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Cobalt(III)- and Rhodium(III)-Catalyzed C−H Amidation and Synthesis of 4-Quinolones: C−H Activation Assisted by Weakly Coordinating and Functionalizable Enaminone

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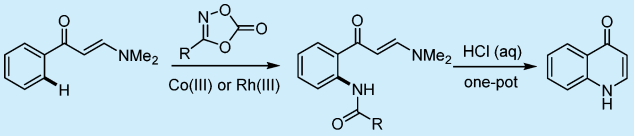
Supporting Information

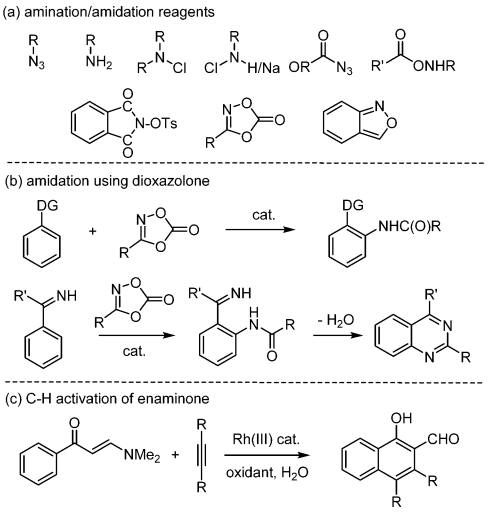
ABSTRACT: Cobalt(III) and rhodium(III) catalysts exhibited complementary scope in C−H amidation of aryl enaminones. The amidation reactions proceeded with broad scope under the assistance of a weakly coordinating and bifunctional enaminone directing group. The electrophilicity of the enaminone group can be further utilized in subsequent hydrolysis−cyclization reactions to afford NH 4-quinolones in telescoping reactions.



The C−N linkage is one of the most important bonds in pharmaceuticals and organic functional molecules.[1] Traditional methods to construct C−N bonds include the Goldberg reaction, the Buchwald−Hartwig coupling, and the Chan−Lam coupling.[2] Although very efficient, these methods require the employment of functionalized arene starting materials. In the past decades, the C−H activation strategy has been extensively explored, which takes advantage of readily available arene substrates.[3] Thus, C−H activation has provided an important avenue to access C−N bonds in high atom- and step-economy,[4] and a variety of nucleophilic and electrophilic amination/amidation reagents have been developed (Scheme 1).[5,6]

In 2015, Chang applied dioxazolone as an amidating reagent for the C−H amidation of arenes for the first time (Scheme 1).[7] Later, Chang and others[8] realized rhodium-, cobalt-, and iridium-catalyzed amidation of a variety of sp^2 and sp^3 C−H bonds using this reagent. These early C−H amidation systems resorted to arenes assisted by nonfunctionalizable directing groups, and consequently, only simple amidation was realized. Shortly afterward, Li,[9] Zhu,[10] Glorius,[11] Ackermann,[12] and others[13] extended it to amidation−cyclization systems where participation of a nucleophilic NH directing group allowed synthesis of quinazolines and their *N*-oxides.[9−12] Despite the progress, the DGs have been mostly limited to nitrogen chelators, while weakly coordinating DGs have been only occasionally used and are mostly limited to secondary benzamides.[5b,8b,14] On the other hand, ketone carbonyl groups are readily functionalizable, but they have been rarely applied in C−H activation due to their low coordinating ability.[15] We reasoned that the carbonyl group in enaminones is more polarized and more coordinating, and it may accommodate C−H amidation. Furthermore, enaminone contains both nucleophilic and electrophilic sites and can be readily functionalized in postcoupling manipulations to allow for cyclization as have been recently demonstrated by Zhu in C−H activation (Scheme 1).[16] We now report cobalt- and rhodium-catalyzed C−H amidation of enaminones and synthesis of 4-quinolones under operationally simple conditions.

