Communication

Enantioselective Synthesis of Chiral Piperidines via the Stepwise Dearomatization/Borylation of Pyridines

Koji Kubota, Yuta Watanabe, Keiichi Hayama, and Hajime Ito

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b01375 • Publication Date (Web): 11 Mar 2016

Enantioselective Synthesis of Chiral Piperidines via the Stepwise Dearomatization/Borylation of Pyridines

Koji Kubota, Yuta Watanabe, Keiichi Hayama and Hajime Ito*

Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan.

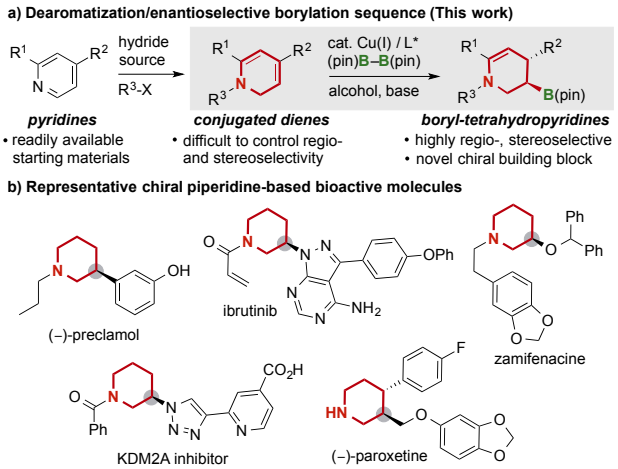
Supporting Information Placeholder

ABSTRACT: We have developed a novel approach for the synthesis of enantioenriched 3-boryl-tetrahydropyridines via the copper(I)-catalyzed regio-, diastereo- and enantioselective protoborylation of 1,2-dihydropyridines, which were obtained by the partial reduction of the pyridine derivatives. This dearomatization/enantioselective borylation stepwise strategy provides facile access to chiral piperidines together with the stereospecific transformation of a stereogenic C–B bond from readily available starting materials. Furthermore, the utility of this method was demonstrated for the concise synthesis of the antidepressant drug (–)-paroxetine. A theoretical study of the reaction mechanism has also been described.

Chiral piperidines are important structural motifs that can be found in a wide variety of naturally occurring bioactive molecules and pharmaceutical drugs.[1] Despite significant progress towards the development of synthetic approaches capable of providing facile access to these molecules, the development of a simple, mild and efficient method for the direct preparation of chiral piperidines remains highly desired. Based on the abundance of readily available nitrogen-containing aromatic compounds, the enantioselective dearomatization of pyridine derivatives represents a powerful and efficient method for the formation of chiral *N*-heterocyclic compounds. Furthermore, the dearomatization of pyridine derivatives can provide direct access to various saturated chiral *N*-heterocyclic structures, making it particularly efficient.[2,3] Recently, several strategies have been developed for the dearomatization of pyridines involving either the nucleophilic addition of a suitable nucleophile to a pyridinium salt or the use of stepwise reduction/enantioselective catalysis.[3,4]

