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Organocatalytic Asymmetric Michael Addition of 1,3-Cyclohexanedione to β,γ-Unsaturated α-Keto Esters

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The Michael reaction is widely recognized as one of the most fascinating and powerful methods for the formation of C-C bonds in organic synthesis,[1] and the development of asymmetric version of 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 addition has been explored intensively in recent years.[3,4] Enantioselective organocatalytic Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds represents a direct and most appealing approach to chiral 1,5-dicarbonyl compounds that are versatile intermediates in organic synthesis.[5] Compared with α,β-unsaturated carbonyl compounds, reactions with β,γ-unsaturated α-keto esters as Michael acceptors are limited. Recently, several groups have reported the asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto esters catalyzed by cinchona-derived organocatalyst, chiral *N,N′*-dioxide copper complexes, and chiral squaramide.[6] There are still some drawbacks in the previously reported procedures, such as high catalyst loading and long reaction time for high enantioselectivity. Therefore, the development of alternative catalysts for enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto esters would be highly desirable.

As part of our research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[7] we recently reported asymmetric Michael addition of active methylenes and methines.[8] Herein, we wish to describe the enantioselective asymmetric Michael addition of 1,3-cyclohexanedione to β,γ-unsaturated α-keto esters promoted by binaphthyl-modified organocatalyst.

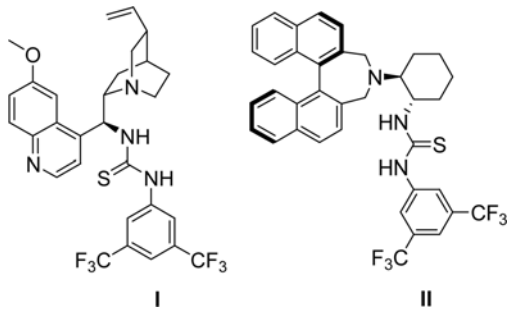
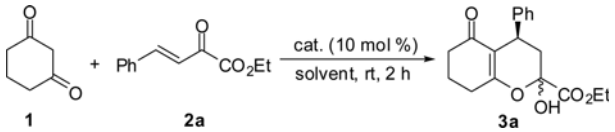


Figure 1. Structure of chiral bifunctional organocatalysts.

Validation of the feasibility of the proposed Michael addition process started by evaluating a model reaction between 1,3-cyclohexanedione (**1**) and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (**2a**) in the presence of 10 mol % bifunctional catalysts (Fig. 1) at room temperature. As shown in Table 1, quinine-derived thiourea catalyst **I** effectively promoted the reaction with moderate enantioselectivity (entry 1). While binaphthyl-modified organocatalyst **II** bearing both central and axial chiral elements gave high enantioselectivity (entry 2). Different solvents were then tested in the presence of 10 mol% of catalyst **II** together with 1,3-cyclohexanedione (**1**) and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (**2a**) in order to further improve the selectivity of the reaction. Aprotic solvents such as toluene, dichloromethane, acetonitrile, THF were well tolerated in this Michael addition without a significant decrease of enantioselectivities (93-80% ee, entries 2-5). Remarkably, MeOH also afforded products with good yields, however, the selectivity dropped significantly (entry 6). Among the solvents probed, the best results (95% yield and 93% ee) were achieved when the

Table 1. Optimization of the reaction conditions

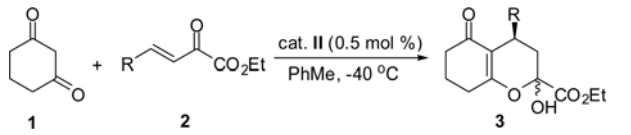


1 **2a** **3a**

Entry	Cat.	Solvent	Yield (%)[a]	ee (%)[b]
1	**I**	PhMe	93	45
2	**II**	PhMe	95	93
3	**II**	CH_2Cl_2	92	86
4	**II**	CH_3CN	95	87
5	**II**	THF	82	80
6	**II**	MeOH	81	43
7[c]	**II**	PhMe	94	93
8[d]	**II**	PhMe	94	93
9[e]	**II**	PhMe	93	93
10[f]	**II**	PhMe	73	81
11[e,g]	**II**	PhMe	93	97

