Cross-Coupling

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Mixed Directing-Group Strategy: Oxidative C−H/C−H Bond Arylation of Unactivated Arenes by Cobalt Catalysis

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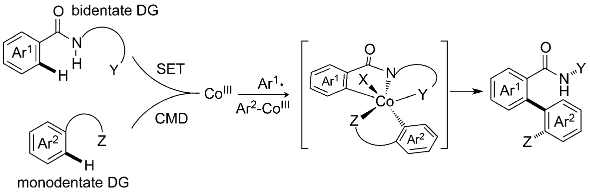
Abstract: *A mixed directing-group strategy for inexpensive [Co(acac)$_3$]-catalyzed oxidative C−H/C−H bond arylation of unactivated arenes has been disclosed. This strategy enables the arylation of a wide range of benzamide and arylpyridines effectively to afford novel bifunctionalized biaryls, which are difficult to achieve by common synthetic routes. Two different pathways, namely, a single-electron-transmetalation process (8-aminoquinoline-directed) and a concerted metalation–deprotonation process (pyridine-directed), were involved to activate two different inert aromatic C−H bonds. Moreover, the aryl radicals have been trapped by 2,6-di-tert-butyl-4-methylphenol to form benzylated products. This unique strategy should be useful in the design of other arene C−H/C−H cross-couplings as well.*

Biaryls are versatile and important structural motifs in medicinal agents, natural products, advanced materials, and other organic molecules.[1] In terms of green and sustainable chemistry, employing C−H bonds as potential functional groups has prevailed in recent years. Especially, transition-metal-catalyzed cross-dehydrogenative C−H/C−H activation arylation has emerged as a more attractive approach to access biaryls.[2] Despite the tremendous achievements in the last decade, unfortunately, cross-dehydrogenative coupling (CDC) has mainly been restricted to palladium[3] and rhodium[4] catalysts with simple arenes as the coupling partners (solvent), and it remains difficult to achieve high regioselectivity on both arene coupling partners.

As a representative of earth-abundant first-row metals, cobalt has exhibited comparable and unique efficiency in C−H functionalization.[5] Over the past decade, in situ generated low-valent cobalt catalysts have been utilized in C−H arylation of arenes with aryl Grignard reagents, aryl halides, and phenol derivatives in the presence of Grignard reagents as the bases and reductants.[6] However, to the best of our knowledge, no cobalt-catalyzed cross-coupling reaction between two aryl C−H bonds has been developed so far.[7] In contrast, the bidentate directing strategy using the relatively cheap Cp*-free (Cp* = C_5Me_5) CoX_n ($n = 2$, 3) salts as catalysts has become a promising methodology for C−H bond functionalization.[8] Recently, cobalt-catalyzed C(sp^2)−H amination and alkoxylation, assisted by a bidentate directing group, was described by our group.[9] Mechanistically, this transformation involves an intermolecular single-electron transfer (SET) process,[10] which is significantly different from the certified concerted metalation–deprotonation (CMD) process. Additionally, such a CMD process assisted by a monodentate directing group has also been extensively investigated for the [Cp*Co^{III}] catalysis.[11] Inspired by the aforementioned progress and based on our continuing research on cobalt-catalyzed C−H bond activation,[8g, 9] we envisaged that a chemoselective cross-coupling reaction between two different C−H substrates could be achieved by incorporating an appropriate monodentate and bidentate directing group into the two respective arene substrates. The SET and CMD pathways might take place in parallel to form a high-valent cobalt intermediate coordinated by two mixed ligands, and then undergo facile reductive elimination to afford unsymmetrical bifunctionalized biaryls (Scheme 1).



Scheme 1. A new strategy for cobalt-catalyzed oxidative C−H/C−H bond arylation of unactivated arenes. DG = directing group.

Although the above speculation seems feasible, several challenges need to be overcome to achieve this ambitious goal. 1) The reactivity of a cobalt catalyst involving twofold SET and CMD processes in one reaction is unprecedented. 2) It is difficult to achieve a chemoselective cross-coupling reaction while avoiding undesired homocoupling products for the two arenes. 3) The complex geometric structure and multiple coordination sites of the substrate and product may inactivate the cobalt catalyst.

