

Influence of β -Substituents in Aldol Reactions of Boron Enolates of β -Alkoxy Methylketones

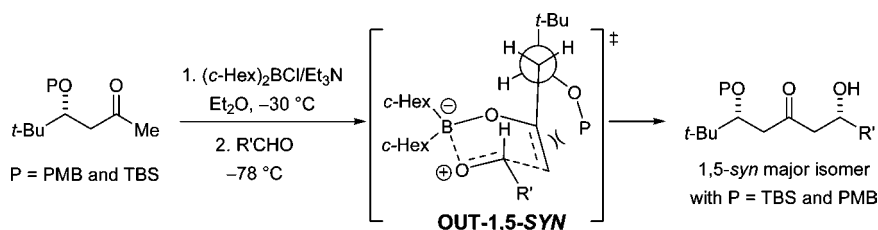
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Received September 24, 2010

ABSTRACT



Moderate to good levels of substrate-based 1,5-*syn*-stereocontrol could be achieved in the boron-mediated aldol reactions of β -*tert*-butyl methylketones with achiral aldehydes, independent of the nature of the β -alkoxy protecting group (P = PMB or TBS). The analysis of the relative energies of the transition structures by theoretical calculations using the density functional B3LYP shows relative energies favoring the corresponding OUT-1,5-SYN transition structures, explaining the observed 1,5-*syn* stereinduction.

The first evidence for 1,5-*anti* asymmetric induction in aldol reactions of boron enolates generated from β -alkoxy methylketones was described in 1989 by Masamune and co-workers in their approach to the synthesis of the AB fragment [C1–C16] of bryostatin 1.¹

Since then, numerous approaches from the research groups of Paterson,² Evans,³ Denmark,⁴ Dias,⁵ and others⁶ have shown that the sense of induction in aldol reactions of boron

enolates of β -alkoxy methylketones with aldehydes favors the formation of the 1,5-*anti* diastereoisomer. However, we demonstrated that it is possible to obtain good levels of 1,5-*syn* induction from β -trifluoromethyl and β -trichloromethyl- β -alkoxy methylketones independent of the nature of the β -alkoxy protecting group (Scheme 1).^{5c,d}

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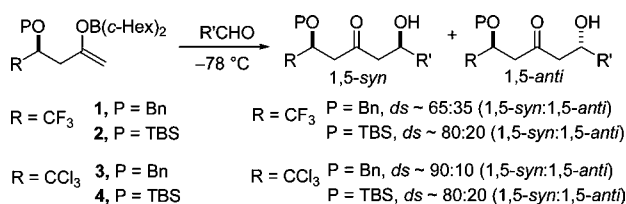
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Scheme 1. 1,5-*syn* Stereinduction in Aldol Reactions of β -Trifluoromethyl and β -Trichloromethyl- β -Alkoxy Methylketones

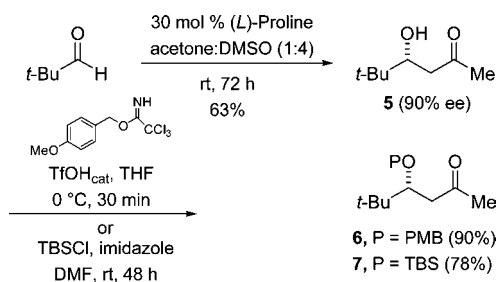


More recently, Yamamoto and co-workers have described that very useful levels of 1,5-*syn* selectivity could be obtained in lithium-mediated aldol reactions employing β -alkoxy methylketones with super silyl protecting groups at the β -oxygen.⁷

At this point, we decided to study the influence of bulky substituents at the β -position in aldol reactions of kinetic boron enolates generated from β -alkoxy methylketones. Methylketones with either *tert*-butyldimethylsilyl (TBS) or *p*-methoxybenzyl (PMB) protecting groups at the β -oxygen were initially employed to evaluate the potential steric and electronic impact of the β -alkoxy protecting group.

