

Research Note

Direct catalytic asymmetric aldol reactions on chiral catalysts assembled in the interface of emulsion droplets

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Abstract

An amphiphilic proline-based organocatalyst was assembled on the interface of water and oil, resulting in a W/O emulsion. The chiral catalyst in emulsion significantly enhances the reactivity and stereoselectivity of the direct asymmetric aldol reactions, which can be attributed mainly to the larger interfacial surface area and uniformly distributed catalyst molecules in the interface of the emulsion droplets.

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1. Introduction

The direct asymmetric aldol reaction is one of the most important C–C bond-forming reactions and has been widely used in constructing natural and nonnatural products [1–3]. Numerous methods based on biologic catalysis, organometallic catalysis, and organocatalysis for this transformation have been reported [4–9]. In particular, organocatalysis has attracted growing interest, and extensive investigations have been conducted to improve the organocatalytic efficiency and enantioselectivity [10–12]. Previous studies have shown that a small amount of water can accelerate the reaction [13–15], whereas a large excess of water is detrimental to the reaction [16–19]. Recently, Hayashi et al. [20] and Barbas III and co-workers [21] independently reported highly diastereoselective and enantioselective aldol reactions in the presence of water without using any organic solvents. Very recently, Hayashi et al. [22] reported successful cross-aldol reactions catalyzed by a combined proline/surfactant organocatalyst in water. However, there is a debate as to whether these reactions are really “all wet,” and

the role of water in these reactions remains unclear [23–25]. Although emulsion and emulsion-related systems have aroused much interest recently because of their significant beneficial effects on the reaction [26–30], whether emulsion formation is a prerequisite for an aldol reaction in the presence of water is not clear [21,22]. For instance, the reactions reported by Barbas III and co-workers [21] and Hayashi et al. [22] were performed almost equally well in DMSO or without water at all. Thus, there clearly exists an incentive to gain more insight into the effect of emulsion on the organocatalytic aldol reaction.

In our previous work on ultra-deep desulfurization of diesel and selective oxidation of alcohols catalyzed by amphiphilic catalysts [31,32], we found that the amphiphilic catalysts can be assembled in the interface of water and oil to form emulsion droplets. The catalyst in the emulsion significantly increases the activity and selectivity of the reactions. These findings have stimulated us to extend the concept of emulsion catalysis to asymmetric aldol reaction with an intention of determining the role of water in the aldol reaction with amino acid catalyst. Herein we report that the reactivity and stereoselectivity of direct asymmetric aldol reactions are significantly enhanced by chiral emulsion catalysis, which can be attributed mainly to the large interfacial area and uniformly distributed catalyst molecules in the emulsion system.

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2. Experimental

All chemicals were obtained commercially. NMR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts are given in δ relative to TMS, and coupling constants, J , are given in Hz. Infrared spectra were recorded on a Nicolet Nexus 470 spectrometer. HPLC was performed on HPLC 1100 using Chiralpak AD-H and Chiralcel OD-H columns. Optical microscopy was performed using a Nikon TE2000-E inverted fluorescence microscope equipped with a Qimaging Ltd. RET-2000R-F-CLR-12-C cooled CCD camera, a 100 W Nikon C-LHG1 mercury lamp, and Nikon B-2A fluorescence filters (excitation filter, 450–490 nm; dichroic mirror, 505 nm; emission filter, >520 nm). Light-scattering measurements were performed on a COULTER N4 Plus Submicron Particle Sizer.

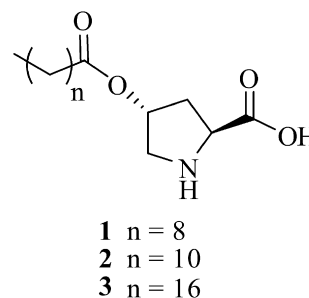
The amphiphilic catalysts were prepared as described previously [22]. Emulsions were formed by the addition of a given amount of catalysts to cyclohexanone, followed by the addition of a specific amount of water under vigorous stirring. The optical microscopy and light scattering of the emulsions were measured immediately thereafter.

