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Synthesis of (*Z*)-alkenyl boronates via a copper(I)-catalyzed linear-selective alkylboration of terminal allenes†

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A copper(I)-catalyzed intermolecular alkylboration of terminal allenes using unactivated alkyl iodides as the carbon electrophiles is reported. The regio- and stereochemistry of the product, (*Z*)-alkenyl boronate, could be constructed without the need to introduce directing groups. A wide range of terminal allenes substituted with *prim-*, *sec-* and *tert-*alkyl groups as well as heteroatoms are suitable for this reaction. Furthermore, the product can be used for the stereoselective synthesis of multi-substituted alkenes via Suzuki–Miyaura cross-coupling reactions. We also demonstrate the formal total synthesis of the marine natural product schizol A by means of the alkylboration of a terminal allene as the key step for the construction of the alkene moiety bearing two alkyl groups in a *cis* orientation. The direct precursor of schizol A was obtained with perfect stereoselectivity.
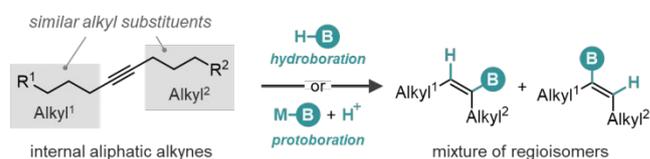
Introduction

Alkenyl boronates are valuable and widely used organometallic reagents owing to the high stereospecificity in their derivatization reactions such as the Suzuki–Miyaura cross-coupling reaction.[1-3] Therefore, the stereoselective synthesis of multi-substituted alkenyl boronates is an important subject. In the context of synthesizing multi-substituted olefins such as the styrene and diene derivatives shown in Scheme 1a, (*Z*)-alkenyl boronates are useful and intuitive precursors for the sterically congested *cis*-alkene moiety.[2,4] However, the synthesis of alkenyl boronates that have similar alkyl substituents (Alkyl[1] and Alkyl[2]) is much more difficult, despite their structural simplicity (Scheme 1b).[2,5] Although catalytic and non-catalytic hydroboration and protoboration of internal alkynes are straightforward and practical ways to access internal alkenyl boronates,[6] these reactions potentially generate products with low regioselectivity unless directing groups such as propargylic heteroatoms are used.[7,8] The recent development of alternative synthetic methods has expanded the variety of accessible alkenyl boronates; however, the diversity of aliphatic (*Z*)-alkenyl boronates remains limited.[9-12] Here, we planned to synthesize alkenyl boronates via a copper(I)-catalyzed three-component coupling between terminal allenes, alkyl halides, and a diboron reagent, i.e., an intermolecular alkylboration of allenes (Scheme 1c).[13] With control over the regio-, stereo-, and chemoselectivity, nucleophilic borylation of the allene moiety

and subsequent alkylation can be expected to furnish (*Z*)-alkenyl boronates that bear two different alkyl groups.

Scheme 1 Potential utility and synthetic strategies of (*Z*)-alkenyl boronates.

The carboboration of allenes is one direct way to access (*Z*)-alkenyl boronates (Scheme 2).[13] The regio- and stereoselective borylcupration of the terminal double bond of the allene generates a (*Z*)-allyl copper(I) intermediate, and the subsequent carbon–carbon bond formation at the α-position with carbon electrophiles furnishes (*Z*)-alkenyl boronates. In 2014, the groups of Tsuji,[14a] Hoveyda,[14b] and Brown[14c] have independently reported the intermolecular carboboration of terminal allenes, and the corresponding products were

