JOC Article

Double Diastereoselection in Aldol Reactions Mediated by Dicyclohexylchloroborane between L-Erythrulose Derivatives and Chiral Aldehydes. The Felkin−Anh versus Cornforth Dichotomy

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Both matched and mismatched diastereoselections have been observed in aldol reactions of the *B,B*-dicyclohexylboron enolate of a protected L-erythrulose derivative with a range of chiral aldehydes. The stereochemical outcome of reactions with α-methyl aldehydes can be adequately explained within the Felkin−Anh paradigm. In the case of α-oxygenated aldehydes, however, strict adherence to this model does not allow for a satisfactory account of the observed results. In such cases, the Cornforth model provides a much better explanation.

Introduction

The aldol reaction is a powerful and general method for the stereocontrolled construction of carbon−carbon bonds.[1] Among the many enolate types investigated thus far, boron enolates have proven to be particularly versatile because of their good reactivity and excellent stereoselectivity.[2] In recent years, we have investigated the outcome of aldol reactions of boron enolates generated from suitably protected L-erythrulose derivatives such as **1** and dicyclohexylboron chloride, Chx_2BCl.[3] With this class of ketone substrates, the latter reagent has been found to promote the formation of *Z* enolates, in contrast with its previously documented behavior.[2,4] We have thus been able to isolate syn aldols **2** with high stereoselectivity (Scheme 1, diastereoisomeric ratio, dr > 95:5) in reactions with achiral aldehydes RCHO.[5]

In these aldol reactions, ketone **1** displays a marked enantiofacial preference whereby the *Re* face of its enolate attacks only the *Re* face of the aldehyde carbonyl. This finding raises the question of whether this facial bias is strong enough to overcome the inherent facial preferences of the carbonyl group in α-chiral aldehydes (double diastereoselection).[1a−e] This would be of great importance, as aldol reactions of this type should allow the synthesis of highly functionalized carbon fragments such as those present in macrolides, polyether antibiotics, and other naturally occurring, biologically relevant molecules.[6] With this in mind, then, we prepared several α-chiral aldehydes in both antipodal forms and investigated their reactions with the *Z* boron enolate of ketone **1**. The results of these reactions and the discussion thereof are the subject of the present paper.

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(3) (a) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677−683. (b) Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron*: *Asymmetry* **2002**, *13*, 2317−2327. (c) Murga, J.; Falomir, E.; González, F.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 9697−9707.

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(6) (a) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno. M., Eds.; Springer, Berlin, Germany, 1990. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114.

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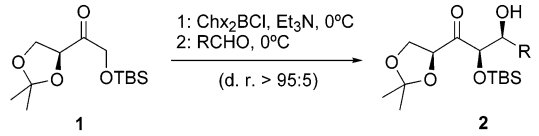
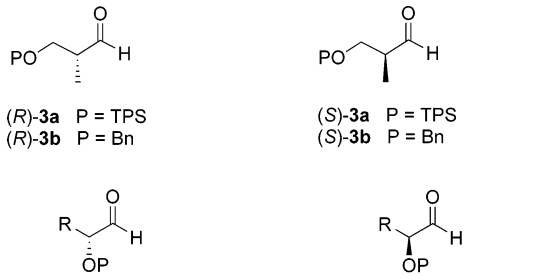
SCHEME 1. Aldol Additions of the Boron Enolate of 1 to Achiral Aldehydes



1 2

SCHEME 2. Chiral Aldehydes Used in This Study



(*R*)-**3a** P = TPS
(*R*)-**3b** P = Bn
(*S*)-**3a** P = TPS
(*S*)-**3b** P = Bn
(*R*)-**4a** R=Me P = TPS
(*R*)-**4b** R=Me P = Bn
(*R*)-**4c** R=CH_2OBn P = Bn
(*S*)-**4a** R=Me P = TPS
(*S*)-**4b** R=Me P = Bn
(*S*)-**4c** R=CH_2OBn P = Bn

Results and Discussion

For the purposes described in the preceding section, five enantiomerically pure aldehydes (**3**−**4**, Scheme 2) were prepared in both antipodal forms according to standard procedures.[7] The derivatives of 3-hydroxy-2-methylpropanal **3a**,**b** and lactaldehyde **4a**,**b** displayed two different protecting groups (*tert*-butyldiphenylsilyl, TPS; benzyl, Bn).[8a]

