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Dedicated to the 100th Anniversary of Corresponding Member of the Russian Academy of Sciences A.A. Petrov

Catalytic Activity of Palladium(II) Diaminocarbene Complexes in the Sonogashira and Suzuki Reactions

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Abstract—Palladium(II) complexes with chelating and non-chelating diaminocarbene ligands were assessed as catalysts in the cross-coupling reactions of haloarenes with oct-1-yne (Sonogashira reaction) and phenylboronic acid (Suzuki reaction). Both complexes exhibited a higher catalytic activity than traditional phosphine ligand-based systems in the Sonogashira reaction, and they ensured cross-coupling not only with iodoarenes but also with bromoarenes activated by electron-withdrawing substituents. The catalytic activities of the examined complexes in the Suzuki reaction were appreciably different: the palladium(II) complex with the chelating ligand turned out to be considerably less active than the complex with the non-chelating ligand.

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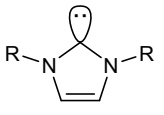
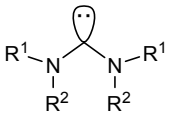
Palladium complexes with cyclic (**A**) [1] and acyclic (**B**) [2] diaminocarbene ligands are used as homogeneous catalysts in cross-coupling reactions.

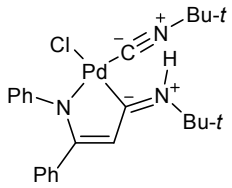


A

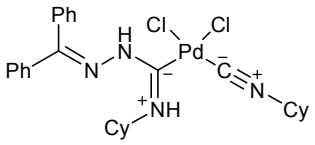


B

Aminocarbene complexes are more stable to oxidation than traditionally used phosphine complexes. In addition, carbene palladium complexes exhibit very high catalytic activity in oxidative addition reactions of haloarenes due to donor properties of the ligands. Therefore, such complexes are highly efficient as catalysts in various cross-coupling reactions with haloarenes, such as Suzuki, Heck, Sonogashira, and other reactions [3–7]. Most procedures for the synthesis of palladium carbene complexes require preliminary preparation of carbene ligand and its subsequent introduction into the metal coordination sphere and are multistep and laborious, which restricts the range of variation of structural parameters of the catalysts. In this connection, the synthesis of diaminocarbene complexes via simple addition of nitrogen-containing nucleophiles to isocyanide palladium complexes attracts increased interest [8–12]. This approach makes it possible to obtain structurally diverse carbene complexes, including chelates (e.g., complex **I**). Such chelates could exhibit unusual catalytic activity in cross-coupling reactions.



I



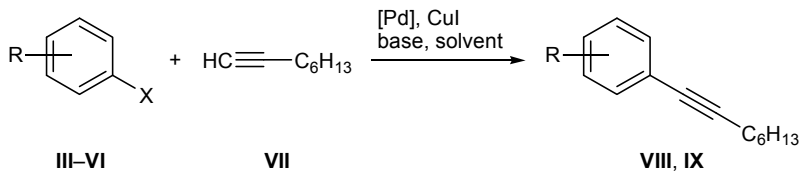
II

Tskhovrebov et al. [13] recently demonstrated that palladium(II) diaminocarbene chelates in the presence of triphenylphosphine are capable of catalyzing the Sonogashira reaction and compared their catalytic activity with the activity of commercially available $PdCl_2(PPh_3)_2$ in the reaction of 1-iodo-2-nitrobenzene (**III**) with oct-1-yne (**VII**) (Scheme 1).

The present study was aimed at comparing the catalytic activities of palladium(II) complexes **I** and **II** with chelating and non-chelating diaminocarbene ligands in the synthesis of arylacetylenes according to Sonogashira and in the Suzuki reaction leading to biphenyl derivatives.

The Sonogashira cross-coupling was studied using 1-iodo-2-nitrobenzene (**III**), 1-bromo-2-nitrobenzene

Scheme 1.



III–**VI** **VII** **VIII**, **IX**

III, **IV**, **VI**, **VIII**, R = 2-NO_2; **V**, **IX**, R = 4-CN; **III**, X = I; **IV**, **V**, X = Br; **VI**, X = Cl.

(**IV**), 4-bromobenzonitrile (**V**), and 1-chloro-2-nitrobenzene (**VI**) as haloarene component and oct-1-yne (**VII**) as terminal alkyne (Scheme 1). *ortho*-Substituted haloarenes were selected mainly as substrates taking into account strong interest in *ortho*-substituted arylacetylenes which are widely used as intermediate products in the synthesis of pharmacologically important substituted heterocycles such as indoles, quinolines, isoquinolines, indolo[1,2-*c*]quinolines, furopyridines, and dihydropyrazoles [14].

