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Highly Enantioselective Organocatalytic Michael Addition of 2-Hydroxy-1,4-naphthoquinone to β,γ-Unsaturated α-Oxo Esters

Yi-Feng Wang,[a] Wei Zhang,[a] Shu-Ping Luo,[a] Guang-Cun Zhang,[a] Ai-Bao Xia,[a] Xiang-Sheng Xu,[a] and Dan-Qian Xu*[a]

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An organocatalytic enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone to β,γ-unsaturated α-oxo esters has been developed. The process was promoted by bifunctional chiral amine derived squaramides according to a hydrogen-bonding mediated activation mechanism and afforded the chiral adducts in high yields (up to 88 %) and excellent enantioselectivity (up to 98 % *ee*) under mild conditions. This organocatalytic asymmetric Michael addition provides an efficient route toward the synthesis of optically active functionalized naphthoquinones.

Introduction

With respect to an increasing need for efficient and new catalytic synthetic methods, organocatalysis represents a powerful field and has found widespread application over the past decade.[1] As a subfield of organocatalysis, hydrogen-bonding catalysis has emerged as an especially important tool for enantioselective synthesis.[2] This is probably attributed to some privileged hydrogen-bonding motifs, such as ureas, thioureas, guanidiniums and squaramides, but is also associated with the compatibility of these hydrogen-bond donators with a range of Brønsted bases or Lewis bases, which allow the development of bifunctional systems,[3] providing new opportunities for simultaneous activation of both the electrophile and the nucleophile. Despite this, further explorations of new asymmetric reactions toward the synthesis of chiral bioactive compounds with use of this activation strategy are still demanding research areas.

Quinones and naphthoquinones have attracted much attention due to the broad scope of their biological activities.[4] The organocatalytic additions of these valuable skeletons to electron-deficient alkenes, which benefited from using secondary amine or tertiary amine–thiourea catalysts, have been investigated in order to provide an alternative process for some novel optically active chemicals with potent pharmacological properties.[5] Both these applied catalysis systems are capable of activating electron-deficient alkenes, either through the formation of an iminium ion intermediate with α,β-unsaturated carbonyl compounds, or through double hydrogen-bonding interaction with nitro alkenes. To the best of our knowledge there are no organocatalytic asymmetric process reported in which β,γ-unsaturated α-oxo esters are employed as electron-deficient alkenes to react with naphthoquinone cores.[6] Nevertheless, β,γ-unsaturated α-oxo esters are very attractive Michael acceptors,[7] since the α-oxo ester moiety is a strong electron-withdrawing group that can be readily transformed into a range of different functionalities. Herein we present our results on the use of simply obtainable tertiary amine–thiourea/squaramide[8] organocatalysts for the first catalytic enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone to β,γ-unsaturated α-oxo esters (Figure 1). This is also a broadening of the strategy employed in our first paper on the application of chiral squaramides in organocatalysis.[8b]

Results and Discussion

The addition of 2-hydroxy-1,4-naphthoquinone (**1**) to β,γ-unsaturated α-oxo ester **2a** was used as the test reaction to explore the feasibility of the enantioselective Michael addition catalyzed by chiral amine derived thioureas and squaramides at room temperature in CH_2Cl_2 as the solvent (Table 1). Gratifyingly, preliminary results showed that good yields and enantioselectivities were obtained when diaminocyclohexane-derived thioureas/squaramides were used as catalysts (Entries 1–2). Whereas thiourea **I** gave a higher enantioselectivity than squaramide **II** did, the reaction rate was higher with squaramide **II**. These results motivated us to optimize these two catalysts simultaneously by screening the catalysts **III**–**IV**. Apparently, these two kinds of bifunctional catalysts were distinctly different in their performance. No improvement in terms of reaction yields and enantioselectivities was observed by using cinchona-de-

[a] State Key Laboratory Breeding Base of Green Chemistry – Synthesis Technology, Zhejiang University of Technology
Hangzhou 310014, China
Fax: +86-0571-88320066
E-mail: chrc@zjut.edu.cn

