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Stereodivergent Addition of 4-Silyloxy-1,2-Allenes to Aldehydes by Hydroboration

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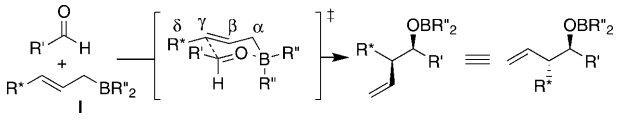
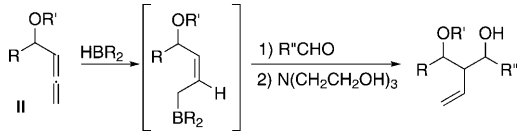
Dedicated to Professor Pelayo Camps on the occasion of his 65th birthday

Chiral allyl- and crotylboron reagents have demonstrated their value for the stereoselective conversion of aldehydes into homoallylic alcohols.[1] Asymmetric induction is usually controlled by terpene[1,2] and tartrate[1,3] ligands linked to boron or by using chiral aldehydes, or by both methods. However, the use of chiral allyl or crotyl moieties has been less explored.[1,4] A careful analysis of the chair-like transition state involved in such additions (Scheme 1) shows that the δ position of the crotyl group can have a direct effect on the stereoselectivity since it is near to the new C–C bond. In fact, this position (R* in Scheme 1) is as close to the new C–C bond as the α carbon of the aldehyde (R′). Since R′ can exert a pivotal role in the stereoselectivity of the reaction in chiral aldehydes,[1] we anticipated that the unexplored use of crotylboron reagents (**I**) with a stereocenter at the δ position would also provide satisfactory stereoselectivity.



Scheme 1. Crotylboron addition to aldehydes.

A serious challenge in the allylboration of aldehydes arises from the stereoselective preparation of the required crotylboron reagents, particularly when they are highly functionalized. In many cases, preparation involves the use of 2-alkenyl metal reagents that are incompatible with some functionalities.[1d] The hydroboration of allenes[5] might be a versatile alternative to the preparation of crotylborane **I** since it obviates the use of transient reactive organometallics.[1d,6] In our search for new methods for the preparation of polyols,[7] we anticipated that the hydroboration of allene **II**, which has a stereocentre next to the allenyl moiety, followed by the addition to an aldehyde would afford 1,3 diols with high stereoselectivity (Scheme 2).



Scheme 2. Allene hydroboration followed by an aldehyde addition.

Our initial proposal for allene **II** was (*S*)-nonan-1,2-dien-3-ol protected as *tert*-butyldimethylsilyl ether ((*S*)-**1**), which is easily obtained from commercially available (*S*)-3-octin-1-ol in two steps.[8] Thus, allene (*S*)-**1**, was hydroborated with dicyclohexylborane (1.1 equiv) in CH_2Cl_2 at RT for two hours (Scheme 3) and then isobutyraldehyde (1.4 equiv) was added at −78 °C. Pleasingly, the reaction afforded the expected 1,3-diol as a major isolable *syn*,*syn*-**3a** stereoisomer (>99:1 e.r.)[9] in good yields. In addition to the major *syn*,*syn* isomer, a small amount of a 7:3 mixture of *anti*,*syn* and *anti*,*anti* was also isolated.

The observed *syn*,*syn* and *anti*,*syn* relative configurations for the major isomer of **3a** agree with those expected for the addition of thermodynamically favoured 2-alkenylborane (*E*)-**2** to both faces of the aldehyde through a chair-like transition state (Scheme 1), whereas the *anti*,*anti* isomer could have arisen in a similar way from (*Z*)-**2**.[10,11] Thus, we

