Guanidine-Urea Bifunctional Organocatalyst for Asymmetric Epoxidation of 1,3-Diarylenones with Hydrogen Peroxide

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Abstract: A highly enantioselective catalytic epoxidation reaction to the electron-deficient α,β-unsaturated olefin moieties of diarylenones was achieved with high chemical yield by using aqueous hydrogen peroxide in the presence of a newly developed guanidine-urea bifunctional organocatalyst. These functional groups were suggested to perform cooperatively by interacting with guanidine–hydrogen peroxide and urea-enones, respectively.

Key words: guanidine, urea, hydrogen peroxide, epoxidation, electron-deficient olefin

Enantioselective catalytic epoxidation of electron-deficient olefins is a powerful method for the preparation of useful chiral building blocks.[1] In the past few decades, a number of efficient methods involving chiral metal and/or metal-free catalysts with various oxidants have been developed.[2] Among them, the use of aqueous hydrogen peroxide as the oxidant has great advantages: it is environmentally friendly, low in cost, safe to handle and provides high atom-efficiency.[3] Since Juliá and Colonna reported the first application of hydrogen peroxide for asymmetric epoxidation,[4] many efforts have been devoted to the development of organocatalysts.[5] Nevertheless, only a few efficient methods have been reported so far. A sterically hindered pyrrolidine organocatalyst was successfully applied to the asymmetric epoxidation to α,β-unsaturated aldehydes with hydrogen peroxide by Jørgensen et al.[6] In the case of α,β-unsaturated ketones, cinchona alkaloid derivatives were reported to catalyze the epoxidation with hydrogen peroxide. Jew et al. reported a highly enantioselective version of this reaction using a dimerized cinchona alkaloid catalyst.[7] Recently, a chiral primary amine salt was reported for the highly asymmetric epoxidation to cyclic enones by List et al.[8]

Guanidine catalysts have also been explored for nucleophilic asymmetric epoxidation.[9] In these reactions, hydrogen peroxide can be used as an oxidant, but enantioselectivity is moderate or poor. We have recently reported a guanidine-hydroxy bifunctional organocatalyst for the asymmetric epoxidation of 1,3-diarylenones.[9h] This catalyst, however, only promoted the reaction with *tert*-butyl hydroperoxide as an oxidant, giving epoxides with moderate enantioselectivity. As a continuation of our work on hetero-bifunctional organocatalysts,[10] we envisaged that a guanidine-urea conjugated catalyst would cooperatively promote the asymmetric epoxidation with aqueous hydrogen peroxide of electron-deficient α,β-unsaturated carbonyl olefins through the interactions of type I, that is, urea–carbonyl group[11] and hydrogen peroxide–guanidine group interactions, or type II, that is, guanidine–carbonyl group[12] and hydrogen peroxide–urea group[13] interactions (Figure 1).

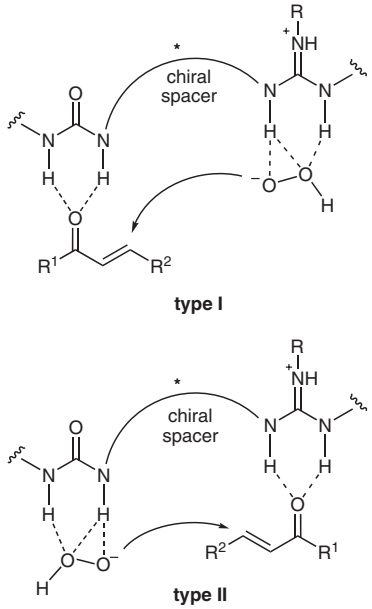

Figure 1 Cooperative interactions of guanidine-urea bifunctional catalyst **1** with enone and hydrogen peroxide

Herein, we describe the highly enantioselective epoxidation of electron-deficient α,β-unsaturated olefins of 1,3-diarylenones with hydrogen peroxide in the presence of a guanidine-urea bifunctional phase-transfer catalyst under mild reaction conditions.

