



# A reinforced Pickering emulsion for cascade reactions†

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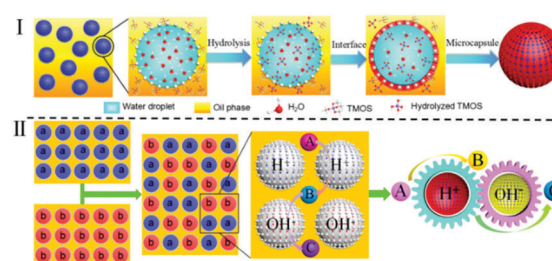
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**Based on an interfacial sol–gel process, a novel reinforced Pickering emulsion has been developed successfully for one-pot cascade reactions involving incompatible catalysts.**

Living cells, as an ingenious outcome of nature evolution, are an excellent platform to perform multistep cascade reactions with unsurpassed efficiency and specificity.<sup>1–5</sup> Among several tactics employed to reconcile different reaction pathways, “compartmentalization” is one of the key strategies. Due to the compartmentalization, incompatible substrates and biocatalytic species are spatially isolated, and undesired interferences between multiple species can be avoided.<sup>5–9</sup>

Inspired by living cells, many artificially compartmentalized systems have been explored for one-pot cascade reactions. The reported strategies mainly rely on the immobilization or encapsulation of different catalytic species on/within polymers or sol-gel materials to avoid direct contact.<sup>8–20</sup> Although encouraging results are obtained, these methods often entail quite complex immobilization/encapsulation procedures.<sup>4,8–11</sup> Moreover, these systems are still embryonic because of the inability to mimic the fundamental aspects of cellular systems.

Pickering emulsions, namely particle-stabilized emulsions, are emerging as an ideal platform for mimicking natural systems.<sup>6,21–30</sup> The spatially separated small droplets of laminated Pickering emulsions have recently been explored to serve as microcompartments to compartmentalize different incompatible reagents, while the continuous phase (outside droplets) allows other reactants to diffuse freely and to access the compartmentalized reagents for chemical reactions.<sup>28</sup> However, due to the thermodynamic instability, droplet coalescence and Ostwald ripening occur unavoidably, leading to the contact of incompatible reagents during the reaction.<sup>31</sup> Another disadvantage of



**Scheme 1** (I) Procedures for the preparation of reinforced Pickering emulsion droplets. (II) Schematic description of a one-pot cascade reaction based on a reinforced Pickering emulsion. a represents an acid-containing reinforced Pickering droplet. b represents a base-containing reinforced Pickering emulsion droplet. A is a starting substrate. B represents an intermediate, and C is a final product.

this system is the requirement of laminating two Pickering emulsions, which ensures sufficiently long distances between droplets containing incompatible reagents. These inherent limitations severely hinder the practical application of the concept.

Herein, we report a novel approach for conducting one-pot cascade reactions based on a reinforced Pickering-emulsion. As shown in Scheme 1(I), water-in-oil Pickering emulsion droplets are reinforced through cross-linking of emulsifier particles, forming an inorganic shell around the droplets. [The emulsifiers were prepared by surface modification of 60–80 nm silica nanospheres with methyltriethoxysilane, as shown in transmission electron microscopy (TEM) images in Fig. S1 in the ESI;† their water contact angle was 92° as shown in Fig. S2 in the ESI;†] Tetramethoxysilane (TMOS) is used as the cross-linking reagent because it can be hydrolyzed and condensed under relatively mild conditions (detailed procedures included in the ESI†). If an acid (for example, H<sub>2</sub>SO<sub>4</sub>) or a base (for example, NH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, which is denoted as EDA hereafter) is added into the water phase before formulating the Pickering emulsions, one can get an acid-containing reinforced Pickering emulsion or a base-containing reinforced Pickering emulsion. These two reinforced Pickering emulsions are brought together and well mixed, leading to an acid/base-coexisting biphasic system, as shown in Scheme 1(II).

