DOI: 10.1002/adsc.200800105

Organocatalytic Asymmetric *syn*-Aldol Reactions of Aldehydes with Long-Chain Aliphatic Ketones on Water and with Dihydroxyacetone in Organic Solvents

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Received: February 15, 2008; Revised: March 23, 2008; Published online: May 16, 2008

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

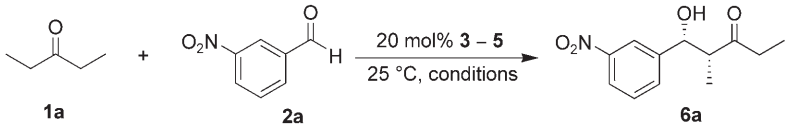
Abstract: An on-water, asymmetric, and direct *syn*-aldol reaction of aliphatic ketones with aromatic aldehydes catalyzed by a primary amino acid-based organocatalyst afforded the *syn*-aldol adducts in high yields with excellent diastereo- and enantioselectivities (up to > 20/1 *dr*, >99% *ee*), and a highly enantioselective *syn*-aldol reaction of dihydroxyacetone with a variety of aldehydes in THF proceeded with 14/1 to >20/1 *dr* and 92 to >99% *ee*. Water not only accelerated the reaction, but also enhanced the enantioselectivity. This positive water effect might arise from the hydrogen bond formed between a pendant hydroxy group of surface water molecules at the hydrophobic interface with the amide oxygen of the organocatalyst, which increases the acidity of the amide NH and thereby strengthens the related hydrogen bond formed with the aldehyde.

Keywords: aldol reaction; aqueous-phase catalysis; asymmetric catalysis; carbohydrates; hydrogen bonds; organic catalysis

Introduction

Since the pioneering reports of the proline-catalyzed asymmetric direct aldol reaction,[1] numerous organocatalysts have been designed and the stereochemistry of these newer reagents has been significantly improved in comparison with the initial organocatalysts.[2] β-Hydroxy carbonyl and polyoxygenated compounds have found widespread applications in organic synthesis. The organocatalytic direct aldol reaction, which straightforwardly generates β-hydroxy carbonyl and/or polyoxygenated compounds, has been the subject of increasing research interest and is viewed as a revolutionary innovation in modern asymmetric organocatalysis.[2] Despite the important advances, some limitations still exist and await a solution. For example, among these studies, simple ketones such as acetone, cyclohexanone, and cyclopentanone have been most commonly used as aldol donors, while organocatalytic direct aldol reactions using long-chain aliphatic ketones have been less investigated. Just recently, a single example of an aldol reaction using linear aliphatic ketones has been reported by Luo and Cheng and co-workers.[3] Of the diastereo- and enantioselective organocatalytic direct aldol reactions, *anti*-selective variants have been readily available with impressive results by using secondary amine-based organocatalysts.[1,2] Recently, a limited number of *syn*-selective asymmetric direct aldol reactions catalyzed by a primary amine have been reported.[3,4] Those aldol reactions employing protected dihydroxyacetone as donor provided an important pathway to access carbohydrates and have also received much attention, leading to the discovery of some organocatalytic asymmetric procedures with excellent levels of stereoselectivity.[5] An even more efficient method for the construction of carbohydrates is undoubtedly the direct aldol reaction of unprotected dihyhydroxyacetone. However, these reactions have not been well established until very recently with a few primary amine-based organocatalysts that appeared to afford the direct aldol reaction of dihydroxyacetone with aldehydes with high stereoselectivity.[6] The development of highly stereoselective organocatalysts for direct aldol reactions with dihydroxyacetone remains an important goal. In this paper, we report a highly enantioselective *syn*-se-

Table 1. Optimization of reaction conditions and screening of organocatalysts.[a]



