

Compartmentalization of Incompatible Reagents within Pickering Emulsion Droplets for One-Pot Cascade Reactions

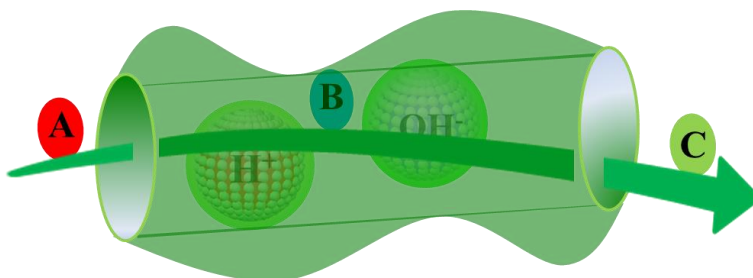
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Supporting Information

ABSTRACT: It is a dream that future synthetic chemistry can mimic living systems to process multistep cascade reactions in a one-pot fashion. One of the key challenges is the mutual destruction of incompatible or opposing reagents, for example, acid and base, oxidants and reductants. A conceptually novel strategy is developed here to address this challenge. This strategy is based on a layered Pickering emulsion system, which is obtained through lamination of Pickering emulsions. In this working Pickering emulsion, the dispersed phase can separately compartmentalize the incompatible reagents to avoid their mutual destruction while the continuous phase allows other reagent molecules to diffuse freely to access the compartmentalized reagents for chemical reactions. The compartmentalization effects and molecular transport ability of the Pickering emulsion were investigated. The deacetalization–reduction, deacetalization–Knoevenagel, deacetalization–Henry and diazotization–iodization cascade reactions demonstrate well the versatility and flexibility of our strategy in processing the one-pot cascade reactions involving mutually destructive reagents.



INTRODUCTION

Living systems can process multistep cascade chemical transformations to produce complex molecules.¹ One key concept living systems adopt is “compartmentalization”, through which incompatible or opposing reagents are spatially isolated to avoid mutual destruction.^{2–5} This concept is, however, still a dream for non-natural systems.^{6–9} Recently, many non-natural systems have been suggested,^{10, 11} which mainly rely on immobilization or encapsulation of incompatible reagents with sol-gel materials,^{12–20} or polymers,^{21–31} avoiding their direct contact. Although these attempts lead to encouraging results, these methods are applied only in particular cases and are not very versatile because they either require relatively complex immobilization/encapsulation procedures or need special polymers. Moreover, these cascade systems are still embryonic because of the inability to mimic the fundamental aspects of natural systems.

Particle-stabilized emulsions [called Pickering emulsions, oil-in-water (o/w) or water-in-oil (w/o)] might make the dream come true,^{32–38} because the whole system is divided into numerous separate droplets that can serve as micro-compartments and even protocells.^{39–42} Moreover, in Pickering emulsions, the oil and water phases are sufficiently mixed leading to a high area of oil-water interface available for chemical reactions.^{43–48} It has recently been found that such a micro-mixing enables

organic-aqueous biphasic reactions to proceed efficiently through the auto-diffusion of reactant molecules (without the need for stirring), and the reaction efficiency is as high as that achieved with vigorous stirring.⁴⁹ We envision that these unique properties of a Pickering emulsion could be helpful to address the obstacles of biomimetic synthesis if its architecture was innovatively constructed so as to effectively compartmentalize incompatible reagents but allow other reactants to diffuse freely in reaction systems. However, Pickering emulsion-based cascade reactions have not been explored up to date.

Herein, we demonstrate a conceptually novel strategy to perform one-pot cascade reactions involving opposing reagents based on Pickering emulsions. As Figure 1 shows, one can first prepare two parent water-in-oil Pickering emulsions using nanoparticles as emulsifier. In one Pickering emulsion, a reagent, *e.g.* acid as catalyst or reactant, is dissolved in the water droplets (dispersed phase) and a reactant A is dissolved in the oil phase (continuous phase, Figure 1a). In the other Pickering emulsion, a reagent, *e.g.* base as catalyst or reactant, is also dissolved in the water droplets (Figure 1b) and other reactants are dissolved in the continuous phase if needed. These two parent Pickering emulsions with opposing reagents are then brought into contact through lamination (Figure 1c), yielding a multi-layered Pickering emulsion system for cascade reactions. The layered

architecture allows the positioning of the emulsion droplets in different regions to avoid direct contact. During the course of reaction, the acid and base are compartmentalized in the water droplets and should not get in contact with each other avoiding destruction. Meanwhile, the reactant A in the continuous (oil) phase can freely move through auto-diffusion, and is converted to the intermediate B upon meeting the acid at the droplet interface, which is subsequently transformed to the final product C after meeting the base-contained droplets located in the neighboring layer. In this scenario, the whole Pickering emulsion reaction system is just like a living system, which can spatially position diverse cells in different regions, compartmentalize the mutually destructive enzymes or molecules in the different cells but allow for the free diffusion of other molecules located outside the cells for biochemical reactions if needed.

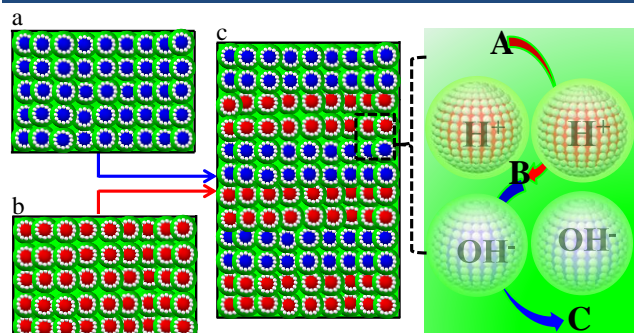


Figure 1. Schematic description of a one-pot cascade reaction based on the proposed Pickering emulsion strategy ($A \rightarrow B \rightarrow C$, where A is the starting substrate, B represents the intermediate and C is the final product). (a) The w/o Pickering emulsion was formulated with water-soluble acid, water, starting substrate A and oil phase. (b) The w/o Pickering emulsion was formulated with water-soluble base, water and oil phase. (c) Mixing a and b through a lamination procedure leads to a layered Pickering emulsion system, which serves as a medium for one-pot cascade reactions.