We recently reported the first C–B bond forming enantioselective dearomatization of indoles under copper(I) catalysis to give the corresponding chiral 3-boryl-indolines with excellent regio-, diastereo- and enantioselectivity.[5-7] Transformations of this type have great numerous potential applications in synthetic and medicinal chemistry because chiral *N*-heterocyclic organoborons are amenable to a wide variety of stereospecific functionalization reactions through their stereogenic C–B bond.[8,9] With this in mind, we became interested in the development of an enantioselective method for the conversion of pyridines to chiral boryl-piperidines, which could be used as novel nucleophiles for the synthesis of piperidine-based bioactive compounds.[9] Our initial efforts focused on the development of a direct C–B bond forming method using an *N*-acyl pyridinium salt as the substrate under copper(I) catalysis with the concomitant dearomatization of the pyridine ring. Although the 1,2-borylation reaction proceeded as anticipated, we failed to isolate the desired product because it decomposed during purification. We subsequently investigated the development of an alternative stepwise strategy involving the combination of Fowler's dearomative reduction of pyridines[10] with the copper(I)-catalyzed enantioselective borylation of the resulting unstable 1,2-dihydropyridines.[4] However, this novel method would be very challenging because of the difficulties associated with controlling the regio-, diastereo- and enantioselectivity for nitrogen-containing conjugated diene substrates. Furthermore, there have been no reports in the literature to date pertaining to the selective borylation of such compounds.[11] Herein, we report the development of a novel method for the enantioselective synthesis of chiral 3-boryl-tetrahydropyridines via the chiral diphosphine/copper(I)-catalyzed regio-, diastereo- and enantioselective protoborylation of 1,2-dihydropyridines, which were derived from the dearomative reduction of readily available pyridines (Scheme 1a). Notably, the subsequent derivatization of the boryl group in these products, as well as the remaining enamine moiety, could provide facile access to complex chiral piperidines bearing a C–3 stereocenter, which are important components in various pharmaceutical drugs (Scheme 1b).[1] In actual fact, the antidepressant drug (–)-paroxetine was successfully synthesized in this study using our newly developed approach. A theoretical study of the reaction mechanism has also been described.

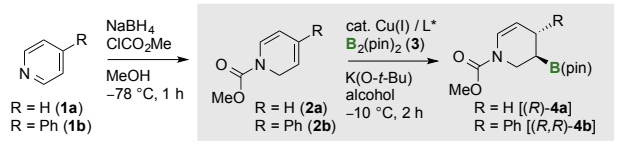
Scheme 1. (a) Stepwise Dearomatization/Enantioselective Borylation Strategy. (b) Representative Bioactive Chiral Piperidines.



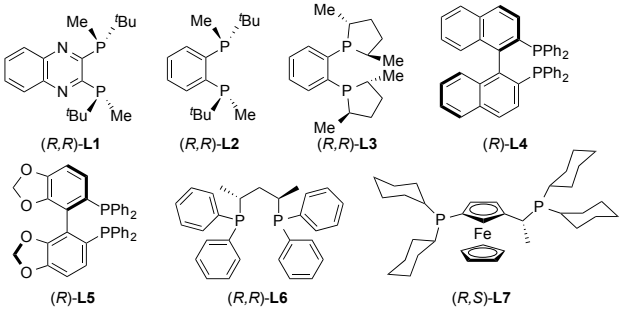
The results of an extensive optimization process revealed that the reaction of methoxycarbonyl-protected 1,2-

dihydropyridine **2a** (R = H), which was isolated from pyridine **1a** using Fowler's reduction method[10], with bis(pinacolato)diboron (**3**) (1.2 equiv) in the presence of CuCl/(*R*,*R*)-QuinoxP* **L1** (5 mol %), K(O-*t*-Bu) (20 mol %) and MeOH (2.0 equiv) in THF at –10°C afforded the chiral 3-boryl-tetrahydropyridine (*R*)-**4a** in high yield with excellent enantioselectivity (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions.[a]



entry	R	chiral ligand	Alcohol	d.r.	yield (%)[b]	ee (%)[c]
1	H (**2a**)	(*R*,*R*)-**L1**	MeOH	–	93	99
2	H (**2a**)	(*R*,*R*)-**L2**	MeOH	–	92	98
3	H (**2a**)	(*R*,*R*)-**L3**	MeOH	–	82	93
4	H (**2a**)	(*R*)-**L4**	MeOH	–	<5	–
5	H (**2a**)	(*R*)-**L5**	MeOH	–	<5	–
6	H (**2a**)	(*R*,*R*)-**L6**	MeOH	–	97	55
7	H (**2a**)	(*R*,*S*)-**L7**	MeOH	–	20	73
8	H (**2a**)	(*R*,*R*)-**L1**	*t*-BuOH	–	92	79
9	H (**2a**)	(*R*,*R*)-**L1**	PhOH	–	40	55
10[d]	H (**2a**)	(*R*,*R*)-**L1**	MeOH	–	92	93
11[e]	H (**2a**)	(*R*,*R*)-**L1**	MeOH	–	96	99
12[f,g]	H (**2a**)	(*R*,*R*)-**L1**	MeOH	–	91	99
13[h]	Ph (**2b**)	(*R*,*R*)-**L1**	MeOH	99:1	83	25
14[h]	Ph (**2b**)	(*R*)-**L5**	*t*-BuOH	97:3	94	92



