

Cobalt(I)-Catalyzed Borylation of Unactivated Alkyl Bromides and Chlorides

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ver the past few decades, the synthetically useful organoboron-containing compounds have become a workhorse for the construction of carbon-carbon bonds via the Suzuki–Miyaura cross-coupling reaction.¹ Of relevance, alkylboronic esters have a broad range of applications in medicinal chemistry² and in the field of organic synthesis.³ A classical approach for the synthesis of alkyl boronic ester derivatives includes transmetalation with organolithium/ magnesium reagents with compatible boron reagents,⁴ hydroboration of olefins,⁵ β -borylation of α,β -unsaturated carbonyls,° or via the C-H activation of alkanes.7 Transition-metalcatalyzed direct borylation of the C-X bond of alkyl halides represents one of the efficient and most straightforward strategies to access alkylboronic esters. In recent years, several reports on transition-metal-catalyzed borylation with Pd,⁸ Ni,⁵ Cu,¹⁰ Zn,¹¹ Fe,¹² and Mn¹³ for alkyl halides borylation (Scheme 1a) have been documented. Very recently, Melchiorre's and Mo's groups reported the transition-metalfree borylation of alkyl halides under photochemical and baseassisted conditions, respectively.¹⁴ Although such approaches are well-established for the synthesis of alkylboronic esters,

Scheme 1. Transition-Metal-Catalyzed Borylation of Unactivated Alkyl Halides



some of them remain limited in electrophile scope, with expensive catalysts and ligands, providing ample incentive to develop a more general strategy.

In view of the high abundance of cobalt in the Earth's crust, its low cost, and low toxicity, the potential benefits of its complexes as practical catalysts in various homogeneous catalytic reactions are significantly explored. In particular, there are several reports detailing the application of cobalt complexes in the borylation reactions by the groups of Chirik, Marder, Ge, Huang and others.¹⁵ However, despite these advances, cobalt-catalyzed borylation of alkyl halides has not been explored yet. Based on our recent findings on the Cobased system, which provides a platform for the synthesis of aryl boronic esters using less reactive aryl chlorides, we sought to explore the possibility of a cobalt-catalyzed alkyl halide borylation reaction.¹⁶ Herein, we describe a mild Co-catalyzed method for the selective borylation of unactivated primary, secondary, and few tertiary alkyl halides (Scheme 1b). This process can be extended to the unactivated alkyl chlorides and shows a broad substrate scope and functional group compatibility.

On the basis of our previous studies on the cobalt-catalyzed aryl halide borylation, we first attempted the borylation of 1bromo-3-phenyl propane, 1a, using $[Co(IMes)_2Cl_2]$ (I; IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) as a catalyst. The GC-MS analysis of the reaction mixture shows the borylated product 3a in 43% yield, along with the formation of hydrodehalogenated (propyl benzene) and homo coupled (1,6-diphenylhexane) byproducts (see the Supporting Information (SI), experiment S1 for more details). Then we

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examined the catalytic performance of the cobalt(I) complex $[Co(IMes)_2CI]$ which exhibited comparable activity to that of I. Deng and co-workers reported that $[Co(IMes)_2CI]$ can be prepared by the addition of 2 equiv of IMes to $[Co(PPh_3)_3CI]$ (A).¹⁷

Hence, for operational simplicity and practicality, we decided to use 5 mol % of $[Co(PPh_3)_3Cl]$ A as the precatalyst. Notably, when A was examined as a catalyst, it produced 3a in 29% yield (Table 1, entry 1), whereas the cobalt catalyst A in

Table 1. Optimization of Reaction Conditions for the Borylation of 1-Bromo-3-phenyl Propane (1a) Catalyzed by Cobalt Complex^a



^{*a*}Reactions were performed with 0.2 mmol of alkyl halide, 0.26 mmol of B_2pin_2 and base, 5 mol % Co(PPh₃)₃Cl, and 10 mol % of ligand at 50 °C in 2 mL of solvent unless otherwise mentioned. ^{*b*}Yields were determined by NMR spectroscopy using nitromethane as an internal standard. ^{*c*}Yield of the isolated product. ^{*d*}2 mol % Co(PPh₃)₃Cl and 4 mol % of ICy ligand were used. MTBE = methyl *tert*-butyl ether; CPME = cyclopentyl methyl ether.

the presence of 10 mol % of IMes as a ligand, KOMe as a base, and $B_2 pin_2$ (2, *bis*(pinacolato)diboron) as the boron source gave the desired alkylboronic ester 3a in 49% yield (entry 2). However, when 10 mol % of ICy (1,3-bis(cyclohexyl)imidazol-2-ylidene) was used as a ligand, a significant increase in the yield of 3a (96%) was observed (entry 3). Other bases, such as KO^tBu, NaO^tBu, LiO^tBu, and LiOMe, resulted in a decrease in the desired product yields (entries 4-7). An excellent yield was obtained when NaOEt was used as a base (3a = >99%)yield; entry 8). A controlled experiment established that the base is essential for the reaction to proceed (entry 9). The use of other solvents, such as THF, CPME (cyclopentyl methyl ether), hexane, and toluene, were less effective (entries 10-13). However, reaction in benzene gave a comparable yield of **3a** (>99%, entry 14). By using 2 mol % of $[Co(PPh_3)_3Cl]$ and 4 mol % of ICy, the borylated product 3a was obtained in >99% yield (entry 15).

