Pd-Catalyzed Copper-Free Carbonylative Sonogashira Reaction of Aryl Iodides with Alkynes for the Synthesis of Alkynyl Ketones and Flavones by Using Water as a Solvent

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Pd-Catalyzed Copper-Free Carbonylative Sonogashira Reaction of Aryl Iodides with Alkynes for the Synthesis of Alkynyl Ketones and Flavones by Using Water as a Solvent

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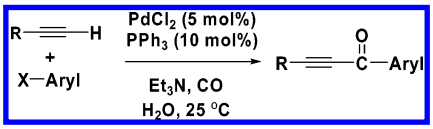

The Pd-catalyzed copper-free carbonylative Sonogashira coupling reaction to synthesize alkynyl ketones from terminal alkynes and aryl iodides was achieved by using water as a solvent. The reaction was carried out at room temperature under balloon pressure of CO with Et_3N as a base. The developed method was successfully applied to the synthesis of flavones.

Alkynyl ketones appear in many biologically active molecules[1] and play crucial roles as intermediates in the synthesis of natural products[2] and druglike molecules.[3] Direct coupling of alkynyl organometallic reagents[4] with acid chlorides has played an important role in making alkynyl ketones. However, these methods have to be handled in dry solvents under an inert atmosphere.

The metal-catalyzed coupling reaction of alkynes or their metalated derivatives (such as alkynylstannanes[5] or alkynylsilanes[6]) with organic halides in the presence of CO provides an alternative approach to the synthesis of alkynyl ketones under atmospheric conditions with atom economy. In this regard, Mori's recent contribution to the direct coupling of terminal alkynes with aryl iodides is a preferred method.[7] This transformation was accomplished by using aqueous ammonia as a base in THF, and the reaction was carried out at room temperature in the presence of $PdCl_2(PPh_3)_2$ with or without CuI.

We recently reported a mild protocol for the copper-free Sonogashira coupling of aryl iodides with terminal alkynes in water under aerobic conditions. The use of $PdCl_2$ (1 mol %) in the presence of pyrrolidine allows the coupling reaction to proceed at room temperature or at 50 °C with good to excellent yields.[8]

Presently, the use of water as a reaction medium for organic synthesis attracts further attention due to its potential ecological impact.[9] We report herein our continual efforts to utilize water as a reaction medium to synthesize alkynyl ketones by the Pd-catalyzed carbonylative reactions of terminal alkynes with phenyl iodides.

We initated our study for the Pd-catalyzed carbonylative coupling reaction in water with 4-iodoanisal and 1-hexyne as substrates and pyrrolidine as a base in the presence of PPh_3 under the conditions listed in Scheme 1. Interestingly, under such conditions, aryl amide **A** was generated as the major product (ca. 40%), jointly with the direct Sonogashira coupling product **B** (ca. 25%). On

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SCHEME 1. Carbonylative Reaction with Pyrrolidine as a Base

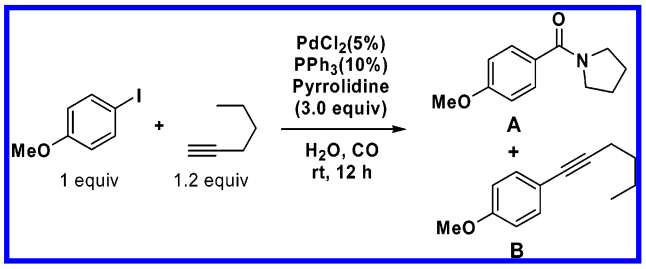
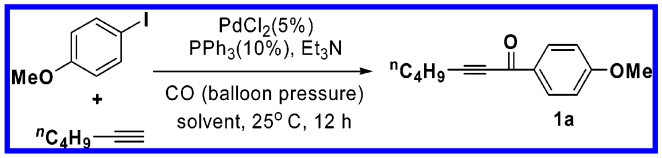


TABLE 1. Pd-Catalyzed Carbonylative Reaction



entry	solvent	base (quiv)	yield (%)[a]
1	H_2O	Et_3N (3.0)	95
2	H_2O	NH_3 (0.5 M)	0
3	THF	Et_3N (3.0)	12[b]
4	CH_2Cl_2	Et_3N (3.0)	30[b]
5	toluene	Et_3N (3.0)	31[b]
6	CH_3CN	Et_3N (3.0)	38[b]

[a] Isolated yield. [b] GC yields.

the other hand, the phosphine-free Pd-catalyzed carbonylative coupling reaction was also tested; however, the palladium precipitate was formed very rapidly under the reductive reaction conditions (CO, H_2O).