[a]Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **2** (0.5 mmol), bis(pinacolato)diboron **3** (0.6 mmol), alcohol (1.0 mmol) and K(O-*t*-Bu) (0.1 mmol) in THF. [b]NMR yield. [c]The ee values of (*R*)-**4a** were determined by HPLC analysis of the corresponding benzoate ester. [d]The reaction was carried out at 30 °C. [e]The reaction was carried out on a 5 mmol scale. [f]1 mol % CuCl and ligand were used. [g]The reaction time was 16 h. [h]The reaction was carried out at 0 °C and the reaction time was 1 h.

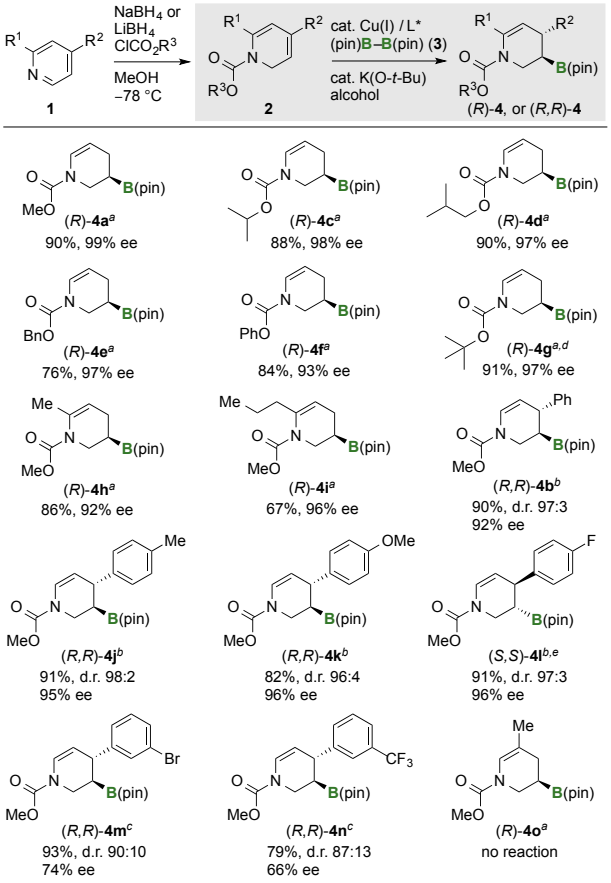
Notably, none of the other regioisomers were detected by ^{1}H NMR analysis of the crude reaction mixture. The use of (*R*,*R*)-BenzP* **L2** or (*R*,*R*)-Me-Duphos **L3** also provided high levels of enantioselectivity (Table 1, entries 2 and 3). No product was observed when a triarylphosphine-type ligand, such as (*R*)-BINAP **L4** or (*R*)-SEGPHOS **L5** was used in the reaction (Table 1, entries 4 and 5). These results suggested that the presence of electron-donating alkyl substituents on the phosphine atoms of the ligand was crucial for the success of the current reaction. Several other chiral ligands, including (*R*,*R*)-BDPP **L6** and (*R*,*S*)-Josiphos **L7**, were also screened in the reaction. Although these ligands both provided access to the desired borylation product, they afforded poor enantioselectivities (Table 1, entries 6 and 7). The nature of the proton source was also found to be important to the reactivity and enantioselectivity of this transformation (Table 1, entries 8 and 9). For example, the use of sterically hindered *t*-BuOH instead of MeOH resulted in a lower enantioselectivity (Table 1, entry 8). Furthermore, the use of PhOH as a proton source provided a low yield and poor enantioselectivity (Table 1, entry 9). Increasing the temperature led to a slight decrease in the enantioselectivity (Table 1, entry 10). Notably, the reaction proceeded smoothly on a 5.0 mmol scale to give gram quantities of the desired product with excellent enantioselectivity (Table 1, entry 11). This enantioselective borylation reaction also proceeded efficiently with a 1 mol % loading of the copper(I) catalyst and showed high enantioselectivity (99% ee), although a longer reaction time was required (Table 1, entry 12). We then proceeded to investigate the borylation of 4-phenyl-1,2-dihydropyridine **2b** in the presence of the QuinoxP* **L1** complex catalyst (Table 1, entry 13). Unfortunately, however, we observed a much lower enantioselectivity (25% ee) than that obtained for the reaction of **2a** under the same conditions, even though the regio- and diastereoselectivity were excellent (d.r. 99:1). Based on this result, we conducted a series of optimization reactions using **2b** as a substrate (see the Supporting Information for details). The results revealed that the use of the (*R*)-SEGPHOS chiral ligand **L5** with *t*-BuOH in a toluene/DME/THF co-solvent system gave the desired chiral 3-boryl-tetrahydropyridine (*R*,*R*)-**4b** bearing consecutive stereogenic centers in good yield (94%) with high diastereo- and enantioselectivity (d.r. 97:3, 92% ee) (Table 1, entry 14).[12] The *anti*-configuration of (*R*,*R*)-**4b** was confirmed by NOE analysis (see Supporting Information for details).

