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# A Ru(II)-catalyzed C–H activation and annulation cascade for the construction of highly coumarinfused benzo[a]quinolizin-4-ones and pyridin-2ones<sup>+</sup>

**HINESE** 

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Jing Wang,<sup>a,b</sup> Xiaoxue Zhang,<sup>a,b</sup> Jianhui Zhou,<sup>a,b</sup> Liping Yan,<sup>a,b</sup> Yuan Li,<sup>b</sup> Naixuan Zhao,<sup>c</sup> Hong Liu, <sup>(D) a,b</sup> He Huang<sup>\*b</sup> and Yu Zhou <sup>(D)</sup>\*<sup>a,b,c</sup>

A reaction involving a Ru(II)-catalyzed C–H activation and annulation cascade was successfully established for constructing coumarin-fused benzo[a]quinolizin-4-ones and pyridin-2-ones. In these constructions, an intriguing 6-6-6-6-6 pentacyclic coumarin-fused scaffold was formed as a result of two successive C–H bond activation/[4 + 2] annulation cascade in a one-pot operation with moderate to good yields, and a broad range of substrates were amenable to the reaction. More importantly, this work was the first time, to the best of our knowledge, that such complex 6-6-6-6-6 pentacyclic coumarin scaffolds were constructed using a successive Ru(II)-catalyzed C–H activation and annulation cascade. The resulting products were further transformed into two new interesting skeletons, and biological evaluations showed the highly fused products having good affinity for the ENL YEATS domain.

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### Introduction

Fused-coumarins represent an important class of privileged structural scaffolds and are extensively and frequently found in natural products, pharmaceutical molecules and functional materials.<sup>1</sup> Some representative examples of such natural and artificial products include defucogilvocarin (M, E and V),<sup>2</sup> lamellarin D, the synthesized derivatives isolamellarins<sup>3</sup> and compounds I–III.<sup>4</sup> These products show extensive biological activities such as HIV-1 integrase inhibition,<sup>5</sup> anticancer,<sup>6</sup> antibacterial,<sup>7,8</sup> and anti-inflammatory activities<sup>8</sup> (Fig. 1). Furthermore, some of these derivatives also show excellent photophysical properties and are widely used as fluorescent labeling probes.<sup>9</sup>

These potential benefits have for a long time attracted the interest of chemists, specifically for developing effective synthetic strategies to construct diverse coumarin-based

<sup>a</sup>School of Chinese Materia Medica, Nanjing University of Chinese Medicine, Nanjing 210023, China

<sup>b</sup>Drug Discovery & Development Center, Shanghai Institute of Materia Medica,

Chinese Academy of Sciences, Shanghai 201203, China. E-mail: hhuang@simm.ac.cn . zhouyu@simm.ac.cn compounds for the purpose of expanding the chemical space of drug discovery or other applications. Recently, a few classic protocols have been used to prepare these intriguing coumarin-based derivatives. For instance, multiple research groups have employed coumarins bearing an electron-withdrawing group (EWG) at the C3 position as the starting point to build cyclopropa[c]coumarins with different single-carbon coupling partners by performing classic Lewis base (LB)-catalyzed cyclopropanations (Scheme 1a, left).<sup>10</sup> The Ye,<sup>11a</sup> Lu<sup>11b</sup> and Lin<sup>11c</sup> groups independently introduced coupling partners each containing two reactive sites (with examples of these part-



Fig. 1 Examples of coumarin-fused heterocyclic derivatives.

<sup>&</sup>lt;sup>c</sup>School of Pharmaceutical Science and Technology, Hangzhou Institute for Advanced Study, UCAS, Hangzhou 310024, China

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Scheme 1 Various methods for synthesizing fused coumarins.

ners including ketenes, allenes, azomethine ylides, *etc.*) to construct tricyclic benzopyrano[3,4-*c*]pyrrolidines *via* classic cycloaddition reaction pathways (Scheme 1a, right).<sup>11</sup> However, in contrast to the above achievements, the construction of highly fused polycyclic coumarin scaffolds has still been full of challenges and lack developed synthetic strategies, with only a few examples having been reported. The Gryko and Tang groups did report a cyclocondensation reaction involving the treatment of coumarin 3-carboxylate with 1,8-diazabicyclo[5.4.0] undec-8-ene (DBU) to synthesize pentacyclic coumarin derivatives displaying fluorescence characteristics, but the substrate scope was very limited.<sup>12,13</sup> The Bu group constructed a 6-6-5-5-6 pentacyclic core by carrying out a Friedel-Crafts alkylation/ cyclization/isomerization sequence between 3-benzoyl coumarins and 3-substituted indoles (Scheme 1b).<sup>14</sup> Similarly, dihydroisoquinoline with classic cycloaddition strategies was used to build polycyclic coumarin-derived 8-oxoprotoberbines.<sup>15</sup> The substrates for these constructions were relatively complex and needed to be prepared using multiple reaction steps. It has so far been rare and difficult to build highly coumarin-fused derivatives by using simple starting materials via a one-pot multi-step reaction strategy involving C-H activation and cyclization cascade steps. As a continuation of our interest and efforts in investigating new strategies for constructing diverse drug-like polycyclic scaffolds,16 we set out in the current work to construct highly coumarin-fused benzo[a]quinolizin-4-ones and pyridin-2-ones using a Ru(II)-catalyzed cascade reaction of 3-carboxamide coumarin and diphenylethyne; this strategy offered high efficiency, a wide substrate scope and potential versatility (Scheme 1c).