Our studies began with the preparation of the β -alkoxy- β -*tert*-butyl methylketones **6** (P = PMB) and **7** (P = TBS) starting with an aldol reaction between acetone and pivalaldehyde mediated by L-proline, providing **5** in 63% yield and 90% ee, as determined by Mosher ester analysis (Scheme 2).⁸ Treatment of methylketone **5** with 4-methoxybenzyl

Scheme 2. Preparation of β -Alkoxy Methylketones **6** and **7**



2,2,2-trichloroacetimidate in the presence of catalytic amounts of TfOH gave methylketone **6** in 90% yield.⁹ Protection of the β -oxygen in **5** as its TBS ether was achieved by using TBSCl and imidazole in DMF at room temperature for 48 h providing **7** in 78% yield¹⁰ (Scheme 2).

The aldol reactions of methylketones **6** and **7** with aldehydes **8a–h** were investigated using (*c*-Hex)₂BCl and

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Et₃N in Et₂O, providing the 1,5-*syn* and 1,5-*anti* aldol adducts (Scheme 3, Table 1). These boron-mediated aldol reactions

Scheme 3. Aldol Reactions of **6** and **7** with R'CHO

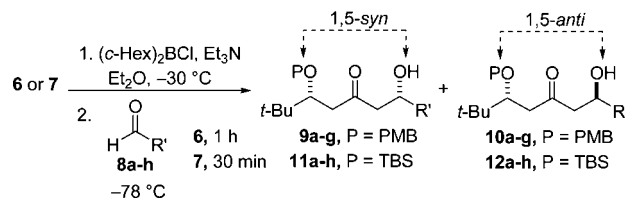


Table 1. Aldol Reactions of **6** and **7** with R'CHO

entry	P	aldehyde		yield (%) ^b
		(R')	(1,5- <i>syn</i> :1,5- <i>anti</i>) ^a	
1	TBS (7)	<i>i</i> -Pr, 8a	65:35	98
2 ^c	TBS (7)	<i>i</i> -Pr, 8a	65:35	79
3	PMB (6)	<i>i</i> -Pr, 8a	80:20	91
4	TBS (7)	Et, 8b	74:26	92
5	PMB (6)	Et, 8b	82:18	85
6	TBS (7)	<i>t</i> -Bu, 8c	66:34	98
7	PMB (6)	<i>t</i> -Bu, 8c	78:22	80
8	TBS (7)	CH ₂ =C(Me), 8d	72:28	86
9	PMB (6)	CH ₂ =C(Me), 8d	81:19	86
10	TBS (7)	Ph, 8e	68:32	71
11	PMB (6)	Ph, 8e	83:17	95
12	TBS (7)	<i>p</i> -NO ₂ C ₆ H ₄ , 8f	62:38	90
13	PMB (6)	<i>p</i> -NO ₂ C ₆ H ₄ , 8f	75:25	85
14	TBS (7)	<i>p</i> -MeOC ₆ H ₄ , 8g	68:32	86
15	PMB (6)	<i>p</i> -MeOC ₆ H ₄ , 8g	79:21	86
16	TBS (7)	PhCH ₂ CH ₂ , 8h	65:35	88

^a Ratio was determined by ¹H and ¹³C NMR analysis of the diastereoisomeric mixture of aldol adducts. ^b Isolated yields of both *syn* and *anti* isomers after SiO₂ gel flash column chromatography. ^c CH₂Cl₂ as solvent.

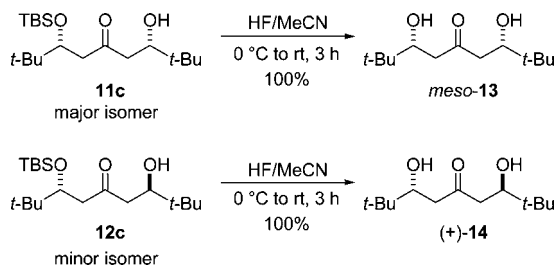
were found to proceed with good yields and good levels of remote 1,5-*syn* stereinduction for methylketone **6** (P = PMB) providing 1,5-*syn* isomers **9a–g** as the major products. In the same way, the boron enolate reactions of methylketone **7** (P = TBS) with aldehydes **8a–h** resulted in a mixture of aldol adducts **11a–h** and **12a–h**, favoring the 1,5-*syn* aldol adducts **11a–h** (Scheme 3, Table 1).

