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# An efficient protocol for copper- and amine-free Sonogashira reactions catalyzed by mononuclear palladacycle complexes containing bidentate phosphine ligands

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#### Abstract

An efficient protocol for copper- and amine-free Sonogashira coupling of aryl halides with phenylacetylene in mild reaction conditions under air are reported using moisture/air-stable and robust palladacycle phosphine complexes as catalyst precursors. The use of 0.001 mol% catalysts in the presence of  $Cs_2CO_3$  allows the coupling reaction to proceed with moderate to good yields. Also, <sup>31</sup>P NMR studies showed that palladacycle **1** can be reduced to zerovalent palladium in methanol, by forming dppe dioxide.

#### Keywords

Palladacycle phosphine complexes

Copper- and amine-free Sonogashira cross-coupling

Mild reaction condition

Efficient protocol

<sup>31</sup>P NMR spectroscopic investigations

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#### **1. Introduction**

Sonogashira coupling reaction of phenylacetylene with aryl halides catalyzed with Pd complexes in the presence of copper reagent is one of the most powerful tools in organic synthesis and has been widely applied to various areas such as natural product synthesis, biologically active molecules and material science [1,2]. In the Sonogashira coupling reaction, copper salts usually play a significant role in transmetalation. The original Sonogashira reaction generally proceeds in the presence of large amount of homogeneous palladium catalyst containing copper as co-catalyst under inert conditions. It has been well-documented that the Sonogashira coupling often suffers from the Glaser-type oxidative dimerization of the alkyne substrate [3] as a side-reaction in the presence of a Cu(I) co-catalyst. The other limitation of Sonogashira reactions arises from the usage of not so environment friendly amines [4] such as piperidine or triethylamine, as solvent [5], which also are used as bases in the coupling reactions [6]. All copper-free methodologies are usually called copper-free Sonogashira couplings. Frequently, these copper-free processes involve the use of excess amine something that diminishes to some extent the environmental and economical advantages of the methodology. Thus, the development of methods which allow the elimination of ligand, copper and amine in the Sonogashira crosscoupling has been pursued in the past few years [6-10]. In addition, there are few catalytic systems to be carried out the Sonogashira coupling reactions under air in low catalyst loading. Therefore, the development of a convenient method in mild conditions is an important objective in this effort. Herein, we report the copper-free, homogeneous Sonogashira reactions catalyzed under air, in methanol by two palladacycle phosphine complexes that we recently developed [11,12]. In these Palladacycle complexes, the phosphorus ylide as a ligand coordinated to the palladium atom via terminal phosphorus atom and methene group and 1,2-

bis(diphenylphosphino)ethane (dppe) via phosphorus atoms to form two five membered chelate rings (Fig. 1).

#### **Insert Figure 1**

#### 2. Results and discussion

It is well established that palladium complexes containing phosphorus ylides, which combine both good donor strength and  $\pi$ -accepting capacity, always have a high catalytic activity [11,13]. In this communication, we attempted to use our palladium (II) complexes as catalyst precursors in Sonogashira reaction. The rate of coupling is dependent on a variety of parameters such as solvent, base and catalyst loading. Preliminary experiments showed that the protocol which we reported recently was not directly applicable to the Sonogashira cross-coupling reaction [13]. Hence, we investigated the effects of different reaction parameters on the catalytic activity in order to optimize the protocol for Sonogashira coupling. In the first, we chose the cross-coupling of 4-bromobenzaldehyde with phenylacetylene as model reaction, and the effects of the catalyst loading were examined. The results were summarized in Table 1. The ability to use small amounts of catalysts and still achieve high yields is a great concern in cross coupling reactions due to the high cost of metals and ligands. Catalyst loading tests were performed to determine the catalytic efficiency of the catalysts 1 and 2 in the presence of methanol and Cs<sub>2</sub>CO<sub>3</sub>. A control experiment indicated that the coupling reaction did not occur in the absence of 1 and 2. Good yields were obtained from catalyst loads down to a level of 0.1 and 0.01 mol% (without homo-coupling products). A moderate yield was obtained even at catalyst loading as low as 0.0005 mol%. Various catalyst concentrations were also tested and 0.001 mol% gave the best result (Table 1, entry 4, 85% and entry 8, 87%).

