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Cobalt(II)-Catalyzed Oxidative C−H Arylation of Indoles and Boronic Acids

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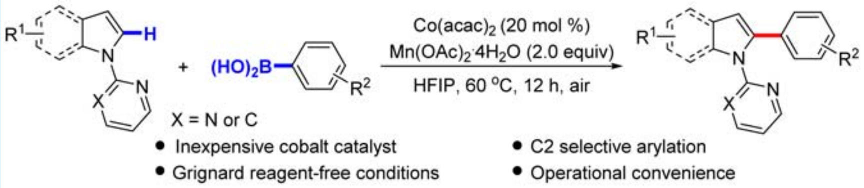
Supporting Information



ABSTRACT: Co(II)-catalyzed C−H C2 selective arylation of indoles with boronic acids through monodentate chelation assistance has been achieved for the first time. The unique features of this methodology include mild reaction conditions, highly C2 regioselectivity, and employment of a Grignard reagent-free catalytic system. A wide range of substrates, including unreactive arenes, are well tolerated, which enables the construction of the coupling products efficiently. This new strategy provides an alternative and versatile approach to construct biaryls using inexpensive cobalt catalyst.

The biaryl framework is a key structural motif with wide applications in pharmaceutical drugs, natural products, and functional materials.[1] The traditional synthetic methodology for aryl−aryl bond formation relied on transition-metal-catalyzed cross-coupling reactions between aryl halides and organometallic reagents.[2] In the past decades, C−H arylation has emerged as a promising and efficient alternative to form $C(sp^2)-C(sp^2)$ bonds, which is more environmentally friendly and atom-economic.[3] Meanwhile, transition-metal-catalyzed oxidative coupling between two different C−H bonds was also developed.[4] However, up to now, the arylation of arenes has been mostly limited to Pd and other noble transition metals.[5] To reduce the costs and toxicity, much attention has been paid to the development of abundant and inexpensive metals for comparable C−H arylation efficiencies.[6]

As a representative first-row transition metal, cobalt-based homogeneous catalysis has been investigated extensively in view of its versatile and unique activities in organic transformations.[7] Since 2011, Shi, Ackermann, and Yoshikai have made pioneering contributions to C−H arylation of unreactive arenes with aryl halides or phenol-derived electrophiles catalyzed by low-valent cobalt catalysts.[8−10] To regenerate in situ active Co−NHC complexes, Grignard regents were utilized as the bases and reductants. Despite the above-mentioned achievements, the use of the strong Grignard reagents as the base is the major limitation, which restricts the scope of aryl electrophiles and leads to undesirable coupling reactions. Thus, it would further expand the catalytic versatility of cobalt catalyst if a Grignard reagent free condition is accomplished.[11]

Recently, a mixed directing-group strategy was employed to achieve oxidative C−H/C−H bond arylation of unreactive arenes via the combination of single-electron transfer (SET) and concerted metalation-deprotonation (CMD) process.[12] However, organoboronates are stable and effective coupling reagents for versatile Pd-, Rh-, and Ru-catalyzed transformations, including the well-known Suzuki−Miyaura coupling.[13] To the best of our knowledge, cobalt-catalyzed direct arylation of aromatics using organoboron reagents as the coupling reagents without Grignard reagents has not been reported. As the continuation of our interest in Co(II)-catalyzed C−H functionalizations,[12,14] we herein report the first example of Co(II)-catalyzed regioselective C-2 arylation of indoles with boronic acids in the absence of Grignard reagents.

We commenced our study on the coupling of 1-(pyrimidin-2-yl)-1*H*-indole **1a** with phenylboronic acid **2a** using the *N*-pyrimidine as a removable directing group. Initially, various solvents were screened, which indicates HFIP is the best choice to afford the desired product **3aa** in 34% yield in the presence of 20 mol % of $Co(OAc)_2·4H_2O$ and 2 equiv of $Mn(OAc)_2·4H_2O$ at 90 °C for 12 h (Table 1, entry 1). Dioxane, CH_3CN, toluene, DMSO, and other alcohols led to only trace or no desired arylated product (see the Supporting Information). Subsequently, other cobalt catalysts, such as $CoC_2O_4·4H_2O$, $Co(acac)_2$, and $Co(acac)_3$ were tested, and $Co(acac)_2$ afforded the arylated **3aa** in 65% yield (Table 1, entry 3). When the reaction was performed at 60 °C, an increased yield of 80% was obtained (Table 1, entry 5). Either elevated or lower temperature was disadvantage for the reaction activity (see the Supporting Information). However, it should be noted that 54% yield could still be achieved at 30 °C for 12 h (Table 1, entry 6). Next, the oxidant effect on the reaction was

