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Asymmetric Epoxidation of 1,4-Naphthoquinones Catalyzed by Guanidine−Urea Bifunctional Organocatalyst

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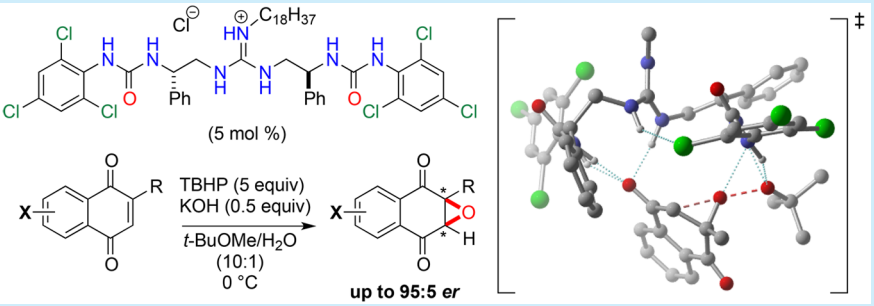
Supporting Information



ABSTRACT: An enantioselective nucleophilic epoxidation of 2-substituted 1,4-naphthoquinones in the presence of a newly developed guanidine−bisurea bifunctional organocatalyst with *tert*-butyl hydroperoxide (TBHP) as an oxidant is presented. 1,4-Naphthoquinones bearing substituents at C6, C7, and C2 were available for the reaction, and the corresponding epoxides were obtained with 88:12−95:5 *er* in 71−98% yields. DFT calculations indicated that substituents at C2 and C6 in the terminal Ar group of the catalyst **9k** play a key role in controlling the stereochemical outcome.

Epoxide is a valuable functional group in synthetic intermediates due to its high reactivity.[1] In addition, epoxy structures are seen in many biologically active natural products, as well as pharmaceuticals.[2] Thus, asymmetric epoxidation has been widely explored. An important landmark was the Katsuki−Sharpless asymmetric epoxidation for allylic alcohols.[3] In this reaction, a hydroxyl group in the allylic alcohol serves as a directing group for the construction of the asymmetric environment by complexation with chiral tartrate and Ti(O*i*-Pr)$_4$.[4] Among the various types of asymmetric epoxidation reactions,[5] epoxidation of electron-deficient enones or enoates with nucleophilic chiral oxidants or oxidants in the presence of a chiral catalyst has also been energetically explored. The carbonyl group in the electron-deficient olefin usually serves as a directing group to control the enantioselectivity of epoxidation. Nevertheless, quinones remain challenging substrates for asymmetric epoxidation, because of their highly symmetric and planar structures with two carbonyl groups, so that it is difficult to differentiate the *si*- and *re*-faces of the olefins with chiral oxidants or catalysts. In particular, 1,4-naphthoquinone epoxides are important synthetic intermediates for biologically active molecules, such as A80915G (**1**),[7c,h] fluostatin C (**2**),[7f,g] and nanaomycin E (**3**)[7a] (Figure 1).[6,7] Currently, asymmetric epoxidation of 1,4-naphthoquinones has been mainly explored with 2-methyl-

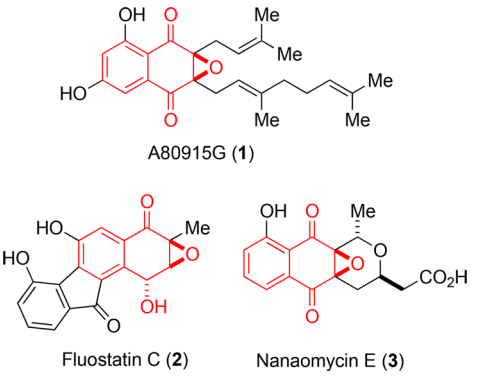


Figure 1. Structures of bioactive molecules containing a naphthoquinone epoxide motif.

