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Asymmetric Organocatalysis: An Efficient Enantioselective Access to Benzopyranes and Chromenes

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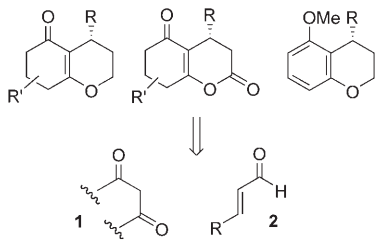
Functionalized chromenes and benzopyranes are important compounds which, due to their biological activity, find wide application in medicinal chemistry. They display not only spasmolytic, diuretic, clotting, antiviral, anti-tumoral, and anti-anaphylactic activity, but can also be used as pigments, photo-active materials, and biodegradable agrochemicals. Furthermore, benzopyranes and chromenes are components of numerous natural products.[1]

Based on their frequent occurrence, extensive application, and the lack of existing enantioselective preparative methods, we decided to develop an asymmetric, organocatalytic, synthetic route starting from 1,3-diketones **1** and α,β-unsaturated aldehydes **2**.



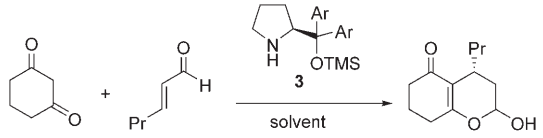
This would not only be a valuable example of such a metal-free, enantioselective reaction but would allow fast and efficient access to these desirable products. We assumed that the reaction of α,β-unsaturated aldehydes **2** with a chiral secondary amine would result in the formation of an intermediary iminium ion.[2] This would subsequently react with a diketone **1** in a 1,4-addition reaction and the following acetalization was anticipated to result in the desired enantiomeric enriched chromenones[3] and their derivatives.[4]

We began our experimental investigations with the transformation of cyclohexane-1,3-dione (**1a**) with α,β-unsaturated aldehyde **2a** employing catalytic amounts of diarylprolinol silyl ethers[5] **3a** and **3b**. Even the initial experiments revealed that catalysis of the transformation could be achieved and that the chromenone **4a** can be isolated in good yields and enantioselectivities if diphenylprolinol ether **3** was employed as the catalyst (Table 1). This is in contrast to the use of tertiary or primary amines,[6] Lewis acids,[7] or Brønsted acids,[8] which result exclusively in the formation of the condensation products.

The addition–cyclization cascade reaction can be carried out in various polar and apolar solvents (Table 1, entries 3–7); very high enantioselectivities are obtained in dichloromethane at −20 °C with catalyst **3b** (Table 1, entry 3).

To further optimize the reaction conditions the catalyst loading of **3a** and **3b**, as well as the temperature, were varied (Table 2). Whereas the use of low catalyst loadings

Table 1. Diarylprolinol ether catalyzed enantioselective synthesis of chromenone **4a** in different solvents.



1a **2a** **3a**: Ar = Ph **3b**: Ar = 3,5-(CF_3)-Ph **4a**

Entry[a]	T [°C]	**3**	Solvent	Yield [%][b]	*ee* [%][c]
1	−20	**3a**	CH_2Cl_2	67	88
2	0	**3a**	CH_2Cl_2	85	88
3	−20	**3b**	CH_2Cl_2	44	98
4	−20	**3a**	toluene	80	92
5	RT	**3a**	DMSO	76	71
6	−20	**3a**	Et_2O	44	92
7	−20	**3a**	Bu_2O	62	94

[a] Reaction conditions: Cyclohexadione **1a**, aldehyde **2a** (1.5 equiv) and 20 mol% **3**. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess was determined by HPLC.

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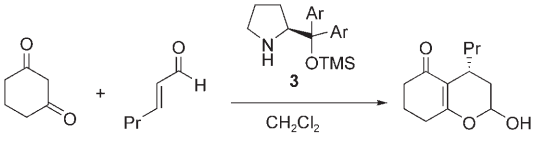
did not alter the observed enantioselectivities, the yield could be considerably increased by using milder temperatures. Interestingly, catalyst **3b** demonstrated better reactivity than catalyst **3a**, which may be due to the electron-withdrawing trifluoromethyl substituents. Hence, the enantioselective addition–cyclization cascade reaction[9] of diketone **1a** with aldehyde **2a** in the presence of 10 mol% of diarylprolinol catalyst **3b** gave the 2-hydroxychromenone (**4a**) in a yield of 78% and a remarkable enantiomeric excess of 96% *ee* (Table 2, entry 5).

Table 2. Influence of catalyst loading and temperature on the enantioselective addition–acetalization cascade.



