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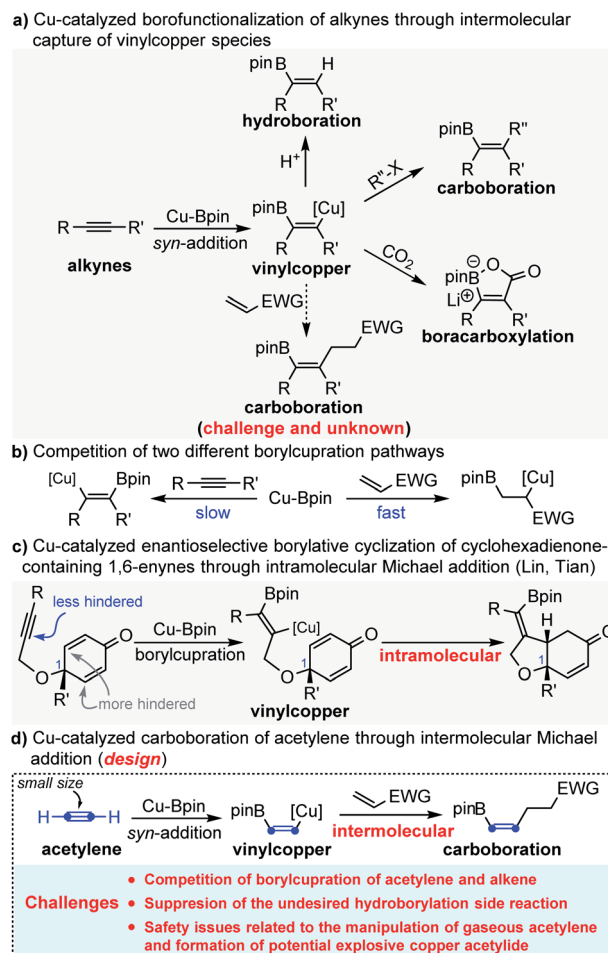
Cu-catalyzed carboboration of acetylene with Michael acceptors†

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A copper-catalyzed three-component carboboration of acetylene with B₂Pin₂ and Michael acceptors is reported. In this reaction, a cheap and abundant C₂ chemical feedstock, acetylene, was used as a starting material to afford *cis*-alkenyl boronates bearing a homoallylic carbonyl group. The reaction was robust and could be reliably performed on the molar scale. Furthermore, the resulting *cis*-alkenyl boronates could be converted to diverse functionalized molecules with ease.

Copper-catalyzed *syn*-1,2-borofunctionalization of alkynes has become a powerful and practical strategy for the installation of both boron and other functional groups across the C≡C bond in excellent regio- and stereoselectivity.¹ The general mechanism is that the borofunctionalization is initiated by the *syn*-addition of nucleophilic Cu-Bpin across the C≡C bond to generate the key intermediate species borylated alkenyl copper, followed by the interception of electrophiles to produce multi-substituted alkenyl boronates (Scheme 1a). So far, different electrophiles, such as H⁺, halides (including alkyl, allyl, aryl and alkynyl halides) and CO₂, have been successfully and efficiently employed to intercept the putative borylated alkenyl copper.^{2–4} In sharp contrast, as excellent electrophiles, Michael acceptors (acrylate, vinyl ketone, acrylonitrile *etc.*) have rarely been employed to capture the *in situ* generated borylated alkenyl copper intermediate. This is not because Michael acceptors are not capable of reacting with the nucleophilic alkenyl copper, but because the electron-deficient Michael acceptors are typically more reactive than the electron-rich alkynes toward the borylcupration of Cu-Bpin species⁵ (Scheme 1b). To circumvent this challenge, Lin and Tian reported a Cu-catalyzed asymmetric borylative cyclization of cyclohexadienone-containing 1,6-enynes through an intramolecular Michael addition.⁶ In this reaction, the authors smartly leveraged the steric hindrance from the quaternary carbon of C1 to suppress the undesired borylcupration of cyclohexadienone (Scheme 1c). Recently, by using the same strategy, Carretero and Mauleón also reported an intramolecular borylative cyclization of 1,6-enynes with a β,β-disubstituted acrylate fragment to provide densely functionalized pyrrolidines.⁷ Despite these elegant studies, due to

the competition between two different borylcupration pathways, copper-catalyzed carboboration of alkynes through intermolecular Michael addition is still challenging and remains unknown.



Scheme 1 Cu-catalyzed borofunctionalization of alkynes.

