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Threonine-surfactant organocatalysts for the highly diastereo- and enantioselective direct *anti*-Mannich reactions of hydroxyacetone

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ABSTRACT

In this work, several new L-threonine derivatives as organocatalysts were synthesized in one step for the first time by the reaction of threonine with acyl chlorides at room temperature in trifluoroacetic acid on a large-scale without protecting groups involved or chromatographic techniques, and those threonine-surfactant organocatalysts mediated the direct asymmetric *anti*-Mannich reactions of hydroxyacetone and anilines with aldehydes to synthesize *anti*-1,2-amino alcohols in good yields (75–93%) and highly enantioselectivities (up to 99% ee).

The catalytic asymmetric Mannich reaction is an effective carbon–carbon bond-forming process for the construction of nitrogen-containing chiral molecules, which are common structural motifs and chiral building blocks for a vast array of biologically active and importantly pharmaceutical compounds.[1] Due to the atom-economy, the direct one-pot three-component asymmetric Mannich reactions are one of the most elegant and synthetically attractive.[2] Shibasaki and co-workers firstly reported the direct enantioselective Mannich-type reactions catalyzed by heterodimetallic complexes.[3] The first example of a direct organocatalytic three-component Mannich reaction was reported by List,[4] and followed by the excellent work of several groups.[5–12] Besides (*S*)-proline,[4–9] proline-derived tetrazole,[10] acylic amino acids and their derivatives,[11] and chiral phosphoric acids[12] were developed as enantioselective organocatalysts for the direct one-pot three-component Mannich reactions. Although 1,2-amino alcohol can be constructed via Mannich reaction of hydroxyketone to imines, hydroxyacetone was seldom used as a donor in the asymmetric-catalyzed direct Mannich reactions.[4,10,11,13] Threonine derivatives were developed as organocatalysts for the direct one-pot three-component asymmetric Mannich reactions of hydroxyketone to imines was reported by Barbas and Lu.[11b,c] However, it should be noted that 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, which created the added hurdles for industrial production, so these organocatalysts were often used in research laboratories. Therefore, the development of a new type of effective asymmetric organocatalysts with natural crude chiral pool, simple preparation procedure, and inexpensive reagents is urgently needed and is also the true challenge.

Here we described a novel, simple and efficient surfactant type of acyl threonine derivatives as the organocatalysts for the asymmetric Mannich reaction of α-hydroxyketones. Threonine seems to be good chiral structural scaffold, as its hydroxy group allows for the easy attachment of various hydrophobic groups such as alkyl, acyl and so on.[14] Trifluoroacetic acid has been used as the best medium for selective acylation of hydroxyproline.[15] In this work, we reported that a series of novel L-threonine derivatives readily available on a large-scale were derived from the one-step O-acylation of L-threonine with acyl chlorides at room temperature in trifluoroacetic acid (Fig. 1), in the synthetic process of the acylthreonines, no protecting method of amino groups and chromatographic technique were involved. The obtained threonine-surfactant organocatalysts were able to smoothly mediate the direct one-step three-component asymmetric *anti*-Mannich reaction of hydroxyacetone with 4-methoxyaniline and 4-nitrobenzaldehyde to give enantiomerical *anti*-1,2-amino alcohols **2a** (Table 1).

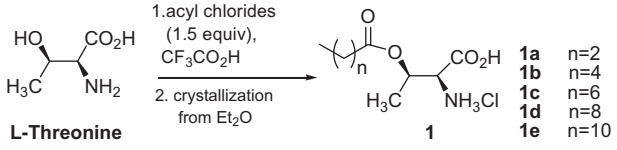

Figure 1. Synthetic figure for acyloxythreonines **1**: (1) acyl chlorides, CF_3CO_2H, 0 °C to room temperature; (2) crystallization from Et_2O.