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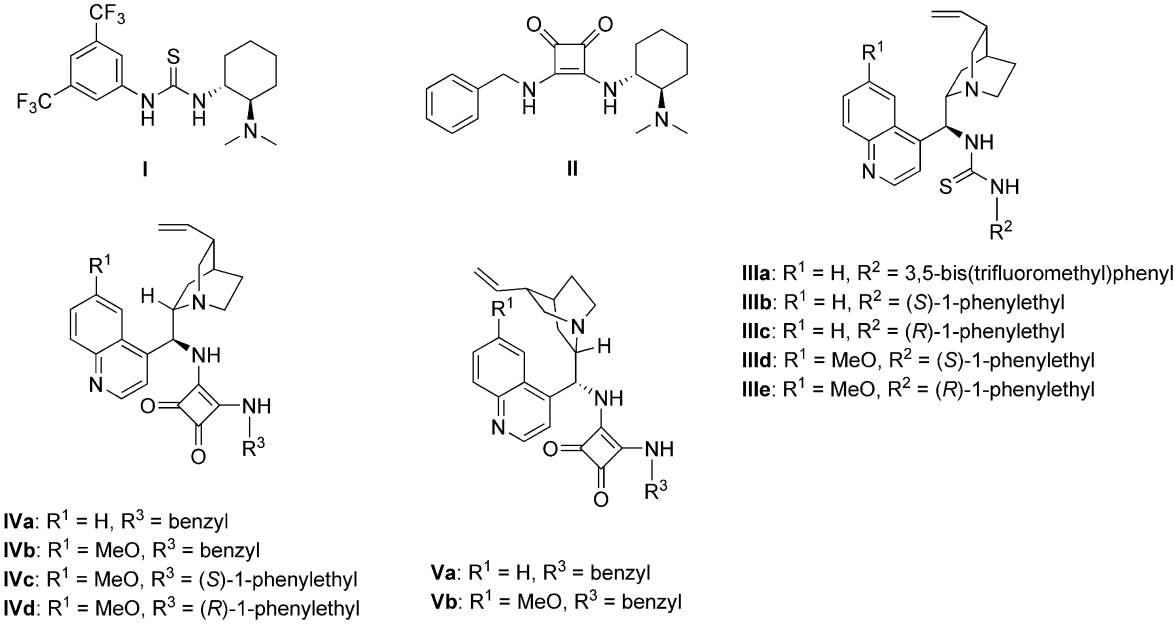


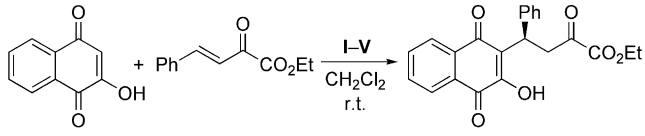
Figure 1. Screened chiral thiourea- and squaramide-based catalysts.

rived thioureas **III** (Entries 3–7). To our delight, promising enantioselectivity and especially high efficiency was achieved when cinchona-derived squaramides **IVa** and **IVb** were employed, which provided 78–81% yields and 80–83% *ee* values after 3 h (Entries 8–9). The pseudo-enantiomers of **IVa** and **IVb** exhibited similar catalytic activity, but the asymmetric inductions were slightly lower (Entries 10–11). Upon further varation of the substituent on one end of the squaramide, catalyst **IVc** afforded an excellent level of enantioselectivity (94% *ee*) and yield (87%) (Entries 12–13). The potential of the catalyst **IVc** was also demonstrated by reducing the catalyst loading in the asymmetric Michael addition; the efficiency was almost maintained even when the amount of the catalyst was decreased to 2.5 mol-% (Entries 14–16). Above observations confirmed that the type of the hydrogen-bond donor motif has a dramatic impact on the catalytic activity.

Subsequently, the solvent effect on the Michael addition reaction was investigated. As shown in Table 2, the reaction proceeded smoothly in most aprotic solvents probed, and encouraging results were obtained with dichloromethane and dioxane as solvents, which afforded 83–85% yields and 94–96% *ee* (Entries 1–7). Nevertheless, protic solvents such as EtOH retarded this process, and both yield and enantioselectivity dropped (Entry 8). Its relatively weak polar homologue *i*PrOH afforded the products with high selectivity, but the yield was low (Entry 9). The lower efficiency of the protic solvents can be attributed to the competitive hydrogen-bond interaction between the alcohols and the organocatalyst or substrates.

The asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone (**1**) to various β,γ-unsaturated α-oxo esters **2** in the presence of organocatalyst **IVc** was investigated under the optimized experimental conditions. As shown in Table 3, a wide array of aromatic β,γ-unsaturated α-oxo esters **2a**–**i**, which bear electron-rich, electron-neutral and electron-withdrawing groups, reacted smoothly with 2-hydroxy-1,4-naphthoquinone (**1**) to afford the corresponding

Table 1. Organocatalytic enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone **1** to β,γ-unsaturated α-oxo ester **2a**.[a]

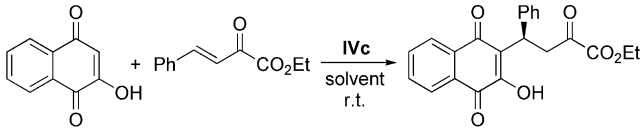


1 **2a** **3a**

Entry	Cat.	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	**I**	12	81	88
2	**II**	6	84	72
3	**IIIa**	12	78	77
4	**IIIb**	12	82	59
5	**IIIc**	12	80	30
6	**IIId**	12	86	53
7	**IIIe**	12	77	21
8	**IVa**	3	81	80
9	**IVb**	3	78	83
10	**Va**	3	79	–76
11	**Vb**	3	80	–78
12	**IVc**	*3*	*87*	*94*
13	**IVd**	3	79	84
14[d]	**IVc**	7	83	93
15[e]	**IVc**	*12*	*85*	*94*
16[f]	**IVc**	24	76	92

