Tetrahedron Letters 50 (2009) 4854–4856

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Organocatalytic asymmetric *syn*-selective direct aldol reactions in water

Yong-Chua Teo [a,*], Guan-Leong Chua [b], Chin-Yee Ong [b], Chai-Yun Poh [b]

[a] Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616, Singapore
[b] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore

ARTICLE INFO

Article history:
Received 17 February 2009
Revised 25 May 2009
Accepted 5 June 2009
Available online 11 June 2009

ABSTRACT

A practical and convenient organocatalytic strategy is developed to provide a direct route to *syn*-selective aldol products in the presence of water. The siloxy serine organocatalyst mediates the direct aldol reaction of TBSO-protected hydroxyacetone with a variety of aldehydes to provide the aldol products in good yields and enantioselectivities up to 92%.

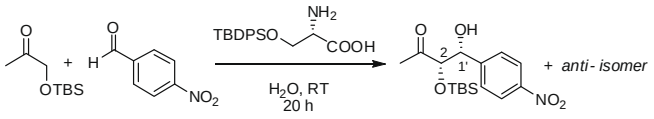
Enantioselective organocatalysis has emerged as a powerful strategy in organic synthesis since it employs small organic molecules that are relatively non-toxic, inexpensive and stable to both air and moisture.[1] The organocatalytic asymmetric direct aldol reaction via enamine intermediates generated in situ is one of the most effective carbon–carbon bond-forming reactions for synthesizing enantiomerically enriched β-hydroxy carbonyl compounds.[2] The potential of this reaction to generate diversity and to construct useful building blocks for pharmaceuticals and natural products has attracted attention from synthetic chemists and the pharmaceutical industry.[3]

Organic reactions in water have attracted significant attention, not only because unique reactivity is often observed in water, but also due to its low-cost, safety and environmentally benign nature.[4] The synthesis of organic molecules via organocatalytic reactions in water[5] is an extensively investigated topic which entails the additional challenges of water tolerance for the catalyst[6] and the associated problem of substrate solubilities and reactivities. Barbas reported the direct asymmetric aldol reaction of ketones and aryl aldehydes in water catalyzed by proline-derived hydrophobic organocatalysts[7] and an amide catalyst derived from threonine that mediated the synthesis of *syn*-aldol products from protected dihydroxyacetone in aqueous media.[8] Hayashi reported that siloxyproline catalyzes effectively the highly diastereo- and enantioselective aldol reaction of ketones and aldehydes in the presence of water,[9] and that a combined proline-surfactant organocatalyst promotes the asymmetric aqueous direct cross-aldol reaction of two different aldehydes.[10] Numerous examples of organocatalytic direct aldol reactions utilizing amino acid derivatives and polymer-supported organocatalysts in the presence of water have been reported.[11,12]

Recently, we reported a siloxy serine organocatalyst that uses a cyclic ketone, predominantly cyclohexanone as the aldol donor, in the presence of water to facilitate the synthesis of *anti*-configured β-hydroxy carbonyl scaffolds.[13] The reaction proceeded via a biphasic system, furnishing a wide variety of aldol products in good yields and excellent enantioselectivities. Based on this precedent and as part of our programme to develop organocatalytic direct aldol reactions to install *syn*-configured 1,2-diols, we investigated protected forms of hydroxyketones as donors. Herein, we report on efficient *syn*-selective syntheses of aldol products based on the protected monohydroxy acetone donors catalyzed by the siloxy serine organocatalyst in the presence of water.

