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# Electrochemical Palladium-Catalyzed Oxidative Sonogashira Carbonylation of Arylhydrazines and Alkynes to Ynones

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**ABSTRACT:** Oxidative carbonylation using carbon monoxide has evolved as an attractive tool to valuable carbonyl-containing compounds, while mixing CO with a stoichiometric amount of a chemical oxidant especially oxygen is hazardous and limits its application in scale-up synthesis. By employing anodic oxidation, we developed an electrochemical palladium-catalyzed oxidative carbonylation of arylhydrazines with alkynes, which is regarded as an alternative supplement of the carbonylative Sonogashira reaction. Combining an undivided cell with constant current mode, oxygen-free conditions avoids the explosion hazard of CO. A diversity of ynones are efficiently obtained using accessible arylhydrazines and alkynes under copper-free conditions. A possible mechanism of the electrochemical Pd(0)/Pd(II) cycle is rationalized based upon cyclic voltammetry, kinetic studies, and intermediates experiments.

Y nones are core skeletons of various natural and bioactive compounds, as well as important synthetic building blocks that can be converted into complex molecules (Scheme 1A).<sup>1</sup> Thus, considerable attention has been focused toward preparing this structural unit.<sup>2</sup> Besides the traditional crosscoupling reactions of terminal alkynes with acyl chlorides, the carbonylative Sonogashira-type reaction which employs easily available aryl halides, alkynes, and CO as coupling partners is a conventional route for the direct preparation of ynones.<sup>3</sup> Despite its great contribution to ynone synthesis, this transformation suffers from the generation of halide-containing chemical wastes, multistep processes, and harsh reaction conditions (Scheme 1B-1).<sup>2e,4</sup> Recently, severe environmental problems motivate chemists to develop new synthetic methodologies to minimize the generation of chemical wastes.

Oxidative carbonylation reactions using O2 have attracted broad interest, which provides a direct route to carbonyl derivatives under mild conditions.<sup>5</sup> However, the mixture of  $CO/O_2$  results in safety issues, limiting practical application in industry. The Beller group developed an efficient strategy for carbonylative Sonogashira reactions of anilines under mild conditions, the strategy proceeds with the assistance of stoichiometric <sup>t</sup>BuONO (Scheme 1B-2).<sup>6</sup> Organo-electrosynthesis that uses electric current as redox reagents attracts increasing attention due to its great potential in the commitment of developing green and sustainable methods. Electrochemical anodic oxidation provides a great opportunity to realize transition-metal catalyzed oxidative carbonylation under external oxidant-free conditions.<sup>8</sup> In the electrocatalytic carbonylation reaction, the challenge is the deactivation of high valent metal species in the cathodic cell, which decreases the catalytic efficiency. Divided cells are used as a solution to prevent the deposition of metal catalysts on the cathode. We envision that the modification of ligand and reaction conditions can tune the potential of the metal complex,

achieving an electrochemical aminocarbonylation of alkynes in the undivided cell.  $^9$ 

As a part of continued interest in oxidative carbonylation and synthetic methods of ynones,<sup>10</sup> herein, we developed an electrochemical palladium-catalyzed oxidative carbonylation of arylhydrazines with alkynes in an undivided cell, which is regarded as an alternative supplement of carbonylative Sonogashira reaction (Scheme 1C). We achieved an external oxidant-free electrochemical oxidation of Pd(0) to Pd(II), avoiding the usage of stoichiometric amounts of chemical oxidants.

Phenylhydrazines which could be easily prepared from anilines have previously proved to be a potential aryl reagent with the release of environmental-friendly  $N_2$  as a byproduct.<sup>1</sup> We started our research by using phenylhydrazine hydrochloride (1a) and phenylacetylene (2a) as a model reaction to investigate the effects of reaction parameters. Optimization of the reaction is shown in Table 1. The reaction was carried out in an undivided cell with a carbon felt anode and a graphite rod cathode under 1.5 mA (4.5 F/mol) in the CO atmosphere. Different Pd salts were used as the catalyst precursors, and only  $Pd(PPh_3)_2Cl_2$  gave a 31% yield to access desired ynone (entries 1-3). Notably, a phosphine ligand was crucial in this transformation. Efforts were also taken to change the ligands using PdCl<sub>2</sub> as the catalyst precursor, indicating that PPh<sub>3</sub> gave the best result (entries 4–7). By combining  $Pd(PPh_3)_2Cl_2$  with  $PPh_3$  ligand, the yield could be raised to 65% (entry 8).