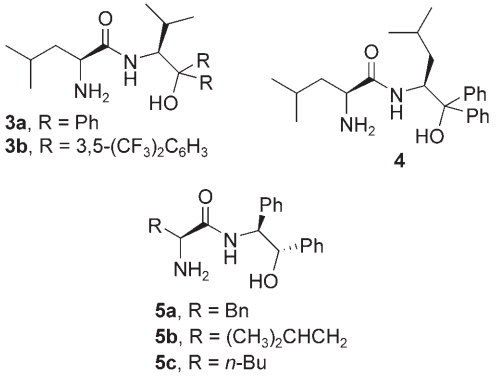
Entry	Solvent	Additive	Catalyst	Time [h]	Yield [%][b]	dr (*syn/anti*)[c]	*ee* [%][d]
1	none	none	**3a**	48	82	4/1	80
2	H_2O	none	**3a**	72	81	6/1	91
3	brine	none	**3a**	72	87	6/1	91
4	brine	4-$NO_2C_6H_4CO_2H$	**3a**	36	93	6/1	98
5	brine	CH_3CO_2H	**3a**	48	35	6/1	80
6	brine	CF_3CO_2H	**3a**	48	54	2/1	94
7	brine	4-$NO_2C_6H_4CO_2H$	**3b**	60	95	4/1	95
8	brine	4-$NO_2C_6H_4CO_2H$	**4**	36	90	6/1	96
9	brine	4-$NO_2C_6H_4CO_2H$	**5a**	60	47	6/1	83
10	brine	4-$NO_2C_6H_4CO_2H$	**5b**	60	62	6/1	90
11	brine	4-$NO_2C_6H_4CO_2H$	**5c**	60	35	4/1	77

[a] The reaction of **2a** (0.30 mmol) with **1a** (3.0 mmol) in the presence of the organocatalysts **3–5** (0.06 mmol) and additive (0.06 mmol) at 25 °C.
[b] Isolated overall yield of *syn* and *anti*-diastereomers.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Measured by chiral HPLC.

lective direct aldol reaction of aldehydes with aliphatic ketones on water[7] and with 1,3-dihydroxyacetone in organic solvents, affording excellent levels of stereoselectivities (up to 7/1 *dr*, 97% *ee* for unfunctionalized aliphatic ketones and 14/1 to >20/1 *dr*, 92 to >99% *ee* for dihydroxyacetone). The finding that water could not only accelerate the reaction, but also enhance the enantioselectivity will also be presented and clarified.

Results and Discussion

In recent years, we have designed a family of organocatalysts on the basis of an "enamine double hydrogen-bonding activation" strategy, which promote direct aldol reactions with high stereoselectivities.[8,9] Of these organocatalysts, primary amino acid-based organic molecules such as **3a** and **3b** provided highly diastereo- and enantioselectivities for *syn*-aldol reactions of aldehydes with hydroxyacetone.[9] However, an aldol reaction of *meta*-nitrobenzaldehyde in neat 3-pentanone catalyzed by 20 mol% of **3a** afforded the *syn*-product with an unsatisfactory enantioselectivity of 80% *ee*, albeit in a high yield (Table 1, entry 1).[9] Strikingly, the use of water to replace the organic solvent significantly enhanced the enantio- and diastereoselectivities with a maintained conversion (entry 2).[10] Further improvement was achieved in the conversion by performing the reaction on brine[11] without a deleterious effect on the stereoselectivity (entry 3). The presence of 20 mol% of *para*-nitrobenzoic acid could apparently enhance both the reaction rate and the enantioselectivity (entry 4). The subsequent investigation into the effect of acid additives revealed that *para*-nitrobenzoic acid served as the best additive, which was able to improve the enantioselectivity from 91% *ee* to 98% *ee*, along with a high conversion within a comparably short reaction time (entries 4–6). Under the optimized conditions, organocatalysts **3a**, **b**, **4**, and **5** were screened for the aldol reaction and **3a** was revealed to exhibit the highest level of enantioselectivity (entries 7–11).



