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Influence of the protecting groups on the *syn/anti* stereoselectivity of boron aldol additions with erythrulose derivatives. A theoretical and experimental study☆

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Dedicated to Professor Emanuel Vogel, former Director of the Institute of Organic Chemistry at the University of Cologne, Germany, on the occasion of his 75th birthday

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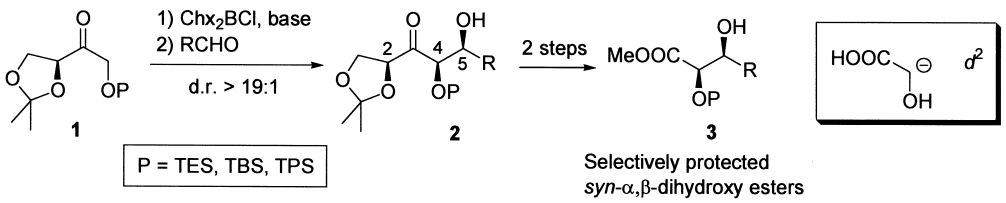
Abstract—We have investigated a series of aldol additions of protected L-erythrulose derivatives mediated by dicyclohexyl boron chloride. The *syn/anti* stereoselectivity has been found to depend on the type of protecting groups on the hydroxyl functions at C-3 and C-4. Thus, erythruloses benzylated at these hydroxyl groups gave only *syn* aldols while the corresponding benzoylated derivatives gave *anti* aldols under the same reaction conditions. The resident chirality of the enolate promoted a complete internal 1,3-induction, which was *syn* in both aldol types. Mechanistic proposals are advanced with support of both theoretical calculations and experimental data.

1. Introduction

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] Our current interest in the development of erythrulose[3] as a useful chiral C_4 building block for the stereocontrolled construction of polyfunctionalized structures has prompted us to investigate the enolization of protected derivatives thereof and the subsequent addition of the resulting enolates to aldehydes. We recently reported that L-erythrulose acetals of the general formula **1** (Scheme 1, protecting group P=triethylsilyl, TES; *t*-butyldimethylsilyl, TBS; or *t*-butyldiphenylsilyl, TPS), readily prepared in two steps from L-erythrulose,[4] were transformed into boron enolates provided that chlorodicyclohexylborane (Chx_2BCl) was used as the enolization reagent.[5–8] The boron enolates were then allowed to react with a range of achiral aldehydes to yield aldol adducts of the general formula **2** with a high degree of *syn* 1,2- and 1,3-induction (which corresponds to the 2,4-*syn*/4,5-*syn* relationship in **2**). It is worth noting here that the observed *syn* 1,2-induction is unexpected for Chx_2BCl as the enolization reagent.[5,6,9] Furthermore, we described the use of aldols **2** for the preparation of selectively protected *syn*-α,β-dihydroxy esters **3** in enantiopure form.[8c] Ketone **1** therefore behaves here as a chiral synthetic equivalent of the d^2 synthon hydroxyacetic (glycolic) acid enolate.[10]

A bibliographic review of the synthetic uses of Chx_2BCl for aldol additions revealed that, prior to our research, only one case of a *syn* aldol addition had been reported with this reagent. Paterson and co-workers described the use of



Scheme 1.

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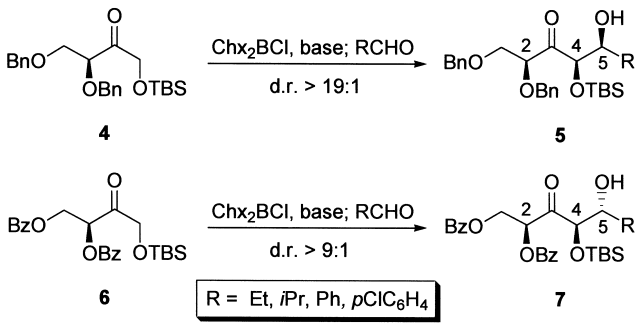
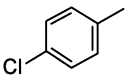


Scheme 2. Aldol reactions of erythrulose derivatives **4** and **6**.

Table 1. Aldol reactions of ketones **4** and **6** with aldehydes RCHO

R	Ketone (% yield of **5** or **7**)
Et	**4** (87) **6** (85)
*i*Pr	**4** (86) **6** (88)
*t*Bu	No reaction
	**4** (83) **6** (85)
	**4** (86) **6** (89)

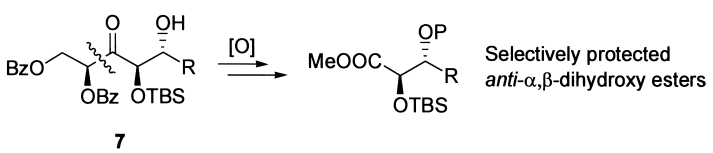
For reaction conditions, see Section 4. Dr's (determined by means of ^{1}H and ^{13}C NMR) were always >9:1 (with **4**, dr's were most often >19:1).

an ethyl ketone bearing an α′-benzyloxy group, where a *syn* aldol was formed with good diastereoselectivity (diastereoisomeric ratio, dr >19:1).[11] The authors related this unanticipated *syn* bias to the formation of a *Z* enolate instead of the expected *E* isomer, a feature attributed in turn to the deprotonation step taking place in a chelate involving the boron, carbonyl oxygen, and α-oxygen atoms.[12] They further reasoned that replacement of the benzyl by a benzoyl group would make the α-oxygen atom electron-poorer and thus inhibit the formation of such a chelate, with subsequent reversal of the stereochemical course to the expected *anti* aldol formation via an *E* enolate. Their conclusions were subsequently supported by experimental results.[11] However, if we assume that a *Z* enolate is also being formed in our case, we would have to imply that the α-oxygen atom of the acetal moiety in **1** participates in the formation of chelates, a conclusion which does not agree with our previous results concerning nucleophilic additions to the carbonyl group of such ketones.[3] In light of these findings, we decided to investigate whether the *syn*/*anti* stereoselectivity of our aldol reactions with erythrulose derivatives was similarly amenable to modulation through the use of protecting groups other than the acetal moiety on the hydroxyl functions at C-3 and C-4. In the present paper, we disclose in full the experimental details of aldol reactions previously reported in preliminary form.[13] Furthermore, we present the results of ab initio calculations aimed at a mechanistic explanation of the observed experimental results.

2. Results and discussion

We initially evaluated the 3,4-di-*O*-benzyl-L-erythrulose derivative **4**.[4] As with **1**, aldol additions of **4** using Chx_2BCl were fruitful, leading to aldol adducts **5** in good chemical yields as essentially single diastereoisomers (Scheme 2 and Table 1). The sterically hindered pivalaldehyde (*t*BuCHO) was the only aldehyde tested which did not react under the described conditions. The stereochemical course of the reaction was the same as for **1**, with only the 2,4-*syn*/4,5-*syn* stereoisomer being detected.[13] Thus, the change of the acetonide moiety to benzyl protecting groups does not change the stereochemical bias of the process. In line with Paterson's mechanistic reasoning, we subsequently investigated the stereochemical outcome of aldol reactions with 1-*O*-*t*-butyldimethylsilyl-3,4-di-*O*-benzoyl-L-erythrulose **6**, readily prepared from L-ascorbic acid.[4,8a,14] It turned out that, under the same reaction conditions used for **1** and **4**, ketone **6** underwent aldol additions with aldehydes to give aldol adducts **7** (relative configuration 2,4-*syn*/4,5-*anti*) with high yield and stereoselectivity (dr's were slightly lower than with **4** but still >9:1, see Scheme 2 and Table 1).[13,15] This result of the aldol reactions with ketone **6** is of great potential use in organic synthesis. For example, oxidative cleavage of the CO–C(OBz) bond under conditions similar to those used in our previous report[8c] should lead to selectively protected *anti* α,β-dihydroxy esters (Scheme 3).[16] In fact, Forsyth and co-workers have recently used **6** in just such a preparative role in their synthetic approach to azaspiracid.[17]

We were interested in understanding the mechanistic aspects of these aldol reactions. The first question we sought to answer concerned the actual configuration of the intermediate enol borane. In the case of **1** (P=TBS), this configuration was unequivocally established as *Z* via boron–silicon interchange as described by Evans and co-workers[18] (in all likelihood, the same result would be observed with α-benzyloxy ketone **4**). We also investigated the influence of some experimental factors on the outcome of the aldol reactions, using **1** (P=TBS) or **4** and benzaldehyde as the model reagents. The results of these studies are shown in Table 2. Under the standard reaction conditions (cond. 1),[8] aldolizations take place smoothly with high yields and only stereoisomers **2** or **5**, respectively, are detected (yields in Table 1). Neither the steric bulk of the base nor the solvent (Et_2O or CH_2Cl_2) plays a determinant



Scheme 3.

