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Efficient Click-Polymer-Stabilized Palladium Nanoparticle Catalysts for Suzuki–Miyaura Reactions of Bromoarenes and Reduction of 4-Nitrophenol in Aqueous Solvents

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Abstract: Palladium nanoparticles (size = 1.6 ± 0.3 nm) stabilized by a polyethylene glycol containing triazolyl rings, synthesized by click reaction in water, are efficient catalysts for the Suzuki–Miyaura coupling of bromoarenes in aqueous ethanol and the borohydride reduction of 4-nitrophenol in water. Turnover numbers (TONs) reach 99,000 and turnover frequencies (TOFs) are up to 198,000 h^{-1} for the C–C cross coupling reactions in water/ethanol.

Keywords: bromoarenes; catalysis; click chemistry; green chemistry; 4-nitrophenol; palladium nanoparticles; polymers; Suzuki–Miyaura reaction

Introduction

Palladium is the most frequently used transition metal in catalysis,[1] especially in the cross-coupling reactions for carbon-carbon bond formation,[2] among which the Suzuki–Miyaura[3] reaction is the most useful one. Metal nanoparticles (NPs) have appeared as a very promising solution towards efficient catalysis under mild, environmentally benign conditions because of their large surface-to-volume ratio and specific surface reactivities.[4] The advantage of the NPs, compared to organometallic catalysts, is that one does not need to use large amounts of catalyst (generally less than 1 mol%),[2a,b,4,5] and ligands (that are often expensive and sometimes toxic) are not required, which is also important for the treatment of the reactions, ligands often being difficult to separate from the final products.

PdNPs with a dimension of less than 10 nm have exhibited high catalytic activities toward different types of reactions.[2a,b,4,5] They are often stabilized by polymers (PVP, PS, PEG, copolymers), dendrimers,[6] cyclodextrins (CDs),[7] inorganic materials,[8] or ionic liquids.[8c,9] For instance, among recent works,[10] Nomura' s group conducted quantitative Suzuki–Miyaura reactions with various substrates in water at 80 °C with PdNPs (1.5 mol% Pd) stabilized by a PS polymer.[10b] Reddy's group carried out Suzuki–Miyaura reactions with various bromoarenes at room temperature, with an amount of catalyst of 0.8–1 mol% Pd, the PdNPs being supported on TiO_2.[10c] Beletskaya's group proposed the term homeopathic Pd catalysis for Heck reactions using PdNP precatalysts.[2a] De Vries used the "homeopathic" concept to investigate the mechanism of high-temperature Heck reactions using low PdNP loading.[10a] Hong's group also used PdNPs stabilized by a bidendate ionic ligand in 0.001 mol% Pd for the Suzuki–Miyaura coupling of activated aryl bromides, the reactions being carried out in only water at 120 °C for a few hours.[10d]

Here we wish to examine the stabilization and catalytic efficiency of PdNPs produced upon $NaBH_4$ reduction of the water-soluble Pd(II) precursor K_2PdCl_4 in the presence specific ethylene glycol oligomer **3** and polymer **5** formed by "click" reactions, i.e., containing 1,2,3-triazolyl (trz) linkages. We are also interested in comparing these properties with those of the known water-soluble arene-centered "click" dendrimer C_6H_3-1,3,5[C{$(CH_2)_3SiMe_2CH_2$-trz-$CH_2OCH_2C_6H_2$-2,3,4-{$(OCH_2CH_2)_3OCH_3$}$_3$}$_3$]$_3$, **6**, that contains 9 trz linkages and 27 TEG termini (TEG = triethylene glycol). Triazolyl rings that were introduced by "click" functionalization in the oligomer, polymer and dendrimer with TEG termini provide the stabilization of the PdNPs after reduction of Pd(II) by $NaBH_4$. The PdNPs stabilized by **6** present a very good activity in the Suzuki–Miyaura reaction of various bromoarenes.[10e,f] Bromoarenes are indeed very important aromatic substrates, because they are often cheaper than their chloroarene analogues, and therefore they are now subjected to further study.

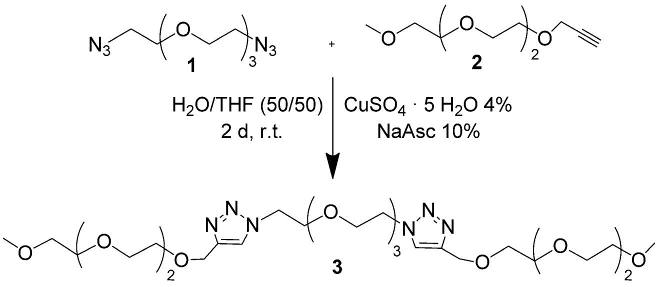
The catalytic activity of PdNPs stabilized by **3** and **5** in the Suzuki–Miyaura coupling of bromoarenes in an aqueous solvent, H_2O:ethanol = 1:1 and the reduction of 4-nitrophenol to 4-aminophenol by sodium borohydride in water have now been examined. 4-Aminophenol is a potential industrial intermediate in the manufacture of many analgesic and antipyretic drugs, anticorrosion lubricants, and hair drying agents. Therefore efficient catalysts for the borohydride reduction of 4-nitrophenol to 4-aminophenol are called for.

Results and Discussion

Synthesis of the PEG-Bis-triazolyl Oligomer 3 and Triazolyl-PEG Polymer 5

New PEG oligomers and polymers have been designed with 1,2,3-triazole rings in their branches in order to provide the mild stabilization of PdNPs by the synergistic combination of triazoles that bind the PdNP surface and PEG that contribute by their steric effect. Click chemistry offers a simple and practical possibility for the synthesis of such oligomers and polymers. The PEG-bis-triazolyl-PEG **3** was synthesized upon clicking tetraethylene glycol bisazide **1** with 2,5,8,11-tetraoxatetradec-13-yne **2** in H_2O/THF (50/50) with 4 mol% of $CuSO_4{\cdot}5H_2O$ as catalyst and 10 mol% sodium ascorbate as reductant of Cu(II) to Cu(I). This reaction leads to **3** in 90% yield (Scheme 1).

