

Iridium catalyzed sp^3 C–H borylation in hydrocarbon solvent enabled by 2,2'-dipyridylarylmethane ligands

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Supporting Information Placeholder

ABSTRACT: Iridium-catalyzed alkane C–H borylation has long suffered from poor atom economy, resulting both from inclusion of only a single boron equivalent from the diboron reagent and a requirement for neat substrate. Appropriately-substituted dipyridylarylmethane ligands are found to give highly active alkane borylation catalysts which facilitate C–H borylation with improved efficiency. This system provides for complete consumption of the diboron reagent, producing two molar equivalents of product at low catalyst loadings. The superior efficacy of this system also enables borylation of un-activated alkanes in hydrocarbon solvent with reduced excess of substrate and improved functional group compatibility. The effectiveness of this ligand is displayed across a selection of functional groups, both under traditional borylation conditions in neat substrate and under atypical conditions in cyclohexane solvent. The utility of this catalytic system is exemplified by the borylation of substrates containing polar functionality, which are unreactive to C–H borylation under neat conditions.

The functionalization of inert C–H bonds has garnered considerable attention as a means of rapidly elaborating abundant chemical feedstocks to higher-value materials.^{1–2} C–H borylation is a versatile functionalization reaction that yields organoborane products which are widely applicable intermediates in organic synthesis. Arene borylation in particular has been developed and studied extensively since its inception,^{3–4} yielding accessible and broadly applicable methods with wide scope. Unfortunately, the analogous iridium-catalyzed sp^3 borylation of aliphatic substrates remains limited by harsh reaction conditions, a requirement for catalysis in neat substrate, and incomplete conversion of the diboron reagent.^{5–9}

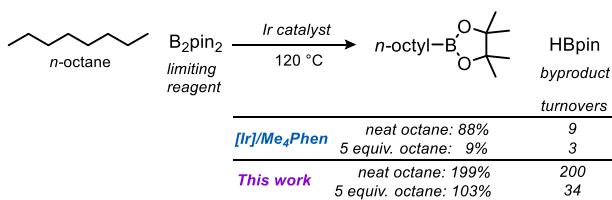


Figure 1. Previously reported conditions for iridium-catalyzed alkane borylation using Me₄Phen with yields reported on a diboron basis.^{8, 10}

Of the limitations of existing systems for alkane borylation, the requirement for catalysis in neat substrate is among the most constraining from the standpoint of usability. There are several reported iridium-catalyzed sp^3 borylation systems that operate on

either smaller excesses of alkane (*ca.* 5 equiv.) or limiting alkane, but each of these cases relies on the increased reactivity of a subset of activated alkane substrates including benzylic^{11–12} or cyclopropane derivatives,^{13–14} alkyl silanes,^{10, 15} or substrates bearing directing groups.^{12, 14, 16–19} Un-activated substrates undergo borylation in reduced yields when smaller excesses are used in solvent. For instance, the tetramethylphenanthroline (Me₄phen)/Ir borylation system gives roughly 1 equivalent of product per equivalent of B₂pin₂ when neat *n*-octane is used as the substrate, but this yield drops to 17% when conducted using 4 equivalents of *n*-octane relative to B₂pin₂ in cyclooctane solvent (Figure 1).^{8, 10}

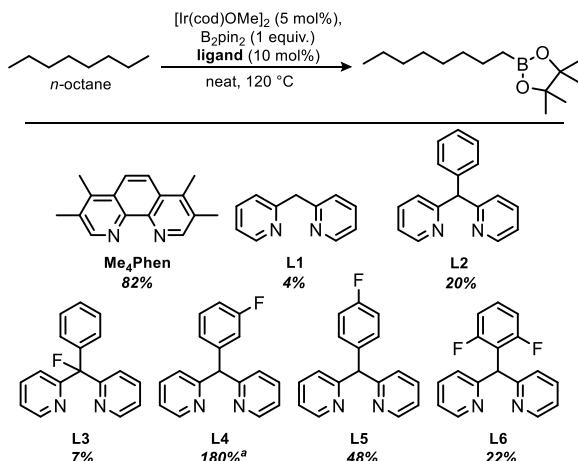


Figure 2. Comparison of ligands for *n*-octane borylation. ^aNMR yields relative to molar equivalents of B₂pin₂.

