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Chlorodicyclohexylborane-Mediated Aldol Additions of α,α′-Dioxygenated Ketones

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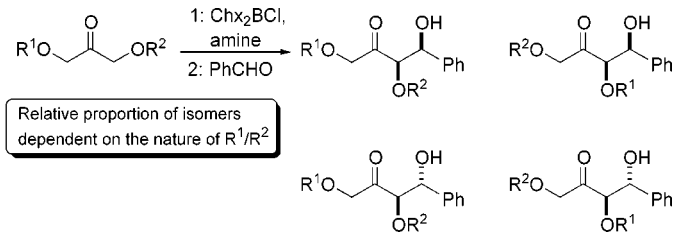
ABSTRACT



Boron aldol additions of variously O-protected α,α′-dioxygenated ketones using dicyclohexylboron chloride and a tertiary amine have been investigated. The stereoselectivity of the process was dependent on the protecting group on the α-oxygen atoms. Notably, ketones with bulky silyloxy groups gave *syn* aldols, most likely via *Z* enolates. This rules out the participation of chelates during the enolization process, at least in the presence of such sterically crowded protecting groups. An alternative explanation is offered.

The aldol reaction[1] has proven to be a powerful and general method for the stereocontrolled construction of carbon−carbon bonds and has relevant application in the synthesis of natural polyoxygenated molecules such as macrolide and polyether antibiotics.[2] We have recently reported on aldol reactions of protected L-(*S*)-erythrulose derivatives using dicyclohexyl boron chloride.[3] The diastereoselectivity (*syn* vs *anti*) was found to be dependent on the type of protecting group used.

A related observation had previously been reported by Paterson et al.[4a] These authors found that the reaction of aldehydes with boron enolates generated from α-benzoyloxy ethyl ketone **1a** and Chx_2BCl gave rise to *anti* aldols, as expected for this reagent, which is assumed to promote the formation of *E* enolates. In contrast, the benzylated analogue **1b** gave *syn* aldols under the same reaction conditions (Scheme 1). The aforementioned authors explained these findings by assuming the formation of a *Z* enolate in the latter case. This was attributed in turn to stereoselective deprotonation of a five-membered chelate involving the boron and the two oxygen atoms of **1b**. Such a chelate would be disfavored if the α-oxygen atom were bound to an electron-withdrawing group (as in **1a**), in which case the

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(1) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203−331. (c) Heathcock, C. H., *Aldrichimica Acta* **1990**, *23*, 99−111. (d) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2. (e) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317−338. (f) Braun, M. In *Houben-Weyl's Methods of Organic Chemistry, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. 3, pp 1603−1666, 1713−1735. (g) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200.

(2) (a) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114.

(3) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677−683.

(4) (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083−9086. (b) Goodman, J. M. *Tetrahedron Lett.* **1992**, *33*, 7219−7222. (c) Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, *33*, 7223−7226.

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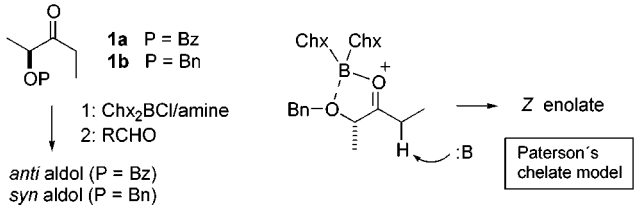
Scheme 1

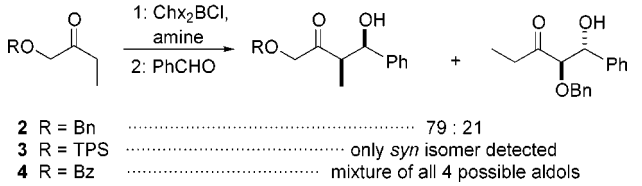


enolization takes place in the expected way to yield an *E* enolate.[4b,c]

We were interested in knowing (a) whether this is a general feature of ketones having donor atoms at C-α and (b) to which extent the steric course of the enolization process can be modulated through the use of appropriate O-protecting groups. The latter were thus selected to either favor (benzyl, Bn) or disfavor (acetate, Ac; benzoate, Bz; pivaloate, Piv; triethylsilyl, TES; *tert*-butyldimethylsilyl, TBS; *tert*-butyldiphenylsilyl, TPS) the formation of chelates.[5]

We initiated a preliminary study on the α-oxygenated ethyl ketones **2**−**4**, which bear an oxygen at only one of the α-carbon atoms. Four aldols can be formed in principle here. These ketones were enolized with Chx_2BCl/triethylamine[6] and then allowed to react with benzaldehyde as the model enolate acceptor. To establish the stereochemical course of the process (*syn* vs *anti*), as well as the regioselectivity,[7] we applied the same methodology used in our previous reports:[3] the aldols were reduced in situ with $LiBH_4$, and the 1,3-diols formed in this way[8] were transformed into the corresponding acetonides. The latter were then analyzed by ^1H and ^{13}C NMR.[9] The results are shown in Scheme 2.