The on-water acceleration observed above was more accurately demonstrated by kinetic studies (Figure 1). In the presence of 20 mol% **3a** and *para*-nitrobenzoic acid, the model aldol reaction was conducted in neat 3-pentanone, on water, and on brine,

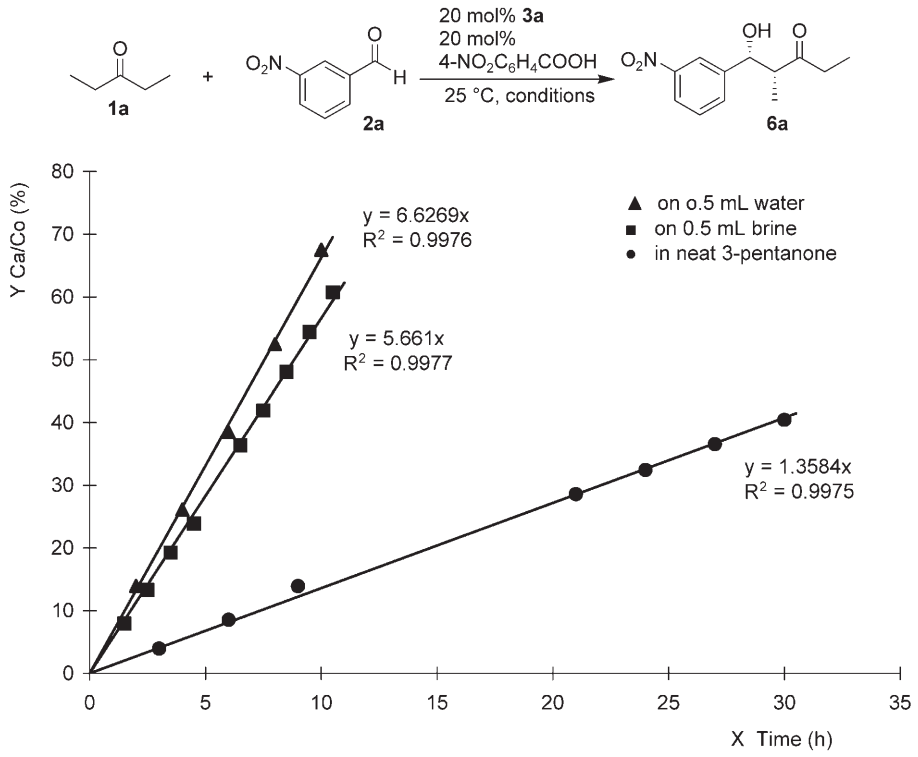


Figure 1. The effect of reaction solvents on the kinetic parameters of the aldol reaction of **2a** with **1a** in the presence of 20 mol% of **3a** and *para*-nitrobenzoic acid.

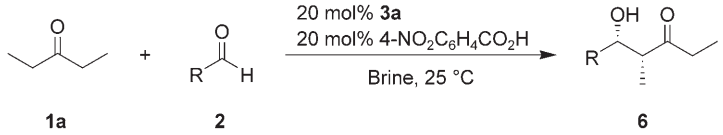
respectively (Figure 1). Surprisingly, a linear correlation between conversion Y (C_α/C_0) and reaction time was observed and indicated a *pseudo zero order* reaction that has not previously been observed in organocatalyzed aldol reactions. Such a trend suggests that the rate-determining step in the reaction cycle is not the addition of enamine to aldehyde that normally leads to a pseudo first order reaction. As butanone was used in a large excess and the on-water aldol reaction occurred in "solvent-free" conditions, the concentration of butanone could be considered a constant in the course of reaction. Thus, the pseudo zero order reaction implied that the formation of enamine from the catalyst and ketone might be the rate-limiting step. The water displayed a significant rate enhancement. Accordingly, the aldol reaction on brine is 5 times faster than that under neat conditions, but has a comparable rate with that conducted on pure water.

