Ligand-Driven Advances in Iridium Catalyzed sp^3 C-H Borylation: 2,2'-Dipyridylarylmethane

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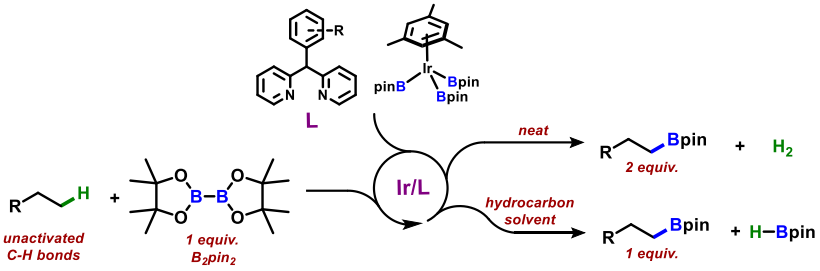


Abstract The field of catalytic C-H borylation has grown considerably since its founding, providing a means for the preparation of synthetically versatile organoborane products. While sp^2 C-H borylation methods have found widespread and practical use in organic synthesis, the analogous sp^3 C-H borylation reaction remains challenging and has seen limited application. Existing catalysts are often hindered by incomplete consumption of the diboron reagent, poor functional group tolerance, harsh reaction conditions, and the need for excess or neat substrate. These challenges acutely affect C-H borylation chemistry of unactivated hydrocarbon substrates, which has lagged in comparison to methods for the C-H borylation of activated compounds. Herein we discuss recent advances in sp^3 C-H borylation of undirected substrates in the context of two particular challenges: (1) utilization of the diboron reagent and (2) the need for excess or neat substrate. Our recent work on the application of dipyridylarylmethane ligands in sp^3 C-H borylation has allowed us to make contributions in this space and has presented an additional ligand scaffold to supplement traditional phenanthroline ligands.

Key words C-H borylation, alkane, iridium catalysis

Introduction

The catalytic borylation of C-H bonds provides a direct method of preparing synthetically valuable organoborane products from readily available chemical feedstocks. Extensive work over the past several decades has led to the development of relatively mature sp^2 C-H borylation methodology for many classes of arene and heteroarene substrates. Modern methods offer a host of strategies aimed at addressing issues of usability, functional group tolerance, and selectivity[1-5]; however, the corresponding borylation of aliphatic sp^3 C-H bonds remains relatively underdeveloped.

Sp^3 C-H borylation can be categorized by substrate type into activated, directed, or unactivated substrate subclasses. Catalysts based on iridium or rhodium have been broadly applied in thermal C-H borylation reactions across these subclasses, while other elements have found more-limited applications in the borylation of activated or directed substrates. Our work in this area aims to address limitations to the borylation of unactivated substrates, therefore we will focus the discussion on systems which operate effectively on alkyl C-H bonds. The unique challenges presented in the C-H bond activation of simple alkanes have been eloquently summarized by Crabtree.[6]

Early reports of thermal, catalytic alkane borylation made use of transition metal pentamethylcyclopentadienyl (Cp*) catalysts with HBpin or B_2pin_2 (pin = pinacolato) as the borylation reagent (Figure 1).[7] These systems show strong selectivity for methyl C-H bonds over methylene or methine positions, mirroring observations in related stoichiometric[8-11] and photochemical[12] systems for sp^3 C-H activation. While Cp* complexes of Re, Ru, and Ir effectively catalyze the transformation, Cp*Rh borylation catalysts provide the greatest efficacy. Cp*Ir and Rh catalysts operate at 150 °C in neat hydrocarbon to give yields in the range of 20-60% and 50-90%, respectively, on a boron basis with limiting B_2pin_2.[7]

