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Journal Name

ARTICLE

Magnetic Nano-organocatalyst: impact of the surface functionalization on catalytic activity.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

E. Nehlig[a], L.Motte[a],and E. Guenin[a]*

Iron oxide nanoparticles (γ-Fe_2O_3) have been synthesized by soft chemistry in aqueous media. Particles have then been stabilized on surface by bifunctional coating agents bearing terminal functions which enables post functionnalization with the desired catalyst (Proline derivatives, peptides). Hybrids nanomaterials have been characterized with various techniques in order to determine their properties. Catalysts activities have been evaluated on Aldolisation and 1,4-Michael addition as model reactions. For both reactions the crucial impact of the nanocatlyst surface functionalisation on catalytic properties is demonstrated. For Michael addition good selectivity was achieved using small amount of nano-catalyst.

Introduction

Nowadays, interest for new catalytic systems increased exponentially thanks to various industrial applications in both fine and pharmaceutical chemistry. Numerous catalysts have been developed for a perpetual increasing number of organic reactions. Lots of homogeneous catalysts are expensive and/or contain noble metals, difficult to adapt for industrial process, due to poor extraction, recycling and many reuse problems. During the last decade, more efficient and greener new catalysts have been developed in organometallic, photocatalytic and organocatalytic areas. Recently immobilization of organocatalysts onto Magnetic nanoparticles (MNPs) has appeared as a really efficient methodology with a low impact on environment.[1-4] Organocatalysts present several advantages like low toxicity, affordability, availability, and robustness.[5-8] Since O'Dalaigh et al.[9] in 2007, many organocatalysts have been grafted onto MNPs, usually with a sturdy link and with or without silica shell. But developing new eco-friendly process is steel a need. Moreover, a precise control of the functionalization and an efficient determination of the average number of catalysts per MNPs is a necessity when having catalytic aims. Another important parameter to control is the possible interaction of the nanoparticle surface during the catalysis as it cannot be consider totally inert as firstly described by Gleeson et al.[10]. As a part of our research on magnetic nanocatalysts,[11,12] we proposed to synthesize, stabilize and functionalize iron oxide NPs in water and anchor different organocatalysts on their surface by simple and efficient click chemistry methodologies[13-17] applicable on nanosurface.[18-22] Using grafting to or grafting from methodologies we prepared several nanocatalyst to be evaluated in aldolization and 1.4 Michael addition reactions.

Results and Discussion

MNPs were synthesized in water by direct micellar process, according to a previously established procedure.[23] Briefly, ferrous dodecyl sulfate was mixed with dimethylamine in water at 28°C for 2 hours, and after several washing steps, bare MNPs were obtained. The as synthesized MNPs are spherical, with an inorganic core size of 10.3 ± 0.25 nm diameter, determined by Transition Electronic Microscopy (TEM). Magnetic properties determined by Vibrating Sample Magnetometer (VSM) measurements confirm their superparamagnetic behavior[24] with magnetization saturation of 55.2 ± 3 $A.m^2.kg^{-1}$ (Figure1).

The bare nanoparticles were then coated in water by small bifunctional molecules from the bisphosphonic family. The bisphosphonic function ensured the anchoring to MNPs surface while lateral chain enabled post functionalization with organocatalysts. Two molecules of the bisphosphonic acid family were used, a homemade Alendronate-Proline**1** for "grafting to" methodology, and an already described bisphosphonic acid bearing a terminal alkyne functionality ((1-hydroxy-1-phosphonohept-6-ynyl)phosphonic acid or BPheptyne) enabling chemoselective functionalization of the MNPs surface.[25] Bisphosphonate **1** was obtained by reacting Alendronate and (Boc)-L-Pro-OSu in a Water/DMF (1/1) mixture in presence of Di-isopropylethylamine (DIPEA) for 4 days at room temperature. After a classic acidic deprotection step using TFA/CH_2Cl_2 (1/1) during 30 min and precipitation, **1** was obtained with good yield and characterized by NMR and HR-MS (see SI). MNPs were then functionalized with **1** using an aqueous grafting process for 2 h at 90°C (Scheme 1).