The aldol additions were performed under the conditions described in our previous papers.[3,8b,9] We started with the aldol reactions of ketone **1** and α-methyl aldehydes (*R*)-**3** and (*S*)-**3**. The results are shown in Scheme 3 and Table 1. The reactions with aldehydes (*S*)-**3** were comparatively rapid (total conversion in 5−6 h) and

SCHEME 3. Aldol Additions of the Boron Enolate of 1 to Aldehydes (*R*)-3 and (*S*)-3

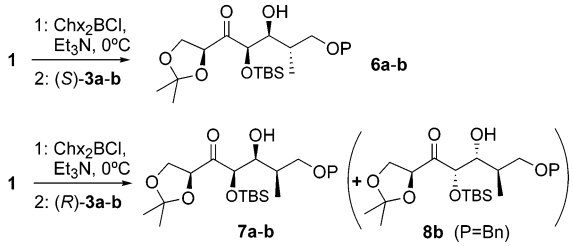


TABLE 1. Stereochemical Outcome of Aldol Additions of Ketone 1 with Aldehydes (*R*)- and (S)-3

entry	aldehyde	% yield	dr
1	(*S*)-**3a**	72	>95:5[a]
2	(*S*)-**3b**	80	>95:5[a]
3	(*R*)-**3a**	88	>95:5[b]
4	(*R*)-**3b**	60	∼80:20[c]

[a] The only diastereoisomer detected was **6a**/**6b**. [b] The only diastereoisomer detected was **7a**. [c] The major diastereoisomer was **7b**.

completely diastereoselective insofar as can be detected with NMR spectroscopic methods (dr > 95:5). Aldols **6** were thus formed via enolate attack to the *Re* aldehyde carbonyl face. For aldehydes (*R*)-**3**, the reactions were also completely diastereoselective when the protecting group P was silyl; the only stereoisomer detected was **7a**, again resulting from enolate attack to the *Re* aldehyde face. For P = benzyl, the minor aldol **8b** was also formed (dr ∼ 80:20). It may thus be concluded that the facial bias of this ketone enolate (attack to aldehyde *Re* faces) is strong enough to overcome the inherent facial preference of the carbonyl group in α-methyl aldehydes **3**, a fact that enhances the synthetic value of this methodology for the preparation of polypropionate fragments.[6]

These results can be understood within the same mechanistic framework presented in one of our recent publications.[3c] For achiral aldehydes we have proposed a cyclic six-membered transition state (TS) of the Zimmerman−Traxler type[12,13] where the *Z* boron enolate of **1** selectively attacks the aldehyde *Re* face to yield syn aldols **2** (Scheme 4), supporting this proposal with theoretical calculations. This TS not only explains the observed syn 1,2-induction (simple diastereoselection), related to the participation of a *Z* enolate, but also the syn 1,3-relationship (induced diastereoselection) with the preexisting stereogenic center.[1m] This 1,3-induction is due

(7) All chiral aldehydes were prepared according to literature procedures. Aldehydes (*R*)-**3a** and (*S*)-**3a**: Roush, W. R.; Palkowitz, A. D.; Palmer, M. A: J. *J. Org. Chem*. **1987**, *52*, 316−318. Aldehyde (*R*)-**3b**: Meyers, A. I.; Babiak, K. A,; Campbell, A. J.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015−5024. Aldehyde (*S*)-**3b**: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873−3888. Aldehydes (*R*)-**4a** and (*S*)-**4a**: Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem*. **1983**, *48*, 5180−5182. Aldehydes (*R*)-**4b** and (*S*)-**4b**: Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767−5790. Aldehyde (*R*)-**4c**: Ohgo, Y.; Yoshimura, J.; Kono, M.; Sato, T. *Bull. Chem. Soc. Jpn*. **1969**, *42*, 2957−2961. Aldehyde (*S*)-**4c** was prepared via Swern oxidation of (*R*)-1,2-di-*O*-benzylglycerol, obtained from L-ascorbic acid as described in: Mikkilineni, A. B.; Kumar, P.; Abushanab, E. *J. Org. Chem*. **1988**, *53*, 6005−6009.