The optimized conditions were then expanded to the direct aldol reactions of 3-pentanone with a range of substituted benzaldehydes (Table 2). As observed previously,[8] the electron-withdrawing substitutent facilitated the direct aldol reaction. Accordingly, high yields were obtained with excellent enantioselectivities for aldehydes bearing a highly electron-withdrawing substituent at the 4-position (entries 1–3). Halogen-substituted benzaldehydes also delivered high yields and enantioselectivities regardless of either the position or number of the substituents (entries 4–11). However, electron-rich aromatic aldehydes such as tolualdehydes and anisaldehydes were much less reactive and therefore unable to undergo the aldol reaction.

Aliphatic linear ketones that differ in their length were next examined in reactions with *m*- and *p*-nitrobenzaldehydes, respectively (Table 3). Interestingly, the diastereo- and enantioselectivities are independent of the size of the ketone in the reaction using *m*-nitrobenzaldehyde as the aldol acceptor (entries 1–4) while in the cases involving *p*-nitrobenzaldehyde as an aldol acceptor, the enantioselectivity gradually drops as the ketone lengthens and thereby becomes more hydrophobic (entries 5–8).

The success of **3a** in catalyzing *syn*-aldol reactions prompted us to apply the conditions to dihydroxyacetone, which would allow an efficient synthesis of carbohydrates.[5] However, no reaction was observed under the aqueous conditions, probably because the dihydroxyacetone was dissolved in the aqueous phase and was thereby isolated from the organocatalyst **3a**, which remained suspended in the water, thus preventing the formation of the enamine. In contrast, in THF, the aldol reactions of aromatic aldehydes **2** with 1,3-dihydroxyacetone (**8**) proceeded smoothly under the influence of the combined catalysis of **3a** (20 mol%) and *p*-nitrobenzoic acid (20 mol%) to afford the *syn*-aldol products in high yields and with excellent stereoselectivities (Table 4). As Barbas and co-workers

Table 2. *syn*-Aldol reactions of benzaldehydes with 3-pentanone.[a]

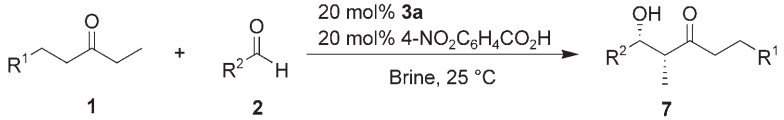


1a 2 6

Entry	6	R	Time [h]	Yield [%][b]	*dr* (*syn/anti*)[c]	*ee* [%][d]
1	**6b**	4-$NO_2C_6H_4$	30	98	5/1	95
2	**6c**	4-$MeO_2CC_6H_4$	48	95	5/1	93
3	**6d**	4-$CF_3C_6H_4$	48	92	3/1	92
4	**6e**	2-BrC_6H_4	72	81	3/1	95
5	**6f**	2-FC_6H_4	48	83	4/1	95
6	**6g**	2-ClC_6H_4	72	82	4/1	95
7	**6h**	3-BrC_6H_4	72	98	4/1	94
8	**6i**	3-ClC_6H_4	72	98	4/1	91
9	**6j**	2,3-$Cl_2C_6H_3$	48	78	4/1	97
10	**6k**	2,3,4-$F_3C_6H_2$	48	83	6/1	84
11	**6l**	3,4,5-$F_3C_6H_2$	48	88	7/1	94

[a] The reaction of **2** (0.30 mmol) with **1a** (3.0 mmol) in the presence of the organocatalysts **3a** (0.06 mmol) and *para*-nitrobenzoic acid (0.06 mmol) was performed in brine (0.5 mL) at 25 °C.
[b] Isolated overall yield of *syn* and *anti*-diastereomers.
[c] Determined by ^{1}HNMR spectroscopy.
[d] Measured by chiral HPLC.

