HETEROCYCLES, Vol. 55, No. 2, 2001, pp. 237 - 242, Received, 17th November, 2000

ASYMMETRIC BAEYER-VILLIGER OXIDATION OF CYCLOBUTANONES USING DIETHYLZINC / OXYGEN / CHIRAL AMINO ALCOHOLS

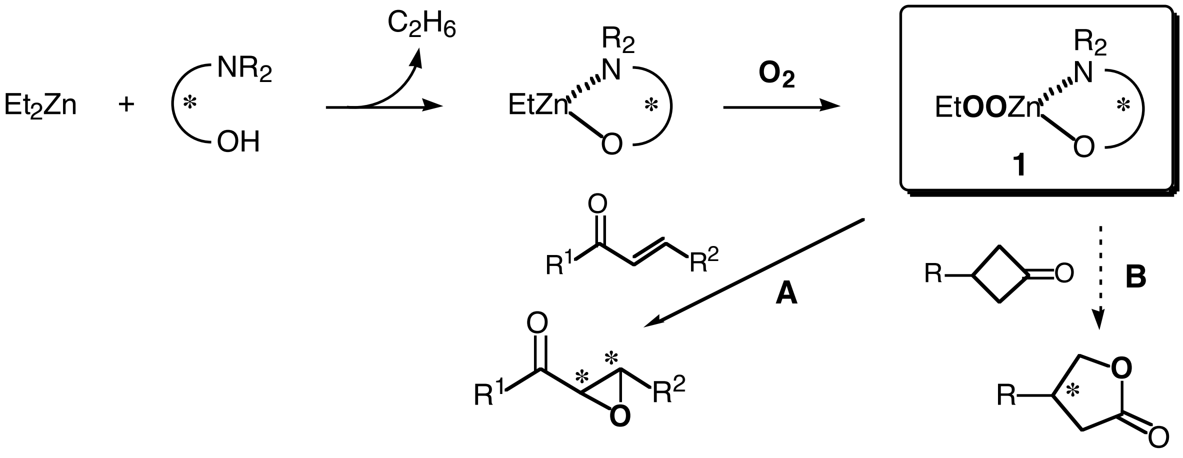
Toshio Shinohara, Shingo Fujioka, and Hiyoshizo Kotsuki*

Laboratory of Natural Products Synthesis, Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan

Abstract - A novel method for the asymmetric Baeyer-Villiger oxidation of cyclobutanones using diethylzinc/oxygen/chiral amino alcohols has been developed. The best result was obtained using (1*R*,2*S*)-*N*,*N*-diethylnorephedrine as the chiral ligand: 3-phenylcyclobutanone was converted into (*S*)-β-phenyl-γ-butyrolactone with 39% ee and in 75% chemical yield.

Since its discovery just 100 years ago,[1] Baeyer-Villiger oxidation has been widely used to transform carbonyl compounds to the corresponding esters or lactones.[2] Surprisingly, until recently only a few papers concerning asymmetric Baeyer-Villiger oxidation[3] have been published, while there are many examples in biological systems.[4] The reported procedures rely on the use of chiral Ni or Cu catalysts/O_2/RCHO,[5] chiral Pt catalysts/H_2O_2,[6] and the Sharpless catalyst.[7] Besides these catalytic methods, Sugimura and coworkers reported that chiral acetals could serve as a convenient substrate to achieve the requisite asymmetric Baeyer-Villiger oxidation using *m*-CPBA/$SnCl_4$.[8]

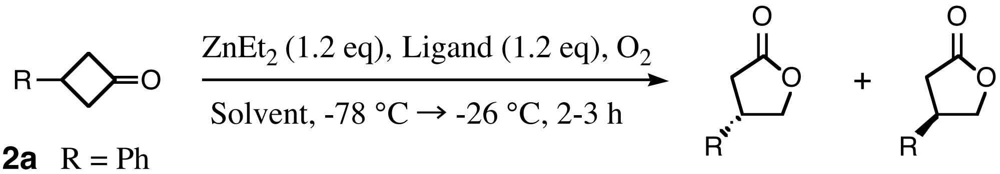
As part of our ongoing research on asymmetric Baeyer-Villiger oxidation,[9] we were particularly interested in Enders' reports[10] on an efficient asymmetric epoxidation of enones using diethylzinc/oxygen/chiral amino alcohols (**Scheme 1**, route **A**). The characteristic chiral zinc ethyl peroxide intermediate (**1**) formed during the reaction sequence prompted us to examine the feasibility of applying this approach to asymmetric



Scheme 1

Baeyer-Villiger oxidation (**Scheme 1**, route **B**), since it is normally considered that there is an inherent relationship between epoxidation and Baeyer-Villiger oxidation, as in the case of Sharpless oxidation.[7] In this Communication, we describe the realization of this expectation. The results are summarized in Table 1.

