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New simple and recyclable O-acylation serine derivatives as highly enantioselective catalysts for the large-scale asymmetric direct aldol reactions in the presence of water

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ABSTRACT

New classes of O-acylation serine derived organocatalysts have been synthesized one-step by rational combination of serine with acyl chlorides at room temperature in trifluoroacetic acid. No protecting groups or chromatographic techniques are involved in any of the procedures, and certain combined serine-surfactant organocatalysts mediate the direct aldol reactions of ketones with a series of aromatic aldehydes to provide the aldol products in high yields (up to 99%) and enantioselectivities (up to 99% ee). The catalyst **1b** can be easily recovered and reused, and without significant decrease of enantioselectivity was observed for five cycles. This novel catalyst can be efficiently used in large-scale reactions with the enantioselectivities being maintained at the same level, which offers a great possibility for application in industry.

1. Introduction

Asymmetric organocatalysis has become an important area of research in organic synthesis.[1] The asymmetric aldol reaction is one of the most powerful methods for constructing carbon–carbon bonds in chiral organic synthesis.[2] A wide range of small organic molecules, including proline[3] and various other chiral pyrrolidine derivatives,[4] have been shown to be efficient catalysts for asymmetric aldol reactions. Hayashi and Cordova demonstrated that acyclic amino acids could effect direct aldol reactions in DMSO (in the presence of a little water).[5a–f] However, their shortcomings have also been realized. One of the major limitations using these amino acids or amino acids surrogates catalyzed aldol reactions was employed in polar solvents, such as DMF, DMSO,[5a–f] and NMP[5g] owing to the solubility, while these high boiling point polar solvents were often created added hurdles for product isolation and environment pollution. Therefore, water had many attractive advantages, such as low cost, safety, and environmentally benign nature. We believe that the development of small organic molecules capable of catalyzing enantioselective reactions using water as reaction medium is attracting great interest. However, the vast majority of organocatalytic reactions would yield racemic products if the reactions took place in the presence of water.[5f,g] Recently, it was shown by the groups of Takabe, Barbas, Hayashi, and Noto that the direct asymmetric aldol reaction and the Michael reaction could be catalyzed by the proline-derived hydrophobic catalysts in the presence of water.[6] Our group recently also reported the 4-phenoxy substituted and 4-tertbutyldimethylsiloxy-substituted prolinamides catalyzed the direct aldol reactions between cyclic ketones and aromatic aldehydes in the presence of water and reported the O-acylation threonine derivatives catalyzed the direct aldol reactions and direct *anti*-mannich reactions.[7] The groups of Teo and Lu reported that the siloxy serine derivatives are highly efficient organocatalysts for asymmetric aldol reactions of ketones in the presence of water and in ionic liquid.[8] Although serine was not efficient organocatalysts in direct aldol reactions between cyclohexanone and benzaldehyde in the presence of water,[8a] their hydrophobic derivatives (e.g., *O*-TBDPS–serine) proved to be very efficient catalysts. The desired aldol products were obtained in excellent yields (up to 95%), and with nearly perfect enantiomeric control (up to 98% ee).[8] From a green chemistry point of view such studies are interesting because the direct aldol reactions are atomically economic, and water as the reactions medium is environment friendly. Meanwhile, it is found that a subtle change in catalyst structure may effect the catalytic activation. However, it should be noted that

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among all of the reported asymmetric organocatalysts, most of them were prepared with strenuous procedure, tiresome purification of chromatography and/or need some expensive reagents,[9] this will also raise a cost concern when large amounts of these chiral organocatalysts are used for a large-scale synthesis in industrial applications, so these organocatalysts were often used in research laboratories. Therefore, the development of novel, simple and highly effective asymmetric organocatalysts with natural crude chiral pool, simple preparation procedure, and inexpensive reagents is urgently needed and is also the true challenge. An alternative strategy is to design recyclable and subsequently reusable organocatalysts. Meanwhile efforts also have been made on organocatalyst recycling using polymer supports,[10] ionic liquid supports,[11] and fluorous chemistry.[12] In this context, we started a research project in order to find new organocatalysts, structurally simple, recoverable and reusable, which are able to catalyze the asymmetric aldol reaction in the presence of water, and these new organocatalysts can be used in large-scale reactions with the enantioselectivities being maintained at the same level.

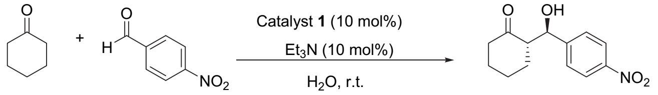
Serine derivatives have been popularly designed to improve the catalytic activity and stereoselectivity. The groups of Lu and Teo reported siloxy serine derivative organocatalysts for the direct asymmetric aldol reactions of various aromatic aldehydes and ketone, and impressive results were obtained.[8] We hypothesized and deduced that incorporation of a simple and cheap aryl group into a natural amino acid could generate a simple, cheap, and highly enantioselective hydrophobic organocatalyst, which may interact favorably with organic substrates in aqueous media due to its hydrophobic nature.[13] Serine seems to be good chiral structural scaffolds, as the hydroxy group allows for the easy attachment of various hydrophobic groups, such as alkyl, aryl, and so on.[8] With the aim to discover new simple and cheap organocatalysts for the direct asymmetric aldol reaction in the presence of water, we prepared eight new serine derivatives **1a**–**h**. The **R** groups were varied in such a way to obtain molecules with increased hydrophobicity going from the *n*-butyl to 3-phenylpropanoyloxy substituent (Fig. 1).

