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EDGE ARTICLE

Tuning the catalytic activity of L-proline functionalized hydrophobic nanogel particles in water†

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L-Proline functionalized PMMA nanogels with a range of catalyst functionalization (0.5–15 wt%) and cross-linking densities (0–50 wt%) were prepared *via* emulsion polymerization. The catalyst efficiency in water was investigated using a model asymmetric aldol reaction and an unprecedented reduction in catalyst loading, whilst maintaining high catalytic activity, is reported. In these reactions, a marked effect on selectivity was observed and determined to be dependent on the hydrophobicity of the nanogel particles. Furthermore, the effect of increasing cross-linking density on the catalytic efficiency of these particles (and their core–shell analogues) was explored and a significant reduction in activity was observed.

Introduction

It is well known that L-proline may be used to effectively catalyze a range of asymmetric organic reactions, yielding products with high stereoselectivity and enantiomeric excess.[1–5] However, although its efficiency in organic solvents has been well documented, there have only been a few examples of its use in water due to the inability of water to dissolve the organic reagents, which are often hydrophobic.[6–8] In cases where the catalyst was modified so as to be more hydrophobic, a concentrated organic microphase was formed around the catalytic site by the reagents, resulting in an observed acceleration in rate of reaction. This was proposed to be driven by the hydrophobic effect where the surrounding water drives the reagents towards the formed organic phase to lower the interfacial energy of the system.[9,10]

Subsequently, nanoreactor systems based on synthetic polymers have been reported to successfully create a favourable nanoenvironment able to concentrate the reagent phase for efficient catalysis.[11] For example, Fréchet and Hawker showed the ability of dendrimeric star polymers to attract reagents based on polarity, calling this the 'concentrator effect'.[12] Similarly, diblock copolymers that consist of a hydrophobic and a hydrophilic block have also been extensively studied for their use in catalytic systems due to their ability to self-assemble in water, providing a protected hydrophobic environment for the supported catalyst.[13] Previous studies have incorporated the

catalyst in the hydrophobic compartment of a micellar assembly by copolymerizing the monomeric derivative with a hydrophobic co-monomer. Recently our group reported the use of such polymeric nanoreactor systems containing 4-dimethylaminopyridine[14] or L-proline[15] that efficiently carried out organic reactions in water. The observed increase in reaction rate was proposed to be due to the ability of the hydrophobic core to effectively sequester the organic reagents from the surrounding water. Although such systems have proven to be highly efficient, the multi-step synthesis of the micelles significantly reduces their potential for use in industrial scale applications.

Related to these systems, microgel particles are excellent candidates for use as catalytic systems because they are unimolecular polymeric nano-sized entities that retain their form under a range of conditions (*i.e.* changes in temperature, solvent or concentration).[16] In addition, their synthesis is scalable and similar procedures are already being performed in industry for the mass production of paints *etc*.[17–19] Previous reports have also shown that microgel particles can be used as catalyst supports by loading metal nanoparticles within the polymeric matrix.[20,21] Other applications involving sub-micron sized cross-linked polymer particles can be found in fields such as drug delivery,[22,23] biotechnology,[24] membranes[25] and cosmetics,[26] as well as biomedical diagnostics (theranostics).[27]

Although the incorporation of L-proline within micron-sized polymer beads (~100 μm) has been reported by Hansen *et al.*[28] the effect of parameters such as the degree of catalyst functionalization within the particles or particle cross-linking density on the catalysis activity have not yet been investigated in detail. We aim to synthesize nano-sized cross-linked particles with a confined hydrophobic core and fully explore their potential as nanoreactors. Minimization of the particle size should enhance the reaction rate due to the increased surface area that enables faster diffusion of the reagents into the

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Fig. 2 Aldol reaction catalyzed by L-proline functionalized PMMA nanogels at 1 mol% catalyst loading and room temperature, in water, (A) CLD 0.5 wt% and DoF 2–15 wt%, (B) DoF 2 wt% and CLDs 0.5–10 wt%.

Table 3 Aldol reaction catalyzed by PMMA nanogels with 0.5 wt% CLD and DoFs of 2–15 wt%.

