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A one-pot organocatalytic asymmetric entry to tetrahydrothioxanthenones

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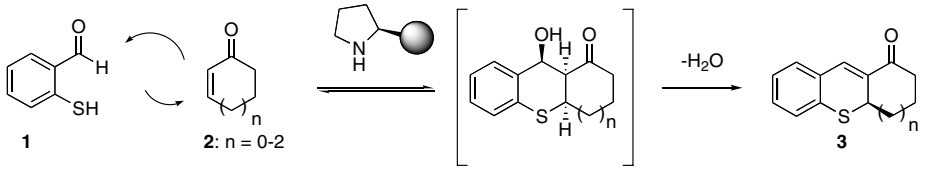
Abstract—A simple catalytic asymmetric synthesis of tetrahydrothioxanthenones is presented. The organocatalytic enantioselective domino reactions between 2-mercaptobenzaldehyde and α,β-unsaturated cyclic ketones proceed with excellent chemoselectivity to give the corresponding tetrahydrothioxanthenones in high yields and moderate to good enantioselectivities.

Xanthones are important classes of natural products that exhibit valuable pharmaceutical activity.[1] The benzothiopyran group is also an important structural motif in the preparation of pharmaceuticals.[2] It may also show a higher biological activity as compared to the corresponding benzopyran.[3] Hence, it would be of significant interest to develop a method for the synthesis of thioxanthones.

Bräse and co-workers have developed a simple catalytic method for the preparation of racemic tetrahydroxanthenones.[4,5] The reaction is mediated by tertiary amines via a Baylis–Hillman reaction pathway. However, there is to our knowledge, no report of a catalytic asymmetric version of this reaction. Recently, organocatalytic asymmetric transformations that involve catalytic domino or cascade reactions via enamine and iminium intermediates were reported.[6,7] Inspired by this research, we developed asymmetric methods for the synthesis of heterocycles via organocatalytic domino oxy-, thia-, and aza-Michael/aldol reactions between 2-heteroatom substituted benzaldehydes and α,β-unsaturated aldehydes.[8] Based on this concept, we envisioned a simple catalytic route to the synthesis of tetrahydrothioxanthenones via an organocatalytic asymmetric domino reaction between 2-mercaptobenzaldehyde **1** and α,β-unsaturated cyclic ketones **2** (Eq. 1).



(1)

Herein, we present the first amine-catalyzed asymmetric synthesis of tetrahydrothioxanthenones.

In an initial catalyst screen, we found that chiral pyrrolidines such as **5**–**7** catalyzed the reaction between 2-mercaptobenzaldehyde **1** (0.30 mmol) and 2-cyclohexen-1-one **2a** (0.25 mmol) with high chemoselectivity to give the corresponding tetrahydrothioxanthenone **3a** in high yields and moderate to good ee's (Table 1).[9]

The corresponding alcohol **4a** was also formed in significant amounts during the domino reaction with excellent diastereoselectivity. Notably, alcohol **4a** was dehydrated upon silica gel column chromatography when a slow gradient system was used. However, use of a lower amount of silica gel in combination with a rapid chromatography eluent system enabled the isolation of **4a** (entry 6).[10] We found that the chiral diamines **5** and **6** catalyzed transformations gave the highest

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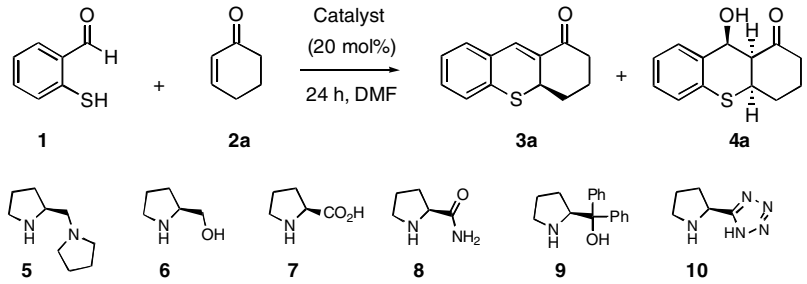
Table 1. Catalyst screen for the enantioselective domino reactions between **1** and **2a**[a]

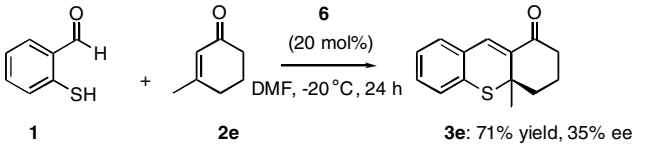


Entry	Cat.	Temp. (°C)	Prod.	Yield (%)[b]	ee (%)[c]	Prod.	Yield (%)[b]	Dr[d]
1	**5**	rt	**3a**	74	27	**4a**	Traces	n.d.
2	**5**	−20	**3a**	69	55	**4a**	Traces	n.d.
3	**5**	−25	**3a**	74	52	**4a**	Traces	n.d.
4	**6**	rt	**3a**	85	45	**4a**	Traces	n.d.
5	**6**	−20	**3a**	74	62	**4a**	Traces	n.d.
6	**6**	−20	**3a**	31	60	**4a**	24[e]	>20:1[e]
7	**7**	rt	**3a**	40	30	**4a**	Traces	n.d.
8	**8**	−20	**3a**	58	39	**4a**	Traces	n.d.
9	**9**	−20	**3a**	0	—	**4a**	0	—
10	**10**	−20	**3a**	Traces	n.d.	**4a**	Traces	n.d.

