Pergamon

Tetrahedron Letters, Vol. 37, No. 12, pp. 1957-1960, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00178-5

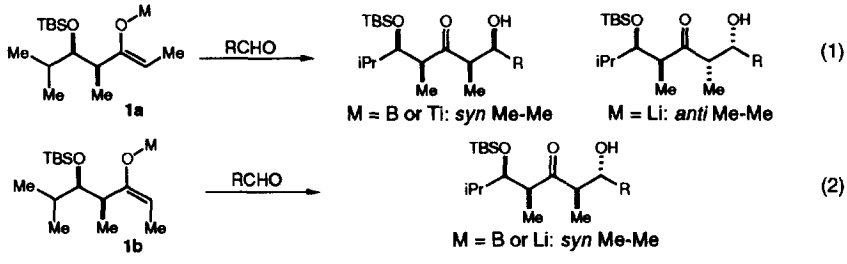
Double Stereodifferentiating Aldol Reactions of (*E*) and (*Z*) Lithium Enolates. Model Reactions for Polypropionate Assemblage

David A. Evans,* Michael G. Yang, Michael J. Dart, and Joseph L. Duffy

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

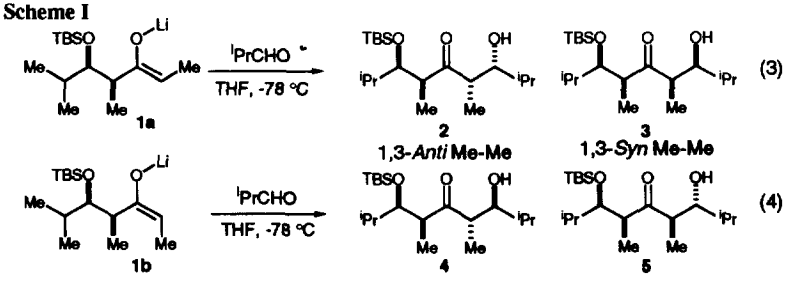
Abstract: A systematic investigation of the double stereodifferentiating aldol reactions of (*E*) and (*Z*) lithium enolates is described. Those reactant pairs that afford aldol adducts inaccessible through other enolate-based aldol reactions are highlighted.

The two important stereochemical attributes of aldol reactions involving chiral substituted enolates are *syn/anti* diastereoselectivity and enolate face selectivity. From the standpoint of design flexibility, it is desirable to be able to independently control both stereochemical aspects of a given bond construction. *Syn/anti* stereoselectivity may be regulated through control of enolate geometry, with high fidelity observed in reactions of dialkylboron enolates and diminished but useful levels of stereochemical correlation for reactions of lithium enolates.[1] With regard to enolate diastereofacial selectivity, complementary *syn* aldol products have been obtained from enolate **1a**. The titanium and boron mediated processes have been documented to afford the *syn* Me-Me relationship, while the (*Z*) lithium enolate has been precedented by McCarthy to preferentially afford the complementary *anti* Me-Me relationship (eq 1).[2] We have also found that both the (*E*) lithium enolate and the (*E*) boron enolate **1b** afford predominantly the *syn* Me-Me relationship (eq 2).[3] In this Letter we report the results of a systematic investigation of the double stereodifferentiating aldol reactions of (*Z*) and (*E*) lithium enolates **1a** and **1b** with chiral aldehydes that model the types of substrates that are encountered in polypropionate fragment coupling. The objective of this and related studies has been to document the advantages and liabilities of specific metal enolates in this family of reactions.[2]



Enolate Component. The face selectivity of the illustrated enolates was documented by addition to isobutyraldehyde (Scheme I).[4] In accord with McCarthy's observation, the (Z) lithium enolate **1a** ($LiN(SiMe_2Ph)_2$, -78 °C, THF)[5] affords a moderately *syn* selective aldol reaction, with primarily *anti* Me-Me product formed among the *syn* aldol diastereomers (eq 3). In the complementary *anti*-selective aldol process, the (*E*) lithium enolate **1b** (LiTMP•LiBr, -78 °C, THF)[6] affords similar levels of stereoselectivity favoring the *anti* aldol diastereomer possessing a *syn* Me-Me relationship (eq 4). Although product equilibration has been demonstrated in the lithium-mediated reactions, control studies on the present system indicate the kinetic product was obtained under the reaction conditions (-78 °C, 30 sec).[7] It must be noted that, while the aldol diastereoselectivity was modest (*syn/anti* = 5-6) in these control studies, a highly diastereoselective coupling might still be obtained in the double stereodifferentiating reactions under the additional influence of stereocontrol elements from the chiral aldehyde component (*vide infra*).

