DOI: 10.1002/ejoc.201001570

Organocatalytic Michael Addition of Naphthoquinone with α,β-Unsaturated Ketones: Primary Amine Catalyzed Asymmetric Synthesis of Lapachol Analogues

Guangcun Zhang,[a] Yifeng Wang,[a] Wei Zhang,[a] Xiangsheng Xu,[a] Aiguo Zhong,[b] and Danqian Xu*[a]

Keywords: Amines / Michael addition / Asymmetric synthesis / Organocatalysis / Natural products

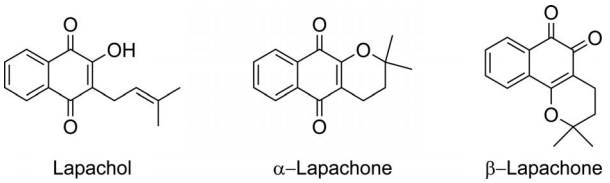
A highly efficient organocatalytic synthesis of lapachol analogues from the Michael addition of naphthoquinone to various α,β-unsaturated ketones catalyzed by primary amines is presented. Good to high yields (up to 93 %) and high to excellent enantioselectivities (up to 98 % *ee*) were obtained for the target compounds. MS (ESI) provided evidence for the key intermediates in the proposed mechanism.

Introduction

Organocatalysis has been one of the focal points of chemical research. The process has been developed to possess special features, and it is atom economic, environmentally benign, and operationally convenient.[1] Many organocatalysts have been applied in a variety of asymmetric reactions; chiral secondary amines, in particular, are extremely powerful reagents and dominated the field of amino catalysis early on.[2] Meanwhile, chiral primary amines have also been demonstrated to be effective catalysts in a wide range of enantioselective organic reactions.[3] Compared to secondary amine-mediated transformations, the use of primary amine organocatalysts has often been shown to be complementary or superior.

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 could be an efficient route for the synthesis of drugs or drug-like bioactive small molecules, which have been the research focus of medicinal or bioorganic chemists and chemical biologists.[4] Further development of new asymmetric reactions with the use of easily available organocatalysts and the discovery of a more practical catalytic asymmetric process to afford novel chiral bioactive compounds are research areas that require attention.

Quinones and their derivatives are used on a large scale as dye reagents, and they often possess biological activities; for example, lapachol and α- and β-lapachone (Scheme 1) are important components of antibacterial, fungicidal, antimalarial, trypanocidal, antiparasitic, and antitumoral agents.[5] Their trypanocidal activity could be to help cure Chagas disease, one of the most important endemic diseases caused by Trypanosoma cruzi, which affects 16–18 million people in large areas of Latin America and Africa.[6] Furthermore, lapachone analogues may present potential inhibitive ability of DNA topoisomerase II, and by this way, they have great cancer-preventing potential.[7] Consequently, the development of an efficient synthesis to obtain these valuable compounds has attracted great interest, and recently, enantioselective organocatalytic reactions of naphthoquinone to electron-withdrawing olefins have been reported.[8] Based on these previous strategies, we introduced a new asymmetric procedure involving primary amine organocatalysts for the synthesis of various lapachol analogues starting from readily available α,β-unsaturated ketones and naphthoquinone.



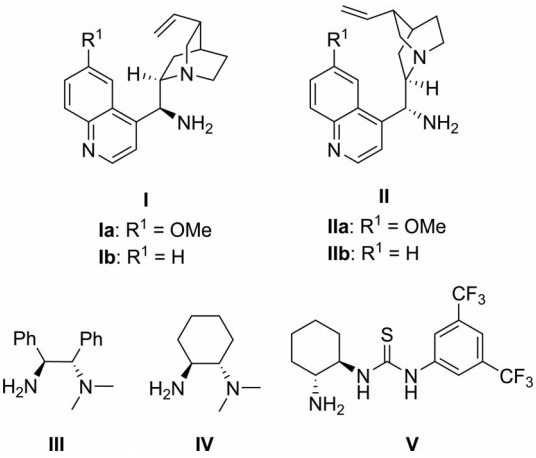
Scheme 1. Structures of lapachol and lapachones.

Results and Discussion

To start, we chose benzalacetone (**1a**) to react with naphthoquinone **2** as the model reaction in the presence of

[a] State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology Hangzhou 310014, China
Fax: +86-571-88320609
E-mail: chrc@zjut.edu.cn
[b] Department of Pharmaceutical and Chemical Engineering, Taizhou College,
Linhai Zhejiang 317000, China
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001570.

primary amine catalysts (Scheme 2), and the representative results are summarized in Table 1.



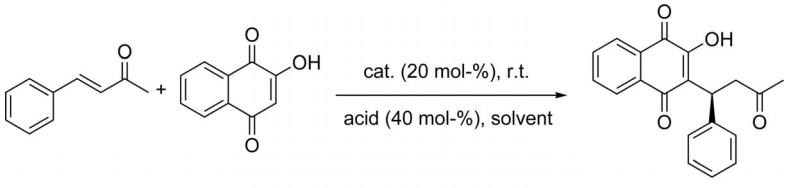
Scheme 2. Primary amine catalysts screened for the reaction.

