A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
International Edition
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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201813490
Angew. Chem. 10.1002/ange.201813490

Link to VoR: http://dx.doi.org/10.1002/anie.201813490
http://dx.doi.org/10.1002/ange.201813490

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Enantioconvergent Synthesis of Tertiary Cyclic Allylboronates Using (Guanidine)copper Complex-Catalyzed Allylic Borylation

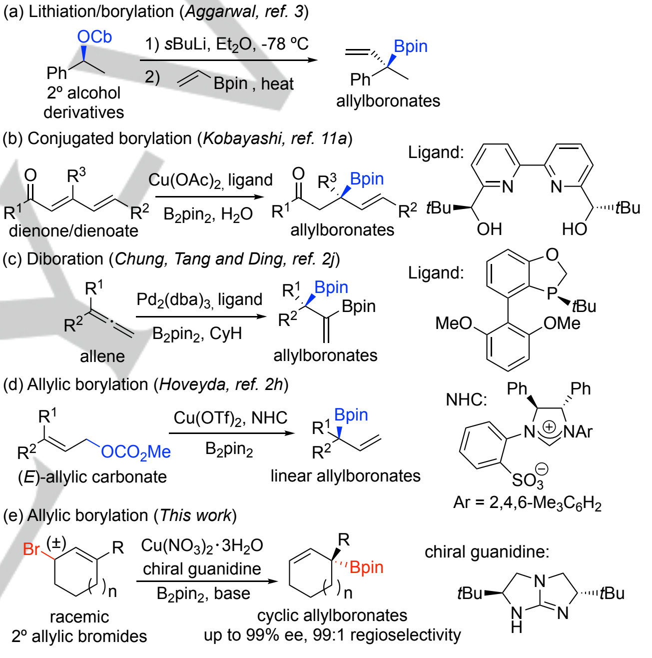
Yicen Ge,[a] Xi-Yang Cui,[a] Siu Min Tan,[b] Huan Jiang,[a] Jingyun Ren,[a] Nicholas Lee,[a] Richmond Lee[b]* and Choon-Hong Tan[a]*

Abstract: An enantioconvergent synthesis of chiral cyclic allylboronates is demonstrated with racemic allylic bromides using a (guanidine)copper catalyst. The allylboronates were acquired with high γ/α regioselectivities (up to 99:1) and enantioselectivities (up to 99% ee) and could be further transformed into diverse functionalized allylic compounds without erosion of optical purity. Experimental and DFT mechanistic studies indicated an S_N2' borylation process catalyzed by a monodentate guanidine-copper(I) complex *via* a special direct enantio-convergent transformation mechanism.

Chiral tertiary allylboronates are useful synthetic building blocks,[1–3] which boryl-substituted stereocenters can be transformed into diverse chiral quaternary functionalities or be utilized to form homoallylic alcohols or amines via allylboration. While there is a myriad of approaches to synthesizing chiral secondary allylboronates,[4–12] ranging from hydroboration to conjugated borylation, direct access to tertiary ones is still very limited (Scheme 1). Using enantio-enriched secondary alcohols, the corresponding vinyl-substituted tertiary allylboronates can be prepared through a lithiation/borylation protocol (Scheme 1a).[3] Separately, tertiary allylboronates can be obtained through conjugated borylation of dienones or dienoates, catalyzed with a chiral copper complex (Scheme 1b)[11a] or through a palladium-catalyzed diboration of allene (Scheme 1c).[2j] Remarkably, enantioselective synthesis of linear tertiary allylboronates was also demonstrated through allylic borylation of trisubstituted allylic carbonates using a Cu-NHC catalyst (Scheme 1d).[2h]

In copper-catalyzed asymmetric allylic borylation, it is often observed that rather than a metal-allyl complex, a copper-boryl intermediate is first formed followed by stereoselective S_N2' attack.[2h,4] Racemic allylic substrates, though easy to obtain, are challenging to be used in stereo-convergent borylation.[13] Only recently Ito developed a direct enantio-convergent transformation (DECT), where two enantiomers of the allylic ethers underwent the *anti*- or *syn*-S_N2' pathways respectively, leading to the same borylated product.[4d]

