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Carbonylation

Palladium-Catalyzed One-Pot Carbonylative Sonogashira Reaction Employing Formic acid as the CO Source

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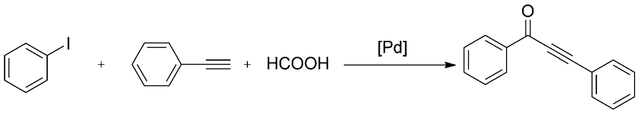
Abstract: A convenient palladium-catalyzed carbonylative coupling of aryl iodides and terminal alkynes with formic acid as the CO precursor has been developed. A variety of alkynones were obtained in good yields in a one-pot manner for the first time.

Palladium-catalyzed carbonylation reactions play a crucial role in advanced chemical synthesis and have drawn much attention in recent years.[1] This strategy has emerged as a straightforward and powerful tool for preparing a variety of organic compounds containing a carbonyl group such as aldehydes, alkynones, amides, carboxylic acids, ketones, and their derivatives.[2] Among these carbonyl compounds, alkynones are of great interest owing to their wide appearance in biologically active molecules[3] and as versatile intermediates in the preparation of natural products.[4] They also have been utilized in the synthesis of numerous heterocycles such as furans, pyrroles, pyrazoles, and quinoline derivatives.[5] Thus, various protocols for alkynones synthesis have been developed, the traditional approach to prepare alkynones relies on transition-metal-catalyzed coupling reaction of acid chlorides with terminal alkynes or alknyl organometallic reagents.[6,7] However, the acid chlorides are not stable and the reactions require relatively harsh conditions. An alternative approach is the transition-metal-catalyzed carbonylative Sonogashira reaction of organic halides with terminal alkynes,[8] which is a more straightforward method. However, the most restricting aspect of these protocols is that gaseous CO is required, which is toxic and difficult to handle. Thus, procedures with alternative CO sources have been developed. The research groups of Kondo and Larhed succeeded in using $Mo(CO)_6$ as the CO source for the carbonylative Sonogashira reaction.[9] Recently, Skrydstrup and co-workers developed a two-chamber system that can realize alkynones synthesis with near stoichiometric amounts of carbon monoxide through ex-situ generation.[10] Herein, we wish to report our newly developed palladium-catalyzed carbonylative Sonogashira method with formic acid as the CO source.[11] Notably, this is the first example of one-pot alkynones synthesis with formic acid as the CO source.

The first carbonylative Sonogashira reaction was carried out with iodobenzene and phenyl acetylene as the model substrates, 1,1′-bis-(diphenylphosphanyl)ferrocene (DPPF) as the ligand, Et_3N as the base in the presence of formic acid, and acetic anhydride with $Pd(OAc)_2$ as the catalyst in toluene at 30 °C. Fortunately, the desired product was obtained in 33% yield (Table 1, entry 1). Encouraged by this result, we continued our studies with various mono- and bidentate phosphine ligands. It was noteworthy that the 1,5-bis(diphenylphosphino)-pentane (DPPPE) ligand gave a slightly higher yield (Table 1, entry 2), but other screened bidentate phosphine ligands provided lower yields (Table 1, entries 3–6). Gratifyingly, PPh_3 appeared to be the best ligand for this reaction, and produced

Table 1. Screening of reaction conditions.[a]



Entry	Ligand	Base	Solvent	Yield [%][b]
1	DPPF	Et_3N	Toluene	33
2	DPPE	Et_3N	Toluene	37
3	DPPP	Et_3N	Toluene	4
4	Xantphos	Et_3N	Toluene	19
5	XPhos	Et_3N	Toluene	1
6	BINAP	Et_3N	Toluene	0
7	PPh_3	Et_3N	Toluene	82 61[c] 0[d]
8	PCy_3	Et_3N	Toluene	3
9	PPh_3	DBU	Toluene	0
10	PPh_3	Pyridine	Toluene	0
11	PPh_3	K_2CO_3	Toluene	0
12	PPh_3	$NaHCO_3$	Toluene	0
13	PPh_3	Et_3N	THF	16
14	PPh_3	Et_3N	DMF	7
15	PPh_3	Et_3N	CH_3CN	39
16	PPh_3	Et_3N	1,4-dioxane	31

[a] Reaction conditions: iodobenzene (1.0 mmol), phenyl acetylene (2.0 mmol), $Pd(OAc)_2$ (3 mol%), ligand (6 mol%), base (5 equiv), HCOOH (2.0 mmol), acetic anhydride (2.0 mmol), solvent (2 mL), 30 °C, 24 h. [b] GC yield, with dodecane as the internal standard. [c] PPh_3 (4 mol%). [d] no ligand, 15 h.

