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Intramolecular cascade annulation triggered by rhodium(III)-catalyzed sequential C(sp^2)–H activation and C(sp^3)–H amination

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Letter

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Abstract

A rhodium(III)-catalyzed intramolecular oxidative annulation of *O*-substituted *N*-hydroxyacrylamides for the construction of indolizinones via sequential C(sp^2)–H activation and C(sp^3)–H amination has been developed. This approach shows excellent functional-group tolerance. The synthesized scaffold forms the core of many natural products with pharmacological relevance.

Introduction

Over the last decade, transition metal-catalyzed C(sp^2)–H activation has emerged as an efficient strategy to access complex molecules [1-6]. Among the methodologies, Rh^{III}-catalyzed oxidative annulation of a C(sp^2)–H bond with 2π components (such as olefins, alkynes) stands out for the construction of carbo(hetero)cycles from easily available starting materials [7-10]. Compared to aromatic C(sp^2)–H bonds, studies on activation of vinylic C(sp^2)–H bonds have been less explored, due to an intrinsic inactivity, tended to undergo polymerization, prone to go through conjugate additions [11,12]. Moreover, the cyclometalation intermediates are unstable, and the β-substitution or α,β-disubstitution of acrylate sterically prevents the cyclometalation [13,14]. Despite these, several approaches have been developed to synthesize pyridones and highly substituted olefins using acrylamides. However, most of them are limited to one-step coupling or annulation and just a single ring is formed [15-22]. Therefore, it is necessary to explore a new cascade annulation of acrylamides to construct a polyfused-heteroarene skeleton in one operational step.

The tricyclic indolizinone scaffold is abundantly present in natural products, as, e.g., in the pharmacologically relevant

mappicine [23,24], camptothecin [25,26], 10-hydroxycamptothecin and topotecan [27,28] (Figure 1). In 2012, Park and co-workers reported a Rh^{III}-catalyzed intramolecular annulation of alkyne-tethered hydroxamic esters for the synthesis of isoquinolones and pyridines without using external oxidants (Scheme 1a) [22]. Recently, we reported an intramolecular annulation of benzamides to synthesize indolizinones through Rh^{III}-catalyzed C(sp^2)–H activation (Scheme 1b) [29-31]. Inspired by this work, we envisaged that tricyclic indolizinones could be built through rhodium(III)-catalyzed sequential C(sp^2)–H activation and C(sp^3)–H amination of *O*-substituted *N*-hydroxyacrylamides (Scheme 1c).

Results and Discussion

We selected *N*-hydroxyacrylamide **1a** as our model substrate under standard conditions. In the presence of $[RhCp^*Cl_2]_2$ (5 mol %) and CsOAc (2 equiv) in 1,4-dioxane (0.1 M) at 60 °C under air, the desired product **3a** was obtained in 40% yield, together with **2a** in 34% yield (Table 1, entry 1). Other solvents could not improve the yield of **3a** (Table 1, entries 2 and 3). $[Ru(p\text{-cymene})Cl_2]_2$ resulted in a very poor yield of **3a** (Table 1, entry 4). Alternative rhodium catalyst $[RhCp^*(CH_3CN)_3](SbF_6)_2$ gave 17% **2a** and 35% **3a** (Table 1, entry 5). Without CsOAc under $[RhCp^*(CH_3CN)_3](SbF_6)_2$ catalysis, just 29% **2a** was isolated (Table 1, entry 6). With

