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

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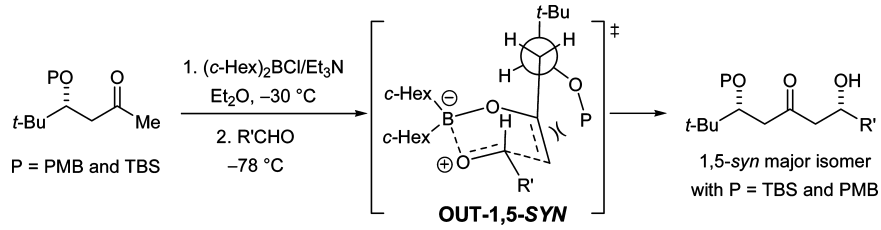
ABSTRACT



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* stereoinduction.

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 coworkers 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 others[6] 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]

(1) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, *54*, 2817.

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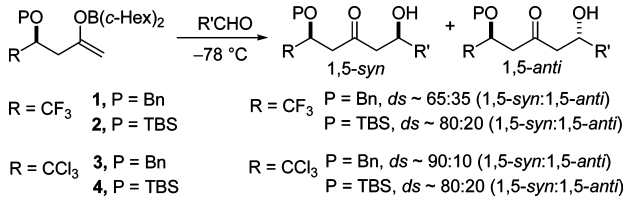
Scheme 1. 1,5-*syn* Stereoinduction in Aldol Reactions of β-Trifluoromethyl and β-Trichloromethyl-β-Alkoxy Methylketones

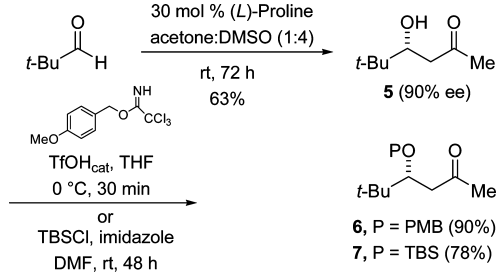


More recently, Yamamoto and co-workers have described that very useful levels of 1,5-*syn* selectivity could be obtained in lithium-mediated aldol reactions employing β-alkoxy methylketones with super silyl protecting groups at the β-oxygen.[7]

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 pivaladehyde 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% yield[10] (Scheme 2).

The aldol reactions of methylketones **6** and **7** with aldehydes **8a**−**h** were investigated using $(c\text{-Hex})_2$BCl and Et_3N in Et_2O, 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

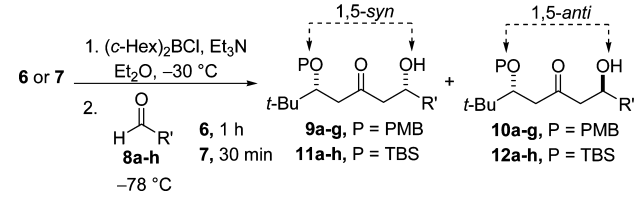


Table 1. Aldol Reactions of **6** and **7** with R′CHO

entry	P	aldehyde (R′)	dr[a] (1,5-*syn*:1,5-*anti*)	yield (%)[b]
1	TBS (**7**)	*i*-Pr, **8a**	65:35	98
2[c]	TBS (**7**)	*i*-Pr, **8a**	65:35	79
3	PMB (**6**)	*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**)	*t*-Bu, **8c**	66:34	98
7	PMB (**6**)	*t*-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**)	*p*-$NO_2C_6H_4$, **8f**	62:38	90
13	PMB (**6**)	*p*-$NO_2C_6H_4$, **8f**	75:25	85
14	TBS (**7**)	*p*-$MeOC_6H_4$, **8g**	68:32	86
15	PMB (**6**)	*p*-$MeOC_6H_4$, **8g**	79:21	86
16	TBS (**7**)	$PhCH_2CH_2$, **8h**	65:35	88

[a] Ratio was determined by ^{1}H and ^{13}C NMR analysis of the diastereoisomeric mixture of aldol adducts. [b] Isolated yields of both *syn* and *anti* isomers after SiO_2 gel *flash* column chromatography. [c] CH_2Cl_2 as solvent.

were found to proceed with good yields and good levels of remote 1,5-*syn* stereoinduction 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* stereoinduction 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 stereoinduction 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]

(7) Yamaoka, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2010**, *132*, 5354.
(8) (a) List, B. *Tetrahedron* **2002**, *58*, 5573. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (c) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. See Supporting Information file for more details.
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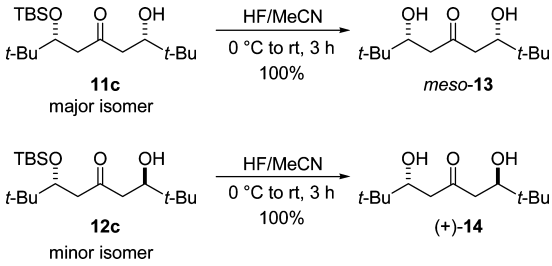
(10) Zou, B.; Wei, J.; Cai, G.; Ma., D. *Org. Lett.* **2003**, *5*, 3503.

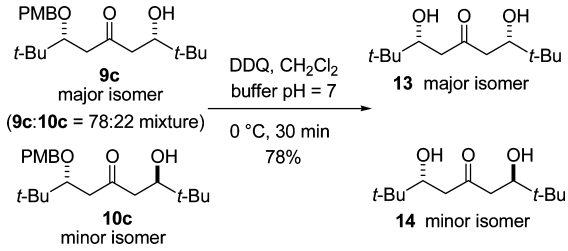
The relative stereochemistry for aldol adducts **11a**−**h** and **12a**−**h** (obtained from methylketone **7**) was unambiguously established after removal of the TBS protecting group in **11c** (major product, obtained after purification by SiO_2 gel *flash* column chromatography) with HF in acetonitrile,[11] 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 isomer) generated the C_2-symmetric 1,5-diol **14**, $[\alpha]_D$ +50 (c = 0.45, CH_2Cl_2), as required by a 1,5-*anti* relationship.

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



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 ^{13}C NMR spectra compared with those of diols prepared in Scheme 4 from **11c** and **12c** (Scheme 5).

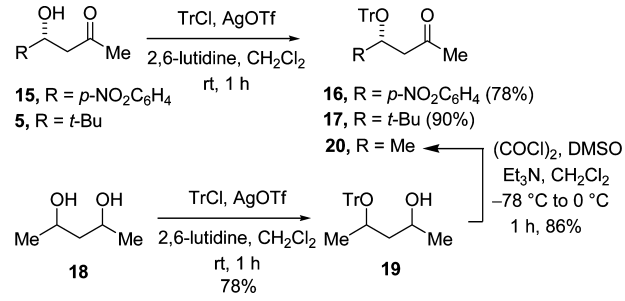
Scheme 5. Proof of Stereochemistry for Aldols **9c** and **10c**



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-$NO_2C_6H_4$, and *t*-Bu). The preparation of the β-alkoxymethylketones **16** (R = p-$NO_2C_6H_4$) 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 CH_2Cl_2 at room temperature for 1 h, providing the corresponding

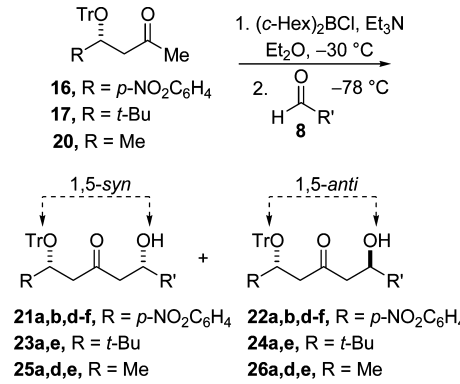
Scheme 6. Preparation of β-Alkoxy Methylketones **16**, **17**, and **20**



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 CH_2Cl_2 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-$NO_2C_6H_4$) 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

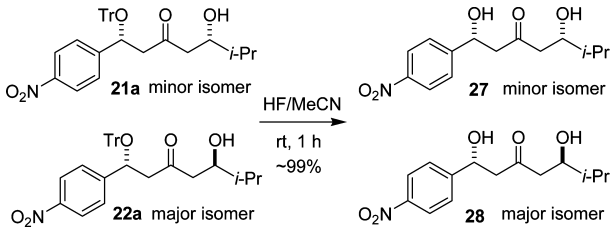
entry	R (MK)	aldehyde (R′)	dr[a] (1,5-*syn*:1,5-*anti*)	yield (%)[b]
1	*t*-Bu (**17**)	*i*-Pr, **8a**	50:50	71
2	Me (**20**)	*i*-Pr, **8a**	50:50	95
3	*p*-$NO_2C_6H_4$ (**16**)	*i*-Pr, **8a**	27:73	51
4	*p*-$NO_2C_6H_4$ (**16**)	Et, **8b**	40:60	55
5	Me (**20**)	CH_2=C(Me), **8d**	50:50	95
6	*p*-$NO_2C_6H_4$ (**16**)	CH_2=C(Me), **8d**	30:70	98
7	*t*-Bu (**17**)	Ph, **8e**	50:50	95
8	Me (**20**)	Ph, **8e**	50:50	77
9	*p*-$NO_2C_6H_4$ (**16**)	Ph, **8e**	33:67	76
10	*p*-$NO_2C_6H_4$ (**16**)	*p*-$NO_2C_6H_4$, **8f**	30:70	76

[a] Ratio was determined by ^{1}H and ^{13}C NMR analysis of the diastereoisomeric mixture of aldol adducts. [b] Isolated yields of both *syn* and *anti* isomers after SiO_2 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* stereoinduction. In this context, methylketone **16** (R = *p*-$NO_2C_6H_4$) shows unexpected selectivities.

To assign the relative stereochemistry for aldol adducts obtained from methylketone **16** (R = *p*-$NO_2C_6H_4$, P = Tr), we treated a 27:73 misture 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 ^{1}H and

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



^{13}C 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).

(13) (a) Paton, R. S.; Goodman, J. M. *Org. Lett.* **2006**, *8*, 4299. (b) Goodman, J. M.; Paton, R. S. *Chem. Commun.* **2007**, 2124. (c) Paton, R. S.; Goodman, J. M. *J. Org. Chem.* **2008**, *73*, 1253.

(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.

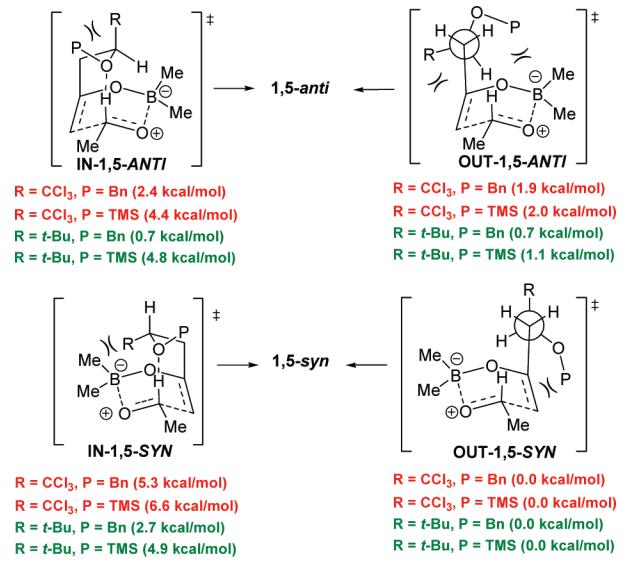


Figure 1. Relative energies for boat-like transition structures obtained using B3LYP/6-31G(d,p). Single-point energy (CPCM-auks) in B3LYP/6-31+G(d,p).

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 = CCl_3 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.

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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.

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