We have synthesized guanidine-urea organocatalysts **1** in which the functional groups are connected with chiral spacers derived from amino acids.[14] With the requirement of a biphasic reaction system because of the use of aqueous hydrogen peroxide, we introduce a long alkyl chain on the guanidine group.[10d] Since the interaction of the urea group with reaction substrates was expected to be one of the key features, catalysts having electron-withdrawing

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groups on the aromatic ring were also synthesized (**1a–c**).[15]

Initial screening was conducted using the reaction of *trans*-chalcone (**4a**) with 30% aqueous hydrogen peroxide (5 equiv) and NaOH (50 mol%) in the presence of 5 mol% of **1** in organic solvents–H_2O (1:1 by volume) at 0 °C. As shown in Table 1, catalysts **1a–e** (Figure 2) all promoted the epoxidation reaction quantitatively (entries 1–5).

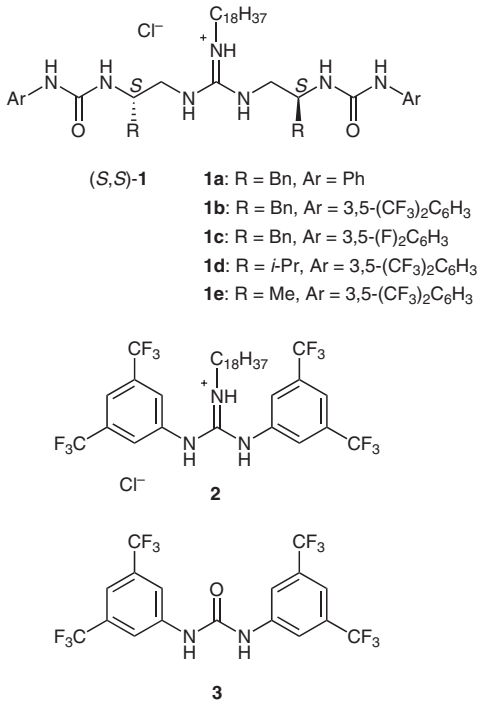
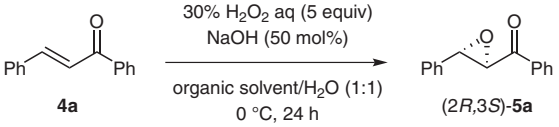


Figure 2 Structures of guanidine-urea bifunctional catalyst **1**, guanidine **2**, and urea **3**

The enantioselectivity varied according to the substituents on the Ar groups and chiral spacers in **1**. The introduction of 3,5-bistrifluoromethyl groups on the phenyl moiety was effective in improving the enantioselectivity (entries 1–3). Among the catalysts **1b**,**d**,**e**, the phenylalanine-derived chiral spacer of **1b** gave the highest enantioselectivity of 78% ee (entries 2 vs. 4 and 5). Next, the solvents in the biphasic system and their ratios were optimized (entries 6–10). Toluene was found to be the best solvent. When the volume ratio of H_2O was decreased to 1:19, enantioselectivity was increased to 90% ee (entry 11). Finally, **5a** was quantitatively obtained with 94% ee by lowering the temperature to –10 °C (entry 12). In this reaction, catalyst **1b** was quantitatively recovered from the reaction mixture by simple silica gel column chromatography, and could be reused without any loss of either catalytic activity or enantioselectivity.[16] Under these reaction conditions, *tert*-butyl hydroperoxide was not effective as an oxidant (entries 13 and 14), which presumably interacts poorly with catalyst because of steric hindrance. Since the catalyst **2**[11a] and **3**,[11a,b] lacking the urea group or guanidine group, did not promote the reaction at all under these conditions, the guanidine and urea groups were revealed to act cooperatively in this asymmetric epoxidation reaction (entries 15 and 16).