All the amine catalysts tested performed well in the model reaction (Table 1, Entries 1–6), but the use of a primary amine thiourea provided disappointing results (Table 1, Entry 7). We were pleased to find **Ib** (20 mol-%) derived from cinchonidine in combination with PhCOOH (40 mol-%) exhibited high catalytic activity for the asymmetric Michael addition (78% yield, 92%*ee*; Table 1, Entry 2). As is known, solvents and acid additives have a notable effect on organocatalytic reactions; therefore, we examined the reaction media and co-catalysts for this reaction. Reactions in polar solvents, such as MeOH and *i*PrOH, provided low yields and *ee* values (Table 1, Entries 8 and 9), and in DMF a trace amount of the product was found (Table 1, Entry 10). When the reaction was performed in less polar solvents, such as THF, $(i\text{Pr})_2\text{O}$, and $PhCH_3$, high yields and *ee* values were afforded (Table 1, Entries 11–13). Having screened various acids, optimum conditions for the Michael reaction (88% yield, 93%*ee*) were discovered when TFA was used as the co-catalyst and THF as the solvent (Table 1, Entry 18). A supplementary screening for solvents was put to trial (Table 1, Entries 19 and 20), but the outcome was inferior to our previous results (Table 1, Entry 18).

On the basis of the above results, further investigations were warranted to examine the capability of the catalysis system to catalyze the asymmetric Michael addition of various α,β-unsaturated ketones with naphthoquinone under the optimized experimental conditions.

As seen from Table 2, a wide array of α,β-unsaturated ketones, which bear electron-donating, electron-neutral, or electron-withdrawing groups at the phenyl group, reacted smoothly with naphthoquinone to afford corresponding products **3a**–**h** in good to high yields (65–93%) and with high levels of enantioselectivity (91–98%*ee*). Generally, electron-withdrawing groups at the *ortho*-, *meta*- or *para*-

Table 1. Screening studies of the organocatalytic asymmetric Michael addition reaction of **1a** to **2**.[a]



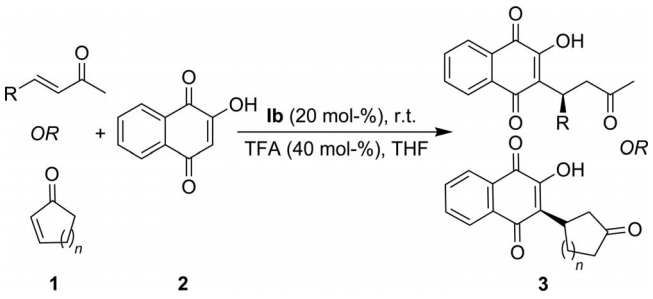
1a **2** **3a**

Entry	Cat.	Acid	Solvent	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	**Ia**	PhCOOH	DCM	60	72	87
2	**Ib**	PhCOOH	DCM	60	78	92
3	**IIa**	PhCOOH	DCM	60	59	–82[d]
4	**IIb**	PhCOOH	DCM	60	70	–84[d]
5	**III**	PhCOOH	DCM	60	55	80
6	**IV**	PhCOOH	DCM	60	70	75
7	**V**	PhCOOH	DCM	60	trace	n.d.[e]
8	**Ib**	PhCOOH	MeOH	72	38	60
9	**Ib**	PhCOOH	*i*PrOH	48	50	37
10	**Ib**	PhCOOH	DMF	72	trace	n.d.
11	**Ib**	PhCOOH	THF	72	86	93
12	**Ib**	PhCOOH	$(i\text{Pr})_2\text{O}$	48	75	66
13	**Ib**	PhCOOH	$PhCH_3$	48	75	72
14	**Ib**	4-MeC_6H_4COOH	THF	40	80	80
15	**Ib**	salicylic acid	THF	48	80	86
16	**Ib**	4-$NO_2C_6H_4COOH$	THF	48	70	85
17	**Ib**	CF_3SO_3H	THF	72	30	75
18	**Ib**	TFA	THF	48	88	93
19	**Ib**	TFA	DCM	48	75	83
20	**Ib**	TFA	DCE	48	60	78

[a] All reactions were carried out with **1a** (0.15 mmol) and **2** (0.10 mmol) in the presence of the catalyst (20 mol-%) and co-catalyst acid (40 mol-%) in solvent (1.0 mL) at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] A minus sign before the *ee* value signifies the enantiomer opposite to that obtained in all other entries in this table. [e] Not detected.

position of the phenyl group were well tolerated and high yields and excellent enantioselectivities were observed (Table 2, Entries 2–7). A moderate yield and *ee* value arose when a methoxy group on the phenyl moiety was present or when furfuralacetone was employed to react with **2** (Table 2, Entries 8 and 9). Reactions of **2** with cycloalkenones were also investigated, which revealed good results with yields exceeding 92% with enantioselectivities ≥92% *ee* (Table 2, Entries 10 and 11). All the above proves that catalyst **Ib** can be perfectly applied to the asymmetric Michael reaction of α,β-unsaturated ketones with 2-hydroxy-1,4-naphthalenedione for the synthesis of lapachol analogues.

