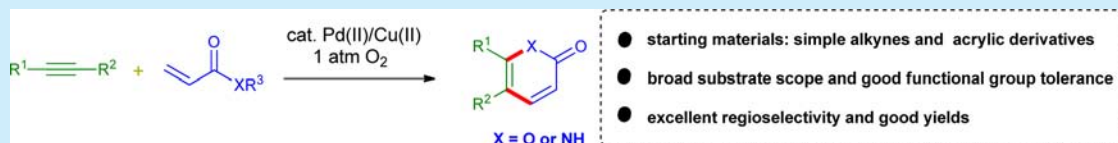


# Palladium-Catalyzed Oxidative Annulation of Acrylic Acid and Amide with Alkynes: A Practical Route to Synthesize $\alpha$ -Pyrones and Pyridones

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**S** Supporting Information

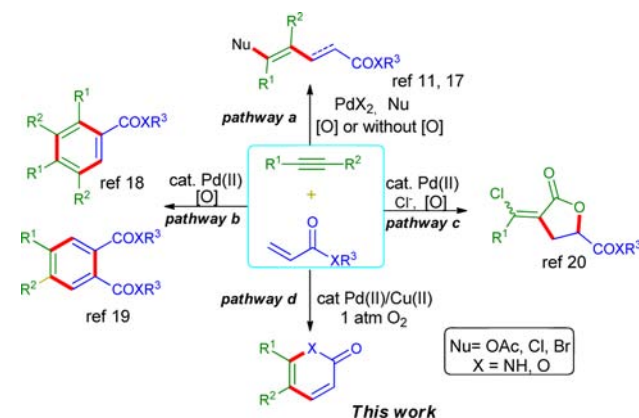


**ABSTRACT:** A range of internal alkynes smoothly underwent palladium-catalyzed oxidative annulations with acrylic acid and amide to afford  $\alpha$ -pyrones and pyridones in good to excellent yields with high regioselectivity. The usage of  $O_2$  (1 atm) as a stoichiometric oxidant with  $H_2O$  as the only byproduct under mild conditions makes this process more attractive and practical.

Efficient and selective synthetic methodologies that include transition metal catalysis and simple starting materials, for the synthesis of complex molecules, occupy a leading position in modern organic chemistry. Unsaturated hydrocarbons, especially alkynes and alkenes, which are important staple products of petroleum and petrochemical industries, can be utilized to build multiple new chemical bonds with maximal atom and step economy.<sup>1</sup> In particular, nucleometalation of carbon–carbon triple bonds has been demonstrated to be one of the most efficient strategies for its high efficiency in constructing nucleophile–carbon and carbon–metal bonds in a single step.<sup>2–4</sup> Yamamoto<sup>5,6</sup> and Zhang<sup>7,8</sup> et al. respectively utilized the carbonyl oxygen atom and other O-containing nucleophiles to attack the triple bond, activated by a Au complex. Lu and others made great contributions to the alkyne conversions initiated by nucleopalladation.<sup>9–16</sup> Recently, our group developed a series of cross-coupling reactions using alkynes and alkenes as substrates to construct 1,3-dienes,<sup>17</sup> substituted benzenes,<sup>18,19</sup> and  $\alpha$ -methylene- $\gamma$ -lactones (Scheme 1).<sup>20</sup> In our continued interest in Pd-catalyzed oxidative coupling between alkynes and alkenes,<sup>17–22</sup> we herein report an efficient and robust strategy to synthesize  $\alpha$ -pyrones and pyridines through the aerobic oxidative annulations between acrylic acids or amides with alkynes (Scheme 1, pathway d).