In our initial study, *tert*-butyldimethylsiloxy hydroxyacetone and 4-nitrobenzaldehyde were chosen as model substrates. Using the optimized conditions developed for the previous protocol,[13a]

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



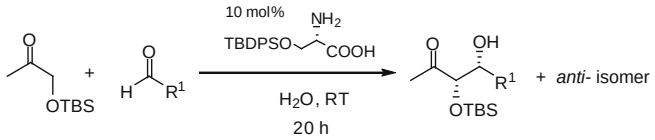
Entry	Cat. loading (mmol %)	H_2O (mL)	Yield[b] (%)	*syn:anti*[c]	ee[d] (%)
1	10	0.1	82	91:9	84
2	10	0.3	83	92:8	88
3	10	0.3	70	91:9	86[e]
4	5	0.3	74	88:12	84

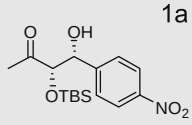
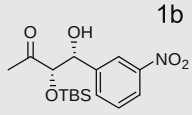
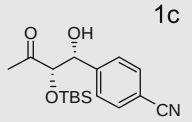
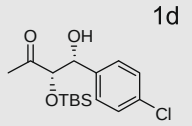
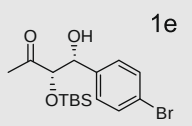
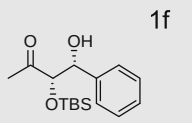
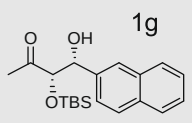
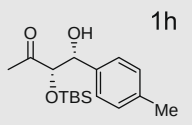
[a] Unless otherwise shown, the reaction was performed with aldehyde (0.5 mmol), ketone (1.0 mmol) and catalyst (0.05 mmol) in H_2O at room temperature for 20 h.
[b] Combined yield of isolated diastereomers.
[c] Diastereoselectivity was determined by ^1H NMR analysis of the reaction mixture.
[d] Enantiomeric excess refers to the *syn* isomer and was determined by HPLC analysis on a chiral phase.
[e] The reaction was performed with 1.1 equiv of ketone donor.

* Corresponding author. Tel.: +65 6790 3846; fax: +65 6896 9414.
E-mail address: yongchua.teo@nie.edu.sg (Y.-C. Teo).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.037

Table 2
The asymmetric direct aldol reaction[a] catalyzed by siloxy-L-serine organocatalyst in water



Entry	Product	Yield[b] (%)	*syn*:*anti*[c] (%)	ee[d] (%)
1		83	92:8	88
2		84	87:13	86
3		90	90:10	90
4		71	84:16	92
5		80	87:13	76
6		62	88:12	92
7		64	81:19	74
8		78	80:20	80[e]

[a] Unless otherwise noted, the reaction was performed with aldehyde (0.5 mmol), ketone (1.0 mmol) and siloxy serine organocatalyst (0.05 mmol) in H_2O (0.3 mL) at room temperature.
[b] Combined yield of isolated diastereomers.
[c] Diastereoselectivity was determined by ^1H 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] Reaction was carried out using 20 mol % catalyst loading.

the direct aldol reaction catalyzed by 10 mol % of the TBDPS-L-serine organocatalyst proceeded in the presence of water to afford the product in a good yield of 82% and enantiomeric excess of 84% (Table 1, entry 1). With an increased amount of water in the reaction mixture, the aldol product was isolated in a comparable yield of 83% and higher enantiomeric excess of 88% (entry 2). To enhance the atom economical value of the current synthetic approach, the reaction was repeated using a reduced amount of the aldol donor. In this experiment, the aldol product was obtained in a good yield of 70% and enantiomeric excess of 86% (entry 3). It is worth noting that the siloxy-L-serine organocatalyst can also catalyze the reaction at 5 mol % catalyst loading, affording the aldol product in good enantiomeric excess, albeit with a slight decrease in yield (entry 4). In summary, the optimum conditions required the use of 10 mol % of the siloxy serine organocatalyst, ketone donor (2 equiv) and water (0.6 ml $mmol^{-1}$) at room temperature for 20 h (entry 2).

