

Aryl Phosphonate-Directed *Ortho* C–H Borylation: Rapid Entry into Highly-Substituted Phosphoarenes

Feiyang Xu,^{†‡} Olivia M. Duke,[†] Daniel Rojas,[†] Hanka M. Eichelberger,^{†‡} Raphael S. Kim,[†] Timothy B. Clark,^{*‡} and Donald A. Watson^{*†}

[†]Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716 (USA)

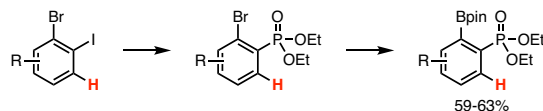
[‡]Department of Chemistry and Biochemistry, University of San Diego, San Diego, CA 92110 (USA)

ABSTRACT: Phosphonate-directed *ortho* C–H borylation of aromatic phosphonates is reported. Using simple starting materials and commercially accessible catalysts, this method provides steady access to *ortho*-phosphonate aryl boronic esters bearing pendant functionality and flexible substitution patterns. These products serve as flexible precursors for a variety of highly-substituted phosphoarenes, and in situ downstream functionalization of the products is described.

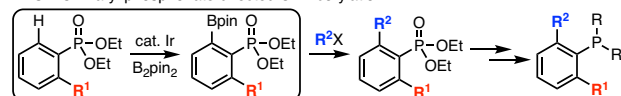
Aryl phosphonates are useful motifs in organic synthesis as their versatility allows for transformation into a number of functional groups, including phosphines, phosphoramidates, and phosphorus oxides.^{1–2} Additionally, some aryl phosphonates and related compounds have also shown interesting bioactivities,^{3–5} including in the clinical treatment of various cancers.⁶

Due to their value, several strategies have been reported to prepare aryl phosphonates. However, current methods to generate functionalized aryl phosphonates typically involve the construction of the C–P bond via pre-functionalized starting materials such as organolithium or Grignard reagents,⁷ (pseudo)halides,^{8–12} boronic acids,^{13–15} carboxylic acids,¹⁶ or hypervalent iodine compounds.^{17–18} These methods are often limited by the availability of the starting materials, and thus only aryl phosphonates with simple structures can be synthesized readily. More complex aryl phosphonates, such as the ones bearing *ortho*-substitutions, are often very challenging to access for this reason. One attractive route to the synthesis of highly-substituted phosphonates is via *ortho*-boryl aryl phosphonates, as these products are readily diversified and are able to be converted into a range of phosphoarenes. However, like the other methods mentioned above, current routes to these intermediates require multiple steps to access (Figure 1).¹⁹

Previous *Ortho*-Boryl Aryl Phosphonate Synthesis: multi-step route required



This Work: aryl phosphonate-directed C–H borylation



- simple catalytic components & easily accessible starting materials
- broad functional group tolerance & flexible substitution pattern
- versatile functionalization of products

Figure 1. Previous Synthesis of *Ortho*-Boryl Aryl Phosphonates and Our Design.

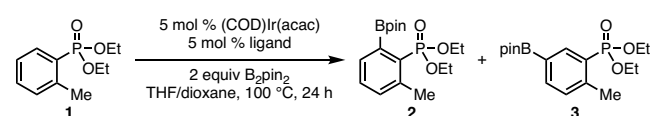
Over the last couple decades, directed C–H borylation has emerged as a powerful tool to prepare *ortho*-substituted aryl boronic esters from simple starting materials.^{20–22} A variety of directing groups have been demonstrated in this field, including a number of carbonyls,^{23–27} Lewis basic nitrogens,^{23, 26–32} phenols,³³ silanes,^{34–35} thianes,^{36–39} ethers,^{23, 26, 40} and halides.²³ We envisioned phosphonate-directed *ortho*-borylation as an attractive platform for the preparation of a variety of *ortho*-functionalized aryl phosphonates (Figure 1). A general method to convert widely accessible simple aryl phosphonates into *ortho*-boryl phosphonates, when combined with the vast chemistry of aryl boronates, would allow for the facile preparation of a wide variety of *ortho*-functionalized aryl phosphonates and their downstream derivatives.