The former example illustrates a second weakness of most iridium catalysts for sp^3 borylation. The diboron source B₂pin₂ contains two equivalents of the pinacolboryl moiety, however, most iridium-catalyzed examples only incorporate one boron equivalent per diboron unit into product. This observation has led to an accepted convention where yields are reported relative to B₂pin₂, occasionally leading to reported yields exceeding 100% when quantities of the HBpin byproduct are also consumed in alkane borylation.⁸ This limitation does not extend to rhodium systems for alkane borylation, some of which can utilize HBpin as the boron source.⁶ The reduced reactivity of HBpin relative to B₂pin₂ has been attributed to differences in enthalpic driving force provided by the two reagents,²⁰ but the success of rhodium catalysts indicates that the primary limitation for iridium systems is kinetic in nature, indicating that a suitable iridium catalyst should be capable of fully consuming the borylating agent.

With the limitations of existing systems in mind, we undertook a study of alkane borylation using dipyridylaryl methane ligands **L2-L6** (Figure 2). Derivatives of the parent dipyridylphenylmethane (**L2**) have been investigated as ancillary ligands in other applications but not previously in catalysis.²¹⁻²³ The dipyridylaryl methane moiety conserves the diimine backbone of typical dtbpy or Me₄Phen ligands, while also allowing for incorporation of substituents that project out of the N-M-N plane.²⁴⁻²⁵ Our intention was that this ligand framework might bind in a facial κ^3 mode upon cyclometalation, a coordination mode which has been observed for complexes of palladium and nickel.²²⁻²³ This facial binding mode (Figure 3) would give a net 5-electron donor analogous to the Cp^* ligand, which was used extensively in early examples of alkane borylation.^{6, 26-27} Facial coordination would also allow for modulation of steric and electronic parameters through substitution on the cyclometalated ring.

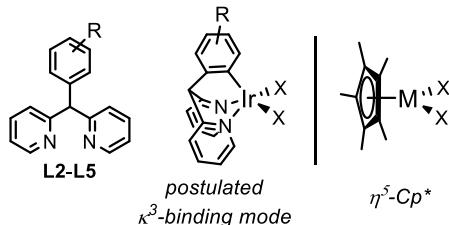


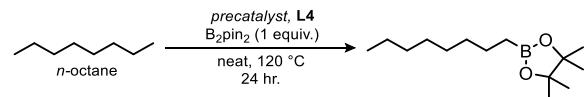
Figure 3. Illustration of a possible κ^3 -binding mode for ligands **L2-L5** and its analogy to Cp^* ligands used in previous examples.

We report that an exploration of dipyridylaryl methane ligands has led to a highly active catalyst for alkane borylation which demonstrates both enhanced catalytic performance and improved conversion efficiency of the boron reagent. These improvements allow for catalysis under non-neat conditions and improved functional group compatibility.

Results

Ligands **L1-L6** were surveyed for the borylation of *n*-octane in combination with the precatalyst $[\text{Ir}(\text{cod})\text{OMe}]_2$ (Figure 2). **L1** produced only trace quantities of octyl-Bpin. **L2** gave improved results relative to the parent scaffold **L1**, but still underperformed Me₄Phen. **L3**, which differs by fluorination of the methine position, is similarly low-yielding to **L1**. Given the poor performance of **L2** and **L3**, we were delighted to find that the fluorinated arene derivatives **L4** and **L5** produce substantial improvements in yield relative to **L1**. The *o*-difluoro derivative, **L6**, cannot cyclometalate to give the κ^3 mode illustrated in Figure 3, and provides poor yields by comparison. Meta fluoro-substituted **L4** displayed remarkable efficacy – providing near-quantitative consumption of both borane equivalents of B₂Pin₂. Following the convention wherein yields of product are calculated based one equivalent of B₂Pin₂, **L4** facilitates a yield of 180%, reflecting significant consumption of the byproduct HBpin. **L4** demonstrates a substantial increase in yield relative to the established ligand Me₄Phen when compared both under analogous conditions and under reported optimized conditions for Me₄Phen. Thus **L4** represents a dramatic improvement relative to established ligands for alkane C-H borylation.

Table 1. Optimization of catalytic C–H borylation under neat conditions.



