Origins of Internal Regioselectivity in Copper-Catalyzed Borylation of Terminal Alkynes

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SUMMARY

Installation of a boron functionality into a more substituted carbon of terminal alkynes has been a challenging issue in chemical synthesis, since inherently Lewis acidic boron moieties, in principle, favor their attachment to a terminal carbon. Herein, we report on the highly internal-selective borylation of terminal alkynes under copper catalysis, wherein diminishment of boron-Lewis acidity and ligand-derived steric bulk around a copper center are the key to the success. In particular, the use of an anthranilamide-substituted boron moiety [B(aam)] is of high synthetic significance, because its properly diminished Lewis acidity enabled the internal regioselectivity and the Suzuki–Miyaura cross-coupling activity to be compatibly achieved. This method provided direct and universal approach to variously substituted branched alkenylboron compounds, regardless of electronic and steric properties of a substituent on terminal alkynes.

INTRODUCTION

In view of the established synthetic significance of organoboron compounds,[1] which serve as essential carbon nucleophiles, endowed with appealing features such as excellent functional group compatibility and high practicality, for undergoing various carbon–carbon and carbon–heteroatom bond-forming reactions, search for effective and reliable borylation reactions has continued to be an important subject in chemical synthesis.[2,3] In this regard, the last decade has experienced remarkable progress in borylation reactions especially with copper catalysis,[3–5] where borylcopper species generated by σ-bond metathesis with diborons have been the mainstay; their versatility has sufficiently been demonstrated by a variety of borylative addition and substitution reactions (Figure 1A). Of particular interest are three-component borylation reactions with alkynes, which provide convenient and direct access to alkenylboron compounds of structural diversity through capturing intermediary *vic*-boryl-substituted alkenylcopper species with suitable electrophiles (Figure 1B).[6–14] Since the addition of borylcopper species across alkynes (borylcupration) generally proceeds in a *syn* stereoselective fashion, and moreover the stereoretentive capture of boryl-substituted alkenylcopper species basically occurs with electrophiles, the most fundamental issue in the copper-catalyzed borylations of alkynes for synthesizing finely stereodefined alkenylboron compounds would be regioselectivity in the borylcupration step.

A: Cu-catalyzed borylative addition and substitution reactions
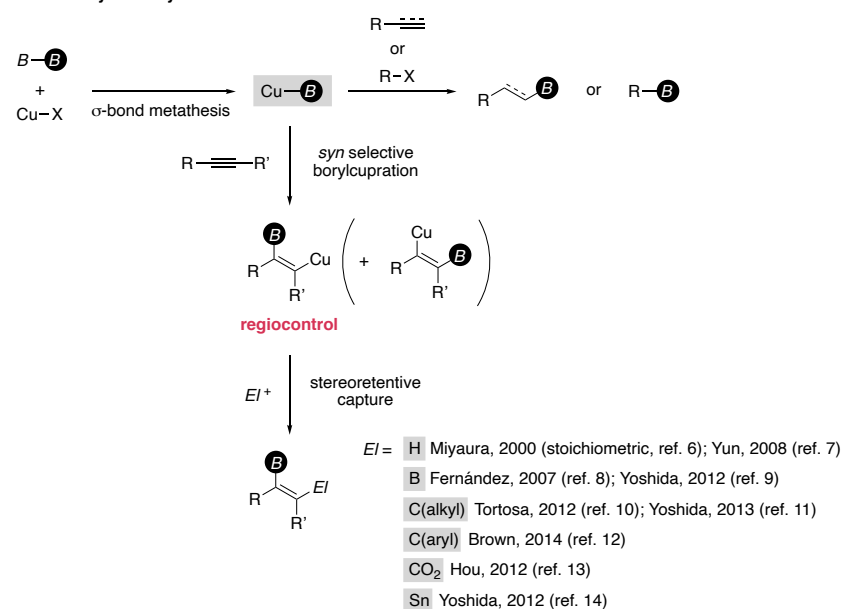
B: Cu-catalyzed three-component borylation reactions of alkynes

Figure 1. Cu-catalyzed borylation reactions with diborons

(A) Cu-catalyzed borylative addition and substitution reactions.

(B) Cu-catalyzed three-component borylation of alkynes, *El*, electrophile.