1,4-naphthoquinones (**4a**) as substrates, and the conditions with a stoichiometric amount of chiral hydroperoxide or oxidants with a chiral organocatalyst have been reported.[8−11] To date, the best enantioselectivity for **4a** was reported by Berkessel and co-workers using sodium hypochlorite as an oxidant in the presence of quinuclidine-derived phase-transfer

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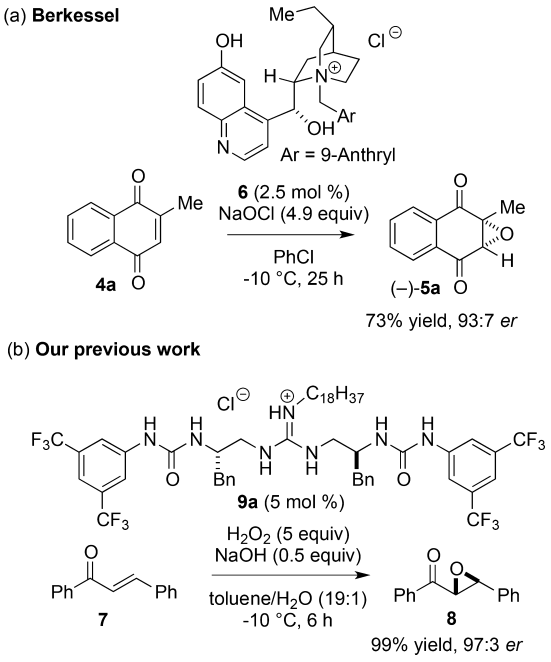
catalyst **6**. They obtained epoxide **5a** with 93:7 *er* in 73% yield (Scheme 1a).[11f]

Scheme 1. (a) Enantioselective Epoxidation of 2-Methyl-1,4-naphthoquinone (4a) Reported by Berkessel et al.; (b) Our Previous Work on Enantioselective Epoxidation of Chalcone (7) in the Presence of 9a

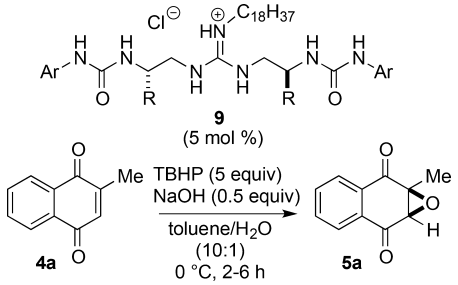


Our group has reported a series of guanidine–bis(thio)urea bifunctional organocatalysts.[12] We previously applied catalyst **9a** to the asymmetric nucleophilic epoxidation of chalcones and obtained high enantioselectivity and high yield (Scheme 1b).[13] Under the conditions used, the interactions of the guanidine and urea groups with chalcones and hydrogen peroxide were proposed to fix the transition state in an optimum three-dimensional structure for the nucleophilic epoxidation reaction.

In the present work, we applied the guanidine–bisurea bifunctional organocatalyst **9** for asymmetric epoxidation of 2-substituted 1,4-naphthoquinones **4**. The transition state of the epoxidation reaction catalyzed by **9** was also investigated by means of DFT calculations.

We initially attempted structural optimization of the catalyst **9** for asymmetric epoxidation of **4a** in the presence of *tert*-butyl hydroperoxide (TBHP) as an oxidant and sodium hydroxide as a base under toluene–H_2O biphasic conditions at 0 °C (Table 1).[13] Under these conditions, the R and Ar groups in **9** were varied. First, the influence of the R group was examined by varying it from benzyl to methyl, isopropyl, and phenyl groups (entries 1–4, respectively). We found that catalyst **9d** with the phenyl group was most effective, and **5a** was obtained with 70:30 *er* in 94% yield. Next, the effect of the Ar group in the catalyst **9d** was investigated. The enantioselectivity was hardly affected by changing the CF_3 group to a F or electron-donating OMe group. In addition, changing the substitution position of the CF_3 group among 2, 3, or 4 did not affect the enantioselectivity (entries 7–9). On the other hand, tribromo or trichloro substitution of the Ar group had a marked influence on the enantioselectivity, and **5a** with 88:12 and 90:10 *er* was obtained, respectively, and without loss of reactivity (entries 10 and 11). Thus, we focused on the catalyst **9k** for the reaction and further investigated the reaction conditions.

