HETEROCYCLES, Vol. 73, 2007, pp. 241 - 247. © The Japan Institute of Heterocyclic Chemistry
Received, 3rd July, 2007, Accepted, 1st October, 2007, Published online, 2nd October, 2007. COM-07-S(U)49

NUCLEOPHILIC ASYMMETRIC EPOXIDATION CATALYZED BY CYCLIC GUANIDINES†

Tetsuya Kita,[2] Bongki Shin,[1] Yuichi Hashimoto,[2] and Kazuo Nagasawa[1]*

[1]Department of Biotechnology and Life Science, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan. knaga@cc.tuat.ac.jp

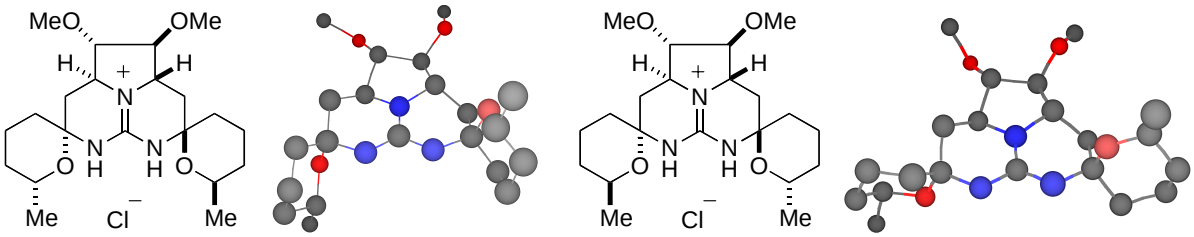
[2]Institute of Molecular and Cellular Biosciences, University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan.

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 C_2-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 enentioselectivity 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

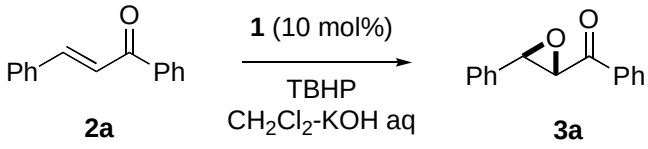
the most important classes of reactions.[3,4] Recently, asymmetric nucleophilic epoxidation reaction in the presence of chiral guanidine catalysts has been reported by Taylor et al.,[5] Murphy et al.,[6] and Ishikawa et al.[7] We first examined our pentacyclic guanidine compounds **1a** and **1b** as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



1a **1b**

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 enantioselectiviy 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).



2a **3a**

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

[a]Enantiomeric 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] [b]Toluene 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 (*2S,3R*)-**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.

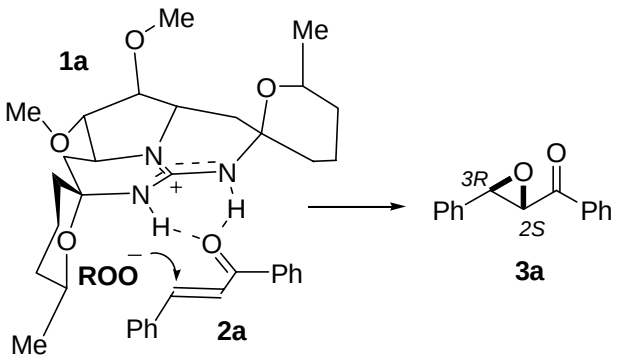
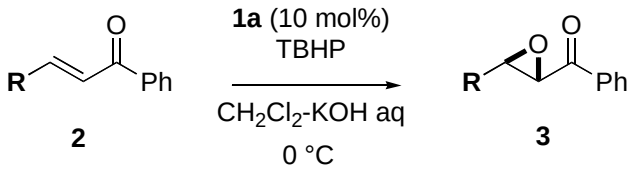


Figure 2. Epoxidation mechanism of **2a** in the presence of pentacyclic guanidine catalysts **1a**.

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-nitorophenyl	**3e**	130	82	38
5	**2f**	4-methoxyphenyl	**3f**	160	22	36

[a]Enantiomeric 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 guandine **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**.