Compounds **1a**–**h** were easily prepared from serine with acyl chlorides on the large-scale at room temperature in trifluoroacetic acid in one-step. Furthermore, in the course of synthetic process, no protecting groups or chromatographic techniques were involved (Fig. 1).[7d,e,f,14]

2. Results and discussion

The organocatalyzed aldol reaction was carried out using cyclohexanone and 4-nitrobenzaldehyde as a model reaction to investigate different parameters, such as the catalysts, the stoichiometry of reactants, loading of the catalysts, and the amount of water. In our initial investigation serine and its derivatives **1a**–**h** were screened as catalysts. As can be seen from the summarized results in Table 1, natural serine as well as other hydrophilic amino acids, such as proline, threonine, valine, leucine, and isoleucine was not efficient organocatalyst in the presence of water (Table 1, entry 1),[8a] probably because they are dissolved in the water phase and thereby separated from the hydrophobic reactants of cyclohexanone and 4-nitrobenzaldehyde.[15] Under the same conditions, the catalysts **1a**–**h** with equivalent triethylamine can catalyze the asymmetric direct aldol reaction of 4-nitrobenzaldehyde and cyclohexanone to give the product in good yields (84–95%) with different ee values (65–98% ee for *anti-isomer*) in the presence of water (Table 1, entries 2–9). Among the eight O-acylation serine derivatives, it was found that the chain length (n) dramatically affected the yields and enantioselectivities (Table 1, entries 2–6). Neither very long (n=6, 8, 14) nor very short carbon chains (n=2) was effective, whereas catalyst **1b** containing the *n*-hexanoyl group (n=4) gave the best yield (95%) and enantioselectivity (98% ee for *anti-isomer*), but among the **1f**,**g**, the chain length did not significantly affected the yields, diastereoselectivities and enantioselectivities (Table 1, entries 7–9). The serine derivative organocatalyst **1b** turned out to be the most efficient catalyst (Table 1, entry 3). These catalyzed process generated 1 equiv of triethylamine HCl salt, which was not removed from the catalyst system. In order to test the effect of triethylamine HCl salt on the aldol reaction in the presence of water, we used the triethylamine HCl salt as organocatalyst catalyzed the direct aldol reaction of cyclohexanone

Table 1
Screening of organocatalysts[a]



Entry	Catalyst	Catalyst loading (%)	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1[8a]	**L-Ser**	10	48	–	–	–
2	**1a**	10	20	90	64/36	65
3	**1b**	**10**	**20**	**95**	**94/6**	**98**
4	**1c**	10	20	94	70/30	91
5	**1d**	10	20	90	72/28	92
6	**1e**	10	20	84	87/13	68
7	**1f**	10	20	90	80/20	73
8	**1g**	10	20	92	83/17	76
9	**1h**	10	20	93	84/16	76
10	**Et$_3$N·HCl**	10	72	–	–	–

[a] The reactions were performed with 4-nitrobenzaldehyde (1 mmol), cyclohexanone (4 mmol), catalyst (0.1 mmol, see Table 1, entries 2–9), and Et$_3$N (0.1 mmol, see Table 1, entries 2–9) in the presence of water (0.2 mL) at room temperature.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H).

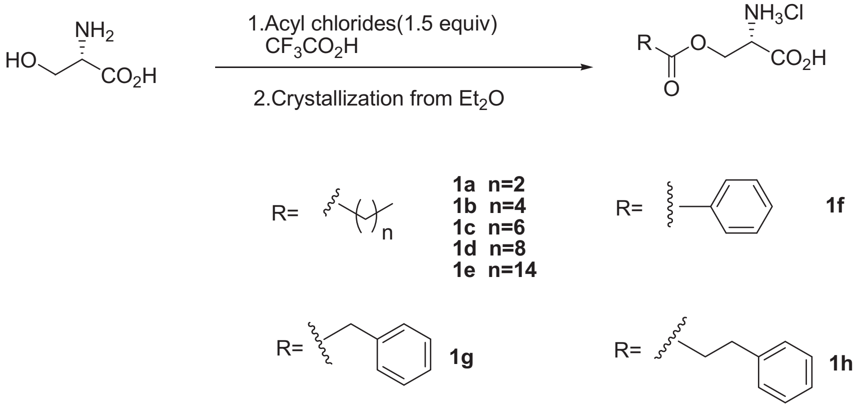


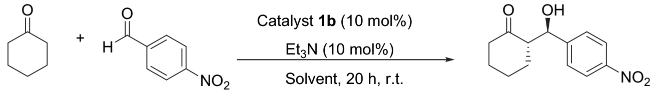
Fig. 1. *O*-Acyl derivatives of serine by selective O-acylation.

and 4-nitrobenzaldehyde in the presence of water. Triethylamine HCl salt was not an efficient organocatalyst in the presence of water (Table 1, entry 10). So the triethylamine HCl salt did not affect the yield, diastereoselectivity, and enantioselectivity.

