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Communication

Rhodium(III)-catalyzed chemodivergent annulations between phenyloxazoles and diazos *via* C–H activation

Xueguo Zhang, Peigen Wang, Liangwei Zhu, Baohua Chen*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

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ABSTRACT

Acid-controlled, chemodivergent and redox-neutral annulations for the synthesis of isocoumarins and isoquinolinones have been realized *via* Rh(III)-catalyzed C—H activation. Diazo compounds act as a carbene precursor, and coupling occurs in one-pot process, where adipic acid and trimethylacetic acid promote chemodivergent cyclizations.

Rhodium-catalysed C—H functionalization has emerged as an effective tool in organic synthesis for the construction of diversified heterocyclic systems [1]. C—H bond functionalization [2] is an attractive alternative to classical cross-coupling reactions (which usually require organohalides and organometallic reagents) due to the abundance and relatively low cost of various hydrocarbons. Thus, merging C—H functionalizations with other efficient and sustainable approaches like multicomponent reactions or cascade transformations, is expected to be an ideal tool in organic synthesis for rapid construction of complex molecules from simple starting materials [3].

Recently, diazo compounds as good partners for C—H activation couplings or cyclizations, are widely used in synthetic organic chemistry (Scheme 1) [4]. In 2012, Yu reported the Rh(III)-catalysed intermolecular cross-coupling of diazomalonates with arene C—H bonds [5]. Subsequent work demonstrated the Rh(III)-catalysed intermolecular cross-coupling of diazo compounds [6]. Although the aforementioned methods are encouraging, a straightforward C—H activation strategy to access isocoumarin and isoquinolinone scaffolds with different substitutions remains highly desireable [7]. To the best of our knowledge, one-pot ring-opening/ring-closure of oxazole *via* Rh(III)-catalyzed C—H activation/cyclization of aromatics with diazo compounds has not been reported.

Isocoumarin and isoquinolinone are heterocyclic compounds [8] that provide the key structural motif for a variety of biologically and pharmacologically important natural products. Despite the vast array of methods to synthesize isocoumarins and isoquinolinones, new methods that efficiently access highly decorated substituted isocoumarins and isoquinolinones remain desirable [9]. Herein, we disclose an acid-controlled [10], one-pot, ring-opening/ring-closure pathway [11] for combining phenyloxazoles with diazos to rapidly and economically stepwise construct polycyclic isocoumarins in high yields.

The envisaged functionalization/cyclization sequence was investigated and optimized using *N*-(2-(4,5-dihydrooxazol-2-yl) phenyl)benzamide (**1a**) and ethyl 2-diazo-3-oxobutanoate (**2a**) as the prototype substrate combination (see Supporting information for details). To our delight, excellent conversions of **1a** were achieved when the reaction was carried out at 100 °C for 20 h in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%) and PivOH (2.0 equiv.) under air and using 1,4-dioxane as the solvent. The corresponding cyclization products **3a** and **4a**, were isolated in 32% and 40% yields, respectively (see Supporting information for details). To improve the yield and selectivity of **3a**, we changed the acid amount. Disappointingly, we found that reducing the amount of acid had little effect on either yield or selectivity. However, there is no doubt that acid plays a decisive role in this process. Several acids were subsequently investigated and to our satisfaction, good selectivities and yields for **3a** were obtained when a binary acid was involved in the reaction system. Propanedioic acid and sebacic acid were both inferior to adipic acid (see Supporting information

* Corresponding author.
E-mail address: chbh@lzu.edu.cn (B. Chen).