Table 2. Michael addition reactions of α,β-unsaturated ketones with naphthoquinone promoted by catalyst **Ib**.[a]



1 2 3

Entry	R	*n*	Time [h]	Adduct	Yield[b] [%]	*ee*[c] [%]
1	Ph	–	48	**3a**	82	94
2	4-BrC_6H_4	–	48	**3b**	93	93.5/ >99[d]
3	3-BrC_6H_4	–	48	**3c**	88	91
4	2-ClC_6H_4	–	72	**3d**	75	92
5	4-ClC_6H_4	–	48	**3e**	87	91.5/ >99[d]
6	2,4-$Cl_2C_6H_3$	–	72	**3f**	78	96
7	4-$NO_2C_6H_4$	–	52	**3g**	85	98
8	3-$MeOC_6H_4$	–	96	**3h**	65	95
9	2-furan	–	72	**3i**	67	84
10	–	1	8	**3j**	93	92
11	–	2	12	**3k**	92	94

[a] All reactions were carried out with **1** (0.15 mmol) and **2** (0.10 mmol) in the presence of **Ib** (20 mol-%) and TFA (40 mol-%) in THF (1.0 mL) at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] After recrystallization from dichloromethane/petroleum ether (1:3).

To determine the absolute configurations of the final adducts, a useful technique by comparing the electronic circular dichroism (ECD) spectra of the chiral product with calculated time-dependent density functional theory (TDDFT) results was adopted.[9] We investigated Michael

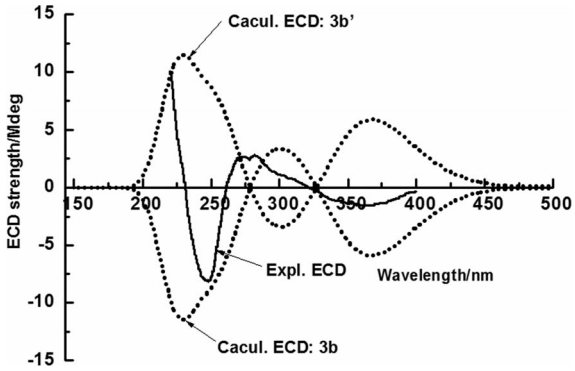


Figure 1. Theoretical ECD spectrum (dotted line) for product **3b** simulated by the TD-DFT/6-311+G*//DFT/6-311+G*method, compared with the experimental spectrum (solid line).

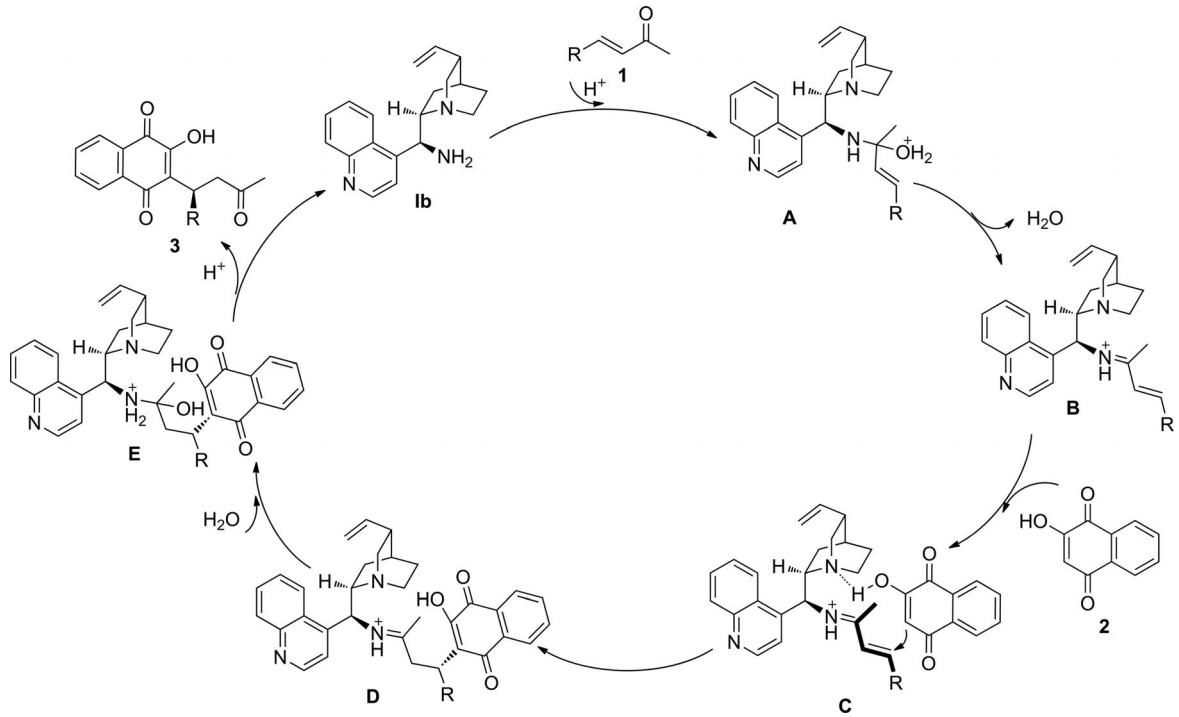


Figure 2. Proposed catalytic mechanism for primary amine catalysis.

adduct **3b** for its absolute stereochemistry (Figure 1), and the experimental ECD spectrum matched the theoretical data of the *S* configuration (Figure 1); they both showed a negative cotton effect around 240 nm. The absolute configuration of the products implies that naphthoquinone should favor attack from the *Re* face of the α,β-unsaturated ketones (Figure 2).

