Pergamon

Tetrahedron Letters 43 (2002) 4481–4485

TETRAHEDRON LETTERS

# Highly enantioselective Baeyer–Villiger oxidation using Zr(salen) complex as catalyst

Akira Watanabe,[a] Tatsuya Uchida,[a] Katsuji Ito[b] and Tsutomu Katsuki[a,*]

[a]*Department of Chemistry, Faculty of Science, Graduate School, Kyushu University 33, CREST JST (Japan Science and Technology), Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan*

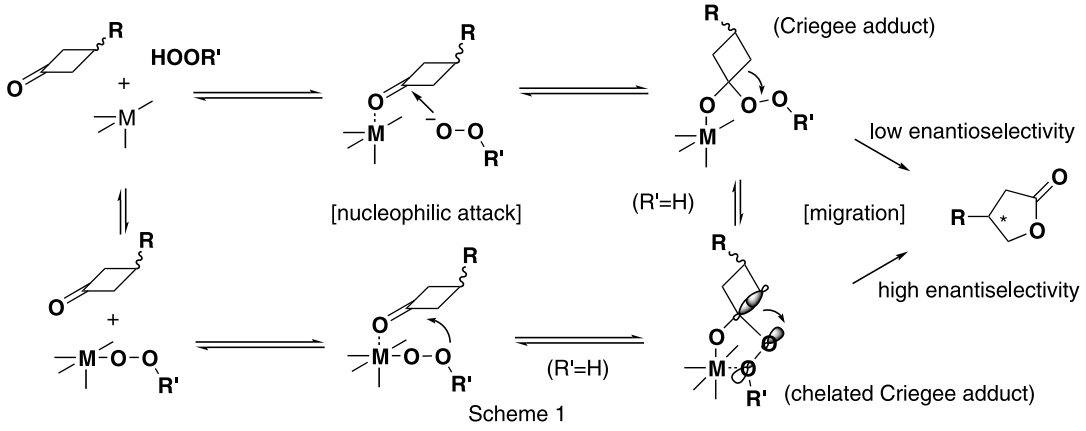
[b]*Department of Chemistry, Fukuoka University of Education, CREST JST, Akama, Munakata, Fukuoka 811-4192, Japan*

Received 25 March 2002; accepted 26 April 2002

**Abstract**—(*R*,*R*)-Zr(salen) complex was found to serve as an efficient catalyst for asymmetric Baeyer–Villiger oxidation of pro-chiral and racemic ketones using urea·hydrogen peroxide as the terminal oxidant: for example, high enantioselectivity of 87% ee was achieved in the Baeyer–Villiger reaction of 3-phenylcyclobutanone. © 2002 Elsevier Science Ltd. All rights reserved.

The Baeyer–Villiger (B–V) reaction, oxidative conversion of carbonyl to ester (or lactone), is of high synthetic value and has been widely used in various syntheses. Although many biocatalyzed asymmetric B–V reactions are known,[1] their chemical versions are still limited in number. In 1994, Bolm et al. reported copper-catalyzed asymmetric B–V reaction.[2] In the same year, Strukul et al. reported platinum-catalyzed asymmetric B–V reaction.[3] Since then, several catalysts have been introduced for asymmetric B–V reaction[4] and high enantioselectivity has been realized in the B–V reactions of some limited substrates.[5] Still, introduction of new methodology for asymmetric B–V oxidation is strongly required.

B–V oxidation is a two-step reaction: (i) nucleophilic addition of an oxidant giving the Criegee adduct and (ii) rearrangement of the adduct to ester (or lactone). If the starting carbonyl compound is a pro-chiral cyclic one, the B–V oxidation product is a pair of enantiomeric lactones (Scheme 1). The stereochemistry of the B–V reaction is dictated by two factors: face selectivity in oxidant addition and enantiotopos selectivity in migration. However, as Criegee adduct formation is a reversible step and its migration to lactone is an irreversible and rate-determining one, topos-selection in the migration step is considered to strongly influence the stereochemistry of B–V reaction.




Scheme 1

**Scheme 1.**

*Keywords*: Zr(salen) complex; asymmetric catalysis; Baeyer–Villiger oxidation; hydrogen peroxide.

