Bulky Bipyridine-Type Ligand-Enabled para-Selective C-H Borylation of Aromatic Compounds

Enta, Taisei
Department of Interdisciplinary Engineering Sciences, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Yoshino, Genki
Department of Interdisciplinary Engineering Sciences, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Kuninobu, Yoichiro
Institute for Materials Chemistry and Engineering, Kyushu University

Bulky Bipyridine-Type Ligand-Enabled *para*-Selective C–H Borylation of Aromatic Compounds

Taisei Enta, Genki Yoshino, and Yoichiro Kuninobu*

[†]Institute for Materials Chemistry and Engineering, Kyushu University, 6-1 Kasugakoen, Kasuga-shi, Fukuoka 816-8580, Japan
[‡]Department of Interdisciplinary Engineering Sciences, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasugakoen, Kasuga-shi, Fukuoka 816-8580, Japan

ABSTRACT: We successfully developed a *para*-selective C–H borylation of aromatic compounds using iridium catalysts with bulky bipyridine-type ligands. The key to success is the introduction of bulky substituents (*m*-terphenyl groups) at the 4- and 4′-positions of the bipyridine-type ligands to sterically protect both sides and back of the catalysts, thereby efficiently preventing substrate orientation that gives *ortho*- and *meta*-borylated products. Using these ligands, higher *para*-selectivity was achieved compared to the conventional iridium-catalyzed *para*-selective C–H borylation. Interestingly, high *para*-selectivity was achieved even when using aromatic compounds with small substituents such as ethyl or isopropyl groups on the aromatic ring.

Site-selective C–H transformations have attracted the most attention in recent years because they enable the synthesis of desired organic compounds in a shorter process and are more efficient than conventional synthetic organic reactions.[1] However, site-selective C–H transformations are generally difficult because there are multiple C–H bonds with similar reactivity in organic compounds, and the reaction proceeds at various reaction sites, resulting in a mixture of regioisomers. Therefore, it is important to control site-selectivity with high efficiency; the "directing group method" controls site-selectivity in C–H transformations, and many C–H transformations at the *ortho*-position of directing groups have been reported.[2] Recently, *meta*[3]- and *para*[4]-selective C–H transformations have been reported by using large, precisely designed directing groups, but there are considerably fewer reports of such reactions than those at the *ortho*-position. The greater the distance between the directing group and the reaction site, the larger the structure of the directing group and the more complicated its synthesis. The greater the freedom due to the bond rotation of each bond of the directing group, the more difficult it becomes to precisely control the site-selectivity.

The most remote position in benzene derivatives is the *para*-position, and the realization of site-selective C–H transformations at this *para*-position is difficult but important. The methods for controlling site-selectivity in *para*-selective C–H transformations so far include (a) a method using directing groups (directing group method, Figure 1a),[4] (b) a method using noncovalent bond between a catalyst and a substrate (noncovalent method,[5] Figure 1b),[6] and (c) a method using steric repulsion between a bulky substituent of a substrate and a bulky ligand or bulky Lewis acids and ligands (Figure 1c).[7] Although the "directing group method" in (a) can achieve *para*-selectivity, it requires the synthesis of directing groups with complex structures in advance, introduction of the directing groups to the substrates before the reactions, and removal of the directing groups from the products after the reactions, which increases the number of reaction steps, and the reaction efficiency is not high due to "substrate control". The "noncovalent method" in (b) is "catalyst control" and therefore more efficient than the substrate-controlled "directing group method," but there are not many examples of *para*-selective C–H borylation to date.[6] In method (c) using steric repulsion, the degree of steric repulsion by the bulky bisphosphine ligand is not sufficient (see Figure 2a),[7a,b,e] so the *para*-selectivity was not satisfactory, and aromatic compounds with bulky substituents had to be used as substrates to achieve high *para*-selectivity (substrate and catalyst control).

Organoboron compounds are important starting materials for synthetic organic reactions (e.g., Suzuki-Miyaura cross-coupling reactions and oxidation reactions),[8] organic functional materials,[9] and pharmaceuticals.[10] Therefore, the development of highly efficient synthetic reactions for boron-containing organic compounds is highly desired. To date, synthetic methods for boron-containing aromatic compounds, such as the reactions of Grignard or organolithium reagents with boron sources[11] and the borylation of aromatic halides (Miyaura–Ishiyama borylation),[12] have been used for the synthesis of various useful boron-containing organic compounds. Direct C–H borylation is a more efficient borylation method that can efficiently introduce boryl groups into organic compounds.[1c,13] However, iridium-catalyzed C–H borylation of monosubstituted aromatic compounds leads to borylation at the *meta*- and *para*-positions, yielding a mixture of isomers.[14] Therefore, the control of site-selectivity is an important issue in C–H borylation.

In this study, to avoid the issue of increased freedom of directing groups, a limitation of the directing group method, we used steric repulsion between the catalyst and the substituent of the substrate. Consequently, we developed a new bulky bipyridine-type ligand with two bulky substituents at the 4- and 4'-positions and succeeded in achieving high *para*-selectivity (Figure 1d). In catalytic C–H borylation using conventional ligands, *para*-selectivity is rarely observed for aromatic compounds with small substituents such as isopropyl and ethyl groups (isopropylbenzene and ethylbenzene).[7] However, by

using the new ligand, C–H borylation at *ortho*- and *meta*-positions could be efficiently inhibited, and *para*-selective C–H borylation was achieved.