Previously, we have shown that benzyl phosphines can be used as directing groups for C–H borylation, which provides access to *ortho*-borylated benzylic phosphines.^{41–42} Later, Shi and Takaya independently reported C–H borylation conditions to prepare *ortho*-borylated phosphines via the use of an aryl phosphine as a directing group.^{43–44} However, these latter methods are limited to phosphines bearing a single type of aromatic group. Moreover, no reactivity was observed with substrates bearing pre-existing *ortho*-substitutions. Thus, there is a clear need to have an alternative way to prepare these *ortho*-borylated phosphoryl aromatic compounds that can overcome these limitations. In this paper, we describe the successful realization of that goal, and report conditions for the preparation of *ortho*-phosphonate aryl boronic esters via a C–H borylation strategy using phosphonate as a directing group. Using easily accessed starting materials and commercially available catalytic components, we show that the reaction enjoys broad functional group tolerance and is highly flexible in regard to substitution patterns.

Our studies began with the borylation of commercially available diethyl phenylphosphonate, and the preliminary screen of iridium catalysts revealed (COD)Ir(acac) as the optimal iridium source (see Supporting Information). The use of [(COD)₂Ir]BF₄ provided comparable results, but the selection of (COD)Ir(acac) is advantageous because it is bench stable and less expensive.

We then examined the effects of ligand with the model substrate **1**, an aryl phosphonate substituted at the *ortho* position (Table 1). The *ortho*-borylation of **1** would produce the highly-substituted phosphonate **2**, whose substitution pattern would be difficult to access using other methods.

Table 1. Reaction Optimization.



entry	ligand	yield of 2	yield of 3
1	no ligand	0%	7%
2	2-picolylamine	0%	4%
3	dtbpy	0%	41%
4	tmphen	0%	38%
5	P[2-Si-(<i>i</i> Pr) ₂ H-C ₆ H ₄](<i>o</i> -tol) ₂	31%	0%
6	PPh ₃	0%	7%
7	P(4-F-C ₆ H ₄) ₃	4%	0%
8	P(4-CF ₃ -C ₆ H ₄) ₃	4%	0%
9	P[3,5-(CF ₃) ₂ -C ₆ H ₃] ₃	84%	0%

^a Yield determined by ¹H NMR analysis with 1,3,5-trimethoxybenzene as internal standard.

Various ligands were examined in conjunction with (COD)Ir(acac) as catalyst. We began by investigating conditions without added external ligand, such as those that had shown success in our previous work on benzyl phosphine-directed C–H borylation.⁴¹ However, with this catalyst system we did not observe any *ortho*-borylation; instead, the borylation took place at the *meta* position to give **3** (Table 1, entry 1).

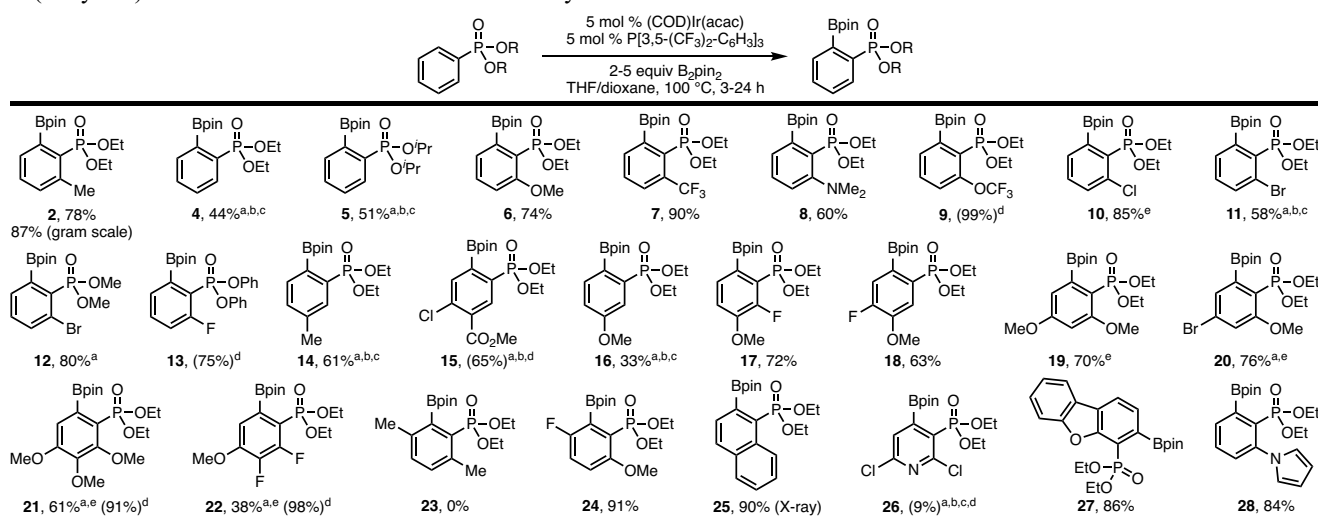
Moving forward, very little reactivity was observed with 2-picolylamine as ligand, the ligand used in our benzyl amine-directed C–H borylation (entry 2).³⁰ Although we found that the borylation was more efficient with bipyridine ligands, such as dtbpy and tmphen that have often been used in aryl borylation, there was still no formation of the desired *ortho*-borylated product (entry 3–4). The selective formation of the *meta*-borylation

