ORGANIC LETTERS

2011
Vol. 13, No. 16
4382–4385

Enantioselective Synthesis of Polycyclic Coumarin Derivatives Catalyzed by an *in Situ* Formed Primary Amine-Imine Catalyst

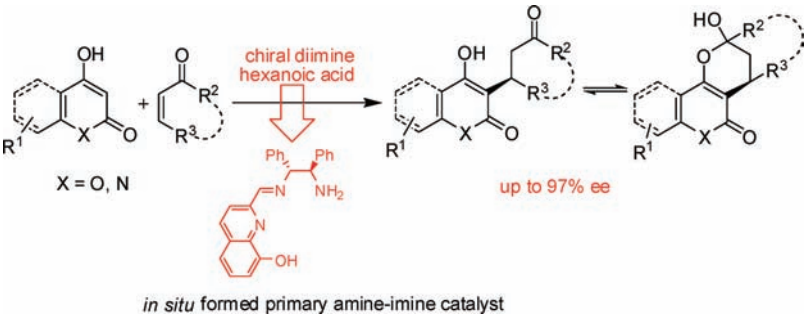
Xi Zhu, Aijun Lin, Yan Shi, Jingyu Guo, Chengjian Zhu,* and Yixiang Cheng*

School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, P. R. China

cjzhu@nju.edu.cn; yxcheng@nju.edu.cn

Received June 27, 2011

ABSTRACT



A facile *in situ* formed primary amine-imine organocatalyst was developed in the asymmetric Michael addition of substituted 4-hydroxycoumarins to cyclic enones. A series of optically active polycyclic coumarin derivatives were obtained in high yields with excellent enantioselectivities up to 97% *ee*.

Coumarin derivatives are distributed in a large number of natural products and are commonly used as versatile intermediates in natural product synthesis.[1] Modification of this class of compound has been of great interest to chemists due to their various biological activities to antimalarial, anticoagulant, and anti-HIV activities, etc.[2] Although most of coumarin derivatives are currently prescribed as the racemate, activity and metabolism are markedly dissimilar for the two enantiomers.[3] Therefore, efficient asymmetric syntheses of coumarins are of long-standing interest.[4] Organocatalysis has proven itself a valuable strategy in the preparation of the synthesis of optically active coumarins[5] since Jørgensen reported a one-step synthesis of enantiomerically pure warfarin in 2003.[6] They presented the first example of an imidazolidine organocatalyst promoted asymmetric Michael reaction of coumarin and α,β-unsaturated ketones.[7] Chin and Chen

(1) (a) Murray, R. D. H.; Mendez, J.; Brown, R. A. *The Natural Coumarins*; Wiley: 1982. (b) Kennedy, R. O.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*; Wiley: 1997. (c) Fylaktakidou, K. C.; Hadjipavlou, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Des.* **2004**, *10*, 3813.

(2) (a) Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A. L.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 78. (b) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K. H. *J. Med. Chem.* **2001**, *44*, 664. (c) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707. (d) Ishikawa, T. *Heterocycles* **2000**, *53*, 453. (e) Ufer, M. *Clin. Pharmacokinet.* **2005**, *44*, 1227. (f) Visser, L. E.; van Schaik, R. H. N.; van Vliet, M.; Trienekens, P. H.; Smet, P. A. G. M. D.; Vulto, A. G.; Hofman, A.; van Duijn, C. M.; Stricker, B. H. C. *Clin. Pharmacol. Ther.* **2005**, *77*, 479.

(3) (a) O'Reilly, R. A. N. *Engl. J. Med.* **1976**, *295*, 354. (b) Wingard, L. B.; O'Reilly, R. A.; Levy, G. *Clin. Pharmacol. Ther.* **1978**, *23*, 212. (c) Rang, H. P.; Dale, M. M.; Ritter, J. M.; Gardner, P. *Pharmacology*, 4th ed.; Churchill Livingstone: Philadelphia, 2001.

(4) (a) Demir, A. S.; Tanyeli, C.; Gklbeyaz, V.; Akgkn, H. *Turk. J. Chem.* **1996**, *20*, 139. (b) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707.

