

# Tandem Catalysis with Antagonistic Catalysts Compartmentalized in the Dispersed and Continuous Phases of a Pickering Emulsion

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Tandem catalysis combines multiple conversion steps, catalysts, and reagents in one reaction medium, offering the potential to reduce waste and time. In this study, Pickering emulsions—emulsions stabilized by solid particles—are used as easy-to-prepare and bioinspired, compartmentalized reaction media for tandem catalysis. Making use of simple and inexpensive acid and base catalysts, the strategy of compartmentalization of two noncompatible catalysts in both phases of the emulsion is demonstrated by using the deacetalization–Knoevenagel condensation reaction of benzaldehyde dimethyl acetal as a probe reaction. In contrast to simple biphasic systems, which do not allow for tandem catalysis and show instantaneous quenching of the acid and base catalysts, the Pickering emulsions show efficient antagonistic tandem catalysis and give the desired product in high yield, as a result of an increased interfacial area and suppressed mutual destruction of the acid and base catalysts.

Biomimicry, that is, science inspired by biological entities and processes, has served catalysis well, for instance by mimicking enzyme active sites for the development of new atom-efficient conversions and the design of new biomimetic catalysts.<sup>[1]</sup> However, less attention has been given to bio-inspired reactor and process design, emulating the efficiency with which living cells are capable of performing multiple sequential and parallel reactions simultaneously.<sup>[2]</sup>

In this study, we aim to emulate nature's strategy of compartmentalization to efficiently perform coupled, one-pot reactions and, in particular, to allow antagonistic orthogonal tandem catalytic reactions.<sup>[3,4]</sup> Orthogonal tandem catalysis has been defined by Lohr et al. as a one-pot reaction in which sequential catalytic processes occur through two or more functionally distinct, and preferably non-interfering catalytic cycles.<sup>[4]</sup> The major challenge of operating tandem reactions for non-interfering catalysts is that the optimal process param-

eters and kinetic regimes for each are typically quite different. Furthermore, noninterference cannot always be avoided and catalyst non-compatibility in fact offers another main challenge for efficient tandem catalysis, for example when combining antagonistic catalysts such as an acid and a base. In that case, the two catalysts need to be kept physically separate, but still be accessible for the substrates. Various approaches have been taken towards the design of bifunctional acid–base catalysts, often relying on the spatial separation of the reactive entities on polymeric or oxidic support materials,<sup>[5,6]</sup> for example, in the form of yolk–shell materials,<sup>[7]</sup> metal–organic frameworks (MOFs),<sup>[8–11]</sup> shell cross-linked micelles,<sup>[12,13]</sup> or star polymers.<sup>[14]</sup> An alternative strategy is to use bio-inspired reaction media and process options in which compartmentalization can be reversibly induced to physically separate soluble antagonistic catalysts. Herein, we report on such a compartmentalization approach in the form of a Pickering emulsion (PE), an emulsion stabilized by solid particles.<sup>[15]</sup> PEs can be obtained as either water-in-oil (w/o), or oil-in-water (o/w) systems, based on the hydrophobic/hydrophilic nature of the particles used.<sup>[16]</sup> These PEs then constitute a special case of a biphasic system, offering the advantage of a higher interfacial area, which is anticipated to result in higher reaction efficiencies even when compared to stirred biphasic systems.<sup>[17]</sup> The PEs also offer wider stability windows than traditional emulsions and are therefore highly interesting media for catalysis.

Although PEs were invented in the early 1900s, their use as reaction media for catalysis is a topic that has only much more recently been explored.<sup>[18–22]</sup> For example, Resasco and co-workers reported on phase-selective catalysis using carbon nanotube–silica nanohybrids stabilized PEs in catalytic hydrogenation reactions<sup>[23,24]</sup> and the catalytic upgrading of biofuels by using hydrophobic zeolites acting as PE stabilizers.<sup>[25]</sup> Recently, Yang et al. were the first to use PE compartmentalization to perform various tandem catalytic reactions by using laminated w/o PEs.<sup>[26]</sup> PEs containing either Brønsted acidic or Brønsted basic water droplets, dispersed in toluene as the continuous phase, were combined in a layered fashion, thus having both incompatible catalyst components compartmentalized in the water phase of the laminated PE. This strategy allowed several tandem catalytic reactions to be performed successfully. Long reaction times in small volumes were required, indicating that mass transfer may be limiting.