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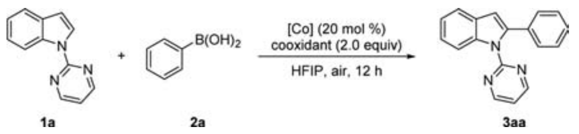
Table 1. Optimization of Cobalt-Catalyzed Arylation Reaction between 1a and 2a[a]



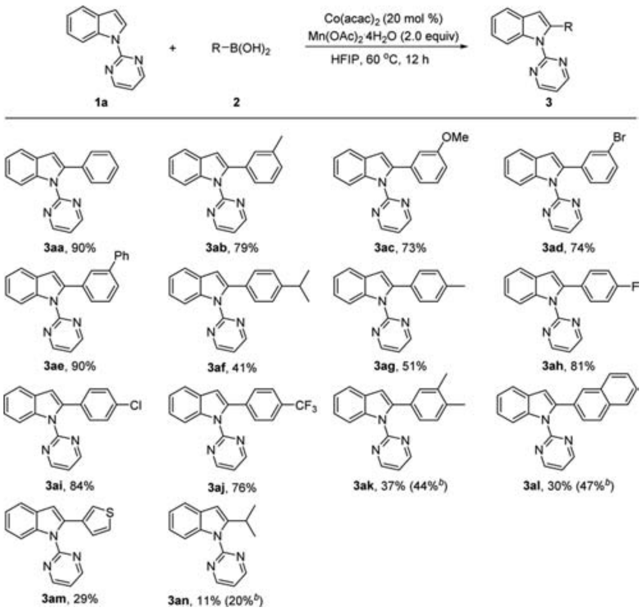
entry	catalyst	cooxidant	temp (°C)	yield[b] (%)
1	$Co(OAc)_2 \cdot 4H_2O$	$Mn(OAc)_2 \cdot 4H_2O$	90	34
2	$CoC_2O_4 \cdot 4H_2O$	$Mn(OAc)_2 \cdot 4H_2O$	90	11
3	$Co(acac)_2$	$Mn(OAc)_2 \cdot 4H_2O$	90	65
4	$Co(acac)_3$	$Mn(OAc)_2 \cdot 4H_2O$	90	60
5	$Co(acac)_2$	$Mn(OAc)_2 \cdot 4H_2O$	60	80
6	$Co(acac)_2$	$Mn(OAc)_2 \cdot 4H_2O$	30	54
7	$Co(acac)_2$	Ag_2O	60	9
8	$Co(acac)_2$	$PhI(OAc)_2$	60	8
9	$Co(acac)_2$	O_2	60	19
10[c]	**$Co(acac)_2$**	**$Mn(OAc)_2 \cdot 4H_2O$**	**60**	**90**

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), [Co] salt (20 mol %), cooxidant (0.4 mmol), HFIP (1.0 mL), air atmosphere, 12 h. [b] Isolated yield. [c] **2a** (0.4 mmol). acac = acetylacetonate, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

investigated, which reveals that $Mn(OAc)_2 \cdot 4H_2O$ was the optimal reagent and showed highest reactivity (Table 1, entries 7–9). Moreover, it was observed that neither basic nor acidic additives were required to fulfill the reaction (see the Supporting Information). Lastly, the catalytic efficiency was further improved by adjusting the amount of **2a** to deliver the corresponding product **3aa** in 90% yield (Table 1, entry 10).

With the optimized conditions in hand, a variety of functionalized boronic acids were first examined in the Co-catalyzed C–H arylation (Scheme 1). The reaction worked well for *meta*- and *para*-substituted arylboronic acids and delivered the desired product **3aa**–**3ai** in moderate to excellent yields, irrespective of electronic effects. Notably, strongly electron-withdrawing CF_3 group was tolerated to afford **3aj** in 76% yield. The current protocol could further expand to other types of (hetero)aromatic and aliphatic boronic acids with arylated product **3ak**–**3an** obtained in moderate yields.

