DIASTEREOSELECTIVE EPOXIDATION OF ALLYLICALLY SUBSTITUTED ALKENES USING METALLOPORPHYRIN CATALYSTS

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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).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
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.


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

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,


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


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 \textit{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. \textit{J. Am. Chem. Soc.} 1999, 121, 1879. For these hydroxy-protected allylic alcohols, \textit{erythro} selectivity was obtained in the epoxidation. The \textit{erythro} selectivity could be attributed to steric effects between the substrates and the catalysts.

In view of the significance of \textit{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.

\textbf{Brief Description of the Drawing}

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

\textbf{Detailed Description of the Invention}

In this invention, highly \textit{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 \textit{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 \textit{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):

![Diagram](https://example.com/diagram.png)

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 $R_5$–$R_{10}$ 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 $R_3$ 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:

\[
\begin{align*}
\text{where } R &= \text{H, alkyl, aryl, heteroalkyl, and hetero aryl; and } n \text{ is 0 to 4;}
\end{align*}
\]
The metalloporphyrin can be a metal complex of the formula (I):

\[
\begin{align*}
&\text{(I)} = \\
&\begin{array}{c}
\text{\includegraphics[width=0.3\textwidth]{porphyrin_diagram.png}}
\end{array}
\end{align*}
\]

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(amide) (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 \((2\text{KHSO}_3\cdot\text{KHSO}_4\cdot\text{K}_2\text{SO}_4)\), 2,6-dichloropyridine \(N\)-oxide, peracids, sodium hypochlorite, \(t\)-butyl hydroperoxide, iodosylbenzene, oxygen and air. When the epoxidation uses hydrogen peroxide or oxone \((2\text{KHSO}_3\cdot\text{KHSO}_4\cdot\text{K}_2\text{SO}_4)\) 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 SiBu(CH₃)₂ protected cyclohexen-1-ol \(3c\) using \([\text{Mn}(\text{TDCPP})\text{Cl}]\) (1) as catalyst and environmentally benign hydrogen peroxide \((\text{H}_2\text{O}_2)\) as oxidant. Manganese porphyrins are known to be effective catalysts for epoxidation of simple alkenes using \(\text{H}_2\text{O}_2\) [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 \(\text{CH}_3\text{CN}\) solution of \(3c\) and 1 (1.2 mol%) with a solution of 35% \(\text{H}_2\text{O}_2\) in aqueous \(\text{NH}_4\text{HCO}_3/\text{CH}_3\text{CN}\) afforded \(\text{trans}\)- and \(\text{cis}\)-epoxides \(4c\) in 88% isolated yield. On the basis of capillary GC analysis, the \(\text{trans}\)-selectivity (i.e., \(\text{trans}\) : \(\text{cis}\)-epoxide ratio) was determined to be 33:1 (Table 1, entry 3). For \(\text{MnSO}_4\) salt catalyzed alkene epoxidation using bicarbonate-activated \(\text{H}_2\text{O}_2\),
Table 1. Diastereoselective Epoxidation of Cycloalkenes 3a-3n by 1 Using H₂O₂

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>R₁</th>
<th>R₂</th>
<th>% yield of epoxide</th>
<th>trans- : cis- epoxide ratio</th>
<th>m-CPBA⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>OH</td>
<td>H</td>
<td>59⁵</td>
<td>4:1</td>
<td>1:7</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>OAc</td>
<td>H</td>
<td>71</td>
<td>5:1</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>OSiBu(CH₃)₂</td>
<td>H</td>
<td>88</td>
<td>33:1⁹</td>
<td>5:1</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>OSiBu(Ph)₂</td>
<td>H</td>
<td>64⁷</td>
<td>16:1</td>
<td>4:1</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>OH</td>
<td>CH₃</td>
<td>52⁸</td>
<td>9:1</td>
<td>1:10</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>OAc</td>
<td>CH₃</td>
<td>69⁶</td>
<td>25:1</td>
<td>3:1</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>OSiBu(CH₃)₂</td>
<td>CH₃</td>
<td>80⁶</td>
<td>&gt;99:1</td>
<td>8:1</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>OSiBu(Ph)₂</td>
<td>CH₃</td>
<td>57⁶</td>
<td>28:1</td>
<td>3:1</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>COOMe</td>
<td>H</td>
<td>97⁶</td>
<td>4:1</td>
<td>1:1</td>
</tr>
<tr>
<td>10</td>
<td>3j</td>
<td>COOC₆H₄</td>
<td>H</td>
<td>92⁶</td>
<td>11:1</td>
<td>1:1</td>
</tr>
<tr>
<td>11</td>
<td>3k</td>
<td>COOCH(Ph)₂</td>
<td>H</td>
<td>74</td>
<td>35:1</td>
<td>1:1</td>
</tr>
<tr>
<td>12</td>
<td>3l</td>
<td>N(Boc)₂</td>
<td>H</td>
<td>90⁶</td>
<td>30:1</td>
<td>n.d.²</td>
</tr>
<tr>
<td>13</td>
<td>3m</td>
<td>OSiBu(CH₃)₂</td>
<td>–</td>
<td>82⁶</td>
<td>18:1</td>
<td>1:1</td>
</tr>
<tr>
<td>14</td>
<td>3n</td>
<td>OCH₂Ph</td>
<td>–</td>
<td>83⁶</td>
<td>10:1</td>
<td>2:1</td>
</tr>
</tbody>
</table>

