

A Highly Diastereo- and Enantioselective Synthesis of Multisubstituted Cyclopentanes with Four Chiral Carbons by the Organocatalytic Domino Michael–Henry Reaction

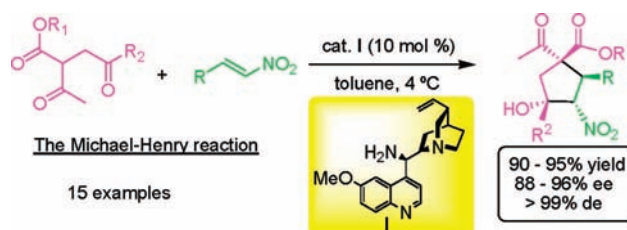
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ABSTRACT



Highly functionalized cyclopentanes with four stereogenic carbons including two quaternary stereocenters have been synthesized in excellent yields (90–95%) with complete diastereoselectivities and excellent enantioselectivities (88–96% ee) by the organocatalyzed asymmetric domino Michael–Henry reaction.

The asymmetric construction of a stereogenic carbon center with a quaternary carbon atom remains one of the most challenging and demanding topics in the synthesis of natural products and chiral drugs.¹ The development of asymmetric methods for the preparation of functionalized cyclopentanes has been of long-standing interest to organic chemists. As a result of their broad applications in organic synthesis, they are widely distributed in a vast array of bioactive molecules.²

(1) For reviews on an enantioselective construction of all carbon quaternary stereocenters, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591.

(2) Reviews of synthesis and bioactivities of cyclopentanes: (a) Silva, L. F. *Tetrahedron* **2002**, *58*, 9137. (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1986**, *25*, 1.

Catalytic enantioselective cascade reactions³ are seen as possible solutions due to the rapid increase in molecular complexity from simple and readily available starting materials to afford enantioenriched compounds in a single operation. Although several elegant organocatalytic⁴ domino

(3) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (e) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(4) For books and selected recent reviews on organocatalysis, see: (a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (b) Ballini, R.; Bosica, G.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.

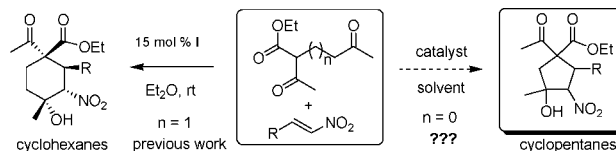
reactions have been reported recently,⁵ the development of new approaches in C–C bond formation with multiple stereogenic centers⁶ in a cascade manner remains a challenge at the forefront of synthetic chemistry.

The Michael reaction is widely recognized as one of the most important C–C bond formation processes in organic chemistry as it is a versatile tool to assemble highly functionalized carbon skeletons.⁷ One of the challenges of such transformation lies in the ability of the catalyst to impart both high enantioselectivity and diastereoselectivity during the formation of the quaternary and tertiary stereocenters in a sterically hindered environment. The Henry reaction is another powerful C–C bond-forming tool that transforms nitro alcohol (nitroaldol) products into a number of nitrogen and oxygen-containing derivatives such as nitroalkenes, amino alcohols, and amino acids.⁸ In addition to substrate-controlled stereospecific nitroaldol reactions, the use of organocatalysts to provide good stereoselectivities has been developed in recent years.⁹ However, to the best of our knowledge, there is no report describing the formation of two quaternary centers in the asymmetric synthesis of cyclopentanes as well as the possibility of using the domino Michael–Henry reaction strategy for the synthesis of multisubstituted chiral cyclopentanes with good results. In this paper, we disclose a facile organocatalytic enantioselective domino Michael–Henry reaction to afford highly functionalized cyclopentane derivatives with four stereogenic centers (two quaternary and two tertiary stereocenters) in complete diastereoselectivities and excellent enantioselectivities (88–96% ee).