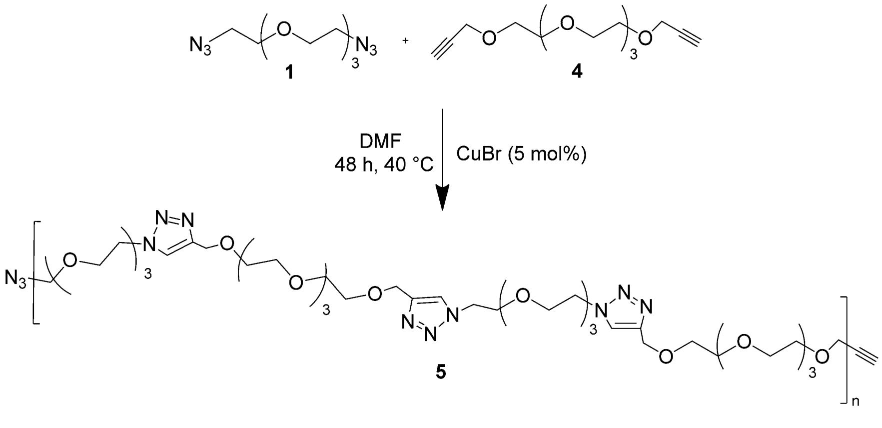
The compound **3** has been characterized by ^{1}H NMR, ^{13}C NMR, heterogeneous single quantum coherence (HSQC), electrospray ionization (ESI) mass spectroscopy, and elemental analysis (see the Supporting Information).



Scheme 1. Synthesis of the PEG-bis-triazolyl oligomer **3** by "click" reaction between tetraethylene glycol bisazide **1** and 2,5,8,11-tetraoxatetradec-13-yne **2**.

"Click" chemistry was also used for the synthesis of the polymer triazolyl-PEG **5**. The reaction between equimolar amounts of the commercial products tetraethylene glycol bisazide **1** and 4,7,10,13,16-pentaoxanonadeca-1,18-diyne **4** in DMF and in the presence of 5 mol% CuBr as catalyst leads to the polymer triazolyl-PEG **5** in 80% yield (Scheme 2). The final polymer has been characterized by ^{1}H NMR, ^{13}C NMR, IR, MALDI TOF mass spectroscopy, size extrusion chromatography (SEC) and dynamic light scattering (DLS, see the Supporting Information).

The SEC analysis provides the polydispersity of the polymer, PDI = 1.3, for this uncontrolled polymerization. The molecular weight, 5×10^4 g mol^{-1}, is determined by SEC using polystyrene as a reference, which corresponds to 97 dimeric units, i.e., 194 triazolyl rings. The mass spectrum shows the presence of small oligomers with 18 triazolyl rings (molecular weight = 4626 g mol^{-1}), but polymers with higher molecular weights cannot be observed due to saturation of the detector with the small oligomers. In ^{1}H NMR, the peak at 2.4 ppm corresponding to the alkyne proton of the starting material is not observed, which allows the conclusion that all the monomeric dialkyne has reacted with the monomeric diazide, but does not



Scheme 2. Synthesis of the triazolyl-PEG polymer **5** by "click" reaction between tetraethylene glycol bisazide **1** and 4,7,10,13,16-pentaoxanonadeca-1,18-diyne **4**.

permit any conclusion concerning the number of units.

The polymer **5** and the oligomer **3** are both soluble in water as expected and desired for the synthesis of PdNPs in water.

PdNP Stabilization

The palladium-polymer complex is prepared in water upon mixing aqueous solutions of the polymer and of K_2PdCl_4 at 20 °C. In previous works with dendrimers containing triazolyl TEG (**6**)[10e] and sulfonated termini,[6c] the stoichiometry between the triazolyl group and the Pd(II) complex was 1:1, and this stoichiometry was explained by the dendritic protection of the interior triazole ligands. In the case of the polymer, the best conditions for the stabilization of PdNPs are a stoichiometry between triazolyl group and Pd(II) around 10:1. In aqueous K_2PdCl_4, a solution of the polymer (or oligomer) is added in this stoichiometry. After five minutes of stirring of Pd(II)/triazole reaction, a solution of sodium borohydride is rapidly added in order to form PdNPs upon reduction of Pd(II) to Pd(0) (see the Experimental Section). The light-yellow solution of Pd(II) instantaneously became orange/brown (see Figure 1), which indicated the quick formation of PdNPs. A fast reduction of Pd(II) to PdNPs is preferred to the dropwise addition leading to a slower reduction, because a high reduction rate results in smaller PdNPs than a slow reduction rate. It is well known that the catalytic activity is improved by reducing the PdNP size within the range of a few nm.[14e]

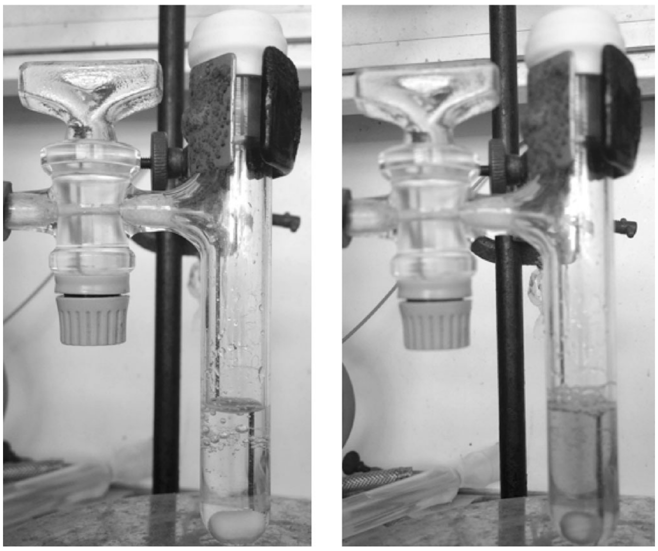
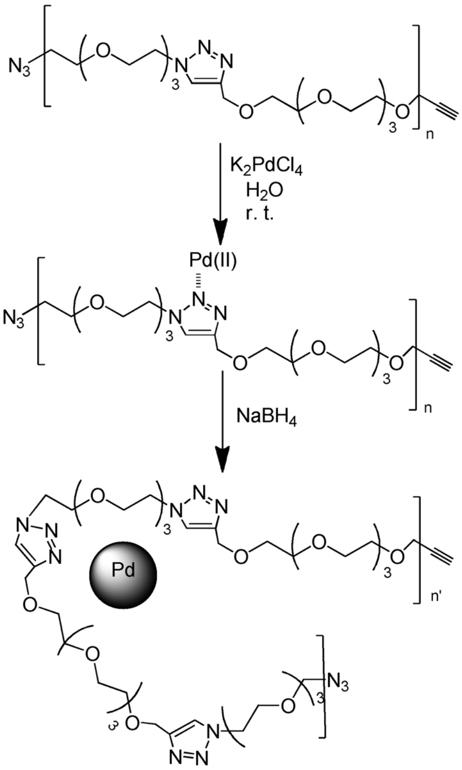