isomer is in itself notable. This result suggests that the primary selectivity is steric in nature, but the fact that borylation *para* to the phosphonate is not observed also suggests a strong electronic differentiation between the methyl and phosphonate groups.

Excitingly, however, when the phosphine/silane-based bidentate ligand previously reported by Smith, Maleczka, and Krska was used, we observed 31% yield of **2** (entry 5).²⁶ Despite the encouraging result using this ligand, we continued to explore other options as we recognized that use of a commercially available ligand would make the method more broadly useful. Therefore, we explored simple phosphine ligands as an alternative. Although PPh₃ did not provide any of the *ortho*-borylation product (entry 6), with more electron-deficient triaryl phosphines we started to observe the desired *ortho* selectivity (entry 7–8). Following this trend, we finally identified the use of P[3,5-(CF₃)₂-C₆H₃]₃ in this reaction, which has the optimal balance of electronic and steric properties, affording **2** in 84% yield (entry 9).^{24,45}

With optimized reaction conditions developed, the scope of this reaction was then investigated (Scheme 1). The borylated phosphonate **2** was isolated in 78% yield on 1 mmol scale. During purification, we observed some loss of product due to the unstable nature of boronic esters, but such an effect can be minimized by running the reaction at larger scales. For example, scaling the same reaction up to gram scale provided 87% isolated yield of **2**.

Substrates without *ortho*-substitution next to the phosphonate require somewhat more stringent conditions, including use of a higher catalyst loading, use of iridium pre-catalyst with a less coordinating counter-ion [(COD)₂Ir]BF₄, and elevated reaction temperature (**4**). Under these conditions, however, we observed a significant amount of bis-borylation at both *ortho* positions.⁴⁶ To avoid the bis-borylation, we hypothesized that the use of larger directing group could restrict the conformational rotation of the phosphonate group in the mono-borylated product and prevent the second C–H activation at the other *ortho* position. This idea is supported by the use of diisopropyl phosphonate, only mono-borylated product is produced (**5**).



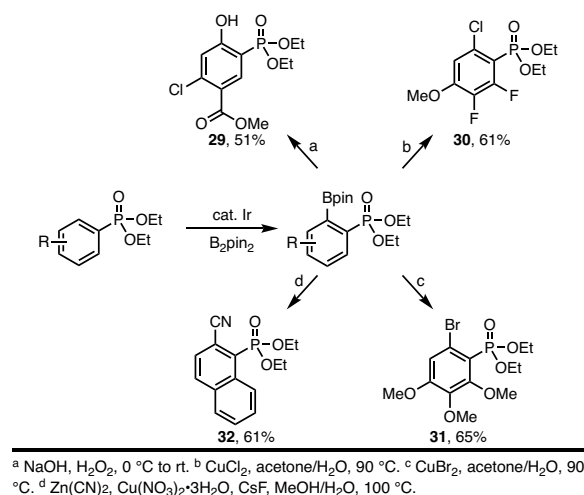
^a Run with [(COD)₂Ir]BF₄. ^b 120 °C. ^c 7.5 mol % catalyst loading. ^d Parenthetical yields calculated by ¹H NMR with 1,3,5-trimethoxybenzene as internal standard. ^e 110 °C.

