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Highly enantioselective synthesis of 2*H*-1-benzothiopyrans by a catalytic domino reaction

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Abstract—A highly enantioselective catalytic asymmetric synthesis of 2*H*-1-benzothiopyrans is presented. The organocatalytic asymmetric domino reactions between 2-mercaptobenzaldehyde and α,β-unsaturated aldehydes proceed with excellent chemo- and enantioselectivities to give the corresponding pharmaceutically valuable benzothiopyrans in high yields with 91–98% ee.

Heterocycles are of immense importance in the design and discovery of new compounds for pharmaceutical applications.[1] The 2*H*-1-benzothiopyran (thiochromenes) group is an important structural motif in the preparation of pharmaceuticals.[2] For instance, the benzothiopyrans exhibit interesting biological properties and have been tested and applied as drugs.[2,3] They may also show higher biological activity as compared to the corresponding benzopyran structural motif, which is also of great importance in the preparation of drugs.[4] There are several methods available for the catalytic synthesis of racemic thiochromene derivatives.[5] However, a catalytic asymmetric synthesis of benzothiochromene derivatives has yet to be developed.

The development of organocatalytic asymmetric reactions is a rapidly growing research field within organic synthesis.[6] Recently, organocatalytic reactions that involve catalytic domino or cascade reactions via enamine and iminium intermediates were reported.[7,8] In this context, Jørgensen and co-workers have reported a catalytic enantioselective Michael reaction with aliphatic thiols as nucleophiles.[7d] Moreover, we recently reported a catalytic asymmetric synthesis of chromene-3-carbaldehyde derivatives via a domino oxa-Michael/aldol reaction.[9] Inspired by the recent development of metal-free catalytic asymmetric domino reactions, we envisioned that a chiral amine catalyzed reaction between 2-mercaptobenzaldehydes and α,β-unsaturated aldehydes could be a new simple entry to 2*H*-1-benzothiopyran derivatives (Scheme 1). Herein, we present a highly enantioselective organocatalytic domino thia-Michael/aldol reaction that gives the corresponding thiochromene derivatives in high yields with 91–98% ee.

In an initial catalyst screen, we found that chiral pyrrolidines such as **4**–**9** catalyzed the reaction between 2-mercapto-benzaldehyde **1** (0.30 mmol) and cinnamic aldehyde **2a** (0.25 mmol) with high chemoselectivity to give the corresponding thiochromene-3-carbaldehyde **3a** in high yield but low enantioselectivity (Table 1).

For instance, (*S*)-proline catalyzed the formation of thiochromene *ent*-**3a** in 87% yield with 7% ee. The chiral diphenylprolinol **8**[10] and its derivative **9a**[11] catalyzed the formation of **3a** in high yield but with modest enantioselectivity. However, the addition of a substoichiometric amount of an organic acid (20 mol %) increased the enantioselectivity of the chiral diarylpyrrolidines **8** and **9a** mediated domino reactions. Based on these initial results, we chose to screen protected diarylprolinols **9** as catalysts in the presence of benzoic acid as an additive under different reaction conditions (Table 1). The thiochromene **3a** was catalytically assembled using **9a** in high yield and good enantioselectivity under all the investigated reaction conditions. The highest enantioselectivity was obtained in $CHCl_3$ and CH_3CN. Furthermore, decreasing the reaction temperature improved the stereoselectivity of the domino reaction in $CHCl_3$. In addition, other chiral protected diarylprolinols **9**