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using chiralpak AD-H column. [c]5 mol % catalyst loading. [d]1 mol % catalyst loading. [e]0.5 mol % catalyst loading. [f]0.25 mol % catalyst loading. [g]This reaction was carried out at −40 °C

Table 2. Enantioselective Michael addition of 1,3-cyclohexanedione (**1**) to β,γ-unsaturated α-keto esters **2**



1 2 3

Entry	**2**, R	Time (h)	Yield (%)[a]	ee (%)[b]
1	**2a**, Ph	2	**3a**, 93	97
2	**2b**, 4-MeC_6H_4	2	**3b**, 95	93
3	**2c**, 4-OMeC_6H_4	6	**3c**, 90	93
4	**2d**, 4-FC_6H_4	6	**3d**, 96	90
5[c]	**2e**, 4-ClC_6H_4	9	**3e**, 89	91
6	**2f**, 2-thienyl	2	**3f**, 93	95
7[c]	**2g**, 2-naphthyl	2	**3g**, 93	87

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using chiralpak AD-H column. [c]2.5 mol % catalyst loading.

reaction was conducted in toluene (entry 2). The present catalytic system tolerates catalyst loading down to 0.5 mol % without compromising both the yield and enantioselectivity (entries 2 and 7-10). Lowering the temperature to −40 °C with catalyst **II** improved the enantioselectivity (97% ee, entry 11).

With optimal reaction conditions, the asymmetric Michael addition of 1,3-cyclohexanedione to several other β,γ-unsaturated α-keto esters was examined, and the results are summarized in Table 2.[9] As demonstrated, organocatalyst **II** catalyzed Michael addition of 1,3-cyclohexanedione (**1**) to β,γ-unsaturated α-keto esters **2** proved to be a general approach for the synthesis of dihydropyran derivatives **3**. Notably, good to high enantiomeric excess was obtained (up to 97% ee). The β,γ-unsaturated α-keto esters **2** bearing substituted aryl and heteroaromatic group in γ-position could effectively participate in this process. Absolute configuration was determined comparison of the optical rotation and chiral HPLC data of the corresponding dihydropyran derivatives **3**.[6]

In conclusion, we have developed organocatalytic enantioselective Michael addition reaction of 1,3-cyclohexanedione (**1**) to β,γ-unsaturated α-keto esters **2** to afford biologically valuable dihydropyran derivatives **3**. Significantly, only 0.5 mol % of binaphthyl-modified organocatalyst **II** is highly effective to give high yields with excellent enantioselectivities (up to 97% ee) under mild reaction conditions.