Scheme 1. Scope of Phosphonate-Directed C–H Borylation

In contrast, substrates bearing varied substitutions at the pre-existing *ortho* position participate in this reaction under standard conditions and result in borylated products efficiently (**6-13**), including ethers (**6, 9**), trifluoromethyl (**7**), aniline (**8**), and halogens (**10-13**). With a bulky substitution at the *ortho* position, such as bromine, we found that the reaction requires higher catalyst loading and temperature to proceed (**11**), presumably due to the limitation of conformational rotation of phosphonate by steric congestion. We found, however, that simply switching to the smaller dimethyl phosphonate group overcomes this limitation and higher yield is observed under milder conditions (**12**). Phosphonates with aromatic substitutions were also easily borylated under the standard conditions (**13**); however, product instability precluded isolation.

With *meta*-substituted aryl phosphonates, the borylation only occurs at the less sterically hindered site (**14**). These reactions are most efficient with weakly donating or electron-withdrawing groups at the *meta* position (**15**). With a strong electron-donating group at the *meta* position, yield of the borylated product is lower (**16**).⁴⁷ However, these electronic effects appear to be very sensitive. Simple inclusion of a weak electron-withdrawing group in the substrate mitigates the effects of the *meta* donor group (**17-18**).

Aryl phosphonates bearing di-substitutions at other positions can also participate in this reaction (**19-20**), and even highly-substituted substrates could be converted to the borylated products with good efficiencies (**21-22**). As with other directed C–H borylation reactions, this reaction is sensitive to steric effects. We did not observe reactivity with alkyl substitution next to the reactive C–H bond (**23**). However, with a smaller substitution, such as fluorine, high yields of the desired product are observed (**24**). A naphthyl substrate also works well under these reaction conditions and can be borylated in 90% isolated yield (**25**). One limitation that we have found with this reaction is that Lewis basic heterocycles, such as pyridine, were not tolerated and resulted in only minimal conversion (**26**). However, less-basic heterocycles are tolerated (**27-28**).

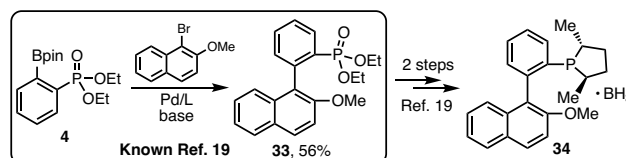


Scheme 2. In Situ Downstream Functionalization

As one of the most versatile functional groups in organic synthesis, boronic esters can be readily converted into a range of other structures. For example, we were rapidly able to prepare aryl phosphonates containing *ortho* phenols (**29**),⁴⁸ chlorides

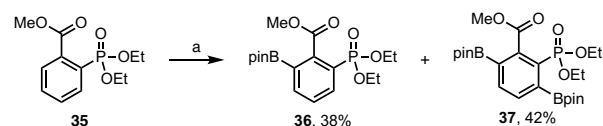
(**30**),⁴⁹ bromides (**31**),⁴⁹ and nitriles (**32**)⁵⁰ by applying known methods from the literature (Scheme 2). It is noteworthy that the purification of the boronic esters is not required prior to many downstream functionalizations. This is particularly important because the purification of some borylated products can cause significant material loss due to their instabilities.

In addition, aryl boronic esters are reliable precursors for substituted biaryl compounds. Previously, Westcott and co-workers reported conditions for Suzuki coupling to transform *ortho*-boryl aryl phosphonates into biarylphosphonate substrates, such as **33**.¹⁹ The further functionalization of **33** led to the synthesis of a dialkyl biarylphosphine ligand **34**, showing the utility of *ortho*-borylated aryl phosphonate products in ligand synthesis (Scheme 3).⁵¹



Scheme 3. Biaryl Phosphonate Synthesis and Their Utility in Ligand Synthesis

Finally, we wished to compare the relative directing group ability of phosphonates to esters (Scheme 4).²⁴ Under the standard and related conditions (see Supporting Information), borylation *ortho* to the ester (**36**) is preferred and mono-borylation *ortho* to the phosphonate was not observed. Interestingly, however, subsequent borylation at that site appears to be competitive (**37**).



