Keto Boronate Reduction: 1,7-Asymmetric Induction

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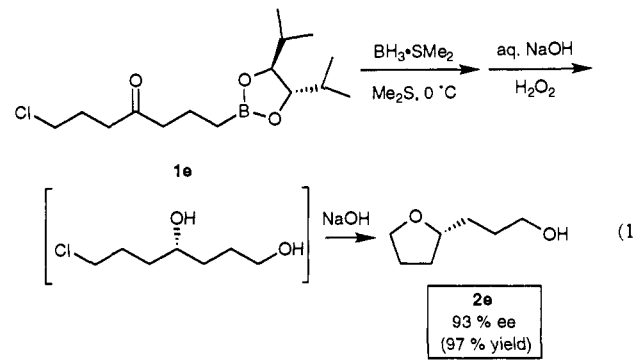
Chiral secondary alcohols in which there is little steric or electronic differentiation between the two alkyl substituents flanking the hydroxyl group represent perhaps the most difficult class of simple molecules to synthesize in high enantiomeric excess.[2] The asymmetric reduction of carbonyl compounds with baker's yeast is often a useful method for the preparation of such stereochemically defined secondary alcohols. However, several factors can greatly influence the synthetic utility of enzymatic procedures, including a complicated dependence of enantiomeric purity of the reaction products on specific reaction conditions and the limitation that only one enantiomer is accessible by these procedures.[3] We now report an alternative procedure for preparing simple enantiomerically enriched secondary alcohols via the reduction of keto boronates utilizing a chiral ligand attached to the boron atom.[4] This procedure constitutes an excellent example of 1,7-asymmetric induction in a carbonyl addition process.[5]

In the present study, (1*S*,2*S*)-1,2-diisopropylethanediol 4-ketoalkyl boronates were used as models to test the hypothesis that an incoming nucleophile might be able to discriminate between the two faces of a ketone carbonyl during stereoelectronically favored axial attack on a kinetically active cyclic complex (Scheme I). Keto boronate starting materials necessary for our investigation were synthesized in straightforward fashion in two steps from diisopropylbromomethyl boronate.[6] Transesterification of this material with the chiral director (1*S*,2*S*)-1,2-diisopropylethanediol[7] provided (1*S*,2*S*)-diisopropylethanediol bromomethyl boronate. This halide was utilized along with zinc metal, CuCN, and trimethylsilyl chloride to effect a conjugate addition to various enones according to the elegant procedure of Knochel,[8] thereby providing the materials needed for the study.

Initial enantioselective reduction experiments employed the protocol used during previous studies when 1,3-asymmetric induction was examined in reduction of keto boronate substrates,[4] i.e., the reduction of **1b** was carried out using BH_3·THF in THF at −78 °C, producing the diol **2b** in 87% ee (*S*-isomer predominant).[9] This auspicious result prompted a systematic investigation to develop optimized conditions for the reduction. After numerous combinations of reducing agents (including $NaBH_4$, DIBAL, Red-Al, and various mono- and dialkylboranes), reaction temperatures, and solvents (Et_2O, THF, CH_2Cl_2) were explored, the investigation was continued with BH_3·SMe_2 in Me_2S at 0 °C, which produced diol **2b** in 92% ee (87% yield).[10] Utilizing these optimized reaction conditions, diverse keto boronates could be reduced efficiently, providing diol products with a high degree of enantiomeric enrichment (Table I).

In addition to the multitude of diverse reaction products which could conceivably be derived from the reduced boronate ester intermediate,[4] the compatibility of functional groups on the keto boronate provides a convenient means for further useful transformations. For example, the diol product derived from substrate **1e** was converted directly to the tetrahydrofuran in 97% overall yield (eq 1). The tolerance of the process for other functional



(1)

groups (entries **1f-h**) suggests that appropriately substituted substrates could also be converted in a straightforward fashion to nitrogen heterocycles, cyclic hemiacetals, and lactones.

As was the case in a related study examining 1,3-asymmetric induction,[4] no direct evidence for the complexed cyclic species was obtained.[11] However, the extraordinary high asymmetric inductions realized point to a highly ordered transition state. The origin of the diastereoselection is thus postulated to result from steric interactions between the isopropyl group of the boronate and the incoming nucleophile in the kinetically active complexed intermediate. The transition structure shown in Scheme I undoubtedly represents a simplified version of the true reaction coordinate traversed during the reaction. Most likely, the borane reducing agent reacts with the complexed ketone via a four-centered transition state. The effect of solvent on the selectivity (with less basic solvents leading to dramatically lower diastereoselectivities) suggests several rationalizations for the observed results. Basic solvents such as dimethyl sulfide form strong complexes with BH_3, making them more sterically demanding than their less tightly bound counterparts. Consequently, there is greater discrimination in the transition state between the two limiting trajectories of attack on the carbonyl. An alternative

