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Organic Solvent–Free Direct Asymmetric Aldol Reactions Catalyzed by a Siloxy Serine Organocatalyst in Brine

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Abstract: A siloxy serine organocatalyst has been developed to catalyze direct asymmetric aldol reactions in aqueous saline media. The asymmetric aldol reactions between a selection of aromatic aldehydes and cyclohexanone afforded the products in good yields and enantioselectivities (up to 92% ee).

Keywords: Asymmetric aldol, enantiomeric excess, β-hydroxy carbonyl compounds, organocatalyst, serine

INTRODUCTION

Organocatalysis has recently emerged as a powerful synthetic methodology for asymmetric synthesis.[1] The development of small organic molecules that avoid the use of expensive and/or toxic metals as useful catalysts in enantioselective reactions is attracting much interest. These organocatalysts provide a ''green'' alternative to transition metals because of their relative nontoxicity. In addition, they are easy to purify and dispose, giving them an added economic advantage over transition-metal catalysts.

The direct catalytic asymmetric aldol reaction[2] is one of the most powerful carbon–carbon bond-forming reactions used for the

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construction of enantiomerically enriched β-hydroxy carbonyl compounds and their derivatives. The intense demand for stereoselective synthesis of aldol products has been fueled by their application as key synthons in numerous natural product syntheses as well as medicinal chemistry.[3] Recently, organocatalytic reactions performed in the presence of water or brine have been reported by a few research groups.[4] These reactions can be catalyzed by a chiral primary or secondary amine that contains a hydrophobic functional group.[5] Henceforth, the development of small molecules that catalyze the asymmetric direct aldol in aqueous media would be a favorable scenario from a green chemistry perspective.

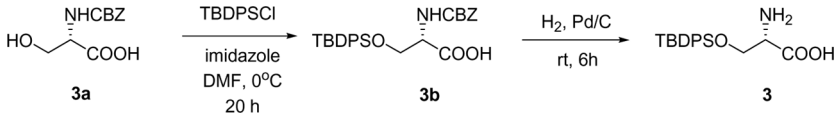
RESULTS AND DISCUSSION

In this article, we disclose a siloxy serine catalyst that can catalyze the direct asymmetric aldol reaction in aqueous saline media. The synthesis of the siloxy serine organocatalyst was carried out according to the synthetic route described in Scheme 1. It was readily accomplished in a simple two-step protocol using commercially available starting materials in good yield and purity.

In our endeavors to develop asymmetric protocols that are environmentally clean and friendly, we got interested in the organocatalytic direct asymmetric aldol reactions of ketones with commonly used aldehyde acceptors. The reaction between cyclohexanone and 4-nitrobenzaldehyde was chosen as the model reaction in our preliminary investigations. The results for the optimization studies are shown in Table 1.

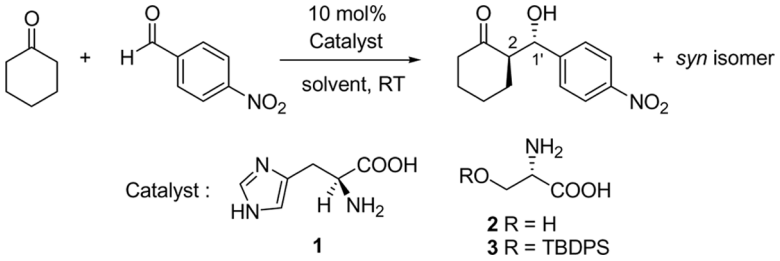
In an initial experiment, the L-histidine (**1**)–catalyzed reaction between cyclohexanone and 4-nitrobenzaldehyde in brine was investigated. However, only a trace amount of the product was detected (Table 1, entry 1). The reaction carried out using L-serine **2** in brine did not afford any product after 2 days of stirring at room temperature (entry 2). Based on these results, an attempt to protect the hydroxyl group of commercially available Z-L-serine with *tert*-butyldiphenylchlorosilane (TBDPSCl) to form TBDPS-L-serine **3** was initiated.

To our delight, the direct aldol reaction catalyzed by 10 mol% of the TBDPS-L-serine **3** organocatalyst in the presence of brine (0.2 mL)



Scheme 1. Synthesis of siloxy serine organocatalyst.

