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Iron-catalyzed carbonylative Suzuki reactions under atmospheric pressure of carbon monoxide†

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The first highly effective iron-catalyzed carbonylative reaction has been developed. Substrates with electron-donating or electron-withdrawing functionality, *ortho*-substitution, as well as active groups proceeded smoothly, affording desired products in high yields. This protocol is economical, environmentally benign and practical for the synthesis of biaryl ketones.

Three-component coupling reactions of arylboronic acids, carbon monoxide, and aryl halides/pseudo-halides, generally known as carbonylative Suzuki reactions,[1] display numerous advantageous features: (1) readily available, and thermally-, air- and water-stable reactants; (2) high regio- and stereoselectivity; (3) wide functional group compatibility; and (4) a broad substrate scope. Nowadays, the reaction represents one of the most straightforward and convenient processes for synthesizing a myriad of symmetrical and unsymmetrical biaryl ketones, which are omnipresent in natural products and manmade compounds with activities related to biology and materials science.[2] Over the past few decades, remarkable advances in this transformation have been achieved, particularly in the substrate scope, functional group tolerance, and design of new catalysts.[3] Nevertheless, the huge majority of the known methods requires relatively high pressure (≥5 bar). Moreover, the cost of ligands is almost always necessary to ensure efficient catalysis.[3] Most disadvantageous of all, the catalyst of choice for carbonylative Suzuki reactions is invariably palladium, which has limited availability (1×10^{-6} wt% in the earth crust),[4] high price (2770 US $ mol^{-1})[5] and significant toxicity.[6] To address these issues, the development of more sustainable, economical and environmentally benign catalysts for the above-named transformation is highly desirable. In this respect, iron is an ideal candidate for catalysis, since it is the second-most-abundant metal in the earth's crust (4.7 wt%), has low cost (<0.5 US Cent per mol)[7] and is present in

diverse biological systems (considered "non-toxic"). Iron has attracted significant attention and emerged as a promising alternative to execute established transition-metal-catalyzed cross-coupling reactions.[8,9]

While a number of stoichiometric iron-mediated carbonylation reactions are known,[10] iron-based catalytic processes are so far underdeveloped and require high pressure of carbon monoxide.[11] The first examples of iron catalyzed carbonylation of aryl iodides with the assistance of a co-catalyst $Co_2(CO)_8$ to prepare symmetrical biaryl ketones were reported by Brunet and co-workers.[12a,b] However, these contributions suffer several limitations, such as a severely limited scope of substrates, low chemoselectivity, and poor functional group tolerance, which make them impractical to organic synthesis. To the best of our knowledge, there is no report of highly effective iron-catalyzed carbonylation of aryl halides so far, although iron has been widely applied in cross coupling reactions of aryl halides.[9] Herein, we report unprecedented, high yielding, iron-catalyzed carbonylative Suzuki reactions of various aryl iodides with arylboronic acids under atmospheric pressure of carbon monoxide (Scheme 1).

Recently, we have successfully launched ligand-free catalytic systems for cross-coupling reactions,[13] utilizing PEG-400 [poly(ethylene glycol) with an average molecular weight of 400 Da][14] as a solvent. Encouraged by the desirable performance of the catalytic systems based on PEG-400, we commenced to determine optimal reaction conditions, employing 4-nitroiodobenzene and phenylboronic acid as model substrates in PEG-400 under ambient pressure of carbon monoxide (Table 1). The first attempted conditions, at 80 °C, with $FeCl_2$, PPh_3 as a ligand, and $NaHCO_3$ as a base (Table 1, entry 1), delivered carbonylated product **3aa** in 36% yield. And without $FeCl_2$, the desired product was not detected (Table 1, entry 2). In the absence of PPh_3, the yield of **3aa** was not affected (Table 1, entry 3). To improve the reactivity, the reaction

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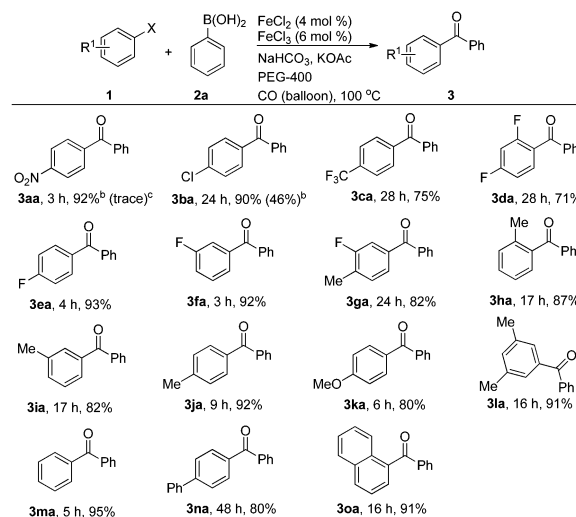**Scheme 1** Iron-catalyzed carbonylative Suzuki reactions of aryl iodides with arylboronic acids.