Our optimization studies commenced with identifying a pair of suitable directing groups (see the Supporting Information). After extensive screening of multiple directing groups, we chose the 8-aminoquinoline amide **1a** and 2-phenylpyridine (**2a**) as the model substrates for optimizing the arylation conditions (Table 1). Solvents play an important role in the reaction activity. When HFIP was used as the solvent, the cross-coupling product **3aa** was obtained in 30% yield (see the Supporting Information).[12] Replacement of

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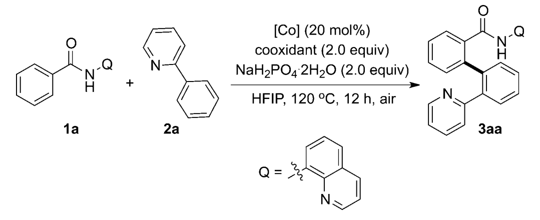
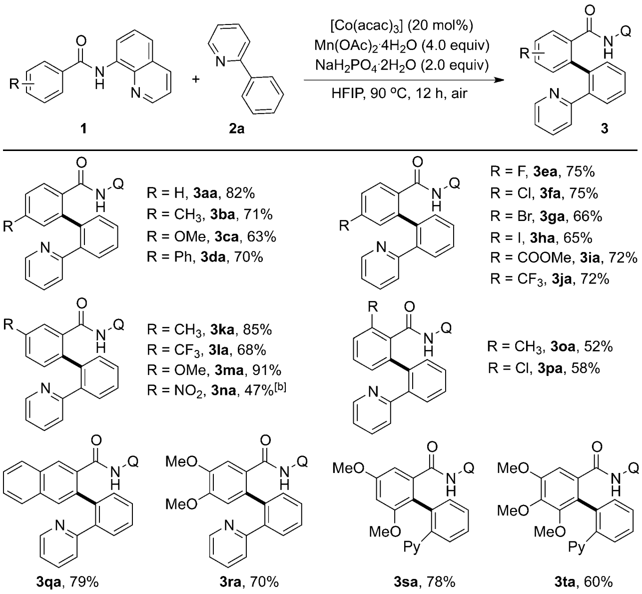
Table 1: Optimization of the cobalt-catalyzed arylation reaction between substrates **1a** and **2a**.[a]



Entry	Catalyst	Cooxidant	Yield [%]
1	$Co(OAc)_2{\cdot}4\,H_2O$	$Mn(OAc)_2{\cdot}4\,H_2O$	32
2	$Co(OAc)_2{\cdot}4\,H_2O$	AgOAc	4
3	$Co(OAc)_2{\cdot}4\,H_2O$	$Mn(OAc)_3{\cdot}2\,H_2O$	9
4[b]	$Co(OAc)_2{\cdot}4\,H_2O$	–	25
5	[Co(acac)$_3$]	$Mn(OAc)_2{\cdot}4\,H_2O$	42
6[c]	[Co(acac)$_3$]	$Mn(OAc)_2{\cdot}4\,H_2O$	61
7[c,d]	[Co(acac)$_3$]	$Mn(OAc)_2{\cdot}4\,H_2O$	74
8[c–e]	[Co(acac)$_3$]	$Mn(OAc)_2{\cdot}4\,H_2O$	82

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), [$Co(OAc)_2{\cdot}4\,H_2O$] (20 mol%), cooxidant (0.4 mmol), $NaH_2PO_4{\cdot}2\,H_2O$ (0.4 mmol), HFIP (1.0 mL), air atmosphere, 12 h, 120 °C. Yield is that of isolated product. [b] O_2 atmosphere. [c] 90 °C. [d] **1a** (0.4 mmol). [e] $Mn(OAc)_2{\cdot}4\,H_2O$ (0.8 mmol). acac = acetylacetonate, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Table 2: Scope with respect to aromatic amides.[a]



R = H, **3aa**, 82%
R = CH$_3$, **3ba**, 71%
R = OMe, **3ca**, 63%
R = Ph, **3da**, 70%

R = F, **3ea**, 75%
R = Cl, **3fa**, 75%
R = Br, **3ga**, 66%
R = I, **3ha**, 65%
R = COOMe, **3ia**, 72%
R = CF$_3$, **3ja**, 72%

R = CH$_3$, **3ka**, 85%
R = CF$_3$, **3la**, 68%
R = OMe, **3ma**, 91%
R = NO$_2$, **3na**, 47%[b]

R = CH$_3$, **3oa**, 52%
R = Cl, **3pa**, 58%

3qa, 79%
3ra, 70%
3sa, 78%
3ta, 60%

[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), [Co(acac)$_3$] (20 mol%), $Mn(OAc)_2{\cdot}4\,H_2O$ (0.8 mmol), $NaH_2PO_4{\cdot}2\,H_2O$ (0.4 mmol), HFIP (1.0 mL), air atmosphere, 12 h, 90 °C. [b] **1** (0.2 mmol), **2a** (0.4 mmol). Py = pyridine.

