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ASYMMETRIC EPOXIDATION OF α,β-UNSATURATED KETONES WITH HYDROGEN PEROXIDE CATALYZED BY AXIALLY CHIRAL GUANIDINE BASE‡

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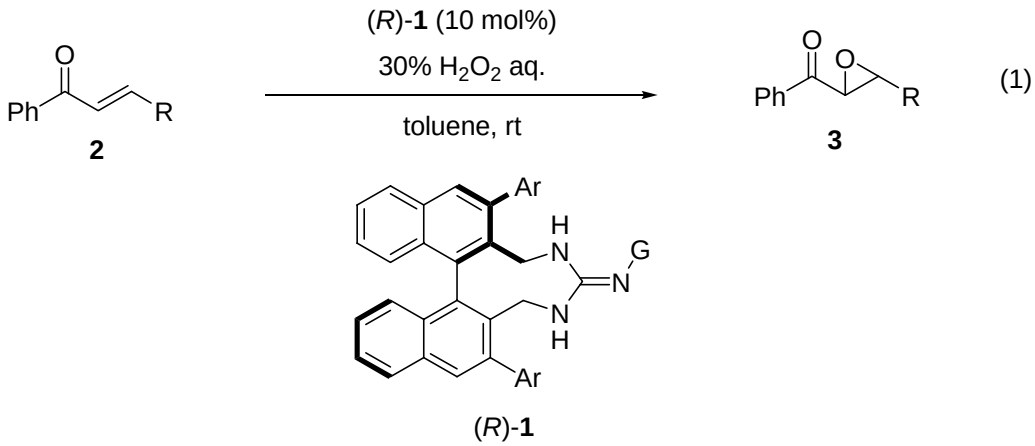
‡Dedication to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract – The enantioselective epoxidation of α,β-unsaturated ketones with hydrogen peroxide was demonstrated using axially chiral guanidine as a base catalyst. Hydrogen peroxide can be utilized as a cost-effective and atom-efficient oxidant in the present catalytic epoxidation even under heterogeneous conditions. The newly developed axially chiral guanidine base bearing an additional central chirality functions as an efficient catalyst to provide epoxides in 51-65% ee.

Catalytic asymmetric epoxidation occupies a privileged position in organic synthesis due to the fundamental importance of enantioenriched epoxides as key synthetic intermediates. A number of efficient protocols for enantioselective epoxidation using chiral metal catalysts and organocatalysts have been reported to date.[1,2] Julia-Colonna epoxidation is one of the most efficient synthetic methods for the enantioselective functionalization of α,β-unsaturated ketones using hydrogen peroxide under basic conditions.[3] Since its discovery in 1980, the enantioselective epoxidation of α,β-unsaturated carbonyl compounds has emerged as an efficient route for preparing highly functionalized synthetic intermediates in bench-top experiments and industrial processes.[4] In recent years, much attention has been devoted to the utilization of aqueous hydrogen peroxide as the terminal oxidant in enantioselective epoxidation because of the distinct advantage that its reduction product is water and the fact that it has high active oxygen content.[5,6]

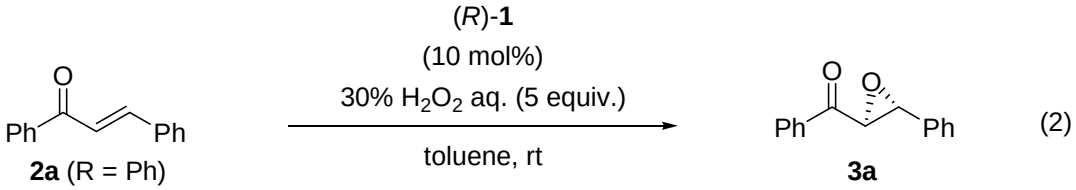
Recently, we successfully developed novel axially chiral guanidines (**1**) as highly efficient Brønsted base catalysts for enantioselective carbon-carbon bond and carbon-heteroatom bond forming reactions.[7] In our continuous studies aimed at extending the synthetic applicability of axially chiral guanidine bases (**1**), we envisioned the activation of hydrogen peroxide by **1** for the asymmetric epoxidation.[8,9] Herein, we report the enantioselective epoxidation of α,β-unsaturated ketones catalyzed by axially chiral guanidine bases (**1**), in which corresponding epoxides were obtained in optically active form by using aqueous hydrogen peroxide as the ecological and atom-efficient oxidant (eq. 1).