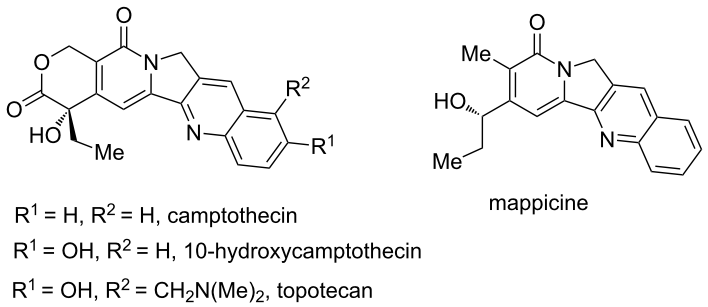
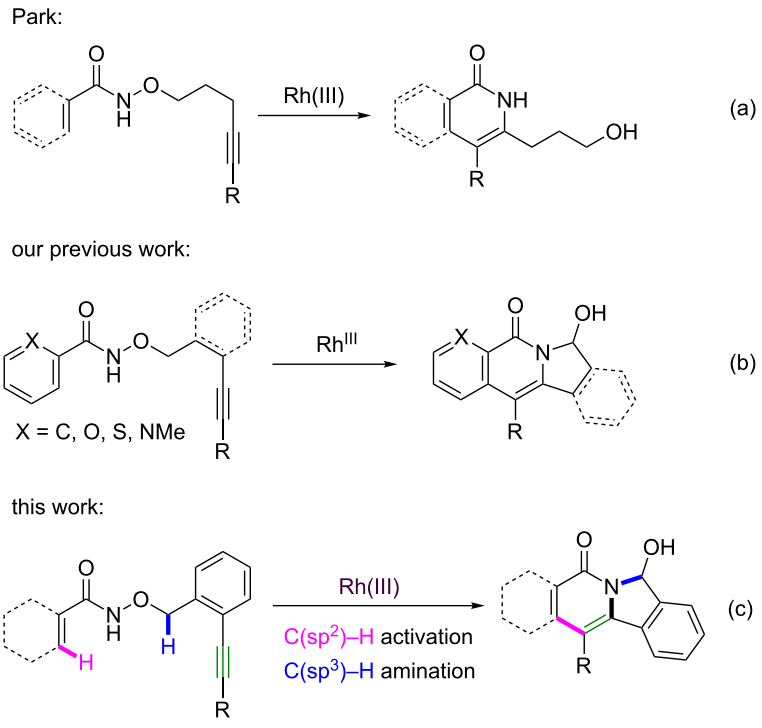
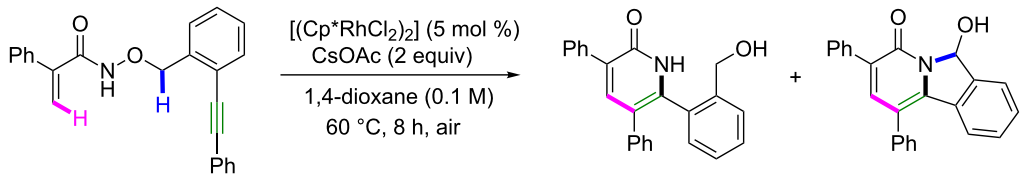


Figure 1: Selected examples of natural products with a tricyclic indolizinone scaffold.



Scheme 1: Previous work and this approach.

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



1a **2a** **3a**

Entry	Changes to standard conditions	Yields (**2a**, **3a**)[b]
1	**none**	**(34%, 40%)**
2	MeOH	(72%, 11%)
3	DCE	(49%, 30%)
4	$[Ru(p\text{-cymene})Cl_2]_2$	(52%, 10%)
5	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	(17%, 35%)
6[c]	$[RhCp^*(CH_3CN)_3](SbF_6)_2$	(29%, 0%)
7	CsOPiv instead of CsOAc	(21%, 32%)
8	without CsOAc	(0%, 0%)
9	0.5 h instead of 8 h	(12%, 14%)

[a]Conditions: **1a** (0.3 mmol), catalyst (0.015 mmol), CsOAc (0.6 mmol), solvent (3.0 mL). [b]Isolated yield. [c]Without CsOAc.

CsOPiv instead of CsOAc, the products **3a** and **2a** were obtained in 32% and 21% yields, respectively (Table 1, entry 7). Without adding CsOAc, no products were formed (Table 1, entry 8). Also, when the reaction was treated under standard conditions for 0.5 h, the products **3a** and **2a** were isolated in 14% and 12% yields, respectively (Table 1, entry 9), which suggested that **3a** was formed as soon as the reaction was performed.