Entry	Precatalyst (mol %)	Variation	Yield ^a
1	$[\text{Ir}(\text{cod})\text{OMe}]_2$ (5%)	None	180%
2	$[\text{Rh}(\text{cod})\text{OMe}]_2$ (5%)	None	6%
3	$[\text{Ir}(\text{cod})\text{Cl}]_2$ (5%)	None	nd
4	-	Catalyst omitted	nd
5	$[\text{Ir}(\text{cod})\text{OMe}]_2$ (1%)	None	143%
6	$[\text{Ir}(\text{cod})\text{OMe}]_2$ (5%)	Me ₄ Phen instead of L4	82%
7	$[\text{Ir}(\text{cod})\text{OMe}]_2$ (5%)	L4 omitted	<1%
8	$[(\text{Mes})\text{Ir}(\text{Bpin})_3]$ (1%)	None	>199%
9	$[(\text{Mes})\text{Ir}(\text{Bpin})_3]$ (1%)	Me ₄ Phen instead of L4	52%
10	$[(\text{Mes})\text{Ir}(\text{Bpin})_3]$ (1%)	L4 omitted	trace
11	$[(\text{Mes})\text{Ir}(\text{Bpin})_3]$ (1%)	HBpin instead of B ₂ Pin ₂	37% ^b
12	$[(\text{Mes})\text{Ir}(\text{Bpin})_3]$ (1%)	0.10 equiv. B ₂ Pin ₂ then 0.80 equiv. HBpin	71% ^b

^aYield determined by GC-FID with dodecane internal standard; based on 1 equiv. B₂Pin₂. ^bPercentage of total boron consumption.

Reaction Optimization and Scope

Optimization of the alkane borylation reaction was performed using **L4** and *n*-octane. In control experiments which omit either pre-catalyst or ligand, no product is formed. Although Cp^* Rh complexes are excellent alkane borylation catalysts,⁴ $[\text{Rh}(\text{cod})\text{OMe}]_2/\text{L4}$ is not an active catalyst system (Table 1, Entry 2). The use of $[(\text{Mes})\text{Ir}(\text{Bpin})_3]$ as the precatalyst produces a quantitative yield at a catalyst loading of only 1 mol% (Table 1, Entry 8). Using $[(\text{Mes})\text{Ir}(\text{Bpin})_3]$, we found that maximal yields were obtained at a reaction temperature of 120 °C for 24 hours.

Following the optimized conditions in Table 1, the reaction scope was explored using the substrates shown in Figure 4. For several substrates, results with the $[(\text{Mes})\text{Ir}(\text{Bpin})_3]/\text{L4}$ system are compared with results using $[(\text{Mes})\text{Ir}(\text{Bpin})_3]/\text{Me}_4\text{Phen}$ under our optimized conditions. Where available, yields for $[(\text{Mes})\text{Ir}(\text{Bpin})_3]/\text{Me}_4\text{Phen}$ using alternate reaction conditions are noted. In all cases we find a substantial increase in product formation using **L4** versus Me₄Phen. This catalytic system is compatible with ethers, tertiary amines, and esters. Butyl ethyl ether shows good β -selectivity,⁵ while cyclopentyl methyl ether and methyl hexanoate undergo selective borylation at the methyl group. Selectivity for C–H bonds β to Lewis bases has been attributed to a directing effect in a previous iridium system.⁵ Importantly, a variety of substrates are found to undergo catalytic sp^3 borylation in yields in excess of 100% on a B₂Pin₂ basis.