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

Entry	[Fe] (mol%)	Base	Solvent	Yield of **3aa** (%)
1[b,c]	FeCl$_2$ (10)	NaHCO$_3$	PEG-400	36
2[b,c]	None	NaHCO$_3$	PEG-400	—
3[c]	FeCl$_2$ (10)	NaHCO$_3$	PEG-400	36
4	FeCl$_2$ (10)	NaHCO$_3$	PEG-400	84
5	FeCl$_2$ (10)	Na$_2$CO$_3$	PEG-400	79
6	FeCl$_2$ (10)	K$_2$CO$_3$	PEG-400	73
7	FeCl$_2$ (10)	Cs$_2$CO$_3$	PEG-400	41
8	FeCl$_2$ (10)	K$_3$PO$_4$	PEG-400	65
9	FeCl$_2$ (10)	KF	PEG-400	59
10	FeCl$_2$ (10)	DBU	PEG-400	—
11	FeCl$_3$ (10)	NaHCO$_3$	PEG-400	71
12	Fe(acac)$_2$ (10)	NaHCO$_3$	PEG-400	62
13	Fe(acac)$_3$ (10)	NaHCO$_3$	PEG-400	11
14	FeF$_3$ (10)	NaHCO$_3$	PEG-400	72
15	**FeCl$_2$ (4) + FeCl$_3$ (6)**	**NaHCO$_3$**	**PEG-400**	**92**
16	FeCl$_2$ (4) + FeCl$_3$ (6)	NaHCO$_3$	PEGDM-190	—
17	FeCl$_2$ (4) + FeCl$_3$ (6)	NaHCO$_3$	DMF	16
18	FeCl$_2$ (4) + FeCl$_3$ (6)	NaHCO$_3$	EtOH	—
19	FeCl$_2$ (4) + FeCl$_3$ (6)	NaHCO$_3$	Dioxane	6
20	FeCl$_2$ (4) + FeCl$_3$ (6)	NaHCO$_3$	DCE	—
21[d]	**FeCl$_2$ (4) + FeCl$_3$ (6)**	**NaHCO$_3$**	**PEG-400**	**94**
22[e]	**FeCl$_2$ (4) + FeCl$_3$ (6)**	**NaHCO$_3$**	**PEG-400**	**94**

[a] Reaction conditions (unless otherwise noted): **1a** (0.5 mmol), **2a** (0.75 mmol), CO (balloon), base (1.0 mmol), FeCl$_2$ (98% based on trace metals, Sigma-Aldrich) and FeCl$_3$ (99% based on trace metals, Sigma-Aldrich), solvent (2.0 mL), 100 °C. [b] With PPh$_3$ (1 mol%). [c] 80 °C. [d] Ultrapure FeCl$_2$ (99.99% based on trace metals, Alfa Aesar) and FeCl$_3$ (99.99% based on trace metals, Sigma-Aldrich) were used. [e] Ultrapure NaHCO$_3$ (99.998% based on trace metals, Alfa Aesar).

Scheme 2 Iron-catalyzed carbonylative Suzuki reactions of **2a** with various aryl iodides. [a] Reaction conditions (unless otherwise noted): **1** (0.5 mmol), **2a** (0.75 mmol), CO (balloon), NaHCO$_3$ (1.0 mmol), KOAc (0.1 mmol), FeCl$_2$ (4 mol%) and FeCl$_3$ (6 mol%), PEG-400 (2.0 mL), 100 °C. [b] Without KOAc. [c] Using the corresponding aryl bromide.

