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Asymmetric aldol reactions using (4*R-trans*)-2-(1-methylethenyl)-1,3,2-dioxaborolane-4,5-dicarboxylic acid, bis-ethyl ester, a chiral precursor of the acetone enolate

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Abstract

(4*R-trans*)-2-(1-Methylethenyl)-1,3,2-dioxaborolane-4,5-dicarboxylic acid, bis-ethyl ester upon oxidation with trimethylamine oxide gives a chiral enol borate that condenses with aldehydes to give optically active 4-hydroxy-2-alkanones in 55–77% yield and 41–65% e.e.

Introduction

In the addition reaction of allylic (or heteroallylic) organometalic compounds to prochiral aldehydes, the absolute configuration of the newly formed stereogenic centres can be controlled by choice of chiral auxiliary ligands bound to the metal. This strategy has been widely exploited in synthesis of optically active homoallylic alcohols using, for example, chiral allylic boranes [1], boronates [2], and stannanes [3]. On the other hand little work has been done along these lines in the case of enolates, which represent a very important class of heteroallylic systems [4].

We describe here the preparation and the condensation with aldehydes of the bis-ethyl ester of (4*R-trans*)-2-(1-methylethenyloxy)-1,3,2-dioxaborolane-4,5-dicarboxylic acid [5*], which acts as a chiral synthetic equivalent of the acetone enolate [6*].

We use as the chiral starting material the vinylic boronate **1**, which is easily accessible on a 20–30 g scale through standard boron chemistry [7] and (*R*,*R*)-diethyl tartrate (DET) as the chiral auxiliary ligand (eq. 1).

* Reference numbers with asterisks indicate notes in the list of references.

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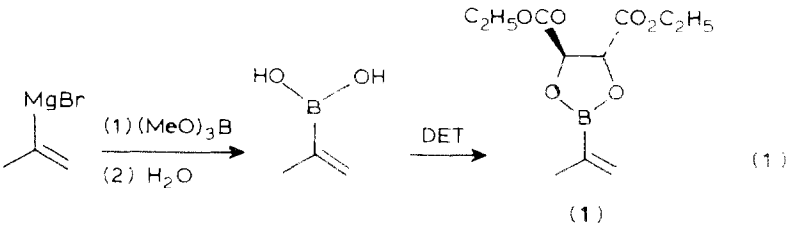
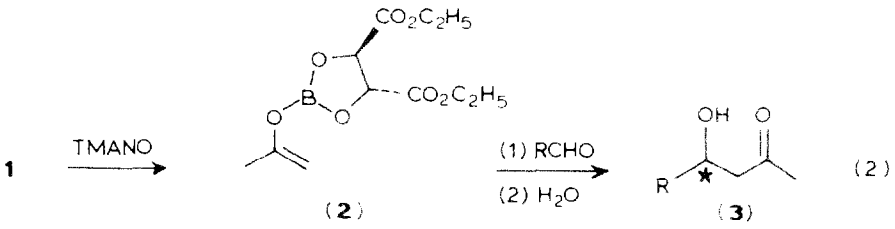


(1)

(1)

Oxidation of **1** by trimethylamine oxide (TMANO) [8] yields the enol borate **2**, which is condensed in situ with aldehydes to give the optically active ketols **3** (eq. 2).



(2)

(2)

(3)

Experimental

General. ^1H NMR spectra were recorded for $CDCl_3$ solutions at 90 MHz on a Varian EM390 instrument; chemical shifts are given in δ units, relative to Me_4Si as internal standard. Infrared (IR) spectra were measured on a Perkin–Elmer PE682 spectrophotometer, and absorptions are given in wavenumbers (cm^{-1}). Optical rotations were measured on a Perkin–Elmer PE241 polarimeter. High pressure liquid chromatography (HPLC) was performed with a Hewlett Packard 1090 Liquid Chromatograph using a 10 cm Hypersil ODS C18 column. Products were purified by flash chromatography on 70–230 mesh silica gel (Merck). All reactions were carried out in flame-dried glassware under argon. Reagents were obtained from Fluka and Aldrich and were used as received. Trimethylamine oxide (TMANO) dihydrate (Aldrich) was dried by Sonderquist's procedure [9].

