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### Introduction

Over the past few decades, the ring-opening reactions of alkylidenecyclopropanes (ACPs) have been vigorously explored, due to their high reactivity endowed by ring strain.<sup>1</sup> In general, the reaction modes of alkylidenecyclopropanes can be mainly classified into the following: transition metal-catalyzed reactions,<sup>2</sup> Lewis or Brønsted acid-catalyzed/mediated reactions,<sup>3</sup> thermal induced cyclizations<sup>4</sup> and free radical additions (Scheme 1A).<sup>5</sup> Since the 1970s, the research on the chemistry of ACPs upon transition metal catalysis has been in progress, and four different reaction patterns have been disclosed thus far (Scheme 1A, a). The distal bond (C3-C4) and proximal bond (C2-C3 or C2-C4) of ACPs can be inserted by transition metal M to undergo the subsequent reactions. On the other hand, the organo-transition metal reagent  $R-ML_n$  can be added into alkylidenecyclopropanes via anti-Markovnikov or Markovnikov addition, leading to the ring opening of cyclopropane or other transformations. In the reaction of ACPs with Lewis or Brønsted acids, the cyclopropyl ring can be activated to undergo ring opening to form two different zwitterionic intermediates, which

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Classical cyclopropylcarbinyl radical clock reactions have been widely applied to conduct mechanistic studies for probing radical processes for a long time; however, alkylidenecyclopropanes, which have a similar molecular structure to methylcyclopropanes, surprisingly have not yet attracted researcher's attention for similar ring opening radical clock processes. In recent years, photocatalytic NHPI ester activation chemistry has witnessed significant blooming developments and provided new synthetic routes for cross-coupling reactions. Herein, we wish to report a non-classical ring opening radical clock reaction using innovative NHPI esters bearing alkylidenecyclopropanes upon photoredox catalysis, providing a brand-new synthetic approach for the direct preparation of a variety of alkynyl derivatives. The potential synthetic utility of this protocol is demonstrated in the diverse transformations and facile synthesis of bioactive molecules or their derivatives and medicinal substances.

can undergo further transformations (Scheme 1A, b). As for thermally induced cyclizations, heating would facilitate the double bond of ACPs to react with a dienophile or dipole to afford spirocyclic derivatives (Scheme 1A, c).

Furthermore, the application of alkylidenecyclopropanes in radical C–C bond forming reactions has also received much

A Traditional reaction modes of alkylidenecyclopropanes

a) Transition metal-catalyzed reactions

$$\mathbb{R}^{\mathsf{R}} \mathsf{ML}_{\mathsf{n}} + \mathbb{R}^{\mathsf{ML}_{\mathsf{n}}} \xrightarrow{\mathsf{R}^{\mathsf{ML}_{\mathsf{n}}}} \left( \begin{array}{c} \mathsf{M} \\ \mathsf{M} \\ \mathsf{M} \end{array} \right) \xrightarrow{\mathsf{M}} \mathsf{M} + \overset{\mathsf{M}}{\longrightarrow} \mathsf{M} + \overset$$

b) Lewis or Brønsted acid-catalyzed reactions

$$\sum_{i=1}^{i} \frac{\operatorname{acid}}{i} + \frac{1}{2} + \frac{1}{2}$$

c) Thermal induced cyclizations

d) Free radical additions

$$\bigvee^{\mathsf{FG}} \overset{\mathsf{R}}{\longleftarrow} \overset{\mathsf{FG}}{\longleftarrow} \overset{\mathsf{R}}{\longleftarrow} \overset{\mathsf{R}}{\longrightarrow} \overset{\mathsf{R}}{\to} \overset{\mathsf{R}}{\to} \overset{\mathsf{R}}{\to} \overset{\mathsf{R}}{\to} \overset{\mathsf{R}}{\to} \overset{\mathsf{R}}{\to} \overset{\mathsf{R}}{\to$$

B Unknown reaction mode of alkylidenecyclopropanes



Scheme 1 Traditional reaction modes of alkylidenecyclopropanes and unknown reaction mode of alkylidenecyclopropanes.



