

# Reversible Switching and Recycling of Adaptable Organic Microgel Catalysts

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**ABSTRACT:** Adaptable enzyme-mimetic catalysts based on temperature-responsive polymer microgels have been developed. By simply changing the temperature, a microgel catalyst can be reversibly switched into its soluble or precipitated form, thus combining the advantages of a homogeneous and heterogeneous catalysis. The responsive microgel reactors show high reactivity and selectivity, as well as good recycling properties in the alcoholysis of *cis*-tetrahydrophthalic anhydride.

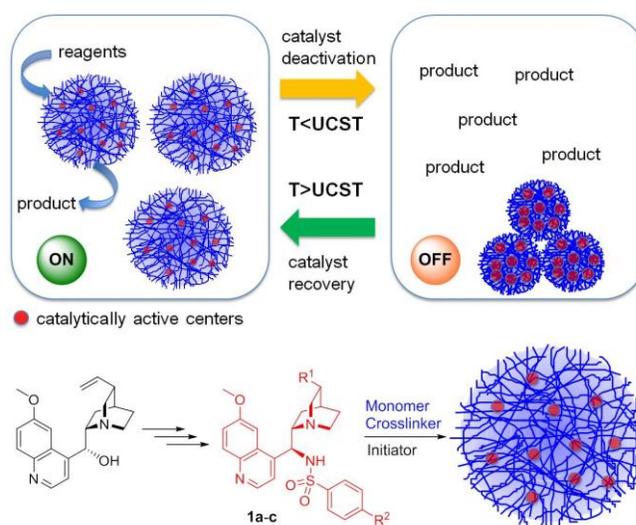
**KEYWORDS:** Switchable Colloidal Catalyst, Temperature-Responsive Microgel, Asymmetric Desymmetrization, Cinchona Alkaloids, Bifunctional Sulfonamides

## ■ INTRODUCTION

Stimuli-responsive polymers, colloids and polymer materials attracted a lot of interest in recent years. Microgels are soft polymer networks consisting of crosslinked polymer chains swollen in a solvent. Microgels exhibit interesting properties that lie between linear polymers and three-dimensional polymer networks (hydrogels).<sup>1-6</sup> Stimuli-responsive microgels can undergo changes in size, softness and surface charge by varying pH, light, solvent or temperature.<sup>7-11</sup> The modification of microgels with metal or metal oxide nanoparticles, ions or proteins results in new materials with enhanced properties.<sup>12-14</sup> Polymer microgels are attractive colloidal carrier systems for application in catalysis. Due to the fact that microgels are highly porous colloids, the functionalization of the particle surface or interior gives a possibility to attach selectively different functionalities.<sup>15-18</sup> Accurately designed microgels adapt to different environments and can be transferred from water to organic environments.<sup>19</sup> The open structure of a swollen microgel allows diffusion of small molecules into the porous colloid and the diffusion rate can be regulated by the swelling degree of the polymer network.<sup>7,20</sup> Compared to molecular catalysts or nanoparticles, microgels are sub-micrometer sized colloids that exhibit stimuli response and adaptable properties and can be adjusted to various reaction conditions and environments which additionally allow convenient purification or separation by simple filtration processes. Hence, we wondered if the material properties of microgels could be unified with homogeneous catalysis. This would provide a new catalyst system, which would not only comprise the properties of the individual components but could potentially lead to new materials with improved performance.

Herein we describe the development of a new adaptable microgel-based colloidal catalyst system. In this system the microgels act as reactive carriers for covalently attached organocatalysts.<sup>21</sup> The particular microgel design allows the catalyst system to remain swollen and colloidally stable at higher reaction temperatures while the reduction in temperature leads to a volume phase transition that induces shrinkage

of microgels and precipitation from the reaction mixture (Figure 1). The critical transition temperature for the precipitation of the colloidal catalysts correlates with the upper critical solution temperature (UCST) of the crosslinked polymer chains and can be flexibly adjusted by the copolymer composition of the microgel. Thus, the new temperature responsive microgel-based colloidal catalysts combine advantages of homogeneous catalysis coupled with temperature-triggered reversible deactivation and separation features, which are very beneficial for catalytic processes on a larger scale.



