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Understanding the Origins of Remote Asymmetric Induction in the Boron Aldol Reactions of β-Alkoxy Methyl Ketones

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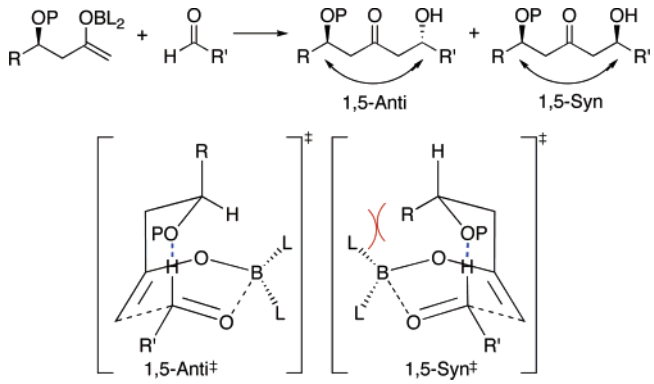
ABSTRACT



We report theoretical studies into the remote 1,5-stereoinduction shown by certain types of β-alkoxy methyl ketones in boron-mediated aldol reactions with achiral aldehydes. For a range of common alkoxy groups, our calculations are in excellent agreement with experimentally observed diastereoselectivities. In the aldol transition structures, a stabilizing hydrogen bond between the alkoxy oxygen and formyl proton leads to preferential formation of the 1,5-adduct, by minimizing steric interactions between the β-alkyl group and one of the ligands on boron.

The boron-mediated aldol reaction is widely used in the stereocontrolled synthesis of polyketide natural products, particularly, those of propionate origin.[1] It has seen less use in the synthesis of polyacetate-derived systems due to the generally lower stereoselectivities observed in the aldol reactions of methyl versus ethyl ketones. Reagent control is usually required to obtain useful levels of asymmetric induction in the addition of unsubstituted boron enolates to achiral aldehydes.[2] Paterson[3] and Evans[4,5] have reported quite remarkable cases of stereoinduction that occur in the boron aldol reactions of certain β-alkoxy methyl ketones, which gives rise to the 1,5-anti aldol adduct with high levels of diastereoselectivity (Table 1). The β-hydroxy ketones obtained may then be reduced in a controlled fashion, leading to the efficient synthesis of long-chain 1,3-polyols. This 1,5-anti aldol methodology has been strategically employed in the synthetic routes toward the natural products phorboxazole B,[6] roxaticin,[6] discodermolide,[8] peloruside A,[9] leucascandrolide A,[10] reidispongiolide A,[11] spongistatin,[12] and dolabelide D.[13]

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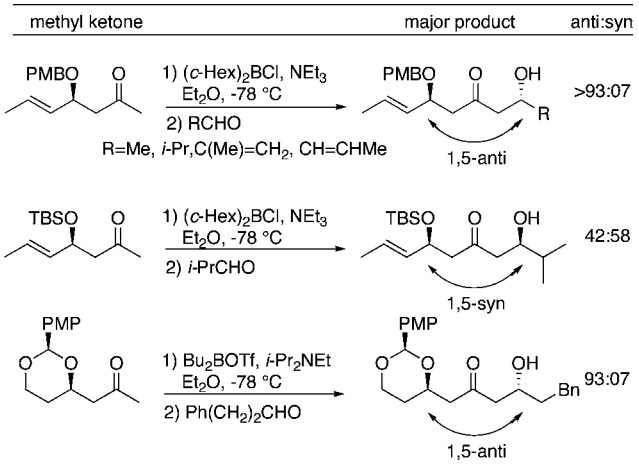
Table 1. Reactions of β-Alkoxy Methyl Ketones: PMB Ethers and PMP Acetals Show High 1,5-Anti Induction, Whereas Silyl Ethers Show Poor Selectivity[3,5]



Typically, high levels of 1,5-induction are obtained with benzylic and benzylidene acetal protecting groups in the β-hydroxy position, whereas silyl groups give rise to little or no selectivity. It is possible to achieve even higher levels of stereocontrol through the reinforcing influence of an Ipc-derived boron enolate. It is likely that electronic rather than steric effects are responsible for the enolate face selectivity and that the nature of the β-oxygen protecting group is critical in determining the level of induction. This is consistent with high 1,5-anti selectivity observed for β-substituents of a similar steric size but differing in their electronic properties and the observation that a decrease in solvent polarity results in higher selectivity.[5] It has been suggested that a π-stacking interaction between benzylic protecting groups and the boron enolate is important in the cyclic aldol transition state.[15] However, this model does not account for 1,5-anti selectivity where both β-substituents possess aromatic groups. It also fails to explain why nonaromatic groups, such as β-methoxy groups and cyclic ethers, also give rise to 1,5-anti selectivity.[9,10]