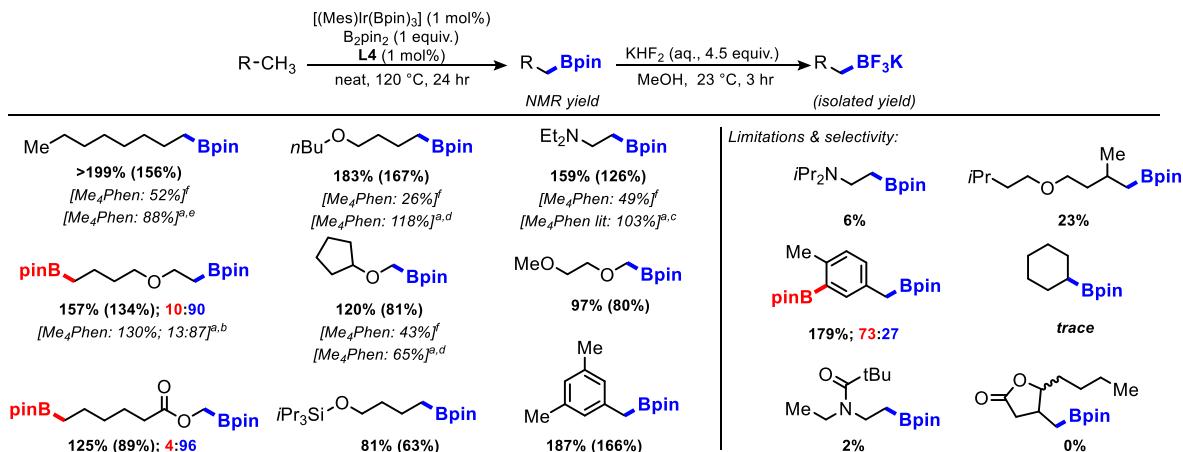


Figure 4. Substrate scope for catalytic borylation under neat conditions. ^aReported GC yield with 1^b, 2^c or 4%^d [(Mes)Ir(Bpin)₃]. ^eReported GC yield with [Ir(cod)OMe]₂ (10% Ir), 120 °C. ^fGC yields using Me₄Phen under our conditions.

The high yields obtained with this catalyst using neat substrate suggested it might be competent for catalysis in solvent at reduced substrate concentrations. Borylation in solvent is common for arene borylation but remain rare in *sp*³ borylation examples. Nearly all previous examples of *sp*³ borylation of simple alkane and ether substrates are performed in neat substrate to obtain reasonable yields of the organoborane.^{5-9,28} Previous attempts at performing this reaction on un-activated substrates in solvent typically give either poor yield of the desired organoborane or extensive borylation of the reaction solvent.^{8,10}

With the poor catalytic performance of [(Mes)Ir(Bpin)₃]/L4 towards secondary²⁹ or branched alkanes (Figure 4, right) in mind, we examined a selection of potential solvents (Table S1), arriving at the optimized conditions used in Figure 5. We find that the [(Mes)Ir(Bpin)₃]/L4 system is capable of productive alkane borylation in cyclohexane with negligible competitive solvent borylation. While the reaction proceeds to 22% yield with a single equivalent of substrate, five molar equivalents of substrate are required for high yields, representing a substantial improvement over the typical requirement for neat substrate.

A survey of substrates for *sp*³ borylation in cyclohexane solvent reveals several interesting features. All substrates which were successful under neat conditions translate well into our conditions in solvent, despite this representing a *ca.* 15-fold decrease in substrate concentration. Additionally, the lactone and amide substrates, which do not undergo catalytic borylation under our neat conditions, can be borylated effectively in cyclohexane. The lactone substrate is borylated at the *α*-branched methyl group rather than on the less hindered *n*-butyl group, which we suspect results from a directing effect analogous to that observed previously for other Lewis-basic substrates.⁵ The success of these relatively polar substrates highlights the importance of pursuing catalysts which are capable of alkane borylation in solvent, as such systems can enable the practical application of C-H borylation to substrates not suitable for neat conditions.

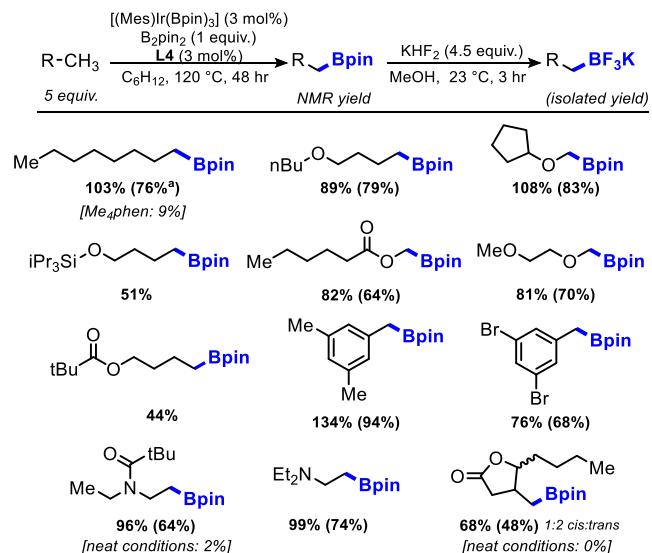


Figure 5. Substrate scope for catalytic C-H borylation conducted in cyclohexane solvent. ^a Isolated as octylBpin.

