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Chiral Squaramide-Catalyzed Highly Enantioselective Michael Addition of 2-Hydroxy-1,4-naphthoquinones to Nitroalkenes

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Abstract: A chiral squaramide-organocatalyzed, highly enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes has been developed. This reaction afforded the chiral naphthoquinones in excellent yields (up to 99%) and excellent enantioselectivity (up to 98% *ee*) under very low catalyst loading (0.25 mol%). This organocatalytic asymmetric Michael addition provides an efficient alternative route toward the synthesis of chiral functionalized naphthoquinones.

Keywords: asymmetric catalysis; Michael addition; naphthoquinones; nitroalkenes; organocatalysis; squaramides

Quinones and naphthoquinones are important structural units in many natural products.[1] Quinones and naphthoquinones exhibit redox properties that influence various regulatory cellular processes. Many quinone-containing compounds have biological activity owing to the presence of the quinone pharmacophore.[2] Quinone-containing antitumor drugs, such as mitoxantrone, ametantrone, and doxorubicin, demonstrate potent antitumor activity and have been used clinically as one of the most effective classes of anticancer agents with broad applications in the treatment of several leukemias and lymphomas.[3] In view of their important biological features in medicinal chemistry, a large number of quinone derivatives and related compounds has been prepared in order to search for novel bioactive agents with improved pharmacological properties.[4] 2-Hydroxy-1,4-naphthoquinones have received particularly attention due to their biological properties and their potential as synthetic precursors of complex carbocyclic and heterocyclic quinones,[5] such as bisannulated indoloquinones, 5*H*-benzo[*b*]carbazole-6,11-diones, which have antineoplastic activity.[6] In consideration of the different bioactivities of enantiomers, the development of highly enantioselective catalytic methodologies for the synthesis of chiral naphthoquinone compounds is an important synthetic target.

The asymmetric Michael addition of nitroalkenes is an important C–C bond-forming reaction, which provides access to synthetically useful enantioenriched nitroalkanes and has attracted significant interest in recent years.[7] 2-Hydroxy-1,4-naphthoquinones have an enol moiety and may serve as good nucleophiles in the Michael addition.[8] The asymmetric conjugate addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes is particularly interesting because it produces chiral nitroalkylated compounds which are precursors of a variety of other functionalized bioactive compounds. After our first report on the chiral thiourea-catalyzed enantioselective Michael addition of 2-hydroxynaphthoquinones to nitroalkenes,[9] Xu reported an organocatalytic enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone to β,γ-unsaturated α-oxo esters, which was promoted by bifunctional chiral amine-derived squaramides.[10] Chiral squaramide organocatalysts pioneered by Rawal's group and later exploited by other groups have been demonstrated to be a new family of efficient and versatile bifunctional organocatalysts for asymmetric chemical transformations such as the enantioselective Michael addition, Friedel–Crafts reaction, and α-amination of 1,3-dicarbonyl compounds.[11] In consideration of the excellent performace of squaramides in asymmetric catalysis as hydrogen-bonding organocatalysts,[11,12] a more powerful catalytic asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes may be possible using squaramide organocatalysts. Herein, we describe our successful applications of squaramide organocatalysts to the highly efficient enantioselective Michael addition of 2-hydroxy-1,4-

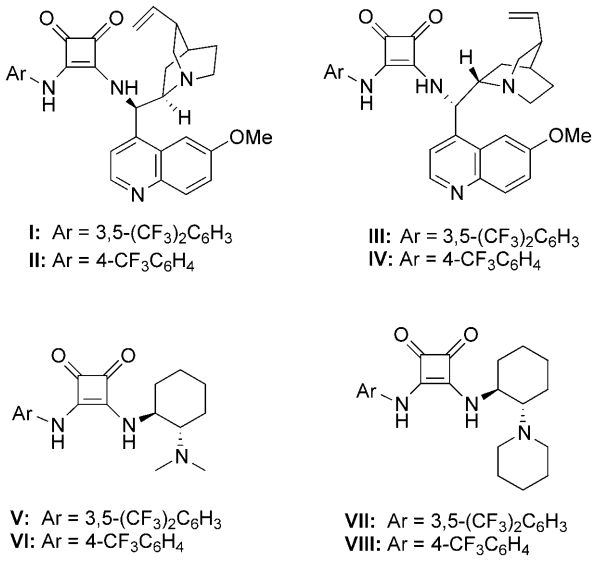
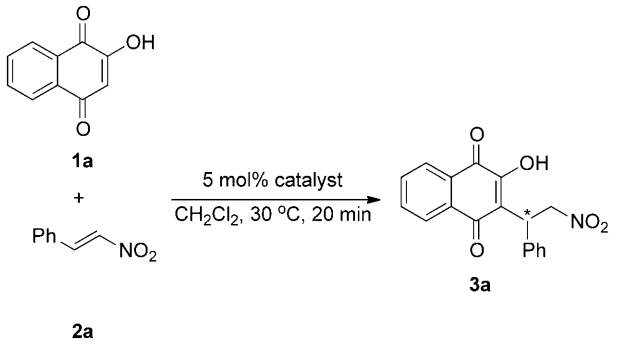


