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Effect of Long Chain Fatty Acids on Organocatalytic Aqueous Direct Aldol Reactions

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Abstract: In an organocatalyzed, aqueous direct aldol reaction, the addition of a long chain fatty acid (1 mol%) such as stearic acid or erucic acid improved the aldol product yield and the enantioselectivity with low catalyst loading (1 mol%). The small particle size of the emulsion (less than 1 μm) was a key to the enhanced reactivity as shown by dynamic light scattering (DLS) analyses.

Keywords: aldol reaction; enantioselectivity; fatty acids; organocatalysis; water

In living organisms, organic reactions and inorganic reactions take place in an aqueous medium, whereas most modern organic syntheses are performed in organic solvents. In aqueous environments, emulsible compounds such as bile acids (Figure 1) are required to facilitate organic reactions of hydrophobic organic substrates. Water has advantages over organic solvents, including cost, safety, synthetic efficiency, simple operation, environmental benefits, and new synthetic methodologies.[1] Therefore, modeling of emulsible natural compounds has been used to direct the synthesis of novel and useful surfactants.[2]

In general, surfactant and catalyst are separately added to the reaction mixture; however, Kobayashi and co-workers reported an interesting "Lewis acid-surfactant combined catalyst" named LASC in 1998.[3,4] Aldol reactions of silyl enol ethers with aldehydes proceeded smoothly in water in the presence of LASCs. Recently we designed the artificial aldolase-surfactant hybrid catalyst **3** (Figure 2) and developed direct asymmetric cross-aldol reactions that can be performed in bulk water without addition of organic co-solvents. The hybrid catalyst **3** afforded the desired aldol products in excellent yields with high enantiomeric excesses, even when only an equal molar ratio of the donor and acceptor was used; however, 10 mol% catalyst loading was required.[5,6,7] Here we report efficient, enamine-based, organocatalytic direct asymmetric aldol reactions in water with low catalyst loading (1 mol%) by addition of long chain fatty acids to the reaction.

Our artificial hybrid organocatalyst **3** formed an emulsion with the organic substrate in water and the aldol reaction occurred smoothly. The catalyst **3** plays an important role as not only a surfactant but also a

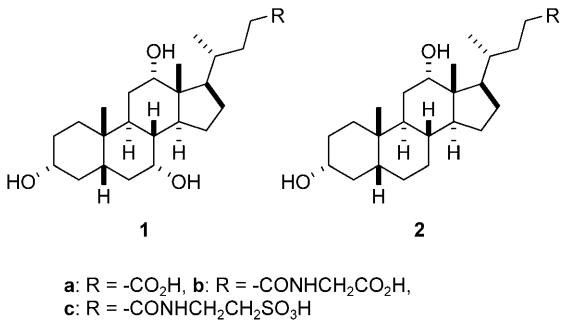


Figure 1. Bile acids in living organisms.

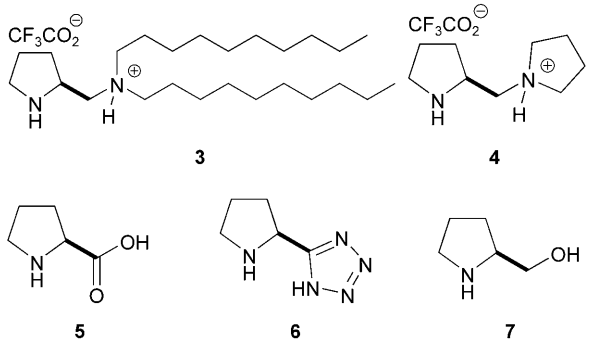
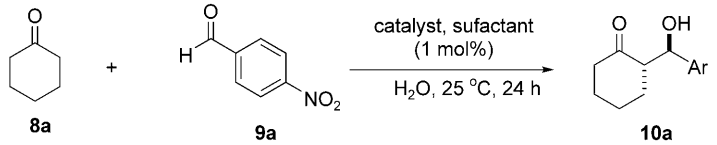


Figure 2. Various organocatalysts.