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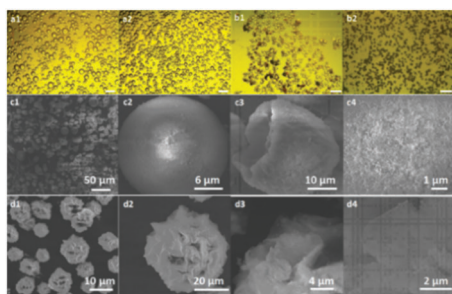
During the reaction, reactant A in the oil phase can be converted to intermediate B upon contact with the acid catalyst, which is subsequently transformed to the final product C after contact with the base catalyst. The good shell permeability of the reinforced droplets ensures contact of the reactants/intermediate with the acid/base catalysts. Since the presence of an inorganic shell around each droplet avoids the thermodynamically driven droplet coalescence and Ostwald ripening, the acid and base can co-exist in the same vessel for a long period of time. Moreover, due to the high stability of the reinforced droplets, the lamination procedures used in the previous method can be avoided completely.<sup>28</sup>

As shown in Fig. 1a, the prepared Pickering emulsion droplets containing the acid or base are spherical and somewhat poly-disperse with a mean diameter of 17 or 39  $\mu\text{m}$  (for the droplet size distribution, see Fig. S3 in the ESI<sup>†</sup>). After cross-linking, the obtained acid-containing or base-containing reinforced Pickering emulsion droplets have a size distribution similar to that of their mother droplets. Upon washing thoroughly with ethanol, the structural integrity of the empty microcapsule was well preserved (Fig. 1b). In contrast, without cross-linking, the droplets were broken after ethanol washing, which was due to ethanol-induced demulsification. Scanning electron microscopy (SEM) indicated that the hollow microcapsules were structurally robust under vacuum. Their shell was several micrometers in thickness (Fig. 1c and d). From the magnified SEM image, one can find that the silica emulsifiers were closely packed on the outer surface of the microcapsules. Interestingly, the microcapsules derived from the acid-containing Pickering emulsion and the microcapsules derived from the base-containing Pickering emulsion differ significantly in surface morphology. The former was broadly spherical, while the latter was spheres with apparent wrinkles. This difference might be attributed to the difference in the hydrolysis and condensation rates.<sup>32–34</sup> With acid as the catalyst, the condensation rate is slower, and the hydrolysed siliceous moieties first condensate with the silanols on the emulsifier surfaces, resulting in a relatively holonomic spherical shell structure. With base as the catalyst, the condensation rate is faster than the

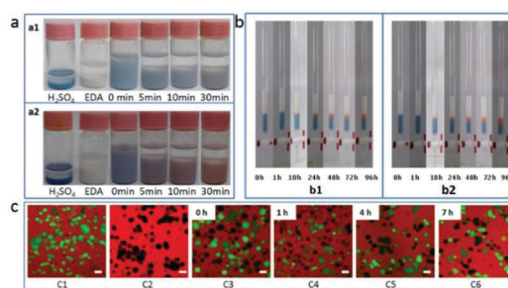
hydrolysis rate, and the self-condensation of the siliceous moieties took place more easily.

The porosity of the shell of the reinforced droplets was determined by nitrogen-sorption measurements. Before measurements, the inner liquid was also washed off. As shown in Fig. S4 (ESI<sup>†</sup>), the microcapsules derived from the acid-containing droplets show a type-IV isotherm, and the microcapsules derived from the base-containing droplets display a type-II isotherm. The BET specific surface area of the former is as high as 537  $\text{m}^2 \text{g}^{-1}$ , and that of the latter is 188  $\text{m}^2 \text{g}^{-1}$ . Their pore size distributions calculated by the BJH method are 4–6 nm and 20–30 nm, respectively. The formation of high surface areas and large pores is very interesting since no surfactants were used as the template during the cross-linking process. These results confirm that the reinforced droplets have a porous shell, which helps the molecules to communicate with the external medium.

