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Co(III)-Catalyzed Enaminone-Directed C−H Amidation for Quinolone Synthesis

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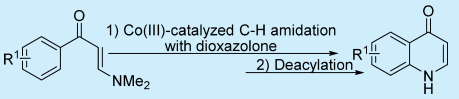
Supporting Information

ABSTRACT: We report herein the development of a Co(III)-catalyzed enaminone-directed C−H amidation method for synthetic access to quinolones, an important heterocyclic scaffold for diverse pharmaceutically active structures. The C−H coupling with dioxazolones and subsequent deacylation of an installed amide group allow consecutive C−N coupling generation of quinolones with wide-ranging compatible substituent patterns.



The quinolin-4(1*H*)-one (abbreviated herein as quinolone) moiety is a nitrogen-containing heterocycle that serves as a privileged core structure for diverse pharmaceutically active reagents (Scheme 1). Their demonstrated therapeutic properties include antibacterial,[1] antiviral,[2] antimalarial,[3] and anticancer[4] activities. For example, norfloxacin has been approved for the treatment of urinary tract infections.[5] Nedocromil is a mast cell stabilizer that acts to prevent breathing problems caused by asthma.[6] Ivacaftor is a drug used to treat cystic fibrosis in people with certain mutations in the cystic fibrosis transmembrane conductance regulator gene.[7] Elvitegravir is an integrase inhibitor used to treat HIV infection.[8] Therefore, increasing efforts have been devoted to the development of efficient protocols for the synthesis of this valuable scaffold. Notable synthetic methods include (1) Conrad-Limpach[9] and Niementowski[10] reactions, involving an initial condensation of amines and carboxyl derivatives and a subsequent cyclization step; (2) the base-promoted cyclization of *N*-(ketoaryl)amides, known as the Camps cyclization;[11] (3) synthesis using transition metals,[12] including palladium-catalyzed carbonylation, titanium-mediated reductive coupling, and ruthenium-catalyzed reduction reactions; and (4) cyclization of 2-nitrophenyl enaminone under catalytic transfer hydrogenation conditions.[13] Unfortunately, these methods can require cumbersome preassembly of a complex set of functional groups, involve harsh reaction conditions, and suffer from a limited substrate scope. Therefore, it is highly desirable to develop new, convenient, and efficient approaches for the synthesis of quinolones from simple starting materials.

Scheme 1. Quinolone Structure and Popular Drugs Containing the Quinolone Unit

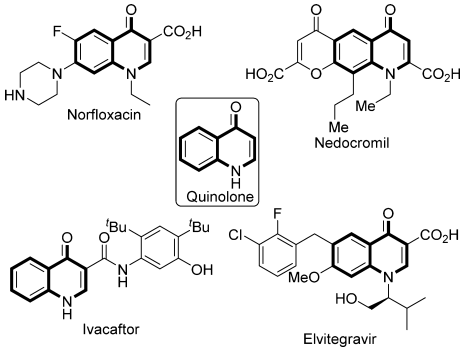
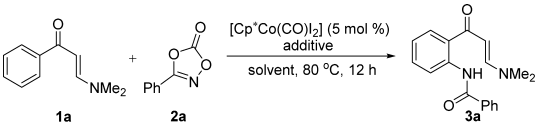


Table 1. Optimization of Reaction Conditions[a,b]



entry	additive (mol %)	solvent	yield (%)
1	$AgSbF_6$ (10)/KOAc (100)	DCE	31
2	$AgSbF_6$ (10)/AgOAc (100)	DCE	64
3	$AgSbF_6$ (10)/HOAc (100)	DCE	62
4		DCE	trace
5	no [Cp*Co(CO)I_2]/$AgSbF_6$ (10)	DCE	0
6	$AgSbF_6$ (10)	DCE	88
7	$AgSbF_6$ (10)	CF_3CH_2OH	19
8	$AgSbF_6$ (10)	1,4-dioxane	37
9	$AgSbF_6$ (10)	toluene	trace
10	$AgSbF_6$ (10)	THF	31
11	$AgBF_4$ (10)	DCE	92
12	$AgPF_6$ (10)	DCE	88
13	$AgNTf_2$ (10)	DCE	85

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Cp*Co(CO)I_2] (5 mol %), solvent (2 mL). [b]Isolated yields.

