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Transition-Metal-Free, Ambient-Pressure Carbonylative Cross-Coupling Reactions of Aryl Halides with Potassium Aryltrifluoroborates

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We disclose an unprecedented transition-metal-free carbonylative cross coupling of aryl halides with potassium aryl trifluoroborates even at atmospheric pressure of carbon monoxide. This protocol is efficient, operationally simple, and shows wide scope with regard to both aryl halides and potassium aryl trifluoroborates containing a series of active functional groups.

Biaryl ketones commonly occur in numerous photosensitizers, advanced organic materials, natural products and drugs.[1] Their extraordinary biological and pharmaceutical properties (e.g. selective estrogen receptor modulation, cholesterol regulation, and anti-inflammatory effects) enable economically pharmaceuticals Evista,[2] Tricor,[3] and Sector[4] that have biaryl ketone units to be among the top 200 best-selling pharmaceutical products by global sales in 2009.[5] Consequently, establishing nonhazardous, practical and effective protocol for the preparation of biaryl ketones bearing active groups that enable versatile synthetic building blocks for structurally complex molecules, is of great significance.

Biaryl ketones are mostly common synthesied by Friedel-Craft-type reactions of active arenes with acyl halides in the presence of overstoichiometric amounts of Lewis acid,[6] or alternatively by the three-component cross-couplings of aryl halides (or pseudo-halides), organometallic reagents, and carbon monoxide (CO) with the use of transition metals as catalysts.[7] Transition-metal-catalyzed carbonylation employing gaseous CO as carbonyl source is a fundamental and key chemical process for the transformations of inexpensive and readily accessible feedstocks to valuable products (typical industrial processes: Oxo process, Monsanto process, and Fischer-Tropsch synthesis).[8] The carbonylative Negishi, Stille, Hiyama, and Suzuki reactions are classical examples of transition-metal-catalyzed carbonylation with CO to deliver biaryl ketones.[9] Among these methods, the carbonylative Suzuki coupling is the most popular protocol.[10] This is attributed in a large degree to unique properties of organoboron reagents (mostly arylboronic acid in the carbonylative Suzuki reaction), such as ready availability, high stabilities toward air, water, and heat, and low toxicities.[11] Although this transformation represents a powerful tool in organic synthesis, the necessity to employ a transition metal and an expensive ligand (often organophosphine or N-heterocyclic carbene).[9] Consequently,

a number of issues are frequently encountered, such as cost of the transition-metal catalyt, deactivation of catalyst (CO is a strong π-acidic ligand), and generation of metal waste that is intractable to remove, particularly in the pharmaceutical industry, in which residual metal contamination can induce severe concerns and must reach stringent specifications.[12] Furthermore, certain functional groups are intolerant of transition-metal system. Therefore, the development of an efficient and practical strategy devoid of metal catalysts is highly attractive but a formidable challenge.[13]

Scheme 1 Metal-free carbonylative Suzuki reactions of aryl iodides with potassium aryl trifluoroborates.

Transition-metal-free strategy for carbonylation of aryl halides (or pseudo-halides) has been scarcely investigated, and previous studies have been limited to radical alkoxycarbonylation.[14] In addition, a high pressure of CO (50–80 atm) is neccessry to ensure efficient catalysis and undermines their practical synthetic value. To the best of our knowledge, there is no example of transition-metal-free carbonylation for carbon-carbon cross coupling. Herein, we uncover unprecedented nonradical transition-metal-free trimodular reaction of aryl halides with potassium aryl trifluoroborates under ambient pressure of CO (Scheme 1). It is worth noting that organotrifluoroborates as surrogates for boronic acids have several advantages, such as enhanced stability, good survivability, and reactive selectivity,[15] which have never been employed in carbonylative Suzuki coupling of aryl halides before.[16]

