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Asymmetric Synthesis using a New Chiral β-Functionalized Allylboronate derived from *endo*-2-phenyl-*exo*-2,3-bornanediol : Preparation and Reactions with Aldehydes.

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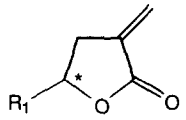
Abstract *: The allylboron reagent* ***4*** *prepared from endo-2-phenyl-exo-2,3-bornanediol reacts with achiral aldehydes to give homoallylic alcohols in good yields and high enantioselectivity (70-85% ee). This new reagent also exhibits good levels of matched and mismatched diastereoselection in reaction with chiral aldehydes. A mechanism is proposed to explained the high regio and stereoselectivity of this carboalkoxyallylboration reaction.* © 1997 Elsevier Science Ltd.

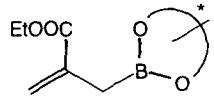
Allylboration of aldehydes with allylic boron reagents and the use of the resulting homoallylic alcohols in the synthesis of complex molecules have been amply demonstrated by several groups.[1,2]

In the course of our interest in the development of new organometallic reagents for the synthesis of α-methylene-γ-lactones derivatives such as **1**, we have recently studied the preparation of new chiral allylboronates of type **2**. However, asymmetric α-methylene-γ-lactones **1** and homoallylic alcohols **3** were obtained with only 5-10% ee on reaction with aldehydes[3] compared to the high ee's obtained with non-functional chiral allylboronates.[1,2]



1

R_1 = COOEt, Et, $(MeO)_3Ph$



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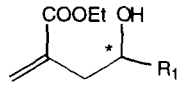


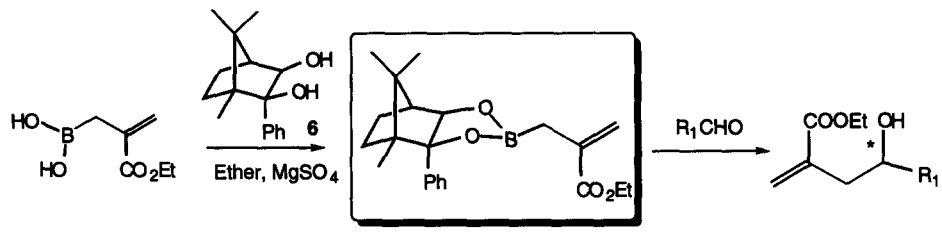
3

R_1 = COOEt, Et, $(MeO)_3Ph$

As an extension of our studies of carboalkoxyallylic boronate aldehyde addition reactions, we have turned our attention to the synthesis of a new chiral β-functionalized allylboronate **4** as a possible solution to increase the enantioselectivity. We wish to report here, the first preparation of a new class of (-)-(1R,2R,3R,4S)-2-*endo*-phenyl-2,3-*exo*-bornanediol β-functionalized allylboronate **4** that exhibits excellent enantio and diastereoselectivities with achiral and chiral aldehydes in order to prepare chiral functionalized homoallylic alcohols **3** in one step.

The preferred method for the synthesis of **4** involves esterification of the allylboronic acid[3] **5** with the chiral (-)-(1R,2R,3R,4S)-2-*endo*-phenyl-2,3-*exo*-bornanediol **6** which has been prepared according to Hoffmann procedure[4] (scheme I).

scheme I



5 4 3

With this method, pure compound **4**[12] has been obtained in 95% yield. The achiral aldehydes, 3,4,5-trimethoxybenzaldehyde **7**, propanal **8** and ethyl glyoxalate **9** were selected for initial screening in a simple asymmetric reaction of reagent **4**. Studies on double diastereoselectivity with **4** were carried out with *D* and *L*-glyceraldehyde acetonide derivatives **10** and **11** now readily available by a two steps sequence from *D*-mannitol or *L*-gulono-1,4-lactone.[5] All carboalkoxyallylboration reactions were carried out at room temperature in solvent on a 1 mmol scale. These reactions are extremely sluggish and hence required one week at room temperature. The crude residue was purified by chromatography on a silica gel column and it should be pointed out that pure enantiomeric chiral auxiliary was recovered in good yield.

