Iridium-Catalyzed Site- and Enantioselective C(sp2)-H Borylation of Benzhydryl Ethers: Enantioselectivity Amplification by Kinetic Resolution Relay

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April 16, 2023

Abstract

We herein report a simple ether-directed iridium-catalyzed site- and enantioselective C(sp2)-H borylation of benzhydryl ethers for the first time. Various chiral benzhydryl ethers were obtained with high enantioselectivities in the presence of a tailor-made chiral bi-dentate boryl ligand. We found that the kinetic resolution relay significantly amplified the enantioselectivity. The synthetic utility of the current method was demonstrated by gram-scale C-H borylation and C-B bond transformations.

Cite this paper:*Chin. J. Chem.* **2023** , *41* , XXX—XXX. **DOI: 10.1002/cjoc.202300XXX**

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Keywords

Asymmetric Catalysis | Benzhydryl Ethers | C-H Borylation | Chiral Bidentate Boryl Ligand | Kinetic Resolution

Comprehensive Summary

We herein report a simple ether-directed iridium-catalyzed site- and enantioselective C(sp^2)-H borylation of benzhydryl eth

Background and Originality Content

Site- and enantioselective C-H functionalization has become a central challenge in modern organic chemistry. In this vein, functional group-directed transition metal-catalyzed C-H activation has emerged as a viable tool to access chiral benzhydryls.[1]Many functional groups can serve as the directing groups (DGs). For example, L-type DGs such as pyridines,[2]imines,[3] and amines,[4]and X-type DGs as exemplified by carboxylic acids,[5] sulfonamides,[6]and silyls[7] are often used (Scheme 1A). The common feature of these DGs is that they can have relatively strong interactions with transition metals. In contrast, less attention has been paid to DGs

that possess extremely weak affinity toward transition metals.[8] For instance, simple ether is one of the most common structural units among bioactive compounds and synthetic intermediates. However, its use as DG in site-selective C-H activation is notoriously difficult, not to mention enantioselective functionalization, due to its extremely low affinity towards transition metals.[9, 10] So far, only a few examples of simple ether-directed site-selective C(sp^2)-H activation have been reported by Hou[10a] and Yu.[10c] Nevertheless, the development of the simple ether-directed site- and enantioselective C(sp^2)-H activation could no doubt provide an attractive and straightforward alternative to valuable chiral benzhydryls.

Scheme 1 Examples of site- and stereoselective *ortho* -C-H borylation of prochiral benzhydryls (**A**) and challenges in simple ether-directed *ortho* -C-H borylation of benzhydryl ethers (**B**).

Functional group-directed transition metal-catalyzed C-H borylation of arenes has been deemd a powerful tool to the synthesis of arylboronates.[11] Accordingly, several catalyst-controlled asymmetric C-H borylation of benzhydryls have been sucessfully developed.[2b, 4, 7, 12] Our laboratory have developed a class of chiral bidentate boryl ligands (**CBL** s) that have shown effectiveness in iridium-catalyzed asymmetric C(sp^2)-H borylation.[4, 13] Recently, we found that simple ether could also serve as a competent DG in the C(sp^3)-H borylation of cyclopropanes.[10e] We envisioned that**CBL** /Iridium catalysis should be suitable for the synthesis of chiral benzhydryl ethers that can be found as important structural motifs among some biologically active molecules.[14] However, two major challenges we must envisage. First, the rather weak affinity of ether function towards transition metals makes the cyclometallation step a daunting challenge, which might cause competitive non-directed C-H borylation (Scheme 1B, i). Second, due to highly reactive of arene C-H bonds, the lack of O-B dative interaction might lead to further directed C-H borylation, which could incur the complexity of the reaction (Scheme 1B, ii). It should be noted that the latter will probably provide us with opportunities to amplify the enantioselectivity through the kinetic resolution (KR) relay if the minor enantiomer undergoes over C-H borylation faster than the major one. Based on our previous study, we surmised that a **CBL**with proper substituents could probably circumvent the problematic issues. Herein, we disclose a general example of simple ether-directed iridium-catalyzed site- and stereoselective C-H borylation of benzhydryl ethers enabled by a tailor-made **CBL** . The KR relay was found crucial to boosting enantioselectivity.

