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Copper-Catalyzed Alkynylboration of Alkenes with Diboron Reagents and Bromoalkynes**

Tian-Jun Gong, Shang-Hai Yu, Kuan Li, Wei Su, Xi Lu, Bin Xiao, * and Yao Fu*

Abstract: A new and efficient method for the synthesis of homopropargylboronates by copper-catalyzed alkynylboration of alkenes with diboron reagents and bromoalkynes has been developed. The alkynylboration reaction features high selectivity and efficiency, mild reaction conditions, wide substrate scope, and functional-group compatibility, and is a highly attractive complement to existing methods for the synthesis of homopropargylboronates. Both the boryl and alkynyl groups are good potential functional groups, for the subsequent manipulations which provide an efficient access to a variety of important molecule structures.

Alkylboronic acid derivatives are versatile intermediates in organic synthesis,^[1a] and also as interesting compounds in medicinal chemistry (e.g., bortezomib).^[1h] The development of new methods to synthesize alkylboronic acid derivatives has been intensively studied in organic chemistry.^[2-7] Transition-metal-catalyzed boration/functionalization of C-C double bonds has been established as an important strategy for the expedient synthesis of complex and reactive boron-containing compounds from readily available starting materials in a single step.^[4-7] One main feature of the process of boration/functionalization is that, in addition to generating the alkylboronates motif, a synthetically versatile group (e.g., boryl,^{[5d,} ^{5g]} amino,^[5k-m] aryl,^[7b-d, 7i, 7n] alkyl,^[6, 7f] alkenyl^[7c]) is also incorporated. For instance, Hoveyda et al. realized the copper-catalyzed carboboration of alkenes (1, 3-envnes and 1, 3-dienes) with B₂pin₂ and aldehydes, aldimines or enoate^[7], 8a]. Brown and Nakao et al., independently, reported synergistic intermolecular arylboration Pd/Cu-catalvzed reactions of vinylarenes, in which C(sp³)-B and C(sp³)-C(sp²) bond formation were realized. Liao reported a Cu/Pd cooperative catalysis for enantioselective allylboration of alkenes.^[7e] More recently, our group reported an example of ligand-controlled regiodivergent copper-catalyzed alkylboration of unactivated alkenes.^[7f] Despite of these pioneering excellent examples of boration/functionalization of alkenes, alkynylboration of alkenes has never been reported.

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Considering that homopropargylboronates are important functional groups in organic synthesis, which provide efficient access to homopropargylalcohol, homopropargylamine and heterocycles,^[8] the development of efficient methods for synthesis of homopropargylboronates is highly demanded.

Herein, we report an example of copper-catalyzed regioselective and enantioselective alkynylboration of alkenes with diboron reagents and bromoalkynes (Scheme 1). This reaction presents a efficient route to construct $C(sp)-C(sp^3)$ and $C(sp^3)$ -B bond in a single step,^[9-10] and tolerates a broad range of substituted alkenes (*styrenes, allene and 1,3-enyne*) and bromoalkynes (*silyl, aryl and aliphatic alkynylbromides*). Both the boryl and alkynyl groups can be subsequent manipulations provide efficient access to a variety of high-value products.





We initially used 4-vinylbiphenyl, bis(pinacolato)diboron (pinB-Bpin) and triisopropylsilylethynyl bromide as model substrates to attempt the alkynylboration reaction. After extensive screening of various reaction parameters, we were pleased to find that the alkynylboration occurred in the presence of a CuCl/PCy3 catalyst and a LiO'Bu base in THF at room temperature, and the desired product 3a was obtained in 34% isolated yield. The yield was not improved when DPPBz was used. With IMes·HCl as ligands, excellent yields of 3a were obtained (entry 3). While ICy·HCl gave moderate yields, only 6% yield of product was obtained when bulky IPr·HCl was used as ligand (entry 5). Moreover, when we used IMesCuCl instead of CuCl and IMes·HCl, the yield of 3a was slightly improved (entry 6). The effects of various bases on the reaction was also tested, whereas other bases such as NaO'Bu, KO'Bu, KOTMS and Cs₂CO₃ afforded the desired product in moderate yields (See SI). When triisopropylsilylethynyl chloride was used instead of triisopropylsilylethynyl bromide, a much lower yield of 3a was obtained (entry 7), while triisopropylsilylethynyl iodine provide only trace amounts of desired

Table 1: Optimization of Reaction Conditions.[a]

