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Cobalt-Catalyzed Aerobic Oxidative C−H/C−H Cross-Coupling of Unactivated Arenes for the Synthesis of Biaryls

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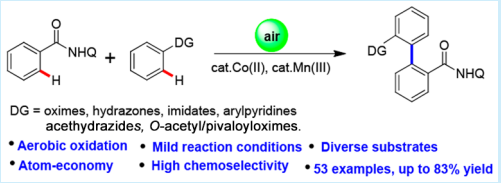
Supporting Information

ABSTRACT: A mild and efficient protocol for the synthesis of 2,2′-difunctional biaryls from readily available benzamides and oximes by $Co(OAc)_2·4H_2O$ catalysis has been developed. The catalytic cycle that includes aerobic oxidation of Co(I) to Co(III) is successfully achieved for the first time through dual-chelation-assisted C−H/C−H coupling with the assistance of catalytic $Mn(acac)_3$. The catalytic system exhibits powerful reactivity and tolerates a large number of sensitive functional groups.



The prevalence of the biaryl structural motif has prompted intense research directed at discovering efficient and high-yielding methods for its preparation.[1,2] Direct arylation of arenes, achieved via cross-coupling of $C(sp^2)$−H bonds, has featured prominently in these efforts, leading to the establishment of a range of useful transition-metal-catalyzed C−H/C−H coupling reactions.[3] For example, by exploiting the advantages of chelation-assisted C−H activation, the biaryl motifs are constructed successfully through the assistance of a directing group to control the regioselectivity and achieve the reactivity.[4−9] These reactions substitute the preactivated arenes with a simple arene and, therefore, avoid the expense and difficulty in preparing organometallic or halide coupling partners. Over the past decade, many catalyst systems have been applied to these transformations, including Pd,[4] Rh,[5] Co,[6] Cu,[7] Ni,[8] and Ru.[9] A common element in all of these processes is the need for distinct electronic effect or sterically controlled substrates, which greatly limits their wider application.

In recent years, the use of a dual-chelation-assisted strategy for the synthesis of biaryls, especially difunctional biaryls which show broad and unique biological activities,[10] has attracted significant scientific attention.[11] The dual-chelation-assisted strategy is expected to precisely control the regioselectivity of both arenes and greatly extend the substrate scope to difunctional biaryls. In this regard, the homocoupling is first explored to successfully attain a high level of regioselectivity.[12] However, the application of the strategy to cross-coupling is relatively limited due to the inevitable formation of undesirable homocoupling byproducts. The large excess of one substrate is often required to increase the chemoselectivity. Another disadvantage is that most of these coupling reactions require a significant excess of hazardous or expensive oxidants such as $K_2S_2O_8$,[11b,d] $NaIO_4$,[11b,d] $AgNO_3$,[11a] and Ag_2CO_3.[11d] Because it is abundant and environmentally benign, oxygen would be a preferred oxidant in these transformations.[13] Herein, we report a new protocol for the synthesis of difunctional biaryls from readily available benzamides and oximes. This new reaction takes place at 65 °C in air and requires 20 mol % $Co(OAc)_2·4H_2O$ and 20 mol % $Mn(acac)_3$ as catalysts.

The low cost cobalt catalysts have attracted much interest recently due to their unique catalytic properties, low toxicity, and industrial prospects.[14] Inspired by our continuous interests in cobalt-catalyzed C−H bond activation,[15] we initially focused on the examination of a cobalt catalytic system without the use of oxidant in air by the use of benzamide **1a** and oxime **2a** as model substrates. Unfortunately, no reaction was observed (see the Supporting Information (SI)). Based on the fact that the metal catalyst is often used to promote the reaction rate in the transformation using oxygen as the oxidant,[16] a series of metals, such as Cu, Ag, Pd, and Mn, were subjected to the reaction (see the SI). To our delight, the coupling product **3a** was obtained in 42% yield by the use of 20 mol % $Mn(acac)_3$. Other metals, including $Cu(OAc)_2$, AgOAc, and $Pd(OAc)_2$, failed to catalyze the reaction. There was no desired product in a nitrogen atmosphere in the presence of 0.2 equiv or 2 equiv of $Mn(acac)_3$, implicating that $Mn(acac)_3$ itself is unable to promote the reaction as an oxidant. Intriguingly, the homocoupling products were not detected by TLC and GC-MS. In order to confirm this result, the parallel experiment was performed to evaluate the reactivity of the homocoupling by subjecting only one substrate under the current catalytic system (see the SI). Unexpectedly, both substrates benzamide **1a** and oxime **2a** are inactive and fail to give the homocoupling products under the standard reaction conditions, which result in high chemoselectivity for this cross-coupling reaction. Further optimization toward the base and solvent revealed that $NaOPiv·H_2O$ showed optimal efficiency and *t*-AmylOH was the best solvent. No reaction was observed in the absence of $Co(OAc)_2·4H_2O$, and the yield decreased obviously when

