Pergamon

Tetrahedron Letters 40 (1999) 1641–1644

TETRAHEDRON LETTERS

Asymmetric Epoxidation of Functionalized cis-Olefins Catalyzed by Chloroperoxidase

Shanghui Hu and Lowell P. Hager*

Department of Biochemistry, University of Illinois, Urbana, Illinois 61801

Received 19 October 1998; accepted 22 December 1998

Abstract: Chloroperoxidase catalyzes the asymmetric epoxidation of functionalized cis-2-alkenes with excellent enantioselectivity and good yields , using tert-butyl hydroperoxide as the terminal oxidant.

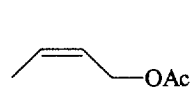
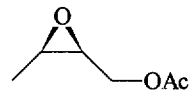
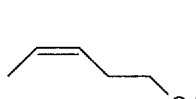
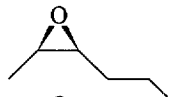
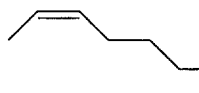
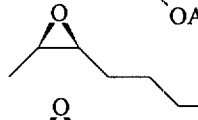
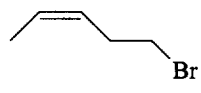
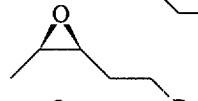
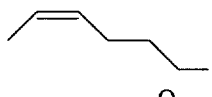
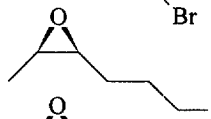
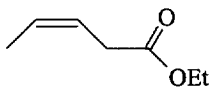
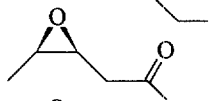
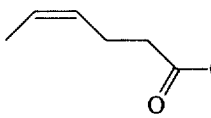
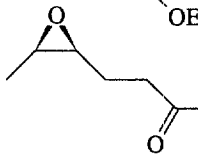
Chiral epoxides are very important intermediates for the synthesis of optically pure complex molecules, in particular, biologically active compounds.[1] Catalytic asymmetric epoxidation of alkenes is one of the most powerful strategies for the preparation of enantionmerically pure epoxides.[2] Several efficient catalysts have been developed for asymmetric epoxidation of allylic alcohols, [3] trans-olefins, [4]trisubstituted olefins, [5] and unfunctionalized cis-olefins.[4a,6] However, there is no general and effective catalyst available for the enantioselective epoxidation of functionalized cis-olefins bearing no allylic alcohol groups.[7]

Chloroperoxidase (CPO)[8] is an efficient and versatile catalyst that catalyzes a large number of oxidative reactions.[9] Since the discovery of CPO mediated epoxidation reactions,[10] we have had a long standing interest in exploring the enantioselectivity and substrate specificity of this enzyme. Our previous work has established unfunctionalized cis-alkenes and 2-methyl-alkenes as good substrates for CPO-catalyzed asymmetric epoxidation.[5c,11] Zaks and Dodds have further expanded the scope of acceptable olefin substrates.[12] The effect of chain length on enantioselectivity and conversion of 2-methyl alkenes has been investigated using ω-bromo-2-methyl-1-alkenes as probe substrates.[11c] We now report on an investigation of the CPO enantioselective epoxidation of functionalized cis-2-alkenes, using tert-butyl hydroperoxide (TBHP) as the terminal oxidant.

We first attempted to use cis-2-buten-1-ol (**1**), cis-3-penten-1-ol (**2**) and cis-4-hexen-1-ol (**3**) as model substrates for CPO epoxidation. However, allylic alcohol **1** was found to be rapidly and completely oxidized to its α,β-unsaturated aldehyde and no epoxide was produced. This result is identical to the early findings showing that CPO catalyses the oxidation of allylic alcohols to aldehydes.[8] Homoallylic alcohols **2** and **3** are not epoxidized by CPO, which suggests that these substrates probably are suicide inhibitors of CPO. It has been found that functionalized olefins **4-6** are effectively converted to epoxides with excellent enantioselectivity (e.e.90-95%) and good yields (51-78%) as shown in Table 1. As the carbon chain lengthens the enantiomeric excesses remain high, while the yields progressively decrease, presumably due to size restrictions in the active site of CPO. The lower yield of epoxide with