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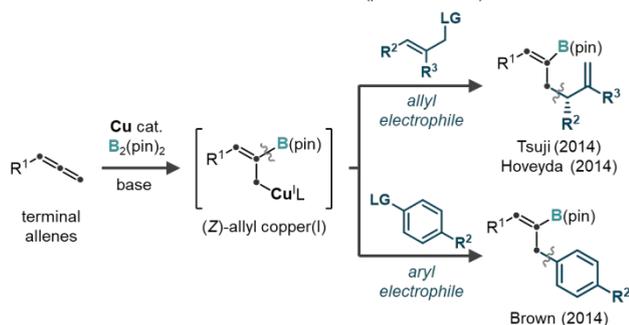b. Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido 060-8628, Japan

obtained with high stereoselectivity (Scheme 2a).[15,16] However, those reactions have only been reported for allyl and aryl electrophiles, which are stable under basic conditions because the competing elimination of the leaving group with the β-proton is avoided in such electrophiles. On the contrary, the use of simple alkyl electrophiles for the carboboration is expected to be more challenging due to potential side reactions caused by the decomposition of the alkyl electrophiles via β-elimination, which would produce alkenes.[8,17] Furthermore, the direct boryl substitution of alkyl electrophiles can also proceed as a major side reaction, which would consume the boron source and the electrophile.[18]

Scheme 2 Copper(I)/diboron-catalyzed synthesis of alkenyl boronates via the carboboration of terminal allenes.

Recently, our group has developed the first intermolecular alkylboration of *gem*-disubstituted allenes for the synthesis of allylic boronates.[17f] The corresponding three-component coupling products were obtained in high yield with suppression of the direct borylation of the alkyl halides. Thus, we anticipated that the reaction of terminal allenes with alkyl halides and a diboron reagent could produce (Z)-alkenyl boronates if the regioselectivity of the borylcupration and subsequent alkylation could be controlled to a high degree (Scheme 2b). Based on these synthetic strategies, we herein report the development of the intermolecular alkylboration reaction of terminal allenes for the synthesis of (Z)-alkenyl boronates. Directing groups were not necessary for allenes and alkyl halides during the stereoselective construction of sterically congested alkenyl boron structures. A variety of R[1] substituents is suitable for this reaction, including *prim*-, *sec*-, and *tert*-alkyl groups, as well as heteroatom substituents.

Table 1 Reaction Optimization[a]
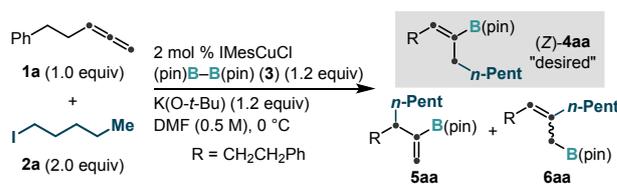
Entry	Variation from the standard conditions shown above	Yield of 4 [%][b]	E/Z of 4 [%][c]	4/5 [%][c]
1	none	90	1:99	>99:1
2	temperature: 30 °C	88	2:98	98:2
3	catalyst: SIMesCuCl	78	1:99	99:1
4	catalyst: IPrCuCl	48	8:92	97:3
5	catalyst: CuCl/PCy$_3$	80	1:99	99:1
6	catalyst: CuCl/Xantphos	19	2:98	67:33
7	solvent: toluene	33	1:99	98:2
8	solvent: THF	73	1:99	99:1
9	base: Li(O-t-Bu)	81	1:99	99:1
10	base: Na(O-t-Bu)	89	1:99	99:1
11	base: KOMe	79	1:99	98:2
12	catalyst loading: 0.5 mol%	76	1:99	99:1
13	w/ 1.0 equiv of reagents[d]	82	1:99	98:2

[a]Standard conditions: IMesCuCl (0.025 mmol), **1a** (0.5 mmol), **2a** (1.0 mmol), **3** (0.6 mmol), and K(O-t-Bu) (0.6 mmol) in DMF (1.0 mL). The consumption of substrate **1a** was confirmed via GC analysis of the reaction mixture. The regioselectivity of the borylcupration (**4**+**5**)/**6** was >99:1, which was determined by GC analysis. [b]Isolated yield. [c]Determined by GC analysis of the reaction mixture. [d]IMesCuCl (0.025 mmol), **1a** (0.5 mmol), **2a** (0.5 mmol), **3** (0.5 mmol), and K(O-t-Bu) (0.5 mmol) in DMF (1.0 mL).