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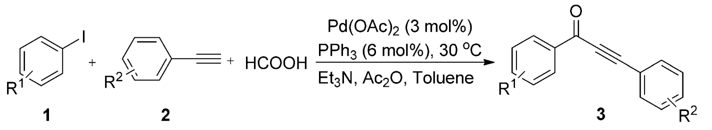
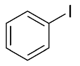
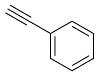
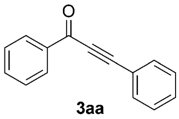
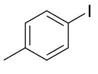
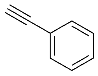
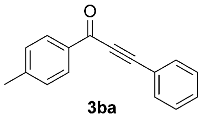
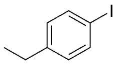
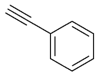
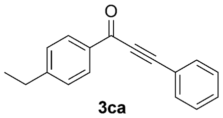
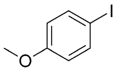
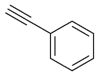
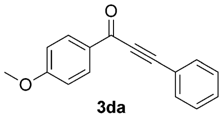
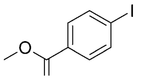
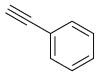
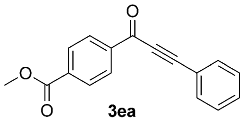
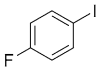
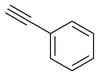
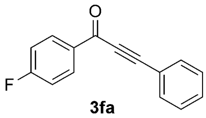
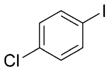
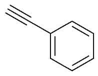
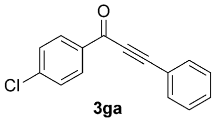
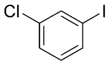
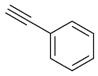
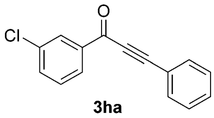
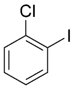
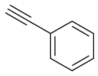
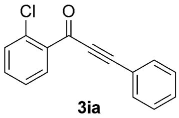
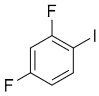
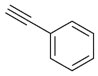
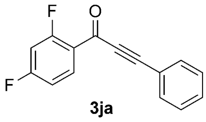
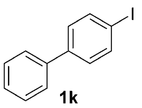
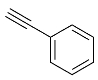
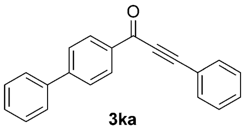
Table 2. Carbonylative Sonogashira reaction of aryl iodides and terminal alkynes.[a]



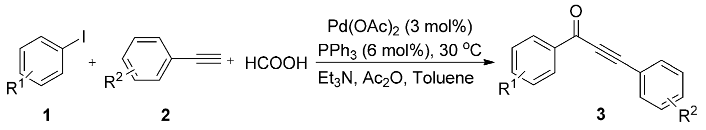
Entry	Aryl iodides	Alkynes	Products	Yield [%][b]
1	 **1a**	 **2a**	 **3aa**	80
2	 **1b**	 **2a**	 **3ba**	68
3	 **1c**	 **2a**	 **3ca**	69
4	 **1d**	 **2a**	 **3da**	51
5	 **1e**	 **2a**	 **3ea**	58
6	 **1f**	 **2a**	 **3fa**	58
7[c]	 **1g**	 **2a**	 **3ga**	62
8	 **1h**	 **2a**	 **3ha**	57
9	 **1i**	 **2a**	 **3ia**	48
10	 **1j**	 **2a**	 **3ja**	43
11	 **1k**	 **2a**	 **3ka**	60

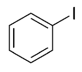
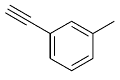
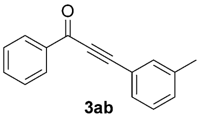
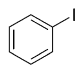
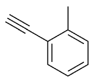
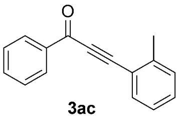
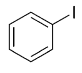
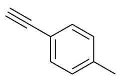
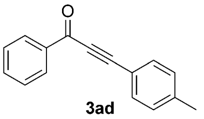
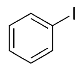
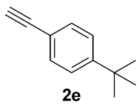
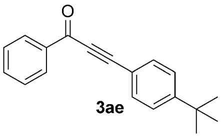
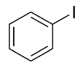
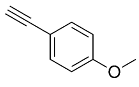
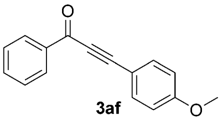
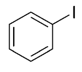
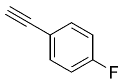
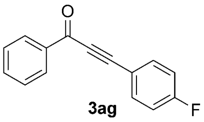
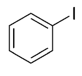
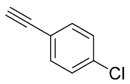
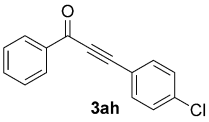
the corresponding product with 82% yield (Table 1, entry 7); while only trace amounts of alkynone was formed with PCy$_3$ as the ligand (Table 1, entry 8). To our surprise, no product was observed with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, K$_2$CO$_3$, or NaHCO$_3$ as the base; this can be explained by the high basicity of DBU and low solubility of inorganic bases (Table 1, entries 9–12). Furthermore, screening of different solvents showed that toluene is the optimal solvent (Table 1, entries 13–16). Additionally, acid anhydrides such as trimethylacetic anhydride, isobutyric anhydride, butyric anhydride, propionic anhydride, and trifluoroacetic anhydride were tested, but improved results were not achieved.

