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The polyethylene glycol–sodium dodecylsulfate–$PdCl_2$–water supramolecular catalytic system for the Suzuki reaction

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The title catalytic system as an uncharged nanosized catalytic complex gives high yields (⩾ 90%) of the aerobic cross-coupling reaction of aryl halides and phenylboronic acid at 25 °C.

Cross-coupling reaction involving aryl halide and organometallic compounds is widely used for introducing asymmetrical biaryl fragments into organic molecules to obtain biologically active compounds (drugs, pesticides and others), conducting polymers, flame retardants, liquid crystalline materials, *etc*.[1–6] Therefore, the improvement of synthetic approaches to the formation of C–C bonds is still of great importance.

The studies of the Suzuki reaction have been carried out in organic solvents under anaerobic conditions and in the presence of ligands.[1–3] The development of new catalytic systems for cross-coupling reactions has been reviewed.[7–10] An effective catalytic system of palladium acetate/polyethylene glycol (PEG) has been proposed for the aerobic ligandless Suzuki reaction at 35–50 °C in water or aqueous organic media.[11–13] Catalytic systems based on surfactants and polymers, including those for cross-coupling reactions, were described previously.[14,15] The aim of this study was (i) to develop new effective catalytic systems based on PEG; (ii) to optimize their composition and reaction conditions for the replacement of palladium acetate by more accessible palladium chloride and to accelerate the reaction in an aqueous medium, at ambient temperature and without phosphine ligands. A correlation between the structure and efficiency of the catalytic composition may be used for controlling the reactivity.

To compare the effectiveness of the PEG/$PdCl_2$ and PEG/$Pd(OAc)_2$ systems, we performed the Suzuki reaction in the presence of $PdCl_2$ in an aqueous PEG solution at 50 °C. Table 1 summarizes the yields of products. Considerable decrease in effectiveness of the PEG catalyst occurs for $PdCl_2$, as compared to $Pd(OAc)_2$, for which quantitative yields of desirable products were obtained under these conditions.[11] Note that higher yields were observed for aryl bromides, as compared to aryl iodides, which is inconsistent with published data.[1–3] However, in some cases, a similar[11] or higher[16,17] reactivity of aryl bromides, as compared to aryl iodides, was documented. To improve the catalytic effect of the PEG/$PdCl_2$ system, it was modified with the anionic surfactant sodium dodecylsulfate (SDS), and the aggregation behavior of supramolecular systems was studied, in particular, the concentration boundaries of aggregation and the sizes and zeta potentials of particles were estimated. PEGs with lower molecular weights were found more effective (Table 1); therefore, PEG-1000 was used in the subsequent experiments. The solution concentrations of PEG are given as a molar concentration on a monomer basis (moles of monomer per liter of solution) in the self-organization study.

Aggregates with a hydrodynamic radius of 2.0 nm are formed in aqueous SDS solution above a critical micelle concentration (cmc) of 0.0085 mol dm^{-3}. According to a current concept,[18] mixed aggregation occurs within the concentration interval between a critical aggregation concentration (cac) and a concentration of polymer saturation (cps) in the solution of anionic surfactant and

Table 1 Yields (HPLC) of cross-coupling products of halogenated toluene and phenylboronic acid in the presence of different polyethylene glycols.[a]

System	Yield of PhC_6H_4Me (%)	
	from MeC_6H_4I	from MeC_6H_4Br
PEG-1000	35	55
PEG-3000	39	56
PEG-10000	23	27
PEG-15000	18	24
PEG-20000	22	27

[a] Na_2CO_3 (0.212 g, 2 mmol), $PdCl_2$ (2 mg, 1 mol%), PEG (3.5 g, 3.5 mmol), and water (3 g), 50 °C, 4 h.

