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## ARTICLE TYPE

# Pd-catalyzed cross-coupling of terminal alkynes with ene-yne-ketones: access to conjugated enynes *via* metal carbene migratory insertion

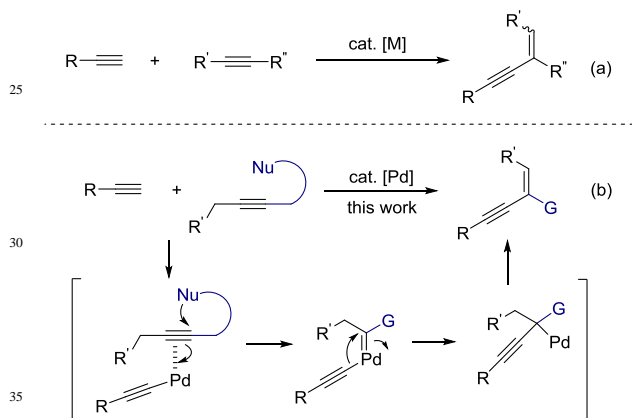Ying Xia,[a] Zhen Liu,[a] Rui Ge,[a] Qing Xiao,[a] Yan Zhang[a] and Jianbo Wang[*ab]

**A novel strategy for alkyne-alkyne cross-coupling has been developed under the palladium catalysis. In this reaction, ene-yne-ketones are employed as carbene precursors, which couple with terminal alkynes through metal carbene
10 migratory insertion process. Furan-substituted enynes were obtained in good yields and in stereoselective manner.**

Conjugated enynes are important structural units which are widely used in synthetic chemistry, medicinal chemistry, and material sciences,[1,2] thus the efficient and selective synthesis of
15 such compounds has attracted much attentions. Among the numerous methods, the transition-metal-catalyzed coupling of two alkynes represents the most straightforward and atom-economical approach to obtain conjugated enynes (Scheme 1, a).[3] Although a series of catalytic systems were developed to achieve
20 this alkyne-alkyne coupling, the regio- and stereoselectivity



**Scheme 1** Transition-metal-catalyzed alkyne-alkyne coupling for the synthesis of conjugated enynes.

40 [a]*Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China. Email: wangjb@pku.edu.cn*

45 [b]*The State Key Laboratory of Organometallic Chemistry, SIOC, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

remains the major challenge.[3] Thus, the development of novel alkyne-alkyne coupling strategy is highly desirable considering the importance of the conjugated enynes.

On the other hand, alkynes can be employed as carbene
55 precursors under the activation of transition-metal catalyst, and a series of novel reactions have been developed based on this concept.[4] Particularly, by using conjugated ene-yne-ketone as the carbene precursor,[5] we have realized the palladium-catalyzed carbene cross-coupling reaction with organic halides,[6] in which
60 carbene migratory insertion is the key step in this reaction.[7] Besides, we have previously reported the palladium-catalyzed cross-coupling of terminal alkynes with diazo compounds as carbene precursors to afford conjugated enynes.[8] As the continuation of our interest in carbene cross-coupling
65 chemistry,[7a,d-f] we conceived that the alkyne-alkyne cross-coupling may be achieved alternatively through a carbene migratory insertion pathway, thus affording a new method for conjugated enynes in stereoselective manner (Scheme 1, b).
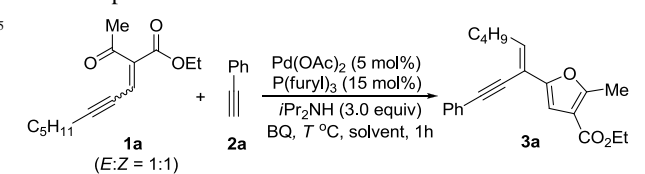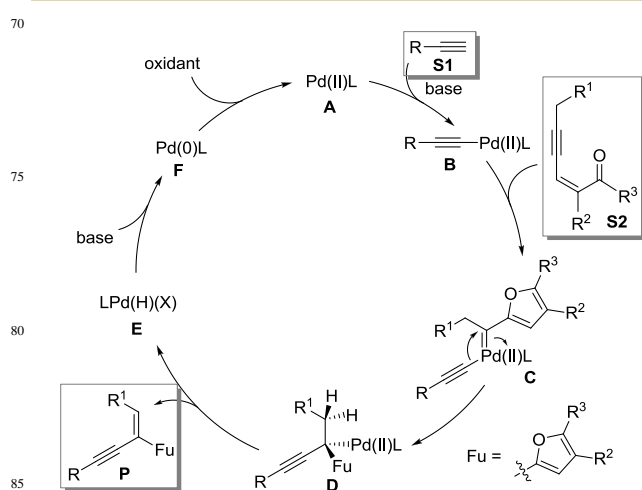


**Scheme 2** A Putative reaction pathway for oxidative coupling

The hypothesized catalytic cycle for this Pd-catalyzed alkyne-
90 alkyne cross-coupling is proposed as shown in Scheme 2. First, with the aid of the base and the ligand, the palladium catalyst **A** reacts with terminal alkyne **S1** to afford an alkynyl palladium(II) intermediate **B**.[3b,9] The intermediate **B** activates the triple bond of the ene-yne-ketone **S2** to undergo cyclization to form furyl Pd-

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carbene species **C**.[5,6] At this point, migratory insertion of the Pd-carbene leads to the formation of intermediate **D**,[7] which undergoes $\beta$-hydride elimination to produce conjugated enyne **P** as the final product. The generated Pd(II) species **E** transforms to Pd(0) species **F** through reductive elimination with the aid of the base. Finally, the catalytic reactive Pd(II) species **A** is regenerated through reoxidation of the Pd(0) species **F** by a suitable oxidant.

