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Direct asymmetric three-component Mannich reactions catalyzed by a siloxy serine organocatalyst in water

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Abstract—A siloxy-L-serine organocatalyst has been developed to catalyze the asymmetric three-component Mannich reactions in the presence of water via a biphasic system, furnishing the Mannich products in good yields and high enantioselectivities.

1. Introduction

The direct asymmetric Mannich reaction is a highly effective carbon–carbon bond forming reaction used for the construction of enantiomerically enriched nitrogenous molecules including amino acids, amino alcohols and their derivatives. The development of asymmetric Mannich reaction has been stimulated by a wide variety of natural products and drugs possessing optically active, nitrogen-containing molecules, which have attracted attention from synthetic chemists and the pharmaceutical industry.[1]

Organocatalysis has recently experienced a renaissance in asymmetric synthesis and emerged as a powerful synthetic methodology.[2] The development of small organic molecules, which avoid the use of expensive and/or toxic metals as useful catalysts in enantioselective reactions, is attracting much interest. List et al. reported the first direct asymmetric three-component Mannich reaction among an aldehyde, 4-methoxyaniline (*p*-anisidine) and a ketone catalyzed by proline.[3] The application of an organocatalytic strategy to the asymmetric Mannich reactions was further broaden by excellent work from the research groups of Barbas, Cordova, Jacobsen and Lu.[4] Some of these methods involve a catalytic indirect asymmetric Mannich reaction, while others involve direct methods. In addition to these aspects, a very recent development has been the use of water as a solvent for organocatalytic asymmetric reactions. Indeed, water is a desirable solvent for catalysis with respect to environmental concerns, safety and cost.[5] Thus, the development of organocatalysts that can catalyze asymmetric Mannich reactions in water is currently a challenge in contemporary asymmetric synthesis.

Herein, we report an efficient and highly enantioselective three-component Mannich reaction catalyzed by an acyclic silyl-protected serine derived organocatalyst in the presence of water, via a two-phase system.

2. Results and discussion

Recently, we have reported an efficient protocol for the asymmetric direct aldol reaction in the presence of water catalyzed by a siloxy serine organocatalyst.[6] This method has proven to be practical and environmentally friendly since it precluded the use of organic solvents and toxic metals. The siloxy serine catalyzed asymmetric direct aldol reaction proceeded via a biphasic system, furnishing a wide variety of β-hydroxy carbonyl scaffolds in good yields and excellent enantioselectivities. Based on this precedent, we envision that a Mannich reaction can also be performed as a three-component reaction utilizing an aldehyde, a ketone and a primary amine since nucleophilic addition of the in situ generated siloxy serine enanamine would be faster to an imine than to an aldehyde.[3]

In an initial study, we examined the three-component Mannich reaction among cyclohexanone, 4-nitrobenzaldehyde and *p*-anisidine catalyzed by a TBDPS-L-serine organocatalyst in the presence of water (Table 1, entries 1–3). The

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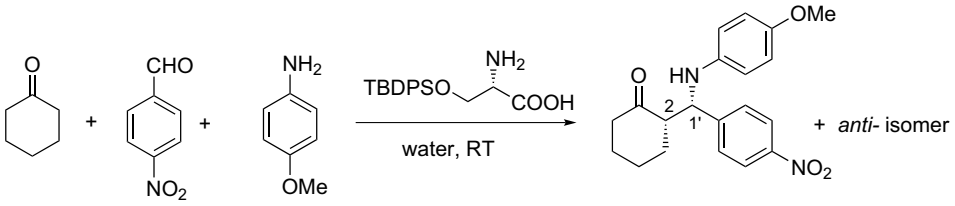
Table 1. Optimization studies on the siloxy-L-serine catalyzed direct asymmetric Mannich reaction[a]



1a **2a** **3a**

Entry	Cat. loading (mol %)	H_2O (μL)	Yield[b] (%)	*syn*:*anti*[c]	ee[d] (%)
1	20	65	82	81:19	78
2	20	100	86	82:18	80
3	20	150	85	82:18	82
4	20	—	81	78:22	40[e]
5	20	65	82	75:25	42[e]
6	10	100	86	84:16	80
7	5	100	86	84:16	82
8	10	100	83	84:16	80[f]

[a] Unless otherwise shown, the reaction was performed with aldehyde (0.5 mmol), ketone (1.5 mmol), *p*-anisidine (0.45 mmol) and catalyst in water at room temperature for 18 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 *syn* isomer and was determined by HPLC analysis on a chiral phase.
[e] 2.0 mL DMSO was used in the reaction.
[f] 2.5 mmol of ketone was used in the reaction.

optimum water concentration was achieved at 56 equiv relative to the catalyst, affording the product in good yield and high enantioselectivity (entry 2). The addition of excess water to the reaction mixture (84 equiv) does not have any significant effects on both the diastereo- and the enantioselectivities of the Mannich product (entry 3). Moreover, the reaction carried out in the absence of water or a mixture of water and DMSO leads to significantly lower diastereo- and enantioselectivities (entries 4 and 5). The optimized conditions were achieved using 5 mol % catalyst loading whereupon the product was isolated in a good yield of 86% and enantiomeric excess of 82% (entry 7).