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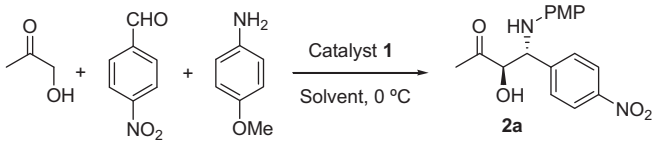
Table 1
Screening of organocatalysts[a]



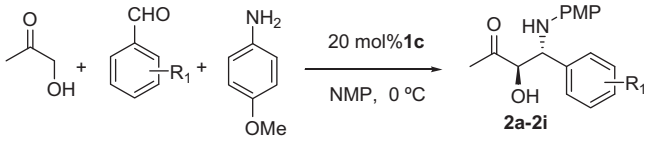
Entry	Catalyst	Cat. loading [%]	Solvent	Yield[b] [%]	*anti*:*syn*[c]	ee[d] [%]
1	**1a**	20	NMP	91	84:16	91
2	**1b**	20	NMP	92	89:11	94
3	**1c**	**20**	**NMP**	**92**	**92:8**	**98**
4	**1d**	20	NMP	89	84:16	92
5	**1e**	20	NMP	79	66:34	73/30
6	**1c**	20	DMSO	91	85:15	92
7	**1c**	20	DMF	90	85:15	90
8	**1c**	20	$ClCH_2CH_2Cl$	75	50:50	27/23
9	L-**Thr**	20	NMP	51	75:25	65
10[e]	**1c**	10	NMP	80	73:27	86/15
11[f]	**1c**	5	NMP	70	53:47	80/36

[a] The reactions were performed with *p*-nitrobenzaldehyde (1.1 mmol), hydroxyacetone (3 mmol), 4-methoxyaniline (1 mmol), Et_3N (0.2 mmol), and catalyst (0.2 mmol) at 0 °C.
[b] Isolated yield.
[c] The ratios of *anti* to *syn* were determined by ^1H NMR analysis of the crude product and by HPLC.
[d] The ee values of the *anti*-isomer were determined by chiral HPLC using a chiralpak AD-H.
[e] The molar ratio of aldehyde/hydroxyacetone/4-methoxyaniline/Et_3N/catalyst was 1.2:3:1:01:0.1.
[f] The molar ratio of aldehyde/hydroxyacetone/4-methoxyaniline/Et_3N/catalyst ratio was 1.2:3:1:0.05:0.05.

In our initial screening, a three-component asymmetric Mannich reaction of hydroxyacetone with 4-nitrobenzaldehyde and 4-methoxyaniline was carried out with 20 mol % of catalyst **1** in NMP at 0 °C (Table 1, entries 1–5). The L-threonine provided the moderate *anti*-selectivity (*anti*:*syn* = 75:25) and enantioselectivity (65% ee) (Table 1, entry 9). Among the five synthesized threonine-surfactant derivatives by the O-acylation of L-threonine with acyl chlorides, it was found that the chain length (*n*) dramatically affected the yields and the enantioselectivities. Neither very long (*n* = 8, 10) nor very short carbon chains (*n* = 2, 4) were effective, whereas catalyst **1c** containing the *n*-octanoic group (*n* = 6) gave the best yield (92%), diastereoselectivity (*anti*:*syn* = 92:8) and enantioselectivity (98% ee) (Table 1, entry 3). Other polar solvents such as DMSO, DMF, and $ClCH_2CH_2Cl$ were less satisfactory in terms of the yields and enantioselectivities (Table 1, entries 6–8). Unfortunately, the yields (70–80%), diastereoselectivities (*anti*:*syn* = 73:27; 54:47), and enantioselectivities (80–86% ee) significantly decreased when the used amount of catalyst **1c** decreased to 10 mol % and 5 mol % in NMP (Table 1, entries 10 and 11).

Under the optimized reaction conditions, the direct *anti*-Mannich reaction in NMP catalyzed by catalyst **1c** was extended to a series of aldehydes to explore the generality of this catalytic system. The catalytic results were summarized in Table 2. The Mannich products were obtained in good yields with up to 99% ee and dr values ranging from 51/49 to 92/8. The stereochemical outcome depended significantly on the electronic properties of the substituted groups on benzaldehydes. The electron-withdrawing groups had a positive effect on the enantioselectivities (entries 1–9).

