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COMMUNICATION

Immobilized Pd on magnetic nanoparticles bearing proline as highly efficient and retrievable Suzuki-Miyaura catalyst in aqueous media.

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A magnetically retrievable nanocatalyst was evaluated for microwave assisted Suzuki-Miyaura reaction in aqueous media. Excellent yields and conversions were obtained with low Pd loadings (down to 0.01 mol% Pd). Stability is up to 6 months in water under aerobic conditions and efficiency remains unaltered even after 7 repeated cycles.

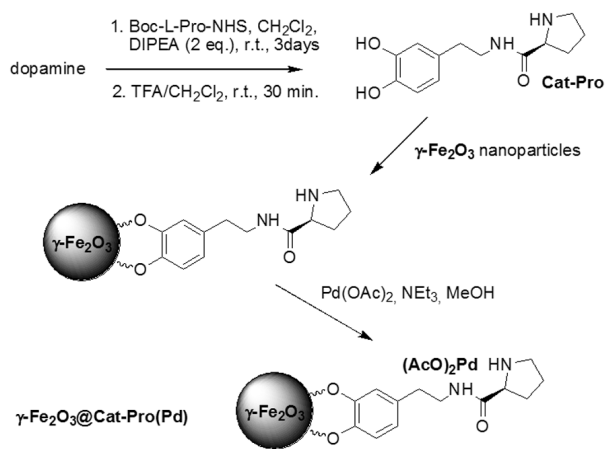
Among the cross coupling reactions catalyzed by noble metals and awarded by the 2010 Nobel prize, the Suzuki-Miyaura reaction remains one of the most important for the obtaining of biaryl compounds owing to its high versatility.¹ This coupling of aryl halides (or tosylates and triflates) with stable and readily available boronic acids has been used for the synthesis of several pharmaceuticals, fungicides, light emitting polymers or organic LED compounds.²⁻⁵ Most of these reactions are done in a homogeneous catalytic manner using various Pd sources and ligands in organic solvents. Nowadays one of the challenges is to be able to recover the catalyst due to the Pd cost (mainly related to its low abundance) and environmental toxicity. That is why an increasing effort was made to develop heterogeneous Pd catalysts using a large variety of solid supports (carbon, zeolites, clays, dendrimers, etc).⁶⁻¹² In addition the replacement of environmentally harmful organic solvent by eco-friendly solvent^{2, 13-17} such as water or mixture of water and alcohol is another area of improvement.

In the last decades more attention has been given to the use of nanomaterials as support¹⁸⁻²⁰ due to their high surface/volume ratio putting them at the frontier between heterogeneous and homogeneous catalysis.²¹ In this field magnetic nanoparticles appear as an ultimate nano-support due to their easiness of recovery.²²⁻²⁴ Hence, the simple use of an external magnet could afford the rapid recovery of the catalyst without the need of filtration or centrifugation.²⁵ When preparing such magnetically retrievable nanocatalyst for Suzuki-Miyaura reaction several strategies have been employed, one of which consisted on binding Pd onto ligands attached to the surface of the magnetic nanoparticles. Most of these ligands are phosphine derivatives²⁶⁻³⁰ or amine based complexes³¹⁻³⁴ that are most of the time already used as conventional ligands in homogeneous reactions. More recently amino acids such as glycine^{35, 36} or proline³⁷ were used as ligands in solution to catalyze C-C coupling. This approach was also used to immobilize palladium

or copper on nanoparticle or solid silica surfaces and to promote C-C coupling or oxidation reactions.³⁸⁻⁴⁰

Ongoing with our work on functionalising magnetic nanoparticles with various derivatives for biomedical or catalysis applications,⁴¹⁻⁴³ we decided to study iron oxide nanoparticles bearing a proline derivative at their surface to complex Pd and to evaluate this new nanocatalyst for Suzuki-Miyaura cross coupling in aqueous media under aerobic conditions.

