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Rhodium-Catalyzed Cascade Reactions of Indoles with 4-Hydroxy-2-Alkynoates for the Synthesis of Indole-Fused Polyheterocycles

Xiaowei Wu,[a,c]‡ Pinyi Li,[a]‡ Yangbin Lu,[b] Jin Qiao,[b] Jingwei Zhao,[a,b]* Xiuwen Jia,[a] Hangcheng Ni,[b] Lichun Kong,[d] Xiaoning Zhang[b]* and Fei Zhao[a,b]*

[a] Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, Chengdu University, 168 Hua Guan Road, Chengdu 610052, China. E-mail: zhaojingwei_siia@126.com; zhaofei@cdu.edu.cn

[b] Jinhua Branch, Sichuan Industrial Institute of Antibiotics, Chengdu University, 888 West Hai Tang Road, Jinhua 321007, China. E-mail: xiaozhangningsunny@163.com

[c] Department of Pharmacology and Chemical Biology, Baylor College of Medicine, 1 Baylor Plaza, Houston, Texas 77030, United States.

[d] Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, Zhejiang Normal University, Jinhua 321004, China.

‡ These authors contributed equally to this work.

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Abstract. Herein, an efficient and regioselective Rh(III)-catalyzed [4+2] annulation/lactonization cascade of indoles with 4-hydroxy-2-alkynoates at room temperature to access the furo[3',4':4,5]pyrimido[1,6-a]indole-1,5(3*H*,4*H*)-diones is described. This method features mild reaction conditions, operational simplicity, excellent regioselectivity, broad substrate scope with good functional group tolerance, and good to excellent yields.

Keywords: Rhodium; C-H activation; Cascade reaction; [4 + 2] annulation; Lactonization

Introduction

Heterocycles widely exist in natural products and pharmaceutical agents.[1] Thus, the development of convenient approaches for the construction of heterocyclic scaffolds is highly desirable. In recent decades, transition metal-catalyzed C-H activation reactions are considered as powerful strategies to construct various heterocycles from simple starting materials.[2] In particular, Rh(III)-catalyzed C-H activation/annulation reactions have attracted wide attention because of their efficiency in heterocycle synthesis.[2d,3] For example, Rh(III)-catalyzed [3+2] cyclizations of aromatic substrates with alkynes for the expeditious synthesis of indoles were disclosed independently by Fagnou, Zhu, Wang and You's groups.[4] Loh and coworkers reported a Rh(III)-catalyzed redox-neutral [4+2] cyclization of *N*-carbamoyl indolines with alkynes to rapidly assemble fused-ring pyrroloquinolinone analogues.[5] Particularly, indole-fused polyheterocycles, which are widely found in natural products (*e. g.* Strychnine, Aspidospermine, Vincamine) and active pharmaceutical ingredients (*e. g.* Ondansetron, 5-HT_3 receptor antagonists, Fluorescent nucleosides),[6]

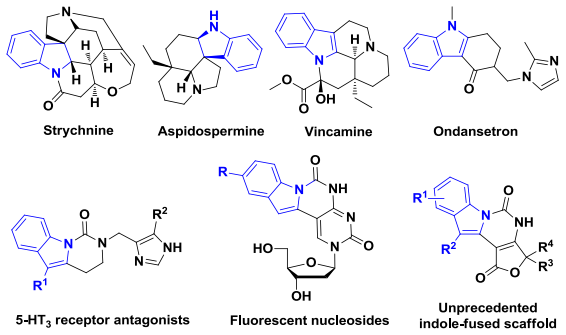
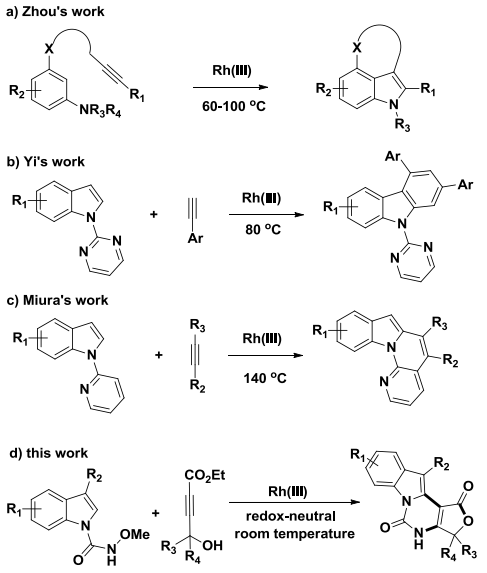


Figure 1. Representative natural products and pharmaceutical agents containing indole-fused polyheterocycle scaffolds.