Scheme I

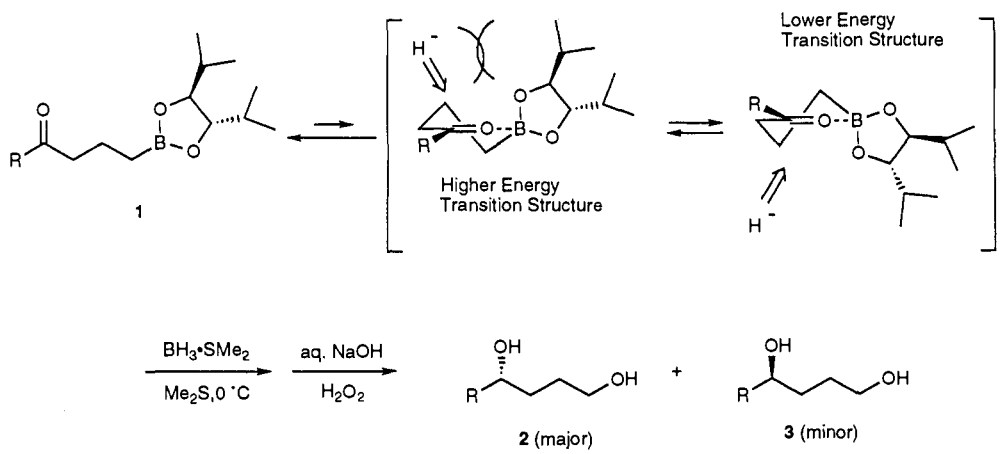


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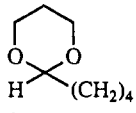
Table I. Results of the Diastereoselective BH_3·SMe_2 Reduction of Keto Boronates **1a–h**

substrate	R	% isolated yield (2 + 3)[a]	enantioselectivity (% ee)[b]
1a	CH_3	83	85[c]
1b	n-C_5H_{11}	87	92
1c	C_6H_{11}	85	>98[c]
1d	C_6H_5	95	97
1e	$Cl(CH_2)_3$	97	93[a,d]
1f	$NC(CH_2)_{10}$	81	97
1g		89	98
1h	$CH_3O_2C(CH_2)_4$	95	>96

[a] Refers to yields of purified diol, except for **2e** (see eq 1). All new compounds have been fully characterized spectroscopically (^1H NMR, ^{13}C NMR, IR), and elemental composition has been established by combustion analysis and/or high-resolution mass spectrometry. [b] Determined by ^{19}F NMR of the crude Mosher diester unless otherwise specified. In all cases, the ^{19}F NMR spectra of the racemic Mosher diesters have also been measured to ensure adequate resolution in the ^{19}F NMR spectra. [c] Determined by 500-MHz ^1H NMR of the multiplet corresponding to the methylene protons adjacent to the primary ester (4.15–4.36 ppm). [d] Determined by capillary GC analysis of the Mosher ester of the tetrahydrofuran derivative.

explanation for the solvent effect is that the acyclic, unactivated form of the keto boronate (which would provide little diastereofacial bias in the reduction process) is less susceptible to reduction by more tightly bound, less reactive reducing agents like BH_3·SMe_2.[12]

The synthetic method described herein represents a unique use of a carbon-bound organometallic/ketone intramolecular complex as a conformational control element in diastereoselective carbonyl addition reactions and should provide a useful method for the synthesis of simple, enantiomerically enriched 2° alcohols in which there is little steric or electronic differentiation between the alkyl groups flanking the prochiral carbonyl unit in the substrate.

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Supplementary Material Available: Complete experimental details and spectral data for synthesis of compounds **1a-h** and **2a-h** (**3a-h**); details for the structure proof outlined within the text (7 pages). Ordering information is given on any current masthead page.

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(9) The enantiomer **3b** depicted in Scheme I was shown to be the minor constituent of the reaction mixture by $LiAlH_4$ reduction of the appropriate lactone prepared by Utaka and subsequent comparison of the spectral data of the di-Mosher ester of this diol with the reaction products produced from our studies. Utaka, M.; Watuba, H.; Takeda, A. *J. Org. Chem.* **1987**, *52*, 4363.

(10) Reductions were performed at 0 °C in Me_2S (distilled from 9-BBN, approximately 1 mmol scale reactions, [**1**] = 0.20 M, 2 equiv of BH_3·SMe_2). Reaction times were 4–5 h, except for **1d** which required a reaction temperature of 20 °C for reasonable reaction times. The reduced boronate was oxidized by the addition of 10 equiv of a 2.0 M $NaOH/H_2O$ solution to the reaction mixture. The solvent (Me_2S) was removed by water aspiration and finally by the addition of 10 equiv of a 30% H_2O_2 solution. Ether was added to a reaction mixture, and the organic layer was washed sequentially with saturated aqueous $NaHCO_3$ and brine. The aqueous layers were extracted five times with *ca.* 10 mL of ethyl acetate and were combined with the ether layer, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo*. The diol was then purified by flash column chromatography.

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(12) This hypothesis has been tested. Thus, the reduction of substrate **1b** in the presence of 1 equiv of 3-heptanone proceeded smoothly, with the 3-heptanone suffering less than 5% reduction under the reaction conditions. This experiment implies that a reactive intramolecular complex such as **1b** may be kinetically significant.