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Boron-Mediated Stereoselective Syntheses of γ,γ-Disubstituted Allenamides

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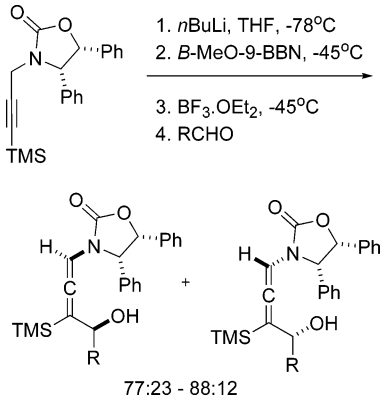


Propargylic boranes generated by lithiation of optically active *N*-propargyloxazolidinones undergo reaction with a range of aldehydes to produce γ,γ-disubstituted allenamides with good diastereoselectivity.

Propargyl **B** and allenyl organometallics **A** can be obtained by deprotonation of propargylic substrates and are important intermediates as they can combine with carbonyl compounds to produce either allenyl alcohols **C** or homopropargylic alcohols **D**, respectively (Figure 1).[1] However, tuning the regioselectivty of this class of reaction is a continuing challenge as **A** and **B** are in rapid equilibrium, especially when M = K, Na, or Li. However, **A** and **B** can both be stabilized by exchanging to a more covalently bound metal such as B, Ti, or Sn, but the issue of regioselectivity during the transmetalation step remains. Furthermore, if R^1 is a strongly chelating group such as carbamoyl, then **B** is favored over **A**, allowing regioselective access to allenyl alcohols.[2]

Toward the goal of regioselective preparation of allenyl organometallics, we have recently developed the synthesis of optically active α-aminoallenylstannane **2**, which is a stable isolable species.[3] Chiral allenamides have recently emerged as versatile synthetic building blocks,[4] which can undergo a variety of useful transformations.[5] α-Aminoallenylstannane **2** undergoes reaction with aldehydes in the presence of $BF_3{\cdot}OEt_2$ via the Felkin−Ahn transition-state model developed by Marshall et al.[6] to produce β-hydroxypropargylamines **3** with high *syn* diastereoselectivity (Scheme 1).

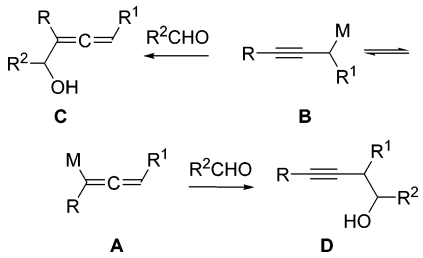
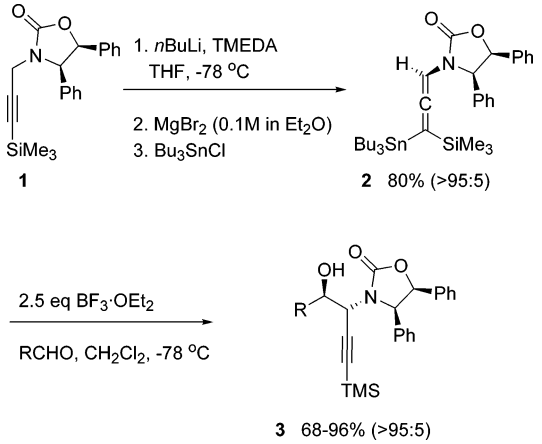


FIGURE 1.

SCHEME 1



Although this methodology represents an efficient synthesis of β-hydroxypropargylamines and a further application of allenamides in synthesis,[4] alternatives that obviate the stoichiometric use of tin are of significant interest. In contrast to organotin compounds, organoboron compounds are easily manipulated and usually do not represent a serious environmental or toxicological hazard. Wang et al. have previously reported that allenylboranes generated in situ from the lithium anion of 3-(*tert*-butyldimethylsilyl)-1-(trimethylsilyl)-1-propyne **4** undergo reaction with allenic aldehydes to yield homopropargylic alcohols **6** in high diastereoselectivity (Scheme 2).[7] This precedent suggested that allenylboranes bearing a chiral oxazolidinone could potentially be synthesized to provide routes to optically active β-hydroxypropargylamines **3**.