Figure 1. During the PdNP synthesis, the reduction of Pd(II) to PdNPs by $NaBH_4$ is visible by the change of a light (yellow) solution (*left*), to a darker (orange/brown) solution (*right*).

TEM analyses (Figure 2) have been conducted on the PdNPs, showing a diameter of 2.0 ± 0.5 nm upon stabilization by **3** and 1.6 ± 0.3 nm upon stabilization by **5**. The bright-grey colour around PdNPs in the TEM pictures shows the stabilizing oligomer or polymer that appears to surround several PdNPs.

The DLS experiments show that the hydrodynamic diameter of the polymer in the absence of PdNPs is in the range 45–55 nm, which corresponds to an agglomerate of **5** in water. When the PdNPs are stabilized by **5**, the hydrodynamic diameter remains unchanged. There is an excess of polymer *vs.* the PdNPs in the synthesis, and it appears in the TEM images that an agglomeration of polymers surrounds the PdNPs. A parallel experiment has been carried out with the same conditions of PdNP synthesis but with the replacement of the new polymer **5** by commercial PEG 2000, and in that case the PdNPs agglomerated several hours after the Pd(II) reduction to Pd(0). Concerning the PdNPs stabilized by the polymer **5**, no trace of Pd aggregation is observed several days after the synthesis. This comparison shows the essential role of the triazole ligands in the PdNP stabilization by **5** (Scheme 3).

On the other hand, when PdNPs are stabilized by the oligomer **3**, some black Pd formation is observed



Scheme 3. Principle of PdNP stabilization. Pd(II) is added to the polymer triazolyl-PEG **5** and is coordinated by nitrogen atoms of the triazolyl ring. Pd(II) is then reduced to Pd(0) forming PdNPs that are stabilized by the overall polymer frameworks including crucial triazole-PdNP interactions.

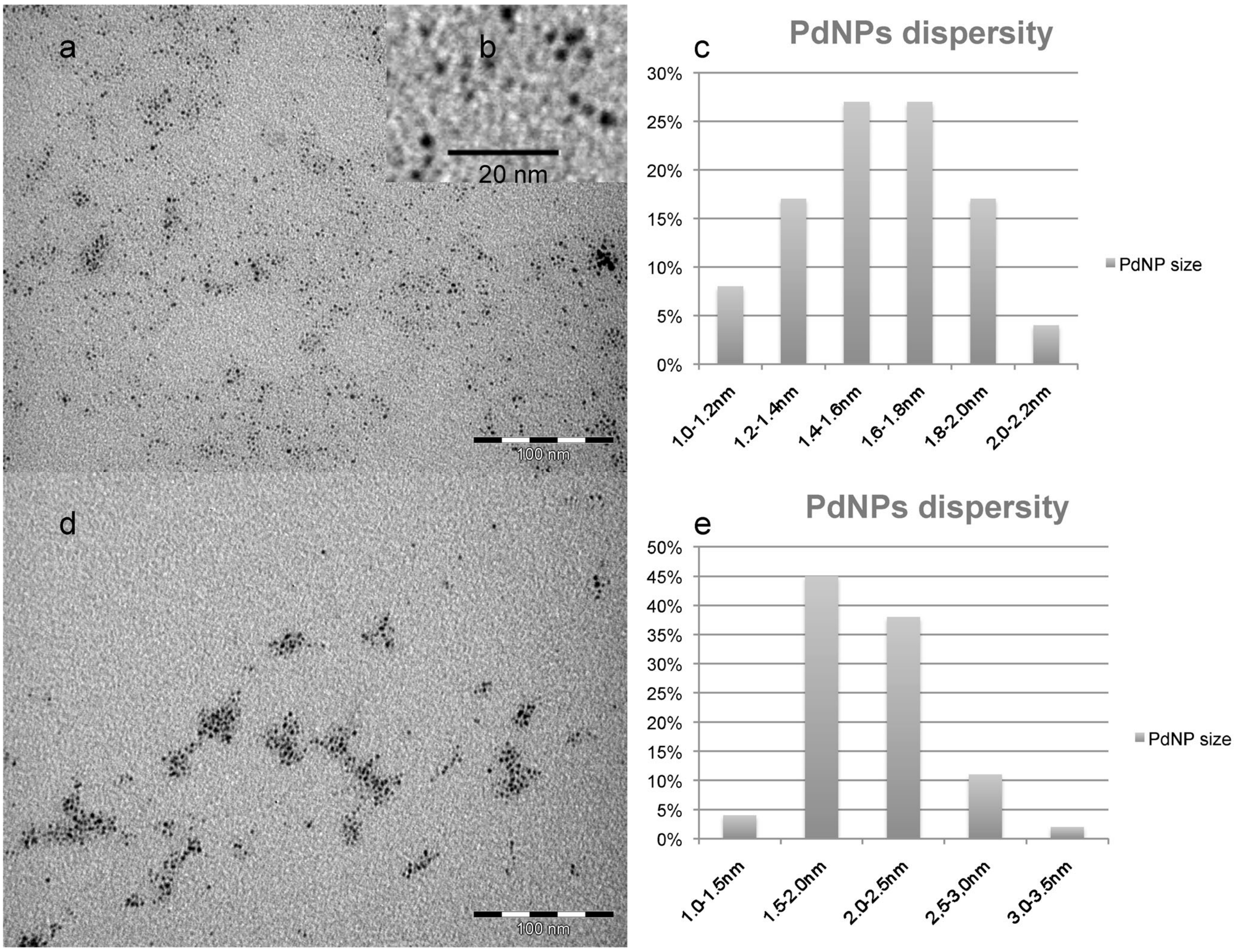
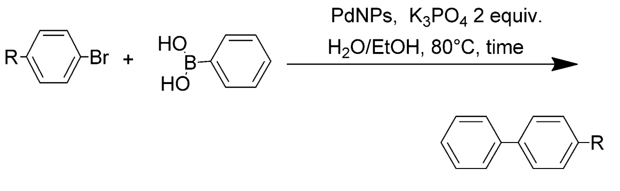


