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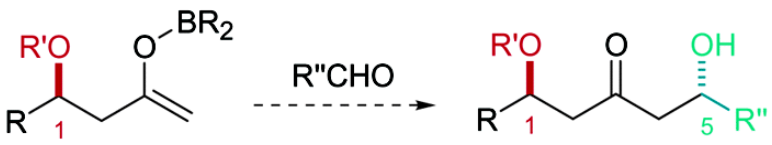

high levels of 1,5-Anti induction

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1,5-Asymmetric Induction in Boron-Mediated β-Alkoxy Methyl Ketone Aldol Addition Reactions

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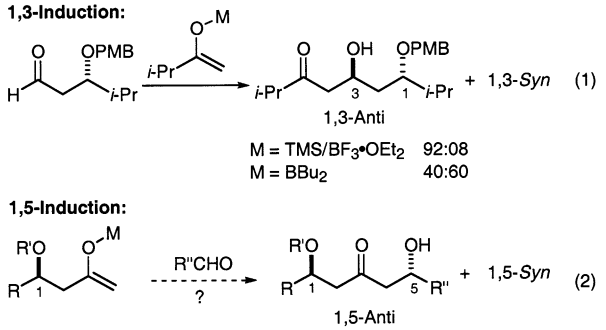
Abstract: This article presents studies that illustrate β-alkoxy methyl ketone-derived boron enolates undergo diastereoselective aldol addition to afford the 1,5-anti diol relationship. The stereochemical outcome of this reaction is documented to be general for a variety of β-alkoxy methyl ketone analogues and aldehyde partners. The double stereodifferentiating reactions of these enolates with chiral β-alkoxy aldehydes have also been investigated in conjunction with the possibility of controlling the absolute stereochemistry of the aldol process. With the proper selection of reaction conditions, the proximal alkoxy substituent on either the aldehyde (1,3-induction) or the enolate fragment (1,5-induction) can be employed to control facial selectivity of the aldol addition. Selection of a boron enolate ensures dominant 1,5-anti induction from the β-alkoxy methyl ketone-derived enolate partner while negating any influence of the β-alkoxy aldehyde substituent. Conversely, if stereochemical control from the β-alkoxy aldehyde is desired, a Lewis acid-catalyzed enolsilane addition ensures dominant 1,3-induction from the aldehyde β-oxygen substituent.

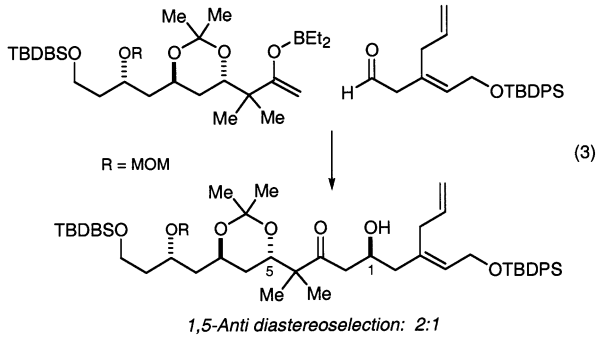
Introduction

The aldol reaction is widely employed in the convergent assembly of polyacetate-derived stereochemical arrays (1,3-polyols).[1] Two control elements that might influence the stereochemical course of these processes are illustrated below (eqs 1 and 2).



In the addition of enol derivatives to β-alkoxyaldehydes, the influence of the β-heteroatom substituent may influence the stereochemical outcome of the aldol process selected (eq 1). It is well-known that good levels of 1,3-anti induction may be realized in the Lewis acid-promoted addition with enolsilanes through either chelate[2] or electrostatic control.[3] In contrast, this same β-substituent imparts no control over the analogous enolborinate additions.

Early evidence that remote induction in enolborane aldol additions might be possible may be found in the bryostatin studies of Masamune (eq 3).[4] While the sense of 1,5-asymmetric induction was low in this complex case, this study remains significant in that remote induction is a possibility.



During the course of our synthesis of altohyrtin, we,[5] and Paterson,[6] evaluated a related set of diastereoselective aldol additions that were quite diastereoselective. In this article, we present our studies that document the scope and limitations of these selective methyl ketone-derived enolborinate aldol reactions (eq 2).

