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

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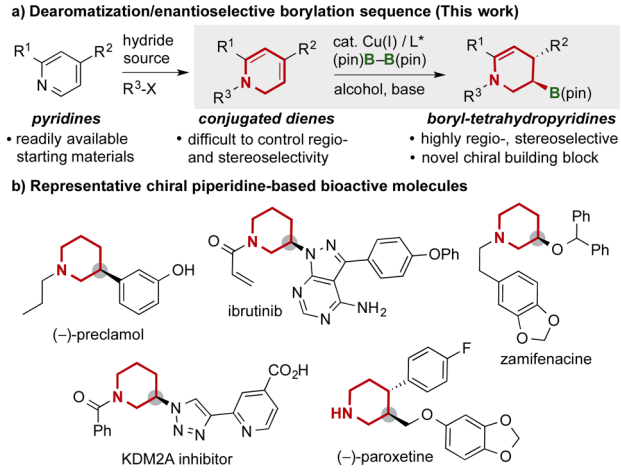
Supporting Information

ABSTRACT: We have developed a novel approach for the synthesis of enantioenriched 3-boryl-tetrahydropyridines via the Cu(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 is demonstrated for the concise synthesis of the antidepressant drug (−)-paroxetine. A theoretical study of the reaction mechanism is also 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 toward 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 Cu(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*-acylpyridinium salt as the substrate under Cu(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 Cu(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/Cu(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

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



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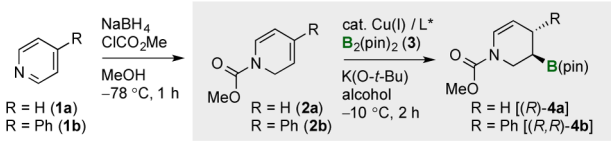
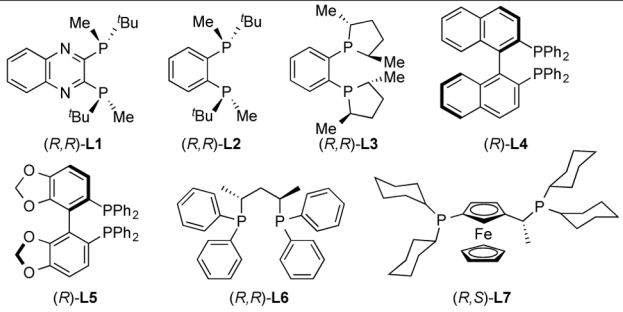
stereocenter, which are important components in various pharmaceutical drugs (Scheme 1b).[1] In actual fact, the antidepressant drug (−)-paroxetine was successfully synthesized in this study using our newly developed approach. A theoretical study of the reaction mechanism has also been described.

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 Cu(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 (dr 99:1). Based on this result, we conducted a series of optimization reactions using **2b** as a substrate (see the Supporting Information (SI) 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 (dr 97:3, 92% ee) (Table 1, entry 14).[12] The *anti*-configuration of (*R*,*R*)-**4b** was confirmed by NOE analysis (see SI 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 Cu(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-dihydropyridines (**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 Cu(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 (dr 96:4−98:2, 93−96% ee). However, the reactions of **2m** and **2n** in the presence of the Cu(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 effect 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

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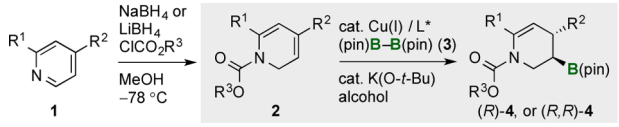
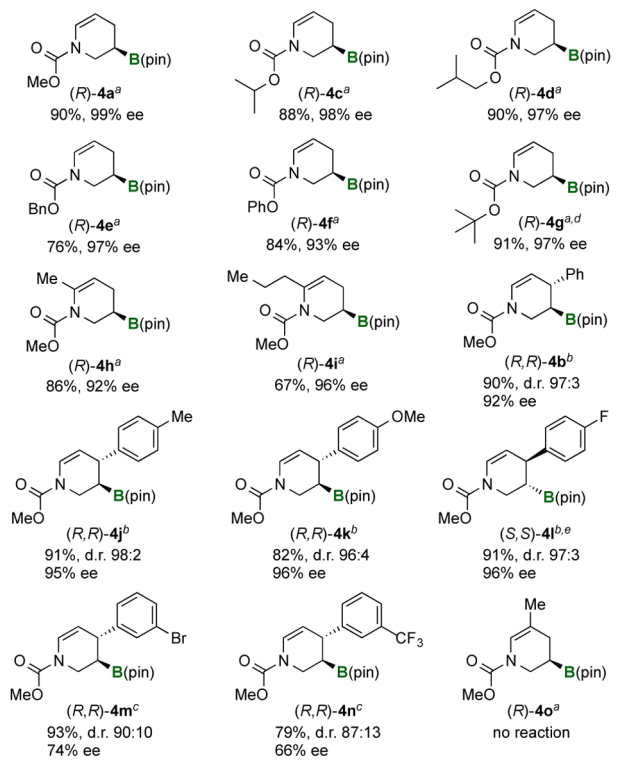
Table 2. Substrate Scope of the Cu(I)-Catalyzed Enantioselective Borylation of 1,2-Dihydropyridines



