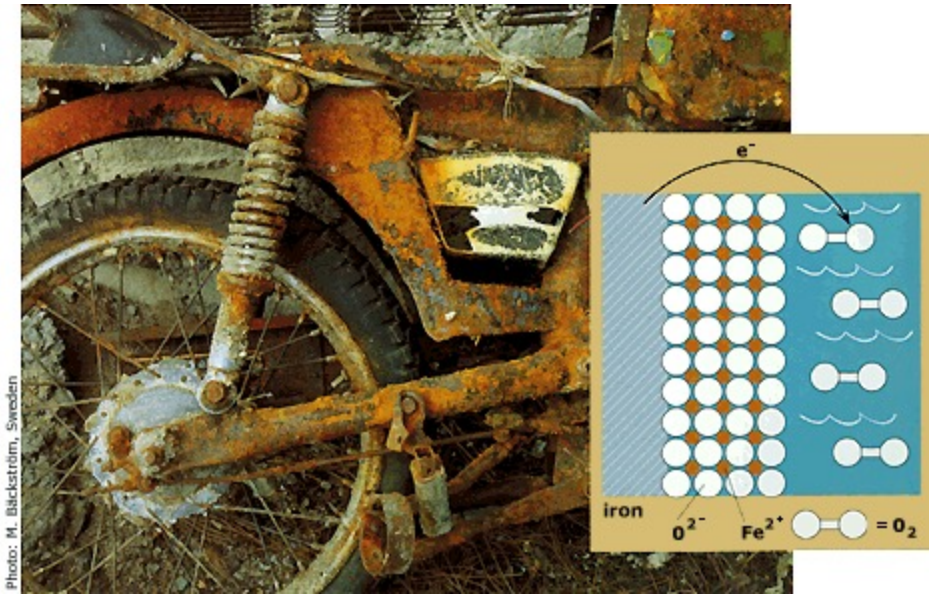
# OXIDATION

Oxidation is one of the major chemical transformations.

There is an increasing demand for selective and mild oxidation methods, in particular catalytic reactions using molecular oxygen as an end oxidant are in focus.




Enantioselective epoxidation of alkenes is an appealing strategy for the synthesis of optically active compounds.

# OXIDATION

Nobel Prize in Chemistry for 2001 for the development of catalytic asymmetric synthesis William S. Knowles, Ryoji Noyori and Barry Sharpless.

**Sharpless's chirally catalyzed oxidations**

Parallel to the progress in catalytic asymmetric hydrogenations Barry Sharpless developed chiral catalysts for very important oxidation reactions. The epoxidation reaction discovered in 1980 by Sharpless and Kazuki is a very fine example of a strategy of using a reagent to achieve stereochemical control.

Using titanium(IV)tetraisopropoxide, *tert*-butyl hydroperoxide, and an enantiomerically pure dialkyltartrate, the Sharpless reaction accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity.

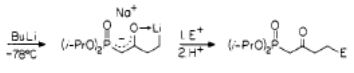
This powerful reaction is very predictable. When the D-(-)-tartrate ligand (D-(-)-DET) is used in epoxidation, the oxygen atom is delivered to the top face of the olefin when the allylic alcohol is depicted as in Figure 1 (i.e. OH group in lower right hand corner).

| ctrophile | product | yield, %[a] |
|---|---|---|
| OD | **7a**, E = D | 70 |
| =CHCH$_2$Br | **7b**, E = CH$_2$=CHCH$_2$ | 75 |
| CH$_2$CH$_2$I | **7c**, E = CH$_3$CH$_2$CH$_2$ | 68 |
| SiCl | **7d**, E = Me$_3$Si | 70 |
| O | **7e**, E = Ph$_2$C(OH) | 72 |
| CONMe$_2$ | **7f**, E = CH$_3$CO | 52 |

efer to pure product after purification on silica gel.

ilization of the organolithium reagent via the intra-chelation of lithium by the enolate oxygen to form a ered cyclic structure (**6**).[13]

nate **4** is a stable compound[14] and was easily prepared eld by the reaction of diisopropyl lithiomethyl-e[2b,15] with methyl 3-(tri-*n*-butylstannyl)propionate.[16] tion of **6** can be followed either by the disappearance




**6** **7**

ing phosphonate (**4**) or by the appearance of tetra-er acid workup of the reaction aliquots. The trans-reaction is essentially complete within 5 min at −78 compound **6** reacts with various electrophiles (Table ly at the δ carbon, giving rise to terminally substituted e esters **7**.[17]

owing experimental procedure is representative of the A dry 35-mL flask (equipped with a septum and a irrer) containing 120 mg (2.5 mmol) of sodium hydride ed with hexanes to remove mineral oil) was flushed and maintained under a positive pressure of argon. mL of freshly distilled dry THF was added, and then mmol) of **4** was added dropwise. The reaction mixture at room temperature for 3 h to allow the formation eaction mixture was cooled to −78 °C, and 2.2 mmol a 2.2 M hexane solution) of *n*-butyllithium was added The resulting light yellow solution was stirred at −78 min. The electrophile (2.2 mmol)[18] was added, and mixture was stirred at −78 °C for 15 min and at room e for 15 min. The reaction was quenched with 10% dimethylacetamide as the electrophile, aqueous NH$_4$Cl and the mixture was extracted with ethyl acetate. The uct[19] was purified by either modified flash chroma-or preparative thin-layer chromatography.

e solution containing **6** (1,4-dianion) was stirred at 0 in, the solution turned red and on reaction with allyl

kind of intramolecular chelated structure of organolithium been postulated in many cases: (a) Klumpp, G. W.; Kool, M.; Schmitz, R. F.; Boutkan, C. *J. Am. Chem. Soc.* **1979**, *101*, 7065. P.; Kostusyk, J. L. *Tetrahedron Lett.* **1979**, 2489. (c) Beak, B. G. *J. Am. Chem. Soc.* **1977**, *99*, 5213. (d) Still, W. C.; T. L. *Ibid.* **1974**, *96*, 5561. (e) Hartmann, J.; Stähle, M.; *Synthesis* **1974**, 888. (f) House, H. O.; Bare, T. M.; Hanners, *Chem.* **1969**, *34*, 2209.

onyl compounds containing the trialkyltin group at the β position able to moisture and treatment with alkali.

Moore, A. H.; Williams, J. H. *J. Chem. Soc.* **1947**, 1465.

erKerk, G. J. M.; Noltes, J. G.; Luijten, J. G. A. *J. Appl. Chem.*

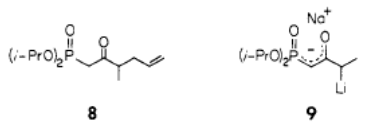
s have not been optimized. In most reactions, 10–20% of pro-ound **7** (E = H) was isolated as the byproduct. As expected, tone **7e** exists predominantly in the cyclic hemiketal structure: .; Zienty, F. B. *J. Am. Chem. Soc.* **1946**, *68*, 1385. The $^1$H nd analytical data of all compounds were in accord with the ctures.

s chlorotrimethylsilane (5.2 mmol) was used for the preparation

crude residue can be partly purified by partitioning between nd hexanes; see: Berge, J. M.; Roberts, S. M. *Synthesis* **1979**,

W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

bromide produced the γ-allyl compound (**8**) as the major product.




**8** **9**


**10**

There was no evidence of **7b** being present in the product. This indicates that **6** is thermodynamically less stable and under conditions conducive to proton transfer gives rise to the more stable 1,3-dianion (**9**).

The generation of **6** shows for the first time that it is possible to generate a homoenolate anion equivalent by tin/lithium exchange when the carbonyl group is protected electronically from nucleophilic attack by butyllithium. The successful transformations reported here, in conjunction with the known reactions of β-ketophosphonates, allow the use of stannane **4** as a synthon for β′-substituted α,β-enones (**10**). The use of **6** to synthesize biologically useful organic molecules and the generation of similar δ-lithio derivatives of other functionalized systems[21] are being investigated.

**Acknowledgment.** I thank Dr. T. H. Whitesides for helpful discussions.

(21) Preliminary experiments show that it is possible to generate $PH_2P^+-^-CHCOCH_2CH_2Li$ similarly. This work will soon be submitted for publication.

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*Received April 21, 1980*

## The First Practical Method for Asymmetric Epoxidation

*Sir:*

As revealed in Scheme I, we have discovered a new metal-catalyzed asymmetric epoxidation process which is far more selective than any of the previously described methods[1] for this type of asymmetric transformation. The simplicity of this new method is one of its more attractive aspects; the necessary components [(+) or (−)-diethyl tartrate,[2] titanium tetraisopropoxide, and

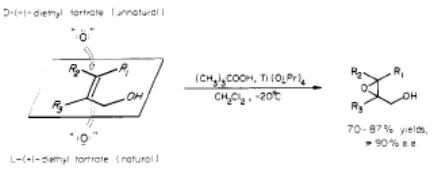
(1) (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, NJ, 1971, pp 258-62; (b) S. Yamada, T. Mashiko, and S. Terashima, *J. Am. Chem. Soc.*, **99**, 1988 (1977); (c) R. C. Michaelson, R. E. Palermo, and K. B. Sharpless, *ibid.*, **99**, 1990 (1977); (d) H. B. Kagan, H. Mimoun, C. Mark, and V. Schurig, *Angew. Chem., Int. Ed. Engl.*, **18**, 485 (1979) [records the highest ee (35%) for a hydrocarbon olefin]; (e) K. Tani, M. Hanafusa, and S. Otsuka, *Tetrahedron Lett.*, 3017 (1979); (f) H. Wynberg and B. Marsman, *J. Org. Chem.*, **45**, 158 (1980); (g) K. Takai, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, 1659 (1980); (h) J. Rebek, *Heterocycles*, in press.

(2) We had earlier examined the effect of chiral alcohols and chiral diols (including L(+)-diethyl tartrate) on the molybdenum- and vanadium-catalyzed TBHP epoxidation of isolated olefins as well as of allylic alcohols. Small (i.e., <10% ee) asymmetric inductions were noted, but they were not deemed worth reporting: R. C. Michaelson and K. B. Sharpless, unpublished results, Massachusetts Institute of Technology, 1974. Otsuka and co-workers have recently described[1g] low (<11% ee) asymmetric inductions in the epoxidation of hydrocarbon olefins with TBHP in the presence of dialkyl tartrate esters and a molybdenum(VI) catalyst.

0002-7863/80/1502-5974$01.00/0 



**Scheme I**




*tert*-butyl hydroperoxide] are all[3] commercially available at low to moderate cost.[4]

This new chiral epoxidation system possesses two especially striking features. First, it gives uniformly high asymmetric inductions throughout a range of substitution patterns[5,17] in the allylic alcohol substrate (Table I). Second, upon use of a given tartrate enantiomer, the system seems obliged to deliver the epoxide oxygen from the same enantioface of the olefin regardless of the substitution pattern. This latter characteristic is highlighted in Scheme I: when the olefinic unit is in the plane of the drawing with the hydroxymethyl substituent at the lower right as shown, the use of (+)-diethyl tartrate leads to addition of the epoxide oxygen from the bottom. Of course, when (−)-diethyl tartrate is employed, the epoxide oxygen is added from the top.

A 500-mL, 1-neck round-bottom flask equipped with a Teflon-coated magnetic stir bar was oven dried and then fitted with a serum cap and flushed with nitrogen. The flask was charged with 200 mL of dry (distilled from $CaH_2$) reagent-grade dichloromethane and cooled by stirring in a −23 °C bath (dry ice/$CCl_4$).[6] Then the following liquids were added sequentially via syringe while stirring in the cooling bath: 5.94 mL (5.68 g, 20 mmol) of titanium tetraisopropoxide (Aldrich); 3.43 mL (4.12 g, 20 mmol)[7] of L(+)-diethyl tartrate (used as received from Aldrich), stirred 5 min before next addition; 3.47 mL (3.08 g, 20 mmol) of geraniol (Aldrich Gold Label); and, finally, ca. 11 mL of a dichloromethane solution (3.67 M in TBHP) containing ca. 40 mmol (2 equiv) of anhydrous *tert*-butyl hydroperoxide (TBHP). (One can just as well use dichloroethane or carbon tetrachloride solutions of anhydrous TBHP. Complete experimental details for preparing these anhydrous TBHP solutions are given elsewhere.[8])

The resulting homogeneous solution was then stored overnight (ca. 18 h) in the freezer at ca. −20 °C in the sealed (serum cap) reaction vessel (the progress of the epoxidation can be monitored by TLC). Then the flask was placed in a −23 °C bath (dry

(3) The diethyl ester of unnatural (−)-tartaric acid has recently become available from Aldrich.

(4) Unnatural D(−)-tartaric acid costs about 34 times more than natural L(+)-tartaric acid when both are purchased in 100-kg quantities; see note 5: E. Hungerbühler, D. Seebach, and D. Wasmuth, *Angew. Chem., Int. Ed. Engl.*, **18**, 958 (1979). This makes it by far the most expensive component since the other three are all available for a few dollars a pound, even in research quantities.

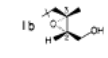
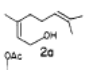
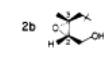
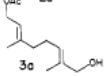
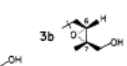
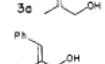
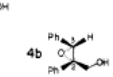
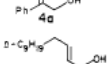
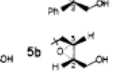
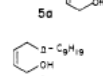
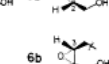
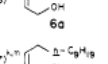
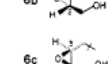
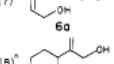
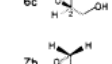
(5) Five of the eight possible basic substitution patterns for a primary allylic alcohol are represented in Table I. We plan to examine the three remaining types, but based on the existing cases no surprises (low ee and/or change in enantioselection pattern) are expected.

