

Cobalt-Catalyzed Benzylic Borylation: Enabling Polyborylation and Functionalization of Remote, Unactivated C(sp³)-H Bonds

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S Supporting Information

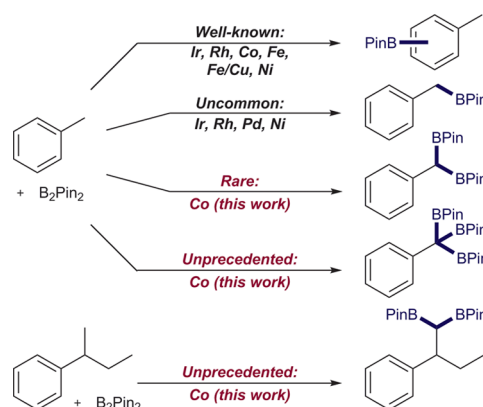
ABSTRACT: Cobalt dialkyl and bis(carboxylate) complexes bearing α -diimine ligands have been synthesized and demonstrated as active for the C(sp³)-H borylation of a range of substituted alkyl arenes using B₂Pin₂ (Pin = pinacolate) as the boron source. At longer reaction times, rare examples of polyborylation were observed, and in the case of toluene, all three benzylic C-H positions were functionalized. Coupling benzylic C-H activation with alkyl isomerization enabled a base-metal-catalyzed method for the borylation of remote, unactivated C(sp³)-H bonds.

Transition-metal-catalyzed C-H functionalization is an enabling strategy for sustainable synthesis and has gained considerable attention due to the ability to streamline the transformation of one of the most fundamental and ubiquitous linkages in organic molecules into an array of functional groups.¹ Applications of C-H functionalization range from natural product synthesis and drug discovery to the preparation of fine and commodity chemicals.² While a number of C-H functionalization reactions are currently available, C-H borylation methods are often preferred and most widely applied³ due to the synthetic versatility of the C-B bond⁴ and predictable selectivity based on steric accessibility rather than directing groups.

A number of precious-metal catalysts are known to promote C-H borylation, with Rh,⁵ Pt,⁶ and Ir-catalyzed^{3,7} methods being the most common. Recent efforts focused on developing catalysts with Earth-abundant metals, and successful iron,⁸ cobalt,⁹ nickel,¹⁰ iron-copper,¹¹ and even metal-free¹² conditions have been described. Selectivity in these reactions typically favors C(sp²)-H bonds, consistent with well-established preferences for oxidative addition.¹³ Methods for selective C(sp³)-H borylation are atypical by comparison and usually rely on directing groups,¹⁴ activated substrates,¹⁵ or use of a large excess of (often neat) alkanes under forcing conditions.^{5a,16}

Rare examples of benzylic borylation were observed either as minor byproducts in arene borylation methods^{10a,17} or as the primary products from Rh¹⁸ or heterogeneous Pd¹⁹ catalysts. Because of the low activity of the latter catalysts, the methylarene was required in large excess, and monoborylated products were observed. In one Rh example, a benzylic diborylation product of toluene was also obtained in low (7%) yield.^{18a} Alteration of the selectivity of traditional Ir-catalyzed borylation to benzylic C-H bonds was also accomplished by using silyl directing groups²⁰ or specialized silyl boronate reagents in combination with a tailored phenanthroline ligand.²¹ With the latter strategy, the non-directed diborylation of a sufficiently activated substrate, 4-CF₃-

Scheme 1. Selectivity of Various Transition-Metal-Catalyzed C-H Borylation Methods



toluene, was accomplished.²¹ Despite advances in altering the selectivity of C-H borylation of alkylarenes, general strategies for non-directed, highly selective mono- and diborylation of C(sp³)-H bonds in this substrate class have not yet been developed. Here we describe α -diimine cobalt catalysts that promote the selective borylation of C(sp³)-H bonds in alkylarenes into polyfunctional products. Coupling the base metal C-H functionalization process to alkyl isomerization enabled multiple functionalization reactions of remote, unactivated C(sp³)-H bonds. This method utilizes readily available, air-stable Co precursors and provides a direct synthetic route to valuable geminal diboronate²² and polyboronate compounds as well as a new strategy to functionalize unactivated C-H positions traditionally inaccessible to most known C-H functionalization methods (Scheme 1).