Our nanocatalyst is obtained by a grafting to methodology. Several small molecules have been described to efficiently coat and stabilize iron oxide nanoparticles. Among them catechol functionalised molecules derived from mussel adhesive proteins are more and more popular coating agents.⁴⁴⁻⁴⁷ We, therefore coupled proline to dopamine in a two steps protocol to obtain a small bifunctional molecule bearing a catechol ring (Cat-Pro). This molecule was then used to chelate the surface of bare maghemite nanoparticles (scheme 1).



Scheme 1 Grafting to methodology for γ -Fe₂O₃@Cat-Pro(Pd) synthesis

Bare maghemite nanoparticles (γ -Fe₂O₃) of a 10 nm mean diameter were obtained using a previously described protocol.^{48, 49} Coating was performed in water at basic pH by simply mixing the

Cat-Pro ligand and γ -Fe₂O₃ nanoparticles. The excess of ligand was then removed by means of magnetic separation. The presence of the Cat-Pro at the surface of the nanoparticles was confirmed by the appearance in Fourier Transform Infra-Red (FTIR) of vibration bands characteristic of the catechol moiety (see SI). The number of molecules bound to the surface was determined by two methodologies: thermogravimetric analysis and amine titration by (o-phthalaldehyde) OPA method. Using both methodologies 450±50 Cat-Pro were found at the γ -Fe₂O₃ surface (corresponding to a 0.69 nm² occupied surface per Cat-Pro molecule). The immobilization of Pd onto the surface was done by applying the conditions described by Allam *et al.*³⁷ for the obtaining of palladium-proline complex. After Pd complexation, the as-obtained nanocatalysts are dispersed in water (see SI). FTIR spectra shown no major changes in the γ -Fe₂O₃@Cat-Pro vibration bands, only a slight difference in intensity of vibrations in the 1600-1400 cm⁻¹ could be noted (see SI). Transmission electron microscope (TEM) micrograph presented in Fig.1 shows that γ -Fe₂O₃@Cat-Pro(Pd) nanoparticles are well dispersed and have unchanged diameter size of 10.5±0.2 nm. Magnetization curve at 300 K confirmed the superparamagnetic behavior of the iron oxide nanoparticle catalyst with a saturate magnetization of 57 +/- 3 emu.g⁻¹ (Fig1) and the same magnetic behavior for the γ -Fe₂O₃@Cat-Pro with or without palladium. The surface composition of the metal-supported nanoparticles has been analyzed by X-ray photoelectron spectroscopy (XPS). Peaks corresponding to carbon, nitrogen, iron, palladium, are clearly observed (see SI). The Pd 3d spectrum of the nanoparticles presented in Fig. 1 shows the peak binding energies of 335.4 eV (Pd 3d5/2) and 340.2 eV (Pd 3d3/2), which confirmed the presence of Pd0. The most intensive peaks were the Pd 3d5/2 and 3d3/2 peaks corresponding to the PdN (or to Pd2+) in a complex with photoelectron energies of 337.4 and 342.6 eV.^{10, 50, 51} The average number of Pd per nanoparticle was deduced by Electron Dispersive X-ray (EDX) analysis. 490 Pd atoms were found per nanoparticle indicating that approximately one Pd is complexed by one ligand at the surface.

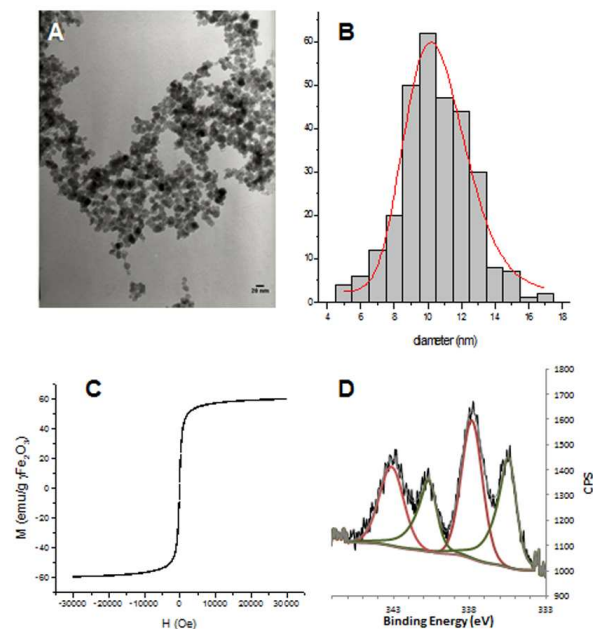


Fig. 1 TEM image, size distribution, magnetization curve and XPS for γ -Fe₂O₃@Cat-Pro(Pd)