Notably, these reactions provided the 1,5-*syn* isomer, opposite to 1,5-*anti* stereinduction observed for boron-mediated aldol reactions of simpler β -alkyl- β -alkoxy methylketones, indicating the overriding contribution, in this special case, from the bulky substituent at the β -position. More surprisingly, independent of the nature of the β -oxygen protecting group, the 1,5-*syn* isomer is always obtained as the major product. The stereinduction observed in these reactions shows that the volume of the substituent in β -position is crucial for control of remote stereochemistry.

Thus, it is clear that the major contribution to the sense of 1,5-*syn* induction observed in aldol reactions involving boron enolates of methylketones **1–4** is due to the volume of the substituent at the β -position and not to electronic effects, as stated previously.⁵

The relative stereochemistry for aldol adducts **11a–h** and **12a–h** (obtained from methylketone **7**) was unambiguously established after removal of the TBS protecting group in **11c** (major product, obtained after purification by SiO₂ gel *flash* column chromatography) with HF in acetonitrile,¹¹ affording the *meso* 1,5-diol **13**, as required by a 1,5-*syn* relationship (Scheme 4). Removal of the TBS group in **12c** (minor

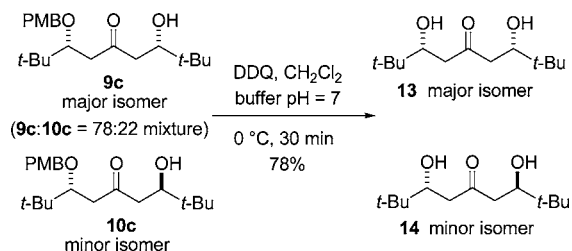
Scheme 4. Proof of Stereochemistry for Aldols **11c** and **12c**



isomer) generated the C₂-symmetric 1,5-diol **14**, [α]_D +50 (*c* = 0.45, CH₂Cl₂), as required by a 1,5-*anti* relationship.

To assign the relative stereochemistry for aldol adducts obtained from methylketone **6** (P = PMB), we treated a 78:22 mixture of adducts **9c** and **10c** (P = PMB) with DDQ providing a mixture of diols **13** and **14** in 78% yield, which had their ¹H and ¹³C NMR spectra compared with those of diols prepared in Scheme 4 from **11c** and **12c** (Scheme 5).

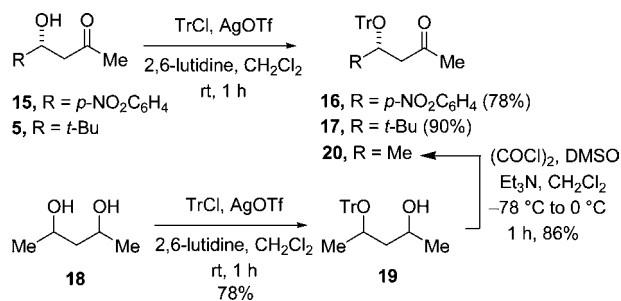
Scheme 5. Proof of Stereochemistry for Aldols **9c** and **10c**



This proved that the 1,5-*syn* isomer is the major product with both TBS and PMB protecting groups.

At this point, we decided to investigate the impact of a bulky protecting group like β -trityl (OTr) at the β -oxygen. To accomplish this, we chose methylketones with different stereoelectronic properties at the β -substituents (R = Me, *p*-NO₂C₆H₄, and *t*-Bu). The preparation of the β -alkoxy-methylketones **16** (R = *p*-NO₂C₆H₄) and **17** (R = *t*-Bu) began with known hydroxy methylketones **15** and **5**, respectively.^{5c,d} Protection of the β -oxygen in **15** and **5** was achieved by using TrCl, AgOTf, and 2,6-lutidine in CH₂Cl₂ at room temperature for 1 h, providing the corresponding

