ORGANIC LETTERS

2007
Vol. 9, No. 3
413−415

Highly Enantioselective Michael Addition of Cyclic 1,3-Dicarbonyl Compounds to α,β-Unsaturated Ketones

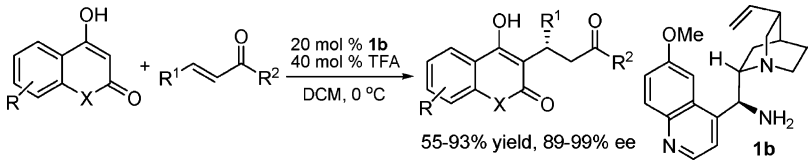
Jian-Wu Xie,[†,‡] Lei Yue,[§] Wei Chen,[§] Wei Du,[§] Jin Zhu,[†] Jin-Gen Deng,[†] and Ying-Chun Chen*[,§,||]

Key Laboratory of Asymmetric Synthesis & Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, China, Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China, and Graduated School of Chinese Academy of Sciences, Beijing, China

ycchenhuaxi@yahoo.com.cn

Received November 7, 2006

ABSTRACT



The highly enantioselective Michael addition of 1,3-cyclic dicarbonyl compounds to α,β-unsaturated ketones was reported to be catalyzed by an organic primary amine derived from quinine. A chiral anticoagulant drug, (*S*)-warfarin, was directly prepared in 96% ee, and other related important adducts were also obtained in excellent enantioselectivity (89–99% ee).

The Michael addition to α,β-unsaturated systems is an important carbon−carbon bond-forming reaction in organic synthesis, and the development of enantioselective catalytic protocols for this reaction has been the subject of intensive research.[1] In addition to the great success catalyzed by metal complexes, the environmentally benign organocatalyst-mediated asymmetric Michael reaction has undergone rapid progress for various useful donor−acceptor combinations in recent years.[2] Among them, MacMillan and other chemists developed a versatile strategy for nonchelating α,β-unsaturated aldehydes and ketones through LUMO-lowering activation catalyzed by chiral secondary amines.[3] Nevertheless, low catalytic efficacy was generally noted for α,β-unsaturated ketones even at room temperature.[4] In an inventive example, Jørgensen et al. reported the enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones catalyzed by an imidazolidine **1a** (Figure 1) derived from chiral 1,2-diphenylethylenediamine, and this process was elegantly applied to make a chiral drug, warfarin, a

[†] Chengdu Institute of Organic Chemistry.
[‡] Graduated School of Chinese Academy of Sciences.
[§] West China School of Pharmacy, Sichuan University.
[||] West China Hospital, Sichuan University.

(1) For reviews, see: (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (b) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171.

(2) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Seayad, J.; List B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. For selected examples, see: (d) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598. (e) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. (f) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032. (g) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948. (h) Xue, D.; Chen, Y. C.; Cun, L. F.; Wang, Q. W.; Zhu, J.; Deng, J. G. *Org. Lett.* **2005**, *7*, 5293. (i) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028. (j) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (k) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (l) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (m) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984.

10.1021/ol062718a CCC: $37.00 © 2007 American Chemical Society
Published on Web 01/06/2007

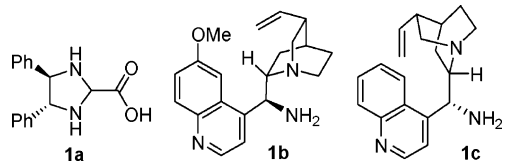
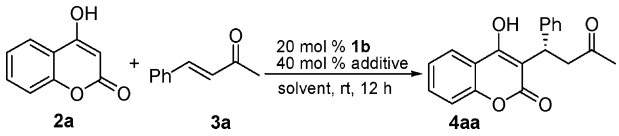


Figure 1. Structure of amine catalysts.

widely prescribed anticoagulant.[4e,5] Unfortunately, less than 90% ee was observed for a range of substrates, and in general, over 6 days were required in order to achieve good yields at ambient temperature. This encouraged us to explore this important asymmetric Michael reaction with our newly developed 9-amino-9-deoxyepicinchona alkaloids as the iminium catalysts (Figure 1).[6]

We were pleased to find that 9-amino-9-deoxyepiquinine **1b** (Figure 1, 20 mol %) in the combination with TFA (40 mol %) exhibited high catalytic activity for the asymmetric Michael addition of 4-hydroxycoumarin **2a** to benzylidene-acetone **3a** in DCM at room temperature. (*S*)-Warfarin **4aa** was cleanly isolated in 90% yield with a promising 92% ee after 12 h (Table 1, entry 1). 9-Amino-9-deoxyepicinchonine **1c** gave the same enantioselectivity while the adduct with opposite configuration was obtained (entry 2). Subsequently, we investigated the effects of solvents and acidic additives with **1b**. Good yields were obtained in THF and DMF but the ee was reduced (entries 3 and 4). Both reactivity and enantioselectivity were decreased in toluene or methanol (entries 5 and 6). The enantioselectivity was decreased in the presence of other acidic additives (entries 7−9). In addition, the coupling reaction could proceed smoothly at 0 °C, and an excellent ee (96%) was obtained in 88% yield after 96 h (entry 10). However, we found that no beneficial effect on ee was observed at 0 °C catalyzed by TFA salt of **1c** (entry 11). Moderate yield was attained catalyzed by 10 mol % of **1b** after 96 h in a more concentrated solution (entry 12).