#### **Insert Table 1**

During the course of our further optimization of the reaction conditions, we examined several different solvents and bases for the Sonogashira coupling reactions. In order to optimize the reaction conditions, the coupling of 4-bromobenzaldehyde with phenylacetylene carried out using 0.001 mol% of palladacycle complexes 1 and 2 under air in the undried solvent, as shown in Table 2. In the present study, non-polar solvents at 110 °C gave moderate yield (entry 1, 56%, entry 5, 52%), whereas polar solvents such as NMP or DMF are found to be more efficient for generating coupling products to 70% and 69% yield, respectively (Table 2, entries 2, 3). On the other hand, polar aprotic solvent at 80 °C (entry 4) gave comparatively good yield. The highest isolated yield was obtained with methanol as solvent at 60 °C (Table 2, entry 6, 85% Cat.1 and 87% Cat. 2). After selecting Methanol as the optimal solvent, we investigated the influence of various bases on the copper-free Sonogashira reaction. The bases including Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaOAc, NaF, and Et<sub>3</sub>N were investigated, as shown in Table 2. The addition of organic bases such as Et<sub>3</sub>N resulted in poor yield (entry 11). It was clear from the results that inorganic bases (entries 6-10) were much better than organic ones (Table 2, entry 11). Among the bases tested, the Cs<sub>2</sub>CO<sub>3</sub> proved to be the most efficient and gave the good isolated yield (entry 6). The yield of product from reaction with phenylacetylene approached 85% for palladacycle 1 as catalyst whereas the same product has been isolated with the yield of 87% for the catalyst 2. So, based on the above results, we selected Cs<sub>2</sub>CO<sub>3</sub> as the base and methanol as the solvent in the presence of 0.001 mol% of the catalysts at 60 °C as the best conditions for the Sonogashira reactions.

#### **Insert Table 2**

Under the determined reaction conditions, a wide range of aryl halides bearing electrondonating and electron-withdrawing groups coupled with phenylacetylene, affording the coupling products in moderate to good yields. The results are summarized in Table 3.

#### **Insert Table 3**

In palladium catalyzed C-C bond formation reactions, it is commonly believed that better yields are achieved for aryl halides with electron-withdrawing rather than electron-donating substituent [14]. This fact is more appropriate for any halides with electron-withdrawing substituent in which the reaction rate of the coupling is faster than the reoxidation of Pd(0). But with electron-rich halides, the corresponding coupling reactions are rather slower. The electronneutral, electron-rich and electron-poor aryl iodides are reacted with phenylacetylene to generate the corresponding cross-coupling products in good yields (Table 3, entries 1, 4 and 7). For instance, by using 4-iodoacetophenone as activated aryl compound, it was not surprising to obtain good yields with the catalytic loading of 0.001 mol % in 24 h (Table 3, entry 7). Interestingly, the Sonogashira coupling of phenylacetylene with aryl bromide bearing electrondonating and electron-withdrawing groups gave the corresponding biarylacetylenes in good yields (Table 3, entries 5, 10 and 12). In the other reaction, 1-methyl-4-(2phenylethynyl)benzene was isolated in good yield for deactivated aryl bromide substrate with this system (entry 5). The electronically neutral bromobenzene (entry 2) produced good amount of desired product. Trying to apply 2-bromothiophene and 1-bromonaphthalene as efficient substrate were successful (Table 3, entries 14 and 16). As can be seen in Table 3, we observed that in all cross-coupling reactions, catalyst 1 and 2 had approximately same catalytic activities and similar yields. To extend the scope of our work, we next investigated the coupling of various aryl chlorides with phenylacetylene. The aryl chlorides with electron-withdrawing groups reacted smoothly, and the corresponding products were obtained in good yields. The coupling products of 4-chloroacetophenone, 4-chlorobenzaldehyde and 4-chloronitrobenzene with phenylacetylene were obtained in good yields by using 0.001 mol% of both catalysts. However,

for chlorobenzene, catalyst **1** and **2** showed low activity under the same conditions (Table 3, entry 3). For 4-methylchlorobenzene with electron-donating group, lower yield was observed (Table 3, entry 6). Increasing the catalyst loading to 0.1 mol % gave moderate yield (Table 3, entry 6 (72 %, Cat. **1**, 75% cat. **2**)) without addition of CuI as a co-catalyst. The stronger C–Cl bond is in fact responsible of the slower reaction rate of aryl halides, because the oxidative addition step was suggested being the rate determining step in cross-coupling catalytic cycles [6]. In all the reactions of aryl halides, the color of the reaction mixture changed very fast (~30 seconds) from light brown to black. Thus, it can be inferred that the reaction mechanism starts with a pre-dissociation and/or reduction step [6]. Furthermore, coupling of 2-chlorothiphene with phenylacetylene using 0.001 mol% of catalyst **1** and **2** afforded the product in 69-73 % yields.

A number of recent studies have paid attention to the mechanism of the Sonogashira reaction, particularly to the simplest copper- and amine-free process; this reaction is still far of being clearly understood. It seems that different catalytic cycles can operate depending on substrates, bases and catalyst precursors [15]. Some of observations made us think about a mechanism being similar to copper-free Sonogashira cross-coupling reactions [15]. There have been few attempts to elucidate the composition of the active species present in the C-C catalytic cycle. Published studies have been limited to the use of electrochemical techniques [16], anionic detection (ESI-MS, EXAFS) [17] together with detailed kinetic studies [18], NMR detections [19] and theoretical study [20].

