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STEREOSELECTIVE ALDOL CONDENSATIONS VIA ALKENYLOXY DIALKOXY-BORANES : MECHANISTIC AND STEREOCHEMICAL DETAILS.

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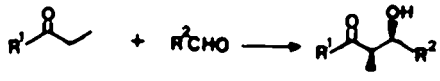
Abstract - A detailed investigation of the enolization of ketones with ethylenechloroboronate (ECB) in the presence of a tertiary amine and the subsequent aldol condensations of these boron enolates was conducted. The enolization with ECB-DPEA system was found to be regioselective except for the case of butanone. The stereochemistry of the enolates derived from ethyl ketones was defined as Z on the basis of ^{1}H-NMR comparison to the Z enolates obtained by a stereodefined route. A mechanistic model for the enolization selectivity. E enolates were found to be more reactive than the Z enolates. The product aldol stereochemistry (syn) was correlated to the enolate geometry via a chairlike transition state (Z enolates) or via a boatlike transition state (E enolates).

Alkenyloxy dialkoxyboranes[1] have recently been shown to be useful reagents for regio- and stereoselective aldol condensations.[2,3,4]



Some aspects of their high selectivity however remained obscure and intriguing and prompted us to a more detailed investigation of the reaction mechanism.

Selective Generation of Alkenyloxy Dialkoxyboranes. Regioselectivity.

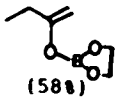
Three different methods can be used to synthesize alkenyloxy dialkoxyboranes at present : oxidation of an alkenyl dialkoxyborane,[4] exchange reaction between a silylenolether and ethylenechloroboronate (ECB), or treatment of carbonyl compounds with the ECB-tertiary amine system.[2,3] Only the last method involves the direct enolization of carbonyl substrates, by the combined use of simple and easy to handle Lewis acid (ECB) and base (DPEA), and under mild conditions.

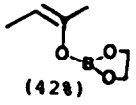
The general procedure for enolate formation involved reaction of 1.0 mol.equiv. of ketone or thioester and ECB (1.1 mol.equiv.) in the presence of 1.15 mol.equiv. of diisopropylethylamine (DPEA) in anhydrous methylene chloride at temperatures ranging from -78°C (ketones) to 0°/+25°C (thioesters). The ECB-DPEA is a regio-

selective system for deprotonating ketones and the selectivity is as follows:[2]

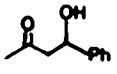
$CH_3 \gtrsim CH_2CH_3$; $CH_3 > CH_2CH_2R$; $CH_3 > CH_2CHR_2$; $CH_3 >> CHR_2$; $CH_2CH_3 >> CHR_2$

Deprotonations are therefore highly regioselective except for the case of butanone where a 58 to 42 terminal vs. internal enolate was obtained at -78°C.


(58%)


(42%)

This ratio was determined both by direct ^{1}H-NMR observation and by reaction with benzaldehyde and subsequent analysis of the resulting condensation products. The methyl vs. ethyl selectivity was also investigated reacting 1.0 mol.equiv. of acetone, 3-pentanone, and benzaldehyde with 1.0 mol equiv. of ECB-DPEA at -78°C: the relative ratio between the acetone and the 3-pentanone addition products was 68 to 32.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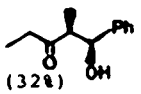
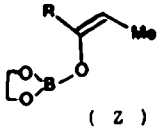

(32%)

Terminal alkenyloxy dialkoxyboranes are somehow more stable and less prone to decompose than the internal: their half-life at RT (checked by ^{1}H-NMR) is longer. Heating up the 58/42 mixture of enolates derived from butanone, from -78°C to 0°C, and then reacting at -78°C with benzaldehyde an improved linear-branched ratio was observed (77: 23) accompanied by a lower yield. Checking the same process by ^{1}H-NMR, warming up the 58/42 mixture of enolates from -78°C to RT, only the linear enolate was still detectable at RT after 15 min, while the internal was totally decomposed.