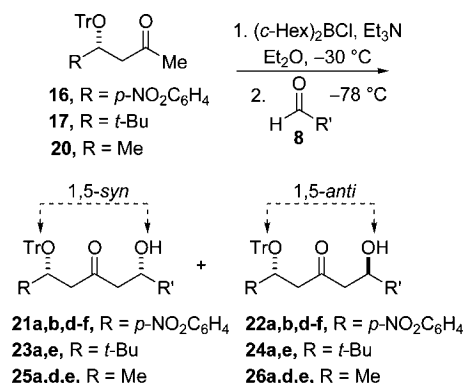
Scheme 6. Preparation of β -Alkoxy Methylketones **16**, **17**, and **20**



β -OTr methylketones **16** and **17** (Scheme 6).¹² The methylketone **20** (R = Me) was obtained by monoprotection of diol **18** with TrCl, AgOTf, and 2,6-lutidine in CH₂Cl₂ providing alcohol **19** followed by Swern oxidation.

The aldol reaction between the boron enolates generated from methylketones **16**, **17**, and **20**, applying the conditions described in Table 1, was performed (Scheme 7, Table 2).

Scheme 7. Aldol Reactions of **16**, **17**, and **20** with R'CHO



Surprisingly, entries 1 and 7 (Table 2) revealed that when the Tr protecting group is introduced in methylketone **17** (R = *t*-Bu) the 1,5-*syn* selectivity previously observed is lost. In the same way, methylketone **20** (R = Me) (entries 2, 5, and 8) led to a 50:50 ratio of diastereoisomers. These results show that the combination of β -alkyl groups with a β -OTr substituent gives rise to no selectivity, independent of the nature of this R group. However, the aldol reactions of methylketone **16** (R = *p*-NO₂C₆H₄) were found to proceed with good yields and low levels of remote 1,5-*anti* stereoinduction providing aldol adducts **22a,b,d–f** as the major products.

This is interesting because in our previous studies we found that high degrees of 1,5-*anti* stereoinduction were obtained in aldol reactions of β -aryl- β -*p*-methoxybenzyl

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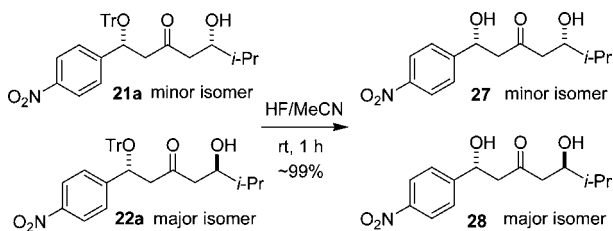
Table 2. Aldol Reactions of **16**, **17**, and **20** with R'CHO

entry	R		dr ^a (1,5- <i>syn</i> :1,5- <i>anti</i>)	yield (%) ^b
	(MK)	(R')		
1	<i>t</i> -Bu (17)	<i>i</i> -Pr, 8a	50:50	71
2	Me (20)	<i>i</i> -Pr, 8a	50:50	95
3	<i>p</i> -NO ₂ C ₆ H ₄ (16)	<i>i</i> -Pr, 8a	27:73	51
4	<i>p</i> -NO ₂ C ₆ H ₄ (16)	Et, 8b	40:60	55
5	Me (20)	CH ₂ =C(Me), 8d	50:50	95
6	<i>p</i> -NO ₂ C ₆ H ₄ (16)	CH ₂ =C(Me), 8d	30:70	98
7	<i>t</i> -Bu (17)	Ph, 8e	50:50	95
8	Me (20)	Ph, 8e	50:50	77
9	<i>p</i> -NO ₂ C ₆ H ₄ (16)	Ph, 8e	33:67	76
10	<i>p</i> -NO ₂ C ₆ H ₄ (16)	<i>p</i> -NO ₂ C ₆ H ₄ , 8f	30:70	76

^a Ratio was determined by ¹H and ¹³C NMR analysis of the diastereoisomeric mixture of aldol adducts. ^b Isolated yields of both *syn* and *anti* isomers after SiO₂ gel *flash* column chromatography.

methylketones.^{5c,d} After introducing TBS and *t*-Bu protecting groups, the aldol reactions proceeded with low levels of 1,5-*syn* stereinduction. In this context, methylketone **16** (R = *p*-NO₂C₆H₄) shows unexpected selectivities.

