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Letter

# Cobalt-Catalyzed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) Suzuki-Miyaura Cross Coupling

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**ABSTRACT:** A cobalt-catalyzed method for the  $C(sp^2)-C(sp^3)$ Suzuki–Miyaura cross coupling of aryl boronic esters and alkyl bromides is described. Cobalt–ligand combinations were assayed with high-throughput experimentation, and cobalt(II) sources with *trans-N,N'*-dimethylcyclohexane-1,2-diamine (DMCyDA, L<sup>1</sup>) produced optimal yield and selectivity. The scope of this transformation encompassed steric and electronic diversity on the aryl boronate nucleophile as well as various levels of branching and synthetically valuable functionality on the electrophile. Radical trap experiments support the formation of electrophile-derived radicals during catalysis.

T he transition-metal-catalyzed cross coupling of an organoboron nucleophile and an organohalide (pseudohalide) electrophile, also known as the Suzuki–Miyaura reaction, is one of the most widely used transformations in synthetic chemistry (Scheme 1A).<sup>1</sup> Broad functional group

# Scheme 1. Overview of Transition-Metal-Catalyzed Suzuki– Miyaura Cross Coupling



tolerance and high success rates have elevated Suzuki–Miyaura coupling to a preferred method for C–C bond formation, in particular, in pharmaceutical applications.<sup>2</sup> The advantages of organoboron nucleophiles include commercial availability, convenient preparation, bench stability, and ease of byproduct



SI Supporting Information

removal following the catalytic reaction,<sup>3</sup> distinguishing the Suzuki–Miyaura variant from other types of couplings.<sup>4</sup>

Historically, palladium complexes have been the dominant catalysts used for Suzuki–Miyaura reactions.<sup>2b,5</sup> The emergence of a detailed mechanistic picture has enabled the evolution of specialized ligands,<sup>2a</sup> positioning palladium catalysis as the state of the art for  $C(sp^2)-C(sp^2)$  coupling. However, extending this approach to include  $C(sp^3)$  coupling partners has been problematic. Whereas some success has been achieved with alkylboron nucleophiles,<sup>6</sup> coupling to more widely available alkyl electrophiles is limited by the  $S_N^2$ -type pathways accessible to low-valent palladium catalysts.<sup>7</sup> Additionally, competing  $\beta$ -hydrogen elimination ( $\beta$ -HE) from intermediate palladium alkyls leads, in some cases, to isomerized products.<sup>8</sup>

First-row transition metals, by virtue of their distinct electronic structures, often mitigate these challenges,<sup>9</sup> and effective methods have been developed for  $C(sp^2)-C(sp^3)$  coupling that rely on more reactive organometallic nucleophiles.<sup>10</sup> Although these methods generate valuable products, many of the benefits associated with using neutral boron reagents are lacking. Notable advancements have been made with nickel- and copper-catalyzed coupling reactions using organoboron coupling partners.<sup>10e-g</sup> One feature common among late transition metals including palladium, nickel, and copper is the facile transmetalation of neutral boron reagents with metal-alkoxide intermediates; analogous reactivity with

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## Table 1. Optimization of Cobalt-Catalyzed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) Suzuki-Miyaura Coupling of 1a and 2a



entry	[Co] ( <i>x</i> )	ligand	base	solvent	conv. (%) <sup><i>a</i></sup>	3a (%) <sup>a</sup>	2a' (%) <sup>a</sup>	$2a'' (\%)^a$
1	$\operatorname{CoCl}_2(10)^{b}$		KOMe	DMA	57	26	7	23
2	$CoBr_2$ (10)		KOMe	DMA	66	31	11	22
3 <sup>c</sup>	$CoBr_2$ (10)	$L^1$	KOMe	DMA	94	61	18	14
4 <sup><i>c</i></sup>	$CoBr_2$ (10)	L <sup>2</sup>	KOMe	DMA	76	37	13	28
5	$CoBr_2$ (10)	$L^3$	KOMe	DMA	72	33	24	19
6 <sup>c</sup>	$L^{1}CoBr_{2}$ (10)		KOMe	DMA	99	59	25	7
7	$L^{1}CoBr_{2}$ (10)		KOMe <sup>d</sup>	DMA	99	49	24	22
8	$L^{1}CoBr_{2}$ (10)		KOEt	DMA	86	38	17	34
9	$L^{1}CoBr_{2}$ (10)		KOMe	THF	91	35	40	6
10	$L^{1}CoBr_{2}$ (10)		KOMe	dioxane	72	37	23	3
11	$L^{1}CoBr_{2}(5)$		KOMe	DMA	89	28	29	32
12	$L^{1}CoBr_{2}$ (15)		KOMe	DMA	99	69	18	5
13	$L^{1}CoBr_{2}(0)$		KOMe	DMA	78	0	0	83
14 <sup>e</sup>	$L^{1}CoBr_{2}$ (10)		KOMe	DMA	62	11	ND	ND
15 <sup>f</sup>	$L^{1}CoBr_{2}$ (10)		KOMe	DMA	ND	5	9	52