Table 2. Influence of experimental factors on the outcome of boron aldol reactions with **1** or **4**

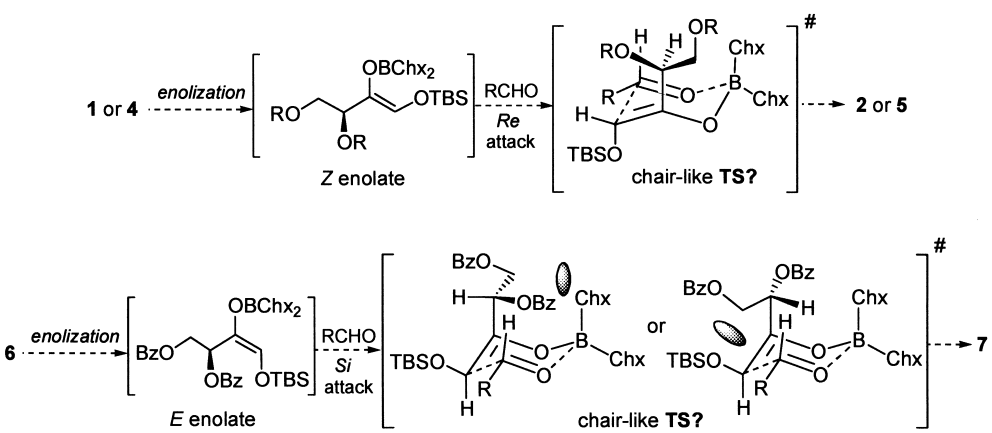
Conditions	1[a]	2[b]	3[c]	4[d]	6[e]	7[f]	8[g]
Reaction product	**2** or **5**[h]	**2** or **5**[h]	**2** or **5**[h]	**2** or **5**[h]	Starting compounds	**2** or **5**[h]	Decomp.

[a] Standard reaction conditions: (i) enolization, Et_3N/1.8 equiv. Chx_2BCl in Et_2O, 0°C, 30 min. (ii) Aldolization: 0°C, 4 h.
[b] As for cond. 1, but replacing $EtNMe_2$ or $EtNiPr_2$ as the base instead of Et_3N, either with Et_2O or with CH_2Cl_2 as the solvent.
[c] As for cond. 1, but aldolization conducted for 5 h at −78°C.
[d] As for cond. 1, but enolization conducted for 6 h at −50°C and aldolization for 5 h at −78°C.
[e] As for cond. 1 but with ≤1.3 equiv. Chx_2BCl.
[f] As for cond. 1 but with 2.5 equiv. Chx_2BCl.
[g] As for cond. 1, but with ≥3 equiv. Chx_2BCl.
[h] Yields and dr's are similar under all these conditions.

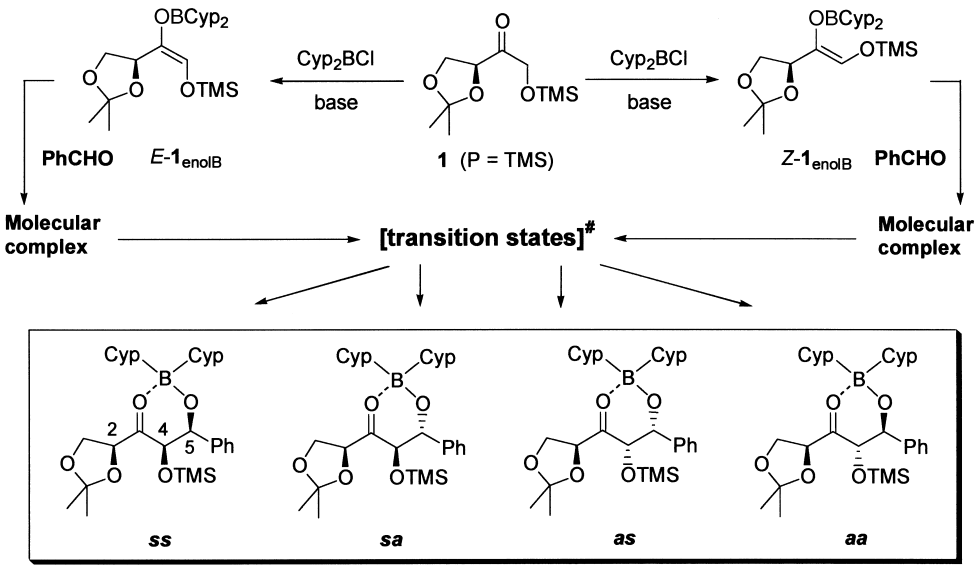
role in the outcome of the aldolization (cond. 2), yields and dr's being the same. We have also found that the aldol addition step takes place readily even at −78°C (cond. 3). However, it is much more comfortable to perform the reaction at 0°C, and neither yields nor dr's are compromised. The enolization step turns out to be rate-determining and requires temperatures ≥−50°C to take place at an acceptable rate (cf. cond. 4). Although the idea of the kinetic formation of an *E* enolate, followed by rapid *E*→*Z* isomerization, is conceivable in principle, such isomerizations have been found to take place at much higher temperatures, so they may ruled out in the present case.[18] The boron aldol reaction requires a minimum of about 1.7 equiv. of Chx_2BCl to work efficiently (we routinely use 1.8 equiv.); an increase of the amount of chloroborane does not change the final result and even begins to cause decomposition above 3 equiv. (cond. 6–8).[19]

On the basis of these experimental facts, the 1,2-*syn* stereopreference of the aldol processes with **1**/**4** can be qualitatively explained by supposing the occurrence of a cyclic, chair-like transition state (TS) of the Zimmermann–Traxler type (Scheme 4),[20] in which the chiral *Z* enolate (more specifically the *Re* side of the reacting enolate carbon) selectively attacks the *Re* side of the aldehyde carbonyl group.[21,22] This TS orients the C–O bond of the secondary OBn group and the C–O bond of the enolate in the electronically more favorable *anti* coplanar arrangement, in which dipolar repulsions are minimized. Moreover, the bulky groups at the stereogenic carbon (OBn and CH_2OBn) point away from the cyclohexyl groups on the boron atom. In this manner, the formation of the 2,4-*syn*/4,5-*syn* stereoisomer would receive a qualitatively reasonable explanation.[18,21] The boron enolate of ketone **6**, however, behaves differently in that: (a) it gives rise to stereoisomer **7** (1,2-*anti* stereopreference). (b) It attacks the *Si* side of the aldehyde carbonyl group (Scheme 2). The formation of an *anti* aldol leads in principle to the suggestion that the enolate of **6** has the *E* configuration. If we thus construct a chair-like TS similar to that of the process **1** (**4**)→**2** (**5**), we no longer find all the favorable features which characterized those TSs. Scheme 4 shows that there is a marked steric crowding between one of the boron ligands and one of the bulky groups at the stereogenic C_α carbon (OBz in the TS depicted in the left). If we try to avoid this by rotation of the C_O–C_α bond, a considerable degree of $A^{(1,3)}$ strain[23] appears between the CH_2OBz and OTBS groups (this factor is much less a concern with the *Z* enolate, where an H atom replaces the OTBS group). Among the various mechanistic alternatives which may be proposed, one of them is that aldol reactions of **6** may take place through a non-chair TS.

In order to find answers to these questions, we have undertaken ab initio quantum-mechanical calculations.[8a,24] In view of the high number of atoms involved in the aldolization step, we used a somewhat reduced model for these theoretical studies. Acetonide **1** (P=$SiMe_3$) was the model ketone, whereas benzaldehyde was the reacting aldehyde (see Scheme 5). For the enolization reagent, the cyclohexyl groups were replaced by cyclopropyl (Cyp) groups.[25] In order to make a complete study, the two possible boron enolates, *E*-$\mathbf{1}_{enolB}$ and *Z*-$\mathbf{1}_{enolB}$, were included in the calculations. The four diastereoisomeric aldols which can be formed, or more precisely the cyclic boron aldolates,



Scheme 4. Tentative mechanistic proposals for aldol additions with ketones **1**/**4** and **6**.



