ORGANIC LETTERS

2004
Vol. 6, No. 10
1597−1599

Highly Diastereoselective Epoxidation of Allyl-Substituted Cycloalkenes Catalyzed by Metalloporphyrins

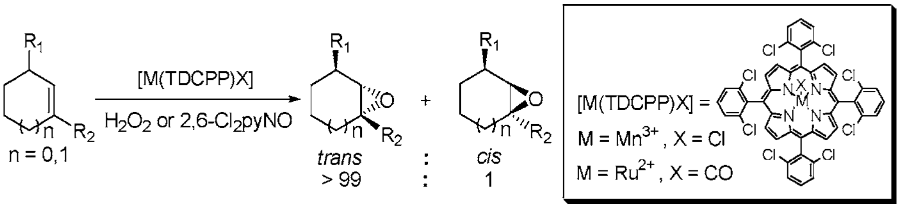
Wing-Kei Chan, Peng Liu, Wing-Yiu Yu, Man-Kin Wong,* and Chi-Ming Che*

Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis,
The University of Hong Kong, Pokfulam Road, Hong Kong, China

cmche@hku.hk

Received February 27, 2004

ABSTRACT



Highly diastereoselective epoxidations of allyl-substituted cycloalkenes including allylic alcohols, esters, and amines using sterically bulky metalloporphyrins [Mn(TDCPP)Cl] (1) and [Ru(TDCPP)CO] (2) as catalysts have been achieved. The “1 + H_2O_2” and “2 + 2,6-Cl_2pyNO” protocols afforded *trans*-epoxides selectively in good yields (up to 99%) with up to >99:1 *trans*-selectivity.

Epoxides of allylic cycloalkenes are versatile building blocks for organic synthesis and construction of biologically active natural products. Significant advances have been achieved in *cis*-selective epoxidation of cyclic allylic alcohols through hydrogen bonding between their *syn*-directing hydroxyl group and oxidants.[1] For epoxidation of cycloalkenes without *syn*-directing groups, *trans*-epoxides would be obtained as major products due to steric interaction. However, the *trans*-selectivities are generally low and rarely exceed 20:1.[2,3] Thus, development of new protocols for highly diastereoselective epoxidation of substituted cyclohexenes poses an important challenge in organic synthesis.

Metalloporphyrin-catalyzed alkene epoxidation has been a subject of extensive investigation.[4] By virtue of the structural diversity of the macrocyclic ligand, steric and electronic properties of metalloporphyrin catalysts can be fine-tuned for stereo- and enantioselective alkene epoxidations.[5] In addition, polyhalogenated metalloporphyrins are robust and recyclable catalysts for alkene epoxidations with exceptionally high turnover numbers.[6] Here, we report that [Mn(TDCPP)Cl] (**1**) and [Ru(TDCPP)CO] (**2**) can effect highly diastereoselective catalytic epoxidation of allyl-substituted cycloalkenes with up to >99:1 *trans*-selectivity.[7]

---

(1) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.

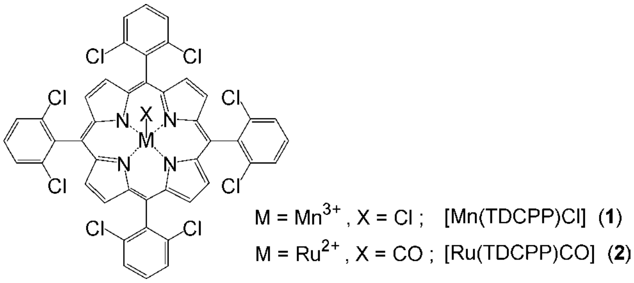
(2) For selected examples on *trans*-selective epoxidations, see: (a) Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*, 1577. (b) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *Tetrahedron Lett.* **1995**, *36*, 2437. (c) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830. (d) Adam, W.; Mitchell, C. M.; Saha-Moller, C. R. *Eur. J. Org. Chem.* **1999**, 785. (e) Yang, D.; Jiao, G.-S.; Yip, Y.-C.; Wong, M.-K. *J. Org. Chem.* **1999**, *64*, 1635. (f) Adam, W.; Corma, A.; Garcia, H.; Weichold, O. *J. Catal.* **2000**, *196*, 339. (g) O'Brien, P.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. M. *Org. Lett.* **2003**, *5*, 4955.