In order to run first evaluation of our nanocatalyst a typical Suzuki-Miyaura reaction was performed coupling 4-tolylboronic acid (0.22 mM) to 4-iodonitrobenzene (0.20 mM). Reactions were performed in water/ethanol (1/1) or in pure water, under aerobic conditions. Microwave irradiation was used for heating the reaction to follow a green chemistry approach and to have a really precise control over the reaction conditions (temperature, stirring, cooling). Test reactions were made with thermal heating giving exactly the same results (data not shown). Two bases were evaluated for these reactions (triethylamine and sodium carbonate). Both gave very similar results (data not shown). Conversions of starting materials in the desired cross coupled product are listed in table 1.

Table 1 Evaluation of Suzuki-Miyaura test reaction conditions

Entry	Pd quantity (mol. %)	Solvent	Time (min.)	Temp (°C)	Conversion ^a (isolated yield) (%)
1	0	H ₂ O/EtOH	30	80	traces
2	0 ^b	H ₂ O/EtOH	30	80	traces
3	1	H ₂ O/EtOH	30	80	100 (98)
4	0.1	H ₂ O/EtOH	30	80	100 (97)
5	0.05	H ₂ O/EtOH	30	80	100 (96)
6	0.01	H ₂ O/EtOH	30	80	95 (90)
7	0.1	H ₂ O	30	80	80 (83)
8	0.1	H ₂ O	30	100	100 (97)
9	0.1	H ₂ O/EtOH	15	80	96
10	0.1 ^c	H ₂ O/EtOH	30	80	100 (95)

^a from ¹H NMR. ^b use of γ -Fe₂O₃@Pro-Cat without Pd. ^c after 7 consecutive run.

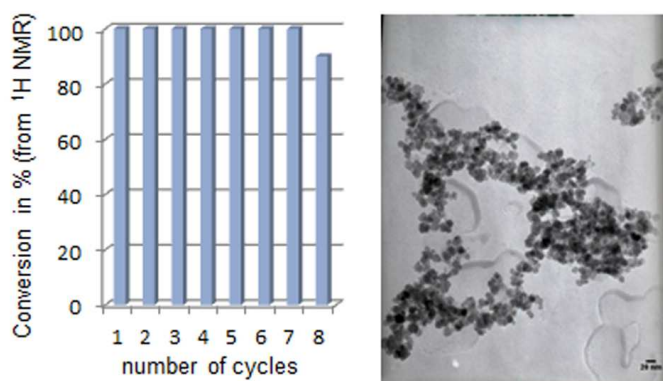
Two blank experiments (entries 1 and 2) were performed to check that no traces of Palladium present on the glass-ware or in the reactants could promote the reaction.⁵² Running the reaction without the nanocatalyst (entry 1) or with a nanocatalyst without Pd (entry 2) only traces of the product could be found indicating that the catalysis is performed only in presence of the active nanocatalyst. On the overall the catalyst system is very efficient in water/ethanol mixture in 30 min. at 80°C, the loading of Pd can be decreased from 1 mol. % down to 0.01 mol. % with still high conversion of starting materials in the desired cross coupled products (entries 3-6). The solvent can be changed for pure water but with an increase in temperature reaction to 100°C (entries 7-8). Decrease of the reaction time induced decrease in conversion (entry 9). Decrease of the temperature also impaired the conversion (data not shown). Reactions were in all cases very clean no secondary products (dehalogenation or homocoupling) were detectable. In fact only the cross coupling product was found on ¹H RMN spectra with the slight excess of boronic acid remaining (see SI for spectra of crude reaction mixture after only extraction). The product was extracted by simply adding diethyl ether to the reaction medium and when conversion was total it was only purified by simple filtration over silica to remove boronic acid. The nanocatalyst was recovered by magnetic separation and washed several times with water and ethanol and could be reused straight away (Fig 2).