Figure 2. TEM pictures of the PdNPs. (a) TEM analysis of PdNPs stabilized by **5**; (b) zoom on several PdNPs; (c) distribution of 1100 PdNPs; average diameter value: 1.6±0.3 nm. (d) TEM analysis of PdNPs stabilized by **3**; (e) distribution of 1250 PdNPs: average diameter value: 2.0±0.5 nm.

after 2–3 days, indicating the decisive role of the bulk of the molecular framework of the polymer **5**.

Catalytic Studies

In order to check the catalytic activity of PdNPs, the Suzuki–Miyaura coupling has been investigated. The Suzuki–Miyaura cross coupling reactions of various bromoarenes [Eq. (1)] have been carried out in the environmentally the friendly mixture water:ethanol (1:1) in the presence of K_3PO_4, with as little palladium as possible. All the results are summarized in Table 1. The most remarkable result is that obtained in the Miyaura-Suzuki reaction of 4-bromoacetophenone and phenylboronic acid that is quantitative with 1 ppm of catalyst during 16 h at 80 °C. Under these or analogous conditions, the TONs vary between 10^3 and 10^6 with various bromoarenes. Of course, the catalysis also works very well with iodoarenes, because they are more easily activated, as it is well known.[11]



(1)

R = H, CH_3, OCH_3, NO_2, CHO, Br, $COCH_3$

The Suzuki–Miyaura reaction works very well with activated (electron-withdrawing substituents) as well as deactivated (electron-donating substituents) bromoarenes with 0.001 mol% of Pd (i.e., 10 ppm). What is very remarkable is the TON up to 99,000 for the reaction with the 4-bromoacetophenone (entry 13),

Table 1. Suzuki–Miyaura of various bromoarenes catalyzed by PdNPs stabilized by **5**.[a]

Entry	R	Time [h]	Pd [mol%]	Yield[c] [%]	TON; TOF [h^{-1}]
1	4-OMe	12	0.1	99	990; 82.5
2	4-OMe	12	0.01	99	9900; 825
3	4-OMe	20	0.002	98	49,000; 2450
4	4-OMe	20	0.001	80	80,000; 4000
5	H	23	0.002	99	49,500; 2152
6[a]	H	23	0.001	99	99,000; 4304
7	4-Me	20	0.002	99	49,500; 2475
8	4-Me	24	0.001	72	72,000; 3000
9[a]	4-NO_2	2.5	0.001	99	99,000; 39,600
10	4-CHO	24	0.01	90	9000; 375
11	4-Br	14	0.002	96	48,000; 3429
12	4-Br	18	0.001	98	98000; 5444
13[b]	4-COMe	0.5	0.001	99	99,000; 198,000

[a] All the reactions have been carried out in 10 mL of H_2O/EtOH (1/1) with 1 mmol of bromoarene, 1.5 mmol of phenylboronic acid, 2 mmol of K_3PO_4 at 80 °C.

[b] The reaction has been also been conducted on a multigram scale ($n = 15$ mmol), and the yield remained the same.

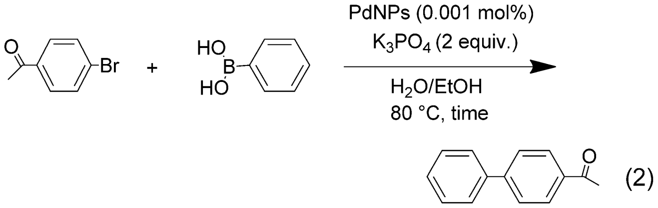
[c] Isolated yields.

and that the reaction is finished in 30 min, which corresponds to a TOF = 198,000 h^{-1} that was never obtained before this study with bromoarenes. The reactions with deactivated arenes such as 1,4-bromoanisole (entry 4) or 1,4-bromotoluene (entry 8) lead to a TON of 80,000 and 72,000, respectively, in a relatively short time too. The reaction with activated bromoarenes such as 1,4-bromonitrobenzene or 1,4-dibromobenzene leads to a quantitative yield for both substrates in a relatively short time (2 h and 14 h, respectively). These results are expected because the oxidative addition on the Pd species is faster when bromoarenes are functionalized with electron-withdrawing groups that weaken the carbon-halogen bond.

These results show the excellent catalytic activity of PdNPs stabilized by the polymer **5** due to ideal stabilization for catalysis by the triazolyl groups (as with dendrimer **6** containing triazolyl TEG termini[10e]). Catalysis with PdNPs stabilized by the oligomer **3** is also efficient down to 0.002 mol% of Pd (quite the same as PdNPs stabilized by the polymer **5**), but then with less than 0.002 mol% the activity is almost nonexistent due to the lack of sufficient stabilization.

We attempted to conduct Suzuki–Miyaura reactions with PdNPs stabilized by the commercial PEG 2000, under the same conditions as those indicated in Table 1 (entry 3, for example), and no C–C coupling was observed.

Suzuki–Miyaura Reaction between 4-Bromoacetophenone and Phenylboronic Acid in EtOH:H_2O = 1:1 [Eq. (2)]



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Kinetic Study of the Reaction

The kinetic study (Figure 3) shows that the reaction between 4-bromoacetophenone and phenylboronic acid is complete in 30 min and that after 10 min the isolated yield is already 72%.