(6) Cooling serves two purposes, the obvious one of optimizing enantioselectivity, and the less obvious one of minimizing transesterification processes. Titanium alkoxides are excellent transesterification catalysts, and there is an extensive patent literature on this subject. We have now found that the rate of transesterification is substantially accelerated by an α-hydroxy substituent. Thus, in the presence of Ti(O-*i*-Pr)$_4$, ethyl mandelate transesterifies much faster than methyl phenylacetate (P. H. J. Carlsen and K. B. Sharpless, unpublished results). As α-hydroxy esters, the tartrates also undergo rather facile transesterification in our reaction system at room temperature. This produces tartrate esters which incorporate 2-propanol and also the allylic alcohol substrate, and gives rise to a multitude of problems at the product isolation stage. Fortunately, transesterification is slow at −20 °C, and running the reactions near that temperature has so far proved a viable solution to the problem. However, other solutions are being sought.[15]

(7) It is important to have at least 1 mol of tartrate per mol of Ti(OR)$_4$. A slight excess of tartrate does not seem to matter, so we sometimes add a small excess (2–5%) to be safe. This consideration is more important for small-scale reactions where it is difficult to measure reagents accurately.

(8) K. B. Sharpless and T. R. Verhoeven, *Aldrichimica Acta*, **12**, 63 (1979). This article also contains the best previous result (80% ee) for asymmetric epoxidation of an allylic alcohol (see eq 32, p 67).

**Table I.** Asymmetric Epoxidation of Allylic Alcohols[a]

| | Allylic Alcohol | Epoxyalcohol | % yield[b] | % ee[c] | Configuration[d] |
|---|---|---|---|---|---|
| (1) |  1a | 1b  | 77 | 95 (Eu, M) | 2(S), 3(S)[g] |
| (2) |  2a | 2b  | 79 | 94 (Eu, M) | 2(S), 3(R)[f] |
| (3) |  3a | 3b  | 70[e] | >95 (Eu) | 6(S), 7(S)[g] |
| (4)[h] |  4a | 4b  | 87 | >95 (Eu) | 2(S), 3(S)[i] |
| (5) |  5a | 5b  | 79 | >95 (M) | 2(S), 3(S)[i] |
| (6)[k] |  6a | 6b  | 82 | 90 (M) | 2(S), 3(R)[i] |
| (7)[k,m] |  6a | 6c  | 80 | 90 (M) | 2(R), 3(S)[m] |
| (8)[n] |  7a | 7b  | 81 | >95 (M) | 2(S)[o] |

[a] Unless otherwise noted, all reactions were performed as described in detail for geraniol (**1a**). In most cases, the scale was smaller (ca. 2 mmol). [b] Isolated yields. All new compounds gave appropriate analytical and spectral data. [c] The enantiomeric excesses were determined by $^1$H NMR on the corresponding epoxy acetates (pyridine/$Ac_2O$) in the presence of Eu(hfbc)$_3$ and/or by conversion to the MTPA ester followed by $^1$H or $^{19}$F NMR analysis. The technique(s) used is(are) indicated in parentheses. When both methods were employed, the % ee reported was an average of the two values. [d] All absolute configurations were proven by chemical correlation as indicated for each case. All of the epoxy alcohols in the table gave a negative rotation in $CHCl_3$ except for **4b** and **6c**. [e] The enantiomer of **1b** has been correlated with (*R*)-(−)-linalool.[1b] [f] The enantiomer of **2b** has been correlated with (*S*)-(+)-linalool.[1b] [g] The alkaline hydrolysis step was omitted in this case; the diethyl tartrate was removed by chromatography. 6(*S*),7(*S*)-(−)-**3b** was correlated with (*S*)-(−)-6,7-epoxygeraniol [S. Yamada, N. Oh-hashi, and K. Achiwa, *Tetrahedron Lett.*, 2557 (1976)]. The 8-hydroxyl group of **3b** was replaced by hydrogen via the following reaction sequence: TsCl/pyridine; NaI/acetone; $NaH_3BCN$/HMPA; LiOH/$CH_3OH$, $H_2O$. [h] Epoxidation was performed at 0 °C and was complete in less than 30 min. [i] Co-worker Victor S. Martin (unpublished results) has correlated **4b** with methyl (*S*)-(+)-2,3-diphenyl-2-hydroxypropionate (ii) [H. R. Sullivan, J. R. Beck, and A. Pohland, *J. Org. Chem.*, **28**, 2381 (1963); see also: E. Bye, *Acta Chem. Scand.*, **27**, 3403 (1973)]. Epoxy alcohol **4b** was transformed to ii by the following steps: $RuO_4$/$CCl_4$, $CH_3CN$, $H_2O$; $CH_2N_2$/$Et_2O$; W-2 Raney nickel, $H_2$/absolute EtOH. [j] **5b** was correlated with (*R*)-(−)-tridecan-3-ol (K. Freudenberg, Stereochemie. Eine Zusammenfassung der Ergebnisse, Grundlagen und Probleme, Franz Deuticke, Ed., Leipzig und Wien, p 696) by the following sequence: TsCl/pyridine; NaI/acetone; Zn/HOAc; $H_2$/$PtO_2$. [k] These results were obtained by B. E. Rossiter during enantioselective syntheses of both natural (+)- and unnatural (−)-disparlure (B. E. Rossiter and K. B. Sharpless, unpublished results). [l] **6b** was correlated with unnatural (−)-disparlure (unpublished results, see ref *k* above). [m] In this case, D(−)-diethyl tartrate (the unnatural enantiomer) was used. **6c** was correlated with natural (+)-disparlure (unpublished results, see ref *k* above). [n] This epoxidation was run for 40 h at −20 °C, and a trace of **7a** still remained. [o] **7b** was correlated with (*R*)-(−)-2-cyclohexyl-2-butanol [D. J. Cram and J. Tadanier, *J. Am. Chem. Soc.*, **81**, 2737 (1959)] through the following steps: $LiAlH_4$/$Et_2O$; TsCl/pyridine; $LiCuMe_2$/$Et_2O$.

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ice/$CCl_4$) and 50 mL of 10% aqueous tartaric acid solution was added while stirring; the aqueous layer solidified. After 30 min, the cooling bath was removed and stirring was continued at room temperature for 1 h or until the aqueous layer became clear. After separation of the aqueous layer, the organic layer was washed once with water,[9] dried ($Na_2SO_4$), and concentrated to afford a colorless oil with an odor revealing contamination by TBHP.[9]

This oil was diluted with 150 mL of ether, and the resulting solution was cooled in an ice bath, and then 60 mL of 1 N sodium hydroxide solution was added. This produced a two-phase mixture which was stirred at 0 °C for $^1/_2$ h.[10] The ether phase was washed with brine, dried ($Na_2SO_4$), and concentrated to give 4.24 g of a clear oil. Chromatography on silica gel afforded 2.6 g (77%) of 2(*S*),3(*S*)-epoxygeraniol, $[\alpha]^{24}_D$ −6.36° (*c* 1.5, $CHCl_3$). Analysis of this material as the MTPA ester[11] gave an enantiomeric excess (ee) of >95% whereas analysis of the derived epoxy acetate by using $Eu(hfbc)_3$ chiral shift reagent gave 94% ee.

The "typical procedure" given for geraniol has a limitation which is important to emphasize. *Very poor yields are realized if the epoxy alcohol produced is fairly water soluble.* For example, although allyl alcohol and crotyl alcohol are epoxidized by this system, it is difficult to extract (even with "salting-out" techniques) more than 10–30% of the intact epoxy alcohol product. We are working on solutions to the isolation problems presented by these and related cases.

The procedure described above for epoxidation of geraniol calls for 1 equiv of both titanium isopropoxide and diethyl tartrate. This is by no means necessary in all cases. With reactive allylic alcohols (**1a**, **2a**, **3a**, and **4a** in Table I), a catalytic amount (e.g., 0.1 equiv) of both $Ti(O\text{-}i\text{-}Pr)_4$ and diethyl tartrate suffices[12] under otherwise identical reaction conditions. However, for the less-reactive substrates in Table I (**5a**, **6a**, and **7a**), the "1-equiv" conditions described above were necessary to achieve reasonable reaction rates. Even under the "1-equiv" conditions, allylic alcohol **7a** required almost 2 days to approach completion. For this first report, the most general method (stoichiometric amount of the chiral catalyst system) was chosen for presentation. The catalytic system (which has some important advantages[13] in addition to the obvious ones) is under further study.

Many other aspects of this unique epoxidation system are also being investigated in our laboratory. Of foremost interest is a good mechanistic rationale for the remarkable selectivities which are seen. Our approach to the mechanism involves both kinetic studies and structural modifications of the chiral ligand. From a synthetic point of view, there are several interesting further developments, among them: (1) this same epoxidation system is effective for the kinetic resolution of racemic allylic alcohols,[14] and (2) predominant inversion of the enantioselectivity pattern shown in Scheme I is observed with certain minor structural modifications of the chiral tartrate ligand.[15] We are also extending our studies to include homo- and bishomoallylic alcohols, and β-hydroxy sulfides.

To the best of our knowledge, this new enantioselective, catalytic process is discriminating to a degree barely[16] rivaled by any other nonenzymatic catalytic process. In its promiscuous acceptance of varied allylic alcohol substrates,[5] it also has some desirable features which would be difficult for even an enzymatic catalyst to achieve.[17]

**Acknowledgments.** We dedicate this work to Professor Harry S. Mosher. Through patient sharing of his unique insights into asymmetric synthesis, he has had a profound influence on us. The National Institutes of Health (GM24551) is thanked for financial support.

(9) Due to the small scale, we have chosen to ignore the excess TBHP. If one wishes to remove it, a number of reductive procedures are available.[8]

(10) Do not expose the reaction mixture to this base treatment for longer than $^1/_2$ h as base-catalyzed rearrangements of the epoxy alcohol may occur: G. B. Payne, *J. Org. Chem.*, **27**, 3819 (1962). Diethyl tartrate is fairly soluble in water and hydrolyzes readily under these conditions. We have found that (+)-dimethyl tartrate (Aldrich) is as effective (>95% ee) as the ethyl ester for epoxidation of **4a**. The methyl ester is much more water soluble and may prove advantageous when the hydrolysis step is unacceptable. The isopropyl ester also works well, but leads to increased trouble at the workup stage.

(11) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969). We used MTPA chloride and DMAP in $CH_2Cl_2$.

(12) Under these catalytic conditions, (0.1 equiv of $Ti(OR)_4$/DET), the yields of **1b**, **2b**, and **4b** were comparable to or somewhat better than those with 1 equiv, and the product isolations were cleaner and easier. The enantiomeric excess was somewhat poorer for **1b** (91% ee) and **2b** (84% ee) but was still >95% ee for **4b**.

(13) The possibilities for product stability problems, transesterification problems, and most other workup and isolation problems are greatly diminished.

(14) M. Ikeda, Y. Yamada, T. Katsuki, V. S. Martin, and K. B. Sharpless,

(16) Asymmetric catalytic hydrogenations can be extremely enantioselective; for an example of 100% ee, see: M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6262 (1977). However, these asymmetric hydrogenation processes appear more sensitive to permutation of the olefin substitution patterns than does the asymmetric epoxidation process we have described here.

(17) **Note Added in Proof.** We now have results for two more of the basic substitution patterns of primary allylic alcohols (see note 5). Allyl alcohol itself affords 2(*S*)-glycidol, ca. 15% yield, 73% ee [performed at 0 °C by using (+)-diisopropyl tartrate and $Ti(OiPr)_4$]; the higher temperature probably contributes to the lower ee observed in this case. (*Z*)-2-Methylhept-2-enol gives the 2(*S*),3(*R*)-epoxy alcohol, 80% yield, 89% ee [performed at −20 °C, using (+)-diethyl tartrate and $Ti(OiPr)_4$]. Thus, both conform to the rules stated in paragraph two and only the tetrasubstituted type of primary allylic alcohol remains to be tried.

