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Communication

# Iridium-Catalyzed Enantioselective #-C(sp3)-H Borylation of Azacycles

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# Iridium-Catalyzed Enantioselective α-C($sp^3$)-H Borylation of Azacycles

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*Supporting Information Placeholder*

**ABSTRACT:** We herein report an iridium-catalyzed enantioselective α-C($sp^3$)-H borylation of a wide range of azacycles. The combination of an iridium precursor and a chiral bidentate boryl ligand has shown effectively differentiating enantiotropic methylene C-H bonds from a single carbon center, affording a variety of synthetically useful azacycles from readily available starting materials with good to excellent enantioselectivities.

Optically active α-functionalized azacycles, particularly tetrahydroisoquinolines (THIQs), pyrrolidines, and piperidines are a large family of natural products with extensive structural diversity and biological activity (Figure 1).[1] The importance of these structures has been evidenced by their frequent use in drug discovery,[1e,2] synthetic chemistry,[3] and organocatalysis.[4] Accordingly, the development of efficient methods for the stereo-controlled synthesis of these frameworks has, therefore, attracted a great deal of attention. Generally, the *de novo* ring-closure is a commonly used strategy to assemble these frameworks.[5] On the other hand, direct asymmetric transformations of readily available azacycles also provide effective methods, including examples of hydrogenations isoquinolines and dihydroisoquinolines,[6,7] deracemizations and cross-dehydrogenative couplings of THIQs,[8,9] dearomatization of pyridinium salt,[10] and α-functionalization of pyrrolidines (Scheme 1A).[11] Another attractive alternative approach to the synthesis of these structures is transition-metal-catalyzed enantioselective α-C($sp^3$)-H functionalization of methylene C-H bonds (Scheme 1B).[12] In this context, Yu and coworkers reported the first elegant example of Pd-catalyzed enantioselective α-C($sp^3$)-H arylation of azacycles with arylboronic acids using thioamides as directing groups.[13] The Glorius group developed a Rh-catalyzed thioamide-directed α-C($sp^3$)-H arylation of azacycles with aryl iodides.[14] Nonetheless, this area is still underexplored and there remain distinct challenges. Firstly, the reaction type is limited to C-Ar bond formations; Secondly, the direct C($sp^3$)-H activation of THIQs' C1 positions remains elusive. In views of the importance of the C1-functionalized THIQs, and the diversity of α-substituents of saturated azacycles, it is appealing to develop novel and complementary α-C($sp^3$)-H functionalization methods. In this regard, the development of C($sp^3$)-H borylation could provide an attractive protocol in combination with well-established stereospecific transformations of the stereogenic C-B bonds.[15] It should also be noted that the borylated products, namely α-aminoboronates, have also served as key constituents in medicinal chemistry (Figure 1),[1e] and their stereo-controlled synthesis usually depends on chiral auxiliaries[1e] and catalytic asymmetric borylation of π-unsaturated bonds.[16] Their atom- and step-economic synthesis remains a formidable challenge.[17]

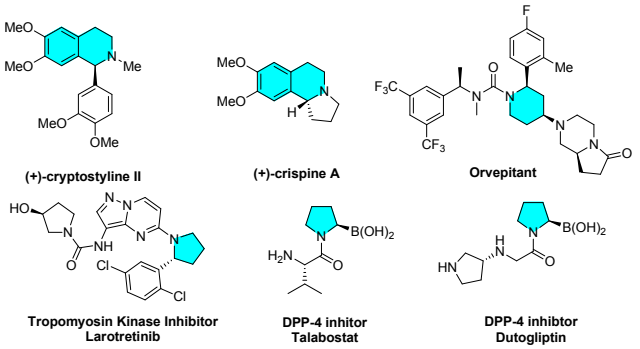
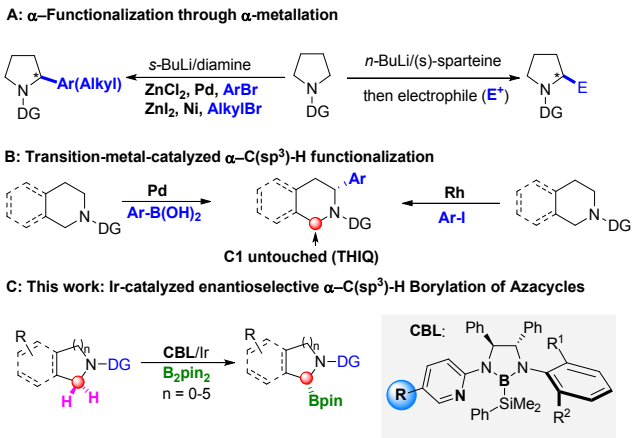


