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Highly Enantioselective Michael Addition of Cyclic 1,3-Dicarbonyl Compounds to α,β-Unsaturated Ketones

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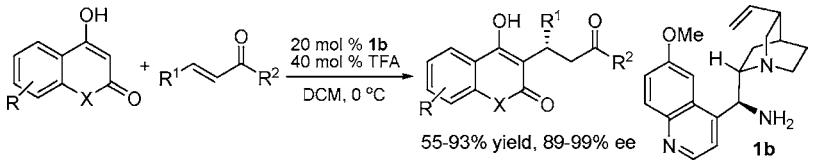
ABSTRACT



The highly enantioselective Michael addition of 1,3-cyclic dicarbonyl compounds to α,β-unsaturated ketones was reported to be catalyzed by an organic primary amine derived from quinine. A chiral anticoagulant drug, (*S*)-warfarin, was directly prepared in 96% ee, and other related important adducts were also obtained in excellent enantioselectivity (89–99% ee).

The Michael addition to α,β-unsaturated systems is an important carbon−carbon bond-forming reaction in organic synthesis, and the development of enantioselective catalytic protocols for this reaction has been the subject of intensive research.[1] In addition to the great success catalyzed by metal complexes, the environmentally benign organocatalyst-mediated asymmetric Michael reaction has undergone rapid progress for various useful donor−acceptor combinations in recent years.[2] Among them, MacMillan and other chemists developed a versatile strategy for nonchelating α,β-unsaturated aldehydes and ketones through LUMO-lowering activation catalyzed by chiral secondary amines.[3] Nevertheless, low catalytic efficacy was generally noted for α,β-unsaturated ketones even at room temperature.[4] In an inventive example, Jørgensen et al. reported the enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated ketones catalyzed by an imidazolidine **1a** (Figure 1) derived from chiral 1,2-diphenylethylenediamine, and this process was elegantly applied to make a chiral drug, warfarin, a

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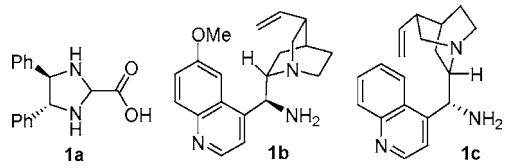
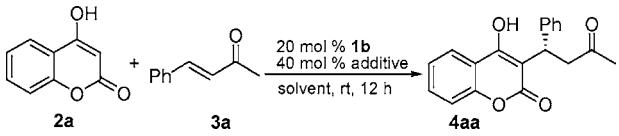


Figure 1. Structure of amine catalysts.

widely prescribed anticoagulant.[4e,5] Unfortunately, less than 90% ee was observed for a range of substrates, and in general, over 6 days were required in order to achieve good yields at ambient temperature. This encouraged us to explore this important asymmetric Michael reaction with our newly developed 9-amino-9-deoxyepicinchona alkaloids as the iminium catalysts (Figure 1).[6]

We were pleased to find that 9-amino-9-deoxyepiquinine **1b** (Figure 1, 20 mol %) in the combination with TFA (40 mol %) exhibited high catalytic activity for the asymmetric Michael addition of 4-hydroxycoumarin **2a** to benzylidene-acetone **3a** in DCM at room temperature. (*S*)-Warfarin **4aa** was cleanly isolated in 90% yield with a promising 92% ee after 12 h (Table 1, entry 1). 9-Amino-9-deoxyepicinchonine **1c** gave the same enantioselectivity while the adduct with opposite configuration was obtained (entry 2). Subsequently, we investigated the effects of solvents and acidic additives with **1b**. Good yields were obtained in THF and DMF but the ee was reduced (entries 3 and 4). Both reactivity and enantioselectivity were decreased in toluene or methanol (entries 5 and 6). The enantioselectivity was decreased in the presence of other acidic additives (entries 7−9). In addition, the coupling reaction could proceed smoothly at 0 °C, and an excellent ee (96%) was obtained in 88% yield after 96 h (entry 10). However, we found that no beneficial effect on ee was observed at 0 °C catalyzed by TFA salt of **1c** (entry 11). Moderate yield was attained catalyzed by 10 mol % of **1b** after 96 h in a more concentrated solution (entry 12).

Table 1. Screening Studies of Organocatalytic Michael Addition of 4-Hydroxycoumarin **2a** to Benzylideneacetone **3a**[a]



entry	solvent	additive	yield[b] (%)	ee[c] (%)
1	DCM	TFA	90	92
2[d]	DCM	TFA	92	−92
3	THF	TFA	88	86
4	DMF	TFA	86	60
5	toluene	TFA	51	85
6	MeOH	TFA	42	65
7	DCM	CF_3SO_3H	15	85
8	DCM	HCl	80	83
9	DCM	$HClO_4$	75	73
10[e]	DCM	TFA	88	96
11[d,e]	DCM	TFA	83	−92
12[f]	DCM	TFA	51	97

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **2a**, 0.15 mmol of **3a**, and 20 mol % of catalyst **1b** in 2 mL of solvent at room temperature for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configuration was determined to be (*S*) according to the optical rotation. [d] Catalyzed by **1c**. [e] At 0 °C for 96 h. [f] Using 10 mol % of **1b** in 1 mL of DCM.

With the optimal reaction conditions in hand, we then examined a variety of cyclic 1,3-dicarbonyl compounds (Figure 2) and α,β-unsaturated ketones to established the

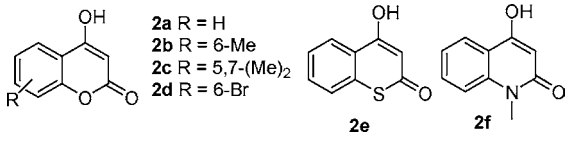


Figure 2. Structures of cyclic 1,3-dicarbonyl compounds.