2. RESULTS AND DISCUSSION

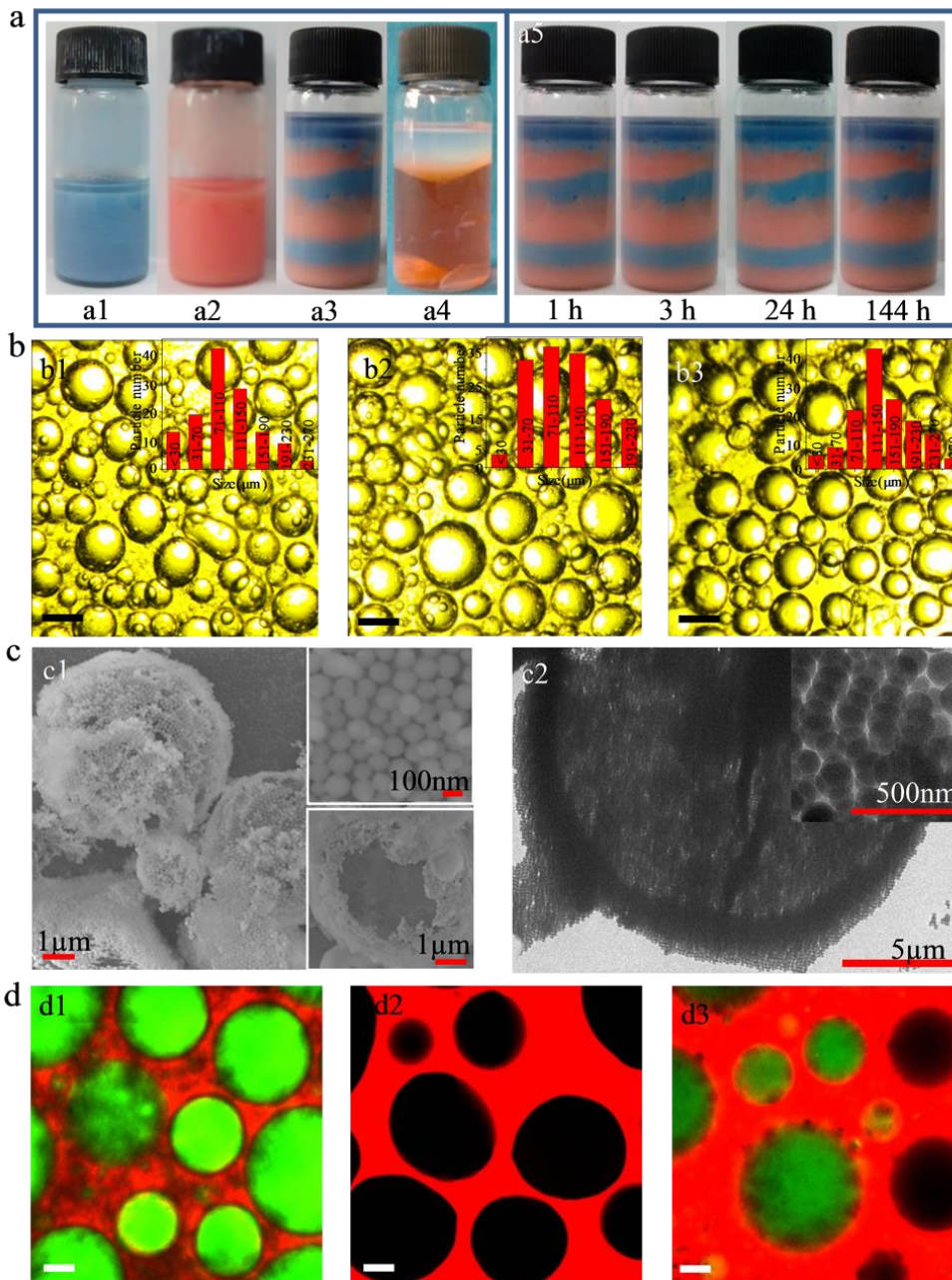
2.1. Compartmentalization effects of water droplets

Although surfactant-stabilized emulsions were reported to have the ability to compartmentalize opposing reagents, the trapping time is only several minutes which is too short to carry out chemical reactions.⁵⁰ The dynamic exchanges of molecular surfactant between emulsion droplets and the presence of free surfactant in the continuous phase probably accelerates mass transport of the molecules between different droplets.^{51, 52} Moreover, after the completion of reaction, the separation of surfactants from products is relatively difficult. These obstacles may be overcome with particle-stabilized emulsions. Partially hydrophobic silica nanospheres with diameters around 200 nm were used as emulsifier, which were easily prepared from bare silica particles through a one-step modification with methyltrimethoxysilane [transmission electron microscopy (TEM) images are included in Figure S1 (Supporting Information)]; the

methyl group loading is estimated to be $0.072 \text{ mmol g}^{-1}$ on the basis of elemental analysis; the thermogravimetric curves are displayed in Figure S2; the air-water contact angle of the particle surfaces measured through water is 91° , as shown in Figure S3].