Figure 1. Structures of the screened organocatalysts.

naphthoquinones to nitroalkenes at very low catalyst loading (0.25 mol%), and excellent yields and enantioselectivities (up to 98% *ee*) could be achieved for most substrates.

A series of chiral squaramide-based organocatalysts **I**–**VIII** (Figure 1) was synthesized to promote the Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes. Remarkably, these squaramides, possessing a high modular nature, can be easily prepared in two or three steps from commercially available dimethyl squarate, aromatic amines and chiral amines (*Cinchona* alkaloids or 1,2-diaminocyclohexane). The highly modular nature and the facile synthesis of chiral squaramides facilitate the fine-tuning of their catalytic activity for asymmetric catalysis. Initially, we selected the Michael addition of 2-hydroxy-1,4-naphthoquinone to β-nitrostyrene as a model reaction and examined the catalytic effects of various squaramide-based organocatalysts. The model reaction was performed in CH_2Cl_2 in the presence of 5 mol% catalyst loading at 30 °C, and the screening results are given in Table 1. To our delight, quinine-derived squaramides **I** and **II** gave the desired products in excellent yields with high enantioselectivities (91% *ee* and 92% *ee*) in 20 min (Table 1, entries 1 and 2). When quinidine-derived squaramides **III** and **IV** were used, the products with the opposite configuration were obtained in lower enantioselectivities (−87% *ee* and −86% *ee*) (Table 1, entries 3 and 4). We then turned our attention to those squaramides derived from chiral 1,2-diaminocyclohexane. Disappointingly, inferior results (89% *ee* and 87% *ee*) were achieved when catalysts **V** and **VI** were employed (Table 1, entries 5 and 6). For investigation of the effect of the tertiary amino group, squaramide-based catalysts **VII** and **VIII** containing a piperidinyl group were prepared and screened. Satisfactorily, catalysts **VII** and **VIII** gave access to the desired products in excellent yields with excellent enantioselectivities (97% *ee* and 98% *ee*) (Table 1, entries 7 and 8). Catalyst **VIII** was slightly better than catalyst **VII**, and was selected as the best catalyst for further optimization.

Table 1. Screening of organocatalysts for the asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to β-nitrostyrene.[a]

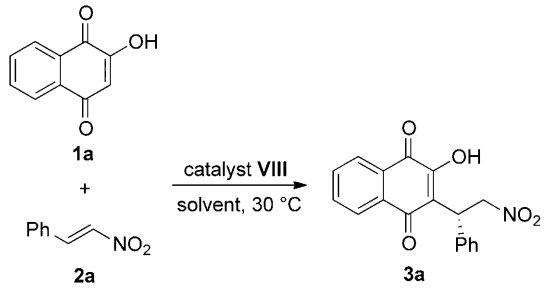


Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**I**	94	91
2	**II**	96	92
3	**III**	96	-87
4	**IV**	96	-86
5	**V**	95	89
6	**VI**	96	87
7	**VII**	97	97
8	**VIII**	97	98

[a] Unless noted otherwise, reactions were carried out with β-nitrostyrene (0.2 mmol) and 2-hydroxy-1,4-naphthoquinone (0.2 mmol) in CH_2Cl_2 (0.5 mL).
[b] Isolated yields after column chromatography purification.
[c] Determined by HPLC using a Daicel Chiralcel OJ-H column.