An initial experiment was performed using chalcone (**2a**) and commercially available 30% hydrogen peroxide in toluene in the presence of 10 mol% nine-membered axially chiral guanidine catalyst (**1aa**), having a phenyl moiety as the aromatic (Ar) substituent introduced at 3,3'-position of the binaphthyl backbone and an *n*-propyl group as the alkyl (G) substituent introduced at the nitrogen atom of the guanidine moiety (eq. 2). To our delight, guanidine catalyst (**1aa**) accelerated the epoxidation under heterogeneous conditions, albeit the low enantioselectivity of 17% ee (Table 1, entry 1). We then explored suitable substituents on axially chiral guanidine bases (**1**) by changing Ar and G substituents. As shown in Table 1, the catalytic activities and enantioselectivities were profoundly dependent on Ar and G substituents. The introduction of substituents at 3,5-position of the phenyl ring (Ar) had negative effects on both catalytic activities and enantioselectivities, regardless of their electronic properties (entries 2 and 3 vs. entry 1). In contrast, the *para*-substitution had marked electronic effects. Catalyst (**1da**) having an electron withdrawing group, CF_3, retarded the reaction markedly (entry 4). In sharp contrast, *tert*-butyl substituted catalyst (**1ea**) accelerated the reaction significantly to provide epoxide (**3a**) in excellent yield, even though the enantioselectivity remained low (entry 5). In order to increase % ee, we further investigated the effect of G substituent introduced at the nitrogen atom of the guanidine moiety (entries 6 – 10). Since the catalyst bearing 4-*tert*-butylphenyl moiety as the Ar substituent exhibited the

highest catalytic activity, a series of alkyl groups were employed as the G substituents (entries 6 – 10). However, neither small nor bulky aliphatic substituents improved enantioselectivities markedly (entries 6 – 8), although good yields were obtained. Benzyl substituted catalyst (**1ee**) also exhibited a similar enantioselectivity (entry 9). In contrast, use of sterically congested benzhydryl moiety as the G substituent, thus **1ef**, resulted in enhancement of enantioselectivity at 51% ee (entry 10), although the yield of product (**3a**) was low. Further derivatisation of the catalyst bearing benzhydryl moiety and a 4-trifluoromethylphenyl as the Ar substituent, **1df**, led to a similar result as observed in the reaction catalyzed by **1ef** (entry 12 vs. 10).

Table 1. Enantioselective epoxidation of chalcone (**2a**) catalyzed by a series of chiral guanidine bases (**1**).[a]



entry	**1** (Ar, G)	time (h)	yield (%)[b]	ee (%)[c]
1	**1aa**: Ar = C_6H_5- , G = *n*-Pr	9	58	17
2	**1ba**: Ar = 3,5-$(CF_3)_2C_6H_3-$, G = *n*-Pr	24	56	8
3	**1ca**: Ar = 3,5-*t*-$Bu_2C_6H_3-$, G = *n*-Pr	24	40	12
4	**1da**: Ar = 4-$CF_3C_6H_4-$, G = *n*-Pr	24	62	19
5	**1ea**: Ar = 4-*t*-BuC_6H_4- , G = *n*-Pr	7	89	14
6	**1eb**: Ar = 4-*t*-BuC_6H_4- , G = Me	7	93	7
7	**1ec**: Ar = 4-*t*-BuC_6H_4- , G = *c*-Hex	18	79	26
8	**1ed**: Ar = 4-*t*-BuC_6H_4- , G = *t*-Bu	9	90	24
9	**1ee**: Ar = 4-*t*-BuC_6H_4- , G = $PhCH_2-$	24	70	25
10	**1ef**: Ar = 4-*t*-BuC_6H_4- , G = Ph_2CH-	24	27	51
11	**1de**: Ar = 4-$CF_3C_6H_4-$, G = $PhCH_2-$	24	57	27
12	**1df**: Ar = 4-$CF_3C_6H_4-$, G = Ph_2CH-	24	35	50

[a] All reactions were carried out using 0.01 mmol of (*R*)-**1** (10 mol%), 0.1 mmol of chalcone (**2a**), and 30% aqueous hydrogen peroxide (5 equiv.) in 1.0 mL of toluene at room temperature. [b] Isolated yield of **3a**. [c] Enantiomeric excess of **3a** was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H). Absolute stereochemistry of **3a** was determined to be 2*S*,3*R*.[10]