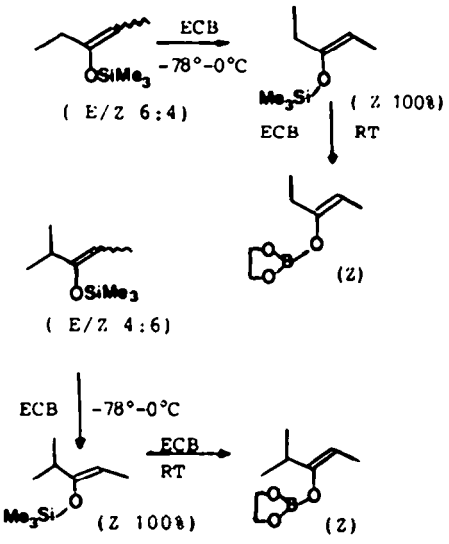
Selective Generation of Alkenyloxy Dialkoxyboranes. Stereoselectivity.

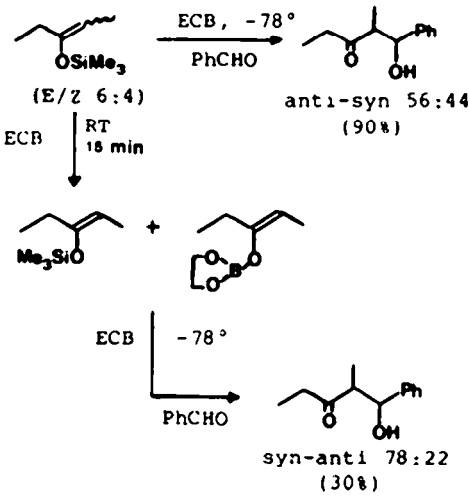
The stereochemistry of alkenyloxy dialkoxyboranes derived from ethylketones was investigated by direct ^{1}H-NMR observation. Only one isomer ($\gtrsim$ 95:5) could be detected from butanone (internal), 3-pentanone, and 2-methyl-3-pentanone, under a variety of experimental conditions (CD_2Cl_2 or $CDCl_3$ as solvent, from -78°C to RT, DPEA or 2,6-lutidine as base). The structure of these enolates was assigned as Z according to the following proofs: a) comparison of the allylic and homoallylic coupling constants to the constants of related systems of known stereochemistry (e.g. alkenyloxy dialkoxyboranes[4], alkenyloxy dialkylboranes[5]). b) comparison of the ^{1}H-NMR spectrum of the alkenyloxy dialkoxyborane derived from butanone to the spectra of the pure Z and E alkenyloxy dialkoxyboranes, formally derived from butanone, obtained via a stereodefined route.[4] c) comparison of the ^{1}H-NMR spectra of the alkenyloxy dialkoxy boranes derived from 3-pentanone and 2-methyl-3-pentanone, to the spectra of the pure Z alkenyloxy dialkoxyboranes obtained treating the corresponding silylenol-ethers with ECB. (See Table in the Experimental Section for comparison of the data). The exchange reaction of acyclic enolsilylethers with ECB to give the corresponding alkenyloxy dialkoxyboranes and Me_3SiCl is rather slow and proceeds significantly only at RT ($T_{1/2}$= ca. 10 min)[6]. Adding ECB to acyclic enolsilyl ethers (E/Z mixtures) in CD_2Cl_2, the signals due to the E isomer rapidly disappeared (from -78°C to 0°C), and only the more stable Z enolsilylether was obser-


(Z)

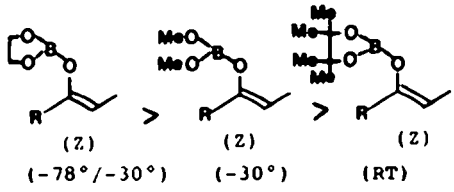
R= Me, Et, i-Pr

ved. The exchange reaction then takes place slowly at RT, but with accompanying extensive decomposition of the products. This reaction is not therefore a good preparative way to synthesize alkenyloxy dialkoxyboranes: the following example emphasizes this point.



