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Application of the Lithiation−Borylation Reaction to the Preparation of Enantioenriched Allylic Boron Reagents and Subsequent In Situ Conversion into 1,2,4-Trisubstituted Homoallylic Alcohols with Complete Control over All Elements of Stereochemistry

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Abstract: The reactions of Hoppe's lithiated carbamates with vinylboranes and boronic esters give allylic boranes/boronic esters, and subsequent addition of aldehydes provides a new route to enantioenriched homoallylic alcohols with high enantiomeric ratios and diastereomeric ratios. Specifically, reactions of sparteine-complexed lithiated carbamates with *trans*-alkenyl-9-BBN derivatives followed by addition of aldehydes gave (*Z*)-*anti*-homoallylic alcohols in greater than 95:5 er and 99:1 dr. However, in the special case of the methyl-substituted lithiated carbamate, diamine-free conditions were required to achieve high selectivity. Reactions of sparteine-complexed lithiated carbamates with (*Z*)-alkenyl pinacol boronic esters and (*E*)-alkenyl neopentyl boronic esters gave (*E*)-*syn*- and (*E*)-*anti*-homoallylic alcohols, respectively, in greater than 96:4 er and 98:2 dr. In these reactions, a Lewis acid ($MgBr_2$ or $BF_3 \cdot OEt_2$) was required to promote both the 1,2-metalate rearrangement and the addition of the intermediate allylic boronic ester to the aldehyde. This methodology provides a general route to each of the three classes of homoallylic alcohols with high selectivity.

Introduction

The asymmetric allylboration of aldehydes is one of the most reliable and useful methods for making carbon−carbon bonds with control over relative and absolute stereochemistry.[1] In particular, Hoffmann's realization that relative stereochemistry could be controlled by the double bond geometry of crotylboronates[2] and Brown's discovery of highly enantioselective allylborations using pinane-derived reagents[3] provided the foundations to this important reaction which continues to evolve to this date.[4] The most notable recent developments include Hall's discovery that Lewis acids promote reactions of allylic boronic esters,[4a,b,5] Roush's use of bisallylboron reagents for the stereocontrolled synthesis of 1,5-diols,[4c,d,6] and the development of a new chiral allylborane by Soderquist which gives high enantioselectivity even with ketones.[7]

However, generally, these powerful transformations are limited to simple allyl or crotylboron reagents, which ultimately lead to terminal alkenes; substitution in the α-position is considerably less common.[8] We recognized that if we could prepare such reagents with control over enantioselectivity, then, by judicious choice of the *achiral* groups on boron and the initial double bond geometry we had the potential to control all of the

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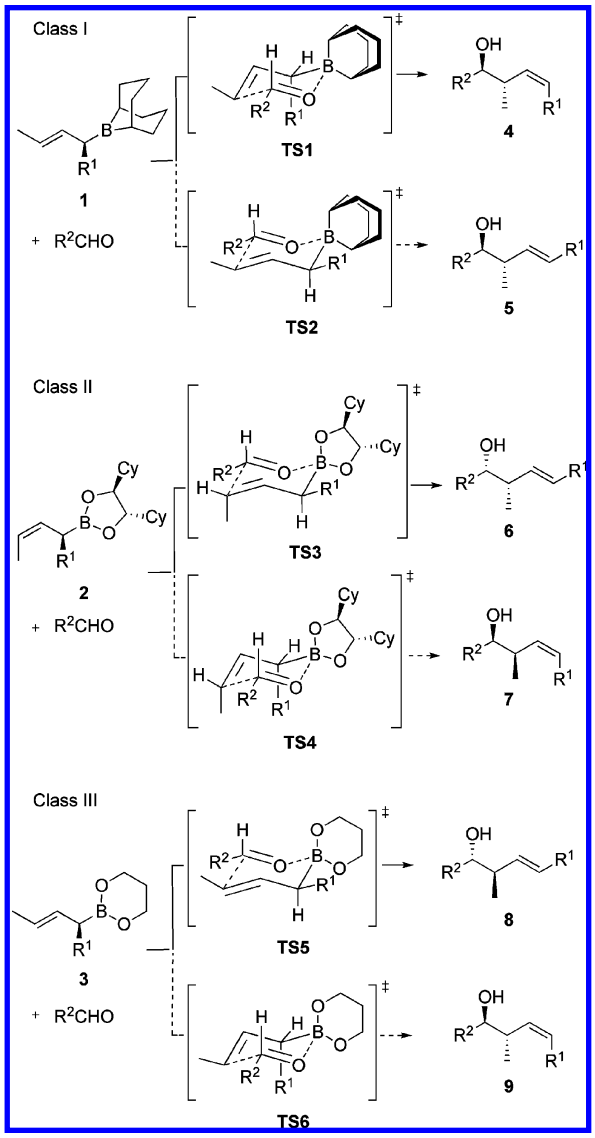
(8) The 2008 comprehensive review of allylation reaction using allylboron reagents by Hall[1c] cites 49 pages of tabulated individual reactions using an α-substituted allylboron reagent compared to 419 pages of reactions using allylboron reagents without α-substitution.