Based on the absolute configuration of the final product and the previous reports of primary amine catalysis,[3] a catalytic mechanism for the reaction is proposed (Figure 2). Firstly, under the catalysis of a protonic acid, the catalytic cycle is initiated by nucleophilic attack of the primary amine to the carbonyl group of substrate **1**. Resultant intermediate **A** then undergoes dehydration to form iminium cation **B**, which furnishes a preorganized structure and controls the enantioselectivity of the reaction. In the cycle, naphthoquinone is assumed to interact with the tertiary amine group of **Ib** through H-bonding, enhancing the nucleophilic character of the reacting carbon center to attack the activated ketones and inducing the Michael addition from the *Re* face of the α,β-unsaturated ketones. That allows the Michael addition of **1** and **2** to take place, providing corresponding iminium intermediate **D**. Ultimately, through hydrolysis, the procedure provides the product and regenerates catalyst **Ib**.

To prove the rationality of the proposed mechanism, we studied the reaction by MS (ESI),[10] which enabled us to identify all critical intermediates in the reaction mixture, especially during dehydration and hydrolysis of the intermediates of the iminium ion (Figure 3). The spectrum of the sample obtained from the reaction mixture of **Ib** (20 mol-%), TFA (40 mol-%), **1a** (0.15 mmol), and **2** (0.1 mmol) after stirring for 2 h revealed ions at *m*/*z* = 294.32, 422.40, 440.22, 596.32, and 614.10, corresponding to the signals for the catalyst ([**Ib** + H]$^+$), iminium intermediate **B**, dehydration intermediate **A** ([**B** + H_2O]$^+$), adduct **D**, and hydrolysis adduct **E** ([**D** + H_2O]$^+$), respectively.

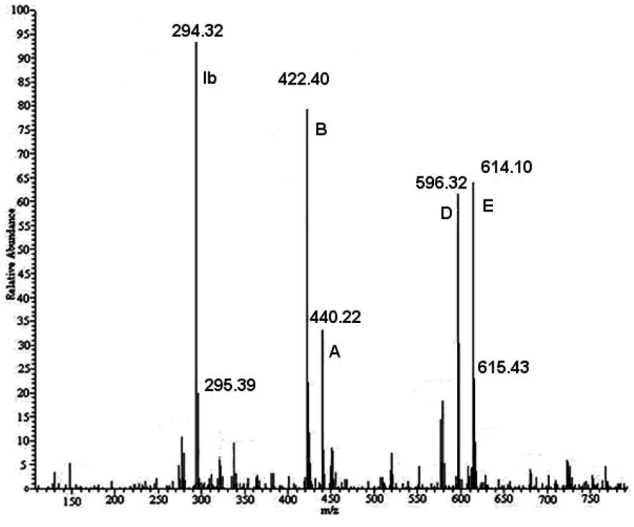


Figure 3. Mass spectrum (ESI) of the reaction 2 h after its start.

Conclusions

In summary, we have developed a highly efficient asymmetric organocatalytic Michael addition reaction of naphthoquinones to a diverse array of α,β-unsaturated ketones in good to high yields and with excellent enantioselectivities. The useful ECD-TDDFT technique was adopted to determine the absolute configuration of the final product. MS (ESI) confirmed the intermediates of the reaction to prove the proposed reaction mechanism. This represents a novel asymmetric synthesis of lapachol analogues, and the corresponding products obtained could be further derivatized for additional applications, which is currently under investigation in our laboratory.

Experimental Section

General Methods: Unless otherwise mentioned, all reagents and solvents were obtained from commercial suppliers and used without further purification. Flash chromatography (FC) was carried out using silica gel (200–300 mesh). Monitoring of reactions was performed by TLC on silica gel precoated on glass plates, and spots were visualized with UV light at 254 nm. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ with a Bruker Avance III (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) at 25 °C. TMS served as internal standard (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ was used as internal standard (δ = 77.0 ppm) for ^{13}C NMR. ^{1}H NMR spectroscopic data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants [Hz], and integration. MS (ESI) spectra were determined with a Thermo LCQ fleet instrument and controlled by Xcalibur software. HRMS spectra were determined with an Agilent 6210 TOF LC–MS. HPLC experiments were carried out using a JASCO LC-2000 Plus system with MD-2010 HPLC diode array detector. CD spectra were measured with a JASCO J-815 CD spectrometer in 0.5 g L^{-1} *i*PrOH.

General Procedure for the Michael Reactions: All reactions were carried out with a mixture of α,β-unsaturated ketones **1** (0.15 mmol), naphthoquinone **2** (0.10 mmol), **Ib** (20 mol-%), and additive TFA (40 mol-%) stirred at room temperature for the corresponding time (TLC; hexane/ethyl acetate, 1:1). The flash column chromatography was carried out over silica gel (petroleum ether/ethyl acetate, 3:1). Enantiomeric excess values of the products were determined by chiral HPLC using a Chiralpak AS-H or OD-H column.