Our laboratory reported that the aryl-substituted α -diimine cobalt allyl complex, (iPrDI)Co(η^3 -C₃H₅) (iPrDI = [2,6-iPr₂C₆H₃N=C(CH₃)₂]₂) was an exceptionally active catalyst for the hydroboration of alkenes.²³ Inspired by this performance, related α -diimine cobalt dialkyl complexes, (DI)CoR₂ were synthesized by straightforward addition of the free ligand to (py)₂Co(CH₂SiMe₃)₂ (py = pyridine).²⁴ With the α -diimine ligand bearing large 2,6-diisopropyl aryl substituents, an S = 1/2, planar cobalt dialkyl complex, (iPrDI)Co(CH₂SiMe₃)₂ (**1**, Figure 1) was isolated and crystallographically characterized. Replacing the aryl imine substituents with cyclohexyl groups resulted in a tetrahedral and hence high spin, S = 3/2 cobalt dialkyl derivative, (CyADI)Co(CH₂SiMe₃)₂ (**2**, Figure 1), the geometry of which was also confirmed by X-ray diffraction (XRD).

Received: November 23, 2015

Published: December 29, 2015

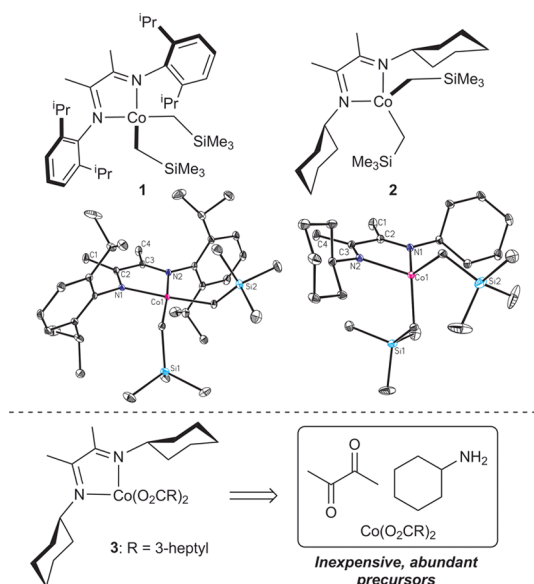


Figure 1. Depictions of the α -diimine cobalt dialkyl and bis(carboxylate) precatalysts used in this work and the solid state molecular structures (30% probability ellipsoids, hydrogens omitted) of dialkyl complexes **1** and **2**.

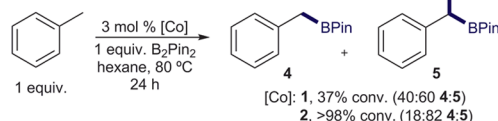
Both (DI)CoR₂ complexes are air-sensitive organometallic compounds and require inert atmosphere techniques for preparation, handling, and use. Alternative Co sources that are more robust would obviate many of these inconveniences. Co(II) carboxylates are some of the most inexpensive, air-stable sources of Co and have been demonstrated to generate catalytically active species upon treatment with borane reagents.²⁵ Our laboratory previously demonstrated that Co(II) acetate in the presence of trialkylphosphine ligands is active for the borylation of benzofuran albeit with modest activity.²⁵ Preparation of an α -diimine cobalt bis(carboxylate) was achieved by stirring the free ^cADI with a pentane solution of Co(II) 2-ethylhexanoate for 5 min at -35 °C followed by concentration and filtration, resulting in the isolation of the air-stable cobalt bis(carboxylate) derivative, **3** (Figure 1), in 60% yield as a pale orange solid.

