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Sonogashira Reaction Catalyzed by Palladium Isocyanide Complex Modified *in situ*

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Abstract—Palladium isocyanide complex modified *in situ* by addition of benzohydrazide as nucleophile was shown to catalyze Sonogashira reactions of phenylacetylene with iodobenzenes in refluxing ethanol in the presence of potassium carbonate. The reactions were complete in 2 h, and neither preliminary degassing nor protection from atmospheric moisture and oxygen was necessary. The yields of the cross-coupling products, unsymmetrical diarylacetylenes were only slightly lower than those obtained with the preliminarily prepared catalyst. The proposed procedure was used to synthesize a series of diarylacetylenes containing both electron-donating and electron-withdrawing substituents in the benzene rings.

Keywords: Sonogashira reaction, palladium bis(isocyanide) complexes, *in situ* catalyst generation

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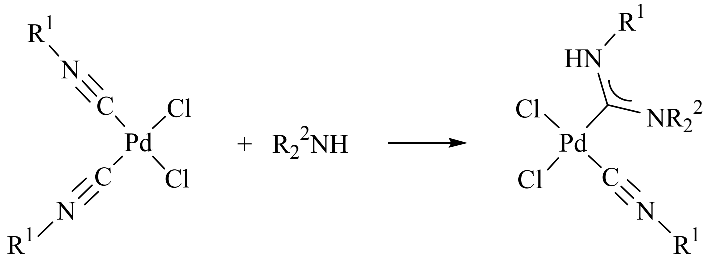
Over the past decades catalysis has been the key factor determining the development of new industrial technologies. The reason is that catalysts allow reactions to be carried out under milder conditions and with higher selectivity. Furthermore, it often becomes possible to synthesize in one step those compounds which were previously available only via multistep procedures. Large-scale efficient manufacture of chemicals is necessary to satisfy demands of fuels, polymers, energy, materials, agrochemicals, and many other items. Homogeneous metal complex catalysis conforms to so-called “green chemistry” principles constituting a paradigm of the development of chemical science in the XXIth century.

Transition metal complexes are extensively used to catalyze organic reactions, in particular due to the possibility of varying the catalytic activity by modifying the ligand structure. Herein, a precatalyst rather than true catalyst is added to the reaction mixture [1–3]. Ligands coordinated to a metal are capable of reacting with other organic and inorganic compounds, thus changing their structure and hence properties of the catalytic center which becomes the true catalyst. This extends the potential of metal-complex catalysis and allows relatively simple transition metal complexes to be used as precatalysts; as a result, practical implementation of catalytic process is facilitated.

The above stated fully applies to palladium(II)–acyclic diaminocarbene complexes (Pd-ADC) that are nowadays among the most efficient cross-coupling catalysts [4, 5]. The most widely used procedure for the synthesis of such complexes is based on the reaction of nitrogen nucleophiles with palladium bis(isocyanide) complexes (Scheme 1) [6–12]. A number of Pd-ADC complexes were previously synthesized in our laboratory, and they turned out to be excellent catalysts of the Suzuki reactions with haloarenes [13, 14], haloalkenes [15], and benzyl halides [16] and copperless Sonogashira reactions [17–21]. In these studies, the catalysts were synthesized preliminarily by reactions of palladium bis(isocyanide) complexes with the corresponding nitrogen nucleophiles in boiling chloroform or methylene chloride.

It has recently been shown that mild conditions of the synthesis of the above complexes make it possible to generate them *in situ* under the Suzuki reaction conditions [22]. In this way, Suzuki cross-coupling was carried out in the presence of dichlorobis(cyclohexyl isocyanide)palladium(II) (**1**) (Scheme 2) and three different nitrogen nucleophiles (4-nitrophenylhydrazine, benzohydrazide, and morpholine) as modifying agents. The best results were obtained with morpholine as modifier taken in a large excess with respect to the palladium complex.

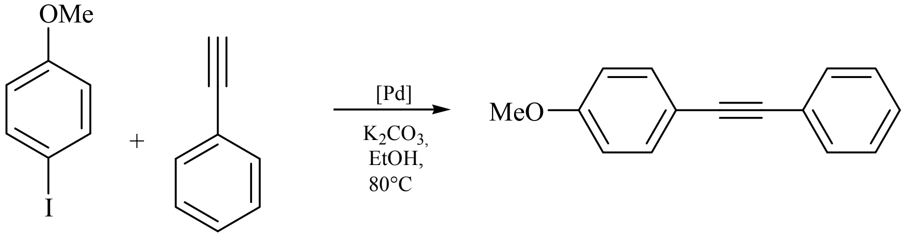
Scheme 1.



