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Copper-catalyzed carbonylative Suzuki coupling of aryl iodides with arylboronic acids under ambient pressure of carbon monoxide†

Laijin Cheng, Yanzhen Zhong, Zhuchao Ni, Hongyan Du, Fengli Jin, Qi Rong and Wei Han*

An efficient and ligandless nanocopper-catalyzed carbonylative cross-coupling of aryl iodides with arylboronic acids at ambient CO pressure in poly(ethylene glycol), has been developed. This protocol is general, practical, and recyclable, and offers an attractive alternative to the corresponding palladium-mediated carbonylative Suzuki process for the construction of biaryl ketone scaffolds.

Cross-coupling of aryl halides, arylboronic acids and carbon monoxide (the carbonylative Suzuki reaction[1]) has been developed as a powerful tool for the construction of biaryl and heterobiaryl ketones. Moreover, these structural motifs are core scaffolds that are found in a tremendous range of pharmaceuticals, advanced organic materials, and photosensitizers.[2] Consequently, establishing a mild, practical, economical, and efficient access to biaryl and heterobiaryl ketones is of great significance.

Since the first example of carbonylative Suzuki reaction was reported by Suzuki *et al.*[1] extensive work has been done to make the transformation more efficient and to widen its substrate scope.[3] However, the overwhelming majority of the reported methods requires a high pressure (often ≥5 bar). Although few examples of carbonylative Suzuki coupling of aryl iodides under ambient pressure of carbon monoxide have been reported,[4] palladium remains the metal of choice in almost all cases, causing several shortcomings, particularly from the perspective of its pragmatic application because of the high cost, toxicity of the metal, and the necessity of utilizing expensive ligands. To address these issues, the development of more sustainable, economical, and eco-friendly protocol for the aforementioned transformation is particularly desirable. Very recently, we first reported iron replaced palladium to catalyze carbonylative Suzuki reaction and satisfactory results can be obtained.[5] However, this protocol is inefficient to catalyzed successive carbonylation of aryl diiodides.

Copper has a strong advantage in terms of cost and toxicity compared to palladium. And copper has been widely applied in organic synthesis and oftentimes emerges as an alternative to conduct established palladium-catalyzed cross-coupling reactions.[6] Copper-based catalysts have been broadly employed in oxidative carbonylation of alcohols with carbon monoxide.[7] Comparatively, copper-catalyzed carbonylation of aryl halide is quite limited. Moreover, the limited examples of aminocarbonylation[8] and carbonylative sonogashira[9] of aryl iodide require high pressures of carbon monoxide and ligands to ensure efficient catalysis. Copper-catalyzed carbonylation of diphenyliodonium tetrafluoroborate with arylboronic acids for the synthesis of biaryl ketones was reported by Kang and co-workers.[10] Since diphenyliodonium tetrafluoroborate is made from phenyl iodide, it would be advantageous to directly carbonylate aryl iodides. Unfortunately, until to date no general copper-catalyzed carbonylative Suzuki reaction of aryl halide exists. We report here first example of copper-catalyzed carbonylative Suzuki reaction of aryl iodide with arylboronic acid under atmospheric pressure of carbon monoxide. Our previous work demonstrated palladium nanoparticles catalyzed carbonylative Suzuki reaction of aryl iodide with a high level of efficacy even in the absence of a ligand in PEG-400 [poly(ethylene glycol) with an average molecular weight of 400 Da].[4a] This work prompts us to search for nanocopper-catalyzed carbonylative Suzuki reaction without the assistance of an additional ligand.

Initially, we employed copper nanoparticles for the catalysis of carbonylative Suzuki reaction of 4-iodonitrobenzene with phenylboronic acid and carbon monoxide (1 atm) to identify optimum reaction conditions. Selected results are summarized in Table 1. On the basis of our previous work of developing PEG-based ligand-free transition metal-catalyzed cross coupling reactions,[4a,5,11] we performed the model reaction in PEG-400

Jiangsu Collaborative Innovation Center of Biomedical Functional Materials, Jiangsu Key Laboratory of Biofunctional Materials, Key Laboratory of Applied Photochemistry, School of Chemistry and Materials Science, Nanjing Normal University, Wenyuan Road no. 1, 210023 Nanjing, China. E-mail: whhanwei@gmail.com; Fax: +86-25-8589-1455

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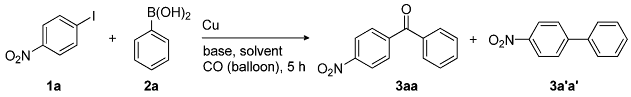
Table 1 Nanocopper-catalyzed carbonylative Suzuki reaction of **1a** with **2a**[a]