Internal/terminal selectivity with terminal alkynes is the typical instance of the regioselectivity, in which a boron functionality is installed into a more/less substituted carbon to give branched or linear alkenylboron compounds, respectively. The addition of the most frequently used pinacolborylcopper species [Cu–B(pin)],[15] formed from (pin)B–B(pin), tend to occur with terminal selectivity (Figure 2),[7,10,13,14,16–25] being quite similar to that observed in the conventional borylation reactions including hydroboration (*anti*-Markovnikov selectivity),[26–28] haloboration,[29] etc., where a Lewis acidic boron center is attached to a less substituted carbon via preferential formation of a more stable alkenyl cationic transition state. These results imply that one of critical factors determining the terminal selectivity in the borylcupration should also be the inherent boron-Lewis acidity, and hence development of internal-selective borylcupration of terminal alkynes, which opens up a potent approach to underexplored copper-catalyzed borylation reactions, has been a challenging issue. In such circumstances, pioneering works on copper-catalyzed Markovnikov selective hydroboration with (pin)B–B(pin) were reported by Hoveyda (2011)[30] and Carretero (2013),[31] where terminal alkynes having a heteroatom functionality at the propargylic position efficiently accepted the internal-selective borylcupration with an *N*-aryl-substituted NHC or *t*-Bu₃P as a ligand (Figure 3A). Although electron-deficient and -neutral aryl alkynes were also found to be smoothly convertible into branched alkenylboron compounds by the copper-catalyzed hydroboration with the Hoveyda's system or with an NHC-capped cyclodextrin ligand (Roland and Sollogoub, 2017)[32] (Figure 3A), the use of electron-rich aryl alkynes and aliphatic alkynes without the electronic bias exerted by the propargylic heteroatom in these methods resulted in significantly poor regiocontrol (Figure 3B), which clearly shows the difficulty in achieving the universal internal-selective borylcupration with commonly used (pin)B–B(pin). On the other hand, we have disclosed that the universal internal-selective borylcupration became feasible by employing an unsymmetrical diboron, (pin)B–B(dan) (dan = naphthalene-1,8-diaminato),[33] in which the B(dan) moiety was

exclusively attachable to an internal carbon, irrespective of electronic and steric factors of a substituent on terminal alkynes (Figure 4).[34,35] Considering that the Lewis acidity of the B(dan) moiety is strongly diminished as compared with that of the B(pin) moiety,[36] the successful internal selectivity may be ascribable to the boron-Lewis acidity diminishment, however validity of this assumption remains to be fully investigated. In addition, from a standpoint of boron-based synthetic transformations, the drawback of using the Lewis acidity-diminished B(dan) is that the C(alkenyl)–B(dan) bonds are directly unusable for alkenyl–carbon (or heteroatom) bond-forming reactions such as the Suzuki–Miyaura coupling (SMC) under standard conditions, thus needing prior deprotection of the dan moiety.[37–39] Herein we report on origins of the internal-selective borylcupration based upon systematic investigations with some boron groups of modified Lewis acidity, leading to an effective solution to a dilemma between the internal selectivity and the activity toward direct SMC by use of a B(aam) group (aam = anthranilamidato).[40]
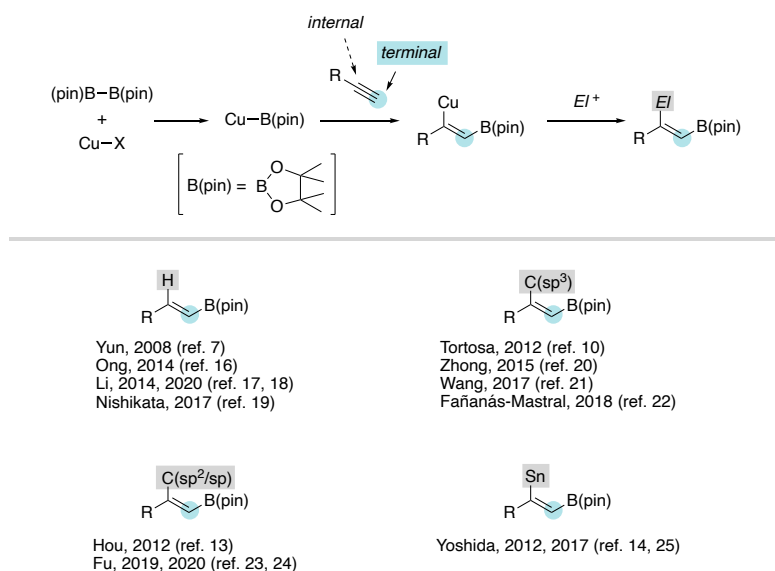

