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Palladium-catalyzed carbene/alkyne metathesis with enynone as carbene precursor: synthesis of fused polyheterocycles

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An unprecedented palladium-catalyzed novel carbene/alkyne metathesis cascade reaction of alkyne-tethered enynones is described. This reaction affords fused polyheterocycles in moderate to good yields. The transformation begins with Pd-catalyzed 5-*exo-dig* cyclization of enynone to form the donor/donor metal carbene; which then undergoes metathesis with alkyne followed by electrophilic aromatic substitution.

Carbene mediated cascade reaction is a powerful tool for building new bonds.¹ In particular, transformations that involve carbene/alkyne metathesis (CAM) have shown high efficiency in bond formations, which leads to direct construction of complex molecular frameworks.²⁻⁶ The pioneering work in this area reported by Padwa involves alkynl-tethered diazo compounds, with silver^{2a} and rhodium complex^{2b,2c} as catalyst. Later, various metal catalysts, including nickel, 3a,3b ruthenium, $^{3c-3f}$ and copper, 4a,4b were disclosed to promote the corresponding cascade transformations. On the other hand, the using of other readily available and relative stable substrates as the initiator, such as, triazole or hydrazone, instead of diazo compound, is developed by Gevorgyan,⁵ May,^{6a} Pla-Quintanaa,^{6b-6c} Zhang and Bruin^{6d} independently (Scheme 1a). Despite the advances of these cascade reactions involving CAM, the substrate scope is still limited, and the development of practicable carbene precursor with compatible catalytic system would certainly be in demand.

As a reliable and useful non-diazo carbenoid precursor, enynone has been applied in a wide range of carbene reactions.⁷ And the key step in these transformations involved a transition metal catalyzed *5-exo-dig* cyclization to generate the donor/donor carbene intermediate (Scheme 1b, **A**).^{8a} Once formed in situ, the metal carbene intermediate can undergo



Scheme 1 Types of metal carbene cascade reactions.

various subsequent reactions such as C-H and X-H insertion,⁸ cycloaddition/annulation,⁹ coupling reactions,¹⁰ and others,¹¹ to provide the corresponding furan derivatives. Inspired by these works and as the continuation of our interest in polycyclic structure construction based on CAM reaction,⁴ herein, we describe a novel carbene/alkyne metathesis cascade reaction with enynone as the carbene precursor. In comparison with the reported Pd-catalyzed general coupling reactions of enynone *via* migratory insertion process by Wang (Scheme 1b),^{10a-10c} this work is the first example of readily available palladium complex catalzyed carbene/alkyne metathesis reaction (Scheme 1c). The 3, 4-disubstituted 2*H*-chromene product generated by this cascade reaction is prevalent in natural products and bioactive molecules.¹²

Alkyne-tethered enynone **1a** was first prepared according to known procedure (see Supporting Information for details),

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Table 1	. Optimization of th	e reaction	conditions ^a
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Me Me	Me Me
0 0 <u>Cat.</u> DCE, rt., 4h	Ph
1a `Ph	2a

Entry	Catalyst (x mol%)	Yield ^b (%)
1	Rh ₂ (OAc) ₄ (1.0 mol%)	20
2	[Rh(COD)OH] ₂ (2.0 mol%)	30
3	Cu(OTf) ₂ (5.0 mol%)	18
4	PPh ₃ AuCl (5.0 mol%)	nr ^c
5	PPh ₃ AuCl (5.0 mol%) +	-
	AgSbF ₆ (5.0 mol%)	<5
6	AgSbF ₆ (5.0 mol%)	<5
7	PPh ₃ AuCl (5.0 mol%) + AgBF ₄	<u>ر ج</u>
	(5.0 mol%)	<5
8	AgBF ₄ (5.0 mol%)	<5
9	ZnCl ₂ (20.0 mol%)	25
10	Pd(OAc) ₂ (5.0 mol%)	37
11	Pd(PPh ₃) ₄ (5.0 mol%)	26
12	Pd ₂ (dba) ₃ (5.0 mol%)	62
13 ^{<i>d</i>}	$Pd_{2}(dba)_{3}(5.0 \text{ mol}\%)$	57
14 ^e	Pd ₂ (dba) ₃ (5.0 mol%)	70

^{*a*} The reaction was conducted with **1a** (0.2 mmol), catalyst (x mol%) in DCE (3.0 mL) at 25 °C under Ar. ^{*b*} Isolated yields. ^{*c*} Most of **1a** was recovered. ^{*d*} The reaction was conducted at 40 °C. ^{*e*} 4 Å Molecular sieve (30 mg) was added as additive. DCE = 1,2-dichloroethane, nr = no reaction.

then utilized as model substrate to probe the cascade reaction: it was mixed with various catalyst (with 1.0-5.0 mol%), including Rh, Au, Zn and Pd (Table 1, entries 1-12) in 1,2dichloroehtane (DCE). Except for PPh₃AuCl, which was turned out no reactivity at all, and majority of the material 1a was recovered (entry 4). Most of the tested catalysts could promote the conversion of 1a, although low selectivities were observed in some cases and the rest of material was decomposed into a complex mixture (entries 5-8). Lower reactivity was found with Pd(PPh₃)₄ (entry 11) compared to Pd(II)-catalyst (entries 10). Using Pd₂(dba)₃ as the catalyst led to a significant improvement of the reaction and 2a was obtained in 62% isolated yield, which may due to it relatively low Lewis acidity (or π -electrophilicity) and weakly coordination ligands of this catalyst (entry 12). Elevating the reaction temperature did not provide better result (entry 13) while introducing 4Å molecular sieve as additive increased the yield to 70% (entry 14).