(4R-trans)-2-(1-Methylethenyl)-1,3,2-dioxaborolane-4,5-dicarboxylic acid, bis-ethyl ester (1). A 1.8 *M* solution of 2-propenylmagnesium bromide in tetrahydrofuran is added dropwise to a cooled solution (−78°C) of trimethylborate (50% excess) in ether. The white suspension formed is stirred overnight as the temperature is allowed to rise to −20°C, and then 0.5 *N* H_2SO_4 is added. The boronic acid is extracted with ether and the extract is dried over anhydrous $MgSO_4$, and the solvent then removed under vacuum. (**Care**: The dried boronic acid is pyrophoric and so must be handled under an inert atmosphere.) The solid residue is dissolved in tetrahydrofuran and the solution treated with (+)-diethyl tartrate. After 15 h stirring at room temperature, the solvent is removed and the residue distilled (115–120°C/0.2 mmHg) to give the vinylic boronate **1** in 45–55% yield based on the amount of Grignard reagent initially taken. Spectroscopic data for **1**: $[\alpha]_D^{20}$ −33.4° (*c* 5.84, $CHCl_3$); ^1H NMR 5.85 (m, 1H), 5.7 (m, 1H), 4.9 (s, 2H), 4.28 (q, *J* 7.5 Hz, 4H), 1.87 (m, 3H), 1.3 (t, *J* 7.5 Hz, 6H); mass spectrum (70 eV, positive ions, rel. abund.) 256 (M^+, 48%), 183 (96%), 155 (25%), 127 (41%), 111 (100%) (all

these ions are preceded by the ^{10}B-containing peak); mass spectrum (negative ions) 228 ($M^- - C_2H_4$, 11%), 227 (100%), 226 (22%), 114 (11%), 113 (31%). The boronate **1** can be stored at 0 °C as a 0.5–0.7 *M* solution in anhydrous CH_2Cl_2 under an inert atmosphere for several weeks without appreciable decomposition.

Synthesis of ketols (3): typical procedure. To a 0.7 *M* solution of **1** in CH_2Cl_2 is added a 1 *M* solution of anhydrous TMANO (1 equiv.) in CH_2Cl_2 at 20 °C. After 45 min the ^1H NMR spectrum of the mixture reveals the disappearance of TMANO (δ 3.2 ppm), and quantitative formation of trimethylamine (δ 2.4 ppm). (Small amounts of acetone are always observed in the ^1H NMR spectrum of the reaction mixture, and are probably due to residual water in the TMANO solution; the drying of commercial TMANO dihydrate is therefore critical for obtaining good chemical yields.) The solvent and the amine are taken off under vacuum, the residue is dissolved in CH_2Cl_2, and the solution cooled to −40 °C. The aldehyde is then added and the mixture stirred for 3 h at −40 °C, and the temperature then allowed to raise to −20 °C. After 2 h at −20 °C the mixture is poured into a pH 7 phosphate buffer solution. After extraction with ether, the ketols are isolated by flash-chromatography on silica gel with 2/8 V/V ether/cyclohexane as eluent.

4-Hydroxy-4-phenyl-2-butanone. IR (CCl_4) 3450, 1702, 700 cm^{-1}; ^1H NMR (CCl_4) 2.0 (s, 3H), 2.6 (m, 2H), 3.6 (m, 1H, OH), 4.8 (m, 1H), 7.1 (s. 5H) ppm.

4-Hydroxy-4-cyclohexyl-2-butanone. IR (neat) 3450, 1700 cm^{-1}; ^1H NMR 0.85–1.9 (11H), 2.2 (s, 3H), 2.5 (m, 1H), 2.6 (m, 1H), 3.0 (s, 1H, OH), 3.8 (m, 1H) ppm.

4-Hydroxy-6-phenyl-2-hexanone. IR (neat) 3450, 1715, 1610, 1500, 700 cm^{-1}; ^1H NMR 1.4–2.0 (m, 2H), 2.1 (s, 3H), 2.3–3.0 (m, 4H), 3.5 (s, 1H, OH), 4.0 (m, 1H), 7.3 (s, 5H) ppm.

(E)-5-Methyl-4-hydroxy-5-hepten-2-one. IR (neat) 3420, 1710, 830 cm^{-1}; ^1H NMR 1.6 (s + d, 6H), 2.2 (s, 3H), 2.5–2.75 (m, 2H), 4.45 (m, 1H), 5.55 (m, 1H) ppm.

4-(4-Quinolyl)-4-hydroxy-2-butanone. IR (Nujol) 3100, 1710, 1590, 1570, 1510, 1360, 1080, 860, 815, 760 cm^{-1}; ^1H NMR 2.2 (s, 3H), 2.5–3.15 (2dd, 2H), 5.5–6.1 (broad, 1H), 5.9–6.1 (m, 1H), 7.35–7.7 (m, 3H), 7.95 (m, 2H), 8.6 (d, *J* 4.5 Hz, 1H) ppm.

Results and discussion

The results of the reaction of **2** with some representative prochiral aldehydes are shown in Table 1. Normally optical yields of 50–60% e.e. are obtained, and this level of enantioselectivity is comparable with that reported for other approaches to optically active ketols lacking substituents in the α position with respect to the carbonyl group [4,6*].