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attention. The addition of radicals into alkylidenecyclopropanes could generate cyclopropyl radicals or cyclopropylcarbinyl radicals. The former can be further transformed to achieve the difunctionalization of alkenes, and the latter can undergo  $\beta$ -scission in the cyclopropyl ring to afford the homoallyl radical known as a *classical radical clock* (Scheme 1A, d). These synthetic methods provide an efficient access to the rapid generation of molecular complexity. However, with increasing exploration on research means and technologies, nearly no breakthrough on the chemical transformation of alkylidenecyclopropanes has been made for a long time. More efforts to develop new reaction modes of alkylidenecyclopropanes are highly desired in current research.

The ring opening of the cyclopropylcarbinyl (CPC) radical to the 3-butenyl radical is a fast radical rearrangement that holds a position of distinction in mechanistic studies involving "radical clocks" and "mechanistic probes". Numerous research studies have adopted potential precursors of this radical or its analogues in attempts to implicate radical intermediates in a reaction pathway by the detection of the products from the radical ring opening process.6 At the same time, it is found that this methodology and the final detected products bearing alkenyl groups can be applied to diverse organic synthesis.<sup>7</sup> Since alkylidenecyclopropanes (ACPs) have a similar molecular structure to methylcyclopropane and the release of ring strain can provide a potent thermodynamic driving force, we designed an unknown radical reaction mode, in which the  $C(sp^2)$ -X bond of alkylidenecyclopropane can be selectively cleaved to afford the alkylidenecyclopropane radical (Scheme 1B). This radical can further undergo the same ring opening rearrangement process to generate the corresponding radical species containing an alkynyl moiety and subsequently play a vital role in mechanistic studies and diverse organic synthesis. Thus, we



**Scheme 2** DFT calculations of the ACP radical clock vs. classical CPC ring opening radical clock process. Alkylidenecyclopropanes and this work.

conducted preliminary density functional theory (DFT) calculations to predict whether the envisaged process is kinetically feasible (Scheme 2A) (see the ESI† for the details). The calculation results showed that the energy barrier for the ringopening process of the alkylidenecyclopropane radical  $(\Delta G_1^{\ddagger} = 5.4 \text{ kcal mol}^{-1})$  is lower than that for the ring-opening process of the CPC radical  $(\Delta G_2^{\ddagger} = 7.1 \text{ kcal mol}^{-1})$ , indicating that the ring-opening process of the alkylidenecyclopropane radical is kinetically favorable. In addition, the ring-opening process of the alkylidenecyclopropane radical is an exergonic process  $(\Delta G_1 = -13.4 \text{ kcal mol}^{-1})$ , suggesting that this is a thermodynamically favorable process. Based on these calculation results, developing reactions involving the ring opening process of the alkylidenecyclopropane radical is feasible.

Recently, NHPI (N-hydroxyphthalimide) esters, as stable and readily accessible compounds, have emerged as a novel and efficient synthon to undergo a number of interesting and practical transformations.8 Due to their redox reactivity, NHPI esters can serve as a radical precursor to accept an electron to trigger a consecutive domino of events that release phthalimidyl anions, CO2 and the corresponding radicals applied for a variety of reactions.9 Photoredox catalysis induced by visible light, owing to the advantages of ease of handling, application safety and natural abundance, is utilized as one of the accesses fulfilling the described process.10 Visible-light induced carboncarbon bond-forming reactions involving NHPI esters were identified as an ideal strategy to construct various interesting compounds. Such reactions can be categorized as follows: (i)  $C(sp^3)-C(sp^3)$  bond formation; (ii)  $C(sp^3)-C(sp^2)$  bond formation; (iii)  $C(sp^3)-C(sp)$  bond formation; (iv)  $C(sp^3)-B$  or Se/S bond formation.8 However, in these reactions, NHPI esters directly release the C(sp<sup>3</sup>) radicals applied for the bond formation. No examples of releasing the highly reactive vinyl radicals as C(sp<sup>2</sup>) radicals have been reported to date. With regard to this aspect, we skillfully take advantage of the high reactivity of  $C(sp^2)$  radicals to fulfill our design. Building on the widely investigated field of classical ring opening radical clock reactions and the successes of photocatalytic NHPI esters in decarboxylative activity chemistry, we are inspired by the possibility of an innovative non-classical ring opening radical clock reaction to provide both terminal and internal alkynes (Scheme 2B). Notably, it is convinced that different levels of saturation of small molecules can cause a broad spectrum of transformations, especially applicable in the areas of pharmaceutical and agrochemical production. Therefore, the transformations of alkynes into alkenes and alkanes fulfilled by our envisaged method would provide a practical synthetic route (Scheme 2B).

