Ph.D. thesis

Development of Copper(I)-Catalyzed Dearomative Borylation and Silylation Reactions of N-Heteroaromatic Compounds

銅(I)触媒による含窒素複素芳香族化合物の

脱芳香族ホウ素化およびケイ素化反応の開発

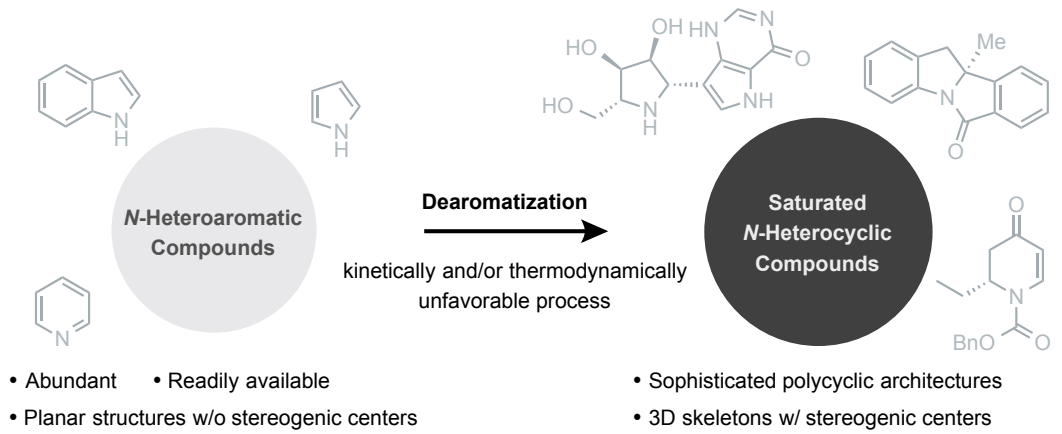
Hokkaido University
Graduate School of Chemical Sciences and Engineering,
Frontier Chemistry Center, Organoelement Chemistry Laboratory

Keiichi Hayama

Contents

General Introduction

N-Heteroaromatic compounds are ubiquitous in nature and readily available as synthesized compounds. The dearomatization reactions of *N*-heteroaromatic compounds are powerful synthetic methods that can be employed to provide direct access to a wide variety of saturated *N*-heterocyclic compounds, which have important structures of pharmaceutical drugs and various bioactive molecules (Scheme 1).[1] Thus, the development of novel dearomatization reactions of *N*-heteroarenes should have important practical implications for organic synthesis. Extensive efforts have already been made on the development of a quite large number of highly efficient synthetic methods for the conversion of planar *N*-heteroaromatic compounds to various saturated *N*-heterocyclic compounds using transition-metal catalytic systems.[1] Despite the rapid and significant progress in this subject, there have been no reports on the C–B bond-forming dearomatization reactions involving aromatic and heteroaromatic compounds.[1] The lack of research of this would be caused by the high activation energy barrier to break the aromatic systems. The development of a C–B bond-forming dearomatization reaction will provide an attractive approach for the synthesis of complicated, functionalized cyclic molecules in combination with the stereospecific functionalization of a stereogenic C–B bonds formed by the dearomative borylations.



Scheme 1. Dearomatization of *N*-heteroaromatic compounds

Organoboron compound is a significant class of compounds in organic synthetic chemistry.[2] They exhibit much higher stability against air and moisture compared with other organometallic reagents such as organolithium reagents or Grignard reagents.[3] That's because of low ionic-character of C–B bond (electronegativity of C: 2.55, B: 2.04 compared with Li: 0.98, Mg: 1.31). On the other hand, organoboron compounds

become also sufficiently reactive for use in organic synthesis when an appropriate activation procedure is employed. They can be used for various transformation reactions such as Suzuki-Miyaura cross-coupling reaction, oxidation, amination, allylboration, and homologation reaction.[4] Moreover, enantioenriched chiral organoboronates have been recognized as important chiral building blocks in organic synthesis because they can be applied to stereospecific transformation of the steregenic C–B bonds to form C–O, C–N or C–C bonds (Figure 1).[4] For these reasons, these derivatives are used as intermediates for constructing agrochemicals, pharmaceuticals and materials chemistry. In addition, some organoboron compounds are important as organic emissive materials (Figure 2a).[5] BODIPY is the most enthusiastically studied organoboron-derived luminophore due to its high fluorescence quantum yields and its derivatives are applied for the biological imaging and labeling. Recently, air-stable triarylboranes are drawing significant interest as materials for EL devices due to their strong π-acceptor properties originating from the vacant p orbital of boron atom. Furthermore, bortezomib, which is the first drug containing boronic acid structure was approved for an anticancer agent by FDA in 2003 (Figure 2b).[2] Tavaborole was also approved as a drug for an antifungal agent recently. Therefore, the development of synthetic methods of organoboron compounds is highly important in organic chemistry.

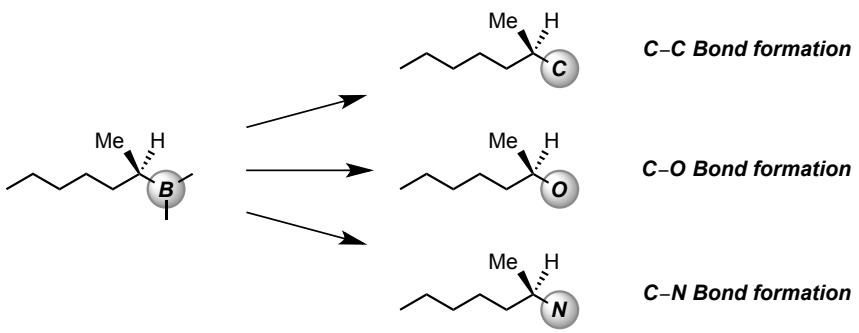


Figure 1. Stereospecific transformations of enantioriched alkylboronate esters

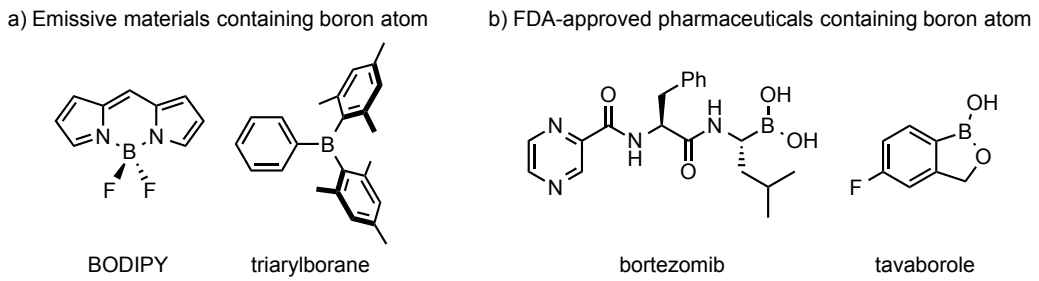
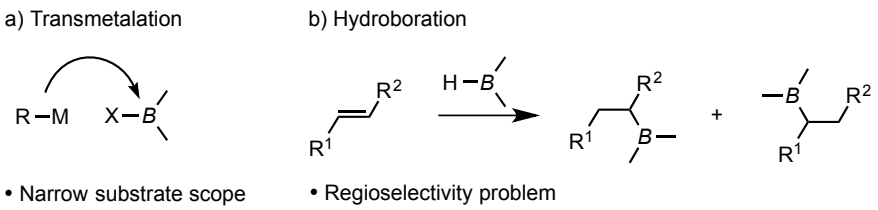


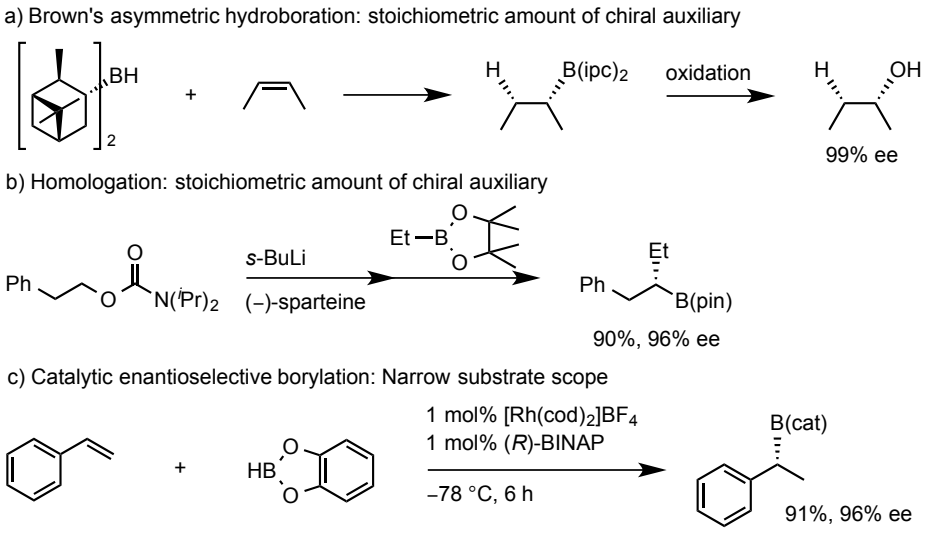
Figure 2. Importance of organoboron compounds for a) boron-containing organic emissive materials and b) boron-containing pharmaceutical drugs.

Organoboronates are most often synthesized through the transmetalation between alkylmagnesium or alkyllithium reagents and electrophilic boron precursors (Scheme 2a). However, these methods suffer from poor functional group tolerance. Hydroboration of alkenes is one of the most efficient and straightforward protocols to access alkylboronic esters. This method has also substantial limitation, such as regioselectivity problem in the case of hydroboration of internal alkenes (Scheme 2b).

Classical synthetic approaches toward chiral organoboronates are shown in Scheme 3. Brown's asymmetric hydroboration using (+)-diisopinocamphenylboran (Ipc_2BH) is one of the most practical and scalable protocols to access optically active organoboron compounds with high enantiomeric excess (Scheme 3a). Homologation methodology using organolithium compound and (−)-sparteine with boron electrophile also produces the chiral organoboronates with high enantiomeric purity (Scheme 3b). However, these reactions require stoichiometric amount of chiral auxiliary. Considering this huge drawback, catalytic asymmetric borylation reaction is a highly desirable method for the construction of stereogenic C–B bonds. In 1989, Hayashi and Ito's group reported the first transition-metal-catalyzed asymmetric hydroboration of stylenes to afford the corresponding chiral organoboron compounds with an excellent enantioselectivity (Scheme 3c).[6] Despite the great utility of this catalytic approach, the development of these methods has been less explored for other prochiral alkenes.

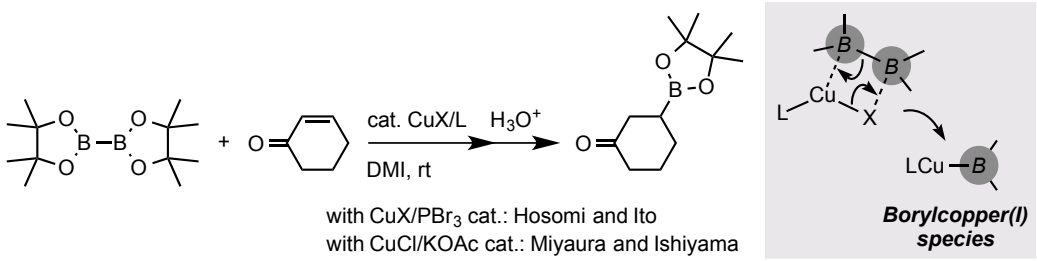


Scheme 2. Conventinal synthetic routes to organoboronate esters



Scheme 3. Selected studies on the synthesis of chiral organoboron compounds

In 2000, the borylation reactions of α,β-unsaturated carbonyl compounds using copper(I)/diboron catalytic system were developed by Hosomi, Ito's group, and Miyaura, Ishiyama's group independently (Scheme 4).[7] These reactions are the first examples of activation of a B–B bond with a copper(I) catalyst to generate borylcopper(I) species. These reactions have great advantages over conventional procedures for the synthesis of organoboron compounds. In the presence of a copper(I) catalyst and diboron, σ-bond metathesis occurs to generate nucleophilic borylcopper(I) intermediates. Unlike classical stoichiometric "boron electrophilic reaction" methods, these reactions don't require stoichiometric amounts of highly reactive carbon nucleophiles such as organolithium compounds or Grignard reagents. Moreover, these reactions can be applied to catalytic asymmetric borylation reactions by using appropriate chiral ligands.



Scheme 4. Copper(I)-catalyzed borylation of conjugated enone

Ito and Sawamura reported several asymmetric borylation reactions of C=C or C=O

unsaturated bonds using chiral copper(I)/diboron catalytic system. In the presence of a chiral copper(I) catalyst and diboron, various novel optically active organoborates were successfully synthesized with high stereoselectivities (Figure 3).[8] However, the target molecules of these asymmetric borylation reactions were limited to electronically active alkenes and carbonyls.

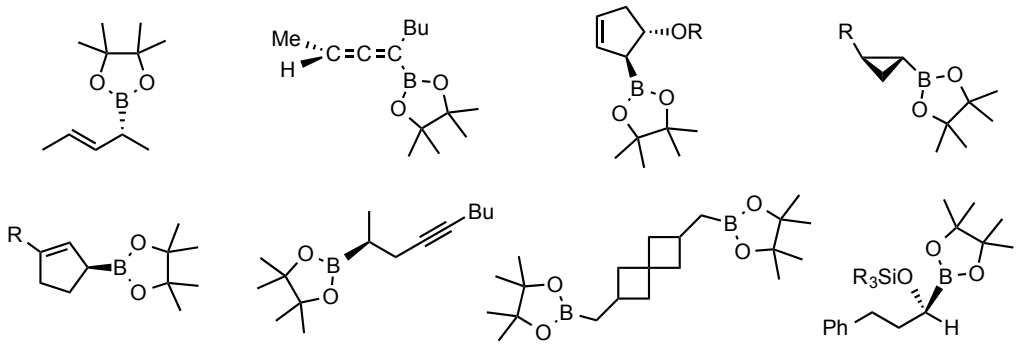
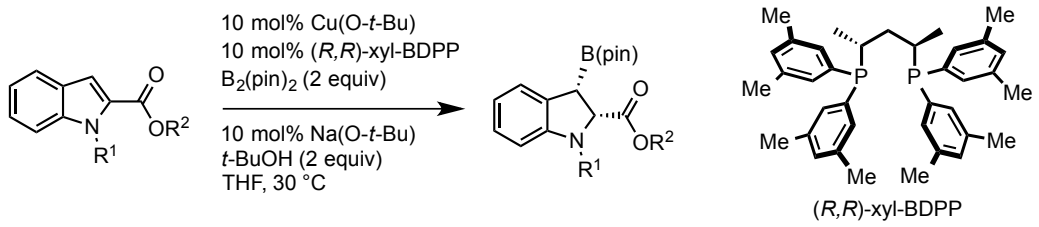


Figure 3. Selected examples of the synthesized optically active organoboron compounds using copper(I) catalysis

Under such a background, the author has previously reported the asymmetric borylative dearomatization reaction of indole-2-carboxylate derivatives using copper(I) catalyst to furnish the corresponding optically active 3-boryl indolines (Scheme 5).[9] This is the first C–B bond-forming asymmetric dearomatization reaction. During the last decade, our group has been involved in the development of new methods for the copper(I)-catalyzed asymmetric borylation of prochiral alkenes. The results of the related research in this field revealed that electron-deficient substrates with low LUMO levels tend to react efficiently with active borylcopper(I) complex in a process involving the formation of a stereogenic C–B bond. With this in mind, we found that an electron-withdrawing group at position 2 in the substrate can facilitate the challenging dearomative borylcupration.



Scheme 5. Copper(I)-catalyzed enantioselective borylative dearomatization of indoles

A plausible reaction mechanism is shown in Figure 4. Cu(O-*t*-Bu) species **A** would initially react with diboron reagent to form the borylcopper(I) species **B**. The coordination of indole to the copper center would result in the formation of π-complex **C**. The subsequent 3,4 addition of **B** into indole would give the copper(I) *C* enolate **D** and then transform to *O* enolate **D'** with concomitant formation of a stereogenic C–B bond. After the formation of **D'**, bulky *t*-BuOH additive would access **D'** from the opposite side of the pinacolate boryl group to avoid steric congestion between the B(pin) and *t*-Bu groups. The subsequent diastereoselective protonation of **D'** would proceed via a six-membered-ring transition state **E** to provide dearomatization product and Cu(O-*t*-Bu) precatalyst **A**.

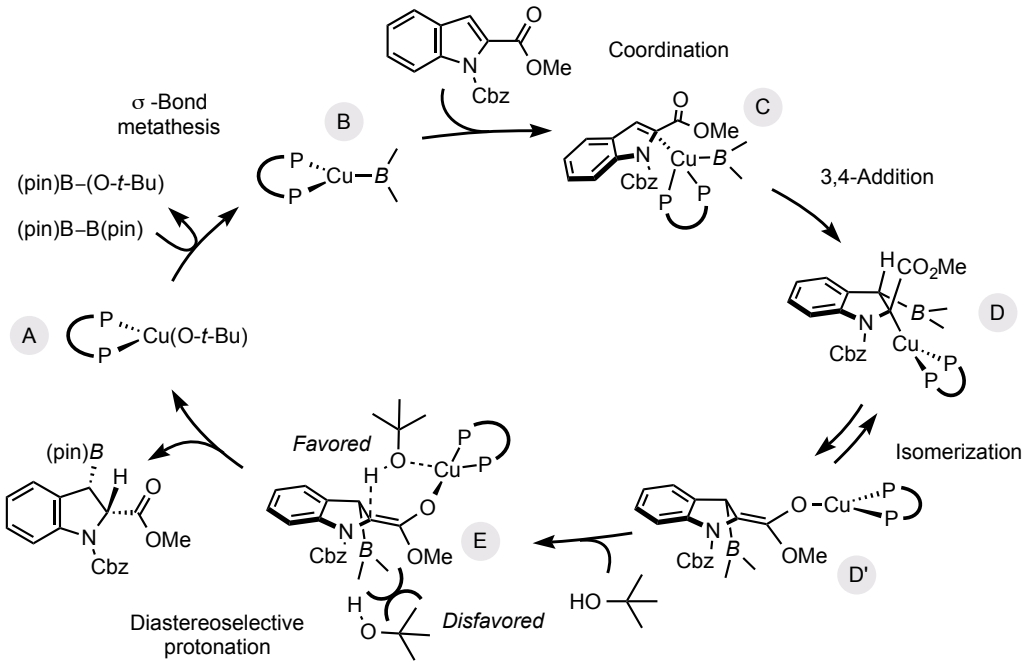
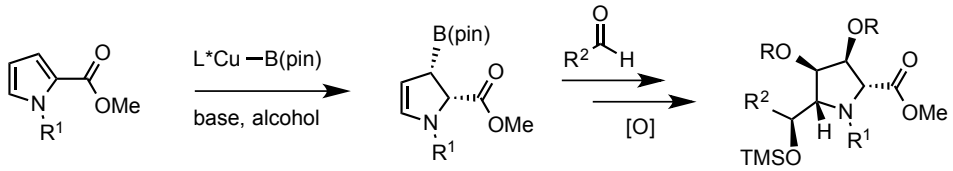


Figure 4. Plausible reaction mechanism of enantioselective borylative dearomatization of indoles

The author extended this borylative dearomatization chemistry to (i) borylative dearomatization of pyrroles, (ii) dearomative carboboration of indoles, and (iii) dearomative silylation of indoles and pyrroles.

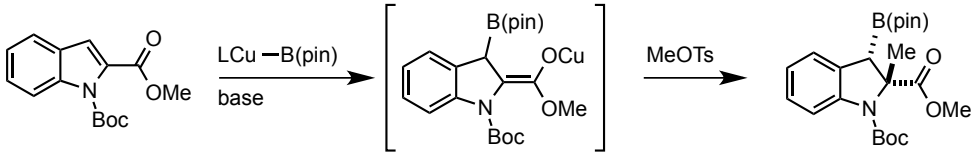
Chapter 1 describes the enantioselective synthesis of five-membered *N*-heterocyclic allylboronates by a C–B bond-forming dearomatization of pyrroles using a copper(I) catalyst and a diboron reagent (Scheme 6).[10] This reaction involves the regio- and enantioselective addition of a borylcopper(I) species to pyrrole-2-carboxylates, followed by the diastereoselective protonation of the resulting copper(I) enolate to afford pyrrolidine-type allylboronates. The newly synthesized organoboron compounds are

highly attractive reagents for the rapid construction of pyrrolidine derivatives that bear five consecutive stereocenters via subsequent allylboration/oxidation processes.



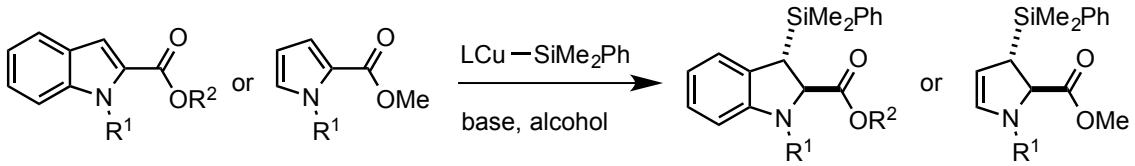
Scheme 6. Copper(I)-catalyzed enantioselective dearomative borylation of pyrroles

Chapter 2 describes the dearomative carboborylation of indoles using a copper(I) catalysis and MeOTs instead of alcohol (Scheme 7).[11] This reaction includes the regioselective addition of a borylcopper(I) intermediate to indoles, followed by the diastereoselective methylation of the resulting copper(I) enolate intermediate to afford the corresponding 3-boryl-2-methyl-indolines bearing a quaternary stereogenic center with excellent regio- and diastereoselectivity.



Scheme 7. Copper(I)-catalyzed diastereoselective dearomative carboborylation of indoles

Chapter 3 describes dearomative silylation of indole-2-carboxylates and pyrrole-2-carboxylates has been achieved using copper(I) catalyst and silylborane without any ligands (Scheme 8).[12] This reaction involves the regioselective addition of silylcopper(I) species to substrates, followed by the diastereoselective protonation of the resulting copper(I) enolate intermediate to afford the corresponding dearomative silylation products with excellent regio- and good to excellent diastereoselectivity.



Scheme 8. Copper(I)-catalyzed diastereoselective dearomative silylation of indoles and pyrroles

References

(1) For reviews of catalytic asymmetric dearomative transformations, see: (a) Zhuo, C. X.; Zhang, W.; You, S.-L. *Angew. Chem. Int. Ed.* **2012.** *51*, 12662. (b) Zhuo, C. X.; Zheng, S.; You, S.-L. C. X. *Acc. Chem. Res.* **2014**, *47*, 2558. (c) Roche, S. P.; Porco, J. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068. (d) Wu, W.-T.; Zhang, L.; You, S.-L. *Chem. Soc. Rev.* **2016**, *45*, 1570.

(2) (a) Boronic Acids: Preparation and Application in Organic Synthesis, Medicine and Materials, 2nd revised ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2011**. (b) Diner, C.; Szabó, K. J. *J. Am. Chem. Soc.* **2017**, *139*, 2–14.

(3) *Organic Synthesis via Boranes*; Brown, H. C.; Wiley-VCH Verlag: Weinheim, **1975**.

(4) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778. (c) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861. (d) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704.

(5) Reviews: (a) Mukherjee, S.; Thilagar, P. J. *Mater. Chem. C* **2016**, *4*, 2647. (b) Frath, D.; Massue, J.; Ulrich, G.; Ziessel, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2290.

(6) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426.

(7) (a) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982.

(8) For examples of the synthesis of optically active organoboron compounds, see: (a) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129,* 14856. (b) Kunii, S.; Sawamura, M. *Nat. Chem.* **2010**, *2*, 972–976. (c) Sasaki, Y.; Zhong, C.; Sawamura, M. Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226–1227. (d) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 560–563.

(9) Kubota, K.; Hayama, K.; Iwamoto, H.; Ito, H. *Angew. Chem. Int. Ed.* **2015**, *54,* 8809–8813.

(10) Hayama, K.; Kojima, R.; Kubota, K.; Ito, H. *Org. Lett.* **2020**, *22*, 739–744.

(11) Hayama, K.; Kubota, K.; Iwamoto, H.; Ito, H. *Chem. Lett.* **2017**, *46*, 1800–1802.

(12) Hayama, K.; Takahashi, R.; Kubota, K.; Ito, H. *manuscript under preparation.*

Chapter 1.

