# Catalyst of Suzuki Cross-Coupling Based on Polymeric Matrix of Amino-Functionalized Hypercrosslinked Polystyrene

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*Abstract:* - This paper is devoted to the synthesis of Pd-containing catalyst based on amino-functionalized polymeric matrix of hypercrosslinked polystyrene and to the investigation of its catalytic properties in the reaction of Suzuki-Miyaura cross-coupling of 4-bromoanisole and phenylboronic acid. It was shown that developed procedure of the catalyst synthesis allows achieving high conversion of 4-bromoanisole (up to 98% for less than 1 h of reaction duration) at relatively low Pd loading (0.72%(mol.)) and mild reaction conditions ($60^oC$ and environmentally friendly solvents) at the absence of phase transfer agent. Besides, proposed method of the catalyst synthesis allows obtaining small Pd nanoparticles (about 3 nm in diameter) after preliminary reduction, which also reveal high activity in Suzuki-Miyaura cross-coupling (conversion of 4-bromoanisole reached up to 84.5% for 3 h of reaction duration).

*Key-Words:* - cross-coupling, Suzuki-Miyaura reaction, ligandless catalysts, palladium, hypercrosslinked polystyrene, nanoparticles, phenylboronic acid, 4-bromoanisole

## 1 Introduction

Cross-coupling reactions are widely used in fine organic synthesis for obtaining of active pharmaceutical ingredients, crop protection substances and polymers. Among all the cross-coupling reactions, the Suzuki-Miyaura reaction is of great importance. Traditionally, Suzuki cross-coupling is catalyzed by homogeneous palladium complexes based on phosphorus- or nitrogen-containing ligands. However, the majority of developed ligands are expensive that significantly limits their application in industry [1]. Besides, common disadvantage of homogeneous palladium catalysts is difficulty of their separation from reaction products for further reuse [2].

The alternative direction is development of ligandless catalytic systems. The most well-known ligandless catalyst is Pd/C [2-6]. In comparison with homogeneous palladium complexes, Pd/C is simple in preparation and can be separated from reaction mixture via filtration or centrifugation. Palladium salts, such as palladium acetate [7] and palladium chloride [1], which are precipitated during the reaction as metal Pd and thus can be filtered, can be also attributed to the ligandless catalysts of Suzuki reaction. The main issue that is due to the use of ligandless catalysts is irreversible leaching of palladium. It was noted that activity of commercial Pd/C decreased more than by 50% at reuse, as a result of Pd leaching and aggregation of catalytically active particles [8].

At present the most perspective catalysts are systems on the basis of palladium nanoparticles (NPs) or complexes stabilized by polymers [9-17]. However, in spite of success achieved in some cases, common disadvantage of heterogeneous, heterogenized and quasi-homogeneous catalysts of Suzuki reaction is loss of catalytic activity as a result of palladium leaching [18]. The molecular forms of palladium formed *in situ* were considered as the most active ones [8], and though the complete prevention of Pd leaching is mechanistically impossible [19], it should be minimized. Besides, the disadvantage of many catalytic systems including polymer-stabilized Pd NPs is the necessity of addition of phase transfer agent in order to achieve high activity in Suzuki reaction proceeding in aqueous medium [17, 20].

This paper is devoted to the synthesis of Pd-containing catalyst based on the polymeric matrix of hypercrosslinked polystyrene (HPS) bearing amino-groups and study of its catalytic properties in Suzuki cross-coupling of 4-bromoanisole and phenylboronic acid (Fig. 1).

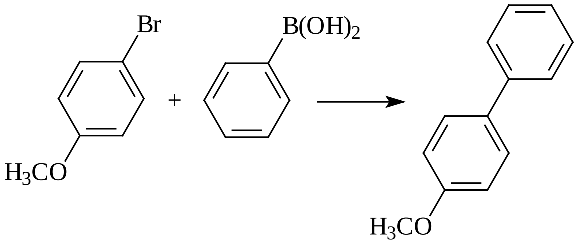

Fig. 1. Scheme of Suzuki cross-coupling of 4-bromoanisole and phenylboronic acid

This kind of HPS has already been used for synthesis of Pd-containing Suzuki catalyst (Pd content was 3.75%(wt.)) by N.A. Lyubimov et al. [21]. Highest conversion (99%) of 4-bromoanisole was achieved for 5 h at a temperature of 100°C in N,N-dimethylformamide or water while using $K_3PO_4$ or $Cs_2CO_3$ as a base. It is noteworthy that the phase transfer agent (tetra-n-butylammonium bromide (TBAB)) was added in reaction mixture. In this work we propose to improve catalytic properties of Pd/HPS system via changing of conditions of the catalyst synthesis and Pd precursor nature, which is shown to allow decreasing Pd loading and at the same time increasing catalytic activity at milder reaction conditions at the absence of TBAB.