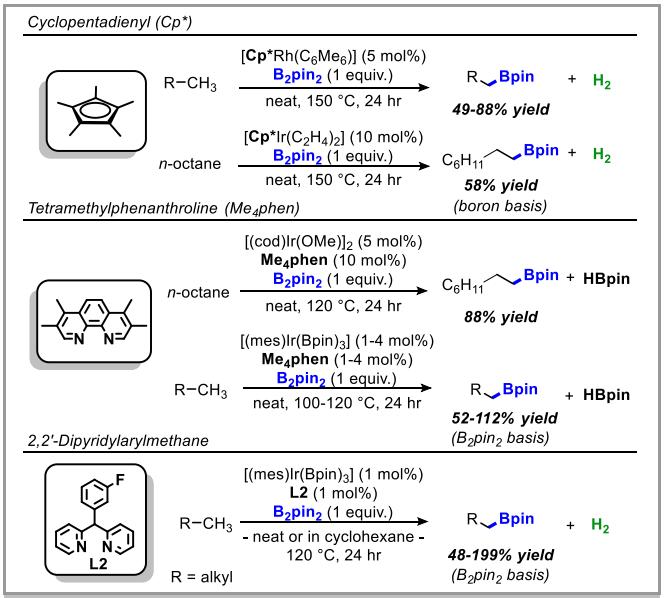


Figure 1 Review of C-H borylation catalysts and ligands for the sp^3 C-H borylation of unactivated substrates: Cp*[7], Me_4phen[13-14], **L2**[15]. Yields reported relative to either 1 equiv. B_2pin_2 or relative to total boron equivalents. See discussion of both conventions below.

A transition to 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4phen)-supported iridium catalysts allowed for C-H borylation at lower temperatures in the range of 100-120 °C (Figure 1).[16-17] Along with reduced temperature requirements, the Me_4phen/Ir system contributed a more accessible catalyst with modest improvements in scope. This system has been studied extensively by Hartwig and others, becoming the benchmark for *sp*³ borylation of unactivated substrates. Despite its advantages, the Me_4Phen/Ir system has significant limitations which remained largely unaddressed until recently.[18] Most notably, C-H borylation of unactivated substrates by Me_4Phen/Ir requires the presence of large excess or neat substrate, with B_2pin_2 serving as the limiting reagent. In contrast to earlier Cp*Rh systems, Me_4Phen/Ir typically gives no more than a single turnover per equivalent of B_2pin_2 reagent. Thus, the Me_4Phen/Ir system shows poor atom economy both with respect to the requirement for neat substrate and the incomplete conversion of both boron equivalents.

Ligand systems for iridium-catalyzed *sp*³ C-H borylation

In a recent publication[15] we detailed a new catalytic system based on a dipyridylarylmethane ligand which offers notable improvements over the Cp*Ir, Rh, and Me_4Phen/Ir systems. Our approach to the design of new ligands for iridium-catalyzed *sp*³ C-H borylation was informed to a significant extent by mechanistic studies published by Hartwig and Sakai. A general catalytic cycle for iridium catalyzed C-H borylation with diimine ligands, such as Me_4Phen, is shown in Figure 2.[19-21] Catalyst activation is proposed to generate 5-coordinate trisboryl Ir complex **A**. This species has been identified as the catalyst resting state in arene borylation,[19] and in that case is believed to react with arene substrates via rate-limiting oxidative addition to give a formal Ir(V) trisborylhydridoaryl **B**.[19,22]

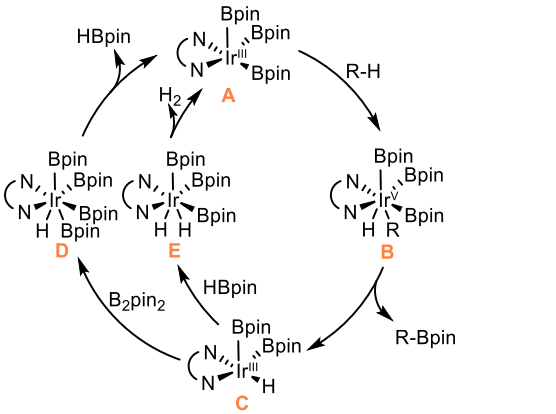


Figure 2. Proposed mechanism for C-H borylation.

