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Artificial metalloenzymes *via* encapsulation of hydrophobic transition-metal catalysts in surface-crosslinked micelles (SCMs)†

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Encapsulation of a hydrophobic rhodium catalyst in crosslinked micelles allowed nonpolar substrates to react in water with unusual selectivity.

Chemists have long marveled at the abilities of enzymes to catalyze reactions under ambient conditions in water with extraordinary selectivity. Water is an attractive green solvent due to its abundance, low cost, nonflammability, and nontoxicity. Aqueous biphasic catalysis, in particular, has the potential benefits of facile product isolation and catalyst recovery as a result of the phase-separated organic products and the reaction medium.[1] The process, however, is limited industrially to a few reactions in which the organic starting material has substantial solubility in water.

The fundamental difficulty in expanding aqueous biphasic catalysis to more hydrophobic substrates lies in the latter's low solubility in water.[1,2] Although many organometallic catalysts can be made water-soluble,[2,3] a nonpolar reactant has difficulty accessing the catalyst in the aqueous phase. Organic co-solvents and surfactants may be added to ease the solubility problem but, inevitably, compromises the phase separation of the product. To solve the dilemma, chemists have investigated many ligands and supports for the catalysts, including water-soluble calixarenes,[4] thermally regulated phase-transfer ligands,[5] cyclodextrin derivatives,[6] polystyrene lattices,[7] and crosslinked polymeric microreactors.[8]

How can we make organometallic catalysts soluble in water without affecting their accessibility by nonpolar organic molecules? We herein report a method to trap conventional *hydrophobic* organometallic catalysts in crosslinked micelles (Fig. 1). The SCMs contained hydrophobic sites near the catalysts, which could bind nonpolar substrates and create unusual selectivity for the catalysis. Moreover, the entrapment protects the catalysts from deactivation pathways such as dimerization.

The SCMs were prepared by crosslinking alkynylated surfactant **1** in the micellar configuration with 1.5 equiv. of **2** in the presence of Cu(I) catalysts.[9] We previously encapsulated

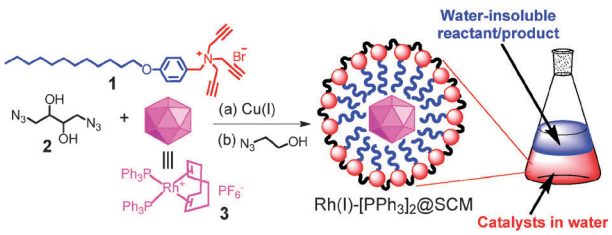

Fig. 1 Preparation of the SCM-encapsulated rhodium catalyst and schematic representation of the biphasic catalytic hydrogenation of water-insoluble alkenes in water.

a hydrophobic fluorescent probe (pyrene) inside the SCMs and found that the probe stayed entrapped for over 6 months.[10] In this work, we solubilized a commercially available bisphosphine rhodium(I) complex (**3**) in water by surfactant **1** at [**3**]/[**1**] = 1/50. With an estimated micellar aggregation number of ~50,[9,11] each SCM should contain one rhodium complex on average. After crosslinking, we "terminated" the residual alkyne groups of the SCMs by reacting with excess 2-azidoethanol and removed the water-soluble impurities such as copper salts by dialysis against water.[12] The concentration of Rh was measured by ICP-MS and translated to 0.92 ± 0.03 rhodium atom per SCM (see the ESI† for details).

It is not enough for the rhodium complex to be solubilized by the SCM. To be useful in aqueous biphasic catalysis, the complex has to be *physically trapped* within the crosslinked micelle—this is the key difference between our method and reported solubilization of organometallic catalysts in surfactant micelles.[13] Fig. 2 shows two aqueous solutions of **3** solubilized by CTAB (*i.e.*, cetyltrimethylammonium bromide) and SCMs, respectively. When the solutions were placed on top of a chloroform layer, the yellow color of the rhodium complex stayed in the

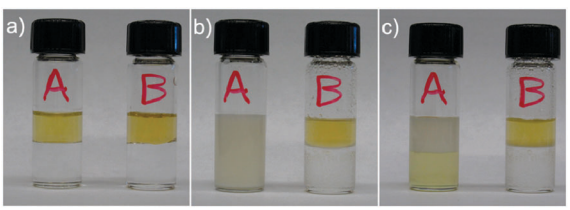

Fig. 2 Comparison of rhodium complex **3** protected by CTAB (A) and SCM (B) in the presence of $CHCl_3$ (a) before, (b) after 2 min of hand-shaking and 1 min of standing, and (c) after standing overnight at room temperature.