Results and Discussion

Our study commenced with optimizing reaction conditions of benzhydryl methyl ether **1aa** . Preliminary experiment of the reaction of**1aa** with 1.0 equivalent of B_2pin_2 (bis(pinacolato)diboron) in the presence of 5.0 mol% **CBL1** and 2.5 mol% $[IrCl(cod)]_2$ (cod: 1,5-cyclooctadiene) in cyclohexane at 60 °C for 12 h resulted in a mixture of directed monoborylated and diborylated products (**2aa** and **4**) as well as non-directed ones (**3** and **5**) (Table 1, entry 1).[15] Although a poor product ratio was observed, we were pleased to see that the desired **2aa** was formed in 24% GC yield with 20% ee. We then focused on the**CBL** 's substituent effect on the reaction performance. When**CBL** s bearing an *N* -*ortho* -arylphenyl group were used, non-directed byproducts **3** and **5** could be substantially inhibited (Table 1, entries 2-4). In particular, the ratio of **2aa** was lifted to 96.4% and 70% ee was observed when using**CBL4** bearing the Ar of 3,5-*t* -Bu_2-C_6H_3(Table 1, entry 4). However, the reactivity was low and only 18% yield was observed. Gratifyingly, introducing a bulky 2,6-$Ph_2C_6H_3$ at pyridine's C5 position (**CBL5**) not only led to **2aa** in a high product ratio (97.0%) and good yield but also resulted in good ee (Table 1, entry 5). The R group of **CBL** also showed an important impact on the product ratio, reactivity, and enantioselectivity (Table 1, entries 6-8). Notably, when **CBL7** bearing R of *t* -Bu was used, complete conversion was observed (Table 1, entry 7), affording**2aa** in 91% yield (83% isolated yield) with 92% ee. Although the ratio of **2aa** was 87.6%, the ratio of directed products (**2aa** +**4**) was excellent (97.5%). Further tuning solvents (Table 1, entries 9 and 10) and temperature (Table 1, entry 11) revealed that cyclohexane and 60 °C were optimal. Interestingly, the amount of B_2pin_2 significantly affected the product ratio and the enantioselectivity (Table 1, entries 12 and 13). Byproduct **4** was substantially inhibited when 0.50 equivalents and 0.75 equivalents of B_2pin_2 were applied. Notably, the ee of**2aa** increased along with the decreasing ratio of **4** , indicating that the KR was involved in the directed over C-H borylation process.[16] As expected, using 1.3 equivalents of B_2pin_2 furnished **2aa** in diminished

yield (53%) with superior enantioselectivity (96%) (Table 1, entry 14).

Table 1 Optimization of reaction conditions for **1aa** .

entry[a]	**CBL**	**2aa: 3: 4: 5**[b]	Yield(%)[b]	ee (%)[c]
1	**CBL1**	45.5: 27.0: 1.9: 25.6	24	20
2	**CBL2**	92.0: 3.2: 3.2: 1.6	32	57
3	**CBL3**	88.5: 5.1: 3.4: 2.7	25	59
4	**CBL4**	96.4: 2.2: 1.4: 0.0	18	70
5	**CBL5**	97.0: 0.0: 2.6: 0.4	85	88
6	**CBL6**	96.5: 0.0: 3.0: 0.5	88	88
7	**CBL7**	87.6: 0.0: 9.9: 2.5	91(83)[d]	92
8	**CBL8**	94.7: 0.0: 5.1: 0.2	94	87
9[e]	**CBL7**	66.0: 0.0: 27.0: 7.0	62	88
10[f]	**CBL7**	87.6: 1.2: 3.4: 5.8	74	84
11[g]	**CBL7**	80.2: 0.0: 15.4: 4.4	74	88
12[h]	**CBL7**	98.8: 0.0: 1.2: 0.0	65	87
13[i]	**CBL7**	96.2: 0.0: 3.1: 0.7	88	88
14[j]	**CBL7**	57.7: 0.0: 38.8: 3.5	53(52)[d]	96