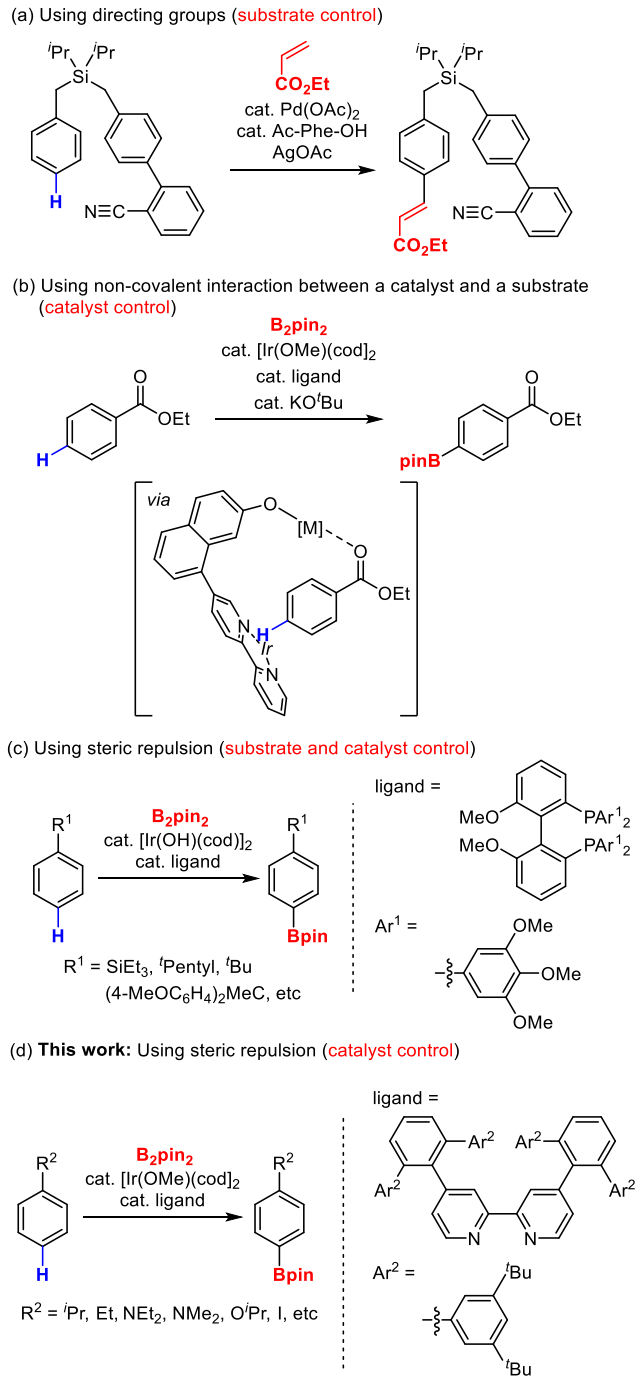


Figure 1. Examples of *para*-selective C–H borylation

Itami, Segawa, and coworkers succeeded for the first time in *para*-selective C–H borylation by steric protection from both sides by aryl groups on the bisphosphine ligand (Figure 2a).[7a,b,e] However, judging from the molecular model, steric protection on both sides appears sufficient but that from the back appears insufficient so that even aromatic compounds with bulky substituents such as isopropyl groups do not have satisfactory *para*-selectivity. To achieve high *para*-selectivity, it is necessary to sterically block not only both sides of the ligand but also the back of the ligand. Therefore, we considered that the introduction of bulky substituents at the 4- and 4'-positions of the bipyridine-type ligand can sterically block both sides and the back of the catalyst. The introduction of these substituents, together with the three boryl groups (Bpin) on the iridium center, may lead to high *para*-selectivity because of the efficient steric repulsion between the catalyst and the substituents on the substrates (Figure 2b).

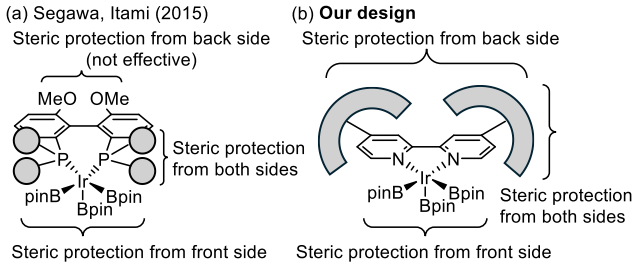
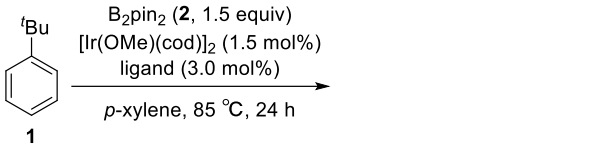


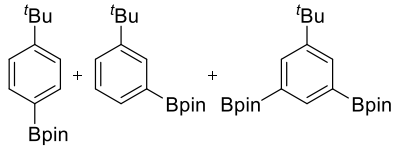
Figure 2. Design of iridium catalysts for *para*-selective C–H borylation

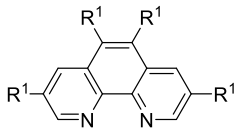
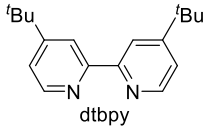
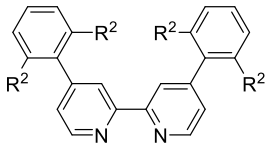
Using *tert*-butylbenzene as the model substrate, several ligands were investigated (Schemes 1 and S1). For phenanthroline ligands often used in iridium-catalyzed C–H borylation reactions, the reaction proceeded preferentially at the *meta*-position rather than at the *para*-position (entry 1). One reason for this is that the *para*-position has a single reaction site, whereas the *meta*-position has two reaction sites; thus, the frequency of the reaction at the *meta*-position is higher than that at the *para*-position. The use of a 1,10-phenanthroline ligand with phenyl groups at the 3-, 5-, 6-, and 8-positions increased the yield; however, the selectivity did not change (entry 2). Although the 1,10-phenanthroline-type ligand with 4-biphenyl groups at 3-, 5-, 6-, and 8-positions did not change the selectivity (entry 3), the phenanthroline ligand with 2-biphenyl groups at 3-, 5-, 6-, and 8-positions significantly increased the selectivity to 96:4 (**3a**:**3a′**), but the reaction hardly proceeded in 2% yield, probably because the ligand was too bulky (entry 4). Next, bipyridine-type ligands were examined, and the dtbpy ligand gave *meta*-borylated product selectively (entry 5). By contrast, 2,2'-bipyridine ligands with 2,6-diarylphenyl groups at the 4- and 4'-positions improved the *para*-selectivity (entries 6–9). Therefore, ligand **L1** was chosen as one of the best ligands, with a good balance between yield and *para*-selectivity (entry 7). Although the yield was slightly lower than that of ligand **L1**, Ligand **L2**, which afforded the highest *para*-selectivity, was selected as the optimal ligand for subsequent studies (entry 9).

