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STEREOSELECTIVE ALDOL REACTIONS OF β-BORONATE CARBONYL DERIVATIVES.

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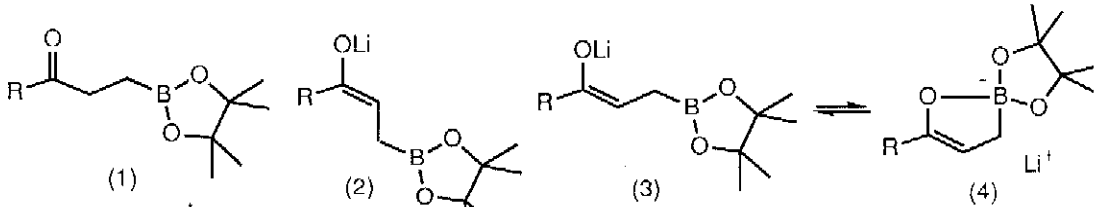
Summary: Deprotonation of β-boronate carbonyl derivatives can be readily achieved using LDA. Reaction of the resulting enolates with aldehydes gives the corresponding Aldol products, with high syn-selectivity for Z-enolates. This result is consistent with chelation enhanced stabilisation of the enolate geometry via the boronate moiety.

The aldol reaction has found countless applications in organic synthesis for the preparation of natural products[1]. The control of the enolate geometry has a profound effect upon the stereoselectivity of the final aldol product, as does the nature of the metal[2]. We have recently developed a general route to β-boronate carbonyl derivatives (1)[3], in the belief that the boronate moiety would participate in the corresponding formation of the enolates of types (2) and (3) *via* intermolecular "ate"-complexation of the enolate oxygen to boron in (2) and intramolecular "ate"-complexation in (3), ie. by formation of (4). We report herein our preliminary results on the lithiation of boronates (1) and the subsequent effect of the boronate ester upon the stereoselectivity of the aldol reaction of the enolate derivatives of (1) with benzaldehyde.



(1)
a; R = OBu^t
b; R = SBu^t
b; R = Ph
c; $R = NMe_2$

(2)
a; R = OBu^t
b; R = SBu^t

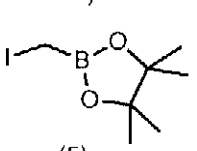
(3)
a; R = Ph
b; $R = NMe_2$

(4)
a; R = Ph
b; $R = NMe_2$

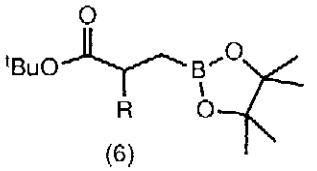
In order to investigate whether the corresponding lithium enolates of carbonyl derivatives (1) could be generated, we treated boronate (1a) with lithium diisopropylamide (LDA) at -78°C for 1h. Quenching the reaction mixture with either iodomethane or iodomethylboronate (5) gave the corresponding alkylated products (6a) and (6b) in 80 and 87% yield respectively[4].

Since the enolate geometry is of prime importance in aldol reactions[2], we lithiated each of the boronates (1) using LDA at -78°C, quenched each of the resulting enolates with chlorotrimethylsilane (TMSCl) (-78°C to RT) and examined the ^1H NMR of the crude TMS enol ethers. In each case the boronate moiety did not significantly change E/Z-stereochemistry of the expected kinetically controlled deprotonation as compared with the corresponding ethyl carbonyl

compounds (see Table 1). From the lack of boron-carbonyl coordination demonstrated by the ^{11}B N.M.R. of each of the starting materials (1)[3], this result is not unexpected. Thus the enolates of esters (1a and b) showed >90% E-selectivity by ^{1}H N.M.R., compared to >90% Z-selectivity for the enolates of (1c and d).



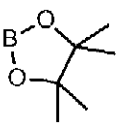
(5)



(6)

a; R = Me

b; R = CH_2B



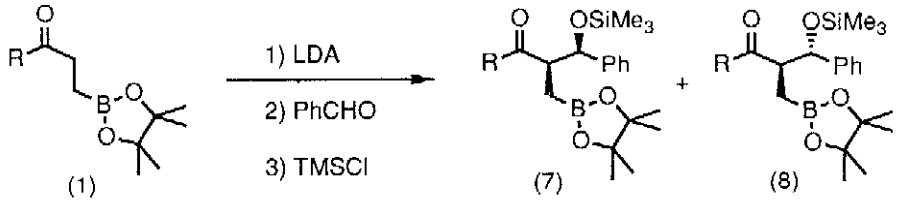
With the knowledge that the lithiation of derivatives (1) was straightforward and that the stereochemical control of the enolisation was essentially unaffected by the boronate moiety, we turned to the aldol reactions of boronates (1) with benzaldehyde (Equation 1)[5]. The resulting syn:anti ratios[6] of each of the aldol reactions are summarised in Table 1, together with the syn:anti ratios of the corresponding non-boron derivatives (Equation 2)[10-13].

