes[a]



1 P = Bn, R = Bn
2 P = Bn, R = *i*-Pr
3 P = TBS, R = *i*-Pr

18 P = Bn, R = Bn
20 P = Bn, R = *i*-Pr
22 P = TBS, R = *i*-Pr

19 P = Bn, R = Bn
21 P = Bn, R = *i*-Pr
23 P = TBS, R = *i*-Pr

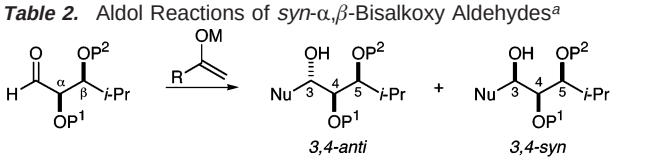
		3,4-anti:3,4-syn[b] (yield)[c]		
aldehyde	R′	M = $TMS/BF_3{\cdot}OEt_2$	M = 9-BBN	M = Li
1	Me	77:23 (67)	68:32 (88)	71:29 (83)
	i-Pr	47:53 (59)	69:31 (93)	64:36 (75)
	t-Bu	42:58 (77)	68:32 (98)	62:38 (73)
2	Me	80:20 (67)	75:25 (79)	**94:06 (88)**
	i-Pr	53:47 (60)	79:21 (89)	**91:09 (84)**
	t-Bu	64:36 (65)	80:20 (81)	**89:11 (76)**
3	Me	82:18 (66)	85:15 (83)	**85:15 (84)**
	i-Pr	75:25 (69)	85:15 (85)	**88:12 (53)**
	t-Bu	50:50 (66)	82:18 (76)	**91:09 (78)**

[a] All reactions were conducted at −78 °C in CH_2Cl_2 except when M = Li (−78 °C in THF). All isolable products were unambiguously characterized. [b] Ratios were determined by HPLC analysis of the unpurified reaction mixture, or by GLC analysis of the derivatized (silylated or acetylated) unpurified reaction mixture. [c] Yields are reported for the mixture of isolated diastereomeric adducts.

(14) The same control elements appear to be operating in the reduction of β-alkoxy ketones: Evans, D. A.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8541−8544.

(15) For a recent double stereodifferentiating Mukaiyama aldol addition see: Keck, G. E.; Knutson, C. E.; Wiles, S. A. *Org. Lett.* **2001**, *3*, 707−710. In this paper, Keck presents a clear three-dimensional representation for merged stereoinduction that is adopted herein.

Table 2. Aldol Reactions of *syn*-α,*β*-Bisalkoxy Aldehydes[a]



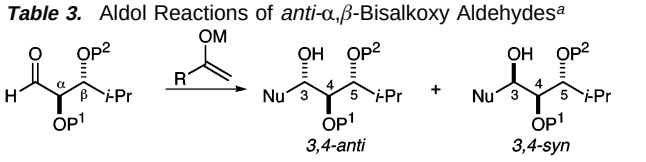
3,4-anti 3,4-syn

4 P^1 = Bn, P^2 = TBS — **24** P^1 = Bn, P^2 = TBS — **25** P^1 = Bn, P^2 = TBS
5 P^1 = Bn, P^2 = PMB — **26** P^1 = Bn, P^2 = PMB — **27** P^1 = Bn, P^2 = PMB
6 P^1 = TBS, P^2 = PMB — **28** P^1 = TBS, P^2 = PMB — **29** P^1 = TBS, P^2 = PMB
7 P^1 = TBS, P^2 = TBS — **30** P^1 = TBS, P^2 = TBS — **31** P^1 = TBS, P^2 = TBS

		3,4-anti:3,4-syn[b] (yield)[c]		
aldehyde	R	M = $TMS/BF_3{\cdot}OEt_2$	M = 9-BBN	M = Li
4	Me	31:69 (50)	40:60 (95)	55:45 (98)
	i-Pr	18:82 (83)	44:56 (91)	69:31 (93)
	t-Bu	25:75 (62)	54:46 (89)	71:29 (77)
5	Me	87:13 (77)	75:25 (93)	74:26 (86)
	i-Pr	49:51 (86)	78:22 (98)	79:21 (87)
	t-Bu	45:55 (61)	83:17 (99)	72:28 (76)
6	Me	67:33 (78)	45:55 (86)	63:37 (90)
	i-Pr	49:51 (67)	36:64 (83)	84:16 (87)
	t-Bu	18:82 (37)	33:67 (86)	66:34 (86)
7	Me	34:66 (69)	**07:93 (90)**	68:32 (79)
	i-Pr	43:57 (61)	**07:93 (87)**	68:32 (83)
	t-Bu	14:86 (61)	**03:97 (91)**	66:34 (70)

[a] All reactions were conducted at −78 °C in CH_2Cl_2 except when M = Li (−78 °C in THF). All isolable products were unambiguously characterized. [b] Ratios were determined by HPLC analysis of the unpurified reaction mixture, or by GLC analysis of the derivatized (silylated or acetylated) unpurified reaction mixture. [c] Yields are reported for the mixture of isolated diastereomeric adducts.