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† Electronic supplementary information (ESI) available: Experimental details and characterization of all compounds, and copies of ¹H and ¹³C NMR spectra. CCDC 2165502 (2t). For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2sc02306g>



Acetylene, with the molecular formula C_2H_2 , is the simplest and smallest alkyne.⁸ Due to its structural simplicity and high reactivity, acetylene represents a unique C_2 alkenyl building block for organic synthesis through addition of its triple bond.⁹ Highly industrially important vinyl-containing monomers, such as vinyl ether,¹⁰ vinyl amine,¹¹ vinyl chloride,¹² acrylic acid and its derivatives,¹³ are being synthesized in millions of tons per year globally. However, in fine chemistry, catalytic protocols directly incorporating acetylene into high value-added chemicals are limited. In fact, while phenylacetylene acts as a model substrate in many state-of-the-art catalytic systems concerning alkyne transformations, acetylene is usually neglected in the substrate scope studies due to its gaseous nature and explosive hazard.^{9a,h} This obscures the true reactivity of acetylene and makes the acetylene chemistry lag behind in the progress of modern catalytic alkyne chemistry.

Inspired by the elegant studies of Lin, Tian, Carretero and Mauleón, in which a steric hindered Michael acceptor was used to suppress the undesired conjugate borylation of Cu-Bpin, we envisioned that the small size of acetylene might also enable the borylcupration of the $C\equiv C$ bond to outcompete the borylcupration of the Michael acceptor, thus allowing the Cu-catalyzed carboboration of acetylene through the challenging intermolecular Michael addition (Scheme 1d). However, the application of acetylene in the copper-catalyzed carboboration reaction through intermolecular Michael addition might encounter the following potential challenges: (1) competition between two different borylcupration processes; (2) suppression of the undesired hydroborylation side reaction; (3) safety issues related to the manipulation of acetylene gas and formation of the potentially explosive copper acetylide.

With this above design in mind, we initially investigated the competition of the borylcupration reaction among different types of alkynes. As shown in Scheme 2, when equal amounts of acetylene, phenylacetylene and 1-pentyne were subjected to the typical borylcupration catalytic system with 1.0 equivalent of B_2pin_2 as the limiting reagent and $IMesCuCl$ as the catalyst, an unexpected reaction selectivity was observed. The hydroborylation product of acetylene (**A1**) was observed in 62% yield, which is about 8 times higher than that of phenylacetylene (**A2**). In addition, no corresponding hydroborylation product of 1-pentyne (**A3**) was detected by NMR. The competition results obviously indicated that the borylcupration of acetylene is much faster than that of both aryl alkynes and alkyl alkynes. More importantly, by comparison of the hydroborylation of acetylene

and 1-pentyne, we can draw the conclusion that the steric hindrance of the substituent does have a significant impact on the borylcupration of the $C\equiv C$ bond by taking into account that both of them are unactivated alkynes.

Encouraged by the above results, we further investigated Cu-catalyzed three-component carboboration of different alkynes in the presence of B_2pin_2 and butyl acrylate **1a** with $IMesCuCl$ as the catalyst and NaO^tBu as the base. As shown in Table 1, when the substituted alkynes, phenylacetylene and 1-pentyne, were used as substrates, the desired three-component carboboration product **2** could not be detected (entries 1–4), even with a large excess of alkynes (12.5 equivalents, entries 2 and 4). The hydroborylation reactions of alkynes and butyl acrylate always dominated, giving the corresponding products **A** and **B**. However, the distribution of **A** and **B** clearly indicated that the hydroborylation of electron-deficient butyl acrylate (Michael acceptor) is much faster than that of substituted alkynes, which echoes their borylcupration reactivities (Scheme 1b). In sharp contrast, the desired three-component carboboration product **2a** could be successfully generated when acetylene was applied as the alkyne component (entries 5 and 6). The carboboration product **2a** could be produced in 38% yield even with 1.0 equivalent of acetylene, which is equal to the yield of hydroborylation product **B** (entry 5). When the amount of acetylene was further increased up to 12.5 equivalents (the gaseous acetylene was supplied with a balloon), the hydroborylation of butyl acrylate was completely suppressed with no byproduct **B** detected, furnishing the desired carboboration product **2a** in 62% yield (entry 6). Taken together, the application of acetylene, due to its small size, could enable the realization of the *syn*-1,2-carboboration of the $C\equiv C$ bond through an intermolecular Michael addition, producing the highly useful alkenyl boronates.

With the initial success achieved, we then systematically screened the reaction conditions and the optimal reaction

Table 1 Cu-catalyzed carboboration of different alkynes



Entry	R	x	A	B	2
1	Ph	1.0	14%	72%	n.d.
2		12.5	34%	40%	n.d.
3	Pr	1.0	n.d.	65%	n.d.
4		12.5	8%	65%	n.d.
5	H	1.0	9%	38%	2a (38%)
6 ^a		12.5	22%	n.d.	2a (62%)

^a The reaction was conducted with a balloon containing acetylene; the saturated solution of acetylene in 1,4-dioxane was about 0.50 M (about 12.5 eq.).



