http://dx.doi.org/10.5012/bkcs.2013.34.6.1623

Organocatalytic Asymmetric Michael Addition of 4-Hydroxycoumarin to β,γ-Unsaturated α-Keto Esters

Chang Won Suh, Tae Hyun Han, and Dae Young Kim*

*Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Korea. *E-mail: dyoung@sch.ac.kr*
Received March 8, 2013, Accepted March 31, 2013

Key Words : 4-Hydroxycoumarin, Asymmetric catalysis, Enones, Michael addition, Organocatalysis

The coumarin core is present as a characteristic structural motif in a large number of natural products and biologically active molecules.[1] Particularly, many of these naturally occurring 4-hydroxycoumarin and their synthetic analogues are important precursors for the synthesis of natural products and pharmaceuticals.[2] Enantioselective organocatalytic conjugate addition of 4-hydroxycoumarin to α,β-unsaturated ketones is a straightforward method to access warfarin which is an effective anticoagulants.[3] Although a number of reactions of α,β-unsaturated ketones as Michael acceptors have been reported,[3,4] the corresponding β,γ-unsaturated α-keto esters have received relatively little attention as Michael acceptors. Recently, several groups have reported the asymmetric Michael addition of 4-hydroxycoumarin to β,γ-unsaturated α-keto esters catalyzed by Cu(II)-bisoxazoline, *N,N'*-dioxide-Ni(II) complexes, thiourea catalysts.[5] Although several efficient methods have been achieved by these systems, an effective method for the synthesis of warfarin analogues is still a challenge.

In the framework of our research program for the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[6] we recently reported asymmetric Michael addition reaction of active methylenes and methines using chiral catalysts.[7] Herein, we wish to describe the enantioselective asymmetric conjugate addition of 4-hydroxycoumarin to β,γ-unsaturated α-keto esters promoted by binaphthyl-modified thiourea organocatalyst.

We initially investigated a reaction system with 4-hydroxycoumarin (**1**) with (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (**2a**) in the presence of 10 mol % bifunctional organocatalysts (Fig. 1) at room temperature. As shown in Table 1, Takemoto's catalyst **I** and quinine-derived thiourea catalyst **II** effectively promoted the reaction with moderate enantioselectivities (entry 1-2). While both of binaphthyl-modified (thio)urea catalysts **III-IV** and squaramide organocatalysts **V-VI** bearing both central and axial chiralities gave high enantioselectivities (entries 3-6). The best result has been obtained with binaphthyl-modified thiourea catalyst **III**. We studied the effect of the ester group of (*E*)-4-phenylbut-3-en-2-one **2** using catalyst **III** in CH_2Cl_2 (entries 3 and 7). When employing synthetically attractive, methyl ester of (*E*)-2-oxo-4-phenylbut-3-enoate (**2b**), the corresponding Michael adduct **3b** was obtained with high enantioselectivity of 93% ee (entry 7). Among the solvents probed, the best results

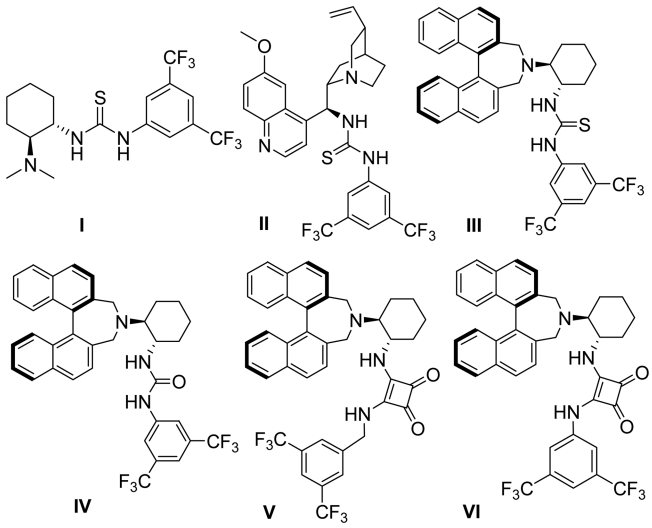
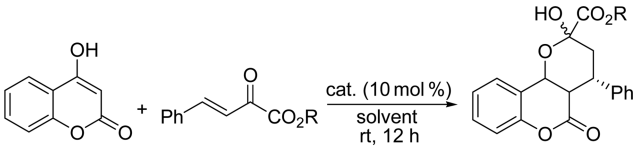


Figure 1. Structure of chiral bifunctional organocatalysts.

