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Direct asymmetric aldol reactions catalyzed by a siloxy serine organocatalyst in water

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Abstract—A siloxy-L-serine organocatalyst has been developed to catalyze direct asymmetric aldol reactions in the presence of water, furnishing the β-hydroxy carbonyl scaffold in high enantio- and diastereoselectivities. The direct aldol reaction between a selection of aromatic aldehydes and cyclohexanone resulted in good yields and high enantioselectivities.

1. Introduction

Catalytic enantioselective reactions using water as a solvent have attracted a great deal of attention mainly due to the low cost, safety and environmentally benign nature of water.[1] The synthesis of enantiopure molecules via enantioselective reactions in water is an extensively investigated topic, which entails the additional challenges of water tolerance for a catalyst.[2] Organocatalysis has recently experienced a renaissance[3] in asymmetric synthesis and excellent progress has been achieved following the discovery of the proline-catalyzed aldol reaction reported by List and Barbas et al.[4] Thus, the development of small organic molecules that catalyze enantioselective reactions in water is currently an important goal amongst today's synthetic community. The organocatalytic asymmetric direct aldol reaction via enamine intermediates generated in situ is one of the most useful carbon–carbon bond forming reactions, furnishing the β-hydroxyl carbonyl scaffold with excellent enantioselectivities.[5] As a step towards the development of enzyme mimics, extensive effort has been directed towards the development of catalytic asymmetric direct aldol in water,[6] which continues to pose a challenge to synthetic chemists.

Herein, we report the first efficient and highly enantioselective organocatalytic system for the direct enamine-based aldol reaction catalyzed by an acyclic silyl-protected serine derivative organocatalyst in the presence of water, via a two-phase system.

2. Results and discussion

In an initial experiment, the L-serine **1**-catalyzed reaction between cyclohexanone and *p*-nitrobenzaldehyde in water was investigated. However, no reaction progress was detected after 2 days in water (Table 1, entry 1). In previously reported studies,[6,7] appropriate hydrophobic interactions between the catalyst and substrates in water were proposed to assemble the hydrophobic reactants and sequester the transition state from water, thus channelling the aldol reaction in an enantiocontrolled fashion. Herein, such an approach was achieved by protecting the hydroxyl group of commercially available L-serine with *tert*-butyldiphenylchlorosilane (TBDPSCl) to form TBDPS-L-serine **2**.

Remarkably, the direct aldol reaction catalyzed by 20 mol % of the TBDPS-L-serine **2** organocatalyst in the presence of water (7.2 equiv) afforded the product in an excellent yield of 95% and good enantiomeric excess of 86% (entry 2). Henceforth, the hydrophobic effects of the serine-derived organocatalyst were essential for the formation of a reaction core in aqua and subsequent catalytic function of the organocatalyst in the presence of water. Moreover, the reactions carried out either with no solvent or in dimethyl sulfoxide (DMSO) resulted in lower enantioselectivities and *anti*:*syn* diastereomeric ratios (entries 3 and 4). These results illustrated that water is important for the high induction of diastereo- and enantiocontrol

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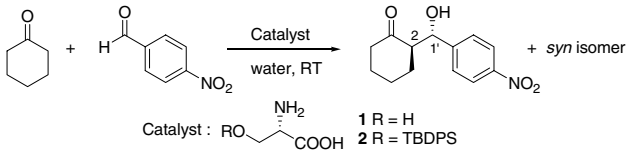
Table 1. Optimization studies on the siloxy-L-serine **2** catalyzed enantioselective direct aldol reaction[a]



Entry	Catalyst	Cat. loading (mmol %)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	**1**	20	—	—	—
2	**2**	20	95	85:15	86
3	**2**	10	89	75:25	84[e]
4	**2**	10	91	78:22	60[f]
5	**2**	10	95	87:13	98
6	**2**	5	92	88:12	92
7	**2**	10	90	85:15	90[g]
8	**2**	10	88	84:16	97[h]

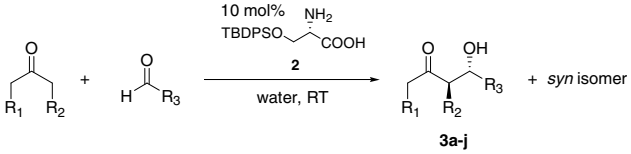
[a] Unless otherwise specified, the reaction was performed with aldehyde (0.5 mmol), ketone (2.5 mmol) and catalyst (0.05 mmol) in water (7.2 equiv) at room temperature for 16 h.
[b] Combined yield of isolated diastereomers.
[c] Diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture.
[d] Enantiomeric excess refers to the *anti*-isomer and was determined by HPLC analysis on a chiral phase.
[e] The reaction was performed neat.
[f] The reaction was performed in 0.1 mL DMSO.
[g] The reaction was performed with 3.3 equiv of water.
[h] The reaction was performed with 16.6 equiv of water.

with the reaction proceeding in a two-phase system. The optimum reaction conditions were achieved with 10 mol % catalyst loading whereupon the aldol product was isolated in an excellent yield of 95% and enantiomeric excess of 98% (entry 5). It is also noteworthy that the siloxy-L-serine organocatalyst **2** can also operate at 5 mol % catalyst loading to afford the product in excellent yield, albeit with a slight decrease in enantioselectivity (entry 6). In addition, it was noted that the addition of a lesser amount of water (3.3 equiv) to the reaction leads to a slight decrease in enantioselectivity, affording the product in 90% ee (entry 7). On the contrary, the addition of excess water (16.6 equiv) relative to the optimum water concentration (7.2 equiv) does not have any significant effect on both the diastereo- and enantioselectivities of the aldol product (entry 8).

