Angewandte International Edition Chemie

DOI: 10.1002/anie.201302662

Supramolecular Catalysis

Supramolecular Assemblies of Amphiphilic L-Proline Regulated by Compressed CO_2 as a Recyclable Organocatalyst for the Asymmetric Aldol Reaction**

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Dedicated to Professor Chunli Bai

Self-assembled nano/micro structures formed by amphiphiles in water, such as micelles, vesicles, and emulsions, have been well-studied and have provided a wide number of applications in the fields of biochemistry,[1] drug delivery,[2] oil recovery,[3] catalysis,[4] and so forth. In terms of the structural regime, these assemblies could serve as nanoreactors with some unique merits. For example, they offer boundaries that separate the reaction space from the environment.[5] They could also assist the preorganization of the reactants in a favored conformation, creating a space where reaction can be selectively controlled.[6] Among these systems, controlling and regulating the assembled nano/microstructures become an important issue to efficiently facilitate applications. Although various ways of regulating the assembled structures, such as temperature,[7] ionic strength,[8] pH value,[9] and additives[10] are generally employed, it still remains a great challenge to regulate the structures dynamically, reversibly, and circularly.

In recent years, with the progress in sustainable chemistry, supercritical or compressed CO_2 has been widely used in many aspects.[11] Compressed CO_2 can trigger the formation of nanoemulsions reversibly,[12] and switch the micelle-to-vesicle transition (MVT)[13] and the liquid-crystal-to-micelle transition.[14] Furthermore, by regulating the pressure, compressed CO_2 favors the separation of the products.[15] Thus, compressed CO_2 is expected to be used in the regulation of the nanostructures as well as reactions.[16] Herein, by combining the merits of the triggering self-assembled nanostructures and the regulation ability of compressed CO_2, we applied compressed CO_2 in a catalytic asymmetric aldol reaction. While metal-assisted catalysts are generally used,[17] supramolecular organocatalysts are attracting great interest recently,[18] and there is still a need to develop a low-cost, safe, and environmentally benign catalyst. In the present case, by aid of compressed CO_2, we have performed the asymmetric aldol reaction in water with great efficiency (Scheme 1). First, although the amphiphilic proline could not be dissolved in water and catalyze the reaction in pure water, by introducing compressed CO_2, the nanostructures can be induced and applied in the catalysis of the aldol reaction. Furthermore, the nanostructure can be regulated by the pressure of CO_2 and subsequently the reaction selectivity, thus providing a dynamic regulation of the nanostructure and reaction. Second, with the aid of compressed CO_2, the products can be separated easily. Third, after simple separation, the amphiphilic proline can be reused for catalyzing the reaction with the formation of nanostructure. Such a process can be repeated several times, thus making the catalyst recyclable. to date, although there are several reports on the regulation of vesicle structures through CO_2,[19] this is the first report that compressed CO_2-induced nanostructures are used to the asymmetric catalysis. Furthermore, such a process is essentially sustainable and recyclable.

The phase behavior of PTC_{12} with a concentration of 8 mM in water was investigated in situ in the presence of compressed CO_2 at 25 °C under different pressure, as shown in Figure 1. The PTC_{12} is practically insoluble in water. Interestingly, as compressed CO_2 was charged into the system to 2.0 MPa, a transparent solution was obtained (Figure 1 A,a), suggesting the formation of a PTC_{12} assembly. A subsequent increase of the CO_2 pressure caused the solution to show a gradual transition from colorless to a slightly bluish color (Figure 1 A,b–e), indicating the increase of the size of assemblies. This process was simultaneously monitored by the turbidity change of the system by UV/Vis spectra (Figure 1 B). Consistent with the continuous phase transition, the transmittance at 500 nm shows dramatic decrease after CO_2 pressure exceeded 2 MPa, and then drops slowly when CO_2 pressure beyond about 6 MPa. The assemblies obtained at all pressures we tested were stable enough and there was no precipitation, even after more than two weeks.

