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Enantioselective Epoxidation of 2,3-Disubstituted Naphthoquinones by a Side Chain Truncated Guanidine–Urea Bifunctional Organocatalyst

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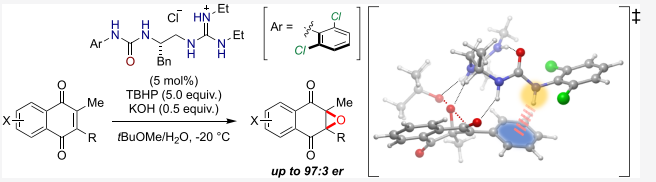
ABSTRACT: An organocatalytic enantioselective epoxidation of 2,3-disubstituted naphthoquinones with *tert*-butyl hydroperoxide as an oxidant was developed using a guanidine–urea bifunctional catalyst lacking C_2 symmetry, which was designed based upon the insights obtained from the DFT calculation model for our previous C_2 symmetric catalyst. The present organocatalytic reaction provides access to a variety of optically active naphthoquinone epoxides bearing aryl and methyl substituents at C2 and C3 in high yields with high enantioselectivities (up to 97:3 er).



INTRODUCTION

Naphthoquinone epoxide is a common structure in diverse natural products, such as phosphatoquinone (**1**), A80915G (**2**), and diospyrin derivative **3** (Figure 1).[1,2] A promising

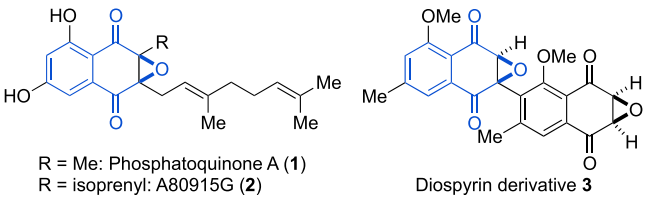


Figure 1. Structures of representative bioactive naphthoquinone epoxides.

approach for the synthesis of the common motif in **1**–**3** (colored blue) would be nucleophilic epoxidation of the corresponding naphthoquinone precursors. So far, various enantioselective epoxidation strategies have been reported, using combinations of oxidants and metal catalysts and/or organocatalysts.[3−6] Asymmetric epoxidation with monosubstituted naphthoquinones has been well explored, but so far, there have been no examples of epoxidation with disubstituted naphthoquinones,[4−6] probably because of the difficulty in differentiating two substituents at highly symmetrical positions in the context of the planar naphthoquinone motif.

Recently, we have reported an enantioselective epoxidation of monosubstituted naphthoquinone **5** by using *tert*-butyl peroxide (TBHP) as an oxidant in the presence of guanidine–bisurea bifunctional organocatalyst **4**.[7,8] Under biphasic conditions (*t*BuOMe/H_2O = 10:1) at 0 °C, the corresponding epoxide **6** was obtained in a 98% yield with a 95:5 er (Figure 2A). Under the same conditions, however, the enantioselectivity decreased to a 87:13 er in the case of disubstituted naphthoquinone **7a** (Figure 2A). In addition, a longer reaction time (8 h) was required to complete the epoxidation. To gain insight into the reason for those differences in reactivity and selectivity of disubstituted naphthoquinone **7a**, transition state (TS) modeling of the epoxidation of **7a** with organocatalyst **4** was conducted at the B3LYP/6-31G* level (Figure 2B, Figure S1).[9,10]

The TS model also suggests that one of the two urea groups in the catalyst has no significant interaction contributing to stabilization of the TS. In addition, the aromatic groups at the chiral center in the urea side chain are orientated in the opposite direction to the reaction pocket for the substrates and should have little impact on the stereocontrol. Those computational insights motivated us to design a more efficient guanidine–urea bifunctional catalyst **9** for the disubstituted naphthoquinone **7a**, in which one urea side chain is truncated, compared with catalyst **4**. Here, we report the first examples of highly enantioselective epoxidation of 2,3-disubstituted naphthoquinones in the presence of catalyst **9** (Figure 2C).

RESULTS AND DISCUSSION

At the outset, we prepared guanidine–urea bifunctional organocatalysts **9a**–**g** by varying the R^1, R^2, and Ar groups,

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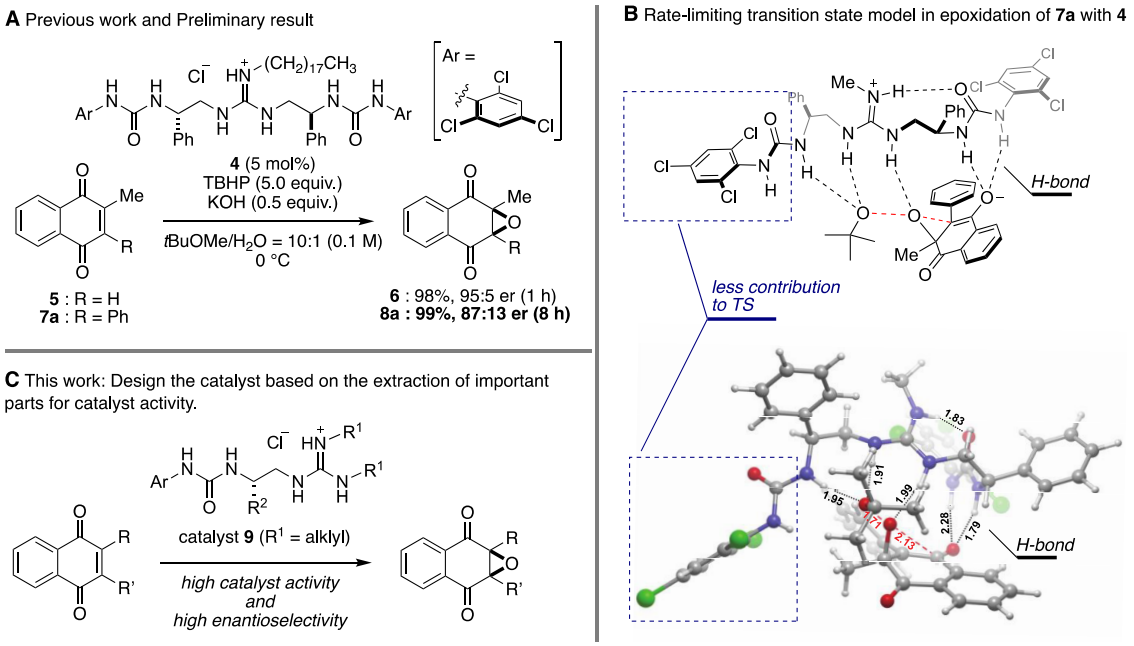
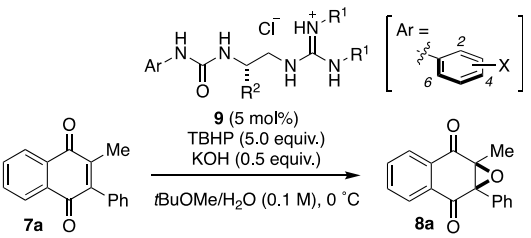


Figure 2. (A) Previous work and preliminary results of asymmetric epoxidation of naphthoquinones **5** and **7a**. (B) Rate-limiting TS model in epoxidation of **7a** with **4**. (C) This work.

and we examined the epoxidation reaction of disubstituted naphthoquinone **7a** bearing a methyl group and a phenyl group under biphasic conditions (*t*BuOMe/H_2O = 10:1) with TBHP as an oxidant and potassium hydroxide in the presence of 5 mol % of catalyst.[11] In all cases, except for **9d** (entry 4), the reactivity of the catalysis was drastically improved compared to the C_2-symmetric catalyst **4**, and epoxide **8a** was obtained in high yields (91−98%) within 2 h (Table 1, entries 1−3, 5−7). In addition, the enantiomeric ratios were improved compared to those obtained with catalyst **4**. Among the catalysts investigated, a high enantiomeric ratio of 94:6 was obtained with **9g**, which has ethyl and benzyl groups on the guanidine, and a 2,6-dichlorophenyl group as the Ar moiety (entry 7). The enantiomeric ratio was improved by lowering the reaction temperature from 0 to −20 °C, and the epoxide **8a** was obtained in a 94% yield with a 97:3 er (entry 8).[12] To demonstrate the practical utility of this reaction, a 5 mmol scale reaction was carried out (entry 9).

The substrate scope of disubstituted naphthoquinones **7** was investigated in the presence of **9g** under the optimized conditions (Table 1, entry 8).[13] The results are summarized in Scheme 1. The electronic nature of the aromatic R group in **7** was not critical, and high enantiomeric ratios of the corresponding epoxides **8b−j** were obtained (93:7 to 97:3 er) with high yields (86−95%). Various substituents (X) at C6 and C7 in **7a** were tolerated, regardless of their electron-donating or withdrawing nature, and the corresponding epoxides **8k−m** were obtained in high yields (87−93%) with high enantioselectivities (92:8 to 95:5 er). Furthermore, the substrate with an *n*-hexyl group at C3 in naphthoquinone was tolerated, and the corresponding epoxide **8p** was obtained in 86% with a 95:5 er. On the other hand, the enantioselectivity was decreased when an alkyl substituent was present at C2, and the epoxides **8n** and **8o** were obtained in 84:16 and 59:41 er, respectively. These results suggest that direct conjugation of the aromatic group at C2 in the substrate is critical for the enantioselective epoxidation in the presence of **9g**.

