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Enantioselective synthesis of the tetrahydro-6*H*-benzo[*c*]chromenes via Domino Michael–Aldol condensation: control of five stereocenters in a quadruple-cascade organocatalytic multi-component reaction

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ABSTRACT

Organocatalytic domino *oxa*-Michael–Michael–Michael–aldol condensation of 2-((*E*)-2-nitrovinyl)phenol and 2 equiv of α,β-unsaturated aldehydes (e.g., cinnamaldehyde) provided tetrahydro-6*H*-benzo[*c*]chromenes in high diastereoselectivity and high enantioselectivity (>99% ee). Structure of the adduct **4a** was confirmed unambiguously by X-ray analysis. The diversity of the protocol was demonstrated by the chemo-differentiating three-component reactions (ABC type) affording the highly functionalized tetrahydro-6*H*-benzo[*c*]chromenes.

Organocatalysis has become the focal point in contemporary organic chemistry.[1] Among the burgeoning organocatalytic reactions explored, vast efforts have been devoted to the enantioselective Michael reactions[2] (conjugate addition) that take place via iminium activation or/and enamine activation. Methodologies relying on the tandem/domino/cascade catalytic strategies for enantioselective synthesis have received increasing attention in the synthetic community recently.[3]The ability to promote cascade/domino reactions by organocatalysts further expands the realm of its synthetic applications.[4,5] There are, however, many fewer examples involving triple cascade reactions[6], of which the pioneering magnum opus was introduced by Enders et al. in 2006. Theoretically, by manipulating the functionality on the molecules with adequate arrangement, much higher-order cascade and multi-component reactions[7] can be achieved. Therefore, the development of more efficient and exquisite higher-order cascade reactions is in great demand by synthetic chemists[8] However, to the best of our knowledge, an effective quadruple-cascade and multi-component organocatalytic reaction for constructing three new C–C bonds and five stereocenters remains elusive. In conjunction with our continuing efforts to explore new organocatalytic annulations[9], we embarked upon a domino strategy in the tandem Michael–aldol condensation to overcome the manqué quadruple-cascade reactions. Herein, we report the enantioselective synthesis of a tetrahydro-6*H*-benzo[*c*]chromene with five contiguous centers[10] by domino oxa-Michael–Michael–Michael–aldol condensation.

Initially, the reactions of **1** and cinnamaldehyde (**2a**) with L-proline (**I**) in various solvents (e.g., CH_3CN, DMF, toluene) gave almost no reaction after 40 h or afforded a complex mixture in the presence of Et_3N (Table 1, entries 1–3). Encouragingly, the same reaction with catalyst **II** and 4-nitrobenzoic acid (PNBA) in CH_2Cl_2 for eight days afforded 30% yield of **3a** and **4a** (ca. 5:95), with more than 99% ee of **4a** isolated and 25% of starting **1** and cinnamaldehyde recovered (Table 1, entry 4). The same reaction was facilitated in toluene (50 h vs 192 h) without lowering the ee of **4a** but affording a 1:1 ratio of **3a**:**4a** (Table 1, entry 5). The yield of **4a** was increased by catalyzing the reaction with **II**-HOAc, and a survey of solvents revealed that the reaction media had significant effects on the yields of the process (Table 1, entries 6–11). For example, the reaction with **II**-HOAc carried out in toluene gave the highest yield (75%) of **4a**, whereas almost no reaction occurred when reacting in polar solvents (e.g., DMF, CH_3CN, and THF) for 50 h. Replacement of HOAc by benzoic acid in the same reaction conditions gave similar yields and selectivity; however, an acid additive was required to facilitate the reaction (Table 1, entry 12), the reaction with **II** without the acid additive gave no reaction for days. Reactions with many other catalysts gave either no reaction or very low yields, while reaction with pyrrolidine–HOAc afforded low yield of racemic **4a** (30% yield); nevertheless, this was a suitable standard for HPLC analysis in determining the ee of **4a** prepared by other catalysts (Table 1, entry 13). The structure of **4a** was assigned unambiguously by single-crystal X-ray analysis, and the ORTEP structure of **4a** is shown in Figure 1.[11]

Although the cascade reaction could generate 32 different stereoisomers, except for the observation trace amount of intermediate **3**, only one enantiomer was observed in this reaction. This high stereoselectivity is probably due to the first oxa-Michael addition, which is known to proceed with high diastereo- and enantioselectivity[12], and the resulting product presumably dictates the stereochemistry of the subsequent reactions (Scheme 1).

