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Suzuki Cross-coupling in Environmentally Friendly Solvents in a Batch Mode Using Hypercrosslinked Polystyrene-supported Pd Catalysts

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This work is devoted to the synthesis of Pd-containing catalysts based on hypercrosslinked polystyrene (HPS) and study of their catalytic properties in Suzuki cross-coupling of 4-bromoanisole (4-BrAn) and phenylboronic acid (PBA). Series of Pd-containing HPS-based catalysts were synthesized at variation of Pd content and tested in Suzuki cross-coupling of 4-BrAn and PBA in a batch mode at ambient pressure while using ethanol (EtOH) and EtOH/water mixtures as solvents.

The highest catalytic activity was observed at EtOH/water ratio of 5 : 1 while using NaOH as a base (the conversion of 4-BrAn has reached higher than 98% for less than 1 h of reaction time). Selectivity was higher than 95 % with respect to 4-methoxybiphenyl. Thus HPS-supported palladium catalysts were found to be promising (active, selective), simple in preparation and stable for at least three consecutive runs for the Suzuki cross-coupling at mild temperatures along with the absence of the necessity to use phase transfer agents.

1. Introduction

The palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids, which are known to reveal low toxicity, is powerful tool for the obtaining of carbon-carbon bonds, in particular for the formation of biaryls (Zharova et al., 2015). There are more than three hundred various commercial compounds, which can react Suzuki. At present, this reaction is widely used in the synthesis of APIs, pesticides, advanced polymeric materials and liquid crystals (Hajipour et al., 2014).

Many heterogeneous and homogeneous Pd catalysts have been developed for Suzuki reaction. Although homogeneous Pd phosphine complexes generally show higher reaction rates and greater selectivity towards the desired products in comparison with heterogeneous catalysts, they are toxic, expensive and difficult to recover and reuse. Besides, homogeneous catalysts of can be also sensitive to oxygen and/or moisture. Furthermore, the contamination of the reaction products with trace amounts of metal represents another major issue associated with the use of transition metal catalysts, and this issue can be particularly problematic following the use of expensive and/or toxic heavy metal complexes. To solve these problems, significant research needs to be conducted towards the development of new heterogeneous catalyst systems that can be easily separated and recycled without any significant loss in efficiency (Liewa et al., 2015).

In the last decade, the attention of many scientists was attracted to the development of new ligand-free catalytic systems that allow for the Suzuki reaction under mild conditions in aqueous medium. One of the most well known ligand-free catalyst is Pd/C (Sołoducho et al., 2013). In comparison with homogeneous palladium complexes, Pd/C is easy to manufacture and can be separated from the reaction mixture by conventional filtration or centrifugation. Palladium salts, e.g. palladium acetate and (Alimardanov et al., 2004) and palladium chloride (Phan et al., 2004), which can be also easily removed from the reaction mixture, are also attributed to ligand-free catalysts of Suzuki reaction.

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However, the main disadvantage of the use of ligand-free catalysts is irreversible leaching of palladium. Therefore, the problem of the search of new ligand-free Suzuki catalysts still exists. Despite the diversity of methods of synthesis of ligand-free catalysts (the use of inorganic supports (metal oxides and salts, zeolites), carbon supports (activated carbon, carbon nanotubes)), nanostructured polymers are considered to be the most promising supports (Sołoducho et al., 2013) and in (Astruć, 2007). The variety of polymer properties (presence of functional groups, molecular weight, degree of crosslinking, hydrophilicity or hydrophobicity, etc.), provides the opportunity to influence the process of catalyst synthesis and metal nanoparticle formation (Pachón et al., 2008)

This work is devoted to the synthesis of Pd-containing hypercrosslinked polystyrene (HPS)-based catalysts and study of their catalytic properties in Suzuki cross-coupling of 4-bromoanisole (4-BrAn) and phenylboronic acid (PBA) (Figure 1). In this reaction, 4-methoxybiphenyl (4-MBP) is the target product of the cross-coupling, while biphenyl formed as a result of homocoupling of PBA is the side product.