2-Hydroxy-3-(3-oxo-1-phenylbutyl)naphthalene-1,4-dione (3a): Yield: 26.8 mg (82%); yellow solid; m.p. 143–145 °C; [*α*] = –38.2 (*c* = 0.10, MeOH). HPLC (Chiralpak OD-H column, hexane/*i*PrOH = 85:15, 1.0 mL/min): t_R = 16.4 (minor), 17.8 (major) min; 94%*ee*. ^{1}H NMR: δ = 2.2 (s, 3 H), 3.3 (dd, *J* = 17.9, 6.0 Hz, 1 H), 3.8 (dd, *J* = 17.8, 9.7 Hz, 1 H), 5.0 (dd, *J* = 9.7, 6.0 Hz, 1 H), 7.2 (t, *J* = 7.37 Hz, 1 H), 7.2–7.3 (m, 2 H), 7.4–7.5 (m, 2 H), 7.7 (t, *J* = 8.1 Hz, 1 H), 7.7 (t, *J* = 7.6 Hz, 1 H), 8.0 (d, *J* = 7.8 Hz, 1 H), 8.1 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 29.9, 35.9, 46.4, 124.4, 124.8, 126.0, 126.7, 127.0, 127.8, 128.1 (2 C), 129.2 (2 C), 132.9, 135.0, 141.1, 152.6, 181.7, 184.3, 207.5 ppm. MS (ESI–): *m*/*z* = 319.2 [M – H]$^-$. HRMS: calcd. for $C_{20}H_{15}O_4$ 319.0973; found 319.0959.

2-[1-(4-Bromophenyl)-3-oxobutyl]-3-hydroxynaphthalene-1,4-dione (3b): Yield: 37.1 mg (93%); yellow solid; m.p. 162–164 °C; [*α*] = –36.4 (*c* = 0.10, MeOH). HPLC (Chiralpak AS-H column, hexane/*i*PrOH = 97:3, 1.0 mL/min); t_R = 70.3 (major), 96.9 (minor) min;

93.5%*ee* (>99% after recrystallization). ^{1}H NMR: δ = 2.2 (s, 3 H), 3.3 (dd, J = 18.0, 6.3 Hz, 1 H), 3.7 (dd, J = 18.0, 9.3 Hz, 1 H), 4.9 (dd, J = 9.3, 6.3 Hz, 1 H), 7.3–7.4 (m, 2 H), 7.4–7.5 (m, 2 H), 7.7 (d, J = 7.6 Hz, 1 H), 7.7 (d, J = 7.8 Hz, 1 H), 8.0 (d, J = 7.7 Hz, 1 H), 8.1 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 29.0, 35.5, 45.8, 123.9, 125.9, 126.7, 127.2, 129.0, 129.9 (2 C), 131.3 (2C), 132.5, 132.8, 134.8, 140.6, 153.0, 181.3, 184.04, 206.8 ppm. MS (ESI–): m/z = 397.1 [M – H]$^-$, 399.3 [M – H]$^-$. HRMS: calcd. for $C_{20}H_{14}BrO_4$ 397.0075; found 399.0084.

2-[1-(3-Bromophenyl)-3-oxobutyl]-3-hydroxynaphthalene-1,4-dione (3c): Yield: 35.2 mg (88%); yellow solid; m.p. 151–154 °C; [α] = –39.5 (c = 0.10, MeOH). HPLC (Chiralpak OD-H column, hexane/*i*PrOH = 97:3, 1.0 mL/min): t_R = 18.2 (major), 21.2 (minor) min; 91%*ee*. ^{1}H NMR: δ = 2.2 (s, 3 H), 3.3 (dd, J = 18.0, 6.1 Hz, 1 H), 3.7 (dd, J = 18.0, 9.5 Hz, 1 H), 4.9 (dd, J = 9.4, 6.2 Hz, 1 H), 7.2 (dd, J = 16.5, 8.5 Hz, 1 H), 7.3–7.4 (m, 2 H), 7.6 (d, J = 7.6 Hz, 1 H), 7.6 (t, J = 7.6, 7.6 Hz, 1 H), 7.7 (dd, J = 5.2, 3.9 Hz, 1 H), 8.0 (d, J = 6.6 Hz, 1 H), 8.1 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 29.9, 36.0, 46.0, 122.5, 123.9, 126.1, 127.0, 127.2, 129.2, 129.9, 130.1, 131.2, 132.8, 133.1, 135.2, 144.0, 152.7, 181.6, 184.1, 206.4 ppm. MS (ESI–): m/z = 397.0 [M – H]$^-$, 399.4 [M – H]$^-$. HRMS: calcd. for $C_{20}H_{14}BrO_4$ 397.0075; found 397.0059.

2-[1-(2-Chlorophenyl)-3-oxobutyl]-3-hydroxynaphthalene-1,4-dione (3d): Yield: 26.7 mg (75%); yellow solid; m.p. 147–150 °C; [α] = –38.0 (c = 0.10, MeOH). HPLC (Chiralpak OD-H column, hexane/*i*PrOH = 97:3, 1.0 mL/min): t_R = 21.2 (major), 16.8 (minor) min; 92%*ee*. ^{1}H NMR: δ = 2.2 (s, 3 H), 3.2 (dd, J = 17.9, 6.3 Hz, 1 H), 3.7 (dd, J = 17.5, 9.0 Hz, 1 H), 4.9 (dd, J = 9.0, 6.6 Hz, 1 H), 7.0–7.1 (m, 2 H), 7.2 (t, J = 1.8, 1.8 Hz, 1 H),7.4 (d, J = 7.9 Hz, 1 H), 7.6 (d, J = 7.6 Hz, 1 H), 7.7 (dd, J = 5.2, 3.9 Hz, 1 H), 8.0 (dd, J = 7.8, 0.7 Hz, 1 H), 8.1 (d, J = 4.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 30.0, 35.9, 46.3, 124.7, 125.9, 126.6, 127.0, 127.8, 128.0, 129.1, 129.2, 129.5, 132.8, 134.9, 136.3, 138.6, 152.6, 181.6, 184.3, 207.4 ppm. MS (ESI–): m/z = 353.2 [M – H]$^-$, 355.2 [M – H]$^-$. HRMS: calcd. for $C_{20}H_{14}ClO_4$ 353.0581; found 353.0595.