(8) (a) The aldol reactions were also made with aldehydes bearing a TBS protecting group. The results were identical with those of TPS protected aldehydes. (b) The stereostructures of the aldol products were established with the aid of the chemical correlation methodology used in our previous papers[3] and, in one case, via X-diffraction analysis.[9] Aldol adducts were reduced in situ with $LiBH_4$ to yield the expected *syn*-1,3-diols.[10] These were subsequently converted into acetonides, which were then studied by means of NMR.[11] Standard manipulations of the protecting groups further permitted the preparation of other cyclic derivatives suitable for similar NMR studies. Descriptions of these chemical correlations and analytical data for the correlation products are given in the Supporting Information.

(9) The stereostructure of compound **6a** was established by means of an X-ray diffraction analysis. Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Center as Supporting Information with reference CCDC-210749. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax +44(0)-1223−336033 or e-mail deposit@ccdc.cam.ac.uk].

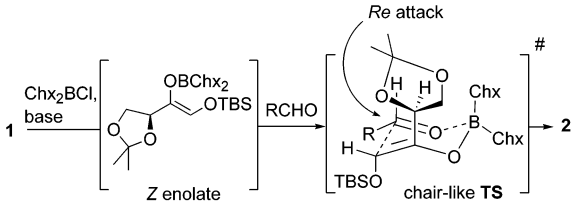
(10) Paterson, I.; Channon, J. A. *Tetrahedron Lett*. **1992**, *33*, 797−800.

(11) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res*. **1998**, *31*, 9−17.

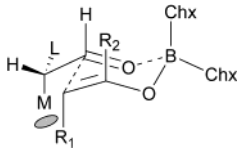
(12) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc*. **1957**, *79*, 1920−1923.

(13) For theoretical studies on boron aldol reactions, see: (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem*. **1990**, *55*, 481−493. (b) Goodman, J. M.; Kahn, S. D.; Paterson, I. *J. Org. Chem*. **1990**, *55*, 3295−3303. (c) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem*. **1990**, *55*, 3576−3581. (d) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471−3484. (e) Bernardi, F.; Robb, M. A.; Suzzi-Valli, G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem*. **1991**, *56*, 6472−6475. (f) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439−4458. (g) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685−696. See also ref 3c.

SCHEME 4. TS of the Aldol Addition of the Boron Enolate of 1 to Achiral Aldehydes



SCHEME 5. *syn*-Pentane Repulsion in the TS of the Aldol Addition of a *Z* Boron Enolate to an α-Chiral Aldehyde



to the π-facial bias of the chiral enolate, related in turn to two energetically favorable features of the depicted TS: the anticoplanar orientation of the C−$O_{enolate}$ and C_α−O bonds (minimized dipolar repulsion)[1e,14] and the spatial allocation of the dioxolane ring away from the bulky boron ligands (minimized steric crowding).[3c]

In the present situation, the chiral aldehydes under study display diastereotopic carbonyl faces, whose relative reactivity toward nucleophiles is dictated by a combination of electronic and steric effects, customarily summarized in the Felkin−Anh model and its later refinements (nucleophile attack anti-coplanar to either the bulkiest aldehyde C_α substituent or that having the lowest lying σ^*_{C-X} orbital), including the most favorable Bürgi−Dunitz trajectory (approach nearer to the smallest C_α substituent, usually an H atom).[15,16] For α-methyl aldehydes such as **3**, this model predicts the formation of the stereoisomer with a syn relationship between the vicinal hydroxy and methyl groups (as in **7**). When the Felkin−Anh model is applied to the doubly diastereoselective aldol additions of erythrulose boron enolates to aldehydes **3**, the essential features of the TS of Scheme 4 have to be combined with those of the model. In addition, another important feature is the avoidance of *syn*-pentane repulsive interactions between the OTBS group at the enolate C=C bond and one substituent at the stereogenic α-aldehyde carbon (Scheme 5 shows this for a dicyclohexylboron enolate; L and M are the large and medium substituents, respectively, at the aldehyde α-carbon atom). This feature, very often associated with aldol TSs involving *Z* enolates, is believed to be a dominant stereocontrol element that determines aldehyde π-facial selectivities in many situations.[1a,17,18]

