Allyl boranes

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Asymmetric Synthesis of α-Substituted Allyl Boranes and Their Application in the Synthesis of Iso-agatharesinol**

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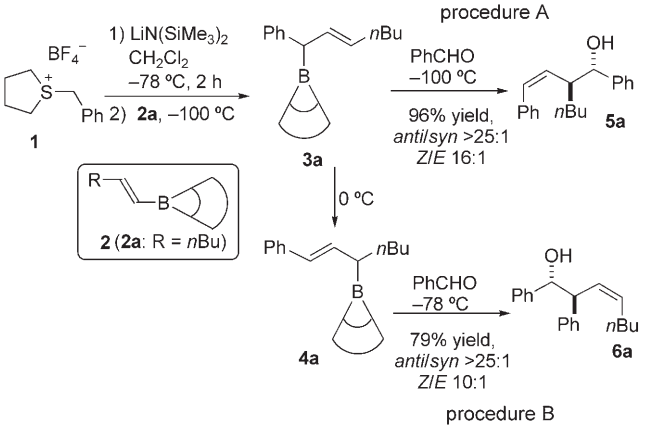
The reaction of chiral allyl boron reagents with aldehydes has played and continues to play a major role in the asymmetric synthesis of complex natural products.[1] Despite the fact that α-substituted allyl boron reagents often react with aldehydes with almost complete stereoinduction, such reagents have not enjoyed the same profile, possibly because their asymmetric synthesis is less facile. Nevertheless, a number of methods have been described for the synthesis of α-substituted allyl borates in enantiomerically enriched form.[2–5] However, the synthesis of the more reactive α-substituted allyl boranes has proved elusive: the only examples that have been reported are those derived from the asymmetric hydroboration of cyclic 1,3-dienes.[6] Herein we describe a simple procedure for the synthesis of α-substituted allyl boranes with very high enantioselectivity and demonstrate their utility in synthesis.

We recently described the reaction of chiral sulfur ylides with symmetrical boranes which after oxidation furnished secondary alcohols with very high enantioselectivity.[7] This study suggested to us a potential solution to the synthesis of α-substituted allyl boranes: the reaction of chiral sulfur ylides with vinyl boranes. Substituted vinyl 9-borabicyclo-[3.3.1]nonanes (9-BBNs) are easily obtained by regioselective hydroboration of terminal alkynes with 9-BBN. However, in the reaction of nonsymmetrical boranes with sulfur ylides, issues of migration ability of the different groups have to be addressed.[8] Although the vinyl group is expected to be a better migrating group than the boracycle,[9] the outcome was not clear, as we had already experienced surprises in the reaction of *B*-phenyl-9-BBN with the ylide derived from **1**, in which we found competing migration of the boracycle.[10]

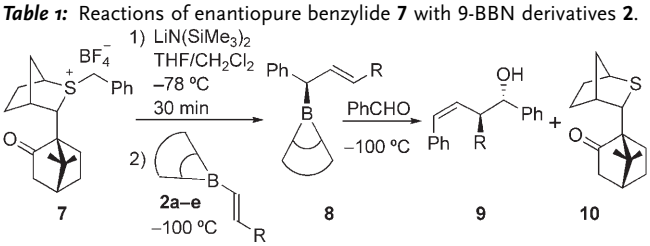
In the event, reaction of the ylide derived from **1** with vinylborane **2a** at −100 °C followed by addition of PhCHO at the same temperature furnished the homoallylic alcohol **5a** in 96% yield as a single diastereomer with high *Z* selectivity (procedure A, Scheme 1). The high yield obtained clearly indicated that the vinyl group migrated exclusively. We also found that warming allylborane **3a** to 0 °C resulted in isomerization to **4a**, which upon recooling to −78 °C and trapping with benzaldehyde furnished another homoallylic alcohol **6a** with similarly high diastereoselectivity (procedure B, Scheme 1).



Scheme 1. The reaction of *B*-hexenyl-9-BBN (**2a**) with sulfonium benzylide **1**.

We applied procedure A to a range of vinyl boranes using the chiral sulfonium salt **7**[11] (Table 1) that had previously been used in highly enantioselective reactions between boranes and sulfur ylides,[7] epoxidations,[12] and other related reactions.[13] In all cases, we observed essentially complete enantio- and diastereoselectivity with very high *Z* selectivity.

Table 1: Reactions of enantiopure benzylide **7** with 9-BBN derivatives **2**.



