

Palladium-Catalyzed Carbonylative Sonogashira Coupling of Aryl Bromides Using Near Stoichiometric Carbon Monoxide

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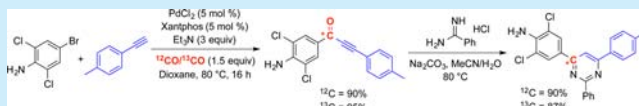
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S Supporting Information

ABSTRACT: A general procedure for the palladium-catalyzed carbonylative Sonogashira coupling of aryl bromides is reported, using near stoichiometric amounts of carbon monoxide. The method allows a broad substrate scope in moderate to excellent yields. The formed alkynone motive serves as a platform for synthesis of various heterocyclic structures, including pyrimidines. Furthermore, the presented strategy allows effective ¹³C labeling.



Alkynones are important structural motifs in organic chemistry, as they serve as key intermediates in the synthesis of many natural products.¹ Furthermore, they represent a platform for the synthesis of various heterocyclic structures, including pyrazoles,² pyridines,³ pyrimidines,⁴ and benzodiazepines.⁵ Traditionally, alkynones have been prepared by the transition-metal-catalyzed cross-coupling of acid chlorides and terminal alkynes.⁶ Recently, reactions between acid chlorides and terminal alkynes without the use of transition metals⁷ have been reported. However, the general stability of acid chlorides is limited, and they are often only accessible with a narrow scope of functional groups.

Palladium-catalyzed carbonylations of aryl halides have within the last decades become an important transformation in organic synthesis.⁸ Therefore, it has been shown that the palladium-catalyzed carbonylative Sonogashira coupling is a viable alternative for the synthesis of alkynones. This method utilizes readily accessible starting materials, such as aryl halides or pseudohalides, and shows good functional group tolerance.⁹ Furthermore, these carbonylative protocols can be performed without the need of adding a copper cocatalyst, which is normally required for the direct Sonogashira couplings. The first palladium-catalyzed carbonylative Sonogashira coupling was published by Kobayashi and Tanaka in 1981,¹⁰ and since then, many groups have reported and improved this particular transformation.¹¹ However, until now, most protocols have been performed using aryl iodides as electrophiles and only one report involves the more challenging aryl bromides as substrates. Recently, Beller and co-workers reported the first general procedure for the carbonylative Sonogashira coupling of aryl bromides.¹² Due to a 10 bar operating pressure of carbon monoxide, their protocol relies on the use of autoclaves. Furthermore, increased pressures of CO (30 bar) were required

for the coupling of a heteroaromatic bromide, and only one example was reported.

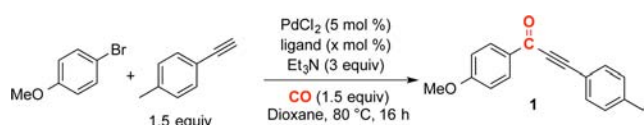
Given our developed expertise in the application of carbonylation chemistry performed in two-chamber reactors, using CO generated from stable precursors,¹³ we decided to investigate if the application of stoichiometric amounts of CO would be sufficient to promote the carbonylative Sonogashira coupling. Despite being a lower pressure protocol, a successful outcome would simultaneously provide direct access to isotope incorporation using ¹³C-labeled CO.

In this paper, we report a new protocol for the palladium-catalyzed carbonylative Sonogashira coupling of aryl bromides with terminal alkynes applying near stoichiometric amounts of CO. The simple application of PdCl₂ in combination with Xantphos as the ligand at 80 °C in dioxane provides a substrate scope with excellent functional group tolerance, including several examples of heteroaromatic bromides. Furthermore, the method proved adaptable to isotope labeling using ¹³C-labeled CO, generated *ex situ* in an analogous manner to CO. Finally, selected alkynones were transformed into their corresponding pyrimidines, by reaction with benzamidine, illustrating the utility of these alkynone building blocks in the synthesis of heteroaromatic structures.

