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# A New Halopropargylation of Alkynes Promoted by Boron Trihalides. Highly Stereo- and Regioselective Syntheses of Substituted (*Z*)-1-Halo-1,4-enyne Derivatives

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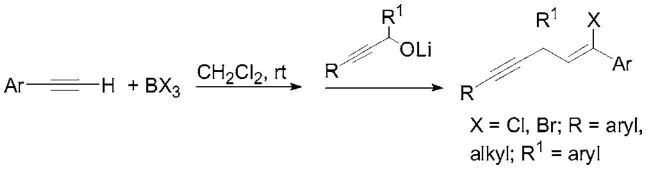
## ABSTRACT



**A new halopropargylation of alkynes promoted by boron trihalides has been developed. Reactions of (*Z*)-2-halo-1-vinylboron dihalides (generated in situ via reaction of alkynes with boron trihalides) with lithium propargyloxides in $CH_2Cl_2$ at room temperature produce the corresponding (*Z*)-1-halo-1,4-enynes in modest to good yields.**

The regio- and stereoselective formation of new carbon−carbon bonds is of fundamental importance in organic synthesis. Development of new coupling reactions that allow stereocontrolled assembly of enynes is especially significant. Propargylation reactions provide important methods for construction of new alkynyl building blocks and have found widespread application in the creation of complex molecular frameworks.[1] The use of transition metals has increased the utility of these reactions enormously. Propargylation reactions usually involve the formation of transition-metal-stabilized propargyl cations.[1c,d] Recent reports outline carbon−carbon bond-forming reactions between propargyl alcohols and alkenes,[2] ketones,[3] alcohols,[4] and allylsilanes.[5] However, these reactions require the use of expensive, and somewhat difficult to prepare, transition-metal catalysts.

Boron halides are very useful Lewis acids[6] and have been widely used in the dealkylation of ethers,[7] the halogenation of alcohols and aryl aldehydes,[8,9] the reduction of carbonyl compounds,[10] and the catalyzation of Friedel−Crafts reactions and aldol condensation.[6,11−14] In recent years, the haloboration of carbon−carbon triple bonds has also been a fruitful area of research.[15] A wide variety of haloboranes have

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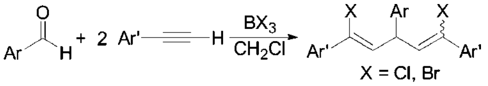
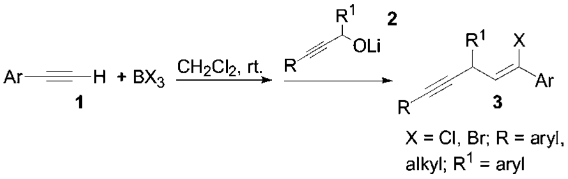
been found to react with terminal alkynes to produce (*Z*)-2-halo-1-alkenylboranes. The reaction occurs in a stereo-, regio-, and chemoselective fashion and has been used to synthesize numerous vinyl halides, alkadienes, alkynes, and a variety of olefinic products.[15] More recently, we reported a unique coupling reaction between alkynes and aldehydes mediated by boron trihalides that stereo- and regioselectively generates a series of (*Z*,*Z*)-1,5-dibromo-1,4-pentadienes and (*Z*,*E*)-1,5-dichloro-1,4-pentadiene derivatives (Scheme 1).[16]

**Scheme 1**



The reaction is believed to proceed through a (2-halovinyl)-(allyloxy)boron halide intermediate.[16] We reasoned that if a (2-halovinyl)(propargyloxide)boron halide intermediate could be formed, it would lead to formation of the 1-halogenated 1,4-enyne product. Therefore, we investigated the reaction of propargyl alcohols with alkynes in the presence of boron trihalides. The reaction stereo- and regioselectively generates (*Z*)-1-halo-1,4-enyne products in modest to good yields (Scheme 2).

