

Copper-Free Sonogashira Cross-Coupling of Aryl Chlorides with (Hetero)arylacetylenes in the Presence of Ppm Molar Loadings of $[\{\text{Pd}(\text{OH})\text{Cl}(\text{NHC})\}_2]$ Complexes. Hydrogen Chloride as a Coupling Product. Co-catalytic Effect of Water

Sylwia Ostrowska , [Szymon Rogalski](#) , [Cezary Pietraszuk](#) *

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Article

Copper-Free Sonogashira Cross-Coupling of Aryl Chlorides with (Hetero)Arylacetylenes in the Presence of ppm Molar Loadings of $[\{\text{Pd}(\text{OH})\text{Cl}(\text{NHC})\}_2]$ Complexes. Hydrogen Chloride as a Coupling Product. Co-Catalytic Effect of Water

Sylwia Ostrowska, Szymon Rogalski and Cezary Pietraszuk *

Adam Mickiewicz University, Poznań, Faculty of Chemistry, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

* Correspondence: cezary.pietraszuk@amu.edu.pl

Abstract: Aryl chlorides and bromides in the presence of NHC palladium hydroxo dimers of the type $[\{\text{Pd}(\mu\text{-OH})\text{Cl}(\text{NHC})\}_2]$ (where NHC = IPr, SIPr, IMes, SIMes) undergo an efficient and selective Sonogashira cross-coupling with terminal acetylenes. For the coupling of 4-chlorotoluene with phenylacetylene TON = 560000 was observed. The procedure enables high-throughput and selective synthesis of a broad spectrum of unsymmetrically substituted 1,2-diarylacetylenes. Nearly a quantitative amount of HCl was detected within cross-coupling products. Water plays the role of the base and is regenerated in the process so that it does not have to be used in stoichiometric amounts (relative to the limiting reactant). Generation of the active Pd(0) complex proceeds via ethanol oxidation.

Keywords: copper-free Sonogashira; cross-coupling; palladium; NHC complexes

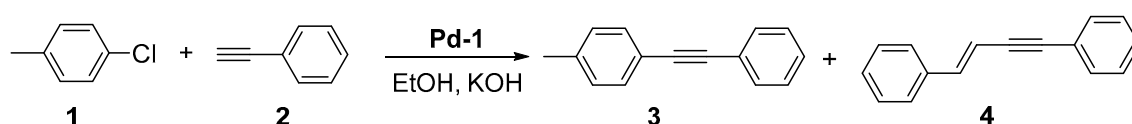
1. Introduction

Palladium-catalysed cross-coupling reactions are among the most useful catalytic transformations in organic synthesis [1–5]. The search for more environmentally friendly ways of catalysing coupling, including the reduction of palladium consumption, is a key driver for ongoing catalyst development [6]. Procedures have been developed that allow the use of catalyst molar loadings from ppm to ppb [7,8]. In particular, they allow efficient transformations of aryl iodides and bromides. In the case of the Sonogashira reaction, more environmentally friendly conditions were achieved by eliminating copper salts from the catalytic system. This led to the development of the so-called copper-free Sonogashira coupling [9], although such systems had already been described in the seminal work of Cassar [10] and Heck [11]. Numerous reports also indicate the beneficial effect of water on the course of the reaction and also point to the possibility of carrying out the reaction in water as a solvent [12,13]. A number of catalytic systems have been described for the highly efficient copper-free coupling of Sonogashira aryl iodides and bromides to terminal acetylenes using small amounts of palladium. For the coupling of aryl chlorides to acetylenes, the use of 1 mol% palladium catalyst is typical. Relatively little progress has been made since Buchwald's work describing the use of $[\text{PdCl}_2(\text{MeCN})_2]$ and bulky electron donating phosphine (XPhos) [14]. The most active procedures described involving soluble precatalysts allow the use of up to 0.001 mol% catalyst for activated aryl chlorides and 0.1 mol% for deactivated ones [15,16]. The most active systems use palladacyclic precatalysts [15–20] and NHC complexes [21,22]. We have recently described synthesis and the high catalytic activity of palladium hydroxo dimer $[\{\text{Pd}(\mu\text{-OH})\text{Cl}(\text{IPr})\}_2]$ (**Pd-1**) in the Suzuki cross-coupling of aryl chlorides with aryl and alkenylboronic acids [23]. Moreover, we demonstrated its high catalytic activity in homo-coupling of aryl and alkenylboronic acids [24] and dimerization of acetylenes [25]. Herein, we report high catalytic activity of **Pd-1** and analogous complexes in the

copper-free Sogashira cross-coupling of (hetero)aryl chlorides and bromides with arylacetylenes. The method we describe allows the efficient formation of a wide range of diarylacetylenes using homeopathic amounts of palladium (up to 1 ppm) and catalytic amounts of a base. In addition, we propose and discuss important aspects of the mechanism of the reaction.

2. Results and discussion

The reaction of 4-chlorotoluene with phenylacetylene was chosen as the test reaction for the copper-free Sonogashira cross-coupling study. This reaction is often used in the scientific literature to study the Sonogashira coupling. For the preliminary tests, ethanol was chosen as the solvent and potassium hydroxide as the base, as dictated by the efficiency of this system in the Suzuki-Miyaura coupling [23] and the homo-coupling of boronic acids [24]. When 1 mol% of hydroxo dimer (**Pd-1**) and 4 mol% of KOH were added at room temperature to an ethanolic solution containing phenylacetylene and an equal molar amount of 4-chlorotoluene, a slow and selective formation of the acetylene dimerization product was observed (Table 1). The use of five times the molar excess of 4-chlorotoluene did not change the reaction outcome. Increasing the reaction temperature to 40 °C resulted in the appearance of small amounts of coupling product in the reaction mixture (Scheme 1). Unexpectedly, at 80 °C, selective and almost quantitative formation of the Sonogashira product was observed (Table 1). To avoid the formation of a dimerization product, the catalyst and KOH as a base were added to the hot reaction mixture.