As a first step, we screened several solvents for the reaction between cyclohexanone and 4-nitrobenzaldehyde (Table 2). Due to its poor solubility in most such solvents, reactions mediated by serine itself are restricted to polar organic solvents, such as dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and *N*-methylpyrrolidone (NMP), while O-acylation serine derived organocatalysts are more soluble than serine in organic solvents. As catalyst we used the most hydrophobic one (**1b**, 10 mol %). Both enantioselectivities and yields were not good when toluene and DMSO were used (Table 2, entries 1 and 2). Chloroform showed increased yield and enantioselectivity (Table 2, entry 3), while water gave the highest stereoselectivity (Table 2, entry 4). This result indicates that water is indispensable for achieving excellent diastereoselectivity and enantioselectivity. Even brine showed a similar behavior (Table 2, entry 5). When the direct aldol reaction was carried out under neat conditions, low diastereoselectivity was observed coupled with a decreased enantioselectivity (Table 2, entry 6). The results summarized in Table 2 suggest that the reaction in the presence of water is different from that in its absence, and that compared to organic solvents, water has a unique beneficial effect.

Table 2

Effect of the solvent on the catalytic aldol reaction between cyclohexanone and 4-nitrobenzaldehydes catalyzed by **1b**[a]



Entry	Solvent	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	Toluene	75	82/18	74
2	DMSO	73	80/20	68
3	$CHCl_3$	86	87/13	91
4	$\mathbf{H_2O}$	**95**	**94/6**	**98**
5	Brine	97	90/10	94
6	None	98	88/12	90

[a] The reactions were performed with 4-nitrobenzaldehyde (1 mmol), cyclohexanone (4 mmol), catalyst **1b** (0.1 mmol), and Et_3N (0.1 mmol) in solvent (0.2 mL, see Table) at room temperature.

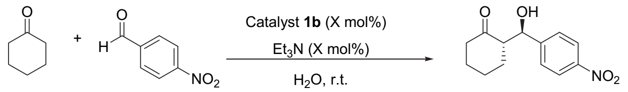
[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H).

Then, using water as reaction medium, we investigated the above reaction employing different amounts of catalyst **1b** with equivalent Et_3N (Table 3). Using a larger amount (15–20 mol %) of catalyst, the reaction was faster but stereoselectivity was lower than in the other cases. The amount was decreased up to 5 mol %. After 20 h the yield was not good but dr and ee values were high. Noticeably, using 10 mol % of catalyst **1b** after 20 h, we obtained an almost good yield and excellent stereoselectivity.

Table 3

Effect of the amount of the catalyst in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalyzed by **1b**[a]



Entry	Catalyst (mol %)	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	20	12	99	84/16	76
2	15	12	98	85/15	80
3	10	20	95	94/6	98
4	5	20	78	93/7	96

[a] The reactions were performed with 4-nitrobenzaldehyde (1 mmol), cyclohexanone (4 mmol), catalyst **1b** (see Table), and Et_3N (see Table) in the presence of water (0.2 mL) at room temperature.

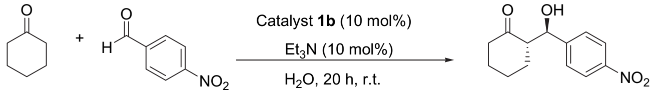
[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H).

Some aldol reactions have been performed under aqueous conditions, with the presence of water reported to increase the reactivity and stereoselectivity.[6,15b] Using catalyst **1b** (10 mol %) with equivalent Et_3N (10 mol %) we investigated the effect of different amount of water (Table 4). When in the presence of only 1 equiv of water (Table 4, entry 1), the aldol product was obtained in a good yield with good diastereo- and excellent enantioselectivity. However, using 5 or more equivalents of water (Table 4, entries 2–4) a highly yield was observed. In each case stereoselectivities were high but, when a large amount of water (17 equiv) was employed, we also obtained excellent diastereo- and enantioselectivity, but the yield was decreased.

Table 4

Effect of the amount of water in aldol reaction between cyclohexanone and 4-nitrobenzaldehydes catalyzed by **1b**[a]



Entry	H_2O (mL)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	0.018	99	85/15	95
2	0.05	97	90/10	96
3	0.1	95	92/8	96
4	0.2	95	94/6	98
5	0.3	86	93/7	97

[a] The reactions were performed with 4-nitrobenzaldehyde (1 mmol), cyclohexanone (4 mmol), catalyst **1b** (0.1 mmol), and Et_3N (0.1 mmol) in the presence of water (see Table) at room temperature.

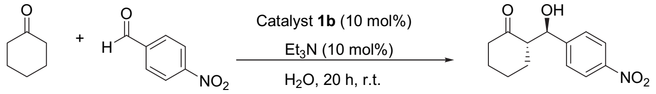
[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H).

We also investigated the affects of ketone loading on the reaction of 4-nitobenzaldehyde and cyclohexanone. When 10 mol % of **1b** with equivalent Et_3N (10 mol %) was used, the reaction could be accelerated by increasing the amount of ketone from 1 to 8 equiv, but dr and ee values were not improved (Table 5, entries 1–4), even with only 1 equiv of cyclohexanone. The aldol product could be obtained in high yield with good stereoselectivity even with only 4 equiv of cyclohexanone.

Table 5

Effect of the amount of cyclohexanone in aldol reaction between cyclohexanone and 4-nitrobenzaldehydes catalyzed by **1b**[a]



Entry	Cyclohexanone (equiv)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	1	84	91/9	95
2	2	93	93/7	96
3	**4**	**95**	**94/6**	**98**
4	8	96	92/8	97

[a] The reactions were performed with 4-nitrobenzaldehyde (1 mmol), cyclohexanone (see Table), catalyst **1b** (0.1 mmol), and Et_3N (0.1 mmol) in the presence of water (0.2 mL) at room temperature.