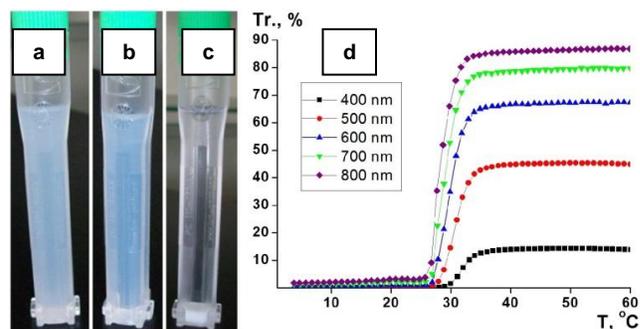
**Figure 1.** Developed switchable catalytic nanoreactors operate with high efficiency at high temperature (ON) and can be isolated from the reaction mixture by precipitation or filtration upon cooling (OFF). A following increase in temperature allows the reuse of the catalyst system. Synthesis of microgels with grafted organocatalysts (**1a**:  $R^1 = \text{vinyl}$ ;  $R^2 = \text{vinyl}$ ; **1b**:  $R^1 = \text{Et}$ ;  $R^2 = \text{vinyl}$ ; **1c**:  $R^1 = \text{vinyl}$ ;  $R^2 = \text{Me}$ ).

## RESULTS AND DISCUSSION

The design strategy of the microgel-based catalysts is presented in Figure 1. We started with the synthesis of catalytically active bifunctional sulfonamides based on naturally occurring quinine. Cinchona alkaloids including quinine and derivatives have been employed as small organic catalysts<sup>22</sup> which are, for instance, able to mimic natural enzymatic reactions and have additionally shown broad applicability in homogeneous catalysis. Their immobilization onto solid supports and their application in heterogeneous catalysis has been achieved.<sup>22-23</sup> However, a general strategy in which both the advantages of homogeneous catalysis (solubility, high reactivity, and selectivity) and heterogeneous catalysis (stability, recycling, and reuse) are unified in a single thermoresponsive polymer system has not been previously established for asymmetric reactions in organic solvents.<sup>24-26</sup>

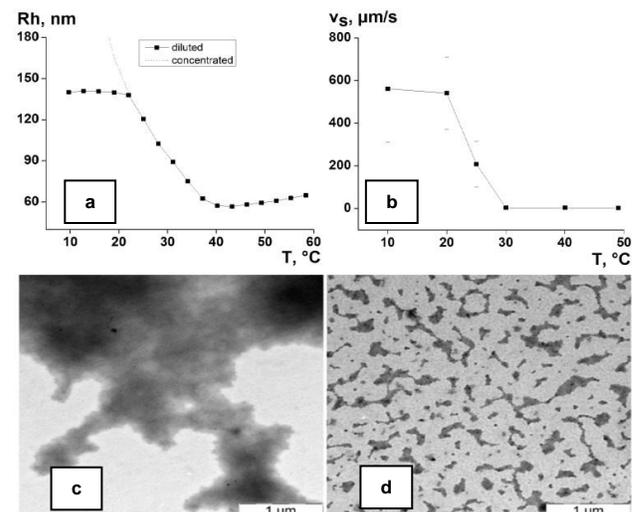
Here we report on the design and use of such a catalyst system, which combines the advantages of homogeneous and heterogeneous catalysis. In order to achieve our goal we synthesized catalyst **1a**, a quinine-derived sulfonamide containing a polymerizable styryl group. This organocatalyst was copolymerized by radical precipitation polymerization with ethyl acrylate (EA) as the main monomer and *N,N'*-methylenebisacrylamide (BIS) as the crosslinker. A series of microgels with 3 mol% crosslinker and organocatalyst contents of 1, 5, and 20 mol% was synthesized (catalysts **A**, **C**, and **D**, respectively). Since **1a** contains two potentially polymerizable groups – a more reactive styryl group on the sulfonamide and a vinyl group on the quinuclidine ring – we performed control experiments to exclude a crosslinking through the organocatalyst. Two additional quinidyl sulfonamides were synthesized: **1b** lacking the vinyl group and **1c** lacking the styryl group (see SI, Scheme S2). **1b** was successfully implemented into microgel catalyst **B**, whereas **1c** could not be incorporated, thus corroborating that no reaction on the vinyl group occurs.