Figure 2. Cu-catalyzed terminal-selective borylation reactions of terminal alkynes with (pin)B–B(pin)
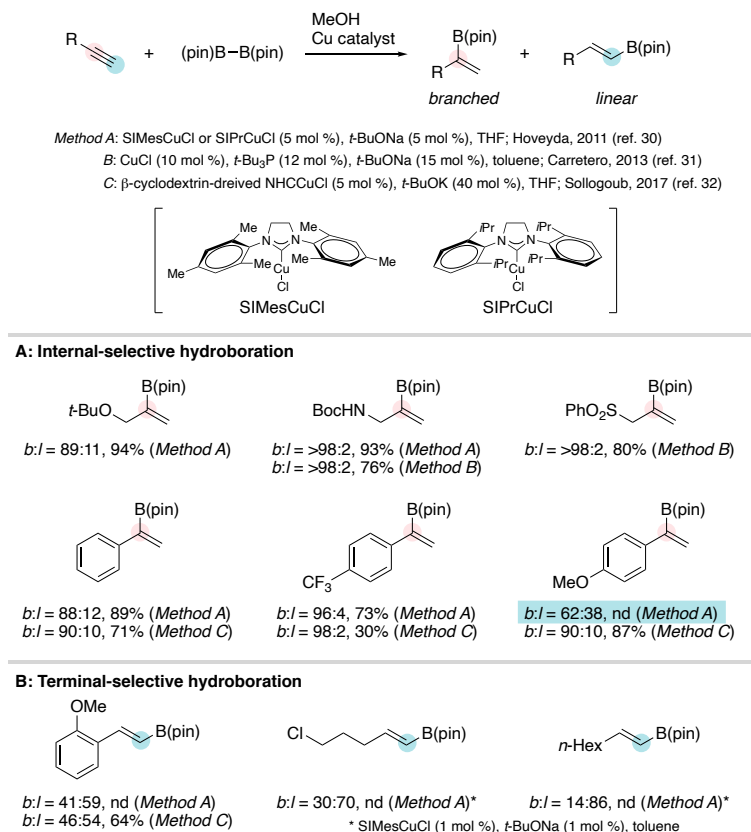
Figure 3. Regioselectivities in Cu-catalyzed hydroboration of terminal alkynes with (pin)B–B(pin)

(A) Internal-selective hydroboration.
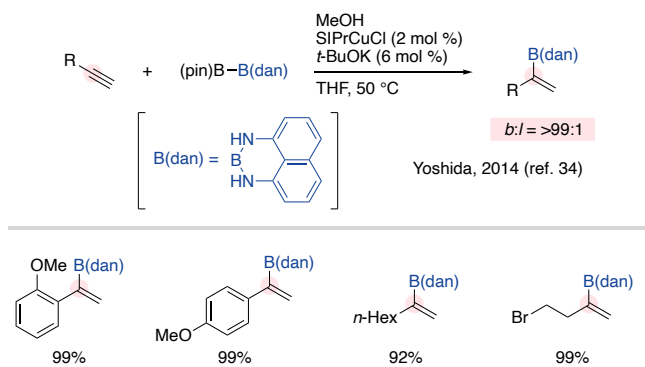(B) Terminal-selective hydroboration.