In this work, we show a new, alternative way of compartmentalizing two antagonistic catalysts in a PE, that is, by confining the acid and base catalyst to the dispersed and continuous phase of the w/o PE, respectively. This would allow the ad-

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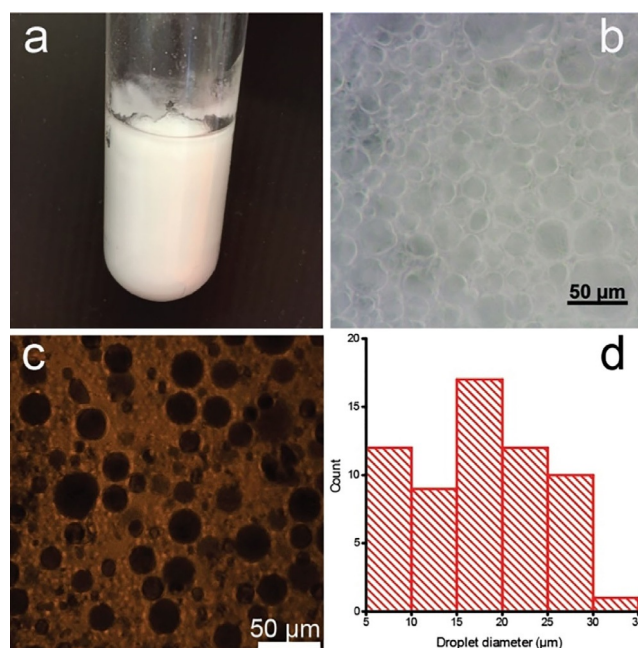
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ditional flexibility of being able to use both phases of the emulsion and minimize transport-related issues. The deacetalization–Knoevenagel reaction, a common probe reaction for bifunctional acid–base catalysis,<sup>[26–29]</sup> was selected to study this general strategy for antagonistic tandem catalysis. To this extent, a water/toluene (w/o) PE stabilized by hydrophobic silica (HDK H20 silica) was prepared, consisting of an aqueous phase containing an inorganic acid (HCl) to catalyze the deacetalization of benzaldehyde dimethyl acetal (**1**) to form the intermediate benzaldehyde (**2**). The oil phase of the PE contains an organic base, piperidine, and malononitrile for the subsequent catalytic Knoevenagel reaction to form benzylidene malononitrile (**3**; Figure 1). The performance of the PE as reaction medium for this tandem reaction is compared to a simple biphasic system with the same components.

PEs formulated with toluene containing 3 wt% silica and water were obtained as milky substances (Figure 2a) and were fully resistant against destabilization phenomena, such as coalescence, creaming, and sedimentation, also under reaction conditions (see the Supporting Information, Figure S1). Optical microscopy images were obtained by using a Zeiss upright microscope (Figure 2b). While the large focal depth precludes a reliable droplet size distribution to be obtained from these images, confocal fluorescence microscopy (CFM) images showed a broad droplet size distribution with droplet diameters varying between 5 and 35  $\mu\text{m}$  (Figure 2c,d). As the organic phase was stained with Nile red, the CFM images confirmed that the PE is of the w/o type (Figure 2c).

First, deacetalization of **1** was monitored in a PE (o/w 6:2 v/v) as function of time and compared to stirred and static biphasic systems of the same composition (Figure 3). Second, the influence of the oil/water ratio in the PE was assessed by comparing the performance of the PE to a 5:3 o/w PE. For these reactions only the substrate (**1**, 1 mmol) and 10 mol% HCl as catalyst were present in the different systems and reactions were executed at 50 °C. As **1** is hardly water soluble and

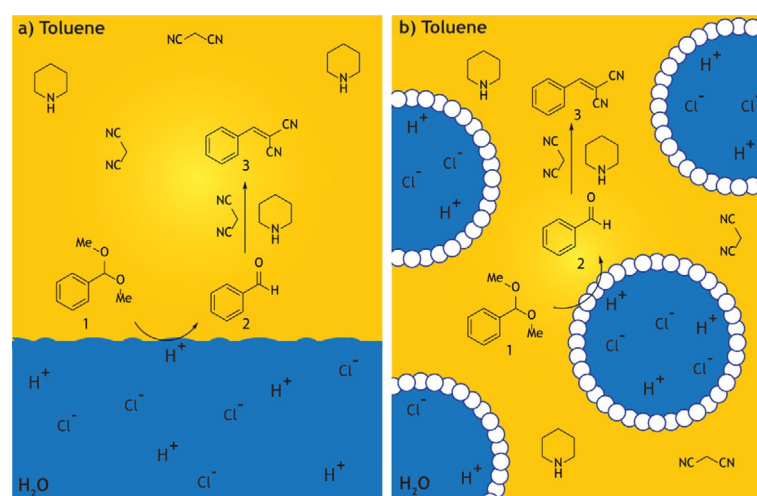


**Figure 2.** a) Physical appearance of the water/toluene PE stabilized with 3 wt% silica immediately after preparation. b) Optical microscopy image of the PE. c) Confocal fluorescence microscopy (CFM) image of the PE with the oil phase stained with Nile red. d) Droplet size distribution of the PE based on the CFM image.

