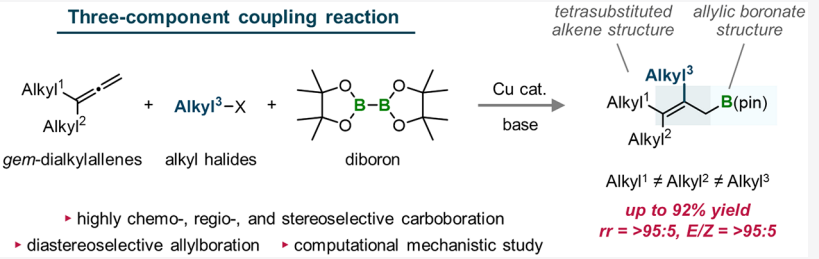
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

Regio- and Stereoselective Synthesis of Multi-Alkylated Allylic Boronates through Three-Component Coupling Reactions between Allenes, Alkyl Halides, and a Diboron Reagent

Yu Ozawa, Kohei Endo, and Hajime Ito*

Cite This: https://doi.org/10.1021/jacs.1c06538
Read Online



ABSTRACT: Multisubstituted allylic boronates are attractive and valuable precursors for the rapid and stereoselective construction of densely substituted carbon skeletons. Herein, we report the first synthetic approach for differentially 2,3,3-trialkyl-substituted allylic boronates that contain a stereodefined tetrasubstituted alkene structure. Copper(I)-catalyzed regio- and stereoselective three-component coupling reactions between *gem*-dialkylallenes, alkyl halides, and a diboron reagent afforded sterically congested allylic boronates. The allylboration of aldehydes diastereoselectively furnished the corresponding homoallylic alcohols that bear a quaternary carbon. A computational study revealed that the selectivity-determining mechanism was correlated to the coordination of a boryl copper(I) species to the allene substrate as well as the borylcupration step.

INTRODUCTION

Allylic boronates are recognized as important building blocks in organic synthesis on account of their synthetic utility, high thermal stability in terms of the C−B bond, and nontoxicity.[1,2] Stereospecific transformations of the boryl group at the γ- or α-position represent a reliable strategy for the construction of carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds in a stereocontrolled manner,[3−18] and several applications of allylic boronates toward total syntheses have been reported.[19−22] Among the many classes of allylic boronates, 2,3,3-all-carbon-trisubstituted allylic boronates that have a stereodefined tetrasubstituted alkene structure are attractive precursors of complex skeletons that contain contiguous and densely substituted sp^2- and sp^3-hybridized carbon atoms, e.g., homoallylic alcohols that bear a quaternary carbon atom as the γ-coupling products with aldehydes, and allylic-functionalized tetrasubstituted alkenes as the α-substitution products (Figure 1A). However, in the synthesis of trisubstituted allylic boronates, the stereoselective construction of sterically congested tetrasubstituted alkene structures, especially those that possess four different substituents, is challenging, and further work remains to be done in terms of reactivity and selectivity.

In 2002, the Hall group first reported a highly regio- and stereoselective synthesis of differentially 2,3,3-all-carbon-trisubstituted allylic boronates via a conjugate addition of organocopper reagents to alkynyl esters and a subsequent coupling reaction with an electrophilic boron source (Figure 1B).[23] After this development, they reported on the synthesis and applications of a series of trisubstituted allylic boronates.[19,24,25] Despite excellent selectivity and functional-group tolerance, the inclusion of an electron-withdrawing group (EWG) and the use of a stoichiometric amount of copper reagent are mandatory in these cases. Additionally, the authors reported that the reaction must be performed at a cryogenic temperature to achieve high stereoselectivity given that the stereochemistry of the alkenyl copper(I) intermediate is unstable above −30 °C.[23] The RajanBabu and Disier groups independently reported enantioselective syntheses of allylic boronates embedded in small rings such as cyclopropene and -butenes.[26−29] In spite of these excellent pioneering studies, the variety of differentially 2,3,3-all-carbon-trisubstituted allylic boronates remains limited.[30,31]

Received: June 24, 2021

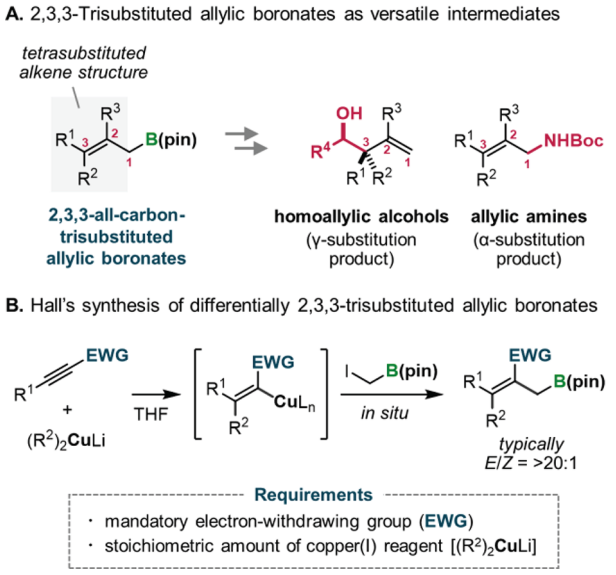


Figure 1. Potential utility and a reported synthesis of differentially 2,3,3-all-carbon-trisubstituted allylic boronates.

The development of copper(I)-catalyzed three-component coupling reactions between allenes, carbon electrophiles, and a boron source, namely, a carboboration of allenes, is an attractive research target due to the great utility of the borylation products and the interest in the regio- and stereodivergence of the borylation and carbo-functionalization reactions, which can provide access to a variety of alkenyl and allylic boronates (Figure 2A).[32−35] To date, most researchers have used the 2,1-borylcupration of mono- and *gem*-disubstituted allenes and developed the subsequent α-C−C bond formation for the preparation of linear alkenyl boronates **I** and γ-C−C bond formation for branched alkenyl boronates **II** (left arrow in Figure 2A and Figure 2B). In these reactions, an allylcopper(I) species generated *in situ* via the regioselective 2,1-borylcupration of allenes is the key intermediate toward the alkenyl boronates. The groups of Tsuji, Hoveyda, Brown, and Liu have reported α-carbo-functionalization reactions from allylcopper(I) intermediates to synthesize linear (*Z*)-alkenyl boronates **I**.[36−39] On the other hand, reaction at the γ-position of the allylcopper(I) intermediates produces the branched alkenyl boronates **II**, which has been reported independently by several research groups including our own.[40−58]

During our previous study of the intramolecular alkylboration of allenes,[49] we became interested in the regiodivergence of the borylcupration. We anticipated that the multisubstituted allylic boronates **III** could be synthesized by generating the alkenyl copper(I) intermediate through the 1,2-borylcupration of the allene substrates and applying the intermediate to the following C−C bond formation reaction (right arrow in Figure 2A). The Ma group has previously demonstrated the stereoselective 1,2-borylcupration of *gem*-dialkylallenes to generate alkenylcopper(I) species and subsequent protonation in a mechanistic study on the hydroboration reaction of allenyl silanes.[59] However, the carboboration reaction, i.e., a three-component coupling reaction that could produce the differentially 2,3,3-all-carbon-trisubstituted allylic boronates **III**, still has not yet been developed (Figure 2B). This reaction is expected to be very challenging on account of the difficulties associated with achieving both high reactivity for the carbo-functionalization to construct the sterically congested tetrasubstituted alkene structure and the high selectivities in terms of the chemoselectivity of the boryl copper(I) intermediate toward allenes rather than carbon electrophiles as well as the regio- and stereoselectivity of the borylcupration of allenes.

In order to address the issues of stereoselectivity and regioselectivity, we envisioned optimizing the ligand of the copper(I) catalyst in such a way that steric repulsion between the ligand and the small substituent R^S would be as low as possible, while the large substituent R^L would clash with the ligand and the B(pin) group (Figure 2C). As a result, 1,2-borylcupration from the top side of the allene would produce the desired stereoisomer of the allylic boronate **III** as the carboboration product. Based on this hypothesis, we developed the first synthetic approach for differentially 2,3,3-trialkyl-substituted allylic boronates via the alkylboration reaction of *gem*-dialkylallenes. The ligands SIMes and Xantphos, which possess a pocket-like structure that is not found in the previously reported ligands for production of alkenyl boronates **I** and **II** listed in the bottom of Figure 2C, realize not only regioselectivity but also stereoselectivity by recognizing the bulk of the two alkyl groups in the substrate. The catalyst is able to differentiate methyl groups from *tert-*, *sec-*, and *prim-*alkyl groups, as well as *prim*-alkyl groups from *tert-* and *sec*-alkyl groups. A directing group is not necessary in this reaction to construct the differentially tetrasubstituted alkene structure. Furthermore, a density functional theory (DFT)-based mechanistic study indicated that the transition state involving the π-coordination of the allenes to borylcopper(I) species is comparable to the borylcupration in terms of activation energy and that both steps are crucial for the regio- and stereo-selectivity.

RESULTS AND DISCUSSION

We started the development of the carboboration reaction using cyclohexyl methyl allene **1a** and alkyl halide **2a** as model substrates under the standard conditions shown in Table 1. The rigid and large-bite-angle bisphosphine Xantphos gave allylic boronate **4aa** with moderate *E*/*Z* selectivity and perfect regioselectivity (entry 1: 88%, *E*/*Z* = 60:40, **4**:**5** > 99:1). The use of bisphosphines dppp or dppf, both of which have greater backbone flexibility, resulted in lower regioselectivity (entry 2: 30%, *E*/*Z* = 70:30, **4**:**5** = 44:56; entry 3: 5%, **4**:**5** = 6:94). Using the monodentate phosphine PCy_3 resulted in a drastically decreased yield (entry 4: 2%, **4**:**5** = 81:19) with a significantly increased yield of the boryl substitution product of alkyl halide **2a**.[60−64] Next, a series of N-heterocyclic carbene (NHC) ligands was investigated. The reactions were performed with lower catalyst loadings and at lower reaction temperatures than the reactions using the phosphine ligands. The saturated-backbone NHC SIMes furnished the product in high yield with high *E*/*Z* and regioselectivity (entry 5: 73%, *E*/*Z* > 95:5, **4**:**5** = 92:8), whereas the yield decreased when the unsaturated NHC IMes was used, even though the selectivities were still high (entry 6: 55%, *E*/*Z* > 95:5, **4**:**5** = 94:6). In contrast, the bulky NHC ligand IAd showed inverted *E*/*Z* selectivity with high regioselectivity (entry 7: 71%, *E*/*Z* = 32:68, **4**:**5** = 98:2). The solvent was then screened with SIMes as the optimal ligand for substrate **1a**. In addition to *N*,*N*-dimethylformamide (DMF), the polar aprotic solvents tetrahydrofuran (THF) and acetonitrile (MeCN) were investigated, although the product was obtained merely in low yield (entry 8: 19%; entry 9: 13%). Although *N*,*N*-

