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To cite this version:

Yang Gao, Nana Kim, Sima Yazdani, Mingyu Liu, Aaron Kendrick, et al.. (CAAC)Copper Catalysis Enables Regioselective Three-Component Carboboration of Terminal Alkynes. 2022. hal-03827967

HAL Id: hal-03827967

https://hal.science/hal-03827967v1

Preprint submitted on 26 Oct 2022

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(CAAC)Copper Catalysis Enables Regioselective Three-Component Carboboration of Terminal Alkynes

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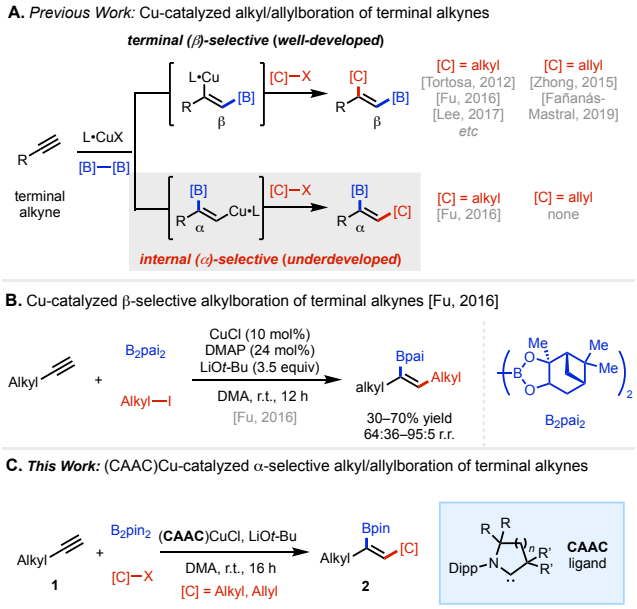
KEYWORDS organoboron, copper, carboboration, CAAC ligand, regioselectivity

ABSTRACT: Cyclic(alkyl)(amino)carbene (CAAC) ligands are found to perturb regioselectivity of the copper-catalyzed carboboration of terminal alkynes, favoring the less commonly observed internal alkenylboron regiosomer through an α-selective borylcupration step. A variety of carbon electrophiles participate in the reaction, including allyl alcohols derivatives and alkyl halides. The method provides a straightforward and selective route to versatile tri-substituted alkenylboron compounds that are otherwise challenging to access.

Organoboron compounds play a unique role in the chemical sciences. Carbon–boron bonds can readily be converted into a diverse array of carbon–carbon and carbon–heteroatom linkages via an ever-expanding battery of methods,[1-4] and organoboron molecules themselves possess myriad of functions in the context of biology[5-6] and materials science.[7-9] The invention of new methods to assemble organoboron compounds from simple chemical inputs streamlines access to important families of molecules. Multi-component catalytic couplings, in which three or more building blocks are united in a single reaction, hold tremendous promise in enabling direct synthesis of densely functionalized organoboron compounds. In this context, copper-catalyzed borylative 1,2-difunctionalization of alkynes is an established means of preparing tri- and tetrasubstitued alkenylboron targets via a mechanism involving migratory insertion of an alkyne into a L_n•Cu^I–boryl intermediate followed by coupling of the resulting L_n•Cu^I(alkenyl) species with an electrophile.[10-13] Controlling the regioselectivity of these processes in a way that grants access to either regioisomer in a predictable manner remains challenging. With terminal alkynes, the vast majority of catalytic systems deliver the boryl group to the terminal (β) position, restricting access to the opposite alkenylboron regioisomers. Here, we demonstrate that appropriately tuned cyclic(alkyl)(amino)carbene (CAAC)-ligated copper catalysts enables regioselective carboboration to give internal (α) alkenylboron compounds with a broad collection of carbon electrophiles.