With the optimized reaction conditions in hand, we went on to explore substrate scope of this reaction, and the results are listed in Table 2. The influence of the aryl group, which is adjacent to the alkyne moiety, was explored first (2a-I). Regardless of the position or electronic property of the



^a Reactions are carried out on a 0.2 mmol scale with Pd₂(dba)₃ (5.0 mol%) 4 Å molecular service (30 mg) in DCE (3.0 mL) at room temperature under Ar atmosphere, and the yields are given in isolated yields. ^b The product was decomposed into a complex mixture during the isolation on column chromatography. ^c Catalyzed by Rh₂(OAc)₄ (2.0 mol%) and running for 12 h.

substitutions on the aryl ring, all the substrates gave the products in moderate to good yields (2a-2k). Interestingly, two diastereoisomers of the product 2l were obtained, which arises from restriction of rotation between the two aromatic planes.¹³ Meanwhile, the aryl-substituted enynones proceeded equally well, and leading to the desired products 2m-p in 60-72% yields. For material 1r, which has a "N" linker instead of "O", although the reaction is quite clean according to the proton NMR of the crude reaction mixture (see Figure S1 in SI), however, the product was decomposed into a complex mixture during the isolation on column chromatography. When 1s, which has a methylene linker, was applied, although no reaction occurred in the presence of either Pd(OAc)₂ or $Pd_2(dba)_3$, we did observe the product when the reaction was catalyzed by Rh₂(OAc)₄, and corresponding product 2s was obtaiend in 55% yields after 12 hours. In addition, these reaction conditions were also successfully applied to the unsymmetrical enynone Z-1q, and mono-carbonyl substrate 1t, which gave 2q and 2t in 62% and 53% yields, respectively. The methyl-substituted alkyne (1u) and terminal alkyne (1v) could not provide the corresponding product and the materials were decomposed into a complex mixture slowly, which may mainly due to the lower stability of the in situ generated carbenoid

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Scheme 2 Scale up and [4+2] cycloaddition.



Scheme 3 Control experiments.

intermediate compared to the corresponding aryl stabilized ones.

To demonstrate the scalability and the practicality of the current method, a gram scale reaction was carried out, and 1.044 g of **2a** was isolated in 61% yield (Scheme 2a). [4+2] Cycloadditions applying the products from the cascade reaction were also investigated (Scheme 2b). Either terminal or internal electron deficient alkynes performed well under thermal conditions, and generated the corresponding addition products with moderate to good yields (**4a**–**d**). The structure of product **4d** was unambiguously determined by single-crystal X-ray diffraction analysis,¹⁴ and the corresponding structure of **2** could be deduced.

To gain insight into the mechanistic details, control experiments were carried out as shown in scheme 3. Firstly, the enyone part in the material was removed, and no reaction occurred with **5** under the standard conditions (Scheme 3a), which means the transformation was initiated with the enynone species. To demonstrate that the donor/donor carbenoid, which was generated from enynone *in situ*, was involved in this transformation, two typical carbene reactions, including C-H insertion and β -H elimination, were designed and performed (Scheme 3b and 3c). Two corresponding products **7** and **9** were obtained in 70% and 55% yields, respectively. These results further confirmed the existing of carbenoid intermediate **B** (Scheme 1c) in this reaction. Based on these information and previous works, ^{2-4,15} we reasoned that the



reaction was initiated by a palladium-catalyzed 5-exo-dig cyclization of enynone to form the donor/donor carbenoid intermediate **B**, followed by carbene/alkyne metathesis (**CAM**), and terminated with electrophilic aromatic substitution (**EAS**) on the newly formed furan ring with the in situ generated carbenoid intermediate **C** (Scheme 4). However, further studies are needed to unambiguously establish the reaction

In summary, we have developed a palladium-catalyzed novel carbene/alkyne metathesis (CAM) cascade reaction of alkynetethered enynone, which provides a straightforward approach for the synthesis of furan fused polyheterocycles in moderate to high yields. In addition, this reaction not only represents the first example of CAM reaction promoted by readily available palladium complex, but also is the only example of the use of enynone as carbene precursor in intramolecular carbene/alkyne metathesis cascade transformation. Potential applications of this strategy for the polycyclic compounds synthesis are under exploration in our laboratory.

Conflicts of interest

transformation.

There are no conflicts to declare.

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