We first checked the feasibility of the coexistence of opposing reagents, *e.g.* HCl and NaOH, in a single vessel with the proposed Pickering emulsion strategy. Congo Red was used as indicator to visualize the pH changes of water droplets because it is exclusively water-soluble (not oil-soluble) and its color varies in response to pH changes (azure at $\text{pH} < 3.0$ and red at $\text{pH} > 5.0$). Two parent water-in-toluene Pickering emulsions were formulated with acidic or basic solutions of Congo Red (the water volume fraction of each Pickering emulsion is *ca.* 70%). The use of a solution of HCl (0.01 M) led to an azure-colored Pickering emulsion (Figure 2, a1), while the use of a solution of NaOH (0.01 M) resulted in a red-colored Pickering emulsion (Figure 2, a2). Mixing these two Pickering emulsions through a lamination procedure yielded a new Pickering emulsion, which exhibited zebra stripes with alternate azure and red colors (Figure 2, a3). The layered architecture was successfully achieved since no agitation is implemented during the course of mixing. However, in a control experiment, mixing two mixtures that were the same as a1 and a2 Pickering emulsions in composition (including toluene, water, particle emulsifier, acid or base, and indicator) but not emulsified, led to a suspension that rapidly changed to red color (Figure 2, a4), which is a result of acid-base reactions. These comparisons underline that Pickering emulsions are crucial to obtain an acid/base-coexisting system. More importantly, after standing for 1, 3 and 24 h, the appearance of layered Pickering emulsions remained virtually the same, and there was still a clear boundary between the layers without color fading (Figure 2, a5). Impressively, after this layered Pickering emulsion stood for 144 h, the zebra stripes of alternate colors were still well maintained indicating the survival of acid and base in the same system. Such a period of time is sufficiently long for most chemical reactions themselves to take place. In contrast, the surfactant-stabilized emulsions have poor ability to achieve the survival of acid and base in a single system (Figure S4).

In order to investigate these results further, optical microscopy, scanning electron microscopy (SEM) and TEM were employed to observe the microstructures of the Pickering emulsions. Before mixing, the Pickering emulsions formulated with HCl and NaOH consist of droplets with diameters ranging from around 10 to 250 μm (Figure 2, b1 and b2). After mixing *via* a lamination procedure and further standing for 24 h, the morphology and size distribution of the emulsion droplets sampled from close to a layer boundary show no apparent changes (Figure 2, b3). This indicates that the layered Pickering emulsions have high stability against droplet coalescence



originated from precursor emulsion droplets. In the more magnified SEM image (Figure 2, upper inset of c₁), silica nanospheres are observed to be closely packed on the surface of these microspheres. As expected, the microspheres are hollow (Figure 2, lower inset of c₁) since freeze-drying involves removal of the inner water directly from a solid to a gas. This is direct evidence for the pronounced micro-compartments. Similar to the SEM image, the TEM image obtained at low temperature further confirmed the droplet microstructure (Figure 2, c₂). The excellent ability to prevent acid-base neutralizations can be attributed to the micro-compartments within Pickering emulsions.

To further confirm the compartmentalization effects of droplets, we used fluorescence microscopy to observe whether reagent molecules transfer between droplets. Two parent Pickering emulsions were formulated in the presence of fluorescent dyes (there is no acid or base in the water in these experiments). The first was prepared with water containing FITC-dextran (green) and toluene containing Nile red (red). Judging by the colors of Figure 2, d₁ (green inside droplets and red outside droplets), this Pickering emulsion is of the water-in-oil type since FITC-dextran is a water-soluble dye while Nile red is an oil-soluble one. The second was prepared with pure water (without FITC-dextran) and toluene containing Nile red. As seen in Figure 2, d₂, the continuous phase is red while the interior of the droplets is black because of the absence of fluorescent dye molecules. These two Pickering emulsions were also put in contact *via* a lamination procedure. After standing for 4 h, the emulsion droplets close to a layer boundary were withdrawn and observed with fluorescence microscopy. Notably, green droplets and black ones were both observed (Figure 2, d₃). That is to say, the FITC-dextran dye molecules did not enter the initially dye-free droplets over this timescale. These findings further confirm that the formulated Pickering emulsion has a good ability to compartmentalize molecules within water droplets and to prevent the transfer of these molecules to other droplets despite the large concentration gradient.

To quantify the effectiveness of the layered architecture in preventing the neutralization of acid and base, we conducted a set of more sensitive experiments in which one Pickering emulsion containing a high concentration of HCl was laminated onto the other Pickering emulsion containing a low concentration of NaOH and Congo Red indicator. In such experiments, if only a small portion of HCl diffuses out from water droplets and across the oil film to react with NaOH at the layer boundary, the color of the layer boundary should change. The concentration of HCl was increased from 0.05 to 0.1, 0.5 and 1 M while the concentration of NaOH was always kept constant (0.001 M). After these two-

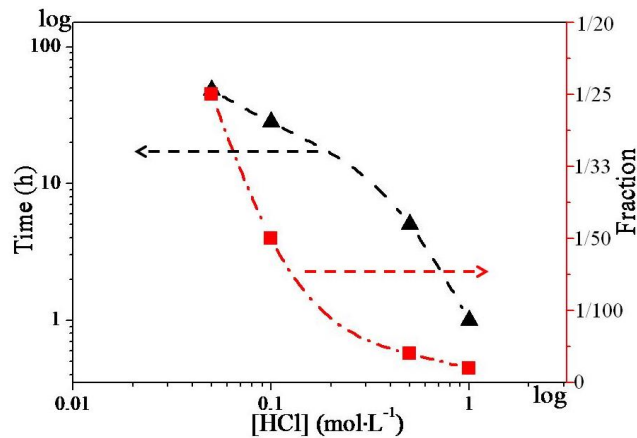


Figure 3. Time for layer boundary to change colour and the fraction of the neutralized acid for the four layered Pickering emulsions system. The layered Pickering emulsions were obtained by lamination of one Pickering emulsion containing a high concentration of HCl onto another Pickering emulsion containing a low concentration of NaOH and Congo Red indicator. [HCl] was changed from 0.05 to 1 M while [NaOH] was kept constant at 0.001 M.