[a] UFR SMBH, Université Paris 13, Sorbonne Paris Cité, 74 Rue Marcel Cachin, 93017 Bobigny Cedex, France

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

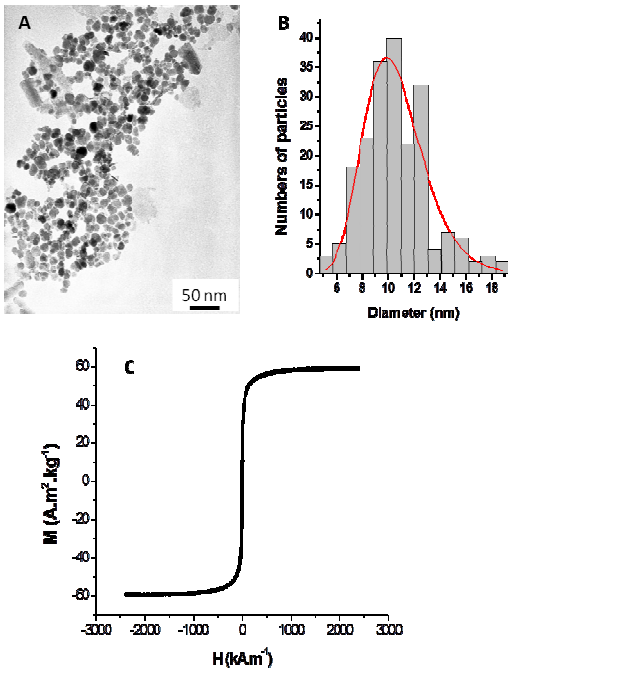
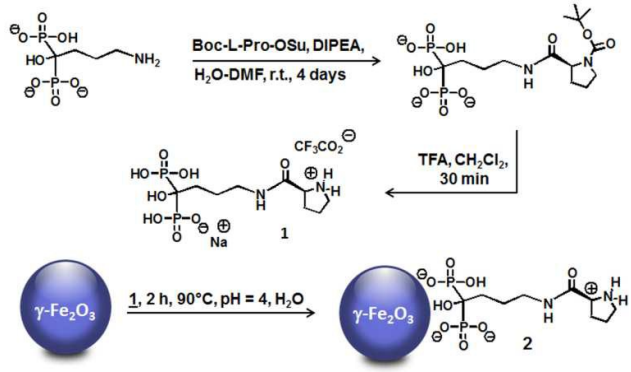


Figure 1. TEM images (A), size distribution (B) and magnetization curve (C) of bare MNPs.

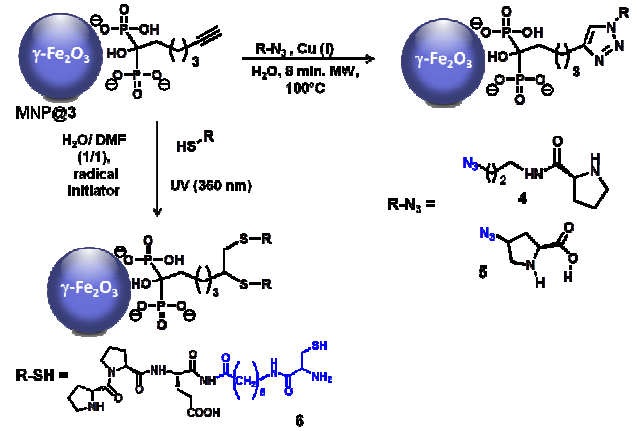


Scheme 1. Synthesis of 1 and preparation of MNP@**2**.

The functionalized MNP@**2** were stable in a wide range of pH (5 < pH < 10) (See SI) At pH 7 the hydrodynamic diameter (Dh) and Zeta Potential (ζ) are respectively 25 ± 5 nm / -36 ± 5 mV. Energy Dispersive X ray spectroscopy (EDX) measurements permitted to evaluate the number of bisphosphonic acid **1** at 400 ± 50 per nanoparticles. This result correspond to a surface area of 26.5 Å^2 occupied by **1**. This result is in accordance with previous observation for such chelating molecules.[26]