Table 1. Optimization of the Structure of Catalyst 9 for Asymmetric Epoxidation of 4a[a]



entry	9	R	Ar	yield (%)[b]	er[c]
1	**9a**	Bn	3,5-$(CF_3)_2$-C_6H_3	87	66:34
2	**9b**	Me	3,5-$(CF_3)_2$-C_6H_3	84	66:34
3	**9c**	*i*-Pr	3,5-$(CF_3)_2$-C_6H_3	70	55:45
4	**9d**	Ph	3,5-$(CF_3)_2$-C_6H_3	94	70:30
5	**9e**	Ph	3,5-F_2-C_6H_3	92	70:30
6	**9f**	Ph	3,5-$(OMe)_2$-C_6H_3	92	76:24
7	**9g**	Ph	2-CF_3-C_6H_4	99	72:28
8	**9h**	Ph	3-CF_3-C_6H_4	93	71:29
9	**9i**	Ph	4-CF_3-C_6H_4	98	65:35
10	**9j**	Ph	2,4,6-Br_3-C_6H_2	98	88:12
11	**9k**	Ph	2,4,6-Cl_3-C_6H_2	93	90:10

[a]Reaction conditions: **4a** (0.1 mmol), TBHP (0.5 mmol), and NaOH (0.05 mmol) in the presence of **9** (5 μmol) in toluene/H_2O (1 mL/0.1 mL) at 0 °C. [b]Yield of isolated product. [c]Determined by HPLC analysis using a chiral stationary phase.

We examined the base in the presence of catalyst **9k** (Table 2, entries 1–6). Among the bases we investigated, none had a significant influence on the enantioselectivity, with the exception of DBU, which provided **5a** with 75:25 *er*. Next, the solvent was varied. Dichloromethane or chloroform did not affect the enantioselectivity. On the other hand, ethers were effective, and 95:5 and 94:6 *er* were observed with *tert*-butyl methyl ether and cyclopentyl methyl ether (CPME), respectively. These reactions proceeded in high yields under biphasic solvent conditions with H_2O (entries 9 and 11).[14] To demonstrate the practical synthetic utility, a 1 mmol scale reaction was carried out (entry 12).

Under the optimal conditions (Table 2, entry 9), we next examined the substrate scope (Scheme 2). The substrates with a methoxy or chloro substituent at C6 gave the corresponding **5b** and **5c** with 92:8 and 94:6 *er* in 90% and 97% yields, respectively. Both electron-donating and -withdrawing groups at C7 were tolerated, and epoxides **5d–5f** were obtained with 91:9–92:8 *er* in 71–93% yields. This asymmetric epoxidation was applicable to compounds with *n*-propyl, *i*-butyl, *i*-propyl, benzyl, 4-methylbenzyl, and 4-chlorobenzyl groups at C2, affording the corresponding epoxides **5g–5l** with 85:15–94:6 *er* in 76–96% yields.

To elucidate the origin of the high enantioselectivity in the guanidine–bisurea-catalyzed asymmetric epoxidation reaction, DFT calculations were conducted.[15] The epoxidation of electron-deficient olefins with peroxides under basic conditions (Weitz–Scheffer epoxidation) is generally agreed to proceed through a stepwise mechanism.[16] In the guanidine–bisurea-catalyzed asymmetric epoxidation of **4a** using TBHP, the first addition of the peroxide anion (TS_{add}) is energetically more