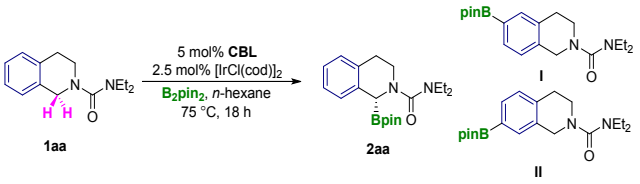

Figure 1. Selected examples of bioactive chiral α-functionalized azacyles.

## Scheme 1. Asymmetric Synthesis of α-Functionalized Azacycles via α-C-H Functionalization



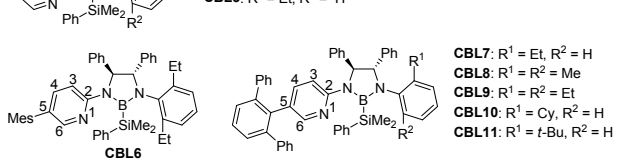
Enantioselective transition-metal-catalyzed C-H borylation has emerged as a viable approach to obtain enantioenriched organoboron compounds with atom- and step-economy.[17,18] However, it still suffers from limited reaction types. For example, although several elegant systems have been established to control regioselectivity of methylene C-H borylation of heterocycles enabled by Ir- and Rh-catalysis,[19] their asymmetric variants remain underdevloped.[17] The deficiency of research may arise from the lack of an adequate catalyst[12b] and difficulty in chiral differentiation of two enantiotopic methylene C-H bonds from a single carbon center.[12a,13, 17,20] Recently, we disclosed Ir-catalyzed asymmetric C($sp^2$)-H borylation of diarylmethylamines[19d] and C($sp^3$)-H borylation of cyclopropanes[19e] using chiral bidentate boryl ligands (**CBL**s). The chiral induction was accomplished by desymmetrization of two enantiotropic carbons. As a continuous effort in this field, we herein report an Ir-catalyzed enantioselective methylene α-C($sp^3$)-H borylation of azacycles using modified **CBL**s for the first time (Scheme 1C). Notably, the borylation occurs at C1 positions of the THIQ substrates.

**Table 1. Optimization of Reaction Conditions for Iridium-Catalyzed Enantioselective C($sp^3$)-H Borylation of 1aa.**[a]




| entry | CBL | rr[b] | yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|
| 1 | **CBL1** | 63:37 | 27 | 30 |
| 2 | **CBL2** | 80:20 | 78 | 53 |
| 3 | **CBL3** | 90:10 | 88 | 64 |
| 4 | **CBL4** | 60:40 | 57 | 72 |
| 5 | **CBL5** | 94:6 | 86 | 85 |
| 6 | **CBL6** | 98:2 | 69 | 82 |
| 7 | **CBL7** | >99:1 | 81 | 88 |
| 8 | **CBL8** | >99:1 | 90 | 88 |
| 9 | **CBL9** | >99:1 | 91 | 93 |
| 10[e] | **CBL9** | >99:1 | 90 | 94 |
| 11[e] | **CBL10** | >99:1 | 73 | 94 |
| 12[e] | **CBL11** | >99:1 | 78 | 94 |

[a]Unless otherwise noted, all the reactions were carried out with **1aa** (0.20 mmol), $B_2pin_2$ (0.30 mmol), **CBL** (0.01 mmol), $[IrCl(cod)]_2$ (0.005 mmol) in *n*-hexane (2.0 mL) at 75 °C for 18 h. [b]rr refers to the regioisomeric ratio of **2aa**/(**I**+**II**) and was determined by GC analysis. [c]Isolated yield. [d]The enantiomeric excesses were determined by HPLC on a chiral stationary AD-H column. [e]The reaction was carried out at 70 ˚C for 18 h.

