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Pd-Catalyzed Selective Carbonylative and Non-carbonylative Couplings of Propiolic Acid: One-Pot Synthesis of Diarylalkynones

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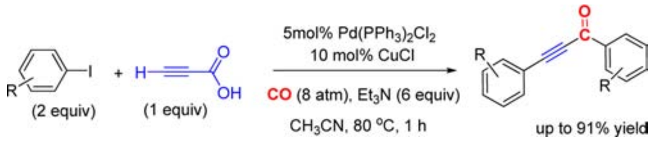
ABSTRACT



Diarylalkynones were synthesized from one-pot Pd-catalyzed carbonylative and noncarbonylative coupling reactions of propiolic acid with aryl iodides under a carbon monoxide atmosphere. Aryl iodide (2.0 equiv), propiolic acid (1.0 equiv), Pd(PPh$_3$)$_2$Cl$_2$ (5 mol %), CuCl (10 mol %), Et$_3$N (6.0 equiv), and CO (8 atm) were reacted under optimized conditions in CH$_3$CN at 80 °C for 1 h. This process afforded good yields and functional group tolerance.

Many bioactive products as well as molecules of medical and material importance are synthesized from ynones.[1] Ynones are transformed into heterocylic compounds such as pyrimidine,[2] quinolone,[3] furan,[4] pyrazole,[5] flavone,[6] and oxime[7] for numerous applications.

Several methods for the synthesis of arylynones have been reported, most commonly using the coupling of acyl halides and terminal alkynes[8] (or alkynyl metal[9]) and the Pd-catalyzed Sonogashira-type carbonylation, which is the coupling reaction of aryl halides and terminal alkyne in the presence of CO atmosphere.[10]

Although acyl halides showed good reactivity in this transformation, they suffer some drawbacks in their storage and limitation in commercial availability, which necessitates a preparation process. As an aryl carbonyl source, aryl ester[11] and Weinreb amide,[12] which are more stable than acyl chloride, were used. However, they showed low functional group tolerance because alkynyllithium was used as the alkyne source. Very recently, the

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coupling of aryl carboxylate salt and alkyne has been reported; however, they still showed a narrow scope of substrates.[13]

Since Kobayashi first reported palladium-catalyzed Sonogashira-type carbonylation,[10] more efficient and improved methodologies have been developed and applied in organic synthesis. As examples, recyclable catalytic systems,[14] reactions in aqueous or ionic liquid,[15] microflow systems,[16] the use of surrogate for carbon monoxide gas,[17] palladium-free systems,[18] and the expansion of substrates have all been reported.[19] However, they all used alkyl- or arylalkynes as the coupling partner. When arylalkyne is used as an alkyne source, it has to be prepared from aryl halides and alkynes through a Sonogashira reaction.

As an alkyne source, acetylene is the simplest synthon and is used in the Sonogashira coupling and Sonogashira-type carbonylation. However, it cannot be easily handled in the general laboratory as it is an explosive gas. To solve these problems, trimethylsilylacetylene,[20] 2-methyl-but-3-yn-2-ol,[21] and bis(tributylstanyl)acetylene[22] have been used as a surrogate in the Sonogashira coupling and carbonylation reactions. However, they have also some drawbacks such as high cost, production of metallic waste, and requirement for strong basic conditions. Recently, we reported the synthesis of symmetric and unsymmetric diaryl alkynes from the coupling reaction of aryl halides with propiolic acid and the site-selective coupling reaction of propiolic acid to produce aryl alkynyl carboxylic acid and arylalkynes.[23] In addition, we first reported the synthesis of diarylynone from the decarboxylative carbonylation of aryl alkynyl carboxylic acid and aryl iodides in the presence of CO.[24]

In terms of cost-effectiveness, nontoxicity of waste and mild conditions in the coupling reaction, propiolic acid as an alkyne source is an attractive alternative as it is easy to handle and store because it is a stable liquid. Considering its structural feature, it has two reactive sp carbon sites, which showed different reactivity in the coupling reaction.

To expand our research of decarboxylative carbonylation, we focused on the carbonylation of propiolic acid. We envisioned that diaryl ynone would be obtained from the one-pot reaction of aryl iodides and propiolic acid under CO atmosphere if noncarbonylative coupling occurs at one site of propiolic acid and carbonylative coupling at the other site of propiolic acid. Herein, we report the one-pot synthesis of diarylynone from the reaction of the aryl iodides, propiolic acid, and carbon monoxide in the presence of palladium catalyst.

