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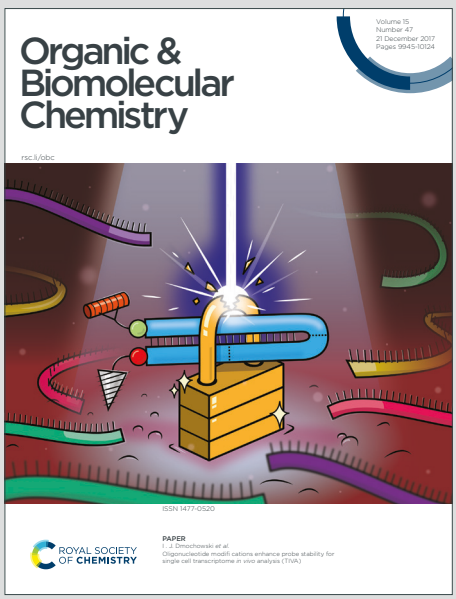

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COMMUNICATION

Construction of isoxazolone-fused phenanthridines *via* Rh-catalyzed cascade C-H activation/cyclization of 3-arylisoxazolones with cyclic 2-diazo-1,3-diketones

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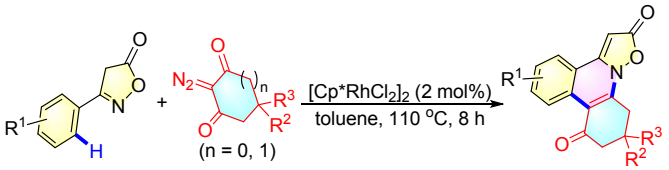
Wangcheng Hu, Xinwei He,* Tongtong Zhou, Youpeng Zuo, Shiwen Zhang, Tingting Yang, Yongjia Shang*

A Rh(III)-catalyzed cascade C-H activation/intramolecular cyclization of 3-aryl-5-isoxazolones with cyclic 2-diazo-1,3-diketones was described, leading to the formation of isoxazolo[2,3-*f*]phenanthridine skeleton. The protocol features the simultaneous one-pot formation of two new C-C/C-N bonds and one heterocycle in moderate-to-good yields with good functional group compatibility. It is amenable to large-scale synthesis and further transformation.

Nitrogen-containing heterocyclic compounds are frequently found as fundamental units in biologically active natural and non-natural products,[1] and designing novel heterocyclic motifs has become an increasingly urgent mission for chemists and biologists.[2] Among them, phenanthridine scaffolds are very important core structural units and possess a wide spectrum of biological activities, such as antitumor,[3] anti-HIV,[4] and antileukemic.[5] In addition, isoxazolones represent an interesting class of heterocycles that display inhibitory activities against *Escherichia coli* and *Yersinia pestis* CDP-ME kinases[6] and as well demonstrate antagonistic antiandrogen activity on human prostate tumor LNCaP cells.[7] Moreover, the *N*-functionalized isoxazolones have been found as core structures in many natural products and pharmaceutical molecules.[8] From a synthetic point of view, to date, methods for obtaining isoxazolone-fused phenanthridine derivatives are still limited.

Transition-metal-catalyzed direct selective conversion of unactivated C–H bonds has emerged as an attractive and arguably ideal new strategy to synthesize heterocyclic molecules,[9] which generally require directing groups (DGs) to resolve the regioselectivity.[10] The heteroatom as a directing group participated in the annulation reaction to avoid the removal of the DGs after transformations.[11] Recently, isoxazol-5(4*H*)-ones have attracted chemists' attention used as DGs mainly because their nitrogen atom could serve as a strong donor atom and undergo cyclometalation at the adjacent position, followed by a subsequent reaction with various partners.[12] Thus 3-aryl-5-isoxazolone could be considered as a novel and facile coupling partner to synthesize diverse isoquinolines through simple C–H bond activation followed by intramolecular annulation.[12b, 13] In continuation of our efforts to enrich transition-metal catalyzed cascade C-H activation/intramolecular cyclization for heterocycle synthesis,[14] We herein disclosed a simple and efficient strategy for the synthesis of isoxazolo[2,3-*f*]phenanthridines *via* the Rh(III)-catalyzed cascade C-H bond activation and sequential intramolecular annulation of 3-aryl-5-isoxazolones and cyclic 2-diazo-1,3-diketones (Scheme 1). Remarkably, one C–C bond and one C–N bond were formed simultaneously with releasing by-products of H_2O and N_2 in the reaction make the process environmentally benign.