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

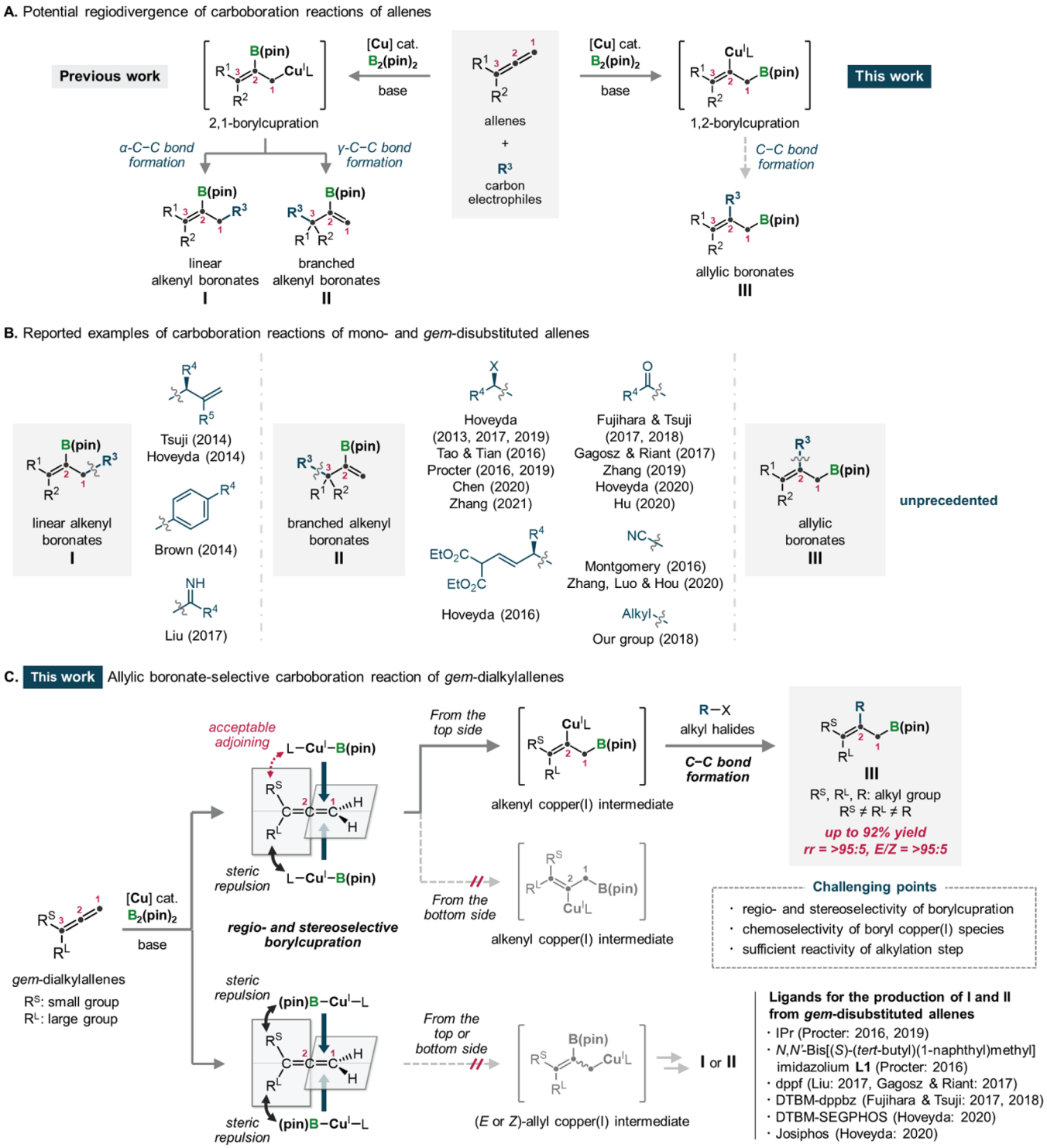
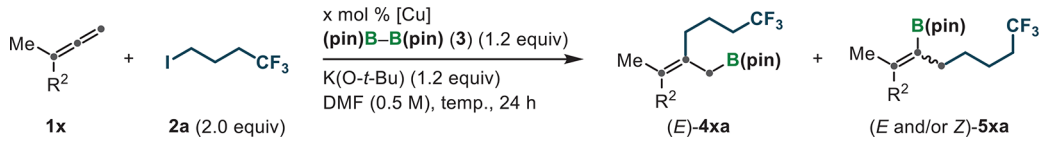


Figure 2. Carboboration reactions of allenes to access alkenyl boronates and allylic boronates.

dimethylacetamide (DMA) gave the alkylboration product in moderate yield, a large amount of the protoboration product was produced (entry 10: 48%, E/Z > 95:5, **4**:**5** = 85:15). In this reaction, the acetyl group in DMA would be the proton source. Conversely, the nonpolar solvents toluene and *n*-hexane afforded less than trace amounts of the product, which should most likely be attributed to the disfavor of S_N2-type reactions in nonpolar solvents, i.e., the alkylation of alkenyl copper(I) species with alkyl halides (entry 11: <1%; entry 12: 5%). Then, potassium methoxide (KOMe) was used as the base instead of potassium *tert*-butoxide [K(O-*t*-Bu)]. The solution turned to jelly over the reaction to furnish a trace amount of the product (entry 13: 5%). During the subsequent temperature screening, the yield and regioselectivity were increased at −5 °C (entry 14: 77%, E/Z > 95:5, **4**:**5** = 93:7). However, the reactivity dropped below −10 °C, despite the higher regioselectivity (entry 15: 51%, E/Z > 95:5, **4**:**5** = 94:6). Low concentration also benefited the regioselectivity, but decreased the yield (entry 16: 68%, E/Z > 95:5, **4**:**5** = 95:5). Therefore, we selected the conditions employed in entry 14 as

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Reaction Optimization[a]



entry	1x (R^2)	[Cu] (*x* mol %)	temp [°C]	variation of other conditions	yield of 4xa (4xa+5xa) [%][b]	*E*/*Z* of 4xa [%][c]	4xa/5xa [%][b]
1	1a (Cy)	CuCl/Xantphos (5)	30	none	88 (88)	60:40	>99:1
2	1a (Cy)	CuCl/dppp (5)	30	none	30 (68)	70:30	44:56
3	1a (Cy)	CuCl/dppf (5)	30	none	5 (80)	n.d.	6:94
4	1a (Cy)	CuCl/PCy_3 (5)	30	none	2 (3)	n.d.	81:19
5	1a (Cy)	SIMesCuCl (2)	0	none	73 (79)	>95:5	92:8
6	1a (Cy)	IMesCuCl (2)	0	none	55 (58)	>95:5	94:6
7	1a (Cy)	IAdCuCl (2)	0	none	71 (72)	32:68	98:2
8	1a (Cy)	SIMesCuCl (2)	0	solvent: THF	19 (22)	n.d.	87:13
9	1a (Cy)	SIMesCuCl (2)	0	solvent: MeCN	13 (16)	n.d.	84:16
10	1a (Cy)	SIMesCuCl (2)	0	solvent: DMA	48 (56)	>95:5	85:15
11	1a (Cy)	SIMesCuCl (2)	0	solvent: toluene	<1 (<1)	n.d.	n.d.
12	1a (Cy)	SIMesCuCl (2)	0	solvent: *n*-hexane	5 (8)	n.d.	60:40
13	1a (Cy)	SIMesCuCl (2)	0	base: KOMe	5 (6)	n.d.	79:21
14	1a (Cy)	SIMesCuCl (2)	−5	none	77 (83)	>95:5	93:7
15	1a (Cy)	SIMesCuCl (2)	−10	none	51 (54)	>95:5	94:6
16	1a (Cy)	SIMesCuCl (2)	0	concentration: 0.25 M	68 (72)	>95:5	95:5
17	1b (*t*-Bu)	SIMesCuCl (2)	−5	none	58[d,e]	77:23 mixture of isomers[f]	
18	1b (*t*-Bu)	CuCl/Xantphos (5)	30	none	83[d]	>95:5	>99:1

[a]Standard conditions: Cu(I) catalyst (0.025 mmol), **1x** (0.5 mmol), **2a** (1.0 mmol), **3** (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in DMF (1.0 mL). [b]Yield values and **4xa**/**5xa** selectivities were determined by GC analysis of the reaction mixture using an internal standard. [c]Determined by ^{13}C NMR analysis of the roughly purified material. [d]Isolated yield. [e]Containing small amounts of protoboration products of **1b** and a boryl substitution product of **2a**. [f]Determined by ^1H NMR analysis of the purified material. The structure of the minor isomer could not be identified.

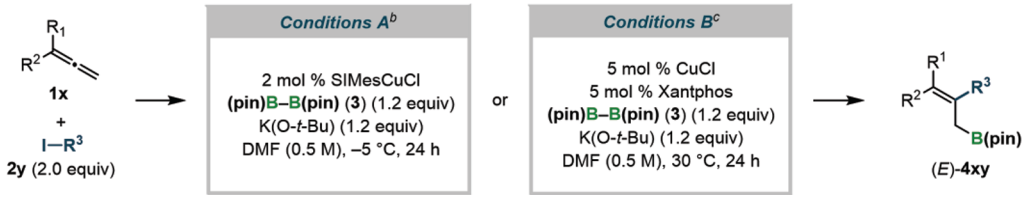
the optimal conditions (conditions **A**) for the following investigations of the substrate scope. The reaction was then applied to the bulkier substrate **1b**, which bears a *tert*-butyl group instead of a cyclohexyl group. However, conditions **A** did not provide adequate reactivity and selectivity (entry 17: 58%, 77:23 mixture of isomers). On the other hand, Xantphos gave the desired product in high yield with excellent *E*/*Z* and regioselectivity (entry 18: 83%, *E*/*Z* > 95:5, **4**:**5** > 99:1). These high selectivities are in good agreement with the mechanistic study reported by the Ma group.[59] Thus, we selected these conditions as the optimized conditions for bulky substrates (conditions **B**).

