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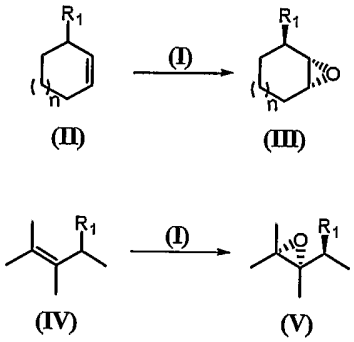
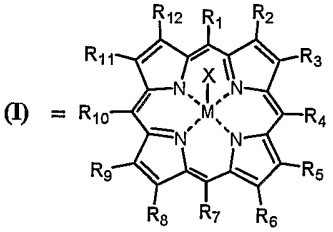
(54) Title: DIASTEREOSELECTIVE EPOXIDATION OF ALLYLICALLY SUBSTITUTED ALKENES USING METALLOPORPHYRIN CATALYSTS





(57) Abstract: Diastereoselective epoxidation of allylically substituted alkenes using metalloporphyrins as catalyst provides high trans-selectivities (i.e., *trans-* : *cis*-epoxide ratio). A diversity of cycloalkenes bearing different allylic substituents are shown to be efficiently epoxidized to afford the corresponding *trans*-epoxides with excellent *trans*-selectivities (up to > 98%) and good yields (up to 99%). Acyclic allylic alkenes bearing different allylic substituents are efficiently epoxidized to afford the corresponding *erythro*-epoxides with good *erythro*-selectivities. The metalloporphyrin-catalyzed reactions exhibit up to 20 times higher *trans*-selectivities than the conventional method using *m*-chloroperoxybenzoic acid as oxidant. Formulae (I), (II), (III), (IV), (V).

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Diastereoselective Epoxidation of Allylically Substituted Alkenes Using Metalloporphyrin Catalysts

This is based on the priority of United States Provisional Application Serial Number 60/553,972, filed March 18, 2004.

Field of The Invention

This invention concerns the use of sterically bulky metalloporphyrins as efficient catalysts for diastereoselective epoxidation of allylically substituted alkenes.

Background of The Invention

Development of efficient methods for highly diastereoselective epoxidation of allylically substituted alkenes is of great importance, as their epoxides are versatile building blocks for organic synthesis as well as construction of biologically active natural products and chiral drugs.

trans-Epoxides of some allylic alkenes are known to be key synthetic intermediates/starting materials in the preparation of synthetically useful chiral 1,2-diamines [Demay, S.; Kotschy, A.; Knochel, P. *Synthesis* 2001, 863], conformationally rigid analogues of Carnitine [Hutchison, T. L.; Saeed, A.; Wolkowicz, P. E.; McMillin, J. B.; Brouillette, W. J. *Bioorg. Med. Chem.* 1999, *7*, 1505], cyclopentane analogues of DNA [Ahn, D.-R.; Mosimann, M.; Leumann, C. J. *J. Org. Chem.* 2003, *68*, 7693], core structure of Neocarzinostain antibiotics [Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett.* 1997, 381], biologically active natural products such as (+)-epiepoformin [Tachihara, T.; Kitahara, T. *Tetrahedron* 2003, *59*, 1773], and several best-selling FDA approved HIV-protease inhibitors [Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* 2001, *15*, 2203].

In addition, some *trans*-epoxides of cycloalkenes are fundamental structural units

of biologically active natural products such as (+)-bromoxone [Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. J. *J. Org. Chem.* 2000, *65*, 716], (-)-cycloepoxydon [Li, C.; Pace, E. A.; Liang, M.-C.; Lobkovsky, E.; Gilmore, T. D.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2001,** *123*, 11308], and (+)-epoxyquinols A and B [Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem. Int. Ed.* 2002, *41*, 3192].

Significant advances have been achieved in *cis*-selective epoxidation of allylic alcohols through hydrogen bonding between their *syn*-directing hydroxyl group and oxidants. In general, highly *cis*-selective epoxides (*cis*:*trans*-epoxide ratio >20 : 1) could be conveniently obtained by using peracids such as *m*-chloroperoxybenzoic acid (*m*-CPBA) as oxidant [for reviews on highly *cis*-selective epoxidation, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* 1993, *93*, 1307. Adam, W.; Wirth, T. *Acc. Chem. Res.* 1999, *32*, 703].

For epoxidation of allylically substituted alkenes without *syn*-directing groups, *trans*-epoxides would be obtained as major product through steric interaction between the substrates and the oxidants. However, the *trans*-selectivity (i.e., *trans*:*cis*-epoxide ratio) obtained by using the common oxidants such as *m*-CPBA and dioxiranes are generally low (i.e., trans:cis < 20 : 1). Thus, the development of efficient methods for highly *trans*-selective epoxidation of allylic alkenes poses an important challenge in organic synthesis.

Recently, a systematic study on *m*-CPBA-mediated diastereoselective epoxidation of some selected *N*-protected 2-cyclohexen-1-ylamines has been reported [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]. Dioxiranes (either isolated or generated *in situ* from ketones and oxone) have been reported as mild and efficient oxidants for *trans*-selective epoxidation of allylically substituted alkenes [see: Miyata, N.; Kurihara, M.; Ito, S.; Tsutsumi, N. *Tetrahedron Lett.* 1994, *35*, 1577. Murray, R. W.; Singh, M.; Williams,

B. L.; Moncrieff, H. M. *Tetrahedron Lett.* 1995, *36*, 2437. Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* 1996, *61*, 1830. Yang, D.; Jiao, G.-S.; Yip, Y.-C.; Wong, M.-K. *J. Org. Chem.* 1999, *64*, 1635]. Methyltrioxorhenium (MTO) has been employed for diastereoselective epoxidation of cyclic allylic alkenes [Adam, W.; Mitchell, C. M.; Saha-Moller, C. R. *Eur. J. Org. Chem.* 1999, 785]. The main reason for their low *trans*-selectivities could be attributed to the weak/moderate steric interaction between the oxidants and the substrates.

Metalloporphyrin-catalyzed alkene epoxidation has been a subject of extensive investigation [Meunier, B. *Chem. Rev.* 1992, *92*, 1411. Mansuy, D. *Coord. Chem. Rev.* 1993, *125*, 129. Dolphin, D.; Traylor, T. G.; Xie, L. Y. *Acc. Chem. Res.* 1997, *30*, 251].

As will be appreciated from the foregoing, metalloporphyrin catalysts have been used for the enantioselective epoxidations of alkenes.

Metalloporphyrins have been used as catalysts for regio- and shape-selective epoxidations of alkenes [Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* 1983, *105*, 5786. Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T.; Raybuck, S. A. *J. Am. Chem. Soc.* 1985, *107*, 2000. Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* 1987, *109*, 5045. Collman, J. P.; Zhang, X.; Hembre, R. T.; Brauman, J. I. *J. Am. Chem. Soc.* 1990, *112*, 5356.]