Readily accessible cinchona alkaloid and derivatives catalysts which were developed recently in several research groups have been identified as efficient bifunctional orga-

nocatalysts in asymmetric Michael reactions,¹⁰ Henry reactions,¹¹ and tandem Michael–Henry reactions (Scheme 1, *n*

Scheme 1. Organocatalytic Synthesis of Cycloalkanes Using Tandem Michael–Henry Reactions Strategy



= 1).¹² These results prompted us to explore the feasibility of employing diamine catalyst **I**¹³ to catalyze tandem Michael–Henry reactions involving a nitroolefin and a rationally designed carbon nucleophiles **1a** to form chiral cyclopentanes (Scheme 1, *n* = 0). To our disappointment, the enantioselectivity of the desired product was only 67% ee (Table 1, entry 1). Despite changing the reaction conditions such as catalysts, solvents, and temperature, the highest enantiomeric excess obtained was 82% (Table 1, entries 1–4). In our bid to get better results, we turned our attention to designed substrates. The investigation of various substrates demonstrated that the domino Michael–Henry reaction proceeded smoothly to afford the desired cyclopentane ring products in high yields (92–95%, Table 1, entries 5, 7–9) with the exception of the less reactive substrate **1c** (Table 1, entry 6). Surprisingly, only one diastereomer was obtained in all of the cases investigated. However, varied enantioselectivities were observed with different substituents on **1**. For example, higher enantiomeric excesses (75% ee) were observed when **1a** was substituted with **1d** or **1e**.

Despite many attempts, the best result achieved was only 83% ee with catalyst **II**. Therefore, it seemed essential to change the organocatalysts for much higher enantioselectivity. To our delight, the product was obtained in 93% yield with 90% ee (Table 1, entry 13) when catalyst **I** was used.

(10) For developments and applications of cinchona-derived bifunctional catalysts, see: (a) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (d) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (e) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932. (f) McCooley, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (g) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206. (h) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831.

(11) (a) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (b) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732.

(12) Tan, B.; Chua, P. J.; Li, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 2437. The results of forming chiral cyclohexanes with excellent enantioselectivities (97 to >99% ee) and high diastereoselectivities (93:7–99:1 dr) were reported.

(13) For some papers related to using this type of catalyst, see: (a) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389. (b) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413. (c) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioi, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (d) McCooley, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (e) Zheng, B.-L.; Liu, Q.-Z.; Guo, C.-S.; Wang, X.-L.; He, L. *Org. Biomol. Chem.* **2007**, *5*, 2913.

(5) For a review of tandem reactions, see: Enders, D.; Grondal, C.; Hüttl, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. For selected examples of tandem reactions, see: (a) Li, H.; Zhang, Y.; Vogel, P.; Sinay, P.; Bleriot, Y. *Chem. Commun.* **2007**, 183. (b) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637. (c) Zhong, G. *Chem. Commun.* **2004**, 626. (d) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387. (e) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. (f) Yamamoto, N.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (g) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (h) Yang, J. W.; Hechavarria, M.; Fonseca, T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (i) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (j) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (k) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (l) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256. (m) Reyes, E.; Jiang, H.; Millesi, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 9202. (n) Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 121.

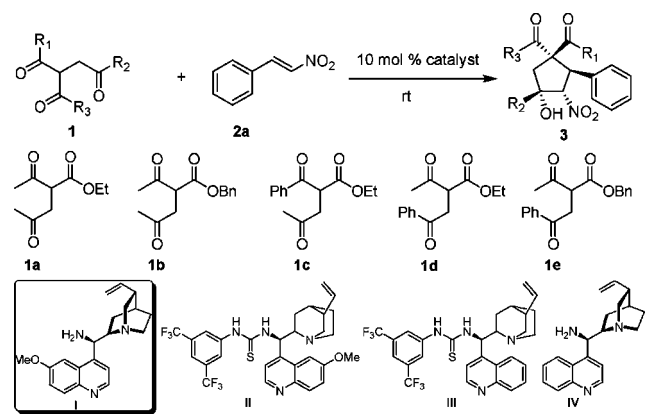
(6) (a) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Enders, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 467. (c) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (d) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (e) Hayashi, Y.; Okano, T.; Aratake, S.; Hazeldard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922. (f) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. *Org. Lett.* **2007**, *9*, 4151.

(7) For selected reviews regarding Michel addition reactions, see: (a) Koichi, M.; Terada, M.; Hiroshi, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3554. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (c) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299.

