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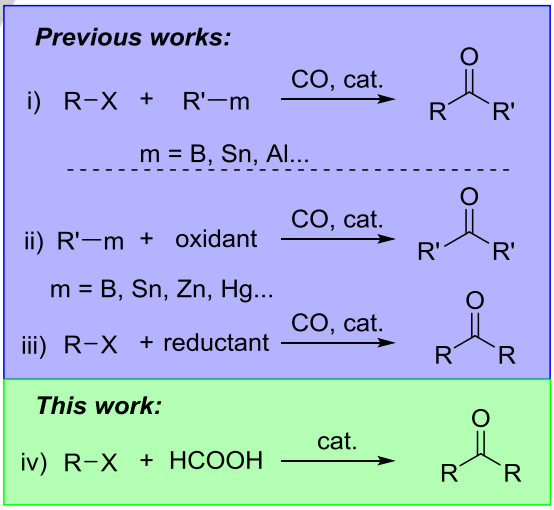
# Palladium-Catalyzed Carbonylative Homo-coupling of Aryl Iodides for the Synthesis of Symmetrical Diaryl Ketones with Formic Acid

Fu-Peng Wu, Jin-Bao Peng,* Xinxin Qi, and Xiao-Feng Wu*[a]

**Abstract:** A convenient palladium-catalyzed carbonylative homo-coupling of aryl iodides was developed. With formic acid as the CO source, various symmetrical diaryl ketones were synthesized in moderate to good yield in the presence of palladium catalyst.

Diaryl ketones are important structure motifs in natural products, pharmaceuticals, materials and fine chemicals.[1] As an ubiquitous synthetic intermediate, the synthesis of diaryl ketone have attracted great attention from the organic chemists. Typically, diaryl ketones are prepared by Friedel-Crafts acylation of arene.[2] However, this method usually suffers the low regio-selectivity, narrow substrate scope as well as the requirement of excess Lewis acid to catalyze the reaction. In this aspect, transition metal catalyzed carbonylative coupling reaction[3] serves as a versatile and straightforward method for constructing polyfunctionalized ketones since it not only retains the advantage of high chemoselectivity of the cross-coupling reactions, but also excluded the usage of carboxylic acid derivatives as the materials. Generally, transition metal catalyzed carbonylative coupling reaction can be classified into three categories: i) carbonylative cross-coupling reaction of organic halides R-X with a nucleophilic organometallic compounds R'-m.[4] This strategy was widely studied and was comparably more mature, both symmetrical and unsymmetrical diaryl ketones could be synthesized using this method. ii) carbonylative homo-coupling reaction of organometallic nucleophiles R'-m in the presence of oxidizing regents.[5] Usually, $Cu^{2+}$ and $O_2$ were used as the oxidant. iii) carbonylative homo-coupling of aryl electrophiles R-X (or $Ar_2I^+$) under reductive conditions with Zn and In as the reducing regent.[6] However, most of these protocols used gaseous CO as the carbonyl source. Although gaseous CO has been abundantly used in industry, the highly toxic and odorless character and the requirement of special high pressure equipment has restricted the wider application of this reaction in synthetic chemistry. Considering the problem of safety and benchtop-friendly manipulation, various caronylation reactions based on CO surrogate had been developed in the past two decades.[7] Metal carbonyls, DMF, chloroform, formic acid and its derivatives were all investigated and successively applied in various carbonylation reactions. Since oxidative carbonylative coupling reaction of organometallics usually requires pre-preparation of the high reactive organometallic reagent, reductive carbonylation of the easily available aryl halides turned out to be a more economic and valuable strategy for the synthesis of symmetric ketones. In 2003, Larhed and co-worker developed a $Co_2(CO)_8$-mediated and microwave-irradiated carbonylation of aryl iodides for the synthesis of symmetric ketones.[8] Later, Iranpoor's group reported a microwave-free $Cr(CO)_6$ mediated carbonylative homo-coupling reaction of aryl iodides.[9] Despite high efficiency, the main drawback of these protocols is that it introduces (sub)stoichiometric metal residuals into the reaction system. Considering the importance of the symmetrical diaryl ketones in organic synthesis and the general lackage of the benchtop-friendly synthesis method, developing a practical gaseous CO-free carbonylative homo-coupling reaction is of great interest. Recently, we have developed a series of carbonylative coupling reactions employing formic acid as the CO source.[10,11] With our continuous interest in developing palladium catalyzed carbonylation reaction, we herein present a convenient carbonylative homo-coupling reactions of aryl halides with formic acid as both the CO source and the reductant.