Each of the Co precatalysts was evaluated for the borylation of toluene with B₂Pin₂ (Pin = pinacolate) (Scheme 2). In hexane solution at 80 °C with equimolar quantities of substrates, **2** proved more active than **1** with the alkyl-substituted α -diimine complex reaching complete conversion of starting material to an 18:82 mixture of mono- and diborylated products, **4** and **5**. Notably, the C-H borylation occurred exclusively at the benzylic C-H bonds with no evidence for C(sp²)-H borylation with either catalyst. Attempts to use analogous α -diimine cobalt monoalkyl complexes²³ or bis(phosphine)cobalt dialkyl complexes²⁶ produced no catalytic turnover highlighting the importance of the Co(II)X₂ motif supported by a redox-active ligand. With **1**, the benzyldiboronate ester, **5**, resulting from two C-H functionalization reactions, was the major product even at low conversions, establishing that the rate of the second C-H borylation is competitive with the first. This observation is consistent with an activating effect of a [BPin] substituent toward subsequent C-H activation, an effect first observed by Marder et al.^{18a}

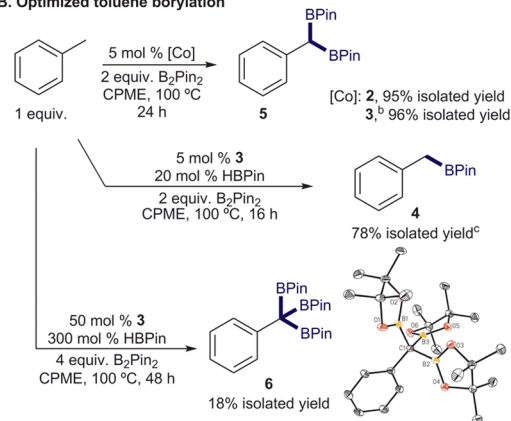
Although conditions to favor exclusive monoborylation directly from the Co-catalyzed reaction have thus far remained elusive, attention was devoted to the preparation of *gem*-diboronate compounds given their value in synthesis and the paucity of methods for their preparation from direct C-H

Scheme 2. Optimization of Toluene Benzylic Borylation Conditions To Access Benzylic Boronate Esters^a