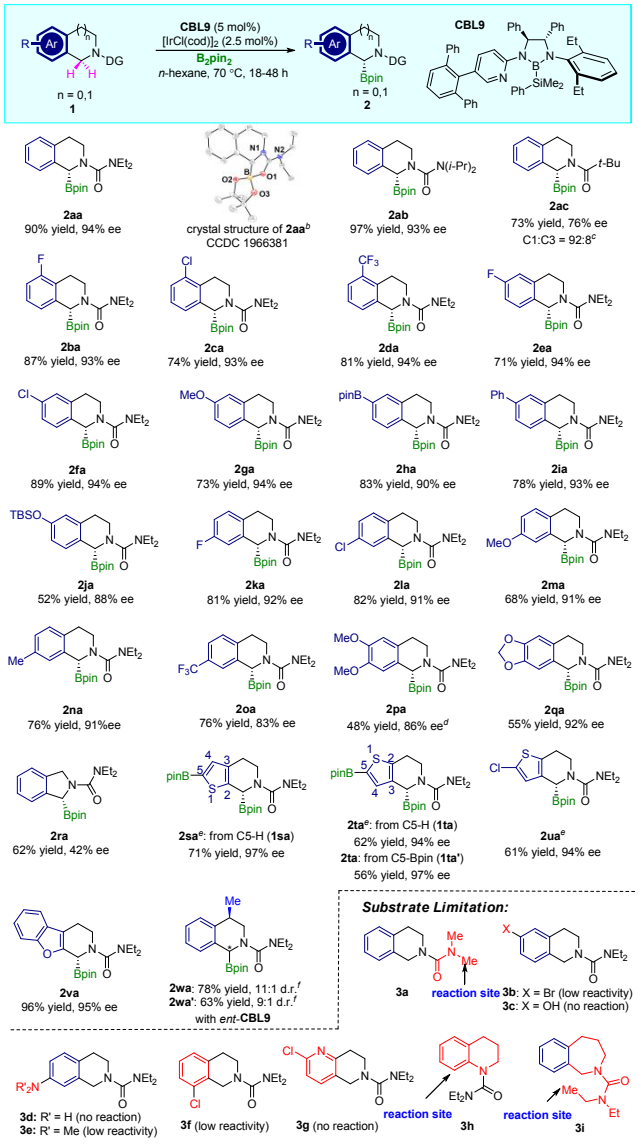



Our research commenced with the optimization of reaction conditions using THIQ **1aa** with the directing group diethylcarbamoy as the pilot substrate. Preliminary experiment of **1aa** with $B_2pin_2$ (Bis(pinacolato)diboron) in the presence of of 2.5 mol% of $[IrCl(cod)]_2$ (cod = 1,5-cyclooctadiene) and 5.0 mol% of **CBL1** ($R^1$ = 3,5-$Me_2C_6H_3$, $R^2$ = H) in *n*-hexane at 75 ˚C for 18 h afforded C1-borylated **2aa** as a sole C($sp^3$)-H product in 27% yield with 30% ee (Table 1, entry 1). Meanwhile, the reaction could not complete and a significant amount of C($sp^2$)-H borylated products **I** and **II** were also observed. The regioisomeric ratio (rr) of **2aa**/(**I**+**II**) is 63:37. These initial results encouraged us to further investigate the effects of ligand substituents on both rr and stereoselectivity. **CBL2** bearing $R^1$ of Me and $R^2$ of H resulted in complete conversion with elevated rr (80:20) and 53% ee (Table 1, entry 2). When **CBL3** containing $R^1$ of Et and $R^2$ of H was used, the reaction performed superiorly in terms of both rr (90:10) and ee (64%) compared to **CBL2** (Table 1, entry 3). Then, we moved on to **CBL** with $R^1$ and $R^2$ being both alkyl substituents. Pleasingly, the use of **CBL5** bearing both $R^1$ and $R^2$ of ethyl groups gave excellent rr (94:6) and good enantioselectivity (Table 1, entry 5). To further suppress C($sp^2$)-H by-products and improve the enantioselectivity, we then focused on the effect of the pyridine ring substituent. To our great delight, **CBL**s with 2,6-$Ph_2C_6H_3$ at pyridine's C5-position could afford **2aa** as a sole product with superior ee (Table 1, entries 7-9). Particularly, **2aa** was obtained in 91% isolated yield with 93% ee when **CBL9** was used (Table 1, entry 9). Further examination of other reaction conditions including temperature and solvent revealed that *n*-hexane and 70 ˚C were optimal,[21] giving **2aa** with 90% yield with 94% ee (Table 1, entry 10). The use of **CBL10** and **CBL11** under otherwise identical reaction conditions showed lower reactivity although almost the same level of enantioselectivities was achieved (Table 1, entries 11 and 12).