It is considered that the low catalytic activity of **1ef** and **1df** observed in the reaction would be ascribed to an unfavorable interaction between sterically hindered benzhydryl substituents (G) and reactants **2a**. In

order to evaluate the steric demand of the benzhydryl moiety, we determined the optimized structure of the guanidinium cation of catalyst **1ef**.[11] The three-dimensional structure of the lowest energy conformer of **1ef** is illustrated in Figure 1a. One phenyl ring of the benzhydryl moiety is oriented above and the other below the basal plane of the guanidinium moiety. We hence speculated that these phenyl substituents would prevent the formation of a transient assembly between chalcone (**2a**) and ion pairs of guanidinium cation and hydroperoxide anion. In contrast, simple benzyl-substituted catalyst (**1ee** and **1de**) exhibited lower enantioselectivity (25 - 27% ee) than **1ef** and **1df**. This result is presumed to be due to the conformational flexibility around the C-N single bond of the benzyl moiety. We therefore attempted to introduce chirality at the benzylic position, i.e., phenethyl amine derivatives, to restrict conformational flexibility around the single bond. Further optimization of G substituents of guanidine catalysts (**1**) was performed by combining axial and central chiralities (Figure 1b).

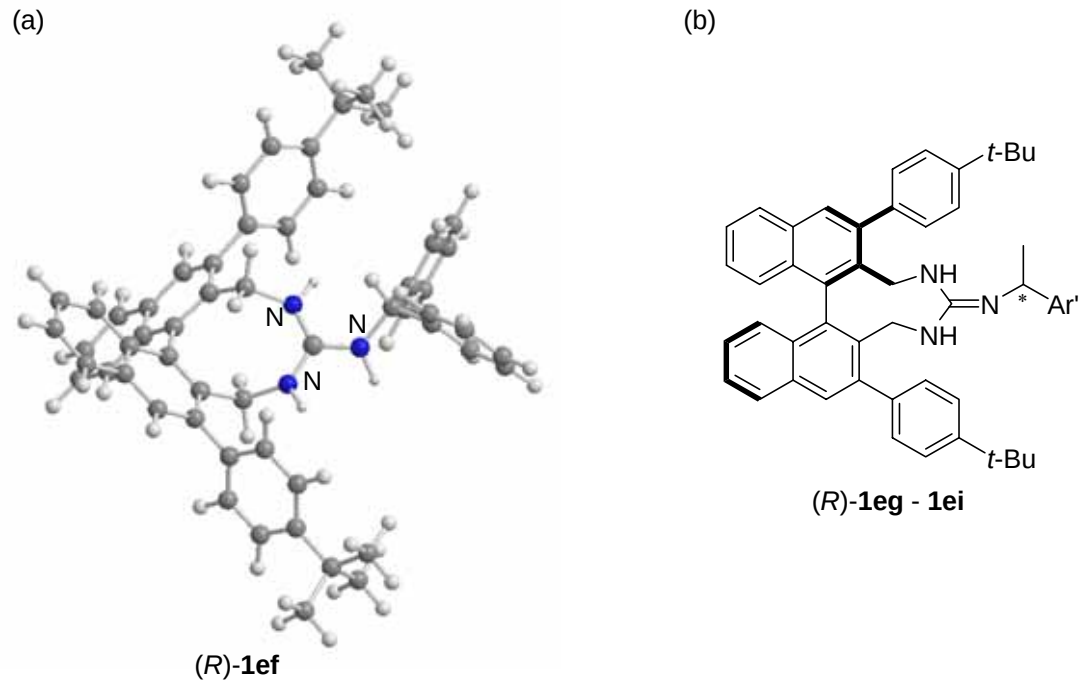
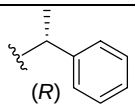
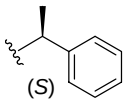
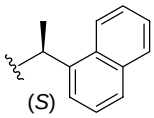


Figure 1. Structure of guanidine catalysts (**1**). (a) Optimized structure of (*R*)-**1ef**. (b) Guanidine catalysts (**1eg** – **1ei**) bearing axial and central chiralities.

The catalyst bearing 4-*tert*-butylphenyl substituent was employed in screening chiral G substituents, because this substituent displayed higher catalytic activity than 4-trifluoromethylphenyl substituent (Table 1, entry 4 vs. 5). Representative results are summarized in Table 2. As expected, catalytic activities and enantioselectivities are markedly dependent on the chirality of G substituents. Introduction of an (*R*)-phenethyl group to catalyst (**1eg**) reduced the enantioselectivity, albeit the modest chemical yield (entry 1). In contrast, diastereomeric catalyst (**1eh**) exhibited better performance than

1eg in terms of catalytic activity and enantioselectivity (entry 2). Further modification of the substituent with a more sterically hindered naphthyl ring, i.e., **1ei**, which has the same absolute configuration at the phenethyl moiety as **1eh**, resulted in enhancement of catalytic activity with almost the same ee (entry 3 vs. 2). Catalyst (**1ei**) is applicable to other α,β-unsaturated ketones (**2b** and **c**) having alkyl substituents (R = Me and *c*-Hex, respectively) (entries 4 and 5). The corresponding products were obtained nearly quantitative yields and ee reached 65% in the reaction of **2c** (R = *c*-Hex) (entry 5).