Table 1 Asymmetric Epoxidation of *trans*-Chalcone Catalyzed by **1–3**



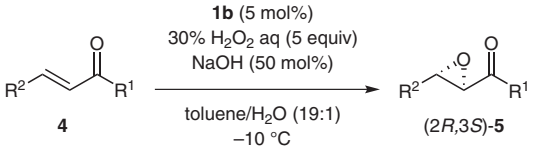
Entry	Catalyst	Organic solvent	Yield (%)[a]	ee (%)[b,c]
1	**1a**	toluene	99	15
2	**1b**	toluene	99	78
3	**1c**	toluene	99	22
4	**1d**	toluene	99	24
5	**1e**	toluene	99	20
6	**1b**	hexane	99	48
7	**1b**	CH_2Cl_2	99	44
8	**1b**	Et_2O	99	25
9	**1b**	THF	99	14
10	**1b**	MeOH	99	4
11[d]	**1b**	toluene	99	90
12[e]	**1b**	toluene	99	94
13[f]	**1b**	toluene	73	21
14[f]	**1b**	CH_2Cl_2	45	19
15	**2**	toluene	0	–
16	**3**	toluene	0	–

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC using a chiral column.
[c] The absolute configuration was determined by comparison of the HPLC retention time with the literature data.
[d] Toluene/H_2O = 19:1 (v/v).
[e] Toluene/H_2O = 19:1 (v/v), –10 °C. Reaction was completed within 6 h.
[f] *tert*-Butyl hydroperoxide in decane (5 equiv) was used as the oxidant.

With the optimized reaction conditions in hand (Table 1, entry 12), the substrate scope of this epoxidation reaction was investigated. As shown in Table 2, a variety of 1,3-diarylenones, having electron-withdrawing and/or donating groups, could be applied under the present reaction conditions. That is, epoxidation of **4b–j** proceeded smoothly within 3–20 hours, and gave the corresponding epoxy ketones **5b–j** in quantitative yield with high enantioselectivity.[18,19]

To clarify the roles of functional groups in **1b**, ^{1}H NMR studies were employed using **4a** with **2** and **3**. As a result,

Table 2 Asymmetric Epoxidation of 1,3-Diarylenones Catalyzed by **1b** under Optimized Conditions



Entry	4	R^1	R^2	Time (h)	Yield (%)[a]	ee (%)[b,c]
1	**4b**	Ph	4-MeC_6H_4	4	99 **5b**	91
2	**4c**	Ph	4-ClC_6H_4	4	99 **5c**	90
3	**4d**	Ph	4-$O_2NC_6H_4$	11	99 **5d**	85
4	**4e**	Ph	1-naphthyl	6	99 **5e**	96
5	**4f**	Ph	2-naphthyl	18	98 **5f**	96
6	**4g**	4-BrC_6H_4	Ph	3	99 **5g**	90
7	**4h**	4-$MeOC_6H_4$	Ph	7	99 **5h**	90
8[d]	**4i**	2-furyl	Ph	20	91 **5i**	86
9	**4j**	4-ClC_6H_4	4-MeC_6H_4	12	98 **5j**	92

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC using a chiral column.
[c] The absolute configuration was determined by comparison of the HPLC retention time with the literature data.[17]
[d] Reaction was carried out at –20 °C.

a downfield shift of NH in **3** was observed from δ = 5.95 to 8.21 ppm in the case of mixture with **4a**.[20,21] These observations suggest the type-I interactions are plausible for the asymmetric epoxidation with **1b**.

In summary, asymmetric epoxidation reaction at the electron-deficient α,β-unsaturated olefins of 1,3-diarylenones was achieved by using aqueous hydrogen peroxide in the presence of a guanidine-urea bifunctional organocatalyst, with high chemical yield and enantioselectivity under biphasic conditions.

Acknowledgment

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(14) **Synthesis of Catalyst 1a and Spectral Data for 1a–e**

To a solution of guanidine (*S*,*S*)-**1f**[10a] (258 mg, 0.317 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (3.0 mL) at 0 °C. The reaction mixture was warmed to r.t. and stirred for 2 h. The resulting mixture was concentrated in vacuo to give diamine. To a solution of the diamine in THF (6.0 mL) was added phenyl isocyanate (0.21 mL, 1.90 mmol), and the mixture was stirred for 12 h. The resulting mixture was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (*n*-hexane–EtOAc = 4:1 to 1:1, $CHCl_3$–MeOH = 9:1) to give **1a** as a TFA salt (Scheme 1). The counteranion of **1a** was exchanged into Cl^- by treatment with sat. aq NH_4Cl and EtOAc solution, and gave **1a** as a HCl form in 81% yield from **1f** (219 mg, 0.257 mmol).