^a 5 mol % (COD)Ir(acac), 5 mol % P[3,5-(CF₃)₂-C₆H₃]₃, 5 equiv B₂pin₂, THF/dioxane, 100 °C, 24 h; yields calculated by ¹H NMR with 1,3,5-trimethoxybenzene as internal standard.

Scheme 4. Comparison Between Phosphonate and Ester

In conclusion, we developed conditions for C–H borylation using phosphonate as a directing group, which allows the preparation of *ortho*-phosphonate aryl boronic esters from simple starting materials. This reaction uses commercially available catalytic components and has a broad functional group tolerance. Using this method, highly-substituted aryl phosphonates can be prepared, which is a known synthetic challenge in this field.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and spectra data (PDF)

Crystallographic data for compound **25** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: dawatson@udel.edu

ACKNOWLEDGMENT

The University of Delaware (UD), the University of San Diego (USD), the Camille and Henry Dreyfus Foundation, the National Science Foundation (CHE-1800011, CHE-1764307) are gratefully acknowledged for support. Dr. Glenn P. A. Yap (UD) and Maxwell I. Martin (UD) are thanked for X-ray crystallography. Data was acquired at UD on instruments obtained with the assistance of NSF and NIH funding (NSF CHE-0421224, CHE-1048367, and CHE-0840401; NIH P20GM104316, P30GM110758, S10RR02692, and S10OD016267).