Scheme 1. Nitrogenation Reagents and C−H Activation of Enaminone



We initiated our investigation with the optimization studies on the coupling of enaminone **1a** and dioxazolone **2a** (Table 1). The expected amidation reaction proceeded in the presence of a rhodium catalyst, but the yield was only moderate (entry 1). While the yield was lower using a $CoCp^*(CO)I_2/AgSbF_6$ catalyst system in DCE (entry 2), introduction of NaOAc additive improved the efficiency (entries 5−7). Further screening returned KOAc as an optimal base additive (entry 8) and 1,4-dioxane as the best solvent (entry 7). In contrast, an acid additive turned out to be essentially ineffective (entries 3

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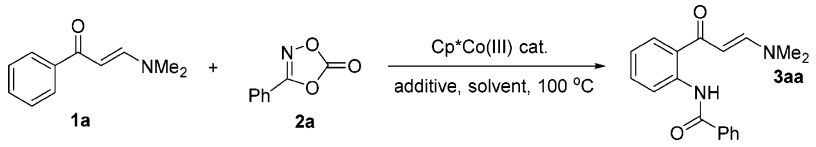
Table 1. Optimization Studies[a]



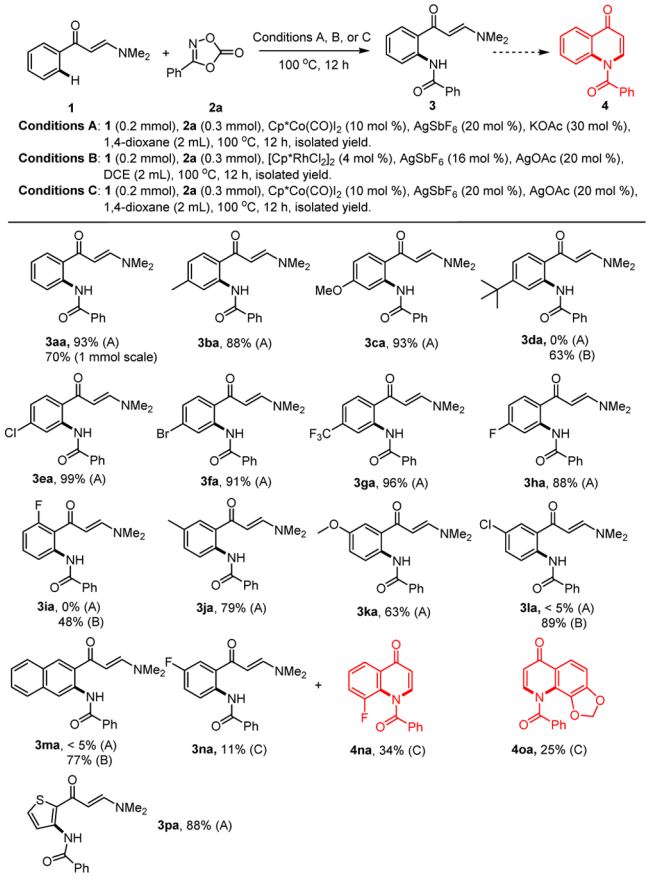
entry	catalyst (mol %)	additive (equiv)	solvent	yield[b] (%)
1[c]	$[RhCp^*Cl_2]_2/AgSbF_6$		DCE	64
2	$CoCp^*(CO)I_2/AgSbF_6$		DCE	50
3	$CoCp^*(CO)I_2/AgSbF_6$	HOAc (2.0)	DCE	64
4	$CoCp^*(CO)I_2/AgSbF_6$	PivOH (2.0)	DCE	47
5	$CoCp^*(CO)I_2/AgSbF_6$	NaOAc (0.3)	DCE	73
6[d]	$CoCp^*(CO)I_2/AgSbF_6$	NaOAc (0.3)	DCE	78
7	$CoCp^*(CO)I_2/AgSbF_6$	NaOAc (0.3)	1,4-dioxane	89
8	$CoCp^*(CO)I_2/AgSbF_6$	KOAc (0.3)	1,4-dioxane	93
9	$CoCp^*(CO)I_2/AgSbF_6$	AgOAc (0.2)	1,4-dioxane	69
10	$CoCp^*(CO)I_2/AgSbF_6$	KOAc (0.3)	1,4-dioxane	68
11	$CoCp^*(CO)I_2/AgSbF_6$	KOAc (0.5)	1,4-dioxane	84
12[e]	$CoCp^*(CO)I_2/AgSbF_6$	KOAc(0.3)	1,4-dioxane	85
13[d]	$CoCp^*(CO)I_2/AgSbF_6$	KOAc (0.3)	1,4-dioxane	69
14	$CoCp^*(CO)I_2/AgNTf_2$	NaOAc(0.3)	1,4-dioxane	trace
15	$AgSbF_6$	KOAc (0.3)	1,4-dioxane	NR