A. Initial borylation results



B. Optimized toluene borylation

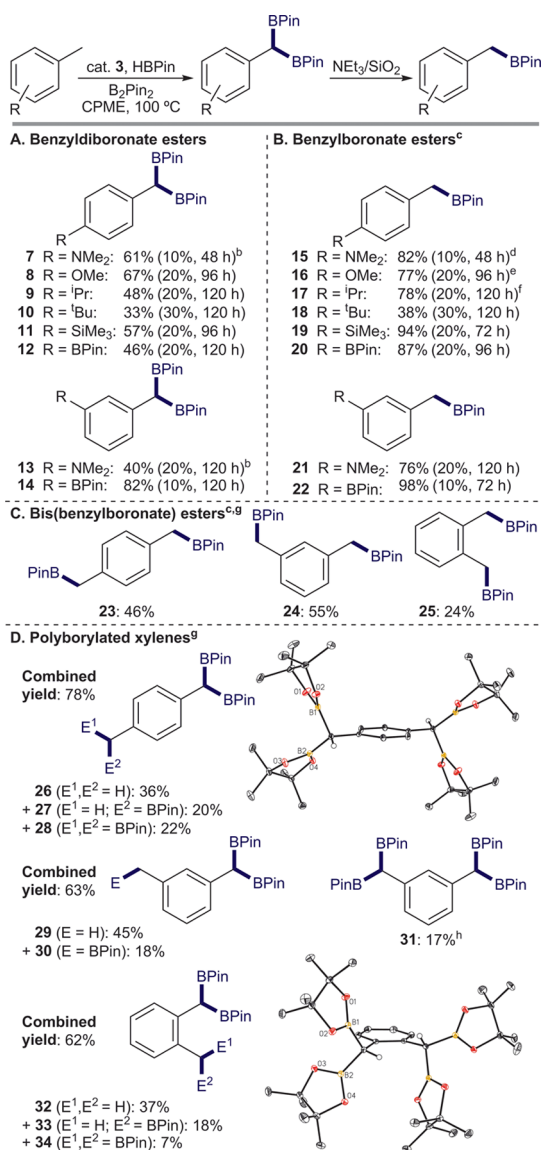


^aSee SI for experimental details. ^b20 mol% HBPin used to activate the catalyst. ^cYield after chromatography on NEt₃-deactivated silica.

functionalization.²⁷ Optimization with **2** revealed that cyclopentyl methyl ether (CPME) was the preferred solvent and resulted in 95% isolated yield of **5** after 24 h at 100 °C using a 1:2 ratio of arene to B₂Pin₂. Using **3** and 20 mol% HBPin for catalyst activation,²⁵ 96% isolated yield of **5** was obtained under otherwise identical conditions, suggesting formation of the same active catalyst. Use of HBPin instead of B₂Pin₂ under identical conditions formed the expected products but with a dramatic reduction in reaction efficiency, yielding 16% and 8% of **4** and **5**, respectively. Under optimized catalytic conditions, the synthesis of **5** was then successfully scaled. Starting with 0.500 g of toluene, 1.601 g (86% yield) of **5** was obtained. During optimization experiments to obtain **5**, it was discovered that purification of the reaction mixture using NEt₃-deactivated silica gel flash column chromatography resulted in high (78%) yield of the monoborylated product, **4**, resulting from protodeborylation on the column. It was also discovered that increasing the catalyst loading to 50 mol% **3** and using 4 equiv of B₂Pin₂ resulted in the *triborylation* of toluene to obtain product **6**, the identity of which was confirmed by X-ray crystallography (Scheme 2).

Because **3** is prepared from abundant and inexpensive precursors and offered improved handling, the scope of the benzylic diborylation was explored with this Co precursor. Each catalytic reaction was conducted with varying catalyst loadings of **3** at 100 °C with a 1:2 ratio of arene to B₂Pin₂ and 4 equiv of HBPin with respect to [Co]. As reported in Scheme 3, a range of 3- and 4-substituted toluenes including those containing amino, methoxy, silyl, alkyl, and boryl groups were tolerated by the reaction. Depending on the conditions used to isolate the product, both mono- and diboronate esters were isolated. In general, the isolated yields of the monoborylated products were higher than the corresponding bis(boronate) esters due to the sensitivity of the latter to protodeborylation, incomplete conversion, or tendency of the products toward autoxidation.

The Co-catalyzed borylation of *o*-, *m*-, and *p*-xylenes highlights the versatility of the method (Scheme 3). With all three isomers of

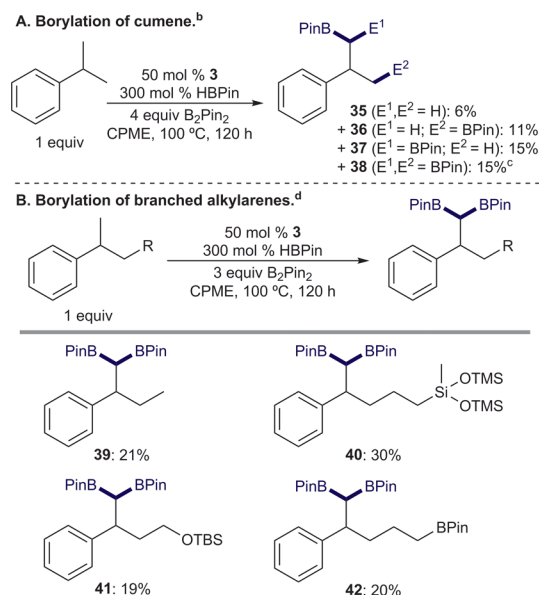
Scheme 3. Borylation of Methylarenes and Xylenes, Isolation of Boronate Products, and Solid-State Structures of 28 and 34^a