Scheme 2 The competition of borylcupration among different alkynes.



conditions were established by using 5 mol% IMesCuCl as the catalyst, 0.5 equivalents of NaO^tBu as the base and 2.5 equivalents of EtOH as the proton source in a solution of 1,4-dioxane (0.04 M) under a 1 atm acetylene atmosphere at room temperature. The desired alkenyl boronate **2a** could be obtained in 90% NMR yield and 72% isolated yield (see the ESI for details).[†]

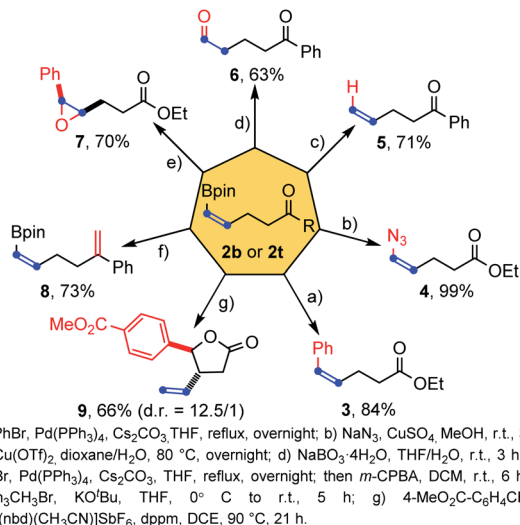
With the optimized reaction conditions in hand, we then explored the generality of this Cu-catalyzed carboboration of acetylene. As shown in Scheme 3, this reaction has a very broad substrate scope and excellent functional group tolerance. Different acrylates, thioacrylates, vinyl ketones, 1,3-dienyl

ketone, acrylonitrile and vinyl sulphones with rich functional groups could be applied as effective substrates for this carboboration reaction. The carboboration of acetylene with acrylates was first demonstrated (**2a–2m**). Simple butyl, ethyl and phenyl acrylate could be transformed to target boronates **2a**, **2b** and **2c** in 72%, 67% and 99% yields, respectively. As a base stronger than NaOH, NaO^tBu has usually been considered to cause poor functional group tolerance. However, the introduction of S_N2-sensitive functional groups such as methylsulfonyloxy, epoxy and alkyl bromide caused no deleterious effect on the reaction efficiency giving the desired products **2e**, **2f**, and **2i** in >82%



Scheme 3 Cu-catalyzed carboboration of acetylene with B₂Pin₂ and Michael acceptors. ^a0.4 mmol of Michael acceptor in 10 mL 1,4-dioxane; ^bthe purity of the product was 93% by weight and the reported yield is based on the pure product; ^cwith 2.0 eq. EtOH; ^dwith 10 mol% IMesCuCl; ^esubstrate diluted with 1,4-dioxane or toluene and added dropwise for about 2 min; ^fwith 15 mol% IMesCuCl; ^gwith 2.5 eq. MeOH instead of EtOH; ^hsubstrate (1.0 mol L⁻¹ in pentane) was added dropwise.



Scheme 5 Synthetic applications of products.¹⁶

direct oxidation of sodium peroxyborate (product 6). Epoxidation of the double bond could be achieved (product 7) once the boron atom is transferred to other oxidation insensitive groups, such as phenyl. Wittig reaction was found to be compatible with the existence of pinacol boron (product 8). Finally, a rhodium-catalyzed allylation tandem intramolecular transesterification reaction with aldehyde forming a five-membered lactone structure was also achieved with good diastereoselectivity and yield (product 9). In general, the three functional groups in the products (pinacol boronate, carbon-carbon double bond and ketone/ester group) could transform individually or synergistically to form other useful structures.

Conclusions

In conclusion, we have developed a copper-catalyzed three-component carboboration of acetylene with B₂Pin₂ and Michael acceptors. In this reaction, the cheap and abundant C₂ chemical feedstock acetylene was used as the starting material to afford the homoallylic carbonyl group-containing *cis*-alkenyl boronates in a regioselective manner. The reaction has high robustness and can be easily and reliably performed on the molar scale. In this reaction, acetylene does not solve the problems encountered with other alkynes, but in turn, the general problems of substituted alkynes may not definitely confine acetylene.¹⁷ Acetylene is acetylene and it is unique in nature. The small size of the acetylene molecule accelerates the rate of borylcupration and also facilitates the following C-C bond formation process through intermolecular Michael addition, which is typically challenging for substituted alkynes. Moreover, the resulting homoallylic carbonyl group-containing *cis*-alkenyl boronates could be converted to diverse functionalized molecules with ease. It is expected that this unique protocol may inspire and prompt chemists to further explore novel catalytic systems using acetylene as the C₂ building block toward the synthesis of valuable chemicals.

Data availability

Experimental procedures, NMR, IR, HRMS spectra, crystallographic data of 2t and some unsuccessful trials are provided in the ESI.†

Author contributions

Conceptualization, funding acquisition, resources and supervision were done or provided by S. Z.; project administration, data curation, investigation and formal analysis were done by T. C.; validation was done by B. L.; writing was done by all authors.

Conflicts of interest

There are no conflicts to declare.

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