Table I summarized the results of the reaction of **4** with achiral aldehydes **7**,**8**,**9**. Best results were obtained when the reactions were performed in toluene. Selectivity dropped slightly in etheral solvents, while significant decreases in enantioselectivity occured in pentane. Consequently, toluene could be considered as the solvent of choice for these reactions. Under these conditions, homoallylic alcohols are obtained with good yields (67-99%) from 3,4,5-trimethoxybenzaldehyde **7** in 82% ee (entry 1), from propanal **8** in 78% ee (entry 6) and from ethyl glyoxalate **9** in 78% ee (entry 10). With **4**, it is noteworthy that the ee's are in the same range with those reported by Hoffmann for reactions of benzaldehyde (68% ee) and propanal (70% ee) with unsubstituted allylbornanediol boronates at a more convenient temperature (-40°C / -78°C) for high stereoselectivity.[4b,6,7]

Table I : Reactions of chiral allylboronate **4** with achiral aldehydes

entry	aldehyde	reaction conditions	Yield[a]	%ee (config)
1		toluene	88%	**82 (R)**
2		ether	100%	76 (R)
3	**7**	THF	91%	80 (R)
4		CH_2Cl_2	80%	82 (R)
5		pentane	89%	71 (R)
6		toluene	99%	**78 (S)**
7		ether	95%	70 (S)
8	**8**	pentane	100%	68 (S)
9		without solvent	99%	67 (S)
10		toluene	67%	**78 (R)**
11		ether	86%	77 (R)
12	**9**[b]	THF	67%	42 (R)
13		CH_2Cl_2	75%	70 (R)
14		pentane	47%	63 (R)

[a]yield of chromatographically purified product, [b]the enantiomeric purities were determined from ^1H N.M.R. spectra ($CDCl_3$ as solvent) by using the Eu(hfc)$_3$.

Enantiomeric excess and absolute configurations of homoallylic alcohols **3** were readily and unambigously established by converting them to the corresponding *O*-methylmandelate ester according to Trost procedure.[8]

The remarkable enantioselectivity of **4** may be interpreted as following : aldehyde addition to chiral allylboronate **4** must proceed through a classical compact cyclic transition state in which boron is primarily coordinated to the carbonyl group of the aldehyde (Figure A). According to such a model few considerations have to be mentioned :

- aldehyde approach was directed by the phenyl group (ring aromatic effect),
- the stability of the transition state could be due to a possible attractive interaction between the aldehyde proton (which is greatly acidified by coordination to the boron) and the eclipsed coplanar oxygen (which is more electron rich because of the negative charge on boron),[9]
- and to a *boron-centered anomeric effect* (n-σ* interactions) between the axial lones pairs of the ring oxygen and the B-O=CHR single bond.[10]

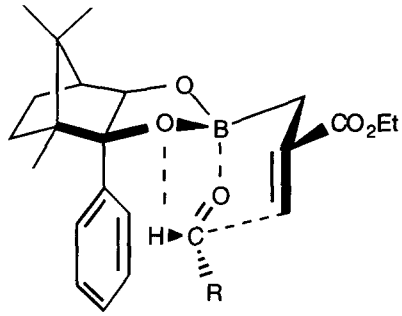
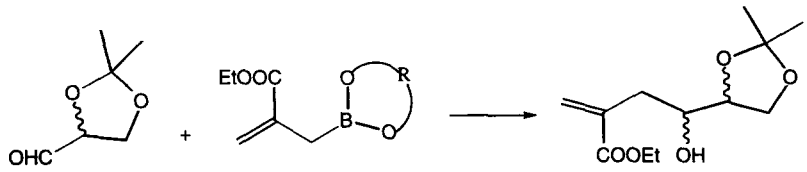


Figure A

These interesting results clearly show that **4** is more highly enantioselective than tartrate derivatives used in our previous work[3] and that enantioselectivity increases as the steric bulk and conformational strain of the chiral auxilliary increase.

