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Cobalt-Catalyzed Benzylic Borylation: Enabling Polyborylation and Functionalization of Remote, Unactivated C(sp^3)-H Bonds.

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Supporting Information Placeholder

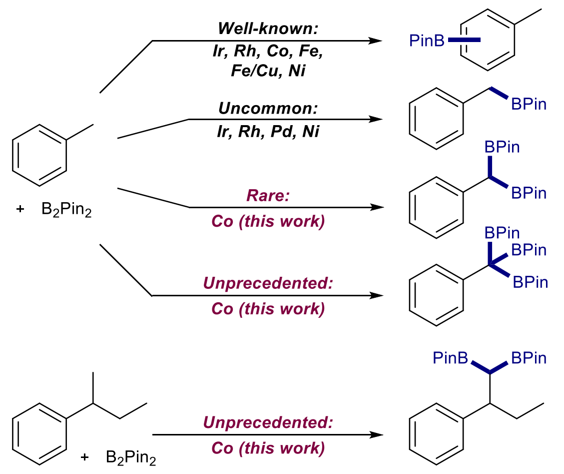
ABSTRACT: Cobalt dialkyl and bis(carboxylate) complexes bearing α-diimine ligands have been synthesized and demonstrated as active for the C(sp^3)-H borylation of a range of substituted alkyl arenes using B_2Pin_2 (Pin = pinacolate) as the boron source. At longer reaction times, rare examples of polyborylation 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 C(sp^3)-H borylation of remote, unactivated C-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 applied[3] due to the synthetic versatility of the C-B bond[4] 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 have focused on developing catalysts with earth abundant metals, and successful iron,[8] cobalt,[9] nickel,[10] iron-copper[11] and even metal-free[12] conditions have been described. Selectivity in these reactions typically favors C(sp^2)-H bonds, consistent with well-established preferences for oxidative addition.[13] Methods for selective C(sp^3)-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 have also been observed either as minor byproducts in arene borylation methods[10a,17] or as the primary products from rhodium[18] or heterogeneous palladium[19] catalysts. Because of the low activity of the latter catalysts, the methylarene was required in large excess and monoborylated products were observed. In one rhodium 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 has also been accomplished by use of silyl directing groups[20] and by use of 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-CF_3-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(sp^3)-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(sp^3)-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(sp^3)-H bonds. This method utilizes readily available, air stable cobalt precursors and provides a direct synthetic route to valuable geminal diboronate[22] 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).

Scheme 1. Selectivity of various transition metal-catalyzed C-H borylation methods.



Our laboratory has reported that the aryl-substituted α-diimine cobalt allyl complex, (^{iPr}DI)Co(η^3-C_3H_5) (^{iPr}DI = [2,6-$^iPr_2C_6H_3N{=}C(CH_3)]_2$) was an exceptionally active catalyst for the hydroboration of alkenes.[23] Inspired by this performance, related α-diimine cobalt dialkyl complexes, (DI)CoR_2 were synthesized by straightforward addition of the free ligand to $(py)_2Co(CH_2SiMe_3)_2$ (py = pyridine).[24] With the α-diimine ligand bearing large 2,6-diisopropyl aryl substituents, an S = 1/2, planar cobalt dialkyl complex, (^{iPr}DI)Co$(CH_2SiMe_3)_2$ (**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, (^{Cy}ADI)Co$(CH_2SiMe_3)_2$ (**2**, Figure 1), the geometry of which was also confirmed by X-ray diffraction.

Both (DI)CoR_2 complexes are air sensitive organometallic compounds and require inert atmosphere techniques for preparation, handling and use. Alternative cobalt sources that are more robust would obviate many of these incoveniences. Cobalt(II) carboxylates are some of the most inexpensive, air-stable sources of cobalt and have been demonstrated to generate catalytically active species upon treatment with borane reagents.[25] Our laboratory has previously demonstrated that cobalt(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 ^{Cy}ADI with a pentane solution of cobalt(II) 2-ethylhexanoate for 5 minutes 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.