Scheme 1 Synthesis of isoxazolo[2,3-*f*]phenanthridines *via* Rh(III)-catalyzed cascade reaction of 3-aryl-5-isoxazolones with cyclic 2-diazo-1,3-diketones.

The study was initiated to establish the optimal conditions with 3-phenylisoxazol-5(4*H*)-one (**1a**) and 2-diazo-5,5-dimethylcyclohexane-1,3-dione (**2a**) as the starting materials. The reaction was performed by $[Cp^*RhCl_2]_2$ as catalyst in DCE at 90 ºC, affording the desired product **3aa** in 39% yield (Table 1, entry 1). However, the replacement of $[Cp^*RhCl_2]_2$ with other Rh- or Ru-catalysts failed to produce the desired product (Table 1, entries 2-6). Increasing or decreasing the loading of catalyst gave inferior outcomes (Table 1, entries 7,8). Next, when the solvent was changed to tetrahydrofuran (THF), ethanol, and acetonitrile, no improvements could be achieved (Table 1, entries, 9, 10, 12). Importantly, higher yield was

Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials (State Key Laboratory Cultivation Base), College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, P.R. China. E-mail: xinweihe@mail.ahnu.edu.cn, shyj@mail.ahnu.edu.cn

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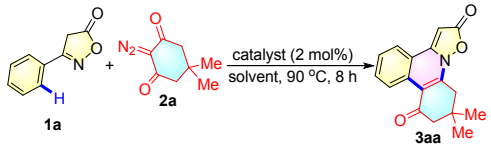
obtained when toluene was used as solvent (Table, entry 11). Furthermore, the yield was improved to 72% when the amount of diazo compound 2a was increased to 2 equivalents as well as the reaction mixture was heated to 110 °C (Table 1, entry 15). Afterward, further optimization of the additive, including $AgSbF_6$, CsOAc, and PivOH, as more competent for this reaction protocol, the product **3aa** was delivered with no remarkable improve in terms of yield (Table 1, entries 17-19).

Table 1 Optimization of the Reaction Conditions.[a]

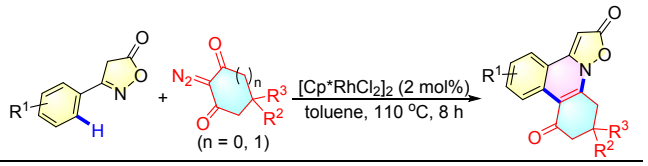


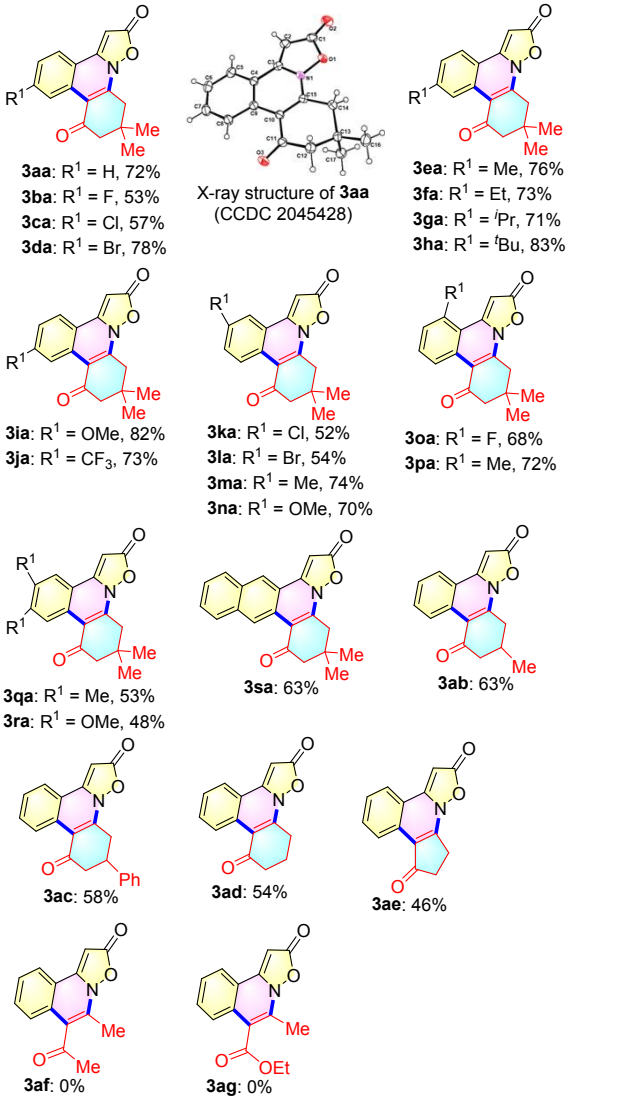
Entry	catalyst	solvent	yield(%)[b]
1	$[Cp^*RhCl_2]_2$	DCE	39
2	$[Cp^*IrCl_2]_2$	DCE	nd
3	$Ru(Ph_3P)_2Cl_2$	DCE	nd
4	$Rh(PPh_3)Cl$	DCE	nr
5	$Rh_2(OAc)_4$	DCE	nr
6	$[(p\text{-cym})RuCl_2]_2$	DCE	nr
7[c]	$[Cp^*RhCl_2]_2$	DCE	27
8[d]	$[Cp^*RhCl_2]_2$	DCE	21
9	$[Cp^*RhCl_2]_2$	THF	13
10	$[Cp^*RhCl_2]_2$	EtOH	nr
11	$[Cp^*RhCl_2]_2$	toluene	48
12	$[Cp^*RhCl_2]_2$	MeCN	nr
13[e]	$[Cp^*RhCl_2]_2$	toluene	58
14[e,f]	$[Cp^*RhCl_2]_2$	toluene	65
15[e,g]	$[Cp^*RhCl_2]_2$	toluene	72
16[e,h]	$[Cp^*RhCl_2]_2$	toluene	68
17[e,i]	$[Cp^*RhCl_2]_2$	toluene	trace
18[e,j]	$[Cp^*RhCl_2]_2$	toluene	33
19[e,k]	$[Cp^*RhCl_2]_2$	toluene	45

