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One-pot Synthesis of Fused *N*,*O*-Heterocycles through Rh(III)-Catalyzed Cascade Reactions of Aromatic/vinylic *N*-Alkoxyamides with 4-Hydroxy-2-alkynoates

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Abstract. A highly efficient and regioselective synthesis of furo[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-diones and furo[3,4-*b*]pyridine-2,5(1*H*,7*H*)-diones *via* Rh(III)-catalyzed one-pot cascade reactions of aromatic/vinylic *N*-alkoxyamides with 4-hydroxy-2-alkynoates is presented. Mechanistically, the formation of the title compounds is triggered by a Rh(III)-catalyzed inert C(sp^2)–H bond activation of the amide substrate followed by its [4+2] annulation and lactonization with 4-hydroxy-2-alkynoate featuring with an oxidizing and partially traceless directing group. To the best of our knowledge, this is the first example in which both the furan-2(5*H*)-one and the pyridin-2(1*H*)-one scaffolds are constructed in one pot under one set of reaction conditions. Compared with literature methods, notable features of this new protocol include facile formation of bis-heterocyclic scaffolds from readily available acyclic substrates, broad substrate scope with good tolerance of a wide range of functional groups, excellent regioselectivity and high efficiency.

Keywords: Heterocycles; Rhodium; *N*-Alkoxyamides; 4-Hydroxy-2-alkynoates; C–H functionalization

Among various kinds of *N*-heterocycles, pyridinones are well known for their frequent uses in medicinal and synthetic chemistry as privileged scaffolds and versatile building blocks.[1,2] Meanwhile, furanone constitutes the structural core of numerous naturally occurring and man-made bioactive compounds and functional molecules.[3,4] Unsurprisingly, many fused heterocycles containing both the pyridinone and the furanone units are endowed with potent biological and medicinal activities, and have thus been used widely in the development of novel physiological and therapeutic agents.[5,6] Owing to their importance, some elegant methods for the synthesis of furan(one) fused pyridin(on)es have been developed.[7,8] In general, these literature methods can be classified into the following two categories: 1) formation of the required furan(one) ring onto a pre-activated pyridin(on)e unit;[7] and 2) formation of the desired pyridin(on)e ring onto a pre-functionalized furan(one) ring.[8] While these literature methods are generally efficient and reliable, new synthetic protocols enabling both the pyridinone and the furanone rings constructed in one pot from easily obtainable acyclic substrates is still urgently needed.

In the past decade, transition metal (TM)-catalyzed direct functionalization of the inert C–H bonds has attracted immense interests since it can significantly improve the atom- and step-economy of organic synthesis by obviating the preactivation of substrates and diminishing the generation of wastes.[9] In this aspect, TM-catalyzed oxidative annulation of alkynes or alkenes with *N*-alkoxybenzamides *via* inert C(sp^2)–H bond activation is thriving as an efficient and atom-economy access toward isoquinolones or their hydrogenated counterparts.[10-13] In these annulation processes, the *N*-alkoxy unit acts as not only an efficient directing group but also an internal oxidant through cleavage of an oxidizing bond, and these unique properties usually result in significant increase in substrate reactivity, enhancement of reaction selectivity, and substantial reduction of waste formation.[14]

Meanwhile, we noted that in Guimond's synthesis of isoquinolones via the annulation of *N*-methoxy benzamides with alkynes, the alkyne substrates could be extended from simple alkynes to 3-phenylprop-2-yn-1-ol to afford 4-(hydroxymethyl)-3-phenyl isoquinolin-1(2*H*)-one in a regioselective manner with the hydroxyl group located on the far end from the amide unit (Scheme 1, eq. 1).[10a] On the other hand, Ma et al disclosed a $[RhCp^*Cl_2]_2$-catalyzed coupling of *N*-methoxybenzamides with nonterminal tertiary 2-alkynylic alcohols affording fully substituted allenes (eq. 2).[15] In another example, Liu et al reported a regio-controlled [4+1] annulation of *N*-methoxy benzamides with α-allenols to form isoindolinones (eq. 3).[16] In addition, Li et al recently reported an efficient Rh(III)-catalyzed coupling of 1-benzoyl