* Corresponding author. Fax: +81-92-642-2607; e-mail: katsuscc@mbox.nc.kyushu-u.ac.jp

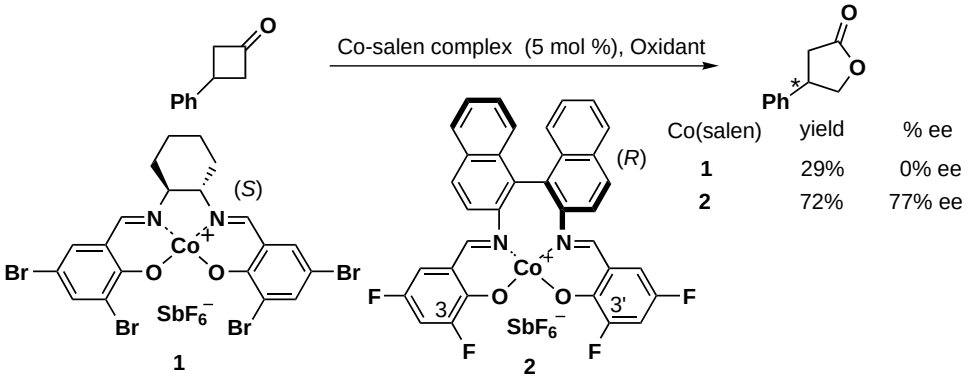

PII: S0040-4039(02)00831-6

Interaction of the σ-orbital of the migrating C–C bond and the σ*-orbital of the O–O bond is crucial for the migration.[1d] Therefore, it was expected that high enantioselectivity would be achieved if the σ-bond interacts with the σ*-bond topos-selectively. It was also considered that the topos-selective interaction would be realized if the Criegee adduct makes a chelate, and the chelate conformation is regulated appropriately. Furthermore, a metallosalen complex [M(salen)] of *cis*-β structure was considered to be a suitable catalyst for this purpose, because it provides two neighboring coordinating sites for chelate formation and its metal center is chiral.[6]

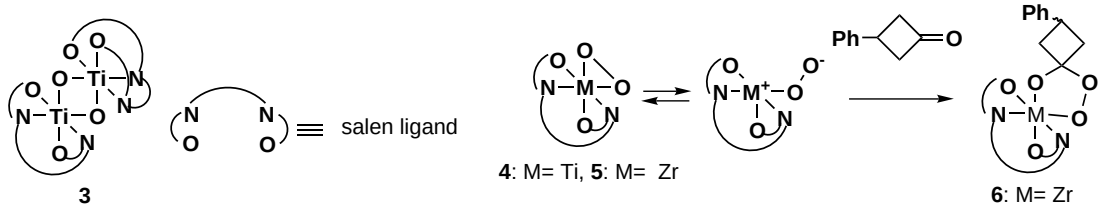
Indeed, Co(salen) **1** of square planar geometry did not show any enantioselectivity in the B–V oxidation of 3-substituted cyclobutanone, while Co(salen) **2** possessing a *cis*-β structure showed good enantioselectivity (up to 78% ee) (Scheme 2).[6] However, this result meant that the control of the chelate conformation by **2** was not sufficient. To strengthen the control, we tried to modify complex **2** by introducing a chiral substituent at its 3- and 3′-carbons but such attempts failed.

We recently reported highly enantioselective sulfoxidation using di-μ-oxo Ti(salen) of *cis*-β structure **3** as the catalyst, which proceeded through a peroxy Ti(salen) intermediate **4**.[7] We expected that complex **3** would also serve as the catalyst for B–V reaction but it showed little catalytic activity. The peroxy ring of **4** must be opened to allow carbonyl coordination for B–V oxidation (Scheme 3). Due to high oxophilicity of titanium ion, however, the ring-opening was considered to be slow. On the other hand, titanium and zirconium ions have similarities in many respects, and we expected that treatment of the Zr(salen) complex with hydrogen peroxide would give a peroxy Zr(salen) complex **5** of *cis*-β structure.[8] Due to the less oxygenophilic nature of the zirconium ion and the longer Zr–O bond, however, a putative peroxy zirconium species **5** was expected to readily undergo ring-opening and to promote B–V oxidation (Scheme 4).