Table 1. Optimization studies on the siloxy-L-serine–catalyzed enantioselective direct aldol reaction in aqueous medium[a]



Entry	Catalyst	Solvent	Yield (%)[b]	*anti*/*syn* (%)[c]	ee (%)[d]
1	**1**	Brine	Trace	—	*nd*
2	**2**	Brine	—	—	*nd*
3	**3**	Brine	82	76:14	80
4	**3**	Brine	91	82:18	86

[a]Unless otherwise shown, the reaction was performed with aldehyde (0.5 mmol), ketone (2.5 mmol), and catalyst (0.05 mmol) at room temperature for 16–22 h.

[b]Combined yield of isolated diastereomers.

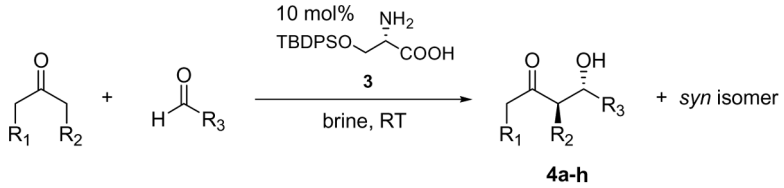
[c]Diastereoselectivity was determined by ^{1}H NMR analysis of the reaction mixture.

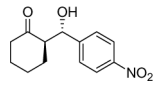
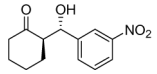
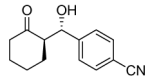
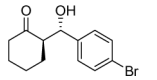
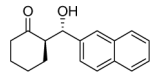
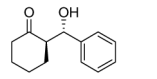
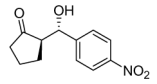
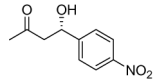
[d]Enantiomeric excess refers to the *anti* isomer and was determined by HPLC analysis on a chiral phase.

afforded the product in a good yield of 82% and enantiomeric excess of 80% (entry 3). Henceforth, the hydrophobic effects of the TDBPS group in the serine-derived organocatalyst were essential for the formation of a reaction core and subsequent catalytic function of the organocatalyst in the presence of brine. This result also illustrates that brine can be employed as an environmentally friendly solvent for the induction of diastereo- and enantiocontrol with the aldol reaction, proceeding in a two-phase system. The optimum reaction condition was achieved with 10 mol% catalyst in the presence of 0.1 mL of brine, whereupon the aldol product was isolated in an excellent yield of 91% and enantiomeric excess of 86% (entry 4). A series of aldehydes was used to explore the generality of this catalytic system in aqueous saline, and the results are summarized in Table 2.

In most cases, the β-hydroxy carbonyl compounds were obtained in good yields and enantioselectivities. The more reactive aldehydes underwent the catalytic process to afford the products in good

Table 2. The asymmetric direct aldol reaction[a] catalyzed by the siloxy-L-serine organocatalyst **3**



Entry	Product		Time (h)	Yield (%)[b]	*anti*/*syn* (%)[c]	ee (%)[d]
1		**4a**	17	91	82:18	86
2		**4b**	24	71	80:20	90
3		**4c**	24	76	70:30	92
4		**4d**	42	62	72:18	72
5		**4e**	24	54	90:10	84
6		**4f**	34	52	82:18	76
7		**4g**	42	71	34:66	84
8		**4h**	48	40	—	35

[a]Unless otherwise shown, the reaction was performed with aldehyde (0.5 mmol), ketone (2.5 mmol) and siloxy serine catalyst **3** (0.05 mmol) in brine (0.1 mL) 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.

enantioselectivities and good *anti* selectivity (Table 2, entries 1 to 4). The direct aldol reaction of neutral aldehydes catalyzed by the siloxy-L-serine catalyst also afforded the products in good enantioselectivities with moderate yields (entries 5 and 6). Good enantioselectivities were also obtained when cyclopentanone was employed as the donor, albeit with low diastereoselectivities (entry 7). Although the aldol reaction of acetone and 4-nitrobenzaldehyde proceeded in the presence of brine, the enantioselectivity and yield obtained was only moderate (entry 8). The stereochemistry of the β-hydroxy group of the aldol adducts **4** derived by the acyclic siloxy-L-serine **3** catalysis was determined as *S* configuration by chiral-phase, high-performance liquid chromatography (HPLC) analysis and comparison with literature.[4]