Scheme 5. Aldolizations of ketone **1** (P=TMS) and benzaldehyde mediated by Cyp_2BCl (Cyp=cyclopropyl).

were designated *ss*/*aa* and *as*/*sa* (Scheme 5; the stereochemical descriptors *s*, *syn*, and *a*, *anti*, refer here in the indicated order to the relative configurations at C_2-C_4 and C_4-C_5).

We first studied the initial step of the aldol addition process, i.e. the formation of the molecular complexes between benzaldehyde and the two boron enolates. These molecular complexes were found to be more stable than the starting molecules, and their formation had a negligible activation barrier. We then calculated the energy barriers of the TSs of the key step, which leads from the molecular complexes to the four boron aldolates. Table 3 shows the calculated energy contents of each molecular complex and of the respective TS, which leads to the final aldolate. The energy barrier for the individual process is the difference between these two energy contents. As shown, when enolate *Z*-$\mathbf{1}_{enolB}$ reacts with the aldehyde carbonyl, the calculations predict that the lowest energy barrier (19.8 kcal/mol) is that leading to the *ss* aldol, in complete agreement with experimental results (Scheme 2). For the corresponding TS, our calculations predict a half-chair geometry (Fig. 1, lower right, and Table 4) very similar in its shape to the chair depicted in Scheme 4 (C=C···C=O dihedral angle, 70.8° vs 60° in an ideal chair). The other three TSs found consisted of another half-chair and two boats of the 'boat A' type.[8a,22c] The calculations further predict that the *aa* aldol is the thermodynamically most stable adduct. All these data confirm the conclusion that boron aldol additions with ketone **1** and **4** are kinetically controlled processes which yield *ss* aldols via the corresponding *Z* enolates.

Aldol reactions of α-benzoyloxy ketone **6** provide *sa* aldols **7**. As commented above, this strongly suggests the intermediacy of an *E* enolate[5] and possibly a non-chair geometry for the key TS. Several years ago, Paterson, Gennari and their groups have performed computational studies on aldol reactions of chiral *E* boron enolates of α′- or β′-oxygenated ethyl ketones with the aid of force-field analysis.[11a,22g] They concluded that such processes are controlled by a range of competing factors such as non-bonded interactions, $A^{(1,3)}$ strain, electrostatic repulsions between lone pairs at the enolate and substituent oxygen atoms, etc. The last factor was said by these authors to be important, as it causes the oxygen-bearing substituent at C_α to point inside the TS pseudocycle, away from the enolate oxygen. They proposed for these aldol reactions two types of competing TSs, one chair-like and another one which

Table 3. HF/6-31G*//3-21G total (au) and relative energies (kcal/mol, in parentheses), relative to the sum enolate+benzaldehyde, for the stationary points of the reaction between enolates *Z*-$\mathbf{1}_{enolB}$ or *E*-$\mathbf{1}_{enolB}$ with benzaldehyde

Enolate	Aldol	Complexes	TS	Products[a]
Z-$\mathbf{1}_{enolB}$	*aa*	−1579.292314 (−16.6)	−1579.237934 (+17.5)	−1579.323101 (−35.9)
Z-$\mathbf{1}_{enolB}$	*as*	−1579.288831 (−14.4)	−1579.242662 (+14.4)	−1579.309724 (−27.5)
Z-$\mathbf{1}_{enolB}$	*sa*	−1579.288845 (−14.4)	−1579.245151 (+13.0)	−1579.300597 (−21.8)
Z-$\mathbf{1}_{enolB}$	*ss*	−1579.277656 (−7.4)	−1579.246008 (+12.4)	−1579.297592 (−19.9)
E-$\mathbf{1}_{enolB}$	*aa*	−1579.281511 (−9.2)	−1579.247061 (+12.4)	−1579.323131 (−35.3)
E-$\mathbf{1}_{enolB}$	*as*	−1579.291385 (−15.4)	−1579.244974 (+13.7)	−1579.309824 (−27.0)
E-$\mathbf{1}_{enolB}$	*sa*	−1579.283213 (−10.3)	−1579.251315 (+9.7)	−1579.300617 (−21.2)
E-$\mathbf{1}_{enolB}$	*ss*	−1579.276658 (−6.2)	−1579.228651 (+23.9)	−1579.297622 (−19.3)

Total energies (hartrees) of the reactants are: *Z*-$\mathbf{1}_{enolB}$=−1235.833459; *E*-$\mathbf{1}_{enolB}$=−1235.834361; benzaldehyde=−343.432438. Geometrical optimizations of stationary points along the potential energy surface have been made at the HF level with the 3-21G basis set. Energy values were then computed at the HF level with the 6-31G* basis set. The energy barrier for each individual process is the difference between the energy contents of its respective TS and complex. All calculations were carried out with the Gaussian 98 suite of programs.[24]

[a] Boron aldolates.

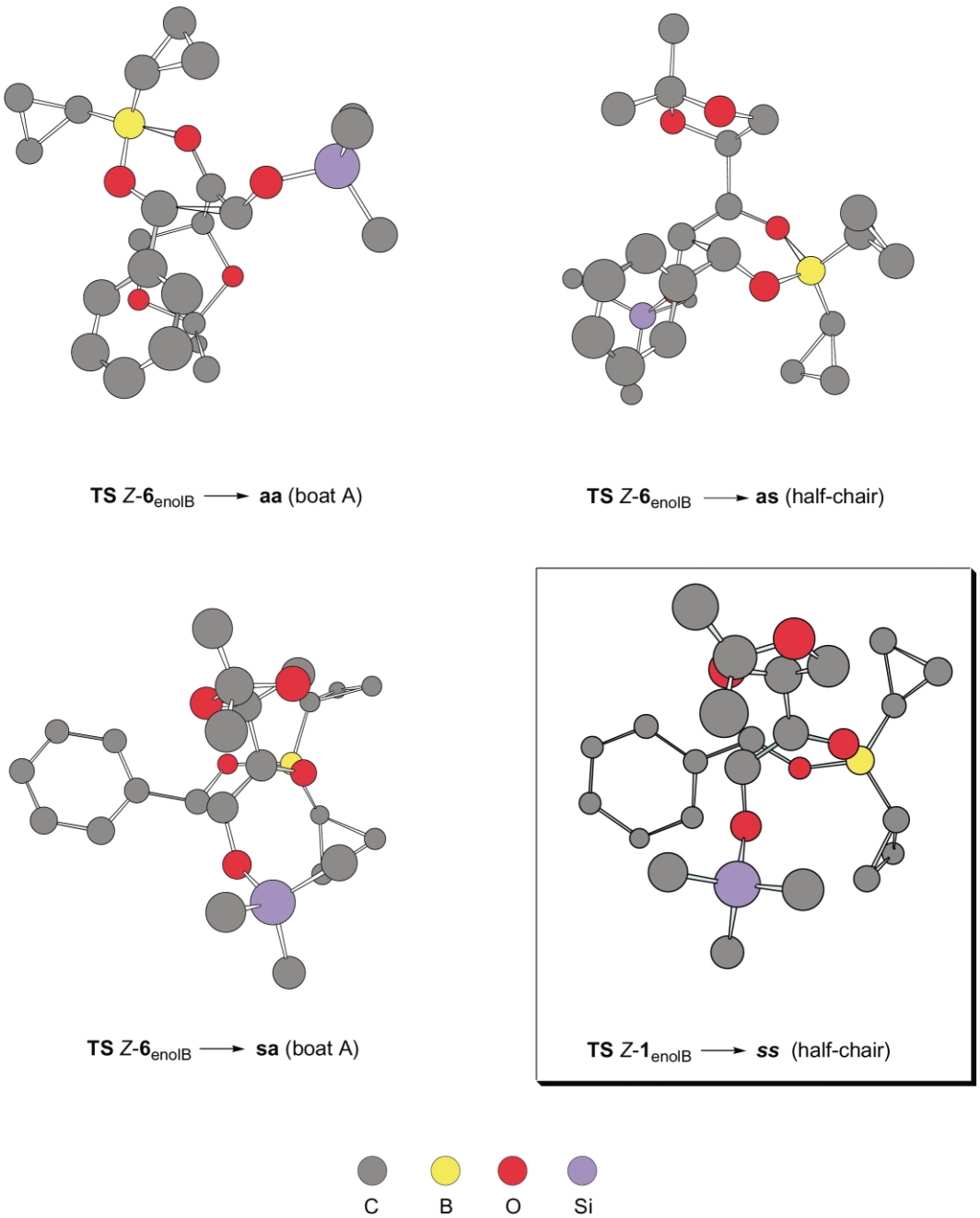


Figure 1. The four TSs for the aldol addition of the *Z* boron enolate of ketone **6** (R=TMS) with benzaldehyde. Hydrogen atoms have been omitted for clarity. The lowest energy barrier corresponds to the reaction leading to the *ss* boron aldolate.