Indeed, all these factors are present in the TSs depicted in Scheme 6. The reaction of aldehydes (*S*)-**3** yields solely stereoisomers **6**, in contrast to the results predicted by the Felkin−Anh model (such addition products are often called, somewhat confusingly, "anti-Felkin" stereoisomers). This can only be explained by assuming a TS such as **TS-2**, which is still of the Felkin−Anh-type (enolate attack anti to the bulky CH_2OP group), but in which the enolate approaches along an unfavorable Bürgi−Dunitz trajectory that pushes the nucleophile toward the methyl group, rather than to the hydrogen atom. This negative feature of the TS is probably of minor importance (see conclusions). The alternative, nonobserved attack of the enolate to the aldehyde *Si* face must take place, under the assumed avoidance of *syn*-pentane interactions, through the non-Anh rotamer **TS-1**,[19] which additionally shows an unfavorable steric crowding between the dioxolane ring and one of the bulky boron ligands. This latter feature can be alleviated by means of bond rotation, but only at the cost of increasing the dipolar repulsion between the C−$O_{enolate}$ and C_α−O bonds. It thus seems that in the present case, stereocontrol is exerted by the π-facial bias of the chiral enolate (preferred attack to aldehyde *Re* faces), which overrides any Felkin−Anh bias of the chiral aldehyde. This is not surprising as this bias is never strong (dr usually < 3:1) for α-methyl aldehydes.[1,16]

In contrast, the aldol reaction with aldehydes (*R*)-**3** led mainly to the Felkin stereoisomer **7**, with the same absolute configuration at the two newly formed stereogenic centers as was found in **6** (Scheme 6). This stereochemical outcome, again the result of preferred enolate attack to the aldehyde *Re* face, can be explained only if the aldol process occurs via the non-Anh rotamer **TS-4**. As mentioned above, this negative feature represents a minor factor and is less destabilizing than the *syn*-pentane interaction present in the true Felkin−Anh rotamer **TS-5**.[17] As in the previous case, enolate attack to the aldehyde *Si* face (**TS-3**) to yield the "anti-Felkin" stereoisomer **8** would suffer from steric crowding between the dioxolane ring and one of the *B*-cyclohexyl groups. It is worth mentioning here that stereoisomer **8** was formed as a minor component when P = benzyl but was not detected when P = silyl (Table 1). This indicates that some remote influence of the β-protecting group may be present here.[20]

We then investigated the aldol reactions of ketone **1** and α-oxygenated aldehydes (*R*)-**4** and (*S*)-**4**. The results

(14) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499−2506. For another example that shows the importance of dipole alignment in aldol TSs, see: Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12368−12369.

(15) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199−2204. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162.

(16) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Pergamon: New York, 1996; Chapters 4 and 5.

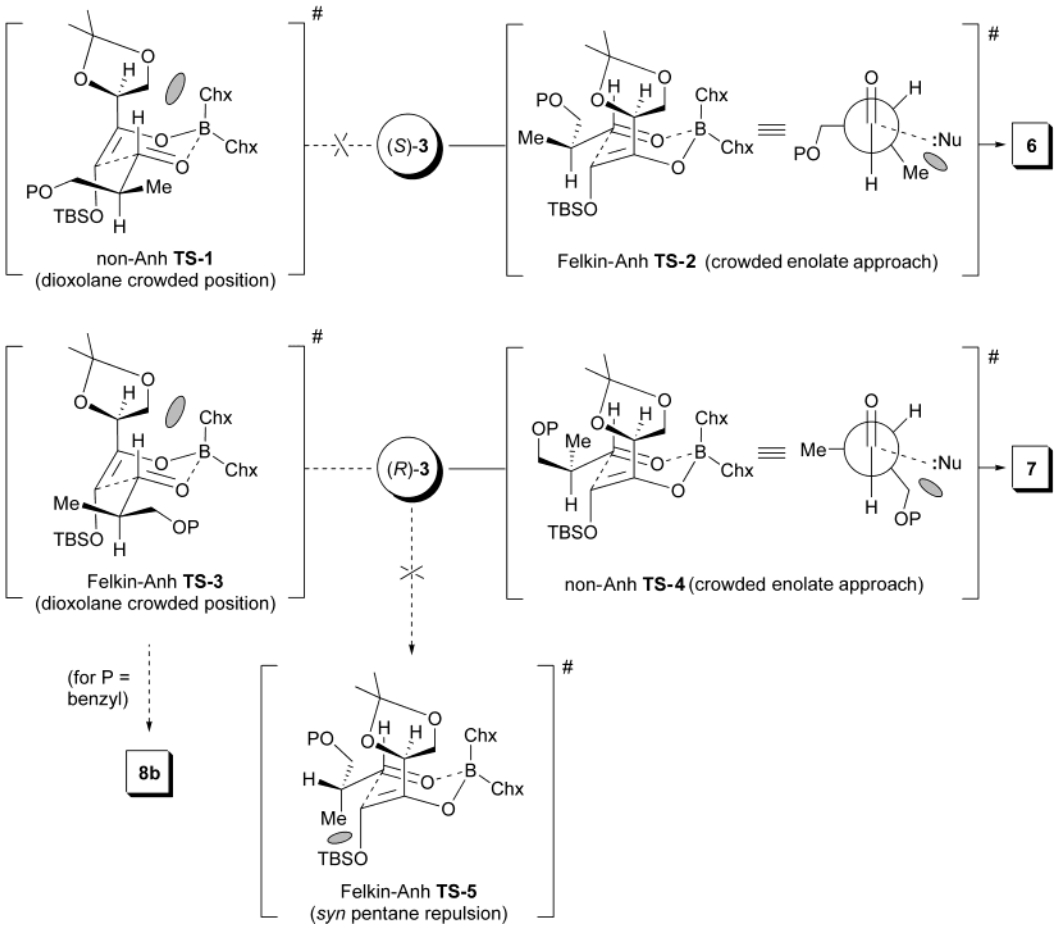
(17) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157.