DoF/%	Conv.[a]/%	Anti/syn ratio[a]	ee[b]/%
0.5	28	98/2	97
2	73	97/3	99
5	32	98/2	89
9	28	99/1	86
15	18	95/5	81

[a] Determined by ^{1}H NMR spectroscopy, in CDCl$_3$. [b] Determined by HPLC, Chiralpak IA, hexane/IPA (90/10), 1 mL min^{-1}.

water.[31] The smaller particle size does not seem to show the anticipated effect as comparable yields and selectivity were shown in Hansen *et al.*'s work with a larger and different (micron-sized) proline-bearing polymeric system with 2% CLD.[28]

Effect of CLD

Changes to the CLD in the 0.5–10 wt% range were found to have less of an effect on the catalyst activity than changes to the DoF (see Fig. 2B and S5†). The selectivity was also unaffected by changes to the CLD in this range (Table 4) and furthermore, leaving the reaction for an additional 2 days resulted in near completion for all systems. In order to investigate the CLD limit, nanogel particles with 25 wt% CLD were synthesized (DoF 2 wt%, 22 nm, PD 0.234). However, the catalyst activity

Table 4 Activity and selectivity of the aldol reaction catalyzed by 1 mol% PMMA nanogels with 2 wt% DoF and a range of CLDs.

CLD/%	Conv.[a]/%	Anti/syn ratio[a]	ee[b]/%
0	41	98/2	94
0.5	73	97/3	99
2	69	95/5	98
5	75	97/3	86
10	49	96/4	95
25	31	97/3	95
50	14	95/5	95
50[c]	<5	—	—

[a] Determined by ^{1}H NMR spectroscopy, in CDCl$_3$. [b] Determined by HPLC, Chiralpak IA, hexane/IPA (90/10), 1 mL min^{-1}. [c] PMMA nanogel with P^{t}BuMA shell.

was not completely shut down and the reaction at 1 mol% still reached 31% conversion after 24 hours. Further increasing the CLD to 50 wt% (DoF 2 wt%, 20 nm, PD 0.108) did cause the expected and dramatic drop in conversion to 14% after 24 hours. We hypothesized that, due to the somewhat hydrophilic nature of the catalyst, the particles remain active even at high CLD due to the presence of L-proline moieties close to the water interface of the nanogels. T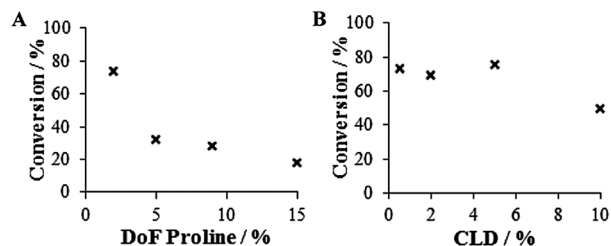o test this rationale, a P^{t}BuMA cross-linked shell was grown using the PMMA nanogels as seeds for the emulsion polymerization (CLD 50 wt%, DoF 2 wt%, 23 nm, PD 0.119, DLS in Fig. S6†), the idea being to render any surface catalyst moieties difficult for the reagents to access. As anticipated, the activity of the double-hydrophobic nanogel was almost eliminated and less than 5% conversion after 24 hours was observed. The influence of CLD was further emphasized when particles without cross-linking (CLD 0 wt%, DoF 2 wt%, 24 nm, PD 0.152) showed low catalytic efficiency (41% conversion) deviating from the observed trend. Although slightly difficult to rationalize, one possible explanation for this observation is that in absence of a cross-linker, the individual polymer chains are unable to form confined hydrophobic pockets that efficiently concentrate reagents and cannot allow such easy diffusion of reagents in and out from the catalytic moieties.

Effect of catalyst concentration/loading

To examine a series in which the number of reactors in the catalysis reactions remained constant (previously carried out at 1 mol% catalyst, leading to variations in the amount of polymeric material present), the same volume of nanogels (*i.e.* same amount of polymeric material, variable amounts of catalyst: 1–8.5 mol%) was used to catalyze the reaction (Table 5). The catalyst efficiency in this case is represented by turnover numbers (TON)[32] and once again results suggest that particles with low DoF catalyze the reaction more efficiently (2 wt% DoF is almost 4 times more efficient than 5 wt% DoF with same CLD, Fig. S7†). The importance of a confined space where the reagents are able to efficiently interact with the chiral catalyst in a chiral space has been studied by Raja *et al.*[33] using inorganic supports. We rationalize that in our case, having a greater number of isolated catalytic sites within the particles allows for efficient formation of the undisrupted transition states responsible for the high activity and enantioselectivity observed in L-proline catalyzed reactions.[34,35] Further lowering the catalyst DoF to 0.5 wt% (CLD 0.5 wt%, 25 nm, PD 0.091), and thus

Table 5 Table showing the efficiency of nanogel particles with the same amount of reagents catalyzed by same number of particles (different catalyst loading) with 0.5 wt% CLD, particles with PMMA core.

