A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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Authors: Rongrong Du, Luhua Liu, and Senmiao Xu

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202016009

Link to VoR: https://doi.org/10.1002/anie.202016009

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Iridium-Catalyzed Regio- and Enantioselective Borylation of Unbiased Methylene C(sp^3)-H Bonds at the Position Beta to a Nitrogen Center

Rongrong Du,[a][b]‡ Luhua Liu,[a][b]‡ and Senmiao Xu*[a][c]

Dedication ((optional))

[a] Ms. R. Du, Mr. L. Liu, and Dr. S. Xu
State Key Laboratory for Oxo Synthesis and Selective Oxidation, Center for Excellence in Molecular Synthesis, Suzhou Research Institute
Lanzhou Institute of Chemical Physics
Chinese Academy of Sciences
Lanzhou 730000, China
E-mail: senmiaoxu@licp.cas.cn
[b] Ms. R. Du, and Mr. L. Liu
University of Chinese Academy of Sciences
Beijing 100049, China
[c] Dr. S. Xu
Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education
Hangzhou Normal University
Hangzhou 311121, China
‡ R. Du and L. Liu contributed equally to this work

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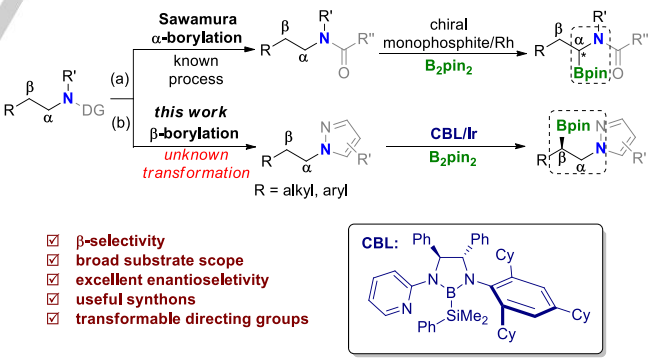
Abstract: Reported here is the first example of pyrazole-directed iridium-catalyzed enantioselective borylation of unbiased methylene C-H bonds at the position beta to a nitrogen center. The combination of a chiral bidentate boryl ligand, iridium precursor, and pyrazole directing group is responsible for achieving high regio- and enantioselectivities. The current method can tolerate a vast array of functional groups, affording corresponding C(sp^3)-H functionalization products in good to excellent enantioselectivities.

Optically active alkyl boronic acid and its derivatives have received considerable interest owing to their diverse applications in synthetic chemistry and drug discovery.[1] Among these, β-aminoboronates are of significant importance as building blocks for many biologically active compounds.[2] Apart from one-carbon homologation of α-aminoboronates,[3] they could also be prepared by means of transition-metal-catalyzed 1,2-aminoboration of alkenes,[4] hydroboration of enamides,[5] conjugate borylation of α-dehydroamino acid derivatives,[6] 1,2-addition of 1,1-diboron compounds to aldimines,[7] and borylative ring opening of 2-arylaziridines.[8] Nevertheless, reactive sites of substrates of the above methods need to be preactivated, which will apparently cost extra reagents and tedious steps.

Recently, transition-metal-catalyzed enantioselective C-H borylation has emerged as an attractive alternative to access chiral organoboron compounds in an atom- and step-economical way.[9] In this context, novel chiral ligands and new strategies developed by Yu,[10] Hartwig,[11] Sawamura,[12] Phipps[13] and our group[14] were capable of enantioselective discrimination of enantiotopic C-H bonds enabled by Pd-, Ir-, and Rh-catalysis. Despite the fact, this area is still underdeveloped compared to asymmetric C-C bond forming reactions. For example, a plethora of α-, β- and γ-selective asymmetric C-H functionalization to form C-C bonds has been accomplished for the amine derivatives.[15-18] In stark contrast, there are only two efficient methods for asymmetric α-C(sp^3)-H borylation (Scheme 1a).[12b, 14d] And, while achiral versions of β-selective reactions have been realized,[19] the enantioselective discrimination of two enantiotopic methylene C(sp^3)-H necessary for asymmetric, β-selective C-H borylation is highly challenging. Thus, it is still appealing to develop novel and complementary methods in this area.