#### Table 1 Optimization of reaction conditions<sup>a,b</sup> catalyst, additives solvent, temp, time 2a 3aa 1a $Yield^{b}$ (%) Entry Catalyst Additive Solvent Ag salt Cp\*RhCl<sub>2</sub>]<sub>2</sub> Cu(OAc)2·H2O DCE 26 1 AgSbF<sub>6</sub> 2 [Ru(p-cymene)Cl<sub>2</sub>]<sub>2</sub> AgSbF<sub>6</sub> Cu(OAc)2·H2O DCE 403 AgSbF<sub>6</sub> Cu(OAc)2·H2O DCE 35 [Ir\*CpCl<sub>2</sub>]<sub>2</sub> NR 4 [Co\*CpCl<sub>2</sub>]<sub>2</sub> AgSbF<sub>6</sub> $Cu(OAc)_2 \cdot H_2O$ DCE

5	$ Ru(p-cymene)Cl_2 _2$	AgSbF <sub>6</sub>	$Cu(OAc)_2$	DCE	42
6	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	AgOAc	DCE	30
7	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	CsOAc	DCE	NR
8	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	$K_2CO_3$	DCE	NR
9	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	HOAc	DCE	25
10	$[Ru(p-cymene)Cl_2]_2$	AgSbF <sub>6</sub>	$Zn(OAc)_2$	DCE	70
11 <sup>c</sup>	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	DCE	60
$12^d$	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	DCE	65
13	$[Ru(p-cymene)Cl_2]_2$	CF <sub>3</sub> PO <sub>2</sub> Ag	$Zn(OAc)_2$	DCE	41
14	$[Ru(p-cymene)Cl_2]_2$	AgNTF <sub>2</sub>	$Zn(OAc)_2$	DCE	32
15	$[Ru(p-cymene)Cl_2]_2$	$AgPF_6$	$Zn(OAc)_2$	DCE	36
16	$[Ru(p-cymene)Cl_2]_2$		$Zn(OAc)_2$	DCE	e
17	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	MeCN	18
18	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	Toluene	37
19	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	Dioxane	20
20	$[Ru(p-cymene)Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	TFE	46
$21^{f}$	$[Ru(p-cymene)Cl_2]_2$	AgSbF <sub>6</sub>	$Zn(OAc)_2$	DCE	60
$22^g$	Ru( <i>n</i> -cymene)Clala	AgShF	Zn(OAc)	DCE	70

<sup>*a*</sup> Reaction conditions: **1a** (0.4 mmol), **2a** (1.2 mmol), [Cp\*RhCI<sub>2</sub>]<sub>2</sub> (4 mol%), Ag salt (16 mol%), additive (2 equiv.) in DCE at 90 °C for 12 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Zn(OAc)<sub>2</sub> (0.5 equiv.). <sup>*d*</sup> Zn(OAc)<sub>2</sub> (3 equiv.). <sup>*e*</sup> Trace. <sup>*f*</sup> 70 °C. <sup>*g*</sup> 110 °C.

#### **Results and discussion**

We started our investigation by using N-methoxy-coumarin-3-carboxamide (1a, 0.4 mmol) and biphenylacetylene (2a, 0.4 mmol) as the model substrates, which were treated with  $[Cp*RhCl_2]_2$  (4 mol%), AgSbF<sub>6</sub> (16 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (2 equiv.) in DCE at 90 °C for 12 h (Table 1, entry 1). Encouragingly, an obvious new product was found, and the corresponding NMR and mass spectroscopy analyses indicated that it may have been a highly fused coumarin derivative with a 6-6-6-6 pentacyclic scaffold (3aa) (Table 1, entry 1). We speculated that the coumarin substrate underwent two successive C-H bond activation/annulation cascade to give this highly fused coumarin derivative, and its structure was unambiguously confirmed from the results of an X-ray crystallographic analysis. In view of this intriguing polycyclic coumarin-fused scaffold, we decided to optimize the reaction conditions to most efficiently construct such skeletons.

