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A novel allylic transfer reaction of chirally modified 2-borylbutadiene: synthesis of chiral homoallenyl alcohols[†]

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An enantioselective synthesis of the homoallenyl alcohols was achieved from the reaction of chiral 2-borylbutadiene with aldehydes through an allylic transfer reaction in good yields and enantioselectivities.

Structurally unique allenes are found in nature and play important biological and chemical roles.¹ Recently allene moieties have been utilized as useful substrates for a variety of chemical transformations.² For example, many advances in the cyclisation using allene moieties mediated by transition metals have been made through a variety of ways in synthetic strategy.³ After all, considerable attention has been paid to synthesizing allenyl compounds.^{1,2} As part of our continuous efforts to utilize allenyl functionality,⁴ we recently disclosed the cyclisation strategies to establish the 5- or 7-membered oxacycles starting from homoallenyl alcohols 2.⁵ The characteristic features of this protocol in terms of chemical efficiency of the three component coupling process and structural features of products have encouraged us to develop an asymmetric method for the preparation of enantiomerically enriched 2, which would expand the scope and utility of our synthetic efforts for allenic alcohols.⁶ As a consequence, we became quite interested in designing an asymmetric process to access 2 from 1 through an intermolecular allylic transfer reaction A with aldehydes as illustrated in Scheme 1. To provide direct access to the product 2, we considered a chirally modified 2-boronylbutadiene 1 as a crucial intermediate. It was envisaged that the method could establish not only center chirality but also axis chirality as shown in Scheme 1.7



Scheme 1 General strategy for a synthesis of homoallenyl alcohol 2.

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and NMR spectra for all products. See DOI: 10.1039/c0cc05751g

In light of widespread advances in synthetic methods for the synthesis of chiral substances, the allylic transfer reactions of carbonyl functionalities using chiral auxiliaries or catalysts led to significant developments in the area of asymmetric synthesis. A number of successful methodologies using stoichiometric amounts of chiral reagents and a catalytic amount of chiral Lewis acid or base have been developed and applied to organic synthesis.⁸ Subsequent to early studies on the use of chirally modified allylic boranes to accomplish asymmetric induction by Hoffmann, many research groups have made important contributions to the extension of this protocol to achieve high levels of stereoselectivity.9 2-Boryldienes have been known in the literature mainly for their utilization as a diene for the Diels-Alder reaction.¹⁰ To the best of our knowledge, there are two reports of asymmetric homoallenylation using 2-boryldiene¹¹ and chromium¹² which appeared during our investigations. We describe herein our preliminary results delineating a practical homoallenylboration for the asymmetric synthesis of homoallenyl alcohols 2.

The first study for preliminary experiments focused on the feasibility of 6 as an allylic transfer reagent and the reactivity of 6 with carbonyl compounds to afford 2 as depicted in Scheme 2. With this issue in mind, our investigations began with 3a for the preparation of the chiral 2-borylbutadiene 6 by the modification of Corey's method¹³ mainly because we had already developed a method for the preparation of 5 as a transmetallating reagent.¹⁴ To investigate the sequence outlined in Scheme 2, several bis-arylsulfonylamides 3 were prepared. The (S,S)-bromoborane 4a (R = p-tolyl) was prepared from **3a** as described in the literature.^{13a} Reaction of 4a with 5 in CH₂Cl₂ at 0 °C for 1 h and 25 °C for 3 h produced the 2-borylbutadiene 6a which was used without isolation for the next stage. Initial attempts to carry out allylic transfer reaction of 6a with hydrocinnamaldehyde at -50 °C for 15 h in CH2Cl2 afforded encouraging but marginal results. Although 2a was produced as a sole product during the reaction, low enantioselectivity (54% ee) and chemical yield (47%) remained to be solved. Unfortunately, reaction did not proceed below -60 °C. Although several solvents such as toluene and propionitrile were introduced as shown in Table 1, reactivity and enantioselectivity were not improved. Introduction of 3b as a ligand turned out to be unpromising in terms of reactivity and stereoselectivity (Table 1, entries 5, 6).