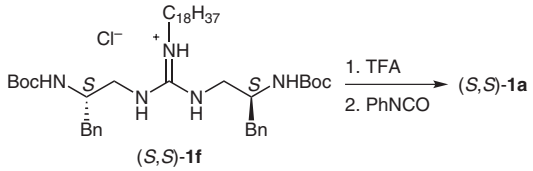
Compound **1a**: $[\alpha]_D^{24}$ –41.2 (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD): δ = 7.33–7.10 (m, 18 H), 6.93 (t, *J* = 7.4 Hz, 2 H), 4.11 (br s, 2 H), 3.45–3.32 (m, 4 H), 3.16 (t, *J* = 7.3 Hz, 2 H), 3.03 (dd, *J* = 4.5, 14.1 Hz, 2 H), 2.79 (dd, *J* = 9.6, 13.7 Hz, 2 H), 1.59 (m, 2 H), 1.34–1.14 (m, 30 H), 0.88 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 158.51, 156.33, 140.52, 138.97, 130.22, 129.83, 129.68, 127.78, 123.67, 120.18, 52.46 (br), 47.63 (br), 43.12, 39.32, 33.09, 30.78 (br), 30.69, 30.66, 30.49, 30.39, 29.75, 27.99, 23.75, 14.48. ESI-HRMS: *m/z* calcd for $C_{51}H_{74}N_7O_2$ [M + H$^+$]: 816.5904; found: 816.5895.

Compound **1b**: $[\alpha]_D^{25}$ –11.3 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD): δ = 7.94 (s, 4 H), 7.44 (s, 2 H), 7.31–7.14 (m, 10 H), 4.14 (br s, 2 H), 3.41 (d, *J* = 5.0 Hz, 4 H), 3.18 (t, *J* = 7.3 Hz, 2 H), 3.07 (dd, *J* = 4.0, 13.9 Hz, 2 H), 2.80 (dd, *J* = 9.5, 13.9 Hz, 2 H), 1.61 (m, 2 H), 1.34–1.08 (m, 30 H), 0.88 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 157.82, 156.31, 142.99, 138.79, 133.13 (q, J_{CF} = 32.6 Hz), 130.14, 129.66, 127.81, 124.76 (d, J_{CF} = 271.3 Hz), 120.70, 118.98, 115.79, 52.66 (br) 47.46, 43.10, 39.20, 33.08, 30.75 (br), 30.61, 30.54, 30.47, 30.16, 29.64, 27.92, 23.74, 14.46. ESI-HRMS: *m/z* calcd for $C_{55}H_{70}F_{12}N_7O_2$ [M + H$^+$]: 1088.5399; found: 1088.5370.

Compound **1c**: $[\alpha]_D^{26}$ –24.5 (*c* 1.4, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD): δ = 7.32–7.17 (m, 10 H), 6.97 (d, *J* = 9.6 Hz, 4 H), 6.46 (t, *J* = 9.2 Hz, 2 H), 4.10 (br s, 2 H), 3.39 (d, *J* = 5.5 Hz, 4 H), 3.18 (t, *J* = 7.3 Hz, 2 H), 3.07 (dd, *J* = 4.6, 13.8 Hz, 2 H), 2.79 (dd, *J* = 9.6, 14.2 Hz, 2 H), 1.63 (m, 2 H), 1.35–1.07 (m, 30 H), 0.88 (t, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 164.61 (dd, J_{CF} = 15.3, 243.4 Hz), 157.77, 156.22, 143.55 (t, J_{CF} = 13.5 Hz), 138.81, 130.18, 129.64, 127.77, 102.09 (dd, J_{CF} = 8.6, 21.1 Hz), 52.54 (br), 47.49 (br), 43.16, 39.22, 33.07, 30.78 (br), 30.71, 30.65, 30.48, 30.38, 29.76, 28.03, 23.74, 14.50. ESI-HRMS: *m/z* calcd for $C_{51}H_{70}F_4N_7O_2$ [M + H$^+$]: 888.5527; found: 888.5572.

