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### Palladium-Catalyzed Oxygenative Cross-Coupling of Ynamides and Benzyl Bromides via Carbene Migratory Insertion\*\*

Yunpeng Gao, Guojiao Wu, Qi Zhou and Jianbo Wang\*

**Abstract:** A Pd-catalyzed oxygenative cross-coupling of ynamides and benzyl bromides has been developed. After subsequent hydrogenation,  $\alpha, \alpha$ -disubstituted amide derivatives were obtained in good yields. Migratory insertion of  $\alpha$ -oxo palladium carbene species generated by intermolecular oxidation is proposed as the key step in this reaction. The study demonstrates the potential of ynamides as carbene precursors in Pd-catalyzed C-C bond-forming crosscoupling reactions.

In recent years, cross-coupling through metal carbene intermediates have been rapidly evolving as general methods for C-C bond construction.<sup>[1,2]</sup> The key steps in these transformation are the formation of the metal carbene intermediate and the subsequent migratory insertions. In the majority of these coupling reactions, the diazo compounds (or their precursors N-tosylhydrazones) are served as the precursors for metal carbene generation (Scheme 1A). In addition to diazo compounds, the unsaturated compounds that can be utilized as metal carbene precursors in transition-metal-catalyzed reactions have attracted significant attentions in recent years.<sup>[3]</sup> Thus, in principle these unsaturated compounds can also be used as reaction partners in carbene-based cross-coupling reactions. In this context, we have previously demonstrated the palladium-catalyzed cross-coupling of enynones and arylhalides. The enynones readily undergo cyclization with aryl palladium species to generate palladium carbenes, which further undergo migratory insertion (Scheme 1B).<sup>[4,5]</sup> In another example, we have demonstrated that allenyl ketones react similarly with arylhalides in the presence of palladium catalyst.<sup>[6]</sup>

Alkynes represent a type of unsaturated compounds that can be utilized as metal carbene precursors, typically initiated by nucleophilic attack on the metal-activated triple bonds. In this context, gold-catalyzed transformations of alkynes via  $\alpha$ -oxo and  $\alpha$ -imino carbenes have recently attracted significant attentions.<sup>[7]</sup> In particular, Zhang and others have established the gold-catalyzed intermolecular oxidation approaches with N-O bond oxidants (Scheme 1C).<sup>[8]</sup> The in situ generated  $\alpha$ -oxo gold carbenes undergo typical carbene transformations, such as cyclopropanation, X-H bond insertion, 1,2-migration and ylide reaction, which renders readily available alkynes as effective alternatives of  $\alpha$ -carbonyl diazo compounds. Aside from intramolecular approaches, several

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A) Cross-couplings via carbene migratory insertion









Scheme 1. Transition-metal-catalyzed cross-coupling with various carbene | precursors

reports also highlight the intermolecular trapping process of  $\alpha$ -oxo gold carbenes generated with external oxidants.<sup>[9]</sup>

In connection to our interest in cross-coupling with carbene pre-cursors, we conceived the possibility of incorporating intermolecular oxidation of C-C triple bond with carbene migratory insertion process to achieve oxygenative coupling. However, compared to gold, palladium is a weaker Lewis acid when activating C-C triple bonds.<sup>[10]</sup> Therefore, the generation of palladium carbenes from simple alkyne is rare.<sup>[11]</sup> Recently, ynamides have emerged as versatile and easily accessible building blocks in organic synthesis.<sup>[12]</sup> Due to its strongly polarized C-C triple bond, ynamide can be converted to keteniminium ion with Lewis or Brønsted acids. Except the transformations via  $\alpha$ -oxo gold carbenes,<sup>[13]</sup> oxygenative reactions of ynamides using zinc<sup>[14]</sup> or Brønsted acid<sup>[15]</sup> as the activating reagent are also known. Thus, we conceived that palladium may be able to activate the triple bonds of ynamides, thus allowing the carbene-based coupling to proceed. Herein we report our investigation on the palladium-catalyzed oxygenative cross-coupling of ynamides and benzyl bromides via sequential intermolecular oxidation and carbene migratory insertion process (Scheme 1D).

Our initial investigations were focused on the reaction of ynamide **1a** and 4-methylbenzyl bromide **2b** with the treatment of pyridine *N*-oxide **3a** and K<sub>2</sub>CO<sub>3</sub> in toluene. Pd(OAc)<sub>2</sub> and P(2-furyl)<sub>3</sub> were utilized as catalyst and ligand respectively (Table 1).<sup>[16]</sup> The reaction was carried out at 90 °C for 4 h, the target product **4a** was obtained in 38% yield (entry 1). Lowering the temperature to 70 °C and prolonging the reaction time resulted in a slightly increased yield (entry 2). However, around half of the starting **1a** was recovered unchanged at 60 °C even after prolonged reaction time (entry 3).