Scheme 1. Sonogashira cross-coupling of 4-chlorotoluene with phenylacetylene catalysed by **Pd-1**. The scheme also shows the formation of enyne (**4**) as the main by-product of the reaction.

Table 1. Sonogashira cross-coupling of 4-chlorotoluene with phenylacetylene catalysed by **Pd-1**. Optimization of reactant ratios, temperature and reaction time.

Entry	[C ₇ H ₇ Cl]/[≡]	[Pd]/[KOH]	Temp. [°C]	Time [h]	Conv. of 2 [%]	Yield [%]
1	1/1	base-free	22	24	0	-
2	1/1	base-free	80	24	84	4 (100)
3	1/1	1/2	22	24	91	4 (100)
4	5/1	1/2	22	24	91	4 (100)
5	5/1	1/2	40	24	93	3 (traces); 4 (98)
6	5/1	1/2	70	24	98	3 (18); 4 (80),
7	5/1	1/2	80	0.25	>99	3 (100)
8	2/1	1/2	80	0.25	>99	3 (60); 4 (40)

Reaction conditions: EtOH (96%), [**Pd-1**] = 1 mol%, argon, dodecane (internal standard); Conversions were calculated from GC analyses; products were identified by GC-MS.

In subsequent tests, conditions were searched for a selective and highly efficient reaction. In a typical experiment, ethanol (96%) (3 ml), acetylene and five times the molar excess of aryl halide were added sequentially to a Schlenk vessel under an argon atmosphere. The mixture was then heated to 80 °C and [**Pd**(μ-OH)Cl(IPr)₂] (0.001 mol%) (1 μL solution in toluene 9.1×10⁻⁶ mol/mL) and KOH (1 μL KOH solution in ethanol, 1.78×10⁻⁴ mol/mL) were added simultaneously. The reactions were carried out at 80 °C with continuous stirring for 2 hours. The results obtained are shown in Table 1.

No Sonogashira coupling (and dimerisation) products were observed in the absence of a base and in the presence of air. The studies revealed that complex **Pd-1** used with twice the molar excess of KOH ([Pd]/[KOH] = 1/2), with a molar ratio of reactants equal to [C₇H₇Cl]/[≡] = 5/1 allowed the test

reaction to proceed completely and selectively (Table 1, entry 7). This was followed by catalyst loading optimization tests (Table 2)

Table 2. Cross-coupling of 4-chlorotoluene with phenylacetylene catalysed by **Pd-1**. Optimization of the catalyst loading.

Entry	Pd-1 [mol%]	[Pd]/[KOH]	Time [h]	Conv. of 2 [%]	Selectivity of 3 [%]	TON
1	0.1	1/2	0.25	>99	100	1000
2	0.01	1/2	0.25	>99	100	10000
3	0.001	1/4	24	97	100	100000
4	0.0001	1/4	24	56	100	560000

Reaction conditions: [ArX]/[≡] = 5/1, EtOH (96%), temp. = 80 °C, argon, dodecane (internal standard); Conversions were calculated from GC analyses; products were identified by GC-MS.

The study showed that the **Pd-1** complex used with twice the molar excess of KOH ([Pd]/[KOH] = 1/2) allowed the test reaction to run completely at loadings up to 0.001 mol%, giving TON = 100000 (Table 2, entry 3). The highest turnover rate (TON = 560000) was observed at a ratio of [Pd]/[KOH] = 1/4. Under these conditions, 1 ppm of catalyst allows the coupling product to be obtained with a yield of 56%, giving TON = 560000 (Table 2, entry 8). To our knowledge, this is the highest value reported in the literature for Sonogashira coupling using aryl chlorides. Following the results of the initial optimization of the reaction conditions, a further series of catalytic tests were carried out to determine the effect of solvent (Table 3) and base (Table 4) on the yield and selectivity of the reaction.

Table 3. Sonogashira cross-coupling of 4-chlorotoluene with phenylacetylene catalysed by **Pd-1**. Effect of solvent on the yield and selectivity of the reaction.

Entry	Solvent	Time [h]	Conversion ^a [%]	Selectivity of 3 [%]
2	EtOH	0.25	100	100
3	EtOH/H ₂ O (1/1)	0.25	100	100
4	MeOH ^b	15	94	100
5	<i>i</i> -PrOH	24	99	100
6	DMF	0.25	89	100
7	THF	24	21	10
8	CHCl ₃ ^b	24	11	30
9	toluene/H ₂ O (9/1)	24	14	100

Reaction conditions: [C₇H₇Cl]:[acetylene] = 5:1, 80 °C, **Pd-1** (0.01 mol%), [**Pd-1**]:[KOH] = 1:2, 24 h, argon; ^a) conversion of phenylacetylene; ^b) reflux. Conversions were calculated from GC analyses, products were identified by GC-MS.

Alcohols, in particular ethanol (96%), gave the best results, as shown in Table 3. Good reaction yields with high selectivity can also be obtained by running reactions in DMF. Using other solvents such as THF, chloroform, toluene or hexane resulted in reduced selectivity and/or conversion.

Table 4. Cross-coupling of 4-chlorotoluene with phenylacetylene catalysed by **Pd-1**. Effect of base on yield and selectivity of the reaction.

Entry	Base	Time [h]	Conversion ^a [%]	Selectivity of 3 [%]
1	KOH	0.25	100	100
2	NaOH	24	0	-
3	K ₂ CO ₃	24	12	40
4	Cs ₂ CO ₃	24	21	100

5	TBAF	24	9	-
6	KO ^t -Bu	24	74	-

Reaction conditions: [ArCl]:[acetylene] = 5:1, 80 °C, **Pd-1** (0.01 mol%), [**Pd-1**]:[base] = 1:2; 24 h, argon, dodecane (internal standard); ^a) conversion of phenylacetylene. Conversions were calculated from GC analyses, products were identified by GC-MS.