EXPERIMENTAL

General Methods

Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Analytical thin-layer chromatography (TLC) was performed using Merck 60 F254 precoated silica-gel plate (0.2 mm thick). Subsequent to elution, plates were visualized using ultraviolet (UV) radiation (254 nm) on Spectroline model ENF-24061/F 254 nm. Flash chromatography was performed using Merck silica gel 60 with AR-grade solvents. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DPX 400 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.2600, singlet). Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe4 (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Infrared (IR) spectra were recorded on a Bio-Rad FTS 165 Fourier transform (FT)–IR spectrometer. HPLC was carried out using a Agilent 110 series LC–G1311A QUAT pump, G1315B DAD detector, and integrator. All aldol reactions were carried out under an atmosphere of air in a closed system.

Organic substrates cyclohexanone, cyclopentanone, 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, 4-cyanobenzaldehyde, 4-bromobenzaldehyde, 2-naphthaldehyde *tert*-butyldiphenylchlorosilane, and Z-Ser-OH were all commercially available and were used without any purification. Benzaldehyde were purified by standard methods and distilled prior to use.

General Procedure for the Synthesis of (2*S*)-2-Benzyloxycarbonyl amino-3-(*tert*-butyl-diphenyl-silanyloxy)-propionic Acid, 3

Imidazole (3.8 g, 55.8 mmol, 2.6 equiv) and TBDPSCl (6.0 mL, 23 mmol, 1.1 equiv) were added to a dimethylformamide (DMF) solution (50 mL) of (2*S*)-2-benzyloxycarbonylamino-3-hydroxy-propionic acid **3a** (5.0 g, 20.9 mmol) at 0°C. The reaction was stirred for 20 h at room temperature and quenched by the addition of water and ether. The aqueous phase was extracted with ether (3×100 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude siloxy ether product was purified by silica-gel column chromatography (hexane–ethyl acetate 2:1) to afford **3b** as a white solid (7.3 g, 73%).

Pd/C (4.89 g, 10 wt%, 4.6 mmol, 0.3 equiv) was added to a methanol solution (100 mL) of (2*S*)-2-benzyloxycarbonylamino-3-(*tert*-butyl-diphenyl-silanyl oxy)-propionic acid **3b** (7.3 g, 15.3 mmol) at room temperature. The reaction mixture was stirred for 6 h at that temperature under a hydrogen atmosphere in a closed system. The filtration of the inorganic materials through celite and removal of methanol under reduced pressure afforded the crude product. Purification by silica-gel chromatography (dichloromethane–methanol 9:1) afforded catalyst **3** as a white solid (4.1 g, 79%). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.98 (s, 9H), 3.35 (dd, $J = 7.6$, 3.2 Hz, 1H), 3.82 (dd, $J = 10.8$, 7.6 Hz, 1H), 3.92 (dd, $J = 10.4$, 3.2 Hz, 1H), 7.40–7.47 (m, 6H), 7.65–7.68 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 19.3, 27.1, 56.7, 64.4, 128.2, 128.3, 130.2, 130.3, 133.1, 133.3, 135.7, 135.8, 168.3.

Representative Procedure for Asymmetric Direct Aldol Reaction: Preparation of (2*R*,1′*S*)-2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone 4a

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 brine (0.1 mL) under air in a closed system. The reaction mixture was stirred at room temperature for 17 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 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 was removed under reduced pressure. The crude aldol product was purified by silica-gel column chromatography (hexane–ethyl acetate 4:1) to

Table 3. ^{1}H NMR ($CDCL_3$-C<u>H</u>OH, δ) of *syn*/*anti* diastereomers

	^{1}H NMR ($CDCl_3$-C<u>*H*</u>OH, δ)	
Product	*Syn*	*Anti*
4a	5.48 (d) ($J = 1.8$ Hz)	4.89 (dd) ($J = 8.4$ Hz)
4b	5.50 (brs)	4.92 (d) ($J = 8.4$ Hz)
4c	5.43 (brs)	4.83 (d) ($J = 8.3$ Hz)
4d	5.30 (d) ($J = 2.6$ Hz)	4.75 (d) ($J = 8.5$ Hz)
4e	5.56 (brs)	4.96 (d) ($J = 8.7$ Hz)
4f	5.39 (d) ($J = 2.3$ Hz)	4.79 ($J = 8.8$ Hz)
4g	5.42 (brs)	4.85 ($J = 8.9$ Hz)

afford **4a** as a white solid (0.1123 g, 91% 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). 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).