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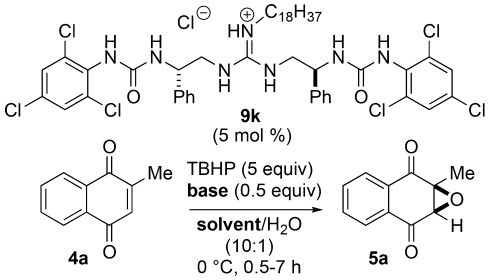
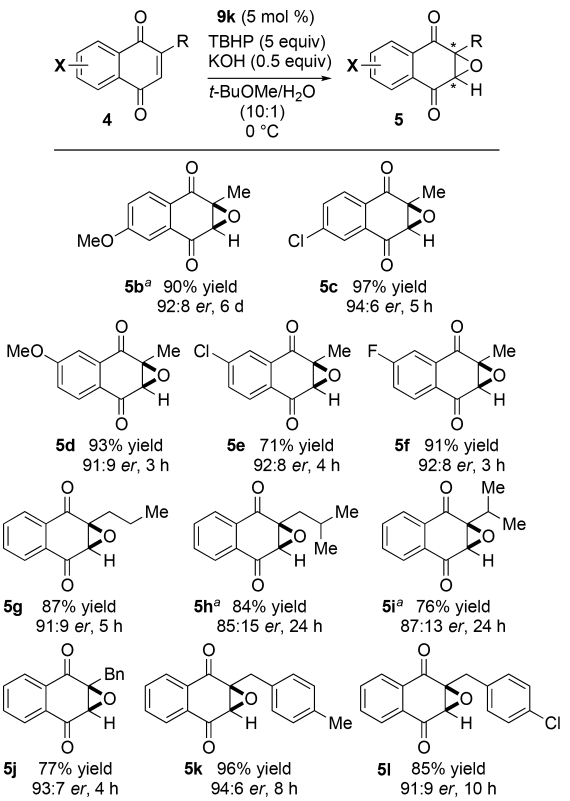
Table 2. Influences of Base and Solvent on the Asymmetric Epoxidation of 4a in the Presence of 9k[a]



entry	base	solvent	time (h)	yield (%)[b]	er[c]
1	NaOH	toluene	3.5	93	90:10
2	LiOH	toluene	3	94	90:10
3	KOH	toluene	3	97	90:10
4	DBU	toluene	1.5	81	75:25
5	Et_3N	toluene	5	80	90:10
6	K_2CO_3	toluene	2.5	88	90:10
7	KOH	CH_2Cl_2	7	88	91:9
8	KOH	$CHCl_3$	7	89	91:9
9	KOH	*t*-BuOMe	0.5	98	95:5
10	KOH	*i*-Pr_2O	1.5	93	92:8
11	KOH	CPME	0.5	99	94:6
12[d]	KOH	*t*-BuOMe	4	89	94:6

[a]Reaction conditions: **4a** (0.1 mmol), TBHP (0.5 mmol), and base (0.05 mmol) in the presence of **9k** (5 μmol) in solvent/H_2O (1 mL/0.1 mL) at 0 °C. [b]Yield of isolated product. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Reaction was carried out on 1 mmol scale for **4a**.

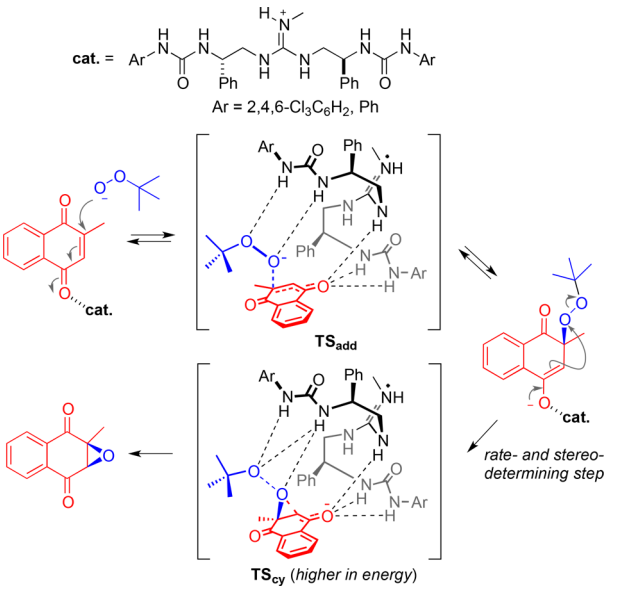
Scheme 2. Substrate Scope for the Asymmetric Epoxidation of 4 under the Optimized Conditions