Having optimized reaction conditions in hand (Table 1, entry 10), we then investigated the additional substrate scope of the current reaction as displayed in Table 2. In addition to the diethylcarbamoyl, pivaloyl group could also result in complete conversion, affording **2ac** with inferior enantioselectivity (76%) along with the formation of 8% C3-borylated by-product. Switching from the diethylcarbamoyl (**1aa**) to the diisopropylcarbamoyl (**1ab**) did not affect the enantioselectivity (**2ab** vs **2aa**). Next, we surveyed THIQs having different substituents on the fused aromatic ring while maintaining *N*-substituent of the diethylcarbamoyl. Most of C5, C6, and C7 substituted substrates gave the corresponding products (**2ba**-**2oa**) in good yields (68-89%) with consistently excellent ee values (90-94%). Disubstituted THIQs **1pa** and **1qa** showed inferior reactivity, affording products **2pa** and **2qa** with 86% and 92% ee, respectively. The chiral induction for the reaction of isoindoline **1ra** was inferior, yielding **2ra** with only 42% ee. Heteroaromatic ring fused substrates could also be well tolerated, giving products **2sa**-**2va** in 94-97% ee. The C($sp^2$)-H borylation of **1sa** and **1ta** is probably caused by more reactive and sterically less hindered C($sp^2$)-H bond of thiophene compared to benzene ring.[22] We also investigated the tolerance of chiral substrate. The reaction of substrate with stereogenic center at C4 position in the presence of **CBL9** gave product **2wa** in 78% yield with 11:1 d.r. (diasteromeric ratio). The diasteromer of **2wa** (**2wa'**) was obtained in 63% yield with 9:1 d.r. when the enantiomer of **CBL9** (*ent*-**CBL9**) was applied. We also tested arene-fused substrates **3a**-**h,** which either showed very low/no reactivity or gave undesired products.

To further extend the generality of the current protocol, we then investigated the reaction scope of saturated azacycles. We chose pyrrolidine **4a** to re-optimize reaction conditions and **CBL10** bearing a cyclohexyl group gave the best results in terms of both reactivity and stereoselectivity, delivering **5a** in 99% yield with 94% ee.[21] Pleasingly, All the reactions of pyrrolidine derivatives underwent smoothly (Table 3), affording most borylated products (**5a-g**) with excellent ee values (90-96%). Other saturated azacycles with

TABLE 2. Substrate Scope of THIQ **1** [a]

