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ARTICLE TYPE

Studying the activity of the MacMillan catalyst embedded within hydrophobic crosslinked polymeric nanostructures

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The immobilization of the MacMillan catalyst within a unique hydrophobic environment created by a lightly cross-linked nanogel structure and its resulting catalytic activity is reported. The catalytic activity and selectivity of the catalyst were evaluated using the Diels-Alder (DA) reaction between cyclopentadiene and cinnamaldehyde. The relatively easy synthetic route applied allowed for the synthesis of a collection of nanogels with catalyst incorporations ranging from 0.5 to 25 wt%. In addition, core-shell type nanogels were synthesized to evaluate potential recovery and reuse of the catalytic system. The influence of the concentrator effect and possible partition coefficient on the catalyst activity was investigated. The results indicate catalyst loading/concentration can be more significantly reduced when the catalyst is embedded within the polymeric nanostructures compared to the small molecule equivalent.

Introduction

The MacMillan catalyst was first reported in 2000[1] and can be classed as a powerful and versatile organocatalyst capable of catalyzing a range of carbon-carbon bond forming reactions. It was first used to catalyze the Diels-Alder (DA)[1, 2] reaction but has since successfully catalyzed the Mukaiyama-Michael,[3] Friedel Crafts alkylation,[4] cascade reactions,[5] transfer hydrogenation reactions[6] and hydride reductions.[7] One of the main focuses of catalyst immobilized polymers has been the potential for recovery and reuse of the catalyst, in an unlimited number of cycles. We have previously demonstrated the successful incorporation of the MacMillan catalyst onto linear polymers prepared by reversible addition fragmentation chain transfer (RAFT) polymerization. These polymers were able to efficiently catalyze the DA reaction and could be re-used in a *pseudo*-continuous process.[8] Key for this was the synthesis of a monomer that contains the MacMillan functionality allowing for a bottom-up approach thus providing control over catalyst loading and environment. Previously reported approaches have been outlined in a review by Kristensen and Hansen which focused mainly on catalyst immobilization onto pre-formed solids[9] including poly(ethylene glycol) (PEG) supports,[10] JandaJel™ systems,[11] mesoceullar foams,[12] sulfonated polystyrene[13] and iron-oxide nanoparticles.[14] Kristensen *et al.*'s work[15] bears the closest resemblance to ours where a polymerizable monomer containing the catalytic MacMillan moiety was synthesized and incorporated into polymeric PEG-based beads *via* a suspension copolymerization process. The beads showed excellent catalytic activity in acetonitrile but unfortunately reported a loss in selectivity after a couple of recycling cycles.

Often in the literature catalysts are purposely incorporated into specific nano-environments to enhance their activity. For instance, placing catalysts into hydrophobic domains in order to exploit the concentrator effect - a term coined by Fréchet in 2005 - allows for the reagents to be brought into closer proximity as they tend towards these hydrophobic regions.[16] This conclusion was drawn from the observation of the catalytic ability of 4-dimethylaminopyridine (DMAP) supported in dendrimers of different polarities. Dendrimers where DMAP was in the most hydrophobic environment achieved the highest conversion. These mirror enzymatic structures found in nature which are well known for their immense catalytic ability due to the active site being buried within a hydrophobic environment surrounded by a hydrophilic shell. Enhanced rates of reactions influenced by local environment have been studied using on-water systems.[17, 18] This has been researched systematically by Sharpless and co-workers in 2005 who demonstrated, amongst others, the rate enhancement of quadricyclane and dimethyl azodicarboxylate; when reacted in toluene the reaction required heating at 80 °C for 24 hours which could be reduced to ambient temperature for a few minutes when the reaction was performed in vigorously stirred water.[19] This rate acceleration has been attributed to a number of effects including hydrophobic aggregation, the same effect as demonstrated by Fréchet.[16] In order to take advantage of how the environment surrounding the catalyst can affect its efficiency, various constructs to support them in hydrophobic domains have been synthesized including star polymers,[20-22] dendrimers,[23, 24] surfactant micelles,[25-27] polymeric micelles[28-31] or even sophisticated folding polymers.[32] These synthetic systems allow the catalyst to be anchored within a hydrophobic environment to promote organic reactions in an overall aqueous media and has been successfully demonstrated by our group for a number of catalysts including DMAP,[29, 33] L-proline[31, 34-36], Cu for click reactions[37] and Pd.[30] The advantages of these types of systems

have been laid out in a recent review by Lu e*t al*.[38]

Interestingly, an approach that has been less explored is the use of cross-linked polymers - namely nanogels - synthesized by emulsion polymerization. Lacking in precision that block copolymers through CRP techniques[39] provide, the overall synthesis is much simpler and scalable. Indeed, these types of structures are successfully used in a myriad of applications,[40-43] including some on industrial scales. The support of catalysts in these structures has also been recently successfully demonstrated in our group using L-proline whereby unprecedented low loadings of catalyst were achieved whilst maintaining high conversions as a result of the concentrator effect. These structures have improved stability, with factors such as temperature, concentration and solvent, over polymeric micelle systems which make them attractive as potential recyclable scaffolds. Unlike most of the previous work, due to the polymerizable nature of our MacMillan catalyst, we are able to immobilize it into a variety of polymeric structures and thus extensively study its ability to catalyze the DA reaction.

Herein we report the immobilization of the MacMillan catalyst into a lightly cross-linked nanogel system *via* an emulsion polymerization process, embedding the catalyst in a hydrophobic environment. The effect of this environment on the catalytic efficiency of the MacMillan catalyst was investigated using a model DA reaction between cinnamaldehyde and cyclopentadiene. The influence of catalyst incorporation within the nanogels with respect to catalyst loading in the reaction was thoroughly examined and revealed an important balance between nanogel, catalyst and substrate concentration to achieve an efficient nanoreactor system.

Experimental

Instrumentation

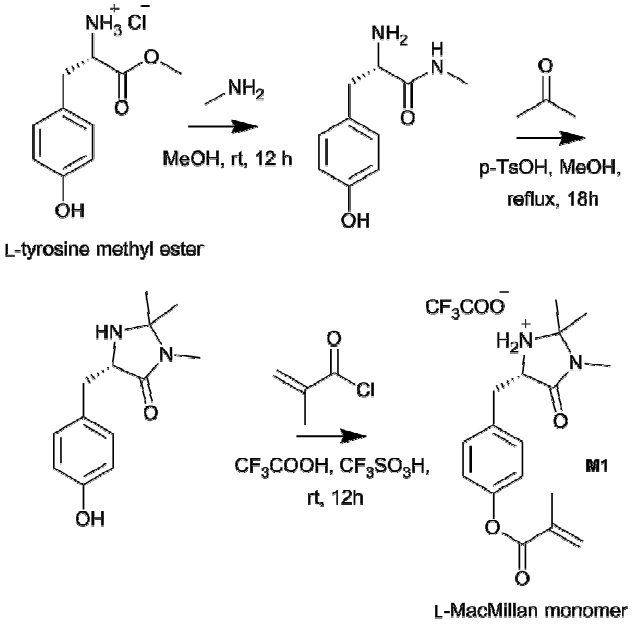
^{1}H NMR spectra were recorded on a 250 or 300 MHz Bruker DPX FT-NMR spectrometer using deuterated solvents. Chemical shifts are reported as δ in parts per million (ppm) relative to the solvent used (d_6-DMSO at 2.50 ppm). Enantiomeric excess (ee %) was measured by gas chromatography (GC) on a Varian 450-GC with a 25 m chirasil-Dex chiral column injection temperature 250 ˚C, column temperature 100 ˚C, ramp to 174 ˚C at 2.0 ˚C min^{-1}. Dialysis tubing was purchased from Spectrum labs with a MWCO of 6 – 8 kDa. Hydrodynamic diameters (D_H) and size distributions were determined by dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS instrument at 25 ˚C equipped with a 4 mW He-Ne 633 nm laser and a detector at 173˚. All measurements were made in triplicate consisting of 10 runs of 10 s each. Variable temperature DLS measurements were carried out using a temperature increment of 10 ˚C between 20 ˚C and 60 ˚C, consisting of 10 x 10 s runs with a 2 min equilibration time held at each temperature. Transmission electron microscopy (TEM) samples were prepared by drop deposition of a 0.1 mg mL^{-1} polymer solution in water onto copper/carbon grids that had been pre-treated with oxygen plasma and analyzed by using a JEOL TEM-2100 microscope operating at 200 kV.

Methods and Techniques

N-isopropylacrylamide (NiPAM) was recrystallized from methanol and stored at 4 ˚C. Cyclopentadiene was prepared from dicyclopentadiene purchased from Sigma-Aldrich and was stored at -20 ˚C. All other chemicals were purchased from Sigma-Aldrich and used without further purification.