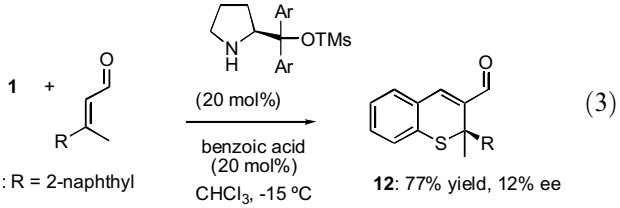
[a] Experimental conditions: A mixture of **1** (0.30 mmol), 2-cyclohexenone **2a** (0.25 mmol) and catalyst (20 mol%) in 0.5 mL solvent was stirred at room temperature under the conditions displayed in the Table.
[b] Isolated yield of pure compound **3a**.
[c] Determined by chiral-HPLC analyzes.
[d] Determined by NMR analysis.
[e] The reaction mixture was directly flushed through a silica gel column.

enantioselectivity in DMF.[11] For instance, (*S*)-prolinol **6** catalyzed the asymmetric formation of **3a** in 74% yield and 62% ee in DMF at −20 °C. Moreover, adding an organic acid additive did not improve further the stereoselectivity of the reaction. Hence, we decided to investigate the scope of the organocatalytic tetrahydrothioxanthenone synthesis using the former reaction conditions and chiral amines **5** and **6** as the catalysts (Table 2).

The catalytic domino reactions with cyclic enones **2a–d** were highly chemoselective and furnished the corresponding tetrahydrothioxanthenones **3a–d** in high yields with 44–67% ee. Moreover, the corresponding alcohols **4a–d** were isolated using a rapid column chromatography eluent system. Crude NMR analyzes revealed that the reactions were highly diastereoselective and only one diastereomer was detected. We also investigated the possibility of generating tertiary chiral centres incorporating thio-substituents by employing 3-methyl-2-cyclohexenone **2e** as an acceptor (Eq. 2).



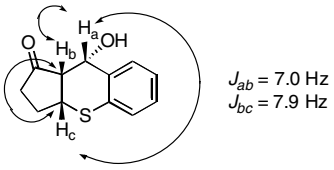
(2)



(3)

To our delight, prolinol **6** catalyzed the formation of hydrothioxanthenone **3e** in 71% yield. In comparison, protected chiral diarylprolinols catalyzed the formation of thiochromene **12** with a tertiary chiral stereocentre in 77% yield but lower enantioselectivity using enal **11** as the substrate.[8b,c,12]

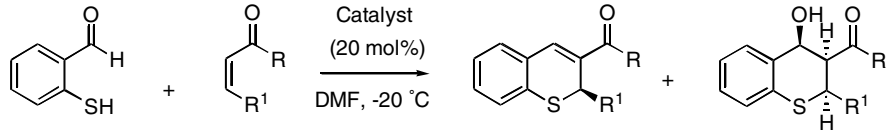
The relative stereochemistry of the alcohols **4** were established by NOE experiments on **4c** and the coupling constants between H_a and H_b and H_b and H_c.



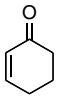
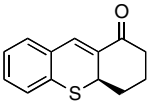
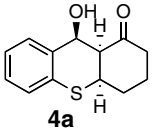
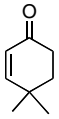
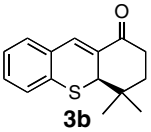
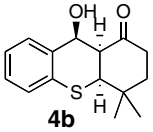
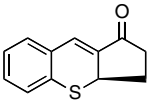
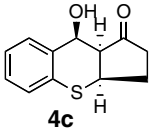
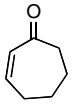
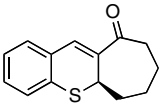
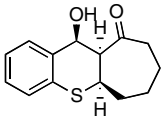
Based on these experiments, we propose the following mechanism for the chiral amine catalyzed reactions. The reaction starts with iminium activation of the α,β-unsaturated cyclic ketone by the chiral pyrrolidine derivatives. Next, stereoselective nucleophilic conjugate attack on the β-carbon by the thiol **1** results in a chiral enamine intermediate, which performs an intramolecular 6-*exo* trig aldol addition from the same face as the incoming thiol, followed by hydrolysis of the resulting iminium intermediate to give the aldol product **4**. Next, elimination of water gives the corresponding tetrahydrothioxanthenone **3**.