Table 3. *syn*-Aldol reactions of *m*- and *p*-nitrobenzaldehydes with various aliphatic ketones.[a]



1 2 7

Entry	7	R^1	R^2	Time [h]	Yield [%][b]	*dr* (*syn/anti*)[c]	*ee* [%][d]
1	**7a**	CH_3	3-$NO_2C_6H_4$	48	84	5/1	93
2	**7b**	CH_2CH_3	3-$NO_2C_6H_4$	48	86	5/1	94
3	**7c**	$(CH_2)_2CH_3$	3-$NO_2C_6H_4$	60	93	5/1	91
4	**7d**	$(CH_2)_3CH_3$	3-$NO_2C_6H_4$	60	85	5/1	94
5	**7e**	CH_3	4-$NO_2C_6H_4$	48	81	5/1	92
6	**7f**	CH_2CH_3	4-$NO_2C_6H_4$	48	84	4/1	92
7	**7g**	$(CH_2)_2CH_3$	4-$NO_2C_6H_4$	60	95	4/1	84
8	**7h**	$(CH_2)_3CH_3$	4-$NO_2C_6H_4$	60	92	4/1	73

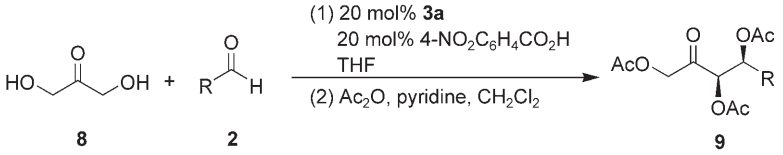
[a] The reaction of **2** (0.30 mmol) with **1a** (3.0 mmol) in the presence of the organocatalysts **3a** (0.06 mmol) and *para*-nitrobenzoic acid (0.06 mmol) was performed on brine (0.5 mL) at 25 °C.
[b] Isolated overall yield of *syn* and *anti*-diastereomers.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Measured by chiral HPLC.

did,[6a] we converted the triols into the corresponding peracetylated compounds **9** by exposure to a mixture of acetyl anhydride and pyridine for measurement of the stereoselectivity. Catalyst **3a** offered high diastereo- and enantioselectivities (14/1 to >20/1 *dr*, 92 to >99% *ee*) for a wide range of aromatic aldehydes (Table 4), and these values are mostly greater than those obtained from similar reactions catalyzed by primary amino acids.[6a] Importantly, unlike amino acid catalysis, which commonly provided the aldol adducts with stereoselectivities highly dependent on the steric or electronic features of aldehydes,[6a] **3a** provided generally high diastereo- and enantioselectivities that seemed less dependent on the substituent of the benzaldehydes.

Transition State Considerations

In our previous work,[9] we proposed a transition state for the *syn*-selective aldol reaction catalyzed by the primary amino acid-derived amino alcohol amides **3–**

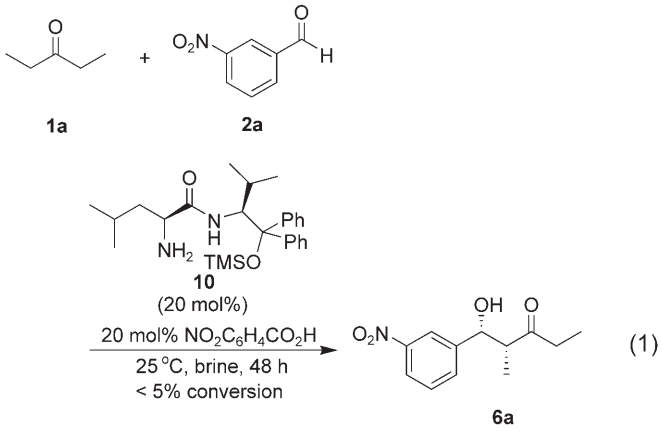
Table 4. *syn*-Selective aldol reactions of dihydroxyacetone catalyzed by **3a**.[a]