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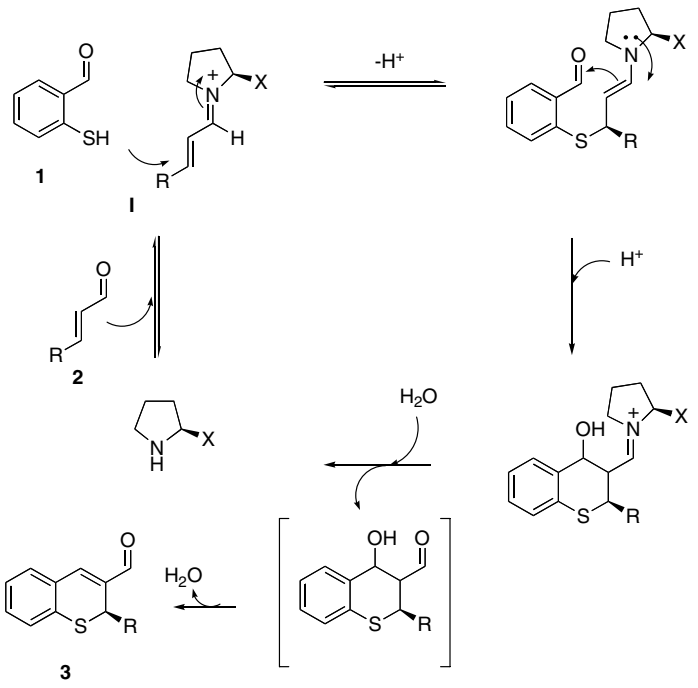
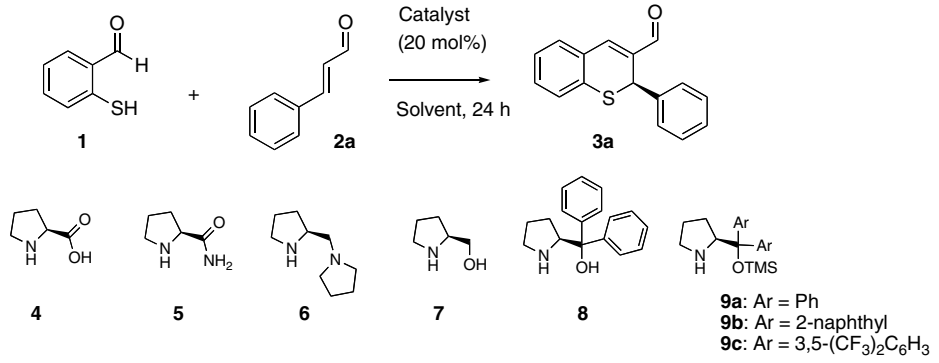


Scheme 1. A plausible reaction pathway for the organocatalytic asymmetric synthesis of thiochromene-3-carbaldehydes.

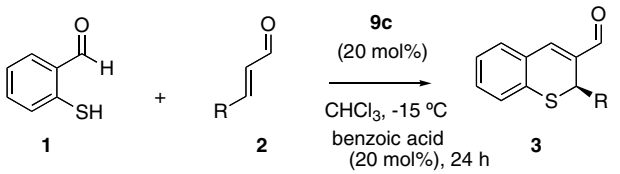
Table 1. Catalyst screen for the enantioselective domino reactions between **1** and **2a**[a]

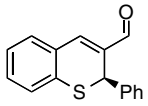
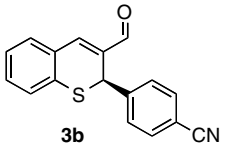
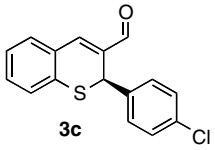
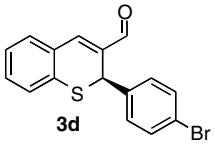
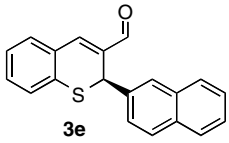
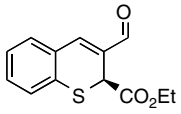
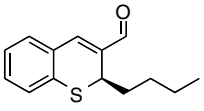
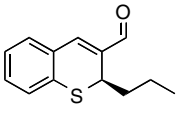
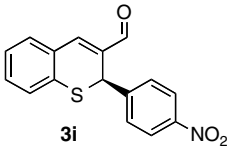