Results and discussion

We first investigated the reaction conditions using allene **1a** and alkyl halide **2a** as model substrates and tested the effect of variations from the standard conditions shown in Table 1. In this reaction, the desired isomer (**4**) was obtained alongside the regioisomers produced by alkylation (**5**) and borylcupration (**6**). However, the regioselectivity of the borylcupration [(**4**+**5**)/**6**] was perfect in most cases. Thus, the regioselectivity is not documented unless otherwise noted. The reaction under the standard conditions selectively produced the alkenyl boronate (Z)-**4aa** in high yield (entry 1: 90%, E/Z = 1:99, **4/5** = >99:1). The yield and selectivity were slightly reduced at a higher temperature of 30 °C (entry 2: 88%, E/Z = 2:98, **4/5** = 98:2). The use of the ligands SIMes and IPr resulted in decreased reactivity and selectivity relative to the IMes ligand (entries 3 and 4: 48–78%, E/Z = 8:92–1:99, **4/5** = 97:3–99:1). The monodentate phosphine PCy$_3$ was also applicable (entry 5: 80%, E/Z = 1:99, **4/5** = 99:1), while the bidentate phosphine ligand Xantphos was not suitable for this reaction (entry 6: 19%, E/Z = 2:98, **4/5** = 67:33). It is worth noting here that the conditions using the SIMes and Xantphos ligands did not produce the allylic boronate **6aa**, although these ligands and conditions are the optimal ones for the synthesis of allylic boronates from *gem*-disubstituted allenes.[17f] In the non-polar aprotic solvent toluene, the product

Table 2 Substrate Scope[a]
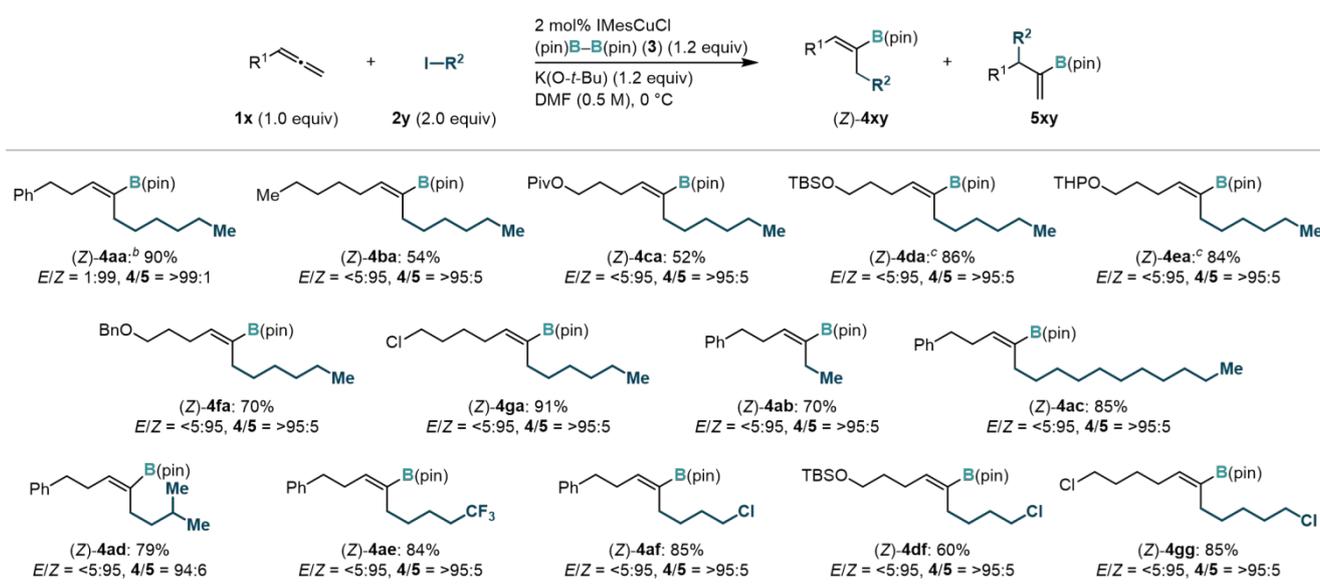
[a]Standard conditions: IMesCuCl (0.025 mmol), **1x** (0.5 mmol), **2y** (1.0 mmol), **3** (0.6 mmol), and K(O-t-Bu) (0.6 mmol) in DMF (1.0 mL). Isolated yield. The E/Z values of **4** and the **4/5** selectivity were determined via ^{1}H NMR analysis after column chromatography on silica gel. [b]The E/Z values of **4** and the **4/5** selectivity were determined via GC analysis of the reaction mixture. [c]10 mol% of IMesCuCl was used.