Changing the ratio of substrates led to significant improvement. Using 1.5 equivalents of 2b and 2.0 equivalents of 3a improved the vield to 62% (entry 5). Subsequently, the effect of the oxidant was investigated. A series of substituted pyridine N-oxides and quinoline screened.<sup>[17]</sup> For *N*-oxides were the *N*-oxide with electron-withdrawing group (3b), most of 1a was recovered unchanged, presumably due to the decreased nucleophilicity of the negatively charged oxygen (entry 6). Pyridine N-oxides with electron-donating groups also led to diminished yields due to the undesirable oxidation of 2b (entries 7 and 8). When screening quinoline N-oxides, we found that keto imide byproduct 4aa was obtained using 3f as oxidant (entry 10). Interestingly, addition of 1 equivalent of water dramatically suppressed the over-oxidation, affording the product 4a in 72% yield (entry 11). Using the oxidant with bulky *i*-Pr group on 8-position of the quinoline ring gave similar result (entry 12). The yield was slightly diminished when the loading of the catalyst was reduced to 5 mol% (entry 13). Thus, the reaction conditions given in entry 11 were chosen as the optimized conditions.

Table 1. Optimization of reaction conditions.<sup>[a]</sup>



Entry	<i>T</i> , ⁰C	1a:2b:3	Oxidant <b>3</b> , R =	<i>t</i> , h	<b>4a</b> , % <sup>[b]</sup>
1	90	1:1:1	<b>3a</b> , H	4	38
2	70	1:1:1	<b>3a</b> , H	10	46
3	60	1:1:1	<b>3a</b> , H	18	35 <sup>[c]</sup>
4	70	1:1.5:1.5	<b>3a</b> , H	10	50
5	70	1:1.5:2	<b>3a</b> , H	10	62
6	70	1:1.5:2	<b>3b</b> , 2,6-Cl <sub>2</sub>	10	trace
7	70	1:1.5:2	<b>3c</b> , 4-Me	10	44
8	70	1:1.5:2	<b>3d</b> , 4-OMe	10	37
9	70	1:1.5:2	<b>3e</b> , H	10	48
10	70	1:1.5:2	<b>3f</b> , Me	10	37 <sup>[d]</sup>
11 <sup>[e]</sup>	70	1:1.5:2	<b>3f</b> , Me	10	72
12 <sup>[e]</sup>	70	1:1.5:2	<b>3g</b> , <i>i-</i> Pr	10	71
13 <sup>[e,f]</sup>	70	1:1.5:2	<b>3f</b> , Me	10	62

[a] The reaction was carried out on 0.1 mmol scale. [b] The yields refer to the combined yield of both isomers. Determined by <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as the internal standard. [c] **1a** was recovered in 53% yield. [d] Keto imide byproduct **4aa** was isolated in 26% yield. [e] 1 equiv of H<sub>2</sub>O was added. [f] The loading of Pd(OAc)<sub>2</sub> and P(2-furyl)<sub>3</sub> was 5 mol% and 20 mol%, respectively.

With the optimized conditions in hand, we started to investigate the substrate scope of this reaction. Since the *E* and *Z* isomers of the alkene products cannot be isolated by flash column chromatography, subsequent hydrogenation was carried out on the crude coupling products, affording hydrogenated products. First, we explored the reaction scope with various benzyl bromides (**2a-n**) by utilizing ynamide **1a** as the carbene precursor (Scheme 2). For most examples the  $\alpha,\alpha$ -disubstituted amide derivatives were obtained with moderate to good yields under optimized reaction conditions. The reaction with benzyl bromide gave the corresponding product (**5a**) in 80% yield. The position of substituents on the aromatic ring had little influence on this reaction. Benzyl bromides bearing methyl groups on different positions were employed in this reaction, and 64-72% yields were obtained (**5b-d**). Electron-donating (**5b-f**) and electron-withdrawing groups (**5g-k**) were both well tolerated in this transformation. Cross-coupling products with fluorine-containing groups at different positions (**5g-j**) were smoothly generated in 54-77% yields. Bromomethylnaphthalenes were also suitable substrates. Compared with  $\beta$ -substituted substrate (**2n**), significant steric effect retarded the reaction when utilizing  $\alpha$ -substrate (**2m**), which led to a diminished yield of 39%.



**Scheme 2.** The reaction scope of benzyl bromides. The reaction was carried out on 0.2 mmol scale. All yields refer to the isolated products after chromatography. Except the cases of **5m** and **5n**, hydrogenation was repeated twice under the same conditions due to incomplete hydrogenation.

Next, a variety of ynamides (**1b-l**) bearing different substituents on the aryl ring was submitted to this transformation (Scheme 3). Substrates with methyl group on the *meta-* and *para-*position of the aryl ring gave similar results (**6a** and **b**), while *ortho-*substituted analog gave trace product with the substrate remained (**6c**), which suggests that the steric effect of the ynamide side is much larger than the benzyl bromide side. Then the electronic effect was investigated. Substrates with electron-donating groups (**6d** and **e**) and weak electron-withdrawing fluoride substituent (**6f** and **g**) afforded the corresponding products in good yields, yet strong electron-withdrawing groups (**6h** and **i**) resulted in diminished yields. Naphthalene substituent was also tolerated in this reaction (**6k**).