Entry	Additive (20 mol %)	Catalyst	Solvent	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	None	**4**	$CHCl_3$	rt	87	−7
2	None	**5**	$CHCl_3$	rt	11	2
3	None	**6**	$CHCl_3$	rt	86	7
4	None	**7**	$CHCl_3$	rt	91	−22
5	None	**8**	$CHCl_3$	rt	75	11
6	$C_6H_5CO_2H$	**8**	$CHCl_3$	rt	86	36
7	None	**9a**	$CHCl_3$	rt	78	39
8	$C_6H_5CO_2H$	**9a**	$CHCl_3$	rt	95	55
9	4-$O_2NC_6H_4CO_2H$	**9a**	$CHCl_3$	rt	86	69
10	2-$FC_6H_4CO_2H$	**9a**	$CHCl_3$	rt	83	50
11	Acetic acid	**9a**	$CHCl_3$	rt	76	50
12	$C_6H_5CO_2H$	**9a**	CH_3CN	rt	70	70
13	$C_6H_5CO_2H$	**9a**	MeOH	rt	67	59
14	$C_6H_5CO_2H$	**9a**	$CHCl_3$	−20	79	69
15	$C_6H_5CO_2H$	**9a**	$CHCl_3$	−15	64	84
16	$C_6H_5CO_2H$	**9b**	$CHCl_3$	−15	71	79
17	$C_6H_5CO_2H$	**9c**	$CHCl_3$	−15	74	98
18	$C_6H_5CO_2H$	**9c**	CH_3CN	−15	51	84

[a] Experimental conditions: A mixture of **1** (0.30 mmol), cinnamic aldehyde **2a** (0.25 mmol) and catalyst (20 mol %) in 0.5 mL solvent was stirred at room temperature under the conditions displayed in the table.
[b] Isolated yield of pure compound **3a**.
[c] Determined by chiral-HPLC analyses.

Table 2. Direct organocatalytic asymmetric domino Michael/aldol condensation between **1** and α,β-unsaturated aldehydes **2**[a]



Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Ph	 **3a**	74	98
2	4-NCC_6H_4	 **3b**	80	98
3	4-ClC_6H_4	 **3c**	53	96
4	4-ClC_6H_4	**3c**	68[d]	94[d]
5	4-BrC_6H_4	 **3d**	93	98
6	2-Naphthyl	 **3e**	68	94
7	CO_2Et	 **3f**	61	91
8	*n*-Butyl	 **3g**	70	96
9	*n*-Propyl	 **3h**	55	94
10	4-$O_2NC_6H_4$	 **3i**	87	96

[a] Experimental conditions: A mixture of **1** (0.30 mmol), α,β-unsaturated aldehyde **2** (0.25 mmol), benzoic acid (20 mol %) and catalyst (20 mol %) in 0.5 mL $CHCl_3$ was stirred at −15 °C for 24 h.
[b] Isolated yield of pure compound **3**.
[c] Determined by chiral-HPLC analysis.
[d] Molecular sieves (0.2 g, 4 Å) were added.

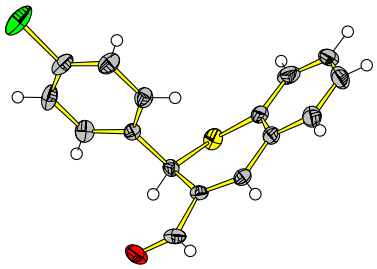


Figure 1. ORTEP picture of thiochromene-3-carbaldehyde **3d**.

catalyzed the reaction with excellent chemoselectivity and furnished thiochromene **3a** in high yield and enantiomeric excess. Notably, catalyst **9c**[7d,11b,c,e] catalyzed the formation of **3a** in 74% yield with 98% ee (entry 15). Encouraged by this excellent result, we decided to investigate the catalytic asymmetric domino thia-Michael/aldol reaction between **1a** and a set of different α,β-unsaturated aldehydes with **9c** as the organocatalyst (Table 2).[12]