Fig. 2 Magnetic recovery of the γ -Fe₂O₃@Cat-Pro(Pd) nanocatalyst



The catalyst was submitted to successive reactions (up to 8 times). After 7 repeated cycles the efficiency was not impaired (entry 10), only on the 8th cycle did un-complete conversion was observed (Fig 3). Nanoparticles were collected after the 8th run and were analyzed by TEM and EDX. The TEM images showed that nanoparticles were un-altered by the treatment and conserved their spherical aspect with low aggregation (Fig 3). The EDX analysis showed that the Pd leaching was relatively low as approximately 400 Pd were found per particle indicating a Pd loss of less than 2.5% in each run. The slight decrease in conversion observed could be explained by gradual loss of the catalyst during washings between each run as a very low amount of the catalyst was used (0.5 mg of nanocatalyst for 0.1 mol. % palladium).

Fig. 3 Recycling efficiency and TEM image after the 8th run.



One must note that our nanocatalyst is also extremely stable. It was kept in aqueous solution, under aerobic conditions at room temperature for more than 6 months after its synthesis and was still active with the same efficiency on our test reaction.

The catalytic efficiency can be quantified for reaction conditions using 0.1 mol. % Pd and 0.01 mol. % Pd. The turnover frequency values (TOF) determined on the basis of the yield of formation of final product per hour were respectively of 1940 and 18000 mol *p*-I-C₆H₄NO₂ (mol Pd)⁻¹ h⁻¹. These results showed the very high efficiency of this nanocatalyst compared to the literature (see table in SI). To the best of our knowledge, similar approaches (where Pd is immobilized onto magnetic nanoparticles) presented a TOF ranging from 5 to 500. The best result so far reached TOF value of 20000 using resin encapsulated Pd nanoparticle catalyst.⁵³ Another data which is also highly important in terms of environmental consideration is that relatively small quantities of nanocatalyst were used. When running catalysis on 40 mg of 4-iodonitrobenzene with 0.1 mol. % Pd the total amount of nanoparticles was 0.5 mg (only 50 μg with 0.01 mol.% Pd). In comparison most of the nanocatalysts described in the literature were used in ranges varying from 2 to 200 mg in comparable conditions. Thus, the total amount of catalyst was drastically decreased in our case.

Finally, to probe the scope of our reaction, using our standard conditions (0.1 mol. % catalyst, 80°C, 30 min in water/ethanol) we try to evaluate several reactants (results are listed in table 2)

Table 2 Cross-coupling evaluation with various reactants

$$\text{R}-\text{C}_6\text{H}_4-\text{X} + (\text{HO})_2\text{B}-\text{Ar} \xrightarrow[\text{NEt}_3 \text{ or } \text{Na}_2\text{CO}_3]{\begin{matrix} \gamma\text{-Fe}_2\text{O}_3 @ \text{Cat-Pro}(\text{Pd}) \\ (0.1 \text{ mol. \%}) \\ \text{H}_2\text{O}/\text{EtOH} \end{matrix}} \text{R}-\text{C}_6\text{H}_4-\text{Ar}$$

Entry	X	R	Ar	Time (min.)	Temp (°C)	Conversion (isolated yield) (%)
1	I	H	4-tolyl	30	80	100 (97)
2	Br	H	4-tolyl	30	80	100 (99)
3	Cl	H	4-tolyl	30	80	20 (15)
4	I	NO ₂		30	80	100 (98)
5	I	NO ₂		30	80	100 (96)
6	I	NO ₂		30	80	traces
7	I	NO ₂		30	80	100 (95)
8	I	NO ₂		30	80	100 (97)
9	I	NO ₂		30	80	67 (60)
10	I	NO ₂		30	80	20 (15)
11	I	NO ₂		30	80	100 (95)

When studying the influence of the nature of the halide (entries 1-3) as expected a drastic decrease in conversion was observed when going from iodide and bromide to chloride. In this latter case, an increase of the reaction time did not permit to improve the conversion and homocoupling byproduct was even detected when reaction time is increased to two hours. Then keeping 4-iodonitrobenzene as substrates we evaluated several carbonyl functionalized phenylboronic acid (entry 4-8). These derivatives, presenting an electron withdrawing group, were used as they represented less reactive boronic acids with some presenting fragile functionalities. Conversions were always total for para substituted derivatives (entries 4,7,8), it stayed total for 3-acetylphenyl boronic acid (entry 5) but no product formation was observed for 2-acetylphenyl boronic acid probably due to steric hindrance (entry 6). Finally two examples of heteroaromatic boronic acids and the 4-vinylphenylboronic acid were evaluated as reactant. For heteroaromatic boronic acids results were contrasted: good conversion was obtained with furan derivative (entry 9) but a low conversion was obtained for thiofuran one (entry 10). In the case of vinylphenylboronic acid (entry 11) total conversion was observed and no byproduct due to possible coupling with the double bond was detected in these conditions.

A new nanocatalyst was synthesized based on a maghemite nanoparticle core bearing proline at the surface that immobilized

palladium. Palladium fixation did not impeded nanoparticles magnetic properties and stability. The resulting catalyst turns out to be extremely efficient for Suzuki-Miyaura reaction in water/ethanol mixture, under aerobic conditions, using as small amount of catalyst as 0.01 mol.% Pd. On the overall good to excellent conversions were obtained with several reactants. Moreover this catalyst was shown to be very stable (up to 6 months in water under aerobic conditions) and reusable up to 7 times with total conversion and small amount of palladium leaching. This nanocatalyst that appears to be one of the most efficient up to date for Suzuki-Miyaura cross coupling will be, now, further studied and evaluated on other C-C reactions such as Heck, Sonogashira or decarboxylative cross coupling. Finally, taking into account the chiral nature of the catechol proline ligand, its used in the case of enantioselective coupling could be evaluated.

Notes and references

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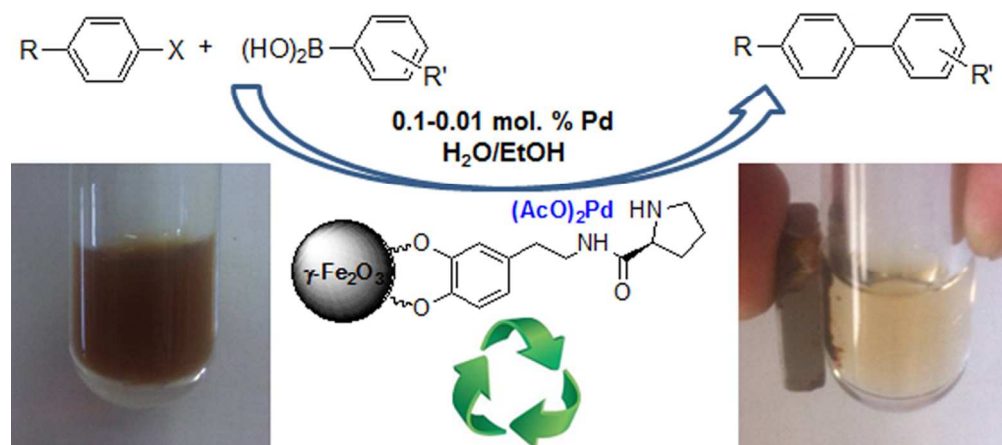
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Electronic Supplementary Information (ESI) available: experimental details, literature examples of TOF values for similar “nanocatalyst” and spectra for nanoparticle and chemicals characterization. See DOI: 10.1039/c000000x/