Entry	Acid	Base	Solvent	Yield of **3aa** (%)	Yield of **3a′a′** (%)
1	—	K_3PO_4	PEG-400	73	14
2	*t*-BuCOOH	K_3PO_4	PEG-400	90(75)[b]	<5
3	CH_3COOH	K_3PO_4	PEG-400	25	<5
4	CF_3COOH	K_3PO_4	PEG-400	43	Trace
5	*t*-BuCOOH	K_2CO_3	PEG-400	55	43
6	*t*-BuCOOH	Na_2CO_3	PEG-400	82	8
7	*t*-BuCOOH	KF	PEG-400	72	Trace
8	*t*-BuCOOH	TBAF	PEG-400	5	—
9	*t*-BuCOOH	AcOK	PEG-400	21	Trace
10	*t*-BuCOOH	K_3PO_4	PEG-200	82	10
11	*t*-BuCOOH	K_3PO_4	PEG-2000	5	—
12	*t*-BuCOOH	K_3PO_4	Ethylene glycol	10	89
13	*t*-BuCOOH	K_3PO_4	PEGDM-190	8	<5
14[c]	*t*-BuCOOH	K_3PO_4	PEG-400	82	<5
15[d]	*t*-BuCOOH	K_3PO_4	PEG-400	45	Trace
16[e]	*t*-BuCOOH	K_3PO_4	PEG-400	47	Trace

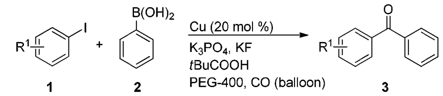
[a] Reaction conditions (unless otherwise stated): **1a** (0.5 mmol), **2a** (0.75 mmol), CO (balloon), base (1.0 mmol), acid (0.25 mmol), nanocopper (20 mol%), solvent (2.0 mL), 80 °C. [b] Nanocopper (10 mol%). [c] Cu_2O (20 mol%). [d] CuCl (20 mol%). [e] CuBr (20 mol%).

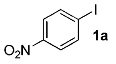
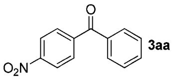
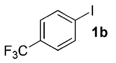
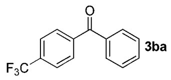
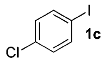
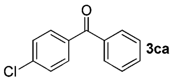
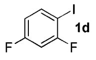
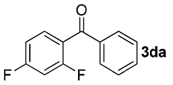
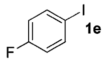
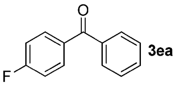
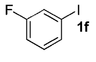
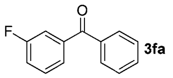
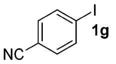
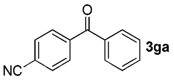
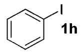
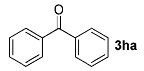
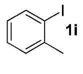
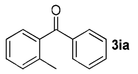
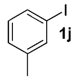
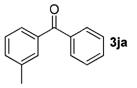
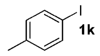
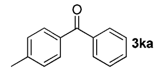
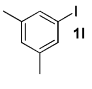
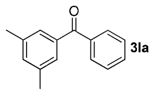
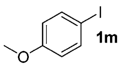
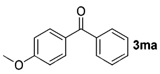
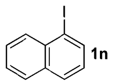
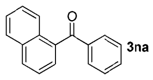
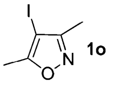
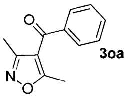
with K_3PO_4 as a base. Consequently, the desired product **3aa** can be obtained in 73% yield, whereas the side product form Suzuki coupling was also formed in 14% yield (Table 1, entry 1). Very recently, we reported pivalic acid effectively suppressed Suzuki coupling and favored carbonylative Suzuki coupling.[4a] As expected, in the presence of the pivalic acid an excellent yield of **3aa** was generated with a little amount of the side product (<5%) (Table 1, entry 2). Other acids such as CH_3COOH and CF_3COOH just gave poor results (Table 1, entries 3 and 4). Successively, other various bases were tested. Na_2CO_3 and KF showed superior results compared with other bases such as K_2CO_3, TBAF, and AcOK (Table 1, entries 5–9), albeit with less efficiency in terms of yields than K_3PO_4. Of the solvents evaluated, PEG-400 gave the best results (Table 1, entry 2). Notably, ethylene glycol and poly(ethylene glycol) dimethyl ether (PEGDM-190) were found to be ineffective (Table 1, entries 12 and 13), suggesting that the unique structure of PEG-400 bearing both hydroxyl groups and a polyether chain played a critical role in this reaction. Other catalysts, such as Cu_2O, CuCl, and CuBr were examined and were observed to be less effective than nanocopper catalyst (Table 1, entries 14–16).