^aIsolated yields. Catalyst loadings and reaction times in parentheses. See SI for experimental details. ^bYield of aldehyde after oxidation with H₂O₂. ^cYields after chromatography on NEt₃-deactivated silica. ^dIsolated with 7% *p*-dimethylaminobenzaldehyde impurity. ^eIsolated with 13% impurity of 4. ^fIsolated with 10% benzyl, homobenzyl diboronate ester impurity (see SI). ^gUsing 20 mol% 3; 96 h reaction time. ^hIsolated from a separate reaction with 17% impurity of 30.

the arene, the *gem*-diboronate product is kinetically preferred again demonstrating the activating effect of a [BPin] substituent. Over the course of 96 h, the formation of tri- and tetraborylated products were also observed along with the diborylated products. Separation using column chromatography allowed isolation of each of the individual components of the reaction mixture. The tetraborylated products, 28 and 34, were characterized by XRD, confirming their identity (Scheme 3).

Previous studies from our laboratory on alkene hydroboration demonstrated that α -diimine cobalt catalysts promote chain migration, whereby alkyl isomerization is fast and C-B formation occurs preferentially from primary cobalt alkyl intermediates to yield terminally functionalized products from internal alkenes.²³

Application of a similar strategy to benzylic C-H borylation would provide a method for the functionalization of remote, unactivated C(sp³)-H bonds in the absence of directing groups. The feasibility of this approach was demonstrated with cumene wherein the presence of 50 mol% 3 and a 1:3:3 ratio of arene:B₂Pin₂:HBPIn, a triboron product, 38, where the homobenzylic positions underwent C-H borylation, was isolated (Scheme 4).

Scheme 4. Selective Homobenzylic Borylation of Branched Alkylarenes as a Strategy for Unactivated C-H Functionalization^a

^aSee SI for experimental details. ^bNMR yields. ^c13% isolated yield. ^dIsolated yields.

and disubstituted products also accompany formation of 38. This selectivity was observed previously with heterogeneous Pd catalysts, but required a large excess of arene and resulted in observation of only 35.¹⁹

The Co-catalyzed method was also extended to other branched alkylarenes to determine the scope of remote C(sp³)-H diborylation (Scheme 4). With *sec*-butyl benzene, exposure to the catalytic conditions resulted in isolation of 39, arising from selective diborylation of the terminal homobenzylic position. The method also proved compatible with silyl, boryl, and silyl ether functional groups at a terminal position of the branched alkyl chain. To determine whether the origin of the second borylation in these reactions could be due to the α -[BPin] activating effect similar to that observed with toluene borylation, *n*-octyl-BPin and Me-BPin were used as substrates. No product was observed at 50% Co loading in either case, suggesting that homobenzylic diborylation likely results from a consecutive benzylic activation/isomerization/borylation sequence. While catalyst loadings are high, the combination of a readily available, inexpensive, and trivial to prepare α -diimine ligand with one of the least expensive sources of Co to enable unprecedented polyfunctionalization of remote, unactivated C(sp³)-H bonds is an attractive new strategy for the elaboration of simple hydrocarbon precursors. Exploring additional substrate scope and the mechanism of this transformation is ongoing in our laboratory.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12249.

Complete experimental details; characterization data for Co complexes and boronate ester products (PDF)
X-ray crystallographic data for 1, 2, 6, 28, and 34 (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

W.N.P. acknowledges the National Science Foundation (CHE-1265988) for financial support. J.V.O. acknowledges the 2014-2015 Bristol-Myers Squibb Graduate Fellowship in Synthetic Organic Chemistry and the Paul Maeder '75 Fund for Energy and the Environment through the Andlinger Center. We thank Allychem for a generous gift of B₂Pin₂.

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