

Catalytic Asymmetric oxa-Michael—Michael Cascade for Facile Construction of Chiral Chromans via an Amino Intermediate

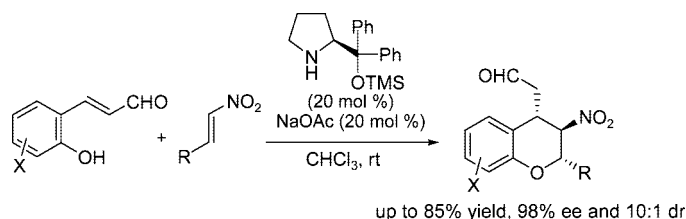
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ABSTRACT



An unprecedented highly enantioselective cascade oxa-Michael–Michael reaction has been developed. The simple and practical process, efficiently catalyzed by chiral diphenylprolinol TMS ether, affords a powerful access to highly functionalized synthetically useful chiral chromans. Moreover, notably a new activation mode involving an amino is disclosed for the first time.

An important goal of asymmetric catalysis is the development of novel activation modes that enable us to promote unprecedented transformations. In the recent past, organocatalysis has significantly advanced the field as a result of the novelty of concept and unique activation modes.¹ Furthermore, the scope of organocatalyzed asymmetric reactions has been dramatically expanded by their ability for catalyzing highly powerful cascade processes that generate complex molecular architectures.² Recently, we and other

groups have reported organocatalyzed oxa-Michael-aldol reactions for forming chromenes.³ In the cascade process, only one stereogenic center in the products was created due

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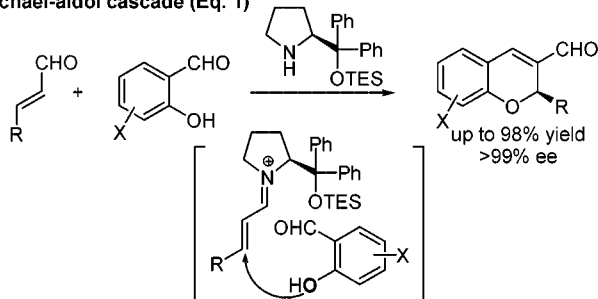
(2) For recent reviews of organocatalytic cascade reactions, see: (a) Enders, D.; Grondal, C.; Hutt, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Yu, X.-H.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2036. And recent selected examples, see: (c) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539. (d) Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 4585. (e) Dodda, R.; Goldman, J. J.; Mandal, T.; Zhao, C.-G.; Broker, G. A.; Tiekink, E. R. T. *Adv. Synth. Catal.* **2008**, *350*, 537. (f) Dodda, R.; Mandal, T.; Zhao, C.-G.

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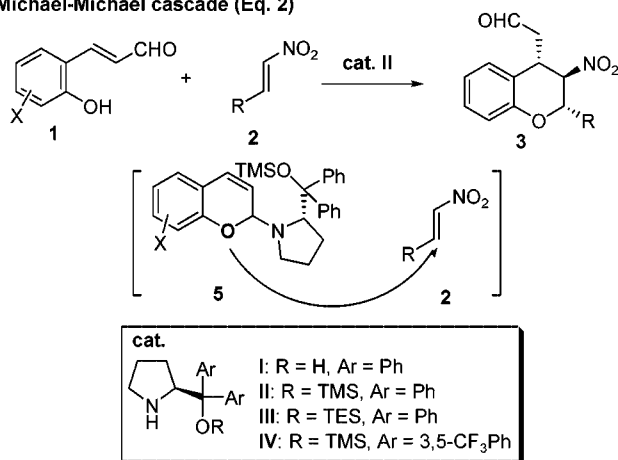
to the spontaneous dehydration of the β -hydroxy aldimine (Scheme 1, eq 1).^{3a} Mechanistically, these reactions share

Scheme 1. Organocatalytic, Asymmetric oxa-Michael-Initiated Cascade Reactions

Michael-aldol cascade (Eq. 1)



Michael-Michael cascade (Eq. 2)



the same pathway, involving the direct conjugate addition of the free phenol –OH group to the activated enal derived iminium.

