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Dual Organocatalytic Ion-Pair Assemblies: A Highly Efficient Approach for the Enantioselective Oxa-Michael–Mannich Reaction of Salicylic Aldehydes with Cyclohexenones

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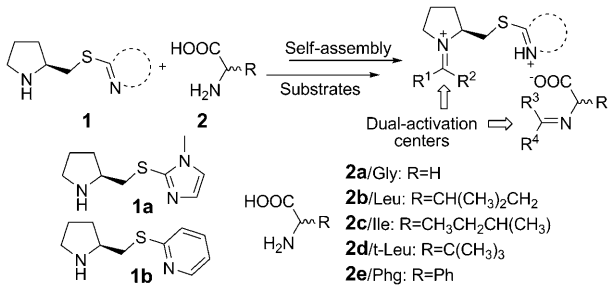
Organocatalysis has made great progress in recent years.[1] However, developing novel types of catalysts and organocatalytic strategies to achieve high activity and enantioselectivity is still a big challenge in asymmetric catalysis.[2] Recently, the synergistic activation by the self-assembly of two or more organocatalysts has been introduced as a useful strategy for high-performance asymmetric catalysis.[3] In comparison with the conventional covalent-bonded multifunctional catalysts, the highly modular nature of the assembly should allow a more convenient optimization of the catalyst, thereby facilitating the achievement of excellent catalytic activity and enantioselectivity.[4] Herein, we present a novel type of bifunctional catalyst generated by the self-assembly of pyrrolidines **1** and readily available primary amino acids **2**.[5–6] As shown in Scheme 1, the protonation of the aromatic nitrogen atom of pyrrolidines **1** by amino acids **2** spontaneously leads to ion-pair assemblies.[7] Notably, the self-assembled catalysts possess dual activation centers and thus, similar to catalysis by enzymes, enable the catalysis of the electrophilic and nucleophilic substrates simultaneously.



Scheme 1. Proposed self-assembly and applied precatalyst modules.

The tricyclic structure moiety of xanthones is found in a variety of natural products with interesting biologic activities.[8] Tetrahydroxanthenones are common motifs in the family of xanthones and are used as versatile intermediates for further transformation in organic and natural product synthesis, and thus their synthesis has attracted considerable attention.[9] Recently, Córdova and co-workers reported the first catalytic asymmetric synthesis of tetrahydroxanthenones from cyclohexenones and salicyclic aldehydes by an oxa-Michael–aldol reaction using a chiral pyrrolidine with moderate yields and up to 91% *ee*.[9g]

We envisaged that the bifunctional catalysts mentioned above should facilitate this asymmetric transformation by a domino oxa-Michael–Mannich reaction. As shown in Scheme 2, the simultaneous activation of cyclohex-2-enone and salicylic aldehyde by pyrrolidines **1** and amino acids **2**, respectively, generates the transient ion pairs through iminiums **6** and imines **7**. The resultant assemblies ensure that the enantioselective domino oxa-Michael addition and intramolecular Mannich reaction proceeded to afford, upon hydrolysis, the corresponding products **8** and release the pyrrolidines **1**. Finally, elimination of the resulting Mannich bases leads to the desired tetrahydroxanthenone, concurrently regenerating the amino acids **2**.

To assess the viability of this domino process, the investigation was started by reacting salicylic aldehyde with cyclohex-2-enone in the presence of various precatalyst modules **1**/**2**. As shown in Table 1, after six days of stirring in MeCN at ambient temperature, less than 5% conversions were observed when **1a** was used alone or in combination with conventional carboxylic acids (Table 1, entries 1–3). In contrast, the assembly of **1a** with **2a** (or L-**2b**, L-**2c**) gave 18–24%

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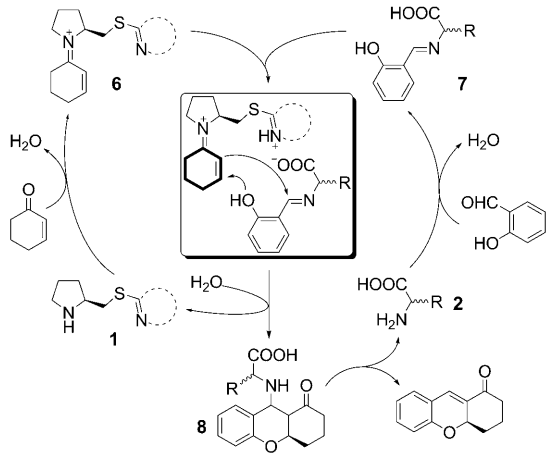
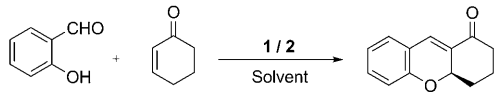


Scheme 2. Proposed catalytic cycle and transition states for the domino reaction.

