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Communications

Enantioselective Michael Addition of 2-Hydroxy-1,4-naphthoquinone to β,γ-Unsaturated α-Keto Esters Catalyzed by Binaphthyl-Modified Squaramide

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The structures of quinone and naphthoquinone exist in a large number of natural products and biologically active molecules.[1] Particularly, many of these naturally occurring naphthoquinones and their synthetic analogues are important precursors for the synthesis of natural products and pharmaceuticals.[2] The Michael reaction is widely recognized as one of the most fascinating and powerful methods for the formation of C-C bonds in organic synthesis[3] and the development of asymmetric version of this reaction has been the subject of intensive research.[4] Enantioselective organocatalytic Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds represents a direct approach to chiral 1,5-dicarbonyl compounds that are versatile intermediates in organic synthesis.[5] Recently, several groups have reported the asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinones to β,γ-unsaturated α-keto esters catalyzed by cinchona-derived organocatalyst and chiral indane thiourea catalyst.[6] Nevertheless, there are still some drawbacks in these procedures, such as high catalyst loading and long reaction time for high enantioselectivity. Accordingly, the development of alternative catalysts for the enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to β,γ-unsaturated α-keto esters is highly desirable.

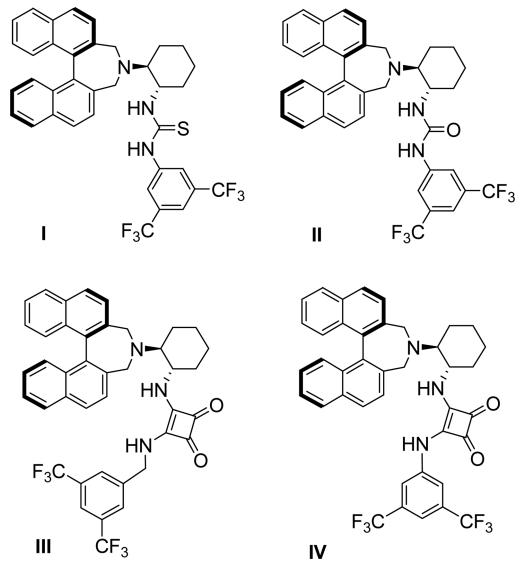
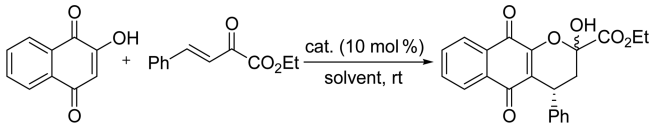


Figure 1. Structure of chiral bifunctional organocatalysts.

As part of our research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[7] we recently reported the asymmetric Michael addition of active methylenes and methines using chiral catalysts.[8] Herein, we wish to describe the enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone to β,γ-unsaturated α-keto esters promoted by binaphthyl-modified organocatalyst.

To determine suitable reaction conditions for the catalytic enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone, we initially investigated a reaction system with 2-hydroxy-1,4-naphthoquinone (**1**) and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate (**2a**) in the presence of 10 mol % binaphthyl-modified organocatalysts **I-IV** (Fig. 1) bearing both central and axial chiral elements. As shown in Table 1,

Table 1. Optimization of the reaction conditions[a]



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

Entry	Cat.	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**I**	CH_2Cl_2	6	65	68
2	**II**	CH_2Cl_2	6	90	62
3	**III**	CH_2Cl_2	6	89	75
4	**IV**	CH_2Cl_2	6	85	81
5	**IV**	THF	10	72	87
6	**IV**	Et_2O	10	94	96
7	**IV**	$MeCO_2Et$	10	81	83
8	**IV**	PhMe	10	81	89
9	**IV**	MeOH	10	86	93
10[d]	**IV**	Et_2O	12	96	95
11[e]	**IV**	Et_2O	12	95	95