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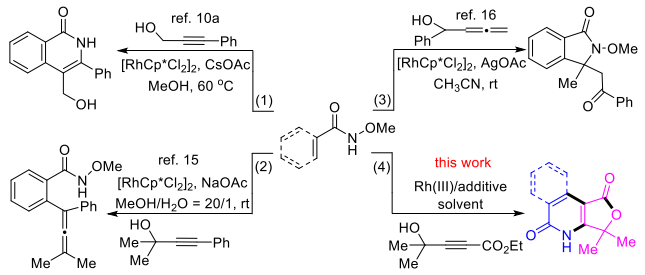
pyrrolidines with propargyl alcohols to afford (4-benzylidene)isochroman-1-ones.[17] Based on these pioneering studies and as a continuation of our own study on Rh(III)-catalyzed inert C(sp^2)−H bond functionalizations,[18] we were interested in exploring the reaction of aromatic/vinylic *N*-alkoxyamides with 4-hydroxy-2-alkynoates with the aim to study the possibility of establishing a one pot construction of both the pyridin-2(1*H*)-one and the furan-2(5*H*)-one units by taking advantages of TM-catalyzed inert C−H bond activation and the unique structural features of 4-hydroxy-2-alkynoates.[19] To our delight, from our study an efficient and regioselective synthesis of furo[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione and furo-[3,4-*b*]pyridine-2,5(1*H*,7*H*)-dione derivatives was successfully established (eq. 4). As far as we aware, the simultaneous construction of both the pyridin-2(1*H*)-one and the furan-2(5*H*)-one units from simple acyclic substrates in one pot under one set of reaction conditions has not been previously reported. Herein, we report our detailed results.

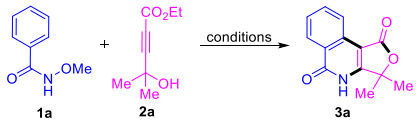


Scheme 1. Reactions of Aromatic/vinylic *N*-Alkoxy amides with Propargyl/allenic Alcohols

At the outset of our investigation, a mixture of *N*-methoxybenzamide (**1a**) and ethyl 4-hydroxy-4-methylpent-2-ynoate (**2a**) as model substrates was treated with [RhCp*Cl_2]$_2$ and CsOAc in dioxane at 100 °C. From this reaction, the desired 3,3-dimethylfuro[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione (**3a**) was obtained in 71% yield (Table 1, entry 1). To improve the efficiency, different solvents including toluene, methanol, isopropanol, CH_3CN and 1,2-dimethoxyethane (DME) were screened (entries 2-6). It turned out that with DME as the reaction medium, the yield of **3a** increased to 79% (entry 6). Subsequent screening of different additives such as KF, AgOAc, NaOAc, KOAc, K_2CO_3, Na_2CO_3, KCl, CsF, KI and TBAI showed that KF was the most effective (entries 7-16). In further optimization, we found that elevating the reaction temperature from 100 °C to 120 °C or reducing it to 80 °C gave reduced yields of **3a** (entries 17 and 18). Control experiments showed that the absence of catalyst or additive resulted in no formation of **3a** (Table 1, entries 19 and 20). It was also found that the yield of **3a** decreased remarkably when the loading of KF was reduced from 2 equiv to 1 equiv (entry 21). Finally, the reaction gave **3a** in a slightly lower yield under air (entry 22).