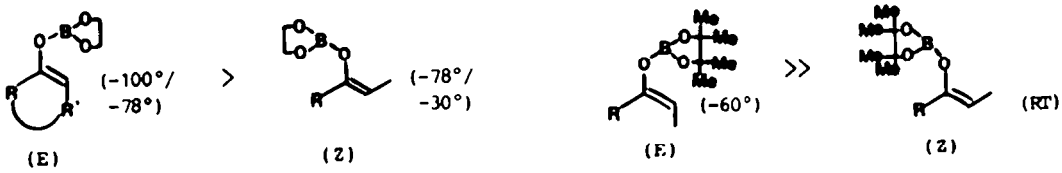


At -78°C the exchange reaction does not proceed, the boron enolate is not involved, and the syn-anti ratio with benzaldehyde is close to 1:1. This reaction is therefore a Lewis acid-catalyzed reaction of enolsilylethers with aldehydes.[7] Instead at RT, a substantial amount of alkenyloxy dialkoxyborane has been synthesized (after 15 min), and the new ratio (syn-anti 78:22) reflects the boron enolate involvement. The yields however are quite low in this case, due to extensive decomposition and selfcondensation of the substrate during the ECB treatment at RT.
In this way we have shown that the reactive species of our aldol reaction are the Z alkenyloxy dialkoxyboranes.



The reactivity of this new class of compounds seems to be extremely dependent on the type of boron ligands: using pinacol[4] or the acyclic dimethoxy[4] the reactivity towards aldehydes is decreased with respect to ethylene glycol. Using therefore the ECB-DPEA system, good yields of the aldol products can be obtained with temperatures ranging from -78°C to -30°C.

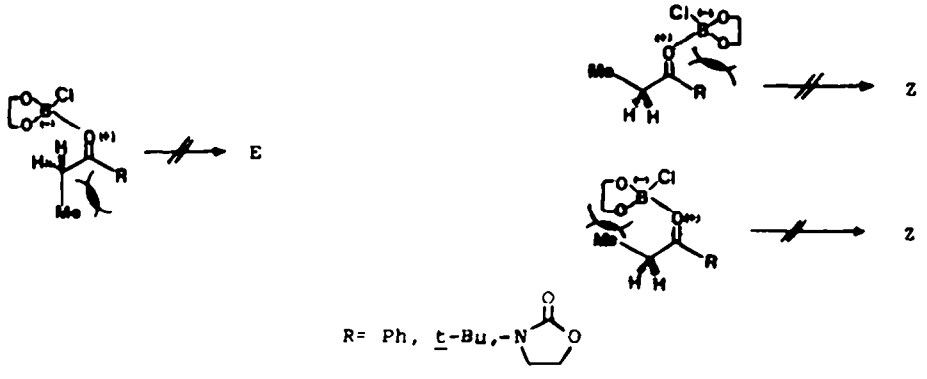
E alkenyloxy dialkoxyboranes are more reactive than the Z, as already observed by Hoffmann and Ditrich[4] in the case of the pinacol derivatives.