Several reports on the existence of highly active soluble palladium(0) colloids (nanoparticles) has established the function of palladacycles as plain Pd(0) reservoirs in high temperature applications like Heck and Sonogashira couplings [21]. The reduction of palladium occurs via insertion into the Pd-C bond followed by a reductive elimination to reduce Pd(II) into

Pd(0), but this is generally followed by formation of Pd(0) nanoparticles. The homogeneous nature of the catalysis was checked by classical mercury test [22]. Addition of a drop of mercury to the reaction mixture did not affect the yield of the reaction (no significant reduction in the reaction yield in presence of mercury under analogous conditions) which suggests that the catalysis is homogeneous in nature, since heterogeneous catalysts would form an amalgam, there by poisoning it (supporting information; Table S1). The fact that metallic Hg does not kill the catalysis is a good point that no metallic Pd is being produced. Electrochemistry is indeed one of the most convenient techniques to detect Pd(0) complexes that are generated in situ from Pd(II) complexes [23]. In the other way, we previously showed that Pd(II) in this palladacycle was reduced to Pd(0) by cyclic voltamnetry [12]. In addition, we investigated the activation of palladacycle phosphine complex **1** to produce active Pd(0) spices with <sup>31</sup>P NMR spectroscopy under the same reaction conditions.

<sup>31</sup>P NMR studies of palladacycle **1** in methanol at various temperatures under air were recorded. <sup>31</sup>P NMR study does not show any dissociation of 1 in methanol even after 4 hours in 25 °C, but after 2 hours in 60 °C we observed a singlet in 34.7 ppm due to dppe dioxide and two doublets in 14.2 and 37.1 ppm (due to  $P_a$  and  $P_b$ , respectively) that can be assigned to unsaturated species **A1** (path I) (Scheme 1 and Fig. 2). We also previously showed that the interaction energy between the phosphorus ylide and  $[Pd(dppe)]^{2+}$  fragment is more than that between dppe and  $[Pd(ylide)]^{2+}$ . The interaction energy of  $Pd^{2+}$  ion and ylide is larger than that with dppe, and both are significantly larger than those between the ylide and  $[Pd(dppe)]^{2+}$ fragment [12]. Other peaks seen in the spectrum (signal of  $P_c$  at 29.3 ppm,  $P_d$  at 39.6 ppm,  $P_e$  at 53.2 ppm and  $P_f$  at 32.4 ppm) can be related to spices **A2** with zero oxidation state (path II)

(Scheme 1 and Fig. 2) [24,25]. Thus, the chemical shifts of observed signals confirm that Pd(II) centre is reduced to Pd(0) in initiated catalytic cycle.

#### **Insert figure 2**

Based on above observations and evidences, we proposed that the formation of active pd(0) catalyst can be done through two possible ways: (*i*) path I may operate through the dechelation of one arm giving a palladacycle bearing a certain structural similarity, that can be concerns the distorted square planer geometry of palladacycle **1** [12], bulkiness of ligands and some of strain in ring like to Herrmann's palladacycles [19]. We expected that by increasing the temperature up to 60 °C, further dechelation of another arm of dppe is done which is accompanied by the reduction of palladium to its zerovalent state and formation of dppe dioxide in aerobic condition. (*ii*) Path II can be done by dechelation of one arm of dppe and also dechelation of P-coordinated arm of phosphorus ylide which is resulted to the formation of active pd(0) catalyst [24,26].

Proposed catalytic cycle for copper-free Sonogashira reaction is presented in Scheme 1. Although the reaction certainly follows the normal oxidative addition-reductive elimination process common to the Pd-catalyzed C–C bond forming reactions, but exact mechanism for the reaction is not known. Two different mechanisms have been proposed for the copper-free Sonogashira reaction: (*i*) deprotonation mechanism [27] and (*ii*) carbopalladation mechanism [28]. The main catalyst precursor formed cis and trans coordinatively unsaturated 14 electron species (Scheme 2, intermediate **A1** (path I) and **A2** (path II)) [11,12,24,26]. A highly reactive Pd(0) species does undergo an oxidative addition with ArX (intermediate **B1** and **B2**). Loss of the dppe creates a vacant coordination site for subsequent ligation of the alkyne, generating the intermediate **C** ( $\pi$ -coordination of the alkyne produces an alkyne–Pd(II) complex containing

phosphorus ylide as a C-coordinated accompanied by the dangling ylide) [29]. Because no copper salt was employed, a transmetalation step could be excluded. Both pathways share to form of intermediate **C**. At this point, the two reaction mechanisms differ in the next steps leading to the final coupled product. In the case of the deprotonation mechanism (Scheme 1) the intermediate **D** can then facilitate deprotonation of the alkyne proton with the leaving group X. Reductive elimination of intermediate **D** with coupling of the aryl halides and alkyne gives the coupling product and regenerates the Pd(0) catalyst **A1** [30]. Alternatively, in the carbopalladation mechanism (Scheme 1) intermediate **E**. This followed by the coordination of the P atom of phosphorus ylide to the Pd center to form intermediate **F**. Subsequent base-mediated reductive elimination also gives the C-C product and **A1** species.