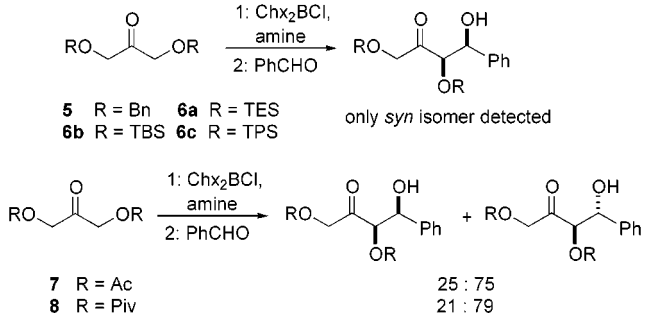
Scheme 2



It is worth noting that ketones **2** and **3** displayed a marked preference for the formation of a *syn* aldol, which in the case of the silylated ethyl ketone **3** was the only isomer detected by high-field NMR.[6] Minor amounts of a second regioisomeric[7] *anti* aldol were formed, however, in the case of **2**. The aldolization was very unselective in the case of ketone **4** (all four possible aldols were formed with none of them being clearly predominant) so that no efforts were undertaken to separate and identify the individual isomers.

We then studied the symmetrical ketones **5**−**8**[10,11] with oxygen atoms at both α-carbon atoms. Regioisomerism is not an issue here, and only two aldols, *syn* or *anti*, can be formed. The results are shown in Scheme 3.

Scheme 3



For ketones **5** and **6a**−**c**, which bear benzyl or bulky silyl groups, *syn* aldols are almost exclusively formed (assumedly via *Z* enolates). It is worth mentioning here that, in contrast to the situation described in a recently reported paper,[12] the three silylated ketones **6a**−**c** behave in the same way,

(5) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc*. **1992**, *114*, 1778−1784.

(6) The appropriate ketone (1 mmol) dissolved in anhydrous ether (3 mL) was added at −78 °C to a stirred solution prepared by mixing Chx_2BCl (neat, 394 μL, ca. 1.8 mmol) and Et_3N (278 μL, 2 mmol) in anhydrous Et_2O (6 mL). After stirring for 10 min, the temperature of the mixture was increased to 0 °C and maintained at this value for 1 h. After recooling to −78 °C, a solution of benzaldehyde (4 mmol) in ether (6 mL) was added, and the reaction mixture was stirred at the same temperature for 5 h. After this time, a 2 M solution of $LiBH_4$ in THF (1.5 mL, 3 mmol) was added via syringe, and the stirring was continued for 2 h. The reaction was then quenched with pH 7 phosphate buffer (6 mL) and MeOH (6 mL), followed by a 30% aqueous H_2O_2 solution (3 mL). After stirring for 1 h at room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried on anhydrous Na_2SO_4. Solvent removal in vacuo afforded an oily residue, which was dissolved in a mixture of acetone (8 mL) and 2,2-dimethoxypropane (2 mL). After *p*-toluenesulphonic acid (20 mg) and activated 3 Å molecular sieves (300 mg) were added, the mixture was stirred overnight under Ar at room temperature, filtered through a pad of silica gel, evaporated in vacuo, and chromatographed on silica gel (hexanes/Et_2O 19:1, then 9:1). This yielded the acetonides, which were then analyzed by means of ^1H and ^{13}C NMR. The chemical yields of the aldolization step and (in parentheses) the overall yields of the aldolization−reduction−acetalization sequence were **2**, 50 (58); **3**, 92 (65); **4**, 87 (−); **5**, 30 (35); **6a**, 85 (48); **6b**, 88 (55); **6c**, 89 (59); **7**, 63 (40); **8**, 85 (51); **9**, 87 (52); **10**, 90 (55). Aldols prepared from ketones **2**, **5**, and **7** were unstable to chromatography on silica gel; this explains the low yields in the isolation of the aldols themselves. The diastereomeric ratios were estimated by $^1H/^{13}C$ NMR of the crude aldolization mixture, prior to chromatography. For ketones **3**, **5**, **6a**−**c**, and **10**, no minor aldols were detected by NMR. At the signal/noise ratio of the measured spectra, this means more than 95% of the major isomer.