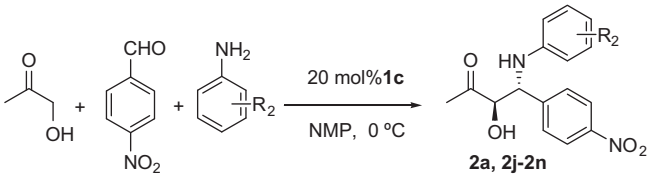
Table 2
The three-component direct asymmetric Mannich reactions of different aldehydes[a]



Entry	R_1	Product	Yield[b] [%]	*anti*:*syn*[c]	ee[d] [%]
1	4-NO_2	**2a**	92	92:8	98
2	3- NO_2	**2b**	93	80:20	90
3	2- NO_2	**2c**	90	86:14	91
4	4-CN	**2d**	91	80:20	>99
5	4-F	**2e**	92	54:46	94
6	4-Cl	**2f**	90	80:20	96
7	2-Cl	**2g**	87	89:11	97
8	4-Br	**2h**	90	90:10	98
9	H	**2i**	75	51:49	70

[a] The reactions were performed with aldehydes (1.1 mmol), hydroxyacetone (3 mmol), 4-methoxyaniline(1 mmol), Et_3N (0.2 mmol) and catalyst**1c** (0.2 mmol) in NMP(3 mL) at 0 °C.
[b] Isolated yield.
[c] The ratio of *anti* to *syn* was determined by ^1H NMR analysis of the crude products and by HPLC.
[d] The ee value of the *anti*-isomer was determined by chiral HPLC using a chiralpak AD-H.

Table 3
The three-component direct asymmetric Mannich reactions of different aniline components[a]



Entry	R_2	Product	Yield[b] [%]	*anti*:*syn*[c]	ee[d] [%]
1	4-MeO	**2a**	92	92:8	98
2	3-MeO	**2j**	91	92:9	99
3	4-Me	**2k**	93	93:7	96
4	2,4-Me_2	**2l**	95	96:4	96
5	4-Cl	**2m**	95	96:4	95
6	H	**2n**	89	90:10	98

[a] The reactions were performed with *p*-nitrobenzaldehyde (1.1 mmol), hydroxyacetone (3 mmol), aniline (1 mmol), Et_3N (0.2 mmol), and catalyst (0.2 mmol) in NMP (3 mL) at 0 °C.
[b] Isolated yield.
[c] The ratio of *anti* to *syn* was determined by ^1H NMR analysis of the crude products and by HPLC.
[d] The ee value of the *anti*-isomer was determined by chiral HPLC using a chiralpak AD-H.

Different aniline components were also investigated and shown in Table 3, all the selected aromatic amines furnished Mannich products in good yields (89–95%) with excellent diastereoselectivities (*anti*:*syn* = 90–96:10–4) and enantioselectivities (95–98% ee).

In conclusions, we have designed and synthesized a new series of simple combined threonine-surfactant organocatalysts in one step for the first time, which were prepared from commercially available and inexpensive threonine and acyl chlorides without using the protecting groups and chromatographic techniques. In the asymmetric direct one-pot three-component *anti*-Mannich reactions of 2-hydroxyacetone with anilines and aldehydes,[16] the high isolated yields (up to 95%), diastereoselectivities (*anti*:*syn* = 96:4), and enantioselectivities (up to 99% ee) were obtained. Hence, it was discovered that L-threonine was successfully utilized in the design of novel and inexpensive organocatalysts for the direct three-component asymmetric *anti*-Mannich reactions. The mechanistic study and catalytic development to a broader range of substrates and other transformations are currently being investigated, and will be reported in due course.

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Supplementary data

Supplementary data (general synthetic method, ^{1}H NMR of the products and HPLC profiles) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.085.