Under optimized conditions in solvent, yields in excess of 100% are observed for fewer substrates than under neat conditions. At present it is not clear what feature of the [(Mes)Ir(Bpin)₃]/L4 catalyst system is responsible for the enhanced consumption of HBpin relative to (Me₄phen)/Ir systems. When HBpin alone is used as the boron source under neat conditions, modest yields of organoborane are observed (Table 1, entry 11). This outcome is lower than expected based on HBpin consumption when B₂Pin₂ is used as the boron source. However when HBPin is added after an initial 1 hour incubation time with B₂Pin₂, substantial HBpin conversion is observed, suggesting differing roles for B₂Pin₂ and HBpin in catalyst activation (Table 1, entry 12). Results from a ¹¹B NMR study on a neat borylation reaction (Figure 6) are consistent with substantial buildup of HBpin during the initial phase of catalysis. At longer reaction times, HBpin incorporation into product becomes evident, confirming that HBpin is still a competent boron source for alkane borylation. A similar difference in reaction rate between B₂Pin₂ and HBpin has been observed in a Cp^{*}Rh system.⁶

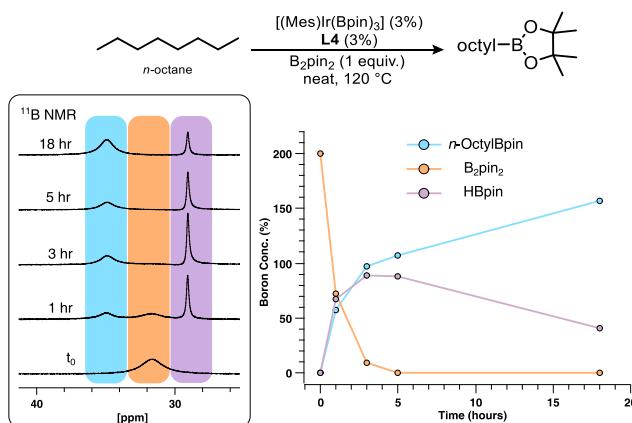


Figure 6. B_2pin_2 and HBpin consumption by ^{11}B NMR spectroscopy. See the Supporting Information.

The enhanced performance of the $[(\text{Mes})\text{Ir}(\text{Bpin})_3]/\text{L4}$ system versus previous iridium catalysts for alkane borylation presumably stems from the structure of the iridium species generated *in situ*. A single major ^{19}F NMR species is observed from the reaction of $[(\text{Mes})\text{Ir}(\text{Bpin})_3]$ with **L4** at $23\text{ }^\circ\text{C}$, which evolves to several species under catalytic conditions. Although we have not been successful in obtaining structural data elucidating the binding mode of **L4** under catalytic conditions, the significant change in reactivity as a function of substitution on the phenyl substituent argues that the aryl group does not remain distal from the metal center during key steps in the catalytic cycle. It is tempting to speculate about a role for a κ^3 binding mode resulting from aryl group cyclometalation, especially in light of the poor performance of **L6**, however it is also possible that sp^2 borylation of the ligand³⁰ could install a pinacolborane group proximal to the metal center. The Hartwig group has previously proposed a role for secondary coordination sphere interactions between metal-boryls and substrate in alkane borylation.⁵

Regardless of the mode by which **L4** enables enhanced alkane borylation catalysis, it is evident that the resulting $[(\text{Mes})\text{Ir}(\text{Bpin})_3]/\text{L4}$ catalyst system possesses major advantages over previously reported iridium catalysts. For many examples under neat conditions, both the B_2pin_2 reagent and its byproduct HBpin are consumed to give borylated product. As B_2pin_2 is typically the limiting reagent under such conditions, the $[(\text{Mes})\text{Ir}(\text{Bpin})_3]/\text{L4}$ system presents an advantage in terms of product yield and efficient utilization of the costly boron source. Additionally, this catalyst allows for the borylation of smaller excesses of substrate in hydrocarbon solvents without need for directing-group strategies. The key enabling advance here is the application of a dipyridylarylmethane ligand. Substitution of the parent ligand is found to impart profound changes to catalyst efficiency, which suggests that dipyridylarylmethane ligands are likely to offer a new and highly-tunable ligand scaffold for alkane borylation catalysis. Our ongoing efforts are directed at understanding the binding mode of dipyridylarylmethane ligands in borylation catalysis in hopes of developing increasingly active catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization of new compounds, and spectroscopic data

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Notes

The authors declare no competing financial interest.