REFERENCES

- Quin, L. D., *A Guide to Organophosphorus Chemistry*. Wiley-Interscience: New York, 2000.
- Iaroshenko, V., *Organophosphorus Chemistry: From Molecules to Applications*. Wiley-VCH: Weinheim, 2019.
- Beugelmans, R.; Bois-Choussy, M.; Gayral, P.; Rigother, M. C., Synthèse par $S_{RN}1$ et évaluation de l'activité amoebicide de nouveaux dérivés quinoléniques. *Eur. J. Med. Chem.* **1988**, *23*, 539–546, 10.1016/0223-5234(88)90097-9.
- Veale, C. A.; Damewood, J. R., Jr.; Steelman, G. B.; Bryant, C.; Gomes, B.; Williams, J., Non-peptidic Inhibitors of Human Leukocyte Elastase. 4. Design, Synthesis, and *in Vitro* and *in Vivo* Activity of a Series of β -Carbolinone-Containing Trifluoromethyl Ketones. *J. Med. Chem.* **1995**, *38*, 86–97, 10.1021/jm00001a014.
- Ortwine, D. F.; Malone, T. C.; Bigge, C. F.; Drummond, J. T.; Humblet, C.; Johnson, G.; Pinter, G. W., Generation of *N*-Methyl-D-aspartate Agonist and Competitive Antagonist Pharmacophore Models. Design and Synthesis of Phosphonoalkyl-Substituted Tetrahydroisoquinolines as Novel Antagonists. *J. Med. Chem.* **1992**, *35*, 1345–1370, 10.1021/jm00086a004.
- Huang, W.-S.; Liu, S.; Zou, D.; Thomas, M.; Wang, Y.; Zhou, T.; Romero, J.; Kohlmann, A.; Li, F.; Qi, J.; Cai, L.; Dwight, T. A.; Xu, Y.; Xu, R.; Dodd, R.; Toms, A.; Parillon, L.; Lu, X.; Anjum, R.; Zhang, S.; Wang, F.; Keats, J.; Wardwell, S. D.; Ning, Y.; Xu, Q.; Moran, L. E.; Mohemmad, Q. K.; Jang, H. G.; Clackson, T.; Narasimhan, N. I.; Rivera, V. M.; Zhu, X.; Dalgarno, D.; Shakespeare, W. C., Discovery of Brigatinib (AP26113), a Phosphine Oxide-Containing, Potent, Orally Active Inhibitor of Anaplastic Lymphoma Kinase. *J. Med. Chem.* **2016**, *59*, 4948–4964, 10.1021/acs.jmedchem.6b00306.
- Eymery, F.; Iorga, B.; Savignac, P., Synthesis of Phosphonates by Nucleophilic Substitution at Phosphorus: The $S_NP(V)$ Reaction. *Tetrahedron* **1999**, *55*, 13109–13150, 10.1016/S0040-4020(99)00822-4.
- Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T., Palladium-catalyzed New Carbon-Phosphorus Bond Formation. *B. Chem. Soc. Jpn.* **1982**, *55*, 909–913, 10.1246/bcsj.55.909.
- Gelman, D.; Jiang, L.; Buchwald, S. L., Copper-Catalyzed C–P Bond Construction via Direct Coupling of Secondary Phosphines and Phosphites with Aryl and Vinyl Halides. *Org. Lett.* **2003**, *5*, 2315–2318, 10.1021/ol0346640.
- Schwan, A. L., Palladium catalyzed cross-coupling reactions for phosphorus–carbon bond formation. *Chem. Soc. Rev.* **2004**, *33*, 218–224, 10.1039/B307538A.
- Bai, Y.; Liu, N.; Wang, S.; Wang, S.; Ning, S.; Shi, L.; Cui, L.; Zhang, Z.; Xiang, J., Nickel-Catalyzed Electrochemical Phosphorylation of Aryl Bromides. *Org. Lett.* **2019**, *21*, 6835–6838, 10.1021/acs.orglett.9b02475.
- Zeng, H.; Dou, Q.; Li, C.-J., Photoinduced Transition-Metal-Free Cross-Coupling of Aryl Halides with H-Phosphonates. *Org. Lett.* **2019**, *21*, 1301–1305, 10.1021/acs.orglett.8b04081.
- Andaloussi, M.; Lindh, J.; Sävmarker, J.; J. R. Sjöberg, P.; Larhed, M., Microwave-Promoted Palladium(II)-Catalyzed C–P Bond Formation by Using Arylboronic Acids or Aryltrifluoroborates. *Chem. Eur. J.* **2009**, *15*, 13069–13074, 10.1002/chem.200901473.
- Zhuang, R.; Xu, J.; Cai, Z.; Tang, G.; Fang, M.; Zhao, Y., Copper-Catalyzed C–P Bond Construction via Direct Coupling of Phenylboronic Acids with H-Phosphonate Diesters. *Org. Lett.* **2011**, *13*, 2110–2113, 10.1021/ol200465z.
- Hu, G.; Chen, W.; Fu, T.; Peng, Z.; Qiao, H.; Gao, Y.; Zhao, Y., Nickel-Catalyzed C–P Cross-Coupling of Arylboronic Acids with P(O)H Compounds. *Org. Lett.* **2013**, *15*, 5362–5365, 10.1021/ol402672e.