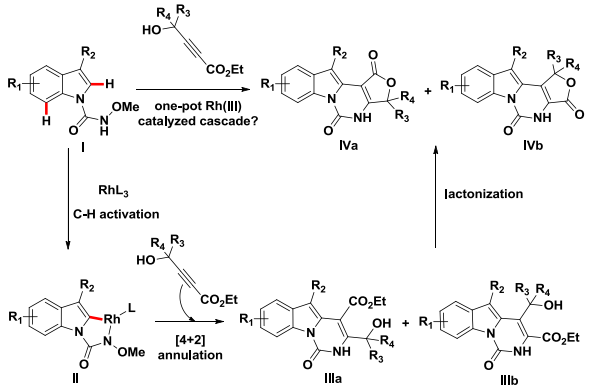
occupy an important place among numerous heterocyclic compounds (Figure 1). Therefore, tremendous efforts have been made to develop efficient methods for synthesis of various indole-fused polyheterocycles. In this context, Rh-catalyzed cyclization reactions have also played an important role. For instance, Zhou *et al*. developed an efficient Rh(III)-catalyzed intramolecular annulation of a tethered alkyne to construct 3,4-fused indoles (Scheme 1a).[7] Yi's group disclosed the assembly of



Scheme 1. Rh-catalyzed annulation reactions of indoles with alkynes.

carbazoles through Rh(III)-catalyzed annulation of indoles with terminal alkynes (Scheme 1b).[8] Miura's group developed the synthesis of indolo[1,2-*a*][1,8]naphthyridine derivatives via Rh(III)-catalyzed dehydrogenative coupling of *N*-pyridylindoles with alkynes (Scheme 1c).[9] However, these methods more or less suffer from some drawbacks such as high temperature, the usage of metal oxidants, unsatisfactory regioselectivities, additional disconnection of the directing group or a single chemical process rather than a cascade.

Despite the remarkable achievements made in the Rh-catalyzed annulations for synthesis of polyheterocycles bearing an indole nucleus, it is still highly demanding to explore new cyclization processes through Rh catalysis to furnish novel indole-fused polyheterocycles, which may find applications in medicinal and material chemistry. Recently, 4-hydroxy-2-alkynoates as coupling partners in C-H activations of arenes were demonstrated.[10] However, these methods still suffer from similar abovementioned disadvantages such as harsh reaction conditions (*e. g.* high temperature, the requirement of stoichiometric amount of metal oxidants), unsatisfactory regioselectivities or additional removal of the directing group. These deficiencies, together with our interests in indole-containing heterocycle synthesis,[11] prompt us to investigate a one-pot, mild, straightforward, redox-neutral and regioselective coupling cascade between 4-hydroxy-2-alkynoates and indoles to construct novel indole-fused polyheterocycles. As shown in Scheme 2, we postulated that the Rh(III)-catalyzed C-H activation of indoles **I** could occur first to provide intermediate **II**, which could undergo a following [4+2] annulation to afford two possible adducts **IIIa** and **IIIb** due to the regioselectivity. The further lactonization of **IIIa** and **IIIb** could deliver the indole-fused polyheterocycle **IVa** and **IVb**,



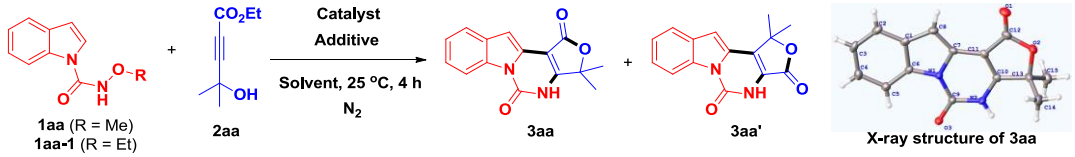
Scheme 2. Concept of Rh(III)-catalyzed C–H activation/[4+2] annulation/lactonization cascade.

respectively. The first challenge of this proposed process is to achieve high levels of C2/C7 site selectivity in C-H activation step, as well as regioselectivity in the addition step, leading to the formation of a single [4+2] annulation intermediate. The second challenge is to realize the further lactonization in the presence of steric hindrance under mild reaction conditions to produce the corresponding cascade product efficiently. In this work, we develop an efficient Rh-catalyzed redox-neutral regioselective C–H activation/[4+2] annulation/lactonization cascade of indoles with 4-hydroxy-2-alkynoates at room temperature to access the unprecedented furo[3',4':4,5]pyrimido[1,6-*a*]indole-1,5(3*H*,4*H*)-diones (Scheme 1d). To the best of our knowledge, this is the first example of the construction of the furo[3',4':4,5]pyrimido[1,6-*a*]indole-1,5(3*H*,4*H*)-dione scaffold described in the literature.