Scheme 1. Regio- and Enantioselective C(sp^3)-H Borylation of Acyclic Amine Derivatives.

Pyrazoles not only possess a broad spectrum of biological activities and pharmaceutical properties,[20] but also are often used as the directing groups in C-H bond functionalization.[21] One benefit of pyrazoles as directing groups is that they could enable the formation of five-membered metallacyclic intermediate to activate C(sp^3)-H bond at the position beta to a nitrogen center. Another distinct advantage is that they could be easily converted to amides through ozonolysis,[22] which makes them synthetically

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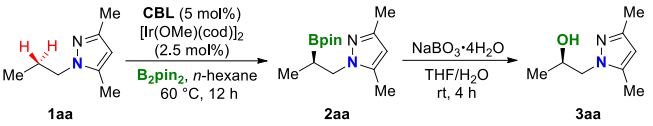
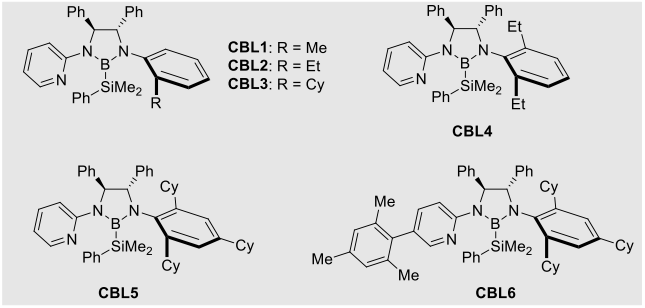
more useful. Thus, the use of pyrazoles in asymmetric C(sp^3)-H functionalization could be poised to provide both optically active pyrazoles and β-chiral amine derivatives. Here, we report our own studies on the use of the chiral bidentate boryl ligand (**CBL**) to enable the pyrazole-directed Ir-catalyzed enantioselective borylation of unbiased methylene C(sp^3)-H bonds at the position beta to a nitrogen center (Scheme 1b).[12,14f,23]