Table 1. Asymmetric Baeyer-Villiger oxidation of 3-substituted cyclobutanones



(*S*)-**3** (*R*)-**3**

2a R = Ph
2b R = 4-ClC$_6$H$_4$
2c R = 4-MeOC$_6$H$_4$
2d R = 2-Naphthyl
2e R = 2-MeOC$_6$H$_4$
2f R = 2-HOC$_6$H$_4$

Entry	2	Ligand	Solvent	Yield (%)	ee (%) of **3**[a]	Configuration[b]
1	**2a**	**A**	toluene	72	14	*S*
2	**2a**	**A**	THF	75	15	*S*
3	**2a**	**A**	CH_2Cl_2	68	7	*S*
4	**2a**	**B**	toluene	75	39	*S* ◀
5	**2a**	**C**	toluene	73	8	*S*
6	**2a**	**D**	toluene	70	6	*S*
7	**2a**	**E**	toluene	60	14	*S*
8	**2a**	**F**	toluene	71	6	*S*
9	**2a**	**G**	toluene	61	2	*S*
10	**2a**	**H**	toluene	64	31	*S*
11	**2a**	**I**	toluene	72	2	*R*
12	**2a**	**J**	toluene	88	26	*S*
13	**2a**	**K**	toluene	72	22	*R*
14	**2a**	**L**	toluene	70	4	*R*
15	**2a**	**M**	toluene	77	6	*R*
16	**2a**	**N**	toluene	74	14	*S*
17	**2a**	**O**	toluene	65	10	*S*
18	**2b**	**B**	toluene	68	31	*S*
19	**2c**	**B**	toluene	69	35	*ND*[c]
20	**2d**	**B**	toluene	85	34	*ND*[c]
21	**2e**	**B**	toluene	75	40	*ND*[c]
22	**2f**	**B**	toluene	73	36	*ND*[c]

[a] Determined by chiral HPLC (DAICEL Chiralpak AD). [b] Determined from the sign of the specific rotation. See Ref. 11. [c] The absolute configuration was not determined. See Ref. 17.

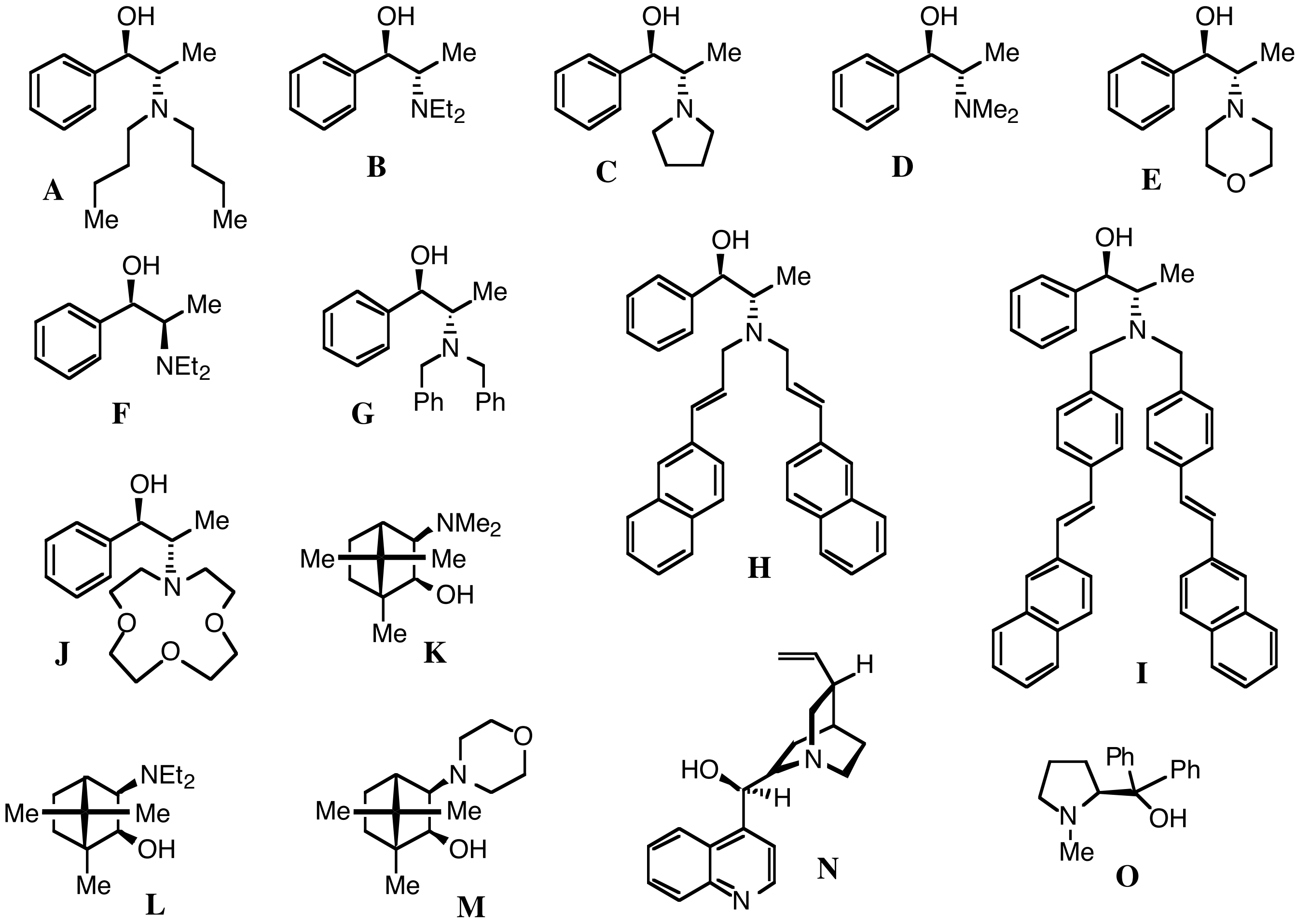
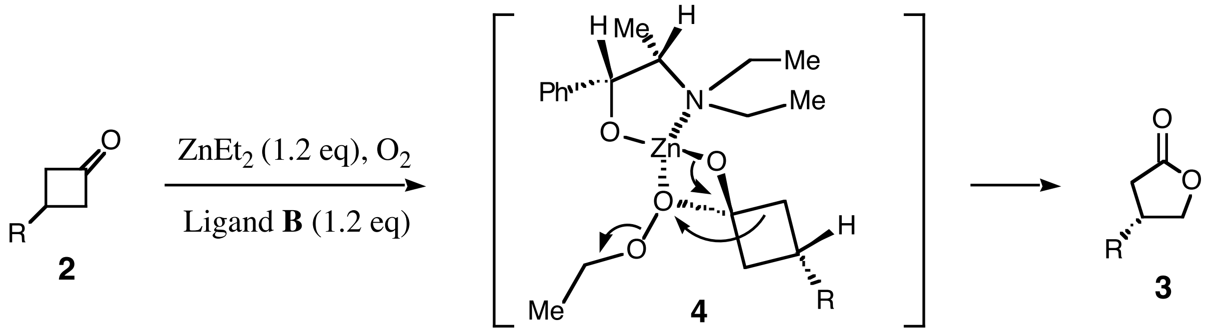


Figure 1. Ligands used in asymmetric Baeyer-Villiger oxidation of cyclobutanones

To identify suitable reaction conditions, treatment of 3-phenylcyclobutanone (**2a**) with 1.2 equiv of diethylzinc in the presence of 1.2 equiv[14] of the chiral ligand (**A**) in dry toluene under an oxygen atmosphere gave the corresponding γ-butyrolactone (**3**) in favor of its (*S*)-isomer, with 14% ee and in 72% chemical yield (Entry 1). A similar result was obtained in THF (Entry 2), while less enantioselectivity was observed in dichloromethane (Entry 3).

Encouraged by this result, we screened over a dozen amino alcoholic chiral ligands.[15] Among several ephedrine-based chiral ligands, (1*R*,2*S*)-*N*,*N*-diethylnorephedrine (**B**) gave the highest ee: 39% ee of (*S*)-**3** (R = Ph) and 75% chemical yield (Entry 4).[16] Disappointingly, however, other ligands which can usually be used for the successful enantioselective alkylation of aldehydes with diethylzinc[17] were found to be less efficient for the present purpose (Entries 13-17). Asymmetric induction with other 3-substituted cyclobutanones such as **2b**-**2f** with the assistance of chiral ligand (**B**) gave around 35% ee with the same *S* configurations (Entries 18-22).[18]

The hypothetical reaction pathway with ligand (**B**) is proposed by invoking the intermediate Criegee-type adduct (**4**) to explain the absolute configuration of the new stereogenic carbon center in **3** (**Scheme 2**). The modest enantioselectivity observed in each case might be due to the weak diastereoselective discrimination at the initial complexation of the prochiral ketone (**2**) with the chiral oxidizing species (**1**) to derive the *anti*-adduct (**4**), and also the nonrigidity of the intermediate adduct (**4**) to control subsequent



Scheme 2

alkyl-group migration. We expected that an introduction of a naphthalene ring on the chiral ligand should stabilize the transition state like **4** through an additional π-π interaction between the phenyl group of **3** and those of the ligand, but only poor results were obtained for **H** and **I** (Entries 10 and 11).

In conclusion, we have examined the first example of a zinc-mediated Baeyer-Villiger oxidation of cyclobutanones with oxygen in the presence of chiral amino alcohols, wherein optically active 3-substituted γ-butyrolactones were produced. Further studies to improve the asymmetric Baeyer-Villiger oxidation using other types of chiral ligands are now in progress.

ACKNOWLEDGMENT.

This work was supported in part by Scientific Research Grants from the Ministry of Education, Science, Sports and Culture of Japan, and a Grant-in-Aid for Special Scientific Research from Kochi University.

REFERENCES AND NOTES

1. A. Baeyer and V. Villiger, *Ber.,* 1899, **32**, 3625.
2. Reviews: C. H. Hassall, *Org. React.,* 1957, **9**, 73; L. B. Lee and B. C. Uff, *Q. Rev., Chem. Soc.*, 1967, **21**, 429; G. R. Krow, *Tetrahedron,* 1981, **37**, 2697; G. R. Krow, in "*Comprehensive Organic Synthesis*," ed. by B. M. Trost and I. Fleming; Pergamon: Oxford, 1991; Vol. 7, Chap. 5.1, pp. 671-688; G. R. Krow, *Org. React.,* 1993, **43**, 251; G. Strukul, *Angew. Chem., Int. Ed. Engl.,* 1998, **37**, 1199; M. Renz and B. Meunier, *Eur. J. Org. Chem.,* 1999, 737.
3. C. Bolm and O. Beckmann, in "*Comprehensive Asymmetric Catalysis*," ed. by E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Springer, Berlin, 1999; Vol. 2, Chap. 22, pp. 803-810; C. Bolm, *Med. Res. Rev.*, 1999, **19**, 348.
4. For recent reviews see: V. Alphand and R. Furstoss, in "*Handbook of Enzyme Catalysis in Organic Synthesis*," ed. by K. Drauz and H. Waldmann, VCH Publishers, Weinheim, 1995; Vol. 2, pp. 744-772; J. D. Stewart, *Curr. Org. Chem.,* 1998, **2**, 195; M. Kayser, G. Chen, and J. Stewart, *Synlett,* 1999, 153; V. Alphand and R. Furstoss, in "*Asymmetric Oxidation Reactions: A Practical Approach*," ed. by T. Katsuki, Oxford University Press, in press.
5. C. Bolm, G. Schlingloff, and K. Weickhardt, *Angew. Chem., Int. Ed. Engl.,* 1994, **33**, 1848; C. Bolm and G. Schlingloff, *J. Chem. Soc., Chem. Commun.,* 1995, 1247; C. Bolm, G. Schlingloff, and F. Bienewald, *J. Mol. Cat. A,* 1997, **117**, 347; C. Bolm, T. K. K. Luong, and G. Schlingloff,

Synlett, 1997, 1151.