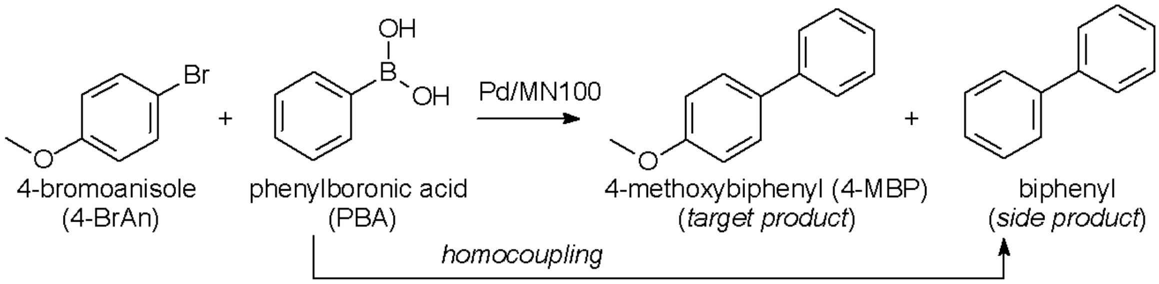

Figure 1: Suzuki cross-coupling reaction of 4-BrAn and PBA

2. Experimental

Series of Pd/HPS catalysts were synthesized via wet-impregnation method according to the procedure described elsewhere (Sulman et al., 2012). In a typical experiment, 1 g of pretreated, dried and crushed (<63 μm) granules of HPS (Macronet MN100 purchased from Purolite Ltd., UK) were impregnated with 2.8 mL of the THF solution of precursor ($PdCl_2(CH_3CN)_2$) of a certain concentration. 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.

Testing of HPS-based catalysts was carried out in a 60 mL isothermal glass batch reactor at vigorous stirring. The total volume of liquid phase was 30 mL. EtOH and EtOH/water mixtures were used as solvent. In each experiment the quantity of 4-BrAn was equal to 1 mmol, 1.5 molar excess of PBA was used. Palladium loading was 0.24 mol.%, 0.47 mol.% or 0.72 mol.% with respect to 4-BrAn, depending on the metal content in the catalyst (0.5wt.%, 1wt.% or 1.5wt.%, respectively). 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, type of atmosphere (air, nitrogen or hydrogen), 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 (100 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).

It is noteworthy that for 1.5 %-Pd/HPS sample, influence of preliminarily gas phase reduction in hydrogen flow (100 mL/min, 300 °C, duration 2 h), which results in Pd nanoparticles formation in HPS matrix, was studied.

Besides, investigation of catalyst stability at multiple reuses was studied for 1.5 %-Pd/HPS sample (both as-synthesized and reduced): after the reaction, catalyst was filtered, washed with EtOH (30 mL), n-hexane (15 mL), and acetonitrile (15 mL), and then dried at 80 °C for 3 h.

3. Results and Discussions

Influence of Pd content was investigated at the following reaction conditions: 70 °C, inert atmosphere (nitrogen), 1.5 mmol of Na_2CO_3. Mixture of EtOH/water at volumetric ratio of 5 : 1 was used as a solvent. It was found that the highest conversion of 4-BrAn (94.7 %) was achieved for as-synthesized (unreduced) 1.5 %-Pd/HPS (see Figure 2) for 55 minutes. Thus, all further experiments were carried out for this catalyst.