(1) For general approaches to the synthesis of 1,3-diol relationships in conjunction with C−C bond formation, see: (a) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753−1765. (b) Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5299−5314. (c) Knochel, P.; Brieden, W.; Rozema, M. J.; Eisenberg, C. *Tetrahedron Lett.* **1993**, *34*, 5881−5884.

(2) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468 and references therein.

(3) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537−8540. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

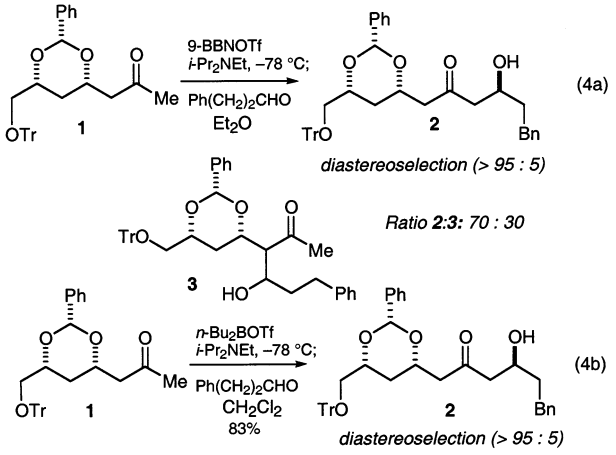
(4) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 2817−2825.

(5) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789.

(6) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

Discussion

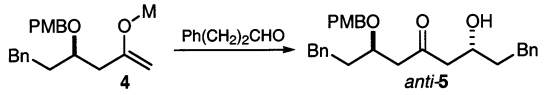
Initial Studies. Remote induction in the methyl ketone aldol addition was first observed by us during the addition of the 9-BBN enolborinate of methyl ketone **1** to dihydrocinnamaldehyde. Two aldol adducts were identified from this reaction (eq 4a). The major product **2** was isolated as a single diastereomer derived from the less-substituted boron enolate. The minor product **3** was also formed as a single stereoisomer. The β-heteroatom substituent on the enolate component is clearly exerting a powerful effect on the stereochemical course of this reaction.[7] Utilization of the more sterically discriminating dibutylboron triflate[8] enforced exclusive generation of the less-substituted enolborinate, which afforded a single aldol adduct with the same high level of diastereoselectivity (eq 4b). The stereochemical relationship of the newly generated stereocenter in the aldol product was determined to be anti with respect to the resident β-heteroatom on the parent methyl ketone **1**.[9]



In view of the relevance of this reaction to the synthesis of polyacetate natural products, we decided to explore the scope of this reaction. This study was initiated with an examination of the aldol reactions of methyl ketone enolates **4** (M = TMS, Li, BR_2) that contain a β-alkoxy substituent (Table 1). To isolate the contribution of electrostatic effects to the diastereoselectivity in these addition processes, enolates **4** were selected bearing β-substituents of similar steric size but different electronic properties ($-OCH_2Ar$ vs $-CH_2CH_2Ar$). In contrast to previous observations on 1,3-induction (eq 1),[3] the dibutyl enolborinates displayed good levels of asymmetric induction in aldol reactions with dihydrocinnamaldehyde, consistently favoring the 1,5-anti diol product anti-**5** (Table 1, entries 1−5). Due to the similar steric requirements of the β-substituents, we speculate that electronic rather than steric effects are responsible for enolate face selectivity.

The observation of a modest solvent effect (Table 1, entries 2−4) that documents a trend toward higher selectivity with a decrease in solvent polarity is consistent with this postulate.[10]

Table 1. 1,5-Induction with Various Metal Enolates



entry	M	*T*, °C	solvent	yield, %[a]	anti/syn[b]
1	Chx_2B[c]	−78	CH_2Cl_2	85	82:18
2	Bu_2B[d]	−78	CH_2Cl_2	80	87:13
3	Bu_2B	−78	PhMe	81	94:06
4	Bu_2B	−78	Et_2O	83	94:06
5	Bu_2B	−115	Et_2O	85	98:02
6	$TMS/BF_3{\cdot}OEt_2$	−78	CH_2Cl_2	85	50:50
7	Li[e]	−78	THF	79	40:60

[a] Yields determined by isolation, HPLC, or NMR analysis with an internal standard. [b] Ratios determined by either HPLC or ^1H NMR analysis of the unpurified product mixture. [c] Enolization conditions: Chx_2BCl, Et_3N, −78 °C, CH_2Cl_2. [d] Enolization conditions: Bu_2BOTf, *i*-Pr_2NEt, −78 °C, solvent (ref 5). [e] LDA enolization.