For the "grafting from" methodology, anchoring of BPhetyne **3** was realized according to previously described procedure.[25] Two click methodologies were used for the functionalization of MNP@**3** with organocatalysts. A prolinamide derivative bearing azide functionality **4**, and a Bocdeprotected commercial azido-proline **5** (See SI) were grafted by Coper Azide Alkyne Cycloaddition (CuAAC).[27,28] Thiol-yne click coupling[25,27] was used in the case of a commercial peptide **6** which derivate from Pr H. Wenemers' peptide sequence[29-31] (Scheme 2). Thermo Gravimetric analysis (TGA) were performed for MNP@**3**-**4** and MNP@**3**-**5** (see SI) indicating the grafting of 150 ± 50, catalyst **4** for MNP@**3**-4 and 250 ± 50 catalyst **5** for MNP@3-5 (see SI). At pH 7 Dh and ζ Potential are 28 ± 5 nm / -37 ± 5 and 26 ± 5 nm / -45 ± 5 respectively for MNP@**3**-**4** and MNP@**3**-**5**. Considering thiol-yne methodology, by EDX, 150 ± 50 catalysts **6** per nanoparticles were found for MNP@**3**-**6** (see SI). The Dh and ζ Potential are 25 ± 5 nm / -44 ± 5 in water at pH 7.

The grafting of the molecule at the surface was further demonstrated by Fourier Transformed Infra-Red (FTIR) analysis. They confirmed the presence of **1** at the MNP surface, as shown on figure 2A as vibration band corresponding to the bisphophonic functions could be found around 1100 cm^{-1}. Moreover the shift observed for the P=O and P-O vibration bands confirms the anchorage via the phosphonate moieties on MNPs' surface.[32] The strong vibration band at 579 cm^{-1} is characteristic for Fe-O vibration typical of maghemite structures. For both MNP@**3**-**4** and MNP@**3**-**5**, the appearance of vibrations bands on FTIR spectra between 1400 and 1800 cm^{-1} is characteristic of triazol rings formation.[28] Furthermore, the apparition of the amide vibration band near 1640 cm^{-1} is observable for MNP@**3**-**4** on the spectra. For MNP@**3**-**5**, the characteristic carboxylic acid vibration bands between 1690 and 1760 cm^{-1} appears after functionalization. All these data confirms presence of **4** and **5** onto MNPs' surface. The large vibration band between 1665 and 1760 cm^{-1} on FTIR spectra confirms that **6** is grafted onto the nanoparticles' surface.



Scheme 2. Preparations of MNP@**3**-**4**, MNP@**3**-**5** and MNP@**3**-**6**.

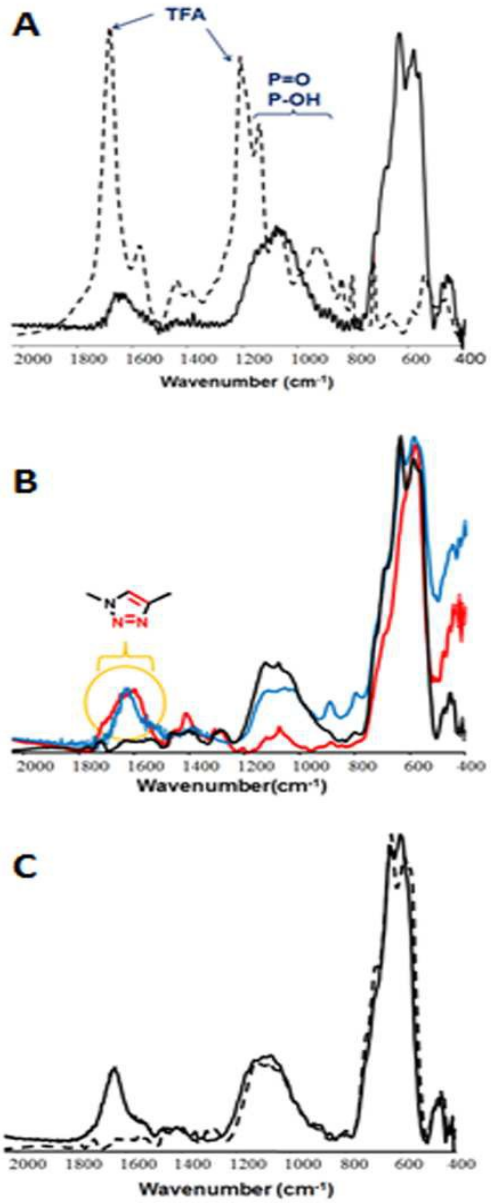
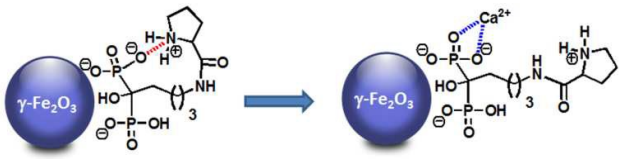


Figure 2. FTIR spectrum of **1** (dash) and **2** (**A**), MNP@**3** (black), MNP@**3**-**4** (red), MNP@**3**-**5** (blue) (**B**), MNP@**3** (dash) and MNP@**3**-**6** (**C**).