Table 1. Organocatalyzed aqueous direct aldol reactions in the presence of various surfactants.[a]



8a 9a 10a

Entry	Catalyst (mol%)[b]	Surfactant	Yield [%]	*anti/syn*[c]	*ee* [%][d]
1	**3** (10)	none	99	89/11	94
2	**3** (1)	none	54	89/11	90
3[e]	**3** (1)	none	0	–	–
4	**3** (1)	SDS	54	90/10	90
5	**3** (1)	DODAC	53	86/14	73
6	**3** (1)	TOMAC	62	88/12	71
7	**3** (1)	Triton X-100	56	90/10	78
8	**3** (1)	monostearin	47	91/9	84
9	**3** (1)	**1a**	64	92/8	91
10	**3** (1)	**2a**	61	89/11	94
11	**3** (1)	Stearic acid	82	89/11	93
12[f]	**4** (1)	Stearic acid	0	–	–
13[f]	**5** (1)	Stearic acid	0	–	–
14[f]	**6** (1)	Stearic acid	52	88/12	81
15[g]	**7** (1)	Stearic acid	98	67/33	11

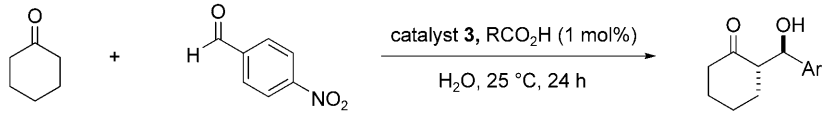
[a] *Conditions:* amine catalyst (0.05 mmol, 1 mol%), surfactant (0.05 mmol, 1 mol%), **8a** (10 mmol), and **9a** (5 mmol) in water (5 mL).
[b] Catalyst structures are shown in Figure 2.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis for *anti*-product.
[e] The reaction was carried out in DMSO.
[f] Reactions were carried out for 72 h.
[g] The reaction was carried out for 48 h.

catalyst. Therefore, a significant amount of **3** (10 mol%) was needed (Table 1, entry 1). Decreasing the amount of catalyst **3** to 1 mol% resulted in low chemical yield but with high stereoselectivity (entry 2). In addition, no formation of the aldol **10a** was observed in a conventional organic solvent such as DMSO (entry 3). To reduce catalyst usage, various surfactants were evaluated. Sodium dodecyl sulphate (SDS, 1 mol%) is known as an efficient surfactant,[8] but addition of SDS did not improve the yield (entry 4). Cationic surfactants such as dioctadecyldimethylammonium chloride (DODAC) and trioctylmethylammonium chloride (TOMAC) provided better chemical yields but decreased the stereoselectivities (entry 5 and 6). In the presence of amphiphilic neutral surfactants, such as Triton X-100 and monostearin, chemical yields and stereoselectivities were low (entries 7 and 8). We found that natural bile acids such as cholic acid (**1a**) and deoxycholic acid (**2a**) improved the chemical yields up to 64% and excellent stereoselectivities were maintained (entries 9 and 10).

Natural bile acids are carboxylic acid derivatives bearing a hydrophobic steroid skeleton; therefore, simple long chain fatty acids should serve as effective surfactants. As we expected, the desired aldol product **10a** was obtained in 82% chemical yield with high diastereo- and enantioselectivities after 24 h in the presence of 1 mol% stearic acid when hybrid organocatalyst **3** was used (entry 11). Under these conditions, diamine catalyst **4** and L-proline **5** did not give the aldol **3** after 72 h (entries 12 and 13). Tetrazole catalyst **6** afforded the aldol **10a** in moderate yield with good enantioselectivity (entry 14). High yield of the aldol **10a** was observed in the presence of L-prolinol **7**, but stereoselectivities were very low (entry 15).

The scope of this class of aldol reactions using hybrid organocatalyst **3** in water was examined with a series of various carboxylic acids (Table 2). Stearic acid enhanced reactivity more than other carboxylic acids tested (entry 12). In the presence of acetic acid, reactivity and stereoselectivities were almost unchanged in comparison with the reaction without carboxylic acid (entry 1 *vs.* 2). Similarly, butyric acid did not affect the reactivity (entry 3). Carboxylic acids (C_6 to C_{16}) showed increased yields relative to the reaction without carboxylic acid (entries 4–10). Erucic acid, which is a monounsaturated fatty acid present in seeds such as rapeseed and wallflower seed, gave the aldol **10a** in 81% yield with 89% *ee* (entry 14). Prolonged reaction times afforded the aldol **10a** in over

Table 2. Effect of various carboxylic acids in organocatalyzed aqueous direct aldol reactions.[a]