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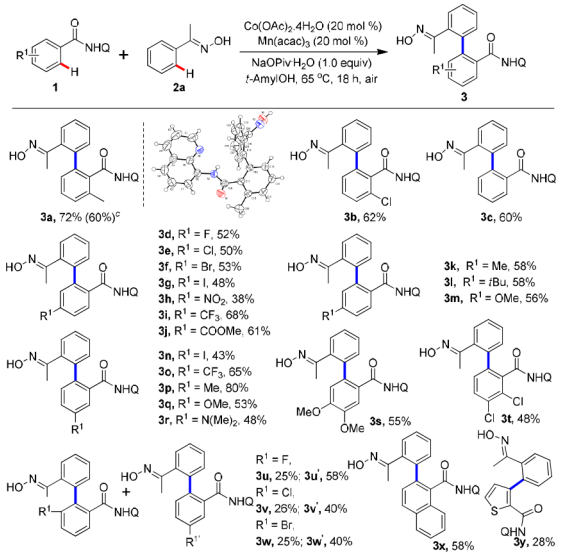
less catalyst was employed (see the SI). The reaction could be performed at 65 °C smoothly.

Various benzamides could be used in this reaction, and some representative results was summarized in Scheme 1. In general,

Scheme 1. Scope of Benzamides[a,b]

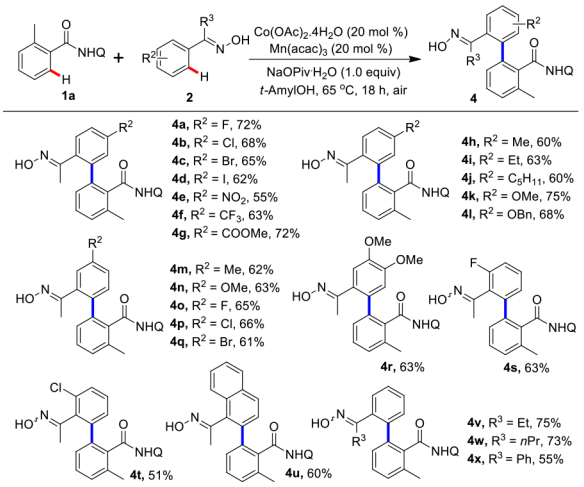


[a]Reaction conditions were optimal conditions in the SI. [b]Isolated yields. [c]1 mmol scale.

the electronic effect and steric effect on benzamides exerted no obvious influence upon the reaction. For example, the electron-rich benzamides showed good reactivity to afford the corresponding biaryls (**3k**−**3m**, **3p**−**3s**). At the same time, the benzamides with electron-withdrawing substituents, including −F, −Cl, −Br, −I, $-CF_3$, and −COOMe, participated in the reaction smoothly (**3b**, **3d**−**3j**, **3n**−**3o**, **3t**−**3w**). When an −I substituted substrate was performed in the reaction, the deiodination had not been observed (**3g**, **3n**). However, the substitution with a strong electron-withdrawing nitro group gave the corresponding biaryls in low yield (**3h**). It is worth mentioning that only monoarylation products were obtained for *para*-substituted benzamide substrates (**3c**−**3m**). And a mixture of biaryls was isolated with regard to several *meta* halo-substituted substrates (**3u**−**w**), which might be attributed to relatively less steric hindrance. Multisubstituted benzamides were successfully converted to their corresponding multisubstituted biaryls under the standard reaction conditions (**3s** and **3t**). Naphthalenecarboxamide was applicable under the standard conditions as well and afforded the desired product (**3x**) in 58% yield. The thiophene-2-carboxamide could serve as a viable substrate in the reaction with lower efficiency (**3y**). Significantly, the transformation could be carried out on a 1 mmol scale in reasonable yield (**3a**), and the structure of the biaryl (**3a**) is clearly confirmed by single-crystal X-ray diffraction (CCDC 1826163).

