

Ligand-Enabled, Copper-Catalyzed Regio- and Stereoselective Synthesis of Trialkylsubstituted Alkenylboronates from Unactivated Internal Alkynes

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S Supporting Information

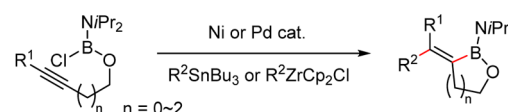
ABSTRACT: We report the first copper-catalyzed regio- and stereoselective borylalkylation of dialkylsubstituted internal alkynes with bis(pinacolato)diboron and alkyl halides. A catalytically generated borylcopper species containing a novel π -accepting N-heterocyclic carbene ligand chemoselectively reacted with unactivated internal alkynes over alkyl halides. The intermediate alkenylcopper species subsequently reacted with alkyl halides, affording the desired products. The copper catalyst differentiated steric demands between the two aliphatic substituents on the $C\equiv C$ triple bond of the alkyne substrates to exhibit high regioselectivity from a wide range of alkyne/alkyl halide combinations. This method is useful for the straightforward synthesis of trialkylsubstituted alkenylboronates, i.e., versatile precursors for tetrasubstituted alkenes containing three or four different alkyl substituents, which are difficult to synthesize by other methods.

Alkenylboronates are synthetically versatile building blocks. Despite many reports of the synthesis of alkenylboronates, regio- and stereoselective synthesis of tetrasubstituted alkenylboronates, which are useful precursors for tetrasubstituted alkenes, is particularly challenging.^{1–8} Suginome et al. reported seminal examples of the regio- and stereoselective synthesis of tetrasubstituted alkenylboronates through nickel- or palladium-catalyzed intramolecular boryl transfer to a $C\equiv C$ triple bond using substrates containing a reactive boryl moiety (Scheme 1a).¹ Soon after, palladium- and nickel-catalyzed intermolecular carboboration of alkynes was reported (Scheme 1b).^{2–4} More recently, copper-catalyzed borylalkylation of alkynes through three-component coupling with bis(pinacolato)diboron [(Bpin)₂] and alkyl halides has emerged as a powerful method to furnish tetrasubstituted alkenylboronates (Scheme 1c).^{5,6} Three main events proceeded in a well-ordered manner in this one-pot, three-component reaction: (1) generation of a borylcopper species from a copper alkoxide catalyst and (Bpin)₂; (2) regioselective borylcupration of alkynes to afford alkenylcopper intermediate **1**; and (3) alkylation of **1** with alkyl halides. To date, however, the substrate scopes of those metal-catalyzed reactions (Scheme 1b,c, previous works) have been predominantly limited to aromatic-substituted alkynes.⁷

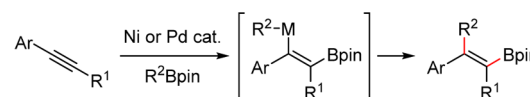
For regio- and stereoselective synthesis of tetrasubstituted alkenylboronates containing three alkyl groups, Nishihara

Scheme 1. Regio- and Stereoselective Synthesis of Tetrasubstituted Alkenylboronates

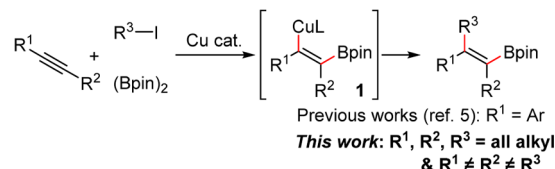
(a) Carboboration of alkynes via intramolecular boryl transfer



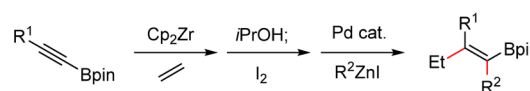
(b) Intermolecular carboboration of aryl alkynes



(c) Copper-catalyzed three-component coupling



(d) Previous synthesis of trialkylsubstituted alkenylboronates



developed a zirconium-mediated stepwise C–C bond formation to alkylsubstituted alkynylboronates (Scheme 1d, R¹ = alkyl).^{8a,c} This method requires multiple steps, however, including regioselective zirconacycle formation, selective protonolysis of an sp³ carbon–metal bond, alkenyl iodide formation, and a Negishi coupling reaction.^{8,9} Here we report the first straightforward synthesis of tetrasubstituted alkenylboronates containing three different alkyl groups by copper-catalyzed regio- and stereoselective borylalkylation of unactivated, dialkylsubstituted internal alkynes (Scheme 1c, this work).