[a]Unless otherwise noted, all reactions were carried out using **1a** (0.20 mmol), **2a** (0.30 mmol), and a cobalt catalyst (10 mol %) in the presence of a silver additive (20 mol %) in a solvent (2.0 mL) at 100 °C for 12 h under Ar. [b]Isolated yield. [c]$[RhCp^*Cl_2]_2$ (4 mol %) and $AgSbF_6$ (16 mol %) were used. [d]The reaction temperature is 120 °C. [e]The reaction temperature is 80 °C.

and 4). Decreasing the loading of the catalyst, variation of the amount of KOAc additive, or lowering the temperature all resulted in somewhat lower yield. Thus, the following optimal reaction conditions (conditions A) have been established for further studies: $Cp^*Co(CO)I_2$ (10 mol %), $AgSbF_6$ (20 mol %), and KOAc (30 mol %) in 1,4-dioxane at 100 °C for 12 h.

With the optimized reaction conditions in hand, we next examined the scope of this system (Scheme 2). The scope of enaminone was explored in the coupling with **2a**. It was found that enaminones bearing an electron-donating (**3ba**, **3ca**), -withdrawing (**3ga**), or halogen group (**3ea**, **3fa**, **3ha**) at the *para* position generally coupled under the cobalt-catalyzed conditions in excellent yields. To our surprise, a *para* *t*-Bu-substituted enaminone failed to undergo any coupling with **2a**, and this negative effect has been observed in our previous indole synthesis via Rh(III)-catalyzed C−H activation of *N*-pyridylanilines.[17] The low yield of Co(III) catalysis is probably due to catalyst decomposition. Gratifyingly, this limitation was resolved when typical Rh(III)-catalyzed amidation conditions were applied (conditions B), and the desired product (**3da**) was isolated in good yield. Introduction of *meta* Me and OMe groups is also tolerated, and the coupling occurred at the less hindered position (**3ja**, **3ka**). Interestingly, the coupling of a *meta* fluoro-substituted enamonine afforded two products. The C−H activation at the less hindered site gave a regular amidated product **3na**, while C−H activation at the more hindered *ortho* site delivered an *N*-benzoyl-4-quinolone (**4na**) as a result of further nucleophilic cyclization of the corresponding amide intermediate. This scenario of amidation−cyclization was also observed in the coupling of an acetal-fused enaminone (**4oa**), indicative of the intrinsic stereoelectronic effect of these two substrates. Introduction of a *m*-Cl group or a fused benzene ring was also allowed (**3la** and **3ma**), but only under the Rh(III)-catalyzed conditions, and the amidated products were isolated in good to high yield. The reaction proved sensitive to steric perturbation at the *ortho* position. Nevertheless, an *o*-fluoro-substituted enaminone reacted with moderate efficiency under our Rh(III)-catalyzed conditions (**3ia**). Furthermore, the C−H activation was not limited to a benzene ring; a thiophene-based enaminone also

