1,5-Asymmetric Induction in Methyl Ketone Aldol Addition Reactions

David A. Evans,* Paul J. Coleman, and Bernard Côté

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

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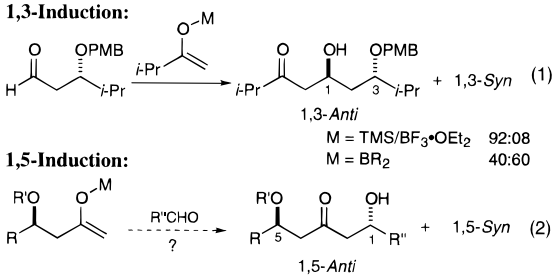
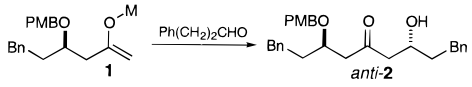
The aldol reaction holds potential as a powerful method for the convergent assembly of polyacetate-derived stereochemical arrays (1,3-polyols).[1] Two possible control elements that might influence the stereochemical course of these processes are illustrated below (eqs 1 and 2).



In the addition of enol derivatives to β-alkoxy aldehydes, the influence of the β-heteroatom substituent may be regulated by the nature of the aldol process selected (eq 1). For example, good levels of 1,3-*anti* induction may be realized in the Lewis acid-promoted addition with enol silanes. In contrast, this same substituent possesses no control over the analogous enol borinate nucleophilic additions.[2] We have speculated that the principal bias exerted by the β-alkoxy substituent is electrostatic in nature. Given the importance of these remote effects on the π-facial selectivity of aldehyde electrophiles, we have now probed the analogous polar effect of a β-heteroatom substituent on the enolate facial bias in these acetate aldol processes (eq 2).[3,4] In this paper, methyl ketone enolates that undergo highly 1,5-diastereoselective aldol addition are identified, and the integration of this control element into double-stereodifferentiating aldol reactions is presented.

This study was initiated with an examination of the aldol reactions of unsubstituted ketone enolates **1** (M = TMS, Li, BR_2) that contain a β-alkoxy substituent (Table 1). To isolate the contribution of electrostatic effects to the diastereoselectivity of these addition processes, enolates **1** were selected bearing β-substituents of similar steric size ($-OCH_2Ar$ vs $-CH_2CH_2Ar$) but different electronic properties. Unlike our previous study on 1,3-induction (eq 1),[2] the dialkylboron enolates[5] displayed

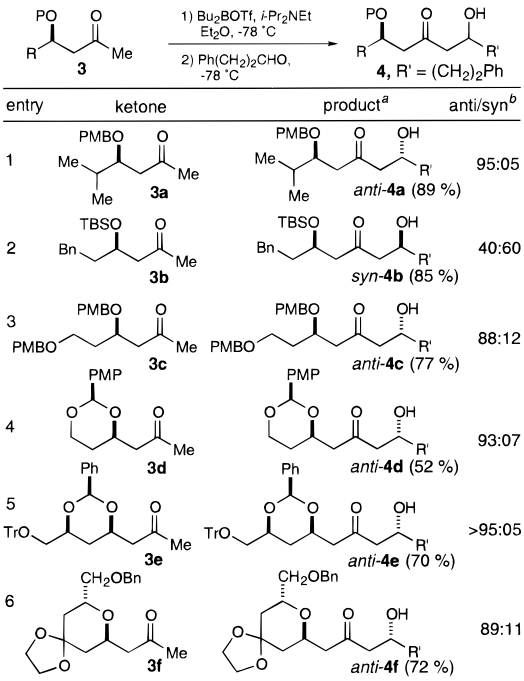
Table 1. 1,5-Induction with Various Metal Enolates



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 either isolation, HPLC, or NMR analysis with an internal standard. Abbreviations: PMB = *p*-(MeO)$C_6H_4CH_2$. [b] Ratios determined either by HPLC or ^{1}H 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.