- Liu, C.; Ji, C.-L.; Zhou, T.; Hong, X.; Szostak, M., Decarbonylative Phosphorylation of Carboxylic Acids via Redox-Neutral Palladium Catalysis. *Org. Lett.* **2019**, *21*, 9256–9261, 10.1021/acs.orglett.9b03678.
- Xu, J.; Zhang, P.; Gao, Y.; Chen, Y.; Tang, G.; Zhao, Y., Copper-Catalyzed P-Arylation via Direct Coupling of Diaryliodonium Salts with Phosphorus Nucleophiles at Room Temperature. *J. Org. Chem.* **2013**, *78*, 8176–8183, 10.1021/jo4012199.
- Lecroq, W.; Bazille, P.; Morlet-Savary, F.; Breugst, M.; Lalevée, J.; Gaumont, A.-C.; Lakhdar, S., Visible-Light-Mediated Metal-Free Synthesis of Aryl Phosphonates: Synthetic and Mechanistic Investigations. *Org. Lett.* **2018**, *20*, 4164–4167, 10.1021/acs.orglett.8b01379.
- Doherty, S.; Knight, J. G.; Ward, N. A. B.; Perry, D. O.; Bittner, D. M.; Probert, M. R.; Westcott, S. A., Palladium-Catalyzed Suzuki–Miyaura Cross-Couplings with 2-Diethylphosphonato-Substituted Aryl- and Naphthylboronate Esters as the Nucleophilic Partner: A Complementary Approach to the Synthesis of Biaryl Monophosphonates. *Organometallics* **2014**, *33*, 5209–5219, 10.1021/om500520z.
- 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, 10.1021/cr900206p.
- Ros, A.; Fernández, R.; Lassaletta, J. M., Functional group directed C–H borylation. *Chem. Soc. Rev.* **2014**, *43*, 3229–3243, 10.1039/C3CS60418G.
- 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, 10.1016/j.tet.2017.11.005.
- Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M., Directed Ortho Borylation of Functionalized Arenes Catalyzed by a Silica-Supported Compact Phosphine–Iridium System. *J. Am. Chem. Soc.* **2009**, *131*, 5058–5059, 10.1021/ja9008419.
- Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N., Ortho-C–H Borylation of Benzoate Esters with Bis(pinacolato)diboron Catalyzed by Iridium–Phosphine Complexes. *Chem. Commun.* **2010**, *46*, 159–161, 10.1039/b910298a.
- Dai, H.-X.; Yu, J.-Q., Pd-Catalyzed Oxidative ortho-C–H Borylation of Arenes. *J. Am. Chem. Soc.* **2012**, *134*, 134–137, 10.1021/ja2097095.
- Ghaffari, B.; Preshlock, S. M.; Plattner, D. L.; Staples, R. J.; Maligres, P. E.; Kraska, S. W.; Maleczka, R. E., Jr.; Smith, M. R., III, Silyl Phosphorus and Nitrogen Donor Chelates for Homogeneous Ortho Borylation Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 14345–14348, 10.1021/ja506229s.
- 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, 10.1021/jacs.6b11867.
- Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M., Rh-Catalyzed Ortho-Selective C–H Borylation of *N*-Functionalized Arenes with Silica-Supported Bridgehead Monophosphine Ligands. *J. Am. Chem. Soc.* **2011**, *133*, 19310–19313, 10.1021/ja208364a.
- Ros, A.; Estepa, B.; López-Rodríguez, R.; Álvarez, E.; Fernández, R.; Lassaletta, J. M., Use of Hemilabile N,N Ligands in Nitrogen-Directed Iridium-Catalyzed Borylations of Arenes. *Angew. Chem. Int. Ed.* **2011**, *50*, 11724–11728, 10.1002/anie.201104544.
- Roering, A. J.; Hale, L. V. A.; Squier, P. A.; Ringgold, M. A.; Wiederspan, E. R.; Clark, T. B., Iridium-Catalyzed, Substrate-Directed C–H Borylation Reactions of Benzylic Amines. *Org. Lett.* **2012**, *14*, 3558–3561, 10.1021/ol301635x.
- Hale, L. V. A.; Emmerson, D. G.; Ling, E. F.; Roering, A. J.; Ringgold, M. A.; Clark, T. B., An ortho-Directed C–H Borylation/Suzuki Coupling Sequence in the Formation of Biphenylbenzylic Amines. *Org. Chem. Front.* **2015**, *2*, 661–664, 10.1039/c4qo00348a.
- Bisht, R.; Chattopadhyay, B., Formal Ir-Catalyzed Ligand-Enabled Ortho and Meta Borylation of Aromatic Aldehydes via *in Situ*-Generated Imines. *J. Am. Chem. Soc.* **2016**, *138*, 84–87, 10.1021/jacs.5b11683.
- Chattopadhyay, B.; Dannatt, J. E.; Andujar-De Sanctis, I. L.; Gore, K. A.; Maleczka, R. E., Jr.; Singleton, D. A.; Smith, M. R., III, Ir-