M1 synthesis

p-[(1-Methyl-2,2-dimethyl-5-oxo-4-imidazolidinyl)methyl] phenyl methacrylate (**M1**) was synthesized following previous literature protocol (Scheme 1).[8]



Scheme 1. The synthetic route the MacMillan monomer M1

Nanogel synthesis

For a typical nanogel synthesis **M1** (0.108 g) (20 wt%) was first dissolved in 800 µL of $CHCl_3$ and added to a solution of sodium dodecyl sulfate (SDS) (0.125 g) in 10 mL H_2O. This heterogeneous mixture was then added dropwise to 40 mL of H_2O stirring at 600 rpm in a 250 mL round bottom flask. Ethyl methacrylate (EMA) (0.469 mL), ethylene glycol dimethacrylate (EGDMA) (0.0026 mL) and potassium persulfate (KPS) (5 mg) were also added and the mixture was purged with nitrogen for 10 min before submerging into a preheated oil bath at 70 ˚C with stirring at 600 rpm overnight. The solution turned to an iridescent solution which was then dialyzed (MWCO = 6 – 8 kDa) against millipure H_2O to remove any excess SDS.

Core-Shell nanogel synthesis

A typical shell synthesis involved the aforementioned nanogels as seeds for the polymerization; the following procedure is for the addition of a large NiPAM shell. The seed nanogel dispersion (25 mL) was purged by bubbling nitrogen and heated at 70 ˚C with rapid stirring (600-800 rpm). In another flask, SDS (0.018 g) was dissolved in water (25 mL) and purged with nitrogen. To that, NiPAM (0.220 g), *N*,*N*'-methylenebisacrylamide (BIS) (1.3 mg) and KPS (2.5 mg) were added. The monomer mixture was then added slowly to the heated seed nanogel dispersion at no faster

than 1 mL min^{-1}. Once the addition was complete, a positive pressure of nitrogen was maintained for the duration of the reaction. The solution was left to stir overnight and then dialyzed against millipure H_2O (MWCO = 6 – 8 kDa) to remove excess reagents.

Diels-Alder reaction

A typical DA reaction was carried out as follows: to the calculated amount of nanogel dispersion for a desired mol%, cinnamaldehyde (22 µL, 1 eq) and cyclopentadiene (30 µL, 1.5 eq) were added, which was then stirred for 24 hours. Over this period, the reaction mixture turned from the iridescent blue solution to yellow. The reagents and products were extracted at the desired time by swelling the hydrophobic nanogels *via* the addition of 3 mL of THF, yielding a clear yellow solution. The THF was then removed under a flow of air and the remaining residues dissolved in d_6-DMSO and analyzed by ^{1}H NMR spectroscopy determining reaction conversion and GC determining enantiomeric excess (ee %). *exo* isomers t_R = 31.7 and 33.1 min, *endo* isomers t_R = 31.9 and 33.4 min. ^{1}H NMR (250 MHz, DMSO): δ 9.54 (1H, d, J = 1.8 Hz, C(O)**H** *exo*), 9.68 (1H, d, J = 7.5 Hz, C(O)**H** starting material), 9.85 (1H, d, J = 2.2 Hz, C(O)**H** *endo*).

Results and Discussion

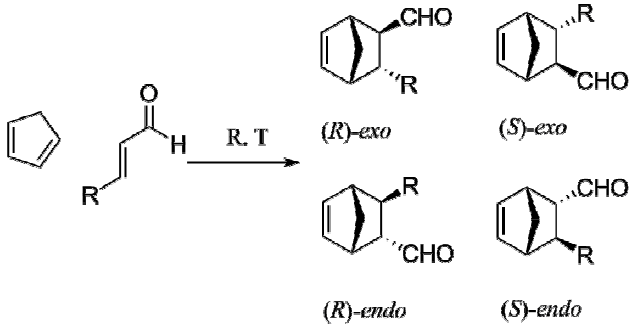
Nanogel Synthesis

A variety of nanogels, prepared by a simple oil-in water emulsion polymerization following the preparation procedure developed by Lu *et al*,[34] that incorporate our MacMillan monomer **M1** have been synthesized, varying the degree of catalyst functionalization (DoF) and nanogel co-monomer. Analysis of the synthesis including kinetics, DLS and TEM can be found in ESI Figure S1 – S3 and show that spherical particles of low size distribution have been produced. The kinetics were obtained by carrying out an identical nanogel synthesis but omitting the crosslinker enabling dissolution into deuterated solvents for ^{1}H NMR analysis. Through sampling the polymerization at regular intervals and disrupting the stabilization through the addition of organic solvent, the relative amount of polymer to monomer could be calculated through ^{1}H NMR spectroscopy. The amount of catalyst incorporation was varied from 0.5 – 25 wt% and the co-monomer was methyl (MMA), ethyl (EMA) or n-butyl methacrylate (nBuMA) increasing the effective hydrophobicity and steric constraint. The details of the synthesized nanogels can be seen in Table 1.