Copper(I)-Catalyzed Enantioselective Dearomative Borylation of Pyrroles: Access to Chiral N-Heterocyclic Allylboronates

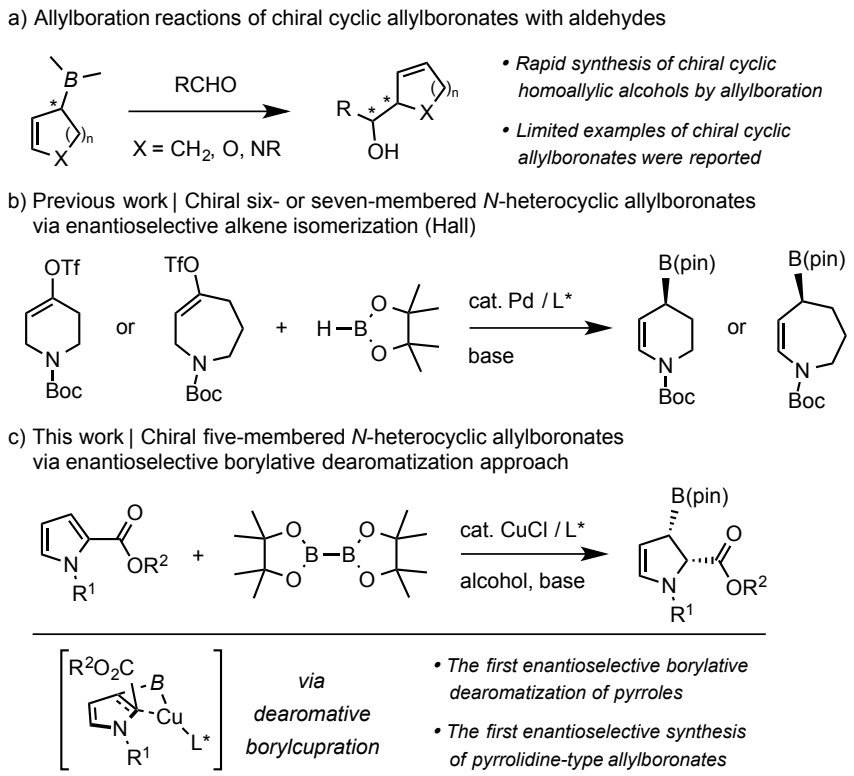
Abstract

The first synthesis of chiral five-membered *N*-heterocyclic allylboronates has been accomplished by a C–B bond-forming dearomatization of pyrroles using a copper(I) salt and a diboron reagent. 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 five-membered *N*-heterocyclic allylboron compounds. The newly synthesized organoboron compounds are greatly attractive reagents for the rapid construction of pyrrolidine derivatives that bear five consecutive stereogenic centers via subsequent allylboration/dihydroxylation processes.

Introduction

Allylboronates have found widespread applications in organic synthesis.[1] Optically active cyclic allylboron compounds are particularly useful synthetic building blocks because their stereoselective addition to carbonyl compounds allows the construction of optically active homoallylic alcohols that bear two consecutive stereogenic centers (Scheme 1-1a).[1] Accordingly, significant efforts have been devoted to the development of catalytic, asymmetric synthetic routes to this class of allylboron compounds. Although lots of excellent procedures have already been reported, the scope of accessible cyclic allylboron compounds remains limited.[2,3]

Chiral *N*-heterocyclic allylic boronates have attracted considerable attention, especially in the context of the allylboration of aldehydes. This provides stereospecific access to functionalized optically active aminoalcohols, which represent a highly prized class of synthetic intermediates for the construction of various naturally occurring complex molecules.[3] Hall and co-workers have reported that the palladium-catalyzed asymmetric borylative alkene isomerization of alkenyl triflates affords optically active *N*-heterocyclic allylboron compounds, which are useful allylation reagents for the efficient synthesis of bioactive molecules (Scheme 1-1b).[3] However, this protocol is limited to the preparation of six- or seven-membered *N*-heterocyclic compounds (Scheme 1-1b). The development of new methods for the synthesis of other *N*-heterocyclic allylboronates (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]



Scheme 1-1. Catalytic enantioselective synthesis of chiral *N*-heterocyclic allylboronates

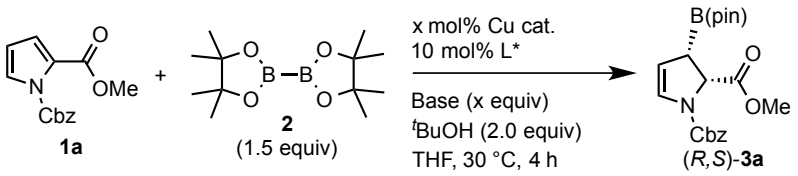
Our group has been recently interested in applying a copper(I)-catalyzed borylation protocol to the synthesis of optically active *N*-heterocyclic organoboron compounds.[5a,6] The author and co-worker have previously reported an asymmetric borylative dearomatization reaction of indole-2-carboxylate derivatives using a copper(I) catalyst to provide the corresponding chiral 3-boryl-indolines.[5,7] The key finding of this study was that an electron-withdrawing group at position 2 in the substrate can facilitate the challenging dearomative borylcupration. Inspired by this finding, the author envisioned that using this method, pyrrole-2-carboxylate derivatives could potentially be converted into novel five-membered *N*-heterocyclic allylboron compounds, which in turn could potentially be transformed into complicated bioactive pyrrolidines via the stereoselective allylboration of aldehydes (Scheme 1-1c).[8,9] The main challenge in the development of such a method is overcoming the high activation 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 experimental section for details). In fact, there is only a limited number of examples of the asymmetric 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, the author reports the first enantioselective synthesis of five-membered *N*-heterocyclic allylboronates via the enantioselective borylative dearomatization of readily available pyrroles.

Results and Discussion

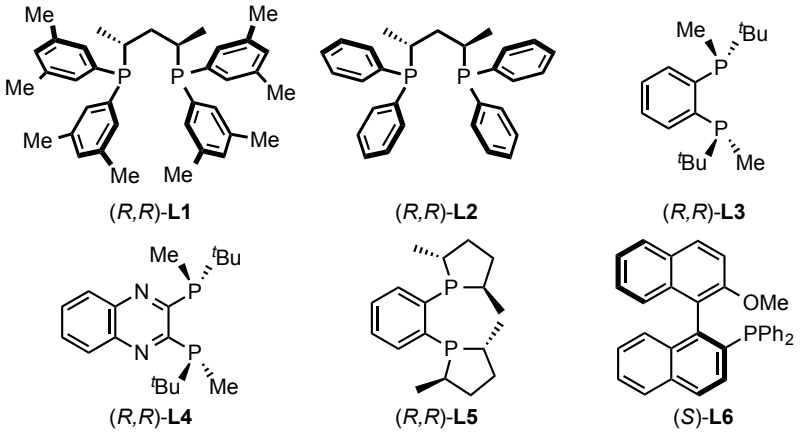
The results of an extensive series of optimization experiments are shown in Table 1-1. Initially, the author applied the previously established optimized reaction conditions for the enantioselective borylative dearomatization of indoles to pyrroles.[5a] The reaction of *N*-benzyloxycarbonyl (Cbz)-protected 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 1-1, entry 1). However, the chemical yield was only moderate (54%). To improve the reactivity, the combination of CuCl and K(O-*t*-Bu) was conducted, albeit that the improvement was merely marginal (64%; Table 1-1, entry 2). Interestingly, the author found that decreasing the amount of the copper catalyst led to significant improvement in the reactivity (81%, d.r. >95:5, 95% ee; Table 1-1, 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 1-1, 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 enantioselectivity (Table 1-1, entries 5–7). No reaction was observed when (*S*)-MOP (**L6**) was used in the reaction (Table 1-1, entry 8). The steric bulkiness of the alcohol was 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 1-1, entry 9). Performing the reaction without any alcohol additive resulted in a significantly decreased chemical yield (7%; Table 1-1, entry 10). The borylation of pyrroles that do not contain an ester group at the 2-position did not proceed (see the Experimental section for details).

Table 1-1. Optimization of the reaction conditions



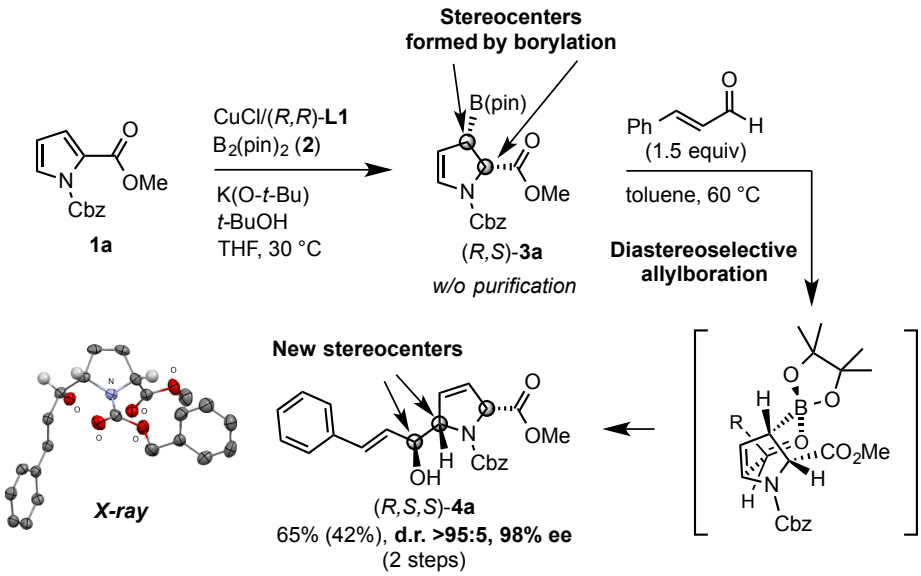
Entry	Cu cat. (mol%)	L*	Base (mol%)	yield (%)[b]	d.r.[c]	ee (%)[d]
1[e]	Cu(O-*t*-Bu) (10)	(*R,R*)-**L1**	Na(O-*t*-Bu) (10)	54	>95:5	96
2	CuCl (10)	(*R,R*)-**L1**	K(O-*t*-Bu) (20)	64	>95:5	96
3	CuCl (5)	(*R,R*)-**L1**	K(O-*t*-Bu) (20)	81	>95:5	95
4	CuCl (5)	(*R,R*)-**L2**	K(O-*t*-Bu) (20)	34	>95:5	80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

[a]Conditions: **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). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using an internal standard. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis. [e]2.0 equiv. of **2** was used. [f]MeOH was used instead of *t*-BuOH. [g]Without alcohol.



The thus obtained chiral 3-boryl-dihydropyrrole (*R,S*)-**3a** can be used for the synthesis of 2,5-substituted pyrrolidines with three stereogenic centers via the diastereoselective allylboration of aldehydes. The author found that the addition of 3-phenylprop-2-enal to the crude mixture of (*R,S*)-**3a**, which was obtained from the

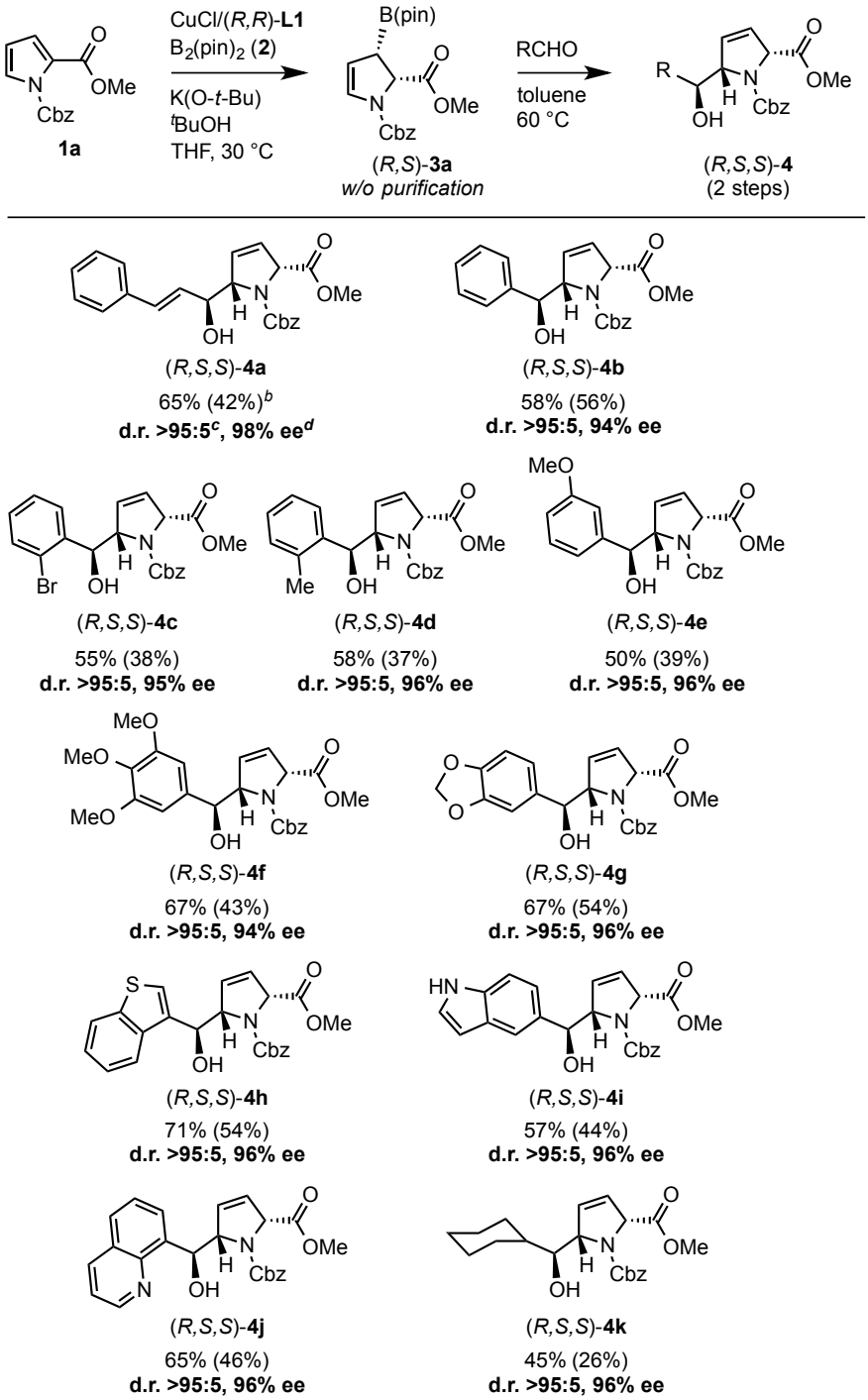
aforementioned reaction, proceeded in a highly diastereoselective manner, probably via a six-membered transition state (vide infra), to give homoallylic alcohol (*R,S,S*)-**4a** in good yield with high diastereoselectivity and without loss of the enantiomeric excess (Scheme 1-2).[2a] Notably, the crude 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 1-2. Allylboration of (*R,S*)-**3a** with cinnamaldehyde

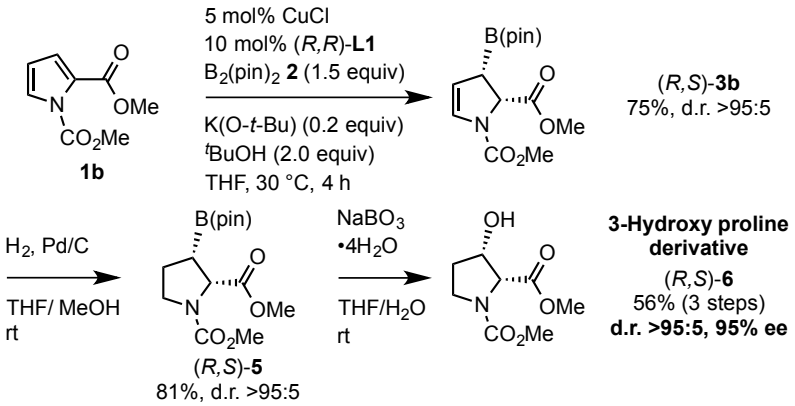
The allylboration of aldehydes with (*R,S*)-**3a** is applicable for a wide range of substrates (Table 1-2). Benzaldehyde smoothly provided the corresponding pyrrolidine derivative (*R,S,S*)-**4b** with excellent stereospecificity. Aromatic aldehydes with electron-withdrawing or -donating functional 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 allylborated with high stereoselectivity [(*R,S,S*)-**4h** − (*R,S,S*)-**4j**]. Allylboration of aliphatic cyclohexane carboxaldehyde provided the product in lower yield (45% NMR yield; 2 steps), albeit with high diastereo- and enantioselectivity (d.r. > 95:5, 96% ee).

Table 1-2. Scope of the allylboration of (*R,S*)-**3a** with respect to aldehyde



[a]Conditions 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). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using an internal standard. Isolated yields are shown in parentheses. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis.

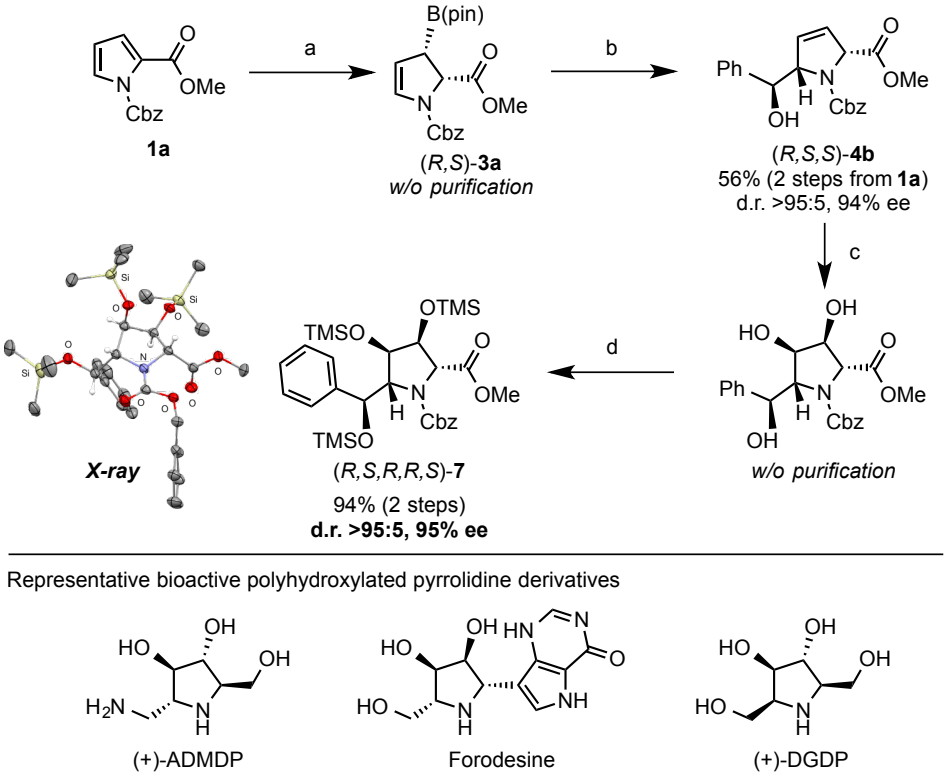
The utility of the borylation of pyrroles was demonstrated by the three-step synthesis of *cis*-3-hydroxy proline derivative (*R,S*)-**6** (Scheme 1-3). *cis*-3-Hydroxy-proline, a rare cyclic β-hydroxy-α-amino acid isolated from carcinoma cell cultures, is a therapeutic agent in the treatment of tumors and collagen disorders.[15] Although both racemic and asymmetric syntheses of *cis*-3-hydroxy proline derivatives have been reported,[16] these protocols are laborious. The author found that the enantioselective borylation of pyrrole **1b,** followed by the sequential hydrogenation of the resulting allylboron compound (*R,S*)-**3b** and oxidation of the boryl group with $NaBO_3$[17] afforded (*R,S*)-**6** in high yield with high diastereo- and enantioselectivity (Scheme 1-3).



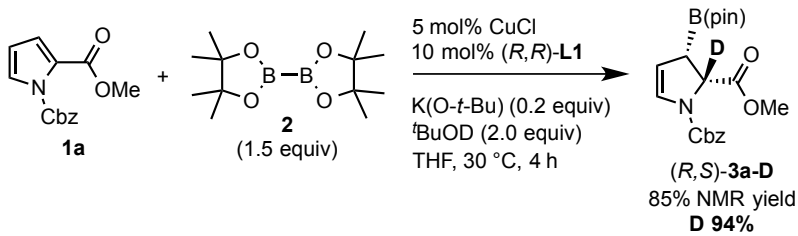
Scheme 1-3. Convenient synthesis of a 3-hydroxy proline derivative via an enantioselective borylative dearomatization

Optically active polyhydroxylated pyrrolidines and their derivatives are potent and selective inhibitors of various glyco-processing enzymes involved in diseases such as cancer and diabete, as well as viral infections and lysosomal storage disorders (Scheme 1-4).[18] To construct these important structural motifs, the author investigated the dihydroxylation of allylboration product (*R,S,S*)-**4b** (Scheme 1-4). Treatment with K_2OsO_4, *N*-methylmorpholine-*N*-oxide (NMO), and citric acid[19], followed by silylation of the hydroxy groups afforded the optically active 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 1-4). The crystallization of racemic **7** from Et_2O afforded single crystals of racemic **7**.[20] The results of an X-ray crystallographic analysis of racemic **7** revealed the relative configuration of its chiral centers. This sequential transformation of borylation/allylboration/dihydroxylation thus enables the rapid construction of this

structural motif, which is commonly encountered in bioactive compounds, from readily available starting materials, highlighting the synthetic utility of the developed method.



Scheme 1-4. Diastereoselective dihydroxylation of (*R,S,S*)-**4b** to provide a chiral pyrrolidine with five consecutive stereocenters. Conditions: (a) standard conditions for the borylation (*cf.* Table 1-1, entry 3); (b) benzaldehyde, toluene, 60 °C; (c) $K_2OsO_4 \cdot 2H_2O$, NMO, citric acid, H_2O/MeCN, rt; (d) Me_3SiCl, imidazole, CH_2Cl_2, rt. See the experimental section for details.



Scheme 1-5. D-Labeling experiment

A deuterium-labeling experiment was tested to probe the reaction mechanism (Scheme 1-5). The borylation of **1a** under the optimal conditions using *t*-BuOD instead of *t*-BuOH afforded the deuterium-labeled product (*R,S*)-**3a-D** (94% D). This result

suggests that the diastereoselective protonation is accomplished by alcohol.

Based on the aforementioned results, the author would like to propose a plausible reaction mechanism for the enantioselective borylative dearomatization of pyrroles (Figure 1-1), 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** with formation of a stereogenic C−B bond. After the formation of **D**, the bulky *t*-BuOH 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**.

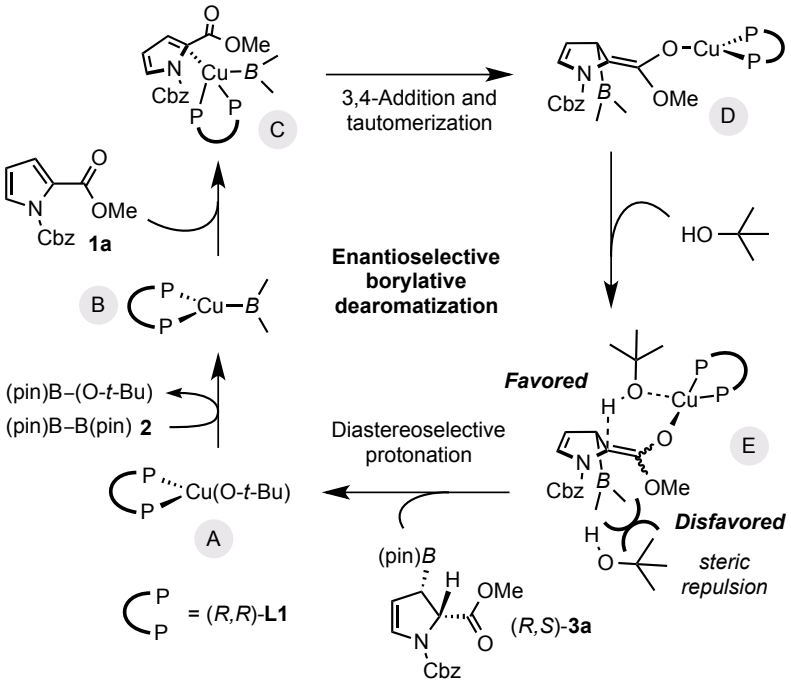


Figure 1-1. Proposed catalytic cycle for the enantioselective borylation of pyrroles

Conclusion

In summary, the author have reported the first synthesis of optically active five-membered *N*-heterocyclic allylboron compounds 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 allylboron compounds represent highly attractive reagents that enable the rapid construction of pyrrolidine derivatives bearing five consecutive stereocenters via sequential allylboration/dihydroxylation processes. The author expects that the results of this study will provide further opportunities for the efficient synthesis of complex molecules with potentially interesting biological activity.

