

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.

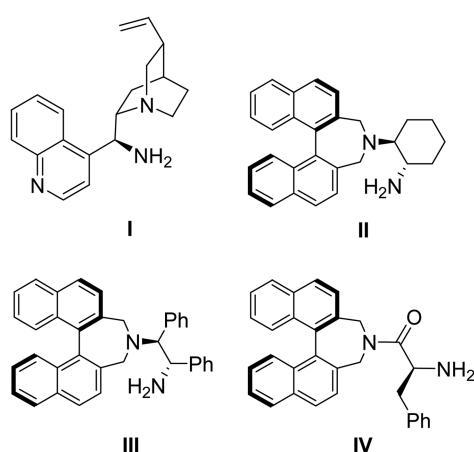


Figure 1. Structure of chiral primary amine catalysts.

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

Entry	Cat.	Additive	Time (h)	Yield (%) ^a	
				ee (%) ^b	ee (%) ^b
1	I	CF ₃ CO ₂ H	5	76	71
2	II	CF ₃ CO ₂ H	18	80	59
3	III	CF ₃ CO ₂ H	15	75	85
4	IV	CF ₃ CO ₂ H	6	73	28
5	III	HCO ₂ H	20	33	25
6	III	CCl ₃ CO ₂ H	14	77	77
7	III	PhCO ₂ H	20	49	17
8	III	<i>p</i> -NO ₂ C ₆ H ₄ CO ₂ H	20	50	42
9	III	maleic acid	23	39	73
10	III	CH ₃ SO ₃ H	33	56	21
11	III	(<i>-</i>)-CSA	20	62	44
12 ^c	III	CF ₃ CO ₂ H	18	73	84
13 ^{c,d}	III	CF ₃ CO ₂ H	40	78	90

^aIsolated yield. ^bEnantiopurity was determined by HPLC analysis using chiralpak IA column. ^c10 mol % catalyst loading. ^dThis reaction was carried out at 0 °C.

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

Entry	2 , Ar, R	Time (h)	Yield (%) ^a	ee (%) ^b
1	2a , Ph, Me	40	78	90
2	2b , <i>p</i> -MeC ₆ H ₄ , Me	38	72	81
3	2c , <i>p</i> -FC ₆ H ₄ , Me	59	78	83
4	2d , <i>p</i> -ClC ₆ H ₄ , Me	46	80	87
5	2e , <i>p</i> -BrC ₆ H ₄ , Me	59	76	73
6	2f , <i>p</i> -NO ₂ C ₆ H ₄ , Me	41	79	79
7	2g , 2-thienyl, Me	65	77	75
8	2i , Ph, Ph	46	68	77

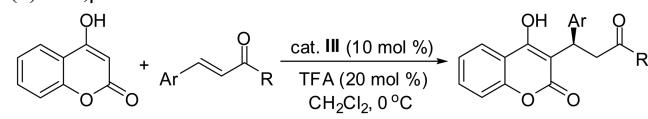
^aIsolated yield. ^bEnantiopurity was determined by HPLC analysis using chiralpak IA column.

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 trifluoroacetic 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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