Scheme 1. Stereoselective Aldehyde Allylation Using Allylic Boron Reagents



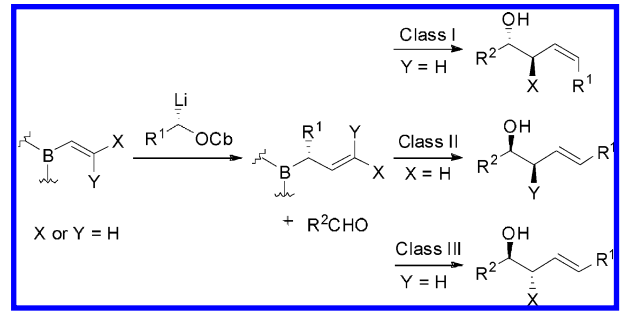
elements of stereochemistry of the homoallylic alcohol products at will (enantioselectivity, *E*/*Z*-stereochemistry and *syn*/*anti*-stereochemistry) without the need for additional stereodirecting reagents (Scheme 1).

The high selectivity in such reactions originates from the closed chair transition-state structures involved and the basic need to minimize nonbonded steric interactions.[2d,9] For example, a hindered borane (e.g., 9-BBN[10] as illustrated) or hindered boronic ester (e.g., tetraphenyl-1,2-ethanediol[6,11]) reacts via **TS1** because **TS2** suffers severe steric interactions between the equatorial substituent and the borane moiety (Scheme 1, class I). A *cis*-Allylic boronic esters, which constitute the most commonly used crotylboronic ester derivatives, reacts via **TS3** as **TS4** suffers severe $A^{1,3}$ strain (Scheme 1, class II).[2,4d,11a,12] As this is the dominant interaction, steric hindrance between the equatorial substituent and boronic ester is tolerated, even if the boronic ester is moderately hindered (e.g., pinacol, dicyclohexyl-1,2-ethanediol).[2] In contrast, *trans*-allylic boronic esters only give good selectivity if the boronic ester is unencumbered (e.g., 1,3-propanediol[4c,d,6]), enabling the reaction to occur via the less hindered **TS5** (**TS6** suffers a degree of $A^{1,3}$ strain). Moderately hindered boronic esters, such as pinacol boronic esters, give low diastereoselectivity and usually in favor of the *Z*-isomer.[12a]

Thus, each class of reagents has the potential to deliver high levels of relative stereocontrol, but absolute control is not equally facile. The best known and utilized reagents are Hoffmann's (*Z*)-crotylboronic esters (class II),[12] which have been prepared in high enantiomeric ratios using Matteson homologation.[13] For class I[9,10a,b] and class III[4c,10c] reagents, only sporadic examples for their generation in enantioenriched form exist.

In this paper, we describe a common general strategy to each class of these reagents, which in the subsequent reactions with aldehydes leads to each class of homoallylic alcohols in >95:5 er and >98:2 dr in all cases. Our common, general strategy involves the reactions of Hoppe's lithiated carbamates[14] with appropriately substituted vinylboranes or boronic ester (Scheme 2).

Scheme 2. Synthesis of α-Substituted Allylic Boron Reagents and In Situ Aldehyde Allylation



A conceptually related reaction had been reported by Hoppe (Scheme 3), in which an enantioenriched carbamoyl-substituted boronic ester was first reacted with a Grignard reagent and subsequent reaction with an aldehyde gave the homoallylic alcohol.[15] However, the diastereomeric ratios were only ~80:20, presumably because pinacol esters had been used, which only leads to low diastereoselectivity in the subsequent allylboration reaction, and the enantiomeric ratio was only 93:7 due to the source of the starting boronic ester.