A series of aldehydes was used to explore the generality of this catalytic system and the results are summarized in Table 2. In most cases, the β-hydroxy carbonyl compounds were obtained in good yields and high enantioselectivities.

The more reactive aldehydes underwent the catalytic process to afford the products in excellent enantioselectivities

Table 2. The catalytic asymmetric direct aldol reaction[a] catalyzed by siloxy-L-serine organocatalyst **2**



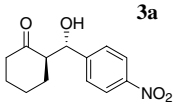
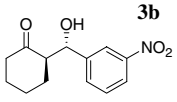
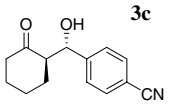
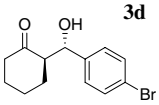
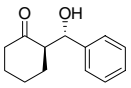
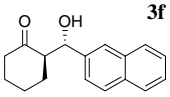
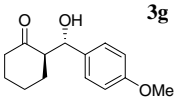
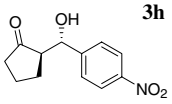
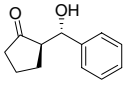
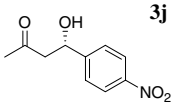
Entry	Product	*t* (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	**3a** 	16	95	87:13	98
2	**3b** 	16	90	86:14	92
3	**3c** 	20	87	87:13	90

Table 2 (*continued*)

Entry	Product	*t* (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
4	**3d** 	20	70	87:13	91
5	**3e** 	22	63	86:14	92
6	**3f** 	22	70	83:17	91
7	**3g** 	26	41	81:19	90
8	**3h** 	6	78	55:45	84
9	**3i** 	18	62	52:48	82
10	**3j** 	42	51	—	38

[a] Unless otherwise specified, the reaction was performed with aldehyde (0.5 mmol), ketone (2.5 mmol) and catalyst **2** (0.05 mmol) in water (7.2 equiv) at room temperature.
[b] Combined yield of isolated diastereomers.
[c] Diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture.
[d] Enantiomeric excess refers to the *anti*-isomer and was determined by HPLC analysis on a chiral phase.

and good *anti*-selectivity (Table 2, entries 1–4). The direct aldol reaction of neutral aldehydes catalyzed by the siloxy-L-serine catalyst also afforded the products in high enantio- and diastereoselectivities (entries 5 and 6). Moreover, the enantioselectivity obtained for a representative electron rich aldehyde gave good enantioselectivity, although the yield was moderate (entry 7). Good enantioselectivities were also obtained when cyclopentanone was employed as the donor albeit with low diastereoselectivities (entries 8 and 9). Although the aldol reaction of acetone and *p*-nitrobenzaldehyde proceeded in water, the enantioselectivity and yield obtained were only moderate (entry 10).

The stereochemistry of the β-hydroxy group of the aldol adducts **3** derived from the acyclic siloxy-L-serine **2** catalysis was determined to have an (*S*)-configuration by chiral-phase HPLC analysis and comparison with the literature.[6] The absolute stereochemical course catalyzed by the siloxy-L-serine **2** can be envisaged in terms of the plausible six-membered chair-like transition state,[8] **4** whereby the catalytically generated enamine favoured a *si*-facial attack on the arylaldehyde (Fig. 1).

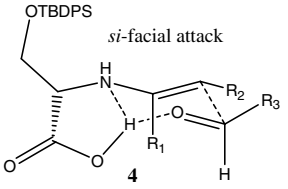


Figure 1. Plausible transition state for the siloxyserine catalyzed asymmetric aldol reaction.

3. Conclusions

In conclusion, we have demonstrated the first efficient asymmetric direct aldol reaction catalyzed by a siloxy-L-serine organocatalyst in the presence of water, via a two-phase system.[9] Noteworthy features in this system include: (1) the direct aldol reaction proceeding in the presence of water via a two-phase system and with simple procedures; (2) high enantioselectivities being attained with most aldehydes; (3) siloxyserine catalyst **2** being easily prepared, economically from commercially available sources, with both enantiomers readily available; and (4) a 5 mol % catalyst

being sufficient enough to furnish the aldol products in excellent yields and enantioselectivities. Further expansion on broadening the scope of the siloxyserine organocatalyst is currently in progress in our laboratory and will be reported in due course.

Acknowledgement

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9. *Representative procedure for the asymmetric direct aldol reaction*: Preparation of (2*R*,1′*S*)-2-[hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **3a**. A catalytic amount of siloxyserine (0.0172 g, 0.05 mmol, 0.1 equiv) was added to a vial containing 4-nitrobenzaldehyde (0.0760 g, 0.5 mmol, 1.0 equiv), cyclohexanone (0.26 mL, 2.5 mmol, 5 equiv) and water (0.065 mL, 3.6 mmol, 7.2 equiv) under air in a closed system. The reaction mixture was stirred at room temperature for 16 h and subsequently poured into an extraction funnel that contained brine (5 mL) and water (5 mL). The reaction vial was also washed with 10 mL of ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The crude aldol product was purified by silica-gel column chromatography (hexane–ethyl acetate 4:1) to afford **3a** as a white solid (0.1183 g, 95% yield). The diastereomeric *anti–syn* ratio was determined by ^{1}H NMR analysis of the reaction mixture: δ 5.48 (d, 1H, $J = 1.8$ Hz, *syn*, minor), 4.89 (d, 1H, $J = 8.8$ Hz, *anti*, major). The enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 95:5, 1 mL/min, $\lambda = 254$ nm, 20 °C): $t_R = 44.8$ min (minor) and 60.5 min (major).