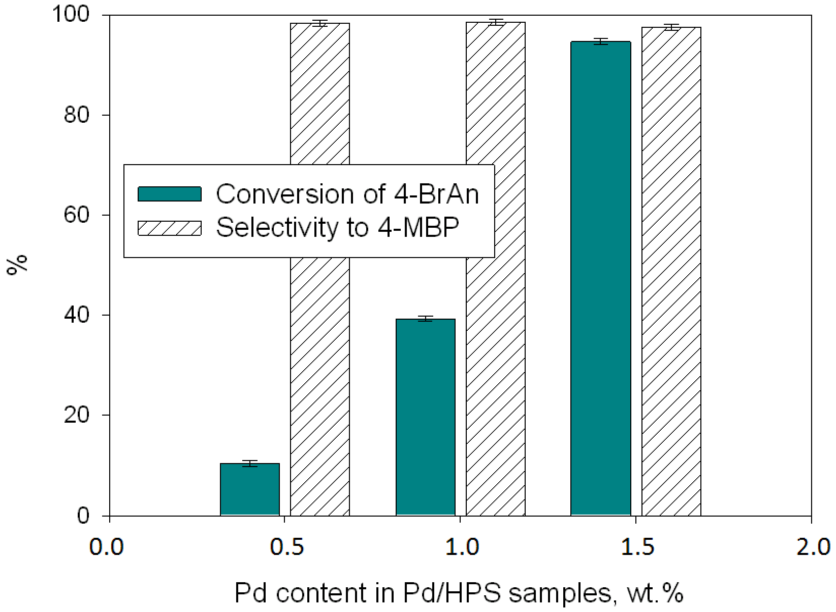

Figure 2: Dependence of 4-BrAn conversion and selectivity with respect to 4-MBP on the Pd content (reaction conditions: nitrogen atmosphere, 70 °C, 1.5 mmol of Na_2CO_3, solvent: EtOH/H_2O = 5 : 1, reaction time 55 min)

Investigation of the effect of solvent composition on the degree of 4-BrAn conversion revealed that the use of pure EtOH as a solvent leads to 89.4 % conversion, while addition of small amounts of water allows increasing 4-BrAn conversion up to 98.4% (Figure 3). Further increase in water content in EtOH/water mixture negatively affects the reaction rate that is likely due to the poor solubility of 4-BaAn in water.

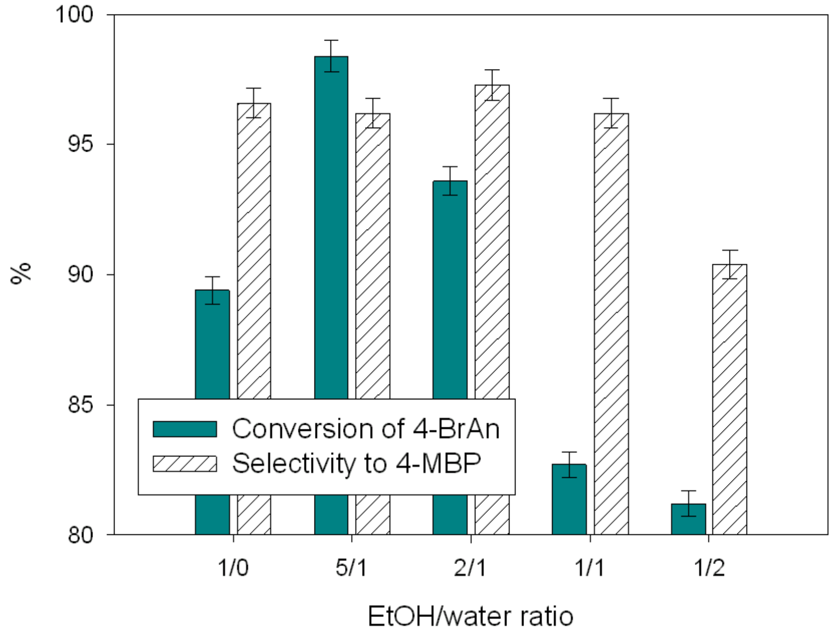

Figure 3: Dependence of 4-BrAn conversion and selectivity to 4-MBP on the EtOH/water ratio for the sample 1.5 %-Pd/HPS (nitrogen atmosphere, 60 °C, 1.5 mmol of NaOH, reaction time 55 min)

