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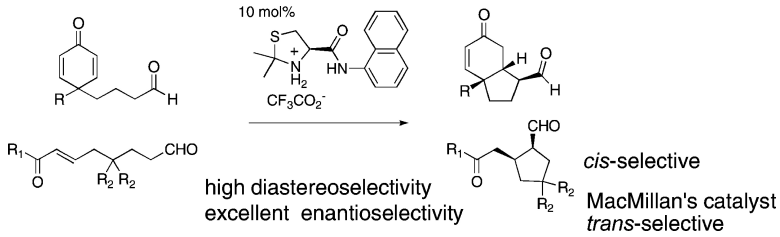

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Cysteine-Derived Organocatalyst in a Highly Enantioselective Intramolecular Michael Reaction

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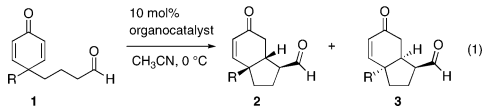
The Michael reaction is an important carbon−carbon bond forming reaction for which the catalytic asymmetric version using metal carbanions has been developed with great success.[1] In recent years, the organocatalyst-mediated Michael reaction has undergone rapid development, and excellent results have been reported for intermolecular reactions.[2] To attain high enantioselectivity, the design of the organocatalyst is crucial, and we have developed diphenylprolinol silyl ether as an efficient catalyst for the Michael reaction of aldehydes and nitroalkenes.[3] Only one excellent report has described the enantioselective, intramolecular, catalytic Michael reaction, an important method for the preparation of chiral, cyclic carbon skeletons from acyclic precursors, in which List and Fonseca reported the synthesis of chiral *trans*-disubstituted cyclopentanes from formyl enones.[4]

The bicyclo[4.3.0]nonene carbon skeleton is found in several natural products, such as the elinacines,[5] axanes,[6] and scabronines,[7] and its asymmetric construction is a synthetic challenge. This skeleton could be synthesized from an achiral precursor, 4-substituted-4-(3-formylpropyl)cyclohexa-2,5-dien-1-one (**1**), via asymmetric intramolecular Michael reaction with creation of three contiguous chiral centers in a single step, if selective reaction of one of the two enantiotopic π-bonds of **1** can be achieved (eq 1).

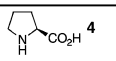
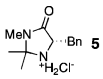
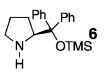
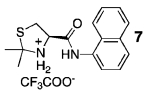


(1)

The achiral **1a** possessing a benzyl group at the 4-position was selected as a model and was prepared from 3-ethoxycyclohex-2-en-1-one in six steps.[8] When **1a** was treated with a catalytic amount of L-proline, the reaction was slow, affording **2a** in low yield and 11% ee (Table 1, entry 1). Low enantiomeric excess was obtained in the case of MacMillan's catalyst **5**,[2c,4a] while prolinol silyl ether, which is an effective catalyst in our aldehyde−nitroalkene Michael reaction,[3] gave good yield and moderate enantiomeric excess. After screening various organocatalysts, the trifluoroacetic acid salt[9] of cysteine-derived amine **7** was found to be the catalyst of choice, affording **2a** in good yield with high diastereo- and excellent enantioselectivity. Moreover, the catalyst loading can be reduced to 5 mol %, without compromising the enantioselectivity. It should be noted that the activity of catalyst **7** is much higher than that of MacMillan's catalyst **5** under the present reaction conditions. The reaction using **7** was complete within 3 h, while the reaction using **5** had not finished even after 24 h.[10]

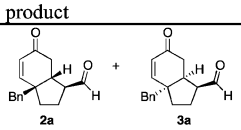
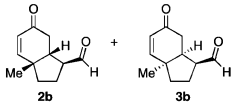
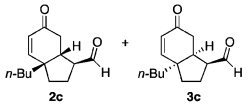
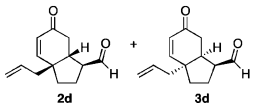
The generality of the present intramolecular Michael reaction was investigated, with the results summarized in Table 2. Not only benzyl but also alkyl groups, such as methyl and butyl, are tolerated in the 4-position. Other synthetically useful substituents, such as the allyl group, are also suitable, affording the bicyclo[4.3.0]nonene skeleton in good yield with high diastereo- and excellent enantioselectivity.

