Nano-Organocatalysts: new magnetically retrievable tools for enantioselective synthesis

E.Nehlig*, L. Motte* and E.Guénin*

*Université Paris 13, Sorbonne Paris Cité, Laboratoire CSPBAT, UMR CNRS 7244
Bureau 330, 74 rue Marcel Cachin, 93017 Bobigny,France, e.nehlig@gmail.com

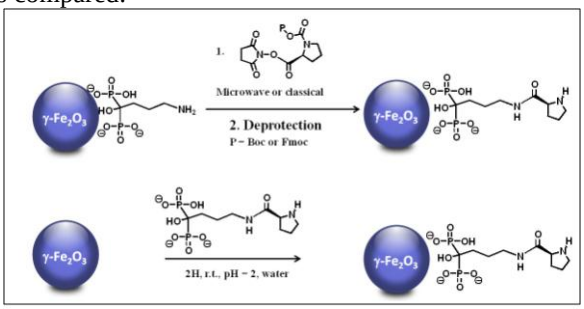
ABSTRACT

Magnetic nanoparticles (mNPs) are attractive candidates for organocatalysis due to there easy removing process. For this kind of application it is crucial to well defined mNPs's surface and to perfectly master the amount of organocatalysts anchoring. That's why synthesis of new anchoring coating agent with an organocatalytic activity is attractive. We report here the elaboration of new organocatalyst functionalized superparamagnetic iron oxide nanoparticles that can act as enantioselective organocatalyst. L-Proline, a well known organocatalysts is grafted using two different methodologies on a nanoplateform constituted of 10 nm maghemite (γFe_2O_3) nanoparticles stabilized by bidendate coating agent such as bisphosphonates (hydroxymethylene bisphosphonic acids (HMBP)). The "grafting to" methodology was also tested in order to modulate the number of catalysts per particles.

Keywords: organocatalysis, nanocatalysts, magnetic nanoparticles, enantioselective reactions, bisphosphonates

1 INTRODUCTION

In Biological and pharmaceutical domains, active molecules often possess one or several stereocenters which are of crucial importance for their activity. The control of the stereoselectivity in the synthesis of active biological molecules[1,2] is therefore a necessity. Interest for stereoselective reaction increase greatly and in the past decades new catalysts were described for an increasing number of stereoselectives organics reactions. Nevertheless, most of the homogenous catalysts are difficult to adapt to industrial process due to separation and regeneration problems. Moreover, though highly efficient, most of the catalysts are containing noble or toxic metals and so new protocols more economically and environmentally friendly need to be developed. That's why organocatalysis[3-6] that uses small costless molecules as metal free catalyst under an aerobic atmosphere with wet solvents is enjoying a huge success. In order to be much more greener[7] and to reduce the amount of catalyst used, immobilize organocatalysts on nanoparticles[8, 9] represent a new challenge for reseachers. The use of magnetic nanoparticles as a catalysts support[10-13] in organic synthesis has become a subject of intense investigation during the last decade[14]. Nanoparticles functionalized with catalysts are used as robust catalyst combining high surface area thanks to their nanometric size, with excellent accessibility[15-21]. They appear as an ideal solution to simplify removing proccess and to reuse the precious catalysts. Magnetic nanoparticles are especially very attractive supports for catalysis as they are robust biocompatible and cheap material that can be removed by simple magnetically driven separation from the reaction solution. Here we report the elaboration and characterization of iron oxide superparamagnetic nanoparticles functionalized with the L-Proline organocatalyst[22]. These nanoparticles, are obtained from two methodologies: a grafting from, and a grafting to. The grafting from approach is consisting on grafting aminoprotected Prolines onto a nanoplateform bearing NH_2 functions at its surface (γFe_2O_3@Alendronate) through a peptidic bond. Two strategies for the amino-protection of the Proline were used (ter-butoxycarbonyl (Boc) and 9-Fluorenylomethoxycarbonyl (Fmoc)). Both classical and microwave[23] conditions were used for the coupling. The grafting to approach is based onto grafting onto mNPs 's surface of a bisphosphonate functionalized with L-Proline by simple ancoring in water (scheme1). This nanohybrids were compared to those obtained from the grafting from methodology.The number of catalysts per nanoparticles was evaluated, and efficency of functionalization startegies and was compared.



Scheme 1: Elaboration of the γFe_2O_3@Alendronate@Proline nanoparticles.

