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The Influence of a β-Electron Withdrawing Substituent in Aldol Reactions of Methylketone Boron Enolates

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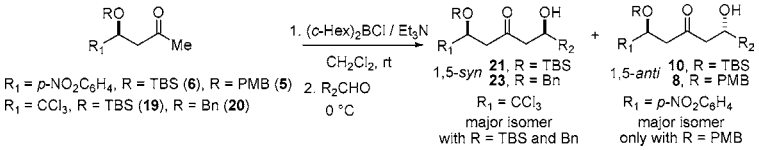
ABSTRACT

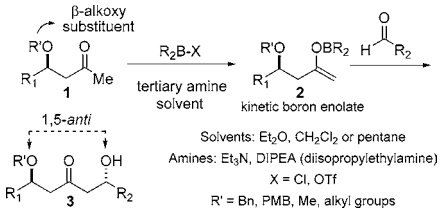


We wish to describe here that good levels of substrate-based, 1,5-*syn*-stereocontrol could be achieved in the boron-mediated aldol reactions of β-trichloromethyl methylketones with achiral aldehydes, independent of the nature of the β-alkoxy protecting group.

The aldol reaction is one of the most powerful and fundamental methods for carbon−carbon bond formation as well as for the creation of 1,3-dioxygen relationships in organic molecules.[1]

In the reactions of β-alkoxy boron enolates of methylketones **1**, the kinetic boron enolate **2** (less-substituted enolate) is generated after treatment of the methylketone with the corresponding diakylborane (boron triflates or dialkyl chloro boranes), followed by addition of a tertiary amine (usually Et_3N or DIPEA) in solvents like CH_2Cl_2, Et_2O, or pentane (Scheme 1).[2] The presence of a β-heteroatom substituent in these boron enolates influences the stereochemical outcome of the corresponding aldol reactions and moderate to high levels of 1,5-*anti* asymmetric induction are observed.[3,4] High selectivities favoring the 1,5-*anti* aldol adduct are obtained in aldol reactions of β-substituted methylketones when the β-alkoxy protecting group is benzylic (OBn, OPMB) or a benzylidene acetal. The nature of

Scheme 1



the β-alkoxy substituent is critical in determining the level of induction as, usually, the use of a β-silicon protecting group gives rise to little or no selectivity.[2−4]

To gain insight into the principles that dictate the 1,5-diastereoselectivity in aldol reactions of kinetic boron enolates generated from methylketones, we decided to study the influence of electron withdrawing groups at the β-position of the boron enolate by using a β-*p*-nitrophenyl group as well as a β-trichloromethyl group.[5,6]

We wish to report here our initial results in the aldol reactions using the kinetic boron enolates of β-alkoxy-β-

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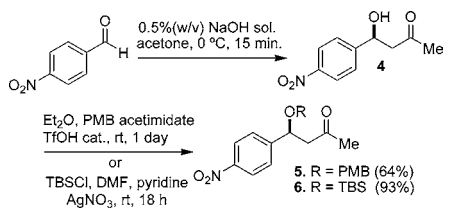
nitrophenyl methylketones and β-alkoxy-β-trichloromethyl methylketones with achiral aldehydes.[7] Notably, especially with a $\beta-CCl_3$ group, these reactions give the 1,5-*syn* isomer, opposite to 1,5-*anti* stereoinduction observed for boron aldol reactions of simple β-alkoxy methylketones, indicating the overriding contribution in this special case from the substituent at the β-position, which is a very strong electron withdrawing group. More surprisingly, independent of the nature of the β-oxygen protecting group, the 1,5-*syn* isomer is obtained as the major product. To the best of our knowledge, this is the first report of boron-mediated aldol reactions of methylketones leading to the 1,5-*syn* isomer with useful levels of diastereoselection, even with a β-OBn substituent.[5] Methylketones with *tert*-butyldimethylsilyl (TBS), benzyl (Bn), and *p*-methoxybenzyl (PMB) protecting groups at the β-positon were employed to evaluate the potential steric and electronic impact of the β-alkoxy protecting group.[8]

Our studies began with the preparation of the β-alkoxy-β-*p*-nitrophenyl methylketones **5** (R = PMB) and **6** (R = TBS) starting with an aldol reaction between acetone and *p*-nitrobenzaldehyde (Scheme 2).[9] Treatment of methyl-

Scheme 2



ketone **4** with PMB-acetimidate in the presence of catalytic amounts of TfOH gave methylketone **5** in 64% yield. Protection of the β-oxygen in **4** as its TBS ether was achieved by using TBSCl and $AgNO_3$ in DMF at room temperature for 18 h providing **6** in 93% yield (Scheme 2).[10]

