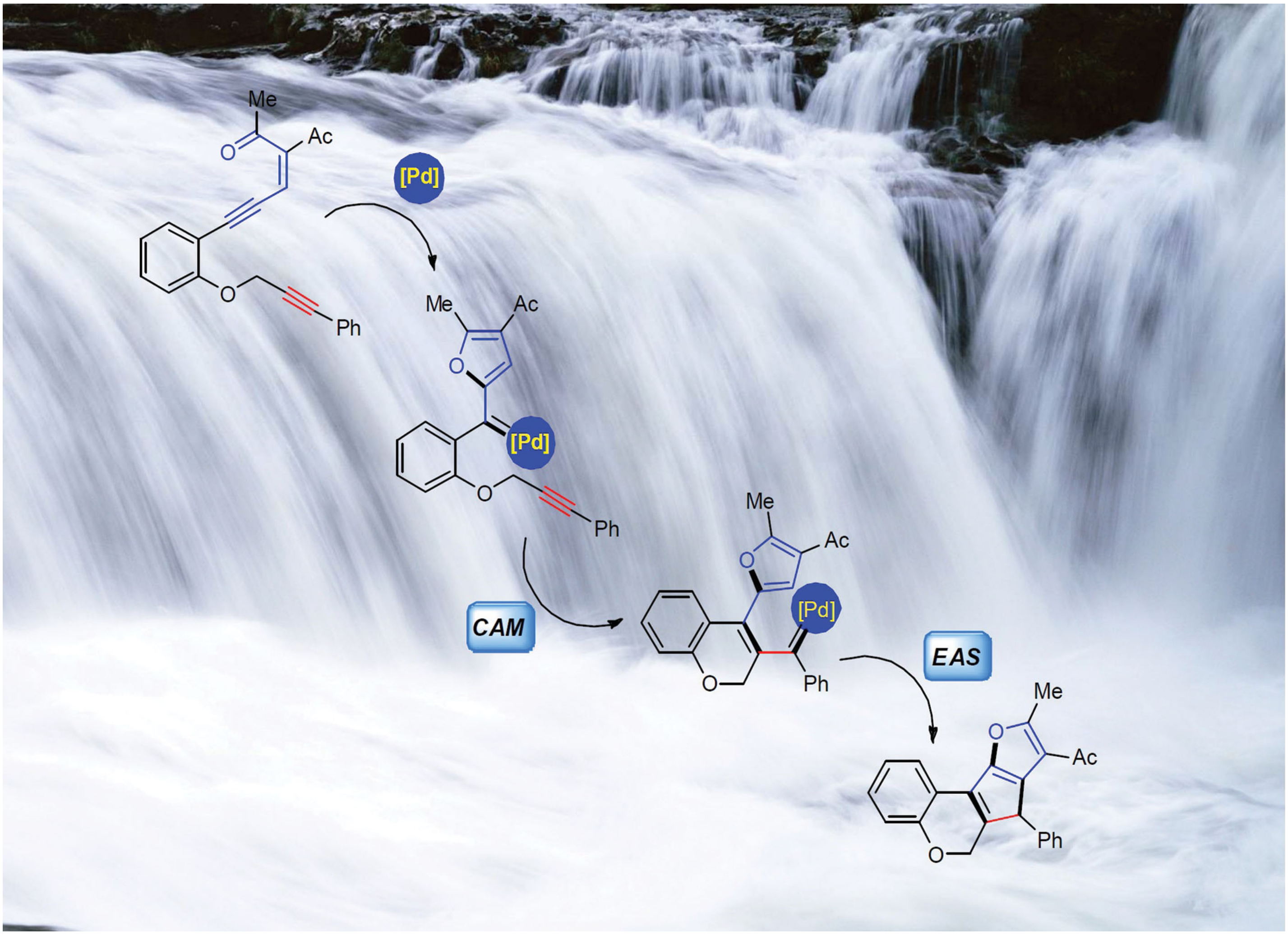

Showcasing the carbene/alkyne metathesis (CAM) cascade research from Prof. Xinfang Xu and co-workers, Department of Chemistry, Soochow University, Suzhou, China

Palladium-catalyzed carbene/alkyne metathesis with enynones as carbene precursors: synthesis of fused polyheterocycles

A palladium-catalyzed novel carbene/alkyne metathesis (CAM) cascade reaction is described, which provides a straightforward approach for the synthesis of polyheterocycles in moderate to high yields. This is the first example of CAM reaction that is promoted by readily available palladium(0) complex with enynone as carbene precursor. Potential advances could be expected due to the highly bond formation efficiency of this cascade strategy.