In addition, the employment of a large excess of ketone in the reaction also afforded the product in good yield, albeit with a slight decrease in both diastereo- and enantioselectivities (entry 8).

The optimized conditions were extended to a series of aldehyde acceptors and ketone donors to explore the generality of this catalytic system and the results are summarized in Table 2. In most cases, the Mannich products were obtained in good yields and high enantioselectivities with only trace amounts of aldol addition side products.

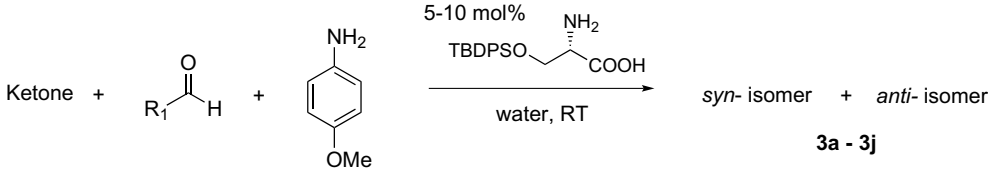
In the case of cyclohexanone **1a** as the cyclic ketone donor, the reactive aldehydes underwent the catalytic process to afford the products with *syn* selectivity with both good yields and enantioselectivities (Table 2, entries 1–3). Moreover, the reaction employing ethyl glyoxylate as the aldehyde acceptor also afforded the corresponding *syn* amino acid derivative in 75% yield and 86% ee (entry 4). To broaden the scope of this transformation, a number of aromatic aldehydes were reacted with the acyclic *O*-benzyl hydroxyacetone **1b** under these conditions to afford the 1,2-protected aminoalcohols. In all the cases, the reaction proceeded regioselectively with the carbon–carbon bond formation occurring at the methylene carbon. Interestingly, the reactions afforded *anti* selectivity and the corresponding 1,2-protected aminoalcohols were obtained in good enantioselectivities and yields (entries 5–8).

The stereochemistry of the Mannich products derived by the acylic siloxy-L-serine catalysis was determined by chiral-phase HPLC analysis and by comparison with the literature.[4] Although the actual mechanism of the Mannich reaction has yet to be elucidated at the moment, the stereochemical course catalyzed by the siloxy-L-serine using cyclohexanone as the cyclic donor can be envisaged in terms of a plausible six-membered chair-like transition state[4f] **4** whereby the catalytically generated enamine favored a *si*-facial attack on the imine (Fig. 1).

3. Conclusions

In summary, the one-pot direct Mannich reaction has been realized with high enantioselectivities in the presence of water by the catalytic use of a siloxy serine organocatalyst. Noteworthy features in this system include (1) the direct Mannich reaction proceeded in the presence of water via a two-phase system and with simple procedures; (2) good enantioselectivities were attained with aromatic aldehydes for both cyclohexanone and *O*-benzyl hydroxyacetone as ketone donors; (3) the siloxy serine catalyst can be easily prepared economically from commercially sources, with both enantiomers readily available.

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



Entry	Ketone	R_1	Product	Catalyst (mol %)	*t* (h)	Yield[b] (%)	*syn*:*anti*[c]	ee[d] (%)
1	**1a**	4-$NO_2C_6H_4$	**3a**	5	18	86	84:16	82
2		4-BrC_6H_4	**3b**	5	20	78	74:26	74
3		4-CNC_6H_4	**3c**	5	22	74	83:17	80
4		CO_2Et	**3d**	10	22	71	72:28	86
5	**1b**	4-$NO_2C_6H_4$	**3e**	10	20	81	14:86	90
6		4-BrC_6H_4	**3f**	10	21	64	18:82	84
7		4-CNC_6H_4	**3g**	10	20	79	14:86	92
8		2-Naphthyl	**3h**	10	25	78	34:66	81

[a] Unless otherwise shown, the reaction was performed with aldehyde (0.5 mmol), ketone (1.5 mmol), *p*-anisidine (0.45 mmol) and catalyst in water (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 major isomer and was determined by HPLC analysis on a chiral phase.

