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Enantioselective Synthesis of Coumarins Catalyzed by a Bifunctional Amine–Thiourea Catalyst

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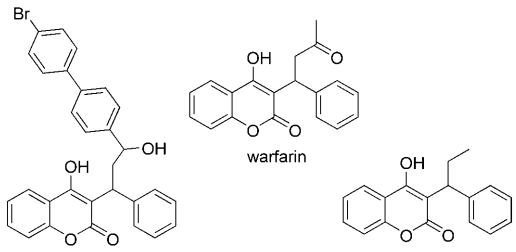
The development of asymmetric methods for the preparation of functionalized coumarins has been of long-standing interest to organic chemists. As a result of their broad applications in organic synthesis they are widely distributed in a vast array of bioactive molecules.[1] Warfarin (see below) has been discovered as an anticoagulant, inhibiting Vitamin K epoxide reductase and thereby decreasing blood coagulation by preventing the vitamin K dependent synthesis of blood-clotting proteins.[2] Bromadiolone is a second-generation 4-hydroxycoumarin derivative, called as a "super-warfarin" for its added potency and tendency to accumulate in the liver of the poisoned organism. It was effective against the populations that had become resistant to the first-generation anticoagulants.[3] Phenprocoumon is another anticoagulant drug



that inhibits coagulation by blocking synthesis of coagulation factors II, VII, IX and X and is frequently used for the prophylaxis and treatment of thromboembolic disorders.[2b,4]

Although currently most of them are formulated as the racemate, activity and metabolism are markedly dissimilar for the two enantiomers, one of the enantiomer being more active than the other.[1f,g,5] For example, warfarin has been used as a racemate for more than fifty years and it is well known that the anticoagulant bioactivity of the *S* enantiomer is about several folds higher than that of the *R* enantiomer.[2a] Furthermore, the two enantiomers are metabolized by different pathways, which are validated by the different half-lives in living organisms. Due to these different pharmacological effects, it may generate a major problem that the delivery of a high dose might cause internal haemorrhages in patients. Thus, it is extremely expected that the treatment of patients with optical pure drug molecule via a low dosage will significantly reduce the potential pharmacological side effects. Most importantly, it can also eventually avoid drug–drug interactions which represent the serious problem with racemic drug molecules.[1f,g,6]

Therefore, efficient asymmetric syntheses of coumarins are of great interest.[7] Obviously, great progress has been made for the synthesis of diversely structured coumarins. Although asymmetric organocatalysis as a powerful tool in particular has proven itself a valuable instrument in the preparation of enantiomerically enriched compounds,[8] the examples that can produce optical pure enantiomer in an organocatalytic asymmetric manner are still extremely rare.[9] Indeed, as early as 2003, Jørgensen reported the first example of imidazolidine organocatalyst-promoted asymmetric Michael reaction of coumarin and α,β-unsaturated ketones (Scheme 1).[9d] Recently, Chin et al.[9a] and Chen et al.[9b] reported a primary amine catalyzed enantioselective Michael reaction of coumarin and α,β-unsaturated ketones, respectively. In summary, all these strategies employed iminium catalysis process to promote the key C–C bond-forming. Recently, hydrogen-bonding-mediated catalysis that achieve the formation of new C–C bond is found as a particularly strategy for the efficient construction of molecular architectures.[10] Especially, there is a remarkable development and application on chiral bifunctional thiourea catalysis.[11] The use of inexpensive and readily synthesized chiral thiourea catalysts has attracted considerable interests and proved to be effective in several asymmetric transformations. Herein,

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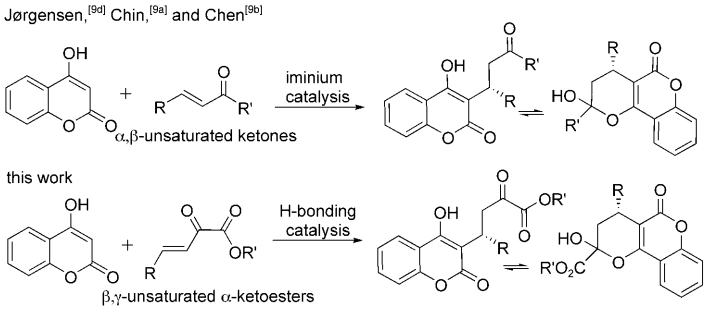
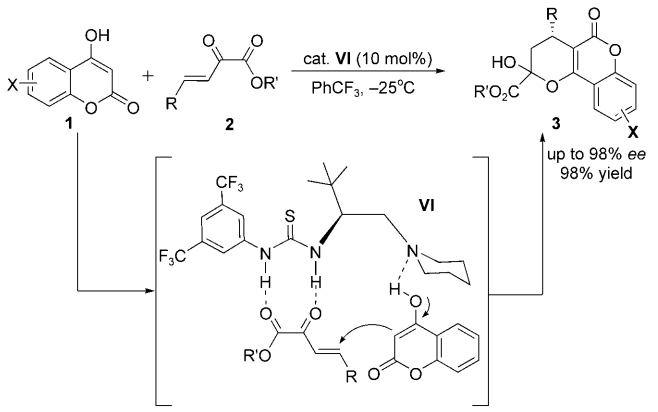


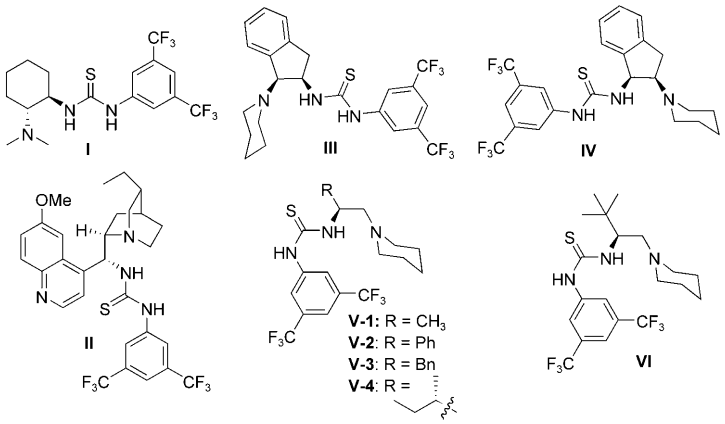
Scheme 1. Organocatalyst-promoted Michael addition of coumarin to α,β-unsaturated system.

we report a novel strategy for the preparation of chiral coumarins through hydrogen-bonding-mediated enantioselective Michael addition reaction via a new chiral amine thiourea catalyst (Scheme 2). Significantly, this strategy enables quick construction of diversely functionalized coumarins with high to excellent enantioselectivity (90–98% *ee*) from readily available starting materials under mild reaction conditions.



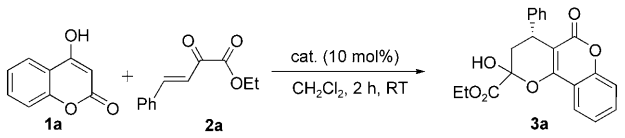
Scheme 2. Strategy for enantioselective synthesis of coumarins.

To probe the feasibility of the proposed strategy, 4-hydroxycoumarin (**1a**) was treated with β,γ-unsaturated α-keto ester (**2a**) in the presence of Takemoto's[11d,e] catalyst **I** (see below) and Connon et al.,[11m] Deng et al.[10a] and Soós et al.[12] developed cinchona alkaloid catalyst **II** (10 mol%). Herein, β,γ-unsaturated α-keto esters are employed as preferred electrophiles in this kind of process due to their high reactivity and the easy convertibility of the resultant products to other useful structures.[13] Furthermore, the α-keto ester functional group can theoretically generate two hydrogen bonds with the catalyst to assist the enantioselective Michael addition process (Scheme 2). As shown in Table 1, in the presence of catalyst **I** and **II**, the process lead to the desired Michael addition product **3a** (compound **3a** was existed as a mixture of anomers in $CDCl_3$, see Supporting Information for details) in high yields (entries 1 and 2, 91 and 98%, respectively, Table 1) but with only moderate selectivities (47 and 63% *ee*, respectively). Further screening of indane catalyst **III** and **IV** (see above), which were recently developed by our group and have been used to catalyze some particular reactions with excellent stereo-control,[14] surprisingly, indane catalyst **IV** can promote this process to afford 96% yield and 79% *ee* in CH_2Cl_2 (entry 4) and even give a higher selectivity in toluene (88% *ee*, entry 4). However, the further optimization of reaction conditions (such as solvent and reaction temperature) based on this catalyst