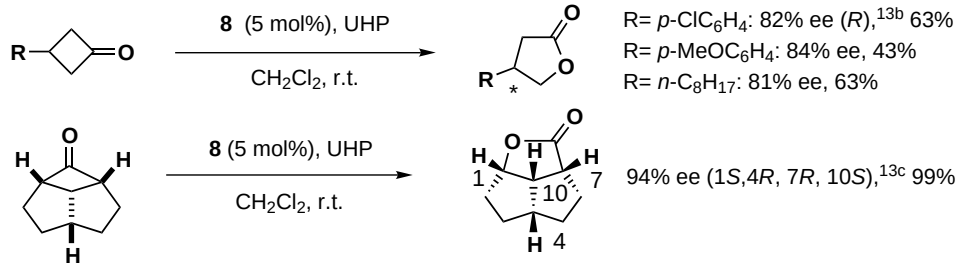
Based on this consideration, we examined Zr(salen)-catalyzed B–V reaction of 3-phenylcyclobutanone using urea·hydrogen peroxide adduct (UHP) as oxidant at room temperature (Table 1). Complexes **7**–**10** were prepared according to the reported procedure with a




**Scheme 2.**

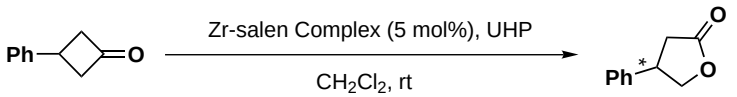



**Scheme 3.**




**Scheme 4.**

**Table 1.** Asymmetric B–V oxidation of 3-phenylcyclobutanone using Zr(salen) complexes as catalyst




| Entry | Catalyst | Yield (%) | % ee[a] | Config.[b] |
|---|---|---|---|---|
| 1 | **7** | 20 | 23 | *S* |
| 2 | **8** | 68 | 87 | *R* |
| 3 | **9** | 13 | 9 | *S* |
| 4 | **10** | 12 | 1 | – |

[a] Determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AD-H, hexane/*i*-PrOH = 49/1).
[b] Configuration was determined by comparison of specific rotation with the reported ones (see Ref. 13a).

slight modification.[9] Among these complexes, complex **8** showed good catalytic activity and high asymmetric induction. On the other hand, its diastereomeric complex **9** was a poor catalyst, suggesting that the chiral binaphthyl unit affected the regulation of the chelate conformation adversely. Complex **10** was also found to be a poor catalyst.[10]

We next examined the effect of the terminal oxidant and solvent on enantioselectivity of the reaction using **8** as the catalyst at room temperature (Table 2). Although the original condition was found to be the best (Table 1), the reaction in chlorobenzene also showed good enantioselectivity (entry 5). Use of a polar solvent such as ether and alcohol reduced enantioselectivity (entries 6 and 7). *t*-Butyl hydrogenperoxide and bis(trimethylsilyl)peroxide were poor oxidants. These results are compatible with the above mechanistic consideration: the presence of bulky *t*-butyl and silyl groups retards chelate formation (Scheme 1). The effect of the reaction temperature was also examined. The reaction rate was enhanced as the temperature rose, but enantioselectivity was diminished at either higher or lower temperature (entries 8 and 9).

Under the best conditions, we examined the reactions of other 3-substituted cyclobutanones using **8** as the catalyst. All the reactions proceeded with high enantioselectivity (Scheme 4). The reaction of tricyclic ketone also proceeded with high enantioselectivity of 94% ee in a good yield.

**Table 2.** Effect of terminal oxidant and solvent on enantioselectivity of B–V reaction with complex **8**

| Entry | Oxidant | Solvent | Yield (%) | % ee[a] |
|---|---|---|---|---|
| 1 | UHP | $CH_2Cl_2$ | 68 | 87 |
| 2 | $H_2O_2$ | $CH_2Cl_2$ | 60 | 56 |
| 3 | TBHP | $CH_2Cl_2$ | Trace | – |
| 4 | TMS-O-O-TMS | $CH_2Cl_2$ | 11 | 4 |
| 5 | UHP | PhCl | 80 | 85 |
| 6 | UHP | $Et_2O$ | 32 | 45 |
| 7 | UHP | EtOH | 44 | 52 |
| 8[b] | UHP | $CH_2Cl_2$ | 58 | 81 |
| 9[c] | UHP | $CH_2Cl_2$ | 78 | 81 |

[a] Determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AD-H, hexane/*i*-PrOH = 49/1).
[b] Reaction was carried out under 0°C.
[c] Reaction was carried out under 40°C.