Compound **1d**: $[\alpha]_D^{25}$ –40.4 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD): δ = 8.04 (s, 4 H), 7.47 (s, 2 H), 3.78 (br s, 2 H), 3.42 (dd, *J* = 13.8, 5.1 Hz, 2 H), 3.25 (m, 2 H), 3.17 (t, *J* = 7.4 Hz, 2 H), 1.94 (br, 2 H), 1.58 (m, 2 H), 1.33–1.08 (m, 30 H), 1.03 (d, *J* = 6.4 Hz, 6 H), 1.01 (d, *J* = 6.4 Hz, 6 H), 0.88 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 158.30, 156.31, 143.15, 133.20 (q, J_{CF} = 32.6 Hz), 128.84, 124.78 (d, J_{CF} = 272.2 Hz), 120.73, 118.84, 115.68, 55.92 (br), 46.04, 43.03, 33.08, 31.04 (br), 30.75 (br), 30.70, 30.62, 30.52, 30.48, 30.19, 29.80, 27.87, 23.74, 20.19, 17.62 14.46. ESI-HRMS: *m/z* calcd for $C_{47}H_{70}F_{12}N_7O_2$ [M + H$^+$]: 992.5399; found: 992.5373.

Compound **1e**: $[\alpha]_D^{26}$ –8.9 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD): δ = 8.04 (s, 4 H), 7.46 (s, 2 H), 3.91 (br s, 2 H), 3.41–3.14 (m, 6 H), 1.64 (m, 2 H), 1.29 (d, *J* = 6.9 Hz, 6 H), 1.27–1.10 (m, 30 H), 0.87 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 157.80, 156.25, 143.11, 133.15 (q, J_{CF} = 32.6 Hz), 128.84, 124.79 (d, J_{CF} = 272.2 Hz), 120.73, 119.00, 115.72, 47.05 (br), 43.13, 33.08, 30.75 (br), 30.70, 30.61, 30.52, 30.48, 30.14, 29.63, 27.90, 23.74, 18.34, 14.46. ESI-HRMS: *m/z* calcd for $C_{43}H_{62}F_{12}N_7O_2$ [M + H$^+$]: 936.4773; found: 936.4734.



Scheme 1

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(16) We recycled the catalyst **1b** five times under the conditions of entry 11 in Table 1. In these reactions, the yields and enantioselectivities were as follows: 2nd run: 95% with 90% ee; 3rd run: 99% with 90% ee; 4th run: 99% with 91% ee; and 5th run: 99% with 89% ee.

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(18) **Typical Procedure for Asymmetric Epoxidation of 4a**

A mixture of enone **4a** (20.8 mg, 0.10 mmol) and guanidine-urea organocatalyst (*S*,*S*)-**1b** (5.6 mg, 0.005 mmol, 5 mol%) in toluene (0.95 mL) was cooled at –10 °C. To the mixture was added 1 M aq NaOH (0.050 mL, 0.050 mmol) and 30% aq H_2O_2 (0.051 mL, 0.50 mmol of H_2O_2). The mixture was stirred vigorously at –10 °C under argon atmosphere for 6 h. To the reaction mixture was added sat. aq NH_4Cl, and the organic layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane–EtOAc = 100:1 to 10:1) to give epoxy ketone **5a** (22.3 mg, 99%) and catalyst **1b** was quantitatively recovered (5.6 mg, >99%). The ee and absolute configuration of the epoxy ketone **5a** was determined by HPLC using a chiral column.

Spectral Data and HPLC Data for Epoxy Ketone 5a

$[\alpha]_D^{24}$ –210.1 (*c* 0.83, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 6.9 Hz, 2 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 2 H), 7.45–7.35 (m, 5 H), 4.31 (d, *J* = 1.8 Hz, 1 H), 4.08 (d, *J* = 1.8 Hz, 1 H). HPLC separation conditions: Chiralcel OD-H, 0.46 cm (ϕ) × 25 cm (L), hexane–2-PrOH = 98:2, 1.00 mL/min, t_R(minor) = 19.5 min (2*S*,3*R*); t_R(major) = 20.4 min (2*R*,3*S*).[17a]

(19) In the case of aliphatic substituted enones, enantioselectivities were moderate to low (ex. R^1 = Me, R^2 = Ph, 99% yield with 41% ee).

(20) NMR studies were performed in C_6D_6.

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