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x-axis: remove the word 'log'

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layered Pickering emulsions stood for a period of time, the color of layer boundary was observed to change from the initial red to the somewhat azure colour (Figure S5). Interestingly, the larger the concentration of HCl, the shorter the time taken for this colour change to occur. As shown in Figure 3, when the HCl concentration increases from 0.05 to 0.1, 0.5 and 1 M, the time taken for the color change at the layer boundary falls from 48 h to 25, 5 and 1 h respectively. This can be explained by the high concentration gradient accelerating HCl diffusion. Based on the color change of the layer boundary, we can estimate that only *ca.* 1/500, 1/250, 1/50 and 1/25 of the initial HCl at the layer boundary of the layered Pickering emulsion reacted with NaOH. Notably, for these Pickering emulsions, the lower red layer and the upper white layer remained unchanged even after standing for at least 35 h, indicating that the neutralized acid and base in the overall Pickering emulsion system is at a negligible level. This set of sensitive experiments sufficiently confirms the high effectiveness of our layered Pickering emulsion strategy.

Our further investigations show that the excellent stability to compartmentalize opposing reagents in water droplets is mainly contributed by three factors: (i) The first is the layered architecture. For the Pickering emulsion system obtained by lamination followed by gentle mixing (3 min, homogeneously mixing the droplets), the coexistence of acid and base in a single vessel was found to be maintained for only 3 h, and after this period the initial azure Pickering emulsion gradually became red as shown in Figure S6. The comparison with the results achieved with the above layered Pickering

emulsion without stirring confirms that the layered architecture is more effective to prevent the destruction of opposing reagents in a single system. The reason may be that the layered architecture significantly decreases the possibility of direct contact of droplets containing opposing reagents. (ii) The second is the concentration of solid particle emulsifier. It was found that a high concentration of solid particle emulsifier is favorable to prevent the mutual destruction of the opposing reagents. As Figure S7 shows, when the concentration of particles was decreased from 7.5 to 0.375 wt% (with respect to water), HCl and NaOH can only survive in a single vessel up to 3 h. (iii) The third is the solubility of compartmentalized reagents. As shown in Figure S8, when NaOH was changed to other bases such as $\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ and $\text{HOCH}_2\text{CH}_2\text{NH}_2$ that are only soluble in water (not oil-soluble), their coexistence with acid-containing droplets without reaction was up to at least 144 h. In contrast, for $\text{NH}(\text{CH}_2\text{CH}_3)_2$ that is both water-soluble and oil-soluble, the acid-base reaction is complete within 3 h. This implies that the solubility of the reagents in the continuous phase plays a key role, and only opposing reagents that are not soluble in the continuous phase can be effectively compartmentalized without destruction. A reasonable explanation is that the continuous phase constitutes an oil film that separates droplets, and the low solubility of compartmentalized reagents in the oil film can significantly impede their mass transport.

2.2. Molecule transport in the continuous phase

We next check the molecular transport ability of the continuous phase of layered Pickering emulsions. The coordination complex N,N' -bis(3,5-di-tert-butylsalicylidene)ethylenediamino-cobalt(II) [Co(Salen)] was chosen as a probe molecule since it is oil-soluble and its red color is helpful to observe molecular transport. A layered Pickering emulsion was obtained by mixing one Pickering emulsion in the presence of Co(Salen) with an equal volume of the other Pickering emulsion in the absence of Co(Salen) (without acid and base in this experiment). By varying the total layer numbers from 2 to 4, 6 and 8, the thickness of each layer was adjusted from 2.0 to 1.0, 0.67 and 0.50 cm, as shown in Figure 4a (a1, a3, a5 and a7 respectively). Initially, these Pickering emulsions were observed to consist of zebra stripes with alternate red and white colors. After standing for a period of time, the white layer became red suggesting that Co(Salen) molecules diffuse throughout the whole volume of the vessel (Figure 4a, a2, a4, a6 and a8; the color changes are displayed in detail in Figure S9). It was found that the thinner the layer, the quicker this takes place. For the Pickering emulsions with layer thickness of 0.5 cm (a7 and a8), it took only 40 min to complete homogeneous distribution, which is relatively short in comparison with the timescale for most chemical reactions. These observations confirm that the continuous phase of a layered Pickering emulsion system allows the transport of molecules through auto-diffusion. The good transport ability of the layered Pickering emulsions is further demonstrated with an alternative

probe molecule benzaldehyde dimethylacetal (only oil-soluble). For ease of monitoring, a two-layered Pickering emulsion was formulated with benzaldehyde dimethylacetal initially in the upper layer (Figure 4b). Gas chromatography (GC) was used to determine the concentration of benzaldehyde dimethylacetal at the bottom of the vessel. It was found that the concentration of benzaldehyde dimethylacetal at the bottom gradually increased with time and leveled off after *ca.* 40 min, suggesting that benzaldehyde dimethylacetal was homogeneously distributed throughout the vial through molecular diffusion. In comparison with the experiment with Co(Salen) (two-layered Pickering emulsion), the time is much shorter, which may be explained in terms of different diffusion coefficients.