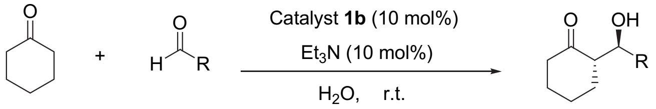
[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H).

In order to test the substrate generality of this organocatalyzed direct aldol reaction, the reactions of various aromatic aldehydes with cyclohexanone were studied under the optimized conditions. The results are summarized in Table 6. It can be seen that a wide range of aromatic aldehydes can effectively participate in the aldol reactions. From Table 6, we were able to access aldol adducts **2**–**18** derived from

Table 6

Organocatalyst **1b**-catalyzed direct aldol reactions in the presence of water[a]



Entry	Product	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	**2**(R=*p*-NO$_2$–C$_6$H$_4$)	20	95	94/6	98
2	**3**(R=*o*-NO$_2$–C$_6$H$_4$)	20	97	97/3	99
3	**4**(R=*m*-NO$_2$–C$_6$H$_4$)	20	98	96/4	96
4	**5**(R=2,4-Dinitrophenyl)	20	96	99/1	96
5	**6**(R=*p*-CN–C$_6$H$_4$)	20	95	92/8	95
6	**7**(R=*p*-CF$_3$–C$_6$H$_4$)	20	89	84/16	96
7	**8**(R=*p*-Cl–C$_6$H$_4$)	30	83	94/6	96
8	**9**(R=*o*-Cl–C$_6$H$_4$)	30	89	94/6	95
9	**10**(R=*p*-Br–C$_6$H$_4$)	30	96	97/3	97
10	**11**(R=*p*-F–C$_6$H$_4$)	30	89	92/8	96
11	**12**(R=*p*-MeO–C$_6$H$_4$)	36	68	98/2	98
12	**13**(R=*m*-MeO–C$_6$H$_4$)	36	56	87/13	94
13	**14**(R=*p*-Me–C$_6$H$_4$)	36	60	90/10	>99
14	**15**(R=2-Naphthyl)	36	67	90/10	96
15	**16**(R=1-Naphthyl)	36	75	97/3	97
16	**17**(R=C$_6$H$_4$)	48	68	95/5	93
17	**18**(R=Pyridinthyl)	24	90	90/10	98

[a] The reactions were performed with aldehyde (1 mmol), cyclohexanone (4 mmol), **1b** (0.1 mmol), and Et$_3$N (0.1 mmol) in the presence of water (0.2 mL) at room temperature.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H, OD-H) and comparison of the retention times with literature data.[7]

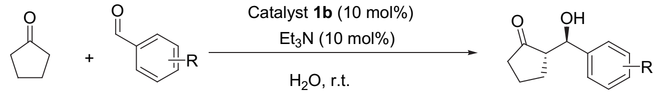
their corresponding aromatic aldehydes and cyclohexanone. In the presence of 10 mol % of catalyst **1b** with equivalent Et$_3$N (10 mol %) and the amount of water (0.2 mL), most reactions between cyclohexanone and various aromatic aldehydes afforded the aldol products in excellent yields and nearly perfect ee values in the presence of water. In general, the reaction between cyclohexanone and aromatic aldehydes bearing electron-withdrawing substituents furnished β-hydroxy carbonyl aldol products in excellent yields (83–98%) and enantioselectivities (95–99% ee for *anti-isomer*) within 20–30 h, especially the *p*-nitrobenzaldehyde and *o*-nitrobenzaldehyde (Table 6, entries 1 and 2, 94/6 to 97/3 *anti*/*syn* ratio and 98–99% ee for *anti*-isomers) (Table 6, entries 1–10). In contrast, longer reaction times (36 h) were required for aromatic aldehydes containing an electron-donating group to give comparatively lower yields (56–68%), but without decrease of enantioselectivities, especially the *p*-tolualdehyde (Table 6, entry 13, 90:10 *anti*/*syn* ratio and >99% ee)(Table 6, entries 11–13). This can be explained in that electron-withdrawing groups enhance the electrophilicity of carbonyl carbons in aldehydes, which facilitates the reaction, while electron-donating groups lessen the electrophilicity. Moreover, the direct aldol reaction of neutral aldehydes catalyzed by the serine derivative organocatalyst **1b** also afforded the aldol products in high enantioselectivities and diastereoselectivities (Table 6, entries 14–17). All the reactions of cyclohexanone with aromatic aldehydes provided the corresponding products with excellent enantioselectivities (94 to >99% ee for *anti*-isomers) and excellent diastereoselectivities(*anti*/*syn* 84/16 to 98/2) (Table 6, entries 1–17).

When cyclopentanone was employed interesting results were obtained (Table 7). In particular, a good yield of 65–98% with excellent enantioselectivities (90–99% for the *anti*-isomer) were received, however, the diastereomeric ratio obtained was only 67/33 to 84/16 dr (*anti*/*syn*).