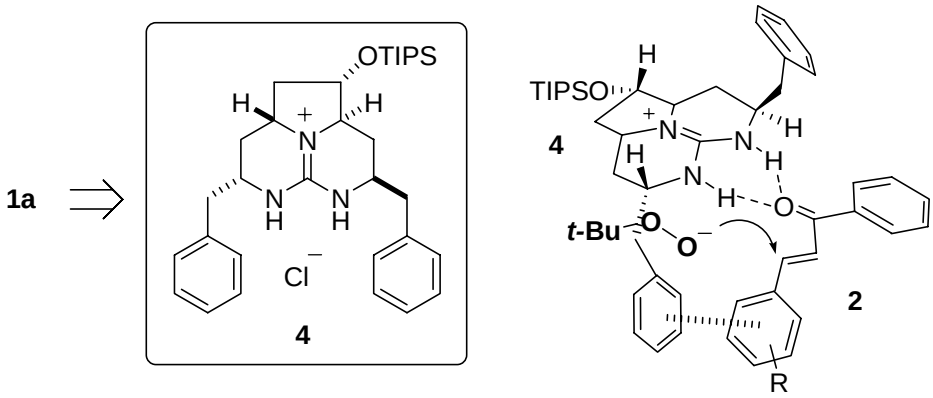
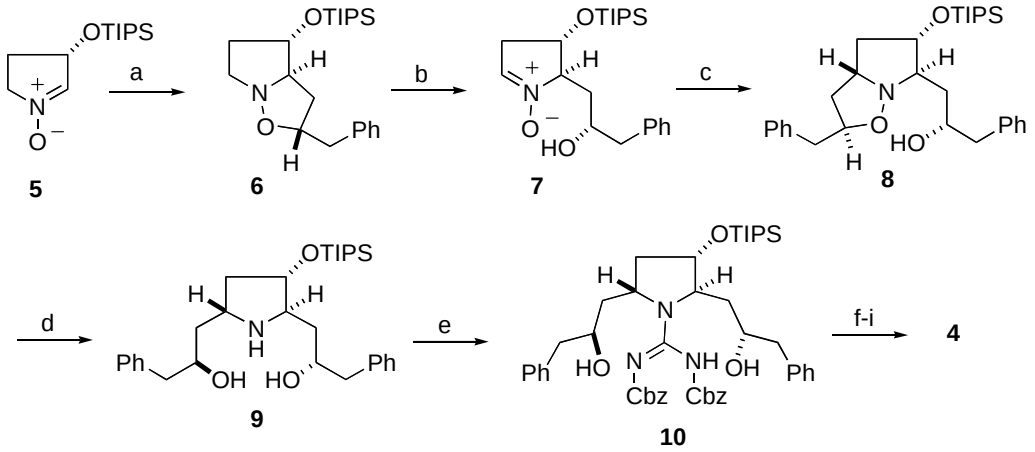


Figure 3. Design of novel tricyclic guanidine **4** and its prospective mechanism for epoxidation.

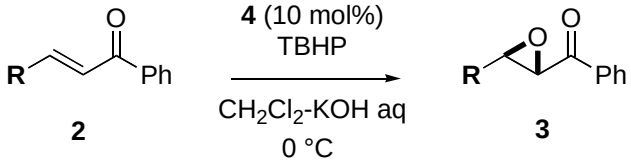
The chiral tricyclic guanidine **4** was synthesized based upon the 1,3-dipolar cycloaddition reaction protocol (Scheme 1).[11] Reaction of the optically active nitrone **5**[12] with allylbenzene gave the isoxazolidine **6** in 79% yield. The oxidation of the isoxazolidine **6** with *m*-CPBA effected 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 $NaBH_4$ 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 $HgCl_2$, tricyclic guanidine was constructed under the Mitunobu 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, CH_2Cl_2, 0°C; (c) Allylbenzene, toluene, 90°C, 60% (2 steps); (d) $NaBH_4$, $Mo(CO)_6$, CH_3CN:H_2O = 7:1, 64%; (e) bis-Cbz-2-methyl-2-pseudourea, $HgCl_2$, NEt_3, DMF, 69%; (f) DEAD, PPh_3, toluene; (g) NaH, MeOH, THF; (h) MsCl, NEt_3, CH_2Cl_2; (i) Pd/C, H_2, MeOH, 30% (4 steps).



entry	**2**	**R**	product	time (h)	yield (%)	ee%[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

[a]Enantiomeric 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.

ACKNOWLEDGEMENTS

This research was supported in part by grants from Mitubishi Chemical Corporation, the Uehara Memorial Foundation, and the Nagase Science and Technology Foundation.