Chiral iron and manganese porphyrins have been employed for enantioselective alkene epoxidations [Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* 1983, *105*, 5791. Mansuy, D.; Battoni, P.; Renaud, J. P.; Guerin, P. *J. Chem. Soc., Chem. Commun.* 1985, 155. O'Malley, S. Kodadek, T. *J. Am. Chem. Soc.* 1989, *111*, 9176. Grove, J. T.; Viski, P. *J. Org. Chem.* 1990, *55*, 3628. Naruta, Y.; Tani, F.; Ishihara, N.; Maruyama, K. *J. Am. Chem. Soc.* **1991**, *113*, 6865. Halterman, R. L.; Jan, S.-T. *J. Org. Chem.* 1991, *56*, 5253. Knoishi, K.; Oda, K.-I.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* 1992, *114*,

1313. Collman, J. P.; Zhang, X.-M.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* 1993, *261*, 1404. Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M. *J. Am. Chem. Soc.* 1999, *121*, 460.]

Chiral ruthenium-porphyrins have been used as efficient catalysts for enantioselective epoxidation of alkenes [Gross, Z.; Ini, S. *J. Org. Chem.* 1997, *62*, 5514. Berkessel, A.; Frauenkron, M. *J. Chem. Soc., Perkin Trans. 1*, 1997, 2265. Gross, Z.; Ini, S. *Org. Lett.* 1999, *1*, 2077. Zhang, R.; Yu, W.-Y.; Lai, T.-S.; Che, C.-M. *Chem. Commun.* 1999, 409. Gross, Z.; Ini, S. *Inorg. Chem.* 1999, *38*, 1446. Zhang, R.; Yu, W.-Y.; Wong, K.-Y.; Che, C.-M. *J. Org. Chem.* 2001, *66*, 8145. Zhang, R.; Yu, W.-Y.; Sun, H.-Z.; Liu, W.-S.; Che, C.-M. *Chem. Eur. J.* 2002, *8*, 2495.]

In addition, it has been reported that supported polyhalogenated metalloporphyrins are robust and recyclable catalysts for alkene epoxidations with exceptionally high turnover numbers [Groves, J. T.; Bonchio, M.; Carofiglio, T.; Shalyaev, K. *J. Am. Chem. Soc.* 1996, *118*, 8961. Liu, C.-J.; Li, S.-G.; Pang, W.-Q.; Che, C.-M. *Chem. Commun.* 1997, 65. Che, C.-M.; Liu, C.-J.; Yu, W.-Y.; Li, S.-G. *J. Org. Chem.* 1998, *63*, 7364. Che, C.-M.; Yu, X.-Q.; Huang, J.-S.; Yu, W.-Y. *J. Am. Chem. Soc.* 2000, *122*, 5337. Che, C.-M.; Zhang, J.-L. *Org. Lett.* 2002, *4*, 1911].

However, there is a paucity of reports of the use of metalloporphyrin catalysts for diastereoselective epoxidation of allylically substituted alkenes. It has been reported that high diastereoselectivity could be obtained in epoxidation of 3,4,6-tri-*O*-acetyl-D-glucal and 2-(Boc-amino)-1-phenylbut-3-ene using ruthenium-porphyrins as catalysts [Che, C.-M.; Liu, C.-J.; Yu, W.-Y.; Li, S.-G. *J. Org. Chem.* 1998, *63*, 7364. Che, C.-M.; Yu, X.-Q.; Huang, J.-S.; Yu, W.-Y. *J. Am. Chem. Soc.* 2000, *122*, 5337. Che, C.-M.; Zhang, J.-L. *Org. Lett.* 2002, *4*, 1911]. There is exclusive formation of α-epoxide in the epoxidation of 3,4,6-tri-*O*-acetyl-D-glucal, which we believe could be attributed to the strong steric

interaction between the bulky porphyrin ligand and the three *O*-acetyl groups on the substrate's ring. On the other hand, the *threo*-selectivity obtained in the epoxidation of 2-(Boc-amino)-1-phenylbut-3-ene appears to be due to the hydrogen bonding formation between the NHBoc group of the substrate and the metal oxo center of the porphyrin catalysts.

Iron porphyrins have been reported as catalysts in diastereoselective epoxidation of some hydroxy-protected acyclic chiral allylic alcohols, see: Adam, W.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc.* 1999, *121*, 1879. For these hydroxy-protected allylic alcohols, *erythro* selectivity was obtained in the epoxidation. The *erythro* selectivity could be attributed to steric effects between the substrates and the catalysts.

In view of the significance of *trans*-selective epoxides of allylically substituted alkenes in the synthesis of natural products and chiral drugs, there exists an urgent need to develop new, practical, and efficient methods for the synthesis of these synthetically useful epoxides.

Brief Description of the Drawing

Figure 1 sets forth five metalloporphyrins which can be used in the present invention.

Detailed Description of the Invention

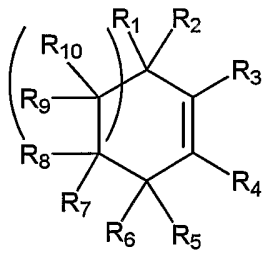
In this invention, highly *trans*-selective epoxidation is achieved based on strong steric interaction between the substrate and the bulky porphyrin ligand when the substrate and ligand are appropriately selected.

In broad terms, the method for synthesizing a *trans-* / *erythro*-epoxide from an allylically substituted alkene involves catalyzing the reaction of an oxidant with the alkene in the presence of a catalytic amount of metalloporphyrin as the catalyst for producing the epoxide. To preferentially achieve a *trans-* / *erythro*-epoxide, the alkene

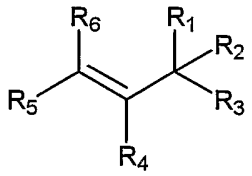
and catalyst must be appropriately selected. Other than in the selection of the alkene and catalyst, the reagents and processes of the prior art can be employed.

The alkene used in this invention is an allylically substituted alkene of the formula R – CH(R_1) – CH = CH – CH - R in which R_1 is a suitable allylic substituent. Each of the carbon atoms in the R groups of these alkenes is optionally substituted and two R groups can be linked to form with the carbon atoms to which they are attached, a 5-, 6-, 7-, 8- or 9- membered ring, which itself can be fused to another ring.

Thus, the alkene can be a cyclic allylically substituted alkene (for example: formula II) or an acyclic allylically substituted alkene (for example: formula IV):



(II)

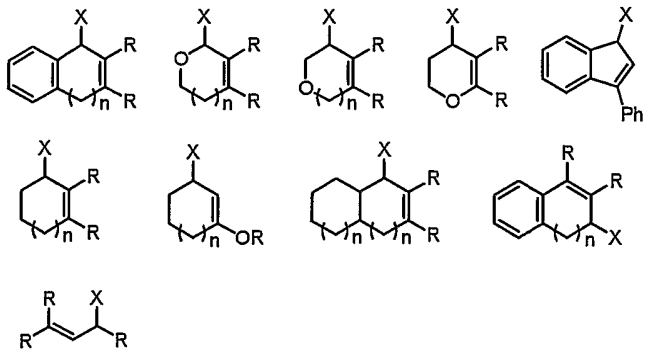


(IV)

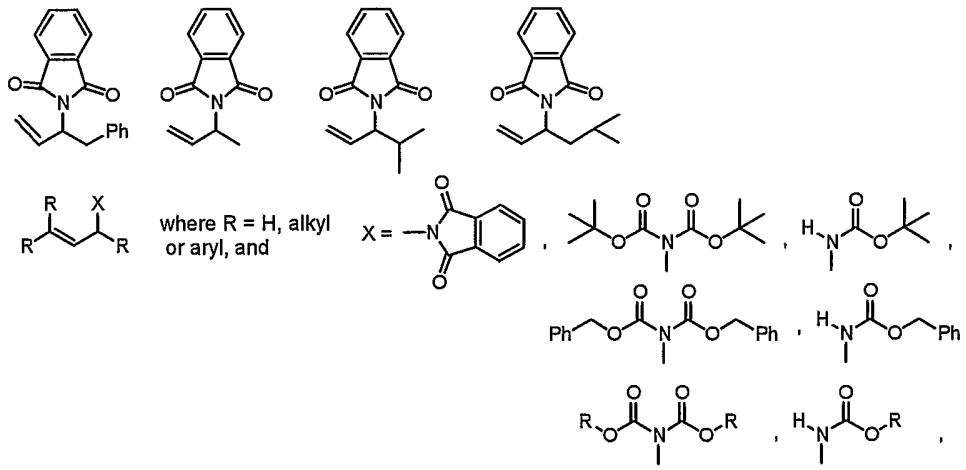
wherein R_1 is an allylic substituent selected from the group consisting of halogen, heteroatom, hydroxy, alkoxy, substituted hydroxy, carboxyl, carbonyl, cyano, silyl, boro, amino, substituted amino, nitro, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl and phosphorus groups ; each of R_2–R_{10} is individually selected from the group consisting of hydrogen, halogen, heteroatom, hydroxyl, alkoxy, substituted hydroxy, carboxyl, carbonyl, cyano, silyl, boro, amino, substituted amino, nitro, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl groups; and R_5 and R_6 in formula II can also be an oxo group. In formula II, the ring can be five-membered, seven-membered, eight-membered, or nine-membered (i.e., n can be 0, 1, 2, 3 or 4), or the R substituents can be linked to form a fused ring. Without limiting the foregoing, the heteroatom can be, for instance, oxygen, nitrogen, silicon, boron, selenium,

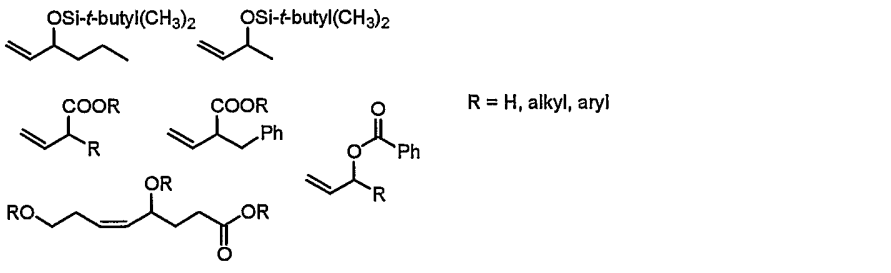
phosphorus or sulfur and the substituents on the various moieties which are substituted can be alkyl, aryl, halogen, hydroxy, oxo, alkoxy, carboxyl, carbonyl, cyano, amino, nitro, heteroalkyl and/or heteroaryl.

Beyond the examples of alkenes described later in this specification, some of the alkenes that can be employed include:

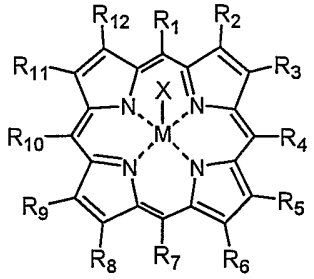


in which X is O, N, C, Br, Cl, I, CN, Si, B, Se, NO_2, SO_2Ph and P; R is H, alkyl, aryl, heteroalkyl, and hetero aryl; and n is 0 to 4;





The metalloporphyrin can be a metal complex of the formula (I):

(I) = 

in which M is selected from Mn, Ru, Fe, Os, Rh, Ir, Nb, Mo, Ti or Re; X is selected from Cl, CO, O^{2-}(oxo), N^{3-}(nitrido), NR(imide) (where R = alkyl, aryl, sulfonyl or acetyl), or a weakly coordination ligand; and where R_1–R_{12} is selected from various substituents that may be the same or different, and are each independently selected from the group consisting of hydrogen, halogen, heteroatom, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl and substituted heteroaryl groups. Without limiting the foregoing, the heteroatom can be, for instance, oxygen, nitrogen or sulfur and the substituents on the various moieties which are substituted can be alkyl, aryl, halogen, hydroxy, oxo, alkoxy, carboxyl, carbonyl, cyano, amino, amino, nitro, heteroalkyl and/or heteroaryl. Typical catalysts are set forth in Figure 1.

Such catalysts can be linked to an inert solid support to function as recyclable catalysts (such as Merrifield resin, polyethylene glycol resin, dendrimer, and MCM-41).

Without being limited to theory, it appears that the relative size of the ortho substituent on the phenyl groups of the porphyrin rings and the R_1 and any substituent adjacent the unsaturation of the alkene have the greatest influence on selectivity. The trans selectivity has been noted to usually increase as the steric size of the alkene R_1 and ortho substituents increased. It is preferred to select these groups so as to permit the

approach of the alkene to the metallic center of the catalyst, whether head-on or side-on, with minimal steric obstruction.

The method can be conducted in the presence of a solvent such as acetonitrile, water, dichloromethane, chloroform, methanol, *t*-butanol, benzene, toluene, xylene, chlorobenzene or their mixtures.

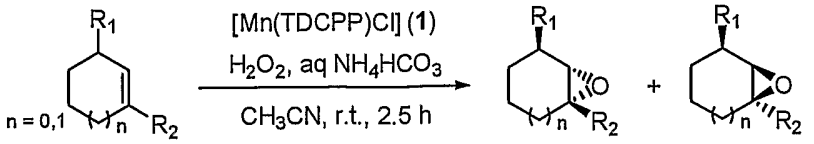
Typical oxidants include hydrogen peroxide and its derivatives, oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), 2,6-dichloropyridine *N*-oxide, peracids, sodium hypochlorite, *t*-butyl hydroperoxide, iodosylbenzene, oxygen and air. When the epoxidation uses hydrogen peroxide or oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as an oxidizing agent, the system is preferably buffered by ammonium bicarbonate or sodium bicarbonate.

Typically, the epoxidation is effected at a temperature ranging from about 0 °C to 60 °C.

The present invention was developed by first conducting an epoxidation of $Si^tBu(CH_3)_2$ protected cyclohexen-1-ol **3c** using [Mn(TDCPP)Cl] (**1**) as catalyst and environmentally benign hydrogen peroxide (H_2O_2) as oxidant. Manganese porphyrins are known to be effective catalysts for epoxidation of simple alkenes using H_2O_2 [see for examples: Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D *J. Am. Chem. Soc.* 1988, 110, 8462. Battioni, P.; Mansuy, D. *J. Chem. Soc., Chem., Commun.* 1994, 1035. Poriel, C.; Ferrand, Y.; Le Maux, P.; Rault-Berthelot, J.; Simonneaux, G. *Tetrahedron Lett.* 2003, *44*, 1759]. 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 afforded *trans*- and *cis*-epoxides **4c** in 88% isolated yield. 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). For $MnSO_4$ salt catalyzed alkene epoxidation using bicarbonate-activated H_2O_2,

see: Burgess, K.; Lane, B. S. *J. Am. Chem. Soc.* 2001, *123*, 2933. Lane, B. S.; Vogt, M.; DeRose, V. J.; Burgess, K. *J. Am. Chem. Soc.* 2002, *124*, 11946.

Table 1. Diastereoselective Epoxidation of Cycloalkenes **3a-3n** 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[e]	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[e,g]	9:1	1:10
6	R1	**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	R2	**3h**	$OSi^tBu(Ph)_2$	CH_3	57[i,f]	28:1	3:1
9		**3i**	COOMe	H	97[e]	4:1	1:1
10		**3j**	$COOC_6H_{11}$	H	92[e]	11:1	1:1
11		**3k**	$COOCH(Ph)_2$	H	74	35:1	1:1
12		**3l**	$N(Boc)_2$	H	90[e]	30:1	n.d.[j]
13	R1	**3m**	$OSi^tBu(CH_3)_2$	–	82[e]	18:1	1:1
14		**3n**	OCH_2Ph	–	83[e]	10:1	2:1

[a] Unless otherwise indicated, all the epoxidation reactions were performed as follows: A solution of alkene (0.25 mmol) and **1** (3 μmol) in CH_3CN (4 mL) was added a pre-mixed 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 based on ^1H NMR analysis. [c] Determined by ^1H NMR. [d] Epoxidations were carried out in CH_2Cl_2 for 3 h with a alkene: *m*-CPBA: $NaHCO_3$ molar ratio of 1: 1.5: 3. [e] Determined by GC. [f] 7–15% of enone was formed based on ^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.

The activities of other manganese porphyrin catalysts for the diastereoselective epoxidation of **3c** were examined under the same reaction conditions. 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](**3**) as catalyst, *trans*-selectivity of 22:1 and epoxide yield of 56% (based on 16% conversion) were observed. While [Mn(TTP)Cl](**5**) was found to exhibit poor catalytic activity (<5% conversion), the perfluorinated analog (i.e., [Mn(TFPP)Cl])(**4**) gave *trans*-selectivity of 12:1 with modest catalytic activity (61% yield based on 25% conversion). It should be noted that all the metalloporphyrin catalysts exhibited higher *trans*-selectivity than *m*-CPBA.

With these promising data in hand, other substrates have been examined by using **1** as catalyst. The catalytic oxidation of **3g** (R_1 = OSi^{t}Bu$(CH_3)_2$, 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. It was 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 [Miyata, N.; Kurihara, M.; Ito, S.; Tsutsumi, N. *Tetrahedron Lett.* **1994**, *35*, 1577] and 20:1 [Yang, D.; Jiao, G.-S.; Yip, Y.-C.; Wong, M.-K. *J. Org. Chem.* **1999**, *64*, 1635], 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. While the **1**-catalyzed epoxidation of **3c** (R_1 = OSi^{t}Bu$(CH_3)_2$, 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^{t}Bu$(Ph)_2$, R_2 = H) was employed

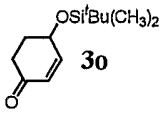
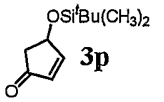
as substrate, the **1**-catalyzed reaction attained a lower diastereoselectivity (16:1) compared to the value for the related reaction of **3c**. Similar dependence on substituent was also encountered for the catalytic epoxidation of **3e–h**. Interestingly, the *trans*-selectivities obtained in the 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, catalytic epoxidation of allylic esters and amines were also performed. 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.

In addition, the catalytic activity of [Ru(TDCPP)CO] (**2**) for epoxidation allylically substituted cyclohexenes was also examined (Table 2). 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. 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). It is worthy to note

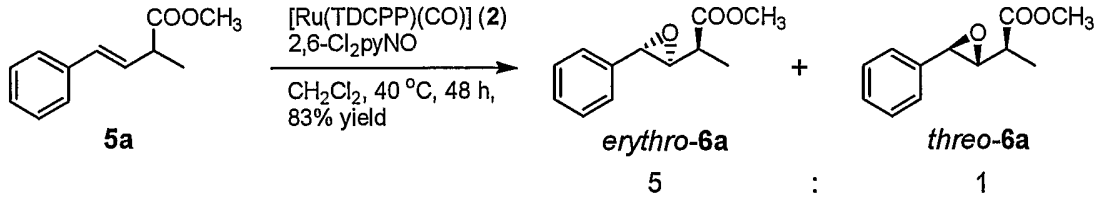
that high product turnover number up to 3,000 could be achieved for the 2-catalyzed epoxidation of **3p** without compromise on the *trans*-selectivity.

Table 2. Diastereoselective Epoxidation of 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 ^{1}H NMR with internal standard.

Apart from cyclic allylic alkenes, diastereoselective epoxidation of acyclic allylically substituted alkene **5a** using 2,6-dichloropyridine-*N*-oxide was also examined.



5a *erythro*-**6a** : *threo*-**6a**

5 : 1

Under the **2**-catalyzed epoxidation conditions, *erythro*-epoxide **6a** was obtained as the major product (*erythro*-**6a** : *threo*-**6a** = 5 : 1) in high yield. This *erythro*-selectivity is higher than the *m*-CPBA mediated epoxidation of **5a** (*erythro*-**6a** : *threo*-**6a** = 1.6 : 1). In addition, using **1** as catalyst and oxone as oxidant, **6a** (*erythro* : *threo* = 6:1) was obtained in 70% yield based on 93% conversion.

As the steric bulky metalloporphyrin catalysts exhibited high diastereoselectivity

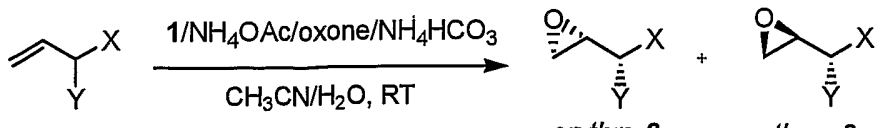
in epoxidation of allylic alkenes, attention was directed to the activity of **1** in epoxidation of allylic terminal alkenes. Using the "**1** + Oxone" approach, terminal allylic alcohol **7a** could be epoxidized to **8a** with *erythro*-selectivity of 5.7:1 (see Table 3 below, entry 1), and higher *erthyro*-selectivity (7.8:1) could be achieved with H_2O_2 as terminal oxidant (entry 2). For a bulkier allylic alcohol **7b**, epoxide **8b** with erythro-selectivities of 7:1 and 9:1 could be obtained in the **1**-catalyzed epoxidations with oxone and H_2O_2 as oxidant, respectively (entries 3 and 4). Notice that *m*-CPBA could only give 1:1 mixtures of *erythro*-and *threo*-epoxides **8a** and **8b**. To the best of our knowledge, the *erythro*-selectivities for the **1**-catalyzed epoxidations of **7a** and **7b** are the best results ever achieved [cf. Kurihara, M.; Ishii, K.; Kasahara, Y.; Kameda, M.; Pathak, A. K.; Miyata, N. *Chem. Lett.* **1997**, 1015].

Diastereoselective epoxidation reactions of other classes of terminal alkenes were also examined. A search of literature revealed that some *erythro*-amino epoxides are key building blocks for the synthesis of several FDA-approved anti-HIV drugs [Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* 2001, *15*, 2203]. Particularly, phenylalanine derived *erythro*-amino epoxides have been used as the key synthetic intermediates for the construction of saquinavir and amprenavir. Currently, these *erythro*-epoxides could be obtained by ring-closure reactions of *β*-halohydrins [Rotella, D. P. *Tetrahedron Lett.* **1995**, *36*, 5453. Albeck, A.; Estreicher, G. I. *Tetrahedron* **1997**, *54*, 5325. 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. Wang, D.; Schwinden, M. D.; Radesca, L.; Patel, B.; Kronenthal, D.; Huang, M.-H.; Nugent, W. A. *J. Org. Chem.* **2004**, *69*, 1629], and other methods [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. et al. *J. Org. Chem.* **1994**, *59*, 3656. Branalt, J.; Kvarnstrom, I.; Classon, B.; Samuelsson, B.; Nillroth, U.; Danielson, U. H.; Karlen, A.;

Hallberg, A. *Tetrahedron Lett.* **1997**, *38*, 3483. Aguilar, N.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 3560. Kurihara, M.; Ishii, K.; Kasahara, Y.; Miyata, N. *Tetrahedron Lett.* **1999**, *40*, 3183]. However, *m*-CPBA epoxidation could only afford *threo*-major epoxides [Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487. Jenmalm, A.; Berts, W.; Li, Y.-L.; Luthman, K.; Csoeregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139. Romeo, S.; Rich, D. H. *Tetrahedron Lett.* **1994**, *35*, 4939]. Before the present invention, there is no direct epoxidation available to access these *erythro*-major amino epoxides.

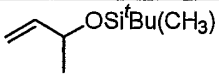
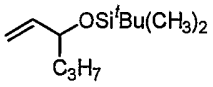
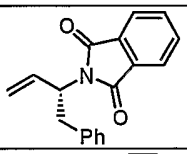
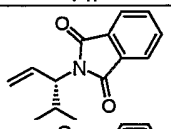
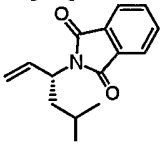
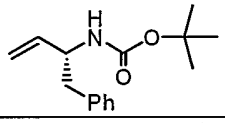
As illustrated in Table 3, the "**1** + oxone" oxidation system could achieve *erythro*-selective epoxidation of phthalimide-protected allylic amines **7c–e** and Boc-protected allylic amine **7f** in high yields. For epoxidation of **7c** bearing a benzyl group, epoxide **8c** with *erythro*-selectivity of 3.4:1 in 96% isolated yield based on 88% conversion could be achieved while *m*-CPBA provided *threo*-major epoxide **8c** with selectivity of 1:3. This is the first example in which erythro-major **8c** can be obtained via direct epoxidation of **7c**. By conducting the epoxidation at 0 °C, *erythro*-selectivity of 3.6:1 could be attained (Table 3, entry 6). For epoxidation of **7d** with an isopropyl group, an increase in *erythro*-selectivity to 5:1 was observed (entry 7), indicating that this epoxidation is sensitive to the steric bulkiness of the α-substituent. For **7e** and Boc-protected **7f**, *erythro*-selectivities of 1.8:1 and 1.4:1 were observed, respectively (entries 8 and 9). It should be noted that *m*-CPBA gave *threo*-major epoxides in the epoxidation of **7d** (1:3), **7e** (1:4) and **7f** (1:13).

Table 3. Epoxidation of Allylic Terminal Alkenes **7** by Mn-porphyrins [a]



7 X = O, N; Y = alkyl

erythro-8 *thero-8*

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

[a] Unless otherwise indicated, all the epoxidation reactions were performed as follows: Alkene (0.1 mmol), NH_4OAc (0.05 mmol) and catalyst (0.5 μmol) in CH_3CN solution was added Oxone (0.13 mmol) and NH_4HCO_3 (0.4 mmol) at room temperature for 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_2 (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.

In summary, general and efficient methods for highly *trans*-selective epoxidation of allylically substituted alkenes by sterically bulky metallo-porphyrin catalysts have been developed. These methods offer an easy assess to a diversity of synthetically useful *trans*-epoxides.

Example 1

A direct method of synthesis of *trans*-selective epoxide using manganese porphyrin (**1**) as catalyst and H_2O_2 as oxidant is as follows. 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.

Example 2

Direct method of synthesis of *trans*-selective epoxide using ruthenium porphyrin (**2**) as catalyst and 2,6-Cl_2pyNO as oxidant: To a dried CH_2Cl_2 solution (4 mL) containing **3c** (53.0 mg, 0.25 mmol) was 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 stirring 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 ^{1}H NMR spectroscopy. The ratio of *trans*-**4c** : *cis*-**4c** was determined to be >99 : 1 by ^{1}H NMR. The yield of epoxides *trans*-**4c** and *cis*-**4c** was 85% based on complete alkene conversion.

The spectral data of cycloalkenes **3b–3d**, **3f–3g**, **3i**, and **3l–3p** are identical with those reported in the following literature:

3b, **3f**	Pearson, A. J.; Hsu, S.-Y. *J. Org. Chem.* **1986**, *51*, 2505.
3c, **3g**	Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
3d	Detty, M. R.; Seidler, M. D. *J. Org. Chem.* **1981**, *46*, 1283.
3i	Davies, S. G.; Whitham, G. H. *J. Chem. Soc. Perkin Trans. 1* **1976**, 2279.
3l	van Benthem, Rolf A. T. M.; Michels, J. J.; Hiemstra, H.; Nico Speckamp, W. *Synlett.* **1994**, 368.
3m	Ahn, D.-R.; Mosimann, M.; Leumann, C. J. *J. Org. Chem.* **2003**, *68*, 7693.
3n	Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Eur. J. Org. Chem.* **1998**, 1675.
3o	Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773.
3p	Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983.

5

The spectral data of epoxides **4a–4g**, **4i** and **4m–4p** are identical with those reported in the literature.

4a, **4b**, **4e**, **4f**, and **4i**	Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830.
4c	Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*. 1577.

4d	Demay, S.; Kotschy, A.; Knochel, P. *Synthesis* **2001**, 863.
4g	Yang, D.; Jiao, G.-S.; Yip, Y.-C.; Wong, M.-K. *J. Org. Chem.* **1999**, *64*, 1635.
4m	Ahn, D.-R.; Mosimann, M.; Leumann, C. J. *J. Org. Chem.* **2003**, *68*, 7693.
4n	Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Eur. J. Org. Chem.* **1998**, 1675.
4o	Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773.
4p	*trans*-**4p**: Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett.* **1997**, 381. *cis*-**4p**: Theil, F. *Tetrahedron: Asymmetry* **1995**, *6*, 1693.

Preparation procedures and characterization data of cycloalkenes **3h**, **3j** and **3k**

3h

A solution of 3-methyl-2-cyclohexen-1-ol (0.49 g, 5 mmol), TBDPSCl (1.01 g, 5.5 mmol), imidazole (0.5 g, 7.3 mmol) in anhydrous DMF (5 mL) was stirred at room temperature for 16 h. The mixture was diluted with EtOAc (50 mL), washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, and concentrated under reduced pressure. The residue was purified by flash column chromatography (1% EtOAc in hexane) to afford alkene **3h** (1.4 g, 4.0 mmol, 80% yield). Colorless oil, analytical TLC (silica gel 60) (10% EA in hexane), R_f = 0.58; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.68 (m, 4H), 7.43–7.24 (m, 6H), 5.35 (s, 1H), 4.21 (br s, 1H), 1.94–1.79 (m, 1H), 1.78–1.72 (m, 2H), 1.61 (s, 3H), 1.60–1.53 (m, 2H), 1.46–1.37 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 136.91, 135.87, 135.82, 134.79, 134.73, 129.41, 129.39, 127.44, 127.42, 125.32, 67.83, 31.93, 30.01, 27.05, 23.59, 19.58, 19.20; IR (KBr) 2931, 1472, 821 cm^{-1}; EIMS *m/z* 360 (M^+), 298 (M^+ – tC_4H_9); HRMS (EI) for $C_{23}H_{30}OSi$, calcd 360.2066, found 360.2062.

3j

A solution of cyclohex-2-enecarboxylic acid (0.4 g, 3.2 mmol), cyclohexanol (0.635 g, 6.4 mmol), DMAP (0.195 g, 1.6 mmol), EDCI (0.92 g, 4.8 mmol) in anhydrous CH_2Cl_2 (10 mL) were stirred at room temperature for 6 h. The reaction mixture was diluted with CH_2Cl_2 (70 mL), washed with H_2O (2 × 10 mL), and dried over anhydrous Na_2SO_4. The reaction mixture was filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (3% EtOAc in hexane) to afford alkene **3j** (0.5 g, 2.4 mmol, 75% yield). Colorless oil, analytical TLC (silica gel 60) (10% EA in hexane), R_f = 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85–5.74 (m, 2H), 4.81–4.77 (m, 1H), 3.06 (m, 1H), 2.02 (m, 2H), 1.92–1.64 (m, 7H), 1.60–1.26 (m, 7H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 174.00, 129.36, 124.65, 72.36, 41.39, 31.51, 25.43, 25.32, 24.67, 23.59, 20.80; IR (KBr) 1722 cm^{-1}; EIMS *m/z* 208 (M^+); HRMS (EI) for $C_{13}H_{20}O_2$, calcd 208.1463, found 208.1443. (Synthesis of cyclohex-2-enecarboxylic acid, see: Davies, S. G.; Whitham, G. H. *J. Chem. Soc. Perkin Trans. 1* **1976**, 2279.)

3k

A solution of cyclohex-2-enecarboxylic acid (0.48 g, 3.8 mmol), benzhydrol (1.4 g, 7.6 mmol), DMAP (0.23 g, 1.9 mmol), EDCI (1.1 mg, 5.7 mmol) and anhydrous CH_2Cl_2 (10 mL) were stirred at room temperature for 6 h. The reaction mixture was diluted with CH_2Cl_2 (70 mL), washed with H_2O (2 × 10 mL), and over anhydrous Na_2SO_4. The reaction mixture was filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (3% EtOAc in hexane) to afford alkene **3k** (0.77 g, 2.6 mmol, 69% yield). Colorless oil, analytical TLC (silica gel 60) (10% EA in

hexane), R_f = 0.58; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 6.88 (s, 1H), 5.86–5.83 (m, 2H), 3.22–3.20 (m, 1H), 2.04–1.75 (m, 5H), 1.63–1.56 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 173.77, 140.85, 140.80, 130.25, 128.91, 128.26, 128.24, 127.49, 127.42, 124.50, 77.20, 41.72, 25.67, 25.07, 21.18; IR (KBr) 1715 cm^{-1}; EIMS *m/z* 292 (M^+), 167 (M^+ - $C_7H_9O_2$); HRMS (EI) for $C_{20}H_{20}O_2$, calcd 292.1463, found 292.1455.

Characterization Data of Epoxides **4h**, and **4j–4l**

A mixture of *trans*-**4h** and *cis*-**4h**

Colorless oil, analytical TLC (silica gel 60) (10% EA in hexane), *trans*-**4h** R_f = 0.28, *cis*-**4h** R_f = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.66 (m, 4H), 7.45–7.34 (m, 6H), 4.02–3.96 (m, 1H), 2.93 (br s, 4/5 × 1H), 2.87 (br s, 1/5 × 1H), 1.85–1.35 (m, 5H), 1.29 (s, 4/5 × 3H), 1.26–1.13 (m, 1H), 1.22 (s, 1/5 × 3H), 1.09 (s, 4/5 × 9H), 1.08 (s, 1/5 × 9H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 135.78, 135.70, 134.04, 133.86, 129.68, 129.65, 129.56, 127.62, 127.55, 127.52, 29.96, 29.39, 28.04, 27.66, 26.95, 26.89, 24.05, 23.36, 19.70, 19.17, 15.68; IR (KBr) 2933, 1472, 822 cm^{-1}; EIMS *m/z* 366 (M^+), 309 ($M^+ - t C_4H_9$); HRMS (EI) for $C_{23}H_{30}O_2Si$, calcd 366.2015, found 366.2015.

trans-**4j**

Colorless oil, analytical TLC (silica gel 60) (10% EA in hexane), R_f = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86–4.80 (m, 1H), 3.41 (d, J = 3.9 Hz, 1H), 3.22–3.20 (m, 1H), 2.87–2.84 (dd, J = 8.6, 5.6 Hz, 1H), 2.08–2.03 (m, 1H), 1.85–1.69 (m, 6H), 1.57–1.25 (m, 9H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 172.97, 72.80, 52.36, 52.24, 40.91, 31.49, 31.43, 25.32, 23.94, 23.78, 23.55, 23.53, 16.80; IR (KBr) 1728 cm^{-1}; EIMS *m/z* 224 (M^+); HRMS (EI) for $C_{13}H_{20}O_3$, calcd 224.1412, found 224.14037.

cis-**4j**

Colorless oil, analytical TLC (silica gel 60) (10% EA in hexane), R_f = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88–4.84 (m, 1H), 3.45 (t, J = 3.5 Hz, 1H), 3.21–3.19 (m, 1H), 2.83–2.78 (m, 1H), 1.90–1.82 (m, 4H), 1.76–1.67 (m, 3H), 1.61–1.23 (m, 9H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 172.24, 72.75, 52.26, 52.18, 41.13, 31.50, 31.47, 25.40, 23.53, 23.58, 23.35, 21.29, 18.91; IR (KBr) 1734 cm^{-1}; EIMS *m/z* 125 ($M^+ - C_6H_{11}O$); HRMS (EI) for $C_7H_9O_2$, calcd 125.0603, found 125.0602.

trans-**4k**

Colorless oil, analytical TLC (silica gel 60) (20% EA in hexane), R_f = 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H), 6.92 (s, 1H), 3.45 (d, 3.5 Hz, 1H), 3.21–3.19 (m, 1H), 3.01 (dd, J = 8.8, 6.5 Hz, 1H), 2.08–2.01 (m, 1H), 1.91–1.87 (m, 1H), 1.86–1.70 (m, 1H), 1.49–1.33 (m, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 172.85, 140.44, 140.37, 128.97,128.95, 128.43, 128.38, 127.46, 127.36, 77.60, 52.65, 52.56, 41.26, 24.29, 24.12, 17.17; IR (KBr) 1732 cm^{-1}; EIMS *m/z* 308 (M^+), 183 ($M^+ - C_7H_9O_2$); HRMS (EI) for $C_{20}H_{20}O_3$, calcd 308.1412, found 308.1407.

cis-**4k**

Colorless oil, analytical TLC (silica gel 60) (20% EA in hexane), R_f = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 10H), 6.94 (s, 1H), 3.54 (t, J = 3.4 Hz, 1H), 3.24–3.21 (m, 1H), 2.95–2.89 (m, 1H), 1.91–1.85 (m, 2H), 1.80–1.64 (m, 1H), 1.61–1.57 (m, 2H), 1.29–1.22 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 171.79, 140.20, 140.13, 128.44, 128.40, 127.87, 127.71, 127.20, 126.82, 77.14, 52.12, 51.95, 41.27, 23.23, 21.32, 18.90; IR (KBr) 1738 cm^{-1}; EIMS *m/z* 308 (M^+), 183 ($M^+ - C_7H_9O_2$); HRMS (EI) for $C_{20}H_{20}O_3$, calcd

308.1412, found 308.1405.

trans-**4l**

Colorless oil; analytical TLC (silica gel 60) (30% EA in hexane), R_f = 0.67; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (dd, J = 10.8, 6.3 Hz, 1H), 3.29 (m, 1H), 3.22 (d, J = 3.9Hz, 1H), 2.12–2.07 (m, 1H), 1.79–1.68 (m, 2H), 1.52 (s, 18H), 1.48–1.43 (m, 2H), 1.42–1.26 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 152.97, 83.31, 57.54, 54.18, 53.25, 28.57, 25.90, 24.68, 16.81; IR (KBr) 1738, 1698 cm^{-1}; EIMS *m/z* 257 ($M^+ + 1 - tC_4H_9$); HRMS (EI) for $C_{12}H_{19}O_5N$ ($M^+ + 1 - C_4H_9$), calcd 257.1263, found 257.1261.

Example 3

A direct method of synthesis of *erythro*-selective epoxide using [Ru(TDCPP)CO] (**2**) as catalyst and 2,6-Cl_2pyNO as oxidant is as follows. To a dried CH_2Cl_2 solution (3 mL) containing **5a** (0.2 mmol) were added [Ru(TDCPP)CO] (**2**) (2 μmol) and 2,6-Cl_2pyNO (0.26 mmol) under nitrogen atmosphere. After being stirred at 40 °C for 48 h, the reaction mixture was 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*-**6a**/*threo*-**6a** was determined to be 5:1 by ^{1}H NMR. The combined yield of *erythro*-**6a** and *threo*-**6a** was 83% based on 82% alkene conversion.

Example 4

A direct method of synthesis of *erythro*-selective epoxide using [Mn(TDCPP)Cl] (**1**) as catalyst and oxone as oxidant is as follows. To a round-bottom flask containing [Mn(TDCPP)Cl] (**1**) (0.5 μmol), **5a** (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 ^1H NMR spectroscopy. The ratio of epoxides *erythro*-**6a**/*threo*-**6a** was determined to be 6:1 by ^1H NMR. The combined yield of *erythro*-**6a** and *threo*-**6a** was 70% based on 93% alkene conversion.

Example 5

A direct method of synthesis of *erythro*-selective epoxide using [Mn(TDCPP)Cl] (**1**) as catalyst and oxone as oxidant is as follows. To a round-bottom flask containing [Mn(TDCPP)Cl] (**1**) (0.5 μmol), **7c** (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 1 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. The residue was added 4-bromochlorobenzene as an internal standard, and the organic products were analyzed and quantified by ^1H NMR spectroscopy. The ratio of epoxides *erythro*-**8c**/*threo*-**8c** was determined to be 3.4:1 by ^1H NMR. The combined yield of *erythro*-**8c** and *threo*-**8c** was 93% based on 88% alkene conversion. The residue was purified by flash column chromatography (20% EtOAc in hexane) to provide a mixture of epoxides *erythro*-**8c** and *threo*-**8c** (24.7 mg, 96% yield based on 88% conversion) as a solid.

Various changes and modification can be made in the present invention without departing from the spirit and scope thereof. The various embodiments described herein were for the purpose of illustration only and were not intended to limit the invention.

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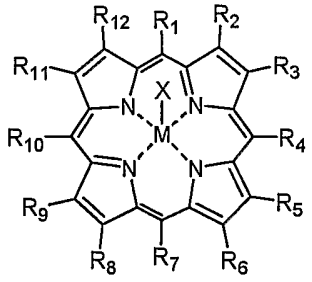
What is claimed is:

1. A method for synthesizing a *trans-* / *erythro*-epoxide from an allylically substituted alkene comprising the step of catalyzing the reaction of an oxidant with said alkene with a catalytic amount of metalloporphyrin as the catalyst for producing the epoxide, wherein said alkene is of the formula R – $CH(R_1)$ – CH = CH – CH - R in which each of the carbon atoms is optionally substituted and two R groups can be linked to form with the carbon atoms to which they are attached, a 5-, 6-, 7-, 8- or 9-membered ring, which itself can be fused to another ring, and R_1 is an allylic substituent selected from the group consisting of halogen, heteroatom, hydroxyl, alkoxy, substituted hydroxy, carboxyl, carbonyl, cyano, silyl, boro, phosphorus containing, sulfur containing, amino, substituted amino, nitro, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl groups.

2. The method of claim 1 wherein the metalloporphyrin is a metal complex of the formula (I):

(I) = 

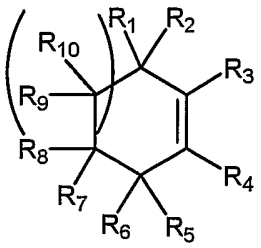
wherein M is selected from Mn, Ru, Fe, Os, Rh, Ir, Nb, Mo, Ti or Re;

wherein X is selected from Cl, CO, O^{2-}(oxo), N^{3-}(nitrido), NR(imide) (where R = alkyl, aryl, sulfonyl or acetyl), or a weakly coordination ligand;

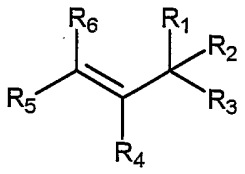
wherein each of R_1–R_{12} is independently selected from the group consisting of hydrogen, halogen, heteroatom, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl groups.

3. The method of claim 2, wherein the catalyst is linked to an inert solid support.

4. The method of claim 3, wherein the alkene is one of



(II)



(IV)

wherein R_1 is an allylic substituent selected from the group consisting of halogen, heteroatom, hydroxyl, alkoxy, substituted hydroxy, carboxyl, carbonyl, cyano, silyl, boro, phosphorus containing, sulfur containing, amino, substituted amino, nitro, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl groups and phosphorous;

wherein each of R_2–R_{10} is individually selected from the group consisting of hydrogen, halogen, heteroatom, hydroxy, alkoxy, substituted hydroxy, carboxyl, carbonyl, cyano, silyl, boro, phosphorus containing, sulfur containing, amino, carboxyl, carbonyl, cyano, amino, substituted amino, nitro, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl groups;

wherein R_5 and R_6 in formula II can also be an oxo group; and

wherein n is 0, 1, 2, 3 or 4.

5. The method of claim 4 conducted in the presence of a solvent selected from the group consisting of acetonitrile, water, dichloromethane, chloroform, methanol, *t*-butanol, benzene, toluene, xylene, chlorobenzene or their mixtures.

6. The method of claim 5 wherein the oxidant is selected from the group consisting of hydrogen peroxide and its derivatives, oxone, 2,6-dichloropyridine *N*-oxide, peracids, sodium hypochlorite, *t*-butyl hydroperoxide, iodosylbenzene, oxygen and air.

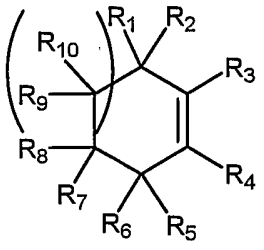
7. The method of claim 6 wherein the reaction is effected at a temperature ranging from about 0 °C to 60 °C.

8. The method of claim 7 wherein the oxidizing agent is hydrogen peroxide or oxone and the reaction is buffered by ammonium bicarbonate or sodium bicarbonate.

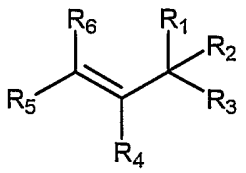
9. The method of claim 1, wherein the catalyst is linked to an inert solid support.

10. The method of claim 2, wherein M is Mn or Ru.

11. The method of claim 1, wherein the alkene is one of



(II)



(IV)

wherein R_1 is an allylic substituent selected from the group consisting of halogen, heteroatom, hydroxyl, alkoxy, substituted hydroxy, carboxyl, carbonyl, cyano, silyl, boro, phosphorus containing, sulfur containing, amino, substituted amino,

nitro, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl groups and phosphorous;

wherein each of R_2–R_{10} is individually selected from the group consisting of hydrogen, halogen, heteroatom, hydroxy, alkoxy, substituted hydroxy, carboxyl, carbonyl, cyano, silyl, boro, phosphorus containing, sulfur containing, amino, substituted amino, nitro, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl groups;

wherein R_5 and R_6 in formula II can also be an oxo group; and

wherein n is 0, 1, 2, 3 or 4.

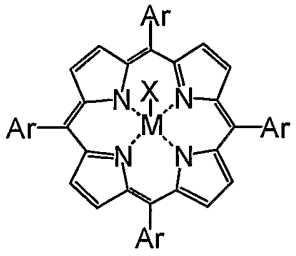
12. The method of claim 1 conducted in the presence of a solvent selected from the group consisting of acetonitrile, water, dichloromethane, chloroform, methanol, *t*-butanol, benzene, toluene, xylene, chlorobenzene or their mixtures.

13. The method of claim 1 wherein the oxidant is selected from the group consisting of hydrogen peroxide and its derivatives, oxone, 2,6-dichloropyridine *N*-oxide, peracids, sodium hypochlorite, *t*-butyl hydroperoxide, iodosylbenzene, oxygen and air.

14. The method of claim 1 wherein the reaction is effected at a temperature ranging from about 0 °C to 60 °C.

15. The method of claim 1 wherein hydrogen peroxide or oxone is used as an oxidizing agent and the reaction is buffered by ammonium bicarbonate or sodium bicarbonate.

16. The method of claim 1 wherein the catalyst exhibits a product turnover number ranging from 50 to 3,000.



1: M = Mn^{3+}; X = Cl; Ar =  Mn(TDCPP)Cl

2: M = Ru^{2+}; X = CO; Ar =  Ru(TDCPP)(CO)

3: M = Mn^{3+}; X = Cl; Ar =  Mn(TMP)Cl

4: M = Mn^{3+}; X = Cl; Ar =  Mn(TPFPP)Cl

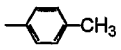
5: M = Mn^{3+}; X = Cl; Ar =  Mn(TTP)Cl

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2005/000342

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D487/22 C07D301/06 B01J31/18 B01J31/26 B01J31/28 B01J31/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI,EPODOC,PAJ,CNPAT,CNKI,CA: porphyrin epoxidation ethyl epo+ Mn Ru cyclohexene allyl oxidation air epoxide oxidant metal diasteroselective trans cis catlyst cat+ oxygen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Catalysis by Metal Complexes, 26(Advances in Catalytic Activation of Dioxygen by Metal Complexes), 1-77 (English) 2003 (CAN 138:309859)	1-16
A	J. Am. Chem. Soc., 114(4), 1313-17 (English) 1992 (CAN 116:83427)	1-16
X	Chemical Communications (Cambridge), (23), 2906-2907 (English) 2002 (CAN 138:337891)	1-3,9
X	US5563263A(examples1-22,table 1,2)	1-16
A	Chem. Commun. (Cambridge), (5), 409-410 (English) 1999 (CAN 130:337962)	1-16
A	Falk J E.Porphyrins And Metalloporphyrins,Amsterdam,Elsevier Pub Co,New York,1964.	1-16
PE	Organic Letters, 6(10), 1597-1599 (English) 2004 (CAN 141:23353)	1-16

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search
08 June 2005 (08.06.2005)

Date of mailing of the international search report
07 · JUL 2005 (07 · 07 · 2005)

Name and mailing address of the ISA/CN
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Authorized officer
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Telephone No. 86-10-62085629

Form PCT/ISA /210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2005/000342

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem. Rev., 93(4), 1307-70 (English) 1993	1-16
A	Chem. Commun. (Cambridge), (5), 409-410 (English) 1999 (CAN 130:337962)	1-16

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2005/000342

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
US5563263A	19961008	WO9608311 A1	19960321