### **Results and discussion**

#### **Experimental investigations**

We began our investigation with easily available NHPI ester **1b** (0.075 mmol, 1.5 equiv.) and phenyl vinyl ketone **2a** (0.05 mmol, 1.0 equiv.) as the model substrates,  $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$  as the photosensitizer, and Hantzsch ester and  ${}^i\text{Pr}_2\text{NEt}$  as additives in dichloromethane (0.75 mL) at room temperature upon the

 Table 1
 Optimization of the reaction conditions<sup>a</sup>

DCE instead of DCM

12 h instead of 3 h

1.0 equiv. 1b



<sup>*a*</sup> Reaction conditions: **1b** (0.075 mmol, 1.5 equiv.), **2a** (0.05 mmol, 1.0 equiv.), Hantzsch ester (HEH) (0.075 mmol, 1.5 equiv.), <sup>*i*</sup>Pr<sub>2</sub>NEt (0.11 mmol, 2.2 equiv.),  $Ru(bpy)_3(PF_6)_2$  (2 mol%), DCM (0.75 mL), rt, 3 h, Ar, and 15 W blue LED. All the reactions were carried out on a 0.05 mmol scale in solvent (0.75 mL) at rt for 3 h unless otherwise specified. <sup>*b*</sup> Isolated yield.

57

66

84

irradiation of a 15 W blue LED for 3 h, giving the desired alkyne 3ba in 87% yield (Table 1, entry 1). The optimization of reaction conditions revealed that the photosensitizer, light and additive were indispensable in this reaction (Table 1, entries 2-4). Other metal-polypyridyl complex photosensitizers were also screened, and the results showed that  $Ru(bpz)_3(PF_6)_2$  was less effective as compared with  $Ru(bpy)_3(PF_6)_2$ , but the use of fac-Ir(ppy)<sub>3</sub> did not afford the desired product (Table 1, entries 5-6). Instead of iPr2NEt, other additives such as DBU and DABCO were tested, which resulted in decreased yields (Table 1, entries 7-8). We further investigated other solvents, such as THF and DCE, providing 3ba in 71% and 57% yields (Table 1, entries 9-10), respectively, identifying DCM as the most suitable solvent. Using 1.0 equiv. of 1b or prolonging the reaction time to 12 h could not effectively improve the yield of 3ba (Table 1, entries 11-12).

With the optimal reaction conditions in hand, we attempted to investigate the substrate scope of various NHPI esters bearing alkylidenecyclopropanes and the results are shown in Table 2. When the substituent R was a hydrogen atom, the reaction could proceed smoothly to provide the terminal alkyne **3aa** in 75% yield. For substrates **1c** and **1d**, ethyl group and propyl group substituted NHPI esters were compatible in this reaction, generating the corresponding internal alkynes **3ca** and **3da** in 89% and 92% yields, respectively. When the R group was changed into the benzyl group bearing different substituents, such as 4-H, 4-OMe, 4-Cl and 3,5-Br (**1e-1h**), the desired products **3ea-3ha** were obtained in 89–93% yields. Moreover, we attempted to introduce featured substituents, such as allyl, propargyl and cinnamyl groups, into the substrates, and found that the reactions also proceeded smoothly to afford the 
 Table
 2
 Substrate
 scope
 of
 NHPI
 esters
 bearing

 alkylidenecyclopropanes<sup>a</sup>



<sup>*a*</sup> Reaction conditions: **1** (0.3 mmol, 1.5 equiv.), **2a** (0.2 mmol, 1.0 equiv.), Hantzsch ester (HEH) (0.3 mmol, 1.5 equiv.), <sup>*i*</sup>Pr<sub>2</sub>NEt (0.44 mmol, 2.2 equiv.), Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (2 mol%), DCM (3 mL), rt, 3 h, Ar, and 15 W blue LED. Yields were determined from isolated products.

corresponding internal alkynes **3ia**, **3ja** and **3ka** in good yields ranging from 80–94%. Notably, the substrate **1la** having an aromatic heterocycle was also suitable for this reaction, affording the desired product **3la** in 85% yield.

