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Yingwei Zhao and Qiuling Song\*

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# Palladium-catalyzed aerobic oxidative cross-coupling of arylhydrazines with terminal alkynes

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A palladium-catalyzed Sonogashira-type aerobic oxidative coupling of arylhydrazines with terminal alkynes via C-N bond cleavage has been developed; internal alkynes were afforded with a broad substrate scope. This reaction proceeds under copper- and base-free conditions with molecular oxygen as the sole oxidant and nitrogen and water as the only byproducts.

Palladium-catalyzed cross-coupling of terminal alkynes with aryl electrophiles, widely known as Sonogashira reaction<sup>1</sup>, has become the most important method to prepare internal arylalkynes or enynes, which are precursors for natural products,<sup>2</sup> pharmaceuticals,<sup>3</sup> and molecular organic materials.<sup>4</sup> Aryl iodides, bromides, triflates, and tosylates are commonly used electrophilic counterparts which undergo oxidative addition to the Pd(0) species smoothly. Although they are successfully applied substrates, the requirement of equivalents of inorganic or organic base leads to the generation of salt waste which could not be avoided (Scheme 1). Also, use of a copper salt as cocatalyst is commonly required. Thus, the development of more economic and environmentally benign arylation reagents and milder reaction conditions are still highly desirable. Arylhydrazines could be a class of ideal candidates due to their good reactivity in generating aryl segments via oxidative C-N bond cleavage for coupling reactions, with nitrogen gas as the byproduct. Meanwhile, they are inexpensive and commercially available, which is important to broaden the application scope. In the past decades, elegant examples have been developed by employing arylhydrazines as an aryl synthon in organic reactions commonly through the formation of free aryl radical<sup>5</sup> or aryl-transition metal complex<sup>6</sup> under oxidative conditions. Early reports showed that stoichiometric amount of high valent metal oxidant such as lead(IV) acetate,<sup>5e</sup> manganese(III) acetate <sup>5f, 5h</sup> and barium ferrate,<sup>7</sup> or hypervalent iodine(V) reagent<sup>5c</sup> could oxidatively decompose phenylhydrazine to produce the phenyl radical. The drawback of these oxidants is obvious. Molecular oxygen is an ideal oxidant to replace the above reagents owing to its abundance, readily availability and sustainability. Recently, some attention has been paid to apply dioxygen as the oxidant in some transition-metalcatalyzed coupling reactions using arylhydrazines as the starting material<sup>5a, 5b, 5k, 5m-o, 6a-c, 6e, 6f</sup>. Herein, we describe our successful

aerobic oxidative cross coupling of arylhydrazines in Sonogashira reactions under copper- and base-free conditions with a broad substrate scope, including the approach of Br-substituted diarylacetylenens which could not be readily obtained in tranditional Sonogashira couplings.



Scheme 1 Sonogashira coupling with different arylation reagents

We began our study with the selection of phenylhydrazine (1a) and phenylacetylene (2a) as model substrates to optimize the reaction conditions (Table 1). Initially in the presence of Pd(OAc)<sub>2</sub> or PdCl<sub>2</sub> catalyst, PPh<sub>3</sub> ligand and 3 equivalents of pivalic acid additive, the desired product diphenylacetylene (3aa) was obtained in low yield when the reaction was carried out in DMF at room temperature for 12 h under air atmosphere (entries 1 and 3). When CuI was used as cocatalyst, a large amount of Glaser-type<sup>8</sup> oxidative homocoupling product (1,4-diphenylbuta-1,3-diyne) of phenylacetylene was obtained (entry 2). To our delight, when the reaction was performed under 1 atm of oxygen, the yield of 3aa was increased to 43% in the absence of a copper salt (entry 4), only a trace amount of homocoupling products and diphenylethylene were detected on GC. Raising the reaction temperature to 50 °C and using of acetic acid instead of pivalic acid led to a satisfactory result (entry 6). We then examined the role of different ligands. It was shown that only PPh<sub>3</sub> was effective, and other ligands such as 1,10-phen, bidentate or bulky phosphanes did not promote this reaction efficiently (entries 7-11). Also, higher or lower loading of PPh<sub>3</sub> ligand led to a decrease in product yield (entries 12 and 13). Next, we found that solvent played an important role for the success of this reaction. In addition to DMF, only DMA gave a modest yield of the desired product. Other solvents severely inhibited the catalytic