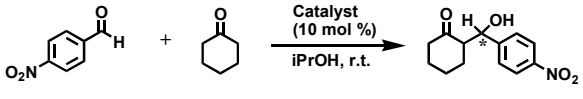
First, we evaluated catalytic activity of **2** in Aldolisation reaction between 4-p-nitobenzaldehyde and cyclohexanone in Isopropanol (iPrOH) at room temperature[33-35] (Table1). Reactions conditions were previously optimized with L-Proline as model catalyst, and 10 mol % of catalyst appear to be the best conditions with full conversion in less than a day (entry 1, other data not shown). Unfortunately, after 7 days using nano-catalyst **2** in the same conditions, no conversion was observed (entry 2). In order to understand the influence of MNPs and/or Bisphosphonic acid, bare nanoparticles and **3** were added separately as additives to L-Proline (entries 3 and 4). Both additions did not impair reactivity, so neither the MNPs, nor the Bisphosphonate has an effect on L-Proline's activity. In fact it appeared that it was the compound **1** itself which was completely unreactive: using 10 mol % of 1, even after 7 days, no conversion was detected (entry 5) even if N-MethylMorpholine (NMM) was added as additive (entry 6). Our hypothesis was that the amine function in compound **1** may interact with bisphosphonic functions in the free molecule as well as on MNP disabling its catalytic efficiency (Scheme 3).

To validate this hypothesis we took advantage of the high affinity of bisphosphonic functions for calcium ion.[36] We hoped that the presence of calcium ion will decrease the interaction thus allowing the catalytic activity. The reaction was so performed with **1** in presence of 10 mol % of anhydrous $CaCl_2$ (entry 7). Conversion of the aldehyde was obtained but with only 40% after 10 days. Conversion rate was still long but tends to confirm our hypothesis. Besides, when $CaCl_2$ was added to L-Proline (entry 9), conversion rate decrease to 64% after 7 days indicating that though having no catalytic efficiency (entry 8), $CaCl_2$ greatly decrease the kinetic of the reaction (entry 9). To further ascertain our findings we performed catalysis with nano-catalyst **2** in presence of 10 mol % of anhydrous $CaCl_2$ (entry 10). Thus, a good conversion (up to 60 %) was achieved after only 3 days. Kinetic was still low comparing to Proline alone but nano-catalyst **2** was more efficient than catalyst **1** when $CaCl_2$ was used. The same phenomenon of complete un-efficiency of the catalysts without presence of calcium ion was found when MNP@**3**-**4** and MNP@**3**-**5** were used (data not shown), again, no activity was observed even though the link between bisphosphonate and Proline was stiffen by the presence of the triazole ring. One must note that several reports documented such interaction between capping agent and nanomaterial core that modify the catalytic performance.[37] The results being deceiving with the aldol reaction we decided to move to another reaction also catalyzed by proline derivatives: the conjugated addition reactions of aldehyde to nitro-olefins.[38,39] This reaction moreover presents another advantage is that it requires lower percentage of catalyst thus allowing the use of smaller amount of MNPs.



Scheme 3. The addition of calcium may prevent catalysts' deactivation.

Table 1. Aldolisation between 4-p-notrobenzaldehyde and cyclohexanone.