The catalyst **2** (11.8 mg, 0.038 mmol) was stirred in 1 ml cyclohexanone for 10 min at room temperature, the 400 μ l of water was added into the mixture under vigorous stirring, resulting in an emulsion. Aldehyde (0.25 mmol) was added into the emulsion and the reaction mixture was vigorously stirred at room temperature for 6–70 h. The reaction mixture was then treated with saturated ammonium chloride solution, and the layers were separated. The aqueous layer was extracted several times with ethyl acetate, and the combined organic layers were dried with anhydrous $MgSO_4$ and evaporated. Purification by

silica gel column chromatography gave the pure aldol product. Ee and dr were determined by HPLC on a Chiralpak AD-H or Chiralcel OD-H column.

3. Results and discussion

Families of the amphiphilic proline-based organocatalysts **1** ((2*S*,4*R*)-4-(decanoyloxy)pyrrolidine-2-carboxylic acid), **2** ((2*S*,4*R*)-4-(dodecanoyloxy)pyrrolidine-2-carboxylic acid) and **3** ((2*S*,4*R*)-4-(stearoyloxy)pyrrolidine-2-carboxylic acid) were synthesized to meet the requirement for the formation of emulsion droplets when the organocatalyst acts as a surfactant (Scheme 1). W/O emulsions were indeed formed by the addition of a given amount of catalyst to cyclohexanone, followed by the addition of a specific amount of water under vigorous stirring. Figs. 1a–1c show an optical microscopy image of the W/O emulsion droplets formed from the amphiphilic catalysts. Metastable emulsions were formed with catalyst **1** and catalyst **2**, whereas catalyst **3** resulted in an unstable emulsion.



Scheme 1. The amphiphilic chiral organocatalysts evaluated in this study.

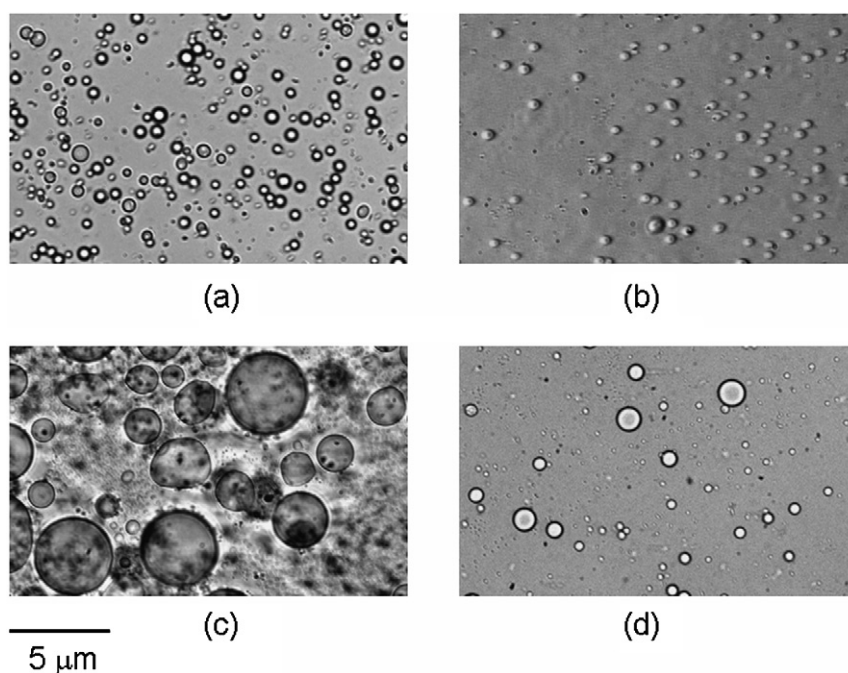
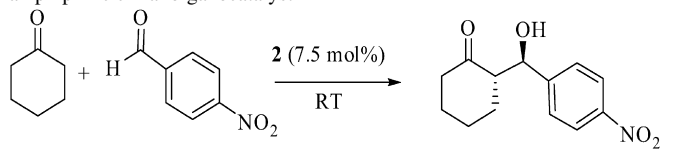


Fig. 1. Optical micrograph of emulsions: (a) mixture of 0.019 mmol catalyst **1**, 400 μ l water and 1 ml cyclohexanone, (b) mixture of 0.019 mmol catalyst **2**, 400 μ l water and 1 ml cyclohexanone, (c) mixture of 0.019 mmol catalyst **3**, 400 μ l water and 1 ml cyclohexanone and (d) mixture of 0.019 mmol catalyst **2**, 500 μ l cyclohexanone and 3.5 ml water.