[a] Unless otherwise noted, all the reactions were carried out with **1aa** (0.20 mmol), B_2pin_2 (0.20 mmol), **CBL** (0.01 mmol), and $[IrCl(cod)]_2$ (0.005 mmol) in cyclohexane (2.0 mL) at 60 °C for 12 h. [b] The ratio and yield were determined by gas chromatograph (GC) with n -octadecane as the internal standard. [c] The enantiomeric excess (ee) was determined by HPLC on a chiral stationary IB column.[d] Yield in parentheses refers to isolated product. [e] n -hexane in lieu of cyclohexane.[f] tetrahydrofuran (THF) in lieu of cyclohexane.[g] 80 °C in lieu of 60 °C.[h] 0.50 equiv B_2pin_2. [i] 0.75 equiv B_2pin_2.[j] 1.30 equiv B_2pin_2.

To gain more insights into the KR relay, we monitored the reaction progress and **2aa** 's ee within 5 h.[15] As illustrated in Scheme 2, the reaction has an approximate 40 min incubation period and **2aa** 's initial ee was less than 80% when**2aa** 's yield was below 10%. As the reaction moved forward, the enantioselectivity gradually climbed. However, diborylated **4**was not detectable at a low yield level of **2aa** . Around 2.5 h, 90% ee was observed when **2aa** reached its highest yield (95%) along with the formation of **4** (5% yield). After that, both**2aa** 's ee and **4** 's yields kept on increasing, whereas**2aa** 's yield dropped slowly. The yield and ee of **2aa**reached 89% and 92% in 5 h, respectively. In addition, several control experiments, as shown in Scheme 3, were conducted to further understand the role of the KR.[15] The reaction of**1aa** with HBpin (pinacolborane) afforded **2aa** in 11% yield with 85% ee (Scheme 3, eq 1), which showed much lower reactivity compared with using B_2pin_2. Notably, byproducts **3** -**5** were not observed. Moreover, we did not observe the KR of enantio-enriched **2aa** (91% ee) using HBpin (Scheme 3, eq 2). In contrast, the KR of enantio-enriched **2aa**(91% ee) using B_2pin_2 afforded directed product **4** (28% yield) along with a tiny amount of non-directed product **5** (**4** : **5** = 91.7: 8.3) (Scheme 3, eq 3). Accordingly, the ee of residual **2aa** was 99%. Meanwhile, the KR of racemic **2aa** using B_2pin_2 resulted in **2aa** with 50% ee, with the concurrent formation of **4** and **5**(**4** : **5** = 97.1: 2.9) (Scheme 2, eq 4). Based on the above results, we could conclude that 1) both B_2pin_2 and HBpin were reactive in the desymmetrization of **1aa** , while the latter showed inferior reactivity but superior enantioselectivity; 2) B_2pin_2 participated in the KR relay to amplify **2aa** 's ee, whereas HBpin was not likely involved in this step; 3) the directed over C-H borylation contributed to the enantioselectivity amplification rather than the non-directed one.

Scheme 2 The reaction progress of **1aa.** Yields were determined by GC analysis.

Scheme 3. Control experiments (B = Bpin). Yields were determined by GC analysis.

Additional substrate scope was then examined, as summarized in Table 2. The dosage of B_2pin_2 depended on the nature of the substituent (See the Supporting Information Table S1 for more details) and superior

performance in terms of enantioselectivity was observed using 1.30 equivalents of B_2pin_2 in most cases. In addition to methyl ether, ethyl and *n* -propyl ethers were also compatible, furnishing respective products **2ab** and **2ac** in 87% and 85% yields with both 91% ee. Interestingly fluoropropyl, chloropropyl, and acetoxyethyl ethers were also compatible, affording corresponding**2ad -af** in 78-87% yields with constantly excellent enantioselectivities (92-98% ee). We next surveyed the tolerance of aryl substituents, showing that most benzhydryl methyl ethers underwent C-H borylation smoothly in the presence of 1.3 equivalents of B_2pin_2 whereas in some cases (**1fa** , **1ma** , **1na** , **1pa** , and**1sa**) the reaction proceeded better using 1.0 equivalent of B_2pin_2. For example,*para* -substituent such as Me, Et, MeO, and Cl worked well, furnishing respective products **2ba -ea** in 49-63% yields with 87-95% ee. The reaction of substrates bearing*meta* -alkyl, MeO, OTBS, NMe_2, Cl, and $SiMe_3$ afforded corresponding **2fa -na** in 47-91% yields with good to excellent enantioselectivities (79-98% ee). In addition, disubstituted aryl groups and naphth-2-yl were also well-tolerated. The corresponding **2oa -ua**

