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Direct, Stereospecific Generation of (*Z*)-Disubstituted Allylic Alcohols

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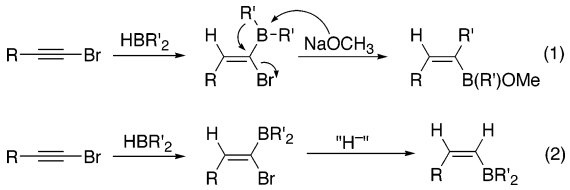
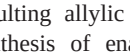
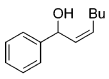
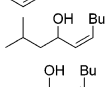
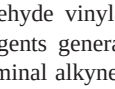
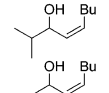
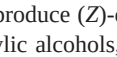
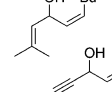
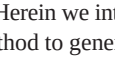
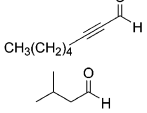
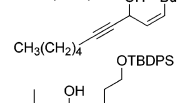
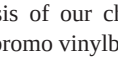
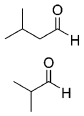
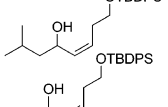
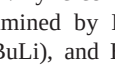
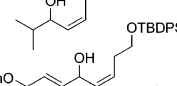
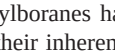
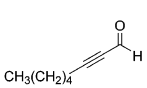
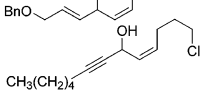
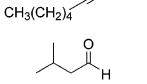
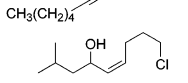
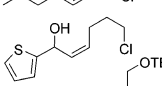
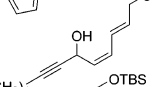
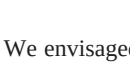
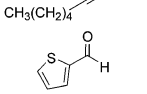
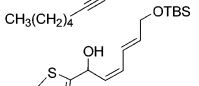
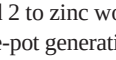
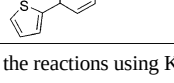
The catalytic asymmetric addition of vinylzinc reagents to aldehydes has recently engendered a great deal of attention.[1] The resulting allylic alcohols are versatile building blocks for the synthesis of enantioenriched allylic amines,[2] α-amino acids,[2] γ-unsaturated β-amino acids,[3] cyclopropyl alcohols,[4] epoxy alcohols,[5−7] and natural products.[8,9] The majority of asymmetric aldehyde vinylations have employed (*E*)-disubstituted vinylzinc reagents generated via hydroboration[10] or hydrozirconation[11] of terminal alkynes and transmetalation to zinc. Analogous methods to produce (*Z*)-disubstituted vinylzinc reagents, and therefore (*Z*)-allylic alcohols, are lacking.

Herein we introduce a practical and general one-pot stereospecific method to generate elaborate (*Z*)-disubstituted allylic alcohols. The basis of our chemistry is Zweifel's addition of nucleophiles to 1-bromo vinylboranes, which forms a C−C bond with inversion at the vinylic center (eq 1).[12] Addition of hydride sources was later examined by Negishi[13] ($LiBEt_3H$, KB(*sec*-Bu)$_3$H), Molander[14] (*t*-BuLi), and Brown[15] (KB(O^{i}Pr)$_3$H) (eq 2). The resulting (*Z*)-vinylboranes have seldom been applied in organic synthesis due to their inherently low reactivity.



We envisaged that transmetalation of the vinylboranes in eqs 1 and 2 to zinc would dramatically increase their reactivity and enable one-pot generation of (*Z*)-trisubstituted[16] and (*Z*)-disubstituted allylic alcohols. To generate (*Z*)-disubstituted allylic alcohols, we initially employed *t*-BuLi as the hydride source and toluene as the solvent. Thus, hydroboration of 1-bromoalkynes with $HBCy_2$ generated analogous 1-bromo vinylboranes (eq 2). Subsequent addition of *t*-BuLi at −78 °C followed by warming to room temperature formed the (*Z*)-disubstituted vinylboranes. Treatment of the vinylborane with Et_2Zn generated the reactive vinylzinc intermediates to which an aldehyde was added. The desired (*Z*)-allylic alcohols were obtained, albeit in low yield with cyclohexyl migrated (*Z*)-trisubstituted allylic alcohol as a major product. We speculated that a lithium borate complex generated in the course of reaction was unstable in the nonpolar toluene. THF was examined in the hope that it would stabilize the proposed borate intermediate. Use of THF to form the (*Z*)-vinylborane was followed by removal of the volatile materials. Toluene, Et_2Zn, and the aldehyde were added to the vinylzinc reagent at low temperature (−78 to 0 °C). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. To our delight, the desired (*Z*)-allylic alcohols were isolated in high yields with no detectable contamination of the (*E*)-diastereomer by ^{1}H NMR spectroscopy (eq 3). The olefinic C−H's exhibit an 11 Hz coupling constant in the ^{1}H NMR spectra, indicative of the *cis* geometry.