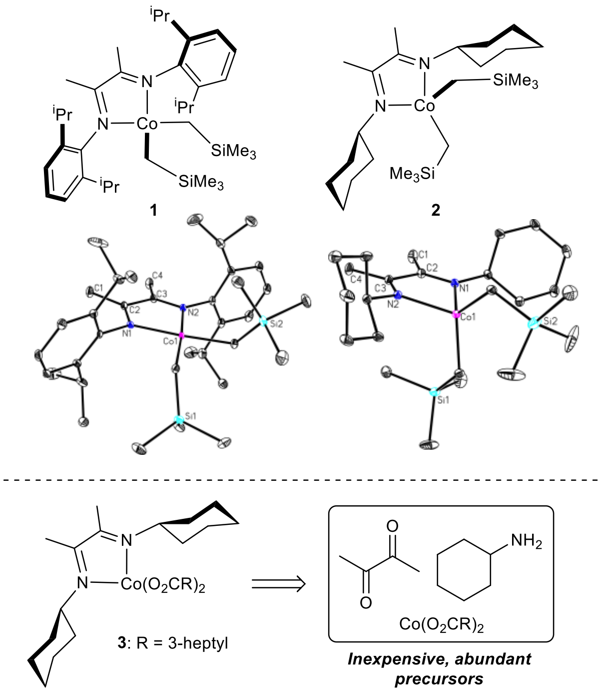
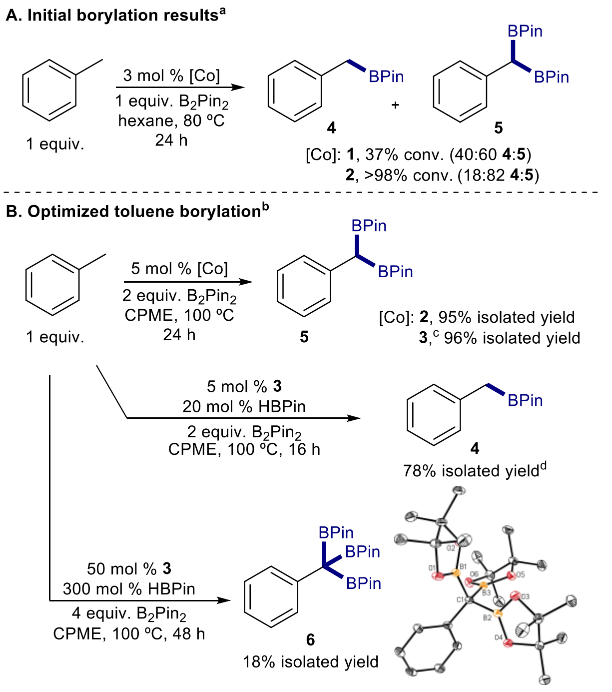


Figure 1. Depictions of the α-diimine cobalt dialkyl and bis(carboxylate) precatalysts used in this work and the solid state molecular structures (30% probability ellipsoids, hydrogens omitted) of dialkyl complexes **1** and **2**.

Each of the cobalt pre-catalysts was evaluated for the borylation of toluene with B_2Pin_2 (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(sp^2)-H borylation with either catalyst. Attempts to use analogous α-diimine cobalt monoalkyl complexes[23] or bis(phosphine)cobalt dialkyl complexes[26] produced no catalytic turnover highlighting the importance of the Co(II)X$_2$ 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 and coworkers.[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 geminal-diboronate compounds given their value in synthesis and the paucity of methods for their preparation from direct C-H 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 hours at 100 °C using a 1:2 ratio of arene to B_2Pin_2. 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 B_2Pin_2 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 NEt$_3$-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 four equivalents of B_2Pin_2 resulted in the *triborylation* of toluene to obtain product **6**, the identity of which was confirmed by X-ray crystallography (Scheme 2). Thus, the cobalt method enables an unprecedented triborylation of toluene.

