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Asymmetric Allylation. An Effective Strategy for the Convergent Synthesis of Highly Functionalized Homoallylic Alcohols

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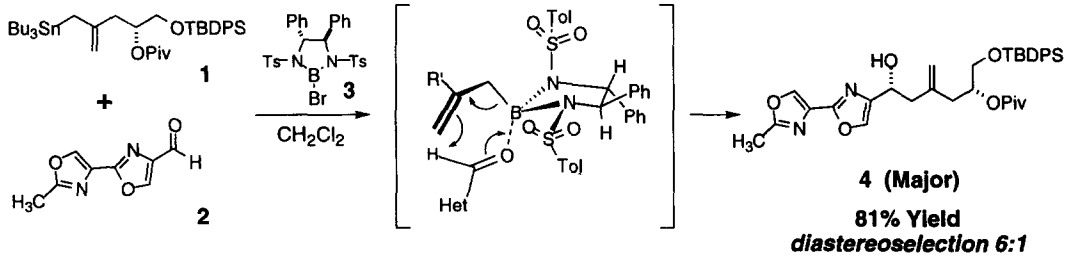
Abstract: A survey of stereoselective syntheses of highly-functionalized homoallylic alcohols is described via asymmetric allylation. Initial transmetalation from an allylic stannane to a C-2 symmetric chiral borane controller is followed by low temperature addition to aldehydes efficiently effecting convergent strategies to complex targets.

The formation of chiral secondary homoallylic alcohols through the enantioselective addition of allyl nucleophiles to aldehydes is a powerful tool for multistep synthesis.[1] Important contributions have shown the effectiveness in achieving excellent selectivity in asymmetric allylations through the use of chiral controllers,[2] chiral Lewis acids,[3] or through substrate control.[4] Studies of natural product synthesis in our laboratories have produced a series of allylstannanes in which the C-2 position is substituted with a densely functionalized carbon segment. Further reactions reveal the rich and somewhat unpredictable chemistry of these nucleophiles.[5] Recent communications have demonstrated the value of C-2 substituted allylstannanes in glycosidation[6] and isoprenoid synthesis.[7] In 1989, E. J. Corey first reported the (*R,R*) and (*S,S*)-1,2-diamino-1,2-diphenylethane controller ligands for enantioselective Diels-Alder, aldol and allylation reactions.[2a,b] Utilizing these readily available and efficiently recovered controllers, the potential of this predictable method for stereocontrolled allylations with simple aldehydes was introduced.

Herein, we have described a survey of our investigations for effective *in situ* transmetalations using the Corey chiral sulfonamide system with functionalized, optically active allylstannanes for stereocontrolled preparation of homoallylic alcohols. These advances in enantioselective allylation technology permit the application of sophisticated C-2 substituted allylstannanes for convergent condensation with a variety of functionalized aldehydes in high yields.



Our initial successes were realized in the course of model studies toward synthesis of the marine alkaloid (–)-hennoxazole A.[8] The expected addition of reactive nucleophiles with the *bis*-oxazole carboxaldehyde **2** led to competing ring deprotonation. Critical formation of the (*R*)-homoallylic alcohol of **4**

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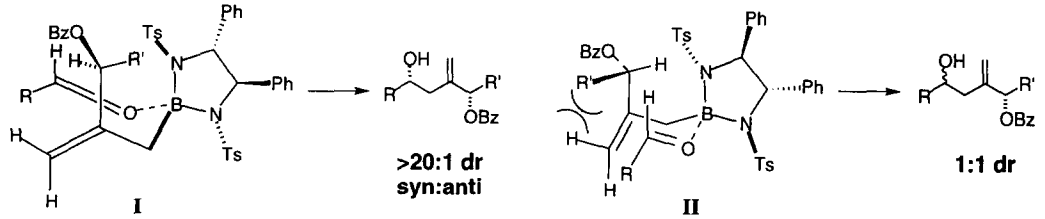
is achieved by transmetalation of the optically pure allylic stannane **1** with (*R,R*)-bromoborane **3**[2a] to yield an intermediate allylic borane for facile condensation with aldehyde **2**. Stereocontrol is principally induced from the sulfonamide (6:1 dr). Lewis acid ($TiCl_4$; CH_2Cl_2; –78 °C) catalyzed reactions of allylstannane **1** with carboxaldehyde **2** produced a mixture of alcohols (40:60 ratio) favoring the corresponding (*S*)-isomer of **4**.