Table 1. One-Pot Synthesis of (*Z*)-Disubstituted Allylic Alcohols

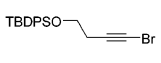
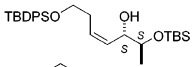
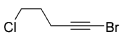
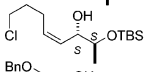
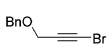
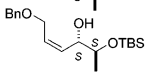
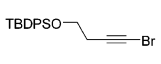
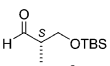
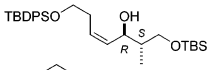
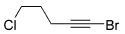
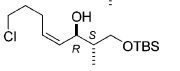
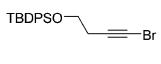
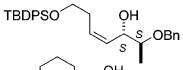
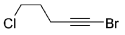
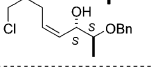
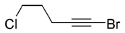
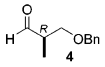
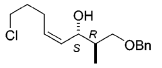
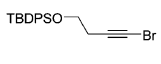
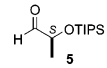
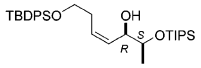
entry	bromoalkyne	aldehyde	product	yield (%)[a]
1				85 (77)
2				95 (83)
3				81 (78)
4				83 (72)
5				95 (72)
6				87 (60)
7				82 (60)
8				86 (64)
9				97 (73)
10				95 (70)
11				95 (70)
12				90 (70)
13				80 (67)

[a] Numbers in parentheses are yields from the reactions using KB(O^{i}Pr)$_3$H as the hydride source.

The broad scope of our tandem reaction is illustrated in Table 1. Aromatic, aliphatic, and α,β-unsaturated aldehydes react smoothly with in situ generated (*Z*)-vinylzinc reagents to provide the corresponding allylic alcohols in high yields (81−97%). Particularly noteworthy is the stereospecific generation of the (*Z*)-double bond in the presence of alkynes (entries 5, 9, and 12). These propargylic alcohols could not be prepared by conventional Lindlar reduction of diynols. Additionally, it is known that sulfur-containing compounds can poison hydrogenation catalysts. The thiophene derivatives in entries 11 and 13 are readily prepared with this tandem

10.1021/ja061973n CCC: $33.50

Table 2. Diastereoselective Additions to Chiral Aldehydes

entry	bromoalkyne	chiral aldehyde	major product[a]	dr[b]	yield (%)
1		 **1**		8 : 1[c]	70
2				8 : 1[c]	82
3				18 : 1	60
4		 **2**		6 : 1[d]	89
5				6 : 1[d]	84
6		 **3**		15 : 1	84
7				15 : 1	81
8		 **4**		11 : 1[c]	85
9		 **5**		1 : 2.3	81

[a] Absolute configurations of secondary alcohols were determined by X-ray crystallography or Mosher ester derivatization method (see Supporting Information). [b] Diastereomeric ratio based on crude ^{1}H NMR. [c] Two equivalents of $BF_3{\cdot}OEt_2$ was premixed with aldehyde at −78 °C for 2 min then added to the reaction mixture. [d] Two equivalents of $ZnBr_2$ was added to the reaction mixture before addition of aldehyde.

method. Stereospecific generation of (*E*,*Z*)-dienes was successfully accomplished, as illustrated in entries 12 and 13. The products in Table 1 were also generated using the mild reducing reagent KB-(O^{i}Pr)$_3$H,[17] which exhibits broad functional group compatibility, although yields were slightly diminished (60−83%).

Diastereoselective C−C bond-forming reactions are crucial to the elaboration of synthetic intermediates. Despite extensive study of such processes, few examples involving organozinc additions to chiral aldehydes have been reported.[18−21] We, therefore, examined additions of our (*Z*)-vinylzinc intermediates to *chiral* aldehydes.

Generation of the vinylzinc reagent from TBDPS-protected 1-bromoalkynol followed by addition to enantioenriched α-TBS-protected hydroxy aldehyde **1** cleanly formed the allylic alcohol in 70% yield with modest dr (4:1). The dr was increased to 8:1 in the presence of $BF_3{\cdot}OEt_2$ (Table 2, entry 1). A similar result was obtained with the chloro-substituted bromoalkyne (entry 2). Surprisingly, in the absence of a Lewis acid, a dr of 18:1 was obtained with the bromoalkyne containing a chelating benzyl group (entry 3). Chiral β-TBS-protected hydroxy aldehyde **2**, a difficult substrate for diastereoselective addition reactions, formed products with 6:1 dr in the presence of $ZnBr_2$. Aldehyde **3**, with a chelating α-benzyloxy group gave product of high dr (15:1). Likewise, β-benzyl-protected hydroxy aldehyde **4** underwent addition in the presence of $BF_3{\cdot}OEt_2$ to provide the allylic alcohol in 85% yield with a dr of 11:1.

Assignment of the stereochemical outcome of the additions in Table 2 (entries 1−8) was based on an X-ray crystal structure of the major diastereomer in entry 3 (see Supporting Information). To our surprise, the *anti*-Felkin product was obtained.[22−24] The stereochemistry of the remaining products was assigned by ^{1}H NMR analysis of the Mosher ester derivatives.[25] Chelation-controlled addition with TBS-protected α- and β-hydroxy aldehydes is rare, due to the steric demands of the TBS group. In our case, the preferential *anti*-Felkin addition (entries 1−8) can be overridden by employing the very bulky TIPS protecting group (entry 9). We are currently investigating the origin of the increased *anti*-Felkin product upon addition of a monodentate Lewis acid ($BF_3{\cdot}OEt_2$).

In summary, we have developed a simple and efficient one-pot procedure for the synthesis of elaborate (*Z*)-disubstituted allylic alcohols from readily available 1-bromoalkynes. An advantage of our method is the generation of the (*Z*)-double bond isomer without contamination from the undesired (*E*)-product. The (*Z*)-vinylzinc reagents have also been shown to undergo addition to chiral α- and β-oxygenated aldehydes with good to excellent control over diastereoselectivity. This tandem addition reaction enables the synthesis of allylic alcohols previously difficult to access, opening up new avenues for complex molecule synthesis. We are currently developing an enantioselective version of these reactions.

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

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