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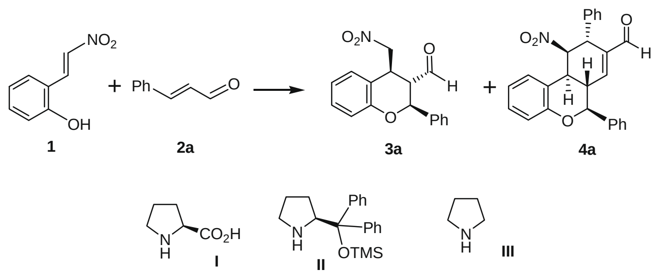
Table 1
Screening of the catalyst, solvent, and reaction conditions for the Domino reaction[a]



Entry	Cat.	Additive[b]	Solvent	*t* (h)	Yield[c] (%)	**3a/4a**[d]	ee[e] (%)
1	**I**	–	CH_3CN	40	~0[f]	n.a.	n.a.
2	**I**	Et_3N	CH_3CN	30	~0[g]	n.a.	n.a.
3	**I**	–	DMF	50	~0[f]	n.a.	n.a.
4	**II**	PNBA	CH_2Cl_2	192	30	5:95	>99
5	**II**	PNBA	Toluene	50	64	1:1	>99
6	**II**	HOAc	CH_2Cl_2	38	70	5:95	>99
7	**II**	HOAc	$CHCl_3$	40	70	5:95	>99
8	**II**	HOAc	Toluene	30	75	5:95	>99
9	**II**	HOAc	CH_3CN	50	~0[f]	n.a.	n.a.
10	**II**	HOAc	DMF	50	~0[f]	n.a.	n.a.
11	**II**	HOAc	THF	50	~0[f]	n.a.	n.a.
12	**II**	$PhCO_2H$	Toluene	40	70	5:95	>99
13	**III**	HOAc	Toluene	24	30	5:95	0

[a] The reactions were performed in 0.06 M of **1** and 3 equiv of **2a** at 25 °C.
[b] 0.2 equiv of catalysts and additive, respectively, were applied.
[c] Isolated yields.
[d] Determined by ^1H NMR prior to work-up.
[e] Enantiomeric excess (ee) of **4a** determined by HPLC with chiral column (Chiracel OD).
[f] No reaction and recovery of starting materials.
[g] Complicated mixture with the decomposition of starting materials.

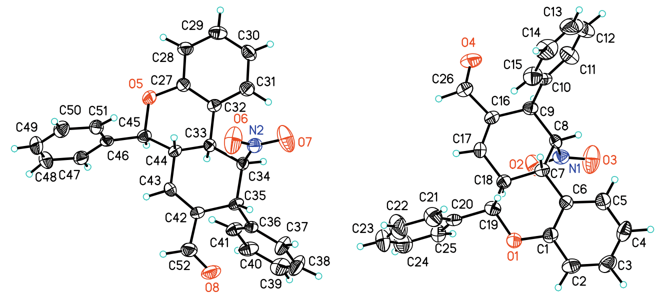
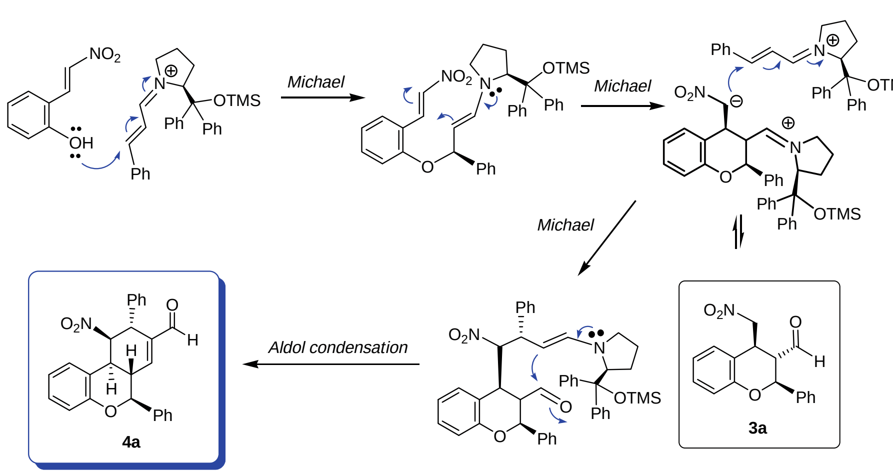


Figure 1. ORTEP plots for X-ray crystal structures of **4a**.