With the optimum reaction conditions in hands, the suitability of a range of diversely substituted *N*-alkoxy benzamides **1** for this novel reaction was studied by

Table 1. Optimization Studies for the Synthesis of **3a**[a]



entry	additive	solvent	T (°C)	yield (%)[b]
1	CsOAc	dioxane	100	71
2	CsOAc	toluene	100	trace
3	CsOAc	MeOH	100	57
4	CsOAc	^{i}PrOH	100	76
5	CsOAc	CH_3CN	100	58
6	CsOAc	DME	100	79
7	**KF**	**DME**	**100**	**87**
8	AgOAc	DME	100	79
9	NaOAc	DME	100	73
10	KOAc	DME	100	78
11	K_2CO_3	DME	100	80
12	Na_2CO_3	DME	100	76
13	KCl	DME	100	-
14	CsF	DME	100	83
15	KI	DME	100	-
16	TBAI	DME	100	-
17	KF	DME	120	85
18	KF	DME	80	80
19[c]	KF	DME	100	-
20	-	DME	100	-
21[d]	KF	DME	100	56
22[e]	KF	DME	100	75

[a] Reaction condition: **1a** (0.5 mmol), **2a** (1.0 mmol), [RhCp*Cl_2]$_2$ (2.5 mol%), additive (2 equiv), solvent (2 mL), N_2, 12 h. [b] Isolated yields. [c] Without catalyst. [d] KF (1 equiv). [e] Under air.

using **2a** as a model substrate. The results listed in Table 2 indicated that all of them took part in this reaction smoothly to afford a number of furo[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-diones **3** in moderate to good yields. Meanwhile, various functional groups, such as methyl, *tert*-butyl, methoxy, fluoro, chloro, or bromo, were well tolerated as demonstrated in the efficient formation of **3b**-**3l**. Notably, the electronic nature of the phenyl unit in benzamides **1** had some effect on the yield of **3** as **1** bearing electron-donating groups (EDG) on the phenyl ring gave the corresponding products in higher yields than those bearing electron-withdrawing groups (EWG) (**3b**, **3c**, **3d** *vs* **3e**). In addition, biphenyl derived amide readily reacted with **2a** to give **3f** in a yield of 79%. When *meta*-methyl substituted *N*-methoxybenzamide was used, regioselective C−H bond functionalization at the less hindered site was observed to afford **3g** exclusively, and the formation of another isomer **3g'** was not observed. However, when *meta*-methoxy, chloro or bromo substituted benzamides were used, a mixture of two regioisomers were obtained (**3h** and **3h'**, **3i** and **3i'**, **3j** and **3j'**). Meanwhile, it is to be noted that the structure of **3j'** was ambiguously confirmed by its single

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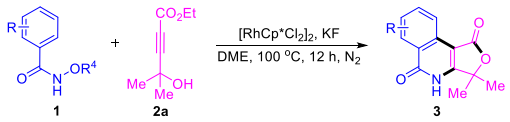
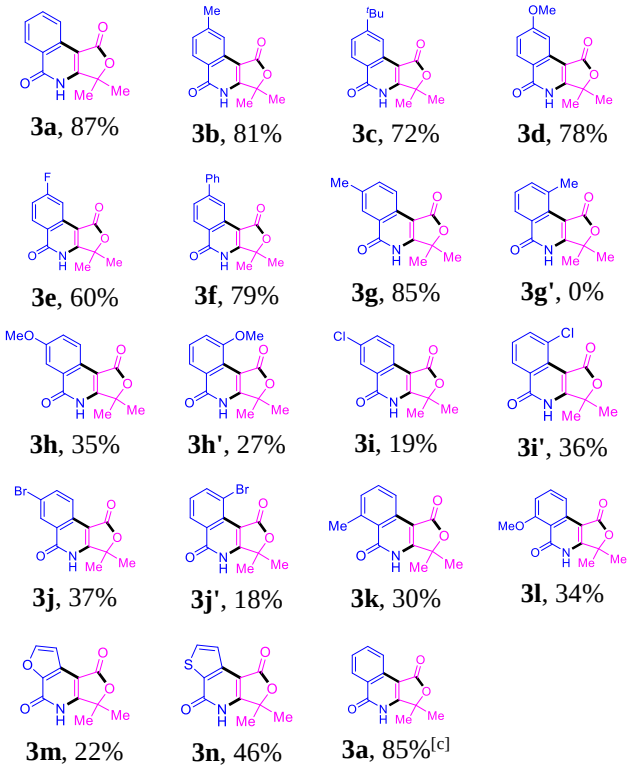
Table 2. Substrate Scope for the Synthesis of **3** (I)[a,b]





