(±)-19, 133627-62-0; (±)-20, 133627-63-1; $PhCOCH_2Li$, 55905-98-1; PhLi, 591-51-5; MeLI, 917-54-4; MeMgBr, 75-16-1; CH_2=CHCH_2MgBr, 1730-25-2; 1-acetylcyclohexene lithium enolate, 128164-71-6; (±)-*epi*-modhephene, 76739-65-6.

Supplementary Material Available: ^{1}H NMR spectra of compounds for which elemental analyses are not reported (8 pages). Ordering information is given on any current masthead page.

Concerning the Diastereofacial Selectivity of the Aldol Reactions of α-Methyl Chiral Aldehydes and Lithium and Boron Propionate Enolates

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Received August 27, 1990

The diastereofacial selectivity of the aldol reactions of α-methyl chiral aldehydes and propionate and ethyl ketone derived lithium and boron enolates is analyzed from the perspective of a transition state model suggested by Evans in 1982. The dominant stereocontrol element in these reactions, as in the mechanistically related reactions of crotylmetal reagents and α-substituted chiral aldehydes (refs 6, 7a), appears to be the minimization of gauche pentane interactions in the competing transition states. Transition structure **35** is viewed as the lowest energy structure in the "anti-Felkin" selective aldol reactions of *Z*(O)-enolates as long as the steric requirements of R are greater than that of the α-Me group. Transition state **36** is similarly the lowest energy structure available in the aldol reactions of *E*(O)-enolates (Felkin selective). The model also reconciles data involving the aldol reactions of Ph(Me)CHCHO (**1a**) and R_2C=CHCH(Me)CHO (**1b**, **1c**) that preferentially provide the 2,3-syn-3,4-syn ("Felkin") diastereomers **3**: the Ph or vinyl substituents are viewed as the smaller of the two α-substituents (Me > Ph or vinyl) since they expose a sterically undemanding, flat surface to the incoming nucleophile in the lowest energy transition structures **39** (for **1a**) and **41** (for **1b**, **1c**).

The aldol reaction has proven to be a very powerful method for the stereocontrolled synthesis of acyclic molecules.[1] The relationship between enolate geometry and product stereostructure (i.e., simple diastereoselection) is well established, and several classes of highly enantioselective chiral enolates have been developed for use in double asymmetric reactions.[2-4] Numerous applications of aldol technology in the synthesis of stereochemically complex natural products have since appeared.[1d] In spite of the attention devoted to this process, the factors that determine aldehyde diastereofacial selectivity in reactions of achiral enolates and chiral aldehydes are less well understood.[1,5] Diastereofacial selectivity is usually rationalized by invoking either the Felkin–Anh or the Cram chelate transition-state models.[1] As has been noted by several investigators, however, the Felkin–Anh paradigm fails to adequately rationalize the results of many aldol reactions involving *Z*(O)-enolates.[1,6a,b] Moreover, the Felkin–Anh model fails to predict the major product obtained in the mechanistically related reactions of (*Z*)-crotylboronates and α-methyl branched chiral aldehydes.[6a,b] Hoffmann stated in his initial paper that "molecular models show that the anti-Cram transition state is less hindered in the case of [the (*Z*)-crotylboronate], and the Cram transition state less hindered in the case of [the (*E*)-crotylboronate]".[6a] Evans provided transition structures for these reactions in his 1982 review of the aldol reaction and suggested that the anti-Felkin behavior of the (*Z*)-crotylboronates was the consequence of destabilizing gauche pentane interactions in the usually favored Felkin–Anh transition state.[1b] This model has been further developed and expanded by Hoffmann and Roush on the basis of a large body of data concerning the reactions of

(1) Reviews of the aldol reaction: (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (d) For a brief review of aldol technology in the context of the synthesis of polypropionate substructures: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.

(2) 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.

(3) Chiral Z(O)-enolates useful for the synthesis of 2,3-syn aldols: (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *Ibid.* **1981**, *103*, 1568. (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *Ibid.* **1981**, *103*, 2127. (d) Evans, D. A.; McGee, L. R. *Ibid.* **1981**, *103*, 2876. (e) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 5807. (f) Paterson, I.; Lister, M. A.; McClure, C. K. *Ibid.* **1986**, *27*, 4787. (g) Paterson, I.; McClure, C. K. *Ibid.* **1987**, *28*, 1229. (h) Paterson, I.; Lister, M. A. *Ibid.* **1988**, *29*, 585. (i) Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* **1989**, 1001. (j) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

(4) Chiral *E*(O)-enolates useful for the synthesis of 2,3-anti aldols: (a) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (b) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (c) Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874. (d) Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699. (e) Davies, S. G.; Dordor-Hedgecock, I. M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125. (f) Masamune, S.; Sato, T.; Kim, B.-M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (g) Short, R. P.; Masamune, S. *Tetrahedron Lett.* **1987**, *28*, 2841. (h) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.

(5) For recent computational studies of aldol transition states: (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481. (b) Leung-Toung, R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1990**, *112*, 1042. (c) Goodman, J. M.; Kahn, S. D.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3295. (d) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *Ibid.* **1990**, *55*, 3576.

(6) (a) Hoffmann, R. W.; Zeiss, H.-J. *Angew Chem., Int. Ed. Engl.* **1980**, *19*, 218. (b) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966. (c) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. Roush, W. R.; Adam, M. A.; Harris, D. J. *J. Org. Chem.* **1985**, *50*, 2000. (d) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881. (e) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (f) For recent experimental and computational investigations of this transition-state model: Hoffmann, R. W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387. Brinkmann, H.; Hoffmann, R. W. *Ibid.* **1990**, *123*, 2395.