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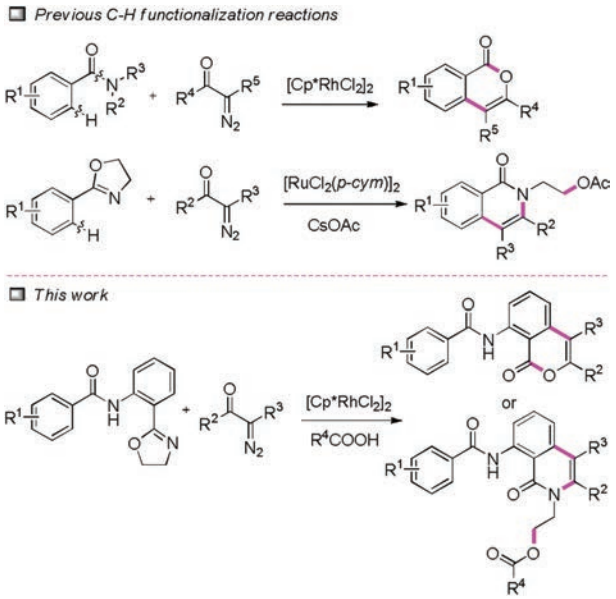


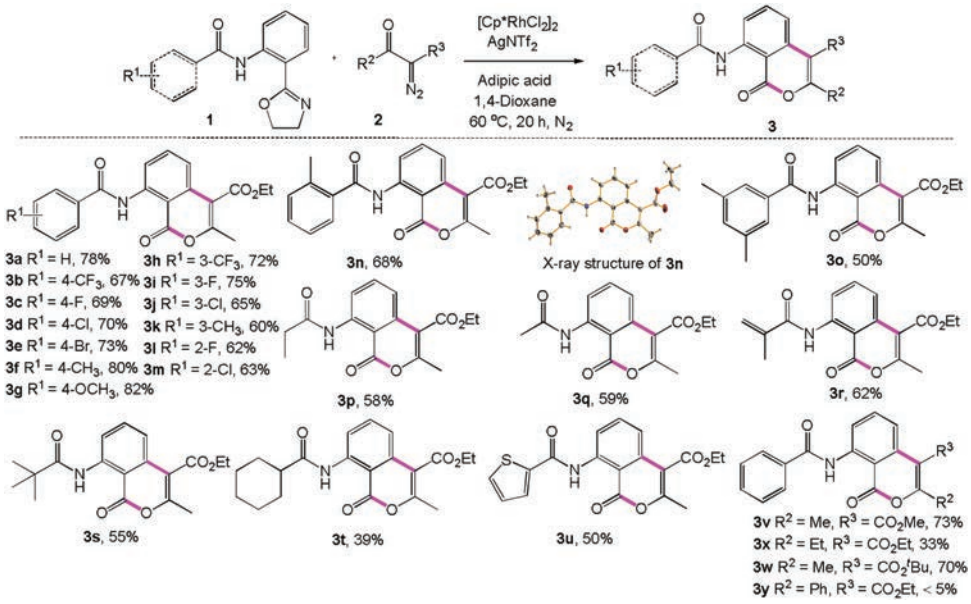
Scheme 1. Rh(III)/Ru(II)-catalysed C–H activation/cyclization using diazo compounds as cyclization partners.

for further details) [12]. We tried different additives to improve the conversion and $AgNTf_2$ was more suitable than others for this transformation. Those results demonstrated that the reaction could be conducted at 60 °C under an inert atmosphere with yields of **3a** reaching 78% yield. Compared with another commonly used organic phase solvent DCE, 1,4-dioxane gave a better yield (see Supporting information for further details). Once an efficient synthesis of **3a** had been established, our attention turned to the preferential formation of **4a**. Solvents effects were initially examined and when the reaction was carried out in DMSO and toluene, only trace amounts of the desired products were obtained. However, when THF was used as the solvent, **4a** was obtained in 55% yield. Lastly, the temperature was changed to 80 °C, which resulted in excellent yields of **4a** (see Supporting information for further details). Further studies on the catalysts revealed that $[Cp^*RhCl_2]_2$ was the most effective, with no isocoumarins products detected using $Rh_2(OAc)_4$, $[Rh(cod)Cl]_2$, $[Ru(p\text{-}cym)Cl_2]_2$ and $[Cp^*IrCl_2]_2$ as catalysts (see Supporting information for further details).

