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Synthesis of Chiral *N*-Heterocyclic Allylboronates via the Enantioselective Borylative Dearomatization of Pyrroles

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Supporting Information Placeholder

ABSTRACT: The first enantioselective synthesis of five-membered *N*-heterocyclic allylboronates has been accomplished by a C–B bond-forming dearomatization of pyrroles using a copper(I) catalyst. This reaction involves the regio- and enantioselective addition of a borylcopper(I) species to pyrrole-2-carboxylates, followed by the diastereoselective protonation of the resulting copper(I) enolate to afford pyrrolidine-type allylboronates. The products are highly attractive reagents for the rapid construction of pyrrolidine derivatives that bear five consecutive stereocenters via subsequent allylboration/oxidation processes.

Allylboron compounds have found widespread applications in organic synthesis.¹ Chiral cyclic allylboronates are particularly useful synthetic building blocks because their stereoselective addition to carbonyl compounds allows the construction of cyclic homoallylic alcohols that bear two consecutive stereogenic centers (Scheme 1a).¹ Accordingly, significant efforts have been devoted to the development of catalytic, enantioselective synthetic routes to this class of allylboron compounds. Although many excellent procedures have already been reported, the scope of accessible cyclic allylboronates remains limited.^{2,3}

Optically active *N*-heterocyclic allylic boronates have attracted considerable interest, especially in the context of the allylboration of aldehydes. This provides sterecontrolled access to functionalized chiral aminoalcohols, which represent a highly prized class of synthetic intermediates for the construction of a wide variety of naturally occurring complex molecules.³ Hall and co-workers have reported that the palladium-catalyzed enantioselective borylative alkene isomerization of alkenyl triflates affords chiral *N*-heterocyclic allylboronates, which are useful allylation reagents for the efficient synthesis of drug molecules (Scheme 1b).³ However, this protocol is limited to the preparation of six- or seven-membered *N*-heterocycles (Scheme 1b). The development of new methods for the synthesis of other *N*-heterocyclic allylic boronates (e.g., five-membered

rings) is also highly desirable in order to provide an attractive route for the rapid construction of complex saturated *N*-heterocycles via stereospecific, boron-based functionalization processes.^{1,2,4}

Our group has been interested in applying a copper(I)-catalyzed nucleophilic borylation protocol to the synthesis of chiral *N*-heterocyclic organoboronates.^{5a,6} We have previously reported an enantioselective borylative dearomatization reaction of indole-2-carboxylate derivatives using a copper(I) catalyst to furnish the corresponding optically active 3-boryl-indolines.^{5,7} The key finding of this study was that an electron-withdrawing group at the 2-position in the substrate can facilitate the challenging dearomative borylcupration. Inspired by this finding, we envisioned that using this method, pyrrole-2-carboxylate derivatives could potentially be converted into novel five-membered *N*-heterocyclic allylic boronates, which in turn could potentially be transformed into complex bioactive pyrrolidines via the stereoselective allylboration of aldehydes (Scheme 1c).^{8,9} The main challenge in the development of such a method is overcoming the high energy barrier associated with the dearomatization process.¹⁰ Our preliminary density functional theory (DFT) calculations of model molecules suggested that the borylation of pyrrole is much less favorable than that of indole in terms of the free energy of formation ($\Delta\Delta G = 10.3$ kcal/mol; see the

Supporting Information for details). In fact, there is only a limited number of examples of the enantioselective dearomatization of pyrroles, including [4+3] cycloadditions,¹¹ hydrogenations,¹² allylic alkylations,¹³ and Heck-type reactions,¹⁴ while the number of reported enantioselective dearomatization reactions of indoles is much higher.¹⁰ Herein, we report the first synthesis of chiral five-membered *N*-heterocyclic allylboronates via the enantioselective borylative dearomatization of readily available pyrroles.