References and notes

1. (a) Denmark, S. E.; Nicaise, O. J. C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; p 923; (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044; (d) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797–5815.
2. For a recent overview on multicomponent reactions, see: (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (b) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41.
3. (a) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307; (b) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857.
4. (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336; (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827; (c) Pojarliev, P.; Biller, W. T.; Martin, H. J.; List, B. *Synlett* **2003**, 1903; (d) Kantam, M. L.; Rajasekhar, C. V.; Gopikrishna, G.; Reddy, K. R.; Choudary, B. M. *Tetrahedron Lett.* **2006**, *47*, 5965–5967.
5. Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III *Adv. Synth. Catal.* **2004**, *346*, 1131.
6. (a) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677; (b) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208; (c) Hayashi, Y.; Urushima, T.; Shoji, M.; Uchimary, T.; Shiina, I. *Adv. Synth. Catal.* **2005**, *347*, 1595.
7. (a) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528; (b) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987; (c) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102; (d) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2839; (e) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3363; (f) Liao, W.-W.; Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 674; (g) Ibrahem, I.; Zou, W.; Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron* **2006**, *62*, 357.
8. Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079.
9. Rodriguez, B.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2888.
10. (a) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2006**, *8*, 2839; (b) Zheng, J. F.; Li, Y. X.; Zhang, S. Q.; Wang, X. M.; Yang, S. T.; Bai, J.; Wang, F.; Zhang, G. L.; Liu, F. A. *Acta Chim. Sinica* **2007**, *65*, 553 (in Chinese); (c) Zhang, X.; Qian, Y. B.; Wang, Y. M. *Eur. J. Org. Chem.* **2010**, *3*, 515–522; (e) Gu, Q.; Jiang, L.-X.; Yuan, K.; Zhang, L.; Wu, X.-Y. *Synth. Commun.* **2008**, *38*, 4198–4206; (f) Gu, Q.; Gong, J.-J.; Feng, J.; Wu, X.-Y.; Zhou, Q.-L. *Chin. J. Chem.* **2008**, *26*, 1902–1906; (g) Pfefferkorn, J. A.; Larsen, S. D.; Huis, C. V.; Sorenson, R.; Barton, T.; Winters, T.; Auerbach, B.; Wu, C. Y.; Wolfram, T. J.; Cai, H. L.; Welch, K.; Esmaiel, N.; Davis, J.; Bousley, R.; Olsen, K.; Mueller, S. B.; Mertz, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 546–553; (h) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 5756–5762.
11. (a) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y. *Chem. Eur. J.* **2005**, *11*, 7024; (b) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288; (c) Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018; (d) Sueki, S.; Igarashi, T.; Nakajima, T.; Shimizu, I. *Chem. Lett.* **2006**, *35*, 682–683; (e) Dirvianskyte, N.; Straukas, J.; Razumas, V.; Butkus, E. *Z. Naturforsch., C: J. Biosci.* **2003**, *58*, 366–370.
12. Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790.
13. Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentanob, G. *Adv. Synth. Catal.* **2002**, *344*, 533.
14. (a) Siyutkin, D. E.; Kucherenko, A. S.; Zlotin, S. G. *Tetrahedron* **2009**, *65*, 1366–1372; (b) Dziedzic, P.; Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2008**, *49*, 803–807; (c) Chen, L.; Han, L. X.; Huang, H. M.; Wong, M. W.; Lu, Y. X. *Chem. Commun.* **2007**, *40*, 4143–4145; (d) Jiang, Z. Q.; Lu, Y. X. *Tetrahedron Lett.* **2010**, *51*, 1884–1886.
15. (a) Kristensen, T. E.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, 387–395; (b) Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett.* **2009**, *11*, 2968–2971.
16. *General procedure for the catalytic asymmetric Mannich reaction in NMP*: A mixture of 1-methyl-2-pyrrolidinone (NMP, 3 mL), *p*-anisidine (1 mmol), *p*-nitrobenzaldehyde (1.2 mmol), hydroxyacetone (3 mmol), and catalyst **1c** (0.2 mmol) was vigorously stirred at 0 °C and monitored with TLC. The reaction mixture was diluted with 5 mL of AcOEt, was added 5 mL of unsaturated ammonium chloride solution and then extracted with AcOEt (3 × 5 mL). The combined organic layers were washed with brine (3 × 3 mL), dried over anhydrous $MgSO_4$, concentrated in vacuo and were purified by flash column chromatography (hexanes/ethyl acetate (v/v = 1:1)) to afford the desired Mannich product **2a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.55 (br s, 1H), 3.69 (s, 3H), 4.56 (br s, 1H), 4.71 (d, 1H, ^3J = 3.5 Hz), 4.88 (d, 1H, ^3J = 3.5 Hz), 6.53 (d, 2H, ^3J = 9.0 Hz), 6.70 (d, 2H, ^3J = 9.0 Hz), 7.46 (d, 2H, ^3J = 9.0 Hz), 8.13 (d, 2H, ^3J = 9.0 Hz). The diastereoselectivities and enantioselectivities were determined by HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 80:20, flow rate 1.00 mL/min, λ = 254 nm): t_R (anti major enantiomer, (3*R*,4*R*)-4) = 27.28 min, t_R (anti minor enantiomer, (3*S*,4*S*)-4) = 21.78 min, t_R (syn major enantiomer, (3*S*,4*R*)-4) = 33.03 min, t_R (syn minor enantiomer, (3*R*,4*S*)-4) = 39.60 min.