This report is based on a serendipitous observation during the investigation of transition-metal-catalyzed carbonylations of aryl halides with aryl boronic acids at ambient pressure of CO and in green solvent poly(ethylene glycol)-400 (PEG-400).[17] Carbonylative product **3aa** was formed in 62% yield, along with 28% yield of side product **3a'a'** when potassium phenyl trifluoroborate (**2a**) took the place of phenyl boronic acid in the presence of Na₂CO₃ (99.5% based on trace metals) in PEG-400 and atmospheric CO without

using any transition metal (Table 1, entry 1). Moreover, ICP-AES confirmed that no transition metal was involved (See ESI). To disclose this original transition-metal-free protocol for the construction of biaryl ketones via activation of inert CO, we

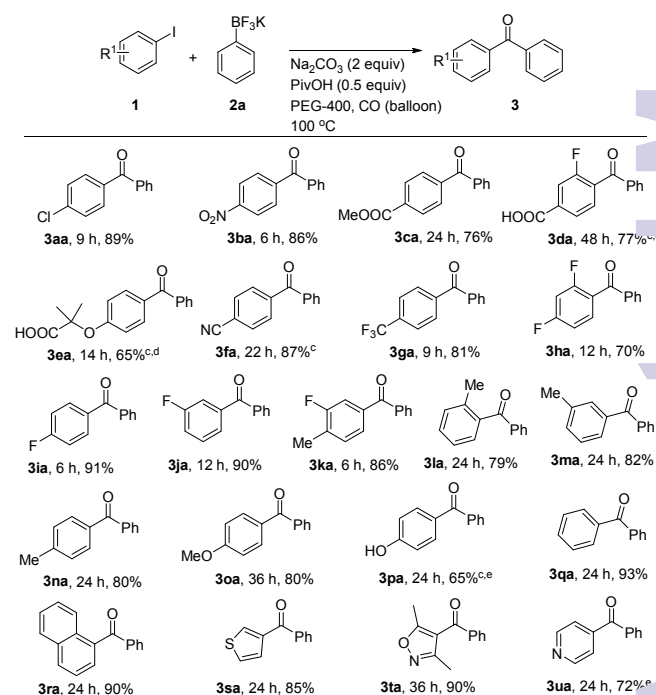**Table 1** Metal-free carbonylative Suzuki reaction of **1a** with **2a**.[a]

Entry	Acid (mol %)	Base	Solvent	Yield of **3aa** (%)	Yield of **3a'a'** (%)
1	-	Na$_2$CO$_3$	PEG-400	62	28
2	PivOH (20)	Na$_2$CO$_3$	PEG-400	79	15
3	**PivOH (50)**	**Na$_2$CO$_3$**	**PEG-400**	**89 (71)[b]**	**5 (7)[b]**
4[c]	**PivOH (50)**	**Na$_2$CO$_3$**	**PEG-400**	**90**	**5**
5	PivOH (100)	Na$_2$CO$_3$	PEG-400	80	8
6	AcOH (50)	Na$_2$CO$_3$	PEG-400	75	8
7	TFA (50)	Na$_2$CO$_3$	PEG-400	64	25
8	PhCOOH (50)	Na$_2$CO$_3$	PEG-400	68	15
9	PivOH (50)	NaHCO$_3$	PEG-400	63	1
10	PivOH (50)	K$_2$CO$_3$	PEG-400	71	15
11	PivOH (50)	Na$_3$PO$_4$	PEG-400	58	2
12	PivOH (50)	K$_3$PO$_4$	PEG-400	51	19
13	PivOH (50)	Cs$_2$CO$_3$	PEG-400	72	21
14	PivOH (50)	DBU	PEG-400	-	-
15	PivOH (50)	NaF	PEG-400	2	-
16	PivOH (50)	KF	PEG-400	-	-
17	PivOH (50)	KOAc	PEG-400	-	-
18	PivOH (50)	K$_2$HPO$_4$	PEG-400	trace	-
19	PivOH (50)	Na$_2$CO$_3$	Dioxane	5	5
20	PivOH (50)	Na$_2$CO$_3$	Glycol	70	25
21	PivOH (50)	Na$_2$CO$_3$	EtOH	5	3
22	PivOH (50)	Na$_2$CO$_3$	Toluene	20	5