Scheme 2. Scope of Enaminones in Amidation



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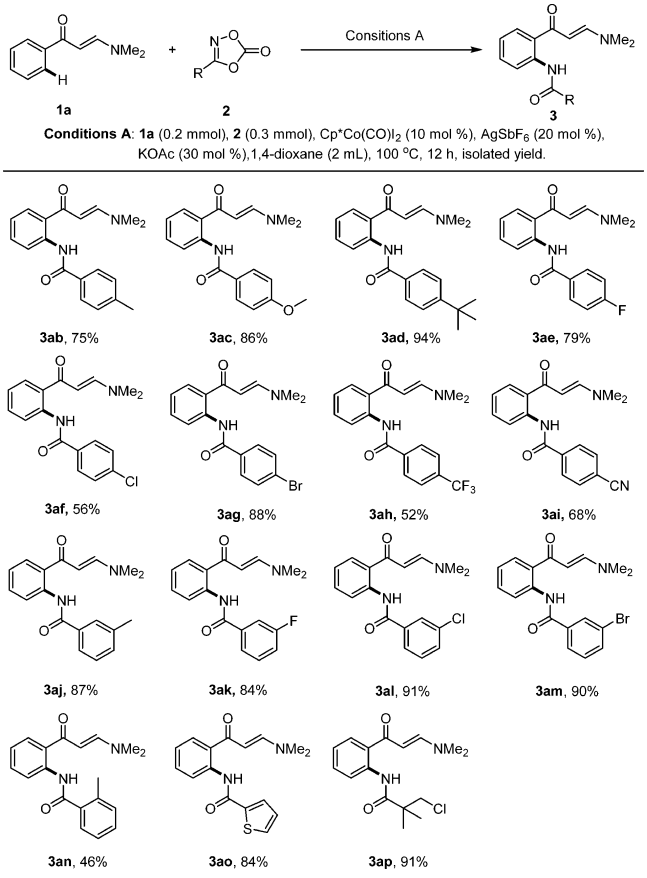
reacted in high efficiency under the cobalt-catalyzed conditions (**3pa**).

The scope of dioxazolone substrates was next explored using **1a** as a coupling partner (Scheme 3). Introduction of both

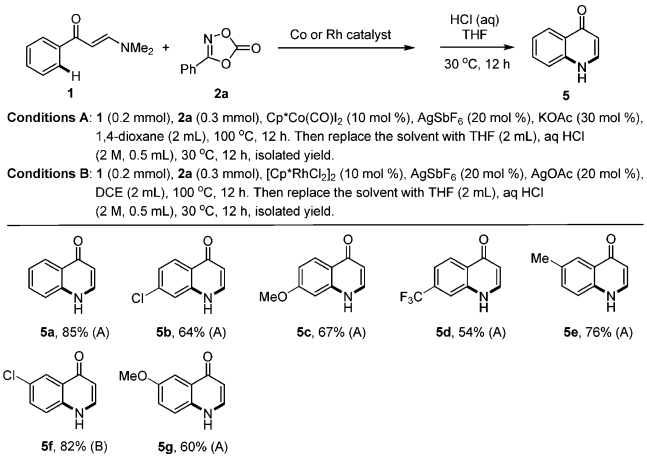
Scheme 3. Scope of Dioxazolones in Amidation Reaction



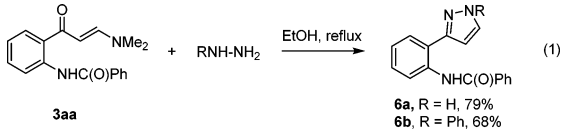
electron-donating and -withdrawing groups to the *ortho*, *meta*, and *para* positions of the 3-aryldioxazolone is fully tolerated, and the amidated product was isolated in moderate to excellent yield as the sole coupled product (**3ab**–**an**, 46–94%), although a relatively lower yield was observed for an *o*-Me substituted dioxazolone (**3an**) due to steric effect. The incorporated halogen and cyano groups should allow further manipulation of the coupled products. In addition, the 3-aryldioxazolone has been extended to 3-heteroaryl (**3ao**) and -alkyl (**3ap**) substitution with essentially no loss of coupling efficiency.