Computational treatments of *sp*³ C-H borylation also support an oxidative addition mechanism for C-H cleavage,[14,23-24] though a σ-bond metathesis mechanism has not been rigorously excluded.[25] The resulting iridium diboryl monohydride **C** is presumed to react with B_2pin_2 to regenerate **A** and extrude HBpin. Under conditions where B_2pin_2 has been fully consumed, byproduct HBpin is proposed to supplant B_2pin_2 in the catalytic cycle, with dihydrogen serving as the terminal byproduct.[21] The utilization of HBpin thus requires a variation in mechanism, which will be discussed later.

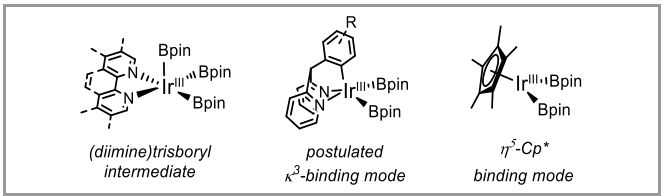


Figure 3. Postulated binding modes for various ligands for *sp*³ C-H borylation.

With the established general mechanism in mind, we hypothesized that a facial, tridentate, monoanionic ligand might serve as a substitute for the diimine and one boryl ligand in **A**, providing a binding mode analogous to that of Cp* (Figure 3). We identified dipyridylarylmethane derivatives as a suitable starting point, anticipating that cyclometalation would confer a κ^3-binding mode. Due to the high *trans* influence of boryl and σ-aryl ligands, dipyridylarylmethane derivatives would be expected to favor a geometry with an open site mutually *cis* to the boryl ligands, and *trans* to the σ-aryl (Figure 3). In this manner we expected dipyridylarylmethane derivatives could mimic the facial binding mode of Cp* systems for alkane borylation while also closely resembling the electronic properties of the highly-effective diimine ligand systems.[16-17] Additionally, cyclometalation of the aryl ring under the reaction conditions would allow for the use of the same pre-catalysts previously found to be effective in diimine systems.

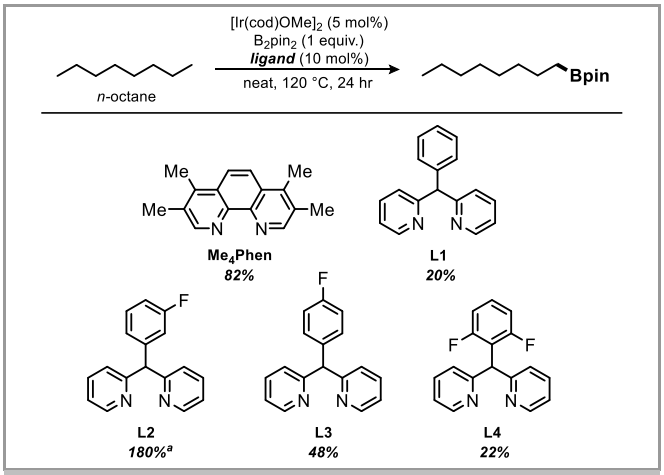


Figure 4. Effect of substitution on dipyridylarylmethane ligands. Conditions: 0.1 mmol B_2pin_2, 1 mL *n*-octane (6 mmol). [a]Yields reported relative to 1 equiv. of B_2pin_2 reagent with yields > 100% indicating consumption of HBpin byproduct.

As we recently reported,[15] we found that while the dipyridylphenylmethane ligand **L1**, does give an active catalyst for *n*-octane borylation, it significantly underperforms the benchmark Me_4Phen/Ir system (Figure 4). As part of an effort to examine the fate of the ligand during catalysis, we prepared the fluorinated derivatives **L2** and **L3**. To our surprise, this modification gives catalyst systems which are substantially more active than the parent ligand **L1**. In particular, *n*-octane borylation with the 3-fluoro analogue **L2** yields up to 2 equivalents of product per B_2pin_2 equivalent, a result which is unusual for diimine-based systems. Additionally, the strong performance of this system under traditional neat substrate conditions for borylation inspired us to examine the much more challenging borylation of substrates in solvent, potentially

allowing us to address a second major limitation of existing *sp*³ C-H borylation catalysts.