Table 4. HF/3-21G geometric parameters (lengths in Å, angles in degrees) for all eight TSs

	Z-**1**$_{enolB}$				*E*-**1**$_{enolB}$			
	aa	*as*	*sa*	*ss*	*aa*	*as*	*sa*	*ss*
Bond lengths								
C···C	2.069	2.111	2.028	2.068	2.158	2.204	2.104	2.167
B–O$_{enolate}$	1.654	1.610	1.687	1.611	1.559	1.557	1.574	1.515
B···O$_{aldehyde}$	1.525	1.528	1.525	1.533	1.578	1.584	1.563	1.634
Dihedral angles								
C=C···C=O$_{aldehyde}$	−4.3	−67.5	2.0	70.8	73.2	45.3	−78.0	−56.4
C=C–O$_{enolate}$–B	−65.6	−51.7	−84.4	46.9	18.9	29.3	−17.2	−14.5
C=C···C–H$_{aldehyde}$	−120.8	55.4	119.5	−51.4	−48.1	164.0	43.1	−174.1

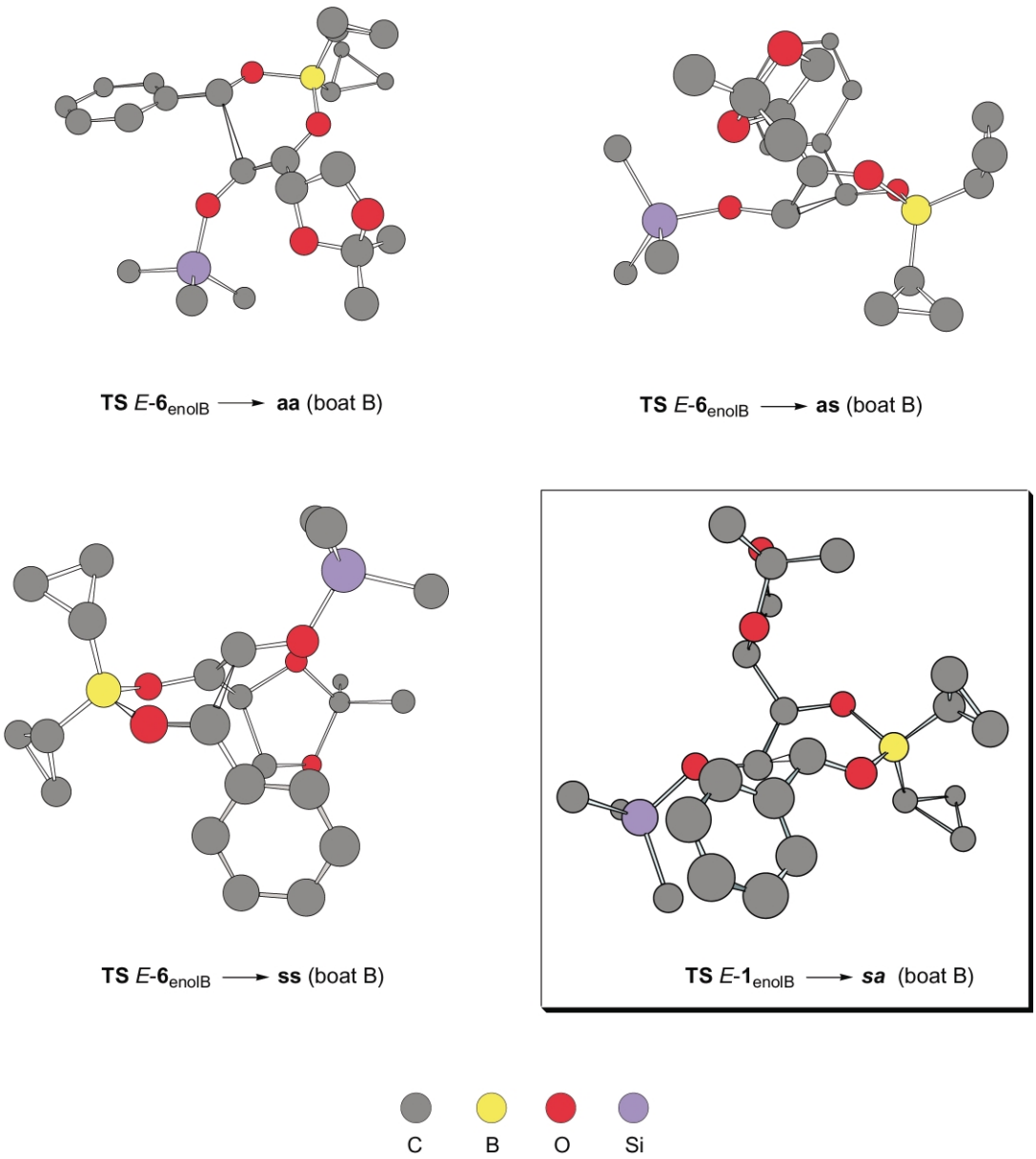
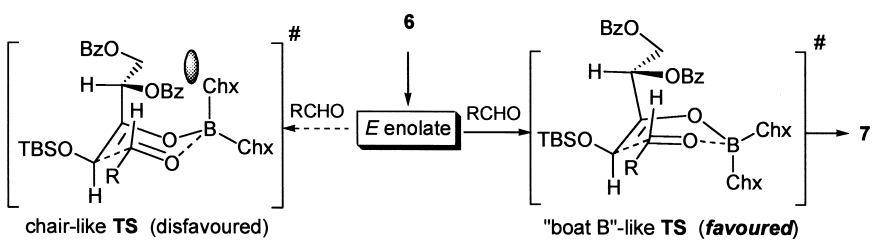


Figure 2. The four TSs for the aldol addition of the *E* boron enolate of ketone **6** (R=TMS) with benzaldehyde. Hydrogen atoms have been omitted for clarity. The lowest energy barrier corresponds to the reaction leading to the *sa* boron aldolate.

could be either chair-like or boat-like, depending of the nature of the groups at the stereogenic α carbon. For our model reaction, Table 3 shows that the lowest energy barrier leading to aldol *sa* is in fact that going through enolate *E*-**1**$_{enolB}$ (20 kcal/mol). Furthermore, the corresponding TS adopts a distorted geometry of the so-called 'boat B' type[22c] (see Fig. 2, lower right, and Table 4). Three further high-energy, boat-like TSs were found in our calculations but no chair-like TSs.[8a] A plausible explanation for a boat-like TS being energetically favored here is that it minimizes the A^{1,3} strain within the allylic moiety, as it is the H atom at C_α which faces the enolate OTBS group (Scheme 6; for the TS *E*-**1**$_{enolB}$⟶aldol *sa*, the calculated H–C_α–C=C dihedral angle is 26.2°). The steric crowding which would exist in the



Scheme 6. TSs for the aldol addition step of the reaction between the *E* boron enolate of ketone **6** and aldehyde RCHO.

chair TS between the OBz moiety and one of the boron cyclohexyl ligands (Scheme 6, left part) is relieved through the rotation of the two B–O bonds and the subsequent spatial separation between these groups. Apparently, these two favorable steric factors are quantitatively more important than the less favourable, non-*anti*coplanar alignment of the C–OBz and C–OB dipoles, which occurs in the boat B TS (see also Scheme 4). However, the relative importance of lone-pair repulsion in the different TSs is difficult to estimate and may not be a decisive factor in our case. In contrast with Paterson's and Gennari's examples,[11a,22g] ketone **6** (and **4** as well) contains oxygen atoms at *both* the C_α and C_β carbon atoms, so that a relative vicinity of one of these oxygen atoms to the enolate oxygen may be difficult to avoid.