was obtained in low yield (entry 7: 33%, E/Z = 1:99, **4/5** = 98:2). On the contrary, in the polar solvent tetrahydrofuran (THF), the product was generated in high yield (entry 8: 73%, E/Z = 1:99, **4/5** = 99:1); however, the yield was lower than that of the reaction in dimethylformamide (DMF). The structure of the base did not greatly affect the reaction results (entries 9–11: 79–89%, E/Z = 1:99, **4/5** = 98:2–99:1). The reaction could also be carried out at a lower loading (0.5 mol%) of the copper(I) catalyst (entry 12: 76%, E/Z = 1:99, **4/5** = 99:1). To the best of our knowledge, the turnover number (TON) of 152 obtained under the conditions of entry 12 is the highest hitherto reported for copper(I)-catalyzed carboboration reactions of multiple bonds. Furthermore, the product was obtained in high yield from a combination of 1.0 equivalent of allene **1a**, alkyl halide **2a**, diboron reagent **3**, and the base K(O-t-Bu) (entry 13: 82%, E/Z = 1:99, **4/5** = 98:2). The results of entries 12 and 13 indicate that the catalyst system and reaction conditions optimized here ensure high reactivity and chemoselectivity.

Then, the substrate scope was investigated using the standard conditions (Table 2). The model substrate and a similar simple prim-alkyl-substituted substrate gave the borylation products in good-to-high yield with excellent regio- and stereoselectivity [(Z)-**4aa**: 90%, E/Z = 1:99, **4/5** = >99:1; (Z)-**4ba**: 54%, E/Z = <5:95, **4/5** = >95:5]. Pivaloyl (Piv), silyl (TBS), tetrahydropyranyl (THP), and benzyl (Bn) groups for protecting hydroxyl groups were tolerated in this reaction [(Z)-**4ca**, (Z)-**4da**, (Z)-**4ea**, (Z)-**4fa**: 52–86%, E/Z = <5:95, **4/5** = >95:5]. A chloride group did not react under these conditions [(Z)-**4ga**: 91%, E/Z = <5:95, **4/5** = >95:5]. However, an aryl-substituted allene, i.e., a phenyl allene, produced a stereo-mixture of products (72%, E/Z = 45:55), which was attributed to the easy 1,3-allylic isomerization of the allyl copper(I) intermediate. Next, we

investigated the scope of alkyl halides. A short and a long alkyl group could be introduced as the R[2] substituent [(Z)-**4ab**, (Z)-**4ac**: 70–85%, E/Z = <5:95, **4/5** = >95:5]. Using iso-butyl iodide as the electrophile, the product was obtained in high yield, although the regioselectivity was slightly reduced [(Z)-**4ad**: 79%, E/Z = <5:95, **4/5** = 94:6]. Trifluoromethyl and chloro groups were also tolerated under these conditions [(Z)-**4ae**, (Z)-**4af**, (Z)-**4df**, (Z)-**4gg**: 60–85%, E/Z = <5:95, **4/5** = >95:5]. It should be noted that the types of alkenyl boronates investigated here are inaccessible via other transition-metal-catalyzed proto- and hydroboration reactions of alkyne substrates, although multi-step procedures have been reported.[6–12] Regardless, the sec-alkyl iodide iodocyclohexane is not suitable for this reaction (<5%).[17e]