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aqueous phase initially (Fig. 2a). After being hand-shaken and left standing for 1 min, the CTAB-containing sample (**A**) turned into an emulsion, whereas the SCM-containing sample (**B**) quickly separated into two layers (Fig. 2b). Most importantly, upon further standing, the rhodium complex migrated to the organic phase completely in sample **A** but remained in the aqueous phase in sample **B** (Fig. 2c). In fact, the yellow color of the SCM sample stayed completely in the aqueous phase even if the solution was stirred with a large amount of chloroform for several days.

Encouraged by the ease of phase-separation and the physical containment of the rhodium complex, we examined the ability of Rh(I)–$[PPh_3]_2$@SCM to catalyze hydrogenation of hydrophobic alkenes. Catalyst optimization was performed with 1-octene and 1-decene as the model substrates. In general, the alkene was mixed with the aqueous solution of SCM-encapsulated catalyst under vigorous stirring at 800 psi H_2. After 24 h at room temperature, 1-octene was converted to the alkane quantitatively but the yield for 1-decene was only 23% (Table 1, entries 1 and 2).

These results were encouraging to us. Although the longer alkene had difficulty approaching the catalyst, 1-octene, being highly hydrophobic, had no problem entering the SCM to react. To improve the reactivity of the longer alkene, we prepared Rh(I)–$[PPh_3]_2$@SCM in the presence of various additives (Table 1). The hypothesis was that the additives would occupy the space inside the micelles of **1** and, after crosslinking could be removed to create hydrophobic sites near the catalyst. However, neither cyclohexane, which was expected to be located in the hydrophobic core of the micelle, nor CTAB, which occupied space both on the surface and within the core of the micelle, afforded better catalysts (Table 1, entries 3–6).

1-Dodecanol turned out to be a much better additive. The catalyst prepared with 25 mol% of the alcohol converted 1-octene and 1-decene quantitatively. Note that, if the additive was not removed after the preparation of Rh(I)–$[PPh_3]_2$@SCM, the hydrogenation was very sluggish (Table 1, entry 9). Clearly, the additive was occupying hydrophobic sites inside the SCM that were critical for the substrate to access the rhodium metal.

We then examined the reactivity of a number of alkenes to understand the selectivity of the SCM-encapsulated catalyst. As shown in Table 2, linear alkenes with 6 to 10 carbons had no difficulty getting to the catalytic site (entries 1–3). An increase of two additional carbons, however, reduced the yield to 21%

Table 1 Optimization of the preparation of Rh(I)–$[PPh_3]_2$@SCM[a]

Entry	Additive[b]	Substrate	Yield (%)
1	None	1-Octene	>95
2	None	1-Decene	23
3	100 mol% cyclohexane	1-Octene	>95
4	100 mol% cyclohexane	1-Decene	Trace
5	10 mol% CTAB	1-Octene	>95
6	10 mol% CTAB	1-Decene	22
7	25 mol% 1-dodecanol	1-Octene	>95
8	25 mol% 1-dodecanol	1-Decene	>95
9	25 mol% 1-dodecanol[c]	1-Decene	35

[a] Catalytic hydrogenation was carried out with 0.2 mol% Rh catalyst at 800 psi H_2 for 24 h. Yields were determined by the ^{1}H NMR spectroscopy after the reaction mixture was extracted with dichloromethane (see ESI for details). [b] The additive was added during the preparation of the Rh(I)–$[PPh_3]_2$@SCM and removed by CH_2Cl_2 extraction after the cross-linking. [c] 1-Dodecanol was *not* removed after the catalyst preparation.