Further results are summarized in the Table. Preparation of the allylic stannane component (compound **1**, entries **1–2, 7–9**) is conveniently carried out via copper-catalyzed Grignard addition of the reagent generated from 2-bromo-3-trimethylsilylpropene[9] to a nonracemic terminal epoxide. Following protection of the resulting secondary alcohol, a two-step protocol[10] converted the allylsilane to the allylic stannane. The precursor silanes did not undergo direct transmetalation with bromoborane **3**. Entries **3–5** were prepared by the deprotonation of the corresponding methallyl alcohol moiety (*n*-BuLi; TMEDA; Et_2O:THF (3:1); 0 °C) and C-alkylation with tri-*n*-butylstannyl iodide.[11]

Reacting components tolerate a wide range of functionality. The presence of Lewis acid sensitive protecting groups in the stannane portion, such as MOM, MEM and ketals, are incompatible with the bromoborane, whereas vinylstannanes, esters, dithioketals, and silyl ethers survive. Transmetalation of the stannane (1.5 eq) with the chiral bromoborane (1.35 eq)[2a] is carried out at ambient temperature for 16 h (CH_2Cl_2), followed by cooling to –78 °C. Addition of aldehyde (1 eq) leads to complete reactions within 2-3 h.[12] Absolute stereochemistry of the newly formed homoallylic alcohol has been established by Mosher ester analysis,[13] and is predicted from a chair-like transition state with minimized steric repulsion.

Stannanes, in which the C-2 branch contains β-asymmetry (entries **7–9**), provide a stereochemical allylation governed solely by the chiral auxiliary. Entries **1–2** demonstrate that the β-tetrahydropyranyl ring in the aldehyde substrate leads to matched and mismatched allylations. However, the presence of a protected alcohol at the α-position of the C-2 substituted stannane has a dramatic effect on diastereoselection (entries **3–4, 6**). One pure product is obtained when the (*R,R*)-auxiliary is matched with the (*S*)-allyl stannane (entry **3**). The corresponding mismatched example of the (*S,S*)-auxiliary affords no diastereoselection. Rationalization of these results can be considered by adaptation of a reactive conformation which minimizes 1,3-allylic strain (Figure **I**), and achieves an antiperiplanar relationship to the allylic benzoate by analogy to the Felkin-Anh model.[14] Figure **II** is destabilized by the unfavorable 1,3-allylic strain. Overall, this technique constitutes a efficient strategy for synthesis of *syn*-1,4-diols.[15] Asymmetry of the α,β-epoxyaldehydes (entries **4** and **5**) provide an inherent preference for Felkin addition. This leads to the triply stereoconvergent process of entry **4**, and the mismatched result of entry **5**.[16]