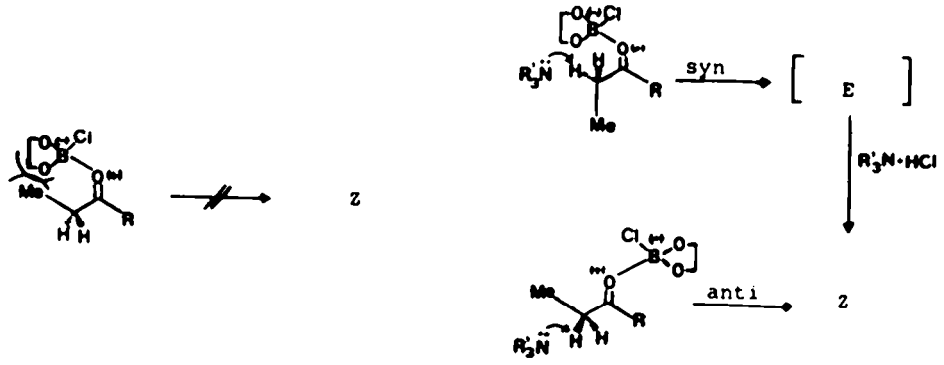
For example the enolate derived from ECB-DPEA treatment of cyclopentanone reacts with benzaldehyde at -78°C to give the condensation product in more than 90% isolated yield. The enolate derived from cyclohexanone is not even stable at -78°C and tends to selfcondense and decompose. When enolization and reaction were carried out from -100° to -78°C, adding the solution of ECB in methylene chloride to a mixture of cyclohexanone, benzaldehyde, and DPEA in CH_2Cl_2, a 4:1 syn-anti ratio of the cross-coupled compound was obtained (46%), together with the self-coupled and other by-products. The reactivity of the cyclohexanone enolate can be decreased using more basic solvents. Generating the enolate at -78°C in CH_2Cl_2-Et_2O 1:1 or CH_2Cl_2-THF 1:1 and then adding PhCHO (following the regular procedure) an enhanced cross-/self-coupling ratio was observed (3:1 with Et_2O, 6:1 with THF) accompanied by a slight lowering of the syn-anti ratio to 3:1.

Mechanistic model for the enolization.

The next question is: are Z alkenyloxy dialkoxyboranes directly obtained by enolization of ketones or do they arise from equilibration of the kinetic E enolates ? Pure, isolated alkenyloxy dialkoxyboranes are known to be configurationally stable even at +70°C.[4] Instead they could easily equilibrate to the more stable Z ones even at -78°C in the presence of the protonated amine (DPEA-HCl).[8] In order to answer this question some interesting observations can be made: acetophenone, 3,3-dimethyl-2-butanone, and 3-methyl-2-butanone were easily enolized at -78°C,[2] while, in the ethyl-ketone series, 2-methyl-3-pentanone was the only enolizable one, propiophenone and 2,2-dimethyl-3-pentanone being completely unreactive.[9] The same puzzling behaviour was encountered for N-acyl-oxazolidinones: N-acetyl-oxazolidinone was easily deprotonated,[10] while N-propionyl-oxazolidinone was totally inert.[9] The common feature of the inert substrates is to give exclusively (>98:2) Z enolates on deprotonation with LDA in THF.[11,12,13] Ground state allylic strain considerations suggest that the E enolization of these substrates is strongly disfavored.[11,12] On the other hand Z enolization could be impeded by the ECB-DPEA system, as shown below.



According to this mechanistic model, ethyl ketones (R= Me,Et,i-Pr) could be deprotonated to give either Z enolates (amine and ECB anti) or E enalates (amine and ECB syn), or mixtures of Z and E enolates. However, if any E enolate is formed, it immediately isomerizes to the more stable Z one (≥ 95:5) in the presence of the protonated amine.[8]



Stereoselective Aldol Condensations.

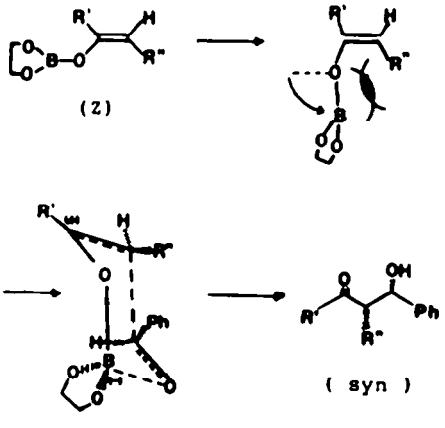
Z Alkenyloxy dialkoxyboranes derived from acyclic ketones react with aldehydes to give syn[14] aldol condensation products with excellent selectivity.[3] A pericyclic chairlike transition state (Zimmerman model)[12] nicely correlates the enolate geometry and the product aldol stereochemistry. E Alkenyloxy dialkoxyboranes derived from cyclic ketones[3] also give syn aldol condensation products with good