Regioselectivity trends in L_n•Cu–boryl alkyne addition processes are complex and reflect an interplay between the steric and electronic properties of the ligand, the identity of the boryl group, and the substituent(s) on the alkyne substrate.[14-16] N-Heterocyclic carbene (NHC) ligands[17-18] have been widely used in catalytic L_n•Cu–



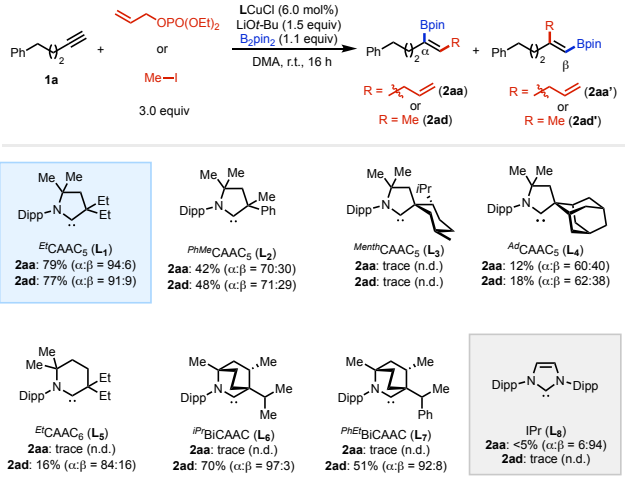
Scheme 1. Overview of Cu-catalyzed regioselective carboboration of terminal alkynes.

boryl catalysis and generally favor boryl transfer to the terminal position of terminal alkynes with Bpin and related boryl groups, though either position can predominate depending on the nature of substrate and the ligand environment around boron. We recently demonstrated that strongly σ-donating CAAC ligands[19-21] override substituent effects of the boryl group and the alkyne, allowing for reliably Markovnikov (α-selective) protoboration of diverse terminal

alkynes with a variety of bis-boron nucleophiles.[22] Based on this result, we questioned whether it would be possible to employ C(sp^3)-based electrophiles in lieu of a proton to develop a three-component carboboration, with regioselectivity and product substitution patterns that would complement existing methodology.[23-32] Of relevance to this proposal, Xiao and Fu disclosed an important study in which the combination of CuCl (10 mol%) as the precatalyst, DMAP (24 mol%) as the ligand, and B_2pai_2 (pai = (+)-pinanediolato) as the bis-boron reagent leads to branched-selective carboboration, though in this case yields and regioselectivities were variable (30–70% yield, 64:36–95:5 r.r.). The less common and more expensive B_2pai_2 nucleophile was employed to maximize regioselectivity, and some synthetically useful carbogenic groups were incompatible with this protocol (e.g., allyl electrophiles).[33]

To reduce this idea to practice, we examined carboboration of model terminal alkyne **1a** with two representative carbon electrophiles, allyl diethyl phosphate and methyl iodide. The former was selected because allyl electrophiles have not been previously employed in α-selective carboboration of alkynes, despite being used in several reports of linear selectivity.[30-32,34] The latter was selected because it was found to be low-yielding under previously published conditions (one example, 87:13 r.r., 32% yield).[33]

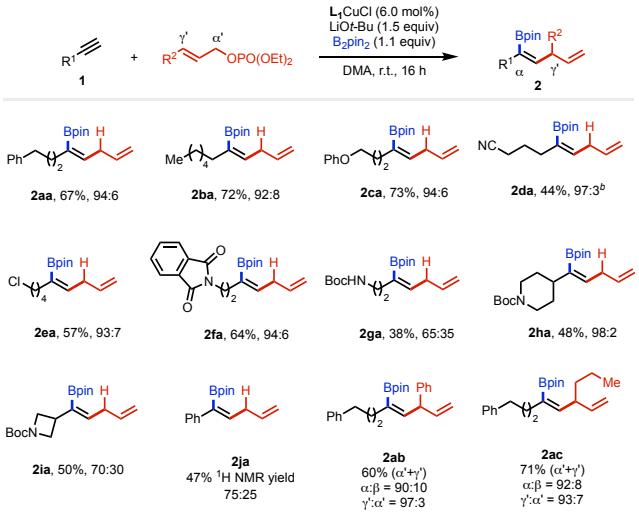
Table 1. Optimization of reaction conditions.[a]



[a]Yields of products (**2aa** or **3aa**) and regioselectivity (±2%) were determined by ^{1}H NMR spectroscopy (600 MHz) using CH_2Br_2 as the internal standard. n.d. = not determined.