Table 1. Effect of Catalyst on Asymmetric Intramolecular Michael Reaction of **1a** (R = $PhCH_2$)[a]

entry	catalyst	time/h	yield/%[b]	**2a**:**3a**[c]	ee of **2a**/%[d]
1[e]	 **4**	24	34	82:18	11
2	 **5**	24	48	96:4	-36
3	 **6**	24	quant.	74:26	71
4	 **7**	3	89	95:5	90
5[f]	**7**	8	85	95:5	93

[a] Unless otherwise shown, reactions were conducted with 10 mol % of catalyst in CH_3CN at 0 °C. [b] Yield of isolated products of **2** and **3**. [c] Determined by ^{1}H NMR (400 MHz). [d] Determined by HPLC using a Chiralpak AS−H column. [e] A 20 mol % of the catalyst was employed. [f] A 5 mol % of the catalyst was employed.

Table 2. Asymmetric Intramolecular Michael Reaction of **1**[a]

entry	product	yield/%[b]	**2**:**3**[c]	ee of **2**/%[d]
1	 **2a** **3a**	89	95:5	90
2	 **2b** **3b**	93	96:4	91
3	 **2c** **3c**	quant.	91:9	90
4	 **2d** **3d**	96	92:8	95

[a] The reactions were conducted with 10 mol % of catalyst **7** in CH_3CN at 0 °C for 3−5 h. [b] Yield of isolated products of **2** and **3**. [c] Determined by ^{1}H NMR (400 MHz). [d] Determined by HPLC using a chiral column.

Next, the catalyst **7** was applied to the reaction of formyl enones **8** for the synthesis of chiral, disubstituted cyclopentane derivatives **9** via intramolecular Michael reaction (eq 2). When **8a** was treated with 10 mol % of **7** at 0 °C, the reaction proceeded smoothly, affording the *cis*-isomer diastereo- and enantioselectively. *Noteworthy is the selective formation of the cis-isomer, which is opposite*

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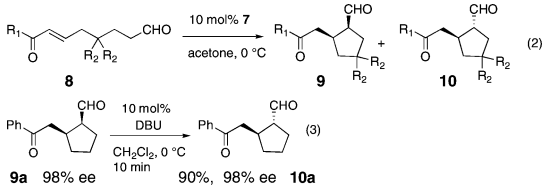
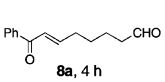
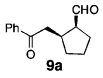
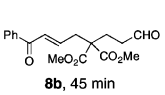
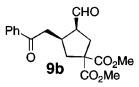
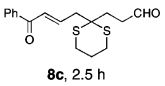
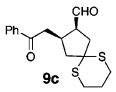
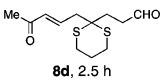
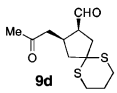


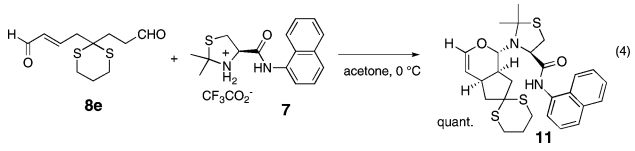
Table 3. Asymmetric Intramolecular Michael Reaction of **8**[a]

entry	starting material reaction time	product	%[b]	*cis:trans*[c]	%ee[d]
1	 **8a**, 4 h	 **9a**	quant	89:11	99
2	**8a**, 23 h	**9a**	quant	42:58[e]	99
3[f]	**8a**, 8 h	**9a**	59	64:36	96
4	 **8b**, 45 min	 **9b**	95	91:9	97
5	 **8c**, 2.5 h	 **9c**	93	>95:5	99
6[g]	 **8d**, 2.5 h	 **9d**	93	>95:5	>99

[a] Reactions were conducted with 10 mol % of catalyst **7** in acetone at 0 °C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR (400 MHz). [d] Determined by HPLC using a chiral column. [e] The *trans*-isomer was obtained in 94% ee. [f] The reaction was conducted in THF at room temperature.[4a] [g] The reaction was conducted at −20 °C.