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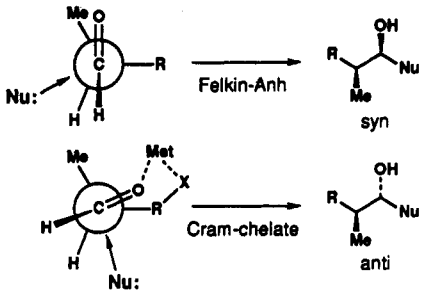
chiral aldehydes and allylboron reagents.[6,7] Evans further predicted the applicability of this model to the aldol reactions of boron enolates, although experimental evidence was not then available.[1b] We analyze herein the diastereofacial selectivity of the aldol reactions of α-methyl chiral aldehydes and propionate and ethyl ketone derived lithium and boron enolates from the perspective of this model. We show further that this transition state analysis adequately rationalizes the majority of aldol reactions of Z(O)-lithium enolates and chiral aldehydes previously thought to proceed by way of Felkin–Anh (e.g., **1a–c**) or Cram chelate transition states (e.g., **5**).

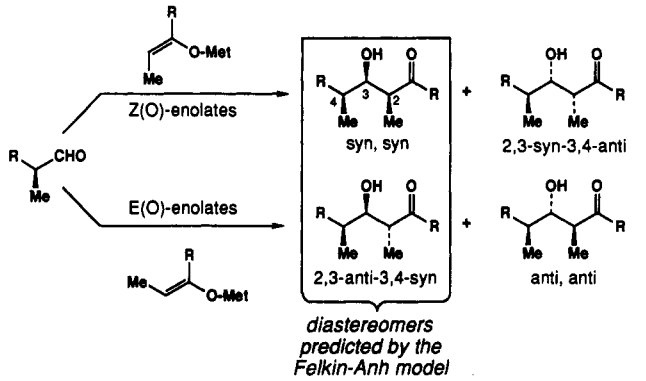
Background

Numerous theoretical and experimental studies of diastereoselective additions of nucleophiles to chiral carbonyl compounds have been reported.[8,9] The two most widely applied[9a] transition state models are the Felkin–Anh[8e,f,j] and Cram chelate[8b] models for reactions that proceed by way of nonchelated and chelated pathways, respectively.[10] Application of these models to the aldol

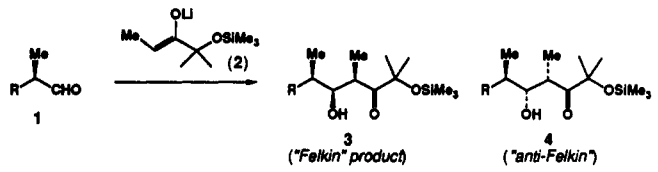


reaction leads to the prediction that the two 3,4-syn diastereomers should predominate in reactions of Z(O)- and E(O)-enolates that proceed by way of chairlike, nonchelated transition states, while the two 3,4-anti diastereomers should predominate in reactions that proceed by way of chelated intermediates. As noted in the introduction, however, the literature reveals many exceptions to predictions based on the Felkin–Anh paradigm for reactions involving Z(O)-enolates.[16b]

For example, the reactions of a series of α-methyl branched chiral aldehydes **1a–h** with the Z(O)-lithium enolate **2** have been reported.[1a,11] While the reactions of



1a–c selectively provide the "predicted" syn,syn ("Felkin") diastereomer **3**, the reactions of **1d–h** provide the 2,3-syn-3,4-anti ("anti-Felkin") diastereomer **4** as the major product.[12] The results with **1d** and **1f–h** have been rationalized by invoking the Cram-chelate model,[1a,11d] although the acetate and TBDMS protecting groups of substrates **1g** and **1h** should disfavor chelate-mediated pathways.[13] The chelation proposal is also weakened by the observation that aldehyde **1e** possessing a cyclohexyl "R" group also displays a ca. 3:1 preference for the 2,3-syn-3,4-anti ("anti-Felkin") diastereomer **4**.



Aldehyde	R	3 (syn,syn) : 4 (syn,anti)	
1a	Ph	81 : 19	
1b	H_2C=CH	75 : 25	
1c	Me_2C=CH	94 : 6	
1d	MeOOCCH(Me)CH_2	45 : 55	
1e	c-C_6H_{11}	27 : 73	anti-Felkin selectivity!!
1f	$PhCH_2OCH_2$	33 : 67	
1g	$AcOCH_2$	23 : 77	
1h	t-$BuMe_2SiOCH_2$	21 : 79	

Masamune considerably expanded the idea of chelation as a stereocontrol strategy in a detailed study of the aldol reactions of a series of β-alkoxy aldehydes **5** and Z(O)-lithium enolates **6** and **7**.[14] The anti-Felkin diastereofacial selectivity observed in these reactions was rationalized in terms of the chelated transition structure **10** that has a boatlike rather than the more frequently invoked chairlike geometry for the pericyclic bond reorganization step.

In a related paper, however, Masamune reported that Z(O)-boron enolates also display anti-Felkin selectivity in reactions with various β-alkoxy aldehydes.[15] For example,

(7) (a) The reactions of Type I and Type III crotylmetal reagents with chiral aldehydes have been analyzed from the perspective of this transition-state model: Roush, W. R. In *Comprehensive Organic Synthesis*, Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, in press. For earlier reviews of the reactions of crotylmetal reagents and aldehydes: (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357.

(8) Transition-state models for diastereoselective carbonyl additions: (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (c) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (d) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. (e) Chêrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (f) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (g) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (h) Wu, Y.-D.; Houk, K. N. *Ibid.* **1987**, *109*, 908. (i) Lodge, E. P.; Heathcock, C. H. *Ibid.* **1987**, *109*, 2819. (j) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456.

(9) For several recent fundamental studies of diastereofacial selectivity in carbonyl addition reactions: (a) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *Ibid.* **1988**, *110*, 3588. (c) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *Ibid.* **1989**, *111*, 8447. (d) Reversal of the normal Felkin or Cram diastereofacial preference occurs in electron transfer mediated reactions: Yamamoto, Y.; Matsuoka, K.; Nemoto, H. *Ibid.* **1988**, *110*, 4475. Yamamoto, Y.; Maruyama, K. *Ibid.* **1985**, *107*, 6411.