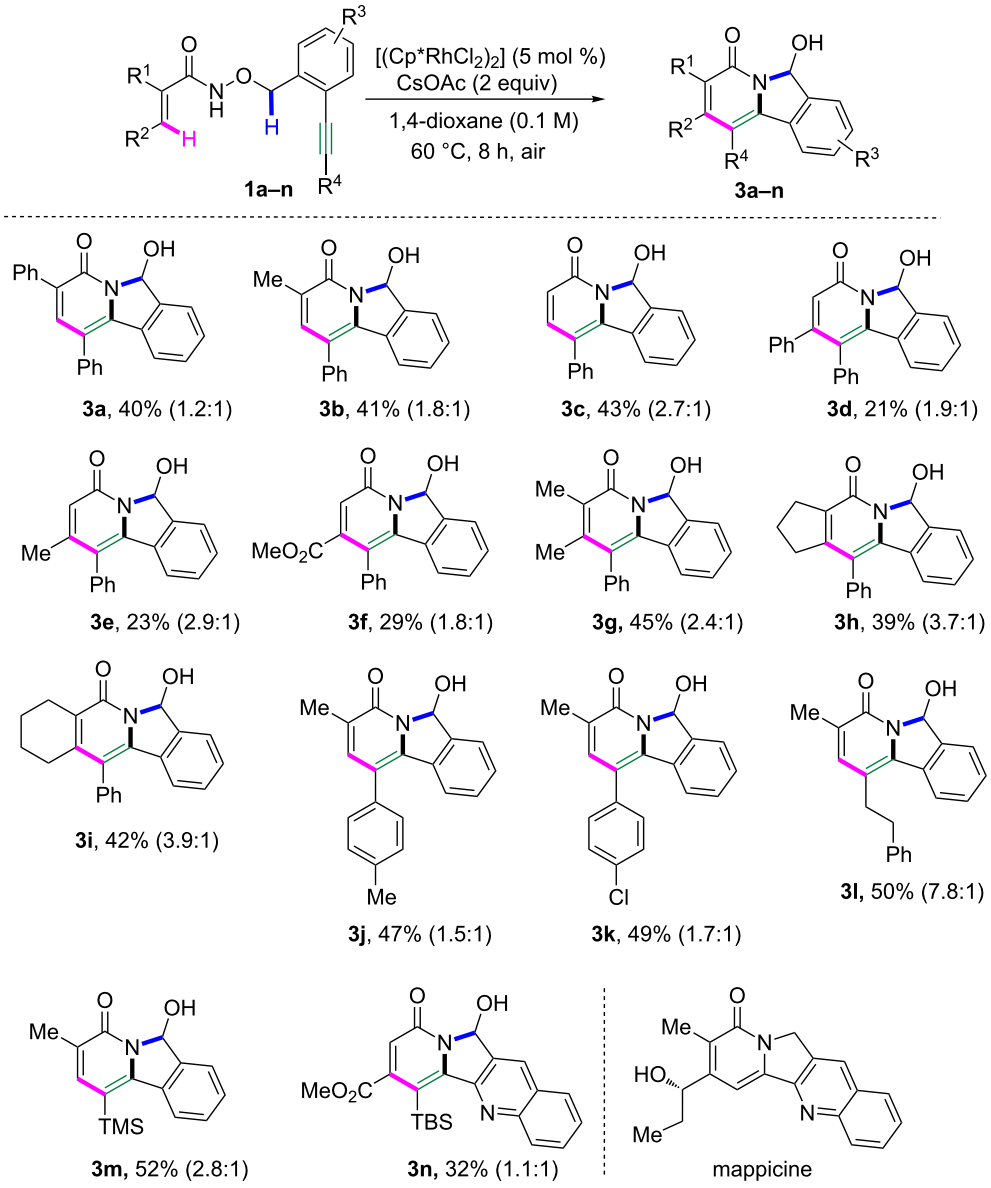
Next, diverse substrates were explored to evaluate the scope of this approach under the optimal reaction conditions (Scheme 2). α-Methylacrylamide smoothly proceeded to give the corresponding indolizinone **3b** in 41% yield. Acrylamide afforded the corresponding indolizinone **3c** in 43% yield. Compared to α-substituted acrylamides, β-substituted acrylamides performed the reaction with lower yields under the same conditions (**3d**–**f**). It should be pointed out that α,β-disubstituted acrylamides were also suitable substrates for this transformation, and the corresponding indolizinones **3g**–**i** were obtained in 39–45% yield. Substrates with different substituents on the alkyne, including 4-methylphenyl, 4-chlorophenyl, phenethyl and a TMS group, could deliver the corresponding indolizinones **3j**–**m** in 47–52% yield. Interestingly, 2-ethynylquinoline as substrate worked well, yielding the corresponding indolizinone **3n** in 32%, which has the same skeleton as mappicine.