We next checked the ability of the reinforced Pickering emulsion to confine opposing reagents ( $\text{H}_2\text{SO}_4$  and EDA) in the same system. Congo red was used as the indicator to visualize the pH changes of the water droplets because it is water-soluble but oil-insoluble and its color varies as the pH changes (azure at  $\text{pH} < 3.0$  and red at  $\text{pH} > 5.0$ ). Acid-containing reinforced droplets were prepared by using 0.5 M  $\text{H}_2\text{SO}_4$  (0.80 mL) in the presence of Congo red. The resultant reinforced Pickering emulsion is azure in color (Fig. 2a, a1). This reinforced Pickering emulsion was then mixed thoroughly with the EDA-containing reinforced Pickering emulsion. If only a small portion of EDA diffuse out from the reinforced droplets and cross the oil phase to react with  $\text{H}_2\text{SO}_4$  within the neighbouring reinforced droplets, the color of the mixture should change. As seen, at the beginning, the mixture was azure (Fig. 2a, a1). After standing for 5 min, the reinforced droplets settled down and the color remained azure. After 30 min, the color still had no visible change, indicating the survival of the acid and base in the same system. For comparison, the same procedure was implemented to mix the acid-containing and the base-containing Pickering emulsions



**Fig. 1** Optical microscopy images of the  $\text{H}_2\text{SO}_4$ -containing reinforced Pickering emulsion before (a1) and after (b1) cross-linking with TMOS. Optical microscopy images of the EDA-containing Pickering emulsion before (a2) and after (b2) cross-linking with TMOS, the scale bar is 100  $\mu\text{m}$ . SEM images of the microcapsules derived from the  $\text{H}_2\text{SO}_4$ -containing (c) and the EDA-containing (d) reinforced Pickering emulsions. (c1 and d1) The morphology of the microcapsules. (c2 and d2) A single microcapsule at high magnification. (c3 and d3) A deliberately broken particle. (c4 and d4) The surface of the shell at high magnification.



**Fig. 2** (a) Comparison of the confining ability of the reinforced Pickering emulsion (a1) and the Pickering emulsion (without cross-linking, a2). (b) Appearance of the columns filled with Cargo red and the  $\text{H}_2\text{SO}_4$ -containing reinforced Pickering emulsion in the lower layer and the EDA-containing reinforced Pickering emulsion in the upper layer (b1) and the corresponding Pickering emulsion system (without cross-linking, b2). (c) The fluorescence microscopy images of the FITC-dextran-stained reinforced Pickering emulsion in a Nile Red solution and (c1) the reinforced Pickering emulsion in a Nile Red solution (c2). Well-mixed c1 and c2 over time (c3–c6). The scale bar is 50  $\mu\text{m}$ .

without cross-linking (Fig. 2a, a2). A rapid color change from azure to red was observed once they were brought together, which was a result of acid–base reactions.

In order to further evaluate the ability of the reinforced droplets to confine acid or base, we packed a column reactor with these two reinforced Pickering emulsions in the lower layer (acid-containing) and in the upper layer (base-containing), respectively. Due to the presence of Congo red, the lower layer was azure. To make the experiment more sensitive, the upper layer was allowed to contain an excess of EDA (4 mL, 500 mM) in comparison to its opposing reagent  $\text{H}_2\text{SO}_4$  (4 mL, 5 mM) in the lower layer. If a trace of the base flows down with the oil phase, the lower layer would change its color. Initially, a clear boundary between these two layers was discerned. After the oil phase flowed for 10 h ( $2 \text{ mL h}^{-1}$ ), a red layer appeared, which resulted from acid–base neutralization. After 96 h of continuous flow, about 1.1 cm of the reinforced Pickering emulsion changed from azure to red. The reason for the escape of EDA from the reinforced droplets is its slight miscibility with toluene. Under the same conditions, the color change length of the Pickering emulsion (without cross-linking) was 1.9 cm, which is about 1.7 fold larger than that of the reinforced Pickering emulsion system. These comparisons underscore that the reinforced Pickering emulsion has enhanced confinement ability.