## 2 Experimental

### 2.1 Materials

HPS Macronet MN100 (Purolite Int., United Kingdom) bearing amino-groups was washed with distilled water and acetone and dried under vacuum as described elsewhere [22]. 4-Bromoanisole (≥98%) was purchased from Merck KGaA. 4-Methoxybiphenyl (>99%) was purchased from Tokyo Chemical Industry Co. Ltd. Phenylboronic acid (95%), diphenylamine (99%), biphenyl (99.5%), bis(acetonitrile)palladium(II)chloride ($(CH_3CN)_2PdCl_2$, >99%), tetrahydrofuran (THF, ≥99.9%), isopropanol (*i*-PrOH, 99.5%), ethanol (EtOH, ≥99.8%), acetonitrile (99.8%), *n*-hexane (≥97%), acetone (>99.9%), potassium carbonate ($K_2CO_3$, ≥99%), sodium carbonate ($Na_2CO_3$, ≥99.5%) and sodium hydroxide (NaOH, ≥98%) were obtained from Sigma-Aldrich. All chemicals were used as received. Distilled water was purified with an Elsi-Aqua water purification system.

### 2.2 Catalyst Synthesis

HPS-based Pd-containing catalyst was synthesized via conventional wet-impregnation method according to the procedure described elsewhere [22]. In a typical experiment, 1 g of pretreated, dried and crushed (<63 μm) granules of MN100 were impregnated with 2.8 mL of the $(CH_3CN)_2PdCl_2$ THF solution (concentration 0.057 mol/L). The Pd-containing polymer was dried at 70°C, treated with 2.7 mL of $Na_2CO_3$ solution (concentration 0.07 mol/L) and dried until the constant weight was achieved. After that the catalyst was washed with distilled water till neutral pH and dried at 70°C.

Thus Pd/MN100 catalyst containing 1.54%(wt.) of Pd was synthesized (the metal content was confirmed by the elemental analysis).

It is noteworthy that in contrast to the procedure described by N.A. Lyubimov et al. [21], the above method of Pd/MN100 catalyst synthesis assumes the use of organic solvent (THF) and $(CH_3CN)_2PdCl_2$ as a precursor (instead of $PdCl_2$ dissolved in water), which likely results in better distribution of Pd inside the relatively hydrophobic polymeric matrix of MN100, and may be responsible for high activity of synthesized catalyst.

Besides, we applied gas-phase reduction in hydrogen flow (at 275°C for 2 h) instead of wet reduction [see ref. 21].

### 2.3 Procedure of Suzuki Cross-Coupling

Catalytic testing of synthesized 1.54%-Pd/MN100 was carried out in inert atmosphere (nitrogen) in a 60 mL isothermal glass batch reactor at vigorous stirring. The total volume of liquid phase was 30 mL. Mixtures of EtOH and water were used as solvents. In each experiment the quantity of 4-bromoanisole was equal to 1 mmol, 1.5 molar excess of phenylboronic acid was used. Palladium loading was varied from 0.35%(mol.) up to 1%(mol.) with respect to 4-bromoanisole. Before the catalyst addition in the reactor, in each experiment the blank test (duration of 60 min) was carried out in order to ensure that the reaction not proceeded at the absence of catalyst.

Influence of solvent composition, type of base, temperature, palladium loading and oxidation state (Pd(II) or Pd(0)) was studied.

Samples were periodically taken and analyzed via GC-MS (Shimadzu GCMS-QP2010S) equipped with a capillary column HP-1MS (30 m × 0.25 mm i.d., 0.25 μm film thickness). Helium was used as a carrier gas at pressure of 74.8 kPa and linear velocity of 36.3 cm/s. Oven temperature was programmed: 120°C (0 min) → 10°C/min (160°C) → 25°C/min (300°C) → 300°C (2.4 min). Temperature of injector, interface and ion source was 260°C, range from 10 up to 500 m/z. The concentrations of the reaction mixture components were calculated using the internal standard calibration method (diphenylamine was used as internal standard).

