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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

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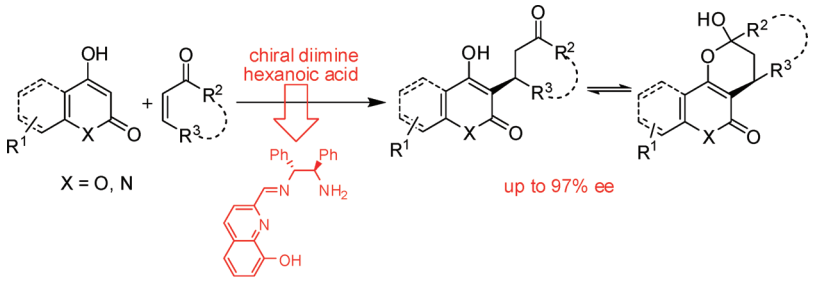
ABSTRACT



in situ formed primary amine-imine catalyst

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

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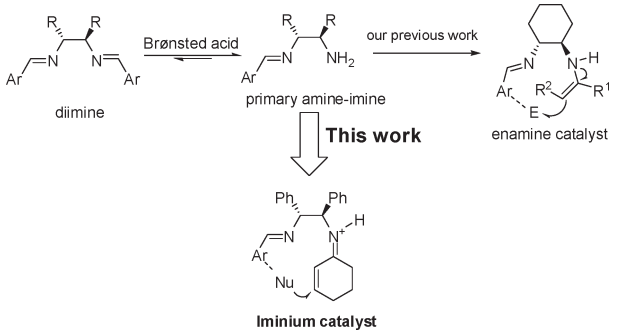
reported the same strategy for the synthesis of pure warfarin catalyzed by a primary amine and diamine, respectively.[8] Recently, Xu and Wang independently developed the procedure by chiral squaramides and an amine-thiourea catalyst.[9] Good yields and excellent enantioselectivities were obtained with 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.

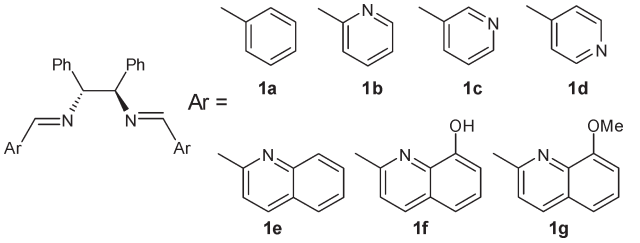


Figure 1. Structure of diimine precatalysts.

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

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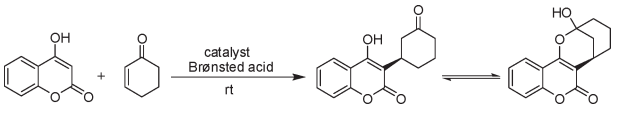
(13) For ESI-MS spectra, see Supporting Information: **1f** was acidified with AcOH in THF.

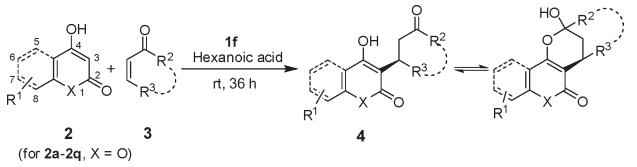
Table 1. Asymmetric Michael Addition of 4-Hydroxycoumarin to 2-Cyclohexen-1-one



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		-C_3H_6-	**4q**	88	95
18		-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,

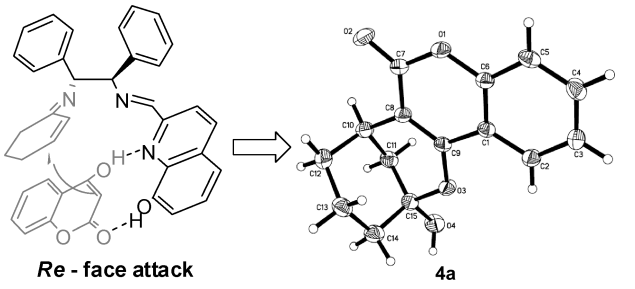


Figure 2. Proposed transition state for the reaction and X-ray crystal structure of compound **4a**.

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.

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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.