This type of oxidative coupling reaction catalyzed by palladium has provided important innovations for synthetic chemistry over the past decades.<sup>23</sup> Recently, similar reactions of oxidative annulation or decarboxylation by rhodium or ruthenium catalysis have been reported by Ackermann, Miura, Jeganmohan, and Rovis et al. since 2007.<sup>24,25</sup> These reactions have greatly supplemented the study of oxidative C–H bond transformations proceeding via C–H/O–H or C–H/N–H bond cleavages, which provide an atom-economical way to synthesize  $\alpha$ -pyrones and pyridines. But oxidative annulations between internal alkynes and acrylic acid or amide by palladium catalysis are still a big challenge, because

## Scheme 1. Pd-Catalyzed Oxidative Coupling between Alkynes and Alkenes



of the relatively less catalytic activity and the different reaction mechanism.

To our delight, the desired oxidative annulation between diphenylethyne **1a** and acrylic acid **2a**, using 10 mol %  $Pd(OAc)_2$  as the catalyst and 30 mol %  $CuBr_2$  at 90 °C under 1 atm of  $O_2$ , afforded the desired product **3a** in 44% yield (Table 1, entry 1). When 2 mL of mixed  $AcOH/Ac_2O$  (1: 3) was used as solvent, the product yield increased to 66% (Table 1, entry 2). Further experiments indicated that  $Pd(OAc)_2$  was the best catalyst for this transformation (Table 1, entries 4–5). Changing the co-oxidant  $CuBr_2$  to other copper salts did not improve the yield (Table 1, entries 6–7). Adjusting the reaction temperature did not increase the yield of the desired product (Table 1, entries 8–9). Interestingly, the yield of **3a** could be enhanced significantly by adding 1 equiv of DABCO to the

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Table 1. Optimization of Reaction Conditions

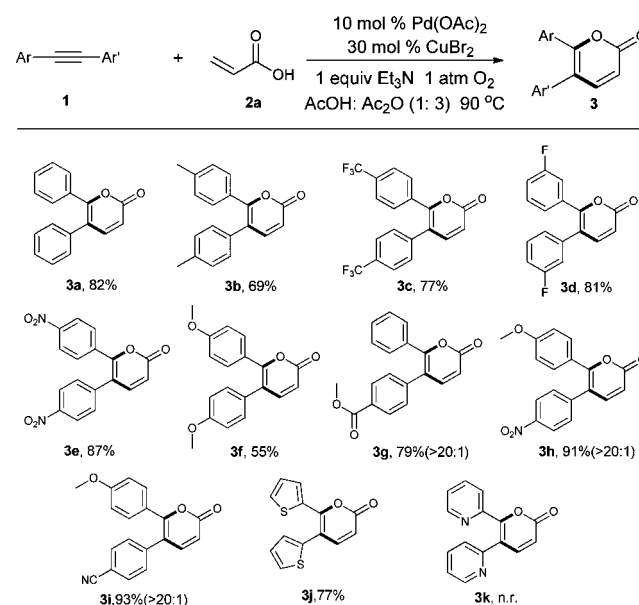
entry	[Pd]	co-oxidant	base	solvent	yield <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	—	Ac <sub>2</sub> O	44
2	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	—	HOAc/Ac <sub>2</sub> O = 1:1	57
3	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	—	HOAc/Ac <sub>2</sub> O = 1:3	66
4	PdCl <sub>2</sub>	CuBr <sub>2</sub>	—	HOAc/Ac <sub>2</sub> O = 1:3	51
5	Pd(TFA) <sub>2</sub>	CuBr <sub>2</sub>	—	HOAc/Ac <sub>2</sub> O = 1:3	37
6	Pd(OAc) <sub>2</sub>	CuCl <sub>2</sub>	—	HOAc/Ac <sub>2</sub> O = 1:3	54
7	Pd(OAc) <sub>2</sub>	Cu(OAc) <sub>2</sub>	—	HOAc/Ac <sub>2</sub> O = 1:3	n.d.
8 <sup>c</sup>	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	—	HOAc/Ac <sub>2</sub> O = 1:3	54
9 <sup>d</sup>	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	—	HOAc/Ac <sub>2</sub> O = 1:3	43
10	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	DABCO	HOAc/Ac <sub>2</sub> O = 1:3	78
11 <sup>c</sup>	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	<i>i</i> -Pr <sub>3</sub> NEt	HOAc/Ac <sub>2</sub> O = 1:3	62
12	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	Et <sub>3</sub> N	HOAc/Ac <sub>2</sub> O = 1:3	82
13	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	HOAc/Ac <sub>2</sub> O = 1:3	50
14	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	Na <sub>2</sub> CO <sub>3</sub>	HOAc/Ac <sub>2</sub> O = 1:3	76
15	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	Li <sub>2</sub> CO <sub>3</sub>	HOAc/Ac <sub>2</sub> O = 1:3	51
16 <sup>e</sup>	Pd(OAc) <sub>2</sub>	CuBr <sub>2</sub>	Et <sub>3</sub> N	HOAc/Ac <sub>2</sub> O = 1:3	64