We also checked the aldol reactions of other ketones (acetone, 4,4-(ethylenedioxy)cyclohexanone, tetrahydro-4*H*-pyran-4-one, 4-methylcyclohexanone, cycloheptanone, and *O*-TBS-hydroxyacetone) with nitrobenzaldehyde using catalyst **1b** (10 mol %)(Table 8). The reaction with acetone was carried out both in the presence and in

Table 7

The direct aldol reactions of cyclopentanone with aromatic aldehydes catalyzed by **1b**[a]



Entry	Product	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	**19**(R=*p*-NO$_2$–C$_6$H$_4$)	20	98	70/30	91/57
2	**20**(R=*o*-NO$_2$–C$_6$H$_4$)	20	96	76/24	99/81
3	**21**(R=*m*-NO$_2$–C$_6$H$_4$)	20	97	74/26	99/31
4	**22**(R=*p*-CF$_3$–C$_6$H$_4$)	20	96	83/17	99/90
5	**23**(R=*p*-Br–C$_6$H$_4$)	30	86	84/16	95/85
6	**24**(R=*p*-Cl–C$_6$H$_4$)	30	86	67/33	98/82
7	**25**(R=*o*-Cl–C$_6$H$_4$)	30	82	75/25	99/95
8	**26**(R=*m*-MeO–C$_6$H$_4$)	36	75	73/27	90/16
9	**27**(R=2-Naphthyl)	36	70	76/24	95/37
10	**28**(R=C$_6$H$_4$)	48	65	75/25	95/81

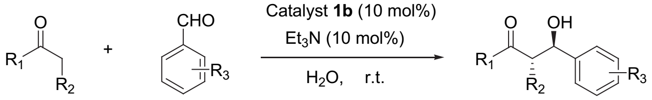
[a] The reactions were performed with aldehyde (1 mmol), cyclopentanone (4 mmol), **1b** (0.1 mmol), and Et$_3$N (0.1 mmol) in the presence of water (0.2 mL) at room temperature.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H, OD-H) and comparison of the retention times with literature data.[6e]

Table 8

Direct asymmetric aldol reactions between ketones and aromatic aldehydes catalyzed by **1b** in the presence of water[a]



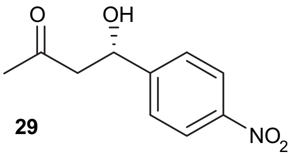
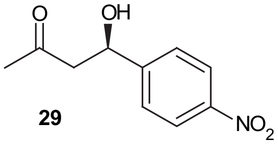
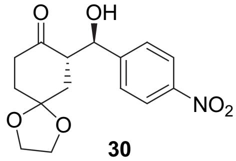
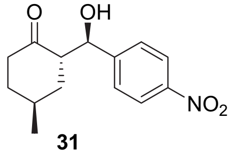
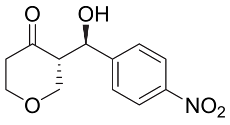
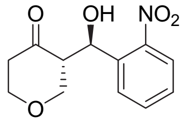
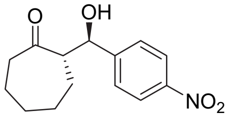
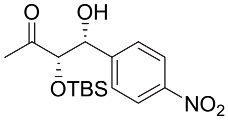
Entry	Product	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	 **29**	36	77	–	18
2[d]	 **29**	36	32	–	73
3	 **30**	48	85	93/7	94
4	 **31**	30	90	95/5	97
5	 **32**	48	68	85/15	92

Table 8 (*continued*)

Entry	Product	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
6	 **33**	48	63	91/9	92
7	 **34**	48	66	52/48	91
8	 **35**	24	95	16/84	97 (*syn*)

[a] The reactions were performed with aldehyde (1 mmol), ketones (4 mmol), **1b** (0.1 mmol), and Et_3N (0.1 mmol) in the presence of water (0.2 mL) at room temperature.

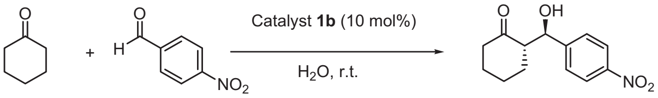
[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H, OD-H and OJ-H) and comparison of the retention times with literature data.[6e,7,8]

[d] Carried out in neat.

Table 9

The recycling and reuse of catalyst **1b**[a]



Run	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1	20	95	94/6	98
2	20	94	94/6	97
3	20	94	97/3	97
4	30	91	93/7	95
5	48	84	91/9	91

[a] The reactions were performed with 4-nitrobenzaldehyde (10 mmol), cyclohexanone (40 mmol), catalyst **1b** (1 mmol), and Et_3N (1 mmol) in the presence of water (2 mL) at room temperature.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis (AD-H).

the absence of water. In the first case we obtained the aldol product in high yield (77%) and low enantioselectivity (18%) (Table 8, entry 1). When we carried out the reaction without water (Table 8, entry 2) we obtained the aldol product in low yield (32%) and good enantioselectivity (73%). However, it is worth noting that the configuration of aldol product was reversed. In our opinion the presence of water increased the activity of the catalyst because the more hydrophilic medium increased the affinity of the hydrophobic aldehyde to the hydrophobic catalyst. When water was absent, the aldehyde was well dissolved in acetone and this caused a lower yield. More difficult to explain is the observed enantioselectivity in the presence of water. By contrast, the reaction between cyclohexanone and 4-nitrobenzaldehyde under neat conditions did not show a reversed enantioselectivity. This is probably due to the different hydrophilicity between the acetone and cyclohexanone. The 4,4-(ethylenedioxy)cyclohexanone and 4-methylcyclohexanone gave high stereoselectivities and good yield (Table 8, entries 3 and 4), whereas excellent enantioselectivities were obtained using tetrahydro-4*H*-pyran-4-one and cycloheptanone both with catalysts **1b**, but lower yields and diastereoselectivities were obtained (Table 8, entries 5–7). Protection of the free hydroxy function with the TBS group furnished a hydrophobic substrate, which then efficiently reacted with the aldehyde *in aqua*, which also gave high stereoselectivities and good yield (Table 8, entry 8).

