Double Stereodifferentiating Aldol Reactions. The Documentation of "Partially Matched" Aldol Bond Constructions in the Assemblage of Polypropionate Systems

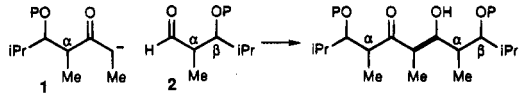
David A. Evans,* Michael J. Dart, Joseph L. Duffy, and Dale L. Rieger

Department of Chemistry, Harvard University Cambridge, Massachusetts 02138

Received April 5, 1995

Significant advances have been made in the union of chiral fragments by the aldol reaction;[1] however, the stereochemical determinants involved in such processes are still not well understood.[2] In the present investigation, ethyl ketone **1** and aldehyde **2** have been selected as model substrates to simulate the complex fragments that one might couple in a polypropionate-derived aldol reaction (Scheme 1). From the aldol union of these substrates we have not only documented the influence of the two stereogenic centers adjacent (α) to the bond construction but also identified the β stereocenter on the aldehyde coupling partner as a third stereochemical determinant for these bond constructions. Recent investigations from this laboratory[3] reinforce the premise that this control element must be integrated into the analysis of double stereodifferentiating reactions.[4]

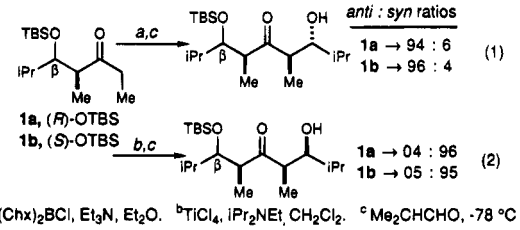
Scheme 1. Double Stereodifferentiating Options: Three Centers



Double Stereodifferentiating Cases	Enolate α	Aldehyde α	Aldehyde β
A Fully matched reaction	(+)	(+)	(+)
B Partially matched reaction	(+)	(+)	(−)
C Partially matched reaction	(+)	(−)	(+)
D Fully mismatched reaction	(+)	(−)	(−)

In this more complex scenario, the chiral enolate may independently adopt either a matched or mismatched relationship with aldehyde substituents both α and β to the bond construction (Scheme 1, cases A−D). In addition to those cases where all three stereocenters are either fully matched (case A) or fully mismatched (case D), there are two instances where the enolate facial bias is matched with either the α or β aldehyde stereocenters, but not both (cases B, C). These intermediate cases we identify as partially matched reactions.[5] The following study provides evidence that this more complex analysis has merit for both *anti* and *syn* double stereodifferentiating aldol reactions.

Reactant Face Selectivities. Previous investigations have documented that boron and titanium enolates derived from ketones **1a** and **1b** undergo diastereoselective *anti*[6] and *syn*[7] aldol reactions, respectively (eqs 1, 2). Enolate face selectivity appears to be dominated by the α-methyl-bearing stereocenter in both sets of aldol reactions.



[a](Chx)$_2$BCl, Et$_3$N, Et$_2$O. [b]TiCl$_4$, iPr$_2$NEt, CH$_2$Cl$_2$. [c]Me$_2$CHCHO, -78 °C

Aldehyde face selectivity in ethyl ketone aldol reactions strongly correlates with enolate geometry.[8] Felkin induction is observed in the addition of (*E*) enolates to α-methyl-substituted aldehydes (eqs 3, 4), whereas (*Z*) enolates typically exhibit a modest anti-Felkin bias (eqs 5, 6) (Scheme 2).[9] We have also found that β stereoinduction can play a significant role in dictating the facial bias of aldehydes such as **3** and **4**. *The intrinsic facial bias imposed by the resident β-alkoxy substituent on the carbonyl addition process results in the preferential formation of the 1,3-anti diol product diastereomer.*[3] It is therefore significant that, within each subset of *anti* and *syn* aldol reactions shown in Scheme 2, higher selectivity is obtained when α and β stereoinductions are mutually reinforcing, and the 1,3-*anti* diastereomer is formed (eqs 3, 5).[10]

Double Stereodifferentiating Reactions. The results from the systematic investigation of double stereodifferentiating *anti* aldol reactions are provided in Scheme 3.[11] When enolate and aldehyde α stereocenters are matched (cases A, B), excellent diastereoselection (>99:1) is observed irrespective of the configuration of the aldehyde β stereocenter. Likewise, the fully mismatched reaction (case D) is found to be nonselective. The partially matched reaction with aldehyde *ent*-**4** (case C) is the most interesting of the stereochemical permutations. In this instance, the enolate facial bias establishes a matched relationship with the aldehyde β heteroatom and a mismatched relationship with respect to the normally dominant aldehyde α stereocenter. Felkin control is overridden in this reaction to provide anti-Felkin aldol adduct **11** with 81:19 diastereoselectivity. Without invoking the role of the β heteroatom as a stereochemical determinant, it is difficult to explain the stereochemical outcome of this reaction. Case C thus demonstrates that useful levels of diastereoselectivity may be obtained in reactions formerly considered to be mismatched.