To further understand such changes, the in situ emission spectra of PTC_{12} were detected (Figure 2 A). PTC_{12} dispersed in pure water shows a weak emission at 333 nm. Upon introducing compressed CO_2, the fluorescence of PTC_{12} increases obviously and shows a shoulder band at 410 nm,

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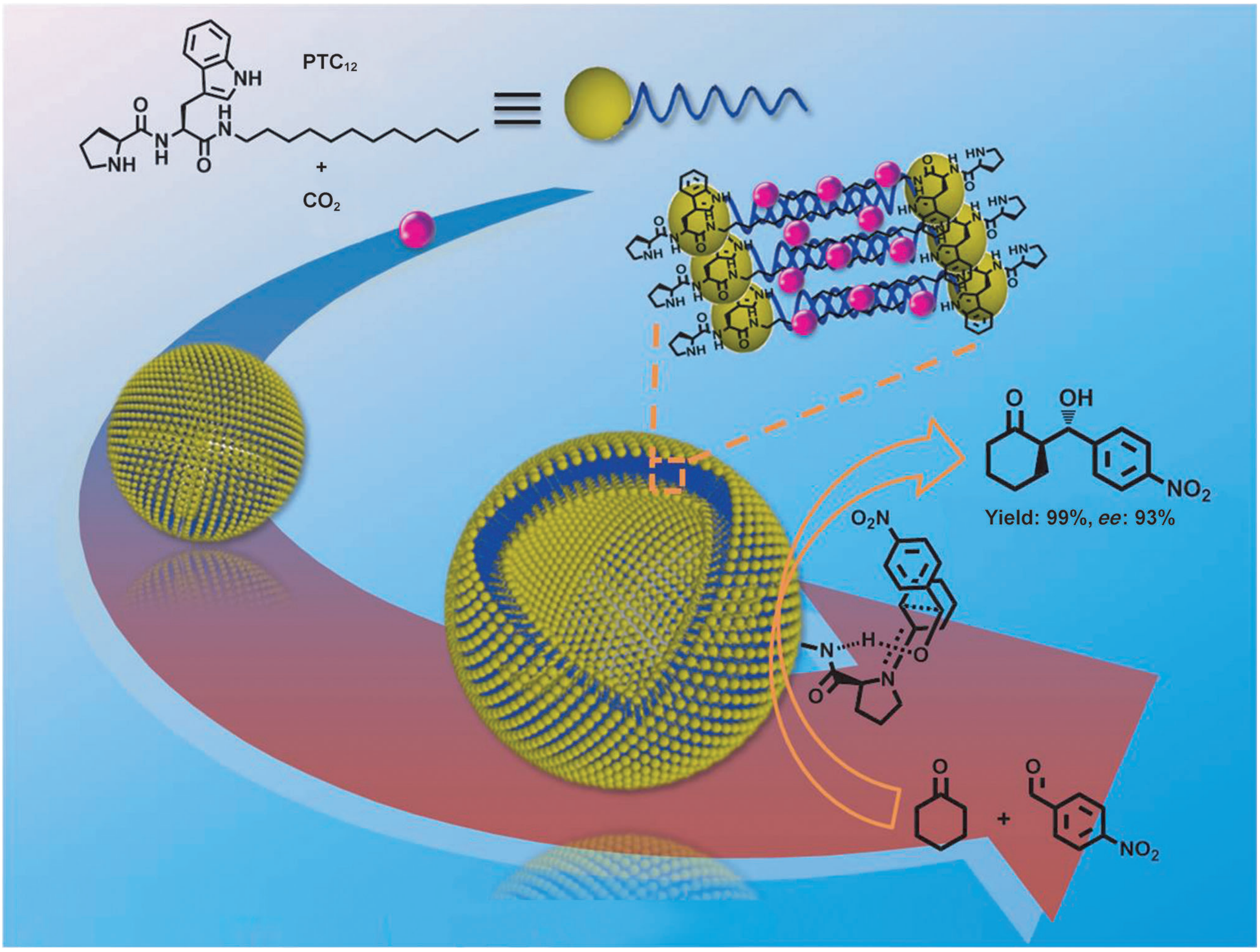
[**] We gratefully acknowledge funding of this research by the Basic Research Development Program (2010CB833305), the National Natural Science Foundation of China (Nos. 91027042, 21021003, 21227802).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201302662.