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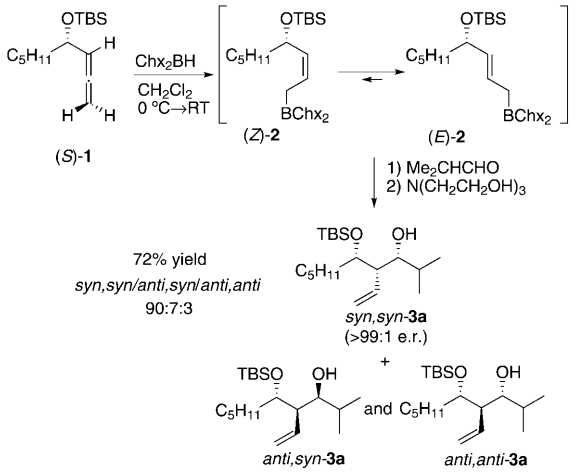


Scheme 3. Hydroboration of **1** followed by the addition of isobutyraldehyde.

concluded that although the *Z* isomer is probably formed faster in the hydroboration step for steric reasons, it undergoes extensive isomerization to its *E* isomer at RT by a known boratropic allylic rearrangement.[12] According to the data, the facial selectivity of the crotyl reagent (*E*)-**2** generated in situ in the addition was 93:7 (ratio *syn*,*syn*/*anti*,*syn*).

We explored the scope of this reaction with a set of representative aldehydes (Table 1). Satisfactory yields of isolable *syn*,*syn*-**3** were consistently obtained for both aliphatic and aromatic aldehydes, again showing the high facial selectivity (ratio *syn*,*syn*/*anti*,*syn*) of the transient *E* crotyl reagent generated by hydroboration (*E*/*Z* ratio ~95:5).[13]

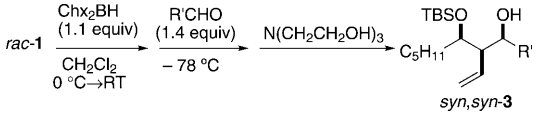
The effect of the protecting group in the allene was also examined. When TBS was replaced by TBDPS in allene **1** similar yields and selectivities were observed in the addition to benzaldehyde. The corresponding homoallylic alcohol was obtained in 77% yield with a 95:5 *syn*,*syn*/*anti*,*syn* diastereomeric ratio. Other *O*-protecting groups on nonan-1,2-dien-3-ol such as acetyl or benzyl or even the unprotected allenol did not afford the expected products.

Major *syn*,*syn* isomer could be also isolated in good yield when we extended our protocol to the addition of other racemic allenes (R = Me, *i*Pr and Ph) to a variety of aliphatic, α,β-unsaturated and aromatic aldehydes. As shown in Table 2, in all the cases the facial selectivity of the major *E* crotyl reagent (*E*/*Z* ratio ~95:5) was at least 92:8.[13]

In an attempt to explain the high facial selectivity of the chiral boron reagent, the reaction of model crotylboron reagent **10** with acetaldehyde was modelled using the Gaussian03[14] series of programs. As shown in Scheme 4 and Figure 1, at the RHF/6-31G** level of theory, the lowest-energy transition state (**TS1**) leads to the observed *syn*,*syn* adduct, while the transition state that leads to the *anti*,*syn* isomer (**TS2**) is 1.4 kcal mol^{-1} higher, in qualitative agreement with the experimental data. These results indicate that the preference for *syn*,*syn* adducts can be attributed to the ability of **TS1** to minimize the interactions of the chain of the aldehyde and the substituents at the chiral center of crotylboron reagent.

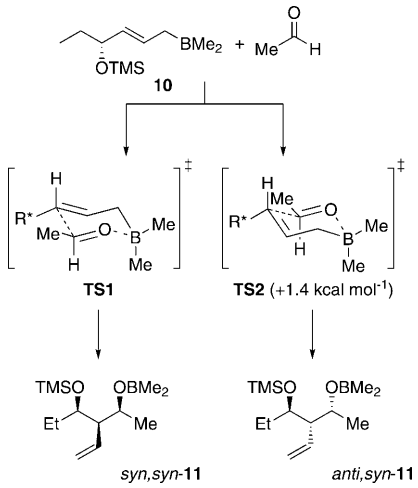
In an effort to improve our control of the *Z*/*E* ratio of the 2-alkenyl borane intermediate, alternative hydroborating agents were considered. Thus, 9-BBN under the conditions

Table 1. Hydroboration of **1** followed by addition of aldehydes.