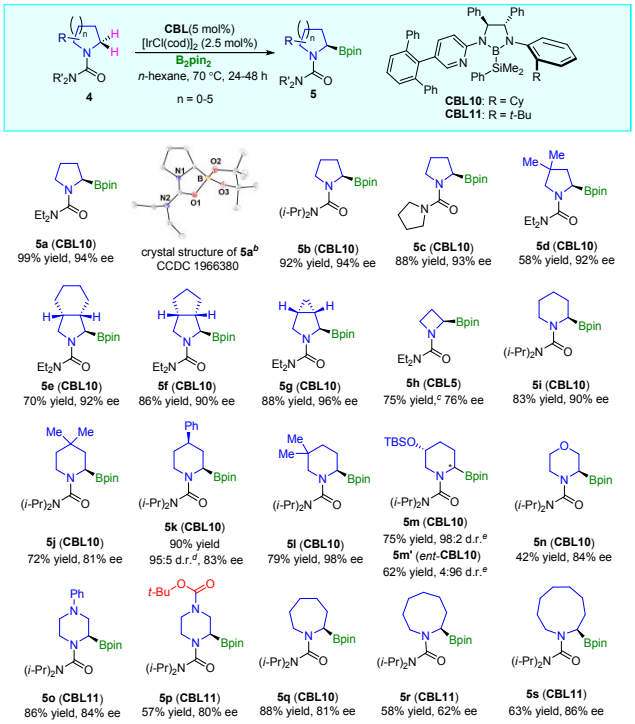



[a]Unless otherwise noted, all the reactions were carried out at 70 °C for 18-48 hours. [b]For the sake of clarity, all the hydrogen atoms are omitted for the crystal structure of **2aa**. [c]The ratio of C1:C3 was determined by GC analysis. [d]The reaction were carried out 80 °C with 10 mol% catalyst. [e]3.0 equivalents of $B_2pin_2$ were used. [f]The d.r. values were determined by $^1H$ NMR.

varying ring size (**4h-s**) were also investigated. For example, borylated azetidine **5h** was obtained in 75% yield with 76% ee in the presence of **CBL5**.[21] In order to suppress competitive methylene C($sp^3$)-H borylation of *N*-ethyl group, directing group *N*,*N*-diisopropylcarbomyl was used when the ring size of saturated azacylcle is greater than five. Piperidine derivatives could afford **5i-m** in good yields with enantioselectivity ranging from 81% to 98%. The current reaction is also compatible with azepane **4q**, providing **5q** in 88% yield with 81% ee. Morpholine and piperazine derivatives could also be well tolerated with adequate ligands,[21] affording **5n-p** with good ee values (80-84%). When the ring size of substrate is greater than 7, inferior both reactivity and enantioselectivity were observed (**5r** and **5s**) with optimized ligand **CBL11** was used.[21] Absolute configurations of **2aa** and **5a** were determined to be *R* by single crystal X-ray diffraction analysis.[23] The configurations of other products were assigned as the same tentatively by analogy.

Next, we examined the borylation of several azacycle related bioactive compounds as shown in Figure 2. Both **CBL9** and *ent*-**CBL9** gave excellent d.r. values for the reaction of *estradiol*-derived THIQ. The borylation of *α-D-galactopyranose*-derived piperidine

Table 3. Substrate Generality Saturated Azacycles **3** [a]




[a]Unless otherwise noted, all the reactions were carried out at 70 °C for 24-48 hours. [b]For the sake of clarity, all the hydrogen atoms are omitted for the crystal structure of **5a**. [c]The yield and ee value of **5h** refer to its vinylation product, see Supporting Information for more details. [d]The relative configuration of **5k** was determined by single crystal X-ray diffraction analysis (CCDC 1998616). [e]The d.r. values were determined by GC analysis.

and the key motif of *Zamifenacine* occurred smoothly using **CBL10**, giving respective products **7** and **8** with >95:5 d.r. values. Inferior performance was observed for when *ent*-**CBL10** was applied. Borylation of *N*-carbamoyl *Paroxetine* and *Lorcaserin* using **CBL10**, however, showed very low reactivity. Borylation of *N*-carbamoyl *Paroxetine* and *Lorcaserin* using *ent*-**CBL10** afforded corresponding products **9'** and **10'** in 54% and 91% yields with 15:85 and 2.5:97.5 d.r. values. These results show that the current protocol provides a promise of enabling late-stage functionalization of azacycle related bioactive compounds.