Table 2. Stereoselective Aldol Reactions with Representative Ketones



[a] Major product (%, yield of aldol adducts). Abbreviations: PMB = *p*-(MeO)$C_6H_4CH_2$; PMP = *p*-(MeO)C_6H_5; TBS = *t*-$BuMe_2Si$; Tr = Ph_3C. [b] Ratios determined by HPLC or ^{1}H NMR analysis of the unpurified product mixture.

good levels of asymmetric induction with dihydrocinnamaldehyde, consistently favoring the 1,5-*anti* diol product **2** (Table 1, entries 1−5). Due to the similar steric requirements of the β-substituents, electrostatic effects might be at least partially responsible for enolate face selectivity. The enolate facial bias may be further enhanced by a decrease in reaction temperatures (Table 1, entry 5). In contrast to our previous study on 1,3-induction (eq 1),[2] the Lewis acid-mediated aldol reaction in this system demonstrated no asymmetric induction (Table 1, entry 6).[6] Similarly, the aldol reactions of metal enolates capable of internal chelation with the β-heteroatom were also nonselective (Table 1, entry 7).[7]

(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) Mora, 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) (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.

(3) (a) 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. (b) Seebach, D.; Misslitz, U.; Uhlmann, P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 472−473.

(4) For 1,4-induction in acetate aldol reactions see: (a) Zibuck, R.; Liverton, N. J.; Smith, A. B. *J. Am. Chem. Soc.* **1986**, *108*, 2451−2453. (b) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24−37. (c) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedreon Lett.* **1989**, *30*, 7121−7124. (d) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982−3983. (e) Roush, W. R.; Bannister, T. D. *Tetrahedron Lett.* **1992**, *33*, 3587−3590. (f) Lagu, B. R.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 4485−4488.

(5) Evans, D. A.; Nelson, J. V.; Vogel, E.; 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.

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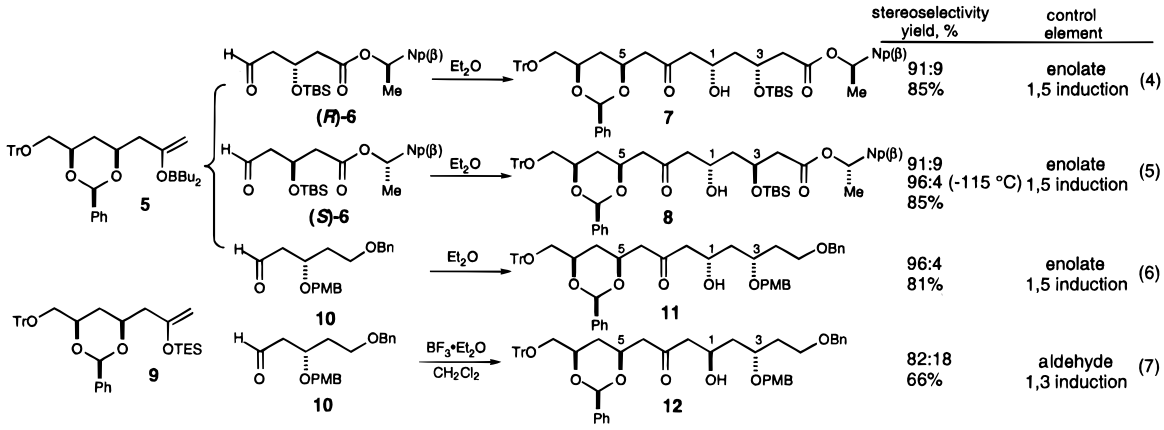
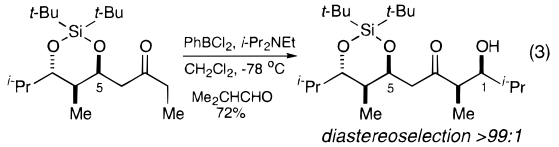
Table 3. Double Stereodifferentiating Aldol Fragment Coupling Reactions[a]



[a] Reactions carried out at −78 °C, except where noted, in the indicated solvent. Abbreviations: PMB = *p*-(MeO)$C_6H_4CH_2$; TES = Et_3Si; TBS = *t*-$BuMe_2Si$; Np(*β*) *β* = naphthyl; Tr = Ph_3C.