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- N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2483.
- R. Franzén and Y. Xu, *Can. J. Chem.*, 2005, **83**, 266-272.
- S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633-9695.
- R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461-1473.
- G. A. Molander and F. Dehmel, *J. Am. Chem. Soc.*, 2004, **126**, 10313-10318.
- D. Astruc, *Tetrahedron-Asymmetry*, 2010, **21**, 1041-1054.
- A. Corma, H. Garcia and A. Leyva, *Appl. Catal. A*, 2002, **236**, 179-185.
- F.-X. Felpin, *Synlett*, 2014, **25**, 1055-1067.
- E. J. Garcia-Suarez, P. Lara, A. B. Garcia, M. Ojeda, R. Luque and K. Philippot, *Appl. Catal. A*, 2013, **468**, 59-67.
- A. Hassine, S. d. Sebti, A. Solhy, M. Zahouily, C. Len, M. N. Hedhili and A. Fihri, *Appl. Catal. A*, 2013, **450**, 13-18.
- M. Poyatos, F. Marquez, E. Peris, C. Claver and E. Fernandez, *New J. Chem.*, 2003, **27**, 425-431.
- T. Sun, Z. Zhang, J. Xiao, C. Chen, F. Xiao, S. Wang and Y. Liu, *Sci. Rep.*, 2013, **3**.
- E. Aktoudianakis, E. Chan, A. R. Edward, I. Jarosz, V. Lee, L. Mui, S. S. Thatipamala and A. P. Dicks, *J. Chem. Educ.*, 2008, **85**, 555.
- A. Fihri, D. Luart, C. Len, A. Solhy, C. Chevrin and V. Polshettiwar, *Dalton Trans.*, 2011, **40**, 3116-3121.
- M. Lamblin, L. Nassar-Hardy, J.-C. Hierso, E. Fouquet and F.-X. Felpin, *Adv. Synth. Catal.*, 2010, **352**, 33-79.
- B. H. Lipshutz, B. R. Taft, A. R. Abela, S. Ghorai, A. Krasovskiy and C. Duplais, *Platin. Met. Rev.*, 2012, **56**, 62-74.
- N. Yan, C. Xiao and Y. Kou, *Coord. Chem. Rev.*, 2011, **254**, 1179-1218.
- L. L. Chng, N. Erathodiyil and J. Y. Ying, *Acc. Chem. Res.*, 2013, **46**, 1825-1837.
- A. Schätz, O. Reiser and W. J. Stark, *Chem. Eur. J.*, 2010, **16**, 8950-8967.
- S. Wittman, J.-P. Majoral, R. N. Grass, W. J. Stark and O. Reiser, *Green Proc. Synth.*, 2012, **1**, 275-279.
- D. Astruc, F. Lu and J. R. Aranzas, *Angew. Chem. Int. Ed.*, 2005, **44**, 7852-7872.
- A. Fihri, M. Bouhrara, B. Nekoueshahraki, J.-M. Basset and V. Polshettiwar, *Chem. Soc. Rev.*, 2011, **40**, 5181-5203.
- V. Polshettiwar, R. Luque, A. Fihri, H. Zhu, M. Bouhrara and J.-M. Basset, *Chem. Rev.*, 2011, **111**, 3036-3075.
- D. Wang and D. Astruc, *Chem. Rev.*, 2014, **114**, 6949-6985.
- D. Zhang, C. Zhou, Z. Sun, L.-Z. Wu, C.-H. Tung and T. Zhang, *Nanoscale*, 2012, **4**, 6244-6255.
- B. Baruwati, D. Guin and S. V. Manorama, *Org. Lett.*, 2007, **9**, 5377-5380.
- P. Li, L. Wang, L. Zhang and G.-W. Wang, *Adv. Synth. Catal.*, 2012, **354**, 1307-1318.
- A. Schätz, T. R. Long, R. N. Grass, W. J. Stark, P. R. Hanson and O. Reiser, *Adv. Funct. Mater.*, 2010, **20**, 4323-4328.
- X. Zhang, P. Li, Y. Ji, L. Zhang and L. Wang, *Synthesis*, 2011, **2011**, 2975-2983.
- S. Shylesh, L. Wang and W. R. Thiel, *Adv. Synth. Catal.*, 2010, **352**, 425-432.
- X. Jin, K. Zhang, J. Sun, J. Wang, Z. Dong and R. Li, *Catal. Commun.*, 2012, **26**, 199-203.
- P. D. Stevens, J. Fan, H. M. R. Gardimalla, M. Yen and Y. Gao, *Org. Lett.*, 2005, **7**, 2085-2088.
- J. Wang, B. Xu, H. Sun and G. Song, *Tetrahedron Lett.*, 2013, **54**, 238-241.
- Z. Yan-Qi, W. Xian-Wen and Y. Rui, *Catal. Lett.*, 2010, **135**, 256-262.
- M. Guo, S. Liu, X. Zhou, M. Lv, S. Chen and D. Xiao, *Molecules*, 2014, **19**, 6524-6533.
- S. Liu, M. Lv, D. Xiao, X. Li, X. Zhou and M. Guo, *Org. Biomol. Chem.*, 2014, **12**, 4511-4516.
- B. K. Allam and K. N. Singh, *Synthesis*, 2014, **2011**, 1125-1131.
- H. Liu, L. Wang and P. Li, *Synthesis*, 2008, **2008**, 2405-2411.
- Z. Wang, L. Wang and P. Li, *Synthesis*, 2008, **2008**, 1367-1372.
- L. Zhang, P. Li, J. Yang, M. Wang and L. Wang, *ChemPlusChem*, 2014, **79**, 217-222.
- J. Bolley, E. Guenin, N. Lievre, M. Lecouvey, M. Soussan, Y. Lalatonne and L. Motte, *Langmuir*, 2013, **29**, 14639-14647.
- P. Demay-Drouhard, E. Nehlig, J. Hardouin, L. Motte and E. Guenin, *Chem. Eur. J.*, 2013, **19**, 8388-8392.
- E. Nehlig, L. Motte and E. Guenin, *Catal. Today* 2013, 90-96.
- D. Ling, W. Park, Y. I. Park, N. Lee, F. Li, C. Song, S.-G. Yang, S. H. Choi, K. Na and T. Hyeon, *Angew. Chem. Int. Ed.*, 2011, **50**, 11360-11365.
- M. Mazur, A. Barras, V. Kuncser, A. Galatanu, V. Zaitzev, K. V. Turcheniuk, P. Woisel, J. Lyskawa, W. Laure, A. Siriwardena,

