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Rh(III)-Catalyzed Three-Component Cascade Annulation to Produce *N*-oxopropyl Chain of Isoquinolone Derivatives

Yuan He,[a] Xian-Zhang Liao,[a] Lin Dong [a],* and Fen-Er Chen [a,b,c]*

Developing powerful methods to introduce the versatile functional groups at the *N*-substituents of isoquinolone scaffolds is still a great challenge. Herein, we report a novel three-component cascade annulation reaction to efficiently construct *N*-oxopropyl chain of isoquinolone derivatives *via* rhodium(III)-catalyzed C–H activation/cyclization/nucleophile attack, with oxazoles using both as the directing group and potential functionalized reagents.

Isoquinolones are an attractive class of structural units, and their extensive prevalence in various biologically active compounds, alkaloids and natural products, such as dorianine, ruprechstyril, protoberberines and benzo[c]phenanthridines.[1] Meanwhile, isoquinolone derivatives as versatile intermediates have widely access to a large variety of chemical molecules and drug structures.[2] Due to these properties, a large number of strategies have paved the way to the formation of different isoquinolone derivatives.[3]

In recent years, transition-metal-catalyzed C–H bond functionalization has received increasing attention because of high atom-economic, activity, selectivity together with great practical worth.[4] Therefore, these highly efficient synthetic methods have been directed to construct the useful isoquinolone skeletons. Most strategies utilized various types of benzamide derivatives direct working with coupling partners such as alkynes, diynes and diazo compounds (Scheme 1, eq 1).[5] Some other reports have appeared on the establishment of the motifs from benzohydrazines, acyl azides and nitriles, etc.[6] Despite these achievements, the further introducing the versatile functional groups at the *N*-substituents of isoquinolone scaffolds during the C–H functionalization/cascade reaction aroused our great interest. Very recently, Cui and Kapur separately featured beautiful oxazoline-directed aromatic C–H activation approaches to build *N*-(2-acetoxyalkyl)isoquinolones from alkynes or diazo compounds (eq 2).[7] Nevertheless, oxazoles serving as a directing group are still very limited, and only one example provided anthracene skeletons from 5-aryl-2-phenyloxazole (eq 3).[8] Therefore, we describe a novel three-component cascade annulation reaction to generate *N*-oxopropyl chain of isoquinolone derivatives *via* rhodium(III)-catalyzed C–H activation/cyclization/nucleophile attack by using oxazoles as the directing group as well as potential functionalized reagents (eq 4).

At the outset of our studies, 5-methyl-2-phenyloxazole (**1a**) and diphenylacetylene (**2a**) were chosen as model substrates to optimize the reaction conditions (Table 1). Initially, no desired product was observed when choosing AgOAc or Cu(acac)$_2$ as the oxidant (entries 1 and 2). To our delight, the desired *N*-oxopropyl chain product **3aa** could be isolated in 57% yield by using Cu(OAc)$_2$·H$_2$O as the oxidant (entries 3 and 4). Silver salt screening showed that AgNTf$_2$ gave the increased result (entries 4-8). Notably, reaction efficiency was increased by adding trace amount of H$_2$O (entry 9). The addition of pivalic acid can effectively promote the reaction activity (entries 10-14). The solvent effect is still obvious in the cascade reaction (entries 15-20). Delightedly, decreasing the loading of catalyst resulted in a higher yield (entry 21). Further decreasing the loading of **2a**, AgNTf$_2$ and PivOH could facilitate the cascade reaction (entry 22). Scaling up the reaction still led to good isolated yield (entry 23).
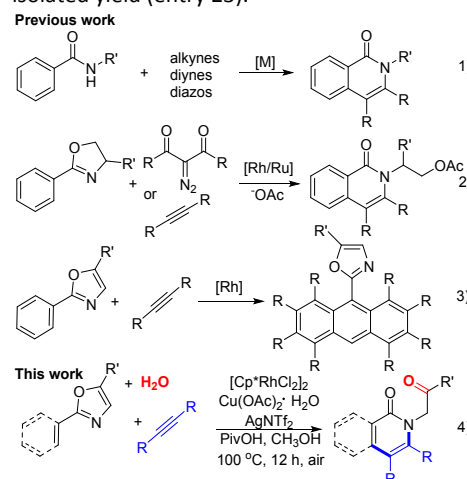
Scheme 1 Strategies to Form Isoquinolone Skeletons *via* C–H Bond Functionalization

With the optimized reaction conditions in hand, we explored the substrate scope of 2-aryloxazolines. As revealed in Scheme 2, in

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Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

general, 2-aryloxazolines bearing electron-donating substituents at *para*-position of phenyl ring were well tolerated, affording the

high regioselectivity.

