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High 1,5-Anti Stereoinduction in Boron-Mediated Aldol Reactions of Methyl Ketones†

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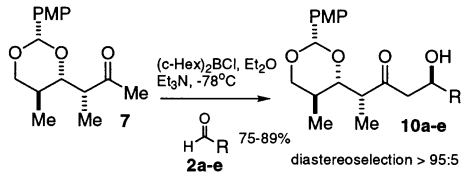
ABSTRACT



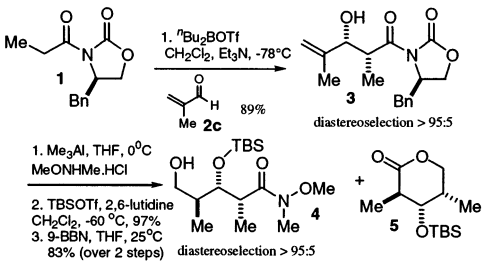
We report herein a very efficient and synthetically useful 1,4-anti-1,5-anti boron-mediated aldol reaction of a chiral α-methyl-β-alkoxy methyl ketone with achiral aldehydes.

The use of enolborinates derived from α-methyl and α-methyl-β-alkoxy methyl ketones for asymmetric aldol reactions generally gives low levels of stereoselectivities when compared with the high selectivities observed with boron enolates of the ethyl ketones.[1,2] 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 methyl ketones to achiral aldehydes, particularly the use of (+)- and (−)-diisopinocampheyboron chlorides (Ipc_2BCl), as described by Paterson et al.[3−5]

We report here that high levels of substrate-based, 1,5-stereocontrol can be achieved in the boron-mediated aldol reactions of α-methyl-β-alkoxy methyl ketones by the proper choice of protecting groups.

Our approach began with the known acyloxazolidinone **1**, which was most conveniently prepared by acylation of the corresponding (*S*)-oxazolidinone (Scheme 1).[6] Asymmetric aldol addition of the boron enolate derived from oxazolidinone **1** with inexpensive methacrolein **2c** gave the aldol adduct **3** as a crystalline solid (mp 57−59 °C) in 89% yield and >95:5 diastereoselectivity (Scheme 1).[7] Exchange of the oxazolidinone auxiliary in *syn*-aldol **3** with *N,O*-

Scheme 1



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† This paper is dedicated to the Brazilian Chemical Society (SBQ).

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§ UFSCar.

(1) For a review on asymmetric aldol reactions using boron enolates, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

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

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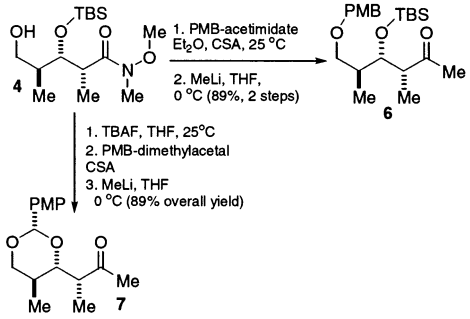
dimethylhydroxylamine generated the Weinreb amide, whose purification was facilitated by isolation of the recyclable oxazolidinone chiral auxiliary (92%) by efficient crystallization from the reaction mixture.[8] Protection of the OH-function as its TBS ether, followed by selective hydroboration with 9-BBN in THF, cleanly provided the primary alcohol **4** (>95:5 diastereoselection) in 83% yield over the two-step sequence, together with small amounts of lactone **5** (~5%).[9]

After a two-step sequence involving protection of the primary alcohol functionality in **4** with PMB−acetimidate in the presence of catalytic amounts of CSA, followed by reaction with methyllithium at 0 °C, methyl ketone **6** was isolated in 89% overall yield (Scheme 2). Amide **4** was

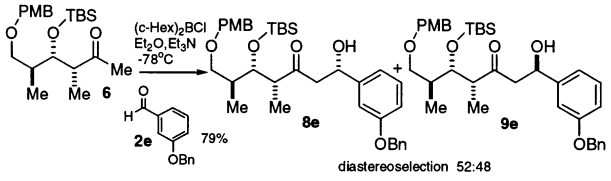
Scheme 2



smoothly converted to methyl ketone **7** after treatment with TBAF in THF and protection of the 1,3-diol as a *p*-methoxybenzylidene acetal followed by reaction with methyllithium at 0 °C (89% overall yeld).

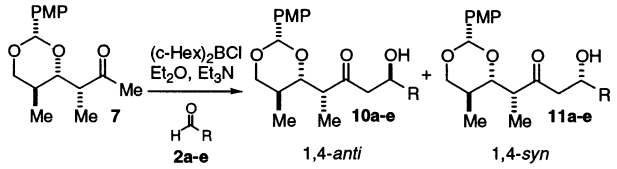
Initially, the aldol reaction of methyl ketone **6**, containing both TBS- and PMB- protected hydroxyl groups, with aldehyde **2e** was explored using (c-Hex)$_2$BCl/Et$_3$N in Et$_2$O for enolization (Scheme 3). As expected, the use of the boron

Scheme 3



enolate formed from methyl ketone **6** showed only modest 1,4-stereoinduction upon addition to aldehyde **2e** to give a

Scheme 4



52:48 mixture of 1,4-syn and 1,4-anti aldol adducts **8e** and **9e**, respectively, in 79% yield.[4]

We next examined the use of methyl ketone **7**. As shown in Scheme 4 and Table 1, these boron-mediated aldol