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References and Notes

1. (a) Leonard, J. *Contemp. Org. Synth*. **1994**, *1*, 387. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
2. For recent reviews of asymmetric Michael addition reactions, see: (a) Christoffers, J.; Baro, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1688. (b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem*. **2002**, 1877.
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. Selected examples: (a) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. (b) M. Rueping, M.; Merino, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3046. (c) Yang, J.; Li, W.; Jin, Z.; Liang, X.; Ye, J. *Org. Lett*. **2010**, *12*, 5218. (d) Zhang, G.; Wang, Y.; Zhang, W.; Xu, X.; Zhong, A.; Xu, D. *Eur. J. Org. Chem.* **2011**, 2142.
6. (a) Calter, M. A.; Wang, J. *Org. Lett.* **2009**, *11*, 2205. (b) Dong, Z.; Feng, J.; Liu, X.; Lin, L.; Feng, X. *Chem. Eur. J*. **2011**, *17*, 1118. (c) Wang, Y.-F.; Wang, K.; Zhang, W.; Zhang, B.-B.; Zhang, C.-X.; Xu, D.-Q. *Eur. J. Org. Chem*. **2012**, 3691.
7. (a) Kim, D. Y.; Park E. J. *Org. Lett*. **2002**, *4*, 545. (b) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem*. **2004**, *69*, 6897. (c) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309. (d) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett*. **2005**, *46*, 3115. (e) Kang, Y. K; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135. (f) Lee, J. H.; Kim, D. Y. *Adv. Synth. Catal*. **2009**, *351*, 1779. (g) Kang, Y. K.; Kim, D. Y. *J. Org. Chem.* **2009**, *74*, 5734. (h) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc*. **2010**, *132*, 11847 (i) Kang, S. H.; Kim, D. Y. *Adv. Synth. Catal*. **2010**, *352*, 2783. (j) Kang, Y. K.; Kim, D. Y. *Curr. Org. Chem.* **2010**, *14*, 917. (k) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2011**, *52*, 2356. (l) Lee, H. J.; Kim, J. H.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 785. (m) Lee, H. J.; Kang, S. H.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 1125. (n) Kang, Y. K.; Yoon, S. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 1195. (o) Kwon, Y. K.; Kang, Y. K.; Kim, E. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 1773. (p) Kang, Y. K.; Kim, H. H.; Koh, K. O.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 3811.
8. (a) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299. (b) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933. (c) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565. (d) Lee, J. H.; Bang, H. T.; Kim, D. Y. *Synlett* **2008**, 1821. (e) Kim, S. M.; Lee, J. H.; Kim, D. Y. *Synlett* **2008**, 2659. (f) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527. (g) Kwon, B. K.; Kim, S. M.; Kim, D. Y. *J. Fluorine Chem*. **2009**, *130*, 759. (h) Mang, J. Y.; Kwon, D. G.; Kim, D. Y. *J. Fluorine Chem*. **2009**, *130*, 259. (i) Oh, Y.; Kim, S. M.; Kim, D. Y. *Tetrahedron Lett.* **2009**, *50*, 4674. (j) Kang, S. H.; Kang, Y. K.; Kim, D. Y. *Tetrahedron* **2009**, *65*, 5676. (k) Moon, H. W.; Kim, D. Y. *Tetrahedron Lett.* **2010,** *51*, 2906. (l) Moon, H. W.; Cho, M. J.; Kim, D. Y. *Tetrahedron Lett.* **2009**, *50*, 4896. (m) Lee, H. J.; Kang, S. H.; Kim, D. Y. *Synlett* **2011**, 1559. (n) Kang, S. H.; Kwon, B. K.; Kim, D. Y. *Tetrahedron Lett.* **2011**, *52*, 3247. (o) Kang, Y. K.; Suh, K. H.; Kim, D. Y. *Synlett* **2011**, 1125. (p) Moon, H. W.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 291. (q) Lee, H. J.; Chae, Y. M.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 2875. (r) Lim, Y. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 1825. (s) Woo, S. B.; Kim, D. Y. *Beilstein J. Org. Chem.* **2012**, *8*, 699. (t) Lee, H. J.; Woo, S. B.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 3374. (u) Lim, Y. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 1825. (v) Lee, H. J.; Woo, S. B.; Kim, D. Y. *Molecules* **2012**, *17*, 7523. (w) Lee, H. J.; Kim, S. M.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 3437.
9. **General procedure for asymmetric conjugate addition 1,3-cyclohexanedione (1) to β,γ-unsaturated α-keto esters 2:** To a stirred solution of β,γ-unsaturated α-keto esters **2** (0.5 mmol), binaphthyl-modified organocatalyst (**II**, 1.6 mg, 0.0025 mmol) in toluene (2 mL) was added 1,3-cyclohexanedione (**1**, 56.0 mg, 0.5 mmol) at −40 °C. The reaction mixture was stirred at −40 °C for a specified reaction time period. The reaction mixture was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 1:1 to give the desired product **3**.