Table 1. Enantioselective Epoxidation of 2,3-Disubstituted Naphthoquinone 7a in the Presence of Side Chain Truncated Organocatalyst 9[a,b,c,d,e]



	catalyst **9**		time	**8a**	
entry	**9a−g**	R^1, R^2, Ar[a]	(h)	yield (%)[b]	er[c]
1	**9a**	$(CH_2)_{17}CH_3$, Ph, 2,4,6-Cl_3-C_6H_2	2	92	87:13
2	**9b**	Et, Ph, 2,4,6-Cl_3-C_6H_2	1	97	91:9
3	**9c**	Cy, Ph, 2,4,6-Cl_3-C_6H_2	2	97	87:13
4	**9d**	Bn, Ph, 2,4,6-Cl_3-C_6H_2	7	96	89:11
5	**9e**	Et, Bn, 2,4,6-Cl_3-C_6H_2	1	93	93:7
6	**9f**	Et, Me, 2,4,6-Cl_3-C_6H_2	1	98	90.5:9.5
7	**9g**	Et, Bn, 2,6-Cl_2-C_6H_3	1	91	94:6
8[d]	**9g**	Et, Bn, 2,6-Cl_2-C_6H_3	3	94	97:3
9[d,e]	**9g**	Et, Bn, 2,6-Cl_2-C_6H_3	6	93	96.5:3.5

[a]Reactions were performed with 0.1 mmol scale of **7a** in *t*BuOMe/H_2O = 10:1. [b]Yield of the isolated product. [c]The ee value was determined by HPLC analysis using a chiral stationary phase. [d]Reaction was performed at −20 °C. [e]Reactions were performed with 5.0 mmol scale of **7a**.

To elucidate the origin of the high enantiomeric ratio obtained with the guanidine−urea catalyst **9**, the epoxidation reaction was computationally revisited. In the epoxidation catalyzed by **9**, the epoxide-forming step, i.e., cyclization step, is the reaction rate- and stereochemistry-determining step, based upon our preliminary calculation.[7] Thus, we explored two diastereomeric TS structures for the cyclization step (*Si*-

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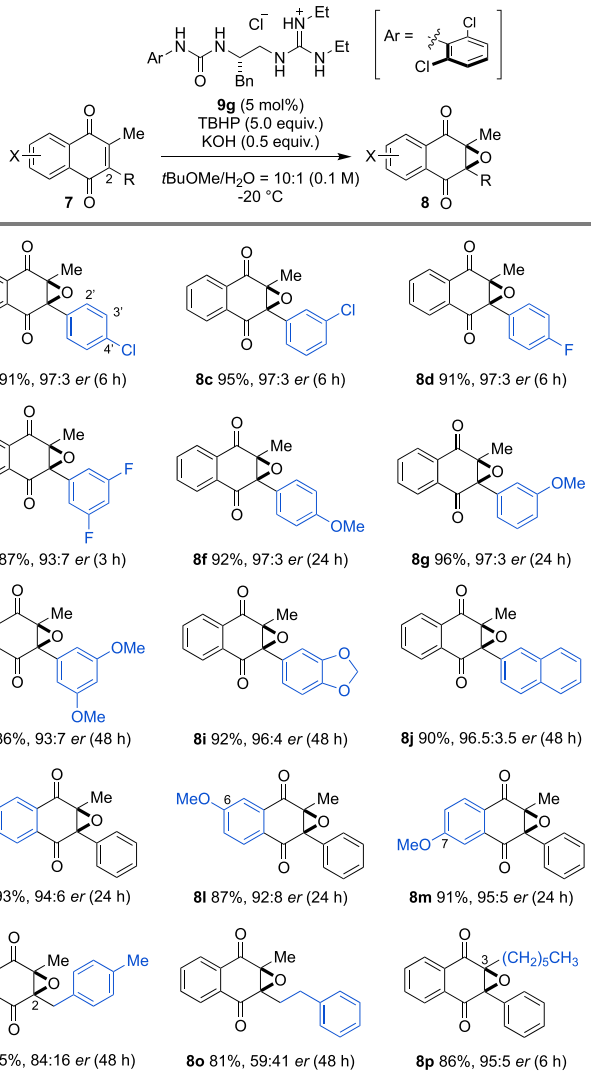
Scheme 1. Substrate Scope of the Enantioselective Epoxidation of Disubstituted Naphthoquinones 7 in the Presence of Catalyst 9g



face (TS_{major}) and *Re*-face (TS_{minor}) modes leading to the major and minor enantiomers of **8a**, respectively) at the B3LYP/6-31G* level in the presence of a simplified catalyst model of **9**. To estimate dispersion interactions, single-point energy calculations of the B3LYP-optimized structures were conducted at the M06-2X/6−311 + G** level. TS_{major} is 2.2 kcal/mol more stable than TS_{minor}, which is consistent with the experimental results. In both TS_{major} and TS_{minor}, the intramolecular hydrogen bond between the NH group of the guanidinium moiety and the carbonyl group of urea constructs the U-shaped catalyst structure. As in the case of the C_2-symmetric catalyst **4**, there are two sets of attractive interactions between the catalyst and the substrates: guanidinium/oxidant and urea/naphthoquinone (Figure 3). An NCI (noncovalent bond interaction)[14] plot indicates that the interacting modes with the naphthoquinone enolate derived from **7a** are significantly different between TS_{major} and TS_{minor} (Figure 4). In the case of TS_{major}, two NH groups in the urea form a hydrogen bond with the enolate and NH−π interaction with the aromatic substituent at C2 in the naphthoquinone, respectively. On the other hand, in the case of TS_{minor}, a two-point hydrogen bonding interaction is formed

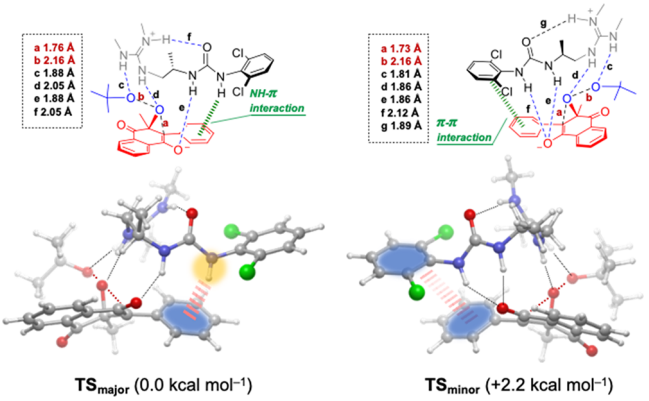


Figure 3. Three-dimensional (3D) structures and relative energies of TS_{major} and TS_{minor} in the reaction with **7a** (M06-2X/6−311 + G**//B3LYP/6-31G*).

between the two NH groups in the urea and the oxygen atom in the enolate. In addition, there is a $\pi-\pi$ interaction between the aromatic group in the catalyst and the aromatic substituents in **7a**.

The difference in the attractive interaction between TS_{major} and TS_{minor} significantly affects the relative stability of the TS models. The NH−π interaction plays one of key roles in stabilizing TS_{major}. If the phenyl substituent at C2 in **7a** is replaced with hydrogen, the relative energy difference between TS_{major} and TS_{minor} decreases to only 0.3 kcal/mol from 2.2 kcal/mol. Indeed, the interaction energy between the catalyst and the substrates decreases more significantly in TS_{major} (3.2 kcal/mol) than in TS_{minor} (1.0 kcal/mol) (see the Supporting Information Figure S2).[14,15] This calculation results also support the low enantioselectivity of the substrates (**8n** and **8o**) with C2-alkyl substituents, which may shift the Ar group from the interacting network with the catalyst **9g**.

To confirm the contribution of the NH−π interactions experimentally, we next examined the epoxidation reaction of monosubstituted naphthoquinone **5** in the presence of guanidine−mono-urea bifunctional catalyst **9g** under the optimized conditions (Scheme 2). In this reaction, epoxide **6** was obtained in an 89% yield with an 88:12 er; i.e., the selectivity was reduced compared to the reaction with catalyst **4** (95:5 er, Figure 2A). This provides experimental support for the significance of the NH−π interaction in the asymmetric epoxidation of disubstituted naphthoquinone **7**.

In conclusion, we have achieved highly enantioselective epoxidation of 2,3-disubstituted naphthoquinones with *tert*-butyl hydroperoxide as an oxidant by using a bifunctional guanidine−urea lacking C_2 symmetry. This catalyst was designed based upon the insights obtained from the DFT calculation model for epoxidation between 2,3-disubstituted naphthoquinone and our previous C_2 symmetric catalyst. Computational studies indicated that the enantiodiscrimination in this reaction depends crucially upon stabilization of the transition state by NH−π interaction between the urea moiety in the catalyst and the aromatic substituent in naphthoquinone.