<sup>a</sup>Unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.6 mmol), Pd catalyst (0.05 mol) and co-oxidant (0.15 mmol), base (0.5 mmol) under O<sub>2</sub> (1 atm) in the indicated solvent (2.0 mL) at 90 °C for 12 h. <sup>b</sup>Determined by GC using dodecane as the internal standard. Yields refer to isolated yields. <sup>c</sup>The temperature was 80 °C. <sup>d</sup>The temperature was 100 °C. <sup>e</sup>The reaction was in air instead of pure O<sub>2</sub>.

reaction system (Table 1, entry 10). During the screening of bases, the yield increased to 82% when DABCO was replaced with Et<sub>3</sub>N (Table 1, entries 11–15). This result suggested that Et<sub>3</sub>N promoted the reaction. We proposed that the salt generated from the reaction of the base with ethylic acid could better stabilize the Pd<sup>II</sup> species. If the reaction was performed in air instead of pure O<sub>2</sub>, the yield would drop to 64% (Table 1, entry 16).

With the optimal reaction conditions in hand, we next expanded the scope of the Pd-catalyzed oxidative annulations with respect to a variety of alkynes (Scheme 2). A series of para-substituted diphenylethyne, including some with electron-withdrawing and -donating groups, went smoothly to afford the corresponding  $\alpha$ -pyrones in good yields (Scheme 2, **3b–c**). The substrate with a substituent on the meta-position of the phenyl ring could also transform to the desired product in 81% yield (Scheme 2, **3d**). Starting materials containing –NO<sub>2</sub> and –OMe, the strong electron biased groups, underwent the transformation efficiently which indicated its good tolerance toward the electron effect (Scheme 2, **3e–f**). To our delight, we found the unsymmetrical diarylethyne could convert to the  $\alpha$ -pyrones with a regioselectivity of >20/1 when strong electron biased groups were present at the para position of the aromatic ring (Scheme 2, **3g–i**). It was worth noting that many synthetically relevant functional groups, including nitro, ester, cyan, and CF<sub>3</sub>, were tolerated under the reaction conditions. Furthermore, the diheteroarylethyne were also subjected to the optimal conditions. 1,2-Di(thiophen-2-yl)-ethyne showed good reactivity, and the desired product was obtained in 77% yield (Scheme 2, **3j**), while the 1,2-di(pyridin-2-yl)ethyne exhibited inertness for this transformation (Scheme 2, **3k**).