Scheme I

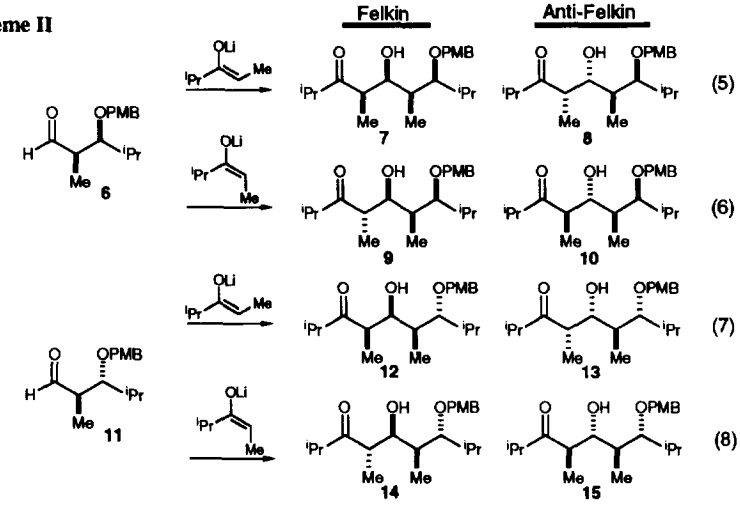


Syn aldol : *Anti* aldol	
2 : 3	(4 + 5)
65 : 21 :	14

Anti aldol : *Syn* aldol	
4 : 5	(2 + 3)
20 : 64 :	16

Aldehyde Component. The face selectivity of the chiral aldehydes **6** and **11** was examined using the (*Z*) and (*E*) lithium enolates of 2-methyl-3-pentanone (Scheme II).[8] For the addition of the (*Z*) lithium enolate (eq 5, 7), primarily *syn* aldol diastereomers were observed, with a consistent preference for addition to the anti-Felkin aldehyde diastereoface. This trend has also been documented for additions of (*Z*) boron enolates and (*Z*) crotylboron reagents.[1a,9] The configuration of the aldehyde β-stereocenter was also found to have a modest effect on the stereoselectivity. The preferred 1,3-*anti* relationship between the newly formed hydroxyl stereocenter and the β-OPMB moiety is in a stereoreinforcing relationship with the anti-Felkin preference in the formation of **8**, while this influence is in a non-reinforcing relationship in the formation of diastereomer **13**.[10] While β-heteroatom chelation has been invoked to explain product diastereoselection in lithium mediated aldol reactions,[5] neither kinetic or stereochemical evidence has been observed for aldehyde chelation in the reactions of lithium enolates in THF, even with α-alkoxy aldehydes.[11]

Scheme II



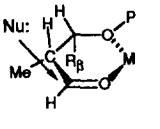
Syn aldol : *Anti* aldol	
7 : 8	(9 + 10)
04 : 87 :	09

Anti aldol : *Syn* aldol		
9 : 10	7	8
51 : 08	11	30

Syn aldol : *Anti* aldol	
12 : 13	(14 + 15)
15 : 80 :	5

Anti aldol : *Syn* aldol	
14 : 15	(12 + 13)
86 : 00 :	14

The influence of 1,3-induction was considerably more evident in the addition of the (*E*) lithium enolate to aldehydes **6** and **11** (Scheme II, eq 6, 8). While a consistent preference was observed for the formation of the Felkin diastereomers **9** and **14** among the *anti* aldol products, this preference was markedly enhanced by a stereoreinforcing 1,3-*anti* influence of the β-OPMB substituent present in the formation of diastereomer **14**. Internal aldehyde chelation may also be precluded in these reactions, even though the (*E*) enolization protocol produces 1 equiv LiBr as an exogenous Lewis acid. Addition to the internally coordinated aldehyde would be expected to form the anti-Felkin diastereomer, with higher selectivity in addition to the *syn* disubstituted aldehyde **6** *via* the illustrated transition state. These predictions are contrary to the experimental results.