To investigate this, the procedure in Scheme 1 was carried out with Et_2BOMe in place of Bu_3SnCl (Scheme

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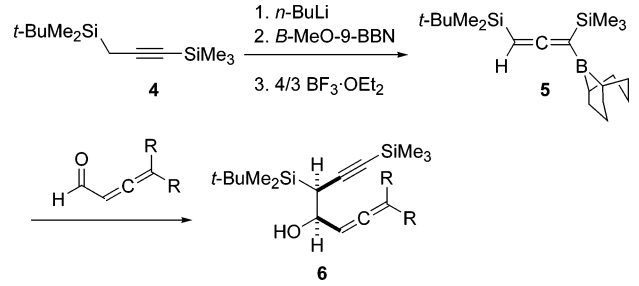
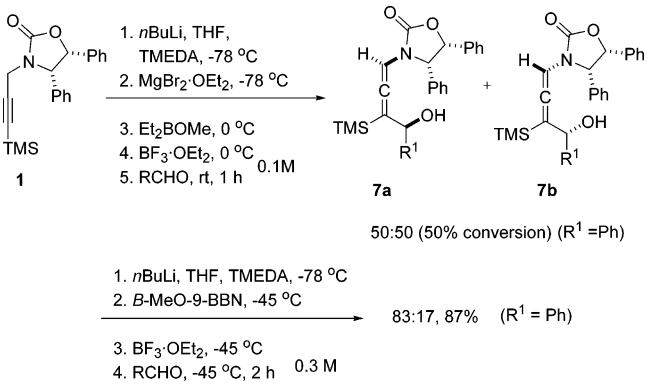
SCHEME 2



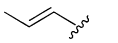
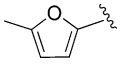
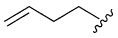
SCHEME 3



3). Because of anticipated instability, the organoborane intermediate was not isolated but allowed to react in situ with PhCHO in the presence of $BF_3{\cdot}OEt_2$ at room temperature for 1 h. Unexpectedly, instead of β-hydroxypropargylamines, allenyl carbinols **7a** and **7b** were obtained in a 1:1 diastereomeric mixture along with 50% recovered starting material. The relative stereochemistry of **7a** and **7b** was determined by single-crystal X-ray diffraction. An earlier report by Wang et al. showed that simple 1-(trimethylsilyl)-1-alkynes can yield allenyl carbinols via propargylic organoboranes,[8] suggesting a strong structure dependency upon the regioselectivity of this class of reaction (Scheme 3).

Allenyl carbinols display a rich organometallic chemistry, typically undergoing efficient cyclization to a variety of ring sizes.[9] However, much of this work has been limited to relatively simple systems, leaving the cyclization of allenamides bearing hydroxyl groups unexamined. Therefore, with a regioselective route to highly functionalized allenyl carbinols in hand, efforts to develop this into an efficient, diastereoselective synthesis were carried out. Optimization studies led to conditions (Scheme 3) that resulted in good yields and acceptable diastereoselectivities. The temperature of the transmetalation step and the aldehyde addition proved critical to the diastereoselectivity of the reaction, and lowering the temperature to −45 °C gave an 83:17 **7a**:**7b** selectivity in 87% isolated yield. For the reaction to proceed efficiently at temperatures below 0 °C, it was necessary to increase the concentration of **1** to 0.3 M. Lowering the temperature below −45 °C did not increase the selectivity and resulted in longer reaction times and poorer conversions.