Table 1. Aldol Reactions of Methyl Ketone **7** with RCHO **2a**−**e**

entry	aldehyde (R)	(c-Hex)$_2$BCl anti:syn[a]	yield (%)[b]
1	**2a**, Me	>95:05	89
2	**2b**, ^{i}Pr	>95:05	77
3	**2c**, C(Me)=CH$_2$	>95:05	75
4	**2d**, Ph	>95:05	77
5	**2e**, *m*-C$_6$H$_4$OBn	>95:05	82

[a] Ratio determined by ^{1}H and ^{13}C NMR analyses of the diastereomeric mixture of adducts. [b] Isolated yields after SiO$_2$ flash chromatography.

reactions were found to proceed with an unexpectedly high degree of remote stereoinduction (1,5-anti:1,5-syn > 95:5).[10] In all cases, the major 1,5-anti adduct **10a**−**e**, corresponding to *re*-face attack on the aldehyde, was obtained with good selectivities using (c-Hex)$_2$BCl.

The 1,5-anti induction obtained in these boron-mediated aldol reactions did not vary significantly with the size of the aldehyde R group, and high levels of stereocontrol were observed even with acetaldehyde (entry 1). These results indicate that the nature of the protecting groups is critical in determining the level of induction and that a cyclic protection of the 1,3-diol proved to be essential for high levels of aldol stereocontrol.

The use of *n*-Bu$_2$BOTf led to similar results in terms of diastereoselectivites, although the yields were lower when compared to the same reactions with (c-Hex)$_2$BCl.

(3) An exception is the aldol reaction of β-alkoxy methyl ketones, which proceeds 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) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187. (d) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (e) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew Chem. Int. Ed. Engl.* **1994**, *33*, 673.

(4) For studies on the synthesis of bafilomycin A using aldol reactions of methyl ketones, see: Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275.

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

(6) (a) Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 83.

(7) (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.

(8) Levin, J. I.; Turos, E.; Weinreb, S. *Synth. Commun.* **1982**, *12*, 989.

(9) Formation of this lactone is in accordance with the results of Smith et al. and Day et al.: (a) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654. (b) Day, B. W.; Kangani, C. O.; Avor, K. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1161.

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

The relative stereochemistry for aldol adduct **10a** (R = Me) was confirmed by a single-crystal X-ray structure determination, as shown in Figure 1.

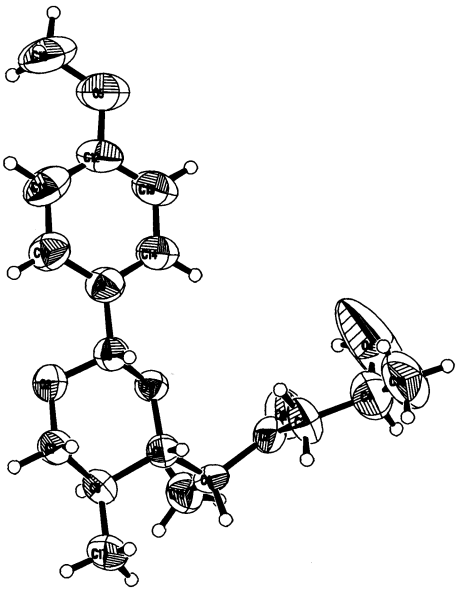
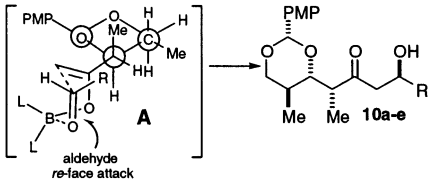


Figure 1.

Although both chairlike and boatlike transition structures must be considered in any transiton-state analysis of methyl ketone aldol reactions, we believe that the origin of the high 1,5-anti selectivity can be explained by the preferred transition state **A** (Scheme 5), which minimizes A(1,3) allylic strain in the boron enolate.[11−13] The enolate α-stereocenter adopts a more favorable rotamer with the methyl group eclipsing the enolate double bond. A boatlike arrangement is proposed, as it avoids steric interactions between the chiral residue of the enolate, the R group in the aldehyde, and a bulky ligand (L = c-Hex) in the chair structure. We believe also that dipole organization is critical to chirality transfer, and the β-alkoxy substituent is oriented anti to the enolate C−O bond. Approach of the aldehyde *re*-face from the less hindered face of the boron enolate provides the observed 1,4-anti-1,5-anti product.

Scheme 5



As this work was in progress, Panek and Arefolov published an example of a similar methyl ketone aldol reaction mediated by *n*-Bu_2BOTf leading to the corresponding 1,4-syn-1,5-anti product.[10]

On the basis of our results and those described by Arefolov and Panek, we believe that the α-stereocenter plays a secondary role in these methyl ketone aldol reactions, with the β-alkoxy substituent being responsible for the enolate facial bias in these aldol processes.

Depending on the relative stereochemistry of the α-methyl-β-alkoxy methyl ketone used, both 1,4-syn and 1,4-anti aldol adducts could be obtained without the need to use a chiral auxiliary.

We reported here that high levels of substrate-based, 1,5-stereocontrol can be achieved in the boron-mediated aldol reactions of methyl ketones by the proper choice of protecting groups. These stereoselective aldol reactions should prove to be valuable in polyketide synthesis, and further studies are underway to explore their generality and origin.[14]

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Supporting Information Available: Spectroscopic data for compounds **3**, **4**, **6**, **7**, and **10a**−**e** and crystallographic data for aldol adduct **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026968C

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(13) (a) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. (b) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

(14) New compounds and the isolatable intermediates gave satisfactory ^{1}H and ^{13}C NMR, IR, HRMS, and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.