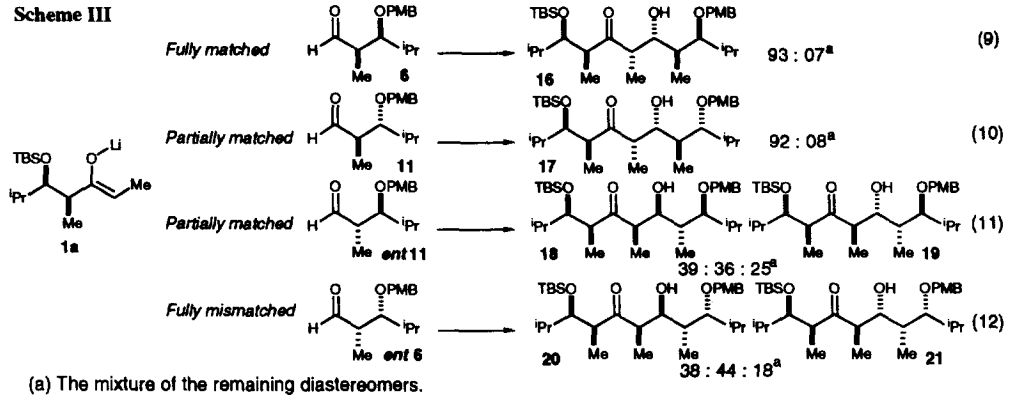


Double Stereodifferentiating Aldol Reactions. In double stereodifferentiating aldol fragment coupling processes,[12] there are at least three identifiable stereocontrol elements that influence the diastereofacial

selectivity of the enolate and aldehyde components: the α-stereocenter on the enolate, the aldehyde α-stereocenter, and the aldehyde β-stereocenter.[13] In the situation where all three control elements direct the forming stereocenters toward the same absolute configuration, the fragment coupling process is termed "fully matched." By analogy, "partially matched" refers to those instances where the α-stereocenter on the enolate is matched with only one of the control elements on the aldehyde, and "fully mismatched" indicates a mismatched relationship between the enolate and both aldehyde stereocontrol elements.

The double stereodifferentiating aldol reactions of (Z) enolate **1a** with chiral aldehydes **6**, **11**, and their respective enantiomers, were investigated (Scheme III).[14] The fully matched reaction (eq 9), and the partially matched reaction (eq 10) afforded highly diastereoselective coupling processes favoring the *syn* aldol anti-Felkin diastereomers **16** and **17** wherein the methyl groups flanking the carbonyl center possess the *anti* Me-Me relationship. These reactions illustrate that the primary aldehyde stereocontrol element in this process is the α stereocenter, with the configuration of the β-OPMB substituent of secondary importance. Furthermore, the adducts **16** and **17** represent complementary stereochemical arrays that cannot be accessed stereoselectively with titanium and boron enolate methodology.[2b] The comparative aldol reactions involving mismatched α-stereocontrol elements on the enolate and aldehyde partners (eq 11, 12) were found to be nonselective, again with minimal influence from the configuration of the β-stereocenter.

Scheme III

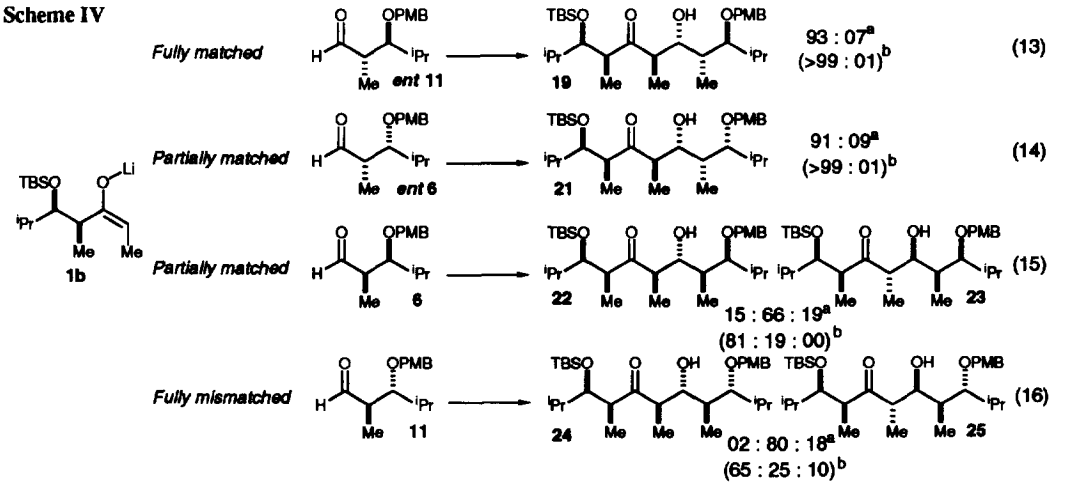


(a) The mixture of the remaining diastereomers.