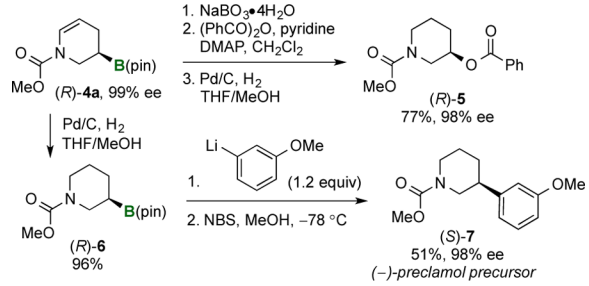


[a]Conditions: CuCl (0.025 mmol), (*R*,*R*)-**L1** (0.025 mmol), **2** (0.5 mmol), **3** (0.6 mmol), MeOH (1.0 mmol), and K(O-*t*-Bu) (0.1 mmol) in THF at −10 °C for 2 h. [b]Conditions: CuCl (0.025 mmol), (*R*)-**L5** (0.025 mmol), **2** (0.5 mmol), **3** (0.6 mmol), *t*-BuOH (1.0 mmol), and K(O-*t*-Bu) (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.

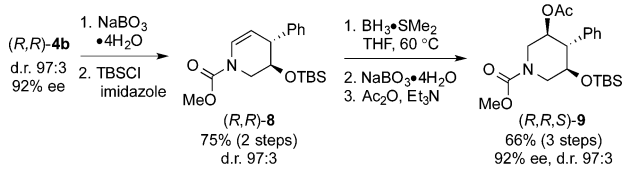
acylation of the resulting alcohol and reduction of the enamine moiety afford the chiral piperidinol (*R*)-**5** with high enantiomeric excess (Scheme 2). Furthermore, the hydrogenation of (*R*)-**4a** gave (*R*)-**6**, which was reacted with (3-methoxyphenyl)lithium under Aggarwal's cross-coupling conditions[14] 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).

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

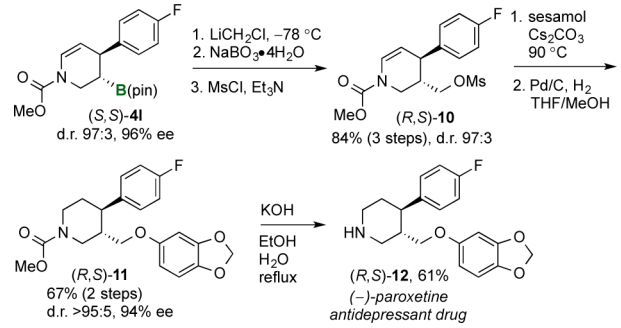
Scheme 2. Derivatization Reactions of (*R*)-4a



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



Scheme 4. Synthesis of (−)-Paroxetine



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.

A deuterium labeling experiment was conducted to probe the reaction mechanism (see the SI 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 (>95% D), 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 borylcupra-

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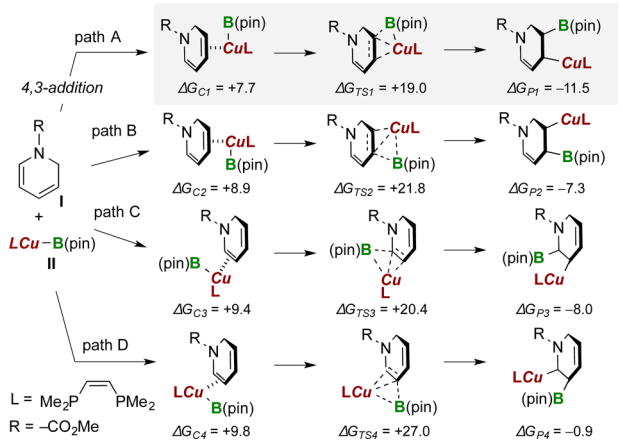

Figure 1. Density functional theory calculations for the four regioisomeric pathways A–D (B3PW91/cc-pVDZ). Relative *G* values (kcal/mol) at 298 K, 1.0 atom in the gas phase.

tion 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]

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 C-3 stereocenter in combination with a stereospecific boron functionalization process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01375.

Experimental procedures and data (PDF)

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Notes

The authors declare no competing financial interest.

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(10) Foowler, 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 Cu(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 SI.

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(16) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.

(17) The reaction pathway is proposed in the SI.

(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 SI.

(19) The details of the calculations are included in the SI.

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