Meanwhile, in order to verify that the serine derivative organocatalyst **1b** could be recovered and reused, we performed a recycling study of **1b** using the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde (Table 9). The catalyst **1b** could be easily recovered from the reaction mixture after completion of the reaction by acid treatment; the aldol product was extracted with ethyl ether (Et_2O), evaporation of the organic solution to obtain the aldol product. The catalyst **1b** exists in the acidic aqueous layer, and then added an equivalent amount of triethylamine (Et_3N), and resulted white suspension. The suspension was filtered under vacuum and the white crystals were used directly in subsequent reaction cycles without adding any new catalyst. In each reuse, the same amounts of substrates were used, and the recovered catalyst **1b** retained essentially its catalytic activity without further purification. No significant decrease in the enantioselectivity was observed over five cycles (Table 9).

We further performed large-scale asymmetric aldol reactions with *2* mol of aromatic aldehydes and 4 equiv of ketones using a 2 L round-bottomed flask. The same catalyst loading of 10 mol % as in the experimental scale was used. The large-scale experiments can be facilely carried out using the same procedure as for the experimental scale reactions. As can be seen from the results summarized in Table 10, to our delightfully, the enantioselectivities maintained at the same level for the large-scale reactions. So the serine derivative organocatalyst **1b** is not only simple, cheap, and prepared easily (one-step) but also the enantioselectivities maintained at the same level for the large-scale aldol reactions, which offers a great possibility for applications in industry.

3. Conclusions

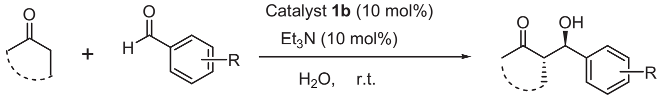
In conclusion, the results from the investigation demonstrate that the O-acylation serine organocatalyst **1b** is a robust and effective catalyst for highly enantioselective aldol reactions. A wide range of aromatic aldehydes with cyclic and acyclic ketones can effectively participate in the direct aldol reactions. The electronic effect of the substituents in substituted benzaldehydes has been discussed. Noteworthy features of this catalysis system are (1) the direct aldol reactions proceeded in the presence of water using simple procedures; (2) O-acylation serine organocatalysts **1a**–**h** can be prepared easily (one-step) and economically from commercially available sources, with both enantiomers readily available; (3) 10 mol % of catalyst **1b** was sufficient to furnish the aldol products in excellent yields (up to 99%) and enantioselectivities (up to 99%); (4) The catalyst can be readily recovered and reused without significant loss of catalytic activity and stereoselectivity; Notably, (5) this organocatalyzed direct asymmetric aldol reaction can be performed on a large-scale with the enantioselectivity being maintained at the same level, which offers a great possibility for applications in industry.

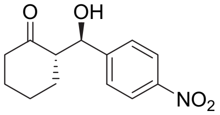
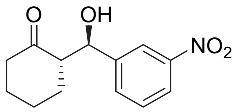
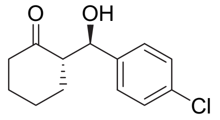
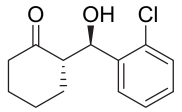
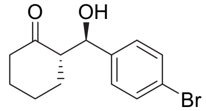
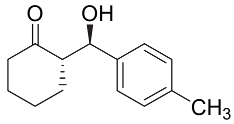
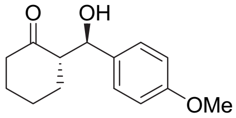
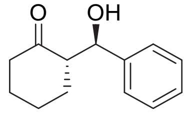
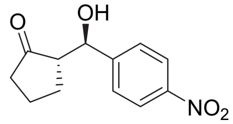
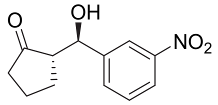
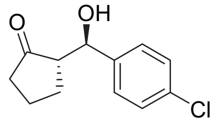
4. Experimental section

4.1. General remarks

All reagents were commercial products. The reactions were monitored by TLC (thin layer chromatography). The column and preparative TLC purification were carried out using silica gel. Flash column chromatography was performed on silica gel (200–300 mesh). NMR spectra were recorded on a 300 MHz instrument (Bruker Avance 300

Table 10
Large-scale asymmetric aldol reactions[a]



Entry	Product	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (%)
1		20	92	91/9	97
2		20	96	94/6	95
3		30	85	92/8	95
4		30	88	91/9	95
5		30	94	92/8	97
6		36	60	93/7	97
7		36	67	94/6	95
8		48	66	95/5	92
9		20	94	70/30	91
10		20	92	60/40	98
11		30	84	66/34	96

[a] The reactions were performed with aldehyde (2 mol), ketone (4 equiv), catalyst **1b** (0.2 mol), and Et_3N (0.2 mol) in the presence of water (400 mL) at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (AD-H, OD-H).

spectrometer). Chemical shifts (d) are given in parts per million relative to TMS as the internal reference, coupling constants (*J*) in Hertz. IR spectra were recorded with a Bruker Tensor 27 FTIR spectrometer. Melting points were measured on a digital melting point apparatus (TAQ100). Mass spectra (MS) were measured with a Bruker HCT mass spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out on Agilent 1200 instrument using Chiralpak AD-H (4.6 mm×250 mm), Chiralpak OJ-H (4.6 mm×250 mm), and Chiralcel OD-H (4.6 mm×250 mm) columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ=589 nm.