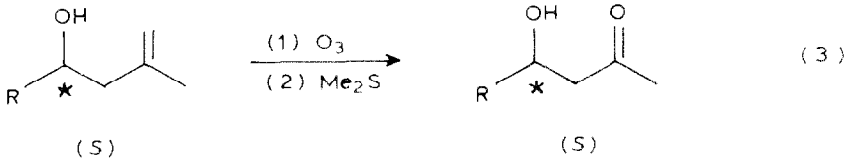
In investigating the absolute stereochemistry of the products obtained in the absence of literature correlations between the ketols reported in this work and stereochemically defined molecules, we established the *S* configuration for the laevorotations of 4-hydroxy-4-phenyl-2-butanone (runs 1,2) and of 4-hydroxy-4-cyclohexyl-2-butanone (run 3) by independent synthesis through ozonization of authentic (*S*)-1-phenyl-3-methyl-3-buten-1-ol and (*S*)-1-cyclohexyl-3-methyl-3-buten-1-ol (eq. 3) prepared by a previously reported method [3b,c].

Table 1

Enantioselective aldol reactions [a]

Run	RCHO	$R^*CH(OH)CH_2COCH_3$				Ref.
	R =	Yield (%) [b]	Absol. configuration	e.e. (%) [c]	$[\alpha]_D^{23}$, deg. (c in $CHCl_3$)	
1	Phenyl [d]	62	*S*	65	−48.8 (1.0)	6c
2	Phenyl [e]	77	*S*	49	−36.9 (1.0)	6c
3	Cyclohexyl	61	*S*	60	−32.4 (1.0) [f]	6e
4	2-Phenylethyl	59	(*R*) [g]	41	−7.0 (1.5)	6d
5	But-2-en-2-yl [h]	64	(*S*) [g]	57 [i]	−16.3 (8.0)	
6	4-Quinolyl [j]	55 [k]	(*S*) [g]	48 [l]	−48.3 (6.1)	

[a] The reactions were carried out on a 5–7 mmol scale of **1** using 1.1 equiv. of aldehyde. For the general procedure see text. [b] Non-optimized isolated yields. [c] Unless otherwise stated the e.e. values were determined by optical rotation measurements. [d] Reaction at −50 °C for 8 h. [e] Reaction at 0 °C for 2 h. [f] Carbon tetrachloride as solvent. [g] These configurations were not determined by chemical correlations with known compounds but are tentatively assigned by analogy to the configurations of the products obtained in runs 1–3. [h] The C=C configuration of tiglic aldehyde is *E*. [i] Determined with an accuracy of ±3% by HPLC analysis (8/2 H_2O/CH_3CN) and by the ratio of the OCH_3 signals in the ^1H NMR spectrum of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenyl acetates. [j] Reaction at −40 °C for 3 h then at −20 °C for 7 h. [k] The ketol was isolated by flash-chromatography with ethyl acetate/cyclohexane 8/2 as eluent. [l] Determined with an accuracy of ±3% by HPLC analysis (6/4 H_2O/MeOH) of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenyl acetates.



(3)

(S) (S)

(R = phenyl, cyclohexyl)

A rationale for the enantioselectivity observed can be derived by inspecting the two trajectories of approach **A** and **B**, of the aldehyde to the enolborate **2** (Fig. 1).

In considering the mode of approach we assumed that (i) the enol borate **2** adopts the planar U-shaped conformation shown in Fig. 1, as suggested by Hoffmann [5b*] on the basis of NOE effects and of ab initio STO-3G calculations on closely related boron derivatives, and (ii) the aldehyde oxygen moves towards the

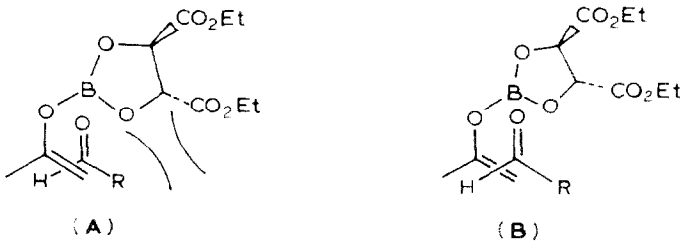


Fig. 1.

boron atom in order to allow a preliminary stabilizing B–O complexation. Formation of the Lewis acid-aldehyde adduct takes place prior to the C–C bond formation in a variety of Lewis acid-mediated additions to aldehydes [10], and this complexation facilitates the nucleophilic attack on the aldehyde by lowering the energy of the π^*(CO) orbital and by increasing the positive charge at the carbonyl carbon. The main difference between pathways **A** and **B** is that the former forces the groups R and $CO_2C_2H_5$ closer together, making it less favourable with respect to **B**. If this is the case, when (*R*,*R*)-diethyl tartrate is used and the priority of R precedes that of the CH_2COCH_3 fragment according to the CIP system, the *S* enantiomer must be formed, exactly as was found in runs 1–3.

The new procedure described here is convenient, it does not require expensive starting materials or tedious preparations of special chiral ligands. In order to improve this procedure we are looking for alternatives to the use of TMANO in the oxidation step, and are seeking other chiral auxiliaries in order to upgrade the enantio-selectivity of the condensation.

Acknowledgements

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