**Scheme 1**. Carbonylative Coupling for the Synthesis of Diaryl Ketones.

Initially, we evaluated the feasibility of the carbonylative homo-coupling reaction by employing iodobenzene as the model substrate. To our delight, heating a solution of iodobenzene and formic acid in the presence of $[(cinnamyl)PdCl]_2$, $PPh_3$ and sodium formate at 120 °C, with DCC as the activator, the desired product benzophenone was obtained in 48% (Table 1, entry 1).

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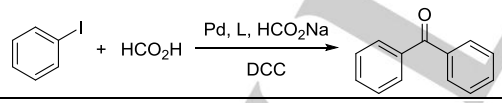
Meanwhile, the direct homo-coupling product biphenyl was detected as one of the byproducts. We then optimized the reaction parameters and selected results were shown in Table 1. First, we examined different phosphine ligands, electron-rich triarylphosphine were successively proceeded the reaction but gave decreased yields (Table 1, entries 2 and 3). However, trialkylphosphine ligands were found not suitable for this reaction, only trace amount of the desired product was detected when $PCy_3$ were used as the ligand (see details in SI). Fortunately, the yield was increased to 51% when DPEphos was used as the ligand (Table 1, entry 4). Compared to $[(cinnamyl)PdCl]_2$, other catalyst precursors such as $Pd(OAc)_2$ and $Pd(PPh_3)_4$ gave the product in trace and 23% yields, respectively (Table 1, entries 5 and 6). Then we tested the effect of the base and found that the usage of sodium formate was essential to this reaction. Combination of sodium formate with inorganic bases as co-bases resulted in decreased yields, while the use of organic base suppressed the reaction and no product was produced (see details in SI). Screening of the solvent showed that THF is the optimal solvent, other solvent such as toluene and acetone gave decreased yields (see details in SI). On the other hand, the reaction temperature played a crucial role in this transformation, lower temperature was unfavorable. Thus, when the reactions were performed at 110 $^oC$ and 100 $^oC$, the yields decreased to 17% and trace, respectively (Table 1, entries 7 and 8). Surprisingly, when the temperature was risen to 130 $^oC$, the yield was decreased compared to that of 120 $^oC$ (Table 1, entry 9 *vs* 1). This might be resulted from the preference of reversed decarbonylation of the acyl-palladium complex at high temperature. Finally, the equivalent of sodium formate also seems to be an important factor to this reaction. Increasing the amount of sodium formate to 3.0 equivalent improved the yield to 68% (Table 1, entry 10). However, 4 equivalent sodium formate gave a decreased yield of 50% (Table 1, entry 11). Increasing the ratio of P:Pd didn't affect the reaction much (Table 1, entry 12).

**Table 1**. Optimizing the reaction condition.[a]




| Entry | Catalyst | Ligand | Temp. ($^oC$) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $[(cinnamyl)PdCl]_2$ | $PPh_3$ | 120 | 48 |
| 2 | $[(cinnamyl)PdCl]_2$ | P(*p*-anisyl)$_3$ | 120 | 17 |
| 3 | $[(cinnamyl)PdCl]_2$ | P(naphthalen-1-yl)$_3$ | 120 | 23 |
| 4 | $[(cinnamyl)PdCl]_2$ | DPEphos | 120 | 51 |
| 5 | $Pd(OAc)_2$ | DPEphos | 120 | trace |
| 6 | $Pd(PPh_3)_4$ | DPEphos | 120 | 23 |
| 7 | $[(cinnamyl)PdCl]_2$ | DPEphos | 100 | trace |
| 8 | $[(cinnamyl)PdCl]_2$ | DPEphos | 110 | 17 |
| 9 | $[(cinnamyl)PdCl]_2$ | DPEphos | 130 | 41 |
| **10**[c] | **$[(cinnamyl)PdCl]_2$** | **DPEphos** | **120** | **68(63**[d]**)** |
| 11[e] | $[(cinnamyl)PdCl]_2$ | DPEphos | 120 | 50 |
| 12[c,f] | $[(cinnamyl)PdCl]_2$ | DPEphos | 120 | 66 |