Table 3. Aldol Reactions of *anti*-α,*β*-Bisalkoxy Aldehydes[a]



3,4-anti 3,4-syn

8 P^1 = Bn, P^2 = TBS — **32** P^1 = Bn, P^2 = TBS — **33** P^1 = Bn, P^2 = TBS
9 P^1 = Bn, P^2 = PMB — **34** P^1 = Bn, P^2 = PMB — **35** P^1 = Bn, P^2 = PMB
10 P^1 = TBS, P^2 = PMB — **36** P^1 = TBS, P^2 = PMB — **37** P^1 = TBS, P^2 = PMB
11 P^1 = TBS, P^2 = TBS — **38** P^1 = TBS, P^2 = TBS — **39** P^1 = TBS, P^2 = TBS

		3,4-anti:3,4-syn[b] (yield)[c]		
aldehyde	R	M = $TMS/BF_3{\cdot}OEt_2$	M = 9-BBN	M = Li
8	Me	**99:01 (86)**	**93:07 (90)**	**99:01 (83)**
	i-Pr	**97:03 (84)**	**92:08 (94)**	**99:01 (95)**
	t-Bu	**97:03 (77)**	**96:04 (94)**	**98:02 (87)**
9	Me	90:10 (81)	86:14 (99)	>**99:01 (99)**
	i-Pr	78:22 (87)	80:20 (96)	**99:01 (94)**
	t-Bu	75:25 (79)	80:20 (99)	>**99:01 (67)**
10	Me	65:35 (83)	91:09 (88)	>**99:01 (95)**
	i-Pr	41:59 (95)	86:14 (92)	>**99:01 (95)**
	t-Bu	09:91 (89)	81:19 (90)	**99:01 (98)**
11	Me	95:05 (82)	**98:02 (83)**	>**99:01 (89)**
	i-Pr	87:13 (82)	**99:01 (78)**	>**99:01 (87)**
	t-Bu	47:53 (69)	**97:03 (83)**	**99:01 (90)**

[a] All reactions were conducted at −78 °C in CH_2Cl_2 except when M = Li (−78 °C in THF). All isolable products were unambiguously characterized. [b] Ratios were determined by HPLC analysis of the unpurified reaction mixture, or by GLC analysis of the derivatized (silylated or acetylated) unpurified reaction mixture. [c] Yields are reported for the mixture of isolated diastereomeric adducts.

***syn*-α,*β*-Bisalkoxy Aldehydes.** The *π*-facial selectivities exhibited by *syn*-α,*β*-bisalkoxy aldehydes (**4**−**7**) in aldol reactions with methyl ketone-derived enolate nucleophiles are presented in Table 2. Although it had been anticipated that the syn diastereomer might contain stereoreinforcing control elements (Figure 3), the levels of selectivity for the 3,4-anti product are surprisingly low. The Lewis acid-promoted enolsilane additions (M = $TMS/BF_3{\cdot}OEt_2$) are the only conditions under which selectivity was significantly affected by the steric encumbrance of the enolate component, with selectivity generally decreasing with the increasing steric size of the enolate substituent (R). This trend is also observed in reactions of α-alkoxy aldehydes (Table 1). On average, the enolsilane additions slightly favor the 3,4-syn product diastereomer. The enolborane aldol reactions (M = 9-BBN) are characterized by a significant protecting group dependence, in which the presence of two TBS protecting groups results in the nearly exclusive formation of the 3,4-syn product. Lithium enolate additions are relatively consistent across all aldehyde and enolate structures, and while the 3,4-anti product is favored, the diastereoselectivity is lower than for aldehydes containing a single α-alkoxy-substituted stereocenter (Table 1). Regarding synthetically useful transformations, the present study reveals the unexpected difficulty in obtaining the 3,4-anti/4,5-syn diastereomer from an aldol-based approach. However, useful levels of selectivity (≥93:07 dr) are available for the construction of the 3,4-syn/4,5-syn diastereomer via enolborane addition to the bis-TBS protected aldehyde **7** (M = 9-BBN).

***anti*-α,*β*-Bisalkoxy Aldehydes.** Reactions of the anti-configured aldehydes **8**−**11** with methyl ketone-derived enolate nucleophiles are presented in Table 3. The immediate conclusion is that this aldehyde family exhibits improved reaction diastereoselectivities when compared to their *syn*-aldehyde counterparts (Table 2). Under Mukaiyama aldol conditions (M = $TMS/BF_3{\cdot}OEt_2$), the diastereoselectivity was significantly affected by both the steric hindrance of the enolate component and the identity of the oxygen protecting groups. Aldehyde **8** exhibits uniformly high selectivity with all enolsilanes, whereas the diastereoselectivity in the reactions of the other aldehydes is sensitive to enolsilane steric hindrance. Enolborane additions show a moderate protecting group dependence, with aldehydes bearing a *β*-OTBS substituent (M = 9-BBN, **8** and **11**) giving superior selectivity relative to *β*-OPMB aldehydes (M = 9-BBN, **9** and **10**).[17] All aldehydes reacting with lithium enolates (M = Li) afford outstanding selectivity for the 3,4-anti diastereomer (>98:02). In addressing the issues of synthesis design, the results indicate the relative ease of establishing the 3,4-anti/4,5-anti stereotriad by an aldol-based strategy.