⁵ Unless otherwise indicated, all the epoxidation reactions were performed as follows: A solution of alkene (0.25 mmol) and 1 (3 μmol) in CH₃CN (4 mL) was added a pre-mixed solution of 0.8 M aqueous NH₄H₂CO₃ (0.5 mL), CH₃CN (0.5 mL) and 35% H₂O₂ (0.125 mL) at room temperature. Isolated yield based on complete alkene consumption, and <5% of enone was formed based on ¹H NMR analysis. Determined by ¹H NMR. Epoxidations were carried out in CH₂Cl₂ for 3 h with a alkene: m-CPBA: NaHCO₃ molar ratio of 1: 1.5: 3. Determined by GC. 7–15% of enone was formed based on ¹H NMR analysis. ¹0% of 3-methyl-2-cyclohexenone was detected by ¹H NMR. Isolated yield based on 87% alkene conversion. Isolated yield based on 84 % alkene conversion. 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(TFP)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 \( 3g \) (\( R_1 = OSi^tBu(CH_3)_2 \), \( R_2 = CH_3 \)) proceeded with 80% epoxide formation and trans-selectivity >99:1 (Table 1, entry 7). It is known that m-CPBA and dioxiranes are common oxidants for alkene epoxidation. 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 \( 3c \) (\( R_1 = OSi^tBu(CH_3)_2 \), \( R_2 = H \)) proceeded with excellent trans-selectivity (trans:cis = 33:1), the related reactions with \( 3a \) (\( R_1 = OH \), \( R_2 = H \)) and \( 3b \) (\( R_1 = OAc \), \( R_2 = H \)) were found to exhibit lower diastereoselectivity (trans:cis ~ 5:1). When \( 3d \) (\( R_1 = OSi^tBu(Ph)_2 \), \( R_2 = H \)) was employed
as substrate, the 1-catalyzed reaction attained a lower diastereoselectivity (16:1) compared to the value for the related reaction of 3c. Similar dependence on substituent was also encountered for the catalytic epoxidation of 3e–h. Interestingly, the trans-selectivities obtained in the epoxidation of 3e–h with R₂ = CH₃ were significantly higher than that of 3a–d with R₂ = 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 (R₁ = COOCH(Ph)₂, R₂ = H). However, with m-CPBA as oxidant, only equimolar mixtures of trans/cis-epoxides were obtained for the oxidation of 3i–k. Amine 3l (R₁ = N(Boc)₂, R₂ = H) can be readily converted to its trans-epoxide selectively (trans:cis = 30:1) under the 1-catalyzed conditions. For 1-catalyzed epoxidation of cyclopent-1-ols 3m (R₁ = OSi′Bu(CH₃)₂) and 3n (R₁ = OCH₂Ph), 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 CH₂Cl₂. 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>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>% conv.</th>
<th>% yield of epoxide</th>
<th>trans: cis-epoxide ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>92</td>
<td>86</td>
<td>1:5</td>
</tr>
<tr>
<td>2</td>
<td>3c</td>
<td>100</td>
<td>85</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>3i</td>
<td>97</td>
<td>65</td>
<td>8:1</td>
</tr>
<tr>
<td>4</td>
<td>3m</td>
<td>100</td>
<td>99</td>
<td>71:1</td>
</tr>
<tr>
<td>5</td>
<td>3o</td>
<td>91</td>
<td>85</td>
<td>trans only</td>
</tr>
<tr>
<td>6</td>
<td>3p</td>
<td>94</td>
<td>85</td>
<td>44:1</td>
</tr>
</tbody>
</table>

*All the epoxidation reactions were carried out in CH₂Cl₂ at 40 °C for 48 h with a 2 : 2,6-Cl₂PyNO : alkene molar ratio of 1 : 150 : 100 under nitrogen atmosphere. *b* Determined by ¹H 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.