To test the feasibility of the proposed design, ene-yne-ketone (**1a**, (*E*)- and (*Z*)-mixtures with about 1:1 ratio)[10] and phenylacetylene (**2**) were used as the model substrates to optimize the reaction conditions (Table 1). In the presence of 5 mol% Pd(OAc)$_2$, 15 mol% P(2-furyl)$_3$, 3 equivalents of *i*Pr$_2$NH as the base and 1.5 equivalents of BQ as the oxidant, we were delighted to obtain the expected enyne **3a** in 45% yield (entry 1). Changing of the solvent from toluene to dioxane resulted in an increased yield (entry 2). Using *i*Pr$_2$NEt as the base afforded an inferior result than that of *i*Pr$_2$NH (entry 3). Then, we adjusted the ratio of the two substrates and the amount of the oxidant BQ, and we found the yields could increase to 73% (entries 4-7). At last, a slight improvement of the yield could be achieved by carrying out the reaction at elevated temperature, and the optimized reaction conditions are shown in entry 8.

**Table 1** Optimization of reaction conditions[a]



| Entry | 1a:2a | Solvent | BQ (equiv) | $T$ ($^o$C) | Yield[b] (%) |
|-------|-------|---------|------------|------|--------------|
| 1 | 1:1.5 | toluene | 1.5 | 80 | 45 |
| 2 | 1:1.5 | dioxane | 1.5 | 80 | 60 |
| 3 | 1:1.5 | dioxane | 1.5 | 80 | 53 |
| 4 | 1:1.3 | dioxane | 1.3 | 80 | 65 |
| 5 | 1:1.1 | dioxane | 1.2 | 80 | 73 |
| 6 | 1.1:1 | dioxane | 1.2 | 80 | 73 |
| 7 | 1:1.1 | dioxane | 1.1 | 80 | 67 |
| 8 | 1:1.1 | dioxane | 1.2 | 90 | 77 |

[a]The reaction was carried out in 0.2 mmol scale in 2.0 mL solvent for 1 h. [b]Isolated yield with column chromatography. BQ = 1,4-benzoquinone

With the established reaction conditions, we then proceeded to investigate the reaction scope of ene-yne-ketones (Scheme 3). To meet the requirement of $\beta$-hydride elimination in the catalytic cycle, all of the ene-yne-ketones should have hydrogen on the carbon adjacent to the alkyne moiety. When R[1] is a pentyl group, the ene-yne-ketones bearing different substituents all show good reactivity, affording the corresponding enyne products in good yields (**3a-d**). When R[1] group contains a phenyl or an ether moiety, slightly diminished yields are observed (**3e-f**, **3g-h**). Ene-yne-ketones bearing secondary alkyl group are also suitable substrates for this reaction, leading to the formation of enynes with a *tetra*-substituted alkene moiety in good yields (**3i-l**). In addition, the second carbonyl moiety on ene-yne-ketones is not

