



Catalytic activity of palladium acyclic diaminocarbene complexes in the synthesis of 1,3-diarylpropynones via Sonogashira reaction: cross- versus homo-coupling

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ABSTRACT

Sonogashira cross-coupling of aryl acetylenes and aroyl chlorides catalyzed by palladium(II) acyclic diaminocarbene complexes was investigated. Reactions were carried out with 0.04 mol % of the catalysts, all of which demonstrated high stability and activity in air. The influence of the reaction conditions (temperature, time, amount of catalyst, solvent) and the structures of the starting compounds on the ratios of cross- (1,3-diarylpropynones) and homo-coupling (1,4-diarylbutadiynes) products was elucidated. The yields of 1,3-diarylpropynones reached 95–98%.

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α,β -Acetylene ketones (propynones) are of significant importance because of their wide use in organic synthesis as bifunctional three-carbon building blocks. For example, they are employed in the preparation of heterocycles,¹ biologically active compounds,² carbocycles,³ functionalized enone systems,⁴ etc. Propynones were applied effectively in the synthesis of unsymmetrical 1-aryl(hetaryl/vinyl) buta-1,3-diynes using the Fritsch–Buttenberg–Wiechell rearrangement according to Tykwinski et al.⁵ In particular, intramolecular cyclization of 1,3-diarylpropynones in Bronsted superacids resulted in the formation of 3-aryl indenones,⁶ which could be easily photo-dimerized into cyclobutane structures.⁷ Hydroarylation of the acetylene bond of 1,3-diarylpropynones in superacids leads to 1,3,3-triaryl substituted propenones.⁸ Oxidative dimerization of these acetylene ketones using the $\text{PbO}_2\text{--CF}_3\text{CO}_2\text{H--CH}_2\text{Cl}_2$ system is a simple one-pot method to prepare synthetically difficult tetraaryl ethylenes, which are used as precursors of pyridazine and 2,3,6,7-tetraaz-anaphthalene derivatives.⁹

Several approaches have been developed for the preparation of 1,3-diarylpropynones using acetylenes (Scheme 1). One of the most effective methods is palladium-catalyzed cross-coupling

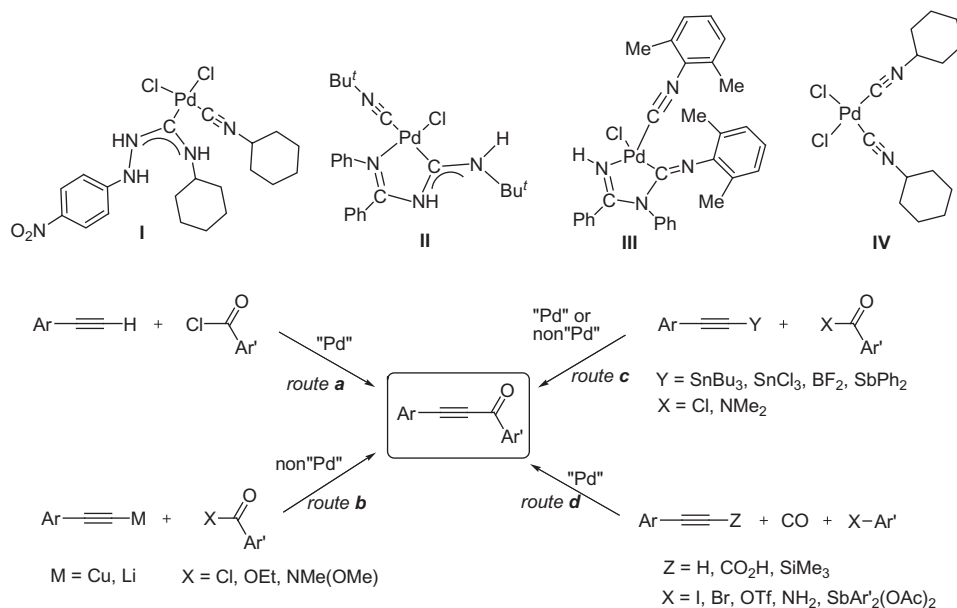
of aryl acetylenes with aroyl chlorides (Scheme 1, route a).^{9,10} This route was discovered by Sonogashira in 1977 in his seminal work.^{10a} Later, non-palladium procedures for this reaction were described.¹¹ Another pathway is the aroylation of copper¹² or lithium¹³ derivatives of aryl acetylenes (Scheme 1, route b). Other methods are the reactions of aroyl chlorides or amides with arylolefinyl stannanes,¹⁴ boranes,¹⁵ or stibines¹⁶ in both palladium-catalyzed^{14a,16} or non-palladium versions^{14b,15} (Scheme 1, route c). Other syntheses are based on carbonylative coupling of aryl acetylenes (or their derivatives) with aryl halides,^{17a–c} triflates,^{17d} amines,^{17e} or triarylantimony(V) diacetate (Scheme 1, route d).^{17f}