To investigate the mechanism of this method, control experiments were carried out (Scheme 3). When **2a** was performed under standard conditions, **3a** could be obtained in 5% yield. Increasing the temperature to 80 °C or 100 °C has no dramatic effect on the yield of **3a**. Other bases, like NaOAc or KOAc, could not improve the yield of **3a** from **2a**. On the contrary, **2a** did not give **3a** in the absence of CsOAc. These results indicate that **3a** could be formed through two pathways, and the one from **2a** is the minor pathway. The main pathway is directly from **1a**.

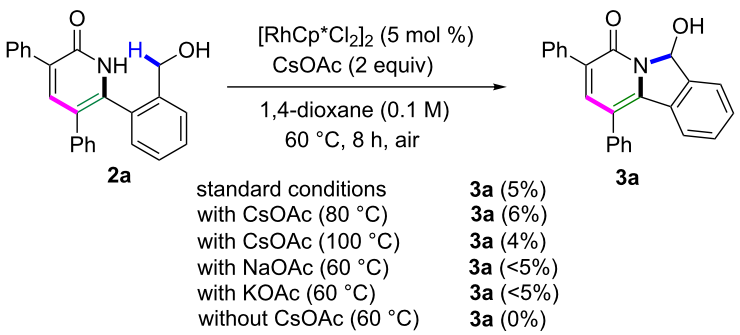
Based on the above results, a plausible mechanism is proposed in Scheme 4 [31]. C(sp^2)–H activation of acrylamide **1a**, followed by subsequent intramolecular coordination of the alkyne gives intermediate **B**. Subsequent intramolecular migratory insertion affords intermediate **C**. Reductive elimination and subsequent oxidative addition give intermediate **D**. Then two pathways are involved in the following steps. In the main pathway (path a), intermediate **D** undergoes β-H elimination and tandem cyclization to give product **3a** and Rh–H intermediate **G**, which could be oxidized by O_2 to regenerate the catalyst. In the minor pathway (path b), intermediate **D** undergoes protonation by acetic acid to give product **2a**, which undergoes deprotonation to form intermediate **D** again, then following the main pathway to give product **3a**.