Table 4 shows that among the bases used, complete conversion of acetylene and exclusive formation of the coupling product was achieved with KOH. It should be noted that the bases were used in catalytic quantities in relation to the catalyst. The efficient course of the reaction does not require the presence of equal amounts of base relative to the reactant. We have reported a similar effect using *N*-heterocyclic hydroxo dimers in Suzuki homo- and cross-coupling reactions [23]. Under conditions considered optimal for the **Pd-1** complex ([ArCl]/[acetylene] = 5/1, 80 °C, [Pd] 0.001 mol%, [Pd]/[KOH] = 1/2, ethanol, argon), the activity of other *N*-heterocyclic hydroxo dimers, i.e. [{Pd(μ-OH)Cl(SIPr)}₂] (**Pd-2**), was investigated, [{Pd(μ-OH)Cl(IMes)}₂] (**Pd-3**), [{Pd(μ-OH)Cl(SIMes)}₂] (**Pd-4**), chloride dimers [{Pd(μ-Cl)Cl(IPr)}₂] (**Pd-5**), [{Pd(μ-Cl)Cl(SIPr)}₂] (**Pd-6**), [{Pd(μ-Cl)Cl(IMes)}₂] (**Pd-7**), [{Pd(μ-Cl)Cl(SIMes)}₂] (**Pd-8**), complexes of the PEPPSI type [26,27] [PdCl₂(IPr)(3-chloropyridine)] (**Pd-9**), [PdCl₂(SIPr)(3-chloropyridine)] (**Pd-10**), [PdCl₂(IMes)(3-chloropyridine)] (**Pd-11**), [PdCl₂(SIMes)(3-chloropyridine)] (**Pd-12**) and selected simple palladium salts PdCl₂ and Pd(OAc)₂. The results are given in Table 5.

Table 5. Cross-coupling of 4-chlorotoluene with phenylacetylene in the presence of different *N*-heterocyclic carbene palladium complexes.

Entry	Catalyst	Conv. of 2 [%]	Selectivity of 3 [%]
1	[{Pd(μ-OH)Cl(IPr)} ₂] (Pd-1)	100 ^a	100 ^a
2	[{Pd(μ-OH)Cl(SIPr)} ₂] (Pd-2)	100 ^a	100 ^a
3	[{Pd(μ-OH)Cl(IMes)} ₂] (Pd-3)	68 ^a (88)	100
4	[{Pd(μ-OH)Cl(SIMes)} ₂] (Pd-4)	48 ^a (61)	100
5	[{Pd(μ-Cl)Cl(IPr)} ₂] (Pd-5)	73	100
6	[{Pd(μ-Cl)Cl(SIPr)} ₂] (Pd-6)	82	100
7	[{Pd(μ-Cl)Cl(IMes)} ₂] (Pd-7)	44	10; 4 (90)
8	[{Pd(μ-Cl)Cl(SIMes)} ₂] (Pd-8)	45	4 (100)
9	[PdCl ₂ (IPr)(3-chloropyridine)] (Pd-9)	55	30; 4 (70)
10	[PdCl ₂ (SIPr)(3-chloropyridine)] (Pd-10)	58	50; 4 (50)
11	[PdCl ₂ (IMes)(3-chloropyridine)] (Pd-11)	59	30; 4 (70)
12	[PdCl ₂ (SIMes)(3-chloropyridine)] (Pd-12)	53	4 (100)
13	PdCl ₂	0	-
14	Pd(OAc) ₂	0	-

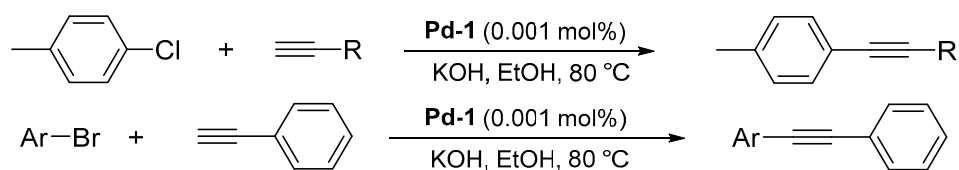
Reaction conditions: [ArCl]/[≡] 5/1, 80 °C, [Pd] (0.01 mol%), [Pd]:[KOH] (1:2); 24 h, argon atmosphere, dodecane (internal standard); (a) 0.25h; Conversions were calculated from GC analyses, products were identified by GC-MS.

All catalysts containing *N*-heterocyclic carbene ligands exhibited catalytic activity. The highest yields with 100% selectivity towards the formation of 1-methyl-4-(phenylethynyl)benzene (3) were observed for the dimeric hydroxo complexes (**Pd-1** - **Pd-4**). The use of chloro dimers (**Pd-7** and **Pd-8**) resulted in a drastic reduction in selectivity and formation of significant amount of alkyne dimerization product. PEPPSI complexes allow medium conversion and give a mixture of coupling and dimerisation products. The exception is the **Pd-12** complex, which allows the dimerization product to be obtained selectively. Simple palladium salts exhibited no activity under the test conditions. Comparison of the progress of the reaction in the presence of [{Pd(μ-OH)Cl(IPr)}₂] (**Pd-1**), [{Pd(μ-Cl)Cl(IPr)}₂] (**Pd-5**) and [PdCl₂(IPr)(3-chloropyridine)] (**Pd-9**) has been shown in Figure S1.

In the presence of [{Pd(μ-OH)Cl(IPr)}₂] (**Pd-1**), almost complete conversion of phenylacetylene occurred after only 15 minutes of reaction. In contrast, no significant difference was observed

between the course of the reaction catalysed by the complexes $[\text{Pd}(\mu\text{-Cl})\text{Cl}(\text{IPr})_2]$ (**Pd-5**) and $[\text{PdCl}_2(\text{IPr})(3\text{-chloropyridine})]$ (**Pd-9**). Reactions proceed much slower and after 2 hours conversions equal to 44% and 26% respectively were observed. A less spectacular, but clear effect on the course of the reaction was observed for the stereoelectronic properties of NHC ligand. As can be observed in Figure S2 the presence of ligands IPr and SIPr present in coordination sphere of **Pd-1** and **Pd-2**, respectively results in higher catalytic activity of these complexes. The **Pd-3** and **Pd-4** complexes showed lower activity in the reaction.