### Insert Scheme 1

For further studies, we investigated the catalytic activity of precursor complex  $[Pd(dppe)(OTf)_2]$  (3) (see ref. [12]) in comparison with palladacycle complexes in Sonogashira coupling reactions. It seems that the precursor complex 3 can also be used to behave as an active resource for producing Pd(0). We used this complex as main catalyst under identical conditions. As can be seen in Table 4, the activity of catalyst 3, with an 'easy' set of substrates (entries 1-3) and a 'difficult' set of substrates (entries 4-6) were tested. The electron-neutral, electron-rich and electron-poor aryl iodides reacted with phenylacetylene in the presence of different loading of catalyst 3 to generate the corresponding cross-coupling products in moderate yields (Table 4, entries 1-3). The Sonogashira coupling of phenylacetylene with aryl chlorides bearing electron-neutral, electron-donating and electron-withdrawing groups gave the corresponding biarylacetylenes in low yields (Table 4, entries 4-6). In the reaction of aryl iodides with

phenylacetylene, we found that increasing the catalyst loading from 0.001 to 0.1 mol% could give good results (Table 4, entries 1-3). Reduction in the amount of the catalyst led to a gradual decrease in the yields under the same reaction conditions (Table 4, entry 1, 70 to 37%). Therefore, the activities of the catalyst **1** and **2** are found to be superior compared with the catalyst **3**.

#### Insert Table 4

The comparison data presented in Table 5 show the efficiency of these new classes of catalysts towards the copper- and amine-free Sonogashira coupling reactions. From an industrial view point, the low catalyst loading, low temperature, aerobic reaction condition, and stable phosphine ligands provide an indisputable advantage than the other catalytic systems.

#### **Insert Table 5**

Although several catalytic systems have been reported to support Sonogashira C-C coupling reaction, a homogeneous catalyst of this type is novel for its P donor of dppe as ligand and P and CH of phosphorus ylide environment. Although acetylene homocoupling reactions are generally useful in synthetic and application point of view [34], formation of homo-coupling products while targeting cross-coupling is undesirable. This is because the terminal acetylene is either very expensive or synthesized through several steps. Therefore, the formation of dimer is considered wasteful. In this protocol, no copper salt was used; the undesired formation of the complexes as homogeneous catalysts, its high solubility in organic solvents, low catalyst loading, and stability toward air make their ideal complexes for Sonogashira coupling. This method proved successful in most cases to give the product in >99% purity. In all of the successful

reactions, the <sup>1</sup>H and <sup>13</sup>C NMR data of the products indicated no homocoupling diyne products. The NMR spectra of the C-C products are given in supporting information.

#### 3. Experimental

#### 3.1. Materials and instruments

The required chemicals were of analytical reagent grade and were purchased from Merck and Alderich. Melting points were measured on a SMPI apparatus and are reported without correction. NMR Spectra were recorded on a 90 MHz Jeol spectrometer (<sup>1</sup>H at 89.60 MHz and <sup>31</sup>P at 36.26 MHz) or 400 MHz Bruker spectrometer (<sup>13</sup>C at 100.62 MHz) in CDCl<sub>3</sub> as solvent at 25 °C. The splitting of proton resonances in the <sup>1</sup>H, <sup>31</sup>P and <sup>13</sup>C NMR spectra are shown as, s = singlet, d = doublet, t = triplet and m = multiplet.

#### 3.2. Characterization of possible Pd–P species in this system

General procedure: To a round-bottom flask equipped with a magnetic stirring bar were added palladacycle **1** (0.04 g) in methanol (2 ml) under air at 60 °C. The mixture was heated for 2 h and recorded <sup>31</sup>P NMR in room temperature. <sup>31</sup>P NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) 14.2 (d, <sup>2</sup>*J*<sub>PP</sub>= 30.3 Hz, **P**<sub>a</sub>), 37.1 (d, <sup>2</sup>*J*<sub>PP</sub>= 31.0 Hz, **P**<sub>b</sub>), 34.7 (s, dppe oxide), 29.3 (d, <sup>2</sup>*J*<sub>PP</sub>= 45.8 Hz, **P**<sub>c</sub>), 32.4 (d, <sup>2</sup>*J*<sub>PP</sub>= 34.7 Hz, **P**<sub>f</sub>), 39.6 (dd, <sup>2</sup>*J*<sub>PP</sub>= 32.5 Hz, <sup>3</sup>*J*<sub>PP</sub>= 17.9 Hz, **P**<sub>d</sub>), 53.2 (dd, <sup>3</sup>*J*<sub>PP</sub>= 25.1 Hz, <sup>3</sup>*J*<sub>PP</sub>= 16.6 Hz, **P**<sub>e</sub>).

#### 3.3. Typical procedure for the copper- and amine-free Sonogashira reactions

General procedure: A mixture of an aryl halide (1 mmol), phenylacetylene (1.3 mmol), Cat. (0.001 mol%),  $Cs_2CO_3$  (2.5 mmol), and methanol (3 ml) was heated to 60 °C for 24 hour. The reaction mixture was then cooled to room temperature and the solvent was removed under

reduced pressure. The combined organic extracts were washed with brine and dried over  $CaCl_2$  and MgSO<sub>4</sub>. The solvent was evaporated and coupling product was obtained. The liquid residues were purified by silica gel column chromatography (n-hexane:EtOAc, 80:20) and The solid residues were purified by re-crystallization from ethanol and water.