The substantial improvement in catalyst performance we observed with **L2** versus **L1** is evocative of recent observations by the Hartwig group on phenanthroline derivatives.[16,18] An exploration of substituent effects resulted in the identification of 2-methylphenanthroline as a particularly effective ligand. 2-methylphenanthroline provides a substantial rate increase over Me_4Phen, which allows for *sp*³ borylation under conditions of limiting alkane in cyclooctane solvent.[18] Subtle perturbations of the phenanthroline core have been shown to have a profound impact on transition state energies and therefore catalyst activity,[16] and it would appear that dipyridylarylmethane derivatives share this remarkable sensitivity to substitution.

Although our studies on **L2** are still ongoing, a comparison of a series of related ligands argues strongly for a role for ligand cyclometalation, and thus a κ^3-coordination mode in the active catalytic species. In particular, the 2,6-difluoro derivative **L4**, which cannot cyclometalate via *ortho*-C-H activation, shows relatively poor performance. The enhanced activity of the 3-fluoro derivative (**L2**) relative to the 4-fluoro (**L3**) variant may be explained by a difference in propensity to cyclometalate, as electron deficient arenes are more susceptible to oxidative addition at iridium boryls.[19] Other differences may result from electronic effects in the σ-systems of the putative κ^3 coordinated iridium complexes formed upon cyclometalation. Alternatively, it is possible that C-H borylation of the ligand serves either an activating or deactivating role in catalysis, as it does in at least one other case,[17] though this hypothesis remains unresolved at this time.

*Sp*³ C-H borylation in solvent

Achieving high reactivity while maintaining selectivity in undirected C-H functionalization is an intrinsic challenge to any approach, owing to the number of C-H bonds in a typical substrate. This challenge is amplified when reactions are conducted with small excess of substrate in organic solvent, since the rate of substrate borylation is likely to be diminished and competitive borylation of solvent must be avoided. Traditional alkane borylation systems including both Cp*Rh/Ir[7,12,26] and (diimine)Ir[13,27] perform quite poorly in solvent. Catalysts have been developed for the *sp*³ borylation of activated (including benzylic, cyclopropane, and alkylsilane substrates)[27-30] or directed substrates,[29,31-35] however, the C-H borylation of unactivated alkyl substrates in solvent was largely unaddressed prior to recent work by Hartwig[18] and ourselves.[15]

The success of the [(cod)IrOMe]$_2$/**L2** system in neat *n*-octane (Figure 4) inspired us to survey potential conditions for borylation in solvent. We ultimately identified a procedure that allowed for the *sp*³ C-H borylation of unactivated substrates in cyclohexane, with a key improvement resulting from a switch in the iridium precursor from [(cod)IrOMe]$_2$ to [(Mes)Ir(Bpin)$_3$]. Although 7 catalyst turnovers could be obtained using a single equivalent of *n*-octane in cyclohexane, we found that using 5 equivalents of *n*-octane relative to B_2pin_2 was sufficient to give high yields of the *n*-octylboronate product. By comparison, attempts at the borylation of *n*-octane with Me_4phen/Ir in cyclooctane give fewer than 2 turnovers. [27]

Furthermore, an examination of the substrate scope of the reaction in solvent revealed increased tolerance of certain functional groups. A lactone substrate and a pivalamide substrate were both unreactive when employed neat, but undergo productive and selective borylation when carried out in small excess in solvent (Figure 5). 3-methyl-4-octanolide undergoes borylation at the α-branched methyl group proximal to the lactone rather than on the less hindered *n*-butyl group, presumably as a result of a directing effect.[14] It is plausible that the failure of these relatively polar substrates under neat conditions stems from dependence of neat reaction conditions on the substrate identity. When diluted in cyclohexane, the solution polarity is attenuated by the bulk hydrocarbon. Under non-neat conditions we observed few yields above 100% (1 equiv. relative to B_2pin_2), reflecting reduced HBpin consumption under the more-challenging reaction conditions. This effect likely stems from the much lower rate of C-H borylation when HBpin is the boron source (*vide infra*).