To investigate the thermo-responsive properties as well as the aggregation and sedimentation behavior of the microgels in solution, four different analytical methods were used: UV-Vis spectroscopy, dynamic light scattering (DLS), transmission electron microscopy (TEM) and sedimentation analysis (LUMiFuge). For the latter technique, microgel dispersions were prepared by redispersing microgels in isopropanol at 60 °C. At temperature of 45 °C the microgel solution is opaque and colloidal stable (Figure 2a) and no sedimentation effect was observed after centrifugation at 4000 rpm (Figure 2b). However, after cooling to 5 °C the same sample can be easily precipitated at the same rotation speed (Figure 2c). To obtain more insight into the temperature-induced aggregation of microgels the light transmission was measured at different temperatures and wavelengths by UV-Vis spectrometry (Figure 2d). Independent of the wavelength a sharp transition is observed around 34 °C indicating a sudden aggregation of microgels and formation of colloidal agglomerates that precipitate and lead to the abrupt change of the light transmission.



**Figure 2.** Aggregation behavior of microgel **A** (poly-EA-**1a** (95:5)) (a) before centrifugation at 45 °C, (b) after centrifugation at 45 °C, (c) after centrifugation at 5 °C. (d) Temperature dependence of optical properties of the microgel dispersions at different wavelengths (microgel concentration 10 mg/ml).

The aggregation of microgels in solution at low temperatures was visualized by TEM (Figure 3 c, d). For these measurements a diluted solution of the microgel in isopropanol was dropped on the TEM grid and dried at 5 °C and 45 °C, respectively. At low temperature the whole grid is covered with big microgel aggregates. In contrast, a homogenous distribution of microgel can be observed by drying at 45 °C.

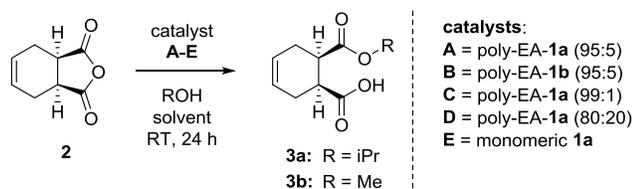


**Figure 3.** Hydrodynamic radius (a) and sedimentation velocity (2000 rpm) (b) of microgel **A** (poly-EA-**1a** (95:5)) in isopropanol as a function of the temperature. TEM image of the same microgel dried at 5 °C (c) and 45 °C (d).

UV-Vis measurements and TEM analysis correlate well with the results of the particle size measurements by DLS (Figure 3a). In the temperature range between 60 °C and 40 °C the hydrodynamic radii ( $R_h$ ) of microgels shrink from 62 to 52 nm. This effect is related to the volume phase transition (VPT) of microgels due to the upper critical solution temperature (UCST) of poly(ethyl acrylate) chains in *iso*-propanol.<sup>27</sup> Upon cooling polymer chains become poorly solvated and undergo coil-globule transitions which lead to the shrinkage of the microgels themselves. Simultaneously, the colloidal stability of the microgels is reduced and they start to aggregate when the temperature decreases below 40 °C. This is reflected in the increase of the hydrodynamic radius below 40 °C (Figure 3a). This increase of  $R_h$  is followed by the increase of the

polydispersity index (PDI) (see SI, Figure S2), which is evident for an aggregation process. As temperature further decreases the microgel aggregates grow in size and become stabilized in diluted solutions reaching the plateau value of  $R_h$  below 22 °C. In concentrated solutions the rapid growth of the aggregate size will result in the macroscopic phase separation and precipitation of the microgels. The measurements of the sedimentation velocity (Figure 3b) performed at different temperatures match perfectly the DLS results in Figure 3a. Above the volume phase transition temperature the microgel solution is stable (sedimentation speed is very low). Decreasing the temperature below the volume phase transition temperature results in aggregates that induce colloidal instability and increase the sedimentation velocity. These experimental data demonstrate that the microgels exhibit a temperature-switchable colloidal stability; they are swollen and colloiddally stable at high temperatures and shrink and precipitate when the solution is cooled.