(7) Throughout the manuscript, we will use the abbreviated expression "regioisomeric aldols" with the actual meaning of "aldols formed through regioisomeric enolates." Predictions of regioselectivity in the enolization of nonsymmetrical α-oxygenated ketones constitute a difficult issue: Paquette, L. A.; O'Neil, S. V.; Guillo, N.; Zeng, Q.; Young, D. G. *Synlett* **1999**, 1857−1866.

(8) Paterson, I.; Channon, J. A. *Tetrahedron Lett*. **1992**, *33*, 797−800.

(9) Relative configurations were deduced from ^1H NMR data (coupling constant values and NOE measurements), as well as from the ^{13}C NMR chemical shift values of the acetonide methyl groups. See: Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res*. **1998**, *31*, 9−17.

(10) Complete experimental procedures, including the preparation of all new model ketones described in this paper and physical data thereof, will be described in a future paper.

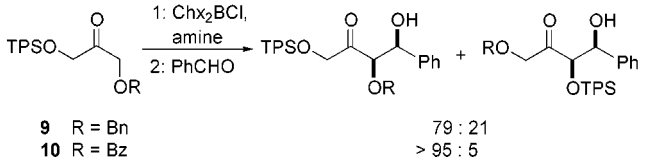
(11) Aldol reactions with dihydroxyacetone derivatives have recently been reported: (a) Majewski, M.; Nowak, P. *J. Org. Chem*. **2000**, *65*, 5152−5160. (b) Kim, K. S.; Hong, S. D. *Tetrahedron Lett*. **2000**, *41*, 5909−5913.

(12) Galobardes, M.; Gascón, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett*. **2000**, 2599−2602.

regardless of the size of the silyl group. Substrates **7** and **8** are α-acyloxy ketones, so that preferred formation of *anti* aldols (via *E* enolates) is not unexpected. However, even here a non-negligible percentage of *syn* isomers (>20%) is also formed.

We finally studied the case of the nonsymmetrical α,α′-dioxygenated ketones **9** and **10** (Scheme 4), where the issue

Scheme 4



9 R = Bn
10 R = Bz

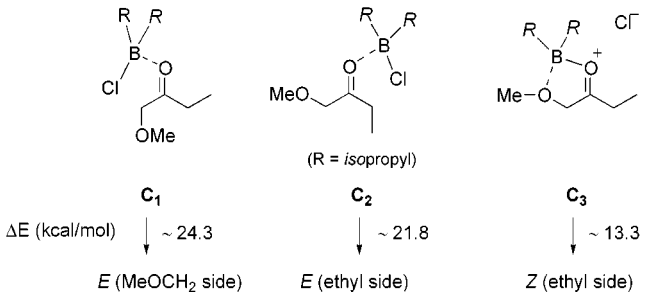
79 : 21
> 95 : 5

of regioisomerism appears again. The behavior of **10** shows a clear point of interest: one single *syn* aldol is formed with complete regio- and stereoselectivity, even though both O-protecting groups at each side of the carbonyl group (TPS, Bz) are expected to prevent chelation. Ketone **9** also gives only *syn* aldols, though the process is not completely regioselective here.

If we try to explain these results, according to Paterson's model,[4] through the formation of a five-membered chelate (Scheme 1), we would have to admit that the extremely bulky TPS group does not prevent the chelation from occurring. This is, however, an unlikely assumption.[5,13] In the case of ketones **3**, **6c**, **9**, and **10**, a chelated intermediate similar to that displayed in Scheme 1 (with TPS instead of Bn) would exhibit a high steric crowding between the boron-bound ligands (cyclohexyl groups) and the TPS group.[13] We must therefore conclude that, at least for these sterically crowded substrates, structural factors other than chelation play a role in controlling the stereochemical outcome of the enolization process.

Quantitative studies are thus needed for a better understanding of the enolboration reaction. Since the enolization process occurs under kinetic control, these studies should be focused on the relative energies of the alternative transition states of the irreversible deprotonation step. As a matter of fact, we have recently performed ab initio calculations on the enolization process of 3-pentanone with trimethylamine and dialkylboron chlorides R_2BCl of variable steric size (R = H, Me, *i*Pr).[14] We are presently extending these ab initio calculations to the enolization of model α-oxygenated ketones with diisopropylboron chloride and trimethylamine. For one model ketone, 1-methoxybutan-2-one (Scheme 5),

Scheme 5



we have already found optimized structures for the two nonchelated complexes $\mathbf{C_1}$ and $\mathbf{C_2}$, as well as for the chelate $\mathbf{C_3}$.[15] Values of energy barriers for transition states have also been calculated.