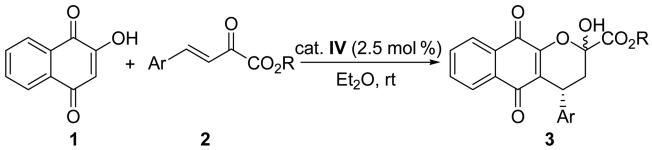
[a]Reaction conditions: 2-hydroxy-1,4-naphthoquinone (**1**, 0.30 mmol), β,γ-unsaturated α-keto ester **2a** (0.36 mmol), catalyst (0.03 mmol), solvent (1.5 mL) at room temperature. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using a Chiralpak IC column. [d]5 mol % catalyst loading. [e]2.5 mol % catalyst loading.

binaphthyl-modified (thio)urea catalysts **I** and **II** effectively promoted the reaction in dichloromethane with moderate enantioselectivities (entries 1-2). Change to the urea-moiety to squaramide organocatalysts **III-IV** improved enantioselectivities (entries 3-4), and the highest enantiselectivities obtained with the binaphthyl-modified squaramide catalyst **IV**. In order to further improve the selectivity, different solvents were then tested in the presence of 10 mol % of catalyst **IV**. Aprotic solvents such as dichloromethane, THF, diethyl ether, ethyl acetate and toluene were well tolerated in this Michael addition without a significant decrease of enantioselectivities (81-96% ee, entries 4-9). Protic solvent such as MeOH also afforded products with high yields with high selectivity (entry 9). Among the solvents probed, the best result was achieved when the reaction was conducted in diethyl ether (94% yield, 96% ee, entry 6). The present catalytic system tolerates catalyst loading down to 5 or 2.5 mol %, and both the yield and enantioselectivity were retained (entries 6 and 10-11).

With the optimal reaction conditions in hand, the asymmetric Michael additions of 2-hydroxy-1,4-naphthoquinone to various β,γ-unsaturated α-keto esters were examined, and the results are summarized in Table 2. As demonstrated, the organocatalyst **IV** catalyzed the Michael addition of 2-hydroxy-1,4-naphthoquinone (**1**) to β,γ-unsaturated α-keto esters **2** providing a general method for the synthesis of optically active naphthoquinone derivatives **3** with high to excellent enantiomeric excess (up to 99% ee). Absolute configurations of products **3** were determined by comparison either of the optical rotation or chiral HPLC data with those of the reported ones.[6]

In conclusion, we have developed organocatalytic enantioselective Michael addition reaction of 2-hydroxy-1,4-naphthoquinone (**1**) to β,γ-unsaturated α-keto esters **2** to afford biologically valuable naphthoquinone derivatives **3**. The binaphthyl-modified squaramide organocatalyst **IV** showed excellent catalytic activity for this reaction to afford **3** in high yields with excellent enantioselectivities (up to 99% ee) under mild reaction conditions.

Table 2. Enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones (**1**) to β,γ-unsaturated α-keto esters **2**[a]



1 **2** **3**

Entry	**2**, Ar, R	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a**, Ph, Et	12	**3a**, 95	95
2	**2b**, Ph, Me	3	**3b**, 93	97
3	**2c**, 4-FC_6H_4, Et	4	**3c**, 85	91
4	**2d**, 4-ClC_6H_4, Et	4	**3d**, 97	95
5	**2e**, 2-ClC_6H_4, Et	12	**3e**, 76	94
6	**2f**, 4-BrC_6H_4, Et	12	**3f**, 78	97
7	**2g**, 4-$NO_2C_6H_4$, Et	3	**3g**, 95	>99
8	**2h**, 4-MeC_6H_4, Et	12	**3h**, 95	91
9[d]	**2i**, 4-$MeOC_6H_4$, Et	12	**3i**, 91	90
10	**2j**, 2-naphthyl, Et	12	**3j**, 91	97

[a]Reaction conditions: 2-hydroxy-1,4-naphthoquinone (**1**, 0.30 mmol), β,γ-unsaturated α-keto ester **2** (0.36 mmol), catalyst (7.5 μmol), Et_2O (1.5 mL) at room temperature. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using a Chiralpak IC column. [d]10 mol % catalyst loading.

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