It is noteworthy that water is an environmentally friendly solvent; however the rate of cross-coupling in pure water is extremely low in comparison with organic solvent-water mixtures (Liu et al., 2011). This fact can be explained not only by insufficient solubility of substrates in water but also by the difficulty of Pd(II) reduction in water that is an essential step of the Suzuki reaction mechanism. In order to achieve high activity in the case of pure water, the addition of phase transfer agents is necessary (Lyubimov et al., 2009). Thus, different polar organic solvents, EtOH in particular, and their mixtures with water in optimum ratio can be applied due to the possibility of enhancing of the catalyst activity and stability.

Experiments on the variation of the type of base were carried out at 70 °C while using the EtOH-water mixture (5 : 1) as a solvent (Table 1). The conversion of 4-BrAn was found to increase from 91.6 % up to 97.7 % while increasing the strength of the base in the series $K_2CO_3 < Na_2CO_3 <$ NaOH. This can be explained by the fact that the base plays two roles: a) acceleration of two rate-limiting steps (transmetallation and reductive elimination) and, at the same time, b) limitation of the formation of unreactive anions. However, the dependence of the rate of the Suzuki cross-coupling on the concentration of NaOH was found to have a maximum (Table 1) corresponding to the value of 1.5 mmol, i.e., the decrease of the NaOH concentration to 1 mmol resulted in the decrease of 4-BrAn conversion to 78.4 %, while the increase of NaOH concentration from 1.5 mmol up to 2 mmol did not provide a further increase of the 4-BrAn conversion.

Table 1: Influence of the type of base on the catalytic behavior of 1.5 %-Pd/HPS in Suzuki cross-coupling

Type of base	Amount of base, mmol	Temperature, °C	Conversion ± 0.5, %	Selectivity ± 0.5, %
K_2CO_3	1.5	70	91.6	97.4
Na_2CO_3,	1.5	70	94.7	97.4
NaOH	1.5	70	97.7	96.8
NaOH	1.5	60	98.4	94.5
NaOH	2	60	98.1	95.1
NaOH	1	60	78.4	96.9

The temperature variation was carried out for 1.5 %-Pd/HPS while using Na_2CO_3 as a base and EtOH/water mixture (5 : 1) as a solvent. Investigation of the effect of temperature (Figure 4) has shown that the use of temperature above 60 °C allows achieving 4-BrAn conversion of >95 % for 55 min of reaction time, while the temperature decrease to 50 °C results in corresponding decrease of 4-BrAn conversion to 93.2%.