EXPERIMENTAL SECTION

General Information. Flash chromatography and preparative-TLC (PLC) were performed using a Silica Gel 60 (spherical, particle size 0.040−0.100 mm; Kanto Chemical Co., Inc., Japan), Chromatorex-NH DM1020 (spherical, particle size 0.007−0.100 mm; Fuji Silysia Chemical Ltd., Japan), and Chromatorex-NH PLC

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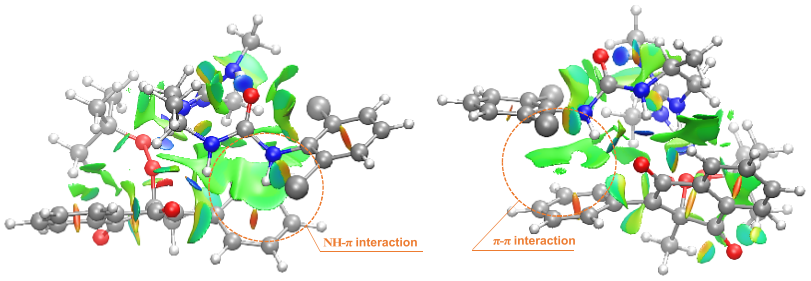
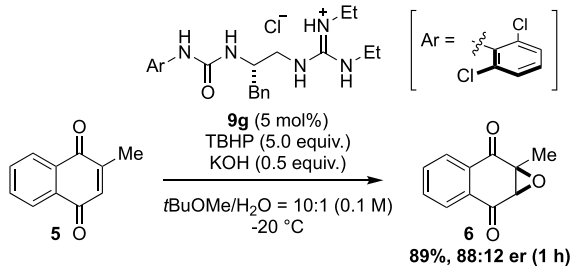


Figure 4. NCI plots of (a) TS_{major} and (b) TS_{minor}. Gradient surfaces correspond to s = 0.25 au and a color scale of $-0.05 < \rho < 0.05$ au (blue, strongly attractive; green, weakly attractive; red, strongly repulsive).

Scheme 2. Asymmetric Epoxidation of Monosubstituted Naphthoquinone 5 in the Presence of Catalyst 9g



05 (0.5 mm; Fuji Silysia Chemical Ltd., Japan). Optical rotations were measured on a JASCO P-2200 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on JEOL ECX-300 instruments. A chemical shift in chloroform-*d* was reported in the scale relative to chloroform-*d* (7.26 ppm) ^{1}H NMR. For ^{13}C NMR, a chemical shift was reported in the scale relative to chloroform-*d* (77.0 ppm) as an internal reference. Mass spectra were recorded on a JEOL JMS-700 spectrometer. HPLC analysis on the chiral stationary phase was performed on JASCO 800-series instruments. Daicel Chiralpak IA, IB, and Chiralcel OD−H columns with *n*-hexane/2-propanol and *n*-hexane/$CHCl_3$ as the eluent were used. X-ray data was obtained from the X-ray single crystal structure analysis system "R-AXIS RAPID" (Rigaku Co.).

Synthesis of 2,3-Disubstituted 1,4-Naphthoquinone Derivatives. 2-Methyl-3-(4-methylbenzyl)-1,4-naphthoquinone (**7n**) and 2-methyl-3-phenethyl-1,4-naphthoquinone (**7o**) was prepared according to literature procedures.[16,17] 2-Methyl-3-aryl-1,4-naphthoquinone derivatives (**7a,d−j**) were prepared according to Method A, and (**7b,c**) were prepared according to Method B. Six or 7-substituted 2-methyl-3-phenyl-1,4-naphthoquinone derivatives (**7k−m**) were prepared according to Method C.

Method A. To a mixture of 3-methyl-4*H*-spiro[naphthalene-1,2′-[1,3]dioxolan]-4-one[18] (1.40 g, 6.47 mmol) and CuI (123 mg, 0.65 mmol) in THF (55 mL) was added dropwise ArMgBr (1.0 M) in THF (9.75 mL, 9.75 mmol) over 30 min at rt, and the resulting mixture was stirred at reflux. After stirred for 3 h, the reaction mixture was quenched by addition of saturated NH_4Cl solution at rt and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and then concentrated *in vacuo*. The residue was used in the subsequent step without purification.

To a solution of the crude residue in 1,4-dioxane (10 mL) was added dropwise HCl (6.0 M) in H_2O (10 mL, 60.0 mmol) over 10 min at rt, and the resulting mixture was vigorously stirred. After stirred for 1.5 h, the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and then concentrated *in vacuo*. The residue was used in the subsequent step without purification.

To a solution of the crude residue in acetonitrile (30 mL) was added DDQ (749 mg, 3.30 mmol) at rt, and the resulting mixture was stirred. After stirred for 10 min, the reaction was quenched with saturated $NaHCO_3$ solution and the mixture was extracted with ethyl acetate, and the organic layer was washed with saturated $NaHCO_3$ solution and brine. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1) to give **7a** (721 mg, 46%, three steps) as a yellow solid.

*2-Methyl-3-phenylnaphthalene-1,4-dione (**7a**).* ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.20−8.06 (m, 2H), 7.80−7.70 (m, 2H), 7.51−7.38 (m, 3H), 7.27−7.20 (m, 2H), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$ δ): 185.8, 184.2, 146.2, 144.1, 133.7, 133.5, 132.1, 129.3, 128.5, 128.1, 126.6, 126.2, 14.7; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{13}O_2$, 248.0837; found, 248.0837.

Method B. To a solution of 2-methylnaphthalene-1,4-dione (2.00 g, 11.62 mmol) and 4-chlorobenzoic acid (3.63 g, 23.18 mmol) in acetonitrile/H_2O (3:1, 76 mL) was added $AgNO_3$ (380 mg, 2.32 mmol) at 85 °C (oil bath). After stirred for 10 min, $(NH_4)_2S_2O_8$ (3.97 g, 17.40 mmol) in acetonitrile/H_2O (3:1, 40 mL) was added dropwise over 20 min, and the resulting mixture was stirred at reflux. After stirred for 2 h, the reaction mixture was cooled to rt and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (toluene only) to give **7b** (189 mg, 21%) as a yellow solid.

*2-(4-Chlorophenyl)-3-methylnaphthalene-1,4-dione (**7b**).* ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.18−8.06 (m, 2H), 7.79−7.70 (m, 2H), 7.48−7.41 (m, 2H), 7.22−7.14 (m, 2H), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$ δ): 185.5, 183.9, 145.0, 144.4, 134.6, 133.8, 133.7, 132.0, 131.9, 131.9, 130.8, 128.5, 126.6, 126.3, 14.7; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{11}ClO_2$, 282.0448; found 282.0451.

Method C. To a solution of 7-chloro-2-methylnaphthalene-1,4-dione[7] (100 mg, 0.45 mmol) and benzoic acid (220 mg, 1.80 mmol) in acetonitrile/H_2O (3:1, 5.0 mL) was added $AgNO_3$ (7.6 mg, 0.045 mmol) at 85 °C. After stirred for 10 min, $(NH_4)_2S_2O_8$ (255 mg, 1.12 mmol) in acetonitrile/H_2O (3:1, 4.0 mL) was added dropwise over 5 min, and the resulting mixture was stirred at reflux. After stirred for 16 h, the reaction mixture was cooled to rt and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (toluene only) to give **7k** (36 mg, 27%) as a yellow solid.

*6-Chloro-3-methyl-2-phenylnaphthalene-1,4-dione (**7k**).* ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.14−8.01 (m, 2H), 7.69 (dd, J = 8.3, 2.1 Hz, 1H), 7.51−7.41 (m, 3H), 7.27−7.20 (m, 2H), 2.12−2.05 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$ δ): 184.7, 183.2, 146.3, 144.1, 140.5, 133.7, 133.2, 130.3, 129.3, 128.7, 128.4, 128.2, 126.2, 14.7; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{11}ClO_2$, 282.0448; found 282.0447.

*2-(3-Chlorophenyl)-3-methylnaphthalene-1,4-dione (**7c**).* Following the procedure (Method B), **7c** was obtained (207 mg, 23%) as a yellow solid from 2-methylnaphthalene-1,4-dione (2.00 g, 11.62 mmol) and 3-chlorobenzoic acid (3.63 g, 23.18 mmol); ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.22−8.03 (m, 2H), 7.83−7.65 (m, 2H), 7.49−7.34 (m, 2H), 7.23 (s, 1H), 7.16−7.07 (m, 1H), 2.09 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$ δ): 185.4, 183.8, 134.1, 133.8, 133.7, 131.9, 131.9, 129.5, 129.3, 128.7, 127.5, 126.6, 126.3, 14.7; HRMS

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(EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{11}ClO_2$, 282.0448; found 282.0443.