As shown in [13], the conversion in the Sonogashira reactions carried out in ethanol depends on the presence of PPh_3 in the reaction mixture. It was presumed that PPh_3 is necessary to enhance the stability of the catalytic system. On the other hand, the catalyst may be stabilized via the use of a complexing solvent. However, in the reaction of haloarene **III** with oct-1-yne (**VII**) in acetonitrile with no PPh_3 the substrate conversion was as low as 20% in 24 h. Addition of 5 mol % of PPh_3 increased the conversion to 100%. Insofar as aminocarbene complexes are considerably more active than classical phosphine catalysts [13], we presumed that the role of PPh_3 is to form a complex with copper and ensure solubility of copper acetylide.

Using compounds **IV** and **V** as examples, we showed that bromoarenes readily react with acetylene **VII** under catalysis by complex **I** in the presence of 5 mol % of PPh_3. After 24 h at room temperature, the conversion of **IV** was 60%, the amount of the catalyst being 0.07 mol %; raising the temperature and increasing the reaction time resulted in more than 80% conversion. The conversion of **V** in 24 h was 64%. Unfortunately, we failed to attain an appreciable conversion of 1-chloro-4-nitrobenzene (**VI**) in the reaction with **VII** in the presence of 0.07 mol % of complex **I** even under prolonged (48 h) heating at 80°C.

Thus the use of 0.07 mol % of palladium complex **I** with chelating aminocarbene ligand in the presence of 5 mol % of PPh_3 ensures considerable conversion in the Sonogashira cross-coupling with both iodo- and bromoarenes.

Aminocarbene complex **II** showed a high efficiency as catalyst in the Suzuki reaction [12]. The catalytic activity of complex **II** in the Sonogashira reaction in

Table 1. Catalytic activity of complexes **I** and **II** in the Sonogashira reaction

ArX	Catalyst (mol %)	Solvent, base	Temperature, °C	Reaction time, h	Yield,[a] %	TON[b]	TOF[c]
III[d]	**I** (0.05) + PPh_3[e]	EtOH, K_2CO_3	60	18	100	2000	111
III	**I** (0.07)	MeCN, Et_3N	60	24	20	290	12
III	**I** (0.07) + PPh_3[e]	MeCN, Et_3N	60	24	100	1400	58
IV	**I** (0.07) + PPh_3[e]	THF, Et_3N	20	24	60	850	35
IV	**I** (0.07) + PPh_3[e]	THF, Et_3N	60	38	81	1150	30
V	**I** (0.07) + PPh_3[e]	Dioxane, Et_3N	80	24	64	900	18
VI	**I** (0.07) + PPh_3[e]	Dioxane, Et_3N	80	48	–	–	–
III	**II** (0.07) + PPh_3[e]	EtOH, K_2CO_3	60	13	100	1400	108
III	**II** (0.018) + PPh_3[e]	EtOH, K_2CO_3	60	72	70	3890	54

[a] According to the ^1H NMR data.
[b] Turnover number.
[c] Turnover frequency, h^{-1}.
[d] Data of [13].
[e] 5 mol % with respect to ArX.

Table 2. Catalytic activity of complexes **I** and **II** in the Suzuki reaction

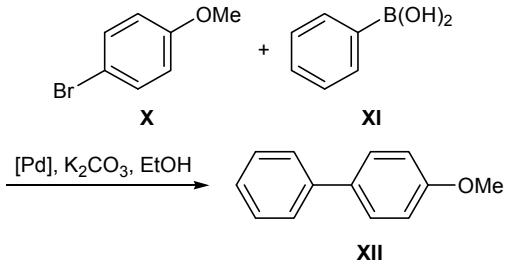
Catalyst (mol %)	Reaction time, min	Yield,[a] %	TON	TOF, h^{-1}
I (1×10^{-3})	10	37	370	2220
I (1×10^{-3})	30	52	520	1040
I (1×10^{-3})	60	60	600	600
I (3×10^{-3})	60	76	250	250
I (1×10^{-2})	60	97	97	97
II[b] (1×10^{-5})	120	97	9.7×10^{4}	4.8×10^{4}

[a] According to the ^{1}H NMR data.
[b] Data of [12].

the presence of 5 mol % of PPh_3 was comparable with the activity of chelate **I**. The conversion of iodoarene **III** in ethanol was complete in 13 h at 60°C.

Having estimated the catalytic activities of complexes **I** and **II** in the Sonogashira reaction, it was interesting to compare their activities in the Suzuki cross-coupling reaction. As model reaction for studying the catalytic activity of palladium aminocarbene chelate **I**, we selected the reaction of 4-bromoanisole (**X**) with phenylboronic acid (**XI**) (Scheme 2). This choice was determined by the fact that the catalytic activity of complex **II** (which is the most efficient among currently known catalyst for the Suzuki reaction) was studied just in the above reaction [12]. The data in Table 2 show that palladium(II) chelate **I** is considerably less active than non-chelate complex **II**.

Scheme 2.