(3) For other methods on the synthesis of *trans*-α,*β*-epoxy alcohols, see: (a) Dubey, S. K.; Kumar, S. *J. Org. Chem.* **1986**, *51*, 3407. (b) Ravikumar, K. S.; Chandrasekaran, S. *Tetrahedron* **1996**, *52*, 9137 and references therein.

(4) (a) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411. (b) Dolphin, D.; Traylor, T. G.; Xie, L. Y. *Acc. Chem. Res.* **1997**, *30*, 251. (c) McLain, J. L.; Lee, J.; Groves, J. T. In *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*; Meunier, B., Ed.; Imperial College Press: London, 2000; pp 91−169.

(5) (a) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786. (b) Tabushi, I.; Morimitsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6871. (c) Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T.; Raybuck, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 2000. (d) Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* **1987**, *109*, 5045. (e) Collman, J. P.; Zhang, X.; Hembre, R. T.; Brauman, J. I. *J. Am. Chem. Soc.* **1990**, *112*, 5356. (f) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S. Brauman, J. I. *Science* **1993**, *261*, 1404.

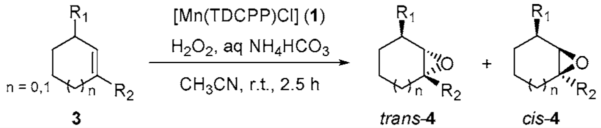
10.1021/ol0496475 CCC: $27.50

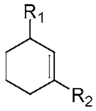
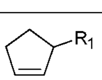


Our working hypothesis for the highly diastereoselective epoxidation is based on strong steric interaction between the substrate and the bulky porphyrin ligand. At the outset, we studied the epoxidation of $Si^tBu(CH_3)_2$-protected cyclohexen-1-ol **3c** using **1** as catalyst and H_2O_2 as oxidant.[8,9] Treatment of a CH_3CN solution of **3c** and **1** (1.2 mol %) with a solution of 35% H_2O_2 in aqueous NH_4HCO_3/CH_3CN[10] afforded *trans*- and *cis*-epoxides **4c** in 88% isolated yield.[11] On the basis of capillary GC analysis, the *trans*-selectivity (i.e., *trans*-/*cis*-epoxide ratio) was determined to be 33:1 (Table 1, entry 3).

The activities of other manganese porphyrin catalysts for the diastereoselective epoxidation of **3c** were examined under the same reaction conditions (Table 2). It was found that [Mn(TDCPP)Cl] (**1**) exhibits the best catalytic activity (88% epoxide yield) and *trans*-selectivity (33:1). With [Mn(TMP)-Cl] as catalyst, lower epoxide yield (56% yield based on 16% conversion) and *trans*-selectivity (22:1) were observed. While [Mn(TTP)Cl] was found to exhibit poor catalytic activity (<5% conversion), the perfluorinated analogue (i.e., [Mn(TFPP)Cl]) gave modest catalytic activity (61% yield based on 25% conversion) and *trans*-selectivity (12:1).

Table 1. Diastereoselective Epoxidation of Substituted Cycloalkenes **3a**−**n** by **1** Using H_2O_2[a]



entry	alkene		R_1	R_2	% yield of epoxide[b]	*trans*- : *cis*-epoxide ratio[c] **1**	*m*-CPBA[d]
1		**3a**	OH	H	59[c]	4:1	1:7
2		**3b**	OAc	H	71	5:1	2:1
3		**3c**	$OSi^tBu(CH_3)_2$	H	88	33:1[e]	5:1
4		**3d**	$OSi^tBu(Ph)_2$	H	64[f]	16:1	4:1
5		**3e**	OH	CH_3	52[c,g]	9:1	1:10
6		**3f**	OAc	CH_3	69[h,f]	25:1	3:1
7		**3g**	$OSi^tBu(CH_3)_2$	CH_3	80[f]	>99:1	8:1
8		**3h**	$OSi^tBu(Ph)_2$	CH_3	57[i,f]	28:1	3:1
9		**3i**	COOMe	H	97[c]	4:1	1:1
10		**3j**	$COOC_6H_{11}$	H	92[c]	11:1	1:1
11		**3k**	$COOCH(Ph)_2$	H	74	35:1	1:1
12		**3l**	$N(Boc)_2$	H	90[c]	30:1	n.d.[j]
13		**3m**	$OSi^tBu(CH_3)_2$	–	82[c]	18:1	1:1
14		**3n**	OCH_2Ph	–	83[c]	10:1	2:1

