

Cobalt-Catalyzed C–H Borylation

Jennifer V. Obligation, Scott P. Semproni, and Paul J. Chirik*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

S Supporting Information

ABSTRACT: A family of pincer-ligated cobalt complexes has been synthesized and are active for the catalytic C–H borylation of heterocycles and arenes. The cobalt catalysts operate with high activity and under mild conditions and do not require excess borane reagents. Up to 5000 turnovers for methyl furan-2-carboxylate have been observed at ambient temperature with 0.02 mol % catalyst loadings. A catalytic cycle that relies on a cobalt(I)–(III) redox couple is proposed.

Carbon–hydrogen bonds are abundant in most organic molecules, and methods for their direct, selective catalytic functionalization are attractive as an efficient means to access more complex molecular entities.^{1–3} The transition-metal-catalyzed borylation of heterocycles and arenes has emerged as one of the most effective and efficient methods for C–H functionalization, in part due to the versatility of the resulting aryl boronate esters in synthesis.^{4–6} Catalytic borylation activity has been observed with several transition-metal complexes, although in most cases the synthetic utility is limited by poor activity or photochemical methods required for catalyst activation.^{4,7} Iridium diene complexes such as [Ir(COD)OMe]₂ (COD = 1,5-cyclooctadiene) in combination with substituted bipyridine or phenanthroline ligands are the most widely used catalysts for C–H borylation.⁸ Silica-supported monophosphine rhodium and iridium catalysts as well as iridium nanoparticles in ionic liquids have also been reported and offer reactivity and selectivity advantages over their soluble counterparts.^{9–12} Despite their widespread application, the number of precious metal catalysts reported in the literature that enable efficient turnover is limited.⁷ Thus, the discovery of new, readily accessible and modular catalyst platforms is attractive as rational changes to the electronic and steric profile of the catalyst may expand the scope and utility of metal-catalyzed C–H borylation.

Base metal compounds are of interest because of their potential cost and environmental advantages but more importantly due to their distinct electronic structures and ability to enable new mechanistic pathways that may ultimately result in new reactivity.¹³ Cyclopentadienyl iron N-heterocyclic carbene,¹⁴ Fe₂O₃ nanoparticles,¹⁵ and heterobimetallic copper complexes¹⁶ have recently been reported for the borylation of aromatic compounds. While important precedents for base metal-catalyzed C–H functionalization, the catalyst loadings are high, and the substrate scope is limited. Also the operating conditions, either continued irradiation or use of sacrificial olefins, present practical disadvantages as compared to the established iridium-catalyzed methods. Here we describe new families of cobalt alkyl complexes supported by different classes

of readily synthesized and modular pincer-type ligands that are active for catalytic C–H borylation under thermal conditions. The base metal-catalyzed C–H functionalization process likely operates via a Co(I)–(III) redox cycle, distinct from known Ir(III)–(V) pathways.

Inspired by recent reports of iron^{17–19} and cobalt-catalyzed alkene hydroboration,²⁰ we reasoned that if a sufficiently electron-rich cobalt center was generated, C–H activation may be enabled and coupled to C–B bond formation. To test this hypothesis, cobalt alkyl complexes with both aryl- and alkyl-substituted redox-active bis(imino)pyridine ligands²¹ were initially evaluated for the catalytic borylation of 2-methylfuran with pinacolborane (HBPin) (Figure 1). Analysis of the products by ¹H NMR spectroscopy and GC-MS established selective borylation of the 5-position of the heterocycle. With the aryl-substituted compound **1**, 59% conversion of the starting material was observed after 72 h at 23 °C. Introduction of a cyclohexyl imine substituent increased the activity of the cobalt catalyst such