The reaction was then applied to other bulkier and functionalized substrates (Table 3). Sec- and tert-alkyl-substituted allenes afforded the corresponding products with perfect selectivity [(Z)-**4ha**, (Z)-**4ia**, (Z)-**4ja**: 52–84%, E/Z = <5:95, **4/5** = >95:5]. We also explored heteroatom-substituted allenes as the substrate of this reaction.[19] After re-optimization of the copper(I) catalyst, CuCl/(o-tol)₃P was found to give the desired carboboration products, i.e., allenamides in moderate yield [(Z)-**4kb**, (Z)-**4ka**, (Z)-**4la**, (Z)-**4mh**: 48–51%, E/Z = ≤5:95, **4/5** = >95:5]. A methylation product of the tosyl-protected amine substrate was obtained in moderate yield with slightly decreased stereoselectivity [(Z)-**4nb**: 60%, E/Z = 17:83, **4/5** = >95:5]. However, the introduction of other alkyl groups, such as an n-pentyl group, could not be achieved; elimination of the tosyl group was observed as the major side reaction. Using IPrCuCl as the copper(I) catalyst furnished the borylation product of an allenyl ether [(Z)-**4ob**: 63%, E/Z = 10:90, **4/5** = >95:5].
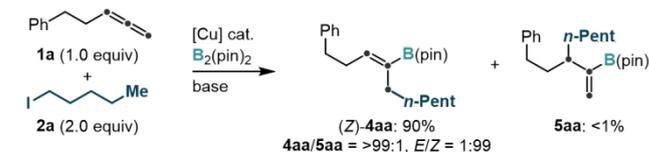
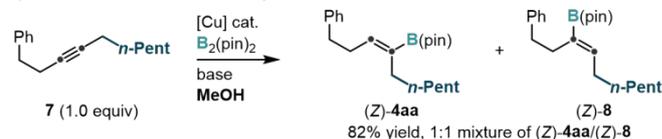Table 3 Substrate scope of bulkier and functionalized allenes[a]
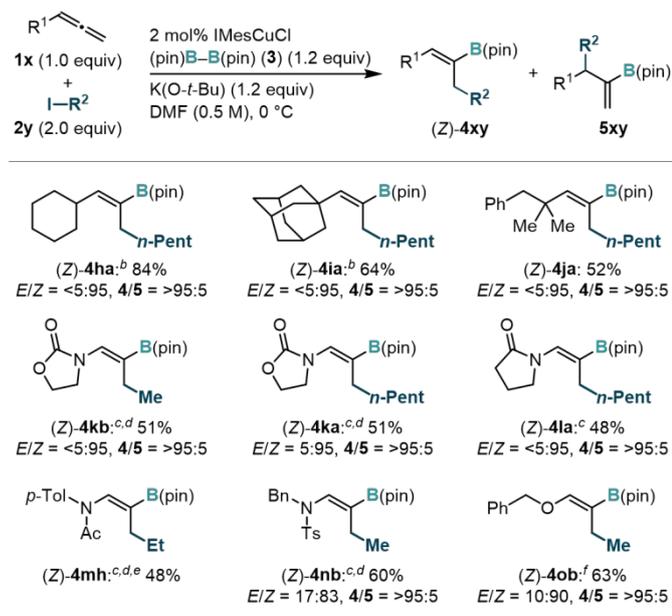
[a]Standard conditions: IMesCuCl (0.025 mmol), **1x** (0.5 mmol), **2y** (1.0 mmol), **3** (0.6 mmol), and K(O-t-Bu) (0.6 mmol) in DMF (1.0 mL). Isolated yield. The E/Z values of **4** and the **4/5** selectivity were determined via ^{1}H NMR analysis after column chromatography on silica gel. [b]10 mol % of IMesCuCl was used. [c]5 mol % of CuCl and (o-tol)$_3$P was used instead of IMesCuCl. The reaction was performed in DMF (0.31 M). [d]The product was isolated after oxidation of the boryl group. [e]The E/Z values of **4** and the **4/5** selectivity could not be determined via GC or NMR analysis. [f]5 mol % of IPrCuCl was used instead of IMesCuCl and the reaction was carried out in THF (0.5 M).