[a] Reaction condition: **1** (0.5 mmol, R^4 = Me), **2a** (1.0 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol%), KF (2 equiv), DME (3 mL), 100 °C, N_2, 12 h. [b] Isolated yields. [c] R^4 = Et.

crystal X-ray diffraction analysis (Figure 1).[20] Notably, the tolerance of chloro and bromo units is of synthetic interest as they could be used as handles for further transformations. It was also observed that *ortho*-substituted benzamides could participate in the reaction to give **3k** and **3l**. Notably, *N*-methoxyfuran-2-carboxamide and *N*-methoxythiophene-2-carboxamide reacted smoothly with **2a** to give fused triheterocyclic compounds **3m** and **3n** albeit the yields were somewhat lower. Finally, it was found that in addition to *N*-methoxybenzamide, *N*-ethoxybenzamide could also react with **2a**, and afforded **3a** in 85% yield.

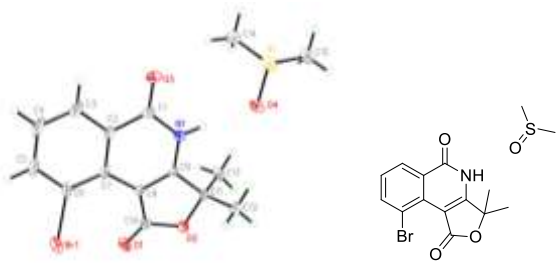


Figure 1. X-ray Crystal Structure of **3j'** with DMSO

Next, the suitability of a range of 4-hydroxy-2-alkynoates **2** for the formation of **3** was studied by using **1a** as a model substrate. It was observed that ethyl 4-ethyl-4-hydroxyhex-2-ynoate (**2b**), 4-hydroxy-4-methylhept-2-ynoate (**2c**), 4-hydroxy-4,6-dimethylhept-2-ynoate (**2d**), and 4-hydroxy-4,5,5-trimethylhex-2-ynoate (**2e**) were compatible with the optimized reaction conditions, and reacted smoothly with **1a** to give **3o**-**3r** in moderate to good yields (Table 3). In addition, 4-hydroxy-4-phenylpent-2-ynoate (**2f**) could also take part in this reaction, but the yield of the corresponding product **3s** was much lower. Interestingly, 3-(1-hydroxycyclopentyl)propiolate (**2g**), 3-(1-hydroxycyclohexyl)propiolate (**2h**) and 3-(1-hydroxycycloheptyl)propiolate (**2i**) were viable substrates, affording spiro products **3t**-**3v** efficiently. Apart from ethyl 4-hydroxy-2-alkynoates, methyl 4-hydroxy-4-methylpent-2-ynoate (**2j**) reacted with **1a** to give **3a** in a yield of 83%.

Having established an efficient synthesis of furo[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-diones **3** from the reactions of *N*-alkoxybenzamides **1** with 4-hydroxy-2-alkynoates **2**, we continued our study by extending the scope of the amide substrate from benzamides **1** to acrylamides **4** to explore the feasibility of an olefinic C−H bond functionalization. If possible, a direct synthesis of furo[3,4-*b*]pyridine-2,5(1*H*,7*H*)-diones **5** from acyclic substrates would be realized. For this purpose, *N*-methoxyacrylamide (**4a**) was treated with **2** under the optimum reaction conditions as listed in Table 1, entry 7. Promisingly, the expected simultaneous construction of both the pyridin-2(1*H*)-one and the furan-2(5*H*)-one scaffolds occurred efficiently to give 7,7-dimethylfuro[3,4-*b*]pyridine-2,5(1*H*,7*H*)-dione (**5a**) in 65% yield (Table 4). Encouraged by this result, the suitability of diversely substituted acrylamides **4** was explored by using **2a** as a model substrate. It turned out that several α-substituted, β-substituted and α,β-disubstituted acrylamides took part in this reaction smoothly to give **5b**-**5g** in moderate to good yields. Notably, the nature of the substituents including methyl, propyl, phenyl and 4-methylphenyl did not show an obvious effect on the reaction efficiency. Meanwhile, the reactions of disubstituted acrylamides were generally of higher efficiency than monosubstituted ones (**5f**, **5g** *vs* **5b**, **5c**, **5d**, **5e**). Interestingly, cyclic acrylamides such as *N*-methoxycyclopent-1-ene-1-carboxamide and *N*-methoxycyclohex-1-ene-1-carboxamide readily participated in this two-fold cyclization process leading to the formation of **5h** and **5i** in good yields. Subsequently, the reaction of a variety of diversely substituted 4-hydroxy-2-alkynoates **2** for the formation of **5** was also studied. It was thus found that **2b**, **2c**, ethyl 4-hydroxy-4,5-dimethylhex-2-ynoate **(2k)**, **2d**, **2e**, **2g**, **2h**, and **2i** were well compatible for this reaction to give **5j**-**5q** in moderate yields.