In order to confirm that the catalyst has been incorporated in the microgel during the copolymerization, we performed sulfur elemental analysis (see SI, Table S1) and FT-IR studies (see SI, Figure S1). Microgels with different amounts of immobilized catalysts were examined and the measurements clearly demonstrated the incorporation of the organocatalyst during the polymerization process. Thus, the new microgel catalyst systems contain bifunctional quindylsulfonamide moieties, which resemble the active sites of an enzyme in the microgel environment. Additionally, its temperature responsive behavior is an efficient tool to switch the solvation state and convert the active catalyst into a recyclable material after the reaction. Considering its temperature dependent swelling/deswelling ability in alcoholic solvents, particularly in *iso*-propanol, we selected the desymmetrization of *meso*-anhydrides<sup>28</sup> as organocatalytic model reaction in order to demonstrate the advanced properties of the newly developed switchable nanoreactors. Thus, we started our investigations with the asymmetric alcoholysis of *cis*-tetrahydrophthalic anhydride **2** (Scheme 1).



**Scheme 1.** General scheme for the asymmetric alcoholysis of *cis*-tetrahydrophthalic anhydride (**2**).

We commenced our studies using catalyst **A** (containing 5 mol% **1a**) and *iso*-propanol as nucleophile in order to open the anhydride. Although *iso*-propanol is a sterically demanding nucleophile and it has been reported to open *meso*-anhydrides with a significantly lower rate compared to less hindered nucleophiles like methanol, we were able to obtain the desired *iso*-propyl hemiester **3a**. Unfortunately, the reaction proceeded slowly and with negligible enantioselectivity (53:47 e.r., Table 1, entry 1). Therefore, we modified the reaction procedure by adding 5 equiv of methanol to the reaction mixture and expected this less sterically demanding nucleophile to react much faster than the solvent *iso*-propanol. The enantiomeric excess of the desired methyl hemiester **3b** was poor (68:32 e.r., entry 2) and a significant background reaction of the

solvent *iso*-propanol was observed. Using methanol as solvent resulted in a lower selectivity (59:41 e.r., entry 3) and the catalyst did not show UCST behavior in this solvent (see SI, Figure S3), preventing a catalyst recycling.

**Table 1.** Evaluation of catalyst loading, solvent mixtures, concentration and equivalents of nucleophile.<sup>a</sup>

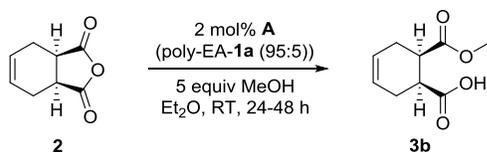
Entry	Cat (mol%)	Solv.	Nu	Equiv.	c [M]	e.r. (%) <sup>b</sup>
1 <sup>c</sup>	<b>A</b> (2)	<i>i</i> PrOH	<i>i</i> PrOH	600	0.02	53:47
2 <sup>c</sup>	<b>A</b> (2)	<i>i</i> PrOH	MeOH	5	0.02	68:32 <sup>d</sup>
3 <sup>e</sup>	<b>A</b> (2)	MeO	MeOH	1200	0.02	59:41
4 <sup>f</sup>	<b>A</b> (2)	Et <sub>2</sub> O <sup>g</sup>	<i>i</i> PrOH	400	0.02	n.r. <sup>h</sup>
5 <sup>f</sup>	<b>A</b> (2)	Et <sub>2</sub> O <sup>i</sup>	<i>i</i> PrOH	200	0.02	n.r. <sup>h</sup>
6	<b>A</b> (2)	Et <sub>2</sub> O <sup>j</sup>	MeOH	800	0.02	62:38
7	<b>A</b> (2)	Et <sub>2</sub> O <sup>k</sup>	MeOH	400	0.02	70:30
8	<b>A</b> (2)	Et <sub>2</sub> O	MeOH	20	0.02	88:12
9	<b>A</b> (2)	Et <sub>2</sub> O	MeOH	10	0.02	90:10
10	<b>A</b> (2)	Et <sub>2</sub> O	MeOH	5	0.02	93:7
11	<b>B</b> (2)	Et <sub>2</sub> O	MeOH	5	0.02	89:11
12	<b>C</b> (2)	Et <sub>2</sub> O	MeOH	5	0.02	91:9
13 <sup>e</sup>	<b>D</b> (2)	Et <sub>2</sub> O	MeOH	5	0.02	94:6
14 <sup>e</sup>	<b>E</b> (2)	Et <sub>2</sub> O	MeOH	5	0.02	96:4
15	<b>A</b> (1)	Et <sub>2</sub> O	MeOH	5	0.02	88:12 <sup>l</sup>
16	<b>A</b> (5)	Et <sub>2</sub> O	MeOH	5	0.02	93:7
17	<b>A</b> (10)	Et <sub>2</sub> O	MeOH	5	0.02	94:6
18	<b>A</b> (20)	Et <sub>2</sub> O	MeOH	5	0.02	94:6
19	<b>A</b> (2)	Et <sub>2</sub> O	MeOH	5	0.01	93:7 <sup>m</sup>
20	<b>A</b> (2)	Et <sub>2</sub> O	MeOH	5	0.05	87:13
21	<b>A</b> (2)	Et <sub>2</sub> O	MeOH	5	0.1	82:18
22	<b>A</b> (2)	Et <sub>2</sub> O	MeOH	5	0.2	75:25