3.4. Characterization of cross-coupling products

3.4.1. 1,2-diphenylethyne (Table 3, entries 1, 2, 3)

White solid, m.p.: 54-55 °C, <sup>1</sup>H NMR (ppm):  $\delta$  = 7.26–8.73 (m, 4H, phenyl), 6.75–7.23 (m, 6H, phenyl). <sup>13</sup>C NMR:  $\delta$  = 88.72, 122.54, 128.38, 128.57, 132.49 [35,36].

3.4.2. 1-methyl-4-(2-phenylethynyl)benzene (Table 3, entries 4, 5, 6)

White solid, m.p.: 71-73 °C, <sup>1</sup>H NMR (ppm):  $\delta = 6.55-7.82$  (m, 9H, Phneyl), 2.40 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (ppm):  $\delta = 21.93$ , 88.80, 89.12, 121.16, 122.76, 128.38, 128.86, 129.89, 130.40, 131.34, 138.53 [35,36].

3.4.3. 1-(4-(2-phenylethynyl)phenyl)ethanone (Table 3, entries 7, 8, 9)

Pale yellow solid, m.p.: 97-99  $^{0}$ C, <sup>1</sup>H NMR (ppm):  $\delta$  = 7.84-7.93 (m, 2H, phenyl), 7.31-7.66 (m, 7H, phenyl), 2.57 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (ppm):  $\delta$  = 197.69, 136.56, 132.29, 132.05, 129.51, 128.82, 128.37, 128.22, 123.09, 92.94, 88.91, 27.04 [35,36].

3.4.4. 4-(2-phenylethynyl)benzaldehyde (Table 3, entries 10, 11)

Pale yellow liquid, <sup>1</sup>H NMR (ppm):  $\delta = 6.61$  (d, 1H, J = 5.3 Hz, phenyl), 7.01-8.04 (m, 8H, phenyl), 9.34 (s, 1H, CHO). <sup>13</sup>C NMR (ppm):  $\delta = 190.45$ , 134.34, 131.95, 131.07, 132.76, 128.57, 127.95, 127.81, 126.16, 92.42, 87.48. [35].

3.4.5. 1-nitro-4-(2-phenylethynyl)benzene (Table 3, entries 12, 13)

Pale yellow solid, m.p. 112–114 °C, <sup>1</sup>H NMR (ppm):  $\delta = 8.04-8.13$  (m, 2H, phenyl), 7.07-7.92 (m, 7H, phenyl). <sup>13</sup>C NMR (ppm):  $\delta = 87.60$ , 94.75, 122.11, 123.66, 128.58, 129.32, 130.27, 131.87, 132.29, 146.96 [35].

3.4.6. 2-(2-phenylethynyl)thiophene (Table 3, entries 14, 15)

Colorless oil, <sup>1</sup>H NMR (ppm):  $\delta$  = 7.01-8.05 (m, 8H, phenyl). <sup>13</sup>C NMR (ppm):  $\delta$  = 131.92, 131.43, 128.44, 128.39, 127.28, 127.12, 123.31, 122.92, 93.03, 82.61 [35].

### 3.4.7. 1-(2-phenylethynyl)naphthalene (Table 3, entry 16)

Pale brown liquid, <sup>1</sup>H NMR (ppm):  $\delta = 8.46$  (d, 1H, J = 8.6 Hz, phenyl), 7.26–7.91 (m, 11H, phenyl and naphthyl). <sup>13</sup>C NMR (ppm):  $\delta = 130.57$ , 129.29, 127.71, 127.38, 127.35, 127.25, 125.73, 125.38, 125.09, 124.22, 122.883, 122.26, 93.28, 86.46 [31].

#### 4. Conclusion

We used palladacycle complexes containing bidentate phosphine ligands as an efficient and well-defined catalyst for the Sonogashira coupling of various aryl halides. Also, we have developed a clean and safe protocol for copper- and amine-free Sonogashira reactions catalyzed by palladacycle complexes under aerobic conditions. The catalyst shows not only high catalytic activity, but also offers many practical advantages such as low catalyst loading and air stability.

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### **Figure Captions**

Figure 1. Structure of Palladacycle phosphine complexes (Catalyst 1 and 2).

Figure 2. <sup>31</sup>P NMR spectrum of Pd (0) species.

Scheme 1. Proposed mechanism for copper-free Sonogashira reaction.







#### Table 1

Entry	Catalyst (mol %)	Isolated	
		yield (%)	
1	None	NR <sup>b</sup>	
2	<b>1</b> (0.1)	85	
3	<b>1</b> (0.01)	80	
4	<b>1</b> (0.001)	85	
5	1 (0.0005)	48	
6	<b>2</b> (0.1)	83	
7	2 (0.01)	82	5
8	2 (0.001)	87	
9	2 (0.0005)	45	$\sim$

## Optimization of catalyst concentrations <sup>a</sup>

<sup>a</sup> *Reaction conditions*: 4-bromobenzaldehyde (1 mmol), phenylacetylene (1.3 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.5 mmol), CH<sub>3</sub>OH (3 ml), 24 h, 60 °C .