Two main hurdles must be overcome to achieve a copper-catalyzed three-component coupling reaction with dialkylsubstituted alkynes, (Bpin)₂, and alkyl halides: chemo- and regioselectivity. The borylcopper species must chemoselectively react with alkynes in the presence of alkyl halides, but the

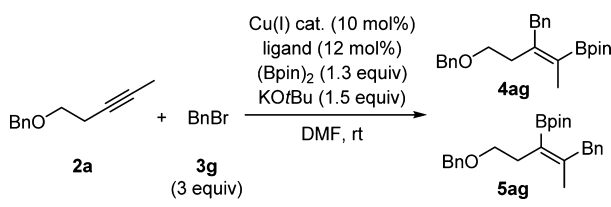
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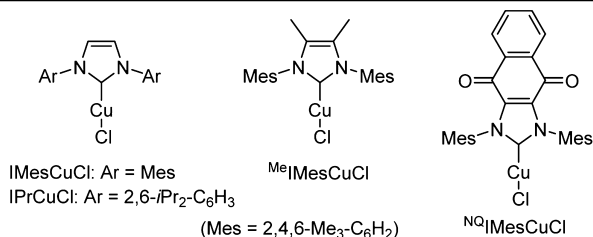
differentiation between the two electrophiles is more difficult in the reaction using dialkylsubstituted unactivated alkynes than when using reactive aromatic-substituted alkynes. Moreover, regioselective borylcupration of electronically unbiased dialkylsubstituted internal alkynes is very difficult to achieve.¹⁰ We envisioned that these two hurdles could be overcome by identifying a proper ligand for the copper catalyst, based on the previous development of ligand-dependent, copper-catalyzed regiodivergent borylalkylation,¹¹ borylamination,¹² and boryloxygenation¹³ of alkenes.

Thus, we began our study by focusing on the ligand effects in the reaction with dialkylsubstituted alkyne **2a**, (Bpin)₂, and benzyl bromide (**3g**) (Table 1). Phosphine ligands were

Table 1. Optimization of Copper-Catalyzed Regioselective Borylalkylation of **2a^a**



entry	Cu(I) cat.	ligand	yield (%) ^b	r.r.
1	CuCl	dppe	3	2.5 : 1
2	CuCl	dppbz	4	1.5 : 1
3	CuCl	Xantphos	1	>20 : 1
4	IMesCuCl	–	15	7.9 : 1
5	IPrCuCl	–	10	2.6 : 1
6	NQIMesCuCl	–	74 (72)	13 : 1
7	MeIMesCuCl	–	12	5.5 : 1
8 ^c	NQIMesCuCl	–	100 (90)	10 : 1



^aGeneral reaction conditions: **2a** (0.10 mmol), **3g** (3 equiv), Cu(I) catalyst (10 mol %), ligand (12 mol %), (Bpin)₂ (1.3 equiv), and KOtBu (1.5 equiv) in DMF (0.5 mL) at rt for 4 h. Yield and r.r. (**4ag**:**5ag**) were determined by ¹H NMR analysis of a crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. ^bCombined yield of **4ag** and **5ag**. Combined isolated yield is shown in parentheses (entries 6 and 8). ^cButyl iodide (**3a**) was used instead of **3g**. Combined yield of **4aa** and **5aa** and r.r. (**4aa**:**5aa**) are shown.

ineffective for the reaction (entries 1–3). In contrast, an N-heterocyclic carbene (NHC)-copper catalyst, IMesCuCl, exhibited potential reactivity and regioselectivity (15% yield, regioisomeric ratio (r.r.) = 7.9:1, entry 4). Use of a bulkier NHC-copper catalyst, IPrCuCl, decreased the regioselectivity (r.r. = 2.6:1, entry 5). This tendency to decrease regioselectivity is likely due to destabilization of the reaction pathway to generate intermediate **1** (R¹ = BnO(CH₂)₂, R² = Me), where the sterically more hindered carbon atom is attached to the copper atom when the ligand is sterically demanding.¹⁴ The low yield in entries 1–5 was due to the lack of chemoselectivity; significant amounts (50–62% based on (Bpin)₂) of BnBpin were generated as a side product through the reaction of borylcopper with benzyl bromide (**3g**), rather than with