Subsequently, we carried out the $PdCl_2$-catalyzed carbonylative coupling reaction using 2 eqiuv of ammonia (0.5 M) as a base.[7] However, the reaction did not occur, and the starting materials were recovered completely.

Finally, we tried to use Et_3N as a base to perform the reaction in water in the presence of Ph_3P. Fortunately, the desired compound **1a** was obtained in 95% yield. However, when the reactions were carried out under identical conditions with organic solvents (such as THF, CH_2Cl_2, toluene, and CH_3CN), the results were less satisfactory (Table 1).

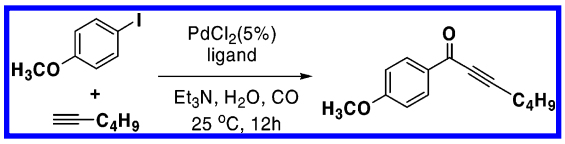
It should be pointed out that in the above carbonylative coupling reaction (see entry 1 in Table 1), 3.0 equiv of Et_3N was used to achieve the high yield, which probably indicates that Et_3N acts not only as a base but also as a cosolvent to help the organic substrates to distribute into water.

To further evaluate the ligand effect on reaction outcome, three additional ligands (dppf, dppp, and BINAP) were screened in the reaction. Among these ligands, PPh_3 proved to be the ideal (Table 2).

As a result of these studies, we were encouraged to examine the reaction with a broad range of substrates to determine the specificity and scope of substrates. Thus, various aryl iodides were reacted with a diverse array of terminal alkynes, and the results are summarized in Table 3.

From the results, it is evident that most of the reactions provided good to excellent yields of coupling products and that many functional groups are tolerated in these reactions. Interestingly, the unprotected *o*-

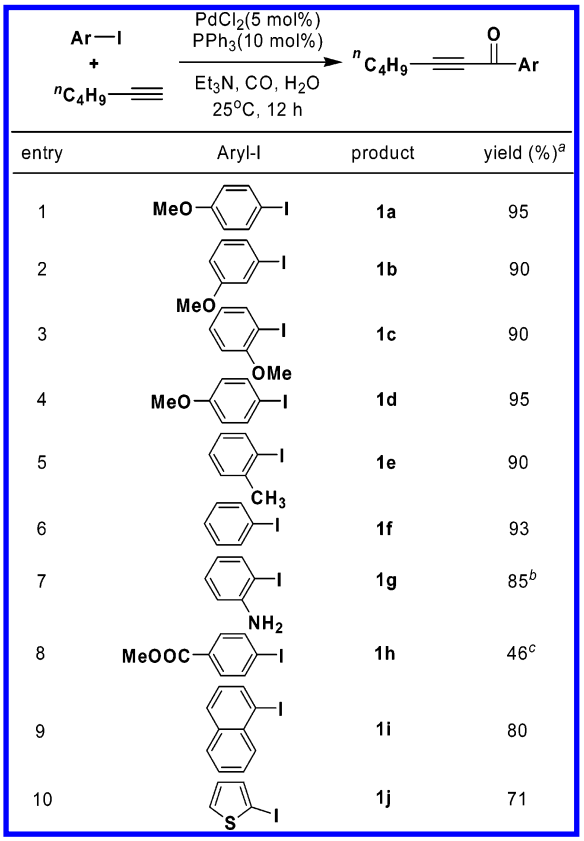
TABLE 2. Pd-Catalyzed Carbonylative Reaction with Different Ligands



entry	ligand	yield (%)[a]
1	PPh_3 (10%)	95
2	DPPF (5%)	91
3	BINAP (5%)	0
4	DPPP (5%)	88

[a] Isolated yield after silica gel chromatography.