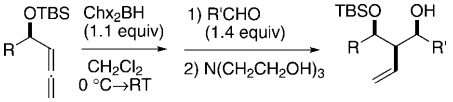
Entry	R′ (aldehyde)	Major product	Facial selectivity[a]	*E*/*Z*[b]	Yield [%]
1	ethyl	*syn*,*syn*-**3b**	91:9	93:7	59
2	*n*-pentyl	*syn*,*syn*-**3c**	89:11	96:4	65
3	phenyl	*syn*,*syn*-**3d**	95:5	95:5	71
4	2-furyl	*syn*,*syn*-**3e**	93:7	97:3	95

[a] *syn*,*syn*/*anti*,*syn* ratio. [b] Ratio of (*syn*,*syn* + *anti*,*syn*)/(*anti*,*anti* + *syn*,*anti*) isomers.



Scheme 4. Reaction of model crotylboron reagent **10** with acetaldehyde.

Table 2. Hydroboration of allenes **4**–**6** followed by addition of aldehydes.



Entry	R (allene)	R′ (aldehyde)	Major product	Facial selectivity[a]	*E*/*Z*[b]	Yield [%]
1	methyl (**4**)	ethyl	*syn*,*syn*-**7a**	93:7	95:5	54
2	methyl (**4**)	isopropyl	*syn*,*syn*-**7b**	93:7	96:4	65
3	methyl (**4**)	2-furyl	*syn*,*syn*-**7c**	93:7	96:4	81
4	isopropyl (**5**)	*n*-pentyl	*syn*,*syn*-**8a**	95:5	96:4	60
5	isopropyl (**5**)	phenyl	*syn*,*syn*-**8b**	96:4	96:4	65
6	isopropyl (**5**)	1-nonenyl	*syn*,*syn*-**8c**	98:2	96:4	83
7	phenyl (**6**)	*n*-pentyl	*syn*,*syn*-**9a**	92:8	96:4	88
8	phenyl (**6**)	isopropyl	*syn*,*syn*-**9b**	95:5	95:5	79

[a] *syn*,*syn*/*anti*,*syn* ratio. [b] Ratio of (*syn*,*syn* + *anti*,*syn*)/(*anti*,*anti* + *syn*,*anti*) isomers.

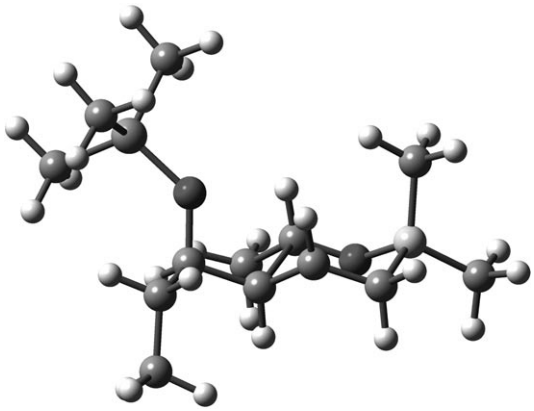


Figure 1. Calculated transition state for adduct *syn*,syn-**11**.