Table 1
Aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde catalyzed by the amphiphilic chiral organocatalyst **2**



Entry	Reaction media	Time (h)	Yield ^a (%)	Dr ^b (%)	Ee ^c (%)	Emulsion stability
1	Organic solvent ^d	14	<5	n.d	n.d	No emulsion
2	Neat	14	<5	n.d	n.d	No emulsion
3	Neat	36	30	86	78	No emulsion
4	W/O emulsion	14	97	94	>99	Metastable
5	W/O emulsion ^e	13	96	92	99	Metastable
6	W/O emulsion ^f	22	97	94	99	Unstable
7	O/W emulsion ^g	24	95	92	99	Metastable

^a Isolated yield after separation by silica gel.

^b Determined by analysis of the mixture of *anti/syn* product.

^c Determined by HPLC (Chiralpak AD-H).

^d DMSO, THF, CH₃CN, or MeOH as solvent.

^e **1** as catalyst.

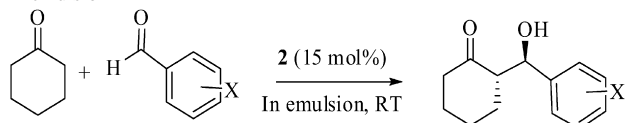
^f **3** as catalyst.

^g 0.5 ml cyclohexanone and 3.5 ml water.

Compared with catalyst **3**, the former two catalysts have shorter alkyl chains and lower hydrophilic-lipophilic balance values. Dynamic light-scattering showed that the sizes of the spherical emulsion droplets formed from **1** and **2** were about 0.1–0.2 μm. Interestingly, a metastable O/W emulsion can be obtained when the ratio of the catalyst to cyclohexanone is optimized (Fig. 1d). The metastable emulsions (either W/O or O/W) can be readily formed using **2** as a surfactant possibly because the chain length of alkyl group in **2** is more suitable for emulsion formation.

The emulsion catalytic system was then tested for the aldol reaction of *p*-nitrobenzaldehyde with cyclohexanone (Table 1). The reaction was very slow in neat or an organic solvent with catalyst **2**, where emulsion was not formed due to the absence of water (Table 1, entries 1 and 2). Prolonging the reaction time to 36 h, the reaction in neat gave the aldol product with only 30% yield, 86% dr, and 78% ee (Table 1, entry 3). However, the reaction in the W/O emulsion formed from **2** (Fig. 1b) was enhanced significantly and gave an aldol product with 97% yield, 94% dr, and >99% ee in 14 h (Table 1, entry 4). The reactivity and stereoselectivity of the reaction also were enhanced significantly when the W/O emulsions formed from **1** (Fig. 1a) and **3** (Fig. 1c) were used as reaction media. The two catalytic emulsion systems showed approximately the same isolated yields and stereoselectivity as the W/O emulsion formed with **2** (Table 1, entries 4–6). The results indicate that emulsion plays a vital role in promoting catalytic activity and stereoselectivity in the aldol reaction. The fact that the metastable emulsions formed from **1** and **2** allowed completion of the aldol reaction more quickly compared with the unstable emulsion formed from **3** further demonstrates the important effect of the emulsion on this reaction (Table 1, entries 4–6). It should be noted that the reaction in the O/W emulsion formed with **2** (Fig. 1d) also was performed efficiently and afforded a product with 95%

Table 2
Cross aldol reactions of cyclohexanone with different aldehydes catalyzed by **2** in emulsion



Entry	X	Time (h)	Yield ^a (%)	Dr ^b (%)	Ee ^c (%)
1	3-NO ₂	12	98	92	98
2	2-NO ₂	18	94	76	93
3	4-Cl	38	40	80	95
4	4-H	38	94	76	90
5	4-MeO	70	70	86	95
6 ^d	4-NO ₂	6	98	74	95

^a Isolated yield after separation by silica gel.

^b Determined by analysis of the mixture of *anti/syn* product.