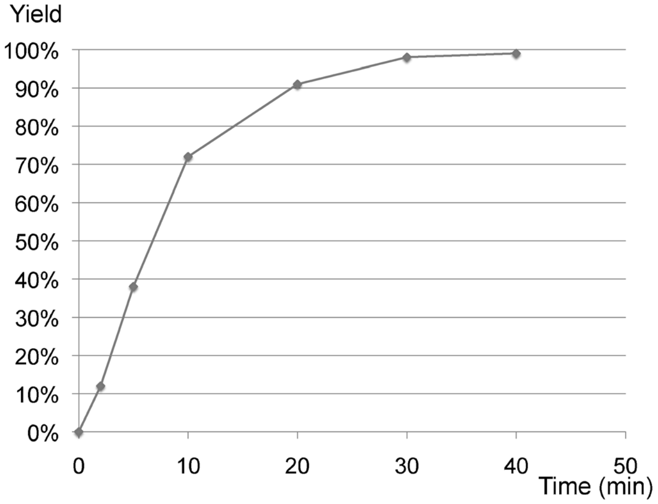


Figure 3. Kinetic study of the Suzuki–Miyaura reaction between 4-bromoacetophenone and phenylboronic acid. The reaction reaches a quantitative yield in 30 min.

Concentration Study

A study of the influence of the concentration has been conducted in order to optimize the reaction conditions (Table 2). It shows that a total volume of the solvent mixture in the range 5–10 mL is necessary for optimized reactions.

The results show that the reaction with 10 ppm Pd (PdNPs) is nearly quantitative with several bromoarenes; therefore the minimal quantity of catalyst necessary for the reaction with the most reactive substrate, 4-bomoacetophenone, has been investigated (Table 3).

The series of TONs data obtained here in Suzuki–Miyaura reactions with various bromoarenes are very

Table 2. Influence of the volume of the solvent mixture EtOH/H_2O: 1/1 on the yield of the Suzuki–Miyaura reactions between 4-bromoacetophenone and phenylboronic acid.[a]

Total volume [mL]	Yield of the reaction [%]
0.2	48
2	90
5	99
10	99
20	60
40	50

[a] The reactions have been carried with 0.001 mol% PdNPs at 80 °C during 1 h.

Table 3. Influence of the PdNPs loading on the TONs and TOFs of the Suzuki–Miyaura reactions between 4-bromoacetophenone and phenylboronic acid.[a]

Entry	Time [h]	Pd [mol%]	Yield [%]	TON; TOF [h^{-1}]
13	0.5	0.001	99	99,000; 198,000
14	2	0.0005	99	198,000; 99,000
15	16	0.0001	99	990,000; 61,875
16	24	0.00005	–	–

[a] All the reactions have been carried out in 10 mL of H_2O/EtOH (1/1) with 1 mmol of 4-bromoacetophenone, 1.5 mmol of phenylboronic acid and 2 mmol of K_3PO_4 at 80 °C.

good in comparison with literature results reported in Table 4, and the TOFs obtained here are superior to those obtained with PdNPs stabilized by dendrimer **6** (Table 5).

In Table 4, the literature data found for Miyaura–Suzuki cross-coupling reactions of bromoarenes in aqueous solutions are summarized, indicating that the PdNP catalysts reported here are among the very best ones reported so far.

Interestingly, the PdNPs stabilized by polymer **5** provide lower TONs, but better TOFs than those with dendrimer **6**. The better TONs obtained with the dendrimer **6** than with the polymer **5** are taken into account by a better protection by encapsulation of the PdNPs in the dendrimer,[10e] whereas the better TOFs obtained with the polymer result from freer access of the substrates to the PdNP surface. See the comparative findings between PdNP stabilized by the dendrimer **6** and PdNP stabilized by **5** (Table 5).

The advantage of this system in comparison with dendrimer **6** is that the polymer needs only one simple synthetic step, and that PdNPs stabilized by the polymer **5** are almost as active for the Suzuki–Miyaura coupling as the dendrimer **6** but with the particular feature of a faster reaction (higher TOFs).

Table 4. Comparison of literature results obtained with PdNP catalysts in aqueous medium for the Miyaura–Suzuki reactions of bromoarenes.

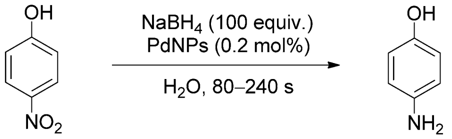
R[ref.]	Catalyst	Temp. [°C]	TON	TOF [h^{-1}]
4-COMe[12a]	PSSA-co-MA-Pd(0)	100	99	1980
4-OMe[12b]	Pd-SDS	100	38	456
4-OMe[12c]	Pd-PVP (MTPs)	100	1680	1680
4-COMe[12d]	Pd-PEG	25	98	49
4-COMe[12e]	Pd-1/FSG	100	950	119
4-OMe[12f]	Fe_3O_4-Pd	50	144	12
4-OMe[12g]	pEVPBr-Pd	90	340	38
4-OMe[12h]	Pd-PS	100	50	10
4-COMe[12i]	HAP-Pd(0)	100	156	39
4-OMe[12j]	$PdCl_2(py)_2$@SHS	60	4681	14050
4-COMe[10d]	Pd/IL	120	970	970
4-OMe[12k]	Pd-MEPI	100	24250	8083
4-COMe[10c]	Pd-salt	90	4250	1062
4-OMe[12l]	Pd@PNIPAM	90	300	30
4-COMe[4c]	Pdx- $([PW_{11}O_{39}]^{7-})_y$	80	92	8
4-OMe[12m]	Pd-block-co-poly	90	310	31
4-COMe[12n]	Pd-G3-p3	80	85000	2125
4-COMe[12o]	Pd@CNPCs	50	990	3960
4-COMe[12p]	Pd-PPy/PS	80	230	77
4-COMe[10a]	PS-PdONPs	80	66	66
4-Me[10b]	Pd-TiO_2	80	115	29
4-OMe[12q]	Pd@PMO-IL	75	475	95
4-NH_2[12r]	Pd-XH-15-SBA	90	96	7
4-OMe[12s]	Pd^{2+}-G0	80	386	99
4-Me[12t]	Pd(0)/Al_2O_3-ZrO_2	60	45	12
4-OMe[12u]	$Pd(OAc)_2$/L	100	19600	2800

Table 5. Comparison between the properties of the PdNPs stabilized by dendrimer **6** properties and those of the PdNPs stabilized by **5**.