Next, we focused on the generality of this protocol regarding  $\alpha$ , $\beta$ -unsaturated carbonyl compounds. As outlined in Table 3, most of the reactions proceeded smoothly under well-established conditions to generate the expected products in moderate to good yields. First, we examined aryl substituted  $\alpha$ , $\beta$ -unsaturated ketones (2b-2i). The mild conditions enabled the tolerance to important functional groups, such as halide, cyano, ester, alkoxy and so on, affording the corresponding alkynes 3bb-3bi, in the yields ranging from 75% to 92%. Moreover, alkyl substituted  $\alpha,\beta$ -unsaturated ketones (2j-2n) were also compatible in this reaction, affording the desired alkynes 3bj-3bn, albeit with moderate yields (36-43%). For the  $\alpha,\beta$ -unsaturated amide 20, the reaction could also proceed smoothly to produce the desired product 3bo in 33% yield. When the  $\alpha$  position of  $\alpha$ , $\beta$ -unsaturated ketones was substituted by ester and phenyl groups, the reaction occurred smoothly to give the expected products 3bp and 3bq in 87% and 81% yields, respectively. For conjugated diene substrate 2r, in which the  $\delta$  position was substituted by a methyl group, the corresponding product 3br was obtained in 92% yield, probably due to the radical addition taking place at the  $\delta$  position and the relative stability of key radical intermediates. It is well known that aromatic heterocycles play an important role in medicinal chemistry; therefore,  $\alpha$ , $\beta$ -unsaturated ketones bearing furyl, thienyl, pyrrole, indolyl, benzofuryl and imidazolyl groups were applied to this reaction to generate alkynes having aromatic heterocycles. To our delight, these reactions also proceeded very well to provide the corresponding alkynes 3bs-3bx in moderate

10

11

12

Table 3 Substrate scope of  $\alpha,\beta$ -unsaturated ketones<sup>a</sup>



<sup>*a*</sup> Reaction conditions: **1b** (0.3 mmol, 1.5 equiv.), **2** (0.2 mmol, 1.0 equiv.), Hantzsch ester (HEH) (0.3 mmol, 1.5 equiv.), <sup>*i*</sup>Pr<sub>2</sub>NEt (0.44 mmol, 2.2 equiv.), Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (2 mol%), DCM (3 mL), rt, 3 h, Ar, and 15 W blue LED. Yields were determined from isolated products.

to good yields. For cyclic exo-methylene ketones 2y and 2z, the desired products 3by and 3bz were obtained in both 78% yields. Notably, when the alkenyl sulfone 2aa was utilized as the substrate, the desulfonylative cross-coupling reaction occurred, resulting in the formation of product 3baa in 97% yield. Finally, we illustrated the utility of this novel non-classical radical clock reaction using the core structures of several bioactive molecules, such as geraniol (2ab), estrone (2ad) and vanillin (2ae), and a mesogenic compound (2ac). All the desired alkynylated products were obtained in good yields (78-88%), irrespective of existing complex molecular structures. In addition, acrylesters, acrylamides, exo-cyclic lactone and simple crotonyl or cinnamoyl substrates were also attempted to use as the radical acceptors to proceed this reaction; however, no desired products were obtained (for unsuccessful examples, see Page S3 in the ESI<sup>†</sup>). Unfortunately, we did not succeed in obtaining an aryl-substituted substrate after several attempts.

#### Synthetic applications

To demonstrate the preparative utility of our methodology, product transformations were conducted (Scheme 3A). The

resulting alkynes can act as versatile forging blocks for diversityoriented synthesis. A rhodium-catalyzed hydrosilylation reaction and gold-catalyzed cyclization of 3baf were conducted to afford the corresponding products, silvlated compound 4 and cyclized product 5 in 87% and 90% yields, respectively. The Sonogashira cross-coupling reaction of 3baf with vinyl bromide also proceeded smoothly, giving the enyne 6 in 99% yield, which could be utilized for the construction of valuable building blocks, such as pyrroles. The click reaction of 3baf with tosyl azide via copper catalysis afforded the [3 + 2] cycloaddition product 7 in 95% yield, demonstrating the potential practicability of the resulting alkynes in medicinal chemistry. Hydrogenation or partial hydrogenation of the obtained alkyne 3baf effectively generated the corresponding alkane 8 and alkene 9. As for the immediate potential in biochemistry and medicinal chemistry, we have easily synthesized five different synthetic precursors 10, 11, 12, 15 and 16 on a gram scale through this methodology (Scheme 3B). Compound 10 was synthesized from 3ba through a two-step reduction procedure in 65% yield (0.91 g), which was regarded as the key intermediate for the synthesis of Fingolimod, mainly available for the treatment of Multiple