Table 2 Substrate scope.[a]

[a] Unless otherwise noted, all the reactions were carried out with **1** (0.20 mmol), B_2pin_2 (0.26 mmol, 1.3 equiv), CBL7 (0.01 mmol), and [IrCl(cod)]2 (0.005 mmol) in cyclohexane (2.0 mL) at 60 °C for 12 h. TBS: tert-butyldimethylsilyl. b 1.0 equiv of B2pin2. c24 h. dFor the sake of clarity, all the hydrogen atoms are omitted.

were obtained in 44-90% yields with 79-96% ee. Unfortunately, branched alkyl ethers such as **1ag** and **1ah** showed no reactivity presumably due to the congested nature around the donor oxygen atom. Only a tiny amount of borylated product was observed for the reaction of bromoalkyl and methoxyalkyl ethers (**1ai** and **1aj**). The absolute configuration of **2la** was unambiguously determined to be *R* by single-crystal X-ray diffraction analysis.[17] The absolute configurations of the other borylated compounds **2** were tentatively assigned the same by analog.

The weak affinity of ether toward transition metals provided us with an opportunity of realizing high turnover numbers (TON). The C-H borylation of **1aa** (1.0 g) in the presence of 0.2 mol% **CBL7** /Ir under concentrated conditions proceeded smoothly, affording **2aa**in 84% yield (TON = 420) with diminished but still acceptable enantioselectivity (91% ee) (Scheme 4). And the turnover numbers (TON) reached 420. Several C-B bond transformations to demonstrate the synthetic utility. As illustrated in Scheme 4, chlorination, bromination, cyanation, and Suzuki-Miyaura coupling of **2aa**under various reaction conditions furnished **6 -9** in 68-84% yields with 92% ee.[13a, 18]

Scheme 4. A gram-scale C-H borylation of **1aa** and transformations of **2aa** . Conditions: (a) $CuCl_2$, $MeOH/H_2O$, 80 °C, 3 h; (b) $CuBr_2$, $MeOH/H_2O$, 80 °C, 3 h; (c) $Cu(NO_3)_23H_2O$, $Zn(CN)_2$, CsF, $MeOH/H_2O$, 90 °C, 3 h; (d) .0 mol $Pd(OAc)_2$, 2.5 mol% SPhos, ArBr, K_3PO_4, THF/H_2O, 80 °C, 5 h.

Conclusions

In summary, we have developed an effective iridium-catalyzed enantioselective C-H borylation of benzhydryl ethers. A variety of chiral benzhydryl ethers were obtained with high enantioselectivities. The initial mechanistic studies showed that the KR relay during over C-H borylation process is important to amplify enantioselectivity. The current reaction was also amenable to gram-scale C-H borylation in the presence of low catalyst loading without compromising on enantioselectivity. We also demonstrated the synthetic utility by the downstream transformation of the C-B bond.

Experimental

To an oven-dried 25-mL Schlenk tube in a nitrogen-filled glovebox charged with **1** (0.20 mmol), **CBL7** (9.7 mg. 0.01 mmol), $[IrCl(cod)]_2$ (3.4 mg, 0.005 mmol), and B_2pin_2 (50.8 mg or 66.0 mg, 0.20 mmol or 0.26 mmol, 1.0 equiv or 1.3 equiv) was added cyclohexane (2.0 mL). The resulting mixture was allowed to stir at 60 °C for 12 h. After removal of the solvent, the residue was purified by column chromatography on silica gel using petroleum ether/EtOAc as the eluent to afford corresponding **2** .

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

Acknowledgement (optional)

We thank the National Natural Science Foundation of China (92256302 and 91956116), the Natural Science Foundation of Jiangsu Province (BK20211092), the Major Program of the Lanzhou Institute of Chemical Physics, CAS (No. ZYFZFX-9), and Lanzhou Institute of Chemical Physics for generous financial support.