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**Tsutomu Katsuki, K. Barry Sharpless*[18]**
*Department of Chemistry, Stanford University*
*Stanford, California 94305*
*Received May 5, 1980*

## 2,3-Di-*n*-propyl-1,4-dehydrobenzene

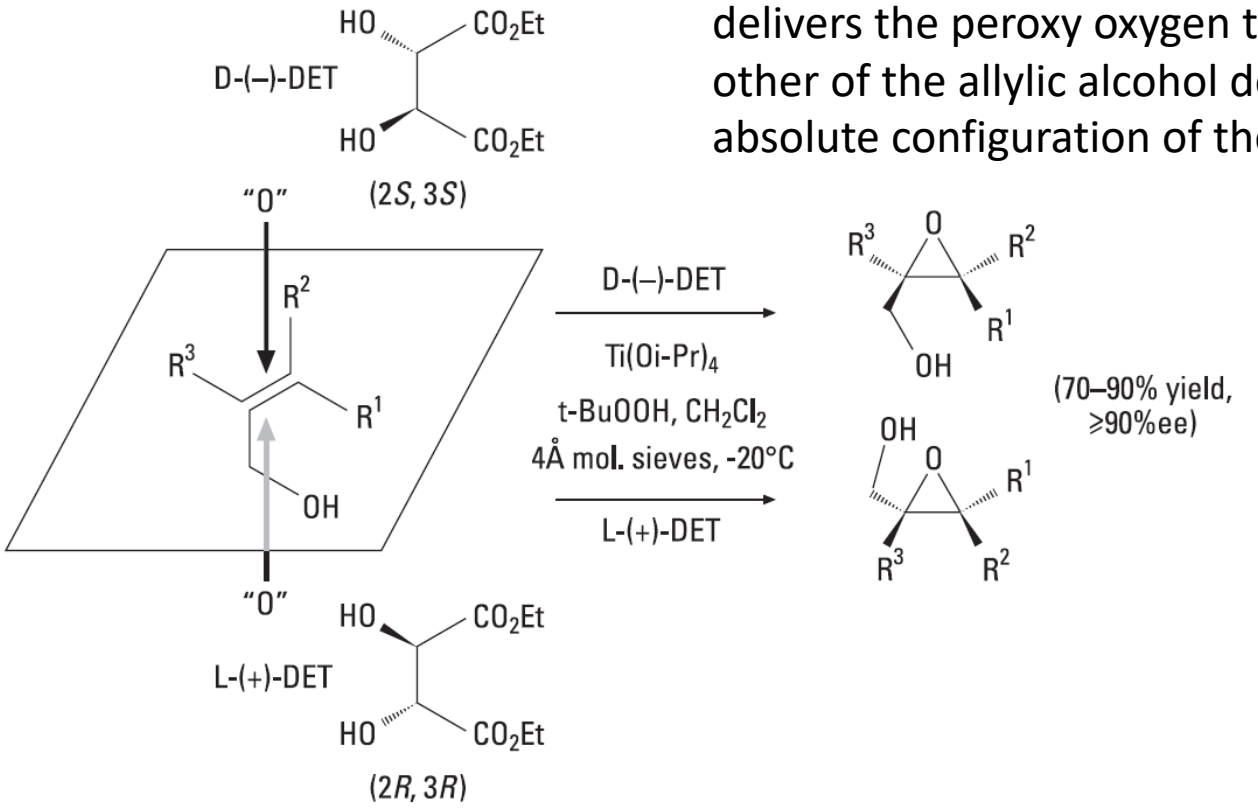
*Sir:*

Rearrangement and trapping studies[1] have implicated an "open" or biradical form (**2**) of 1,4-dehydrobenzene as an intermediate in the thermal reaction of (*Z*)-hexa-1,5-diyn-3-ene (**1**, R = H; Scheme I). Attempts to obtain kinetic evidence for the existence of a true intermediate in this reaction, however, have been frustrated by the low yield of aromatic products obtained in solution pyrolyses of several compounds of type **1**. In this paper, we report a detailed study of the thermolysis of (*Z*)-4,5-diethynyl-4-octene (**4**).[2] This reaction gives high yields of products formed by rearrangement and intramolecular and intermolecular trapping of the intermediate 1,4-dehydrobenzene **5**. The kinetics of the solution pyrolysis of **4** in the presence and absence of trapping agent establish that the 1,4-dehydrobenzene is a discrete intermediate on the pathway leading to products. By following this reaction in the probe of an NMR spectrometer at high temperature, we have, for the first time, observed CIDNP in a 1,4-dehydrobenzene reaction. This observation, along with kinetic and chemical trapping evidence, indicates the subsequent formation of two additional intermediates on the pathway to products. The observation of CIDNP, coupled with the reactivity exhibited by **5** and the other two intermediates, implicates a biradical description of these molecules.

(1) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (c) Johnson, G. C.; Stofko, J. J.; Lockhart, T. P.; Brown, D. W.; Bergman, R. G. *J. Org. Chem.* **1979**, *44*, 4215. See also, however: (d) Breslow, R.; Napierski, J.; Clarke, T. C. *J. Am. Chem. Soc.* **1976**, *98*, 570. (e) Breslow, R.; Khanna, P. L. *Tetrahedron*

# CATALYTIC OXIDATION

The asymmetric complex formed from titanium alkoxide and a chiral tartrate ester delivers the peroxy oxygen to one face or the other of the allylic alcohol depending on the absolute configuration of the tartrate used.



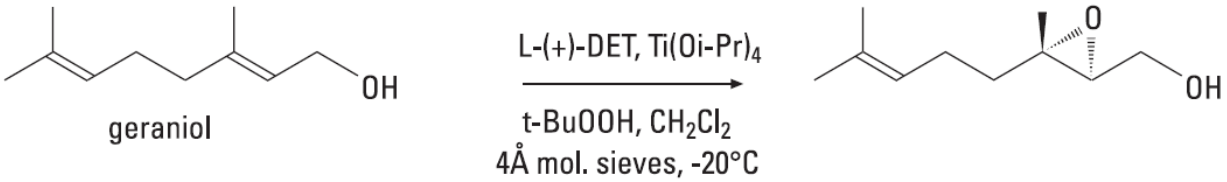
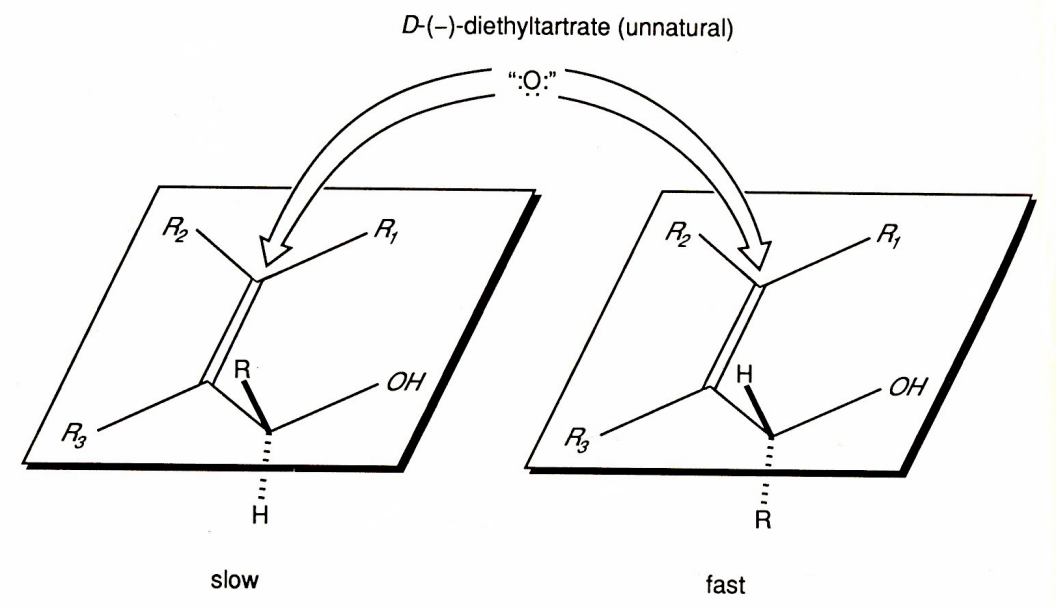




Figure 1: The predictive stereoselectivity of the Sharpless epoxidation is shown together with an example of its regioselectivity.

# CATALYTIC OXIDATION

If allylic alcohol has substituents, the order of the enantioselectivity might change.

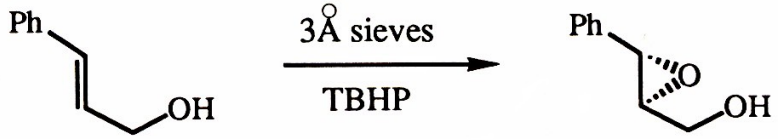
For example, a substituent is placed in $C_1$ as shown in the figure. Oxygen is now delivered at different rates to the two enantiomers depending on the orientation of the R group.




Often the difference in rates is of sufficient magnitude that one enantiomer is completely oxidized while other remains largely unoxidized. *The slow reacting enantiomer has the R group to the direction of "oxygen" delivery.*
Opposite enantiomer will be obtained, if D(+) diethyltartrate complex is used instead.

# CATALYTIC OXIDATION

**Table 2** Dependence of Enantioselectivity on Catalyst Stoichiometry




| Entry | $Ti(O\text{-}i\text{-}Pr)_4$, mole % | (+)-DIPT mole % | % ee |
|---|---|---|---|
| 1 | 5.0 | 6.0 | 92 |
| 2 | 4.0 | 5.2 | 87 |
| 3 | 2.0 | 2.5 | 69 |

The success in the use of titanium tartrate catalyzed asymmetric epoxidation depends on the presence of the hydroxyl group of the allylic alcohol; the hydroxyl group enhances the rate of the reaction, thereby providing selective epoxidation of the allylic olefin in the presence of other olefins, it is also essential for the achievement of asymmetric induction.

*The need for a hydroxyl group necessarily limits the scope of the epoxidation to a fraction of olefins.* On the other hand allylic alcohols are easily introduced to synthetic intermediates and are very versatile in organic synthesis.

# CATALYTIC OXIDATION

The ligands on titanium are in rapid exchange. When equimolar solutions of a titanium alkoxide and dialkyl tartrate are mixed, equilibrium is quickly reached.

$$Ti(OR)_4 + \text{tartrate} \rightleftharpoons Ti(\text{tartrate})(OR)_2 + 2\ ROH$$

The equilibrium is far right because a chelating diol has a much higher binding constant (also higher acidity enhanced by ester groups) for titanium than do monodentate alcohols.

Rapid ligand exchange continues as hydroperoxide (oxidant) and allylic alcohol are added.

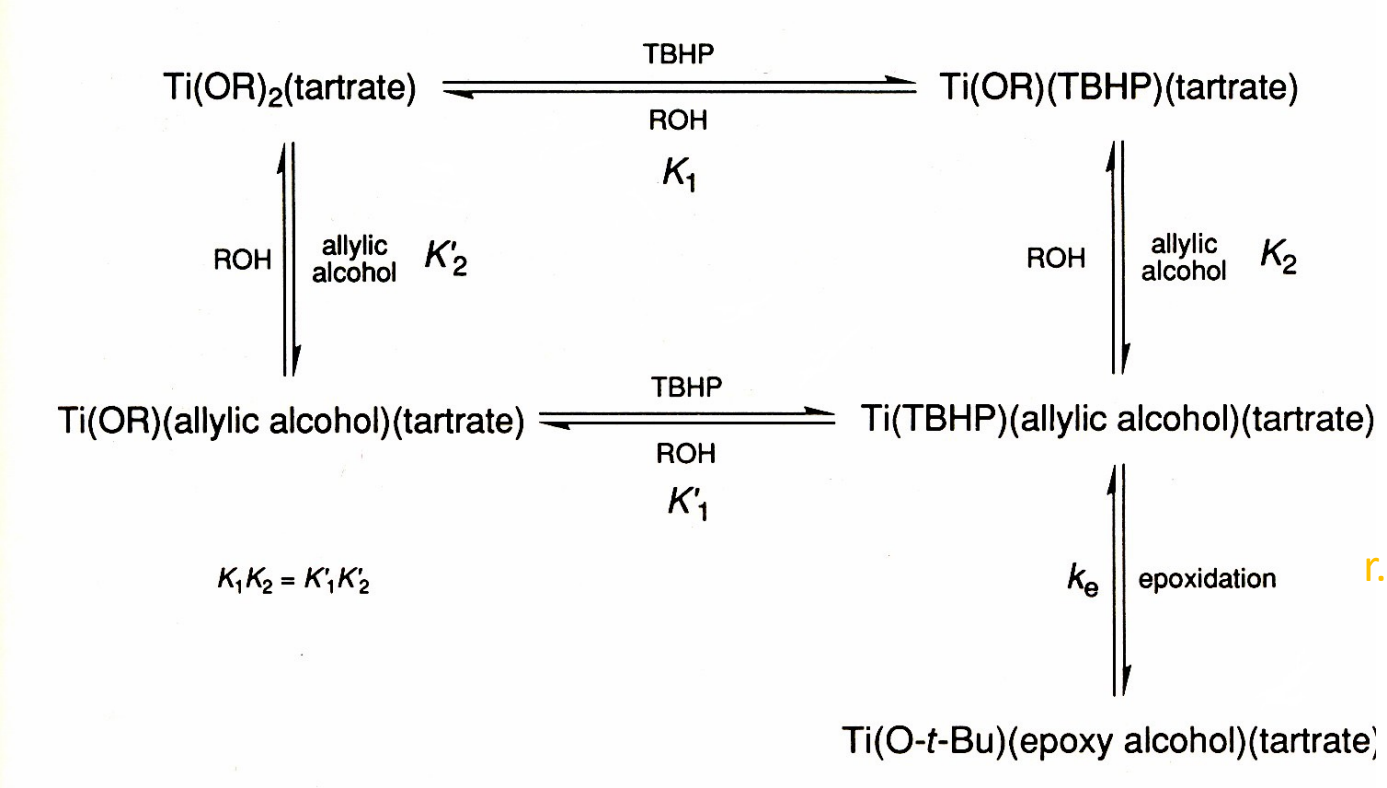
Rate law clearly illustrates that the ligand exchange process is essential for catalytic epoxidation.

$$\text{Rate} = k\frac{[Ti(\text{tartrate})(OR)_2][TBHP][\text{allylic alcoho}}{[\text{ligand alcohol}]^2}$$

Because achiral $Ti(OR)_4$ complexes are also active in epoxidation, it is important to suppress their concentration ($Ti(\text{tartrate})_2$ is inactive; 10-20%$_{mol}$ excess of tartrate is optimal for high yields and selectivity).

# CATALYTIC OXIDATION

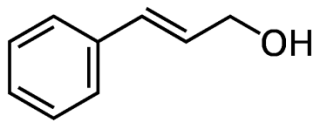
After forming the tartrate complex, the two remaining alkoxide ligands are replaced by hydroperoxide and allylic alcohol.



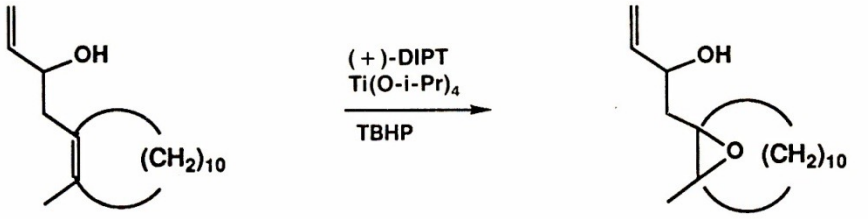

Epoxy alcohols are replaced by more allylic alcohol and TBHP to regenerate the "loaded" (active) complex and complete the catalytic cycle.

