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NUCLEOPHILIC ASYMMETRIC EPOXIDATION CATALYZED BY CYCLIC GUANIDINES[†]

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Abstract – Asymmetric nucleophilic epoxidation of chalcone and its derivatives was studied using chiral cyclic guanidine compounds. Pentacyclic guanidine **1a**, which has a characteristic closed-type cavity, catalyzed the reaction to give epoxides with 39-60% *ee*. The newly developed tricyclic guanidine **4** drastically accelerated the reaction, and induced the asymmetric induction of chalcones with almost the same level of **1a**.

Development of novel efficient catalysts for asymmetric reactions is one of the important and challenging topics in synthetic organic chemistry. Phase-transfer catalysts (PTCs) are particularly attractive since they have some advantages over homogeneous catalysts, and many efficient asymmetric PTCs have been explored.¹ In the course of our studies aimed at the development of PTCs, we have reported the pentacyclic guanidine catalyst **1** (Figure 1).² The structures of **1** were rationally designed to have a C₂-symmetrical chiral reaction cavity around the guanidine group; i.e., a substrate recognition/activation site. One of these catalysts, **1a**, which has a closed-type cavity and methyl substituents on its ether rings, was found to induce the high enantioselectivity in the alkylation reaction of the Schiff base imine.^{2b} In this communication, we describe the asymmetric nucleophilic epoxidation to α,β -unsaturated ketones catalyzed by **1** and newly synthesized tricyclic guanidine **4**.

Among asymmetric epoxidation, catalytic asymmetric epoxidation of electron-deficient olefins is one of

the most important classes of reactions.^{3,4} Recently, asymmetric nucleophilic epoxidation reaction in the presence of chiral guanidine catalysts has been reported by Taylor et al.,⁵ Murphy et al.,⁶ and Ishikawa et al.⁷ We first examined our pentacyclic guanidine compounds **1a** and **1b** as catalyst for the epoxidation reaction to the electron deficient alkenes.

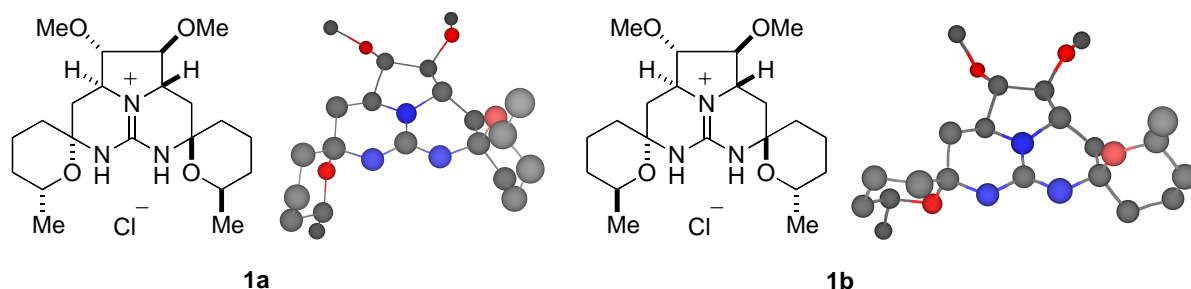
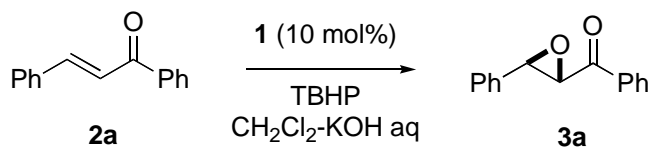


Figure 1. Structures of chiral pentacyclic guanidine **1a** and **1b**, and their X-ray.

