

Palladium-catalyzed carbonylative coupling of benzyl chlorides with terminal alkynes to give 1,4-diaryl-3-butyn-2-ones and related furanones†

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A general palladium-catalyzed carbonylative Sonogashira coupling of benzyl chlorides with terminal acetylenes has been established. Depending on the alkyne 1,4-diaryl-3-butyn-2-ones or substituted furanones are obtained in moderate to good yields. Best catalytic performance is achieved applying a mixed Pd(PPh₃)₂Cl₂/P(OPh)₃ catalyst system.

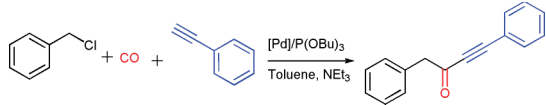
Palladium-catalyzed coupling reactions have become an indispensable tool in modern organic synthesis. These methodologies are of significant value for the preparation of pharmaceuticals and agrochemicals, as well as advanced materials.¹ Hence, both academic as well as industrial laboratories constantly explore new applications of the different coupling reactions.² Clearly, this area constitutes one of the major topics in homogeneous catalysis and organic synthesis, which is also demonstrated by the recent Nobel Prize in 2010.³ Along with the different coupling reactions, palladium-catalyzed carbonylative-coupling reactions are also attracting increasing attentions within the last decade.⁴ They allow for the direct incorporation of CO, the most inexpensive and readily available C1-source, into parent molecules. The resulting building blocks can be easily refined further on.⁵ One of the notable examples of CO-incorporating coupling reactions is the carbonylative Sonogashira reaction.⁶ While the coupling of aryl halides with carbon monoxide and alkynes has been well explored, carbonylative reactions of benzyl halides with terminal acetylenes to produce alkynones and furanones are scarcely known. In fact, to the best of our knowledge, only two reports deal with the synthesis of 1,4-diarylbutynones using such a methodology.^{6a,10}

In 2011, we described an improved protocol for the synthesis of furanones starting from aryl bromides/triflates and benzyl acetylenes.⁷ In that work we failed to perform similar carbonylations using inexpensive benzyl chlorides as starting material. Based on our continuous interest in palladium-catalyzed carbonylation reactions^{6a,7,8} here we wish to report novel carbonylative Sonogashira reactions of benzyl chlorides with aryl acetylenes as well as the carbonylative coupling with benzyl acetylenes to give furanones.⁹

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Table 1 Carbonylative coupling of benzyl chloride with phenyl acetylene: testing of palladium sources^a




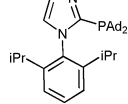
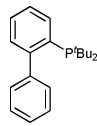
Entry	Pd [2 mol%]	Conv [%] ^b	Yield [%] ^b
1	PdCl ₂	6	6
2	PdBr ₂	19	10
3	Pd(OAc) ₂	1	1
4	Pd(TFA) ₂	15	10
5	Pd(PhCN) ₂ Cl ₂	10	10
6	Pd(MeCN) ₂ Cl ₂	16	9
7	Na ₂ PdCl ₄	20	13
8	K ₂ PdCl ₄	10	8
9	[Pd(cinnamyl)Cl] ₂	0	0
10	Pd(PPh ₃) ₂ Cl ₂	50	42

^a Benzyl chloride (1 mmol), phenyl acetylene (1 mmol), CO (10 bar), toluene (2 ml), NEt₃ (2 mmol), [Pd] (2 mol%), P(OPh)₃ (4 mol%), 100 °C, 16 h. ^b Conversion and yield were determined by GC-MS using hexadecane as internal standard.

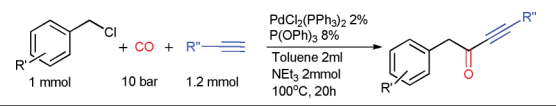
At the start of our investigations, we reacted benzyl chloride with phenyl acetylene under 10 bar of CO pressure in the presence of a PdCl₂/P(OPh)₃ catalyst system. Despite some conversion, the product yield was disappointingly low (only 6% yield of the desired product) (Table 1, entry 1). Testing different palladium precursors gave no considerable improvement of yield and conversion (Table 1, entries 2–9). However, applying Pd(PPh₃)₂Cl₂ led to a significant improvement in yield of the desired product (Table 1, entry 10). Interestingly, no reaction took place when the reaction was performed without P(OPh)₃ as ligand.

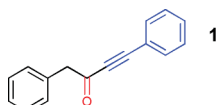
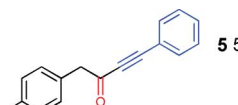
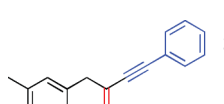
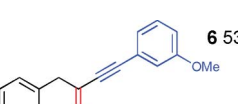
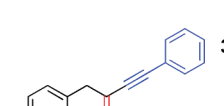
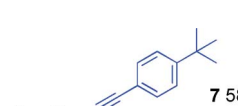

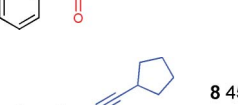
In order to improve the product yield further, the influence of different reaction parameters such as pressure, temperature, ligand, and base was tested (Table 2). Unfortunately, the addition of different phosphine ligands resulted in a low yield of the target product (Table 2, entries 1–4). On the other hand, in the presence of P(OPh)₃ the product was obtained in 72% yield (Table 2, entries 5–7). Next, we attempted to improve the yield by changing the base (Table 2, entries 8–11). Here, NEt₃ proved to be optimal. Finally, the best yield (85%) was realized by increasing the amount of phenyl acetylene to 1.2 equiv (Table 2, entry 12). Notably, at a lower pressure of CO (5 bar), 68% of 1,4-diphenylbutynone was still achieved (Table 2, entry 13). In the case of high

