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Organocatalytic Highly Enantioselective Michael Addition of 2-Hydroxy-1,4-naphthoquinones to Nitroalkenes

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ABSTRACT

The first organocatalytic enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes for the direct synthesis of chiral nitroalkylated naphthoquinone derivatives was investigated. Good yields and excellent enantioselectivities (up to >99% ee) could be achieved. This organocatalytic asymmetric Michael addition provides an efficient route toward the synthesis of optically active functionalized naphthoquinones.

In recent years, organocatalysis has been the subject of intensive development, and many organocatalysts have been applied in a variety of asymmetric reactions.[1] Organocatalysis has been recognized as having special features such as being environmentally benign and having atom economy and convenient operation. Among the organocatalysts used currently, proline derivatives, thioureas, and Cinchona alkaloids are recognized as the privileged catalysts.[2] Further development of the new asymmetric reaction with use of easily available organocatalysts and the discovery of a more practical catalytic asymmetric process toward the synthesis of novel chiral bioactive compounds are still demanding research areas.

Quinones and naphthoquinones are important structural units in many natural products, which can undergo many important biological transformations. Naphthoquinones are also used in industry on a large scale as dye reagents or components. Many quinone-containing compounds have biological activity owing to the presence of the quinone pharmacophore.[3] Quinone-containing antitumor drugs, such

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as mitoxantrone, ametantrone, and doxorubicin, demonstrate potent antitumor activity and have been used in clinics as one of the most effective classes of anticancer agents with broad application in the treatment of several leukemias and lymphomas.[4] In view of their important biological features in medicinal chemistry, a large number of quinone derivatives and related compounds have been prepared in order to search for novel bioactive agents with improved pharmacological properties.[5]

The asymmetric Michael addition with nitroalkenes as Michael acceptor is an important C−C bond-forming reaction, which provides access to synthetically useful enantioenriched nitroalkanes and has attracted significant interest in recent years.[6] Nitroalkanes can be transformed into a variety of functionalities due to the strong electron-withdrawing nature of the nitro group.[7] The conjugate addition of naphthoquinone to nitroalkenes is particularly interesting because it produces nitroalkylated compounds which are precursors of a variety of other functionalized bioactive compounds. However, to the best of our knowledge, no studies on the catalytic asymmetric synthesis of nitroalkylated naphthoquinones has been reported.[8]

As one part of our continuing research program on the catalytic asymmetric addition of nitroalkane and heteroaromatics to nitroalkenes,[9] we would like to report the first organocatalytic enantioselective Michael addition of 2-hydroxynaphthoquinones to nitroalkenes for the direct synthesis of chiral nitroalkylated naphthoquinone derivatives herein. Good yields and excellent enantioselectivities (up to >99% ee) could be achieved for most substrates.

Initially, we studied the model Michael addition reaction of 2-hydroxy-1,4-naphthoquinone **6a** to β-nitrostyrene **7a** by the catalysis of 10 mol % of a series of readily available organocatalyst **1**−**5** (Figure 1) at room temperature. The

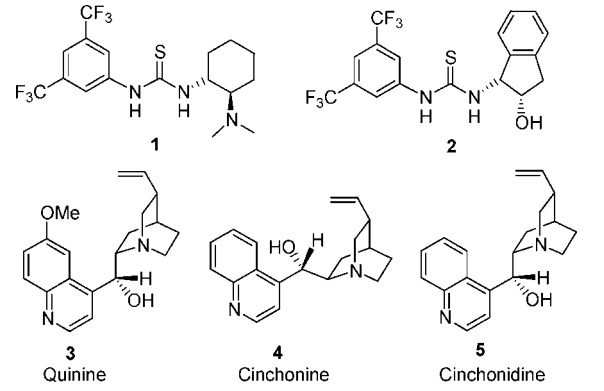

Figure 1. Thiourea and cinchona alkaloid organocatalysts.

results are presented in Table 1. During the screening of catalysts, we first performed the reaction by the catalysis of thiourea catalyst **1** in CH_2Cl_2. Gratifyingly, we found that the reaction was completed within 12 h and the corresponding addition product was obtained in 82% yield with excellent enantioselectivity (>99% ee). Thiourea catalyst **2** cannot give high enantioselectivity. Such a phenomenon can be ascribed to the lack of tertiary amine groups, which work as the activator of the pronucleophile. The cinchona alkaloid

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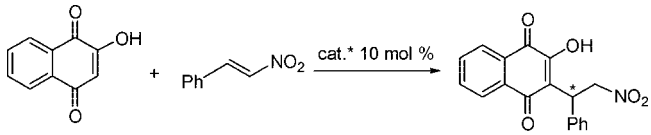
Table 1. Screening of the Reaction Condition of Asymmetric Michael Addition of 2-Hydroxy-1,4-naphthoquinone to β-Nitrostyrene[a]