- Catalyzed *ortho*-Borylation of Phenols Directed by Substrate-Ligand Electrostatic Interactions: A Combined Experimental/in Silico Strategy for Optimizing Weak Interactions. *J. Am. Chem. Soc.* **2017**, *139*, 7864–7871, 10.1021/jacs.7b02232.
34. Robbins, D. W.; Boebel, T. A.; Hartwig, J. F., Iridium-Catalyzed, Silyl-Directed Borylation of Nitrogen-Containing Heterocycles. *J. Am. Chem. Soc.* **2010**, *132*, 4068–4069, 10.1021/ja1006405.
 35. Boebel, T. A.; Hartwig, J. F., Silyl-Directed, Iridium-Catalyzed *ortho*-Borylation of Arenes. A One-Pot *ortho*-Borylation of Phenols, Arylamines, and Alkylarenes. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535, 10.1021/ja8015878.
 36. Kalläne, S. I.; Braun, T., Catalytic Borylation of SCF₃-Functionalized Arenes by Rhodium(I) Boryl Complexes: Regioselective C–H Activation at the *ortho*-Position. *Angew. Chem. Int. Ed.* **2014**, *53*, 9311–9315, 10.1002/anie.201406424.
 37. Li, H.-L.; Kanai, M.; Kuninobu, Y., Iridium/Bipyridine-Catalyzed *ortho*-Selective C–H Borylation of Phenol and Aniline Derivatives. *Org. Lett.* **2017**, *19*, 5944–5947, 10.1021/acs.orglett.7b02936.
 38. Li, H. L.; Kuninobu, Y.; Kanai, M., Lewis Acid–Base Interaction-Controlled *ortho*-Selective C–H Borylation of Aryl Sulfides. *Angew. Chem. Int. Ed.* **2017**, *56*, 1495–1499, 10.1002/anie.201610041.
 39. Liu, L.; Wang, G.; Jiao, J.; Li, P., Sulfur-Directed Ligand-Free C–H Borylation by Iridium Catalysis. *Org. Lett.* **2017**, *19*, 6132–6135, 10.1021/acs.orglett.7b03008.
 40. Xue, C.; Luo, Y.; Teng, H.; Ma, Y.; Nishiura, M.; Hou, Z., *Ortho*-Selective C–H Borylation of Aromatic Ethers with Pinacol-borane by Organo Rare-Earth Catalysts. *ACS Catal.* **2018**, *8*, 5017–5022, 10.1021/acscatal.8b01364.
 41. Crawford, K. M.; Ramseyer, T. R.; Daley, C. J. A.; Clark, T. B., Phosphine-Directed C–H Borylation Reactions: Facile and Selective Access to Ambiphilic Phosphine Boronate Esters. *Angew. Chem. Int. Ed.* **2014**, *53*, 7589–7593, 10.1002/anie.201402868.
 42. Wright, S. E.; Richardson-Solorzano, S.; Stewart, T. N.; Miller, C. D.; Morris, K. C.; Daley, C. J. A.; Clark, T. B., Accessing Ambiphilic Phosphine Boronates through C–H Borylation by an Unforeseen Cationic Iridium Complex. *Angew. Chem. Int. Ed.* **2019**, *58*, 2834–2838, 10.1002/anie.201812857.
 43. Wen, J.; Wang, D.; Qian, J.; Wang, D.; Zhu, C.; Zhao, Y.; Shi, Z., Rhodium-Catalyzed P^{III}-Directed *ortho*-C–H Borylation of Arylphosphines. *Angew. Chem. Int. Ed.* **2019**, *58*, 2078–2082, 10.1002/anie.201813452.
 44. Fukuda, K.; Iwasawa, N.; Takaya, J., Ruthenium-Catalyzed *ortho* C–H Borylation of Arylphosphines. *Angew. Chem. Int. Ed.* **2019**, *58*, 2850–2853, 10.1002/anie.201813278.
 45. Attempts to use HBpin as borylating reagent did not provide any desired product. See the Supporting Information for more details.
 46. Due to the instability of bis-borylation product it could not be purified chromatography.
 47. Vanchura, B. A., II; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, J. R. E.; Singleton, D. A.; Smith, M. R., III, Electronic effects in iridium C–H borylations: insights from unencumbered substrates and variation of boryl ligand substituents. *Chem. Commun.* **2010**, *46*, 7724–7726, 10.1039/C0CC02041A.
 48. Brown, H. C.; Zweifel, G., A Stereospecific *cis* Hydration of the Double Bond in Cyclic Derivatives. *J. Am. Chem. Soc.* **1959**, *81*, 247–247, 10.1021/ja01510a059.
 49. 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, 10.1021/ja076498n.
 50. Liskey, C. W.; Liao, X.; Hartwig, J. F., Cyanation of Arenes via Iridium-Catalyzed Borylation. *J. Am. Chem. Soc.* **2010**, *132*, 11389–11391, 10.1021/ja104442v.
 51. Yin, J.; Buchwald, S. L., A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052, 10.1021/ja005622z.

TOC Graphic:

