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# ARTICLE TYPE

### "Click" dendrimers as efficient nanoreactors in aqueous solvent: Pd nanoparticles stabilization for sub-ppm Pd catalysis of Suzuki-Miyaura reactions of aryl bromides

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Palladium nanoparticles (PdNPs) with a size of 1.4 nm are stabilized by dendritic nanoreactors containing 1,2,3-triazole ligands with hydrophilic triethylene glycol (TEG) termini. These PdNPs are stable for months under air and are extremely active for the Suzuki-Miyaura reaction of aryl bromides down to subppm level.

The concept of nanoreactor arose in the early 1970's with 15 Breslow's seminal work on artificial enzymes based on transition-metal complexes derivatives of cyclodextrins<sup>1</sup>, and has more recently been elegantly persued with appropriately designed supramolecular containers.<sup>2</sup> Crooks' group has pioneered catalysis by PAMAM-encapsulated Pd nanoparticles (PdNPs),<sup>3</sup> 20 and these PdNPs as well as various other polymer- and inorganic substrate-stabilized PdNPs are good catalysts for Suzuki-Miyaura reactions of aryl iodides and activated bromides with Pd catalyst amounts of the order of 10<sup>-1</sup>-10<sup>-2</sup> mol %.<sup>4</sup> Such reactions are useful, especially with aryl bromides, because they are usually 25 inexpensive and often cheaper than aryl chlorides. The Suzuki-Miyaura' cross-coupling reaction has indeed become one of the most powerful synthetic methods for preparing biaryl compounds, such as natural products, pharmaceuticals and polymers etc. Another important issue is the use of minimum 30 amounts of catalysts, because metal contamination tolerated in organic products does not overtakes a few ppm. Along this line only very few authors have reported PdNPs than can be active with 10<sup>-3</sup> Pd mol %.<sup>6</sup> Among them, we have already noted that click ferrocenyl dendrimers<sup>6b</sup> can catalyze this reaction of aryl 35 iodides with quite good TONs, but very low TOFs.

We now report that when such dendrimers are terminated by triethyleneglycol groups, the PdNPs are stabilized, retain their catalytic activity for months and present an extraordinary activity even in air, for the first time down to the sub-ppm level of Pd as

- <sup>40</sup> pre-catalysts for the Suzuki-Miyaura reactions of aryl bromides in 50% EtOH/water, a "green" solvent. Moreover, these dendrimers are easily recycled. Such reactions can also be conducted on multi-gram scales with the same very high TONs and optimized efficiency, which is promising in view of industrial applications.
- <sup>45</sup> The water-soluble click dendrimers **1** and **2** have been synthesized and are represented in Figure 1. They contain respectively 9 (for G0) and 27 (for G1) 1,2,3-triazolyl groups linking the dendritic core to Percec-type dendrons<sup>7</sup> and respectively 27 and 81 TEG termini. The dendrimer **1** is already
- <sup>50</sup> known,<sup>8</sup> whereas the new dendrimer 2 has now been synthesized via "click" chemistry (see S.I.; elemental analysis: calcd for C<sub>1125</sub>H<sub>1947</sub>N<sub>81</sub>O<sub>360</sub>Si<sub>36</sub>: C57.79, H8.39, N4.85, found C57.78,

H8.32, N4.82). Inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis confirms the indication of <sup>55</sup> elemental analyses according which Cu ions used for click syntheses of these dendrimers have been totally removed (< 0.1 ppm, the ICP-OES detection limit).



Figure 1. Dendrimer G0-27 TEG 1 (up) and dendrimer G1-TEG 2 (down).

PdNPs are stabilized in water by **1** and **2** after reduction of Pd<sup>II</sup> in <sup>130</sup> Pd<sup>0</sup>. Firstly the dendrimer-Pd<sup>II</sup> complexes are synthesized in water by adding to the dendrimer one equiv.  $K_2PdCl_4$  per dendritic triazole group (the optimized stoichiometry for further

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PdNP catalysis). The nature of the Pd<sup>II</sup> complexation sites in the dendrimer has been examined by UV-vis. spectroscopy. An absorption band is observed at 217 nm when K<sub>2</sub>PdCl<sub>4</sub> is added to the dendrimer in water (figure 2), which is assigned to a ligands to-metal charge transfer (LMCT) transition of Pd<sup>II</sup>. Here, it is associated to the complexation of the metal interior.

associated to the complexation of the metal ions to the interior triazole of 1 (S.I.). Previously, a band at 225 nm has already been associated to the complexation of Pd<sup>II</sup> to the intradendritic tertiary amine of the PAMAM dendrimer.<sup>3a,3c</sup>



<sup>10</sup> **Figure 2.** UV-vis. spectra of Pd(II) salt, 1/ Pd<sup>II</sup> complex and PdNPs stabilized by 1. The three spectra have been recorded using 1 as a blank.