Entry	9	R	Time [h]	Yield [%][b]	*dr* (*syn/anti*)[c]	*ee* [%][d]
1	**9a**	4-$NO_2C_6H_4$	40	78	14/1	95
2	**9b**	4-$CF_3C_6H_4$	40	75	>20/1	96
3	**9c**	4-$MeO_2CC_6H_4$	72	86	>20/1	98
4	**9d**	4-CNC_6H_4	60	90	19/1	>99
5	**9e**	4-BrC_6H_4	120	81	>20/1	96
6	**9f**	3-$CF_3C_6H_4$	48	82	>20/1	98
7	**9g**	3-$NO_2C_6H_4$	40	85	>20/1	98
8	**9h**	3-FC_6H_4	60	83	>20/1	99
9	**9i**	3-BrC_6H_4	108	65	>20/1	92
10	**9j**	3-ClC_6H_4	120	70	>20/1	99
11	**9k**	2-$NO_2C_6H_4$	60	90	17/1	>99
12	**9l**	2-$CF_3C_6H_4$	72	89	>20/1	98
13	**9m**	2-FC_6H_4	48	86	>20/1	94
14	**9n**	2-BrC_6H_4	108	72	>20/1	98
15	**9o**	2,3-$Cl_2C_6H_3$	72	89	>20/1	98
16	**9p**	1-$BrC_{10}H_6$	96	74	>20/1	99

[a] The reaction of **2** (0.30 mmol) with dihydroxyacetone (0.6 mmol) in the presence of the organocatalyst **3a** (0.06 mmol) and 4-nitrobenzoic acid (0.06 mmol) in THF was performed at room temperature.
[b] Overall yield of *syn* and *anti*.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Measured by chiral HPLC.

5 in an organic solvent, in which the aldehyde was activated by double hydrogen bonds formed with the amide and the hydroxy group of the organocatalyst. Basically, water breaks the hydrogen bond required for activation of the substrates. As neither the reactants nor the organocatalyst is soluble in the water, we surmised that the organocatalytic aldol reaction might take place in a concentrated organic phase environment, suspended in the water. The hydrophobic substituents of the organocatalyst **3a** surrounding the hydrogen-bonding site and the enamine may provide a protective environment for the enamine and the hydrogen bonds that activate the aldehyde, thereby sequestering them from water. Thus, a transition state similar to that proposed for the *syn*-aldol reaction in organic solvent is still possible, that is, the *Z*-enamine and double hydrogen bonds exist in the transition state of the on-water aldol reaction.[11] To further demonstrate the possibility of the double hydrogen bonds used for the activation of the aldehyde, we investigated the model reaction [Eq. (1)] in the presence of 20 mol% of organocatalyst **10**, which differs from **3a** by the absence of one hydrogen donor. However, very little conversion (<5%) was observed by ^{1}H NMR measurement after the reaction was conducted for 48 h. This result clearly showed that the hydroxy formed hydrogen bond with the aldehyde and the double hydrogen bonds that are critical to the catalysis are not interrupted either by water or by the carboxylic acid additive.



(1)

The fact that the most concentrated reaction, namely a neat reaction, proceeded more slowly and afforded much less enantioselective *syn*-aldol adduct than the on-water reactions implied that water participates in the control of enantioselectivity of the on-water aldol reaction. However, the experimental observation that the compound **10** is unable to catalyze the aldol reaction indicated that water and the car-

boxylic acid additive have very little effect on the transition state. The conflict between the conclusions drawn from these experiments leads to an interesting and important question: how does the water influence the **3a**-catalyzed on-water aldol reaction? Elegant studies on the hydrophobic surface structure of water[12] and on the on-water organic reactions[13] have shown that the dangling hydroxy groups of surface molecules at the hydrophobic interface can hydrogen bond with the carbonyl of the reactants of the on-water reactions.[13a] In the **3a**-catalyzed aldol reaction, the dangling OH might form a hydrogen bond with the amide oxygen, but not with either NH or OH of the catalyst due to the hydrophobic substituents, leading to **TS-1b**, which differs from **TS-1a** in that the *syn*-aldol reaction proceeds in the organic phase by forming an additional hydrogen bond with water (Figure 2). In this transition state, the hydrogen