In the past decade, we have developed asymmetric transformations using chiral guanidines as Brønsted base catalysts, as well as guanidinium salts as phase-transfer or ion-pairing catalysts.[14] It is still rare to employ chiral guanidine as ligands or co-catalysts in transition metal-catalyzed asymmetric reactions.[15] Recently, an efficient dynamic kinetic copper-catalyzed asymmetric allylic alkynylation reaction was reported by our group using chiral bicyclic guanidine.[16a] Such (guanidine)copper complex was also found to catalyze the formation of secondary and tertiary allylboronates. This regioselective S_N2' allylic borylation was achieved using various racemic allylic bromides in good yields and excellent enantioselectivities (Scheme 1e).



Scheme 1. Synthesis of enantio-enriched tertiary allylboronates.

Initially, we employed commercially available (±)-3-bromocyclohexene **1a** and bis(pinacolate)diboron (B_2pin_2) as model substrates. After exploring several guanidinium catalysts and investigating various reaction conditions, we obtained the best results when copper nitrate was used in combination with bicyclic guanidinium **CG1** (for full optimization details see Supporting Information S26). Under the optimized conditions, (±)-3-bromocyclohexene **1a** was completely converted to the desired allylboronate **2a** with 97% ee (Table 1, entry 1). The yield and enantioselectivity remained the same when the counter-anion of guanidinium catalyst was changed to PF_6^- (entry 2). Dimethylated guanidinium salt **CG3** led to a dramatic decrease in both yield and enantioselectivity (entry 3), as did the use of **PN** and **BG** (entries 8 and 9). Less bulky guanidiniums **CG4**–**6** furnished the product in high yields but with diminished ee values (entries 4–6), whereas the usage of bisguanidinium salt **BCG** rendered the reaction sluggish (entry 7).

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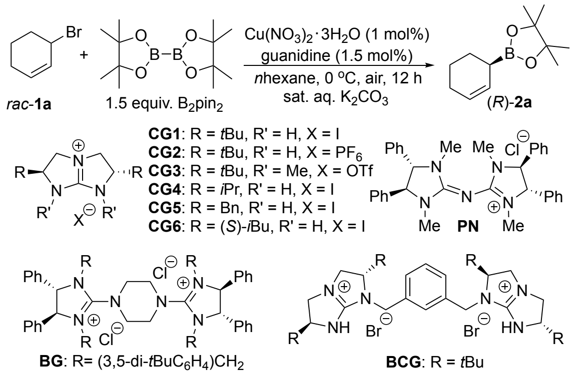
Table 1. Allylic borylation of (±)-3-bromocyclohexene **1a**.[a]



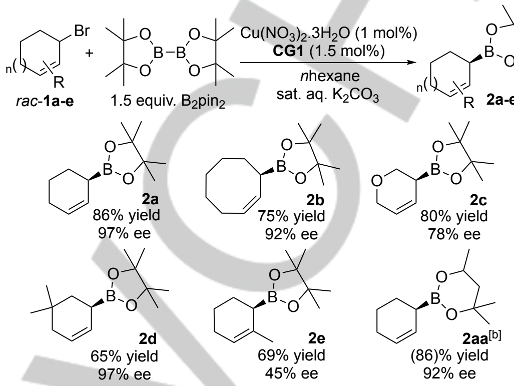
Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**CG1**	> 99	97
2	**CG2**	> 99	97
3	**CG3**	12	11
4	**CG4**	> 99	71
5	**CG5**	86	77
6	**CG6**	71	72
7	**BCG**	31	90
8	**PN**	25	17
9	**BG**	22	23

[a] Reagents and conditions: *rac*-**1a** (0.10 mmol), $Cu(NO_3)_2\cdot 3H_2O$ (0.001 mmol), catalyst (0.0015 mmol), bis(pinacolato)diboron (0.15 mmol), 0.2 mL saturated K_2CO_3 aqueous solution in *n*hexane (1 mL) at 0 °C for 12h. [b] Calibrated GC yield with biphenyl as internal standard. [c] Determined by GC analysis with a chiral column.