Figure 4. Cu-catalyzed internal-selective hydroboration of terminal alkynes with (pin)B–B(dan)

RESULTS AND DISCUSSION

We initially carried out the reaction of an electronically unbiased aliphatic alkyne, 1-octyne (**1a**), with diborons of varied Lewis acidity and methanol using SIPrCuCl as a catalyst (Figure 5); the use of (pin)B–B(pin) (**2a**) resulted in the terminal-selective installation of the Lewis acidic B(pin) moiety, as was the case with the Hoveyda's system,[30] giving a linear alkenylboron compound (**3'aa**) preferentially (branched:linear

= 12:88, 62%). In stark contrast, the copper-catalyzed hydroboration with Lewis acidity-diminished B(dan) [(pin)B–B(dan) (**2b**)] or B(aam) [(pin)B–B(aam) (**2c**)][41] proceeded with internal-selectivity to afford **3ab** (b:l = >99:1, 92%)[34] or **3ac** (b:l = 89:11, 91%), which strongly implies that the boron-Lewis acidity diminshment is the key to achieving the internal-selectivity. Furthermore, it should be noted that the regioselectivity of the borylcupration correlates closely with the degree of the diminishment, which can be qualitatively determined by theoretical calculation-based FIA (Fluoride Ion Affinity).[42,43] The calculated FIA, by means of Ph–BX$_2$ as model compounds, showed somewhat increased Lewis acidity of the B(aam) moiety (FIA = 236 kJ/mol), bearing a less donative amide substituent, in comparison to the B(dan) moiety (FIA = 216 kJ/mol), which is in good accordance with its higher hydrolyzablity,[40,44] and the results clearly demonstrates that the stronger boron-Lewis acidity [B(pin) ≫ B(aam) > B(dan)] is, the lower internal-selectivity becomes. This regiochemical tendency was further confirmed by the reaction of a new diboron [(pin)B–B(mdan) (**2d**), mdan = N,N'-dimethyl-naphthalene-1,8-diaminato], in which the B(mdan) moiety of sufficiently diminished Lewis acidity (FIA = 229 kJ/mol) provided **3ad** (b:l = >99:1, 64%) with perfect internal-selectivity. Despite its widely accepted Lewis acidic character of the B(pin) moiety as is evident from the chemoselectivity in the σ-bond metathesis between (pin)B–B(dan/aam/mdan) and a Cu–X (see Figure 9A below), and from the significantly higher reactivitity in SMC (transmetalation),[33,36] sterically encumbered complexation of a fluoride ion and Ph–B(pin) resulted in the decreased FIA (197 kJ/mol), which may lead to underestimation of the real B(pin)-Lewis acidity.[45,46]
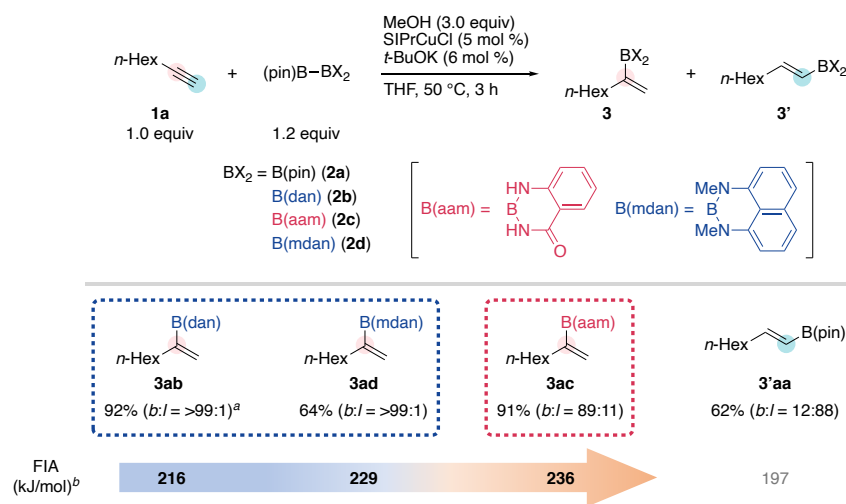

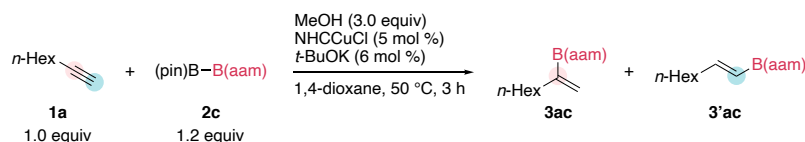**Figure 5. Regioselectivities in Cu-catalyzed hydroboration of 1-octyne with diborons of varied Lewis acidity**

Standard conditions: 1-octyne **1a** (1.0 equiv), diboron **2** (1.2 equiv), MeOH (3.0 equiv), SIPrCuCl (5 mol %), t-BuOK (6 mol %), THF (0.5 mL), 50 °C, 3 h; NMR yield; regioisomeric ratios (b:l) were determined by ^{1}H NMR spectroscopy of the crude reaction mixture; only the major regioisomer was drawn.
[a]SIPrCuCl (2 mol %); Isolated yield.
[b]DFT calculations were carried out at the B3LYP/6-31+G(d,p) level.