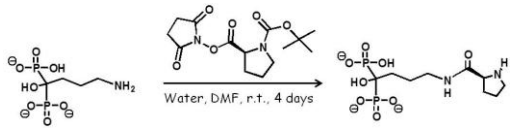
2 MATERIALS AND METHODES

Alendronate was synthesized following literature protocols[24]. Alendronate@Proline was synthesized by reacting for 72h Alendronate and an excess of commercial activated N-hydroxysuccinimide (NHS) ester Boc-L-Proline in a water/N,N dimethylformamide (DMF) mixture at room temperature. After washing with organic solutions

twice, the product was precipitated at acidic pH and washed several time. The desired product was obtained as a white powder and characterized by NMR, FTIR and HRMAS. The syntesis of γFe_2O_3 nanocrystals and their surface coating with hydroxy methylene bisphosphonate molecules was done as previously described[25-27]. Free HMBPs were removed from coated particles thanks to a magnetic field. The peptidic bond formation between Protected-Proline and γFe_2O_3@Alendronate was performed in water or water/DMF, in a two step procedure (activation and conjugation) at room temperature or assisted by microwaves. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and NHS were used as coupling agent. The deprotection step was performed with a CH_2Cl_2/trifluoroacetic acid (TFA) (1/1) mixture for Boc protection. For Fmoc removing, a classic mixture of DMF/piperidine (70/30) was used. UV-visible and IR spectra were respectively recorded on a Varian Cary 50 Scan UV-Visible spectrophotometer and on a Thermo Electron Corporation Nicolet 380 FTIR (KBr pellet) respectively. The size and the zeta potential of the nanocomplex were determined by dynamic laser light scattering (DLS) on a Nano-ZS (Red Badge) ZEN 3600 device (Malvern Instruments, Malvern, UK. The magnetic behaviour at room temperature of the as-synthesized nanoparticles is characterized using MIAtek® reader (Magnisense). Energy-dispersive X-ray (EDX) microanalyses were performed using a TM 3000 tabletop microscope equipped with a Swift EDX-ray 3000 microanalysis system (Oxford Instruments). TEM images were obtained using a FEI CM10 Microscope (Philips) and samples were prepared by depositing a drop of nanoparticles suspension on carbon coated copper grids placed on a filter paper.

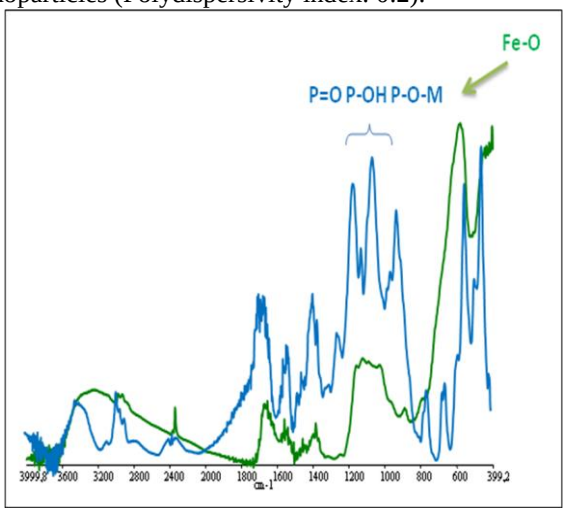
3 RESULTS

The γFe_2O_3@Alendronate nanoplateform was used in order to evaluated a grafting from strategy for anchoring organocatalyst on nanoparticles's surface. The amine groups present on the nanoplateform surface were covalently conjugated with the carboxylic function of protected L-Proline via the EDC/NHS activation method. Depending on the Proline amino deprotection, acidic labile Boc or basic labile Fmoc were used[28]. Acidic Boc deprotection was found to be incompatible with our nanoparticles because of their degradation. Otherwise, Fmoc deprotection led to the desired products and allowed us to indirectly quantify the number of grafted Proline onto the nanoparticles by UV measurement. After deprotection the supernantent was evaluated by UV for Fluorenyl containt. Comparison to a calibration curve permited to quantify the number of fluorenyl deprotected. It so gave indirect access to the number of Proline function per particles. As previously described in ou group for such a nanoplateform, microwave assisted coupling was far more efficient for the grafting: a grafting of ≈5 L-Prolines per nanoparticles whas osberved when using classical conditions, and about 150 L-Prolines per nanoparticles were obtained using microwave conditions. In order to modulate the number of catalysts per nanoparticles and also to avoid severals synthesis steps due to protection/deprotection stategies, a grafting to methodology was also evaluated. An HMBP Alendronate@L-Proline was synthesized (Scheme 2). Alendronate with was reacted with an excess of activated Boc-L-Proline at room temperature in a water/DMF medium for 4 days. Then precipitation in acidic conditions and filtration led to the desired product. Nanoparticles were synthesized by mild conditions in water according to reverse micelle process[27]. Coating with Alendronate@L-Proline was performed in water (pH = 2) during two hours and the excess of catalyst was removed thanks to a magnetic field. The coupling efficency was investigated qualitatively using various measurements methods: infrared spectroscopy, dynamic light scattering, TEM, MIAtek, and quantitatively using UV absorption, TGA and EDX measurements.