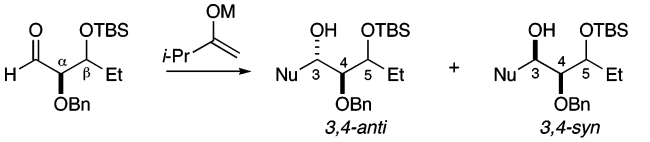
Unbranched *β*-Alkyl Substituent. The effect of the relative size of the *β*-alkyl substituent on diastereofacial selectivity was examined in aldehydes **12** and **13** (Table 4). The *syn*-aldehyde **12** is observed to provide aldol adducts favoring the 3,4-syn diastereomer for both enolsilane and enolborane nucleophiles, while modest selectivity for the 3,4-anti diastereomer is observed with the lithium enolate. In contrast, the anti-configured aldehyde **13** is observed to provide aldol adducts with good to excellent selectivity for the 3,4-anti diastereomer. While the differences in selectivity between *syn*- and *anti*-aldehydes is still

(16) Heathcock and co-workers have previously reported highly diastereoselective aldol addition reactions between the lithium enolate of pinacolone and α-alkoxy aldehydes. See ref 10b.

(17) For a report of a *β*-oxygen protecting group effect in the addition of boron enolates to α-methyl-*β*-alkoxy aldehydes, see: Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443−3446.

quite large, aldehyde **13** does exhibit slightly lower selectivity relative to the corresponding β-*iso*-propyl-substituted aldehyde **8** (Table 3).

Table 4. Aldol Reactions of β-Ethyl-α,β-bisalkoxy Aldehydes[a]



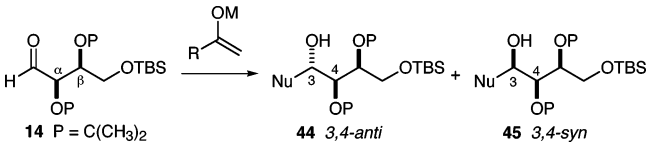
12 α,β-*syn* **13** α,β-*anti* **40** *4,5-syn* **42** *4,5-anti* **41** *4,5-syn* **43** *4,5-anti*

		3,4-anti:3,4-syn[b] (yield)[c]		
aldehyde	α,β-	M = TMS/BF_3·OEt_2	M = 9-BBN	M = Li
12	syn	07:93 (83)	22:78 (96)	71:29 (88)
13	anti	84:16 (91)	83:17 (88)	**95:05 (76)**

[a] All reactions were conducted at −78 °C in CH_2Cl_2 except when M = Li (−78 °C in THF). All isolable products were unambiguously characterized. [b] Ratios were determined by integration of the ^{1}H NMR spectra of the unpurified reaction mixtures. [c] Yields are reported for the mixture of isolated diastereomeric adducts.

Acetonide Protecting Group. The *syn*- and *anti*-α,β-bisalkoxy aldehyde acetonides corresponding to erythrose and threose[18] were investigated to determine the effect of a cyclic protecting group and relative configuration on diastereofacial selectivity (Tables 5 and 6). Acetonide **14**, corresponding to a *syn*-α,β-bisalkoxy configuration, reacts with low to moderate diastereoselectivity in Lewis acid-promoted and enolborane aldol reactions. Again, the selectivity of the lithium enolate aldol reaction is significantly better, and is the first example of high levels of 3,4-anti diastereoselectivity from a *syn*-α,β-bisalkoxy aldehyde in this study. Acetonide **15** corresponding to an *anti*-α,β-bisalkoxy configuration exhibits similar trends, with the average diastereoselectivity being slightly higher than that observed for the syn-configured aldehyde **14**. The similar behavior of the *syn*- and *anti*-acetonide aldehydes is noteworthy, since the majority of *syn*- and *anti*-aldehydes studied exhibit significant differences in π-facial selectivity.

Table 5. Aldol Reactions of *syn*-α,β-Bisalkoxy Aldehyde Acetonides[a]



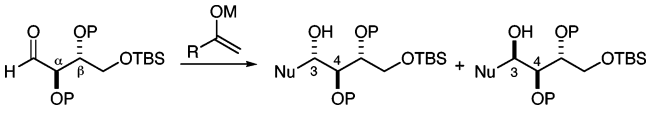
14 P = $C(CH_3)_2$ **44** *3,4-anti* **45** *3,4-syn*

	44:**45**[b] (yield)[c]		
R	M = TMS/BF_3·OEt_2	M = 9-BBN	M = Li
Me	65:35 (61)	49:51 (74)	**89:11 (62)**
i-Pr	67:33 (69)	54:46 (91)	**92:08 (48)**
t-Bu	54:46 (28)	54:46 (72)	**90:10 (58)**

[a] All reactions were conducted at −78 °C in CH_2Cl_2 except when M = Li (−78 °C in THF). All isolable products were unambiguously characterized. [b] Ratios were determined by HPLC analysis of the unpurified reaction mixture, or by GLC analysis of the derivatized (silylated or acetylated) unpurified reaction mixture. [c] Yields are reported for the mixture of isolated diastereomeric adducts.

(18) Acetonides corresponding to aldehydes **4**−**11** were initially studied. Unfortunately, it was found that when subjected to a BF_3·OEt_2-promoted enolsilane addition reaction, the *anti*-α,β-alkoxy aldehyde acetonide underwent acetonide migration. This rearrangement greatly complicated the analysis of the reaction diastereoselectivity. Fortunately, the aldehyde acetonides related to erythrose and threose were not observed to undergo migration.