### 2.4 Catalyst Characterization

Pd/HPS catalyst was characterized by liquid nitrogen physisorption, X-Ray Photoelectron Spectroscopy (XPS) and Transmission Electron Microscopy (TEM).

Liquid nitrogen physisorption was carried out using Beckman Coulter SA 3100 (Coulter Corporation, USA). Prior to the analysis, samples were degassed in Becman Coulter SA-PREP at 120°C in vacuum for 1 h.

XPS data were obtained using Mg Kα (hν = 1253.6 eV) radiation with ES-2403 spectrometer (Institute for Analytic Instrumentation of RAS, St. Petersburg, Russia) equipped with energy analyzer PHOIBOS 100-MCD5 (SPECS, Germany) and X-Ray source XR-50 (SPECS, Germany). All the data were acquired at X-ray power of 250 W. Survey spectra were recorded at an energy step of 0.5 eV with an analyzer pass energy 40 eV, and high resolution spectra were recorded at an energy step of 0.05 eV with an analyzer pass energy 7 eV. Samples were allowed to outgas for 180 min before analysis and were stable during the examination. The data analysis was performed by CasaXPS.

Pd NPs sizes were evaluated by TEM using a JEOL JEM1010 instrument at electron accelerating voltage of 80 kV. Samples were prepared by embedding the catalyst in epoxy resin with following microtomming at ambient temperature. Images of the resulting thin sections (*ca*. 50 nm thick) were collected with the Gatan digital camera and analyzed with the Adobe Photoshop software package and the Scion Image Processing Toolkit.

## 3 Results and Discussion

### 3.1 Characterization of Pd/HPS Catalyst

Initial MN100 and the Pd/MN100 catalyst (both as-synthesized and reduced) were characterized by the low-temperature nitrogen physisorption, XPS and TEM.

The BET surface area (SSA) of MN100 after impregnation with $(CH_3CN)_2PdCl_2$ changed negligibly: from 793 $m^2/g$ to 746 $m^2/g$, respectively, indicating that almost no pore blockage took place after incorporation of the Pd compound. The Barrett-Joyner-Halenda (BJH) pore size distribution suggested the presence of micro- (< 2 nm), meso- (2-50 nm) and macro-pores (> 50 nm) with predominant microporosity. After the reduction the porosity was slightly decreased to 721 $m^2/g$ mainly due to the decrease of the fraction of meso- and macropores (from 148 $m^2/g$ to 119 $m^2/g$ according to the *t*-plot), while SSA of micropores changed negligibly (from 597 $m^2/g$ up to 603 $m^2/g$). This observation can be due to the location of Pd NPs in mesopores of MN100.

XPS data revealed that the surface of Pd/HPS catalyst contains chlorine, carbon, oxygen, nitrogen and palladium. According to the high resolution spectrum of Pd 3d, the values of the binding energy of Pd $3d_{5/2}$ are 338.6 eV (binding energy of $(CH_3CN)_2PdCl_2$ was found to be equal to 338.7 eV), 337.7 eV ($PdCl_2$) [23], 336.1 eV (small clusters of Pd) [24]. The existence of $PdCl_2$ in the catalyst composition can be ascribed to the transformation of $(CH_3CN)_2PdCl_2$ during the catalyst synthesis, as was also observed for hydrogenation catalysts in one of our previous studies [25]. XPS investigation was also carried out for the catalyst samples taken after first use in Suzuki reaction. In the case of unreduced catalyst, it was found that the share of $PdCl_2$ on the catalyst surface decreased slightly while the percentage of $(CH_3CN)_2PdCl_2$ drastically decreased (in about 24 times). These changes were in line with approximately three-fold increase of percentage of Pd clusters. Besides, traces of Pd(0) appeared (about 0.3%(at.)), which correspond to Pd NPs. This observation can be explained by the peculiarities of catalytic cycle of Suzuki cross-coupling [8, 18], when palladium changes its oxidation state from (II) to (0) and vice versa, and small Pd clusters are responsible for catalytic activity and can result in NP formation.

Fig. 2 shows TEM image of as-synthesized Pd/MN100 catalyst (Fig. 2 (a)). No NPs are formed in as-synthesized Pd/MN100, presumably, due to high affinity of $(CH_3CN)_2PdCl_2$ to the MN100 pore walls. TEM image was also obtained for reduced Pd/MN100 (see Fig. 2 (b)). It can be seen formation of small NPs with mean diameter of 3.3 ± 0.8 nm. Thus it can be concluded that mesopores of HPS are responsible for NP formation.