*2-(4-Fluorophenyl)-3-methylnaphthalene-1,4-dione (**7d**).* Following the procedure (Method A), **7d** was obtained (654 mg, 38%, 3steps) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.26−7.99 (m, 2H), 7.82−7.69 (m, 2H), 7.30−7.11 (m, 4H), 2.10 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.6, 184.1, 164.3, 161.1, 145.1, 144.4, 133.8 (d, J = 7.2 Hz), 132.0 (d, J = 7.2 Hz), 131.3 (d, J = 8.7 Hz), 129.3 (d, J = 2.9 Hz), 126.4 (d, J = 26.0 Hz), 115.3 (d, J = 21.7 Hz), 14.7; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{11}FO_2$, 266.0743; found 266.0739.

*2-(3,5-Difluorophenyl)-3-methylnaphthalene-1,4-dione (**7e**).* Following the procedure (Method A), **7e** was obtained (552 mg, 30%, 3steps) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.21−7.96 (m, 2H), 7.83−7.72 (m, 2H), 6.89 (tt, J = 8.9, 2.3 Hz, 1H), 6.83−6.72 (m, 2H), 2.09 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.1, 183.4, 164.4 (d, J = 13.0 Hz), 161.1 (d, J = 12.3 Hz), 144.9, 144.1, 136.6 (t, J = 10.1 Hz), 133.9 (d, J = 7.2 Hz), 131.9 (d, J = 10.8 Hz), 126.5 (d, J = 18.1 Hz), 112.5 (q, J = 8.7 Hz), 104.1 (t, J = 24.9 Hz), 14.6; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{10}F_2O_2$, 284.0649; found 284.0643.

*2-(4-Methoxyphenyl)-3-methylnaphthalene-1,4-dione (**7f**).* Following the procedure (Method A), **7f** was obtained (756 mg, 42%, 3steps) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.18−8.05 (m, 2H), 7.78−7.68 (m, 2H), 7.19 (dt, J = 9.1, 2.4 Hz, 2H), 6.99 (dt, J = 9.1, 2.4 Hz, 2H), 3.89 (s, 3H), 2.12 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.8, 184.4, 159.7, 145.7, 143.8, 133.6, 133.6, 132.1, 131.0, 126.6, 126.1, 125.6, 113.6, 55.3, 14.8; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{14}O_3$, 278.0943; found 278.0937.

*2-(3-Methoxyphenyl)-3-methylnaphthalene-1,4-dione (**7g**).* Following the procedure (Method A), **7g** was obtained (720 mg, 40%, 3steps) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.22−8.01 (m, 2H), 7.82−7.69 (m, 2H), 7.49−7.29 (m, 1H), 6.96 (dd, J = 8.3, 2.4 Hz, 1H), 6.88−6.69 (m, 2H), 3.86 (s, 3H), 2.11 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.7, 184.0, 159.3, 146.1, 144.2, 134.9, 133.7, 133.5, 132.0, 129.3, 126.5, 126.2, 121.5, 114.9, 113.9, 55.2, 14.6; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{14}O_3$, 278.0943; found 278.0948.

*2-(3,5-Dimethoxyphenyl)-3-methylnaphthalene-1,4-dione (**7h**).* Following the procedure (Method A), **7h** was obtained (419 mg, 21%, 3steps) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.18−8.08 (m, 2H), 7.79−7.71 (m, 2H), 6.52 (t, J = 2.2 Hz, 1H), 6.34 (d, J = 2.4 Hz, 2H), 3.81 (s, 6H), 2.09 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.7, 184.0, 160.6, 146.3, 144.3, 135.6, 133.7, 133.5, 132.1, 126.6, 126.2, 107.2, 100.4, 55.4, 14.6; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{19}H_{16}O_4$, 308.1049; found 308.1057.

*2-(Benzo[d][1,3]dioxol-5-yl)-3-methylnaphthalene-1,4-dione (**7i**).* Following the procedure (Method A), **7i** was obtained (567 mg, 30%, 3steps) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.20−8.03 (m, 2H), 7.78−7.67 (m, 2H), 6.98−6.79 (m, 1H), 6.79−6.59 (m, 2H), 6.01 (s, 2H), 2.12 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.7, 184.2, 147.8, 147.5, 145.8, 144.2, 133.6, 133.5, 132.1, 127.0, 126.6, 126.2, 123.3, 110.0, 108.2, 101.3, 29.7, 14.7; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{12}O_4$, 292.0736; found 292.0737.

*3-Methyl-[2,2′-Binaphthalene]-1,4-Dione (**7j**).* Following the procedure (Method A), **7j** was obtained (753 mg, 39%, 3steps) as a yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.24−8.10 (m, 2H), 8.00−7.81 (m, 3H), 7.81−7.68 (m, 3H), 7.62−7.48 (m, 2H), 7.34 (dd, J = 8.4, 1.5 Hz, 1H), 2.16 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.9, 184.4, 146.3, 144.6, 133.8, 133.7, 133.2, 133.0, 132.3, 132.2, 131.3, 129.0, 128.4, 127.9, 127.8, 127.1, 126.8, 126.7, 126.5, 126.4, 14.9; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{14}O_2$, 298.0994; found 298.0984.

*6-Methoxy-3-methyl-2-phenylnaphthalene-1,4-dione (**7l**).* Following the procedure (Method C), **7l** was obtained (45 mg, 36%) as a yellow oil from 7-methoxy-2-methylnaphthalene-1,4-dione (91 mg, 0.45 mmol); ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.06 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.52−7.37 (m, 3H), 7.27−7.18 (m, 3H), 3.96 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.9, 183.3, 163.8, 146.2, 143.6, 134.0, 133.7, 129.3, 129.0, 128.4, 128.0, 125.6, 120.3, 109.3, 55.9, 14.6; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{14}O_3$, 278.0943; found 278.0937.

*7-Methoxy-3-methyl-2-phenylnaphthalene-1,4-dione (**7m**).* Following the procedure (Method C), **7m** was obtained (43 mg, 34%) as a yellow oil from 6-methoxy-2-methylnaphthalene-1,4-dione (91 mg, 0.45 mmol); ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.10 (d, J = 8.6 Hz, 1H), 7.54 (d, J = 2.8 Hz, 1H), 7.51−7.38 (m, 3H), 7.27−7.18 (m, 3H), 3.93 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 184.8, 184.2, 163.9, 145.8, 144.4, 134.1, 133.7, 129.3, 128.7, 128.4, 128.1, 125.7, 120.1, 109.8, 55.9, 14.7; HRMS (EI-TOF) m/z: $[M]^+$calcd for $C_{18}H_{14}O_3$, 278.0943; found 278.0937.

Synthesis of 2-Hexyl-3-phenylnaphthalene-1,4-dione (7p). To a solution of 2-phenylnaphthalene-1,4-dione (105 mg, 0.45 mmol) and heptanoic acid (234 mg, 1.80 mmol) in acetonitrile/H_2O (3:1, 5.0 mL) was added $AgNO_3$ (7.6 mg, 0.045 mmol) at 85 °C (oil bath). After stirred for 10 min, $(NH_4)_2S_2O_8$ (255 mg, 1.12 mmol) in acetonitrile/H_2O (3:1, 4.0 mL) was added dropwise over 5 min, and the resulting mixture was stirred at reflux. After stirred for 16 h, the reaction mixture was cooled to rt and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (toluene only) to give **7p** (69 mg, 48%) as a yellow oil.

*2-Hexyl-3-phenylnaphthalene-1,4-dione (**7p**).* ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.21−8.03 (m, 2H), 7.84−7.66 (m, 2H), 7.58−7.36 (m, 3H), 7.32−7.16 (m, 2H), 2.58−2.35 (m, 2H), 1.56−1.36 (m, 2H), 1.36−1.06 (m, 6H), 0.82 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 185.4, 184.6, 148.3, 146.2, 133.6, 133.5, 133.4, 132.2, 132.0, 128.9, 128.3, 128.1, 126.4, 126.2, 31.2, 29.5, 29.4, 28.1, 22.3, 13.9; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{22}O_2$, 318.1620; found 318.1630.

General Procedure for the Asymmetric Epoxidation. To a solution of **7a** (24.8 mg, 0.100 mmol) and **9g** (2.5 mg, 0.005 mmol) in methyl *tert*-butyl ether (1.0 mL) was added a 1.0 M KOH solution (50.0 μL, 0.050 mmol) and *tert*-butyl hydroperoxide (7.5 M) in H_2O (66.0 μL, 0.500 mmol) at −20 °C. After stirring for 3 h, the reaction mixture was quenched by addition of saturated NH_4Cl solution at −20 °C and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1 to 10:1) to give epoxide **8a** (25.2 mg, 94%) as a colorless oil.

*(1aS,7aR)-1a-Methyl-7a-phenyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8a**).* $[\alpha]_D^{25}$ + 77.6 (*c* 1.2, $CHCl_3$, er = 97:3); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, τ_1 (major) = 8.6, τ_2 (minor) = 9.9; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.05−7.98 (m, 2H), 7.79−7.72 (m, 2H), 7.48−7.42 (m, 3H), 7.42−7.35 (m, 2H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.5, 191.6, 134.4, 134.3, 132.4, 132.0, 130.1, 129.0, 128.3, 128.0, 127.3, 127.1, 69.2, 66.9, 12.3; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{12}O_3$, 264.0786; found 264.0794.