Having the optimized conditions in hand, we evaluated a series of alkyl bromides to determine the substrate scope. As illustrated in Scheme 2, several acyclic primary alkyl bromides

Scheme 2. Substrate Scope of Co-Catalyzed Borylation of Unactivated Alkyl Bromides^a



^{*a*}Reactions were performed with 1.0 mmol of alkyl halide, 1.3 mmol of B_2pin_2 and NaOEt, 2 mol % of Co(PPh₃)₃Cl, and 4 mol % of ICy in MTBE as a solvent at 50 °C unless otherwise mentioned. Yields determined by NMR spectroscopy using nitromethane as an internal standard were given in parentheses. ^{*b*}Using 1.1 equiv of B_2pin_2 and NaOEt. ^{*c*}Reaction was performed for 24 h. ^{*d*}Reaction was performed using 1.3 equiv of B_2cat_2 as the boron reagent, followed by transesterification with pinacol.

(1a-1c) were able to produce the alkylboronate products in good yields. Borylation of substrates having ether substituents, such as (2-bromoethoxy)benzene (1d), 1-(3-bromopropyl)-4-methoxybenzene (1e), 2-(2-bromoethyl)-1,3-dioxane (1f), silylether (1g), and 1-bromo-2-methoxyethane (1i), afforded excellent yields of the corresponding alkylboronic esters (3d-3g and 3i).

Many other synthetically important functional groups, such as CF_3 (1h), esters (1j), and hydroxyl (1k) were well tolerated and gave the desired products in moderate to good yields. The alkyl halide having a heterocycle is also amenable to the borylation reaction, furnishing boronate product 3l in 66% yield. It is noteworthy that the catalyst showed excellent selectivity for the bromo- group over the chloro- group (1m) to produce (3m) exclusively, using 1.1 equiv of B_2pin_2 and NaOEt. Similar to primary alkyl halides, secondary alkyl bromides were also borylated in excellent yields, albeit with a

slightly longer reaction time (24 h). The borylation of bromocyclopentane (1n) and bromocyclohexane (1o) proceeded smoothly, affording the alkylboronates in good-toexcellent yields. In addition, sterically demanding *exo*-2bromonorborane (1p) reacted to give the borylation product (3p) in excellent yield (86%). The reaction proceeded well in the case of an alkyl halide with a protected amine group (1q). Interestingly, the reaction of cyclohexenyl bromide (1r)exclusively produced the alkyl halide borylation product (3r), leaving the olefin moiety intact.

To date, very few examples exist for the borylation of tertiary halides. For instance, Fu and co-workers developed a nickelbased method^{9a} and Cook and co-workers developed iron-^{12a} and manganese-based methods,¹³ which offer the only examples beyond 1-bromoadamantane.^{10g,11} Our method enables the borylation of 1-bromoadamantane (1s) using B₂cat₂ as a diboron reagent, giving an excellent yield of 3s. However, the reaction of (3-bromo-3-methylbutyl)benzene (1t) gave a lower yield of 3t (24%). Even a higher temperature, longer reaction time, and change in the optimized NHC to less sterically hindered IMe (1,3-dimethylimidazol-2-ylidene) did not improve the reaction outcome.

Next, we investigated the compatibility of alkyl chloride using this cobalt system, since the examples of borylation of unactivated alkyl chlorides remain rare. To date, only two systems exist for the direct borylation of alkyl chlorides, allowing access to a range of alkyl boronic esters. The Mnbased system was developed by Cook et al. for the borylation of alkyl chlorides, using 1.3 equiv of the Grignard reagent, EtMgBr.¹³ Subsequently, Marder et al. reported a Cu(II)-NHC catalytic system for the borylation of alkyl chlorides.^{10g} Further, Ito et al. has also reported the copper-catalyzed borylation of alkyl halides, but only with two examples of alkyl chlorides.^{10b} When the reaction of 4a was performed using B_2pin_2 as a boron source, the alkylboronate 3a was obtained in only 21% yield, together with a trace amount of hydrodehalogenation byproduct. A brief optimization revealed $B_2 neop_2$ (5, *bis*(neopentylglycolato)diboron) as the boron reagent successfully affording alkyl boronates in good yields (Scheme 3). The alkyl chlorides bearing acyclic substituents (4a-4c) reacted well to afford the desired products 6a-6c in good yields. The reaction proceeded well in the presence of heterocycles (4d-4f) and produced the corresponding borylated products in moderate to good yields. Silylether (4g) as a functional group furnished the desired boronate ester in good yield (63%). Reaction with secondary alkyl chlorides, such as cyclohexyl chloride (4h) and acyclic chloride (4i), proceeded smoothly to furnish the borylation products 6h in 83% yield and 6i in 76% yield. The tertiary alkyl chloride, 1chloroadamentane (4j), also readily participated in the reaction and provided the desired product 3s in good yield (76%). However, similar to the tertiary bromide 1t, tertiary chloride 4k produced inferior results. It should be also noted that gram scale reactions of 1a proceeded smoothly to produce 89% of the isolated borylated product 3a, under the optimized reaction conditions.

