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Enantioselective Organocatalytic Double Michael Addition Reactions

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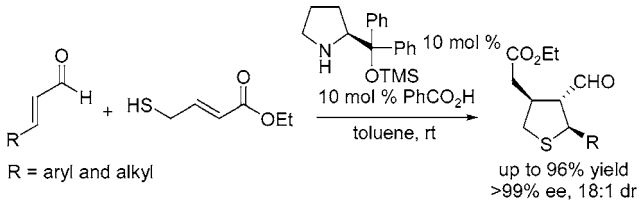
ABSTRACT



A novel organocatalytic, enantioselective domino double Michael addition reaction of α,β-unsaturated aldehydes with ethyl 4-mercapto-2-butenoate has been developed. The process is promoted by chiral diphenylprolinol TMS ether to give chiral tetrahydrothiophenes in high to excellent levels of enantioselectivities.

The development of new methodologies aimed at improving synthetic efficiency is an important goal in contemporary organic synthesis. A domino process, which involves several bond-forming reactions in a single manipulation, represents an attractive strategy in the facile assembly of molecular architecture. These processes are operational simple, atom economic, and minimize the generation of chemical waste and the use of energy.[1] Domino Michael−Michael (also called "double Michael") reactions have been intensively explored and demonstrated as a powerful tool in organic synthesis.[1,2] Efficient asymmetric double Michel processes have been achieved by relying on the use of chiral auxiliaries[3] and chiral precursors[4] for stereocontrol. However, the development of catalytic enantioselective versions of the reactions proved to be a challenging task, and such processes are sparse.[5]

Chiral tetrahydrothiophenes display a broad spectrum of biological activities, serving as essential enzyme cofactor,[6a] potent CCK,[6b] HIV,[6c] and copper amine oxidase inhibitors,[6d] hypocholesterolemic agent,[6e] and plant growth regulators.[6f]

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(2) Review of double Michael reactions, see: Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1010.

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(5) Recently Takemoto and co-workers have developed a thiourea via H-bonding mediated double Michael reaction. Although it is claimed to be a cascade process, the addition of a base 1,1,3,3-tetramethylguanidine or KOH is essential for the second Michael reaction: Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365.

(6) (a) Essential enzyme cofactor: De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755. (b) CCK inhibitors: Page, P. C. B.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett* **2003**, 1022. (c) HIV inhibitors: Wirsching, J.; Voss, J.; Adiwidjaja, G.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1049. (d) Copper amine oxidase inhibitors: Qiao, C.; Ling, K.-Q.; Shepard, E. M.; Dooley, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2006**, *128*, 6206. (e) Hypocholesterolemic agent: Smith, A. B., III; Empfield, J. R. *Chem. Pharm. Bull.* **1999**, *47*, 1671. (f) Plant growth regulators: Tsygoanko, V. A.; Blume, Y. B. *Biopolim. Kletka* **1997**, *13*, 484.

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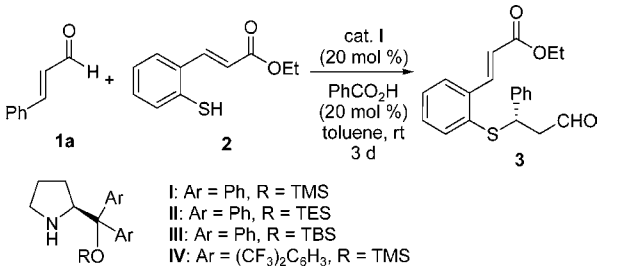
Moreover, these scaffolds also have been used as ligands in catalysis.[7] Given the increasing applications of this class of molecules, however, very few asymmetric methods have been described.[8] Recently we have initiated a program aimed at the development of new organocatalyzed, asymmetric domino reactions for the rapid construction of complex structures.[9] In this context, we wish to report the results of the effort, which has led to a novel organocatalytic, enantioselective domino thio-Michael−Michael process. This process is efficiently catalyzed by a readily available, robust (*S*)-diphenylprolinol TMS ether under a mild reaction condition to furnish the synthetically useful chiral tetrahydrothiophenes from simple achiral substances in excellent enantioselectivities (94−99% ee) and good dr (6:1 to 18:1).

Michael addition reactions have been established as a powerful platform for the development of new domino processes.[1d] Recently, a great deal of effort has focused on the development of organocatalytic asymmetric domino Michael-aldol reactions.[10−14] We have developed highly enantioselective thio-, oxa-, and aza-Michael-aldol reactions, which are efficiently catalyzed by chiral diarylprolinol silyl ethers.[9,13] However, organocatalyzed asymmetric double Michael processes have not been reported in spite of their broad synthetic utility. Having established the capacity of chiral diarylprolinol silyl ethers as efficient promoters for the domino thio-Michael-aldol−dehydration reaction,[9b] we envisioned that positioning an α,β-unsaturated ester instead of an aldehyde into the 2-mercapto aromatic system could porduce a novel double Michael process with an α,β-unsaturated aldehyde (Scheme 1). Unfortunately, the reaction

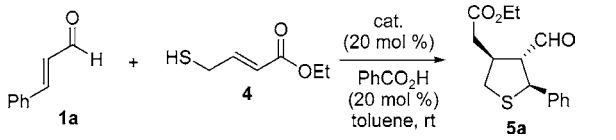
Scheme 1. Organocatalytic, Asymmetric Michael Reaction



of *trans*-α,β-unsaturated aldehyde **1a** with *trans*-3-(2-mercaptophenyl)-2-propenoic acid ethyl ester **2** in the presence of catalyst **I**[15,16] and benzoic acid did not lead to the desired Michael−Michael product. Instead, a single Michael addition adduct **3** was obtained.

We surmised that the steric hindrance of the rigid substrate **2** might prevent the second Michael addition process. Accordingly, a linear, flexible *trans*-ethyl 4-mercapto-2-butenoate **4** was designed and exploited for the double Michael addition reaction with α,β-unsaturated aldehyde **1a** under the same reaction conditions (Table 1). Gratifyingly,

Table 1. Organocatalytic Asymmetric Domino Thio-Michael−Michael Reaction of 3-Phenylpropenal (**1a**) with *trans*-Ethyl 4-Mercapto-2-butenoate (**4**)[a]



entry	cat.	time (d)	% yield[b]	% ee[c]	dr[d]
1	**I**	2	75	>99	15:1
2[e]	**I**	3	76	>99	15:1
3	**II**	2.5	73	99	15:1
4	**III**	2.5	84	98	15:1
5	**IV**	2.5	0	ND[f]	ND[f]

[a] Reaction conditions: unless specified, a mixture of **1a** (0.20 mmol), **4** (0.20 mmol), catalyst (0.04 mmol), and $PhCO_2H$ (0.04 mmol) in toluene (0.5 mL) was stirred for a certain period of time. [b] Isolated yields. [c] Ee determined by chiral HPLC analysis (Chiralcel OD-H). [d] Determined by ^1H NMR. [e] 10 mol % catalyst used. [f] Not determined.

it was found that the reaction proceeded smoothly to furnish the desired Michael−Michael adduct **5a** in 75% yield and

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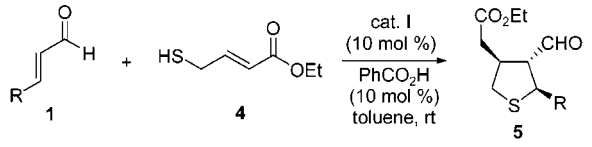
with a remarkably high ee (>99%) and high dr (15:1) (entry 1). Encouraged by the promising results, we probed other diarylprolinol silyl ethers **II**−**IV** as well (Scheme 1 and Table 1). Catalysts **II** and **III** with TES and TBS group afforded similar results to that of catalyst **I** (Table 1, entries 3 and 4). However, no reaction occurred when catalyst **IV**, a more bulky and strong electron-withdrawing $(CF_3)_2C_6H_3$ moiety, was employed (entry 5). Catalyst loading of **I** could be reduced to 10 mol % without affecting enantio- and diastereoselectivity (entry 2). Screening reaction solvents revealed that toluene was the optimal medium for the process.[17]

Table 2. Catalyst **I** Promoted Domino Thio-Michael−Michael Reactions of α,β-Unsaturated Aldehydes (**1**) with *trans*-Ethyl 4-Mercapto-2-butenoate (**4**)[a]



entry	R	time (d)	% yield[b]	% ee[c]	dr[d]
1	Ph (**5a**)	3	76	>99	15:1
2	4-$NO_2C_6H_4$ (**5b**)	2.5	84	99	7:1
3	2-$NO_2C_6H_4$ (**5c**)	3	84	99	6:1
4	4-FC_6H_4 (**5d**)	3	81	96	11:1
5	4-$CF_3C_6H_4$ (**5e**)	3	69	98	11:1
6	4-CNC_6H_4 (**5f**)	3	65	>99	18:1
7	2-ClC_6H_4 (**5g**)	3	85	99	10:1
8	4-$MeOC_6H_4$ (**5h**)	2.5	87	95	15:1
9	2-$MeOC_6H_4$ (**5i**)	2.5	96	98	18:1
10	3-MeO-4-$AcOC_6H_3$ (**5j**)	2.5	89	99	17:1
11	2-furanyl (**5k**)	2	88	98	6:1
12	2-naphthyl (***5l***)	4	55	96	8:1
13	$BnOCH_2$ (**5m**)	2.5	62	94	7:1

[a] Reaction conditions: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H, or AD and Chiralcel OD-H). [d] Determined by ^{1}H NMR.

Our first goal was to show that this new organocatalytic double Michael addition process could serve as a facile route for the preparation of a wide range of tetrahydrothiophenes **5** with high to excellent degrees of enantioselectivities (94−99% ee) and good to high diastereoselectivities (6:1 to 18:1) (Table 2). The reaction scope proved to be quite a broad scope with respect to α,β-unsaturated aldehydes **1**. The use of aromatic ring substituents with neutral groups (entry 1), electron-withdrawing groups (entries 2−7), electron-donating groups (entries 8 and 9), or those in combination (entry 10) is well tolerated in the reaction. It is also realized that the steric hindrance (entries 2, 7, and 9) has a very limited effect on the domino reactions. Furthermore, heteroaromatic (entry 11) and conjugated aromatic (entry 12) systems and alkyl enal (entry 13) can be applicable to the domino processes as well. The absolute configuration of the product **5*l*** is determined based on X-ray crystal structure analysis (Figure 1).

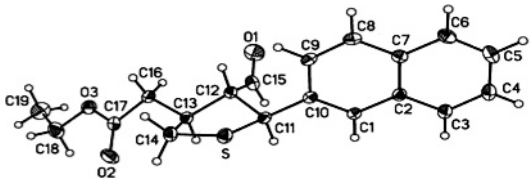


Figure 1. X-ray crystal structure of **5*l***.

In summary, we have developed a novel and simple organocatalytic thiol initiated domino double Michael addition reaction between a variety of α,β-unsaturated aldehydes and *trans*-ethyl 4-mercapto-2-butenoate. The process, efficiently catalyzed by readily available and robust (*S*)-diphenylprolinol TMS ether, furnishes highly functionalized chiral tetrahydrothiophenes with generation of three new stereogenic centers in high and excellent enantioselectivities and high stereoselectivities. The reaction conditions are mild and practical. Further investigation is underway to expand the scope and application of this efficient domino process.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR and HRMS data for products **5** and X-ray crystal date (CIF file) for **5*l***. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) CH_2Cl_2: 3 d, 81% yield, 97% ee, 10:1 dr. $Cl(CH_2)_2Cl$: 3 d, 89% yield, 90% ee, 11:1 dr. Xylenes: 3 d, 79% yield, >99% ee, 15:1 dr.