(18) For a lucid analysis of the various factors which may influence the stereochemical outcome of aldol reactions, see: Lee, C. B.; Wu, Z.; Zhang, F.; Chappell, M. D.; Stachel, S. J.; Chou, T.-C.; Guan, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 5249−5259.

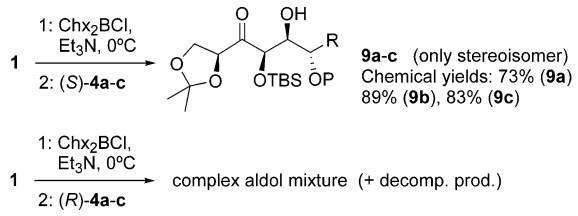
(19) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361. The "non-Anh" label refers to transition structures in which attack takes place anti to a substituent that neither has the lowest lying σ^*_{C-X} orbital (for α-heteroatom-substituted aldehydes) nor is the sterically bulkiest one (for aldehydes not bearing α-heteroatoms). See also ref 16.

(20) Effects of β-protecting groups at either the enolate or the aldehyde on the degree of diastereoselectivity of aldol reactions have been previously described. In some cases, such effects were attributed to various origins (chelation, conformational effects, etc.) while in others they remained unexplained. See, for example: (a) Paterson, I.; Bower, S.; Tillyer, R. D. *Tetrahedron Lett.* **1993**, *34*, 4393−4396. (b) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871−6874. (c) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459. (d) Martin, S. F.; Lee, W.-C.; Pacofsky, G. J.; Gist, R. P.; Mulhern, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 4674−4688. (e) Roush, W. R.; Dilley, G. J. *Tetrahedron Lett.* **1999**, *40*, 4955−4959. Sometimes, influence of still more remote protecting groups has been observed: Roush, W. R.; Bannister, T. D.; Wendt, M. D. *Tetrahedron Lett.* **1993**, *34*, 8387−8390.

SCHEME 6. Felkin−Anh TSs for Aldol Additions of the Boron Enolate of 1 to Aldehydes (*R*)-3 and (*S*)-3



SCHEME 7. Aldol Additions of the Boron Enolate of 1 to Aldehydes (*R*)-4 and (*S*)-4



are given in Scheme 7. The reactions with aldehydes (*S*)-**4** were highly diastereoselective and gave aldols **9** (dr > 95:5), once again through enolate attack to the aldehyde *Re* face. In contrast, the reactions of aldehydes (*R*)-**4** were extremely slow (less than 50% conversion after 12 h), yielding complex mixtures of 3−4 stereoisomeric aldols together with extensive decomposition.[21]

This last result was both unanticipated and disappointing, especially in view of the aforementioned findings and literature precedents.[22] For nucleophilic attacks to α-oxygenated aldehydes of general structure RCH(OP)-CHO, the Felkin−Anh model predicts the formation of the stereoisomer with an anti relationship between the vicinal hydroxy and OP groups, as observed in **9**. At first sight then, it seems that the π-facial bias of aldehydes (*S*)-**4** should work together with that of the chiral enolate (matched double diastereoselection) to react across a standard Felkin−Anh TS. However, this is not the case. As shown in Scheme 8, the Felkin−Anh **TS-6** suffers from steric crowding that arises from a *syn*-pentane interaction[1a,17] between the enolate OTBS group and the R group in the aldehyde moiety. If this repulsion is avoided by means of a C_α−CHO bond rotation, a non-Anh rotamer[19] results (**TS-7**) in which enolate attack takes place through a trajectory that is anti to the R group. Although we have commented above that this may be a factor of minor importance with α-alkyl aldehydes such as **3**, this is not necessarily so for α-heteroatom-substituted aldehydes.[22,23]