Scheme 1. Catalytic Enantioselective Synthesis of Chiral *N*-Heterocyclic Allylboronates

a) Allylboration reactions of chiral cyclic allylboronates with aldehydes

b) Previous work | Chiral six- or seven-membered *N*-heterocyclic allylboronates via enantioselective alkene isomerization (Hall)

c) This work | Chiral five-membered *N*-heterocyclic allylboronates via an enantioselective borylative dearomatization approach

The results of an extensive series of optimization experiments are shown in Table 1. Initially, we applied the previously established optimal reaction conditions for the borylative dearomatization of indoles to pyrroles.^{5a} The reaction of *N*-benzyloxycarbonyl (Cbz)-protected methyl pyrrole-2-carboxylate (**1a**) with bis(pinacolato)diboron (**2**) (2.0 equiv) in the presence of Cu(O-*t*-Bu) (10 mol%)/chiral bisphosphine ligand (*R,R*)-**L1** (10 mol%), Na(O-*t*-Bu) (10 mol%), and *t*-BuOH (2.0 equiv) in THF at 30 °C afforded the desired 3-boryl-dihydropyrrole (*R,S*)-**3a** with excellent diastereo- and enantioselectivity (d.r. >95:5, 96% ee; Table 1, entry 1). However, the chemical yield was only moderate (54%). To improve the reactivity, the combination of CuCl and K(O-*t*-Bu) was investigated, albeit that the improvement was merely marginal (64%; Table 1, entry 2). Interestingly, we found that decreasing the amount of the copper salt led to a more substantial improvement in the reactivity (81%, d.r. >95:5, 95% ee; Table 1, entry 3). The use of the sterically less hindered ligand (*R,R*)-**L2** led to not only a lower enantioselectivity but also a lower yield (34%, 80% ee; Table 1, entry 4). Several other chiral bisphosphine ligands, including (*R,R*)-BenzP* (**L3**), (*R,R*)-QuinoxP* (**L4**), and (*R,R*)-Me-Duphos (**L5**), were also tested but afforded the product in poor stereoselectivity (Table 1, entries 5–7). No reaction was observed when (*S*)-MOP (**L6**) was used in the reaction (Table 1, entry 8). The steric bulk of the alcohol was also found to affect the diastereoselectivity of this reaction,

i.e., the use of sterically undemanding MeOH led to moderate diastereoselectivity (d.r. 81:19; Table 1, entry 9). Performing the reaction without any alcohol additive resulted in a significantly decreased product yield (7%; Table 1, entry 10). The borylation of pyrroles that do not contain an ester group at the 2-position did not proceed (see the Supporting Information for details).

Table 1. Optimization of the Reaction Conditions^a

Entry	Cu cat. (mol%)	L*	base (mol%)	yield (%) ^b	d.r. ^c	ee (%) ^d
1 ^e	Cu(O- <i>t</i> -Bu) (10)	(<i>R,R</i>)- L1	Na(O- <i>t</i> -Bu) (10)	54	>95:5	96
2	CuCl (10)	(<i>R,R</i>)- L1	K(O- <i>t</i> -Bu) (20)	64	>95:5	96
3	CuCl (5)	(<i>R,R</i>)- L1	K(O- <i>t</i> -Bu) (20)	81	>95:5	95
4	CuCl (5)	(<i>R,R</i>)- L2	K(O- <i>t</i> -Bu) (20)	34	>95:5	80
5	CuCl (5)	(<i>R,R</i>)- L3	K(O- <i>t</i> -Bu) (20)	15	>95:5	28
6	CuCl (5)	(<i>R,R</i>)- L4	K(O- <i>t</i> -Bu) (20)	30	>95:5	22
7	CuCl (5)	(<i>R,R</i>)- L5	K(O- <i>t</i> -Bu) (20)	53	>95:5	46
8	CuCl (5)	(<i>S</i>)- L6	K(O- <i>t</i> -Bu) (20)	<5	n.d.	n.d.
9 ^f	CuCl (5)	(<i>R,R</i>)- L1	K(O- <i>t</i> -Bu) (20)	41	81:19	86
10 ^g	CuCl (5)	(<i>R,R</i>)- L1	K(O- <i>t</i> -Bu) (20)	7	n.d.	n.d.