Experimental

Instrumentation and Chemicals

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{13}C) were employed as external standards, respectively.

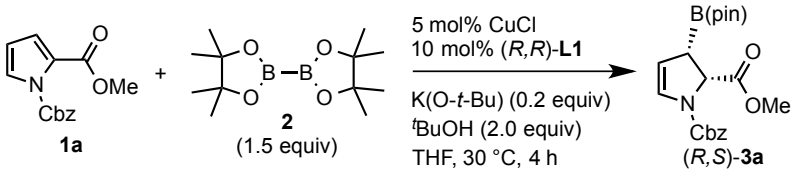
CuCl (ReagentPlus® grade, 224332-25G, ≥99%) was purchased from Sigma-Aldrich Co. and used as received. Tetrachloroethane and mesitylene were used as internal standards to determine NMR yields. Recycle preparative gel permeation chromatography (GPC) was conducted with a JAI LC-9101 using $CHCl_3$ as an eluent with JAIGEL-1H. HPLC analyses with chiral stationary phase were carried out using a Hitachi Chromaster HPLC system [Daicel CHIRALPAK® IA-3 (4.6 x 250 mm), Daicel CHIRALPAK® IBN-3 (4.6 x 250 mm), Daicel CHIRALPAK® IC-3 (4.6 x 250 mm), Daicel CHIRALPAK® ID-3 (4.6 x 250 mm), Daicel CHIRALPAK® IE-3 (4.6 x 250 mm), or Daicel CHIRALPAK® IF-3 (4.6 x 250 mm)]. Specific optical rotations were measured with HORIBA SEPA-30. Medium-pressure column chromatography was carried out on a Biotage Flash Purification System Isolera, which is equipped with a UV detector. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

X-ray diffraction analyses: Single crystal X-ray structural analyses were carried out on a Rigaku XtaLAB PRO MM007 or XtaLAB-Synergy diffractometer using graphite monochromated Cu-Kα radiation. The structure was solved by direct methods and expanded using Fourier techniques. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the Olex2 crystallographic software package except for refinement, which was performed using SHELXL-2018.[20] Simulated powder patterns were generated with Mercury 4.1 from the structures determined by the single-crystal diffraction analyses.

General Experimental Procedures

^{1}H and ^{13}C NMR spectra for borylation products contain conformational isomers, which is caused by the restricted C–N bond rotation around the carbamate group.

Procedure for the Copper(I)-Catalyzed Enantioselective Borylative Dearomatization of 1a (Table 1-1).



Bis(pinacolato)diboron (**2**) (190.5 mg, 0.75 mmol), CuCl (2.5 mg, 0.025 mmol) and (*R,R*)-**L1** (27.6 mg, 0.050 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (0.9 mL) and a THF solution of K(O-*t*-Bu) (1.0 M, 0.10 mL, 0.10 mmol) were added in the vial through the rubber septum. After **1a** (129.6 mg, 0.50 mmol) was added to the mixture at 30 °C, ^{t}BuOH (94.9 μL, 1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column (15 mm×40 mm) eluting with Et_2O. The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 0:100– 10:90) within 10 min to give the corresponding borylation product (*R*,S)-**3a** (111.8 mg, 0.29 mmol, 58%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.23 and 1.24 (a pair of s, 12H), 2.93 and 2.98 (a pair of d, J = 12.6 Hz, 1H), 3.55 and 3.75 (a pair of s, 3H), 4.84 and 4.88 (a pair of d, J = 13.0 Hz, 1H), 4.98–5.26 (m, 3H), 6.58 and 6.67 (a pair of t, J = 3.6 Hz, 1H), 7.27–7.42 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.6 and 24.8 (a pair of s, CH_3), 30.0 (br, B–*C*H), 51.8 and 52.0 (a pair of s, CH_3), 60.4 and 60.5 (a pair of s, *C*H), 67.1 and 67.3 (a pair of s, CH_2), 84.0 (*C*), 108.6 and 108.7 (a pair of s, *C*H), 127.8 and 128.0 (a pair of s, *C*H), 128.1 (*C*H), 128.37 and 128.43 (a pair of s, *C*H), 128.7 (*C*H), 136.07 and 136.14 (a pair of s, *C*), 151.9 (*C*), 171.4 and 171.6 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{26}O_6N^{10}BNa$, 409.1782; found, 409.1786. $[\alpha]_D^{29}$ +25.5 (*c* 0.96, $CHCl_3$). Daicel CHIRALPAK® IA-3, 2-PrOH/Hexane = 7/93, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 13.5 min., (*R,S*)-isomer: t_R = 23.0 min.

General Procedure for the Allylboration Reaction of (*R,S*)-3a with Aldehydes

(Table 1-2).

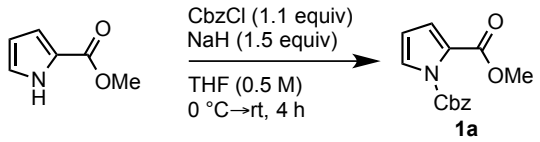
Borylation product (*R*,*S*)-**3a** was submitted to the subsequent allylboration reaction without further purification. In a reaction vial, the crude material of (*R,S*)-**3a** was dissolved in toluene (0.5 M) at room temperature. An aldehyde (1.5 equiv) was added to this solution and stirred over night at 60 °C. The reaction mixture was quenched by CH_2Cl_2 solution of triethanolamine (10% v/v, 3.0 mL) at room temperature. The mixture was separated with water and EtOAc, and then extracted three times with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 0:100– 30:70) to give the corresponding allylboration product.

Preparation of Chiral Ligands

(*R*,*R*)-**L1** was synthesized according to the literature procedure.[21] Other chiral ligands were obtained from commercial suppliers without further purification.

Substrate Preparation

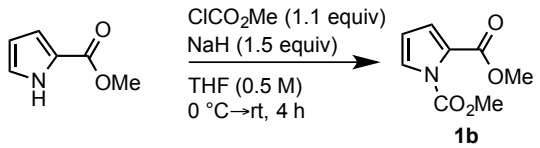
Preparation of 1-Benzyl 2-methyl 1*H*-pyrrole-1,2-dicarboxylate (1a).



In a 200 mL round bottomed flask, NaH (1.8 g, 60%, dispersion in paraffin liquid, 45 mmol) was dissolved in dry THF (60 mL) and the mixture was cooled to 0 °C under nitrogen atmosphere. Methyl pyrrole-2-carboxylate (3.75 g, 30 mmol) was added in three separate times. Benzyl chloroformate (4.65 mL, 33 mmol) was then added dropwise. After stirred for 4 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 three times. The combined organic layer was then dried over $MgSO_4$. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 3:97–20:80) to obtain **1a** (4.58 g, 17.7 mmol, 59%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.76 (s, 3H), 5.37 (s, 2H), 6.20 (t, J = 3.4 Hz, 1H), 6.88 (q, J = 1.8 Hz, 1H), 7.33–7.46 (m, 6H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 51.7 (CH_3), 69.6 (CH_2), 110.6 (*C*H), 121.2 (*C*H), 125.3 (*C*), 126.4 (*C*H), 128.43 (*C*H), 128.45 (*C*H), 128.6 (*C*H), 134.2 (*C*), 149.5 (*C*), 160.9 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{13}O_4NNa$, 282.0737; found, 282.0736.

Preparation of Dimethyl 1*H*-pyrrole-1,2-dicarboxylate (1b).



In a 200 mL round bottomed flask, NaH (440 mg, 60%, dispersion in paraffin liquid, 11 mmol) was dissolved in dry THF (20 mL) and the mixture was cooled to 0 °C under nitrogen atmosphere. Methyl pyrrole-2-carboxylate (1.25 g, 10 mmol) was added in three separate times. Methyl chloroformate (0.927 mL, 12 mmol) was then added dropwise. After stirred for 4 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 three times. The combined organic layer was then dried over $MgSO_4$. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 3:97–20:80) to obtain **1b** (1.80 g, 9.8 mmol, 98%) as a colorless oil.

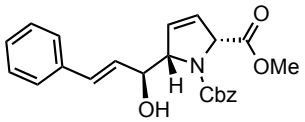
^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.86 (s, 3H), 3.98 (s, 3H), 6.21 (t, J = 3.4 Hz, 1H),

6.89 (q, J = 1.6 Hz, 1H), 7.35 (dd, J = 3.2, 1.8 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 51.3 (CH_3), 54.1 (CH_3), 110.2 (*C*H), 120.9 (*C*H), 124.9 (*C*), 126.2 (*C*H), 149.8 (*C*), 160.4 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_8H_9O_4NNa$, 206.0424; found, 206.0426.

Allylboration Product Characterization

^{1}H and ^{13}C NMR spectra for all allylboration products contain conformational isomers, which is caused by the restricted C–N bond rotation around the carbamate group. Diastereomer ratios of the allylboration products were determined by ^{1}H NMR analysis of the crude reaction mixture.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*,*E*)-1-hydroxy-3-phenylallyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R*,*S*,*S*)-4a].

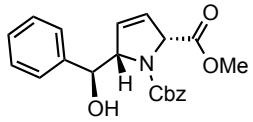


(*R*,*S*,*S*)-**4a**

The product (*R,S,S*)-**4a** was obtained in 42% 2-step yield (82.6 mg, 0.21 mmol, white solid) with d.r. >95:5, 98% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.69 and 3.77 (a pair of s, 3H), 4.42–4.54 (m, 1H), 4.86 and 4.91 (a pair of d, J = 7.4, 4.0 Hz, 2H), 5.10–5.28 (m, 3H), 5.79–5.98 (m, 2H), 6.31 (dd, J = 15.7, 6.3 Hz, 1H), 6.63 and 6.69 (a pair of d, J = 17.2, 15.7 Hz, 1H), 7.18–7.44 (m, 10H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.6 and 52.8 (a pair of s, CH_3), 67.1 and 67.6 (a pair of s, *C*H), 67.7 (CH_2), 69.6 and 71.3 (a pair of s, *C*H), 73.1 and 76.2 (a pair of s, *C*H), 124.8 and 125.0 (a pair of s, *C*H), 126.4 and 126.5 (a pair of s, *C*H), 127.3 and 127.4 (a pair of s, *C*H), 127.7 (*C*H), 128.1 (*C*H), 128.4 (*C*H), 128.8 (*C*H), 129.7 and 130.4 (a pair of s, *C*H), 130.8 and 131.0 (a pair of s, *C*H), 135.7 and 135.8 (a pair of s, *C*), 136.8 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{23}O_5NNa$, 416.1468; found, 416.1468. $[\alpha]_D^{27}$ –28.6 (*c* 1.06, $CHCl_3$). Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*R,S,S*)-isomer: t_R = 28.2 min., (*S,R,R*)-isomer: t_R = 36.0 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-hydroxy(phenyl)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R*,*S*,*S*)-4b].

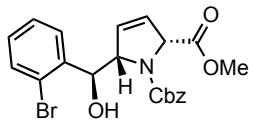


(*R,S,S*)-**4b**

The product (*R,S,S*)-**4b** was obtained in 56% 2-step yield (102.9 mg, 0.28 mmol, colorless oil) with d.r. >95:5, 94% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.71 and 3.83 (a pair of s, 3H), 4.25 and 4.79 (a pair of d, J = 7.4, 7.2 Hz, 1H), 4.28–4.33 and 4.87–4.93 (a pair of m, 1H), 4.94–5.32 (m, 4H), 5.70–5.75 and 5.84–5.94 (a pair of m, 1H), 5.86 (s, 1H), 7.14–7.42 (m, 10H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.6 and 52.9 (a pair of s, CH_3), 67.3 and 67.6 (a pair of s, *C*H), 68.0 (CH_2), 71.2 and 73.0 (a pair of s, *C*H), 75.6 and 80.0 (a pair of s, *C*H), 124.4 and 124.9 (a pair of s, *C*H), 126.1 and 126.9 (a pair of s, *C*H), 127.3 and 127.9 (a pair of s, *C*H), 127.8 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 130.5 and 131.4 (a pair of s, *C*H), 135.7 (*C*), 140.9 and 141.8 (a pair of s, *C*), 155.2 and 156.9 (a pair of s, *C*), 170.1 and 172.2 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{21}O_5NNa$, 390.1312; found, 390.1310. $[\alpha]_D^{27}$ +44.7 (*c* 1.07, $CHCl_3$). Daicel CHIRALPAK® IA-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*S,R,R*)-isomer: t_R = 39.3 min., (*R,S,S*)-isomer: t_R = 43.9 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-(2-bromophenyl)(hydroxy)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4c].



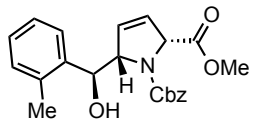
(*R,S,S*)-**4c**

The product (*R,S,S*)-**4c** was obtained in 38% 2-step yield (85.2 mg, 0.19 mmol, colorless oil) with d.r. >95:5, 95% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.75 and 3.89 (a pair of s, 3H), 4.95 and 4.98 (a pair of d, J = 6.3, 5.4 Hz, 1H), 5.02–5.09 (m, 1H), 5.07 and 5.11 (a pair of s, 1H), 5.18 (s, 1H), 5.18–5.23 and 5.29–5.34 (a pair of m, 1H), 5.34–5.40 and 5.68–5.74 (a pair of m, 1H), 5.47 and 5.78 (a pair of d, J = 5.8 Hz, 1H), 5.92 and 6.07 (a pair of d, J = 6.3, 5.8 Hz, 1H), 6.98 and 7.14 (a pair of t, J = 7.6, 7.2 Hz, 1H), 7.04–7.10 (m, 1H), 7.23–7.41 and 7.57–7.63 (a pair of m, 6H), 7.53 (t, J = 7.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.7 and 53.2 (a pair of s, CH_3), 67.3 and 67.7 (a pair of s, CH_2), 67.4 and 67.7 (a pair of s, *C*H), 68.2 and 71.8 (a pair of s, *C*H), 72.9 and 76.2 (a pair of s, *C*H), 121.7 and 122.6 (a pair of s, *C*), 124.7 and 125.0 (a pair of s, *C*H), 127.1 and 127.6 (a pair of s,

*C*H), 127.6 and 128.0 (a pair of s, *C*H), 127.7 and 128.1 (a pair of s, *C*H), 128.0 and 128.4 (a pair of s, *C*H), 129.0 (*C*H), 130.2 (*C*H), 131.9 and 132.0 (a pair of s, *C*H), 132.5 (*C*H), 135.4 and 135.8 (a pair of s, *C*), 140.4 and 141.3 (a pair of s, *C*), 155.1 and 156.2 (a pair of s, *C*), 170.8 and 173.7 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{20}O_5NBrNa$, 468.0417; found, 468.0419. $[\alpha]_D^{27}$ +95.5 (*c* 1.02, $CHCl_3$). Daicel CHIRALPAK® IA-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*S,R,R*)-isomer: t_R = 29.5 min., (*R,S,S*)-isomer: t_R = 41.3 min.

1-Benzyl 2-methyl(2*R*,5*S*)-5-((*S*)-hydroxy(*o*-tolyl)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4d].

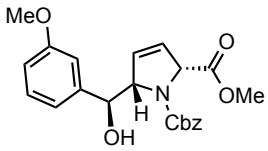


(*R,S,S*)-**4d**

The product (*R,S,S*)-**4d** was obtained in 37% 2-step yield (70.7 mg, 0.19 mmol, colorless oil) with d.r. >95:5, 96% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 2.26 (s,3H), 3.70 and 3.85 (a pair of s, 3H), 4.18 and 4.95 (a pair of d, *J* = 12.9, 7.2 Hz, 1H), 4.34–4.44 and 4.96–5.06 (a pair of m, 1H), 5.12–5.34 (m, 4H), 5.64–5.71 and 5.82–5.86 (a pair of m, 1H), 5.81 and 5.89 (a pair of s, 1H), 6.96–7.64 (m, 9H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 19.3 and 19.7 (a pair of s, CH_3), 52.6 and 53.1 (a pair of s, CH_3), 67.5 and 67.7 (a pair of s, *C*H), 68.0 and 69.4 (a pair of s, CH_2), 72.0 and 73.4 (a pair of s, *C*H), 75.5 (a pair of s, *C*H), 124.6 and 125.0 (a pair of s, *C*H), 125.8 and 126.4 (a pair of s, *C*H), 126.0 and 126.7 (a pair of s, *C*H), 127.1 and 127.5 (a pair of s, *C*H), 127.9 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 130.1 and 130.3 (a pair of s, *C*H), 130.5 and 131.5 (a pair of s, *C*H), 134.1 and 134.9 (a pair of s, *C*), 135.7 (*C*), 139.3 (*C*), 156.8 (*C*), 170.2 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{23}O_5NNa$, 404.1468; found, 404.1467. $[\alpha]_D^{28}$ +30.4 (*c* 0.99, $CHCl_3$). Daicel CHIRALPAK® IA-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*R,S,S*)-isomer: t_R = 32.6 min., (*S,R,R*)-isomer: t_R = 34.5 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-hydroxy(3-methoxyphenyl)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4e].

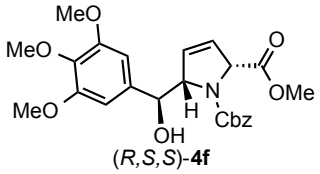


(*R,S,S*)-**4e**

The product (*R,S,S*)-**4e** was obtained in 39% 2-step yield (77.3 mg, 0.20 mmol, colorless oil) with d.r. >95:5, 96% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.71 and 3.75 (a pair of s, 3H), 3.81 (s, 3H), 4.22 and 4.76 (a pair of d, *J* = 7.2, 5.9 Hz, 1H), 4.40 and 4.88 (a pair of d, *J* = 11.0, 7.4 Hz, 1H), 4.92–5.32 (a pair of m, 4H), 5.68–5.74 and 5.80–5.85 (a pair of m, 1H), 5.88 (s, 1H), 6.72–6.78 and 6.80–6.86 (a pair of m, 1H), 6.91 and 6.93 (a pair of s, 1H), 6.96 (s, 1H), 7.16–7.42 (m, 6H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.6 and 52.9 (a pair of s, *C*H_3), 55.2 (*C*H_3), 67.4 and 67.5 (a pair of s, *C*H), 68.0 (*C*H_2), 71.1 and 72.9 (a pair of s, *C*H), 75.8 and 80.0 (a pair of s, *C*H), 111.5 and 112.1 (a pair of s, *C*H), 113.1 and 113.6 (a pair of s, *C*H), 118.5 and 119.4 (a pair of s, *C*H), 124.4 and 125.0 (a pair of s, *C*H), 127.8 and 128.15 (a pair of s, *C*H), 128.24 (*C*H), 128.4 and 128.5 (a pair of s, *C*H), 129.1 and 129.3 (a pair of s, *C*H), 130.6 and 131.3 (a pair of s, *C*H), 135.7 (*C*), 142.5 and 143.4 (a pair of s, *C*), 155.2 and 156.9 (a pair of s, *C*), 159.7 (*C*), 170.0 and 172.1 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{23}O_6NNa$, 420.1418; found, 420.1418. $[\alpha]_D^{28}$ +32.5 (*c* 1.08, $CHCl_3$). Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*S,R,R*)-isomer: t_R = 51.4 min., (*R,S,S*)-isomer: t_R = 58.8 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-hydroxy(3,4,5-trimethoxyphenyl)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4f].



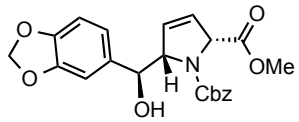
(*R,S,S*)-**4f**

The product (*R,S,S*)-**4f** was obtained in 43% 2-step yield (99.0 mg, 0.22 mmol, colorless oil) with d.r. >95:5, 94% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.72 and 3.81 (a pair of s, 3H), 3.83 (s, 3H), 3.86 (s, 6H), 4.19 and 4.69 (a pair of d, *J* = 7.6 Hz, 1H), 4.51 and 4.86 (a pair of d, *J* = 11.2, 6.3 Hz, 1H), 4.90–5.02 and 5.12–5.32 (a pair of m, 4H), 5.70–5.76 and 5.80–5.84 (a pair of m, 1H), 5.91 (s, 1H), 6.60 (s, 2H), 7.16–7.42 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.3 and 52.6 (a pair of s, *C*H_3), 55.7 and 55.8 (a pair of s, *C*H_3), 60.5 (*C*H_3), 67.1 and 67.3 (a pair of s, *C*H), 67.8 (*C*H_2), 70.7 and 72.6 (a pair of s, *C*H), 75.5 and 80.0 (a pair of s, *C*H), 102.9 and 103.5 (a pair of s, *C*H), 124.3 and 124.8 (a pair of s, *C*H), 127.6 and 127.8 (a pair of s, *C*H), 128.0 (*C*H), 128.2 (*C*H), 130.2 and 130.9 (a pair of s, *C*H), 135.4 (*C*), 136.4 and 136.5 (a pair of s, *C*), 137.2 and 137.3 (a pair of s, *C*), 152.7 and 152.9 (a pair of s, *C*), 154.9 and 156.8 (a pair of s, *C*), 169.8 and 171.8 (a pair of s, *C*).

HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{27}O_8NNa$, 480.1629; found, 480.1628. $[\alpha]_D^{28}$ +10.6 (*c* 1.06, $CHCl_3$). Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 15/85, 0.5 mL/min, 40 °C, (*S,R,R*)-isomer: t_R = 28.0 min., (*R,S,S*)-isomer: t_R = 38.7 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-benzo[*d*][1,3]dioxol-5-yl(hydroxy)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4g].

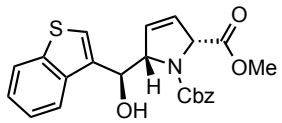


(*R,S,S*)-**4g**

The product (*R,S,S*)-**4g** was obtained in 54% 2-step yield (110.5 mg, 0.27 mmol, colorless oil) with d.r. >95:5, 96% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.70 and 3.81 (a pair of s, 3H), 4.04–4.14 and 4.66–4.74 (a pair of m, 1H), 4.60–4.66 and 4.80–4.84 (a pair of m, 1H), 4.86–5.30 (m, 4H), 5.68–5.74 and 5.74–5.80 (a pair of m, 1H), 5.84 (s, 1H), 5.89 and 5.95 (a pair of s, 2H), 6.77 (q, 7.3 Hz, 2H), 6.91 (s, 1H), 7.20–7.42 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.6 and 52.9 (a pair of s, CH_3), 67.3 and 67.7 (a pair of s, *C*H), 68.0 (CH_2), 71.3 and 73.0 (a pair of s, *C*H), 75.9 and 79.8 (a pair of s, *C*H), 119.6 and 120.4 (a pair of s, *C*H), 124.5 and 125.0 (a pair of s, *C*H), 127.8 and 128.0 (a pair of s, *C*H), 128.2 (*C*H), 128.5 (*C*H), 130.5 and 131.1 (a pair of s, *C*H), 135.0 (*C*), 135.6 and 135.7 (a pair of s, *C*), 146.9 and 147.1 (a pair of s, *C*), 147.5 and 147.7 (a pair of s, *C*), 155.2 and 156.9 (a pair of s, *C*), 170.0 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{21}O_7NNa$, 434.1210; found, 434.1213. $[\alpha]_D^{29}$ +6.7 (*c* 1.06, $CHCl_3$). Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*R,S,S*)-isomer: t_R = 44.0 min., (*S,R,R*)-isomer: t_R = 50.6 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-benzo[*b*]thiophen-3-yl(hydroxy)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4h].



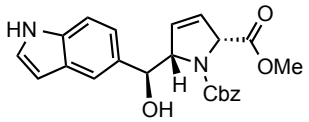
(*R,S,S*)-**4h**

The product (*R,S,S*)-**4h** was obtained in 54% 2-step yield (114.0 mg, 0.27 mmol, colorless oil, small amount of impurities were contained) with d.r. >95:5, 96% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.73 and 3.84 (a pair of s, 3H), 3.90 and 4.51 and 5.10–5.24 (pairs of m, 4H), 5.02 and 5.31 (a pair of d, *J* = 12.2, 4.5 Hz, 1H), 5.29 (s,

1H), 5.66–5.74 and 5.90–5.94 (a pair of m, 1H), 5.88 and 5.93 (a pair of s, 1H), 6.82 and 7.19 (a pair of d, J = 7.8, 5.5 Hz, 1H), 7.30–7.44 (m, 6H), 7.47 and 7.51 (a pair of s, 1H), 7.73–7.80 and 7.80–7.92 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.6 and 53.0 (a pair of s, CH_3), 67.3 and 67.5 (a pair of s, *C*H), 67.6 and 68.0 (a pair of s, CH_2), 69.2 and 72.6 (a pair of s, *C*H), 71.3 and 75.2 (a pair of s, *C*H), 121.5 and 122.7 (a pair of s, *C*H), 122.8 (*C*H), 123.9 (*C*H), 124.16 (*C*H), 124.23 (*C*H), 124.7 and 125.1 (a pair of s, *C*H), 127.8 (*C*H), 128.0 and 128.2 (a pair of s, *C*H), 128.5 (*C*H), 130.4 and 131.2 (a pair of s, *C*H), 135.4 and 135.6 (a pair of s, *C*), 136.3 (*C*), 137.3 (*C*), 140.7 (*C*), 155.1 and 156.7 (a pair of s, *C*), 170.2 and 172.7 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{21}O_5NNaS$, 446.1033; found, 446.1035. $[\alpha]_D^{29}$ +45.3 (*c* 1.02, $CHCl_3$). Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*S,R,R*)-isomer: t_R = 40.7 min., (*R,S,S*)-isomer: t_R = 54.7 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-hydroxy(1*H*-indol-5-yl)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4i].