Scheme 1. The self-assembly of vesicles regulated by compressed CO_2 and the proposed transition-state model for the direct asymmetric aldol reaction. Top: molecular structure of amphiphilic proline derivative, abbreviated as PTC_{12}. The PTC_{12} can be induced to form vesicle structure in water under compressed CO_2, the size of which depended on the pressure of CO_2. The direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde was catalyzed in the vesicle structures, and high enantiomeric selectivity was achieved.

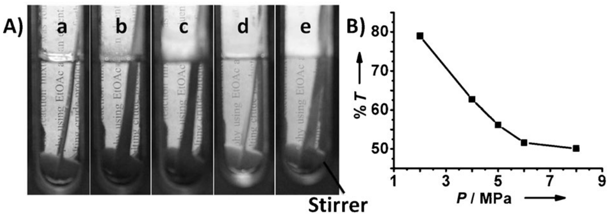


Figure 1. A) Photographs of PTC_{12} aqueous system at 25 °C and under CO_2 pressure of a) 2, b) 4, c) 5, d) 6, e) 8 MPa; B) Variation in UV transmittance at 25 °C with corresponding CO_2 pressure.

suggesting the formation of excimer.[20] With a further increase of CO_2 pressure, the emission spectra shows a gradual decrease at around 336 nm and increase around 410 nm. Dynamic light scattering (DLS) measurements were carried out for the PTC_{12} assemblies in water immediately after removal of CO_2 (Figure 2B). An average apparent hydrodynamic diameter of about 110 nm for PTC_{12} assembly was observed under 2 MPa. Together with the transparent appearance of the solution and the amphiphilic nature of PTC_{12}, we suggest that vesicles are formed. The diameter of the vesicles gradually increased to about 353 nm and 429 nm, as the system pressure was at 5 and 8 MPa respectively. The ionic strength of the system also has a profound effect on PTC_{12} assembly. The hydrodynamic diameter of about 290 nm was obtained in saturated aqueous NaCl solution under 5 MPa pressure.

The fluorescence-probe technique[21] was utilized to investigate the vesicular assemblies of PTC_{12} induced by compressed CO_2. Figure 2C shows the fluorescence spectra of Nile red (NR) incorporated in the PTC_{12} aqueous system under compressed CO_2. A weak emission of NR close to 664 nm was recorded at 0 MPa, which indicated that NR was distributed among a range of polar environment.[22] However, a blue shift in emission and increase of fluorescence intensity were observed when CO_2 was charged into the system to 2 MPa, suggesting that NR was located in hydrophobic environment. After this point, the emission intensity gradually decreased and the emission peak continuously shifted slightly to a shorter wavelength, from $\lambda_{max} = 625$ to 617 nm, with a further increase in CO_2 pressure (Figure 2D). This

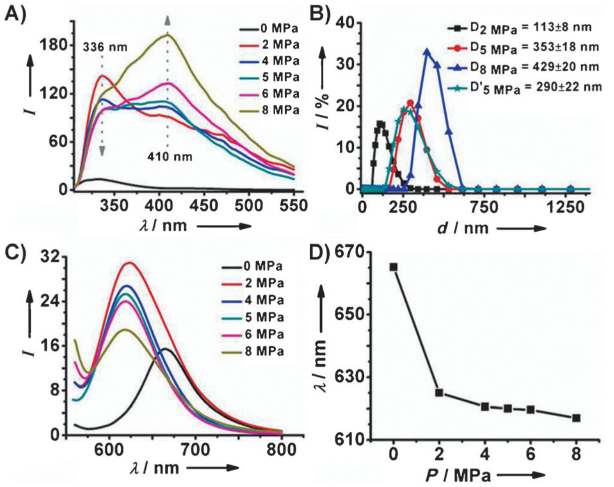


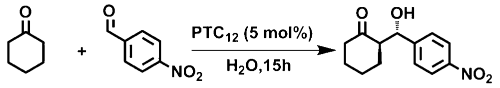
Figure 2. A) Emission spectra of PTC_{12} (8 mM, $\lambda_{ex} = 280$ nm) at some typical CO_2 pressures; B) DLS of PTC_{12} with the same concentration under different pressures and system ($D'_{5\,MPa}$ refers to DLS data obtained in saturated NaCl aqueous solution); C) Fluorescence spectra of Nile red (5 μM, $\lambda_{ex} = 550$ nm) in PTC_{12} aqueous solution; D) Dependence of maximum emission wavelength of Nile red under different CO_2 pressure at 25 °C.