References

[1] a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Transition metal-catalyzed C–H activation reactions: diastereoselectivity and enantioselectivity. *Chem. Soc. Rev.***2009** , *38* , 3242-3272; b) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C–H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017** , *117* , 8908-8976; c) Jerhaoui, S.; Colobert, F.; Wencel-Delord, J. in *C-H Activation for Asymmetric Synthesis* , 2019, pp. 175-192; d) Achar, T. K.; Maiti, S.; Jana, S.; Maiti, D. Transition Metal Catalyzed Enantioselective C(sp2)–H Bond Functionalization. *ACS Catal.* **2020** , *10* , 13748-13793; e) Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. From $Pd(OAc)_2$ to Chiral Catalysts: The Discovery and Development of Bifunctional Mono-*N* -Protected Amino Acid Ligands for Diverse C–H Functionalization Reactions. *Acc. Chem. Res.***2020** , *53* , 833-851; f) Zhang, Q.; Wu, L.-S.; Shi, B.-F. Forging C-heteroatom bonds by transition-metal-catalyzed enantioselective C–H functionalization. *Chem* **2022** ,*8* , 384-413.

[2] a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. PdII-Catalyzed Enantioselective Activation of $C(sp^2)$-H and $C(sp^3)$-H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem. Int. Ed.* **2008** , *47* , 4882-4886; b) Song, P.; Hu, L.; Yu, T.; Jiao, J.; He, Y.; Xu, L.; Li, P. Development of a Tunable Chiral Pyridine Ligand Unit for Enantioselective Iridium-Catalyzed C–H Borylation. *ACS Catal.***2021** , *11* , 7339-7349.

[3] Grosheva, D.; Cramer, N. Enantioselective Access to 1H-Isoindoles with Quaternary Stereogenic Centers by Palladium(0)-Catalyzed C-H Functionalization. *Angew. Chem. Int. Ed.* **2018** , *57* , 13644-13647.

[4] Zou, X.; Zhao, H.; Li, Y.; Gao, Q.; Ke, Z.; Xu, S. Chiral Bidentate Boryl Ligand Enabled Iridium-Catalyzed Asymmetric $C(sp^2)$-H Borylation of Diarylmethylamines. *J. Am. Chem. Soc.* **2019** , *141* , 5334-5342.

[5] a) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. Pd(II)-Catalyzed Enantioselective C-H Olefination of Diphenylacetic Acids. *J. Am. Chem. Soc.* **2010** , *132* , 460-461; b) Xiao, K.-J.; Chu, L.; Yu, J.-Q. Enantioselective C-H Olefination of α-Hydroxy and α-Amino Phenylacetic Acids by Kinetic Resolution.*Angew. Chem. Int. Ed.* **2016** , *55* , 2856-2860.

[6] a) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. Pd-Catalyzed Enantioselective C–H Iodination: Asymmetric Synthesis of Chiral Diarylmethylamines. *J. Am. Chem. Soc.***2013** , *135* , 16344-16347; b) Chu, L.; Xiao, K.-J.; Yu, J.-Q. Room-temperature enantioselective C–H iodination via kinetic resolution. *Science* **2014** , *346* , 451-455; c) Laforteza, B. N.; Chan, K. S. L.; Yu, J.-Q. Enantioselective*ortho* -C–H Cross-Coupling of Diarylmethylamines with Organoborons. *Angew. Chem. Int. Ed.* **2015** , *54* , 11143-11146; d) Xiao, K.-J.; Chu, L.; Chen, G.; Yu, J.-Q. Kinetic Resolution of Benzylamines via Palladium(II)-Catalyzed C–H Cross-Coupling. *J. Am. Chem. Soc.* **2016** , *138* , 7796-7800; e) Plata, R. E.; Hill, D. E.; Haines, B. E.; Musaev, D. G.; Chu, L.; Hickey, D. P.; Sigman, M. S.; Yu, J.-Q.; Blackmond, D. G. A Role for Pd(IV) in Catalytic Enantioselective C–H Functionalization with Monoprotected Amino Acid Ligands under Mild Conditions. *J. Am. Chem. Soc.* **2017** , *139* , 9238-9245.