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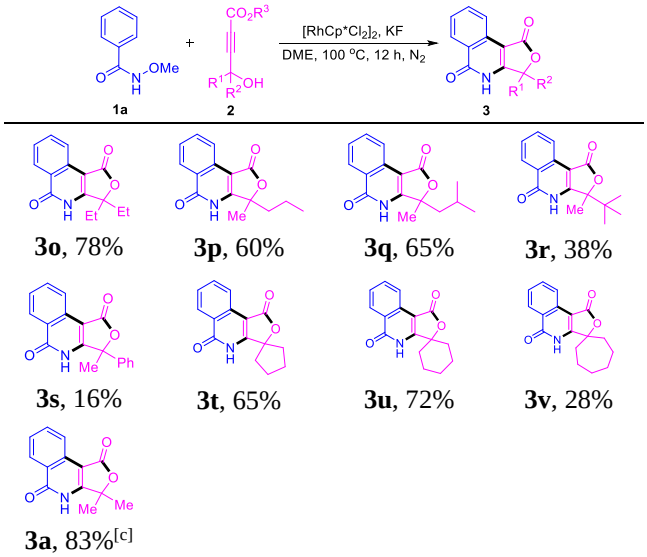
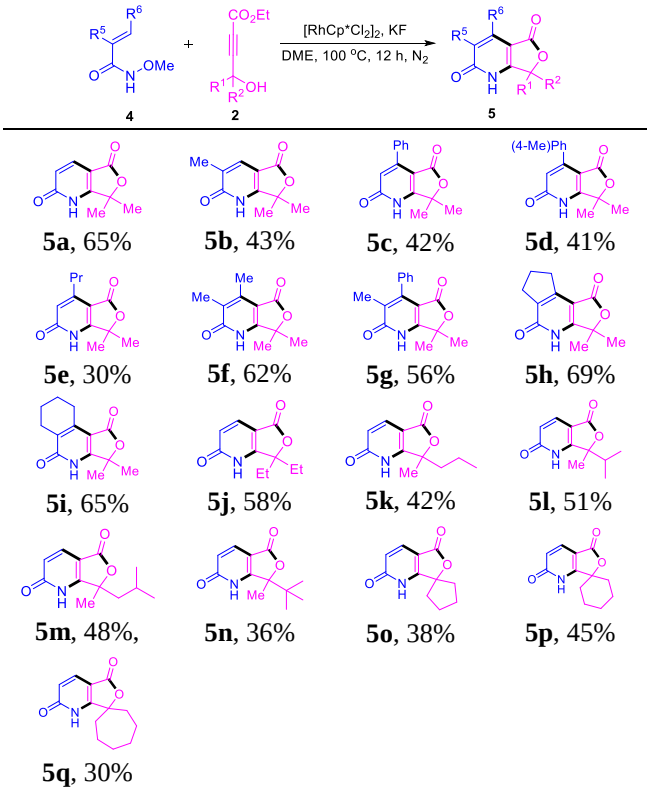
Table 3. Substrate Scope for the Synthesis of **3** (II)[a,b]



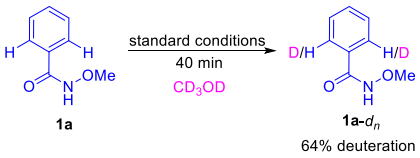
[a] Reaction condition: **1a** (0.5 mmol), **2** (1.0 mmol, R^3 = Et), $[RhCp^*Cl_2]_2$ (2.5 mol%), KF (2 equiv), DME (3 mL), 100 °C, N_2, 12 h. [b] Isolated yields. [c] R^3 = Me.