The optimized conditions were used for further evaluation of the substrate scope (Table 2). The reactions of 1,2-dihydropyridines bearing various carbamate-type protecting groups (**2a**, **2c**–**2g**) in the presence of the copper(I)/(*R*,*R*)-QuinoxP* **L1** catalyst system proceeded to give the desired products [(*R*)-**4a**, (*R*)-**4c**–(*R*)-**4g**] with high enantioselectivities (Table 2). The 6-substituted 1,2-dipydropyridines (**2h** and **2i**) were also borylated to afford the corresponding chiral 3-boryl-tetrahydropyridines [(*R*)-**4h** and (*R*)-**4i**] with excellent enantioselectivities without any of the other undesired regioisomers being detected (Table 2). The copper(I)/(*R*)-SEGPHOS complex catalyzed the enantioselective borylation of various 4-aryl-1,2-dihydropyridines (**2b**, **2j**–**2l**) to provide the corresponding borylated products bearing consecutive stereogenic centers with high diastereo- and enantioselectivities (d.r. 96:4–98:2, 93–96% ee). However, the reactions of **2m** and **2n** in the presence of the copper(I)/(*R*)-SEGPHOS **L5** catalyst resulted in low yields (10%). Fortunately, however, we found that the use of (*R*,*R*)-BDPP **L6** allowed for the successful synthesis of the corresponding products [(*R*,*R*)-**4m** and (*R*,*R*)-**4n**], albeit with moderate enantioselectivities (74% ee and 66% ee, respectively). Finally, the current catalytic system failed to affect the borylation of the 3-substituted 1,2-dihydropyridine **2o**.[13]

The borylation products could be used as versatile building blocks for the preparation of chiral piperidines. For example, the oxidation of (*R*)-**4a** with $NaBO_3$, followed

by the sequential acylation of the resulting alcohol and reduction of the enamine moiety afford the chiral piperidinol (*R*)-**5** with high enantiomeric excess (Scheme 2). Furthermore, the hydrogenation of (*R*)-**4a** gave (*R*)-**6**, which was reacted with (3-methoxyphenyl)lithium under Aggarwal's cross-coupling conditions[14] to afford (–)-preclamol precursor (**S**)-7 with excellent stereospecificity (Scheme 2). The diastereoselective hydroboration of the remaining enamine moiety, followed by an oxidation gave the chiral piperidine (*R*,*R*,*S*)-**9** bearing three consecutive stereogenic centers (Scheme 3).