<sup>a</sup>Reaction conditions: reaction conditions: 0.2 mmol substrate **2**, catalyst **A-E**, solvent, RT, 24 h; <sup>b</sup>determined after derivatization of the free carboxylic acid into the corresponding (*R*)-1-(naphthalen-1-yl)ethyl amide (see supporting information) by SFC using Chiralcel OJ-H column; <sup>c</sup>reaction performed at 40 °C; <sup>d</sup>44% isopropyl hemiester byproduct (48:52 e.r.); <sup>e</sup>catalyst is not temperature-responsive in this solvent mixture, therefore no recycling possible; <sup>f</sup>reaction performed at 30 °C; <sup>g</sup>Et<sub>2</sub>O/ *i*PrOH 1:2; <sup>h</sup>no reaction; <sup>i</sup>Et<sub>2</sub>O/ *i*PrOH 2:1; <sup>j</sup>MeOH/ Et<sub>2</sub>O 2:1; <sup>k</sup>Et<sub>2</sub>O/ MeOH 2:1; <sup>l</sup>incomplete conversion after 24 h; <sup>m</sup>incomplete conversion after 120 h.

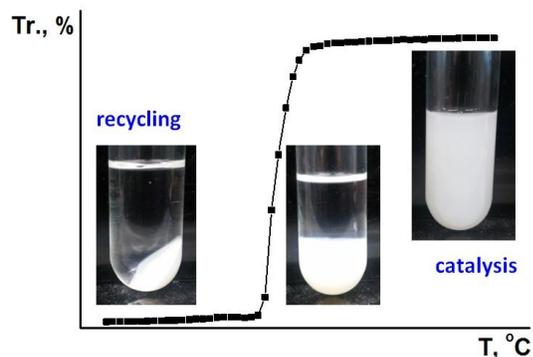
Previous reports on the desymmetrization of *meso*-anhydrides found less polar solvents to be better for the enantio-differentiating pathways. For the same reason the amount of added nucleophile is important as a large excess of nucleophile can lead to reduced enantiomeric excess. Taking this into account, we varied the solvent system further by successively adding diethyl ether and observed an UCST in the UV-Vis for solvent mixtures of diethyl ether and *iso*-propanol (see SI, Figures S4c and S4e). However, the transition becomes broad and therefore the microgel catalyst is not well solvated under catalysis condition, resulting in no product formation (Table 1, entries 4 and 5). For mixtures of diethyl ether and MeOH on the other hand, we observed a relatively sharp UCST behavior at 6 °C (see SI, Figures S4d and S4f). This allowed us to efficiently recycle the microgel catalyst upon cooling to 0 °C. The precipitated catalyst was separated by centrifugation, washed,

and recharged with fresh solvent and substrate to perform another catalytic cycle.