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Cite this: *Chem. Commun.*, 2018, **54**, 350

Received 25th October 2017,
Accepted 4th December 2017

DOI: 10.1039/c7cc08221e

rsc.li/chemcomm

Palladium-catalyzed carbene/alkyne metathesis with enynones as carbene precursors: synthesis of fused polyheterocycles†

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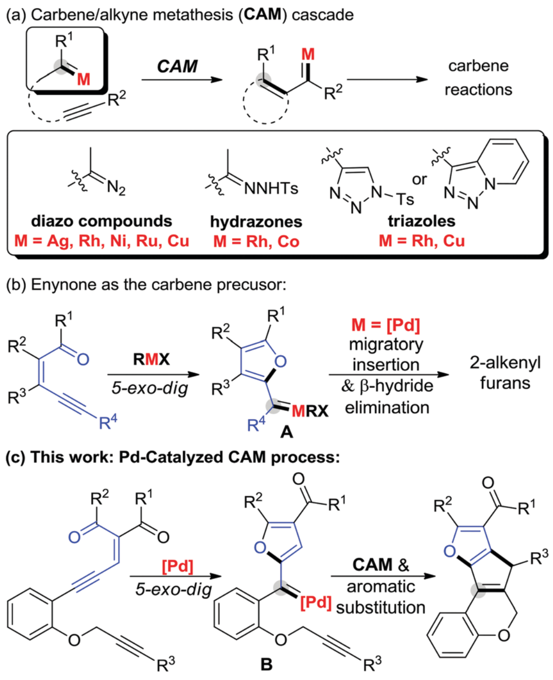
An unprecedented palladium-catalyzed novel carbene/alkyne metathesis cascade reaction of alkyne-tethered enynones is described. This reaction affords fused polyheterocycles in moderate to good yields. The transformation begins with Pd-catalyzed 5-*exo*-dig cyclization of the enynone to form the donor/donor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

A 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 alkyne-tethered diazo compounds, with silver[2a] and rhodium complexes[2b,c] as catalysts. Later, various metal catalysts, including nickel,[3a,b] ruthenium,[3c–f] and copper,[4a,b] were disclosed to promote the corresponding cascade transformations. On the other hand, the use of other readily available and relatively stable substrates as the initiator, such as, triazole or hydrazone, instead of diazo compounds, was developed by Gevorgyan,[5] May,[6a] Pla-Quintanaa,[6b,c] and Zhang and Bruin[6d] independently (Scheme 1a). Despite the advances in these cascade reactions involving CAM, the substrate scope is still limited, and the development of a practicable carbene precursor with a compatible catalytic system would certainly be in demand.

As a reliable and useful non-diazo carbenoid precursor, enynones have been applied in a wide range of carbene reactions.[7] And the key step in these transformations is 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 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 the CAM reaction,[4] herein, we describe a novel carbene/alkyne metathesis cascade reaction with enynones as the carbene precursor. In comparison with the Pd-catalyzed general coupling reactions of enynones *via* a migratory insertion process reported by Wang (Scheme 1b),[10a–c] this work shows the first example of a readily available palladium complex catalyzed carbene/alkyne metathesis reaction (Scheme 1c). The 3,4-disubstituted 2*H*-chromene product generated *via* this cascade reaction is prevalent in natural products and bioactive molecules.[12]



Scheme 1 Types of metal carbene cascade reactions.