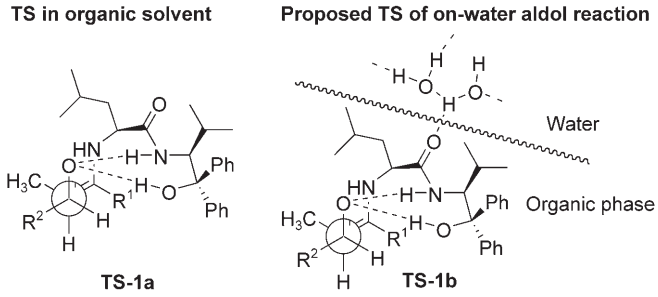


Figure 2. Rationale for the effect of water on the enantioselectivity.

bond between the dangling OH and the amide oxygen[8e] makes the NH of amide group more acidic and thereby strengthens the hydrogen bond formed between the NH and the aldehyde. The stronger hydrogen bond is able to improve both the catalytic efficiency and the enantioselectivity, as we indicated previously.[8b,c]

The plausible transition state shown in Figure 3 could explain the highly stereoselective *syn*-aldol reaction of dihydroxyacetone with aldehydes in THF. The aldehyde was activated by double hydrogen bonds formed with NH and OH of the catalyst on the basis of the previous studies.[8,9] As Barbas and coworkers indicated,[6a] the *Z*-enamine in **TS-2b** is stabilized by a hydrogen bond, which favors transition state **TS-2b** over **TS-2a**, and leads to the predominant formation of *syn*-aldol adducts.

Conclusions

We have disclosed an on-water, organocatalytic *syn*-aldol reaction of acyclic aliphatic ketones with aromatic aldehydes, providing highly diastereo- and enantioselectivities. The aldol reaction on-water provided much higher enantioselectivity than the reaction conducted in organic solvents. The enhancement of water in the enantioselectivity might stem from the hydrogen bond formed between a dangling hydroxy group of surface water molecules at the hydrophobic interface with the amide oxygen of the organocatalyst, which increases the acidity of the amide NH and thereby strengthens the related hydrogen bond formed with the aldehyde. In organic solvents, *syn*-aldol reactions of dihydroxyacetone with aldehydes afforded triols with 14/1–>20/1 *dr* and 92–99% *ee*.

Experimental Section

General Procedure for the Aldol Reaction on-Water

After a suspension of an aldehyde (0.3 mmol), catalyst **3a** (20 mol%), 4-nitrobenzoic acid (20 mol%), and a ketone (3 mmol) in brine (0.5 mL) had been stirred at room temperature for 30–120 h, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (1×10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent under the reduced pressure, the residue was purified by flash column chromatography on silica gel to give the desired aldol product.

General Procedure for the Aldol Reaction of Dihydroxyacetone with Aldehydes Catalyzed by 3a

To a solution of aldehyde (0.3 mmol) in anhydrous THF (1.0 mL) was added dihydroxyacetone dimer (0.3 mmol) followed by catalyst **3a** (0.06 mmol), and 4-nitrobenzoic acid (0.06 mmol) at room temperature. The reaction solution was stirred at room temperature until the aldehyde was consumed (monitored by TLC). The mixture was purified (with-

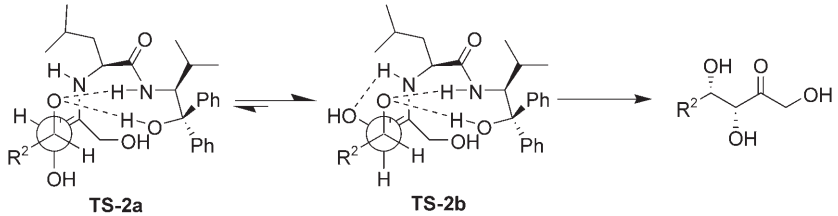


Figure 3. Proposed transition state of the *syn*-aldol reaction of dihydroxyacetone with aldehydes.

out work-up) through flash column chromatography (mixtures of hexanes/ethyl acetate) to give the aldol product.