Table 1 Optimization of the Reaction Conditions[a]

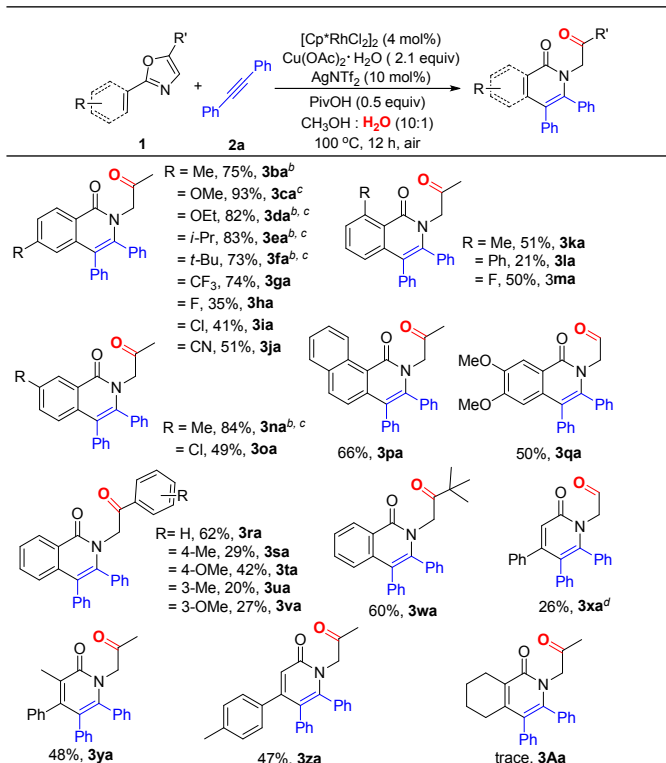| Entry	Oxidant	Additive	Solvent	Yield[b]
1	AgOAc	AgNTf$_2$	CH$_3$OH	ND
2	Cu(acac)$_2$	AgNTf$_2$	CH$_3$OH	ND
3	Cu(OAc)$_2$	AgNTf$_2$	CH$_3$OH	Trace
4	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$	CH$_3$OH	57%
5	Cu(OAc)$_2$·H$_2$O	AgOTf	CH$_3$OH	14%
6	Cu(OAc)$_2$·H$_2$O	AgSO$_3$CH$_3$	CH$_3$OH	40%
7	Cu(OAc)$_2$·H$_2$O	AgBF$_4$	CH$_3$OH	51%
8	Cu(OAc)2·H$_2$O	AgSbF$_6$	CH$_3$OH	52%
9	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/H$_2$O	CH$_3$OH	65%
10	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/Na$_2$CO$_3$/H$_2$O	CH$_3$OH	40%%
11	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/HOAc/H$_2$O	CH$_3$OH	42%
12	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PhCOOH/H$_2$O	CH$_3$OH	65**%**
13	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/1-AdCOOH/H$_2$O	CH$_3$OH	66%
14	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	CH$_3$OH	74%
15	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	THF	56%
16	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	DCE	41%
17	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	CH$_3$CN	57%
18	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	Toluene	Trace
19	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	1,4-Dioxane	42%
20	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	EtOH	64%
21[c]	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	CH$_3$OH	53%
22[d]	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	CH$_3$OH	52%
21[e]	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	CH$_3$OH	80%
22[f]	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	CH$_3$OH	86%
23[g]	Cu(OAc)$_2$·H$_2$O	AgNTf$_2$/PivOH/H$_2$O	CH$_3$OH	64%