*(1aR,7aS)-1a-(4-Chlorophenyl)-7a-methyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8b**).* Following the general procedure, **8b** (27.2 mg, 91%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 62.5 (*c* 1.0, $CHCl_3$, er = 97:3); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, τ_1 (major) = 16.3, τ_2 (minor) = 18.7; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.06−7.96 (m, 2H), 7.82−7.72 (m, 2H), 7.44 (d, J = 8.9 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 1.40 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.1, 191.3, 135.1, 134.5, 134.3, 132.2, 131.9, 129.5, 128.6, 127.3, 127.2, 68.8, 66.9, 12.3; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{11}ClO_3$, 298.0397; found 298.0400.

*(1aR,7aS)-1a-(3-Chlorophenyl)-7a-methyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8c**).* Following the general procedure, **8c** (28.2 mg, 95%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 48.9 (*c* 2.1, $CHCl_3$, er = 97:3); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, τ_1 (major) = 17.8, τ_2 (minor) = 20.9; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.08−7.98 (m, 2H), 7.83−7.73 (m, 2H), 7.47−7.36 (m, 3H), 7.27 (s, 1H), 1.41 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 191.9, 191.1, 134.6, 134.4, 132.2, 132.2, 131.9, 129.6, 129.3, 127.4, 127.2, 68.6, 66.9, 12.3;

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HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{11}ClO_3$, 298.0397; found 298.0400.

*(1aR,7aS)-1a-(4-Fluorophenyl)-7a-methyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8d**).* Following the general procedure, **8d** (25.7 mg, 91%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 68.4 (*c* 2.0, $CHCl_3$, er = 97:3); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, τ_1 (major) = 14.5, τ_2 (minor) = 18.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06−7.96 (m, 2H), 7.80−7.71 (m, 2H), 7.42−7.33 (m, 2H), 7.19−7.10 (m, 2H), 1.38 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.2, 191.5, 164.7, 161.4, 134.4 (d, *J* = 10.1 Hz), 132.1 (d, *J* = 27.5 Hz), 129.9 (d, *J* = 7.9 Hz), 127.2 (d, *J* = 13.0 Hz), 125.9 (d, *J* = 3.6 Hz), 115.5 (d, *J* = 21.7 Hz), 68.8, 66.9, 12.3; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{11}FO_3$, 282.0692; found 282.0701.

*(1aR,7aS)-1a-(3,5-Difluorophenyl)-7a-methyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8e**).* Following the general procedure, **8e** (26.1 mg, 87%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 49.9 (*c* 1.1, $CHCl_3$, er = 93:7); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, τ_1 (major) = 13.1, τ_2 (minor) = 16.6; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.06−7.96 (m, 2H), 7.80−7.71 (m, 2H), 7.42−7.33 (m, 2H), 7.19−7.10 (m, 2H), 1.38 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 191.5, 190.5, 164.5 (d, *J* = 12.3 Hz), 161.2 (d, *J* = 12.3 Hz), 134.6 (d, *J* = 16.6 Hz), 134.0 (t, *J* = 9.4 Hz), 131.9 (d, *J* = 18.8 Hz), 127.4 (d, *J* = 7.2 Hz), 111.5 (d, *J* = 24.6 Hz), 104.8 (t, *J* = 24.9 Hz), 68.4, 66.9, 12.2; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{10}F_2O_3$, 300.0598; found 300.0598.

*(1aR,7aS)-1a-(4-Methoxyphenyl)-7a-methyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8f**).* Following the general procedure, **8f** (27.1 mg, 92%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 32.0 (*c* 1.0, $CHCl_3$, er = 97:3); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, τ_1 (major) = 24.4, τ_2 (minor) = 30.3; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.07−7.97 (m, 2H), 7.80−7.71 (m, 2H), 7.39−7.27 (m, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 1.40 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.7, 192.0, 160.0, 134.3, 134.2, 132.5, 132.0, 129.3, 127.3, 127.0, 121.9, 113.8, 69.1, 67.1, 55.3, 12.3; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{14}O_4$, 294.0892; found 294.0881.

*(1aR,7aS)-1a-(3-Methoxyphenyl)-7a-methyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8g**).* Following the general procedure, **8g** (28.2 mg, 96%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 48.1 (*c* 2.0, $CHCl_3$, er = 97:3); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, τ_1 (major) = 12.2, τ_2 (minor) = 14.8; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.07−7.97 (m, 2H), 7.80−7.71 (m, 2H), 7.39−7.27 (m, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 1.40 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.4, 191.4, 159.5, 134.4, 134.3, 132.4, 131.9, 131.6, 129.4, 127.3, 127.1, 120.4, 114.7, 113.5, 69.2, 66.8, 55.3, 12.3; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{14}O_4$, 294.0892; found 294.0881.

*(1aR,7aS)-1a-(3,5-Dimethoxyphenyl)-7a-methyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8h**).* Following the general procedure, **8h** (27.9 mg, 86%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 59.3 (*c* 1.1, $CHCl_3$, er = 93:7); HPLC analysis: Daicel Chiralpak IA, *n*-hexane/$CHCl_3$ = 80:20, flow rate = 1.0 mL/min, τ_1 (major) = 16.6, τ_2 (minor) = 15.7; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.06−7.99 (m, 2H), 7.81−7.72 (m, 2H), 6.49 (s, 3H), 3.81 (s, 6H), 1.44 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.4, 191.3, 160.7, 134.4, 134.3, 132.4, 132.3, 131.8, 127.4, 127.1, 106.1, 101.2, 69.3, 66.8, 55.4, 12.3; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{19}H_{16}O_5$, 324.0998; found 324.1010.

*(1aR,7aS)-1a-(Benzo[d][1,3]dioxol-5-yl)-7a-methyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8i**).* Following the general procedure, **8i** (28.4 mg, 92%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 101.5 (*c* 2.6, $CHCl_3$, er = 96:4); HPLC analysis: Daicel Chiralpak IA, *n*-hexane/$CHCl_3$ = 70:30, flow rate = 1.0 mL/min, τ_1 (major) = 18.4, τ_2 (minor) = 10.2; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.08−7.94 (m, 2H), 7.84−7.65 (m, 2H), 6.93−6.79 (m, 3H), 6.09−5.98 (m, 2H), 1.45 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.4, 191.7, 148.2, 147.7, 134.4, 134.2, 132.4, 132.0, 127.3, 127.1, 123.7, 121.9, 108.6, 108.3, 101.4, 69.2, 67.1, 12.3; HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{12}O_5$, 308.0685; found 308.0692.

*(1aS,7aR)-1a-Methyl-7a-(naphthalen-2-yl)-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8j**).* Following the general procedure, **8j** (28.3 mg, 90%) was obtained as a white solid; $[\alpha]_D^{25}$ + 162.8 (*c* 1.6, $CHCl_3$, er = 96.5:3.5); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, τ_1 (major) = 14.9, τ_2 (minor) = 13.2; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.12−7.98 (m, 2H), 8.00−7.84 (m, 4H), 7.84−7.73 (m, 2H), 7.62−7.41 (m, 3H), 1.43 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.5, 191.7, 134.4, 134.3, 133.5, 132.9, 132.5, 132.1, 128.2, 128.1, 127.8, 127.7, 127.4, 127.2, 126.7, 126.5, 125.2, 69.5, 67.1, 12.3; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{14}O_3$, 314.0943; found 314.0946.

*(1aS,7aR)-4-Chloro-1a-methyl-7a-phenyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8k**).* Following the general procedure, **8k** (27.8 mg, 93%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 64.1 (*c* 1.0, $CHCl_3$, er = 94:6); HPLC analysis: Daicel Chiralpak IB, *n*-hexane/$CHCl_3$ = 90:10, flow rate = 1.0 mL/min, τ_1 (major) = 11.6, τ_2 (minor) = 16.7; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.02−7.94 (m, 2H), 7.70 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.49−7.44 (m, 3H), 7.41−7.34 (m, 2H), 1.40 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 191.5, 190.6, 141.3, 134.3, 133.2, 130.6, 129.8, 129.2, 129.1, 128.4, 128.1, 127.1, 69.3, 67.0, 12.3; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{11}ClO_3$, 298.0397; found 298.0387.

*(1aS,7aR)-4-Methoxy-1a-methyl-7a-phenyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8l**).* Following the general procedure, **8l** (25.6 mg, 87%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 68.9 (*c* 2.0, $CHCl_3$, er = 92:8); HPLC analysis: Daicel Chiralpak IB, *n*-hexane/$CHCl_3$ = 90:10, flow rate = 1.0 mL/min, τ_1 (major) = 20.1, τ_2 (minor) = 11.0; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 7.98 (d, *J* = 8.6 Hz, 1H), 7.50−7.42 (m, 4H), 7.41−7.33 (m, 2H), 7.25−7.18 (m, 1H), 3.94 (s, 3H), 1.38 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.5, 190.3, 164.5, 134.1, 130.5, 129.8, 128.9, 128.3, 128.0, 125.6, 121.2, 110.1, 69.1, 66.7, 55.9, 12.4; HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{14}O_4$, 294.0892; found 294.0890.