In addition to the boron-Lewis acidity, steric properties of a ligand on a copper center turned out to affect the regioselectivity significantly (Figure 6); treatment of **1a** and **2c** in an optimum solvent (1,4-dioxane) by employing sterically less hindered IMesCuCl (%V_{bur} = 38.1)[47] led to the formation of **3'ac** as the major product (b:l = 40:60, 42%), whereas the reaction with IPrCuCl (%V_{bur} = 48.5) took place with similar internal-

selectivity (b:l = 88:12, 84%) to that with sterically comparable SIPrCuCl (%V_{bur} = 50.1, b:l = 91:9, 92%). Finally, perfect internal-selectivity in the B(aam)-installing hydroboration was achieved with sterically more hindered six-membered 6DippCuCl (%V_{bur} = 53.4) to give **3ac** in 96% yield. These results obtained by the use of various diborons and ligands clearly show that key factors governing the internal regioselectivity in the borylcupration of terminal alkynes are the diminishment of boron-Lewis acidity and the ligand-derived steric bulk around a copper center. Although the reaction with sterically less bulky Cl-substituted IPr (%V_{bur} = 47.1) also led to the sole formation of **3ac** in a lower yield, ligand electronic effects on the regioselectivity remain to be elusidated.

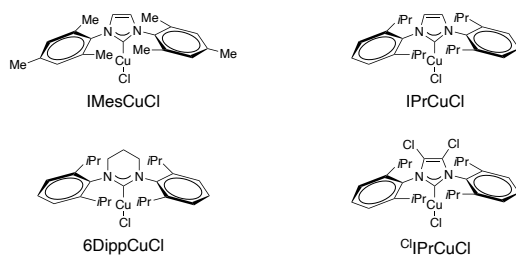| NHCCuCl	%V_{bur}	NMR yield (%)	b:l
IMesCuCl	38.1	42	40:60
IPrCuCl	48.5	84	88:12
SIPrCuCl	50.1	92	91:9
6DippCuCl	53.4	96	>99:1
ClIPrCuCl	47.1	77	>99:1

Figure 6. Regioselectivities in Cu-catalyzed hydroboration of 1-octyne with (pin)B–B(aam) by use of various NHC ligands

The exclusive attachment of a boron functionality to an internal carbon of terminal alkynes with the B(aam) would be of high synthetic value, since its slightly residual Lewis acidity enables the resulting branched alkenyl–B(aam) to be directly utilized for SMC under standard conditions with a weak base (K₃PO₄),[48] being in marked contrast to the cases with the B(dan) that needs acidic deprotection[36,37,49] or activation by strongly basic t-BuOK.[38,39] Thus, with the optimized reaction conditions using 6DippCuCl, the substrate scope of the internal-selective hydroboration was investigated (Figure 7). A variety of electronically unbiased aliphatic alkynes including 1-hexyne (**1b**), 1-docecyne (**1c**), 4-methyl-1-pentyne (**1d**), and cyclopentylacetylene (**1e**) were smoothly convertible into the respective branched alkenyl–B(aam) (**3bc**–**3ec**) with perfect internal-selectivity, and a high yield of *gem*-boryl(silyl)ethene (**3fc**) was produced from trimethylsilylacetylene (**1f**). In contrast to the previous B(pin)-installing hydroboration, which required a heteroatom functionality at a propargylic position for the internal-selectivity,[30,31] the present method universally allowed more remote position-functionalized terminal alkynes (**1g**–**1k**) to accept the B(aam)-installation solely at their internal carbon with demonstrating the high functional group compatibility. Besides the successful transformation of phenylacetylene (**1l**) or 4-bromophenylacetylene (**1m**), it is noteworthy that even MeO-substituted electron-rich