7 8 9 10

Entry	R	Yield (**9**) [%][a]	*Z*/*E*[b]	d.r. [%][b,c]	*ee* [%][c]
1	*n*Bu **a**	79	15:1	>95	>99
2	Me **b**	81	40:1	>95	>99
3	H **c**	61[d]	>40:1	>95	>99
4	$TMSOCH_2$[e] **d**	61[f,g]	>40:1	>95	>99
5	$AcOCH_2CH_2$ **e**	72[h]	>40:1	>95	>99

[a] Yield of isolated product. [b] The ratios were obtained by ^{1}H NMR spectroscopy. [c] Data for *Z* isomers only. [d] The product from boracycle migration, 1-phenyl-1-(5-hydroxycyclooctyl)methanol, was also isolated in 15% yield. [e] TMS = trimethylsilyl. [f] The product from boracycle migration was also isolated in 20% yield. [g] The compound was isolated as the corresponding diol. [h] The product from boracycle migration was also isolated in 12% yield.

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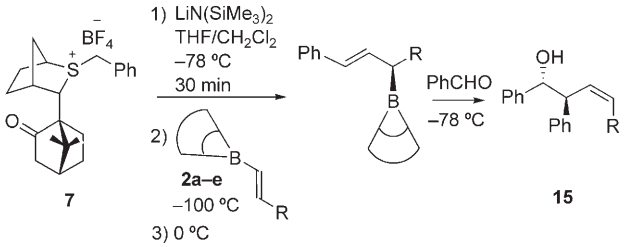
Furthermore, the chiral sulfide **10** could be reisolated in greater than 90% yield in all cases. The reaction was compatible with substituted and unsubstituted vinyl boranes, and tolerated both ether and ester functionalities. Interestingly, with the less electron-rich vinyl groups (entries 3–5), competing migration of the boracycle, which led to 1-phenyl-1-(5-hydroxycyclooctyl)methanol was also observed, thereby resulting in somewhat reduced yields of the homoallylic alcohols **9c–e**.

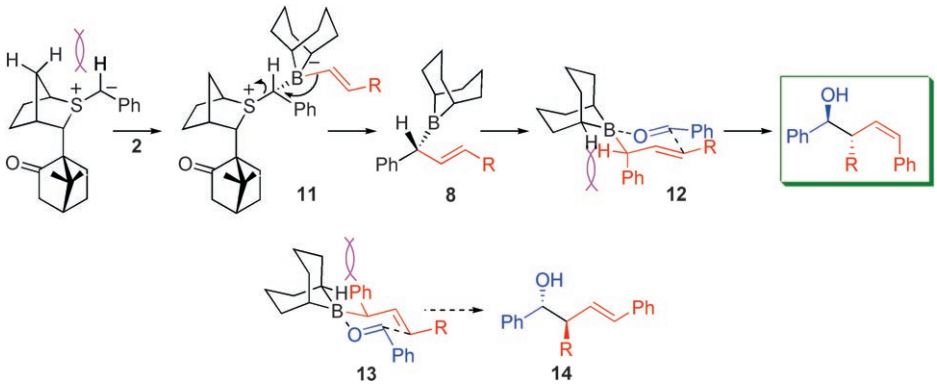
The absolute stereochemistry of allylborane **8** originates from the established high level of control of ylide conformation and face selectivity, followed by stereospecific 1,2-metalate rearrangement of **11** (Scheme 2).[7] The high selectivity in the subsequent reaction with the aldehyde across all three elements of stereogenicity is believed to arise from the chair transition state **12** (which is favored over transition state **13,** which leads to the minor *E* isomer **14** with opposite absolute stereochemistry).[14] In transition state **12**, the α substituent occupies an axial position to minimize steric interactions with the bulky and conformationally locked 9-BBN moiety (Scheme 2).

Table 2: Stereocontrolled synthesis of the homoallylic alcohols by procedure B.



Entry	R	Yield (**15**) [%][a]	*Z*/*E*[b]	d.r. [%][b,c]	*ee* [%][c]
1	*n*Bu **a**	81	10:1	>95	>99
2	Me **b**	76	30:1	>95	>99
3	$TMSOCH_2$ **d**	49[d,e]	>30:1	>95	>99
4	$AcOCH_2CH_2$ **e**	56[f]	13:1	>95	>99

[a] Yield of isolated product. [b] The ratios were obtained by ^{1}H NMR spectroscopy. [c] Data for *Z* isomers only. [d] The product from boracycle migration was also isolated in 19% yield. [e] The yield of the corresponding diols. [f] The product from boracycle migration was also isolated in 12% yield.