Table 2 Testing of ligands and bases^a


Entry	Ligand [4 mol%]	Base [2 mmol]	Conv [%] ^b	Yield [%] ^b
1	BuPAd ₂	NEt ₃	1	0
2	PCy ₃	NEt ₃	20	17
3		NEt ₃	19	10
4		NEt ₃	15	6
5	P(OPh) ₃	NEt ₃	70	60
6 ^c	P(OPh) ₃	NEt ₃	84	72
7 ^d	P(OPh) ₃	NEt ₃	77	50
8 ^e	P(OPh) ₃	DABCO	100	0
9 ^e	P(OPh) ₃	DMAP	75	0
10 ^e	P(OPh) ₃	NBu ₃	22	1
11 ^e	P(OPh) ₃	DBU	100	0
12 ^e	P(OPh) ₃	NEt ₃	99	85 (80 ^g)
13 ^f	P(OPh) ₃	NEt ₃	90	68

^a Benzyl chloride (1 mmol), phenyl acetylene (1 mmol), CO (10 bar), toluene (2 ml), base (2 mmol), Pd(PPh₃)₂Cl₂ (2 mol%), ligand (4 mol%), 100 °C, 16 h. ^b Conversion and yield were determined by GC-MS using hexadecane as internal standard. ^c P(OPh)₃ (8 mol%). ^d P(OPh)₃ (20 mol%). ^e P(OPh)₃ (8 mol%), phenyl acetylene (1.2 mmol), 20 h. ^f P(OPh)₃ (8 mol%), phenyl acetylene (1.2 mmol), CO (5 bar), 20 h. ^g Isolated yield.

Table 3 Palladium-catalyzed synthesis of 1,4-diaryl-3-alkyn-2-ones^a


	1 80% ^c		5 50% ^b
	2 65% ^b		6 53% ^b
	3 60% ^b		7 58% ^b
	4 58% ^b		8 45% ^b

^a Benzyl chlorides (1 mmol), terminal acetylenes (1.2 mmol), CO (10 bar), toluene (2 ml), NEt₃ (2 mmol), Pd(PPh₃)₂Cl₂ (2 mol%), P(OPh)₃ (8 mol%), 100 °C, 20 h. ^b Yields were determined by NMR. ^c Isolated yield.

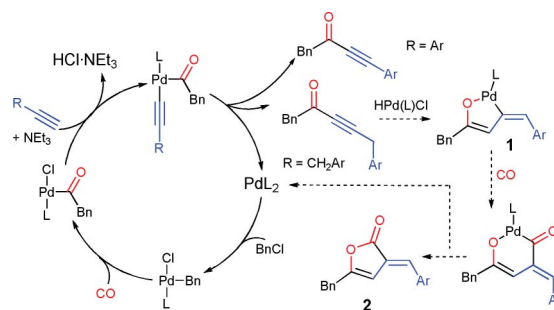
conversion but low or no desired product yield, benzyl chloride was decomposed and phenyl acetylene was still detected as it is.

With the best conditions in hand, we studied the scope and limitations of this methodology (Table 3). Methyl-, *tert*-butyl-, and fluoro-substituted benzyl chlorides successfully gave the corresponding products with phenyl acetylene in 50–80% yield (Table 3, entries 1–5).

Not only aromatic acetylenes, but also cyclopentyl acetylene as an example of an aliphatic alkyne worked in this reaction (Table 3, entry 8). On the other hand, activated benzyl chlorides such as 4-nitrobenzyl chloride and acetylenes, e.g. 4-bromophenylacetylene, did not work and gave mainly the non-carbonylative products.

Using benzyl acetylenes instead of aryl acetylenes resulted in the formation of potentially bio-active furan-2(3*H*)-ones¹¹ in moderate yields (Table 4). Both electron-withdrawing and electron-donating functionalized benzyl chlorides can be used in the coupling with benzyl acetylene and furnished the corresponding 5-benzyl-3-benzylidene-furan-2(3*H*)-ones in moderate to good yields.

The different reactivity of aromatic and benzylic alkynes is explained by a subsequent carbonylation in the case of the latter substrates. As shown in Scheme 1, we propose an initial oxidative addition of the benzyl chloride to Pd(0) to give the corresponding benzylpalladium(II) complex. Subsequent forma-

**Scheme 1** Proposed reaction mechanism.

tion of the acylpalladium complex takes place by CO insertion. Base-induced substitution of the chloride by the acetylide occurs and the alkynone is formed *via* reductive elimination. After the carbonylative Sonogashira coupling took place with benzyl acetylene, further reaction with hydridopalladiumchloride, which is generated within the first cycle (see Scheme 1), results in the formation of the isomerized complex **1**. Subsequent second carbonylation and final reductive elimination led to furanone **2**.

In conclusion, novel protocols for the carbonylation of benzyl chlorides and alkynes have been established. Applying an unusual Pd(PPh₃)₂Cl₂/P(OPh)₃ catalyst system eight different alkynones are produced in moderate to good yields (45–80%). Benzyl acetylene gave the corresponding furanones in moderate yield (45–68%) *via* palladium-catalyzed domino double carbonylation reactions.

Table 4 Palladium-catalyzed synthesis of furanones^a

Entry	Furanones	Yield [%] ^b
1		68 ^c
2		65
3		68
4		50
5		63
6		45
7		56
8		63
9		67

^a Benzyl chlorides (1 mmol), terminal acetylenes (1.2 mmol), CO (10 bar), toluene (2 ml), NEt₃ (2 mmol), Pd(PPh₃)₂Cl₂ (2 mol%), P(OPh)₃ (8 mol%), 100 °C, 20 h. ^b Yields were determined by NMR. ^c Isolated yield.

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