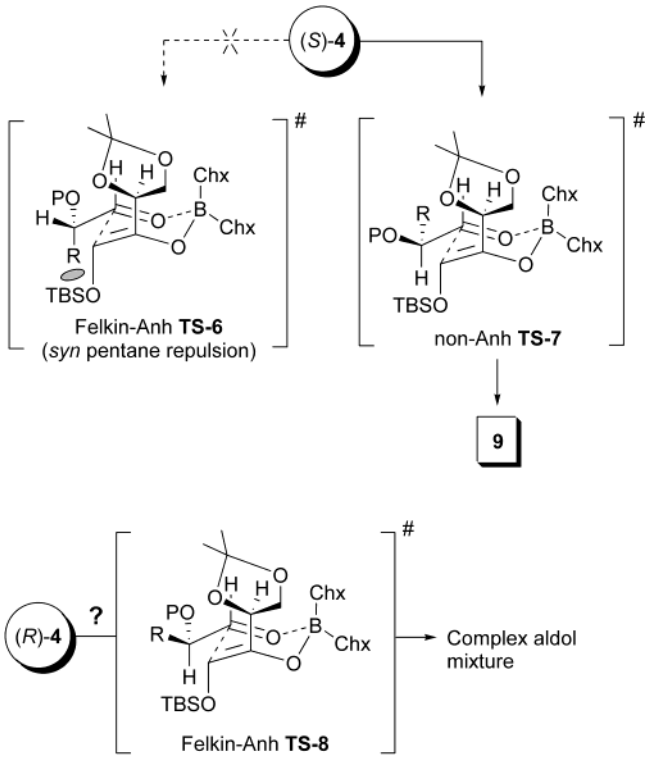
The reactions of aldehydes (*R*)-**4** are even more difficult to rationalize within the Felkin−Anh paradigm. Even if a well-matched Felkin−Anh TS can be proposed in this

(21) This was established upon examination of NMR data for the crude aldol mixtures. In view of this synthetically useless result, we did not attempt to isolate individual compounds.

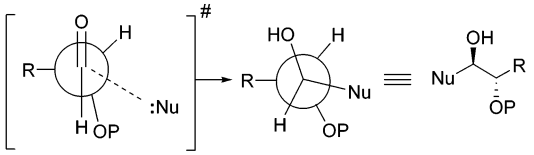
(22) Provided that chelation is not involved in the transition state, achiral enolates react with α-oxygenated aldehydes to yield predominantly, albeit with variable diastereoselectivity, the Felkin aldols. See refs 1 and 2. For more recent cases, see, for example: (a) Esteve, C.; Ferrerò, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 5079−5082. (b) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 843−853. However, it is worth noting that Felkin aldols have been found to predominate in some reactions where chelation is likely to occur: Grandel, R.; Kazmaier, U.; Rominger, F. *J. Org. Chem.* **1998**, *63*, 4524−4528.

(23) For nucleophilic additions to aldehydes bearing α-heteroatoms other than oxygen, see, for example: (a) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162 (α-amino aldehydes). (b) Enders, D.; Piva, O.; Burkamp, F. *Tetrahedron* **1996**, *52*, 2893−2908 (α-sulfenyl aldehydes). (c) Enders, D.; Adam, J.; Klein, D.; Otten, T. *Synlett* **2000**, 1371−1384 (α-silyl aldehydes). See also: Enders, D.; Burkamp, F. *Collect. Czech. Chem. Commun.* **2003**, *68*, 975−1006.