We tested the new solvent system for its catalytic performance and observed satisfying stereoselectivity. A screening of the amount of added nucleophile revealed that 5 equivalents of methanol are optimal, providing a significantly enhanced enantiomeric excess of 93:7 e.r. (entry 10). In comparison, catalyst **B** (containing **1b**) performed slightly worse than catalyst **A** (89:11 e.r., entry 11). A lowered degree of functionalization of EA/**1a** 99:1 in polymer catalyst **C** resulted in a decreased enantioselectivity (91:9 e.r., entry 12). On the other hand, a functionalization degree of EA/**1a** 80:20 caused catalyst **D** to lose its thermoresponsive behavior and recycling properties (entry 13). Having a promising catalyst system in hands, we screened additional parameters in order to optimize the enantiocontrol further. We started off with the catalyst loading and found 10 mol% catalyst to be optimal (94:6 e.r., entry 17). Decreasing the catalyst loading had only little impact on the enantioselectivity, however at 1 mol% a dramatically lowered reactivity was observed. Therefore, we decided to move on with the 2 mol% conditions and found in a subsequent concentration screening (entries 19-22) that 0.02 M provides an optimal balance between reactivity and high enantioselectivity (93:7 e.r.). In comparison, the non-immobilized variant **1a** provided similar enantiomeric excess (entry 14).



Run	Yield [%]	e.r. (%)
1	96	92:8
2	95	93:7
3	96	91:9
4	97	92:8
5	96	93:7
6	95	93:7
7	96	91:9
8	94	92:8
9	95	92:8
10	96	93:7



**Figure 4.** Reversible switching and recycling of adaptable organic nanoreactors **A** (poly-EA-**1a** (95:5)).

With the optimal reaction conditions we performed 10 subsequent reaction runs, each followed by catalyst recovery and obtained the products with excellent yields (94-97%) and a stable enantiocontrol (91:9 - 93:7 e.r.) demonstrating the efficacy of the reversible switching and recycling properties of the adaptable organic nanoreactors (Figure 4).

## CONCLUSIONS

In summary, we have developed switchable colloidal catalysts based on temperature-responsive polymer microgels that combine advantages of homogeneous and heterogeneous catalysts. The new adaptable catalyst system consists of a porous microgel structure in which a covalently attached organocatalyst acts as a catalysis center mimicking the active site of an enzyme. Compared to enzymes, the temperature responsiveness of the microgel leads to distinct advantages. The catalyst activity can be simply reversibly switched on and off by adjustment of the temperature. At reaction temperature ( $T > VPTT$ ) the microgels are swollen and colloidally stable which ensures a large surface area, high reaction speed and selectivity. With decreasing temperature to  $T < VPTT$  the microgels collapse and form aggregates in solution and the catalytic activity is switched off. The colloidal aggregates can be easily separated from the reaction mixture by filtration or centrifugation and, hence, no further work-up is needed. The catalyst can be recycled several times as the microgel aggregates solubilize again to provide the active catalyst system. This provides a unique possibility of fast recovery and re-use of the colloidal microgel catalyst what results in the lowering of the production costs and reduction of the product pollution risk often observed in metal catalyzed processes. In addition, microgel-based catalysts exhibit superior thermal and chemical resistance. As a representative example we demonstrated the application of this temperature-responsive enzyme-mimicking microgel containing a bifunctional quinidylsulfomamide moiety as the active catalysis site in the desymmetrization of *meso*-anhydrides. Under reaction conditions, above its UCST, the catalytically active microgel is swollen and well solvated and therefore acts as a homogeneous catalyst with advantages of high reaction yield (>95%) and good enantiocontrol. After the reaction has finished, the catalyst can be switched off by simply decreasing the temperature below the UCST, which leads to shrinking, aggregation and precipitation of the microgel. We performed several subsequent catalytic cycles by cooling the reaction mixture and separating the precipitated microgel by filtration. The experimental data indicate that high efficiency and selectivity of the colloidal catalyst remains unaltered after many separation cycles. Thus, the interesting properties of these new switchable and recyclable microgel-based catalysts opens up new possibilities and opportunities for designing and preparing new adaptable organic nanoreactors with high efficiency.

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## Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

## Notes

The authors declare no competing financial interests.

## ASSOCIATED CONTENT

**Supporting Information.** Detailed experimental procedures and spectral data are available in the supporting information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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