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Stereochemistry of the Reactions of Pinacol Allylboronate with Two α,β-Dialkoxyaldehydes

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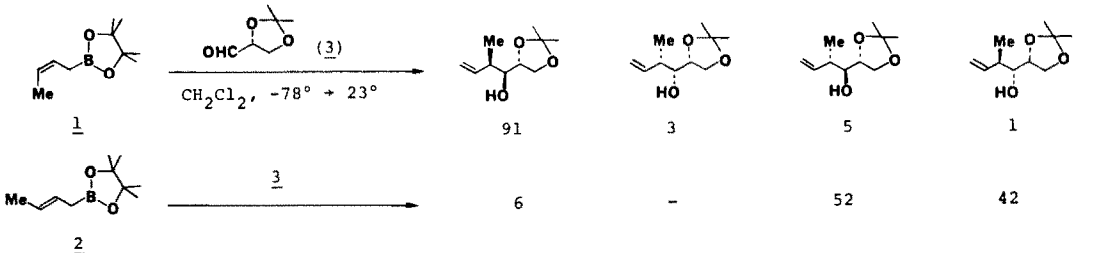
Summary: The stereochemistry of the reactions of pinacol allylboronate 5 with α,β-dialkoxyaldehydes 3 and 4 is described. The results are contrasted with data for the reactions of crotylboronates 1 and 2 with the same aldehydes.

The reaction of allyl and crotylboronic esters with aldehydes constitutes a potentially powerful method for control of acyclic stereochemistry.[2,3a] A variety of 3-substituted allylic boronates are available with high stereochemical purity,[3] and during reactions with aldehydes the olefin geometry is transmitted predictably via cyclic transition states to a syn (from (Z)) or anti (from (E)) relationship around the newly formed C-C bond in the product.[3a] A challenging and as yet unsolved problem, however, involves control of facial selectivity in reactions of allylic boronic esters with chiral aldehydes.[4,5]

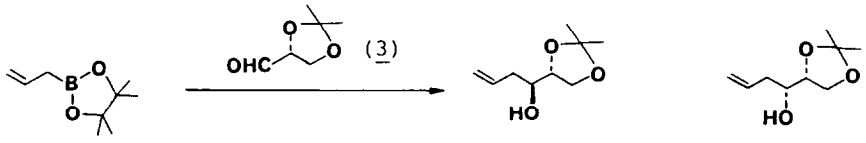
We recently described the stereochemistry of the reactions of several (Z)- and (E)-crotylboronates with α,β-dialkoxyaldehydes 3 and 4.[4] In general, the reactions involving (Z)-crotylboronates (e.g., 1) are highly stereoselective, with aldehyde facial selectivities in the range of 20-90:1. In contrast, the (E)-reagents (e.g., 2) proved to be disappointingly non-



selective, with approximate 1:1 mixtures of facial addition isomers being produced. In order to further probe the factors controlling aldehyde facial selectivity, we have examined and report herein the stereochemical features of the reactions of allylboronate (5) with aldehydes 3 and 4.[6,7]

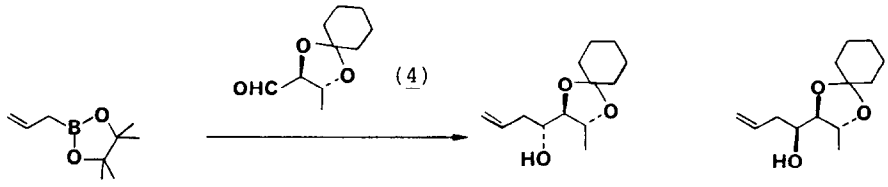
The results of this study are summarized in Table I. It is readily apparent that the reactions of 5 with 3 or 4 are more selective than those involving (E)-crotylboronates, but less so than with the (Z)-crotyl isomers.[4] Maximal selectivity for erythro-adduct 6 (80:20) using D-glyceraldehyde acetonide 3 as substrate was realized in CH_2Cl_2 at -78°C (entry 1). This reaction was slightly less selective when performed at 23°C (77:23, entry 2). Interestingly, the reactions in toluene and hexane were slightly more selective at room temperature