At the outset of the mechanistic investigation, we speculated the possibility of a radical based mechanism, since we observed a significant drop in the yield of 3a, when the reaction was performed in toluene as a solvent (Table 1, entry 13). The GC-MS analysis of the crude reaction mixture revealed the formation of 3a, propyl benzene (hydrodehalogenation byproduct), and PhCH₂Bpin (benzylic C-H borylation Scheme 3. Substrate Scope of Co-Catalyzed Borylation of Unactivated Alkyl Chlorides^a



^{*a*}Reactions were performed with 1.0 mmol of alkyl chloride, 1.3 mmol of B₂neop₂ and NaOEt, 2 mol % Co(PPh₃)₃Cl, and 4 mol % of ICy in MTBE as a solvent at 50 °C unless otherwise stated. Yields determined by NMR spectroscopy using nitromethane as internal standard were given in parentheses. ^{*b*}Reaction was performed using 1.3 equiv of B₂cat₂ as the boron reagent, followed by transesterification with pinacol.

product of toluene; Scheme 4). However, when the reaction was performed in the absence of 1a, using toluene as a solvent,

Scheme 4. Borylation of 1-Bromo-3-Phenyl Propane (1a) in Toluene as a Solvent

a) Ph Br + Bapina	Co(PPh ₃) ₃ Cl (5 mol%) ICy (10 mol%)	Ph Bnin + Ph
(0.2 mmol) (1.3 equiv) (1a)	NaOEt (1.3 equiv) Toluene, 50 °C, 16 h	(3a) 48% 28% + Ph Bpin 24%

formation of PhCH₂Bpin was not observed, which eliminates the possibility of the benzylic C–H bond activation of toluene (see SI, experiment S2-b).¹⁸ These results suggest that the alkyl halide might be the source for the benzyl radical in this cobalt-mediated catalytic reaction.^{9,19}

Further, to explore the possibility of a radical-mediated process, the borylation reaction was performed using 6bromohex-1-ene that exclusively afforded the cyclized product cyclopentylmethylboronate (Scheme 5, entry 1). Similar results were reported for Mn-,¹³ Zn-,¹¹ and Cu-catalyzed systems.^{10a,g} Similarly, the reaction of (bromomethyl)-cyclopropane produced an acyclic isomeric mixture of borylated products under standard reaction conditions (Scheme 5, entry 2). The intermediacy of alkyl radicals was further tested using TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) and 1,10-dihydroanthracene as radical trapping reagents. When the substrate **1a** was subjected to standard reaction conditions in the presence of TEMPO (1 equiv), the adduct, 3-phenyl-1-(2',2',6',6'-tetramethyl-1'-piperidinyloxy)-propane was obtained and no **3a** was observed (entry 3). Similarly, Scheme 5. Mechanistic Investigations of Co-Catalyzed Borylation of Unactivated Alkyl Halides on a Radical Mediated Process



when 1,10-dihydroanthracene was used under standard borylation conditions, the yield of **3a** reduced to 28%, and 14% of anthracene formation was observed (entry 4). All these observations are consistent with the hypothesis that a radical intermediate is involved in the oxidative-addition step.^{9,12a}

Furthermore, several additional experiments were performed in order to elucidate the composition of the active catalyst. Since ICy was used as a ligand for this transformation, to examine the possibility of the *in situ* formation of the $[Co(ICy)_3CI]^{20}$ complex, and it serving as an active catalyst for this transformation, we explored the catalytic reaction using **1a** as a substrate, which produced only a 28% yield of **3a**. Attempts to synthesize the pure form of the active catalyst through the reaction of $[Co(PPh_3)_3CI]$ with 2 equiv of the ICy ligand was unsuccessful. Therefore, further studies are needed for a full explanation of the reaction mechanism.

In summary, we have developed a novel and efficient borylation reaction of alkyl halides, including the effective couplings of unactivated alkyl chlorides, catalyzed by a cobalt(I) complex to produce alkyl boronic esters. To the best of our knowledge, this is the first reported catalytic procedure to synthesize alkylboronates using cobalt as a catalyst. The reaction is mild and efficient, thereby making this an attractive methodology for the preparation of alkylboronic esters with diverse functional groups. In view of the remarkable diversity of alkylboronates, we anticipate that our strategy and discovery could expand the development of versatile catalysts for a wide range of cross-coupling processes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00038.

Experimental and spectroscopic data, copies of ¹H, ¹³C, and ¹¹B NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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