Subsequently, several other solvents were investigated (Scheme 2). When the reaction was performed in cyclohexane or hexane using ligand **L1**, the reaction proceeded at the *para*-position selectively (**3a**:(**3a′**+**3a″**) = ca. 7:3), yielding the borylated products in moderate yield (entries 1 and 2). The use of *p*-xylene as the solvent increased the yield of the borylated product to 76% (entry 3). Furthermore, the use of more polar ether solvents, such as dioxane and THF, significantly increased the yield, producing 89% and 95% borylated products, respectively (entries 4 and 5). Interestingly, the *para*-selectivity was similar, regardless of the solvent polarity. These results suggest that the site-selectivity of C–H borylation is controlled by steric repulsion rather than by noncovalent interactions.[5]

Scheme 1. Screening of Several Ligands

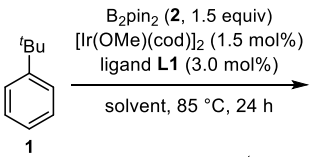


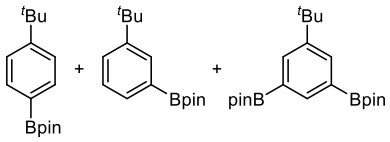


entry	ligand	yield/% (**3a**+**3a'**+**3a''**)[a]	**3a**:(**3a'**+**3a''**)[a]
			
1	R^1 = H	79	28:72
2	R^1 = Ph	93	28:72
3	R^1 = 4-biphenyl	82	30:70
4	R^1 = 2-biphenyl	2	96:4
5	 dtbpy	99	28:72
			
6	R^2 = Ph	99	51:49
7	R^2 = 4-^{t}BuC$_6$H$_4$ (**L1**)	76	70:30
8	R^2 = 3,5-Me$_2$C$_6$H$_3$	73	42:58
9	R^2 = 3,5-^{t}BuC$_6$H$_3$ (**L2**)	70	90:10

[a]Determined by ^{1}H NMR.

Scheme 2. Screening of Several Solvents

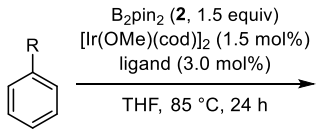


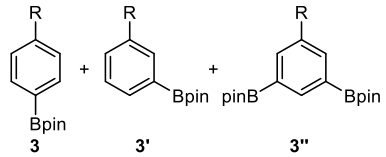


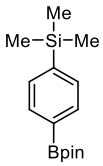
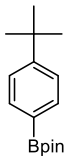
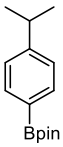
entry	solvent	yield/% (**3a**+**3a'**+**3a''**)	**3a**:(**3a'**+**3a''**)
1	cyclohexane	43	72:28
2	hexane	58	70:30
3	*p*-xylene	76	70:30
4	dioxane	89	68:32
5	THF	95	67:33

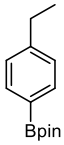
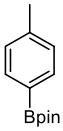
Before investigating the substrate scope using ligands **L1** and **L2**, the yields and *para*-selectivities of four ligands (dtbpy, xyl-MeO-BIPHEP,[7a] and ligands **L1** and **L2**) were compared to clarify the selectivity of ligands **L1** and **L2** compared to previously reported ligands in the C–H borylation of trimethylsilylbenzene, *tert*-butylbenzene, isopropylbenzene, ethylbenzene, and toluene (Scheme 3). The dtbpy ligand gave the borylated products in high yields; however, the selectivity (**3**:(**3'**+**3''**)) was approximately 3:7 in all cases, and the reaction was *meta*-selective. The xyl-MeO-BIPHEP ligand gave high *para*-selectivity for trimethylsilylbenzene and *tert*-butylbenzene; however, the selectivity for isopropylbenzene and ethylbenzene with smaller substituents was lower, and the selectivity for ethylbenzene was comparable to that of dtbpy. Ligand **L1** showed a selectivity comparable to that of xyl-MeO-BIPHEP. Interestingly, ligand **L2** showed *para*-selectivity not only with trimethylsilylbenzene and *tert*-butylbenzene but also with isopropylbenzene and ethylbenzene. The use of ligand **L2** also

Scheme 3. Comparison of Yields and *para*-Selectivity Among dtbpy, xyl-MeO-BIPHEP, and Ligands L1 and L2

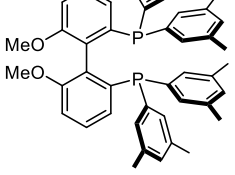




3b	**3a**	**3c**
		
95% [31:69][a]	93% [28:72][a]	94% [28:72][a]
94% [88:12][b]	84% [90:10][b]	82% [58:42][b]
95% [90:10][c]	85% [70:30][c]	90% [45:55][c]
62% [93:7][d]	**85% [92:8]**[d]	**92% [80:20]**[d]

3d	**3e**
	
94% [28:72][a]	86% [33:67][a]
80% [31:68][b]	—
95% [36:64][c]	96% [39:61][c]
95% [62:38][d]	**95% [52:48]**[d]

[a]**3**:(**3'**+**3''**), dtbpy. [b]**3**:(**3'**+**3''**), xyl-MeO-BIPHEP. [c]**3**:(**3'**+**3''**), ligand **L1**. [d]**3**:(**3'**+**3''**), ligand **L2**.