Transition-metal-catalyzed C−H functionalization promises shortened reaction steps and has recently been explored for building desired valuable C−C/C−heteroatom bonds or heterocyclic skeletons.[14] The activation of arene C−H bonds typically entails the presence of a proximal directing group.[15] The effective utilization of this strategy[16] has permitted efficient construction of a diverse range of heterocycles, including

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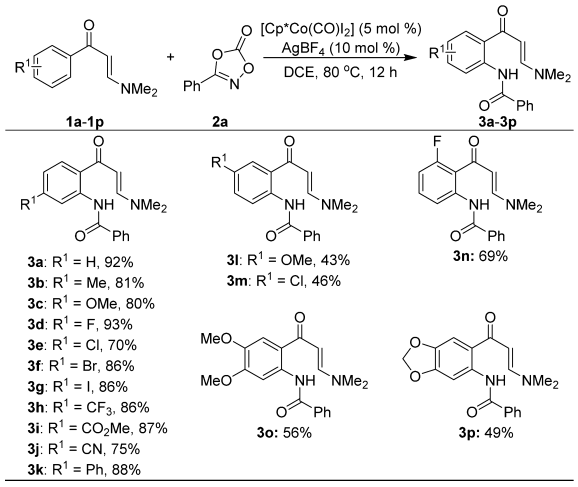
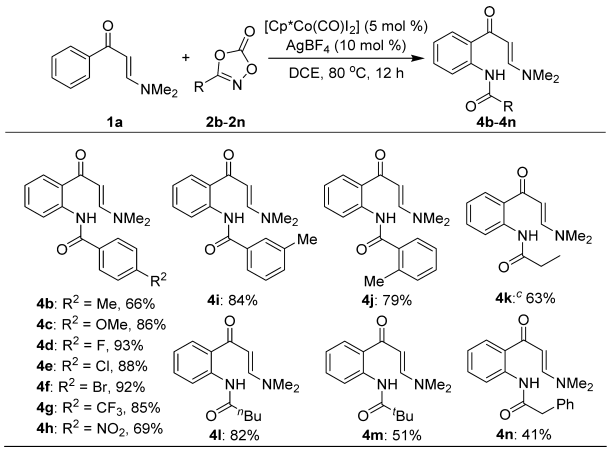
Scheme 2. Substrate Scope for Enaminones[a,b]



[a]Conditions: **1a**−**1p** (0.2 mmol), **2a** (0.3 mmol), DCE (2 mL). [b]Isolated yields.

Scheme 3. Substrate Scope for Dioxazolones[a,b]



[a]Conditions: **1a** (0.2 mmol), **2** (0.3 mmol), DCE (2 mL). [b]Isolated yields. [c]The reaction was conducted with [Cp*Co(CO)I_2] (10 mol %), $AgBF_4$ (20 mol %), DCE (2 mL) at 80 °C for 12 h.

isoquinolines,[17] isoquinolones,[18] indoles,[14c,19] etc.[20] Despite the advances, directing groups reported thus far are still limited with respect to the synthesis of certain important heterocyclic skeletons. For example, no directed C−H functionalization method has been documented for the synthesis of quinolones.

Recently, we have launched a synthetic program with enaminones acting as the directing group for C−H functionalization.[21] The unique push−pull electronic structure[22] has allowed the exploitation of the enaminone system for Rh(III)-catalyzed C−C coupling and synthesis of naphthalenes. We are interested in the extension of the reactivity profile of enaminones to C−heteroatom coupling en route to the synthesis of heterocycles. In addition, our synthetic endeavor also aims at the development of viable catalysis with earth-abundant metal species. We now report herein Co(III)-catalyzed, enaminone-directed C−H amidation, using 1,4,2-dioxazol-5-ones[23] (abbreviated as dioxazolones herein) as the coupling partners, for the synthesis of quinolones.