Nucleophilic epoxidation reaction of *trans*-chalcone (**2a**) using *tert*-butyl hydroperoxide (TBHP) (5 equivalents) in the presence of **1a** and/or **1b** (10 mol%) was examined in an aqueous 1M KOH/dichloromethane biphasic solution conditions (Table 1). In the case of the reaction with **1a** at room temperature, **3a** was obtained in 76% yield and 22% *ee* (entry 2). Lowering the temperature at 0 °C improved the enantioselectivity up to 39% *ee* (entry 3). When toluene was used instead of dichloromethane, no enantioselectivity was observed (entry 4). In the case of the catalysts **1b**, which has an open-type cavity, **3a** was obtained in 95%, although enantiomeric excess was only 10% (entry 5).



entry	1	temp (°C)	time (h)	yield (%)	ee% ^a
1	---	rt	26	10	---
2	1a	rt	26	76	22
3	1a	0	110	35	39
4	1a	0	40	55	4 ^b
5	1b	0	130	95	10

^aEnantiomeric excess of **3a** was determined by HPLC analysis (DAICEL Chiralcel OD-H). Absolute configuration was determined by comparison of the HPLC retention time and $[\alpha]_D$ value with reported authentic sample data.^{ref 8} ^bToluene was used instead of dichloromethane.

Table 1. Nucleophilic epoxidation of **2a** in the presence of chiral pentacyclic guanidine **1**.

These results are interpreted as follows based upon the alkylation reaction of Schiff base imine in the presence of **1** (Figure 2).^{2b} Carbonyl group in chalcone (**2a**) coordinates with guanidine in **1** through hydrogen bonding, and a nucleophilic attack of the oxidant (TBHP) takes place from the less hindered side to give (2*S*,3*R*)-**3a** as the major product. The structure of **1a**, which has a closed-type cavity and methyl substituents on the ether rings, effectively controlled the nucleophile approach. On the other hand, control of the nucleophile approach was not sufficient by the structure of **1b**, which has open-type cavity, although it was effective for the acceleration of the reaction.

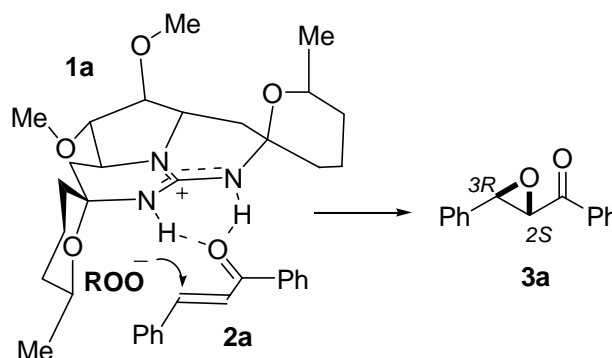
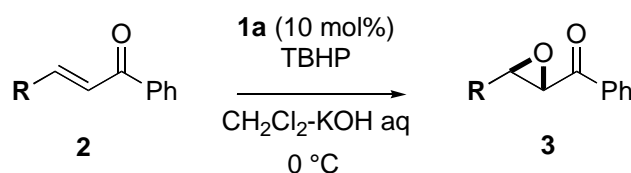


Figure 2. Epoxidation mechanism of **2a** in the presence of pentacyclic guanidine catalysts **1a**.

Epoxidation reaction of the chalcone derivatives **2b-f** was examined in the presence of catalyst **1a** (Table 2). The 2-naphthyl and 1-naphthyl substituted derivatives **2b** and **2c** gave **3b** and **3c** in 50% and 60% *ee*, respectively (entries 1 and 2).^{8,9} On the other hand, the enantiomeric excess was 35% in case of anthracenyl derivative **2d** (entry 3).¹⁰



entry	2	R	product	time (h)	yield (%)	ee% ^a
1	2b	2-naphthyl	3b	140	51	50
2	2c	1-naphthyl	3c	140	77	60
3	2d	9-anthracenyl	3d	140	>99	35
4	2e	4-nitrophenyl	3e	130	82	38
5	2f	4-methoxyphenyl	3f	160	22	36

^aEnantiomeric excess of **3** was determined by HPLC analysis.

Table 2. Nucleophilic epoxidation of **2** in the presence of chiral pentacyclic guanidine **1a**.