**Scheme 2**



1,4-Enynes are usually prepared via stoichiometric reactions of allyl halides with alkyne metal salts or metal-catalyzed cross-coupling reactions of allyl halides with alkynes or alkynylborates.[17−19] Silylated 1,4-enynes have been synthesized via carbosilylation of alkynes catalyzed by $EtAlCl_2$.[20] To our knowledge, the direct halopropargylation of alkynes using propargyl alcohols mediated by boron halides has not been reported. Moreover, 1-halo-1,4-enynes are valuable synthetic intermediates because of the multitude of functional groups they contain that can be subjected to further synthetic manipulations, such as coupling reactions. Significantly, the reaction predominantly produces (*Z*)-1-halo-1,4-enynes.

The reaction was initially carried out by introducing 1 equiv of the lithium salt of 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-ol (generated in situ by adding *n*-butyllithium to the propargylic alcohol) to boron trichloride (1:1 ratio) followed by the addition of 1 equiv of phenylacetylene in methylene chloride at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was hydrolyzed. Surprisingly, a modest yield of (*Z*)-1-chloro-4-(3-chloro-3-phenylethynylallyl)benzene (**3a**) was obtained along with a small amount of (*E*)-1-chloro-4-(3-chloro-3-phenylethynylallyl)benzene. However, the chlorination of 1,3-diphenylprop-2-yn-1-ol by boron trichloride to form the corresponding propargylic chloride also occurred. To improve the yield of this novel coupling reaction, an alternative reaction procedure was developed (Scheme 2). First, 1 equiv of phenylacetylene was treated with boron trichloride at room temperature to form (*Z*)-(2-chloro-2-phenyl-1-vinyl)dichloroborane at room temperature. Then 1 equiv of lithium 1-(4-chlorophenyl)-3-phenylpropynoxide (generated by reaction of the corresponding alcohol with *n*-butyllithium in $CH_2Cl_2$) was introduced to the (*Z*)-(2-chloro-2-phenyl-1-vinyl)dichloroborane at room temperature. (*Z*)-1-Chloro-4-(3-chloro-3-phenylethynylallyl)benzene (**3a**) was isolated in excellent yield.

A series of propargylic alcohols were subjected to the reaction sequence. Modest to good yields of the corresponding 1-chloro-1,4-enyne products were obtained (Table 1). Subsequently, the reaction was extended to include boron tribromide since the bromide derivatives are generally more reactive intermediates in organic synthesis. The reactions using boron tribromide gave modest to good yields of (*Z*)-1-bromo-1,4-enyne products (Table 1). All compounds were characterized by elemental analysis and NMR spectroscopy. The NMR data revealed that the $^1H$ chemical shifts of the vinyl (ca. 6.30 ppm) and methine (ca. 5.30 ppm) protons in (*Z*)-1-halo-1,4-enynes are very close to those reported for (*Z*,*Z*)-1,5-dihalo-1,4-pentadiene compounds.[16] In some cases, the NMR spectra revealed the presence of small quantities of (*E*)-1-halo-1,4-enynes in which the $^1H$ chemical shifts of the vinyl (ca. 6.00 ppm) and methine (ca. 4.80 ppm) protons are shifted upfield compared to those in the corresponding (*Z*)-isomers. Similar trends have been observed in the NMR data of (*Z*,*E*)-1,5-dihalo-1,4-diene compounds in previous reports.[16]

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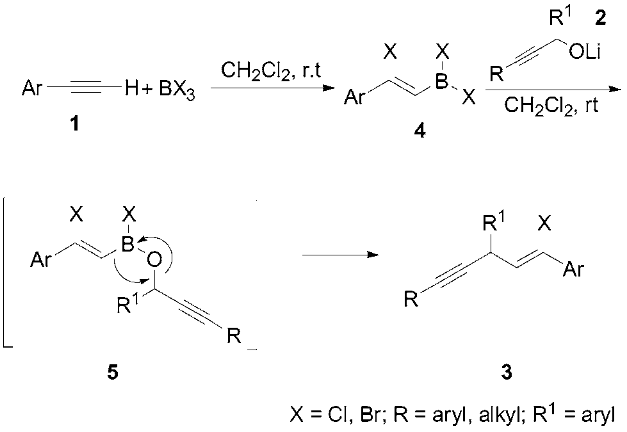
**Table 1.** Stereo- and Regioselective Synthesis of Substituted (*Z*)-1-Halo-1,4-enynes