We can use Fick's second law to estimate the time taken for organic reactants to reach homogeneous distribution between layers, which is given by the equation:

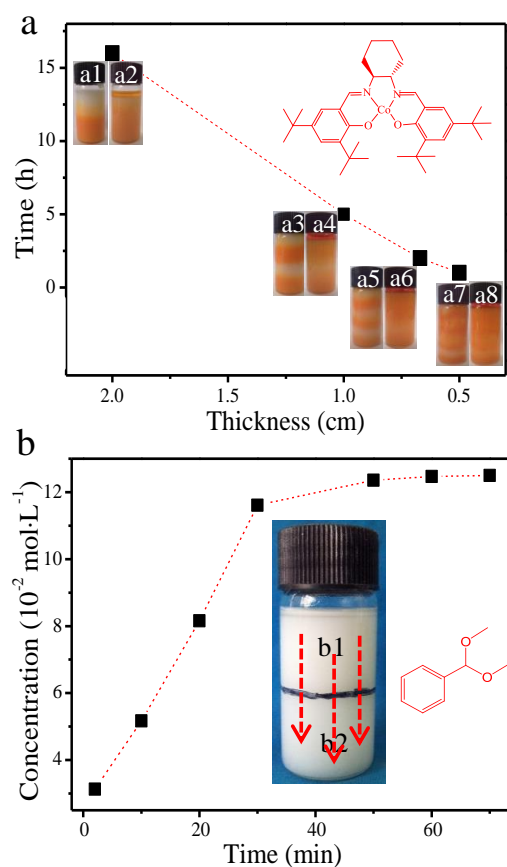


Figure 4. Molecular transport in the continuous phase of layered Pickering emulsions. (a) The time taken by Co(Salen) to diffuse throughout the whole volume of the vessel as a function of the layer thickness. The insets are photos of the vessels initially (left) and **? state the time** h later (right). The structure of Co(Salen) is also given. The detailed procedure is included in Supporting Materials. (b) Concentration of benzaldehyde dimethylacetal at the bottom of vial as a function of time. The detailed procedure for this experiment is included in Supporting Information. b1 represents the upper layer of Pickering

emulsion where benzaldehyde dimethylacetal is initially dissolved; b2 is the lower layer of Pickering emulsion where benzaldehyde dimethylacetal is initially absent.

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \quad (1)$$

where C is the concentration of diffusing species, t the time, D the diffusion coefficient of the diffusing species and x is the distance diffused. Assuming that no reaction occurs and the presence of droplets is ignored, the solution to the equation with initial boundary conditions $C_0(x,0) = C_0$ in even layers and $C(x,0) = 0$ in odd layers is $C(x,t)$

$$= \frac{1}{2}C_0 + \sum_{n=0}^{\infty} \frac{(-1)^n}{(2n+1)\pi} \exp\left\{-\frac{\pi^2(2n+1)^2Dt}{4L^2}\right\} \cos\left\{\frac{\pi(2n+1)x}{2L}\right\} \quad (2)$$

where the sum is over all values of n from 0 to ∞ , and L is the half layer thickness? explain better. This is an infinite series with terms getting smaller as n increases.

$C(x,t)$

$$= \frac{1}{2}C_0 + \frac{2C_0}{\pi} \exp\left\{-\frac{\pi^2Dt}{4L^2}\right\} \cos\left\{\frac{\pi x}{2L}\right\} - \frac{2C_0}{3\pi} \exp\left\{-\frac{9\pi^2Dt}{4L^2}\right\} \cos\left\{\frac{3\pi x}{2L}\right\}$$

$$+ \frac{2C_0}{5\pi} \exp\left\{-\frac{25\pi^2Dt}{4L^2}\right\} \cos\left\{\frac{5\pi x}{2L}\right\} - \frac{2C_0}{7\pi} \exp\left\{-\frac{49\pi^2Dt}{4L^2}\right\}$$

+ ... (3)

A program for the solution of this equation was written in Excel. It can be estimated that the time for a reactant to reach homogeneous distribution between layers is 0.07-7 h for a layer thickness of 0.5 cm and a diffusion coefficient D in the range of 1×10^{-8} - $10^{-10} \text{ m}^2 \text{ s}^{-1}$. Such a timescale is acceptable for most reactions since the diffusion timescale and reaction timescale are the order of magnitude. Moreover, we believe for a given reaction, this time may be significantly shortened because the local concentration gradients caused by chemical reactions can accelerate the molecular diffusion since the molecular diffusion rate scales with the square of concentration gradient.

2.3. One-pot cascade reactions

Given the above encouraging results, we next examined this Pickering emulsion strategy with one-pot cascade reactions. A deacetalization-reduction cascade reaction was first chosen, in which deacetalization was catalyzed with HCl and reduction required NaBH_4 (Reaction I in Figure 5). HCl and NaBH_4 is a pair of opposing reagents because they rapidly react with each other. Normally, it is impossible to combine these two reactions in a single vessel. To validate the examination, we conducted a set of control experiments and all reactions were carried out without stirring at room temperature. The reaction systems were formulated by mixing two mixtures. In the first control experiment, one mixture consisted of an aqueous solution of HCl, toluene, silica particle emulsifier, and benzaldehyde dimethylacetal, while the other comprised an aqueous solution of NaBH_4 , toluene and silica particle emulsifier. Despite the presence of particle

emulsifier, these two mixtures were not emulsified before mixing, thereby consisting of toluene and water layers. It was observed that bubbles were rapidly produced upon mixing, caused by the reaction of HCl with NaBH_4 releasing H_2 . After standing for 30 min,