A library of CAAC•CuCl precatalysts with different steric and electronic properties was tested, and a summary of the data is shown in Table 1. To our delight, ^{Et}CAAC$_5$-ligated Cu complex (**L$_1$**CuCl) promoted both transformations with high conversion and high α-selectivity. Replacement of the ethyl groups on the α-carbon of **L$_1$**[35] with either an electron-withdrawing group (**L$_2$**) [36] or more sterically bulky groups (**L$_3$**, **L$_4$**) [35,37] led to decreased yield and α:β ratio. ^{Et}CAAC$_6$ ligand (**L$_5$**), [38] a much stronger electron-donor than **L$_1$**, gave poor yields in both transformations, though high α:β ratio (84:16) was observed in the methylboration reaction. Interestingly, BiCAAC ligands,[39] $^{i\text{-}Pr}$BiCAAC (**L$_6$**) and ^{PhEt}BiCAAC (**L$_7$**), which are also strong electron-donors, furnished the desired product methylborylated product **2ad** with high α-selectivity (97 % and 92 %, respectively). But neither of them could deliver any desired allylborylated product **2aa**. Moreover, further exploration of substrate scope for methylboration using **L$_6$** suggested that this ligand could not tolerate the presence of Lewis basic functional groups. For

Table 2. Scope of α-selective allylboration of terminal alkynes.[a]



[a]Conditions: **1** (0.10 mmol), B_2pin_2 (0.11 mmol), allyl electrophile (0.30 mmol), **L$_1$**CuCl (0.006 mmol), LiO*t*-Bu (0.15 mmol) and DMA (0.60 mL), r.t. Ratios of α:β (±2) were determined via ^{1}H NMR spectroscopy (600 MHz) of the crude reaction mixtures. Percentages represent isolated yields of the α-borylated product. [b]The corresponding protoboration side product (23%) was observed by ^{1}H NMR analysis of the crude reaction mixture.

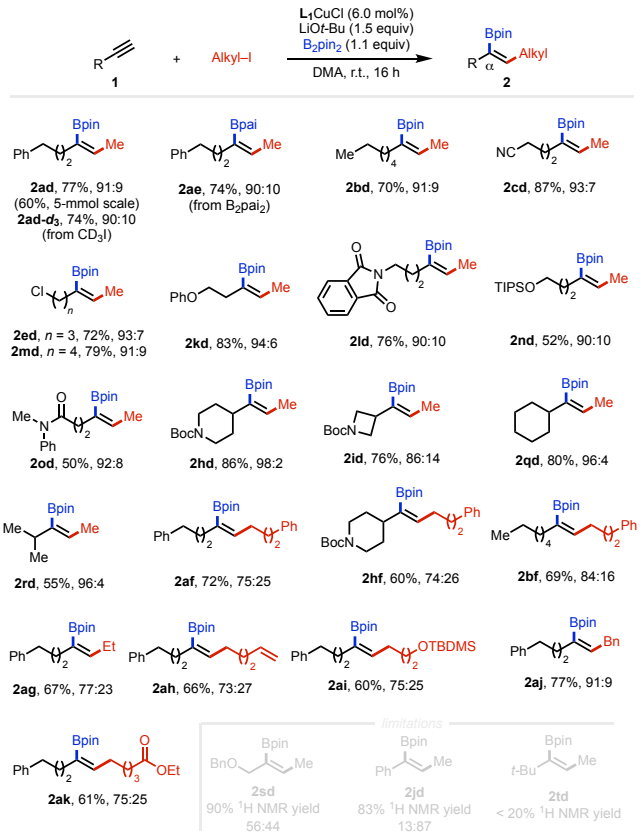
example, when an ether-containing substrate was attempted (see **2kd** below), only 23% yield and 47% α-selectivity were observed. A control experiment with IPr (**L$_8$**), a representative N-heterocyclic carbene ligand commonly used in copper–boryl chemistry,[10–13] led to low yield with both electrophiles.