Table 2 Catalytic hydrogenation with Rh(I)–$[PPh_3]_2$@SCM prepared with 25 mol% 1-dodecanol as the additive[a]

Entry	Substrate	Yield (%)
1	1-Hexene	>95
2	1-Octene	>95
3	1-Decene	>95
4	1-Dodecene	21
5	Styrene	78
6	Cyclohexene	22
7	Butyl acrylate	>95
8	*t*-Butyl acrylate	79
9	Allyl alcohol	26
10	Pent-4-en-1-ol	28
11	2-*trans*-Octene[b]	22
12	3-*trans*-Octene[b]	10
13	4-*trans*-Octene[b]	18

[a] Catalytic hydrogenation was carried out with 0.2 mol% Rh catalyst at 1200 psi H_2 for 24 h. Yields were determined by ^{1}H NMR spectroscopy after the reaction mixture was extracted with dichloromethane. [b] Yields were determined by GC. GC-MS was used to identify the identity of the products.

for 1-dodecene. Heating the reaction mixture at 60 °C gave essentially the same results. The inherent chemical reactivity of 1-decene and 1-dodecene could not explain the large difference in the yields. Neither substrate has significant solubility in water. It seems that the crosslinked micelle, limited by the chain length of the hydrophobic tail, could only accommodate hydrocarbons with a certain chain length. 1-Dodecene was probably too long to fit within the hydrophobic sites of the SCM (Fig. 3). Exposure of a hydrophobic compound to water is unfavorable. If a large section of 1-dodecene has to be exposed to water in order to react with the entrapped rhodium, the hydrogenation is expected to be disfavored by the hydrophobic effect.

We also prepared an analogue of **1** with a C16 hydrocarbon tail and used cetyl alcohol as the additive to prepare Rh(I)–$[PPh_3]_2$@SCM. We were hoping that the longer hydrocarbon tail might allow the longer alkene to be accommodated. Unfortunately, the longer surfactant had difficulty forming micelles at room temperature. Although the catalyst entrapment could be performed at higher temperature (*ca.* 50 °C), no improvement in the hydrogenation of 1-dodecene was observed. Since the catalysts prepared at different temperatures could be different, other factors might have contributed to the results (*i.e.*, lack of improvement).

It seems to us that, even if a surfactant with a longer hydrocarbon tail is used successfully in the SCM preparation,

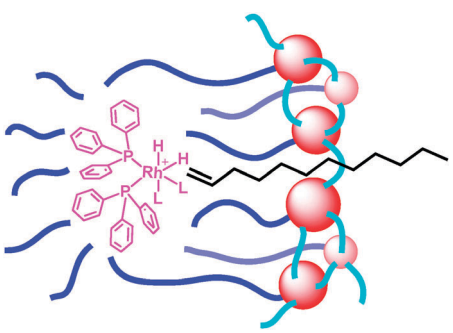

Fig. 3 Schematic representation of the hypothesized chain-length selectivity.

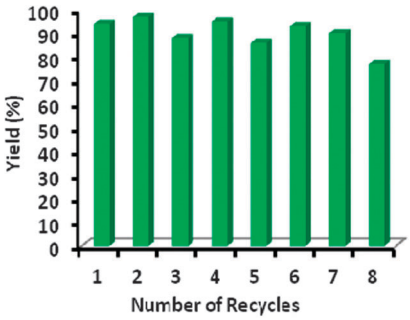

Fig. 4 Reusing of Rh(I)–$[PPh_3]_2$@SCM in the hydrogenation of 1-octene.

the longer tail does not necessarily translate to a deeper location of the catalyst. The hydrophobic tails of the surfactants need to aggregate tightly to maximize hydrophobic interactions. In the presence of a bulky rhodium complex, these tails would kink and possibly wrap around the catalyst, diminishing the potential "depth" of the catalyst in the SCM. Besides, there is no reason for the catalyst to stay in the center of the SCM. Possibly, the selectivity in the Rh(I)–$[PPh_3]_2$@SCM was caused by small "crevices" in the crosslinked micelles formed after the removal of the alcohol additive. Linear alkenes can squeeze into these crevices to access the metal center. If the alkenes are too bulky or too long, they will have difficulty fitting into these crevices, making them less reactive.