Although the amidated product failed to undergo cyclization in situ in most cases, we reasoned that this can be possible under ex situ conditions. Although attempts to cyclize product **3aa** met with failure when catalyzed by Lewis acidic metals such as Au(I) or Au(III), treatment of **3aa** with hydrochloric acid led to formation of an NH quinolone **5a** in 92% yield as a result of hydrolysis–cyclization. In contrast, treatment of thiophene-based amination product **3pa**, however, gave no desired product. Nevertheless, these two processes have been successfully combined in a telescoping synthesis for seven examples (Scheme 4). Thus, the two-stage synthesis of NH quinolones was realized in good to high yield. In these reactions, both electron-donating and -withdrawing groups at the *para* and *meta* positions of the enaminone substrate were well tolerated. Besides formation of quinolones, heating amide

Scheme 4. Telescoping Synthesis of NH Isoquinolones

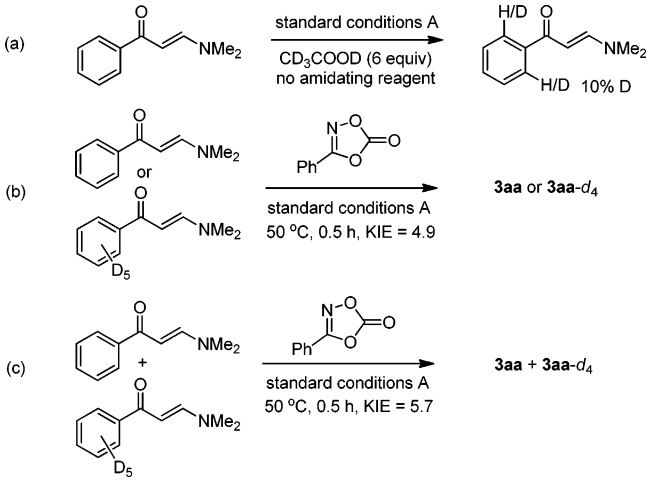


3aa with a simple hydrazine or a phenylhydrazine afforded a pyrazole in good to high yield, with the amide functionality being intact (eq 1).



Several experiments have been performed to briefly probe the mechanism (Scheme 5). H/D exchange experiment has

Scheme 5. Preliminary Mechanistic Studies



been performed between enaminone **1a** and CD_3COOD under conditions A in the absence of any amidating reagent. ^1H NMR analysis of the recovered (94% yield) enaminone revealed slight H/D exchange (10% D) at both *ortho* positions, and no exchange at any other position has been observed, indicative of relevancy of C–H activation. To further understand this C–H activation process, the kinetic isotope effect has been measured using both a side-by-side reaction (KIE = 4.9) and an intermolecular competition reaction (KIE = 5.7). Consistent large values of KIE have been obtained from these two reactions, suggesting that C–H activation is involved in the turnover-limiting process (see the SI for a proposed catalytic cycle).

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In summary, we have applied enaminone as a weakly coordinating directing group to realize the amidation of a broad scope of arenes. Cobalt and rhodium catalysts are both efficient for this transformation, and they offered complementary scope of substrates. In most cases, only simple amidation was achieved. Occasionally, the C−H amidation was followed by cyclization to give *N*-acyl 4-quinolones under the catalytic conditions. The enaminone acts as an electrophilic directing group as in subsequent hydrolysis−cyclization reactions to afford diverse NH quinolones in telescoping reactions. Given the broad scope of substrates, ready functionalization of the enaminone, and diversity of the coupled products, this method may find applications in the synthesis of complex structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00583.

Detailed experimental procedures, characterization of new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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