

Synthesis of Vinyl-, Allyl-, and 2-Boryl Allylboronates via a Highly Selective Copper-Catalyzed Borylation of Propargylic Alcohols

Lujia Mao,[†] Rüdiger Bertermann,[†] Katharina Emmert,[†] Kálmán J. Szabó,^{*,‡} and Todd B. Marder^{*,†}®

[†]Institut für Anorganische Chemie and Institute for Sustainable Chemistry & Catalysis with Boron, Julius-Maximilians-Universität Würzburg, 97074 Würzburg, Germany

[‡]Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-10691 Stockholm, Sweden

S Supporting Information

ABSTRACT: An efficient methodology for the synthesis of vinyl-, allyl-, and (*E*)-2-boryl allylboronates from propargylic alcohols via Cu-catalyzed borylation under mild conditions is reported. In the presence of commercially available $Cu(OAc)_2$ or $Cu(acac)_2$ and Xantphos, the reaction affords the desired products in up to 92% yield with a broad substrate scope (43 examples). Isolation of an allenyl boronate as the reaction intermediate suggests that an insertion-elimination-type reaction, followed by borylcupration, is involved in the borylation of propargylic alcohols.



lcohols constitute a highly attractive class of starting Amaterials as they are inexpensive and often easily derived from natural sources.¹ In particular, propargylic alcohols are useful building blocks in organic synthesis,² as they possess inherent alkynyl and hydroxyl functional groups and can be easily accessed from terminal alkynes and aldehydes or ketones. Meyer–Schuster rearrangement of propargylic alcohols to $\alpha_{\beta}\beta$ unsaturated aldehydes or ketones promoted by Brønsted or Lewis acids has been extensively applied to convert readily available materials into versatile enone products.^{2a} Recently, significant progress has been made to synthesize allene derivatives via trapping of allenyl intermediates, generated from propargylic alcohols and their derivatives, with various reagents, such as B₂pin₂.³ Cu(I)-catalyzed synthesis of allenyl boronates via borylation of propargylic carbonates was reported.^{3a} A Pd/Cu bimetallic system was also developed for the catalyzed synthesis of allenyl boronates from propargylic carbonates.^{3b} The first Cucatalyzed borylation of benzyl-, allyl-, and propargyl alcohols providing the corresponding organic boronates using a commercially available Cu catalyst under mild condition was recently reported.³⁰

Vinyl boronates are widely used in Suzuki–Miyaura coupling reactions,^{4a} and allyl boronates are valuable building blocks for the synthesis of homoallyl alcohols.^{4b–d} Among other approaches,⁵ borylcupration of allenes,⁶ which can be synthesized from propargylic alcohols,⁷ has been established^{8–10} as an efficient means to synthesize vinyl- and allylboronates. Note that bis(boronate) esters are useful synthetic intermediates in a number of one-pot C–C bond-forming sequences.¹¹ Alkenes and alkynes are well-known feedstocks for metal-catalyzed diborations,¹² and diboration of allenes has emerged as a powerful tool for the preparation of bis(boronate) esters.¹³ Miyaura developed the first Pt-catalyzed diboration of allenes with B₂pin₂ providing 2-boryl allylboronates,^{13a} and Cheng reported diboration of allenes

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catalyzed by Pd(dba)₂ and organic iodides, which afforded (*Z*)-2boryl allylboronates with C=C bonds at an internal position as major products.^{13b} Subsequently, Morken developed enantioselective diborations of allenes employing Pd₂(dba)₃ as a catalyst precursor to provide 2-boryl allylboronates with C=C bonds at the terminal position.^{11a,c,13c,d} Recently, borylative opening of strained rings was reported (e.g., cyclopropanes and epoxides) with an allenyl moiety affording boryl allylboronates.¹⁴ A general protocol for the selective synthesis of vinyl-, allyl-, and (*E*)-2-boryl allylboronates from more readily available propargylic alcohols via Cu catalysis has not been established. Marder and others have developed Cu-^{15a-e} or Zn-catalyzed^{15f-i} borylations of organic halides, as Cu and Zn have relatively low toxicity and are inexpensive. Herein, we used catalytic borylation of propargylic alcohols to synthesize vinyl-, allyl-, and (*E*)-2-boryl allylboronates (Scheme 1).