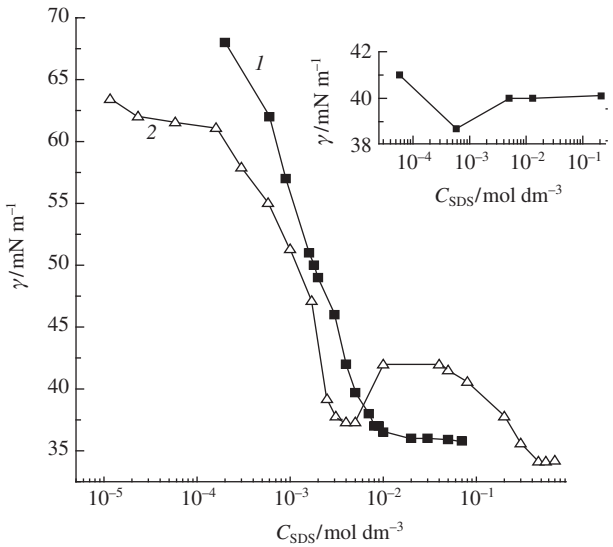


Figure 1 Surface tension isotherms for (*1*) an SDS solution and (*2*) aqueous binary PEG–SDS system; 4.4 mmol dm^{-3} PEG, 25 °C. The binary PEG–SDS system is studied at lower polymer concentrations as compared to other experiments (insert: surface tension isotherm for aqueous binary PEG–SDS system; C_{PEG} = 0.13 mol dm^{-3}).

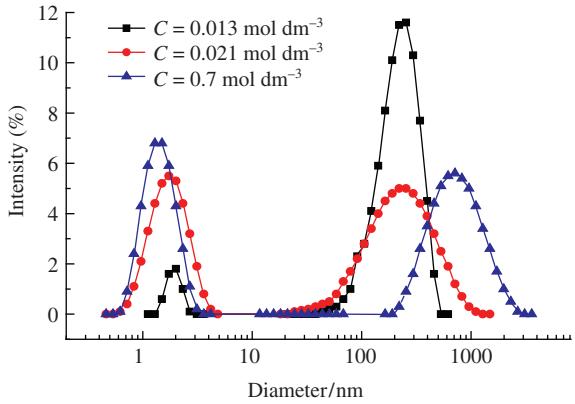


Figure 2 Size distribution analysis in the aqueous PEG–SDS solution at 4.4 mmol dm^{-3} PEG and different SDS concentrations; 25 °C; dynamic light scattering; the intensity parameter.

uncharged polymers; while after the cps single surfactant micelles exist. Optimal SDS concentrations covering mixed aggregation were determined by tensiometry (Figure 1). The values of cac and cps are 0.0036 and 0.42 mol dm^{-3}, respectively. Single PEG solution, the PEG–SDS and PEG–SDS–$PdCl_2$ systems were studied by dynamic light scattering. The autocorrelation function was found bimodal in all cases; therefore, two types of aggregates were observed in solutions, *i.e.*, small aggregates with the hydrodynamic diameter D_h = 1.5–2.5 nm and large aggregates ($D_h \geqslant 100$ nm) (Figure 2).

In the PEG solution, the contribution of small aggregates can be attributed to free PEG molecules, as supported by calculations of the radius of gyration (R_g) for PEG-1000. R_g makes it possible to estimate roughly the size of the PEG particles using the model of statistic coil for flexible polymer:[19]

$$R^2_{e\text{-}e} = 0.006M, \quad (1)$$

$$R^2_g = R^2_{e\text{-}e}/6, \quad (2)$$

where $R_{e\text{-}e}$ is the mean end-to-end distance (nm), M is the molecular weight, and R_g is the radius of gyration of the polymer (nm).

For PEG-1000, the calculated R_g is 2 nm, which agrees well with the experimental values of D_h = 1.5–2.5 (Figure 2).

In the binary PEG–SDS system, an increase in cac occurs as compared to single SDS solution (Figure 1), which provides evidences for the interaction of components resulting in the formation of mixed aggregates. A bimodal size distribution is due to the presence of either polymer-bound or polymer-free SDS micelles (small particles) and aggregated macromolecules (large particles). The diameter of the latter increased with PEG and SDS concentrations from 100–130 nm to several micrometers (Figure 2).

Figure 3 shows the zeta potential for the ternary PEG–SDS–$PdCl_2$ system. Since palladium chloride shows poor solubility in water, the ternary mixture was stirred for 1 h and then filtered. Palladium in solution was determined by atomic emission spectroscopy. As can be seen, the potential is close to zero (–1.4 mV). The charge compensation of the SDS aggregates can be due to the interactions of anionic head groups with other species or a high degree of counterion binding. The latter seems more probable since a high concentration of PEG in the system decreases the dissociative capacity of the solvent. In this case, the sulfate head group exists as an ionic pair with the sodium cation. However, further investigations are required to elucidate the nature of interactions involved.