(5) (a) Tsuchiya, Y.; Hamashima, Y.; Sodeoka, M. *Org. Lett.* **2006**, *8*, 4851. (b) Halland, N.; Velgarard, T.; Jøgensen, K. A. *J. Org. Chem.* **2003**, *68*, 5067.

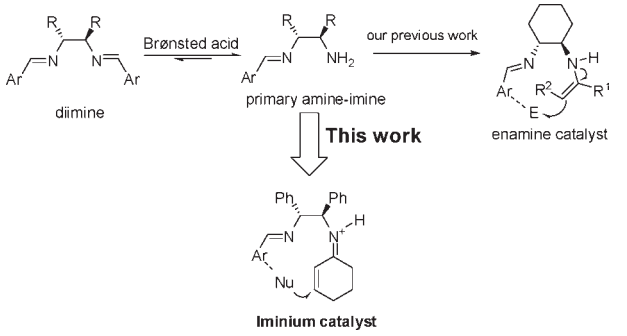
(6) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955.

(7) For selected organocatalytic conjugate additions to α,β-unsaturated ketones, see: (a) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4541. (b) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (c) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958. (d) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598. (e) Yang, J. Y.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (f) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028. (g) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897. (h) Deiana, L.; Zhao, G. L.; Lin, S. Z.; Dziedzic, P.; Zhang, Q.; Leijonmarck, H.; Cordova, A. *Adv. Synth. Catal.* **2010**, *18*, 3201. (i) Yanai, H.; Takahashi, A.; Taguchi, T. *Chem. Commun.* **2010**, *46*, 8728.

10.1021/ol201715h
Published on Web 07/19/2011

reported the same strategy for the synthesis of pure warfarin catalyzed by a primary amine and diamine, respectively.[8] Recently, Xu and Wang independently developed the procedure by chiral squaramides and an amine-thiourea catalyst.[9] Good yields and excellent enantioselectivities were obtained with the synthesis strategy above. However, most of the previous research efforts have been limited to a Michael addition reaction with unsubstituted coumarins to modified acyclic enones. Cyclic enones, a special α, β-unsaturated system, still remain as difficult substrates and have been rarely employed as electrophiles in this process. Even for the only example with a 2-cyclohexen-1-one as a cyclic enone donor, the reaction activity was obviously low and a long reaction time (6 days, 78% yield) was required.[8a] Since the conjugate addition to cyclic enones is an important strategy for the synthesis of active cyclic building blocks, it is therefore of great demand to develop a more effective method to improve the tolerance of cyclic enones and explore more coumarin substrates.

Scheme 1. Application of the *in Situ* Prepared Primary Amine-Imine



Recently, the primary amine-imine catalyst with an (*R*,*R*)-cyclohexane backbone was first described by our group as an efficient aminocatalyst for the aldol reaction of α-keto esters with excellent enantioselectivity.[10] The primary amine-imine catalyst (Scheme 1), which is unable to be isolated due to instability,[11] can be *in situ* generated by taking advantage of the hydrolization of a chiral diimine under acidic conditions. This could be identified obviously using ESI-MS. A catalytic amount of chiral diimine with AcOH afforded the active catalyst, which efficiently promoted the aldol reaction *via* an enamine process. Inspired by the finding, we considered that the procedure could be extended to activate the cyclic α,β-unsaturated ketones *via* an iminium process in the Michael reaction.[12] Herein, we describe an asymmetric Michael reaction of 4-hydroxycoumarins and 2-cyclohexen-1-one catalyzed by the *in situ* formed primary amine-imine catalyst with an (*R*,*R*)-diphenylethane backbone to give polycyclic coumarin derivative adducts in high yields and excellent enantioselectivities under mild conditions.

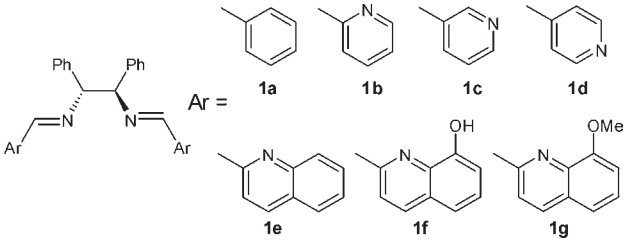


Figure 1. Structure of diimine precatalysts.