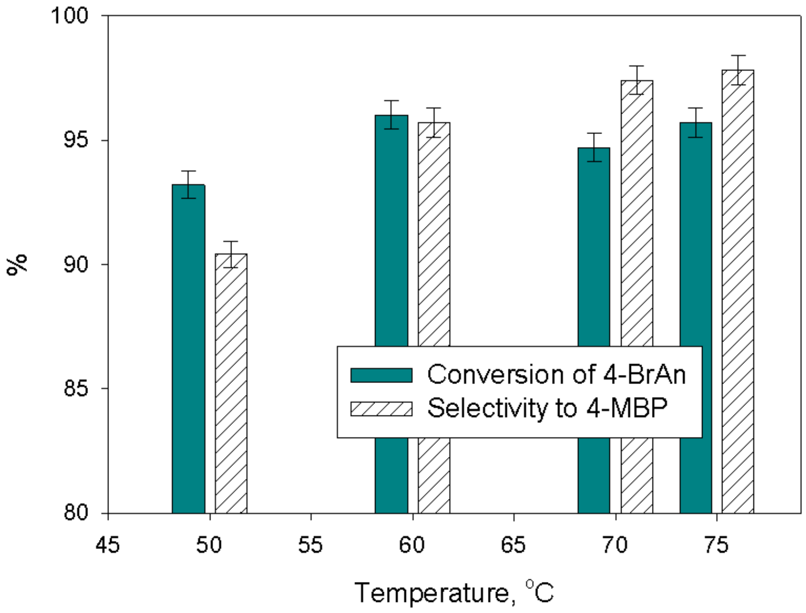

Figure 4: Dependence of 4-BrAn conversion and selectivity to 4-MBP on temperature for the sample 1.5 %-Pd/HPS (nitrogen atmosphere, 1.5 mmol of Na_2CO_3, solvent: EtOH/H_2O = 5 : 1, reaction time 55 min)

It is noteworthy that the temperature increase results in an increase of selectivity with respect to 4-MBP due to the corresponding decrease of biphenyl content. However, the influence of temperature on 4-BrAn conversion is negligible at the temperatures higher than 60 °C. The temperature effect can be explained by the influence on the equilibrium between different forms of Pd participating in the reaction, i.e., the temperature decrease provides the increase of the stability of palladium complexes in solution while the higher temperatures increase the rate of the Pd reduction and precipitation in the form of nanoparticles, which are much less active in Suzuki cross-coupling in comparison with small Pd_n clusters formed *in situ* from Pd(II) species.

Moreover, while comparing the yield of 4-MBP obtained at different reaction temperatures, it was found that the yield of 4-MBP changed slightly in the temperature range of 60 - 75 °C (from *ca.* 92% up to *ca.* 94%). Thus 60 °C was chosen as the optimum temperature for further study.

Gas atmosphere also influences the degree of 4-BrAn conversion. For example (Table 2), the replacement of inert atmosphere of nitrogen by the air resulted in slight decrease of 4-BrAn conversion. Whereas the use of hydrogen led to a sharp decrease of 4-BrAn conversion, almost in 4 times in comparison with an inert atmosphere, which is likely due to the fact that in the case of hydrogen atmosphere, palladium was quickly reduced and precipitated as nanoparticles resulting in lower catalytic activity.

Table 2: Influence of the atmosphere on the catalytic behaviour of 1.5 %-Pd/HPS in Suzuki cross-coupling (temperature 60 °C, 1.5 mmol of NaOH, solvent: EtOH/H_2O = 5 : 1)

Atmosphere	Conversion ± 0.5, %	Selectivity ± 0.5, %
N_2	98.4	96.2
H_2	34.6	98.7
Air	96.8	95.0

When the 1.5 %-Pd/HPS catalyst was reduced prior to the Suzuki reaction, its activity dropped by half (Figure 5) in comparison with the as-synthesized (unreduced) catalyst. However, the investigation of the catalyst stability in three repeated uses showed that the reduced sample is more stable than the unreduced one.