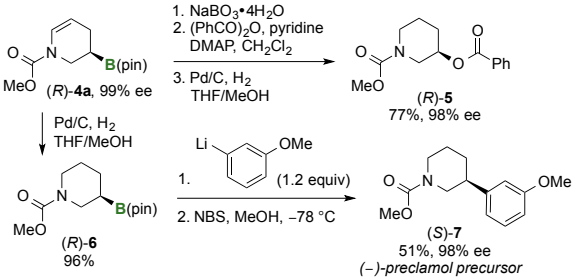
Table 2. Substrate Scope of the Copper(I)-Catalyzed Enantioselective Borylation of 1,2-Dihydropyridines.



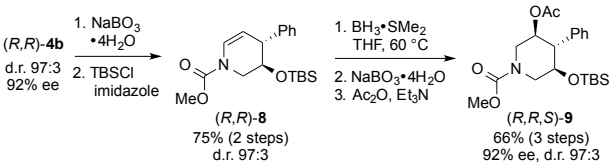
[a]Conditions: CuCl (0.025 mmol), (*R*,*R*)-**L1** (0.025 mmol), **2** (0.5 mmol), **3** (0.6 mmol), MeOH (1.0 mmol) and K(O-*t*-Bu) (0.1 mmol) in THF at –10°C for 2 h. [b]Conditions: CuCl (0.025 mmol), (*R*)-**L5** (0.025 mmol), **2** (0.5 mmol), **3** (0.6 mmol), *t*-BuOH (1.0 mmol) and K(O-*t*-Bu) (0.1 mmol) in THF/toluene/DME (1:6:6 - v/v/v) at 0°C for 1 h. [c]Conditions: CuCl (0.025 mmol), (*R*,*R*)-**L6** (0.025 mmol), **2** (0.5 mmol), **3** (0.6 mmol), *t*-BuOH (1.0 mmol) and K(O-*t*-Bu) (0.1 mmol) in THF at 0°C for 1 h. [d]**2g** was prepared by the treatment of **2f** with K(O-*t*-Bu). [e](*S*)-**L5** was used.

To demonstrate the applicability of this newly developed methodology to the synthesis of bioactive molecules, we completed the synthesis of the antidepressant drug (–)-paroxetine (*R*,*S*)-**12** using the borylated product (*S*,*S*)-**4l** (Scheme 4).[8,15] Briefly, the boryl group in (*S*,*S*)-**4l** was successfully functionalized through a one carbon homologation reaction.[16] Subsequent oxidation and mesyl protection steps afforded the corresponding mesylate (*R*,*S*)-**10**, which was subjected to sequential etherification and hydrogenation steps to give (*R*,*S*)-**11** with high enantiomeric purity (94% ee). Finally, the deprotection of the methyl carbamate moiety with KOH provided (–)-paroxetine (*R*,*S*)-**12**. It is envisioned that these novel chiral boronates will find further application in synthetic and medicinal chemistry.

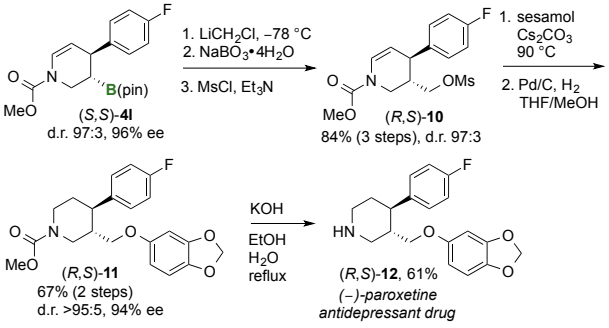
Scheme 2. Derivatization Reactions of (*R*)-**4a**.



Scheme 3. Construction of Three Consecutive Stereocenters via a Diastereoselective Hydroboration Reaction.



Scheme 4. Synthesis of (–)-Paroxetine.



