ORGANIC LETTERS

2006
Vol. 8, No. 20
4629−4632

# Chiral Boron Enolate Aldol Additions to Chiral Aldehydes†

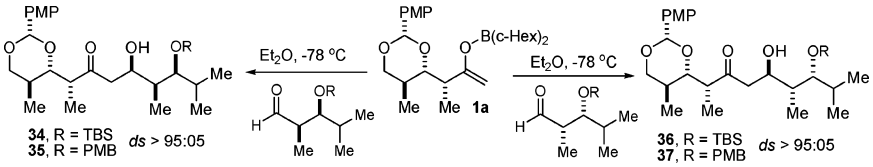
**Luiz C. Dias* and Andrea M. Aguilar**

*Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, CEP 13084-971, Campinas SP, Brazil*

*ldias@iqm.unicamp.br*

**Received July 28, 2006**

## ABSTRACT




**We have examined the double-diastereodifferentiating aldol addition reactions of chiral enolborinate 1a with chiral aldehydes leading to the corresponding aldol adducts with excellent levels of 1,5-*anti* diastereoselection.**

The aldol reaction is one of the most powerful transformations for the creation of the 1,3-dioxygen relationships in organic molecules.[1] As the resulting aldol adducts resemble the 1,3-polyol fragments, this reaction has been applied for the synthesis of a wide variety of natural products with biological and pharmacological significance.

The incorporation of convergence into the construction of complex polyketides requires that large fragments must be joined together at some point in the synthesis. The aldol reaction provides an attractive method for such a convergent assembly.[2] The key aldol assemblage reactions that join large fragments with high and predictable levels of stereocontrol still lack the guidance of refined models and reaction methodology.[3] The use of boron enolates derived from α-methyl and α-methyl-β-alkoxy methyl ketones for asymmetric aldol reactions usually give low levels of diastereoselectivity when compared with the high selectivities observed with the use of boron enolates prepared from ethyl ketones.[4,5] Usually, reagent control using chiral ligands on boron is required to obtain useful levels of asymmetric induction in the addition of boron enolates of α-methyl ketones to achiral aldehydes.[4−6] To gain insight into the principles that dictate diastereoselectivity in double-stereodifferentiating[7,8] aldol reactions, we have investigated the use of chiral methyl ketone **1** in boron-mediated aldol reactions with chiral aldehydes **2**−**12** (Scheme 1).[9] These substrates were chosen to be representative of the complex fragments that might be coupled in polyacetate and polypropionate-

* To whom correspondence should be addressed. Fax: +55-019-3788-3023.

† This paper is dedicated to Prof. Angelo da Cunha Pinto (UFRJ) for his outstanding contributions to the field of organic synthesis in Brazil.

(1) Reviews of the aldol reaction: (a) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (b) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317. (c) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 181. (d) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 239. (e) Paterson, I. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 301. (f) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(2) (a) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581. (b) Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893.

(3) Denmark, S. E.; Fujimori, S.; Pham, S. M. *J. Org. Chem.* **2005**, *70*, 10823.

(4) (a) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997. (b) Paterson, I.; Florence, G. J. *Tetrahedron Lett.* **2000**, *41*, 6935.

(5) An exception is the aldol reaction of β-alkoxy methyl ketones which proceed with high 1,5-stereoinduction under substrate control: (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *29*, 8671. (c) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew Chem., Int. Ed. Engl.* **1994**, *33*, 673. (d) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275. (e) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (f) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187.

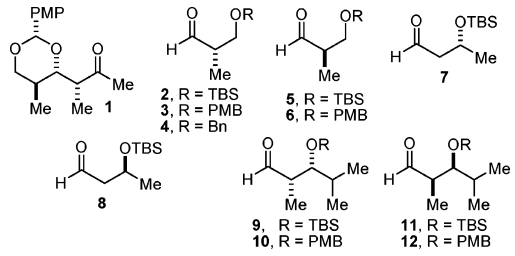
(6) For aldol reactions of chiral methyl ketone trichlorosilyl enolates under base catalysis see: Denmark, S. E.; Fujimori, S. *Synlett* **2001**, 1024.