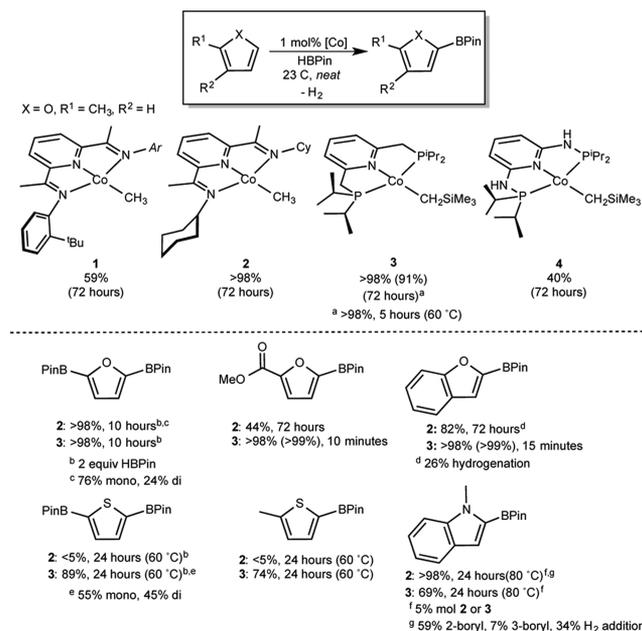


Figure 1. Evaluation of cobalt pincer complexes for the catalytic borylation of five-membered heterocycles with HBPin. Reported values are % conversions with respect to the five-membered heterocycle as determined by gas chromatography using mesitylene as an internal standard. Product ratios were determined by NMR spectroscopy, and the values in parentheses are isolated yields.

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that quantitative conversion was observed in the same time frame, suggesting that more electron-donating ligands²² increase the rate of catalytic C–H functionalization.

To generate a more electron-rich base metal center, the supporting pincer ligand was modified by replacing the relatively π -acidic imine arms with more σ -donating phosphines. The cobalt alkyl complexes, **3** and **4** were synthesized by straightforward alkylation of the corresponding cobalt chloride complexes,^{23–25} and the solid-state structure of **3** was confirmed by X-ray diffraction (Figure S1). The [CH₂SiMe₃] hydrocarbyl substituent was chosen due to its commercial availability and demonstrated success in cobalt catalysis.²⁶ In the solid state, **3** is diamagnetic yet the ¹H NMR spectrum recorded in toluene-*d*₈ exhibits paramagnetically shifted and broadened resonances (Figures S2 and S3). Cooling the sample to –75 °C resulted in sharpening of the peaks and shifting to expected diamagnetic references values. This behavior is likely a result of thermal population of a low-lying triplet state upon warming.

Both **3** and **4** were active for the borylation of 2-methylfuran, reaching >98% and 40% conversion after 72 h, respectively. Importantly, no solvent was needed, and efficient conversion and high yields were observed with stoichiometric quantities of HBPIn. Cobalt precatalyst **3** also functions using B₂Cat₂ (Cat = catechol) as the boron source. In the presence of 1 mol % of **3**, the selective borylation of 2-methylfuran was accomplished in THF solution over the course of 1 h at 80 °C.^{27,28}

To further evaluate catalyst performance, the borylation of a family of representative five-membered heterocycles containing oxygen, sulfur, and nitrogen was studied with **2** and **3**. The phosphine-substituted pincer precatalyst, **3**, was superior in each case, likely due to a more electron-rich cobalt center, which facilitates oxidative addition of the C–H bonds of the substrate. Up to 5000 turnovers have been observed with the borylation of methyl furan-2-carboxylate at 23 °C over the course of 6 h in the presence of 0.02 mol % of **3**. Isolated yields for the borylation products of 2-methylfuran, methyl furan-2-carboxylate, and benzofuran were 91%, >99%, and >99%, respectively. The bis(imino)pyridine compound, **2** proved incompatible with sulfur-containing heterocycles perhaps a result of increased electrophilicity. Precatalyst **2** was effective for the borylation of furans and *N*-methyl indole, although in some cases competing substrate reduction was observed, consistent with the known hydrogenation activity of this class of cobalt alkyl.^{29,30} With **3**, exclusive borylation of the position adjacent to the heteroatom was observed with each substrate correlating with the relative acidity of the C–H bonds.^{4,31} For parent furan and thiophene, the borylation of the initial product was sufficiently rapid that the 2,5-disubstituted product was also observed.