### 3.2 Catalytic Testing in Suzuki Cross-Coupling

#### 3.2.1 Influence of Temperature

During the variation of reaction temperature (1.5 mmol of $Na_2CO_3$, 0.72%(mol.) of Pd, solvent –

EtOH/water mixture (5:1)), 60$^{o}$C was found to be optimal (95.5% of 4-bromoanisole conversion was achieved) for as-synthesized Pd/MN100 (Fig. 3). Though the results obtained at 70$^{o}$C for 55 min of reaction duration were rather close, we supposed the lower temperature to be preferable.

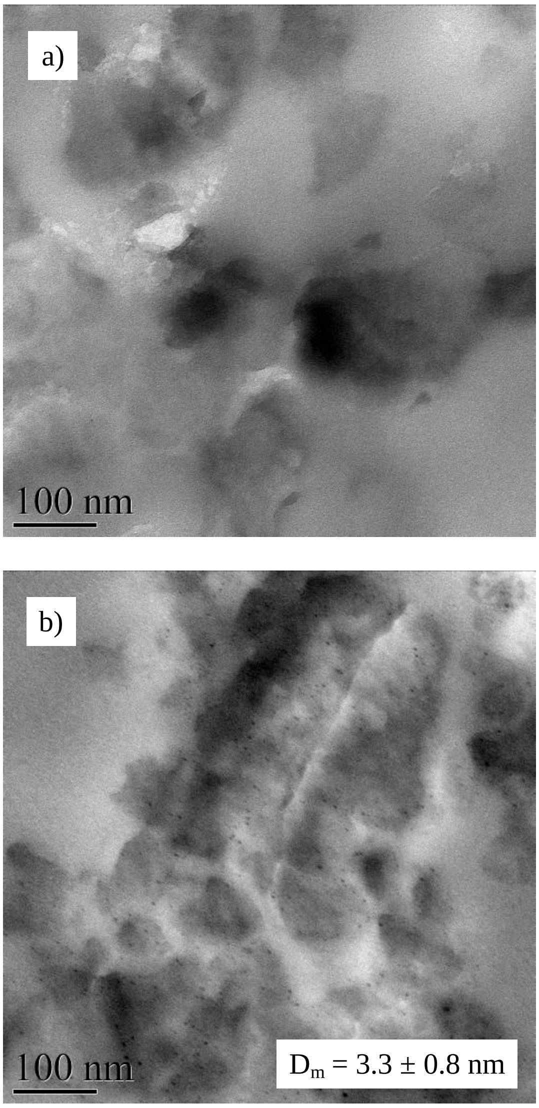

Fig. 2. TEM images of Pd/MN100 (as-synthesized (a) and reduced (b))

### 3.2.2 Influence of the Type and Concentration of Base

Experiments on variation of the type and concentration of base were carried out for as-synthesized Pd/MN100 (0.72%(mol.) of Pd) at 70$^{o}$C while using EtOH/water mixture (5 : 1) as a solvent. Conversion of 4-bromoanisole was found to increased from 89% up to 97% while increasing the strength of base in the series $K_2CO_3$ < $Na_2CO_3$ < NaOH. This observation can be explained by the fact that base plays multiple roles: acceleration of two rate-limiting stages (transmetallation and reductive elimination) and, at the same time, limitation of formation of unreactive anions. Thus the increase of OH-group concentration allows increasing the degree of 4-bromoanisole conversion.

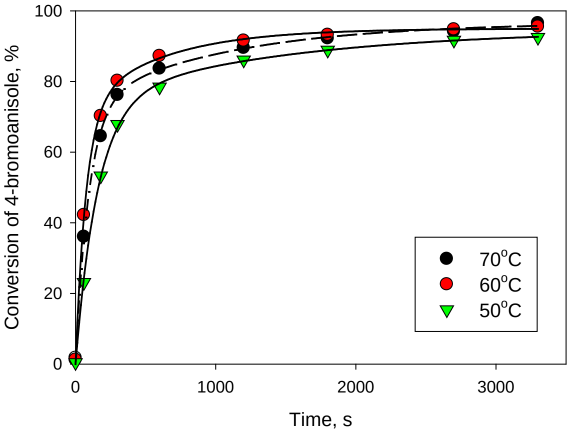

Fig. 3. Dependence of conversion of 4-bromoanisole on time at variation of solvent composition

### 3.2.3 Influence of Solvent Composition

The influence of solvent composition was investigated for as-synthesized Pd/MN100 at the following reaction conditions: temperature of 60$^{o}$C, 1.5 mmol of NaOH, 0.72%(mol.) of Pd. The data of the influence of solvent composition are presented in Fig. 4. It is noteworthy that the use of complex solvent allowed us avoiding the necessity of application of phase transfer agent.