2-[1-(4-Chlorophenyl)-3-oxobutyl]-3-hydroxynaphthalene-1,4-dione (3e): Yield: 31.0 mg (87%); yellow solid; m.p. 158–159 °C; [α] = –42.5 (c = 0.10, MeOH). HPLC (Chiralpak AS-H column, hexane/*i*PrOH = 97:3, 1.0 mL/min): t_R = 52.4 (major), 70.6 (minor) min; 91.5%*ee* (>99% after recrystallization). ^{1}H NMR: δ = 2.2 (s, 3 H), 3.3 (dd, J = 18.0, 6.3 Hz, 1 H), 3.7 (dd, J = 17.9, 9.3 Hz, 1 H), 4.9 (dd, J = 8.9, 6.6 Hz, 1 H), 7.2–7.3 (m, 2 H), 7.4–7.5 (m, 2 H), 7.7 (d, J = 7.6 Hz, 1 H), 7.8 (d, J = 7.8 Hz, 1 H), 8.0 (d, J = 7.7 Hz, 1 H), 8.1 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 29.0, 35.5, 45.8, 123.9, 125.9, 126.8, 127.2, 128.7, 129.0, 129.9 (2 C), 131.3 (2 C), 132.8, 134.9, 140.6, 153.0, 181.3, 184.1, 206.9 ppm. MS (ESI–): m/z = 353.2 [M – H]$^-$. HRMS: calcd. for $C_{20}H_{14}ClO_4$ 353.0581; found 353.0593.

2-[1-(2,4-Dichlorophenyl)-3-oxobutyl]-3-hydroxynaphthalene-1,4-dione (3f): Yield: 30.3 mg (78%); yellow solid; m.p. 151–154 °C; [α] = –43.7 (c = 0.10, MeOH). HPLC (Chiralpak OD-H column, hexane/*i*PrOH = 97:3, 1.0 mL/min): t_R = 11.6 (minor), 13.0 (major) min; 96%*ee*. ^{1}H NMR: δ = 2.2 (s, 3 H), 3.3 (dd, J = 17.9, 6.0 Hz, 1 H), 3.8 (dd, J = 17.8, 9.7 Hz, 1 H), 5.0 (dd, J = 9.7, 6.0 Hz, 1 H), 7.2 (t, J = 7.4, 7.4 Hz, 1 H), 7.3 (d, J = 7.5 Hz, 1 H), 7.5 (d, J = 7.6 Hz, 1 H), 7.7 (t, J = 7.6, 7.6 Hz, 1 H), 7.7 (t, J = 7.6, 7.6 Hz, 1 H), 8.0 (d, J = 7.8 Hz, 1 H), 8.1 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 29.6, 34.0, 45.9, 122.6, 126.2, 127.1, 127.6, 129.1, 129.5, 130.3, 132.9, 133.0, 133.1, 134.4, 135.3, 137.7, 153.4, 181.4, 184.1, 206.2 ppm. MS (ESI–): m/z = 387.1 [M – H]$^-$. HRMS: calcd. for $C_{20}H_{13}Cl_2O_4$ 387.0191; found 387.0189.

2-Hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]naphthalene-1,4-dione (3 g): Yield: 31.2 mg (85%); yellow solid; m.p. 172–174 °C; [α] = –46.3 (c = 0.10, MeOH). HPLC (Chiralpak AD-H column, hexane/*i*PrOH = 90:10, 1.0 mL/min): t_R = 92.0 (major), 64.2 (minor) min; 98%*ee*. ^{1}H NMR: δ = 2.2 (s, 3 H), 3.4 (dd, J = 18.1, 6.6 Hz, 1 H), 3.7 (dd, J = 18.4, 8.9 Hz, 1 H), 5.1 (dd, J = 8.2, 7.1 Hz, 1 H), 7.6 (d, J = 8.7 Hz, 2 H), 7.7–7.8 (m, 2 H), 8.0–8.1 (m, 2 H), 8.3 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR: δ = 29.8, 36.2, 45.6, 123.8 (2 C), 124.3, 126.3, 126.4, 127.2, 129.2 (2 C), 133.2, 133.3, 135.3, 146.8, 149.2, 152.9, 181.3, 183.9, 205.7 ppm. MS (ESI–): m/z = 364.1 [M – H]$^-$. HRMS: calcd. for $C_{20}H_{14}NO_6$ 364.0821; found 364.0812.

