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Identification of a Boron-Containing Intermediate in the Boron Tribromide Mediated Aryl Propargyl Ether Cleavage Reaction

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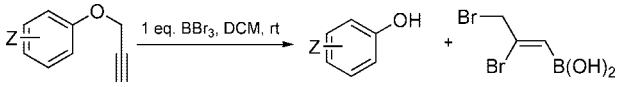
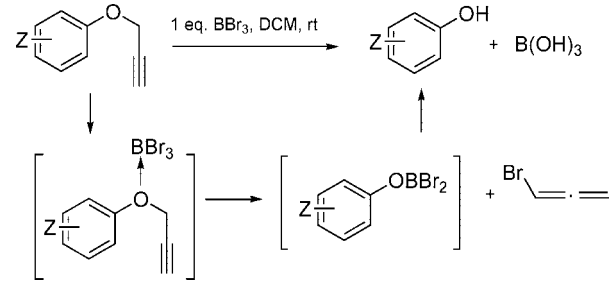


An alternate reaction mechanism for the boron tribromide mediated deprotection of aryl propargyl ethers based on the isolation of a key boron-containing byproduct is proposed. On the basis of the new mechanistic insight, we discovered that $HBBr_2 \cdot SMe_2$ can also be used for cleaving aryl propargyl ethers.

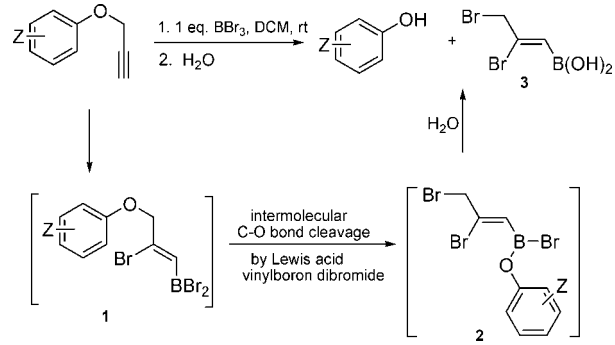
Recently, a boron tribromide mediated aryl propargyl ether deprotection reaction was reported (Scheme 1).[1] The reaction proceeds smoothly at room temperature, and a variety of functional groups (-Br, $-CO_2Et$, $-NO_2$, -OMe) are tolerated by the reaction conditions. The stability of aryl methoxy groups under the reaction conditions is notable because boron tribromide is known to be an effective reagent for cleaving aryl ethers.[2] A mechanism involving the delivery of bromine to the propargyl terminus, to generate a bromoallene, was proposed on the basis of a NMR study of the reaction (Scheme 1).[3]

In recent years, we have developed a number of novel reactions involving boron halide derivatives. Examples include a boron trihalide mediated alkyne-aldehyde coupling reaction leading to stereodefined 1,4-pentadienes[4] that proceeds through an unprecedented C−O bond cleavage originating from an alkoxyboron monohalide intermediate.[5] Further investigations of these novel reactions led us to develop reactions in which hydroxyl groups were substituted by stereodefined halovinyl,[6] alkynyl,[7] and allyl[8] moieties using boron halides. In these studies, we found that aryl methoxy groups were stable in the presence of either preformed or in situ generated vinylboron dibromides.[5,6] In view of the fact that the *syn* addition of boron tribromide to terminal alkynes is a fast process at −78 °C,[9] we felt that the aryl propargyl ether cleavage reaction might proceed through a pathway that differed from the one proposed earlier (Scheme 2): addition of boron tribromide to the terminal alkyne would first generate the vinylboron dibromide intermediate **1** (consistent with the reported NMR study[3]); then C−O bond cleavage would occur as a result of the presence of the vinylboron dibromide (a Lewis acid) and afford intermediate **2**; hydrolysis of intermediate **2**[10] would then give the observed products (phenol and bromovinylboronic acid **3**). Notably, the pathway we propose is also consistent with the observed failure of boron tribromide to react with a propargyl ether containing an internal alkyne because boron tribromide is known to react only slowly with internal alkynes.[9]