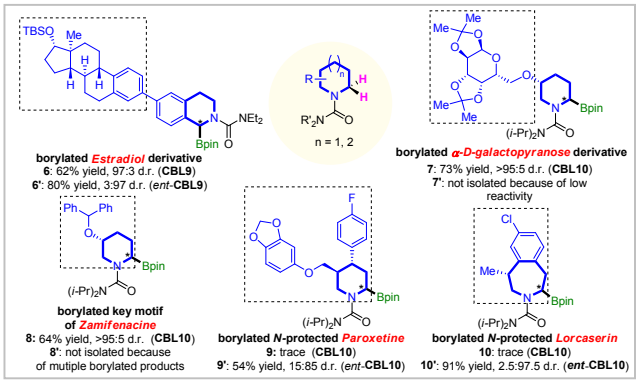



Figure 2. C($sp^3$)-H borylation of bioactive related azacycles.

The current reaction is also amendable to gram-scale synthesis with 1 mol% catalyst loading while maintaining enantioselectivity (Figure 3). To further demonstrate the synthetic utility, a series of transformations of **2** were conducted as depicted in Figure 2. The pinacol group of **2aa** could be easily removed by $KHF_2$ to afford difluoroborane **11** in 94% yield with 95% ee.[24] The C-B bond of compound **2aa** could undergo arylation, homologation, and homologation/oxidation, affording corresponding products **12**-**15** in 62-80% yields without erosion of stereochemistry under various reaction conditions.[18d,25] Importantly, the diethylcarbamoyl group of **16** could be easily removed by LiOH, providing alkaloid (+)-*calycotomine*[26] **17** in 87% yield.

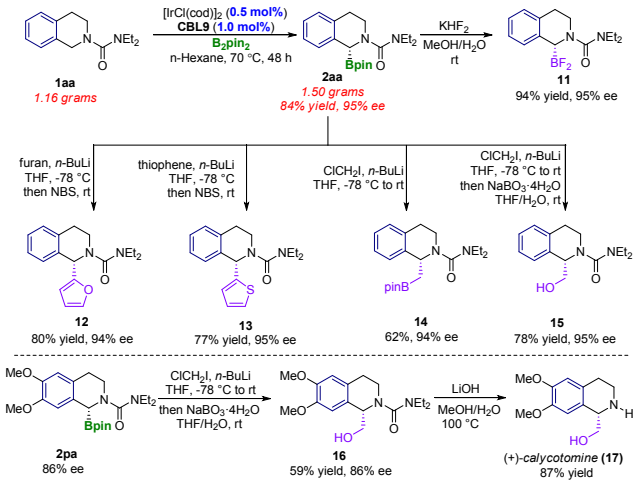



Figure 3. Gram-scale C($sp^3$)-H borylation of **1aa** and synthetic utility of borylated product **2**.

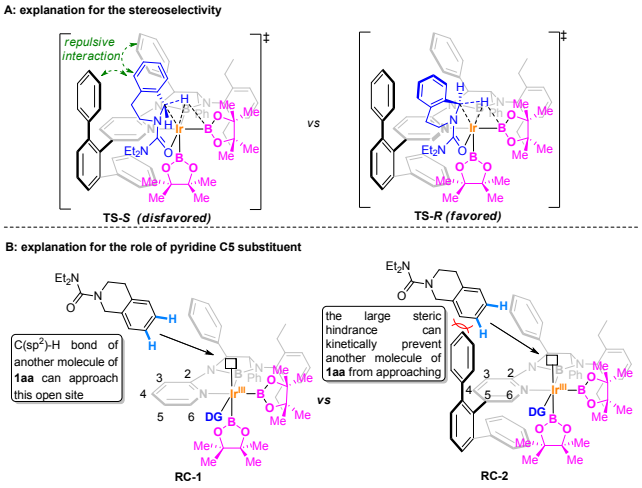



Figure 4. A) Explanation of the origin of stereoselectivity. B) Putative reactant complexes (**RC**) to explain the effect of pyridine C5 substituent on regioselectivity.