<sup>*a*</sup>Yields and conversions measured by UPLC using 1,3,5-tri-*tert*-butylbenzene as an internal standard. <sup>*b*</sup>99.99% purity. <sup>*c*</sup>For L<sup>1</sup> and L<sup>2</sup>, the racemic trans diastereomer was used. For the isolated precatalyst, L<sup>1</sup>CoBr<sub>2</sub>, the enantiopure (R,R) ligand was used. <sup>*d*</sup>1.5 equiv of base was used. <sup>*e*</sup>PhB(OH)<sub>2</sub> was used instead of PhB(neo). <sup>*f*</sup>PhB(pin) was used instead of PhB(neo). ND = not determined. Cbz = benzyloxycarbonyl.

earlier transition metals is sometimes complicated by the aggregation of alkoxide complexes.<sup>11</sup> New methods that employ Earth-abundant transition metals as catalysts with organoboron coupling partners and common, readily used bases are attractive to extend both the scope and utility of  $C(sp^2)-C(sp^3)$  coupling as well as to provide a fundamental understanding of what types of metal complexes promote the transformation.

For cobalt, few methods have been reported that utilize neutral organoboron coupling partners, and those that are known have been exclusively applied to biaryl synthesis (Scheme 1B). The first was reported by our laboratory in 2016 and relied on the well-defined cobalt(I) pincer complex, (<sup>iPr</sup>PNP)CoCl, as a precatalyst for the coupling of a limited selection of heteroaryl pinacol boronate esters and aryl triflates.<sup>12</sup> Subsequently, Duong and coworkers reported the coupling of a broader range of aryl neopentyl glycol boronate esters and (hetero)aryl halides using a terpyridine ligand (<sup>Ph</sup>Tpy) and CoCl<sub>2</sub> as a precatalyst mixture.<sup>13a</sup> Bedford has also reported N-heterocyclic carbene-supported cobalt catalysts for the coupling of alkyl-lithium-activated aryl boronic esters with aryl chlorides and bromides.<sup>13b</sup> As interest grows in molecules with increased  $C(sp^3)$  content, specifically for applications in medicinal chemistry<sup>14</sup> and organic synthesis,<sup>15</sup> so does motivation for new  $C(sp^2)-C(sp^3)$  cross coupling methods. Here we describe the discovery of a diamine-ligated cobalt precatalyst for the  $C(sp^2)-C(sp^3)$  Suzuki-Miyaura coupling of arylboronic ester nucleophiles and alkyl bromide electrophiles.

The discovery of a cobalt-catalyzed  $C(sp^2)-C(sp^3)$  Suzuki– Miyaura reaction began with an investigation of the coupling of PhB(neo) **1a** and 4-bromo-*N*-Cbz-piperidine **2a**. (See the Supporting Information for complete optimization details.) **2a** was chosen as the electrophile due to the prevalence of piperidines in biologically active molecules<sup>16</sup> and the ability of the [N-Cbz] group to facilitate characterization.<sup>17</sup> Furthermore, the cyclic nature of **2a** makes it particularly prone to elimination, suggesting that the optimal conditions for this electrophile would likely extend to other alkyl bromides.

Application of the previously reported cobalt precatalysts (Scheme 1B) for  $C(sp^2)-C(sp^2)$  coupling did not provide synthetically useful amounts of the desired 4-aryl piperidine 3a (Table S4); however, control experiments with cobalt(II) salts in the absence of added ligand provided up to 31% yield of 3a (Table 1). These observations raised concerns about trace metal impurities; however, ultrapure (99.99%) CoCl<sub>2</sub> performed similarly to CoBr<sub>2</sub> (entries 1 and 2), and ICP-MS analysis of each component of the reaction mixture established that no other metal was present above 10 ppm (Tables S5 and S7).

