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Visible-light promoted intramolecular carboamination of alkynes for the synthesis of oxazolidinone-fused isoquinolinones†

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An efficient method for the synthesis of isoquinolinone derivatives via photopromoted carboamination of alkynes is developed. Starting from the readily available propargyl alcohol derivatives, the polycyclic isoquinolinone derivatives could be obtained with good aryl and heterocycle tolerance. Both terminal and alkyl substituted alkynes could be employed. This protocol is operationally easy, and easily conducted on a gram-scale. A possible mechanism involving radical addition and cyclization following aromatization was proposed.

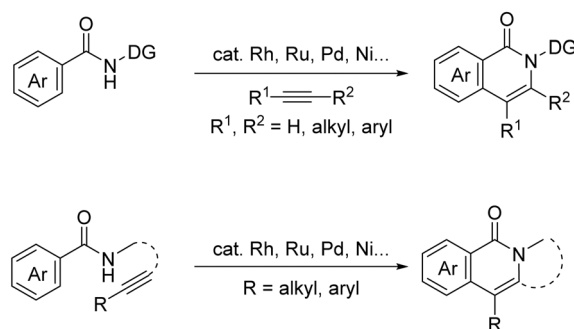
As an important nitrogen-containing heterocycle, isoquinolinone is widely found in natural products, pharmaceutical agents, and biologically active molecules.¹ Therefore, the methods of efficient construction of isoquinolinones have attracted extensive attention. In recent years, the transition metals, including rhodium,² ruthenium,³ palladium,⁴ nickel,⁵ cobalt,⁶ and so on, have been able to catalyze C–H bond activation inter-/intramolecular [4+2] cycloaddition reaction of benzamides and alkynes affording straight forward methods to construct substituted isoquinolinones (Scheme 1a).⁷ In addition, the research groups of Ackermann,^{8a,b} Lei,^{8c} and others developed a dual catalytic approach to synthesize isoquinolinones by combination of metal catalysis and electrosynthesis.⁸

As a safe, inexpensive, abundant, and nonpolluting energy source, visible light has attracted extensive attention.⁹ Recently, interests in visible-light photoredox catalysis have provided a number of approaches for C–N bond formation.¹⁰ The difunctionalization of olefins initiated by a nitrogen radical is a direct strategy to construct molecules containing a nitrogen heterocycle.¹¹ However, because of the strong bond energy of alkynes and the

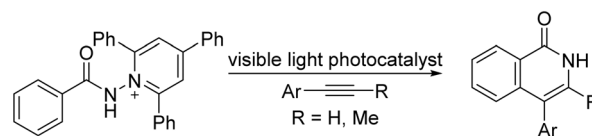
instability of vinyl radicals derived from radical additions, there are few examples of the synthesis of nitrogen heterocycles using difunctionalization of alkynes initiated by a nitrogen radical.¹² The development of methods for the difunctionalization of alkynes is still highly desirable.

In our previous work,¹³ an amidyl radical intermediate generated from hydroxylamines has been studied for visible light-catalyzed diastereodivergent intramolecular oxyamination of alkenes and intramolecular unactivated C(sp³)–H amination

(a) Transition metal-catalyzed strategies:



(b) Xia's method:



(c) This work:



Scheme 1 Synthesis of isoquinolinone derivatives via metal-catalysis and photocatalysis.

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to construct nitrogen-containing compounds. Here, the difunctionalization of alkynes was proposed. The photoinduced synthesis of isoquinolinones from *N*-amidepyridinium and alkynes was reported by Xia and co-workers in 2020 (Scheme 1b).¹⁴ However, there are still some challenges: (1) it is difficult to control the regioselectivity based on unsymmetrical alkynes. (2) There is no construction of polycyclic structures, which are widely found in nature products.¹⁵ (3) The reaction is limited to aryl alkynes, and the results using terminal alkynes and alkyl alkynes have not been discussed. Alternatively, intramolecular [4+2] reactions can avoid the problem of regioselectivity for the construction of complex polycyclic structures. Here, we report a visible-light-promoted intramolecular radical-type cycloaddition of alkynes with benzamide to construct isoquinolinone skeletons (Scheme 1c).

At the beginning of our study by using 2-methylbut-3-yn-2-yl benzoyl(benzoyloxy)carbamate **1a** as a model substrate, DIPEA as an electron sacrificial donor, and MeCN as a solvent at 50 °C under the irradiation of an 18 W cold fluorescent lamp (CFL), a variety of photocatalysts were screened (Table S1 in ESI†). The reaction using *fac*-Ir(ppy)₃ as a photocatalyst without DIPEA could occur smoothly (entry 1, Table 1). After the optimization of the solvents (entries 1–12, Table 1), the reaction using DMSO as a solvent could give **2a** in 64% yield (entry 12). Using 5 W blue LEDs at 60 °C, the reaction could deliver **2a** in 88% yield (entries 13 and 14). Based on these results, the standard reaction conditions were determined. Specifically, benzoyl(benzoyloxy)carbamate **1** with 2 mol% of Ir(ppy)₃ in DMSO (0.05 M) were stirred at 60 °C under 5 W blue LEDs for 12 h.