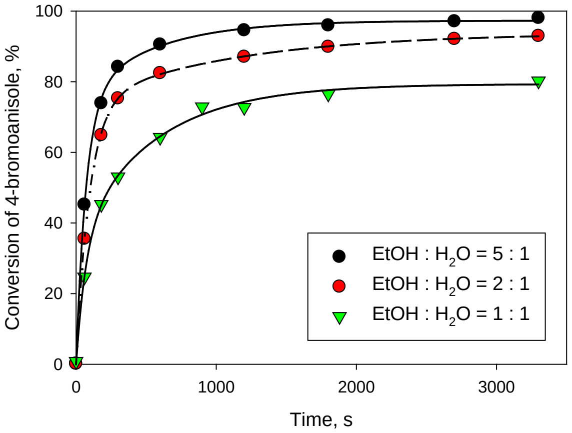

Fig. 4. Dependence of conversion of 4-bromoanisole on time at variation of solvent composition

It can be seen that the increase of EtOH content results in corresponding increase of 4-bromoanisole conversion. The optimal ratio of EtOH/water was found to be equal to 5 (conversion of 4-bromoanisole was found to be 98%).

It is worth noting that product of homocoupling of phenylboronic acid (biphenyl) was also found, but its content was less than 2%(wt.) by the end of each experiment.

### 3.2.4 Influence of the Catalyst Loading and Palladium Oxidation State

Increase of the catalyst loading from 0.35%(mol.) up to 0.72%(mol.) was found to result in corresponding increase of 4-bromoanisole conversion from 93.2% up to 95.5% ($60^oC$, 1.5 mmol of $Na_2CO_3$) for 55 min. Reduction was found to result in the decrease of reaction rate (see Fig. 5) that is in accordance with the reported data [see e.g. ref. 6, 26].

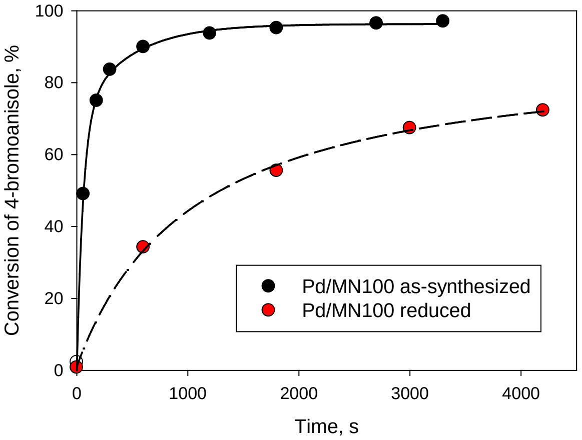

Fig. 5. Influence of preliminarily reduction of Pd/MN100 on conversion of 4-bromoanisole

For the reduced sample, the increase of the catalyst loading from 0.72%(mol.) up to 1%(mol.) resulted in increase of 4-bromoanisole conversion from 71% up to 84.5%, respectively ($60^oC$, 1.5 mmol of NaOH) for 180 min.

It is noteworthy that in spite of lower activity in comparison with the as-synthesized sample, the reduced catalyst revealed nearly twofold increase of activity in comparison with the data reported elsewhere [21] at milder reaction conditions at the absence of TBAB.

### 3.2.4 Catalyst Reuse

As-synthesized catalyst was stable during three repeated use, conversion of 4-bromoanisole changed slightly (by about 1%). Reduced sample revealed higher stability (up to 5 cycles).

## 4 Conclusion

HPS-based catalysts of Suzuki cross-coupling were synthesized. In spite of mild reaction conditions and the absence of phase transfer agents, more than 90% conversion of aryl halide was achieved. Formation of small Pd clusters and NPs was found to be responsible for observed catalytic activity.

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