We have investigated the effects of the alkoxy group (−OMe, OPMB, PMP acetal, and OTBS) in the boron enolate on the level and sense of remote 1,5-stereoinduction. Transition structures have been located and the relative energies calculated using Jaguar[16] with the B3LYP[17] functional and the 6-31G** basis set.[18] Initially, competing transition structures for the reaction of a simple achiral β-alkoxy methyl ketone with ethanal were investigated, and the low energy structures are shown in Figure 1.

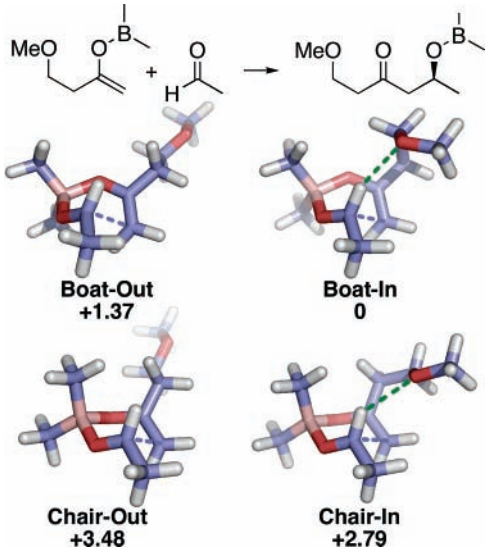


Figure 1. B3LYP/6-31G** transition structures and relative energies (kcal/mol) for the boron aldol reaction shown above.

As shown previously by Houk[20] and Bernardi,[21] the boron aldol reactions of methyl ketones can proceed through both boat-like and chair-like transition structures. We located boat and chair transition structures and investigated all conformers arising from rotation about the extra-annular bonds. Here we show the low energy structures for which the alkoxy group can be oriented either away (Boat-Out, Chair-Out) or back toward (Boat-In, Chair-In) the cyclic core. The most favorable conformation (Boat-In) is boat-shaped with the alkoxy side chain folded back in toward the C···C forming bond. On steric grounds, this is an unexpected result. However, the distance between the alkoxy oxygen and formyl proton is noticeably short (2.355 Å). We therefore postulate that there is a favorable formyl hydrogen bonding (C−H···O) interaction between the two atoms, a concept previously

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explored in boron Lewis acids by Corey[22] and ourselves.[23] The Paterson group has previously proposed this as a working model of 1,5-anti induction via an internal formyl hydrogen bond,[24] and a related formyl hydrogen bond argument has been also used by Paterson to rationalize the high stereoselectivity observed in the boron aldol reactions of certain α-acyloxy ketones.[25] The magnitude of this interaction was assessed by natural bond order (NBO)[19] analysis of the optimized structures. The energy associated with oxygen lone pair donation into the C−H σ*-orbital is 3.2 kcal/mol, and there is a resultant increase in the electronic occupancy of the C−H σ*-orbital. The same favorable interaction exists in the chair structure (Chair-In), although the C−H···O separation is greater and was calculated to provide only 0.91 kcal/mol of stabilization. The extent of delocalization in the chair is less pronounced because in achieving a close C−H···O contact the β-carbon eclipses the enolate double bond, resulting in allylic 1,3-strain. In the boat structure, a close C−H···O contact is achieved, while a proton eclipses the enolate double bond, which is particularly favorable. At −78 °C, only the boat transition structure is populated.