Table 4. Substrate Scope for the Synthesis of **5**[a,b]



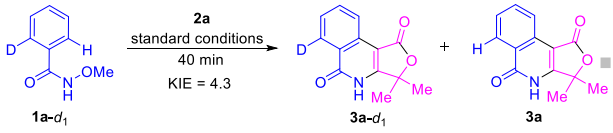
[a] Reaction condition: **4** (0.5 mmol), **2** (1.0 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol%), KF (2 equiv), DME (3 mL), 100 °C, N_2, 12 h. [b] Isolated yields.

To gain some insight into the mechanism of this cascade reaction, several experiments were performed. First, **1a** was treated with CD_3OD under standard reaction conditions for 40 min in the absence of **2**, which led to a significant level of deuterium incorporation (64%) at the *ortho*-position of **1a** (Scheme 2). This result indicates that this Rh(III)-catalyzed C−H bond cleavage is reversible.



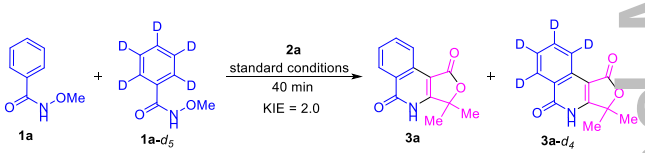
Scheme 2. Reversibility of C−H Bond Activation

Second, the intramolecular kinetic isotope effect was measured on the basis of the reaction of **1a**-d_1 with **2a** (Scheme 3). The observed KIE value (K_H/K_D = 4.3) indicates that cleavage of the C−H bond is probably involved in the rate-limiting step.



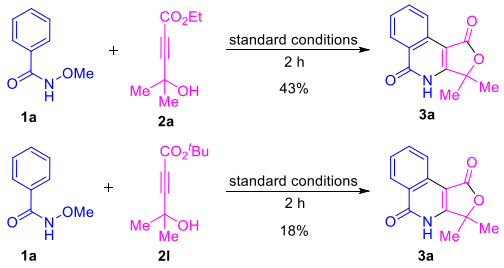
Scheme 3. Intramolecular Kinetic Isotope Effect Study

Third, the intermolecular kinetic isotopic effect was measured on the basis of competition reactions between **1a** with **2a** and **1a**-d_5 with **2a**. From this study, a notable KIE (K_H/K_D = 2.0) was observed (Scheme 4). This result is in consistence with what was observed in the intramolecular KIE study (as shown in Scheme 3), both of which indicate that the cleavage of the C−H bond is probably involved in the rate-limiting step.



Scheme 4. Intermolecular Kinetic Isotope Effect Study

Fourth, a competitive experiment was performed by running two side by side reactions of **1a** with **2a** and **1a** with *tert*-butyl 4-hydroxy-4-methylpent-2-ynoate (**2l**). The reactions were let to proceed under standard reaction conditions for 2 h. From the resulting mixtures, **3a** was obtained in yields of 43% and 18%, respectively (Scheme 5). The fact that 4-hydroxy-2-alkynoate **2** with less steric congestion on the ester moiety was kinetically more favored indicates that the lactonization step should be another key factor in determining the overall rate of this cascade process.