8a **9a** **10a**

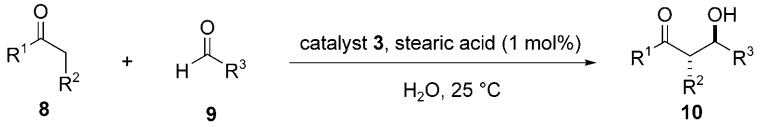
Entry	RCO_2H	Yield [%]	*anti/syn*[b]	*ee* [%][c]
1	None	54	89/11	90
2	Acetic acid (C_2)	55	91/9	86
3	Butyric acid (C_4)	60	92/8	89
4	Hexanoic acid (C_6)	71	92/8	91
5	Benzoic acid (C_7)	57	92/8	89
6	Caprylic acid (C_8)	68	91/9	91
7	Decanoic acid (C_{10})	63	92/8	90
8	Lauric acid (C_{12})	75	91/9	94
9	Myristic acid (C_{14})	71	91/9	85
10	Palmitic acid (C_{16})	73	91/9	91
11	Oleic acid (C_{18})	72	91/9	90
12	Stearic acid (C_{18})	82	89/11	93
13[d]	Stearic acid (C_{18})	91	86/14	85
14	Erucic acid (C_{22})	81	91/9	89
15[d]	Erucic acid (C_{22})	92	91/9	90
16	Decane (C_{10})	66	87/13	83
17	Eicosane (C_{20})	64	79/21	85

[a,b,c] See footnotes in Table 1.
[d] The reaction was carried out for 48 h.

90% yield (entries 13 and 15). In order to confirm the effect of the carboxylic acid functionality, long-chain hydrocarbons such as decane and eicosane were examined. Chemical yields in the presence of long-chain hydrocarbons were slightly better than that in the absence of the additive (entries 16 and 17 *vs.* entry 1), however, significantly lower than those in the presence of the most closely related fatty acids (entries 16 and 17 *vs.* entries 12 and 14).

The scope of this class of aldol reactions using the catalyst **3** (1 mol%) in the presence of stearic acid (1 mol%) in water was examined with a series of arylaldehyde acceptors **9** and ketone donors **8** (Table 3). Although aldol reactions in the absence of stearic acid afforded the aldol products in 0–54% yields,[9] in

Table 3. Aqueous direct aldol reactions of donors **8** with acceptors **9**.[a]



8 **9** **10**

Entry	R^1	R^2	R^3	Product	Time [h]	Yield [%]	*anti/syn*[b]	*ee* [%][c]
1	$-(CH_2)_4-$		$4\text{-}NO_2C_6H_4$	**10a**	48	91	86/14	85
2	$-(CH_2)_4-$		$3\text{-}NO_2C_6H_4$	**10b**	48	90	88/12	92
3	$-(CH_2)_4-$		$2\text{-}NO_2C_6H_4$	**10c**	48	75	89/11	94
4	$-(CH_2)_4-$		$4\text{-}CNC_6H_4$	**10d**	96	96	86/14	82
5	$-(CH_2)_4-$		$4\text{-}CO_2MeC_6H_4$	**10e**	96	65	87/13	85
6	$-(CH_2)_4-$		$4\text{-}BrC_6H_4$	**10f**	96	30	82/18	78
7	$-(CH_2)_4-$		$4\text{-}ClC_6H_4$	**10g**	96	44	83/17	82
8	$-(CH_2)_4-$		Ph	**10h**	96	12	79/21	79
9	$-(CH_2)_3-$		$4\text{-}NO_2C_6H_4$	**10i**	48	99	51/49	70
10	$-(CH_2)_5-$		$4\text{-}NO_2C_6H_4$	**10j**	96	28	48/52	71
11	Me	H	$4\text{-}NO_2C_6H_4$	**10k**	96	93	–	38

[a,b,c] See footnotes in Table 1.

most cases, reactions afforded *anti*-aldol products **10** in reasonable yields (entries 1–8). Reactions with cyclopentanone (**8b**) afforded a quantitative yield (entry 9), while a low yield was observed in the reaction with the less reactive cycloheptanone donor (entry 10). The reaction of acyclic acetone donor yielded the aldol product **10k** in 93% yield with 38% *ee* (entry 11).[10] These tendencies of reactivity correspond with the previous data in the presence of the catalyst **3** (10 mol%).[5]

Due to hydrophobic interactions, the liquid organic donor **8a** forms an emulsion with the catalyst **3** and fatty acid in water. Aggregation of the organic molecules excludes water from the organic phase and drives the equilibrium toward enamine formation. The enamine intermediate **11** is more hydrophobic than catalyst **3**, therefore the enamine intermediate moves into organic phase from the liquid-liquid interface. Carbon-carbon bond formation between the enamine intermediate and the aldehyde acceptor **9** occurs quickly in this highly concentrated organic phase through a transition state **12** similar to that observed in organic solvents,[11] before hydrolysis of the enamine intermediate proceeds.

