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Copper(I)-catalysed regio- and diastereoselective intramolecular alkylboration of terminal allenes via allylcopper(I) isomerization

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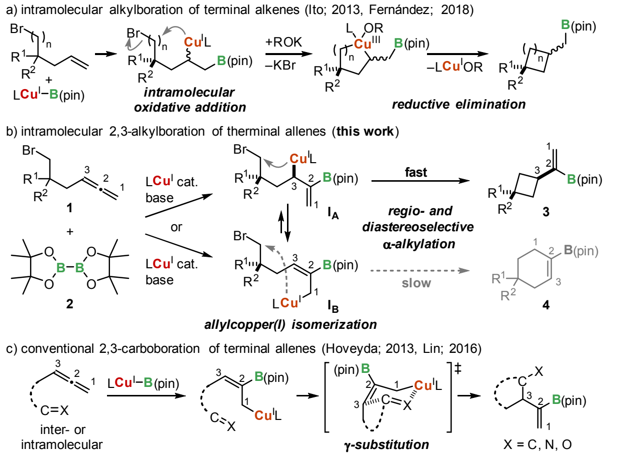
We report the first copper(I)-catalysed intramolecular alkylboration of terminal allenes with an alkyl halide moiety. The reaction provides alkenylboronates bearing a four-membered ring structure with high regio- and diastereocontrol. A possible reaction mechanism is proposed, involving the facile isomerization of an allylcopper(I) intermediate. A DFT study explains the experimental regio- and diastereoselectivity.

Carboboration of multiple bonds is a useful method for the synthesis of multifunctional organoboron compounds.[1] Intramolecular carboboration reactions afford cyclic organoboron compounds,[2,3] which are versatile building blocks for the rapid construction of complex skeletons. Recently, our group reported the intramolecular alkylboration of alkenes with an alkylhalide using a copper(I)/diboron catalyst system (Scheme 1a).[4–6] The alkylboron compounds containing a small ring structure are constructed by forming a new C–C bond at the α-position of the alkylcopper(I) species generated *in situ* through substitution of the C–Br bond.

We planned to synthesize alkenyl boron compounds **3**, containing a four-membered ring, through intramolecular 2,3-alkylboration of terminal allenes **1** (Scheme 1b). Previously, Hoveyda and co-workers reported the first intermolecular 2,3-carboboration reaction of terminal allenes via an allylcopper(I) intermediate using carbonyl compounds as the electrophiles (Scheme 1c).[7] More recently, Lin and co-workers reported the synthesis of alkenylboron compounds bearing a *cis*-decalin structure using an intramolecular reaction with a similar catalyst system.[8] These reactions were thought to proceed through the γ-substitution of the 3-position to the unsaturated double bond (C=X) via a chair-like transition state.[7–10] However, there are no reports of a reaction using an alkyl halide as the carbon electrophile that has the α-substitution reactivity to access the small ring structure,[4,5] rather than γ-substitution reactivity.

One challenge for this transformation is the controlling the regioselectivity between **3** and the six-membered ring product **4**, as the allylcopper(I) intermediate formed by addition of the borylcopper(I) species to the terminal allene can isomerize between the thermodynamically less stable **I**$_A$ and the more stable **I**$_B$ (Scheme 1b).[11] Intramolecular α-alkylation at the 3-position of **I**$_A$ gives **3**, and α-alkylation at the 1-position of **I**$_B$ gives **4**. Herein, we report the first copper(I)-catalysed regio- and diastereoselective intramolecular alkylboration of terminal allenes. The carbon atom at the 3-position was regioselectively alkylated via the thermodynamically less stable allylcopper(I) intermediate **I**$_A$ under kinetic control at the cyclization step. Furthermore, the reaction proceeded diastereoselectively, influenced by substituents R^1 and R^2 during the isomerization between allylcopper(I) intermediates **I**$_A$ and **I**$_B$. This is also the first example of four-membered-ring borylative cyclizations demonstrating high diastereoselectivity at the 1,3-position.[4,5] These selectivities were investigated by density functional theory (DFT) calculations.



Scheme 1 Intra- and intermolecular carboboration of allenes and alkenes.