aryl alkynes (**1n** and **1o**), which only gave a mixture of isomers with poor regiocontrol under the B(pin)-installing conditions,[30,32] underwent the internal-selective hydroboration to afford **3nc** and **3oc** in ≧95% regioselectivity.
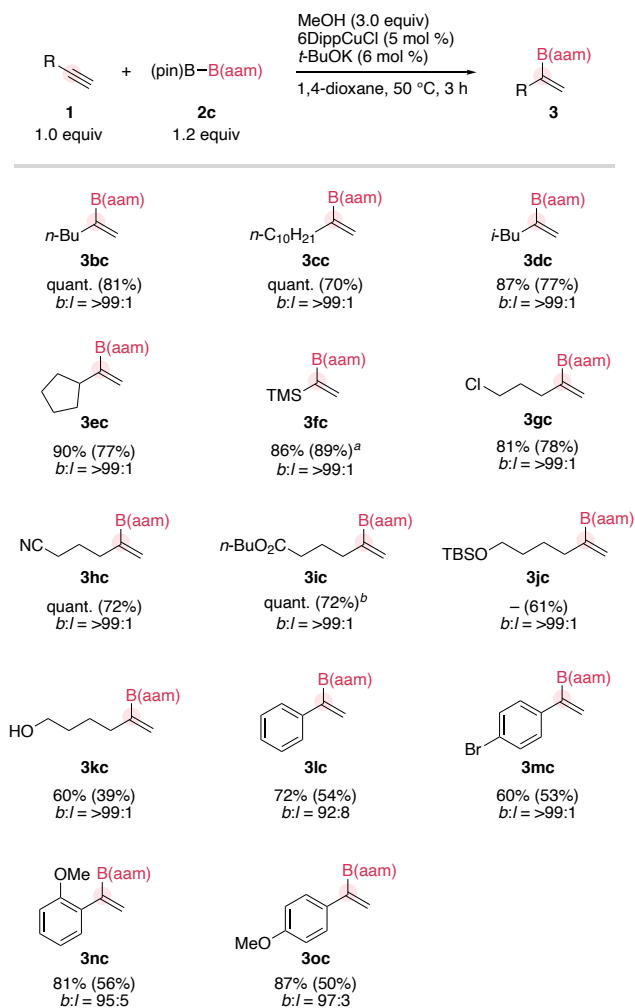

Figure 7. Cu-catalyzed internal-selective hydroboration of various terminal alkynes with (pin)B–B(aam)

Standard conditions: terminal alkyne **1** (1.0 equiv), (pin)–B(aam) **2c** (1.2 equiv), MeOH (3.0 equiv), 6DippCuCl (5 mol %), *t*-BuOK (6 mol %), 1,4-dioxane (0.5 mL), 50 °C, 3 h; NMR yield (Isolated yield); regioisomeric ratios (*b:l*) were determined by ^{1}H NMR spectroscopy of the crude reaction mixture; only the major regioisomer was drawn.
[a]24 h.
[b]*n*-BuOH was used instead of MeOH.