In order to check the scope of the reaction, a series of tests were carried out using aryl chlorides, bromides and acetylenes with different stereoelectronic properties. The results obtained are shown in Scheme 2 and Figures 1 and 2. A detailed description of the synthesis and isolation of 1,2-disubstituted acetylenes and their analytical data are presented in the experimental section.



Scheme 2. Sonogashira cross-coupling of 4-chlorotoluene with terminal acetylenes in the presence of **Pd-1** (a) and Sonogashira cross-coupling of (hetero)aryl bromide with phenylacetylene in the presence of **Pd-1** (b).

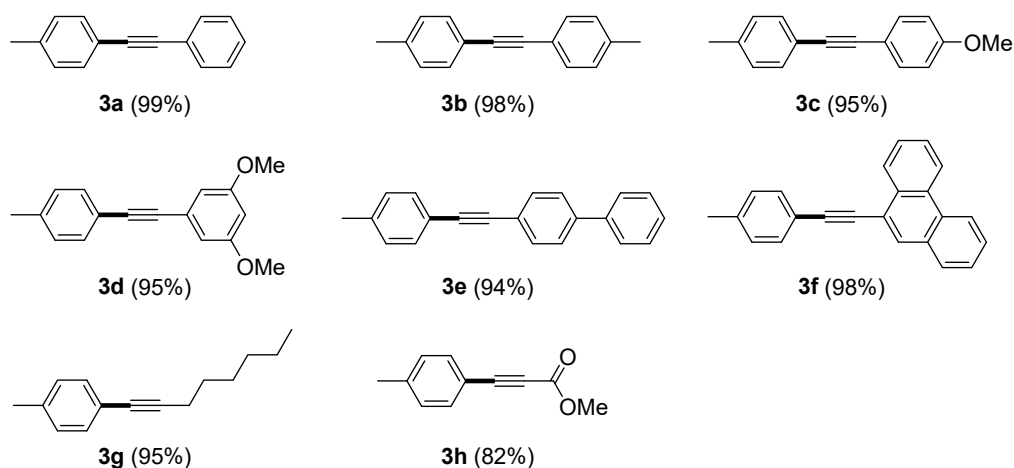


Figure 1. Cross-coupling of 4-chlorotoluene with terminal acetylenes Scope of the reaction. Conditions are detailed in Scheme 2a. Isolation yields are given in parentheses.

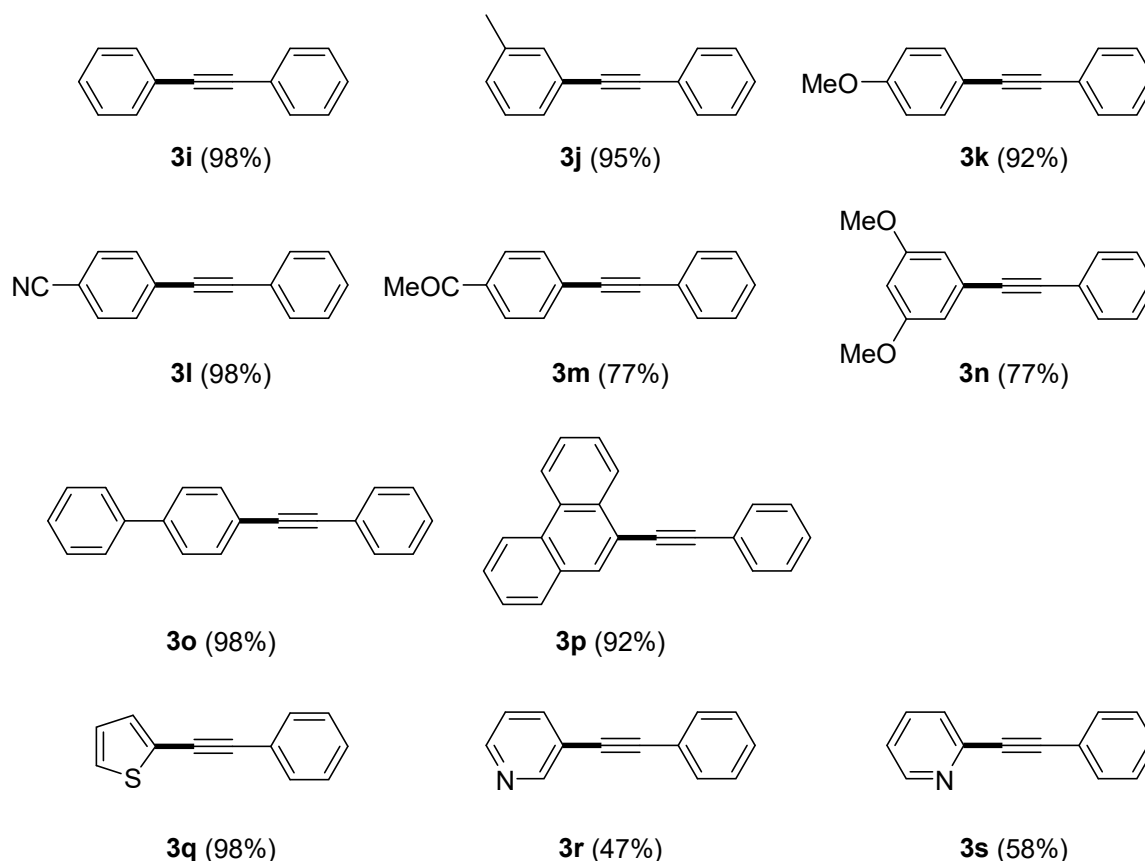


Figure 2. Cross-coupling of (hetero)aryl bromide with phenylacetylene Scope of the reaction. Conditions are detailed in scheme 2b. Isolation yields are given in parentheses.