Using these optimized reaction conditions, the scope of allenes and halides was investigated (Table 2). Some of the borylation products were isolated and characterized after oxidation of the boryl group as the borylation products were inseparable from the byproducts, i.e., the protoboration product of the allene and the boryl-substitution product of the alkyl halides. The borylation products of allene **1a** with some halides were obtained with excellent *E*/*Z* and regioselectivity [(*E*)-**4aa**, (*E*)-**4ab**, (*E*)-**4ac**, (*E*)-**4ad**: 49−66%, *E*/*Z* > 95:5, **4**:**5** > 95:5]. We confirmed the stereochemistry of (*E*)-**4aa** as a representative borylation product synthesized under conditions **A** using a NOESY experiment (for details, see the Supporting Information). To investigate the effect of a *sec*-alkyl group as R^2 in allene substrate **1**, an acyclic *sec*-alkyl group was used in the reaction instead of a cyclohexyl group. The reaction of allene **1c** under conditions **A** resulted in a somewhat complex mixture, while conditions **B** gave the corresponding product in high yield with high *E*/*Z* and excellent regioselectivity regardless of the length of the alkyl halide {(*E*)-**4cb**, (*E*)-**4cc**: 88−89%, *E*/*Z* = 88:12, **4**:**5** > 95:5}. Subsequently, the substituent R^1 was screened with *n*-propyl, *n*-octyl, and isobutyl groups. The yields decreased slightly in the order *n*-propyl > *n*-octyl > isobutyl, while the selectivities remained high [(*E*)-**4db**, (*E*)-**4dc**, (*E*)-**4eb**, (*E*)-**4ec**, (*E*)-**4fb**, (*E*)-**4fc**: 50−87%, *E*/*Z* = 87:13−91:9, **4**:**5** > 95:5]. The catalyst is able to recognize *α*- and *β*-branched alkyl groups as R^1 and R^2 substituents, as shown in (*E*)-**4fb** and (*E*)-**4fc**. Subsequently, methyl *tert*-alkyl allenes and a *prim*-alkyl *tert*-alkyl allene were examined, and these afforded the corresponding products with perfect selectivities [(*E*)-**4ga**, (*E*)-**4ba**, (*E*)-**4ha**, (*E*)-**4hc**: 64−92%, *E*/*Z* > 95:5, **4**:**5** > 95:5]. We confirmed the stereochemistry of (*E*)-**4ga** as a representative borylation product synthesized under conditions **B** using a single-crystal X-ray diffraction analysis. Moreover, an even more challenging group of substrates, methyl *prim*-alkyl allenes, was found to be suitable for this reaction. The products were obtained in moderate yield with high selectivities [(*E*)-**4ia**, (*E*)-**4ic**, (*E*)-**4ja**, (*E*)-**4jc**: 46−64%, *E*/*Z* = 89:11−94:6, **4**:**5** ≥ 95:5]. However, the catalyst was unable to distinguish between two *prim*-alkyl groups, such as an ethyl vs a benzyl group. Under conditions **B**, the product was obtained with no stereoselectivity [(**4kc**: 67%, *E*/*Z* = 50:50, **4**:**5** > 95:5], whereas conditions **A** resulted in a low conversion and gave a mixture of isomers. It should be noted here that the optimized conditions for *gem*-dialkylallenes are not suitable for aryl-substituted allenes (for details, see the Supporting Information).

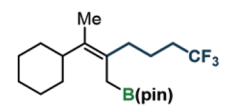
Next, we investigated the scope and limitations of alkyl halides **2**. In addition to ethyl and *n*-pentyl groups, a longer alkyl chain, the *n*-decyl group, could be introduced as the R^3 substituent in high yield [(*E*)-**4bb**, (*E*)-**4bc**, (*E*)-**4be**: 75−88%, *E*/*Z* > 95:5, **4**:**5** > 95:5]. Isobutyl iodide also showed high

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

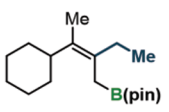
Table 2. Screening the Substrate Scope[a]



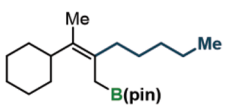
scope of allenes



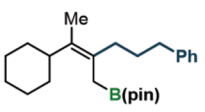
(*E*)-**4aa**, 66%[b,d]
E/*Z* = >95:5, **4**:**5** = >95:5



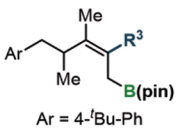
(*E*)-**4ab**, 62%[b,d]
E/*Z* = >95:5, **4**:**5** = >95:5



(*E*)-**4ac**, 49%[b,d,e]
E/*Z* = >95:5, **4**:**5** = >95:5

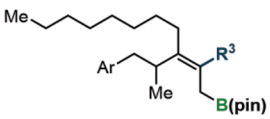


(*E*)-**4ad**, 63%[b,d]
E/*Z* = >95:5, **4**:**5** = >95:5

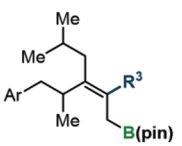


Ar = 4-*t*Bu-Ph
R[3] = **Et**: (*E*)-**4cb**, 88%[c,f]
E/*Z* = 88:12, **4**:**5** = >95:5
R[3] = ***n*-Pent**: (*E*)-**4cc**, 89%[c,f]
E/*Z* = 88:12, **4**:**5** = >95:5

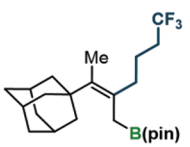
Ar = 4-*t*Bu-Ph
R[3] = **Et**: (*E*)-**4db**, 87%[c,f]
E/*Z* = 89:11, **4**:**5** = >95:5
R[3] = ***n*-Pent**: (*E*)-**4dc**, 87%[c,f]
E/*Z* = 89:11, **4**:**5** = >95:5



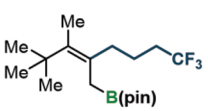
Ar = 4-*t*Bu-Ph
R[3] = **Et**: (*E*)-**4eb**, 82%[c,f]
E/*Z* = 89:11, **4**:**5** = >95:5
R[3] = ***n*-Pent**: (*E*)-**4ec**, 50%[c,d]
E/*Z* = 87:13, **4**:**5** = >95:5



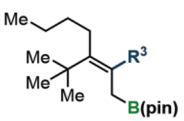
Ar = 4-*t*Bu-Ph
R[3] = **Et**: (*E*)-**4fb**, 79%[c,f]
E/*Z* = 89:11, **4**:**5** = >95:5
R[3] = ***n*-Pent**: (*E*)-**4fc**, 76%[c,f]
E/*Z* = 91:9, **4**:**5** = >95:5



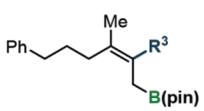
(*E*)-**4ga**, 64%[c,g]
E/*Z* = >95:5, **4**:**5** = >95:5



(*E*)-**4ba**, 83%[c]
E/*Z* = >95:5, **4**:**5** = >95:5

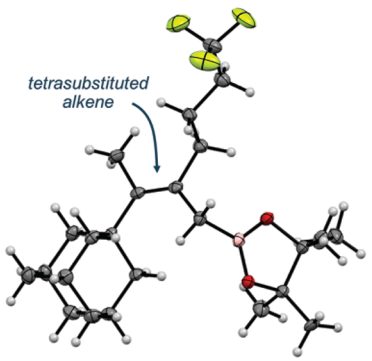


R[3] = $(CH_2)_3CF_3$: (*E*)-**4ha**, 69%[c,h]
E/*Z* = >95:5, **4**:**5** = >95:5
R[3] = ***n*-Pent**: (*E*)-**4hc**, 92%[c]
E/*Z* = >95:5, **4**:**5** = >95:5

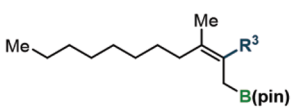


R[3] = $(CH_2)_3CF_3$: (*E*)-**4ia**, 59%[b,d,i]
E/*Z* = 89:11, **4**:**5** = >95:5
R[3] = ***n*-Pent**: (*E*)-**4ic**, 52%[b,d]
E/*Z* = 90:10, **4**:**5** = >95:5

III

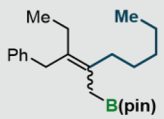


X-ray structure



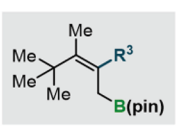
R[3] = $(CH_2)_3CF_3$: (*E*)-**4ja**, 64%[b,d]
E/*Z* = 92:8, **4**:**5** = >95:5
R[3] = ***n*-Pent**: (*E*)-**4jc**, 46%[b,d]
E/*Z* = 94:6, **4**:**5** = 95:5

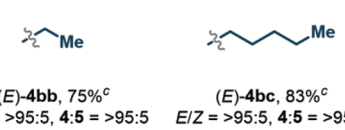
unsuccessful allene



4kc, 67%[c,d]
E/*Z* = 50:50
4:**5** = >95:5
no stereoselectivity

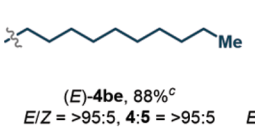
scope of alkyl halides





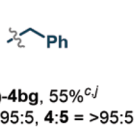
(*E*)-**4bb**, 75%[c]
E/*Z* = >95:5, **4**:**5** = >95:5

(*E*)-**4bc**, 83%[c]
E/*Z* = >95:5, **4**:**5** = >95:5



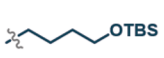
(*E*)-**4be**, 88%[c]
E/*Z* = >95:5, **4**:**5** = >95:5

(*E*)-**4bf**, 81%[c]
E/*Z* = 91:9, **4**:**5** = >95:5

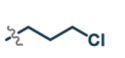


(*E*)-**4bg**, 55%[c,j]
E/*Z* = >95:5, **4**:**5** = >95:5

(*E*)-**4bh**, 74%[c]
E/*Z* = >95:5, **4**:**5** = >95:5

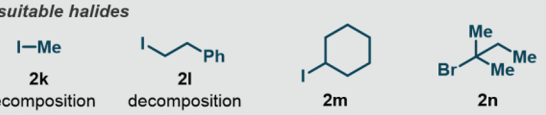


(*E*)-**4bi**, 44%[c,d]
E/*Z* = >95:5, **4**:**5** = >95:5



(*E*)-**4bj**, 51%[c,d,k]
E/*Z* = >95:5, **4**:**5** = >95:5

unsuitable halides



[a]Isolated yield of the borylation product unless otherwise noted. The *E*/*Z* values of **4** and the **4**/**5** selectivity were determined by ^{1}H NMR analysis after column chromatography unless otherwise noted. [b]Conditions A: SIMesCuCl (0.01 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) at −5 °C for 24 h. [c]Conditions B: CuCl (0.025 mmol), Xantphos (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) at 30 °C for 24 h. [d]Isolated yield after oxidation of the boryl group. [e]The reaction was performed at 30 °C. [f]The regio- and stereoselectivity were determined by GC analysis after silica gel column chromatography. [g]A small amount of byproduct, possibly the borylation product of the alkyl iodide, was removed by selective oxidation. [h]The reaction was performed for 48 h. [i]The reaction was performed at 0 °C. [j]Benzyl bromide was used instead of benzyl iodide. [k]The selectivity of C−C bond formation at iodide and chloride was 86:14.

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

reactivity to produce the corresponding borylation product in high yield with slightly decreased stereoselectivity [(*E*)-**4bf**: 81%, *E*/*Z* = 91:9, **4**:**5** > 95:5]. A benzyl group could be introduced by using benzyl bromide as the carbon electrophile instead of the iodide [(*E*)-**4bg**: 55%, *E*/*Z* > 95:5, **4**:**5** > 95:5]. Some functionalized alkyl halides were then examined. A methoxy group was tolerated in this reaction [(*E*)-**4bh**: 74%, *E*/*Z* > 95:5, **4**:**5** > 95:5]. However, the reaction of compounds including halides with a silyl ether or chloride group produced a mixture of the alkylboration product and unidentified side products [(*E*)-**4bi**, (*E*)-**4bj**: 44−51%, *E*/*Z* > 95:5, **4**:**5** > 95:5]. Additionally, methyl iodide **2k** decomposed in the reaction, probably via a reaction with the base K(O-*t*-Bu) or direct boryl substitution of the alkyl iodide moiety. Phenethyl iodide **2l** also decomposed, probably via *β*-elimination, to produce styrene as a side product. Finally, *sec*- and *tert*-alkyl halides **2m** and **2n** were found to be inapplicable to this reaction due to their lack of reactivity in the S_N2-type alkylation step.