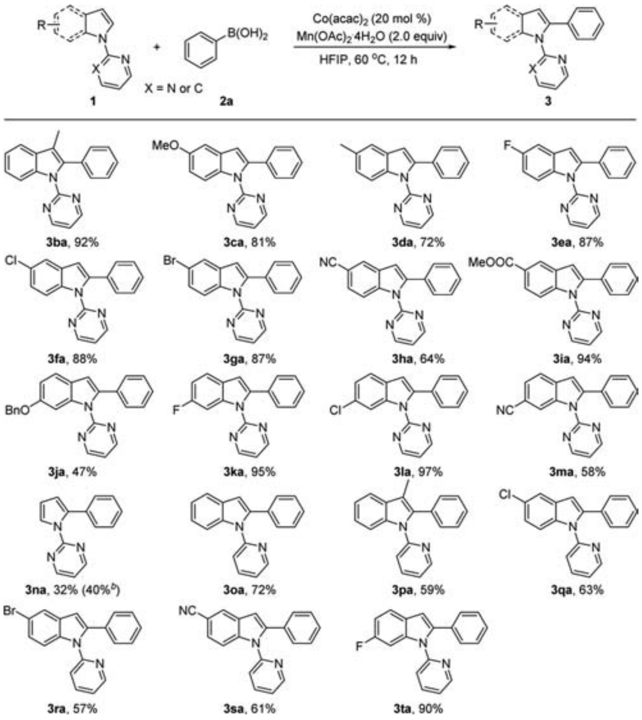
Scheme 1. Co(II)-Catalyzed Direct Arylation of Indole with Various Boronic Acids[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Co(acac)_2$ (20 mol %), $Mn(OAc)_2 \cdot 4H_2O$ (0.4 mmol), HFIP (1.0 mL), air atmosphere, 12 h, 60 °C. [b] **2** (0.8 mmol), $Co(acac)_2$ (30 mol %), 48 h.

Encouraged by the above results, the scope of indole substrates was investigated to test the generality of current methodology (Scheme 2). To our delight, a range of substrates bearing various functional groups proceeded smoothly and gave the corresponding products in good yields. Notably, both electron-donating and electron-withdrawing groups, including methoxy (**3ca**), phenylmethoxy (**3ja**), methyl (**3ba** and **3da**), fluoro (**3ea** and **3ka**), chloro (**3fa** and **3la**), bromo (**3ga**), cyano (**3ha** and **3ma**), and ester (**3ia**) substituents were well tolerated. Another substrate, such as pyrrole **1n**, was employed, and the corresponding products **3na** was obtained in 40% yield. Moreover, this protocol was not restricted to pyrimidine directing group. The pyridine equipped indoles **1o**–**1t** could still react with **2a** effectively to provide the arylated products in 57–90% yields.

Scheme 2. Co(II)-Catalyzed Direct Arylation of Various Indoles with Phenylboronic Acid[a]

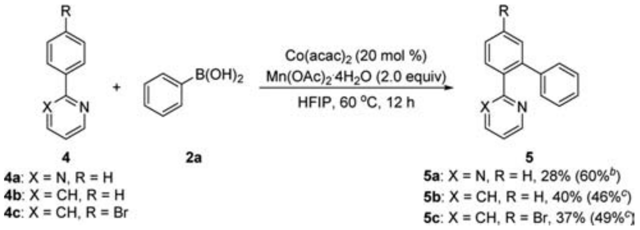


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Co(acac)_2$ (20 mol %), $Mn(OAc)_2 \cdot 4H_2O$ (0.4 mmol), HFIP (1.0 mL), air atmosphere, 12 h, 60 °C. [b] $Co(acac)_2$ (30 mol %), 80 °C.

The current Co-catalyzed C–H transformation could further be extended to arene-containing substrates, which delivered the arylated product **5a**–**5c** in 46–60% yields (Scheme 3). Overall, compared with other metal catalysts, similar efficiencies could be achieved for indole substrates, while lower yields were achieved for unreactive arenes with limited substrate scopes.

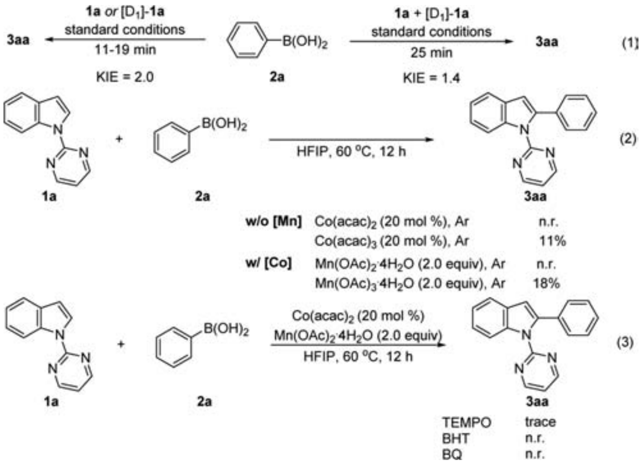
To gain insight into the reaction mechanism, a set of control experiments was conducted (Scheme 4). In the competitive studies, when an equimolar mixture of **1a** and $[D_1]$-**1a** was