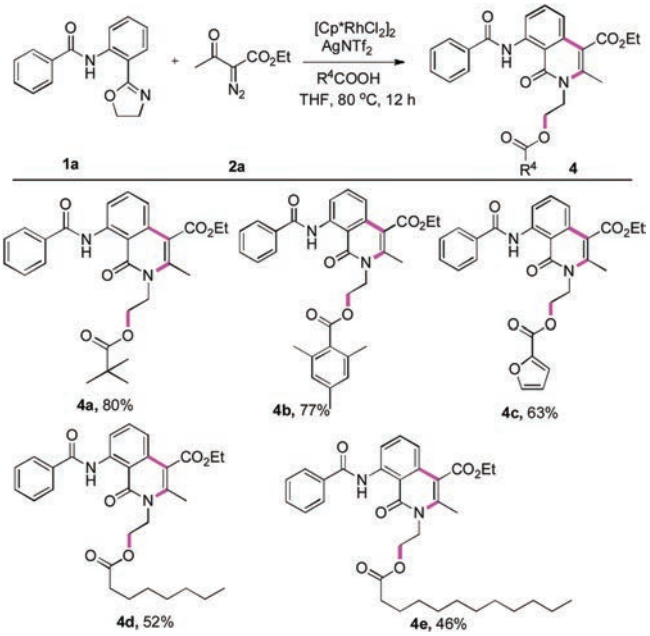
As shown in Scheme 2, the scope and limitations for the formation of isocoumarins **3a–3z** were investigated using systematic variation of phenyloxazoles (**1a–1u**) and diazo compounds (**2a–2d**). Ethyl 2-diazo-3-oxobutanoate (**2a**) was chosen as a representative coupling partner. Phenyloxazoles bearing a variety of substituted groups on the benzene ring, which included both electron-rich groups (methyl, methoxy) and electron-deficient groups (trifluoromethyl, fluoride, chloride and bromide), exhibited high reactivity with **2a** under the optimised reaction conditions (**3a-3n**, 60%–82%). Moreover, the chemical structure of **3n** was unambiguously confirmed by X-ray crystallography (Crystal Structure submitted to Cambridge Cystallographic Data Centre. CCDC: 1961003). Furthermore, substrate bearing 3,5-dimethyl substituent (**1o**) was also well tolerated, furnishing the required isocoumarin in moderate yield (**3o**, 50%). Additionally, the less sterically demanding wide range of alkyl substituted such as ethyl and methyl, also provided the corresponding product in good yield (**3p**, 58% and **3q**, 59%). Moreover, a wide range of alkyl substituted phenyloxazoles performed well and furnished the corresponding products in satisfactory yields (**3r**, 62%, **3s**, 55% and **3t**, 39%). Heterocyclic derivatives were also well tolerated in this transformation, and moderate yields of the corresponding products **3u** were obtained (**3u**, 50%).

Next, we investigated the scope and reactivity of diazo compounds using *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)-benzamide (**1a**) as a representative coupling partner. When R^3 was a methyl ester or a tertiary-butyl ester, the reaction proceeded smoothly and gave the corresponding products in 73% and 70% yields, respectively (**3v** and **3w**). However, the ethyl substituted substrate (**2c**) gave the desired product **3x** was obtained in only 33% yield. Furthermore, the reaction did not produce the corresponding product when the phenyl substituted substrate (**2d**) was used, probably due to the steric hindrance.

Finally, we explored the scope of this Rhodium-catalysed cyclization of *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamide (**1a**) and ethyl 2-diazo-3-oxobutanoate (**2a**) with a variety of



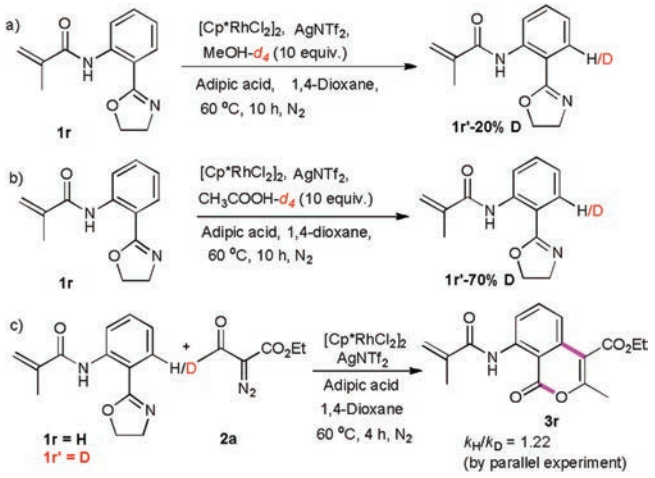
Scheme 2. Substrate scope. Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgNTf_2$ (10 mol%), 1,4-dioxane (2 mL), 20 h, under N_2 atmosphere. Isolated yields.