The enolate facial bias may be further enhanced by a decrease in reaction temperature (Table 1, entry 5). Again, in contrast to our previous study on 1,3-induction (eq 1), the Lewis acid-mediated aldol reaction in this system demonstrated no asymmetric induction (Table 1, entry 6).[3b] Similarly, the aldol reactions of metal enolates capable of internal chelation with the β-heteroatom were also found to be nonselective (Table 1, entry 7).[11]

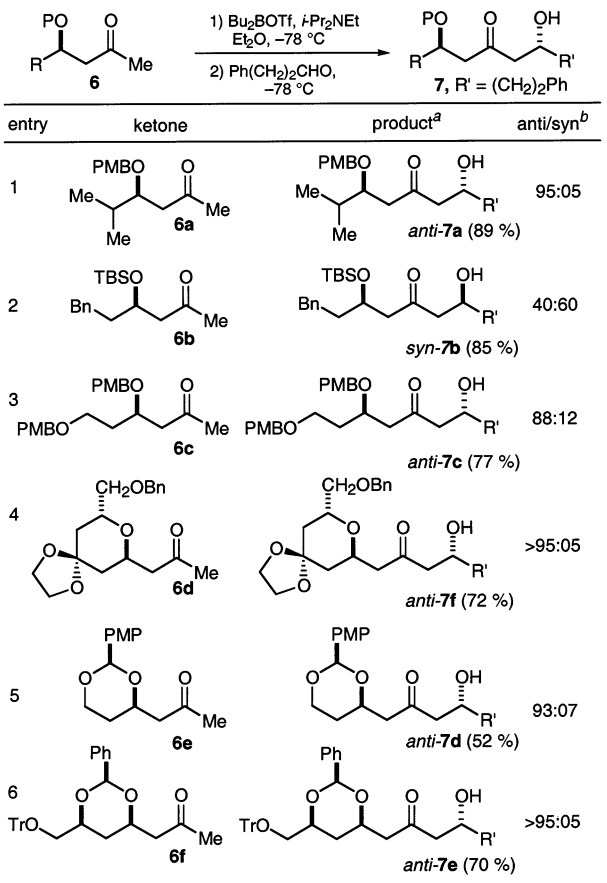
Reaction Scope. The generality of 1,5-enolate induction was probed in the examples illustrated in Table 2. Not surprisingly, the structure of the β-oxygen protecting group plays an important role in reaction diastereoselectivity.[12] Accordingly, silicon protecting groups may be used to neutralize this β-alkoxy control element (Table 2, entry 2). The aldol reactions of methyl ketones **6d**, **6e**, and **6f**, highlight the fact that the β-oxygen substituent may be constrained within a ring without a significant alteration in reaction diastereoselection (Table 2, entries 4−6).

Table 3 demonstrates the variety of aldehydes that participate in this reaction. Hindered alkyl and aromatic aldehydes provide aldol adducts in good yield and stereoselectivity, even when the reaction temperature is not lowered below −78 °C.

Temperature Effects. Diastereoselectivity in this and related aldol reactions is the product of both the degree of enolate diastereoface selectivity and the integrity of the transition state through which the reaction proceeds. A significant temperature effect was noted in this reaction (Table 4). Reaction diastereoselectivity drops significantly when the temperature is increased. Examination of an Eyring plot clearly shows a nonlinear relationship between reaction temperature and selectivity. This suggests the intermediacy of more than one set of competing diastereomeric transition states contributing to the observed product ratios.[13] If the reaction is run in CH_2Cl_2 for the purposes of maintaining a fully homogeneous solution, this nonlinear effect is still observed.[14]