The generality of 1,5-enolate induction was probed in the examples illustrated in Table 2. Dihydrocinnamaldehyde was selected as the common aldehyde for purposes of comparison; however, it appears that these results may be generalized to other aldehydes.[8] Not surprisingly, the structure of the *β*-oxygen protecting group plays an important role in reaction diastereoselectivity (Table 2, entry 2).[9] Accordingly, silicon protecting groups may be employed to neutralize this control element. Finally, the aldol reactions of methyl ketones **3d**−**f** illustrate that the *β*-oxygen substituent may be constrained within an oxygen heterocycle without a significant alteration in reaction diastereoselection (Table 2, entries 4−6).[10,15]

Aldol reaction diastereoselectivity in this and related reactions (cf. eq 3) is the product of both the degree of enolate diastereoface selectivity and the integrity of the transition state through which the reaction proceeds. For the present reactions, the sense of asymmetric induction (1,5-*anti*) may be reconciled with our previous observations on the related addition reactions of substituted enolates that exhibit exceptionally high levels of 1,5-*syn* diastereoselection (eq 3)[11] if the two reactions proceed through different transition structures: (twist-boat→1,5-*anti vs* chair→1,5-*syn*). The implication of a twist-boat-



preferred transition structure in the reactions of the methyl ketone-derived enolates was first suggested by Houk, who has reported *ab initio* calculations at the 3-21G level that indicate the twist-boat is favored over the chair transition structure by 1.4 kcal/mol for the reaction of $H_2BOCH{=}CH_2 + CH_2{=}O$.[12] We have extended these calculations to the more relevant reaction of $Me_2BOC(Me){=}CH_2$ + MeCH=O and find that the twist-boat, while still favored, differs from the chair geometry by only 0.4 kcal/mol.

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) since face selectivity in either reaction component can be regulated by the proper selection of aldol reaction type. For example, the preceding data suggest that selection of a boron enolate 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 enol silane addition will ensure dominant 1,3-induction from the aldehyde *β*-oxygen substituent (eq 1).[2a] The double-stereodifferentiating aldol processes illustrated in Table 3 confirm this premise. The aldol reactions of enantiomerically pure methyl ketone **5** with the illustrated enantiopure aldehydes[13] illustrate the degree of stereochemical control attainable in these double stereodifferentiating processes. The application of this methodology in the synthesis of polyol natural products will be reported shortly.[14]

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Supporting Information Available: Experimental procedures for all reactions, product stereochemical proofs, and characterization of all new compounds (16 pages).

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(6) $TiCl_4$, $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, $SnCl_4$, $ZnCl_2$, $TrCl/SnCl_2$, and $TrClO_4$ were also found to give extremely low levels of stereochemical induction.

(7) Mg(II), Ti(IV), and Sn(II) enolates were also nonselective.

(8) Selectivity and isolated yields for the 1,5-*anti* product with boron enolate **1** was high regardless of the structure of the aldehyde: isovaleraldehyde (90:10, 88%), isobutyraldehyde (94:6, 84%), pivaldehyde (95:5, 88%), and benzaldehyde (94:6, 88%).

(9) This trend has also been noted in the addition of enolsilanes to *β*-alkoxy aldehydes. See ref 2a.

(10) The authors wish to thank Mr. Duke Fitch for carrying out the reaction illustrated in entry 3, Table 2.

(11) (a) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871−6874. (b) Evans, D. A.; Fitch, D. *J. Org. Chem.* **1997**, *62*, in press.

(12) Li, Y.; Padden-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481−493.

(13) Since submission of this manuscript, a related study has been reported: Paterson, I; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

(14) The author has deposited atomic coordinates for ketone **4f** with the Cambridge Crystallographic Date Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(15) (*R*)-**6** amd (*S*)-**6** were prepared in analogy to the Heathcock procedure: (a) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374−2378. (b) We have found that commerically available 2(*R*)- and 2(*S*)-naphthylethanol work well in this esterification process: Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513.