As the starting point for the optimization, the coupling of 4-bromoanisole with 4-ethynyltoluene was chosen (Table 1). Based on preliminary work performed in our group, the combination of PdCl₂ with triethylamine in dioxane was applied. CO was generated *ex situ* from COgen by applying the two-chamber reactor (COware) previously reported.¹³ With

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Table 1. Ligand Screening of the Carbonylative Sonogashira Reaction^a

entry	ligand (mol %)	conversion ^b (%)
1	HBF ₄ (tBu) ₃ P (10.0)	37
2	HBF ₄ PCy ₃ (10.0)	0
3	CataCXium A (10.0)	27
4	PPh ₃ (10.0)	25
5	P(<i>o</i> -Tol) ₃ (10.0)	trace
6	Xantphos (5.0)	>95 (90) ^c
7	dppf (5.0)	25
8	dppp (5.0)	trace
9 ^d	Xantphos (2.5)	50

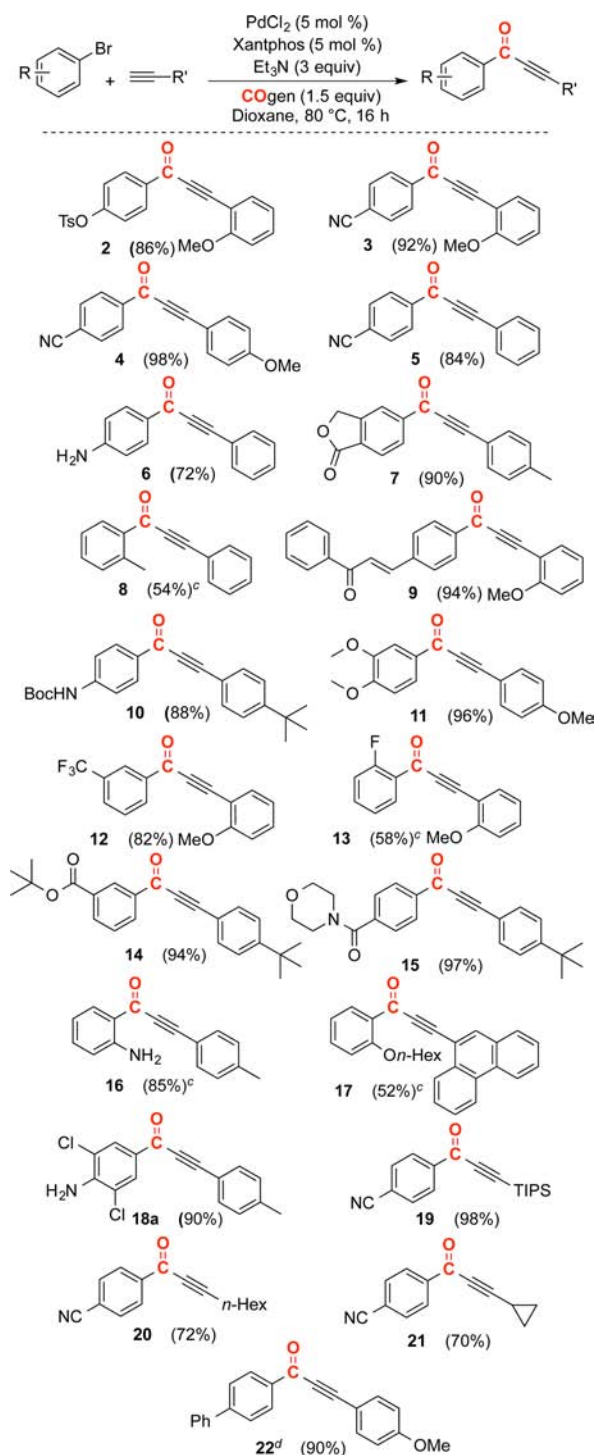
^aChamber A: COgen (0.75 mmol), HBF₄(tBu)₃P (1 mol %), Pd(cod)Cl₂ (1 mol %), Cy₂NMe (1.5 mmol) in dioxane (3 mL). Chamber B: 4-bromoanisole (0.5 mmol), 4-ethynyltoluene (0.75 mmol), PdCl₂ (5 mol %), ligand (x mol %), Et₃N (1.5 mmol) in dioxane (3 mL). ^bDetermined by ¹H NMR. ^cIsolated yield shown in brackets. ^dUsing 2.5 mol % of PdCl₂.

this setup in hand, different ligands were tested, the results of which are shown in Table 1.

First, alkyl phosphine ligands were tested, as these were previously shown to provide good conversions of both aryl iodides and aryl bromides (Table 1, entries 1–3).^{9g,12,14} However, in this case, these ligands did not provide satisfactory conversions. Another attempt was undertaken using PPh₃, a typically applied ligand in the carbonylative Sonogashira reaction with aryl iodides (Table 1, entry 4). However, only low conversion of 4-bromoanisole was observed, presumably due to a difficult oxidative addition step using PPh₃ as ligand. Changing to the more active ligand P(*o*-Tol)₃ only provided trace amounts of **1** (Table 1, entry 5).

