Palladium Colloid Stabilized by Block Copolymer Micelles as an Efficient Catalyst for Reactions of C−C and C−Heteroatom Bond Formation

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Palladium nanoparticles stabilized in micelles formed by polystyrene-*co*-poly(ethylene oxide) and cetylpyridinium chloride as a surfactant were investigated as a catalyst in the following reactions: the Heck reaction of 2-ethylhexyl acrylate with iodobenzene and *p*-bromoacetophenone and heterocyclization of *N*-methylsulfonyl-*o*-iodoaniline with phenylacetylene and of methyl *o*-iodobenzoate with diphenylacetylene leading to formation of substituted indole and isocoumarin, respectively. The activity of the colloidal palladium catalytic system is comparable to that of the low-molecular-weight palladium complexes, whereas the stability of the colloidal palladium system is much higher. The reuse of the catalyst was demonstrated in the experiments with fresh starts as well as by thermomorphous separation of the catalyst from products.

Introduction

Transition-metal-catalyzed reactions have become an important tool of modern organic synthesis due to their high efficiency, selectivit,y and wide diversity of possible transformations. Homogeneous catalysts are of high activity, but insufficient stability and high cost are major drawbacks often preventing their application in industry.[1] Heterogeneous catalysts are more stable, cheaper, and easier to separate from products, which is an important advantage in industrial processes. However, the activity and selectivity of heterogeneous catalysts is usually lower than that of homogeneous catalysts, while the scope of catalyzed reactions is not as wide. Therefore, major efforts of researchers now are to develop novel catalysts combining the advantages of both homogeneous and heterogeneous catalytic systems. The creation of immobilized homogeneous catalysts allowing the recovery and reuse of the system is a direct way to realize this idea. This is also coupled with the current emphasis on green chemistry aimed tt minimizing waste and the use of toxic materials.

The application of polymer-supported transition-metal complexes is a highly explored technique to immobilize homogeneous catalysts and has been extensively reviewed.[2] However, we have discovered a number of drawbacks associated with this approach: lengthy and expensive synthesis of the polymer-bound ligand and low reactivity of the catalyst because of catalytic centers being enveloped by the polymer, as well as low stability of the catalysts. Another problem of supported catalysts arises from metal leaching, which limits reuse of the catalyst.[3]

Recently transition-metal nanoparticles have drawn much attention as catalytic systems.[4] It has been shown that in many catalytic reactions the true catalyst is not the original transition-metal complex but metal nanoparticles formed in situ.[5] In classic homogeneous catalysis the nanoparticles aggregate to form large inactive moieties or bulk metal. The nanoparticles stabilized by some sort of support (such as an immobilized colloidal catalytic system) could have several important advantages over both traditional homogeneous and supported transition-metal catalysts: lower cost, absence of toxic and expensive phosphine ligands, high activity of the homogeneous system, and ability for reuse. A number of metal colloidal systems have been created.[6] Among them, metal nanoparticles stabilized within the micelles of amphiphilic block copolymers or dendrimers are especially promising.[7] In contrast to colloids stabilized by surfactants or coordinating solvents, metal colloids stabilized by block copolymers are far more stable and easier to separate from reaction products. Catalysts based on palladium nanoparticles have been used mostly in hydrogenation reactions and a few works dealing with oxidation reactions[7] and coupling

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reactions such as Heck,[3,8,9] Suzuki,[10,11] Sonogashira,[12] Stille,[12] and allylic substitution reactions.[13] However, the great potential of nanoparticles has still not been utilized in important catalytic transformations.

This work is aimed at extending the scope of application of the palladium nanocatalytic systems to more complex synthetic reactions such as heterocyclizations, leading to potentially biologically important heterocycles. An aqueous solution of palladium nanoparticles stabilized by micelles of polystyrene−poly(ethylene oxide) copolymer (PS-PEO) with cetylpyridinium chloride (CPC) was used to catalyze reactions performed in dimethylacetamide (DMA).