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#### Table 2

Optimization of base and solvent for Sonogashira cross-coupling reactions of 4bromobenzaldehyde with phenylacetylene.<sup>a</sup>

Entry         Base         Solvent         Temp. (°C)         Catalyst (Yield %) <sup>b</sup> 1 $Cs_2CO_3$ Dioxane         110         1 (56)           2 $Cs_2CO_3$ NMP         110         1 (70)           2 $Cs_2CO_3$ DMF         110         1 (70)           3 $Cs_2CO_3$ DMF         110         1 (69)           4 $Cs_2CO_3$ CH <sub>3</sub> CN         80         1 (73)           5 $Cs_2CO_3$ Toluene         110         1 (52)           6 $Cs_2CO_3$ Methanol         60         1 (85)           7 $K_2CO_3$ Methanol         60         1 (71)           8         Na <sub>2</sub> CO <sub>3</sub> Methanol         60         1 (65)           9         NaOAc         Methanol         60         1 (55)           10         NaF         Methanol         60         1 (55)	°	Br +	Cat. (0.001 mol%)	°	
EntryBaseSolventTemp. (C)Catalyst (Field %)1 $Cs_2CO_3$ Dioxane1101 (56)2 $Cs_2CO_3$ NMP1101 (70)3 $Cs_2CO_3$ DMF1101 (69)4 $Cs_2CO_3$ CH_3CN801 (73)5 $Cs_2CO_3$ Toluene1101 (52)6 $Cs_2CO_3$ Toluene1101 (52)7 $K_2CO_3$ Methanol601 (85)8Na_2CO_3Methanol601 (65)9NaOAcMethanol601 (55)10NaFMethanol601 (55)2 (58)10NaFMethanol601 (55)	Enter	Daga	Solvent	Tomp (°C)	Catalyst (Viald 0/)b
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	<u>Enu y</u>		Diamana	110	
2 $Cs_2CO_3$ NMP       110       1 (70)         3 $Cs_2CO_3$ DMF       110       1 (69)         3 $Cs_2CO_3$ DMF       110       1 (69)         4 $Cs_2CO_3$ CH_3CN       80       1 (73)         5 $Cs_2CO_3$ Toluene       110       1 (52)         6 $Cs_2CO_3$ Methanol       60       1 (85)         7 $K_2CO_3$ Methanol       60       1 (71)         8       Na_2CO_3       Methanol       60       1 (65)         2 (53)       Methanol       60       1 (55)         2 (59)       9       NaOAc       Methanol       60       1 (55)         10       NaF       Methanol       60       1 (55)         2 (58)       10       NaF       Methanol       60       1 (55)	1	$Cs_2CO_3$	Dioxane	110	1(50)
2 $Cs_2CO_3$ NMP110 $1 (70)$ $2 (68)3Cs_2CO_3DMF1101 (69)2 (72)4Cs_2CO_3CH_3CN801 (73)2 (72)5Cs_2CO_3Toluene1101 (52)2 (56)6Cs_2CO_3Methanol601 (85)2 (87)7K_2CO_3Methanol601 (71)2 (63)8Na_2CO_3Methanol601 (65)2 (59)9NaOAcMethanol601 (55)2 (58)10NaFMethanol601 (55)2 (63)$	2	0,00		110	2 (55) 1 (70)
$\begin{array}{cccccccc} & & & & & & & & & & & & & & & $	2	$Cs_2CO_3$	NMP	110	$\mathbf{I}(70)$
3 $Cs_2CO_3$ DMF       110       1 (69)         4 $Cs_2CO_3$ $CH_3CN$ 80       1 (73)         5 $Cs_2CO_3$ Toluene       110       1 (52)         6 $Cs_2CO_3$ Toluene       110       1 (52)         6 $Cs_2CO_3$ Methanol       60       1 (85)         7 $K_2CO_3$ Methanol       60       1 (71)         8 $Na_2CO_3$ Methanol       60       1 (65)         9       NaOAc       Methanol       60       1 (55)         2 (58)       10       NaF       Methanol       60       1 (55)         2 (58)       10       NaF       Methanol       60       1 (55)		~ ~ ~	5105	110	2 (68)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3	$Cs_2CO_3$	DMF	110	1 (69)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$					<b>2</b> (72)
5 $Cs_2CO_3$ Toluene       110       1 (52)         6 $Cs_2CO_3$ Methanol       60       1 (85)         6 $Cs_2CO_3$ Methanol       60       1 (85)         7 $K_2CO_3$ Methanol       60       1 (71)         8 $Na_2CO_3$ Methanol       60       1 (65)         9       NaOAc       Methanol       60       1 (55)         2 (59)       10       NaF       Methanol       60       1 (55)         2 (63)       10       10       10       10       10       10       10       10	4	$Cs_2CO_3$	CH <sub>3</sub> CN	80	1 (73)
5 $Cs_2CO_3$ Toluene       110       1 (52)         6 $Cs_2CO_3$ Methanol       60       1 (85)         7 $K_2CO_3$ Methanol       60       1 (71)         7 $K_2CO_3$ Methanol       60       1 (71)         2 (63)       10       Na2CO_3       Methanol       60       1 (65)         9       NaOAc       Methanol       60       1 (55)       2 (58)         10       NaF       Methanol       60       1 (55)       2 (53)					<b>2</b> (72)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	5	$Cs_2CO_3$	Toluene	110	1 (52)
6 $Cs_2CO_3$ Methanol       60       1 (85)         7 $K_2CO_3$ Methanol       60       1 (71)         7 $K_2CO_3$ Methanol       60       1 (71)         8 $Na_2CO_3$ Methanol       60       1 (65)         9       NaOAc       Methanol       60       1 (55)         10       NaF       Methanol       60       1 (55)         2 (53)       2 (58)       2 (53)       2 (53)					<b>2</b> (56)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	6	$Cs_2CO_3$	Methanol	60	1 (85)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$					<b>2</b> (87)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	7	$K_2CO_3$	Methanol	60	<b>1</b> (71)
8       Na <sub>2</sub> CO <sub>3</sub> Methanol       60       1 (65)         9       NaOAc       Methanol       60       1 (55)         2 (59)       2 (59)       2 (58)       2 (58)         10       NaF       Methanol       60       1 (55)         2 (58)       2 (63)       2 (63)					<b>2</b> (63)
9       NaOAc       Methanol       60       1 (55)         10       NaF       Methanol       60       1 (55)         2 (58)       2 (58)       2 (63)	8	Na <sub>2</sub> CO <sub>3</sub>	Methanol	60	1 (65)
9         NaOAc         Methanol         60         1 (55)         2 (58)           10         NaF         Methanol         60         1 (55)         2 (58)           2 (58)         2 (63)         2 (63)         2 (63)					2 (59)
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	9	NaOAc	Methanol	60	1 (55)
10       NaF       Methanol $60$ $1 (55)$ 2 (63)	-				2(58)
$\frac{1}{2} (63)$	10	NaF	Methanol	60	1 (55)
					$\frac{1}{2}(63)$
11 Et <sub>2</sub> N Methanol $60$ <b>1</b> (47)	11	Et <sub>2</sub> N	Methanol	60	1(47)
1 (47)			1.1.Culuitor	00	$\frac{1}{2}(52)$