(7) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871−6874
(8) Evans, D. A.; Nelson, J. V.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111. The regiochemistry (CH_3 vs CH_2) of the enolization process with Bu_2BOTf and Chx_2BCl with these methyl ketone substrates is high (>95:5). In certain cases, 9-BBNOTf is nonselective in this enolization process.
(9) A detailed discussion of the procedures that were followed for the assignment of the aldol-related stereochemical relationships is contained in the Supporting Information.
(10) Based on dielectric constants, it is not clear why the more polar diethyl ether ($e = 4.3$) is a better solvent than toluene ($e = 2.4$). However, ether was typically used because it provided the cleanest reaction mixtures.
(11) $TiCl_4$, $Ti(Oi\text{-}Pr)_2Cl_2$, $SnCl_4$, $ZnCl_2$, $TrCl/SnCl_2$, and $TrClO_4$ were also found to give extremely low levels of stereochemical induction.
(12) This observation has also been noted in the addition of enolsilanes to β-alkoxyaldehydes. See ref 3.
(13) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477−515.
(14) The optimal solvent for these reactions is diethyl ether. However, the reaction mixture is heterogeneous from the point of enolization until the quench.

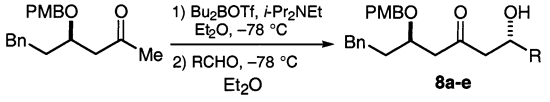
Table 2. 1,5-Induction with Various Methyl Ketones

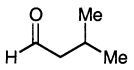
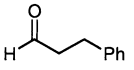
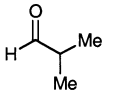
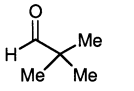
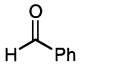


entry	ketone	product[a]	anti/syn[b]
1	**6a**	*anti*-**7a** (89 %)	95:05
2	**6b**	*syn*-**7b** (85 %)	40:60
3	**6c**	*anti*-**7c** (77 %)	88:12
4	**6d**	*anti*-**7f** (72 %)	>95:05
5	**6e**	*anti*-**7d** (52 %)	93:07
6	**6f**	*anti*-**7e** (70 %)	>95:05

[a] Major product (% yield of aldol adducts). [b] Ratios determined by either HPLC or ^{1}H NMR analysis of the unpurified product mixture.

Table 3. Diastereoselective Aldol Additions to Representative Aldehydes

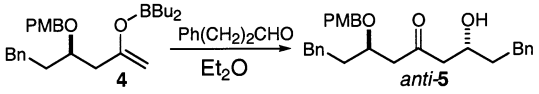


entry	RCHO	yield	anti/syn
1		88%	90:10
2		83%	94:06
3		84%	94:06
4		82%	95:05
5		88%	96:04

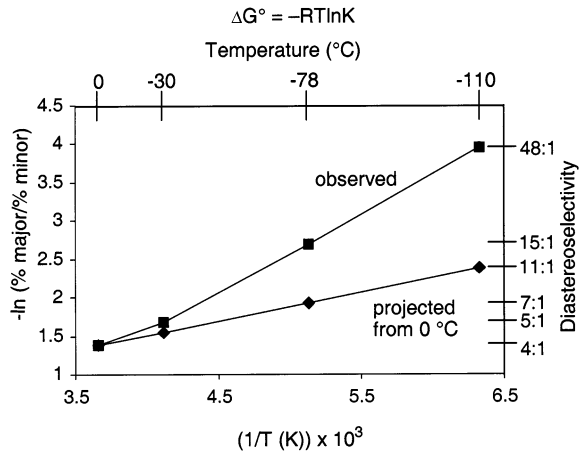
[a] Yields determined by isolation, HPLC, or NMR analysis with an internal standard. [b] Ratios determined by either HPLC or ^{1}H NMR analysis of the unpurified product mixture.

Double Stereodifferentiation. Although high levels of 1,5-induction may be obtained with dibutyl enolborinate in these methyl ketone aldol reactions (Table 3), no induction from the enolate β-stereocenter was observed under Mukaiyama (enolsilane/Lewis acid) conditions (Table 1, entry 6). Since facial selectivity in either reaction component can be regulated by the proper selection of aldol reaction type (enolborinate or enolsilane), the double stereodifferentiating reactions of these enolates with chiral β-alkoxy aldehydes offer the possibility of controlling the absolute stereochemistry of the aldol process from the proximal alkoxy substituent on either the aldehyde (1,3-induction) or the enolate fragment (1,5-induction). For example, the preceding data suggest that selection of a enolborinate will ensure 1,5-anti induction from the enolate partner while negating the influence of the β-oxygen aldehyde substituent. Conversely, if stereochemical control from the chiral aldehyde is desired, selection of a Lewis acid-catalyzed enolsilane addition will ensure dominant 1,3-induction from the aldehyde β-oxygen substituent (eq 1).[3] These double stereodifferentiating aldol processes (Table 5) of enantiomerically pure enolborinate **9** with the illustrated enantiopure aldehydes document the degree of stereochemical control attainable in these double stereodifferentiating processes. In summary, it is rather remarkable that 1,5-induction from the enolate component is more pronounced (eq 5−7) than than 1,3-induction from the aldehyde component (eq 8).