Table 6. Aldol Reactions of *anti*-α,β-Bisalkoxy Aldehyde Acetonides[a]



15 P = $C(CH_3)_2$ **46** *3,4-anti* **47** *3,4-syn*

	46:**47**[b] (yield)[c]		
R	M = TMS/BF_3·OEt_2	M = 9-BBN	M = Li
Me	83:17 (81)	67:33 (98)	**96:04 (81)**
i-Pr	63:37 (61)	76:24 (85)	**96:04 (85)**
t-Bu	25:75 (69)	78:22 (74)	**94:06 (90)**

[a] All reactions were conducted at −78 °C in CH_2Cl_2 except when M = Li (−78 °C in THF). All isolable products were unambiguously characterized. [b] Ratios were determined by HPLC analysis of the unpurified reaction mixture, or by GLC analysis of the derivatized (silylated or acetylated) unpurified reaction mixture. [c] Yields are reported for the mixture of isolated diastereomeric adducts.

Model for Asymmetric Induction. Our observations (Tables 2 and 3) reveal that the *anti*-aldehyde diastereomers exhibit significantly higher reaction diastereoselectivities than their *syn*-aldehyde counterparts. This trend runs counter to preliminary expectations based on a summation of the individual contributions of the α- and β-stereocenters to π-facial selectivity (Figure 3). It is apparent that the presence of multiple oxygen stereocenters affects aldehyde π-facial selectivity in a manner that is not encountered in aldehydes with single oxygen-substituted stereocenters.

The aldehydes under study have considerable conformational flexibility, and the generation of transition state models that correlate with our data can be simplified by the application of well-established paradigms for asymmetric induction to select appropriate O=C−C_α torsion angles. Both the Cornforth and PFA torsion angle constraints are applied in this regard. To determine the likelihood of a transition structure contributing to product formation, the following assumptions are made: (**A**) fully developed sy*n*-pentane interactions between the α-OP substituent and the non-hydrogen β-substituents are prohibitive;[19] (**B**) developing sy*n*-pentane interactions between the nucleophile and substrate are prohibitive;[20] (**C**) fully developed *syn*-pentane interactions are energetically more costly than developing *syn*-pentane interations within the reacting electrophile; (**D**) developing *syn*-pentane interactions between C=O and β-C−R are energetically more costly than between C=O and β-C−O.[13] Prohibitive *syn*-pentane interactions are highlighted in red, while developing *syn*-pentane interactions are shown in blue.

As the aldehydes under consideration contain vicinal alkoxy substituents, it is possible that aldehyde conformations containing a gauche arrangement of alkoxy substituents may be stabilized relative to aldehydes containing an anti arrangement of these groups.[21] By means of NMR spin−spin coupling measurements of 1,2-dimethoxyethane in the liquid phase, it has been established that the gauche OCCO tgt conformer is 0.5 kcal/mol more stable than the trans OCCO ttt conformer.[22]

(19) The *syn*-pentane arrangement for methyl propyl ether (COCC and OCCC dihedral angles of +60 and −60°) has been calculated to be +6.2 kcal/mol: Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4821−4828.

(20) For the reaction of acetaldehyde enolborane with 2-methoxypropanal (ref 9), it has not been possible to generate calculated structures which contain a *syn*-pentane relationship between the forming C−C bond and the O−CH_3 bond, suggesting that this arrangement is prohibitively high in energy.

(21) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 2−111.

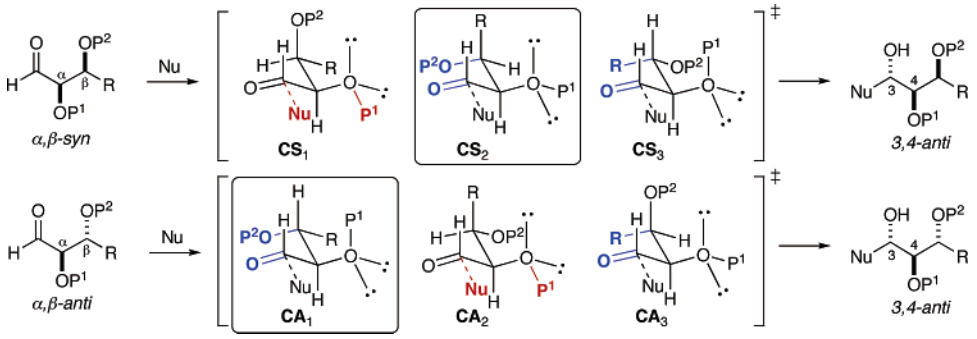
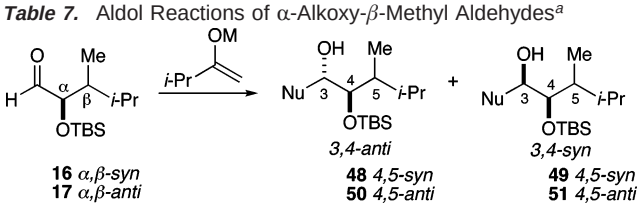


Figure 4. Cornforth transition structures for nucleophilic addition to *syn*- and *anti*-α,*β*-alkoxy aldehydes.