Next, we demonstrated the synthetic utility of the multisubstituted allylic boronates synthesized via the above method (Figure 3). First, a gram-scale synthesis of (*E*)-**4hc** was performed. Similar to the small-scale reaction, the allylic boronate was obtained in high yield [(*E*)-**4hc**: 88% (1.86 g), *E*/*Z* > 95:5, **4**:**5** > 95:5; Figure 3A]. The oxidative transformations afforded the corresponding allylic alcohol and allylic amine in moderate to high yield [(*Z*)-**6hc** 89%, *E*/*Z* > 95:5; (*Z*)-**7hc**: 46%, *E*/*Z* > 95:5; Figure 3B]. The Matteson homologation also successfully furnished the homoallylic boronate in high yield [(*E*)-**8hc**: 73%, *E*/*Z* > 95:5; Figure 3B].

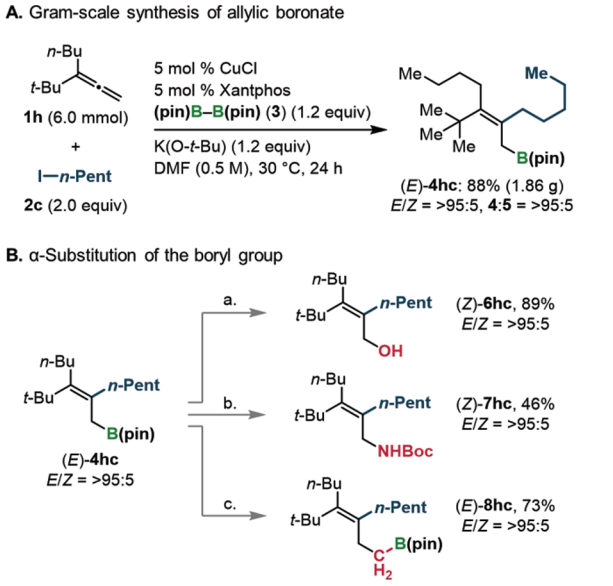


Figure 3. Synthetic applications of 2,3,3-trialkylsubstituted allylic boronates. (A) Gram-scale carboboration reaction of *gem*-dialkylallenes. (B) *α*-Selective transformations of the boryl group: (a) $NaBO_3 \cdot 4H_2O$, THF/H_2O, rt, 21 h. (b) H_2NOMe, *n*-BuLi, −78 to 60 °C, 48 h; then $(Boc)_2O$, rt, 2 h. (c) CH_2ClBr, *n*-BuLi, −78 °C to rt, 21 h.

We then carried out allylboration reactions using the differentially 2,3,3-trisubstituted allylic boronates (Figure 4). Heating a mixture of allylic boronate (*E*)-**4hc** and formaldehyde furnished the corresponding homoallylic alcohol in high yield (**9a**: 90%; Figure 4A).[65] The product contains vicinal quaternary carbon atoms, which are difficult to construct via C−C bond formation reactions such as aldol or

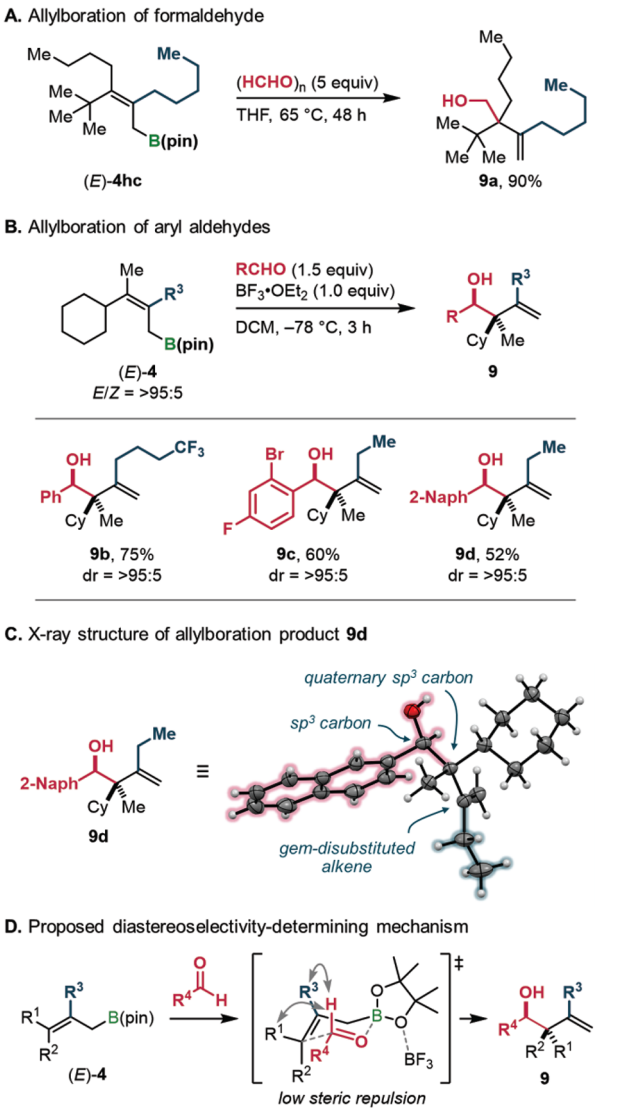


Figure 4. Allylboration of 2,3,3-trialkyl-substituted allylic boronates.

Grignard reactions, due to steric congestion.[66,67] Lewis-acid-mediated conditions allowed the allylboration of aryl aldehydes (Figure 4B).[25,68,69] The allylation of benzaldehydes furnished the product in high yield with high diastereoselectivity (**9b**, **9c**, **9d**: 52−75%, dr > 95:5). The stereochemistry of allylboration product **9d** was confirmed by a single-crystal X-ray diffraction analysis (Figure 4C). Considering the structure of the vicinal stereodefined sp^3-hybridized carbon atoms in the allylboration product, the relative configuration of the substituents in the transition state (TS) was estimated as illustrated in Figure 4D. Substituent R^4 of the aldehyde should be at an equatorial position in the TS, thus avoiding steric repulsion with R^1 and R^3 of the allylic boronate.

We also applied this borylation reaction to exocyclic allenes (Figure 5). For a model study, the simple exocyclic allene **1l** was chosen as the substrate. The alkylboration product was obtained in high yield with high regioselectivity under conditions **B** (**4la**: 69%, **4**:**5** > 95:5; Figure 5A). The reaction of a steroid-type substrate proceeded stereo- and regioselectively to afford the products in high yield [(*E*)-**4ma**, (*E*)-**4mb**: 78−90%, *E*/*Z* > 95:5, **4**:**5** > 95:5; Figure 5B]. The stereochemistry of (*E*)-**4mb** was confirmed by a single-crystal

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

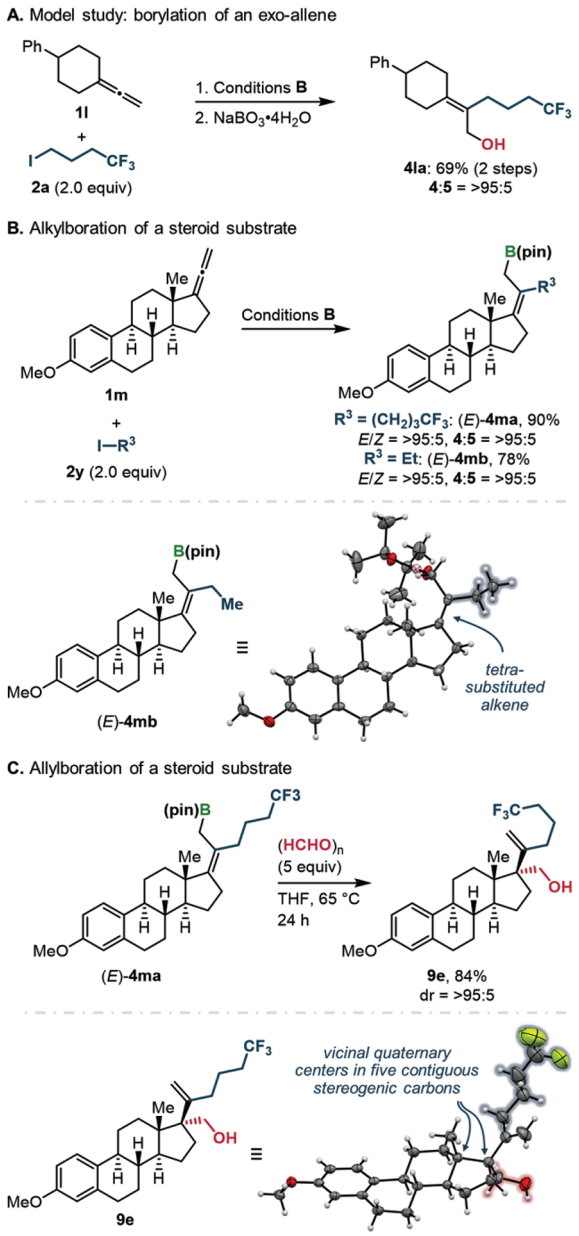


Figure 5. Alkylborylation and allylboration of exo-allenes.

X-ray diffraction analysis. Furthermore, the allylboration of formaldehyde using (*E*)-**4ma** afforded the homoallylic alcohol **9e**, which bears five contiguous stereocenters (including two vicinal quaternary carbon atoms) in high yield with perfect diastereoselectivity (**9e**: 84% dr > 95:5; Figure 5C). The stereochemistry of **9e** was determined by a single-crystal X-ray diffraction analysis. These results demonstrate that this synthesis of multisubstituted allylboron compounds is useful for the rapid construction of stereocongested structures in a stereoselective manner.

We then moved on to analyze the regio- and stereoselectivity-determining mechanism of this reaction. The proposed catalytic cycle based on the past studies of copper(I)-catalyzed alkylboration reactions is shown in Figure 6A.[34,49,70,71] Prior to the on-cycle catalytic reaction, copper(I) alkoxide **Int1** is formed *in situ* via the reaction between copper(I) chloride and K(O-*t*-Bu). The boryl copper(I) intermediate **Int2** is then generated via a σ-bond metathesis between **Int1** and diboron reagent **3**. The subsequent coordination and borylcupration of allene **1x** with **Int2** gives the alkenyl copper(I) species **Int3**. In general, the borylcupration is highly exothermic and exergonic; that is, this is the regio- and stereodetermining step. The cuprate species **Int4** is then generated by coordination of the alkoxide to the copper(I) center in intermediate **Int3**.[72−83] The nucleophilic cuprate can undergo S_N2-type oxidative addition to alkyl halide **2y** to afford the organocopper(III) intermediate **Int5**. However, the high-valent copper(III) species could be a transient species or a transition state of the concerted mechanism.[49,71] Finally, reductive elimination forms the new C−C bond to produce the alkylboration product **4xy** with concomitant restoration of copper(I) alkoxide **Int1**.