Table 1. Reaction of salicylic aldehyde with cyclohex-2-enone catalyzed by the assemblies **1/2**.[a]



3a **4a** **5a**

Entry	**1**	**2**	Solvent	*t* [day]	C[b] [%]	*ee*[c] [%]
1	**1a**	none	MeCN	6	trace	–
2	**1a**	CH_3COOH	MeCN	6	1	72
3	**1a**	4-$NO_2C_6H_4CO_2H$	MeCN	6	<5	71
4	**1a**	**2a**	MeCN	1.5	24	75
5	**1a**	L-**2b**	MeCN	1.5	18	74
6	**1a**	L-**2c**	MeCN	1.5	24	72
7	**1a**	L-**2d**	MeCN	1.5	35	82
8	**1a**	D-**2d**	MeCN	1.5	2	80
9	**1a**	L-**2e**	MeCN	1.5	17	73
10	**1a**	D-**2e**	MeCN	1.5	2	75
11	**1b**	L-**2d**	MeCN	1.5	3	84
12	**1b**	D-**2d**	MeCN	1.5	37	86
13	**1b**	D-**2d**	MeOH	3	10	74
14	**1b**	D-**2d**	DMSO	3	20	72
15	**1b**	D-**2d**	PhMe	3	>99	76
16	**1b**	D-**2d**	CH_2Cl_2	3	>99	79
17	**1b**	D-**2d**	Et_2O	3	>99	75
18	**1b**	D-**2d**	THF	3	>99	80
19	**1b**	**D-2d**	**Diox**[d]	**3**	**>99**	**88**
20	**1b**	D-**2d**	Diox	2	96	88
21[e]	**1b**	**D-2d**	**Diox**	**2**	**96**	**92**
22[f]	**1b**	D-**2d**	Diox	2	93	89
23	none	D-**2d**	Diox	6	trace	–
24	**1b**	none	Diox	6	48	60
25	Boc-**1b**[g]	D-**2d**	Diox	2	trace	–
26	**1b**	Boc-D-**2d**[h]	Diox	2	43	85
27	**1b**	D-**2d**-ester[i]	Diox	6	<5	31 (*S*)

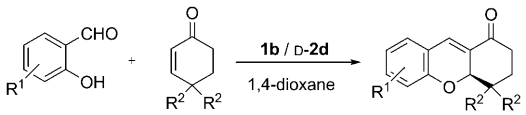
[a] Unless otherwise indicated, all reactions were conducted in solvent (1 mL) using salicylic aldehyde **3a** (1 mmol) and cyclohex-2-enone **4a** (3.5 mmol) in the presence of 30 mol% **1** and 30 mol% **2** at room temperature with stirring. [b] Conversion of **3a** to the product, less than 5% conversion of **4a** to the self Michael addition product was found, as determined by GC-MS. [c] Determined by HPLC analysis on a chiralcel OD-H column. [d] 1,4-Dioxane. [e] 20 mol% each of **1b** and D-**2d** was used. [f] 15 mol% each of **1b** and D-**2d** was used. [g] N-Boc-protected **1b**. [h] N-Boc-protected D-**2d**. [i] The methyl ester of D-**2d**.

conversions after only 1.5 days (Table 1, entries 4–6). Further experiments revealed that the enantiomers of amino acids **2** showed strong matching and mismatching effects with pyrrolidines **1**. Though similar enantioselectivies were observed, L-**2d** and L-**2e** together with **1a**, respectively, exhibited superior activities to their D-enantiomers, leading to increased conversions of 35% and 17% (Table 1, entries 7 and 9 vs. entries 8 and 10). Whereas in the case of the assembly of **1b** with **2d**, D-**2d** gave the superior results (Table 1, entry 11 vs. entry 12). Notably, all assemblies tested afforded the desired tetrahydroxanthenone **5a** with the same *R* configuration,[10] implying that the modules **1** in the assembly play a leading role in the enantioselectivity of the oxa-Michael addition step.