[7] a) Su, B.; Zhou, T.-G.; Xu, P.-L.; Shi, Z.-J.; Hartwig, J. F. Enantioselective Borylation of Aromatic C-H Bonds with Chiral Dinitrogen Ligands. *Angew. Chem. Int. Ed.* **2017** , *56* , 7205-7208; b) Park, D.; Baek, D.; Lee, C.-W.; Ryu, H.; Park, S.; Han, W.; Hong, S. Enantioselective $C(sp^2)$–H borylation of

diarylmethylsilanes catalyzed by chiral pyridine-dihydroisoquinoline iridium complexes. *Tetrahedron* **2020** , 131811.

[8] Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak coordination as a powerful means for developing broadly useful C-H functionalization reactions. *Acc. Chem. Res.* **2012** , *45* , 788-802.

[9] Alvarez, S. Coordinating Ability of Anions, Solvents, Amino Acids, and Gases towards Alkaline and Alkaline-Earth Elements, Transition Metals, and Lanthanides. *Chem. Eur. J.* **2020** ,*26* , 4350-4377.

[10] a) Oyamada, J.; Nishiura, M.; Hou, Z. Scandium-Catalyzed Silylation of Aromatic C?H Bond. *Angew. Chem. Int. Ed.***2011** , *50* , 10720-10723; b) Iglesias, Á.; Álvarez, R.; de Lera, A. R.; Muniz, K. Palladium-Catalyzed Intermolecular C(sp^3)-H Amidation. *Angew. Chem. Int. Ed.***2012** , *51* , 2225-2228; c) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. Ether-Directed ortho-C–H Olefination with a Palladium(II)/Monoprotected Amino Acid Catalyst. *Angew. Chem. Int. Ed.* **2013** , *52* , 1245-1247; d) Tanaka, K.; Ewing, W. R.; Yu, J.-Q. Hemilabile Benzyl Ether Enables γ-C(sp^3)–H Carbonylation and Olefination of Alcohols. *J. Am. Chem. Soc.***2019** , *141* , 15494-15497.

[11] a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. C-H Activation for the Construction of C-B Bonds.*Chem. Rev.* **2010** , *110* , 890-931; b) Hartwig, J. F. Regioselectivity of the borylation of alkanes and arenes. *Chem. Soc. Rev.* **2011** , *40* , 1992-2002; c) Ros, A.; Fernandez, R.; Lassaletta, J. M. Functional group directed C–H borylation.*Chem. Soc. Rev.* **2014** , *43* , 3229-3243; d) Xu, L.; Wang, G.; Zhang, S. Wang, H.; Wang, L.; Liu, L.; Jiao, J.; Li, P. Recent advances in catalytic C-H borylation reactions. *Tetrahedron***2017** , *73* , 7123-7157; e) Wang, Y.-X.; Zhang, P.-F.; Ye, M. Well-Designed Chiral Ligands for Enantioselective Ir-Catalyzed C(sp2)–H Borylation. *Chin. J. Chem.* **2020** , *38* , 1762-1766; f) Bisht, R.; Haldar, C.; Hassan, M. M. M.; Hoque, M. E.; Chaturvedi, J.; Chattopadhyay, B. Metal-catalysed C–H bond activation and borylation. *Chem. Soc. Rev.* **2022** , *51* , 5042-5100; g) Hoque, M. E.; Hassan, M. M. M.; Haldar, C.; Dey, S.; Guria, S.; Chaturvedi, J.; Chattopadhyay, B. Catalyst Engineering through Heterobidentate (N–X-Type) Ligand Design for Iridium-Catalyzed Borylation. *Synthesis* **2022** , *54* , 3328-3340.

[12] a) Genov, G. R.; Douthwaite, J. L.; Lahdenperä, A. S. K.; Gibson, D. C.; Phipps, R. J. Enantioselective remote C-H activation directed by a chiral cation. *Science* **2020** , *367* , 1246-1251; b) Su, B.; Hartwig, J. F. Development of Chiral Ligands for the Transition-Metal-Catalyzed Enantioselective Silylation and Borylation of C-H Bonds. *Angew. Chem. Int. Ed.* **2022** ,*61* , e202113343.