With the optimized conditions, we first investigated the scope of the reaction with racemic cyclic allylic bromides bearing various ring structures and functionalities. A series of secondary allylboronates **2a**-**2e** was successfully prepared with moderate yields and good ee values (Table 2). Substituents at the 2-position led to a significant decrease in enantioselectivity (Table 2, **2e**). In most cases, NMR yields were excellent and the isolation of these unstable products were successful but precarious. When racemic allylic chloride was used instead, the (guanidine)copper catalyst gave satisfactory results but more diboron reagents were required (SI S29). Interestingly, switching to bis(hexyleneglycolato)diboron (B_2hex_2) as the boryl source did not affect the reaction significantly; the additional chiral center on the Bhex group did not perturb the reaction (Table 2, **2aa**).

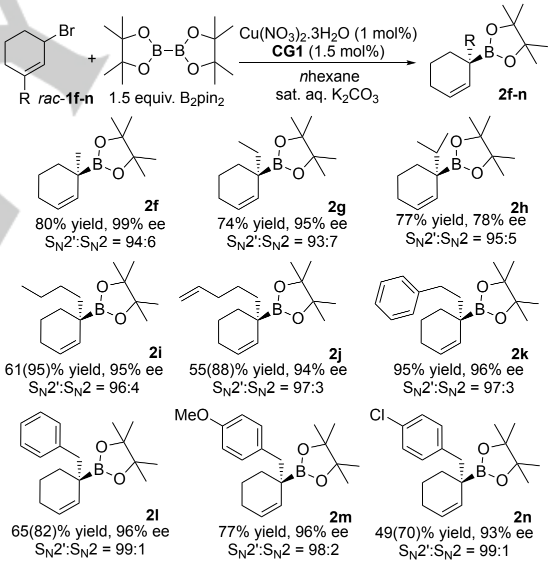
Excited by the good reaction profile, we next examined the more attractive scenario of preparing allylic boronates bearing boryl-substituted quaternary stereocenters (Table 3). Various racemic 1-substituted cyclic allylbromides **1f**–**1n** were evaluated and those carrying methyl **1f**, ethyl **1g** and *n*butyl **1i** substitutions were all converted into the desired tertiary allylboronates with high ee values. The high α/γ regioselectivity (above 1:20) suggested that the borylation proceeded in a regioselective S_N2' substitution pathway. Notably, the sterically bulky substrate **1h** led to a decreased enantioselectivity. Use of a radical-probe **1j**, did not lead to cyclized by-products, indicating that the reaction was unlikely to undergo pathways involving radical intermediates. 1-Benzylic allylic bromides gave **2l**–**2n** with good enantioselectivities regardless of the electron density on the aryl groups.

Table 2. Enantioconvergent synthesis of secondary allylboronates. [a]



[a] Reagents and conditions: allylbromide (0.10 mmol), $Cu(NO_3)_2\cdot 3H_2O$ (0.001 mmol), catalyst (0.0015 mmol), bis(pinacolato)diboron (0.15 mmol), 0.2 mL saturated K_2CO_3 aqueous solution in *n*hexane (1 mL) at 0 °C for 12~24h. Isolated (NMR) yields reported. Enantiomeric excesses were determined by chiral GC analysis. [b] Bis(hexyleneglycolato)diboron was used instead.

Table 3. Enantio-convergent synthesis of tertiary allylboronates.



Reagents and conditions: allylbromide (0.10 mmol), $Cu(NO_3)_2\cdot 3H_2O$ (0.001 mmol), catalyst (0.0015 mmol), bis(pinacolato)diboron (0.15 mmol), 0.2 mL saturated K_2CO_3 aqueous solution in *n*hexane (1 mL) at 0 °C for 18h. Isolated (NMR) yields reported. Enantiomeric excesses were determined by the chiral GC or HPLC analysis of the corresponding alcohols. The α/γ regioselectivities were identified by GC.

To obtain a clearer picture of the reaction mechanism, a series of control experiments were conducted (SI S52). The formation of metallic copper was observed without air, which resulted in lower yields and enantioselectivities (Table S2, entry 4). Besides copper, base and guanidine catalyst, water was also found essential to afford the desired borylation products (Table S2, entry 5). Intrigued by the above observations, we carried out further studies using electronic paramagnetic resonance (EPR) to distinguish the oxidation state of the copper catalytic species (SI S53). When treated with basified guanidine **CG1'** and B_2pin_2, the EPR signal of paramagnetic Cu(II) species was diminished rapidly but recovered if the resulting mixture was exposed to air. We proposed that Cu(II) was reduced to diamagnetic Cu(I) species by B_2pin_2 with the aid of basic guanidine, which acted as the catalyst in borylation process.