result demonstrated that CO_2 was situated within alkyl chains and provided a more hydrophobic environment, which restricted motion of NR molecules.

It is well-known that compressed CO_2 is soluble in water and consequently the pH value of the system can be easily regulated.[23] Generally, the pH value could be decrease to 3.4; after that, the pH will drop slightly.[24] In the present case, upon introduction of compressed CO_2, it seemed that the PTC_{12} experienced the protonation to form the bicarbonate salts first,[25] which increased the hydrophilicity of PTC_{12} and then facilitated the formation of the assembly in water. The hydrogen bonds of amide between headgroup may force to decrease the surface area per surfactant headgroup, causing the packing parameter to probably exceed the critical value of 0.5, which led to the formation of vesicles.[26] Subsequently, compressed CO_2 will regulate the size of these vesicles dynamically upon inserting CO_2 into the hydrophobic area of packed amphiphiles.

The PTC_{12} vesicles induced by compressed CO_2 were subsequently employed to catalyze the direct asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. After reaction, the products precipitated from system owing to poor solubility in water, and organocatalyst PTC_{12} was still well-dissolved in the aqueous system under compressed CO_2. The difference of solubility of products and PTC_{12} in water offered the possibility of simple separation between products and catalysts without any organic extraction agents. The reaction products were easily collected after the aqueous organocatalyst system was released while the CO_2 pressure was kept (for the aldol reaction and separation process, see the Supporting Information, Figure S6). The DLS of the recycled residual aqueous system was then measured after the reaction (Supporting Information, Figure S7). Compared to the size of plain PTC_{12} assemblies, the similar apparent hydrodynamics diameter distribution was obtained, which confirmed the assembly structure being preserved during the reaction.

Table 1: Screening of reaction conditions in the direct asymmetric aldol reaction of cyclohexanone with 4-nitrobenzaldehyde in presence of compressed CO_2.[a]



Entry	*P* [MPa]	*T* [°C]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	0	25	0	–	–
2	2	25	81	81/19	37
3	4	25	92	82/18	39
4	5	25	94	81/19	51
5	6	25	93	80/20	48
6	8	25	93	83/17	28
7[e]	8	40	69	77/23	23
8	5	40	72	79/21	24
9	5	10	98	86/14	76
10	5	0	98	86/14	83
11[f]	5	0	99	84/16	71
12[g]	5	25	99	84/16	93
13[h]	5	25	0	–	–
14[i]	0	25	35	63/37	22

[a] Reaction conditions: 4-nitrobenzaldehyde (0.5 mmol), cyclohexanone (1 mmol), H_2O (3 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral-phase HPLC. [e] Under supercritical CO_2. [f] catalyst load: 2 mol%. [g] Saturated NaCl aqueous solution as solvent. [h] L-Proline as catalyst. [i] PTC_{12} in the presence of 1 mM trifluoroacetic acid (TFA).