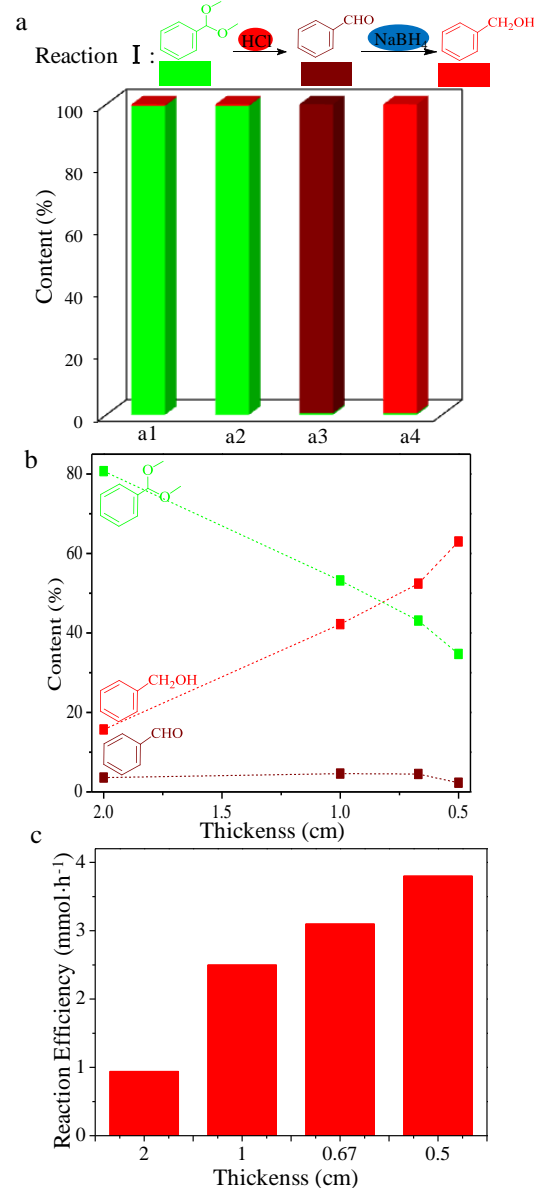


Figure 5. The results of one-pot deacetalization-reduction cascade reaction. (a) Final compositions of the deacetalization-reduction reactions in different systems. Green represents benzaldehyde dimethylacetal; brown represents benzaldehyde and red represents benzyl alcohol. Composition of the reaction system: 0.5 mmol benzaldehyde dimethylacetal, 4 mL water, 1.8 mL toluene, 0.02 mmol HCl (if used), 1.5 mmol NaBH_4 (if used), and 0.3 g methyl-modified SiO_2 . Reaction conditions: 25 °C and 30 min. a1) The reaction system in the presence of both HCl and NaBH_4 but without emulsification; a2) The Pickering emulsion system in the absence of HCl; a3) The Pickering emulsion system in the absence of NaBH_4 ; a4) The Pickering emulsion system in the presence of both HCl and NaBH_4 . (b) The reaction results versus the layer thickness. The contents of benzaldehyde dimethylacetal,

benzaldehyde and benzyl alcohol were determined by GC when the reaction proceeded for 10 min. Their total contents are 100%. (c) The reaction efficiency (moles benzyl alcohol generated/h) versus the layer thickness.

(b) and (c): x-axis label is mis-spelled, should be thickness

the content of benzaldehyde dimethylacetal in the reaction mixture was determined to be more than 99% (first bar of Figure 5a) and the content of the final product benzyl alcohol was less than 0.5%. In the second control experiment, these two mixtures were first emulsified (stirring for 2 min) and were then mixed through a lamination procedure (0.67 cm in layer thickness, 3 + 3 layers), but in the first Pickering emulsion HCl is absent. After the same time, the content of benzaldehyde dimethylacetal in the reaction mixture was also more than 99% (second bar of Figure 5a) and the reaction did not occur. In the third control experiment, these two mixtures were emulsified and were then mixed through the same procedure as the second control experiment, but in the second Pickering emulsion NaBH₄ was not introduced. After 30 min, benzaldehyde dimethylacetal was completely converted to the intermediate benzaldehyde, but the final product benzyl alcohol was not detected (third bar of Figure 5a). These control experiments suggest that both the emulsification and combination of HCl and NaBH₄ are absolutely necessary for this cascade reaction. We then checked this one-pot cascade reaction in the presence of both HCl and NaBH₄ with our layered Pickering emulsion strategy (0.67 cm in layer thickness, 3 + 3 layers). After the same period of time, benzaldehyde dimethylacetal was fully transformed to the final product benzyl alcohol via a deacetalization–reduction cascade (final bar of Figure 5a). These comparisons confirm the effectiveness of our Pickering emulsion strategy in one-pot cascade reactions involving opposing catalyst and reactant.

To clarify the impact of the layer thickness on the reaction systems we varied the layer number from 2 to 4, 6 and 8. The thickness of each layer was correspondingly changed from 2.0 to 1.0, 0.67 and 0.50 cm. After a period of 10 min, the contents of benzaldehyde dimethylacetal, benzaldehyde and benzyl alcohol in each Pickering emulsion system were determined. The layer thickness-dependent contents for the reactant, intermediate and product are reflected in Figure 5b. As the layer thickness decreases, the content of benzaldehyde dimethylacetal decreases progressively from 80% to 53%, 43% and 35%, and the content of benzyl alcohol increases progressively from 16% to 42%, 52% and 63%. Notably, in each Pickering emulsion system, the content of the intermediate benzaldehyde was always lower than 5% and the accumulation of the intermediate did not occur during the whole course of reaction. This means that once the deacetalization reaction starts the reduction reaction occurs and these two reactions proceed simultaneously, which is a feature of one-pot cascade reactions.

Based on the content of the generated final product benzyl alcohol, one can estimate the reaction

efficiency of the Pickering emulsion systems, defined as the moles of the final product per hour. As displayed in Figure 5c, the reaction efficiency of the layered Pickering emulsion system is closely related to the layer thickness of the reaction systems, and it increases upon decreasing the layer thickness. When the layer thickness is decreased down to 0.33 cm, the reaction efficiency no longer increases significantly (coming soon). Such a dependence can be interpreted with the aforementioned molecular diffusion equation. The shorter the diffusion distance, the shorter the time for the reactant to complete the homogeneous distribution. However, when the layer thickness decreases to a certain level for a given reaction, the reaction rate is no longer suppressed by the reactant diffusion rate. These findings suggest that the reaction efficiency of one-pot cascade systems can be regulated through changing the layer thickness..