TABLE 1. Reactions of 1 with RCHO (Scheme 3)

R	product	yield, %[a]	time, h	diastereoselectivity[b]
Ph	**7a,b**	87	1	83:17[c]
*i*Pr	**8a,b**	87	24	77:23
n-pentyl	**9a,b**	65	24	88:12
	**10a,b**	72	2	81:19
	**11a,b**	61	4	83:17[d]
	**12a,b**	86	12	83:17
	**13a,b**	78	48	88:12
	**14a,b**	81	48	88:12

[a] Reported yields are for isolated, purified compounds. [b] Estimated from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Stereochemistry determined by single-crystal X-ray diffraction. [d] Reaction run at −25 °C

The reaction proved general for a range of aldehydes (Table 1). Aromatic-, staight-, and branched-chain aliphatic and α,β-unsaturated aldehydes all underwent reaction in high yields and good diastereoselectivities. Of note is the accessibility of ene-allene **12a** from 4-pentenal, which potentially allows access to highly functionalized ring systems via the recently developed Rh(I)-catalyzed ene-allene carbocylization for the formation of seven-membered rings.[10] Electron-poor 5-methyl-furfural also underwent diastereoselective allene formation but required higher temperatures of −25 °C for the reaction to be efficient. The reaction was also relatively insensitive to α-chirality in the aldehyde, with both *S* and *R* enantiomeric aldehydes, R = $CH_3CH(OBn)$, undergoing diastereoselective condensation. It is important to note that in all cases the major and minor diastereomers have a sufficiently different R_f to allow straightforward separation by flash chromatography. Although Wang et al. have reported that simple propargylic organoboranes undergo reaction with imines,[11] attempts to carry out the condensation in Scheme 3 with the *N*-tosylimine of benzaldehyde and the *N*-benzylimine of benzaldehyde resulted in recovered starting material or decomposition. The same result was observed when the condensation was attempted with acetophenone. However, work is currently underway to extend the scope of the reaction to other electrophiles.

The regiochemical outcome of the reaction can be tentatively explained assuming that the presumed intermediate propargylic borane is configurationally stable as the result of a strong Lewis acid−base interaction between boron and the carbonyl group of the oxazolidinone. This then reacts with benzaldehyde in an *anti*-S_E2' process to produce allenyl carbinols. The stereochemical outcome of the reaction is of interest as it is opposite to that reported by Seebach in his elegant synthesis of allenyl carbinols via propargylic titanium species.[12] See-

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(9) For reviews, see: (a) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (b) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701.
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(11) Wang, K. K.; Nikam, S. S. *J. Org. Chem.* **1985**, *50*, 2193.
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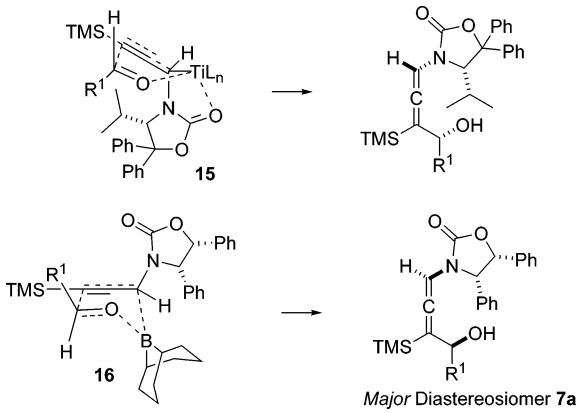

FIGURE 2.

bach proposed that coordination of the titanium to the oxazolidinone leads to the chairlike transition state **15**, in which the isopropyl group blocks one face of the alkyne from attack and the R group of the aldehyde assumes a pseudo-equitorial position. In contrast, simultaneous interaction with the carbonyl group of the oxazolidinone and the aldehyde cannot occur with boron as there is only one empty p-orbital leaving the oxazolidinone uncoordinated, potentially disfavoring transition state **15** (Figure 2). As such, it is tentatively proposed that the diastereoselective outcome in the case of boron arises through the favored transition state **16**,[2] which has the R group of the aldehyde positioned in a pseudo-equitorial position to avoid unfavorable interactions with both the bulky borane fragment.[13] Further work is ongoing in these laboratories to elucidate the exact nature of the selectivity of the reaction.