# CATALYTIC OXIDATION

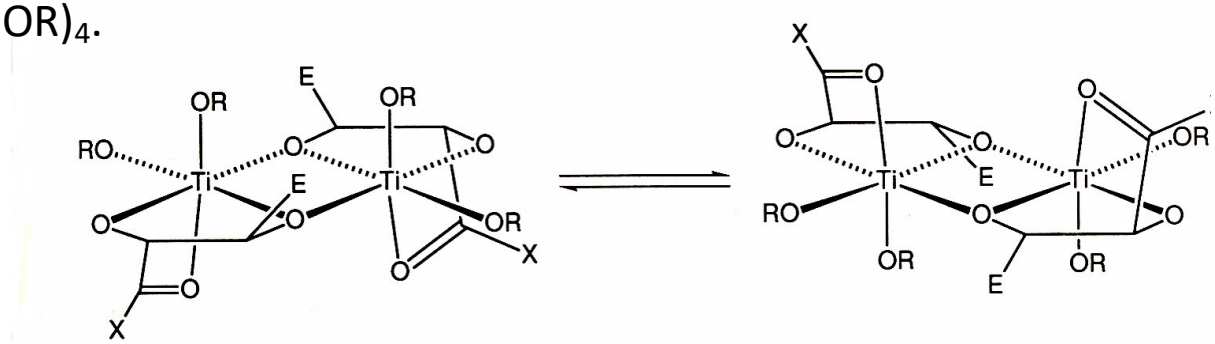
The olefin works as a nucleophile toward the activated peroxide oxygen in the epoxidation:
unsubstituted cinnamyl alcohol ; the relative rate =1.0
Electron withdrawing *p*-nitro group; the relative rate = 0.4
Electron donating p-MeO group; the relative rate 4.4




If two double bonds are available, the epoxidation takes place rather on a propenyl than a vinyl group. This is consistent with the nucleophilic role of olefin.



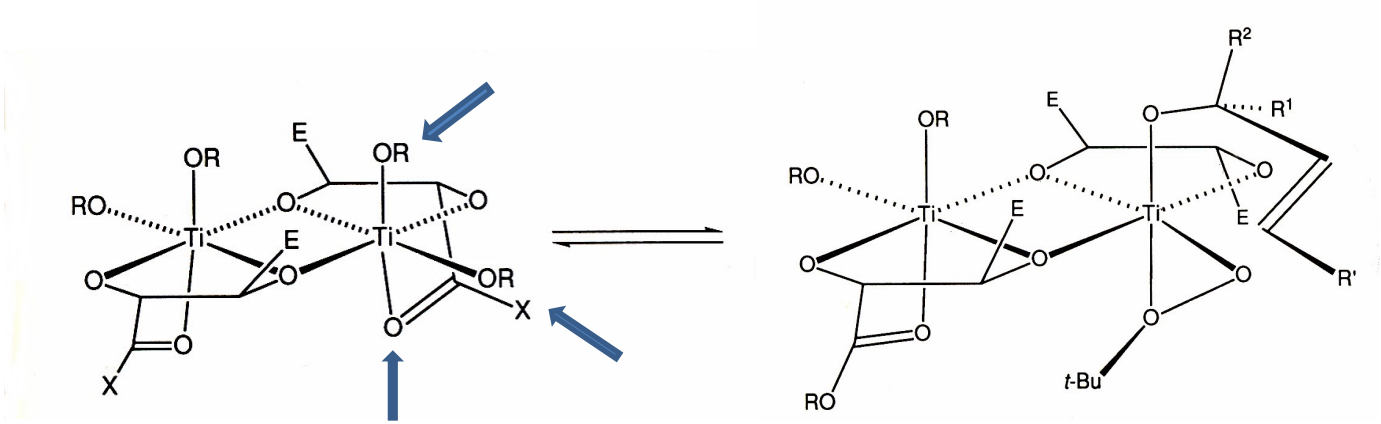

Rapid exchange reactions make the characterization of the catalyst structure extremely difficult. The major molecular species in solution is dimeric composite $Ti_2(tartrate)_2(OR)_4$.

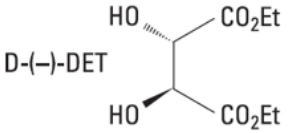



This structure has $C_2$ axis of symmetry (with two titanium atoms in identical stereochemical environments). Fluxional equilibrium proposed is shown in the figure.

# CATALYTIC OXIDATION

In active form the orientation of the hydroperoxide and substrate is a crucial issue. Three coordination sites, two axial and one equatorial become available by exchange of two isopropoxides and dissociation of the coordinated ester carbonyl group.



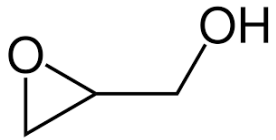




The reactions cause only minimal disturbance to the rest of the molecule.

Coordination of the hydroperoxide is considered to bidentate. It must occupy the equatorial and one of the available axial coordination sites, with allylic in the remaining axial site.

To achieve the oxygen transfer, the distal oxygen is placed to equatorial site. The axial site is at lower face of the complex is chosen for the peroxide because of the large steric demand of the t-Bu group in comparison to allylic alcohol.

# CATALYTIC OXIDATION




The L-(+)-tartrate ligand (L-(+)-DET), on the other hand, allows the bottom face of the olefin to be epoxidised. When achiral allylic alcohols are employed, the Sharpless reaction exhibits exceptional enantiofacial selectivity (ca. 100:1) and provides convenient access to synthetically versatile epoxy alcohols.

The emergence of the powerful Sharpless asymmetric epoxidation in the 1980s has stimulated major advances in both academic and industrial organic synthesis. Through the action of an enantiomerically pure titanium-tartrate complex, a myriad of achiral and chiral allylic alcohols can be epoxidised with exceptional stereoselectivity. Interest in the Sharpless epoxidation as a tool for industrial organic synthesis increased substantially after Sharpless *et al.* had discovered that the asymmetric epoxidation process can be conducted with catalytic amounts of the enantiomerically pure titanium-tartrate complex simply by adding molecular sieves to the epoxidation reaction mixture.

Using this practical and reproducible catalytic variant, an industrial process for ton-scale productions of (*S)- and (R)-glycidol and (S)- and (R)-methylglycidol has been* developed. These low molecular weight epoxy alcohols are versatile building blocks for the synthesis of a number of chiral molecules. As an example glycidol is used in the pharmaceutical industry to produce β-blockers, used as heart medicines.
Another successful industrial application of the Sharpless epoxidation, is the synthesis of (7*R,8S)-disparlure,* the pheromone of the gypsy moth.

# CATALYTIC OXIDATION

The *cis* dihydroxylation of olefins first reported early last century is another most useful oxidation reaction. It converts an olefin to a vicinal diol present in many natural products and unnatural molecules. The original dihydroxylation reaction used stoichiometric amounts of osmium tetroxide ($OsO_4$), which is expensive, volatile and toxic, with the result that even small-scale reactions were inconvenient.

**Asymmetric Dihydroxylation via Ligand-Accelerated Catalysis**[†]

Eric N. Jacobsen, István Markó, William S. Mungall, Georg Schröder, and K. Barry Sharpless*

*Department of Chemistry*
*Massachusetts Institute of Technology*
*Cambridge, Massachusetts 02139*

*Received December 29, 1987*

The addition of osmium tetroxide to olefins may be both the most selective and reliable of known organic transformations.[1] The added utility of stereospecifically imbedding two hydroxyl groups in a hydrocarbon framework (cis vicinal dihydroxylation) accounts for osmium tetroxide's popularity in organic synthesis, but osmium's expense and toxicity call for a catalytic solution.[1c,2]

# CATALYTIC OXIDATION

The *cis* dihydroxylation of olefins first reported early last century is another most useful oxidation reaction. It converts an olefin to a vicinal diol present in many natural products and unnatural molecules. The original dihydroxylation reaction used stoichiometric amounts of osmium tetroxide ($OsO_4$), which is expensive, volatile and toxic, with the result that even small-scale reactions were inconvenient.

However, the dihydroxylation shows specificity for double bonds and has no particular substrate requirements, which were advantages. Over the years, the original dihydroxylation procedure has been modified to operate catalytically, more rapidly, and in better yield.

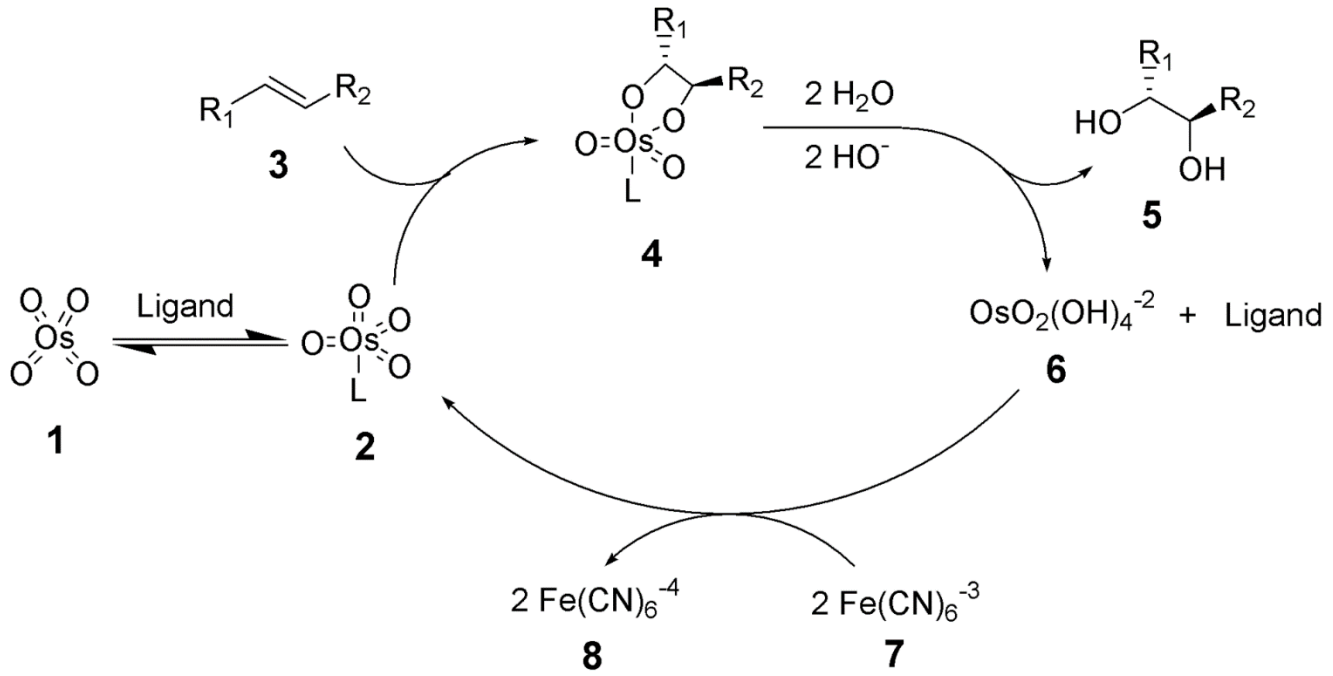
Methods for the conversion of olefins to diols with only catalytic amounts of osmium tetroxide and a stoichiometric co-oxidant have been known almost as long as the reaction itself. Criegee first observed that the addition of amines, such as pyridine, to the dihydroxylation reaction increases its rate. Presumably this is due to the formation of an electron-rich coordination complex with the osmium atom. A useful stoichiometric co-oxidant is *N-methylmorpholine N-oxide (NMO).*

# CATALYTIC OXIDATION

The first attempt at non-enzymatic asymmetric dihydroxylation utilized a chiral, enantiomerically pure pyridine to determine if this induced asymmetry in the diol.
A modest ee was obtained. However, the cinchona alkaloid ligands proved to have more balanced properties and gave more pronounced ”ligand accelerated catalysis”.

This concept was introduced by Sharpless in the same paper where he reported the first catalytic asymmetric dihydroxylation. The seemingly trivial marriage of the Sharpless cinchona alkaloid stoichiometric dihydroxylation process (now optimized with the ligand) with the practical qualities of NMO resulted in good yields and moderate to good enatiomeric excesses.