![Chemical structure](image)

Under the 2-catalyzed epoxidation conditions, erythro-epoxide 6a was obtained as the major product (*erythro-6a : threeo-6a = 5 : 1*) in high yield. This erythro-selectivity is higher than the *m*-CPBA mediated epoxidation of 5a (*erythro-6a : threeo-6a = 1.6 : 1*). In addition, using 1 as catalyst and oxone as oxidant, 6a (*erythro : threeo = 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 erythro-selectivity (7.8:1) could be achieved with H₂O₂ 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 H₂O₂ 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].


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

*
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 access 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 H₂O₂ as oxidant is as follows. To a round-bottom flask containing [Mn(TDCCP)Cl] (1) (3.0 mg, 0.003 mmol) and 3c (53.0 mg, 0.25 mmol) in CH₃CN (4 mL) was added a premixed solution of 35% H₂O₂ (0.125 mL), aqueous NH₄HCO₃ (0.8 M, 0.5 mL) and CH₃CN (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 Na₂S₂O₃ (1 mL) and extracted with n-hexane (4 × 20 mL). The combined organic layers were dried over anhydrous MgSO₄, 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-Cl₂pyNO as oxidant: To a dried CH₂Cl₂ solution (4 mL) containing 3c (53.0 mg, 0.25 mmol) was added [Ru(TDCCP)(CO)(MeOH)] (2) (2.6 mg, 0.0025 mmol) and 2,6-Cl₂pyNO (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 ¹H NMR spectroscopy. The ratio of trans-4c : cis-4c was determined to be >99 : 1 by ¹H NMR. The yield of epoxides trans-4c and cis-4c was 85% based on complete alkene conversion.
The spectral data of cycloalkenes 3b–3d, 3f–3g, 3i, and 3l–3p are identical with those reported in the following literature:


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. |
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), TBDPS-Cl (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 NaHCO₃ 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<sub>f</sub> = 0.58; <sup>1</sup>H NMR (400 MHz, CDCl₃) 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); <sup>13</sup>C NMR (75.47 MHz, CDCl₃) 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⁺ - tC₄H₉); HRMS (EI) for C<sub>25</sub>H₅₀OΣi, calcld 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 CH₂Cl₂ (10 mL) were stirred at room temperature for 6 h. The reaction mixture was diluted with CH₂Cl₂ (70 mL), washed with H₂O (2 × 10 mL), and dried over anhydrous Na₂SO₄. 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), R₇ = 0.50; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75.47 MHz, CDCl₃) 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 C₁₃H₂₀O₂, 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 CH₂Cl₂ (10 mL) were stirred at room temperature for 6 h. The reaction mixture was diluted with CH₂Cl₂ (70 mL), washed with H₂O (2 × 10 mL), and over anhydrous Na₂SO₄. 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), Rf = 0.58; 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75.47 MHz, CDCl3) 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\(_7\)H\(_8\)O\(_2\)); 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 Rf = 0.28, cis-4h Rf = 0.25; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100.61 MHz, CDCl3) 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\(^+\) – tC\(_4\)H\(_9\)); HRMS (EI) for C\(_{20}\)H\(_{20}\)O\(_2\)Si, calcd 366.2015, found 366.2015.

trans-4j

Colorless oil, analytical TLC (silica gel 60) (10% EA in hexane), Rf = 0.31; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100.62 MHz, CDCl3) 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\(_{19}\)H\(_{20}\)O\(_5\), calcd 224.1412, found 224.14037.
cis-4j

Colorless oil, analytical TLC (silica gel 60) (10% EA in hexane), Rf = 0.25; 1H NMR (400 MHz, CDCl₃) 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); 13C NMR (100.62 MHz, CDCl₃) 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⁺ – C₆H₁₄O); HRMS (EI) for C₇H₁₂O₄s, calcd 125.0603, found 125.0602.