[a] Unless otherwise specified, all reactions were carried out with 2-hydroxy-1,4-naphthoquinone (0.125 mmol), β,γ-unsaturated α-oxo ester **2a** (0.125 mmol), catalyst (0.025 mmol, 20 mol-%) in CH_2Cl_2 (1.0 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*PrOH = 70:30 containing 0.15% TFA); a minus sign before the *ee* signifies the enantiomer opposite that obtained in all other entries in this table. [d] With 10 mol-% catalyst loading. [e] With 5 mol-% catalyst loading. [f] With 2.5 mol-% catalyst loading.

Table 2. Screening of the solvents for the enantioselective Michael addition reaction catalyzed by squaramide **IVc**.[a]



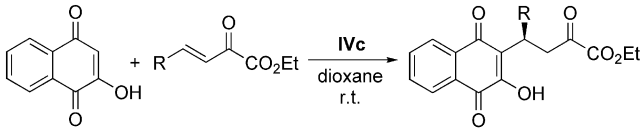
1 2a 3a

Entry	Solvent	Yield[b] [%]	*ee*[c] [%]
1	CH_2Cl_2	85	94
2	$CHCl_3$	51	84
3	DCE[d]	81	92
4	Et_2O	50	93
5	THF	78	94
6	*dioxane*	*83*	*96*
7	PhMe	77	91
8	EtOH	66	76
9	*i*PrOH	35	94

[a] All reactions were carried out with 2-hydroxy-1,4-naphthoquinone (0.125 mmol), β,γ-unsaturated α-oxo ester **2a** (0.125 mmol), catalyst **IVc** (0.0625 mmol, 5 mol-%) in the solvent (1.0 mL) at room temperature for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*PrOH = 70:30 containing 0.15% TFA). [d] DCE: 1,2-dichloroethane.

products **3a**–**i** with high levels of yield (73–88%) and enantioselectivity (90–98% *ee*) (Entries 1–10). It is noted that oxo esters with an electron-neutral or electron-withdrawing group at the aromatic ring could react quite effectively with only 2.5 mol-% catalyst loading (Entries 4–10). Other aromatic oxo esters, derived from naphthalene, furan and thiophene, could also be applied in this reaction to provide 81–86% yields and 93–96% *ee* (Entries 11–13). Moreover, aliphatic oxo esters react also in this catalytic system and give rise to the corresponding products in good yield and high enantioselectivity (Entry 14).

Table 3. Squaramide **IVc** promoted enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone (**1**) to β,γ-unsaturated α-oxo ester **2**.[a]

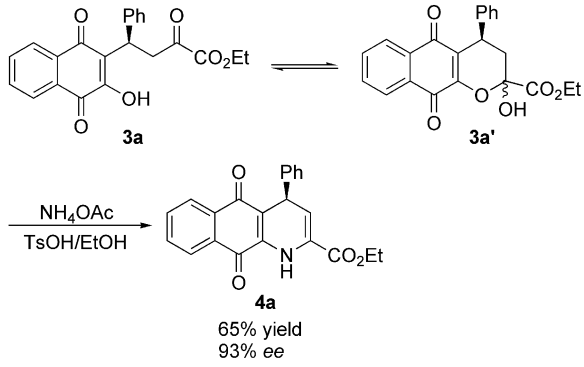


1 2 3

Entry	R	Product	Yield[b] [%]	*ee*[c] [%]
1	Ph (**2a**)	**3a**	83	96
2	4-MeC_6H_4 (**2b**)	**3b**	88	91
3	4-$MeOC_6H_4$ (**2c**)	**3c**	82	94
4[d]	4-ClC_6H_4 (**2d**)	**3d**	87	95
5[d]	2-ClC_6H_4 (**2e**)	**3e**	86	91
6[d]	4-BrC_6H_4 (**2f**)	**3f**	81	94
7[d]	3-BrC_6H_4 (**2g**)	**3g**	85	93
8[d]	2,4-$Cl_2C_6H_3$ (**2h**)	**3h**	86	90
9[d]	4-$CF_3C_6H_4$ (**2i**)	**3i**	73	93
10[d]	4-$NO_2C_6H_4$ (**2j**)	**3j**	83	98
11	naphthalen-2-yl (**2k**)	**3k**	86	93
12	furan-2-yl (**2l**)	**3l**	81	93
13	thien-2-yl (**2m**)	**3m**	83	96
14	Me (**2n**)	**3n**	78	87

[a] Unless otherwise specified, all reactions were carried out with 2-hydroxy-1,4-naphthoquinone (0.125 mmol), β,γ-unsaturated α-oxo ester **2** (0.125 mmol), catalyst **IVc** (0.0625 mmol, 5 mol-%) in dioxane (1.0 mL) at room temperature for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H). [d] With 2.5 mol-% catalyst loading.