Reaction with **2e** and **2f**, which have similar molecular sizes as **2a**, gave similar levels of asymmetric induction as **2a**.⁹

In all cases, the enantiomeric excesses of **3** were moderate, however, reaction times were long (130-160 h). To improve the catalytic activity of **1a**, we designed the novel tricyclic guanidine **4** (Figure 3). The tricyclic guanidine **4** has an open-type cavity similar to **1b**, and two benzyl groups overhang to the up and/or down direction with respect to the tricyclic guanidine plane. The open-type cavity in **4** was expected to improve the reactivity, and the two benzyl groups were anticipated to control the nucleophile approach. The π - π interaction of phenyl groups between **4** and **2** was also expected to fix the reactive complex conformation of **4** and **2**.

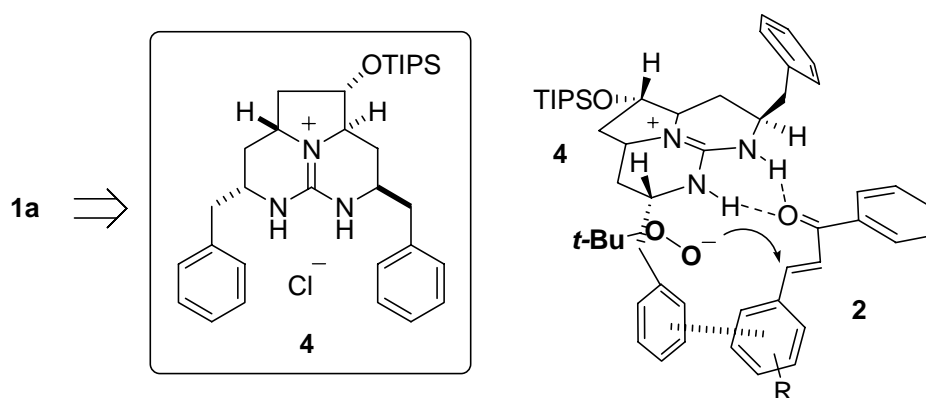
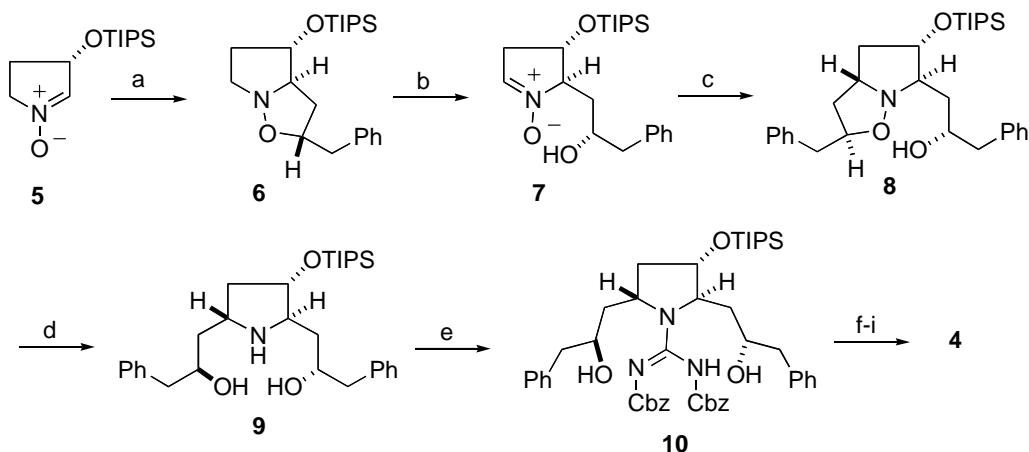


Figure 3. Design of novel tricyclic guanidine **4** and its prospective mechanism for epoxidation.

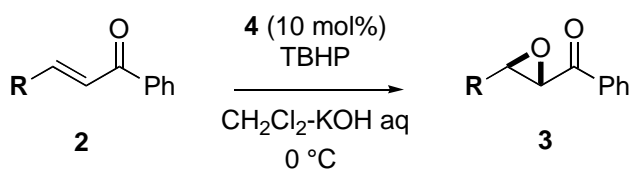
The chiral tricyclic guanidine **4** was synthesized based upon the 1,3-dipolar cycloaddition reaction protocol (Scheme 1).¹¹ Reaction of the optically active nitrone **5**¹² with allylbenzene gave the isoxazolidine **6** in 79% yield. The oxidation of the isoxazolidine **6** with *m*-CPBA effected regioselective ring cleavage to give the nitrone **7**. A second 1,3-dipolar cycloaddition reaction of **7** with allylbenzene was conducted, and subsequent reduction of the N-O bond with NaBH₄ in the presence of Mo(O)₆ gave the 2,5-disubstituted pyrrolidine **9** in 38% yield (3 steps). After guanylation of **9** with bis-Cbz-2-methyl-2-pseudourea in the presence of HgCl₂, tricyclic guanidine was constructed under the Mitsunobu conditions followed by mesylation. Finally, Cbz group was deprotected with hydrogen over 10% Pd/C to give **4** in 30% yield (4 steps).