Table 1. Optimization of the reaction conditions[a]

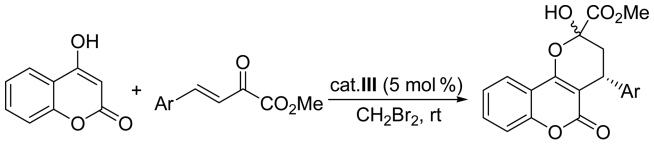


1 2 3

Entry	Cat.	**2**, R	Solvent	Yield (%)[b]	ee (%)[c]
1	**I**	**2a**, Et	DCM	**3a**, 87	59
2	**II**	**2a**, Et	DCM	**3a**, 91	67
3	**III**	**2a**, Et	DCM	**3a**, 88	87
4	**IV**	**2a**, Et	DCM	**3a**, 84	83
5	**V**	**2a**, Et	DCM	**3a**, 86	81
6	**VI**	**2a**, Et	DCM	**3a**, 82	87
7	**III**	**2b**, Me	DCM	**3b**, 93	93
8	**III**	**2b**, Me	DCE	**3b**, 82	94
9	**III**	**2b**, Me	CH_2Br_2	**3b**, 92	96
10	**III**	**2b**, Me	CH_3CN	**3b**, 91	91
11	**III**	**2b**, Me	Et_2O	**3b**, 91	90
12	**III**	**2b**, Me	PhMe	**3b**, 92	84
13[d]	**III**	**2b**, Me	CH_2Br_2	**3b**, 90	96

[a]Reaction conditions: 4-hydroxy coumarin **1** (0.30 mmol), β,γ-unsaturated α-keto ester (**2a**, 0.30 mmol), catalyst (0.03 mmol), solvent (1.2 mL) at room temperature. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using a Chiralpak AD-H column. [d]5 mol % catalyst loading.

Table 2. Enantioselective conjugate addition of 4-hydroxycoumarin (**1**) to β,γ-unsaturated α-keto esters **2**[a]



1 **2** **3**

Entry	**2**, Ar	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2b**, Ph	12	**3b**, 90	96
2[d]	**2c**, 4-FC_6H_4	15	**3c**, 96	95
3	**2d**, 4-ClC_6H_4	12	**3d**, 80	90
4	**2e**, 4-BrC_6H_4	7	**3e**, 90	97
5	**2f**, 4-$NO_2C_6H_4$	6	**3f**, 77	99
6	**2g**, 4-MeC_6H_4	12	**3g**, 92	92
7	**2h**, 4-$MeOC_6H_4$	9	**3h**, 96	87
8	**2i**, 2-furyl	7	**3i**, 88	90
9	**2j**, 2-thienyl	9	**3j**, 60	91
10	**2k**, 1-naphthyl	2	**3k**, 96	93

[a]Reaction conditions: 4-hydroxy coumarin **1** (0.30 mmol), β,γ-unsaturated α-keto ester (**2**, 0.30 mmol), catalyst (0.015 mmol), CH_2Br_2 (1.2 mL) at room temperature. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using Chiralpak AD-H (for **3b-3j**) and IA (for **3k**) columns. [d]This reaction was carried out at −20 °C.

were achieved when the reaction was conducted in dibromomethane (entry 9). The present catalytic system tolerates catalyst loading down to 5 mol % without compromising both the yield and enantioselectivity (entries 9 and 13).