Scheme 5. Steric Effect of the Lactonization

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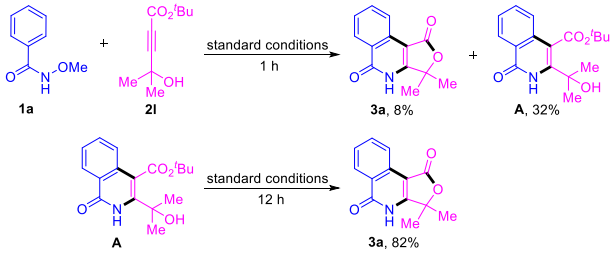
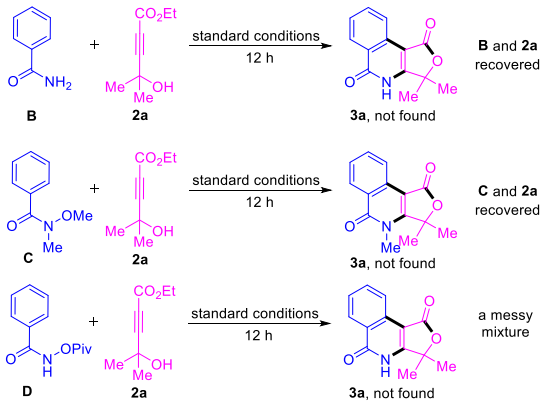
Fifth, **1a** was treated with **2l** under the standard reaction conditions for 1 h. From the resulting mixture, **3a** was isolated in 8% yield. Meanwhile, the isoquinoline intermediate **A** was obtained in a yield of 32%. Next, **A** was subjected to the standard reaction conditions for 12 h, from which **3a** was obtained in a yield of 82% (Scheme 6).



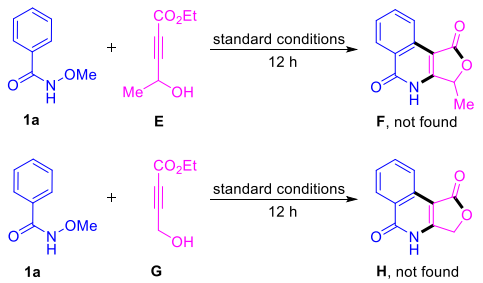
Scheme 6. Isolation and Transformation of Intermediate **A**

Sixth, benzamide (**B**) was treated with **2a** under standard conditions for 12 h, but **3a** was not obtained. Meanwhile, **B** and **2a** remained intact, indicating that the -OMe unit in **1a** is indispensable for the formation of **3a**. It was also observed that when *N*-methoxy-*N*-methylbenzamide (**C**) or *N*-(pivaloyloxy)benzamide (**D**) was used as the amide substrate, no **3a** was obtained (Scheme 7).



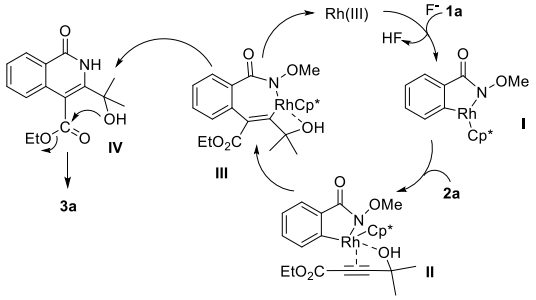
Scheme 7. Control Experiments (**I**)

Seventh, ethyl 4-hydroxypent-2-ynoate (**E**) or ethyl 4-hydroxybut-2-ynoate (**G**) was tried as the 4-hydroxy -2-alkynoate substrate to react with *N*-methoxy benzamide (**1a**) under standard conditions for 12 h. It turned out the desired product **F** or **H** was not obtained while most of the starting materials remained intact (Scheme 8).