With the demonstration that cobalt was effective for  $C(sp^2)-C(sp^3)$  coupling, a library of ligands<sup>10c</sup> was explored to suppress the side reactions that produce 2a' and 2a" (Figure S1, Tables S1–S3). In addition to reducing the overall yield and efficiency of the reaction, side products like these, which are common in cross-coupling reactions of this type, are often problematic for the separation of byproducts from the desired compound. High-throughput experimentation identified *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine (DMCyDA, L<sup>1</sup>) as an optimal ligand for cross coupling, generating 3a in 61% yield (entry 3). The cobalt(II) complex, (DMCyDA)CoBr<sub>2</sub>, was prepared and provided similar results; therefore, it was used in

subsequent experiments for operational simplicity and consistency (entry 6). Modest modifications to  $L^1$  such as replacing the hydrogen on each nitrogen with an *N*-methyl group (TMCyDA,  $L^2$ )—importantly, a ligand that has been successfully used in previously reported, cobalt-catalyzed cross-coupling methods—<sup>18</sup> or the removal of the cyclohexane backbone (DMEDA,  $L^3$ ) resulted in diminished yields of 37 and 33%, respectively (entries 4 and 5). Because the yields for reactions with  $L^2$  and  $L^3$  are comparable to the yield for CoBr<sub>2</sub> alone (31%, entry 2), inefficient complexation may be responsible for the low yields; however, other effects might also be operative.

With a suitable ligand identified, additional reaction parameters were investigated. Relatively strong alkoxide bases were required to promote cross coupling (entries 7 and 8), as weaker phenoxide or silanolate derivatives resulted in elimination with the former and overall poor conversion with the latter (Table S8). The stoichiometry of the base also proved important, as increasing the equivalents of KOMe from 1.25 to 1.5 had a deleterious effect on the formation of **3a** with increased elimination (entry 7).

Optimal cross coupling was observed with a slight excess of aryl boron reagent 1a (1.5 equiv) relative to KOMe (1.25 equiv). This likely reduces the amount of base in solution, thereby minimizing side products. An evaluation of common solvents established DMA as optimal (entry 6), likely a result of its high polarity that solubilizes all of the reaction components. Ethereal solvents are widely used in other cobalt-catalyzed cross coupling reactions;<sup>10c</sup> however, C-Br reduction 2a' was a significant side product in both THF and 1,4-dioxane, with 2a' being the major product in THF (entries 9 and 10). Increasing the amount of the cobalt precursor to 15 mol % resulted in a modest improvement in yield (entries 11 and 12) and no coupling product was observed in the absence of cobalt (entry 13). Finally, PhB(OH), and PhB(Pin), more commonly encountered aryl boron reagents, afforded only small amounts of 3a (entries 14 and 15), demonstrating the unique efficacy of ArB(neo) reagents for transmetalation with cobalt.

With the optimized conditions established, the scope of the cobalt-catalyzed cross coupling with various nucleophiles 1 and electrophiles 2 was explored (Scheme 2). Reactivity trends were determined for both 1 and 2 while keeping the other coupling partner constant. Coupling products 3b-g derived from a number of sterically and electronically differentiated aryl B(neo) reagents were prepared. Specifically, sterically demanding 2-methylphenyl 3b and 1-naphthyl 3c aromatic rings were tolerated, along with alkoxy- (3g), phenoxy- (3d), and trifluoromethyl-substituted (3f) arenes. Branched alkyl electrophiles were effective partners, providing 3h-j in up to 73% yield. A set of electrophiles of constant chain length between the site of C-C bond formation and a synthetically versatile functional group provided products with an ester (3k), a protected alcohol (3l), and a protected amine (3m), each in good yield. The scope of this method was expanded to include diversely functionalized coupling partners into the final Suzuki products. Highlights include nucleophile- (3q) and electrophile- (3p and 3s) derived heterocycles, adamantyl-<sup>19</sup> (30) and oxetane- $^{20}$  (3p) based bioisosteres, and compounds with functional groups that can be directly used for (-Ac 3n,-CN 30, and 3r), or deprotected prior to (-OTBS 3r and -NBoc 3s), further synthetic manipulation.

Scheme 2. Scope of Cobalt-Catalyzed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) Suzuki-Miyaura Cross Coupling<sup>c</sup>



<sup>*a*</sup>Yield determined by <sup>1</sup>H NMR spectroscopy using mesitylene as an internal standard. <sup>*b*</sup>Diastereomeric ratio (dr) of 4:1 measured by crude <sup>1</sup>H NMR spectroscopy; major diastereomer shown. <sup>*c*</sup>Yield of isolated product shown unless otherwise stated.