Also, we used confocal fluorescence microscopy to observe whether the fluorescent molecules transfer between the reinforced droplets. A water-soluble dye (toluene-insoluble), fluorescein isothiocyanate (FITC-dextran), was loaded into a reinforced Pickering emulsion during the preparation. Its oil phase (toluene) was also stained with another dye, fluorescein Nile red (water-insoluble). As seen in Fig. 2c, the fluorescence images reveal that the FITC-dextran is distributed within the interior of the reinforced droplets as evidenced by green zones. After mixing the FITC-dextran/Nile red co-stained reinforced Pickering emulsion with only the Nile red-stained reinforced Pickering emulsion, green and black zones were observed concomitantly. After standing for 7 h, this situation remained almost unchanged. That is to say, the FITC-dextran molecules did not initially enter the dye-free reinforced droplets. These findings further confirm that the reinforced droplets have good ability to compartmentalize molecules within their interiors and prevent the transport of oil-phase-insoluble molecules between different reinforced droplets.

To evaluate the stability of the reinforced Pickering emulsion against coalescence, a thermal treatment was implemented. As shown in Fig. S5 (ESI<sup>†</sup>), after thermal treatment at  $100^\circ\text{C}$  for 3 h, the reinforced droplets remained almost the same as those before the thermal treatment, whereas the droplets of the Pickering emulsion (without cross-linking) were completely destroyed. This difference indicates that the cross-linking was indeed successful and the resulting reinforced droplets have high stability against coalescence.

As demonstrated above, the coupling of good compartmentalization ability with excellent shell permeability probably enables one-pot cascade reactions in this reinforced Pickering emulsion. To test this potential, a deacetalization–Knoevenagel condensation cascade reaction was chosen for investigation,

in which deacetalization requires an acid as the catalyst and Knoevenagel condensation requires a base as the catalyst.<sup>28</sup> The cascade reaction system was formulated by mixing together an acid-containing reinforced Pickering emulsion, a base-containing reinforced Pickering emulsion, and the reactants.

To validate the examination, we conducted a set of control experiments. In the first control experiment, only a  $\text{H}_2\text{SO}_4$ -containing reinforced Pickering emulsion was present in the reaction system (without EDA). After 3 h, the content of benzaldehyde dimethylacetal in the reaction mixture was determined to be less than 0.5%, and that of the intermediate product was more than 99%, and no final product was detected (Fig. 3). In the second control experiment, the reaction system consisted of only an EDA-containing reinforced Pickering emulsion without  $\text{H}_2\text{SO}_4$ . After the same period of time, the content of benzaldehyde dimethylacetal in the reaction mixture was also more than 85% and the second reaction did not occur. These two control experiments suggest that the combination of  $\text{H}_2\text{SO}_4$  and EDA is absolutely necessary for this chosen cascade reaction. In the third control experiment, a  $\text{H}_2\text{SO}_4$ -containing Pickering emulsion and an EDA-containing Pickering emulsion (both without cross-linking) were mixed together. Under the same reaction conditions, only 30% of benzaldehyde dimethylacetal was converted to the intermediate benzaldehyde and the final product was approximately 20%. This outcome suggests that a Pickering emulsion without cross-linking has no ability to process this cascade reaction. For the reinforced Pickering emulsion system, benzaldehyde dimethylacetal was fully transformed to the final product *via* a deacetalization–Knoevenagel cascade after the same period of time (Fig. 3 and Table 1, entry 1). This set of experiments confirms the effectiveness of the reinforced Pickering emulsion in performing one-pot cascade reactions involving opposing reagents.