<sup>a</sup> Reaction conditions: 4-bromobenzaldehyde (1 mmol), phenylacetylene (1.3 mmol), base (2.5 mmol), solvent (3 ml), 24 h, 60 °C , under air. <sup>b</sup> Isolated yield.

Entry	Ar-X	Product	Catalyst <sup>b</sup> (Yield %) <sup>c</sup>
1		Ph	<b>1</b> (84) <b>2</b> (86)
2	Br	Ph Ph	<b>1</b> (85) <b>2</b> (81)
3	Ci		<b>1</b> (65) <b>2</b> (68)
4	H <sub>a</sub> C	H <sub>3</sub> C-Ph	1 (79) 2 (78)
5	H <sub>4</sub> C Br	H	<b>1</b> (75)
6			<b>2</b> (75) <b>1</b> $72^{d}(54)$
7	H <sub>3</sub> C Cl	H <sub>3</sub> C Ph	<b>2</b> 75 <sup>d</sup> (59)
Ι	H <sub>3</sub> C	H <sub>1</sub> C Ph	1 (88) 2 (87)
8	o Br	оРh	1 (85) 2 (88)
9		H <sub>3</sub> C Ph	<b>1</b> (79)
10	H <sub>a</sub> C O	H <sub>3</sub> C	<b>2</b> (77)
	Br	H Ph	<b>1</b> (83) <b>2</b> (87)
11		Ph	<b>1</b> (80) <b>2</b> (79)
12	O <sub>2</sub> N Br	O <sub>2</sub> N-Ph	1 (86) 2 (85)
13		0 <sub>2</sub> NPh	<b>1</b> (81) <b>2</b> (80)
14			<b>1</b> (74)
15	Br	Ph	2 (78)
	CI	Ph	<b>1</b> (69) <b>2</b> (73)
16			<b>1</b> (74)
	Br	Ph	2 (74)

Table 3. copper- free Sonogashira cross-coupling reaction of aryl halides with phenylacetylene catalyzed by Pd complex 1 and  $2^{a}$ .

<sup>a</sup> *Reaction conditions*: aryl halides (1 mmol), phenylacetylene (1.3 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.5 mmol), CH<sub>3</sub>OH (3 ml), 24 h, 60 °C , under air. <sup>b</sup> Catalyst loading (0.001 mol%) <sup>c</sup> Isolated yield.