IV was ineffective for selectivity enhancement. From the above pre-screened results, we envisioned that the dihedral angle and the relative crowded two functional groups from catalyst might play the key role in this case. To investigate this hypothesis, a series of other amine–thiourea catalysts **V1–4** and **VI** (see above) has been synthesized. The survey revealed that we found the new catalyst **VI** to give the best selectivity (entry 9, 90% *ee*) in high yield (97%). Changing the moiety of R group in catalyst **V1–4** framework, the reaction can afford the high yields (Table 1, entries, 5–8, 93–96%) but without any enhancement on enantiomeric excess (entries, 5–8, 68–79% *ee*).

Table 1. Evaluation of the bifunctional organocatalyst and optimization of asymmetric cyclization reaction conditions.[a]

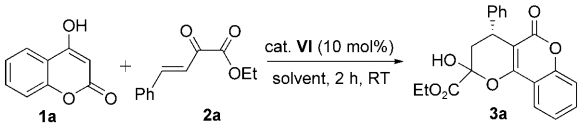


Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**I**	91	47
2	**II**	98	63
3	**III**	95	59
4	**IV**	96	79 (88[d])
5	**V-1**	96	72
6	**V-2**	93	68
7	**V-3**	95	75
8	**V-4**	96	79
9	**VI**	97	90

[a] Reaction was conducted on 0.1 mmol scale in CH_2Cl_2 (0.5 mL) catalyzed by 10 mol% catalyst, and the ratio of **1a/2a** is 1:1. [b] Yield of isolated product after column chromatography. [c] *ee* values were determined by HPLC. [d] Toluene as solvent.

Accordingly, catalyst **VI** was then used for further investigation of solvent and temperature effects in this process. It was discovered that in general the reactions proceeded well in less polar solvents with high yields and high enantioselectivities (Table 2, entries 2–10, 95–98% yields, 86–91% *ee*).

Table 2. Influence of solvent and temperature on the enantioselective reaction.[a]



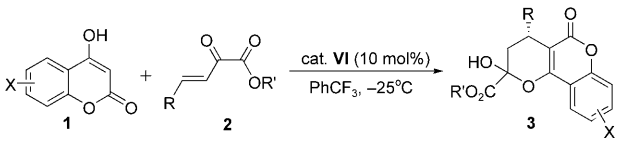
Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	DMSO	95	6
2	$Cl(CH_2)_2Cl$	98	89
3	CH_2Cl_2	97	90
4	$CHCl_3$	95	87
5	anisole	96	86
7	Et_2O	95	89
8	toluene	96	86
9	xylenes	97	87
10	$PhCF_3$	96	91
11[d]	$PhCF_3$	96	93
12[e]	$PhCF_3$	96	93
13[f]	$PhCF_3$	96	96

[a] Unless specified, see the Experimental Section for reaction conditions. [b] Yield of isolated product after column chromatography. [c] *ee* values were determined by HPLC. [d] Reaction was performed at 0°C for 3 h. [e] Reaction was performed at −10°C for 5 h. [f] Reaction was performed at −25°C for 24 h.

Trifluorotoluene was identified as the ideal solvent and afforded the best selectivity (entry 10, 91% *ee*). Lower temperature (−25°C) can slightly improve the selectivity with loss of reaction yield in a reasonable time (entry 13, 96% yield, 96% *ee*, 24 h). Meanwhile a convenient and efficient synthesis of catalyst **VI** has also been constructed through a five-step synthesis with an overall 75% yield in our group (see Supporting Information for details).

Having established the optimal conditions for this Michael addition reaction, we then investigated the scope of this process. As shown in Table 3, the process promoted by catalyst **VI** serves as a general and atom-economical approach to construct the chiral coumarins with the formation of one C–C bond and one stereogenic center, and the incorporation of α-keto ester functional group that is available for further elaboration. A number of α,β-unsaturated α-keto esters **2a**–**q** that bear alkyl, and aromatic ring as well as heteroaromatic ring were involved in the process (entries 1–17). Notably, in all cases, the reactions promote smoothly to afford designed Michael adducts **3a**–**h** in high yields (90–98%) and high to excellent enantioselectivities (90–98% *ee*). It appears that the position and electronic properties of substituents on aromatic rings have a limited effect on the efficiency and selectivity of this process. Heteroaromatic 2-thiophene-substituted α-keto ester was also effectively engaged in the process (entry 13, 90% yield, 93% *ee*). Notably, γ-alkyl-substituted α-keto ester **2q** also gave high yield