With the optimized conditions in hand, we examined the scope of the allylboration reaction. Terminal alkynes bearing primary alkyl groups provided the corresponding products in excellent yields with high levels of regioselectivity (**2aa** and **2ba**). In addition, functional groups such as ether (**2ca**), cyano (**2da**), halogen (**2ea**), protected amines (**2fa** and **2ga**) and pendant piperidine (**2ha**) and azetidine (**2ia**) were well tolerated, furnishing desired products in good yields and high α-selectivity, except in the case of **2ga** and **2ia**, where moderate α-selectivity (65% and 70%, respectively) was observed. Notably, when phenylacetylene was subjected to the optimal reaction conditions, the desired product **2ja** was generated with 75% α-selectivity. Allyl electrophiles with phenyl and *n*-propyl groups substituted at γ-position were also compatible under the reaction conditions, furnishing desired products in high yields (60–71%) and excellent regioselectivity (>90% α-borylation, 93–97% S_N2' allylation) (**2ab** and **2ac**).

We next explored the scope of terminal alkynes for alkylboration. Alkynes containing different primary alkyl chains readily underwent efficient methylboration with high α-selectivity (**2ad** and **2bd**). In addition, a range of functional groups, including ether (**2kd**), chloro (**2ed**, **2md**), cyano (**2cd**), amide (**2od**) and protected amino group (**2ld**), were tolerated, furnishing the desired products in good yields and high regioselectivity. The reactions of alkynes bearing secondary alkyl groups at the α-position (**2qd** and **2rd**) gave high α-selectivity as well. However, similarly to the previous reported (CAAC)Cu-catalyzed protoboration reactions, *tert*-butyl acetylene (**2td**) has very low reactivity under the optimal conditions. Alkynes with medicinally relevant functional groups such as pendant piperidine and azetidine were both competent coupling partners (**2hd** and **2id**).

Unfortunately, poor α-selectivity was observed when benzyl protected propargyl alcohol (**2sd**) or phenylacetylene (**2jd**) were used as substrates.

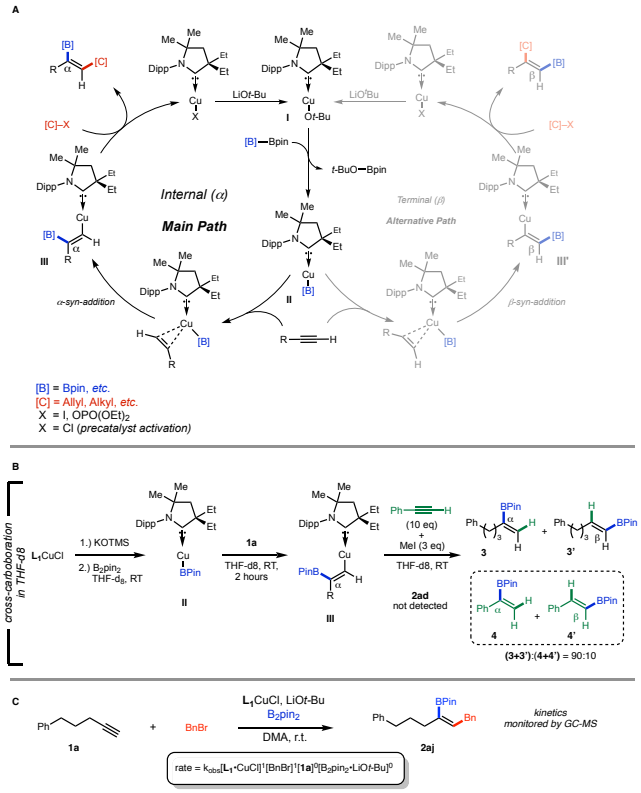
Table 3. Scope of α-selective alkylboration of terminal alkynes.[a]



[a]Conditions: **1** (0.10 mmol), B_2pin_2 (0.11 mmol), alkyl iodide (0.30 mmol), $\mathbf{L_1}$CuCl (0.006 mmol), LiO*t*-Bu (0.15 mmol) and DMA (0.60 mL), r.t. Ratios of α:β (±2) were determined via ^{1}H NMR spectroscopy (600 MHz) of the crude reaction mixtures. Percentages represent isolated yields of the α-borylated products.