(7) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953. (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10. (d) Seebach, D.; Prelog, V. *Angew. Chem.* **1982**, *21*, 654.

(8) (a) Izumi, Y.; Tai, A. in *Stereodifferentiating Reactions*, Academic Press: New York, 1977. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. K.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

10.1021/ol0618712 CCC: $33.50 
**Published on Web 08/29/2006**

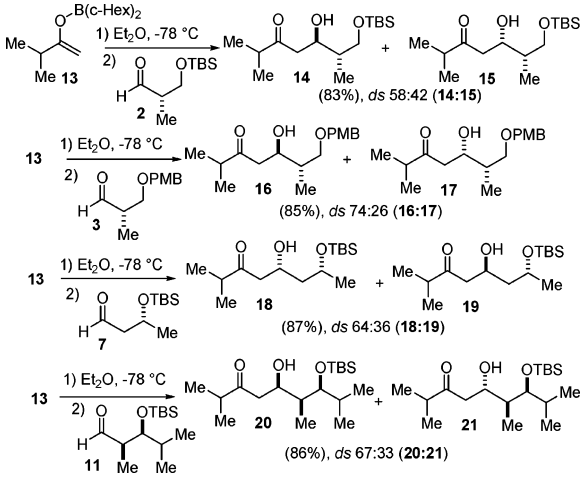
**Scheme 1**




derived aldol-type reactions. Aldehydes with *tert*-butyldimethylsilyl (TBS), benzyl (Bn) and *p*-methoxybenzyl (PMB) protecting groups were employed to evaluate the potential steric and electronic impact of the protecting group.[2d,10] Aldehydes **2**−**6** were prepared from (2*S*)- and (2*R*)-methyl 3-hydroxymethylpropionate and aldehydes **7** and **8** were prepared from (3*S*)- and (3*R*)-1,3-butanediol.[11] The 1,2-*syn* (**9**−**12**) aldehydes were easily prepared by using *syn*-selective aldol reactions as the key steps.[12]

To successfully predict the viability of double stereodifferentiating reactions, the key stereocontrol elements in each of the chiral reacting partners must be identified.[13] To check the facial selectivities of aldehydes **2**, **3**, **7**, and **11**, we reacted them with achiral boron enolate **13** in $Et_2O$ at low temperatures (Scheme 2).[13]

**Scheme 2**



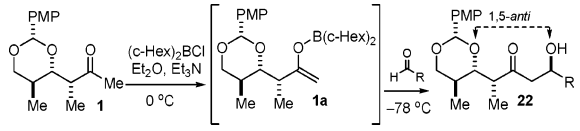

These reactions were characterized by poor levels of diastereoselectivity. The achiral boron enolate **13** reacted with chiral α-methyl aldehyde (*S*)-**2** in $Et_2O$ at −78 °C to give the corresponding 1,2-*anti* product **14** as the major product in good yield but with only 58:42 diastereoselectivity (Scheme 2).[13,16]

The boron enolate addition to aldehyde (*S*)-**3** containing a PMB protecting group gave a mixture of aldol adducts **16** and **17** in a 74:26 ratio favoring the *anti*-Felkin aldol adduct **16**.[13−16] The stereoinduction observed in these reactions shows that the reaction weakly favored the *anti*-Felkin product, indicating that there is a mild inherent selectivity toward the 1,2-*anti* product by the resident α-stereogenic center, especially with a PMB protecting group at the aldehyde *β*-oxygen.[13−16]