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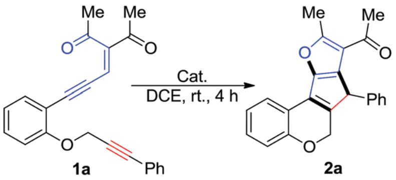
† Electronic supplementary information (ESI) available. CCDC 1545526 (**4d**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc08221e

Alkyne-tethered enynone **1a** was first prepared according to a known procedure (see the ESI† for details) and then utilized as a model substrate to probe the cascade reaction: it was mixed with various catalysts (with 1.0–5.0 mol%), including Rh, Au, Zn and Pd (Table 1, entries 1–12), in 1,2-dichloroethane (DCE). Except for PPh_3AuCl, which exhibited 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 the material was decomposed into a complex mixture (entries 5–8). Lower reactivity was found with $Pd(PPh_3)_4$ (entry 11) compared to the Pd(II)-catalyst (entry 10). Using $Pd_2(dba)_3$ as the catalyst led to a significant improvement in the reaction and **2a** was obtained in 62% isolated yield, which may due to the relatively low Lewis acidity (or π-electrophilicity) and weakly coordinating ligands of this catalyst (entry 12). Elevating the reaction temperature did not provide a better result (entry 13); however, introducing a 4 Å molecular sieve as an additive increased the yield to 70% (entry 14).

With the optimized reaction conditions in hand, we went on to explore the 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–l**). Regardless of the position or electronic properties of the 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 the restriction of rotation between the two aromatic planes.[13] Meanwhile, the reaction of the aryl-substituted enynones proceeded equally well, leading to the desired products **2m–p** in 60–72% yields. For material **1r**, which has an "N" linker instead of "O", although the reaction is quite clean according to the proton NMR of the crude reaction mixture (see Fig. S1 in the ESI†), however, the product was decomposed into a complex mixture during the isolation using 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 $Rh_2(OAc)_4$, and the corresponding product **2s** was obtained in 55% yield 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 products and the materials were decomposed into a complex mixture slowly, which may be mainly due to the lower stability of the *in situ* generated carbenoid 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

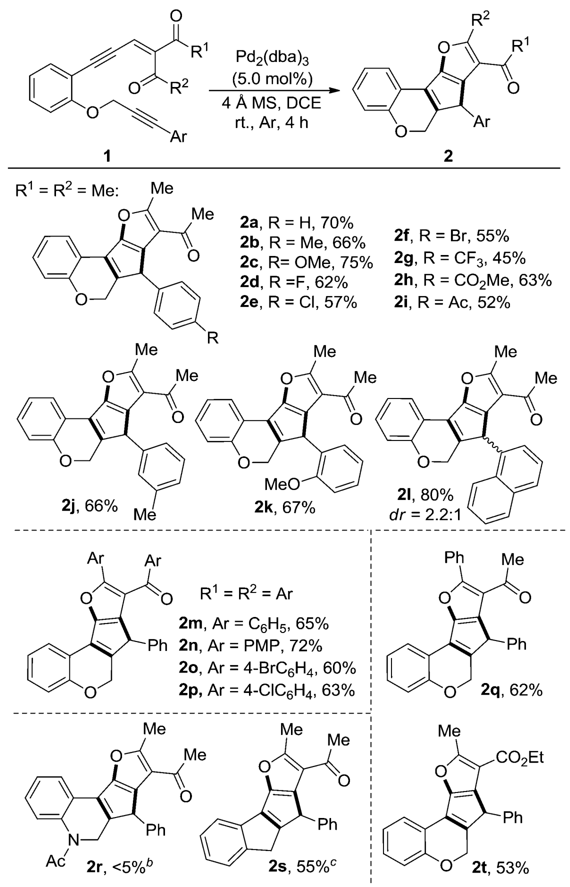
Table 1 Optimization of the reaction conditions[a]



