Tetrahedron Letters 50 (2009) 2946–2948

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Enatioselective organocatalytic synthesis of highly functionalized tetrahydrothiophenes by a Michael-aldol cascade reaction

Guangshun Luo [a], Shilei Zhang [a], Wenhu Duan [a,b,*], Wei Wang [a,b,c,*]

[a] Department of Pharmaceutical Science, School of Pharmacy, East China University of Science & Technology, Shanghai 200237, People's Republic of China
[b] Shanghai Institute of Materia Medica, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Graduate School of the Chinese Academy of Sciences, Shanghai 201203, People's Republic of China
[c] Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, NM 87131-0001, USA

ARTICLE INFO

Article history:
Received 4 March 2009
Revised 19 March 2009
Accepted 31 March 2009
Available online 5 April 2009

Keywords:
Cascade reactions
Michael-aldol
Organocatalysis
Tetrahydrothiophenes

ABSTRACT

A catalytic asymmetric Michael-aldol cascade process for efficient synthesis of trisubstituted tetrahydrothiophenes is reported with high enantio- and diastereo-selectivities. Notably, three consecutive stereogenic centers including one chiral quaternary carbon center are efficiently created in the 'one-pot' operation.

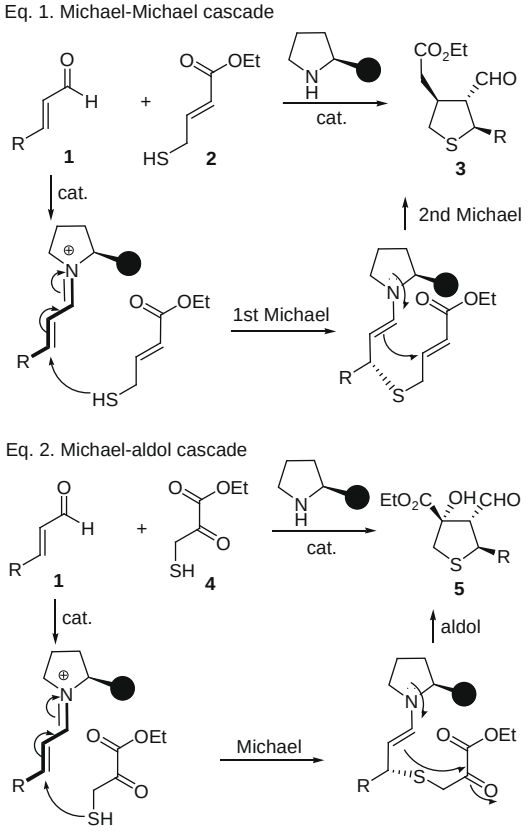
The development of new cascade strategies for the efficient construction of biologically important complex molecular architectures remains a challenging goal in modern organic synthesis.[1,2] Substituted tetrahydrothiophenes display a broad spectrum of intriguing biological activities, ranging from the essential enzyme cofactor,[3] potent CCK,[4] HIV,[5] copper amine oxidase inhibitors,[6] hypocholesterolemic agent,[7] or plant growth regulators.[8] Given the importance of this scaffold, however, very few asymmetric methods have been reported.[9] In this Letter, we wish to disclose a recent investigation, which has resulted in a new organocatalytic, enantioselective cascade Michael-aldol reaction. The process affords highly functionalized tetrahydrothiophenes with high enantioselectivities (91–97%) and good diastereoselectivity (8:1 to >20:1) from simple achiral substances despite relatively low yields (25–59%). Significantly, in the cascade sequence, new C–S and C–C bonds are created with forming a chiral quaternary carbon.

Recently we have developed a series of organocatalyzed enantioselective cascade processes for 'one-pot' assembly of complex molecules.[10,11] The motivation of this investigation came from our recent study in exploring double Michael addition reactions catalyzed by (*S*)-diphenylprolinol TMS ether for the synthesis of functionalized chiral tetrahydrothiophenes **3** (Scheme 1, Eq. 1).[10f] To generate the stereochemical and functional diversity based on the important scaffold, we envisioned that employing 3-mercapto α-carbonyl esters **4** instead of ethyl 4-mercapto-2-butenoate **2** could create a novel thia-Michael-aldol cascade (Eq. 2). Such cascade would produce products **5** with new structural components. A chiral quaternary carbon center and a new α-hydroxy ester group were efficiently assembled in 'one-pot' operation. It is noted that the construction of chiral quaternary carbons has long been a challenge in organic synthesis.