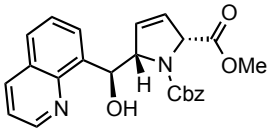


(*R,S,S*)-**4i**

The product (*R,S,S*)-**4i** was obtained in 44% 2-step yield (88.5 mg, 0.22 mmol, colorless oil) with d.r. >95:5, 96% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.70 and 3.76 (a pair of s, 3H), 4.44 and 4.88 (a pair of d, J = 12.2, 7.6 Hz, 1H), 4.96 (dd, J = 7.6, 1.8 Hz, 1H), 4.78–4.84 and 5.12–5.24 (a pair of m, 3H), 5.06 and 5.29 (a pair of d, J = 12.6, 11.8 Hz, 1H), 5.64–5.70 and 5.70–5.78 (a pair of m, 1H), 5.85 and 5.90 (a pair of s, 1H), 6.52 (s, 1H), 7.06–7.44 (m, 8H), 7.62 (s, 1H), 8.25 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.6 (CH_3), 67.4 and 67.6 (a pair of s, *C*H), 68.0 (CH_2), 73.4 (*C*H), 80.8 (*C*H), 102.5 (*C*H), 111.1 (*C*H), 119.2 (*C*H), 120.9 (*C*H), 123.9 (*C*H), 124.6 (*C*H), 127.7 (*C*), 127.9 (*C*H), 128.2 (*C*H), 128.5 (*C*H), 131.2 (*C*H), 132.4 (*C*), 135.7 (*C*), 135.8 (*C*), 157.1 (*C*), 170.2 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{23}H_{22}O_5N_2Na$, 429.1421; found, 429.1426. $[\alpha]_D^{29}$ −1.4 (*c* 0.95, $CHCl_3$). Daicel CHIRALPAK® ID-3, 2-PrOH/Hexane = 17/83, 0.5 mL/min, 40 °C, (*S,R,R*)-isomer: t_R = 94.2 min., (*R,S,S*)-isomer: t_R = 114.1 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-hydroxy(quinolin-8-yl)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4j].

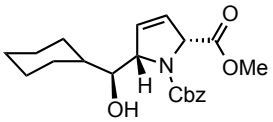


(*R,S,S*)-**4j**

The product (*R,S,S*)-**4j** was obtained in 46% 2-step yield (95.3 mg, 0.23 mmol, colorless oil) with d.r. >95:5, 96% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.66 and 3.81 (a pair of s, 3H), 4.89 and 4.99 (a pair of d, J = 12.1 Hz, 1H), 5.06–5.86 (m, 5H), 5.90 and 6.16 (a pair of d, J = 5.8 Hz, 1H), 6.72–7.80 (m, 9H), 8.02 and 8.17 (a pair of d, J = 8.1, 7.6 Hz, 1H), 8.76 and 8.85 (a pair of d, J = 2.7 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.5 and 52.9 (a pair of s, CH_3), 66.8 and 67.1 (a pair of s, CH_2), 67.4 and 67.8 (a pair of s, *C*H), 70.4 and 71.8 (a pair of s, *C*H), 72.9 and 75.0 (a pair of s, *C*H), 120.7 (*C*H), 123.9 and 124.2 (a pair of s, *C*H), 126.2 and 126.8 (a pair of s, *C*H), 127.0 (*C*H), 127.2 and 127.7 (a pair of *C*H), 127.6 and 127.9 (a pair of s, *C*H), 128.1 and 128.4 (a pair of s, *C*H), 131.6 and 132.3 (a pair of s, *C*H), 135.6 (*C*), 136.3 and 136.6 (a pair of s, *C*H), 137.8 (*C*), 139.1 (*C*), 145.9 (*C*), 148.4 (*C*H), 155.2 and 155.5 (a pair of *C*), 172.7 (*C*). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{24}H_{23}O_5N_2$, 419.1602; found, 419.1604. $[\alpha]_D^{29}$ +76.5 (*c* 1.05, $CHCl_3$). Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 15/85, 0.5 mL/min, 40 °C, (*S,R,R*)-isomer: t_R = 31.2 min., (*R,S,S*)-isomer: t_R = 49.4 min.

1-Benzyl 2-methyl (2*R*,5*S*)-5-((*S*)-cyclohexyl(hydroxy)methyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate [(*R,S,S*)-4k].



(*R,S,S*)-**4k**

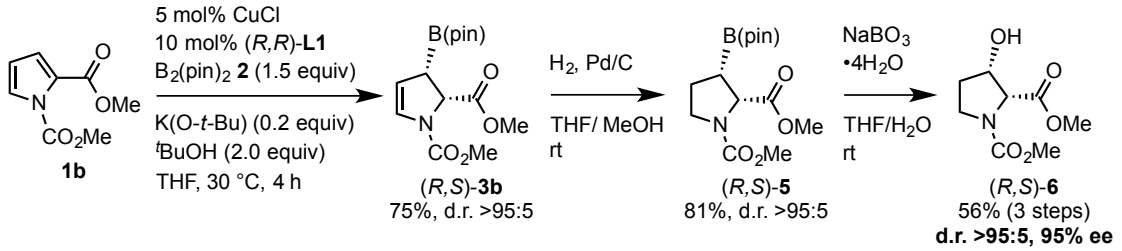
The product (*R,S,S*)-**4k** was obtained in 26% 2-step yield (48.3 mg, 0.13 mmol, colorless oil) with d.r. >95:5, 96% ee.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.80–2.06 (m, 11H), 3.11 and 3.46 (a pair of d, J = 4.0 Hz, 1H), 3.69 and 3.80 (a pair of s, 3H), 4.48 (d, J = 4.0 Hz, 1H), 4.87 (s, 1H), 5.00–5.36 (m, 3H), 5.82 and 5.88 (a pair of s, 2H), 7.26–7.42 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 25.9 and 26.1 (a pair of s, CH_2), 26.2 (CH_2), 26.4 and 26.5 (a pair of s, CH_2), 28.7 and 30.0 (a pair of s, CH_2), 66.6 and 67.1 (a pair of s, *C*H), 67.7 and 67.9 (a pair of s, CH_2), 69.4 (*C*H), 79.5 (*C*H), 124.1 and 124.5 (a pair of s, *C*H), 127.7 (*C*H), 128.1 (*C*H), 128.3 and 128.5 (a pair of s, *C*H), 130.7 and 132.3 (a pair of s, *C*H), 135.9 (*C*), 156.4 (*C*), 170.8 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{27}O_5NNa$, 396.1781;

found, 396.1783. $[\alpha]_D^{29}$ +11.7 (*c* 1.06, $CHCl_3$). Daicel CHIRALPAK® IA-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*S,R,R*)-isomer: t_R = 19.6 min., (*R,S,S*)-isomer: t_R = 21.5 min.

Procedures for Functionalization of Borylation Products

Procedure for the Synthesis of Chiral 3-Hydroxy Proline Derivative (*R,S*)-6 through the Borylation following Sequential Hydrogenation and Oxidation of 1b.



Bis(pinacolato)diboron (**2**) (190.5 mg, 0.75 mmol), CuCl (2.5 mg, 0.025 mmol) and (*R,R*)-**L1** (27.6 mg, 0.050 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (0.9 mL) and a THF solution of K(O-*t*-Bu) (1.0 M, 0.10 mL, 0.10 mmol) were added in the vial through the rubber septum. After **1b** (91.6 mg, 0.50 mmol) was added to the mixture at 30 °C, ^{t}BuOH (94.9 μL, 1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et_2O. The crude mixture was roughly purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 10:90– 50:50) to give the corresponding borylation product (*R,S*)-**3b** as a colorless oil. The flash column chromatography should be done within 10 min after the crude mixture was applied on the silica gel surface. Their longer retention time in the column may have resulted in decomposition of products, leading to a lower isolated yield.

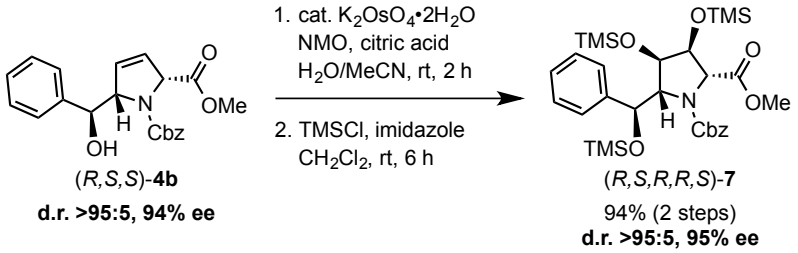
In a reaction vial, 10% Pd/C (15 mg) was dissolved in MeOH (1.0 mL). The crude material of (*R,S*)-**3b** in THF (1.0 mL) was then added to this solution. After stirred for 3 h at room temperature under H_2 atmosphere (H_2 balloon), the mixture was passed through a short silica gel column eluting with Et_2O and concentrated under reduced pressure. The resulting product (*R,S*)-**5** was used in the next reaction without further purification.

The oxidation was performed according to the literature procedure.[22] In a reaction vial, the crude material of (*R,S*)-**5** was dissolved in THF/H_2O (1:1, 2 mL). $NaBO_3$•$4H_2O$ (188.3 mg, 1.22 mmol) was then added at room temperature. After stirred for 3 h, the reaction mixture was extracted three times with $CHCl_3$, dried over $MgSO_4$, and filtered. The crude mixture was purified by flash column chromatography (SiO_2, ethyl

acetate/hexane, 30:70–100:0) to afford (*R,S*)-**6** (56.4 mg, 0.278 mmol, 56%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.96–2.30 (m, 3H), 3.46–3.74 (m, 2H), 3.68 and 3.72 (a pair of s, 3H), 3.78 and 3.80 (a pair of s, 3H), 4.43 and 4.47 (a pair of d, J = 6.7 Hz, 1H), 4.58–4.70 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 31.9 and 32.8 (a pair of s, CH_2), 44.1 and 44.4 (a pair of s, CH_2), 52.3 (CH_3), 52.7 (CH_3), 63.5 and 63.7 (a pair of s, *C*H), 71.3 and 72.2 (a pair of s, *C*H), 155.0 and 155.5 (a pair of s, *C*), 170.5 and 170.6 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_8H_{13}O_5NNa$, 226.0686; found, 226.0688. $[\alpha]_D^{29}$ +35.2 (*c* 1.06, $CHCl_3$). Daicel CHIRALPAK® IA-3, 2-PrOH/Hexane = 15/85, 0.5 mL/min, 40 °C, (*R,S*)-isomer: t_R = 16.1 min., (*S,R*)-isomer: t_R = 18.8 min.

Procedure for the Synthesis of All Carbon-Substituted Chiral Pyrrolidine (*R,S,R,R,S*)-7 through the Dihydroxylation of Allylboration Product (*R,S,S*)-4b.



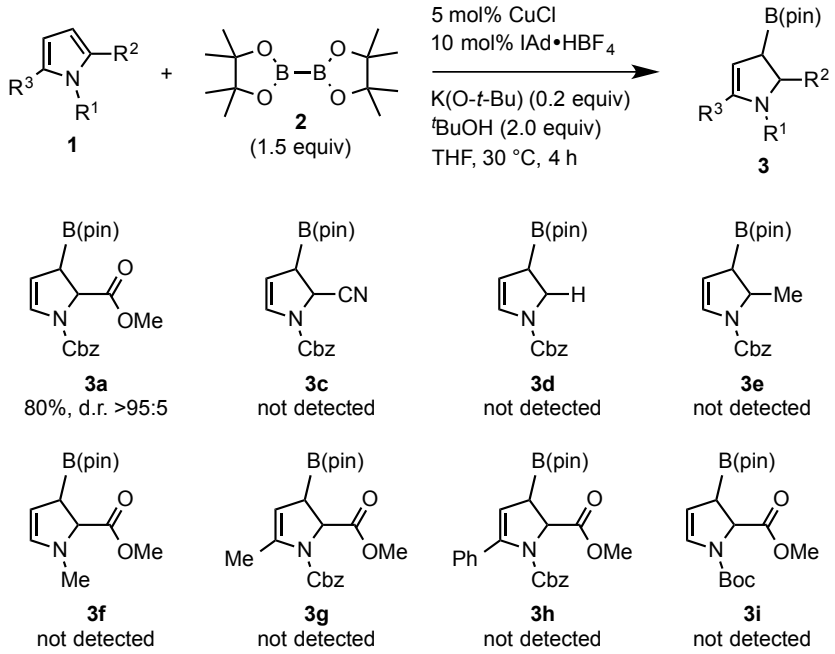
The dihydroxylation of (*R,S,S*)-**4b** was performed according to the literature procedure.[23] In a reaction vial, Allylboration product (*R,S,S*)-**4b** (36.7 mg, 0.10 mmol) was dissolved in H_2O/MeCN (4:1, 2 mL). NMO (15.6 mg, 0.133 mmol), citric acid (14.4 mg, 0.075 mmol), K_2OsO_4•$2H_2O$ (3.7 mg, 0.001 mmol) were added. The mixture was stirred at room temperature for 2 h, then extracted with EtOAc (4×10 mL). The organic phase was dried over $MgSO_4$, and concentrated.

To a solution of the crude product and imidazole (68.1 mg, 1.0 mmol) in CH_2Cl_2 (1.5 mL) was added TMSCl (75.8 μL, 0.60 mmol) at 0 °C, and then stirred at room temperature for 6 h. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et_2O. The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 1:99– 10:90) to give the corresponding product (*R,S,R,R,S*)-**7** (57.9 mg, 94%, 2 steps) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): −0.20 and −0.17 (a pair of s, 9H), −0.09 and 0.13 (a pair of s, 9H), 0.11 and 0.14 (a pair of s, 9H), 2.77 and 2.82 (a pair of dd, J = 9.4, 3.8 Hz, 1H), 3.81 and 3.94 (a pair of d, J = 4.1, 4.0 Hz, 1H), 3.96–4.12 (m, 2H), 5.00–5.28 (m, 3H), 7.22–7.48 (m, 10H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): −0.63 and −0.55 (a pair of s, CH_3), −0.42 and −0.19 (a pair of s, CH_3), 0.31 (CH_3), 51.3 and 51.7 (a pair of s, CH_3),

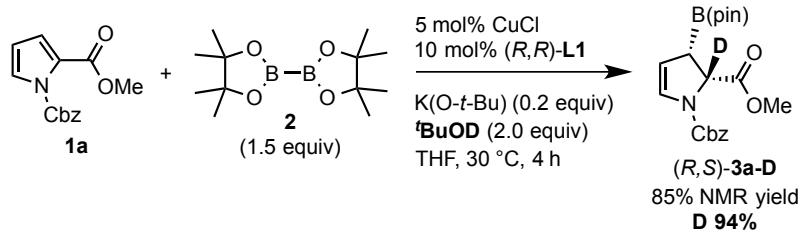
62.9 and 63.2 (a pair of s, *C*H), 67.4 and 67.8 (a pair of s, CH_2), 71.4 and 72.0 (a pair of s, *C*H), 71.8 and 72.6 (a pair of s, *C*H), 72.7 and 73.4 (a pair of s, *C*H), 73.7 and 74.2 (a pair of s, *C*H), 127.1 and 127.3 (a pair of s, *C*H), 127.5 and 127.7 (a pair of s, *C*H), 127.6 and 127.8 (a pair of s, *C*H), 127.9 (*C*H), 128.3 (*C*H), 128.5 and 128.6 (a pair of s, *C*H), 135.9 and 136.0 (a pair of s, *C*), 139.8 and 140.1 (a pair of s, *C*), 155.8 and 155.9 (a pair of s, *C*), 171.2 and 171.4 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{30}H_{47}O_7NNaSi_3$, 640.2553; found, 640.2552. $[\alpha]_D^{29}$ −60.8 (*c* 0.98, $CHCl_3$). Daicel CHIRALPAK® IC-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S,R,S,S,R*)-isomer: t_R = 8.7 min., (*R,S,R,R,S*)-isomer: t_R = 11.6 min.

Effect of Substituents in Pyrroles



Borylative dearomatization of various pyrroles was investigated. While borylation of the pyrrole bearing the ester group at 2-position proceeded efficiently, the substrate bearing a cyano group did not react. No reactions occurred when the pyrroles that do not bear an electron-withdrawing group were used as substrates. Substituents at 5 position significantly decreased the reactivity. The borylation of Boc-protected pyrrole was investigated, but it resulted in no reaction due to the steric bulkiness of the Boc group.

Deuterium Labeling Experiment



The borylation of **1a** under the optimized conditions using *t*-BuOD instead of *t*-BuOH gave the deuterium labeling product (*R,S*)-**3a-D** (94% D). This result is consistent with our proposed reaction mechanism shown in Figure 1.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.24 (s, 12H), 2.93 and 2.98 (a pair of s, 1H), 3.55 and 3.76 (a pair of s, 3H), 4.98–5.26 (m, 3H), 6.58 and 6.67 (a pair od s, 1H), 7.27–7.42 (m, 5H).

Single Crystal X-ray Structural Analyses

The absolute configuration of the compound (*R,S,S*)-**4a** and the relative configuration of the compound (*rac*)-**7** were determined based on X-ray crystallographic analyses. The absolute configurations of other products were deduced by these products. The details were summarized in Figure S1-1, S1-2 and Table S1-1, S1-2.

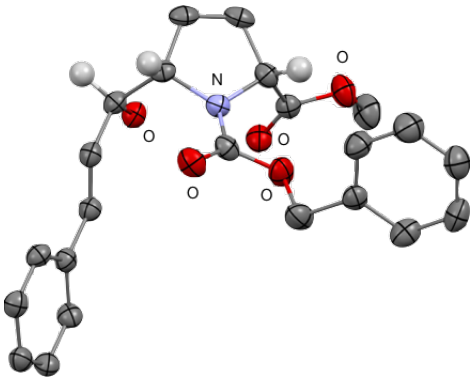


Figure S1-1. Molecular structure of (*R,S,S*)-**4a**. Thermal ellipsoids set at 50% probability.

Table S1-1. Summary of X-ray crystallographic data for (*R,S,S*)-**4a**.

CCDC	1962364
Empirical formula	$C_{23}H_{23}NO_5$
Formula weight	393.42
Temperature/K	123
Crystal system	monoclinic
Space group	*P*21
a/Å	11.60227(18)
b/Å	5.83150(9)
c/Å	14.7816(2)
α /°	90
β /°	97.2697(14)
γ /°	90
Volume/Å^3	992.06(3)
Z	2
ρ_{calc} g/cm^3	1.317
μ /mm^{-1}	0.761
F(000)	416.0
Crystal size/mm^3	0.316 × 0.047 × 0.026
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	6.028 to 147.356
Index ranges	$-14 \leq h \leq 14$, $-7 \leq k \leq 7$, $-18 \leq l \leq 18$
Reflections collected	24413
Independent reflections	3979 [R_{int} = 0.0772, R_{sigma} = 0.0371]
Data/restraints/parameters	3979/1/264
Goodness-of-fit on F^2	1.079
Final *R* indexes [I>=2σ (I)]	R_1 = 0.0488, wR_2 = 0.1282
Final R indexes [all data]	R_1 = 0.0527, wR_2 = 0.1316
Largest diff. peak/hole / e Å^{-3}	0.34/−0.21
Flack parameter	−0.29(13)

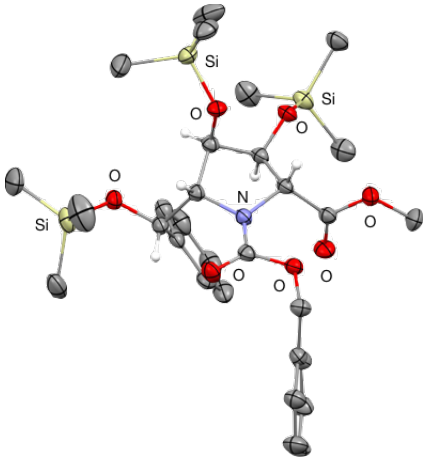


Figure S1-2. Molecular structure of (*rac*)-**7**. Thermal ellipsoids set at 50% probability.

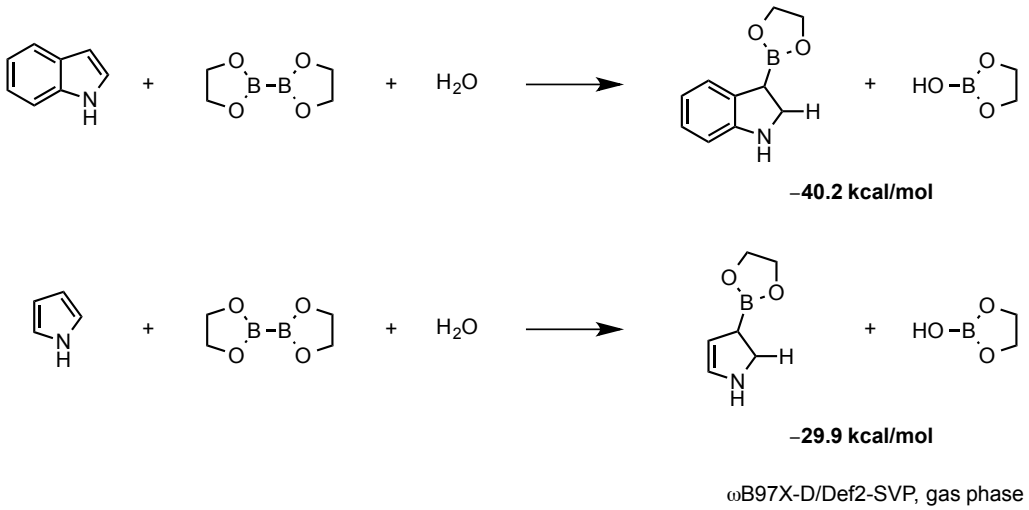
Table S1-2. Summary of X-ray crystallographic data for (*rac*)-**7**.

CCDC	1962365
Empirical formula	$C_{30}H_{47}NO_7Si_3$
Formula weight	617.95
Temperature/K	123
Crystal system	triclinic
Space group	*P*-1
a/Å	11.4127(2)
b/Å	12.59660(10)
c/Å	13.9030(2)
α /°	99.4810(10)
β /°	110.4930(10)
γ /°	103.0100(10)
Volume/Å^3	1758.02(4)
Z	2
ρ_{calc} g/cm^3	1.167
μ /mm^{-1}	1.586
F(000)	664.0
Crystal size/mm^3	0.15 × 0.15 × 0.05
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.044 to 153.136
Index ranges	$-14 \leq h \leq 12$, $-15 \leq k \leq 15$, $-17 \leq l \leq 17$
Reflections collected	101897
Independent reflections	7078 [R_{int} = 0.0382, R_{sigma} = 0.0145]
Data/restraints/parameters	7078/0/381
Goodness-of-fit on F^2	1.059
Final *R* indexes [I>=2σ (I)]	R_1 = 0.0311, wR_2 = 0.0801
Final R indexes [all data]	R_1 = 0.0331, wR_2 = 0.0814
Largest diff. peak/hole / e Å^{-3}	0.27/−0.28

Density Functional Theory (DFT) Calculations

All calculations were performed with the Gaussian 09 (revision D.01) suite of programs.[24] Geometry optimizations were carried out at ωB97X-D[25] level of theory with Def2-SVP[26] basis set. Frequency calculations were conducted at the same level of theory on the optimized geometries to check the all stationary points as either minima to obtain zero-point energy (ZPE), thermal energy and Gibbs free energy corrections at 298.1 K (1.0 atm). We choose indole and pyrrole as a model substrate. In the calculations, B(eg) group was used as a model catalyst system of B(pin).

The results 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).



References

(1) (a) Boronic Acids: Preparation and Application in Organic Synthesis, Medicine and Materials, 2nd revised ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2011**. (b) Diner, C.; Szabó, K. J. *J. Am. Chem. Soc.* **2017**, *139*, 2–14.