essential for this transformation, although the yield is diminished (**3m**). Notably, replacing the Ph substituent of **2a** with TMS does not affect the reaction (**3n**).
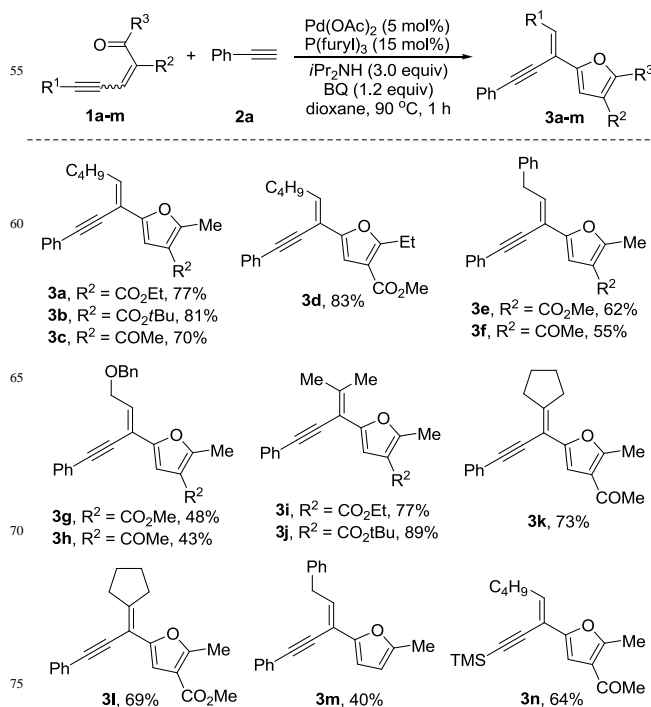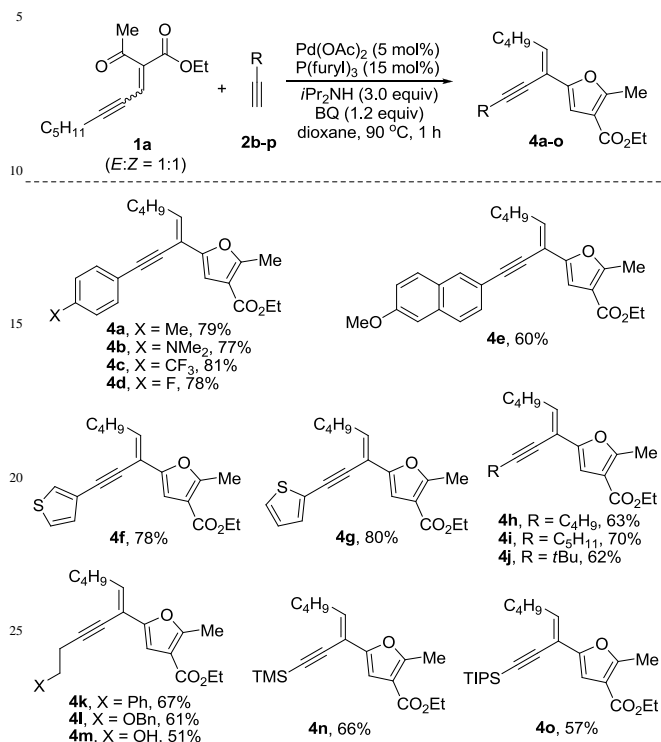


**Scheme 3** Reaction scope of ene-yne-ketones. [a]Reaction conditions: Pd(OAc)$_2$ (5 mol%), P(2-furyl)$_3$ (15 mol%), **1a-n** (0.2 mmol), **2a** (0.22 mmol), BQ (0.24 mmol), *i*Pr$_2$NH (0.6 mmol) in dioxane (2.0 mL) was stirred under N$_2$ at 90 $^o$C for 1 h. [b]Ene-yne-ketones **1a**, **b**, **d**, **e**, **g**, **i**, **j**, **l** were used as mixtures of (*E*)- and (*Z*)-isomers. [c]Isolated yield with column chromatography. [d]The stereoselectivity is >20:1 based on the analysis of GC-MS and ^{1}H NMR.

Notably, all the products are obtained with greater than 20:1 stereoselectivity as judged by GC-MS and ^{1}H NMR. According to the previous report on similar reactions, the newly-formed double bond is proposed to have (*E*)-configuration.[8,11] In the transition state of the *cis* $\beta$-H elimination from intermediate **D** shown in Scheme 2, the R[1] group should prefer to eclipse with the less bulky linear alkyne moiety rather than the furyl moiety, thus leading to the product with high stereoselectivity of (*E*)-configuration.

Subsequently, we examined the scope of terminal alkynes by using ene-yne-ketone **1a** as the substrate, and a series of terminal alkynes **2b-p** were smoothly converted to the corresponding enynes in good yields with high stereoselectivity under the optimized reaction conditions (Scheme 4). For the aryl-substituted terminal alkynes, both electron-withdrawing and -donating groups on the aromatic ring are tolerated (**4a-e**), and the heteroaryl terminal alkynes are also suitable substrates (**4f, g**). Reactions of terminal alkynes bearing alkyl groups afforded the corresponding enynes smoothly (**4h-m**). It is noteworthy that the free hydroxyl group is tolerated in this transformation (**4m**). In

addition, the reaction conditions are also suitable for silyl substituted terminal alkynes, although the substrate bearing bulky TIPS group gives a slightly diminished yield (**4o**).



**Scheme 4** Reaction scope of terminal alkynes. $^{a}$Reaction conditions: Pd(OAc)$_2$ (5 mol%), P(2-furyl)$_3$ (15 mol%), **1a** (0.2 mmol), **2b-p** (0.22 mmol), BQ (0.24 mmol), $i$Pr$_2$NH (0.6 mmol) in dioxane (2.0 mL) was stirred under N$_2$ at 90 $^{o}$C for 1 h. $^{b}$Ene-yne-ketone **1a** was used as mixtures of (*E*)- and (*Z*)-isomers. $^{c}$Isolated yield with column chromatography. $^{d}$The stereoselectivity is >20:1 based on the analysis of GC-MS and $^{1}$H NMR.

In summary, we have reported the palladium-catalyzed oxidative cross-coupling reaction of conjugated ene-yne-ketones with terminal alkynes. This reaction shows broad substrate scope for both alkyne partners and affords furan-substituted conjugated enynes in good yields and with high stereoselectivity. The key to achieve this novel alkyne-alkyne cross-coupling is the use of ene-yne-ketones as the carbene precursors, which undergo carbene migratory insertion process. Further studies on the exploitation of alkyne as carbene precursor in similar transition-metal-catalyzed cross-coupling reactions are undergoing and the results will be reported in due course.

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