Results and Discussion

As shown in Table 1, *N*-methoxy-1*H*-indole-1-carboxamide **1aa** and ethyl 4-hydroxy-4-methylpent-2-ynoate **2aa** were employed as model substrates to optimize the reaction conditions. Initially, compounds **1aa** and **2aa** were treated with various metal catalysts in 1,4-dioxane at 25 °C for 4 h employing CsOAc as the additive. $MnBr(CO)_5$, $Pd(OAc)_2$, $[Cp^*IrCl_2]_2$ and $[RuCl_2(p\text{-cymene})]_2$ were found to be ineffective but with the recovery of the starting materials (entries 1-4). Pleasingly, $[Cp^*RhCl_2]_2$ could catalyze the [4+2] annulation/lactonization highly regioselectively, affording **3aa** as the only product in an excellent yield, in which indole C2 was dominantly located at the α position of the ester group (entry 5). The structure of **3aa** was unambiguously confirmed by X-ray crystallography.[12] Next, using $[Cp^*RhCl_2]_2$ and CsOAc as the catalyst and additive respectively, a variety of solvents were screened. Toluene, CH_2Cl_2, THF, DCE and acetone were also proved to be suitable solvents, in which product **3aa** was obtained with excellent regioselectivity and good to excellent yields (entries 6-10). Interestingly, no desired product

Table 1. Optimization of the reaction conditions.[a]