*(1aR,7aS)-4-Methoxy-7a-methyl-1a-phenyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8 m**).* Following the general procedure, **8m** (26.8 mg, 91%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 61.6 (*c* 1.0, $CHCl_3$, er = 95:5); HPLC analysis: Daicel Chiralpak IA, *n*-hexane/$CHCl_3$ = 90:10, flow rate = 1.0 mL/min, τ_1 (major) = 9.3, τ_2 (minor) = 11.9; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.01 (d, *J* = 8.6 Hz, 1H), 7.48−7.42 (m, 4H), 7.41−7.33 (m, 2H), 7.24 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.92 (s, 3H), 1.37 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 191.6, 191.1, 164.4, 134.5, 130.4, 129.6, 128.9, 128.3, 128.0, 125.2, 121.3, 110.4, 69.2, 66.7, 55.9, 12.4; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{14}O_4$, 294.0892; found 294.0881.

*(1aS,7aR)-1a-Methyl-7a-(4-methylbenzyl)-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8n**).* Following the general procedure, **8n** (27.8 mg, 95%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 9.2 (*c* 5.3, $CHCl_3$, er = 84:16); HPLC analysis: Daicel Chiralcel OD−H, *n*-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, τ_1 (major) = 10.7, τ_2 (minor) = 14.0; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.04−7.92 (m, 2H), 7.77−7.67 (m, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 3.74 (d, *J* = 14.8 Hz, 1H), 3.18 (d, *J* = 15.1 Hz, 1H), 2.30 (s, 3H), 1.83 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.8, 191.9, 136.3, 134.2, 134.2, 132.4, 132.1, 131.8, 129.2, 129.1, 127.2, 127.0, 67.6, 65.7, 31.4, 21.0, 12.6; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{19}H_{16}O_3$, 292.1099; found 292.1093.

*(1aS,7aR)-1a-Methyl-7a-phenethyl-1a,7a-dihydronaphtho[2,3-b]oxirene-2,7-dione (**8o**).* Following the general procedure, **8o** (23.7 mg, 81%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 12.7 (*c* 6.0, $CHCl_3$, er = 59:41); HPLC analysis: Daicel Chiralpak IA, *n*-hexane/$CHCl_3$ = 95:5, flow rate = 1.0 mL/min, τ_1 (major) = 18.1, τ_2 (minor) = 8.9; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.06−7.94 (m, 2H), 7.80−7.70 (m, 2H), 7.37−7.18 (m, 5H), 2.99−2.79 (m, 2H), 2.72−2.58 (m, 1H), 2.23−2.08 (m, 1H), 1.63 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.9, 192.4, 140.9, 134.2, 134.2, 132.1, 131.9, 128.6, 128.4, 127.0, 126.3, 67.1, 65.5, 31.5, 28.4, 11.8; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{19}H_{16}O_3$, 292.1099; found 292.1093.

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*(1aS,7aR)-1a-Hexyl-7a-phenyl-1a,7a-dihydronaphtho[2,3-b]-oxirene-2,7-dione (**8p**).* Following the general procedure, **8p** (28.8 mg, 86%) was obtained as a colorless oil; $[\alpha]_D^{25}$ + 107.9 (*c* 2.2, $CHCl_3$, er = 95:5); HPLC analysis: Daicel Chiralcel AD-H, *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, τ_1 (major) = 10.6, τ_2 (minor) = 7.5; ^{1}H NMR (300 MHz, $CDCl_3$ δ): 8.13−7.95 (m, 2H), 7.84−7.67 (m, 2H), 7.54−7.34 (m, 5H), 1.82−1.67 (m, 1H), 1.67−1.54 (m, 2H), 1.54−1.39 (m, 1H), 1.39−1.24 (m, 1H), 1.24−1.01 (m, 5H), 0.80 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$ δ): 192.1, 191.7, 134.3, 134.2, 132.4, 132.3, 129.9, 128.9, 128.1, 127.3, 127.1, 69.7, 69.6, 31.1, 29.2, 26.0, 24.4, 22.3, 13.9; HRMS (EI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{22}O_3$, 334.1569; found 334.1558.

The Procedure for the Asymmetric Epoxidation Carried out on a Large Scale. To a solution of **7a** (1.24 g, 5.0 mmol) and **9g** (120 mg, 0.25 mmol) in methyl *tert*-butyl ether (50 mL) was added a 1.0 M KOH solution (2.50 mL, 2.5 mmol) and *tert*-butyl hydroperoxide (7.5 M) in H_2O (3.30 mL, 25 mmol) at −20 °C. After stirring for 6 h, the reaction mixture was quenched by addition of saturated NH_4Cl solution at −20 °C and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1 to 10:1) to give epoxide **8a** (1.23 g, 93%) as a colorless oil.

Synthesis of Guanidine−Urea Bifunctional Organocatalysts. A suspension of 1,3-dioctadecylthiourea (332 mg, 0.57 mmol), *tert*-butyl (*S*)-(2-amino-1-phenylethyl)carbamate (90 mg, 0.38 mmol), $HgCl_2$ (155 mg, 0.57 mmol), and Et_3N (0.16 mL, 1.14 mmol) in DMF (4 mL) was stirred at 80 °C (oil bath) for 16 h under a nitrogen atmosphere, and then allowed to cool to room temperature. The reaction mixture was diluted with $CHCl_3$, filtered through Celite, and then concentrated *in vacuo*. The crude residue was used in the subsequent step without purification.

To a solution of the crude residue in CH_2Cl_2 (3 mL) was added TFA (1 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h, and then concentrated *in vacuo*, and then to a solution of the residue in THF (3 mL) was added Et_3N (0.10 mL, 0.69 mmol) and 1,3,5-trichloro-2-isocyanatobenzene (85 mg, 0.38 mmol) at 0 °C. The mixture was stirred for 24 h, and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/methanol = 20:1 to 10:1) to give a colorless solid. The solution of this colorless solid in $CHCl_3$ (30 mL) was washed with saturated NH_4Cl solution. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give **9a** (36 mg, 27%) as a white solid.

*(S,E)-N-((Octadecylamino)((2-phenyl-2-(3-(2,4,6-trichlorophenyl)ureido)ethyl)amino)methylene)octadecan-1-aminium Chloride (**9a**).* $[\alpha]_D^{25}$ + 2.0 (*c* 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$ δ): 8.35 (br, s, 1H), 8.23 (s, 1H), 7.75 (br, s, 1H), 7.54−7.39 (m, 2H), 7.33−7.27 (m, 3H), 7.24 (s, 2H), 6.55 (br, s, 1H), 5.03 (br, s, 1H), 3.82 (br, s, 1H), 3.59 (br, s, 1H), 3.09 (s, 4H), 1.36−1.00 (m, 64H), 0.83 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ δ): 156.9, 154.9, 138.7, 134.8, 132.3, 132.1, 128.7, 127.9, 127.8, 126.8, 53.9, 49.1, 42.4, 31.9, 29.7, 29.4, 29.2, 26.7, 22.7, 14.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{52}H_{89}Cl_3N_5O$, 904.6133; found 904.6105.

*(S,E)-N-((Ethylamino)((2-phenyl-2-(3-(2,4,6-trichlorophenyl)-ureido)ethyl)amino)methylene)ethanaminium Chloride (**9b**).* Following the procedure from **9a**, **9b** was obtained (90 mg, 48%, 3steps) as a white solid from 1,3-diethylthiourea (75 mg, 0.57 mmol) and *tert*-butyl (*S*)-(2-amino-1-phenylethyl)carbamate (90 mg, 0.38 mmol); $[\alpha]_D^{25}$ + 10.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6 δ): 8.50 (s, 1H), 8.36 (s, 1H), 7.67 (s, 2H), 7.66−7.52 (m, 2H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.1 Hz, 1H), 4.98 (dd, *J* = 14.4, 8.5 Hz, 1H), 3.61−3.45 (m, 2H), 3.25−3.11 (m, 4H), 1.06 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 δ): 154.9, 153.7, 140.4, 134.5, 133.2, 131.1, 128.4, 128.0, 127.4, 126.9, 53.1, 46.8, 36.0, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{25}Cl_3N_5O$, 456.1125; found 456.1125.

*(S,Z)-N-((Cyclohexylamino)((2-phenyl-2-(3-(2,4,6-trichlorophenyl)ureido)ethyl)amino)methylene)-cyclohexanaminium Chloride (**9c**).* Following the procedure from **9a**, **9c** was obtained (66 mg, 29%, three steps) as a white solid from 1,3-dicyclohexylthiourea (137 mg, 0.57 mmol) and *tert*-butyl (*S*)-(2-amino-1-phenylethyl)carbamate (90 mg, 0.38 mmol); $[\alpha]_D^{25}$ − 3.7 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6 δ): 8.59 (s, 1H), 8.37 (s, 1H), 7.88−7.71 (m, 1H), 7.67 (d, *J* = 10.5 Hz, 2H), 7.57 (t, *J* = 5.0 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.33−7.25 (m, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 4.97 (q, *J* = 7.3 Hz, 1H), 3.72−3.50 (m, 2H), 1.86−1.46 (m, 10H), 1.42−1.12 (m, 8H), 1.04 (t, *J* = 11.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 δ): 155.1, 152.5, 140.2, 134.5, 133.3, 131.0, 128.4, 127.9, 127.4, 127.0, 53.1, 50.5, 47.3, 32.2, 24.8, 24.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{37}Cl_3N_5O$, 564.2064; found 564.2089.

