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Highly Diastereoselective Epoxidation of Allyl-Substituted Cycloalkenes Catalyzed by Metalloporphyrins

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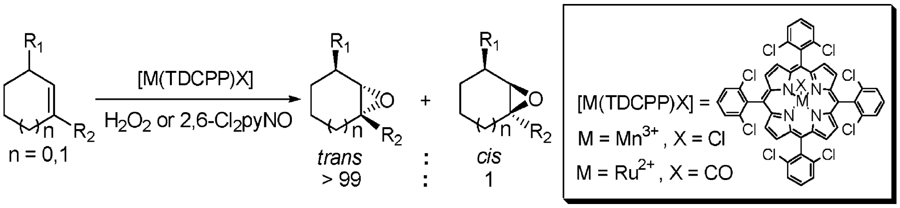
ABSTRACT



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]

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(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.

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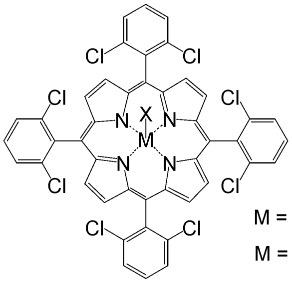
10.1021/ol0496475 CCC: $27.50

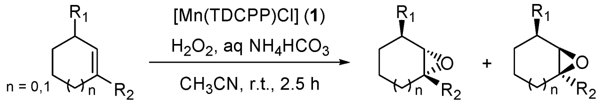


M = Mn^{3+}, X = Cl ; [Mn(TDCPP)Cl] (**1**)
M = Ru^{2+}, X = CO ; [Ru(TDCPP)CO] (**2**)

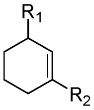
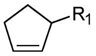
Our working hypothesis for the highly diastereoselective epoxidation is based on strong steric interaction between the substrate and the bulky porphyrin ligand. At the outset, we studied the epoxidation of $Si^{t}Bu(CH_3)_2$-protected cyclohexen-1-ol **3c** using **1** as catalyst and H_2O_2 as oxidant.[8,9] 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]



3 *trans*-**4** *cis*-**4**

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**	$OSi^{t}Bu(CH_3)_2$	H	88	$33:1^{e}$	5:1
4		**3d**	$OSi^{t}Bu(Ph)_2$	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**	$OSi^{t}Bu(CH_3)_2$	CH_3	80^{f}	>99:1	8:1
8		**3h**	$OSi^{t}Bu(Ph)_2$	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**	$OSi^{t}Bu(CH_3)_2$	–	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.

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(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**.

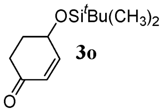
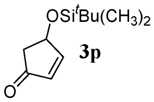
With these data in hand, other substrates have been examined by using **1** as catalyst. *The catalytic oxidation of* ***3g*** *($R_1 = OSi^tBu(CH_3)_2$, $R_2 = CH_3$) proceeded with 80% epoxide formation and trans-selectivity >99:1 (Table 1, entry 7).* It is known that *m*-CPBA and dioxiranes are common 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.

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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.

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(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.