

Cascade Reactions

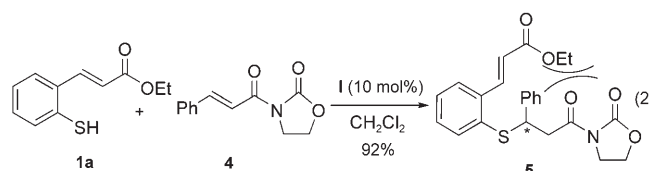
A Highly Stereoselective Hydrogen-Bond-Mediated Michael–Michael Cascade Process through Dynamic Kinetic Resolution**

Jian Wang, Hexin Xie, Hao Li, Liansuo Zu, and Wei Wang*

The ability of organocatalyzed asymmetric reactions to promote cascade reactions has expanded their scope significantly in the past few years, and a number of elegant cascade reactions have been reported.^[1] The predominant strategy is the use of cascade reactions that are driven by the formation of covalent bonds through the action of a chiral amine catalyst.^[1,2] In contrast, the use of noncovalent hydrogen bonds as an activation force for such processes has been much less explored, with only a handful of examples reported.^[3–5]

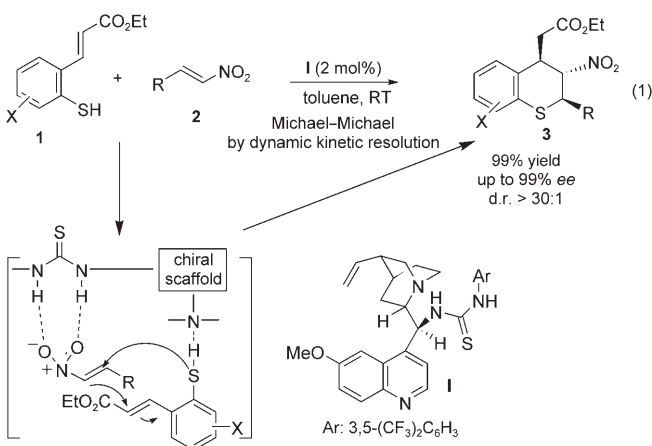
Herein we report a novel asymmetric Michael–Michael cascade reaction [Eq. (1)]. Notably, the cascade process is efficiently catalyzed by a cinchona alkaloid amine thiourea at

acid ethyl ester (**1a**) was treated with *trans*- α,β -unsaturated oxazolidinone **4** in the presence of catalyst **I** in CH₂Cl₂ at room temperature [Eq. (2)]. Unfortunately, the process did



not lead to the desired Michael–Michael product. Instead, a single Michael adduct **5** was obtained in 92 % yield, possibly because the steric hindrance in **5** might obstruct the second Michael addition.

Accordingly, the less hindered *trans*- β -nitrostyrene (**2a**) was then used for the Michael–Michael reaction with **1a** in the presence of **I** (5 mol%) under the same reaction conditions as above (Table 1, entry 1). Gratifyingly, this reaction proceeded smoothly to furnish the desired Michael adduct **3a** in 93 % yield and with good selectivity (86 % *ee*, d.r. 15:1). Further investigation of other bifunctional organo-catalysts revealed that **I** gave the best conversion and selectivity.^[6] A survey of reaction media showed that toluene was the optimum solvent for the reaction (Table 1, entry 6). In this case, the process was complete within 4 h and afforded



a low catalyst loading (2 mol %) and affords one-pot access to enantioenriched thiochromanes with the creation of three new stereogenic centers in remarkably high efficiency and stereoselectivity. More significantly a novel activation mode of the chiral amine thiourea catalyzed dynamic kinetic resolution (DKR) has been identified for this highly stereoselective cascade process.

To probe the feasibility of the proposed Michael–Michael cascade reaction, *trans*-3-(2-mercaptophenyl)-2-propenoic

Table 1: Effects of solvent and catalyst loading on the Michael–Michael reaction.^[a]

Entry	Solvent	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]	d.r. ^[d]
1	CH ₂ Cl ₂	6	93	86	15:1
2	Cl(CH ₂) ₂ Cl	6	89	93	27:1
3	1,4-dioxane	6	92	91	18:1
4	Et ₂ O	9	76	95	25:1
5	PhOMe	9	81	94	27:1
6	toluene	4	91	97	> 30:1
7 ^[e]	toluene	8	90	97	> 30:1
8 ^[f]	toluene	15	86	97	> 30:1
9	xylenes	4	88	95	> 30:1
10	DMF	4	87	8	17:1

[a] Reaction conditions: unless otherwise specified, see the Experimental Section. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H). [d] Determined by ¹H NMR spectroscopy. [e] 2 mol % catalyst loading. [f] 1 mol % catalyst loading. DMF = *N,N*-dimethylformamide.