The discovery of an effective  $C(sp^2)-C(sp^3)$  cross-coupling method that is compatible with some common organic functional groups inspired studies into the mechanism of the reaction. Observation of the reduction product 2a', derived from the electrophile, suggested the intermediacy of radicals that likely undergo competing H-atom abstraction. The intermediacy of carbon-centered radicals is well established for cross-coupling reactions using first-row transition-metal catalysts including cobalt.<sup>10c</sup> Such intermediates are often derived from organohalide halogen atom abstraction or single electron transfer to some other type of activated C-X bond by a reduced metal intermediate. A series of radical trap experiments were performed to determine if radical intermediates are formed in the present system. Cobalt-catalyzed cross coupling of 4 with 6-bromo-1-hexene 5, a wellestablished radical clock,<sup>21</sup> produced a 7:1 mixture of cyclized 6a to linear 6b coupling products in 74% overall yield (Scheme 3A). This supports a pathway where the rate of direct radical cross coupling to give linear product 6b is approximately the same order of magnitude as the rate of initial radical cyclization that occurs prior to C-C bond formation for cyclized product **6a**.<sup>22</sup> Intramolecular migratory insertion of the tethered alkene of the Co-alkyl intermediate that occurs prior to reductive

Scheme 3. Experimental Support for Electrophile-Derived Radical Intermediates in Cobalt-Catalyzed  $C(sp^2)-C(sp^3)$ Suzuki-Miyaura Cross Coupling



"Yield determined by GC-FID using dodecane as an internal standard.  $^b$ Yield determined by  $^1$ H NMR spectroscopy using mesitylene as an internal standard.

elimination could also account for the formation of **6a**. To distinguish these possibilities, an additional experiment was conducted with 1,1-diphenylethylene,<sup>23</sup> an established trap due to the formation of a stabilized radical.<sup>24,25</sup>

Conducting the catalytic reaction of PhB(neo) and 1bromo-2-methylpropane in the presence of 1,1-diphenylethylene, addition products 7b and 7c were obtained, along with the expected coupling product 7a, as the major electrophile-containing products (Scheme 3B). Whereas direct C-H abstraction by radical 7r yielded saturated product 7b, alkene 7c constitutes the product of a formal alkyl Heck reaction, a known pathway in cobalt catalysis.<sup>26</sup> Taken together, these results support the intermediacy of an electrophile-derived radical during cobalt-catalyzed  $C(sp^2) C(sp^3)$  Suzuki-Miyaura cross coupling.

The role of borates was explored in the cobalt-catalyzed reaction to gain insight into the nucleophile; the interaction of KOMe with the arylboronate could generate this type of intermediate under catalytic conditions. Duong and coworkers have implicated borates as the reducing species for cobalt precatalyst activation, although no direct evidence to support these claims was reported.<sup>13</sup> The potassium aryl borate **8a** was prepared from PhB(neo) and KOMe; **8a** proved competent in cobalt-catalyzed cross coupling, although a slightly lower yield of **3e** was obtained (Scheme 4A). With hydroxide-derived aryl borate **8b**, only trace **3e** was obtained, likely as a result of cobalt catalyst decomposition due to incompatibility with [OH] groups.

With borates established as proficient coupling partners, competition experiments with electronically differentiated aryl boronates were conducted (Scheme 4B). The combination of 1.25 equiv of KOMe and 1.5 equiv each of the 4-carboxy 4- and 4-methoxy 9-substituted aryl B(neo) reagents produced the 4-carboxy coupling product **3h** in 66% yield and the 4-methoxy product **10** in 5% yield. Notably, if the same conditions were used albeit with 2.5 equiv of KOMe instead of

#### Scheme 4. Reactivity and Selectivity of Aryl Borates in Cobalt-Catalyzed Cross Coupling

A. Borate synthesis and reactivity



<sup>*a*</sup>Trace coupling product **3e** detected by GC-MS. Yields of **3h** and **10** determined by <sup>1</sup>H NMR spectroscopy using mesitylene as an internal standard.

1.25, then the preference for 3h decreased to 34% yield versus 20% for 10. Collectively, these experiments suggest that coupling is favored with a more Lewis-acidic boron center.

In summary, a versatile cobalt-catalyzed  $C(sp^2)-C(sp^3)$ Suzuki–Miyaura cross-coupling reaction has been developed. While cobalt salts promoted the reaction, the introduction of the diamine ligand DMCyDA, L<sup>1</sup>, significantly improved selectivity for cross-coupling over side reactions. A substrate scope compatible with common organic functional groups was discovered. Radical clocks and trapping experiments support the intermediacy of electrophile-derived radicals, and aryl borates were shown to be competent nucleophilic coupling partners. Future studies will focus on the development of new catalysts with improved performance and will be coupled to efforts to gain deeper insight into the mechanism of the transformation.

## ASSOCIATED CONTENT

#### **1** Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02934.

Complete experimental procedures including general considerations and characterization data and NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

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