Table I[a]



5 6 7

Entry	Solvent	Temperature	Ratio 6:7[b,c]
1	CH_2Cl_2	-78°	80:20[d]
2	CH_2Cl_2	23°	77:23
3	toluene	-78°	71:29
4	toluene	23°	73:27
5	hexane	-78°	75:25
6	hexane	23°	79:21
7	ether	23°	77:23
8	THF	23°	71:29
9	DMF	0-23°	58:42



5 8 9

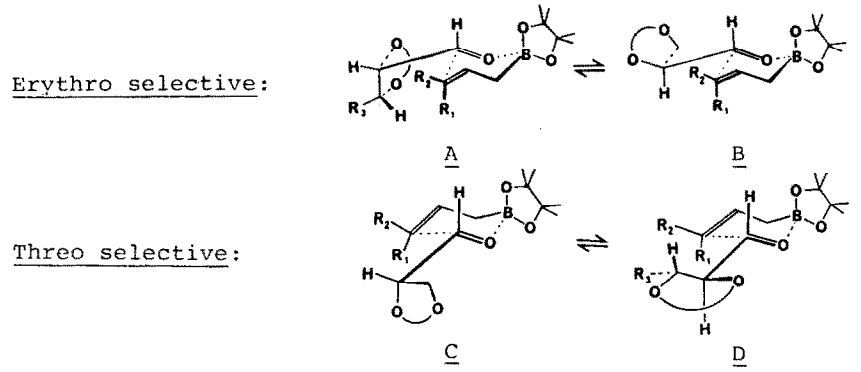
			Ratio 8:9[b,e]
10	CH_2Cl_2	-78°	90:10[f]
11	CH_2Cl_2	23°	87:13
12	toluene	-78°	90:10
13	toluene	23°	87:13
14	THF-nBuLi (1 equiv.)[g]	-78°→23°	79:21

(a) All analytical scale reactions were performed by addition of 1.5 equiv. of aldehyde to a solution of 5 (0.2M) at the indicated temperature. The reactions were allowed to proceed to completion (generally 12-24h), and then were worked up by dilution with water and extraction with ether.
(b) Ratios of 6:7 and 8:9 were determined by gas chromatographic analysis (0.25"x10' 4.1% Carbowax on Chrom. G column) before chromatographic purification.
(c) Alcohols 6 and 7 are known compounds (ref. 5d,9).
(d) The isolated yield of 6 and 7 was 75-79% in preparative scale experiments (1.0 equiv. of 3, 1.2 equiv. of 5; product purified by chromatography and distillation).
(e) Alcohols 8 and 9 were separated by careful preparative TLC. Spectroscopic and analytical data for both isomers is reported in ref. 10. Stereochemical assignments were confirmed by methanolysis (1:1 MeOH-HOAc, reflux) to the corresponding triols which were compared with authentic samples (ref. 11).
(f) The yield of a 90:10 mixture of 8 and 9 was 85% in preparative scale experiments (see (d))
(g) One equiv. of n-BuLi in hexane was added to 5 in THF at -78° followed by addition of 4.

than at -78°C (entries 3-6). Although the reaction in ether proved also to be reasonably discriminating (77:23), use of increasingly polar solvents such as THF or DMF resulted in diminished stereoselectivity (compare entries 7-9). This may well reflect a change in mechanism associated with coordination of the boron atom by solvent.[8]

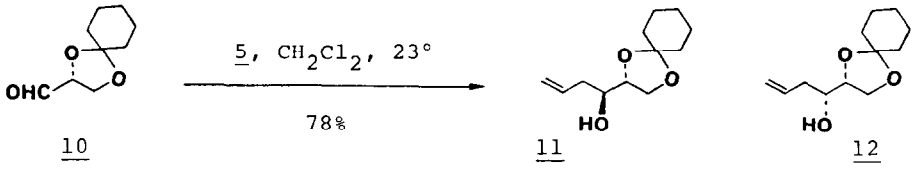
In contrast, the condensation of 5 and 4-deoxythreose ketal 4 is considerably more selective (90:10) and apparently less solvent dependent. Identical product ratios were obtained using CH_2Cl_2 or toluene solutions, with maximal selectivity being realized at -78°C (entries 10-13). The selectivity was significantly affected only when an ate complex[8] derived from 5 was used (entry 14).