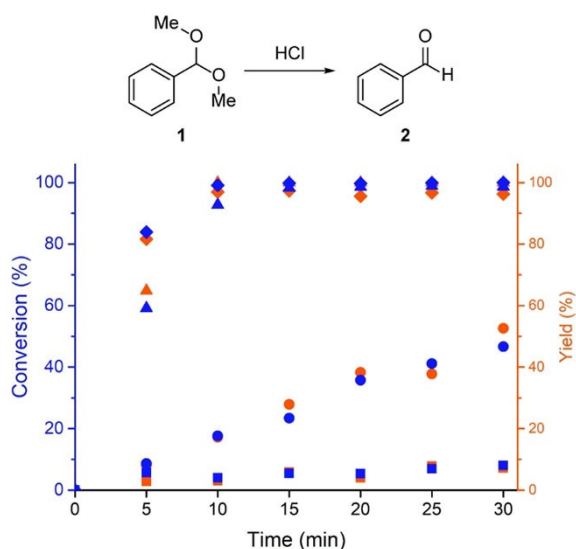
deacetalization requires the acid catalyst, the higher interfacial area between the organic and the aqueous phase in the PE was expected to lead to faster conversion. This was truly the case, as the conversion of **1** in the biphasic system without or with stirring reached only 12% or 46%, respectively, after 30 min, while the 6:2 toluene/water PE showed full conversion within 15 min. With a higher water content PE (5:3) the reaction proceeded even faster, with full conversion being reached in 10 min. This clearly shows the beneficial effect of the use of the PE for biphasic catalysis, as has been shown before for other types of reactions.<sup>[17]</sup>

The conversion of **2** into **3** was also followed over time at room temperature in a static and stirred biphasic system and in a PE (Figure S2). The Knoevenagel condensation part of the tandem reaction is an all-organic phase reaction, using excess malononitrile as second substrate. The differences in performance between the static and stirred biphasic system and the 6:2 o/w PE in this second step is less pronounced than for the first deacetalization reaction, with all reaching about 80–90% conversion of **2** in 2 h. Therefore, only the static biphasic system and a PE were compared in further studies of the influence of catalyst concentration on efficiency, using only base (Figure 4a) or both acid and base (Figure 4b).

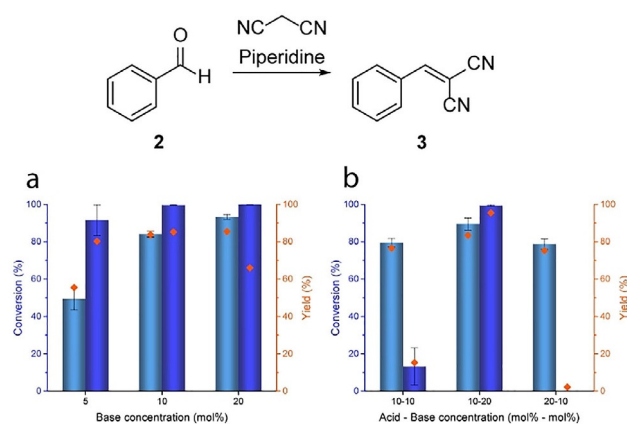
When only piperidine, and no hydrochloric acid, was present as catalyst in the biphasic system, a conversion of **2** of 49% was reached with 5 mol% of base. Increasing the piperidine concentration to 10 and 20 mol% increased conversion to 84 and 93%



**Figure 1.** Schematic representations of an orthogonal tandem reaction with compartmentalized, antagonistic catalysts, exemplified by a deacetalization–Knoevenagel tandem probe reaction in a) a biphasic system and b) a Pickering emulsion (PE).



**Figure 3.** Conversion of **1** and yield of **2** followed over time in a stirred biphasic system (1250 rpm; ●), static biphasic system (■), static PE with 6:2 toluene/water (▲), and a static PE with 5:3 toluene/water (◆) as a function of time. All systems contain 1 mmol of **1** and 10 mol% of HCl at  $t=0$  min, 50 °C.