Pd-ADC

R^1 = Alk, Ar; R^2 = H, Alk, Ar, NR^1_2.

Scheme 2.



2a **3** **4a**

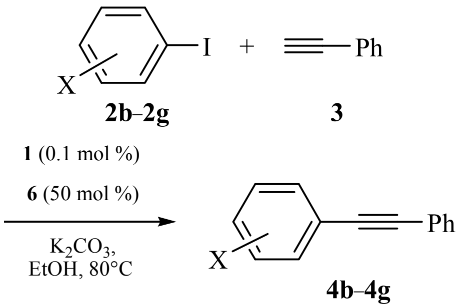
[Pd]: $(CyNC)_2PdCl_2$ (**1**) + $(CH_2CH_2OCH_2CH_2)NH$ (**5**); $(CyNC)_2PdCl_2$ (**1**) + $PhCONHNH_2$ (**6**).

In this work, the possibility of *in situ* modification of a palladium bis(isocyanide) complex was studied in the Sonogashira cross-coupling of 4-methoxy-1-iodobenzene (**2a**) with phenylacetylene (**3**) (Scheme 2) as a model reaction. When the reaction was carried out under the conditions reported previously for the copperless Sonogashira reaction catalyzed by Pd-ADC [19–21] but using a mixture of complex **1** with morpholine (**5**) as the most efficient modifier in the Suzuki reaction [22], the yield of cross-coupling product **4a** was low. Satisfactory results were obtained with the use of another modifier, benzohydrazide (**6**). In this case, the yield of **4a** was comparable with that reported for the catalysis with preliminarily synthesized Pd-ADC complex [21]. Table 1 compares the yields of **4a** obtained using different catalytic systems.

The difference of the relative catalytic activities of the examined systems in the Snogashira reaction from their catalytic activities in the Suzuki reaction is likely to be related to the presence in the reaction mixture of compounds containing a triple bond [22]. The low yield of **4a** in the reaction catalyzed by the system complex **1**–morpholine may be rationalized assuming that morpholine partially reacts (probably, in a reversible manner) with the triple bond of initial phenylacetylene (**3**) and/or cross-coupling product **4a**.

To estimate the scope of the proposed procedure, phenylacetylene (**3**) was reacted with substituted iodobenzenes **2b**–**2g** under the given conditions (Scheme 3). In all cases, the corresponding cross-coupling products **4b**–**4g** were obtained (Table 2). Regardless of the substituent nature in the initial iodobenzene, the cross-coupling products were isolated in satisfactory yields, which provides one more evidence for the efficiency of the proposed catalytic system in the copperless Sonogashira reaction. The presence of a substituent in the *ortho* position with respect to iodine did not interfere with the reaction provided that this substituent is incapable of

Scheme 3.



2b–**2g** **3** **4b**–**4g**

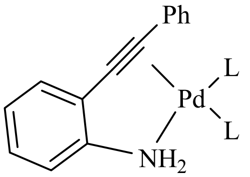
X = 4-Me (**b**); X = 4-CHO (**c**); X = 2,6-Me_2 (**d**); X = 4-NH_2 (**e**); X = 2-NH_2 (**f**); X = 2,4,6-Cl_3 (**g**).

Table 1. Sonogashira reaction of 1-iodo-4-methoxybenzene (**2a**) with phenylacetylene (**3**) in different catalytic systems[a]

Catalyst (0.001 mol per mole of **2a**)	Added nitrogen nucleophile (mol per mole of **2a**)	Yield of **4a**,[b] %
Pd-ADC [21]	–	$93^{\text{в}}$
1 + 5	0.5	15
1 + 6	0.5	86 (80[c])

[a] Reaction conditions: **2a**, 0.3 mmol; **3**, 0.5 mmol; K_2CO_3, 0.7 mmol; EtOH, 2 mL; 80°C, 2 h. [b] GC/MS data. [c] Isolated yield.

specifically interacting with the metal center. The low yield of **4f** in the reaction with 2-iodoaniline (**2f**) is likely to be determined by the formation of strong acetylene amine chelate complex **7**, which hampers further reaction.