<sup>d</sup> Using 0.1 mol% catalysts. Table 4

The copper-free Sonogashira coupling of aryl halides with phenylacetylene catalyzed by precursor

complex **3**.<sup>a</sup>

Entry	Ar-X	Product	Catalyst loading <sup>b</sup> (Yield %) <sup>c</sup>
1			0.1 (70)
		PhPh	0.01 (53)
			0.001 (37)
2			0.1 (62)
	H <sub>3</sub> C	H <sub>3</sub> C Ph	0.01 (50)
			0.001 (32)
3			0.1 (75)
		Ph	0.01 (64)
	H <sub>3</sub> C	H <sub>3</sub> C	0.001 (48)
4			0.1 (51)
	CI	Ph	0.01 (40)
			0.001 (23)
5			0.1 (41)
	H <sub>3</sub> C CI	H <sub>3</sub> C Ph	0.01 (32)
			0.001 (10)
6			0.1 (52)
		Ph	0.01 (47)
	H <sub>3</sub> C′	Hac	0.001 (29)

<sup>a</sup> *Reaction conditions*: aryl halides (1 mmol), phenylacetylene (1.3 mmol), catalyst precursor [Pd(dppe)(OTf)<sub>2</sub>] (ref. [12] ), Cs<sub>2</sub>CO<sub>3</sub> (2.5 mmol), CH<sub>3</sub>OH (3 ml), 24 h, 60 °C , under air.

<sup>b</sup> mol%

° Isolated yield.

#### Table 5

Comparison catalytic activity of some palladacycles complexes that promote the copper- and amine-free Sonogashira coupling between phenylacetylene and aryl halides.

	A 37		(D 1)	D	0.1	C I'''	X7' 11	DC
Entry	Ar-X	Pd catalyst		Base	Solvent	Conditions	Yield	Ref.
			mol%	<u> </u>	<b>E</b>		(%)	603
I	Ph-Br	Pd-NHC complex	1	CsOAc	DMA	100 °C, in air, 15 h	40	[8]
2	4-MePhBr	Pd-diphosphane complex	2	$K_2CO_3$	DMF	130 °C, in argon, 20 h	97	[7]
3	4-NO <sub>2</sub> PhBr	Pd-NHC complex	3	$Cs_2CO_3$	$DMF/H_2O$	90 °C, in air, 1 h	58	[10]
4	4-MePhBr	Pd-phosphinite complex	1	Et <sub>3</sub> N	$H_2O$	40 °C, in argon, 4 h	48	[14]
5	4-MePhBr	Pd-phosphine imine complex	0.1	TBAOAc	NMP	110 °C, in air, 1 h	99	[31]
6	4-MePhBr	PCN pincer Pd complexes	1	Cs <sub>2</sub> CO <sub>3</sub>	MeOH	70 °C, in air, 12 h	39	[32]
7	Ph-Br	Pd-aminophosphine complexes <sup>a</sup>	0.005	K <sub>3</sub> PO <sub>4</sub>	Glycol <sup>b</sup>	140 °C, in N <sub>2</sub> , 3 h	71	[33]
8	Ph-Br	Pd-phosphine ylide complex <sup>c</sup>	0.001	$Cs_2CO_3$	MeOH	60 °C, in air, 24 h	85	This work
9	4-MePhBr	Pd-phosphine ylide complex	0.001	Cs <sub>2</sub> CO <sub>3</sub>	MeOH	60 °C, in air, 24 h	75	This work
<sup>a</sup> Catalys	st added in solution	(dioxane).				, ,		
<sup>b</sup> Ethyle	ne glycol.							
° Using o	catalyst 1.							
			$\sim$					

### **Graphical Abstract**

An efficient protocol copper- and amine-free palladium-catalyzed Sonogashira reaction of various aryl halides with phenylacetylene in mild reaction condition has been developed. Various aryl halides were coupled with phenylacetylene under air in the presence of 0.001 mol% of the moisture-stable and homogeneous catalysts to afford corresponding C-C products in moderate to good yields. <sup>31</sup>P NMR studies showed that palladacycle **1** can be reduced to zerovalent palladium in methanol, by forming dppe dioxide.

Palladacycle Catalysts 0.001 mol% Phenylacetylene MeOH, Cs<sub>2</sub>CO<sub>3</sub>, 60 °C 54-88% Copper- and amine-free  $R = H, NO_2, CH_3, C(O)H, C(O)Me$ Low catalyst loading BrC<sub>4</sub>H<sub>3</sub>S, BrC<sub>10</sub>H<sub>7</sub> Mild conditions X = CI, Br, IUnder air С  $Ph_2$ PPh<sub>2</sub> Pď Ph2 Ph2F Catalyst precursors  $X = Br(1), NO_2(2)$ 

### Highlights

- New classes of homogenous catalysts for the Sonogashira reactions were used for the first time.
- > The reactions carried out under aerobic and copper- and amine-free conditions.
- The ease of preparation of the complexes and low catalyst loading make their ideal complexes for Sonogashira reaction.
- > Proposed catalytic cycle for copper-free Sonogashira reaction is presented.

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