The scope of alkyne carboamination was investigated under the standard conditions (Scheme 2). The substrates (**1b–1e**) with electron-withdrawing and electron-donating substituents could be converted into alkyne carboamination products in



Scheme 2 Photo-promoted alkyne difunctionalization. ^a Reaction conditions: **1** (1.0 equiv.) and *fac*-Ir(ppy)₃ (2 mol%) in DMSO (0.05 M) were stirred at 60 °C under 5 W blue LEDs for 12 h. The yield of the isolated product after column chromatography on a silica gel. ^b 80 °C, 60 h.

Table 1 Optimization of the reaction conditions^a

| Entry | Solvent | 2a (%) | Recovery of 1a (%) |
|------------------|-------------------|---------------|---------------------------|
| 1 | MeCN | 20 | 70 |
| 2 | Toluene | 34 | 46 |
| 3 | PhCl | 30 | 59 |
| 4 | PhCF ₃ | 36 | 59 |
| 5 | THF | 17 | 5 |
| 6 | Dioxane | 42 | 3 |
| 7 | DME | 32 | 40 |
| 8 | DCM | 27 | 63 |
| 9 | DCE | 24 | 67 |
| 10 | DMF | 57 | — |
| 11 | DMA | 48 | — |
| 12 | DMSO | 64 | 16 |
| 13 ^b | DMSO | 83 | — |
| 14 ^{bc} | DMSO | 88 | — |

^a Reaction conditions: **1a** (1.0 equiv.) and photocatalyst (2 mol%) in solvent (0.05 M) were stirred at 50 °C under an 18 W compact fluorescent lamp (CFL) for 12 hours. ^b 5 W blue LEDs. ^c 60 °C.

70–79% yields. The substrate containing naphthalen-1-yl could give **2f** in 52% yield. Other heterocycles, such as indole (**2g**) and thiophene (**2h**), could give 62–64% yields. The dimethyl group in the substrate can be replaced by diethyl, cyclopentyl, cyclohexyl, and menthol derivatives (**2i–2m**). The reactions of the internal alkyne derivative **1n** gave carbo-amination products in 77% yield. For aryl-terminal alkynes, the reaction only gave trace product. Secondary alcohol derivatives could be transformed to **2o** and **2p** in 26% and 33% yield, respectively.

The 5 mmol-scale reaction of **1a** could be conducted to afford **2a** in 79% yield (Scheme 3a). To further investigate the mechanism of the reaction, a control experiment was conducted. When 3 equivalents of radical inhibitor TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl) were added under the standard reaction conditions, the reaction was almost inhibited (Scheme 3b). This result indicated that the reaction process might contain a radical-initiated process. Prop-2-yn-1-yl(benzoyloxy)carbamate **3** could give alkyne oxyamination product **4** in 15% NMR yield under the standard conditions (Scheme 3c). The product configuration was determined by the nuclear Overhauser effect (NOE). The hydrogen bond between the



Scheme 3 Scale-up reaction and mechanistic studies.

N-H in the oxazolidin-2-one and the benzoate might lead to this selectivity. The light-on-off experiment demonstrated that the radical chain mechanism was less likely involved (Scheme 3d).

The quantum yield of this reaction was 1 (see in ESI[†]), so the radical chain mechanism was less likely involved.

Based on the above experimental results and previously reported literature using photo-/electro-catalysis to construct azaheterocycles,^{11,16} a possible reaction mechanism was proposed (Scheme 4). Firstly, the substrate **1a** could be reduced by PC^{*} species generated by photoexcitation of the visible light photocatalyst to generate the high valence photocatalyst PC⁺ and afford the radical ion intermediate, which might undergo O–N bond cleavage to form a distonic radical ion **A** and benzoic acid anion. The intramolecular addition reaction between the nitrogen radical intermediate **A** and the alkyne gave the enyl radical intermediate **B**. Subsequently, the enyl radical intermediate **B** underwent intramolecular cyclization to give the aryl radical intermediate **C**. This intermediate could undergo



Scheme 4 Proposed mechanism.

one-electron oxidation by PC⁺ and dehydrogenation to afford **2a** and regenerate PC simultaneously.

In summary, by using the visible-light-promoted intramolecular carboamination of alkynes, we developed an alternative way to construct aryl and heterocycle polycyclic isoquinolinone derivatives. Both terminal and alkyl substituted alkynes could be tolerated. This reaction could be easily scaled up to 5 mmol. Control experiments and light-on-off experiments indicated that the reaction process might contain a radical-initiated process and the radical chain mechanism was less likely involved.

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Conflicts of interest

There are no conflicts to declare.

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