With regard to the various assemblies **1/2**, the assembly of **1b** with D-**2d** appeared to be the most suitable for this transformation in terms of conversion and enantioselectivity, and functioned most effectively in 1,4-dioxane as solvent to afford almost complete conversion and 88% *ee* after three days (Table 1, entries 12–19). The domino reaction proceeded also smoothly in lower catalyst loading (Table 1, entries 20–22). In contrast, even when the reaction was carried out in dioxane, poor catalytic performance was observed when **1b** or D-**2d** were used alone, or when **1b** and D-**2d** were N-Boc-protected (Table 1, entries 23–26). In addition, the combination of **1b** and the methyl ester of D-**2d** gave the desired product in very low yields (Table 1, entry 27). These results clearly indicated the importance of the dual activation and catalyst assembly.

A range of salicylic aldehydes were then surveyed to determine the scope of the methodology. As shown in Table 2, the assembly of **1b** and D-**2d** was highly effective in promoting the domino reaction of cyclohexenone with a variety of

Table 2. The enantioselective reaction of salicylic aldehydes with cyclohexenones promoted by the assembly of **1b**/D-**2d** in dioxane.[a]



3 **4** **5**

Entry	R^1	R^2	Prod	*t* [h]	C[b] [%]	Yield[c] [%]	*ee*[d] [%]
1	H	H	**5a**	48	96	89	92
2	3-MeO	H	**5b**	40	97	90	95
3	5-MeO	H	**5c**	20	>99	95	92
4	3-F	H	**5d**	12	>99	95	91
5	5-F	H	**5e**	12	>99	95	93
6	5-Cl	H	**5f**	12	>99	91	93
7	5-Br	H	**5g**	12	95	86	93
8	3-MeO-5-Br	H	**5h**	12	94	89	98
9	3,5-DiCl	H	**5i**	12	94	87	97
10	3,5-DiBr	H	**5j**	12	95	86	97
11[e]	3-MeO-5-Br	Me	**5k**	72	95	88	80

[a] All reactions were conducted in 1,4-dioxane (1 mL) using **3** (1 mmol) and **4** (3.5 mmol) in the presence of 20 mol% **1b** and 20 mol% D-**2d** at room temperature. [b] Conversion to the product, as determined by GC-MS. [c] Isolated yield. [d] Determined by HPLC analysis on a chiralcel OD-H column or chiralcel AD-H column. [e] Reacted at 30°C.

salicylic aldehydes (Table 2, entries 1–10). It appeared that the electronic property and the position of the substituents on the phenyl ring of salicylic aldehydes had a very limited influence on the enantioselectivity of the reaction, and the desired tetrahydroxanthenones **5** were obtained with 91–98% *ee*. Likewise, the assembly was also reactive for 4-dimethylcyclohex-2-enone to give 88% yield and 80% *ee* within 72 h (Table 2, entry 11).

Results of mass spectrometry experiments confirmed the proposed catalytic cycle.[11] As shown in Figure 1 and Figure 2, the ESI mass spectra showed the signals for the key transition states **6–8** involved in this domino reaction. These results were further confirmed by accurate mass data using Fourier-transform ion cyclotron resonance mass spectrometry in Table 3.

In summary, we have developed a highly efficient approach for the asymmetric oxa-Michael–Mannich reaction of salicylic aldehydes with cyclohexenones to generate versatile tetrahydroxanthenones in up to 98% *ee*. The special feature of the approach is the first application of bifunctional catalysts formed from the ion-pair assembly of pyrrolidines and readily available primary amino acids, which simultaneously activate the two substrates. The key intermediates in this domino reaction were fully characterized by using mass spectrometry. We believe that the present strategy will aid the development of future asymmetric transformations.

Table 3. High-resolution mass data of detected intermediates **6–8**.