It is noteworthy that chiral chromenes and chromans are important “privileged” structures found in a myriad of biologically intriguing molecules.⁴ In our continuing effort on the construction of the synthetically useful scaffold with stereochemical and functional diversity, herein we wish to disclose an unprecedented organocatalyzed asymmetric cascade oxa-Michael–Michael reaction, which affords chiral

highly functionalized chromans with the creation of three new stereogenic centers (eq 2).⁵ The cascade process is efficiently catalyzed by a commercial diphenylprolinol silyl ether from simple achiral substances and provides one-pot access to enantioenriched chromans. Significantly, a novel activation mode of the chiral amine-catalyzed cascade process involving formation of aminal **5**, which serves as a nucleophile, rather than a free phenol –OH group for the Michael addition, has been identified for the first time.

In our exploratory study, we decided to choose 2-hydroxy cinnamaldehyde **1a** and *trans*- β -nitrostyrene **2a** as substrates for the proposed cascade oxa-Michael–Michael reaction in the presence of a chiral amine in CH₂Cl₂ at rt since the aldehyde and nitro groups are highly versatile functionalities in organic transformations (Table 1). Initial optimization

Table 1. Organocatalytic Asymmetric Cascade Michael–Michael Reaction of 2-Hydroxy-3-phenyl-propenal (**1a**) with *trans*- β -Nitrostyrene (**2a**)^a

entry	cat.	additive	% yield ^b	% ee ^c	dr ^d
1	I	none	<5	ND ^e	ND ^e
2	II	none	65	96	4:1
3	II	PhCO ₂ H	78	96	4:1
4	II	NaOAc	80	96	5:1
5 ^f	II	NaOAc	78	98	6:1
6	III	NaOAc	77	97	4:1
7	IV	NaOAc	<5	ND ^e	ND ^e

^a Reaction conditions: unless specified, a mixture of **1a** (0.12 mmol), **2a** (0.10 mmol), additive (0.02 mmol), and a catalyst (0.02 mmol) in CH₂Cl₂ (0.2 mL) was stirred at rt. ^b Isolated yields. ^c Determined by HPLC analysis (Chiralcel OD-H). ^d Determined by ¹H NMR. ^e Not determined. ^f CHCl₃ as solvent.

investigation revealed that the catalyst reactivity varied significantly among the commonly used chiral secondary amines probed. It was found that the class of chiral diarylprolinol silyl ethers was promising for the cascade process (eq 2).⁶ No reaction occurred when diphenylprolinol **I** was employed (entry 1). Nevertheless, the encouraging results (65% yield, 96% ee and 4:1 dr, entry 2) were obtained

(3) For examples of organocatalytic asymmetric oxa-Michael-aldol reaction, see: (a) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507. (b) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (c) Li, H.; Zu, L.-S.; Xie, H.-X.; Wang, J.; Jiang, W.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732. (d) Sundén, H.; Ibrahim, I.; Zhao, G. L.; Eriksson, L.; Córdova, A. *Chem.–Eur. J.* **2007**, *13*, 574. (e) Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3046. (f) Liu, K.; Chougnet, A.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5827. (g) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704.

(4) For reviews of chromans: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Keay, B. A. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 395. (c) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, *126*, 11966, and references cited therein. (d) Nicolaou, K. C.; Pfeifferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939, and references cited therein.

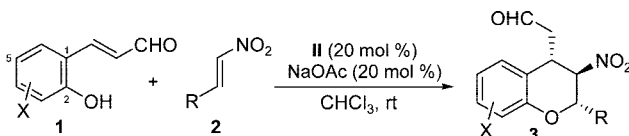
(5) There are only a handful of examples of organocatalytic cascade Michael–Michael reactions: (a) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. (b) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928. (c) Sun, X.; Sengupta, S.; Petersen, J. L.; Wang, H.; Lewis, J. P.; Shi, X.-D. *Org. Lett.* **2007**, *9*, 4495. (d) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732. (e) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177.