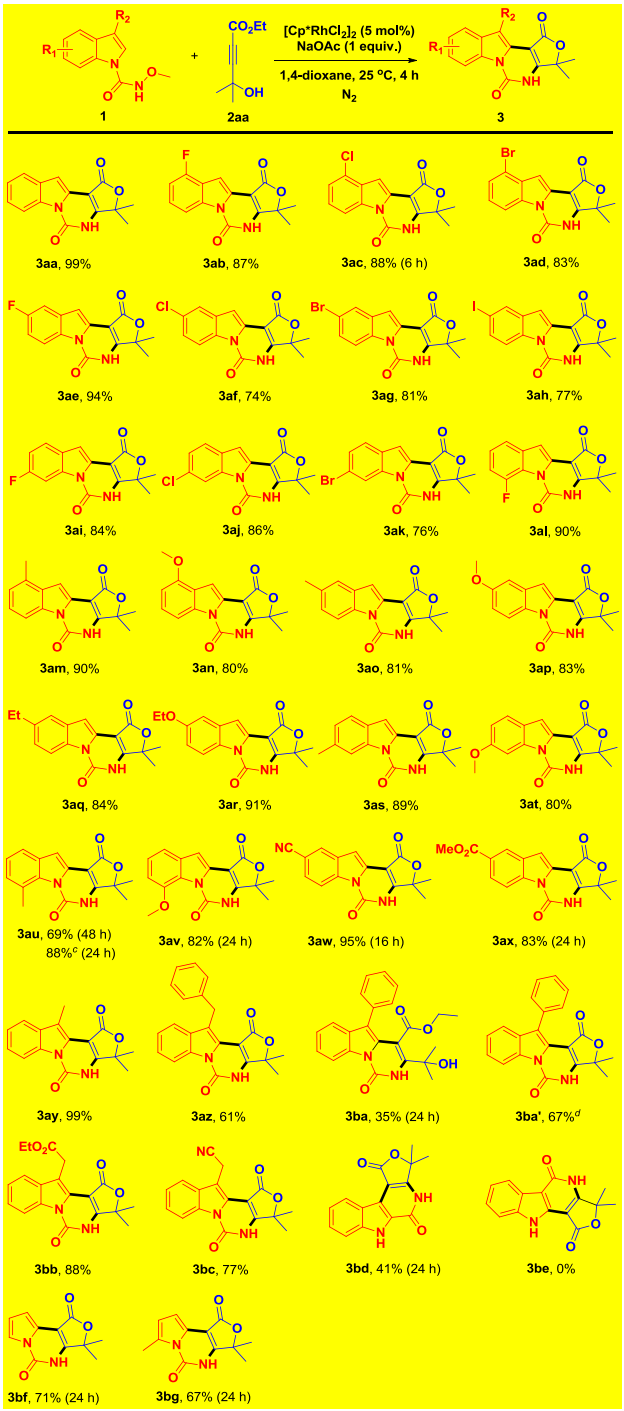


Entry	Catalyst	Additive	Solvent	Conv. (%)[b]	Yield of **3aa** (%)[c]	**3aa**/**3aa'**[d]
1	$MnBr(CO)_5$	CsOAc	1,4-dioxane	<5	0	/
2	$Pd(OAc)_2$	CsOAc	1,4-dioxane	<5	0	/
3	$[Cp^*IrCl_2]_2$	CsOAc	1,4-dioxane	<5	0	/
4	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	1,4-dioxane	<10	trace	/
5	$[Cp^*RhCl_2]_2$	CsOAc	1,4-dioxane	>99	97	100:0
6	$[Cp^*RhCl_2]_2$	CsOAc	Toluene	>99	95	100:0
7	$[Cp^*RhCl_2]_2$	CsOAc	CH_2Cl_2	>99	95	100:0
8	$[Cp^*RhCl_2]_2$	CsOAc	THF	>99	80	100:0
9	$[Cp^*RhCl_2]_2$	CsOAc	DCE	>99	89	100:0
10	$[Cp^*RhCl_2]_2$	CsOAc	Acetone	>99	75	100:0
11	$[Cp^*RhCl_2]_2$	CsOAc	CH_3CN	<1	0	/
12	$[Cp^*RhCl_2]_2$	CsOAc	MeOH	53	32	100:0
13	$[Cp^*RhCl_2]_2$	CsOAc	EtOH	72	43	100:0
14	$[Cp^*RhCl_2]_2$	CsOAc	DMF	54	33	100:0
15	$[Cp^*RhCl_2]_2$	CsOAc	DMSO	49	37	100:0
16	$[Cp^*RhCl_2]_2$	Na_2CO_3	1,4-dioxane	88	80	100:0
17	$[Cp^*RhCl_2]_2$	KOAc	1,4-dioxane	>99	83	100:0
18	**$[Cp^*RhCl_2]_2$**	**NaOAc**	**1,4-dioxane**	**>99**	**99**	**100:0**
19	$[Cp^*RhCl_2]_2$	K_2CO_3	1,4-dioxane	81	72	100:0
20	$[Cp^*RhCl_2]_2$	NaOH	1,4-dioxane	93	88	100:0
21	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	1,4-dioxane	97	92	100:0
22	$[Cp^*RhCl_2]_2$	$NaHCO_3$	1,4-dioxane	<5	trace	/
23	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	1,4-dioxane	47	40	100:0
24[e]	$[Cp^*RhCl_2]_2$	NaOAc	1,4-dioxane	>99	97	100:0
25[f]	$[Cp^*RhCl_2]_2$	NaOAc	1,4-dioxane	>99	98	100:0
26[g]	$[Cp^*RhCl_2]_2$	NaOAc	1,4-dioxane	90	86	100:0
27[h]	$[Cp^*RhCl_2]_2$	NaOAc	1,4-dioxane	93	91	100:0
28[i]	$[Cp^*RhCl_2]_2$	NaOAc	1,4-dioxane	85	79	100:0
29	—	CsOAc	1,4-dioxane	<1	0 (0[j])	/
30	$[Cp^*RhCl_2]_2$	—	1,4-dioxane	<1	0 (0[j])	/

[a]Reaction conditions: **1aa** (0.25 mmol), **2aa** (0.325 mmol), catalyst (5 mol%), additive (0.25 mmol), solvent (4.0 mL), 25 °C, 4 h, N_2 atmosphere. [b]The conversion was calculated based on the recovery amount of substrate **1aa** or **1aa-1**. [c]Isolated yield. [d]The ratio was determined by ^{1}HNMR integration of the crude reaction mixture. [e]The reaction was run for 3 h using **1aa-1** instead of **1aa** as the substrate. [f]The reaction was performed under air atmosphere. [g]$[Cp^*RhCl_2]_2$ (2.5 mol%) was used. [h]NaOAc (0.125 mmol) was used. [i]NaOAc (0.025 mmol) was used. [j]Data after 24 h.