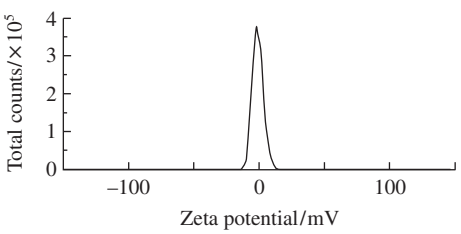
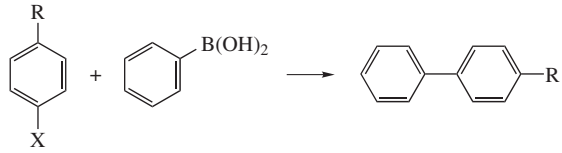


Figure 3 Electrokinetic potential for the aqueous PEG–SDS–$PdCl_2$ system [3.5 g (3.5 mmol) of PEG, 0.0556 g (0.19 mmol) of SDS; 2 mg (1 mol%) $PdCl_2$; 25 °C]. (The ternary mixture: 3.5 g of PEG; 0.0556 g of SDS and 2 mg of $PdCl_2$ in 3 ml of water were stirred for 1 h and then filtered).

The ternary system [3.5 g (3.5 mmol) of PEG, 0.0556 g (0.19 mmol) of SDS, 2 mg (1 mol%) $PdCl_2$] was studied in the catalysis of the aerobic Suzuki reaction (Scheme 1)† in water. The reaction of substituted aryl halides **1a–e**, **2a–e** was carried out at 50 °C for 4 h, *i.e.*, under conditions described previously.[11] The quantitative monitoring of the yields of target products and contributions of homo-coupling was conducted at this stage. The exploration of the reaction mixture by atomic force microscopy revealed the presence of large particles (of a micrometer size). High yields were reached under these conditions in all cases (Figure 4); however, the formation of a by-product due to the homo-coupling of phenylboronic acid was observed. This undesirable process grows



1a–e, 2a–b

a R = H
b R = Me
c R = OMe
d R = OH
e R = NH_2

1 X = Br
2 X = I

Scheme 1

† The following reagents were used: SDS (Sigma), phenylboronic acid, substituted bromo- or iodoaryls (Acros), $PdCl_2$ (Panreac Quimica SA), Na_2CO_3 (analytical grade), and PEG-1000, PEG-3000, PEG-10000, PEG-15000 and PEG-20000 (Sigma–Aldrich). Aqueous solutions were prepared using twice-distilled water.

General procedure for the Suzuki reaction. A mixture of Na_2CO_3 (0.212 g, 2 mmol), $PdCl_2$ (2 mg, 1 mol%), PEG (3.5 g), SDS (0.0556 g, 0.19 mmol) and water (3 g) was stirred at 25 or 50 °C. Afterward, aryl halide (1 mmol) and phenylboronic acid (1.5 mmol) were added to the solution, and the reaction was carried out for the specified time. Then, the resulting suspension was extracted two to four times with diethyl ether (2–4×15 ml). The ether phase was analyzed by the following methods. HPLC (column C_{18}, 150×3 mm, 5 μm; methanol) was used for determining the yields of products by means of calibration plots. ^{1}H NMR experiments (a Bruker AVANCE-600 spectrometer operating at 600.13 Hz) were performed to estimate the conversion of substrates, the ratio of components in reaction mixtures, and absolute amounts of components using cyclohexane as a reference substance. GC/MS with electron ionization [a DFS mass spectrometer (Thermo Fisher Sci. Co.) with a DB-1 capillary column (30 m); the column temperature, 160 °C; the injector temperature, 280 °C; the transfer line temperature, 280 °C; the carrier gas (helium) flow rate, 1.0 ml min^{-1}, and the mass range, 40–210 a.m.u. (scan speed of 0.5 s dec^{-1})] was used for controlling the qualitative and quantitative composition of reaction mixtures based on the ratio of component peaks and the use of an external probe (*tert*-butylbenzene). For an additional control of the results obtained, products were separated from reaction mixtures. The data on conversions of substrates and yields of products obtained by different methods vary by 5–7%. Surface tension measurements were carried out using the du Nouy ring detachment method. The experimental details are described elsewhere.[20] Dynamic light scattering measurements were performed with the Malvern Instrument Zetasizer nano. A He–Ne laser operating at 633 nm and emitting under 173° polarized light was used as a light source (for the experimental details, see ref. 21).