Table 1. Optimization of reaction conditions



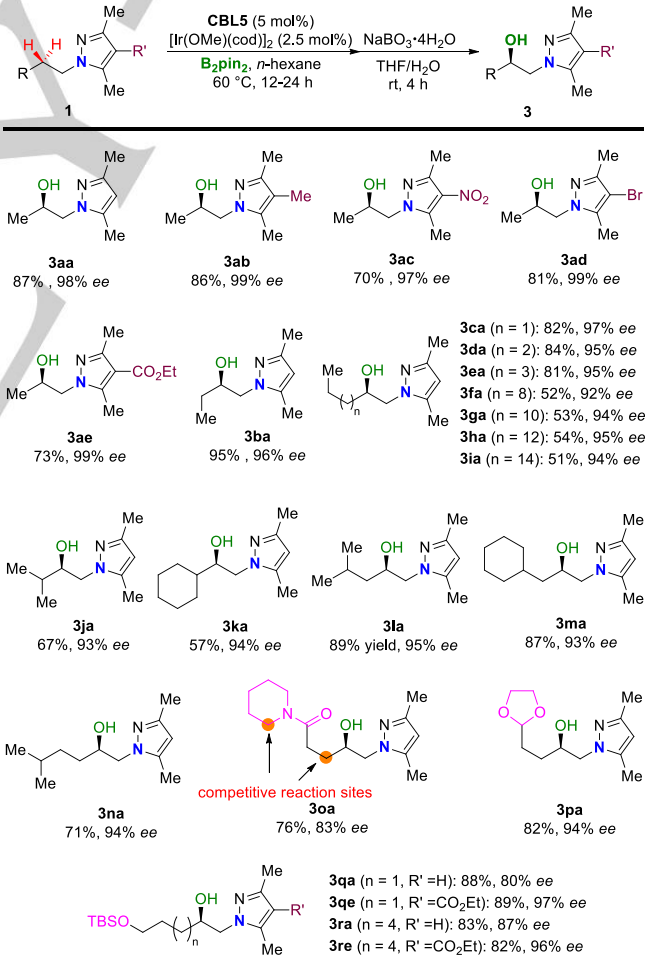


Entry[a]	CBL	Yield (%)[b]	*ee* (%)[c]
1	**CBL1**	71	63
2	**CBL2**	67	67
3	**CBL3**	32	45
4	**CBL4**	23	78
5	**CBL5**	87	98
6	**CBL6**	85	96
7[d]	**CBL5**	74	95
8[e]	**CBL5**	83	95
9[f]	**CBL5**	73	94
10[g]	**CBL5**	trace	n.d.

[a] Unless otherwise noted, all the borylation reactions were carried out with **1aa** (0.2 mmol), B_2pin_2 (0.3 mmol), **CBL** (0.01 mmol), and $[Ir(OMe)(cod)]_2$ (0.005 mmol) at 60 °C in *n*-hexane (2.0 mL) for 12 h. [b] Yield refers to isolated product. [c] Enantiomeric excess (*ee*) value was determined by HPLC on a chiral stationary column OD-H. [d] $[IrCl(cod)]_2$ was used instead of $[Ir(OMe)(cod)]_2$. [e]The reaction was carried out at 70 °C. [f] Cyclohexane was used. [g] Tetrahydrofuran (THF) was used as the solvent.

Our research commenced with the optimization of the reaction conditions using 3,5-dimethyl-1-propyl-1*H*-pyrazole **1aa** as the model substrate as shown in Table 1.[24] Preliminary examination of borylation of **1aa** (0.20 mmol) with B_2pin_2 (bis(pinacolato)diboron) (0.30 mmol, 1.5 equiv) in the presence of 2.5 mol% $[Ir(OMe)(cod)]_2$ (cod: 1,5-cyclooctadiene) and 5.0 mol% **CBL1** in *n*-hexane (2.0 mL) at 60 °C for 12 h resulted in good conversion (Table 1, entry 1). Due to the instability of the borylated product **2aa** during isolation by chromatography on silica gel, the crude reaction mixture was treated with $NaBO_3{\cdot}4H_2O$ to afford **3aa** in 71% isolated yield with 63% *ee*. Notably, no desired product was observed when the reaction was carried out without **CBL1** under otherwise identical reaction conditions. These initial findings encouraged us to further investigate the impact of **CBL**'s substituent on the reaction performance. For example, switching methyl (Me) group to bulkier groups ethyl (Et) (**CBL2**) and cyclohexyl (Cy) (**CBL3**) did not further improve both reactivity and enantioselectivity (Table 1, entries 2 and 3). **CBL** bearing *N*-aryl groups of 2,6-Et_2-C_6H_3 (**CBL4**) resulted in low yield (23%) and moderate enantioselectivities (Table 1, entry 4). To our great delight, when **CBL5** bearing a 2,4,6-Cy_3-C_6H_2 group was used, **3aa** could be obtained in 87% isolated yield with 98% *ee* (Table 1, entry 5). Further tuning the substituent at the pyridine ring resulted in product with slightly lower *ee* value (Table 1, entry 6). With the optimized ligand **CBL5** in hand, we then further surveyed the effect of iridium precursor, temperature, and solvent on the catalytic performance (Table 1, entries 7-10, which indicates $[IrOMe(cod)]_2$, 60 °C and *n*-hexane were optimal in terms of both reactivity and chiral induction.

Table 2. Substrate scope generality



Conditions: all the borylation reactions were carried out with substrate (0.2 mmol), B_2pin_2 (0.3 mmol), **CBL5** (0.01 mmol), and $[Ir(OMe)(cod)]_2$ (0.005 mmol)in *n*-hexane at 60 °C for 12 - 24 h. The crude reaction mixture was then treated with $NaBO_3{\cdot}4H_2O$ (5.0 equiv) in THF/H_2O at rt for 4 h. TBS = *tert*-butyldimethylsilyl.