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In summary, the possibility of carrying out copperless Sonogashira cross coupling catalyzed by palladium(II) bis(isocyanide) complex modified by addition of a nitrogen nucleophile has been demonstrated for the first time. The proposed procedure is advantageous due to mild conditions (reflux in ethanol in the presence of potassium carbonate without preliminary degassing and protection from atmospheric moisture and oxygen) and the use of a simple catalytic system.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance II+ spectrometer (400.13 MHz) at room temperature using $CDCl_3$ as solvent. Gas chromatographic–mass spectrometric analysis was performed with a Shimadzu GCMS QP-2010 SE instrument [electron impact, 70 eV; a.m.u. range 35–500; detector temperature 200°C; Rtx-5MS column, 30 m × 0.32 mm, film thickness 0.25 μm; carrier gas argon, flow rate 0.8 mL/min; oven temperature programming from 50 (2 min) to 250°C at a rate of 25 deg/min and 20 min at 250°C].

Sonogashira reaction *(general procedure).* A solution of comple **1** in ethanol with a required concentration was added with stirring to a mixture of iodoarene **2a**–**2g** (0.3 mmol), phenylacetylene (**3**, 0.5 mmol), potassium carbonate (0.7 mmol), and ethanol (2 mL). The mixture was heated for 2 h on an oil bath at a bath temperature of 80°C. After cooling to room temperature, the mixture was diluted with 10 mL of water and extracted with hexane–methylene chloride (5 : 1, 2 × 5 mL), and the combined extracts were dried over anhydrous sodium sulfate and analyzed by GC/MS. The solvent was evaporated, and the product was isolated by silica gel column chromatography using *n*-hexane as eluent.

The properties of the isolated compounds were in agreement with the data given in [23–27].

1-Methoxy-4-(phenylethynyl)benzene (4a). Yield 166 mg (80%), colorless solid, mp 57°C. ^{1}H NMR spectrum, δ, ppm: 3.86 s (3H, OCH_3), 6.91 d (2H, J = 8.8 Hz), 7.33–7.39 m (3H), 7.51 d (2H, J = 8.8 Hz), 7.51–7.55 m (2H).

1-Methyl-4-(phenylethynyl)benzene (4b). Yield 157 mg (82%), colorless solid, mp 71°C. ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 7.18 d (2H, J = 7.8 Hz), 7.34–7.38 m (3H), 7.45 d (2H, J = 7.8 Hz), 7.53–7.56 m (2H).

4-(Phenylethynyl)benzaldehyde (4c). Yield 161 mg (78%), colorless solid, mp 95°C. ^{1}H NMR spectrum, δ, ppm: 7.39–7.41 m (3H), 7.57–7.60 m (2H), 7.70 d (2H, J = 8.2 Hz), 7.89 d (2H, J = 8.4 Hz), 10.04 s (1H, CHO).

Table 2. Sonogashira reactions of iodobenzenes **2b**–**2g**[a]

Substrate	X	Yield of **4**,[b] %
2b	4-Me	82
2c	4-CHO	78
2d	2,6-Me_2	72
2e	4-NH_2	62
2f	2-NH_2	33
2g	2,4,6-Cl_3	73

[a] Reaction conditions: **2a**, 0.3 mmol; **3**, 0.5 mmol; K_2CO_3, 0.7 mmol; EtOH, 2 mL; 80°C, 2 h. [b] Isolated yield.

1,3-Dimethyl-2-(phenylethynyl)benzene (4d). Yield 148 mg (72%), light yellow oily material. ^{1}H NMR spectrum, δ, ppm: 2.58 s (6H, CH_3), 7.11–7.18 m (3H), 7.39–7.41 m (3H), 7.59–7.61 m (2H).

4-(Phenylethynyl)aniline (4e). Yield 120 mg (62%). ^{1}H NMR spectrum, δ, ppm: 3.89 br.s (2H, NH_2), 6.66 d (2H, J = 8.5 Hz), 7.33–7.37 m (5H), 7.53 d (2H, J = 9.5 Hz).

2-(Phenylethynyl)aniline (4f). Yield 58 mg (33%), colorless solid, mp 87°C. ^{1}H NMR spectrum, δ, ppm: 4.30 br.s (2H, NH_2), 6.76 d (1H, J = 8.0 Hz), 7.15–7.19 m (1H), 7.34–7.40 m (5H), 7.55–7.57 m (2H).

1,3,5-Trichloro-2-(phenylethynyl)benzene (4g). Yield 211 mg (75%), colorless solid, mp 120°C. ^{1}H NMR spectrum, δ, ppm: 7.40–7.42 m (5H), 7.62–7.64 m (2H).

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