3aa was detected in CH_3CN but with the recovery of substrates (entry 11). This may be attributed to the coordination of CH_3CN to $[Cp^*RhCl_2]_2$ which deactivates the catalyst. In addition, this cascade reaction could also take place in MeOH, EtOH, DMF or DMSO regioselectively, but with incomplete consumption of the starting materials which led to low yields of product **3aa** (entries 12-15). Therefore, the screening of solvents revealed that 1,4-dioxane is the best of choice. Subsequently, a series of additives were screened in 1,4-dioxane (entries 16-23), and NaOAc turned out to be the most suitable additive resulting in a quantitative yield of **3aa** (99%) with excellent regioselectivity (entry 18). Moreover, compound **1aa-1** was also tested as the substrate. It could undergo this transformation with **2aa** as well to produce the desired product **3aa** in 97% yield in a shorter time (3 h), and again, an excellent regioselectivity was observed (entry 24). Besides, the reaction was not sensitive to oxygen as a high yield (98%) was still obtained when the reaction was carried out under air atmosphere (entry 25). Reducing the amount of $[Cp^*RhCl_2]_2$ from 5 mol% to 2.5 mol% or NaOAc from 1 equivalent to 0.5 or 0.1 equivalent led to the incomplete conversion of the substrates (entries 26-28). Finally, in order to determine the role of the catalyst and additive in this cascade reaction, a set of blank experiments, in which $[Cp^*RhCl_2]_2$ or NaOAc was selectively removed from the reaction, were performed. As a result, no formation of the product **3aa** was observed in the presence of single catalyst or additive even after a longer reaction time (entries 29 and 30). These results clearly confirmed the crucial catalytic role of the

Table 2. Scope of *N*-methoxy-1*H*-indole-1-carboxamides.[a,b]



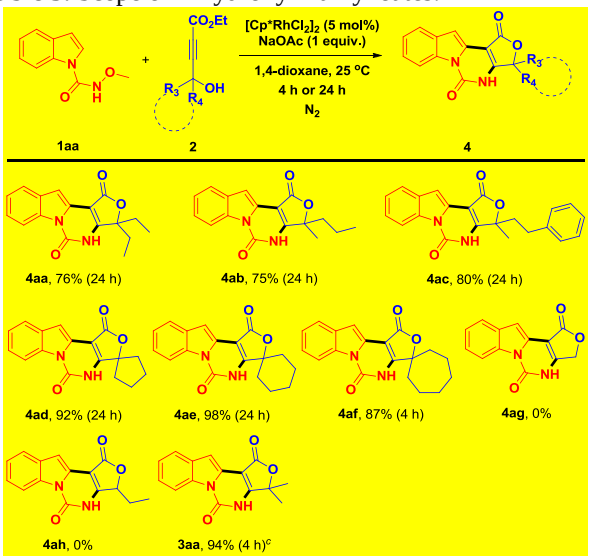
[a]Reaction conditions: **1** (0.25 mmol), **2aa** (0.325 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), NaOAc (0.25 mmol), 1,4-dioxane (4.0 mL), 25 °C, 4 h, N_2 atmosphere. [b]Isolated yields are reported. [c]The yield of reaction carried out at 40 °C for 24 h. [d]The reaction was carried out at 80 °C for 7 h.

$[Cp^*RhCl_2]_2$/NaOAc system in this reaction. It is noteworthy that no regioisomer **3aa'** was detected in any reaction, indicating the excellent regiochemical control of this reaction.