(8) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561.

(9) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.

Table 1. Organocatalytic Domino Michael–Henry Reactions of Ethyl 2-Acetyl-4-oxo-4-phenylbutanoate (**1a**) and *trans*- β -Nitrostyrene^a

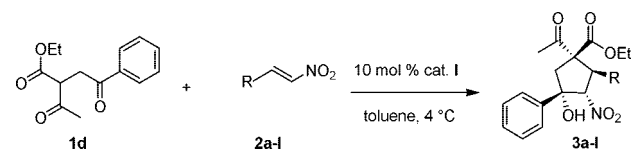


entry	1	catalyst	solvent	time (h)	yield ^b (%)	ee ^c (%)
1	1a	I	Et ₂ O	18	92	67
2	1a	II	neat	3	94	71
3	1a	II	toluene	10	92	80
4 ^d	1a	II	toluene	18	90	82
5	1b	II	neat	3	92	70
6	1c	II	neat	3	NR ^e	NA ^f
7	1d	II	neat	3	95	75
8	1e	II	neat	3	94	75
9	1d	II	toluene	10	92	80
10 ^d	1d	II	toluene	18	93	83
11	1d	III	toluene	10	94	75
12	1d	IV	toluene	18	93	65
13	1d	I	toluene	18	93	90
14	1d	I	Et ₂ O	18	92	88
15 ^d	1d	I	toluene	36	93	95

^a Unless otherwise specified, all the reactions were carried out using **1** (1.0 mmol, 2.0 equiv) and **2a** (0.5 mmol, 1.0 equiv) with 10 mol % of catalysts at room temperature. ^b Isolated yields. ^c Determined by chiral HPLC analysis. ^d Reaction at 4 °C. ^e No reaction. ^f Not applicable.

When catalyst **IV** was used, the lower enantiomeric excess indicated that the OMe group on the catalyst was critical for stereoselectivity (Table 1, entry 12). Although the reaction time was prolonged to 36 h, higher ee (95% ee) was afforded when the reaction temperature was lowered to 4 °C (Table 1, entry 15). The domino Michael–Henry reaction indeed proceeded smoothly to yield the desired cyclopentane ring product in excellent yield (95%) and good enantioselectivity (75% ee). With the optimized reaction conditions, we embarked on the investigation of the generality of the domino Michael–Henry process by using a variety of nitroalkenes. It was observed that all of the reactions were completed within 72 h, giving adducts in excellent yields (90–95%) and with complete diastereoselectivities and excellent enantioselectivities (88–96% ee). It appeared that the position and the electronic property of the substituents for aromatic rings had a very limited influence on the stereoselectivities of the reactions (Table 2, entries 2–7). Electron-withdrawing (entries 6, 7 and 11, 12), electron-donating (entries 2–5), and neutral (entries 1 and 10) groups, as well as substrates containing a variety of substitution patterns (para, meta and

Table 2. Organocatalytic Domino Michael–Henry Reactions of Ethyl 2-Acetyl-4-oxo-4-phenylbutanoate (**1d**) and Nitroolefins Catalyzed by Catalyst **I**^a

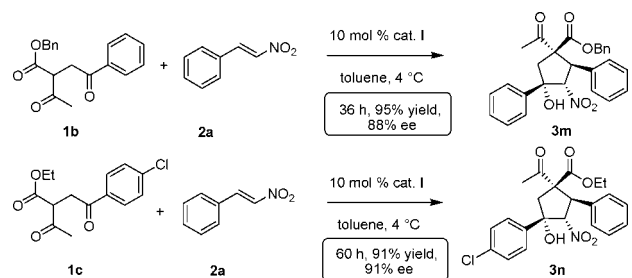


entry	R	3	time (h)	yield (%) ^b	ee (%) ^c
1	Ph	3a	36	93	95
2	3-MeO-C ₆ H ₄	3b	48	91	92
3	4-MeO-C ₆ H ₄	3c	60	93	92
4	2-Me-C ₆ H ₄	3d	48	90	90
5	4-Me-C ₆ H ₄	3e	48	91	95
6	4-Br-C ₆ H ₄	3f	40	94	91
7	4-Cl-C ₆ H ₄	3g	36	95	95
8	2-thienyl	3h	40	93	93
9	2-furyl	3i	48	91	92
10	1-naphthyl	3j	60	91	96
11	4-O ₂ N-C ₆ H ₄	3k	72	90	91
12	4-CF ₃ -C ₆ H ₄	3l	48	95	92