To explore the possibility of the proposed cascade Michael-aldol process, we carried out a model reaction between *trans*-cinnamaldehyde **1a** and ethyl 3-mercapto-2-oxopropanoate **4** in toluene at rt in the presence of an organocatalyst (Fig. 1 and Table 1). Screening of organocatalysts revealed that (*S*)-diarylprolinol silyl ethers **II**, **III**, and **VI** (Table 1, entries 2, 3, and 6) afforded promising results in terms of reaction yields (46–71%) and enantioselectivity (82–87% ee).[12] Nevertheless, low catalytic activities were observed with other pyrrolidine derivatives (entries 1, 4, 5, and 7–10). We decided to choose catalyst **VI** for further optimization of the reaction conditions. Investigation of solvent effect indicated that the use of a mixture of CH_2Cl_2 and H_2O was the optimal for the process (entry 11). The water helped to slightly improve the reaction yield (49% yield vs 55% yield, entries 11 and 12) without compromising ee and dr presumably owing to the minimization of by-products formed. It

* Corresponding authors. Tel.: +86 21 5080 6032 (W.D.); tel.: +1 505 277 0756; fax: +1 505 277 2609 (W.W).
E-mail addresses: wduan@mail.shcnc.ac.cn (W. Duan), wwang@unm.edu (W. Wang).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.218



Scheme 1. Organocatalytic asymmetric thia-Michael-initiated cascade reactions.

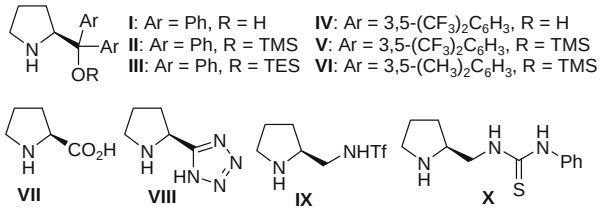
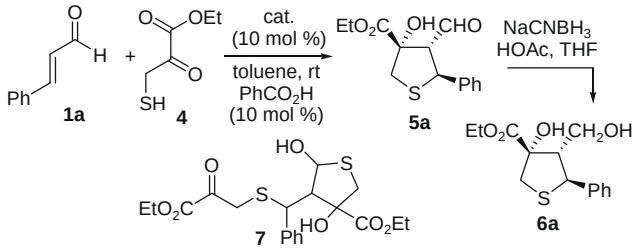


Figure 1. Structures of organocatalysts screened.

was found that the use of 10 equiv of water was optimal.[13] The improvement of both enantioselectivity (95% ee) and diastereoselectivity (11:1 dr) (entry 13) was achieved when catalyst loading was reduced to 5 mol %. No further gain was observed when the catalyst loading was reduced to 1 mol % (entry 14). It should be pointed out that the low reaction yield of the Michael-aldol cascade process resulted from a significant amount of by-product **7** (10–20%), which was formed from a three-component reaction. In addition, unidentified oligomers were found. It is noteworthy that the reduction of the aldehyde (**5a**) to alcohol (**6a**) was necessary for convenient chiral HPLC analysis with good resolution.

With the optimized reaction conditions in hand, we next probed the scope of asymmetric Michael-aldol cascade reaction promoted by **VI**. The new methodology provides a facile access to a range of trisubstituted tetrahydrothiophenes **6** in high enantiomeric excess (91–97% ee) and high diastereoselectivities

Table 1
Organocatalytic asymmetric cascade thia-Michael-adol reaction of 3-phenylpropenal (**1a**) with ethyl 3-mercapto-2-oxopropanoate (**4**)[a]



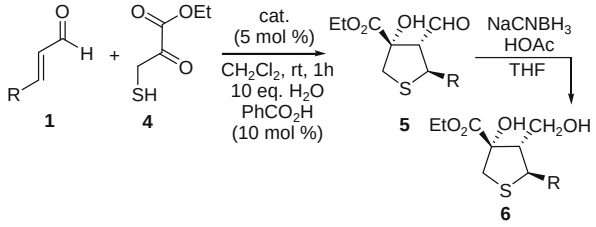
Entry	Cat	*t* (h)	Yield[b] (%)	ee[c] (%)	dr[d]
1	**I**	22	10	0	8:1
2	**II**	3.5	46	83	7:1
3	**III**	1	71	82	9:1
4	**IV**	96	<5	Nd[e]	Nd[e]
5	**V**	96	<5	Nd[e]	Nd[e]
6	**VI**	1	66	87	7:1
7	**VII**	3	<5	Nd[e]	Nd[e]
8	**VIII**	96	<5	Nd[e]	Nd[e]
9	**IX**	3	53	−6	10:1
10	**X**	96	32	−32	6:1
11[f]	**VI**	1	49	92	10:1
12[g]	**VI**	1	55	92	10:1
13[g,h]	**VI**	1	42	95	11:1
14[g,i]	**VI**	24	29	95	10:1