Support: Properties	Dendrimer **6**	Polymer **5**
Size PdNP	1.4 ± 0.7 nm	1.6 ± 0.3 nm
TON (Suzuki–Miyaura)	2.7×10^6	9.9×10^5
TOF (Suzuki–Miyaura)	4.5×10^4 h^{-1}	1.98×10^5 h^{-1}
Storage	Several months	Several weeks
Air stable	yes	yes
Easy synthesis of the support	yes	yes
Synthesis of the support	8 steps	1 step

Reduction of 4-Nitrophenol to 4-Aminophenol

The high efficiency of PdNPs described above in the Suzuki–Miyaura-catalyzed C–C coupling and the fact that the rate of this catalysis clearly depends on the size of the nanoparticles led to the idea that such catalysts might also be efficient for nitrophenol reduction. This reaction is very fast and simple, with the advantage of the possibility of monitoring by UV-vis.



(3)

spectroscopy. Indeed, a typical peak at 400 nm is directly linked to 4-nitrophenol (corresponding to 4-nitrophenolate that instantaneously appears in the presence of NaBH$_4$) and at 300 nm to 4-aminophenol. The disappearance of the yellow colour in the solution shows the reaction progress. The reduction of 4-nitrophenol has been carried out in the presence of an excess of NaBH$_4$ (100 equiv.) and 0.2 mol% of PdNPs/**5** in water in the presence of catalytic amounts of Pd from the above PdNPs.

The reaction is completed in 240 seconds, which corresponds to a K_{app} value of $6.0 \times 10^{-3}\ s^{-1}$ (Figure 4). When the reduction of 4-nitrophenol is carried out in a concentration that is increased four times, the K_{app} value is nearly ten times higher ($K_{app} = 5.5 \times 10^{-2}\ s^{-1}$), and the reaction is completed in less than 80 seconds. The reaction rate constant K_{app} is calculated using the rate equation $-\ln(C_t/C_0) = K_{app} \cdot t$ (the catalyst exhibits a pseudo-first order kinetics).

The results obtained with the catalyst **5** are among the best results ever recorded (here only Pd catalysts have been compared in Table 6, but Au catalysts are less impressive too) in terms of high TOF values, low amounts of catalyst and similar to the literature in term of rate constant K_{app}.

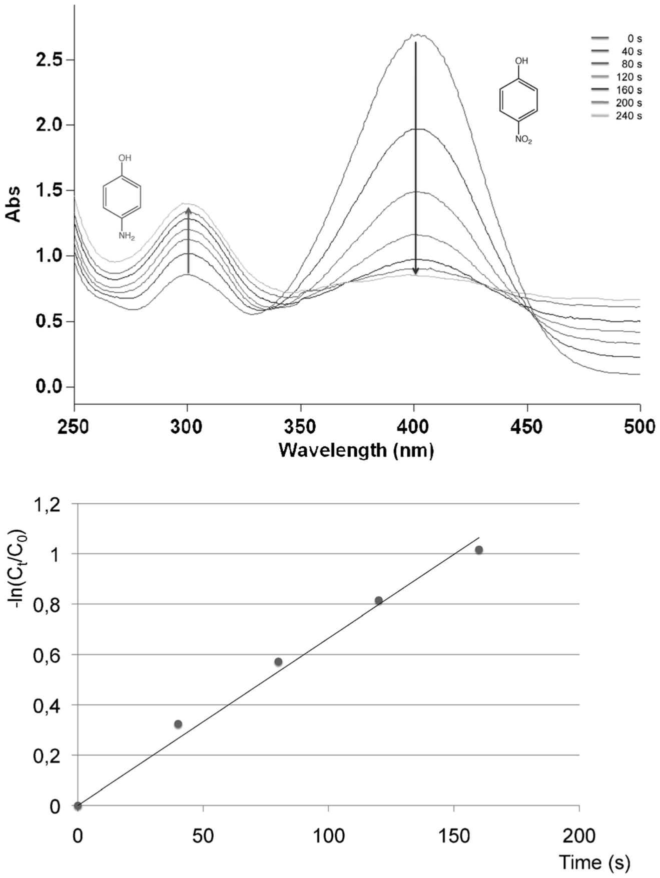


Figure 4. Kinetic study of the 4-nitrophenol reduction by NaBH$_4$ using UV-vis. spectroscopy at 400 nm (*top*) and plot of $-\ln(C_0/C_t)$ *vs.* time (s) for its disappearance (*bottom*).

Concluding Remarks

The polymer **5** has been synthesized by a "click" reaction between commercial PEG diazide and PEG diyne and shown to be a very good stabilizer of PdNPs of 1.6 nm diameter in comparison with PEG 2000 that leads to PdNP aggregation. The combination of triazolyl rings and PEG offers a compromise for an excellent activity in the Suzuki–Miyaura reaction of bromoarenes in EtOH:H$_2$O = 1:1 with a very low amount of catalyst confirming results with the triazolyl-TEG dendrimer **6**. The use of only 1 ppm Pd leads to a quasi-quantitative reaction with 4-bromoacetophenone (entry 15, Table 3 TON: 990,000), and by increasing the amount of catalyst, this reaction is complete in 30 min. The results obtained in the reduction of 4-nitrophenol are also ex-

Table 6. Comparison of literature results obtained with PdNP catalysts for the reduction of 4-nitrophenol in water.