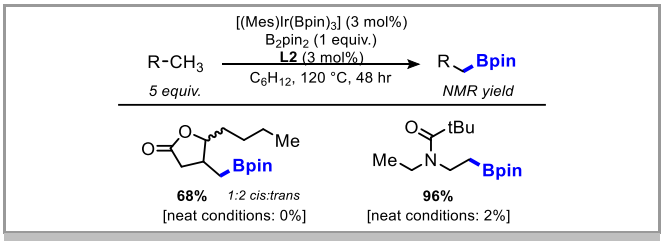
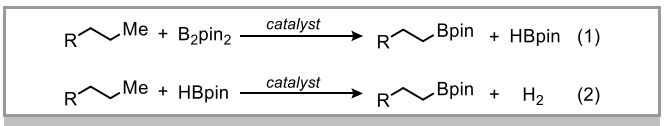


Figure 5. Catalysis in solvent on polar substrates. NMR yields given relative to B_2pin_2.

While our group was successful in reducing the required substrate excess to 5 equivalents and carrying out borylation in cyclohexane solvent, a coincident report by the Hartwig group showed that the 2-methylphenanthroline ligand enables *sp*³ borylation of unactivated substrates in stoichiometric quantities in cyclooctane.[18] In both cases, the success of cycloalkane solvents reflects the intrinsic selectivity of iridium *sp*³ C-H borylation catalysts for methyl C-H bonds over methylene C-H bonds. Substantial limitations remain for both systems however, leaving space for the development of improved catalysts for *sp*³ C-H borylation chemistry in solvent.

Consumption of the diboron reagent B_2pin_2



Equations 1 & 2. Consumption of boron equivalents from B_2pin_2.

C-H borylation using the diboron reagent B_2pin_2 comprises two separate but analogous catalytic reactions. In the first reaction shown in eqn. 1, B_2pin_2 is consumed to give one equivalent of product and one equivalent of HBpin. In the second (eqn 2), the byproduct HBpin serves as the borylating agent to produce H_2 as the terminal byproduct of C-H cleavage, along with a second equivalent of organoborane. Early Cp* Rh/Ir examples of alkane sp³ borylation catalyze both reactions to different extents, exhibiting complete consumption of B_2pin_2 as well as conversion of byproduct HBpin to H_2 in select cases.[7,12,26] While the Me_4phen/Ir system for *sp*³ C-H borylation is capable of effecting

eqn. 1 at lower temperatures (*ca.* 100-120 °C), poor conversion of HBpin by this catalyst system has given rise to the convention of reporting alkane borylation yields relative to molar equivalents of B_2pin_2.[13] Thus, a system that produces 2 equiv. of alkyl boronate from 1 equiv. B_2pin_2 is often reported as achieving 200% yield.