A last question to be addressed here is why the formation of the *aa* aldol through a boat B TS is not favored in the case of **6**. In fact, an examination of the corresponding TS in the model reaction (Scheme 5, *E*-$\mathbf{1}_{enolB}$→aldol *aa*) does not reveal a high degree of $A^{(1,3)}$ strain nor an important steric crowding between the boron ligands and the dioxolane ring. However, it reveals sizeable non-bonding interactions, not present in the TS leading to aldol *sa*, between the dioxolane ring and the OTMS group (the counterparts of the 1,2-dibenzoyloxyethyl and OTBS moieties in **6**). Attempts at relieving this steric interaction through rotation of a C–C or a C–O bond would make other sources of internal strain (non-bonded interactions or dipolar repulsion within the $O–C_\alpha–C–O_{enolate}$ fragment) to increase their value. It is possible that the dioxolane ring of the model reaction is not a sufficiently good surrogate for the 1,2-dibenzoyloxyethyl moiety of **6**, as the latter fragment is less rigid and more capable of internal rotations. However, an ab initio modelization of the full molecule of **6** with its 61 atoms is beyond our computer capabilities.

3. Conclusions

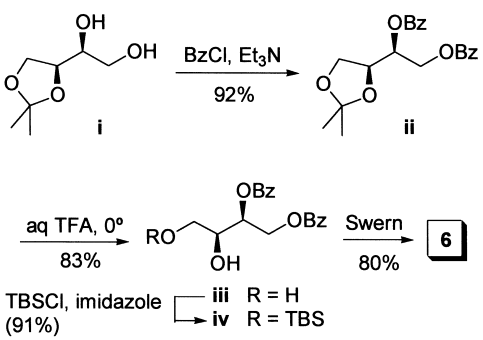
In summary, we have performed highly stereoselective aldol additions of two readily available erythrulose derivatives bearing different protecting groups. The nature of the latter has been found to play a decisive role as regards the sterochemical outcome of the process; when suitably chosen, these protecting groups make possible the preparation of either *syn* or *anti* aldols, precursors in turn of selectively protected *syn* or *anti* α,β-dihydroxy esters, respectively: Erythrulose therefore turns out to behave here as a synthetic equivalent of the chiral d^2 synthon hydroxyacetic (glycolic) acid enolate. This opens a range of synthetic possibilities which are currently being explored within our group.

4. Experimental

4.1. General

NMR spectra were measured at 400 or 500 MHz in $CDCl_3$ solution at 25°C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Unambiguous assignments of ^1H and ^{13}C NMR signals were made with a combination of spin decoupling, DEPT and HMQC experiments. Mass spectra were run by the electron impact (EIMS, 70 eV) or with the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR spectra were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25°C. Reactions which required an inert atmosphere were carried out under argon with flame-dried glassware. Et_2O was freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Chx_2BCl was generated by hydroboration of cyclohexene with monochloroborane as reported[26] and used neat. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, extraction with the indicated solvent, additional washing with 5% aqueous $NaHCO_3$, (if acids had been utilized in the reaction) or with 5% aqueous HCl (if bases had been utilized), then again with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and elimination of the solvent in vacuo. The obtained material was then chromatographed on a silica gel column (Süd-Chemie AG, 60–200 μ) with the indicated eluent.

4.1.1. Preparation of (*S*)-3,4-dibenzoyloxy-1-(*tert*-butyldimethylsilyloxy)butan-2-one (6). A solution of L-threitol 1,2-acetonide (**i**)[14] (4.86 g, ca. 30 mmol) in dry CH_2Cl_2 (75 mL) was ice-cooled under Ar and treated sequentially with triethyl amine (8.5 mL, ca. 60 mmol), DMAP (36 mg, 0.3 mmol) and benzoyl chloride (8.1 mL, ca. 70 mmol). After removal of the ice bath, the mixture was stirred overnight at room temperature, then poured onto brine and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous ammonium chloride, then again with brine and finally dried on anhydrous sodium sulfate. Solvent removal in vacuo was followed by chromatography on silica gel (hexane–EtOAc 9.1) to furnish dibenzoate (**ii**) (10.2 g, 92%) as a colorless oil, $[\alpha]_D=-24.6$ (*c* 1.5; $CHCl_3$); ^1H NMR (500 MHz) δ 8.10–8.00 (m, 4H), 7.60–7.35 (m, 6H), 5.62 (dt, 1H, *J*=7, 4.2 Hz), 4.68 (dd, 1H, *J*=11.8, 4.2 Hz), 4.64 (dd, 1H, *J*=11.8, 7 Hz), 4.52 (ddd, 1H, *J*=6.8, 6, 4.2 Hz), 4.15 (dd, 1H, *J*=8.5, 6.8 Hz), 3.96 (dd, 1H, *J*=8.5, 6 Hz); ^{13}C NMR (125 MHz) δ 166.16, 166.0, 133.2, 133.1, 129.8, 129.7, 129.6, 128.4, 128.3, 110.0, 74.5, 71.2, 65.5, 63.5, 26.3, 25.2; IR (NaCl) 3450 (br), 3064, 2988, 2937, 2890, 1724, 1602, 1585, 1452, 1382, 1372, 1316, 1284, 1264, 1110, 1070, 1026, 910, 847, 735, 712 cm^{-1}.



Compound (**ii**) (10 g, 27 mmol) was dissolved in ice-cooled 1:1 aqueous trifluoroacetic acid (100 mL) and stirred at 0°C for 30 min (note of caution: if this time is exceeded, migration of benzoyl groups may take place with the corresponding decrease in the yield of (**iii**). The mixture was then brought to neutral pH through slow and careful addition of aqueous Na_2CO_3 at 0°C (pH control!) and subsequently poured onto brine. After extraction with CH_2Cl_2, the organic layer was washed with brine and dried on anhydrous Na_2SO_4. Column chromatography on silica gel afforded L-threitol dibenzoate (**iii**) (7.4 g, 83%) as a colorless oil, $[\alpha]_D=-24$ (*c* 1.1; $CHCl_3$); ^1H NMR (400 MHz) δ 8.10–8.00 (m, 4H), 7.60–7.35 (m, 6H), 5.59 (ddd, 1H, *J*=6.9, 4.4, 3.8 Hz), 4.76 (dd, 1H, *J*=11.8, 4.4 Hz), 4.64 (dd, 1H, *J*=11.8, 6.9 Hz), 4.09 (m, 1H), 3.74 (m, 1H), 2.90 (br s, 1H), 2.60 (br s, 1H); ^{13}C NMR (100 MHz) δ 166.6, 166.4, 133.6, 133.3, 129.9, 129.4, 129.2, 128.6, 128.5, 72.2, 71.0, 63.1, 63.0; IR (NaCl) 3450 (br), 3065, 3031, 2958, 1721, 1601, 1584, 1432, 1316, 1266, 1070, 803 cm^{-1}.

The previous compound (6.6 g, ca. 20 mmol) was dissolved under Ar in dry DMF (10 mL), cooled to 0°C and treated with imidazole (1.7 g, 25 mmol) and *t*-butyldimethylsilyl chloride (3.32 g, ca. 22 mmol). The mixture was then stirred for about 8 h at the same temp. (TLC monitoring!), poured onto brine and extracted with Et_2O. The combined organic layers were washed with satd. aqueous ammonium chloride, then again with brine and finally dried on anhydrous sodium sulfate. Solvent removal in vacuo was followed by chromatography on silica gel (hexane–EtOAc 9.1) to yield the silylated derivative (**iv**) (8.09 g, 91%) as a colorless oil, $[\alpha]_D=-23.2$ (*c* 1.2; $CHCl_3$); ^1H NMR (500 MHz) δ 8.10–8.00 (m, 4H), 7.60–7.35 (m, 6H), 5.64 (dt, 1H, *J*=6.9, 4.2 Hz), 4.74 (dd, 1H, *J*=12, 4.2 Hz), 4.64 (dd, 1H, *J*=12, 6.9 Hz), 4.07 (ddd, 1H, m), 3.82 (dd, 1H, *J*=10, 4.5 Hz), 3.78 (dd, 1H, *J*=10, 5.6 Hz), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz) δ 166.3, 166.0, 133.26, 133.1, 129.9, 129.8, 129.7, 129.6, 128.4, 128.3, 72.1, 70.8, 63.7, 63.4, 25.8, 18.2, −5.6; IR (NaCl) 3450 (br), 3060, 3030, 2954, 1720, 1600, 1538, 1315, 1260, 1110, 1066, 700 cm^{-1}.