process (entries 15-20). Finally, this reaction did not occur under a nitrogen atmosphere, indicating the essential role of dioxygen in this catalytic process (entry 21).

a

$\square$		· =_√¯	catal	yst / ligand	•	
\	/ 1a	2a	/ O <sub>2</sub> , a	dditive, 12 h	\ <u> </u> /	Saa 🔪
Entry	Catalyst	Ligand	Solvent	Additive	Temp. (°C)	Yield (%)
1 <sup><i>b</i></sup>	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	DMF	Piv-OH	25	21
2 <sup><i>b</i></sup>	Pd(OAc) <sub>2</sub> /CuI	PPh <sub>3</sub>	DMF	Piv-OH	25	16 (30) <sup>c</sup>
3 <sup><i>b</i></sup>	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMF	Piv-OH	25	25
4	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMF	Piv-OH	25	43
5	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMF	Piv-OH	50	56
6	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMF	AcOH	50	82 (74) <sup>d</sup>
7	PdCl <sub>2</sub>	1,10-phen	DMF	Piv-OH	50	6
8	PdCl <sub>2</sub>	PCy <sub>3</sub>	DMF	AcOH	50	9
9	PdCl <sub>2</sub>	P <sup>t</sup> Bu <sub>3</sub>	DMF	AcOH	50	18
10	PdCl <sub>2</sub>	dppb	DMF	AcOH	50	5
11	PdCl <sub>2</sub>	dppf	DMF	AcOH	50	28
12 <sup>e</sup>	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMF	AcOH	50	40
13 <sup><i>f</i></sup>	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMF	AcOH	50	50
14	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMF	AcOH	80	43
15	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMA	AcOH	50	53
16	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMSO	AcOH	50	trace
17	PdCl <sub>2</sub>	PPh <sub>3</sub>	toluene	AcOH	50	trace
18	PdCl <sub>2</sub>	PPh <sub>3</sub>	NMP	AcOH	50	16
19	PdCl <sub>2</sub>	PPh <sub>3</sub>	dioxane	AcOH	50	0
20	PdCl <sub>2</sub>	PPh <sub>3</sub>	MeCN	AcOH	50	0
21 <sup>g</sup>	PdCl <sub>2</sub>	PPh <sub>3</sub>	DMF	AcOH	50	0

<sup>*a*</sup> Reaction conditions: **1a** (1.75 mmol), **2a** (0.5 mmol), catalyst (0.025 mmol), ligand (0.15 mmol), additive (1.5 mmol), O<sub>2</sub> (1 atm), solvent (1.5 mL). Yields were based on the GC analysis with dodecane as the internal standard. <sup>*b*</sup> The reactions were carried out under open air. <sup>*c*</sup> The yield in the bracket was that of the oxidative homocoupling product from **2a**. <sup>*d*</sup> Isolated yield. <sup>*e*</sup> 0.25 mmol of PPh<sub>3</sub> (50 mol %) was used. <sup>*f*</sup> 0.075 mmol of PPh<sub>3</sub> (15 mol %) was used. <sup>*g*</sup> The reaction was carried out under nitrogen.