of Scheme 3 gave the same major stereoisomer (*syn*,*syn*-**3a**) but in lower yield and diasteromeric ratio (83:17). Interestingly, when (*S*)-**1** was hydroborated at RT with (−)-Ipc_2BH the *anti*,*anti*-**3a** isomer, presumably arising from the (*Z*)-**2** borane intermediate, was obtained (d.r. 85:15)[15] in 54% yield. The diastereomeric ratio was improved to 91:9 when the same reaction was performed at −25°C (55% yield). The mismatch reaction with (+)-Ipc_2BH at RT yielded a disappointing mixture (40 (*anti*,*anti*): 40 (*syn*,*anti*): 20 (*anti*, *syn*)). On the other hand, we also explored the effect of the temperature on the selectivity of the hydroboration. Surprisingly, when the hydroboration of **1** with dicyclohexylborane was performed at lower temperature (−40°C) the stereoselectivity switched to the *anti*,*anti*-**3a** isomer (d.r. 88:12)[11] but in low yield (17%) probably due to the fact that the hydroboration was incomplete under these conditions.

These experiments suggest that when dicyclohexylborane or 9-BBN was used, (*Z*)-**2** was first formed in the hydroboration step (probably between −40 and −20°C) but it easily isomerized at RT to the more stable isomer (*E*)-**2**. However, at lower temperatures or when a more hindered hydroborating agent is involved (Ipc_2BH), the *Z*/*E* isomerization could be slow enough to achieve the addition of (*Z*)-**2** to the aldehyde.[1d,16]

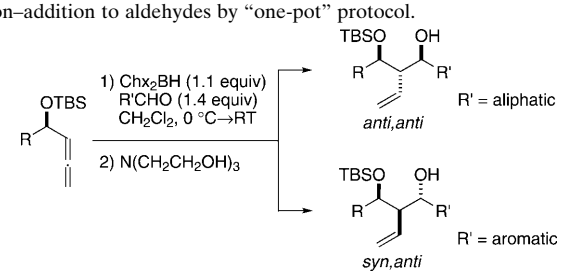
Nevertheless, none of these attempts to control the *Z*/*E* configuration of the boron intermediate during the hydroboration step was completely satisfactory. Neither the change of the temperature[17] nor the use of other hydroborating agent[18] was successful.

Although borane or alkylborane species can reduce aldehydes and ketones, this process is slow at low temperatures.[19] Thus, we envisaged that the hydroboration of the allene might be possible in the presence of the aldehyde. We hypothesized that when the allene was hydroborated to form the kinetic *Z* boron reagent it would be immediately trapped by the aldehyde. Therefore, the unprecedented idea of hydroborating the allene in the presence of the aldehyde should allow us to isolate *anti*,*anti*-**3** or *syn*,*anti*-**3** as major isomers rather than the *syn*,*syn*-**3**. As expected, when dicyclohexylborane (1.1 eq) was added to a mixture of allene **1** and ethanal in CH_2Cl_2 at 0°C *anti*,*anti*-**3b** (entry 1, Table 3) was isolated as major isomer at RT. The analysis of the minor stereoisomers revealed a notable 6:94 facial diastereoselectivity (*syn*,*anti*/*anti*,*anti* ratio) in the addition of the *Z* alkenyl borane intermediate to the aldehyde.[20] The main minor isomer detected was *syn*,*syn*-**3b** possibly resulting from the partial isomerization of (*Z*)-**2** to (*E*)-**2** (*Z*/*E* ratio 86:14). The same behavior was observed for the addition of a number of racemic allenes to aliphatic, aromatic and heteroaromatic aldehydes (Table 3).[13]

Remarkably, the facial stereoselectivity in the addition to aromatic aldehydes was very good (up to >99:1) but with opposite facial bias (*syn*,*anti* products) to that noted for the aliphatic ones (*anti*,*anti* products). This behavior is observed for both electron-rich (*p*-methoxybenzaldehyde or furfural) and electrondeficient aldehydes (*p*-nitrobenzaldehyde). This unexpected effect could be explained by assuming a twist-boat transition state that can overcome the more usual chair-like arrangement in such cases. In fact, this situation has been suggested for the reaction of (*Z*)-2-alkenyl metals with hindered aldehydes.[21,22]

In conclusion, we have established a new stereodivergent approach to 2-vinyl-1,3-diols based on a hydroboration of

Table 3. Hydroboration–addition to aldehydes by "one-pot" protocol.