Reaction development was initiated with the screening of experimental conditions for the coupling of (*E*)-3-dimethylamino-1-phenylprop-2-en-1-one (**1a**) with 3-phenyl-1,4,2-dioxazol-5-one (**2a**). Initial screening of the reaction conditions with [Cp*Co(CO)I_2],[24] $AgSbF_6$, and additionally either KOAc, AgOAc, or HOAc leads to the low-yield production of **3a** after 12 h of reaction in dichloroethane (DCE) (Table 1, entries 1−3). Essentially no conversion is observed in the absence of [Cp*Co(CO)I_2] and $AgSbF_6$ (entries 4 and 5), suggesting, most likely, that a cationic Co(III) complex is involved in the

Scheme 4. Proposed Catalytic Cycle

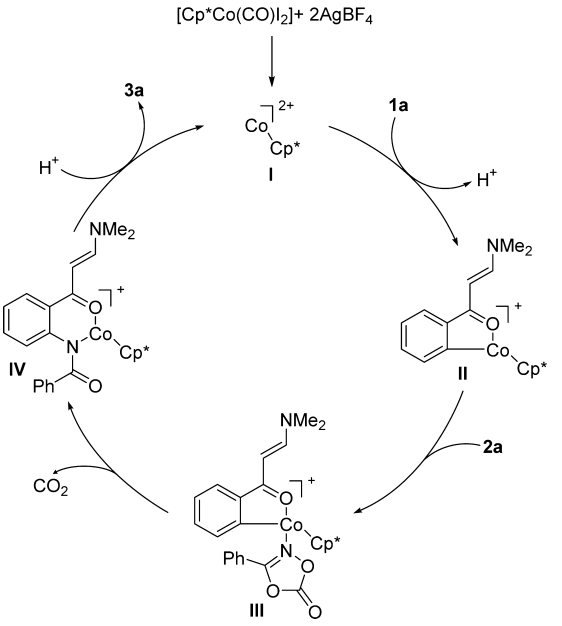
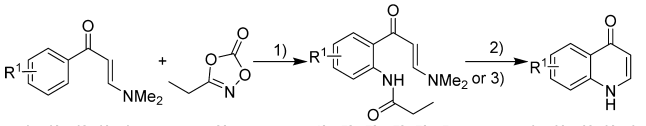


Table 2. Synthesis of Quinolones[a,b]



substrate	product 4k, 5b-5o	yield (%) 1)	product 6a-6o	yield (%) 2)	3)
1a	**4k**, R^1 = H	63	**6a**, R^1 = H	72	86
1b	**5b**, R^1 = Me	63	**6b**, R^1 = Me	80	86
1c	**5c**, R^1 = OMe	69	**6c**, R^1 = OMe	67	81
1d	**5d**, R^1 = F	93	**6d**, R^1 = F	74	95
1e	**5e**, R^1 = Cl	84	**6e**, R^1 = Cl	92	78
1f	**5f**, R^1 = Br	78	**6f**, R^1 = Br	78	82
1g	**5g**, R^1 = I	80	**6g**, R^1 = I	96	87
1h	**5h**, R^1 = CF_3	89	**6h**, R^1 = CF_3	85	65
1j	**5j**, R^1 = CN	91	**6j**, R^1 = CN	79	76
1k	**5k**, R^1 = Ph	87	**6k**, R^1 = Ph	92	85
1o	**5o**	56	**6o**	75	79

[a]Conditions: 1) **1** (0.2 mmol), **2k** (0.3 mmol), [Cp*Co(CO)I_2] (10 mol %), $AgBF_4$ (20 mol %), DCE (2 mL), 80 °C, 12 h; 2) **4k**, **5b**−**5o** (0.1 mmol), 1.2 N HCl (2 mL), reflux, 9 h; 3) **4k**, **5b**−**5o** (0.1 mmol), TMSOTf (1.45 equiv), Cy_2NMe (1.4 equiv), CH_2Cl_2, 0 °C to rt, 2 h. [b]Isolated yields.

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catalytic cycle. With $AgSbF_6$ loaded as the sole additive, the yield of **3a** is increased to 88% (entry 6). The switching of solvent from DCE to various other reaction media (entries 6−10) proves DCE as the optimum solvent. Further examination of the effect of silver salt (entries 6, 11−13) indicates that $AgBF_4$ gives the best result (entry 11), with the optimized product yield reaching 92%.