With the best catalyst in hand, we further screened the effect of solvents, catalyst loading, substrate concentration and temperature for the optimal reaction conditions. The screening results are summarized in Table 2. Variation of the solvents had a limited effect on the yields and enantioselectivities of the reaction. The common solvents such as CH_2ClCH_2Cl, $CHCl_3$, toluene and THF gave excellent yields and enantioselectivities (96–98% *ee*) (Table 2, entries 2–5). As expected, MeOH led to a decrease in the enantioselectivity (92% *ee*) because it is often a poor solvent in hydrogen bond-controlled organocatalysis (Table 2, entry 6). No solvent tested was found to be obviously superior to CH_2Cl_2. The above observation demonstrated that the catalytic system for the Michael addition was not very sensitive to solvents. Subsequently, the effect of catalyst loading was investigated. The excellent enantioselectivities were still maintained with a reduced catalyst loading from 1 to 0.1 mol%, and

Table 2. Optimization of the reaction conditions for the asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to β-nitrostyrene.[a]



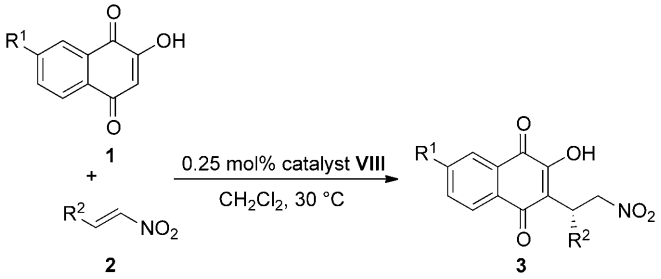
Entry	Solvent	Loading [mol%]	Time	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	5	20 min	97	98
2	CH_2ClCH_2Cl	5	20 min	96	97
3	$CHCl_3$	5	20 min	97	97
4	$PhCH_3$	5	20 min	99	96
5	THF	5	20 min	98	97
6	MeOH	5	20 min	98	92
7	CH_2Cl_2	1	1 h	97	98
8	CH_2Cl_2	0.50	3 h	96	98
9	CH_2Cl_2	0.25	6 h	94	98
10	CH_2Cl_2	0.10	24 h	91	98
11[d]	CH_2Cl_2	0.25	6 h	96	98
12[e]	CH_2Cl_2	0.25	24 h	91	98
13[f]	CH_2Cl_2	0.25	24 h	70	98

[a] Unless noted otherwise, reactions were carried out with β-nitrostyrene (0.20 mmol) and 2-hydroxy-1,4-naphthoquinone (0.20 mmol) in solvent (0.5 mL).
[b] Isolated yields after column chromatography purification.
[c] Determined by HPLC using a Daicel Chiralcel OJ-H column.
[d] 0.25 mL of CH_2Cl_2 was used.
[e] 1.0 mL of CH_2Cl_2 was used.
[f] Reaction was carried out at 0 °C.

high yields were also achieved in the corresponding extended reaction times (Table 2, entries 7–10). Compromising with the yield and reaction time, 0.25 mol% catalyst loading was chosen for further optimization. Variation of the substrate concentration did not affect the enantioselectivities, but had a slight effect on the yields (Table 2, entries 11 and 12). As expected, a high substrate concentration led to a slight increase in the yield. When the reaction was performed at 0 °C, a moderate yield (70%) and comparable enantioselectivity were observed in a prolonged time (Table 2, entry 13).

The scope of this Michael reaction was explored under the optimized reaction conditions, and the results are summarized in Table 3. Various nitroalkenes bearing either electron-withdrawing or electron-donating groups (F, Cl, Br, Me and OMe) at the *para* or *ortho* position on the phenyl ring reacted smoothly

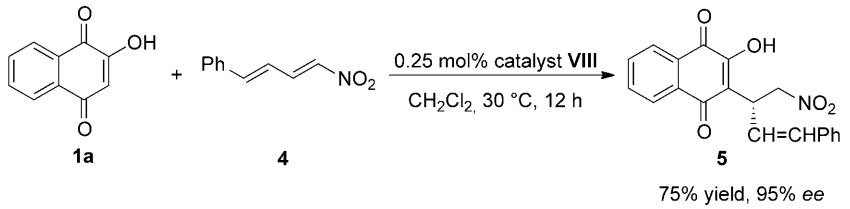
Table 3. Scope of the Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes.[a]



