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A One-Pot Multicomponent Coupling Reaction for the Stereocontrolled Synthesis of (*Z*)-Trisubstituted Allylic Alcohols

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Allylic alcohols are among the most versatile intermediates in organic synthesis and are pervasive in natural products. Thus, development of new multicomponent coupling reactions that allow assembly of allylic alcohols in a stereocontrolled manner is in high demand. Although substantial progress has been made in the synthesis of (*E*)-di- and (*E*)-trisubstituted allylic alcohols,[1−5] the direct synthesis of (*Z*)-trisubstituted allylic alcohols remains a formidable challenge.[6]

Among the most frequently employed methods to access (*Z*)-trisubstituted olefins are the Still−Gennari[7] modification of the Horner−Wadsworth−Emmons (HWE) olefination, and other variants of the Wittig reaction. The Still−Gennari method, however, is generally a linear two-carbon homologation and not a viable method for the direct coupling of larger fragments.

The addition of (*Z*)-vinylorganometallic reagents to aldehydes, such as the Nozaki−Hiyama−Kishi (NHK) reaction,[8] is also an attractive route to (*Z*)-allylic alcohols. The NHK reaction is rarely used in this construction, however, because the synthesis of the requisite stereochemically pure (*Z*)-trisubstituted vinyliodides is difficult.[9]

As part of our continuing program in the application of vinylzinc reagents in organic synthesis,[5,10,11] we report a one-pot, multicomponent coupling method for the direct synthesis of (*Z*)-trisubstituted allylic alcohols. The underpinning strategy is based on the addition of organometallic reagents to 1-bromo-1-alkenyboranes with concurrent migration of an alkyl group from boron to the alkene terminus. This crucial migration occurs with inversion at the vinylic center (Scheme 1).[12] Subsequent in situ transmetalation of the newly formed (*Z*)-vinylborane with the dialkylzinc reagent generates a stereodefined (*Z*)-vinylzinc species that undergoes addition to aldehydes to provide isomerically pure (*Z*)-allylic alcohols.

Hydroboration of 1-bromoalkynes is known to proceed with high regioselectivity to generate 1-bromo-1-vinylboranes (Scheme 1).[12−15] We initially examined use of diethylborane (generated in situ from Et_3B and $BH_3{\cdot}SMe_2$) and dicyclohexylborane. We propose that treatment of the resulting 1-bromo-1-vinylboranes with excess diethylzinc (2.2 equiv) at −78 °C followed by warming to 0 °C generates (*Z*)-trisubstituted vinylzinc reagents. On following the reaction by ^{11}B NMR, the only boron-containing product was observed at 86 ppm, indicating formation of Et_3B. Trapping the vinylzinc intermediates with 2 equiv of formaldehyde gave good yields of the allylic alcohol. Use of other aldehydes, however, resulted in 30−40% yields of the isolated allylic alcohols. A byproduct of these reactions was formed by ethyl addition to the aldehydes. This side reaction may be promoted by a zinc bromide species formed during the migration step (Scheme 1). Fortunately, the yield of the coupling was greatly improved when the volatile contents of the reaction mixture, including excess Et_2Zn, were evacuated prior to introduction of the aldehyde. Thus, use of 1-bromo-1-hexyne to generate the (*Z*)-vinylzinc reagent, followed by addition of isovaleraldehyde, afforded the (*Z*)-trisubstituted allylic alcohol in 61% yield, (eq 1, Table 1, entry 2).

Scheme 1. Proposed Coupling Mechanism

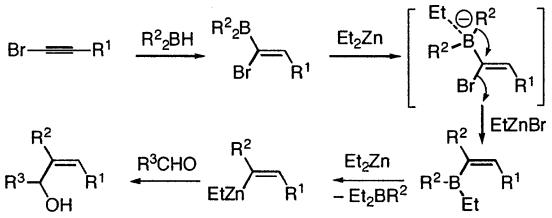
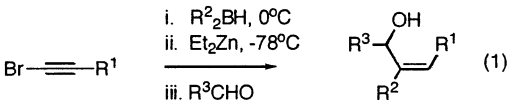


Table 1. Multicomponent Synthesis of Allylic Alcohols

entry	R^1	R^2	R^3CHO	yield %
1	*n*-Bu	Et	CH_2O	70[a]
2	*n*-Bu	Et	Me_2CHCH_2CHO	61
3	$CH_2OTBDPS$	Et	Me_2CHCH_2CHO	71
4	$CH_2OTBDPS$	Et	*p*-ClC_6H_4CHO	84
5	CH_2OBn	Et	*p*-ClC_6H_4CHO	65
6	CH_2OBn	Et	CH_2O	61[a]
7	CH_2CH_2OTBS	Et	*p*-MeC_6H_4CHO	82
8	CH_2CH_2OTBS	Et	*p*-MeC_6H_4CHO	84
9	*n*-Bu	Cy	*p*-MeC_6H_4CHO	60
10	*n*-Bu	Cy	*o*-$MeOC_6H_4CHO$	63

[a] Two equivalents of paraformaldehyde was added without removal of the volatile materials.