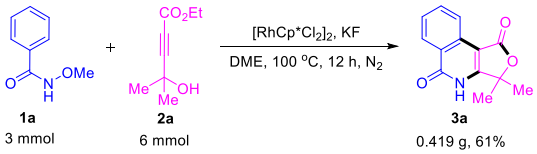
Scheme 8. Control Experiments (**II**)

On the basis of the above mentioned experimental results and previous reports,[10-19] a plausible mechanism is proposed for the formation of **3a** (Scheme 9). Firstly, a C−H bond cleavage of **1a** assisted by Rh(III) takes place to form a five-membered rhodacycle **I**. Complexation of **I** with **2a** gives rise to intermediate **II**. Next, the regioselective insertion of the alkyne triple bond into the C−Rh bond provides a seven-membered rhodacycle intermediate **III**. During this process, it is believed that the steric effect of the congested tertiary alcohol moiety of **2a** and the binding affinity of the hydroxyl group onto Rh(III) help to guide the regioselective migratory insertion of the unsymmetrical triple bond.[16] Next, a concerted or stepwise C−N bond forming/N−O bond cleaving event occurs, affording the annulation product **IV**, and releasing the Rh(III) catalyst. Next, the in situ formed **IV** undergoes an intramolecular lactonation to afford the final product **3a**. Notably, it is postulated that in the formation of intermeidate **I**, KF should have acted as a base in helping to remove the proton of NH generating the N−Rh bond.



Scheme 9. Proposed Mechanism for the Formation of **3a**

Finally, to demonstrate that this newly developed method is suitable for large scale synthetic missions, the preparation of **3a** was carried out in an enlarged scale of 3 mmol. We were delighted to find that the corresponding reaction proceeded smoothly to afford **3a** in a yield of 61% (Scheme 10).



Scheme 10. Large Scale Synthesis of **3a**

In summary, we have developed a novel strategy for the one-pot synthesis of furo[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione and furo[3,4-*b*]pyridine-2,5(1*H*,7*H*)-dione derivatives via a Rh(III)-catalyzed cascade process consisting C(sp^2)–H bond activation, [4+2] annulation and lactonization. This protocol employed readily available aromatic/vinylic *N*-alkyloxyamides and 4-hydroxy-2-alkynoates as starting materials, providing a straightforward and economic strategy to access biologically important hybrid compounds containing both the pyridinone and the furanone units.

Interestingly, this reaction is highly regioselective for the unsymmetrical triple bond insertion, which is originated from the prevention of the steric congestion associated with the tertiary alcohol unit of 4-hydroxy-2-alkynoates and the coordination of the hydroxyl oxygen with the transition metal catalyst. With the merits as described above, we expect this new method will be useful in related rearch areas.

Experimental Section

Typical Procedure for the Synthesis of 3,3-Dimethylfuro[3,4-*c*]isoquinoline-1,5(3*H*,4*H*)-dione (3a)

To a reaction tube equipped with a stir bar were added *N*-methoxybenzamide (**1a**, 75.6 mg, 0.5 mmol), DME (3 mL), ethyl 4-hydroxy-4-methylpent-2-ynoate (**2a**, 156.2 mg, 1.0 mmol), $[RhCp^*Cl_2]_2$ (7.7 mg, 0.0125 mmol), and KF (58.1 mg, 1.0 mmol) with stirring. The mixture was stirred under N_2 at 100 °C. Upon completion, it was cooled to room temperature. The resulting mixture was filtered through a pad of celite, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using dichloromethane/methanol (200:1) as eluent to afford **3**a in a yield of 87%. **3b**-**3v**, **5a**-**5q** were obtained in a similar manner.

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[20] CCDC 1820589 (**3j'**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk /data_request/cif.

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COMMUNICATION

One-pot Synthesis of Fused *N*,*O*-Heterocycles through Rh(III)-Catalyzed Cascade Reactions of Aromatic/vinylic *N*-Alkoxyamides with 4-Hydroxy -2-alkynoates

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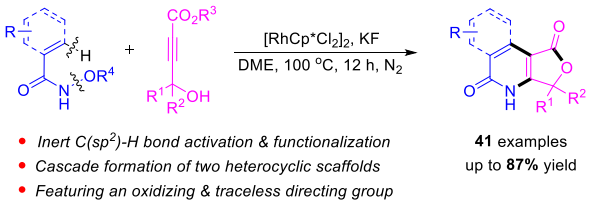

- *Inert C(sp^2)-H bond activation & functionalization*
- *Cascade formation of two heterocyclic scaffolds*
- *Featuring an oxidizing & traceless directing group*

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