A deuterium labeling experiment was conducted to probe the reaction mechanism (see the Supporting Information for further details). The borylation of **2e** under the optimized conditions using MeOD instead of MeOH gave (*R*)-**4e'**, bearing a deuterium label at its 4-position (D >95%), with high enantioselectivity (98% ee). The *syn* configuration between the boryl group and the deuterium atom at the 4-position was confirmed by NOE analysis. These results therefore suggested that the current borylation proceeds via the regio- and enantioselective *syn*-4,3-addition of an active borylcopper(I) to the substrate, followed by the stereoretentive S_E2 protonation of the allylcopper(I) intermediate by the alcohol additive.[17]

Density functional theory calculations (B3PW91/cc-pVDZ) were performed to understand the unprecedented regioselectivity of this borylation process (Figure 1). This reaction could potentially proceed via four different borylcupration pathways (paths A–D, Figure 1). All of the borylation pathways were calculated using the achiral borylcopper(I)/$Me_2PCH{=}CHPMe_2$ model complex with **2a** as a substrate. The results showed that the activation energies for pathways A (ΔG_{TS1}) and C (ΔG_{TS3}), leading to the

corresponding stable allylcopper(I) intermediates, were lower than those of pathways B and D. For pathway C, steric congestion between the B(pin) and carbamate moieties would destabilize the complex during the borylcupration process.[18] The current borylation process would therefore most likely proceed via a 4,3-borylcupration process (path A) to form intermediate P1 with high selectivity. The similar calculations in the case of **2b** also indicated that the activation energy for the 4,3-addition was lower than those of other pathways.[19]

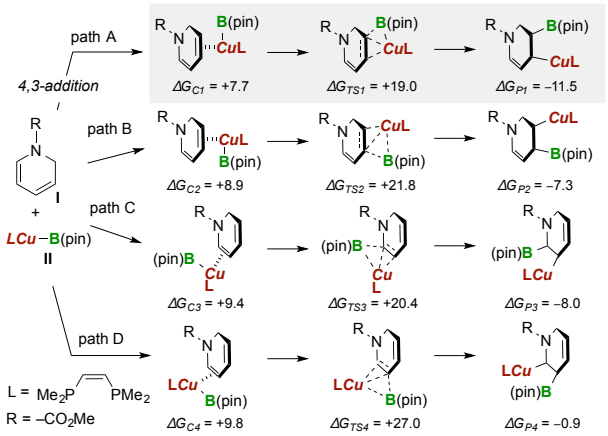


Figure 1. Density functional theory calculations for the four regioisomeric pathways A–D (B3PW91/cc-pVDZ). Relative *G* values (kcal/mol) at 298 K, 1.0 atom in the Gas Phase.

In summary, we have developed a novel stepwise dearomatization/enantioselective borylation strategy for the preparation of chiral 3-boryl-tetrahydropyridines from pyridines with excellent enantiomeric purity. This reaction involves the unprecedented regio- and enantioselective borylcupration of 1,2-dihydropyridines, followed by the stereoretentive S_E2 protonation of the resulting allylcopper(I) intermediates by an alcohol additive. The current methodology represents a simple and direct method for the synthesis of optically active piperidines bearing a C3-stereocenter in combination with a stereospecific boron functionalization process.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

hajito@eng.hokudai.ac.jp

Notes

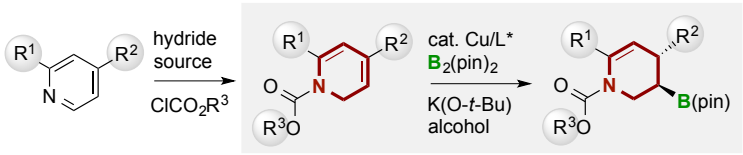
The authors declare that there are no competing financial interests.

ACKNOWLEDGMENTS

This study was financially supported by the MEXT (Japan) program (Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions) of Hokkaido University, as well as the JSPS (KAKENHI Grant Numbers 15H03804 and 15K13633). K.K. would like to thank the JSPS for their scholarship funding (KAKENHI Grant Number 14J02341).