| entry | Ar | R | $R^1$ | X | time (h) | product | *Z*/*E* | yield[a–c] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Ph | 4-ClPh | Cl | 2 | **3a** | 98/2 | 90 |
| 2 | Ph | Ph | 4-BrPh | Cl | 2 | **3b** | 96/4 | 86 |
| 3 | Ph | Ph | 3-BrPh | Cl | 1 | **3c** | 99/1 | 82 |
| 4 | Ph | Ph | 2-MePh | Cl | 1 | **3d** | 99/1 | 66 |
| 5 | Ph | Ph | 4-$NO_2$Ph | Cl | 6 | **3e** | 99/1 | 52 |
| 6 | Ph | *n*-Bu | Ph | Cl | 4 | **3f** | 97/3 | 60 |
| 7 | 4-MePh | Ph | 4-ClPh | Cl | 2 | **3g** | 98/2 | 85 |
| 8 | Ph | Ph | Ph | Br | 2 | **3h** | 99/1 | 68 |
| 9 | Ph | Ph | 4-FPh | Br | 4 | **3i** | 99/1 | 85 |
| 10 | Ph | Ph | 4-ClPh | Br | 2 | **3j** | 98/2 | 72 |
| 11 | Ph | Ph | 4-MePh | Br | 1 | **3k** | 98/2 | 65 |
| 12 | Ph | Ph | 2-MePh | Br | 2 | **3l** | 99/1 | 62 |
| 13 | Ph | *n*-Bu | Ph | Br | 4 | **3m** | 98/2 | 40 |
| 14 | Ph | *n*-Bu | 4-ClPh | Br | 4 | **3n** | 99/1 | 45 |

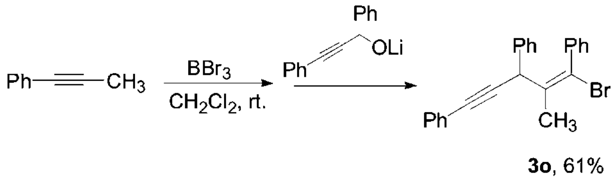
[a] Isolated yield based on starting propargyl alcohols. [b] Bromide compounds slightly decompose on a silica gel column. [c] All compounds have been characterized by elemental analysis and NMR spectroscopy.

The reactions tolerate a variety of functional groups (Table 1). Reactions of alcohols and alkynes containing electron-withdrawing substituents on the phenyl rings tend to proceed at a slower rate. Also, aliphatic propargylic alcohols (Table 1, entries 6, 13, and 14) require longer reaction times. Primary propargylic alcohols and aliphatic alkynes do not give the desired products.

**Scheme 3**



**Scheme 4**



Although a detailed study of the reaction mechanism has not been undertaken, the reaction presumably proceeds through the haloboration of the alkyne to form a (*Z*)-2-halo-1-vinylboron dihalide (**4**), which then reacts with lithium propargyloxide to generate a (halovinyl)(propargyloxy)-boronhalide (**5**) intermediate. Migration of the halovinyl group with retention of configuration affords the final (*Z*)-1-halo-1,4-enyne product **3** (Scheme 3).

In an effort to rule out the possibility of an ionic reaction mechanism ($S_N1$), we have investigated reactions of internal alkynes such as phenylpropyne with lithium propargyloxide in the presence of $BBr_3$. These reactions produce the *E*-isomer predominantly (Scheme 4). The structure of product **3o**, (*E*)-1-bromo-1,4-enyne, has been confirmed by X-ray crystallography (Figure 1 in Supporting Information). Since internal alkynes do not react with boron trihalides to form (*Z*)-halovinylborane intermediates, the reaction presumably proceeds through an ionic mechanism ($S_N1$) to generate the corresponding (*E*)-1,4-enyne. This result supports the proposed mechanism suggested in Scheme 3.

In conclusion, we have developed a unique and simple halopropargylation of alkynes using propargylic alcohols that is promoted by boron trichloride and tribromide. The reaction produces a variety of useful (*Z*)-1-halo-1,4-enyne derivatives with high stereo- and regioselectivity under mild conditions. Efforts to define the reaction mechanism, the scope of the reaction, and the use of the alternative Lewis acids are currently underway.

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**Supporting Information Available:** Detailed experimental procedures, spectroscopic data for all compounds, and X-ray data for **3o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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