SCHEME 8. Felkin−Anh TSs for Aldol Additions of the Boron Enolate of 1 to Aldehydes (*R*)-4 and (*S*)-4



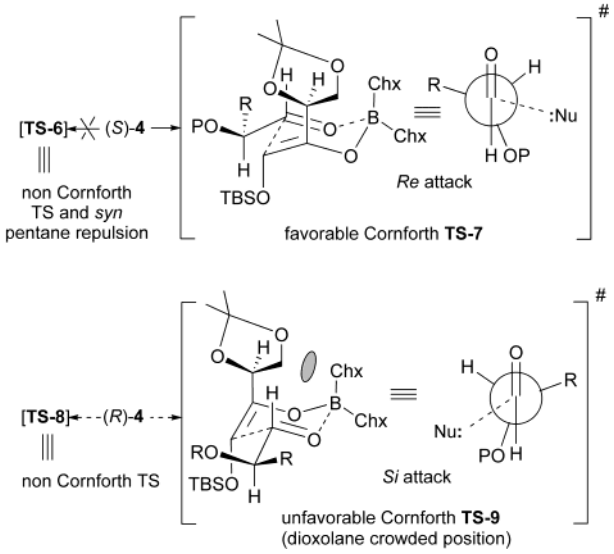
SCHEME 9. Cornforth TS of Nucleophilic Additions to α-Oxygenated Aldehydes



case with no unfavorable features (**TS-8**), the process turns out to be very slow in practice, as commented above, and is both nonstereoselective and accompanied by a great amount of decomposition. It thus appears that the standard Felkin−Anh model does not provide a satisfactory explanation for these kinds of aldol additions to α-oxygenated aldehydes **4**.

A very recent publication by Evans and co-workers called our attention to an alternative explanation.[24] To account for the stereochemical outcome of aldol additions to aldehydes of general formula R−CH(X)−CHO (X = electronegative heteroatom), these authors proposed a resurrection of the classic Cornforth model.[16,25] According to this model, nucleophilic additions to such carbonyl compounds take place in a conformation in which the C=O and C−X dipoles are at maximum opposition (anticoplanar, Scheme 9), thus minimizing dipolar repulsion. Nucleophilic attacks then take place from the sterically

SCHEME 10. Cornforth TSs for Aldol Additions of the Boron Enolate of 1 to Aldehydes (*R*)-4 and (*S*)-4



less crowded face of the C=O function. As shown in Scheme 9, this model predicts the formation of the same 1,2-anti configurated adduct for simple nucleophiles as the Felkin−Anh model. It is perhaps for this reason that the Cornforth model has to a great extent been supplanted by the theoretically more grounded Felkin−Anh paradigm, which has become the standard explanation for such processes. The contribution of Evans and co-workers,[24] which specifically deals with aldol reactions assumed to proceed through cyclic, chairlike transition states of the Zimmerman−Traxler type, is the first case where both models have been found to predict different outcomes. The aforementioned authors demonstrated that although the stereochemical outcome of aldol additions of the lithium and boron enolates of ethyl isopropyl ketone to a range of chiral, α-oxygenated aldehydes could not be conveniently accounted for with the Felkin−Anh model, they did receive a satisfactory explanation within the Cornforth paradigm.[26]

We thus applied Cornforth's model to the case of aldehydes **4**. A reexamination of the transition structures proposed above (Scheme 8) reveals that for reactions with (*S*)-**4**, only **TS-7** displays the geometry proposed by the Cornforth model (Scheme 10). In addition, this TS (a "non-Anh" TS in Heathcock's nomenclature[19]) not only shows none of the other previously mentioned destabilizing features, but also implies the formation of stereoisomers **9**, as experimentally observed. The alternative rotameric **TS-6** also predicts the formation of **9**, but shows an unfavorable *syn*-pentane repulsion. We can thus conclude that a Cornforth-type geometry is intrinsically more favorable in additions to α-heteroatom-substituted aldehydes than that predicated by the Felkin−Anh model. This conclusion seems to be bolstered by the results of the slow and nonstereoselective aldol additions with aldehydes (*R*)-**4**. That the seemingly ideal Felkin−

(24) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761−1765.

(25) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112−127. See also: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162−7166.

(26) The Cornforth model, as an alternative to the Felkin−Anh model, has already been proposed to explain the stereochemical outcome of additions of allylboranes to α-heteroatom-substituted aldehydes. See: Brinkmann, H.; Hoffmann, R. W. *Chem. Ber.* **1990**, *123*, 2395−2401 and references therein.