Using the bidentate ligand, Xantphos provided full conversion to the desired product (Table 1, entry 6), with a 90% isolated yield of the desired alkynone (**1**). Other bidentate ligands, such as dppf and dppp, proved less reactive (Table 1, entries 7 and 8). Lowering the ligand and catalyst loadings only afforded 50% conversion (Table 1, entry 9).

Having developed optimal reaction conditions for the carbonylative Sonogashira coupling of aryl bromides, we explored the scope of the reaction by examining combinations of various aryl bromides and terminal alkynes (Scheme 1). Electron-rich aryl bromides were coupled successfully in high yields (compounds **2**, **10**, and **11**), including 4-bromoaniline, which could be successfully isolated in a 72% yield (compound **6**). Electron-deficient aryl bromides were also coupled to the desired alkynone structures in yields ranging from 82 to 98% (compounds **3–5**, **7**, **12**, **14**, and **15**). The use of aryl bromides carrying *ortho* substituents turned out to be more challenging, but by increasing the reaction temperature to 100 °C and applying DIPEA as the base, we could secure the desired products in moderate to good yields (compounds **8**, **13**, **16**, and **17**). Both free anilines and Boc-protected anilines were tolerated under the developed conditions with isolated yields ranging from 72 to 95% (compounds **6**, **10**, **16**, and **18**). Especially the motive found in compound **16** is interesting as it provides an expedient access to various quinolone structures.¹⁵

Scheme 1. Scope of the Carbonylative Sonogashira Coupling with Aryl Bromides^{a,b}

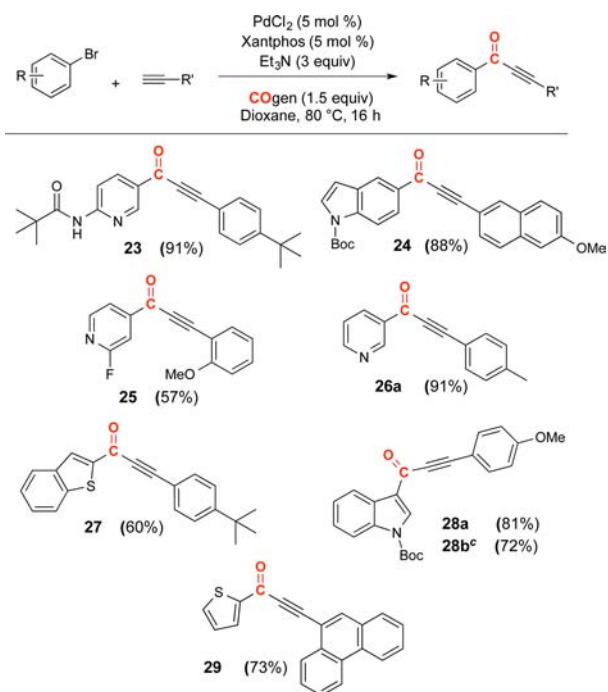
^aChamber A: COgen (0.75 mmol), HBF₄(tBu)₃P (1 mol %), Pd(cod)Cl₂ (1 mol %), Cy₂NMe (1.5 mmol) in dioxane (3 mL). Chamber B: aryl bromide (0.5 mmol), alkyne (0.75 mmol), PdCl₂ (5 mol %), Xantphos (5 mol %), Et₃N (1.5 mmol) in dioxane (3 mL). ^bIsolated yields. ^cReaction conducted at 100 °C using DIPEA (1.5 mmol) as base in both chambers. ^dStarting from 1,1'-biphenyl triflate.

The substrate scope also demonstrates that a variety of terminal alkynes can be tolerated; aromatic alkynes with *ortho* and *para* substituents and aliphatic alkynes perform well under the catalytic conditions (e.g., compounds **3**, **4**, **20**, and **21**).

TIPS-protected acetylene also underwent successful coupling, affording **19** in an excellent 98% isolated yield. Finally, substituting the aryl bromide for the corresponding aryl triflate did not impede the carbonylative coupling (compound **22**).