# CATALYTIC OXIDATION



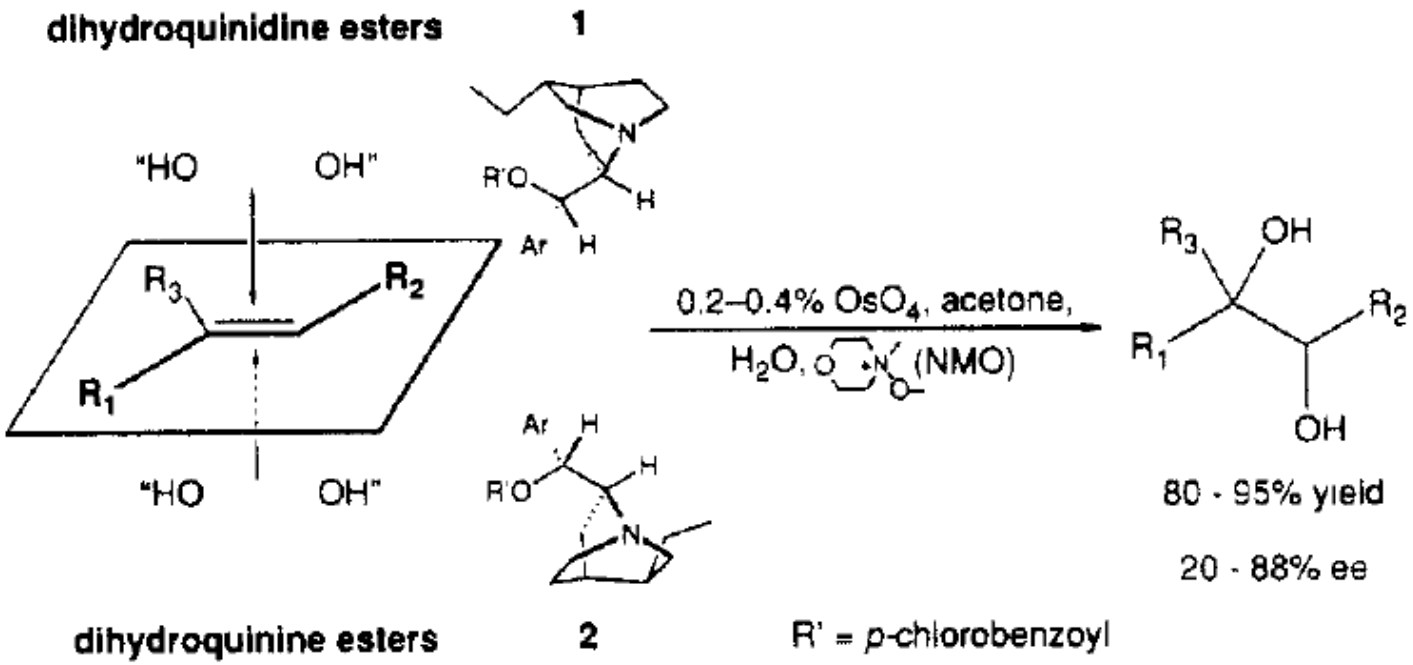

A [3+2]-cycloaddition with the alkene (**3**) gives the cyclic intermediate **4**. Basic hydrolysis liberates the diol (**5**) and the reduced osmate (**6**). Finally, the stoichiometric oxidant regenerates the osmium tetroxide – ligand complex (**2**).

# CATALYTIC OXIDATION

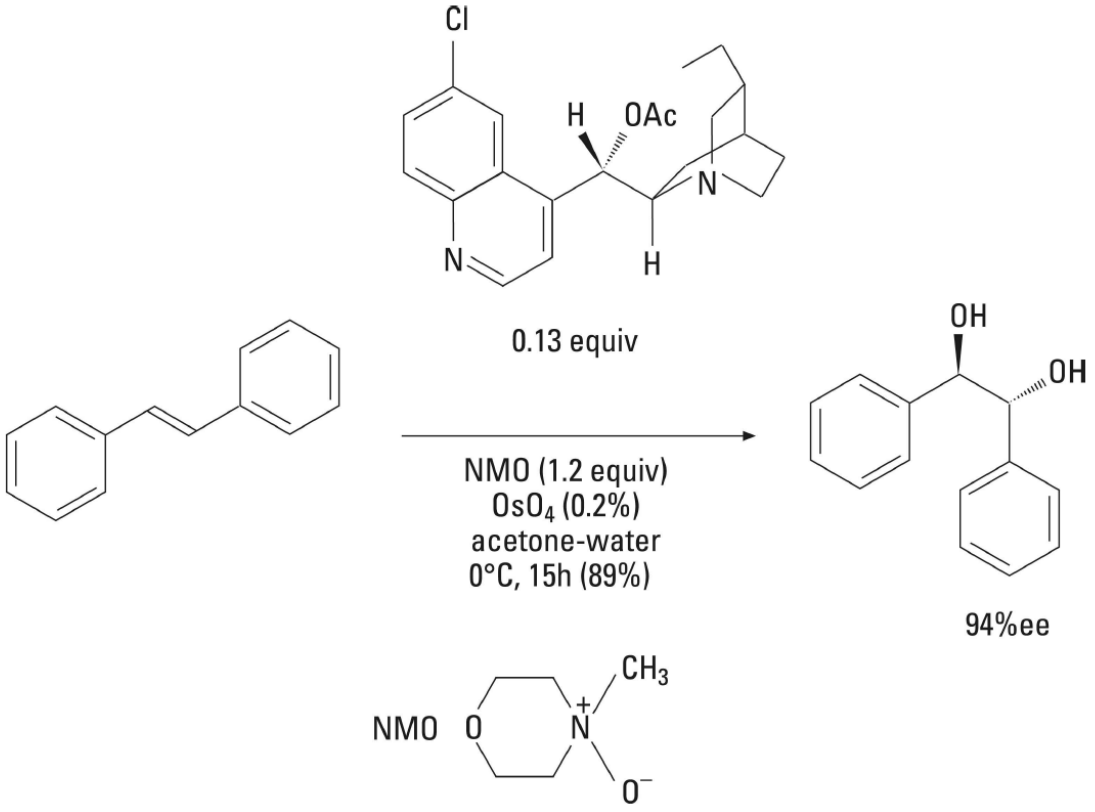
The first attempt at non-enzymatic asymmetric dihydroxylation utilized a chiral, enantiomerically pure pyridine to determine if this induced asymmetry in the diol.

A modest ee was obtained. However, the cinchona alkaloid ligands proved to have more balanced properties and gave more pronounced ”ligand accelerated catalysis”.

**Scheme I**



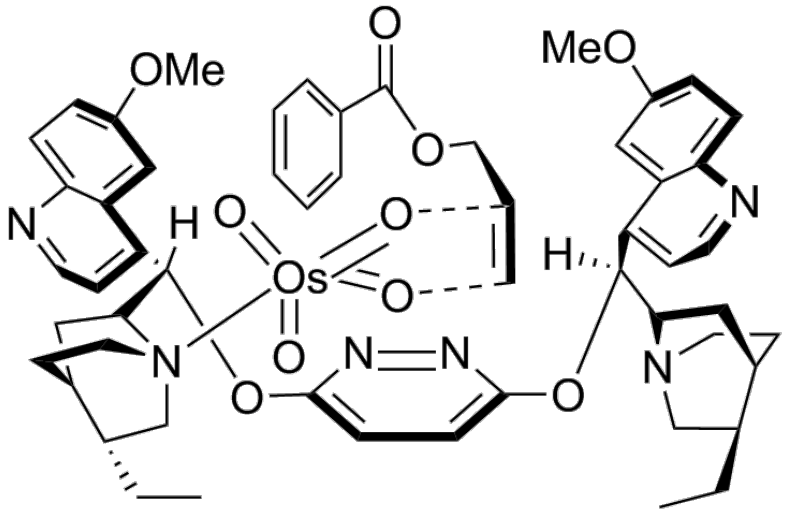
# CATALYTIC OXIDATION



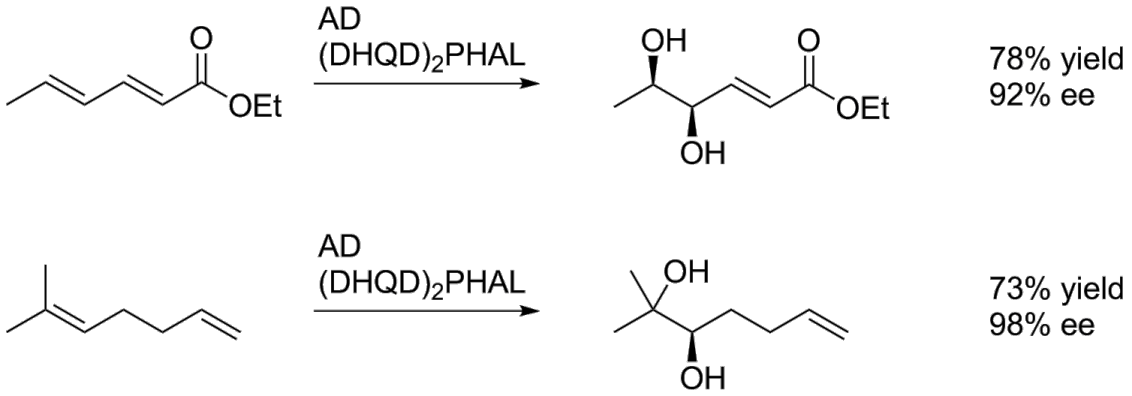

Since Sharpless's discovery of the chirally catalyzed dihydroxylations, there has been considerable progress with respect to the understanding of the reaction mechanism.

Better ligands have been designed and procedures have been improved making Sharpless's catalytic asymmetric dihydroxylation an extremely useful reaction.

# CATALYTIC OXIDATION




In general, Sharpless asymmetric dihydroxylation favors oxidation of the more electron-rich alkene

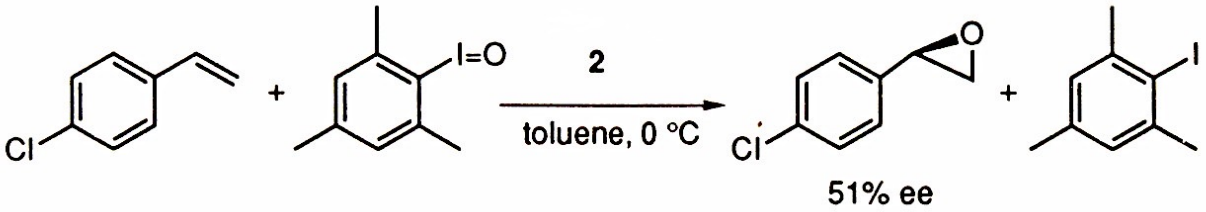


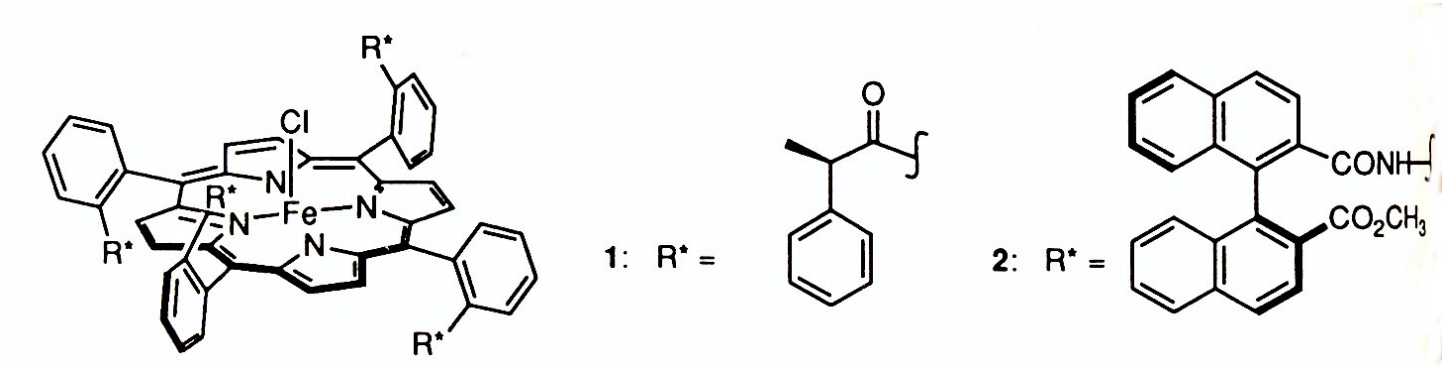
# CATALYTIC OXIDATION

EPOXIDATION OF UNFUCTIONALIZED OLEFINS

Enantioselective epoxidation of unsubstituted alkenes is an appealing strategy for the synthesis of optically active compounds.

Iodosylmesitylene as a stoichiometric oxidant

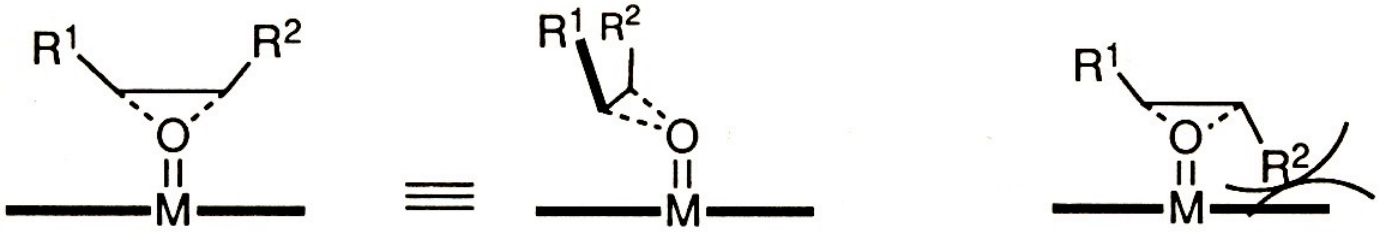



After Sharpless results, the methods for epoxidation of unsubstituted alkenes were looked for. Fe(III) porphyrin complexes are model for cytochrome P450 and received a lot attention for the reaction.

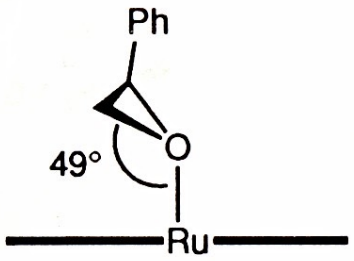
# CATALYTIC OXIDATION

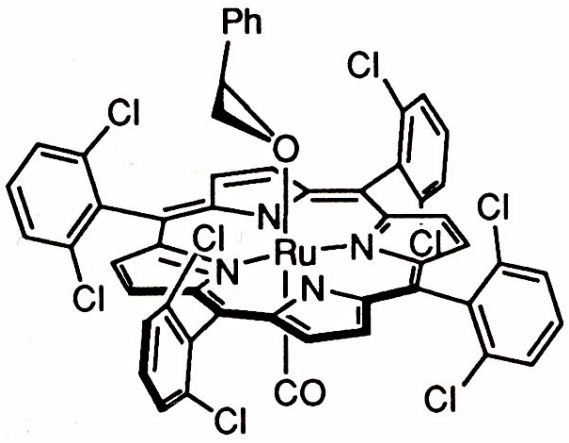
*Cis* olefins are more reactive than *trans* olefins. This suggests a side-on approach of the olefin towards iron-oxo intermediate.