With the optimized reaction conditions in hand, we next investigated a variety of aryl iodides and alkynes (Table 2). Both electron-donating and electron-withdrawing groups are tolerated well to give the desired alkynone products in good yields (Table 2, entries 2–5). Aryl iodides with fluoro and chloro groups can smoothly provide the desired products in 58% and 62% yields (Table 2, entries 6 and 7). The substrates bearing an *ortho*-group resulted in lower yield compared to *meta*- and *para*-substituted substrates; this can be explained by the steric hindrance (Table 2, entries 7 and 8 vs 9). The substrate with a difluoro group at the *ortho*- and *meta*-position decreased the yield to 43% (Table 2, entry 10). Remarkably, the substrates containing a phenyl moiety also worked well to provide the corresponding product in 60% yield (Table 2, entry 11). Furthermore, various terminal alkynes were examined subsequently (Table 2, entries 12–18). It was noteworthy that those substrates bearing a *meta*-substituted aryl group worked better than *ortho*- and *para*-substitution (Table 2, entries 12 vs 13 and 14). We also tested other electron-rich groups including methyl, *tert*-butyl, and methoxy, the desired alkynones can be isolated in good yields (Table 2, entries 14–16). Moreover, substrates with fluoro and chloro moieties gave the desired products in 53% and 58% yields, respectively (Table 2, entries 17 and 18). Bromobenzene was tested as well, but no product was detected. However, a trace amount of the desired alkynone can be produced with 1-acetyl-4-bromobenzene as the coupling partner with phenyl acetylene under the same reaction conditions.

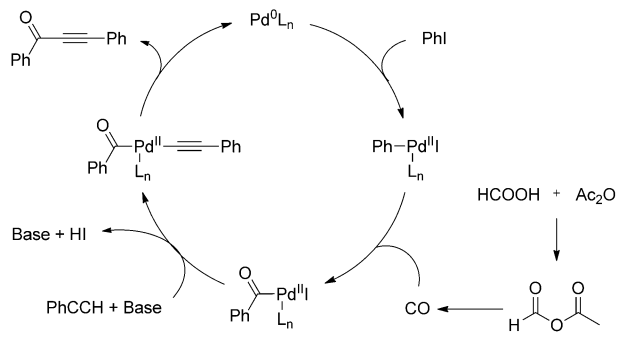
Concerning the reaction pathway, a plausible mechanism is proposed and shown in Scheme 1. The catalytic cycle starts with the oxidative addition of aryl iodide to Pd^{0}L$_n$ to give an arylpalladium complex and then forms an acylpalladium intermediate after the coordination and insertion of CO. The final alkynones will be eliminated after reductive elimination and meanwhile give Pd^0 for the next catalyst cycle. Here the CO is in situ produced from acetic formic anhydride, which was in situ obtained by the reaction of formic acid and acetic anhydride.

Table 2. (Continued)



Entry	Aryl iodides	Alkynes	Products	Yield [%][b]
12	 **1a**	 **2b**	 **3ab**	82
13	 **1a**	 **2c**	 **3ac**	57
14	 **1a**	 **2d**	 **3ad**	54
15	 **1a**	 **2e**	 **3ae**	73
16	 **1a**	 **2f**	 **3af**	50
17	 **1a**	 **2g**	 **3ag**	53
18	 **1a**	 **2h**	 **3ah**	58

[a] Reaction conditions: iodobenzene (1.0 mmol), phenyl acetylene (2.0 mmol), Pd(OAc)$_2$ (3 mol%), PPh$_3$ (6 mol%), Et$_3$N (5 equiv), HCOOH (2.0 mmol), acetic anhydride (2.0 mmol), toluene (2 mL), 30 °C, 17–24 h. [b] Yield of isolated product.



Scheme 1. Proposed reaction mechanism.

In conclusion, we have developed a convenient palladium-catalyzed Sonogashira carbonylative coupling reaction for the synthesis of alkynones. Formic acid has been used as the CO source; the desired alkynones can be isolated in moderate-to-good yields under mild reaction conditions. Notably, this is the first example of a one-pot carbonylative Sonogashira reaction with formic acid as the CO source.

Experimental Section

Typical reaction procedure for carbonylative Sonogashira reaction: Pd(OAc)$_2$ (3 mol%) and PPh$_3$ (6 mol%) were transferred into an oven-dried tube and then flashed with nitrogen. Toluene (2.0 mL), iodobenzene (1.0 mmol), phenylacetylene (2.0 mmol), and Et$_3$N (5.0 mmol) were added into the reaction tube via syringe. Then a mixture of formic acid (2.0 mmol) and acetic anhydride (2.0 mmol) was stirred at 30 °C for 1.5 h, and added drop wise to the reaction tube. The final mixture was stirred at 30 °C for another 17–24 h. After the reaction was complete, the reaction mixture was filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate 50:1) to give the pure product.

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Keywords: alkynones · carbonylation · carbonylative sonogashira reaction · CO · palladium

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