The coupling products of 4-chlorotoluene with all the arylacetylenes tested, including 9-ethylphenanthrene, 1-heptyne and methyl acetylene carboxylate, were obtained in very good yields. The reaction conditions used also allow highly efficient and selective coupling of a number of substituted aryl chlorides and bromides and 2-bromothiophene with phenylacetylene. Only for *N*-heteroaromatic halides (2-bromo/chloro-pyridine, 3-bromo/chloro-pyridine) lower yields were obtained.

We have carried out many experiments to better understand this reaction system. One of its peculiarities is that it does not require an equimolar amount of base with respect to the limiting reagent. There are few examples in the literature of Pd-catalysed Sonogashira coupling without Cu, carried out in a base-free system [28,29]. The use of acid scavengers (propylene oxide) [30] or an aqueous extract of banana peel ash [31] as a substitute for the base has been reported in the literature. The generally accepted view is that the role of the base in the reaction is (i) to enable/facilitate the formation of the σ -alkyne complex via deprotonation of the π -acetylene complex and (ii) to ensure the irreversibility of the reductive elimination of hydrogen halide responsible for regeneration of the active Pd(0) catalyst. We assumed that conducting the reaction in boiling ethanol would allow efficient removal of hydrogen halide from the reaction vessel via the absorption/desorption cycle. To verify this assumption, we decided to detect the possible HCl gas evolved during the reaction. Indeed, we were able to detect HCl as a Sonogashira coupling product and show that it is formed with (almost) theoretical yield. Although the literature on Sonogashira coupling is, to our knowledge, extremely rich, this is the first observation of hydrogen chloride formation in the Sonogashira reaction. Analysing the system under study in the context of the σ -alkyne complex formation pathway, we decided to investigate the effect of water on the reaction. According to Table 3, there was no change in the yield or selectivity in the presence of a vol. 1/1 mixture of ethanol and water compared to the reaction carried out in 96% ethanol. We decided to see if removing the water from the system as fully as possible would affect the outcome of the reaction. This was done by comparing the course of test

reactions carried out in anhydrous ethanol (99.99%) [32] see experimental for and ethanol (96%) under the conditions described in Table 3 (Figure 3). This result clearly shows that the presence of water in the reaction system affects the reaction rate.

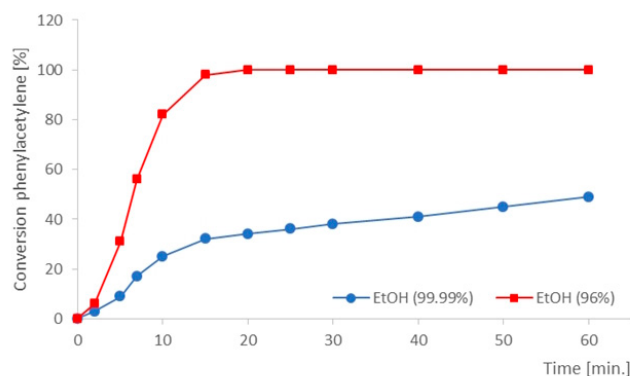
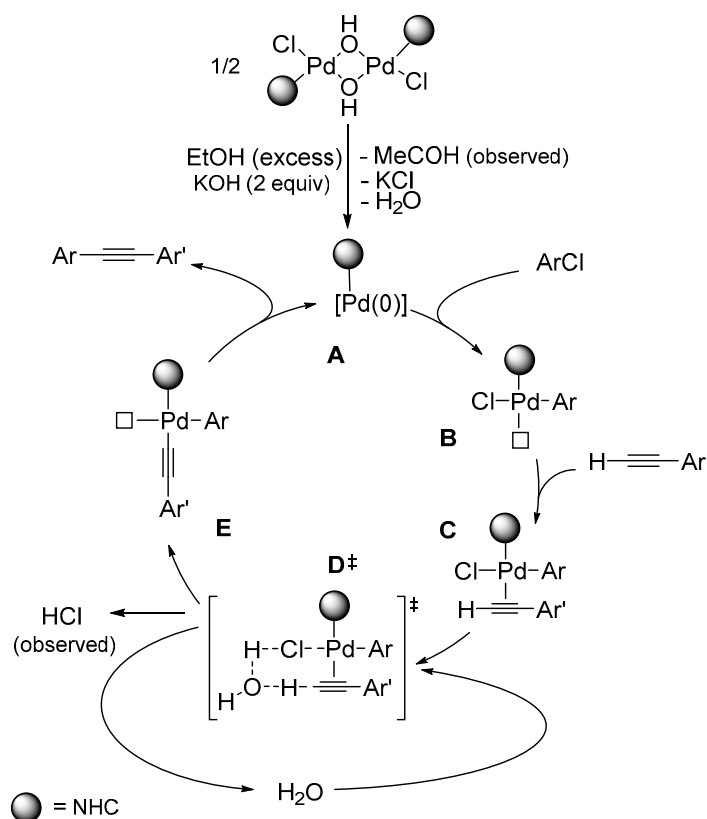


Figure 3. Conversion vs time plot for Sonogashira cross-coupling from phenylacetylene with 4-chlorotoluene in the presence of **Pd-1**. Reaction conditions: [ArCl]:[acetylene] = 5:1, 80 °C, [Pd] (0.01 mol%), [Pd]:[KOH] = 1:2; 24 h, argon, dodecane (internal standard); Conversions were calculated from GC analyses.

A reasonable catalytic cycle that is in agreement with the experimental data is proposed in Scheme 3. This is a modification of the Cu-free Sonogashira coupling deprotonation mechanism calculated and proposed by Nájera, Lledós and Ujaque [33]. According to the proposed scheme, the initiation of the actual catalyst from the hydroxo dimer involves the oxidation of ethanol to acetaldehyde by palladium(II) which leads, in the presence of KOH, to the formation of the catalytically active complex (A). The reduction of palladium precatalysts from Pd(II) to Pd(0) with isopropanol or metanol has been reported and elucidated in the literature e.g. [34]. However, we could not find the analogous study on the formation of the active Pd(0) complex in cross-coupling processes occurring by reduction of Pd(II) with ethanol. To support such an initiation pathway, we demonstrated that the oxidation of ethanol takes place by detecting an acetaldehyde in the reaction system (see experimental and Figures S5 and S6).