Unlike 1,2-dimethoxyethane, however, the aldehydes under consideration contain a C_3-C_6 butane fragment, and we believe that the conformational preference of this fragment is more significant, as *trans*-butane is known to be 0.9 kcal/mol more stable than gauche-butane, a value considerably larger than the gauche preference for 1,2-dimethoxyethane. The finding that the trends in diastereoselectivity observed in α,*β*-bisalkoxy aldehydes persist among α-alkoxy, *β*-methyl aldehydes **16** and **17** (Table 7), in which vicinal alkoxy substituents are not present, supports this view.

Table 7. Aldol Reactions of α-Alkoxy-*β*-Methyl Aldehydes[a]



16 α,*β*-*syn*
17 α,*β*-*anti*
48 4,5-*syn*
50 4,5-*anti*
49 4,5-*syn*
51 4,5-*anti*

		3,4-anti:3,4-syn[b] (yield)[c]		
aldehyde	α,*β*-	M = TMS/BF_3·OEt_2	M = 9-BBN	M = Li
16	syn	47:53 (63)	78:22 (87)	81:19 (83)
17	anti	70:30 (87)	87:13 (93)	98:02 (90)

[a] All reactions were conducted at −78 °C in CH_2Cl_2 except when M = Li (−78 °C in THF). All isolable products were unambiguously characterized. [b] Ratios were determined by GLC analysis of the silylated unpurified reaction mixture. [c] Yields are reported for the mixture of isolated diastereomeric adducts.

Cornforth Model. Conformational representations of transition structures based on the Cornforth model are depicted in Figure 4. In all representations, the reacting *π*-face of C═O corresponds to the formation of 3,4-anti products, and the α-C−O and C═O bonds are in an antiparallel arrangement. In this orientation, three transition structures are possible due to rotation about the C_4-C_5 bond for both the syn-configured aldehyde (**CS_1**−**CS_3**) and the anti-configured aldehyde (**CA_1**−**CA_3**). A unique consequence of the α-oxygen substituent is that the protecting group P^1 is coupled to rotation about the C_4-C_5 bond due to potential *syn*-pentane interactions with the non-hydrogen *β*-substituents. Beginning with the *β*-alkyl group in an optimal position anti to the reacting carbonyl, transition state **CS_1** contains the same favorable nonparallel arrangement of *β*-C−O and C═O that is implicated in the 1,3-polar model of asymmetric induction (Figure 2) while the corresponding transition state for the *anti*-aldehyde **CA_1** contains a parallel arrangement of *β*-C−O and C═O. This would likely make addition to the *syn*-aldehyde via **CS_1** a very favorable situation, were it not for the prohibitive *syn*-pentane interaction between O−P^1 and the forming C−C bond. This interaction was not accounted for in our simple prediction (Figure 3), and is likely responsible for the failure of this prediction. Rotation about the C_4-C_5 bond results in additional transition structures **CS_2** and **CS_3** in which P^1 does not experience prohibitive interactions with the nucleophile, but this comes at the expense of additional gauche interactions involving the *β*-alkyl substituent. *According to criterion **D**, transition structure **CS_2** is proposed to be the most likely for addition to the syn-aldehyde*. Corresponding transition structures for addition to the *anti*-aldehyde (**CA_2** and **CA_3**) can also be considered, but suffer from significant destabilizing interactions relative to **CA_1**. Comparison of the most likely transition structures for addition to the *syn*- and *anti*-aldehydes, **CS_2** and **CA_1**, respectively, reveals an identical developing *syn*-pentane interaction between *β*-C−O and C═O. *The suboptimal position of the β-alkyl substituent in the transition state for addition to the syn-aldehyde, compared to an optimal positioning of this group for addition to the anti-aldehyde, suggests that addition to the anti-aldehyde should be more favorable*. This finding is consistent with our observations (Tables 1 and 2) and we conclude that evaluation of the Cornforth transition structures of *syn*- and *anti*-α,*β*-bisalkoxy aldehydes leading to the 3,4-anti product diastereomer provides a sufficient explanation for the observed differences in diastereofacial selectivity.

Polar Felkin-Anh Model. Conformational representations of transition structures based on the Polar Felkin-Anh model are illustrated in Figure 5. In all representations, the reacting *π*-face of C═O corresponds to the formation of 3,4-anti products, and the α-C−O and C═O bonds are in a perpendicular arrangement. In this orientation, three transition structures are possible due to rotation about the C_4-C_5 bond for both the syn-configured aldehyde (**FS_1**−**FS_3**) and the anti-configured aldehyde (**FA_1**−**FA_3**). Transition structures **FS_2**, **FS_3**, **FA_1**, and **FA_3** are observed to contain prohibitive *syn*-pentane interactions between the forming C−C bond and non-hydrogen *β*-substituents, and it is unlikely that these contribute to product formation. The remaining transition structures, **FS_1** for addition to the *syn*-aldehyde, and **FA_2** for addition to the *anti*-aldehyde, exhibit developing *syn*-pentane interactions between C═O and either OP^2 or R, respectively. To the extent that C═O↔R is more destabilizing than C═O↔OP^2 (criterion **D**), the polar Felkin-Anh transition structures suggest that addition to the *anti*-aldehyde is less favorable than the analogous addition to the *syn*-aldehyde. This

(22) (a) Viti, V.; Indovina, P. L.; Podo, F.; Radics, L.; Nemethy, G. *Mol. Phys.* **1974**, *27*, 541−559. (b) Tasaki, K.; Abe, A. *Polym. J.* **1985**, *17*, 641−655. (c) Abe, A.; Tasaki, K.; Mark, J. E. *Polym. J.* **1985**, *17*, 883−893.