Results and Discussion

Block copolymers consisting of hydrophobic and hydrophilic blocks form micelles upon dissolution in selective solvents (good solvents for only one type of block).[7] In nonpolar solvents hydrophilic blocks form the micelle core, while the hydrophobic blocks form the corona. The opposite is true in water. Metal nanoparticles stabilized in the block copolymers are usually bonded to hydrophilic blocks bearing heteroatoms. In nonpolar solvents the nanoparticles are trapped inside the core, thus hindering access to them. Palladium nanoparticles stabilized by polystyrene−poly(4-vinylpyridine) (PS-PVP) copolymer in toluene showed lower activity compared to homogeneous palladium complexes in the Heck reaction due to slow mass transport to the core.[8] Amphiphilic block copolymers form a hydrophobic core, while the nanoparticles are distributed in the hydrophilic corona in water. Polystyrene−poly(sodium acrylate) copolymer stabilized palladium nanoparticles in water efficiently catalyzed the Suzuki coupling of phenyl iodide with arylboronic acids but showed unsatisfactory results with aryl bromides.[10] We investigated a novel block copolymer based catalytic system holding nanoparticles at the surface of the micelle core, which are more defined and stable compared to the nanoparticles distributed in the diffuse corona and more accessible to reactants compared to the nanoparticles trapped inside the core. The structure and formation of the micellar stabilized nanoparticles were investigated earlier.[14] Amphiphilic PS-PEO copolymer was dissolved in water, leading to the formation of micelles with a hydrophobic PS core and hydrophilic PEO corona. The cationic surfactant CPC, which was added to the micellar solution, penetrates into the hydrophobic micellar cores of block copolymers. The surface of the micelle cores is thereby charged positively with headgroups of the surfactant. Addition of K_2PdCl_4 salt leads to adsorption of $PdCl_4^{2-}$ anions on the micelle core surface (Figure 1). Subsequent reduction of palladium(II) by $NaBH_4$ results in the formation of metal nanoparticles on

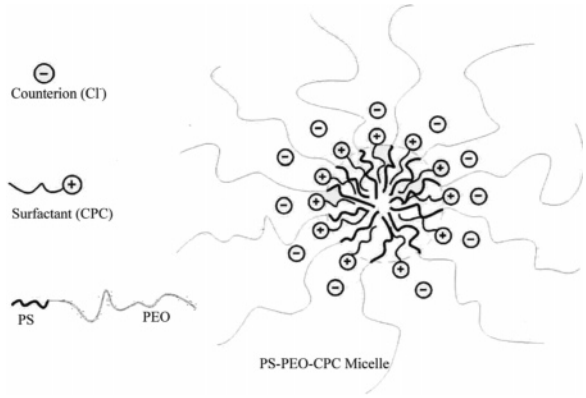
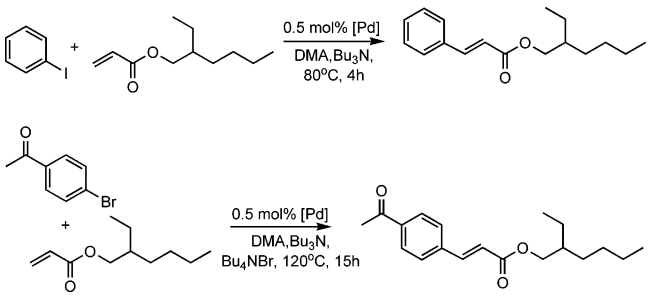


Figure 1.

Scheme 1



the surface of the micellar core.[14] The resulting palladium colloid solution in water (PS-PEO-CPC-Pd) was added as a catalyst to DMA solutions of reactants. It shows remarkable stability. We observed no change of activity after 1 year of storage in aqueous solution.