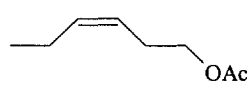
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00056-8

Table 1. Enantioselective Epoxidation of Functionalized cis-2-Alkenes Catalyzed by Chloroperoxidase [a]

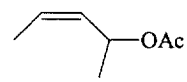
Entry	Alkene	Epoxide [b,c]	e.e. (%) [d]	Yield (%)[e]	Conversion (%)[e]
4			95	64	96
5			90	78	81
6			91	51	71
7			91	53	78
8			90	50	74
9			96	95	100
10			68	28	30

[a]Chloroperoxidase was provided by Chirazyme Laboratories, 2004 S. Wright St., Urbana, IL 61801. General Procedures: Alkene (0.8 mmol) and 20 mg of CPO was stirred vigorously with t-BuOOH (1.6 mmol) in 8.0 ml of 10 mM Na citrate buffer adjusted to pH 5.5. The reaction vial was capped, and the reaction was stirred for 1.5 h at room temperature, after which $Na_2S_2O_3$ was added and the mixture was extracted with dichloromethane. Combined organic extracts were dried over $MgSO_4$, and were purified by flash chromatography using pentane/ether as eluent. [b]Structures were confirmed by ^1H and ^{13}C-NMR and MS spectra and always compared with MCPBA epoxidations. [c]Absolute configurations were determined by correlation to the corresponding (R)-mono or diol available by chemical conversions. Entry **4** correlates to (R)-2-butanol, entries **5** and **7** correlate to (R)-2-pentanol, entries **6** and **8** correlate to (R)-2-hexanol. Entry **9** correlated to (R)-pentan-1,4-diol and entry **10** was assigned by analogy to entry **9**. [d]The e.e. values were determined by gas chromatography using a chiral G-TA column. [e]Total substrate consumption determined by GC analysis.

cis-olefin **4** must be due to the fact that under the reaction conditions **4** readily isomerizes and the trans isomer is not a substrate. TBHP is an efficient terminal oxidant for these epoxidation reactions. When a terminal bromine atom is present (entries **7** and **8**), the enantioselectivity of CPO epoxidation is good (e.e. 90% and 91%, respectively), although the yields are moderate. The unsaturated carboxylic ester **9** was found to be an excellent substrate and the epoxide is produced with very high stereoselectivity and good yield (e.e. 96%, 95% yield). However, the e.e. value and yield dramatically decrease with olefin **10.** It is apparent that the presence of one additional carbon in olefin **10** hinders the interaction of this olefin with the active site residues of CPO. Alkene **11** is a poor CPO epoxidation substrate, the e.e. value is only moderate (68%) and the yield is very low (ca.3%). CPO tolerates branching on the alkyl substituents remote from the C=C bond for unfunctionalized olefins,[5c] but alkene **12** contains an α-methyl branching group and was found to be unreactive for CPO epoxidation. This observation further indicates that the active site of CPO is very sterically restricted.



11



12

For functionalized straight chain cis-olefins, the stereocontrol of substrate orientation in the active site of CPO appears to largely depend upon the substituents adjacent to the double bond. In all of the products the chiral carbon atom adjacent to the terminal methyl group is of the R-configuration. This also is true for unfunctionalized cis-olefins and 2-methyl olefins, the products are of the R-configuration. The functionalized olefins require that a methyl group be attached to the C=C double bond. The presence of the methyl group is essential for the selectivity and efficiency of the epoxidation reaction. This observation is similar to for unfunctionalized olefins.[5c,12] In all cases the length of carbon chain plays an important role in the selectivity and yields, however, this study shows that CPO can tolerate a variety of functional groups (Table 1).