Scheme 3. Proposed mechanism of the copper-free Sonogashira cross-coupling of aryl halide with arylacetylene catalysed by $[\{\text{Pd}(\mu\text{-OH})\text{Cl}(\text{NHC})\}_2]$.

Oxidative addition of aryl halide to the active $\text{Pd}(0)$ complex (A) initiates the catalytic cycle and leads to the formation of complex (B). The addition of phenylacetylene to B leads to the formation of π -acetylene complex (C). Complex (C) is then converted to σ -acetylene complex (E) via the proposed transition state $\text{D}^\ddagger$ (or similar) assuming the involvement of a water molecule(s). The formation of hydrogen chloride also takes place at this stage of the reaction. Finally, complex E undergoes reductive elimination to form a cross-coupling product and regenerate the active catalyst (A). Our study of the Suzuki reaction [23] shows that, in an analogous catalytic system, an oxidative addition of aryl chlorides to the palladium(0) complex takes place at room temperature. The same applies to the reductive elimination of the product. Therefore we postulate the process $\text{C} + \text{H}_2\text{O} \rightarrow \text{E} + \text{HCl} + \text{H}_2\text{O}$ is a step that limits the rate of the reaction. As this is a $\text{C}_{\text{sp}}\text{-H}$ bond cleavage process, a primary kinetic isotopic effect would be expected. Indeed, a comparison of the course of the reaction of 4-chlorotoluene with phenylacetylene and its deuterium labelled isotopomer in the acetylene position (Figure S4) indicates the occurrence of $\text{KIE} = 9.7$. Although this value appears to be overestimated, the occurrence of a high positive primary KIE confirms that C-H bond cleavage occurs in the rate determining step.

3. Conclusions

Aryl chlorides and bromides in the presence of NHC palladium hydroxo dimers of the type $[\{\text{Pd}(\mu\text{-OH})\text{Cl}(\text{NHC})\}_2]$ (where NHC = IPr, SIPr, IMes, SIMes) undergo an efficient and selective Sonogashira coupling reaction with terminal acetylenes. Catalyst loading of 1 ppm allows for the coupling of 4-chlorotoluene with phenylacetylene to achieve $\text{TON} = 560000$. The procedure enables high-throughput and selective synthesis of a broad spectrum of unsymmetrically substituted 1,2-diarylacetylenes. Nearly a quantitative amount of HCl was found within cross-coupling products. Water plays the role of a base and is regenerated in the process. Generation of the active $\text{Pd}(0)$ complex proceeds via ethanol oxidation and requires 2 equivalents of KOH (in relation to palladium).

The procedure does not require the use of stoichiometric amounts of the base (in relation to the limiting reactant).

4. Experimental

Representative procedure for catalytic test.

Test reactions were carried out in a 2 mL glass reactor equipped with a reflux condenser, magnetic stirrer and gas introduction cap. The degassed solvent (2 mL), phenylacetylene (1 equiv.), 4-chlorotoluene (1-10 equiv.) and dodecane (10 μ L) were introduced sequentially into the reactor under an argon atmosphere. The prepared mixture was then heated to the reaction running temperature (22-80 °C) and an appropriate amounts of $[\text{Pd}(\mu\text{-OH})\text{Cl}(\text{IPr})_2]$ (1-0.001 mol%) and base ($[\text{Pd}]/[\text{base}] = 1/1\text{-}4/1$) were added simultaneously. Reactions were carried out for 24 hours with continuous stirring while monitoring the reaction by gas chromatography (GC) and gas chromatography with mass detection (GC-MS). The reaction products were identified by mass spectra. All parameter variables are collected in Tables 1-3.

General procedure for the synthesis of Sonogashira cross-coupling products

Ethanol (96%) (3 mL), acetylene (1.83×10^{-3} mol), halide (9.13×10^{-3} mol) were introduced sequentially into a Schlenk vessel under an argon atmosphere. The mixture was then heated to 80 °C and $[\text{Pd}(\mu\text{-OH})\text{Cl}(\text{IPr})_2]$ (0.001 mol%) (1 μ L of solution in toluene 9.1×10^{-6} mol/mL), and KOH (1 μ L of KOH solution in ethanol 1.78×10^{-4} mol/mL) were added simultaneously. Reactions were carried out at 80 °C with continuous stirring for 2 hours. Products were separated by column chromatography using a suitable SiO_2 /eluent system.

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1-methyl-4-(phenylethynyl)benzene (3a) [35–38]. White solid. Yield (99%). Purified by column chromatography (hexane : EtOAc = 10 : 1). ^1H NMR (300 MHz, CDCl_3) δ : 7.57 – 7.51 (m, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.39 – 7.31 (m, 3H), 7.17 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ : 138.36, 131.52, 131.48, 129.09, 128.29, 128.04, 123.47, 120.17, 89.53, 88.70, 21.49. MS (EI) m/z (%) = 192 (M^+).

1,2-di-p-tolylethyne (3b) [35]. White solid. Yield (98%). Purified by column chromatography (hexane : EtOAc = 10 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 7.41 (d, J = 7.6 Hz, 4H), 7.14 (d, J = 7.6 Hz, 4H), 2.35 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ : 138.22, 131.41, 129.19, 120.44, 88.91, 21.51. MS (EI) m/z (%) = 206 (M^+).

1-methoxy-4-(p-tolylethynyl)benzene (3c) [35,37,38]. Pale yellow solid. Yield (95%). Purified by column chromatography (hexane : CH_2Cl_2 = 9 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 7.48–7.44 (m, 2 H), 7.40 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 7.8 Hz, 2 H), 6.88–6.86 (m, 2 H), 3.82 (s, 3 H), 2.36 (s, 3 H). ^{13}C NMR (100 MHz, CDCl_3) δ : 159.5, 138.0, 132.9, 131.3, 129.1, 120.5, 115.4, 113.9, 88.6, 88.2, 55.3, 21.5. MS (EI) m/z : 222 (M^+).