To study the catalytic properties of this catalytic system, the Heck coupling as a simple model test reaction was carried out first. Iodobenzene and *p*-bromoacetophenone reacted with 2-ethylhexyl acrylate in dimethylacetamide with Bu_3N as a base at 80 and 120 °C, respectively, in the presence of PS-PEO-CPC-Pd to give the corresponding cinnamic esters with quantitive trans stereoselectivity and high yields (Scheme 1). As can be seen from Table 1, the activity of the palladium colloid is comparable to that of $PdCl_2(MeCN)_2$ (compare entries 1 and 2 and entried 5 and 6). The reaction with 4-bromoacetophenone proceeds more slowly compared to that with iodobenzene, and higher temperatures are required (entry 10). The addition of Ph_3P increases the product yield in the reaction, but the Bu_4NBr additive works much better, leading to an almost quantitive yield of the product and a higher rate of the reaction (entries 11 and 12, Table 1). The activity of PS-PEO-PC-Pd catalyst in the Heck reaction is comparable to the activity of palladium nanoparticles stabilized by quaternary ammonium salts, taking into account different reaction conditions.[5b]

In the case of homogeneous palladium complexes fast degradation of the catalyst occurs during reaction and palladium metal precipitation. In contrast, there was no palladium black formation observed in the reaction catalyzed by the PS-PEO-CPC-Pd system even after many hours at 120 °C. This indicates a much higher stability for this catalyst.

The reuse of the catalyst was investigated by two methods. After the reaction was complete, fresh portions of all the reagents except for the catalyst were added to the reaction mixture and this mixture was reheated (fresh start). Three cycles of the fresh start showed that the reaction proceeds with the almost the same yield and speed without degradation of the catalyst (entries 2−4).

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Table 1. Reactions of 2-Ethylhexyl Acrylate with Aryl Halides[a]

entry	ArHal	solvent	cat.	temp, °C	time, h	yield, %[b]
1	PhI	DMA	PS-PEO-PC-Pd	80	2	52
2	PhI	DMA	PS-PEO-PC-Pd	80	4	83 (cycle 1)
3	PhI	DMA	PS-PEO-PC-Pd	80	4	79 (cycle 2)
4	PhI	DMA	PS-PEO-PC-Pd	80	4	87 (cycle 3)
5	PhI	DMA	$PdCl_2(MeCN)_2$	80	2	70
6	PhI	DMA	$PdCl_2(MeCN)_2$	80	4	86
7	PhI	DMA/heptane[c]	PS-PEO-PC-Pd	90	2	90 (cycle 1)
8	PhI	DMA/heptane[c]	PS-PEO-PC-Pd	90	2	86 (cycle 2)
9	PhI	DMA/heptane[c]	PS-PEO-PC-Pd	90	2	94 (cycle 3)
10	4-AcC_6H_4Br	DMA	PS-PEO-PC-Pd	120	15	73
11	4-AcC_6H_4Br	DMA	PS-PEO-PC-Pd[d]	120	15	87
12	4-AcC_6H_4Br	DMA	PS-PEO-PC-Pd[e]	120	13	98

[a] Reaction conditions: 2-ethylhexyl acrylate, 0.6 mmol; ArHal, 0.5 mmol; Bu_3N, 1 mmol; [Pd], 0.5 mol %; DMA, 1 mL; mole percent and yields are relative to ArHal. [b] Determined by GLC. [c] 10% H_2O in DMA/heptane (1:2 v/v), 1 mL. [d] In the presence of 2 mol % Ph_3P. [e] In the presence of 20 mol % Bu_4NBr.

The recovery of the catalyst was investigated with Bergbreiter's thermomorphic heptane−10% aqueous DMA (2:1) mixture as the reaction media.[15] At room temperature the system is biphasic. When it is heated to 90 °C, the solution becomes homogeneous and the reaction proceeds. After the solution is cooled to room temperature, the catalyst remains in the polar layer and the hydrophobic product stays in heptane, allowing them to be separated from each other. For the next run a new portion of the reagents dissolved in heptane was added to the DMA solution and the mixture heated again. Three cycles of catalyst reuse showed no change in activity and no palladium black formation (entries 7−9).

Thus, the new catalytic system showed high activity and recycling ability in the Heck reaction. Usually activity or stability or recycling ability was sacrificed in the catalytic systems employed. Reetz et al. reported that palladium nanoparticles stabilized by tetraalkylammonium salts showed high catalytic activity in cross-coupling reactions.[5b] Highly active palladium nanoparticles stabilized by ammonium or phosphonium salts were much more stable compared to catalysts based on low-molecular-weight palladium complexes (such as traditional $Pd(OAc)_2PPh_3$) but are still less stable in comparison with block copolymer colloidal systems and are not reusable.[5a] Moreover, reusable PS-PVP stabilized nanoparticles are less active.[8] The Pd/C system is very stable but less active, and the reuse of the catalyst is limited, due to considerable leaching of palladium from the support into the reaction solution.[3b] Our catalytic system was found to be stable and active in the Heck reaction, which prompted us to investigate the catalyst in synthetically more interesting and valuable heterocyclization reactions.