[a]Unless otherwise stated, reaction conditions are as follows: **1a** (0.05 mmol), **2a** (2 equiv), [Cp*RhCl$_2$]$_2$ (5 mol%), oxidant (2.1 equiv), silver salt (20 mol%), acid (1 equiv), solvent (0.5 mL), H$_2$O (50 μL), 100 ˚C, 12 h, under air. [b] Isolated yield. [c]80 ℃. [d]120 ℃. [e][Cp*RhCl$_2$]$_2$ (4 mol%). [f]**2a** (1.5 equiv), [Cp*RhCl$_2$]$_2$ (4 mol%), AgNTf$_2$ (10 mol%), PivOH (0.5 equiv). [g]**1a** (1 mmol).

corresponding products (**3ba**-**3fa**) in higher yields than electron-poor ones (**3ha**-**3ja**), except **3ga**, probably because trifluoromethyl groups are more stable than other electron-absorbing groups in catalytic system. Due to the influence of steric hindrance, *ortho* substituted substrates were sluggish in the catalytic system, giving the products (**3ka**-**3ma**) ranging from 21% to 51% yields. Excellent regioselectivity was isolated because of steric reasons, when *meta*-substituted substrates (**3na** and **3oa**) were used under the conditions. Naphthalene ring and dimethoxy substituted substrates were also compatible, affording **3pa** and **3qa** in 66% and 50% yields, respectively. Aryl group substituted oxazole proceeded successfully, providing *N*-acetophenone chain products in acceptable yields (**3ra**-**3va**). Tertiary butyl group substituted oxazole also gave **3wa** in useful yield. In particular, Csp²-H still showed good reactivity, affording triphenylpyridin (**3xa**-**3za**) in modest yields, while dialkyl substituted olefin **1A** nullified reactivity.
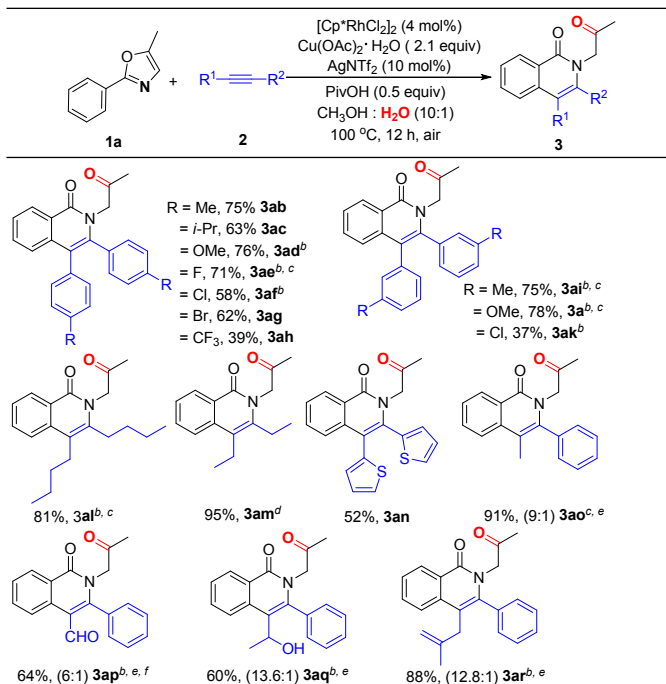
Subsequently, diverse alkynes coupling with 5-methyl-2-phenyloxazole **1a** were explored, and the results were showed in Scheme 3. Pleasingly, moderate to good yields from symmetrical diarylacetylenes (**3ab**-**3ak**) were obtained, whether the substituent was electron-rich or -poor. Dialkyl alkynes were excellent coupling partners in the reaction (**3al** and **3am**). Dithiophene alkyne could also react with **1a** to give the heteroaryl product **3an** in 52% yield. To our delight, the unsymmetrical alkynes could work smoothly with **1a** to give the products **3ao**-**3ar** in good yields together with

Scheme 2 Substrate Scope of 2-Aryloxazolinea[a]