SCHEME 1. Proposed Reaction Mechanism



SCHEME 2. Currently Proposed Reaction Mechanism



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‡ Graduate School of Medicine, The University of Tennessee.
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(1) Punna, S.; Meunier, S.; Finn, M. G. *Org. Lett.* **2004**, *6*, 2777.
(2) (a) Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719. (b) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (c) Benton, F. L.; Dillon, T. E. *J. Am. Chem. Soc.* **1942**, *64*, 1128.
(3) NMR monitoring of the reaction clearly demonstrated that the alkyne unit participated in the propargyl ether bond cleavage (the absence of alkyne resonances along with the appearance of several vinyl protons).
(4) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2002**, *4*, 1491.
(5) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.; Ju, Y.; Quick, T. *J. Org. Chem.* **2008**, *73*, 2668.
(6) (a) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2004**, *6*, 3929. (b) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z. *Chem. Commun.* **2005**, 2492. (c) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z. *Org. Lett.* **2005**, *7*, 2865.
(7) (a) Kabalka, G. W.; Yao, M.-L.; Borella, S. *Org. Lett.* **2006**, *8*, 879. (b) Kabalka, G. W.; Borella, S.; Yao, M.-L. *Synthesis* **2008**, 325.
(8) (a) Kabalka, G. W.; Yao, M.-L.; Borella, S. *J. Am. Chem. Soc.* **2006**, *128*, 11320. (b) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Goins, L. K. *Organometallics* **2007**, *26*, 4112.
(9) Lappert, M. F.; Prokai, B. *J. Organomet. Chem.* **1964**, *1*, 384.
(10) The detection of phenol by TLC, before quenching of the reaction either with water or with saturated aqueous $NaHCO_3$ at 0 °C, indicates that the C-O bond cleavage most likely occurred in the reaction process, as opposed to the cleavage being induced by the HBr formed during the hydrolysis process.

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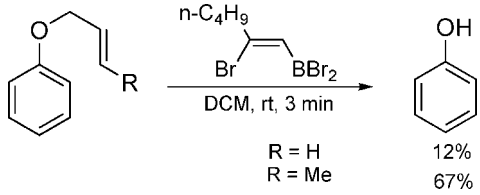
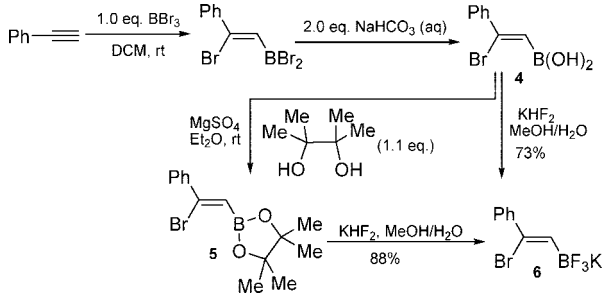
SCHEME 3. C−O Bond Cleavage Using Vinylboron Dibromide



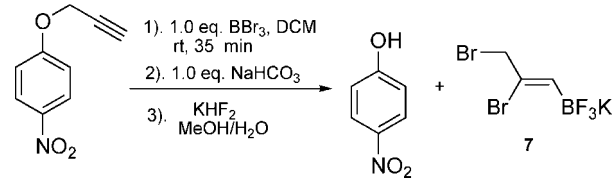
SCHEME 4. Transformations of Bromovinylboron Dibromide



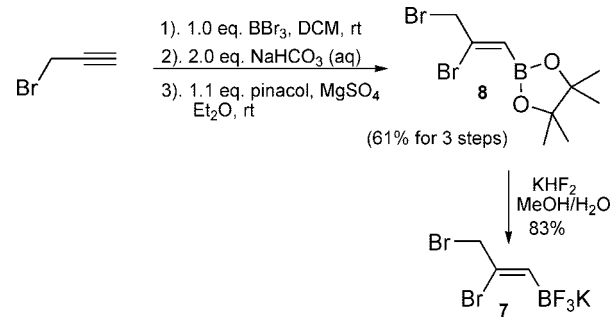
To test the hypothesis that a vinylboron dibromide could cleave a C−O ether bond,[11] preformed vinylboron dibromide was allowed to react with phenyl allyl ether (Scheme 3). The cleavage reaction occurred rapidly at room temperature and the phenyl allyl ether was consumed within 3 min. For phenyl allyl ether (bearing a terminal alkene), the Claisen rearrangement product is formed (61% yield) along with the anticipated phenol (in 12% yield). For a phenyl allyl ether bearing an internal alkene (structurally similar to intermediate **1**), the reaction gives the expected phenol in 67% yield along with some of the Claisen product. Thus, vinylboron dibromide reagents readily cleave the C−O bond in allyl ethers.