In conclusion, a new method for the diastereoselective synthesis of allenylcarbinols via propargylic boranes has been developed. The complimentary stereochemical outcome of the reaction compared to related titanium methodology is of particular interest and allows access to alternative diastereoisomers. Further work investigating the transition metal catalyzed reactions of these highly functionalized allenes is currently being carried out.

(13) It has been suggested by a referee that R^1 might be subject to eclipsing interactions with the TMS group and that the aldehyde might alternatively approach with the R1 group in a pseudoaxial position. We acknowledge this possibility; however, as the observed diastereoselectivity of the reaction does not fit in with this, it is presumed that the linear nature of the propargyl unit combined with the length of the C-TMS bond causes any interaction to be diminished. Additionally, placing R1 in an axial position might result in deleterious interactions with the bulky borane fragment.

Experimental Section

General Procedure for Preparation of the Allenyl Carbinols. A solution of (trimethylsilyl)-propargyloxazolidinone (1 equiv) **1** in THF (0.1 or 0.3 M) was cooled to −78 °C with a dry ice−acteone bath, and *n*BuLi (1.2 equiv) was added dropwise. After stirring at this temperature for 10 min, *B*-MeO-9-BBN (1.0 equiv) was added dropwise, and the mixture was transferred to a cryocool controlled bath at −45 °C. The reaction was left to stir at this temperature for 45 min, and then boron trifluoride etherate (1.34 equiv) was added dropwise, followed by the aldehyde (1.05 equiv) after an additional 20 min. After the starting material had been consumed, the reaction was quenched by the addition of aqueous NaOH and aqueous H_2O_2 and allowed to warm to room temperature over 1 h. The resulting mixture was extracted with diethyl ether, and the combined organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc/hexanes) gave the two diastereomeric allenycarbinols

(4*S*,5*R*)-3((4*S*)-4-Hydroxy-3-(trimethylsilyl)-4-phenylbuta-1,2-dienyl)-4,5-diphenyloxazolidin-2-one 7a. This compound was made according to the general procedure, using benzaldehyde at 0.1 M concentration, which gave the major diastereoisomer **7a** (87 mg) and the minor diastereoisomer **7b** (24 mg) (total 87% yield) both as white solids. **7a**. Mp 145−147 °C. $[\alpha]^{25}_D$ = +111.8 (c 0.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.10−7.22 (m, 9H), 6.89−7.00 (m, 7H), 5.97 (d, J = 7.4 Hz, 1H), 5.13 (d, J = 7.4 Hz, 1H), 4.56 (br s, 1H), 1.07 (d, J = 5.1 Hz, 1H), −0.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.2, 155.4, 142.0, 134.1, 134.0, 128.7, 128.6, 128.3, 128.2, 127.6, 127.5, 126.6, 126.4, 117.6, 94.6, 80.4, 75.5, 64.8, −0.5; IR 3459, 1751 cm^{-1}. Anal. Calcd for $C_{28}H_{29}NO_3Si$: C, 73.81; H, 6.50; N, 3.07. Found: C, 74.02; H, 6.46; N, 3.03. **7b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26−7.41 (m, 6H), 7.03−7.08 (m, 6H), 6.90−6.93 (m, 2H), 6.76 (m, 2H), 5.83 (d, J = 8.1 Hz, 1H), 5.16 (m, 1H), 4.73 (d, J = 8.1 Hz, 1H), 2.43 (br s, 1H), −0.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.1, 155.3, 142.5, 134.1, 133.9, 128.5, 128.4, 128.4, 128.3, 128.1, 127.3, 127.2, 126.5, 119.0, 97.0, 80.9, 73.2, 64.3, −1.8; IR 1753 cm^{-1}

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Supporting Information Available: Characterization data and X-ray structural data for **7a** and **7b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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