trans-4k

Colorless oil, analytical TLC (silica gel 60) (20% EA in hexane), Rf = 0.38; 1H NMR (300 MHz, CDCl₃) δ 7.35–7.26 (m, 10H), 6.92 (s, 1H), 3.45 (d, J = 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); 13C NMR (75.47 MHz, CDCl₃) 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⁺ – C₇H₅O₂); HRMS (EI) for C₂₀H₂₀O₅s, calcd 308.1412, found 308.1407.

cis-4k

Colorless oil, analytical TLC (silica gel 60) (20% EA in hexane), Rf = 0.30; 1H NMR (300 MHz, CDCl₃) 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); 13C NMR (75.47 MHz, CDCl₃) 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⁺ – C₇H₅O₂); HRMS (EI) for C₂₀H₂₀O₅s, 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\(_3\)) \( \delta 4.32 \) (dd, \( J = 10.8, 6.3 \) Hz, 1H), 3.29 (m, 1H), 3.22 (d, \( J = 3.9 \) Hz, 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\(_3\)) \( \delta 152.97, 83.31, 57.54, 54.18, 53.25, 28.57, 25.90, 24.68, 16.81 \); IR (KBr) 1738, 1698 cm\(^{-1}\); EIMS \( m/z \) 257 (\( M^+ + 1 – tC\(_2\)H\(_4\)\)); HRMS (EI) for C\(_{12}\)H\(_{13}\)O\(_2\)N (\( M^+ + 1 – tC\(_2\)H\(_4\)\)), 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\(_2\)pyNO as oxidant is as follows. To a dried CH\(_2\)Cl\(_2\) solution (3 mL) containing 5a (0.2 mmol) were added [Ru(TDCPP)CO] (2) (2 \( \mu \)mol) and 2,6-Cl\(_2\)pyNO (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 \( \mu \)mol), 5a (0.1 mmol) and ammonium acetate (0.05 mmol) in
a solution of CH$_3$CN (3 mL) and H$_2$O (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$_2$S$_2$O$_3$ solution (1 mL), and extracted with n-hexane (4 × 20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, 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-6a/threo-6a was determined to be 6:1 by $^1$H 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$_3$CN (3 mL) and H$_2$O (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$_2$S$_2$O$_3$ solution (1 mL), and extracted with n-hexane (4 × 20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, 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 $^1$H NMR spectroscopy. The ratio of epoxides erythro-8c/threo-8c was determined to be 3.4:1 by $^1$H 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.
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(R₁) – 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 R₁ 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):

\[ (I) = \text{structure diagram} \]

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 R₁–R₁₂ 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

\[ \text{(II)} \]

\[ \text{(IV)} \]

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 \( R_4 \) and \( R_8 \) 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

![Diagram](attachment:image.png)

wherein Rₙ 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 $R_3$–$R_{15}$ 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 $R_3$ and $R_4$ 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**

**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, EPDOC, PAI, CNPAT, CNKI, CA: porphyrin epoxidation ethyl epo+ Mn Ru cyclohexene allyl oxidation air epoxide oxidant metal diastereoselective trans cis catalyst cat+ oxygen

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>Catalysis by Metal Complexes, 26(Advances in Catalytic Activation of Dioxygen by Metal Complexes), 1-77 (English) 2003 (CAN 138:309859)</td>
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<td>A</td>
<td>J. Am. Chem. Soc., 114(4), 1313-17 (English) 1992 (CAN 116:83427)</td>
<td>1-16</td>
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<td>X</td>
<td>Chemical Communications (Cambridge), (23), 2906-2907 (English) 2002 (CAN 138:337891)</td>
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<td>X</td>
<td>US5563263A(examples1-22,table 1,2 )</td>
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<td>PE</td>
<td>Organic Letters, 6(10), 1597-1599 (English) 2004 (CAN 141:23353)</td>
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* Further documents are listed in the continuation of Box C.  
[See patent family annex.]

- **“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
- **“L”** document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **“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**  
28 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  
The State Intellectual Property Office, the P.R.China  
6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China  
100088  
Facsimile No. 86-10-62019451

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>Chem. Rev., 93(4), 1307-70 (English) 1993</td>
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<td>Chem. Commun. (Cambridge), (5), 409-410 (English) 1999 (CAN 130:337962)</td>
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