temperature was elevated to 100 °C, resulting in a remarkable increase in the yield of **3aa** to 84% (Table 1, entry 4). Other bases, such as Na$_2$CO$_3$, K$_2$CO$_3$, Cs$_2$CO$_3$, K$_3$PO$_4$, KF, and DBU, were tested and were found to be less effective (Table 1, entries 5–10). We then examined other iron sources and observed that **3aa** was obtained in 11–72% yield (Table 1, entries 11–14). Interestingly, using the combination of FeCl$_2$ (4 mol%) and FeCl$_3$ (6 mol%) as a catalyst, an excellent yield (92%) of **3aa** was accessible (Table 1, entry 15).[15] However, in the poly(ethylene glycol) dimethyl ether solvent, the reaction didn't give **3aa** (Table 1, entry 16). Poor results were obtained when the reaction was performed in other pure organic solvents (Table 1, entries 17–20). The use of FeCl$_2$ (99.99% based on trace metals) and FeCl$_3$ (99.99% based on trace metals) with high purity resulted in a slightly better yield of **3aa** to eliminate the influence of the trace quantities of other metals in the iron sources on the investigation (Table 1, entry 21). Meanwhile, using NaHCO$_3$ with high purity (99.998% based on trace metals) didn't affect the result at all (Table 1, entry 22). These experiments suggest that the catalytic system is based on iron.

With this newly established iron-catalyzed carbonylative Suzuki coupling procedure in hand, we conducted carbonylative Suzuki reactions on a variety of commercially available aryl iodides (Scheme 2). Gratifyingly, all reactions delivered desired biaryl ketones **3** in good to excellent yields in the presence of an external promoter KOAc (0.2 equiv.) (**3ba**),[16] as long as aryl iodides were used as the educts. Indeed, 4-bromonitrobenzene afforded carbonylative product

3aa in a trace amount when coupled with phenylboronic acid under ambient pressure of carbon monoxide. The electronic nature of the aryl iodides was found to be only loosely correlated with their reactivity. Sterically hindered 2-iodotoluene did not hamper the transformation and furnished product **3ha** in 87% yield. 2-Naphthyl iodide also underwent an efficient carbonylative Suzuki reaction and provided desired product **3oa** in an excellent yield.

To further ascertain that the iron-catalyzed carbonylative Suzuki reactions are generally applicable to a broad range of arylboronic acids, we examined the carbonylative transformation of various aryl iodides with representative arylboronic acids under the standard conditions (Scheme 3). A variety of electronically diverse arylboronic acids underwent carbonylative Suzuki reactions smoothly and delivered desired products in 78–97% yields. Notably, sensitive functional groups, such as hydroxyl, chloro, bromo, and nitrile, were well tolerated (e.g., **3aj**, **3hl**, **3jl**, **3ag**, **3ac**, **3ec**, and **3kc**) in the reactions. Arylboronic acids with ortho substituents also underwent this transformation successfully and provided desired products in high yields (e.g., **3ah**, **3ag**, **3ha**, **3hl**, **3jl**, and **3kh**). A 92% yield of the corresponding product **3ak** was obtained when 2-naphthylboronic acid was used in the transformation. To our delight, a heterocyclic boronic acid, dibenzofuran-4-ylboronic acid (**2n**) successfully transformed to desired product **3an** in 70% yield within 6 h [eqn (1)].


(1)
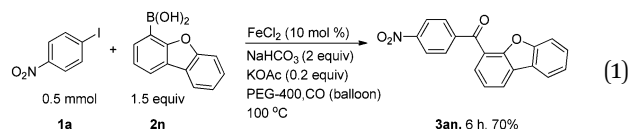
To gain insight into this reaction mechanism, control experiments were performed. In the absence of **2a** any carbonylated product was not detected under normal conditions [eqn (2)], whereas **2a** gave a carbonylated product benzophenone in 23% yield in the absence of **1a** under the same conditions [eqn (3)]. These experiments suggest that the catalytic cycle of the iron-catalyzed carbonylative Suzuki
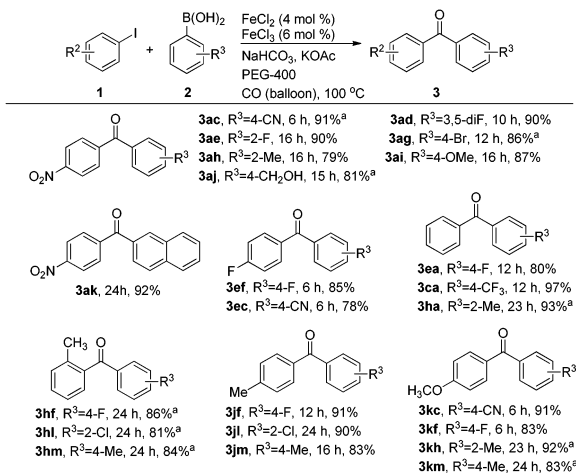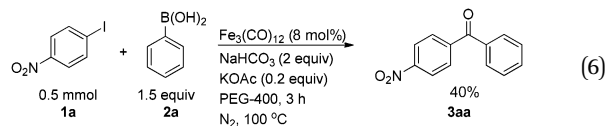
Scheme 3 Iron-catalyzed carbonylative Suzuki reactions of aryl iodides with various arylboronic acids. Reaction conditions (unless otherwise noted): **1a** (0.5 mmol), **2a** (0.75 mmol), CO (balloon), NaHCO$_3$ (1.0 mmol), KOAc (0.1 mmol), FeCl$_2$ (4 mol%) and FeCl$_3$ (6 mol%), solvent (2.0 mL), 100 °C. Isolated yields after column chromatography are given. [a] Without FeCl$_3$ (6 mol%).