An illustrative set of double stereodifferentiating *syn* aldol reactions is illustrated in Scheme 4.[12] When the chiral (*Z*) enolate establishes a matched relationship with the aldehyde α

(1) For a review of double asymmetric synthesis: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−76.

(2) For recent examples illustrating this point, see: (a) Evans, D. A.; Polniaszek, R. P.; DeVries, K. E.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613−7630. (b) Martin, S. F.; Lee, W.-C.; Pacofsky, G. J.; Gist, R. P.; Mulhern, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 4674−4688. (c) Nakata, M.; Ishiyama, T.; Akamatsu, S.; Suzuki, R.; Tatsuta, K. *Synlett* **1994**, 601−604.

(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.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619−6620.

(4) The β-alkoxy substituent on the enolate partner represents a possible fourth stereochemical determinant; however, with these enolates, the influence of this substituent appears to be negligible (eqs 1, 2).

(5) For an earlier study of aldol reactions involving three stereochemical determinants, see: Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357−7360. The authors suggest the label "matched-mismatched" for similar partially matched cases.

(6) All (*E*) boron enolates utilized in this investigation were synthesized by the methodology reported by Brown: (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singraram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441−3442. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127−2142. (c) For a paper concerning the origins of π-facial selectivity of chiral (*E*) boron enolates, see: Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685−696.

(7) The chlorotitanium enolates were generated by the standard procedure reported by us: Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049. These substrates exhibit the stereochemical attributes of (*Z*) enolates; however, the enolization of **1a** afforded a complex mixture of four vinyl proton resonances by ^{1}H NMR spectroscopy (−78 °C, CD_2Cl_2).

(8) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157 and references cited therein.

(9) The stereochemical assignments and analytical and spectroscopic data for the aldol adducts illustrated in Schemes 2−4 are provided in the supporting information.

(10) We have found that 1,3-stereoinduction is attenuated by a TBS (*tert*-butyldimethylsilyl) protecting group relative to a PMB (*p*-methoxybenzyl) ether. See ref 3.

(11) For a recent example of a double stereodifferentiating ethyl ketone *anti* aldol reactions, see: Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608−1610.

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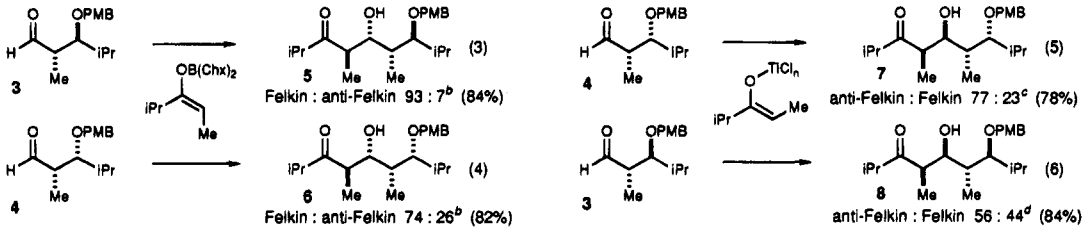
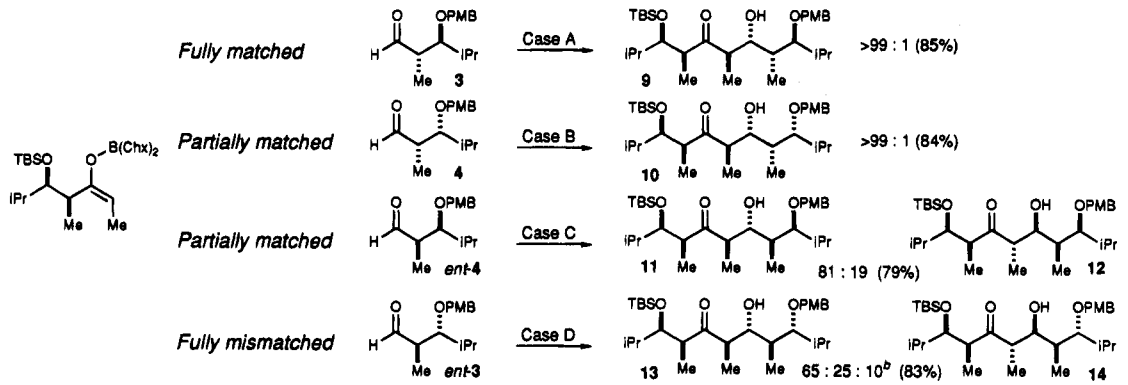
Scheme 2.[a] Diastereoselective Aldol Reactions between Chiral Aldehydes and Achiral Enolates