A solution of oxalyl chloride (2.7 mL, ca. 30 mmol) in dry CH_2Cl_2 (50 mL) was cooled under Ar to −60°C and treated dropwise with a solution of DMSO (2.5 mL, ca. 35 mmol) in dry CH_2Cl_2 (25 mL). The mixture was then stirred for 2 min at the same temperature and treated sequentially with compound iv (6.67 g, ca. 15 mmol) dissolved in dry CH_2Cl_2 (50 mL) and, 15 min later, triethyl amine (10 mL, ca. 70 mmol). The mixture was stirred for 15 min a −60°C and then for 1 h at 0°C. After pouring onto brine and extraction with CH_2Cl_2, the organic layer was washed with 5% aqueous HCl, then again with brine, dried on anhydrous Na_2SO_4, evaporated in vacuo and chromatographed on silica gel (hexane–EtOAc 9.1). This furnished ketone **6** (5.31 g, 80%) as a colorless oil, $[\alpha]_D=-25.3$ (*c* 1; $CHCl_3$); ^1H NMR (500 MHz) δ 8.10–8.00 (m, 4H), 7.60–7.40 (m, 6H), 5.98 (t, 1H, *J*=4.1 Hz), 4.90 (m, 2H), 4.49 (s, 2H), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz) δ 203.2, 166.0, 165.6, 133.6, 133.4, 130.0, 129.7, 129.4, 129.0, 128.5, 128.4, 75.0, 68.4, 62.7, 25.8, 18.3, −5.6; IR (NaCl) 3440 (br), 3069, 2930, 2857, 1726, 1452, 1316, 1262, 1177, 1109, 1070, 1026, 838, 781, 709 cm^{-1}; HR FABMS *m/z* 443.1899 [M+H$^+$], calcd for $C_{24}H_{31}O_6Si$, 443.1890. Anal. Calcd for $C_{24}H_{30}O_6Si$: C, 65.13; H, 6.83. Found, C, 65.00; H, 6.99.

4.2. Experimental procedure for aldol additions of ketones 4 or 6 promoted by dicyclohexyl boron chloride

Chx_2BCl (395 μL, ca. 1.8 mmol) was added under Ar via syringe to an ice-cooled solution of Et_3N (280 μL, 2 mmol) in anhydrous Et_2O (5 mL). Erythrulose derivative **4** or **6** (1 mmol) was dissolved in anhydrous ether (5 mL) and added dropwise via syringe to the reagent solution. The reaction mixture was then stirred for 30 min. After addition of a solution of the aldehyde (1.5 mmol) in ether (6 mL), the reaction mixture was stirred at 0°C for 4 h. Then phosphate buffer solution (pH 7, 6 mL) and MeOH (6 mL) were added, followed by 30% aqueous H_2O_2 solution (3 mL). After stirring for 1 h at room temperature, the mixture was worked up (extraction with Et_2O). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexane–EtOAc 9:1, then 4:1) afforded the corresponding aldol addition product **5** or **7**. Chemical yields and dr are given in the paper (Table 1). When Et_2O was replaced by THF or CH_2Cl_2, or when Et_3N was replaced by $EtNMe_2$ or $EtNiPr_2$, yields and dr's remained essentially unchanged. When the TBS group at C-1 was replaced by a TES or a TPS group, yield and stereoselectivity also remained practically unchanged, even though the reaction with the TPS derivative was slower. The aldol addition step still takes place at −78°C although it requires a longer time (about 6–8 h). This low temperature may become necessary in the case of sensitive aldehydes.

4.2.1. (2*S*,4*R*,5*S*)-1,2-Bis(benzyloxy)-4-(*t*-butyldimethylsilyloxy)-5-hydroxyheptan-3-one (5, R=Et). Colorless oil, $[\alpha]_D=-61.4$ (*c* 3.7; $CHCl_3$); ^1H NMR (400 MHz) δ 7.35–7.25 (m, 10H), 4.75 (d, 1H, *J*=11.5 Hz), 4.68 (d, 1H, *J*=2 Hz), 4.57 (d, 1H, *J*=11.5 Hz), 4.56, 4.52 (AB system, 2H, *J*=12 Hz), 4.29 (dd, 1H, *J*=4.7, 3.3 Hz), 3.87 (dd, 1H, *J*=10.5, 3.3 Hz), 3.80 (m, 2H), 1.50 (m, 2H), 0.90 (s, 9H), 0.87 (t, 3H, *J*=7.5 Hz), 0.05 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz) δ 207.6, 137.8, 137.2, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 81.6, 77.9, 73.6, 73.1, 72.5, 69.4, 27.6, 25.8, 18.3, 10.2, −4.5, −5.4; IR (NaCl) 3470 (br), 3065, 3032, 2935, 2860, 1735, 1500, 1455, 1390, 1365, 1255, 1216, 1093, 1028, 887, 838, 780, 737, 700 cm^{-1}; HR FABMS *m/z* 495.2530 [M+Na$^+$], calcd for $C_{27}H_{40}O_5NaSi$, 495.2543. Anal. Calcd for $C_{27}H_{40}O_5Si$: C, 68.61; H, 8.53. Found, C, 68.81; H, 8.57.

4.2.2. (2*S*,4*R*,5*S*)-1,2-Bis(benzyloxy)-4-(*t*-butyldimethylsilyloxy)-5-hydroxy-6-methylheptan-3-one (5, R=*i*Pr). Colorless oil, $[\alpha]_D=-34.8$ (*c* 1.2; $CHCl_3$); ^1H NMR (400 MHz) δ 7.35–7.25 (m, 10H), 4.90 (d, 1H, *J*=1 Hz), 4.77 (d, 1H, *J*=11.2 Hz), 4.60–4.50 (m, 3H), 4.22 (dd, 1H, *J*=4.5, 3.1 Hz), 3.87 (dd, 1H, *J*=10.5, 3.1 Hz), 3.81 (dd, 1H, *J*=10.5, 4.5 Hz), 3.48 (br d, 1H, *J*=9 Hz), 1.70 (m, 1H), 0.96 (d, 3H, *J*=6.5 Hz), 0.89 (s, 9H), 0.74 (d, 3H, *J*=6.5 Hz), 0.06 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz) δ 207.5, 137.8, 137.1, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 81.9, 76.7, 76.4, 73.6, 72.5, 69.4, 31.5, 25.9, 19.3, 18.8, 18.4, −4.3, −5.4; IR (NaCl) 3450 (br), 3065, 3032,

2930, 2860, 1732, 1497, 1455, 1389, 1362, 1255, 1107, 1028, 837, 779, 737, 698 cm^{-1}; HR FABMS *m/z* 509.2715 M+Na^+], calcd for $C_{28}H_{43}O_5NaSi$, 509.2699. Anal. Calcd for $C_{28}H_{42}O_5Si$: C, 69.10; H, 8.70. Found, C, 69.00; H, 8.77.

4.2.3. (1*S*,2*R*,4*S*)-4,5-Bis(benzyloxy)-2-(*t*-butyldimethylsilyloxy)-1-hydroxy-1-phenylpentan-3-one (5, R=Ph). Colorless oil, $[\alpha]_D=-59$ (*c* 4.3; $CHCl_3$); ^1H NMR (400 MHz) δ 7.40–7.20 (m, 15H), 5.18 (d, 1H, *J*= 1.5 Hz), 4.89 (d, 1H, *J*=2 Hz), 4.79 (d, 1H, *J*=11.3 Hz), 4.60–4.50 (m, 3H), 4.28 (dd, 1H, *J*=4.5, 3.1 Hz), 3.90 (dd, 1H, *J*=10.5, 3.1 Hz), 3.84 (dd, 1H, *J*=10.5, 4.5 Hz), 0.72 (s, 9H), −0.18 (s, 3H), −0.44 (s, 3H); ^{13}C NMR (100 MHz) δ 206.8, 141.4, 137.8, 137.2, 128.6, 128.5, 128.4, 128.2, 128.0, 127.8, 127.3, 125.7, 82.3, 80.3, 73.6, 72.7, 69.4, 25.6, 18.2, −5.2, −5.9; IR (NaCl) 3470 (br), 3065, 3032, 2927, 2929, 2857, 1703, 1598, 1584, 1496, 1455, 1390, 1313, 1255, 1204, 1112, 1026, 837, 780, 745, 699 cm^{-1}; HR FABMS *m/z* 543.2531 [M+Na^+], calcd for $C_{31}H_{40}O_5NaSi$, 543.2542. Anal. Calcd for $C_{31}H_{40}O_5Si$: C, 71.50; H, 7.74. Found, C, 71.70; H, 7.77.