With the optimal reaction conditions in hand, we then examined the scope of *N*-methoxy-1*H*-indole-1-carboxamides at first (Table 2). In general, this rhodium(III)-catalyzed [4+2] annulation/lactonization was compatible with diverse indole substrates carring halogens, electron-donating or electron-withdrawing groups. Their reactions with **2aa** underwent smoothly to afford the desired products in good to excellent yields with excellent regioselectivity irrespective of the electronic nature and position of the substituents on the indole ring. For example, indoles bearing halogens (F, Cl, Br, I) at different positions of the benzene ring reacted well with **2aa** to regioselectively provide the corresponding products **3ab**-**3al** in 74-94% yields. Likewise, various substrates having electron-donating groups (Me, MeO, Et, EtO) at C4, C5, C6 or C7 position of the indole ring could participate in this cascade reaction efficiently and regioselectively, leading to the formation of the desired products **3am**-**3av** in high yields. Similarly, indoles containing electron-withdrawing groups (CN, CO_2Me) at C5 position were well tolerated and converted into the products **3aw**-**3ax** in high yields. Pleasingly, substrates with methyl or even the bulky benzyl groups at C3 position could undergo this transformation to deliver the products **3ay** and **3az** in 99% and 61% yields, respectively. Interstingly, under standard conditions, the reaction of substrate carrying a phenyl substituent at C3 position only gave the [4+2] annulation product **3ba** rather than [4+2] annulation/lactonization product **3ba'** in a lower yield. We speculated that the huge phenyl group may prevent **3ba** from further lactonization. However, carrying out the same reaction at a higher temperature (80 °C) for 7 h could produce the cascade product **3ba'** instead of **3ba** in a good yield (67%). Notably, this protocol was also compatible with indoles bearing various functional groups like ester and cyano groups at C3 position, which produced the products **3bb**-**3bc** in good to high yields. Indole-2-carboxamide **1bd** could also take part in this reaction to deliver the corresponding product **3bd** in a moderate yield, while indole-3-carboxamide **1be** failed to react with **2aa**. Gratifyingly, pyrroles are also suitable substrates. Their reactions with **2aa** took place successfully to provide the corresponding pyrrole-fused products **3bf**-**3bg** in good yields.

Next, the scope of 4-hydroxy-2-alkynoates was explored (Table 3). Overall, this tandem process tolerated a variety of 4-hydroxy-2-alkynoates bearing substituents at R_3 and R_4. They reacted well with **1aa** to afford the desired products in good to excellent yields with perfect regioselectivity. For instance, symmetrically or unsymmetrically dialkyl-substituted 4-hydroxy-2-alkynoates could undergo this cascade reaction regioselectively to give the corresponding products **4aa**-**4ac** in 75-80% yields. Likewise, the reactions of cyclopentyl, cyclohexyl, or cycloheptyl substituted 4-hydroxy-2-alkynoate derivatives appeared to be reactive and provided the desired spiro products **4ad**-**4af** in high yields without affecting the regioselectivity of products. By contrast, methyl 4-hydroxybut-2-ynoate or ethyl 4-hydroxyhex-2-ynoate failed to react with **1aa** to produce the desired products **4ag** or **4ah**. This result is similar to the

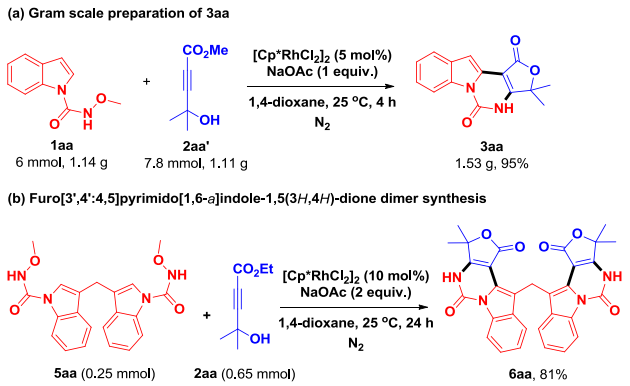
Table 3. Scope of 4-hydroxy-2-alkynoates.[a,b]



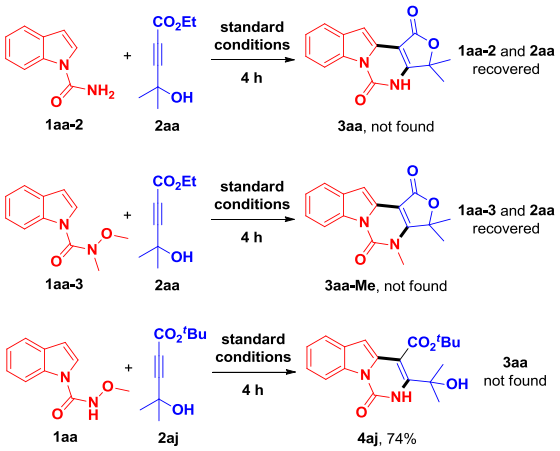
[a]Reaction conditions: **1aa** (0.25 mmol), **2** (0.325 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), NaOAc (0.25 mmol), 1,4-dioxane (4.0 mL), 25 °C, 4 h or 24 h, N_2 atmosphere. [b]Isolated yields are reported. [c]Methyl 4-hydroxy-4-methylpent-2-ynoate was used.