Although the results are still preliminary, we can now assert that the preferred conformations of these complexes are very different from each other, and the pertinent α-hydrogen atoms are left in different degrees of steric exposure to the deprotonating base. Preliminary values of the energy barriers (Scheme 5) for the alternative deprotonation processes (calculated at the HF/6-31G** level) have recently been obtained.[15] They predict that *E* enolates should be preferentially formed from complexes $\mathbf{C_1}$ and $\mathbf{C_2}$ (on the methoxymethyl side for $\mathbf{C_1}$ and on the ethyl side for $\mathbf{C_2}$). Furthermore, it is predicted that a *Z* enolate (on the ethyl side) will be formed from chelate $\mathbf{C_3}$ through deprotonation taking place *anti* to the boron atom. Since the calculated energy barrier in the latter case is also lower than those for $\mathbf{C_1}$ and $\mathbf{C_2}$, the *syn* isomer (ethyl side) is predicted to be the main aldol, in agreement with the experimental result observed for the closely related ketone **2** (Scheme 2).

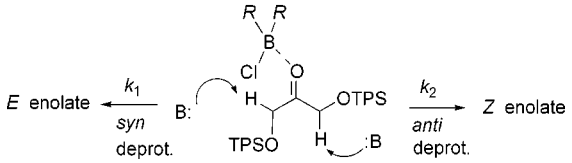
It thus seems that the chelation model reasonably explains the results observed with unhindered α-alkoxy ketones. However, it still remains to be seen which results will be derived from calculations with model ketones bearing bulky α-silyloxy groups, where chelation is unlikely. In the absence of the final results of these calculations,[15] we now propose an alternative deprotonation model (Scheme 6) presented in a qualitative way for ketone **6c**. It is assumed that the ketone−boron chloride complex predominantly adopts the conformation depicted below in which the dialkylboron chloride fragment and the two bulky TPS groups are located as far away from each other as possible. According to the Paterson−Goodman mechanism, *syn* deprotonation (i.e., proximal to the boron fragment) leads to the *E* enolate.[4] However, *anti* deprotonation (away from the boron moiety)

(13) It has been proposed that even the oxygen atom of the bulky OTIPS group can participate in chelations during additions of certain tin enolates to aldehydes: Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233−4236. More recently, the OTBS group has been claimed to be involved in chelates during additions of enol silanes to *β*-silyloxy aldehydes, provided that Me_2AlCl or $MeAlCl_2$ are used as Lewis acids: Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457−4460. However, while the steric crowding in the assumed six-membered chelates containing relatively long O−Sn or O−Al bonds might be possibly tolerable, this may not be true for the presently discussed five-membered chelate, which contains the shorter O−B bonds.

(14) Murga, J.; Carda, M.; Falomir, E.; Marco, J. A., submitted for publication.

(15) Murga, J.; Carda, M.; Falomir, E.; Marco, J. A., calculations on α-oxygenated ketones are still underway. Preliminary calculations on the molecular complex of *tert*-butyldiphenylsilyloxyacetaldehyde and diisopropyl boron chloride have shown that, in its preferred geometry, the C=O and the C_α−O bonds are almost antiperiplanar. In this geometry, which would lead by deprotonation to an *E* enolate, the TPS group and the boron ligands are spatially separated. The two protons at C_α are sterically shielded to a very similar degree by the bulky silyl group. This preliminary result led us to conceive the qualitative proposal depicted in Scheme 6.

Scheme 6



is expected to lead to the *Z* enolate. As a result of the steric crowding caused by the bulky OTPS group, the approach of the base to the *syn* α-hydrogen atom is very hindered, so that the *anti* α-hydrogen atom now becomes more accessible to deprotonation (i.e., $k_2 \gg k_1$), with the formation of the *Z* enolate and, consequently, the *syn* aldol being observed. This qualitative proposal is now being investigated at a quantitative level by means of ab initio studies, which will be reported in due course.[15]

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Supporting Information Available: Experimental conditions of the aldolization-reduction-acetalization procedure. Spectroscopic data of acetonides prepared in this way with stereochemical proof of their relative configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

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