The boron enolate **13** reacted with chiral *β*-alkoxy aldehyde (*R*)-**7** in $Et_2O$ at −78 °C to give a mixture of aldol adducts **18**/**19** in a 64:36 ratio, respectively (Scheme 2).[13a] We next examined the stereochemical impact of both α and *β*-aldehyde substituents with chiral *syn*-disubstituted α-methyl-*β*-alkoxy aldehyde **11**. Boron enolate **13** reacted with chiral *syn*-α,*β*-disubstituted aldehyde **11** to give the corresponding 1,2-*syn*-1,3-*syn* product **20** in 86% yield, with a small stereoinduction (67:33 diastereoselectivity) resulting from the stereogenic centers (Scheme 2).[13−16] This example shows that under these conditions a 1,2-*syn* aldehyde has a small preference to give the product of Felkin addition as well as 1,3-*syn* addition. The reactions of **13** with both **7** and **11** show that 1,3-asymmetric induction imposes an intrinsic facial bias on the carbonyl that results in the formation of a 1,3-*syn*-dioxygen relationship.[13a] The results observed with 1,2-*syn* aldehyde are in accordance with previous observations made by Roush et al. (see **18:19**, Scheme 2).[16] The intrinsic facial selectivity of the boron enolate **1a** generated from methyl ketone **1** has been investigated before in our laboratories.[9] For this purpose, we reacted **1a** with achiral aromatic, olefinic, and aliphatic aldehydes.

We were delighted to find that this reaction led to the formation of 1,5-*anti* products **22** as the major isomers (up to >95:5 diastereoselectivity) (Scheme 3).[9] These studies

**Scheme 3**




showed a remarkable influence of the resident *β*-alkoxy stereocenter on the stereochemical course of the aldol reactions.[9,17]

(9) Dias, L. C.; Baú, R. Z.; de Sousa, M. A.; Zuckerman-Schpector, J. *Org. Lett.* **2002**, *4*, 4325.

(10) For a discussion of the coordinating abilities of various ether substituents, see: (a) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (b) Chen, X. N.; Hortellano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130. (c) Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055. (d) Schreiber, S. L.; Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.

(11) (a) Dias, L. C.; Steil, L. J. *Tetrahedron Lett.* **2004**, *45*, 8835. (b) Dias, L. C.; dos Santos, D. R.; Steil, L. J. *Tetrahedron Lett.* **2003**, *44*, 6861.

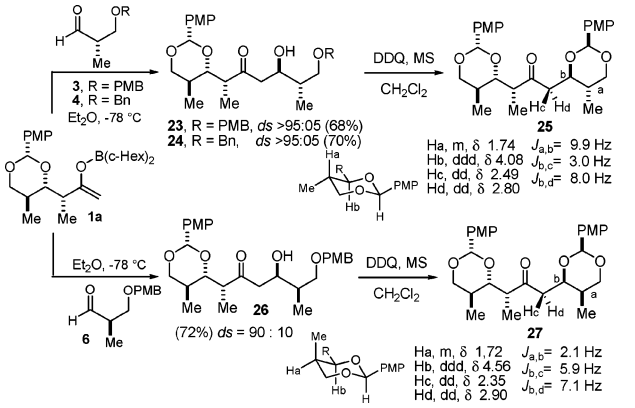
(12) (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675. (d) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(13) For similar investigations, see: (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322. (b) Gustin, D. J.; VanNieuwenhze, M. D.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443.

(14) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (c) We use the "Felkin" descriptor to refer to the diastereomer predicted by the Felkin-Ahn paradigm. The "*anti*-Felkin" descriptor refers to diastereomers not predicted by this transition state model.

At this point we initiated a double-stereodifferentiating study.[7,8] Boron enolate **1a** reacted with aldehyde (*S*)-**3** (R = PMB) to give *anti*-Felkin product **23** as the major product, with excellent diastereoselectivities (ds >95:5) (Scheme 4).