A series of aromatic aldehydes were used to explore the generality of this catalytic system and the results are summarized in Table 2. In most cases, the expected β-hydroxy carbonyl compounds were obtained in good yields and high diastereo- and enantioselectivities. The more reactive aldehydes afforded the aldol products in good to excellent enantioselectivities and high *syn*-selectivities (Table 2, entries 1–3). Aldehyde substrates with a *para*-substituted halogen moiety underwent the catalytic process to afford the aldol products in moderate yields and good enantioselectivities (entries 4 and 5). The direct aldol reaction between benzaldehyde and *tert*-butyldimethylsiloxy hydroxyacetone catalyzed by the siloxy-L-serine organocatalyst gave the corresponding product in high enantio- and diastereoselectivity (entry 6). However, only moderate enantioselectivity was obtained in the case of 2-naphthaldehyde as the aldol acceptor (entry 7). The catalytic process was also efficient for a representative aldehyde with a *para*-electron-donating group, affording the product in good yield and enantioselectivity (entry 8). Currently, the catalytic system is limited only to aryl aldehydes as acceptors as we were unable to obtain satisfactory results with aliphatic aldehydes. The stereochemistry of the β-hydroxy group of the aldol adducts derived from the acyclic siloxy-L-serine catalysis was determined as *S* by chiral-phase HPLC analysis and by comparison with the literature.[11]

In conclusion, we have demonstrated an efficient direct asymmetric *syn*-selective aldol reaction between a variety of aromatic aldehydes and *tert*-butyldimethylsiloxy hydroxyacetone as donor in the presence of water, catalyzed by a siloxy-L-serine organocatalyst.[14] Features worth noting include (1) the direct aldol reaction proceeded efficiently in the presence of water to afford a variety of valuable compounds from commercially available substrates; (2) the procedure is simple to perform and requires mild conditions; (3) the siloxy-L-serine organocatalyst is prepared easily and economically from commercially available sources, with both enantiomers readily available; (4) a 5 mol % catalyst loading is sufficient to furnish the aldol products in good yields and enantioselectivities. Further extension of the siloxy serine organocatalyst to other asymmetric reactions is ongoing in our laboratory and the results will be reported in due course.

Acknowledgements

We would like to thank the National Institute of Education (RP5/06 TYC), Nanyang Technological University for their generous financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.037.