Scheme 2: Elaboration of HMBP Alendronate@Proline.

Figure 1 presents IR spectra comparision between Alendronat@Proline and γFe_2O_3@Alendronate@Proline. The appearance of iron–oxide vibration bands at 579 cm−1 and the shift of P=O and P-O vibration bands indicating that the Alendronate@Proline molecule binds to the γFe_2O_3 nanoparticles through the phosphonate moiety. Zeta potential measurements at pH 7 in water before coupling is about +30mV, and -45mV after coupling indicating efficienty functionalization by the phosphonate organic molecule. DLS measurements shown an increase of the hydrodynamical diameter of the particles: 15.7 nm for "naked" nanoparticles and 21.30 nm for the passived nanoparticles (Polydispersivity index: 0.2).



Firgure 1 : Infra red spectra of Alendronat@Proline (blue) and γFe_2O_3@Alendronate@Proline (green).

TEM image shows that particles are stable and well dispersed. A size distribution of 10 nm was measure for the Alendronate@Proline nanoparticles (figure 2). The nanoparticles are stable from pH 4 to 10. The ferrofluids presented good magnetic property after functionalization step, and no significant variations were observed.

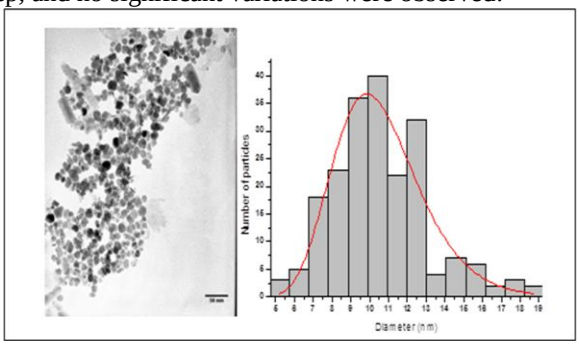


Figure 2: TEM image and size distribution for γFe_2O_3@Alendronate@Proline.

In order to quantify the average number of catalysts per nanoparticles, EDX analysis was done (figure 3). The average number of phosphorus molecules per nanoparticles is 800 ± 150. So a grafting increase of about 5 (compared to microwave Fmoc startegy) is obtained when the catalyst is previsously coupled on the bisphosphonate stabilizing agent and then grafted on the nanoparticles's surface. Moreover one must note that secondary amine function are still disposable onto particles's surface with the grafting from way, and could maybe disturbed the enantioselective catalytic activity.

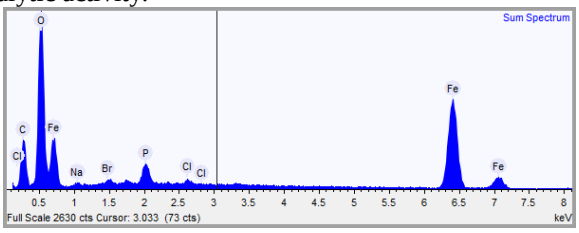


Figure 3: EDX analysis for γFe_2O_3@Alendronate@Proline.

4 CONCLUSIONS

Magnetic nanoparticles functionalized with L-Proline were successfully obtained from two different manners. The grafting from approach combined with microwave irradiation led to a 30 times grafting increase using the Fmoc strategy compared to classical conditions. Indirect quantification by UV measurement permits to evaluated at 150 the average number of catalysts per nanoparticles. A coating agent with organocatalytic activity: Alendronate@Proline, was also obtained and passivation of nanoparticles was performed quikly in one step. By EDX we evaluated the amount of Proline at 800 per particles. The catalytic potenty of these nanohybrids toward enantioselective reactions such as aldolization is still in evaluation yet. The amount of organocatalysts per particles is a paramater to take into account for an efficent catalysis. We here will be able to evaluate two different functionalization loading and find if the optimum for catalysis reaction is to completely covered the surface of the nanoparticle with catalysts or to have uncompletly functionalization. Further intermediate loading will also be evaluated using a ligand exchange methodology.