4.2.4. (1*S*,2*R*,4*S*)-4,5-Bis(benzyloxy)-2-(*t*-butyldimethylsilyloxy)-1-hydroxy-1-(4-chlorophenyl)-pentan-3-one (5, R=4-chlorophenyl). Colorless oil, $[\alpha]_D=-65.8$ (*c* 0.8; $CHCl_3$); ^1H NMR (400 MHz) δ 7.40–7.30 (m, 10H), 7.17 (d, 2H, *J*=8.5 Hz), 7.03 (d, 2H, *J*=8.5 Hz), 5.14 (d, 1H, *J*=1 Hz), 4.83 (d, 1H, *J*=1.5 Hz), 4.81 (d, 1H, *J*=11 Hz), 4.60–4.50 (m, 3H), 4.30 (dd, 1H, *J*=4.3, 3.2 Hz), 3.91 (dd, 1H, *J*=10.5, 3.2 Hz), 3.84 (dd, 1H, *J*=10.5, 4.3 Hz), 0.72 (s, 9H), −0.16 (s, 3H), −0.43 (s, 3H); ^{13}C NMR (100 MHz) δ 206.5, 140.2, 137.7, 137.1, 133.0, 128.7, 128.6, 128.5, 128.4, 128.1, 127.8, 127.2, 82.5, 80.1, 73.7, 72.7, 72.1, 69.2, 25.6, 18.2, −5.1, −5.9; IR (NaCl) 3450 (br), 3030, 2930, 2857, 1730, 1575, 1495, 1360, 1254, 1090, 940, 780 cm^{-1}; HR FABMS *m/z* 577.2169 [M+Na^+], calcd for $C_{31}H_{39}^{35}ClO_5NaSi$, 577.2153. Anal. Calcd for $C_{31}H_{39}ClO_5Si$: C, 67.07; H, 7.08. Found, C, 67.00; H, 7.21.

4.2.5. (2*S*,4*R*,5*R*)-1,2-Bis(benzoyloxy)-4-(*t*-butyldimethylsilyloxy)-5-hydroxyheptan-3-one (7, R=Et). Colorless oil, $[\alpha]_D=+27.1$ (*c* 5.2; $CHCl_3$); ^1H NMR (400 MHz) δ 8.10–8.00 (m, 4H), 7.60–7.30 (m, 6H), 6.01 (dd, 1H, *J*=5.6, 2.5 Hz), 4.96 (dd, 1H, *J*=12.3, 2.5 Hz), 4.80 (dd, 1H, *J*=12.3, 5.6 Hz), 4.30 (d, 1H, *J*=4.7 Hz), 3.80 (m, 1H), 3.10 (br s, 1H), 1.70–1.50 (m, 2H), 1.02 (t, 3H, *J*=7.5 Hz), 0.94 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz) δ 203.3, 166.3, 166.1, 133.7, 133.3, 130.0, 129.9, 129.7, 129.4, 128.7, 128.5, 128.4, 81.3, 76.3, 75.9, 63.0, 25.8, 25.7, 18.2, 10.4, −4.5, −4.8; IR (NaCl) 3490 (br), 3019, 2958, 2931, 2859, 1725 (br), 1602, 1452, 1264, 1216, 1112, 1070, 1026, 840, 757, 712 cm^{-1}; HR FABMS *m/z* 501.2306 [M+H^+], calcd for $C_{27}H_{37}O_7Si$, 501.2308. Anal. Calcd for $C_{27}H_{36}O_7Si$: C, 64.77; H, 7.25. Found, C, 64.81; H, 7.37.

4.2.6. (2*S*,4*R*,5*R*)-1,2-Bis(benzoyloxy)-4-(*t*-butyldimethylsilyloxy)-5-hydroxy-6-methylheptan-3-one (7, R=*i*Pr). Colorless oil, $[\alpha]_D=+20.5$ (*c* 3.2; $CHCl_3$); ^1H NMR (400 MHz) δ 8.10–8.00 (m, 4H), 7.60–7.30 (m, 6H), 6.04 (dd, 1H, *J*=6, 2.4 Hz), 4.98 (dd, 1H, *J*=12.2, 2.4 Hz), 4.80 (dd, 1H, *J*=12.2, 6 Hz), 4.49 (d, 1H, *J*=4.8 Hz), 3.51 (dt, 1H, *J*=7.5, 4.8 Hz), 3.00 (br d, 1H, *J*=7.5 Hz), 1.83 (m, 1H), 1.00 (d, 6H, *J*=6.5 Hz), 0.94 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz) δ 203.7, 166.3, 166.1, 133.7, 133.3, 130.0, 129.9, 129.8, 129.7, 129.5, 128.8, 128.6, 128.5, 79.9, 79.0, 76.6, 63.1, 29.5, 25.7, 19.8, 18.1, 17.9, −4.5, −4.8; IR (NaCl) 3470 (br), 3028, 2959, 1725, 1720sh, 1585, 1470, 1317, 1111, 840 cm^{-1}; HR FABMS *m/z* 515.2477 [M+H^+], calcd for $C_{28}H_{39}O_7Si$, 515.2465. Anal. Calcd for $C_{28}H_{38}O_7Si$: C, 65.34; H, 7.44. Found, C, 65.47; H, 7.57.

4.2.7. (1*R*,2*R*,4*S*)-4,5-Bis(benzoyloxy)-2-(*t*-butyldimethylsilyloxy)-1-hydroxy-1-phenylpentan-3-one (7, R=Ph). Colorless oil, $[\alpha]_D=-22.7$ (*c* 1.4; $CHCl_3$); ^1H NMR (400 MHz) δ 8.10–8.00 (m, 4H), 7.60–7.30 (m, 11H), 6.08 (dd, 1H, *J*=6.5, 2.8 Hz), 5.00 (dd, 1H, *J*=12.2, 2.8 Hz), 4.99 (d, 1H, *J*=7.5 Hz), 4.77 (dd, 1H, *J*=12.2, 6.5 Hz), 4.48 (d, 1H, *J*=7.5 Hz), 0.79 (s, 9H), −0.10 (s, 3H), −0.45 (s, 3H); ^{13}C NMR (100 MHz) δ 203.4, 166.1, 166.0, 140.3, 133.7, 133.3, 130.0, 129.8, 129.5, 128.9, 128.6, 128.4, 128.3, 127.3, 81.4, 76.3, 75.1, 62.9, 25.7, 18.1, −4.9, −5.9; IR (NaCl) 3440 (br), 3065, 3032, 2958, 2859, 1732, 1704sh, 1472, 1455, 1384, 1256, 1106, 838, 779 cm^{-1}; HR FABMS *m/z* 571.2135 [M+Na^+], calcd for $C_{31}H_{36}O_7NaSi$, 571.2128. Anal. Calcd for $C_{31}H_{36}O_7Si$: C, 67.86; H, 6.61. Found, C, 68.00; H, 6.75.

4.2.8. (1*R*,2*R*,4*S*)-4,5-Bis(benzoyloxy)-2-(*t*-butyldimethylsilyloxy)-1-hydroxy-1-(4-chlorophenyl)-pentan-3-one (7, R=4-chlorophenyl). Colorless oil, $[\alpha]_D=-30.2$ (*c* 0.8; $CHCl_3$); ^1H NMR (400 MHz) δ 8.10–8.00 (m, 4H), 7.60–7.30 (m, 10H), 6.03 (dd, 1H, *J*=6.5, 2.8 Hz), 4.99 (dd, 1H, *J*=12.1, 2.8 Hz), 4.97 (d, 1H, *J*=7.5 Hz), 4.75 (dd, 1H, *J*=12.1, 6.5 Hz), 4.40 (d, 1H, *J*=7.5 Hz), 0.81 (s, 9H), −0.07 (s, 3H), −0.41 (s, 3H); ^{13}C NMR (100 MHz) δ 203.0, 166.2, 166.1, 138.6, 134.1, 133.8, 133.3, 130.0, 129.7, 129.4, 128.6, 128.5, 128.4, 81.5, 75.6, 75.0, 62.8, 25.7, 18.1, −4.8, −5.8; IR (NaCl) 3490 (br), 3059, 2956, 2931, 2887, 2858, 1727 (br), 1602, 1584, 1493, 1452, 1265, 1177, 1110, 1094, 1015, 840, 781, 712 cm^{-1}; HR FABMS *m/z* 583.1944 [M+H^+], calcd for $C_{31}H_{36}^{35}ClO_7Si$, 583.1919. Anal. Calcd for $C_{31}H_{35}ClO_7Si$: C, 63.85; H, 6.05. Found, C, 64.00; H, 6.20.