**Figure 4.** Conversion (bars) of benzaldehyde (**2**) and yield (◆) of benzylidene malononitrile (**3**) in static biphasic system (left bars; light blue) and PE (right bars; dark blue) with a) only base or b) acid and base catalysts present. Reaction conditions: **2** (1 mmol), malononitrile (2.5 equiv.), RT, 3 h.

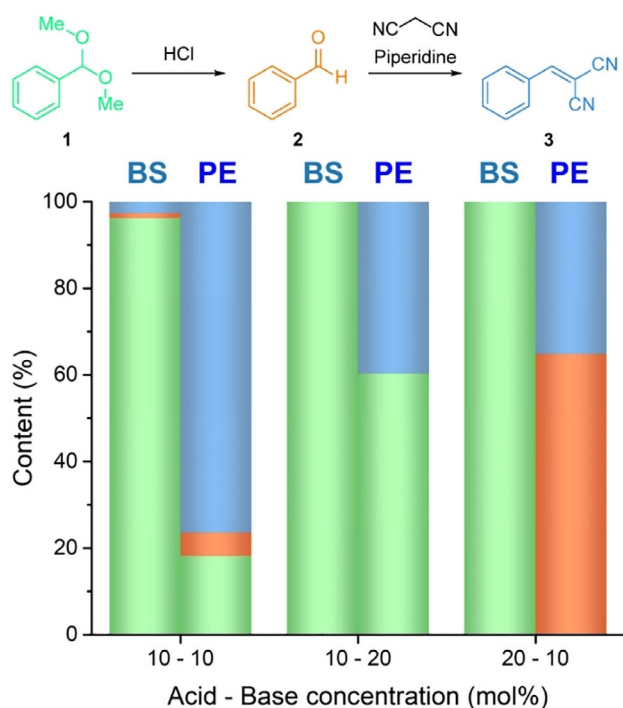
respectively. For the PE, higher conversions were observed of 91% with 5 mol% base and full conversion when 10 or 20 mol% base was used. However, the yield of **3** dropped on increasing base concentration, owing to the formation of side products. As piperidine is somewhat water soluble, this results in some alkalinity of the water phase, allowing for benzaldehyde to react in a Cannizzaro reaction to form benzoic acid and benzyl alcohol.<sup>[30,31]</sup> These products are highly soluble in the aqueous phase and are therefore not detected in the GC analysis of the organic phase.

Using an acidified aqueous phase clearly impacts the conversion of **2** in the organic phase in both the biphasic system and the PE (Figure 4b). The decrease in conversion observed when equimolar amounts acid and base or excess acid are used can be contributed to some interface quenching of the

antagonistic catalysts, with this effect being more pronounced in PE than in the biphasic system due to the higher interfacial area. The use of an excess of base (10 mol% acid, 20 mol% base), led to a marginal increase in conversion in the biphasic system, but a significant improvement for the PE with conversion shooting up to 99%. The 10 mol% excess of base present in the system explains the similarity in conversion to the reaction with 10 mol% base only. These results emphasize the balance that needs to be struck to achieve efficient coupling between the two tandem catalytic steps. Indeed, where the larger interfacial area of the PE was advantageous in the first step of the reaction in terms of kinetics, the opposite is seen in the second step if the acid and base are not present in the appropriate ratio, most likely because of more extensive quenching. Even though some recombination of acid and base and consequent salt formation thus may occur, this does not adversely affect the stability of the PE as no sedimentation or creaming was observed during the reaction (Figure S1). The 10–20 mol% acid–base experiments, however, suggested that actual PE tandem catalysis should be possible, provided that the acid–base ratio is properly tuned. It should also be noted that in all experiments with both acid and base catalysts present, the yield of **3** closely matched the conversion of **2**, indicating that the presence of acid prevents the formation of side products.

Having established the subtle (dis)advantageous effects of Pickering emulsification on the individual steps of the tandem reaction, the influence on the overall tandem catalytic conversion of **1** with both acid and base present in the systems was assessed. The tandem reactions were run for 3 h at room temperature in both static biphasic systems and PE. The normalized product distributions are shown in Figure 5.