To assign the relative stereochemistry for aldol adducts obtained from methylketone **16** (R = *p*-NO₂C₆H₄, P = Tr), we treated a 27:73 mixture of *syn* and *anti* aldol adducts **21a** and **22a** with HF in acetonitrile, giving a mixture of diols **27** and **28**, respectively (Scheme 8). After comparison of their ¹H and

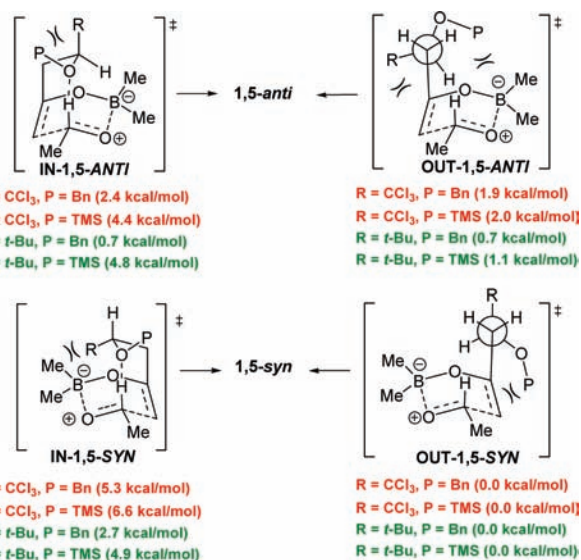
Scheme 8. Proof of Stereochemistry for Aldols **21a** and **22a**

¹³C NMR spectra with spectroscopic data previously reported,^{5c,d} we observed that the 1,5-*anti* isomer is the major product (see Supporting Information for full details).

Recently, Paton and Goodman proposed that the aldol reactions of boron enolates generated from β -alkoxy methylketones proceed via boat-like transition states involving a hydrogen bonding interaction.^{13,14} This intriguing formyl hydrogen bond stabilizes the transition state **IN-1,5-ANTI**, leading to the 1,5-*anti* isomer, and shows steric interactions between the β -alkyl R group and the boron ligands in the boat-like transition state **IN-1,5-SYN**, leading to the 1,5-*syn* isomer (Figure 1).

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(14) The theoretical calculations were performed with the corresponding *S* enantiomer of the β -alkoxy methylketone. For similar theoretical calculations performed in our group, see ref 5e.

**Figure 1.** Relative energies for boat-like transition structures obtained using B3LYP/6-31G(d,p). Single-point energy (CPCM-auks) in B3LYP/6-31+G(d,p).

On the basis of the results described here, the 1,5-*syn* selectivities observed in aldol reactions of β -bulky boron enolates cannot be explained via Goodman's proposed **IN-1,5-SYN** transition state. We have performed theoretical calculations using density functional theory (B3LYP) on the competing transition structures leading to both 1,5-*anti* and 1,5-*syn* aldol adducts. We studied the simple aldol transition structures for the dimethylboron enolates and acetaldehyde. For R = CCl₃ and *t*-Bu, the competitive boat-like transition states containing stabilizing hydrogen bonds are higher in energy when compared with the corresponding **OUT-1,5-ANTI** and **OUT-1,5-SYN** transition states, lacking the formyl H-bond. The analysis of the relative energies of these transition states shows relative energies favoring the corresponding **OUT-1,5-SYN** transition structure, thus preventing the steric interactions of bulky R groups and supporting the formation of the 1,5-*syn* diastereoisomer. The results presented in Figure 1 are in agreement with our experimental results. Further details about the theoretical studies will be described in a full account of this work.

Acknowledgment. We are grateful to FAEP-UNICAMP, FAPESP, CNPq, and INCT-INOVAR (Proc. CNPq 573.564/2008-6) for financial support and to Prof. Carol H. Collins (IQ-UNICAMP) for helpful suggestions about English grammar and style.

Supporting Information Available: Experimental procedures and spectral data for the prepared compounds as well as Cartesian coordinates of transition structures with gas-phase and solution-phase SCF absolute energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL102303P