To gain deeper insight into the regio- and stereoselectivity-determining mechanism, we performed DFT calculations (Figure 6B). A simplified SIMes ligand in which the 4-methyl groups of the mesityl groups are replaced with hydrogen atoms and allene **1a** were chosen as the model ligand and substrate, respectively (for the case of Xantphos and allene **1b**, see the Supporting Information). The respective transition states of the borylcupration (**TS2**) for the four regio- and stereoisomers were successfully located 16−21 kcal/mol higher than the precursor state **EQ1**, which consists of boryl copper(I) species **Int2** and the substrate **1a** (**EQ1**: ΔG = 0.0 kcal/mol). It should be noted that, during the calculation of **TS2**, we found that the transition states for the coordination of allene **1a** to **Int2** (**TS1**s) are comparable to those of the **TS2**s. Although the activation barriers of the coordination steps prior to the borylcuprations are generally small, and even negligible in many cases, this relative energy profile suggests that the coordination step could be a regio- and stereodetermining step.[84,85] We envisioned that the substituents R^1 and R^2, which are perpendicular to the double bond where the borylcupration proceeds, can cause steric repulsion toward the boryl copper(I) species in the case of *gem*-disubstituted allenes. For the path of the experimental major isomer, (*E*)-**4**, the intermediate state **EQ2**$^{\text{allyl-}E}$ is energetically higher than the precursor state **EQ1**, while the product state, alkenyl copper(I) **Int3**$^{\text{allyl-}E}$, is relatively stable (**EQ2**$^{\text{allyl-}E}$: ΔG = 12.4 kcal/mol; **Int3**$^{\text{allyl-}E}$: ΔG = −25.3 kcal/mol). However, **TS2**$^{\text{allyl-}E}$ for the borylcupration step is smaller than **TS1**$^{\text{allyl-}E}$ for the coordination step of the boryl copper(I) species to the allene (**TS1**$^{\text{allyl-}E}$: $\Delta G^{\ddagger}$ = 17.0 kcal/mol; **TS2**$^{\text{allyl-}E}$: $\Delta G^{\ddagger}$ = 16.4 kcal/mol). Therefore, once **EQ2**$^{\text{allyl-}E}$ is formed, the intermediate is more easily converted to **Int3**$^{\text{allyl-}E}$ rather than **EQ1**; that is, the coordination step is assumed to be irreversible. However, the energy difference between **TS1**$^{\text{allyl-}E}$ and **TS2**$^{\text{allyl-}E}$ is small; thus the reverse reaction from **EQ2**$^{\text{allyl-}E}$ to **EQ1** could potentially proceed to some extent. Likewise, the path of the minor *E*/*Z*-isomer, (*Z*)-**4**, is also irreversible, and **TS1**$^{\text{allyl-}Z}$ is the selectivity-determining step of this path (**TS1**$^{\text{allyl-}Z}$: $\Delta G^{\ddagger}$ = 18.9 kcal/mol; **EQ2**$^{\text{allyl-}Z}$: ΔG = 13.0 kcal/mol; **TS2**$^{\text{allyl-}Z}$: $\Delta G^{\ddagger}$ = 16.5 kcal/mol; **Int3**$^{\text{allyl-}Z}$: ΔG = −28.0 kcal/mol).

In contrast, the paths to regioisomers (*Z*)- and (*E*)-**5** exhibit more unstable borylcupration transition states than those to allylic boronates (*E*)- and (*Z*)-**4**. In these paths, **TS2** is higher than **TS1** [for (*Z*)-**5**; **TS1**$^{\text{alkenyl-}Z}$: $\Delta G^{\ddagger}$ = 16.0 kcal/mol, **EQ2**$^{\text{alkenyl-}Z}$: ΔG = 9.4 kcal/mol, **TS2**$^{\text{alkenyl-}Z}$: $\Delta G^{\ddagger}$ = 20.1 kcal/mol, **Int3**$^{\text{alkenyl-}Z}$: ΔG = −26.7 kcal/mol; for (*E*)-**5**; **TS1**$^{\text{alkenyl-}E}$: $\Delta G^{\ddagger}$ = 14.7 kcal/mol, **EQ2**$^{\text{alkenyl-}E}$: ΔG = 9.6 kcal/mol, **TS2**$^{\text{alkenyl-}E}$: $\Delta G^{\ddagger}$ = 19.4 kcal/mol, **Int3**$^{\text{alkenyl-}E}$: ΔG = −27.6 kcal/mol]. Due to the relatively high **TS2**$^{\text{alkenyl}}$ and low

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

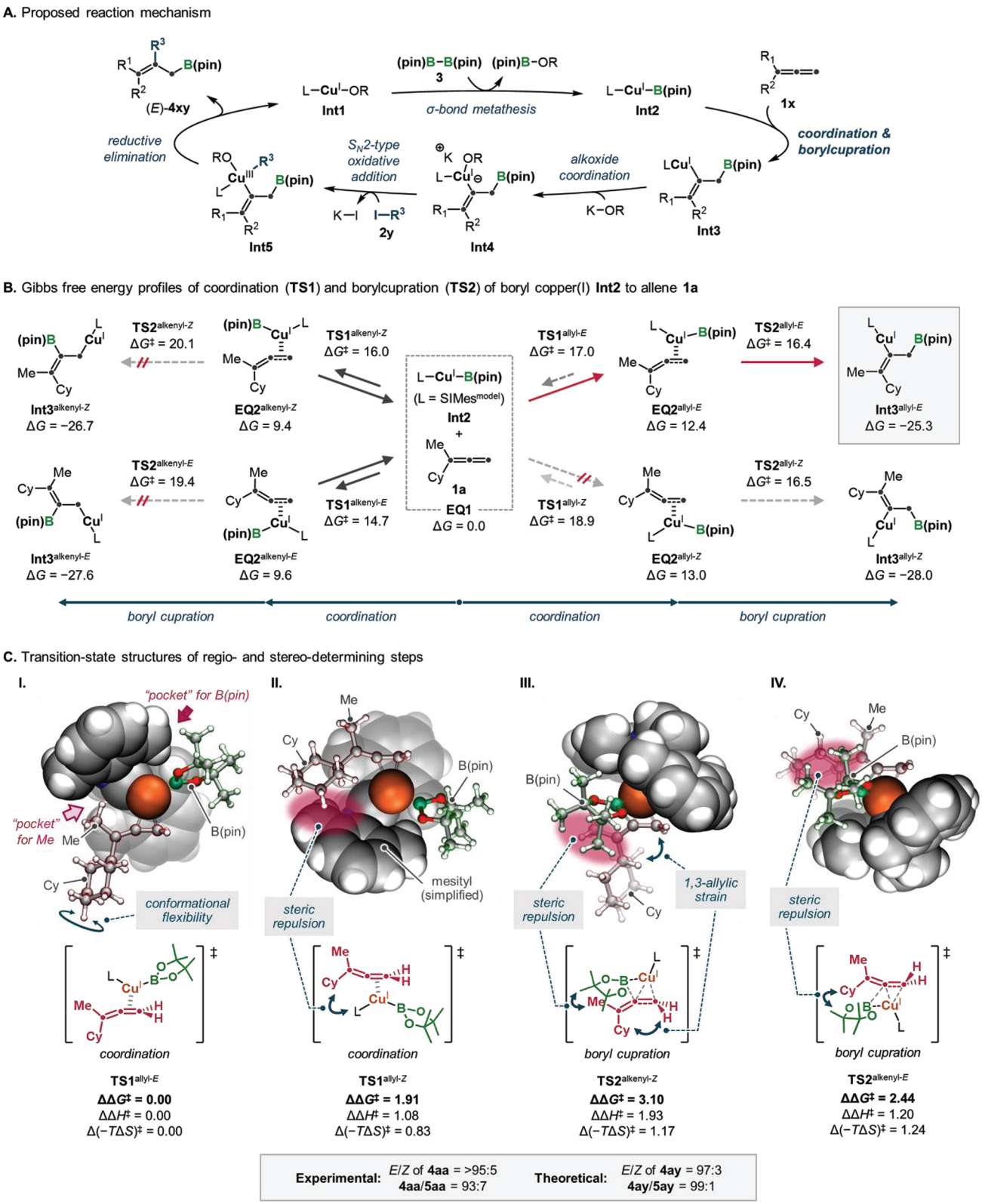


Figure 6. Proposed catalytic cycle and DFT study of the regio- and stereoselectivity-determining mechanism; energy values are given in kcal/mol.

TS1$^{\text{alkenyl}}$, the formation of **EQ2**$^{\text{alkenyl-}Z}$ and **EQ2**$^{\text{alkenyl-}E}$ is reversible, and **TS2**$^{\text{alkenyl-}Z}$ and **TS2**$^{\text{alkenyl-}E}$ are the selectivity-determining steps of these paths. In summary, the transition states of coordination, **TS1**$^{\text{allyl-}E}$ and **TS1**$^{\text{allyl-}Z}$, are the selectivity-determining steps for the formation of allylic boronates, whereas **TS2**$^{\text{alkenyl-}Z}$ and **TS2**$^{\text{alkenyl-}E}$ are the selectivity-determining steps for the formation of alkenyl boronates. Among these TSs, **TS1**$^{\text{allyl-}E}$ is kinetically the most favorable to reach the major product (*E*)-**4**.

Next, we analyzed the thermochemical properties of the selectivity-determining TSs illustrated in Figure 6C. The relative energies, Gibbs free energy ($\Delta\Delta G^{\ddagger}$), enthalpy