After examining the compatibility of the coupling reaction with various benzamides, then we explored the reactivity of different oximes (Scheme 2). A series of *para* substituted oximes bearing electron-withdrawing or -donating groups were reactive to furnish the biaryl products in moderate to good yields (**4a**−**4l**). The tolerance of several halogen substituents offered the opportunity of further derivatization of the obtained biaryls. When the −I substituted oxime substrate

Scheme 2. Scope of Oximes[a,b]

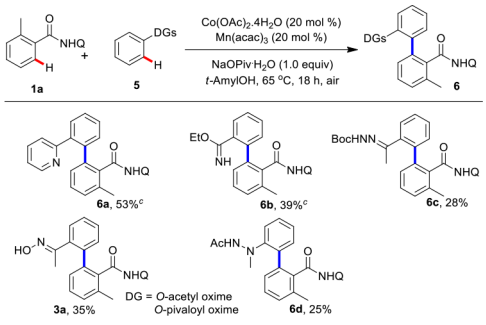


[a]Reaction conditions were optimal conditions in the SI. [b]Isolated yields.

was used in the reaction, the deiodination had not been observed (**4d**). The comparable reactivity was attained with diverse *meta* substituted, disubstituted, or *ortho* substituted oximes (**4m**−**4t**), exhibiting the good compatibility of the methodology. With respect to the 1-naphthoxime substrate, the reaction proceeded well to provide the coupling product **4u** in 60% yield. The other complicated aryl oximes could participate in the reaction to deliver the desired products in good yields as well (**4v**−**4x**).

As part of a research program targeted at the development of general direct arylation reactions, we explored the reactivity of the current catalytic system to verify the availability of an efficient reaction with various directing group substrates. We first explored 2-phenylpyridine, which is a popular model molecule for the chelation assisted C−H activation reaction. Initial investigations revealed that the current catalytic system enabled the selective formation of the corresponding cross-coupling biaryls in moderate yield (Scheme 3, **6a**). Encouraged

Scheme 3. Scope of Variant Directing Groups[a,b]



[a]Reaction conditions were optimal conditions in the SI. [b]Isolated yields. [c]Using TFE as solvent.

by this initial discovery, the scope with variant chelation substrates was investigated. To our delight, most nitrogen-containing directing groups, including benzimidate, hydrazone, *O*-acetyl/pivaloyloxime, and acethydrazide showed reactivity to give diverse difunctional biaryls (**6b**−**d**), greatly highlighting the good compatibility of the protocol. The homocoupling byproduct was not observed in these transformations.

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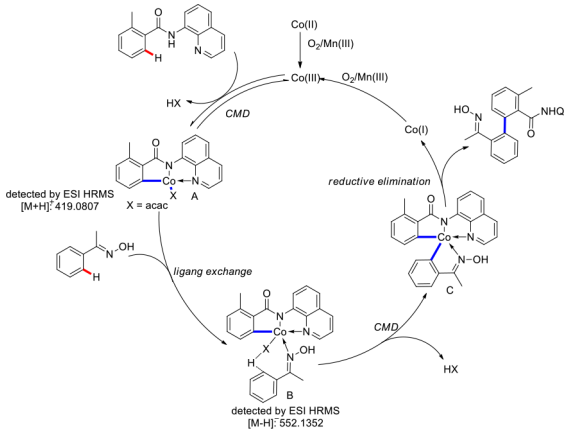
To gain insight into the reaction mechanism, the intermolecular competition experiment of electronically differentiated **1h** and **1k** with **2a** was performed. It is observed that the electronic effect of benzamides does not significantly impact the reaction. In contrast, the electron-donating group on the oximes facilitates the transformation (see the SI). The experiments in the presence of 20 equiv of D_2O led to the formation of a 19% H/D exchange of benzamide, suggesting a reversible process of C−H cleavage of benzamide. In contrast, no H/D exchange was observed for the oxime substrate. The intermolecular deuterium-labeling experiments with respect to benzamide and oxime were performed as shown in the SI. A kinetic isotope effect (KIE) value of 4.0 was observed from the competitive reaction of **1c** and **D_5-1c**. These data demonstrate that the C−H activation process might be involved in the rate-determining step.