Then reduction of Pd<sup>II</sup> (1 equiv. per triazolyl group) to Pd<sup>0</sup> is <sup>15</sup> carried out in aqueous solution using 10 equiv. NaBH<sub>4</sub> per Pd (see the color change in the S.I.). Finally, dialysis is conducted for 1 day in order to remove excess NaBH<sub>4</sub> and eventually purify the PdNPs from any Pd derivatives. Thereafter, ICP-OES analysis indicates that the Pd loading in the PdNPs is 96% of starting Pd. <sup>20</sup> It is known that NaBH<sub>4</sub> inhibits catalytic activity by the formation

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of borides at the particle surface,<sup>6c</sup> but this is not the case in aqueous media, because the borohydride is then fully hydrolyzed. Catalysis results (*vide infra*) are the same with and without dialysis, however, thus dialysis is not indispensible in view of <sup>25</sup> catalysis experiments. So after reduction of Pd<sup>II</sup> in PdNPs, the water solution of PdNPs is ready for catalysis experiments.

The polydispersities of these PdNPs shown by DLS are good, and the TEM and HRTEM (S.I.) reveal that the PdNPs are very small,  $1.4 \pm 0.7$  nm in 1 (Figure 3 and S.I. troncaded bipyramid, 100

- atoms per NP) and 2.7 nm  $\pm$  1 nm in **2** (S.I. figure S4) thus of optimal size for their use in catalysis. The hydrodynamic diameters of the TEG dendrimers determined by DOSY NMR and DLS are 5.5  $\pm$  0.2 nm<sup>8</sup> and 9 nm respectively for 1 and 13.2  $\pm$  0.2 nm and 16 nm respectively for **2** (S.I.). The actual size is best
- <sup>35</sup> reflected by the DOSY NMR values, and it is expected that the DLS values take into account the water solvation around the dendrimers that increases the apparent dendrimer size. These DLS values are much larger than what is expected for a single dendrimer, which means that a number of dendrimers aggregate
- <sup>40</sup> in water to form a supramolecular assembly of dendrimers. The aggregation of TEG dendrimers is facilitated by the amphiphilic nature of the TEG termini so that the TEG-terminated dendrimers interpenetrate one another because of the supramolecular forces attracting the TEG tethers among one another. What is
- <sup>45</sup> remarkable is that, when the PdNPs are formed, the DLS size value considerably increases for G0 from 9 nm to 31 nm, whereas it only increases from 16 nm to 18 nm for G1 (see S.I. figure S7). This strongly argues for a full encapsulation of the stabilized PdNPs for the large dendrimer G1 that undergoes a modest size <sup>50</sup> change upon PdNP formation and, on the opposite, for an
- assembly of small dendrimers 1 (11\*1/PdNPs) stabilizing a PdNP. Note that the PdNPs stabilized by the TEG dendrimers are stable under air condition for several months without any sign of

aggregation and that the size determined by TEM and the ss catalytic activity (vide infra) remain the same after such prolonged periods of time (see S.I. figure S3). View Article Online DOI: 10.1039/C3CC45132A





The Suzuki-Miyaura reactions were conducted in  $H_2O/EtOH$ : 1/1 with iodo-, bromo- and chloroarenes (equation (1)).



As the Suzuki-Miyaura coupling works very well at 28°C with 65 iodoarenes even with less than 1 ppm of Pd‡ we decided to focus on bromoarenes

**Table 1.** Isolated yields and TONs for the catalysis by G0 PdNPs of the Suzuki-Miyaura reactions beween bromoarenes  $[p-RC_6H_4Br]$  and phenylboronic acid.

R	entry	Pd (%)	Time (h)	Yield (%)	TON
Н	1	0.1	15	99	990
	2 <sup>b</sup>	0.1	96	66	660
	3	0.01	24	99	9900
	4 <sup>a,c</sup>	0.0001	60	99	990000
CH <sub>3</sub> O	5	0.1	15	94	940
	6	0.01	24	99	9900
	7	0.001	24	60	60000
	8	0.001	48	99	99000
	9	0.0001	60	63	630000
NH <sub>2</sub>	10	0.1	15	96	960
	11	0.01	24	31	3100
	12	0.01	48	40	4000
NO <sub>2</sub>	13	0.1	15	99	990
	14 <sup>b</sup>	0.1	240	80	800
	15	0.001	24	87	87000
	16	0.001	36	98	98000
	17 <sup>c</sup>	0.0001	60	91	910000
	18 <sup>a</sup>	0.00003	60	82	2700000
CH <sub>3</sub>	19	0.1	24	99	990
	20	0.001	48	99	99000
	21	0.0001	48	46	460000
СНО	22	0.1	24	99	990
	23	0.01	24	80	8000
	24	0.001	24	20	20000
Each reactio	n is cond	lucted with 1	mmol bror	noarene, [p-]	RC <sub>6</sub> H <sub>4</sub> Br] in
0.05 M as final concentration, 1.5 mmol of phenylboronic acid and 2					
equiv. K <sub>3</sub> PO <sub>4</sub> in EtOH/H <sub>2</sub> O (10mL/10mL) at 80°C. <sup>a</sup> : same conditions					
but in EtOH/H <sub>2</sub> O (5mL/5mL), $C[RC_6H_4Br] = 0.1$ M. <sup>b</sup> : standard					
conditions but at 28°C instead of 80°C. "The reaction is also conducted					
on a larger scale (10 g of $p$ -RC <sub>6</sub> H <sub>4</sub> Br), leading to similar isolated vields.					