(2) For examples of the synthesis of chiral cyclic allylic boronates, see: (a) Ito, H.; Kunii, S.; Sawamura, M. *Nat. Chem.* **2010**, *2*, 972–976. (b) Sasaki, Y.; Zhong, C.; Sawamura, M. Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226–1227. (c) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 560–563. (d) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc.* **2014**, *136*, 16515–16521. (e) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308–9309. (f) Gao, X.; Hall, D. G.; Deligny, M.; Favre, A.; Carreaux, F.; Carboni, B. *Chem.-Eur. J.* **2006**, *12*, 3132–3142. (g) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612–9613. (h) Lee, H.; Han, J. T.; Yun, J. *ACS Catal.* **2016**, *6*, 6487–6490. (i) Ge, Y.; Cui, X.-Y.; Tan, S. M.; Jiang, H.; Ren, J.; Lee, N.; Lee, R.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2019**, *58*, 2382–2386.

(3) For examples of the synthesis of chiral six- or seven-membered *N*-heterocyclic allylic boronates, see: (a) Ding, J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 8069–8073. (b) Ding, J.; Rybak, T.; Hall, D. G. *Nat. Commun.* **2014**, *5*, 5474. (c) Kim, Y.-R.; Hall, D. G. *Org. Biomol. Chem.* **2016**, *14*, 4739–4748. (d) Clement, H. A.; Hall, D. G. *Tetrahedron Lett.* **2018**, *59*, 4334–4339.

(4) Wang, Y.; Noble, A.; Sandford, C.; Aggarwal, V. K. Enantiospecific Trifluoromethyl-Radical-Induced Three-Component Coupling of Boronic Esters with Furans. *Angew. Chem., Int. Ed.* **2017**, *56*, 1810–1814.

(5) For borylative dearomatization reactions of indoles reported by our group, see: (a) Kubota, K.; Hayama, K.; Iwamoto, H.; Ito, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 8809‑8813. (b) Hayama, K. Kubota, K.; Iwamoto, H.; Ito, H. *Chem. Lett.* **2017**, *46*, 1800–1802.

(6) (a) Kubota, K.; Watanabe, Y.; Hayama, K.; Ito, H. *J. Am. Chem. Soc.* **2016**, *138*, 4338–4341. (b) Kubota, K.; Watanabe, Y.; Ito, H. *Adv. Synth. Catal.* **2016**, *358*, 2379–2384.

(7) For borylative dearomatization reactions of indoles reported by other groups, see: Chen, L.; Shen, J.-J.; Gao, Q.; Xu, S. *Chem. Sci.* **2018**, *9*, 5855–5859.

(8) Modern Alkaloids: Structure, Isolation, Synthesis and Biology. Fattorusso, E.; Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim, **2008**.

(9) For general reviews on the synthesis of pyrrolidine derivatives, see: (a) Pichon, M.; Figadére, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964. (b) Bellina, F.; Rossi, R. *Tetrahedron*, **2006**, *62*, 7213–7256. (c) Yu, J.; Zhou, Y.; Chen, D.-F.; Gong, L.-Z. *Pure Appl. Chem.* **2014**, *86*, 1217–1226.

(10) For reviews of catalytic asymmetric dearomative transformations, see: (a) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662–12686. (b) Zhuo, C.-X.; Zheng, C.; You, S.-L. *Acc. Chem. Res.* **2014**, *47*, 2558–2573. (c) Zheng, C.; You, S.-L. *Chem*, **2016**, *1*, 830–857.

(11) For catalytic asymmetric [4+3] cycloaddition reactions of pyrroles, see: (a) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095–1105. (b) Reddy, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10312–10313.

(12) For catalytic asymmetric hydrogenation reactions of pyr-roles, see: (a) Kuwano, R.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* **2008**, *130*, 808–809. (b) Wang, D.-S.; Ye, Z.-S.; Chen, Q.-A.; Zhou, Y.-G.; Yu, C.-B.; Fan, H.-J.; Duan, Y. *J. Am. Chem. Soc.* **2011**, *133*, 8866–8869.

(13) For catalytic asymmetric allylic dearomatization reactions of pyrroles, see: (a) Zhuo, C.-X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Chem. Sci.* **2012**, *3*, 205–208. (b) Zhuo, C.-X.; Zhou, Y.; You, S.-L. *J. Am. Chem. Soc.* **2014**, *136*, 6590–6593. (c) Zheng, C.; Zhuo, C.-X.; You, S.-L. *J. Am. Chem. Soc.* **2014**, *136*, 16251–16259.

(14) Yang, P.; You, S.-L. *Org. Lett.* **2018**, *20*, 7684–7688.

(15) For reviews on hydroxyprolines, see: (a) Mauger, A. B.; Witkop, B. *Chem. Rev.* **1966**, *66*, 47–86. (b) Adams, E.; Frank, L. *Annu. Rev. Biochem.* **1980**, *49*, 1005–1061. (c) Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205. (d) El-Ashry, E.-S. H.; Nemr, A. E. *Carbohydr. Res.* **2003**, *338*, 2265–2290.

(16) For selected examples of the synthesis of cis-3-hydroxyproline derivatives, see: (a) Mulzer, J.; Meier, A. *J. Org. Chem.* **1996**, *61*, 566–572. (b) Gryko, D.; Prokopowicz, P.; Jurczak, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1103–1113. (c) Kalamkar, N. B.; Kasture, V. M.; Dhavale, D. D. *Tetrahedron Lett.* **2010**, *51*, 6745–6747. (d) Davies, S. G.; Fletcher, A. M.; Linsdall, S. M.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2018**, *20*, 4135–4139.

(17) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930–5933.

(18) (a) Iminosugars as glycosidase inhibitors. Stütz, A. E. Wiley-VCH: Weinheim, **1999**. (b) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541–560.

(19) Priem, C.; Geyer, A. *Org. Lett.* **2018**, *20*, 162–165.

(20) Unfortunately, we could not obtain single crystals of enantiopure (*R,S,R,R,S*)-**7**. The ^{1}H NMR analysis confirmed that the relative configuration of racemic **7** and enantiopure (*R,S,R,R,S*)-**7** is the same.
(21) Sheldrick, G. M. *Acta Cryst. Sect. C*, **2015**, *71*, 3.
(22) Bakos, J.; Tóth, I.; Heil, B.; Markó, L. *J. Organometallic Chem.* **1985**, *279*, 23.
(23) Kaabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989***, 54,* 5930.
(24) Priem, C.; Geyer, A. *Org. Lett.* **2018**, *20*, 162.
(25) Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.
(26) J.-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, **2008**, *10*, 6615.
(27) F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, **2005**, *7*, 3297.

Chapter 2.

Copper(I)-Catalyzed Diastereoselective Dearomative Carboborylation of Indoles

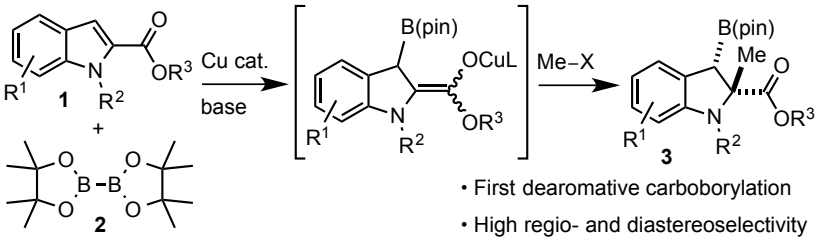
Abstract

The first dearomative carboborylation of heteroaromatic compounds has been achieved using copper(I)/diboron catalytic system. This reaction involves the regioselective addition of a borylcopper(I) intermediate to indoles, followed by the diastereoselective methylation of the resulting copper(I)-enolate intermediate to afford the corresponding 3-boryl-2-methyl-indolines bearing a quaternary stereogenic center with excellent regio- and diastereoselectivity.

Introduction

Indolines have received significant attention as important structures in naturally occurring bioactive molecules and drugs.[1-4] Thus, the development of an efficient synthetic protocol for the preparation of these compounds is an important subject in organic synthesis.[5-6] Dearomatization reaction of indoles is a powerful and attractive approach for the straightforward preparation of indoline derivatives, which has been extensively studied over the past decade.[7-10]

Recently, the author and co-worker reported the first C−B bond forming dearomatization of indoles using chiral copper(I) catalyst and diboron to give the corresponding chiral 3-boryl-indolines.[11] This reaction involved the regioselective addition of a borylcopper(I) intermediate to an indole-2-carboxylate, followed by the diastereoselective protonation of the resulting copper(I)-enolate by alcohol additives to give the corresponding 3-boryl-indoline. Based on this result, the author envisioned that alkylation of the copper(I) enolate intermediate would proceed to afford the corresponding carboboration product when an alkyl electrophile is used instead of alcohol additive.[12-17] Herein, chapter 2 describes the development of a copper(I)-catalyzed regio- and diastereoselective dearomative carboborylation of indole-2-carboxylate **1** to afford the corresponding indoline derivative **3** bearing a quaternary stereogenic center with excellent regio- and diastereoselectivity (Scheme 2-1).

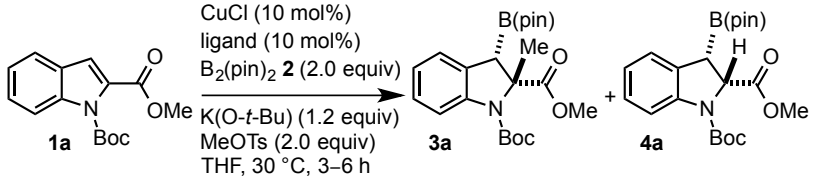


Scheme 2-1. Copper(I)-catalyzed regio- and diastereoselective dearomative carboborylation of indoles.

Results and Discussion

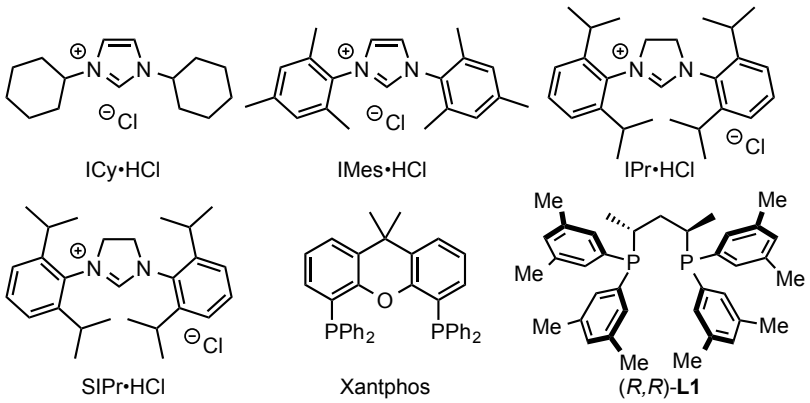
The results of an extensive series of optimization revealed that the reaction of Boc-protected methyl indole-2-carboxylate **1a** with bis(pinacolato)diboron **2** (2.0 equiv) in the presence of CuCl/ICy (10 mol%), K(O-*t*-Bu) (1.2 equiv), and MeOTs (2.0 equiv), which was used as alkyl electrophile, in THF at 30°C provided the desired carboborylation product **3a** in a good yield (60%), with an excellent diastereoselectivity (d.r. >95:5; Table 2-1, entry 1). Undesired protoborylation product **4a** was also produced with low yield (20%; Table 2-1, entry 1). Unfortunately, **4a** was not easy to separate from **3a** by flash column chromatography, and suppression of **4a** failed in any other conditions. Therefore, isolation of the dearomatization products (**5a**) was carried out after oxidation of **3a** to confirm the product structure (See Experimental section).[18] Several other NHC ligands were also tested in the reaction, including IMes, IPr, and SIPr, but they all resulted in poor yields (Table 2-1, entries 2−4). The yield was dramatically decreased when the bisphosphine type ligands Xantphos and (*R,R*)-**L1** were used in the reaction although they were effective for the dearomative protoborylation of indoles in our previous work (Table 2-1, entries 5 and 6).[11]

Table 2-1. Optimization of the ligands.[a]



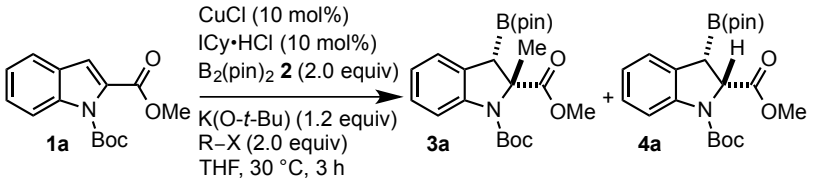
Entry	ligand	Yield of **3a** [%][b]	Yield of **4a** [%][b]
1[c]	ICy・HCl	60	9
2	IMes・HCl	11	30
3	IPr・HCl	<5	–
4	SIPr・HCl	<5	–
5	Xantphos	<5	12
6	(*R,R*)-**L1**	10	11

[a]Conditions: **1a** (0.5 mmol), CuCl (0.05 mmol), ligand (0.05 mmol), bis(pinacolato)diboron **2** (1.0 mmol), K(O-*t*-Bu) (0.6 mmol), and MeOTs (1.0 mmol) in THF (2.0 mL). [b]NMR yield. [c]Almost no minor diastereomer was detected by ^{1}H NMR.



Next, the author investigated the effect of the electrophiles with ICy as an optimal ligand (Table 2-2). Several other alkylation reagents **6**, **7** and **8** also provided the desired product **3a** with slightly lower yield (Table 2-2, entries 1−4).[19] Unfortunately, MeI and BnBr were not suited as an electrophile for this reaction (Table 2-2, entry 5 and 6). More reactive electrophiles might react with borylcopper(I) species or diborons prior to copper(I)-enolate intermediate.

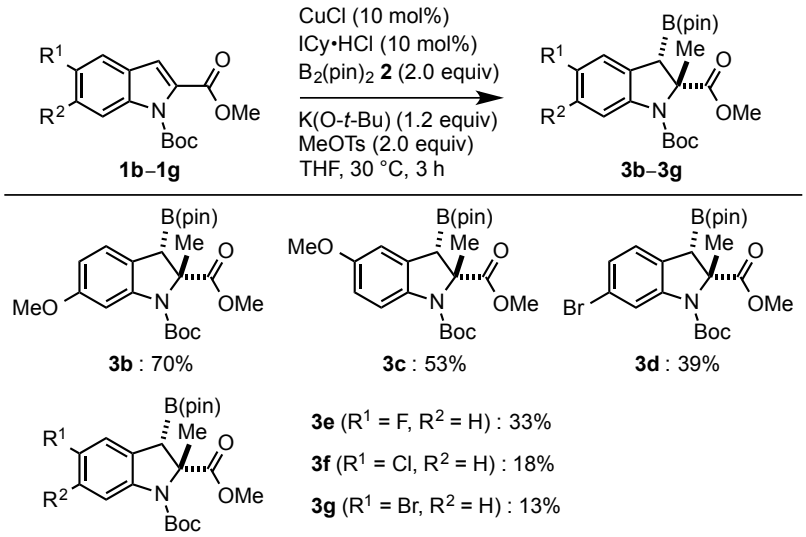
Table 2-2. Optimization of the electrophiles.[a]



Entry	R–X	Yield of **3a** [%][b]	Yield of **4a** [%][b]
1[c]	MeOTs	60	20
2[c]	*p*-F-PhSO$_3$Me (**6**)	53	27
3[c]	*p*-MeO-PhSO$_3$Me (**7**)	58	20
4[c]	*p*-Ph-PhSO$_3$Me (**8**)	46	25
5	MeI	<5	–
6	BnBr	<5	–

[a]Conditions: **1a** (0.5 mmol), CuCl (0.05 mmol), ligand (0.05 mmol), bis(pinacolato)diboron **2** (1.0 mmol), K(O-*t*-Bu) (0.6 mmol), and MeOTs (1.0 mmol) in THF (2.0 mL). [b]NMR yield. [c]Almost no minor diastereomer was detected by ^{1}H NMR.

With the optimal reaction conditions in hand, the scope of indole substrates was investigated (Scheme 2-2). Indoles bearing methoxy substituent at their 5 or 6 positions reacted with good yield, respectively (**3b**, **3c**). The introduction of halide at the 5 or 6 position of the indole was tolerated, but with a lower product yield (**3d–g**).



Scheme 2-2. Substrate scope. Conditions: **1** (0.5 mmol), CuCl (0.05 mmol), ICy・HCl (0.05 mmol), bis(pinacolato)diboron **2** (1.0 mmol), K(O-*t*-Bu) (0.6 mmol), and MeOTs (1.0 mmol) in THF (2.0 mL). NMR yields are reported.

The product stereochemistry was checked by single crystal X-ray crystallography. The compound **3d** was oxidized by $NaBO_3 \cdot H_2O$ to give **5d**. The X-ray analysis of this product unambiguously revealed the trans configuration of the dearomatization product (Figure 2-1, S2-1).

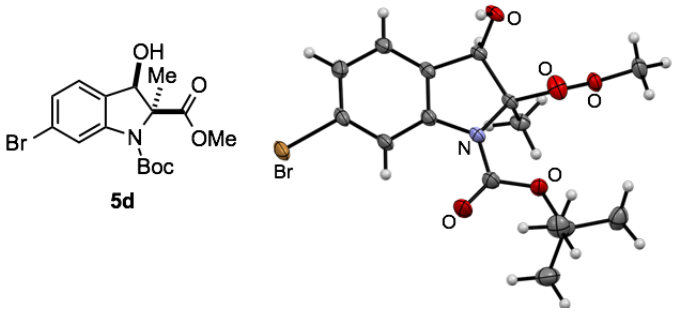


Figure 2-1. Molecular structure of **5d** (thermal elipsoids are drawn at the 50% probability level).

Based on the aforementioned results, a plausible mechanism for the reaction of **1a** with **2** and MeOTs is illustrated in Figure 2-2. The Cu(O-*t*-Bu) precatalyst **A** would initially react with diboron **2** to afford the borylcopper(I) intermediate **B**. Next, the coordination of indole **1a** to the intermediate **B** would result in the formation of π-complex **C**. A subsequent 3,4 addition of **B** to **1a** would give the copper(I) *C*-enolate, which could then transform to the *O*-enolate **D** under concomitant formation of a C−B bond. After the formation of **D**, MeOTs would approach **D** from the opposite side of the pinacol boryl group to avoid steric congestion between the bulky B(pin) and MeOTs. Subsequent diastereoselective methylation of **D** would proceed to afford dearomatization product and copper(I) alkoxide precatalyst **A**.

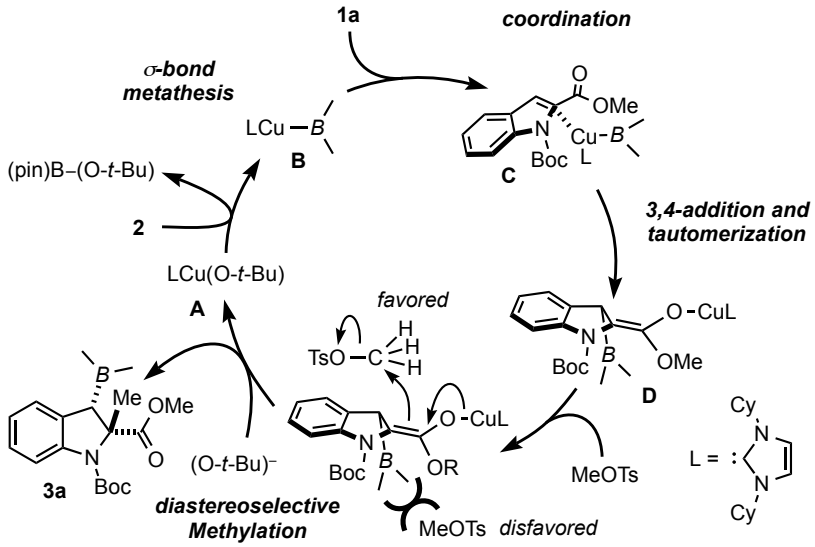
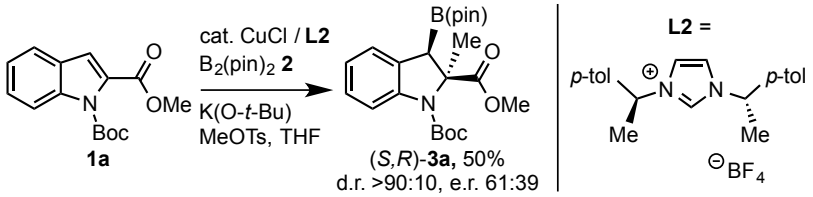


Figure 2-2. Proposed catalytic cycle.

The attempt for the asymmetric synthesis of enantioenriched 3-boryl-2-methyl-indoline with a chiral copper(I) catalyst (10 mol% of CuCl/**L2**) resulted in a moderate e.r. value with excellent diastereoselectivity (e.r. 61:39, d.r. >90:10; Scheme 2-3).[20-21] Absolute configuration of major enantiomer was determined by Mosher method.[22] Further investigation to improve the enantioselectivity of such reaction is under way.



Scheme 2-3. Asymmetric dearomative carboborylation of indole **1a**. Condition: **1a** (0.5 mmol), CuCl (0.05 mmol), **L2** (0.05 mmol), **2** (1.0 mmol), K(O-*t*-Bu) (0.6 mmol), and MeOTs (1.0 mmol) in THF (2.0 mL) at 30°C for 24 h. NMR yields are reported. The enantiomeric ratio was determined by HPLC analysis of the oxidation product derived from (*S,R*)-**3a**.

Conclusion

In summary, the author has developed a copper(I)-catalyzed regio- and diastereoselective dearomative carboborylation reaction of indoles. This reaction involves the regioselective addition of a borylcopper(I) intermediate to indoles, followed by the diastereoselective alkylation of the resulting copper(I) enolate intermediate to afford the corresponding boryl indolines bearing a quaternary stereogenic center with excellent diastereoselectivity, which could be useful synthetic intermediates in the combination of boron functionalization processes.

Experimental

Instrumentation and Chemicals

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{13}C) were employed as external standards, respectively.

CuCl (ReagentPlus® grade, 224332-25G, ≥99%) and K(O-*t*-Bu)/THF (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. 1,1,2,2-Tetrachloroethane were used as an internal standard to determine ^{1}H NMR yields. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. Recycle preparative gel chromatography (GPC) was conducted with JAILC-9101 using $CHCl_3$ as an eluent. HPLC analyses with chiral stationary phase were carried out using a Hitachi LaChrome Elite HPLC system with a L-2400 UV detector. High-resolution mass spectra were recorded at the Global Facility Center for Instrumental Analysis, Hokkaido University.

A typical procedure for the copper(I)-catalyzed dearomative carboborylation (Table 2-1, 2-2 and Scheme 2-2)

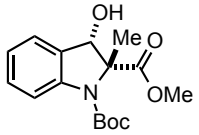
Indole **1** (0.50 mmol), bis(pinacolato)diboron (253.9 mg, 1.0 mmol), CuCl (5.0 mg, 0.050 mmol) and ligand (0.050 mmol) were placed in an oven-dried reaction vial. After being sealed with a screw cap containing a teflon-coated rubber septum, the vial was connected to a nitrogen line through a needle. THF (1.4 mL) and K(O-*t*-Bu)/THF (1.0 M, 0.6 mL, 0.60 mmol) were added to the mixture through the rubber septum at 30 °C. Then electrophile (1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et_2O/CH_2Cl_2 (50:50). The resulting crude material was used in the next oxidation reaction without further purification.

The oxidation was performed according to the literature procedure.[18] In a reaction vial, crude material was dissolved in THF/H2O (1:1, 2 mL). $NaBO_3$•$4H_2O$ (307.7 mg, 2.0 mmol) was then added at room temperature. After the reaction was complete, the reaction mixture was extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The crude mixture was purified by flash column chromatography (SiO_2, ethyl

acetate/hexane, 13:87–18:82). In many cases, side product generated by protonation was contaminated in the product. Further purification for checking the structure was conducted by GPC to afford the pure oxidation product **5** as colorless oil.

Analytical data of products

1-(*tert*-Butyl) 2-methyl 3-hydroxy-2-methylindoline-1,2-dicarboxylate (5a).

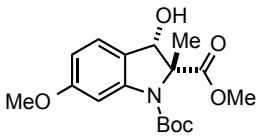


5a

5a was prepared from the corresponding indole according to the procedure described above (yield of **5a** after GPC is 8%).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.45–1.63 (m, 9H), 1.67 (s, 3H), 2.21–2.40 (m, 1H), 3.76 (s, 3H), 4.87 (d, J = 10.3 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.40 (d, J = 7.2 Hz, 1H), 7.54 and 7.99 (a pair of d, J = 7.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.2 (CH_3), 28.2 (CH_3), 52.3 (CH_3), 73.0 (*C*), 80.1 (*C*H), 81.8 (*C*), 115.5 (*C*H), 123.1 (*C*H), 125.7 (*C*H), 128.4 (*C*), 130.7 (*C*H), 142.4 (*C*), 151.0 (*C*), 170.6 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{21}N_1O_5$, 307.14197; found, 307.14260.