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REFERENCES

- Wencel-Delord, J.; Glorius, F., "C–H bond activation enables the rapid construction and late-stage diversification of functional molecules." *Nature Chemistry* **2013**, *5* (5), 369–375.
- Goldberg, K. I.; Goldman, A. S., "Large-Scale Selective Functionalization of Alkanes." *Acc. Chem. Res.* **2017**, *50* (3), 620–626.
- 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* (51), 7123–7157.
- Hartwig, J. F., "Borylation and Silylation of C–H Bonds: A Platform for Diverse C–H Bond Functionalizations." *Acc. Chem. Res.* **2012**, *45* (6), 864–873.
- Li, Q.; Liskey, C. W.; Hartwig, J. F., "Regioselective Borylation of the C–H Bonds in Alkylamines and Alkyl Ethers. Observation and Origin of High Reactivity of Primary C–H Bonds Beta to Nitrogen and Oxygen." *J. Am. Chem. Soc.* **2014**, *136* (24), 8755–8765.
- Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F., "Thermal, Catalytic, Regiospecific Functionalization of Alkanes." *Science* **2000**, *287* (5460), 1995–1997.
- Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F., "Regiospecific Functionalization of Methyl C–H Bonds of Alkyl Groups in Reagents with Heteroatom Functionality." *J. Am. Chem. Soc.* **2004**, *126* (47), 15334–15335.
- Liskey, C. W.; Hartwig, J. F., "Iridium-Catalyzed Borylation of Secondary C–H Bonds in Cyclic Ethers." *J. Am. Chem. Soc.* **2012**, *134* (30), 12422–12425.
- Ohmura, T.; Torigoe, T.; Suginome, M., "Iridium-catalysed borylation of sterically hindered $\text{C}(\text{sp}^3)\text{–H}$ bonds: remarkable rate acceleration by a catalytic amount of potassium tert-butoxide." *Chem. Commun.* **2014**, *50* (48), 6333–6336.
- Ohmura, T.; Torigoe, T.; Suginome, M., "Functionalization of Tetraorganosilanes and Permethyloligosilanes at a Methyl Group on Silicon via Iridium-Catalyzed $\text{C}(\text{sp}^3)\text{–H}$ Borylation." *Organometallics* **2013**, *32* (21), 6170–6173.
- Larsen, M. A.; Wilson, C. V.; Hartwig, J. F., "Iridium-Catalyzed Borylation of Primary Benzylic C–H Bonds without a Directing Group: Scope, Mechanism, and Origins of Selectivity." *J. Am. Chem. Soc.* **2015**, *137* (26), 8633–8643.
- Cho, S. H.; Hartwig, J. F., "Iridium-Catalyzed Borylation of Secondary Benzylic C–H Bonds Directed by a Hydrosilane." *J. Am. Chem. Soc.* **2013**, *135* (22), 8157–8160.
- Liskey, C. W.; Hartwig, J. F., "Iridium-Catalyzed C–H Borylation of Cyclopropanes." *J. Am. Chem. Soc.* **2013**, *135* (9), 3375–3378.
- Shi, Y.; Gao, Q.; Xu, S., "Chiral Bidentate Boryl Ligand Enabled Iridium-Catalyzed Enantioselective $\text{C}(\text{sp}^3)\text{–H}$ Borylation of Cyclopropanes." *J. Am. Chem. Soc.* **2019**, *141* (27), 10599–10604.
- Ohmura, T.; Torigoe, T.; Suginome, M., "Catalytic Functionalization of Methyl Group on Silicon: Iridium-Catalyzed $\text{C}(\text{sp}^3)\text{–H}$ Borylation of Methylchlorosilanes." *J. Am. Chem. Soc.* **2012**, *134* (42), 17416–17419.
- Yamamoto, T.; Ishibashi, A.; Suginome, M., "Boryl-Directed, Ir-Catalyzed $\text{C}(\text{sp}^3)\text{–H}$ Borylation of Alkylboronic Acids Leading to Site-Selective Synthesis of Polyborylalkanes." *Org. Lett.* **2019**, *21* (16), 6235–6240.
- Kawamorita, S.; Murakami, R.; Iwai, T.; Sawamura, M., "Synthesis of Primary and Secondary Alkylboronates through Site-