[*] Dr. J. Wang, H. Xie, Dr. H. Li, L.-S. Zu, Prof. Dr. W. Wang
Department of Chemistry & Chemical Biology
University of New Mexico, MSC03 2060
Albuquerque, NM 87131-0001 (USA)
Fax: (+1) 505-277-2609
E-mail: wwang@unm.edu

[**] Financial support of this research was provided by the NSF (CHE-0704015) and the ACS Petroleum Research Fund.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

thiochromane **3a** in 91 % yield and with excellent selectivity (97 % *ee*, d.r. > 30:1). Remarkably, the reaction also proceeded efficiently with a catalyst loading of only 1 mol % (Table 1, entry 8).

We then selected the use of **I** (2 mol %) in toluene at room temperature to evaluate the generality of our cascade process (Table 2). The results demonstrate that the cascade process

Table 2: Scope of the Michael–Michael cascade reaction catalyzed by **I**.^[a]

Entry	X	R	t [h]	Product (yield) [%] ^[b]	<i>ee</i> [%] ^[c]	d.r. ^[d]
1	H	Ph	8	3a (90)	97	> 30:1
2	H	4-FC ₆ H ₄	12	3b (92)	97	30:1
3	H	4-ClC ₆ H ₄	12	3c (99)	97	> 30:1
4	H	2,6-Cl ₂ C ₆ H ₃	12	3d (98)	94	16:1
5	H	4-BrC ₆ H ₄	12	3e (91)	97	> 30:1
6	H	3-BrC ₆ H ₄	12	3f (83)	97	> 30:1
7	H	4-MeOC ₆ H ₄	15	3g (88)	97	> 30:1
8	H	4-BnOC ₆ H ₄	12	3h (95)	97	> 30:1
9	H	2-MeOC ₆ H ₄	18	3i (90)	99	> 30:1
10	H	3-BnO, 4-MeOC ₆ H ₃	24	3j (87)	92	> 30:1
11	H	2-thiophene	12	3k (97)	98	> 30:1
12 ^[e]	H	<i>n</i> C ₄ H ₉	96	3l (32) 91 ^[g]	93	> 30:1
13	5-Me	Ph	36	3m (93)	99	> 30:1
14 ^[f]	5-OMe	Ph	72	3n (42)	97	> 30:1

[a] Reaction conditions: unless otherwise specified, see the Experimental Section. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralpak AS-H, Chiralpak AD, Chiralcel OD-H, or Chiralcel OJ-H). [d] Determined by ¹H NMR spectroscopy. [e] 10 % catalyst loading. [f] 5 % catalyst loading. [g] Yield of the recovered product.

catalyzed by **I** serves as a general approach to afford thiochromanes with the highly efficient creation of three new stereogenic centers. It was found that an extensive range of nitroalkenes can effectively participate in the process (Table 2, entries 1–12), irrespective of the electronic nature and the substitution pattern of the aromatic system. For example, the reaction takes place with aromatic systems that possess electron-neutral (Table 2, entry 1), -withdrawing (Table 2, entries 2–6), or -donating (Table 2, entries 7–10) groups at the *o*, *m*, or *p* positions of the nitroalkene without substantial loss in yield (83–98 %) or selectivity (92–99 % *ee*, d.r. 16:1 to > 30:1). Moreover, the heteroaromatic nitroolefin (Table 2, entry 11) can also be tolerated. A high *ee* value (93 %) and good diastereoselectivity (> 30:1) were obtained with this less reactive aliphatic nitroalkene, in spite of the slow conversion (Table 2, entry 12). Finally, the system also seems inert to any electronic changes to the aromatic ring of **1** (Table 2, entries 13 and 14). The absolute configuration of the products was determined by single-crystal X-ray analysis of **6** (an amide derived from **3c**; Figure 1).^[7]

Initially a Michael–Michael cascade process was proposed for the formation of the highly stereocontrolled products **3**