1-(*tert*-Butyl) 2-methyl 3-hydroxy-6-methoxy-2-methylindoline-1,2-dicarboxylate (5b).

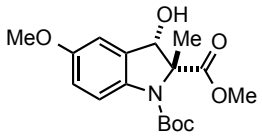


5b

5b was prepared from the corresponding indole according to the procedure described above (yield of **5b** after GPC is 33%).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.47–1.64 (broad m, 9H), 1.66 (s, 3H), 2.07 (broad d, J = 9.0 Hz, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 4.81 (d, J = 11.3 Hz, 1H), 6.62 (dd, J = 2.0 and 8.3 Hz, 1H), 7.16 and 7.63 (a pair of s, 1H) 7.29 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.1 (CH_3), 28.1 (CH_3), 52.1 (CH_3), 55.5 (CH_3), 73.9 (*C*), 79.6 (*C*H), 81.8 (*C*), 100.2 (*C*H), 110.4 (*C*H), 120.5 (*C*), 126.2 (*C*H), 143.8 (*C*), 151.0 (*C*), 161.9 (*C*), 170.6 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{17}H_{23}N_1O_6$, 337.15254; found, 337.15255.

1-(*tert*-Butyl) 2-methyl 3-hydroxy-5-methoxy-2-methylindoline-1,2-dicarboxylate (5c).

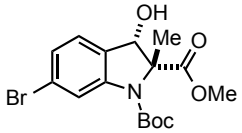


5c

5c was prepared from the corresponding indole according to the procedure described above (yield of **5c** after GPC is 5%).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.45–1.64 (m, 9H), 1.66 (s, 3H), 2.18 (broad d, J = 11.3 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.84 (d, J = 10.3 Hz, 1H), 6.84–6.98 (m, 2H), 7.45 and 7.91 (a pair of d, J = 9.0 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.2 (CH_3), 28.2 (CH_3), 52.3 (CH_3), 55.8 (CH_3), 73.1 (*C*), 80.2 (*C*H), 81.6 (*C*), 110.5 (*C*H), 116.3 (*C*H), 116.7 (*C*H), 129.4 (*C*), 136.0 (*C*), 150.1 (*C*), 156.0 (*C*), 170.6 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{17}H_{23}N_1O_6$, 337.15254; found, 337.15252.

1-(*tert*-Butyl) 2-methyl 6-bromo-3-hydroxy-2-methylindoline-1,2-dicarboxylate (5d).



5d

5d was prepared from the corresponding indole according to the procedure described above (yield of **5d** after GPC is 8%).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.45–1.64 (m, 9H), 1.67 (s, 3H), 2.26 (broad s, 1H), 3.77 (s, 3H), 4.82 (d, J = 9.0 Hz, 1H), 7.18 and 7.20 (a pair of d, J = 1.4, 1.8 Hz, 1H), 7.24 (s, 1H), 7.73 and 8.22 (a pair of s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.2 (CH_3), 28.1 (CH_3), 52.4 (CH_3), 73.5 (*C*), 79.6 (*C*H), 82.4 (*C*), 118.7 (*C*H), 124.7 (*C*), 126.2 (*C*H), 126.8 (*C*H), 127.5 (*C*), 143.6 (*C*), 150.8 (*C*), 170.2 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{20}Br_1N_1O_5$, 385.05248; found, 385.05164.

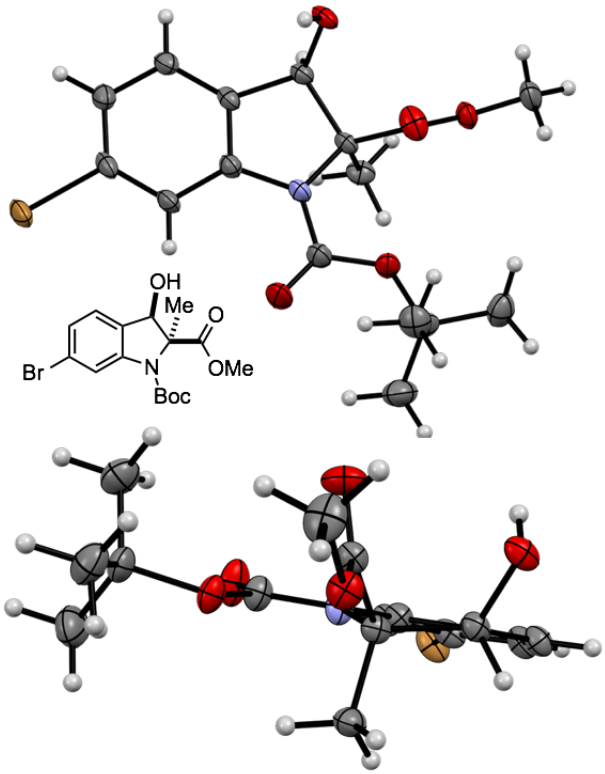
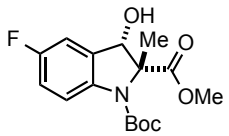


Figure S2-1. X-ray structure of **5d**. Thermal ellipsoids are drawn at the 50% probability level. Crystal data (CCDC 798073): triclinic, *P*-1 (#2), a = 11.5584(7) Å, b = 12.3697(7) Å, c = 13.3852(8) Å, α = 80.8713(15) °, β = 86.8081(17) °, γ = 65.1225(17) °, V = 1714.04(17) Å^3, Z = 4, T = 123 K, $2\theta_{max}$ = 54.9°, R_1 = 0.0334 (I>2.00σ(I)), wR_2 = 0.1025, GOF = 1.085.

1-(*tert*-Butyl) 2-methyl 5-fluoro-3-hydroxy-2-methylindoline-1,2-dicarboxylate (5e).

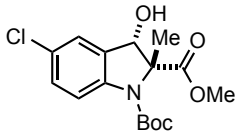


5e

5e was prepared from the corresponding indole according to the procedure described above (yield of **5e** after GPC is 13%).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.44–1.64 (m, 9H), 1.67 (s, 3H), 2.61 (broad s, 1H), 3.76 (s, 3H), 4.85 (s, 1H), 6.99–7.14 (m, 2H), 7.41–7.57 and 7.87–8.01 (a pair of m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.2 (CH_3), 28.2 (CH_3), 52.3 (CH_3), 73.3 (*C*), 79.6 (*C*H), 82.0 (*C*), 112.4 (*C*–F, d, *J* = 23.5 Hz, *C*H), 116.4 (*C*–F, d, *J* = 7.5 Hz, *C*H), 117.3 (*C*–F, d, *J* = 22.5 Hz, *C*H), 129.8 (*C*), 138.4 (*C*), 151.0 (*C*), 158.9 (*C*–F, d, *J* = 240.5 Hz, *C*), 170.4 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{20}F_1N_1O_5$, 325.13255; found, 325.13205.

1-(*tert*-Butyl) 2-methyl 5-chloro-3-hydroxy-2-methylindoline-1,2-dicarboxylate (5f).

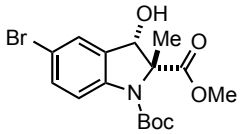


5f

5f was prepared from the corresponding indole according to the procedure described above (yield of **5f** after GPC is 3%).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.44–1.64 (m, 9H), 1.67 (s, 3H), 2.19–2.48 (m, 1H), 3.77 (s, 3H), 4.85 (s, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 1.8 Hz, 1H), 7.53 and 7.94 (a pair of d, *J* = 8.1 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.2 (CH_3), 28.2 (CH_3), 52.4 (CH_3), 73.3 (*C*), 79.6 (*C*H), 82.2 (*C*), 116.6 (*C*H), 125.7 (*C*H), 128.0 (*C*), 128.8 (*C*), 130.7 (*C*H), 141.1 (*C*), 150.9 (*C*), 170.2 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{20}Cl_1N_1O_5$, 341.10300; found, 341.10287.

1-(*tert*-Butyl) 2-methyl 5-bromo-3-hydroxy-2-methylindoline-1,2-dicarboxylate (5g).



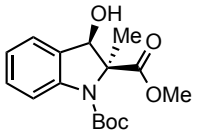
5g

5g was prepared from the corresponding indole according to the procedure described

above (yield of **5g** after GPC is 4%).

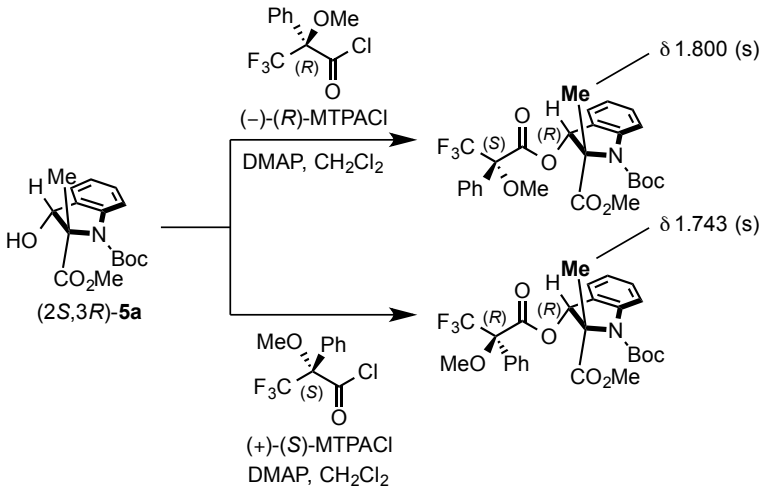
^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.44–1.65 (m, 9H), 1.73 (s, 3H), 2.36 (s, 1H), 3.79 (s, 3H), 4.59 (s, 1H), 7.36–7.46 (m, 2H), 7.67–7.75 and 7.76–7.92 (a pair of m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 28.1 (CH_3), 28.6 (CH_3), 52.3 (CH_3), 72.6 (*C*H), 77.2 (*C*H), 82.2 (*C*), 115.3 (*C*), 116.4 (*C*H), 126.2 (*C*H), 133.1 (*C*H), 135.7 (*C*), 140.8 (*C*), 151.0 (*C*), 168.9 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{20}Br_1N_1O_5$, 385.05248; found, 385.05227.

(2*S*,3*R*)-1-(*tert*-Butyl) 2-methyl 3-hydroxy-2-methylindoline-1,2-dicarboxylate [(2*S*,3*R*)-5a].



(2*S*,3*R*)-5a

Following a typical procedure for the copper(I)-catalyzed dearomative carboborylation**,** the reaction was conducted with **1a** (137.7 mg, 0.50 mmol) and bis(pinacolato)diboron (253.9 mg, 1.0 mmol) in the presence of CuCl (5.0 mg, 0.050 mmol) and **L2** (20.81 mg, 0.050 mmol). (2*S*,3*R*)-**3a** was derived to the corresponding alcohol (2*S*,3*R*)-**5a** through $NaBO_3$ oxidation with retention of the configuration. ^{1}H and ^{13}C NMR of (2*S*,3*R*)-**5a** are identical with those of (*rac*)-**5a**. The absolute configuration of major enantiomer (2*S*,3*R*)-**5a** was determined by Mosher method as shown in the following scheme. The ee value was determined by HPLC analysis. $[\alpha]_D^{22.6}$ −20.87 (*c* 1.5 in $CHCl_3$, 22% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, major isomer: t_R = 15.34 min., minor isomer: t_R = 18.33 min.



References

(1) S. Kobayashi, G. Peng, T. Fukuyama, *Tetrahedron Lett.* **1999**, *40*, 1519.

(2) J. L. Pinder, S. M. Weinreb, *Tetrahedron Lett.* **2003**, *44*, 4141.

(3) D. Crich, A. Banerjee, *Acc. Chem. Res.* **2007**, *40*, 151.

(4) Y. Sasaki, D. Kato, D. L. Boger, *J. Am. Chem. Soc.* **2010**, *132*, 13533.

(5) W. Zi, Z. Zuo, D. Ma, *Acc. Chem. Res.* **2015**, *48*, 702.

(6) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614.

(7) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; *Angew. Chem.* **2012**, *124*, 12834.

(8) Q. Ding, X. Zhou, R. Fan, *Org. Biomol. Chem.* **2014**, *12*, 4807.

(9) C.-X. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2014**, *47*, 2558.

(10) C. Zheng, S.-L. You, *Chem* **2016**, *1*, 830.

(11) K. Kubota, K. Hayama, H. Iwamoto, H. Ito, *Angew. Chem. Int. Ed.* **2015**, *54*, 8809; *Angew. Chem.* **2015**, *127*, 8933.

(12) H. Ito, Y. Kosaka, K. Nonoyama, Y. Sasaki, M. Sawamura, *Angew. Chem. Int. Ed.* **2008**, *47*, 7424; *Angew. Chem.* **2008**, *120*, 7534.

(13) C. Zhong, S. Kunii, Y. Kosaka, M. Sawamura, H. Ito, *J. Am. Chem. Soc.* **2010**, *132*, 11440.

(14) H. Yoshida, I. Kageyuki, K. Takaki, *Org. Lett.* **2013**, *15*, 952.

(15) T. Jia, P. Cao, B. Wang, Y. Lou, X. Yin, M. Wang, J. Liao, *J. Am. Chem. Soc.* **2015**, *137*, 13760.

(16) L. Jiang, P. Cao, M. Wang, B. Chen, B. Wang, J. Liao, *Angew. Chem. Int. Ed.* **2016**, *55*, 13854; *Angew. Chem.* **2016**, *128*, 14058.

(17) I. Kageyuki, I. Osaka, K. Takaki, H. Yoshida, *Org. Lett.* **2017**, *19*, 830.

(18) G. W. Kabalka, T. M. Shoup, N. M. Goudgaon, *J. Org. Chem.* **1989**, *54*, 5930.

(19) S. Alunni, M. Pica, G. Reichenbach, *J. Phys. Org. Chem.* **2001**, *14*, 265.

(20) C. L. Winn, F. Guillen, J. Pytkowicz, S. Roland, P. Mangeney, A. Alexakis, *J. Organomet. Chem.* **2005**, *690*, 5672.

(21) Y. Sato, Y. Hinata, R. Seki, Y. Oonishi, N. Saito, *Org. Lett.* **2007**, *9*, 5597.

(22) See Supporting Information.

Chapter 3.

Copper(I)-Catalyzed Diastereoselective Dearomative Silylation of Indoles and Pyrroles

Abstract

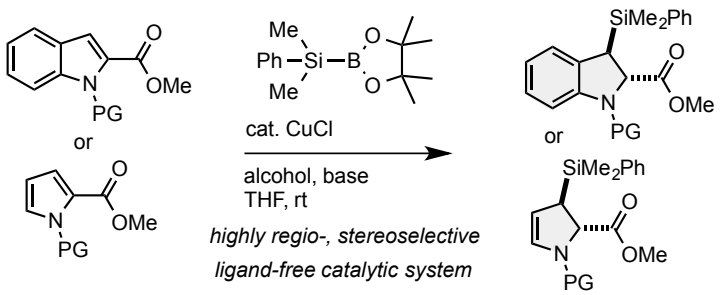
Silylative dearomatization reaction of indole-2-carboxylates has been accomplished using copper(I) catalyst and silylboranes. This reaction presumably proceeds through the regioselective addition of silylcopper(I) species to the substrates, followed by the diastereoselective protonation of the resulting copper(I) enolate intermediate to afford the corresponding dearomative silylation products with high regio- and diastereoselectivity. The first silylative dearomatization of pyrroles using the developed catalytic system has also been described.

Introduction

Organosilicon compounds are widely utilized as an important building unit in synthetic, medical, polymer, and materials chemistry.[1] Among them, saturated *N*-heterocyclic organosilicon compounds have received particular attention because they are useful synthetic intermediates for the construction of core skeletons found in biologically active natural and synthetic alkaloids.[2-4] In this context, the development of carbon−silicon bond-forming reactions of readily available *N*-heteroaromatic compounds is of great interest.[5] In 2011, Suginome, Ohmura and co-workers reported the highly regioselective palladium-catalyzed silaboration of pyridines to form dihydropyridines bearing a carbon−silicon bond at the C2- or C4-positions.[6] In 2014, Park, Chang and co-workers developed a metal-free catalytic procedure using $B(C_6F_5)_3$ catalyst for the carbon−silicon bond-forming reduction of quinolines.[7] In continuing their efforts, the system was successfully applied to the silylative reduction of pyridines.[8] More recently, Xu and co-workers reported the carbon−silicon bond-forming dearomatization of 3-acylindoles using *N*-heterocyclic carbene(NHC)-copper(I) complex catalyst.[9] Despite such an impressive advance, the scope of accessible *N*-heterocyclic organosilicon compounds remains limited.

Our group has been interested in applying a copper(I)-catalyzed nucleophilic borylation protocol to the synthesis of *N*-heterocyclic organoboronate esters.[10,11] In 2015, the author and co-workers have reported the first dearomative borylation reaction of indole-2-carboxylate derivatives to furnish the corresponding 3-boryl-indolines.[10a] More recently, we have also achieved the dearomative borylation reaction of pyrrole-2-carboxylate derivatives to give the corresponding five-membered *N*-heterocyclic allylboronates.[12] These reactions involved the regioselective addition of

a borylcopper(I) intermediate to the substrate, followed by diastereoselective protonation of the resulting copper(I) enolate by alcohol additives to give the corresponding dearomatization product. The key finding of these studies was that an electron-withdrawing group at the 2-position in the substrate can facilitate the challenging dearomative borylcupration process. Based on these results, we envisioned that carbon − silicon bond-forming dearomatizations of these *N*-heteroaromatic compounds would proceed via the similar reaction pathway to produce the corresponding silylation products when a silylborane is employed instead of diboron compound.[13,14] Herein, we describe the development of a ligand-free copper(I)-catalyzed regio- and diastereoselective silylative dearomatization reactions of indole-2-carboxylates to afford the corresponding *N*-heterocyclic organosilicon compounds with high regio- and diastereoselectivity (Scheme 3-1). Notably, the first silylative dearomatization of pyrroles has also been achieved by using the developed catalytic system.



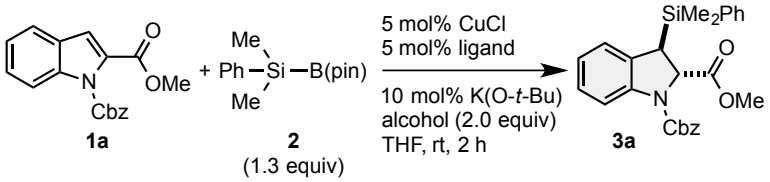
Scheme 3-1. Carbon–silicon bond-forming dearomatization reactions of indoles and pyrroles using copper catalyst

Results and Discussion

The results of an extensive series of optimization experiments are shown in Table 3-1. The reaction of *N*-benzyloxycarbonyl (Cbz)-protected methyl indole-2-carboxylate (**1a**) with (dimethylphenylsilyl)boronic acid pinacol ester (**2**) (1.3 equiv) in the presence of CuCl (5 mol%)/ICy (ICy・HCl: 1,3-dicyclohexylimidazolium chloride) (5 mol%), K(O-*t*-Bu) (10 mol%), and MeOH (2.0 equiv) in THF at room temperature afforded the desired 3-silyl-indoline derivative (**3a**) in low yield (8%; Table 1, entry 1). The improvement of the reactivity was merely marginal when IAd・HBF_4 [1,3-di(1-adamantyl) imidazolium tetrafluoroborate] was used (27%; Table 3-1, entry 2). No reaction was occurred without copper salt (Table 3-1, entry 3). Surprisingly, we

found that the use of CuCl without any ligands resulted in dramatic yield improvement and excellent diastereoselectivity was observed (95%, d.r. >99:1; Table 3-1, entry 4). The bulkiness of the alcohol was found to affect the diastereoselectivity of this reaction. The use of bulky alcohols led to loss of the diastereoselectivity (Table 3-1, entry 4-7).

Table 3-1. Optimization of the reaction conditions

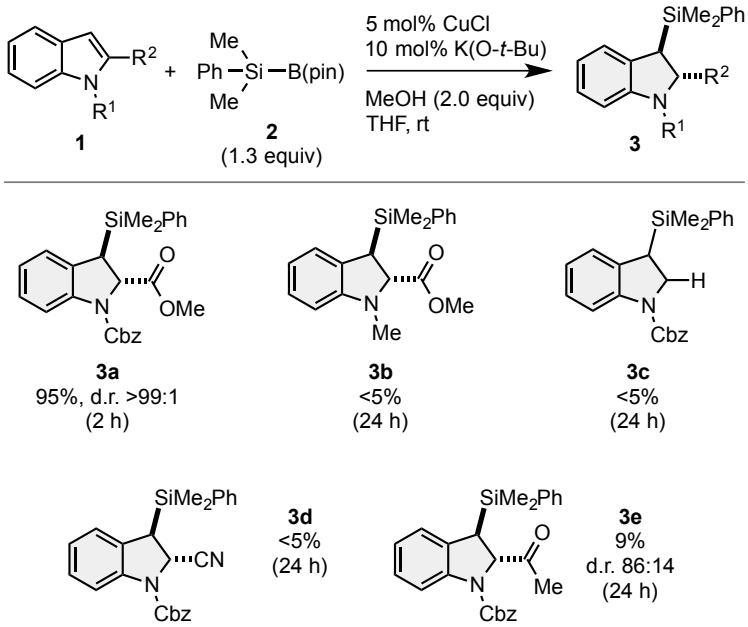


Entry	Ligand	alcohol	yield (%)[b]	d.r.[c]
1	ICy・HCl	MeOH	8	–
2	IAd・HBF_4	MeOH	27	–
3[d]	IAd・HBF_4	MeOH	<5	–
4	–	MeOH	95 (95)[e]	>99:1
5	–	1-PrOH	94	97:3
6	–	2-PrOH	93	94:6
7	–	*t*-BuOH	96	77:23

[a]Conditions: **1a** (0.25 mmol), **2** (0.325 mmol), CuCl/Ligand (0.0125 mmol), K(O-*t*-Bu) (0.025 mmol) and alcohol (0.50 mmol) in THF (1.0 mL). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture with an internal standard. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Without CuCl. [e]Isolated yield is shown in the parentheses. 0.5 mmol scale.

With the optimized procedure in hand, we proceeded to investigate the effect of electron-withdrawing groups on the reactivity (Table 3-2). As a result, both electron-withdrawing substituents at nitrogen and the C2 position are necessary for this reaction (**3a**–**3c**). We also found that substrates bearing cyano group or acetyl group at the C2 position were not applicable to this protocol (**3d** and **3e**).

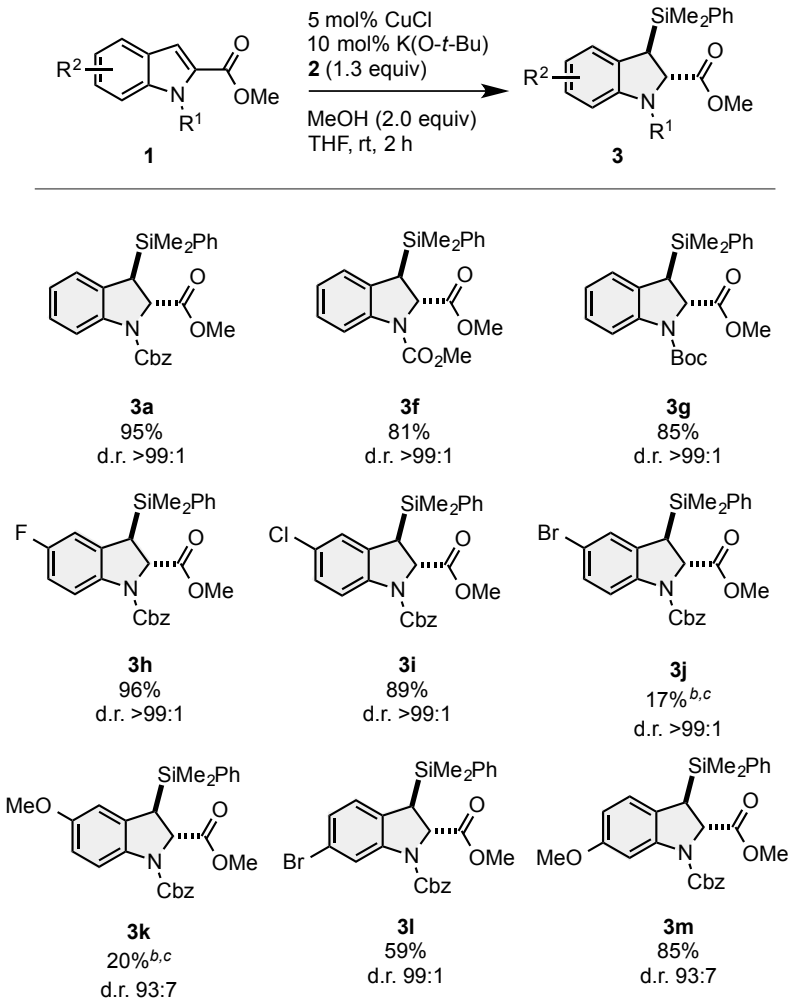
Table 3-2. Effect of electron-withdrawing groups[a]



[a]Conditions: **1** (0.50 mmol), **2** (0.65 mmol), CuCl (0.025 mmol), K(O-*t*-Bu) (0.050 mmol) and MeOH (1.0 mmol) in THF (2.0 mL). Yields and diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

Next, the scope of the silylation reaction using a variety of indole substrates was investigated (Table 3-3). The silylation reactions of *N*-CO_2Me-protected and *N*-*tert*-butoxycarbonyl (Boc)-protected indoles proceeded smoothly to afford the corresponding dearomatization product (**3f** and **3g**). The introduction of a fluoro or chloro substiuent at the C5 position of the indole was well tolerated, with the silylation reaction affording consistently excellent diastereoselectivity (**3h** and **3i**). The silylation of indoles bearing a bromo or methoxy substituent at their 5 position provide the desired products with high diastereoselectivity, although the yields were significantly decreased (**3j** and **3k**). Indoles bearing a bromo or methoxy substituent at their C6 position also reacted in good yield with high levels of diastereoselectivity (**3l** and **3m**).