Results and Discussion

We began our investigations with the class I reactions. The key intermediate allylboron reagents could potentially be

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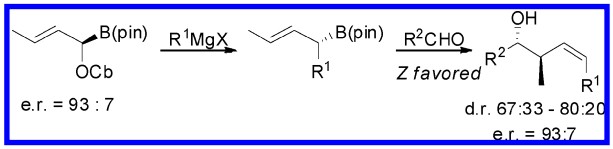
Scheme 3. Hoppe's Synthesis of α-Substituted Allylic Boronic Esters and Reaction with Aldehydes

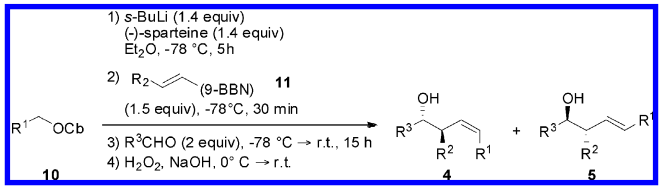


prepared by the reaction of lithiated carbamates with vinylboranes or boronic esters.[16] We had previously shown that α-aryl allylboranes bearing the 9-BBN group (Scheme 1, R^1 = aryl) could be easily obtained through reaction of an aryl-stabilized sulfur ylide with a vinylborane and that the allylic borane generated reacted with aldehydes with high enantio- and diastereoselectivity.[17] This reaction was limited to aryl-stabilized ylides; simple alkyl-substituted ylides reacted with boranes with low enantioselectivity.[18] However, more recently, we have shown that lithiated alkyl carbamates could react with boranes with high enantioselectivity.[16b,c]

In extending this transformation to vinylboranes, it was important that the conditions required for 1,2-metalate rearrangement did not result in isomerization of the labile allylic borane that was generated. We believed that this could be achieved by adding the aldehyde to the ate complex at low temperature. Upon warming, the ate complex would undergo a 1,2-metalate rearrangement, giving the allyl borane which would be immediately trapped by the aldehyde before isomerization could occur. This protocol was found to be successful with a range of representative *trans*-vinylboranes **11**, carbamates, and aldehydes (Table 1, entries 1−9). In all cases, high enantiomeric ratios and perfect diastereomeric ratios were observed except for the simplest carbamates (R^1 = Me, entries 10 and 11), which gave much lower enantiomeric ratio. This was surprising as we had previously found that the same carbamate reacted with B-Ph-(9-BBN) with high enantiomeric ratio.[16] After some experimentation, we discovered that the diamine-free lithiated carbamate generated from the corresponding stannane[19] **12** rescued this important substrate, giving the homoallylic alcohol with excellent enantiomeric ratios and perfect diastereomeric ratios for a range of aldehydes and alkenyl 9-BBN derivatives (Table 2).[20]

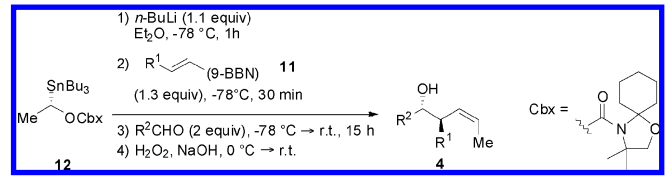
The high diastereoselectivity observed in the allylation reaction can be rationalized by the increased steric encumbrance in transition-state structure **TS2** compared to that in **TS1** (Figure 1).[5a,9,21] Severe hindrance between the 9-BBN ring and R^1 would force the α-carbon substituent into a pseudoaxial position, resulting in the *anti*-diastereoisomer and (*Z*)-alkene geometry.

Table 1. Aldehyde Allylation Using α-Substituted Allyl-(9-BBN) Reagents



entry	R^1	R^2	R^3	yield **4** (%)	er (**4**)	dr (**4**/**5**)
1	$Ph(CH_2)_2$	Me	Cy	84	96:4	>99:1
2	$Ph(CH_2)_2$	Me	Ph	82	97:3	>99:1
3	$Ph(CH_2)_2$	Bu	Ph	91	98:2	>99:1
4	$Ph(CH_2)_2$	Bu	Cy	78	98:2	>99:1
5	$Ph(CH_2)_2$	CH_2OSiMe_3	Ph	73	98:2	>99:1
6	$Ph(CH_2)_2$	Me	Bu	80	98:2	>99:1
7	*i*-Pr	Me	Ph	58	98:2	>99:1
8	*i*-Pr	Me	Cy	54	96:4	>99:1
9	*i*-Pr	Bu	Ph	60	95:5	98:2
10	Me	Me	Ph	88	60:40	>99:1
11	Me	Me	Cy	65	88:12	>99:1