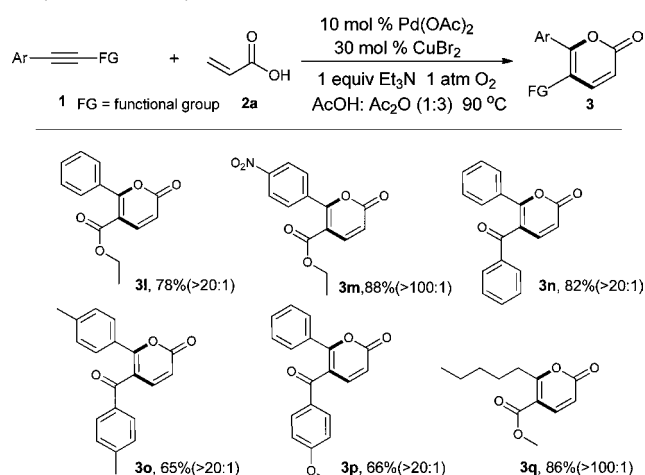
To further explore the utility of this newly developed reaction for the synthesis of functional molecules, we tested the oxidative annulations of acrylic acids with alkynes, containing functional groups (Scheme 3). When the functional group was ester, no matter whether there are substitutions on the aromatic

Scheme 2. Pd-Catalyzed Oxidative Annulations between Diarylethyne and Acrylic Acid<sup>a</sup>

<sup>a</sup>Unless otherwise noted, all reactions were performed with **1** (0.5 mmol), **2a** (0.75 mmol), Pd(OAc)<sub>2</sub> (0.05 mmol), CuBr<sub>2</sub> (0.15 mmol), and Et<sub>3</sub>N (0.5 mmol) in 2 mL of solvent (HOAc/Ac<sub>2</sub>O = 1:3) under 1 atm of O<sub>2</sub> at 90 °C for 12 h. Yields refer to isolated yields.

ring or not, the transformation afforded the desired products in good to high yields (Scheme 3, **3l–m**). The situation was similar to the alkynoates when the functional group was ketone for this transformation (Scheme 3, **3n–p**). Finally, the alkanoates could transfer to the corresponding products with excellent regioselectivity in 86% yield (Scheme 3, **3q**). Inspired by the recent nucleopalladation of haloalkynes of Zhu,<sup>26–28</sup> we tried to use haloalkynes as a substrate but failed.

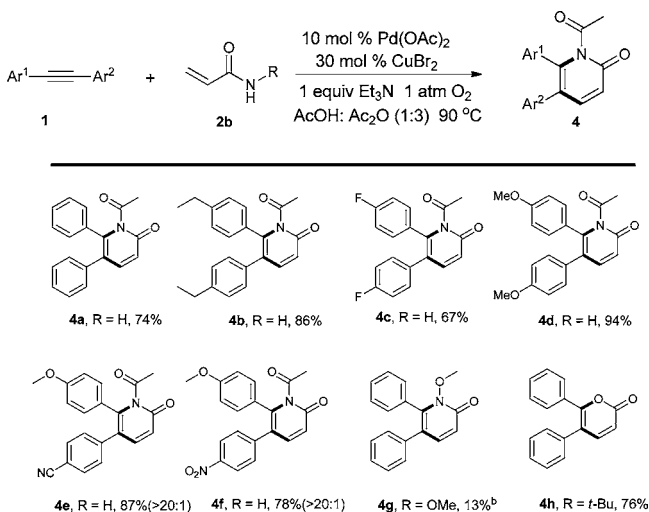
### Scheme 3. Pd-Catalyzed Oxidative Annulations between Alkynes and Acrylic Acid<sup>a</sup>



<sup>a</sup>Unless otherwise noted, all reactions were performed with **1** (0.5 mmol), **2a** (0.75 mmol), Pd(OAc)<sub>2</sub> (0.05 mmol), CuBr<sub>2</sub> (0.15 mmol), and Et<sub>3</sub>N (0.5 mmol) in 2 mL of solvent (HOAc/Ac<sub>2</sub>O = 1:3) under 1 atm of O<sub>2</sub> at 90 °C for 12 h. Yields refer to isolated yields.