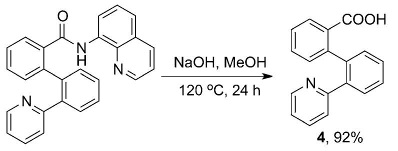
HFIP with other common solvents, such as THF, DMF, DMSO, and arenes dramatically lowered the reactivity. Various bases and acids were also investigated afterwards and $NaH_2PO_4{\cdot}2H_2O$ was found to be the optimal choice (entry 1). Oxidants have a significant influence on the cross-coupling product. When either AgOAc or $Mn(OAc)_3{\cdot}2\,H_2O$ was used as an oxidant, the reaction was mostly inhibited (entries 2 and 3). Moreover, the reactivity of cobalt could be realized under an oxygen atmosphere (entry 4). As for other catalysts, [Co(acac)$_3$] showed superior result compared with $Co(OAc)_2{\cdot}4\,H_2O$ (entry 5). A slightly improved yield was observed when the temperature was elevated to 90 °C (entry 6). Further improvement was achieved by adjusting the amount of **1a** and cooxidant (entries 7 and 8), thus affording **3aa** in 82% yield. It is noteworthy that negligible homocoupled product (< 5%) of **1a** and no homocoupled product of **2a** were observed (see the Supporting Information).

To assess the generality of this strategy, the scope with respect to the benzamide substrates were firstly explored (Table 2). A variety of substituted benzamides reacted to afford the corresponding biaryls with high chemoselectivity. The *para*-substituted benzamides bearing both electron-donating and electron-withdrawing groups were compatible with the optimized reaction conditions, thus affording the arylation products in 63–84% yields (**3aa–ja**). Various functionalities, including halides (**3ea–ha**) and carbomethoxy (**3ia**) were well tolerated, thus providing an opportunity for potential post-transformations. For *meta*-substituted benzamides (**3ka–na**) and 2-naphthamide (**3qa**), the arylation took place at the sterically less-hindered position. Additionally, the strong electron-withdrawing functional group (NO_2) was compatible with the transformation (**3na**). The efficiency of the arylation was not impeded by *ortho*-substituents (**3oa,pa**). Di- and trisubstituted amides could also react to deliver the desired products in 60–78% yields (**3ra–ta**).

Subsequently, the strategy was applied to a variety of 2-arylpyridines (Table 3). Substrates with *ortho*-, *para*-, and *meta*-methoxy groups exhibited similar reactivities (**3ab–ad**), thus indicating that steric bulk did not significantly affect the reaction efficiency. Halogenated arylpyridines were compatible with the transformation (**3ae–ag**). Furthermore, we were delighted to find that the unprotected OH in **2h**, a group which is frequently problematic for cross-coupling methods, was also tolerated under the optimized reaction conditions (73% yield). For *meta*-substituted substrates and 2-(naphthalen-2-yl)pyridine, the arylation occurred at the less hindered *ortho*-position (**3ab**, **3ai–aj**). The reaction of substituted pyridines (**2k–m**) and other N-based directing groups, such as benzo[*h*]quinoline (**2n**) and pyrimidine (**2o**), were also found to proceed smoothly. Interestingly, benzoxazole bearing an activated C–H bond could successfully be coupled with the amide substrate by deprotonation of the acidic C–H atom under the modified reaction conditions, thus furnishing the heteroarylated product in 32% yield (**3ap**).[13]

Finally, the 8-aminoquinoline auxiliary could be easily removed by the simple base hydrolysis to afford the bifunctional pyridine- and carboxy-containing biaryls **4** (Scheme 2).