To better understand the role of bicyclic guanidine in this transformation, the crystal of Cu(**CG1'**)Cl complex **I** was obtained. X-ray crystallographic studies showed the existence of two ligand-coordination patterns in a 1:1 ratio (Figure 1). Form **A** (Figure 1, left) was a simple mono-ligated CuCl complex with **CG1'**, bearing a weak Cu–Cu interaction. However, form **B** (Figure 1, right) was shown to be a dichloridocuprate salt with bis-ligated Cu(I) cation as the counterion, which was detected by CSI-MS in our previous work.[16a] Such an observation indicated a possible isomerization between the two structures in solution. Based on the absence of non-linear effect (NLE) observed in the reaction (SI S55), we proposed that the mono-ligated Cu(I) complex is the active catalyst.

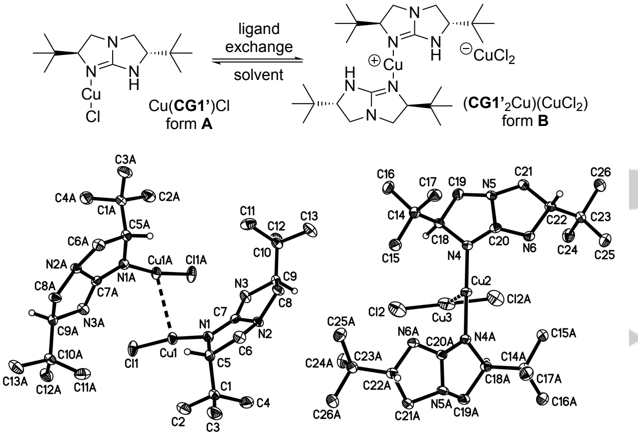
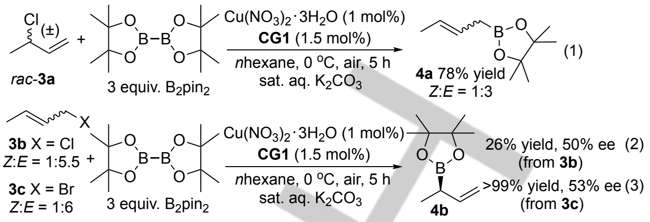


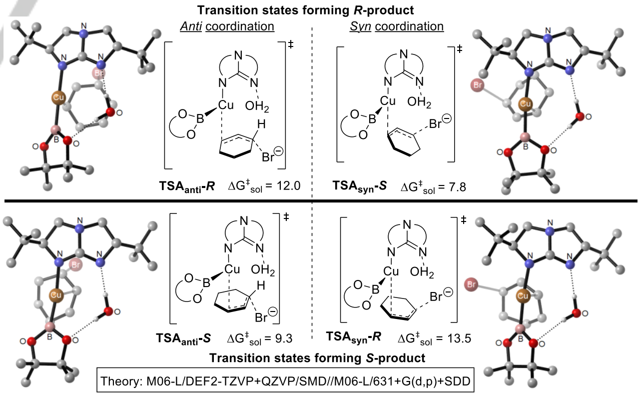
Figure 1. The crystal structure of Cu(**CG1'**)Cl complex **I** and its ORTEP representation (50% possibility level). Most of the hydrogen atoms have been omitted for clarity.

Borylation of organohalides was previously reported by Fu[18] to undergo a radical pathway; however, no cyclization product was observed when a radical probe **1j** was used. Radical scavengers such as TEMPO and BHT did not significantly affect both yield and enantioselectivity of the reactions (SI S56). High regioselectivity on gamma-position of allylic bromides indicated an S_N2' allylic substitution, similar to previous reported examples on copper-catalyzed allylic borylation.[2h,4] The S_N2' selectivity of the reaction was demonstrated using acyclic allylic halides. When branched allylic chloride *rac*-**3a** was employed, a mixture of *Z*/*E* isomers of **4a** was obtained, without the detection of any branched allylboronate (Scheme 2, eqn. 1). On the other hand, when linear allylic chloride **3b** and allylic bromide **3c** was used, boronate **4b** was obtained with up to 53% ee (Scheme 2, eqn. 2 and 3). Reactions of linear allylic chloride **3b** was much slower than with allylic bromide **3c**.