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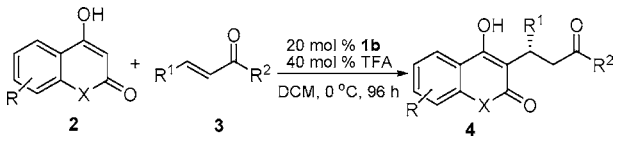
general utility of the catalytic transformation. The Michael reaction was generally conducted with 20 mol % of **1b** at 0 °C for 96 h. As illustrated in Table 2, for the reactions of

Table 2. Asymmetric Michael Addition of 1,3-Dicarbonyl Compounds **2** to α,β-Unsaturated Ketones **3**[a]



entry	2	R^1	R^2 (3)	4	yield[b] (%)	ee[c] (%)
1	**2a**	Ph	Me (**3a**)	**4aa**	88	96
2	**2a**	*p*-Cl-Ph	Me (**3b**)	**4ab**	87	97
3	**2a**	*p*-MeO-Ph	Me (**3c**)	**4ac**	81	95
4	**2a**	2-furanyl	Me (**3d**)	**4ad**	81	94
5	**2a**	2-thienyl	Me (**3e**)	**4ae**	83	93
6[d]	**2a**	Ph	Et (**3f**)	**4af**	90	99
7[d]	**2a**	Ph	*n*-Pr (**3g**)	**4ag**	82	97
8[d]	**2a**	*n*-Pr	Me (**3h**)	**4ah**	93	95
9[d]	**2a**	*i*-Pr	Me (**3i**)	**4ai**	88	98
10[d,e]	**2a**	*n*-Pr	Et (**3j**)	**4aj**	55 (95)	90
11[d]	**2a**	$-C_4H_8-$ (**3k**)		**4ak**	78	94
12	**2b**	Ph	Me (**3a**)	**4ba**	87	99
13	**2c**	Ph	Me (**3a**)	**4ca**	80	98
14	**2d**	Ph	Me (**3a**)	**4da**	82	98
15	**2e**	Ph	Me (**3a**)	**4ea**	68	89
16	**2f**	Ph	Me (**3a**)	**4fa**	71	99

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **2**, 0.15 mmol of **3**, and 20 mol % of catalyst **1b** in 2 mL of DCM at 0 °C for 96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configuration of **4aa** was (*S*), and the other adducts were assigned accordingly. [d] For 6 days. [e] Yield in parentheses is based on recovered **2a**.

4-hydroxycoumarin **2a**, excellent results were achieved with α,β-unsaturated ketones **3b**−**e** bearing various β-aryl or heteroaryl substitutions (entries 2−5). Other bulkier alkyl enones **3f** and **3g** were also well tolerated to give excellent ee while longer time was required (entries 6 and 7). On the other hand, the enantioselectivity was quite satisfying when β-alkyl α,β-unsaturated ketones **3h**−**j** were applied (entries 8−10), and a high yield was observed even for enone **3i** with a branched substitution after 6 days (entry 9). Nevertheless, the isolated yield was moderate for ethyl enone **3j** (entry 10). A high ee was also received in the case of cyclic enone **3k** (entry 11). Subsequently, a few 4-hydroxycoumarin derivatives **2b**−**d** with different substitutions were investigated. The electronic effect was very marginal and remarkable enantioselectivity was achieved (entries 12−14). 4-Hydroxythiocoumarin **2e** exhibited slightly lower reactivity, while a high ee (89%) was still obtained (entry 15). In comparison, only moderate ee (75%) was received in the same reaction of **2e** catalyzed by **1a**.[4e] In addition, we tested the asymmetric Michael addition reaction of 1-methyl-4-hydroxycarbostyril **2f**.[7] Although sluggish reaction was observed even at room-temperature due to the very low solubility of **2f** in DCM, gratifyingly, the Michael reaction proceeded very well at 40 °C, and an excellent ee (99%) was achieved in 71% yield after 24 h (entry 16).

As previously reported, the ketimine cation intermediate from **1b**-$(TFA)_2$ salt and benzylideneacetone **3a** in the asymmetric Michael addition would adopt a *trans* conformation (Figure 3, **a**).[6a,8] The desired (*S*)-product could be obtained through the *si*-face attacking of the iminium ion.

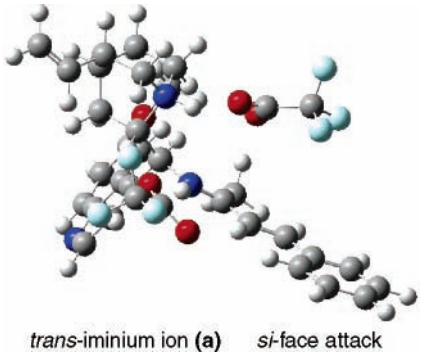


Figure 3. Possible iminium intermediate in the Michael reaction.

In conclusion, we have successfully demonstrated that 9-amino-9-deoxyepiquinine is an excellent iminium organocatalyst for the enantioselective Michael addition reaction of cyclic 1,3-dicarbonyl compounds and α,β-unsaturated ketones under mild conditions. The reaction scopes were quite broad, and excellent enantioselectivity (89−99% ee) was achieved for a number of cyclic 1,3-dicarbonyl compounds and substituted α,β-unsaturated ketones. Moreover, a chiral drug, (*S*)-warfarin, was directly prepared in high ee (96%) and yield. Current studies are actively and well underway to expand the synthetic utility of this reaction, as well as of this catalytic system in other asymmetric transformations.

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Supporting Information Available: Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The computational studies were conducted with hyperchem 7.5 software, see ref. 6a, Supporting Information