- R. Boukherroub and S. Szunerits, *Nanoscale*, 2013, **5**, 2692-2702.
46. Q. Ye, F. Zhou and W. Liu, *Chem. Soc. Rev.*, 2011, **40**, 4244-4258.
47. A. K. L. Yuen, G. A. Hutton, A. F. Masters and T. Maschmeyer, *Dalton Trans.*, 2012, **41**, 2545-2559.
48. J. Bolley, Y. Lalatonne, O. Haddad, D. Letourneur, M. Soussan, J. Perard-Viret and L. Motte, *Nanoscale*, 2013, **5**, 11478-11489.
49. Y. Lalatonne, C. Paris, J. M. Serfaty, P. Weinmann, M. Lecouvey and L. Motte, *Chem. Commun.*, 2008, 2553-2555.
50. T. Borkowski, A. M. Trzeciak, W. Bukowski, A. Bukowska, W. Tylus and L. Kepinski, *Appl. Catal. A*, 2010, **378**, 83-89.
51. J. P. Mathew and M. Srinivasan, *Eur. Polym. J.*, 1995, **31**, 835-839.
52. N. E. Leadbeater, *Nat. Chem.*, 2010, **2**, 1007-1009.
53. H. Kaur, D. Shah and U. Pal, *Catal. Commun.*, 2011, **12**, 1384-1388.



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80x35mm (300 x 300 DPI)