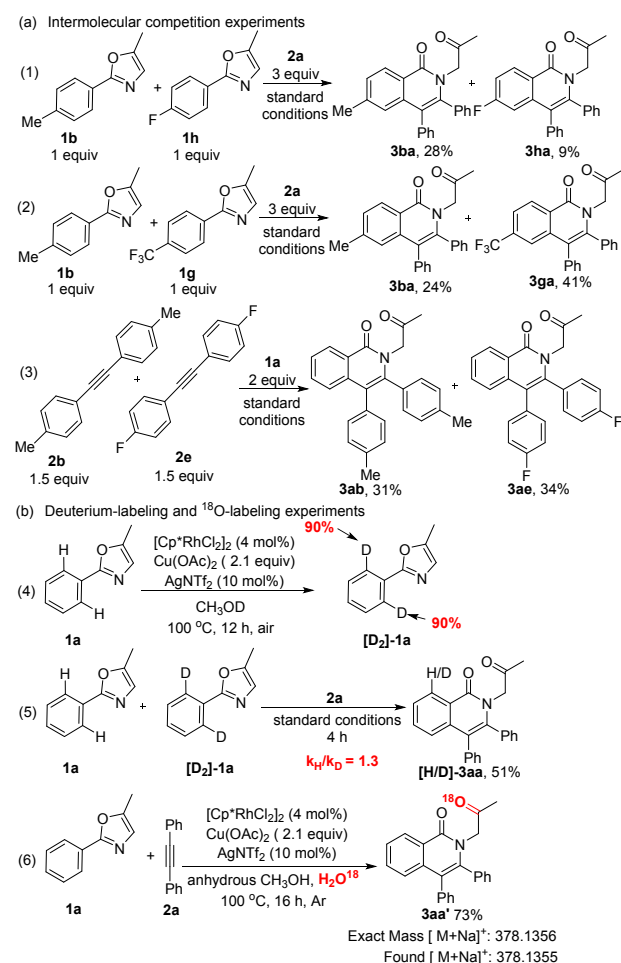[a]Reaction conditions: **1** (0.05 mmol), **2a** (1.5 equiv), [Cp*RhCl$_2$]$_2$ (4 mol%), Cu(OAc)$_2$·H$_2$O (2.1 equiv), AgNTf$_2$ (10 mol%), PivOH (0.5 equiv), CH$_3$OH (0.5 mL), H$_2$O (50 μL), 100 ˚C, 12 h, under air, isolated yield. [b]**2a** (1.2 equiv). [c]10 h. [d] (*E*)-5-methyl-2-styryloxazole was used.

Scheme 3 Substrate Scope of Alkynes[a]

[a]Reaction conditions: **1a** (0.05 mmol), **2** (1.5 equiv), [Cp*RhCl$_2$]$_2$ (4 mol%), Cu(OAc)$_2$·H$_2$O (2.1 equiv), AgNTf$_2$ (10 mol%), PivOH (0.5 equiv), CH$_3$OH (0.5 mL), 50 μL H$_2$O, 100 ℃, 12 h, under air, isolated yield. [b]**2** (1.2 equiv). [c]10 h.

2o (2.0 equiv), Cu(OAc)$_2$·H$_2$O (3.0 equiv). *e*ratio determined by ^{1}H NMR of the crude reaction mixture, only the major isomer was shown. *f*(3,3-diethoxyprop-1-yn-1-yl)benzene was used.

The intermolecular competition reaction between the F- and Me-substituent on the *para*-position of aryl ring with **2a** under standard conditions indicated that the electron-donating substituent exhibited a little bit better reaction activity in the one-pot competition reaction (Scheme 4, eq 1). While the yield of **3ga** was higher than **3ba**, which indicate that the special strong electron-poor substituent CF$_3$ exhibited better reaction activity in the one-pot competition reaction (eq 2). Furthermore, **3ab** and **3ae** were obtained in a ratio of 1:1.1, which implied that there was no obvious reactivity difference in this reaction system (eq 3). Subsequently, some deuterium-labeling experiments were carried out to further investigate the catalytic mechanism. 90% deuterium was observed at both *ortho*-positions when the reaction was performed in the absence of **2a** using CH$_3$OD as the solvent, showing that the possibility of the reaction pathway *via ortho*-C–H bond activation (eq 4). In addition, a kinetic isotope effect (KIE) was determined to be 1.3, indicating that the cleavage of the *ortho* C–H bond might be not involved in the rate-determining step (eq 5). Then the reaction was performed in the presence of H$_2$O^{18} (eq 6), which unambiguously proving the nucleophilic attack of water step and suggesting that the carbonyl oxygen on the oxopropyl chain of the isoquinolone derivative comes from the water used in the reaction conditions.