Here, we report a CPO catalyzed enantioselective epoxidation of functionalized cis-alkenes, using TBHP as a convenient terminal oxidant. The overall scope of substrate specificity for CPO epoxidations remains limited. Usually, CPO utilizes functionalized cis-2-olefins containing short carbon chains with excellent enantioselectivity and good yields. Current research in this laboratory is aimed at the modification of the active site of CPO by random and site directed mutagenesis. This research offers an approach for broadening the substrate specificity and improving the selectivity of the epoxidation reaction.

Acknowledgment. This research has been supported by a grant from the National Institutes of Health, GM 07768. We thank Bedoukian Research Inc., CT, USA for providing cis-4-hexen-1-ol as a gift.

References

1. Besse, P.; Veschambre, H. *Tetrahedron*. **1994**, 50, 8885.
2. (a) Noyori, R. Asymmertic Catalysis in Organic Synthesis; John Wiley & Sons; New York, 1994. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.
3. (a) Katsuki, K.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, 102, 5974. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ed.; VCH: New York, 1993.
4. (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ed.; VCH: New York, 1993. (b) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, 112, 2801. (c) Collman, J. P.; Lee, V. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1993**, 115, 3834. (e) Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, 116, 6937. (d) Collman, J. P.; Lee, V. J.; Kellen-Yuen, C. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1995**, 117, 692. (e) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, 118, 7004. (f) Yang, D.; Yip, Y.-C.; tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, 118, 491. (g) Yang, D.; Wang, X.-C.; Wong, M.-W.; Yip, Y.-C.; Tang, M-W. *J. Am. Chem. Soc.* **1996**, 118, 11311. (h) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, 118, 9806. (I) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, 119, 2329.
5. (a) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, 59, 4378. (b) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, 36, 5457. (c) Allain, E. J.; Hager, L. P.; Deng, L.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1993**, 115, 4415. (d) Koch, A.; Reymond, J.; Lerner, R. A. *J. Am. Chem. Soc.* **1994**, 116, 803.
6. (a) Collman, J. P; Zhang, X.; Lee, V. J.; Uffelman, E. S. Brauman J. I. *Science*, **1993**, 261, 1404. (b) Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, 37, 4389.
7. (a) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, 103, 7690. (b) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, 49, 3707. (c) Ikegami, S.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1987**, 83.
8. (a) Shaw, P. D.; Hager, L. P. *J. Biol. Chem.* **1961**, 236, 1626. (b) Hager, L. P.; Morris, D. R.; Brown, F. S.; Eberwein, H. *J. Biol. Chem.* **1966**, 241, 1769. (c) Morris, D. R.; Hager, L. P. *J. Biol. Chem.* **1966**, 241, 3582.
9. (a) Franssen, M. C. R.; van der Plas, H. C. *Adv. Appl. Microbiol.* **1992**, 37, 41. (b) Van Deurzen, M. P. J.; van Rantwijk, F.; Sheldon, R. A. *Tetrahedron*. **1997**, 53, 13183.
10. McCarthy, M. B.; White, R. E. *J. Biol. Chem.* **1983**, 258, 9153.
11. (a) Dexter, A. F.; Lakner, F. J.; Campbell, R. A.; Hager, L. P. *J. Am. Chem. Soc.* **1995**, 117, 6412. (b) Lakner, F. J.; Hager, L. P. *J. Org. Chem.* **1996**, 61, 3923. (c) Lakner, F. J.; Cain, K. P.; Hager, L. P. *J. Am. Chem. Soc.* **1997**, 119, 443. (d) Lakner, F. J.; Hager, L. P. *Tetrahedron: Asymmetry*. **1997**, 8, 3547.
12. Zaks, A.; Dodds, D. R. *J. Am. Chem. Soc.* **1995**, 117, 10419.
13. (a) Geigert, J.; Dalietos, D. J.; Neidelman, S. L.; Lee, T. D.; Wadsworth, J. *Biochem. Biophys. Res. Commun.* **1983**, 114, 1104. (b) Miller, V. P.; Tschirret-Guth, R. A.; Ortiz de Montillano, P. R. *Arch. Biochem. Biophys*. **1995**, 319, 333.