Folding the alkyl chain inside is sterically unfavorable, but the stabilizing C−H···O interaction more than compensates for this. Therefore, one would expect to see an increase in energy as this distance is increased. This is exactly what is observed, and in the absence of a short C−H···O distance, the transition structure is indeed higher in energy when the alkyl group is pointing back inside (Figure 2). The difference

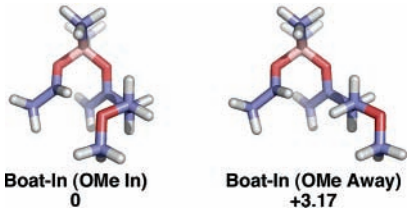

Figure 2. Boat transition structures differing in orientation of methoxy group (relative energies in kcal/mol).

in energy between the transition structures in Figure 2 is explained perfectly by the calculated NBO delocalization energy of 3.17 kcal/mol. In comparison, formyl hydrogen bonding in boron Lewis acids has previously been calculated (MP2/6-31G**) to confer 2.2 kcal/mol of stability.[23] It is worth noting that the dipolar arrangement of the two conformers is very similar. Finally, we note that our formyl hydrogen bond postulate is also consistent with the experimental observation that 1,5-anti diastereoselectivity is lower in dichloromethane than in diethyl ether. Competing transition structures where the β-center is now chiral (possessing isopropyl and benzyl ether substituents) are shown in Figure 3.

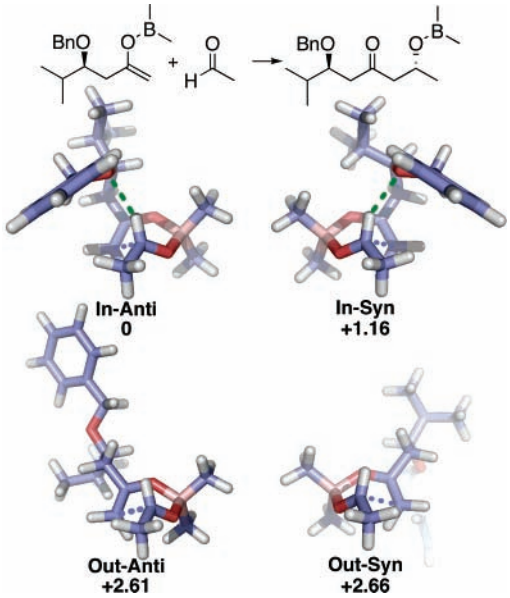

Figure 3. Competing transition structures with a stereogenic β-center (relative energies in kcal/mol).

As in the achiral case, a boat-shaped transition structure, where the alkoxy group is folded back inside, is favored. However, the presence of a stereogenic β-center leads to discrimination between diastereomeric 1,5-anti and 1,5-syn transition structures. The 1,5-syn structure is disfavored due to a steric interaction between the β-alkyl group and one of the ligands on boron. This analysis can be reduced to a schematic working model (Figure 4). The formyl hydrogen

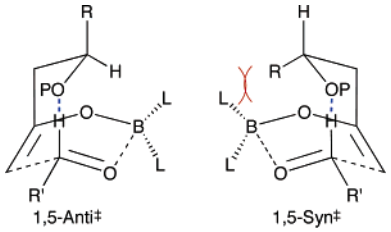

Figure 4. Predictive model for diastereomeric 1,5-anti and 1,5-syn transition structures, with the unfavorable steric interaction highlighted.

bond is part of a seven-membered ring with the enolate and the forming C−C bond of the aldol reaction. This model