Rh(III)-catalyzed cascade reactions of aromatic *N*-alkoxyamides with 4-hydroxy-2-alkynoates reported by Fan and coworkers.[10b] In addition, methyl 4-hydroxy-4-methylpent-2-ynoate **2aa'** was also proved to be a suitable alkyne component without changing the reaction results. Interestingly, the reactions of **1aa** and alkynes which do not contain a hydroxyl group such as ethyl pent-2-ynoate gave totally different products.[13]

To further illustrate the practicality of this methodology, the Rh-catalyzed [4+2] annulation/lactonization reaction between **1aa** and **2aa'** was performed on a gram scale under the optimal conditions. Impressively, the desired product **3aa** was achieved in 95% yield (Scheme 3a), indicating the efficiency and potential of industrial application of this cascade process. Interestingly, a furo[3',4':4,5]pyrimido[1,6-*a*]indole-1,5(3*H*,4*H*)-dione dimer **6aa** was synthesized when substrates **5aa**



Scheme 3. Gram scale experiments and furo[3',4':4,5]pyrimido[1,6-*a*]indole-1,5(3*H*,4*H*)-dione dimer synthesis.



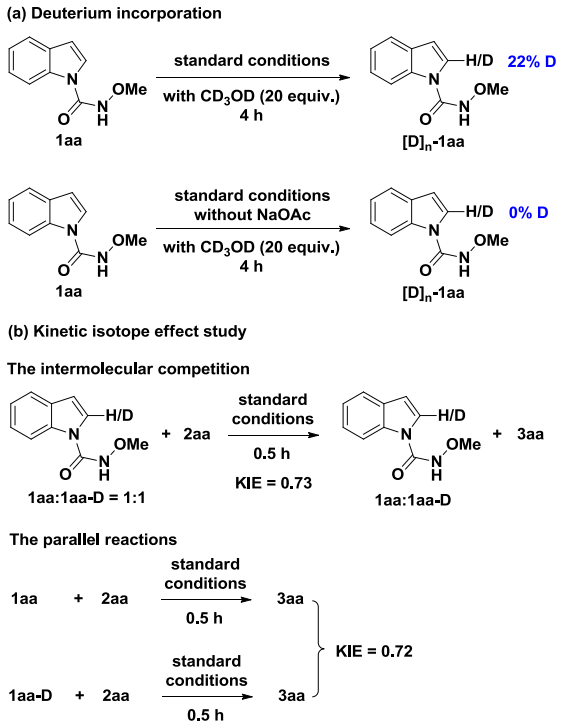
Scheme 4. Control experiments.

and **2aa** were subjected to the standard conditions (Scheme 3b). These findings further highlight the advantages and potential applications of this approach.

Additionally, control experiments (Scheme 4) show that the OMe unit attached to the nitrogen atom in the substrate is indispensable for this [4+2] annulation as the reaction of 1*H*-indole-1-carboxamide **1aa-2** with **2aa** failed to give the desired product **3aa** under standard conditions, but with the recovery of starting materials. Moreover, *N*-methoxy-*N*-methyl-1*H*-indole-1-carboxamide **1aa-3** also failed to react with **2aa** under standard conditions to give the corresponding product, but with the substrates untouched, indicating the free hydrogen on the amide nitrogen is essential for this reaction. At last, when **1aa** and *tert*-butyl 4-hydroxy-4-methylpent-2-ynoate **2aj** were subjected to the standard conditions, the [4+2] annulation product **4aj** rather than the [4+2] annulation/lactonization product **3aa** was obtained. This means the final lactonization step does not favor poor leaving groups like ^{t}BuO, which presents a bigger steric hindrance for the OH group to attack as compared with EtO or MeO.