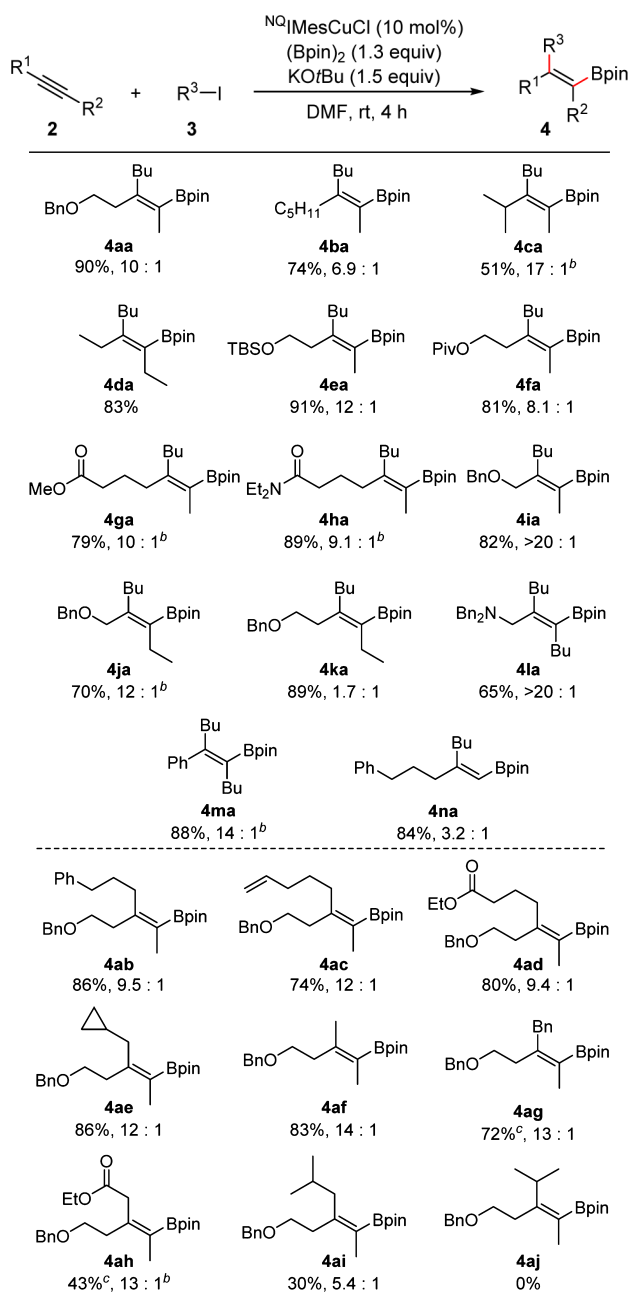
alkyne **2a**. We hypothesized that a π -accepting NHC-copper catalyst would exhibit increased affinity toward the π -electrons of alkynes,¹⁵ leading to chemoselective promotion of the desired borylcupration of **2a**, rather than undesired borylation of **3g**. As expected, use of a π -accepting naphthoquinone-conjugated NHC-copper catalyst, NQIMesCuCl,¹⁶ dramatically improved both the yield and regioselectivity (74% yield, r.r. = 13:1, entry 6) while markedly suppressing the undesired BnBpin generation (18%). In contrast, use of a simple methyl-substituted NHC-copper catalyst, MeIMesCuCl, as a control provided almost the same yield of borylalkylation products (12%, entry 7) as IMesCuCl (entry 4). When a less reactive alkylating reagent, BuI (**3a**), was used instead of BnBr (**3g**), product **4aa** was obtained in quantitative yield with high regioselectivity under the optimized conditions using the NQIMesCuCl catalyst (r.r. = 10:1, entry 8).

With the optimized conditions in hand, we next examined the substrate scope of this three-component coupling reaction (Table 2). A nonfunctionalized simple alkyne, 2-octyne (**2b**), afforded a synthetically useful yield and regioselectivity (**4ba**, 74% yield, r.r. = 6.9:1). A larger difference in the steric demand between two alkyl substituents on the C≡C triple bond (**2c**) led to increased regioselectivity (**4ca**, 17:1). The reaction proceeded without any difficulties with 3-hexyne (**2d**) bearing two symmetric ethyl substituents (**4da**). Silyl ether (**2e**), ester (**2f** and **2g**), and amide (**2h**) functionalities were tolerated, and the products were obtained in high yield and regioselectivity (**4ea**, **4fa**, **4ga**, and **4ha**). In the cases of propargyl ethers **2i** and **2j** and propargyl amine **2l**, the alkylation proceeded predominantly at the proximate carbons to the hetero atoms, independent of the steric bulkiness of the substituents on the C≡C triple bonds (**4ia**, **4ja**, and **4la**). In homopropargyl ether **2k**, however, the directing effect of the heteroatom was not operative (**4ka**, 1.7:1). For alkyl-aromatic-disubstituted internal alkyne **2m**, the alkylation proceeded predominantly at the benzylic position (**4ma**). Terminal alkyne **2n** afforded a trisubstituted alkenyl boronate **4na** in high yield, albeit with moderate regioselectivity (3.2:1).