Table 3-3. Substrate scope[a]



[a]Conditions: **1** (0.50 mmol), **2** (0.65 mmol), CuCl (0.025 mmol), K(O-*t*-Bu) (0.050 mmol) and MeOH (1.0 mmol) in THF (2.0 mL). [b]NMR yield determined by ^{1}H NMR analysis of the crude reaction mixture using an internal standard. [c]Reaction was conducted for 24 h.

A single-crystal X-ray diffraction analysis confirmed the structure of **3f** and unambiguously indicated the *trans* configuration of its stereocenters (Figure 3-1).

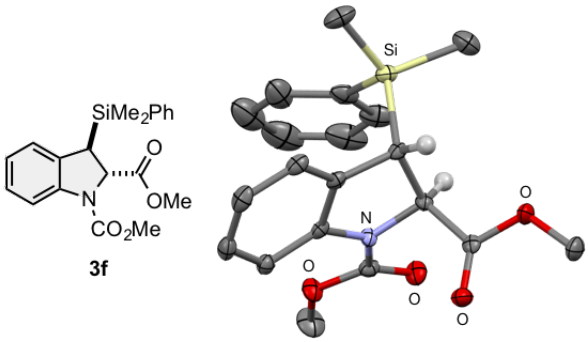
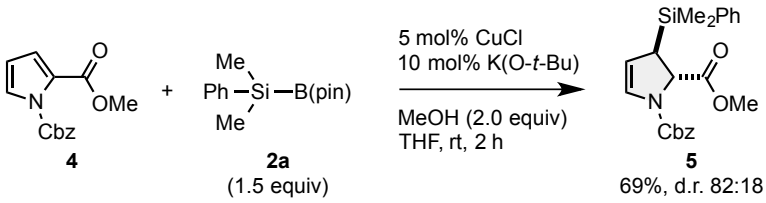


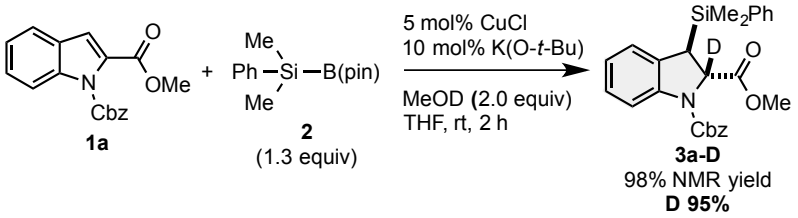
Figure 3-1. Molecular structure of **3f** with thermal elipsoids at 50% probability; hydrogen atoms have been omitted for clarity and only selected atoms have been labeled.

Notably, the first silylative dearomatization of pyrroles has also been achieved by applying the optimized reaction protocol (Scheme 3-2). The silylation reaction of *N*-benzyloxycarbonyl (Cbz)-protected methyl pyrrole-2-carboxylate (**4**) under optimized conditions afforded the desired 3-silyl-dihydropyrrole (**5**) in good yield with good diastereoselectivity. The anti configuration of its stereocenters of the major isomer was confirmed by nucler Overhauser effect (NOE) ^{1}H NMR analysis.



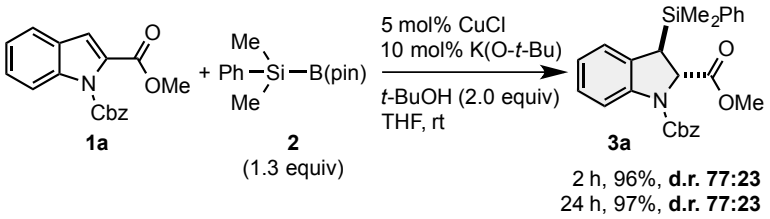
Scheme 3-2. Silylative dearomatization of pyrrole-2-carboxylates

A deuterium-labeling experiment was conducted to probe the reaction mechanism (Scheme 3-3). The silylation of **1a** under the optimized conditions using MeOD instead of MeOH furnished the deuterium-labeled product **3a-D** (95% D). This result suggests that the diastereoselective protonation is accomplished by the alcohol additive.



Scheme 3-3. D-labeling experiment

To gain insight into the origin of diastereoselectivity of this transformation, we monitored the reaction progress of the silylation between **1a** and **2**. (Scheme 3-4). As a result, the reaction was completed within 2 h, and the diastereomeric ratio of **3a** did not change after 24 h. This result suggests that an epimerization from *cis*-**3a** (minor) to *anti*-**3a** (major) could not occur under the reaction conditions and the diastereoselectivity determining step is likely the protonation of the resulting copper(I) enolate intermediate.



Scheme 3-4. Diastereoselectivity at different time points

On the basis of the above observations, we proposed a plausible reaction mechanism as shown in Figure 3-2. At first, in situ generated Cu(O-*t*-Bu) species **A** reacts with silylborane **2** to form the silylcopper(I) species B.[13] The coordination of indole substrate **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 **D**. The stereoretentive protonation of **D** could rapidly proceed to afford the dearomatization product *anti*-**3a** and the Cu(O-*t*-Bu) precatalyst **A**. When bulky alcohol was used, the protonation would become relatively slow due to the steric repulsion between alcohol and silyl group of **D**. Thus, the isomerization from **D** to **D'** could proceed before the protonation, which may lead to the decrease of the diastereoselectivity of this reaction.

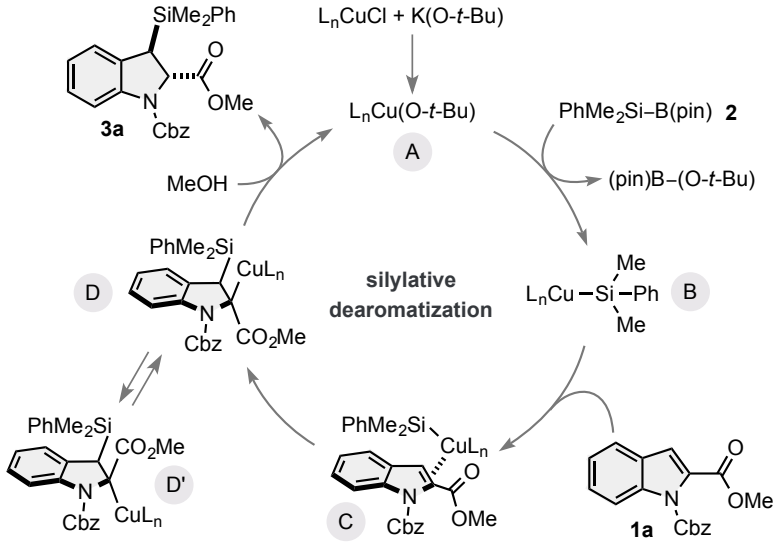


Figure 3-2. Proposed reaction mechanism

Conclusion

In summary, we have developed the ligand-free copper(I)-catalyzed silylative dearomatization of indole-2-carboxylates to give the silylated indolines with high diastereoselectivity. Notably, the first silylative dearomatization of pyrroles has also been achieved by using the developed catalytic system.

Experimental

Instrumentation and Chemicals

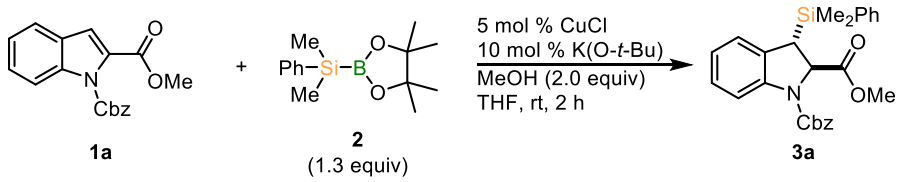
Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{13}C) were employed as external standards, respectively.
CuCl (ReagentPlus® grade, 224332-25G, ≥99%) was purchased from Sigma-Aldrich Co. and used as received. Tetrachloroethane, mesitylene and dibromomethane were used as internal standards to determine NMR yields. Recycle preparative gel permeation chromatography (GPC) was conducted with a JAI LC-9101 using $CHCl_3$ as an eluent with JAIGEL-1H. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

X-ray diffraction analyses: Single crystal X-ray structural analyses were carried out on a Rigaku XtaLAB PRO MM007 or XtaLAB-Synergy diffractometer using graphite monochromated Mo-Kα radiation. The structure was solved by direct methods and expanded using Fourier techniques. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the Olex2 crystallographic software package except for refinement, which was performed using SHELXL-2018.[15] Simulated powder patterns were generated with Mercury 4.1 from the structures determined by the single-crystal diffraction analyses.

General Experimental Procedures

^{1}H and ^{13}C NMR spectra for silylation products contain conformational isomers, which is caused by the restricted C–N bond rotation around the carbamate group.

General Procedure for the Copper(I)-Catalyzed Stereoselective Silylative Dearomatization of Indole 1a (Table 3-1).

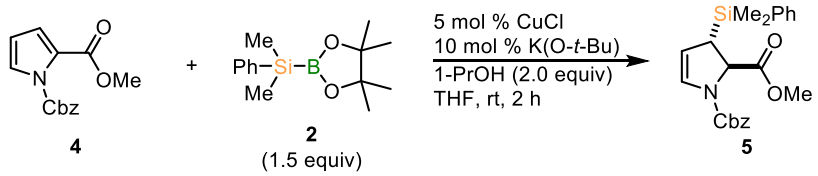


CuCl (2.5 mg, 0.025 mmol) was placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (0.95 mL) and a THF solution of K(O-*t*-Bu) (1.0 M, 50 μL, 0.05 mmol) were added in the vial through the rubber septum. The resulting mixture was allowed to stir at room temperature for 15 min. (Dimethylphenylsilyl) boronic acid pinacol ester (**2**) (170.7 mg, 0.65 mmol) was then introduced and the reaction was allowed to stir at room temperature for 15 min. After **1a** (154.5 mg, 0.50 mmol) and THF (1 mL) were added to the mixture at room temperature, MeOH (40.5 μL, 1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column (15 mm× 40 mm) eluting with EtOAc. The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 4:96– 12:88) within 15 min and distillation by kugelrohr to give the corresponding silylation product **3a** (211.8 mg, 0.48 mmol, 95%) as a yellow oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.31–0.37 (m, 6H), 2.93 (s, 1H), 3.53 and 3.68 (a pair of s, 3H), 4.76 and 4.87 (a pair of d, J = 3.2, 2.3 Hz, 2H), 5.07–5.26 (m, 2H), 6.69 (d, J = 7.7 Hz, 1H), 6.83 and 6.86 (a pair of t, J = 6.8, 7.5 Hz, 1H), 7.02 and 7.12 (a pair of t, J = 7.7, 7.7 Hz,1H), 7.29–7.37 (m, 10H), 7.82 (d, J = 7.7 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –5.9 and –5.8 (a pair of s, CH_3), –5.1 (CH_3), 34.8 and 35.4 (a pair of s, *C*H), 52.3 and 52.4 (a pair of s, *C*H), 62.3 and 62.6 (a pair of s, *C*H), 66.9 and 67.8 (a pair of s, CH_2), 114.6 and 114.9 (a pair of s, *C*H), 128.0 and 128.1 (a pair of s, *C*H), 127.8 and 127.9 (a pair of s, *C*H), 126.4 and 126.5 (a pair of s, *C*H), 123.2 and 123.6 (a pair of s, *C*H), 122.6 and 122.7 (a pair of s, *C*H), 128.4 and 128.5 (a pair of s, *C*H), 129.6 and 129.7 (a pair of s, *C*H), 130.8 and 131.7 (a pair of s, *C*), 133.9 (*C*H), 134.7 and 134.8 (a pair of s, *C*), 135.8 and 136.1 (a pair of *C*), 139.9 and 141.1 (a pair of s, *C*), 151.4 and

153.3 (a pair of s, *C*), 172.1 and 172.2 (a pair of s, *C*). HRMS–EI$^+$ (m/z): [M] calcd for $C_{26}H_{27}O_4N^{28}Si$, 445.1709; found, 445.1711.

Procedure for the Copper(I)-Catalyzed Stereoselective Silylative Dearomatization of Pyrroles 4 (Scheme 3-2).



CuCl (2.5 mg, 0.025 mmol) was placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (1.95 mL) and a THF solution of K(O-*t*-Bu) (1.0 M, 50 μL, 0.05 mmol) were added in the vial through the rubber septum. The resulting mixture was allowed to stir at room temperature for 15 min. (Dimethylphenylsilyl)boronic acid pinacol ester (**2**) (197.1 mg, 0.75 mmol) was then introduced and the reaction was allowed to stir at room temperature for 15 min. After **4** (130.2 mg, 0.50 mmol) was added to the mixture at room temperature, 1-PrOH (75 μL, 1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column (15 mm×40 mm) eluting with EtOAc. The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 4:96– 12:88) within 15 min and GPC was conducted to give the corresponding silylation product **5** 136.8 mg, 0.35 mmol, 69%) as a yellow oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.32–0.36 (m 6H), 2.48 and 2.54 (a pair of quint, J = 2.5, 2.5 Hz, 1H), 3.54 and 3.70 (a pair of s, 3H), 4.52 and 4.62 (a pair of d, J = 5.0, 4.6 Hz, 1H), 4.83–5.22 (m, 3H), 6.45 and 6.56 (a pair of q, J = 2.3, 2.3 Hz, 1H), 7.25–7.39 (m, 8H), 7.47–7.51 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –5.9 and –5.7 (a pair of s, CH_3), –5.4 (CH_3), 36.8 and 38.1 (a pair of s, *C*H), 52.1 and 52.3 (a pair of s, CH_3), 60.1 and 60.2 (a pair of s, *C*H), 67.0 and 67.2 (a pair of s, CH_2), 108.5 and 108.8 (a pair of s, *C*H), 126.4 (*C*H), 127.1 and 127.4 (a pair of s, *C*H), 127.7 and 127.8 (a pair of s, *C*H), 128.0 (*C*H), 128.3 and 128.4 (a pair of s, *C*H), 129.5 and 129.5 (a pair of s, *C*H), 133.7 (*C*H), 135.3 (*C*), 136.1 (*C*), 151.9 and 152.0 (a pair of s, *C*), 171.9 and 172.1 (a pair of s, *C*). HRMS–EI$^+$ (m/z): [M] calcd for $C_{22}H_{25}O_4N^{28}Si$, 395.1553; found, 395.15370.

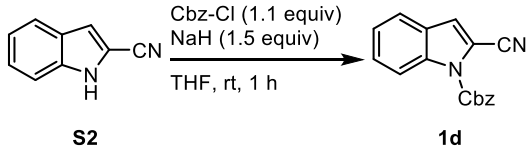
Preparation of Silylboron reagent 2

Silylboron reagent **2** was synthesized according to the literature procedure.[16]

Substrate Preparation

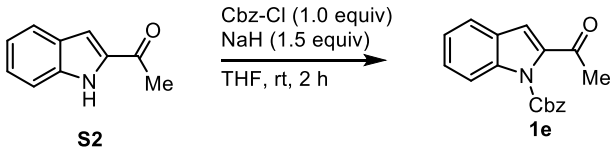
Unless otherwise noted, all substrates were synthesized according to the literature procedure.[10a,12]

Preparation of benzyl 2-cyano-1H-indole-1-carboxylate (1d).



1H-indole-2-carbonitrile (**S1**) was performed according to the literature procedure.[19] The Cbz-protection was performed according to the literature procedure.[18] In a 50 mL round bottomed flask, NaH (185.5 mg, 60%, dispersion in paraffin liquid, 3.3 mmol) was dissolved in dry THF (6 mL) and the mixture was cooled to 0 °C under nitrogen atmosphere. **S1** (548.6 mg, 3.0 mmol) was added in three separate times. Benzyl chloroformate (470 µL, 4.5 mmol) was then added dropwise. After stirred for 2 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 three times. The combined organic layer was then dried over $MgSO_4$. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 2:98–30:70) to obtain **1d** (228.7 mg, 0.83 mmol, 27%) as a white solid.

Preparation of benzyl 2-acetyl-1*H*-indole-1-carboxylate (1e).



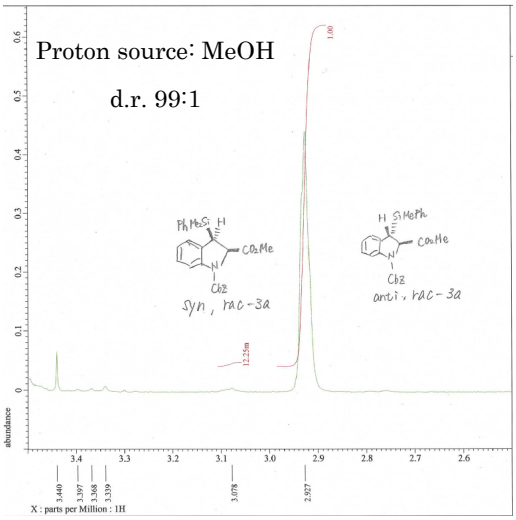
1-(1*H*-Indole-2-yl) ehane-1-one (**S2**) was prepared according to the literature procedure.[17] The Cbz-protection was performed according to the literature procedure.[18] In a 50 mL round bottomed flask, NaH (185.4 mg, 60%, dispersion in paraffin liquid, 3.3 mmol) was dissolved in dry THF (20 mL) and the mixture was cooled to 0 °C under nitrogen atmosphere. **S2** (486.6 mg, 3.1 mmol) was added in three separate times. Benzyl chloroformate (475 µL, 4.5 mmol) was then added dropwise. After stirred for 2 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 three times. The combined organic layer was then dried over $MgSO_4$. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 0:100–20:80) and GPC to obtain **1e** (745.2 mg, 2.4 mmol, 12%) as a black oil.

Determination of Diastereomeric Ratio Values

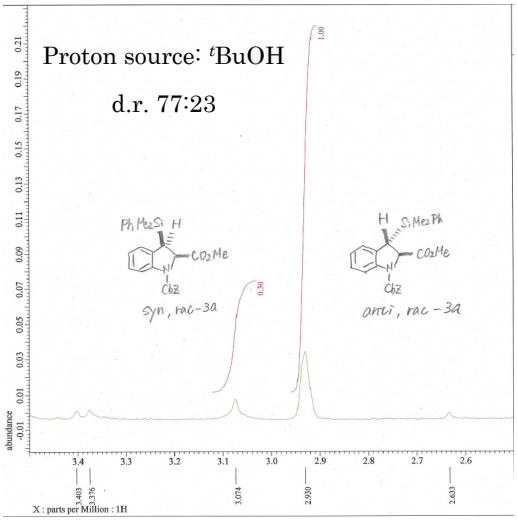
Diastereomeric ratio values of the silylation products were determined by ^{1}H NMR analysis of the crude reaction mixture (Figure S3-1). In the case of **1a**, the use of MeOH as a proton source provided a high diastereoselectivity (>99:1, Figure S3-1a). In contrast, the reaction using *t*-BuOH resulted in a poor diastereoselectivity (77:23, Figure S3-1b). Diastereomeric ratio values of other silylation products were determined in the similar way.

Figure S3-1. Determination of diastereomeric ratio values by crude ^{1}H NMR.

a)



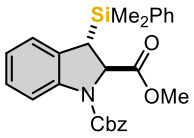
b)



Silylation Product Characterization

^{1}H and ^{13}C NMR spectra for all silylation products contain conformational isomers, which is caused by the restricted C–N bond rotation around the carbamate group. Diastereomer ratios of the silylation products were determined by ^{1}H NMR analysis of the crude reaction mixture.

1-Benzyl 2-methyl-3-(dimethyl(phenyl)silyl) indoline-1,2-dicarboxylate (3a).

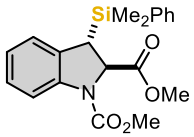


3a

The product **3a** was purified by flush column chromatography (SiO_2, ethyl acetate/hexane, 4:96–12:88) and obtained in 95% (211.8 mg, 0.48 mmol, yellow oil) with d.r. >99:1.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.31 and 0.32 (a pair of s, 6H), 2.93 (s, 1H), 3.53 and 3.68 (a pair of s, 3H), 4.76 and 4.87 (a pair of d, J = 3.2, 2.3 Hz, 2H), 5.07–5.26 (m, 2H), 6.69 (d, J = 7.7 Hz, 1H), 6.83 and 6.86 (a pair of t, J = 6.8, 7.5 Hz, 1H), 7.02 and 7.12 (a pair of t, J = 7.7, 7.7 Hz, 1H), 7.29–7.37 (m, 10H), 7.82 (d, J = 7.7 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –5.9 and –5.8 (a pair of s, CH_3), –5.1 (CH_3), 34.8 and 35.4 (a pair of s, *C*H), 52.3 and 52.4 (a pair of s, *C*H), 62.3 and 62.6 (a pair of s, *C*H), 66.9 and 67.8 (a pair of s, CH_2), 114.6 and 114.9 (a pair of s, *C*H), 128.0 and 128.1 (a pair of s, *C*H), 127.8 and 127.9 (a pair of s, *C*H), 126.4 and 126.5 (a pair of s, *C*H), 123.2 and 123.6 (a pair of s, *C*H), 122.6 and 122.7 (a pair of s, *C*H), 128.4 and 128.5 (a pair of s, *C*H), 129.6 and 129.7 (a pair of s, *C*H), 130.8 and 131.7 (a pair of s, *C*), 133.9 (*C*H), 134.7 and 134.8 (a pair of s, *C*), 135.8 and 136.1 (a pair of *C*), 139.9 and 141.1 (a pair of s, *C*), 151.4 and 153.3 (a pair of s, *C*), 172.1 and 172.2 (a pair of s, *C*). HRMS–EI^{+} (m/z): [M] calcd for $C_{26}H_{27}O_4N^{28}Si$, 445.1709; found, 445.1711.

Dimethyl-3-(dimethyl(phenyl)silyl) indoline-1,2-dicarboxylate (3f).



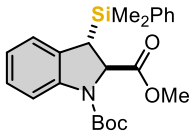
3f

The product **3f** was purified by flush column chromatography (SiO_2, ethyl acetate/hexane, 5:95–20:80) and obtained in 96% (149.7 mg, 0.41 mmol, white solid)

with d.r. >99:1.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.32–0.34 (m, 6H), 2.92 and 2.93 (a pair of s, 1H), 3.68–3.83 (m, 6H), 4.71 and 4.84 (d and s, *J* = 2.7 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.86 (q, *J* = 7.7 Hz, 1H), 7.02 and 7.12 (a pair of t, *J* = 8.2, 7.9 Hz,1H), 7.31–7.40 (m, 5H), 7.80 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –5.9 and –5.7 (a pair of s, *C*H_3), –5.1 (*C*H_3), 34.8 and 35.5 (a pair of s, *C*H), 52.5 and 52.6 (a pair of s, *C*H), 62.3 and 62.5 (a pair of s, *C*H), 114.6 and 114.7 (a pair of s, *C*H), 122.7 (*C*H), 127.8 (*C*H), 129.6 and 129.7 (a pair of s, *C*H), 130.7 (*C*), 134.0 (*C*H), 134.4 (*C*), 141.2 (*C*H), 152.7 (*C*), 172.3 (*C*). HRMS–EI$^+$ (m/z): [M] calcd for $C_{20}H_{23}O_4N^{28}Si$, 369.1396; found, 369.1382.

1-(tert-Butyl) 2-methyl-3-(dimethyl(phenyl)silyl) indoline-1,2-dicarboxylate (3g).