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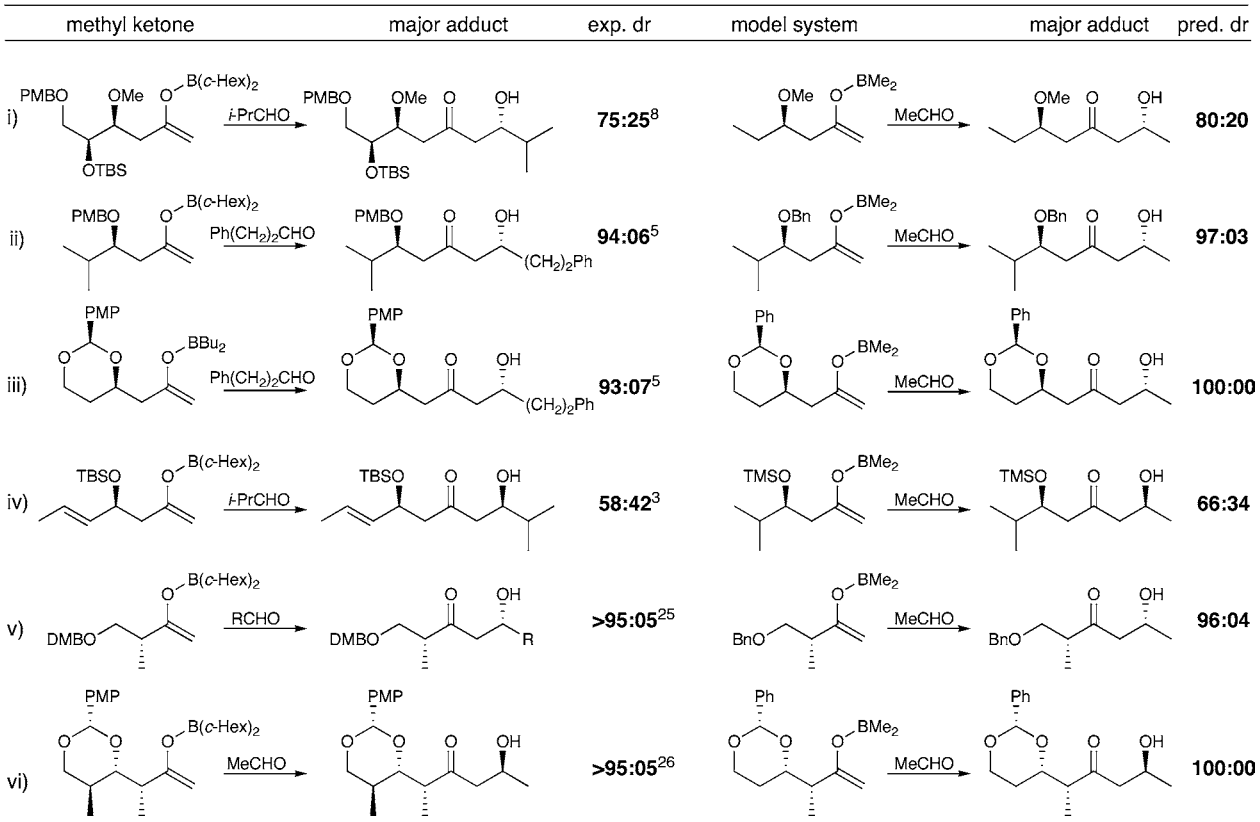
Table 2. Comparison of Experimental and Predicted Diastereoselectivity for a Range of Protecting Groups



illustrates how the small and large groups in the β-position control the stereochemistry of the product. On the basis of this figure, we expect the α-position to have less of an effect.

We investigated a series of reactions for which experimental data are available, testing both the density functional analysis, which we expect to give quantitatively accurate results, and the predictive model transition state, which should give the correct qualitative picture. The predicted diastereoselectivities were calculated from Boltzmann factors at −78 °C of competing (B3LYP/6-31G**) transition structures and are tabulated in Table 2.

Our calculations show excellent agreement with experiment. Methoxy, PMB ether, and PMP acetal groups are all predicted to show 1,5-anti selectivity due to internal hydrogen bond formation in the transition structures, which favors the 1,5-adduct. For silyl ethers, however, there is no preference for an internal hydrogen bond due to the bulky protecting group and the electron-poor oxygen. The NBO calculated CH···O delocalization energy is just 1.46 kcal/mol (cf. 3.29 and 4.07 kcal/mol for benzyl ether and benzylidene acetal, respectively). Significant delocalization into the adjacent silicon atom is predicted, however. Hence, the more open transition structures are preferred, leading to little diastereofacial discrimination. Interestingly, our calculations also rationalize the excellent levels of 1,4-syn selectivity observed in the reactions of α-methyl enolboranes[26] (Table 2, entry v) and correctly predict that where there is a competition between 1,4- and 1,5-stereoinduction the latter will dominate (Table 2, entry vi).[27]

In summary, calculations show that the boron aldol reactions of methyl ketones proceed via a boat transition structure. For β-alkoxy methyl ketones, a stabilizing formyl hydrogen bond exists that leads to disfavoring of the 1,5-syn adduct by minimizing steric interactions between the β-alkyl group and one of the ligands on boron. Silyl protecting groups prevent formyl hydrogen bonding due to their large size and electron-deficient oxygen. The prediction of diastereoselectivity from calculated Boltzmann factors in each example is in excellent agreement with experiment. A schematic working model of the boat transition state gives the correct qualitative interpretation in all cases.

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Supporting Information Available: Cartesian coordinates, absolute energies, and imaginary frequencies of all transition structures reported in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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