The resultant aldol product was dissolved in anhydrous CH_2Cl_2 (2 mL) and pyridine (0.5 mL) and acetic anhydride (0.3 mL) were added to the solution at room temperature. After stirring for 4 h at the same temperature, the mixture was diluted with CH_2Cl_2 (2 mL) and washed with 1 N HCl. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by flash column chromatography on silica gel to give the acetylated aldol product.

Supporting Information

Experimental details and characterization data of new compounds are given in the Supporting Information.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (grants 20732006 and 20325211) and CAS.

References

[1] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; b) U. Eder, R. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496; c) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; d) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260; e) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386.

[2] For reviews: a) B. List, *Tetrahedron* **2002**, *58*, 5573; b) B. List, *Synlett* **2001**, 1675; c) B. Alcaide, P. Almendros, *Angew. Chem.* **2003**, *115* 884; *Angew. Chem. Int. Ed.* **2003**, *42*, 858; d) B. List, *Acc. Chem. Res.* **2004**, *37*, 548; e) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580; f) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570; g) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, *33*, 65; h) *Modern Aldol Reactions*, Vols. 1 and 2, (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**; i) S. Mukherjee, Y. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; j) G. Guillena, C. Najera, D. J. Ramon, *Tetrahedron: Asymmetry* **2007**, *18*, 2249.

[3] S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074.

[4] a) S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288; b) T. Kano, Y. Yamaguchi, Y. Tanaka, K. Maruoka, *Angew. Chem.* **2007**, *119*, 1768; *Angew. Chem. Int. Ed.* **2007**, *46*, 1738; c) P. Diner, M. Amedjkouh, *Org. Biomol. Chem.* **2006**, *4*, 2091; d) N. Utsumi, M. Imai, F. Tanaka, S. S. V. Ramasastry, C. F. Barbas III, *Org. Lett.* **2007**, *9*, 3445; e) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812.

[5] For an excellent review, see: M. Markert, R. Mahrwald, *Chem. Eur. J.* **2008**, *14*, 40.

[6] a) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2007**, *119*, 5668; *Angew. Chem. Int. Ed.* **2007**, *46*, 5572; b) after completion of this manuscript, a paper by Luo and Cheng concerning syn-aldol reaction of dihydroxyacetone published on the web: S. Luo, H. Xu, L. Zhang, J. Li, J.-P. Cheng, *Org. Lett.* **2008**, *10*, 653.

[7] For the concept of the "on-water" reaction, see: S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.

[8] a) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262; b) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5755; c) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285; d) X.-Y. Xu, Y.-Z. Wang, L.-F. Cun, L.-Z. Gong, *Tetrahedron: Asymmetry* **2007**, *18*, 237; e) X.-H. Chen, S.-W. Luo, Z. Tang, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Chem. Eur. J.* **2007**, *13*, 689; f) L. He, Z. Tang, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Tetrahedron* **2006**, *62*, 346.

[9] X.-Y. Xu, Y.-Z. Wang, L.-Z. Gong, *Org. Lett.* **2007**, *9*, 4247.

[10] For recent reports and discussions on the aldol reactions in aqueous media, see: a) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734; b) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972; *Angew. Chem. Int. Ed.* **2006**, *45*, 958; c) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem.* **2006**, *118*, 5653; *Angew. Chem. Int. Ed.* **2006**, *45*, 5527; d) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100; e) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103; f) J. Huang, X. Zhang, D. W. Armstrong, *Angew. Chem.* **2007**, *119*, 9231; *Angew. Chem. Int. Ed.* **2007**, *46*, 9073.

[11] a) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966; b) V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 293.

[12] Y.-R. Shen, V. Ostroverkhov, *Chem. Rev.* **2006**, *106*, 1140.

[13] a) Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492; b) J. Chandrasekhar, S. Shariffskul, W. L. Jørgensen, *J. Phys. Chem. B.* **2002**, *106*, 8078.