The observed effect of chelation on the catalytic activity in cross-coupling reactions is likely to be related to specific features of the reaction mechanisms. The Suzuki reaction mechanism [15] requires the presence of a palladium complex with *trans* arrangement of the ligands Ar and X at the transmetalation step of the catalytic cycle [16]. Stronger binding of the chelating ligand in complex **I** hampers formation of such complexes during the reaction. This is consistent with the results of calculations [17], according to which phosphine complexes where the neutral ligand occupies only one rather two sites in the coordination sphere exhibit higher catalytic activity. From this viewpoint, the chelating ligand in complex **I** should also hinder Suzuki reaction.

The Sonogashira reaction mechanism does not impose so severe constraints on mutual arrangement of the ligands in the arylpalladium complex formed by oxidative addition. Although in this case the transmetalation step remains more favorable for the complexes with *trans* orientation of the ligands Ar and X, this effect is compensated by the complexity of *cis/trans* isomerization of the alkynylarylpalladium intermediate generated in the transmetalation step [18]. Presumably, this factor eliminates advantages of the *trans* orientation of the anionic ligands Ar and X, thus reducing the catalytic activity of the non-chelate complex to a level comparable with the activity of the palladium chelate.

On the whole, the Sonogashira reaction catalyzed by palladium(II) complex **I** with chelating diaminocarbene ligand possessing an amidine fragment requires a considerably smaller amount of the catalyst as compared to the classical $PdCl_2(PPh_3)_2$-based catalytic system to ensure equally high yield. The reaction in the presence of complex **I** readily occurs not only with iodoarenes but also with bromoarenes having electron-withdrawing substituents. Complex **II** with non-chelating diaminocarbene ligand shows a comparable catalytic activity. On the other hand, the use of chelate **I** to catalyze Suzuki reaction is unreasonable, since its activity is appreciably lower than that of complex **II** with non-chelating ligand. A probable reason is specific features of the *cis*/*trans* isomerization of intermediate arylpalladium complexes.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 instrument at 300.13 and 75.5 MHz, respectively, using $CDCl_3$ as solvent. Commercial re-

agents of analytical grade were used without additional purification. The solvents were purified according to standard procedures.

Typical procedure for the Sonogashira reaction of haloarenes III–VI with oct-1-yne (VII). Haloarene **III–VI,** 2.5 mol, and oct-1-yne (**VII**), 5.0 mmol (55 mg), were dissolved in 10 ml of appropriate solvent, 14.5 mol of the corresponding base was added, palladium catalyst, 0.24 mol (45 mg) of CuI, and (if necessary) 0.11 mol (30 mg) of PPh_3 were added, and the mixture was stirred under the conditions indicated in Table 1. The mixture was then cooled to room temperature, 2 ml of diethyl ether and 4 ml of water were added, the organic layer was separated, washed with water (2×5 ml), dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was analyzed by ^{1}H NMR.

1-Nitro-2-(oct-1-yn-1-yl)benzene (VIII) [19]**.** ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, CH_3, J = 6 Hz), 1.25–1.40 m [4H, $(CH_2)_2$], 1.41–1.58 m (2H, CH_2), 1.63 m (2H, ≡$CCH_2C\mathbf{H}_2$), 2.49 t (2H, ≡CCH_2, J = 7 Hz), 7.39 t (1H, H_{arom}, J = 7 Hz), 7.49–7.65 m (2H, H_{arom}), 7.96 d (1H, H_{arom}, J = 7 Hz).

4-(Oct-1-yn-1-yl)benzonitrile (IX) [20]**.** ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, CH_3, J = 6 Hz), 1.26–1.48 m [4H, $(CH_2)_2$], 1.54 m (2H, ≡$CCH_2C\mathbf{H}_2$), 2.42 t (2H, ≡CCH_2, J = 7 Hz), 7.44 d (2H, H_{arom}, J = 7 Hz), 7.54 d (2H, H_{arom}, J = 7 Hz).

Typical procedure for the Suzuki reaction of 4-bromoanisole (X) with phenylboronic acid (XI). A mixture of 0.20 mol (39 mg) of 4-bromoanisole (**X**), 0.22 mol (27 mg) of phenylboronic acid (**XI**), 0.20 mol (6.2 mg) of acenaphthene (internal standard for NMR), 0.72 mol (100 mg) of K_2CO_3, and 1 ml of ethanol was heated to 80°C, a solution of a required amount of complex **I** or **II** in 0.1 ml of ethanol was added, and the mixture was stirred at 80°C for a time indicated in Table 1. The mixture was then cooled to room temperature, 2 ml of carbon tetrachloride and 4 ml of water were added, and the organic layer was separated, washed with water (2×5 ml), dried over Na_2SO_4, and analyzed by ^{1}H NMR.

4-Methoxybiphenyl (XII) [21]**.** ^{1}H NMR spectrum, δ, ppm: 3.88 s (3H, OCH_3), 7.02 d (2H, H_{arom}, J = 8.6 Hz), 7.31–7.36 m (1H, H_{arom}), 7.42–7.47 m (2H, H_{arom}), 7.60–7.65 m (4H, H_{arom}).

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