We then analyzed the yield and the *ee* value of the products by chiral HPLC; the results are summarized in Table 1. No product was obtained in the absence of CO_2, while a good catalytic activity but poor enantioselectivity were obtained under 2 MPa (entry 2). The reaction yield and enantioselectivity gradually increased with the pressure from 2 to 5 MPa (entries 3 and 4), which was attributed to the larger size of assemblies affording more active catalytic sites. A further increase of the pressure to 6 or 8 MPa showed no obvious impact on the reaction yield; however, the *ee* value decreased rapidly (entries 5 and 6). All these results indicated that the curvature of the PTC_{12} vesicles may play an important role in determining the enantioselectivity. The curvature of vesicles varies with the size change and the suitable curvature will be favorable for the enhancement of enantioselectivity through stabilizing the transition state between enamine and aldehydes.[27] The effect of temperature and catalyst load on the reaction was then investigated under 5 MPa (Table 1, entries 8–11). As expected, the reaction gave the desired aldol products in high yield and *ee* value at lower temperature. When the catalyst load was decreased by 60%, the system still exhibited good catalytic activity and selectivity. The best result was obtained when the reaction medium was replaced by the saturated NaCl aqueous solution, which could be attributed to the increment of hydrophobic interaction of nonpolar group through salting-out effect.[28] All asymmetric aldol reactions in this experiment afforded the *anti* configuration as the main product, and the *syn*/*anti* ratio had no significant change under different reaction conditions. In comparison with amphiphilic proline, the L-proline-catalyzed aldol reaction in water under compressed CO_2 was turned out to be ineffective (entry 13). This result indicates that the self-assembled vesicle formed by amphiphilic proline was really an efficient nanoreactor for the direct aldol reaction. The addition of acid, especially TFA, has been shown to enhance the yield and *ee* value of aldol reaction in water.[29] However, the amount of TFA should be higher than the organocatalyst to reach high catalytic activity and enantiomeric selectivity. If the TFA concentration was lowered to 1 mM (pH 3), the yield and *ee* value of product would be much lower than that at 5 MPa CO_2 (pH 3; entry 14). This result indicated that compressed CO_2 not only provided an acidic environment for the PTC_{12} organocatalyst system, but afforded a suitable catalytic microenvironment for direct aldol reaction through the formation of vesicles.

The organocatalyst PTC_{12} for the aldol reaction was simply reused without any other treatment by recovering the aqueous phase accompanied by simultaneous release of CO_2. This process provided a direct recycling method without loading catalysts on polymer or inorganic materials, or introducing any organic extract solvents into system.[30] Reintroduction of starting reactants into the catalyst residual aqueous layer began the next catalytic cycle. This process can be repeated at least five times (Figure 3). The catalytic activity corresponding to the aldol reaction was constantly kept in a high level at the first four repeats. A slightly decrease of yield was detected at fifth run. However, it had no obvious effect on enantioselectivity of the organocatalyst in five cycles, which suggested that the recycling of PTC_{12} was qualified as practicable. It should be noted that the recycling was not carried out in saturated NaCl solution, as the salt would affect the separation of products and catalysts.

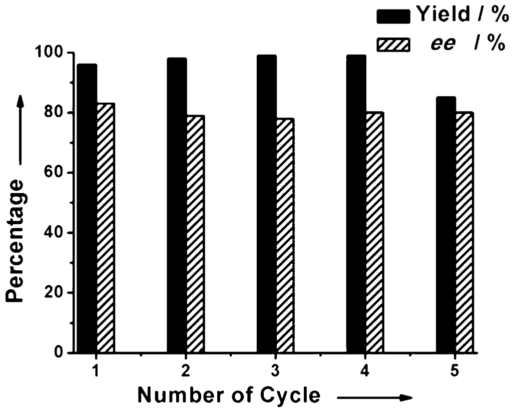


Figure 3. Recycling experiment of PTC_{12} at 0 °C under 5 MPa compressed CO_2 in water.

In summary, we have developed a dynamic self-assembly of vesicle structures that is regulated by compressed CO_2 and we utilized this process as a sustainable catalytic system to the direct asymmetric aldol reaction. The vesicle structures turned out to be an efficient nanoreactor and showed high activities to catalyze the direct asymmetric aldol reaction with 93 % *ee* and 99 % yield. Furthermore, the simple separation of products was benefit from removing reaction medium followed with the release of CO_2. The recycling of organocatalyst was realized over several cycles with constant catalytic activity and enantioselectivity at a high level.

Received: March 31, 2013
Revised: May 1, 2013

Keywords: carbon dioxide · L-proline · organocatalysis · sustainable chemistry · vesicles

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