The deacetalization–reduction cascade reaction (Reaction I) can be applied to other substrates, as summarized in Table 1. All examined reactions were formulated with a layer thickness of 0.33 cm (3 + 3 layers) and carried out without stirring. Methoxybenzaldehyde dimethylacetal was completely converted to the final product methoxybenzyl alcohol within 0.5 h at room temperature, and the intermediate methoxybenzaldehyde was not detected. Cyclohexanone dimethylacetal was also fully transformed to the final product cyclohexanol within 2 h. For the less reactive acetals such as benzaldehyde propylene glycolacetal and butaldehyde diethylacetal, the content of the final products were determined as 99% within 2 h at 50 °C. These findings demonstrate the versatility and effectiveness of the Pickering emulsion strategy.

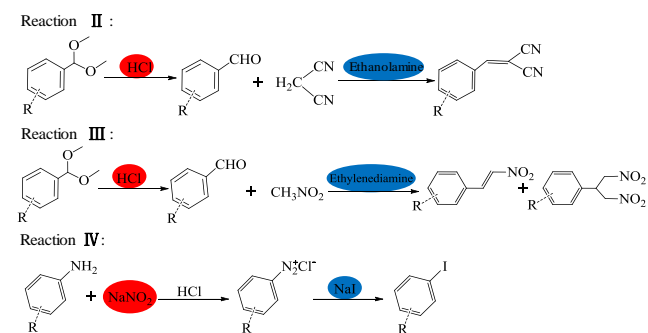


Figure 6. The extended one-pot cascade reactions in the presence of a pair of opposing reagents. Reaction II: the deacetalization–Knoevenagel cascade reaction in the presence of HCl/ethanolamine pair; Reaction III: the deacetalization–Henry cascade in the presence of HCl/ethylenediamine pair; Reaction IV: the diazotization–iodization cascade in the presence of NaNO₂/NaI pair.

The versatility and effectiveness of the Pickering emulsion strategy is further demonstrated by other cascade reactions involving different pairs of opposing reagents. Figure 6 displays another three cascade reactions in which opposing reagents are marked with different colors: deacetalization–Knoevenagel condensation cascade

Cascade reactions	Reactants	Intermediates	Products	T/°C	T/h ^b	B/% ^c	C/% ^d
I				25	0.5	0	>99
				25	2	0	>99
II				50	2	1	99
				50	2	1	99

Table 1. The results of four one-pot cascade reactions with different pair of opposing reagents^a

III				25	10	5	84
				60	10	13	75
				60	10	13	78
IV				70	10	0	0.3 ^e
				70	10	12	0.3 ^e
				70	10	12	40
				70	10	12	40
				70	18	28	28
				70	18	28	38
				70	18	16	58
				70	18	16	22
				25	24	/	0.8 ^e
				25	2.5	/	91
				25	1	/	93
				25	5	/	86
			25	4	/	72	

^aReaction I is shown in Figure 5 and its reaction conditions are similar to the statements in Figure 5; Reactions II, III and IV are displayed in Figure 6; The reaction conditions are described in Supporting Information. ^bReaction time. ^{c,d}The yields of the intermediate B and the final product C except Reaction I; For Reaction I, the data are the contents of the intermediate B and the final product C in the final mixture. ^eControl experiments without preparing a Pickering emulsion.

(Reaction II, acid/base pair); deacetalization–Henry cascade (Reaction III, acid/base pair), and diazotization–iodination cascade (Reaction IV, oxidant/reductant pair). The results of these three cascade reactions are also summarized in Table 1. For Reaction II, in the absence of emulsion droplets or HCl or ethanolamine, it is impossible to get the final product in a satisfactory yield (Figure S10). However, with the Pickering emulsion strategy, all the investigated acetals were found to undergo a complete deacetalization and the isolated yields of final dicyano compounds were between 75 and 84% within 10 h. For Reaction III, the control experiment also shows that without emulsification very little product was detected. In contrast, with the Pickering emulsion strategy the final products including α , β -unsaturated nitro and dinitro compounds were obtained. Their total yields were up to 66–80% within 10–18 h.

Reaction IV was explored here to synthesize aryl iodides in one-pot. The conventional process of synthesizing aryl iodide consists of two separate reactions: diazotization and iodination. Only after the diazotization is complete can NaI be added for the second reaction

because NaI is otherwise quickly oxidized by NaNO_2 under the reaction conditions. Moreover, there is a