4.2. Typical experimental procedure for the preparation of the O-acylation serine organocatalysts 1a–h[14]

A 500 mL round bottom flask was charged with CF_3CO_2H (120 mL) and placed in an ice/water bath. Powdered serine (250 mmol, dried at 70–75 °C for 24 h) was added in small portions under vigorous stirring to give a viscous solution (leaving some small pieces of undissolved material). The reaction mixture was stirred for 15 min, and then removed from the ice/water bath. After 5 min of stirring, acyl chloride (375 mmol) was added in one portion. The reaction flask was fitted with a loose glass stopper, and the reaction mixture was stirred at room temperature without any external temperature adjustment for 12 h, giving a clear and colorless solution. The reaction flask was then cooled in an ice/water bath, and Et_2O (360 mL) was added under vigorous stirring over a period of 20 min, slowly at first. The resulting white suspension was stirred at 0–5 °C for 15 min after completed addition, and then filtered by vacuum. The crystals were washed with two portions of Et_2O and dried at room temperature for 23 h in a ventilated hood to give O-acylation serine hydrochloride **1a**–**h**. This essentially pure material was used for the next step without further purification.

*4.2.1. (S)-O-(n-Butyl)-L-serine hydrochloride (**1a**).* White solid; 50.79 g, yield: 96%, mp: 121–123 °C; $[\alpha]_D^{20}$ +17.2 (*c* 1, MeOH). IR (KBr): ν=2969, 1742, 1622, 1557, 1463, 1256, 1176, 1100, 1046, 751, 594 cm^{-1}; ^1H NMR (300 MHz, DMSO) δ=0.82–0.87 (m, 3H), 1.45–1.57 (m, 2H), 2.26–2.31 (m, 2H), 4.25 (dd, *J*=6.4 Hz and 3.7 Hz, 1H), 4.35 (m, 2H) ppm. ^{13}C NMR (75.5 MHz, DMSO) δ=13.5, 17.7, 35.1, 51.3, 61.4, 168.3, 172.4 ppm. MS (ESI): 175.52.

*4.2.2. (S)-O-(n-Hexanoyl)-L-serine hydrochloride (**1b**).* White solid; 58.13 g, yield: 97%, mp: 125–127 °C; $[\alpha]_D^{20}$ +14.3 (*c* 1, MeOH). IR (KBr): ν=2961, 2932, 1753, 1631,1598, 1463, 1256, 1176, 1100, 1046, 751, 594 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ=0.78–0.82 (m, 3H), 1.22–1.23 (m, 4H), 1.51–1.56 (m, 2H), 2.29–2.40 (m, 2H), 4.168 (dd, *J*=6.4 Hz and 3.6 Hz, 1H), 4.41(m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO) δ=13.7, 21.2, 23.4, 30.0, 33.0, 33.4, 54.2, 61.4, 169.7, 175.7 ppm. MS (ESI): 203.52.

*4.2.3. (S)-O-(n-Octanoyl)-L-serine hydrochloride (**1c**).* White solid; 63.59 g, yield: 95%, mp: 128–129 °C; $[\alpha]_D^{20}$ +11.3 (*c* 1, MeOH). IR (KBr): ν=2956, 2927, 2856, 1749, 1650,1598, 1463, 1256, 1163, 1100, 1046, 751, 594 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ=0.84–0.86 (m, 3H), 1.25 (br, 8H), 1.52 (m, 2H), 2.31–2.35 (m, 2H), 4.28 (dd, *J*=6.4 Hz and 3.7 Hz, 1H), 4.36 (m, 2H). ^{13}C NMR (75 MHz, DMSO): δ=14.0, 22.2, 24.2, 28.5, 31.2, 33.3, 51.3, 61.5, 168.4, 172.5 ppm. MS (ESI): 231.52.

*4.2.4. (S)-O-(n-Decanoyl)-L-serine hydrochloride (**1d**).* White solid; 70.99 g, yield: 96%, mp: 128–130 °C; $[\alpha]_D^{20}$ +12.5 (*c* 1, MeOH). IR (KBr): ν=2957, 2923, 2851, 1748, 1633, 1598, 1463, 1256, 1163, 1100, 1046, 751, 594 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ=0.90–0.95 (m, 3H), 1.33 (br, 12H), 1.62–1.67 (m, 2H), 2.41–2.45 (m, 2H), 4.40 (dd, *J*=6.3 Hz and 3.8 Hz, 1H), 4.56 (m, 2H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ=14.5, 23.7, 25.7, 30.1, 30.2, 30.4, 30.5, 33.0, 24.5, 53.3, 62.6, 169.0, 174.4 ppm. MS (ESI): 259.56.

*4.2.5. (S)-O-(n-Palmitoyl)-*L*-serine hydrochloride (**1e**).* White solid; 89.29 g, yield: 94%, mp: 130–131 °C; $[\alpha]_D^{20}$ +10.6 (*c* 1, MeOH). IR (KBr): ν=2957, 2922, 2850, 1749, 1691, 1417, 1354, 1165, 1122, 1066, 750, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ=0.83–0.85 (m, 3H), 1.23 (br, 24H), 1.51 (br, 2H), 2.32 (t, *J*=7.1 Hz, 2H), 4.29 (dd, *J*=6.4 Hz and 3.7 Hz, 1H), 4.45 (m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO): δ=14.0, 22.1, 24.1, 28.5, 28.8, 28.8, 29.0, 29.1, 31.3, 33.1, 51.2, 61.4, 168.3, 172.4 ppm. MS (ESI): 343.51.