(a) Intermolecular competition experiments

(b) Deuterium-labeling and ^{18}O-labeling experiments

Scheme 4 Study on Characteristics and Mechanism

The transformations of the products were undertaken in Scheme 5. Compound **3aa** could build the product **4** in 95% yield via second C–H functionalization with methyl acrylate (eq 7). Additionally, condensation of carbonyl functionalized long chain with formamide precursor generated the key ethenamine **5** in 68% yield, which could be further subjected cyclization to give pyrazole derivative **6** (eq 8).[9] Moreover, phenylhydrazone compound **7** introducing from *N*-carbonyl chain of **3aa**, converted to novel heterocyclic compound **8** using Vilsmeier–Haack reagent (DMF-POCl$_3$) in 86% yield (eq 9).[10]
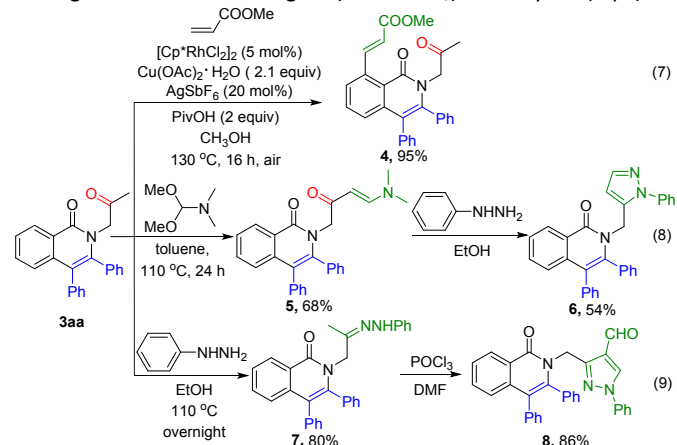
Scheme 5 Synthetic Applications

A plausible mechanism for the reaction were proposed in Scheme 6. First, a coordination of nitrogen of **1a** by rhodium and C–H bond activation occurred to afford a rhodacyclic intermediate **I**. Subsequently, coordination of diphenylacetylene **2a** to rhodacyclic intermediate **I** was followed by insertion of the C-Rh bond to give complex **III**, which underwent reductive elimination to generate oxazolinium salt **IV**. Then the reduced rhodium(I) was oxidized to regenerate rhodium(III) participating in the next catalytic cycle. Finally, H$_2$O as a nucleophile attacked oxazolinium salt **IV** and living cationic ring-opening to afford the final product **3aa**.
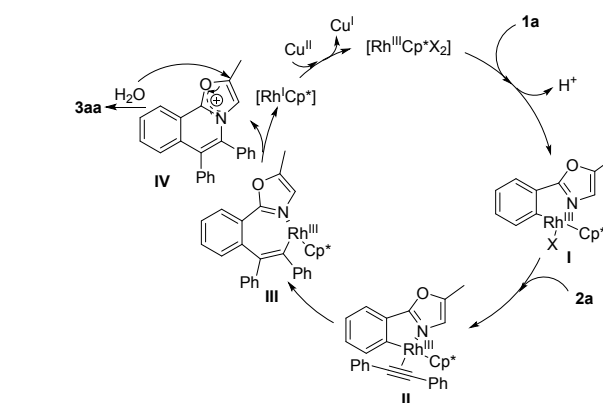
Scheme 6 Plausible Mechanism

Conclusions

In summary, we highly efficiently synthesized isoquinolone derivatives bearing functional *N*-oxopropyl chain via chelation assistance of oxazoline ring. Novel three-component cascade

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annulation involving rhodium(III)-catalyzed C–H activation/cyclization/ nucleophile attack has been well developed. In particular, oxazoles worked as the directing group as well as potential functionalized reagents. This approach showed excellent regioselective and a broad functional group tolerance. Further work is ongoing to form more complex isoquinolone derivatives.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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Rh(III)-Catalyzed Three-Component Cascade Annulation to Produce *N*-oxopropyl Chain of Isoquinolone Derivatives

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Functionalized chain
Wide substrate scope