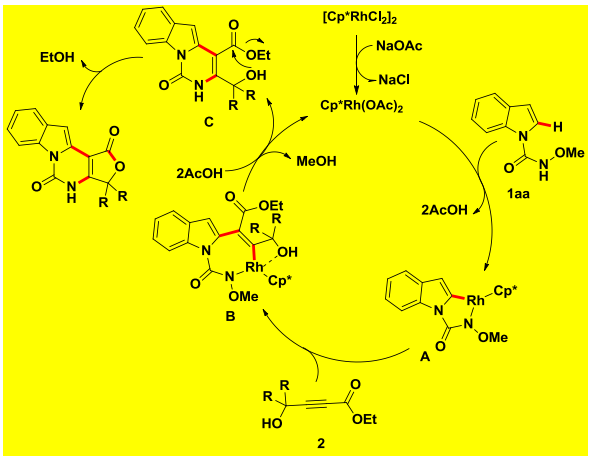
To gain some insights into the mechanism of this reaction, we conducted deuterium-labeling experiments (Scheme 5a). At first, **1aa** was treated with methanol-d_4 under standard reaction conditions without **2aa**, which led to 22% deuteration at the C2 position of indole. This result indicated that the step of C-H bond cleavage is reversible. Next, carrying out the same reaction in the absence of NaOAc resulted in no deuteration at the C2 position of indole, which suggested that NaOAc was crucial for the step of C-H bond activation. Besides, kinetic isotope effect (KIE) experiments were also conducted (Scheme 5b). The intermolecular KIE with k_H/k_D = 0.73 was measured on the basis of competition reactions. Two parallel reactions using **1aa** and **1aa-D** gave a KIE value of 0.72. The results indicated that the step of the C−H bond cleavage was not likely involved in the rate-limiting step.

Based on previous reports[10] and the preliminary mechanistic studies, a plausible mechanism was proposed (Scheme 6). Initially, an active Rh catalyst,



Scheme 5. Preliminary mechanism studies.

which is generated through the ligand exchange of $[Cp^*RhCl_2]_2$ with the additive NaOAc, binds to substrate **1aa** and selectively activates the *ortho*-C-H bond of indole substrate to form the rhodium complex **A**. Subsequently, the regioselective coordination and insertion of alkyne into the Rh-C bond of rhodium complex **A** afford intermediate **B** exclusively. Then, reductive elimination of intermediate **B** provides intermediate **C** and regenerates the active rhodium catalyst to enter the next catalytic cycle. Finally, the *in-situ* formed intermediate **C** undergoes an intramolecular lactonization to give the final product.



Scheme 6. Proposed mechanism.

Conclusion

In conclusion, we have developed a robust and highly regioselective Rh(III)-catalyzed [4+2] annulation/lactonization cascade reaction between indoles and 4-hydroxy-2-alkynoates for the synthesis of the unprecedented furo[3',4':4,5]pyrimido[1,6-a]indole-1,5(3*H*,4*H*)-diones. This protocol has various advantageous features, such as broad substrate scope, excellent regioselectivity, good functional tolerability, good to excellent yields, mild reaction conditions, operational simplicity and step economy. This method is particularly attractive because it allows the efficient assembly of a variety of furo[3',4':4,5]pyrimido[1,6-a]indole-1,5(3*H*,4*H*)-diones under redox-neutral conditions at room temperature. Further bioactivity studies of the indole-fused polyheterocycles presented in this paper are currently in progress in our laboratory, and we anticipate these novel heterocyclic compounds incorporating the bioactive indole motif may find their pharmaceutical applications.

Experimental Section

General Procedure for the Preparation of products 3, 4 and 6aa

To a mixture of **1** (0.25 mmol), $[Cp^*RhCl_2]_2$ (5 mol%) and NaOAc (0.25 mmol) in a 25 mL dry Schlenk tube was added a solution of **2** (0.325 mmol) in 1,4-dioxane (4.0 mL). Then the tube was capped with septa, evacuated and backfilled with N_2. After that, the resulting mixture was stirred at 25 ^oC for the time indicated in Table 2 and 3. After removal of the solvent, the residue was purified by flash chromatography on silica gel to give the desired products **3** and **4**. Product **6aa** was prepared similarly with the conditions indicated in Scheme 3b.

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[12] CCDC-1983959 (compound **3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre viawww.ccdc.cam.ac.uk/data_request/cif.

[13] The reaction of **1aa** and ethyl pent-2-ynoate gave a totally different product (*E*)-ethyl 2-(1*H*-indol-2-yl)-3-(methoxycarbamoyl)pent-2-enoate, to be submitted soon.

Rhodium-Catalyzed Cascade Reactions of Indoles with 4-Hydroxy-2-Alkynoates for the Synthesis of Indole-Fused Polyheterocycles

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Xiaowei Wu,[a,c]‡ Pinyi Li,[a]‡ Yangbin Lu,[b] Jin Qiao,[b] Jingwei Zhao,[a,b]* Xiuwen Jia,[a] Hangcheng Ni,[b] Lichun Kong,[d] Xiaoning Zhang[b]* and Fei Zhao[a,b]*