Scheme 3. Co(II)-Catalyzed Direct Arylation of Arene-Containing Substrates[a]



^{a}Reaction conditions: **4** (0.2 mmol), **2a** (0.4 mmol), Co(acac)$_2$ (20 mol %), Mn(OAc)$_2$·4H$_2$O (0.4 mmol), HFIP (1.0 mL), air atmosphere, 12 h, 60 °C. ^{b}Co(acac)$_2$ (30 mol %), 80 °C. ^{c}**2a** (0.8 mmol), Co(acac)$_2$ (30 mol %), 48 h.

Scheme 4. Mechanistic Studies

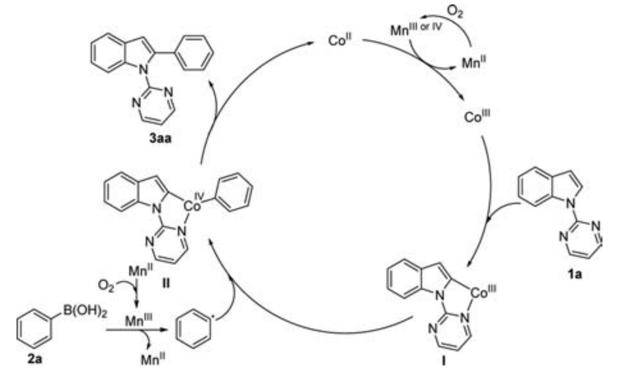


employed, a kinetic isotope effect (KIE) value of 1.4 was obtained. Also, a KIE value of 2.0 was observed between **1a** *or* [D$_1$]-**1a** with **2a**, respectively, in the parallel experiments, which indicates that Co-catalyzed C−H bond cleavage is the rate-determining step (Scheme 4, eq 1). In the absence of Mn(OAc)$_2$·4H$_2$O, the employment Co(acac)$_2$ alone led to no desired product, while 11% yield was obtain when Co(acac)$_3$ was utilized under the Ar atmosphere. In the presence of Co(acac)$_2$, no product was detected when Mn(OAc)$_2$·4H$_2$O was introduced under Ar, while **3aa** was isolated in 18% yield with Mn(OAc)$_3$·4H$_2$O applied (Scheme 4, eq 2). These results indicate that the reaction probably commenced from an in situ generated Co(III) species in the presence of Mn(OAc)$_2$·4H$_2$O and oxygen (from air).[12] Next, when the radical quencher, including TEMPO, BHT, or BQ, was added, no desired product **3aa** was formed, which implies that a SET pathway might be involved during the reaction (Scheme 4, eq 3).

On the basis of the above mechanistic studies and previous reports,[12] a plausible catalytic cycle is illustrated in Scheme 5. Initially, oxygen oxidized Mn$^{\text{II}}$ to Mn$^{\text{III}}$ or Mn$^{\text{IV}}$ complex, which reacted with Co$^{\text{II}}$ to generate Co$^{\text{III}}$ species. Next, complex **1a** underwent a CMD process to produce intermediate **I**. The reaction between phenylboronic acid **2a** and Mn$^{\text{III}}$ provided a phenyl radical,[15] which attacked the intermediate **I** to form intermediate **II**. Lastly, the desired product **3aa** was obtained by reductive elimination, accompanied by the regeneration of Co$^{\text{II}}$ to fulfill the catalytic cycle.

In conclusion, we have developed a Co(acac)$_2$-catalyzed oxidative C2 arylation of indoles with boronic acids in the presence of Mn(OAc)$_2$·4H$_2$O as the cooxidant under an air atmosphere. This methodology enables the facile construction of various arylated indoles, which is operationally convenient, cost-effective, and Grignard reagent-free. The pyrimidine auxiliary could be easily removed under the basic hydrolysis. This protocol could provide new insight into Co-catalyzed arylation, which paves the way for other types of inexpensive Co-catalyzed C−C cross-coupling reactions.

Scheme 5. Proposed Reaction Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03746.

Experimental procedures and NMR spectra data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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