Although the mechanism through which the fatty acids improve yields and stereoselectivities is presumably complex, we assume that the long chain fatty acid plays two roles. One is acceleration of enamine intermediate formation and the other is stabilization of the emulsion. It is well known that enamine formation is effectively catalyzed by acids; indeed previously we reported that addition of carboxylic acid accelerates the formation of enamine intermediate derived from isobutyraldehyde and pyrrolidine.[12] The proposed mechanism for the direct aldol reaction catalyzed by **3** in water in the presence of fatty acid is shown in Figure 3.[13]

In order to confirm the properties of the emulsion, dynamic light scattering (DLS) measurements were performed (Figure 4).[14] A narrow distribution of diameter was observed in the emulsion of water and the donor **8a** in the presence of 10 mol% catalyst **3**; the average cumulant diameter was 195 nm. This emulsion was stable, since diameter did not significantly change over 30 min without stirring (Figure 5). In contrast, a broad distribution of diameter was observed in the presence of 1 mol% catalyst **3** with an average cumulant diameter of 1,307 nm. Similarly, in the presence of 1 mol% acetic acid, a broad distribution and a large average diameter were observed. Addition of stearic acid (1 mol%) changed these properties. The particle size distribution shifted to an average diameter of 600 nm. In addition, the particle stability was higher in the presence of stearic acid than that without (Figure 5). These observations support our hypothesis that the emulsion is stabilized with 1 mol% of long chain fatty acid providing good yields

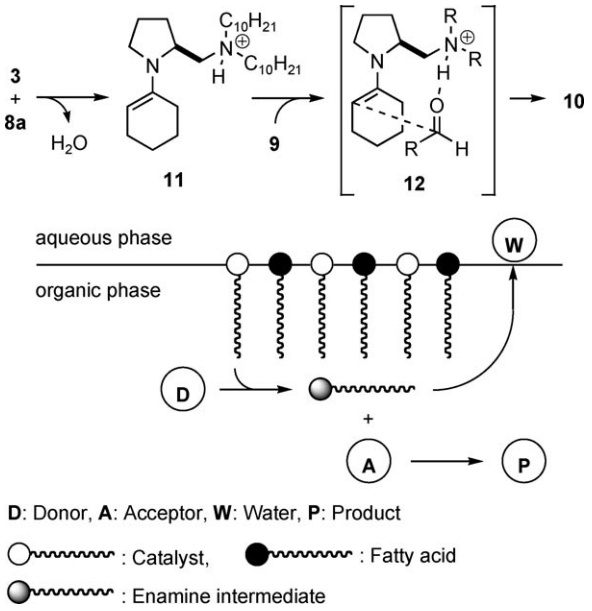


Figure 3. Proposed mechanism for organocatalyzed aqueous direct aldol reaction.

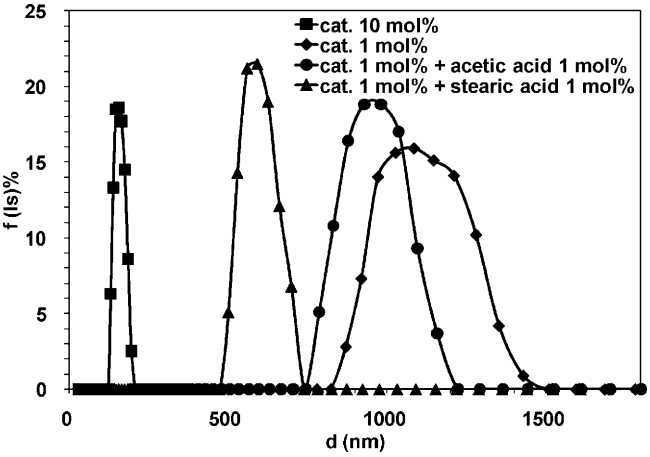


Figure 4. Dynamic light scattering (DLS) histogram analyses of emulsions. Prior to analysis, a mixture of catalyst **3**, carboxylic acid, water (0.5 mL), and **8a** (0.1 mL) was vigorously stirred for 10 min.

for the aqueous direct aldol reaction even when only 1 mol% of catalyst **3** was used.

In summary, we have shown that yields and stereoselectivity of organocatalyzed aqueous direct asymmetric aldol reactions are enhanced by addition of long chain fatty acids. At 1 mol%, a long chain fatty acid improved reactivity at low catalyst loading (1 mol%). The small particle size of the emulsion (less than 1 μm, as shown by DLS) was a key to the enhanced reactivity. Further studies focusing on the full scope of this catalyst-aqueous media system and related systems are currently under investigation and will be reported in due course.