B–V reaction of racemic bicyclo[4.2.0]octan-7-one was then examined in chlorobenzene. The reaction proceeded to give normal and abnormal rearrangement products (**A** and **B**).[5a,8,11] Enantiomeric excess of major normal product **A** was diminished as the reaction proceeded, while that of minor product **B** was constantly greater than 99% (Table 3). The relative reaction ratio ($k_{rel}$) of fast and slow isomers of the racemic ketone was

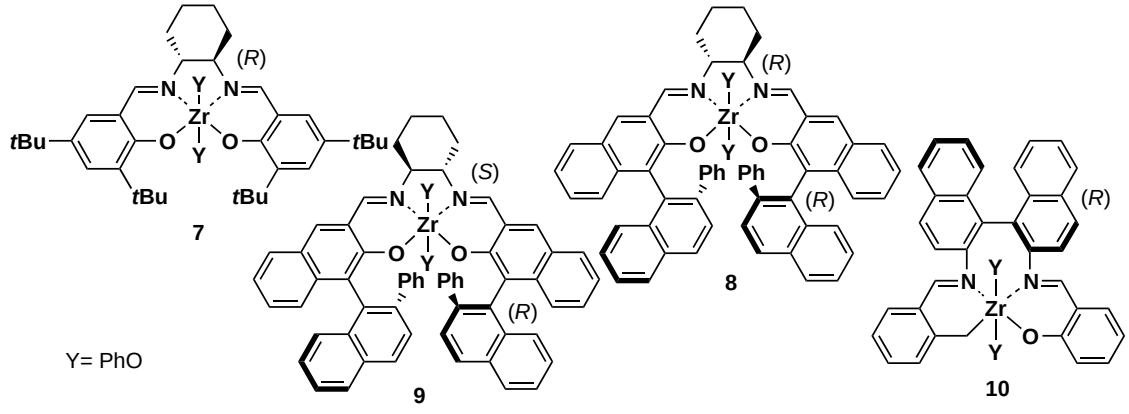
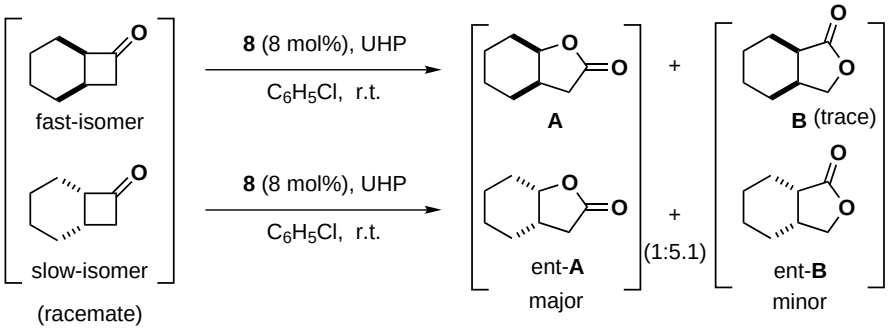


**Table 3.** B–V oxidation of racemic bicyclooctanone using Zr(IV)–salen complex **8** as the catalyst




| Run | Ketone | | | A | | B | |
|---|---|---|---|---|---|---|---|
| | Conv. (%)[a] | % ee[b] | $k_{rel}$ | Yield (%)[a] | % ee[b] | Yield (%)[a] | % ee[b] |
| 1 | 76 | 86 | 4.2 | 54 | 82 | 22 | >99 |
| 2 | 83 | 92 | 3.8 | 51 | 82 | 24 | >99 |
| 3 | 76 | 82 | 3.5 | 53 | 85 | 21 | >99 |
| 4 | 71 | 77 | 4.1 | 48 | 85 | 20 | >99 |
| 5 | 83 | 94 | 4.1 | 55 | 80 | 25 | >99 |

[a] Conversion of racemic ketone and yields of lactones were determined by GLC analysis using bicyclohexyl as the internal standard.
[b] Determined by GLC analysis using optically active column (SUPELC BETA-DEX-255).

determined to be ca. 4 according to Kagan's equation.[12] These results suggested that the reaction of the fast isomer gave normal product **A** exclusively, while the reaction of the slow isomer gave ent-**A** and abnormal product (ent-**B**) in a ratio of 1:5.1. The reaction of the optically pure slow isomer with complex **8** provided normal product **A** of >99% ee and abnormal product **B** of >99% ee in a 1:6.6 ratio. This indicates that the topos selection by **8** overrides the migratory attitude of the carbonyl substituent in Baeyer–Villiger reaction.[11]

*General procedure for asymmetric Baeyer–Villager reaction with Zr(salen) complex **8***: 3-Phenylcyclobutanone (14.6 mg 0.1 mmol) was dissolved in $CH_2Cl_2$ (1.0 ml). To the solution were added complex **8** (5.5 mg, 5.0 μmol) and UHP (12 mg, 0.12 mmol) successively and the resulting mixture was stirred at room temperature for 24 h. The mixture was concentrated on a rotary evaporator and chromatographed on silica gel using a mixture of hexane and AcOEt (6.5:1) as the eluate to give β-phenyl-γ-butyrolactone (10.9 mg, 68%). The enantiomeric excess of the product was determined by HPLC analysis using DAICEL CHIRALPAK AD-H (hexane:*i*-PrOH = 49:1).

