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A simple and concise catalytic asymmetric entry to tetrahydroxanthenones

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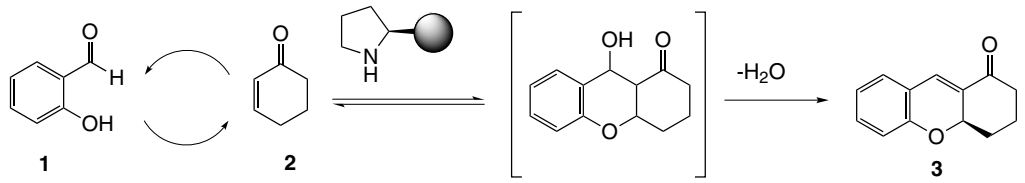
Abstract—The first catalytic asymmetric synthesis of tetrahydroxanthenones is presented. The simple organocatalytic enantioselective domino reactions between salicylic aldehyde derivatives and α,β-unsaturated cyclic ketones proceed with excellent chemoselectivity to give the corresponding tetrahydroxanthenones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

Xanthones have attracted much attention from a broad area of science, including medicinal chemistry, physical chemistry, synthetic organic chemistry and natural product chemistry, because of their distinctive structure and the potential for further transformations.[1] Tetrahydroxanthenones are among the most important classes in the family of xanthones.[2] There are different methods reported for the racemic synthesis of tetrahydroxanthenones. For example, Bräse and co-workers have described a very efficient approach to tetrahydroxanthenones, adopting the condensation between salicylic aldehydes and 2-cyclohexen-2-ones.[3] The reaction is mediated by tertiary amines via a Baylis–Hillman reaction pathway. More recently, Shi reported a new approach to the synthesis of tetrahydroxanthenones using *N*-tosylimines to replace salicylic aldehydes and dimethylphenylphosphine as a catalyst.[4] 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.[5,6] 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.[7] We have also recently developed methodology for the synthesis of tetrahydrothioxanthenones.[8] Based on this concept, we envisioned a simple catalytic route to the synthesis of tetrahydroxanthenones via an organocatalytic asymmetric domino reaction between salicylic aldehyde derivatives **1** and α,β-unsaturated cyclic ketones **2** (Eq. 1).



(1)

Herein, we present the first amine-catalyzed asymmetric synthesis of tetrahydroxanthenones, in good to moderate yields with 85–91% ee.

In an initial catalyst screen, we found that chiral pyrrolidines such as **4**, **5** and **7** catalyzed the reaction between 2-hydroxybenzaldehyde **1a** (0.30 mmol) and 2-cyclohexen-1-one **2a** (0.25 mmol) with high chemoselectivity to give the corresponding tetrahydroxanthenone **3a** in moderate yields and moderate to good ee's (Table 1).[9]

We found that the chiral diamine **4** catalyzed transformations gave the highest enantioselectivity in CH_3CN and MeOH. For instance, (*S*)-1-(2-pyrrolidinyl-

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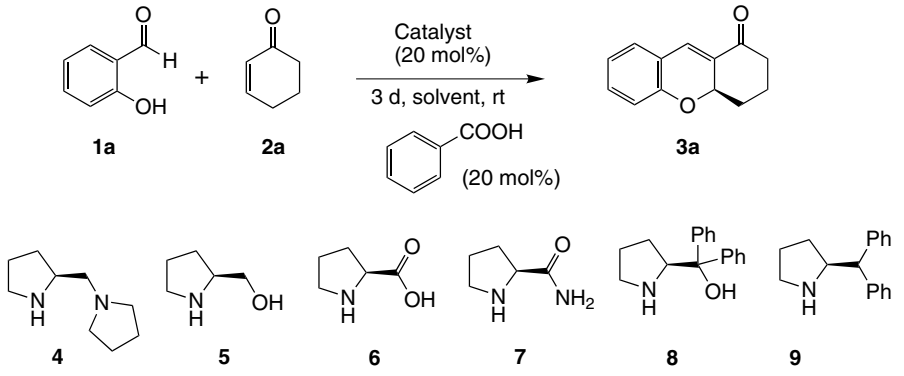
Table 1. Catalyst screen for the enantioselective domino reactions between **1** and **2a**[a]



Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**4**	CH_3CN	48	75
2	**4**	Toluene	56	30
3	**4**	MeOH	58	77
4	**4**	DMF	Traces	n.d.
5	**5**	CH_3CN	22	54
6	**6**	CH_3CN	N.R.	—
7	**7**	CH_3CN	16	39
8	**8**	CH_3CN	N.R.	—
9	**9**	CH_3CN	N.R.	—

[a] Experimental conditions: a mixture of **1** (0.25 mmol), 2-cyclohexenone **2a** (0.30 mmol), benzoic acid (20 mol %) and catalyst (20 mol %) in 1 mL of 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.

methyl)pyrrolidine **4** catalyzed the asymmetric formation of **3a** in 58% yield and 77% ee in MeOH at rt.[10] Moreover, adding an organic acid additive improved the stereoselectivity of the reaction. Hence, we decided to investigate the use of various organic acids and different reaction conditions to enhance the enantioselectivity of the reaction using the chiral diamine **4** as a catalyst (Table 2).

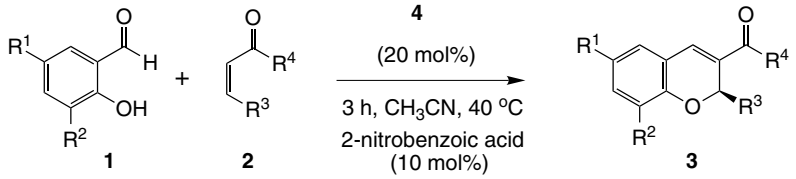
Tetrahydroxanthenone **3a** was catalytically assembled using **4** in moderate yield and good enantioselectivity when 2-nitrobenzoic acid was used as an additive. The highest enantioselectivity was obtained in CH_3CN at room temperature. Furthermore, increasing the reaction temperature improved the yield and decreased the reaction time without significant loss of enantioselectivity (entry 10).[11] Encouraged by this result, we decided to

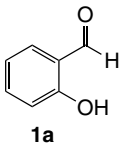
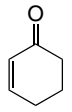
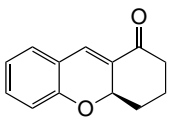
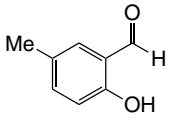
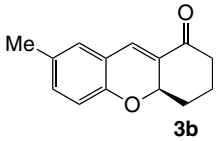
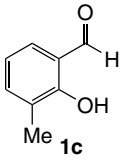
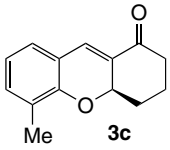
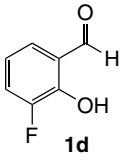
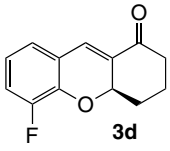
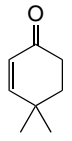
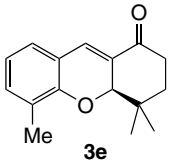
Table 2. Acid screen for the enantioselective domino reactions between **1** and **2a**[a]

Entry	Acid	Solvent	Time (h)	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	C_6H_5COOH	CH_3CN	72	rt	48	75
2	2-$NO_2C_6H_4COOH$	CH_3CN	120	rt	46	85
3	C_6H_5COOH	MeOH	72	rt	58	77
4	2-$NO_2C_6H_4COOH$	MeOH	120	rt	56	77
5	2-FC_6H_4COOH	CH_3CN	120	rt	46	78
6	3,5-$(NO_2)_2C_6H_3COOH$	MeOH	120	rt	56	78
7	3,5-$(NO_2)_2C_6H_3COOH$	CH_3CN	120	rt	42	91
8	No acid added	MeOH	120	rt	Traces	76
9	No acid added	CH_3CN	120	rt	Traces	86
10[d]	2-$NO_2C_6H_4COOH$	CH_3CN	3	40	52	89

[a] Experimental conditions: a mixture of **1** (0.25 mmol), 2-cyclohexenone **2a** (0.30 mmol), organic acid (20 mol %) and catalyst (20 mol %) in 1 mL of 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.
[d] 10% of 2-nitrobenzoic acid and 0.50 mmol of 2-cyclohexenone were employed.