To achieve our goal, we first screened a variety of reaction parameters in the coupling reaction of iodobenzene and propiolic acid in the presence of carbon monoxide. The results are summarized in Table 1.

The carbonylative reactions in DBU and DMSO, which showed good yield in the synthesis of diarylalkynes, afforded only noncarbonylative product even under 1 and 5 atm of CO (Table 1, entries 1 and 2). The use of Et_3N, which is a suitable base in the decarboxylative carbonylation, showed unsatisfactory results in DMSO and toluene (entries 3 and 4). The addition of 10 mol % of CuI produced the desire product in 12% yield (entry 5). DBU and toluene were not suitable as base and solvent, respectively (entry 6). Among the solvents tested, CH_3CN showed 65% yield of **2a** and 5% yield of **3a** (entry 10). Instead of CuI, CuBr and CuCl afforded the desired product in 55% and 71% yield, respectively (entries 11 and 12). Keeping CuCl, Et_3N, and CH_3CN as the additive, base, and solvent, respectively, a carbon monoxide atmosphere of 8 bar showed a better result with a low amount of **3a** (entry 13), compared to 10 bar. When the amount of CuCl was decreased to 5 mol %, the product yield was decreased to 54% (entry 15). No product was formed when the reaction was run at 50 °C (entry 16). These results revealed optimized conditions in which aryl iodide (2.0 equiv), propiolic acid (1.0 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuCl (10 mol %), Et_3N (6.0 equiv), and CO (8 atm) were reacted in CH_3CN at 80 °C for 1 h.

Next, to evaluate the effectiveness of our new reaction system, a range of aryl iodides was examined using the preliminary optimized reaction conditions as shown in Scheme 1. As expected, iodobenzene afforded 1,3-diphenylprop-2-yn-1-one (**2a**) in 84% yield (entry 1). Alkyl-substituted aryl iodides showed good yields (entries 2–4). 2-Iodoanisole provided the desired product in lower yield than 4-iodoanilsole, which may have been due to the steric hindrance (entries 5 and 6). We found that the survival of the halides, such as bromide, chloride and fluoride, presented an opportunity for further coupling with others (entries 7–9). 4-Trifluoromethyl iodobenzene gave 69% product yield (entry 10). Aryl iodides bearing ketone and

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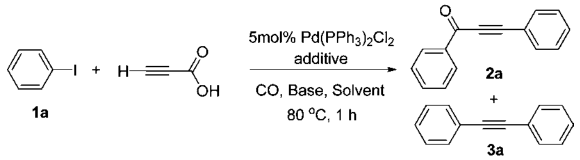
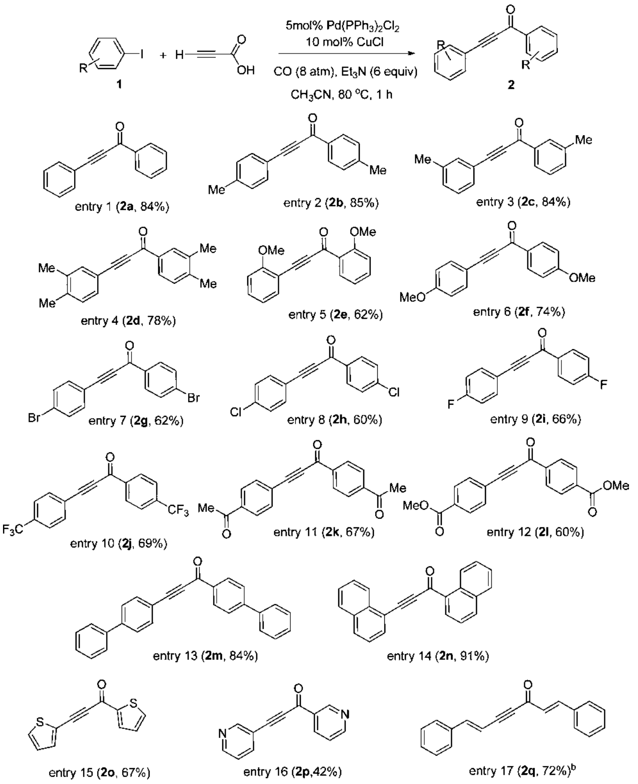
Table 1. Optimized Conditions for the Synthesis of **2a** from Propiolic Acid[a]