DoF/%	mol%	Conv.[a]/%	Anti/syn[a]	ee[b]/%	TON
2	1	73	97/3	99	73
5	3	51	97/3	88	17
9	5	57	97/3	81	11
15	8.5	53	98/2	67	6

[a] Determined by ^{1}H NMR spectroscopy, in CDCl$_3$. [b] Determined by HPLC, ChiralPak IA, hexane/IPA (90/10), 1 mL min^{-1}.

reducing the catalyst loading in the reaction to 0.15 mol% resulted in a great increase in TON to 187 (whilst maintaining excellent selectivity, anti/syn 98/2, ee 97%). This highlights the potential for effectively reducing the catalyst loading and maximizing product output in these nanogel systems. In addition, control experiments with unfunctionalized PMMA nanogels, which provided no conversion whatsoever, further highlighting the importance of having the catalyst tethered within the particles, bringing reaction components with different solubilities together within the same reaction sphere (Table S2†).

Effect of nanogel hydrophobicity

The results presented so far are interesting, as they show a dramatic decrease in enantioselectivity with increasing L-proline DoF (Table 5). We hypothesize that this effect is related to the reduced hydrophobicity of the core as well as the formation of less isolated catalytic sites.

To probe reaction dependence on nanogel core hydrophobicity, nanogels based on four more hydrophobic monomers were synthesized: ethyl, n-butyl, tert-butyl and lauryl methacrylate. Particle size of the new nanogels was found to be in a similar range to those previously reported for the PMMA nanogels (DLS, Fig. S8 and TEM, Fig. S9†) and analogous aldol reactions were carried out using the same number of nanogel particles (resulting in different catalyst loadings vide supra). The same trend in TON was observed for each, confirming the high efficiency of nanogel particles with lower catalyst DoF (Fig. S10†). However, a dramatic decrease in enantioselectivity with increasing DoF was not observed for any of these, more hydrophobic, nanogel systems (Table 6). We propose that the high enantioselectivity observed for more hydrophobic nanogels is a direct result of their ability to more efficiently sequester the reagents. The difference in core hydrophobicity was investigated by relative uptake of the hydrophobic dye Nile Red (Fig. S11†) and the efficient uptake of the reaction reagents was also demonstrated by an increase in particle size upon re-dispersing the nanogels in cyclohexanone after removal of water (Fig. S12†). The considerably lower catalytic activity achieved by the lauryl methacrylate-based nanogels is most likely a result of greater steric hindrance. On the other hand, the greater catalytic efficiency observed for the ethyl methacrylate based system compared to both the ^{n}butyl and ^{t}butyl methacrylate systems is attributed to the hydrophobic–hydrophilic balance within the nanogel core (Fig. S13†). Although at low DoF the activity and selectivity seem unaffected by the slight difference in steric bulk introduced by ^{t}butyl compared to ^{n}butyl side groups, at higher DoF a greater difference in activity is observed. These results suggest that the overall core hydrophobicity is an important factor in achieving high stereoselectivity in L-proline catalyzed aldol reactions.

Conclusions

In summary, the synthesis of a range of hydrophobic nanogels with embedded L-proline catalytic functionality via emulsion polymerization is reported. The catalytic efficiency with respect to modifications to cross-linking density and degree of catalyst functionalization is demonstrated. The importance of local core environment design is also highlighted by the enantioselectivity dependence on degree of functionalization and core hydrophobicity as shown by the use of different monomers. PMMA, being the least hydrophobic in the range, showed a decrease in enantioselectivity with increasing L-proline content and hence a proposed increase in water content within the core. However, the same effect was not observed when using more hydrophobic nanogels. The ability to completely shut down the catalytic activity via the preparation of double-hydrophobic core–shell nanogels was also demonstrated. Successful organocatalytic reactions were reported at loadings as low as 0.15 mol%, highlighting the efficiency of the functionalized nanogel system to catalyze organic reactions in water.

Table 6 Table showing the catalytic efficiency of nanogel particles with 0.5 wt% CLD, a range of DoF and different cores, catalysis carried out using the same number of particles.

Core	DoF/%	mol%	Conv.[a]/%	Anti/syn[a]	ee[b]/%	TON
EMA	2	1	99	99/1	99	99
	5	3	97	98/2	99	32
	9	5	95	98/2	99	19
	15	8.5	95	98/2	97	11
^{n}BuMA	2	1	78	99/1	99	78
	5	3	63	99/1	99	21
	9	5	79	97/3	99	16
	15	8.5	78	98/2	99	9
^{t}BuMA	2	1	79	97/3	93	79
	5	3	48	99/1	94	16
	9	5	44	99/1	95	9
	15	8.5	53	99/1	92	6
LMA	2	1	16	95/5	99	16
	5	3	19	96/4	98	6
	9	5	13	95/5	97	3
	15	8.5	14	98/2	89	2

[a] Determined by ^{1}H NMR spectroscopy, in CDCl$_3$. [b] Determined by HPLC, ChiralPak IA, hexane/IPA (90/10), 1 mL min^{-1}.

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