Entry[a]	3	Mol% 3	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**3a**	10	0	89	88
2	**3a**	20	−20	67	88
3	**3b**	10	RT	69	92
4	**3b**	10	10	67	96
5	**3b**	10	0	78	96
6	**3b**	20	−20	44	98

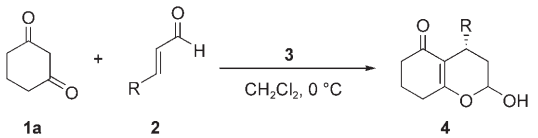
[a] Reaction conditions: Cyclohexadione **1a**, **2a** (1.5 equiv) in dichloromethane. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess was determined by HPLC.

Using these optimized conditions, we examined the scope of the new diarylprolinol ether catalyzed enantioselective reaction of diketone **1** with various α,β-unsaturated aldehydes **2** (Table 3).

In general, aliphatic as well as aromatic α,β-unsaturated aldehydes can for the first time be successfully applied in this transformation, and a variety of 2-hydroxychromenones **4a–h** can be isolated in good yields and with excellent enantioselectivities (up to 97%).

This efficient and highly enantioselective method was also successfully applied to other diketones, such as dimedone **1b** (Table 4). Yet again the organocatalytic addition–acetalization sequence provided a series of 2-hydroxychromenones **5a–l** with various aliphatic (Table 4, entries 1–5) and aromatic (Table 4, entries 6–12) substituents with excellent enantiomeric excesses (87–96% *ee*).

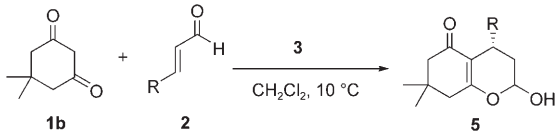
Table 3. Scope of the diarylprolinol ether catalyzed enantioselective synthesis of chromenones.



Entry[a]	Product	3	R	Yield [%][d]	*ee* [%][e]
8	**4a**	**3b**	C_3H_7	78	96
2	**4b**	**3b**	C_7H_{15}	66	96
3	**4c**	**3b**	$C_{10}H_{21}$	67	96
4	**4d**[b]	**3a**	2-NO_2Ph	77	94
5	**4e**[c]	**3a**	2-ClPh	51	93
6	**4f**[b]	**3a**	2-BrPh	78	96
7	**4g**[b]	**3a**	3-BrPh	95	87
8	**4h**[b]	**3a**	4-BrPh	76	97

[a] Reaction conditions: Cyclohexadione **1a**, **2** (1.3 equiv) and 10 mol% **3b**. [b] With 20 mol% **3a.** [c] With 20 mol% **3a** at room temperature. [d] Yield of isolated product after column chromatography. [e] Enantiomeric excess was determined by HPLC.

Table 4. Extended scope of the diarylprolinol catalyzed enantioselective addition-cyclisation cascade.

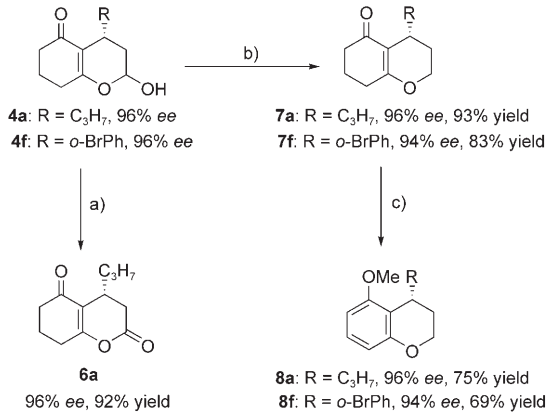


Entry[a]	Product	3	R	Yield [%][e]	*ee* [%][f]
1	**5a**	**3b**	C_2H_5	62	94
2	**5b**	**3b**	C_3H_7	73	95
3	**5c**	**3b**	C_4H_9	68	96
4	**5d**	**3b**	C_7H_{15}	67	96
5	**5e**	**3b**	$C_{10}H_{21}$	67	96
6	**5f**[b]	**3a**	Ph	89	94
7	**5g**[b]	**3a**	2-NO_2Ph	49	92
8	**5h**[c]	**3a**	2-ClPh	64	92
9	**5i**[c]	**3a**	2-BrPh	63	92
10	**5j**[b]	**3a**	2-CH_3Ph	69	88
11	**5k**[b]	**3a**	2,4-$(CH_3)_2$Ph	76	87
12	**5l**[d]	**3b**	3-BrPh	48	92

[a] Reaction conditions: Cyclohexadione **1b**, aldehyde **2** (1.3 equiv) and 10 mol% **3b**. [b] With 20 mol% **3a** at 0°C. [c] With 20 mol% **3a** at room temperature. [d] With 20 mol% **3b**. [e] Yield of isolated product after column chromatography. [f] Enantiomeric excess was determined by HPLC.