Under the obtained optimal reaction conditions mentioned above, we explored the applicability of diversely substituted enaminones **1a−1p** in the transformation by adopting **2a** as the representative reaction partner (Scheme 2). The *para*-substituted enaminones, bearing both electron-donating substituents (**1b**, Me; **1c**, OMe; **1k**, Ph) and electron-withdrawing substituents (**1d**, F; **1e**, Cl; **1f**, Br; **1g**, I; **1h**, CF_3; **1i**, COOMe; **1j**, CN), exhibit excellent reactivity. The reaction proceeds effectively for *meta*-substituted enaminones (**1l**, OMe; **1m**, Cl), resulting in the production of a single regioisomer. Substitution in the *ortho*-position as in **1n** proves to be compatible with the synthesis. The reaction can also be applied to disubstituted (**1o**) and polycyclic (**1p**) substrates, and the corresponding products are acquired in moderate yields.

With the enaminone substrate scope explored, we next examined the substrate scope for dioxazolones (**2b−2n**), with **1a** employed as the reaction partner (Scheme 3). Dioxazolone reagents bearing different electron-donating (**2b**, **2c**, **2i**, **2j**) and electron-withdrawing (**2d−2h**) groups at different positions of the phenyl ring can all couple smoothly with **1a**. Substituents on the dioxazolones are not limited to aromatic structures, as ethyl (**2k**), butyl (**2l**), *tert*-butyl (**2m**), and benzylic (**2n**) substitution also allows the delivery of respective target products effectively.

Several experiments were then conducted to examine the C−H activation process. A competition reaction was performed to evaluate the electronic preference for the transformation (see Supporting Information). A one-pot reaction between **1b**/**1d** and **2a** reveals a preferred reaction for electron-rich **1b** (product distribution: **3b**/**3d** = 2.27), providing evidence for an electrophilic aromatic substitution pathway. A large kinetic isotope effect ($k_H/k_D = 4$) is observed in an experiment between **1a**/**1a**-d_5 and **2a**, suggesting that C−H activation is turnover-limiting.

Based on these results and the previously documented observations,[21] a plausible mechanism is proposed (Scheme 4). In the presence of $AgBF_4$, a cationic Co(III) species (**I**) is generated *in situ* as the active catalyst; **I** coordinates to the carbonyl group of **1a** and activates the *ortho*-C−H bond to deliver a five-membered metallocyclic intermediate **II**; **2a** coordinates to **II** to form **III**, and then migratory insertion occurs, resulting in the production of **IV** and release of CO_2; **IV** undergoes proto-demetalation to give target product **3a** and simultaneously regenerate **I** for a new catalytic cycle.

As a demonstration of the synthetic utility of our protocol, we next examined the amenability of the coupling products for further elaboration. As mentioned earlier, enaminones possess a unique push−pull electronic property. The amide group in the coupling products can, in principle, be deacylated, allowing the generation of an amino group that can undergo nucleophilic attack at the alkene moiety of enaminone to produce a diversity of N-heterocyclic compounds. To take atom economy into consideration and minimize the size of the deprotected group, we produced the coupling products (**4k**, **5b−5h**, **5j**, **5k**, **5o**) in high yields by using 3-ethyl-1,4,2-dioxazol-5-one (**2k**) as the reaction partner. The propionyl group in the coupling products can indeed be removed under the condition of either 1.2 N hydrochloric acid solutions[25] or trimethylsilyl trifluoromethanesulfonate (TMSOTf)/*N*,*N*-dicyclohexylmethylamine (Cy_2NMe),[26] enabling the synthesis of a diverse range of quinolone derivatives (**6a−6h**, **6j**, **6k**, **6o**) (Table 2).

In conclusion, we have developed herein an efficient Co(III)-catalyzed enaminone-directed C−H amidation method for synthetic access to quinolones. The distinct reactivity between the alkene moiety of the enaminone group and the amino group generated by deacylation of the amide group has allowed the incorporation of a diverse range of substituent patterns into the quinolone molecular skeleton. Given the unique electron push−pull property exhibited by the enaminones, we anticipate that this valuable synthon will further prove its utility in more C−H functionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00968.

Experimental and synthetic details (PDF)
^1H and ^{13}C NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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