Table 4. Temperature Profile



Temp.	Observed *anti:syn* Ratio	$\Delta\Delta G^{\ddagger}$ (kcal/mol)	Expected *anti:syn* Ratio
0 °C	4 : 1	0.752	(4 : 1)
−30 °C	5.2 : 1	0.796	4.7 : 1
−78 °C	15 : 1	1.05	6.9 : 1
−115 °C	48 : 1	1.25	11 : 1



Synthetic Utility. We first applied this boron-mediated aldol reaction to a total synthesis of the marine natural product Altohyrtin C (Spongistatin 2), where we carried out the aldol bond construction illustrated in eq 6 (Table 5).[15] The ability of this methodology to mediate related complex fragment couplings is illustrated in Table 6. In studies directed toward a total

(15) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726.

Table 5. Double Diastereoselective Aldol Reactions

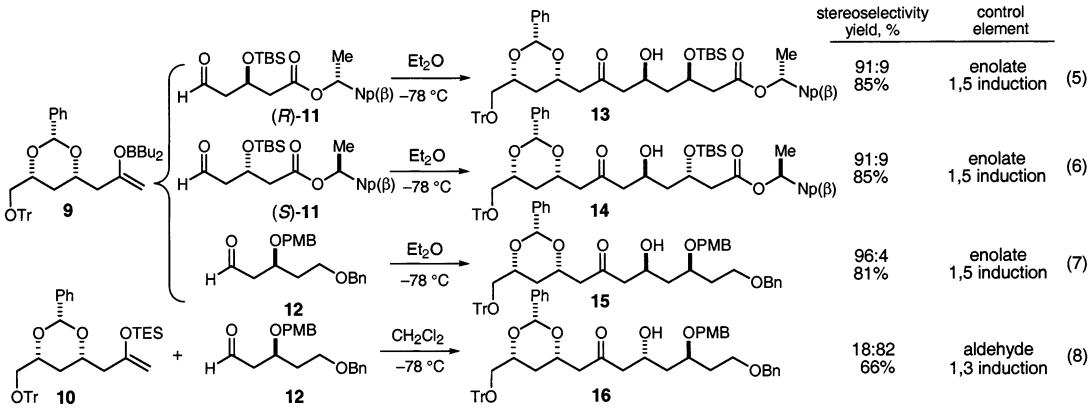
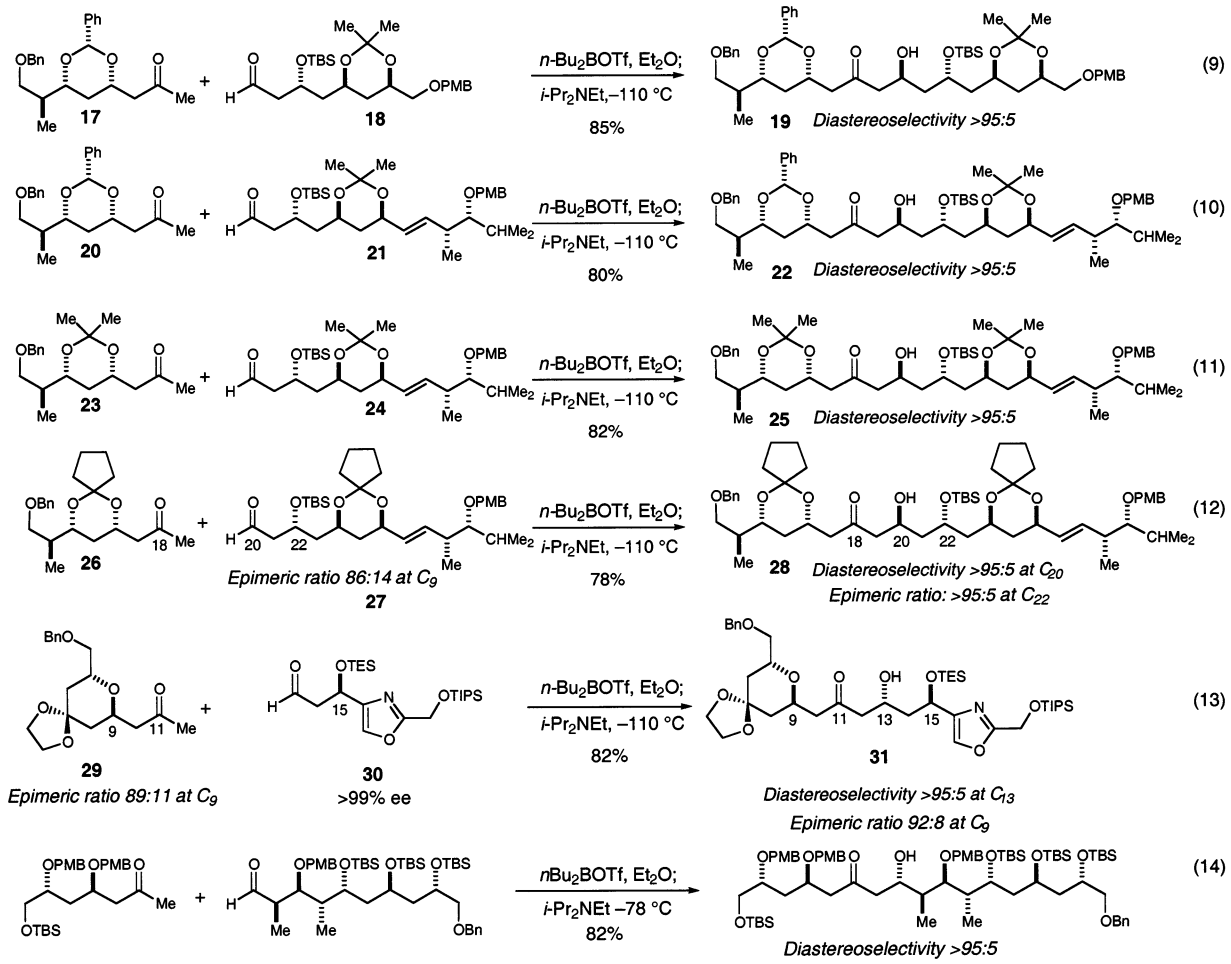