reactions starting from arylboronic acids is reasonable. Recently, Ryu and co-workers reported that an iron-carbonyl complex could be *in situ* generated from FeCl$_2$ and carbon monoxide.[17] To gain some understanding of the real active catalyst, a commercially available triirondodecacarbonyl was applied to catalyze the model reaction under otherwise identical conditions and afforded desired product **3aa** in 30% yield [eqn (4)]. Furthermore, iron powder replacing the triirondodecacarbonyl to catalyze the same reaction produced **3aa** in 39% yield [eqn (5)], indicating that iron(0) may be the center of active species. Notably, without carbon monoxide, 8 mol% of triirondodecacarbonyl can catalyzed the model reaction to afford the carbonylated product **3aa** in 40% yield [eqn (6)]. These results not only further demonstrate iron carbonyl species present in the catalytic loop, but also reveal that carbon monoxide firstly formed the iron carbonyl species and then transferred from the iron carbonyl species to the expected product.

$$(2)$$

$$(3)$$

$$(4)$$

$$(5)$$
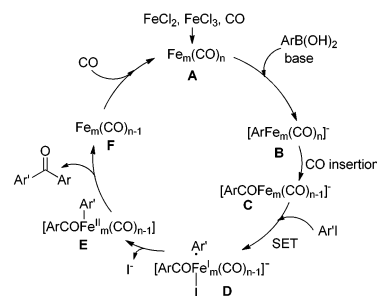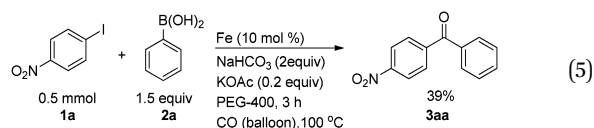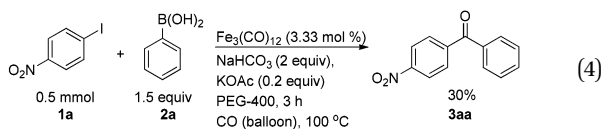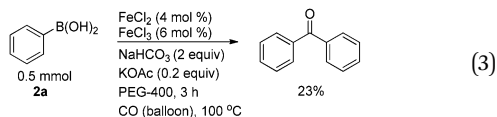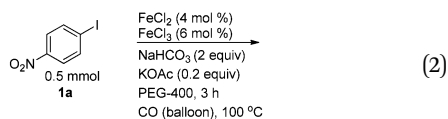
Scheme 4 Proposed catalytic loop.

$$(6)$$

Based on our experimental results and previous studies,[9f,17] we propose a mechanism for this iron-catalyzed carbonylative Suzuki reactions (Scheme 4). Fe$_m$(CO)$_n$ (**A**) is generated *in situ* from FeCl$_3$ and FeCl$_2$ with carbon monoxide under normal conditions. Then, aryboronic acid with the assistance of base undergoes an addition reaction to **A** to form highly nucleophilic organoiron complex **B**,[18] which further gives organoiron complex **C** by intramolecular carbon monoxide migratory insertion. The organoferrate compound can react with ArI through a S$_N$R1 type nucleophilic oxidative addition.[12] Subsequently, **C** proceeds with the S$_N$R1 type reaction with aryl iodide to afford organoiron complex **D**. Finally, reductive elimination gives rise to the desired carbonylated product and regenerates the catalytically active **A** in a carbon monoxide atmosphere.

In summary, we have demonstrated that a novel catalytic system composed of catalytic amounts of FeCl$_3$ and FeCl$_2$ in conjunction with PEG-400 is highly effective for carbonylative Suzuki reactions of aryl iodides under atmospheric pressure in the absence of an additional ligand. The use of iron catalysts instead of the generally utilized palladium ones makes the novel process more economical and environmentally friendly, and thus attractive to industry.

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