We next explored the scope of the alkyl electrophile. Deuterated methyl iodide works well, showing the ability of this method to assemble specifically labelled compounds efficiently. The reactions of primary alkyl electrophiles with **1a** afforded the α-selective alkylboration products with high yield, though relatively lower α:β ratios were observed compared to the reaction using methyl iodide (**2af**, **2ag**). Notably, the alkyl electrophiles with functional groups, such as terminal alkene, silyl ether and ester, were compatible under our reaction conditions, giving 60%–66% yield and 73%–75% α-selectivity (**2ah**–**2aj**). When benzyl bromide was used as electrophile, the desired product (**2ak**) was generated in excellent yield and high α-selectivity. Similar α:β ratio was observed when an alkyne bearing secondary alkyl groups at the α-position was applied (**2hf**).

A plausible catalytic cycle for this reaction is depicted in Scheme 2A. One possible explanation for the observation that regioselectivity varies across the different C(sp^3) electrophiles tested in Table 3 is that the borylcupration step could be reversible. Under such a scenario, the nature of the C(sp^3) electrophile and the rate of C–C bond formation may influence regioselectivity. To test this hypothesis, we performed a cross-over experiment between alkyne **1a** and **1j**. In this case, we observed formation of protoboration products **3**/**3'** and **4**/**4'** in a 9:1 ratio after reacting with *in situ*-generated complex **III** in THF-d8 (Scheme 2B). In parallel we also performed kinetic studies of the reaction of alkyne **1a** and BnBr and found first order rate dependence in catalyst [$\mathbf{L_1}$•CuCl] and electrophile [BnBr], meanwhile a 0th order rate was observed from the alkyne [1a] and the borane partner [B_2pin_2•LiO*t*-Bu] (Scheme 2C). The resulting rate law would be consistent with the mechanism proposed in Scheme 2A wherein a fast and reversible borylcupration precedes the regio- and rate-determining electrophile substitution. These studies taken together support the proposed mechanism wherein a reversible borylcupration would account for the change in regioselectivity as a function of electrophile identity.



Scheme 2. Mechanistic studies.

In conclusion, we have extended our investigations of (CAAC)Cu–boryl catalysis to the three-component carboboration of terminal alkynes and have found that high levels of α-selectivity are maintained across different carbon electrophiles, including allyl electrophiles, which have not been previously employed in an α-selective reaction system. The generality of the method across different alkyne substrates offers a convenient means of preparing tri-substituted alkenylboron compounds with established utility in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was financially supported by the National Institutes of Health (5R35GM125052-04 and diversity supplement, 5R35GM125052-04S1) and an ACS PRF Doctoral New Investigator Grant (K.M.E.). This work was also supported by the U.S. Department of Energy, Office of Science, Basic Energy Sciences, Catalysis Science Program, under Award No. DE-SC0009376 (G.B.), National Science Foundation Award No. CHE-1800598 (D.B.G.), and the Agence Nationale de la Recherche Award No. ANR-19-276CE07-0017 (R.J). Thanks are due to San Diego State University for initial support of this work by a SDSU University Graduate Fellowship (S.Y.)

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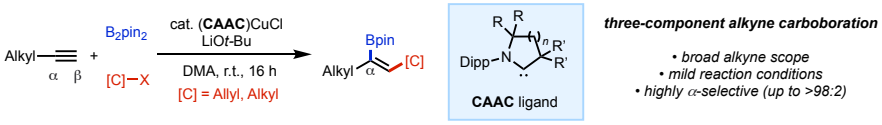
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Bpin
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R
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Dipp
N
CAAC ligand
three-component alkyne carboboration
• broad alkyne scope
• mild reaction conditions
• highly α-selective (up to >98:2)