Organocatalytic Asymmetric Michael Addition of β-Ketoesters to Nitroalkenes

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The Michael addition reaction is widely recognized as one of the most general and versatile methods for formation of C-C bonds in organic synthesis,[1] and the development of enantioselective catalytic protocols for this reaction has been subject of intensive research.[2] In addition to the great success catalyzed by metal complexes, the powerful and environmentally friendly organocatalyst-mediated asymmetric Michael reaction has been explored intensively in recent years.[3,4] Michael reaction of nucleophiles to nitroalkenes represents a direct and most appealing approach to chiral nitroalkanes that are versatile intermediates in organic synthesis, which can be transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen *etc.*[5] The conjugate addition of α-substituted dicarbonyl compounds to suitable acceptor represents an important approach to generate all-carbon quaternary stereogenic centers. Takemoto *et al.* applied their bifunctional thiourea catalyst in asymmetric Michael addition of β-ketoester compounds to nitroolefins.[6] Also, Deng *et al.* reported the construction of quaternary stereogenic centers by conjugate addition of β-ketoesters mediated by cinchona alkaloid catalyst.[7]

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[8] we recently reported chiral amine-thiourea **I** (Fig. 1) to be a highly selective catalyst for the enantioselective amination of active methines.[9] We envision that the rigid binaphthyl structure can serve as an efficient stereocontrolling axial chiral element. Herein, we wish to describe the direct asymmetric Michael reaction of β-ketoesters to nitroalkenes with catalyzed by bifunctional organocatalysts bearing both central and axial chiral elements.

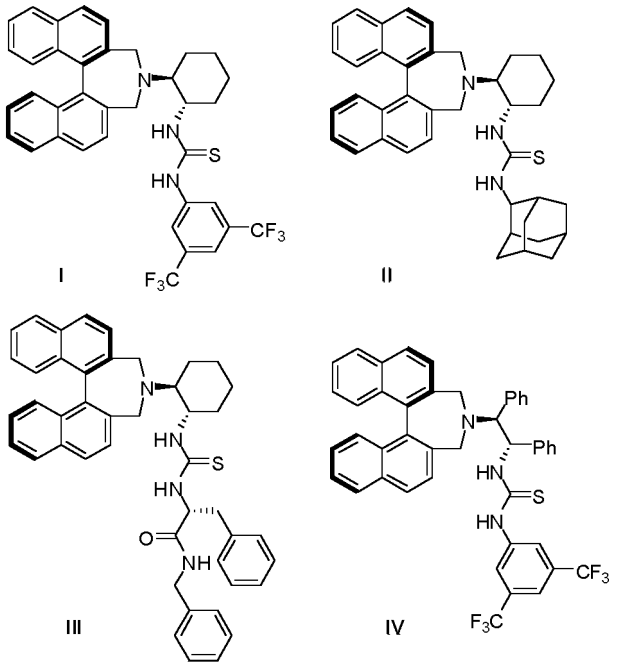
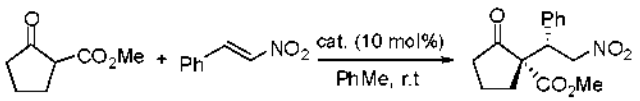


Figure 1. Structure of chiral thiourea-tertiary amine catalysts.

A survey of some reaction parameters was performed, and some representative results are presented in Table 1. Our investigation began with the catalytic asymmetric Michael addition of methyl cyclopentanone 2-carboxylate (**1a**) with nitrostyrene (**2a**). When the reaction was performed in toluene at room temperature in the presence of 10 mol% catalyst **I**, product **3a** was isolated in high yield with 85% ee (Table 1, entry 1). We first examined the impact of the structure of catalysts **I-IV** on enantioselectivity (Table 1, 60-85% ee, entries 1-4). The best results have been obtained with catalysts **I** and **IV**. Concerning the solvent (entries 1, 5-7), the use of halogenated solvents, especially, dibromomethane gave the best result in the yield and the enantiomeric excess (> 99% ee, entry 6).

We then explored the possibility of using wide range of para-substituted aromatic and heteroaromatic nitroalkenes **2** with β-ketoester **1a** under the optimized reaction condition.

Table 1. Optimazation of the reaction conditions

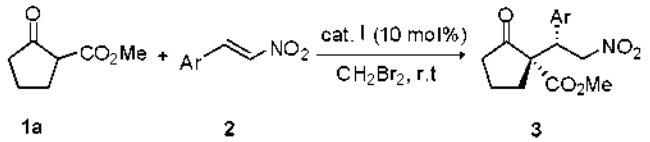


1a **2a** **3a**

entry	cat.	time (h)	yield[a] (%)	dr[b] (*syn*/*anti*)	ee[c] (%)
1	**I**	12	95	85:15	85
2	**II**	32	93	90:10	73
3	**III**	48	92	77:23	60
4	**IV**	120	90	94:6	83
5[d]	**I**	6	95	86:14	91
6[e]	**I**	4	98	86:14	> 99
7[f]	**I**	10	93	85:15	89

[a]Refers to the isolated mixture of diastereomers. [b]Determined from crude ^{1}H NMR spectra. [c]Enantiomeric excess of the major isomer, determined by chiral HPLC analysis. [d]The reaction was run in CH_2Cl_2 as solvent. [e]The reaction was run in CH_2Br_2 as solvent. [f]The reaction was run in $CHCl_3$ as solvent.