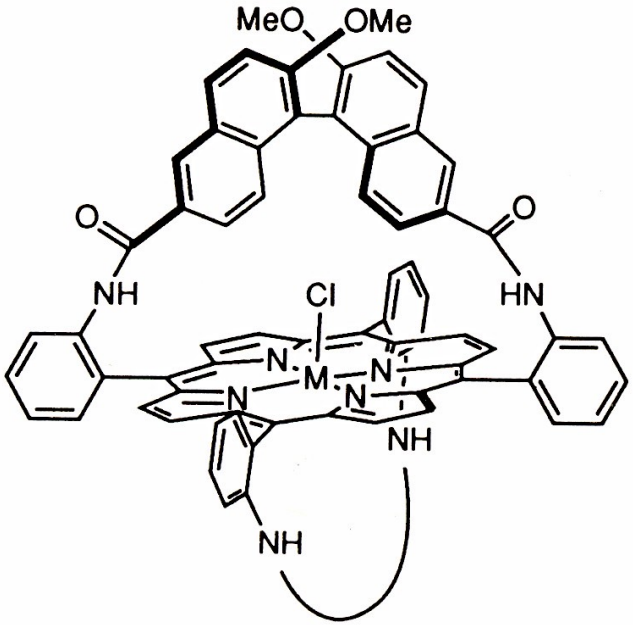

The porphyrine ligand is symbolized by the heavy line.

The side-on approach is supported by the X-ray structure below.



# CATALYTIC OXIDATION

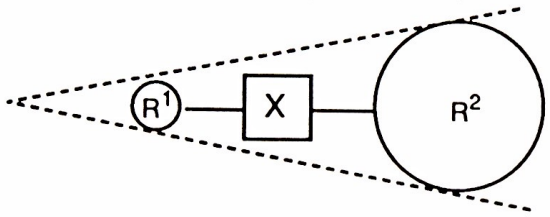


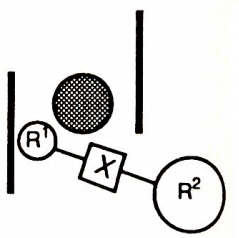

Vaulted binaphthyl derivatives were developed:
79 ee for p-Cl- styrene
72% ee for β-methyl styrene (-15 ˚C)

**4**: M = Fe

**5**: M = Mn

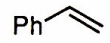
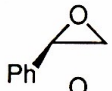
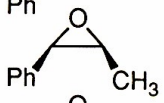
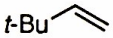
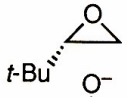
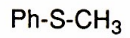
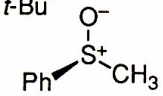
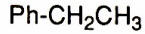
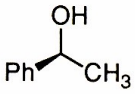
The wedgelike pocket (sterics) was rationalized as a reason for ee.



# CATALYTIC OXIDATION

**Table 1** Asymmetric Oxidation Reactions Catalyzed by **3**

| Substrate | Major Product | % ee | Yield (%)[a] |
|---|---|---|---|
|  |  | 30 | 23 |
|  |  | 58/20°C<br>72/-15°C | 64<br>9 |
|  |  | 40 | 14 |
|  |  | 24 | 84 |
|  |  | 40 | 40 |

[a] Yields based on iodosylbenzene.

The lack of selectivity with *tert*-butyl ethylene suggests that epoxidation by oxo-transfer reaction might proceed with an different mechanism.

# CATALYTIC OXIDATION

An impressive series of other chiral porphyrin derivatives bearing conformationally restricted bridged ligands.

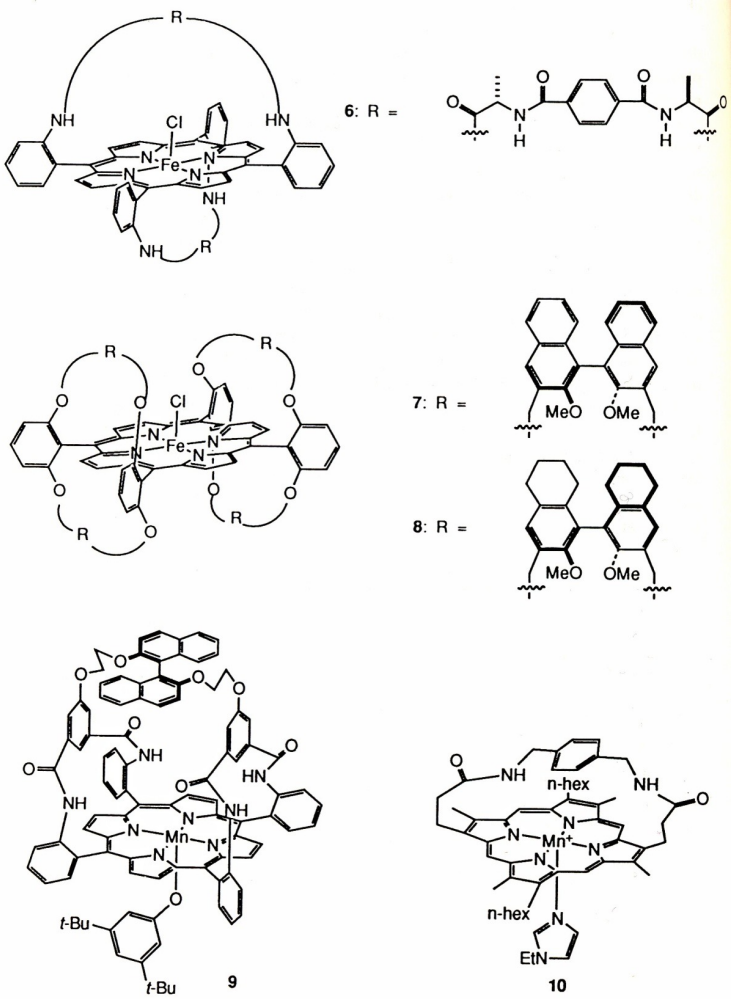



**Table 2** Asymmetric Epoxidations with Catalysts 6–10

| Substrate | Catalyst | % ee | Turnover # |
|---|---|---|---|
| *p*-$ClC_6H_4$ | **6** | 50 | a |
| Ph | **7** | 22 | 50 |
| *o*-$MeOC_6H_4$ | **7** | 0 | 32 |
| *o*-$NO_2C_6H_4$ | **7** | 80 | 26 |
| | **8** | 89 | 46 |
| $C_6F_5$ | **7** | 74 | 36 |
| Ph | **9** | 13 | a |
| Ph | **10** | 50[b] | a |

[a] Not reported. [b] Reaction carried out in the presence of 10 mol% added 1-ethylimidazole.

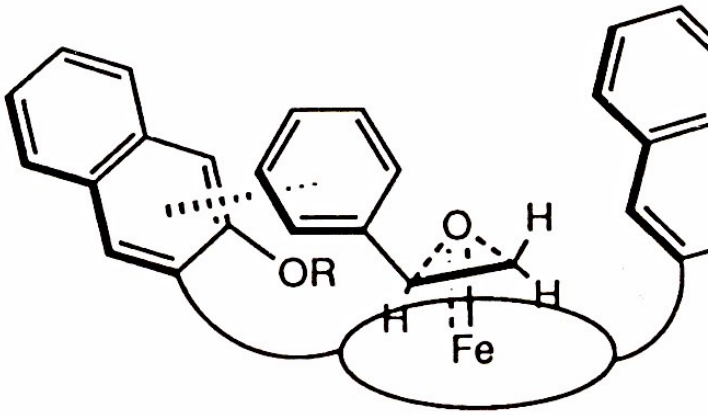
# CATALYTIC OXIDATION

The catalysts tend to be unstable in the oxidation conditions

ees were low

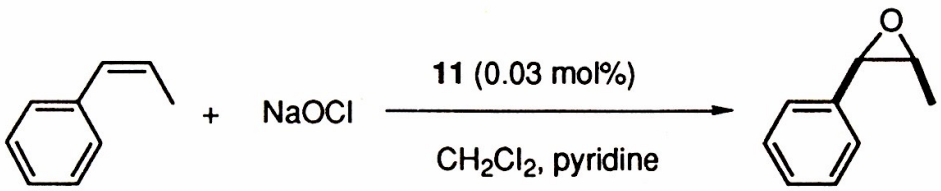
Conversions were low

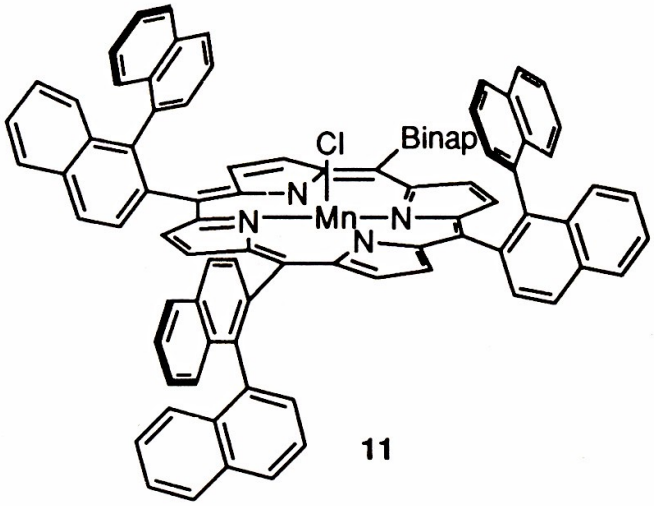
(extremely) low yields in complex synthesis



# CATALYTIC OXIDATION

To avoid sensitivity in oxidation a “chiral wall” catalyst was designed.



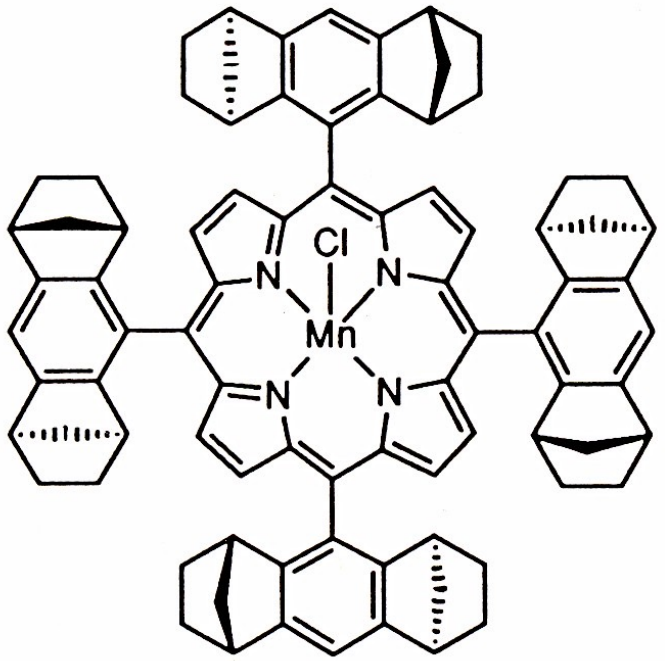

11

Unfortunately, ees were below 40%
Even for cis-β-methyl styrene.

TON= 3000

# CATALYTIC OXIDATION

Oxidation is one of the major chemical transformations.



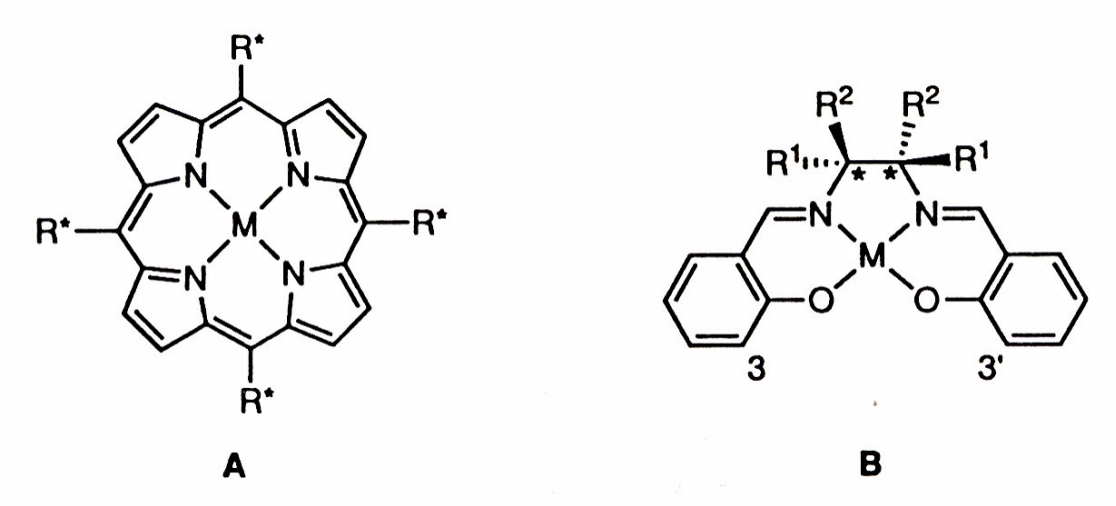

12

An example of the D4 symmetric systems.