Species	Formula	Mass (measured)	Mass (calculated)	Error [ppm]
6	$C_{16}H_{21}N_2S$	273.1415	273.1420	1.8
7	$C_{13}H_{16}NO_3$	234.1140	234.1130	4.3
8	$C_{19}H_{24}NO_4$	330.1711	330.1705	1.8

Experimental Section

Typical experimental procedure for the oxa-Michael–Mannich reaction of salicylic aldehydes 3 and cyclohexenones 4 (Table 1, entry 21): 2-Hydroxybenzaldehyde (112 mg, 1 mmol) and the amino acid D-**2d** (26.2 mg, 0.2 mmol) were added to 1,4-dioxane (1 mL) at room temperature with vigorous stirring. After the D-**2d** had dissolved in the solution, cyclohex-2-enone (336 mg, 3.5 mmol) and pyrrolidine **1b** (38.8 mg, 0.2 mmol) were added to the solution. The reaction conversion was monitored by GC-MS. After reaction at room temperature for 2 days, the reaction mixture was extracted with EtOAc (3×10 mL), washed with water, dried, and concentrated. The residue was purified by flash chromatography, eluted with ether/petroleum ether to give the desired oxa-Michael-Mannich product **5a**. The enantiomeric ratio was determined by HPLC analysis on Daicel Chiralpak OD-H; hexane/2-propanol (90:10, 1.0 mL min^{-1}); retention time: 11.92 (minor), 9.07-(major). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, J = 2.0 Hz, 1H), 7.28–7.22 (m, 2H), 6.98–6.95 (m, 1H), 6.90–6.88 (d, J = 8.5 Hz, 1H), 5.03–4.99 (m, 1H), 2.54–2.50 (m, 1H), 2.43–2.41 (m, 1H), 2.35–2.28 (m, 1H), 2.05–1.99 (m, 1H), 1.97–1.89 (m, 1H), 1.68–1.58 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.5, 155.9, 132.0, 131.5, 130.4, 129.8, 122.1(×2), 116.0, 74.6, 38.8, 29.7, 18.0 ppm; GC-MS: m/z: 200.1, 199.1, 197.1, 144.1-(100), 115.1; HRMS: (EI+) m/z calcd for $[C_{13}H_{12}O_2]^+$ 200.0837, found 200.0846.

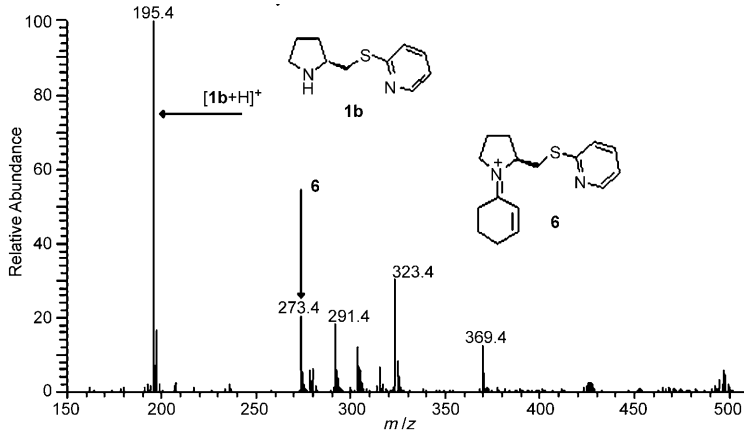


Figure 1. ESI mass spectrum (positive mode) of the domino reaction, 2 h after the start of the reaction.

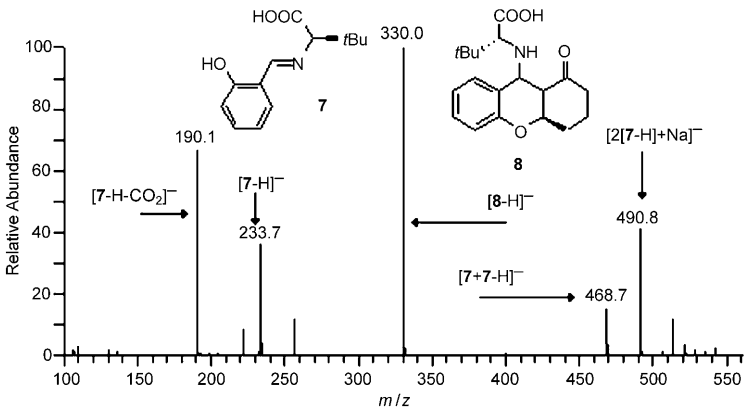


Figure 2. ESI mass spectrum (negative mode) of the domino reaction, 2 h after the start of the reaction.

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Keywords: asymmetric synthesis · dual activation · organocatalysis · oxa-Michael–Mannich reaction · self-assembly

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