We have previously suggested that the stereochemical course of crotylboronate carbonyl addition reactions is strongly influenced by nonbonded interactions in the competing transition states.[4] The observation that the reactions of allylboronate 5 displays intermediate selectivity relative to the extrema defined by the (Z)- and (E)-crotyl reagents is consistent with this analysis. Consider, for example, erythro selective transition states A and B from which 6 and 8 are produced. These transition states are more accessible in reactions involving 5 (R_1=R_2=H) than 2 (R_1=H, R_2=Me) since interactions involving R_2 are less serious when



R_2=H.[12a] On the other hand, transition state C, from which approximately 50% of the product is produced during reactions of 2, is less significantly affected by changing R_2 from Me to H.[12b] Consequently, the reactions of 5 are somewhat more erythro selective than those of 2. Similarly, comparison of transition states B, C, and D for 5 and (Z)-crotylboronate 1 (R_1=Me, R_2=H) reveals that threo selective transition states C and D are considerably more accessible for 5, consistent with our finding that 5 is less erythro selective than 1. Although the nonbonded interactions appear to be comparable in B and C for 5, the net erythro selectivity may be due to the involvement of Felkin transition state A in this series.[12a]

The greater erythro facial preference of 4 relative to 3 (also apparent in their reactions with (Z)-crotylboronates[4]) appears to be a function of the C(4)-methyl group of 4. Indeed, the reaction of ketal 10[13] and 5 afforded a mixture of 11 and 12 in a ratio essentially identical to that recorded in entry 2 of the Table. Presumably, then, the greater erythro selectivity realized with 4 is a consequence of enhanced destabilization of threo-selective transition state D when R_3 = Me. When R_3 = H, D is more accessible and the overall erythro selectivity is diminished.[12b]



10 11 12

78 : 22

Data beginning to appear from a number of laboratories now suggests that high facial selectivity in the reactions of allylic boronates with chiral carbonyl compounds is the exception rather than the rule.[4,5f] A general solution to this problem probably will require the development of efficient chiral reagents.[14] Our initial contribution to this area will be described in due course.

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10. Data for 8: $[\alpha]_D^{19}$ + 9.7° (c=2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 5.84 (m, 1H), 5.15 (br d, J=16 Hz, 1H), 5.14 (br d, J=11 Hz, 1H), 4.09 (dq, J=7.7, 6.1 Hz, 1H), 3.75 (br m, 1H), 3.49 (dd, J=5.5, 7.8 Hz, 1H), 2.37 (m, 1H), 2.20 (m, 1H), 1.97 (d, J=3 Hz, -OH), 1.7-1.5 (m, 9H), 1.48-1.3 (m and overlapping d, J=6 Hz, 5H total); IR (neat) 3450 (br), 3080, 2940, 2870, 1642; mass spectrum, m/e 226 (M^+). Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.72; H, 9.80. Data for 9: $[\alpha]_D^{19}$ + 7.9° (c=0.2, $CHCl_3$); ^1H NMR δ 5.85 (m, 1H), 5.12 (br d, J=17 Hz, 1H), 5.10 (br d, J=10 Hz, 1H), 4.04 (dq, J=7.9, 6.1 Hz), 3.60-3.45 (two m, 2H), 2.30 (br t, J=7.1 Hz, 2H), 2.12 (d, J=7.7 Hz, 1H), 1.7-1.5 (m, 8H), 1.48-1.3 (m, 2H), 1.27 (d, J=6.0 Hz, 3H); high resolution mass spectrum, obsd. 226.1568, $C_{13}H_{22}O_3$ requires 226.1569.
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