*(S,E)-N-((Benzylamino)((2-phenyl-2-(3-(2,4,6-trichlorophenyl)-ureido)ethyl)amino)methylene)-1-phenylmethanaminium Chloride (**9d**).* Following the procedure from **9a**, **9d** was obtained (82 mg, 35%, 3steps) as a white solid from 1,3-dibenzylthiourea (146 mg, 0.57 mmol) and *tert*-butyl (*S*)-(2-amino-1-phenylethyl)carbamate (90 mg, 0.38 mmol); $[\alpha]_D^{25}$ − 125.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6 δ): 8.56 (s, 1H), 8.40 (s, 1H), 7.89 (t, *J* = 5.5 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 1H), 7.67 (s, 2H), 7.40 (d, *J* = 6.9 Hz, 2H), 7.37−7.23 (m, 10H), 7.18 (s, 3H), 5.01 (q, *J* = 7.5 Hz, 1H), 4.62−4.37 (m, 4H), 3.68−3.58 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 δ): 155.1, 154.3, 140.2, 137.1, 134.6, 133.3, 131.2, 128.3, 128.1, 127.4, 127.2, 127.1, 126.9, 66.4, 53.2, 47.1, 44.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{30}H_{29}Cl_3N_5O$, 580.1438; found 580.1465.

*(S,E)-N-((Ethylamino)((3-phenyl-2-(3-(2,4,6-trichlorophenyl)-ureido)propyl)amino)methylene)ethanaminium Chloride (**9e**).* Following the procedure from **9a**, **9e** was obtained (87 mg, 45%, 3steps) as a white solid from 1,3-diethylthiourea (75 mg, 0.57 mmol) and *tert*-butyl (*S*)-(1-amino-3-phenylpropan-2-yl)carbamate (95 mg, 0.38 mmol); $[\alpha]_D^{25}$ − 35.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6 δ): 8.34 (s, 1H), 8.20 (s, 1H), 7.65 (s, 2H), 7.61−7.47 (m, 2H), 7.32−7.25 (m, 3H), 7.21 (q, *J* = 4.6 Hz, 1H), 6.83 (d, *J* = 7.3 Hz, 1H), 3.99 (s, 1H), 3.28 (t, *J* = 5.7 Hz, 2H), 3.24−3.11 (m, 4H), 2.88 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.73 (dd, *J* = 13.7, 9.6 Hz, 1H), 1.10 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 δ): 155.3, 153.9, 138.3, 134.6, 133.2, 131.1, 129.1, 128.2, 128.0, 126.1, 50.8, 45.8, 37.8, 36.1, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{27}Cl_3N_5O$, 470.1281; found 470.1280.

*(S,E)-N-((Ethylamino)((2-(3-(2,4,6-trichlorophenyl)ureido)-propyl)amino)methylene)ethanaminium Chloride (**9f**).* Following the procedure from **9a**, **9f** was obtained (69 mg, 42%, 3steps) as a white solid from 1,3-diethylthiourea (75 mg, 0.57 mmol) and *tert*-butyl (*S*)-(1-aminopropan-2-yl)carbamate (66 mg, 0.38 mmol); $[\alpha]_D^{25}$ − 39.6 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6 δ): 8.56 (s, 1H), 8.42 (s, 1H), 7.73−7.65 (m, 1H), 7.63 (s, 2H), 7.15 (d, *J* = 6.9 Hz, 1H), 3.83−3.69 (m, 1H), 3.26−3.16 (m, 4H), 3.09−2.98 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 δ): 155.5, 153.8, 134.5, 133.2, 131.0, 128.0, 47.1, 45.3, 36.1, 18.3, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{23}Cl_3N_5O$, 394.0968; found 394.0944.

*(S,E)-N-(((2-(3-(2,6-Dichlorophenyl)ureido)-3-phenylpropyl)-amino)(ethylamino)methylene)ethanaminium Chloride (**9g**).* Following the procedure from **9a**, **9g** was obtained (86 mg, 48%, 3steps.) as a white solid from 1,3-diethylthiourea (75 mg, 0.57 mmol), *tert*-butyl (*S*)-(1-amino-3-phenylpropan-2-yl)carbamate (95 mg, 0.38 mmol), and 1,3-dichloro-2-isocyanatobenzene (71 mg, 0.38 mmol); $[\alpha]_D^{25}$ − 18.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6 δ): 8.59−8.36 (m, 2H), 7.71 (s, 2H), 7.64 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.36−7.14 (m, 5H), 7.07 (d, *J* = 7.0 Hz, 1H), 3.97 (s, 1H), 3.40−3.28 (m, 2H), 3.28−3.14 (m, 2H), 3.09−2.97 (m, 2H), 2.93 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.74 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 δ): 155.6, 153.9, 138.4, 133.8, 133.7, 129.2, 128.3, 128.1, 127.9, 126.1, 51.0, 45.9, 45.2, 37.8, 36.1, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{28}Cl_3N_5O$, 436.1671; found 436.1673.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02084.

Experimental procedures and characterization data, including the X-ray crystal structure of a diol derived from **8b**, DFT calculations, and HPLC analysis (PDF)

Accession Codes

CCDC 1917081 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Miyashita, K.; Imanishi, T. Syntheses of Natural Products Having an Epoxyquinone Structure. *Chem. Rev.* **2005**, *105*, 4515−4536.

(2) Isolation of representative naphthoquinone epoxides, see: (a) Kasai, M.; Shirahata, K.; Ishii, S.; Mineura, K.; Marumo, H.; Tanaka, H.; Omura, S. Structure of nanaomycin E, a new nanaomycin. *J. Antibiot.* **1979**, *32*, 442−445. (b) Shiomi, K.; Iinuma, H.; Hamada, H.; Naganawa, H.; Manabe, M.; Matsuki, C.; Takeuchi, T.; Umezawa, H. Novel antibiotics napyradiomycins. Production, isolation, physicochemical properties and biological activity. *J. Antibiot.* **1986**, *39*, 487−493. (c) Kagamizono, T.; Hamaguchi, T.; Ando, T.; Sugawara, K.; Adachi, T.; Osada, H. Phosphatoquinones A and B, Novel Tyrosine Phosphatase Inhibitors Produced by Streptomyces sp. *J. Antibiot.* **1999**, *52*, 75−80. (d) Kara, M.; Soga, S.; Shono, K.; Eishima, J.; Mizukami, T. UCF76 Compounds, New Inhibitors of Farnesyltransferase Produced by Streptomyces. *J. Antibiot.* **2001**, *54*, 182−186. (e) Feroj Hasan, A. F. M.; Furumoto, T.; Begum, S.; Fukui, H. Hydroxysesamone and 2,3-epoxysesamone from roots of Sesamum indicum. *Phytochemistry* **2001**, *58*, 1225−1228. (f) Schneider, K.; Nicholson, G.; Ströbele, M.; Baur, S.; Niehaus, J.; Fiedler, H.-P.; Süssmuth, R. D. The Structures of Fluostatins C, D and E, Novel Members of the Fluostatin Family. *J. Antibiot.* **2006**, *59*, 105−109. (g) Baur, S.; Niehaus, J.; Karagouni, A. D.; Katsifas, E. A.; Chalkou, K.; Meintanis, C.; Jones, A. L.; Goodfellow, M.; Ward, A. C.; Beil, W.; Schneider, K.; Süssmuth, R. D.; Fiedler, H.-P. Fluostatins C∼E, Novel Members of the Fluostatin Family Produced by *Streptomyces* Strain Acta 1383. *J. Antibiot.* **2006**, *59*, 293−297. (h) Motohashi, K.; Irie, K.; Toda, T.; Matsuo, Y.; Kasai, H.; Sue, M.; Furihata, K.; Seto, H. Studies on Terpenoids Produced by Actinomycetes. *J. Antibiot.* **2008**, *61*, 75−80. (i) Das Sarma, M.; Ghosh, R.; Patra, A.; Hazra, B. Synthesis and antiproliferative activity of some novel derivatives of diospyrin, a plant-derived naphthoquinonoid. *Bioorg. Med. Chem.* **2007**, *15*, 3672−3677.