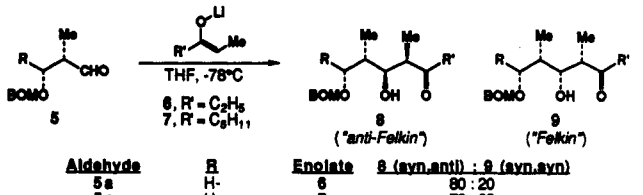
(10) Reviews of chelation controlled carbonyl additions: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 125.

(11) (a) Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 8109. (b) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23. (c) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. (d) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (e) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *Ibid.* **1985**, *50*, 2095.

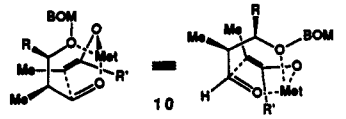
(12) We use the "Felkin" descriptor to refer to the diastereomer predicted by the Felkin-Anh paradigm. The "anti-Felkin" descriptor refers to diastereomers not predicted by this transition state model. While the so-called "anti-Felkin" diastereomers could conceivably arise via Cram-chelate pathways for reactions involving lithium or magnesium enolates, this is not possible for aldol reactions involving boron enolates.

(13) For studies on the influence of protecting groups on chelate controlled carbonyl additions: (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847. (b) Frye, S. V.; Eliel, E. L.; Cloux, R. *Ibid.* **1987**, *109*, 1862. (c) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (d) Keck, G. E.; Castellino, S. *Ibid.* **1987**, *28*, 281. (e) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478. (f) Reetz, M. T.; Hüllmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477.

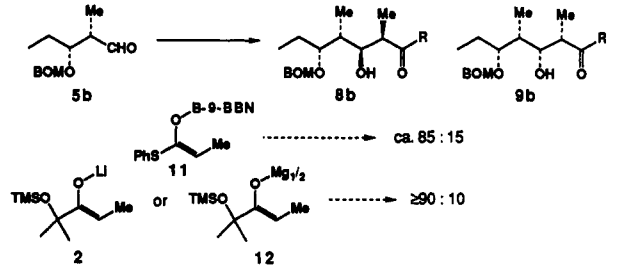
(14) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.



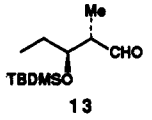
Aldehyde	R	Enolate	8 (syn,anti) : 9 (syn,syn)
5a	H-	6	80 : 20
5a	H-	7	78 : 22
5b	Et-	6	83 : 17
5b	Et-	7	90 : 10
5c	i-Pr-	6	87 : 13
5c	i-Pr-	7	92 : 8
5d	TBDMSOCH2CH2-	6	93 : 7
5d	TBDMSOCH2CH2-	7	95 : 5



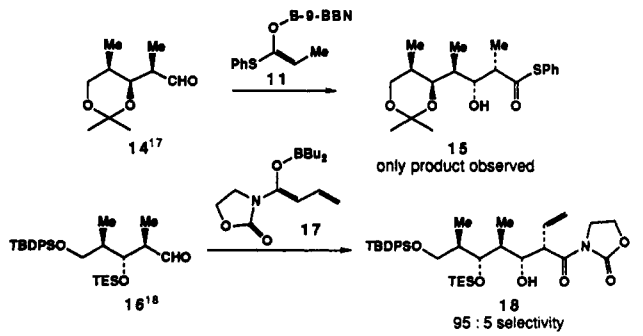
the aldol reaction of **5b** and boron enolate **11** provides the anti-Felkin diastereomer **8b** with ca. 85:15 selectivity; qualitatively similar levels of selectivity (≥90:10) for **8b** were realized when the lithium and magnesium enolates (**2** and **12**) were used. This observation is significant since



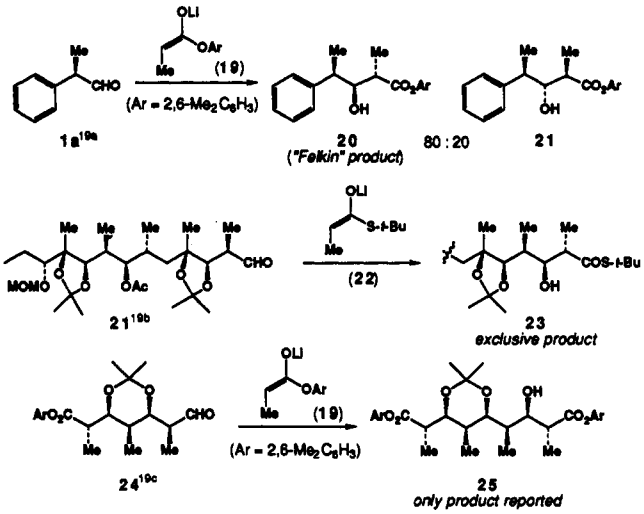
boron enolates are incapable of reacting by way of internally chelated transition structures such as **10** (Met = BR_2). Other published data indicate that *Z*(O)-lithium and boron enolates sometimes display qualitatively similar levels of anti-Felkin selectivity in reactions with chiral β-alkoxy aldehydes. For example, the reactions of **13** and *Z*(O)-enolates **2** and **11** provide the 2,3-syn-3,4-anti (anti-Felkin) diastereomers with 73:27 and 71:29 selectivity, respectively.[16]



Finally, it is noteworthy that several other examples of aldol reactions of *Z*(O)-boron enolates have been reported that proceed with outstanding levels of anti-Felkin diastereoselectivity (cf. the aldol reactions of **14** and **16** summarized below).[17,18]