With the optimal reaction conditions in hand, we then carried on evaluating the generality of this protocol. The results of a representative selection of β,γ-unsaturated α-keto esters for the Michael addition are summarized in Table 2. As demonstrated, organocatalyst **III** catalyzed the Michael addition of 4-hydroxycoumarin (**1**) to β,γ-unsaturated α-keto esters **2** proved to be a general approach for the synthesis of Michael adducts **3** with high to excellent enantiomeric excess (up to 99% ee). Absolute configuration of products **3** was determined comparison of the optical rotation and chiral HPLC data with the literature values.[5]

In conclusion, we have developed organocatalytic enantioselective conjugate addition reaction of 4-hydroxycoumarin (**1**) to β,γ-unsaturated α-keto esters **2** to afford biologically valuable warfarin derivatives **3**. The process is efficiently catalyzed by a binaphthyl-modified thiourea organocatalyst.

Acknowledgments. This research was supported in part by the Soonchunhyang University.

References and Notes

1. For selected reviews on coumarin, see: (a) Manolov, I.; Danchev, N. D. *Eur. J. Med. Chem.* **1995**, *30*, 531. (b) Shen, H. C. *Tetrahedron* **2009**, *65*, 3931.
2. Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Des.* **2004**, *10*, 3813.
3. Selected examples: (a) O'Reilly, R. A. N. *Engl. J. Med.* **1976**, *295*, 354. (b) Thomassigny, C.; Prim, D.; Greck, C. *Tetrahedron Lett.* **2006**, *47*, 1117. (c) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. (d) Yang, J.; Li, W.; Jin, Z.; Liang, X.; Ye, J. *Org. Lett.* **2010**, *12*, 5218.
4. For selected examples: (a) Dong, Z.-H.; Wang, L.-J.; Chen, X.-H.; Liu, X.-H.; Lin, L.-L.; Feng, X.-M. *Eur. J. Org. Chem.* **2009**, 5192. (b) Zhu, X.; Lin, A.; Shi, Y.; Guo, J.; Zhu, C.; Cheng, Y. *Org. Lett.* **2011**, *13*, 4382. (c) Lim, Y. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 1825.
5. (a) Xu, D.-Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A.-G.; Xia, A.-B.; Xu, Z.-Y. *Chem. Eur. J.* **2010**, *16*, 4177. (b) Chen, X.-K.; Zheng, C.-W.; Zhao, S.-L.; Chai, Z.; Yang, Y. Q.; Zhao, G.; Cao, W.-G. *Adv. Synth. Catal.* **2010**, *352*, 1648. (c) Gao, Y.; Ren, Q.; Wang, L.; Wang, J. *Chem. Eur. J.* **2010**, *16*, 13068. (d) Wang, J.-J.; Luo, J.-H.; Hu, Z.-P.; Lu, R.-J.; Nie, S.-Z.; Du, Q.-S.; Yan, M. *ARKIVOC* **2010**, 229. (e) Dong, Z.; Feng, J.; Cao, W.; Liu, X.; Lin, L.; Feng, X. *Tetrahedron Lett.* **2011**, *52*, 3433.
6. (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) Kang, Y. K.; Kim, H. H.; Koh, K. O.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 3811. (m) Kwon, B. K.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 2481. (n) Lee, H. J.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 6984.
7. (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) Lee, H. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 3537.(q) Woo, S. B.; Kim, D. Y. *Beilstein J. Org. Chem.* **2012**, *8*, 699. (r) Lee, H. J.; Woo, S. B.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 3374. (s) Moon, H. W.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 2845. (t) Lee, H. J.; Woo, S. B.; Kim, D. Y. *Molecules* **2012**, *17*, 7523. (u) Lee, H. J.; Kim, S. M.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 3437. (v) Lee, H. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 3171. (w) Moon, H. W.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 6569. (x) Kang, Y. K.; Lee, H. J.; Moon, H. W.; Kim, D. Y. *RSC Adv.* **2013**, *3*, 1332.