Indoles and isocoumarins are important natural products and biologically active compounds. The pharmacological properties of such molecules have led to an increasing number of publications aimed at the improvement of the synthetic methods utilizing such reactions.[16] Homogeneous palladium complexes catalyzing the annelation of *o*-haloanilines with alkynes have been widely used for the synthesis of indoles.[16] We investigated the reaction of phenylacetylene with *o*-iodoaniline protected by a methylsulfonyl group catalyzed by PS-PEO-PC-Pd. The reaction proceeds as the cascade process of Sonogashira coupling of phenylacetylene with *o*-iodoaniline protected by a methylsulfonyl group, followed by cyclization[17] (Scheme 2).

Scheme 2

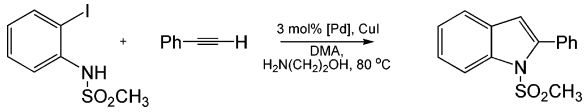

Table 2. Reactions of Phenylacetylene with *N*-(Methylsulfonyl)-2-iodoaniline[a]

entry	cat.	ligand (L)	amt of L, equiv	time, h	yield, %[b]
1	PS-PEO-PC-Pd			2	52
2	PS-PEO-PC-Pd			4, 5	79 (cycle 1)
3	PS-PEO-PC-Pd			4, 5	84 (cycle 2)
4	PS-PEO-PC-Pd			4, 5	73 (cycle 3)
5	PS-PEO-PC-Pd	Ph_3P	4	3	70
6	PS-PEO-PC-Pd	Ph_3P	4	7	78 (cycle 1)
7	PS-PEO-PC-Pd	Ph_3P	4	7	80 (cycle 2)
8	PS-PEO-PC-Pd	Ph_3P	4	7	85 (cycle 3)
9	$PdCl_2(CH_3CN)_2$	Ph_3P	4	4	91
10	PS-PEO-PC-Pd			3	20[c]
11	PS-PEO-PC-Pd	Ph_3P	4	3	42[c]

[a] Reaction conditions: *N*-(methylsulfonyl)-2-iodoaniline, 0.1 mmol; phenylacetylene, 0.27 mmol; 2-ethanolamine, 0.33 mmol; [Pd], 3 mol %; CuI, 6 mol %; DMA, 0.53 mL; 80 °C. [b] Determined by GLC. [c] In water.

Both unprotected aniline and (trifluoroacetyl)aniline gave lower yields because the 2-phenylindole that formed was consumed in a side reaction, as reported.[18] The product with a methylsulfonyl protecting group is stable in the reaction mixture and in the purification process.

The reaction was carried out at 80 °C in DMA with ethanolamine as a base in the presence of of PS-PEO-PC-Pd (3 mol % Pd) and 6 mol % of CuI. As can be seen from Table 2, the reaction is complete after 4.5 h to give a high yield of *N*-(methylsulfonyl)-2-phenylindole (entry 2). The activity of the colloidal catalyst is just slightly lower than that of the low-molecular-weight complex (entry 9). Reuse of the catalyst by the fresh start technique shows stable activity (entries 2−4 and 6−8). Water was also used as a reaction solvent, but heterogeneous conditions slow the reaction (entries 10 and 11). In this case the reaction occurred in the emulsion, as the reagents are not soluble in water. The addition of a Ph_3P ligand leads to a considerably increased yield in water solution (entry 11) but does not influence the reaction in DMA (compare entries 2−4 and 6−8).