REFERENCES

(1) Pyridine and its Derivatives in Heterocycles in Natural Product Synthesis, Majumdar, K. C.; Chattopadhyay, S. K., Ed.; Wiley-VCH, Weinheim, 2011, Chap. 8, pp. 267.
(2) General reviews on piperidines, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.
(3) Recent reviews on catalytic enantioselective dearomatization reactions, see: (a) Zhuo, C.; Zhang, W.; You, S. –L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662. (b) Ding, Q.; Zhou, X.; Fan, R.; *Org. Biomol. Chem.* **2014**, *12*, 4807. (c) Zhuo, C. –X.; Zheng, C.; You, S. –L. *Acc. Chem. Res.* **2014**, *47*, 2558.
(4) Reviews on the synthesis and applications of 1,2-dihydropyridines, see: (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (b) Silva, E. M. P.; Varandas, P. A. M. M.; Silva, A. M. S. *Synthesis* **2013**, 3053. (c) Tanaka, K.; Fukase, K.; Katsumura, S. *Synlett* **2011**, 2115.
(5) Kubota, K.; Hayama, K.; Iwamoto, H.; Ito. H. *Angew. Chem., Int. Ed.* **2015**, *54*, 8809.
(6) For selected examples of copper(I)-catalyzed enantioselective borylations from our group, see: (a) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (b) Ito, H.; Kunii, S.; Sawamura, M. *Nat. Chem.* **2010**, *2*, 972. (c) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc.* **2014**, *136*, 16515. (d) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2015**, *137*, 420.
(7) For selected examples of the copper(I)-catalyzed enantioselective protoboration reaction, see: (a) Lillo, V.; Prieto, A.; Bonet, A.; Diaz-Requejo, M. M.; Ramirez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659. (b) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160. (c) Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6062. (d) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894. (e) He, Z. T.; Zhao, Y. S.; Tian, P.; Wang, C. C.; Dong, H. Q.; Lin, G. Q. *Org. Lett.* **2014**, *16*, 1426. (f) Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; Ruano, J. L. G.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833.
(8) Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials, 2 nd revised ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2011.
(9) For examples of the synthesis of chiral 4-boryl-piperidines, see: (a) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612. (b) Ding, J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 8069. (c) Ding, J.; Rybak, T.; Hall, D. G. *Nat. Commun.* **2014**, *5*, 5474.
(10) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321. The 1,2-dihydropyridines were isolated prior to the next borylation step, but should be used immediately in order to prevent decomposition.
(11) We have reported the first copper(I)-catalyzed regio- and enantioselective protoborylation of carbocyclic 1,3-dienes, see: Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226.
(12) The triarylphosphine type ligand showed high enough reactivity toward 4-aryl-1,2-dihydropyridines because an aryl group at 4-position could lower the LUMO levels of 1,2-dihydropyridines by extension of the conjugated system in the substrate, which could promote the insertion reaction of a borylcopper(I) intermediate.
(13) The results of further investigation on the substrate scope have been described in the Supporting Information.
(14) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nat. Chem.* **2014**, *6*, 584.
(15) Recent syntheses of (–)-paroxetine, see: (a) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389. (b) Kim, M. –H.; Park, Y.; Jeong, B. –S.; Park, H. –G.; Jew, S. –S. *Org. Lett.* **2010**, *12*, 2826. (c) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, 136, 3020. (d) White, N. A.; Ozboya, K. E.; Flanigan, D. M.; Rovis, T. *Asian J. Org. Chem.* **2014**, *3*, 442.
(16) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.
(17) The reaction pathway is proposed in the Supporting Information.
(18) DFT calculations also suggest that the electronic properties of dienes would be important for high regioselectivity. The details and calculated structures are included in the Supporting Information.
(19) The details of the calculations are included in the Supporting Information.



- ***Unprecedented regio-, diastereo- and enantioselective***
- ***Readily available starting materials***
- ***Chiral boryl-tetrahydropyridines: Novel building blocks***