Song and Niu recently reported a cobalt-catalyzed SET and CMD C−H/C−H coupling reaction for biaryl synthesis and the addition of a radical scavenger drastically suppressed the reaction.[11c] However, it was found that the addition of an excessive amount of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) did not influence the reaction at all and a good yield was always obtained (see the SI). This result indicated that a radical catalytic pathway might not be involved in our reaction. It should be emphasized that the reaction was totally inhibited with the addition of 2 equiv of BHT (2,4-di*tert*-butyl-4-methylphenol) due to the reaction between the oxime and BHT (see the SI).

Based on previous reports[11,16] and preliminary mechanistic studies, a plausible mechanism is proposed as shown in Scheme 4. Because the reaction failed in the presence of 20 mol % $Co(OAc)_2·4H_2O$ and 2 equiv $Mn(acac)_3$ in a nitrogen atmosphere, it is presumed that the key oxidant for the oxidation of Co(II) to Co(III) cycle is the $O_2/Mn(acac)_3$ system. The formed Co(III) reacts with benzamide with the assistance of an 8-aminoquinolyl auxiliary to enable the formation of intermediate **A** through an *ortho*-C−H cleavage by a concerted metalation deprotonation process (CMD), which was detected by ESI-HRMS (see the SI). The H/D exchange experiment revealed that this activation process is reversible. The subsequent ligand exchange of oxime into Co(III) provides the species **B** (detected by ESI-HRMS; see the SI), which undergoes the second CMD process to abstract the inert *ortho*-hydrogen of the oxime to generate species **C**.

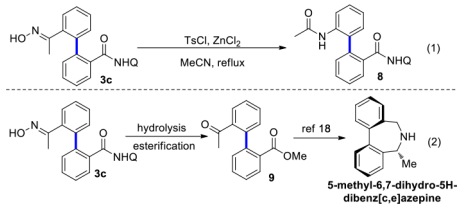
Scheme 4. Proposed Reaction Mechanism



The reductive elimination of species **C** produces the cross-coupling biaryl product and liberates Co(I) species. The latter could be oxidized to Co(III) through the $O_2/Mn(acac)_3$ system to fulfill the catalytic cycle.

The obtained coupling product could undergo Beckmann rearrangement to give the useful 2-amino-2′-carboxybiaryls, which possess versatile biological activities and medicinal properties (Scheme 5, eq 1).[17] Furthermore, by using our biaryl product, the key intermediate **9** for the synthesis of valuable pharmaceutical[18] 5-methyl-6,7-dihydro-5*H*-dibenz-[*c*,*e*]azepine, which is often synthesized through Suzuki coupling reaction, could be prepared by hydrolysis and esterification (Scheme 5, eq 2). The preparation of the Suzuki coupling partners for compound **9** is quite complicated with multiple steps.[19]

Scheme 5. Further Applications



In summary, we have developed a new protocol for synthesis of difunctional biaryls by cobalt-catalyzed aerobic oxidative cross-coupling of C−H/C−H from readily available benzamides and oximes. For the first time, hazardous and expensive oxidants, such as $K_2S_2O_8$, $NaIO_4$, $AgNO_3$, and Ag_2CO_3, have been successfully replaced by oxygen/cat.Mn(III). In view of the rare utility of oxygen as an oxidant in biaryl synthesis, the current results should provide a meaningful opportunity for process development in avoiding the use of large amounts of oxidants. This protocol is distinguished by its broad substrate scope and intriguing chemoselectivity in cross-coupling. Furthermore, this catalytic system is compatible with a few variant directing group substrates, which provides a pathway to obtain diverse difunctional biaryls. Further investigations on a related mechanism will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02526.

Experimental and characterization details; mechanistic investigations; synthetic application; ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1826163 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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