Scheme 3. Substrate scope. Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgNTf_2$ (10 mol%), THF (2 mL), 12 h. Isolated yields.

commercially available acids to afford the corresponding isoquinolinones. To our delight, we observed that both alkyl, aryl and heterocyclic acids were well-tolerated (Scheme 3, **4a**-**4c**). In particular, when long-chain-fatty-acids were participated, the reaction still took place (**4d** and **4e**). Synthesis of these compounds certainly have applications in the medical field. In fact, isoquinolinones were formed the core of several medicines currently in development.

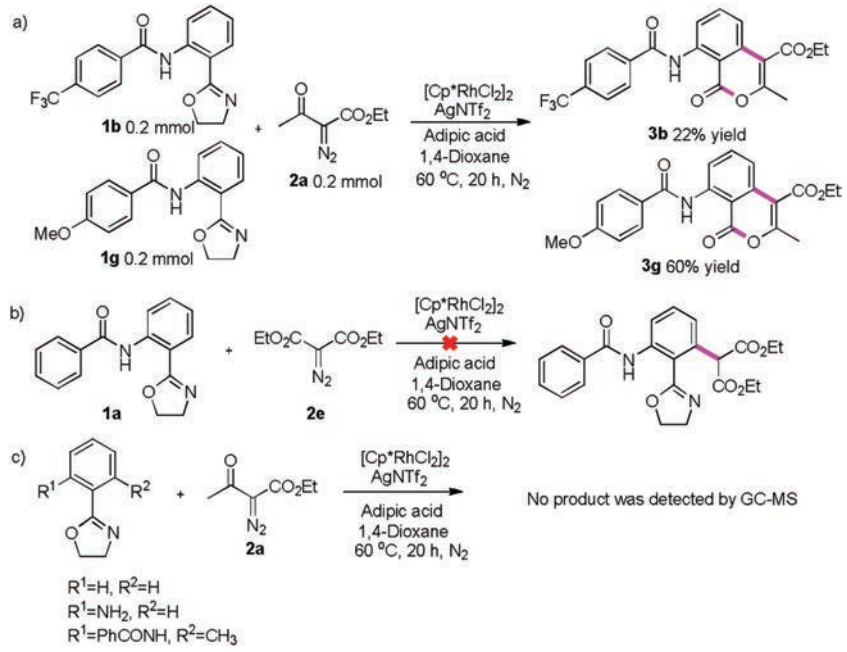
To better understand the versatile reactivity of Rh(III)-catalysed C–H activation and to gain insight into the mechanism of this transformation, we conducted several control experiments. The competition experiment between **1b** and **1g** was performed under