The aldol reactions of the methylketones **5** and **6** with aldehydes **7a-f** were investigated using $(c\text{-Hex})_2BCl/Et_3N$ in Et_2O or CH_2Cl_2 for enolization and were optimized in CH_2Cl_2 as solvent, to give the 1,5-*anti* and 1,5-*syn* aldol adducts (Scheme 3, Table 1).[11]

Scheme 3

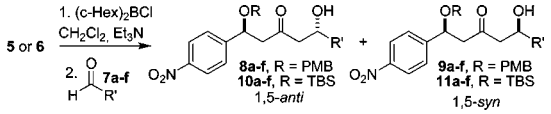


Table 1. Aldol Reactions of **5** and **6** with R′CHO

entry	R	aldehyde (R′)	dr[a] (1,5-*anti*:1,5-*syn*)	yield (%)[b]
1[c]	PMB	**7a**, ^{i}Pr	96:04	57
2	PMB		96:04	78
3	TBS		39:61	90
4	PMB	**7b**, Ph	>95:05	65
5[d]	PMB		87:13	74
6	TBS		29:71	81
7	PMB	**7c**, Et	92:08	34
8	TBS		41:59	50
9	PMB	**7d**, C(Me)=CH_2	93:07	54
10	TBS		41:59	70
11	PMB	**7e**, *p*-C_6H_4OMe	>95:05	63
12	TBS		37:63	67
13	PMB	**7f**, *p*-$C_6H_4NO_2$	>95:05	56
14	TBS		43:57	69

[a] Ratio was determined by ^1H NMR analysis of the diastereoisomeric mixture of adducts. [b] Isolated yields of both syn and anti isomers after SiO_2 flash chromatography. [c] Et_2O as solvent. [d] Aldehyde addition at 0 °C.

The enolizations were performed at 0 °C and the addition of the aldehyde at −78 °C. These boron-mediated aldol reactions were found to proceed with good yields and high degrees of remote 1,5-*anti* stereoinduction for methylketone **5** (R = PMB) providing **8a**−**f** as the major products. In all the cases studied, 1,5-*anti* isomers **8a**−**f** were isolated as the major products.

The boron enolate addition of methylketone **6** (with a β-TBS protecting group) to aldehydes **7a**−**f** gave a mixture of aldol adducts **10** and **11** favoring the 1,5-*syn* aldol adducts **11a**−**f** (Scheme 3, Table 1).[11] The stereoinduction observed in these reactions (with a TBS protecting group at the β-oxygen) shows that the reaction weakly favored the 1,5-*syn* product, indicating that there is a mild inherent selectivity by the resident electron-withdrawing β-nitrophenyl group. The best selectivity was observed with benzaldehyde (entry 6, anti/syn = 29:71). It is noteworthy that the presence of a β-OTBS leads to the 1,5-*syn* isomer.

The 1,5-*anti* relative stereochemistry for aldol adducts **8a**−**f** was then unambiguously established after conversion

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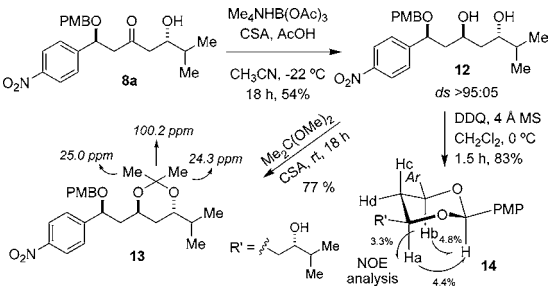
(11) (a) The ratios were determined by ^1H and ^{13}C-NMR spectroscopic analysis of the unpurified product mixture. (b) All of the percentage values represent data obtained from at least three individual trials.

of **8a** to the corresponding isopropylidene acetal **13** and benzylidene acetal **14** (Scheme 4).[12] Selective reduction of

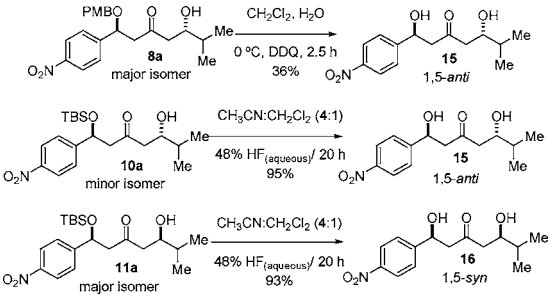
Scheme 4



8a to the 1,3-*anti* diol **12** (54% yield) followed by treatment of **12** with $Me_2C(OMe)_2$ and CSA catalyst provided acetal **13** (Scheme 4). Analysis of the ^{13}C NMR spectra showed resonances at 25.0, 24.3, and 100.2 for **13**, characteristic of a 1,3-*anti* acetonide.[13] Treatment of **12** with DDQ in CH_2Cl_2 gave benzylidene acetal **14** in 83% yield (Scheme 4).[14] Analysis of the ^1H NMR coupling constants, specifically $J_{Ha-Hc} = 11.2$ Hz, $J_{Ha-Hd} = 2.7$ Hz, $J_{Hb-Hc} = 11.2$ Hz and $J_{Hb-Hd} = 2.5$ Hz, proved that Ha, Hb, and Hc are all axial in **14**. This was supported by the illustrated NOE interactions.

To assign the stereochemistry for aldol adducts obtained from methylketone **6** (R = TBS), we first treated aldol **8a** (R = PMB) with DDQ, to give diol 1,5-*anti* **15** in 36% nonoptimized yield (Scheme 5). The 39:61 mixture of syn

Scheme 5



and anti aldol adducts **10a** and **11a** (R = TBS) was separated by flash column chromatography and both aldols were independently treated with HF in CH_3CN to give diols **15** and **16**, respectively, in good yields. The diol **15**, prepared from the minor aldol **10a** was identical in all respects with the 1,5-*anti* aldol prepared from PMB removal of **8a**. This proved that the 1,5-*syn* isomer is the major product in the aldol reactions with a TBS protecting group.

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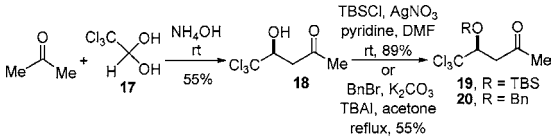
At this point we decided to investigate the stereochemical impact of a β-trichloromethyl substituent. The β-trichloromethyl methylketone **18** was prepared by an aldol reaction of acetone with chloral hydrate **17** (Scheme 6).[15] The best

Scheme 6



conditions involved treatment of **18** with TBSCl, $AgNO_3$, and pyridine in DMF (Scheme 6).[10] This supports the notion that the basic nature of the β-oxygen atom is sufficiently attenuated owing to the strong electron withdrawing capability of the trichloromethyl group.

Enolization of methylketone **19** (R = TBS) with $(c\text{-Hex})_2BCl$ and Et_3N in CH_2Cl_2 at room temperature, proceeded smoothly providing the corresponding kinetic enol borinate, which was used in the aldol reactions with aldehydes **7a**−**e** (Scheme 7, Table 2).

Scheme 7

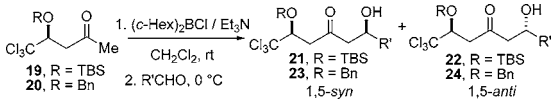


Table 2. Aldol Reactions of **19** and **20** with R′CHO

entry	R	aldehyde (R′)	dr[a] (1,5-*anti*:1,5-*syn*)	yield (%)[b]
1	TBS	**7a**, ^{i}Pr	18:82	92
2	Bn		19:81	76
3	TBS	**7b**, Ph	17:83	82
4	Bn		22:78	72
5	TBS	**7c**, Et	19:81	60
8	Bn		20:80	85
7	TBS	**7d**, C(Me)=CH_2	20:80	87
8	Bn		20:80	72
9	TBS	**7e**, p−C_6H_4OMe	20:80	53

[a] Ratio was determined by ^1H NMR analysis of the diastereoisomeric mixture of adducts. [b] Isolated yields of both syn and anti isomers after SiO_2 flash chromatography.

We were delighted to find that this reaction led to the formation of 1,5-*syn* products **21a**−**e** as the major isomers (up to 83:17 diastereoselectivity) in moderate to high yields (Scheme 7, Table 2). These studies showed a remarkable influence of the resident β-trichloromethyl group on the stereochemical course of these aldol reactions.