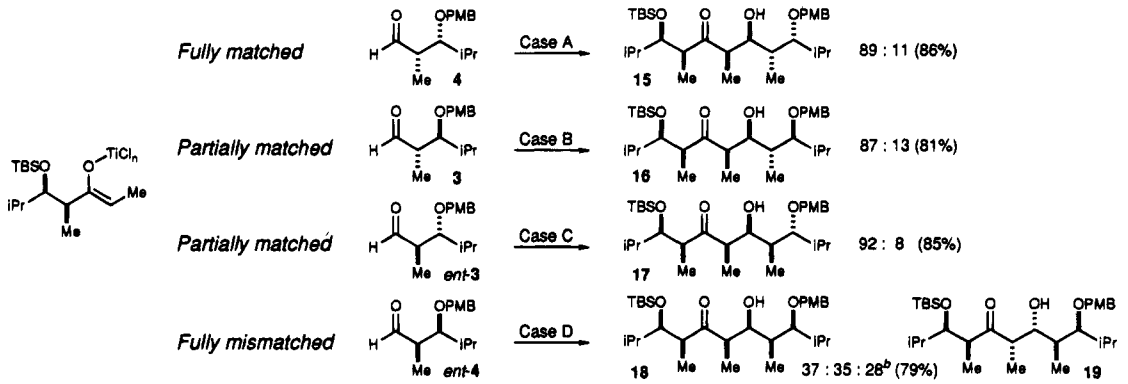
[a] Ratios were determined by GLC analysis after silylation of the unpurified reaction mixtures. Yields refer to combined yield of all diastereomers. Complete characterization and structural proofs of the illustrated diastereomers are available in the supporting information. [b]Only *anti* aldol diastereomers were detected. [c]8% of a mixture of *anti* aldol diastereomers was detected. [d]10% of *anti* aldol adduct **5** was detected.

Scheme 3.[a] Double Stereodifferentiating *Anti* Aldol Reactions between Chiral Reaction Partners



[a] See footnote a in Scheme 2. [b]The minor diastereomer was not isolated in sufficient quantities for complete characterization.

Scheme 4.[a] Double Stereodifferentiating *Syn* Aldol Reactions between Chiral Reaction Partners



[a] See footnote a in Scheme 2. [b]The third unpictured diastereomer is anti aldol diastereomer **11**.

stereocenter (cases A, B), diastereoselective *syn* aldol reactions result. Once more, the partially matched case C is the most interesting stereochemical variant. In this reaction, the matched relationship between the enolate substituent and the aldehyde β heteroatom affords a Felkin-selective reaction, in spite of the inherent anti-Felkin preference associated with *syn* aldol reactions (Scheme 2, eqs 5, 6).[13] Again, the stereochemical outcome of this reaction is difficult to explain without invoking the influence of the β heteroatom stereochemical determinant. Finally, the fully mismatched reaction (case D) is nonselective and affords a mixture of aldol adducts.[14]

Although the influence of the more remote enolate substituent has been held constant in this study, it is reasonable that other families of enolates will respond more strongly to remote structural changes. In these instances, the introduction of a fourth stereochemical determinant will add further complexity to the stereochemical analysis of the bond construction.

Acknowledgment. Support has been provided by the National Institutes of Health and the National Science Foundation. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities.

Supporting Information Available: General experimental procedures for all reactions, product stereochemical proofs, and characterization of all new compounds (37 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) For some recent examples of double stereodifferentiating ethyl ketone *syn* aldol reactions, see: (a) Evans, D. A.; Sheppard, G. S. *J. Org. Chem.* **1991**, *55*, 5192–5194. (b) Andersen, M. W.; Hildebrandt, B.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 97–99. (c) Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801–804. (d) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233–4236. (e) Martin, S. F.; Lee, W.-C. *Tetrahedron Lett.* **1993**, *34*, 2711–2714. (f) Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Patron, A. P; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1151–1152.

(13) (a) For a preliminary discussion of these results, see: Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446–11459. (b) Evans, D. A.; Ng, H. P. *Tetrahedron Lett.* **1993**, *34*, 2229–2232. (c) A very similar bond construction has also been carried out by White and co-workers: White, J. D.; Porter, W. J.; Tiller, T. *Synlett* **1993**, 535–538.

(14) Improved stereoinduction is observed in the fully mismatched variant (Scheme 4, case D) utilizing the (*Z*) dialkylboron enolate of ketone **1a**. This reaction affords a 77:14:9 ratio of aldol adducts **18**:**11**:**19**, respectively.