Having established the optimal reaction conditions, a series of arylacrylaldehydes (**2**) were reacted with **1** in the presence of **II**-HOAc in toluene at ambient temperature to probe the generality of this asymmetric cascade reaction (Table 2, entries 2–6). Significantly, regardless of the electron-donating or -withdrawing substituents on **2**, most of the reactions gave **4** in excellent enantioselectivity and diastereoselectivty[13] (>30:1). However, some of the reaction conditions need to be adjusted for optimization of yields and enantioselectivities. For example, reaction of **1** and **2b** in toluene was slower (75 h) than that with **2a**, but the reaction was facilitated in $CHCl_3$ (35 h), with the same yield and enantioselectivity. Noteworthily, owing to the low solubility of **2f** in toluene, the reaction of **1** and **2f** was carried out in $CHCl_3$ and took place optimally at 0 °C, as a fast consumption of **1** and lower yield of **4f** (20%) was obtained at ambient temperature. Interestingly, reaction of **1** with β-disubstituted aldehyde, 3-methylbut-2-enal (**2g**) was very fast, completing in 30 min; however, it afforded predominately the oxa-Michael–Michael adduct **5g** (65% yields), without the observation of quadruple-cascade product **4g** (Table 2, entry 7). Addition of excess **2g** or prolonging the reaction (30 h) yielded no observable **4g**. The premature termination of the cascade reaction is probably due to the steric hindrance of the *gem*-dimethyl (R_3 and R_4) groups on **2′g**. Nevertheless, such chemo-differentiating reactivity provides a useful venue of multi-component cross reaction (ABC MCR) to achieve structurally complex and diverse products. For demonstrating the three-component reaction (ABC 3CR), the series of aldehydes **2′a**/**2′b**/**2′f** and **2g** was reacted with **1**, providing the MCR adducts with excellent enantioselectivity (Table 2, entries 8–10). For example, reaction of **1**, **2g**, and **2′a** under the same reaction condition for 50 h gave **4ga** in 51% yield with >99% ee (Table 2, entry 8).

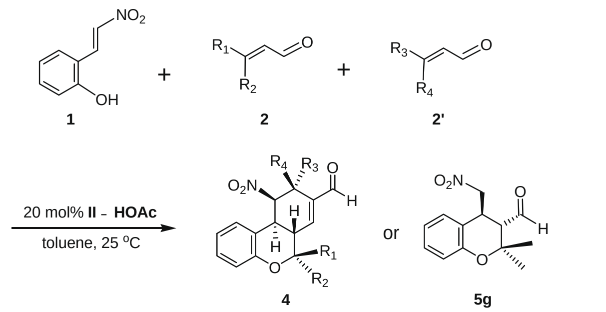
The hexahydro-6,6-dimethyl-6*H*-benzo[*c*]chromene systems can be found in a variety of natural products and biologically active agents, including (−)-heterophylol,[14] (+)-murrayamine-P, (−)-murrayamine-O[15], and nabilone.[16] Other hexahydro-6*H*-benzo[*c*] chromenes, such as sauchinone A,[17] machaeriol A, machaeriol B,[18] clusiacitran A, and clusiacitran B,[19,18] are also the natural occurring compounds and are known for their biological activities. The successful cascade multi-component reactions provide a useful methodology in the synthesis of these compounds and derivatives.

In summary, we have developed a highly diastereoselective and enantioselective quadruple-cascade organocatalytic reaction, constructing four new bonds and five stereocenters, that provides expedited access to highly functionalized and enantiomeri-



Scheme 1. Proposed mechanism for the cycloaddition.

Table 2
Triple Michael–aldol condensation of **1** and **2**[a]



Entry	Product	t (h)	Yield[b] (%)	ee[c] (%)
1	**4a** $R_1 = R_3$ = Ph, $R_2 = R_4$ = H	30	75	>99
2	**4b** $R_1 = R_3$ = 4-OMeC_6H_4, $R_2 = R_4$ = H	35[d]	73	>99
3	**4c** $R_1 = R_3$ = 2-MeC_6H_4, $R_2 = R_4$ = H	40	63	>99
4	**4d** $R_1 = R_3$ = 4-BrC_6H_4, $R_2 = R_4$ = H	10	55	>99[g]
5	**4e** $R_1 = R_3$ = 4-MeC_6H_4, $R_2 = R_4$ = H	24	67	>99
6	**4f** $R_1 = R_3$ = 4-$NO_2C_6H_4$, $R_2 = R_4$ = H	62[d,e]	53	>99[g]
7	**5g** $R_1 = R_2$ = Me	0.5	65	>99
8	**4ga** $R_1 = R_2$ = Me, R_3 = Ph, R_4 = H	50	51	>99
9	**4gb** $R_1 = R_2$ = Me, R_3 = 4-OMeC_6H_4, R_4 = H	24[d]	54	>99
10	**4gf** $R_1 = R_2$ = Me, R_3 = 4-$NO_2C_6H_4$, R_4 = H	48[d,f]	47	>99

[a] Unless otherwise noted, reactions proceeded at 25 °C.
[b] Isolated yields.
[c] Enantiomeric excesses (ee) were measured by HPLC with chiral column (Chiracel OD).
[d] Reaction in $CHCl_3$.
[e] Reaction at 0 °C.
[f] Reaction at 10 °C.
[g] With chiral column (Chiralpak IA).

cally enriched tetrahydro-6*H*-benzo[*c*]chromenes (>99% ee). The structure was confirmed by X-ray analysis of adduct **4a**. Chemo-differentiating three-component reaction has been achieved, demonstrating the synthetic versatility of this protocol and making it highly appealing for asymmetric synthesis. Further applications of this methodology toward total synthesis of natural products and pharmaceutical agents are currently under active investigation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.106.

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