[13] a) Song, S.-Y.; Li, Y.; Ke, Z.; Xu, S. Iridium-Catalyzed Enantioselective C-H Borylation of Diarylphosphinates. *ACS Catal.***2021** , *11* , 13445-13451; b) Zou, X.; Li, Y.; Ke, Z.; Xu, S. Chiral Bidentate Boryl Ligand Enabled Iridium-Catalyzed Enantioselective Dual C-H Borylation of Ferrocenes: Reaction Development and Mechanistic Insights. *ACS Catal.* **2022** , *12* , 1830-1840; c) Song, S.-Y.; Zhou, X.; Ke, Z.; Xu, S. Synthesis of Chiral Sulfoximines via Iridium-Catalyzed Regio-and Enantioselective C-H Borylation: A Remarkable Sidearm Effect of Ligand. *Angew. Chem. Int. Ed.* **2023** , *62* , e202217130; d) Zhao, H.; Chen, L.; Xia, C.; Xu, S. Enantioselective C-H Borylation for the Synthesis of Axially Chiral N-Aryl phthalimides. *Asian. J. Org. Chem.***2023** , *12* , e202200695.

[14] a) Lepola, U.; Wade, A.; Andersen, H. F. Do equivalent doses of escitalopram and citalopram have similar efficacy? A pooled analysis of two positive placebo-controlled studies in major depressive disorder.*Int. Clin. Psychopharmacol.* **2004** , *19* , 149-155; b) Zat'ura, F.; Všetiča, J.; Abadías, M.; Pavlík, I.; Schraml, P.; Brod'ák, M.; Villoria, J.; Sust, M. Cizolirtine Citrate Is Safe and Effective for Treating Urinary Incontinence Secondary to Overactive Bladder: A Phase 2 Proof-of-Concept Study. *Eur. Urol.* **2010** , *57* , 145-153; c) Li, M.; Zhang, J.; Ma, S.; Jiang, Z.; Di, X.; Guo, X. Chiral separation of five antihistamine drug enantiomers and enantioselective pharmacokinetic study of carbinoxamine in rat plasma by HPLC-MS/MS.*New J. Chem.* **2020** , *44* , 5819-5827.

[15] For the identification of byproducts, see the Supporting Information for more details.

[16] a) Kelly, P.; Lawrence, S. E.; Maguire, A. R. Asymmetric Synthesis of Aryl Benzyl Sulfoxides by

Vanadium-Catalysed Oxidation: A Combination of Enantioselective Sulfide Oxidation and Kinetic Resolution in Sulfoxide Oxidation. *Eur. J. Org. Chem.* **2006** ,*2006* , 4500-4509; b) Yang, X.-H.; Xie, J.-H.; Liu, W.-P.; Zhou, Q.-L. Catalytic Asymmetric Hydrogenation of δ-Ketoesters: Highly Efficient Approach to Chiral 1,5-Diol. *Angew. Chem. Int. Ed.***2013** , *52* , 7833-7836; c) Guo, W.; Luo, Y.; Sung, H. H. Y.; Williams, I. D.; Li, P.; Sun, J. Chiral Phosphoric Acid Catalyzed Enantioselective Synthesis of α-Tertiary Amino Ketones from Sulfonium Ylides. *J. Am. Chem. Soc.* **2020** , *142* , 14384-14390.

[17] Crystallographic data for **2la** could be found in the Supporting Information. CCDC 2232676 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.

[18] a) Murphy, J. M.; Liao, X.; Hartwig, J. F. Meta Halogenation of 1,3-Disubstituted Arenes via Iridium-Catalyzed Arene Borylation.*J. Am. Chem. Soc.* **2007** , *129* , 15434-15435; b) Liskey, C. W.; Liao, X.; Hartwig, J. F. Cyanation of Arenes via Iridium-Catalyzed Borylation. *J. Am. Chem. Soc.* **2010** ,*132* , 11389-11391.

Manuscript received: XXXX, 2023 Manuscript revised: XXXX, 2023 Manuscript accepted: XXXX, 2023 Accepted manuscr

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A chiral bidentate boryl ligand (**CBL**)/iridium catalyst was found effective to enable simple ether-directed iridium-catalyze