Table 1 The synthesized nanogels **N1** - **N9** detailing the DoF (wt%), co-monomer, hydrodynamic size (nm) and dispersity

Nanogel	DoF (wt%)	Co-monomer	D_H (nm), ($Đ$)[a]
N1	0.5	EMA	48 (0.085)
N2	1	EMA	54 (0.213)
N3	2	EMA	48 (0.045)
N4	15	EMA	38 (0.219)
N5	20	EMA	35 (0.074)
N6	25	EMA	63 (0.081)
N7	15	MMA	33 (0.193)
N8	15	^{n}BuMA	35 (0.252)
N9	0	EMA	35 (0.096)

[a] Measured by DLS analysis.



Scheme 2. The DA reaction between cyclopentadiene and cinnamaldehyde and the four possible products.

Table 2 The conversions of DA reaction between cinnamaldehyde and cyclopentadiene catalyzed by nanogels **N1** – **N6** at various mol%, in water (maintaining a reaction volume of 2 mL)

Entry	Nanogel	DoF (%)	mol %	Conversion (%)[a]
1	**N1**	0.5	0.25	0
2	**N2**	1	0.5	0
3	**N3**	2	1	5
4	**N4**	15	7.2	40
5	**N5**	20	9.8	92
6	**N6**	25	12.3	100

[a] Determined by ^{1}H NMR spectroscopy after 24 hours.

Nanogels **N1**-**N6** were synthesized with the co-monomer EMA and the DoF varied from 0.5% to 25%. **N7** and **N8** have been synthesized at the same DoF as **N4** but with different co-monomers; MMA and nBuMA respectively. Nanogel **N9** contains no catalyst for comparison.

Table 3 Conversion of the DA reaction between cinnamaldehyde and cyclopentadiene catalyzed by **N3** – **N6** at 5 mol%, carried out at room temperature

Entry	Nanogel	DoF (%)	Amount of Nanogel (mL)	Conversion (%)[a]
1	**N3**	2	2	5
2	**N4**	15	1.365	26
3	**N5**	20	1.02	72
4	**N6**	25	0.815	82

[a] Determined by ^{1}H NMR spectroscopy after 24 hours.

Diels-Alder catalysis

The catalytic efficiency of the MacMillan functionalized hydrophobic nanogel was investigated using the DA reaction

between cyclopentadiene and cinnamaldehyde (Scheme 2). It has previously been shown that hydrophobic molecules are able to enter the hydrophobic domain of a supramolecular nanostructure as a result of hydrophobic effects or what has now been coined the concentrator effect.[16] Thus, a high concentration of reaction substrate is expected to diffuse into the MacMillan decorated nanogel core.

Initially, catalysis reactions were carried out at the same concentration of nanogels (i.e. same nanogel volume) resulting in different catalyst concentrations (Table 2).

The DA reaction was most efficiently catalyzed by **N6**, reaching completion in 24 hours. This was not unexpected as the reaction was carried out with the highest concentration of catalyst and thus catalyst loading (Table 1, Entry 6). Comparatively, **N5** and **N4** reached 92 and 40% conversion in the same reaction time with **N3** only reaching 5% conversion at 1 mol% catalyst loading. Unfortunately, **N2** and **N1** were not able to catalyze the reaction at all in 24 hours.

Following these experiments, the catalytic activity of **N3**, **N4**, **N5** and **N6** were compared at the same catalyst loading (5 mol%). This was accomplished by varying the volume of nanogel which resulted in the use of different concentrations of nanogels (Figure 1, B). In other words, a greater number of **N3** nanoreactors are required to make up 5 mol% catalyst loading compared to **N6**. The importance of concentration/number of nanoreactors has previously been reported by our group,[34] and the reverse trend seems to be true for this system. **N6** is once again the most efficient system despite the lower concentration of nanogels (Table 3, Entry 4). We propose this is a partition coefficient effect, which has previously been observed with less hydrophobic substrates[29] where a small portion of substrates remain in the surrounding aqueous environment. As all the reactions detailed in Table 3 were conducted using the same volume of reaction substrates, the substrate to water ratio is smallest for **N6**, perhaps explaining its efficiency.

This hypothesis was investigated by carrying out reactions catalyzed by **N5** and **N6** under more dilute conditions (Figure 1, C). Firstly, catalysis was carried out at a total nanogel volume of 1.365 mL, matching that of **N4** (Table 3, Entry 2), without altering the catalyst loading which remained at 5 mol%. As expected, a drop in conversion was observed for both **N5** and **N6** reaching 60 and 62% conversion respectively in 24 hours (ESI, Table S1). The more dramatic drop in conversion for **N6** further supports our hypothesis that a partition coefficient effect is