Ph + B_2pin_2 + TIPS 1a 2 THF, rt, 12 h PPh ₂ dppbz R = 2,4,6-trimethylphenyl, IMes-HCI CIO R = Cy, ICy-HCI THS $R = 2,4,6-trimethylphenyl, IMes-HCI CIO R = Cy, ICy-HCI$				
entry	X	Ligand+Cat.[Cu]	Base	Yield (%) [b]
1	Br	$PCy_3 + CuCl$	LiO'Bu	34
2	Br	DPPBz + CuCl	LiO ^t Bu	12
3	Br	IMes·HCl + CuCl	LiO ^t Bu	85
4	Br	ICy·HCl + CuCl	LiO ^t Bu	57
5	Br	$IPr {\cdot} HCl + CuCl$	LiO ^t Bu	6
6	Br	IMesCuCl	LiO'Bu	90
7	Cl	IMesCuCl	LiO ^t Bu	60
8	Ι	IMesCuCl	LiO ^t Bu	Trace
9 ^c	Br	IMesCuCl	LiOtBu	81

[a] Reaction conditions: alkene **1a** (0.1 mmol), $(Bpin)_2$ (0.15 mmol), haloalkynes **2** (0.2 mmol), CuCl (0.01 mmol), ligand (0.011 or 0.022 mmol), and LiO'Bu (0.2 mmol) were stirr in THF (0.5 mL) at room temperature for 12 h. [b] Isolated yield of pure **3a**. [c] haloalkynes **2** (0.15 mmol). B₂pin₂ = bis(pinacolato)diboron.

product (entry 8). Lower yield of product was obtained when 1.5 equivalents of alkynyl bromide was used (entry 9). In all the above reactions, this reaction performed excellent regio-selectivity.

With the optimized conditions identified, we first investigated the scope of bromoalkynes (Scheme 2). A variety of silylated alkynylbromides were well tolerated in this reaction (3a-3d). In addition to silylated alkynylbromides, the reaction proceeded well with aryl and aliphatic alkynylbromides bearing different functional groups, giving products bearing a phenyl group (3f, 68% yield) or benzyl-protected propargylic alcohols (3h, 73%). We were surprised to find that a steroid group, useful biologically active compounds, can smoothly survive the alkynylboration process (3k). Other diboron reagents, such as bis(neopentyl glycolato)diboron and bis[(+)-pinanediolato]diboron, can also be applied in the reaction with acceptable yields. Then, we tested the scope of styrenes. As to the electronic effects of the substituents on the reaction, both electron-donating (3m) and withdrawing groups (3n) could be tolerated. The fluoro-containing groups that are frequently found in agrochemical and pharmaceutical products were well compatible with the alkynylboration processes (30, 3p). Moreover, the aryl-halogen (Cl, Br) and OTs groups were well tolerated in the alkynylboration reaction (3q-s), which made additional functionalization possible at these positions. For a di-vinyl substrate, we can obtain the product 3u carrying a vinyl group by using 1.5 equivalent B₂pin₂ and 2 equivalent bromoalkyne. As for the substrates containing an indole (3v) or benzothiophene (3w), the present reaction occurred smoothly. In addition, sterically hindered styrenes such as ortho-Me (3x) and ortho-OMe (3y) styrene posed no problem during the cross-coupling process. α-Quaternary homopropargyl-



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Scheme 2: Substrate Scope. [a] Reaction conditions: alkenes (0.1 mmol), B₂pin₂ (0.15 mmol), haloalkynes (0.2 mmol), IMesCuCl (0.01 mmol), and LiO'Bu (0.2 mmol) were stirr in THF (0.5 mL) at room temperature for 12 h. Isolated yields of pure **3** or **4** are shown. [b] Bis(neopentyl glycolato)diboron (0.15 mmol) was used instead of B₂pin₂. [c] Bis[(+)-pinanediolato]diboron (0.15 mmol) was used instead of B₂pin₂. [d] Cs₂CO₃ (0.2 mmol) was used instead of LiO'Bu. [e] KO'Bu (0.2 mmol) was used instead of LiO'Bu. [f] NaBO₃·4H₂O, THF/H₂O, rt., 4h. B₂pin₂ = bis(pinacolato)diboron.

boronate can be obtained by alkynylboration with sterically hindered 1,1-disubstituted alkenes (**3z**), which is difficult to obtained by Ito's hydroboration of an enyne.^[8b] To our delight, macrocyclic alkyne could be synthesized from intramolecular alkynylboration (**3aa**). It presents the first example of macro-sized-ring synthesis in carboboration. In line with the expected reaction result, 1,2-disubstituted alkene and alkyl-substituted alkenes are ineffective substrates.



Besides styrenes, other types of alkenes were also examined in this reaction. Gratifyingly, when oxabenzonorbornadiene was used as alkene for the alkynylboration, the reaction proceeded smoothly without the formation of ring-opened side products (4a, 4b), which were consistent with the recent work of Miura and co-workers.^[51] Furthermore, terminal vinyl silane also underwent the alkynylboration reaction to provide the desired product in 40% yield (4c). To be pointed out that, silicon compounds are very important synthetic reagents and intermediates in modern organic synthesis. When cyclohexyl allene was used, the product was obtained in 51% yield (4d). Interestingly, when 1,3-envne was used as alkene for the alkynylboration,[11] 1,4-alkynylboration product was obtained (Eq.1, As comparison, 3,4-carboboration^[8a] **4e**). а and 3,4-hydroboration^[8b, c] to 1,3-enynes is the most common reaction pattern .