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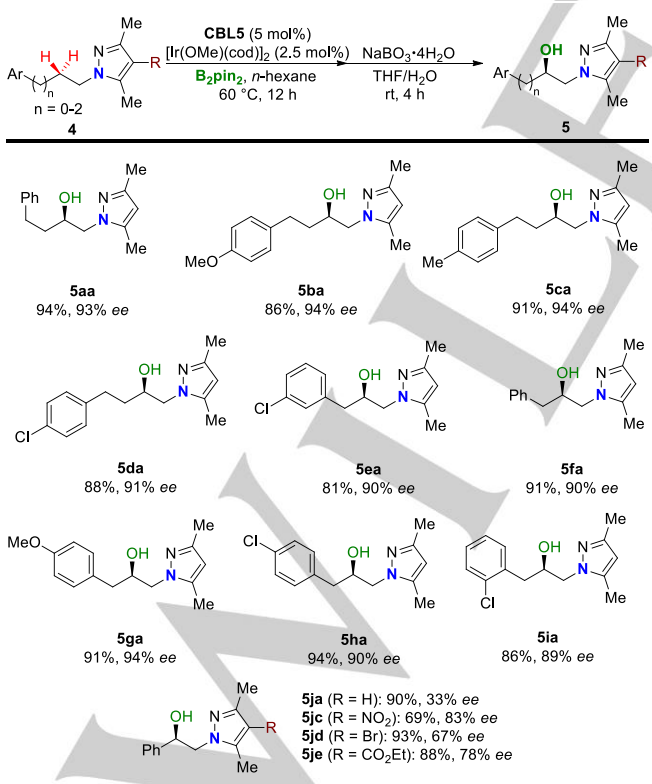
With the optimized reaction conditions in hand, we then determined the additional substrate scope of the current C(sp^3)-H borylation reactions as shown in Table 2. Firstly, we surveyed the tolerance of substituent on the pyrazole ring. Groups such as Me, NO_2, Br, and CO_2Et at C4 position of pyrazole are compatible with the reaction conditions. Corresponding products **3ab**-**3ae** were obtained in 70-86% yields with constantly excellent *ee* values ranging from 97% to 99%. We then focused on the performance of substrates bearing the varying chain length of linear *N*-alkyl group. All the reactions with chain length ranging from four to eighteen carbon atoms proceeded smoothly under standard reaction conditions. Accordingly, products **3ba**-**3ia** were obtained in 51-95% yields with excellent enantioselectivities (92-97%). We then turned our attention to the substrates containing branched *N*-alkyl chain. Pleasingly, products **3ja**-**3na** were obtained in 57-89% yields with excellent *ee* values (93-95%) although the reaction sites are more congested. The current method could also be compatible with substrate containing transformable group such as amide, acetal, and TBS-protected hydroxyl. For example, although there are two amide-directed competitive reaction sites α-C(sp^3)-H of piperidine motif[12b,14d] and β-C(sp^3)-H bond of amide[14f] in substrate **1oa**, **3oa** could be obtained as exclusive product in 76% yield with 83% *ee*. Excellent enantioselectivity (**3pa**: 94%) and good yield was observed when an acetal group resides on the *N*-alkyl chain. Although TBS-protected alcohol derivatives **1qa** and **1ra** gave respective products **3qa** and **3ra** with 80% and 87% *ee*s, excellent enantioselectivities (**3qe**: 97%; **3re**: 96%) were observed when the substrate contains a CO_2Et group at its pyrazole's C4 position.[25]