In the preliminary investigation, a series of diimine precatalysts with an (*R*,*R*)-diphenylethane backbone were prepared (Figure 1, **1a**−**1g**). When acidified with AcOH in THF, the diimines largely converted to the primary amine-imine, which could be obviously detected by the ESI-MS analysis of the mixture.[13] The addition of 4-hydroxycoumarin **2a** to 2-cyclohexen-1-one was selected as a model reaction to explore the feasibility of the proposed strategy catalyzed by a chiral primary amine-imine catalyst. The results are summarized in Table 1.

Initially, diimine **1a** was investigated as the precatalyst, and the reaction failed to proceed without any additive. When added with 10 equiv of AcOH, **1a** afforded the desired product in 96% yield with 86% *ee* in THF at room temperature (entry 1). The product was found to exist in rapid equilibrium with a pseudodiastereomeric hemiketal form in solution. The equilibrium is very rapid, and therefore no pseudodiastereomers are observed during HPLC analysis.[7−9] (*R*,*R*)-dpen as catalyst was also investigated but gave the desired adduct with a lower *ee* value (entry 2). Subsequently, different diimines **1b**−**1g** were probed as precatalysts, and **1f** exhibited the best result (entry 7). We then investigated the effects of solvents with catalyst **1f**. The results (entries 7 and 9−12) showed that the best solvent was THF. To further improve the enantioselectivity, the effect of

(8) (a) Xie, J. W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J. G.; Chen, Y. C. *Org. Lett.* **2007**, *9*, 413. (b) Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239.

(9) (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) Gao, Y. J.; Ren, Q.; Wang, L.; Wang, J. *Chem.—Eur. J.* **2010**, *16*, 13068.

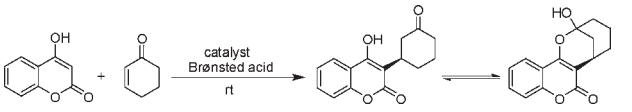
(10) Zhu, X.; Lin, A. J.; Fang, L.; Li, W.; Zhu, C. J.; Cheng, Y. X. *Chem.— Eur. J.* **2011**, *17*, 8281.

(11) For the instability of the primary amine-imine, see: (a) Xia, Q.; Ge, H.; Ye, C.; Liu, Z.; Su, K. *Chem. Rev.* **2005**, *105*, 1603. (b) Lopez, J.; Liang, S.; Bu, X. *Tetrahedron Lett.* **1998**, *39*, 4199. (c) Campbell, E. J.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 1221. (d) Sun, Y.; Tang, N. *J. Mol. Catal. A: Chem.* **2006**, *255*, 171. (e) Daly, A. M.; Dalton, C. T.; Renehan, M. F.; Gilheany, D. G. *Tetrahedron Lett.* **1999**, *40*, 3617. (f) Renehan, M. F.; Schanz, H. J.; McGarrigle, E. M.; Dalton, C. T.; Daly, A. M.; Gilheany, D. G. *J. Mol. Catal. A: Chem.* **2006**, *231*, 205.

(12) For examples of asymmetric reactions of α,β-unsaturated ketones catalyzed by primary amines, see: (a) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (b) 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. (c) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49. (d) Yang, Y. Q.; Zhao, G. *Chem.—Eur. J.* **2008**, *14*, 10888. (e) Liu, C.; Lu, Y. X. *Org. Lett.* **2010**, *10*, 2278. (f) Xue, F.; Liu, Lu.; Zhang, S. L.; Duan, W. H.; Wang, W. *Chem.—Eur. J.* **2010**, *27*, 7979. (g) Zhu, Q.; Lu, Y. X. *Chem. Commun.* **2010**, *13*, 2235.

(13) For ESI-MS spectra, see Supporting Information: **1f** was acidified with AcOH in THF.