First, we investigated the effects of different catalysts (Table 1, entries 1-4). Of the catalysts tested, [Ru(p-cymene) Cl<sub>2</sub>]<sub>2</sub> showed the best catalytic effect, with the yield of 3aa reaching 40% (Table 1, entry 2). The screening of reaction additives was subsequently carried out (Table 1, entries 5-10). When using  $Zn(OAc)_2$  as the additive, the yield of 3aa was 70% (Table 1, entry 10). To further improve the effect of additives, we changed the number of equivalents of the additive from 2 to 0.5 in one test and to 3 in another (Table 1, entries 11 and 12), but both tests showed reduced yields of 3aa. In a screening of silver salts, AgSbF<sub>6</sub> provided the highest yield and the removal of silver salts resulted in no target product (Table 1, entries 13-16). Subsequently, we kept the optimal catalytic system to investigate reaction solvents. The originally used DCE remained the best reaction solvent for this transformation (Table 1, entries 17-20). Finally, the reaction temperature was investigated. We found a lower yield of 3aa when lowering the reaction temperature from 90 °C to 70 °C (Table 1, entries 21 and 22), and the most suitable temperature was hence determined to be 90 °C. Based on these screenings, the optimal conditions for this reaction were determined to involve stirring  $[\operatorname{Ru}(p\text{-cymene})\operatorname{Cl}_2]_2$  (4 mol%), AgSbF<sub>6</sub> (16 mol%), Zn(OAc)<sub>2</sub> (2 equiv.) in DCE at 90 °C for 12 h (Table 1, entry 10).

Under the optimal reaction conditions, we set out to assess the scopes of the two substrates (Table 2). First, we investigated the influences of different substituents of the biphenylacetylene on this reaction (2a–2g). We tested groups with different electron properties introduced into the *para*-position of phenyl group of biphenylacetylene 2a. Substituting in electron-donating groups and halogen atoms had almost no effect on the target product yield (3ab–3af), but including a trifluoromethyl group resulted in a large decrease in the yield (3ag), indicating that the electron-withdrawing groups may be detrimental for this transformation. We next evaluated the influences of the substituents of the coumarin ring on the yields of target pentacyclic coumarin derivatives. For instance, we introduced independently methyl, methoxy, fluoro, chloro and trifluoro groups into the benzene ring of the coumarin scaffold,

 Table 2
 Scope of the two substrates<sup>a,b</sup>



<sup>*a*</sup> Reaction conditions: **1** (0.4 mmol) and **2** (1.2 mmol),  $[Ru(p\text{-cymene}) Cl_2]_2$  (4 mol%), AgSbF<sub>6</sub> (16 mol%), Zn(OAc)<sub>2</sub> (2 equiv.) in DCE at 90 °C, for 12 h. <sup>*b*</sup> Isolated yields.

mainly involving 6-position and 7-position substitutions, and the results demonstrated that all these substrates could be easily transformed to corresponding products with good yields (**3ba-3ge**), indicating a good substrate tolerance for this strategy.

In order to further investigate the reaction scope of this strategy, we introduced examples of symmetric aliphatic alkynes instead of arylalkynes for this transformation (Table 3). As we expected, the coumarin-fused pyridin-2-one scaffold could also be formed via a single C-H bond activation and annulation cascade under Ru(II) catalysis. First, 3-carboxamide coumarins (1a, 1b, 1d and 1e) were investigated to couple alkyl alkynes (2h and 2i) under the standard reaction conditions, respectively, and the corresponding coumarinfused pyridin-2-one products were obtained with good yields (3ah-3eh). We tried to react diethyl acetylenedicarboxylate with N-methoxy-2-oxo-2H-chromene-3-carboxamide, but target product 3ak was obtained in only 15% yield. When replacing symmetric alkynes with asymmetric alkynes, such as 1-phenyl-1-propyne, the reaction afforded three products, but only 3aj as a major product was isolated; its structure was confirmed from the results of an X-ray crystallographic analysis.

To assess the efficiency of these methods and their potential for being utilized, a gram-scale experiment for model substrates **1a** and **2a** was performed, and target product **3aa** was

 Table 3
 Aliphatic alkyne substrate scope<sup>a,b</sup>



<sup>*a*</sup> Reaction conditions: 1 (0.4 mmol), 2 (1.2 mmol),  $[Ru(p-cymene)Cl_2]_2$  (4 mol%), Ag salt (16 mol%),  $Zn(OAc)_2$  (2 equiv.) in DCE at 90 °C, for 12 h. <sup>*b*</sup> Isolated yields.