Scheme 3 Synthetic applications of the non-classical ring opening radical clock reaction. (A) Product transformations of **3baf**. (a) NaBH<sub>4</sub>, MeOH,  $0 \degree C - rt$ ; DMAP, imidazole, TBSCl, DCM,  $0 \degree C - rt$ , and 12 h; Rh(COD)<sub>2</sub>BF<sub>4</sub>, PPh<sub>3</sub>, Et<sub>3</sub>SiH, acetone, rt, and 20 h. (b) AuCl<sub>3</sub>, AgOTf, toluene, rt, and 8 h. (c) Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, Cul, Et<sub>3</sub>N, THF, rt, 12 h. (d) CuTc, toluene, rt, and 8 h. (e) Pd/C, MeOH, H<sub>2</sub>, rt, and 4 h. (f) Lindlar catalyst, MeOH, H<sub>2</sub>, rt, and 8 h. (b) Synthesis of drugs applying our methodology. (g) Pd/C, MeOH, H<sub>2</sub>, rt, and 4 h; NaBH<sub>4</sub>, AlCl<sub>3</sub>, THF, and  $0 \degree C - 65 \degree C$ . (h) ethylene glycol, *p*-TsOH, toluene, and 110 °C; *n*-BuLi, propyl chloroformate, THF, and  $-78 \degree C$ ; Pd/C, MeOH, H<sub>2</sub>, rt, and overnight; LiOH, THF, H<sub>2</sub>O, and rt; DMAP, DCC, Et<sub>3</sub>N, DCM, DMF, and  $0 \degree C - rt$ ; 6-(1-aminoethyl)pyridazin-3(2H)-one **S6**, POCl<sub>3</sub>, DCE, reflux, and 3 h. (i) BH<sub>3</sub>·THF, cyclohexene, THF,  $0 \degree C$ , and 2 h; NaBO<sub>3</sub>·4H<sub>2</sub>O, H<sub>2</sub>O, and 2 h. (j) Pd/C, MeOH, H<sub>2</sub>, rt, and 4 h; TiCl<sub>4</sub>, (CH<sub>3</sub>)<sub>2</sub>Zn, DCM,  $-50 \degree C$ , and 2 h; BBr<sub>3</sub>, DCM,  $0 \degree C$ , and 12 h.

Sclerosis (MS).<sup>11</sup> Starting from **3aa**, the two vital precursors **11** and **12** were synthesized in 46% (0.56 g) and 43% (0.49 g) yields, respectively. Precursors **11** and **12** could be further transformed into substituted imidazo [1,5-*b*] pyridazine **13** and its analogue **14**, which are proved to be exceptionally active against the reverse transcriptase of HIV-1, in 64% (0.68 g) yield and 62% (0.64 g) yield, respectively<sup>12</sup> (for details on the formal synthesis or total synthesis of bioactive molecules, see Pages S13 and S14 in the ESI†). Since 1977, Tramadol has been used as a painkiller

by serving as a weak  $\mu$ -opioid receptor agonist;<sup>13</sup> therefore, we synthesized the vital precursor **15** through a one-pot selective hydroboration and oxidation of alkyne **3baf** in 59% yield (0.69 g). Furthermore, on the basis of Razdan's protocol,<sup>14</sup> we prepared the building block **16** in 79% yield (0.63 g) through the reduction and demethylation of alkyne **3baf**, which could be applied to assemble the novel tetrahydrocannabinol/ananda-mide (THC/AEA) hybrid ligand. This modified ligand could significantly improve its binding affinity to the CB1 receptor in



Fia. 1



Scheme 4 Mechanistic investigations

biological research. In summary, these diverse transformations exhibit the strong capability of our non-classical radical clock reaction coupled with various subsequent manipulations for

generating terminal or internal alkynes and their derivatives, which would be synthetically very useful along with excellent functional group tolerance.