[a] Unless otherwise indicated, all the epoxidation reactions were performed as follows: To a solution of alkene (0.25 mmol) and **1** (3 μmol) in CH_3CN (4 mL) was added a premixed solution of 0.8 M aqueous NH_4HCO_3 (0.5 mL), CH_3CN (0.5 mL), and 35% H_2O_2 (0.125 mL) at room temperature. [b] Isolated yield based on complete alkene consumption, and <5% of enone was formed on the basis of ^1H NMR analysis. [c] Determined by ^1H NMR. [d] Epoxidations were carried out in CH_2Cl_2 for 3 h with an alkene/*m*-CPBA/$NaHCO_3$ molar ratio of 1:1.5:3. [e] Determined by GC. [f] 7−15% of enone was formed on the basis of ^1H NMR analysis. [g] 10% of 3-methyl-2-cyclohexenone was detected by ^1H NMR. [h] Isolated yield based on 87% alkene conversion. [i] Isolated yield based on 84% alkene conversion. [j] No epoxide was detected.

Table 2. Diastereoselective Epoxidation of **3c** Catalyzed by Mn Porphyrins[a]

entry	catalyst	% conv.[b]	% yield of epoxide[c]	*trans*-:*cis*-epoxide ratio[d]
1	[Mn(TDCPP)Cl] (**1**)	100	88	33:1
2	[Mn(TMP)Cl]	16	56	22:1
3	[Mn(TFPP)Cl]	28	61	12:1
4	[Mn(TTP)Cl]	<5	n.d.	n.d.

[a] Unless otherwise indicated, all epoxidation reactions were conducted at room temperature: To a solution of 0.25 mmol of alkene and 0.003 mmol of **1** in 4 mL of CH_3CN was added a premixed solution of 0.5 mL of 0.8 M aqueous NH_4HCO_3, 0.5 mL of CH_3CN, and 0.125 mL of 35% H_2O_2. [b] Determined by GC with internal standard. [c] Isolated yield based on substrate conversion, and a trace amount of enone was observed by ^1H NMR. [d] Determined by GC.

---

(6) (a) Che, C.-M.; Liu, C.-J.; Yu, W.-Y.; Li, S.-G. *J. Org. Chem.* **1998**, *63*, 7364. (b) Liu, C.-J.; Yu, W.-Y.; Che, C.-M.; Yeung, C.-H. *J. Org. Chem.* **1999**, *64*, 7365. (c) Che, C.-M.; Yu, X.-Q.; Huang, J.-S.; Yu, W.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 5337. (d) Zhang, R.; Yu, W.-Y.; Wong, K.-Y.; Che, C.-M. *J. Org. Chem.* **2001**, *66*, 8145. (e) Che, C.-M.; Zhang, J.-L. *Org. Lett.* **2002**, *4*, 1911. (f) Zhang, R.; Yu, W.-Y.; Sun, H.-Z.; Liu, W.-S.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 2495.

(7) For selected examples on the synthetic utilities of *trans*-epoxides of cycloalkenes in organic synthesis, see: (a) Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* **1997**, 381. (b) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Eur. J. Org. Chem.* **1998**, 1675. (c) Hutchison, T. L.; Saeed, A.; Wolkowicz, P. E.; McMillin, J. B.; Brouillette, W. J. *Bioorg. Med. Chem.* **1999**, *7*, 1505. (d) Demay, S.; Kotschy, A.; Knochel, P. *Synthesis* **2001**, 863. (e) Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773. (f) Ahn, D.-R.; Mosimann, M.; Leumann, C. J. *J. Org. Chem.* **2003**, *68*, 7693.

(8) Manganese porphyrins are known to be effective catalysts for epoxidation of simple alkenes using H_2O_2; see for examples: (a) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110*, 8462. (b) Battioni, P.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1994**, 1035. (c) Poriel, C.; Ferrand, Y.; Le Maux, P.; Rault-Berthelot, J.; Simonneaux, G. *Tetrahedron Lett.* **2003**, *44*, 1759. See also ref 4b.