Catalyst/support	Pd [mol%]	Size Pd [nm]	NaBH$_4$ [equiv.]	K_{app} [s^{-1}]	TOF [h^{-1}]
CNT/PiHP[14a]	4	2.7	80	5×10^{-3}	300
Fe$_3$O$_4$[14b]	10	16.9 ± 1.3	139	3.3×10^{-2}	300
PEDOT-PSS[14c]	77	< 9	excess	6.6×10^{-2}	13
SPB[14d]	0.36	2.4 ± 0.5	100	4.41×10^{-3}	819
Microgels[14e]	2.1	3.8 ± 0.6	100	1.5×10^{-3}	139
PPy/TiO$_2$[14f]	2.6	2.0	11	1.22×10^{-2}	326
SBA-15[14g]	100	~8	1000	1.2×10^{-2}	6
CeO$_2$[14h]	0.56	3–5	83	8×10^{-3}	1 068
5	0.2	1.6	100	6×10^{-3}	7 500
5	0.2	1.6	100	$5.5x\ 10^{-2}$	22 500

cellent. Macromolecules such as dendrimer **6** or polymer **5** are outstanding for a compromise between stabilization and catalytic activity of PdNPs, whereas small molecules such as the oligomer **3** are not sufficiently efficient stabilizers to provide active PdNPs. This is due to the fact that PdNPs can take shelter in the holes of the dendrimer or can be enveloped by several polymer molecules **5**. The comparison between the triazole-containing dendrimer **6** and polymer **5** interestingly shows that the polymer provides higher TOF values because of freer access than the dendrimer, whereas the higher protection in the dendrimer interior offers higher TONs than with the polymer due to the better PdNP protection.

The extremely low amount of Pd catalyst and the biocompatibility of the PEG polymers opens an access to biological applications without the need for treatment of the product in order to remove the metal. The multi-gram scale reaction reported here is also very useful for potential industrial applications of the Miyaura–Suzuki reactions of bromoarenes, especially given their modest cost among the halogenoarenes.

Experimental Section

General Data

All the solvents (THF, EtOH, DMF, CH_2Cl_2, Et_2O) and chemicals were used as received. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C with a Bruker AC 200, 300 or 400 (200, 300 or 400 MHz) spectrometer. All the chemical shifts are reported in parts per million (δ, ppm) with reference to Me_4Si (TMS) for the ^{1}H NMR spectra. The infrared (IR) spectra were recorded on an ATI Mattson Genesis series FT-IR spectrophotometer. Size exclusion chromatography (SEC) of the polymer **5** was performed using a JASCO HPLC pump type 880-PU, TOSOHAAS TSK gel columns (G4000, G3000, G2000 with pore sizes of 20,75, and 200 Å respectively, connected in series), a Varian (series RI-3) refractive index detector, with DMF as the mobile phase and calibrated with polystyrene standard. MALDI-TOF mass spectra were recorded with a PerSeptive Biosystems Voyager Elite (Framingham, MA) time-of-flight mass spectrometer. This instrument is equipped with a nitrogen laser (337 nm), a delayed extraction, and a reflector. It was operated at an accelerating potential of 20 kV in both linear and reflection modes. The mass spectra shown represent an average over 256 consecutive laser shots (3 Hz repetition rate). Peptides were used to calibrate the mass scale using the two points calibration software 3.07.1 from PerSeptive Biosystems. Mentioned *m/z* values correspond to monoisotopic masses. Elemental analysis (EA) results were obtained with a Thermo Flash 2000 EA; the sample is introduced in a tin container for CHS analysis.

Synthesis of the PEG-bis-triazolyl Oligomer 3

Bisazide **1** (0.122 g, 0.5 mmol) and **2** (0.202 g, 1 mmol, 2 equiv.) were dissolved in 2 mL THF in a Schlenk tube. $CuSO_4{\cdot}5H_2O$ was added (0.0048 g, 0.02 mmol, 0.04 equiv.) after dissolving in 1 mL of water, followed by the dropwise addition of a freshly prepared solution of sodium ascorbate (0.0124 g, 0.1 mmol, 0.1 equiv.) in order to set a 1:1 THF:water ratio. The reaction mixture was stirred for 2 days at 25 °C under N_2. After removing THF under vacuum, CH_2Cl_2 (100 mL) and an aqueous ammonia solution (2.0 M, 50 mL) were successively added. The mixture was allowed to stir for 10 min in order to remove all the Cu(II) trapped inside the trimer as $[Cu(NH_3)_2(H_2O)_2]$ $[SO_4]$. The organic phase was washed twice with water. The organic phase was dried with sodium sulfate, and the solvent is removed under vacuum to afford **3**; yield: 0.290 g (90%). The product was fully characterized by ^{1}H NMR, ^{13}C NMR, HSQC, ESI, EA (see the Supporting Information).

Synthesis of Triazolyl-PEG Polymer 5

Bisazide **1**[13] (0.244 g, 1 mmol) and **4**[13] (0.270 g, 1 mmol, 1 equiv.) were dissolved in 1 mL DMF in a Schlenk tube. CuBr was added in the vessel (0.0102 g, 0.05 equiv.). The reaction mixture was stirred for 2 days at 40 °C under N_2. The solution was then added to 200 mL of Et_2O in order to precipitate the polymer formed. The precipitate was filtered, and CH_2Cl_2 (100 mL) and an aqueous ammonia solution (2.0 M, 50 mL) were successively added. The mixture was allowed to stir for 10 min in order to remove all the Cu(II) trapped inside the polymer as $[Cu(NH_3)_2(H_2O)_2]$ $[SO_4]$. The organic phase was washed twice with water, then this operation was repeated once more to ensure the complete removal of copper ions. The organic phase was dried with sodium sulfate, and the solvent was removed under vacuum to afford **5**; yield: 0.410 g (80%). The product has been fully characterized by ^{1}H NMR, ^{13}C NMR, IR, MALDI TOF, DLS, SEC (see the Supporting Informatoin).