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## Scheme 1. (A) Bioactive Products with Ynones Structure; (B) Carbonylative Sonogashira Reaction; (C) Electrochemical Pd-Catalyzed Oxidative Carbonylation of Arylhydrazines and Alkynes



Furthermore, several iodine sources were used as additives to enhance the reaction efficiency (entries 9–11). Delightfully, adding an additional 30 mol % of NH<sub>4</sub>I led to an excellent yield (entry 11). A trace amount of product could be detected when using O<sub>2</sub>, 1,4-Benzoquinone (BQ), or other oxidation reagents as the oxidant but switching off the electricity (entries 12–13 and Table S1), indicating the specialty of electrosynthesis to distinguish from the traditional oxidation method. Pd(PPh<sub>3</sub>)<sub>4</sub> was examined as the Pd(0) catalyst, and a satisfactory yield could be also obtained (entry 14). Control experiments showed that Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> was indispensable for the electrooxidative carbonylation (entry 15).

Encouraged by these results, we next investigated the scope of this electrooxidative carbonylative Sonogashira-type reaction. Various alkynes were tested under the standard reaction conditions (Table 2). First, the reaction of *para-, meta-,* and *ortho*-methyl-substituted phenylacetylene all proceeded well and afforded the corresponding ynones in 92–85% yields (**3b**–**3d**), indicating that steric hindrance of phenylacetylene has little influence on reaction efficiency. Notably, halogens such as F, Cl, and Br were all tolerated in this transformation, thus providing a possibility for further functionalization (**3e**–

Table 1. Summary of the Effects of Reaction Parameters and Conditions on the Reaction Efficiency  $\!\!\!\!^a$ 

		<b>I<sup>II</sup>I</b> undivided (+) carbon felt I gra 5 mol% <b>[P</b> 10 mol% <b>lig</b> a	$\sim$	
<u>\_</u> /"		30 mol% add		
		MeCN, 1 atm. C		
	1a 2a			3a
Entry	[Pd]	Ligands	Additives	Yield (%) <sup>b</sup>
1	PdCl <sub>2</sub>	-	_	trace
2	$Pd(OAc)_2$	-	-	trace
3	$Pd(PPh)_2Cl_2$	-	-	31
4	PdCl <sub>2</sub>	PPh <sub>3</sub>	_	56
5	PdCl <sub>2</sub>	$P(p-tol)_3$	-	53
6	PdCl <sub>2</sub>	$P(m-tol)_3$	_	20
7	PdCl <sub>2</sub>	Xantphos	-	trace
8	$Pd(PPh_3)_2Cl_2$	PPh <sub>3</sub>	-	65
9	$Pd(PPh_3)_2Cl_2$	PPh <sub>3</sub>	KI	70
10	$Pd(PPh_3)_2Cl_2$	PPh <sub>3</sub>	TBAI	57
11	$Pd(PPh_3)_2Cl_2$	PPh <sub>3</sub>	$NH_4I$	84(83) <sup>c</sup>
12 <sup>d</sup>	$Pd(PPh_3)_2Cl_2$	PPh <sub>3</sub>	$NH_4I$	trace
13 <sup>e</sup>	$Pd(PPh_3)_2Cl_2$	PPh <sub>3</sub>	$NH_4I$	21
14	$Pd(PPh_3)_4$	PPh <sub>3</sub>	$\rm NH_4I$	58
15	-	PPh <sub>3</sub>	$\rm NH_4I$	n.d.

<sup>*a*</sup>Reaction conditions: **1a** (0.40 mmol), **2a** (0.25 mmol), [Pd] (5.0 mol %), ligands (10 mol %), additives (30 mol %), "Bu<sub>4</sub>NBF<sub>4</sub> (0.20 mmol), NEt<sub>3</sub> (0.75 mmol), and CH<sub>3</sub>CN (6 mL) in an undivided cell with a carbon felt anode, a graphite rod cathode, CO balloon, 25 °C, 1.5 mA, 20 h, 4.5 F/mol. <sup>*b*</sup>The yield of **3a** was determined by GC analysis with biphenyl as the internal standard; n.d. = not detected. <sup>*c*</sup>Isolated yield. <sup>*a*</sup>No electricity, CO/O<sub>2</sub> = 1/1. <sup>*e*</sup>No electricity, BQ was used as the oxidant.