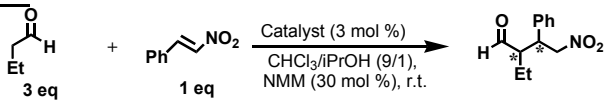
Entry	Catalyst	Additive (mol %)	Time (day)	Conversion[a] (%)
1	L-Proline	-	< 1	100

2	**2**	-	7	0
3	L-Proline	**3** (10)	< 1	100
4	L-Proline	MNPs (10)	< 1	100
5	**1**	-	7	0
6	**1**	NMM (20)	7	0
7	**1**	$CaCl_2$ (10)	10	40
8	-	$CaCl_2$ (10)	7	0
9	L-Proline	$CaCl_2$ (10)	7	60
10	**2**	$CaCl_2$ (10)	3	> 60

[a)]determined by 1H NMR

We first used the three parent molecules **4**, **5** and **6** to evaluate their catalytic activities on conjugated addition reactions of aldehyde to nitro-olefins and to serve as reference. The reaction consisted on condensation n-butyraldehyde on trans-β-Nitrostyrene.[31,38,39] Reactions conditions were optimized (data not shown) and ideal conditions were found to be reaction in a $CHCl_3$/*i*PrOH (9/1) medium in presence of 30 mol % of NMM using 3 mol% of catalyst (Table 2). After less than a day, **4, 5** and **6** led to full conversion (entries 1, 2 and 3). Both **4** and **5** led to full conversion in 18h with good diastereoselectivities of 14:1 and reasonable to good enantioselectivities for **4** (ee = 60 %) and **5** (ee = 75%). Results were more deceiving for peptide **6** which gave a lower diastereoselectivity of 7:1 and a lower enantioselectivity (ee = 55%). It appeared that compared to the parent peptide described by Wennemer's group the adjunction of the extra amino-acids at the N-terminus to allow the thiol-yne coupling greatly impaired its catalytic activities. When MNP@**3-4,** MNP@**3-5** and MNP@**3-6** were evaluated an important decrease of the reaction kinetic and lower conversion yields in general were observed. For MNP@**3-4** a still good conversion of 70 % was achieved (entry 4) but in 6 days. For MNP@**3-5** a complete conversion was obtained after 4 days (entry 5) and for MNP@**3-6** a maximum conversion of 45% was reached after 6 days. Though kinetics were lower the diastereoselectivity as well as the ee were globally conserved for the three catalysts after anchoring them to the MNPs indicating that their stereoselective abilities were not lost in the grafting process. One hypothesis to explain the slowing down of kinetics could be that in the organic media, the dispersion of the nanoparticles is not optimal inducing some aggregation and decreasing the catalyst accessibility. The differences between MNP3-4 and MNP3-5 could be found in the variation of the linker rigidity which in the case of MNP3-5 would allow for better stability and/or orientation of the catalyst. Thus it could also lessened hypothetical deactivation as observed in the case of MNP2. Recyclability experiments were conducted with MNP3-5. The MNPs were recovered after the first run owing to their magnetic properties washed several time and reused. During the second run the results were unchanged after 96 h, same yield, enantioselectivity and diastereoselectivity were found. However, after the third run though stereoselectivities were unmodified conversion was lower reaching only 80%. This decrease cannot be attributed to leaching of the catalyst as TGA and EDX measurement didn't show any blatant modification (data not shown). When kept for longer time conversion improved showing that this result could be explained by partial deactivation or loss of nanocatalyst during the washing steps. No further experiment was run as the kinetic of the reaction was already low and we preferred to try to optimize the catalyst.

Table 2. Michael Addition between n-butyraldehyde and tran-β-Nitrostyrene.

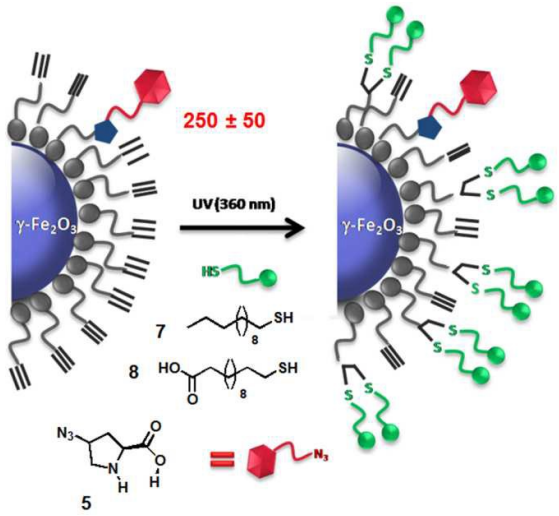


	Catalyst	Time (h)	Conversion [a)]	Anti/ Syn[a)]	ee[b)]
1	**4**	18	100	14:1	60
2	**5**	18	100	14:1	75
3	**6**	24	100	7:1	55
4	MN@**3**-**4**	144	70	14:1	60
5	MN@**3**-**5**	96	100	14:1	80
6	MN@**3**-**6**	144	45	7:1	55
7	MN@**3**-**5**-**7**	144	100	14:1	75
8	MN@**3**-**5**-**8**	72	100	14:1	70

[a)]determined by 1H NMR. b) determined by HPLC.