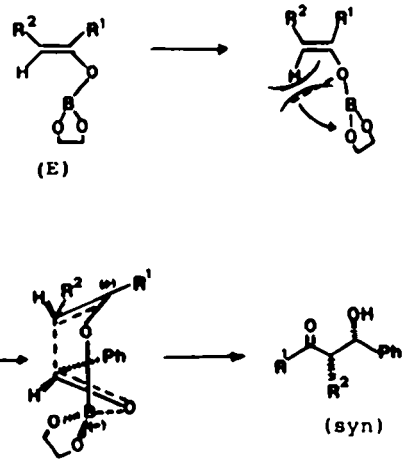
$R^1COCH_2CH_3$	R^2CHO	syn-anti	Yield (%)
	PhCHO	>99:1	85[a]
	PhCHO	>99:1	82
	n-$C_5H_{11}CHO$	97:3	88
	PhCHO	>99:1	71

a Linear-branched ca. 58:42 (see text).

Ketone	Aldehyde	syn-anti	Yield(%)
	PhCHO	96:4	90
	PhCHO	81:19	46[a]

a To the mixture of cyclohexanone, benzaldehyde (2mol.equiv.), and DPEA in CH_2Cl_2 at -100°C, the solution of ECB in CH_2Cl_2 was slowly added (see text).





selectivity. A pericyclic boatlike process could therefore be involved in the case of E enolates. This is in striking contrast to the case of alkenyloxy dialkylboranes[12,15] which give a good correlation between the enolate geometry and the product aldol stereochemistry via a chairlike transition state. A similar syn selectivity, independent of the enolate geometry, has been reported for tin,[16] zirconium,[17] titanium[18], and tris(dialkylamino)sulfonium (TAS)[19] enolates. Either an acyclic transition state[16c,17b,19] or a cyclic one[17a,18a] has been considered for explaining the results. A similar stereoconvergent behaviour has been reported[4] for the E and Z alkenyloxy dialkoxyboranes (syn selectivity) formally derived from butanone. We are now trying to evaluate the geometries and the energies of the possible transition states (acyclic, chairlike, boatlike) using theoretical methods, in order to gain a deeper insight into the reaction mechanism.

The reasons why E enolates are more reactive than Z enolates can be rationalized in terms of the energy difference between the ground state conformations and the reactive conformations. The ground state conformation for the Z isomer is nearly planar s-trans[20] (ω C_{sp2}-C_{sp2}-O-B ca. 180°) while for the E isomer is nearly planar s-cis[20] (ω ca. 0°). In order to reach the reactive conformation (ω ca.90°) the bulky boron substituent has to move towards R" (R"=Me) in the case of Z enolates, and away from H in the case of E enolates. Different energy barriers during this process (lower for the E enolates) could account for the different reactivity of the Z and E enolates.

ACKNOWLEDGMENT

C.G. wishes to especially thank Prof. W. Clark Still (Columbia University) for fruitful discussion and constructive comments. All authors thank Mr. Sergio Crippa for running the low temperature ^{1}H-NMR spectra.

EXPERIMENTAL

General procedure for the aldol condensations: to a stirred solution of ECB (see ref 2) (1.1 mmol) and DPEA (1.15 mmol) in methylene chloride (2.5 ml), at -78°C, under nitrogen, the ketone (1.0 mmol) was added dropwise. The mixture was stirred at -78°C for 30 min, then the aldehyde (1.0 mmol non-enolizable; 1.2 mmol enolizable) was added at -78°C. The reaction was then stirred at the temperature and for the time stated (see ref.2,3), and quenched at that temperature by adding pH 7-phosphate buffer. The product was extracted into methylene chloride, the extracts were dried (Na_2SO_4) and evaporated. The crude product was analyzed by ^{1}H- and ^{13}C-NMR spectroscopy (see ref. 11,21) and, (in the case of alyphatic aldehydes) by capillary VPC for determining ratios. The compound was then isolated by flash-chromatography (see ref 22) for determining yields. The spectra and analytical data of the compounds synthesized are identical with those reported in the literature (see ref. 11, 15, 21).