Table 2. Diamine-Free Aldehyde Allylation Using α-Stannylated *O*-Ethyl Carbamate



entry	R^1	R^2	yield **4** (%)	er (**4**)	dr (**4**/**5**)
1	Me	Ph	84	95:5	>99:1
2	Me	Cy	78	94:6	>99:1
3	Bu	Ph	64	93:7	>99:1

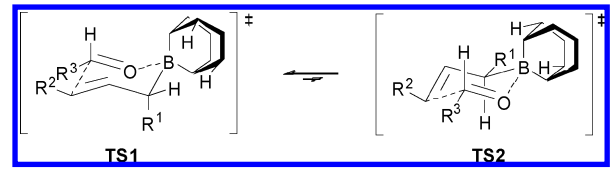


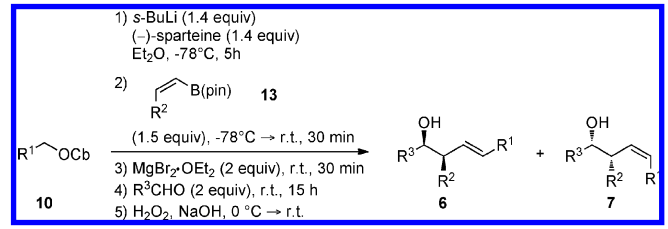
Figure 1. Competing transition-state structures in the addition of α-substituted allyl-(9-BBN) reagents to aldehydes.

In order to target class II reactions, we chose *cis*-vinyl pinacol boronic esters **13**, which were easily prepared by esterification of commercially available vinylboronic acids. In this case, the presence of the boronic ester in place of the borane presents additional challenges: (i) the 1,2-metalate rearrangement is now much slower; and (ii) the allylic boronic ester is much slower at allylboration. Fortunately, both processes can be accelerated with Lewis acid catalysis.[5a,22] After optimization of the reaction conditions, a protocol was developed which showed broad generality for a representative range of boronic esters, aldehydes, and carbamates leading to the (*E*)-*syn*-homoallylic alcohol with high diastereomeric ratio and enantiomeric ratio in all cases (Table 3).

The stereochemical outcome can be rationalized by considering the Lewis acid activated closed TS for the reaction. In this case, the *cis* R^2 substituent imposes severe $A^{1,3}$ strain and forces R^1 into a pseudoequatorial position, **TS8**, thus leading to the *E*-*syn*-isomer (Figure 2).

In order to obtain the *E*-*anti*-isomer, we would "simply" require the (*E*)-allylic boronic ester. However, this is one of the most challenging diastereoisomers to prepare selectively

Table 3. Aldehyde Allylation Using (*Z*)-Allylic Boronic Esters



entry	R^1	R^2	R^3	yield **6** (%)	er (**6**)	dr (**6**/**7**)
1	$Ph(CH_2)_2$	Bu	Ph	54	99:1	>99:1
2	$Ph(CH_2)_2$	Me	Ph	46	99:1	>99:1
3[a]	$Ph(CH_2)_2$	Me	Cy	59	99:1	>99:1
4	Me	Me	Ph	56	99:1	>99:1
5[a]	Me	Me	Cy	46	99:1	>99:1

[a] Four equivalents of $MgBr_2 \cdot OEt_2$ used.

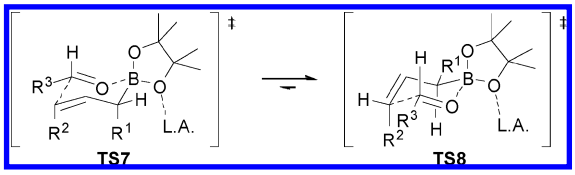


Figure 2. Stereoselectivity of (*Z*)-allylic-boronic esters.

since the two competing closed transition-state structures both suffer from different forms of steric interactions (Figure 3): **TS9** suffers from $A^{1,3}$ interactions between R^1 and the vinyl proton, while **TS10** suffers from steric hindrance between R^1 and the boronic ester diol group.