6. A. Gusso, C. Baccin, F. Pinna, and G. Strukul, *Organometallics,* 1994, **13**, 3442; G. Strukul, A. Varagnolo, and F. Pinna, *J. Mol. Cat. A,* 1997, **117**, 413; C. Paneghetti, R. Gavagnin, F. Pinna, and G. Strukul, *Organometallics,* 1999, **18**, 5057.
7. M. Lopp, A. Paju, T. Kanger, and T. Pehk, *Tetrahedron Lett.,* 1996, **37**, 7583; T. Kanger, K. Kriis, A. Paju, T. Pehk, and M. Lopp, *Tetrahedron: Asymmetry,* 1998, **9**, 4475.
8. T. Sugimura, Y. Fujiwara, and A. Tai, *Tetrahedron Lett.,* 1997, **38**, 6019.
9. H. Kotsuki, T. Araki, K. Arimura, and T. Shinohara, *Synlett,* 1999, 462.
10. D. Enders, J. Zhu, and G. Raabe, *Angew. Chem., Int. Ed. Engl.,* 1996, **35**, 1725; D. Enders, J. Zhu, and L. Kramps, *Liebigs Ann./Recueil,* 1997, 1101.
11. The specific rotation for the known (*S*)-**3**: R = Ph, $[\alpha]_D^{20}$ +50.4° (*c* 5, MeOH);[12] R = 4-ClC_6H_4, $[\alpha]_D^{20}$ +46.5° (*c* 0.5, $CHCl_3$).[13]
12. G. Helmchen and G. Nill, *Angew. Chem., Int. Ed. Engl.,* 1979, **18**, 65.
13. I. W. Lawston and T. D. Inch, *J. Chem. Soc., Perkin Trans. 1,* 1983, 2629.
14. The use of more amounts of the ligand did not increase the ee or the chemical yield.
15. Among these ligands, **H** {$[\alpha]_D^{26}$ -92.7° (*c* 0.73, $CHCl_3$)}, **I** {$[\alpha]_D^{26}$ -199.0° (*c* 0.96, $CHCl_3$)}, **J** {$[\alpha]_D^{26}$ -7.42° (*c* 0.54, EtOH)}, and **L** {$[\alpha]_D^{20}$ +15.6° (*c* 1.15, EtOH)}, are unknown and were readily prepared from commercially available (1*R*,2*S*)-(-)-norephedrine or D-camphor. For ligand **A**, K. Soai, S. Yokoyama, K. Ebihara, and T. Hayasaka, *J. Chem. Soc., Chem. Commun.*, 1987, 1690. For ligands **A**-**D**, K. Soai, S. Yokoyama, and T. Hayasaka, *J. Org. Chem.,* 1991, **56**, 4264. For ligand **E**, K. Soai, T. Hatanaka, and T. Miyazawa, *J. Chem. Soc., Chem. Commun.*, 1992, 1097. For ligand **F**, see ref 10. For ligand **G**, R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, V. Molteni, and L. Raimondi, *Tetrahedron*, 1995, **51**, 8941. For ligand **K**, M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, 1986, **108**, 6071. For ligand **M**, W. A. Nugent, *Chem. Commun.*, 1999, 1369. For ligand **N**, Ab. A. Smaardijk and H. Wynberg, *J. Org. Chem.,* 1987, **52**, 135. For ligand **O**, K. Soai, S. Yokoyama, K. Ogawa, and T. Kaba, *J. Chem. Soc., Chem. Commun.*, 1987, 467; K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111.
16. Typical experimental procedure for the asymmetric Baeyer-Villiger oxidation of 3-phenylcyclobutanone (**2a**): To a solution of (1*R*,2*S*)-*N*,*N*-diethylnorephedrine **B** (250 mg, 1.2 mmol)[14] in dry toluene (3 mL) at 0 °C was added diethylzinc (1.2 mL, 1.2 mmol; 1.0 M solution in toluene) with stirring under an argon atmosphere. After 80 min, the connection to the argon cylinder was replaced by a balloon filled with oxygen. After stirring for 2.5 h, the reaction mixture was cooled to -78 °C and a solution of **2a** (146 mg, 1.0 mmol) in dry toluene (1 mL) was introduced. The reaction mixture was stirred for 2 h at this temperature and then warmed to -26 °C. After completion, the reaction was quenched by addition of satd NH_4Cl and the aqueous layer was extracted with AcOEt. The extracts were washed with satd NaCl, and dried (Na_2SO_4). The crude product was purified by flash SiO_2 column chromatography (elution with hexane/AcOEt = 2 : 1) to give **3a** (122 mg, 75%, mp 50-52 °C) as colorless crystals, which showed 39% ee by chiral HPLC

analysis (DAICEL Chiralpak AD, elution with hexane / 2-propanol = 90 : 10).

17. K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833; R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.,* 1991, **30**, 49.

18. The absolute configuration of **3** (R = 4-MeOC_6H_4, 2-naphthyl, 2-MeOC_6H_4, 2-HOC_6H_4) is unknown: W. H. Pirkle and P. L. Spence, *J. Chromatogr. A,* 1997, **775**, 81; K. Nymann and J. S. Svendsen, *Acta Chem. Scand.,* 1998, **52**, 338.