2-Hydroxy-3-[1-(3-methoxyphenyl)-3-oxobutyl]naphthalene-1,4-dione (3h): Yield: 22.8 mg (65%); yellow solid; m.p. 148–150 °C; [α] = –45.2 (c = 0.10, MeOH). HPLC (Chiralpak OD-H column, hexane/*i*PrOH = 97:3, 1.0 mL/min): t_R = 21.3 (major), 19.9 (minor) min; 95%*ee*. ^{1}H NMR: δ = 2.2 (s, 3 H), 3.2 (dd, J = 17.9, 6.0 Hz, 1 H), 3.7 (dd, J = 18.0, 9.9 Hz, 1 H), 3.8 (s, 3 H), 4.9 (dd, J = 9.7, 6.0 Hz, 1 H), 6.7 (dd, J = 7.9, 2.4 Hz, 1 H), 7.0–7.1 (m, 2 H), 7.2 (t, J = 7.9, 7.9 Hz, 1 H), 7.7 (d, J = 8.7 Hz, 1 H), 7.8 (d, J = 7.6 Hz, 1 H), 8.0 (d, J = 7.5 Hz, 1 H), 8.1 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 29.9, 36.4, 46.3, 55.2, 111.9, 114.3, 120.6, 124.5, 126.0, 127.1, 129.2, 129.5, 132.9,132.9, 135.0, 143.3, 152.7, 159.7, 181.7, 184.2, 207.0 ppm. MS (ESI–): m/z = 349.2 [M – H]$^-$. HRMS: calcd. for $C_{21}H_{17}O_5$ 349.1076; found 349.1061.

2-[1-(Furan-2-yl)-3-oxobutyl]-3-hydroxynaphthalene-1,4-dione (3i): Yield: 20.8 mg (67%); yellow solid; m.p. 131–133 °C; [α] = –27.3 (c = 0.10, MeOH). HPLC (Chiralpak OD-H column, hexane/*i*PrOH = 90:10, 1.0 mL/min): t_R = 25.1 (major), 28.3 (minor) min; 84%*ee*. ^{1}H NMR: δ = 2.2 (s, 3 H), 3.3 (dd, J = 17.8, 6.3 Hz, 1 H), 3.5 (dd, J = 17.8, 8.9 Hz, 1 H), 5.1 (dd, J = 8.8, 6.4 Hz, 1 H), 6.1 (d, J = 3.2 Hz, 1 H), 6.3 (dd, J = 3.1, 1.9 Hz, 1 H), 7.5 (dd, J = 5.7, 3.3 Hz, 1 H), 7.7–7.8 (m, 2 H), 8.1 (d, J = 7.4 Hz, 1 H), 8.2 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 29.8, 30.1, 44.6, 105.8, 110.4, 122.0, 126.2, 126.4, 127.2, 129.3, 133.0, 135.2, 141.3, 153.1, 154.2, 181.5, 183.7, 206.2 ppm. MS (ESI–): m/z = 308.9 [M – H]$^-$. HRMS: calcd. for $C_{18}H_{13}O_5$ 309.0763; found 309.0773.

2-Hydroxy-3-(3-oxocyclopentyl)naphthalene-1,4-dione (3j): Yield: 23.6 mg (92%); yellow solid; m.p. 168–169 °C; [α] = –49.2 (c = 0.10, MeOH). HPLC (Chiralpak AS-H column, hexane/*i*PrOH = 97:3, 1.0 mL/min): t_R = 50.3 (major), 46.7 (minor) min; 92%*ee*. ^{1}H NMR: δ = 2.2–2.6 (m, 5 H), 2.9 (dd, J = 18.3, 10.6 Hz, 1 H), 3.9 (dd, J = 16.9, 8.6 Hz, 1 H), 7.7 (t, J = 7.6, 7.6 Hz, 1 H), 7.8 (t, J = 7.6, 7.6 Hz, 1 H), 8.1 (d, J = 7.6 Hz, 1 H), 8.2 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 27.0, 32.0, 38.5, 41.6, 123.9, 126.2, 127.0, 129.2, 132.9, 133.1, 135.2, 153.3, 181.2, 184.3, 218.9 ppm. MS (ESI–): m/z = 255.2 [M – H]$^-$. HRMS: calcd. for $C_{15}H_{11}O_4$ 255.0657; found 255.0666.

2-Hydroxy-3-(3-oxocyclohexyl)naphthalene-1,4-dione (3k): Yield: 25.2 mg (93%); yellow solid; m.p. 181–183 °C; [α] = –59.2 (c = 0.10, MeOH). HPLC (Chiralpak OD-H column, hexane/*i*PrOH = 97:3, 1.0 mL/min): t_R = 13.79 (major), 12.93 (minor) min; 94%*ee*. ^{1}H NMR: δ = 1.6–2.5 (m, 8 H), 3.5 (s, 1 H), 7.7 (dd, J = 13.0, 6.9 Hz, 1 H), 7.9 (t, J = 7.5, 7.5 Hz, 1 H), 8.1 (t, J = 14.5 Hz, 1 H), 8.2 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 19.2, 25.7, 35.1, 39.3, 43.9, 123.3, 126.1, 126.4, 129.0, 133.0, 134.1, 135.2, 155.7, 181.3, 183.0, 210.8 ppm. MS (ESI–): m/z = 269.1 [M – H]$^-$. HRMS: calcd. for $C_{16}H_{13}O_4$ 269.0814; found 269.0814.

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

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 20772110).

[1] a) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; b) A. Berkessel, H. Greger. *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**.

[2] For reviews of asymmetric reactions catalyzed by secondary amines, see: a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.