We chose aliphatic terminal allene **1a** as the model substrate for optimizing the reaction conditions (Table 1). Subjecting

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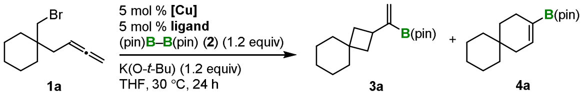
substrate **1a** to the reaction conditions, using (*o*-tol)$_3$P as a ligand for the copper(I) catalyst for the borylative cyclization of alkynes, which our group previously reported,[6b] resulted in full conversion of **1a** but a low yield of four-membered-ring cyclization product **3a** (entry 1: 32%). However, when the reaction was performed at lower concentrations, the desired product **3a** was obtained in higher yield with excellent regioselectivity, along with a trace amount of the six-membered-ring cyclization product **4a** (entry 2: 70%, **3a**/**4a** = 98:2, entry 3: 75%, **3a**/**4a** = 98:2). This implies that the intermolecular side reaction was supressed at low concentrations. The reaction using the monophosphine ligands PPh$_3$ and PCy$_3$, which have smaller cone angles than that of (*o*-tol)$_3$P,[12] afforded the product in moderate yield (entry 4: 46%, **3a**/**4a** = 96:4, entry 5: 62%, **3a**/**4a** = 99:1), suggesting that the steric effect was important. Sterically more demanding ligand (mes)$_3$P[13] and XPhos[14] were also effective in the reaction, affording the product in high yields (entry 6: 74%, **3a**/**4a** = 97:3, entry 7: 70%, **3a**/**4a** = 98:2). Although the bisphosphine ligand dppp showed moderate reactivity (entry 8: 44%, **3a**/**4a** = 97:3), Xantphos was not suitable for this reaction (entry 9: 8%). We then investigated the impact of the copper(I) precursor. The use of CuI furnished the desired product in high yield with excellent regioselectivity in the cyclization reaction, whereas cationic copper(I) salt (MeCN)$_4$CuBF$_4$ was less effective (entry 10: 81%, **3a**/**4a** = 98:2, entry 11: 63%, **3a**/**4a** = 98:2).

Table 1 Optimization of the reaction conditions[a]

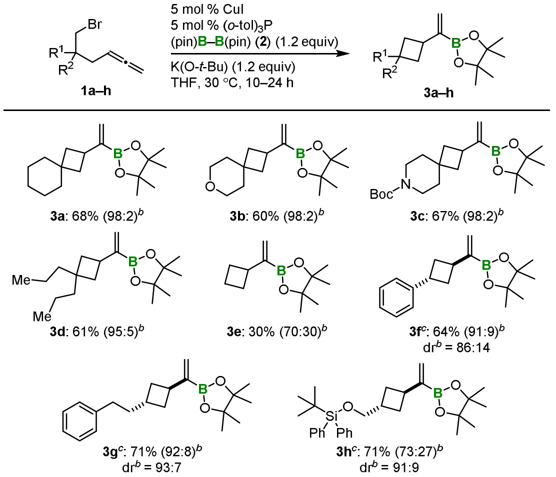


Entry	[Cu]	Ligand	Conc. (M)	Yield[b] (%)	**3a/4a**[c]
1	CuCl	(*o*-tol)$_3$P	0.50	32[d]	nd[e]
2[f]	CuCl	(*o*-tol)$_3$P	0.25	70	98:2
3	CuCl	(*o*-tol)$_3$P	0.10	75	98:2
4	CuCl	PPh$_3$	0.10	46	96:4
5	CuCl	PCy$_3$	0.10	62	99:1
6	CuCl	(mes)$_3$P	0.10	74	97:3
7	CuCl	XPhos	0.10	70	98:2
8	CuCl	dppp	0.10	44	97:3
9	CuCl	Xantphos	0.10	8	nd[e]
10[g]	CuI	(*o*-tol)$_3$P	0.10	81	98:2
11	(MeCN)$_4$CuBF$_4$	(*o*-tol)$_3$P	0.10	63	98:2

[a] Conditions: CuI (0.0125 mmol), ligand (0.0125 mmol), **1a** (0.25 mmol), bis(pinacolato)diboron (**2**) (0.30 mmol) and K(O-*t*-Bu) (0.30 mmol) in THF (2.5 mL). [b] GC yield was determined by GC analysis of the reaction mixture using an internal standard. [c] Determined by GC analysis of the reaction mixture. [d] Determined by ^{1}H NMR analysis of the crude material using an internal standard. [e] nd = not determined. [f] 0.20 mmol of **1a** was used. [g] 0.50 mmol of **1a** was used.