[a] Reaction conditions: unless specified, to a mixture of *trans*-cinnamaldehyde (**1a**) (0.135 mmol), 10 mol % catalyst, benzoic acid (0.1 equiv) in toluene (0.5 mL) was added 3-mercapto-2-oxopropanoate (**4**) (0.135 mol) in one portion. The reaction mixture was stirred at rt for a specified time. The aldehyde was directly reduced to alcohol for chiral HPLC analysis.
[b] Isolated yield for two steps.
[c] Determined by chiral HPLC analysis (Chiralpak AD-H) after reduced by $NaCNBH_3$.
[d] Determined by ^1H NMR.
[e] Not determined.
[f] CH_2Cl_2 as a solvent.
[g] CH_2Cl_2 as a solvent and H_2O (10 equiv) added.
[h] 5 mol % catalyst used.
[i] 1 mol % catalyst used.

(8:1 to >20:1 dr) (Table 2). The cascade processes were tolerant of a variety of Michael acceptors *trans*-3-arylpropenals **1**, which possess electron-neutral (entry 1), withdrawing (entries 2–7), donating (entries 8 and 11), a combination of withdrawing-donating (entries 9 and 10), and heteroaromatic (entry 12) groups. It appeared that the steric effect imposed by these substituents (entries 3, 7, and 11) in **1** on the process was also limited. The limitation of the cascade process was also realized. A complicated reaction mixture was obtained when aliphatic α,β-unsaturated aldehydes were employed. The absolute configuration of **6b** is determined based on X-ray crystal structure analysis (Fig. 2).[14]

In conclusion, we have developed a novel and simple organocatalytic thiol initiated cascade Michael-aldol reaction between a variety of derivatives of cinnamic aldehydes and 3-mercapto-2-oxopropanoate. The process, efficiently catalyzed by readily available (*S*)-di(3,5-dimethylphenyl)prolinol TMS ether, furnishes highly functionalized chiral tetrahydrothiophenes with generation of three new consecutive stereogenic centers including a chiral quaternary carbon center in high enantioselectivities and high stereoselectivities in 'one-pot' transformation. The reaction conditions are mild and practical. Further investigation is underway to expand the scope and application of this efficient cascade process.

Table 2
Scope of catalyst **VI** catalyzed asymmetric thia-Michael aldol cascade reactions of enals (**1**) with ethyl 3-mercapto-2-oxopropanoate (**4**)[a]



Entry	R	Yield[b] (%)	ee[c] (%)	dr[d]
1	Ph	**6a**, 42	95	10:1
2	4-BrC_6H_4	**6b**, 34	93	12:1
3	2-BrC_6H_4	**6c**, 31	92	8:1
4	4-FC_6H_4	**6d**, 46	94	13:1
5	4-$NO_2C_6H_4$	**6e**, 25	94	>20:1
6	3-$NO_2C_6H_4$	**6f**, 25	93	>20:1
7	2-$NO_2C_6H_4$	**6g**, 37	91	9:1
8	4-MeOC_6H_4	**6h**, 57	97	12:1
9	3,4-$(MeO)_2C_6H_3$	**6i**, 41	97	>20:1
10	3,4-$(OCH_2O)C_6H_3$	**6j**, 51	97	>20:1
11	2-MeOC_6H_4	**6k**, 47	97	>20:1
12	2-Furanyl	**6l**, 59	93[e]	>20:1

[a] Unless stated otherwise, see Supplementary data.
[b] Isolated yield for two steps.
[c] Determined by chiral HPLC analysis (Chirapak AD, AS or chiralcel OJ-H column).
[d] Determined by ^{1}H NMR.
[e] Determined by converting to corresponding α,β-unsaturated ester with triethyl phosphonacetic acid.

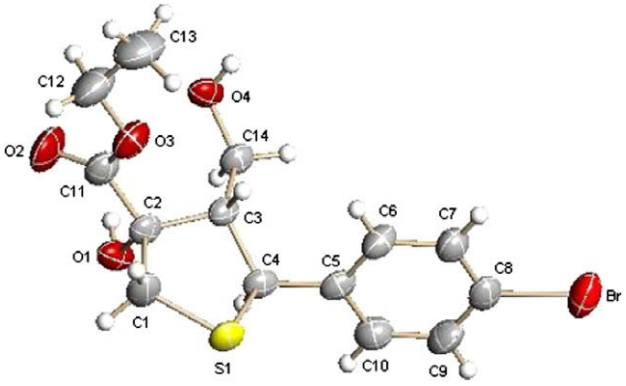


Figure 2. X-ray crystal structure of **6b**.