In further support of the proposed mechanism, we decided to isolate bromovinylboronic acid **3** as the corresponding trifluoroborate derivative. Interestingly, no literature report for the conversion of halovinylboron dihalides to the corresponding trifluoroborate derivatives could be found.[12] Therefore, we investigated the feasibility of this transformation using the readily available 2-phenyl-2-bromovinylboron dibromide (Scheme 4). The bromovinylboron dibromide was first converted to bromovinylboronic acid **4** by reaction with an aqueous mixture of $Et_2O/NaHCO_3$ at 0 °C. Attempts to purify vinylboronic acid **4** via recrystallization in water induced dehaloboration (phenyl acetylene formed).[13] Therefore, crude **4** was used directly to synthesize the corresponding boron pinacolate ester. Boron pinacolate **5** was isolated in 67% yield (in three steps based on phenyl acetylene) using silica gel column chromatography. The preparation of organotrifluoroborate **6**, either from the crude vinylboronic acid **4** or the boron pinacolate ester **5**, was successful using reported procedures.[14] Good yields were obtained in both cases (Scheme 4).

SCHEME 5. Evidence Supporting the New Mechanism: Isolation of a Vinyl Trifluoroborate Product



SCHEME 6. Preparation of Authentic Sample



With the knowledge that bromovinylboronic acids could be isolated as their stable trifluorobonate salts, we then investigated the reaction of 4-nitrophenyl propargyl ether with boron tribromide. (The goal being the validation of the newly proposed reaction mechanism.) The reaction was carried out according to the literature procedure[1] and was quenched by transferring the reaction mixture, under an argon atmosphere, to an aqueous $Et_2O/NaHCO_3$ mixture at 0 °C. Three equivalents of KHF_2 were then added, and the mixture was stirred for 20 min. Removal of the solvents under vacuum afforded a brown solid. After washing the solid with dry diethyl ether to remove the coproduct, 4-nitrophenol, and a trace amount of propargyl ether, a white solid was obtained. Extraction of the white solid three times with hot acetone, followed by solvent removal, yielded organotrifluoroborate **7** in 41% yield. The resonances observed at 6.26−6.28 ppm (m) and 4.28 ppm (s) in the ^1H NMR spectrum and at 44.5 ppm in the ^{13}C NMR spectrum fit well with the structural assignment for compound **7**. The vinyl carbon was not visible in the ^{13}C NMR spectrum owing to the nearby fluorine nucleus. In addition, the observed HRMS analysis (266.8644 for $[M - K]^-$ peak) supports the structural assignment.

For structural identification purposes, a standard organotrifluoroborate sample **7** was synthesized from fully characterized boron pinacolate ester **8** (Scheme 6). The NMR data demonstrated that the organotrifluoroborate obtained was identical to the material obtained in the reaction outlined in Scheme 5.

On the basis of the newly proposed reaction mechanism, we deduced that $HBBr_2$ would also be suitable for cleaving propargyl ethers bearing terminal alkynes. The facile addition of $HBBr_2$ to the terminal alkyne moiety in propargyl ether would generate intermediate **9**, which is similar in structure to the earlier proposed intermediate **1**. The experimental results confirmed our hypothesis (Scheme 7).

In summary, an alternate reaction mechanism is proposed for the boron tribromide mediated deprotection of aryl propargyl ethers. A key boron-containing byproduct, which strongly

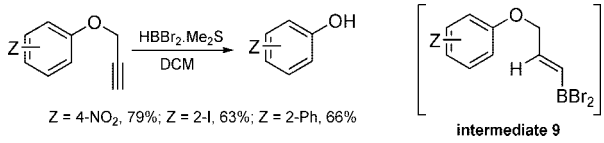
(11) The C-O ether bond cleavage mediated by organoboron halides, such as $PhBCl_2$ and 9-Br-9-BBN is known,[2b] but C-O bond cleavage using bromovinylboron dibromide had not been previously reported.

(12) (a) Hara, S.; Ishimura, S.; Suzuki, A. *Synlett* **1996**, 993. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798. (c) Batey, R. A.; MacKay, D. B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075.

(13) For other 2-halovinylboron compounds that undergo dehaloboration reaction, see: (a) Suzuki, A.; Miyaura, N.; Abiko, S.; Itoh, M.; Brown, H. C.; Sinclair, J. A.; Midland, M. M. *J. Am. Chem. Soc.* **1973**, *95*, 3080. (b) Eisch, J. J.; Gonsior, L. J. *J. Organomet. Chem.* **1967**, *8*, 53.

(14) (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020. (b) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424.

SCHEME 7. Propargyl Ether Cleavage Using $HBBr_2 \cdot SMe_2$ Complex



supports the newly proposed mechanism, was isolated by converting it into organotrifluoroborate **7**. Based on the proposed reaction mechanism, we discovered that $HBBr_2$ is also an effective cleaving reagent for propargyl ethers bearing terminal alkyne moieties.