obtained with an isolated yield of 65%; and when substrate **2h** was used, product **3ah** with an isolated yield of 34% was obtained (Scheme 2a). More interestingly, products **3aa** and **3ga** were further converted into biaryl compound **4a** and **4b** in DMF-POCl<sub>3</sub> mixed solvent under heated conditions. Here, this transformation may have each undergone amide bond breakage and subsequent intramolecular cyclization (Scheme 2b). The structure of **4a** was verified by carrying out an X-ray crystallographic analysis. Additionally, product **3ah** was easily converted into pyridine-fused coumarin derivative **5** in a rapid reduction reaction with borane-methyl sulfide complex; this derivative may have some potential pharmacological activities and fluorescence properties (Scheme 2c).<sup>17</sup>

In order to investigate the potential biological value of these highly fused coumarin scaffolds, we evaluated their affinities for the ENL YEATS domain. Histone acylation modification and gene transcriptional activity are closely related to the recognition of acetylation modification (Kac) or croton acylation modification (Kcr) on lysine residues by YEATS domain. The dysregulation of the YEATS (YAF9, ENL, AF9, TAF14 and SAS5)-domain-containing proteins correlates with the onset and progression of cancers. In particular, interest in the ENL YEATS domain has been very high due to the reported significant involvement of this domain in acute leukemia pathophysiology.<sup>18a</sup> Therefore, the development of small-molecule





**Scheme 2** Synthesis application and biological evaluation (the YEATS domain inhibitor SGC as a positive control).<sup>18b</sup>

inhibitors targeting the ENL YEATS domain may provide a new strategy for the treatment of ENL-dependent leukemia. In order to investigate the potential biological value of these highly coumarin-fused scaffolds, pull-down experiments were carried out to verify the binding inhibitory activities of these compounds against the ENL YEATS domain and H3K9cr (which has a high affinity for the ENL YEATS domain), and the results indicated good inhibitory activities displayed by compounds **3aa** and **3ba** (Scheme 2d), which laid a foundation for subsequent studies.

Then, we performed mechanism studies. First, a competition experiment between the electron-withdrawing substituted substrate **1d** and electron-donating substituted substrate **1c** with diphenylalkyne **2a** was performed. The results showed that the electron-withdrawing substrate reacted faster than did the electron-donating substrate with a ratio of 1.35:1; a similar result was also observed when reacting substrates **1d** 



and **1b** with dec-5-yne (**2h**), and a ratio of 3.15:1 was measured (Scheme 3a). These results indicated that the C–H activation might proceed through a concerted metalation-deprotonation (CMD) mechanism.<sup>19</sup> Also, by decreasing the number of equivalents of biphenylacetylene and shortening the reaction time, we trapped intermediate **VI** (Scheme 3b). In addition, we performed an H/D exchange experiment to attempt to gain insights into the preliminary mechanism of this reaction. First, when treating the model substrate **1a** without substrate **2a** under standard reaction conditions with D<sub>2</sub>O for 12 h, we found that in about 10% of the product molecules, the 4-position of the 3-carboxamide coumarin scaffold



Scheme 4 Proposed reaction mechanism.

was exchanged with a deuterium atom (Scheme 3c), indicating that this C–H bond activation was reversible.

Based on literature reports<sup>20</sup> and the H/D exchange experiment, we derived a speculative yet plausible mechanism for this transformation (Scheme 4). According to this mechanism, the first step was the activation of the ruthenium catalyst under the effect of  $AgSbF_6$  and  $Zn(OAc)_2$ , inducing then a C4 metalation of coumarin 1a to form a 5-membered ring I with the activated catalyst. Diphenylalkyne complexed with I, followed by the coordination of alkyne to the cyclometalation complex II and insertion to give a seven-membered Ru-metallacycle III, with III becoming converted into IV through an internal oxidation, and with reductive elimination of IV forming V. When R was an alkyl group, the catalytic cycle afforded coumarin-fused pyridin-2-one scaffold VI. When R was an aryl group, another C-H bond activation catalytic cycle occurred to construct complex 6-6-6-6 pentacyclic coumarin scaffold 3aa.

#### Conclusions

In conclusion, we have successfully established a novel and effective strategy to construct two kinds of highly fused coumarin scaffolds with a benzo[a]quinolizin-4-one core or pyridin-2-one core by carrying out a Ru(II)-catalyzed C-H activation and annulation cascade, in which the construction of a 6-6-6-6 pentacyclic coumarin scaffold underwent two successive C-H bond activation/[4 + 2] annulation cascade in a onepot operation with good yields. In this reaction, the Ru(II)-catalyzed C-H activation and annulation cascade strategy was for the first time performed, to the best of our knowledge, to construct such complex 6-6-6-6 pentacyclic coumarin scaffolds. Additionally, this transformation was shown to tolerate a broad range of substrates, and provide moderate to good yields, with the resulting polycyclic compounds containing an important drug-privileged scaffold, and perhaps having potential biological applications for further drug discovery.

#### Conflicts of interest

There are no conflicts to declare.

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