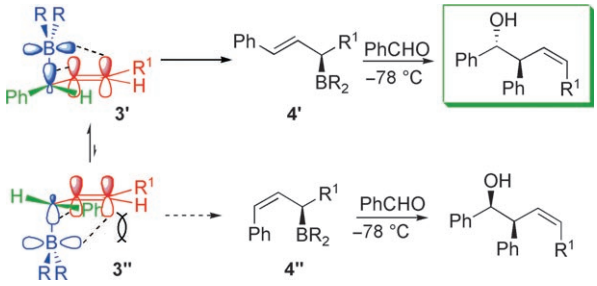


Scheme 2. Rationale for the observed stereochemistry.

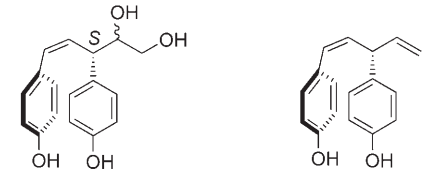
Procedure B was also applied to the same range of vinyl boranes and chiral sulfonium salt **7** (Table 2). Again, essentially complete enantio- and diastereoselectivity was observed with high *Z* selectivity. Since procedures A and B share common borate intermediates **11**, the competing migration of the boracycle, previously seen with less electron-rich vinyl boranes, was again observed (Table 2, entries 3 and 4). The relative and absolute stereochemistry of **9b** and **15a** were determined by transformation into known diols (see the Supporting Information).[4]

The complete selectivity observed following procedure B is consistent with the 1,3-borotropic rearrangement being a highly stereoselective, intramolecular process which leads to **4′** rather than **4″** (Scheme 3). The preferred formation of **4′** over **4″** results from minimization of the $A^{1,3}$ strain[15] in the conformations required (**3′** and **3″**) for the borotropic rearrangement to occur. Crotyl borane reagents are known to rapidly isomerize,[16] and racemization of allyl boranes has also been noted,[17] but such observations do not provide any information on the nature of the rearrangement. Theoretical calculations have suggested that the 1,3-borotropic rearrangement occurs through a pseudopericyclic transition state,[18] but as far as we are aware, this study provides the first experimental proof of the complete stereoselectivity and suprafacial nature of this rearrangement (Scheme 2).[19]

This stereocontrolled three-component-coupling reaction was applied to a short synthesis of iso-agatharesinol, isolated from the roots of asparagus gobicus.[20] Members of this family of nor-lignans show potent cytotoxicity against human ovarian carcinoma and human hepatoma.[18] However, the relative and absolute stereochemistry of one member of this family, iso-agatharesinol, has not yet been established (Scheme 4).[20] To determine the structure of the natural product, we set about synthesizing both diastereomers of iso-agatharesinol with the 3*S* configuration because this absolute stereochemistry had been established in related compounds such as nyasol.[21]

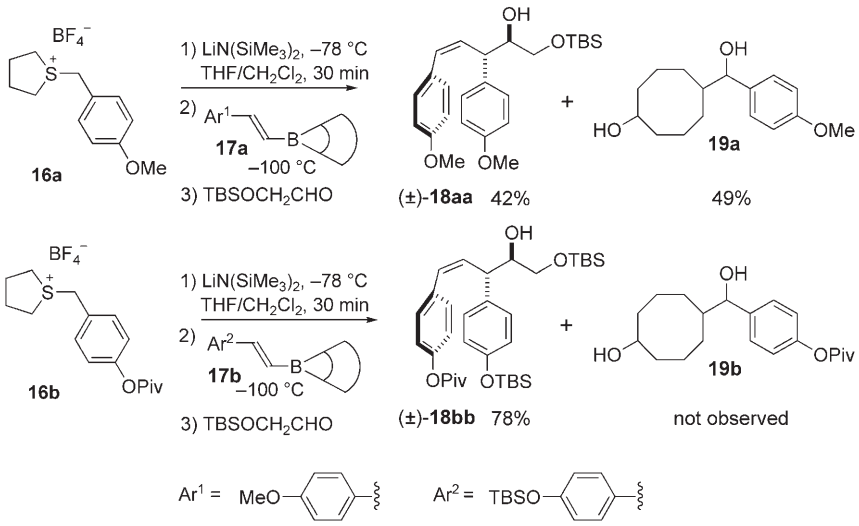


Scheme 3. Proposed [1,3]-borotropic rearrangement.