Previously, allenylboronates were prepared from multisubstituted propargylic alcohols catalyzed by 10 mol % of $[Cu(CH_3CN)_4]^{2+}[BF_4^{-}]_2$ with 1.2 equiv of B_2pin_2 at 40–60 °C.^{3c} However, when the reaction was carried out with **1a** as the starting material, 30% of diboration product **2a** was obtained instead of the expected allenylboronate (Table S1, entry 2). Therefore, we explored the borylation of propargylic alcohols using other Cu salts as catalyst precursors and Xantphos as the ligand (Table 1). (*E*)-2-Boryl allylboronate **2a** was obtained in 66% yield when we employed 10 mol % of Cu(acac)₂ as catalyst precursor, 13 mol % of Xantphos as ligand, and 1 equiv of Ti(OⁱPr)₄ as a Lewis acid (Table 1, entry 1). However, the yield of **2a** dropped to 57% when $[Cu(CH_3CN)_4]^+[BF_4]^-$ was used instead of Cu(acac)₂ (Table 1, entry 2). Control experiments revealed that the diboration reaction is catalyzed by Cu, with

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Scheme 1. Transition-Metal-Catalyzed Borylation of Propargylic Alcohols



Table 1. Condition Screening^a



^{*a*}All reactions were carried out on a 0.2 mmol scale. Reaction conditions: Cu(acac)₂ (10 mol %), Xantphos (13 mol %), **1a** (1 equiv), B₂pin₂ (2.2 equiv), Ti(OⁱPr)₄ (1 equiv), MTBE (1 mL), 60 °C, 18 h. ^{*b*}Yields determined by GC-MS analysis vs a calibrated internal standard and are averages of two experiments. ^{*c*}Geometry of C=C bonds determined by ¹H-¹H NOESY NMR. ^{*d*}Unreacted starting material. ^{*c*}Not detected. ^{*f*}Isolated yield.

Xantphos as the ligand (Table 1, entries 3 and 4). Yield of **2a** dropped to 20% in the absence of $Ti(O^{i}Pr)_{4}$, which turns the OH moiety into a good leaving group (Table 1, entry 5).^{16a} When we replaced MTBE with CH₂Cl₂ as the solvent, **1a** was fully converted and **2a** was obtained in 87% yield (Table 1, entry 6; for details see SI).

With optimized conditions in hand, we investigated the scope of the diboration reaction (Scheme 2). Desired products 2b-e were obtained in 86–91% yield from diboration of 1b-e. Yields of 2f and 2g dropped to 74 and 63%, respectively, when bulkier

Scheme 2. Synthesis of (E)-2-Boryl Allylboronates^{*a,b,c*}



^aStandard conditions: 1 (0.20 mmol), Cu(acac)₂ (10 mol %), Xantphos (13 mol %), B₂pin₂ (0.44 mmol), Ti(OⁱPr)₄ (0.20 mmol), CH₂Cl₂ (1 mL), 60–80 °C, 18–24 h. ^bIsolated yield. ^cGeometry of C=C bonds determined by ¹H–¹H NOESY NMR.

functional groups, such as isopropyl or cyclohexyl, were present. Diboration products 2h-j were obtained in good to excellent yields of 81–92% upon replacement of "Bu by ethyl or phenethyl groups. Propargylic alcohols bearing aromatic substituents were also good substrates for diboration, giving 2k-n in good yields of 69-78%. With a phenyl ring bearing an OMe group at the meta position, **20** was formed 71% yield. Yields of 2p-r dropped to 60, 54, and 57%, respectively, when OMe, Me, and F were introduced at the ortho position. Naphthyl-containing substrate 1s gave 2s in 72% yield. Again, the "Bu group can be replaced by a phenethyl group, and corresponding products 2t and 2u were formed in 76 and 72% yields, respectively. The regio- and stereoselectivity of our Cu-catalyzed diborations are different from those of Pd-catalyzed allene diborations,^{13b-d} which afforded (E)-2-boryl allylboronates. Pd-catalyzed allene diborations give either (Z)-2boryl allylboronates^{13b'} or 2-boryl allylboronates with C=C bonds at the terminal position.^{13c,d} The regioselectivity of our diborations also suggests that a cascade involving the insertion/ elimination^{16b,c} and a borylcupration of the resulting allenyl boronates might be taking place.⁸⁻¹⁰

When 1,1-disubstituted propargyl alcohols as substrates and 1.5 equiv of ⁱPrOH were added, allyl boronates were obtained from the borylation reaction (Scheme 3). With 2-phenylbut-3-yn-2-ol (3a) as the starting material, desired allyl boronate 4a was formed in 74% yield. Allyl boronates 4b-f were obtained in moderate to good yields of 68–82% with the phenyl ring bearing different substituents (3b-f). 3g, with a fused ring system, provided 4g in 83% yield. The geometry of the C==C bonds was determined by ¹H-¹H NOESY, and NMR data are identical to those in the literature.¹⁷ When the phenyl ring system was replaced by aliphatic substituents, such as 3h-j, allyl boronates 4h-j were also afforded in 44–61% yields. Because alkylsubstituted allyl boronates are unstable on silica gel and are