The aldol reactions involving (*E*) lithium enolate **1b** with this same set of aldehydes was also investigated (Scheme IV). For purposes of comparison, the diastereoselectivity of the corresponding (*E*) dicyclohexylboron enolate aldol reactions are provided in parenthesis.[2b] In those instances where the enolate and aldehyde α stereocenters are paired in a matched relationship (eq 13, 14), excellent diastereoselection was observed regardless of the enolization method. However, the remaining two reactions (eq 15, 16) demonstrate the importance of the coordinating metal center on the relative stereochemical influence of the reacting partners. The double stereodifferentiating reactions involving the (*E*) boron enolate reveal that enolate diastereoface control dominates the process. On the other hand, in the mismatched lithium mediated processes, the aldehyde component overrides the opposing enolate bias affording modest selectivity for adducts **23** and **25**. *Thus the relative influence of the enolate or aldehyde component may be enhanced depending on the coordinating metal employed in the double stereodifferentiating aldol reaction.*

It is evident from this study that lithium enolates, in spite of their modest *syn/anti* selectivity, are effective in double stereodifferentiating aldol coupling reactions. The unique advantage provided by (Z) lithium enolates is highlighted in Scheme III. In the matched and partially matched cases (eq 9, 10) enolate face selectivity is opposite to that found for the analogous boron and titanium processes. Improved *syn/anti* aldol diastereoselection is another attribute of these examples. It is noteworthy that the modest diastereoselectivity exhibited by **1a** and **1b** with isobutyraldehyde (eq 3, 4) is improved through stereoamplification when paired with matched or partially matched chiral aldehyde coupling partners (eq 9, 10, 13, 14).

Scheme IV



(a) The mixture of the remaining diastereomers. (b) The product ratios of the analogous boron enolates.

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.

References and Footnotes

1. (a) Evans, D. A.; Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 1-115. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, Ch. 2, pp 111-212. (c) Paterson, I. in *Comprehensive Organic Synthesis: Additions to C-X π-Bonds Part 2;* Trost, B. M.; Fleming, I.; Heathcock, C. Eds.; Pergamon Press; NY, 1991; Ch 1.9.
2. Titanium enolates: (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.*, **1995**, *117*, 9073-9074. (Z) Boron enolates: (c) Evans, D. A.; Duffy, J. L. unpublished results, Chemistry Department, Harvard University. See also: (d) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229-1232. (Z) Lithium enolates: (e) McCarthy, P.; Kageyama, M. *J. Org. Chem.* **1987**, *52*, 4681-4686.
3. (a) Evans, D. A.; Ng., H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127-2142. (b) ref 2(b). For a complementary double stereodifferentiating *anti* aldol reaction, see: (c) Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608-1610.
4. The chiral lithium enolates **1a** and **1b** were prepared by the indicated methods in ≥ 92:8 geometric purity as determined by capillary GC analysis of the corresponding enolsilanes.
5. Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526-5528.
6. Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571-9574.
7. The reaction illustrated in eq 14 afforded an identical diastereomeric product mixture after 30 sec or 30 min at -78 °C, however warming to -30 °C for 30 min produced a 1:1:1 mixture of diastereomers. For lithium aldol equilibration examples see: (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe. J. *J. Org. Chem.* **1980**, *45*, 1066-1081. (b) Abdel-Magid, A. F.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595-4602. (c) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3447-3450.
8. Diastereoselectivity was determined by capillary GC analysis of the silylated or acetylated product mixtures prior to purification. The yields of all reactions were 63-86%. Stereochemical proofs were carried out on each product as in ref 2(b).
9. Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151-4157 and references cited therein.
10. (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.
11. (a) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302-1312. (b) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846-3856.
12. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew Chem. Int. Ed. Engl.* **1985**, *24*, 1-30.
13. The enolate β stereocenter may represent a fourth stereocontrol element. However, the relative configuration of the enolate β-stereocenter has been held constant for the present study.
14. For double asymmetric lithium aldol reactions see: (a) Martin, S. F.; Lee, W. C.; Pacofsky, G. J.; Gist, R. P.; Mulhern, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 4674-4688. (b) Martin, S. F.; Lee, W-C. *Tetrahedron Lett.* **1993**, *34*, 2711-2714. (c) Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, N. K. *Tetrahedron.* **1991**, *47*, 2317-2336. (d) ref 7(c). (e) ref 12.

(*Received in USA* 27 *November* 1995; *accepted* 12 *January* 1996)