J|A|C|S
ARTICLES
Published on Web 10/28/2006

Asymmetric Synthesis of Highly Functionalized Tetrahydrothiophenes by Organocatalytic Domino Reactions

Sven Brandau, Eddy Maerten, and Karl Anker Jørgensen*

Contribution from the Danish National Research Foundation, Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Received July 31, 2006; E-mail: kaj@chem.au.dk

Abstract: A simple approach for the formation of optically active highly functionalized tetrahydrothiophenes, which might find important use in biochemistry, pharmaceutical science, and nanoscience is presented. Development of new organocatalytic Michael−aldol domino reactions is outlined, and with the appropriate choice of additives it is possible to control the regioselectivity of these domino reactions, yielding diastereomerically pure (tetrahydrothiophen-2-yl)phenyl methanones or tetrahydrothiophene carbaldehydes in good yields and with excellent enantioselectivities up to 96% ee. The stereochemical outcome of these reactions is investigated, and the mechanism of these organocatalytic domino processes is presented.

Introduction

Substituted tetrahydrothiophenes and optically active tetrahydrothiophenes are endowed with a large spectrum of biological activities, ranging from the essential coenzyme biotin,[1] inhibitor of copper amine oxidases,[2] antioxidant activities,[3] leukotriene antagonism,[4] or plant growth regulations.[5] Tetrahydrothiophenes have been also used as building blocks for new chiral ligands in asymmetric metal catalysis[6] and organocatalysis[7] and in natural product synthesis.[8] In addition, adsorption and properties of the related achiral, aromatic thiophenes on gold surfaces are well known[9] for their benefit for the synthesis of gold nanoparticles.[10] More recently chiral sulfur compounds have also shown new and interesting properties when adsorbed to Au(110) surfaces.[11] Investigations of chiral tetrahydrothiophenes in these research areas are just beginning, and the properties of functionalized chiral tetrahydrothiophenes will probably provide new advantages and possibilities in these fields. Despite their high benefits in numerous applications, very few examples for asymmetric synthesis have been developed yet.[12]

Asymmetric domino reactions have become a powerful tool for the synthetic chemist building up efficient complex cyclic and acyclic molecules in an easy way.[13] They can form multiple stereogenic centers and fulfill in an exemplary manner one demand of modern organic synthesis, namely, minimizing the number of manual operations and purifications in a synthetic sequence.[14] However, during the past few years the field of asymmetric domino reactions has been dominated by metal catalysis,[15] and only few examples have been published using organocatalysis.[16] Organocatalysis is usually a nontoxic, metal-free, and selective powerful approach for the preparation of important optically active building blocks; therefore, the field of organocatalysis is a rapidly progressing area with a large number of new asymmetric reactions.[17,18]

(1) (a) Imwinkelried, R. *Chimia* **1997**, *51*, 300. (b) Begley, T. P. *Nat. Prod. Rep.* **2006**, *23*, 15. (c) Zempleni, J. *Annu. Rev. Nutr.* **2005**, *25*, 175. (d) Ward, T. R. *Chem.—Eur. J.* **2005**, *11*, 3798. (e) Fernandez-Mejia, C. *J. Nutr. Biochem.* **2005**, *16*, 424.
(2) Qiao, C.; Ling, K.-Q.; Shepard, E. M.; Dooley, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2006**, *128*, 6206 and references therein.
(3) Kato, T.; Tsuzuki, K. Patent Application JP 1992-147881, CAN 120: 106750; 1992.
(4) Chorghade, M. S.; Gurjar, M. K.; Palakodety, R. K.; Lalitha, S. V. S.; Sadalapure, K.; Adhikari, S. S.; Murugaiah, A. M. S.; Rao, B. V.; Talukdar, A.; Talukdar, A.; Islam, A. Hariprasad, C.; Rao, A. V. R. Patent Application WO 1999-US15050, CAN 132:93203; 1999.
(5) Tsygoanko, V. A.; Blume, Y. B. *Biopolim. Kletka* **1997**, *13*, 484.
(6) (a) Mukaiyama, T.; Asanuma, H.; Hachiya, I.; Harada, T.; Kobayashi, S. *Chem. Lett.* **1991**, *7*, 1209. (b) Hauptman, E.; Shapiro, R.; Marshall, W. *Organometallics* **1998**, *17*, 4976.
(7) See, for example: (a) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222. (b) Li, A.-H.; Dai, L. X.; Hou, X. L.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem.* **1996**, *61*, 489. (c) Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532. (d) Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731. (d) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620. (e) Zanardi, J.; Lamazure, D.; Miniere, S.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2002**, *67*, 9083.
(8) Williams, D. R.; Jass, P. A.; Tse, H. L. A.; Gaston, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4552.
(9) (a) Higai, S.; Nara, J.; Ohno, T. *Surf. Sci.* **2006**, *600*, 685. (b) Sako, E.; Kondoh, H.; Nakai, I.; Nambu, A.; Nakamura, T.; Ohta, T. *Chem. Phys. Lett.* **2005**, *413*, 267. (c) Nagamatsu, S.; Kaneto, K.; Azumi, R.; Matsumoto, M.; Yoshida, Y.; Yase, K. *J. Phys. Chem. B* **2005**, *109*, 9374. (d) Noh, J.; Ito, E.; Nakajima, K.; Kim, J.; Lee, H.; Hara, M. *J. Phys. Chem. B* **2002**, *106*, 7139. (e) Liu, G.; Rodriguez, J. A.; Dvorak, J.; Hrbek, J.; Jirsak, T. *Surf. Sci.* **2002**, *505*, 295.
(10) Huang, H.; Yang, X. *Colloids Surf. A, Physicochem. Eng. Aspects* **2005**, *255*, 11.
(11) (a) Kühnle, A.; Linderoth, T.; Hammer, B.; Besenbacher, F. *Nature* **2002**, *415*, 891. (b) Kühnle, A.; Linderoth, T.; Besenbacher, F. *J. Am. Chem. Soc.* **2003**, *125*, 14680.
(12) (a) Ponce, A. M.; Overman, L. E. *J. Am. Chem. Soc.* **2000**, *122*, 8672. (b) Desmaële, D.; Delarue-Cochin, S.; Cavé, C.; d'Angelo, J.; Morgant, G. *Org. Lett.* **2004**, *6*, 2421. (c) Popsavin, V.; Beric, O.; Velimirovic, S.; Miljkovic, D. *J. Serb. Chem. Soc.* **1993**, *9*, 717. (d) 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. (e) Dehmlow, E. V.; Westerheide, R. *Synthesis* **1992**, *10*, 947.
(13) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (d) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (e) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (f) Pellisier, H. *Tetrahedron* **2006**, *62*, 2143. (g) Nicolaou, K. C.; Montagnon, T.; Synder, S. A. *Chem. Commun.* **2003**, 551.
(14) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
(15) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.

10.1021/ja065507+ CCC: $33.50

Here we report the development of a new organocatalytic Michael−aldol domino reaction for the synthesis of diastereo- and enantiomerically pure tetrahydrothiophenes, building up highly functionalized tetrahydrothiophenes with three stereocenters in one step. We will present how the regioselectivity can be controlled, leading to formation of different tetrahydrothiophenes, namely, tetrahydrothiophene carbaldehydes **1** or (tetrahydrothiophen-2-yl)phenyl methanones **2**, by the appropriate choice of simple additives to the organocatalytic system (Scheme 1). The common intermediate **3** for both tetrahydrothiophenes is synthesized by the first reaction in this domino reaction, a Michael addition of a nucleophilic thiol **5**[19] to different aliphatic α,β-unsaturated aldehydes **4**.

Results and Discussion

Acid-Catalyzed Domino Reactions. The organocatalytic Michael−aldol domino reaction of thiol **5** with different aliphatic α,β-unsaturated aldehydes **4** was first investigated under acidic conditions. The enantioselective formation of tetrahydrothiophene carbaldehydes **1** was initially developed by reaction of (*E*)-4-methylpent-2-enal **4a** and 2-mercapto-1-phenylethanone **5** in different solvents in the presence of the L-proline derivative (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]-pyrrolidine (*S*)-**6**[20] as the catalyst (Table 1).

The reaction performed well in toluene at room temperature (Table 1, entry 1), yielding the tetrahydrothiophene carbaldehyde **1a** in 40% overall yield and 92% ee as a single regio- and diastereomer. Spectroscopic experiments revealed that the domino reaction of (*E*)-4-methylpent-2-enal **4a** and 2-mercapto-1-phenylethanone **5** needs 5 days for completion. It turned out that in the presence of benzoic acid, the reaction time is shortened from 5 to 2 days without any loss of selectivity in **1a**, which is obtained now in 56% yield and 94% ee as a single isomer (entry 2). Screening of different solvents in Table 1 showed that the reaction gave the highest yield and enantioselectivity of the desired product **1** in aromatic solvents (entries 2−4). Using *n*-pentane, product **1a** was formed in a good yield of 63% over two steps but in slightly lower enantioselectivity (entry 5). Decomposition products were detected in polar, aprotic solvents; therefore, the desired tetrahydrothiophene **1a** was obtained in lower yields (entry 6−10). The enantioselectivity of **1a** in these solvents was between 10% and 80% ee, showing that conjugate addition of the thiol to the α,β-unsaturated aldehyde is accomplished in a more nonstereoselective way than in nonpolar solvents. Performing the reaction in H_2O (entry 11), we observe formation of two regioisomers, the tetrahydrothiophene carbaldehyde **1a** in 26% yield and 96% ee and the (tetrahydrothiophen-2-yl)phenyl methanone **2a** in 16% yield

(16) For selected organocatalytic domino reactions involving conjugate additions, see, for example: (a) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature (London)* **2006**, *441*, 861. (b) Eder, U.; Sauer, G.; Wichert, R. *Angew. Chem.* **1971**, *83*, 492. (c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (d) Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S. J.; Barbas, C. F., III *J. Am. Chem. Soc.* **1997**, *119*, 8131. (e) List, B.; Lerner, R. A.; Barbas, C. F., III *Org. Lett.* **1999**, *1*, 59. (f) Bui, T.; Barbas, C. F., III *Tetrahedron Lett.* **2000**, *41*, 6951. (g) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2003**, *5*, 4301. (h) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (i) Pukkinen, J.; Aburel, P. S.; Halland, N.; Jørgensen, K. A. *Adv. Synth. Catal.* **2004**, *346*, 1077. (j) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (k) Huang, Y.; Walji, A.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (l) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (m) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (n) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (o) Sundén, H.; Ibrahem, I.; Erikson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877. (p) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354.

(17) For recent reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) *Acc. Chem. Res.* **2004**, *37* (8), special issue on organocatalysis.

(18) For some recent feature articles of enamine- and imine-catalysis, see, for example: (a) List, B. *Chem. Commun.* **2006**, 819. (b) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. For application of enamine catalysis in Michael additions, see, for example: (c) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253. (d) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598. (e) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (f) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077. (g) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093. (h) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (i) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966. For application of enamine catalysis in Mannich reactions, see, for example: (j) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 1040. (k) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (l) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (m) Enders, D.; Grondal, C.; Vrettou, M. *Angew. Chem., Int. Ed.* **2005**, *117*, 4147. For application of enamine catalysis in fluorinations, see, for example: (n) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991. (o) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (p) Steiner, D. D.; Mase, N.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2005**, *44*, 3706. (q) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (r) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chem.−Eur. J.* **2006**, *12*, 6039. For application of enamine catalysis in chlorinations, see, for example: (s) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (t) Halland, N.; Braunton, A.; Bachmann, S.; Marigo. M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (u) Halland, N.; Lie, M. A.; Kjærsgaard, A.; Marigo, M.; Schiøtt, B.; Jørgensen, K. A. *Chem.−Eur. J.* **2005**, *11*, 7083. (v) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507. For application of enamine catalysis in brominations, see, for example: (w) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821. For application of enamine catalysis in sulfenylations, see, for example: (x) Wang, J.; Li, H.; Mei, Y.; Lou, B.; Xu, D.; Xie, D.; Gou, H. Wang, W. *J. Org. Chem.* **2005**, *70*, 5678. (y) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. For application of enamine catalysis in oxygenations, see, for example: (z) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (aa) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (ab) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293. (ac) Kumarn, S.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Lett.* **2005**, *7*, 4189. (ad) Cordova, A.; Sunden, H.; Enqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914. (ae) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317. For application of enamine catalysis in hydroxyaminations, see, for example: (af) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046. For application of enamine catalysis in alkylations, see, for example: (ag) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450. For applications of iminium-ion catalysis in cycloadditions, see, for example: (ah) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240. (ai) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616. For applications of iminium-ion catalysis in reductions, see, for example: (aj) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32. For applications of iminium-ion catalysis in Mukaiyama−Michael reactions, see, for example: (ak) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. For applications of iminium-ion catalysis in Michael reactions, see, for example: (al) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897. (am) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955. (an) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66 and references therein.

(19) (a) Wilde, R. G.; Billheimer, J. T.; Germain, S. J.; Hausner, E. A.; Meunier, P. C.; Munzer, D. A.; Stoltenberg, J. K.; Gillies, P. J.; Burcham, D. L.; Huang, S.-M.; Klaczkiewicz, J. D.; Ko, S. S.; Wexler, R. R. *Bioorg. Med. Chem.* **1996**, *4*, 1493. (b) Vedejs, F.; Eberlein, T. H.; Varic, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445. (c) Vedejs, F.; Eberlein, T. H.; Mazur, D. J.; McClure, C.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556.

(20) Recent examples using catalyst **6**, see, for example: (a) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6964. (b) Marigo, M.; Fránzen, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 4790. For application of **6** in enamine-catalyzed reactions, see: (c) Fránzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (d) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (e) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (f) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804. (g) Ibrahem, I.; Zhao, G.-L.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 4659.

Scheme 1. Domino Reactions to Chiral Tetrahydrothiophenes

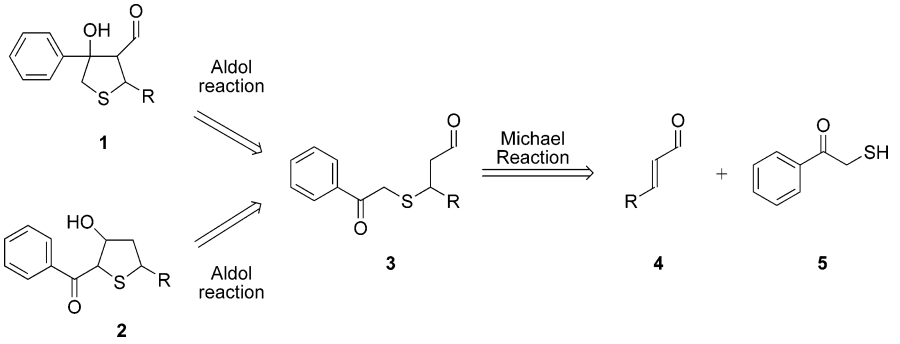
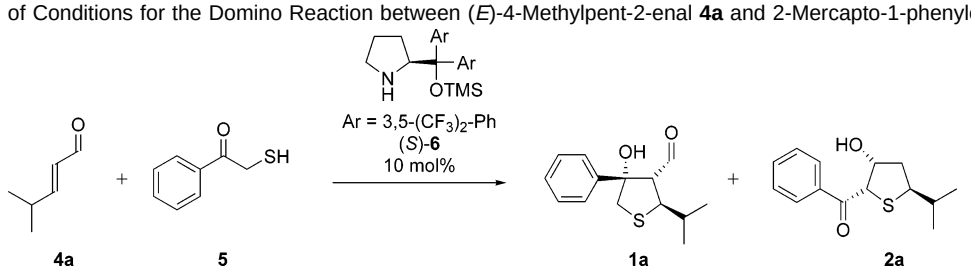


Table 1. Screening of Conditions for the Domino Reaction between (*E*)-4-Methylpent-2-enal **4a** and 2-Mercapto-1-phenylethanone **5**[a]



entry	additive	solvent	yield **1a** (%)[b]	ee (%)[c]	yield **2a** (%)[b]	ee(%)[d]
1[e]		toluene	40	92		
2[f]	$PhCO_2H$	toluene	56	94		
3	$PhCO_2H$	*o*-xylene	54	93		
4	$PhCO_2H$	benzene	57	95		
5	$PhCO_2H$	*n*-pentane	63	92		
6	$PhCO_2H$	CH_2Cl_2	9	76		
7	$PhCO_2H$	THF	30	10		
8	$PhCO_2H$	DCE	17	80		
9	$PhCO_2H$	Et_2O	24	60		
10	$PhCO_2H$	DME	20	37		
11	$PhCO_2H$	H_2O	26	96	16	80

[a] All reactions were performed on a 0.25 mmol scale at room temperature for 2 days. [b] Yield of isolated product. [c] Determined by chiral HPLC after reduction to the corresponding alcohol (see below). [d] Determined by chiral HPLC. [e] Five days reaction time. [f] At 0 °C we obtained under these reaction conditions **1a** in 54% yield with 95% ee; at 50 °C we observe partial decomposition.

and 80% ee. Each regioisomer is formed as a single diastereomer. Formation of the second regioisomer will be explained in detail in the mechanistic section. However, avoiding the toxicity of benzene and the harsh conditions to remove *o*-xylene in the crude products, we decided to use toluene as solvent for further investigations.

The reaction is general for aliphatic α,β-unsaturated aldehyde bearing different groups (Table 2). Excellent enantioselectivities were obtained for all tetrahydrothiophenes **1a**−**h** ranging from 90% to 96% ee. No other regioisomer was detected under these reaction conditions, leading to a stereoselective domino reaction of diastereomerically pure, highly functionalized tetrahydrothiophenes **1**.

Use of the enantiomeric catalyst (*R*)-**6** for the domino reaction of thiol **5a** and α,β-unsaturated aldehyde **4a** afforded the enantiomeric product *ent*-**1a** in 51% yield and with an enantioselectivity of 89% ee (Table 2, entry 5). Use of L-proline as catalyst in this domino reaction gave product **1a** in 52% yield as a single isomer but only in 2% ee (entry 6). For the Michael addition step of this domino reaction, the organocatalyst 2-[bis-(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]-pyrrolidine **6** could highlight the fact that this catalyst is effective in iminium-ion activation of α,β-unsaturated aldehydes, and through a steric shielding of one side of the α,β-unsaturated aldehyde, a high asymmetric induction is obtained.

The absolute configuration of the tetrahydrothiophene carbaldehydes **1** was confirmed by a single-crystal X-ray analysis of **1d** (Figure 1).[21]

Tetrahydrothiophenols are sensitive compounds with regard to oxidation and elimination processes, catalyzed by, for example, acids, leading to aromatic thiophenes.[22] During our studies we observed no transformation of the tetrahydrothiophenols **1** to the aromatic thiophenes. One reason for the stability of compounds **1** could be strong intra- or intermolecular hydrogen bondings. The crystal structure of **1d** revealed intermolecular hydrogen bonds with a distance of 2.07(0) Å, which might prevent aromatization (Figure 2).

We were pleased to find that the tetrahydrothiophene car-

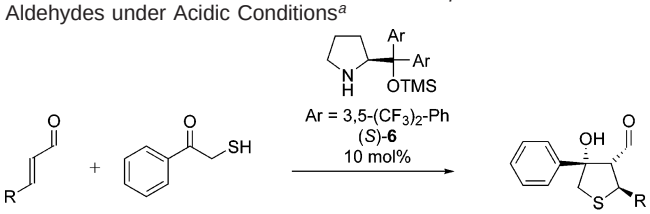
(21) X-ray crystal structure analysis of **1d**: Formula $C_{14}H_{18}O_2S$, weight 250.36 g mol^{-1}. See Supporting Information.

(22) (a) Fevig, T. L.; Philips, W. G.; Lau, P. H. *J. Org. Chem.* **2001**, *66*, 2493. (b) Kaneko, H.; Yamato, Y.; Kurokawa, M. *Chem. Pharm. Bull.* **1968**, *16*, 1200. (c) Nehlsen, J.; Benzinger, J.; Kevrekidis, I. *Ind. Eng. Chem. Res.* **2006**, *45*, 518. (d) Pocar, D.; Rossi, L. M.; Stradi, R.; Trimarco, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2337.

(23) X-ray crystal structure analysis of **2c**: Formula $C_{13}H_{16}O_2S$, weight 236.33 g mol^{-1}. See Supporting Information.

(24) Zhuang, W.; Marigo, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3883.

Table 2. Reaction of Thiol **5a** with Different α,β-Unsaturated Aldehydes under Acidic Conditions[a]



entry	R	catalyst	yield (%)[b]	ee (%)[c]
1	Me (**4b**)	(*S*)-**6**	**1b** = 59	90
2	Et (**4c**)	(*S*)-**6**	**1c** = 73	95
3	*n*-Pr (**4d**)	(*S*)-**6**	**1d** = 74	95
4	*i*-Pr (**4a**)	(*S*)-**6**	**1a** = 56	94
5[d]	*i*-Pr (**4a**)	(*R*)-**6**	*ent*-**1a** = 51	−89
6	*i*-Pr (**4a**)	L-proline	*ent*-**1a** = 52	−2
7	*n*-Bu (**4e**)	(*S*)-**6**	**1e** = 62	90
8	*n*-Hept (**4f**)	(*S*)-**6**	**1f** = 44	90
9	(*Z*)-*n*-hex-3-en (**4g**)	(*S*)-**6**	**1g** = 61	93
10	$CH_2CH_2OTBDMS$ (**4h**)	(*S*)-**6**	**1h** = 44	96

[a] All reactions were performed on a 0.25 mmol scale in toluene, 10 mol % catalyst, and $PhCO_2H$ as additive. [b] Yields of isolated product. [c] Determined by chiral HPLC after reduction to the corresponding alcohol (see below). [d] Catalyst contains small amounts of inpurities (~5%).

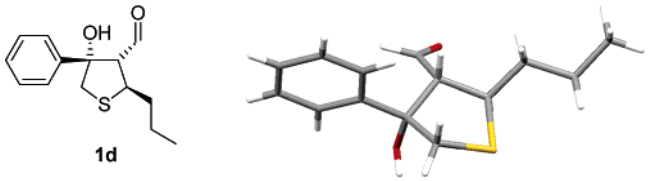


Figure 1. X-ray crystal structure of (2*R*,3*R*,4*S*)-4-hydroxy-4-phenyl-2-propyltetrahydrothiophene-3-carbaldehyde **1d**.

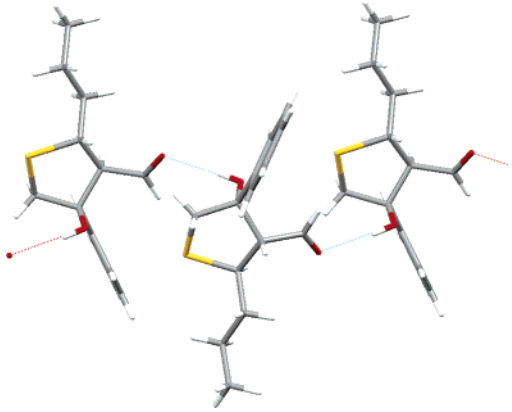
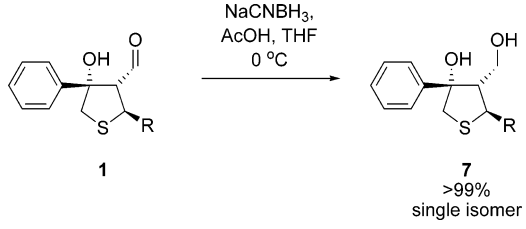


Figure 2. Hydrogen bonds in (2*R*,3*R*,4*S*)-4-hydroxy-4-phenyl-2-propyltetrahydrothiophene-3-carbaldehyde **1d**.

Scheme 2. Reduction of Tetrahydrothiophene Carbaldehydes 1 to Tetrahydrothiophen-3-ols **7**



baldehydes **1** undergo a smooth quantitative reduction to the corresponding alcohols **7** without any racemization (Scheme 2). Even in the presence of AcOH we observed no elimination reaction leading to dihydrothiophenes which could then spontaneously oxidize to the more stable aromatic thiophenes.

Base-Catalyzed Domino Reaction. The course of the organocatalytic domino reaction is dependent on variations in the cyclization reaction step. Temperature and solvent have an influence on yield and enantioselectivity, and the additive benzoic acid increases the rate of the domino reaction path to the tetrahydrothiophene carbaldehydes **1**. Changing the additive benzoic acid to a base, we observed in several cases a competing reaction path and formation of tetrahydrothiophene **2**. Therefore, we tested the effect of different additives on the conversion and regioselectivity of the domino reaction of (*E*)-4-methylpent-2-enal **4a** with 2-mercapto-1-phenylethanone **5**. The results are presented in Table 3.

No cyclization reaction was observed in the case of NaOH as additive (Table 3, entry 1). The domino cyclization reaction proceeds to the tetrahydrothiophenes with low conversion using LiOH, Na_2HPO_4, Na_2CO_3, Cs_2CO_3, or Et_3N (Table 3, entries 2, 3, and 5−7), while applying $NaHCO_3$ as the additive leads in the reaction of (*E*)-4-methylpent-2-enal **4a** and 2-mercapto-1-phenylethanone **5** to 97% conversion (entry 4). The regioselectivity for the latter reaction was determined by ^{1}H NMR spectroscopy to be 98:2 in favor to the tetrahydrothiophene **2a**. Isolation provided the single diastereoisomer **2a** in 61% yield and 80% ee.

Experiments that probe the scope of the α,β-unsaturated aldehyde component for this domino reaction are summarized in Table 4.

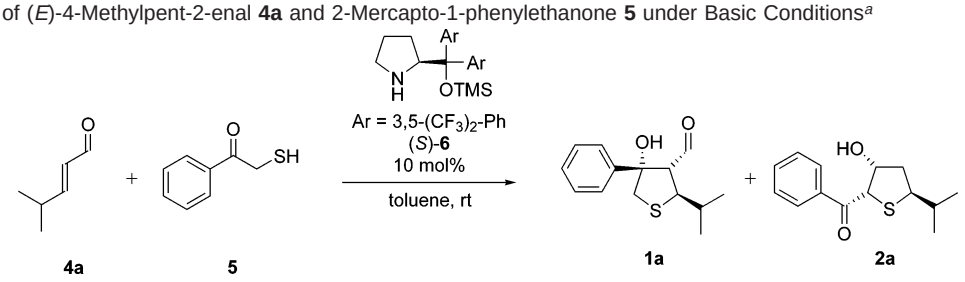
The tetrahydrothiophen-3-ols **2** are formed as a single diastereomer in good yields of 43−66% yield over two steps and with 64−82% ee. The domino process, providing tetrahydrothiophen-3-ols **2**, starts with a Michael addition of the thiol **5** to the α,β-unsaturated aldehyde **4**, as in the asymmetric domino reaction for the formation of **1**. However, the enantiomeric excess of the final products **2** (64−82% ee) is lower than the tetrahydrothiophene carbaldehydes **1** (90−96% ee), derived from the acid-catalyzed domino reaction. Including the result from performing the reaction in water with benzoic acid as additive (Table 1, entry 11), it demonstrates the existence of two different pathways in the second step, the aldol reaction. One catalytic cycle is probably an asymmetric aldol reaction, catalyzed by (*S*)-**6**, which leads to an enantioenrichment for the product **1** after the Michael addition whereby the second catalytic cycle to formation of **2** is a simple enolization of the Michael adduct by $NaHCO_3$ without further asymmetric induction. Therefore, the enantiomeric excess of **2** reflects the asymmetric induction of the Michael addition of **5** to the α,β-unsaturated aldehyde **4**.

An X-ray crystal structure with anomalous diffraction revealed the absolute configuration of (2*S*,3*R*,5*R*)-(5-ethyl-3-hydroxytetrahydrothiophen-2-yl)phenyl methanone **2c** (Figure 3).[23]

An intramolecular hydrogen bond with a distance of 2.20(0) Å stabilizes the tetrahydrothiophenes, which might prevent elimination of water, leading to aromatic compounds.

Mechanistic Insights. The proposed mechanisms for the two domino reactions are summarized in Scheme 3. Michael addition of thiol **5** and the α,β-unsaturated aldehyde **4** follows the known

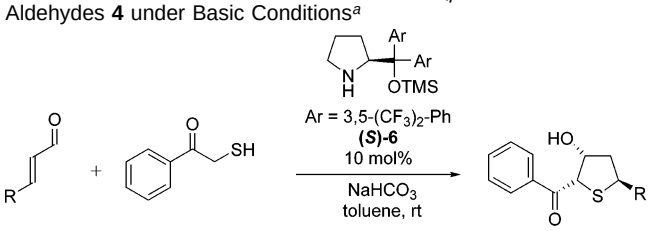
Table 3. Reaction of (*E*)-4-Methylpent-2-enal **4a** and 2-Mercapto-1-phenylethanone **5** under Basic Conditions[a]



entry	additive	conversion (%)[b]	1a:2a	ee (%)[c]
1	NaOH	no reaction		
2	LiOH	22	0:100	nd
3	Na_2HPO_4	22	100:0	nd
4	$NaHCO_3$	97	2:98	80
5	Na_2CO_3	48	83:17	nd
6	Cs_2CO_3	17	0:100	nd
7	Et_3N	54	50:50	nd

[a] All reactions were performed on a 0.25 mmol scale in toluene with 10 mol % catalyst (*S*)-**6**. [b] Determined by ^{1}H NMR after 48 h. [c] Determined by chiral HPLC.

Table 4. Reaction of Thiol **5a** with Different α,β-Unsaturated Aldehydes **4** under Basic Conditions[a]



entry	R	yield (%)[b]	ee (%)[c]
1	Me (**4b**)	**2b** = 59	74
2	Et (**4c**)	**2c** = 44	72
3	*n*-Pr (**4d**)	**2d** = 43	82
4	*i*-Pr (**4a**)	**2a** = 61	80
5	*n*-Bu (**4e**)	**2e** = 66	64
6	(*Z*)-*n*-hex-3-en (**4g**)	**2f** = 57	76
7	$(CH_2)_2$OTBDMS (**4h**)	**2g** = 61	70

[a] All reactions were performed on a 0.25 mmol scale in toluene, 10 mol % catalyst, and $NaHCO_3$ as additive. [b] Yields of isolated product. [c] Determined by chiral HPLC.

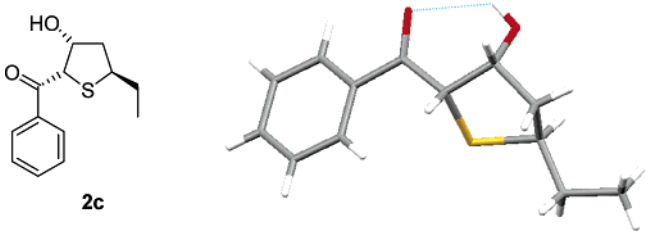


Figure 3. X-ray crystal structure of (2*S*,3*R*,5*R*)-(5-ethyl-3-hydroxytetrahydrothiophen-2-yl)phenyl methanone **2c**.

pathway of related organocatalytic transformations.[16a,m,n,20c,d,24] The TMS-protected proline derivative (*S*)-**6** generates, with the α,β-unsaturated aldehyde **4**, the iminium-ion **8** shielding the *si* side of the reactive intermediate. Nucleophilic attack of the thiol **5** approaches from the *re* side, leading to formation of a (*R*)-configured stereocenter in the enamine **9**. The diastereotopic differentiation of the nucleophile is directed from the catalyst, yielding a diastereomeric ratio of ~6:1. Hydrolysis of the product **10** in aqueous media or in the presence of $NaHCO_3$ releases the catalyst (*S*)-**6** and the thioether **11**, which can, after a fast enolization to **12**, react in a diastereospecific aldol reaction leading to tetrahydrothiophene **2**.

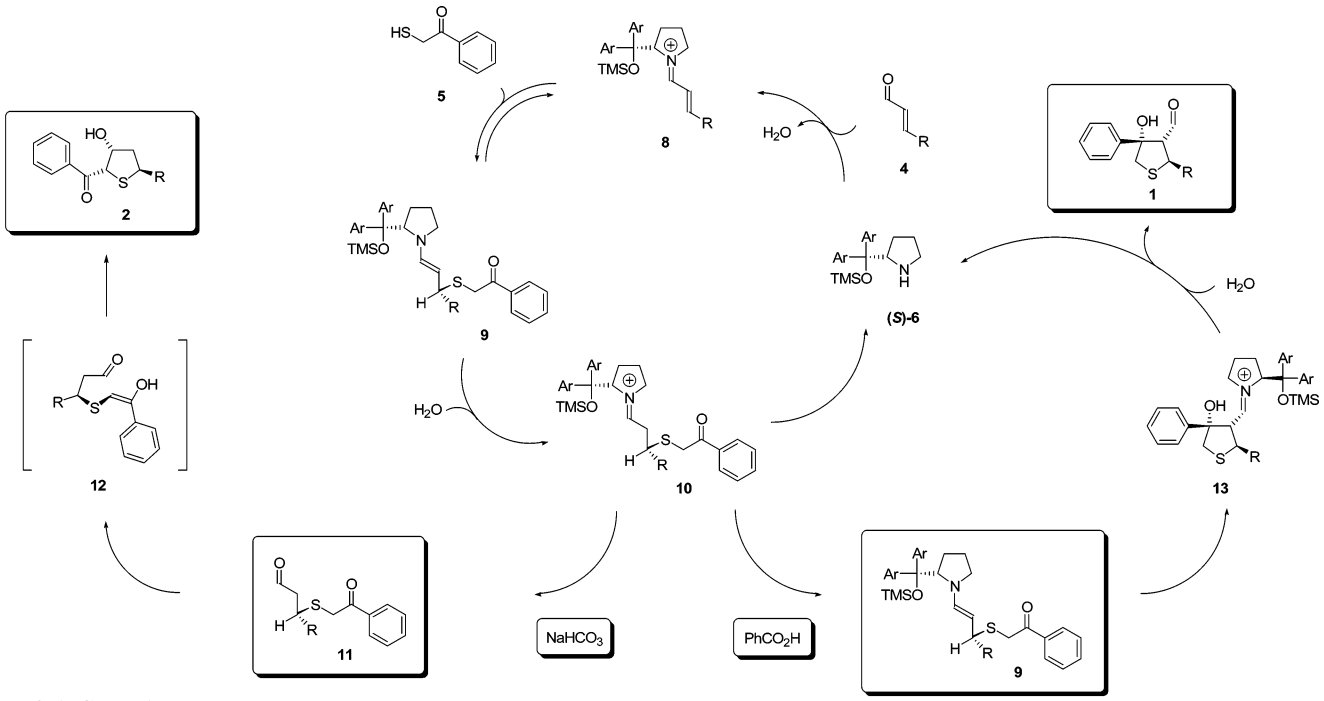
Assuming a thermodynamic-controlled (*E*)-enol in intermediate **12** with a pseudoequatorial group R, hydrogen bonding between the enol and the aldehyde supports formation of the syn relationship of the substituents in product **2**. The role of $NaHCO_3$ as additive is therefore to promote hydrolysis of **10** and enolization. No asymmetric induction through the catalyst (*S*)-**6** is observed for the second catalytic step in the formation of (tetrahydrothiophen-2-yl)phenyl methanones **2**.

In the presence of benzoic acid as additive in toluene we propose that no hydrolysis to the thioether **11** takes place. The catalyst remains in the catalytic cycle, forming the enamine **9** as reactive intermediate. Due to the steric hindrance of the chiral substituent in the pyrrolidine ring the enamine **9** reacts from an (*E*)-enamine state, attacking selectively the carbonyl moiety from the *re* side, leading to the observed (2*R*,3*R*,4*S*)-configuration of the tetrahydrothiophenes **1**. Hydrolysis of the iminium-ion intermediate **13** gives the diastereomerically pure product **1** and sets the catalyst (*S*)-**6** free. The increase of the reaction rate using benzoic acid as an additive can be explained by a possible protonation of the carbonyl group of the intermediate **9** forming a more reactive intermediate. Within this mechanistic cascade the catalyst has a multiple asymmetric induction, yielding products **1** with higher enantioenrichment (>90% ee) than the tetrahydrothiophenes **2** (70−80% ee).[16k]

Conclusion

In summary, we have developed new and simple organocatalytic domino reactions for formation of highly functionalized optically active tetrahydrothiophenes. The catalytic domino reaction can be controlled by addition of benzoic acid, yielding tetrahydrothiophene carbaldehydes **1** in good yields and with excellent enantio- and diastereoselectivity, or $NaHCO_3$, giving (tetrahydrothiophen-2-yl)phenyl methanones **2** in moderate yields with very good selectivity. Furthermore, we were able

Scheme 3. Mechanism of the Domino Michael−Aldol Reaction for Formation of Optically Active Tetrahydrothiophenes



Ar = 3,5-$(CF_3)_2$-Ph

to explain the stability of these classes of compounds by hydrogen bonding and could show easy, highly efficient transformations of these compounds as a synthetic application.

Acknowledgment. This work was made possible by a grant from The Danish National Research Foundation. Thanks are expressed to Dr. Jacob Overgaard and Professor Finn Krebs Larsen from the Department of Chemistry, Aarhus University, for performing the X-ray crystal structure analysis.

Supporting Information Available: Complete experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JA065507+