In order to improve the catalytic efficiency we decide to evaluate the modification of the lipophilicity of the nanoparticle surface on the catalysis. To prepare more lipophilic catalyst we take advantages of the possibility to multi-functionalized the surface of our MNPs. Indeed we previously described the possibility to chemoselectively di-functionalized the MNP@3 nanoplatform using two sequential click chemistry reactions: CuAAC and thiol-yne. Here we applied this double click functionalization to further graft two thioalkanes differing by their terminal group on the surface of MNP@**3**-**5**. Dodecanthiol **7** and 1-mercapto-dodecanoïc acid 8 were thus added to MNP@**3**-**5** in a second functionalization step by thiol-yne reaction not impairing the catalytic sites (scheme 4). Both molecules have long alkyl chains which could create a promiscuous environment near the catalyst enhancing accessibility of the reactant and thus improving the kinetic of the reaction. **7** and **8** were grafted using the protocol previously described and the number of grafted molecules was determined by EDX measurements (see SI). 170 ± 25 molecules of **7** and 250 ±25 molecules of **8** were respectively found at the surface of MNP@**3**-**5**-**7** and MNP@**3**-**5**-**8**. It is to note that the adjunction of **7** modified the zeta potential from -45 mV to -14 mV (see S.I.) on the resulting nanoparticles, whereas addition of **8** only slightly modified it to -39 mV.

The two modified catalysts were then evaluated in the same conditions (Table 2). Results were contrasted as for MNP@**3**-**5**-**7** the full conversion was obtained (entry **7**) but with an increased length of time (6 days of reactions instead of 4 days). Once again the kinetic was modified but without impairing the stereoselective ability as comparable diastereoselectivity and enantioselectivity were found. On another hand, when MNP@**3**-**5**-**8** was evaluated this time full conversion was achieved in 3 days instead of 4 previously. Diastereoselectivity was unchanged and a negligible decrease of ee was observed. To explain these results it could be hypothesized that though improving the lipophilicity of the nanocatalyst the addition of **7** decreased the electrostatic repulsion between nanoparticles as it shield surface charges. This phenomenon would thus impair the catalyst accessibility by increasing particle interaction through possible chain inter-digitation in the organic media. It is consistent with the fact that when adding **8** the presence of the terminal carboxylate still ensures the electrostatic repulsion between nanoparticles, thus preventing alkyl chains interaction and improving the catalyst access to the reactants. Finally this double controlled click functionalization permitted to achieve good conversion using a small amount of catalyst (3 mol %) in 3 days.



Scheme 4. Double click methodology for MNP@**3**-**5**-**7** and MNP@**3**-**5**-**8**.

Experimental

4.1. General

Boc-Pro-Osu (≥ 98 %), 1-mercapto-dodecanoic acid 996%), 1-dodecanthiol (≥ 98%), dimethylamine (40 wt% in H_2O), and tris(trimethyl-silyl) phosphite were purchased from Sigma-Aldrich, and were used without further purification. 4-p-nitobenzaldehyde (99%), cyclohexanone(99%), n-butyraldehyde(99%), trans-β-Nitrostyrene, TFA (99%), DMF (99%), were purchased from Alpha Aesar and were used without further purification. Peptide **6** (H-L-Pro-L-Pro-Glu-AHX-Cys-NH2 (HPLC > 95%) was purchased from Eurogentec. Solvents: methanol (RS HPLC), isopropanol (HPLC), dichloromethane (RE amylenestabi-lized), ethyl acetate, hexane and diethylether (RE stabilized) were purchased from Carlo Erba SDS. All the other reagents were obtained from current commercial suppliers and were used without purification. Water was purified with a millipore system (resistivity 18.2 MΩ.cm).^{1}H NMR spectra (400 MHz), proton-decoupled ^{13}C NMR spectra (100.63 MHz) were recorded on a Bruker Advance III 400 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale. The residual solvent peaks were used as internal references (^{1}H NMR: $CHCl_3$ 7.26 ppm, H_2O 4.79 ppm; ^{13}C NMR: $CDCl_3$ 77.2 ppm). Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet and coupling constant(s) are given in Hz. FTIR spectra were recorded as KBr pellets or between NaCl plates (for liquid product) on a Thermo Scientific Nicolet 380 FTIR spectrophotometer and are reported in wave numbers (cm^{-1}). TEM images were obtained using a FEI CM10 microscope (Philips). HPLC was performed with an Agilent 1200 Infinity device, using a Daicel AD-H chiral column, fitted with guard column. The Aldolisation and Michael adducts are known and their spectroscopic data were in accordance with literature. [29-31,38,39]