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

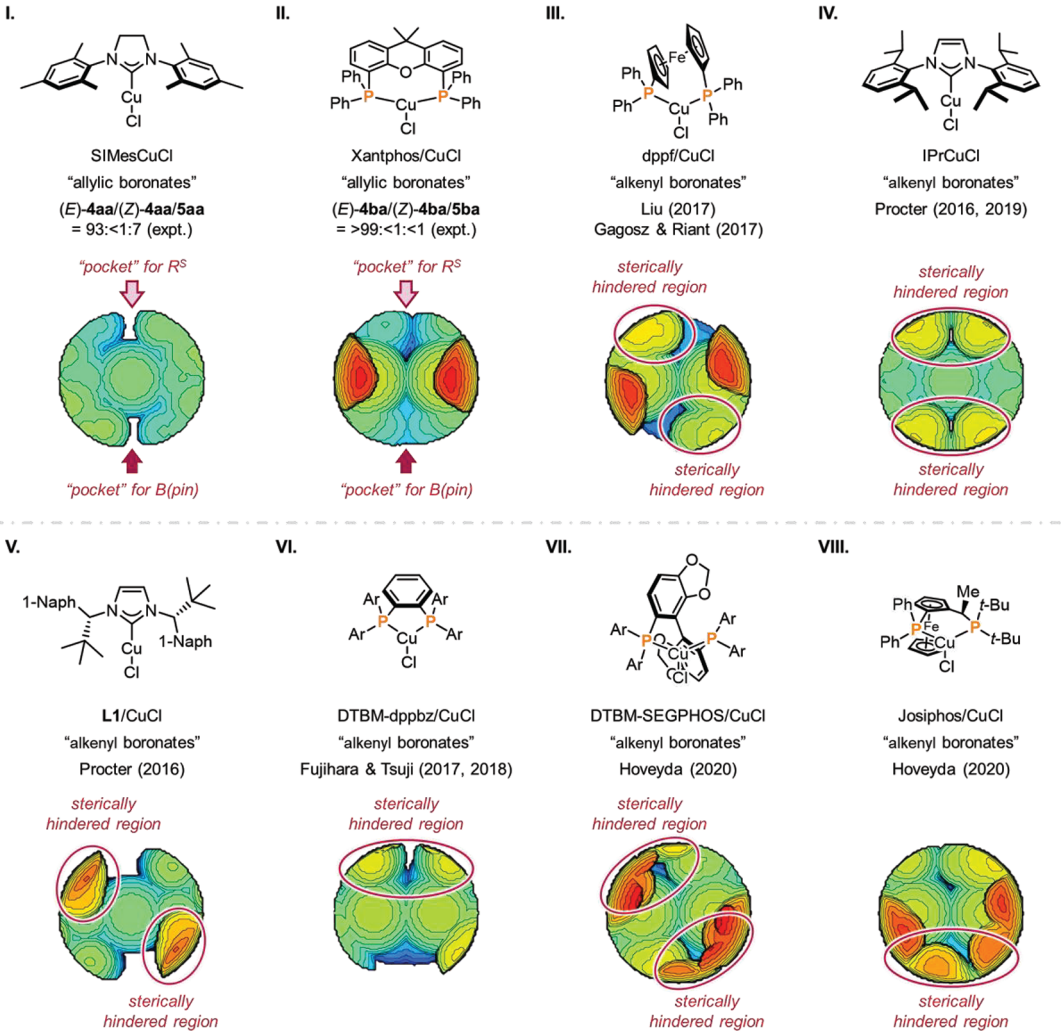


Figure 7. Comparison of ligands used in carboboration reactions of *gem*-disubstituted allenes.

($\Delta\Delta H^{\ddagger}$), and entropy $\{\Delta(-T\Delta S^{\ddagger})\}$ were calculated relative to those of the **TS1**$^{\text{allyl-}E}$ of the major product [$\Delta\Delta G^{\ddagger}$ = 0.00 kcal/mol, $\Delta\Delta H^{\ddagger}$ = 0.00 kcal/mol, $\Delta(-T\Delta S^{\ddagger})$ = 0.00 kcal/mol; Figure 6C, I]. The **TS1**$^{\text{allyl-}E}$ of the major path is enthalpically and entropically more favorable than those of the other paths. The **TS1**$^{\text{allyl-}Z}$ to give the minor stereoisomer (*Z*)-**4** is disfavored compared to the major TS, which gives an estimated stereoselectivity of *E*/*Z* = 97:3 [$\Delta\Delta G^{\ddagger}$ = 1.91 kcal/mol, $\Delta\Delta H^{\ddagger}$ = 1.08 kcal/mol, $\Delta(-T\Delta S^{\ddagger})$ = 0.83 kcal/mol; Figure 6C, II]. The TSs for the regioisomer, **TS2**$^{\text{alkenyl-}Z}$ and **TS2**$^{\text{alkenyl-}E}$, also exhibit higher relative enthalpies and entropies than that of the major TS [$\Delta\Delta G^{\ddagger}$ = 3.10 kcal/mol, $\Delta\Delta H^{\ddagger}$ = 1.93 kcal/mol, $\Delta(-T\Delta S^{\ddagger})$ = 1.17 kcal/mol; Figure 6C, III, $\Delta\Delta G^{\ddagger}$ = 2.44 kcal/mol, $\Delta\Delta H^{\ddagger}$ = 1.20 kcal/mol, $\Delta(-T\Delta S^{\ddagger})$ = 1.24 kcal/mol; Figure 6C, IV]. Considering these relative Gibbs free energies, the estimated regioselectivity is **4**:**5** = 99:1. The calculated selectivities are in good agreement with the experimental values (for **4aa**: experimental *E*/*Z* > 95:5, **4**:**5** = 93:7; theoretical *E*/*Z* = 97:3, **4**:**5** = 99:1).

Finally, we investigated the structures of the selectivity-determining TSs (Figure 6C). We speculated that the enthalpic effect for the destabilization of the minor TSs comes from steric repulsion, while the entropy effect is attributable to the difference in the degree of structural flexibility. In the case of the major TS, **TS1**$^{\text{allyl-}E}$, the methyl (Me) group and B(pin) group can be located in the pocket of the ligand to avoid steric repulsion (Figure 6C, I). Conversely, in the structure of the minor TS for the stereoisomer, **TS1**$^{\text{allyl-}Z}$, the steric repulsion between the mesityl group in the ligand and the cyclohexyl (Cy) group in the allene substrate contributes to the destabilization of this TS (Figure 6C, II). The steric repulsion between the substrate and the boryl group is also found to destabilize the minor **TS2**$^{\text{alkenyl-}Z}$ and **TS2**$^{\text{alkenyl-}E}$ (Figure 6C, III and VI). Furthermore, the increasing 1,3-allylic strain during the borylcupration via **TS2**$^{\text{alkenyl-}Z}$ causes extra destabilization of this minor TS. On the other hand, the entropic effect is assumed to result from the conformational flexibility of the Cy group. The rotational mode of the Cy group would be retained in **TS1**$^{\text{allyl-}E}$ because the Cy group is located far from the catalyst (Figure 6C, I). Conversely, the interaction between the Cy group and the catalyst or B(pin) group in **TS1**$^{\text{allyl-}Z}$ and **TS2**$^{\text{alkenyl-}E}$ locks the rotation of the Cy group, causing entropic destabilization of the structures (Figure 6C, II and IV). For the minor **TS2**$^{\text{alkenyl-}Z}$, the 1,3-allylic interaction should induce the same locking effect, although the Cy group is oriented in the opposite direction to the catalyst (Figure 6C, III).

To understand the differences in selectivity among the ligands, the steric hindrances of the ligands SIMes and Xantphos, which selectively produce allylic boronates, and

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

those of previously reported ligands for the production of alkenyl boronates were illustrated using a steric map (Figure 7).[86] The pocket-like structure around the top side for the smaller substituent R^S (R^1) of the allene substrate and bottom side for the B(pin) group in SIMes and Xantphos affords a high level of regio- and stereoselectivity to produce allylic boronates by avoiding significant steric repulsion (Figure 7, I and II). Conversely, several ligands that selectively produce alkenyl boronates through carboboration reactions of *gem*-disubstituted allenes via the 2,1-borylcupration have been reported to date. In 2017, the groups of Gagosz and Riant[47] and Liu[39] independently reported that the dppf ligand shows high regioselectivity in the reaction producing alkenyl boronates, which is similar to our results (Figure 7, III, and Table 1, entry 3). The dppf ligand contains two sterically hindered regions that can cause steric repulsions toward the R^S substituent and the B(pin) group, which would destabilize **TS1**$^{allyl\text{-}E}$. In 2016, the Procter group reported racemic and enantioselective carboboration reactions of *gem*-dialkylallenes with aldimines as the carbon electrophile.[41,42] One of the optimal ligands, IPr, exhibits steric hindrance around the top and bottom sides (Figure 7, IV). On the other hand, another optimal ligand, **L1**, contains deep pockets around the top and bottom sides, although the protruded steric hindrances of the 1-naphthyl groups might induce steric repulsion (Figure 7, V). Alternatively, it can be assumed that the "twisted" (C_2 symmetric) steric environment, such as those found in dppf, stabilizes **TS2**$^{alkenyl\text{-}Z}$ and **TS2**$^{alkenyl\text{-}E}$, which would result in the production of alkenyl boronates. In 2017 and 2018, the group of Fujihara and Tsuji reported the bora-formylation, -acylation, and -alkoxyoxalylation of *gem*-dialkylallenes.[46,50] In their reports, bulky dppbz-type ligands, DTBM-dppbz, showed excellent reactivity and regioselectivity to produce the corresponding alkenyl boronates. The ligand DTBM-dppbz exhibits steric hindrance around the top side, which can be expected to destabilize **TS1**$^{allyl\text{-}E}$ (Figure 7, VI). In 2020, the Hoveyda group reported that the DTBM-SEGPHOS and Josiphos ligands give alkenyl boronates via the carboboration of *gem*-dialkylallenes.[57] The ligand DTBM-SEGPHOS forms a steric environment similar to those of dppf and **L1** (Figure 7, VII). The Josiphos ligand contains a large sterically hindered region on the bottom (Figure 7, VIII). In conclusion, we assumed that the two pockets for the B(pin) group and the small substituent R^S around the top and bottom regions are crucial for the high regioselectivity of the 1,2-borylcupration and the resulting allylic boronates.

CONCLUSIONS

In summary, we have developed a regio- and stereoselective alkylboration of *gem*-dialkylallenes, which is a highly challenging intermolecular three-component coupling reaction, to access unprecedented multisubstituted allylic boronates that contain a differentially tetrasubstituted alkene structure. This reaction was applied to a wide variety of *gem*-dialkylallenes bearing *prim*-, *sec*-, and *tert*-alkyl groups. The optimal ligands SIMes and Xantphos can differentiate the bulk of the above alkyl substituents on the allene moiety to realize regio- and stereoselective borylcuprations. Furthermore, the allylboration of aldehydes allows the diastereoselective construction of quaternary carbon atoms. Further studies that aim at expanding the substrate scope to include functionalized allenes and carbon electrophiles other than *prim*-alkyl halides are currently in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c06538.

Experimental procedure, compound characterization, NMR spectra, and computational data (PDF)

Calculated structures (ZIP)

Accession Codes

CCDC 2062673, 2067460, 2067461, and 2070912 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Hajime Ito − *Division of Applied Chemistry, Graduate School of Engineering and Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido 060-8628, Japan;* orcid.org/0000-0003-3852-6721; Email: hajito@eng.hokudai.ac.jp

Authors

Yu Ozawa − *Division of Applied Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan;* orcid.org/0000-0002-0299-7073

Kohei Endo − *Division of Applied Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c06538

Author Contributions

The manuscript was prepared by contributions from all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by the Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), which was established by the World Premier International Research Initiative (WPI), MEXT, Japan, as well as by JSPS KAKENHI grants 17H06370 and 18H03907, and JST CREST grant JPMJCR19R1. Y.O. would like to thank the JSPS for a scholarship (19J20823) and the "Program for Leading Graduate Schools" (Hokkaido University "Ambitious Leaders Program"). The authors would like to thank Dr. Tomohiro Seki, Dr. Mingoo Jin, Dr. Kenta Kato, Mr. Chi Feng, Mr. Naoki Toyoshima, and Ms. Satsuki Matsuura for support with the X-ray diffraction analyses. Parts of the computational calculations were carried out on the supercomputer of the Research Center for Computational Science, Okazaki, Japan.

REFERENCES

(1) *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2006; Vols *1 and 2*.