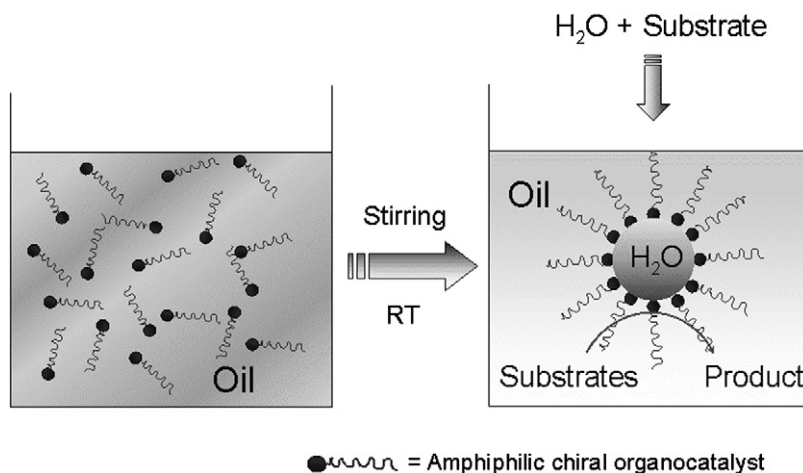
^c Determined by HPLC (Chiralpak AD-H and Chiralcel OD-H).

^d Cyclopentanone as ketone donor.

yield, 92% dr, and 99% ee (Table 1, entry 7). Interestingly, the two types of emulsions (W/O and O/W) formed from **2** resulted in an aldol product with the nearly same yield and stereoselectivity (Table 1, entries 4 and 7), indicating that the aldol reaction can occur efficiently in emulsion even if with an excess amount of water. It should be noted that all of the aldol reactions in emulsion (W/O or O/W) were performed under continuous stirring because the emulsion is metastable. As long as the emulsion was formed, the change in stirring rate did not make a significant difference in the reaction rate.

Although the reaction mechanism of the aldol reaction in emulsions (W/O and O/W) is not very clear at this moment, we can propose that the assembly of the amphiphilic chiral organocatalyst in emulsion is an indispensable requirement for enhancing the activity and stereoselectivity of the aldol reaction. The catalyst molecules in nonemulsion media (neat or organic solvent) are distributed randomly, whereas the catalyst molecules in emulsion are distributed uniformly on the emulsion droplet surface at the molecule level. Thus, the surface area of active catalyst is increased, and more uniform active centers are created. The catalyst on the interface of emulsion droplets also could be beneficial for the reaction if water acts as a weak Brønsted acid to accelerate the reaction, because the catalyst in either W/O or O/W can intimately contact the water [20]. As a result, emulsion catalysis has higher activity and stereoselectivity than nonemulsion catalysis [26–34].

The direct asymmetric aldol reactions using the amphiphilic organocatalyst **2** in emulsion also was examined for cyclohexanone and different aldehydes (Table 2). Generally, the reaction of cyclohexanone with reactive aldehydes gives aldol products with high yields and stereoselectivities. More than 90% ee was obtained in the case of an electron-rich aldehyde, although the yield was modest. The reaction with cyclopentanone, another water-immiscible ketone, also was performed efficiently in emulsion, affording an aldol product with high yield and enantioselectivity (Table 2, entry 6). These results demonstrate that chiral emulsion can act as an efficient reaction media for the direct asymmetric aldol reactions.



Scheme 2. Schematic description of direct asymmetric aldol reaction using an amphiphilic chiral organocatalyst assembled on emulsion droplets.

The direct asymmetric aldol reactions in the W/O emulsion are depicted schematically in Scheme 2. The amphiphilic chiral organocatalyst with proper hydrophilic–lipophilic balance values can be distributed uniformly in the water–oil interface, forming an assembly around the water droplets. The amphiphilic catalyst acts as a surfactant to maintain stable emulsion droplets and so provides high interfacial surface areas, resulting in high reactivity. The catalyst in emulsion can be organized as a well-ordered two-dimensional chiral surface, which may be responsible for the high activity and enantioselectivity observed in the direct aldol reactions [28,33–35].

4. Conclusion

We have developed emulsion catalytic systems (W/O and O/W) using chiral amphiphilic organocatalysts as surfactants. The direct asymmetric aldol reactions were found to occur in the emulsion where the catalyst molecules are distributed uniformly in the water–oil interface and form a chiral surface. The chiral catalyst in emulsion significantly enhanced the reactivity and stereoselectivity of the reactions, which can be attributed mainly to the large interfacial area and uniformly distributed catalyst molecules in the emulsion system. The chiral emulsion catalysis may provide a general and efficient approach for asymmetric synthesis.

Acknowledgments

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