4.2. MNPs synthesis

For MNPs synthesis refer to Lalatone et al.[23] and S.I.

4.3. Synthesis of 1

Sodium Alendronate (500 mg, 1.85 mmol) was dissolved in 50 mL pure water and pH was adjusted to 7 with NaOH (1M) (10 mL). (Boc)-L-Pro-OSu (1.20 mg, 3.7 mmol) previously dissolved in 10 mL of DMF and DIPEA (700 µL, 4.1 mmol) were added to the water solution. The resulting mixture was stirred for 4 days and then washed twice with 15 mL Et_2O. The white product was obtained after acidic precipitation with 75% yield. Classical deprotection was performed using 6 mL of CH_2Cl_2/TFA (1/1) mixture for 30 min at room temperature. Then solvents were removed by reduced pressure. The product was washed twice with 10 mL Et_2O. After crystallization, a white powder was obtained with 75% yield. The product (**1**) is obtained as a TFA salt. ^{1}H (D_2O, 25°C): δ = 4.20 (dd, 1H,); 3.35-3.10 (m, 4H); 2.34-2.2 (m, 2H); 2-1.62 (m, 6H) ppm. ^{13}C{1H} (D_2O, 25°C): δ = 169.33; 73.35 (t, JC,P = 138.3 Hz,) ; 59.78; 46.34; 40.02; 30.79; 29.64; 23.50; 23,16 ppm. ^{31}P{1H} (D2O, 25°C): δ = 18.26 ppm. IR (KBr): 3400 ; 3294 ; 3103 ; 2983 ; 2786 ; 2394 ; 1685 ; 1681 ; 1573 ; 1441 ; 1435 ; 1385 ; 1206 ; 1138 ; 1068 ; 930 ; 840 ; 801 ; 722 ; 667 ; 580 ; 538 ; 461 cm-1. HRMS: (ESI-Q Tof) $C_9H_{21}N_2O_8P_2$ m/z (M + H) $^{+}$: 347.08; calc: 347.08. $[\alpha D]^{25}$ (589 nm acidic pH, H_2O) = -91.3°.

4.4. Synthesis of MNPs 2

To 4 mL of an aqueous solution of **1** (43 mg, 83 µmol, pH = 4), an aqueous solution of bare MNPs (4 mL, [Fe] = 0.16 M, pH = 4) was added. The resulting mixture was vigorously stirred for 2 h at 90°C. The nanoparticles **2** were then washed 5 times by

filtration using 30KDa Amicon filters, in order to remove the excess of unbidden **1**. MNPs **2** are dispersed in pure water and pH of the solution was adjusted to 7 using NaOH solution (0.1M).

4.5. General procedure for CuAAC

For BPheptyne synthesis refer to Demay-Drouard et al.[25]. CuAAC procedure is performed according to [27,28]. Briefly, 5 equivalents of Azido-Proline (**4** or **5**), Copper Sulfatehexahydrate (5%) and sodium ascorbate (20%) were added to 2.5 mL of MNP@**3** ([Fe] = 0.1 – 0.2M, [**3**] = 2 – 5 mM) and reacted in a sealed vial under microwave irradiations for 8 min ($T°C_{max}$ = 100°C). The as synthesized nanoparticles were washed 5 times by magnetic separation with acidic pure water (pH = 2) and then dissolved in water at pH 7. The same protocol was used for double functionalization, see S.I.