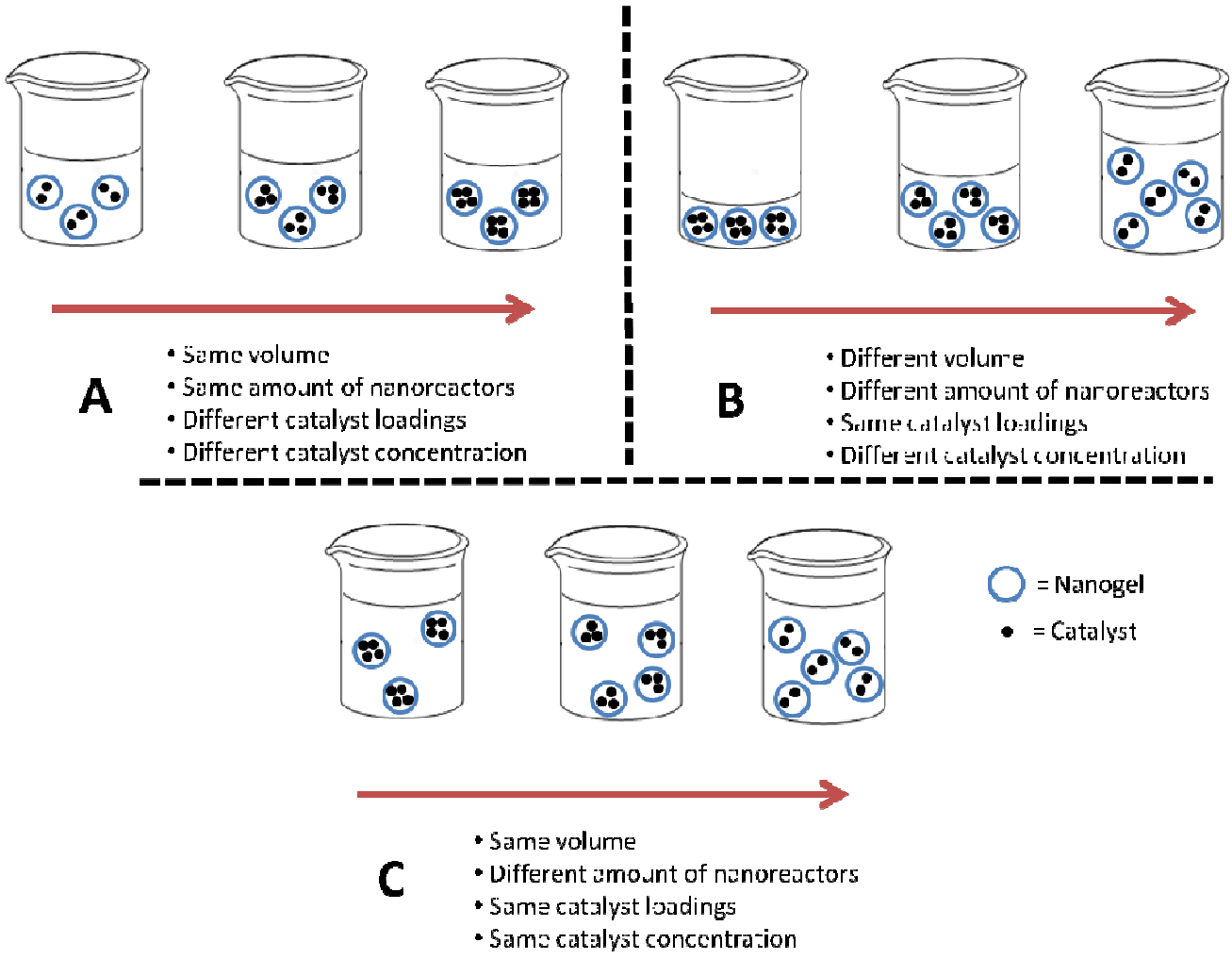


Fig. 1 A schematic representation of reactions carried out varying the nanogel concentration and catalyst concentration (as affected by the difference in catalyst DoF)

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Table 4 Conversion of DA reaction between cinnamaldehyde and cyclopentadiene catalyzed by **N4** – **N6** at 1 mol%, carried out at room temperature

Nanogel	DoF (%)	Reaction volume (mL)	Water added (mL)	Conversion (%)[a]
N4	15	0.275	1.725	11
N5	20	0.255	1.745	2
N6	25	0.205	1.795	8

[a] Determined by ^{1}H NMR spectroscopy after 24 hours.

involved. Further dilution of the nanogel concentration and reducing catalyst loading to 1 mol% resulted in a remarkable drop in conversion to ≤ 11% conversion for **N4**-**N6** (Table 4). Further dilutions were not carried out as conversions as low as 2% were observed.