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 Table 1
 Selected preliminary investigations^a

Entry	z	Solvent	t/h	$T/^{\circ}\mathbf{C}$	$ee, \%^b$	Yield, % ^c
1	3a	CH ₂ Cl ₂	15	-50	54	47
2	3a	Toluene	15	-50	37	41
3	3a	EtCN	15	-50	nd	15
4	3a	CH_2Cl_2	15	-78	nd	Trace
5	3b	CH_2Cl_2	15	-50	57	51
5	3b	Toluene	15	-50	37	44
7	3c	CH_2Cl_2	5	-78	91	78
3	3c	Toluene	15	-78	77	44
)	3d	CH_2Cl_2	15	-78	88	55
10	3d	Toluene	15	-78	83	51
^a As ou OD-H. ^c	tlined i Refers	in Scheme 2 s to isolated j	. ^b Dete product	ermined b	y HPLC a	nalysis with

We subsequently speculated that the modification of 3 might be needed to enhance reactivity. After surveying numerous conditions with a variety of chiral ligands, we were delighted to find that 3c could be a suitable chiral ligand in terms of chemical conversion and enantioselectivity as shown in Table 1 (entry 7).

During the orienting experiments, key findings emerged as follows: (1) the use of **3c** proved to be most effective for the homoallenylboration; (2) reaction performed at -78 °C in CH₂Cl₂ resulted in the best chemical yields in comparison with other solvents such as toluene; (3) reaction produced solely the homoallenyl alcohol **2a** without formation of dienylalcohol. This observation clearly indicated that the formation of **6c** was regiospecific.

With the notion that this approach might lead to a general and efficient method for the synthesis of 2 as shown in Scheme 3, we set out to determine the scope to produce various products. Indeed, the method is successful with a variety of aldehydes to yield the cyclic products 2b-j as a single isomer, respectively, in moderate to high yields with high levels of enantioselectivity as can be seen in Table 2.

Table 2	Asymmetric homoallenylboration of aldehydes	
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^{*a*} Refers to yield after production. ^{*b*} Determined by HPLC analysis with Daicel OD-H and/or ¹H NMR analysis of (+)-MTPA esters in comparison with samples prepared from (*R*,*R*)-3c.

Absolute configuration of products was verified by the comparison of specific rotation data with literature values.^{5,12} The products obtained can be accounted for by the intervention of the pseudopericyclic stereochemical model **A** with minimum steric interactions and optimal orbital interactions, which leads to a major reaction pathway as illustrated in Scheme 3.

This method for the synthesis of homoallenyl alcohols could be valuable because many useful functional group transformations can be foreseen.¹⁵ In light of the above results for the asymmetric homoallenylboration, we next turned our attention to the application of this approach for an enantioselective synthesis of *cis*-2-methyl-5-hexanolide **8**, a naturally occurring pheromone of the carpenter bee.¹⁶ Cyclocarbonylation of **2a** and **2b** with Ru₃(CO)₁₂ in the presence of Et₃N under CO atmosphere (20 atm) at 100 °C in dioxane resulted in the formation of lactone **7a** and **7b**,



Scheme 3 A plausible stereochemical and reaction route.



Scheme 4 Synthesis of natural product 8.

respectively.¹⁷ Hydrogenation of **7b** with Pd/C at 0 $^{\circ}$ C in EtOAc provided **8** in 88% yield (Scheme 4).

In summary, this communication describes an asymmetric homoallenylboration of aldehydes through the intermolecular allylic transfer reaction, which promises to be synthetically useful. This transformation involves the formation of 2-dienylborane from chirally modified bromoborane with homoallenyl tin reagent, and subsequently the intermolecular allylic transfer reaction with aldehydes. Further studies including synthetic applications and extension of this method with substituted 2-boryldienes are in progress.

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