6a **7a** **8a**

entry	catalyst	solvent	t (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1**	CH_2Cl_2	25	12	82	>99
2	**2**	CH_2Cl_2	25	24	65	6
3	**3**	CH_2Cl_2	25	12	72	25
4	**4**	CH_2Cl_2	25	12	75	−64
5	**5**	CH_2Cl_2	25	12	72	56
6	**1**	THF	25	12	71	87
7	**1**	CH_3CN	25	12	65	86
8	**1**	CH_3OH	25	12	72	69
9	**1**	toluene	25	12	59	97
10	**1**	CH_2Cl_2	0	12	73	>99
11	**1**[d]	CH_2Cl_2	25	12	78	95

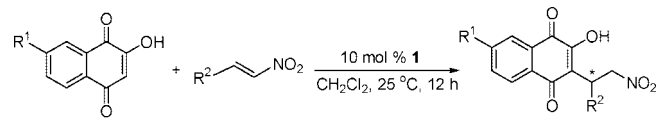
[a] Reaction conditions: **6a** (0.2 mmol), **7a** (0.2 mmol), and 10 mol % of organocatalyst in 2 mL of solvent. [b] Isolated yields after chromatography. [c] Determined by HPLC analysis on Chiralcel OJ-H column. [d] With 5 mol % catalyst.

catalysts **3**−**5** gave lower enantioselectivity than thiourea **1**. Cinchona alkaloid catalysts **3**−**5** gave modest enantioselectivities (35−64% ee), though the reaction can also be completed within 12 h (Table 1, entries 3−5). This observation indicates that the cooperation of thiourea and tertiary amine functionalities is significant to the enantiocontrol in this asymmetric addition. From this comparative study, the bifunctional thiourea catalyst **1** is the best choice.

For further optimization of the reaction condition, we screened the effect of solvents, temperature, and catalyst loading. The investigation on the solvent showed that good to excellent enantioselectivities (86−97% ee) of nitroalkylated naphthoquinones were also obtained in CH_3CN, THF, and toluene. As proton solvent, methanol gave a lower yield and enantioselectivity, which can be attributed to the competive hydrogen bond interaction between methanol and the organocatalyst or the substrate. The screening identified dichloromethane as the optimal solvent for the reaction (>99% ee). The yield decreased slightly when the reaction temperature was reduced to 0 °C, while the enantioselectivity was not affected significantly (Table 1, entry 10). When the catalyst loading was lowered to 5 mol %, though the yield decreased slightly, high enantioselectivity (95% ee) can still be achieved (Table 1, entry 11), which demonstrates the high catalytic activity of thiourea catalyst **1**.

With the optimized conditions in hand, the scope of the organocatalyzed asymmetric Michael addition was explored. A wide range of nitroalkenes were tested under the optimized reaction conditions (10 mol % **1** in CH_2Cl_2 at room temperature for 12 h), and the results are summarized in Table 2. A series of nitroalkylated naphthoquinones **8a**−**n** were obtained in good yields with excellent enantioselectivities (up to >99% ee). For para-substituted aromatic nitroalkenes, the ee values are higher than 99% (Table 2, entries 2−6). The aromatic nitroalkene with ortho substitution gives a little lower enantioselectivity (Table 2, entry 7). Such a phenomenon can be attributed to the unfavored interaction between the ortho-substituted group and nucleophile. The electronic nature of the substitutions has little effect on the enantioselectivity. Other aromatic nitroalkenes derived from furan and thiophene can also be applied in this reaction: 89% and >99% ee can be achieved respectively (Table 2, entries 8 and 9). The aliphatic nitroalkenes can also work as good substrates in the Michael addition of 2-hydroxy-1,4-naphthoquinone, but the ee value determination of most products is very difficult since the enantiomers cannot be separated on many columns. For aliphatic nitroalkenes, such as 1-nitro-4-phenyl-1-butene and 1-cyclohexyl-2-nitroethylene, higher than 93% ee values can be obtained, which are determined through their *O*-methyl derivatives (Table 2, entries 10 and 11).