Entry	R (allene)	R′ (aldehyde)	Major product	Facial selectivity[a]	*Z*/*E*[b]	Yield [%]
1	*n*-pentyl (**1**)	ethyl	*anti*,*anti*-**3b**	6:94	86:14	65
2	*n*-pentyl (**1**)	phenyl	*syn*,*anti*-**3d**	92:8	88:12	70
3	*n*-pentyl (**1**)	2-furyl	*syn*,*anti*-**3e**	>99:1	84:16	90
4	*n*-pentyl (**1**)	*p*-MeO-C_6H_4	*syn*,*anti*-**3f**	>99:1	93:7	58
5	methyl (**4**)	isopropyl	*anti*,*anti*-**7b**	9:91	84:16	87
6	methyl (**4**)	2-furyl	*syn*,*anti*-**7c**	97:3	80:20	66
7	isopropyl (**5**)	*n*-pentyl	*anti*,*anti*-**8a**	15:85	80:20	86
8	isopropyl (**5**)	phenyl	*syn*,*anti*-**8b**	>99:1	91:9	65
9	isopropyl (**5**)	*p*-MeO-C_6H_4	*syn*,*anti*-**8d**	98:2	80:20	67
10	isopropyl (**5**)	*p*-NO_2-C_6H_4	*syn*,*anti*-**8e**	99:1	84:16	56
11	phenyl (**6**)	*n*-pentyl	*anti*,*anti*-**9a**	11:89	85:15	53
12	phenyl (**6**)	isopropyl	*anti*,*anti*-**9b**	11:89	85:15	60

[a] *syn*,*anti*/*anti*,*anti* ratio. [b] Ratio of (*anti*,*anti* + *syn*,*anti*)/(*syn*,*syn* + *anti*,*syn*) isomers.

allene/addition of aldehyde tandem process. The stereocenter present next to the allenyl moiety (C1) in the starting allene effectively determines the configuration of the new formed carbinol (C3) whereas the relative configuration of C2 and C3 is determined by the configuration (*E*/*Z*) of the transient 2-alkenylborane intermediate. It should be noted that the order of mixing of the reagents and the kind of aldehyde used allowed us to obtain three out of the four possible diastereomers of the 1,3-diol.

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Keywords: aldehydes · allenes · asymmetric synthesis · hydroboration

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[9] The enantiomer of *syn*,*syn*-**3a** was also prepared from allene (*R*)-**1**. The enantiomeric purity was >99:1 as determined by HPLC analysis of the corresponding benzoates using a Chiralpak IA column (see the Supporting Information).

[10] An analogous cyclic transition state for (*Z*)-**2** was assumed to account the formation of *anti*,*anti*- and *syn*,*anti*-**3a**.

[11] For the relative configurational assignments, see the Supporting Information.

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[15] The main minor isomer was *syn*,*syn*-**3a**.

[16] The sterically hindered disiamylborane gave also *anti*,*anti*-**3a** (d.r. 80:9:11 *anti*,*anti*/*syn*,*syn*/*anti*,*syn*) as the major isomer.

[17] For a successful control of the *E*/*Z* configuration by changing the temperature, see: reference [6g].

[18] For the stereoselective formation of (*Z*)-boron intermediates by hydroboration, see: references [6d,f].

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[20] Major *anti*,*anti* and *syn*,*anti* products of Table 3 were easily separated from the mixture of the rest of minor isomers by flash chromatography. The same applies for the *syn*,*syn* major compounds in Tables 1 and 2.

[21] Reference [1b], pp. 1361–1364.

[22] In contrast with the performed ab initio calculations for the addition of (*E*)-2-alkenylboranes to aldehydes in which the chair-like transition states are predicted to dominate over boat-like arrangements, the situation is less clear for the (*Z*)-2-alkenyl boranes where different transition states of similar energy could be found.

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