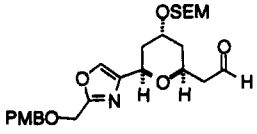
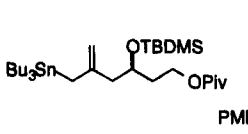
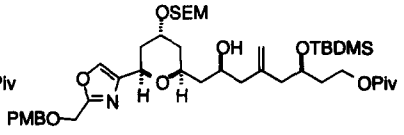
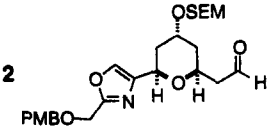
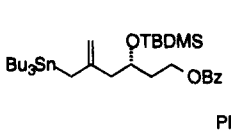
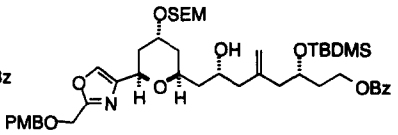
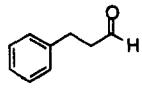
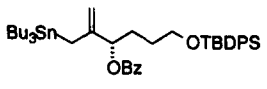
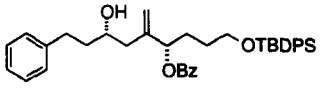
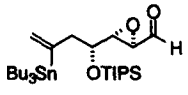
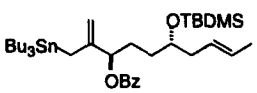
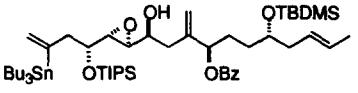
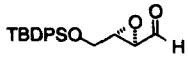
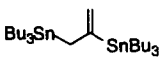
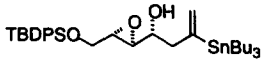
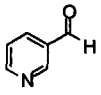
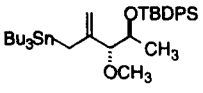
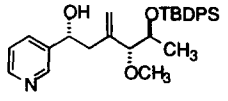
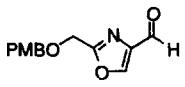
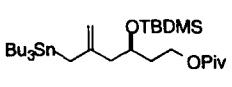
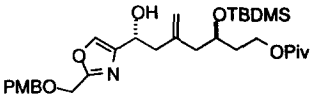
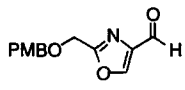
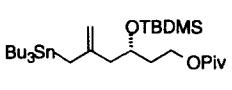
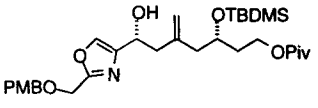
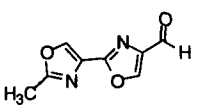
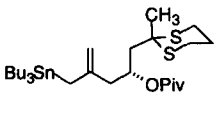
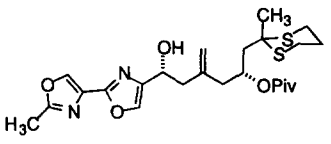


I **II**

(*R,R*)-sulfonamide **(*S,S*)-sulfonamide**

A powerfully convergent strategy for the diastereoselective synthesis of homoallylic alcohols with chiral allylic stannanes has been described. Further advancements are in progress.

Table: Enantioselective Allylations

Entry	Aldehyde	Stannane	Product	Aux.	Yield, dr
1				(S,S)	99% 11.4:1
2				(R,R)	88% 4:1
3				(R,R) (S,S)	96% > 20:1 94% 1:1
4				(S,S)	75% 17:1
5				(R,R)	85% 3.2:1
6				(R,R)	55% >20:1
7				(R,R)	92% >20:1
8				(R,R)	98% >20:1
9				(R,R)	95% 10.5:1[17]

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10. General Procedure: 1. NBS, CH_2Cl_2, –78 °C, 4h; 2. $Bu_3SnCuLi$, THF, –78 °C→ –40 °C
11. Trost, B.M.; King, S.A. *J. Am. Chem. Soc.* **1990**, *112*, 408.
12. Optimum yields and diastereoselectivities were achieved using new bottles of boron tribromide (1.0 M solution in CH_2Cl_2 purchased from Acros) to generate the boron sulfonamide. Diastereoselectivity ratios (dr) were determined by 500 MHz ^1H NMR analysis of the crude reaction mixture. Isolated product yields were determined following flash silica chromatography.
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14. Maguire, R.J.; Mulzer, J.; Bats, J.W. *Tetrahedron Lett.* **1996**, *37*, 5487. Maguire, R.J.; Mulzer, J.; Bats, J.W. *J. Org. Chem.* **1996**, *61*, 6936. Boron trifluoride etherate-catalyzed reactions provided no diastereoselection for substrates in entry **3** (yield 93%).
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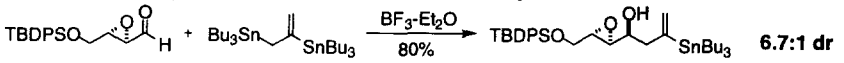
16. The observed diastereoselection in entry **4** reflects the purity of the starting epoxy-aldehyde (89% ee; ratio 17:1). When this is taken into account, the allylation proceeds in >40:1 diastereoselection. Boron trifluoride etherate-catalyzed reactions for substrates in entry **5** illustrate Felkin addition.



17. When the enantiomeric purity of the starting stannane (90% ee) is taken into account, the allylation proceeds in >20:1 diastereoselection for the (*R*)-isomer.