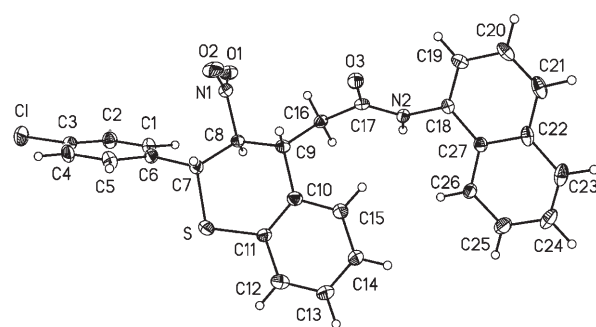
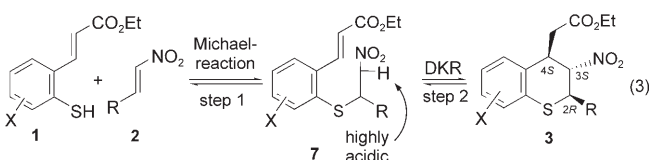
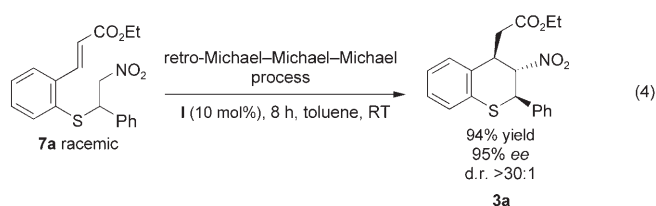


Figure 1. X-ray crystal structure of **6**.

[Eq. (1)]. However, we suspected that the reaction might follow an alternative pathway because low enantioselectivity was generally observed with **I** for the single conjugate addition reaction of thiols with nitroolefins.^[8] In an effort to reconcile the unusual observation, we propose a novel DKR-mediated Michael–retro-Michael–Michael–Michael cascade pathway [Rauhut–Currier reaction; Eq. (3)].^[9–11] We ration-



alized that the initially formed Michael adduct **7** could undergo a DKR process in the presence of **I**: where deprotonation of the highly acidic nitroalkane proton of **7** by the chiral bifunctional amine thiourea **I** would lead to a reversible and highly stereoselective retro-Michael–Michael–Michael process. The above hypothesis was confirmed by treatment of racemic **7a** with **I** (10 mol %) under the standard reaction conditions, that is, in toluene at room temperature [Eq. (4)]. Product **3a** was formed in 94 % yield (95 % *ee*,



d.r. > 30:1) and with the same 2*R*,3*S*,4*S* configuration that was observed from the direct reaction of **1a** with **2a** (Table 2, entry 1). Notably, however, the previous **I**-promoted Michael–aldol cascade reaction did not undergo the DKR process.^[5a,12]

In conclusion, we have developed a novel and highly stereoselective Michael–Michael cascade reaction that is catalyzed by a cinchona alkaloid thiourea. An unprecedented cascade process, which involved dynamic kinetic resolution, is described. Our study, with a new activation mode, expands the scope of organocatalyzed reactions. Further applications

of this activation mode, with respect to other organic transformations, will be reported shortly together with detailed mechanistic aspects.

Experimental Section

General procedure (Table 2, entry 1): A solution of 3-(2-mercapto-phenyl)-2-propenoic acid ethyl ester (**1a**; 21 mg, 0.1 mmol), *trans*- β -nitrostyrene (**2a**; 15 mg, 0.1 mmol), and **I** (3 mg, 0.002 mmol) in toluene (0.2 mL) was stirred at room temperature for 8 h. The crude product was purified by column chromatography on silica gel with hexanes/EtOAc (20:1) as eluent to afford the desired product as a clear oil (32 mg, 90% yield); d.r. > 30:1 (determined by ^1H NMR spectroscopy); 97% *ee* (HPLC on a Chiralcel OD-H column, eluted with hexanes/*i*PrOH (70:30) at 0.5 mL min $^{-1}$, λ = 254 nm); retention time: 14.7 min (major product) and 16.5 min (minor product); $[\alpha]_{\text{D}}^{25}$ = -88.6 deg cm 3 g $^{-1}$ dm $^{-1}$ (c = 0.90 g cm $^{-3}$, CHCl $_3$).