Anh **TS-8** is not able to determine the stereochemical outcome of the process can be explained if we assume that its deviation from the Cornforth geometry increases its energy content to such an extent as to make this pathway very slow. Attempts to achieve a Cornforth-type geometry through C_α−CHO bond rotation would only cause a *syn*-pentane repulsion between the OTBS and the R group (cf. Scheme 8, TS not depicted). Furthermore, enolate attack to the *Si* aldehyde face through a Cornforth geometry would lead to **TS-9** (Scheme 10), with the same type of steric crowding observed in both **TS-1** and **TS-3**. Since this pathway is also expected to be slow, this explains not only the overall lack of stereoselectivity of this aldol process, but also its sluggishness and resulting proclivity to decomposition.

Conclusions

The Cornforth model has now been applied for the first time to a doubly diastereoselective aldol reaction.[27,28] We can summarize the results disclosed above within a unified general concept in which several factors must be taken into account to predict the stereochemical outcome of boron aldol reactions of ketones such as **1** with α-chiral aldehydes. Cyclic transition states of the Zimmerman−Traxler type are assumed with no chelation issues involved. In order of energetically decreasing importance, these factors are the following:

(a) For α-heteroatom-substituted aldehydes, Cornforth TSs (**TS-7**) are markedly preferred.

(b) *syn*-Pentane repulsions between the OTBS group and one aldehyde non-hydrogen α-substituent are energetically important interactions (**TS-5**, **TS-6**) that must be avoided through C−C bond rotation.

(c) Steric crowding between the dioxolane ring and one B-cyclohexyl group arises when attack takes place from the enolate *Si* face (**TS-1**, **TS-3**, **TS-9**). Suitable C−C bond rotation relieves this interaction but simultaneously increases the dipolar repulsion between the $C-O_{enolate}$ and C_α−O bonds.

(d) The Felkin−Anh π-facial bias is not very strong for aldehydes bearing only carbon α-substituents. In this case, stereocontrol is frequently exerted by the chiral enolate rather than by the aldehyde. This may give rise to rotameric TSs in which a steric repulsion develops between the incoming enolate and one aldehyde non-hydrogen α-substituent due to approach along an unfavorable Bürgi−Dunitz trajectory (**TS-2**, **TS-4**).

Taking all these factors into consideration, we propose that α-methyl aldehydes (*S*)-**3** react with the boron enolate of **1** to yield aldols **6** selectively through **TS-2** whereas aldehydes (*R*)-**3** generate mainly or exclusively aldols **7** through **TS-4** (Scheme 6), in both cases due to control by the chiral enolate. The α-oxygenated aldehydes (*S*)-**4** react to yield aldols **9** exclusively through the Cornforth transition state **TS-7** (Scheme 10). Their enantiomers (*R*)-**3** react sluggishly and nonstereoselectively because the energy of the Cornforth-type **TS-9** (Scheme 10) is increased by factor (c). The energy of the alternative **TS-8** is also increased by its deviation from the Cornforth geometry, i.e. factor (a) prevails. In view of these and of the recent results described by Evans and co-workers,[24] it seems that the Cornforth model will have to be revitalized to explain the stereochemical outcome of aldol additions to α-heteroatom-substituted carbonyl groups.[26−28]

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Note Added after ASAP Posting. Page S7 of the Supporting Information file posted ASAP October 7, 2003, contained errors. A corrected Supporting Information file was posted October 9, 2003.

Supporting Information Available: Description of experimental procedures; tabulated physical and spectral data of aldols **6a**, **6b**, **7a**, **9a**, **9b**, and **9c**; description of the chemical correlations used to establish the configurations of the aldols and spectral data of several selected correlation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Doubly diastereoselective aldol reactions of chiral enolates with chiral α-oxygenated aldehydes are not extensively documented in the literature. Matched and mismatched processes have been reported, with the full range from total stereocontrol by the enolate to complete dominance of the aldehyde being observed. See refs 1 and 2 and, for more recent cases: (a) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318−333. (b) Kobayashi, S.; Furuta, T. *Tetrahedron* **1998**, *54*, 10275−10294. (c) Esteve, C.; Ferrerò, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 5083−5086. (d) Nicolaou, K. C.; Pihko, P. M.; Diedrichs, N.; Zou, N.; Bernal, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 1262−1265. (e) Forsyth, C. J.; Hao, J.; Aiguade, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3663−3667.

(28) Excluded from this discussion are chiral enolates in which the chirality resides in the ligands bound to the heteroatom. In these cases, stereocontrol by the chiral auxiliary is usually observed. See, for example: Gennari, C.; Pain, G.; Moresca, D. *J. Chem. Org.* **1995**, *60*, 6248−6249.