Table 6. Complex Aldol Fragment Aldol Couplings

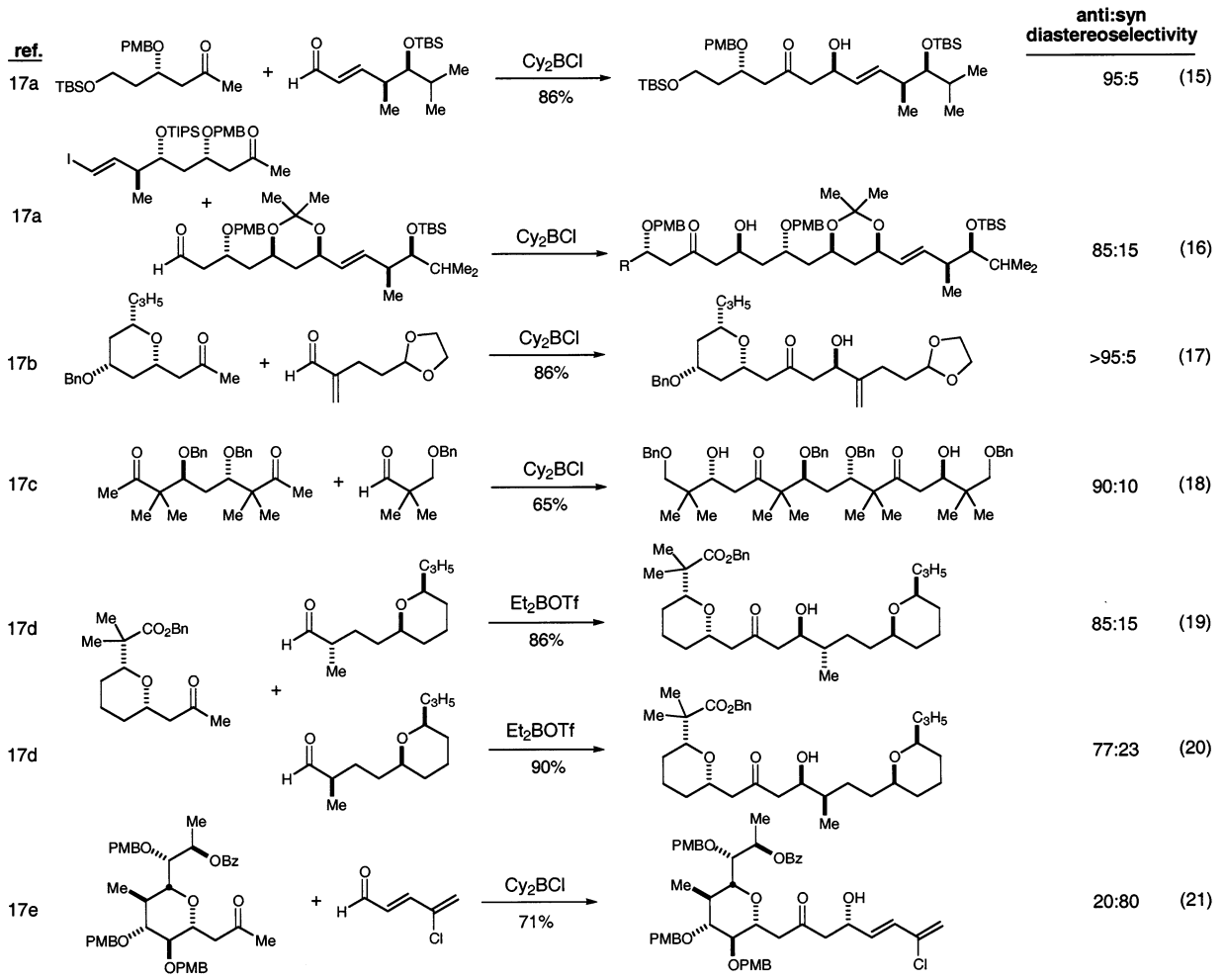


synthesis of the antifungal macrolide roxaticin,[16] the ketones illustrated in eqs 9−12 were successfully coupled to the indicated aldehyde in good yield and high (>95:5) diastereoselectivity. In each of these cases, the aldehyde was employed as a 5−9:1 mixture of diastereomers at the β-position. It is interesting to note that a kinetic resolution took place over the course of these reactions, affording the desired product in preference to the adduct derived from reaction of the undesired aldehyde epimer. The observed product contained both the 1,5-anti and the 1,3-anti stereochemistry in the polyol array. An excess of the aldehydic isomers was employed in the reaction and was typically recovered from the reaction as a 1:1 epimeric ratio at the β-position.

A kinetic resolution was also observed in the reaction depicted in eq 13. An excess of ketone **29**, as an 89:11 diastereomeric mixture at C_9, was transformed into the derived boron enolate and treated with aldehyde **30** (>99% ee) to deliver **31** as a 92:8 mixture favoring the desired C_9 isomer. No evidence of a C_{13}

(16) Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, preceding article.

Table 7. Other Examples of Complex 1,5-Induction



All reactions were carried out at −78 °C in diethyl ether with the indicated borane reagent and triethylamine as base.

diastereomer was observed. Recovered ketone **29** was shown to be an 80:20 mixture of diastereomers at the β-stereocenter. The product β-hydroxy ketone **31** has been elaborated to the antitumor macrolide phorboxazole B.[17] Finally, eq 14 illustrates a complex aldol cross-coupling reaction recently carried out in our laboratory.[18] In this reaction, the aldehyde α-methyl and β-OR substituents individually contribute to the aldehyde face selectivity with the syn diastereomeric relationship for the substituents being nonreinforcing.[3b,19] In this double stereodifferentiating reaction, dominant stereochemical control from the enolate substituent affords the anti-Felkin aldol adduct. Subordinate reinforcing stereocontrol is being provided by the β-alkoxy substituent to override the facial bias of the methyl substituent.