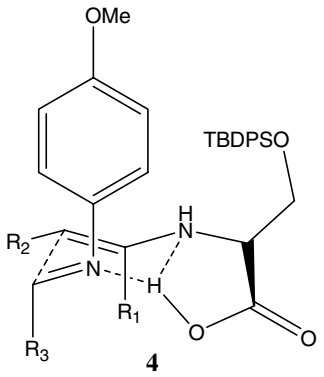


Figure 1. Plausible transition state for the siloxyserine catalyzed asymmetric Mannich reaction.

Further research to elucidate the mechanism of this reaction and broaden the scope of the siloxyserine catalyst to other asymmetric reactions is currently under investigation.

4. Experimental

4.1. 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 thickness). Subsequent to elution, plates were visualized using 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 $SiMe_4$ (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 $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet). Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. HPLC was carried out using a AGILENT 110 series LC—G1311A QUAT pump, G1315B DAD detector and integrator. All Mannich reactions were carried out under an atmosphere of air in a closed system.

Organic substrates cyclohexanone, hydroxyacetone, 4-nitrobenzaldehyde, 4-cyanobenzaldehyde, 4-bromobenzaldehyde, 2-naphthaldehyde, *tert*-butyldiphenyl chlorosilane and Z-Ser-OH were all commercially available and were used without any purification.

The Mannich adducts **3a**–**3h** are all known compounds that exhibited spectroscopic data identical to those reported in the literature.[4] The diastereomeric *anti–syn* ratio was determined by ^{1}H NMR analysis of the reaction mixture and comparison to the known literature. The absolute configuration of the Mannich products was extrapolated by comparison of the HPLC data with those of **3a**–**3h** whose absolute configuration is known.

4.2. General procedure for the synthesis of siloxyserine catalyst

4.2.1. Typical procedure for the synthesis of (2*S*)-2-benzyloxycarbonylamino-3-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid. To a DMF solution (50 mL) of (2*S*)-2-benzyloxycarbonylamino-3-hydroxy-propionic acid **2a** (5.0 g, 20.9 mmol) were added imidazole (3.8 g, 55.8 mmol, 2.6 equiv) and TBDPSCl (6.0 mL, 23 mmol, 1.1 equiv) at 0 °C. The reaction was stirred for 18 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 removed under reduced pressure. The crude siloxy ether product was purified by silica gel column chromatography (hexane/ethyl acetate 2:1) to afford **2b** as a white solid (7.3 g, 73%).

To a methanol solution (100 mL) of (2*S*)-2-benzyloxycarbonylamino-3-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid **2b** (7.3 g, 15.3 mmol) was added Pd/C (4.89 g, 10 wt %, 4.6 mmol, 0.3 equiv) 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 2 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 $[\alpha]_D^{23} = +2.6$ (*c* 1.94, MeOH).

4.3. General procedure for the asymmetric direct Mannich reaction

4.3.1. Representative procedure for asymmetric direct Mannich reaction: Preparation of (2*S*,1′*S*)-2-[(4-methoxy-phenylamino)-(4-nitro-phenyl)-methyl]-cyclohexanone 3a. A catalytic amount of siloxyserine (7.75 mg, 0.0225 mmol, 0.05 equiv) was added to a vial containing 4-nitrobenzaldehyde (0.0760 g, 0.5 mmol, 1.1 equiv), *p*-anisidine (0.055 g, 0.45 mmol, 1.0 equiv), cyclohexanone (0.16 mL, 1.5 mmol, 3.3 equiv) and water (0.1 mL, 5.55 mmol, 12.3 equiv) under air in a closed system. The reaction mixture was stirred at room temperature for 18 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 Mannich product was purified by silica gel column chromatography (hexane/ethyl acetate 4:1) to afford **3a** as a brown oil (0.1370 g, 86% yield).

4.3.2. Representative data of 3a

4.3.2.1. (2*S*,1′*S*)-2-[(4-Methoxy-phenylamino)-(4-nitro-phenyl)-methyl]-cyclohexanone 3a. Brown oil (137 mg,

86%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.60–2.15 (m, 4H), 2.03–2.06 (m, 2H), 2.30–2.46 (m, 2H), 2.79–2.84 (m, 1H), 3.67 (s, 3H), 4.34 (br s, 1H), 4.79 (d, $J = 4.1$ Hz, 1H), 6.46 (d, $J = 8.7$ Hz, 2H), 6.66 (d, $J = 8.7$ Hz, 2H), 7.54 (d, $J = 8.7$ Hz, 2H), 8.212 (d, $J = 8.7$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 27.0, 28.9, 42.6, 55.5, 56.3, 57.9, 114.7, 115.5, 123.6, 128.5, 140.7, 147.0, 149.8, 152.6, 210.6 ppm.