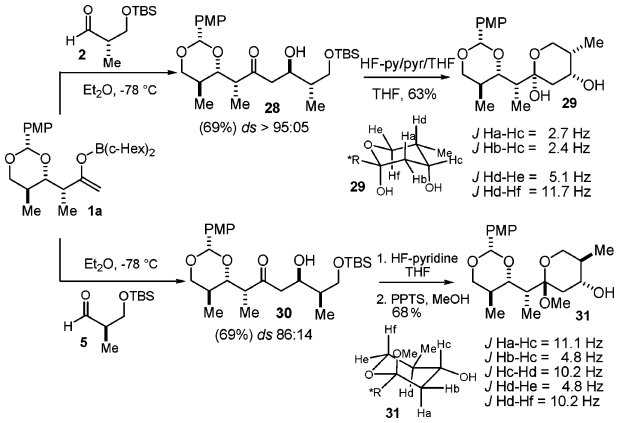
**Scheme 4**




Reaction of aldehyde (*S*)-**4** (R = Bn) led to similar results in terms of yields and diastereoselectivities.[15,16] The facial bias of chiral boron enolate **1a** is dominated by the $\beta$-alkoxy stereocenter and tends to give the 1,5-*anti* isomer.[9] As the facial bias of these particular aldehydes is for the *anti*-Felkin product, there is an enhancement of the 1,5-*anti* selectivity because the sense of stereoinduction by the boron enolate and that of the aldehyde are the same. These two examples represent "matched cases" of double stereodifferentiation.[7,8] The aldol adducts **23** and **24** appeared ideally suited for stereochemical analysis by using the very simple method for assigning the relative stereochemistry of $\beta$-hydroxy ketones reported in 2002 by Roush and co-workers.[16,18] Recently, we reported a refinement of Roush's model, in which we show that $^1$H HMR ABX pattern analysis is not applicable to $\beta$-hydroxy ketones (e.g., aldols) derived from aldehydes lacking $\beta$-branches.[19] The relative stereochemistry for aldol adduct **23** was then unambiguously established after conversion to the corresponding benzylidene acetal **25** by treatment of **23** with DDQ in $CH_2Cl_2$ (Scheme 4).[20] Analysis of the $^1$H NMR coupling constants, specifically $J = 9.9$ Hz, proved that Ha and Hb were both axial in **25** (Scheme 4). This indicated that benzylidene acetal **25** derived from an *anti*-Felkin aldol product. On the other hand, the use of enantiomeric aldehyde **6** led to the formation of aldol adduct **26** as the major isomer with 90:10 diastereoselectivity (Felkin addition). This aldehyde gives rise to lower selectivity because the stereoinduction caused by the aldehyde is opposite to the effect of the $\beta$-alkoxy stereocenter in the boron enolate **1a**. Apparently, this represents a "partially matched case" of double stereodifferentiation, as aldehyde **6** has a small preference for *anti*-Felkin addition. The relative stereochemistry of aldol **26** was determined after conversion to the *p*-methoxybenzylidene acetal **27** by DDQ oxidation of the PMB ether.[21] The coupling constant measured between Ha−Hb ($J = 2.1$ Hz) in **27** confirmed the Felkin stereochemistry for aldol **26**.

With enantiomeric aldehydes **2** and **5** we observed the same trend and the overall diastereoselection of the process was again controlled by the strong facial bias of the boron enolate to give the 1,5-*anti* product (Scheme 5).

**Scheme 5**




Addition of the chiral boron enolate **1a** to aldehyde (*S*)-**2** led to aldol adduct **28** as the major isomer, with >95:05 diastereoselectivity (Scheme 5). As the facial bias of the aldehyde **2** was to give the 1,2-*anti* product, we expected a matched case and high levels of diastereoselectivity in the reaction of **1a** with (*S*)-**2**, which was in fact observed. The relative stereochemistry for aldol adduct **28** was determined after conversion to the corresponding acetal **29** (63%) by treatment of **28** with HF·pyr in THF (Scheme 5). Analysis of the $^1$H NMR coupling constants, specifically $J_{Ha-Hc} = 2.7$ Hz, $J_{Hb-Hc} = 2.4$ Hz, $J_{Hd-He} = 5.1$ Hz, and $J_{Hd-Hf} = 11.7$ Hz, proved that Ha, Hd, and Hf were all axial in **29**. This indicated that acetal **29** derived from a 1,5-*anti*-Felkin aldol product.