Table 1. Screening Studies of Organocatalytic Michael Addition of 4-Hydroxycoumarin **2a** to Benzylideneacetone **3a**[a]



entry	solvent	additive	yield[b] (%)	ee[c] (%)
1	DCM	TFA	90	92
2[d]	DCM	TFA	92	−92
3	THF	TFA	88	86
4	DMF	TFA	86	60
5	toluene	TFA	51	85
6	MeOH	TFA	42	65
7	DCM	CF_3SO_3H	15	85
8	DCM	HCl	80	83
9	DCM	$HClO_4$	75	73
10[e]	DCM	TFA	88	96
11[d,e]	DCM	TFA	83	−92
12[f]	DCM	TFA	51	97

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **2a**, 0.15 mmol of **3a**, and 20 mol % of catalyst **1b** in 2 mL of solvent at room temperature for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configuration was determined to be (*S*) according to the optical rotation. [d] Catalyzed by **1c**. [e] At 0 °C for 96 h. [f] Using 10 mol % of **1b** in 1 mL of DCM.

With the optimal reaction conditions in hand, we then examined a variety of cyclic 1,3-dicarbonyl compounds (Figure 2) and α,β-unsaturated ketones to established the

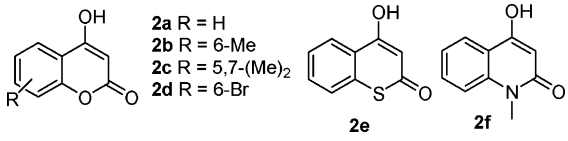


Figure 2. Structures of cyclic 1,3-dicarbonyl compounds.

(3) (a) For a review, see: List, B. *Chem. Commun.* **2006**, 819. For selected examples, see: (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (c) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (d) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894. (e) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (f) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. (g) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660. (h) Wang, W.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 1637. (i) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437. (j) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (k) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (l) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (m) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305. (n) Xie, J.-W.; Yue, L.; Xue, D.; Ma, X.-L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Chem. Commun.* **2006**, 1563. (o) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354.

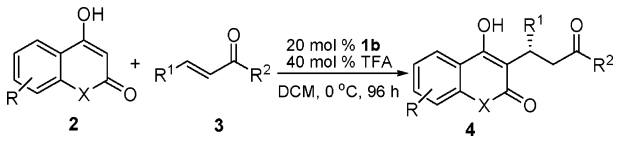
(4) For asymmetric reactions of α,β-unsaturated ketones catalyzed by secondary amines, see: (a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975 and references therein. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (c) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (d) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661. (e) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955. (f) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (g) Pulkkinen, J.; Aburel, P. S.; Halland, N.; Jørgensen, K. A. *Adv. Synth. Catal.* **2004**, *346*, 1077. (h) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897. (i) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66. (j) Li, D.-P.; Guo, Y.-C.; Ding, Y.; Xiao, W.-J. *Chem. Commun.* **2006**, 799. (k) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.

(5) During the preparation of this paper, a vicinal diamine-catalyzed synthesis of (*R*)-warfarin (92% ee) was reported, see: (a) Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239. For other reports on stereoselective warfarin synthesis, see: (b) Demir, A. S.; Tanyeli, C.; Gülbeyaz, V.; Akgün, H. *Tur. J. Chem.* **1996**, *20*, 139. (c) Robinson, A.; Li, H.-Y.; Feaster, J. *Tetrahedron Lett.* **1996**, *37*, 8321. (d) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707. (e) Tsuchiya, Y.; Hamashima, Y.; Sodeoka, M. *Org. Lett.* **2006**, *8*, 4851. Optical resolution, see: (f) West, B. D.; Preis, S.; Schroeder, C. H.; Link, K. P. *J. Am. Chem. Soc.* **1961**, *83*, 2676.

(6) (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. For other examples of primary amines as iminium catalysts, see the following. For α,β-unsaturated aldehydes: (b) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (c) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229. For α,β-unsaturated ketones: (d) Tsogoeva, S.; Jagtap, S. B. *Synlett* **2004**, 2624. (e) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368. (f) See ref 5a.

general utility of the catalytic transformation. The Michael reaction was generally conducted with 20 mol % of **1b** at 0 °C for 96 h. As illustrated in Table 2, for the reactions of