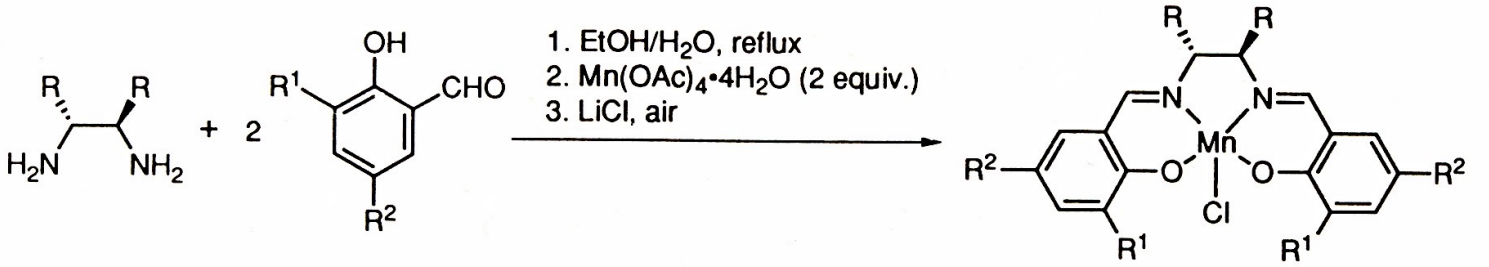
It is robust (TON = 2000) and ees are up to 76% for β-methyl styrene.

# CATALYTIC OXIDATION

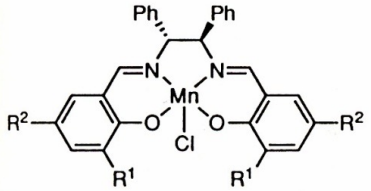
Chiral salen complexes bear tetravalent and thus potentially stereogenic carbon atoms in the vicinity of the metal centre.



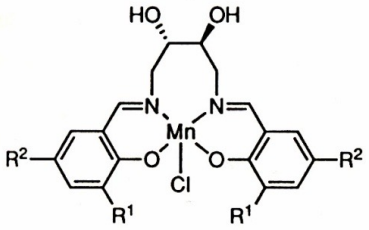

They are easy to synthesize.



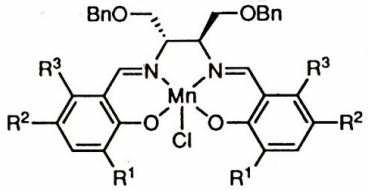
# CATALYTIC OXIDATION



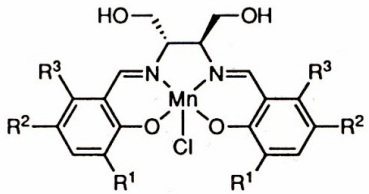

**13** $R^1$ = H, $R^2$ = H
**14** $R^1$ = *t*-Bu, $R^2$ = H
**15** $R^1$ = *t*-Bu, $R^2$ = Cl
**16** $R^1$ = *t*-Bu, $R^2$ = OMe
**17** $R^1$ = 1-methylcyclohexyl, $R^2$ = Me
**18** $R^1$ = $C(Ph)_2Me$, $R^2$ = H
**19** $R^1$ = $C(Et)_2Me$, $R^2$ = H
**20** $R^1$ = $Me_3Si$, $R^2$ = H
**21** $R^1$ = *t*-Bu, $R^2$ = Me
**22** $R^1$ = 9-methyl-9-fluorenyl, $R^2$ =Me
**23** $R^1$ = 1-adamantyl, $R^2$ =Me
**24** $R^1$ = $R^2$ = Br
**25** $R^1$ = *t*-Bu, $R^2$ = $NO_2$



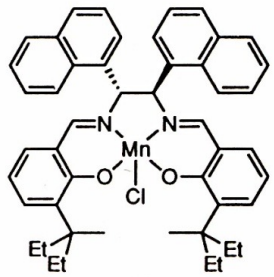

**26** $R^1$ = $R^2$ = H
**27** $R^1$ = H, $R^2$ = $NO_2$
**28** $R^1$ = *t*-Bu. $R^2$ = Me




**29** $R^1$ = $R^2$ = $R^3$ = H
**30** $R^1$ = $R^3$ = H, $R^2$ = *t*-Bu
**31** $R^1$ = $R^3$ = H, $R^2$ = $NO_2$
**32** $R^1$ = $R^2$ = Br, $R^3$ = H
**33** $R^1$ = H, $R^2$, $R^3$ = -CH=CH-CH=CH-
**34** $R^1$ = *t*-Bu, $R^2$ =Me, $R^3$ = H

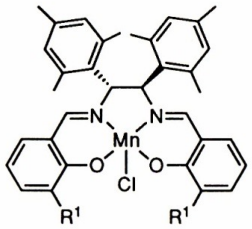



**35** $R^1$ = $R^2$ = $R^3$ = H
**36** $R^1$ = $R^3$ = H, $R^2$ = *t*-Bu
**37** $R^1$ = $R^3$ = H, $R^2$ = $NO_2$
**38** $R^1$ = $R^2$ = Br, $R^3$ = H
**39** $R^1$ = H, $R^2$, $R^3$ = -CH=CH-CH=CH-
**40** $R^1$ = *t*-Bu, $R^2$ = Me, $R^3$ = H

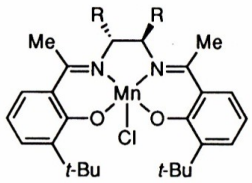



**41**

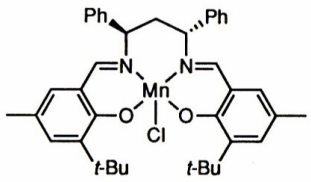
# CATALYTIC OXIDATION



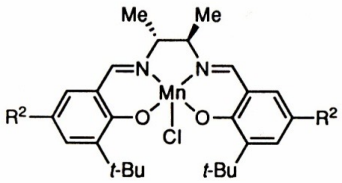
**42** $R^1$ = *t*-Bu
**43** $R^1$ = $C(Ph)_2Me$



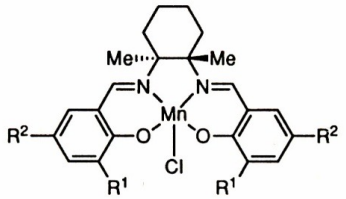
**44** R = H
**45** R = Ph (unstable)



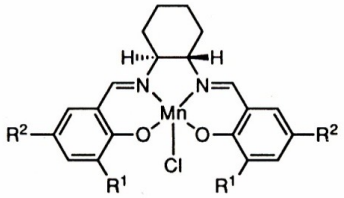
**46**



**47** $R^2$ = Me
**48** $R^2$ = *t*-Bu

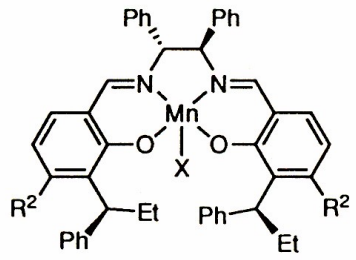


**49** $R^1$ = $R^2$ = H
**50** $R^1$ = $C(Ph)_2Me$, $R^2$ = H
**51** $R^1$ = $R^2$ = *t*-Bu
**52** $R^1$ = *t*-Bu, $R^2$ = Me
**53** $R^1$ = 1-methylcyclohexyl, $R^2$ = Me

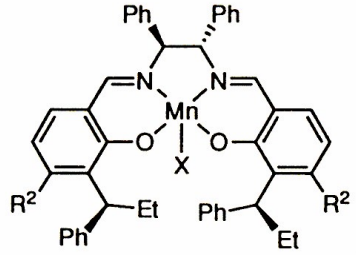


**54** $R^1$ = H, $R^2$ = H
**55** $R^1$ = *t*-Bu, $R^2$ = Me
**56** $R^1$ = *t*-Bu, $R^2$ = Cl
**57** $R^1$ = *t*-Bu, $R^2$ = H
**58** $R^1$ = *t*-Bu, $R^2$ = OMe
**59** $R^1$ = *t*-Bu, $R^2$ = $NO_2$
**60** $R^1$ = 1-methylcyclohexyl, $R^2$ = Me
**61** $R^1$ = 9-methyl-9-fluorenyl, $R^2$ =Me
**62** $R^1$ = 1-adamantyl, $R^2$ =Me
**63** $R^1$ = $R^2$ = *t*-Am
**64** $R^1$ = $R^2$ =Br
**65** $R^1$ = $R^2$ = *t*-Bu

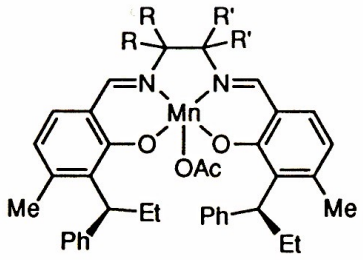
# CATALYTIC OXIDATION



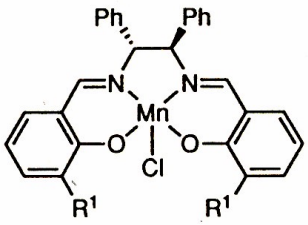

**66** $R^2$ = H, X = OAc
**67** $R^2$ = Me, X = $PF_6$



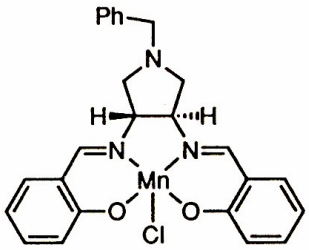

**68** $R^2$ = H, X = OAc
**69** $R^2$ = Me, X = $PF_6$




**70** $R^1$ = $R^2$ = H
**71** $R^1$ = $R^2$ = Me
**72** $R^1$ = H, $R^2$ = Me




**73** $R^1$ =TMS
**74** $R^1$ =TBDMS

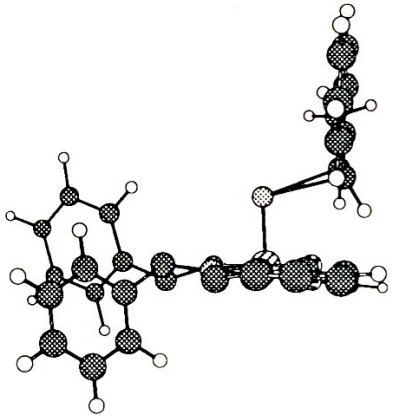



**75**

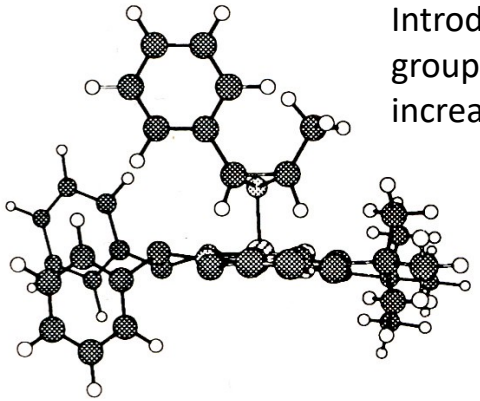
# CATALYTIC OXIDATION

Diphenylethylenediamine derivative 13 was one of the first chiral epoxidation catalysts based on Mn salen. Trans-stilbene afforded promising (33% ee) results.

(salen)Mn(V) oxo-intermediate



A

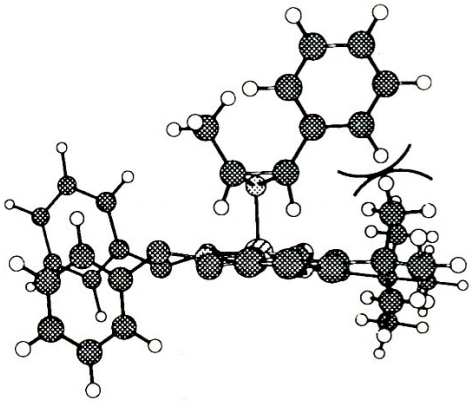


B (favored)

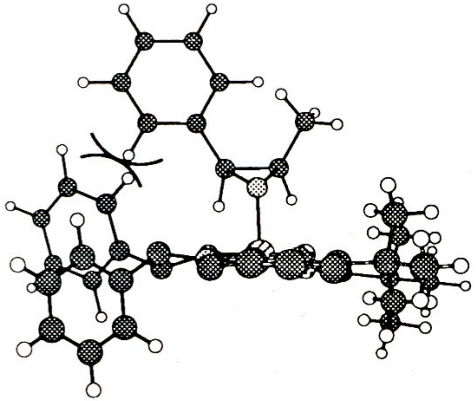
Introduction of tert-butyl groups to 3,3’ positions increased the selectivity.

To improve selectivity, bulky substituents like in 41-43 were introduced. No success, even the activity went down.

How about unhindered catalysts (49-53)? No success.



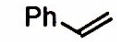
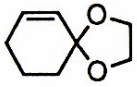
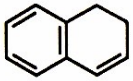
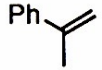
C (disfavored)



D (disfavored)

# CATALYTIC OXIDATION

**Table 3** Asymmetric Epoxidation Reactions Catalyzed by **14**

| Entry | Olefin | Method[a] | Isolated Yield(%) | % ee | Configuration[b] |
|---|---|---|---|---|---|
| 1 |  | A | 75 | 57 | *R*-(+) |
| 2 |  | B | 65 | 94 | (–)[c] |
| 3 |  | A | 73 | 81 | 1*R*,2*S*-(–) |
| 4 |  | B | 72 | 78 | 1*R*,2*S*-(+) |
| 5 |  | A | 36 | 30 | *R*-(+) |

[a]Method A: NaOCl (pH 11.3), $CH_2Cl_2$ solvent, 0 °C. Method B: Same as method A but with 0.2 equiv 4-phenylpyridine *N*-oxide employed as additive. [b]The sign corresponds to that of $[\alpha]_D$. [c]Absolute configuration not ascertained.