[a] Reaction conditions (unless otherwise stated): **1a** (0.25 mmol), **2a** (0.375 mmol), CO (balloon), base (0.5 mmol), solvent (2.0 mL), 100 °C, and 9 h. [b] 80 °C. [c] Ultrapure Na$_2$CO$_3$ (99.997% based on trace metals, Alfa Aesar).

continued to identify the optimal conditions. From the Table 1, a challenge had to be addressed: the problematic chemoselectivity between carbonylative Suzuki coupling and Suzuki coupling. To our delight, PivOH that had been proved to be effective in the suppression of side Suzuki coupling in our previous studies,[17b-d] was equally helpful to enhance selectivity of the carbonylative Suzuki coupling (Table 1, entry 3). The use of ultrapure Na$_2$CO$_3$ (99.997% based on trace metals) resulted in a slight better yield of **3aa** to eliminate the influence of trace transition metal elements in the Na$_2$CO$_3$ on the investigation (Table 1, entry 4). Of all other examined bases, NaHCO$_3$, K$_2$CO$_3$, Na$_3$PO$_4$, K$_3$PO$_4$, and Cs$_2$CO$_3$ resulted in moderate yields of **3aa** (Table 1, entries 9–13), whereas DBU, NaF, KF, KOAc, and K$_2$HPO$_4$ were totally ineffective for this transformation (Table 1, entries 14–18). None of other solvents 1,4-dioxane, glycol, ethanol, and toluene could substitute the PEG-400 (Table 1, entries 19–22). Additionally, at 5 mmol scale, 70% yield of **3aa** can be obtained in 31 h.

With a facile and practical protocol in hand, we explored the scope of aryl halides as coupling partners to potassium phenyl

trifluoroborate under the optimized conditions (Scheme 2). To our delight, broad scope of aryl halides was tested to give desired products in high yields with high selectivities. Electron-poor aryl iodides proceeded smoothly and afforded biaryl ketones in good to excellent yields within short times, while electron-rich aryl iodide need retardation times to achieve the comparable results. Notably, aryl iodides with electron-withdrawing substituents (Cl, NO$_2$, COOMe, and CN), known to readily direct Suzuki coupling to give biaryls, were able to undergo highly selective carbonylation coupling to generate the desired products in 89%, 86%, 76% and 87% yields respectively (**3aa–3ca**, and **3fa**). A series of trifluoromethyl- or fluoro- substituted aryl iodides underwent facile carbonylative Suzuki coupling to furnish fluorinated biaryl ketones (**3ga–3ka**) that are potentially useful intermediates in the synthesis of pharmceuticals and organic materials. Iodotoluene are productive coupling partners regardless of the position of methyl group at
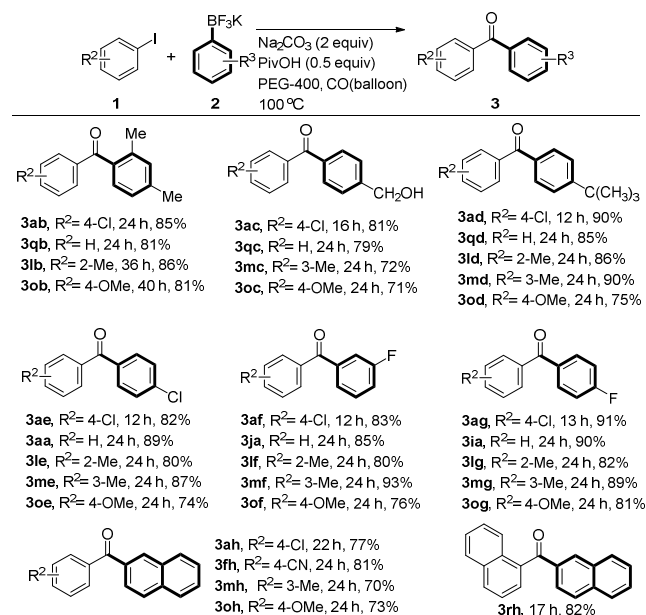