The catalytic activity of **N5** and **N6** was further compared at a range of catalyst loadings, 1-10 mol% which was carried out by either changing the nanogel concentration or substrate concentration. Interestingly, regardless of which parameter was changed, volume of nanogels or substrates, in all cases an increase in catalyst loading was accompanied by an increase in conversion. This does not correlate with trends previously observed by our group with L-proline functionalized nanogels (ESI, Table S2). In this case when the catalyst was more isolated and the reactions performed at a lower mol% an increase in efficiency was observed, although the change in mol% in this case was achieved through alterations in DoF.

Across all systems the general trend is a higher conversion at higher mol%. The two methods have not given the same conversion for the same mol% with the reactions conducted at the larger volumes always achieving a greater conversion. Indeed repeating **N5** at 5 mol% on an increased scale of 2.04 mL compared to 1.02 mL improved the conversion to 80%. As from a chemical perspective these reactions are the same, the result must be from a physical change. A potential reason could be the changing effect of stirring on the increased volume; as all reactions have been carried out in the same size flask with similar stirrer bars at similar stirring speeds the larger volumes may offer a system that becomes more homogenized, promoting the entry of reagents into the core.

Table 5 The selectivities of the DA reaction after 24 hours between cinnamaldehyde and cyclopentadiene. Catalyzed by **N4** to which the sets of catalysis are compared. Entries 1and 2 are the small molecule reaction, entries 3-5 are different co-monomer nanogels, entries 6 and 7 are different mol % reactions, entry 8 different DoF nanogel and entries 9 and 10 different DoFs of nanogels with the same volume resulting in different mol%

Entry	Catalyst	Co-monomer	Conversion (%)[a]	Mol%	*exo*:*endo*[a]	*exo* ee %[b]	*endo* ee %[b]
1	**MacMillan[1]**		99	5	0.8	93	93
2	**M1 at reported conditions**		62	5	0.8	85	88
3	**N4**	EMA	26	5	0.8	73	72
4	**N7**	MMA	40	5	0.7	83	90
5	**N8**	nBUMA	38	5	0.6	78	85
6	**N4**	EMA	38	2.5	0.8	66	76
7	**N4**	EMA	24	1	0.9	58	65
8	**N5**	EMA	72	5	0.8	70	77
9	**N5**	EMA	92	9.8	0.9	85	80
10	**N6**	EMA	100	12.3	0.9	77	79

[a] Determined by ^{1}H NMR spectroscopy after 24 hours [b] Determined by GC using the ^{1}H NMR spectroscopy sample.

The scope of this catalytic system was also investigated by varying the R group on the dieneophile (Scheme 2). Therefore the DA reaction between cyclopentadiene and acrolein (R = H), *trans* 2-hexen-1-al (R = C_3H_7) and *trans* 2-nonen-1-al (R = C_6H_{13}) was investigated at 5 mol% with **N5**. The conversions of the *trans* 2-hexen-1-al and *trans* 2-nonen-1-al gave conversions of 40% and 49% respectively after 24 hours. However, the less hydrophobic acrolein failed to react in this time period resulting in 0% conversion, which has been attributed to the reagent not entering the hydrophobic cavity. These reactions have been further detailed in ESI Table S3.

Selectivity

In order to further investigate if catalyst immobilization was successful, catalyst stereoselectivity after immobilization was evaluated. Firstly, the monomer was compared to MacMillan's original catalyst under his conditions.[1] **M1** showed both lower

activity and enantioselectivity compared to MacMillan's catalyst at the same catalyst loading and reaction conditions (Table 5, entries 1 and 2), this lower activity could be attributed to the change in structure which could have an effect on the sterics around the active site altering both the accessibility and the enantioselectivity. A further drop in enantioselectivity was observed after the catalyst was incorporated into the nanogel scaffold which is attributed to steric crowding around the catalytic sites.