Addition of the boron enolate **1a** to the enantiomeric aldehyde (*R*)-**5** led to the formation of aldol adduct **30** as the major isomer with 86:14 diastereoselectivity (Felkin product). Again, this represents a "partially matched case" of double stereodifferentiation, as aldehyde **5** has a small preference for *anti*-Felkin addition. The relative stereochemistry for aldol adduct **30** was established after conversion to acetal **31** (68%, two steps) by treatment of **30** with HF·pyr followed by PPTS in MeOH (Scheme 5). Analysis of the

(15) (a) The ratios were determined by $^1$H and $^{13}$C NMR spectroscopic analysis of the unpurified product mixture; (b) All of the percentage values represent data obtained from at least three individual trials.

(16) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; VanNieuwenhze, M. S.; Gustin, D. J.; Dilley, G. J.; Lane, G. C.; Scheidt, K. A.; Smith, W. J., III. *J. Org. Chem.* **2002**, *67*, 4284.

(17) Arefolov, A.; Panek. J. S. *Org. Lett.* **2002**, *4*, 2397.

(18) Liu, C. M.; Smith, W. J., III; Gustin, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 5770.

(19) Dias, L. C.; Aguilar, A. M.; Salles, A. G., Jr.; Steil. L. J.; Roush, W. R. *J. Org. Chem.* **2005**, *70*, 10461.

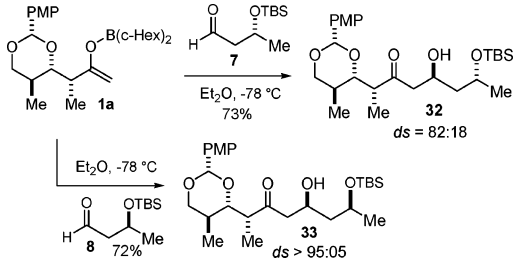
(20) Having confirmed the relative relationship between boron enolate-derived stereogenic centers, the absolute stereochemistry of the newly formed hydroxyl substituent was determined by ascertaining its relationship to the known stereocenter originating from the aldehydes.

(21) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

$^1$H NMR coupling constants, specifically $J_{Ha-Hc} = 11.1$ Hz, $J_{Hb-Hc} = 4.8$ Hz, $J_{Hc-Hd} = 10.2$ Hz, $J_{Hd-He} = 4.8$ Hz, and $J_{Hd-Hf} = 10.2$ Hz, proved that acetal **31** derives from a Felkin aldol product.

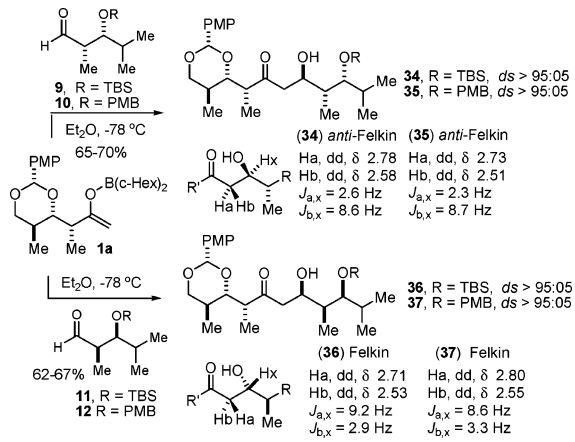
The next step involved the use of aldehyde (*R*)-**7**, and the addition of boron enolate **1a** proceeded smoothly providing aldol **32** with 82:18 diastereoselectivity. Chiral boron enolate **1a** reacted with aldehyde (*S*)-**8** to give *β*-hydroxy ketone **33** with >95:05 diastereoselectivity (Scheme 6).

**Scheme 6**




The stereochemical outcome of these reactions seems to be controlled mainly by the resident *β*-alkoxy stereogenic center of boron enolate, although the result with aldehyde **7** was interesting as it shows a mismatched situation. We next examined the addition of chiral boron enolate **1a** to chiral *syn*-disubstituted α-methyl-*β*-alkoxy aldehydes **9**−**12** (Scheme 7). Chiral boron enolate **1a** reacted with aldehydes **9** and **10**