Results of double asymmetric reactions of **4** with *L* and *D*-glyceraldehyde acetonide derivatives **10** and **11** are summarized in Table II. These aldehydes have been used intensively as probes of diastereofacial selectivity in reactions with various nucleophiles.[11] It is noteworthy that an appropriate adjustment of the chiralities of both aldehydes and the 2-phenyl-2,3-bornanediol residue effectively enhances individual stereodifferenciation as observed in reaction with achiral pinacol allylboronate **12**, thereby making possible the selective preparation of *anti* alcohols. Thus, whereas glyceraldehyde acetonide displays only moderate facial preference in reaction with **12** (70:30, entry 1), selectivity for the *anti* alcohol (matched case, entry 3) is enhanced to 98:2 by using **4**, while in the mismatched case a reverse selectivity (35:65) for the *syn* alcohol has been found (entry 2).

Table II : Reactions of chiral allylboronate **4** with chiral aldehydes **10** and **11**



entry	aldehyde	allylboronate	product ratio (yield)
1	**10** (R)	pinacol **12**	**70**:30 (**SR**,RR) (89%)
2	**10** (R)	2-phenyl-3,4 bornanediol **4**	35:**65** (SR,**RR**) (99%)
3	**11** (S)	2-phenyl-3,4-bornanediol **4**	**98**:02 (**RS**,SS) (99%)

The asymmetric induction realized is consistent with major product formation occuring via the above proposed transition state which is favored as a consequence of steric interactions involving acetonide function and phenyl group present in the bornanediol ligand.

Moreover, reagents **12** and **4** induce opposite diastereoselectivity in reactions with the same (R) glyceraldehyde acetonide **10** (Table II, entries 1 and 2, mismatched case). The reason is that the asymmetric induction is due to only one of the reaction partners, namely aldehyde in the first case (Table II, entry 1), while an antagonist effect of both partners is supposed in the second case (Table II, entry 2).

In conclusion, we have clearly demonstrated the use of β-functionalized allylbornanediolboronate for enantioselective synthesis of β-functional secondary homoallylic alcohols and have thereby increased the potential usefulness of allylboronate reagents, hence our choice of β-functionalized allylbornanediolboronate as target for asymmetric lactone synthesis.

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12. Characterization data : (**4**) NMR ^{1}H (200MHz, $CDCl_3$) δ (ppm) : 0.8-2.2 (m; 5H) ; 0.92 (s; 3H) ; 0.93 (s; 3H) ; 1.02 (t; 3H; ^{3}J=7.1Hz) ; 1.23 (s; 3H) ; 1.93 (se; 2H) ; 3.84 (dq; 1H; ^{2}J=-10.8Hz; ^{3}J=7.1Hz) ; 3,98 (dq; 1H; ^{2}J=-10.8Hz; ^{3}J=7.1Hz) ; 4.72 (s; 1H); 5.44 (bd; 1H; ^{2}J=1.4Hz) ; 6.08 (bd; 1H; ^{2}J=1.4Hz) ; 7.2-7.5 (m; 5H). NMR ^{13}C (50MHz, $CDCl_3$) δ (ppm): 9.3 ; 13.8 ; 17.1 ; 20.7; 23.5; 24.6; 29.5 ; 48.7; 50.1; 51.9 ; 60.4 ; 88.7 ; 95.7 ; 124.0 ; 126.6; 127.1; 127.3 ; 137.3 ; 141.6 ; 167.2
MS m/e (I%) : 368 (1) ; 258 (100) ; 230 (28) ; 162 (19) ; 141 (34) ; 105 (21) ; 95 (19) ; 68 (23) ; 29 (14).

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