^aConditions: **1a** (0.5 mmol), **2** (0.75 mmol), Cu catalyst, chiral ligand (0.05 mmol), base, and alcohol (1.0 mmol) in THF (1.0 mL). ^bDetermined by ¹H NMR analysis of the crude reaction mixture using an internal standard. ^cDetermined by ¹H NMR analysis of the crude reaction mixture. ^dDetermined by HPLC analysis. ^e2.0 equiv. of **2** was used. ^fMeOH was used instead of *t*-BuOH. ^gWithout alcohol.

The thus obtained optically active 3-boryl-dihydropyrrole (*R,S*)-**3a** can be used for the synthesis of 2,5-substituted pyrrolidine derivatives with three stereogenic carbon centers via the diastereoselective allylboration of aldehydes. We found that the addition of cinnamaldehyde (3-phenylprop-2-enal) to the crude mixture of (*R,S*)-**3a**, which was obtained from the aforementioned reaction, proceeded in a highly diastereoselective manner, probably via a six-membered transition state (*vide infra*), to give homoallylic alcohol (*R,S,S*)-**4a** in good yield with high diastereoselectivity and without loss of the enantiomeric purity (Scheme 2).^{2a} Notably, the crude mixture of the borylation product

(*R,S*)-**3a** can be used for the allylboration, which allows the rapid construction of molecular complexity from readily available pyrrole derivatives. A single-crystal X-ray diffraction analysis confirmed the structure of **4a** and revealed the absolute configuration of its stereogenic centers as (*R,S,S*)-**4a**.

Scheme 2. Allylboration of (*R,S*)-3a** with Cinnamaldehyde**

The allylboration of aldehydes with (*R,S*)-**3a** is possible for a wide range of substrates (Scheme 3). Benzaldehyde smoothly produced the corresponding pyrrolidine derivative (*R,S,S*)-**4b** with excellent stereospecificity. Aromatic aldehydes with electron-withdrawing or -donating functional groups afforded the corresponding pyrrolidine derivatives in good yield with high diastereo- and enantioselectivity [(*R,S,S*)-**4c**–(*R,S,S*)-**4g**]. Heteroaromatic aldehydes are also allylbored with high stereoselectivity [(*R,S,S*)-**4h**–(*R,S,S*)-**4j**]. Allylboration of the aliphatic cyclohexane carboxaldehyde provided the product in lower yield (45%, NMR; 2 steps), albeit with high stereoselectivity (d.r. > 95:5, 96% ee). This borylation/allylboration sequence of **1a** can be carried out at a 1 mmol scale (See the Supporting Information for details).

The utility of the borylation of pyrroles was further demonstrated by the three-step synthesis of *cis*-3-hydroxy proline derivative (*R,S*)-**6** (Scheme 4). *cis*-3-Hydroxy-proline, a rare cyclic β -hydroxy- α -amino acid isolated from carcinoma cell cultures, is a therapeutic agent in the treatment of tumors and collagen disorders.¹⁵ Although both racemic and asymmetric syntheses of *cis*-3-hydroxy proline derivatives have been reported,¹⁶ these methods are laborious. We found that the enantioselective borylation of pyrrole **1b**, followed by the sequential hydrogenation of the resulting allylboration product (*R,S*)-**3b** and oxidation of the boryl group with NaBO₃¹⁷ afforded (*R,S*)-**6** in high yield with high diastereo- and enantioselectivity (Scheme 4).

Scheme 3. Scope of the Allylboration of (*R,S*)-3a** with Respect to Aldehydes^a**

^aConditions of the borylation reactions: **1a** (0.5 mmol), **2** (0.75 mmol), CuCl (0.025 mmol), chiral ligand (0.05 mmol), K(O-*t*-Bu) (0.1 mmol), and *t*-BuOK (1.0 mmol) in THF (1.0 mL). Conditions of the allylboration reactions: crude borylation product (*R,S*)-**3a** and aldehyde (1.5 equiv) in toluene (0.5 M). ^bDetermined by ¹H NMR analysis of the crude reaction mixture using an internal standard. Isolated yields are shown in parentheses. ^cDetermined by ¹H NMR analysis of the crude reaction mixture. ^dDetermined by HPLC analysis.