Having identified the optimized reaction conditions, we next explored the scope and generality of this process (Scheme 2). First, a

variety of substituted aryl acetylenes were allowed to react with phenylhydrazine (1a). It could be seen that 4-alkysubstituted phenylacetylenes were transformed to the corresponding diaryl acetylenes in high yields (3ab and 3ac). Good yields could be obtained when other electron-donating groups such as phenyl and alkoxyl were on the phenyl ring (3ad and 3ae). The electrondeficient aryl acetylenes also exhibited good reactivity (**3af-3ak**). It is noteworthy that the potentially labile Br and Cl were inert in this reaction (3ag and 3ai). Next, the scope of arylhydrazines was also surveyed. Initially, the direct use of commercially available arylhydrazine hydrochlorides as the substrates did not lead to the desired products. Pretreatment of these hydrochloride salts with NaOH is required. Different substituted arylhydrazines and alkynes were evaluated under the optimal reaction conditions. Either electron-rich (3bi-3di) or electron-deficient group (3ei-3gl) substituted arylhydrazines worked well for this reaction to give the corresponding diarylacetylenes in good to excellent yields. The bromine-substituted products (3bi-3fi), which could not be readily obtained in tranditional Sonogashira couplings, were obtained successfully by our protocol. This effect was known in many coupling reactions under base-free9 or acidic conditions.10 Last not the least, the substrate 4-hydrazinylbenzonitrile (1g) was able to react with aliphatic alkynes. The reaction with benzyl acetylene (2m) led to the desired product 3gm in 58% yield. Simple 1-octyne was also feasible, though the yield of 3gn was low.



Scheme 2 Substrate Scope. Reaction conditions: 1 (1.75 mmol), 2 (0.5 mmol), PdCl<sub>2</sub> (0.025 mmol), PPh<sub>3</sub> (0.15 mmol), AcOH (1.5 mmol),  $O_2$  (1 atm), DMF (1.5 mL). Yields were based on the isolated products.

This reaction was also compatible with a larger scale (5 mmol of alkyne substrate **2i**) under the optimized condition. (Scheme 3). The desired product **3ai** was obtained in 52% yield.

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Based on the above studies and discussions on palladium complexes containing N-N multiple bonds in previous reports,<sup>11</sup> and the detailed study on the reaction of Pd<sup>II</sup> complex with phenylhydrazine (1a) carried out by Loh et al.,<sup>6e</sup> a general mechanism is illustrated in Scheme 4. Initially, ligand exchange precursor by phenylhydrazine affords the of the Pd<sup>II</sup> palladadiaziridine (I), which allows the oxidative addition with Pd<sup>0</sup> to afford the two Pd<sup>II</sup>-centered complex **II**. Protonolysis of releases the arylpalladium complex III and the Π palladiaziridine complex IV, which collapses to give Pd<sup>0</sup>, nitrogen gas, and water in the presence of oxygen. The reaction of palladium complex III with terminal alkyne 2a might experience a typical complexation-dehydropalladationreductive elimination to afford the product 3aa. The anionic ligand X (OAc) might play the role of internal base.<sup>12</sup> However, a carbopalladation-β-hydride elimination step is also feasible, which could be found in many base-free cases.<sup>13</sup> Finally, the catalytic cycle is closed upon reoxidation of  $Pd^0$  to  $Pd^{II}$  by oxygen with the assistance of acetic acid.



Scheme 4 Plausible reaction mechanism

### Conclusions

In summary, we have developed a new type of Sonogashira cross coupling reaction by using commercially available arylhydrazines as the arylation reagents to prepare internal alkynes. This reaction is performed under mild conditions without the addition of copper salt or base. The substrate scope is broad and also, the utilization of 1 atm of  $O_2$  as the environmentally benign oxidant makes the protocol very attractive for both academia and industry. Further investigations to gain a detailed mechanistic understanding of this reaction are currently underway.

### Notes and references

<sup>*a*</sup> Institute of Next Generation Matter Transformation, College of Chemical Engineering at Huaqiao University, 668 Jimei Blvd, Xiamen, Fujian, 361021, P. R. China. E-mail: qsong@hqu.edu.cn

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