Table 3. Preliminary substrate scope of the asymmetric synthesis of coumarin derivatives reaction catalyzed by amine–thiourea **VI**.[a]



Entry	X	R′	R	Yield [%][b]	*ee* [%][c]
1	H	Et	Ph (**3a**)	96	96
2	H	Et	4-FC_6H_4 (**3b**)	98	95
3	H	Et	4-ClC_6H_4 (**3c**)	98	96
4	H	Et	4-$MeOC_6H_4$ (**3d**)	96	95
5	H	Et	4-$MeSC_6H_4$ (**3e**)	97	96
6[d]	H	Et	3-$MeSC_6H_4$ (**3f**)	98	96
7	H	Et	4-allyloxyC_6H_4 (**3g**)	97	95
8[d]	H	Et	2-allyloxyC_6H_4 (**3h**)	91	90
9[d]	H	Et	4-$BnOC_6H_4$ (**3i**)	95	95
10	H	Et	4-*i*PrC_6H_4 (**3j**)	96	96
11[d]	H	Et	2-MeC_6H_4 (**3k**)	95	92
12[d]	H	Et	1-naphthyl (**3l**)	95	95
13[d]	H	Et	2-thiophene (**3m**)	90	93
14	6-Cl	Et	Ph (**3n**)	97	96
15	6-CH_3	Et	Ph (**3o**)	97	98
16	H	Me	Ph (**3p**)	96	94
17	H	Et	Et (**3q**)	93	92

[a] Unless specified, see the Experimental Section for reaction conditions. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Reaction was performed at −20°C.

and excellent enantioselectivity (entry 17, 93% yield, 92% *ee*). Moreover, the scope of the reaction can be successfully extended utilizing to 4-hydroxycoumarin analogues **2n** and **2o** which lead to differently substituted α-keto esters **3n** and **3o** with 96 and 98% *ee*, respectively (entries 14 and 15). The absolute configuration of product **3c** was determined to be *R* by using single crystal X-ray diffraction (Figure 1).[15]

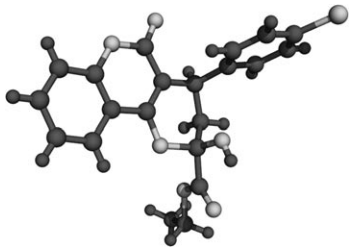


Figure 1. X-ray crystal structure of compound **3c**.

In conclusion, we have developed an efficient and convenient enantioselective Michael addition reaction for the synthesis of coumarin complex with high yields and excellent enantioselectivities (up to 98% *ee*). This protocol proceeded through a new and simple amine–thiourea-catalyst-promoted conjugated addition strategy. We believe that the catalytic system and strategy demonstrated here might be applied to other asymmetric transformations to efficiently assemble chiral materials with complex structures. Further elaboration of the products to other types of biologically active com-

pounds and the potential application of the catalytic system are now ongoing in our group.

Experimental Section

General procedure: To a solution of 4-hydroxycoumarin (**1a**; 16.2 mg, 0.1 mmol) in $PhCF_3$ (0.45 mL) was added β,γ-unsaturated α-keto ester **2a** (20.4 mg, 0. 1 mmol) at −25 °C, followed by addition of pre-cooled catalyst **VI** solution (50 μL; 4.6 mg in 50 μL $PhCF_3$, 0.01 mmol). The reaction mixture was stirred at −25 °C for 24 h. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc 2:1 to afford (35 mg, 96%) of the desired product **3a** as white solid. HPLC analysis (Chiralpak IB, isopropanol/hexane 20:80, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): $t_{major} = 8.8$ min, $t_{minor} = 15.0$ min, $ee = 96\%$.

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Keywords: asymmetric catalysis · coumarins · Michael addition · organocatalysis · thioureas

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[14] Our group successful uncovered a series of indene scaffold based amine–thiourea catalysts and applied to catalyze some novel reactions with excellent stereocontrol.

[15] CCDC 784873 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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