Recently heterocyclization of *o*-iodoanilines with phenylacetylenes to give good yields of the indoles has been achieved using a heterogeneous catalyst (Pd/C-Ph_3P) in a water−ethanolamine mixture but no attempts to recycle the catalyst

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Scheme 3

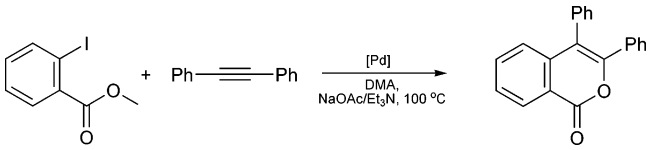

Table 3. Reactions of Methyl *o*-Iodobenzoate with Diphenylacetylene[a]

entry	cat.	time, h	amt of Pd, mol %	yield, %[b]
1	PS-PEO-CPC-Pd	4	0.3	48 (cycle 1)
2	PS-PEO-CPC-Pd	4	0.3	48 (cycle 2)
3	PS-PEO-CPC-Pd	4	0.3	52 (cycle 3)
4	PS-PEO-CPC-Pd	10	0.5	68 (cycle 1)
5	PS-PEO-CPC-Pd	10	0.5	71 (cycle 2)
6	PS-PEO-CPC-Pd	10	0.5	74 (cycle 3)
7	PS-PEO-CPC-Pd	10	0.5	74[c]
8	PS-PEO-CPC-Pd	24	0.3	22[d]
9	$PdCl_2(PPh_3)_2$	8	6	75
10	$PdCl_2(MeCN)_2$	8	5	61

[a] Reaction conditions: methyl *o*-iodobenzoate, 0.13 mmol; diphenylacetylene, 0.29 mmol; NaOAc, 0.18 mmol; Et_3N, 0.05 mL; DMA, 5 mL; 100 °C. [b] Determined by GLC. [c] With 10 mol % Ph_3P. [d] In DMA with 10% H_2O (v/v).

have been reported.[18] Our catalyst showed comparable activity but good recycling ability and stability in the indole synthesis.

Another important investigated model heterocyclization reaction is the interaction of methyl *o*-iodobenzoate with diphenylacetylene, leading to the cascade formation of substituted isocoumarin.This reaction reported by Heck and developed by Larock was catalyzed by palladium acetate with tri-*o*-tolylphosphine ligand.[17] We carried out the reaction catalyzed by aqueous PS-PEO-PC-Pd in DMA at 100 °C using an excess of tolane (2 equiv) in the presence of Et_3N and sodium acetate. The low-molecular-weight complexes $[PdCl_2(MeCN)_2]$ and $[PdCl_2(PPh_3)_2]$ were used for the comparison. Diphenylisocoumarin is formed as a result of the cascade process of palladium insertion into the aryl−iodide bond followed by arylpalladium iodide addition to the triple bond with subsequent cyclization through a palladacyclic intermediate.[17a] As can be seen from Table 3, the activity of the colloidal catalyst is remarkably high compared to that of low-molecular-weight palladium complexes. An average 70% yield can be achieved with 0.5 mol % of our catalyst or with 5−6 mol % of the $PdCl_2$ complexes (entries 9 and 10) for practically the same time. The reaction proceeds fairly quickly, achieving 50% yield after 4 h with 0.3 mol % of the catalyst (entries 1−3), but the completion of the reaction demands longer times and/or more catalyst (entries 4−6). Inactivation of homogeneous palladium complexes through palladium black formation necessitates higher palladium loading to complete the reaction. As our colloidal catalyst carries constant activity, it can be used at lower loadings and reused many times. Reuse of the catalyst by the fresh start technique showed no change in activity after three cycles (entries 1−3 and 4−6). The stability of the catalyst is very high, as even a long time at an elevated temperature does not affect the activity of the catalyst and no palladium black was formed. The addition of Ph_3P has no influence upon the reaction (compare entries 4 and 7), but water acts as an inhibitor (entry 8).

In conclusion, we have examined the novel palladium nanoparticle based catalyst PS-PEO-PC-Pd. The activity of the catalyst is as high as that observed for low-molecular-weight complexes, whereas the stability is much higher. No palladium black was observed in all the reactions investigated. Reuse of the catalyst showed no loss of activity. These results promise rich perspectives of utilizing such systems in other catalytic reactions. Ph_3P addition does not affect any of the reactions investigated, except for the Heck reaction with aryl bromide at higher temperatures. It is most important to note that PS-PEO-PC-Pd catalysts do not require the use of toxic and unstable phosphine ligands. The system is relatively cheap and simple. The development of the catalyst recycling is in progress.