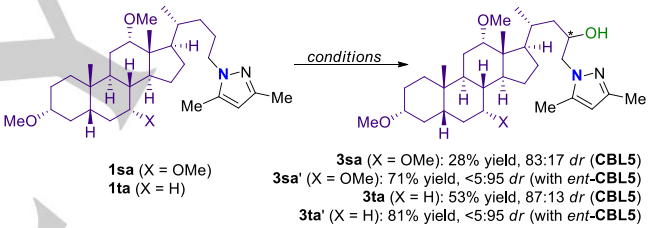
Table 3. Substrate scope generality



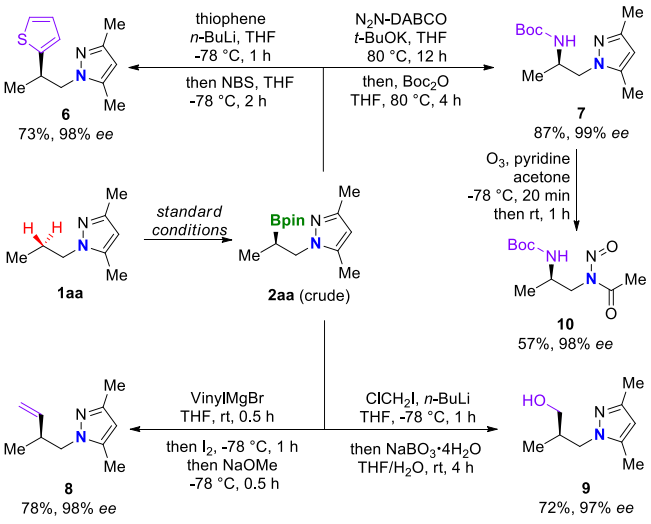
Conditions: all the borylation reactions were carried out with substrate (0.2 mmol), B_2pin_2 (0.3 mmol), **CBL5** (0.01 mmol), and $[Ir(OMe)(cod)]_2$ (0.005 mmol)in *n*-hexane at 60 °C for 12 h. The crude reaction mixture was then treated with $NaBO_3$·$4H_2O$ (5.0 equiv) in THF/H_2O at rt for 4 h.

To further extend the generality of the current reaction, we then moved to substrate bearing an aryl group at the terminal position of linear *N*-alkyl group as shown in Table 3. When the reaction occurred at the non-benzylic position using 3,5-dimethylpyrazole as the directing group, high *ee* values ranging from 89% to 94% were observed for the corresponding products **5aa**-**5ia**. On the other hand, the benzylic functionalized product **5ja** was obtained with low enantioselectivity (33%) probably due to the significant background reaction.[25] Fortunately, the background reaction could be significantly reduced when pyrazole possesses an electron-withdrawing group at its C4 position (**4jc**-**4je**).[25] Particularly, product **5jc** could be obtained in 69% yield with 83% *ee* when a nitro group resides at pyrazole's C4 position.

Next, we applied the current method for the C(sp^3)-H functionalization of cholic and deoxycholic acids derived pyrazoles **1sa** and **1ta** as shown in Scheme 2. Moderate reactivity and diastereomeric ratio (*dr*) were observed when **CBL5** was applied. As a comparison, the use of the enantiomer of **CBL5** (*ent*-**CBL5**) resulted in diastereomers **3sa'** and **3ta'** in 71% and 81% yields with excellent *dr* values. These results not only indicate the stereochemistry of the formation of C-B bonds is predominantly controlled by the catalyst, but also provide a promise of late-stage modification of pyrazole-tethered bioactive compounds.



Scheme 2. Late-stage C(sp^3)-H functionalization of bioactive cholic and deoxycholic acids derived pyrazoles.



Scheme 3. Transformations of crude borylated product **2aa**. NBS = *N*-bromosuccinimide, Boc_2O = di-*tert*-butyl decarbonate, DABCO = 1,4-diazabicyclo[2.2.2]octane.

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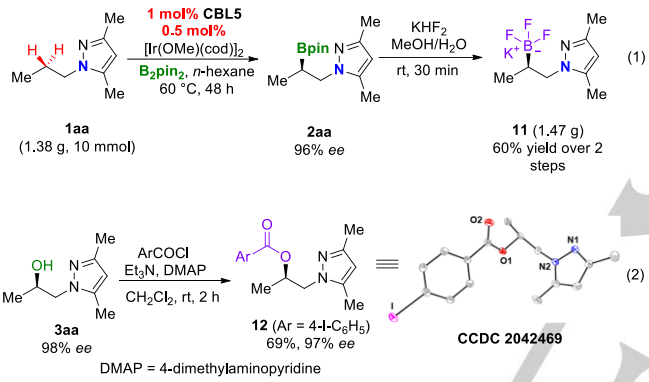
In order to demonstrate the synthetic utility of the current methods, several stereospecific transformations of C-B bond are conducted as shown in Scheme 3. Although borylated product **2aa** is difficult to isolate, the C-B bond of crude **2aa** could undergo a series of stereospecific C-C and C-heteroatom bonds forming reactions under various reaction conditions,[26] providing corresponding β-functionalized pyrazoles **6**-**9** in overall 72-87% yields with 98-99% *ee*. Interestingly, ozonolysis of aminated pyrazole **7** could afford chiral vicinal diamine derivative **10** in 57% yield and 98% *ee* (eq 2).[21f]