The epoxidation reaction of **2a-d** was then examined in the presence of **4** (Table 3).¹³ In all cases, the reaction was drastically accelerated to give **3a-d** in quantitative yield, and the enantiomeric excesses were

found to be 52, 52, 41 and 30% *ee*, respectively. Thus, the catalytic activity of **1a** was improved by the tricyclic guanidine **4** without losing the moderate enantioselection of **1a**.



Scheme 1. Synthesis of novel tricyclic guanidine **4**. (a) Allylbenzene, toluene, 90°C, 79%; (b) *m*-CPBA, CH₂Cl₂, 0°C; (c) Allylbenzene, toluene, 90°C, 60% (2 steps); (d) NaBH₄, Mo(CO)₆, CH₃CN:H₂O = 7:1, 64%; (e) bis-Cbz-2-methyl-2-pseudourea, HgCl₂, NEt₃, DMF, 69%; (f) DEAD, PPh₃, toluene; (g) NaH, MeOH, THF; (h) MsCl, NEt₃, CH₂Cl₂; (i) Pd/C, H₂, MeOH, 30% (4 steps).



entry	2	R	product	time (h)	yield (%)	<i>ee</i> % ^a
1	2a	phenyl	3a	26	>99	52
2	2b	2-naphtyl	3b	20	>99	52
3	2c	1-naphtyl	3c	20	>99	41
4	2d	anthracenyl	3d	24	>99	30

^aEnantiomeric excess of **3a** was determined by HPLC analysis.

Table 3. Nucleophilic epoxidation of **2** in the presence of chiral tricyclic guanidine **4**.

In summary, nucleophilic epoxidation reaction of chalcone and its derivatives was examined in the presence of chiral cyclic guanidine catalysts **1** and **4**. In case of the pentacyclic guanidine **1**, closed-type **1a** was effective for the asymmetric induction, and moderate enantiomeric excess of **3** was obtained. The newly developed tricyclic guanidine **4** drastically accelerated the reaction, and induced the chirality of epoxide **3** with almost the same level of **1a**. Further improvements of the catalyst based upon the structure of **4** are in progress.

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†We would like to dedicate this communication to Professor Ivar Ugi.

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10. Absolute configuration of **3d** was not determined. Spectral Data for **3d**: $[\alpha]_D^{23} = -26.3$ (*c* 0.9, CHCl₃). ¹H NMR (500 Mhz, CDCl₃) δ 8.50-8.45 (m, 3H), 8.25 (m, 2H), 8.05-8.03 (m, 2H), 7.71 (m, 1H), 7.60-7.49 (m, 6H), 5.01 (d, *J* = 2.1 Hz, 1H), 4.49 (d, *J* = 2.1 Hz, 1H). HPLC (DAICEL Chiral OD-H): 7% dioxane-hexane, 0.5 mL/min, 46.5 min (minor), 69.2 min (major).
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13. Typical procedure for epoxidation of **2a** in the presence of **4**. A mixture of **2a** (10 mg, 0.05 mmol) and **4** (3 mg, 0.005 mmol) in dichloromethane (0.2 mL) and 1M KOH solution (0.25 mL) was cooled at 0 °C. To the mixture was added TBHP (5M in decane, 0.05 mL, 0.25 mmol), and the resulting mixture was stirred at 0 °C for 26 h. The reaction mixture was added H₂O, and extracted with dichloromethane. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **3a** (11 mg, 99%, 52% *ee*).