We next employed a series of 1-bromo-1-alkynes bearing protected alcohols to demonstrate the compatibility of these protecting groups with the reaction conditions. The reaction of TBDPS-protected 1-bromo-propargyl alcohol, Et_2BH, and Et_2Zn with either isovaleraldehyde or *p*-chlorobenzaldehyde provided (*Z*)-allylic alcohols in 71% and 84% yield (entries 3 and 4). The reaction was equally effective for benzyl protected 1-bromopropargyl alcohol, which furnished (*Z*)-trisubstituted allylic alcohols with *p*-chlorobenzaldehyde and paraformaldehyde in 65% and 61% yield (entry 5 and 6). 1-Bromo-1-butyn-4-ol, protected as TBS-ether, was also effective as an alkyne source. Trisubstituted allylic alcohols were isolated in good yield with *p*-methylbenzaldehyde and *p*-chlorobenzaldehyde (entries 7 and 8).

Dicyclohexylborane was employed to examine the transfer of secondary alkyl groups. As highlighted in entries 9 and 10, hydroboration of 1-bromo-1-hexyne with dicyclohexylborane was followed by treatment with Et_2Zn under the standard conditions. (*Z*)-Trisubstituted allylic alcohols derived from *o*-methoxybenzaldehyde and *p*-tolualdehyde were produced in good yields (entries 9 and 10). It should be noted that up to 20% ethyl migration was

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Scheme 2

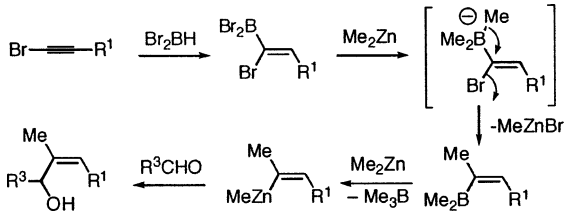


Table 2. Multicomponent Synthesis of Allylic Alcohols

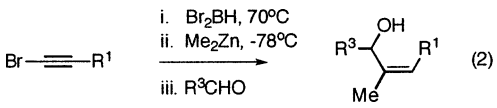
entry	R^1	R^3CHO	yield %
1	*n*-Bu	CH_2O	75[a]
2	$CH_2CH_2OTBDPS$	CH_2O	77[a]
3	*n*-Bu	Me_2CHCH_2CHO	92
4	*n*-Bu	*p*-MeC_6H_4CHO	71
5	*n*-Bu	*p*-ClC_6H_4CHO	70

[a] Two equivalents of paraformaldehyde was added without removal of the volatile materials.

observed when addition of Et_2Zn was performed at higher temperature (0 °C). At −78 °C, however, ethyl migration is negligible.

The most common class of (*Z*)-allylic alcohols found in natural products is the α-methyl substituted (*Z*)-allylic alcohols. The ability to synthesize such groups would greatly broaden the synthetic utility of our method. Therefore, we examined the use of dimethylborane as described in Scheme 1; however, low yields of the coupling products were obtained. This reaction is experimentally difficult, because the preparation of Me_2BH is tedious. Our recourse was to substitute Br_2BH for Me_2BH in the hydroboration (Scheme 2).

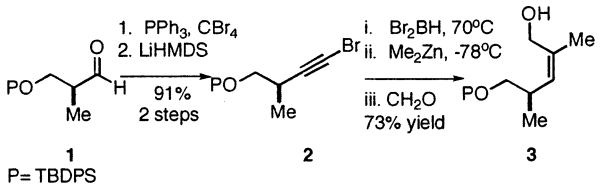
Reaction of the resulting 1-bromo-1-vinyldibromoborane with excess Me_2Zn was envisioned to begin with boron−halogen exchange. Further reaction of the resultant vinyldimethylborane with Me_2Zn induces migration, which is followed by transmetalation and addition to the aldehyde.



Hydroboration of 1-bromohexyne with Br_2BH was accomplished at either ambient temperature for 12 h or upon heating to 70 °C in toluene for 1 h (eq 2). The resulting vinyldibromoborane was treated with 4.0 equiv of Me_2Zn at −78 °C. After removal of volatile materials under vacuum, aldehyde was added. As highlighted in Table 2, (*Z*)-trisubstituted allylic alcohols derived from paraformaldehyde, isovaleraldehyde, *p*-tolualdehyde, and *p*-chlorobenzaldehyde were afforded in good to excellent yields (70−92%). The NMR spectrum of the allylic alcohol in entry 1 is identical to the previously published data.[16]

To illustrate the synthetic potential of our methodology, we synthesized (*Z*)-trisubstituted allylic alcohol **3**, a segment that is

Scheme 3. Potential Building Block for Migrastatin and Discodermolide



common to both (+)-migrastatin and (+)-discodermolide (Scheme 3). Aldehyde **1** was converted to the corresponding bromoacetylene **2** in two steps (91% yield) using a modified Corey−Fuchs[17] protocol. Subjecting **2** to the conditions outlined above gave **3**[18] in 73% yield as a single enantiomer (as determined by ^1H NMR spectroscopy of the Mosher ester). Compound **3** was an intermediate in the total synthesis of (−)-hennoxazole A.[18]

In summary, a new one-pot, multicomponent coupling reaction that allows facile access into (*Z*)-trisubstituted allylic alcohols in a stereocontrolled manner is reported. The advantage of this methodology over the Still−Gennari[7] modification of the HWE olefination is that it allows coupling of larger fragments. We are currently examining the application of these novel vinylzinc reagents to other reactions.

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Supporting Information Available: Procedures and full characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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