To demonstrate the advantages of this reaction compared to other synthetic methods for (Z)-alkenyl boronates, three types of copper(I)-catalyzed borylation reactions were carried out: (a) the alkylboration of terminal allene **1a**, (b) the protoboration of internal alkyne **7**, and (c) the protoboration of internal allene **9** (Scheme 3). The three-component coupling reaction between allene **1a**, alkyl halide **2a**, and diboron reagent **3** selectively furnished the corresponding alkenyl boronate (Z)-**4aa** in high yield [(Z)-**4aa**: 90%, E/Z = 1:99, **4/5** = >99:1; Scheme 3a]. Conversely, the protoboration of internal alkyne **7** using methanol as the proton source produced the desired product (Z)-**4aa** and the regioisomer (Z)-**8** with no regioselectivity [82% in total, 1:1 mixture of (Z)-**4aa**/(Z)-**8**; Scheme 3b].[20] Furthermore, the protoboration of internal allene **9** furnished various regio- and stereoisomers of the borylation product [78% in total, 3:2:2:1 mixture of isomers; Scheme 3c].[20] Although other synthetic approaches, including catalytic reactions using transition-metal catalysts and some multi-step synthetic routes, are conceivable, we would like to argue that the copper(I)-catalyzed three-component coupling reaction developed in this study is one of the most efficient and general approaches to obtain (Z)-alkenyl boronates in the absence of directing groups.
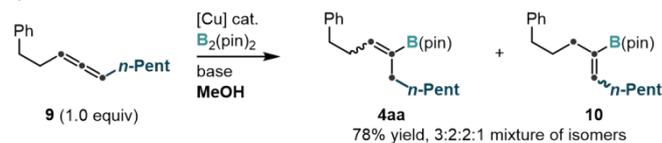
Scheme 3 Comparison of synthetic routes to (Z)-alkenyl boronates.

We then performed the Suzuki–Miyaura cross-coupling reactions for the derivatization of alkenyl boronates synthesized via this method (Table 4). Coupling with an aryl bromide and an alkenyl bromide afforded the corresponding styrene and diene derivatives, respectively [(E)-**12a**, (E)-**12b**: 82–99%, E/Z = >95:5]. The coupling products of enamide and alkenyl ether substrates were also obtained in good yield with high stereospecificity [(E)-**12c**, (E)-**12d**: 73–76%, E/Z = >95:5].

Table 4 Suzuki–Miyaura cross-coupling of (Z)-alkenyl boronates[a]
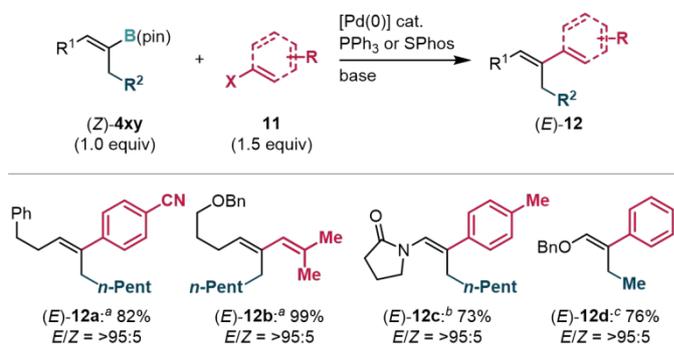
[a]Isolated yield. [b]Conditions: [Pd]/SPhos cat. and NaOH in THF/H$_2$O. [c]Conditions: [Pd]/PPh$_3$ cat. and Cs$_2$CO$_3$ in THF. [d]Conditions: [Pd]/PPh$_3$ cat. and KOH in THF/H$_2$O.