The performance of **3** for the catalytic borylation of a family of substituted pyridines was also examined. These substrates were of interest due to their prevalence in pharmaceuticals³² and the enabling impact that direct C–H functionalization methods have on elaboration of lead compounds in medicinal chemistry. Each catalytic reaction was conducted in a 0.55 M THF solution of substrate in the presence of B₂Pin₂ and 3 mol % **3** at 80 °C (Figure 2). Experiments in solution were selected over neat conditions as substituted pyridines are often solids or valuable and therefore sometimes available in only limited quantities.

Two sets of catalytic conditions were selected that varied by the ratio of B₂Pin₂ to the substrate. The first, termed condition **A**, employed 0.5 equiv of B₂Pin₂ (1 BPIn unit per pyridine) and generated H₂ as the reaction byproduct. Using this protocol, HBPIn is formed during catalytic turnover and is known to be a

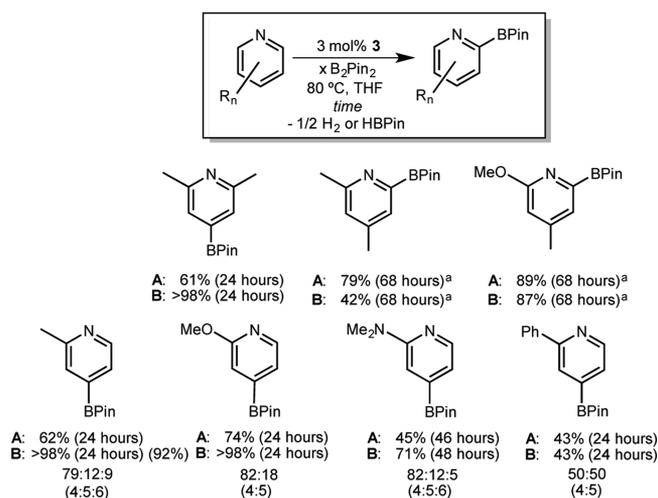


Figure 2. Cobalt-catalyzed borylation of pyridines with **3**. Conditions **A** with 0.5 equiv B₂Pin₂ and **B** with 1.0 equiv of B₂Pin₂. Reported numbers are % conversions of the corresponding pyridine derivative determined by GC analysis using mesitylene as an internal standard, and the value in parentheses is the isolated yield. Product ratios were determined by NMR analysis. Values under the % conversions are selectivities, and the numbers in parentheses denote the position of borylation. Selectivities were the same for both conditions **A** and **B**.

less effective borylation agent, accounting for the reduced activity of the catalyst. These conditions are useful, however for the differentiation of the relative rates of reaction among the different pyridines. Condition **B** employed 1 equiv of B₂Pin₂ (2 BPIn equivalents per pyridine) relative to substrate and was designed to maintain the diboron species as the active borylating agent, forming HBPIn as a byproduct.

The cobalt-catalyzed borylation of 2,6-lutidine with 3 mol % of **3** selectively borylated the 4-position of the ring, consistent with functionalization of the most sterically accessible C–H bond. Notably, 2,4-lutidine and 2-methoxy-4-methyl pyridine also underwent smooth catalytic borylation in the presence of **3** to selectively yield the 2-borylated products. To our knowledge, a successful iridium-catalyzed borylation of these two substrates has not been published. In our hands, applying the reported published conditions for the iridium-catalyzed borylation of 2,6-lutidine³³ for the 2,4-isomer furnished a complex mixture of products. The desired 2-borylated product accounted for only 28% of the mixture, highlighting one of the benefits of the cobalt-catalyzed method. One curiosity of the cobalt method is the higher yields observed with condition **A** during the same time frame as condition **B**. The origin of this anomaly under investigation.