Next, attention was turned to the heteroaromatic bromides as electrophiles in the coupling (Scheme 2). Applying *N*-Boc-

Scheme 2. Scope of the Carbonylative Sonogashira Coupling with Heteroaryl Bromides^{a,b}



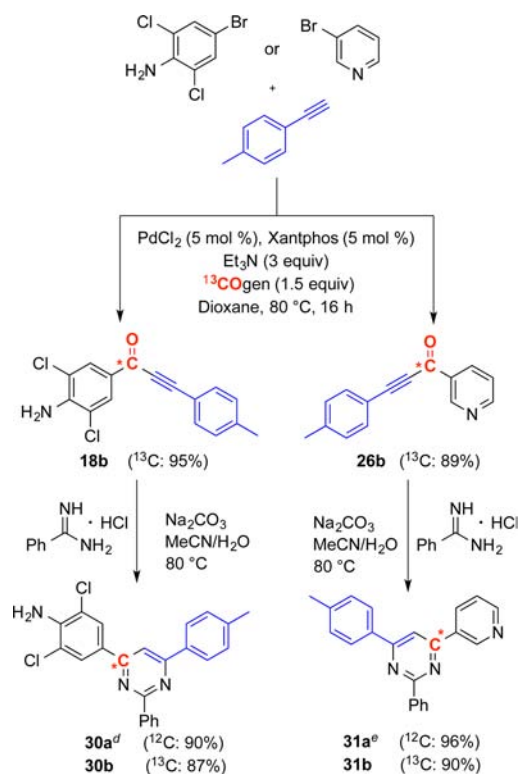
^aChamber A: COgen (0.75 mmol), HBF₄(*t*Bu)₃P (1 mol %), Pd(cod)Cl₂ (1 mol %), Cy₂NMe (1.5 mmol) in dioxane (3 mL). Chamber B: aryl bromide (0.5 mmol), alkyne (0.75 mmol), PdCl₂ (5 mol %), Xantphos (5 mol %), Et₃N (1.5 mmol) in dioxane (3 mL). ^bIsolated yields. ^cUsing ¹³COgen (0.75 mmol).

protected bromoindoles furnished the alkynones in good overall yields (compounds **24** and **28**). Different bromopyridines were also tolerated in moderate to excellent yields (compounds **23**, **25**, and **26**). Using 2-bromobenzothiophene as the electrophile yielded the desired product **27** in a 60% isolated yield. Finally 2-bromothiophene was successfully coupled to alkyne **29** in a 73% yield.

Finally, to illustrate the applicability of the synthesized alkynones, it was decided to synthesize pyrimidines and their labeled counterparts. The synthesis of the intermediary alkynone structures was carried out using ¹³C-labeled ¹³COgen (compounds **18b** and **26b**, Scheme 3). Müller and co-workers have demonstrated how to access various heterocyclic structures starting from the alkynone motif.^{2b,4} Hence, employing their method provided an efficient route to highly substituted pyrimidines in only two steps with overall good yields (Scheme 3).

In conclusion, we have developed a new and efficient procedure for the carbonylative Sonogashira coupling of various aryl- and heteroaryl bromides. Noteworthy, is the excellent functional group tolerance, illustrating the generality of the developed procedure. The substrate scope also includes several examples of heteroaromatic bromides, which have not been

Scheme 3. Synthesis of ¹³C-Labeled Pyrimidines from Selected Carbonylative Sonogashira Products^{a,b,c}



^aCarbonylative Sonogashira. Chamber A: COgen (0.75 mmol), HBF₄(*t*Bu)₃P (1 mol %), Pd(cod)Cl₂ (1 mol %), Cy₂NMe (1.5 mmol) in dioxane (3 mL). Chamber B: aryl bromide (0.5 mmol), alkyne (0.75 mmol), PdCl₂ (5 mol %), Xantphos (5 mol %), Et₃N (1.5 mmol) in dioxane (3 mL). ^bPyrimidine synthesis: alkynone (0.3 mmol), benzamidine hydrochloride (0.36 mmol), Na₂CO₃ (0.72 mmol) in MeCN (2 mL) and H₂O (0.3 mL). ^cIsolated yields. ^dFrom **18a**, Scheme 1 ^eFrom **26a**, Scheme 2.

accessed before. Finally, this setup is highly suitable for ¹³C isotope labeling by applying ¹³COgen as the CO precursor.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental details and copies of all the ¹H NMR and ¹³C NMR spectra for all the coupling products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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