^a All the reactions were carried out using **1d** (1.0 mmol, 2.0 equiv) and **2** (0.5 mmol, 1.0 equiv) in the presence of 10 mol % of **I** at 4 °C with toluene (0.5 mL). ^b Isolated yields. ^c Determined by chiral HPLC analysis.

ortho), participated in this reaction efficiently. Not only aromatic groups but also heteroaromatic groups such as furyl and thienyl could be successfully employed to afford the respective cyclopentane derivatives with excellent enantioselectivity (entries 8 and 9). To our surprise, the presence of the nitro group on the aromatic ring (entry 11) did not decrease the enantiomeric excess. This demonstrates the point that the primary amine group in the catalyst is able to capture one of the two nitro groups selectively. Furthermore, the domino reaction also proceeded smoothly when **1a** was replaced with either **1b** or **1c**, as displayed in Scheme 2.

Scheme 2. Organocatalytic Domino Michael–Henry Reactions of Trisubstituted Carbon Nucleophiles (**1b** or **1c**) to *trans*- β -Nitrostyrene Catalyzed by Catalyst **I**



The dual activation model was proposed¹⁴ where the two substrates involved in the reaction are activated simulta-

(14) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

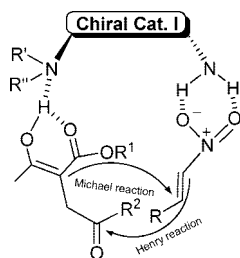


Figure 1. Proposed action of catalyst.

neously by catalyst **I** as shown in the Figure 1. Nitroolefins have been assumed to interact with the primary amine moiety of **I** via multiple H-bonds, thus enhancing the electrophilic character of the reacting carbon center. However, the enolic form of **I** is assumed to interact with the tertiary amine group and a subsequent deprotonation results in a highly nucleophilic enolate species. The carbonanion adjacent to the nitro group then attacks the carbonyl group to afford Henry products. The absolute configuration of **3f** was determined by X-ray crystallography (Figure 2, see the Supporting

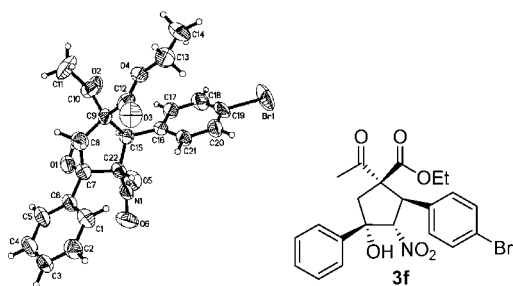


Figure 2. X-ray crystal structure of **3f**.

Information). The stereochemistry of this domino reaction was then established by analysis of the X-ray crystal structures together with analysis of the NMR data.

In summary, we have described a facile organocatalytic, enantioselective synthesis of highly functionalized chiral cyclopentanes with four stereogenic centers (two quaternary and two tertiary stereocenters) in excellent yields (90–95%), enantioselectivities (88–96% ee), and complete diastereoselectivities by the domino Michael–Henry reaction strategy. The domino reaction was efficiently catalyzed by readily available catalyst **I** (9-amino-9-deoxyepiquinine) to give synthetically valuable multifunctionalized chiral cyclopentanes, where the organocatalytic *intramolecular* Henry reaction of common ketones was employed for the cyclopentane ring-closing step in excellent stereoselectivities. This domino synthesis is quite useful in natural product synthesis since we know that there are many types of biologically active natural substances that bear optically active cyclopentane derivatives. We hope that this strategy of developing a practical and efficient domino Michael–Henry reaction can spark further efforts into the designing of such organocatalytic domino reactions. This approach constitutes our future direction aimed at expanding the scope and applications of these powerful tandem processes.

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Supporting Information Available: Experimental procedures, characterization, spectra, chiral HPLC conditions, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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