Next, we investigated the first copper-catalyzed method for carbonylative Suzuki reactions of various aryl iodides. However, we observed that more unactivated substrates compared with 4-iodonitrobenzene were unsuitable to the above-established reaction conditions. In the Table 1, KF as a base gave a better selectivity than K_3PO_4, albeit with moderate efficiency (entry 3). After a concise reevaluation, we found out that the addition of KF (0.5 equiv.) can ensure effective catalysis at an elevated temperature (100 °C) (Table 2). The carbonylative Suzuki reactions of aryl iodides with phenylboronic acid demonstrated that electron-deficient as well as electron-rich aryl iodides worked well. And the electronic nature of the aryl iodides had a minor impact on the observed yields. Fluoro- and trifluoromethyl-substituted aryl iodides were reactive and afforded the corresponding products in 75–91% yields (Table 2, entries 2, and 4–6), which are potentially useful for the synthesis of pharmaceuticals and advanced materials.[12] Sterically hindered 2-iodotoluene also proceeded smoothly (Table 2, entry 9). We were pleased to find that a heterocyle 4-iodo-3,5-dimethylisoxazole (**1o**) and 1-iodonaphthalene were suitable substrates and provided the expected products in 90% and 87%, respectively (Table 2, entries 15 and 14). Intriguingly, 1,4-diiodobenzene (**1p**) and 1,3-diiodobenzene (**1q**) could undergo successive carbonylation effectively and furnish corresponding diketones that are important intermediates for advanced functional materials,[2a,2d] in 87% and 75% yields, respectively (Scheme 1).

To further explore the scope, we extensively surveyed the carbonylative Suzuki reactions of various aryl iodides with representative arylboronic acids under the optimized conditions (Scheme 2). In general, unsubstituted, *para*-, *meta*-, and *ortho*-substituted arylboronic acids afforded desired products in good to excellent yields. The electronic nature of the arylboronic acids was observed to be loosely correlated with their reactivity. The reaction conditions were compatible with methyl, methoxy, aldehyde, cyano, fluoro, and chloro groups. Treatment of

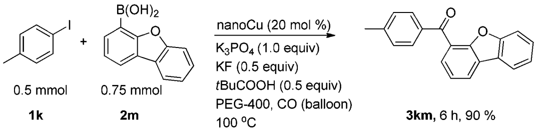
Table 2 Nanocopper-catalyzed carbonylative Suzuki reaction of **2a** with various aryl iodides[a]



Entry	Aryl iodide	Product	Time (h)	Yield[b] (%)
1[c]	 **1a**	 **3aa**	5	90
2	 **1b**	 **3ba**	9	75
3	 **1c**	 **3ca**	12	89
4	 **1d**	 **3da**	12	91
5	 **1e**	 **3ea**	12	90
6	 **1f**	 **3fa**	4	91
7	 **1g**	 **3ga**	9	80
8	 **1h**	 **3ha**	5	95
9	 **1i**	 **3ia**	24	93
10	 **1j**	 **3ja**	9	81
11	 **1k**	 **3ka**	9	91
12	 **1l**	 **3la**	9	92
13	 **1m**	 **3ma**	12	83
14	 **1n**	 **3na**	12	87
15	 **1o**	 **3oa**	9	90

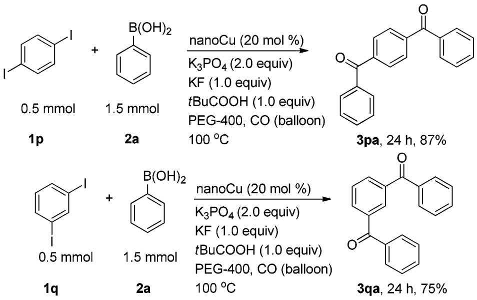
[a] Reaction conditions (unless otherwise stated): **1a** (0.5 mmol), **2a** (0.75 mmol), CO (balloon), K_3PO_4 (0.5 mmol), KF (0.25 mmol), *t*BuCOOH (0.25 mmol), nanoCu (20 mol%), PEG-400 (2.0 mL), 100 °C. [b] Yield of isolated product after column chromatography. [c] **1a** (0.5 mmol), **2a** (0.75 mmol), CO (balloon), K_3PO_4 (1.0 mmol), *t*BuCOOH (0.25 mmol), nanocopper (20 mol%), PEG-400 (2.0 mL), 80 °C.

naphthalen-2-ylboronic acid (**2k**) with **1n** produced desired product (**3nk**) in 82% yield. To our delight, a heterocyclic boronic acid **2m** was quite effective and provided desired product **3km** in 90% yield [eqn (1)].