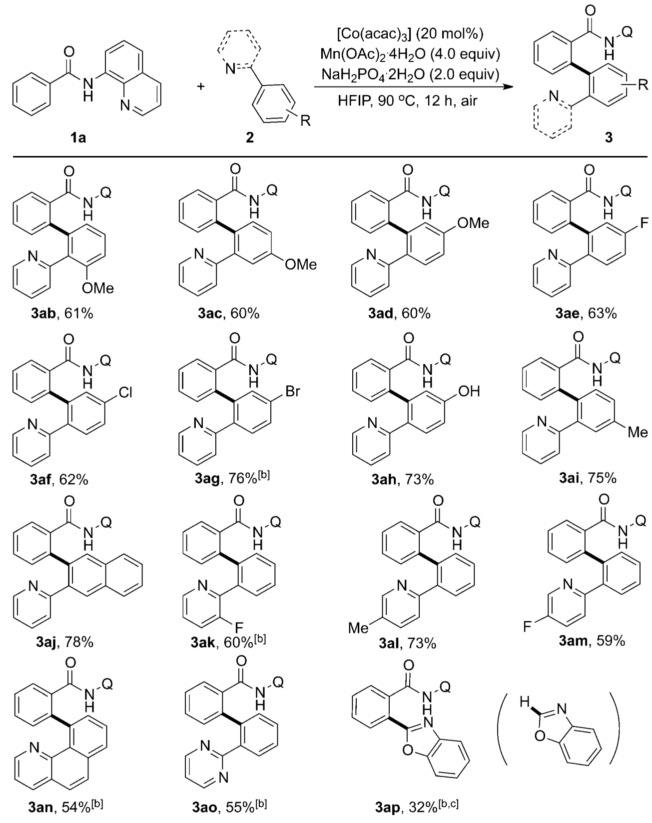
To examine the role of cobalt and manganese salts, a sequence of control experiments were performed (for



4, 92%

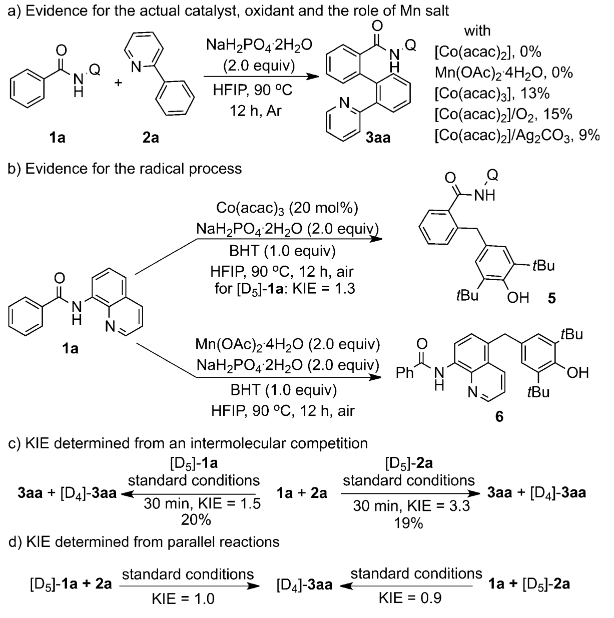
Scheme 2. Removal of the 8-aminoquinoline auxiliary.

Table 3: Scope with respect to arylpyridines.[a]



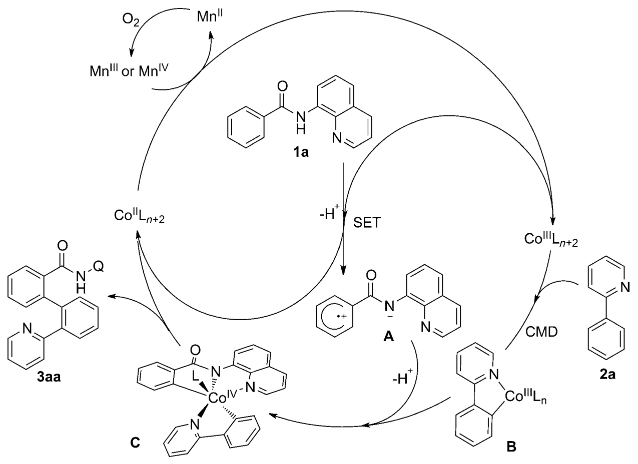
[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), [Co(acac)$_3$] (20 mol%), Mn(OAc)$_2$·4 H$_2$O (0.8 mmol), NaH$_2$PO$_4$·2 H$_2$O (0.4 mmol), HFIP (1.0 mL), air atmosphere, 12 h, 90°C. [b] **1a** (0.2 mmol), **2** (0.4 mmol). [c] Ag$_2$O (0.2 mmol) instead of Mn(OAc)$_2$·4 H$_2$O, 110°C.

