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Enantioselective Conjugate Addition of 4-Hydroxycoumarin to Enones Catalyzed by Binaphthyl-Modified Primary Amine Organocatalyst

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The Michael addition reaction is widely recognized as one of the most general methods for formation of C-C bonds in organic synthesis,[1] and the development of enantioselective catalytic conjugate addition reaction has been subject of intensive research.[2] In addition to the great success catalyzed by metal complexes, the powerful and environmentally friendly organocatalyst-mediated asymmetric conjugate addition reaction has been explored intensively in recent years.[3,4] Enantioselective organocatalytic conjugate addition reaction of β-ketoesters to α,β-unsaturated carbonyl compounds represents a direct and most appealing approach to chiral 1,5-dicarbonyl compounds that are versatile intermediates in organic synthesis.[5] Particularly, the addition of 4-hydroxycoumarin to α,β-unsaturated ketones is a straightforward method to access warfarin which is an effective anticoagulants. Further investigation showed that (*S*)-warfarin had higher anticoagulant activity than the *R* enantiomer.[6] As a result, achieving the optically pure *R* or *S* enantiomer of warfarin would be of great importance. Among the established strategies for the synthesis of chiral warfarin, chiral auxiliary strategy, hydrogenation, and hetero-Diels-Alder reaction have been intensively studied.[7] Recently, several groups reported an enantioselective conjugate addition reaction of 4-hydroxycoumarin to enones, catalyzed by chiral secondary amines, primary amines, and bifunctional primary-amine thioureas.[8] Although several efficient methods have been achieved by these systems, an effective method for the synthesis of warfarin is still a challenge.

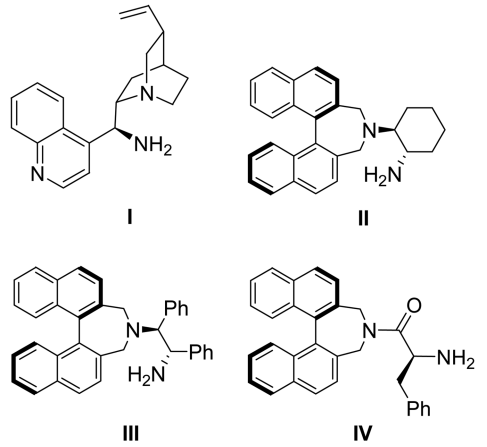
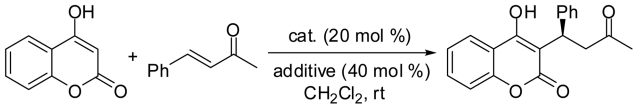


Figure 1. Structure of chiral primary amine catalysts.

As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[9] we recently reported asymmetric conjugate addition reaction of active methylenes and methines.[10] Herein, we wish to describe the enantioselective asymmetric conjugate addition of 4-hydroxycoumarin to α,β-unsaturated ketones promoted by binaphthyl-modified primary amine organocatalyst.

Validation of the feasibility of the proposed Michael addition process started by evaluating a model reaction between 4-hydroxycoumarin (**1**) with (*E*)-4-phenylbut-3-en-2-one (**2a**) in the presence of 20 mol % bifunctional catalysts (Fig. 1) and 40 mol % of TFA as additive at room temperature. As shown in Table 1, 9-amino-9-deoxyepicinchonidine (**I**) effectively promoted the reaction with high enantioselectivity (entry 1). While chiral primary amine organocatalysts (**II**-**IV**) bearing both central and axial chiral elements gave moderate to high enantioselectivity (entries 2-4). The best result has been obtained with binaphthyl-modified 1,2-diphenylethylenediamine catalyst (**III**). We examined our

Table 1. Optimization of the reaction conditions

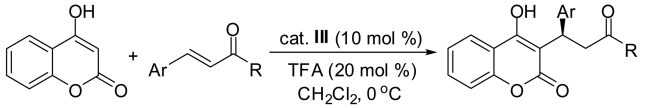


1 **2a** **3a**

Entry	Cat.	Additive	Time (h)	Yield (%)[a]	ee (%)[b]
1	**I**	CF_3CO_2H	5	76	71
2	**II**	CF_3CO_2H	18	80	59
3	**III**	CF_3CO_2H	15	75	85
4	**IV**	CF_3CO_2H	6	73	28
5	**III**	HCO_2H	20	33	25
6	**III**	CCl_3CO_2H	14	77	77
7	**III**	$PhCO_2H$	20	49	17
8	**III**	*p*-$NO_2C_6H_4CO_2H$	20	50	42
9	**III**	maleic acid	23	39	73
10	**III**	CH_3SO_3H	33	56	21
11	**III**	(-)-CSA	20	62	44
12[c]	**III**	CF_3CO_2H	18	73	84
13[c,d]	**III**	CF_3CO_2H	40	78	90

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using chiralpak IA column. [c]10 mol % catalyst loading. [d]This reaction was carried out at 0 °C.

Table 2. Enantioselective conjugate addition of 4-hydroxycoumarin (**1**) to α,β-unsaturated ketones **2**



1 **2** **3**

Entry	**2**, Ar, R	Time (h)	Yield (%)[a]	ee (%)[b]
1	**2a**, Ph, Me	40	78	90
2	**2b**, *p*-MeC_6H_4, Me	38	72	81
3	**2c**, *p*-FC_6H_4, Me	59	78	83
4	**2d**, *p*-ClC_6H_4, Me	46	80	87
5	**2e**, *p*-BrC_6H_4, Me	59	76	73
6	**2f**, *p*-$NO_2C_6H_4$, Me	41	79	79
7	**2g**, 2-thienyl, Me	65	77	75
8	**2i**, Ph, Ph	46	68	77

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using chiralpak IA column.

investigations by examining the reactivity and selectivity with organocatalyst **III** in the presence of different acids, such as formic acid, trihaloacetic acids, benzoic acids, maleic acid, and sulfonic acids as additives (entries 3 and 5-11). Among the additives probed, the best results (85% ee) were achieved when the reaction was conducted in trifluoroactic acid (entry 3). The present catalytic system tolerates catalyst loading down to 10 mol % without compromising both the yield and enantioselectivity (entries 3 and 12). Lowering the temperature to 0 °C with catalyst **III** improved the enantioselectivity (90% ee, entry 13).

As demonstrated in Table 2, organocatalyst **III** catalyzed Michael addition of 4-hydroxycoumarin (**1**) to α,β-unsaturated ketones **2** proved to be a general approach for the synthesis of warfarin derivatives. Notably, good to high enantiomeric excess was obtained (up to 90% ee). The α,β-unsaturated ketones bearing substituted aryl and heteroaromatic group in b-position could effectively participate in the process (entries 1-8). Absolute configuration was determined comparison of the optical rotation and chiral HPLC data of the corresponding warfarin derivatives **3**.[8]

In conclusion, we have developed organocatalytic enantioselective conjugate addition reaction of 4-hydroxycoumarin (**1**) to α,β-unsaturated ketones **2** to afford biologically valuable warfarine derivatives **3**. The process is efficiently catalyzed by a binaphthyl-modified primary amine organocatalyst. Further details and application of this asymmetric Michael addition of 4-hydroxycoumarin will be presented in due course.

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