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3. Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Castillo, E.; Murga, J. *J. Org. Chem.* **1998**, *63*, 698–707, and references cited therein.
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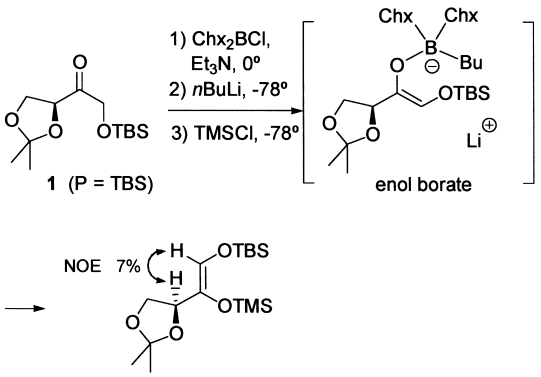
5. For a general review of boron aldol reactions: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200.
6. For the enolization of ketones with Chx_2BCl/tertiary amine to yield *E* boron enolates, see, for example: (a) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147–153. (b) Paterson, I.; Nowak, T. *Tetrahedron Lett.* **1996**, *37*, 8243–8246.
7. Aldol reactions with **1** proved unfeasible with the following enolization systems: (a) $Sn(OTf)_2$/*i*Pr_2NEt: Mukaiyama, T. *Aldrichim. Acta* **1996**, *29*, 59–76. $TiCl_4$/*i*Pr_2NEt: (b) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868. $SnCl_4$/*i*Pr_2NEt: (c) Rossi, T.; Marchioro, C.; Paio, A.; Thomas, R. J.; Zarantonello, P. *J. Org. Chem.* **1997**, *62*, 1653–1661. *n*-Bu_2BOTf/tertiary amine: (d) Mukaiyama, T.; Inoue, T. *Bull. Chem. Soc. Jpn* **1980**, *53*, 174–178. *n*-$BuBCl_2$/tertiary amine: (e) Ramachandran, P. V.; Xu, W.-C.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 769–772. While no aldolization was observed in several cases, extensive decomposition took place in reactions involving the Lewis acids $TiCl_4$ and $SnCl_4$, which attacked the acetal ring.[3]
8. (a) Falomir, E. PhD Thesis, University of Castellón, Spain, 1998. (b) Marco, J. A.; Carda, M.; Falomir, E.; Palomo, C.; Oiarbide, M.; Ortiz, J. A.; Linden, A. *Tetrahedron Lett.* **1999**, *40*, 1065–1068. (c) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677–683.
9. We have recently reported our first results of ab initio theoretical calculations on the enolization process with Chx_2BCl. These calculations predict the predominant formation of an *E* enolate in the case of a simple ketone (3-pentanone) bearing no further heteroatoms: Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2001**, *57*, 6239–6247. We are presently extending these theoretical investigations to the case of α-oxygenated ketones with the aim of testing Paterson's chelate hypothesis.
10. For further recent examples of the same chiron type, see: (a) Enders, D. In *Stereoselective Synthesis*; Ottow, E., Schöllkopf, K., Schulz, B.-G., Eds.; Springer: Berlin, 1993; pp 63–90. (b) Mukaiyama, T. *Aldrichim. Acta* **1996**, *29*, 59–76. (c) Díez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem. Int. Ed.* **2001**, *40*, 2906–2909.
11. (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083–9086. (b) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639–652. After our results, a further example of preparation of syn aldols using Chx_2BCl has appeared in the literature: (c) Galobardes, M.; Gascón, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2000**, *2*, 2599–2602.
12. Recent experimental findings of our group seem to indicate that this behavior may be general with α-oxygenated ketones, even in cases where the formation of chelates is unlikely: Murga, J.; Falomir, E.; Carda, M.; González, F.; Marco, J. A. *Org. Lett.* **2001**, *3*, 901–904.
13. Carda, M.; Falomir, E.; Murga, J.; Castillo, E.; González, F.; Marco, J. A. *Tetrahedron Lett.* **1999**, *40*, 6845–6848. The configurations of all aldol adducts were established through chemical correlations described in this paper.
14. L-Ascorbic acid was first converted into L-threitol 1,2-acetonide as reported: (a) Wei, C. C.; De Bernardo, S.; Tengi, J. P.; Borgese, J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3462–3467. (b) Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598–2602. L-Threitol 1,2-acetonide was then converted into **6** as described in Section 4.
15. Like **1**, ketones **4** and **6** did not yield aldol products with $Sn(OTf)_2$/EtN*i*Pr_2, $TiCl_4$/EtN*i*Pr_2, LDA or LDA/LiCl; instead, either decomposition or recovery of the starting product was observed. Aldolizations with *n*-Bu_2BOTf or *n*-$BuBCl_2$ failed also with **4** and **6**. In contrast to **1**, however, aldolizations performed with $SnCl_4$ in the presence of a tertiary amine[7c] were successful with **4** and afforded aldols **5**. Yields and

stereoselectivities were similar to those observed with Chx_2BCl.[8a]

16. There are not many alternatives in the literature for the preparation of such esters in enantiopure form. See, for example: (a) Andrus, M. B.; Sekhar, B. B. V. S.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035–3037. (b) Dixon, D. J.; Ley, S. V.; Polara, A.; Sheppard, T. *Org. Lett.* **2001**, *3*, 3749–3752. For previous work, see references cited in these papers.
17. Forsyth, C. J.; Hao, J.; Aiguadé, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 3663–3667.
18. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111(b) Enol borane formation from **1** (P=TBS) under the standard conditions was followed by addition of BuLi at −78°C and capture of the intermediate enol borate with trimethylsilyl chloride at the same temperature. Examination of the NMR spectra of the crude mixture showed the presence of only one enol silane. Its structure was determined from the spectral properties, whereas its configuration was ascertained by means of NOE experiments. We have also tried to perform an *E*→*Z* isomerization in our substrates. A solution of **1** (P=TBS) in hexanes was thus enolized under the standard conditions, and the solution was then heated at reflux for 3 h. However, extensive decomposition was the only result observed



19. Before the result of the boron–silicon interchange experiment was known, we had considered the possibility of a non-cyclic, extended TS with participation of an *E* enolate and two molecules of Chx_2BCl (see: Walker, M. A.; Heathcock, C. H.; *J. Org. Chem.* **1991**, *56*, 5747–5750). This alternative was made unlikely by the results of Table 2 and definitively ruled out after the *Z* enolate configuration was secured.
20. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.
21. For discussions on mechanistic models of aldol reactions with chiral enolates, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. (b) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99–111. (c) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499–2506. (d) Figueras, S.; Martín, R.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*, 1637–1640. (e) Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5593–5608. See also Refs. 5, 18 and 22.
22. For computational studies on boron aldol reactions, see, for example: (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481–493. (b) Goodman, J. M.; Kahn, S. D.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3295–3303. (c) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576–3581. (d) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471–3484. (e) Bernardi, F.; Robb, M. A.; Suzzi-Valli, G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1991**, *56*, 6472–6475. (f) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439–4458. (g) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685–696.
23. (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
24. Calculations have been carried out with the Gaussian 98 suite of programs: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseris, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrezewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Peterson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, R.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; González, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andrés, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian* 98 (Revision A.1); Gaussian Inc.: Pittsburgh, PA, 1998.
25. While the size of the boron-bonded alkyl groups has been shown to have a marked influence on the outcome of the enolization step,[5,9] this is not the case with the aldol addition step.[18,21,22] It may also be assumed that the size of these boron ligands is more decisive than its electronic nature in determining the energy of the TS of the aldol addition step. For this reason, we considered that a cyclopropyl group was a suitable model for a cyclohexyl group, even if they have different electronic features. We further considered that the dioxolane moiety of **1** (P=TMS) was an acceptable surrogate for either the bisbenzyloxyethyl fragment of **4** or the bisbenzoyloxyethyl of **6** and would simplify the calculations, as it contains fewer atoms.
26. Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287–11314.