**3h**). The electron-rich aryl alkynes bearing -Pentyl,  $-{}^{t}Bu$ , -Ph, and -OMe were well tolerated, furnishing 3i-3l in 70– 87% yields. Strongly electron-withdrawing groups such as  $-CF_3$ , -COOMe, -COMe, and -CN proved compatible but afforded generally lower yields as a result of lower conversion (3m-3p). Substrates bearing naphthalenyl or thiophene were suitable under the reaction conditions and provided corresponding products 3q and 3r in 66% and 71% yields, respectively. Both aliphatic acyclic and cyclic terminal alkynes could be introduced as substrates for this process (3s and 3t).

Variation of the arylhydrazine hydrochlorides were also examined, and the results were shown in Table 2. It appeared that the position of the substituents on the phenyl ring has a limited effect on the reaction efficiency (3aa-3ac). Disubstituted substrates such as 3, 5-dimethyl phenylhydrazine hydrochlorides could also successfully undergo the electrochemical oxidative carbonylation reaction to afford moderate yield (3ad). Halogen-substituted phenylhydrazine hydrochlorides could give desired products in moderate yields under the standard reaction conditions (3ae-3ag), providing us the opportunities for further functionalization. Both electron-rich and electron-deficient phenylhydrazines were well tolerated in this transformation (3ah-3am). Substrates bearing 1-naphthalenyl or 2-naphthalenyl were compatible with this electrochemical process.

The potential of the strategy was further documented by the late-stage functionalization of bioactive molecules. For this purpose, various alkyne-containing compounds were examined. It was found that a herbicide molecule, propyzamide, could







<sup>*a*</sup>Reaction conditions: **1** (0.40 mmol), **2** (0.25 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5.0 mol %), PPh<sub>3</sub> (10 mol %), NH<sub>4</sub>I (30 mol %), "Bu<sub>4</sub>NBF<sub>4</sub> (0.20 mmol), NEt<sub>3</sub> (0.75 mmol), and CH<sub>3</sub>CN (6 mL) in an undivided cell with a carbon felt anode, a graphite rod cathode, 25 °C, 1.5 mA, 20 h, 4.5 F/mol. Isolated yields are reported. <sup>*b*</sup>10 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and 4 mL of CH<sub>3</sub>CN used.

react with phenylhydrazine hydrochloride smoothly and afforded the ynone derivative in 87% yield  $(3\mathbf{u})$ . Satisfyingly, this reaction also enables the functionalization of estrone-, naproxen-, and ibuprofen-containing alkyne, which highlighted the potential of the strategy in the pharmaceutical intermediate  $(3\mathbf{v}-3\mathbf{x})$ . Additionally, the alkyne derived from levulinic acid was smoothly converted into the desired products in 69% yield  $(3\mathbf{y})$ .

A 10 mmol scale synthesis was performed to demonstrate the synthetic utility of this electrochemical approach. As shown in Scheme 2, the reaction with 1a and 2a furnished the





corresponding ynone (3a) in 51% yield (1.05 g) by using 20 mA (3.0 F/mol) (Scheme 2A). Furthermore, one of the antiinflammatory and analgesic drugs FSY could be obtained in 60% yield under standard electrochemical conditions, indicating that this electrosynthesis strategy had some potential in drug preparation (Scheme 2B).

To verify the role of electricity and possible active intermediates in the reaction system, stoichiometric reactions were performed (Scheme 3). The arylpalladium species Pd-1 were isolated through the reaction between  $Pd(PPh_3)_4$  and  $PhNHNH_2$  under electrochemical conditions (Scheme 3A). In addition, stoichiometric Pd-1 and acyl palladium Pd-2 reacted with 2a smoothly to give a moderate yield under the standard conditions but without electricity (Scheme 3B). Based on the stoichiometric results, electric current is key for the oxidation of Pd(0) to Pd(II) and activation of arylhydrazines. Aryl-Pd and acyl palladium are the possible intermediates for the electrochemical carbonylative reactions.