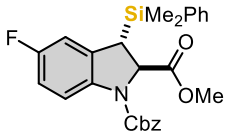


3g

The product **3g** was purified by flush column chromatography (SiO_2, ethyl acetate/hexane, 0:100–8:92) and obtained in 85% (175.2 mg, 0.43 mmol, colorless oil) with d.r. >99:1.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.33 and 0.36 (a pair of s, 6H), 1.44 and 1.54 (a pair of s, 9H), 2.89 (s, 1H), 3.67 (s, 3H), 4.64 and 4.82 (m, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 6.82 (t, *J* = 7.3 Hz, 1H), 7.05–7.11 (m, 1H), 7.31–7.37 (m, 5H), 7.78 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –6.0 and –5.8 (a pair of s, *C*H_3), –5.0 and –4.8 (*C*H_3), 28.2 and 28.3 (a pair of s, *C*H), 34.5 and 35.1 (a pair of s, *C*H), 52.2 (*C*H_3), 62.2 and 62.6 (a pair of s, *C*H), 81.0 and 82.0 (a pair of s, *C*), 114.4 and 114.6 (a pair of s, *C*H), 122.2 (*C*H), 123.2 and 123.6 (a pair of s, *C*H), 126.3 and 126.5 (a pair of s, *C*H), 127.8 and 129.6 (a pair of s, *C*H), 129.7 and 134.0 (a pair of s, *C*H), 130.7 and 131.7 (a pair of s, *C*), 133.0 and 135.1 (a pair of s, *C*), 140.6 and 141.5 (a pair of s, *C*), 151.4 and 152.4 (a pair of s, *C*), 172.4 and 172.6 (a pair of *C*). HRMS–ESI (m/z): [M+Na]$^+$ calcd for $C_{23}H_{23}O_5NNaSi$, 434.1758; found, 434.1754.

1-Benzyl 2-methyl-3-(dimethyl(phenyl)silyl)-5-fluoroindoline-1,2-dicarboxylate (3h).

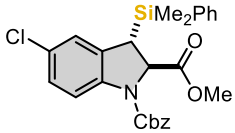


3h

The product **3h** was purified by flush column chromatography (SiO_2, ethyl acetate/hexane, 4:96–12:88) and obtained in 96% (221.6 mg, 0.48 mmol, yellow oil) with d.r. >99:1.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.32 and 0.35 (a pair of s, 6H), 2.89 (s, 1H), 3.55 and 3.70 (a pair of s, 3H), 4.77 and 4.88 (a pair of s, 2H), 5.06–5.25 (m, 2H), 6.37 and 6.35 (a pair of s, 1H), 6.69 and 6.79 (a pair of sxt, J = 4.0, 4.1 Hz, 1H), 7.23–7.41 (m, 10H), 7.74 (q, J = 4.5 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –6.1 and –5.9 (a pair of s, CH_3), –5.1 (CH_3), 35.1 and 35.5 (a pair of s, *C*H), 52.3 and 52.5 (a pair of s, CH_3), 62.6 and 62.9 (a pair of s, *C*H), 67.0 and 67.9 (a pair of s, CH_2), 110.5 (s, *C*H), 110.8 and 111.1 (a pair of s, *C*H), 112.4, 112.5, 112.6 and 112.7 (a pair of d, *C*H), 115.1, 115.2, 115.4 and 115.5 (a pair of d, *C*H), 127.8–127.9 (m, *C*H), 128.1 and 128.2 (a pair of s, *C*H), 128.4 and 128.5 (a pair of s, *C*H), 132.9–134.2 (m, *C*), 133.8 (*C*H), 133.6 and 136.0 (a pair of s, *C*), 137.2 (*C*), 151.9 and 153.0 (a pair of s, *C*), 157.5 and 157.6 (a pair of s, *C*), 160.0 and 160.1 (a pair of s, *C*), 171.9 and 172.0 (a pair of *C*). HRMS–EI$^+$ (m/z): [M] calcd for $C_{26}H_{26}O_4N^{28}SiF$, 463.1615; found, 463.1615.

1-Benzyl 2-methyl-5-chloro-3-(dimethyl(phenyl)silyl) indoline-1,2-dicarboxylate (3i).



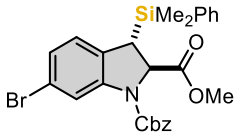
3i

The product **3i** was purified by flush column chromatography (SiO_2, ethyl acetate/hexane, 2:98–10:90) and obtained in 89% (213.5 mg, 0.44 mmol, yellow oil) with d.r. >99:1.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.33–0.35 (m, 6H), 2.87 (s, 1H), 3.54 and 3.69 (a pair of s, 3H), 4.75 and 4.86 (d and s, J = 2.7 Hz, 1H), 5.06–5.25 (m, 2H), 6.59 and 6.61 (a pair of s, 1H), 6.97 and 7.08 (a pair of d, J = 10.5, 7.2 Hz, 1H), 7.22–7.40 (m, 10H), 7.73 (d, J = 8.6 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –6.0 and –5.9 (a pair of s, CH_3), –5.3 (CH_3), 34.9 and 35.4 (a pair of s, *C*H), 52.4 and 52.5 (a pair of s, CH_3), 62.5

and 62.8 (a pair of s, *C*H), 67.1 and 68.0 (a pair of s, *C*H_2), 115.4 and 115.7 (a pair of s, *C*H), 123.3 and 123.6 (a pair of s, *C*H), 126.3 and 126.4 (a pair of s, *C*H), 127.7 (*C*), 127.8 (*C*H), 127.9 and 127.9 (a pair of s, *C*H), 128.1 and 128.2 (a pair of s, *C*H), 128.4 and 128.5 (a pair of s, *C*), 129.8 and 129.9 (a pair of s, *C*H), 133.0 (*C*), 133.8 (*C*), 134.0 and 134.1 (a pair of s, *C*), 135.5 and 135.9 (a pair of s, *C*), 138.7 and 139.9 (a pair of s, *C*), 151.8 and 152.9 (a pair of s, *C*), 171.8 and 171.9 (a pair of s, *C*). HRMS–EI$^+$ (m/z): [M] calcd for $C_{26}H_{26}O_4N^{28}SiCl$, 479.1320; found, 479.1309.

1-Benzyl 2-methyl-6-bromo-3-(dimethyl(phenyl)silyl) indoline-1,2-dicarboxylate (3l).

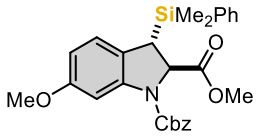


3l

The product **3l** was purified by flush column chromatography (SiO_2, ethyl acetate/hexane, 0:100–8:92) and GPC, then it was obtained in 59% (155.5 mg, 0.30 mmol, yellow oil) with d.r. 99:1.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.30–0.36 (m, 6H), 2.85 and 2.86 (a pair of s, 1H), 3.54 and 3.69 (a pair of s, 3H), 4.75 and 4.85 (a pair of d, J = 3.2, 2.3 Hz, 1H), 5.06, 5.09, 5.24 and 5.27 (two pairs of s, 2H), 6.46–6.50 (m, 1H), 6.94–6.99 (m, 1H), 7.26–7.34 (m, 10H), 8.01 (d, J = 0.9 Hz, 10H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –6.1 and –6.0 (a pair of s, *C*H_3), –5.1 (*C*H_3), 34.6 and 35.2 (a pair of s, *C*H), 52.4 and 52.5 (a pair of s, *C*H_3), 62.7 and 62.9 (a pair of s, *C*H), 67.2 and 68.1 (a pair of s, *C*H_2), 117.8 and 118.2 (a pair of s, *C*H), 119.6 and 119.9 (a pair of s, *C*), 124.2 and 124.6 (a pair of s, *C*H), 125.5 and 125.6 (a pair of s, *C*H), 127.9 (*C*H), 128.2 and 128.3 (a pair of s, *C*H), 128.5 and 128.5 (a pair of s, *C*H), 129.8 and 129.9 (a pair of s, *C*H), 130.1 and 131.1 (a pair of s, *C*), 133.9 (*C*H), 134.2 and 134.3 (a pair of s, *C*), 135.5 and 135.9 (a pair of s, *C*), 141.2 and 142.5 (a pair of s, *C*), 151.8 and 152.9 (a pair of s, *C*), 171.9 (*C*). HRMS–EI$^+$ (m/z): [M] calcd for $C_{26}H_{26}O_4N^{28}SiBr$, 523.0815; found, 523.0815.

1-Benzyl 2-methyl-3-(dimethyl(phenyl)silyl)-6-methoxyindoline-1,2-dicarboxylate (3m).



3m

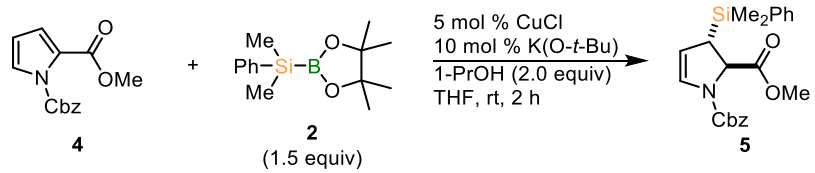
The product **3m** was purified by flush column chromatography (SiO_2, ethyl acetate/hexane, 8:92–12:88) and obtained in 85% (203.1 mg, 0.43 mmol, colorless oil) with d.r. 93:7.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.30–0.34 (m, 6H), 2.84 and 2.85 (a pair of s, 1H), 3.54 and 3.60 (a pair of s, 3H), 3.69 and 3.79 (a pair of s, 3H), 4.76 and 4.86 (d and s, *J* = 3.2, 1H), 5.06–5.27 (m, 2H), 6.37–6.44 (m, 1H), 6.54 and 6.56 (a pair of s, 1H), 7.00 and 7.51 (a pair of s, 1H), 7.29–7.38 (m, 10H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –6.0 and –5.9 (a pair of s, *C*H_3), –5.1 (*C*H_3), 33.7 and 34.3 (a pair of s, *C*H), 52.2 and 52.3 (a pair of s, *C*H_3), 55.1 and 55.3 (a pair of s, *C*H_3), 63.0 and 63.2 (a pair of s, *C*H), 66.9 and 67.9 (a pair of s, *C*H_2), 100.9 and 101.7 (a pair of s, *C*H), 108.2 and 108.8 (a pair of s, *C*H), 122.4 (*C*), 123.4 and 123.7 (a pair of s, *C*H), 127.7 and 127.7 (a pair of s, *C*H), 127.9 and 128.0 (a pair of s, *C*H), 128.2 (*C*H), 128.4 (*C*H), 129.5 and 129.6 (a pair of s, *C*H), 133.9 (*C*H), 134.9 and 134.9 (a pair of s, *C*), 135.6 and 136.0 (a pair of s, *C*), 141.0 and 142.3 (a pair of s, *C*), 151.9 and 153.0 (a pair of s, *C*), 158.6 and 158.9 (a pair of s, *C*), 172.1 and 172.2 (a pair of s, *C*). HRMS–EI$^+$ (m/z): [M] calcd for $C_{27}H_{29}O_5N^{28}Si$, 475.1815; found, 475.1807.

Reaction Optimization for the Silylation of Pyrroles

Optimization of the Reaction Conditions (Table S3-1)

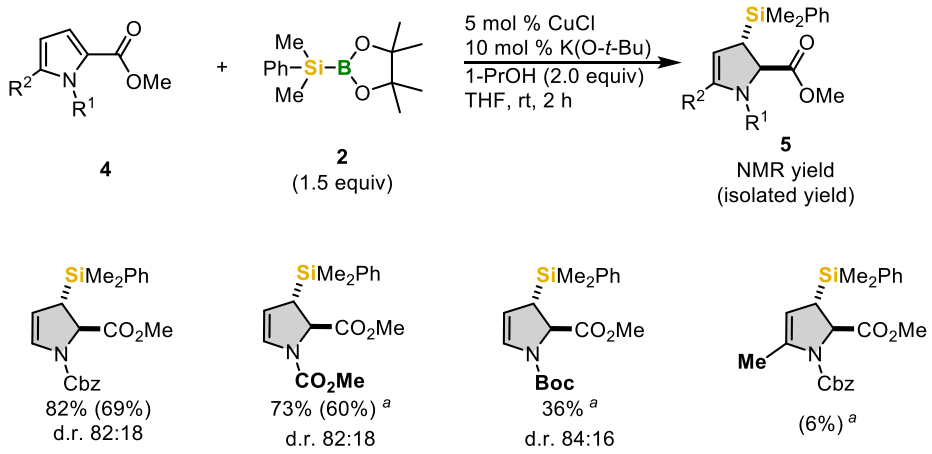
Table S1. Optimization of the reaction conditions in pyrroles



entry	alcohol	time (h)	conversion (%)	NMR yield (%)	d.r.
1	MeOH	4	75	49	87:13
2	EtOH	3	76	70	84:16
3	**1-PrOH**	2	**91**	**77**	**85:15**
4	1-BuOH	4	86	74	84:16
5	2-PrOH	1	95	82	67:33
6	*t*-BuOH	2	99	79	53:47

The series of alcohol were tested as shown in Table S3-1. When MeOH was used as a proton source, the desired 3-silyl-dihydropyrrole (**5**) was obtained in moderate yield with good diastereoselectivity. When EtOH was used, the reactivity was improved and the desired product was afforded in good yield with good diastereoselectivity. Finally, the use of 1-PrOH resulted in the best yield with good diastereoselectivity. The bulkier alcohol led to loss of the diastereoselectivity as similar to indoles silylation.

Effect of the Protecting Groups and Substituents in Pyrroles.

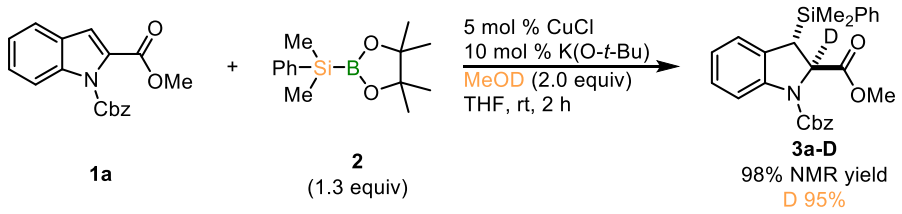


[a] Reaction was conducted for 24 h.

Silylative dearomatization of various pyrroles was investigated. Silylation of the pyrrole bearing the ester group at 2-position proceeded efficiently. When the pyrroles protected by Cbz and CO_2Me were used, the silylation products were provided at good

yield. However, the reactivity was lowered when using the pyrrole protected by Boc. Substituents at 5 position significantly decreased the reactivity.

Deuterium Labeling Experiment



The silylation of **1a** under the optimized conditions using MeOD instead of MeOH gave the deuterium labeling product **3a-D** (95% D). This result is consistent with our proposed reaction mechanism shown in Figure 3-2.

Single Crystal X-ray Structural Analyses

The configuration of the compound (*rac*)-**3f** was determined based on X-ray crystallographic analyses. The configurations of other products were deduced by these products. The details were summarized in Figure S3-2 and Table S3-2.

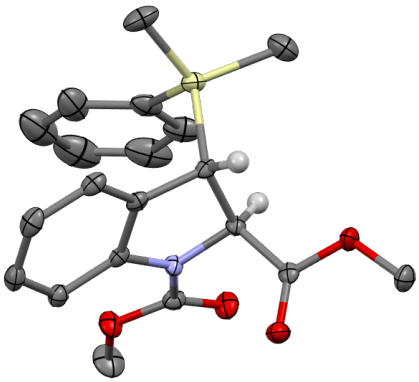
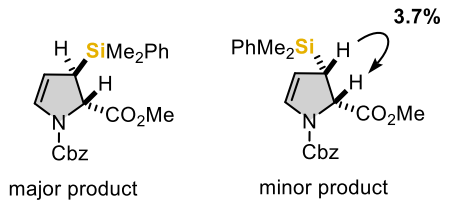


Figure S3-2. Molecular structure of (*rac*)-**3f**. Thermal ellipsoids set at 50% probability.

Table S3-1. Summary of X-ray crystallographic data for (*rac*)-**3f**.

CCDC	xxx
Empirical formula	$C_{20}H_{23}NO_4Si$
Formula weight	369.48
Temperature/K	123
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.8037(9)
b/Å	9.5888(4)
c/Å	13.7868(9)
α /°	90
β /°	113.574(7)
γ /°	90
Volume/Å^3	1914.9(2)
Z	4
ρ_{calc} g/cm^3	1.282
μ /mm^{-1}	0.147
F(000)	784.0
Crystal size/mm^3	0.15 × 0.1 × 0.05
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	5.094 to 56.526
Index ranges	$-20 \leq h \leq 19$, $-11 \leq k \leq 12$, $-15 \leq l \leq 17$
Reflections collected	14451
Independent reflections	4030 [R_{int} = 0.0367, R_{sigma} = 0.0373]
Data/restraints/parameters	4030/72/239
Goodness-of-fit on F^2	1.032
Final *R* indexes [I>=2σ (I)]	R_1 = 0.0436, wR_2 = 0.1022
Final R indexes [all data]	R_1 = 0.0569, wR_2 = 0.1078
Largest diff. peak/hole / e Å^{-3}	0.61/−0.38

We also confirmed the relative configuration of the silylation product (*rac*)-**5** by nucler Overhauser effect (NOE) ^{1}H NMR analysis. The result was shown as below.



References

(23) a) T. Hiyama, T. Kusamoto, *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming, Eds.; Pergamon: Oxford, U.K., **1991**.; Chapter 3.12, Vol. 8. b) *The Chemistry of Organo Silicon Compounds*; Z. Rappoport, Y. Apeloig, Eds.; Wiley: New York, **1998**. c) E. Langkopf, D. Schinzer, *Chem. Rev.* **1995**, *95*, 1375-7408. d) V. B. Pukhnarevich, E. Lukevics, L. T. Kopylova, M. G. Voronkov, *Perspectives of Hydrosilylation*; E. Lukevics, Ed.; Institute of Organic Synthesis: Riga, **1992**. e) M. A. Brook, *Silicon in Organic, Organometallic, and Polymer Chemistry*; Wiley: New York, **2000**. f) I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063-2192. g) M. Mortensen, R. Husmann, E. Veri, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 1002-1010. h) A. K. Franz, *Curr. Opin. Drug Discov. Devel.* **2007**, *10*, 654-671.

(24) *Modern Alkaloids: Structure, Isolation, Synthesis and Biology.* E. Fattorusso, O. Taglialatela-Scafati, Eds.; Wiley-VCH: Weinheim, **2008**.

(25) For a review and selected examples of the synthesis of the indoline scaffold, see: a) W. Zi, Z. Zuo, D. Ma, *Acc. Chem. Res.* **2015**, *48*, 702-711. b) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614-7615.

(26) For general reviews on the synthesis of pyrrolidine derivatives, see: a) M. Pichon, B. Figadére, *Tetrahedron: Asymmetry* **1996**, *7*, 927-964. b) F. Bellina, R. Rossi, *Tetrahedron*, **2006**, *62*, 7213-7256. c) J. Yu, Y. Zhou, D.-F. Chen, L.-Z. Gong, *Pure Appl. Chem.* **2014**, *86*, 1217-1226.

(27) S. Park, S. Chang, *Angew. Chem., Int. Ed.* **2017**, *56*, 7720-7738.

(28) K. Oshima, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2011**, *133*, 7324-7327.

(29) N. Gandhamsetty, S. Joung, S.-W. Park, S. Park, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 16780-16783.

(30) N. Gandhamsetty, S. Park, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 15176-15184.

(31) Y. Shi, Q. Gao, S. Xu, *J. Org. Chem.* **2018**, *83*, 14758-14767.

(32) For borylative dearomatization reactions of indoles reported by our group, see: a) K. Kubota, K. Hayama, H. Iwamoto, H. Ito, *Angew. Chem., Int. Ed.* **2015**, *54*, 8809-8813. b) K. Hayama, K. Kubota, H. Iwamoto, H. Ito, *Chem. Lett.* **2017**, *46*, 1800-1802.

(33) a) K. Kubota, Y. Watanabe, K. Hayama, H. Ito, *J. Am. Chem. Soc.* **2016**, *138*, 4338-4341. b) K. Kubota, Y. Watanabe, H. Ito, *Adv. Synth. Catal.* **2016**, *358*, 2379-2384.

(34) K. Hayama, R. Kojima, K. Kubota, H. Ito, *Org. Lett.* **2020**, *22*, 739–744.

(35) For general reviews of silylboranes see: a) A. B. Cuenca, R. Shishido, H. Ito, E. Fernández. *Chem. Soc. Rev.* **2017**, *46*, 415-430. b) M. Oestreich, E. Hartmann, M. Mewald, *Chem. Rev.* **2013**, *113*, 402-441.

(36) J. R. Wilkinson, C. E. Nuyen, T. S. Carpenter, S. R. Harruff, R. V. Hoveln, *ACS Catal.* **2019**, *9*, 8961-8979.

(37) Sheldrick, G. M. *Acta Cryst. Sect. C*, **2015**, *71*, 3–8.

(38) Cirriez, V.; Rasson, C.; Hermant, T.; Petrignet, J.; Álvarez, J. D.; Robeyns, K.; Riant, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 1785–1788.

(39) Mietke, T.; Cruchter, T.; Larionov, V. A.; Faber, T.; Harms, K.; Meggers, E. *Adv. Synth. Catal*. **2018**, *360*, 2093–2100.

(40) U. Jacquemard, V. Bénéteau, M. Lefoix, S. Routier, J. –Y. Mérour, G. Coudert, *Tetrahedron* **2004**, *60*, 10039–10047.

(41) Lopchuk, J. M.; Montgomery, W. L.; Jasinski, J. P.; Gorjifard, S.; Gribble, G. W. *Tetrahedron Letters* **2013**, *54,* 6142–6145.

List of Publications

Chapter 1

"Synthesis of Chiral *N*-Heterocyclic Allylboronates via the Enantioselective Borylative Dearomatization of Pyrroles"
Hayama, K.; Kojima, R.; Kubota, K.; Ito, H.
Org. Lett. **2020**, *22*, 739–744.

Chapter 2

"Copper(I)-Catalyzed Diastereoselective Dearomative Carboborylation of Indoles"
Hayama, K.; Kubota, K.; Iwamoto, H.; Ito, H.
Chem. Lett. **2017**, *46*, 1800–1802.

Chapter 3

"Copper(I)-Catalyzed Stereoselective Silylative Dearomatization of Indoles and Pyrroles with Silylboranes"
Hayama, K.; Takahashi, R.; Kubota, K.; Ito, H.
manuscript under preparation.

Other Publications

1. "Enantioselective Borylative Dearomatization of Indoles through Copper(I) Catalysis"
   Kubota, K.; Hayama, K.; Iwamoto, H.; Ito, H.
   Angew. Chem., Int. Ed. **2015**, *54*, 8809–8813.

2. "Enantioselective Synthesis of Chiral Piperidines via the Stepwise Dearomatization/Borylation of Pyridines"
   Kubota, K.; Watanabe, Y.; Hayama, K.; Ito, H.
   J. Am. Chem. Soc. **2016**, *138*, 4338–4341.

3. "Copper(I)-Catalyzed Stereo- and Chemoselective Borylative Radical Cyclization of Alkyl Halides Bearing an Alkene Moiety"
   Iwamoto, H.; Akiyama, S.; Hayama, K.; Ito, H.
   Org. Lett. **2017**, *19*, 2614–2617.

4. "Transition-Metal- and Light-Free Directed Amination of Remote Unactivated C(sp^3)–H Bonds of Alcohols"
   Kurandina, D.; Yadagiri, D.; Rivas, M.; Kavun, A.; Chuentragool, P.; Hayama, K.; Gevorgyan, V.
   J. Am. Chem. Soc. **2019**, *141*, 8104–8109.

Acknowledgements

The studies presented in this thesis have been carried out under the direction of Professor Doctor Hajime Ito at the Faculty of Engineering of Hokkaido University during 2014–2020. The studies are concerned with the development of copper(I)-catalyzed dearomative borylation and silylation reactions of N-heteroaromatic compounds.

At first and foremost the author would like to express his deepest gratitude to Prof. Hajime Ito, whose constant guidance, enormous supports and insightful comments were invaluable during the course of his study. The author is particularly indebted to Prof. Koji Kubota for his kind and helpful advice and stimulating discussions during the course of his study. The author also would like to thank Prof. Tatsuo Ishiyama for his kind advice and encouragement during the course of his study. The author would also like to thank Prof. Tomohiro Seki, Mr. Toshiki Sumitani, and Mr. Takaki Mashimo for their help analyzing the X-ray crystallography data. The author is grateful to thank Mr. Ryoto Kojima, Hiroaki Iwamoto, Sota Akiyama, Yuta Watanabe, Rikuro Takahashi, and other members of the Prof. Ito's research group for their good collaboration and for providing a good working atmosphere. This work supported by Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

Keiichi Hayama

Graduate school of chemical sciences and engineering,
Frontier chemistry center, organoelement chemistry laboratory
Hokkaido University
2020