With reference to Table 5, the selectivities were found to be highly dependent on the reaction conditions. For entries 1 and 2, the small molecules of the reported MacMillan catalyst and **M1,** have achieved comparable selectivity (although **M1** is slightly lower) operating in the same conditions with *endo* ee% of 93% and 88% respectively. However, the enantioselectivity decreases when the catalyst is placed in the nanogel (entry 3) with *endo* ee% dropping to 72%, possibly due to steric crowding interfering with the efficiency of the catalyst. **N7** and **N8** (entries 4 and 5) which have different hydrophobicity and different steric hindrance based on the co-monomers (MMA and nBuMA respectively) have produced different selectivities. **N7** with an MMA core and the lowest steric constraints offers the best enantioselectivity of 83% and 90% ee for *exo* and *endo* respectively. This is much more comparable to the catalysis performed by **M1**, when not immobilized into the nanogel, suggesting that the lower crowding inside the nanogel is favourable for increased selectivity. Entries 6 and 7 show different catalyst loading (mol%) of the reaction, where a drop in mol% (high concentration of reagents) results in a drop in conversion. At 1 mol%, 58% ee and 65% ee for *exo* and *endo* respectively were observed. As the reagents are in high concentration it is likely that there is increased steric crowding inside the nanogel leading to this drop. Interestingly the conversions do not seem to follow a trend with the highest conversion obtained for 2.5 mol%, however, when the turnover number (TON) is examined a clearer trend is observed (1 mol% = 24, 2.5 mol% = 15 and 5 mol% = 5). Comparing the different DoF between entry 3 and 8 we observe that this change does not affect enantioselectivity as **N4** and **N5** (DoF = 15% and 20% respectively) both give ee's for *exo* and *endo* in the 70%s. When the mol% was increased by increasing the volume of nanogel (Table 2) we observe a slight increase in selectivity (Table 5, entries 9 and 10). When **N5** and **N6** were used in catalysis, giving catalyst loadings of 9.8 and 12.3 mol% respectively, the *endo* and *exo* ee% increased. Comparing **N5** at 5 mol% and 9.8 mol% we saw an increase in *endo* ee% from 72% to 80%; further

Table 6 Conversions of DA reaction between cinnamaldehyde and cyclopentadiene catalyzed by **M1**, **N4** and **N6** under different conditions, determined after 24 hours

Catalyst	Vol. H_2O (mL)	[Catalyst][M]	mol %	Conversion (%)
MacMillan[a]		1.0	5	99
M1[a]		1.0	5	62
M1[b]	0.1	0.7	5	62
M1[c]	0.1	0.7	5	9
M1[b]	0.1	0.7	1	29
M1[b]	1.38	0.5×10^{-3}	5	0
N4	1.38	0.5×10^{-3}	5	26
N9	1.38	0.5×10^{-3}	-	0

[a] Performed in reported conditions in CH^3OH:H_2O (95:5 v/v%) at 1.0 M [b] **M1** as TFA salt [c] **M1** with TFA salt removed [d] Determined by ^1H NMR spectroscopy after 24 hours.

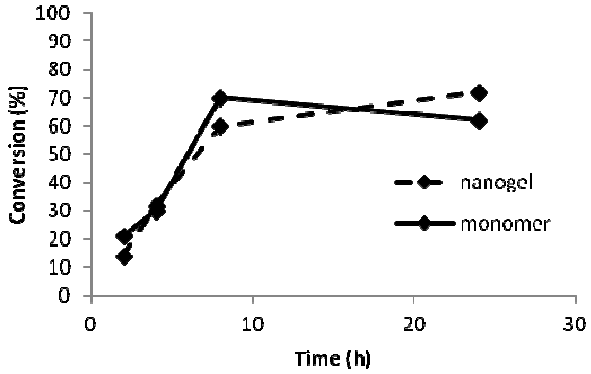

Fig. 2 The conversion against time of **M1** (solid line) in 100 µL H_2O and **N5** (dashed line) in 1.02 mL H_2O. Final conversion **M1,** Table 6.

demonstrating that when the catalyst is less hindered it works more efficiently, as has been demonstrated by previous work where isolated catalysts have resulted in greater yields.[44]

Hydrophobic effect/concentrator effect

To further demonstrate the advantages of catalyst immobilization into polymeric nanostructures, the concentrator effect was further explored. In relatively concentrated conditions (i.e. 100 µL reaction volume) products are observed at both 5 and 1 mol%, reaching 62 and 29% conversion respectively (Table 6). If diluted, to achieve the catalyst concentration observed in the nanogel reactions (i.e. 1.38 mL), no products are observed after 24 hours whereas 26% conversion is observed for **N4**.

The kinetics of the **N5** and **M1** were also investigated to highlight this effect. Both sets of catalysis were carried out at 5 mol%, with **M1** in 100 µL of water and **N5** in 1.02 mL. The conversions were measured from different reactions as sampling the nanogel, with its emulsion type behaviour, led to anomalous results. The conversions can be seen in Figure 2. The two systems have similar rates of reaction, which is significant as **N5** has the catalyst at a much lower concentration. This is a clear observation of the power of the concentrator effect. It is also interesting to note that even though this work has been conducted sampling the conversion at 24 hours to ensure comparisons, high conversions were observed already after 8 hours.