The catalytic domino reactions proceeded with excellent chemo- and enantioselectivities and the corresponding thiochromene-3-carbaldehydes **3a–i** were obtained in high yields with 91–98% ee. We found that the catalytic asymmetric reaction was highly chemoselective for reactions with both aromatic and aliphatic α,β-unsaturated aldehydes. For instance, chiral amine **9c** catalyzed the asymmetric reaction between **1** and 2-hept-2-enal with high chemoselectivity and thiochromene **3g** was isolated in 70% yield and 96% ee (entry 8). The yield was further improved by the addition of molecular sieves (4 Å) without affecting the enantioselectivity of the reaction (entry 4). Moreover, the reactions were operationally simple and were performed in parallel. Hence, the organocatalytic enantioselective domino reactions may be suitable for the generation of thiochromene libraries.

X-ray analysis of the thiochromene-3-carbaldehyde **3d** supported the absolute configuration at C2 as *R* (Fig. 1).[13]

Based on the X-ray analysis, we propose the following mechanism to be responsible for the stereochemical outcome of the chiral arylprolinol **9**-catalyzed reactions (Scheme 1).

The direct organocatalytic asymmetric domino thia-Michael/aldol reaction starts with iminium activation of the α,β-unsaturated aldehyde by the chiral pyrrolidine derivative **9**. The efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups leads to stereoselective *Re*-facial nucleophilic conjugate attack on the β-carbon by the thiol **1** resulting in a chiral enamine intermediate (Scheme 1). Next, the chiral enamine undergoes an intramolecular 6-*exo* trig aldol addition, followed by hydrolysis of the resulting iminium intermediate to give the aldol product. Next, elimination of water gives the corresponding thiochromene-3-carbaldehyde **3**. This is further supported by the fact that the aldol intermediate was observed when the reaction was monitored by NMR analyses of the crude reaction mixture.

In summary, we have reported a simple highly enantioselective organocatalytic asymmetric domino thia-Michael/aldol reaction. The chiral pyrrolidine catalyzed domino reactions between thiosalicylic aldehyde and α,β-unsaturated aldehydes proceeded with high chemo- and enantioselectivities to furnish thiochromene-3-carbaldehydes in high yields with 91–98% ee. Further elaboration of this novel transformation, its synthetic application and mechanistic studies are ongoing in our laboratory.[14]

Acknowledgement

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12. To a stirred solution of catalyst **9c** (20 mol %) and benzoic acid (20 mol %) in chloroform (0.5 mL) at −15 °C were added cinnamic aldehyde (1.0 equiv, 0.25 mmol) and 2-mercaptobenzaldehyde (1.2 equiv, 0.3 mmol). The reaction was vigorously stirred for 24 h and then purified by silica gel chromatography (pentane–EtOAc 10:1) to give the thiochromene-3-carbaldehyde **3a** in 74% yield as a light yellow solid. The ee of **3a** was 98% as determined by chiral-phase HPLC analysis. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.66$ (s, 1H), 7.46 (s, 1H), 7.39 (d, 1H, $J = 7$ Hz), 7.27–7.16 (m, 8H), 5.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.07$, 145.05, 141.62, 134.37, 134.04, 131.70, 130.95, 129.83, 128.59, 127.77, 127.54, 126.44, 125.80, 38.29. $[\alpha]_D^{25}$ +408.4 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD with *iso*-hexane/*i*-PrOH (97:3) as the eluent; flow: 0.5 mL/min; minor isomer: $t_R = 30.4$ min; major isomer: $t_R = 27.3$ min. HRMS (ESI): calcd for $(C_{16}H_{12}OS + H) = 253.0682$. Found 253.0677.
13. CCDC 615363 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
14. After our original submission of this manuscript to *Angewandte Chemie* on the 19th of July, a paper by Wang et al. (Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *ASAP*) appeared on the web on 26th July.