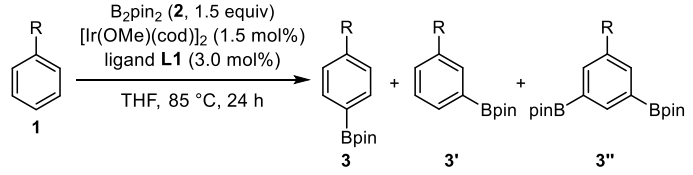
xyl-MeO-BIPHEP

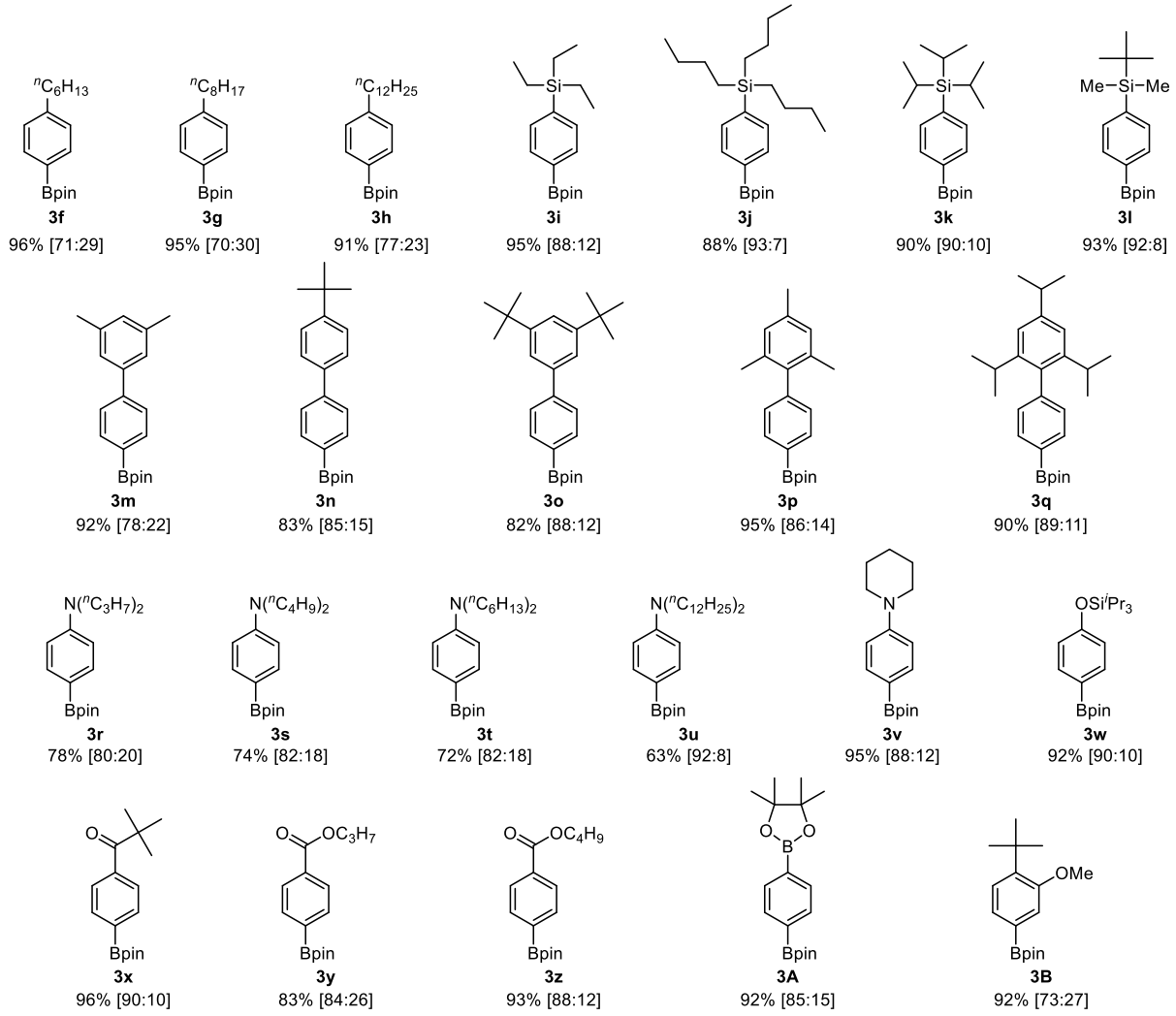
improved *para*-selectivity when toluene was used as the substrate. In the reactions with isopropylbenzene and ethylbenzene, ligands **L1** and **L2** also improved the yield compared to xyl-MeO-BIPHEP.

For all substrates, the highest *para*-selectivity was observed for the ligand **L2**, but the yields tended to decrease for substrates with bulky substituents. Therefore, the substrate scope was investigated using ligand **L1** for substrates with bulky substituents and ligand **L2** for substrates with small substituents.

The substrate scope was investigated using **L1** (Scheme 4). For all substrates, the dtbpy ligand, which is often used in C–H borylation, showed a selectivity of approximately 3:7 (**3a**:(**3a′**+**3a″**)), with preference for the *meta*-position (probably owing to the presence of two reaction sites at the *meta*-position compared to one at the *para*-position). By contrast, ligand **L1** exhibited significantly improved *para*-selectivity. For all substituents, the *para*-selectivity tended to increase as the bulkiness of the substituents increased; for aromatic substrates **1f–1h** with a primary alkyl group, the corresponding *para*-C–H borylated products **3f–3h** were selectively obtained. For substrates **1i–1l** with a silyl group, the reaction proceeded with high *para*-selectivity. The reaction also proceeded with good *para*-selectivity for substrates **1m–1q** having aryl groups, and the corresponding borylated products **3m–3q** were obtained. C–H borylation proceeded using substrates **1r–1v** having an amino group, **1w** with a siloxy group, and **1x–1z** with a carbonyl group. The corresponding *para*-borylated products **3r–3z** were obtained in good yield and *para*-selectivity without inhibition by the functional groups. The reactions proceeded without any loss of functional groups in the case of the siloxy and boryl group-containing substrates **1w** and **1A**. Next, the reaction was performed with substrate **1B** bearing both large and small substituents; the reaction proceeded preferentially at the *para*-position of the bulkier substituent (*tert*-butyl group).