1,3-dimethoxy-5-(p-tolylethynyl)benzene (3d) [37]. Pale yellow solid. Yield (95%). Purified by column chromatography (hexane : CH_2Cl_2 = 9 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 7.42 (d, J = 8.0 Hz, 2 H), 7.15 (d, J = 7.8 Hz, 2 H), 6.68 (d, J = 2.3 Hz, 2 H), 6.45 (t, J = 4.5 Hz, 1 H), 3.81 (s, 6 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3) δ : 160.51, 138.50, 131.55, 129.12, 124.72, 120.00, 109.30, 101.78, 89.13, 88.71, 55.41, 21.5 MS (EI) m/z : 252 (M^+).

4-(p-tolylethynyl)-1,1'-biphenyl (3e). Pale yellow solid. Yield (94%). Purified by column chromatography Purified by column chromatography (hexane : EtOAc = 10 : 1). ^1H NMR (300 MHz,

CDCl_3) δ : 7.65 – 7.53 (m, 8H), 7.50 – 7.43 (m, 3H), 7.41 – 7.34 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ : 140.74, 140.37, 138.39, 132.53, 131.93, 131.48, 129.11, 128.82, 127.56, 126.98, 122.38, 120.20, 90.25, 88.63, 21.50. MS (EI) m/z (%) = 269 (M^+).

9-(p-tolylethynyl)phenanthrene (3f). Pale orange solid. Yield (98%). Purified by column chromatography (hexane : CH_2Cl_2 = 4 : 1). ^1H NMR (300 MHz, CDCl_3) δ : 8.83 – 8.58 (m, 5H), 8.31 – 8.18 (m, 1H), 8.13 (s, 1H), 7.86 – 7.55 (m, 8H), 7.26 (d, J = 1.7 Hz, 2H), 7.12 – 6.79 (m, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ : 138.60, 132.20, 131.59, 131.32, 131.19, 130.23, 130.13, 129.20, 128.93, 128.80, 128.51, 127.32, 127.01, 126.55, 122.74, 122.60, 120.29, 119.86, 94.16, 87.05, 21.53. MS (EI) m/z : 292(M^+).

1-methyl-4-(oct-1-yn-1-yl)benzene (3g) [39]. Colorless oil. Yield (95%). Purified by column chromatography (hexane). ^1H NMR (300 MHz, CDCl_3) δ : 7.29 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 2.39 (t, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.67 – 1.52 (m, 2H), 1.49 – 1.25 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ : 137.35, 131.37, 128.89, 120.99, 89.60, 80.51, 31.12, 28.52, 22.22, 21.35, 19.37, 13.97. MS (EI) m/z : 186 (M^+).

methyl 3-(p-tolyl)propiolate (3h) [39]. Colorless liquid. Yield (82%). Purified by column chromatography (hexane : CH_2Cl_2 = 9 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 7.46 (d, J = 6.8 Hz, 2H), 7.16 (d, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 154.4, 141.2, 132.8, 129.2, 116.3, 86.9, 79.9, 52.5, 21.37. MS (EI) m/z : 174(M^+).

1,2-diphenylethyne (3i) [35–38]. White solid. Yield (98%). Purified by column chromatography (hexane : EtOAc = 10 : 1). ^1H NMR (403 MHz, CDCl_3) δ : 7.57 – 7.52 (m, 4H), 7.39 – 7.31 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ : 131.58, 128.32, 128.23, 123.24, 89.33. MS (EI) m/z (%) = 178 (M^+).

1-methyl-3-(phenylethynyl)benzene (3j) [35,37,38,40]. Colorless oil. Yield (95%). Purified by column chromatography (hexane : EtOAc = 10 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 7.61 – 7.56 (m, 2H), 7.44 – 7.34 (m, 5H), 7.28 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 138.0, 132.2, 131.6, 129.2, 128.7, 128.3, 128.3, 128.2, 123.4, 123.1, 89.6, 89.1, 21.2. MS (EI) m/z (%) = 192 (M^+).

1-methoxy-4-(phenylethynyl)benzene (3k) [35,38,40]. Pale yellow solid. Yield (92%). Purified by column chromatography (hexane : CH_2Cl_2 = 6 : 1). ^1H NMR (300 MHz, CDCl_3) δ : 7.43–7.36 (m, 4H), 7.23–7.20 (m, 3H), 6.76 (d, J = 8.7 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ : 159.81, 133.34, 131.71, 128.62, 128.20, 123.84, 115.67, 114.21, 89.72, 88.31, 55.52. MS (EI) m/z (%) = 208 (M^+).

4-(phenylethynyl)benzonitrile (3l) [35–38]. Yellow solid. Yield (98%). Purified by column chromatography (hexane : EtOAc = 5 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 7.67 – 7.58 (m, 4H), 7.58 – 7.50 (m, 2H), 7.41 – 7.35 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ : 132.04, 132.02, 131.76, 129.10, 128.48, 128.23, 122.20, 118.49, 111.46, 93.76, 87.69. MS (EI) m/z : 203(M^+).

1-(4-(phenylethynyl)phenyl)ethan-1-one (3m) [35,37,40]. Yellow solid. Yield (77%). Purified by column chromatography (hexane : EtOAc = 9 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 7.93 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.40 – 7.34 (m, 3H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ : 197.21, 136.24, 132.54, 131.79, 131.71, 128.82, 128.48, 128.24, 128.20, 122.71, 92.74, 88.62, 26.63. MS (EI) m/z (%) = 220 (M^+).

1,3-dimethoxy-5-(phenylethynyl)benzene (3n) [36]. Pale yellow solid. Yield (77%). Purified by column chromatography (hexane : CH_2Cl_2 = 9 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 7.55 – 7.52 (m, 2H), 7.37 – 7.33 (m, 3H), 6.70 (d, J = 2.3 Hz, 2H), 6.47 (t, J = 2.3 Hz, 1H), 3.81 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ : 160.61, 131.83, 131.70, 128.54, 124.64, 123.21, 109.48, 101.91, 89.51, 89.00, 55.51. MS (EI) m/z : 238(M^+).