With the optimized conditions in hand, we next investigated the substrate scope of this intramolecular borylative cyclization reaction using a variety of allene substrates bearing a bromine leaving group (Table 2). The model substrate **1a** was successfully converted to the alkenylboronate **3a** bearing a spiro[3.5]nonane structure (**3a**: 68%, **3a**/**4a** = 98:2). Heteroatom-containing spirocycles incorporating a four-membered ring were also obtained with excellent regioselectivity (**3b**: 60%, **3b**/**4b** = 98:2, **3c**: 67%, **3c**/**4c** = 98:2). A trisubstituted cyclobutane was formed in slightly lower yield with high regioselectivity (**3d**: 61%, **3d**/**4d** = 95:5). However, a monosubstituted cyclobutane was obtained in low yield with moderate regioselectivity (**3e**: 30%, **3e**/**4e** = 70:30). We then investigated the diastereoselective cyclization of allene substrates (**3f**–**3h**). A *trans*-disubstituted cyclobutane, *trans*-**3f**, was obtained with good regio- and diastereoselectivity (**3f**: 64%, **3f**/**4f** = 91:9, dr = 86:14). The reactions with alkyl-substituted substrates proceeded with higher diastereoselectivity (**3g**: 71%, **3g**/**4g** = 92:8, dr = 93:7, **3h**: 71%, **3h**/**4h** = 73:27, dr = 91:9).

Table 2 Substrate scope of the intramolecular alkylboration of terminal allenes[a]



[a] Conditions: CuI (0.025 mmol), ligand (0.025 mmol), **1a** (0.50 mmol), bis(pinacolato)diboron (**2**) (0.60 mmol) and K(O-*t*-Bu) (0.60 mmol) in THF (5.0 mL). [b] **3**/**4** ratio is shown in parenthesis (the **3**/**4** ratio and diastereoselectivity were determined by GC analysis of the reaction mixture). [c] The product was isolated as a mixture of the regioisomer and the diastereomer.

To demonstrate the utility of the alkenylboronates synthesized by this intramolecular alkylboration reaction of allenes, we conducted a Suzuki–Miyaura cross-coupling reaction of the borylation products (Scheme 2, eq. 1 and 2). The reaction of alkenylboronate **3a** with an aryl bromide afforded the corresponding coupling product **5** in high yield (**5**: 87%). The reaction between alkenylboronate **3b** and an alkenyl bromide also proceeded smoothly to produce diene **6** in moderate yield (**6**: 60%). Recently, our group reported a novel method for the transformation of alkenylboronates to acylboron compounds,[15] which can be used for amide-forming bioconjugation.[16] Acylboron **8** was obtained in high yield through ozonolysis of alkenyl MIDA boronate **7** under mild reaction conditions (Scheme 2, eq. 3, **8**: 83%).

To gain insight into the reaction mechanism, we first conducted protonolysis of the organocopper(I) intermediate generated *in situ* under the standard reaction conditions (Scheme 3). The corresponding protoboration product, alkenylboron compound **9**, retaining the alkyl halide moiety,

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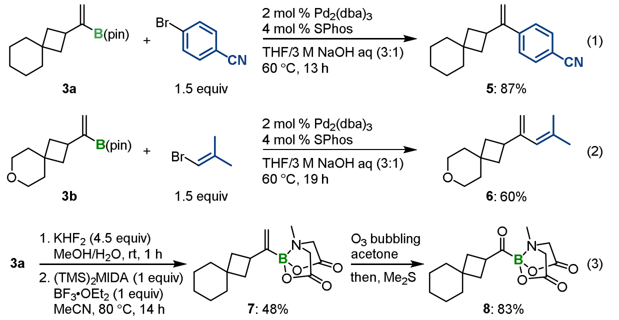
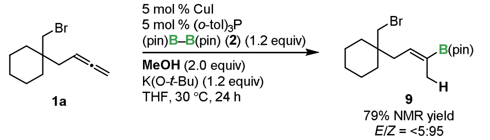
was obtained in high yield (**9**: 79%); this indicates that the allene is more reactive than the alkyl halide under these reaction conditions. Thus, a radical cyclization initiated by the reaction between borylcopper(I) and the C–Br bond can be eliminated from the possible reaction pathways.[2b,17]



Scheme 2 Derivatization of borylation products.