By prolonging the reaction time, current method is also amendable to gram-scale borylation of **1aa** (1.38 g, 10 mmol) in the presence of reduced catalyst loading (1.0 mol%) with 96% *ee* (eq 1) which is comparable to that obtained from standard reaction conditions (98% *ee*). The subsequent one-pot treatment of crude **2aa** with KHF_2 afforded potassium trifluoroborate **11** (1.47 g) in 60% yield (eq 1).[27] Finally, the absolute configuration of **3aa** was unambiguously confirmed to be *R* by X-ray single-crystal diffraction analysis of its acyl protected derivative **12** (eq 2).[28]



In summary, we have developed the **CBL**/Ir-catalyzed enantioselective borylation of unbiased methylene C(sp^3)-H bonds at the position beta to a nitrogen center using pyrazole as the directing group. A broad spectrum of functional groups could be well tolerated, affording a variety of β-functionalized chiral pyrazoles with good to excellent enantioselectivities under mild reaction conditions. Both the C-B bond and the pyrazole group of the borylated product could undergo downstream transformations, which shows the potential synthetic utility of the current C(sp^3)-H borylation. Further applications of **CBL**s in other contexts of asymmetric catalysis are currently underway in our laboratory.

Acknowledgements

We thank National Natural Science Foundation of China (21873261 and 91956116), Natural Science Foundation of Jiangsu Province (BK20170422), Hangzhou Normal University (KFJJ2021001), and Lanzhou Institute of Chemical Physics for generous financial support.

Keywords: C-H borylation • asymmetric catalysis • pyrazoles • organoboron • chiral amines

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[24] The use of non-substituted 1-propylpyrazole results in a mixture of multiple mono- and di-borylated products.

[25] *Racemic*-**3qa**, *racemic*-**3ra**, and *racemic*-**5ja** were observed in 8%, 3% and 91% ^{1}H NMR yields without **CBL5** under otherwise identical reaction conditions. While reduced background reactions were observed for substrates **1qe**, **1re**, and **4jc**-**4je** (See supporting information Table S1 for more details). The electron-withdrawing feature of C4 substituent could probably reduce the coordination ability of the C2 nitrogen atom of the pyrazole moiety, which may be the reason for the deceleration of the background reaction.

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[28] Crystallographic data for **12** could be found in the Supporting Information. CCDC 2042469 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

10.1002/anie.202016009

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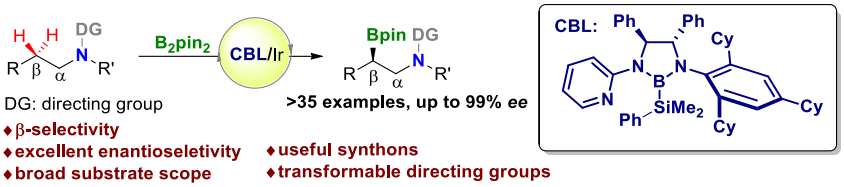

Beta to Nitrogen: Unbiased methylene C(sp^3)-H bonds at the position beta to a nitrogen center could be borylated in an enantioselective manner in the presence of a catalytic amount of the chiral bidentate boryl ligand (**CBL**) and iridium precursor. The method could tolerate a broad spectrum of functional groups, furnishing a variety of C(sp^3)-H functionalized products in good yields with excellent enantioselectivities.