In summary, we report a simple organocatalytic asymmetric stereoselective synthesis of tetrahydrothioxanthenones. The simple chiral pyrrolidine catalyzed domino

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



1 **2** **3a** **4a**

Entry	Cat.	Ketone	Prod.	Yield (%)[b]	ee (%)[c]	Prod.	Yield (%)[b]	Dr[d]
1	**6**	 **2a**	 **3a**	74	62	 **4a**	Traces	n.d.
2	**6**	**2a**	**3a**	31	60	**4a**	24[e]	>20:1[e]
3	**6**	 **2b**	 **3b**	77	48	 **4b**	Traces	n.d.
4	**6**	**2b**	**3b**	50	40	**4b**	30[e]	>20:1[e]
5	**5**	 **2c**	 **3c**	78	38	 **4c**	Traces	n.d.
6	**5**	**2c**	**3c**	58	44	**4c**	n.d.[e]	>20:1[e]
7	**5**	 **2d**	 **3d**	70	60	 **4d**	Traces	n.d.
8	**5**	**2d**	**3d**	37	67	**4d**	39[e]	>20:1[e]

[a] Experimental conditions: A mixture of **1** (0.30 mmol), ketone **2** (0.25 mmol) and catalyst (20 mol%) in 0.5 mL solvent was stirred in DMF at −20 °C.
[b] Isolated yield of pure compound **3a**.
[c] Determined by chiral-HPLC analyzes.
[d] Determined by NMR analysis.
[e] The reaction mixture was rapidly flushed through a silica gel column.

thia-Michael/aldol reaction between 2-mercaptobenzaldehyde and α,β-unsaturated cyclic ketones proceeds with high chemo- and diastereoselectivities and furnishes the corresponding tetrahydrothioxanthenones in high yields with moderate to good ee's. Further investigations of this novel transformation and its synthetic applications are ongoing in our laboratory.

Acknowledgements

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9. To a stirred solution of catalyst (20 mol%) in DMF (0.5 mL) at −20 °C were added α,β-unsaturated ketone **2** (1.0 equiv. 0.25 mmol) and 2-mercaptobenzaldehyde **1** (1.2 equiv. 0.3 mmol). The reaction was vigorously stirred for 24 h and then purified by silica gel chromatography (pentane/EtOAc 20:1) to give the corresponding tetrahydrothioxanthenone **3**.
Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.52$ (d, $J = 2.1$ Hz, 1H), 7.40–7.10 (m, 3H), 4.27 (ddd, $J = 2.4$ Hz, $J' = 5.7$ Hz, $J'' = 11.1$ Hz, 1H), 2.70–2.60 (m, 1H), 2.50–2.40 (m, 1H), 2.30–1.80 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.2$, 135.5, 135.4, 131.7, 131.4, 130.5, 130.1, 126.6, 126.0, 39.2, 38.3, 28.4, 20.9. $[\alpha]_D^{25}$ −38.2 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD–H with *iso*-hexane/*i*-PrOH (98:2) as the eluent. Flow: 1.0 mL/min; minor isomer: $t_R = 17.0$ min; major isomer: $t_R = 15.3$ min.
10. Compound **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$ (d, $J = 5.6$ Hz, 1H), 7.18–7.08 (m, 3H), 5.12 (d, $J = 4$ Hz, 1H), 4.20 (m, 1H), 3.15 (t, $J = 4$ Hz, 1H), 2.40–1.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 207.9$, 132.6, 132.0, 130.5, 128.4, 126.7, 125.0, 67.2, 53.6, 40.6, 38.0, 28.8, 22.4. $[\alpha]_D^{25}$ −3.3 (*c* 0.24, $CHCl_3$).
11. The reaction also works in other solvents. The following are the results from the diamine **5** catalyzed reactions at room temperature: 74% yield, 18% ee ($CHCl_3$); 80% yield, 14% ee (toluene); 90% yield, 8% ee (MeOH); 60% yield, 32% ee (DMSO); 61% yield, 28% ee (CH_3CN).
12. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.57$ (s, 1H), 7.86 (d, $J = 1.8$ Hz, 1H), 7.80–7.75 (m, 3H), 7.73 (d, $J = 1.8$ Hz, 1H), 7.50–7.15 (m, 7H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.2$, 145.8, 141.0, 139.6, 134.9, 132.8, 132.4, 131.8, 130.9, 130.1, 129.1, 128.3, 127.9, 127.5, 126.2, 126.1, 125.7, 125.4, 125.1, 49.9, 27.1; HRMS (ESI) calcd. for ($C_{21}H_{16}OS$+H) = 317.0994. Found 317.0995. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD–H with *iso*-hexane/*i*-PrOH (95:5) as the eluent. Flow: 1.0 mL/min; minor isomer: $t_R = 14.9$ min; major isomer: $t_R =$ 12.1 min.