We found that the ee value of **2aa** is not only independent of the ratio of **CBL9**/$[IrCl(cod)]_2$, but also proportional to the optical purity of **CBL9,**[27] indicating that the most plausible reactive catalytic species is a monomeric Ir complex in which the ratio of **CBL9**/Ir is 1:1. Together with in-situ NMR evidence,[27] the plausible catalytic scenario is similar to C-H borylation that we previously reported,[18d,18e] in which a 14-electron chiral trisboryl Ir complex is responsible for both regio- and enantioselectivity.[28] According to the known reaction mechanism, the C-H activation step is synergistically assisted by Ir-B bond.[18d,29] Thus, two putatively transition states TS-*S* and TS-*R* that lead to S and *R* isomers, respectively, are proposed in Figure 4A to explain the origin of enantioselectivity. In TS-*S*, the THIQ ring points to the phenyl group of the (1*S*,2*S*)-DPEN ((1S,2S)-diphenylethylenediamine) moiety and pyridine's C5 substitution, which causes the repulsive interaction. On the other hand, there is no such repulsion in the TS-*R*. Therefore, it should be lower in energy barrier to undergoing oxidative addition, favoring the product with *R* configuration. To explain why **CBL9** could prohibit C($sp^2$)-H borylation, two putative reactant complexes (**RC**) **RC-1** and **RC-2** for the **CBL5** and **CBL9** are proposed respectively in Figure 4B. Obviously, the planarity of the pyridine ring in **RC-1** causes the apical vacancy of the iridium center to be exposed to the external C($sp^2$)-H bonds approaching from pyridine's side, while the other directions are blocked by Bpin, **1aa** (DG), ligand scaffold, and *N*-aryl substitution. This 16-electron trisboryl iridium complex is similar to that in the dtbpy/iridium system (dtbpy = 4,4'-di-tert-butyl-2,2'-bipyridine),[27a] which could cleave sterically less hindered C($sp^2$)-H bond of another molecule of **1aa**. In contrast, the vacant site of **RC-2** is in part shielded by the group of 2,6-$Ph_2C_6H_3$ of the pyridine ring. As a result, it could kinetically prevent another molecule of **1aa** from approaching to suppress competitive C($sp^2$)-H borylation.

In summary, we have developed a highly efficient Ir-catalyzed enantioselective α-C($sp^3$)-H borylation of azacycles using **CBL**s for the first time. This method could tolerate a wide range of functional groups, providing a series of enantioenriched α-borylated products in good yields with good to excellent enantioselectivities. Further utilization of products and application of **CBL**s in other contexts of asymmetric transformations are currently underway in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxx.
Experimental procedures, spectroscopic data. (PDF)
Crystallographic data of **2aa**, **5a, 5k**, and **S6h.** (CIF)

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### Author Contributions

§L. Chen and Y. Yang contributed equally to this work.

### Notes

The authors declare no competing financial interests.

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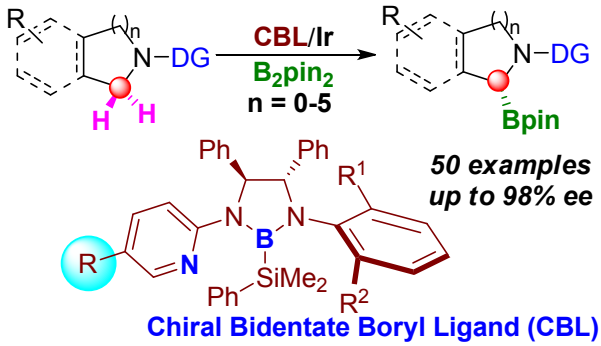
R
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SiMe2
Ph
R2
50 examples
up to 98% ee
Chiral Bidentate Boryl Ligand (CBL)