Scheme 2 Metal-free carbonylative Suzuki reactions of **2a** with various aryl iodides. Reaction conditions (unless otherwise stated): **1** (0.25 mmol), **2a** (0.375 mmol), CO (balloon), Na$_2$CO$_3$ (0.5 mmol), PivOH (0.125 mmol), PEG-400 (2.0 mL), and 100 °C. [b] Yields of the isolated products are given. [c] 120 °C. [d] Na$_2$CO$_3$ (0.75 mmol) and without acid additive. [e] PivOH (0.25mmol).

phenyl ring (**3la–3na**). Gratifyingly, quite reactive carboxyl and phenolic hydroxyl groups were well tolerated (**3da–3ea**, and **3pa**), which scarcely reported in carbonylative Suzuki coupling. In addition, 4-hydroxybenzophenone (**3pa**) is the key intermediate for the synthesis of the prescribed drug Clomifene.[18] Naphthyl and heteroaryl iodides also served as highly suitable coupling partners (**3ra–3ua**). Importantly, the carbonylative coupling of 1-bromo-4-nitrobenzene (**1a'**) could
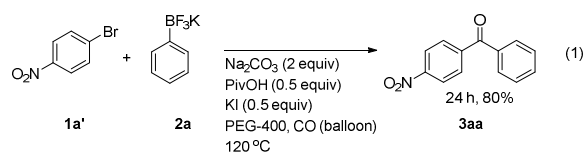
take place successfully in the presence of additional additive KI[19] and at elevated temperature [eqn (1)]. However, other unactivated aryl bromides reacted sluggishly.

Next, the carbonylative coupling of various potassium aryl trifluoroborates was investigated (Scheme 3). They could effectively couple with typical aryl iodides at atmospheric pressure of CO to deliver biaryl ketones in good to excellent yields. Notably, reactive groups, such as OH, Cl, and F, are all compatible (**2c**, **2e**, **2f**, and **2g**). The sterically hindered potassium 2,4-dimethylphenyl trifluoroborate (**2b**) was proved to be good coupling partners. Additionally, when potassium naphthalen-2-yl trifluoroborate (**3h**) was used as substrate, the expected products were produced in satisfactory yields (**3ah**, **3fh**, **3mh**, **3oh**, and **3rh**).


Scheme 3 Metal-free carbonylative Suzuki coupling of aryl iodides with various potassium aryl trifluoroborates. Reaction conditions (unless otherwise stated): **1** (0.25 mmol), **2** (0.375 mmol), CO (balloon), Na$_2$CO$_3$ (0.5 mmol), PivOH (0.125 mmol), PEG-400 (2.0 mL), and 100 °C. ^{b} Yields of the isolated products are given.

Furthermore, by employing this protocol, the marketed drug Fenofibrate (Tricor) (triglyceride and cholesterol regulator) was readily accessed in 81% yield at elevated temperature 120 °C [eqn (2)]. To highlight the applicability of this method to bioactive or drug-like molecule, an iodo estrone derivative (**1w**) underwent carbonylative coupling to provide **3wa** in 80% yield [eqn (3)]. In addition, 1,4-diiodobenzene (**1x**) readily furnished
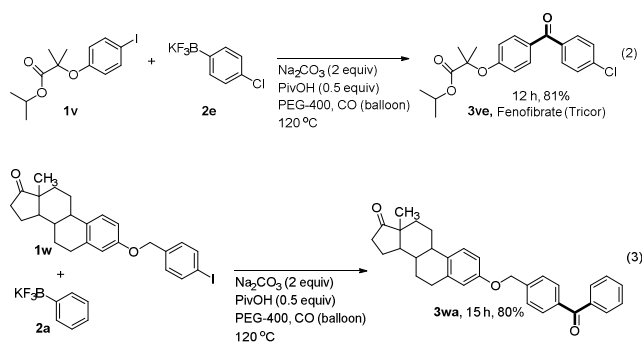
successive carbonylated product **3xa** (Scheme 4) which is the key intermediate for the construction of the efficient light emitter TPTPE.[1b]
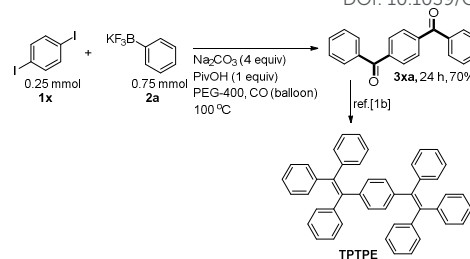
Scheme 4 Successive carbonylation of 1,4-diiodobenzene (**1x**).