(6) For a review of diarylprolinol ether catalysis, see: (a) Vicario, J. L.; Reboredo, S.; Badia, D.; Carrello, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (b) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (c) Mielgo, A.; Palomo, C. *Chem. Asian. J.* **2008**, *3*, 922. And leading references, see: (d) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (e) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (f) Chi, Y.-G.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804.

with silyl ether **II**. Additives could improve the reaction yields (entries 3 and 4) without sacrificing enantioselectivity. Slightly better dr (5:1) was achieved with base additive NaOAc (entry 4). Under the same reaction conditions, a similar trend was observed for the analogue **III** (entry 6), while the **IV** catalyzed process proceeded very sluggishly (entry 7). Examination of solvents showed that comparable outcomes were provided for CH₂Cl₂ and CHCl₃, but CHCl₃ was chosen for probing the scope of the cascade process owing to the enhanced dr (entry 5).

The **II**-promoted cascade oxa-Michael–Michael reaction between a variety of 2-hydroxy cinnamaldehydes **1** and nitroolefins **2** under the optimized conditions was investigated. As revealed in Table 2, the new methodology provided

Table 2. Scope of Catalyst **II** Promoted Cascade oxa-Michael–Michael Reactions^{a,b}



entry	X, R	time (h)	% yield ^c	% ee ^d	dr ^e
1	H, Ph (3a)	12	78	98	6:1
2	H, 4-MeOC ₆ H ₄ (3b)	24	75	97 ^f	5:1
3	H, 2-MeOC ₆ H ₄ (3c)	36	80	98 ^g	4:1
4	H, 4-ClC ₆ H ₄ (3d)	12	85	97	5:1
5	H, 3-BrC ₆ H ₄ (3e)	12	73	95 ^f	4:1
6	H, 2-furanyl (3f)	24	73	96 ^f	6:1
7	H, 2-thienyl (3g)	24	79	94 ^g	5:1
8	3-Cl, Ph (3h)	72	61	95 ^g	10:1
9	3-MeO, Ph (3i)	72	60	96 ^g	10:1
10	4-MeO, Ph (3j)	48	65	96 ^g	8:1
11	5-Me, Ph (3k)	20	71	93 ^g	6:1
12	H, <i>i</i> -Pr (3l)	12	73	93 ^f	2:1

^a Reaction conditions: unless specified, see footnote *a* in Table 1.

^b Absolute configuration of the products determined by single X-ray analysis of a derivative **8** of **3d** (see Figure 1 and Supporting Information). ^c Isolated yields. ^d Determined by chiral HPLC analysis (Chiralpak AS-H or Chiralcel OD-H). ^e Determined by ¹H NMR. ^f Determined by converting to corresponding alcohol for HPLC analysis. ^g Determined by converting to corresponding enone with Ph₃P=CHCOPh for HPLC analysis.

a facile and general approach to a range of trisubstituted, highly functionalized chiral chromans with the generation of three new stereogenic centers in excellent levels of enantiomeric excess (93 to 98% ee) and good to high diastereoselectivities (2:1 to 10:1). The reactions were applicable to a variety of nitroolefins **2** bearing different aryl groups with good yields and excellent enantioselectivities. Significant variation of 2-hydroxy cinnamaldehydes **1** in their electronic and steric features could be tolerated for the **II**-catalyzed cascade processes. Moreover, the process was applicable for less reactive aliphatic enals with high efficiency (entry 12).