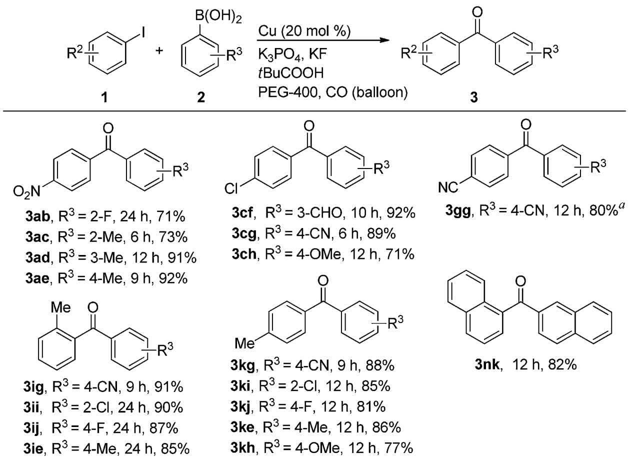


(1)

To check the reusability of PEG-400 and nanocopper catalyst, the model reaction of 4-iodonitrobenzene (**1a**) with phenylboronic acid (**2a**) and carbon monoxide (1 atm) was tested (Fig. 1). The reaction mixture was extracted with diethyl ether, and then, the nanocopper-PEG-400 proceeded to the second run by charging with the same substrates under carbon monoxide (1 atm). Gratifyingly, the catalytic system can be recycled up to ten times with good yields (Fig. 1). And Cu leaching in the



Scheme 1 Successive carbonylative Suzuki reactions of diiodobenzenes.



Scheme 2 Carbonylative Suzuki reactions of aryl iodides with arylboronic acids. Reaction conditions (unless otherwise stated): **1** (0.5 mmol), **2** (0.75 mmol), CO (balloon), K_3PO_4 (0.5 mmol), KF (0.25 mmol), *t*BuCOOH (0.25 mmol), nano-Cu (20 mol%), PEG-400 (2.0 mL), 100 °C. Yield of isolated product after column chromatography was given. [a] **1g** (0.5 mmol), **2g** (0.75 mmol), CO (balloon), K_3PO_4 (1.0 mmol), *t*BuCOOH (0.25 mmol), nanocopper (20 mol%), PEG-400 (2.0 mL), 80 °C.

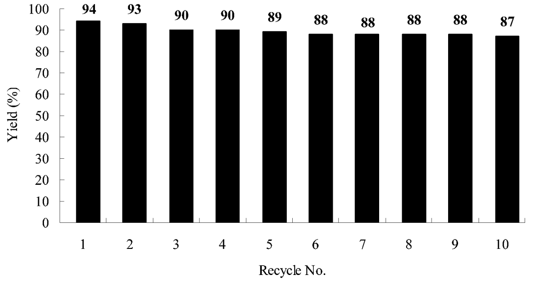
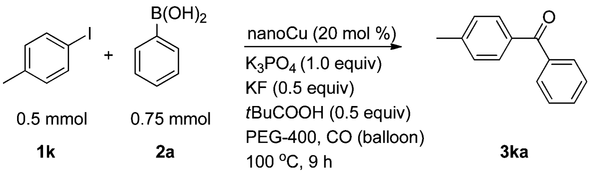


Fig. 1 Reusability of catalyst. Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), CO (balloon), K_3PO_4 (1.0 mmol), *t*BuCOOH (0.25 mmol), nanocopper (20 mol%), PEG-400 (2.0 mL), 80 °C.



No additive: 91%

Additive: 200 equiv Hg (per Cu): <5%

Scheme 3 The effect of the presence of Hg additive.

organic phase (using ICP-MS) was observed to be 1.2% of the starting Cu.

Although commercially available nanocopper was directly employed to catalyzed the carbonylative Suzuki reactions, we still wondered whether the catalysis occurred on the cluster surface or by leached copper species.[13] A mercury additive was used to test nano-metal catalyst.[14] Control experiments were conducted, as shown in Scheme 3. The reaction of **1k** with **2a** under carbon monoxide (1 atm) was almost completely inhibited when 200 equiv. of Hg(0) with respect to copper was added. Thus, it is likely that copper nanoparticles are the real working catalyst.

In conclusion, we have developed the first copper-catalyzed carbonylative Suzuki reactions of aryl iodides with arylboronic acids, which affords the best product yields in the absence of a ligand and under atmospheric pressure of carbon monoxide. The transformation tolerates a variety of functional groups on both coupling partners. Diiodobenzenes such as 1,4-diiodobenzene (**1p**) and 1,3-diiodobenzene (**1q**) can also undergo successive carbonylative Suzuki reactions. Notably, the catalytic system is based on environmentally benign solvent and can be recycled up to ten times with satisfactory yields. Control experiments suggest that copper nanoparticles likely catalyzed the reactions.

Acknowledgements

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Notes and references

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