From the results shown in Table 1, we can see that the syn:anti ratios for each of the two E-enolates (2a) and (2b) remain relatively unchanged from their non-boron substituted counterparts, with minor increases of the syn-aldol products [Entries 1 and 2, Table 1]. However, when the Z-enolates (3a) and (3b) are used, the syn:anti ratios for the boron substituted enolates are greatly enhanced over their non-boron containing counterparts [Entries 3 and 4, Table 1]. This effect is particularly notable for the amide derived aldol product (7d).

Although the degree of stereoselectivity of lithium mediated aldol reactions is strongly dependant upon the enolate geometry, E-lithium enolates generally give poorer diastereoselectivity than the corresponding Z-enolates[2a]. However, when the boronate moiety is incorporated into the enolate and is capable of coordination to the enolate alkoxide, as in (3a) and (3b), we see enhanced syn-stereoselectivity in the aldol reaction. This effect is particularly enhanced with amide (1d) (Table 1). The reason for this effect is not totally clear at present, however we suggest two possible effects which may well be acting independantly, or more likely in concert: 1) The enolates (3a) and (3b) may be "locked" into the Z-stereochemistry by formation of an intramolecular "ate"-complex, effectively stopping Z/E-isomerisation. Enolates (2a) and (2b) may also be affected by formation of a boronate "ate"-complex, but by weaker intermolecular coordination[7]. 2) Once the aldol reaction has occured, the resulting aldolate alkoxide may coordinate to the boronate moiety, resulting in slowing or effectively stopping retro-aldol/aldol precesses, which is comparable to normal boron enolate-mediated aldol processes[8].

In summary, we have found that incorporation of a boronate group in the β-position to a carbonyl moiety, provides a new method for achieving high syn-selectivity in the aldol reaction of Z-enolates with benzaldehyde. In view of ease of conversion of the boronate group into a variety of other functions[14], we believe that this methodology will prove highly applicable for stereoselective synthesis. Further investigations towards these goals are underway and will be reported in due course.

Equation 1

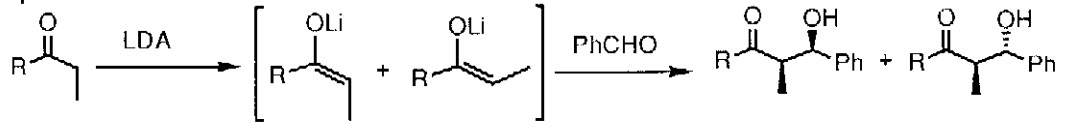


(1) a; R = OBu^t b; R = SBu^t c; R = Ph d; R = NMe_2

(7) a; R = OBu^t b; R = SBu^t c; R = Ph d; R = NMe_2

(8) a; R = OBu^t b; R = SBu^t c; R = Ph d; R = NMe_2

Equation 2



(9) a; R = OBu^t b; R = SBu^t c; R = Ph d; R = NMe_2

(10) a; R = OBu^t b; R = SBu^t c; R = Ph d; R = NMe_2

(11) a; R = OBu^t b; R = SBu^t c; R = Ph d; R = NMe_2

(12) a; R = OBu^t b; R = SBu^t c; R = Ph d; R = NMe_2

(13) a; R = OBu^t b; R = SBu^t c; R = Ph d; R = NMe_2

Table 1

Entry	Boron TMS Enolate Ratio[a], Z:E, (3):(2)	Boron Aldol Ratio[b] Syn:Anti, (7):(8)	Non-BoronTMS Enolate Ratio, Z:E, (11):(10)	Non-Boron Aldol Ratio Syn:Anti, (12):(13)
1	<2:98	(7a):(8a), **60:40**	<2:98[c]	(12a):(13a), **51:49**[d]
2	<10:90	(7b):(8b), **53:47**	10:90[c]	(12b):(13b), **60:40**[e]
3	>98:2	(7c):(8c), **96:4**	>98:2[d]	(12c):(13c), **88:12**[d]
4	>95:5	(7d):(8d), **95:5**	>97:3[a,f]	(12d):(13d), **54:46**[f]

a, Determined by 300 MHz ^1H n.m.r. after quenching the lithium enolate with TMSCl. b, References 5, 6 and 9. c, Reference 10. d, Reference 11. e, Reference 12. f, Reference 13.