The G0-PdNP catalyst is extremely active and efficient for the Suzuki-Miyaura coupling reactions of bromoarenes even at 28°C. At 80°C, the reaction between 1,4-bromonitrobenzene and phenyl boronic acid with only 0.3 ppm of Pd reaches a TON of 2.7 x  $10^6$  after 2.5 days (TOF = 4.5 x  $10^4$  h<sup>-1</sup>). With only 1 ppm of Pd from

the G0-PdNP catalyst, the cross-coupling with phenylboronic acid is quantitative with bromobenzene: TON =  $0.99 \times 10^6$ ; TOF =  $1.65 \times 10^4 \text{ h}^{-1}$ , and the yield is 63% for 1,4-bromoanisole (TON =  $0.63 \times 10^6$ ; TOF =  $1.05 \times 10^4 \text{ h}^{-1}$ ).

- <sup>5</sup> The results of the Suzuki-Miyaura reactions of bromoarenes are gathered in Table 1. In conclusion, for bromoarenes, the TONs are very impressive at 80°C, sometimes even larger than 10<sup>6</sup>. Concerning the G1-PdNP catalyst, reactions under the same conditions as in Table 1, (80°C, 2.5 days) between bromoarenes
- <sup>10</sup> and phenylboronic acid using 1 ppm Pd give yields of 20% with bromobenzene, 27% with bromoanisole and 39% with 1,4bromonitrobenzene. The catalytic efficiency of G1-PdNPs is lower than that of the G0-PdNPs, which is taken into account by the fact that PdNPs prepared in G1-81 TEG **2** are larger than that
- <sup>15</sup> in G0-27 TEG 1. This also is in accord with the leaching mechanism.<sup>4e</sup> With chloroarenes, the results with G0 are less impressive than with the other halogenoarenes, because high temperatures (> 100°C) are required to activate chloroarenes under these conditions, and at such temperatures these PdNPs
- <sup>20</sup> aggregate more rapidly that the activation reactions.

#### Conclusions

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In conclusion, the TEGylated click dendrimer assemblies represent a new type of nanoreactors for PdNPs that provide <sup>25</sup> stability and catalytic activity during several months without the strain of inert atmosphere. The TEG termini of the dendrimer tethers are responsible for this high degree of intradendritic PdNP stabilization, because they interact interdendritically to form large assemblies. The intradendritic PdNPs are loosely liganded by the

- <sup>30</sup> 1,2,3-triazoles, which present an excellent compromise between stabilization and lability for an optimized catalytic activity. The catalytic activity of these PdNPs is exceptionally high with bromoarenes, reaching TONs that are equal to or larger than 10<sup>6</sup> never reached with PdNPs stabilized with ferrocene<sup>6c</sup> or
- <sup>35</sup> sulfonated<sup>6d</sup> dendrimers' termini, which enhances the role of the TEG termini (see S.I. table S4). The catalyst 1-PdNPs is the most active for the Suzuki-Miyaura reaction in aqueous solvent, in terms of TONs for bromoarenes,<sup>4-6</sup> (see S.I. table S3) with longstanding catalytic activity on multi-gram scales of <sup>40</sup> substrates. We suggest that the reasons for this exceptional catalytic activity of the dendritic nanorector 1 are (i) the loose intradendritic stabilization of PdNPs by the triazole ligands
- combined with the inter-dendritic assembly provided by the TEG termini better protects the PdNPs than a single dendrimer, (ii) the <sup>45</sup> leaching mechanism<sup>4c</sup> generates very active Pd atoms in solution that are less easily quenched by the mother PdNPs because of the protection by the nanoreactor, and (iii) the leaching is easier for
- protection by the nanoreactor, and (iii) the leaching is easier for small PdNPs ( $1.4 \pm 0.7$  nm, truncated bipyramid, high proportion of reactive Pd atoms on the edges and summits) than for larger <sup>50</sup> ones. As a consequence, extremely high TONs are reached,
- <sup>50</sup> ones. As a consequence, extremely high TONs are reached, because the catalytic activity is retained at extremely high substrate/catalyst ratios. Finally, these water-soluble dendrimers are very stable and easy to recover<sup>8</sup> whenever needed when they are used in substantial quantity, and they can indefinitely be re-<sup>55</sup> used.

### Notes and references

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- In the case of iodobenzene, the Suzuki-Miyaura react **View Articles** at 28°C even with a very small quantity of Pd (PANPs stabilized by G0-27)
- TEG), down to 3 x  $10^{-5}$  mol %, i.e. 0.3 ppm Pd in 80% yield (TON = 2.7 x  $10^{6}$ ; TOF = 2.8 x  $10^{4}$  h<sup>-1</sup>.
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