TABLE 3. Carbonylative Coupling of Terminal Alkynes and Substituted Aryl Iodide



entry	Aryl-I	product	yield (%)[a]
1		**1a**	95
2		**1b**	90
3		**1c**	90
4		**1d**	95
5		**1e**	90
6		**1f**	93
7		**1g**	85[b]
8		**1h**	46[c]
9		**1i**	80
10		**1j**	71

[a] Isolated yield after silica gel chromatography. [b] Reaction time = 24 h. [c] $PdCl_2$ (6%) and Ph_3P (12%) were used; the reaction was carried out at 15 °C for 36 h.

amino-phenyl iodide (entry 7 in Table 3) can participate in the reaction, and a good result can be obtained. On the other hand, as discussed in Mori's research,[7] a mixture of carbonylative and noncarbonylative coupling products were obtained when electron-deficient aryl iodide was used as the electrophile in the coupling reaction, presumably because the alkyne reacts too rapidly with the palladium complex derived from the oxidative addition of aryl iodide to palladium without insertion of CO. Thus, to get the desired carbonylative product, we eventually carried out the reaction at 15 °C, and product **1h** was obtained in 46% yield (entry 8 in

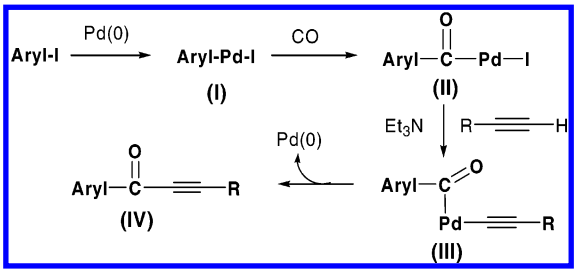
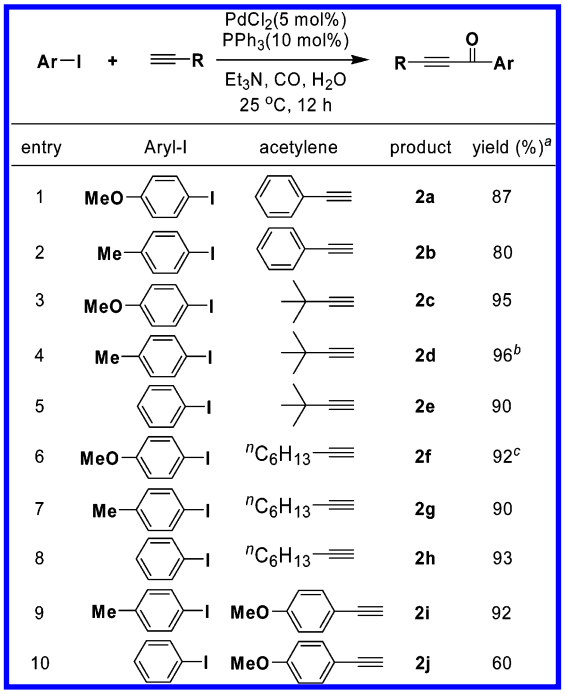


FIGURE 1. Possible Explanation for Carbonylative Coupling Reactions.

TABLE 4. Carbonylative Coupling of Acetylene and Aryl Iodides



entry	Aryl-I	acetylene	product	yield (%)[a]
1	MeO—C6H4—I	C6H5—≡	2a	87
2	Me—C6H4—I	C6H5—≡	2b	80
3	MeO—C6H4—I		2c	95
4	Me—C6H4—I		2d	96[b]
5	C6H5—I		2e	90
6	MeO—C6H4—I	^{n}C$_6$H$_{13}$—≡	2f	92[c]
7	Me—C6H4—I	^{n}C$_6$H$_{13}$—≡	2g	90
8	C6H5—I	^{n}C$_6$H$_{13}$—≡	2h	93
9	Me—C6H4—I	MeO—C6H4—≡	2i	92
10	C6H5—I	MeO—C6H4—≡	2j	60

[a] Isolated yield after silica gel chromatography. [b] Reaction time = 24 h. [c] Reaction time = 16 h.

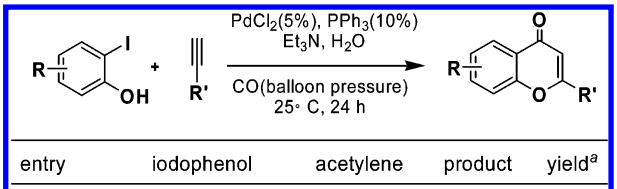
Table 3), along with 32% yield of noncarbonylative coupling product.