The most common palladium catalysts for the Sonogashira reaction are $\text{PdCl}_2(\text{PPh}_3)_2$ or $\text{Pd}(\text{PPh}_3)_4$.¹⁸ More recently, attention has been paid to palladium aminocarbene species as catalysts for versatile organic transformations,¹⁹ including the Sonogashira synthesis of dialkylacetylenes,^{20a} alkylarylacetylenes,^{20b,c} diarylacetylenes,^{20b,d–g} and alkylarylbutadiynes.^{20c}

Based on our studies on the preparation^{9a} and chemical reactions^{6–9} of 1,3-diarylpropynones, herein we report a synthesis of these substrates via the palladium acyclic diaminocarbene complex catalyzed Sonogashira coupling of arylacetylenes with aroyl chlorides. This is the first example of the use of such palladium species in the synthesis of acetylene ketones.

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Scheme 1.

Four complexes (**I–IV**) have been studied as catalysts in the described reaction. Acyclic diaminocarbene complexes **I–III** are readily available from palladium(II) isonitrile complexes by addition of the corresponding *N*-nucleophiles to a CN triple bond.¹⁹ The complexes **II** and **III** were obtained recently and tested in Sonogashira cross-coupling of acetylenes with iodoarenes.^{20c} Complex **I** was synthesized analogously by reaction of isonitrile complex **IV** with *p*-nitrophenylhydrazine.²¹ Starting complex **IV** was also tested in the presence of secondary amines to investigate the possibility of the in situ generation of catalytic Pd-aminocarbene species.²²

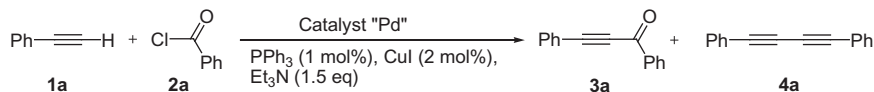
It is known that the Pd/Cu catalyzed cross-coupling is usually accompanied by competitive homo-coupling, which leads to the formation of butadiynes from terminal acetylenes.¹⁸ Thus, it is necessary to use an excess of the terminal acetylene and to separate the target cross-coupling products from homo-coupling by-prod-

ucts. In this study we also investigated the selectivity of complexes **I–IV** toward cross- and homo-couplings.

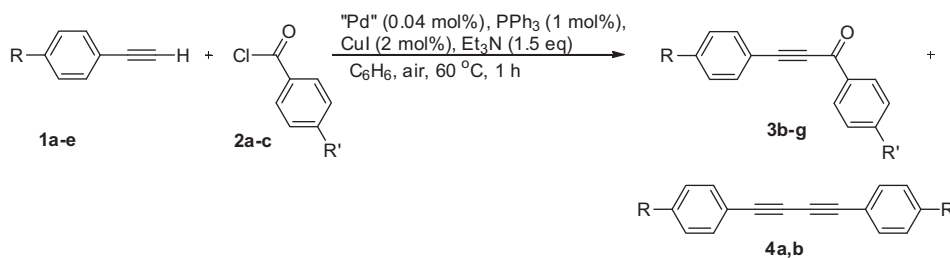
To study and compare the catalytic activity complexes **I–IV**, we chose the reaction of phenyl acetylene (**1a**) with benzoyl chloride (**2a**) using complexes **I–IV** instead of PdCl₂.^{6b,9} (Table 1). The ratio of the two reaction products, 1,3-diphenylpropynone (**3a**) (the cross-coupling product) and 1,4-diphenylbutadiyne (**4a**) (the homo-coupling product), was determined by ¹H NMR spectroscopy and GC-MS after work-up of the reaction mixtures.²³