#### Mechanistic studies

To gain more insights into the reaction mechanism, the fluorescence quenching experiments of  $Ru(bpy)_3(PF_6)_2$  with **1b** were performed and its Stern-Volmer analysis is depicted in Fig. 1, indicating that 1b could not be photo-excited by the photocatalyst effectively. In addition, we carried out several control experiments (Scheme 4). First, when TEMPO as a radical scavenger was subjected to our model reaction, the non-classical radical clock reaction was inhibited completely and a new product 17 generated from the resultant alkyl radical trapped by TEMPO was obtained in 49% yield (Scheme 4, a). Subsequently, a reaction using deuterium-labeled Hantzsch ester  $d_3$ -2af was conducted, and the deuterium atom was incorporated exclusively at the  $\alpha$  position of alkyne  $d_1$ -3ba, showing that SET and HAT processes were both involved in the last step<sup>15</sup> (Scheme 4, b). Substrate 1a ( $E_{1/2} = -1.18$  V vs. SCE, see Page S18 in the ESI<sup>†</sup>) and radical clock substrate  $\mathbf{1m} (E_{1/2} = -1.24 \text{ V} \text{ vs. SCE}$ , see Page S18 in the ESI<sup>†</sup>) were mixed together to undergo the reaction, affording the corresponding products 3aa and 18 in 48% and 16% yield, respectively (Scheme 4, c). This reaction outcome basically agrees with the prediction of DFT calculations, which indicate that the ring-opening process of the alkylidenecyclopropane radical is kinetically more favorable.

On the basis of generally accepted mechanisms for NHPI ester's decarboxylative activity,<sup>8,15</sup> a plausible catalytic cycle is proposed in Scheme 5. The initial excitation of Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> produces the excited state  $Ru(bpy)_3(PF_6)_2^*$ , which undergoes SET with  ${}^{i}Pr_{2}NEt$  or Hantzsch ester to generate the Ru(1), amine radical cation or Hantzsch ester radical cation. The N-(acyloxy) phthalimide **1** receives an electron from  $\operatorname{Ru}(I)$  ( $E_{1/2} = -1.33$  V vs.



Scheme 5 Proposed reaction mechanisms.

SCE), to transiently form radical anionic intermediate A. Next, an entropically favored decarboxylation can proceed via two plausible pathways to generate the desired radical intermediate D: (i) rapid homolytic fragmentation and decarboxylation from A to release the phthalimide anion, CO<sub>2</sub> and the radical intermediate **B**. As a central design element, we postulated that **B** would undergo the ring-opening process to produce the nucleophilic carbon-centered radical bearing alkynyl D, or (ii) homolytic fragmentation of the N-O bond to furnish intermediate C, which can further undergo decarboxylation and radical rearrangement to D. The addition of this nucleophilic radical to a conjugate acceptor 2 generates a stabilized radical E, which then undergoes SET and HAT processes to successfully form the functionalized alkyne 3. Notably, the radical intermediate E was not engaged in a fast 5-exo-dig-cyclization to afford the cyclized product; therefore, we assumed that the cyclization is reversible and reduction only occurred on the ring-opened isomer.

### Conclusions

In conclusion, we have successfully established a robust methodology to access alkynes *via* the versatile and practical non-classical ring-opening radical clock reactions of NHPI esters bearing ACPs inspired by conventional photocatalytic NHPI ester's activation and classical radical clock reactions. Compared with the traditional reaction modes of alkylidenecyclopropanes, this method is totally new and its prospect will be prosperous for the rapid generation of molecular complexity in organic synthesis. Most importantly, since the carboncarbon triple bond can serve as a versatile functional group for diverse organic synthesis, the resulting alkynes can be transformed into a variety of bioactive molecules and natural products. Further studies for discovering detailed mechanisms and novel reaction types to synthesize other useful compounds are underway.

### Author contributions

X.-Y. Z., C.N. and B. M. contributed to the experimental work; Y. W. contributed to the computational work. X.-Y. Z., Y. W. and M. S. contributed to ideation and writing of the paper.

## Conflicts of interest

There are no conflicts to declare.

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