The scope of alkyl halides was also broad. Unactivated alkyl iodide **3b** afforded **4ab** in high yield and regioselectivity. The C=C double bond (**3c**) and ester (**3d**) functionalities in the alkylation reagents were compatible with the reaction conditions. The reaction using (iodomethyl)cyclopropane (**3e**) solely produced the desired borylalkylation product **4ae** and no ring-opening product, indicating that the alkylation step from alkenylcopper species **1** proceeds through a nonradical process.¹⁷ Using highly reactive methyl iodide (**3f**) as an alkylating reagent, **4af** was obtained in high yield and regioselectivity when **3f** was added dropwise over 1 h. For introduction of other activated alkyl groups, such as benzyl and ethoxycarbonylmethyl groups, use of the corresponding alkyl bromides produced a higher yield (**4ag** and **4ah**). Sterically congested isobutyl iodide (**3i**) gave **4ai** in moderate yield and regioselectivity. A secondary alkyl iodide, isopropyl iodide (**3j**), was considerably unreactive, and the desired product was not obtained.

To demonstrate that the products are versatile precursors to tetrasubstituted alkenes, we conducted Suzuki–Miyaura coupling of **4ia** with iodobenzene and 1-bromododecane (Scheme 2). Tetrasubstituted alkenes **6** and **7**, containing three and four different alkyl substituents, respectively, were stereoselectively obtained in high yield. Therefore, the two-step sequence, i.e., copper-catalyzed regio- and stereoselective

Table 2. Scope of Copper-Catalyzed Regioselective Borylalkylation of Dialkylsubstituted Internal Alkynes^a

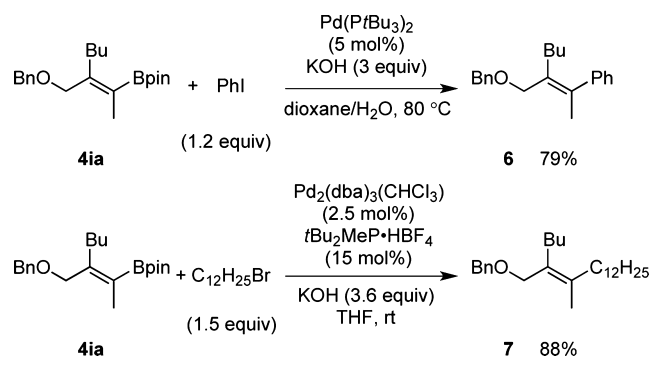


^aGeneral reaction conditions: **2** (0.20 mmol), **3** (3 equiv), ^{NQ}IMesCuCl (10 mol%), (Bpin)₂ (1.3 equiv), and KOtBu (1.5 equiv) in DMF (1.0 mL) at rt for 4 h. Combined isolated yield of **4** and **5** and r.r. (**4**:**5**) are shown. Regioisomeric ratio was determined by ¹H NMR analysis of a crude mixture. ^bRegioisomeric ratio was determined after isolation. ^cCorresponding alkyl bromides were used instead of alkyl iodides.

borylalkylation, followed by Suzuki–Miyaura coupling, is a useful method for the straightforward synthesis of tetrasubstituted alkenes containing three or four different alkyl substituents, which are difficult to synthesize by other methods.^{8a,18}

In conclusion, we developed the first straightforward catalytic method for regio- and stereoselective synthesis of trialkylsubstituted alkenylboronates, versatile precursors for tetrasubstituted alkenes containing three or four different alkyl groups. This group of alkenes comprises useful building blocks for

Scheme 2. Synthesis of Tetrasubstituted Alkenes Containing Three or Four Alkyl Substituents



organic synthesis, but their efficient and concise synthesis has remained challenging. The π -accepting ability of the ^{NQ}IMes ligand on the copper(I) catalyst was found to be essential for controlling the high regio- and chemoselectivity in the three-component, one-pot borylalkylation process of dialkylsubstituted internal alkynes with (Bpin)₂ and alkyl halides. Studies are in progress to elucidate the origin of the high selectivity exhibited by the π -accepting NHC ligand in copper(I) chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04646.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Consistent with this explanation, regioselectivity decreased according to the decreased steric demand of boronates. When less bulky bis[(-)-pinanediolato]diboron and bis(hexylene glycolato) diboron were used instead of (Bpin)₂, regioselectivity decreased to 5.9:1 and 1:1.5, respectively, using a ^{NQ}IMesCuCl catalyst (cf. 10:1 with (Bpin)₂, see Table 1, entry 8).

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