Acknowledgments

We are grateful for the financial support from School of Pharmacy, East China University of Science and the National Science Foundation of China (Nos. 03772648 and 30721005), and the Chinese National Programs for High Technology Research and Development (Nos. 2006AA020602 and 2007AA02Z147).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.218.

References and notes

1. For recent reviews of cascade reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (b) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967; (c) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (d) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354; (e) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143; (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.
2. For recent reviews of organocatalytic cascade reactions, see: (a) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570; (b) Yu, X.-H.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2036.
3. De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.
4. Page, P. C. B.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett* **2003**, 1022.
5. Wirsching, J.; Voss, J.; Adiwidjaja, G.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1049.
6. Qiao, C.; Ling, K.-Q.; Shepard, E. M.; Dooley, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2006**, *128*, 6206.
7. Smith, A. B., III; Empfield, J. R. *Chem. Pharm. Bull.* **1999**, *47*, 1671.
8. Tsygoanko, V. A.; Blume, Y. B. *Biopolim. Kletka* **1997**, *13*, 484.
9. (a) Dehmlow, E. V.; Westerheide, R. *Synthesis* **1992**, *10*, 947; (b) Rao, A. V. R.; Reddy, K. A.; Srinivas, N. R.; Gurjar, M. K.; Padmaja, N.; Ramakumar, S.; Viswamitra, M. A.; Swapna, G. V. T.; Jagannadh, B.; Kunwar, A. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1255; (c) Popsavin, V.; Beric, O.; Velimirovic, S.; Miljkovic, D. *J. Serb. Chem. Soc.* **1993**, *9*, 717; (d) Ponce, A. M.; Overman, L. E. *J. Am. Chem. Soc.* **2000**, *122*, 8672; (e) Desmaele, D.; Delarue-Cochin, S.; Cave, C.; Angelo, J.; Morgant, G. *Org. Lett.* **2004**, *6*, 2421; (f) Barco, A.; Baricordi, N.; Benetti, S.; De Risi, C.; Pollini, G. P. *Tetrahedron Lett.* **2006**, *47*, 8087; (g) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986.
10. (a) Li, H.; Zu, L.-S.; Xie, H.-X.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636; (b) Wang, J.; Xie, H.-X.; Li, H.; Zu, L.-S.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177; (c) Zu, L.-S.; Xie, H.-X.; Li, H.; Wang, J.; Yu, X.-H.; Wang, W. *Eur. Chem. J.* **2008**, *14*, 6333; (d) Zu, L.; Xie, H.; Li, H.; Wang, J.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882; (e) Wang, J.; Li, H.; Xie, H.; Zhu, L.; Shen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9050; (f) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833; (g) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036; (h) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965; (i) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354; (j) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2006**, 507.
11. For recent selected examples, see: (a) Zhong, C.; Chen, Y.; Petersen, L.; Akhmedov, N. G.; Shi, X.-D. *Angew. Chem., Int. Ed.* **2009**, *48*, 1279; (b) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539; (c) Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 4585; (d) Dodda, R.; Goldman, J. J.; Mandal, T.; Zhao, C.-G.; Broker, G. A.; Tiekink, E. R. T. *Adv. Synth. Catal.* **2008**, *350*, 537; (e) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012; (f) de Figueiredo, R. M.; Froelich, R.; Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1450; (g) Vo, N. T.; Pace, R. D.; O'Hara, M. F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404; (h) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336; (i) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922; (j) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498; (k) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168; (l) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *47*, 1101; (m) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830; (n) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256; (o) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. *Org. Lett.* **2007**, *9*, 4151; (p) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861; (q) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683; (r) Wang, Y.; Liu, X.-F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928; (s) Huang, Y.; Walji, M. C.; Larsen, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051; (t) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036; (u) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962; (v) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S.; Barbas, C. F., III *J. Org. Chem.* **2004**, *69*, 5838; (w) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2003**, *42*, 4233.
12. For reviews of diaryl prolinol ethers catalysis, see: (a) Vicario, J. L.; Reboredo, S.; Badia, D.; Carrello, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168; (b) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876; (c) Mielgo, A.; Palomo, C. *Chem. Asian. J.* **2008**, *3*, 922.
13. One equivalents of water: 49% yield, 90% ee; 10:1 dr; 2.0 equiv of water: 48% yield, 91% ee; 10:1 dr; 20.0 equiv of water: 42% yield, 91% ee; 10:1 dr.
14. CCDC 723406 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk.