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Enantioselective Organocatalytic Tandem Michael−Aldol Reactions: One-Pot Synthesis of Chiral Thiochromenes

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Despite the fact that the chemistry of thiopyrans has been much less explored than that of the analogous pyrans, recently the interest in the sulfur-containing heterocycles has been significantly surged since a wide range of biological activities associated with the scaffold have been identified.[1] For example, 1-benzothiopyrans exhibit anti-inflammatory,[2] anti-bacteria,[3] anti-hyperplasia,[4] anti-psychiatric,[5] analgesic, and anti-cancer[6] activities. Accordingly, the development of new and facile synthetic strategies to access such heterocycles is of considerable interest. Various methods for their preparation have been reported.[1,7] However, survey of the literature reveals that these approaches involve multistep sequences; moreover, to date, to the best of our knowledge, only two studies of the asymmetric version for synthesis of the scaffold have been described using either optically pure starting material[8] or a chiral auxiliary.[9]

Tandem or cascade reactions are a powerful tool for rapid assembly of complex structures.[10] Unlike stepwise bond formation toward a target molecule, such a process has the advantages of greatly enhanced synthetic efficiency, while producing less waste and minimizing the excessive handling. Organocatalytic enantioselective tandem processes are even more appealing because of their operational simplicity and environmental friendliness.[11] In this communication, we wish to disclosure a new organocatalyzed enantioselective tandem Michael−aldol reaction by furnishing synthetically useful thiochromenes in high yields (72−97%) and good to high enantioselectivities (85−95% ee).

Our strategy for developing a one-pot synthesis of chiral thiochromenes is described in Scheme 1.[10,12,13] Activation of α,β-unsaturated aldehyde **1** by a chiral organocatalyst produces iminium **A**. Conjugate addition of a nucleophilic thiolphenol aldehyde **2** to the resulting active iminium **A** triggers a cascade Michael−aldol process to afford intermediate **B**, which subsequently undergoes a dehydration reaction to give α,β-unsaturated aldehyde **3**.

To explore the possibility of the proposed tandem Michael−aldol process, a model reaction between *trans*-cinnamaldehyde **1a** and 2-mercaptobenzaldehyde **2a** was performed in toluene at room temperature in the presence of an organocatalyst (Figure 1 and Table 1). Seven chiral pyrrolidines **I**−**VII** were screened for promoting the cascade reactions because they can activate α,β-unsaturated aldehydes by formation of active iminium species (Figure 1).[14−18] The results showed that the catalysts probed exhibited significantly different catalytic activity and enantioselectivity toward the process (Table 1). L-Proline **I**[14] and (*S*)-pyrrolidine trifluoromethanesulfonamide **II**[15] were good promoters for the process, achieving high yields (80 and 87%, respectively) but giving poor to moderate enantioselectivities (10 and 51% ee, respectively, entries 1 and 2). No enantioselectivity for diamine **III**[16] (entry 3) and poor catalytic activity for MacMillan's catalyst **IV**[17] (entry 4) were observed. Among the organocatalysts surveyed, (*S*)-pyrrolidine silyl ethers **V**−**VII**[18] showed promising results (entries 5, 6, and 8). It was realized that catalyst **VI**[18a] was found to be the best one for catalyzing the cascade process (entry 6). In this instance, the reaction

Scheme 1. Tandem Organocatalyzed Enantioselective Michael−Aldol Reaction

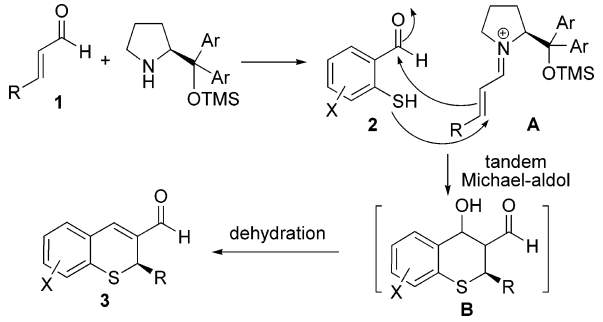
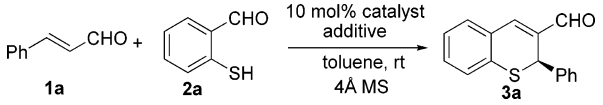


Table 1. Organocatalytic Asymmetric Cascade Michael−Aldol−Dehydration Reaction of 3-Phenylpropenal (**1a**) with 2-Mercaptobenzaldehyde (**2a**)[a]



entry	catalyst	additive	*t* (h)	% yield[b]	% ee[c]
1	**I**	none	12	80	−10
2	**II**	none	12	87	−50
3	**III**	$PhCO_2H$	12	93	0
4	**IV**	HCl	48	<10	ND[e]
5	**V**	$PhCO_2H$	4	90	53
6	**VI**	$PhCO_2H$	1	62	86
7[d]	**VI**	$PhCO_2H$	16	85	94
8	**VII**	$PhCO_2H$	12	92	83

[a] Reaction conditions: unless specified, a mixture of 3-phenylpropenal (**1a**) (0.1 mmol), 2-mercaptobenzaldehyde (**2a**) (0.15 mmol), 10 mol % catalyst, benzoic acid (0.1 equiv), and 4 Å MS (50 mg) in toluene (0.5 mL) was stirred at room temperature for a specified time. [b] Isolated yields. [c] Enantiomeric excess was determined by HPLC analysis (Chiralpak AS-H). [d] Reaction at 0 °C. [e] Not determined.

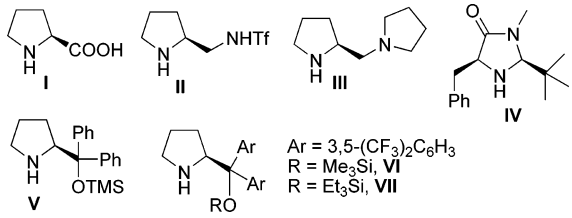


Figure 1. Screened organocatalysts.

was completed within 1 h to give product **3a** with 86% ee. When the reaction temperature was lowered to 0 °C, both reaction yield (85%) and ee (94%) were improved, although reaction time was prolonged (16 h, entry 7). The analogue **VII** with a TES group displayed similar results (92% yield and 83% ee, entry 8) under the same reaction conditions, but with long reaction time even at room temperature. After extensive optimization of reaction condi-

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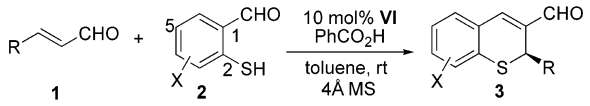
Table 2. Catalyst **VI**-Promoted Cascade Michael−Aldol Reactions of α,β-Unsaturated Aldehydes (**1**) to 2-Mercaptobenzaldehydes (**2**)[a]



1 2 3

entry	R	X	t (h)	% yield[b]	% ee[c]
1[d]	Ph	H	16	85	94
2[d]	4-MeO−C_6H_4	H	16	82	85
3	2-MeO−C_6H_4	H	12	96	94
4	4-F−C_6H_4	H	12	93	86
5	4-NO_2−C_6H_4	H	12	95	92
6	Me	H	12	90	92
7[d]	Et	H	12	81	95
8	*n*-C_3H_7	H	12	96	94
9	*n*-C_5H_{11}	H	12	94	93
10	Me	5-Cl	12	91	91
11	Me	5-MeO	12	80	93
12	Me	5-Me	12	97	90
13	Me	3,4-$(CH)_4$	12	72	89
14	Me	4,6-$(MeO)_2$	12	96	89

[a] Reaction conditions: unless specified, see footnote a in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H and Chiralcel OD-H or OJ-H). [d] Reaction performed at 0 °C.

tions, including screening reaction media and acid additives, we found that the use of toluene as solvent and $PhCO_2H$ as additive gave the best results (entries 6 and 7). The absolute configuration of **3a** prepared under the conditions was determined by X-ray crystallography to be *R* (see Supporting Information).

The **VI**-promoted tandem Michael−aldol−dehydration processes between a variety of α,β-unsaturated aldehydes **1** and various 2-mercaptobenzaldehydes **2** under optimized conditions (10 mol % of **VI** in toluene) were investigated (Table 2). The results showed that, in general, the reactions took place efficiently in high yields (72−97%) with good to excellent levels of enantioselectivity (85−95% ee). The reactions were applicable to a variety of α,β-unsaturated aldehydes **1**, bearing both aryl and alkyl groups (entries 1−14). Aromatic α,β-unsaturated aldehydes, regardless of electron-donating (Table 2, entries 2 and 3) and electron-withdrawing substituents (entries 4 and 5) on the phenyl ring and the substitution pattern (entries 2−5, ortho vs para), participated in this process in high efficiency (82−96% yield and 85−94% ee). More significantly, generally, even higher enantioselectivities for less reactive alkyl α,β-unsaturated aldehydes **1** (entries 6−14, 89−95% ee) were observed. The investigation of 2-mercaptobenzaldehydes **2** with variation in their electronic and steric features (entries 10−14) revealed that the **VI**-catalyzed processes proceeded smoothly with high ee values (89−93%) and high yields (72−97%).

In summary, the new organocatalytic tandem Michael−aldol reaction, promoted by organocatalyst **VI**, described above serves as an efficient method for preparation of synthetically useful chiral thiochromenes with good to high enantioselectivities. A broad range of α,β-unsaturated aldehydes and 2-mercaptobenzaldehydes can be tolerated in the process. Further investigation of the scope of the cascade reaction and its application to the synthesis of biologically interesting molecules is underway.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR and HRMS data for products **3** and X-ray crystallographic information of **3a** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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