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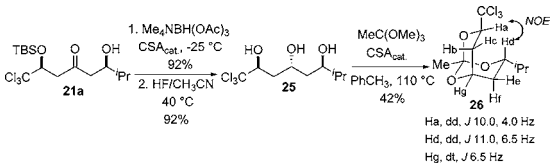
With methylketone **20** (R = Bn) we observed the same trend and the overall diastereoselection of the process was again controlled by the strong facial bias of the β-trichloromethyl group of boron enolate to give the 1,5-*syn* products **23a**−**e** as the major isomers (Scheme 7, Table 2).[11]

The relative stereochemistries of the major aldol adducts **21** were determined by ^{1}H NMR and NOESY analysis of the bicyclic derivative **26** (Scheme 8). Diastereoselective 1,3-

Scheme 8

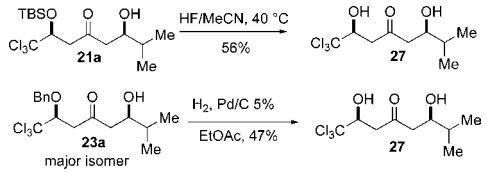


anti reduction of **21a** with $Me_4NBH(OAc)_3$ gave the corresponding diol, which after removal of the TBS protecting group with HF/CH_3CN provided triol **25** (Scheme 8).[13]

Treatment of triol **25** with trimethylorthoacetate and catalytic amounts of CSA gave the bicyclic derivative **26**. Analysis of the ^{1}H NMR coupling constants, specifically $J_{Ha-Hc} = 4.0$ Hz, $J_{Ha-Hb} = 10.0$ Hz, $J_{Hd-He} = 6.5$ Hz, $J_{Hd-Hf} = 11.0$ Hz and $J_{Hg-Hb} = J_{Hg-Hf} = 6.5$ Hz, proved that Ha and Hd were both axial in **26**. This was also supported by the illustrated NOE interaction.

To assign the stereochemistry for aldol adducts **23a**−**e** obtained from methylketone **20** (R = Bn), we first treated aldol **21a** (R = TBS) with HF in CH_3CN to give diol **27** in 56% yield (Scheme 9). The mixture of syn and anti aldol

Scheme 9

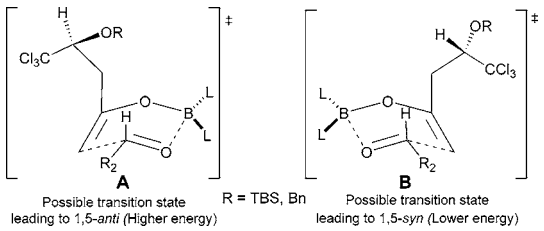


adducts **23a** and **24a** (R = Bn) was submitted to hydrogenolysis to give diol **27** as the major isomer. This diol was identical in all respects with the 1,5-*syn* diol prepared from TBS removal of **21a**. This proved that the 1,5-*syn* isomer is the major product in the aldol reactions with both TBS and Bn protecting groups at the β-oxygen of **19** and **20**. The stereochemical outcome of these reactions with both TBS and Bn protecting groups at the β-position seems to be controlled mainly by the resident β-trichloromethyl substituent of boron enolate and tends to give the 1,5-*syn* isomer.

In 2006, Paton and Goodman published very interesting theoretical studies in order to explain the origins of the 1,5-*anti* asymmetric induction in boron-mediated aldol reactions of methylketones.[16] They concluded that these reactions proceed via boatlike transition states.[16,17] For boron enolates with a β-alkoxy substituent, it is proposed that a stabilizing formyl hydrogen bond favors the 1,5-*anti* aldol adduct by minimizing steric interactions between the β-alkyl group and one of the ligands on boron.

In our case, because of the lower intrinsic basicity of the oxygen with electron withdrawing groups at the β-position, this formyl hydrogen bonding is prevented and probably the transition state proposed by Paton and Goodman is not possible. Then, we believe that the main factor controlling the preference for the 1,5-*syn* isomer is minimization of dipole moments in the corresponding boatlike transition states **A** and **B** (Scheme 10). Transition state **A**, with the β-CCl_3

Scheme 10



group anti to the C−O bond of the enolate and anti to the aldehyde C=O bond has the approach of the aldehyde from the same side of the OR group (R = TBS, Bn) and should be disfavored. In transition state **B**, the aldehyde approaches from the side opposite to the OR group, leading to the 1,5-*syn* isomer. Theoretical studies are underway to clarify this.

We have described here that good levels of substrate-based, 1,5-*syn*-stereocontrol could be achieved in the boron-mediated aldol reactions of β-trichloromethyl methylketones with achiral aldehydes. The moderate internal stereoinduction of the corresponding kinetic boron enolates dominated the overall stereochemical outcome of these aldol addition reactions. Independent of the nature of the β-protecting group, the 1,5-*syn* diastereoisomer was always isolated as the major product when boron enolates generated from β-trichloromethyl methylketones were used. Further studies in this direction are underway to explore and better understand their generality and origin and will be described in due course.

Acknowledgment. We are grateful to FAPESP and CNPq for financial support and to Prof. Carol H. Collins (IQ−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.

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