REFERENCES AND NOTES

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

1. a) E. V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed.; VCH:Weinheim, 1993. b) C. M. Starks, C. L. Liotta, and M. Halpern, *Phase-Transfer Catalysis*; Chapman and Hall: New York, NY, 1994. c) *Handbook of Phase-Transfer Catalysis*; ed. by Y. Sasson and R. Neumann; Blackie Academic and Professional: London, 1997. d) *Phase-Transfer Catalysis*; ed. by M. E. Halpern; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997. Recent reviews on asymmetric phase-transfer catalysis, see: e) T. Shioiri, *Handbook of Phase-Transfer Catalysis*; ed. by Y. Sasson and R. Neumann; Blackie Academic and Professional: London, 1997, Chapter 14. f) M. J. O'Donnell, *Catalytic Asymmetric Syntheses*, 2nd ed.; ed. by I. Ojima; Wiley-VCH: New York, NY, 2000; Chapter 10. g) T. Shioiri and S. Arai, *Stimulating Concepts in Chemistry*; ed. by F. Vogtle, J. F. Stoddart, and M. Shibasaki; Wiley-VCH: Weinheim, 2000; p. 123 h) M. J. O'Donnell, *Aldrichimica Acta*, 2001, **34**, 3. i) K. Maruoka and T. Ooi, *Chem. Rev*., 2003, **103**, 3013. j) M. J. O'Donnell, *Acc. Chem. Res*., 2004, **37**, 506. k) B. Lygo and B. I. Andrews, *Acc. Chem. Res*., 2004, **37**, 518.
2. a) K. Nagasawa, A. Georgieva, and T. Nakata, *Tetrahedron*, 2001, **57**, 8959. b) T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, and K. Nagasawa, *Angew. Chem. Int. Ed*., 2002, **41**, 2832.
3. For recent reviews on asymmetric epoxidation of electrone deficient olefins, see: a) M. J. Porter and J. Skidmore, *Chem. Commun*., 2000, 1215. b) T. Nemoto, T. Ohshima, and M. Shibasaki, *J. Synth. Org. Chem. Jpn.*, 2002, **60**, 94. c) Y. Shi, *Acc. Chem. Res*., 2004, **37**, 488.
4. a) M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, and M. Shibasaki, *J. Am. Chem. Soc*., 1997, **119**, 2329. b) T. Nemoto, T. Ohshima, K. Yamaguchi, and M. Shibasaki, *J. Am. Chem. Soc*., 2001, **123**, 2725.
5. a) J. C. McManus, J. S. Carey, and R. J. K. Taylor, *Synlett*, 2003, **3**, 365. b) J. C. McManus, T. Genski, J. S. Carey, and R. J. K. Taylor, *Synlett*, 2003, **3**, 369.
6. M. T. Allingham, A. H.-Jones, P. J. Murphy, D. A. Thomas, and P. W. R. Caulkett, *Tetrahedron Lett*., 2003, **44**, 8677.
7. T. Kumamoto, K. Ebine, M. Endo, Y. Araki, Y. Fushimi, I. Miyamoto, T. Ishikawa, T. Isobe, and K. Fukuda, *Heterocycles*, 2005, **66**, 347.
8. a) B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1998, **39**, 1599. b) B. Lygo and P. G.

Wainwright, *Tetrahedron*, 1999, **55**, 6289. c) B. Lygo and D. C. M. To, *Tetrahedron Lett.*, 2001, **42**, 1343.

9. a) E. J. Corey and F. Y. Zhang, *Org. Lett*., 1999, **1**, 1287. b) T. Ooi, D. Ohara, M. Tamura, and K. Maruoka, *J. Am. Chem. Soc*., 2004, **126**, 6844.
10. Absolute configuration of **3d** was not determined. Spectral Data for **3d**: $[\alpha]_D^{23}$ = - 26.3 (*c* 0.9, $CHCl_3$). ^1H NMR (500 Mhz, $CDCl_3$) 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).
11. a) K. Nagasawa, T. Ishiwata, Y. Hashimoto, and T. Nakata, *Tetrahedron Lett*., 2002, **43**, 6383. b) T. Ishiwata, T. Hino, H. Koshino, Y. Hashimoto, T. Nakata, and K. Nagasawa, *Org. Lett*., 2002, **4**, 2921. c) J. Shimokawa, K. Shirai, A. Tanatani, Y. Hashimoto, and K. Nagasawa, *Angew. Chem. Int. Ed.*, 2004, **43**, 1559. d) J. Shimokawa, T. Ishiwata, K. Shirai, H. Koshino, A. Tanatani, T. Nakata, Y. Hashimoto, and K. Nagasawa, *Chem. Eur. J*., 2005, **11**, 6878.
12. A. Goti, M. Cacciarini, F. Cardona, and A. Brandi, *Tetrahedron Lett*., 1999, **40**, 2853.
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 H_2O, and extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **3a** (11 mg, 99%, 52% *ee*) .