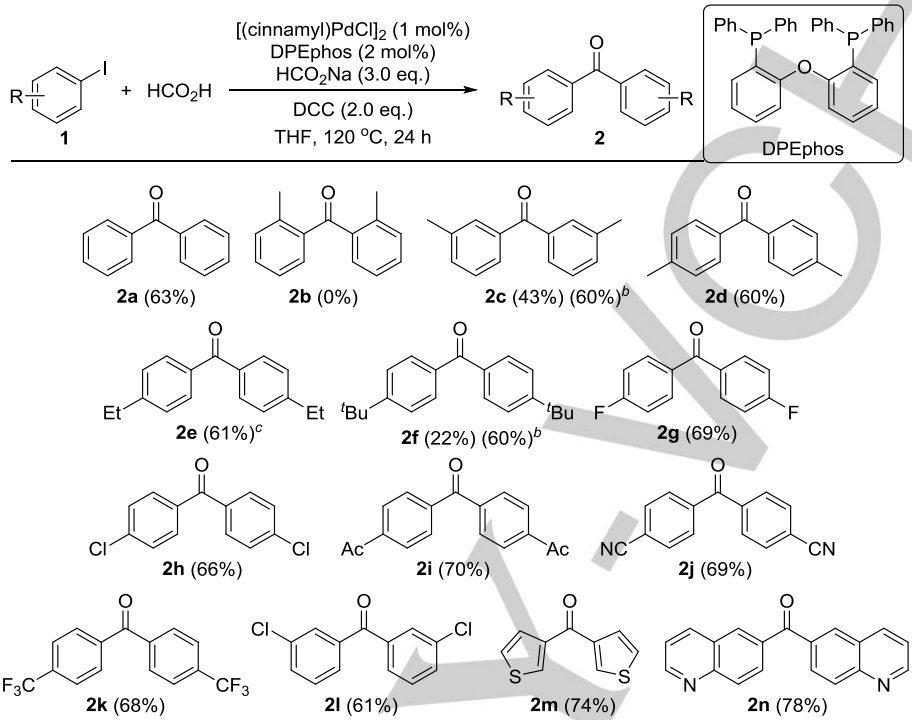
[a]Reaction condition: Iodobenzene (0.5 mmol), [Pd] (2 mol%), $HCO_2Na$ (1.0 mmol), DPEphos (2 mol%), $HCO_2H$ (1.0 mmol), DCC (1.0 mmol), THF (2 mL), 120 $^oC$. 20h. [b]GC yield. [c]$HCO_2Na$ (1.5 mmol). [d]Isolated yield. [e]$HCO_2Na$ (2.0 mmol). [f]P:Pd=4:1. P(*p*-anisyl)$_3$: tris(*p*-methoxyphenyl)phosphine. P(naphthalen-1-yl)$_3$: tri-1-naphthylphosphine. DPEphos: bis[(2-diphenylphosphino)phenyl] ether.

With the optimized reaction conditions in hand (Table 1, entry 10), we turned our attention to evaluate the substrate scope of the carbonylative homo-coupling reaction. As illustrated in Table 2, various substituted aryl iodides were employed to test the generality of the reaction. The steric effect of the substituent at different position of the benzene ring has a pronounced influence on the reaction yield. *p*-methyl iodobenzene gave a higher yield than *m*-methyl iodobenzene, while *o*-methyl iodobenzene was not able to undergo the homo-coupling reaction and no desired product was detected (Table 2, **2b**-**2d**). This might be resulted from the steric effect during the transmetalation process. Both electron-donating and electron-withdrawing group substituted aryl iodides were tolerated in the transformation and gave the corresponding products in moderate yields. Generally, substrates with electron-withdrawing groups (Table 2, **2g**-**2l**) gave higher yields than that of electron-donating groups (Table 2, **2b**-**2f**). It should be mentioned that when *m*-methyl iodobenzene and *p*-*tert*-butyl iodobenzene were subjected to the optimized reaction condition, only 43% and 22% yields of the desired products were produced, respectively. Fortunately, the yields could be improved by increasing the reaction temperature to 130 $^oC$ (Table 2, **2c** and **2f**). Interestingly the fluoro- and chloro-substituted iodobenzene were well tolerated in this transformation (Table 2, **2g** and **2h**).[12] Furthermore, heterocyclic aryl iodides such as 3-iodothiophene and 6-iodoquinoline also underwent the reaction smoothly and delivered the desired ketones in 74% and 78% yields, respectively (Table 2, **2m** and **2n**). However, in the case of bromobenzen and 4-bromobenzotrifluoride, no or very low conversion of substrates were observed.

With these homo-coupling results in hand, we were interested in the application of this method in the carbonylative cross-coupling reaction. Unfortunately, when a mixed substrate (0.5 mmol iodobenzene **1a** and 0.5 mmol *p*-ethyl iodobenzene **1e**) were subjected to the optimized condition, a mixture of homo- and cross-coupling products were generated with poor selectivity (Scheme 2, eq. 1). Considering that the difference of electronic properties on the substrates might play an important role in the reaction selectivity, a mixture of **1e** and **1i** was employed in the standard condition. However, there was no

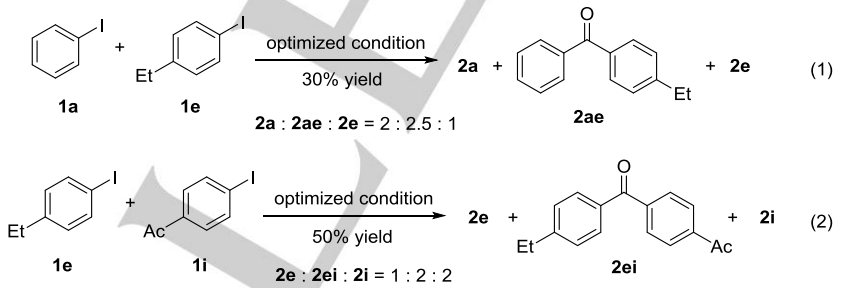
significant improvement of the selectivity of homo- and cross-products (Scheme 2, eq. 2).

**Table 2**. Substrate Scope of the Carbonylative Homo-Coupling Reaction.[a]

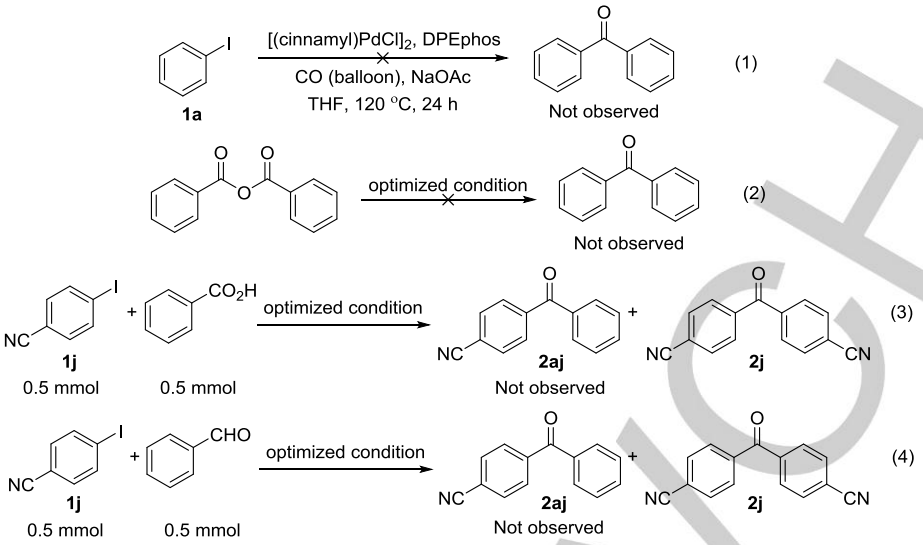



[a]Reaction condition: Iodobenzene (0.5 mmol), [(cinnamyl)PdCl]$_2$ (1 mol%), $HCO_2Na$ (1.5 mmol), DPEphos (2 mol%), $HCO_2H$ (1.0 mmol), DCC (1.0 mmol), THF (2 mL), 120 °C. 20h. [b]130 °C. [c]30h.