[a]Reaction was carried out at −10 °C with 10 mol % of **9k**.

favored than the second cyclization step (elimination of the alkoxide anion, TS_{cy}) (Scheme 3; details are shown in Figure

Scheme 3. Proposed Reaction Mechanism, Based on DFT Calculation



S1). An induced-fit-type structural change of the guanidine–bisurea catalyst efficiently holds **4a** and TBHP via hydrogen bonding networks through the sequential addition/cyclization process.[17]

Focusing on the rate- and stereodetermining cyclization step, we also obtained deep insight into the stereocontrol mechanism for the asymmetric induction by comparing four diastereomeric TSs corresponding to regioselectivity (**TS-a**, **TS-b**) and facial selectivity (*Si*-face, **TS-1**; *Re*-face, **TS-2**) for Ar = 2,4,6-$Cl_3C_6H_2$ and Ph (Figure 2, Figure S2). The **TS-a** tends to be more stable than **TS-b** due to the steric repulsion between the methyl group in **4a** and the urea side chain of the catalyst. In the case of Ar = 2,4,6-$Cl_3C_6H_2$, **TS-a1** is more stable than **TS-a2**. Exchange of 2,4,6-$Cl_3C_6H_2$ with Ph (as a model for 4- or 3,5-substituted Ar group) considerably decreased the energy difference between the diastereomeric TSs (**TS-a1*** and **TS-a2***). These computational results are qualitatively consistent with the experimentally observed enantiomer ratio values. To clarify the energy difference between **TS-a1** and **TS-a2**, structural and energetic features of these TS models were investigated in detail. In both **TS-a1** and **TS-a2**, the S-shaped catalyst constructs similar hydrogen-bonding networks with **4a** and the peroxide anion (*a*–*f* in Figure 2a). Whereas three NH residues of the guanidinium/urea groups coordinate with one carbonyl group of **4a** (*a*–*c*), two NH residues of the other urea group hold the peroxo moiety in place via multiple hydrogen bonds (*d*–*f*). An intramolecular hydrogen bond (*i* in **TS-a1**) between the noncoordinated NH residue of the guanidinium group and a Cl atom of the 2,4,6-$Cl_3C_6H_2$ group is seen only in **TS-a1**. The aromatic ring moiety of **4a** induces significant conformational changes of the catalyst through a relay of sterically repulsive interactions along the Ph (colored in orange, Figure 2a) and 2,4,6-$Cl_3C_6H_2$ groups in **TS-a2**. The terminal 2,4,6-$Cl_3C_6H_2$ group is kicked out by the conformationally changed Ph group to a position far from the NH residue of the guanidinium group in **TS-a2**. Consequently, the intramolecular NH···Cl hydrogen