[a] Reaction conditions: 3-phenylisoxazol-5(4*H*)-one (**1a**) (0.25 mmol), 2-diazo-5,5-dimethylcyclohexane-1,3-dione (**2a**) (0.25 mmol), and catalyst (2 mol%) in solvent (4 mL) at 90 °C for 8 h under air atmosphere. [b] Isolated yields. [c] 1 mol% of catalyst. [d] 4 mol% of catalyst. [e] **1a**:**2a** = 1:2. [f] 100 °C. [g] 110 °C. [h] 120 °C. [i] 8 mol% of $AgSbF_6$ as additive. [j] 20 mol% of CsOAc as additive. [k] 20 mol% of PivOH as additive. nd = not detected. nr = no reaction.

After establishing the optimal reaction conditions (Table 1, entry 15), the substrate scope was examined for the preparation of various functionalized isoxazolo[2,3-*f*]phenanthridine derivatives (Table 2). In general, the reaction proceeded smoothly with a broad spectrum of 3-arylisoxazol-5(4*H*)-ones. Electron–deficient (e.g., -F, -Cl, -Br, and $-CF_3$), –neutral (e.g., -Me, -Et, -^{i}Pr, and -^{t}Bu), and –rich (e.g., -OMe) groups at the *para*-position of beneze ring in substrate **1** were well-tolerated, affording the corresponding products **3aa**-**3ja** in 53-83% yields. In addition, changing the substituents to *meta*- and *orth*-position of beneze ring in the starting material **1** could also generated the desired products **3ka**-**3pa** in 52-74% yields. Moreover, the disubstituted 3-arylisoxazol-5(4*H*)-ones were found to react with diazo-5,5-dimethylcyclohexane-1,3-dione **2a** yielding the corresponding products **3qa**, **3ra** in 53% and 48% yields, respectively. Furthermore, it was found that the aryl framework could be extended to naphthalene, affording the desired product **3sa** with a percentage yield of 63%. Next, the suitability of cyclic diazo compounds was investigated under the standard conditions. Both H, alkyl (e.g., methyl) and aryl (e.g., phenyl) R^2 groups were well-tolerated affording the corresponding products **3ab**-**3ad** in 63%, 58%, and 54% yields, respectively. Additionally, 2-diazocyclopentane-1,3-dione was also found to undergo this transformation, generating the corresponding product **3ae** in 46% yield. However, the protocol is not suitable for noncyclic diazo substrates, such as 3-diazopentane-2,4-dione and ethyl 2-diazo-3-oxobutanoate.

Table 2. Substrate scope.[a,b]





[a] Reaction conditions: 3-arylisoxazol-5(4*H*)-one **1** (0.25 mmol), cyclic 2-diazo-1,3-diketones **2** (0.5 mmol), and $[Cp^*RhCl_2]_2$ (2 mol%) in toluene (4 mL) at 110 °C for 8 h under air atmosphere. [b] Isolated yields.