4.6. General procedure for thiolyne reaction

Thiolyne reaction procedure is performed according to Demay-Drouard et al.[25] . An aqueous solution of MNP@**3** ([Fe] = 0.1-0.15 M, [**3**] = 2.5-3.8 mM, pH = 7, V = 3 mL) and 3 mL of DMF were mixed with radical initiator, 1-hydroxycyclohexylphenylketone (10 %). Thiol molecules were added (2 equivalents per **3**, 10 for double functionalization) and the mixture was stirred for one and an half hour under UV irradiation (360 nm). The as functionalized MNPs are then washed 5 times with ethanol and 5 times with HCl 0.01M by magnetic separation (for **6**, only two ethanol washing were performed). MNPs are dispersed in water and pH is adjusted to **7**.

4.7. General procedure aldolisation

Catalyst (10 mol %, 0.04 mmol) was dissolved in 420 µL iPrOH. To this mixture, 60.4 mg of 4-p-nitrobenzaldehyde (0.4 mmol) and 210 µL of cyclohexanone (2 mmol) were added. The resulting mixture was mechanically mixed (600 rpm) at room temperature. The reaction was monitored by ^{1}H NMR. After reaction, crude mixture was extract tree times with Et_2O. Organic phase was then wash and dried with $MgSO_4$ and solvent was removed under reduced pressure. The product, orange powder, was purified on silica column using hexane/AcOEt gradient. With MNPs: catalyst (2 µmol), 4-p-nitrobenzaldehyde (0.02 mmol) and cylohexanone (0.1 mmol), iPrOH (21 µL).Water was remove from MNPs by magnetic separation.

4.8. General procedure for Michael addition

Catalyst (18.8 µmol) was first dissolved in 1 mL $CHCl_3$/iPrOH (9/1) and NMM (0.188 mmol, 23 µL) and mechanically stirred (600 rpm) for 5 min. at room temperature. Then trans-β-Nitrostyrene (0.7 mmol, 105 mg) and n-butyraldehyde (2.1 mmol, 191 µL) were added. The reaction was monitored by ^{1}H NMR. After reaction, crude mixture was extract tree times with CH_2Cl_2, and three times with water. Organic phase was then dried with $MgSO_4$ and solvent and excess of aldehyde were removed under reduced pressure. The yellow-orange product was purified on silica column (Hexane/AcOEt). With MNPs: catalyst (1 µmol), trans-β-Nitrostyrene (32.3 µmol, 4.8 mg), n-butyraldehyde (97 µmol, 8.8 µL), $CHCl_3$/iPrOH (9/1) (50 µL), NMM (30 mol %). Water was removed from MNPs by centrifugation.

Conclusions

In conclusions, new nano-catalysts were developed using two methodologies. A grafting to methodology on one hand that permits to anchor numerous catalytic moieties on MNPs' surface. On another hand, grafting from click methodology led to easy functionalized nano-catalysts and allows for controlled multi-functionalization of the nanoparticle surface. Evaluating the obtained catalysts we showed that the nature of the surface has a crucial impact on the catalysis efficiency. Use of **2** on aldolisation as put in evidence a deactivation mechanism of the catalyst probably due to strong interaction with the anionic charges present at the surface. On 1.4 Michael addition reaction we observed a decrease of the kinetic of the reaction when grafting the catalyst onto the nanoparticle surface but with a maintaining of their diastereoselectivity and enantioselectivity. Double controlled click methodology permits to improve kinetic and emphasized the fact that once again the activity was closely related to the tailoring of the nanoparticle surface. Finally nano-catalyst MNP@3-5-8 was shown to be efficient on 1.4 Michael addition reaction with complete conversion after 72 h and good diastereoselectivity and enanioselectivity, using small amount of catalyst (3 mol %).

Acknowledgements

This work was supported by Région Ile de France. We are grateful to N. Liévre (University of Paris 13) for TEM observations, J. Perard (Paris 5 University) for specific optical rotation measurements and J. Hardouin (Rouen University) for Mass spectrometry measurements.

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Nano-organocatalysts were synthesized by controlled click chemistry and studied on aldolization and michael addition. It was shown that small modifications of the nanosurface can have drastic effect on the catalysis.