Considering the contingent effect of trace amounts of metal contaminants on the transformation,[20] we carried out control experiments through the addition of transition metals that are used to catalyzed carbonylative Suzuki coupling to reaction system (See ESI, table S1). As illustrated in table S1, PdCl$_2$ and Pd(OAc)$_2$, the most, common and effective species in carbonylative Suzuki coupling, resulted in the worst chemoselectivity among the tested transition metals (Table 1, entries 2−3). Other metals such as Cu, NiCl$_2$, and FeCl$_2$, didn't contribute to a positive effect on the original reaction, and rather caused somewhat lower selectivity (Table S1, entries 4−6).

Recently, transition-metal-free alkoxycarbonylations of aryl halides with CO were proposed to invole a radical process.[14] To gain further insight into our transition-metal-free carbonylative transformation, the model reaction was carried out in the presence of a radical scavenger TEMPO or 1,1-diphenylethylene under otherwise identical reaction conditions (See ESI, Scheme S1). Consequently, the reaction was almost not affected at all. Thus, a radical pathway could be ruled out. In addition, the model reaction generated carbonylated product benzoic acid in 23% yield without reactant aryl halide [See ESI, eqn (S1)], whereas any carbonylated product wasn't observed in the absence of potassium aryl trifluoroborate [See ESI, eqn (S2)]. These results suggest that the carbonylative Suzuki coupling initiating from potassium aryl trifluoroborate is plausible.

We further ran competition experiments to find out the effect of substrate electronics on the reaction (See ESI). A more electron-deficient iodide **1b** is consumed ~4.2 times faster than an iodide **1n** [See ESI, eqn (S3)], while an electron-deficient trifluoroborate **2e** and an electron-rich trifluoroborate **2d** show little difference in reactivity [See ESI, eqn (S4)]. These competition experiments imply that the cleavage of C-X bond in aryl halide is likely to be the rate limiting step. Additionally, on switching the solvent PEG-400 to MeO-PEG-OMe (PEM 250: polyethylene glycol dimethyl ether with an average molecular weight of 250 Da) [See ESI, eqn (S5)], the model reaction proceeded sluggishly under otherwise standard conditions, implying that the effect of hydrogen bonding maybe play a critical role in activation of CO.[21] A mechanism was proposed (See ESI), however, it still remains to be elucidated.

In summary, we report here the first transition-metal-free carbonylative cross couplings of aryl halides, potassium aryl trifluoroborates, and CO. Notably, this transition-metal-free carbonylation proceeds efficiently at ambient pressure, which has never been achieved before. Moreover, the versatile method possesses high functional group tolerance, shows wide scope of aryl halides and potassium aryl trifluoroborates partners, and

enables the synthesis of biaryl ketones in high yields with high selectivities. Importantly, the operationally simple method has been succesfully applied to the synthesis of the marketed drug Fenofibrate, and a complex druglike molecule. Studies to expand this transition-metal-free carbonylation process to other carbonylative cross-couplings as well as elucidate the detailed mechanism are ongoing.

Notes and references

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