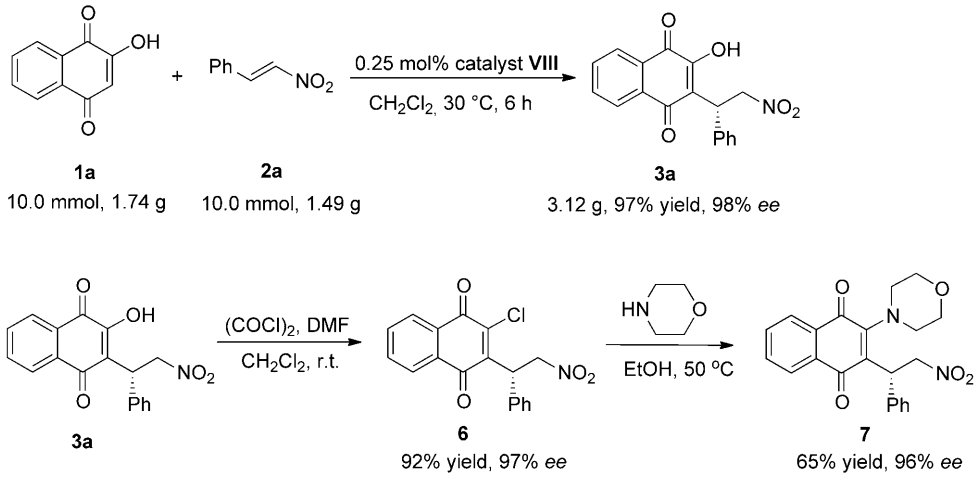
Entry	R^1	R^2	Product	Yield [%][b]	*ee* [%][c,d]
1	H	C_6H_5	**3a**	96	98
2	H	4-FC_6H_4	**3b**	95	98
3	H	4-ClC_6H_4	**3c**	99	97
4	H	4-BrC_6H_4	**3d**	94	98 (*R*)
5	H	4-MeC_6H_4	**3e**	97	97
6	H	4-$MeOC_6H_4$	**3f**	95	97
7	H	2-ClC_6H_4	**3g**	92	98
8	H	2-$MeOC_6H_4$	**3h**	90	95
9	H	3,4-$(MeO)_2C_6H_3$	**3i**	89	96[e]
10	H	2-furanyl	**3j**	92	97
11	H	2-thienyl	**3k**	93	98
12[f]	H	2-phenylethyl	**3l**	89	97 g]
13[f]	H	cyclohexyl	**3m**	78	96[e]
14	Me	C_6H_5	**3n**	95	98
15	Me	4-MeC_6H_4	**3o**	96	97
16	OMe	C_6H_5	**3p**	75	97

[a] Unless noted otherwise, reactions were carried out with nitroalkenes (0.20 mmol) and 2-hydroxy-1,4-naphthoquinones (0.20 mmol) in CH_2Cl_2 (0.25 mL) for 6 h.
[b] Isolated yields after column chromatography purification.
[c] Determined by HPLC using a Daicel Chiralcel OJ-H column.
[d] The configuration of product **3d** was assigned by comparation with the previous X-ray crystal structure of its enantiomer, others were assigned by analogy.[9]
[e] Determined by HPLC using a Chiralpak IA column through its *O*-methyl derivative.
[f] Reaction was carried out for 12 h.
[g] Determined by HPLC using a Daicel Chiralcel OJ-H column through its *O*-methyl derivative.

with 2-hydroxy-1,4-naphthoquinone to afford the desired products with excellent yields (90–99%) and enantioselectivities (95–98% *ee*) (Table 3, entries 2–8). When the 3,4-dimethoxy-substituted nitroalkene was used as an acceptor, a comparable result (89% yield and 96% *ee*) was observed (Table 3, entry 9). In the cases of other aromatic nitroalkenes derived from furan and thiophene, the desired products were also obtained with high yields and excellent enantioselectivities (Table 3, entries 10 and 11). The aliphatic nitroalkenes can also gave comparable excellent enantioselectivities (97% and 96% *ee*), which were deter-



Scheme 1. Further investiagtion of the substrate scope.



Scheme 2. The gram-scale preparation of **3a** and its synthetic transformations.

mined through their *O*-methyl derivatives, but these compounds required a longer time (12 h) due to their lower reactivity (Table 3, entries 12 and 13). 2-Hydroxy-1,4-naphthoquinones with electron-donating groups (Me and OMe) on the 6-position were also tested, and the corresponding products were obtained with excellent enantioselectivities (Table 3, entries 14–16).

As shown in Scheme 1, further exctension of the substrate scope to a nitrodiene was investigated. The catalytic asymmetric addition of 2-hydroxy-1,4-naphthoquinone **3a** to [(1*E*,3*E*)-4-nitrobuta-1,3-dienyl]benzene **4** was also effective to give the desired product **5** in good yield with excellent enantioselectivity (95% *ee*) under the above optimized conditions for 12 h.

