

# The role of $\beta$ -bulky alkyl substituents in aldol reactions of boron enolates of methylketones with aldehydes

Emílio Carlos de Lucca Júnior and Luiz Carlos Dias\*

Instituto de Química, Universidade Estadual de Campinas, C.P. 6154, 13084-971, Campinas, SP, Brasil

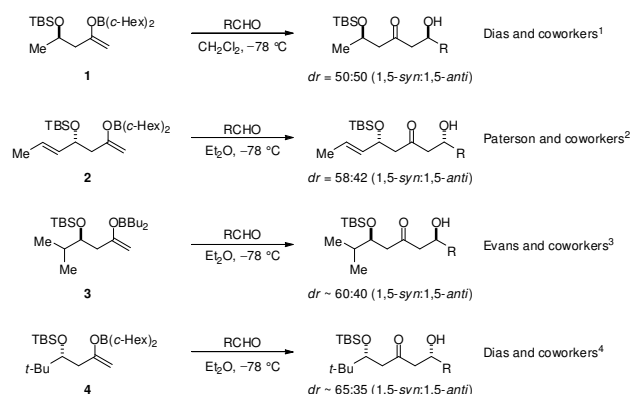
\* [ldias@iqm.unicamp.br](mailto:ldias@iqm.unicamp.br)

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## INTRODUCTION

Recently, we described that the levels of 1,5-syn selectivities in aldol reactions involving boron enolates of  $\beta$ -alkoxy methylketones, where the  $\beta$ -alkoxy protecting group is TBS, are dependent on the volume of the alkyl substituent in  $\beta$ -position (Scheme 1).

Scheme 1. Aldol reactions.

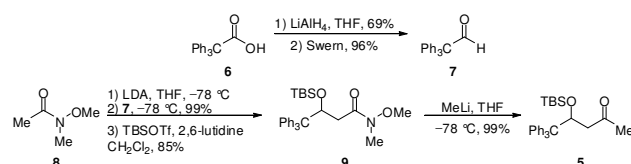


Based on these results, we prepared methylketone **5** in order to assess the steric contribution of the  $\beta$ -alkyl substituent in reactions of the corresponding boron enolates with achiral aldehydes.

## RESULTS AND DISCUSSION

Our studies began with the preparation of methylketone **5**. Treatment of acid **6** with  $\text{LiAlH}_4$  (69%) followed by Swern oxidation (96%) provided **7**. Aldol reaction between **7** and **8** (99%) followed by treatment with TBSOTf (85%) lead to the formation of **9**. Finally, treatment of **9** with MeLi gave methylketone **5** in 99% yield (Scheme 2).

Scheme 2. Preparation of methylketone **5**.



The aldol reactions of methylketone **5** with aldehydes **10a-g** were investigated using

$(c\text{-Hex})_2\text{BCl}$  and  $\text{Et}_3\text{N}$  in  $\text{Et}_2\text{O}$ , providing the 1,5-syn and 1,5-anti aldol adducts (Scheme 3, Table 1).

Scheme 3. Aldol reactions of **5** with RCHO.

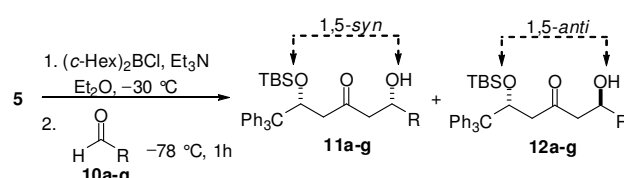


Table 1. Aldol reactions of **5** with RCHO.

ent	aldehyde (R)	dr <sup>a</sup> (1,5-syn:1,5-anti)	yield (%) <sup>b</sup>
1	<i>i</i> -Pr, <b>10a</b>	> 95:05	95
2	Et, <b>10b</b>	> 95:05	92
3	<i>t</i> -Bu, <b>10c</b>	> 95:05	98
4	$\text{CH}_2=\text{C}(\text{Me})$ , <b>10d</b>	> 95:05	94
5	Ph, <b>10e</b>	91:09	89
6	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> , <b>10f</b>	> 95:05	84
7	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> , <b>10g</b>	91:09	78

<sup>a</sup> Ratio was determined by <sup>1</sup>H and <sup>13</sup>C NMR analysis of the diastereoisomeric mixture of aldol adducts. <sup>b</sup> Isolated yields of both isomers after SiO<sub>2</sub> gel flash column chromatography.

These boron-mediated aldol reactions were found to proceed with good yields and excellent levels of remote 1,5-syn stereoselection.

The relative stereochemistry for aldol adducts **11a-g** and **12a-g** was unambiguously established on the basis of Kishi methodology.<sup>5</sup>

## CONCLUSION

The stereoselection observed in these reactions shows that the levels of 1,5-syn selectivities in aldol reactions are really dependent on the volume of the alkyl substituent at the  $\beta$  position.

## ACKNOWLEDGEMENTS

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