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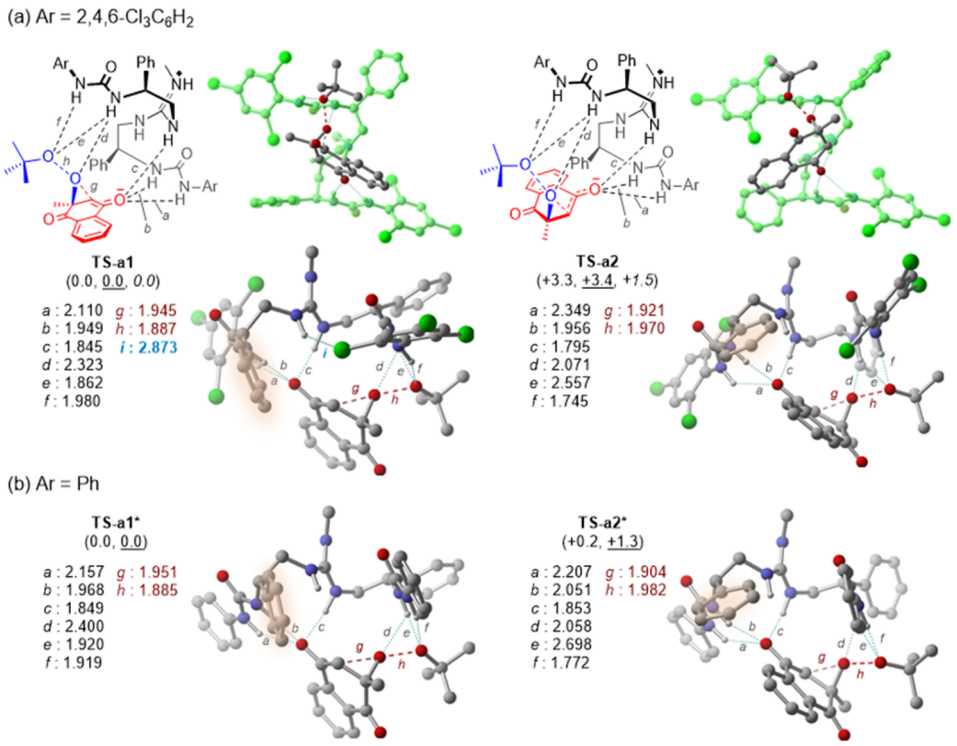

Figure 2. 3D models and relative energies (kcal/mol) of (a) **TS-a1** and **TS-a2** (Ar = 2,4,6-$Cl_3C_6H_2$, catalyst moieties are highlighted in green) and (b) **TS-a1*** and **TS-a2*** (Ar = Ph). The relative electronic energies at the B3LYP/6-31G* and B3LYP-D3/6-31+G** (italics) levels and the relative Gibbs free energies (underlined) at the B3LYP/6-31G* level are shown in parentheses. Bond lengths are in Å.

bond is completely lacking in **TS-a1*** and **TS-a2***, albeit with no change in the gross structure or the hydrogen-bonding network between **4a** and the catalyst (Figure 2b). Therefore, the arrangement of the terminal 2,4,6-$Cl_3C_6H_2$ group plays a key role in determining the stability of the TS. The **TS-a1** is mainly stabilized by the intramolecular NH···Cl hydrogen bond in the catalyst (see also the distortion/interaction analysis in Figure S3).

In conclusion, we have developed an enantioselective nucleophilic epoxidation of 2-substituted 1,4-naphthoquinones with TBHP in the presence of our newly developed guanidine–bisurea bifunctional organocatalyst. Various substituents at C6 and C7, as well as C2, are tolerated, and the corresponding epoxides were obtained with 85:15–95:5 *er* in 71–98% yields. DFT calculations revealed that substituents at C2 and C6 in the terminal Ar group of the catalyst **9k** are key players in controlling the stereochemical outcome.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00641.

Experimental procedures and detail of the optimization reaction conditions; characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Some oxidants and their amounts for the epoxidation reaction were investigated; see Supporting Information, sections 4.1 and 4.3. By reducing the equivalents of TBHP from 5 to 1.2, the yield of **5a** decreased to 64% (4 h) while retaining the *er* (92:8).
(15) Computational details are shown in the Supporting Information.
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(17) Guanidine−bis(thio)urea catalysts activate substrates in a similar manner to that shown in our previous reports; see: Odagi, M.; Furukori, K.; Yamamoto, Y.; Sato, M.; Iida, K.; Yamanaka, M.; Nagasawa, K. *J. Am. Chem. Soc.* **2015**, *137*, 1909−1915.

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