Scheme 3 Protonolysis of the allylcopper(I) intermediate.

The proposed reaction mechanism is shown in Fig. 1. At the beginning of the reaction, borylcopper(I) intermediate **V** selectively reacts with the allene moiety rather than the alkyl halide moiety in substrate **1** to generate the allylcopper(I) intermediate $\mathbf{I_A}$ or $\mathbf{I_B}$ via boryl cupration of the internal or terminal double bond of the allene, respectively. The resulting intermediates, allylcopper(I) species $\mathbf{I_A}$ and $\mathbf{I_B}$, are easily interchanged at room temperature. Cuprates $\mathbf{II_A}$ and $\mathbf{II_B}$ are then formed through reversible coordination of an alkoxide to the copper(I) center.[18] The subsequent intramolecular oxidative addition then produces cupracycles $\mathbf{III_A}$ and $\mathbf{III_B}$,[19] with five-membered cupracycle $\mathbf{III_A}$ being kinetically favoured over seven-membered cupracycle $\mathbf{III_B}$ (see the ESI† for the detailed discussion).[20] As potassium bromide is precipitated from the solution, this oxidative addition step is irreversible, and determines the regioselectivity of the cyclization. Reductive elimination of $\mathbf{III_A}$ gives the product **3** and copper(I)-alkoxide **IV**. Borylcopper(I) intermediate **V** is regenerated by the reaction of **IV** and diboron reagent **2**.

Based on the above-proposed reaction mechanism, we then carried out detailed DFT calculations to describe the diastereoselectivity of the reaction producing the *trans*-disubstituted cyclobutane ring as the major product (Fig. 2). We used allene **1x** and $Me_3PCuB(en)$ catalyst system **V'** instead of (*o*-tol)$_3$PCuB(pin) (**V**) as simpler model substrates. All calculations were conducted at ωB97X-D/def2-SVP/SMD(THF) level of theory (see the ESI† for the computational details and the full list of references). The relative energies based on **1x** and **V'** are illustrated in Fig. 2. Borylcupration of the allene moiety in substrate **1x** can potentially produce four isomers of allylcopper(I) species: *trans*-$\mathbf{I_A}$ (–31.4 kcal/mol), *cis*-$\mathbf{I_A}$ (–31.7 kcal/mol) , *trans*-$\mathbf{I_B}$ (–36.7 kcal/mol) and *cis*-$\mathbf{I_B}$ (–33.9 kcal/mol). The *trans*-$\mathbf{I_A}$ isomer is directly connected to *trans*-$\mathbf{I_B}$ and *cis*-$\mathbf{I_B}$ with a low energy barrier, but not to *cis*-$\mathbf{I_A}$ (see the ESI† for a detailed discussion). In the same way, *cis*-$\mathbf{I_A}$ directly connects with *trans*-$\mathbf{I_B}$ and *cis*-$\mathbf{I_B}$, but not with *trans*-$\mathbf{I_A}$. Coordination of an alkoxide to intermediates **I** leads to the metastable intermediates **II**, which is an exothermic reaction by 14.1–15.0 kcal/mol. In this structure, copper(I) has a trigonal planar geometry and the potassium cation is chelated by two oxygen atoms from the alkoxide and boronic acid ester. The cuprate *trans*-$\mathbf{II_A}$ is isomerized to *cis*-$\mathbf{II_A}$ through the transient intermediates **I**, for example, in the sequence of *trans*-$\mathbf{II_A}$, *trans*-$\mathbf{I_A}$, *cis*-$\mathbf{I_B}$, *cis*-$\mathbf{I_A}$ and *cis*-$\mathbf{II_A}$.