experiment details see the Supporting Information). Under an argon atmosphere, the use of either [Co(acac)$_2$] or Mn(OAc)$_2$·4H$_2$O alone could not promote the reaction, whereas this transformation could occur in the presence of [Co(acac)$_3$] without oxidants. When either Ag$_2$CO$_3$ or an oxygen atmosphere was introduced, the desired arylation product was obtained in the presence of [Co(acac)$_2$]. These facts indicate that the reaction process probably initiates from a cobalt(III) species and oxygen (from air) should be the actual oxidant (Scheme 3 a). The addition of a radical quencher, either 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), or *p*-benzoquinone (BQ), under standard reaction conditions, suppressed the formation of **3aa**. Notably, the utilization of BHT led to trapping of aryl radicals, thus resulting in the formation of two regioisomers, **5** and **6**,[12] which might result from different SET pathways initiated by either [Co(acac)$_3$] or Mn(OAc)$_2$·4 H$_2$O catalysts. The treatment of **1a** with BHT in the presence of [Co(acac)$_3$] afforded the coupled product **5** at the *ortho*-position of benzamide, while the reaction with Mn(OAc)$_2$·4 H$_2$O led to the quinolinyl coupled product **6** at C5. These data suggest that the aryl radical is generated by a cobalt(III) catalyst and manganese(II) is a cooxidant. Furthermore, a kinetic isotope effect (KIE) value of 1.3 was observed in the reaction of **1a** and [D$_5$]-**1a** with BHT. These results indicate the C–H activation of **1a** could occur by a SET mechanism (Scheme 3 b). Competitive coupling of **2a** with an equimolar mixture of **1a** and [D$_5$]-**1a** at a low conversion gave a KIE value of 1.5. Likewise, when an equimolar mixture of **2a** and [D$_5$]-**2a** was used in the presence of **1a**, a notable KIE value of 3.3 was obtained (Scheme 3 c). Meanwhile, the KIE values (1.0 for **1a**, 0.9 for **2a**) observed in parallel reactions suggest that the C–H bond cleavage of **1a** and **2a** is not involved in the rate-limiting step (Scheme 3 d).



Scheme 3. Control experiments and mechanistic studies.

Based on the above mechanistic studies and relevant literature,[5b,10] we propose that the cobalt catalyst plays a twofold role in the oxidative C–H/C–H bond arylation (Scheme 4). In the first catalytic cycle, an intermolecular SET process between **1a** and Co^{III} provides the intermediate **A** and regenerates Co^{III} in the presence of Mn(OAc)$_2$·4H$_2$O and oxygen. In the second catalytic cycle, directed C–H activation through a CMD process produces the intermediate **B**, which is attacked by deprotonated **A** to form the key intermediate



Scheme 4. Proposed reaction mechanism.

species **C**. The cross-coupling product **3aa** is obtained by reductive elimination and Co^{III} is regenerated by the oxidant (O_2) and cooxidant ($Mn(OAc)_2{\cdot}4H_2O$).[14]

In conclusion, we have successfully demonstrated Cp*-free cobalt-catalyzed oxidative C–H/C–H bond arylation of unactivated arenes, in which the commercially available [$Co(acac)_3$] was utilized as the catalyst and $Mn(OAc)_2{\cdot}4H_2O$ as the cooxidant to accomplish the unsymmetrical biaryls. The significant aspects of our work are: 1) Inert C–H bonds between two arenes could be identified by the same cobalt catalyst through SET and CMD processes. 2) High selectivity, mild temperature, and operational convenience are the key features for the cross-coupling reaction. 3) A variety of functional groups are compatible with the current methodology which affords novel bifunctionalized biaryls. This mixed directing-group strategy should provide unique insights for a synthetically valuable direct arylation. Extension of this strategy to other oxidative $C(sp^3)$–H/$C(sp^2)$–H couplings and asymmetric reactions is currently in progress in our laboratory.

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Keywords: arylation · biaryls · cross-coupling · cobalt · reaction mechanisms

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[14] At present, other pathways could not be completely excluded, including: 1) two C–H activation steps occurring within a single cobalt center in a sequential manner. 2) Co^I/Co^{III} cycle (see Ref. [13b]): **1a** undergoes an intramolecular SET process and an intermolecular SET process to form a cyclometalated Co^{III} intermediate.

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