(2) Diner, C.; Szabó, K. J. Recent Advances in the Preparation and Application of Allylboron Species in Organic Synthesis. *J. Am. Chem. Soc.* **2017**, *139*, 2−14.
(3) Hoffmann, R. W. Diastereogenic Addition of Crotylmetal Compounds to Aldehydes. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555−566.
(4) Kennedy, J. W. J.; Hall, D. G. Recent Advances in the Activation of Boron and Silicon Reagents for Stereocontrolled Allylation Reactions. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732−4739.
(5) Marek, I.; Sklute, G. Creation of Quaternary Stereocenters in Carbonyl Allylation Reactions. *Chem. Commun.* **2007**, 1683−1691.
(6) Hall, D. G. New Preparative Methods for Allylic Boronates and Their Application in Stereoselective Catalytic Allylborations. *Pure Appl. Chem.* **2008**, *80*, 913−927.
(7) Yus, M.; González-Gómez, J. C.; Foubelo, F. Diastereoselective Allylation of Carbonyl Compounds and Imines: Application to the Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, 5595−5698.
(8) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. Catalytic Asymmetric Allylation of Carbonyl Compounds and Imines with Allylic Boronates. *Org. Chem. Front.* **2014**, *1*, 303−320.
(9) Scott, H. K.; Aggarwal, V. K. Highly Enantioselective Synthesis of Tertiary Boronic Esters and Their Stereospecific Conversion to Other Functional Groups and Quaternary Stereocentres. *Chem. - Eur. J.* **2011**, *17*, 13124−13132.
(10) Leonori, D.; Aggarwal, V. K. Lithiation−Borylation Methodology and Its Application in Synthesis. *Acc. Chem. Res.* **2014**, *47*, 3174−3183.
(11) Leonori, D.; Aggarwal, V. K. Stereospecific Couplings of Secondary and Tertiary Boronic Esters. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082−1096.
(12) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. Direct Stereospecific Amination of Alkyl and Aryl Pinacol Boronates. *J. Am. Chem. Soc.* **2012**, *134*, 16449−16451.
(13) Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. Synthesis of Adjacent Quaternary Stereocenters by Catalytic Asymmetric Allylboration. *J. Am. Chem. Soc.* **2015**, *137*, 11262−11265.
(14) Alam, R.; Diner, C.; Jonker, S.; Eriksson, L.; Szabó, K. J. Catalytic Asymmetric Allylboration of Indoles and Dihydroisoquinolines with Allylboronic Acids: Stereodivergent Synthesis of up to Three Contiguous Stereocenters. *Angew. Chem., Int. Ed.* **2016**, *55*, 14417−14421.
(15) García-Ruiz, C.; Chen, J. L.-Y.; Sandford, C.; Feeney, K.; Lorenzo, P.; Berionni, G.; Mayr, H.; Aggarwal, V. K. Stereospecific Allylic Functionalization: The Reactions of Allylboronate Complexes with Electrophiles. *J. Am. Chem. Soc.* **2017**, *139*, 15324−15327.
(16) Jonker, S. J. T.; Diner, C.; Schulz, G.; Iwamoto, H.; Eriksson, L.; Szabó, K. J. Catalytic Asymmetric Propargyl- and Allylboration of Hydrazonoesters: A Metal-Free Approach to Sterically Encumbered Chiral α-Amino Acid Derivatives. *Chem. Commun.* **2018**, *54*, 12852−12855.
(17) Kiyokawa, K.; Hata, S.; Kainuma, S.; Minakata, S. Electrophilic Cyanation of Allylic Boranes: Synthesis of β,γ-Unsaturated Nitriles Containing Allylic Quaternary Carbon Centers. *Chem. Commun.* **2019**, *55*, 458−461.
(18) Hari, D. P.; Madhavachary, R.; Fasano, V.; Haire, J.; Aggarwal, V. K. Highly Diastereoselective Strain-Increase Allylborations: Rapid Access to Alkylidenecyclopropanes and Alkylidenecyclobutanes. *J. Am. Chem. Soc.* **2021**, *143*, 7462−7470.
(19) Elford, T. G.; Hall, D. G. Total Synthesis of (+)-Chinensiolide B via Tandem Allylboration/Lactonization. *J. Am. Chem. Soc.* **2010**, *132*, 1488−1489.
(20) Wohlfahrt, M.; Harms, K.; Koert, U. Asymmetric Allylboration of *vic*-Tricarbonyl Compounds: Total Synthesis of (+)-Awajanomycin. *Angew. Chem., Int. Ed.* **2011**, *50*, 8404−8406.
(21) Beveridge, R. E.; Batey, R. A. An Organotrifluoroborate-Based Convergent Total Synthesis of the Potent Cancer Cell Growth Inhibitory Depsipeptides Kitastatin and Respirantin. *Org. Lett.* **2014**, *16*, 2322−2325.
(22) Allais, C.; Roush, W. R. Enantio- and Diastereoselective Synthesis of 1,5-*syn*-(Z)-Amino Alcohols via Imine Double Allylboration: Synthesis of *trans*-1,2,3,6-Tetrahydropyridines and Total Synthesis of Andrachcine. *Org. Lett.* **2017**, *19*, 2646−2649.
(23) Kennedy, J. W. J.; Hall, D. G. Novel Isomerically Pure Tetrasubstituted Allylboronates: Stereocontrolled Synthesis of α-Exomethylene γ-Lactones as Aldol-Like Adducts with a Stereogenic Quaternary Carbon Center. *J. Am. Chem. Soc.* **2002**, *124*, 898−899.
(24) Zhu, N.; Hall, D. G. Effect of Additives on the Stereochemical Integrity and Reactivity of α-Alkoxycarbonyl Alkenylcopper Intermediates. Optimal Conditions for the Synthesis of Isomerically Pure Tetrasubstituted Alkenes. *J. Org. Chem.* **2003**, *68*, 6066−6069.
(25) Kennedy, J. W. J.; Hall, D. G. Lewis Acid Catalyzed Allylboration: Discovery, Optimization, and Application to the Formation of Stereogenic Quaternary Carbon Centers. *J. Org. Chem.* **2004**, *69*, 4412−4428.
(26) Baumann, A. N.; Music, A.; Karaghiosoff, K.; Didier, D. Highly Diastereoselective Approach to Methylenecyclopropanes via Boron-Homologation/Allylboration Sequences. *Chem. Commun.* **2016**, *52*, 2529−2532.
(27) Eisold, M.; Kiefl, G. M.; Didier, D. Single-Pot Asymmetric Approach toward Enantioenriched Quaternary Stereocenter-Containing Alkylidenecyclobutanes. *Org. Lett.* **2016**, *18*, 3022−3025.
(28) Eisold, M.; Baumann, A. N.; Kiefl, G. M.; Emmerling, S. T.; Didier, D. Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes. *Chem. - Eur. J.* **2017**, *23*, 1634−1644.
(29) Parsutkar, M. M.; Pagar, V. V.; RajanBabu, T. V. Catalytic Enantioselective Synthesis of Cyclobutenes from Alkynes and Alkenyl Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 15367−15377.
(30) The platinum-catalyzed diboration of *gem*-disubstituted allenes is an alternative strategy for the preparation of differentially 2,3,3-trisubstituted allylic boronates that have an alkenyl boronate structure instead of an all-carbon tetrasubstituted alkene structure; for details, see ref 31.
(31) Guo, X.; Nelson, A. K.; Slebodnick, C.; Santos, W. L. Regio- and Chemoselective Diboration of Allenes with Unsymmetrical Diboron: Formation of Vinyl and Allyl Boronic Acid Derivatives. *ACS Catal.* **2015**, *5*, 2172−2176.
(32) Pulis, A. P.; Yeung, K.; Procter, D. J. Enantioselective Copper Catalysed, Direct Functionalisation of Allenes via Allyl Copper Intermediates. *Chem. Sci.* **2017**, *8*, 5240−5247.
(33) Fujihara, T.; Tsuji, Y. Cu-Catalyzed Borylative and Silylative Transformations of Allenes: Use of β-Functionalized Allyl Copper Intermediates in Organic Synthesis. *Synthesis* **2018**, *50*, 1737−1749.
(34) Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M. Copper-Catalyzed Borylative Difunctionalization of π-Systems. *ACS Catal.* **2020**, *10*, 11578−11622.
(35) Talbot, F. J. T.; Dherbassy, Q.; Manna, S.; Shi, C.; Zhang, S.; Howell, G. P.; Perry, G. J. P.; Procter, D. J. Copper-Catalyzed Borylative Couplings with C−N Electrophiles. *Angew. Chem., Int. Ed.* **2020**, *59*, 20278−20289.
(36) Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. Copper-Catalyzed Cross-Coupling of Boronic Esters with Aryl Iodides and Application to the Carboboration of Alkynes and Allenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 3475−3479.
(37) Semba, K.; Bessho, N.; Fujihara, T.; Terao, J.; Tsuji, Y. Copper-Catalyzed Borylative Allyl−Allyl Coupling Reaction. *Angew. Chem., Int. Ed.* **2014**, *53*, 9007−9011.
(38) Meng, F.; McGrath, K. P.; Hoveyda, A. H. Multifunctional Organoboron Compounds for Scalable Natural Product Synthesis. *Nature* **2014**, *513*, 367−374.
(39) Xiong, M.; Xie, X.; Liu, Y. Copper-Catalyzed Borylative Cyclization of in Situ Generated *o*-Allenylaryl Nitriles with Bis(pinacolato)diboron. *Org. Lett.* **2017**, *19*, 3398−3401.
(40) Meng, F.; Jang, H.; Jung, B.; Hoveyda, A. H. Cu-Catalyzed Chemoselective Preparation of 2-(Pinacolato)Boron-Substituted Allylcopper Complexes and Their In Situ Site-, Diastereo-, and