References and notes

1. (a) Alexakis, A.; Bernardinelli, G.; Andrey, O. *Org. Lett.* **2003**, *5*, 2559; (b) Barbas, C. F., III; Chowdari, N. S.; Suri, J. T. *Org. Lett.* **2004**, *6*, 2507; (c) Northrup, A. B.; Mangion, I. K. F.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4138; (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (e) List, B. *Chem. Commun.* **2006**, 819; (f) Berkssel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005; (g) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001; (h) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79; (i) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8; (j) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416; (k) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471; (l) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; (m) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. *Chem. Rev.* **2007**, *107*, 5759.
2. (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352; (b) Sathivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260; (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798; (d) List, B. *Tetrahedron* **2002**, *28*, 5573; (e) Suzuki, N.; Hayashi, Y.; Shoji, M.; Tsuboi, W. *J. Am. Chem. Soc.* **2003**, *125*, 11208; (f) Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; (g) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580; (h) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65; (i) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 1383; (j) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249; (k) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471; (l) Schwab, R. S.; Galetto, F. Z.; Azeredo, J. B.; Braga, A. L.; Lüdtke, D. S.; Paixão, M. W. *Tetrahedron Lett.* **2009**, *49*, 5094.
3. (a) Trost, B. M. *Science* **1991**, *254*, 147; (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259; (c)*Modern Aldol Reactions*; Marhrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vols. 1–2, (d) Kim, B. M.; Williams, S. F.; Masamune, S.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2,.
4. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159; (b) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219; (c)*Organic Synthesis in Water*; Grieco, P., Ed.; Blackie: London, 1998; (d) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751; (e) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209; (f) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (g) Pirrung, M. C. *Chem. Eur. J.* **2006**, *12*, 1312. and references cited therein.
5. (a) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093; (b) Palomo, C.; Vera, S.; Mielgo, A.; Gomez Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984; (c) Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559; (d) Mosse, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577; (e) Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135; (f) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599; (g) Barros, M. T.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2007**, 178; (h) Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.
6. Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221.
7. Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734.
8. Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas, C. F., III *Org. Lett.* **2008**, *10*, 1621.
9. Hayashi, Y.; Sumiya, T.; Takashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958.
10. Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527.
11. (a) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586; (b) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sundén, H.; Córdova, A. *Chem. Commun*, **2005**, 4946; (c) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103; (d) Mase, N.; Wattanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966; (e) Jiang, Z.-Q.; Liang, Z.; Wu, X.-Y.; Lu, Y.-X. *Chem. Commun.* **2006**, 2801; (f) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383; (g) Dziedzic, P.; Zou, W.; Ibrahem, I.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 6657; (h) Chimni, S. S.; Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108; (i) Dziedzic, P.; Zou, W.; Hffren, J.; Cordova, A. *Org. Biomol. Chem.* **2006**, *4*, 38; (j) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687; (k) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417; (l) Guillena, G.; Hita, M. D. C.; Tjera, C. N. *Tetrahedron: Asymmetry* **2006**, *17*, 1493; (m) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317; (n) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653; (o) Guilenna, G.; Hita, M. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 729; (p) Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 3351; (q) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247; (r) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957; (s) Wu, X.; Jiang, Z.; Shen, M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812; (t) Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 4710; (u) Huang, J. M.; Zhang, X. T.; Armstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073; (v) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593; (w) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Tetrahedron* **2007**, *63*, 1923; (x) Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R. *Tetrahedron Lett.* **2007**, *48*, 255; (y) Amedjkouh, M. *Tetrahedron: Asymmetry* **2007**, *18*, 390.
12. (a) Gryko, D.; Saletra, W. J. *Org. Biomol. Chem.* **2007**, *5*, 2148; (b) Wang, C.; Jiang, Y.; Zhang, X.; Huang, Y.; Li, B.; Zhang, G. *Tetrahedron Lett.* **2007**, *48*, 4281; (c) Aratake, S.; Itoh, T.; Okano, T.; Usui, T.; Shoji, M.; Hayashi, Y. *Chem. Commun.* **2007**, *24*, 2524; (d) Chen, X.-H.; Luo, S.-W.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Chem. Eur. J.* **2007**, *13*, 689; (e) Carrie, E. A.; Scott, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 256; (f) Nagamine, T.; Inomata, K.; Enso, Y.; Paquette, L. A. *J. Org. Chem.* **2007**, *72*, 123.
13. (a) Teo, Y.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 1155; (b) Teo, Y.-C.; Lau, J.-J.; Wu, M.-C. *Tetrahedron: Asymmetry* **2007**, *19*, 186; (c) Teo, Y.-C.; Chua, G.-L. *Tetrahedron Lett.* **2008**, *49*, 4235.
14. *Representative procedure for the direct asymmetric aldol reaction*: A catalytic amount of siloxyserine (0.05 mmol, 0.1 equiv) was added to a vial containing the aldehyde (0.5 mmol, 1.0 equiv), *tert*-butyldimethyl-siloxyhydroxyacetone (1.0 mmol, 2.0 equiv) and water (0.3 mL) under air in a closed system. The reaction mixture was stirred at room temperature for 20 h and subsequently poured into an extraction funnel containing brine (5 mL) and water (5 mL). The reaction vial was also washed with ethyl acetate (5 mL). 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, 9:1) to afford the product. The diastereomeric *anti*-*syn* ratio for **1a** was determined by ^{1}H NMR analysis of the crude reaction mixture: δ 4.17 (d, 1H, J = 2.8 Hz, *syn*, major), 4.10 (d, 1H, J = 6.2 Hz, *anti*, minor). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/*i*-PrOH = 90:10, 0.5 mL/min, λ = 254 nm, 20 °C): t_R = 14.5 min (minor) and 15.7 min (major).