Synthetic versatility of the present borylation was further enhanced by a combination of direct SMC at generated alkenyl–B(aam) bonds conducted in one-pot (Figure 8); *gem*-boryl(silyl)ethene (**3fc**) produced from **1f** and **2c** underwent sequential SMC with 4-bromobiphenyl without isolation to provide aryl(silyl)ethene (**4a**) in total 51% yield. Moreover, a two-step total synthesis of *iso*-Combretastatin A4 (**4b**), a highly promising cytotoxic and antitubulin agent,[50,51] was also achieved depending upon the procedure by using 3,4,5-trimethoxyphenylacetylene (**1p**) and 3-HO-4-MeO-bromobenzene.
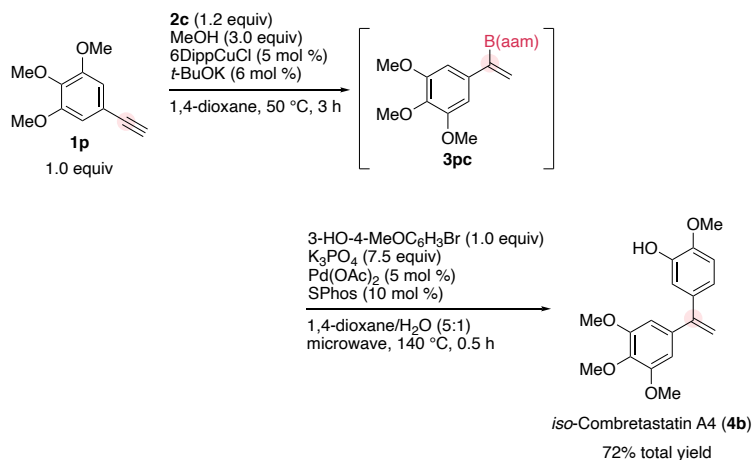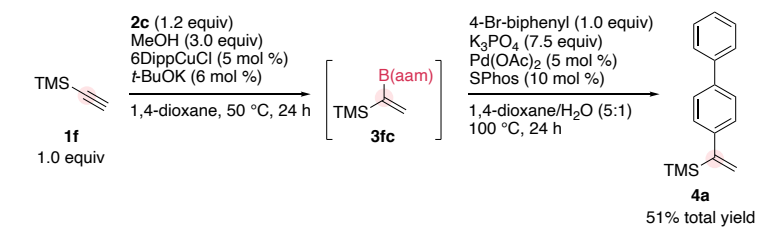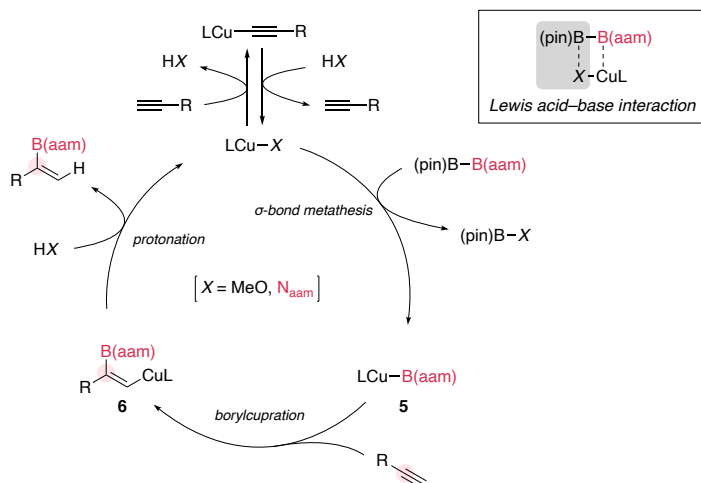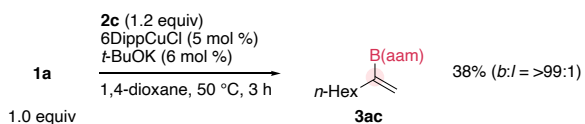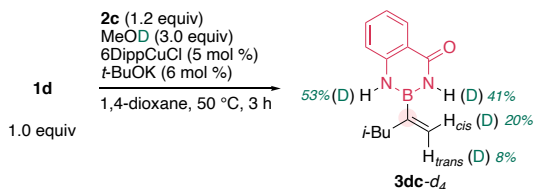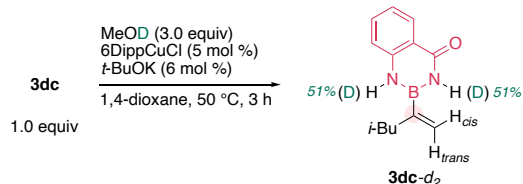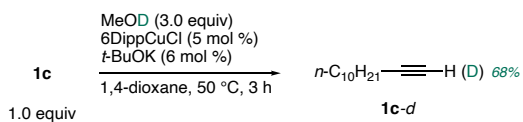
Figure 8. One pot sequential internal-selective hydroboration–Suzuki–Miyaura cross-coupling