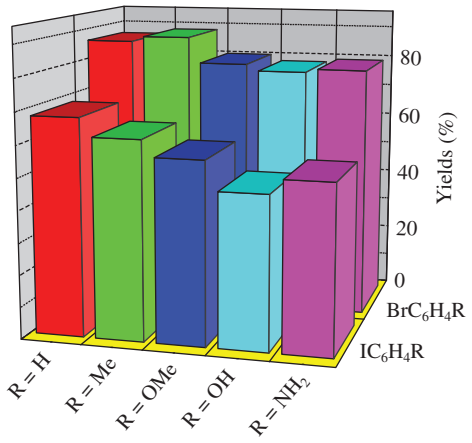


Figure 4 Yields of cross-coupling products of aryl halides and phenylboronic acid in the presence of the PEG–SDS–$PdCl_2$ catalytic system: Na_2CO_3 (0.212 g, 2 mmol), $PdCl_2$ (2 mg, 1 mol%), PEG (3.5 g, 3.5 mmol), SDS (0.0556 g, 0.19 mmol), water (3 g), 50 °C, 4 h; reaction mixtures were analyzed by ^{1}H NMR spectroscopy and HPLC.

with time and the yield of by-product can reach 9 mol% with respect to the target product. In the reactions of substrates **1a–d** at 25 °C, high yields of cross-coupling products were obtained in 3–4 h with a minimal contribution of by-products (Table 2), the usual conversion of aryl bromides being 100% after 3 h.

To study the possibility of reusing the catalyst, the residual after extraction was subjected to the second run by charging with the same substrates. The yields of the first three–five cycles were close to 90%. Further, the yield dropped down to 70–80%. The catalytic systems were examined at different PEG concentrations. The yields of cross-coupling products were 80–90% at 25 °C. Good yields of target products (up to 70%) were obtained in the presence of a trace amount of $PdCl_2$. These results make it possible to predict the maintenance or even growth of catalytic capacity of the PEG–SDS–$PdCl_2$ system at the decrease of component dosage.

Thus, the application of the new PEG–SDS–$PdCl_2$ supramolecular system provides high yields of cross-coupling aerobic reaction of aryl halides with electron-donating substituents and phenylboronic acid. The system has obvious advantages over the majority of those used in routine procedures: (i) it is based on accessible and environmentally friendly components, *i.e.*, $PdCl_2$ as a catalyst and water as a solvent; (ii) it is a ligandless, aerobic, and proceeding at ambient temperature. Based on the correlation between the structural behavior of the supramolecular system and its effectiveness, the ways of further improvement are outlined. They are the use of ppb amounts of the palladium-based catalyst, a decrease in the amounts of other catalytic components, diminishing the reaction time and covering the inactivated substrates.

Table 2 Yields of cross-coupling products of substituted aryl bromides and phenylboronic acid.[a]

Time/h	Yields of cross-coupling product PhC_6H_4R/ homo-coupling product (mol%)[b]		
	R = Me	R = OMe	R = OH
1	86/<1	90/<1	85/1
2	91/<1	95/1	91/1
3	93/1	95/3	93/2
4	93[c]/4, 90[d], 92[e]	95/4	95/3

[a] Na_2CO_3 (0.212 g, 2 mmol), $PdCl_2$ (2 mg, 1 mol%), PEG (3.5 g, 3.5 mmol), SDS (0.0556 g, 0.19 mmol) and water (3 g), 25 °C. [b] Average of three methods, *i.e.*, GC/MS, ^{1}H NMR spectroscopy and HPLC. [c] GC/MS. [d] ^{1}H NMR spectroscopy. [e] HPLC.

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