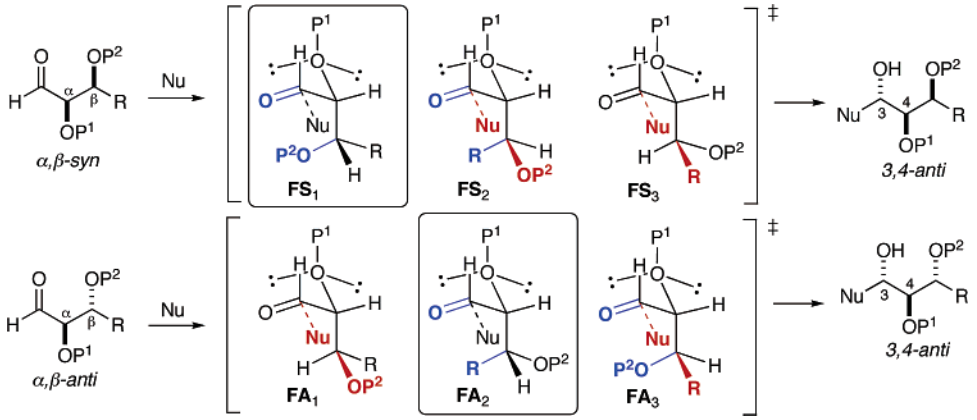


Figure 5. Polar Felkin-Anh transition structures for nucleophilic addition to *syn*- and *anti*-α,*β*-alkoxy aldehydes.

finding is inconsistent with our observations (Tables 1 and 2) and we conclude that evaluation of the PFA transition structures of *syn*- and *anti*-α,*β*-bisalkoxy aldehydes leading to the 3,4-anti product diastereomer is insufficient in accounting for the observed differences in diastereofacial selectivity.

Cornforth Model: Acetonide-Protected Aldehydes. In contrast to the dramatic differences in diastereofacial selectivity observed for *syn*- and *anti*-aldehydes with independent protecting groups (Tables 2 and 3), the *syn*- and *anti*-acetonides (Tables 5 and 6) exhibited comparable levels of selectivity in aldol addition reactions. Examination of the Cornforth transition structures for addition to *syn*- and *anti*-aldehyde acetonides (Figure 6) indicates that the acetonide linkage serves to remove the offending Nu↔P[1] interaction in the transition state for nucleophilic addition to the *syn*-aldehyde (compare **CS**$_1$, Figure 4, with **C**$_S$, Figure 6). The steric environment in the vicinity of the nucleophile is now similar for both *syn*-(**C**$_S$) and *anti*-aldehydes (**C**$_A$), consistent with the comparable aldehyde *π*-facial selectivity.

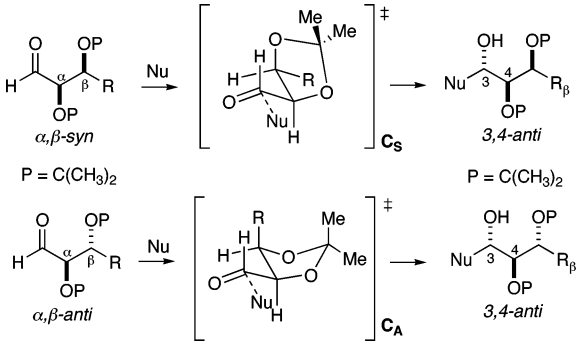


Figure 6. Cornforth transition structures for nucleophilic addition to α,*β*-alkoxy aldehyde acetonides.

Additions to α-Alkoxy-*β*-Methyl Aldehydes. The influence of the configuration at the *β*-stereocenter on aldehyde *π*-facial selectivity is proposed to be due in part to the conformational constraint imposed by the *β*-alkoxy substituent on the α-oxygen protecting group, which effectively removes any contribution from transition state **CS**$_1$ (Figure 4). Since this is primarily a steric effect, it follows that a methyl substituent in place of the *β*-alkoxy substituent should result in the same trend in *π*-facial selectivity (Figure 7), with lower 3,4-anti selectivity for the *syn*-aldehyde. To investigate these predictions, *syn*- and *anti*-α-silyloxy-*β*-methyl aldehydes **16** and **17** were constructed and subjected to aldol addition reactions (Table 7). The syn-configured aldehyde exhibits lower diastereoselectivity for the 3,4-anti product diastereomer in every case. This finding lends additional support to the steric interactions identified in the Cornforth transition states for addition to α,*β*-bisalkoxy aldehydes.

The preceding analysis has established that Cornforth transition structures leading to the formation of 3,4-anti product diastereomers provide a plausible explanation for the relative differences in asymmetric induction observed for *syn*- and *anti*-α,*β*-bisalkoxy aldehydes. For the *syn*-aldehydes, the 3,4-syn-diastereomer often constitutes a significant part (and in some cases, major part) of the observed product distribution. This implies the existence of transition structures leading to the 3,4-syn-product that compete effectively with the favored transition structure for the formation of the 3,4-anti product (**CS**$_2$, Figure 4). Figure 8 illustrates several transition structures for the formation of the 3,4/4,5-syn-product in which prohibitive *syn*-pentane interactions are absent. **NCS** and **NFS** are formally related to the Cornforth and polar Felkin-Anh models, respectively, due to the relationship of C=O and α-C−O. **NS**$_1$ and **NS**$_2$, on the other hand, contain a synparallel arrangement of C=O and α-C−O. The developing *syn*-pentane interactions are so similar, and the orientations of the α-stereocenter so different, that it is difficult to determine the most likely transition structure without performing a more sophisticated computational analysis.