To further study the applicability of this strategy by preparation of compound **3aa** on a scale-up synthesis (3 mmol of **1a** with 6 mmol of **2a**) under the standard conditions as

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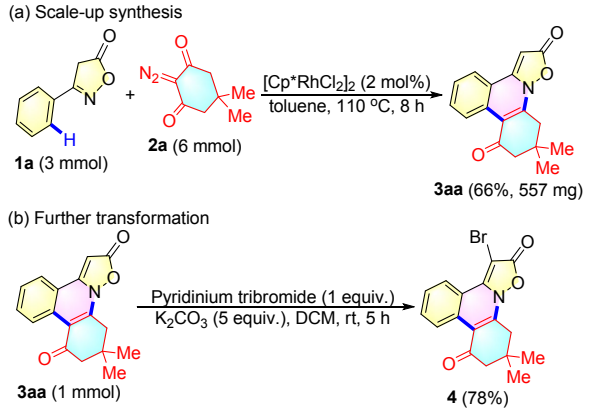
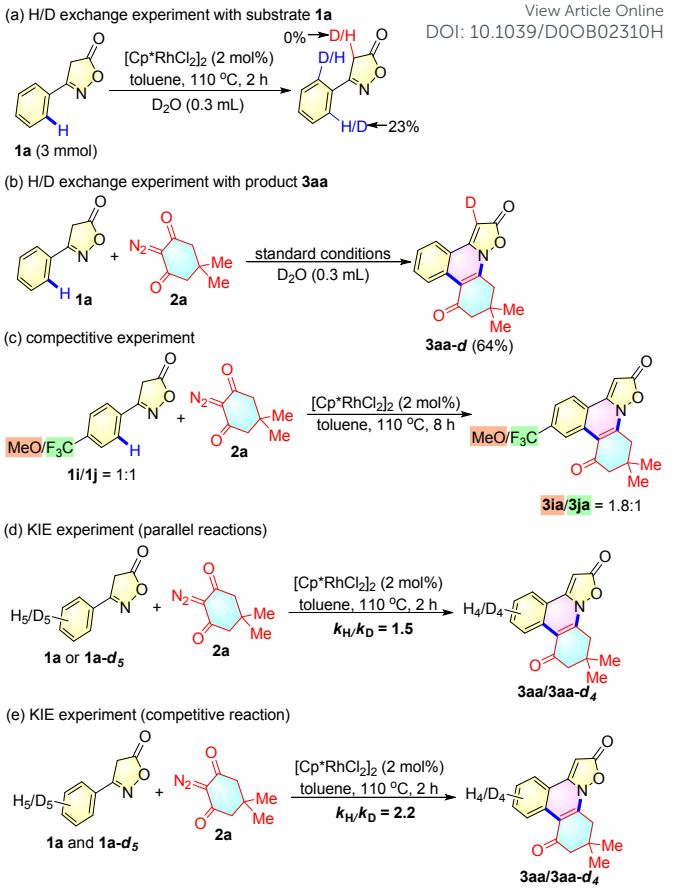
described above (Scheme 2a). The large-scale synthesis proceeded smoothly to give the desired product **3aa** in 66% yield (557 mg). In addition, derivatization of **3aa** was performed by reacting with pyridinium tribromide in the presence of K_2CO_3 in DCM (dichloromethane) at room temperature for 5 h, affording the bromo-substituted product **4** in 78% yield (Scheme 2b).



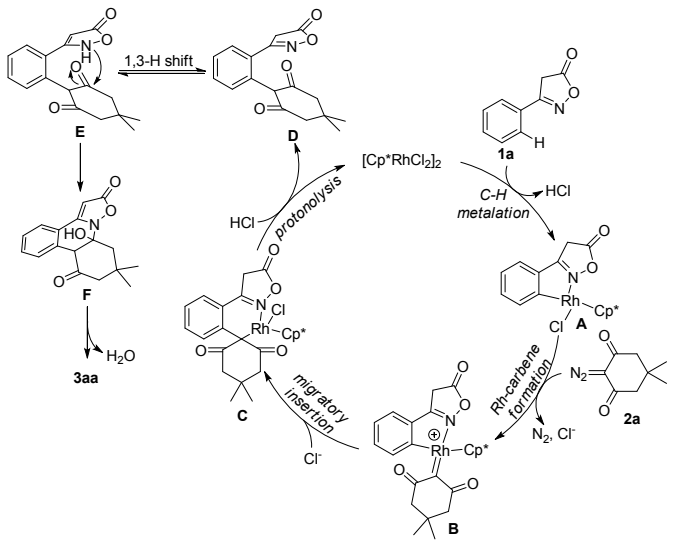
Scheme 2. Scale-up synthesis and further synthetic transformation.