Preparation of the PdNPs for Catalysis

a): 1.62×10^{-2} mmol of polymer triazolyl PEG **5** (dimer MW = 514 g.mol^{-1}, 0.8368 mg) were dissolved in 0.3 mL of water in a Schlenk flask, and an orange solution of K_2PdCl_4 (3.2×10^{-5} mmol in 0.11 mL water) was added to the solution of **5**. Then 2.8 mL of water were added, and the solution was stirred for 5 min at 20 °C. 0.1 mL of an aqueous solution containing 3.2×10^{-4} mmol of $NaBH_4$ was added dropwise, provoking the formation of a brown/black colour corresponding to the reduction of Pd(II) to Pd(0) and PdNP formation [Figure S13 in the Supporting Inromation shows the full reduction of Pd(II) in Pd(0)]. The use of $NaBH_4$ is essential in order to obtain small, active PdNPs for efficient catalysis. When PdNPs are formed *in situ* (without $NaBH_4$) during the Suzuki–Miyaura reaction, the catalytic activity of the PdNPs is much lower. The same reaction as entry 13 was carried out with PdNPs formed *in situ*, and 22 h were needed for a quantitative reaction instead of 2 h with PdNPs reduced by $NaBH_4$.

b): 1.3×10^{-3} mmol of oligomer PEG **3** (MW = 648 g.mol^{-1}, 0.8368 mg) were dissolved in 0.3 mL of water in a Schlenk flask, and an orange solution of K_2PdCl_4 (3.2×

10^{-5} mmol in 0.11 mL water) was added to the solution of **5**. Then 2.8 mL of water were added, and the solution was stirred for 5 min at 20 °C. 0.1 mL of an aqueous solution containing 3.2×10^{-4} mmol of $NaBH_4$ was added dropwise, provoking the formation of a brown/black colour that corresponds to the reduction of Pd(II) to Pd(0) and PdNP formation.

The stoichiometry, 10 triazolyl groups per Pd(II), is necessary in order to avoid PdNPs aggregation. When the stoichiometries 1:1, 2:1, and 5:1 are used, PdNPs precipitate after several hours due to aggregation.

General Procedure for the Suzuki–Miyaura Catalysis

In a Schlenk flask containing tribasic potassium phosphate (2 equiv.), phenylboronic acid (1.5 equiv.), the aryl halide (1 equiv.) and 5 mL of EtOH (volume ratio of H_2O:EtOH = 1:1) were successively added. Then the solution containing the PdNPs was added. The suspension was allowed to stir under N_2 or air. After the reaction time (see Table 1), the reaction mixture was extracted twice with diethyl ether (Et_2O; all the reactants and final products are soluble in Et_2O), the organic phase was dried over Na_2SO_4, and the solvent was removed under vacuum.

In parallel, the reaction was checked using TLC in only petroleum ether as eluent in nearly all the cases, and ^{1}H NMR. Purification by flash chromatography column was conducted with silica gel as stationary phase and petroleum ether as mobile phase. Another purification procedure consists in cooling the Schlenk flask at the end of the reaction. The product precipitates, and a simple filtration allows one to obtain the product that is then washed with a cold solution of H_2O/EtOH (this is not the case of all the bromoarenes). With 1 ppm of catalyst, the reuse of the catalyst shows a very slow reaction, which indicates that after 24 h hours at 80 °C the catalyst is deactivated in solution. The aqueous phase obtained after filtration cannot be reused, because the polymer-stabilized catalyst is not stable for a long time.

After each reaction, the Schlenk flask was washed with a solution of aqua regia (3 volumes of hydrochloric acid for 1 volume of nitric acid) in order to remove traces of Pd. All the reactions have been carried out with 1 mmol of bromoarene. Three other reactions with 15 mmol of bromoarenes have been conducted in order to check the efficiency of the system on a multigram scale. The yields obtained with 15 mmol of bromobenzene, 1,4-nitrobenzene or 4-bromoacetophenone are the same as that obtained with 1 mmol.

General Procedure for the Reduction of 4-Nitrophenol

In a beaker, 7 mg of 4-nitrophenol (5.03×10^{-5} mol) were mixed with 195 mg of $NaBH_4$ (5.13×10^{-3} mol) in 20 mL water, 1 mL of PdNPs was added to the reaction mixture (0.2 mol%), and the reaction was completed in 80 seconds. Alternatively, 0.5 mL of the total solution was diluted with 1.5 mL of water before the reaction started in order to follow the reaction by UV-vis. spectroscopy. This reaction was complete in 240 seconds.

Purification by Flash Chromatography of the Coupling Products of the Suzuki–Miyaura Reactions

Biphenyl (white powder): reaction between bromobenzene and phenylboronic acid was followed by simple flash chromatography with petroleum ether as mobile phase and silica as stationary phase; yield: 152 mg (99%) when 1 mmol of bromoarene is used.

4-Methylbiphenyl (colourless crystals): reaction between 4-bromotoluene and phenylboronic acid was followed by simple flash chromatography with petroleum ether as mobile phase and silica as stationary phase; yield: 166 mg (99%) when 1 mmol of bromoarene is used.

4-Methoxybiphenyl (white powder): reaction between bromoanisole and phenylboronic acid was followed by flash chromatography with petroleum ether as mobile phase and silica as stationary phase at the beginning and then 95% petroleum ether/5% diethyl ether; yield: 183 mg (99%) when 1 mmol of bromoarene is used.

4-Nitrobiphenyl (yellow crystals): reaction between 1,4-bromonitrobenzene and phenylboronic acid is followed by flash chromatography with 95% petroleum ether/5% dichloromethane as mobile phase and silica as stationary phase; yield: 197 mg (99%) when 1 mmol of bromoarene is used.

4-Biphenylcarboxaldehyde (light yellow crystals): reaction between bromobenzaldehyde and phenylboronic acid was followed by flash chromatography with 95% petroleum ether/5% dichloromethane as mobile phase and silica as stationary phase; yield: 164 mg (90%) when 1 mmol of bromoarene is used.

p-Terphenyl (white powder): reaction between 1,4-dibromobenzene and phenylboronic acid was followed by simple flash chromatography with petroleum ether as mobile phase and silica as stationary phase; yield: 226 mg (908%) when 1 mmol of bromoarene is used.

4-Acetylbiphenyl (white powder): reaction between 4-bromoacetophenone and phenylboronic acid was followed by flash chromatography with 95% petroleum ether/5% diethyl ether as mobile phase and silica as stationary phase; yield: 195 mg (99%) when 1 mmol of bromoarene is used.

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Efficient Click-Polymer-Stabilized Palladium Nanoparticle Catalysts for Suzuki–Miyaura Reactions of Bromoarenes and Reduction of 4-Nitrophenol in Aqueous Solvents

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