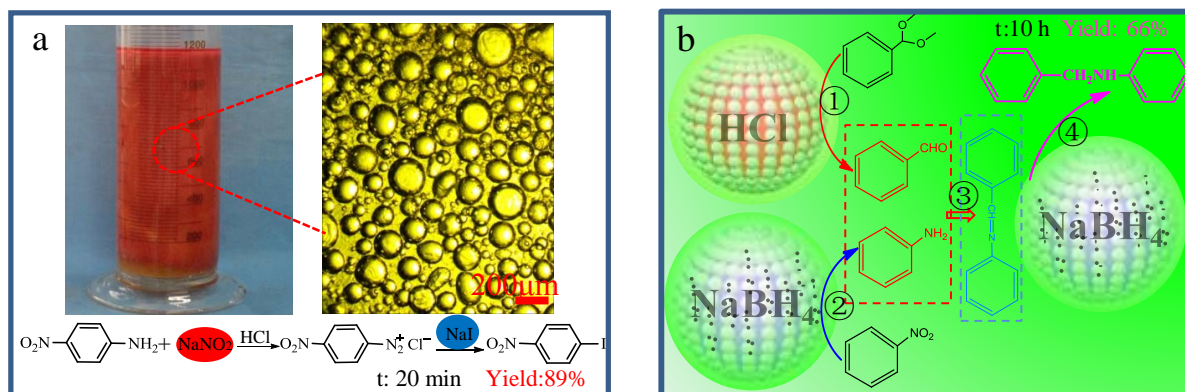


Figure 7. Scaling-up of a one-pot cascade reaction and a one-pot four-step cascade reaction in the presence of solid catalyst. (a) The diazotization-iodization cascade scaled up to 1 L, for which the reaction conditions are included in Supporting Information. The photo of vessel was taken at the end of reaction. (d) The one-pot four step cascade reaction for synthesizing *N*-alkyl aniline, of which the reaction conditions are included in the experimental section.

serious risk of explosion due to the accumulation of unstable diazonium in the reaction system.⁵⁴ With the Pickering emulsion strategy (0.33 cm layer thickness, 3 + 3 layers), NaNO₂ and NaI were compartmentalized in the different droplets. As shown in Table 1 for the investigated reactants, the iodide yields are as high as 72–90% in a one-pot reaction. In our multiple experiments, explosion was not observed. As Figure S11 exhibits, the concentration of diazonium intermediate was always kept below 5×10^{-5} M during the course of reaction. The accumulation of unstable diazonium in the reaction system does not occur in our cascade systems. The intermediate diazonium formed is transformed instantaneously into iodides, which significantly decrease the risk of explosion.

2.5. Scaling up one-pot cascade reactions

In order to examine the practical application feasibility of our Pickering emulsion strategy, the scale of the diazotization-iodization cascade (Reaction IV) was increased up to 1 L (Figure 7a). The scaled-up reaction system was easily obtained through mixing two Pickering emulsions with a lamination procedure (0.7 cm thickness, 12 + 12 layers), similar to the milliliter-scaled reaction. After standing for 30 min, the conversion of 4-aminonitrobenzene was complete. About 20 grams of 4-iodo nitrobenzene were obtained and the isolated yield was as high as 89%. The reaction efficiency does not significantly decrease after scaling-up in terms of reaction time and yield. This may be ascribed to the fact that the Pickering emulsion phase and emulsion droplet sizes were well maintained despite scale-up (Figure 7a) creating large reaction interface areas. Notably, during the reaction process, N₂ bubbles were observed to be released progressively, as diazonium is smoothly transformed into iodide. Moreover, the silica nanoparticles were easily separated from products through a filtrate step for re-use. In the second batch, the isolated yield of 4-iodo nitrobenzene was still up to 85% within the same reaction time.

2.6. One-pot multiple cascade reactions

The versatility of our Pickering emulsion strategy is further highlighted by a one-pot four cascade reaction for

synthesizing mono *N*-alkyl amine in the presence of solid catalysts. Using nitrobenzene and benzaldehyde dimethylacetal as starting materials, the whole synthesis process comprises four separate reactions: ① reduction of nitrobenzene to aniline with NaBH₄ in the presence of a Pd catalyst, ② deacetalization of benzaldehyde dimethylacetal to benzaldehyde in the presence of HCl, ③ condensation of aniline with benzaldehyde to yield imine and ④ reduction of imine with NaBH₄ to the final product mono *N*-alkyl amine. Normally, the four reaction cascade is impossible to realize because of the destruction of NaBH₄ and HCl. As shown in Figure 7b (and Figure S12), the cascade reaction system was obtained by mixing two Pickering emulsions. In one, methyl-modified silica blended with a small amount of an interfacially active catalyst Pd/SiO₂-CN(4) was used as emulsifier,⁴⁴ where Pd/SiO₂-CN(4) also acted as catalyst for the nitrobenzene and imine reduction. After standing for 10 h at 60 °C, the starting materials benzaldehyde dimethylacetal and nitrobenzene were not detected, and the final product *N*-alkyl amine was obtained in a yield of 66% (the yield of main side product benzyl alcohol was 21%). The high reaction efficiency is attributed to the formation of a Pickering emulsion, which enables multiple reagents including water-soluble reagents, oil-soluble ones and solid catalysts to be sufficiently mixed. These results further demonstrate that our Pickering emulsion strategy is highly flexible to allow multi-component, multi-step cascade reactions even in the presence of solid catalysts.

3. CONCLUSIONS

We have demonstrated a novel strategy for one-pot cascade reactions based on the lamination of Pickering emulsions. The droplets of this working Pickering emulsion system have proven able to separately compartmentalize incompatible or opposing reagents to avoid mutual destruction while its continuous phase allows other reagent molecules to diffuse freely to access the compartmentalized reagents for chemical reactions. Such compartmentalization and efficient mass transport under static conditions constitute the fundamental

features of biomimetic multistep synthesis to some extent, which are difficult to obtain with the existing methods. As a proof of the concept, the deacetalization–reduction, deacetalization–Knoevenagel, deacetalization–Henry and diazotization–iodization cascade reactions demonstrate well the applicability, versatility and flexibility of our strategy in processing one-pot cascade reactions involving incompatible reagents. Being simple, versatile and efficient, our strategy provides an unprecedented opportunity to practical cascade reactions with mutually destructive reagents.

ASSOCIATED CONTENT

Supporting Information

Experimental details; TEM images; TG curves; Water contact angles; Appearance of various Pickering emulsions; Results of the deacetalization–Knoevenagel cascade reaction in different systems; Results of monitoring diazonium concentration; Optical microscopy image; NMR and MS data for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

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