Gram-scale syntheses of **3a** and **3e** were also carried out to test the scalability of the transformation: The alkynylboration of **1a** on a 3.0 mmol scale afforded **3a** and **3e** in 80% yield and 68% yield, respectively, with 2 mol% catalyst loading. We then demonstrated the versatility of the alkynylboration products (Scheme 6). These products could be efficiently converted into 4-biphenyl-3-butyn-1-ol (**5**) at 80% yield in two steps. This terminal alkynes can further transformed to heteroaryl ring under Click reaction and Sonogashiya reaction conditions (**6**, **7**).^[12a,b] The boronic esters can be easily transformed to amine (**8**),^[12c] while homopropargylamines are useful building blocks in organic synthesis. By oxidation and Au(PPh₃)₂Cl₂



Scheme 3. Transformations of Alkynylboration Products. [a] NaBO₃.4H₂O, THF/H₂O, r. t.; [b] TBAF, THF, r. t.; [c] CuSO₄·5H₂O, BnN₃, N₂H₄·H₂O, r. t.; [d] Pd(PPh₃)₂Cl₂, CuI, 2-bromophenol, NEt₃, 90 °C; [e] BCl₃, BnN₃, DCM, r. t.; [f]

Au(PPh₃)₃Cl, AgSbF₆, TsOH·H₂O, MeOH, r. t.; [g] Ni(cod)₂, CsF, ZnMe₂, CO₂ balloon, 60 °C.

/AgSbF₆catalyzed *endo*-cyclization reaction, the tetrahydrofuran derivatives was obtained in 67% yield (9).^[12d] Moreover, γ -butyrolactones derivatives can be obtained by using Ni-catalyzed *exo*-cyclization reaction (10).^[12e] Thus, the Cu-catalyzed alkynylboration of alkenes is synthetically useful and the homoalkynylboronic esters products can be readily converted to diverse useful molecules.

Inspired by the high efficiency of this reaction, we applied the present protocol to catalytic enantioselective alkynylboration by using an appropriate optically active ligand (Scheme 4, See SI). Alkynylboration of 1, 1-disubstituted alkenes with **2a** in the presence of NHC precursor afforded the α -quaternary homopropargylboronate in 44% yield with 92.9:7.1 er.^[13] It provides an efficient method to construct chiral quaternary carbon.



Scheme 4. Preliminary Results of Enantioselective Alkynylboration.

To study the mechanism of the alkynylboration of alkenes, we sought to gain evidence for the possible reactive intermediates involved in the reaction (Scheme 5). When alkynylborane (11) was subjected to the optimized reaction conditions for 4-vinylbiphenyl, **3a** was not produced.^[14] Then, bis(borylated) derivative (12) was subjected to the reaction, without obtaining the **3a**. These observations exclude the possibility that bis(borylated) or alkynylborane derivatives were intermediates in the alkynylboration of alkenes.^[15]



Scheme 5. Mechanistic Insights.

On the basis of these experiments, a possible reaction mechanism was proposed (Scheme 6). First, IMesCuO'Bu complex was generated from the reaction of IMesCuCl and LiO'Bu. Then σ -bond metathesis with pinB-Bpin generates borylcopper species **I**. Subsequent insertion of the alkene into the Cu-B bond of **I** furnishes a borylated alkylcopper intermediate **II**.^[16] Akynylation with the bromoalkyne then occurs, which forms the desired alkynylboration product along with the regeneration of the Cu(I) catalyst. As for 1,3-enyne, 1,3-isomerization of the propargylcopper **III** affording an allenylcopper intermediate **IV**,^[8a, 11] then oxidative addition with the bromoalkyne to form intermediate **V**, which undergoes a reductive elimination to furnish the target product.

In summary, we have reported the an example of copper-catalyzed regioselective alkynylboration of alkenes for synthesis of homopropargylboronates. This protocol provides an effective means to access an array of synthetically versatile building blocks that can be easily transformed into a variety of important molecules. Chiral α -quaternary homopropargylboronate was obtained by using hindered 1, 1-disubstituted alkene. this reaction provides an efficient method to construct chiral quaternary carbon. Moreover, this reaction presents the first example of macro-sized-ring synthesis in carboboration.



Scheme 6. Possible Reaction Mechanism.

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Copper-Catalyzed Alkynylboration of Alkenes with Diboron Reagents and Bromoalkynes



A new and efficient method for the synthesis of homopropargylboronates by copper-catalyzed alkynylboration of alkenes with diboron reagents and bromoalkynes has been developed. The alkynylboration reaction features high selectivity and efficiency, mild reaction conditions, wide substrate scope, and functional-group compatibility, and is a highly attractive complement to existing methods for the synthesis of homopropargylboronates. Both the boryl and alkynyl groups are good potential functional groups, for the subsequent manipulations which provide an efficient access to a variety of important molecule structures.



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