The 5-alkylresorcinol derivative schizol A is a marine natural product that was first isolated and characterized in 2017 by the Zubía group (Scheme 4a, right).[21] It is structurally unique due to the presence of a trisubstituted alkene moiety with two long alkyl groups in a cis orientation. The Zubía group also attempted to synthesize schizol A from commercially available aldehyde **13** (Scheme 4a). For that purpose, the direct precursor of schizol A, (E)-**12e**, was synthesized via a Julia–Koscienski olefination as the key step for the construction of the alkene moiety. However, the stereoselectivity was very low for the desired (E)-stereoisomer (E/Z = 1:4).

We decided to apply our selective synthesis of (Z)-alkenyl boronates to synthesize (E)-**12e** via the alkylboration of
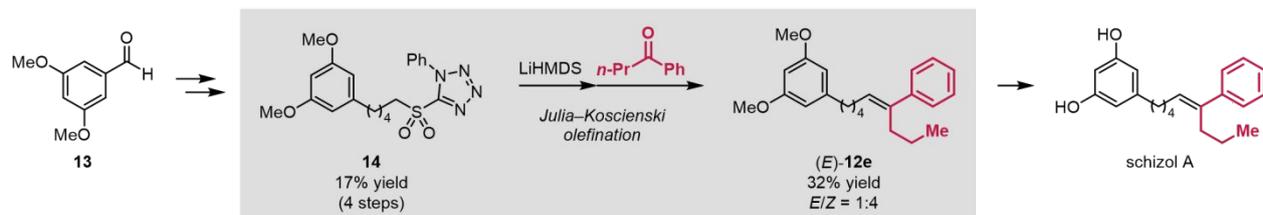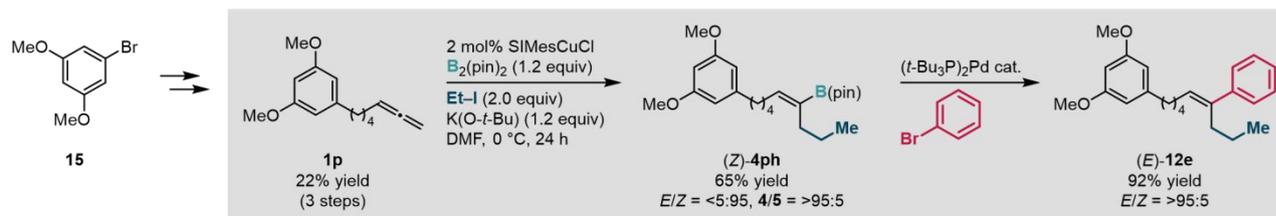
Scheme 4 Comparison of synthetic approaches for the precursor of schizol A, (*E*)-**12e**.

terminal allene **1p** (Scheme 4b). First, terminal allene **1p** was synthesized in three steps from commercially available aryl bromide **15** in 22% yield. Then, the alkylboration was performed under standard conditions with ethyl iodide as the alkyl electrophile. The product (*Z*)-**4ph** was obtained in moderate yield with high regio- and stereoselectivity (65% yield, *E/Z* = <5:95, **4/5** = >95:5). The subsequent Suzuki–Miyaura cross-coupling reaction furnished (*E*)-**12e** in high yield (92% yield, *E/Z* = >95:5). Thus, we succeeded in the stereoselective synthesis of a trisubstituted alkene for schizol A. This result demonstrates the validity of this alkylboration reaction for the construction of trisubstituted alkene moieties.

A plausible reaction mechanism is proposed in Scheme 5a. A σ-bond metathesis between diboron reagent **3** and the copper(I) alkoxide **Int1**, which is generated *in situ* from the copper(I) chloride complex and the alkoxide base, produces boryl copper(I) species **Int2**. The borylcupration of allene **1** forms allyl copper(I) intermediate **Int3**.[22] After the coordination of the alkoxide to the copper(I) center to form cuprate **Int4**,[23,24] S$_N$2-type oxidative addition to alkyl halide **2** gives a transient copper(III) intermediate **Int5**, which could be a transition state (TS) of the concerted alkylation mechanism.[25] Finally, reductive elimination generates copper(I) alkoxide **Int1** and product **4**.