Table 2. Enantioselective epoxidation of **2** catalyzed by guanidine bases (**1**) having axial and central chiralities.[a]

entry	**1** (Ar, G)	**2**	time (h)	Yield[b] (%)	ee[c] (%)
1	**1eg**: Ar = 4-*t*-BuC_6H_4−, G =  (*R*)	**2a**	18	44	31
2	**1eh**: Ar = 4-*t*-BuC_6H_4−, G =  (*S*)	**2a**	18	57	50
3	**1ei**: Ar = 4-*t*-BuC_6H_4− , G =  (*S*)	**2a**	24	77	52
4	**1ei**	**2b**: R= Me	14	98	51
5	**1ei**	**2c**: R = c-Hex	14	98	65

[a] All reactions were carried out using 0.01 mmol of (*R*)-**1** (10 mol%), 0.1 mmol of chalcone (**2a**), and 30% aqueous hydrogen peroxide (5 equiv.) in 1.0 mL of toluene at room temperature. [b] Isolated yield of **3**. [c] Enantiomeric excess of **3** was determined by chiral HPLC analysis (Daicel Chiralpak AD-H). Absolute stereochemistry of either **3a**[10] or **3b**[12] was determined to be 2*S*,3*R*. Absolute stereochemistry of **3c** was assigned to be 2*S*,3*R* by analogy.[13]

In conclusion, we have demonstrated the enantioselective epoxidation of α,β-unsaturated ketones with hydrogen peroxide catalyzed by an axially chiral guanidine base. Although the enantioselectivities are moderate in the series of guanidine catalysts tested, the newly developed axially chiral guanidine base bearing an additional central chirality functions as an efficient catalyst for asymmetric epoxidation under heterogeneous conditions. In addition, hydrogen peroxide can be utilized as a cost-effective and atom-efficient oxidant in the present catalytic epoxidation. The present catalytic method is expected to contribute to the further development of an environmentally benign process for the asymmetric epoxidation of α,β-unsaturated carbonyl compounds.[14] Further studies to elucidate the mechanisms of the enantiofacial selection are in progress in our laboratory.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. For selected reviews on metal-catalyzed asymmetric epoxidations, see: E. McGarrigle and D. G. Gilheany, *Chem. Rev.*, 2005, **105**, 1563; E. N. Jacobsen and M. H. Wu, 'Comprehensive Asymmetric Catalysis,' Vol. 2, ed. by E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Springer, Heidelberg, 1999, pp. 649-677; T. Katsuki, 'Comprehensive Asymmetric Catalysis,' Vol. 2, ed. by E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Springer, Heidelberg, 1999, pp. 621-648.
2. For selected reviews on organocatalytic asymmetric epoxidations, see: P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2004, **43**, 5138; P. Merino and T. Tejero, *Angew. Chem. Int. Ed.*, 2004, **43**, 2995; A. Armstrong, *Angew. Chem. Int. Ed.*, 2004, **43**, 1460; Y. Shi, *Acc. Chem. Res.*, 2004, **37**, 488; D. Yang, *Acc. Chem. Res.*, 2004, **37**, 497; A. Berkessel and H. Gröger, 'Asymmetric Organocatalysis,' Wiley-VCH, Weinheim, 2005, pp. 277-313.
3. S. Juliá, J. Masana, and J. C. Vega, *Angew. Chem., Int. Ed. Engl.,* 1980, **19**, 929; S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annunziata, and H. Molinari, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1317.
4. For a recent review on asymmetric epoxidation of α,β-unsaturated carbonyl compounds, see: M. J. Porter and J. Skidmore, *Chem. Commun.*, 2000, 1215.
5. For leading reviews on epoxidation of olefins with hydrogen peroxide see: G. Grigoropoulou, J. H. Clark, and J. A. Elings, *Green Chem.*, 2003, **5**, 1; R. Noyori, M. Aoki, and K. Sato, *Chem. Commun.*, 2003, 1977; K. Burgess and B. S. Lane, *Chem. Rev.*, 2003, **103**, 2457; I. W. C. E. Arends, *Angew. Chem. Int. Ed.*, 2006, **45**, 6250.
6. For recent examples of organocatalytic asymmetric epoxidations using hydrogen preroxide, see: M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964; W. Z. Zhuang, M. Marigo, and K. A. Jørgensen, *Org. Biom. Chem.*, 2005, 3883; H. Sundén, I. Ibrahem, and A. Córdova, *Tetrahedron Lett.*, 2006, **47**, 99; G.-L. Zhao, I. Ibrahem, H. Sundén, and A. Córdova, *Adv. Synth. Catal.*, 2007, **349**, 1210; C. P. Burke, L. Shu, and Y. Shi, *J. Org. Chem.*, 2007, **72**, 6320.
7. M. Terada, H. Ube, and Y. Yaguchi, *J. Am. Chem. Soc.*, 2006, **128**, 1454; M. Terada, M. Nakano, and H. Ube, *J. Am. Chem. Soc.*, 2006, **128**, 16044; H. Ube, M. Terada, and D. Uraguchi, *J.*