Selective C(sp₃)-H Activation with Silica-Supported Monophosphine-Ir Catalysts." *J. Am. Chem. Soc.* **2013**, *135* (8), 2947-2950.

(18) Mita, T.; Ikeda, Y.; Michigami, K.; Sato, Y., "Iridium-catalyzed triple C(sp₃)-H borylations: construction of triborylated sp₃-carbon centers." *Chem. Commun.* **2013**, *49* (49), 5601-5603.

(19) Reyes, R. L.; Iwai, T.; Maeda, S.; Sawamura, M., "Iridium-Catalyzed Asymmetric Borylation of Unactivated Methylene C(sp₃)-H Bonds." *J. Am. Chem. Soc.* **2019**, *141* (17), 6817-6821.

(20) M Khalid, 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* (2), 890-931.

(21) Hierlinger, C.; Cordes, D. B.; Slawin, A. M. Z.; Jacquemin, D.; Guerchais, V.; Zysman-Colman, E., "Phosphorescent cationic iridium(III) complexes bearing a nonconjugated six-membered chelating ancillary ligand: a strategy for tuning the emission towards the blue." *Dalton Transactions* **2018**, *47* (31), 10569-10577.

(22) Malekis, A.; Sanford, M. S., "Facial tridentate ligands for stabilizing palladium(IV) complexes." *Organometallics* **2011**, *30* (24), 6617-6627.

(23) Chong, E.; Kampf, J. W.; Ariafard, A.; Carty, A. J.; Sanford, M. S., "Oxidatively Induced C-H Activation at High Valent Nickel." *J. Am. Chem. Soc.* **2017**, *139* (17), 6058-6061.

(24) Sberegaeva, A. V.; Zavalij, P. Y.; Vedernikov, A. N., "Oxidation of a Monomethylpalladium(II) Complex with O₂ in Water: Tuning Reaction Selectivity to Form Ethane, Methanol, or Methylhydroperoxide." *J. Am. Chem. Soc.* **2016**, *138* (4), 1446-1455.

(25) Vasko, P.; Kinnunen, V.; Moilanen, J. O.; Roemmele, T. L.; Boere, R. T.; Konu, J.; Tuononen, H. M., "Group 13 complexes of dipyridylmethane, a forgotten ligand in coordination chemistry." *Dalton Transactions* **2015**, *44* (41), 18247-18259.

(26) Chen, H.; Hartwig, J. F., "Catalytic, Regiospecific End-Functionalization of Alkanes: Rhenium-Catalyzed Borylation under Photochemical Conditions." *Angew. Chem. Int. Ed.* **1999**, *38* (22), 3391-3393.

(27) Iverson, C. N.; Smith, M. R., "Stoichiometric and Catalytic B-C Bond Formation from Unactivated Hydrocarbons and Boranes." *J. Am. Chem. Soc.* **1999**, *121* (33), 7696-7697.

(28) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F., "Ruthenium-Catalyzed Regiospecific Borylation of Methyl C-H Bonds." *J. Am. Chem. Soc.* **2006**, *128* (42), 13684-13685.

(29) Wei, C. S.; Jiménez-Hoyos, C. A.; Videau, M. F.; Hartwig, J. F.; Hall, M. B., "Origins of the Selectivity for Borylation of Primary over Secondary C-H Bonds Catalyzed by Cp*-Rhodium Complexes." *J. Am. Chem. Soc.* **2010**, *132* (9), 3078-3091.

(30) Yang, Y.; Gao, Q.; Xu, S., "Ligand-Free Iridium-Catalyzed Dehydrogenative ortho C-H Borylation of Benzyl-2-Pyridines at Room Temperature." *Adv. Synth. Catal.* **2019**, *361* (4), 858-862.

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