As expected from the results of the deacetalization reaction, independent of the acid–base ratio applied, little to no conversion of **1** was observed for the static biphasic system, precluding any further tandem catalytic conversion. Importantly, when a stirred biphasic system with high acid and base concentrations (20 mol% acid, 20 mol% base) was used, no conversion of **1** was observed either (Figure S3). Gratifyingly, the PE reactions did show tandem catalysis, however, with efficiency, as expected, depending greatly on the relative acid and base concentrations. When equimolar amounts of acid and base were used (10 mol% acid, 10 mol% base), the conversion of **1** reached 82% with a yield of **3** of 76%. Only 6% of the product distribution was attributable to the intermediate **2**, implying that under these conditions deacetalization is rate limiting. With excess base (10 mol% acid, 20 mol% base), the conversion of **1** was rather low, because of partial quenching of the limiting amount of acid. Nevertheless, **3** was still produced in 40% yield. Under these conditions, intermediate **2** was not detected in the final reaction mixture, in line with deacetalization being rate limiting. Using an excess of acid (20 mol% acid, 10 mol% base) led to full conversion of **1** into **2** but limited conversion of **2** into **3**, reflecting the effect of partial quenching of the limiting amount of base, resulting in 35% yield of **3**. Equimolar amounts of acid and base thus gave the best tandem catalytic conversion of **1** into **3** in the PE. The compari-



**Figure 5.** Normalized product distributions of the tandem catalytic reactions in static biphasic systems (left bars) and PEs (right bars). Green bars show benzaldehyde dimethyl acetal (1), orange bars benzaldehyde (2) and blue bars benzylidene malononitrile (3) content in the reaction mixture. Reaction conditions: **1** (1 mmol), malononitrile (2.5 equiv.), RT, 3 h.

son with the biphasic system shows that the mutual destruction of acid and base, which is to an extent unavoidable, is thus clearly offset by the higher efficiency of the deacetalization reaction. Overall, this results in the complete tandem catalytic reaction performing much better in the PE than in the (stirred or static) biphasic system.

When the tandem catalytic activity of our simple, compartmentalized PE is compared to that of the more complex laminated one reported by Yang et al.,<sup>[26]</sup> we show that confining the acid and base catalysts to both phases rather than only the aqueous phase, results in a more rapid reaction, even at lower temperature. Mass transport and the desired partitioning are also expected to benefit from the higher oil/water ratio and lower silica loading, leading to a reduced viscosity, used in the reactions reported herein.

In conclusion, we have demonstrated a new, alternative method for the compartmentalization of simple acid and base catalysts in the two phases of a PE, a strategy that resulted in efficient tandem catalysis. This compartmentalization strategy thus allowed antagonistic catalysts to be used and accelerated phase transfer of reagents over the interface. Using the deacetalization–Knoevenagel condensation tandem reaction as a probe reaction, the PE system was shown to clearly outperform the simple biphasic one. All tandem reactions were executed at room temperature using inexpensive, commercially available catalysts in easily obtainable PEs as reaction media. Furthermore, the stability of the PEs was not influenced by the presence of substrate, catalysts, or products formed. The larger

interfacial area of the PE, compared to a simple biphasic system, obtained by the stable dispersion of the acidic aqueous phase inside the continuous organic phase, was highly beneficial for the rate of the acid-catalyzed reaction and therefore for the overall tandem catalytic reaction. The scope can be expanded to other substrates that benefit from acid–base tandem catalysis, including the conversion of biomass-derived compounds. Conversion of this type of compounds requires higher reaction temperatures and operates under different reaction mechanisms. The application of our simple compartmentalized PEs on such substrates and reactions is currently under investigation.

### Conflict of interest

The authors declare no conflict of interest.