Scheme 2. Investigation of S_N2' selectivity using allylic-isomeric halides.

In contrast to our previous studies on alkynylation of allyl bromides,[16a] we found that the ee of allyl bromides increased over time as the borylation reaction proceeded (SI S59). This observation indicates that if the racemization of allylbromides is taking place, it is much slower than borylation and the rates of borylation for (*R*)- and (*S*)-**1a** are different. More insights into the resolution process were provided with density functional theory (DFT) calculations. Based on current experimental observations and previous mechanistic studies (SI S60), we postulated that the active catalyst to be an anionic Cu(I)-guanidine species.[16] The rate determining step involves oxidative addition of allylbromide **1a** to the anionic catalytic species **[LCuBpin(OH$_2$)]$^-$**, where **L** represents the guanidine motif. Based on the solution free energies, the kinetically competitive pathways transforming (*R*)- and (*S*)-**1a** to the allylboronate product are transition states **TSA$_{anti}$-*R*** and **TSA$_{syn}$-*S*** (Scheme 3). After oxidative addition and the release of bromide, the transition states lead to a common intermediate **intB-*R*** (SI S62), which ultimately forms the (*R*)-product. Although the reaction is different from Ito's previous report, we propose that a direct enantio-convergent transformation mechanism is plausible, and consistent with the definition as no erasure of the substrate chiral center is involved.[13f]



Scheme 3. Transition states for the rate determining oxidative addition of **1a** and **[LCuR(OH$_2$)]$^-$**.

In summary, we reported the preparation of enantiopure secondary and tertiary cyclic allylboronates from racemic allylic bromides. Chiral guanidine and easily accessible copper salts were used as catalysts under mild conditions. EPR experiments and X-ray crystallographic analysis suggested that a mono-ligated Cu(I)-guanidine complex to be the active catalytic specie. We also proposed after experimental investigations and DFT calculations that the borylation proceeded *via* a selective S_N2'

pathway with a rare example of direct enantio-convergent transformation.

Acknowledgements

We are grateful to the Nanyang Technological University (M4011633), Ministry of Education Tier 2 Grant (MOE2016-T2-1-087) and Singapore University of Technology and Design (T1MOE1706 & IDG31800104) for financial support. Computational resources from National Supercomputing Centre (Singapore) are also gratefully acknowledged.

Keywords: chiral tertiary allylboronate • asymmetric allylic borylation • enantio-convergent synthesis • copper-guanidine catalyst • direct enantio-convergent transformation

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[17] Hoveyda also employed Cu(II) salts as catalysts but no investigation of true catalytic species was conducted (ref. 2h); while Kobayashi

believed that the reaction proceeded through a borylcopper(II) intermediate (ref. 11a).

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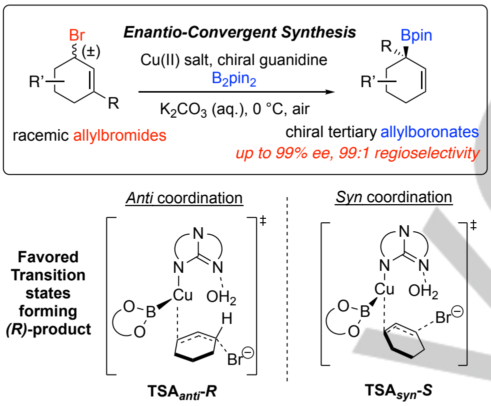
Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

An enantioconvergent synthesis of chiral cyclic allylboronates is demonstrated with racemic allylic bromides using a (guanidine)copper catalyst. The allylboronates were acquired with high γ/α regioselectivities (up to 99:1) and enantioselectivities (up to 99% ee). The reaction is believed to go through an S_N2' borylation process catalyzed by a monodentated guanidine-copper(I) complex with DECT mechanism.



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