Chiral polyhydroxylated pyrrolidines and their derivatives are potent and selective inhibitors of various glycoprocessing enzymes involved in diseases such as diabetes and cancer, as well as viral infections and lysosomal storage disorders (Scheme 5).¹⁸ To construct these important structural motifs, we investigated the dihydroxylation of allylboration product (*R,S,S*)-**4b** (Scheme 5). Treatment with K₂OsO₄, *N*-methylmorpholine-*N*-oxide (NMO), and citric acid¹⁹, followed by silylation of the hydroxy groups afforded the chiral polyhydroxylated pyrrolidine derivative (*R,S,R,R,S*)-**7**, which bears five consecutive stereocenters, in excellent yield with high diastereoselectivity and without loss of enantiomeric purity (Scheme 4). The crystallization of racemic **7** from Et₂O afforded single crystals of racemic

7.²⁰ The results of an X-ray crystallographic analysis of racemic **7** revealed the relative configuration of its stereogenic centers. This sequential transformation of borylation/allylboration/oxidation thus enables the rapid construction of this structural motif, which is commonly encountered in bioactive molecules, from readily available starting materials, highlighting the synthetic utility of the developed protocol.

Scheme 4. Convenient Synthesis of a 3-Hydroxy Proline Derivative via an Enantioselective Borylative Dearomatization

Scheme 5. Diastereoselective Dihydroxylation of (R,S,S)-**4b** to Provide a Chiral Pyrrolidine with Five Consecutive Stereocenters

Representative bioactive polyhydroxylated pyrrolidine derivatives

Conditions: (a) standard conditions for the borylation (cf. Table 1, entry 3); (b) benzaldehyde, toluene, 60 °C; (c) K₂O₈·2H₂O, NMO, citric acid, H₂O/MeCN, rt; (d) Me₃SiCl, imidazole, CH₂Cl₂, rt. See the Supporting Information for details.

A deuterium-labeling experiment was conducted to probe the reaction mechanism (Scheme 6). The borylation of **1a** using *t*-BuOD instead of *t*-BuOH furnished the deuterium-labeled product (R,S)-**3a-D** (94% D). This result suggests that the diastereoselective protonation is accomplished by the alcohol additive.

Scheme 6. D-Labeling Experiment

Based on the aforementioned results, we would like to propose a plausible reaction mechanism for the enantioselective borylation of pyrroles (Figure 1), in which Cu(O-*t*-Bu) species **A** initially reacts with diboron reagent **2** to form the borylcopper(I) species **B**. The coordination of pyrrole **1a** to the copper center then results in the formation of π -complex **C**. A subsequent 3,4 addition of **B** to **1a** would afford the copper(I) *C*-enolate, which could then transform into the *O*-enolate **D** under concomitant formation of a stereogenic C–B bond. After the formation of **D**, the bulky *t*-BuOH additive approaches **D** from the opposite side of the pinacolate boryl group to avoid steric repulsion between the B(pin) and *t*-Bu groups. The subsequent diastereoselective protonation of **D** would then proceed via six-membered-ring transition state **E** to provide the dearomatization product (R,S)-**3a** and the Cu(O-*t*-Bu) precatalyst **A**.

Figure 1. Proposed catalytic cycle for the enantioselective borylation of pyrroles.

In summary, we have reported the first enantioselective synthesis of five-membered *N*-heterocyclic allylboronates via the enantioselective C–B bond-forming dearomatization of pyrroles. This reaction involves the unprecedented regio- and enantioselective borylcupration of pyrrole-2-carboxylates, followed by diastereoselective protonation of the resulting copper(I) *O*-enolate intermediates by a sterically demanding alcohol additive. The newly synthesized cyclic allylboronates represent highly attractive reagents that enable the rapid construction of pyrrolidine derivatives that bear five consecutive stereocenters via sequential allylboration/oxidation processes. We expect that the results of this study will provide further opportunities for the efficient synthesis of complex molecules with potentially interesting biological activity.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of new compounds are provided in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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