The unusual organocatalytic cascade process stimulated us to carry out a preliminary mechanistic investigation

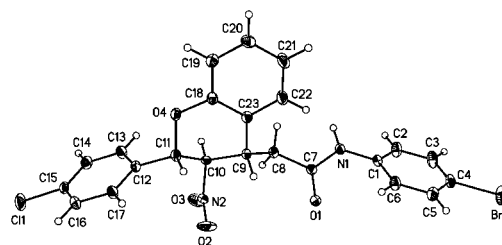
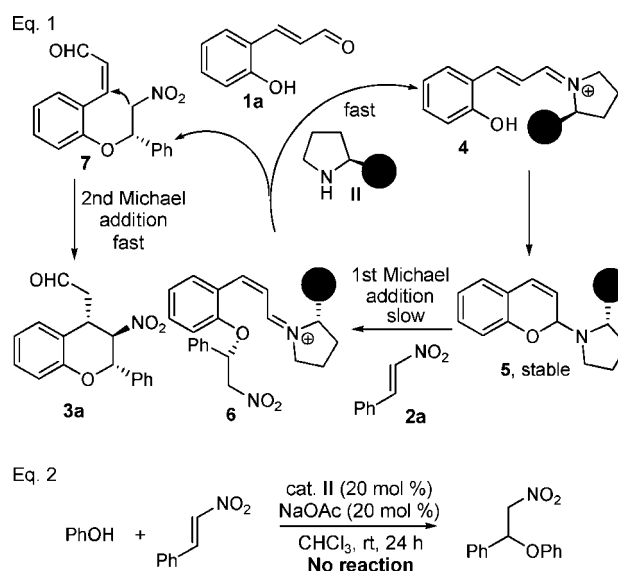


Figure 1. X-ray crystal structure of **8**.

(Scheme 2, eq 1).⁷ An aminal intermediate **5**, which was isolated and characterized (see Supporting Information), was

Scheme 2. Reaction Mechanism of the Cascade oxa-Michael–Michael Reactions



involved in the reaction pathway. Compound **5** was formed very quickly from reaction of **1a** with catalyst **II** in an almost quantitative yield. It is believed that it was produced through an iminium **4**-activated isomerization of the C=C bond and subsequent intramolecular “O” addition to the iminium sequence. The formation of an aminal from an amine has been reported.⁸ However, its function as a nucleophile involved in the organocatalysis is unprecedented. Specifically, it was conceived that the aminal **5** served as a nucleophile for the first Michael addition to nitroolefin **2a** to produce intermediate **6**. We believed that the “O” of the aminal **5** was more active as a nucleophile than that of the “OH” of a phenol. This assumption was confirmed by a controlled study (Scheme 2). In the presence of catalyst **II**, under the same reaction conditions, no reaction occurred

(7) A Diels–Alder pathway was also possible, but it was ruled out.

(8) A recent study related to proline-catalyzed reactions involved aminals. See: Seebach, D.; Beck, A. K.; Badine, D. M.; Limbachi, M.; Eschemoser, A.; Treasuryswala, A. M.; Hobi, R. *Helv. Chim. Acta* **2007**, 90, 425.

between phenol and *trans*- β -nitrostyrene (eq 2), indicating that the “OH” of phenol was not a nucleophile for the first Michael reaction. This observation was in contrast to that seen in the oxa-Michael-aldol reactions,³ where the phenol was directly added to the enal due to the significant activation by a chiral amine via formation of an iminium (see above). We also isolated and characterized the relatively stable **6** (see Supporting Information). The catalyst **II** was released for the next cycle reaction via exchange of **6** with **1a**, and meanwhile compound **7** was produced. Therefore, it is essential to use a slight excess of **1a** (e.g., 1.2 equiv) in the cascade process. Finally, an intramolecular Michael reaction in **7** gave rise to the product **3a**.

In summary, we have developed a new powerful catalytic cascade oxa-Michael–Michael strategy for the facile construction of biologically significant, heavily functionalized chiral chromans containing multiple stereogenic centers. Moreover, an unprecedented aminal serving as an activated nucleophile in the cascade process is first discovered. The study significantly expands the scope of organocatalyzed

reactions with the new activation mode. Further application of this organocatalytic activation mode in new organic transformations, the elaboration of the highly versatile chiral chromans in organic synthesis, and the detailed mechanistic aspects will be reported in due course.

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Supporting Information Available: Experimental procedures and ¹H and ¹³C NMR and HRMS data for experimental procedures and characterization of the products **3**, **4**, and **6** and X-ray crystal data (CIF file) for **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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