[3] For reviews of asymmetric reactions catalyzed by primary amines, see: a) L. W. Xu, J. Luo, Y. X. Lu, *Chem. Commun.* **2009**, 1807–1821; b) F. Z. Peng, Z. H. Shao, *J. Mol. Catal. A* **2008**, *285*, 1–13; c) Y. C. Chen, *Synlett* **2008**, *13*, 1919–1930; for selected examples, see: d) C. Liu, Y. X. Lu, *Org. Lett.* **2010**, *12*, 2278–2281; e) L. Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7332–7335; *Angew. Chem. Int. Ed.* **2009**, *48*, 7196–7199; f) L. T. Dong, R. J. Lu, Q. S. Du, J. M. Zhang, S. P. Liu, Y. N. Xuan, M. Yan, *Tetrahedron* **2009**, *65*, 4124–4129; g) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem.* **2008**, *120*, 7768–7771; *Angew. Chem. Int. Ed.* **2008**, *47*, 7656–7658; h) F. Xue, S. L. Zhang, W. H. Duan, W. Wang, *Adv. Synth. Catal.* **2008**, *350*, 2194–2198; i) S. H. Luo, H. Xu, L. Zhang, J. Y. Li, J. P. Cheng, *Org. Lett.* **2008**, *10*, 653–656.

[4] For reviews of Michael additions, see: a) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, *2*, 171–196; b) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061; for selected examples, see: c) P. F. Li, S. G. Wen, F. Yu, Q. X. Liu, W. J. Li, Y. C. Wang, X. M. Liang, J. X. Ye, *Org. Lett.* **2009**, *11*, 753–756; d) H. W. Moon, M. J. Cho, D. Y. Kim, *Tetrahedron Lett.* **2009**, *50*, 4896–4898; e) M. Rueping, E. Merino, E. Sugiono, *Adv. Synth. Catal.* **2008**, *350*, 2127–2131; f) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600; g) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105–5107; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955–4957.

[5] For selected examples, see: a) M. Glänzel, R. Bültmann, K. Starke, A. W. Frahm, *Eur. J. Med. Chem.* **2005**, *40*, 1262–1276; b) V. K. Tandon, D. B. Yadav, R. V. Singh, A. K. Chaturvedi, P. K. Shukla, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5324–5328; c) V. F. de Andrade-Neto, M. O. F. Goulart, J. F. da. S. Filho, M. J. da Silva, M. do. C. F. R. Pinto, A. V. Pinto, M. G. Zalis, L. H. Carvalhoa, A. U. Krettlia, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1145–1149; d) E. P. Sacau, A. Estévez-Braun, Á. G. Ravelo, E. A. Ferro, H. Tokuda, T. Mukainaka, H. Nishino, *Bioorg. Med. Chem.* **2003**, *11*, 483–488.

[6] C. Salas, R. A. Tapia, K. Ciudad, V. Armstrong, M. Orellana, U. Kemmerling, J. Ferreira, J. D. Mayab, A. Morello, *Bioorg. Med. Chem.* **2008**, *16*, 668–674.

[7] a) P. Wei, X. H. Zhang, S. J. Tu, S. Yan, H. J. Ying, P. K. Ouyang, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 828–830; b) Y. Z. Li, X. G. Sun, J. T. Lamont, A. B. Pardee, C. J. Li, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 2674–2678.

[8] a) Y. F. Wang, W. Zhang, S. P. Luo, G. C. Zhang, A. B. Xia, X. S. Xu, D. Q. Xu, *Eur. J. Org. Chem.* **2010**, 4981–4985; b) M. Rueping, E. Sugiono, E. Merino, *Angew. Chem.* **2008**, *120*, 3089–3092; *Angew. Chem. Int. Ed.* **2008**, *47*, 3046–3049; c) W. M. Zhou, H. Liu, D. M. Du, *Org. Lett.* **2008**, *10*, 2817–2820.

[9] For recent examples of the use of this technique to assign the absolute configurations of organic molecules, see: a) S. Abbate, L. F. Burgi, E. Castiglioni, F. Lebon, G. Longhi, E. Toscano, S. Caccamese, *Chirality* **2009**, *21*, 436–441; b) D. Casarini, L. Lunazzi, M. Mancinelli, A. Mazzanti, P. Scafato, *Chirality* **2009**, *21*, 16–23; c) P. L. Polavarapu, N. Jeirath, S. WalIb, *J. Phys. Chem. A* **2009**, *113*, 5423–5431; d) L. Lunazzi, M. Mancinelli, A. Mazzanti, *J. Org. Chem.* **2009**, *74*, 1345–1348; e) M. Humam, P. Christen, O. Muz, K. Hostettmann, D. Jeannerat, *Chirality* **2008**, *20*, 20–25; f) P. J. Stephens, J. J. Pan, F. J. Devlin, M. Urbanová, O. Julínek, J. Hájícek, *Chirality* **2008**, *20*, 454–470; g) T. Grkovic, Y. Ding, X. C. Li, V. L. Webb, D. Ferreira, B. R. Copp, *J. Org. Chem.* **2008**, *73*, 9133–9136; h) J. Haesler, I. Schindelholz, E. Riguet, C. G. Bochet, W. Hug, *Nature* **2007**, *446*, 526–529.

[10] For a review, see: L. S. Santos, *Eur. J. Org. Chem.* **2008**, 235–253. For recent applications in organocatalysis, see: a) W. Schrader, P. P. Handayani, J. Zhou, B. List, *Angew. Chem.* **2009**, *121*, 1491–1494; *Angew. Chem. Int. Ed.* **2009**, *48*, 1463–1466; b) W. Schrader, P. P. Handayani, C. Burstein, F. Glorius, *Chem. Commun.* **2007**, 716–718.

Received: November 22, 2010
Published Online: March 1, 2011