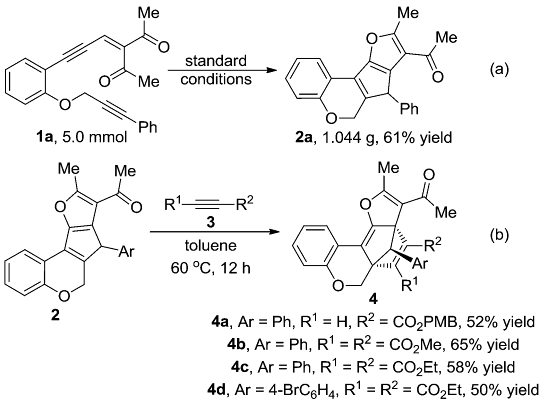
Entry	Catalyst (*x* mol%)	Yield[b] (%)
1	$Rh_2(OAc)_4$ (1.0)	20
2	$[Rh(COD)OH]_2$ (2.0)	30
3	$Cu(OTf)_2$ (5.0)	18
4	PPh_3AuCl (5.0)	nr[c]
5	PPh_3AuCl (5.0) + $AgSbF_6$ (5.0)	<5
6	$AgSbF_6$ (5.0)	<5
7	PPh_3AuCl (5.0) + $AgBF_4$ (5.0)	<5
8	$AgBF_4$ (5.0)	<5
9	$ZnCl_2$ (20.0)	25
10	$Pd(OAc)_2$ (5.0)	37
11	$Pd(PPh_3)_4$ (5.0)	26
12	$Pd_2(dba)_3$ (5.0)	62
13[d]	$Pd_2(dba)_3$ (5.0)	57
14[e]	$Pd_2(dba)_3$ (5.0)	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 an additive. DCE = 1,2-dichloroethane, nr = no reaction.

Table 2 Substrates scope[a,b]



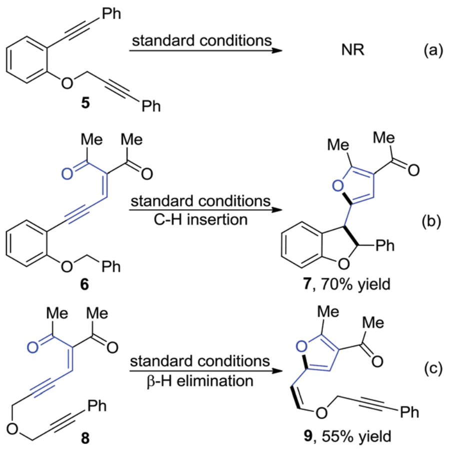
[a] Reactions are carried out on a 0.2 mmol scale with $Pd_2(dba)_3$ (5.0 mol%), 4 Å molecular sieve (30 mg) in DCE (3.0 mL) at room temperature under an Ar atmosphere, and the yields are given in isolated yields. [b] The product was decomposed into a complex mixture during the isolation using column chromatography. [c] Catalyzed by $Rh_2(OAc)_4$ (2.0 mol%) and running for 12 h.



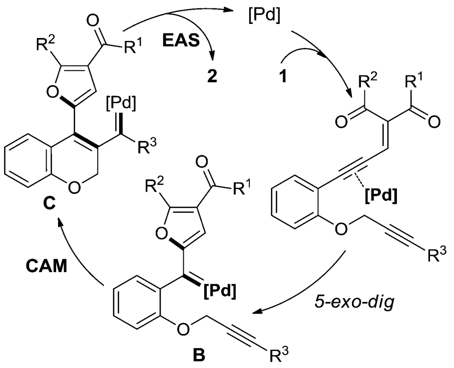
Scheme 2 Scale up and [4+2] cycloaddition.

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 in 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 enynone part in the material was removed, and no reaction occurred with **5** under the standard conditions (Scheme 3a), which means that the transformation was initiated by the enynone species. To demonstrate that the donor/donor carbenoid, which was generated from the 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 c). Two corresponding products **7** and **9** were obtained in 70% and 55% yields, respectively. These results further confirmed the existence of the carbenoid intermediate **B** (Scheme 1c) in this reaction. Based on this information and previous works,[2–4,15] we reasoned that the reaction was initiated by a palladium-catalyzed 5-*exo*-dig cyclization of the 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 transformation.



Scheme 3 Control experiments.



Scheme 4 Proposed reaction mechanism.

In summary, we have developed a palladium-catalyzed novel carbene/alkyne metathesis (CAM) cascade reaction of alkyne-tethered enynones, 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 a CAM reaction promoted by a readily available palladium complex, but also is the only example of the use of enynones as the carbene precursor in intramolecular carbene/alkyne metathesis cascade transformation. Potential applications of this strategy for polycyclic compounds synthesis are under exploration in our laboratory.

Support for this research from the National Natural Science Foundation of China and the NSFC of Jiangsu (NSFC21602148, BK20150315, and 15KJD150004), and the Priority Academic Program Development (PAPD) of Jiangsu Higher Education Institutions is gratefully acknowledged.

Conflicts of interest

There are no conflicts to declare.

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