It is noteworthy that the coupling reaction of aryl iodides with *the alkynes bearing alkyl substituents* was achieved by running the reaction without CuI as a cocatalyst. We reasoned that in the absence of CuI, the less reactive alkyne (compared with its corresponding alkynyl copper ate complex) would easily react with the electron-deficient acylpalladium (II) rather than its precursor palladium complex (I) derived from the oxidative addition of aryl iodide to palladium (Figure 1); thus, the desired carbonylative coupling reaction could be secured.

To further evaluate the reaction, the methyl- and methoxyl-substituted aryl iodides were used to couple with aryl- and alkyl-substituted terminal acetylenes. The results listed in Table 4 show that good to excellent yields were obtained under aqueous conditions.

Flavone represents a major class of naturally occurring products,[10] and a number of routes to its synthesis have been published.[11] Recent advances in the palladium-catalyzed carbonylation of *o*-iodophenol derivatives with terminal acetylenes to synthesize flavones have shown

TABLE 5. Syntheses of Flavones



entry	iodophenol	acetylene	product	yield[a]
1	A	^{n}C$_4$H$_9$—≡ B	3a	91%
2	A		3b	47%
3	A	TMS—≡		55%[b]
4	A	^{n}C$_6$H$_{13}$—≡	3d	70%
5	^{t}Bu—C6H3(I)(OH)	B	3e	70%
6	Me—C6H3(I)(OH)	B	3f	78%
7	Ph—C6H3(I)(OH)	B	3g	95%
8	Cl—C6H3(I)(OH)	B	3h	90%
9	EtOOC—C6H3(I)(OH)	B	3i	35%[c]

[a] Isolated yield after silica gel chromatography. [b] Performed with 2 equiv of acetylene for 48 h. [c] Reaction time = 48 h.

this method to be particularly attractive.[12] We, therefore, started to test the feasibility of synthesizing flavones by the sequential carbonylative coupling of *o*-iodophenols with terminal acetylenes to make α,β-unsaturated ketones, followed by an intramolecular cyclization to afford flavones in a one-pot operation.

To our satisfaction, all the selected substrates gave the desired flavones in good to acceptable yields (Table 5).

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Importantly, the reaction with alkyl-substituted terminal acetylenes can also give the expected flavones, a result that was not achieved in our previous approach by using iodophenyl acetates as substrates for flavone synthesis.[12g] It is interesting to notice that unlike our previous investigation for the synthesis of flavones from iodophenols,[12g] the side reaction for the competitive formation of five-membered aurones did not occur using the present procedure.

In summary, the copper-free Pd-catalyzed carbonylative coupling reaction to synthesize various alkynyl ketones from phenyl iodides and terminal acetylenes was achieved by using water as a solvent. This reaction was carried out at room temperature under balloon pressure of CO with Et_3N as a base. Application of this synthetic method to generate flavones from iodophenols and terminal alkynes was also achieved. This protocol will serve as an efficient way to synthesize alkynyl ketones and 2-substituted flavones.

Experimental Section

General Procedure for the Carbonylative Sonogashira Coupling in Water. To a 25 mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2$ (17.7 mg, 0.1 mmol), PPh_3 (52.4 mg, 0.2 mmol), 4-iodoanisole (468 mg, 2.0 mmol), and H_2O (2.5 mL), and then Et_3N (0.84 mL, 6.0 mmol) was injected into the tube. The mixture was first stirred for 5 min, and then 1-hexyne (0.28 mL, 2.4 mmol) was added to the tube. The reaction mixture was stirred at room temperature for 12 h under a balloon pressure of CO. The mixture was extracted with ethyl acetate (5 × 5 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (hexane/ethyl acetate = 40/1) to give product **1a** (410 mg) in 95% yield as a colorless oil.

General Procedure for Synthesis of Flavone. To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2$ (17.7 mg, 0.1 mmol), PPh_3 (52.4 mg, 0.2 mmol), 2-iodophenol (440 mg, 2.0 mmol), and H_2O (2.5 mL), and then Et_3N (0.84 mL, 6.0 mmol) was injected into the tube. After the mixture was stirred for 5 min, 1-hexyne (0.28 mL, 2.4 mmol) was added to the tube, and the mixture was stirred under a balloon pressure of CO for 12 h. The reaction mixture was extracted with ethyl acetate (4 × 5 mL), and the combined organic phases were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (hexane/ethyl acetate = 8/1) to give the product **3a** (368 mg) in 91%.

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Supporting Information Available: Experimental procedures and NMR and LC-MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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