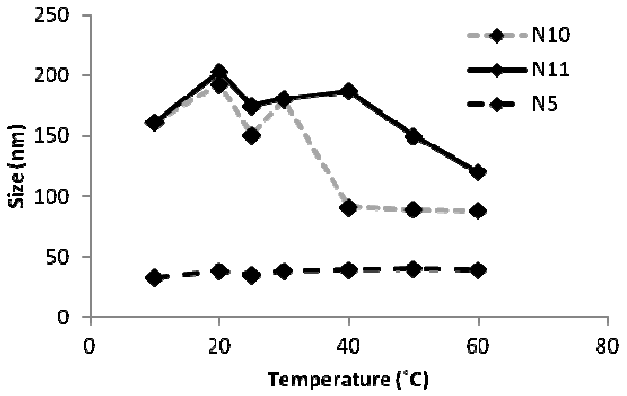

Fig. 3 Change in particle size with temperature, as determined by DLS for **N10**, **N11** and **N5**

Core-shell nanogels

One of the main advantages of using a polymer scaffold for catalyst immobilization is the possibility of catalyst recovery and reuse. This has previously been accomplished using core-shell nanogels with immobilized metal nanoparticles[44] and more recently for the organocatalyst L-proline.[45] These systems require the introduction of a cross-linked steric stabilizer as upon extraction of starting materials and products with an organic solvent the static SDS stabilizer will be solubilized; reducing the ability to re-suspend the polymeric nanogel into water. The presence of a soluble water shell allows for this re-suspension after the removal of the organic small molecules. Encouraged by these previous results, a similar system was designed for the MacMillan catalyst using two different thermo-responsive shells, NIPAM and triethylene glycol di-methacrylate (TEGMA). **N5** (EMA, 20 wt% DoF) was used as the hydrophobic core in both cases yielding PEMA/PNIPAM and PEMA/PTEGMA core-shell nanogels, labelled **N10** and **N11** respectively. An increase in nanogel D_H after addition of the thermo-responsive shell from 35 nm to 151 and 175 for **N10** and **N11** was observed confirming a successful process, determined at 25 °C.

The change in particle size with respect to temperature was monitored by DLS observing a transition from a swollen to shrunken state (Figure 3). A clear and relatively sharp transition was observed for **N10** (30 ˚C) and a less sharp transition for **N11** (40 ˚C). A change in particle size with temperature was not observed for **N5**, consisting of simply the hydrophobic core.

The results of the catalysis performed with the synthesized gels, including a more concentrated system can be seen in ESI Table S4 – S7. Disappointingly the conversion was ≤ 10% after 24 hours, carried out at room temperature. In a further attempt to increase catalyst activity in the supported system, core-shell nanogels with a thinner PNIPAM shell, **N12** was synthesized. At 25 ˚C, the particle size was determined as 85 nm compared to 151 nm for **N10**. Despite the thinner shell, only 10% conversion was achieved at 5 mol% catalyst loading. Addition of the shell had an equally detrimental effect on the selectivity of the catalyst, dropping as low as 50% *endo* ee for **N10** and 35% for **N11** (ESI, Table S5). Due to both the activity and selectivity, the recovery and reuse of the systems were not investigated.

An interesting observation with this system is that catalysis can be switched off by increasing the temperature. For both systems when the temperature was increased from 4 ˚C to 20 ˚C there was an increase in conversion (ESI Table S6), for **N10** an increase from 10 to 13%. It would be anticipated that increasing the temperature further would lead to another increase. However, upon raising the temperature to 40 ˚C, making the shells more hydrophobic, and in the case of **N10** completely hydrophobic, the conversion for **N10** dropped to zero conversion. We propose that, as the shells become hydrophobic they collapse onto the nanogel blocking the core and thus retaining the reagents in the shell. To check that the catalysis was not affected by an increase in temperature the DA reaction was carried out with **M1** in 100 µL of water at 40 ˚C: after 24 hours the conversion had reached 83% with the *endo* ee% dropping to 56%.

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Conclusions

In conclusion we have synthesized hydrophobic polymeric nanostructures that place the MacMillan catalyst into a unique hydrophobic environment. The ease of synthesis has allowed for variation in catalytic loading and steric hindrance (through co-monomers) of the environment. The catalytic ability of the nanostructures was investigated using the DA reaction and shows that these structures offer the concentrator effect required to enhance the performance of organocatalysts. However, the system is greatly affected by the reagents partition coefficient and the catalyst has been shown to lose selective control when placed in these confined environments. Further modifications to the system are currently on the way to improve the catalytic activity and selectivity of the system.

Notes and references

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† Electronic Supplementary Information (ESI) available: Characterization of synthesized nanogels. Conversions of DA reactions for: 5 mol% reactions at the same volume and various mol% for **N5** and **N6** achieved by varying the concentration of substrates and nanogels. Conversions and selectivities of the reaction of cyclopenatdiene with different dieneophiles catalyzed by **N5**. Details of the characterization of the core-shell nanaogels along with their conversions and selectivities in the DA reaction. See DOI: 10.1039/b000000x/

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