A catalytic cycle of the B(aam)-installing hydroboration would be similar to that of the well-established hydroboration with (pin)B–B(pin) (**2a**),[3–5] and thus chemoselective formation of a Cu–B(aam) species (**5**), which obviously implies that the B(pin) moiety of **2c** is more Lewis acidic, triggers the reaction (Figure 9A). On the other hand, the NH moieties of the B(aam) were found to serve as a proton source for capturing an alkenylcopper intermediate (**6**) by the result that **3ac** was produced even in the absence of MeOH under highly dehydrated conditions (the water content of 1,4-dioxane was determined to be 5×10^{-4} wt% by Karl Fischer titration) (Figure 9B). In addition, the reactions with methanol-*d* (MeOD) offered further insights into the reaction pathway; treatment of **1d** with **2c** in the presence of MeOD resulted in deuterium-incorporation into both of the alkenyl–H*cis/trans* moieties as well as into the N–H moieties (Figure 9C). Among these, the N–H moieties proved to be readily exchangeable for N–D by the reaction of isolated **3dc** with MeOD under the copper catalysis, while the alkenyl–H*cis/trans* moieties totally remained unchanged (Figure 9D). These results in conjunction with copper-catalyzed smooth H–D exchange at the alkynyl–H of **1c** (Figure 9E) illustrate that the alkenyl–D*trans* of **3dc**-*d4* would derive from *in situ*-generated 4-methyl-1-pentyne-*d* (**1d**-*d*).

A: Plausible catalytic cycle

B: Hydroboration in the absence of MeOH

1a 1.0 equiv

2c (1.2 equiv)
6DippCuCl (5 mol %)
t-BuOK (6 mol %)
1,4-dioxane, 50 °C, 3 h

3ac 38% (*b:l* = >99:1)

C: Hydroboration in the presence of MeOD

1d 1.0 equiv

2c (1.2 equiv)
MeOD (3.0 equiv)
6DippCuCl (5 mol %)
t-BuOK (6 mol %)
1,4-dioxane, 50 °C, 3 h

3dc-*d₄*
53% (D) H ... H (D) 41%
H*cis* (D) 20%
H*trans* (D) 8%

D: Treatment of 3dc with MeOD

3dc 1.0 equiv

MeOD (3.0 equiv)
6DippCuCl (5 mol %)
t-BuOK (6 mol %)
1,4-dioxane, 50 °C, 3 h

3dc-*d₂*
51% (D) H ... H (D) 51%

E: Treatment of 1c with MeOD

1c 1.0 equiv

MeOD (3.0 equiv)
6DippCuCl (5 mol %)
t-BuOK (6 mol %)
1,4-dioxane, 50 °C, 3 h

n-C₁₀H₂₁——H (D) 68%

1c-*d*

Figure 9. Mechanistic studies on a catalytic cycle

(A) Plausible catalytic cycle.
(B) Hydroboration in the absence of MeOH.
(C) Hydroboration in the presence of MeOD.
(D) Treatment of hydroboration product **3dc** with MeOD.
(E) Treatment of terminal alkyne **1c** with MeOD.

Conclusions

We have disclosed that the key factors governing internal-selective borylcupration of terminal alkynes are diminishment of boron-Lewis acidity and ligand (NHC)-derived steric bulk around a copper center. The system provides us a universal way of transforming diverse terminal alkynes, irrespective of substituent nature, into branched alkenylboron compounds catalytically with almost perfect regiocontrol, which cannot be accomplished by a commonly used B(pin) moiety. The characteristic feature of the B(aam) moiety to be installed is slightly residual Lewis acidity that allows its direct use for SMC under standard conditions, and thus this was applied to the two-step total synthesis of biologically active *iso*-Combretastatin A4 conducted all in one-pot. In view of versatility of the boryl-substituted alkenylcopper intermediate, which can be captured by various electrophiles, the present results would open new avenues for catalytic borylations with rare regioselectivity.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact
Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Hiroto Yoshida (yhiroto@hiroshima-u.ac.jp).

Materials availability
This study did not generate new unique reagents.

Data and code availability
Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under reference numbers CCDC: 2085995 and 2085996. These data can be obtained free of charge from CCDC at http://www.ccdc.cam.ac.uk/data_request/cif.

Full experimental procedures are provided in the Supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

T.T. and H.Y. designed and analyzed all experiments. T.T. performed all experiments. H.T. conducted DFT calculations. K.N. conducted X-ray crystallographic analysis. M.N. provided advice for DFT calculations. H.Y. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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