entry	additive[b]	base[c]	solvent	atm[d]	yield[e] (%) **2a**	**3a**
1		DBU	DMSO	1	0	96
2		DBU	DMSO	5	0	35
3		Et_3N	DMSO	5	0	71
4		Et_3N	toluene	5	5	6
5	CuI	Et_3N	toluene	5	12	5
6	CuI	DBU	toluene	5	0	27
7	CuI	Et_3N	diglyme	5	27	3
8	CuI	Et_3N	NMP	5	39	28
9	CuI	Et_3N	DMF	5	49	17
10	CuI	Et_3N	CH_3CN	5	65	5
11	CuBr	Et_3N	CH_3CN	5	55	18
12	CuCl	Et_3N	CH_3CN	5	71	3
13	CuCl	Et_3N	CH_3CN	8	86	trace
14	CuCl	Et_3N	CH_3CN	10	83	2
15	CuCl[f]	Et_3N	CH_3CN	8	54	3
16[g]	CuCl	Et_3N	CH_3CN	8	trace	

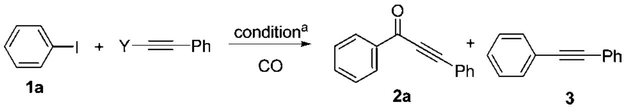
[a] Reaction conditions: **1a** (0.6 mmol), propiolic acid (0.3 mmol), and $Pd(PPh_3)_2Cl_2$ (0.015 mmol) were reacted in the presence of carbon monoxide at 80 °C for 1 h. [b] 10 mol %. [c] 6 equiv was used. [d] Pressure of carbon monoxide. [e] Determined by gas chromatography with internal standard. [f] 5 mol % was used. [g] Reaction temperature was 50 °C.

Scheme 1. Synthesis of Diarylalkynones from the Propiolic Acid[a]



[a] Reaction conditions: aryl iodide (6.0 mmol), propiolic acid (3.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.15 mmol), CuCl (0.3 mmol), Et_3N (18.0 mmol), and CO (8 atm) were reacted in acetonitrile at 80 °C for 1 h. [b] β-Bromostyrene was used.

Table 2. Effect of Copper in the Carbonylative Coupling of Phenylpropiolic Acid and Phenylacetylene[a]



entry	alkyne, Y =	additive	yield[b] (%) **2a**	**3**
1	CO_2H	CuCl	81	4
2	CO_2H		78	
3	H	CuCl		99
4	H		68	29

[a] PhI (3.0 mmol), alkyne (3.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.15 mmol), Et_3N (18.0 mmol), and CO (8 atm) were reacted in the presence or absence of CuCl (0.3 mmol) in acetonitrile at 80 °C for 1 h. [b] After aqueous workup, the crude product was analyzed by gas chromatography with internal standard and ^1H and ^{13}C NMR.

ester groups also afforded the desired products (entries 11 and 12). 4-Iodobiphenyl and 1-iodonaphthalene showed good yields (entries 13 and 14). Heteroaromatic iodides such as 2-iodothiophene and 3-iodopyridine gave **2o** and **2p** in 67%, 42% yield, respectively (entries 15 and 16). When we attempted to expand this method to aryl bromides, only β-bromostyrene gave the desired product **2q** in 72% yield (entry 17).

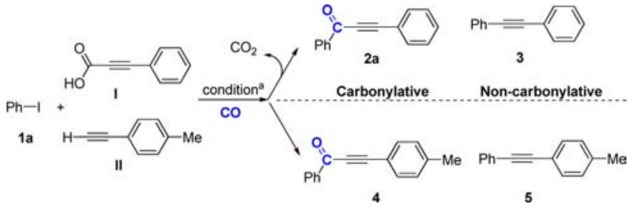
To study the selective carbonylative and noncarbonylative coupling reaction toward propiolic acid, we investigated the carbonylative reaction of phenyl propiolic acid and phenyl acetylene in the presence or absence of CuCl, as shown in Table 2.

Phenylpropiolic acid afforded the carbonylative product as the major product both in the presence and absence of CuCl (entries 1 and 2). In the case of phenylacetylene, the reaction with CuCl afforded only noncarbonylative coupling product (entry 3); however, carbonylative product was formed in 68% with 29% yield of **3** in the absence of CuCl. These results revealed that phenylpropiolic acid preferred the carbonylative coupling, whereas phenylacetylene preferred the carbonylative coupling in the absence of CuCl and noncarbonylative coupling in the presence of CuCl.