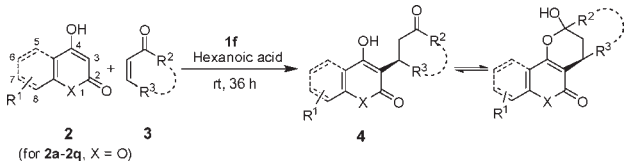
Table 1. Asymmetric Michael Addition of 4-Hydroxycoumarin to 2-Cyclohexen-1-one



entry[a]	catalyst	solvent	additive	t (h)	yield (%)[b]	ee (%)[c]
1	**1a**	THF	--/AcOH	24	--/92	--/86
2	(*R*, *R*)-dpen	THF	--/AcOH	24	92/96	49/75
3	**1b**	THF	AcOH	36	93	88
4	**1c**	THF	AcOH	36	91	87
5	**1d**	THF	AcOH	36	90	86
6	**1e**	THF	AcOH	36	92	89
7	**1f**	THF	AcOH	36	94	91
8	**1g**	THF	AcOH	36	92	88
9	**1f**	Toluene	AcOH	48	68	79
10	**1f**	MeOH	AcOH	72	57	63
11	**1f**	CH_2Cl_2	AcOH	48	90	88
12	**1f**	Et_2O	AcOH	72	9	68
13	**1f**	THF	C_2H_5COOH	36	93	92
14	**1f**	THF	C_3H_7COOH	36	94	93
15	**1f**	THF	hexanoic acid	36	94	95
16	**1f**[d]	THF	hexanoic acid	36	94	90
17	**1f**[e]	THF	hexanoic acid	36	94	95
18	**1f**[f]	THF	hexanoic acid	72	78	95
19	**1f**[g]	THF	hexanoic acid	36	76	91
20	**1f**[h]	THF	hexanoic acid	36	78	92

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol of 2-cyclohexen-1-one, 0.1 mmol of 4-hydroxycoumarin, 10 equiv of a Brønsted acid, and a 10 mol % loading of diimine in 0.5 mL of THF at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC. The absolute configurations were established as *R*. [d] With 5 mol % loading of **1f**. [e] With 20 mol % loading of **1f**. [f] Carried out at 0 °C. [g] With 5 equiv of hexanoic acid loading. [h] With 20 equiv of hexanoic acid loading.

Table 2. Asymmetric Michael Addition of 4-Hydroxycoumarins to Cyclic Enones



entry[a]	2	3 (R^2, R^3)	product	yield (%)[b]	ee (%)[c]
1	**2a** R^1=H	-C_3H_6-	**4a**	94	95(*R*)[d]
2	**2b** R^1=8-Me	-C_3H_6-	**4b**	91	97
3	**2c** R^1=6-Me	-C_3H_6-	**4c**	94	94
4	**2d** R^1=6-OMe	-C_3H_6-	**4d**	91	95
5	**2e** R^1=6-tBu	-C_3H_6-	**4e**	87	96
6	**2f** R^1=6, 8-$(tBu)_2$	-C_3H_6-	**4f**	86	95
7	**2g** R^1=6-Cl	-C_3H_6-	**4g**	92	95
8	**2h** R^1=6-Br	-C_3H_6-	**4h**	94	91
9	**2i** R^1=7-F	-C_3H_6-	**4i**	93	95
10	**2j** R^1=7, 8-benzo	-C_3H_6-	**4j**	82	95
11	**2k** R^1=5, 6-benzo	-C_3H_6-	**4k**	84	95
12	**2l** R^1=H	-C_4H_8-	**4l**	91	94
13	**2m** R^1=H	-C_5H_{10}-	**4m**	88	95
14	**2n** R^1=H	R^2=Me, R^3=Ph	**4n**	96	91
15	**2o** R^1=H	R^2=Ph, R^3=Ph	**4o**	61	94
16	**2p** R^1=H	-$C(CH_3)_2C_2H_4$-	**4p**	94	95
17	**2q** 	-C_3H_6-	**4q**	88	95
18	**2r** 	-C_3H_6-	**4r**	83	88

[a] Carried out with 0.1 mmol of enone, 0.1 mmol of substituted 4-hydroxycoumarin compounds, 10 equiv of hexanoic acid, and a 10 mol % loading of diimine **1f** in 0.5 mL of THF at room temperature for 36 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The absolute configuration was established as *R*.

additives was investigated. A series of Brønsted acids screened showed that aliphatic acids had a slight effect on enantioselectivity enhancement. Hexanoic acid was the best additive which afforded the adduct with 95% *ee* (entries 13−15). Decreasing the catalyst loading of **1f** to 5 mol % led some loss of *ee* value while increasing the **1f** loading to 20 mol % provided no improvement of enantioselectivity (entries 16−17). The reaction temperature was also studied. It seems that lowering the reaction temperature to 0 °C led to little improvement of the enantioselectivity and caused low reactivity (entry 18). In addition, the loading of hexanoic acid is probed and 10 equiv of hexanoic acid to 4-hydroxycoumarin afforded the product with the highest enantioselectivity (entries 19−20). Optimization of reaction conditions revealed that the reaction carried out with a 10 mol % loading of **1f** and 10 equiv of hexanoic acid in 0.5 mL of THF at room temperature afforded the adduct with the best reactivity (94% yield) and enantioselectivity (95% *ee*) in 36 h (entry 15).