First of all, experiments with each aminocarbene complex were carried out under argon at 20 °C according to the procedure previously developed by us.^{9a} In the presence of only 0.04 mol % of catalysts **I–IV** the reactions were rapid. However even under an inert atmosphere and using THF or benzene as the solvents, diphenylbutadiyne **4a** was formed as the major product (Table 1, en-

Table 1
Reaction of phenyl acetylene (**1a**) with benzoyl chloride (**2a**): catalysts, conditions, yields, and ratios of reaction products **3a** and **4a**



Entry	Catalyst (mol %)	Reaction conditions				Yield of 3a + 4a (%)	Ratio of 3a : 4a
		Solvent	Atmosphere	Temperature (°C)	Time (h)		
1	I (0.04)	THF	Argon	20	7	93	44:56
2	I (1)	C ₆ H ₆	Argon	20	5	87	20:80
3	II (0.04)	THF	Argon	20	1	52	7:93
4	III (0.04)	C ₆ H ₆	Argon	20	24	91	50:50
5	IV (1)	C ₆ H ₆	Argon	20	5	75	9:91
6	IV (0.04) + NHEt ₂ (20 mg)	THF	Argon	20	24	91	6:94
7	I (0.04)	C ₆ H ₆	Air	20	12	95	59:41
8	II (0.04)	C ₆ H ₆	Air	20	24	89	28:72
9	III (0.04)	C ₆ H ₆	Air	20	24	86	13:87
10	III (1)	C ₆ H ₆	Air	20	24	93	15:85
11	IV (0.04) + NHEt ₂ (20 mg)	C ₆ H ₆	Air	20	24	98	44:56
12	I (0.04)	C ₆ H ₆	Air	60	1	98	67:33
13	II (0.04)	C ₆ H ₆	Air	60	1	94	77:23
14	III (0.04)	C ₆ H ₆	Air	60	1	98	89:11
15	IV (0.04)	C ₆ H ₆	Air	60	1	90	80:20
16	IV (0.04) + NHEt ₂ (20 mg)	C ₆ H ₆	Air	60	1	96	72:28

Table 2Reactions of aryl acetylenes **1a–e** with benzoyl chlorides **2a–c**

Entry	Substituents in 1–4		Initial compounds		Catalyst	Reaction products			
	R	R'	Alkyne	Chloride		Ketone	Diyne	Yield of 3 + 4 (%)	Ratio of 3a:4a
1	H	Me	1a	2b	II	3b	4a	89	23:77
2	H	NO_2	1a	2c	II	3c	4a	92	38:62
3	Me	H	1b	2a	I	3d	–	95	100:0
4	MeO	H	1c	2a	I	3e	–	98	100:0
5	Br	H	1d	2a	II	3f	–	97	100:0
6	NO_2	H	1e	2a	II	3g	4b	90	77:23

tries 1–6). Increasing the amount of the catalyst from 0.04 to 1 mol % (Table 1, entry 2) did not change the situation significantly.

Next, experiments were performed under similar conditions at $20\text{ }^\circ C$ in air (Table 1, entries 7–11) with the use of the benzene as the solvent. Previously it was shown that complexes **II** and **III** demonstrated high catalytic activity in Sonogashira cross-couplings of acetylenes with iodoarenes in air.^{20c} Surprisingly, despite the fact that the homo-coupling product prevailed, the amount of the hetero-coupling product **3a**, except that from the reaction catalyzed by **III** (Table 1, entries 9 and 10), was increased. We assume that benzene favors formation of the cross-coupling product (compare entries 1 and 7 or 3 and 8, Table 1). It was also noted that complete conversion of the starting compounds required more time (up to 24 h).

In the subsequent experiments, the temperature was increased to $60\text{ }^\circ C$. Under these conditions, all the reactions were complete in one hour. Moreover the increased temperature led to an inversion in the ratio of the homo- and hetero-coupling products and higher yields of the latter were observed (Table 1, entries 12–16). The complexes **I–III** showed approximately equal catalytic activity. The isonitrile compound **IV** could also be used as a catalyst (Table 1, entry 15), or with addition of Et_2NH (Table 1, entries 6, 11 and 16). It should also be mentioned that the increased temperature had a beneficial effect on the reactions catalyzed by complexes **II** and **III** (Table 1, entries 13 and 14 vs entries 8 and 9).