**Scheme 7**




to give a >95:05 ratio favoring the *anti*-Felkin isomers **34** and **35**, respectively (Scheme 7). In this latter case, the *β*-alkoxy stereocenter in the boron enolate (propensity for 1,5-*anti* addition) exerts a dominant influence on aldehyde facial selectivity, by overriding the low intrinsic bias imposed by the α and *β*-stereocenters in the aldehyde, to give the 1,2-*syn*-1,3-*syn* products. Chiral aldehydes **11** and **12** were next employed in anticipation that their preference for forming adducts **36** and **37**, combined with the same intrinsic preference of the substrate **1a**, would lead to high selectivities. Indeed, this was found to be the case. The reaction of chiral boron enolate **1a** with aldehyde **11** gave aldol **36** as the major isomer (Felkin addition, matched case) (Scheme 7). Under the same conditions as described before, chiral boron enolate **1a** reacted with aldehyde **12** to give isomer **37** with >95:05 diastereoselectivity (Scheme 7). The stereochemical assignment of compounds **34**−**37** was determined by their $^1$H NMR analysis, according to Roush's model.[16,18,19] This method involves analysis of the ABX system for the methylene unit α to the carbonyl group in the $^1$H NMR spectra of the *β*-hydroxy ketones.[16,18,19] The $^1$H NMR spectra (measured in $C_6D_6$) of aldol adduct **34** (or *anti*-Felkin) exhibit a characteristic doublet of doublet for Ha (2.78 ppm) with a small $J_{a,x}$ (2.6 Hz) downfield of the resonance for Hb (2.58 ppm), which shows a large $J_{b,x}$ (8.6 Hz). Similar results were observed for aldol adduct **35**. For Felkin aldol adduct **36** (R = TBS), the $^1$H NMR displays a downfield resonance for Ha (2.71 ppm) with a large $J_{a,x}$ (9.2 Hz), and a higher resonance for Hb (2.53 ppm), with a small $J_{b,x}$ (2.9 Hz).

For Felkin aldol adduct **37** (R = PMB), the $^1$H NMR displays a downfield resonance for Ha (2.80 ppm) with a large $J_{a,x}$ (8.6 Hz), and a higher resonance for Hb (2.55 ppm), with a small $J_{b,x}$ (3.3 Hz). These results are consistent with the aldols adopting internally hydrogen bonded conformations, as proposed by Roush and co-workers.[16,18,19]

We have described here that high levels of substrate-based, 1,5-*anti*-stereocontrol could be achieved in the boron-mediated aldol reactions of α-methyl-*β*-alkoxy methyl ketones with chiral aldehydes, leading to both Felkin and anti-Felkin aldol addition products. The examples presented in this work show that the levels of facial selection are independent of the absolute stereochemistries of the aldehydes although dependent on the absolute stereochemistry of the chiral boron enolate. The strong internal stereoinduction of chiral enolate **1a** dominated the overall stereochemical outcome of these aldol addition reactions. These stereoselective aldol reactions should prove valuable in polyketide synthesis and we believe they will allow synthetic chemists to confidently pursue more aggressive convergent approaches toward assembling complex polyacetate arrays in the synthesis of natural products. Further studies in this direction are underway to explore their generality and origin and will be described in due course.[22,23]

**Acknowledgment.** We are grateful to FAPESP and CNPq for financial support. We thank also Prof. Carol H. Collins (Institute of Chemistry, UNICAMP) for helpful suggestions about English grammar and style.

**Supporting Information Available:** Product characterization for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0618712

(22) Several computational studies indicate that chairlike and boatlike transiton states in methyl ketone aldol reactions are relatively close in energy: (a) Li, Y.; Paddow-Row: M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 1535. (b) Bernardi, F.; Robb, M. A.; Suzzi-Vall, G.; Tagliavini, E.; Trombin, C.; Umani-Ronchi, A. *J. Org. Chem.* **1991**, *56*, 6472.

(23) For papers dealing with the origins of remote asymmetric induction in these reactions, see: (a) Paton, R. S.; Goodman, J. M. *Org. Lett.* **2006**, *8*, 4299−4302. (b) Stocker, B. L.; Teesdale-Spittle, P.; Hoberg, J. O. *Eur. J. Org. Chem.* **2004**, 330.