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Enantioselective Additions to Aldehydes and Ketones. *Angew. Chem., Int. Ed.* **2013**, *52*, 5046−5051.
(41) Rae, J.; Yeung, K.; McDouall, J. J. W.; Procter, D. J. Copper-Catalyzed Borylative Cross-Coupling of Allenes and Imines: Selective Three-Component Assembly of Branched Homoallyl Amines. *Angew. Chem., Int. Ed.* **2016**, *55*, 1102−1107.
(42) Yeung, K.; Ruscoe, R. E.; Rae, J.; Pulis, A. P.; Procter, D. J. Enantioselective Generation of Adjacent Stereocenters in a Copper-Catalyzed Three-Component Coupling of Imines, Allenes, and Diboranes. *Angew. Chem., Int. Ed.* **2016**, *55*, 11912−11916.
(43) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. Catalytic Enantioselective 1,6-Conjugate Additions of Propargyl and Allyl Groups. *Nature* **2016**, *537*, 387−393.
(44) Zhao, Y.-S.; Tang, X.-Q.; Tao, J.-C.; Tian, P.; Lin, G.-Q. Efficient Access to *cis*-Decalinol Frameworks: Copper(I)-Catalyzed Borylative Cyclization of Allene Cyclohexanediones. *Org. Biomol. Chem.* **2016**, *14*, 4400−4404.
(45) Zhao, W.; Montgomery, J. Cascade Copper-Catalyzed 1,2,3-Trifunctionalization of Terminal Allenes. *J. Am. Chem. Soc.* **2016**, *138*, 9763−9766.
(46) Fujihara, T.; Sawada, A.; Yamaguchi, T.; Tani, Y.; Terao, J.; Tsuji, Y. Boraformylation and Silaformylation of Allenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 1539−1543.
(47) Boreux, A.; Indukuri, K.; Gagosz, F.; Riant, O. Acyl Fluorides as Efficient Electrophiles for the Copper-Catalyzed Boroacylation of Allenes. *ACS Catal.* **2017**, *7*, 8200−8204.
(48) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H. Catalytic Diastereo- and Enantioselective Additions of Versatile Allyl Groups to N−H Ketimines. *Nat. Chem.* **2017**, *9*, 1269−1275.
(49) Ozawa, Y.; Iwamoto, H.; Ito, H. Copper(I)-Catalysed Regio- and Diastereoselective Intramolecular Alkylboration of Terminal Allenes *via* Allylcopper(I) Isomerization. *Chem. Commun.* **2018**, *54*, 4991−4994.
(50) Sawada, A.; Fujihara, T.; Tsuji, Y. Copper-Catalyzed Bora-Acylation and Bora-Alkoxyoxalylation of Allenes. *Adv. Synth. Catal.* **2018**, *360*, 2621−2625.
(51) Yeung, K.; Talbot, F. J. T.; Howell, G. P.; Pulis, A. P.; Procter, D. J. Copper-Catalyzed Borylative Multicomponent Synthesis of Quaternary α-Amino Esters. *ACS Catal.* **2019**, *9*, 1655−1661.
(52) Han, J.; Zhou, W.; Zhang, P.-C.; Wang, H.; Zhang, R.; Wu, H.-H.; Zhang, J. Design and Synthesis of WJ-Phos, and Application in Cu-Catalyzed Enantioselective Boroacylation of 1,1-Disubstituted Allenes. *ACS Catal.* **2019**, *9*, 6890−6895.
(53) Zhang, S.; del Pozo, J.; Romiti, F.; Mu, Y.; Torker, S.; Hoveyda, A. H. Delayed Catalyst Function Enables Direct Enantioselective Conversion of Nitriles to NH 2 -Amines. *Science* **2019**, *364*, 45−51.
(54) Shen, B.-X.; Min, X.-T.; Hu, Y.-C.; Qian, L.-L.; Yang, S.-N.; Wan, B.; Chen, Q.-A. Copper-Catalyzed Boroacylation of Allenes to Access Tetrasubstituted Vinylboronates. *Org. Biomol. Chem.* **2020**, *18*, 9253−9260.
(55) Li, Z.; Zhang, L.; Nishiura, M.; Luo, G.; Luo, Y.; Hou, Z. Enantioselective Cyanoborylation of Allenes by N-Heterocyclic Carbene-Copper Catalysts. *ACS Catal.* **2020**, *10*, 11685−11692.
(56) Zhao, C.-Y.; Zheng, H.; Ji, D.-W.; Min, X.-T.; Hu, Y.-C.; Chen, Q.-A. Copper-Catalyzed Asymmetric Carboboronation of Allenes to Access α-Quaternary Amino Esters with Adjacent Stereocenters. *Cell Rep. Phys. Sci.* **2020**, *1*, 100067.
(57) del Pozo, J.; Zhang, S.; Romiti, F.; Xu, S.; Conger, R. P.; Hoveyda, A. H. Streamlined Catalytic Enantioselective Synthesis of α-Substituted β,γ-Unsaturated Ketones and Either of the Corresponding Tertiary Homoallylic Alcohol Diastereomers. *J. Am. Chem. Soc.* **2020**, *142*, 18200−18212.
(58) Deng, H.; Dong, Y.; Shangguan, Y.; Yang, F.; Han, S.; Wu, J.; Liang, B.; Guo, H.; Zhang, C. Copper-Catalyzed Three-Component Carboboronation of Allenes Using Highly Strained Cyclic Ketimines as Electrophiles. *Org. Lett.* **2021**, *23*, 4431−4435.
(59) Yuan, W.; Song, L.; Ma, S. Copper-Catalyzed Borylcupration of Allenylsilanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 3140−3143.
(60) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. Alkylboronic Esters from Copper-Catalyzed Borylation of Primary and Secondary Alkyl Halides and Pseudohalides. *Angew. Chem., Int. Ed.* **2012**, *51*, 528−532.
(61) Ito, H.; Kubota, K. Copper(I)-Catalyzed Boryl Substitution of Unactivated Alkyl Halides. *Org. Lett.* **2012**, *14*, 890−893.
(62) Iwamoto, H.; Kubota, K.; Yamamoto, E.; Ito, H. Copper(I)-Catalyzed Carbon−Halogen Bond-Selective Boryl Substitution of Alkyl Halides Bearing Terminal Alkene Moieties. *Chem. Commun.* **2015**, *51*, 9655−9658.
(63) Iwamoto, H.; Akiyama, S.; Hayama, K.; Ito, H. Copper(I)-Catalyzed Stereo- and Chemoselective Borylative Radical Cyclization of Alkyl Halides Bearing an Alkene Moiety. *Org. Lett.* **2017**, *19*, 2614−2617.
(64) We have previously demonstrated that PCy_3 is a "halide-selective" ligand over alkenes in a copper(I)/diboron catalyst system. Likewise, PCy_3 is considered to be more reactive toward alkyl halides than allenes under these reaction conditions; for details, see refs 62 and 63.
(65) Zanghi, J. M.; Liu, S.; Meek, S. J. Enantio- and Diastereoselective Synthesis of Functionalized Carbocycles by Cu-Catalyzed Borylative Cyclization of Alkynes with Ketones. *Org. Lett.* **2019**, *21*, 5172−5177.
(66) Long, R.; Huang, J.; Gong, J.; Yang, Z. Direct Construction of Vicinal All-Carbon Quaternary Stereocenters in Natural Product Synthesis. *Nat. Prod. Rep.* **2015**, *32*, 1584−1601.
(67) Zhou, F.; Zhu, L.; Pan, B.-W.; Shi, Y.; Liu, Y.-L.; Zhou, J. Catalytic Enantioselective Construction of Vicinal Quaternary Carbon Stereocenters. *Chem. Sci.* **2020**, *11*, 9341−9365.
(68) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. Acceleration Effect of Lewis Acid in Allylboration of Aldehydes: Catalytic, Regiospecific, Diastereospecific, and Enantioselective Synthesis of Homoallyl Alcohols. *J. Am. Chem. Soc.* **2002**, *124*, 12414−12415.
(69) Sakata, K.; Fujimoto, H. Quantum Chemical Study of Lewis Acid Catalyzed Allylboration of Aldehydes. *J. Am. Chem. Soc.* **2008**, *130*, 12519−12526.
(70) Kubota, K.; Iwamoto, H.; Ito, H. Formal Nucleophilic Borylation and Borylative Cyclization of Organic Halides. *Org. Biomol. Chem.* **2017**, *15*, 285−300.
(71) Royes, J.; Ni, S.; Farré, A.; La Cascia, E.; Carbó, J. J.; Cuenca, A. B.; Maseras, F.; Fernández, E. Copper-Catalyzed Borylative Ring Closing C−C Coupling toward Spiro- and Dispiroheterocycles. *ACS Catal.* **2018**, *8*, 2833−2838.
(72) In the catalytic cycle, the detailed mechanism of the alkylation step from **Int3** to **Int1** is still unclear at present. However, we would like to propose a mechanism that involves the formation of cuprate species **Int4** and a subsequent S_N2-type oxidative addition to alkyl halides based on refs 34, 49, 70, 71, and 73−80 and stoichiometric reactions as a mechanistic study (for details, see the Supporting Information). Alternatively, the formation of borates rather than cuprates was also reported in refs 81 and 82. A direct alkylation (methylation) of **Int3** has been proposed in ref 83.
(73) Nakamura, E.; Mori, S. Wherefore Art Thou Copper? Structures and Reaction Mechanisms of Organocuprate Clusters in Organic Chemistry. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750−3771.
(74) Mori, S.; Nakamura, E.; Morokuma, K. Mechanism of S_N2 Alkylation Reactions of Lithium Organocuprate Clusters with Alkyl Halides and Epoxides. Solvent Effects, BF_3 Effects, and Trans-Diaxial Epoxide Opening. *J. Am. Chem. Soc.* **2000**, *122*, 7294−7307.
(75) Yoshikai, N.; Nakamura, E. Mechanisms of Nucleophilic Organocopper(I) Reactions. *Chem. Rev.* **2012**, *112*, 2339−2372.
(76) Posner, G. H.; Sterling, J. J. Reaction of α,α'-Dibromo Ketones with Organocopper Reagents. New Method for α Alkylation of Ketones. *J. Am. Chem. Soc.* **1973**, *95*, 3076−3077.
(77) Posner, G. H.; Whitten, C. E.; Sterling, J. J. New Class of Mixed Cuprate(I) Reagents, Lithium Hetero(Alkyl) Cuprate(I), Which Allow Selective Alkyl Group Transfer. *J. Am. Chem. Soc.* **1973**, *95*, 7788−7800.

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(78) Posner, G. H.; Whitten, C. E. Substitution and Conjugate Addition Reactions Using New Lithium -Butoxy-Alkylcuprate(I) Reagents. *Tetrahedron Lett.* **1973**, *14*, 1815−1818.
(79) Please see our comments on a mechanistic study in the reference section of one of our previous reports (ref 80).
(80) Ito, H.; Toyoda, T.; Sawamura, M. Stereospecific Synthesis of Cyclobutylboronates through Copper(I)-Catalyzed Reaction of Homoallylic Sulfonates and a Diboron Derivative. *J. Am. Chem. Soc.* **2010**, *132*, 5990−5992.
(81) Kim-Lee, S. H.; Alonso, I.; Mauleón, P.; Arrayás, R. G.; Carretero, J. C. Rationalizing the Role of NaOtBu in Copper-Catalyzed Carboboration of Alkynes: Assembly of Allylic All-Carbon Quaternary Stereocenters. *ACS Catal.* **2018**, *8*, 8993−9005.
(82) Lin, S.; Lin, Z. DFT Studies on the Mechanism of Copper-Catalyzed Boracarboxylation of Alkene with CO2 and Diboron. *Organometallics* **2019**, *38*, 240−247.
(83) Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M. Copper(I)-Catalyzed Formal Carboboration of Alkynes: Synthesis of Tri- and Tetrasubstituted Vinylboronates. *J. Am. Chem. Soc.* **2012**, *134*, 15165−15168.
(84) Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. DFT Studies on the Mechanism of the Diboration of Aldehydes Catalyzed by Copper(I) Boryl Complexes. *J. Am. Chem. Soc.* **2008**, *130*, 5586−5594.
(85) Han, L.; Xu, B.; Liu, T. Mechanisms of the Synthesis of Trialkylsubstituted Alkenylboronates from Unactivated Internal Alkynes Catalyzed by Copper: A Theoretical Study. *J. Organomet. Chem.* **2018**, *864*, 154−159.
(86) Falivene, L.; Cao, Z.; Petta, A.; Serra, L.; Poater, A.; Oliva, R.; Scarano, V.; Cavallo, L. Towards the Online Computer-Aided Design of Catalytic Pockets. *Nat. Chem.* **2019**, *11*, 872−879.

https://doi.org/10.1021/jacs.1c06538
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX