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Metalloporphyrin-Catalyzed Diastereoselective Epoxidation of Allyl-Substituted Alkenes

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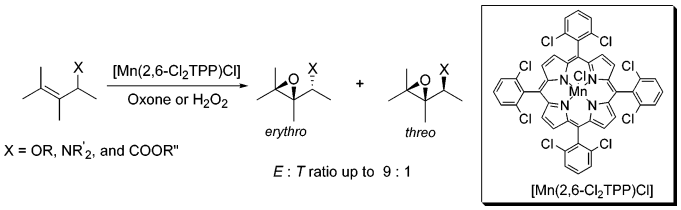

By using [Mn(2,6-Cl_2TPP)Cl] (**1**) as a catalyst and Oxone/H_2O_2 as an oxidant, we have developed an efficient method for *erythro*-selective epoxidation of acyclic allyl-substituted alkenes, including allylic alcohols, amines, and esters. Up to 9:1 *erythro* selectivities for terminal allyllic alkenes could be achieved, which are significantly higher than that achieved using *m*-CPBA as an oxidant. In addition, the synthetic utilities of this epoxidation method were highlighted in stereoselective synthesis of key anti-HIV drug intermediates and epoxidation of glycals.

Introduction

Epoxides of allyl-substituted alkenes are versatile synthetic building blocks for organic synthesis and important structural moieties of biologically active natural products.[1] Diastereoselective alkene epoxidation remains one of the most efficient methods for stereoselective synthesis of these epoxides. Through hydrogen-bonding between oxidizing agents and the syn-directing group of allyl-substituted alkenes, excellent syn selectivity can be achieved.[2] For allyl-substituted alkenes without syn-directing groups, *anti*-epoxides would be obtained as the major product due to steric interaction. However, the anti selectivities are generally low and rarely exceed 20:1.[3,4] The key to achieving high anti selectivities is to develop sterically bulky oxidizing agents possessing strong steric interaction with the substrates and yet sufficient reactivity for epoxidation.

Metalloporphyrin-catalyzed alkene epoxidation has been extensively investigated for decades.[5] Metalloporphyrin complexes containing a wide variety of bulky/chiral substitutents can catalyze alkene epoxidations with excellent regio- and enantioselectivities.[6] In addition, exceptionally high turnover numbers can be achieved with polyhalogenated metalloporhyrins as catalysts.[7] Recently, we have reported that sterically bulky poly-

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(2) (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.

(3) For selected examples on anti-selective epoxidations of cycloalkenes, 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.

(4) For selected examples of anti-selective epoxidations of acyclic alkenes, see: (a) Adam, W.; Brunker, H.-G.; Kumar, A. S.; Peters, E.-M.; Peters, K.; Schneider, U.; von Schnering, H. G. *J. Am. Chem. Soc.* **1996**, *118*, 1899. (b) Kurihara, M.; Ishii, K.; Kasahara, Y.; Kameda, M.; Pathak, A. K.; Miyata, N. *Chem. Lett.* **1997**, 1015. (c) Yang, D.; Jiao, G.-S.; Yip, Y.-C.; Lai, T.-H.; Wong, M.-K. *J. Org. Chem.* **2001**, *66*, 4619.

(5) (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.

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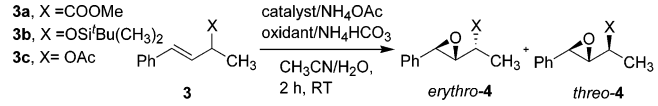
TABLE 1. Epoxidation of *trans*-Alkenes 3a–c by Mn–porphyrins[a]



entry	alkene	catalyst	% conversion[b]	% yield [b]	*E*:*T* epoxide ratio[b] catalyst	*E*:*T* epoxide ratio[b] *m*-CPBA[c]
1	**3a**	**1**	93	70	6:1	1.6:1
2		[Mn(F_{20}-TPP)Cl]	100	62	1.7:1	
3		[Mn(TTP)Cl]	60	64	1.4:1	
4	**3b**	**1**	91	<5 (58)[d]	n.d.	1:1
5[e]		**1**	57	<5 (49)[d]	n.d.	
6		[Mn(F_{20}-TPP)Cl]	97	51 (15)[d]	5:1	
7		[Mn(TTP)Cl]	72	35 (9)[d]	4:1	
8	**3c**	**1**	49	35	1:1	1:1
9[e]		**1**	<5	n.d.	n.d.	
10		[Mn(F_{20}-TPP)Cl]	95	86	1.4:1	

[a] Unless otherwise indicated, all the epoxidation reactions were performed as follows: To a CH_3CN/H_2O solution of alkene (0.1 mmol), NH_4OAc (0.05 mmol) and catalyst (0.5 μmol) was added Oxone (0.13 mmol) and NH_4HCO_3 (0.4 mmol) at room temparture (Reaction time: 2 h). [b] Conversion and yield were analyzed and quantified by ^{1}H NMR spectroscopy with 4-bromochlorobenzene or 1,1-diphenylethylene as an internal standard. [c] Epoxidations were conducted in CH_2Cl_2 with an alkene/*m*-CPBA/$NaHCO_3$ molar ratio of 1:2:3. [d] Percent yield of *trans*-4-phenyl-3-buten-2-one. [e] To a solution of alkene (0.2 mmol), NH_4OAc (0.03 mmol), and **1** (2 μmol) in CH_3CN (4 mL) was added a premixed solution of NH_4HCO_3 (0.6 mmol), CH_3CN (0.5 mL), H_2O (0.5 mL), and 35% H_2O_2 (0.1 mL) at room temperature (reaction time: 2 h).

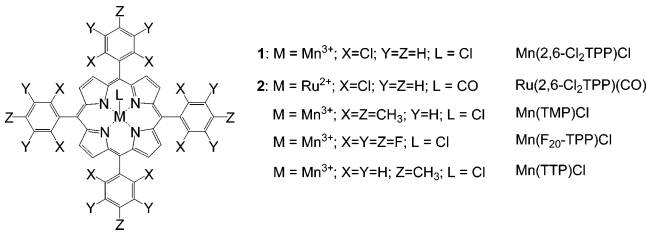


FIGURE 1. Structures of metalloporphyrins.

halogentated metalloporphyrins [Mn(2,6-Cl_2TPP)Cl] (**1**) and [Ru(2,6-Cl_2TPP)(CO)] (**2**) (Figure 1) could catalyze highly diastereoselective epoxidation of allyl-substituted cycloalkenes in good yields (up to 99%) with up to >99:1 trans selectivity.[8] The exceptionally high trans selectivity could be attributed to the strong steric interaction between the substrates and the bulky porphyrin ligands.

As part of our continuing effort to develop efficient methods for diastereoselective alkene epoxidation under mild reaction conditions, we have expanded the substrate scope to acyclic allyl-substituted alkenes including allylic alcohols, amines, and esters (Figure 2). By using [Mn-(2,6-Cl_2TPP)Cl] (**1**) as a catalyst, we achieved *erythro* selectivities of up to 9:1 for epoxidation of allyl-substituted terminal alkenes, which are significantly higher than that achieved using *m*-CPBA as an oxidant.

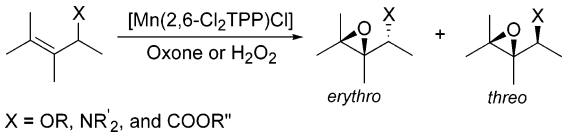


FIGURE 2. Diastereoselective epoxidation with [Mn(2,6-Cl_2TPP)Cl] (**1**) as a catalyst.

Results and Discussion

Diastereoselective Epoxdation of Allyl-Substituted *trans*-Alkenes. Recently, we have reported that highly trans-selective epoxidation of cycloalkenes could be attained by using [Mn(2,6-Cl_2TPP)Cl] (**1**) as a catalyst and H_2O_2 as a terminal oxidant. It has been reported that Oxone could also be used as a green oxidant for manganese porphyrin-catalyzed epoxidation.[5a,9] Thus, apart from H_2O_2, Oxone was also employed as the oxidant in our studies.

At the outset, we studied the epoxidation of allylic ester **3a** using **1** as a catalyst and Oxone as an oxidant. Treatment of a CH_3CN solution of **3a** (0.1 mmol) and **1** (0.5 μmol) with NH_4OAc (0.05 mmol), Oxone (0.13 mmol), and NH_4HCO_3 (0.4 mmol) afforded epoxide **4a** in 70% yield based on 93% conversion. The *erythro*:*threo* ratio of **4a** was 6:1 as determined by ^{1}H NMR analysis (Table 1, entry 1), whereas poor *erythro* selectivity (1.6:1) was obtained with *m*-CPBA.[10,11] The activities of other Mn–porphyrin catalysts for the diastereoselective epoxidation of **3a** were also examined under the same reaction

(6) (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.

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(8) Chan, W.-K.; Liu, P.; Yu, W.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2004**, *6*, 1597.

(9) (a) de Pooter, B.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1735. (b) Robert, A.; Meunier, B. *New J. Chem.* **1988**, *12*, 885. (c) Liu, J.-Y.; Li, X.-F.; Li, Y.-Z.; Chang, W.-B.; Huang, A.-J. *J Mol. Catal.* **2002**, *187*, 163.

(10) Structure of *erythro*-**4a** is similar to the epoxide moiety of crytophycins (cytotoxic macrocyclic depsipeptides). The *erythro*-epoxide of crytophycins could be prepared by *m*-CPBA or dimethyl dioxirane epoxidation with 2–3:1 *erythro* selectivity; see: (a) Salamonczyk, G. M.; Han, K.; Guo, Z.-W.; Sih, C. J. *J. Org. Chem.* **1996**, *61*, 6893. (b) White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem.* **1999**, *64*, 6206. (c) Liang, J.; Moher, E. D.; Moore, R. E.; Hoard, D. W. *J. Org. Chem.* **2000**, *65*, 3143. (d) Buck, S. B.; Huff, J. K.; Himes, R. H.; Gerog, G. I. *J. Med. Chem.* **2004**, *47*, 696.

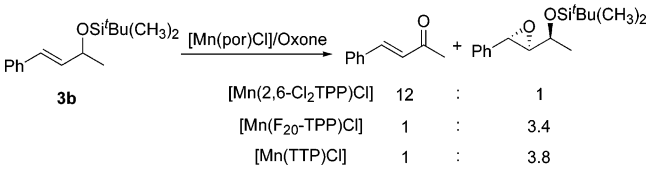


FIGURE 3. Oxidation of **3b** catalyzed by Mn−porphyrins.

conditions. It was found that **1** exhibited the highest *erythro* selectivity in the epoxidation of **3a**, while [Mn(F$_{20}$-TPP)Cl] and [Mn(TTP)Cl] provided *erythro* selectivities of 1.7:1 and 1.4:1, respectively (Table 1, entries 2 and 3).

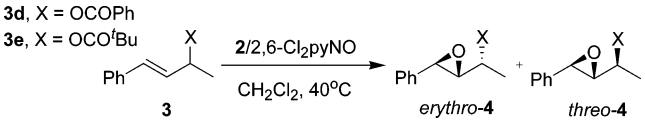
Then, we proceeded to investigate the epoxidation of allylic alcohol **3b** by using the "**1** + Oxone" approach (Table 1). Note that epoxidation of **3b** bearing an allylic OSi^{t}Bu(CH$_3$)$_2$ group unexpectedly afforded *trans*-4-phenyl-3-buten-2-one (58% yield based on 91% conversion) (Figure 3) as the major product with less than 5% yield of epoxide **4b** (Table 1, entry 4). The same enone was found to be the major product with H_2O_2 as a terminal oxidant (49% yield based on 57% conversion).[12] Yet, [Mn(F$_{20}$-TPP)Cl] and [Mn(TTP)Cl] with smaller ortho substituents on the porphyrin-phenyl group provided epoxide **4b** as the major product and [Mn(F$_{20}$-TPP)Cl] provided **4b** with *erythro* selectivity of 5:1 in 51% yield, while [Mn(TTP)Cl] gave **4b** with *erythro* selectivity of 4:1 in 35% yield based on 72% conversion. It should be noted that only a 1:1 mixture of *erythro*- and *threo*-epoxides with no enone formation was obtained with *m*-CPBA as an oxidant.

For allylic alcohol **3c** with an OAc group, no enone was detected either using **1** or [Mn(F$_{20}$-TPP)Cl] as a catalyst (entries 8−10). Using the "**1** + Oxone" approach, epoxide **4c** was obtained in 49% yield based on 35% conversion, whereas less than 5% conversion was observed with H_2O_2 as an oxidant (entries 8 and 9). [Mn(F$_{20}$-TPP)Cl] could provide **4c** with *erythro* selectivity of 1.4:1 with 86% yield based on 95% conversion (entry 10).

Despite the importance of −OSi^{t}Bu(CH$_3$)$_2$ as a versatile protecting group in organic synthesis,[13] there are only limited methods for its oxidative desilylation.[14] As shown in Table 1, the Mn−porphyrins could achieve oxidative desilylation by using H_2O_2 or Oxone as an oxidant. In addition, our results indicated that the ratio of epoxides to enones could be varied by proper choice of Mn−porphyrins (Figure 3).

Apart from Mn−porphyrins, we also examined the catalytic activity of [Ru(2,6-Cl$_2$TPP)(CO)] (**2**). With **2** (1 mol %) as a catalyst, alkene **3a** could be epoxidized to **4a** with *erythro* selectivity of 5:1 (Table 2, entry 1), which is similar to that of **1**. As depicted in Table 2, **2** could

TABLE 2. Epoxidation of *trans*-Alkenes 3 by [Ru(2,6-Cl$_2$TPP)CO] (2)[a]



				E:*T* epoxide ratio[b]	
entry	alkene	% conversion[b]	% yield[b]	**2**	*m*-CPBA[c]
1	**3a**	82	72	5:1	1.6:1
2	**3b**	28	(95)[d]		1:1
3	**3c**	100	70	2.2:1	1:1
4	**3d**	100	87	1.6:1	1:1
5	**3e**	100	85	2.3:1	1:1

[a] Unless otherwise indicated, all the epoxidation reactions were carried out at 40 °C for 48 h with a **2**/2,6-Cl$_2$pyNO/alkene molar ratio of 1:130:100 under a nitrogen atmosphere. [b] Determined by ^{1}H NMR. [c] Epoxidations were performed in CH_2Cl_2 with an alkene/*m*-CPBA/$NaHCO_3$ molar ratio of 1:2:3. [d] Percent yield of *trans*-4-phenyl-3-buten-2-one.

effect chemoselective desilylation of **3b** to provide the enone in 95% yield based on 28% conversion (entry 2). For epoxidation of allylic alcohols **3c**−**e**, **2** could afford *erythro* selectivity of 2:1, while *m*-CPBA provided 1:1 mixtures of *erythro*- and *threo*-epoxides (entries 3−5).

Diastereoselective Epoxdation of Allylic Terminal Alkenes. It has always been a challenge to attain high *erythro* selectivity for epoxidation of allylic terminal alkenes, and the reason is twofold. In contrast to cyclic alkenes, acyclic alkenes are conformationally nonrigid. In addition, the conformation of terminal alkenes is particularly flexible due to the lack of 1,2- or 1,3-allylic strains.[2a] The highly flexible conformation of the allylic terminal alkenes would lead to additional competing transition state geometries during the oxygen transfer process, resulting in poor diastereoselectivity (see later section).

As the sterically bulky metalloporphyrin catalysts have exhibited high diastereoselectivity in epoxidation of allylic alkenes, we were interested to examine the activity of **1** in epoxidation of allylic terminal alkenes. Using the "**1** + Oxone" approach, terminal allylic alcohol **5a** could be epoxidized to **6a**[15] with an *erythro* selectivity of 5.7:1 (Table 3, entry 1), and higher *erythro* selectivity (7.8:1) could be achieved with H_2O_2 as a terminal oxidant (entry 2). *For a bulkier allylic alcohol **5b**, epoxide **6b** could be obtained with erythro selectivities of 7.1:1 and 9:1 in the **1**-catalyzed epoxidations with Oxone and H_2O_2 as an oxidant, respectively (entries 3 and 4).* Notice that *m*-CPBA could only give 1:1 mixtures of *erythro*-and *threo*-epoxides **6a** and **6b**. To the best of our knowledge, the *erythro* selectivities for the **1**-catalyzed epoxidations of **5a** and **5b** are the best results ever achieved.[4b]

With these promising findings in hand, we proceeded to examine diastereoselective epoxidation reactions of other classes of terminal alkenes. A search of the literature revealed that some *erythro*-amino epoxides are key building blocks for the synthesis of several FDA-approved anti-HIV drugs.[16] Particularly, phenylalanine-derived *erythro*-amino epoxides have been used as the

(11) For other methods to obtain *erythro*-epoxides of crytophycins, see: (a) Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett.* **2002**, *4*, 1813. (b) Al-awar, R. S.; Ray, J. E.; Schultz, R. M.; Andis, S. L.; Kennedy, J. H.; Moore, R. E.; Liang, J.; Golakoti, T.; Subbaraju, G. V.; Corbett, T. H. *J. Med. Chem.* **2003**, *46*, 2985.

(12) Manganese porphyrins were known to catalyze alkane hydroxylation; see ref 5a.

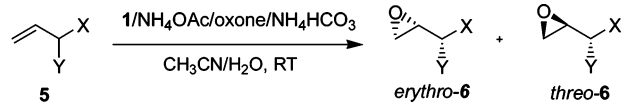
(13) For the use of −OSi^{t}Bu(CH$_3$)$_2$ as a protecting group, see: *Protective Group in Organic Synthesis*, 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons: New York, 1999; Chapter 3.

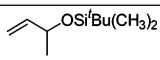
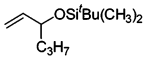
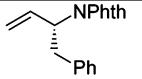
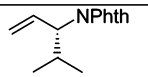
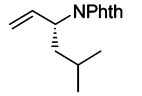
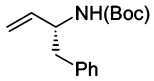
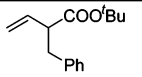
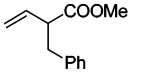
(14) (a) Muzart, J.; N'Ait Ajjou, N. *Synlett* **1991**, *7*, 497. (b) Muzart, J.; Ajjou, A. N. *Synth. Commun.* **1992**, *22*, 1993. (c) Firouzabadi, H.; Shiriny, F. *Synth. Commun.* **1996**, *26*, 423. (d) Heravi, M. M.; Ajami, D.; Tabar-Heydar, K. *Synth. Commun.* **1999**, *29*, 1009.

(15) Hindupur, R. M.; Panicker, B.; Valluri, M.; Avery, M. A. *Tetrahedron Lett.* **2001**, *42*, 7341.

(16) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis*, **2001**, 2203.

TABLE 3. Epoxidation of Allyic Terminal Alkenes 5 by Mn−porphyrins[a]



Entry	Alkene		% Conv.[b]	% yield[b]	*E* : *T* − epoxide ratio.[b] 1	*m*-CPBA[c]
1		**5a**	100	35	5.7:1	1:1
2[d]			93	62	7.8:1	
3		**5b**	100	61	7.1:1	1:1
4[d]			77	78	9:1	
5		**5c**	88	93(96)[e]	3.4:1	1:3
6[f]			80	91	3.6:1	
7[g]			81	82	1.3:1	
8		**5d**	86	87	5:1	1:3
9		**5e**	85	82	1.8:1	1:4
10		**5f**	89	88	1.4:1	1:13
11		**5g**	100	92	1:1	2:1
12		**5h**	82	96	1:1	1:1

[a] Unless otherwise indicated, all the epoxidation reactions were performed as follows: To a CH_3CN/H_2O solution of alkene (0.1 mmol), NH_4OAc (0.05 mmol) and catalyst (0.5 μmol) was added Oxone (0.13 mmol) and NH_4HCO_3 (0.4 mmol) at room temperature (Reaction time: 1 h). [b] Determined by ^1H NMR. [c] Epoxidations were carried out in CH_2Cl_2 with an alkene/*m*-CPBA/$NaHCO_3$ molar ratio of 1:2:3. [d] To a solution of alkene (0.2 mmol), NH_4OAc (0.03 mmol), and **1** (2 μmol) in CH_3CN (4 mL) was added a premixed solution of NH_4HCO_3 (0.6 mmol), CH_3CN (0.5 mL), H_2O (0.5 mL), and 35% H_2O_2 (0.1 mL) at room temperature (Reaction time: 2 h). [e] Isolated yield based on 88% conversion. [f] At 0 °C for 5 h. [g] $Mn(F_{20}$-TPP)Cl was used instead of **1**.

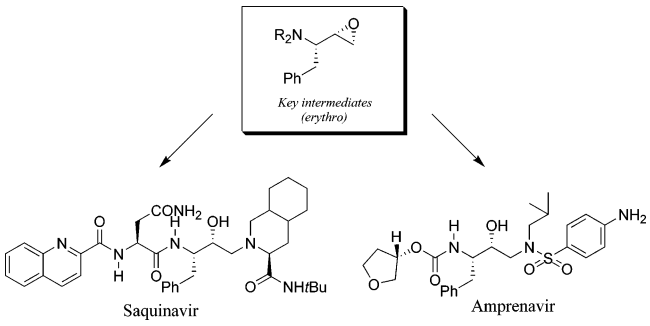


FIGURE 4. Synthetic utilities of *erythro*-allyic amino epoxides.

key synthetic intermediates for the construction of Saquinavir and Amprenavir (Figure 4). Currently, these *erythro*-epoxides have been obtained by ring-closure reactions of β-halohydrins.[17,18] However, *m*-CPBA epoxidation could only afford *threo*-epoxides as major products.[19,20] Up to now, there is no direct epoxidation method available to access these *erythro*-amino epoxide major products.

As illustrated in Table 3, the "**1** + Oxone" oxidation system could achieve *erythro*-selective epoxidation of phthalimide-protected allylic amines **5c**−**e** and Boc-protected allylic amine **5f** in high yields. For epoxidation of **5c** bearing a benzyl group, epoxide **6c**[18a,c] could be achieved with *erythro* selectivity of 3.4:1 in 96% isolated yield based on 88% conversion, while *m*-CPBA provided major product *threo*-epoxide **6c** with a selectivity of 1:3. It should be noted that this is the first example in which major product *erythro* **6c** was obtained via direct epoxidation of **5c**. By conducting the epoxidation at 0 °C, *erythro* selectivity of 3.6:1 could be attained (Table 3, entry 6). With $[Mn(F_{20}$-TPP)Cl] as the catalyst, *erythro* selectivity of 1.3:1 was obtained (entry 7). For epoxidation of **5d** with an isopropyl group, an increase in *erythro* selectivity to 5:1 was observed (entry 8), indicating that this epoxidation is sensitive to the steric bulkiness of the α-substituent. For **5e** and Boc-protected **5f**, *erythro* selectivities of 1.8:1 and 1.4:1 were observed, respectively (entries 9 and 10). It should be noted that *m*-CPBA gave *threo*-epoxides as major products in the epoxidation of **5d** (1:3), **5e** (1:4), and **5f** (1:13). For epoxidation of allylic esters **5g** and **5h** using **1** as a catalyst, 1:1 mixtures of epoxides were observed (entries 11 and 12) in 1 h.[21]

Stereoselective Epoxidation of Glycals. Glycal epoxides have been shown to be important intermediates for oligosaccharide synthesis and could be prepared by dimethyl dioxirane-mediated glycal epoxidation.[22] However, the isolation and large-scale preparation of dimethyl dioxirane would be tedious. In addition, poor facial selectivity resulted in epoxidation of glycals bearing small substituents such as tri-*O*-acetylglycal **7**.[22a,23] In this regard, we were interested to examine the activity of **1** in epoxidation of **7**.[24] To minimize the possibility of epoxide hydrolysis by water, urea−H_2O_2 was used as the

(17) (a) Rotella, D. P. *Tetrahedron Lett.* **1995**, *36*, 5453. (b) Albeck, A.; Estreicher, G. I. *Tetrahedron* **1997**, *53*, 5325. (c) Kim, B. M.; Bae, S. J.; So, S. M.; Yoo, H. T.; Chang, S. K.; Lee, J. H.; Kang, J. *Org. Lett.* **2001**, *3*, 2349. (d) Wang, D.; Schwinden, M. D.; Radesca, L.; Patel, B.; Kronenthal, D.; Huang, M.-H.; Nugent, W. A. *J. Org. Chem.* **2004**, *69*, 1629.

(18) For other methods, see: (a) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656. (b) Branalt, J.; Kvarnstrom, I.; Classon, B.; Samuelsson, B.; Nillroth, U.; Danielson, U. H.; Karlen, A.; Hallberg, A. *Tetrahedron Lett.* **1997**, *38*, 3483. (c) Aguilar, N.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 3560. (d) Kurihara, M.; Ishii, K.; Kasahara, Y.; Miyata, N. *Tetrahedron Lett.* **1999**, *40*, 3183.

(19) Using *m*-CPBA as the oxidant, mixtures of *erythro*- and *threo*-epoxides were obtained, see: (a) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487. (b) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127. (c) Li, Y.-L.; Luthman, K.; Hacksell, U. *Tetrahedron Lett.* **1992**, *33*, 4487. (d) Romeo, S.; Rich, D. H. *Tetrahedron Lett.* **1993**, *34*, 7187. (e) Albeck, A.; Persky, R. *J. Org. Chem.* **1994**, *59*, 653. (f) Jenmalm, A.; Berts, W.; Li, Y.-L.; Luthman, K.; Csoeregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139. (g) Romeo, S.; Rich, D. H. *Tetrahedron Lett.* **1994**, *35*, 4939.

(20) For the use of a polymer-supported ruthenium porphyrin catalyst to synthesize *threo*-**6f**, see ref 7c.

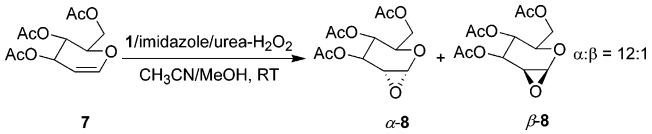
(21) For a selected example on the synthetic utility of *erythro*-**6g**, see: Chung, S. J.; Chung, S.; Lee, H. S.; Kim, E.-J.; Oh, K. S.; Choi, H. S.; Kim, K. S.; Kim, Y. J.; Hahn, J. H.; Kim, D. H. *J. Org. Chem.* **2001**, *66*, 6462. Note that with *m*-CPBA as the oxidant, epoxidations of **5g** and **5h** required a few days for complete conversion.

(22) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. (b) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380.

(23) Kim, H. M.; Kim, I. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 35.

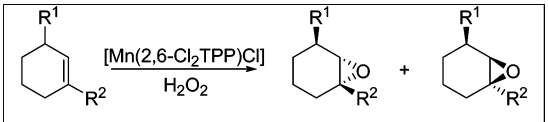
(24) For the use of a ruthenium porphyrin catalyst in α-selective epoxidation of glycal, see ref 7a.

SCHEME 1



oxygen source, and imidazole was used as an axial ligand instead of hydroscopic ammonium acetate.[25] Reaction of **7** (0.1 mmol) with **1** (2 mol %), imidazole (0.04 mmol), and urea−H_2O_2 (3 equiv) in CH_3CN/MeOH afforded the corresponding glycal epoxide, which underwent subsequent methanolysis (with an inversion of configuration) to give methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside in 84% yield based on 53% conversion. On the basis of ^{1}H NMR analysis, the facial selectivity (α:β) of this glycal epoxidation was found to be 12:1 (Scheme 1).

Proposed Transition State Models for 1-Catalyzed Diastereoselective Epoxidation of Cyclohexen-1-ols. Previously, we have reported that **1** could catalyze highly diastereoselective epoxidation of allyl-substituted cycloalkenes with up to >99:1 trans selectivity,[8] and the results are summarized in Figures 5 and 6. Three



Entry	alkene	R^1	R^2	*trans- : cis-* epoxide ratio
1	**9a**	OH	H	4:1
2	**9b**	OAc	H	5:1
3	**9c**	OSi^{t}Bu$(CH_3)_2$	H	33:1
4	**9d**	OSi^{t}Bu$(Ph)_2$	H	16:1
5	**9e**	OH	CH_3	9:1
6	**9f**	OAc	CH_3	25:1
7	**9g**	OSi^{t}Bu$(CH_3)_2$	CH_3	>99:1
8	**9h**	OSi^{t}Bu$(Ph)_2$	CH_3	28:1

FIGURE 5. Diastereoselective epoxidation of cyclohexen-1-ols **9a**−**h** with **1**.

interesting trends were observed: (1) The trans selectivities increased as the steric size of the cyclohexene substituent (R^1) increased from OH to OAc to OSi^{t}Bu$(CH_3)_2$ and decreased when R^1 = OSi^{t}Bu$(Ph)_2$ (Figure 5, entries 1−4 and 5−8). (2) The trans selectivities decreased as the steric size of the ortho substituents X (Cl, CH_3, and F) on the phenyl group of porphyrin rings

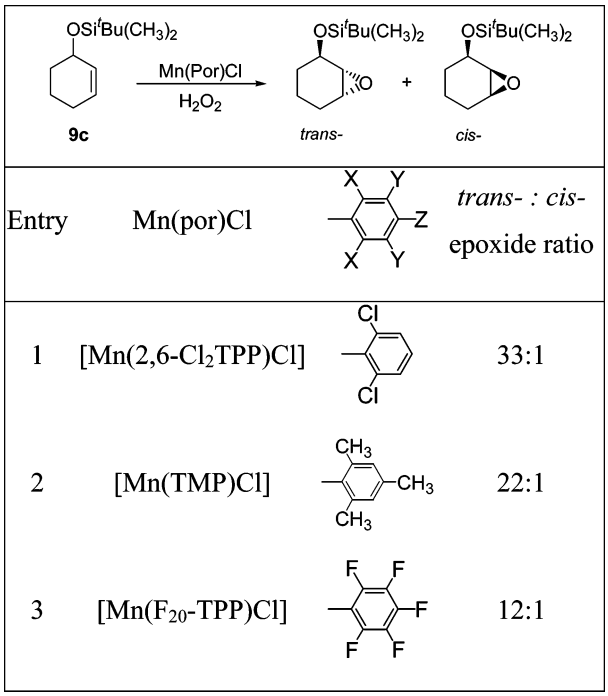


FIGURE 6. Diastereoselective epoxidation of **9c** with Mn−porphyrins.

decreased (Figure 6, entries 1−3). (3) The trans selectivities of **9e**−**h** with $R^2 = CH_3$ are much higher than that of **9a**−**d** with R^2 = H (Figure 5, entries 1 vs 5, 2 vs 6, 3 vs 7, and 4 vs 8). On the basis of the experimental findings, here we propose transition-state models for the **1**-catalyzed diastereoselective epoxidation of cyclohexen-1-ols.

Trend 1. The side-on approach was employed to explain the stereoselectivity obtained in metalloporphyrin-catalyzed epoxidation of *cis*-alkenes.[6a,26] This model has gained a widespread acceptance in the oxidation chemistry of metalloporphyrins and has been successfully applied to explain the enantioselectivity of the chiral Mn(salen)-catalyzed asymmetric epoxidation of unfunctionalized alkenes.[27]

On the basis of the side-on approach, **1** can transfer an oxygen atom to the C=C double bond of the cyclohexenes from both faces, and hence two possible transition states are discernible (Figure 7). In the favored transition state (TS) leading to *trans*-epoxides, there is little or no steric interactions between the X group of **1** and the R^1 group of cyclohexenes. However, severe steric interaction between the X group of **1** and the R^1 group of cyclohexenes are anticipated in the disfavored TS, leading to *cis*-epoxides. The energy difference between the favored and disfavored TS determines the diastereoselectivity. As a result, *trans*-epoxides are obtained as the major diastereoisomers in **1**-catalyzed epoxidation of all the substrates tested.

According to Figure 7, as the steric size of the R^1 group of cyclohexenes increases, more severe steric interactions between the X and R^1 groups are expected in the

(25) Using an axial ligand as a cocatalyst for manganese porphyrin-catalyzed oxidation reaction, see: (a) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110*, 8462. (b) Thellend, A.; Battioni, P.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1994**, 1035.

(26) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.

(27) Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G. W., Stone, F. G. A., Abel, E. W., Hegedus, L. S., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 11.1.

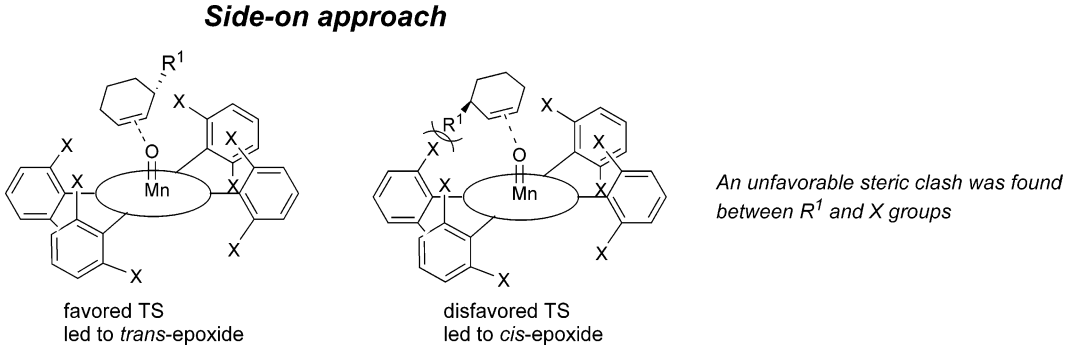


FIGURE 7. Transition-state geometries for epoxidation of cyclohexen-1-ols **9a**−**d** with **1**.

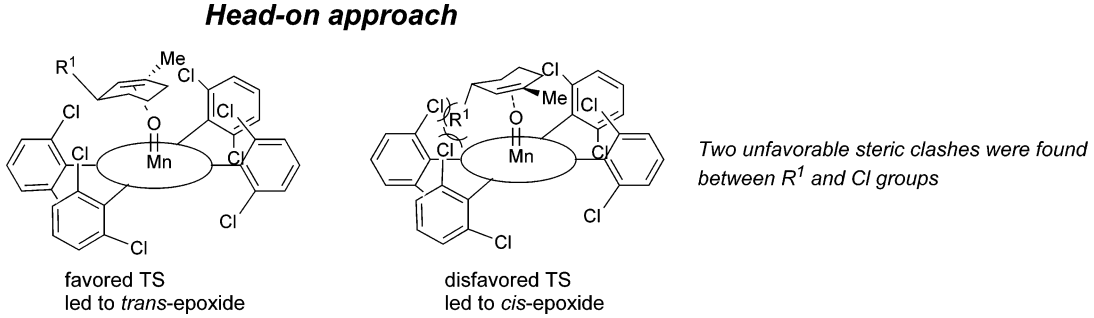


FIGURE 8. Transition-state geometries for epoxidation of cyclohexen-1-ols **9e**−**h** with **1**.

disfavored TS, which lead to an increase in trans selectivity. This notion is supported by the fact that **9c** bearing an $OSi^tBu(CH_3)_2$ group has a higher trans selectivity than **9a** (R^1 = OH) and **9b** (R^1 = OAc). However, when the size of R^1 continues to increase and up to a certain size (i.e., from $OSi^tBu(CH_3)_2$ to $OSi^tBu(Ph)_2$), lower trans selectivity was observed, indicating that $OSi^tBu(CH_3)_2$ would be the optimum substituent for achieving high selectivity.

Trend 2. As depicted in Figure 7, when the X group of the porphyrins becomes smaller (i.e., X changes from Cl to CH_3 to F), less unfavorable steric interactions were found between the X group and the R^1 group in the disfavored TS. In this regard, lower trans selectivities were obtained.

Trend 3. Due to the steric bulkiness of trisubstituted alkenes **9e**−**h**, the head-on approach (instead of the side-on approach) was employed to rationalize the **1**-catalyzed epoxidation.[7b] As shown in Figure 8, **9e**−**h** would approach the metal center from the top of the porphyrin ring. In the favored TS, there is little or no steric interaction between the Cl group of the porphyrin and the R^1 group of the cyclohexenes, leading to *trans*-epoxides. However, severe steric interaction between the Cl group of porphyrins and the R^1 group of cyclohexenes are expected in the disfavored TS, giving rise to *cis*-epoxides. Note that in the disfavored TS, the R^1 group has *two* unfavorable steric clashes with the Cl groups of the porphyrin. The *extra one* steric clash may account for the higher trans selectivity observed in the epoxidation of **9e**−**h** compared with **9a**−**d** (Figure 5, entries 1 vs 5, 2 vs 6, 3 vs 7, and 4 vs 8).

Proposed Transition State Models for 1-Catalyzed Diastereoselective Epoxidation of Terminal Alkene 5a. Due to the lack of 1,2- or 1,3-allylic strains of **5a**, the two most stable conformations **A** and **B** are

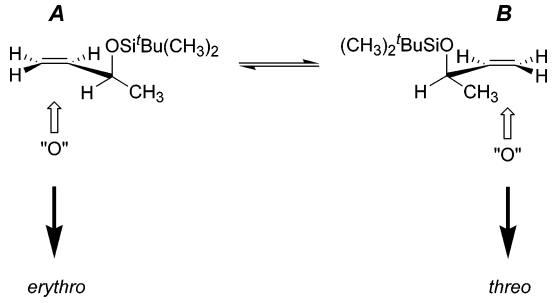


FIGURE 9. Conformers **A** and **B** of substrate **5a**.

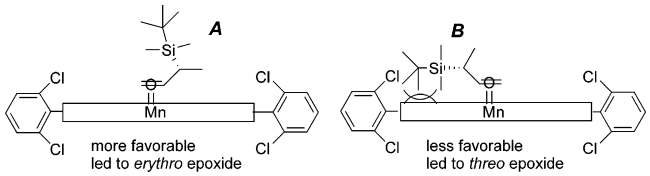


FIGURE 10. Transition-state geometries for epoxidation of **5a** with **1**.

discernible with comparable free energies (Figure 9). As depicted in Figure 9, *erythro*-epoxide would be the major product from conformer **A**, while *threo*-epoxide from conformer **B**. As conformers **A** and **B** are interchangeable, equimolar mixtures of *erythro*- and *threo*-epoxides would be resulted. Therefore, to achieve diastereoselective epoxidation of terminal alkenes, the oxidants must be able to distinguish the conformers **A** and **B**.

On the basis of the side-on approach, **1** would transfer an oxygen atom to **5a** anti to the bulky silyl group, and two possible transition states are proposed (Figure 10). For conformer **A**, the sterically bulky silyl group of **5a** positions itself away from the porphyrin ring, leading to *erythro*-epoxide. In contrast, for conformer **B**, severe

steric interactions are found between the silyl group of **5a** and the porphyrin ring. As a result, *erythro*-epoxide, coming from the epoxidation of conformer **A**, is obtained as the major diastereoisomer.

Conclusion

Furthering our previous work on metalloporphyrin-catalyzed diastereoselective epoxidation, we have successfully extended this method toward *erythro*-selective epoxidation of acyclic allyl-substituted alkenes using Oxone/H_2O_2 as oxidants. Up to 9:1 *erythro* selectivities could be achieved for terminal allyl-substituted alkenes, which are much higher than that achieved using *m*-CPBA. This epoxidation method provides a convenient assess to synthetically useful epoxides including *erythro*-amino epoxides (important anti-HIV drug intermediates) and α-glycal epoxide major products. Future work will be directed toward the application of this method to natural product synthesis.

Experimental Section

General Procedure for "[Mn(2,6-Cl_2TPP)Cl] (1) + Oxone"-Catalyzed Epoxidation of *trans*-Alkene (Table 1, Entry 1). To a round-bottom flask containing [Mn(2,6-Cl_2TPP)Cl] (**1**) (0.5 μmol), **3a** (0.1 mmol), and ammonium acetate (0.05 mmol) in a solution of CH_3CN (3 mL) and H_2O (2 mL) was added a mixture of Oxone (0.13 mmol) and ammonium bicarbonate (0.4 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with saturated aqueous $Na_2S_2O_3$ solution (1 mL) and extracted with *n*-hexane (4 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. To the residue was added 1,1-diphenyl ethylene as an internal standard, and the organic products were analyzed and quantified by ^{1}H NMR spectroscopy. The ratio of epoxides *erythro*-**4a**/*threo*-**4a** was determined to be 6:1 by ^{1}H NMR. The combined yield of *erythro*-**4a** and *threo*-**4a** was 70% on the basis of 93% alkene conversion.

General Procedure for "[Mn(2,6-Cl_2TPP)Cl] (1) + H_2O_2"-Catalyzed Epoxidation (Table 1, Entry 5). To a round-bottom flask containing [Mn(2,6-Cl_2TPP)Cl] (**1**) (2 μmol), **3b** (0.2 mmol), and ammonium acetate (0.03 mmol) in CH_3CN (4 mL) was added a premixed solution of 35% H_2O_2 (0.1 mL), ammonium bicarbonate (0.6 mmol), CH_3CN (0.5 mL), and H_2O (0.5 mL) in 3 portions for 1 h at room temperature. After stirring for an additional 1 h, the reaction mixture was diluted with saturated aqueous $Na_2S_2O_3$ solution (2 mL) and extracted with *n*-hexane (4 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. To the residue was added 1,1-diphenyl ethylene as an internal standard, and the organic products were analyzed and quantified by ^{1}H NMR spectroscopy. The yield of *trans*-4-phenyl-3-buten-2-one was determined to be 49% on the basis of 57% alkene conversion.

General Procedure for [Ru(2,6-Cl_2TPP)(CO)] (2)-Catalyzed Epoxidation (Table 2, Entry 1). To a dried CH_2Cl_2 solution (3 mL) containing **3a** (0.2 mmol) were added [Ru(2,6-Cl_2TPP)(CO)] (**2**) (2 μmol) and 2,6-Cl_2pyNO (0.26 mmol) under a nitrogen atmosphere. After being stirred at 40 °C for 48 h, the reaction mixture was concentrated under reduced pressure. The residue was added 1,1-diphenyl ethylene as an internal standard, and the organic products were analyzed and quantified by ^{1}H NMR spectroscopy. The ratio of epoxides *erythro*-**4a**/*threo*-**4a** was determined to be 5:1 by ^{1}H NMR. The combined yield of *erythro*-**4a** and *threo*-**4a** was 72% on the basis of 82% alkene conversion.

Procedure for 1-Catalyzed Epoxidation of Glycal 7. To a solution of dried CH_3CN (2 mL) and MeOH (1 mL) containing glycal **7** (0.1 mmol) and imidazole (0.04 mmol) were added **1** (2 μmol) and urea−H_2O_2 (0.3 mmol) under a nitrogen atmosphere. After being stirred at room temperature for 5 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with ether (50 mL) and filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure, and 4-bromochlorobenzene was added as an internal standard. The yield of methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside was determined to be 84% on the basis of 53% conversion by ^{1}H NMR. The ratio of epoxides α-**8**/β-**8** was determined to be 12:1.

Acknowledgment. This work was supported by The University of Hong Kong (University Development Fund), the Hong Kong Research Grants Council (HKU-7384/02P), and the Area of Excellence Scheme (AoE/P-10-01) established under the University Grants Council (HKSAR).

Supporting Information Available: Characterization data of **4** and **6**; ^{1}H NMR determinations of the *erythro*-/*threo*-epoxide ratio; and ^{1}H and ^{13}C NMR spectra of **4a**−**e**, **6b**, and **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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