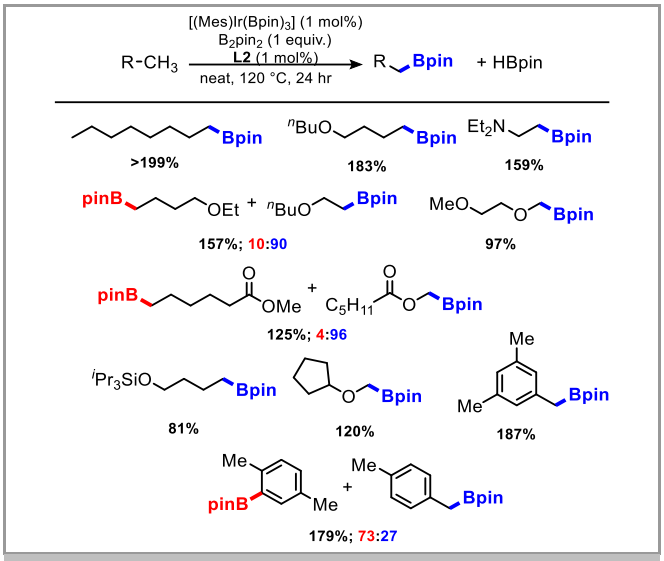


Figure 6. C-H borylation of neat substrates. Conditions: 0.3 mmol B_2pin_2, 3 mL substrate. [a]Yields reported relative to 1 equiv. of B_2pin_2 reagent with yields > 100% indicating consumption of HBpin byproduct.

Since the vast majority of alkane borylation systems (including our own) use B_2pin_2 as the limiting reagent, conversion of the HBpin byproduct of eqn 1. is an important goal for the atom economy of the process. Especially in the case of simple, unactivated hydrocarbon substrates, the diboron reagent can be more valuable than the substrate. The challenges to HBpin utilization likely stem both from differences in the thermodynamic driving force[1] for eqns. 1 and 2 and from kinetic challenges arising from distinct elementary steps in the two catalytic cycles.[21] For instance, although the (diimine)Ir trisboryl species **A** is the presumed resting state of the catalytic reaction associated with eqn 1, the role of **A** and the identity of the resting state are less clear when HBpin is used. At a minimum, HBpin consumption requires the extrusion of molecular dihydrogen – either by reductive elimination of an iridium dihydride intermediate such as **E,** or by σ-bond metathesis of an iridium hydride with an equivalent of HBpin.[21]

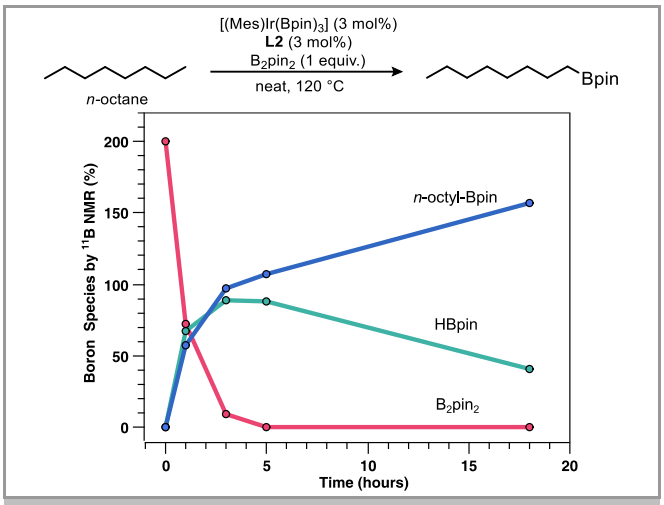
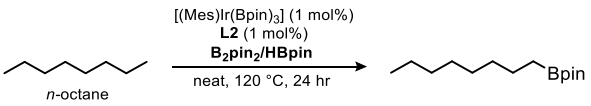


Figure 7. Boron species by ^{11}B NMR during catalysis.

Under our optimized conditions with [(Mes)Ir(Bpin)$_3$]/**L2**, significant consumption of byproduct HBpin is only observed under neat conditions. Borylation of *n*-octane proceeds quantitatively, while a variety of other substrates give yields consistent with modest to excellent HBpin conversion (Figure 6). Consumption of HBpin appears to be substrate dependent, mirroring observations with previous Cp*Rh catalysts.[36] When a catalytic reaction is monitored by ^{11}B NMR, essentially quantitative consumption of B_2pin_2 is observed prior to any notable HBpin conversion, suggesting that at the halfway point of catalysis the B_2pin_2 has been fully consumed. (Figure 7).