Table 2. Catalytic Asymmetric Michael Addition of 2-Hydroxy-1,4-naphthoquinones to Nitroalkenes[a]



6 **7** **8**

entry	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	H	C_6H_5	**8a**	82	>99
2	H	4-MeC_6H_4	**8b**	75	>99
3	H	4-$MeOC_6H_4$	**8c**	75	>99
6	H	4-FC_6H_4	**8d**	71	>99
4	H	4-ClC_6H_4	**8e**	75	>99
5	H	4-BrC_6H_4	**8f**	81	>99
7	H	2-$MeOC_6H_4$	**8g**	75	89
8	H	2-furanyl	**8h**	85	89
9	H	2-thienyl	**8i**	77	>99
10	H	2-phenylethyl	**8j**	77	93[d]
11	H	cyclohexyl	**8k**	63	95[e]
12	Me	C_6H_5	**8l**	77	94
13	Me	4-MeC_6H_4	**8m**	73	94
14	MeO	C_6H_5	**8n**	61	95

[a] Reaction conditions: **6** (0.2 mmol), **7** (0.2 mmol), and catalyst **1** (10 mol %) in CH_2Cl_2 (2 mL) for 12 h at 25 °C. [b] Isolated yields after chromatography. [c] Determined by HPLC analysis on Chiralcel OJ-H column. [d] Determined through its *O*-methyl derivative. [e] Determined by HPLC analysis on Chiralcel AD column through its *O*-methyl derivative.

Adding electron-rich substituents on the 7-position of the 2-hydroxy-1,4-naphthoquinone does not affect the efficiency of the reaction (Table 2, entries 12−14), 7-methyl- or 7-methoxy-substituted 2-hydroxy-1,4-naphthoquinone can also afford high enantioselectivities (94% and 95% ee, respectively). Other quinone derivatives, such as 2-bromo-1,4-naphthoquinone, 2-morphorlinyl-1,4-naphthoquinone, 2-methoxy-1,4-naphthoquinone, and *p*-benzoquinone, were also tested in the reaction. In these cases, no Michael addition products can be obtained, which indicates the importance

of the 2-hydroxy group in the activation mode of the nucleophile.[10]

The absolute configuration of product **8f** was determined to be *S* on the basis of the X-ray crystallographic analysis (CCDC deposition number 682469).[11] In this crystal structure, there are hydrogen bonds between the 2-hydroxy group of one molecule and the carbonyl group of another molecule (Figure 2).

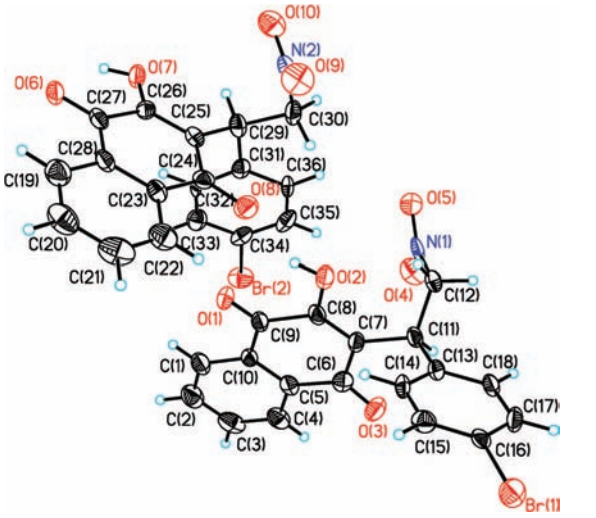


Figure 2. X-ray crystal structure of 1,4-naphthoquinone **8f**.

A mechanism as illustrated in Figure 3 is proposed to explain the observed results. The nitro group forms hydrogen bonds with the thiourea segment of organocatalyst **1**. The hydroxy group of the 2-hydroxy-1,4-naphthoquinone is deprotonated by the tertiary amine segment of the catalyst and the newly formed anion is associated with the catalyst through charge interactions. The double interaction between the hydrogen and the two vicinal oxygen atoms of naththoquinone fixes the conformation of the nucleophile and

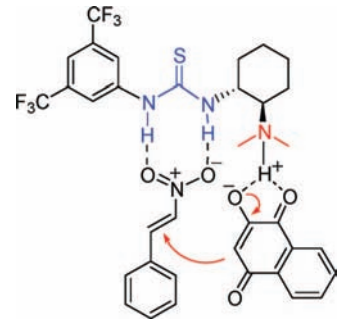


Figure 3. Proposed transition state for the Michael addition.

enhances the enantiocontrol in the transition state. The nucleophile approaches the β-carbon of the nitroalkene from the *Re* face under the direction of the tertiary amine group and forms the *S* product.

In summary, we developed the first highly enantioselective asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes by using thiourea **1** as the organocatalyst. In this efficient catalytic asymmetric reaction, only 10 mol % of catalyst is sufficient to afford chiral 2-hydroxy-3-functionalized naphthoquinone derivatives in good yields with excellent enantioselectivities (up to >99% ee). This reaction provides a valuable route for the synthesis of chiral naphthoquinone derivatives. Considering the potent transformations and biological activity of the optically pure nitroalkylated 1,4-naphthoquinone derivatives, further investigation on the application of the products is underway in our group.

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Supporting Information Available: Experimental procedures and characterizations, copies of ^{1}H NMR and ^{13}C NMR of new compounds, HPLC profiles, and the crystal data of **8f** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) CCDC 682469 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.