(3) For the enantioselective epoxidation of 1,4-naphthoquinone with a stoichiometric amount of chiral hydroperoxide, see: (a) Colonna, S.; Manfredi, A.; Annunziata, R.; Gaggero, N.; Casella, L. Biomimetic asymmetric synthesis. Enantioselective Weitz-Scheffer epoxidation of vitamin K3 and analogs in the presence of cyclodextrins. *J. Org. Chem.* **1990**, *55*, 5862−5866. (b) Lattanzi, A.; Cocilova, M.; Iannece, P.; Scettri, A. Enantioselective epoxidation of chalcones and naphthoquinones mediated by (+)-norcamphor-derived hydroperoxide. *Tetrahedron: Asymmetry* **2004**, *15*, 3751−3755. (c) Bundu, A.; Berry, N. G.; Gill, C. D.; Dwyer, C. L.; Stachulski, A. V.; Taylor, R. J. K.; Whittall, J. The design and synthesis of novel anomeric hydroperoxides: influence of the carbohydrate residue in the enantioselective epoxidation of quinones. *Tetrahedron: Asymmetry* **2005**, *16*, 283−293. (d) Kośnik, W.; Stachulski, A. V.; Chmielewski, M. New stable anomeric hydroperoxides derived from 2-deoxysugars; enantioselective epoxidation of 2-methyl-1,4-naphthoquinone. *Tetrahedron: Asymmetry* **2005**, *16*, 1975−1981. (e) Bunge, A.; Hamann, H.-J.; McCalmont, E.; Liebscher, J. Enantioselective epoxidation of 2-substituted 1,4-naphthoquinones using gem-dihydroperoxides. *Tetrahedron Lett.* **2009**, *50*, 4629−4632. (f) Blumenthal, H.; Liebscher, J. Isoquinoline- and piperazinedione-derived α-acylamino peroxide moieties in asymmetric oxidation of sulphides and epoxidation of naphthoquinones. *ARKIVOC* **2009**, *2009*, 204−220.

(4) For the enantioselective epoxidation of 1,4-naphthoquinone with an enzyme, see: Colonna, S.; Manfredi, A.; Annunziata, R.; Spadoni, M. Catalytic asymmetric weitz-scheffer epoxidation promoted by bovine serum albumin. Part II. *Tetrahedron* **1987**, *43*, 2157−2164.

(5) For the enantioselective epoxidation of 1,4-naphthoquinone with a transition-metal catalyst, see: Prasetyanto, E. A.; Khan, N.-U. H.; Seo, H.-U.; Park, S.-E. Asymmetric Epoxidation of α,β-Unsaturated Ketones over Heterogenized Chiral Proline Diamide Complex

Catalyst in the Solvent-Free Condition. *Top. Catal.* **2010**, *53*, 1381−1386.

(6) For the enantioselective epoxidation of 1,4-naphthoquinone with an organocatalyst, see: (a) Baba, N.; Oda, J.; Kawaguchi, M. Asymmetric Epoxidation of Cyclic Enones under Chiral Phase Transfer Conditions. *Agric. Biol. Chem.* **1986**, *50*, 3113−3117. (b) Arai, S. Catalytic Asymmetric Epoxidation of Naphthoquinone Derivatives Under Phase-Transfer Catalyzed Conditions. *Synlett* **1998**, *1998*, 1201−1202. (c) Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. Catalytic asymmetric epoxidation of enones under phase-transfer catalyzed conditions. *Tetrahedron* **2002**, *58*, 1623−1630. (d) Dehmlow, E. V.; Düttmann, S.; Neumann, B.; Stammler, H.-G. Monodeazacinchona Alkaloid Derivatives: Synthesis and Preliminary Applications as Phase-Transfer Catalysts. *Eur. J. Org. Chem.* **2002**, *2002*, 2087−2093. (e) Berkessel, A.; Guixà, M.; Schmidt, F.; Neudörfl, J. M.; Lex, J. Highly Enantioselective Epoxidation of 2-Methylnaphthoquinone (Vitamin K_3) Mediated by New *Cinchona* Alkaloid Phase-Transfer Catalysts. *Chem. − Eur. J.* **2007**, *13*, 4483−4498.

(7) Kawaguchi, K.; Nakano, K.; Hosoya, K.; Orihara, T.; Yamanaka, M.; Odagi, M.; Nagasawa, K. Asymmetric Epoxidation of 1,4-Naphthoquinones Catalyzed by Guanidine-Urea Bifunctional Organocatalyst. *Org. Lett.* **2018**, *20*, 2811−2815.

(8) For leading reviews, see: (a) Nagasawa, K.; Sohtome, Y. The Design of Chiral Double Hydrogen Bonding Networks and Their Applications to Catalytic Asymmetric Carbon-Carbon and Carbon-Oxygen Bond-Forming Reactions. *Synlett* **2010**, *1*, 1−22. (b) Sohtome, Y.; Nagasawa, K. Dynamic asymmetric organocatalysis: cooperative effects of weak interactions and conformational flexibility in asymmetric organocatalysts. *Chem. Commun.* **2012**, *48*, 7777−7789. (c) Sohtome, Y.; Nagasawa, K. Sequential stereodivergent organocatalysis and programmed organocascades. *Org. Biomol. Chem.* **2014**, *12*, 1681−1685.

(9) *Gaussian 09*, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc.: Wallingford CT, 2013.

(10) *CYLview, 1.0b*, Legault, C. Y. Université de Sherbrooke, 2009.

(11) Details of the structure-activity relationship (SAR) studies on catalyst **9** and the optimization of reaction conditions are given in the Supporting Information.

(12) Absolute configuration was determined by X-ray crystallography of a diol derived from **8b**. A single crystal suitable for X-ray diffraction analysis was obtained by slow evaporation of a solution of the diol in CH_2Cl_2/*n*-hexane at room temperature. See Supporting Information for the X-ray structure. The crystallographic data (CCDC1917081) can be obtained free of charge from The Cambridge Crystallographic Data Center.

(13) The epoxidation reaction of naphthoquinones with methoxy group at *ortho* position on the aromatic group and with alkenyl group at C2 was investigated. See the Supporting Information for details.

(14) Johnson, E. R.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A. J.; Yang, W. Revealing Noncovalent Interactions. *J. Am. Chem. Soc.* **2010**, *132*, 6498−6506.

(15) The original distortion/interaction analysis, see: (a) Morokuma, K.; Kitaura, K. in *Chemical Applications of Atomic and Molecular Electrostatic Potentials*, Politzer, P., Truhlar, D. G., Eds.; Plenum: New York, 1981. (b) Ess, D. H.; Houk, K. N. Distortion/Interaction Energy Control of 1,3-Dipolar Cycloaddition Reactivity. *J. Am. Chem. Soc.* **2007**, *129*, 10646−10647. (c) Ess, D. H.; Houk, K. N. Theory of 1,3-Dipolar Cycloadditions: Distortion/Interaction and Frontier Molecular Orbital Models. *J. Am. Chem. Soc.* **2008**, *130*, 10187−10198. (d) Lam, Y.-H.; Cheong, P. H.-Y.; Blasco Mata, J. M.; Stanway, S. J.; Gouverneur, V.; Houk, K. N. Diels-Alder Exo Selectivity in Terminal-Substituted Dienes and Dienophiles: Experimental Discoveries and Computational Explanations. *J. Am. Chem. Soc.* **2009**, *131*, 1947−1957. (e) Paton, R. S.; Kim, S.; Ross, A. G.; Danishefsky, S. J.; Houk, K. N. Experimental Diels-Alder Reactivities of Cycloalkenones and Cyclic Dienes Explained through Transition-State Distortion Energies. *Angew. Chem., Int. Ed.* **2011**, *50*, 10366−10368. (f) Green, A. G.; Liu, P.; Merlic, C. A.; Houk, K. N. Distortion/Interaction Analysis Reveals the Origins of Selectivities in Iridium-Catalyzed C-H Borylation of Substituted Arenes and 5-Membered Heterocycles. *J. Am. Chem. Soc.* **2014**, *136*, 4575−4583. (g) Yang, Y.-F.; Liang, Y.; Liu, F.; Houk, K. N. Diels-Alder Reactivities of Benzene, Pyridine, and Di-, Tri-, and Tetrazines: The Roles of Geometrical Distortions and Orbital Interactions. *J. Am. Chem. Soc.* **2016**, *138*, 1660−1667.

(16) Sidorov, P.; Desta, I.; Chessé, M.; Horvath, D.; Marcou, G.; Varnek, A.; Davioud-Charvet, E.; Elhabiri, M. Redox Polypharmacology as an Emerging Strategy to Combat Malarial Parasites. *Chem. Med. Chem.* **2016**, *11*, 1339−1351.

(17) El-Hout, S. I.; Suzuki, H.; El-Sheikh, S. M.; Hassan, H. M. A.; Harraz, F. A.; Ibrahim, I. A.; El-Sharkawy, E. A.; Tsujimura, S.; Holzinger, M.; Nishina, Y. Tuning the redox potential of vitamin K_3 derivatives by oxidative functionalization using a Ag(I)/GO catalyst. *Chem. Commun.* **2017**, *53*, 8890−8893.

(18) Nyangulu, J. M.; Nelson, K. M.; Rose, P. A.; Gai, Y.; Loewen, M.; Lougheed, B.; Quail, J. W.; Cutlera, A. J.; Abrams, S. R. Synthesis and biological activity of tetralone abscisic acid analogues. *Org. Biomol. Chem.* **2006**, *4*, 1400−1412.

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