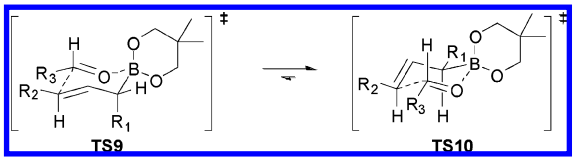
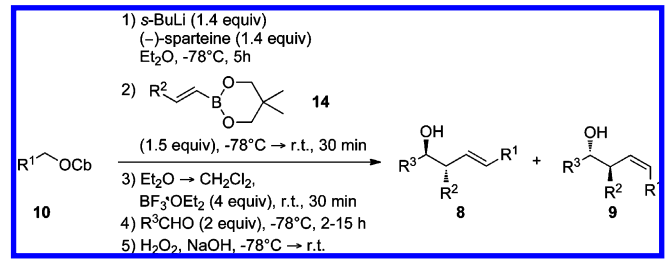


Figure 3. Stereoselectivity within the allylation reaction using (*E*)-allylic boronic esters.

In order to favor **TS10**, we required an unhindered boronic ester and chose the neopentyl boronic ester for the class III reactions. These boronic esters have similar steric hindrance to propane-1,3-diol boronic esters but are more robust and can even be purified by silica gel chromatography in many cases. These were easily prepared by hydroboration of an alkyne with $HBBr_2$ followed by addition of neopentyl glycol.[23] After some experimentation, a general protocol was again found that gave moderate to high yields, high enantiomeric ratios, and very high diastereomeric ratios in this most challenging of cases. The optimum conditions involved addition of the boronic ester **14** to the lithiated carbamates followed by solvent exchange ($Et_2O \rightarrow CH_2Cl_2$), addition of $BF_3 \cdot OEt_2$ (4 equiv) at room temperature, cooling to −78 °C, addition of the aldehyde, and quenching at −78 °C, after completion of the reaction. We believe the excess Lewis acid is required as some is sequestered by the diamine and LiOCb which are present in the reaction mixture. Without the solvent exchange, the reaction times are considerably longer.[24] Under the optimized conditions, a representative range of carbamates, *trans*-vinylboronic esters, and aldehydes all gave excellent results (Table 4).

Table 4. Allylation of Aldehydes Using (*E*)-Allylic Boronic Esters



entry	R^1	R^2	R^3	yield **8** (%)	er (**8**)	dr (**8**/**9**)
1	$Ph(CH_2)_2$	Me	Ph	67	98:2	>99:1
2	$Ph(CH_2)_2$	Me	Cy	60	98:2	>99:1
3	$Ph(CH_2)_2$	Bu	Ph	58	99:1	>99:1
4	$Ph(CH_2)_2$	Bu	Cy	67	99:1	>99:1
5	Me	Me	Ph	51	95:5	>99:1
6	Me	Me	Cy	58	99:1	>99:1

Conclusion

In conclusion, we have developed a general and convergent protocol for combining lithiated carbamates, vinylboranes/boronic esters, and aldehydes to give 1,2,4-substituted homoallylic alcohols with control over relative and absolute stereochemistry. The absolute stereochemistry is controlled through sparteine-mediated lithiation of the carbamate, a reaction where the other enantiomer is also easily accessible through the use of the (+)-sparteine surrogate.[25] The relative stereochemistry is controlled by the nature of the boron substituent and the geometry of the initial vinylboron reagent: (i) the hindered 9-BBN combined with (*E*)-vinylborane leads to the *Z-anti*-isomer (class I); (ii) the relatively hindered pinacol boronic ester combined with the (*Z*)-vinylboronic ester leads to the *E-syn*-isomer (class II); and (iii) the unhindered neopentyl boronic ester combined with the (*E*)-vinylboronic ester gives the *E-anti*-isomer (class III). The new processes described significantly expand the scope of allylboron reactions as it not only introduces substitution in the alkene of the homoallylic alcohol product with control of double bond geometry but also achieves exquisite levels of stereocontrol. The predictable stereochemical outcome and ease of access to the reagents are features that readily lend this protocol to use in complex natural product synthesis. Studies in this area are ongoing.

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Supporting Information Available: Full experimental and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) This observation was also seen in the reactions with B-β-trimethylsilylvinyl-9-BBN substrates but to an even greater extent. Full details will be published shortly.
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