Reactions for the other alkenes seemed to be consistent with the above explanation. In general, linear, "slimmer" alkenes were more reactive than bulkier ones (Table 2). Although the difference was not large, butyl acrylate was clearly more reactive than *t*-butyl acrylate. Hydrophilic alcohols (allyl alcohol and pent-4-en-1-ol) were unreactive, fully in line with the hydrophobic microenvironment around the catalyst.

The most interesting selectivity was the terminal *versus* internal for the linear alkenes. Although the hydrogenation of 1-octene proceeded smoothly (Table 2, entry 2), none of the internal octenes gave good yields (entries 11–13). When the reactions were performed in methanol homogenously, 1-octene was more reactive than the other octenes by 2–3-fold (data not shown). The highest selectivity among the octenes was >9 with the SCM-encapsulated rhodium (entries 2 and 12), clearly due to the *supramolecular control of the reactivity*. The rhodium catalyst was confirmed to be physically trapped inside the SCM. In addition to the chloroform extraction experiment (Fig. 2), we analyzed the methylene chloride extract after the hydrogenation. The concentration of Rh determined by ICP-MS was 1.05 ± 0.08 ppb, which corresponded to *ca.* 0.01% of Rh leaching.

Catalytically active rhodium(I) species can be deactivated easily in homogeneous solution by dimerization.[14] Such deactivation will be difficult with the catalyst protected by the SCM. Indeed, the Rh(I)–$[PPh_3]_2$@SCM catalyst could be reused many times in the biphasic catalysis (Fig. 4). Only in the eighth cycle, a significant decrease in yield (to 77%) occurred.[15] The turn-over frequency (TOF) of the catalyst stayed largely unchanged in the repeated reactions, either at the end of 24 h when the reaction was near completion (Table S1, ESI†) or at 6 h at relatively low conversions (Table S2, ESI†). Considering the harsh treatment of the samples in between the reactions,[16] the rhodium catalyst was extremely robust when encapsulated inside the SCM.

In conclusion, physical entrapment of a conventional hydrophobic transition metal catalyst within the water-soluble surface-crosslinked micelle provided a hydrophobic microenvironment around the catalyst. In comparison to other methods to prepare water-soluble transition metal catalysts,[1–3] our method requires no structural modification of the catalyst and enables hydrophobic substrates to access the catalyst in water. The activity of the catalyst was still rather low, as the complete reaction required 24 h at room temperature.[17] Although rudimentary in comparison to the substrate selectivity found in biocatalysts, the chain-length and terminal/internal selectivity displayed by the SCM-encapsulated rhodium demonstrated the potential power of the supramolecular confinement. Overall, the Rh(I)–$[PPh_3]_2$@SCM catalyst has remarkable resemblance to natural metalloenzymes with water-solubility, modifiable surface groups,[9] an internal catalytic site, and hydrophobic binding sites. Further modification of these catalytic nanoparticles should endow them with additional features, possibly creating useful, reusable catalysts for aqueous biphasic catalysis.

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15 The reaction conditions were not optimized. The fluctuation in the yields in the first several cycles of reaction most likely resulted from variations in the stirring conditions resulted from the heterogeneous nature of the reaction.
16 After each cycle of hydrogenation, the aqueous phase (2 mL), where the catalyst was, was extracted with methylene chloride (3×3 mL) and heated at 50 °C for ~2 min to evaporate the residual methylene chloride before the next cycle of hydrogenation. The extraction and evaporation were performed in air without special protection.
17 The low reactivity was probably caused by steric hindrance around the catalyst and possibly also the difficulty of the nonpolar alkene to migrate in the aqueous phase.