Table 1 Comparison of boron reagents for the borylation of *n*-octane

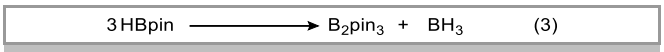


Entry	Boron Source	Yield (Boron Basis)[a]
1	B_2pin_2	>99%
2	HBpin	37%
3	0.10 equiv. B_2Pin_2 0.80 equiv. HBpin	36%
4	0.10 equiv. B_2Pin_2 then 0.80 equiv. HBpin after 1 hr.	71%

[a]Yield based on percentage of total boron consumption. Conditions: 0.2 mmol total boron, 1 mL n-octane. For instance: 0.1 mmol (0.1 M) B_2pin_2 and 0.2 mmol (0.2M) HBpin for entries 1 and 2 respectively.

Although B_2pin_2 is completely consumed in the case of *n*-octane, HBpin alone is a poor reagent for octane borylation with [(Mes)Ir(Bpin)$_3$]/**L2** – giving only 37% of the expected yield (Table 1). The poor performance with HBpin alone can only be explained by a difference in catalyst speciation or activation between the two boron reagents. Indeed, initial incubation of the pre-catalyst reagents with 0.1 equiv. B_2pin_2 followed by addition of HBpin gave significantly improved yield, arguing for an important role for B_2pin_2 in catalyst activation. The poor performance of the HBpin reagent is not remedied by simultaneous addition of a catalytic quantity of B_2pin_2, suggesting HBpin may be detrimental to precatalyst activation. Our ^{11}B NMR monitoring study also shows that the second phase of catalysis during which HBpin is consumed proceeds at a significantly

diminished rate when compared to the first phase with B_2pin_2, which reinforces the point that catalysis with HBpin should be considered as a second kinetic regime.



Equation 3. HBpin disproportionation observed by the Hartwig group.[18]

The Hartwig group has also published a ^{11}B NMR study of an alkane borylation reaction in progress for their highly-active 2-methylphenanthroline/Ir system.[18] They found that a buildup of byproduct HBpin leads to inhibition of catalysis, and that conducting catalysis in an open system resulted in increased yields of organoborane. Their NMR experiments demonstrate that under such conditions HBpin undergoes a redistribution reaction according to eqn 3, driven by loss of the volatile BH_3 byproduct. Continuous removal of HBpin by redistribution was apparently key to the success of the 2-methylphenanthroline/Ir catalytic system. However, NMR studies of the [(Mes)Ir(Bpin)$_3$]/**L2** system do not support a role for HBpin redistribution in our case, as the B_2pin_3 byproduct is not detected during borylation using the [(Mes)Ir(Bpin)$_3$]/**L2** catalyst. Taken together, the ^{11}B NMR studies by the Hartwig group and ourselves provide a useful pair of examples for monitoring both the fate of boron equivalents and byproducts during catalysis and for elucidating differing effects of HBpin concentration.

Conclusion and Future Outlook

The [(Mes)Ir(Bpin)$_3$]/**L2** system enables the *sp³* C-H borylation of small excess of substrate in solvent, which increases the scope of suitable substrates. When applied to neat substrates, C-H borylation occurs even with the HBpin byproduct of borylation by B_2pin_2, leading to drastically improved conversion on a boron basis. Catalyst performance has been shown to be highly sensitive to ligand substitution, mirroring results on related diimine systems. Further development of *sp³* C-H borylation systems should be performed with the sensitivity of catalyst performance to ligand substitution in mind.

Although significant strides have been made towards both the efficient utilization of the diboron reagent and the functionalization of stoichiometric quantities of substrate, no catalytic system yet offers a complete solution. It is clear that further development is still needed for *sp³* C-H borylation catalysis to overcome its longstanding limitations. The demonstrated success of suitably-substituted dipyridylarylmethane ligands in the *sp³* C-H borylation of unactivated substrates therefore offers an additional dimension for ligand design, optimization, and tuning that we expect will play an important role moving forward.

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