**Keywords:** bifunctional catalysis · biomimicry · biphasic catalysis · Pickering emulsions · tandem reactions

- [1] A. E. Rawlings, J. P. Bramble, S. S. Staniland, *Soft Matter* **2012**, *8*, 6675–6679.
- [2] S. B. P. E. Timmermans, J. C. M. van Hest, *Curr. Opin. Colloid Interface Sci.* **2018**, *35*, 26–35.
- [3] M. J. Climent, A. Corma, S. Iborra, M. J. Sabater, *ACS Catal.* **2014**, *4*, 870–891.
- [4] T. L. Lohr, T. J. Marks, *Nat. Chem.* **2015**, *7*, 477–482.
- [5] Z. Jia, K. Wang, B. Tan, Y. Gu, *ACS Catal.* **2017**, *7*, 3693–3702.
- [6] Z. Weng, T. Yu, F. Zaera, *ACS Catal.* **2018**, *8*, 2870–2879.
- [7] Y. Yang, X. Liu, X. Li, J. Zhao, S. Bai, J. Liu, Q. Yang, *Angew. Chem. Int. Ed.* **2012**, *51*, 9164–9168; *Angew. Chem.* **2012**, *124*, 9298–9302.
- [8] A. Dhakshinamoorthy, H. Garcia, *ChemSusChem* **2014**, *7*, 2392–2410.
- [9] M. H. Qi, M. L. Gao, L. Liu, Z. B. Han, *Inorg. Chem.* **2018**, *57*, 14467–14470.
- [10] Y. Zhang, Y. X. Wang, L. Liu, N. Wei, M. L. Gao, D. Zhao, Z. B. Han, *Inorg. Chem.* **2018**, *57*, 2193–2198.
- [11] S. Mistry, A. Sarkar, S. Natarajan, *Cryst. Growth Des.* **2019**, *19*, 747–755.
- [12] L. C. Lee, J. Lu, M. Weck, C. W. Jones, *ACS Catal.* **2016**, *6*, 784–787.
- [13] M. Kuepfert, A. E. Cohen, O. Cullen, M. Weck, *Chem. Eur. J.* **2018**, *24*, 18648–18652.
- [14] B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, C. J. Hawker, J. M. J. Fréchet, *Angew. Chem. Int. Ed.* **2005**, *44*, 6384–6387; *Angew. Chem.* **2005**, *117*, 6542–6545.
- [15] S. U. Pickering, *J. Chem. Soc. Trans.* **1907**, *91*, 2001–2021.
- [16] R. Aveyard, B. P. Binks, J. H. Clint, *Adv. Colloid Interface Sci.* **2003**, *100*, 503–546.
- [17] W. Zhang, L. Fu, H. Yang, *ChemSusChem* **2014**, *7*, 391–396.
- [18] M. Pera-Titus, L. Leclercq, J. M. Clacens, F. De Campo, V. Nardello-Rataj, *Angew. Chem. Int. Ed.* **2015**, *54*, 2006–2021; *Angew. Chem.* **2015**, *127*, 2028–2044.
- [19] J. Cho, J. Cho, H. Kim, M. Lim, H. Jo, H. Kim, S.-J. Min, H. Rhee, J. W. Kim, *Green Chem.* **2018**, *20*, 2840–2844.
- [20] M. Zhang, R. Ettelaie, T. Yan, S. Zhang, F. Cheng, B. P. Binks, H. Yang, *J. Am. Chem. Soc.* **2017**, *139*, 17387–17396.
- [21] T. Yang, L. Wei, L. Jing, J. Liang, X. Zhang, M. Tang, M. J. Monteiro, Y. I. Chen, Y. Wang, S. Gu, D. Zhao, H. Yang, J. Liu, G. Q. M. Lu, *Angew. Chem. Int. Ed.* **2017**, *56*, 8459–8463; *Angew. Chem.* **2017**, *129*, 8579–8583.
- [22] F. Xue, Y. Zhang, F. Zhang, X. Ren, H. Yang, *ACS Appl. Mater. Interfaces* **2017**, *9*, 8403–8412.
- [23] M. Shen, D. E. Resasco, *Langmuir* **2009**, *25*, 10843–10851.
- [24] S. Crossley, J. Faria, M. Shen, D. E. Resasco, *Science* **2010**, *327*, 68–72.
- [25] P. A. Zapata, J. Faria, M. P. Ruiz, R. E. Jentoft, D. E. Resasco, *J. Am. Chem. Soc.* **2012**, *134*, 8570–8578.
- [26] H. Yang, L. Fu, L. Wei, J. Liang, B. P. Binks, *J. Am. Chem. Soc.* **2015**, *137*, 1362–1371.

- [27] H. Liu, F. G. Xi, W. Sun, N. N. Yang, E. Q. Gao, *Inorg. Chem.* **2016**, *55*, 5753–5755.
- [28] J. Park, J.-R. Li, Y.-P. Chen, J. Yu, A. A. Yakovenko, Z. U. Wang, L.-B. Sun, P. B. Balbuena, H.-C. Zhou, *Chem. Commun.* **2012**, *48*, 9995–9997.
- [29] L. Zhong, C. Anand, K. S. Lakhi, G. Lawrence, A. Vinu, *Sci. Rep.* **2015**, *5*, 1–8.
- [30] T. A. Geissman, *Org. React.* **1944**, 94–113.
- [31] C. G. Swain, A. L. Powell, W. A. Sheppard, C. R. Morgan, *J. Am. Chem. Soc.* **1979**, *101*, 3576–3583.

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