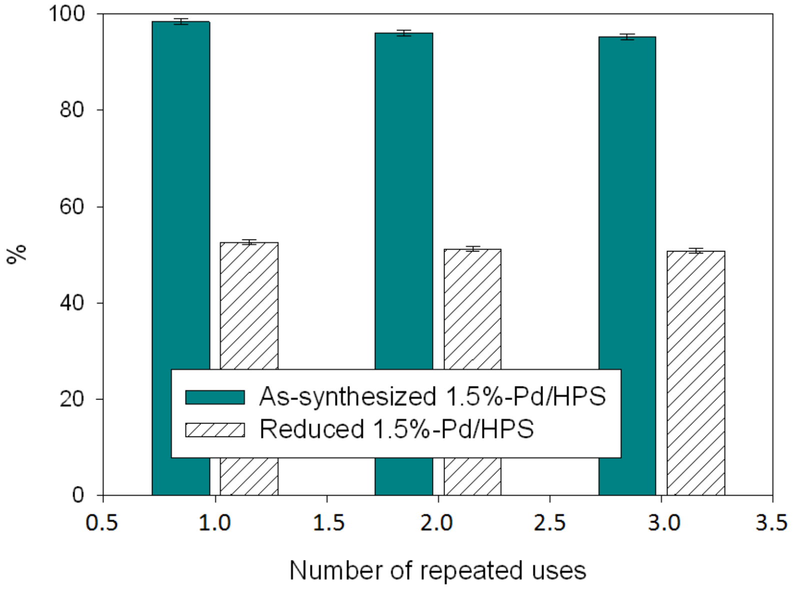

Figure 5: Influence of the Pd oxidation state and the repeated uses on the catalytic behavior of 1.5 %-Pd/HPS sample in Suzuki cross-coupling (temperature 60 °C, 1.5 mmol of NaOH, solvent: EtOH/H_2O = 5 : 1, reaction time 55 min)

It should be mentioned that this kind of HPS has already been used for synthesis of Pd-containing Suzuki catalyst (Lyubimov et al., 2009) while using aqueous solution of $PdCl_2$ as a precursor (Pd content was 3.75 %(wt.)). Highest conversion (99%) of 4-BrAn was achieved for 5 h at a temperature of 100°C in water while using Cs_2CO_3 as a base. It is noteworthy that the phase transfer agent (tetra-n-butylammonium bromide) was added in reaction mixture.

Regarding the results obtained with 1.5 %-Pd/HPS in this work, in spite of the lower activity in comparison with the as-synthesized sample, the 1.5 %-Pd/HPS catalyst preliminarily reduced in hydrogen flow revealed much higher activity at milder reaction conditions at the absence of transfer agent in comparison with the data reported elsewhere (Lyubimov et al., 2009). For comparison, the activity of 3.75%-Pd/HPS was about 10 h^{-1} in

Suzuki cross-coupling of 4-BrAn and PBA at the above mentioned reaction conditions, while for 1.5 %-Pd/HPS synthesized in this work the activity was *ca.* 79 h^{-1} (calculated as mol(4-BrAn)*$X_{4\text{-BrAn}}$/(molPd*t*100), where "$X_{4\text{-BrAn}}$" is conversion of 4-BrAn, %; "t" is reaction time, h) at 60 °C while using EtOH/H_2O mixture as a solvent. The observed activity of the reduced 1.5 %-Pd/HPS catalyst can be attributed to the presence of small Pd nanoparticles as well as to the existence of a large number of Pd clusters formed during gas-phase catalyst reduction.

It is noteworthy that the increase of the Pd loading from 0.72 mol.% up to 1.1 mol.% for the preliminarily reduced 1.5 %-Pd/HPS allowed increasing of the 4-BrAn conversion from 73.3 % up to 90.2 % for 3 h: a promising result for the reduced ligand-free catalyst working in the absence of phase transfer agent.

4. Conclusions

Thus HPS-supported palladium catalysts were found to be promising (active, selective), simple in preparation and stable for at least three consecutive runs for the Suzuki cross-coupling at mild temperatures along with the absence of the necessity to use phase transfer agents. At mild reaction conditions (temperature 60 °C, 1.5 mmol of NaOH, solvent EtOH-water mixture at volumetric ratio of 5 : 1) and in the absence of phase transfer agents, 98.4% conversion of 4-BrAn was achieved for the as-synthesized (unreduced) 1.5 %-Pd/HPS catalyst for 55 minutes of the reaction time. The use of the HPS of MN100 type as a support in combination with thoroughly chosen conditions of the catalyst synthesis (type of the Pd precursor, solvent nature) allowed synthesizing catalytic system containing Pd nanoparticles as well as of Pd_n clusters after the gas-phase reduction with hydrogen, which were likely responsible for the observed activity in cross-coupling of 4-BrAn and PBA. The activity of the reduced 1.5 %-Pd/HPS catalyst was shown to be much higher than that reported in the literature for the analogous catalytic system.

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