Scheme 3. Synthesis of Allyl Boronates^{*a,b,c*}



^{*a*}Standard conditions: **3** (0.2 mmol), Cu(OAc)₂ (10 mol %), Xantphos (13 mol %), B₂pin₂ (0.4 mmol), Ti(OⁱPr)₄ (0.20 mmol), ⁱPrOH (0.3 mmol), MTBE (1 mL), 60 °C, 18 h. ^{*b*}Isolated yield. ^{*c*}Geometry of C=C bonds determined by ¹H–¹H NOESY NMR. ^{*d*}Z/E isomer ratios were determined by ¹H NMR spectroscopy of the crude products, and isolated yields of (Z)-4a–g are given in the table.

volatile compounds, flash chromatography and rotary evaporation of solvents contribute to yield losses to varying extents. Regio- and stereoselectivity of the above borylation reaction suggest mechanistic similarities to the borylcupration of allenylsilanes^{8c} (for a detailed mechanism, see SI).

Monosubstituted propargyl alcohols with 1.5 equiv of ⁱPrOH afforded vinyl boronates from the borylation reactions (Scheme 4).



"Standard conditions: **5** (0.20 mmol), $Cu(OAc)_2$ (10 mol %), Xantphos (13 mol %), B_2pin_2 (0.21 mmol), $Ti(O'Pr)_4$ (0.20 mmol), "PrOH (0.3 mmol), toluene (1 mL), 60 °C, 18 h. "Isolated yield." "Reaction carried out on a 1 mmol scale.

When we employed 1-phenylprop-2-yn-1-ol (**5a**) as the starting material, vinyl boronate **6a** was obtained in 79% yield.^{18a} Vinyl boronates **6b** and **6c** were formed in 83 and 80% yields, respectively, with the phenyl ring bearing electron-donating groups. **6d** and **6e** were formed in 75 and 69% yields, respectively, when the *para* substituents were F or Cl, and **6f** was formed in 84% yield with an OMe group at the *meta* position. With an OMe group at the *ortho* position, **6g** was formed in 71% yield. With other groups at the *ortho* position, **6h**–j were obtained in yields of 50–64%. Compound **5k**, bearing a fused ring system, and

heterocyclic compound **51** gave corresponding products **6k** and **6l** in 71 and 78% yields, respectively. Regioselectivity of the borylation reaction agrees with a mechanism reported for the borylcupration of alkynes (for a detailed mechanism, see SI).^{18b,c}

Based on preliminary results (see SI), a plausible mechanism is shown in Scheme 5.

Scheme 5. Plausible Mechanism for the Diboration of Propargylic Alcohols



Propargylic alcohols 1 can be activated by $Ti(O^{i}Pr)_{4}$ to generate I and ⁱPrOH (eq 1).^{16a} We hypothesize that the active catalyst is a Cu(I) species.^{19a} Active Cu(I) species A could be generated via reduction by an electron-rich anionic adduct of B_2pin_2 or a boryl anion nucleophile.^{19b} Transmetalation between A and B_2pin_2 affords Cu-Bpin species B.^{3c,Sh} Via intermediates C and D, an insertion/elimination occurs between B and I to provide allenylboronates E,^{16b,c} and catalytic species A is regenerated. Transmetalation between A and B_2pin_2 regenerates B. Borylcupration of E affords F.^{8a,b,9a} Because the *E*-geometry is thermodynamically more stable than the *Z*-geometry, (*E*)-2-boryl allylboronates 2 were afforded via γ -alcoholysis of F.^{8a,b,9a}

In summary, we developed methodology for the synthesis of vinyl-, allyl-, and 2-boryl allylboronates from propargyl alcohols under mild conditions, broadening the utility of alcohols in synthetic methodology. An insertion/elimination followed by a borylcupration of the allenyl boronate intermediate is apparently involved in the overall mechanism.

Supporting Information

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Experimental procedures and compound characterization data (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: kalman@organ.su.se.

*E-mail: todd.marder@uni-wuerzburg.de.

ORCID [©]

Todd B. Marder: 0000-0002-9990-0169

Notes

The authors declare no competing financial interest.

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