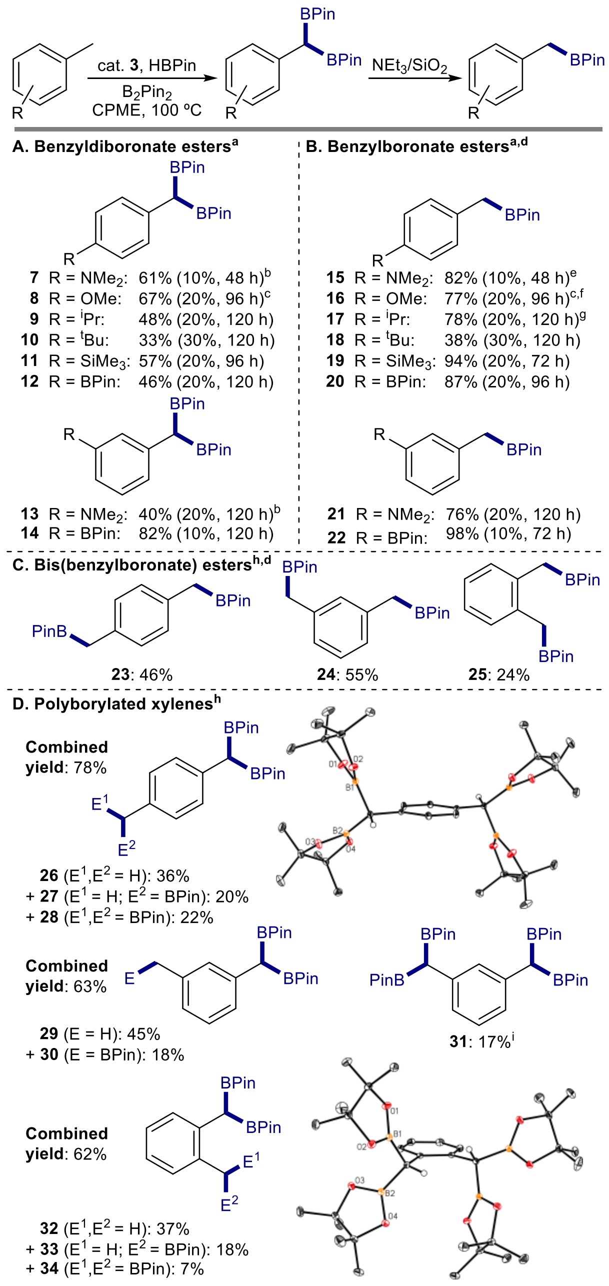
Scheme 2. Optimization of toluene benzylic borylation conditions to access benzylic mono-, di- and triboronate esters.



[a]Reactions carried out using 0.55 mmol of toluene in 1.0 mL hexanes. See SI for complete experimental details. [b]Reactions carried out using 0.55 mmol toluene in 0.55 mL CPME. [c]20 mol % HBPin used to activate the catalyst. [d]Yield after chromatography on NEt$_3$-deactivated silica.

Because **3** is prepared from abundant and inexpensive precursors and offered improved handling, the scope of the benzylic diborylation was explored with this cobalt precursor. Each catalytic reaction was conducted with varying catalyst loadings of **3** at 100 °C with a 1:2 ratio of arene to B_2Pin_2 and four equivalents 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 towards autoxidation.

Scheme 3. Borylation of methylarenes and xylenes, isolation of mono-, di-, tri- and tetraboronate products, and the solid state structures (30% probablility ellipsoids, hydrogens except for benzylic C-H omitted for clarity) of **28** and **34**.



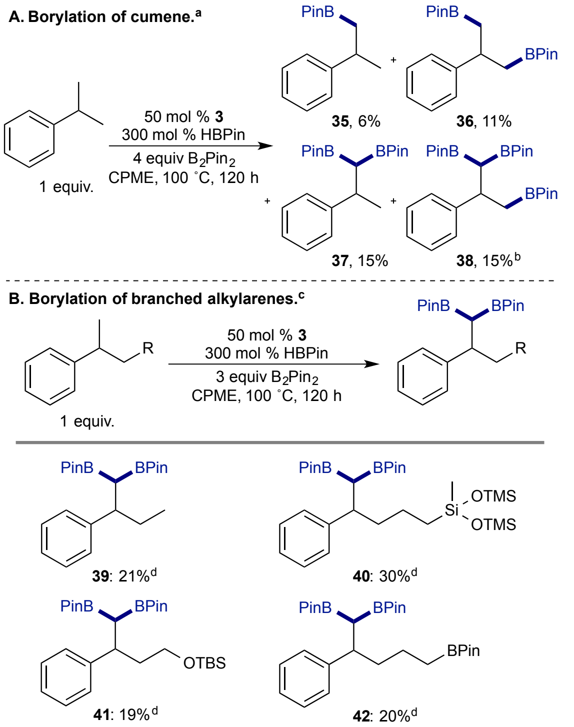
[a]Isolated yields. Reactions conducted with 0.55 mmol methylarene, 1.10 mmol B_2Pin_2, 0.55 mL CPME at 100 ºC. Catalyst loadings and reaction times included in parentheses. 4 equiv. of HBPin with respect to **3** was added. [b]Isolated yield of aldehyde after oxidation with H_2O_2. [c]1.65 mmol B_2Pin_2 used. [d]Yields after chromatography on NEt_3-deactived silica. [e]Isolated with 7% *p*-dimethylaminobenzaldehyde impurity. [f]Isolated with 13% impurity of **4**. [g]Isolated with 10% benzyl,homobenzyl-diboronate ester impurity (see SI for details). [h]Isolated yields. Reactions conducted with 0.55 mmol xylene, 2.20 mmol B_2Pin_2, 0.55 mL CPME, 20 mol % **3**, and 80 mol % HBPin at 100 ºC for 96 h. [i]Isolated from a separate reaction with 17% impurity of **30**.