To further study the different reactivity of alkynyl carboxylic acid and terminal alkyne toward carbonylation, comparative experiments were conducted, as shown in Table 3. An equal amount of iodobenzene, phenylpropiolic acid, and 4-tolylacetylene were reacted in one reaction vessel. Both in the presence and absence of CuCl, terminal alkyne **II** was more reactive than alkynyl carboxylic acid **I**.

However, in the presence of CuCl, iodobenzene selectively reacted with 4-tolylacetylene which has a terminal alkyne to give noncarbonylative product **5** in 97% yield (entry 1). In the absence of CuCl, terminal alkyne **II** afforded carbonylative product **4** as the major product (entry 2). When the amount of iodobenzene increased to 2 equivalent, phenyl propiolic acid (**I**) gave the carbonylative product **2a** in 45% yield and 4-tolylacetylene gave the noncarbonylative product **5** in 49% yield in the presence of CuCl (entry 3). However, in the absence of CuCl, both **I** and **II** afforded the corresponding carbonylative product **2a** and **4**, respectively (entry 4).

Table 3. Comparative Experiments with Phenylpropiolic Acid and *p*-Tolylacetylene[a]

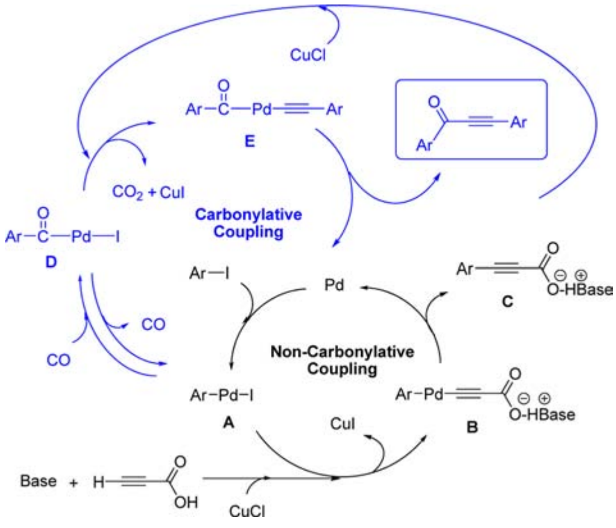


			yield (%)[b]			
			product from **I**		product from **II**	
entry	ratio of **1a**:**I**:**II**	additive	**2a**	**3**	**4**	**5**
1	1:1:1	CuCl	2			97
2	1:1:1		7		74	15
3	2:1:1	CuCl	45	2		49
4	2:1:1		35		48	4

[a] PhI (3.0 mmol), **I** (1.5 or 3.0 mmol), **II** (1.5 or 3.0 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.15 mmol), Et$_3$N (18.0 mmol), and CO (8 atm) were reacted in the presence or absence of CuCl (0.3 mmol) in acetonitrile at 80 °C for 1 h. [b] After aqueous workup, the crude product was analyzed by gas chromatography with internal standard and ^{1}H and ^{13}C NMR.

From these results, we proposed the mechanism presented in Scheme 2. First, palladium complex **A**, produced by the oxidative addition of aryl iodide to palladium, was reacted with alkynylcopper complex that was formed in the presence of CuCl and base to afford palladium complex **B**. Reductive elimination of **B** afforded the aryl alkynyl carboxylic acid salt **C**. This is the catalytic cycle for noncarbonylative coupling, with another catalytic cycle for carbonylative coupling. The oxidative palladium complex **A** reacted with carbon monoxide to produce complex **D** and then afforded the palladium complex **E** through the decarboxylative coupling of aryl alkynyl carboxylic acid **C**. Finally, the reductive elimination of **E** gave the desired product.

Scheme 2. Proposed Mechanism



In summary, we developed the one-pot synthesis of diarylalkynone from the palladium-catalyzed noncarbonylative Sonogashira coupling and decarboxylative carbonylative coupling reaction of propiolic acid with aryl iodide. This method showed good yields and functional group tolerance. We report the following findings. (1) Alkynyl carboxylic acid prefers decarboxylative carbonylation to noncarbonylative coupling under carbon monoxide atmosphere. (2) Terminal alkyne provides carbonylative product in the presence of CuCl and noncarbonylative product in the absence of CuCl. (3) The reactivity of terminal alkyne and noncarbonylation is better than that of alkynyl carboxylic acid and carbonylation, which provide the selective carbonylative coupling products.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.