to the result obtained with MacMillan's catalyst ***5***, which was reported to give the *trans*-isomer stereoselectively with excellent enantioselectivity.[4a] Careful examination of the *cis/trans* ratio at different reaction times indicated that the *cis*-isomer is the kinetic product, while the *trans*-isomer is thermodynamically more stable. That is, the *cis*-isomer was obtained in good yield and excellent enantioselectivity after 4 h, but this yield decreased with time, with a concomitant increase in the *trans*-isomer. Both isomers are formed with excellent enantioselectivity (entry 2). As efficient isomerization can be realized by treatment of the isolated *cis*-isomer **9a** with a catalytic amount of DBU in 10 min at 0 °C, affording the *trans*-isomer **10a** in 90% yield without loss of optical purity (eq 3), the present Michael reaction is a powerful method for the preparation of both *cis*- and *trans*-isomers in synthetically useful yield with very high optical purity. When the reaction was carried out in THF at room temperature under List's conditions[4a] using catalyst **7**, the reaction was slow, affording cyclopentanes in moderate diastereomeric excess and excellent enantiomeric excess after 8 h (entry 3). The reaction is fairly general and could be used to prepare several synthetically useful disubstituted cyclopentane and cyclopentanone derivatives with high *cis*-selectivity and excellent enantioselectivity; these results are summarized in Table 3. Both aromatic and aliphatic α,β-enones are suitable substrates, affording almost enantiomerically pure cyclized product.

α,β-Unsaturated aldehyde **8e** gave different results (eq 4). When **8e** was treated with **7**, dihydropyran **11** was obtained quantitatively as a single isomer. The generation of **11** indicates that a chiral enamine is involved in the reaction,[2c,4a] and that possible mechanisms for this transformation include not only the Michael reaction but also the inverse-electron demand Diels−Alder reaction.[11]



In summary, the naphthylamide catalyst **7** derived from cysteine has been developed to act as an efficient organocatalyst of two different types of asymmetric intramolecular Michael reaction. In one, there is discrimination between two enantiotopic π-bonds, and a bicyclo[4.3.0]nonene is formed, and, in the other, between the enantiofaces of an α,β-enone giving *cis*-disubstituted cyclopentane skeletons. These compounds, containing three and two contiguous chiral centers, respectively, are formed in good yield with high diastereo- and excellent enantioselectivities. There is another noteworthy feature to this reaction: in the synthesis of the cyclopentane skeleton, the *cis*-isomer is synthesized diastereo- and enantioselectively, which is complementary to the intramolecular Michael reaction using Enders' SAMP/RAMP-hydrazone methodology,[4c] and that using MacMillan's catalyst,[4a] both of which afford the *trans*-isomer selectively.

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Supporting Information Available: Detailed experimental procedures, full characterization, copies of ^{1}H, ^{13}C NMR, and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, pp 1105−1120. (b) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, pp 1121−1139. (c) Tomioka, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004; Supplement 2, pp 109−124. (d) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; pp 569−592. (e) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (f) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171. (g) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.

(2) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (c) Recently, **5** was found to be an effective catalyst of an intermolecular aldehyde−enone Michael reaction; see: Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598.

(3) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(4) (a) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958. For intramolecular Michael reaction catalyzed by stoichiometric amount of chiral promoter or auxiliary, see: (b) Hirai, Y.; Terada, T.; Yamazaki, T. *J. Am. Chem. Soc.* **1988**, *110*, 958. (c) Enders, D.; Scherer, H. J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1664. (d) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 509. For intramolecular aza-Michael reaction catalyzed by organocatalyst, see: (e) Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51.

(5) Kenmoku, H.; Tanaka, K.; Okada, K.; Kato, N.; Sassa, T. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1789 and the references therein.

(6) Cafieri, F.; Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Tetrahedron* **1973**, *29*, 4259.

(7) (a) Ohta, T.; Kita, T.; Kobayashi, N.; Obara, Y.; Nakahata, N.; Ohizumi, Y.; Takaya, Y.; Oshima, Y. *Tetrahedron Lett.* **1998**, *39*, 6229. (b) Kita, T.; Takaya, Y.; Oshima, Y.; Ohta, T.; Aizawa, K.; Hirano, T.; Inakuma, T. *Tetrahedron* **1998**, *54*, 11877.

(8) See Supporting Information for details.

(9) The free amine itself scarcely promoted the reaction.

(10) The reaction of **5** in THF under List's conditions[4a] is also slow.

(11) (a) Asymmetric catalytic inverse electron-demand hetero-Diels−Alder reaction using organocatalyst: Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498. (b) Stoichiometric use of chiral amine: Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198. (c) The Lewis acid-catalyzed enantioselective inverse-electron demand hetero-Diels−Alder reaction: Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059 and the references therein.

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