Observations in Related Systems. Other groups have reported the addition of enolate nucleophiles[23] to α,*β*-bisalkoxy aldehydes.[24] While syn- and anti-configured aldehydes of the same structure are not directly compared, the following examples highlight the importance of the principles established by this systematic study.

***syn*-α,*β*-Bisalkoxy Aldehydes.** Kobayashi and co-workers have reported that addition of a polymer-supported silylketene thioacetal to a *syn*-α,*β*-silyloxy aldehyde provides exclusively the 3,4-*syn*-product diastereomer (eq 7),[25] a result that is inconsistent with the Cornforth/polar Felkin-Anh models for asymmetric induction. A similar case has been documented by Paterson and co-workers (eq 8).[26] These unexpected syn selectivities can now be understood as a consequence of the aldehyde configuration, in which the *β*-alkoxy substituent forces the large α-silyloxy group to project into the path of the nucleophile at what would otherwise be the preferred *π*-face of the aldehyde (**CS**$_1$, Figure 4). In contrast, *syn*-α,*β*-alkoxy

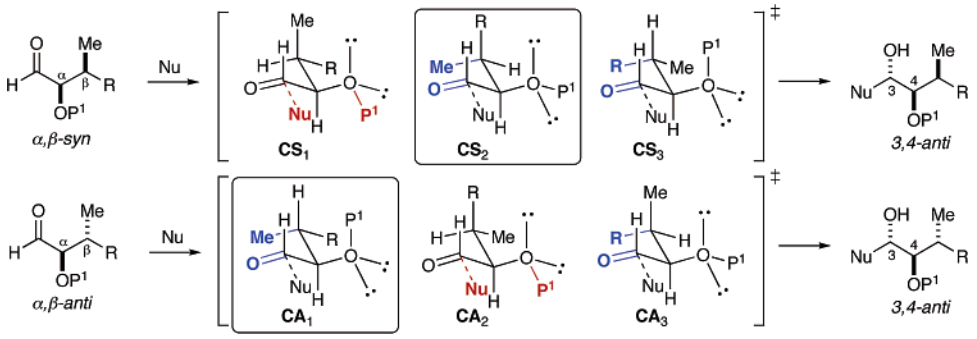


Figure 7. Cornforth transition structures for nucleophilic addition to *syn*- and *anti*-α-alkoxy-*β*-methyl aldehydes.

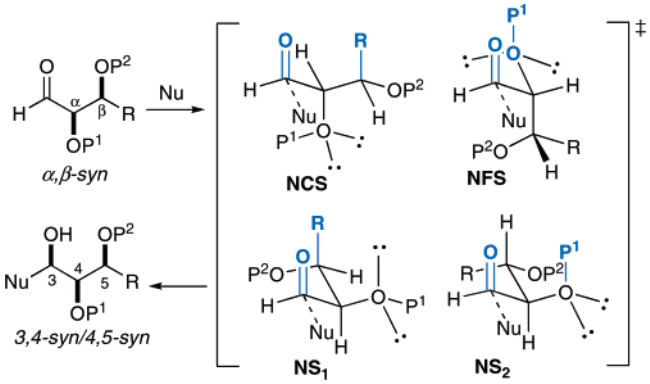
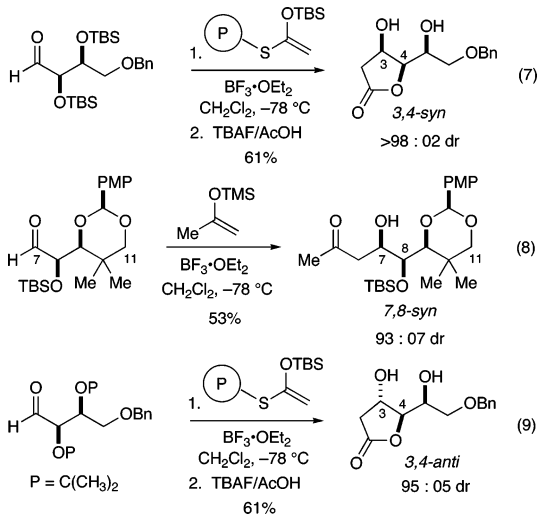
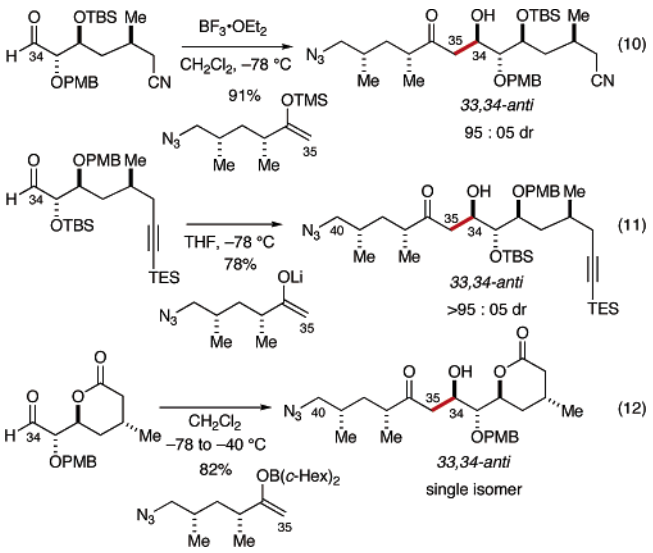