REFERENCES

[1] J. Novacek, and M. Waser, *European Journal of Organic Chemistry* **2013**, (4), 637-648 (2012).
[2] J. Aleman, and S. Cabrera, *Chemical Society Reviews* **42**, (2), 774-793 (2012).
[3] S. Bertelsen, and K. A. Jorgensen, *Chemical Society Reviews* **38**, (8), 2178-2189 (2009).
[4] P. I. Dalko, and L. Moisan, *Angewandte Chemie International Edition* **40**, (20), 3726-3748 (2001).
[5] P. I. Dalko, and L. Moisan, *Angewandte Chemie International Edition* **43**, (39), 5138-5175 (2004).
[6] P. Melchiorre, M. Marigo, A. Carlone, and G. Bartoli, *Angewandte Chemie International Edition* **47**, (33), 6138-6171 (2008).
[7] R. A. Sheldon, *Chemical Society Reviews* **41**, (4), 1437-1451 (2012).
[8] G. Chouhan, D. Wang, and H. Alper, *Chemical Communications*, (45), 4809-4811 (2007).
[9] A. V. Malkov, M. Figlus, G. Cooke, S. T. Caldwell, G. Rabani, M. R. Prestly, and P. Kocovsky, *Organic & Biomolecular Chemistry* **7**, (9), 1878-1883 (2009).
[10] O. Gleeson, G.-L. Davies, A. Peschiulli, R. Tekoriute, Y. K. Gun'ko, and S. J. Connon, *Organic & Biomolecular Chemistry* **9**, (22), 7929-7940 (2011).
[11] O. Gleeson, R. Tekoriute, Y. K. Gun'ko, and S. J. Connon, *Chemistry – A European Journal* **15**, (23), 5669-5673 (2009).
[12] S. Luo, X. Zheng, H. Xu, X. Mi, L. Zhang, and J.-P. Cheng, *Advanced Synthesis & Catalysis* **349**, (16), 2431-2434 (2007).
[13] A. K. Tucker-Schwartz, and R. L. Garrell, *Chemistry – A European Journal* **16**, (42), 12718-12726 (2010).
[14] Q. Dai, and A. Nelson, *Chemical Society Reviews* **39**, (11), 4057-4066 (2010).
[15]G. Centi, and S. Perathoner, *Coordination Chemistry Reviews* **255**, (13â€“14), 1480-1498 (2011).
[16] C. W. Lim, and I. S. Lee, *Nano Today* **5**, (5), 412-434 (2010).
[17] V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara, and J.-M. Basset, *Chemical Reviews* **111**, (5), 3036-3075 (2011).
[18] V. Polshettiwar, and R. S. Varma, *Tetrahedron* **66**, (5), 1091-1097 (2010).
[19] V. Polshettiwar, and R. S. Varma, *Green Chemistry* **12**, (5), 743-754 (2010).

[20] A. Schätz, O. Reiser, and W. J. Stark, *Chemistry – A European Journal* **16**, (30), 8950-8967 (2010).
[21] Y. Zhu, L. P. Stubbs, F. Ho, R. Liu, C. P. Ship, J. A. Maguire, and N. S. Hosmane, *ChemCatChem* **2**, (4), 365-374 (2010).
[22] B. List, R. A. Lerner, and C. F. Barbas, *Journal of the American Chemical Society* **122**, (10), 2395-2396 (2000).
[23] F. Benyettou, E. Guénin, L. Lalatonne, and L. Motte, *Nanotechnology* **22**, (5), 055102 (2011).
[24] G. R. Kieczykowski, R. B. Jobson, D. G. Melillo, D. F. Reinhold, V. J. Grenda, and I. Shinkai, *J. Org. Chem.* **60**, 8310-8312 (1995).
[25] F. Benyettou, Y. Lalatonne, O. Sainte-Catherine, M. Monteil, and L. Motte, *International Journal of Pharmaceutics* **379**, (2), 324-327 (2009).
[26] Y. Lalatonne, C. Paris, J. M. Serfaty, P. Weinmann, M. Lecouvey, and L. Motte, *Chemical Communications*, (22), 2553-2555 (2008).
[27] L. Motte, F. Benyettou, C. de Beaucorps, M. Lecouvey, I. Milesovic, and Y. Lalatonne, *Faraday Discussions* **149**, (0), 211-225 (2011).
[28] E. Nehlig, L. Motte, and E. GuÃ©nin, *Catalysis Today*, (0), (2012).