To further understand the mechanism, some control experiments were carried out. When the catalytic amount of Pd species Pd-1 and Pd-2 were utilized as the catalysts, satisfied yields could also be obtained (Scheme 3C). These catalytic results further verified that Pd-1 and Pd-2 are key intermediates in the transformation. The intermolecular KIE experiment proved that the C-H bond cleavage of phenyl-acetylene was not involved in the rate-determining step (Scheme 3D). The influence of the concentration has been evaluated as shown in Scheme 3E. The reaction rate remained unchanged when the concentration of 2a was halved, further confirming the C-H bond activation step is fast.

Cyclic voltammetry (CV) experiments were carried out to gain insights into this carbonylation reaction as shown in Scheme 4. First, the substrates and the additives were tested. No obvious oxidation peaks were observed within the range 0 to 2 V for phenylacetylene and phenylhydrazine hydrochloride (Figure S1 red and blue lines), which indicated that these substrates are difficult to activate directly. The mixture of phenylhydrazine hydrochloride and 1 equiv of NEt<sub>3</sub> showed an obvious peak at 0.65 V (Figure S1, green line). Moreover, the oxidation peaks of NEt<sub>3</sub>, PPh<sub>3</sub> and NH<sub>4</sub>I were recorded under the optimized conditions showed 1.05, 1.03, and 0.42 V respectively (Scheme 4A). The oxidation potential of the NH<sub>4</sub>I is the lowest among these substrates and additives. Next, the

# Scheme 3. Preliminary Mechanistic Studies

A) Stoichiometric Pd(0) react with phenylhydrazine under electricity



B) Stoichiometric Pd species react with alkyne under standard condition but without electricity





E) Kinetic profiles under different concentrations of 2a/1a



oxidation potentials of catalytic species were investigated. An inconspicuous peak was observed at 0.11 V for  $Pd(MeCN)_2Cl_2$  under a CO atmosphere (Scheme 4B, black line). However,

#### Scheme 4. Cyclic Voltammetry Studies

A) CV of substrate and additives



B) CV of catalytic species



Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> with 2 equiv of PPh<sub>3</sub> displayed no peaks within the range 0 to 0.5 V due to the poor solubility (Scheme 4B, red line). Furthermore, the mixture of Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>, 2 equiv of PPh<sub>3</sub>, and 3 equiv of NH<sub>4</sub>I showed an obvious peak at 0.22 V, indicating that the oxidation from Pd(0) species was generated by the reduction of NH<sub>4</sub>I under a CO atmosphere to Pd(II) species (Scheme 4B, blue line).<sup>12</sup> Pd(0) species were also formed from the reaction between Pd(II) species and PhNHNH<sub>2</sub> because the mixture of Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>, 2 equiv of PPh<sub>3</sub>, and 1 equiv of PhNHNH<sub>2</sub> revealed an oxidation peak of Pd(0)/Pd(II) at 0.14 V (Scheme 4B, green line).

The oxidation potentials during the whole reaction process were recorded by an external voltmeter. As shown in Scheme 5, the range of oxidation potential was between 0 to 0.1 V for the first 16 h. The oxidation potential then increased gradually to 0.45 V for the last 4 h. These results indicated that only





Pd(0) species were oxidized by anode for most of the time until substrates were used up.

A proposal mechanism is provided according to the above experiments and previous related work.<sup>10b,13</sup> As shown in Scheme 6,  $Pd^{II}$  precursor A prefers to react with 1 to give the

Scheme 6. Proposal Mechanism



aryl Pd species **B** along with the release of N<sub>2</sub>. Subsequent CO insertion into the C–Pd bond of **B** affords the palladium carbamoyl intermediate **C**. Terminal alkynes **2** then react with species **C** to give ynones **3** and Pd(0) species **D** by reductive elimination. Pd(0) species **D** may also be generated by the reduction of NH<sub>4</sub>I. Finally, Pd catalysts undergo recycle by anodic oxidation along with hydrogen evolution on cathode.

In summary, a novel palladium-catalyzed electrochemical carbonylative Sonogashira-type cross-coupling reaction has been developed. Various arylhydrazines and alkynes were well tolerated under mild reaction conditions, giving biologically important ynones as the products. Through mechanistic studies, key Pd reactive intermediaters were verified and an electric current served as a reagent for the oxidation of Pd(0) to Pd(II). We suppose that this transformation would contribute significantly to the development of electrochemical carbonylative Sonogashira-type reactions.

## ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c06036.

The experimental procedure, characterization data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

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