Conclusion

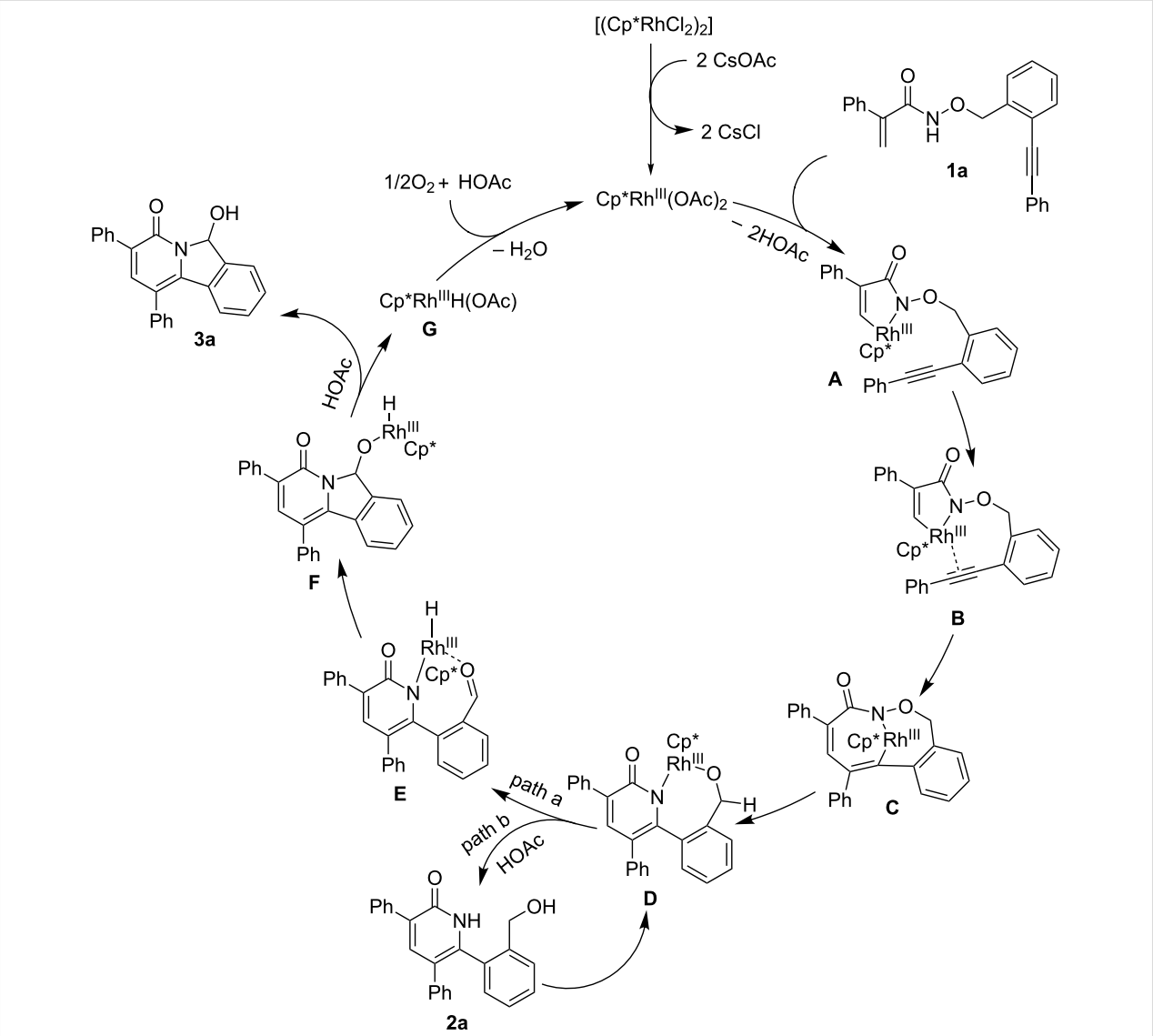
In summary, we have developed a rhodium(III)-catalyzed sequential C(sp^2)–H activation and C(sp^3)–H amination of *O*-substituted *N*-hydroxyacrylamides for the synthesis of



Scheme 2: Reaction scope. Reaction conditions: **1** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.015 mmol), CsOAc (0.6 mmol), 1,4-dioxane (3.0 mL), the ratio of isolated **3**:**2** was shown in parenthesis.



Scheme 3: Control experiments.



Scheme 4: Proposed mechanism.

indolizinones. This method shows excellent functional-group tolerance. The family of indolizinone products represents potential bioactive molecules for further studies.

Supporting Information

Supporting Information File 1

Experimental details and characterization data.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-52-S1.pdf]

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