**Scheme 2**. Carbonylative Cross-Coupling.

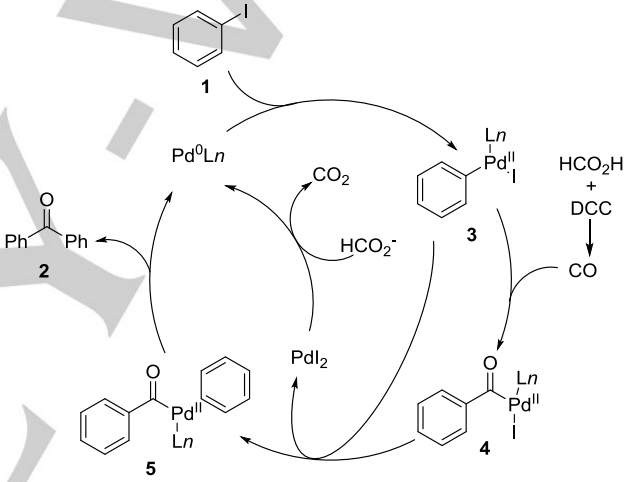



**Scheme 3**. Control Reactions for Exploring the Mechanism.




To gain a better understanding of the reaction pathway, a set of supporting experiments were carried out (Scheme 3). First, sodium formate was essential for this reaction, when the reaction was performed with gaseous CO with NaOAc as the base, no carbonylation product was detected (Scheme 3, eq. 1). It was known that the decarboxylation of anhydrides would generate the ketone under thermal condition. However, when acid anhydride was subjected to the optimized condition, no decarboxylated product was detected (Scheme 3, eq. 2). Besides, when a mixture of *p*-iodobenzonitrile **1j** and benzoic acid was used in this reaction, only homo-coupling product **2j** was produced and no cross-product **2aj** was observed (Scheme 3, eq. 3). These excluded the possibility of the anhydride formation/decarboxylation pathway. Additionally, the presence of aldehyde in the reaction also didn't afford the cross-coupling product (Scheme 3 eq. 4).

On the basis of the above experimental results, a plausible mechanism was proposed in Scheme 4. The catalytic cycle starts with the oxidative addition of the in-situ generated $Pd^0$ with aryl iodide **1** to give the corresponding aryl-palladium complex **3**. Subsequently, coordination and insertion of **3** with one molecule of carbon monoxide, which was generated in-situ from the reaction of formic acid and DCC, forms an acyl-palladium intermediate **4**. Then, a transmetalation between **3** and **4** generates the acyl-palladium intermediate **5** and $PdI_2$. Finally, reductive elimination of **5** delivers the product **2** and regenerate the active $Pd^0$ species for the next catalytic cycle. On the other hand, $PdI_2$ would be reduced by sodium formate to give the active $Pd^0$.




**Scheme 4**. Plausible Reaction Mechanism

In conclusion, a novel palladium catalyzed carbonylative homo-coupling reaction for the synthesis of symmetrical diaryl ketone has been developed. This method uses formic acid as the CO source, various (hetero)aryl iodides were conveniently transformed into the corresponding ketones in moderate to good yields.

## Experimental Section

[(cinnamyl)PdCl]$_2$ (1 mol %), DPEphos (2 mol%), NaOOCH (1.5 mmol), DCC (1.0 mmol), were transferred into an oven-dried tube which was filled with nitrogen. THF (2.0 mL) and iodobenzene (0.5 mmol) were added to the reaction tube. After formic acid (1.0 mmol) was added, the tube was sealed and the mixture was stirred at 120 °C for 24 h. After the reaction finished, the reaction system was cooled to room temperature and the reaction mixture was filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel column using EtOAc/petroleum ether (1/200 to 1/50) to give the desired product.

## Acknowledgements

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**Keywords:** palladium • carbonylation • ketone • formic acid • aryl iodide

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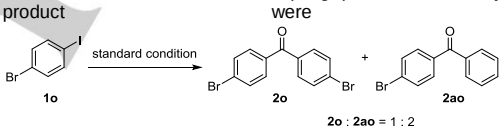
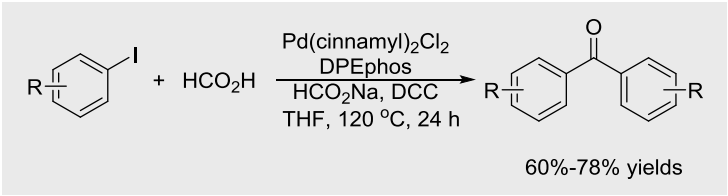
[12] When 1-bromo-4-iodobenzene was used as the substrate in this reaction, a mixture of homo-coupling products with major reduced product were obtained.




**2o** : **2ao** = 1 : 2

# COMMUNICATION

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