^{1}H-NMR determination of the enolate geometry: alkenyloxydialkoxyboranes were generated in the NMR tube at temperatures ranging from -78°C to +33°C, using CD_2Cl_2 or $CDCl_3$ as solvent, and DPEA or 2,6-lutidine as base.

Table. Comparison of the ^{1}H-NMR data of alkenyloxy dialkoxyboranes and alkenyloxy dialkylboranes. (selected values).

Compound	δ C<u>H</u>=C, multip., J (Hz)	δ <u>Me</u>-C=C, multip., J (Hz)
(Z)i-PrC(OB<O-CHMe>O)	4.66, dq, 6.80, 0.82	1.40, dd, 6.80, 1.10
(Z)EtC(OB<O-CHMe>O)	4.64, tq, 6.72, 0.98	1.43, td, 6.72, 1.40

(Z)MeC(OB<O-CHMe-O>)	4.56, qq, 6.70, 1.20	1.45, qd, 6.70, 1.50
EtC(OB<O-CH$_2$-O>)	4.20, m, 1.22	---
(Z)MeC(OB<O-CHMe-O>)	4.70, qq, 7.0, 1.0	1.51, qd, 7.0, 1.5 (ref.4)
(E)MeC(OB<O-CHMe-O>)	4.99, qq, 7.0, 1.0	1.55, qd, 7.0, 1.0 (ref.4)
(Z)EtC(OBEt$_2$)CHMe	4.63, tq, 6.8, 1.1	1.36, td, 6.8, 1.4 (ref.5)
(E)EtC(OBEt$_2$)CHMe	a , tq, 7.0, b	1.54, td, 7.0, b (ref.5)

a not reported; b very small, <0.5 Hz.

Reactions of silylenolethers with ECB.

A. ^{1}H-NMR. A solution of the silylenolether in CD_2Cl_2 at -78°C was treated with ECB. The temperature was slowly raised to +25°C while several spectra were recorded. Only Z silylenolethers were observed at that time. From 3-pentanone δ 4.52 (tq) J=6.59, 1.0 Hz; from 2-methyl-3-pentanone δ 4.54 (dq) J=6.76, 1.0 Hz. The exchange reaction to give the Z alkenyloxy dialkoxyboranes was then observed, recording one spectrum every 5 min.

B. Condensations with benzaldehyde. A solution of the silylenolether (1.0 mmol) in methylene chloride (1.4 ml), at -78°C, under nitrogen, was treated with 1M solution of ECB in methylene chloride (1.0 ml), and immediately after with PhCHO (1.0 mmol). After 1 h at -78°C the reaction was quenched with pH 7-phosphate buffer, worked-up and analyzed as described above.

NOTES AND REFERENCES

1. Nomenclature: the use of the terms borate ester, borinic ester and boronic ester is outmoded and scientifically confusing. In this paper we use: R_3B=trialkylborane, $ROBR_2$=alkoxy dialkylborane, $(RO)_2BR$= alkyl dialkoxyborane, $(RO)_3B$=trialkoxyborane. For sake of simplicity we use the name ethylenechloroboronate (ECB) instead of the IUPAC name 2-chloro-1,3,2-dioxaborolane.
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8. See for example: S. Masamune, S.Mori, D. Van Horn, D.W. Brooks, Tetrahedron Letters, 1979, 1665 (E-Z isomerization of alkenyloxy dialkylboranes); C.S. Wilcox, R.E. Babston, J.Org. Chem., 1984, 49, 1451(E-Z isomerization of silyl ketene acetals).
9. No enolate formation was detected by ^{1}H-NMR under a variety of experimental conditions. No condensation product was obtained using benzaldehyde or n-hexanal.
10. Deprotonation was conducted at -78°C with 1.1 mol.equiv. of ECB and 1.15 mol. equiv. of DPEA in CH_2Cl_2. Subsequent addition of benzaldehyde and quenching at -78°C gave the aldol condensation product in 55% isolated yield.
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