Table 3. Direct organocatalytic asymmetric domino oxo-Michael/aldol condensation between hydroxybenzaldehydes **1** and α,β-unsaturated ketones **2**[a]



Entry	2-Hydroxybenzaldehyde	Ketone	Product	Yield[b] (%)	ee[c] (%)
1	 **1a**	 **2a**	 **3a**	52 (42)[d]	89 (91)[d]
2	 **1b**	**2a**	 **3b**	51	86
3	 **1c**	**2a**	 **3c**	53	87
4	 **1d**	**2a**	 **3d**	56	85
5	**1c**	 **2b**	 **3e**	51	88

[a] Experimental conditions: a mixture of **1** (0.25 mmol), 2-cyclohexenone **2a** (0.50 mmol), 2-nitrobenzoic acid (10 mol %) and catalyst (20 mol %) in 1 mL of solvent was stirred at 40 °C for 3 h.
[b] Isolated yield of pure compound **3**.
[c] Determined by chiral-HPLC analyses.
[d] Reaction run at room temperature. 3,5-$(NO_2)_2C_6H_3COOH$ was used as the additive.

investigate the catalytic asymmetric domino oxo-Michael/aldol reaction between **1a** and various α,β-unsaturated ketones with **4** as the organocatalyst and 10% of 2-nitrobenzoic acid (Table 3) at 40 °C.

The catalytic domino reactions with cyclic enones **2a** and **b** were highly chemoselective and furnished the corresponding tetrahydroxanthenones **3a**–**e** in moderate yields and excellent enantioselectivities (85–89% ee). The only products were the tetrahydroxanthenones **3** and the unreacted starting materials which could be recovered.

Based on our previous work,[7,8] 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. Stereoselective nucleophilic conjugate attack on the β-carbon by alcohol **1** results in a chiral enamine intermediate, which performs an intramolecular 6-*exo* trig aldol addition from the same face as the incoming alcohol, followed by hydrolysis of the resulting iminium intermediate to give the aldol product **4**. Elimination of water gives the corresponding tetrahydroxanthenone **3**.

In summary, we have reported the first organocatalytic asymmetric stereoselective synthesis of tetrahydroxanthenones. The simple chiral pyrrolidine catalyzed domino oxo-Michael/aldol reaction between 2-hydroxybenzaldehyde and α,β-unsaturated cyclic ketones proceeds with high chemo- and diastereoselectivity and furnishes the corresponding tetrahydroxanthenones in moderate yields with high ee's (up to 91% ee). Further

investigations on 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 CH_3CN (1.0 mL) at rt was added α,β-unsaturated ketone **2** (1.2 equiv, 0.30 mmol) and 2-hydroxybenzaldehyde **1** (1.2 equiv, 0.3 mmol). The reaction was vigorously stirred for 72 h and then purified by silica gel chromatography (pentane/EtOAc 20:1) to give the corresponding tetrahydroxanthenone **3**.
10. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, $J = 2.0$ Hz, 1H), 7.30–7.20 (m, 2H), 6.95 (dt, $J = 7.6$ Hz, $J' = 1.2$ Hz, 1H), 6.87 (d, $J = 7.6$ Hz, 1H), 5.00 (m, 1H), 2.61–2.38 (m, 2H), 2.16–1.96 (m, 2H), 1.78–1.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 155.8, 132.0, 131.5, 130.4, 129.8, 122.1, 121.5, 116.1, 74.6, 39.3, 29.8, 18.7. HRMS (ESI): calcd for $[M+Na]^+$ ($C_{13}H_{12}O_2Na$) requires m/z 223.0730, found 223.0730. $[\alpha]_D$ −20.3 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with *iso*-hexane/*i*-PrOH (90:10 as the eluent. Flow: 0.5 mL/min; minor isomer: $t_R =$ 15.8 min; major isomer: $t_R = 19.6$ min).
11. Longer reaction times do not increase the yield of the reaction and decrease the enantioselectivities.