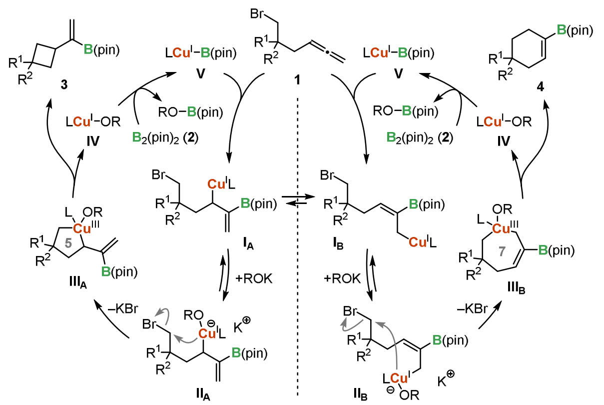


Fig. 1 Proposed reaction mechanism.

We next elucidated the origin of diastereoselectivity of the cyclization. The oxidative addition step is irreversible to produce the five-membered cupracycles **III** with the release of KBr. In this step, copper(I) is oxidized to copper(III), with a square planar geometry. The difference in the activation energy between these two steps $\Delta\Delta G^{\ddagger}_{cis}$–$\Delta\Delta G^{\ddagger}_{trans}$ is 1.0 kcal/mol, which is in good agreement with the value derived from the experimental results (1.1–1.5 kcal/mol, *cis*/*trans* = 86:14–93:7). It is assumed that the stability of the transition states is affected by the conformation of resulting cupracycles **III**. Furthermore, we were unable to find an energetically reasonable pathway from *cis*-$\mathbf{III_A}$ to *trans*-$\mathbf{III_A}$, which implies that isomerization of allylcopper(III) would not occur.[19] Accordingly, the diastereoselectivity is determined at the oxidative addition step with kinetic control.

In conclusion, we have developed an intramolecular 2,3-alkylboration of terminal allenes to produce alkenylboronates bearing a four-membered ring structure. The reaction proceeded in a highly regio- and diastereoselective manner, which was enabled by facile allylcopper(I) isomerization. These kinetic control selectivities were explained using a DFT study. Further studies towards the development of an enantioselective version of this reaction are currently in progress.

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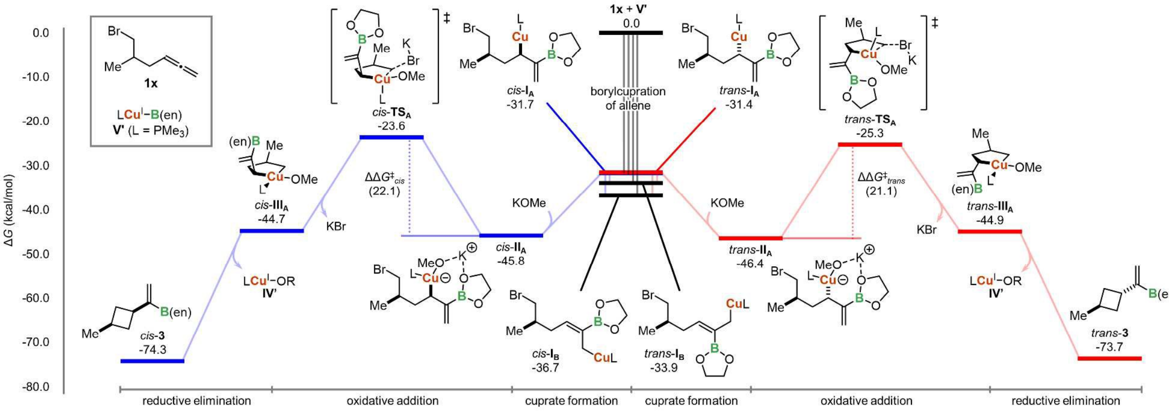

Fig. 2 Free energy diagram of the diastereoselective intramolecular 2,3-alkylboration of terminal allenes.

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Conflicts of interest

There are no conflicts to declare.

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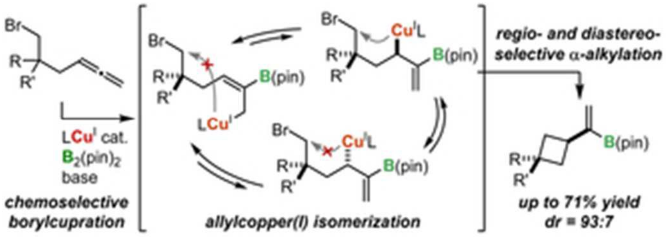

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