In contrast to these results with *Z*(O)-enolates is the behavior of the isomeric *E*(O)-enolates in reactions with α-methyl chiral aldehydes: to our knowledge, the major product of all such reactions is the one predicted by the Felkin-Anh paradigm (i.e., the 2,3-anti-3,4-syn diastereomer). Three such examples are summarized below.[19]



A similar dichotomy has been observed in the reactions of α-methyl chiral aldehydes and crotylboronates: (*Z*)-crotylboronates preferentially provide the anti-Felkin diastereomer whereas the (*E*)-crotyl reagents consistently provide the diastereomer predicted by the Felkin–Anh model.[6,7a] Several examples from Hoffmann's study are provided in the following equations.[6b] It may be concluded, therefore, that the anti-Felkin behavior demonstrated in the aldol reactions of *Z*(O)-enolates is reflective of a general trend in diastereoselection and that it is not necessary a priori to invoke chelation (c.f., **10**) to rationalize the anti-Felkin preference observed in the reactions of most α-methyl chiral aldehydes and *Z*(O)-lithium enolates summarized above.

A detailed analysis of transition states of these reactions is presented in the following section.

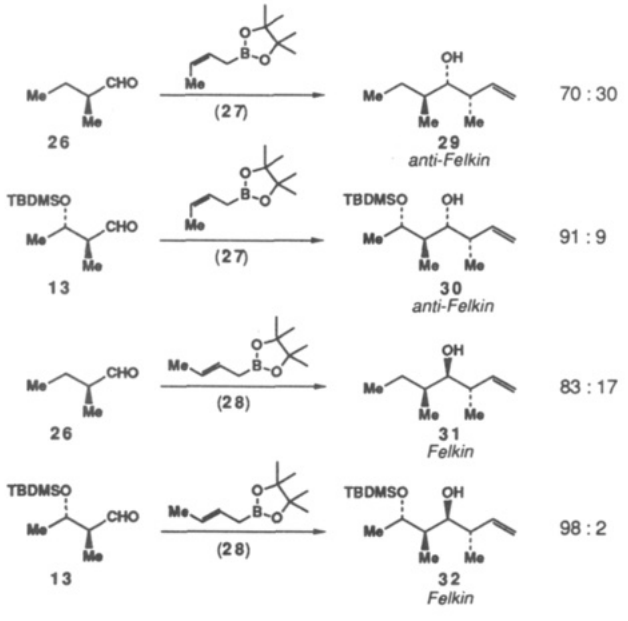
Discussion

The analysis of transition states of aldol and crotylmetal carbonyl addition reactions derives ultimately from the pioneering contribution of Zimmerman and Traxler who first postulated the involvement of cyclic, internally chelated transition states in Reformatsky and Ivanov reactions.[20] Dubois and co-workers established that the aldol reaction is subject to kinetic diastereoselection, with aldol stereostructure depending on the stereochemistry of the enolate.[21] Subsequent studies by Heathcock defined experimental conditions and structural requirements necessary for achieving virtually complete simple diastereo-

(15) Masamune, S. In *Organic Synthesis Today and Tomorrow*, Trost, B. M., Hutchinson, C. R., Eds.; Pergamon-Press: New York, 1981; p 199.
(16) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, *23*, 4991.

(17) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603. These authors rationalize the outcome of this aldol reaction by comparing transition structures analogous to **35** (favored) and **33**, which they note is destabilized by syn pentane interactions between the two methyl groups.
(18) Roush, W. R.; Palkowitz, A. D. *J. Org. Chem.* **1989**, *54*, 3009.
(19) (a) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087. (b) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210. (c) Tschamber, T.; Waespe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 621.
(20) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(21) (a) Dubois, J.-E.; Dubois, M. *Tetrahedron Lett.* **1967**, 4215. (b) Dubois, J.-E.; Fellmann, P. *C. R. Acad. Sci. Ser. C* **1972**, *274*, 1307. (c) Dubois, J.-E.; Fellmann, P. *Tetrahedron Lett.* **1975**, 1225.

selection with lithium enolates.[22] The now familiar chairlike transition state for reactions of lithium enolates appeared for the first time in this 1977 communication. Evans provided a more detailed transition state analysis for aldol reactions of boron enolates in 1979.[23] Evans also established that simple diastereoselectivity is significantly enhanced in aldol reactions of boron vs lithium enolates, owing to the considerably shorter B–O and B–C bond lengths that lead to much tighter transition states.[23,24] Heathcock provided the first bridge of thought connecting simple diastereoselectivity in aldol reactions with that in the crotylmetal arena in his analysis of transition states for the reaction of the crotylchromium(III) reagent and aldehydes.[25] Subsequent transition-state analyses of the reactions of aldehydes and crotylmetal reagents have drawn analogy to the related aldol processes.[7b,26] As noted in the introduction to this paper, the connection between diastereofacial selectivity in aldol and crotylmetal carbonyl addition reactions was established by Evans in his 1982 review article in which he provided a transition state analysis of Hoffmann's initial results concerning the anti-Felkin behavior of (*Z*)-crotylboronates in reactions with α-methyl branched aldehydes.[1b,6a] This diastereofacial selectivity model has been further developed and expanded by Hoffmann and Roush for the reactions of chiral aldehydes and allylboron reagents.[6,7a]



Central to this analysis is the suggestion[1b] that *the dominant stereocontrol element that determines aldehyde diastereofacial selectivity is the minimization of gauche pentane interactions in the competing cyclic, chairlike transition states.*[6,7,17,27,28] The significance of these interactions becomes apparent upon inspection of transition states **33**–**35** for the aldol reaction of *Z*(O)-enolates and α-methyl chiral aldehydes (Figure 1). Structure **33** is a three-dimensional representation of the Felkin–Anh transition state: the carbonyl is aligned syn to the α-methyl substituent, and the developing C–C bond is anti to the largest α-substituent designated as "R".[29] This transition structure, however, contains a serious gauche$^+$–gauche$^-$ (g^+g^-) pentane interaction (also referred to as a "syn-pentane" conformation)[28] between the methyl substituents on the enolate and the aldehyde α-carbon atom (highlighted for emphasis). The magnitude of this interaction is probably less than that in ground state gauche$^+$–gauche$^-$ pentane,[27] or that of the 1,3-interaction that destabilizes the diaxial conformation of 1,3-dimethylcyclohexane,[27a] since the developing C–C bond must be longer than a fully developed C–C bond.[6b,f] Nevertheless, it is clear from an examination of space-filling molecular models that this interaction is sufficiently large that it is difficult for the enolate and carbonyl carbon atoms to make direct contact with one another. This g^+g^- interaction is relieved by a 120° rotation about the O=C—C_α single bond that provides rotamer **34**. *Transition structure **34**, however, is destabilized relative to the diastereomeric "anti-Felkin" arrangement **35** by the indicated gauche pentane interactions, to the extent that the R substituent is more sterically demanding than Me.* All other transition structures generated by 120° rotations

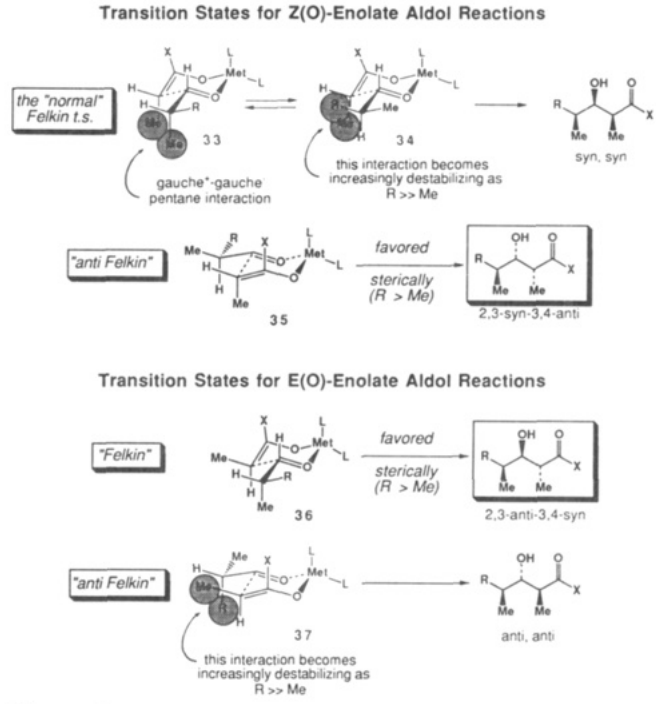


Figure 1.

(22) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247.

(23) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.

(24) Stereoselective aldol condensations via boron enolates were simultaneously developed by Masamune and co-workers: (a) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. (b) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, 2225. (c) Van Horn, D. E.; Masamune, S. *Tetrahedron Lett.* **1979**, 2229. (d) Hirama, M.; Garvey, D. S.; Lu, L. D.-L; Masamune, S. *Tetrahedron Lett.* **1979**, 3937.

(25) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685.

(26) See, for example: (a) Hayashi, T.; Fujitaka, N.; Oishi, T.; Takeshima, T. *Tetrahedron Lett.* **1980**, 303. (b) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309. (c) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1982**, *23*, 845.

(27) (a) Allinger, N. L.; Miller, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 2145. (b) Abe, A.; Jernigan, R. L.; Flory, P. J. *Ibid.* **1966**, *88*, 631. (c) Scott, R. T.; Scheraga, H. A. *J. Chem. Phys.* **1966**, *44*, 3054. (d) Sy'korn, S. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3514.

(28) The minimization of gauche$^+$–gauche$^-$ pentane interactions has proven to be a useful stereocontrol stragety: (a) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105. (b) Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618. (c) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *Ibid.* **1984**, *106*, 2738. (d) Schreiber, S. L.; Wang, Z. *Ibid.* **1985**, *107*, 5303. (e) Kurth, M. J.; Brown, E. G. *Ibid.* **1987**, *109*, 6844. (g) Kurth, M. J.; Beard, R. L.; Olmstead, M.; Macmillan, J. C. *Ibid.* **1989**, *111*, 3712. (h) For one example in which a gauche$^+$–gauche$^-$ pentane interaction has a deleterious effect: Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *Ibid.* **1981**, *103*, 7690.

(29) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438.

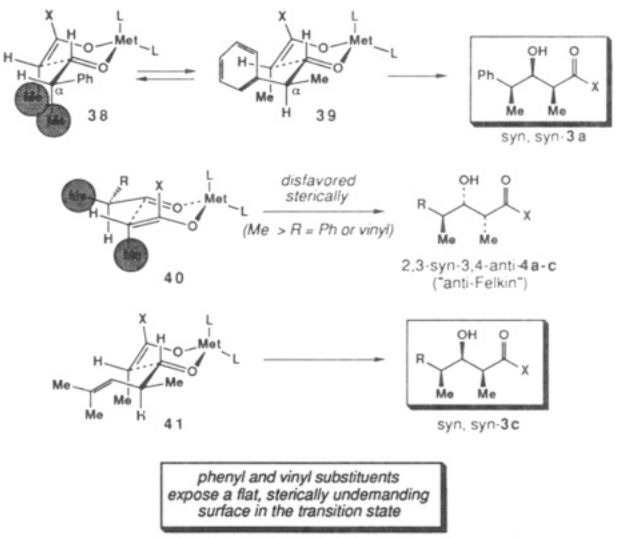
about the O=C—C_α bonds of **33**/**34** or **35** possess destabilizing g^+g^- interactions involving the "R" or Me substituents of the chiral aldehyde and must therefore be considerably higher in energy.

Thus transition structure **35** is expected (predicted)[16] to be the lowest energy transition state available for aldol reactions of α-methyl chiral aldehydes and *Z*(O)-enolates, *as long as the steric requirements of Me are smaller than R*. This transition structure nicely accounts for the preferential production of the 2,3-syn-3,4-anti aldol ("anti-Felkin") diastereomers from the majority of *Z*-(O)-enolate aldol reactions summarized in the Background section of this paper. Further comparison of **34** and **35** leads to the prediction that diastereofacial selectivity should increase as the steric requirements of "R" increase relative to Me, a prediction that is consistent with experimental results (diastereofacial selectivity in reactions with *Z*(O)-enolates increases in the series **1** < **5** < **14**, **16**). That is, the energy of **35** should be relatively unaffected by an increase in the size of "R", while the gauche interactions highlighted in **34** should increase in magnitude as the steric demands of "R" also increase. This analysis directly parallels the previously described transition state model for the reactions of chiral aldehydes and (*Z*)-crotylboron reagents.[6e,7a]

The analysis of the aldol reactions involving *E*(O)-enolates (Figure 1) is more straightforward since the Felkin–Anh transition state (**36**) corresponds to the transition structure with the fewest serious gauche pentane interactions (ts **36** has two Me···H and one Me···Me interactions, while ts **37** has one Me···H, one R···H and one R···Me interactions). Transition state **36** also benefits from favorable stereoelectronic effects (σ^* orbital energies). Thus, the developing C–C bond is anti to the largest substituent ("R") in **36**, and the gauche Me–Me interaction in **36** is certainly less destabilizing than the Me–R interaction in the "anti-Felkin" transition structure **37**. It is to be expected that the level of diastereofacial selectivity in aldol reactions involving *E*(O)-enolates should increase as the steric requirements of "R" increase relative to Me, a prediction that again appears to be consistent with available experimental data.

The diastereofacial selectivity of the aldol reactions of chiral aldehydes and acetate or methyl ketone enolates has not been addressed in this analysis since this topic has already been examined in detail by Heathcock.[9a] While the Felkin–Anh model correctly predicts the outcome of the majority of the acetate/methyl ketone aldol reactions, Heathcock concluded that steric effects are at least as important as stereoelectronic effects (e.g., σ^* orbital energies) in determining the group that occupies the "large" position anti to the incoming enolate nucleophile. Heathcock's data thus are supportive of the model we present here—specifically that nonbonded interactions in the form of the syn pentane interactions highlighted in transition structures **33**, **34**, and **37** play a very significant role in determining aldehyde diastereofacial selectivity.

The interplay of σ^* orbital energies vs the minimization of gauche pentane interactions is relevant to the analysis of the aldol reactions of aldehydes **1a–c** and *Z*(O)-lithium enolate **2**. While the preferential formation of syn,syn diastereomers **3a–c** in these reactions is superficially consistent with the Felkin–Anh transition state **33** (**38** for the reactions of aldehyde **1a**), the syn pentane interaction between the two eclipsing methyl groups must be as destabilizing in these reactions as they are for all other *Z*-(O)-enolate aldol reactions discussed in the Background section. Is the stabilization of the developing C–C bond by the σ^* orbital of the C–Ph bond sufficiently large that the destabilizing gauche pentane interactions may be ignored? We think not, especially since in the mechanistically related reactions of crotylboronates and α-alkoxy aldehydes it has been concluded that syn pentane considerations indeed override competing stereoelectronic effects in determining the stereochemical outcome of these carbonyl addition processes.[6b,c,7a]



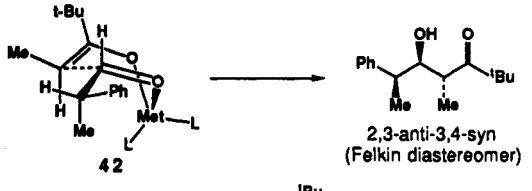
The preferential formation of **3a–c** from **1a–c** is thus better explained by invoking transition structure **39** (for **1a**) or **41** (for **1c**) rather than **40** (cf. **35**), which is the lowest energy transition structure in aldol reactions when R is a bulky substituent (R > Me). *That is, the data for the aldol reactions of* ***1a–c*** *may be rationalized if it is assumed that Me is the largest of the α-substituents (Me > Ph or vinyl for the reactions with* ***2***). This assumption flies in the face of conventional wisdom that, for example, a phenyl group has a greater steric requirement than Me.[30] It must be recognized, however, that *A* values assessing the relative steric size of substituents are weighted averages of the energies of all conformations (including rotational isomers) available to the ground-state structures. Transition state **39** is but one of a family of transition structures that differ conformationally (and energetically) by rotations about the Ph–C_α bond.[29] Those in which the phenyl group eclipses the C_α–Me or the C_α–(C=O) units necessarily suffer from nonbonded interactions between the phenyl substituent and the incoming enolate, and undoubtedly will be higher in energy than **40**. On the other hand, the conformation depicted in rotamer **39** in which the phenyl group eclipses the C_α–H bond suffers no significant nonbonded interactions since the phenyl group exposes a flat, sterically undemanding surface to the incoming enolate. It is probably this one specific conformation of **39**, and not the usual Felkin–Anh arrangement described by **38**, that accounts for the preferential formation of **3a** from the aldol reaction of **1a** and *Z*(O)-enolate **2**. There may be an entropic cost for selecting this single rotational isomer, but this presumably is easily paid as long as the destabilizing interactions between Ph and Me in **39** are less than the Me···Me interactions in **40**.

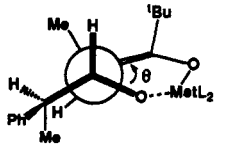
These arguments are supported by the data for the aldol reactions of *Z*(O)-enolate **2** and aldehydes **1b** and **1c** that possess vinyl substituents. Vinyl groups are generally assumed to be less sterically demanding than Me.[30] It is also curious that the aldol reaction of **1c**, which possesses

(30) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

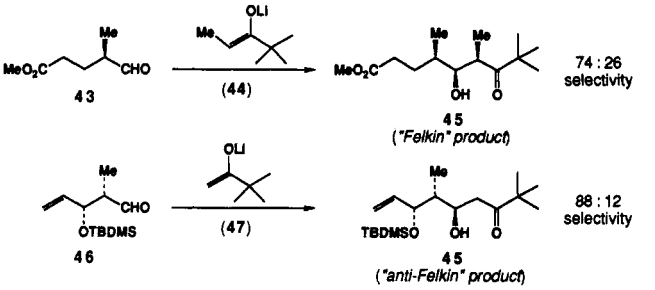
a β,β-dimethyl vinyl "R" substituent, is significantly more stereoselective than those of either **1a** or **1b**.[11e] This result is consistent with **41** (cf. **39**) as the lowest energy transition structure, especially since allylic strain considerations lead one to conclude that the conformation with the vinyl appendage eclipsing C_α–H as indicated in **41**, *thereby exposing the "flat" surface of the vinyl appendage to the incoming nucleophile*, should be the most favorable (lowest energy) one.[31] The *Z*-methyl substituent in **1c** will thus raise the energy of all other C_α rotamers due to the increased allylic strain interactions.[31] The absence of *Z* olefinic substituents in **1a** or **1b** implies that the preference for transition states with the α-phenyl or α-vinyl groups syn to H, as indicated in **39**, may not be as great as for **1c** (see **41**), and therefore that the aldol reactions of **1a** or **1b** should be less stereoselective, as is observed experimentally.

If the preceding arguments are accepted that phenyl and vinyl substituents are less sterically demanding than methyl groups in the aldol reactions of *Z*(O)-enolates, then why does the aldol reaction of **1a** and *E*(O)-enolate **19** evidently proceed by way transition state **36**, in which the phenyl substituent is anti to the developing C–C bond, and not **37**? Experimental[1,32] and computational[5] studies suggest that twist-boat transition structures are relatively close in energy to the chairlike ones in the aldol reactions of *E*(O)-enolates. It may well be then that twist boat transition structures like **42** are competitive in the *E*-(O)-aldol reactions under consideration here (but not in the *Z*(O)-enolate reactions discussed earlier). Because the geometry about the developing C–C bond in twist boat structures (e.g., **42**) has been calculated to be closer to eclipsed than staggered ($\theta = -20°$ to $-30°$),[5a] the distance between the methyl groups in **42** is greater than in chairlike transition structures **35** or **36** (which are expected to have essentially staggered developing C–C bonds, $\theta = -55$ to $-59°$).[5a] That is, gauche pentane interactions may well be less significant in the aldol reactions of *E*(O)-enolates especially if twist-boat transition structures such as **42** are involved. If so, one would expect that stereoelectronic effects would have a greater, and gauche pentane interactions a lesser, impact on the stereochemical course of *E*(O)-enolate aldol reactions, compared to the *Z*(O)-enolate reactions discussed previously.





While the transition-state analysis presented here is consistent with the vast majority of known aldol (and crotyl metal) reactions that proceed by way of chairlike cyclic transition states, there are several cases that are not in agreement with the model. One is the reaction of **43** and *Z*(O)-enolate **44** that provides the syn, syn ("Felkin") diastereomer **45** as the major component of a 74:26 mixture.[11a] This result is clearly inconsistent with the data reported for the reactions of **1d–h** and the related enolate **2**. The second aberrant example is the reaction of **46** and **47** that provides the "anti-Felkin" diastereomer **48** with 88% selectivity.[33] This case deviates from the stereochemical pattern by Heathcock for the aldol reactions of methyl ketones and other chiral aldehydes.[9a] We are not able at present to offer a reasonable rationalization for either result.

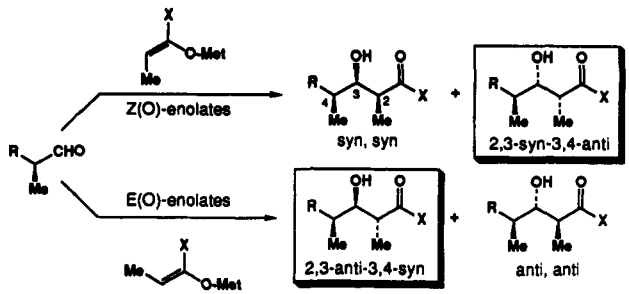


These last two examples suggest that the stereochemical course of aldol reactions of lithium enolates may well be more complicated than implied by the transition-state analysis discussed in this paper. Lithium enolates are well known to exist as aggregates in solution, and the dimeric forms are believed to be the most reactive species in solution.[34] This important structural feature has not been considered in this analysis. It is also conceivable that chelation effects, owing to the presence of polar substituents in either the enolate or aldehyde components and the involvement of aggregates as kinetically significant reaction intermediates, could alter the "predicted" stereochemical course of aldol reactions involving lithium enolates.

In summary, we have shown that the transition-state model first presented by Evans almost a decade ago is consistent with the vast majority of known aldol (and crotylmetal)[6,7a] reactions that proceed by way of chairlike cyclic transition states. The main utility of this transition-state analysis obviously lies in the ability to predict the outcome of aldol (and crotylmetal) reactions that are of interest in numerous synthetic endeavors. The model further predicts that diastereofacial selectivity in favor of the two 2,4-anti methyl diastereomers will increase as the steric requirements the aldehydic R substituent increases; indeed, several of the aldol and crotylmetal addition reactions summarized in the Background section of this paper exhibit outstanding levels of diastereofacial selectivity. Unfortunately, however, it is not always possible to predict the absolute level of stereoselectivity that a particular chiral aldehyde/achiral enolate (or crotylmetal reagent) pair will exhibit. Several studies indicate that this depends not simply on reduced mass considerations, but rather on the three dimensional structure (stereochemistry and conformation) of the R substituent.[7a,35] Nevertheless, since it can be assumed that the two 2,4-anti methyl diastereomers will be the intrinsically favored products of reactions of α-methyl chiral aldehydes and enolate/crotylmetal reagents of appropriate *Z* or *E* geometry, one can always resort to the strategy of double asymmetric synthesis to achieve outstanding levels of stereocontrol. These two diastereomers will, by definition, correspond to the products of matched double asymmetric reactions.[2] In this way, we believe, the process of analyzing complex synthetic