In conclusion, we were able to demonstrate that asymmetric Bayer–Villiger reaction can be effected in a highly enantioselective manner by using suitably designed Zr(salen) complex **8** as the catalyst.

## References

1. For recent reviews, see: (a) Alphand, V.; Furstoss, R. In *Handbook of Enzyme Catalysis in Organic Synthesis*; Drauz, K.; Waldmann, H., Eds.; VCH: Weinheim, 1995; Vol. 2, pp. 744–772; (b) Stewart, J. D. *Curr. Org. Chem.* **1997**, *2*, 211–232; (c) Kayser, M.; Chen, G.; Stewart, J. *Synlett* **1999**, 153–158; (d) Kelly, D. R. *Chem. Oggi/Chem. Today* **2000**, *18*, 33–39 and 52–56; (e) Alphand, V.; Furstoss, R. In *Asymmetric Oxidation Reactions: A Practical Approach*; Katsuki, T., Ed.; Oxford University Press: Oxford, 2001; pp. 214–226.
2. Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1848–1849.
3. Gusso, A.; Baccin, C.; Pinna, F.; Strukul, G. *Organometallics* **1994**, *13*, 3442–3451.
4. (a) Bolm, C.; Beckmann, O. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp. 803–810; (b) Strukul, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1198–1209.
5. (a) Bolm, C.; Luong, K. K.; Schlingloff, G. *Synlett* **1997**, 1151–1152; (b) Bolm, C.; Beckmann, O.; Cosp, A.; Palazzi, C. *Synlett* **2001**, 1461–1463; (c) Bolm, C.; Beckmann, O.; Palazzi, C. *Can. J. Chem.* **2001**, *79*, 1593–1597.
6. Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 6911–6914.
7. (a) Saito, B.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3873–3876; (b) Saito, B.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 8333–8336.
8. Zirconium-mediated Baeyer–Villiger oxidation has been reported. See: Bolm, C.; Beckmann, O. *Chirality* **2000**, *12*, 523–525.
9. (a) Schweder, B.; Walther, D.; Döhler, T.; Klobs, O.; Görls, H. *J. Prakt. Chem.* **1999**, *341*, 736–746; (b) Woodman, P. R.; Munslow, I. J.; Hitchcock, P. B.; Scott, P. *J. Chem. Soc., Dalton Trans.* **1999**, 4069–4076.
10. Although the structure of **10** has not been determined yet, the structure of the corresponding dichloro complex (Y = Cl) has been determined to take a *cis*,*cis*-structure by X-ray analysis (Ref. 9b).

11. Migratory attitude of the carbonyl substituent in B–V oxidation is in the order of tertiary>secondary>primary.
12. Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S. H., Eds.; John Wiley & Sons: New York, 1988; Vol. 18, pp. 249–330.
13. (a) Specific rotation of 4-phenylbutyrolactone (87% ee): $[\alpha]_D^{20}=-41.4$ (*c* 0.6, $CHCl_3$); lit.[14a] [96% ee (*S*)-isomer]; $[\alpha]_D^{20}=+46.0$ (*c* 0.95, $CHCl_3$); (b) Specific rotation of 4-(*p*-chlorophenylbutyrolactone (82% ee): $[\alpha]_D^{20}=-35.9$ (*c* 0.5, $CHCl_3$); lit.[14b] [>99% ee (*R*)-isomer]; $[\alpha]_D^{25}=-51.0$ (*c* 0.5, $CHCl_3$); (c) Specific rotation of 2-oxatricyclo-[5.2.1.0$^{4,10}$]decan-3-one (94% ee): $[\alpha]_D^{25}=-66.7$ (*c* 0.28, $CHCl_3$); lit.[14c] [>98% ee (1*R*,4*S*,7*S*,10*R*)-isomer]; $[\alpha]_D^{25}=+62.0$ (*c* 1.0, $CHCl_3$).
14. (a) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047–4056; (b) Mazzini, C.; Lebreton, J.; Alphand, Y.; Furstoss, R. *Tetrahedron Lett*. **1997**, *38*, 1195–1196; (c) Kelly, D. R.; Knowles, C. J.; Mahdi, J. G.; Wright, M. A.; Taylor, I. N.; Hibbs, D. E.; Hursthouse, M. B.; Mish'al, A. K.; Roberts, S. M.; Wan, P. W. H.; Grogan, G.; Willetts, A. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2057–2066.