The products were found to exist in solution in a rapid equilibrium with their pseudo-diastereomeric hemiketal forms, which could be converted into tetrahydrobenzoquinolines by a simple one-step treatment. Therefore, reaction of **3a** with ammonium acetate yielded tetrahydrobenzoquinoline **4a** (Scheme 1). The hemiketal of compound **3f′** was crystallized, and its absolute configuration was determined to be (*R*) on the basis of a single-crystal X-ray analysis[9] (Figure 2).



Scheme 1. Conversion of **3a** into tetrahydrobenzoquinoline **4a**.

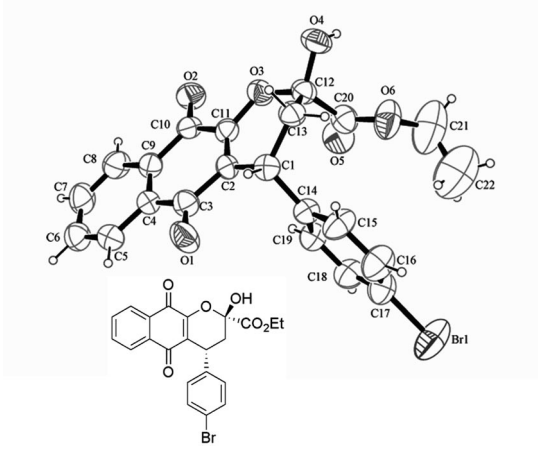


Figure 2. X-ray crystal structure of adduct **3f** in its hemiketal form.

According to above experimental results and previous reported dual activation model, the two substrates involved in the reaction are activated by catalyst **IVc** as proposed in Figure 3. The α-oxo ester **2a** has been assumed to interact with the squaramide moiety of **IVc** through two hydrogen bonds, which activates the γ-carbon atom of the substrate

but also constrains it to a well-defined orientation, which is furthermore enhanced by the two chiral substituted ends of the squaramide. The deprotonated form of 2-hydroxy-1,4-naphthoquinone (**1**) is assumed to interact with the tertiary amine group of the catalyst through the hydrogen bonds between the protonated amine and the two vicinal oxygen atoms of **1**, which is also activated and fixed by a bidentate interaction. The well-induced transition state facilitates the nucleophile **1** to attack the oxo ester **2a** from the *re* face and to form the (*R*) product.

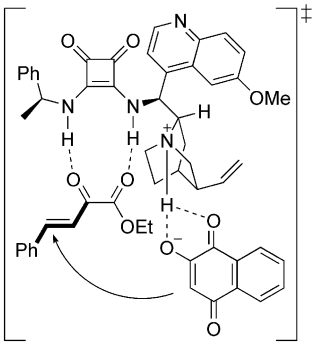


Figure 3. Proposed transition state of the organocatalytic enantioselective Michael reaction.

Conclusions

We have developed a novel highly enantioselective organocatalytic Michael addition of 2-hydroxy-1,4-naphthoquinone to β,γ-unsaturated α-oxo esters catalyzed by readily available cinchona-derived squaramides with low catalyst loading (2.5–5 mol-%) to provide an expeditious access toward highly functionalized naphthoquinone derivatives in good yields (73–88%) and with excellent enantioselectivities (87–98% *ee*). Considering the high efficiency of the potent transformations, further investigation on the application of chiral squaramides in organocatalysis is in progress in our laboratory.

Experimental Section

Typical Procedure for the Organocatalytic Asymmetric Michael Reaction: To a solution of catalyst **IVc** (0.0625 mmol, 5 mol-%) in dioxane (1.0 mL), 2-hydroxy-1,4-naphthoquinone (**1**) (0.125 mmol) and β,γ-unsaturated α-oxo ester **2a** (0.125 mmol) were added sequentially. The reaction mixture was then stirred at room temperature (about 25 °C) for 12 h. The crude mixture was purified by flash chromatography to furnish a yellow solid in 83% yield. The process was clear and no 1,2-addition or oxa-Michael addition product formed. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column [hexane/*i*PrOH = 70:30 containing 0.15% TFA; flow rate 1.0 mL/min; t_R(major isomer) = 9.9 min, t_R(minor isomer) = 13.6 min].

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra, mass spectra, HPLC analysis data.

Acknowledgments

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[9] CCDC-759808 (**3f′**) 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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