Scheme 4. Scope of Substrates with Bulky Substituent Using Ligand L1[a]

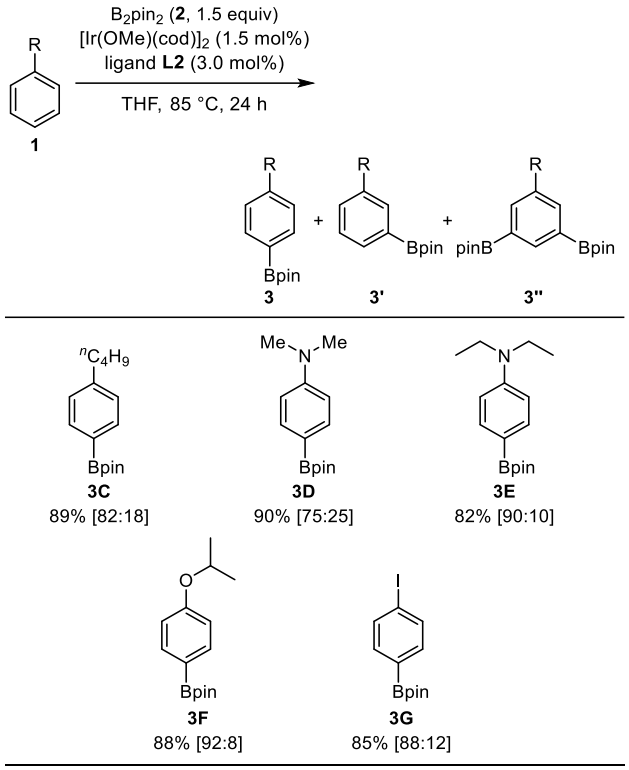




[a]The ratio between **3** and (**3′**+**3″**) is reported in square brackets.

High *para*-selectivity was not observed for substrates with small substituents when ligand **L1**. To improve *para*-selectivity, we used ligand **L2**, which is bulkier than **L1**, and performed C–H borylation (Scheme 5). Consequently, the *para*-selectivity was expressed for all the substrates using **L2**. The reaction was not inhibited by amino or alkoxy groups. In addition, the corresponding borylated product **3G** was obtained without loss of the iodine atom.

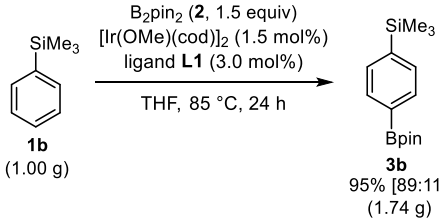
Scheme 5. Scope of Substrates with Small Substituent Using Ligand L2[a]



[a]The ratio (**3**:(**3′**+**3′′**)) is reported in square brackets.

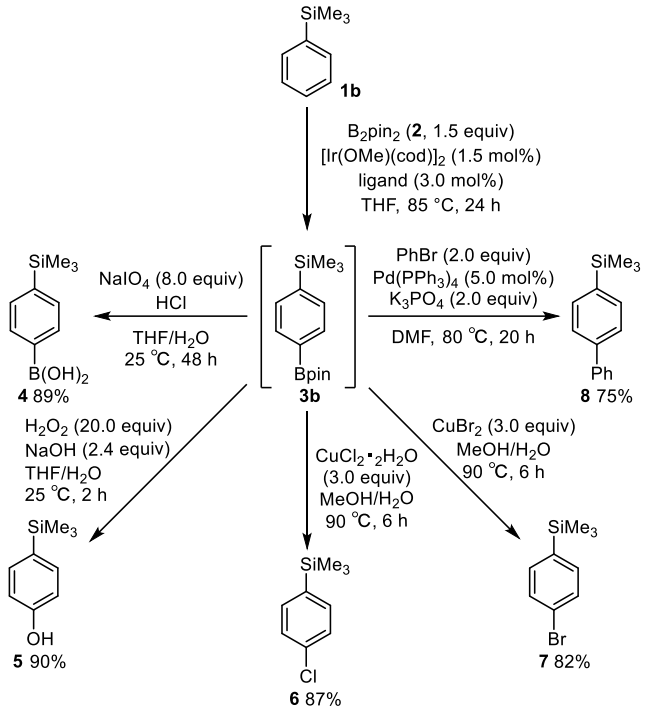
C–H borylation proceeded without the loss of yield or site-selectivity for the borylated product, even on the gram scale (Scheme 6). In the presence of iridium catalyst $[Ir(OMe)(cod)]_2$, 1.00 g of trimethylsilylbenzene **1b** reacted with B_2pin_2 (**2**) in THF at 85 °C for 24 h, 1.74 g of *para*-borylation product **3b** was obtained in 95% yield (**3#**:(**3#′**+**3#′′**) = 89:11).

Scheme 6. Gram-scale Synthesis



Following the *para*-selective C–H borylation, various transformations were performed without isolating the borylated product **3b**, allowing the introduction of various functional groups at the *para*-position (Scheme 7).[15] Treatment of the reaction mixture of the C–H borylation with $NaIO_4$ led to the deprotection of the Bpin group and the corresponding boronic acid **4** was obtained in 89% yield. The oxidation reaction proceeded by treating the reaction mixture with H_2O_2 and NaOH, and the corresponding phenol derivative **5** was produced in 90% yield. Treatment of the reaction mixture with $CuCl_2$ or $CuBr_2$ promoted halogenation, yielding chlorides **6** and **7** in 87% and 82% yields, respectively. Furthermore, the reaction with bromobenzene in the presence of a palladium catalyst proceeded to a carbon–carbon bond formation reaction, yielding the phenylated product **8** in 75% yield.