Table 2. Asymmetric Michael Addition of 1,3-Dicarbonyl Compounds **2** to α,β-Unsaturated Ketones **3**[a]



entry	2	R^1	R^2 (3)	4	yield[b] (%)	ee[c] (%)
1	**2a**	Ph	Me (**3a**)	**4aa**	88	96
2	**2a**	*p*-Cl-Ph	Me (**3b**)	**4ab**	87	97
3	**2a**	*p*-MeO-Ph	Me (**3c**)	**4ac**	81	95
4	**2a**	2-furanyl	Me (**3d**)	**4ad**	81	94
5	**2a**	2-thienyl	Me (**3e**)	**4ae**	83	93
6[d]	**2a**	Ph	Et (**3f**)	**4af**	90	99
7[d]	**2a**	Ph	*n*-Pr (**3g**)	**4ag**	82	97
8[d]	**2a**	*n*-Pr	Me (**3h**)	**4ah**	93	95
9[d]	**2a**	*i*-Pr	Me (**3i**)	**4ai**	88	98
10[d,e]	**2a**	*n*-Pr	Et (**3j**)	**4aj**	55 (95)	90
11[d]	**2a**	$-C_4H_8-$ (**3k**)		**4ak**	78	94
12	**2b**	Ph	Me (**3a**)	**4ba**	87	99
13	**2c**	Ph	Me (**3a**)	**4ca**	80	98
14	**2d**	Ph	Me (**3a**)	**4da**	82	98
15	**2e**	Ph	Me (**3a**)	**4ea**	68	89
16	**2f**	Ph	Me (**3a**)	**4fa**	71	99

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **2**, 0.15 mmol of **3**, and 20 mol % of catalyst **1b** in 2 mL of DCM at 0 °C for 96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configuration of **4aa** was (*S*), and the other adducts were assigned accordingly. [d] For 6 days. [e] Yield in parentheses is based on recovered **2a**.

4-hydroxycoumarin **2a**, excellent results were achieved with α,β-unsaturated ketones **3b**−**e** bearing various β-aryl or heteroaryl substitutions (entries 2−5). Other bulkier alkyl enones **3f** and **3g** were also well tolerated to give excellent ee while longer time was required (entries 6 and 7). On the other hand, the enantioselectivity was quite satisfying when β-alkyl α,β-unsaturated ketones **3h**−**j** were applied (entries 8−10), and a high yield was observed even for enone **3i** with a branched substitution after 6 days (entry 9). Nevertheless, the isolated yield was moderate for ethyl enone **3j** (entry 10). A high ee was also received in the case of cyclic enone **3k** (entry 11). Subsequently, a few 4-hydroxycoumarin derivatives **2b**−**d** with different substitutions were investigated. The electronic effect was very marginal and remarkable enantioselectivity was achieved (entries 12−14). 4-Hydroxythiocoumarin **2e** exhibited slightly lower reactivity, while a high ee (89%) was still obtained (entry 15). In comparison, only moderate ee (75%) was received in the same reaction of **2e** catalyzed by **1a**.[4e] In addition, we tested the asymmetric Michael addition reaction of 1-methyl-4-hydroxycarbostyril **2f**.[7] Although sluggish reaction was observed even at room-temperature due to the very low solubility of **2f** in DCM, gratifyingly, the Michael reaction proceeded very well at 40 °C, and an excellent ee (99%) was achieved in 71% yield after 24 h (entry 16).

As previously reported, the ketimine cation intermediate from **1b**-$(TFA)_2$ salt and benzylideneacetone **3a** in the asymmetric Michael addition would adopt a *trans* conformation (Figure 3, **a**).[6a,8] The desired (*S*)-product could be obtained through the *si*-face attacking of the iminium ion.

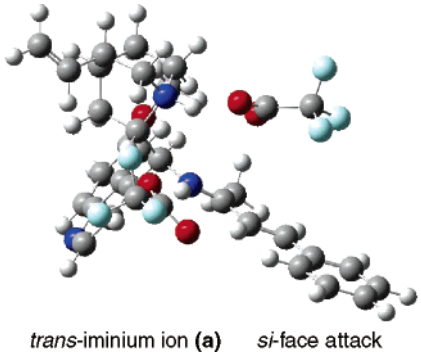


Figure 3. Possible iminium intermediate in the Michael reaction.

In conclusion, we have successfully demonstrated that 9-amino-9-deoxyepiquinine is an excellent iminium organocatalyst for the enantioselective Michael addition reaction of cyclic 1,3-dicarbonyl compounds and α,β-unsaturated ketones under mild conditions. The reaction scopes were quite broad, and excellent enantioselectivity (89−99% ee) was achieved for a number of cyclic 1,3-dicarbonyl compounds and substituted α,β-unsaturated ketones. Moreover, a chiral drug, (*S*)-warfarin, was directly prepared in high ee (96%) and yield. Current studies are actively and well underway to expand the synthetic utility of this reaction, as well as of this catalytic system in other asymmetric transformations.

Acknowledgment. We are grateful for financial support from the National Natural Science Foundation of China (20502018), Ministry of Education of China (NCET-05-0781), Fok Ying Tung Education Foundation (101037), and Sichuan University. We thank Dr. Rui Li for his help with the computational calculation studies.

Supporting Information Available: Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062718A

(7) For the Michael reaction of 4-hydroxycarbostyrils and benzylideneacetone in a racemic form, see: Boetius, M.; Carstens, E.; Meyer, C. 4-Hydroxycarbostyril derivatives. Patent DD 13870, 1957.

(8) The computational studies were conducted with hyperchem 7.5 software, see ref. 6a, Supporting Information