The aldol adducts **4a–h** are all known compounds that exhibited spectroscopic data identical to those reported in the literature. The diastereomeric *anti*/*syn* ratio (Table 3) was determined by ^{1}H NMR analysis of the reaction mixture and comparison to known literature.[2k,4a–b,6]

The absolute configuration of aldol products was extrapolated by comparison of the HPLC data with those of **4a–h**, whose absolute configurations are known.

Representative Data of (2*R*,1′*S*)-2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone 4a

White solid (112 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.31–2.12 (m, 6H), 2.32–2.49 (m, 2H), 2.57–2.63 (m, 1H), 4.07 (s, 1H), 4.89 (d, $J = 8.4$ Hz, 1H), 7.50 (d, $J = 8.7$ Hz, 2H), 8.20 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.7, 27.7, 30.8, 42.7, 57.2, 74.0, 123.5, 127.9, 147.6, 148.4, 214.8.

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).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min, $\lambda = 254$ nm, 20°C): $t_R = 44.8$ min (minor) and 60.5 min (major).

The absolute of configuration of **4a** was extrapolated by comparison of the HPLC data to the literature[1–4] compound, whose absolute configuration is known.

HPLC Data for Aldol Products 4b–h

(2*R*,1′*S*)-2-[Hydroxy-(3-nitro-phenyl)-methyl]-cyclohexanone **4b**

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min, $\lambda = 254$ nm, 20°C): $t_R = 35.5$ min (major) and 47.0 min (minor).

(2*R*,1′*S*)-4-[Hydroxy-(2-oxo-cyclohexyl)-methyl]-benzonitrile **4c**

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min, $\lambda = 254$ nm, 20°C): $t_R = 21.6$ min (minor) and 27.1 min (major).

(2*R*,1′*S*)-2-[(4-Bromo-phenyl)-hydroxy-methyl]-cyclohexanone **4d**

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min, $\lambda = 254$ nm, 20°C): $t_R = 13.5$ min (minor) and 15.7 min (major).

(2*R*,1′*S*)-2-(Hydroxy-naphthalen-2-yl-methyl)-cyclohexanone **4e**

Enantiomeric excess was determined by HPLC with a Chiralcel AS-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min, $\lambda = 254$ nm, 20°C): $t_R = 27.5$ min (major) and 32.1 min (minor).

(2*R*,1′*S*)-2-(Hydroxy-phenyl-methyl)-cyclohexanone **4f**

Enantiomeric excess was determined by HPLC with a Chiralcel AS-H (hexane/*i*-PrOH = 95/5, 1.0 mL/min, $\lambda = 254$ nm, 20°C): $t_R = 20.8$ min (major) and 22.5 min (minor).

(2*R*,1′*S*)-2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone **4g**

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 97/3, 1.0 mL/min, $\lambda = 254$ nm, 20°C): $t_R = 71.9$ min (minor) and 76.9 min (major).

(*S*)-4-Hydroxy-4-(4-nitro-phenyl)-butan-2-one **4h**

Enantiomeric excess was determined by HPLC with a Chiralcel AS-H (hexane/*i*-PrOH = 60/40, 1 mL/min, $\lambda = 254$ nm, 20°C): $t_R = 9.2$ min (major) and 11.3 min (minor).

CONCLUSION

In conclusion, we have demonstrated an efficient asymmetric direct aldol reaction catalyzed by a siloxy-L-serine organocatalyst in the presence of brine via a two-phase system. Noteworthy features in this system include (1) the direct aldol reaction proceeded in the presence of brine via a two-phase system and with simple procedures without the need of an organic cosolvent; (2) good enantioselectivities were attained in most aldehydes; and (3) the siloxy serine catalyst **3** can be easily prepared economically from commercially available sources, with both enantiomers readily available. Further investigation on broadening the scope of the siloxy serine organocatalyst is currently ongoing in our laboratory and will be reported in due course.

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