(9) **General Procedure for 1-Catalyzed Epoxidation Reactions (Table 1, Entry 3).** To a round-bottom flask containing [Mn(TDCPP)Cl] (**1**) (3.0 mg, 0.003 mmol) and **3c** (53.0 mg, 0.25 mmol) in CH_3CN (4 mL) was added a premixed solution of 35% H_2O_2 (0.125 mL), aqueous NH_4HCO_3 (0.8 M, 0.5 mL), and CH_3CN (0.5 mL) via a syringe pump for 1.5 h at room temperature. After being stirred for 1 h, the reaction mixture was diluted with saturated aqueous $Na_2S_2O_3$ (1 mL) and extracted with *n*-hexane (4 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. The ratio of *trans*-**4c** to *cis*-**4c** was determined to be 33:1 by capillary GC analysis. The residue was purified by flash column chromatography (5% EtOAc in *n*-hexane) to provide a mixture of epoxides *trans*-**4c** and *cis*-**4c** (49 mg, 88% yield based on complete alkene conversion) as a colorless oil.

(10) For $MnSO_4$ salt catalyzed alkene epoxidation using bicarbonate-activated H_2O_2, see: (a) Burgess, K.; Lane, B. S. *J. Am. Chem. Soc.* **2001**, *123*, 2933. (b) Lane, B. S.; Vogt, M.; DeRose, V. J.; Burgess, K. *J. Am. Chem. Soc.* **2002**, *124*, 11946.

(11) In control experiments, no epoxidation of **3c** was observed either in the absence of NH_4HCO_3 or **1**. The H_2O_2/NH_4HCO_3 mixture alone (i.e., without catalyst **1**) did not effect epoxidation of **3c**.

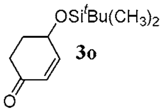
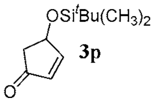
With these data in hand, other substrates have been examined by using **1** as catalyst. *The catalytic oxidation of* ***3g*** *(R_1 = $OSi^tBu(CH_3)_2$, R_2 = CH_3) proceeded with 80% epoxide formation and trans-selectivity >99:1 (Table 1, entry 7).* It is known that *m*-CPBA and dioxiranes are common oxidants for alkene epoxidation. We found that **3c** and **3g** reacted with *m*-CPBA to give *trans*-**4c** and *trans*-**4g** with *trans*-selectivities of 5:1 and 8:1, respectively. According to the literature, the *trans*-selectivities obtained in dioxirane mediated epoxidation of **3c** and **3g** are 13:1[2a] and 20:1,[2e] respectively. To our knowledge, the *trans*-selectivity for the **1**-catalyzed epoxidation of **3c** and **3g** are the best results ever achieved.

The *trans*-selectivity was found to be dependent upon the size of the substituents R_1 and R_2. Noting that the **1**-catalyzed epoxidaiton of **3c** (R_1 = $OSi^tBu(CH_3)_2$, R_2 = H) proceeded with excellent *trans*-selectivity (*trans*/*cis* = 33:1), the related reactions with **3a** (R_1 = OH, R_2 = H) and **3b** (R_1 = OAc, R_2 = H) were found to exhibit lower diastereoselectivity (*trans*/*cis* ~ 5:1). When **3d** (R_1 = $OSi^tBu(Ph)_2$, R_2 = H) was employed as substrate, the **1**-catalyzed reaction attained a lower diastereoselectivity (16:1) compared to the value for the related reaction of **3c**. Similar dependence on substituent was also encountered for the catalytic epoxidation of **3e**−**h**. Interestingly, the *trans*-selectivities obtained in the epoxidation of **3e**−**h** with R_2 = CH_3 were significantly higher than that of **3a**−**d** with R_2 = H. It should be noted that in all cases *trans*-epoxides were obtained selectively in moderate to good yields with much better *trans*-selectivity than the *m*-CPBA-mediated reactions.