Table 7 illustrates the reactions and selectivities obtained utilizing this aldol reaction that have been reported from other laboratories.[20] The yields are all good, and in most cases, the selectivities are good to excellent. However, when steric bulk is added to the vicinity of the β-heteroatom, selectivities often diminish. In fact, in extreme cases (eq 21), the selectivity is inverted to favor the 1,5-syn aldol product. This point has been previously highlighted in Table 2 (entry 2).

A number of new applications of this boron aldol reaction have recently appeared. For example, this reaction has been recently incorporated into recent syntheses of leucascandrolide A.[21] In addition, the continued application of this fragment coupling process directed toward the synthesis of peloruside has just appeared.[22] Finally, Leighton has employed a complimentary double stereodifferentiating Mukaiyama aldol variant (Table 5, eq 8) in his synthesis of mycoticin A.[23]

Conclusion

In summary, diastereoselective aldol addition reactions of chiral β-alkoxy methyl ketones have been documented. Eno-

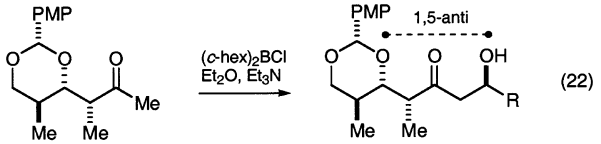
(17) Evans, D. A.; Fitch D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046.
(18) This reaction has been carried out by Dr. Kenneth J. McRae (Harvard University).
(19) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129−6132.
(20) (a) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187−1191. (b) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755−758. (c) Trieselmann, T.; Hoffman, R. W. *Org. Lett.* **2000**, *2*, 1209−1212. (d) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481−484. (e) Paterson, I.; Chen, D. Y. K.; Coster, M. J.; Acena, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4055−4060.
(21) (a) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755−758. Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670−13671. (b) Fettes, A.; Carreira, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 4098−4101. (c) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343−347.
(22) Paterson, I.; Di Fransesco, M. E.; Kuhn, T. *Org. Lett.* **2003**, *5*, 599−602.
(23) Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341−342.

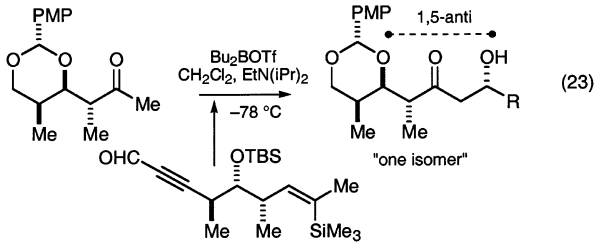
lization with either *n*-Bu_2BOTf or *c*-Hex_2BCl[6] allows exclusive formation of the less-substituted enolborinate that participates in highly distereoselective 1,5-anti aldol addition reactions to a variety of aldehydes under mild conditions. This diastereocontrol element can be eliminated, if so desired, by choice of a metal counterion other than boron. This strategy allows other stereocontrol elements to dominate, such as the 1,3-anti induction derived from addition of an enolsilane to a β-alkoxy aldehyde.

In the analysis of more complex methyl ketone aldol reactions such as those illustrated below (eqs 22 and 23),[24,25] it is tempting to speculate that the β-alkoxy substituent could also be playing a dominant role in directing the stereochemical course of the indicated transformations. Indeed, Dias has drawn this conclusion on the basis of the cited examples.[24,26] A systematic study that firmly documents this point would be a valuable contribution.

Acknowledgment. Support has been provided by the NIH and NSF. The authors also thank the Merck Research Laboratories for student support.

Supporting Information Available: Full experimental details, characterization data, and product stereochemical assignments.





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(24) Dias, L. C.; Bau, R. Z.; de Sousa, M. A.; Zukerman-Schpector, J. *Org. Lett.* **2002**, *4*, 4325−4327.

(25) Arefolov, A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2397−2400.

(26) In the aldol reaction reported by Panek (eq 23), the indicated configurations of the acetal centers in both reactant and product are currently in question. This reaction has been reinvestigated by Professor L. C. Dias (Universidade Estadual de Campinas, Instituto De Quimica-UNICAMP, Caixa Postal 6154 Campinas SPBRAZIL) who has kindly informed me of his results and of the indicated configuration reassignment.