Experimental Section

General Comments. Reagents were supplied by Lancaster. Solvents were purified by standard techniques. *N*-(Methylsulfonyl)-*o*-iodoaniline was prepared according to literature routes.[19] Standard samples for GLC were prepared by column chromatography of a reaction mixture on silica with a petroleum−ethyl acetate mixture as an eluent. Analysis of the reaction mixture was performed by GLC. Qualitative GLC analysis was performed on a Hewlett-Packard 5890 Series II Plus chromatograph with an HP-1701 capillary column (15 m length, 0.32 mm diameter, 0.25 μm phase layer thickness).

Catalyst Preparation. The micelle system was prepared from polystyrene−poly(ethylene oxide) copolymer (M_n = 4000, N_{ps} = 9.6, D = 1.55) and cetylpyridinium chloride. Palladium colloid was prepared by reduction of K_2PdCl_4 in a water solution of the micelle system by $NaBH_4$ (0.245 mmol of Pd for 1 g of copolymer) according to the reported procedure.[14]

Heck Reaction. A 0.08 mL portion of an aqueous solution of colloidal palladium (2.5 μmol of Pd) was placed into the reactor. The reactor was filled with argon, and 0.056 mL (0.5 mmol) of iodobenzene, 0.125 mL (0.6 mmol) of 2-ethylhexyl acrylate, 0.143 mL (1 mmol) of tributylamine, 0.04 mL of tetradecane (internal standard), and 1 mL of DMA were placed into the reactor. The mixture was stirred at 80 °C. Samples of the reaction mixture were diluted with 1 mL of brine, extracted with ether, and dried with Na_2SO_4. Reaction with 4-bromoacetophenone was performed at 120 °C in a sealed ampule.

Heck Reaction under the Thermomorphic Conditions. A 0.056 mL portion (0.5 mmol) of iodobenzene, 0.125 mL (0.6 mmol) of 2-ehthylhexyl acrylate, 0.143 mL (1 mmol) of Bu_3N, 2 mL of heptane, 0.9 mL of DMA, 0.1 mL of water, and 0.08 mL of an aqueous solution of colloidal palladium (2.5 μmol of Pd) was placed into the reactor under an argon atmosphere. The reaction mixture was stirred at 90 °C. Then the reaction mixture was cooled and the heptane phase was separated and analyzed by GLC as described before. A new portion of the reagents excluding the catalyst was added in heptane solution to the water−DMA phase containing the catalyst, and the reaction mixture was reheated.

Indole Synthesis. A 0.096 mL portion of an aqueous solution of colloidal palladium (3 μmol of Pd) was placed into the reactor. Then the reactor was filled with argon and 31.7 mg (0.1 mmol) of *N*-(methylsulfonyl)-*o*-iodoaniline, 0.0195 mL (0.33 mmol) of ethanolamine, 0.01 mL of tetradecane (internal standard), 1.2 mg (0.0063 mmol) of CuI, and 0.6 mL of DMA were placed into the reactor and strirred for 1 h at room temperature. At this point 0.029 mL (0.27 mmol) of phenylacetylene was added, and the reaction mixture was heated to 80 °C. Samples for GLC were prepared as in the Heck reaction.

Isocoumarin Synthesis. A 35 mg portion (0.13 mmol) of methyl *o*-iodobenzoate, 51 mg (0.29 mmol) of diphenylacetylene, 15 mg of sodium acetate, 0.05 mL of Et_3N, 0.026 mL of tetradecane (internal standard), 5 mL of DMA, and 0.021 mL of an aqueous solution of colloidal palladium (0.65 μmol of Pd) was placed into the reactor under an argon atmosphere and stirred at 100 °C. Samples for GLC analysis were prepared as follows: 0.1 mL of

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the reaction mixture passed through the silica filter with 5 mL of dichloromethane as an eluent.

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