The cascade reaction system is applicable to other substrates, as summarized in Table 1 (entries 3 and 4). Benzaldehyde dimethylacetal was also transformed to the final product with 96.6% of conversion within 6 h at  $70^\circ\text{C}$ . For less reactive

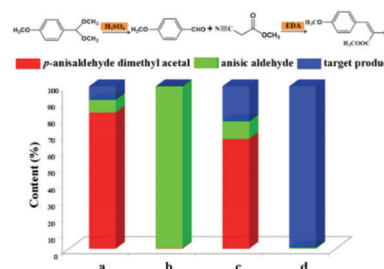
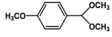
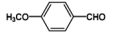
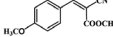








Fig. 3 Comparison of the compositions in different reaction systems for the *p*-anisaldehyde dimethyl acetal deacetalization–Knoevenagel cascade reaction. (a) Only a  $\text{H}_2\text{SO}_4$ -containing reinforced Pickering emulsion was present in the reaction system (without EDA). (b) Only an EDA-containing reinforced Pickering emulsion without  $\text{H}_2\text{SO}_4$ . (c) A  $\text{H}_2\text{SO}_4$ -containing Pickering emulsion and an EDA-containing Pickering emulsion (both without cross-linking) were mixed together. (d) The mixed acid- and base-containing reinforced Pickering emulsion systems. Reaction conditions: 0.4 mL  $\text{H}_2\text{SO}_4$  (0.5 M), 1.0 mL EDA (0.5 M), 2 mmol *p*-anisaldehyde dimethyl acetal, 3 mmol methyl cyanoacetate, and 70 rpm rotating.

Table 1 Results of deacetalization–Knoevenagel cascade reactions of the reinforced Pickering emulsions

Entry	Reactions	Intermediates	Products	T/°C	Time <sup>e</sup> (h)	Yield <sup>f</sup> (%)	Yield <sup>g</sup> (%)
1 <sup>a</sup>				50	3	0.0	> 99.9
2 <sup>b</sup>				50	8	< 20	> 80.0
3 <sup>c</sup>				70	6	3.1	96.6
4 <sup>d</sup>				80	12	3.6	85.5

Reaction conditions: 0.4 mL H<sub>2</sub>SO<sub>4</sub> (0.5 M), 1.0 mL EDA (0.5 M), 70 rpm.<sup>a</sup> 2 mmol *p*-anisaldehyde dimethyl acetal and 3 mmol methyl cyanoacetate.

<sup>b</sup> The second reaction cycle of the reinforced Pickering emulsion under the same conditions as those of the case of *a*. <sup>c</sup> 2 mmol benzaldehyde dimethyl acetal and 3 mmol methyl cyanoacetate. <sup>d</sup> 1 mmol benzaldehyde propylene glycol acetal and 1.5 mmol methyl cyanoacetate. <sup>e</sup> Reaction time. <sup>f</sup> Yield of the intermediates. <sup>g</sup> Yield of the final target product.

acetals such as benzaldehyde propylene glycolacetal, the content of the final products was determined to be 85.5% within 12 h at 80 °C. These findings further demonstrate the effectiveness of the Pickering emulsion based encapsulation strategy.

Furthermore, the reinforced droplets can easily settle down at the bottom of the vessel soon after stopping the rotation, which allows their recovery for multiple reaction cycles. As listed in Table 1 (entry 1), in the second run, above 80% yield of the final product could still be obtained after prolonging the reaction time to 8 h. Though the recyclability is not very good, it is the first time to realize the recycling of incompatible liquid acid and base co-involved cascade reactions, which is otherwise unattainable for the reported system. The shell of the reinforced droplets plays an important role in this success.

In summary, taking advantaging of the interfacial sol–gel (cross-linking) process, a reinforced Pickering emulsion has first been developed successfully for the construction of cascade reaction systems. This method was shown to enable the facile encapsulation of liquid acid and base catalysts within the reinforced droplets. The grown shell is proven to be able to compartmentalize incompatible reagents to avoid mutual interferences even in the same vessel, while its porous shell allows the reactant molecules to diffuse freely to access the compartmentalized catalysts. These merits constitute the key features of biomimetic multistep synthesis to some extent. The investigation of the deacetalization–Knoevenagel cascade reaction demonstrates the applicability of our strategy in processing one-pot cascade reactions involving incompatible reagents. The present approach will serve as a platform for mimicking biocatalytic systems.

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## Conflicts of interest

There are no conflicts to declare.

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