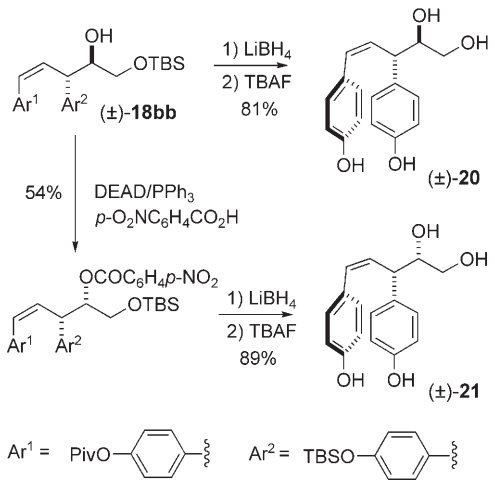
Scheme 4. Structures of iso-agatharesinol and nyasol.

We initially explored the racemic synthesis of iso-agatharesinol using the achiral sulfonium salt **16a** (Scheme 5). Thus, treatment of sulfonium salt **16a** with base followed by reaction with vinylborane **17a** and subsequent addition of the required aldehyde furnished the homoallylic alcohol **18aa**, but in only 42% yield. Product **18aa** was also accompanied by 49% of the eight-membered-ring diol **19a**, which resulted from migration of the boracycle followed by oxidation. We believe that the competing migration of the boracycle originates from the rearrangement process becoming more facile when the ylidic carbon atom is substituted with an electron-rich aromatic group (which helps expel the sulfide leaving group) and so the benefit of the higher migratory ability of the vinyl group on the borane is attenuated.[10] As the methoxy groups were also difficult to remove without destroying the sensitive *cis* olefin, we substituted the strongly electron-donating methoxy group on the ylide for the much weaker pivalate (Piv) group **16b**. This time, reaction of ylide **16b** with vinylborane **17b** followed by the aldehyde gave homoallylic alcohol **18bb** in 78% yield (*Z*/*E* 10:1), with no migration of the boracycle observed (Scheme 5).



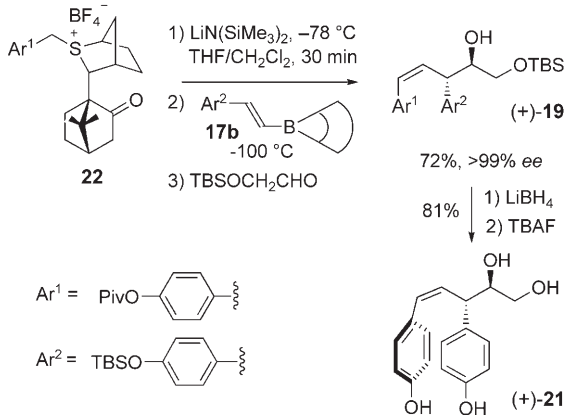
Scheme 5. Establishment of suitable protecting groups on the phenol function. TBS = *tert*-butyldimethylsilyl.

Deprotection of **18bb** gave the required polyol **20** in 81% yield (Scheme 6). The other diastereomer **21** was prepared by Mitsunobu inversion[22] of alcohol **18bb** followed by deprotection as before (Scheme 6). Of the two isomers, the reported data for the natural product most closely matched polyol **20**. In particular, the diastereotopic methylene protons in **20** appeared close together as a multiplet in the ^{1}H NMR spectrum (similar to that reported) whereas in **21** they were widely separated in a classic ABX system.[23]



Scheme 6. Racemic synthesis of both possible diastereomers of iso-agatharesinol. DEAD = diethylazodicarboxylate, TBAF = tetra-*n*-butylammonium fluoride.

Having established the relative stereochemistry of iso-agatharesinol, the asymmetric synthesis was carried out beginning with the chiral sulfonium salt **22** (Scheme 7). The key ylide addition, 1,2-metalate rearrangement,[24] and trapping with the aldehyde occurred in 72% yield and with greater than 99% *ee*, and without migration of the boracycle. Deprotection furnished iso-agatharesinol whose data ($[\alpha]_D^{20} = +50.7$ ($c = 0.75$, acetone)) corresponded with those reported ($[\alpha]_D^{20} = +49.7$ ($c = 5.40$, acetone)).[20] We



Scheme 7. Synthesis of (+)-iso-agatharesinol.

have thus established the relative and confirmed the absolute stereochemistry of isoagatharesinol.

In conclusion, we have described a new method for the stereocontrolled synthesis of allyl boranes and their subsequent reactions with aldehydes which occur with almost complete selectivity over the three elements of stereogenicity created. Furthermore, we have shown that the allyl boranes also undergo a stereospecific 1,3-borotropic rearrangement leading to new allyl boranes which also show almost complete selectivity in reactions with aldehydes. The efficiency of this process has been demonstrated by a short synthesis of the norlignan, iso-agatharesinol, which also confirmed its structure.

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