Received: January 24, 2008

Published online: April 17, 2008

Keywords: cascade reactions · kinetic dynamic resolution · Michael addition · organocatalysis

- [1] For reviews of organocatalytic cascade reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; b) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477.
- [2] For recent selected examples of cascade reactions catalyzed by chiral amines, see: a) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem.* **2003**, *115*, 4365; *Angew. Chem. Int. Ed.* **2003**, *42*, 4233; b) D. B. Ramachary, K. Anebuselvy, N. S. Chowdari, C. F. Barbas III, *J. Org. Chem.* **2004**, *69*, 5838; c) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962; d) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; e) J. W. Yang, M. T. H. Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036; f) M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710; g) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; h) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986; i) M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475; j) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354; k) R. Rios, H. Sundén, I. Ibrahim, G.-L. Zhao, L. Eriksson, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 8547; l) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471; *Angew. Chem. Int. Ed.* **2007**, *46*, 467; m) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101; n) H. Li, J. Wang, H. Xie, L. Zu, W. Jiang, E. N. Duesler, W. Wang, *Org. Lett.* **2007**, *9*, 965; o) H. Sundén, I. Ibrahim, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 574; p) H. Li, L. Zu, H. Xie, J. Wang, W. Jiang, W. Wang, *Angew. Chem.* **2007**, *119*, 3806; *Angew. Chem. Int. Ed.* **2007**, *46*, 3732; q) Y. Hayashi, T. Okano, S. Aratake, D. Hazeldard, *Angew. Chem.* **2007**, *119*, 5010; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922; r) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168; s) D. Enders, A. A. Narine, T. Benninghaus, G. Raabe, *Synlett* **2007**, 1667; t) X. Sun, S. Sengupta, J. L. Petersen, H. Wang, J. P. Lewis, X.-D. Shi, *Org. Lett.* **2007**, *9*, 4495.
- [3] For reviews of hydrogen-bond-mediated catalysis, see: a) S.-K. Tian, Y.-G. Chen, J.-F. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621; b) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; c) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; e) T. Akiyama, J. Itoh, K. Fuchibe, *Chem. Rev.* **2007**, *107*, 5744; f) X.-H. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516.
- [4] For examples of hydrogen-bond-catalyzed cascade reactions, see: a) S. Kaneko, T. Yoshino, T. Katoh, S. Terashima, *Tetrahedron* **1998**, *54*, 5471; b) Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185; c) Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe, Y. Takemoto, *Tetrahedron* **2006**, *62*, 365; d) Y. Wang, X.-F. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928; M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; e) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070; f) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; g) B. Wang, F. Wu, Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768; h) M. M. Biddle, M. Lin, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 3830; i) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334; j) J. Zhou, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 7498; k) M. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 10336.
- [5] a) L.-S. Zu, J. Wang, H. Li, H.-X. Xie, W. Jiang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 1036; b) L.-S. Zu, H.-X. Xie, H. Li, J. Wang, W. Jiang, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 1882.
- [6] See Table S1 of the Supporting Information for details.
- [7] CCDC 675590 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.
- [8] The reaction of thiophenol with *trans*- β -nitrostyrene under the same reaction conditions and in the presence of catalyst **I** gave only 12% *ee*. We found that the process proceeded very quickly even without **I**.
- [9] For recent reviews of dynamic kinetic resolutions, see a) G. R. Cook, *Curr. Org. Chem.* **2000**, *4*, 869; b) F. F. Huerta, A. B. E. Minidis, J.-E. Backvall, *Chem. Soc. Rev.* **2001**, *30*, 321; c) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291.
- [10] For examples of organocatalytic dynamic kinetic resolutions, see: a) J. Liang, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 3154; b) J. Hang, H. Li, L. Deng, *Org. Lett.* **2002**, *4*, 3321; c) L. Tang, L. Deng, *J. Am. Chem. Soc.* **2002**, *124*, 2870; d) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem.* **2005**, *117*, 817; *Angew. Chem. Int. Ed.* **2005**, *44*, 807; e) A. Berkessel, F. Cleemann, S. Mukherjee, *Angew. Chem.* **2005**, *117*, 7632; *Angew. Chem. Int. Ed.* **2005**, *44*, 7466; f) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074; g) Y.-J. Wang, Z.-X. Shen, B. Li, Y. Zhang, Y.-W. Zhang, *Chem. Commun.* **2007**, 1284; h) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988.
- [11] For recent examples of organocatalytic Rauhut–Currier reactions, see: a) L.-C. Wang, A. L. Luis, K. Agapiou, H.-Y. Jang, M. J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 2402; b) S. A. Frank, D. J. Mergott, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 2404; c) D. J. Mergott, S. A. Frank, W. R. Roush, *Org. Lett.* **2002**, *4*, 3157; d) K. Agapiou, M. J. Krische, *Org. Lett.* **2003**, *5*, 1737; e) C. E. Aroyan, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 256.
- [12] Treatment of racemic **8** in the presence of **I** (20 mol%) in toluene at room temperature did not result in the formation of **9**. Instead, only starting material was recovered.