**Scheme 3.** The reaction scope of aryl substituents of ynamides. The reaction was carried out on 0.2 mmol scale. All yields refer to the isolated products after chromatography. Except the cases of **6g** and **6h**, hydrogenation was repeated twice under the same conditions due to incomplete hydrogenation.

It is worth mentioning that the substituents on the nitrogen have significant influence on the reactivity of the ynamides. Thus, the scope of *N*-substituents was preliminarily studied (Scheme 4). Since chiral oxazolidinone auxiliaries are widely used in stereoselective construction of chiral molecules,<sup>[18]</sup> auxiliaries derived from *L*-phenylalanine and *L*-valine were introduced to ynamides and resulted in moderate yields (**7a** and **b**). However, only a low diastereoselectivity of 3:2 for **7a** and 1:1 for **7b** was observed after the hydrogenation. The structure of the (*S*,*S*) diastereoisomer of **7b** was unambiguously established by X-ray crystallography.<sup>[16]</sup> Ynamides bearing sulfonyl groups were also proved to be suitable substrates for this reaction (**7c** and **7d**).



**Scheme 4.** The reaction scope of *N*-substituents of ynamides. The reaction was carried out on 0.2 mmol scale. All yields refer to the isolated products after chromatography. Diastereomeric ratio was determined by isolated products.

To gain insights into the mechanism of this reaction, diazo compound **8** was prepared and submitted to the palladium-catalyzed reaction with benzyl bromide. As shown in Scheme 5, it was observed that **8** reacted smoothly with benzyl bromide **2a**, affording **4a** with 75% yield. A similar ratio of two isomers (E:Z = 4:1) with the reaction of **1a** and **2a** (E:Z = 3:1) was also obtained. Then, 1.0 equivalent of 8-methylquinoline *N*-oxide (**3f**) was added to simulate the standard conditions of the investigated reaction. It is noteworthy that a slightly improved yield of 85% was obtained. This phenomenon could be explained by the stabilization effect due to the electron donation from heteroaromatic *N*-oxide to the palladium carbene species.<sup>[19]</sup> Moreover, a similar water effect was also observed. In the absence of water, the yield of **4a** decreased significantly and the keto imide byproduct **4aa** was formed.



**Scheme 5.** Cross-coupling of diazo compound **8** and benzyl bromide. The reaction was carried out on 0.1 mmol scale. [a] Yield and *E*/*Z* ratio were determined by <sup>1</sup>H NMR using CH<sub>2</sub>Br<sub>2</sub> as the internal standard. [b] The reaction was conducted without H<sub>2</sub>O. [c] *E*:*Z* = 4:1. [d] *E*/*Z* ratio was not determined.

Based on the results, the following mechanism is proposed (Scheme 6).  $Pd(OAc)_2$  is first reduced to Pd(0) species **A**, then oxidative addition of benzyl bromide **2** to Pd(0) takes place to generate benzylpalladium(II) species **B**. The C-C triple bond of ynamide **1** is activated by **B**, which leads to the generation of reactive keteniminium ion **D**. Intermolecular oxidation by **3f** affords intermediate **E**, which undergoes  $\gamma$ -elimination and then the nucleofugal part of the oxidant is expelled. A subsequent migratory insertion occurs to Pd(II) carbene species **F**, thus forming Pd(II) species **G**. Finally, with the aid of base, Pd(0) catalyst **A** is regenerated by  $\beta$ -H elimination and the coupling product **4** is formed.



Scheme 6. Proposed reaction mechanism.

In conclusion, we have developed a novel palladium-catalyzed oxygenative cross-coupling between ynamides and benzyl bromides. The reaction is a straightforward method for the efficient synthesis of  $\alpha, \alpha$ -disubstituted amide derivatives. Mechanistically, an intermolecular oxidation and carbene migratory insertion sequence is involved. This methodology reveals the possibility of utilizing alkynes as  $\alpha$ -oxo palladium carbene precursors, which is a significant expansion of gold-catalyzed oxidative transformations of alkynes. This study also demonstrates the generality of carbene migratory insertion process in C-C bond formation regardless of carbene precursors.

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#### **Cross-Coupling**

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Palladium-Catalyzed Oxygenative Cross-Coupling of Ynamides and Benzyl Bromides via Carbene Migratory Insertion



**Ynamide as palladium carbene precursor**: A palladium-catalyzed oxygenative cross-coupling between ynamides and benzyl bromides is reported. An orderly organized intermolecular oxidation/carbene migratory insertion sequence is most likely involved in the mechanism, which renders ynamide as a novel palladium carbene precursor.