(31) For recent review of 1,3-allylic strain as a stereocontrol element in organic synthesis: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(32) (a) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343. (b) Hoffmann, R.; Ditrich, K.; Froech, S.; Cremer, D. *Tetrahedron* **1985**, *41*, 5517.
(33) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129.
(34) (a) For a review of the structure and reactivity of lithium enolates: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) For a recent disclosure of an aldol reaction of a lithium enolate in the solid state: Wei, Y.; Bakthavatchalam, R. *Tetrahedron Lett.* **1991**, *32*, 1535.
(35) Lewis, M. S.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343.

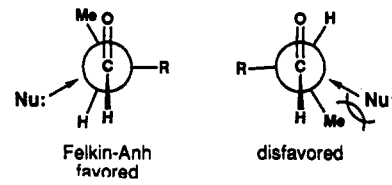
Scheme I[a]



[a] The two 2,4-anti methyl diastereomers are intrinsically favored as long as the steric requirements of R are greater than Me. Further, the intrinsic diastereofacial selectivity is expected to increase as the steric requirements of R increase relative to Me. Finally, as long as the first condition is met, the two 2,4-anti diastereomers will correspond to the products of "matched" double asymmetric reactions when appropriate chiral enolates are utilized.

targets is greatly simplified.[36,37]

In closing we wish to stress that the transition-state model discussed herein does not contradict the major precepts of the Felkin–Anh paradigm, specifically the stereoelectronic requirement that the developing C–C bond must overlap with and be stabilized by the σ^* orbital of one of the substituents α to the carbonyl.[8,29] The influence of steric effects was recognized early on by Anh and Eisenstein,[8f] who noted that if nucleophilic addition proceeds according to the Bürgi–Dunitz trajectory,[38] then the stereodifferentiation that occurs in the carbonyl addition step may be rationalized by the differential interactions of the nucleophile and the small (H) and medium sized groups (Me) in the two transition structures reproduced below. The present transition-state model simply expands the notion that steric interactions involving the nucleophile must be considered carefully, since, as is apparent by inspection of the three-dimensional transition structure **33**, interactions may indeed occur between the methyl substituent of propionate enolate and the carbonyl α-methyl group; the "normal" Felkin–Anh transition state thus may not necessarily be the lowest energy one. The lowest energy transition state will most certainly be the one that maximizes stereoelectronic stabilization, in the form of σ_{C-C}/σ^* interactions, and minimizes all nonbonded interactions, including the syn or gauche pentane interactions highlighted in this paper. When these effects are dissonant, as in the aldol reactions of *Z*(O)-enolates or the reactions of (*Z*)-crotylboronates and α-methyl chiral aldehydes, it appears that stereoelectronic stabilization plays a lesser role than the minimization of syn and gauche pentane interactions. Finally, we close by noting that other carbonyl addition reactions are known in which the usual stereochemical course is altered as a result of remote steric effects.[9b]



Acknowledgment. The author gratefully acknowledges support provided by the National Institute of General Medical Sciences (GM 38436), and fruitful discussions with Professor Evans during the final revisions of the manuscript.

(36) This point has been discussed in detail in connection with the reactions of α-methyl chiral aldehydes and crotylboronates (ref 6e).

(37) These considerations are also relevant to the analysis of fragment assembly steps involving aldol reactions of chiral enolates and chiral aldehydes. For two illustative examples: (a) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568 (conversion of **5** + **6** → **4**). (b) Evans, D. A.; Sheppard, G. S. *J. Org. Chem.* **1990**, *55*, 5192 (conversion of **4** + **7** → **8**).

(38) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *Ibid*, **1974**, *96*, 1956. (c) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

On the Maximum Rotation and the Solvobromination and -mercuration of Enantioenriched 1,3-Dimethylallene

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Received January 23, 1991

The prior assignments of the maximum rotation of enantiomerically pure 1,3-dimethylallene (13DMA) based on the methoxybromination and -mercuration of enantioenriched 13DMA are shown to be drastically in error. A value of $[\alpha]_{589}$ of 81.0 ± 0.2° (25 °C in diethyl ether) has been determined directly on enantioenriched samples of 13DMA by the use of a chiral NMR shift reagent. The methoxybromination and -mercuration reactions, which were previously suggested to be completely stereospecific, are shown to occur with substantial losses in ee, suggesting that the intermediate onium ion intermediates undergo competitive ring opening to achiral substituted allyl cations thus resulting in loss of ee.

Introduction

Current studies in our laboratories investigating the stereochemical details of the (2 + 2) cycloaddition reactions of chiral allenes have initially focused on the cycloaddition reactions of enantioenriched (scalemic) 1,3-dimethylallene (13DMA), a reasonably readily available, simple chiral allene. Enantioenriched (*S*)-(+)-13DMA has been prepared by the partial asymmetric hydroboration of racemic 13DMA with diisopinocampheylborane prepared from (+)-α-pinene following the procedure of Waters and Caserio,[1] Waters, Linn, and Caserio,[2] and Rossi and Diversi[3] and modified by Brown and Singaram.[4] The enantiomeric

(1) Waters, W. L.; Caserio, M. C. *Tetrahedron Lett.* **1968**, 5233.

(2) Waters, W. L.; Linn, W. S.; Caserio, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6741.

(3) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25.

0022-3263/91/1956-4157$02.50/0