

# IRIDIUM-CATALYZED C-H BORYLATION

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## INTRODUCTION

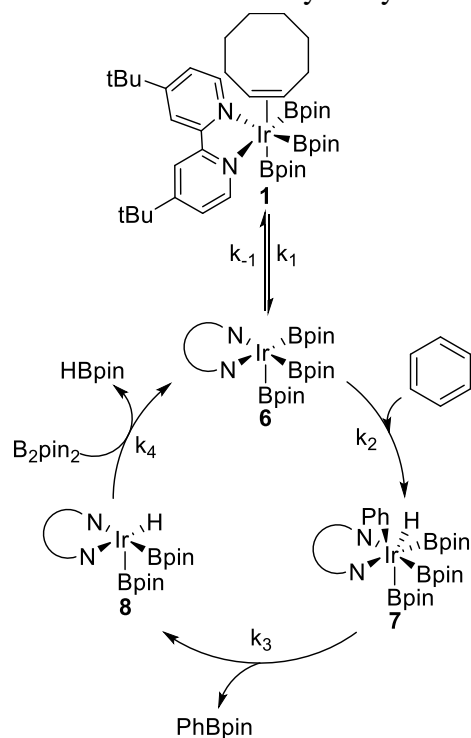
C-H bonds are one of the most abundant functional groups in organic chemistry. However, functionalizing these bonds can be difficult without the use of activating groups or forcing reaction conditions. By contrast, boronic acid or boronic ester functional groups are useful for various modifications including in the widely used Suzuki-Miyaura cross-couplings.<sup>1</sup> Traditionally, two types of reactions have been used to place boron on organic molecules: organometallic transformations with highly reactive intermediates or Miyaura borylations. These reactions require previously installed functionality or the use of highly reactive reagents limiting substrate compatibility.<sup>2</sup> The use of transition metals can provide a route to better atom economy, catalyst-driven selectivity, and improved compatibility for reactive functional groups.

Initial reports of C-H borylations using iron and tungsten catalysts required stoichiometric quantities of metal. Similar rhodium, manganese, and rhenium catalysts required high reaction temperatures, reducing the reaction scope.<sup>2</sup> Two separate iridium-catalyzed C-H borylations were discovered by Milton Smith and John Hartwig.<sup>2</sup> These seminal discoveries sparked further mechanistic understanding and reaction development.

## MECHANISM DETERMINATION

With initial observations of a potential Ir(III) catalyst complex, Ishiyama, Miyaura, and Hartwig performed an extensive analysis of the reaction mechanism. The observed intermediate implicated an unusual Ir(III)-Ir(V) cycle requiring further supporting evidence. Using the bipyridine-ligated trisboryl complex (**1**) and either pinacol borane (HBpin) or bis(pinacol)diborane (B<sub>2</sub>pin<sub>2</sub>)(**Scheme 1**) Ishiyama, Miyaura, and Hartwig sought to justify the proposed cycle. Through labeling, competition, and kinetic experiments along with computation from Sakaki and coworkers, the Ir(III)-Ir(V) cycle was verified. Dissociation of cyclooctene initiates the cycle producing a 16-electron iridium(III) complex (**6**). This complex oxidatively adds the arene to produce the 18-electron iridium(V) species (**7**). Reductive elimination of the product results in the 16-electron iridium(III) hydride species (**8**) which then oxidatively

**Scheme 1: Catalytic Cycle**



adds  $B_2pin_2$  and reductively eliminates  $HBpin$  to regenerate the 16-electron iridium(III) complex (**6**) (Scheme 1).<sup>2</sup> This mechanistic understanding provided an avenue for further reaction development for regio- and stereospecific C-H borylation.

## DEVELOPED REACTIONS

In simple mono- or di-substituted arenes, regioselectivity required steric hindrance from substituents on the ring. Therefore, borylation was disfavored at the *ortho* position on 6-membered mono-substituted aryl rings, with low *meta* and *para* selectivity in the absence of another driving force.<sup>2</sup> The placement of silicon directing groups allowed for selective *ortho* borylation. Subsequently, ammonium sulfate salts provided selective *para* borylation through steric interactions. *Meta* selective borylations required further ligand design.<sup>3</sup> Similar strategies have been used to direct borylation on heteroarenes.<sup>4</sup>

Until recent years, iridium-catalyzed  $sp^3$  C-H borylations remained elusive due to the strength of such bonds. Only recently was borylation observed on primary  $sp^3$  C-H bonds. This transformation reveals the possibility for undirected borylations using iridium catalysis despite the incompatibility with arene rings.<sup>5</sup> With ligand modification, enantioselective  $sp^3$  C-H borylation was observed. Compared to primary  $sp^3$  C-H borylation, these conditions were compatible with arene rings.<sup>4</sup> This type of selectivity is currently limited to substrates with specific directing groups and is likely to be a continued point of study.

## CONCLUSION

Iridium-catalyzed C-H borylation allows for functionalization at various positions of arenes, and is under development in  $sp^3$  C-H bonds. Further developments may rely on the mechanism to continue to broaden the capabilities of iridium-catalyzed borylations. Broadening the scope of such reactions would not only improve understanding, but allow for wider variations of substrates in medicine or synthesis.

## REFERENCES

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