Table 2. Variation of the nitroalkene

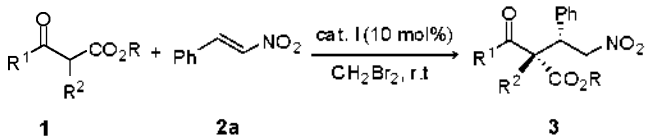


1a 2 3

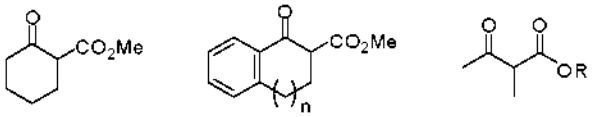
entry	2, Ar	time (h)	yield[a] (%)	dr[b] (*syn*:*anti*)	ee[c] (%)
1	**2a**, Ph	4	**3a**, 98	86:14	> 99
2	**2b**, *p*-F-Ph	3	**3b**, 96	86:14	93
3	**2c**, *p*-Cl-Ph	3	**3c**, 97	84:16	95
4[d]	**2d**, *p*-Me-Ph	36	**3d**, 91	85:15	91
5	**2e**, *p*-MeO-Ph	18	**3e**, 90	82:18	88

[a]Refers to the isolated mixture of diastereomers. [b]Determined from crude ^{1}H NMR spectra. [c]Enantiomeric excess of the major isomer, determined by chiral HPLC analysis. [d]This reaction was carried out at -40 °C.

Table 3. Variation of the β-ketoester



1 2a 3



1b **1c** : n = 0, **1d** : n = 1 **1e** : R = Et, **1f** : R = *t*-Bu

entry	1	time (h)	yield[a] (%)	dr[b] (*syn*:*anti*)	ee[c] (%)
1	**1b**	144	**3f**, 75	92:8	96
2	**1c**	1	**3g**, 95	45:55	> 99
3	**1d**	96	**3h**, 89	92:8	95
4	**1e**	168	**3i**, 90	97:3	95
5	**1f**	192	**3j**, 85	56:44	97

[a]Refers to the isolated mixture of diastereomers. [b]Determined from crude ^{1}H NMR spectra. [c]Enantiomeric excess of the major isomer, determined by chiral HPLC analysis.

As shown in Table 2, the products **3a-e** were formed in high yields (90-98%), high diastereoselectivities, and excellent enatioselectivities (88 - > 99%).

To examine the generality of the catalytic asymmetric Michael reaction of β-ketoesters **1** by using new bifunctional organocatalyst **I**, we studied the addition of various β-ketoesters **1** to nitrostyrene (**2a**). As it can be seen by the results summarized in Table 3, the corresponding products **3f-j** were obtained in high to excellent yields, high diastereoselectivities, and excellent enantioselectivities. The absolute configuration of adducts **3** has been determined for some derivatives by comparison of their optical and HPLC properties with literature values.[6,7]

In conclusion, we have developed a highly efficient catalytic asymmetric Michael reaction of β-ketoesters to nitroalkenes using bifunctional organocatalyst **I**. The desired γ-nitro carbonyl compounds were obtained in good to high yields, excellent diastereoselectivities (up to 86:14), and excellent enantioselectivities (up to > 99% ee) were observed. Further study of these bifunctional organocatalysts in asymmetric reactions is being under investigation.

References

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
2. For recent reviews of asymmetric Michael addition reactions, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Christoffers, J.; Baro, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1688.
3. For selected recent reviews for bifunctional organocatalysts, see: (a) Connon, S. J. *Synlett* **2009**, 354. (b) Yu, X.; Wang, W. Chem. *Asian J.* **2008**, *3*, 516. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.
4. For recent reviews of organocatalytic asymmetric Michael addition, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Almasi, D.; Alonso, D. A.; Najera, D. *Tetrahedron: Asymmetry* **2007**, *18*, 299.
5. (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017. (c) Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 612.
6. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.
7. (a) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 105. (b) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 947.
8. (a) Mang, J. Y.; Kwon, D. G.; Kim, D. Y. *J. Fluorine Chem.* **2009**, *130*, 259. (b) Lee, N. R.; Kim, S. M.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 829. (c) Mang, J. Y.; Kwon, D. G.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 249. (d) Kim, D. Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 2036. (e) Kang, Y. K.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 2093. (f) Lee, J. H.; Bang, H. T.; Kim, D. Y. *Synlett* **2008**, 1821. (g) Kang, Y. K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135. (h) Kim, S. M.; Kang, Y. K.; Cho, M. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2435. (i) Cho, M. J.; Kang, Y. K.; Lee, N. R.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2191. (j) Kim, S. M.; Kang, Y. K.; Lee, K.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 423. (k) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4265. (l) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115. (m) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309. (n) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897. (o) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545. (p) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299. (q) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933.
9. (a) Kim, S. M.; Lee, J. H.; Kim, D. Y. *Synlett* **2008**, 2659. (b) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527. (c) Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 2091.