Pyridines bearing substituents at the 2-position such as methyl, methoxy, dimethylamino, or phenyl also underwent smooth catalytic borylation, all yielding monoborylated products as a mixture of positional isomers (Figure 2). In each case, the aryl boronate ester resulting from borylation of the 4-position was the major product. For 2-phenylpyridine, this product was obtained in an equimolar ratio to the 5-position isomer. No borylation of the phenyl ring was observed under these conditions. For the Me and NMe₂ functionalized substrates, small quantities of 6-position borylation was observed, demonstrating the ability of cobalt to functionalize positions adjacent to sp² hybridized nitrogen atoms.

The cobalt-catalyzed borylation of pure hydrocarbon arenes was also studied with **3** (Figure 3). Conditions employed a 20:1

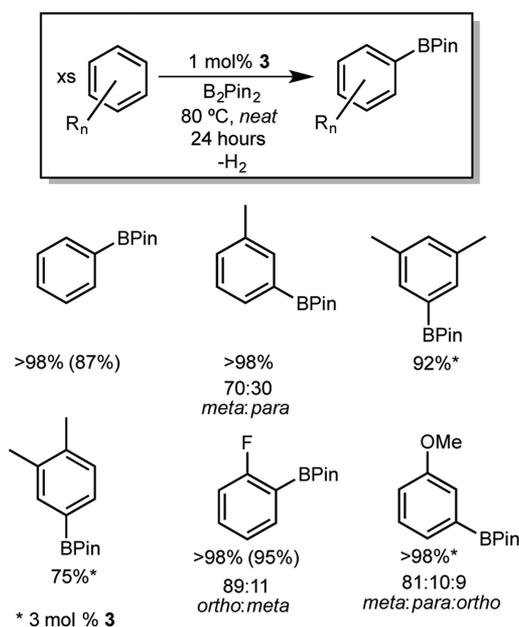


Figure 3. Arene borylation with **3** and B_2Pin_2 . Reported values are % conversions of B_2Pin_2 determined by GC using mesitylene as an internal standard. Product ratios were determined via NMR analysis. Isolated yields are reported in parentheses.

ratio of arene to B_2Pin_2 and 1 mol % of **3** at 80 °C for 24 h. The reported conversions are based on the consumption of B_2Pin_2 , and no other boron products were observed. The borylation of benzene and toluene proceeded smoothly. For the latter, a 70:30 selectivity of *meta*- and *para*-substituted products was obtained. The functionalization of *meta*-xylene required a slightly higher catalyst loading of 3 mol % and exclusively occurred at the 5-position of the ring. These data are consistent with borylation likely arising from the C–H oxidative addition step in the catalytic cycle. Electron-poor arenes such as fluorobenzene were borylated more readily than electron-rich examples such as anisole likely as a result of the relative acidity of the C–H bonds, similar to the trend observed in iridium-catalyzed reactions.⁴ Unfortunately, reasonable turnover was observed for this substrate class only when the reactions were conducted in neat arene.

The rich catalytic chemistry associated with **3** prompted investigation into the mechanism of turnover. Treatment of a diethyl ether solution of the cobalt alkyl compound with 2 equiv of HBPIn resulted in loss of one equivalent of $\text{Me}_3\text{SiCH}_2\text{BPIn}$ with concomitant formation of a new cobalt species identified as *trans*-(^{Pr}PNP)CoH₂(BPIn). The toluene-*d*₈ ¹H NMR spectrum exhibits a single broadened hydride resonance at –8.71 ppm at 23 °C; cooling the same solution below 0 °C resulted in sharpening of the signal to a well-resolved triplet (Figure S5). Single ³¹P and ¹¹B NMR resonances were observed at 103.5 and 41.1 ppm, respectively, consistent with formation of a single isomer of the cobalt product. Single crystals suitable for X-ray diffraction were obtained from a concentrated diethyl ether solution stored at –35 °C. The data were of sufficient quality such that the two cobalt-hydrides were located and freely refined providing definitive structural evidence for formation of a Co(III) oxidative addition product and the *trans*-dihydride isomer. Notably, this species is an active catalyst precursor for

catalytic borylation, and monitoring borylations by NMR spectroscopy reveals this compound is the catalyst resting state.