Scheme 7. Several Transformations of Borylated Product without Isolation of Borylated Product



In summary, we have successfully promoted *para*-selective C–H borylation using our originally developed bulky bipyridine-type ligands. In previous reports, *para*-selectivity was observed in aromatic compounds with bulky substituents but not in those with smaller substituents, such as isopropyl and ethyl groups. By contrast, using a bulky bipyridine-type ligand, we succeeded in developing *para*-selective C–H borylation, even for aromatic compounds with small substituents. The key to the high *para*-selectivity in this reaction is the use of bipyridine-type ligands with bulky *meta*-terphenyl groups introduced at the 4- and 4'-positions, which efficiently and sterically block both sides and the back of the iridium center. This reaction proceeded with good functional group tolerance, even on the gram scale. In addition, several functional groups can be introduced at the *para*-position of the aromatic compound by conversion of the introduced boryl group without isolation of the borylated compound. These results provide useful insights for the design of catalysts for site-selective C–H transformations at remote positions, such as the *para*-position.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedure and characterization data for C–H borylated products (PDF)

AUTHOR INFORMATION

Corresponding Author

Yoichiro Kuninobu − Institute for Materials Chemistry and Engineering and Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasuga-shi, Fukuoka 816-8580, Japan; orcid.org/0000-0002-8679-9487; Email: kuninobu@cm.kyushu-u.ac.jp

Authors

Taisei Enta − Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasuga-shi, Fukuoka 816-8580, Japan

Genki Yoshino − Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasuga-shi, Fukuoka 816-8580, Japan

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported in part by JSPS KAKENHI Grant Numbers JP 21H01941, 22H05370, and 24K01489.

REFERENCES

(1) For several recent reviews, see: (a) Karimov, R. R.; Hartwig, J. F. Transition-Metal-Catalyzed Selective Functionalization of C(sp^3)–H Bonds in Natural Products. *Angew. Chem. Int. Ed.* **2018**, *57*, 4234-4241. (b) Zhang, L.; Ritter, T. A Perspective on Late-Stage Aromatic C–H Bond Functionalization. *J. Am. Chem. Soc.* **2022**, *144*, 2399-2414. (c) 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. (d) Bellotti, P.; Huang, H.-M.; Faber, T.; Glorius, F. Photocatalytic Late-Stage C–H Functionalization. *Chem. Rev.* **2023**, *123*, 4237-4352.

(2) For several reviews, see: (a) Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp^2)–H and C(sp^3)–H Bonds by Using Bidentate Directing Group. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743. (b) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C–H Bond Functionalization Chemistry for the Expedient Construction of C–C Bonds. *Chem. Rev.* **2020**, *120*, 1788–1887. (c) Rej, S.; Das, A.; Chatani, N. Strategic evolution in transition metal-catalyzed directed C–H bond activation and future directions. *Coord. Chem. Rev.* **2021**, *431*, 213683.

(3) (a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. Activation of remote *meta*-C–H bonds assisted by an end-on template. *Nature* **2012**, *486*, 518-522. (b) Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. Pd(II)-Catalyzed *ortho*- or *meta*-C–H Olefination of Phenol Derivatives. *J. Am. Chem. Soc.* **2013**, *135*, 7567-7571. (c) Lee, S.; Lee, H.; Tan, K. L. Meta-Selective C–H Functionalization Using a Nitrile-Based Directing Group and Cleavable Si-Tether. *J. Am. Chem. Soc.* **2013**, *135*, 18778-18781. (d) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. Pd(II)-Catalyzed *meta*-C–H Olefination, Acylation, and Acetoxylation of Indolines Using T-Shaped Template. *J. Am. Chem. Soc.* **2014**, *136*, 10807-10813. (e) Bera, M.; Modak, A.; Patra, T.; Maji, A.; Maiti, D. *Meta*-Selective Arene C−H Bond Olefination of Arylacetic Acid Using a Nitrile-Based Directing Group. *Org. Lett.* **2014**, *16*, 5760-5763. (f) Bera, M.; Maji, A.; Sahoo, S. K.; Maiti, D. Palladium(II)-Catalyzed *meta*-C−H Olefination: Constructing Multisubstituted Arenes through Homo-Diolefination and Sequential Hetero-Diolefination. *Angew. Chem. Int. Ed.* **2015**, *54*, 8515-8519.

(4) (a) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. Remote *para*-C−H Functionalization of Arenes by a D-Shaped Biphenyl Template-Based Assembly. *J. Am. Chem. Soc.* **2015**, *137*, 11888-11891. (b) Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 7751-7755. (c) Maji, A.; Guin, S.; Feng, S.; Dahiya, A.; Singh, V. K.; Liu, P.; Maiti, D. Experimental and Computational Exploration of para-Selective Silylation with a Hydrogen-Bonded Template. *Angew. Chem. Int. Ed.* **2017**, *56*, 14903-14907. (d) Maji, A.; Dahiya, A.; Lu, G.; Bhattacharya, T.; Brochetta, M.; Zanoni, G.; Liu, P.; Maiti, D. H-bonded reusable template assisted *para*-selective ketonisation using soft electrophilic vinyl ethers. *Nat. Commun.* **2018**, *9*, 3582.

(5) (a) Kuninobu, Y. The Development of Novel C–H Bond Transformations and Their Application to the Synthesis of Organic Functional Molecules. *J. Synth. Org. Chem. Jpn.* **2016**, *74*, 1058-1068. (b) Davis, H. J.; Phipps, R. J. Harnessing non-covalent interactions to exert control over regioselectivity and site-selectivity in catalytic reactions. *Chem. Sci.* **2017**, *8*, 864-877. (c) Kuninobu, Y. Development of Novel C–H Bond Transformations and Their Application to the Synthesis of Organic Functional Molecules. *Synlett* **2018**, *29*, 2093-2107. (d) Mihai, M. T.; Genov, G. R.; Phipps, R. J. Access to the meta position of arenes through transition metal catalysed C–H bond functionalisation: a focus on metals other than palladium. *Chem. Soc. Rev.* **2018**, *47*, 149-171. (e) Ghosh, M.; Sarkar, S. D. *meta*- and *para*-Selective C–H Functionalization using Transient Mediators and Noncovalent Templates. *Asian J. Org. Chem.* **2018**, *7*, 1236-1255. (f) Haldar, C.; Hoque, M. E.; Bisht, R.; Chattopadhyay, B. Concept of Ir-catalyzed C–H bond activation/borylation by noncovalent interaction. *Tetrahedron Lett.* **2018**, *59*, 1269-1277. (g) Kuroda, Y.; Nakao, Y. Catalyst-enabled Site-selectivity in the Iridium-catalyzed C–H Borylation of Arenes. *Chem. Lett.* **2019**, *48*, 1092-1100. (h) Kuninobu, Y.; Torigoe, T. Recent progress of transition metal-catalysed regioselective C–H transformations based on noncovalent interactions. *Org. Biomol. Chem.* **2020**, *18*, 4126-4134. (i) Meng, G.; Lam, N. Y. S.; Lucas, E. L.; Saint-Denis, T. G.; Verma, P.; Chekshin, N.; Yu, J.-Q. Achieving Site-Selectivity for C−H Activation Processes Based onDistance and Geometry: A Carpenter's Approach. *J. Am. Chem. Soc.* **2020**, *142*, 10571-10591. (j) Fanourakis, A.; Docherty, P. J.; Chuentragool, P.; Phipps, R. J. Recent Developments in Enantioselective Transition Metal Catalysis Featuring Attractive Noncovalent Interactions between Ligand and Substrate. *ACS Catal.* **2020**, *10*, 10672-10714. (k) Olivo, G.; Capocasa, G.; Giudice, D. D.; Lanzalunga, O.; Stefano, S. D. New horizons for catalysis disclosed by supramolecular chemistry. *Chem. Soc. Rev.* **2021**, *50*, 7681-7724. (l) Dutta, U.; Maiti, S.; Bhattacharya, T.; Maiti, D. Arene diversification through distal C(sp^2)–H functionalization. *Science* **2021**, *372*, eabd5992. (m) Ali, R.; Siddiqui, R. Recent Developments in Remote *Meta*-C–H Bond Functionalization. *Adv. Synth. Catal.* **2021**, *363*, 1290-1316. (n) Haldar, C.; Hoque, M. E.; Chaturvedi, J.; Hassan, M. M. M.; Chattopadhyay, B. Ir-catalyzed proximal and distal C–H borylation of arenes. *Chem. Commun.* **2021**, *57*, 13059-13074. (o) Pachisia, S.; Gupta, R. Supramolecular catalysis: the role of H-bonding interactions in substrate orientation and activation. *Dalton Trans.* **2021**, *50*, 14951-14966. (p) Sinha, S. K.; Guin, S.; Maiti, S.; Biswas, J. P.; Porey, S.; Maiti, D. Toolbox for Distal C–H Bond Functionalizations in Organic Molecules. *Chem. Rev.* **2022**, *122*, 5682-5841. (q) Fernández-Figueiras, A.; Ravutsov,

M. A.; Simeonov, S. P. Site-Selective C−H Functionalization of Arenes Enabled by Noncovalent Interactions. *ACS Omega* **2022**, *7*, 6439-6448. (r) Jiao, Y.; Chen, X.-Y.; Stoddart, J. F. Weak bonding strategies for achieving regio- and site-selective transformations. *Chem* **2022**, *8*, 414-438. (s) Reek, J. N. H.; de Bruin, B.; Pullen, S.; Mooibroek, T. J.; Kluwer, A. M.; Caumes, X. Transition Metal Catalysis Controlled by Hydrogen Bonding in the Second Coordination Sphere. *Chem. Rev.* **2022**, *122*, 12308-12369. (t) Gillespie, J. E.; Fanourakis, A.; Phipps, R. J. Strategies That Utilize Ion Pairing Interactions to Exert Selectivity Control in the Functionalization of C−H Bonds. *J. Am. Chem. Soc.* **2022**, *144*, 18195-18211. (u) Kuninobu, Y. Non-Covalent Interaction-Controlled Site-Selective C−H Transformations. *Chem. Rec.* **2023**, *23*, e202300149. (v) Hassan, M. M. M.; Guria, S.; Dey, S.; Das, J.; Chattopadhyay, B. Transition metal-catalyzed remote C−H borylation: An emerging synthetic tool. *Sci. Adv.* **2023**, *9*, eadg3311.

(6) (a) Hoque, E.; Bisht, R.; Haldar, C.; Chattopadhyay, B. Noncovalent Interactions in Ir-Catalyzed C−H Activation: L-Shaped Ligand for Para-Selective Borylation of Aromatic Esters. *J. Am. Chem. Soc.* **2017**, *139*, 7745-7748. (b) Lu, S.; Zheng, T.; Ma, J.; Deng, Z.; Qin, S.; Chen, Y.; Liang, Y. *para*-Selective C−H Borylation of Aromatic Quaternary Ammonium and Phosphonium Salts. *Angew. Chem. Int. Ed.* **2022**, *61*, e202201285. (c) Wang, Y.; Chang, W.; Qin, S.; Ang, Q. H.; Ma, J.; Lu, S.; Liang, Y. Diversification of Aryl Sulfonyl Compounds through Ligand-Controlled *meta*- and *para*-C−H Borylation. *Angew. Chem. Int. Ed.* **2022**, *61*, e202206797. (d) Chang, W.; Chen, Y.; Lu, S.; Jiao, H.; Wang, Y.; Zheng, T.; Shi, Z.; Han, Y.; Lu, Y.; Wang, Y.; Pan, Y.; Yu, J.-Q.; Houk, K. N.; Liu, F.; Liang, Y. *Chem* **2022**, *8*, 1775-1788. (e) Douwaite, J. L.; Phipps, R. J. *Tetrahedron* **2022**, *117-118*, 132831.

(7) (a) Saito, Y.; Segawa, Y.; Itami, K. *para*-C–H Borylation of Benzene Derivatives by a Bulky Iridium Catalyst. *J. Am. Chem. Soc.* **2015**, *137*, 5193-5198. (b) Haines, B. E.; Saito, Y.; Segawa, Y.; Itami, K.; Musaev, D. G. Flexible Reaction Pocket on Bulky Diphosphine–Ir Complex Controls Regioselectivity in *para*-Selective C–H Borylation of Arenes. *ACS Catal.* **2016**, *6*, 7536-7546. (c) Yang, L.; Semba, K.; Nakao, Y. *para*-Selective C-H Borylation of (Hetero)Arenes by Cooperative Iridium/Aluminum Catalysis. *Angew. Chem. Int. Ed.* **2017**, *56*, 4853-4857. (d) Mihai, M. T.; Williams, B. D.; Phipps, R. J. *Para*-Selective C–H Borylation of Common Arene Building Blocks Enabled by Ion-Pairing with a Bulky Countercation. *J. Am. Chem. Soc.* **2019**, *141*, 15477-15482. (e) Saito, Y.; Yamanoue, K.; Segawa, Y.; Itami, K. Selective Transformation of Strychnine and 1,2-Disubstituted Benzenes by C–H Borylation. *Chem* **2020**, *6*, 985-993. (f) Ju, G.; Huang, Z.; Zhao, Y. Trialkoxysilane-Induced Iridium-Catalyzed *para*-Selective C–H Bond Borylation of Arenes. *Nat. Commun.* **2024**, *15*, 2847.

(8) Grams, R. J.; Santos, W. L.; Scorei, I. R.; Abad-García, A.; Rosenblum, C. A.; Bita, A.; Cerecetto, H.; Viñas, C.; Soriano-Ursúa, M. A. The Rise of Boron-Containing Compounds: Advancements inSynthesis, Medicinal Chemistry, and Emerging Pharmacology. *Chem. Rev*. **2024**, *124*, 2441-2511.

(9) (a) Shimomura, N.; Egawa, Y.; Miki, R.; Fujihara, T.; Ishimaru, Y.; Seki, T. A red fluorophore comprising a borinate-containing xanthene analogue as a polyol sensor. *Org. Biomol. Chem.* **2016**, *14*, 10031-10036. (b) Zhou, X.; Lesiak, L.; Lai, R.; Beck, J. R.; Zhao, J.; Elowsky, C. G.; Li, H.; Stains, C. I. Chemoselective Alteration of Fluorophore Scaffolds as a Strategy for the Development of Ratiometric Chemodosimeters. *Angew. Chem., Int. Ed.* **2017**, *56*, 4197-4200. (c) Ando, N.; Soutome, H.; Yamaguchi, S. Near-infrared fluorescein dyes containing a tricoordinate boron atom. *Chem. Sci*. **2019**, *10*, 7816-7821.

(10) Diaz, D. B.; Yudin, A. K. *Nat. Chem*. **2017**, *9*, 731-742.

(11) (a) Khotinsky, E.; Melamed, M. Die Wirkung der magnesiummorganischen Verbindungen auf die Borsäureester. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3090-3096. (b) Letsinger, R. L.; Skoog, I. H. The preparation and some properties of 2-methyl-1-propene-1-boronic acid. *J. Org. Chem.* **1953**, *18*, 895-897.

(12) (a) Ishiyama, T.; Miyaura, N. Metal-Catalyzed Reactions of Diborons for Synthesis of Organoboron Compounds. *Chem. Rec.* **2004**, *3*, 271-280. (b) Chow, W. K.; Yuen, O. Y.; Choy, P. Y.; So, C. M.; Lau, C. P.; Wong, W. T.; Kwong, F. Y. A decade advancement of transition metal-catalyzed borylation of aryl halides and sulfonates. *RSC Adv.* **2013**, *3*, 12518-12539.

(13) (a) 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. (b) Veth, L.; Grab, H. A.; Dydio, P. Recent Trends in Group 9 Catalyzed C–H Borylation Reactions: Different Strategies to Control Site-, Regio- and Stereoselectivity. *Synthesis* **2022**, *54*, 3482-3498. (c) Guria, S.; Hassan, M. M. M.; Chattopadhyay, B. C–H borylation: a tool for molecular diversification. *Org. Chem. Front.* **2024**, *11*, 929-953.

(14) (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith III, M. R. Remarkably selective iridium catalysts for the elaboration of aromatic C–H bonds. *Science* **2002**, *295*, 305-308. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. Mild Iridium-Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature Reactions, and Isolation of a Potential Intermediate. *J. Am. Chem. Soc.* **2002**, *124*, 390-391.

(15) (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. (c) Wang, G.; Liu, L.; Wang, H.; Ding, Y.-S.; Zhou, J.; Mao, S.; Li, P. N,B-Bidentate Boryl Ligand-Supported Iridium Catalyst for Efficient Functional-Group-Directed C−H Borylation. *J. Am. Chem. Soc.* **2017**, *139*, 91-94. (d) Wang, J.; Torigoe, T.; Kuninobu, Y. Hydrogen-Bond-Controlled Formal *Meta*-Selective C–H Transformations and Regioselective Synthesis of Multisubstituted Aromatic Compounds**.** *Org. Lett.* **2019**, *21*, 1342-1346.

We successfully developed a *para*-selective C–H borylation of aromatic compounds using iridium catalysts with bulky bipyridine-type ligands. The key to success is the introduction of bulky substituents (*m*-terphenyl groups) at the 4- and 4′-positions of the bipyridine-type ligands to sterically protect both sides and back of the catalysts, thereby efficiently preventing substrate orientation that gives *ortho*- and *meta*-borylated products. Using these ligands, higher *para*-selectivity was achieved compared to the conventional iridium-catalyzed *para*-selective C–H borylation. Interestingly, high *para*-selectivity was achieved even when using aromatic compounds with small substituents such as ethyl or isopropyl groups on the aromatic ring.