The scope of this oxidative annulation was further expanded to acrylic amide with internal alkynes (Scheme 4).<sup>29</sup> The

### Scheme 4. Pd-Catalyzed Oxidative Annulations between Diarylethyne and Acrylic Amide<sup>a</sup>



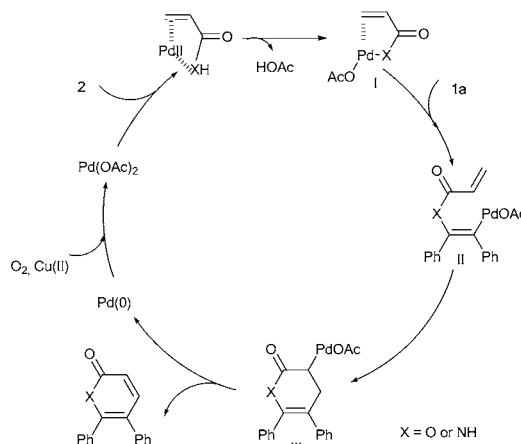
<sup>a</sup>Unless otherwise noted, all reactions were performed with **1** (0.5 mmol), **2b** (0.75 mmol), Pd(OAc)<sub>2</sub> (0.05 mmol), CuBr<sub>2</sub> (0.15 mmol), and Et<sub>3</sub>N (0.5 mmol) in 2 mL of solvent (HOAc/Ac<sub>2</sub>O = 1:3) under 1 atm of O<sub>2</sub> at 90 °C for 12 h. Yields refer to isolated yields. <sup>b</sup>Determined by GC using dodecane as the internal standard. Yields refer to isolated yields.

compatibility of this catalytic system with different functional groups, including alkyl, halogen, esters, cyan, and nitriles, was established (Scheme 4, **4b–f**). The regioselectivity of the reaction was excellent when the para substituents of the aromatic ring were strong electron biased groups, such as OMe, CN, and NO<sub>2</sub> (Scheme 4, **4e–f**). Particularly, it was noteworthy that if the substituent R is OMe, which is a weak electron-withdrawing group in this situation, it also can transform to the corresponding product while the yield is too

low (Scheme 4, **4g**). Then, if R is *tert*-butyl, the acrylic amide will be easy to hydrolyze to acrylic acid, resulting in the product **4h**, with the same structure as that of **3a**. In order to confirm whether the acylation occurred before or after the cyclization, we tried to test the reaction of acrylic amide under the standard conditions in the absence of the catalyst and alkyne, and the acylate was found, which suggested that the acylation occurred before the cyclization.

On the basis of the above results, a plausible mechanism for the Pd-catalyzed oxidative annulations is illustrated in Scheme 5. We proposed that the initial step involved the coordination

### Scheme 5. Proposed Catalytic Cycle



and ligand exchange of the acrylic derivative **2** with Pd<sup>II</sup> to provide X–Pd intermediate **I**.<sup>30,31</sup> Then, exo coordination of **1a** and insertion of the diarylethyne molecule into **I** gave the vinyl–palladium complex **II**. Subsequently, the intramolecular Heck-type process afforded the alkyl–palladium species **III**,<sup>32</sup> which would undergo  $\beta$ -hydride elimination to release product **3** and Pd<sup>0</sup>. Finally, the catalyst was regenerated to complete the catalytic cycle. Under the assistance of Cu(II), the oxygen oxidized the Pd<sup>0</sup> to Pd<sup>II</sup>. When acrylic amide was used as the starting material, the annulation product would undergo acylation under the acid conditions and afford the observed product **4**.

In summary, we have developed a highly efficient strategy for the synthesis of  $\alpha$ -pyrones and pyridones via Pd-catalyzed oxidative [4 + 2] annulations between acrylic derivatives and internal alkynes with high regioselectivity. The usage of O<sub>2</sub> (1 atm) as a stoichiometric oxidant with H<sub>2</sub>O as the only byproduct under mild conditions makes this process more attractive and practical. The detailed mechanistic studies and further applications of this reaction are currently underway in our laboratory.

### ■ ASSOCIATED CONTENT

#### Supporting Information

Experimental section, characterization of all compounds, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## Author Contributions

<sup>†</sup>Y.Y. and L.H. contributed equally.

## Notes

The authors declare no competing financial interest.

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