Experimental Section

All glassware was dried in an oven heated to 120 °C for at least 12 h and then cooled prior to use. Dichloromethane was distilled over CaH_2 prior to use. Reactions were magnetically stirred and monitored by TLC. Products were purified by flash chromatography, using silica gel (230−400 mesh, 60 Å). Boron tribromide (1.0 M in methylene chloride), dibromoborane dimethyl sulfide complex solution (1.0 M in methylene chloride), phenylacetylene, and propargyl bromide solution (80 wt % in toluene) were used as received.

Synthesis of Compound 5. To a solution of phenylacetylene (10 mmol, 1.02 g) in CH_2Cl_2 (20 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 10 mmol, 10 mL). The mixture was stirred at room temperature for 15 min. The resulting red-purple reaction mixture was transferred by a double-ended needle to a mixture of diethyl ether (5 mL) and aqueous $NaHCO_3$ (1.70 g of $NaHCO_3$ in 15 mL of water) at 0 °C. The mixture was stirred at room temperature for 15 min. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic phase was washed with cold water and then brine. The organic phase was subsequently dried over anhydrous magnesium sulfate. Removal of solvents under vacuum followed by washing with hexanes (15 mL) yielded crude boronic acid **4** as a pale yellow solid. Crude **4** was then added to a solution of pinacol (11.0 mmol, 1.30 g) in ethyl ether (40 mL). Anhydrous magnesium sulfate (20.0 mmol, 2.40 g) was added, and the mixture was stirred overnight at room temperature. After filtration and removal of the solvent under vacuum crude compound **5** was obtained. The product (2.07 g) was isolated in 67% yield by flash column chromatography. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.58−7.62 (m, 2H), 7.31−7.33 (m, 3H), 6.43 (s, 1H), 1.34 (s, 12H). ^{13}C NMR: δ 140.9, 140.1, 129.3, 128.3, 128.1, 127.5, 83.8, 24.8. Anal. Calcd for $C_{14}H_{18}BBrO_2$: C, 54.42; H, 5.87. Found: C, 54.48; H, 5.63.

Isolation of Compound 7 from the BBr_3-Mediated Propargyl Deprotection Reaction. To a solution of the propargyl ether, 1-nitro-4-prop-2-ynyloxybenzene (2.0 mmol, 354 mg), in dry CH_2Cl_2 (6 mL) under argon atmosphere was added BBr_3 (1.0 M in CH_2Cl_2, 2.0 mmol, 2.0 mL) dropwise at room temperature. The reaction mixture was stirred for 35 min at room temperature and then transferred by a double-ended needle to a mixture of diethyl ether (5 mL) and aqueous $NaHCO_3$ (168 mg of $NaHCO_3$ in 3 mL of water) at 0 °C. The mixture was stirred at room temperature for another 15 min. Subsequently, methanol (2 mL) and aqueous KHF_2 (6.0 mmol, 468 mg in 3 mL of water) was added, and the mixture was stirred for another 20 min. Removal of the solvents under vacuum afforded a brown solid. After washing the solid with dry diethyl ether to remove the coproduct 4-nitrophenol and a trace amount of propargyl ether, a white solid was obtained. Extraction of the white solid with hot acetone (3 × 10 mL), followed by solvent removal, yielded organotrifluoroborate **7** in 41% yield. ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.26−6.28 (m, 1H), 4.28 (s, 2H). ^{13}C NMR: δ 44.5. Calcd HRMS for $C_3H_3BBr_2F_3K$: 266.8627 ([M − K]$^-$ peak). Found: 266.8644.

Synthesis of Compound 8. The procedure paralleled that described for compound **5**. The reaction was carried out on a 10 mmol scale, and compound **8** was purified by column chromatography (silica-gel, EtOAc−hexanes, 1:5) as a colorless liquid (1.97 g, 61% for three steps). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.35 (s, 1H), 4.24 (s, 2H), 1.30 (s, 12H). ^{13}C NMR: δ 136.0, 83.4, 39.4, 24.7. IR (film, ν_{max}/cm^{-1}): 2979, 2919, 1629, 1380, 1372, 1348, 1142, 967, 848, 764, 749. Anal. Calcd for $C_9H_{15}BBr_2O_2$: C, 33.18; H, 4.64. Found: C, 33.47; H, 4.71.

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Supporting Information Available: ^{1}H and ^{13}C NMR data for all new compounds reported, preparation of starting material propargyl ether. This material is available free of charge via the Internet at http://pubs.acs.org.

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