A deuterium-labeling experiment was also conducted. The cobalt-catalyzed borylation of 2-methylfuran was conducted with DBPin in the presence of 1 mol % of **3**. Analysis of the starting furan and the resulting borylated product by quantitative ¹³C NMR spectroscopy at 40% conversion established no deuterium incorporation into either organic molecule. Analysis of the isotopic composition of the remaining pinacolborane revealed formation of HBPIn, and sampling of the headspace and analysis by ¹H NMR spectroscopy also confirmed formation of HD gas (Figure S6). It is also likely that D₂ gas was formed. These results are consistent with reversible oxidative-addition and reductive elimination of the B–H(D) bonds.

A working mechanism consistent with the experimental observations is presented in Figure 4. Following formation of

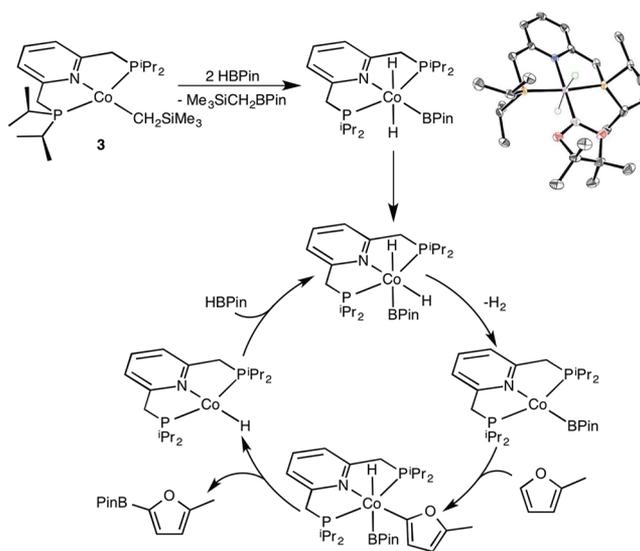


Figure 4. Proposed mechanism for cobalt-catalyzed borylation with **3** using methylfuran as a representative substrate.

trans-(^{Pr}PNP)CoH₂(BPIn), reductive elimination of H₂ either by isomerization to the *cis* isomer or by dissociation of a phosphine ligand³⁶ generates the active species in the cycle. The isomerization pathway is shown for illustrative purposes. The observation of a broad cobalt hydride signal by ¹H NMR spectroscopy at 23 °C suggests that a dynamic process may be operative. Following H₂ elimination, the resulting cobalt(I) boryl complex, (^{Pr}PNP)CoBPIn promotes the oxidative addition of a C–H bond of the substrate.³⁷ Reductive elimination of the B–C bond furnishes the observed product and oxidative addition of HBPIn regenerates *cis*-(^{Pr}PNP)CoH₂(BPIn). It is also plausible that the cobalt hydride (^{Pr}PNP)CoH formed from B–H reductive elimination from (^{Pr}PNP)CoH₂(BPIn) could promote the oxidative addition of the C–H bond. An alternative pathway highlighting this possibility is presented in Figure S7.

One notable feature of the proposed mechanism is that the base metal-catalyzed C–H functionalization operates via a Co(I)–(III) redox couple. These electronic structure requirements are distinct from iridium, where a cycle involving Ir(III)–(V) intermediates is now well-established.^{4,7,35} The cobalt intermediate responsible for C–H activation, likely the boryl

compound (^{Pr}PNP)CoBPIn but also possibly (^{Pr}PNP)CoH, is four-coordinate and coordinatively unsaturated and presents the opportunity, by virtue of vacant coordination sites, for substrate directed reactions.³⁴ These mechanistic principles serve as the centerpiece for further interrogation and future catalyst development and optimization.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental details and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

pchirik@princeton.edu

Notes

The authors declare no competing financial interest.

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