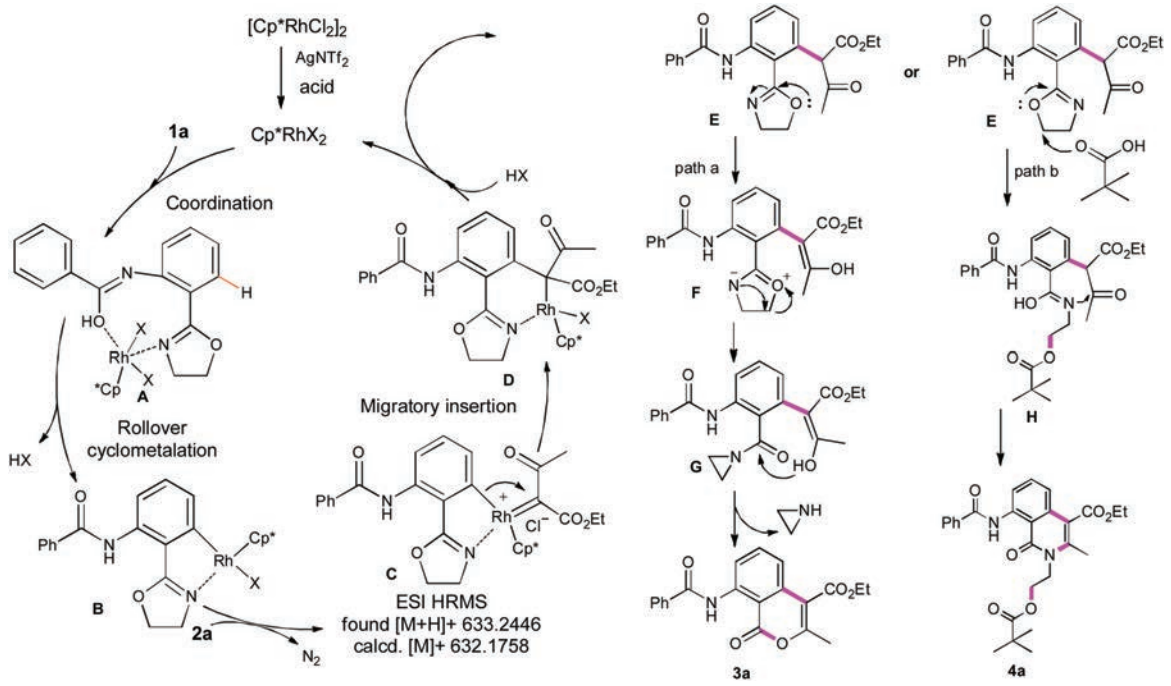
Scheme 5. Kinetic isotope effect experiments.

standard conditions and gave products **3b** and **3g** in 22% and 60% yields, respectively (Scheme 4a). These results indicated that electron-donating substituents were favoured for this transformation. Furthermore, when we used diethyl 2-diazomalonate **2e**, the reaction did not proceed (Scheme 4b). This implied that the ketone plays an important role in this lactonization progress. To investigate the role of amides, we replaced amides with hydrogen and amidogen groups, however, no target products were obtained. This led us to conclude that the amide group was necessary (Scheme 4c). Similarly, Rh(III)-catalysed *ortho*-positions C—H activation was proved (Scheme 2c).

To further probe the C–H activation process, we carried out kinetic isotope effect (*KIE*) experiments. To eliminate the interference of other hydrogen of benzene ring, we choose **1r** as the model substrate for *KIE* experiments. Methanol-d_4 and acetic acid-d_4 were separately subjected to the optimized reaction conditions over 10 h. We obtained the products **1r'**-20%D and **1r'**-70%D at the *ortho*-positions (Schemes 5a and b). These results showed that acid is beneficial for C–H metalation. A low k_H/k_D (1.22) value was



Scheme 4. Mechanistic studies.



Scheme 6. Plausible mechanism.

obtained for parallel experiments, and indicated that C–H cleavage was not the rate-determining step (Scheme 5c).

Based on these preliminary experimental results and literature precedents [4,13–15], we propose a plausible mechanism in Scheme 6. First, the coordination of **1a** with Rh(III) forms Rh(III) complexes **A**, which undergo a reversible rollover cyclometalation to give complexes **B**. Subsequent combination with ethyl 2-diazo-3-oxobutanoate **2a** produces a rhodium-carbene intermediate **C**. Migratory insertion of the Rh-C bond into the activated carbene forms the six-membered rhodacycle **D**. The intermediate **E** produces **3a** *via* enolization and esterification with the release of ethyleneimine (Scheme 6, path a). Meanwhile, **E** produces **4a** by nucleophilic attack through the intermediate **H** in the presence of PivOH (Scheme 6, path b).

In conclusion, we have developed a one-pot, ring-opening/ring-closure, Rh(III)-catalysed, C–H functionalization of phenyloxazoles with diazo compounds to produce isocoumarins and isoquinolinones. This transformation features acid-controlled chemodivergent annulation, operational simplicity and excellent functional group tolerance. Further applications of this Rh(III)-catalytic system to other more challenging C—H functionalizations continue in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.06.011.

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