To further evaluate the synthetic potential of the catalytic system, the gram-scale preparation of **3a** was performed in the presence of 0.25 mol% of catalyst **VIII** under the optimized conditions. As shown in Scheme 2, the catalytic asymmetric Michael addition of **1a** to **2a** was accomplished with excellent results (3.12 g, 97% yield, 98% *ee*). In addition, the product **3a** can also be easily transformed into the optically active product **6** in 92% yield with 97% *ee*. Compound **6** may serve as a versatile building block owing to the existence of carbonyl, chloro, and nitro groups. For example, the nucleophilic substitution of compound **6** with morpholine can afford the corresponding heterocyclic-substituted chiral naphthoquinone **7** in 65% yield with 96% *ee*.

On the basis of the experimental results described above, a possible transition state model was hypothesized and shown in Figure 2. The model has no significant difference with the one in our previous report. We envisioned that the chiral squaramide **VIII** acts as a bifunctional catalyst. The 2-hydroxy-1,4-naphthoquinone is deprotonated by the basic nitrogen atom of the tertiary amine. Meanwhile, the nitroalkene is fixed and activited by the squaramide moiety through double hydrogen bonding between the NH groups and the nitro group. The deprotonated 2-hydroxy-1,4-

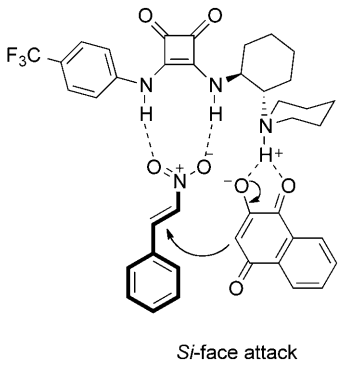


Figure 2. Proposed transition state model.

naphthoquinone attacks the fixed nitroalkene from the *Si*-face to afford the *R*-configured product, which is consistent with the observed results.

In summary, we have synthesized a series of chiral squaramide-based bifunctional organocatalysts, which have been successfully applied to promoting the asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes. Significantly, only 0.25 mol% of catalyst **VIII** is highly effective to give good-to-excellent yields and excellent enantioselectivities (95–98% *ee*) under mild reaction conditions. This catalytic asymmetric reaction provides a valuable and easy access to chiral naphthoquinone derivatives, which possess the versatile transformation possibilites and potential biological activity. Given the highly modular nature and facile synthesis, chiral squaramides may represent a kind of good hydrogen-bonding organocatalyst, and current studies are underway in our group to broaden their application in asymmetric catalysis.

Experimental Section

General Procedure for the Enantioselective Michael Addition Reaction

Organocatalyst **VIII** (8.4 mg) was added to dichloromethane to afford a solution of catalyst **VIII** (10.0 mL, 2.0 mmol/L). To a solution of nitroalkenes **2** (0.20 mmol) in 0.25 mL of the above catalyst **VIII** solution (0.0005 mmol) was added 2-hydroxy-1,4-naphthoquinone **1** (0.20 mmol). The reaction mixture was stirred at 30 °C for 6 h or 12 h. Then the mixture was concentrated and purified by silica gel column chromatography (CH_2Cl_2) to afford the desired products **3**.

2-Hydroxy-3-(2-nitro-1-phenylethyl)naphthalene-1,4-dione (3a): Compound **3a** was obtained according to the general procedure as an orange solid; yield: 61.9 mg (96%); mp 152–153 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OJ-H column (*n*-hexane:2-propanol 70:30 v/v, flow rate 1.0 mL·min^{-1}, 254 nm): minor enantiomer $t_r = 17.3$ min, major enantiomer $t_r = 31.6$ min, 98% *ee*; $[\alpha]_D^{25}$: −34.0 (*c* 1.46 g/100 mL, CH_3COCH_3); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.11$ (d, $J = 7.5$ Hz, 1H), 8.06 (d, $J = 7.5$ Hz, 1H), 8.00 (br s, 1H), 7.77 (dt, $J_1 = 1.0$ Hz, $J_2 = 7.5$ Hz, 1H), 7.69 (dt, $J_1 = 1.0$ Hz, $J_2 = 7.5$ Hz, 1H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.32 (t, $J = 7.5$ Hz, 2H), 7.28–7.25 (m, 1H), 5.48 (dd, $J_1 = 9.0$ Hz, $J_2 = 13.5$ Hz, 1H), 5.34–5.30 (m, 1H), 5.16 (dd, $J_1 = 6.5$ Hz, $J_2 = 13.5$ Hz, 1H).

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