The cobalt-catalyzed borylation of *ortho*-, *meta*- and *para*-xylenes highlights the versatility of the method (Scheme 3). With all three isomers of the arene, the geminal-diboronate product is kinetically preferred again demonstrating the activating effect of a [BPin] substituent. Over the course of 96 hours, 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 X-ray diffraction, confirming their identity (Scheme 3). Thus, the cobalt-catalyzed method allows synthesis of di-, tri- and tetrasubstituted boronate derivatives of xylenes by manipulation of reaction and isolation conditions.

Previous studies from our laboratory on alkene hydroboration have 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(sp^3)-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:B_2Pin_2:HBPin, a triboron product, **38**, where the homobenzylic positions underwent C-H borylation, was isolated (Scheme 4). Mono- and disubstituted products also accompany formation of **38**. This selectivity has only been observed previously with heterogeneous palladium catalysts, but required a large excess of arene due to the low activity of the catalyst, and resulted in observation of only monoborylated products.[19]

The cobalt-catalyzed method was also extended to other branched alkylarenes to determine the scope of remote C(sp^3)-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% cobalt 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 cobalt to enable unprecedented polyfunctionalization of remote, unactivated C(sp^3)-H bonds is an attractive new strategy for the elaboration of simple hydrocarbon precursors.

Scheme 4. Selective homobenzylic borylation of branched alkylarenes as a strategy for unactivated C-H functionalization.[a]



[a] Yields determined by NMR spectroscopy. Reaction conducted with 0.55 mmol of cumene and 2.20 mmol B_2Pin_2 in 0.55 mL CPME. [b] 13% isolated yield. [c] Isolated yields. Reactions conducted with 0.55 mmol of alkylarene and 1.65 mmol B_2Pin_2 in 0.55 mL CPME.

In summary, a new cobalt-catalyzed method for the selective borylation of benzylic and unactivated C(sp^3)-H bonds of alkylarenes has been discovered that allows for the synthesis of polyfunctionalized products from simple hydrocarbons. The catalysts are readily prepared from abundant and inexpensive starting materials and provide direct access to a valuable class of synthetic intermediates poised for use in complex molecule synthesis.[22] The mechanism of the reaction and the origin of the unusual selectivity are currently under investigation.

ASSOCIATED CONTENT

Supporting Information

Complete experimental details, characterization data of cobalt complexes and of boronate ester products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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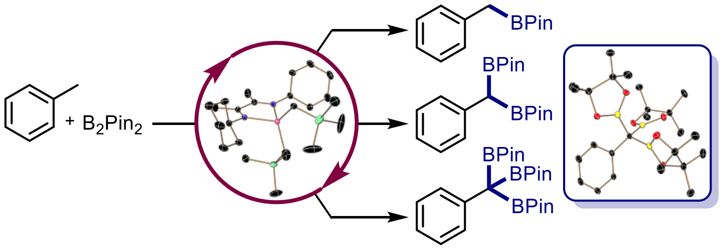
(27) For examples in which geminal-diboronates have been observed or isolated via C(sp^3)-H borylation using directing groups, see references 14a-c, 20b



Highly selective cobalt catalyzed C(sp^3)-H functionalization.