Figure 8. Transition structures for the formation of the 3,4-syn/4,5-syn-product diastereomer.

aldehyde acetonides are observed to provide aldol adducts with high selectivity for the anti product diastereomer,[27] as the example from Kobayashi and co-workers demonstrates (eq 9).[25] As noted previously ($\mathbf{S_C}$, Figure 6), the acetonide protecting group minimizes destabilizing interactions with the nucleophile, resulting in selectivity for the 3,4-anti product diastereomer.



***anti*-α,*β*-Alkoxy Aldehydes.** The azaspiracid class of natural products[28] has inspired a number of aldol-based approaches for the construction of the $C_{34}-C_{35}$ bond. Three research groups have independently found that the addition of a $C_{35}-C_{40}$ methyl ketone enolate to the indicated structurally diverse *anti*-α,*β*-bisalkoxy aldehydes (eqs 10−12) results in extremely high selectivity for the unnatural 33,34-anti diastereomer.[29] These examples are consistent with the favorable features identified in the proposed transition state ($\mathbf{CA_1}$, Figure 4) for nucleophilic addition to *anti*-α,*β*-bisalkoxy aldehydes.



Conclusions

A systematic study of asymmetric induction in aldol addition reactions of α-alkoxy and α,*β*-bisalkoxy aldehydes has been presented. We find that asymmetric induction in lithium enolate additions to α-alkoxy aldehydes is superior to that obtained from the corresponding enolborane and enolsilane nucleophiles. The levels of asymmetric induction in the lithium enolate additions are relatively insensitive to both the identity of the α-oxygen protecting group and the steric hindrance of the enolate nucleophile. These additions are, however, sensitive to the nature

(23) Only enolate nucleophiles reacting under conditions where chelation is unlikely are included in this discussion. While a large number of examples exist for the addition of organometallic reagents to α,*β*-alkoxy aldehydes, the analysis of the observed diastereoselectivity is greatly complicated by the ambiguous nature of the nucleophile and the unknown contribution from chelated transition states.

(24) Aldol addition reactions of α,*β*-alkoxy aldehydes in which the α-oxygen is part of a tetrahydrofuran or tetrahydropyran ring system have been reported. Due to the lack of comparable cases from our study, these examples will not be discussed. For α-THP aldehydes see: (a) Dondoni, A.; Ianelli, S.; Kniezo, L.; Merino, P.; Nardelli, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1231−1239. (b) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 9007−9010. For an α-THF aldehyde, see: (c) Anderson, O. P.; Barrett, A. G. M.; Edmunds, J. J.; Hachiya, S.-I.; Hendrix, J. A.; Horita, K.; Malecha, J. W.; Parkinson, C. J.; VanSickle, A. *Can. J. Chem.* **2001**, *79*, 1562−1592.

(25) Kobayashi, S.; Wakabayashi, T.; Yasuda, M. *J. Org. Chem.* **1998**, *63*, 4868−4869.

(26) Enolborane and lithium enolate additions are also reported: Paterson, I.; Di Francesco, M. E.; Kuhn, T. *Org. Lett.* **2003**, *5*, 599−602.

of the β-alkyl substituent. For α,β-bisalkoxy aldehydes, the relationship between relative configuration and π-facial selectivity has been established. Aldehydes with an *anti*-α,β-bisalkoxy configuration reacted with methyl ketone-derived enolates to give 3,4-anti products with consistently superior diastereoselectivity relative to the *syn*-α,β-bisalkoxy aldehydes. This trend is observed in aldehydes containing a wide range of protecting groups, branched or unbranched β-alkyl substituent, and is even evident in nucleophilic additions to α-alkoxy-β-methyl aldehydes. The only exception is the case of the acetonide-protected α,β-bisalkoxy aldehydes, which exhibit similar levels of diastereoselection regardless of relative configuration. A Cornforth transition-state model is proposed to account for these observations in which the β-alkoxy substituent dictates the position in space occupied by the α-oxygen protecting group, which in turn governs aldehyde π-facial selectivity due to its proximity to the approaching nucleophile. The systematic study presented here provides a comprehensive data set for the synthesis of vicinal alkoxy stereotriads by an aldol-based approach, and should lead to greater sophistication in the synthesis of poly-hydroxylated structures.

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Supporting Information Available: Experimental details, analytical data, and stereochemical proofs for all new compounds (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) (a) Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967−9968. (b) Nicolaou, K. C.; Vyskocil, S.; Koftis, T. V.; Yamada, Y. M. A.; Ling, T.; Chen, D. Y.-K.; Tang, Wenjun; Petrovic, G.; Frederick, M. O.; Li, Y.; Satake, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4312−4318. (c) Nicolaou, K. C.; Koftis, T. V.; Vyskocil, S.; Petrovic, G.; Ling, T.; Yamada, Y. M. A.; Tang, W.; Frederick, M. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 4318−4324.

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