*4.2.6. (S)-O-(Benzoyloxy)-*L*-serine hydrochloride (**1f**).* White solid; 55.27 g, yield: 90%, mp: 119–120 °C; $[\alpha]_D^{20}$ −11.5 (*c* 1, MeOH). IR (KBr): ν=3500–2600, 1750, 1691, 1417, 1354, 1165, 1122, 1066, 750, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ=4.48 (dd, *J*=6.4 Hz and 3.7 Hz, 1H), 4.81 (m, 2H), 7.55–7.58 (m, 2H), 7.68–7.73 (m, 1H), 8.08–8.10 (m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO): δ=51.4, 62.5, 128.7, 128.9, 129.8, 133.8, 165.2, 168.3 ppm. MS (ESI): 209.47.

*4.2.7. (S)-O-(2-Phenylacetoxy)-*L*-serine hydrochloride (**1g**).* White solid; 59.07 g, yield: 91%, mp: 118–119 °C; $[\alpha]_D^{20}$ +16.5 (*c* 1, MeOH). IR (KBr): ν=3500–2600, 2850, 1748, 1691, 1417, 1354, 1165, 1122, 1066, 750, 699 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ=3.83 (d, *J*=2.2 Hz, 2H), 4.31 (dd, *J*=6.4 Hz and 3.7 Hz, 1H), 4.40 (m, 2H), 7.25–7.34 (m, 5H) ppm. ^{13}C NMR (75 MHz, DMSO): δ=39.8, 51.4, 62.5, 128.7, 128.9, 129.8, 133.8, 165.2, 168.4 ppm. MS (ESI): 223.50.

*4.2.8. (S)-O-(3-Phenylpropanoyloxy)-*L*-serine hydrochloride (**1h**).* White solid; 64.17 g, yield: 94%, mp: 120–122 °C; $[\alpha]_D^{20}$ +15.5 (*c* 1, MeOH). IR (KBr): ν=3500–2600, 2850, 1755, 1691, 1417, 1354, 1165, 1122, 1066, 750, 720 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$OD): δ=2.75 (t, *J*=7.6 Hz, 2H), 2.97 (t, *J*=7.6 Hz, 2H), 4.37 (dd, *J*=6.3 Hz and 3.6 Hz, 1H), 4.55 (m, 2H), 7.19–7.32 (m, 5H) ppm. ^{13}C NMR (75 MHz, CD$_3$OD): δ=31.6, 36.3, 53.4, 62.8, 127.3, 129.3, 129.3, 129.5, 133.8, 141.7, 169.0, 173.6 ppm. MS (ESI): 237.49.

4.3. Representative procedure for direct asymmetric aldol reactions of ketones with aldehydes

To a mixture of catalyst **1b** (0.1 mmol) with equivalent triethylamine (0.1 mmol), water (0.2 mL), and ketone (4.0 mmol) were added aromatic aldehyde (1.0 mmol). The resulting mixture was stirred at room temperature, an emulsion was formed. 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.[15b,c] The reaction was monitored by TLC. It was then quenched with 5 mL saturated NH$_4$Cl solution, extracted with EtOAc (3×5 mL), and dried over Na$_2$SO$_4$. Purification by flash chromatography afforded the corresponding pure products.

4.4. Procedure for catalyst recovery

To a mixture of catalyst **1b** (0.2397 g, 1 mmol) with equivalent triethylamine (1 mmol), water (2 mL), and cyclohexanone (40 mmol) were added 4-nitrobenzaldehyde (1.5120 g, 10 mmol). The mixture was stirred at room temperature as specified in Table 9. The reaction mixture is quenched with aqueous HCl (1 mmol, 6 mol/L) and then diluted with diethyl ether (25 mL) and the reaction mixture was vigorously stirred for 5 min. The reaction mixture was placed in an ethanol bath (−20 °C) for 1 h. The organic layer was concentrated in vacuo to afford the crude aldol product, which was purified by column chromatography (ethyl acetate:hexane=1/10 to 1/2). The catalyst **1b**, which exits in the acidic aqueous layer, was added amount of triethylamine (1 mmol), and the resulting white suspension was stirred at room temperature for 10 min after completed addition. The suspension was filtered under vacuum and the white crystals were used directly in subsequent reaction cycles without adding any new catalyst. In each reuse, the same amounts of substrates were used.

4.5. General procedure for large-scale aldol reactions

To a mixture of catalyst **1b** (0.2 mol) with equivalent triethylamine (0.2 mol), water (400 mL), and ketone (8 mol) were added aromatic aldehyde (2 mol) using a 2 L round-bottomed flask. The resulting mixture was stirred at room temperature. The reaction was monitored by TLC. It was then quenched with 200 mL saturated NH$_4$Cl solution, extracted with EtOAc (3×500 mL), and dried over Na$_2$SO$_4$. Purification by flash chromatography afforded the corresponding pure products.

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Supplementary data

Complete experimental procedures are provided, including ^{1}H and ^{13}C spectra, of all new compounds. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.083.

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