With **1** as catalyst, we also studied the catalytic epoxidation of allylic esters and amines. As shown in Table 1, *trans*-selectivity of 35:1 was attained for the epoxidation of **3k** (R_1 = $COOCH(Ph)_2$, R_2 = H). However, with *m*-CPBA as oxidant, only equimolar mixtures of *trans*-/*cis*-epoxides were obtained for the oxidation of **3i**−**k**. Amine **3l** (R_1 = $N(Boc)_2$, R_2 = H) can be readily converted to its *trans*-epoxide selectively (*trans*/*cis* = 30:1) under the **1**-catalyzed conditions. For **1**-catalyzed epoxidation of cyclopenten-1-ols **3m** (R_1 = $OSi^tBu(CH_3)_2$) and **3n** (R_1 = OCH_2Ph), *trans*-selectivities of 18:1 and 10:1 were attained, respectively.

We also examined the catalytic activity of [Ru(TDCPP)-CO] (**2**) for cyclohexene epoxidation (Table 3).[12] The **2**-catalyzed epoxidation of **3a** furnished *cis*-epoxide as major product (*trans*/*cis* = 1:5). Assuming a metal−oxo intermediate, the observed *cis*-selectivity is probably due to the hydrogen-bonding effect of the *syn*-directing OH group in CH_2Cl_2.[13] Compared to **1**, **2** was found to afford much higher *trans*-selectivities in the catalytic epoxidation of **3c** (>99:1), **3i** (8:1), and **3m** (71:1). Interestingly, under the **2**-catalyzed epoxidation conditions, enone **3o** was converted to *trans*-epoxide exclusively, while the analogous reaction of enone **3p** gave the corresponding *trans*-epoxide as major product (*trans*/*cis* = 44:1).

Table 3. Diastereoselective Epoxidation of Substituted Cycloalkenes by **2** Using 2,6-Dichloropyridine *N*-Oxide[a]

entry	alkene	% conv.[b]	% yield of epoxide[b]	*trans*- : *cis*- epoxide ratio[b]
1	**3a**	92	86	1:5
2	**3c**	100	85	>99:1
3	**3i**	97	65	8:1
4	**3m**	100	99	71:1
5	 **3o**	91	85	trans only
6	 **3p**	94	85	44:1

[a] All the epoxidation reactions were carried out in CH_2Cl_2 at 40 °C for 48 h with a **2**/2,6-Cl_2pyNO/alkene molar ratio of 1:150:100 under nitrogen atmosphere. [b] Determined by ^1H NMR with internal standard.

In summary, we have developed general and efficient methods for highly diastereoselective epoxidation of allylically substituted cycloalkenes by sterically bulky Mn- and Ru-porphyrin catalysts. Our protocols offer an easy assess to a diversity of synthetically useful *trans*-epoxides of cycloalkenes. Application of the diastereoselective epoxidation methods for natural product synthesis and kinetic resolution of the substituted cycloalkenes using chiral metal catalysts are under investigation.

Acknowledgment. This work was supported by The University of Hong Kong (University Development Fund), the Hong Kong Research Grants Council (HKU7384/02P), and the Areas of Excellence Scheme (AoE/P-10-01) established under the University Grants Council (HKSAR).

Supporting Information Available: Characterization data of **3** and **4**; GC and ^1H NMR determinations of the *trans*-/*cis*-epoxide ratios; ^1H and ^{13}C NMR spectra of **3h**,**j**,**k** and **4h**,**j**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0496475

---

[12] **General Procedure for 2-Catalyzed Epoxidation Reactions (Table 3, Entry 2).** To a dried CH_2Cl_2 solution (4 mL) containing **3c** (53.0 mg, 0.25 mmol) were added [Ru(TDCPP)(CO)(MeOH)] (**2**) (2.6 mg, 0.0025 mmol) and 2,6-Cl_2pyNO (61.5 mg, 0.38 mmol) under an nitrogen atmosphere. After being stirred at 40 °C for 48 h, the reaction mixture was concentrated under reduced pressure. The residue was added 4-bromochlorobenzene as an internal standard, and the organic products were then analyzed and quantified by ^1H NMR spectroscopy. The ratio of *trans*-**4c**/*cis*-**4c** was determined to be >99:1 by ^1H NMR. The yield of epoxides *trans*-**4c** and *cis*-**4c** was 85% based on complete alkene conversion.

[13] For highly *threo* selective epoxidation of allylic alcohols via *syn*-directing hydrogen bonding effect, see: Adam, W.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **1999**, *121*, 1879.