To gain insight into the regio- and stereoselectivity of the borylcupration of terminal allenes in this reaction, **TS**^{alkenyl} and the resulting allyl copper(I) intermediate **Int3** were examined theoretically using DFT calculations (Scheme 5b). The calculations were conducted on IMesCuB(pin) and methyl allene as the model catalyst and substrate, respectively. The TS leading to (*Z*)-**Int3** is located 3.7 kcal/mol lower than that leading to (*E*)-**Int3**, indicating that the formation of (*Z*)-**Int3** is kinetically more favorable than that of (*E*)-**Int3**. Furthermore, (*Z*)-**Int3** is thermodynamically more stable than (*E*)-**Int3** and another allyl copper(I) isomer (**Int3'**) that generates **5**; they are connected to each other by 1,3-allylic isomerization of the allyl copper(I) species. Therefore, we assume that the formation of (*Z*)-**Int3** and thus (*Z*)-**4** is both kinetically and thermodynamically

advantageous relative to the paths for other isomers, albeit that further computational studies for the subsequent alkylation steps are needed to elucidate the full energy diagram of this reaction.
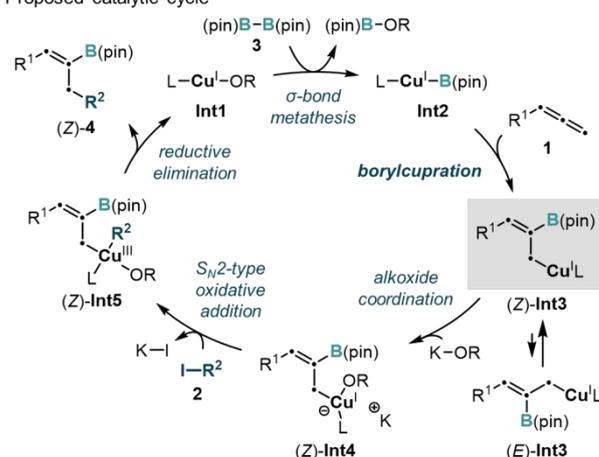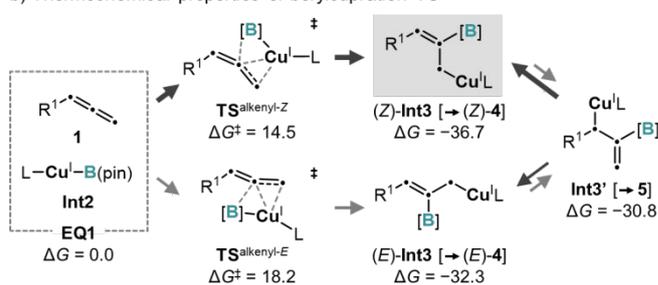
Scheme 5 Mechanistic overview of the alkylboration of terminal allenes. The DFT calculations were performed at the ωB97X-D/SDD and 6-311+G(d,p)/SMD(DMF)//ωB97X-D/SDD and 6-31G(d)/SMD(DMF) level of theory.

Conclusions

We have developed a copper(I)-catalyzed intermolecular alkylboration of terminal allenes that provides access to (Z)-alkenyl boronates. A wide variety of allenes and alkyl iodides, including allenamides and an allenyl ether, could be used as substrates. This method allows preparing (Z)-alkenyl boronates that contain two similar alkyl groups, which are difficult to synthesize via other borylation reactions of multiple bonds, such as hydroboration or protoboration of internal alkynes and allenes. The further development of copper(I)-catalyzed reactions to generate tetrasubstituted alkenyl boronates from *gem*-disubstituted allenes is currently in progress.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. #These authors contributed equally.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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