With the optimized conditions, the substrate generality was investigated. As summarized in Table 2, generally, the Michael reactions proceeded smoothly with a variety of substituted 4-hydroxycoumarins and 2-cyclohexen-1-one to generate the corresponding adducts with high enantioselectivities. The 4-hydroxycoumarins with electron-donating substituents (entries 2−6) and electron-withdrawing substituents (entries 7−9) on aromatic rings were introduced and showed good toleration in the reaction. It appears that the position and electronic properties of substituents on aromatic rings have a limited effect on the activity and selectivity of this process. Benzo-4-hydroxycoumarins were also investigated (entries 10−11). Although slightly lower yields of the Michael adducts were obtained, high enantioselectivities were maintained. 2-Cyclohepten-1-one and 2-cycloocten-1-one were employed as electrophiles in the process and showed good enantioselectivities (entries 12−13). Benzalacetone and chalcone as acyclic enones were also introduced and were well-tolerated (entries 14−15). Moreover, we probed the asymmetric Michael addition reaction of 4,4-dimethylcyclohex-2-enone, which gave the adduct in a high yield with 95% ee (entry 16). In addition, the reaction can be successfully extended utilizing 4-hydroxy-6-methyl-2-pyrone as the Michael donor, which afforded an excellent result (entry 17). 1-Methyl-4-hydroxycarbostyril, a 4-hydroxycoumarin analogue, was also employed,

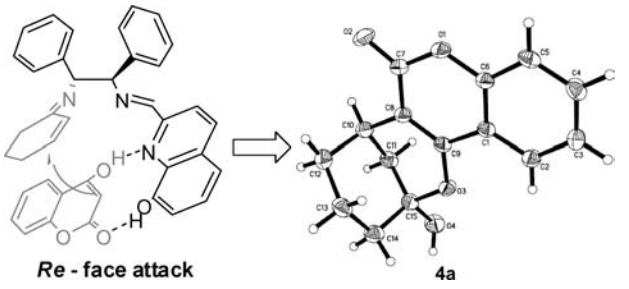


Figure 2. Proposed transition state for the reaction and X-ray crystal structure of compound **4a**.

and high enantioselectivity (88% ee) was achieved with a little reduction of yield (entry 18).

The absolute configuration of product **4a** was determined to be *R* by using single-crystal X-ray diffraction (Figure 2).[14] Based on the result, we proposed a transition state for the catalytic asymmetric Michael reaction. The chiral diimine is hydrolyzed under acidic conditions and converted to a primary amine-imine catalyst. The interaction between enone and amine gives the active iminium. The 4-hydroxycoumarin introduced by hydrogen bonding is much more accessible to attack the active iminium from the *Re* face, affording the major stereoisomer.

In conclusion, we have successfully demonstrated that the *in situ* formed primary amine-imine catalyst is an excellent aminocatalyst for an enantioselective Michael addition reaction of substituted 4-hydroxycoumarin compounds and cyclic enones. High yields and excellent enantioselectivities were achieved for a series of substituted 4-hydroxycoumarin compounds. Cyclic enones showed excellent toleration in the process, which explored a new strategy for the synthesis of optically active polycyclic coumarin derivatives.

Acknowledgment. We gratefully acknowledge the National Natural Science Foundation of China (20832001, 20972065, 21074054) and the National Basic Research Program of China (2007CB925103, 2010CB923303) for their financial support. Fundamental Research Funds for the Central Universities (1082020502) is also acknowledged.

Supporting Information Available. Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products, and CIF file of enantiopure **4a**. The material is available free of charge via the Internet at http://pubs.acs.org.

(14) CCDC 823543 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc. cam.ac.uk/data_request/cif.