In order to gain insight into the reaction mechanism, we initially performed the H/D exchange experiment in deuterium oxide under the standard conditions (Scheme 3a). The deuteration reaction of **1a** mainly occurs at the C(sp^2)-H bond (D, 23%) on the benzene ring, while no deuterated product was detected at the C(sp^3)-H on the isoxazol-5(4*H*)-one ring. This result showed that the activation process of the C(sp^2)-H bond is favorable and fast and no alkenylation occurred on the isoxazol-5(4*H*)-one ring at the initial stage of the reaction. As we expect, more than 99% of product **3aa**-*d* was deuterated at the α-H of carbonyl group on the isoxazol-5(4*H*)-one ring when the reaction of substrates **1a** with **2a** in the presence of deuterium oxide under the standard conditions (Scheme 3b). Furthermore, an intermolecular competition experiment was conducted to examine the electron-rich substrate **1i** and its electron-deficient counterpart **1j** (Scheme 3c). The higher yield for **1i** than **1j** highlights the fact that electron-rich substrates are inherently more reactive, implying that stronger coordination ability of the N-atom in these substrates with the Rh(III) catalyst, which in turn facilitates the following C-H activation step. Furthermore, we determined the kinetic isotope effect (KIE) of this cascade C-H activation/cyclization. A KIE value of 1.5 was determined from two parallel reactions (Scheme 3d), and a KIE value of 2.2 was determined from a competition reaction (Scheme 3e). These results suggested that C(sp^2)–H bond cleavage might be the limiting step.



Scheme 3. Mechanistic studies.

On the basis of the above control experiment results and literature reports,[15] a plausible mechanism is proposed for the formation of product **3aa** (Scheme 4). Initially, the reaction of the Rh-catalyst with the substrate **1a** leads to the five-membered rhodacycle intermediate **A** by deprotonation. Subsequently, the cyclic 2-diazo-1,3-diketone **2a** coordinates with intermediate **A** to form the intermediate **B** by releasing N_2. Then, migratory insertion of carbine into Rh-C bond completes the C-C coupling and affords the six-membered intermediate **C**, which can be protonated with hydrochloric acid to generate intermediate **D** and release the Rh(III)-catalyst. In the next stage of this cascade process, an alkenylation occurs with the *in situ* generated intermediate **E** *via* 1,3-H shift. Finally, the desired product **3aa** was formed through an intramolecular nucleophilic addition of the amino group to carbonyl in intermediate **E** to form intermediate **F**, followed by water elimination.



Scheme 4. A plausible mechanism.

Conclusions

In summary, we have developed rhodium-catalyzed cascade C-H activation/intramolecular cyclization of 3-aryl-5-isoxazolones with cyclic 2-diazo-1,3-diketones. Under the reaction conditions, structurally diverse isoxazolo[2,3-*f*]phenanthridine scaffolds could be produced in moderate-to-good yields. The advantages of the current strategy include additive-free conditions, good functional tolerance, and broad substrate scope. Particularly noteworthy is that the by-products of N_2 and H_2O in the reaction make the process environmentally benign. In addition, a large-scale synthesis and further transformation are also presented to show the practicality and potential of the current reaction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgement

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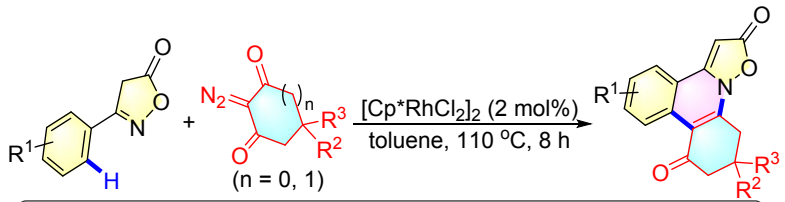

- *mild conditions, scalability & practicality*
- *N_2 & H_2O as the only by-products*
- *two new bonds and one heterocycle formation in one-pot*
- *good functional group tolerance, e.g. -F, -Cl, -Br, -CF_3, -OMe, alkyl.....*

A Rh(III)-catalyzed cascade C-H activation/intramolecular cyclization of 3-aryl-5-isoxazolones with cyclic 2-diazo-1,3-diketones was described, leading to functional isoxazolone-fused phenanthridine derivatives in moderate to good yields.