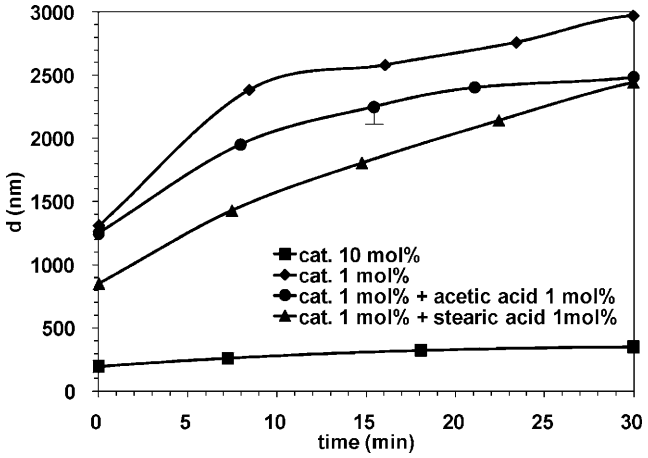


Figure 5. Time course of average cumulant diameter of the emulsion. Samples were not stirred during the time course of the analysis.

Experimental Section

Typical Procedure for the Aqueous Direct Aldol Reaction using Catalyst 3 in the Presence of Fatty Acid

To a mixture of the catalyst **3** (19.0 mg, 0.05 mmol) in water (5 mL) aqueous trifluoroacetic acid solution (1.0 M, 50 μL, 0.05 mmol) was added at 25 °C under air in a closed system. The reaction mixture was stirred for 10 min, then cyclohexanone (**8a**, 1.05 mL, 10 mmol) and fatty acid (0.05 mmol) were added. After additional stirring for 10 min, *p*-nitrobenzaldehyde (**9a**, 770 mg, 5 mmol) was added. The reaction mixture was stirred for 24 h. The reaction mixture was an emulsion and the solid aldol product gradually formed from the emulsion mixture. Water was removed by centrifugal separation. If extraction was needed, the water phase was extracted with ethyl acetate (3×1 mL), and organic extracts were dried over Na_2SO_4. Diastereoselectivity and conversion were determined by ^{1}H NMR analysis of the crude aldol product after short column chromatography purification (SiO_2, 1 g) to remove the catalyst. Purification by flash column chromatography (silica gel, hexane/AcOEt) gave the aldol product **10a** as a colourless solid.

The enantiomeric excess (*ee*) of **10a** was determined by chiral-phase HPLC analysis. The absolute configuration of aldol products **10a** was extrapolated by comparison of the HPLC data with those of **10a** whose absolute configuration is known: Registry numbers: (2*R*,1′*S*) – 501417-31-8, (2*S*,1′*S*) – 501417-28-3, (2*S*,1′*R*) – 351533-35-2, (2*R*,1′*R*) – 349628-69-9, *rel*-(2*S*,1′*R*) – 71444-30-9, *rel*-(2*R*,1′*R*) – 71444-29-6, racemic – 61235-16-3; R_f = 0.29 (*anti* product), 0.37 (*syn* product) (hexane:ethyl acetate = 70:30); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.20–1.95 (m, 5H), 2.05–2.20 (m, 1H), 2.26–2.72 (m, 3H), 3.23 (d, J = 2.4 Hz, 1H, *syn*-OH), 4.10 (brs, 1H, *anti*-OH), 4.91 (d, J = 8.3 Hz, 1H, *anti*-C*H*OH), 5.49 (brs, 1H, *syn*-C*H*OH), 7.41–7.59 (m, 2H, Ar), 8.16–8.25 (m, 2H, Ar); HPLC (Mightysil, hexane/2-PrOH = 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 15.892 min (*syn*), 20.092 min (*anti*); HPLC (CHIRALPAK AD-H, hexane/2-PrOH = 80:20, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 24.892 (*syn* minor), 27.792 (*syn* major), 30.275 (*anti*, 2*R*,1′*S*), 39.300 (*anti*, 2*S*,1′*R*).

Acknowledgements

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[9] The less reactive benzaldehyde acceptor did not give the aldol product at all in the absence of stearic acid.

[10] Less reactive acyclic donors such as 2-butanone and 2-octanone in the presence of both catalyst **3** and stearic acid afforded the aldol products **10** in 9% and 15% yields after 96 h, respectively.

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[13] The enamine could not be detected by ^{1}H NMR under conditions of emulsion formation. However, the carboxylic acid functionality should affect the reactivity, as even short chain carboxylic acid such as butyric acid (C_4) and hexanoic acid (C_6) improve chemical yields.

[14] Optical micrograph analyses of emulsions were also performed; however, clear differences were not observed among investigated reaction conditions. See Supporting Information.