4-(phenylethynyl)-1,1'-biphenyl (3o) [35]. Pale yellow solid. Yield (98%). Purified by column chromatography (hexane : EtOAc = 10 : 1). ^1H NMR (400 MHz, C_6D_6) δ : 7.60 – 7.56 (m, 3H), 7.38 – 7.30 (m, 4H), 7.20 – 7.15 (m, 5H), 7.04 – 6.99 (m, 2H). ^{13}C NMR (101 MHz, C_6D_6) δ : 141.39, 140.65, 132.45, 131.97, 129.04, 128.69, 128.47, 127.79, 127.41, 127.34, 123.98, 122.74, 90.83, 90.19. MS (EI) m/z : 254 (M^+).

9-(phenylethynyl)phenanthrene (3p) [36]. Yellow solid. Yield (92%). Purified by column chromatography (hexane : CH_2Cl_2 = 4 : 1). ^1H NMR (300 MHz, C_6D_6) δ : 8.90 – 8.73 (m, 1H), 8.51 – 8.24 (m, 2H), 8.00 (s, 1H), 7.56 – 7.25 (m, 6H), 7.13 – 6.98 (m, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ : 132.44, 132.07,

131.75, 130.81, 130.70, 128.92, 128.74, 128.60, 127.62, 127.41, 127.37, 127.34, 127.12, 124.00, 123.25, 122.99, 120.24, 94.64, 88.58. Sygnał dla jednego atomu węgla nie został zlokalizowany. MS (EI) m/z : 278(M^+).

2-(phenylethynyl)thiophene (3q) [35,37,38,40]. Pale yellow solid. Yield (98%). Purified by column chromatography (hexane : EtOAc = 5 : 1). ^1H NMR (403 MHz, CDCl_3) δ : 7.55 – 7.52 (m, 2H), 7.38 – 7.34 (m, 3H), 7.30 (d, J = 4.1 MHz, 2H), 7.04 – 7.01 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ : 131.85, 131.37, 128.38, 128.33, 127.21, 127.06, 123.28, 122.88, 92.99, 82.57. MS (EI) m/z (%) = 184 (M^+).

3-(phenylethynyl)pyridine (3r) [35,38]. Brown oil. Yield (47%). Purified by column chromatography (hexane : EtOAc = 99:1). ^1H NMR (300 MHz, CDCl_3) δ : 8.77 (s, 1H), 8.54 (d, J = 3.8 Hz, 1H), 7.81–7.79 (m, 1H), 7.56–7.53 (m, 2H), 7.37–7.36 (m, 3H), 7.29–7.26 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ : 152.17, 148.46, 138.38, 131.64, 128.75, 128.39, 122.98, 122.47, 120.45, 92.62, 85.87. MS (EI) m/z (%) = 179 (M^+).

2-(phenylethynyl)pyridine (3s) [37,40]. Brown oil. Yield (58%). Purified by column chromatography (hexane : EtOAc = 4 : 1). ^1H NMR (400 MHz, CDCl_3) δ : 8.61 (s, 1H), 7.65 (td, J = 7.7, 1.7 Hz, 1H), 7.60 (dd, J = 6.7, 3.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.24 – 7.19 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ : 150.02, 143.54, 136.11, 132.02, 128.93, 128.41, 127.17, 122.78, 122.32, 89.25, 88.74. MS (EI) m/z (%) = 179 (M^+).

Detection of HCl. The test reaction was carried out in a 10 mL Schlenk tube equipped with a magnetic stirring bar and a glass stopper. The Schlenk tube was charged under argon with degassed EtOH 96% (2 mL), phenylacetylene (329 μL , 3 mmol), 4-chlorotoluene (1.77 mL, 15 mmol) and dodecane (100 μL). The prepared mixture was then heated to 80 $^\circ\text{C}$ and $[(\text{IPr})\text{Pd}(\mu\text{-OH})\text{Cl}]_2$ (0.3 μM , 0.01 mol%) (10 μL of catalyst was added as a solution prepared from 33 mg of **Pd-1** dissolved in 1 mL of toluene) and the KOH (0.6 μM) (10 μL of catalyst was added as a solution prepared from 3.4 mg of KOH dissolved in 1 mL of EtOH) were added. The glass stopper was then replaced by a silicone stopper with a gas discharge tube connected to a water washer. The reaction was carried out for 1 h. The indicator paper placed at the outlet of the tube turned red. When an aliquot of AgNO_3 was added to the water scrubber, an immediate formation of a white precipitate was observed. The precipitate was filtered and dried under vacuum. 0.281 g AgCl was obtained, representing 78% of the theoretical amount of HCl released in the reaction.

Pd(II) reduction via ethanol oxidation. An NMR tube equipped with a rotaflo valve was charged under argon with 0.65 mL of CD_2Cl_2 and 2.6 μL (0.0436 mmol) of 96% EtOH, after which an initial ^1H NMR spectrum was recorded. Then 0.011 g (0.01 mmol) of $[(\text{Pd}(\mu\text{-OH})\text{Cl}(\text{IPr}))_2]$ and 0.0012 g (0.0214 mmol) of solid KOH has been added under argon to the reaction mixture. The reaction was performed at 25 $^\circ\text{C}$ for 24 h. The progress of the reaction was monitored by ^1H NMR. Acetaldehyde formation was indicated by a quartet at 9.74 ppm (J = 2.9 Hz), visible after 4 h of reaction and continuously increasing in intensity. The quartet is accompanied in the spectrum by a doublet at 2.15 ppm (J = 2.9 Hz) (Figures S5 and S6). After 24 h the mixture was additionally analyzed by GC-MS. GC-MS (EI): m/z (rel. intensity): 44 (100, M^+).

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