Acknowledgements

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References and Notes

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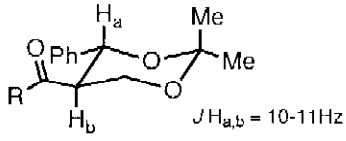
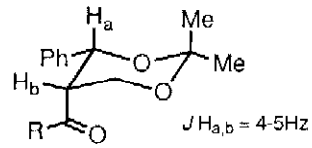
2. a) See C.H. Heathcock in "Asymmetric Synthesis", J.D. Morrison ed., Vol. 3, p. 111, Academic Press, London (1984), b) D. Seebach, *Angew. Chem., Int. Edn. Engl., 27*, 1624 (1988),
3. See preceeding communication.
4. Product (6a) purified by SiO_2 chromatography; δ(^{1}H, 300MHz, $CDCl_3$) 0.85 (1H, dd, J = 15.9 and 7.4 Hz, B.CHH), 1.08 (1H, dd, J = 15.9 and 7.4 Hz, B.CHH), 1.14 (3H, d, J = 7.0 Hz, O:C.CH.Me), 1.22 and 1.23 (each 6H, s, 2xC.Me$_2$), 1.42 (9H, s, C.Me$_3$) and 2.54 (1H, tq, J =7.4 and 7.0 Hz, O:C.CH). Product (6b) purified by Kugelruhr distillation at 150-155°C, 0.2 mmHg; δ(^{1}H, 300MHz, $CDCl_3$) 0.94 (2H, dd, J = 15.8 and 6.7 Hz, 2xB.CHH), 1.11 (2H, dd, J = 15.8 and 8.1 Hz, 2xB.CHH), 1.22 and 1.23 (each 12H, s, 4xC.Me$_2$), 1.42 (9H, s, C.Me$_3$) and 2.64 (1H, m, O:C.CH).
5.Typical Procedure: To a stirred solution of LDA (prepared from 0.383ml, 2.75mmol of diisopropylamine, 1.10ml of 2.5M solution of n-BuLi in hexanes and 4.0ml of dry, redistilled THF) at -78°C under argon, was added neat 2.5mmol of (1). After 1h, 0.279ml, 2.75mmol of benzaldehyde was added and the mixture stirred for a further 2h. The mixture was quenched with 0.347ml, 2.75mmol TMSCl at -78°C[a], allowed to warm to RT, treated with saturated ammonium chloride, extracted with EtOAc, dried ($MgSO_4$) and evaporated. Crude aldol products (7) and (8) were isolated in essentially quantitive yield and the diastereomeric ratios were determined by 300MHz ^{1}H N.M.R.[9]. Purification was carried out by SiO_2 chromatography. a) The aldol reactions were also quenched with saturated ammonium chloride directly. Under these conditions the syn:anti ratios were approximately the same, but the unsilylated products are less stable to SiO_2 chromatography.
6. The identity of the syn and anti-products (7) and (8) respectively was unambiguously established by oxidative cleavage of the boronate group and preparation of the resulting acetonide derivatives (i) and (ii). 300MHz ^{1}H N.M.R. showed that (i) was derived from the syn-aldol (7) and (ii) from the anti-aldol (8), by examination of the $H_{a,b}$ coupling constants. Further details will be provided in due course.



(i)



(ii)

7. That intermolecular boronate "ate"-complexes intervene in the formation of compounds (1) has been discussed[3].
8. For a discussion of the effect of boron upon slowing retro-aldol processes, see reference 2a.
9. All new compounds had satisfactory analytical and spectroscopic properties: (7a) and (8a), δ(^{1}H, 300MHz, $CDCl_3$) 4.18(0.4H, d, J = 7.0Hz, Ph.CH.O) and 4.88(0.6H, d, J = 6.1 Hz, Ph.CH.O) ; (7b) and (8b), δ(^{1}H, 300MHz, $CDCl_3$) 4.76(0.47H, d, J = 8.7Hz, Ph.CH.O) and 4.96(0.53H, d, J = 5.5Hz, Ph.CH.O) ; (7c) and (8c), δ(^{1}H, 300MHz, $CDCl_3$) 4.90(0.04H, d, J = 9.3Hz, Ph.CH.O) and 4.99 (0.96H, d, J = 6.4Hz, Ph.CH.O); (7d) and (8d), δ(^{1}H, 300MHz, $CDCl_3$) 4.57(0.05H, d, J = 2.2Hz, Ph.CH.O) and 4.62(0.95 H, d, J = 9.3 Hz, Ph.CH.O).
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