Organomet. Chem., 2007, **692**, 545; M. Terada, T. Ikehara, and H. Ube, *J. Am. Chem. Soc.*, 2007, **129**, 14112.

8. For reviews of chiral guanidine catalysts, see: T. Ishikawa and T. Isobe, *Chem. Eur. J.*, 2002, **8**, 552; T. Ishikawa and T. Kumamoto, *Synthesis*, 2006, 737.
9. For asymmetric epoxidation promoted by chiral guanidines, see: J. C. McManus, J. S. Carey, and R. J. K. Taylor, *Synlett*, 2003, 365; J. C. McManus, T. Genski, J. S. Carey, and R. J. K. Taylor, *Synlett*, 2003, 369; M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas, and P. W. R. Caulkett, *Tetrahedron Lett.*, 2003, **44**, 8677; T. Kumamoto, K. Ebine, M. Endo, Y. Araki, Y. Fushimi, I. Miyamoto, T. Ishikawa, T. Isobe, and K. Fukuda, *Heterocycles*, 2005, **66**, 347; T. Kita, B. Shin, Y. Hashimoto, and K. Nagasawa, *Heterocycles*, 2007, **73**, 241.
10. B. M. Choudary, M. L. Kantam, K. V. S. Ranganath, K. Mahendar, and B. Sreedhar, *J. Am. Chem. Soc.*, 2004, **126**, 3396; C. L. Elston, R. F. W. Jackson, S. J. F. MacDonald, and P. J. Murray, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 410; B. Lygo and P. G. Wainwright, *Tetrahedron*, 1999, **55**, 6289.
11. Geometry optimization was conducted using density functional theory (B3LYP) at the 6-31G* level.
12. O. Meth-Cohn, R. M. Horak, and G. Fouché, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1517; W. Adam, P. B. Rao, H.-G. Degen, and C. R. Saha-Möller, *J. Am. Chem. Soc.*, 2000, **122**, 5654.
13. S. Arai, Y. Shirai, T. Ishida, and T. Shioiri, *Tetrahedron*, 1999, **55**, 6375.
14. Representative procedure for guanidine-catalyzed asymmetric epoxidation of chalcone (**2a**): To a toluene solution (1.0 mL) of guanidine catalyst [(*R*)-**1ei**] (7.56 mg, 0.01 mmol) and chalcone (**2a**) (20.8 mg, 0.10 mmol) was added H_2O_2 solution (52 μL, 30% aqueous solution, 0.5 mmol). The reaction mixture was vigorously stirred at room temperature and the progress of the reaction was monitored by TLC. The resulting solution was quenched with Na_2SO_3 aq. and extracted with AcOEt. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexane/AcOEt = 20/1 to 10/1) to afford *trans*-epoxy-1,3-diphenylpropan-1-one (**3a**) in 77% yield (17.2 mg, 52% ee). Enantiomeric excess was determined by chiral HPLC analysis. (2*S*,3*R*)-**3a**: HPLC analysis: Daicel Chiralpak AD-H (hexane/EtOH = 85/15, 1.0 mL/min, 254 nm, 10 °C) 21.4 (major), 27.8 (minor) min; and Daicel Chiralcel OJ-H (hexane/2-propanol = 90/10, 1.0 mL/min, 254 nm, rt) 28.2 (minor), 30.5 (major) min; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.07 (1H, d, J = 1.9 Hz), 4.29 (1H, d, J = 1.9 Hz), 7.35-7.63 (8H, m), 8.00-8.03 (2H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 59.9, 61.5, 126.3, 128.9, 129.3, 129.4, 129.6, 134.5, 136.0, 193.6. These spectral data are consistent with previous reports.[10]