Having developed favorable conditions for the preparation of 1,3-diarylpropynones (Pd-catalyst 0.04 mol %, air, $60\text{ }^\circ C$, benzene, 1 hour), we next explored the reaction of aryl acetylenes **1a–e** and aryl chlorides **2a–c** with the complexes **I** and **II** (Table 2).²³ Acetylene substrates **1b–d** with electron-donating (Me, MeO) or the weakly electron-withdrawing Br groups reacted with benzoyl chloride (**2a**) to form exclusively the ketones **3d–f** without any of the corresponding 1,4-diarylbutadiynes (Table 2, entries 3–5). On the other hand, even acetylene **1e**, bearing a strong electron-accepting NO_2 substituent, gave propynone **3g** as the major reaction product and diyne **4b** as a minor product (Table 2, entry 6). Reactions of substituted aryl chlorides **2b,c** led to ketones **3b,c** and diyne **4a** with a predominant formation of the latter (Table 2, entries 1 and 2).

The formation of diynes, as products of homo-coupling, is one outcome of the catalytic cycle of the Sonogashira reaction.¹⁸ In our study, the formation of large amounts of diynes **4a,b** revealed deep mechanistic problems related to the abilities of copper acetylides and aryl chlorides to coordinate with catalytic palladium

species and the different stabilities of the so-formed reaction intermediates under the various reaction conditions investigated (argon, oxygen, temperature, solvent). This complex problem of Pd-catalyzed couplings has been discussed, and the formation of a 'cocktail'-like mixture of the catalysts in such reactions was proposed.²⁴

In conclusion, palladium acyclic diaminocarbene complexes can be used as catalysts in Sonogashira cross-couplings to give 1,3-diarylpropynones. Compared to other similar syntheses of 1,3-diarylpropynones, where $PdCl_2$ (2 mol %)^{6b,9} or $PdCl_2(PPh_3)_2$ (0.9 mol %)^{10b} were used, in this study the quantity of complexes **I–III** was extremely low 0.04 mol %. Also the palladium acyclic diaminocarbene complexes reacted in air, yielding the target 1,3-diarylpropynones in yields up to 95–98%. The scope, limitations, and mechanistic aspects of this reaction are currently under investigation.

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21. *Characterization of complex I*: $^1\text{H NMR}$ (CDCl_3 , δ): 9.90 (s, 1H, C=NH), 8.10 (d, $2\text{H}_{\text{arom.}}$, $J = 8.7$ Hz), 7.75 (s, 1H, ArNH), 7.05 (d, 1H, NH, $J = 10.2$ Hz), 6.90 (d, $2\text{H}_{\text{arom.}}$, $J = 8.7$ Hz), 4.44 (m, 1H, CH), 4.01 (m, 1H, CH), 2.20–1.24 (m, 20H, 10CH_2). IR (KBr, ν , cm^{-1}): 2934–2856 (C–H); 2230 (C≡N); 1330 (NO_2). HRMS: ESI $^+$ -MS, found: 514.1092 [M-Cl] $^+$; calcd for $\text{C}_{20}\text{H}_{28}\text{ClN}_5\text{O}_2\text{Pd}$: 514.1049. ESI $^-$ -MS, found: 548.08 [M-H] $^-$; calcd for $\text{C}_{20}\text{H}_{28}\text{Cl}_2\text{N}_5\text{O}_2\text{Pd}$: 548.07.
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23. *General procedure for the coupling of aryl acetylenes with aroyl chlorides*. Catalyst (0.04 mol %, as 0.35–0.5 ml aliquot of THF or benzene solutions), PPh_3 (8 mg, 1 mol %), CuI (11 mg, 2 mol %), and Et_3N (1.5 equiv) were added to a solution of the aryl acetylene (3 mmol) and aroyl chloride (3 mmol) in benzene (10 ml) under stirring at 60 °C. The mixture was stirred at 60 °C for 1 h, then cooled to room temperature, and diluted with CHCl_3 (100 ml). The organic layer was washed with H_2O (20 ml), aqueous NaHCO_3 solution (2×10 ml), and H_2O (20 ml), and dried over Na_2SO_4 . After evaporation of the solvent under vacuum, the residue was analyzed by $^1\text{H NMR}$ and GC–MS. Individual reaction products were separated by column chromatography on silica gel (eluent hexanes/EtOAc). 1,3-Diarylpropynones **3a–g** were previously obtained and characterized by ourselves.^{6b,9}
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