The chromenones **4** are not only important biologically active compounds and components of natural products,[10] but also valuable substrates for the synthesis of further pharmacologically interesting compounds. For instance, the 2-hydroxychromenones **4a** can readily be oxidized to the lactones **6a** in the presence of PCC and without loss of enantiomeric excess (Scheme 1a). The chromenones can also be directly transformed into the corresponding cyclic ethers, the oxadecalinones **7**. The reaction proceeds with good yields as demonstrated for the first time with compounds **4a** and **4f**. Hence, the transformation of **4a** and **4f** with sodium borohydride results in the intermediary alcohol which, following an acid catalyzed substitution, gives the oxadecalinones[11] **7a** and **7f** (Scheme 1b). Furthermore, the compounds **7a** and **7f** could be transformed under oxidative conditions into the enantiomerically enriched benzopyranes **8a** and **8f**, whereby no loss of enantiomeric excess occurs (Scheme 1c).

The constitution und configuration of the products was determined by using X-ray crystallography. Suitable crystals



Scheme 1. Reaction conditions: a) PCC, CH_2Cl_2, RT; b) $NaBH_4$, H_2SO_4; c) I_2, MeOH, reflux.

of compound **5i** were obtained which enabled the assignment of the absolute configuration (Figure 1).

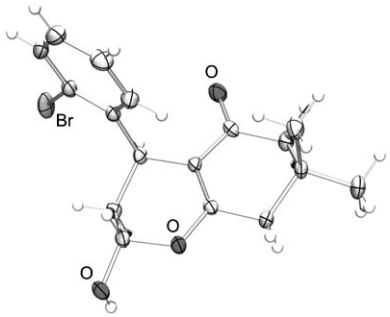
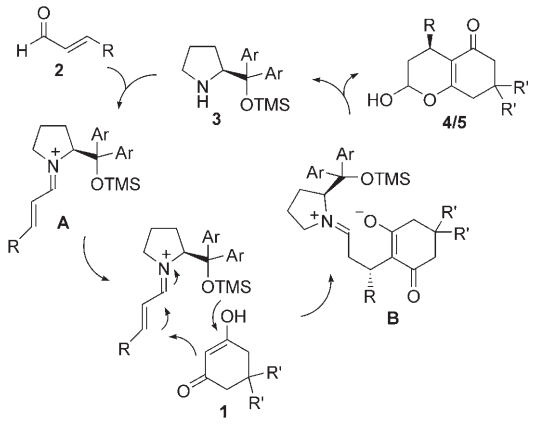


Figure 1. Molecular structure of compound **5i**.[12]

With regards to the mechanism, we assume that organocatalytic, highly enantioselective addition–cyclization sequence starts with the activation of the α,β-unsaturated aldehydes **2** by the prolinol ether **3** forming the iminum ion **A**. This then reacts with the diketone **1** in a 1,4-addition to give intermediate **B**. Subsequent hydrolysis and half acetalization provides the desired hydroxychromenone **4** or **5**, and the catalyst **3** is regenerated (Scheme 2).

In summary we report the development of a diaryl prolinol ether catalyzed, enantioselective reaction of diketones with α,β-unsaturated aldehydes that provides valuable, biologically active chromenones. In these efficient addition–acetalization cascade reactions, diverse aliphatic and aromatic α,β-unsaturated aldehydes, as well as various diketones, can be successfully applied and the 2-hydroxychromenones can be isolated in good yields and with excellent enantioselectivities (87–98% *ee*) (Tables 3 and 4). The 2-hydroxychromenones can subsequently be transformed not only into the corresponding lactones but also into useful oxadecalinones and benzopyranes (Scheme 1). No change in the enantiomeric excess is observed and generally good yields are obtained.



Scheme 2. Diarylprolinol ether catalyzed enantioselective synthesis of hydroxylchromenones.

The catalytic, enantioselective, addition–acetalization reaction presented here should also enable enamides to be applied in these efficient yet mild transformations. Furthermore, this organocatalytic reaction should allow facile access to various natural products and biologically active derivatives, which is the focus of our current research.

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Keywords: asymmetric catalysis · Brønsted acids · chromenes · domino reactions · organocatalysis

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[11] Oxadecalinones are constituents of interesting natural products, including arisugacin, phomactin A, penostatin A, pyripyropen, and orevactaene.

[12] CCDC-690679 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.

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