The diastereomeric *anti–syn* ratio was determined by ^{1}H NMR analysis of the reaction mixture: δ (ppm) 4.79 (d, 1H, $J = 4.1$ Hz, *syn*, major), δ 4.64 (d, 1H, $J = 8.2$ Hz, *anti*, minor).

Enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 85/15, 0.5 mL/min, $\lambda = 254$ nm, 20 °C): $t_R = 71.1$ min (minor) and 74.7 min (major).

The absolute configuration of **3a** was extrapolated by comparison of the HPLC data of the literature[4f] whose absolute configuration is known.

4.3.3. HPLC data for Mannich products 3b–3h

4.3.3.1. (2*R*,1′*S*)-2-[(4-Bromo-phenyl)-(4-methoxy-phenylamino)-methyl]-cyclohexanone. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H (hexane/*i*-PrOH = 80/20, 0.5 mL/min, $\lambda = 254$ nm, 20 °C): $t_R = 26.9$ min (major) and 32.1 min (minor).

4.3.3.2. (2*S*,1′*S*)-4-[(4-Methoxy-phenylamino)-(2-oxo-cyclohexyl)-methyl]-benzonitrile. 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): $t_R = 80.6$ min (minor) and 108.4 min (major).

4.3.3.3. (2*S*,1′*S*)-(4-Methoxy-phenylamino)-(2-oxo-cyclohexyl)-acetic acid ethyl ester. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H (hexane/*i*-PrOH = 96/4, 0.5 mL/min, $\lambda = 254$ nm, 20 °C): $t_R = 42.1$ min (major) and 55.1 min (minor).

4.3.3.4. (3*R*,4*R*)-3-Benzyloxy-4-(4-methoxy-phenylamino)-4-(4-nitro-phenyl)-butan-2-one. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 85/15, 1.0 mL/min, $\lambda = 254$ nm, 20 °C): $t_R = 20.9$ min (minor) and 25.3 min (major).

4.3.3.5. (3*R*,4*R*)-3-Benzyloxy-4-(4-bromo-phenyl)-4-(4-methoxy-phenylamino)-butan-2-one 3f. 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): $t_R = 11.5$ min (minor) and 16.8 min (major).

4.3.3.6. (3*R*,4*R*)-4-[2-Benzyloxy-1-(4-methoxy-phenylamino)-3-oxo-butyl]-benzonitrile. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H (hexane/*i*-PrOH = 90/10, 1.0 mL/min, $\lambda = 254$ nm, 20 °C): $t_R = 27.6$ min (minor) and 32.9 min (major).

4.3.3.7. (3*R*,4*R*)-3-Benzyloxy-4-(4-methoxy-phenylamino)-4-naphthalen-2-yl-butan-2-one. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H (hexane/*i*-PrOH = 90/10, 0.5 mL/min, $\lambda = 254$ nm, 20 °C): $t_R = 33.9$ min (major) and 40.6 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.60–2.15 (m, 4H), 2.03–2.06 (m, 2H), 2.30–2.46 (m, 2H), 2.79–2.84 (m, 1H), 3.67 (s, 3H), 4.34 (br s, 1H), 4.79 (d, $J = 4.1$ Hz, 1H), 6.46 (d, $J = 8.7$ Hz, 2H), 6.66 (d, $J = 8.7$ Hz, 2H), 7.54 (d, $J = 8.7$ Hz, 2H), 8.212 (d, $J = 8.7$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 27.0, 28.9, 42.6, 55.5, 56.3, 57.9, 114.7, 115.5, 123.6, 128.5, 140.7, 147.0, 149.8, 152.6, 210.6 ppm. The diastereomeric *anti–syn* ratio was determined by ^{1}H NMR analysis of the reaction mixture: δ (ppm) 4.79 (d, 1H, $J = 4.1$ Hz, syn, major), δ 4.64 (d, 1H, $J = 8.2$ Hz, anti, minor). Enantiomeric excess was determined by HPLC with a Chiralcel AD-H (hexane/*i*-PrOH = 85/15, 0.5 mL/min, $\lambda = 254$ nm, 20 °C): $t_R = 71.1$ min (minor) and 74.7 min (major).

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