# CATALYTIC OXIDATION

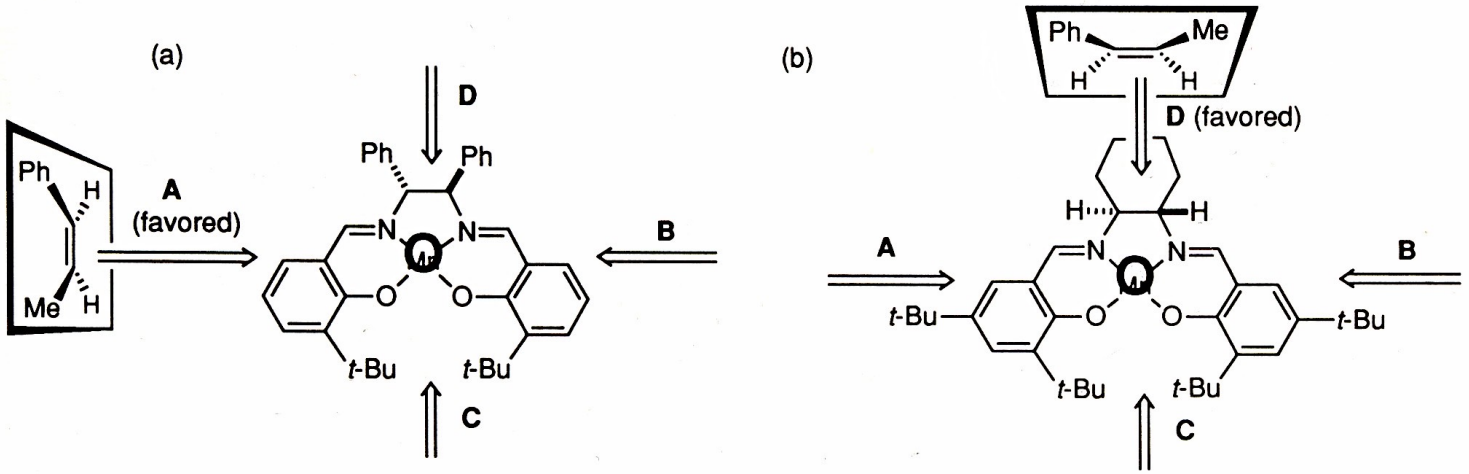
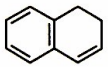
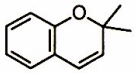
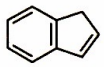
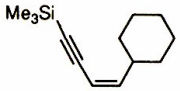
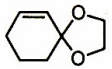
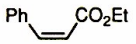



**Figure 7** Side-on approaches of *cis*-β-methylstyrene to (a) **14** and (b) **65**. In both cases the oxo ligand is oriented out of the plane of the page.

# CATALYTIC OXIDATION

**65** was designed to prevent all side on approaches except D. In deed this is the most selective catalyst so far.

**Table 4** Asymmetric Epoxidation of Representative Olefins by Catalyst **65**

| Entry | Olefin | Method[a] | Isolated Yield (%) | % ee of major epoxide | Equiv. **65** Required for Complete Reaction |
|---|---|---|---|---|---|
| 1 |  | A | 84[b] | 92 | 0.04 |
| 2 |  | B | 67 | 86 | 0.04 |
| 3 |  | A | 87 | 98 | 0.02 |
| 4 |  | A | 80 | 88 | 0.01 |
| 5 |  | A | 65[c] | 98 | 0.04 |
| 6 |  | B | 63 | 94 | 0.15 |
| 7 |  | B | 67[e] | 97 | 0.08 |

[a]See Table 3. [b]Isolated yield of epoxide mixture (cis:trans = 11.5:1). [c]Isolated yield of epoxide mixture (cis:trans
[d]Isolated yield of epoxide mixture (cis:trans = 5:1).

# CATALYTIC OXIDATION

Because the ees are so high, epoxidation seems to go via a single pathway.

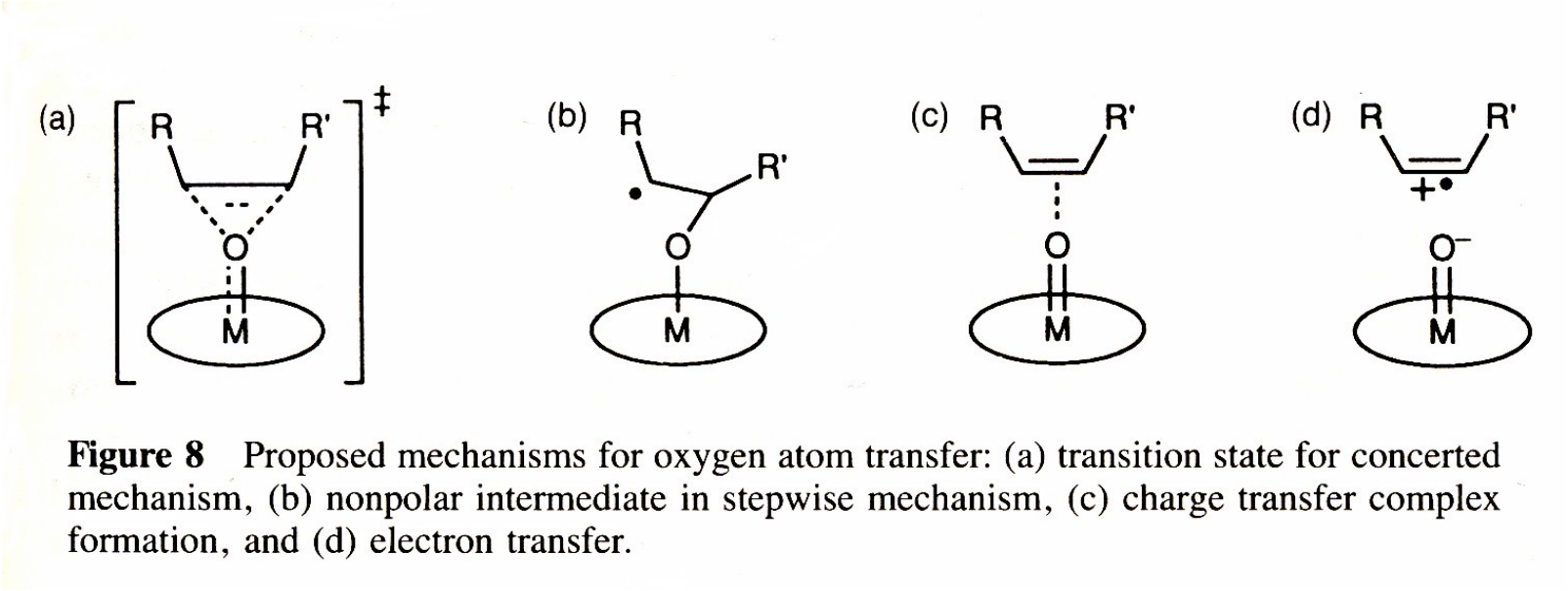
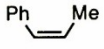
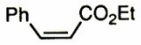
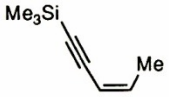
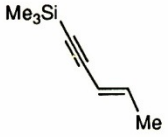
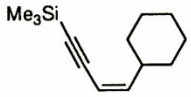
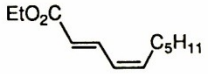



**Figure 8** Proposed mechanisms for oxygen atom transfer: (a) transition state for concerted mechanism, (b) nonpolar intermediate in stepwise mechanism, (c) charge transfer complex formation, and (d) electron transfer.

Because of high ee, last two mechanisms seem unlike. High ee needs a highly ordered stereo-determining transition state (with covalent bonding?)

# CATALYTIC OXIDATION

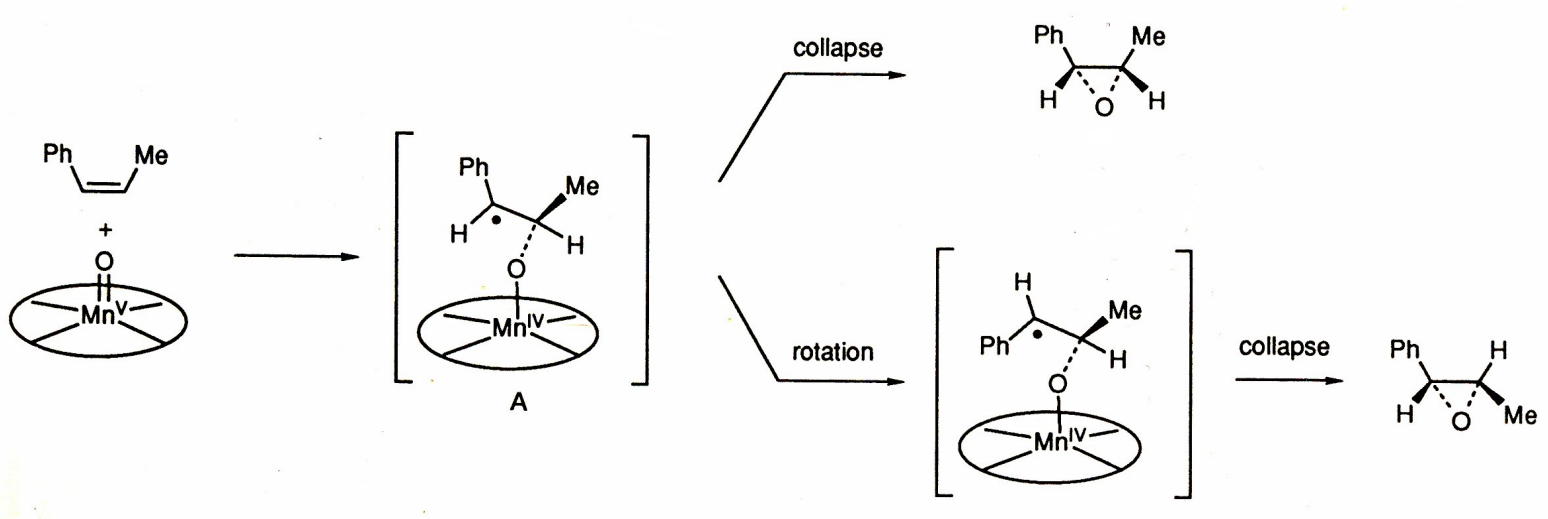
**Table 5** Nonstereospecific Epoxidation Reactions Catalyzed by **65**

| Entry | Olefin | cis epoxide/ trans epoxide | cis epoxide % ee | trans epoxide % ee |
|---|---|---|---|---|
| 1 |  | >99:1 | 34 | -- |
| 2 |  | 92:8 | 92 | 83 |
| 3 |  | 78:22 | 97 | 78 |
| 4 |  | 29:71 | 48 | 90 |
| 5 |  | 33:67 | 28 | 46 |
| 6 |  | 16:84 | 64 | 98 |
| 7 |  | 10:90 | 60 | 87 |

Because alkyl substituted cis olefins are reacted stereospecifically, but cis aryl substituted olefins give varying amounts of trans epoxides, the results discriminate the (a) mechanism.

# CATALYTIC OXIDATION

Formation of trans epoxides from cis olefins.



# CATALYTIC OXIDATION

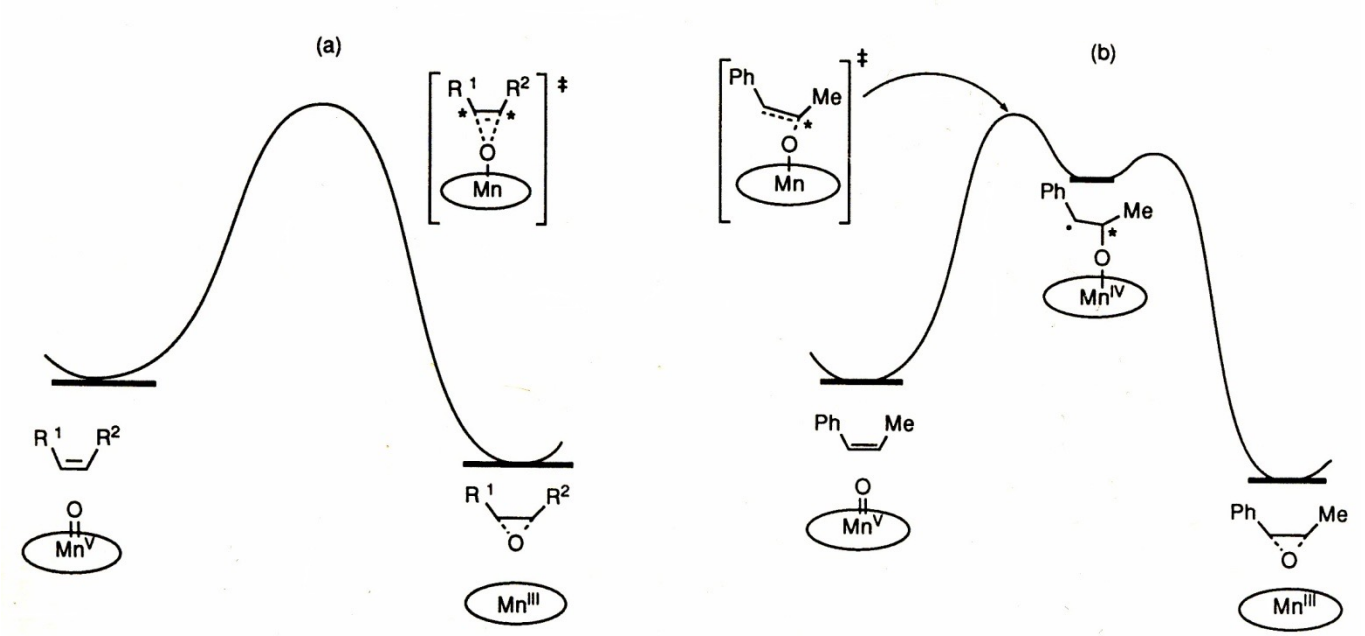
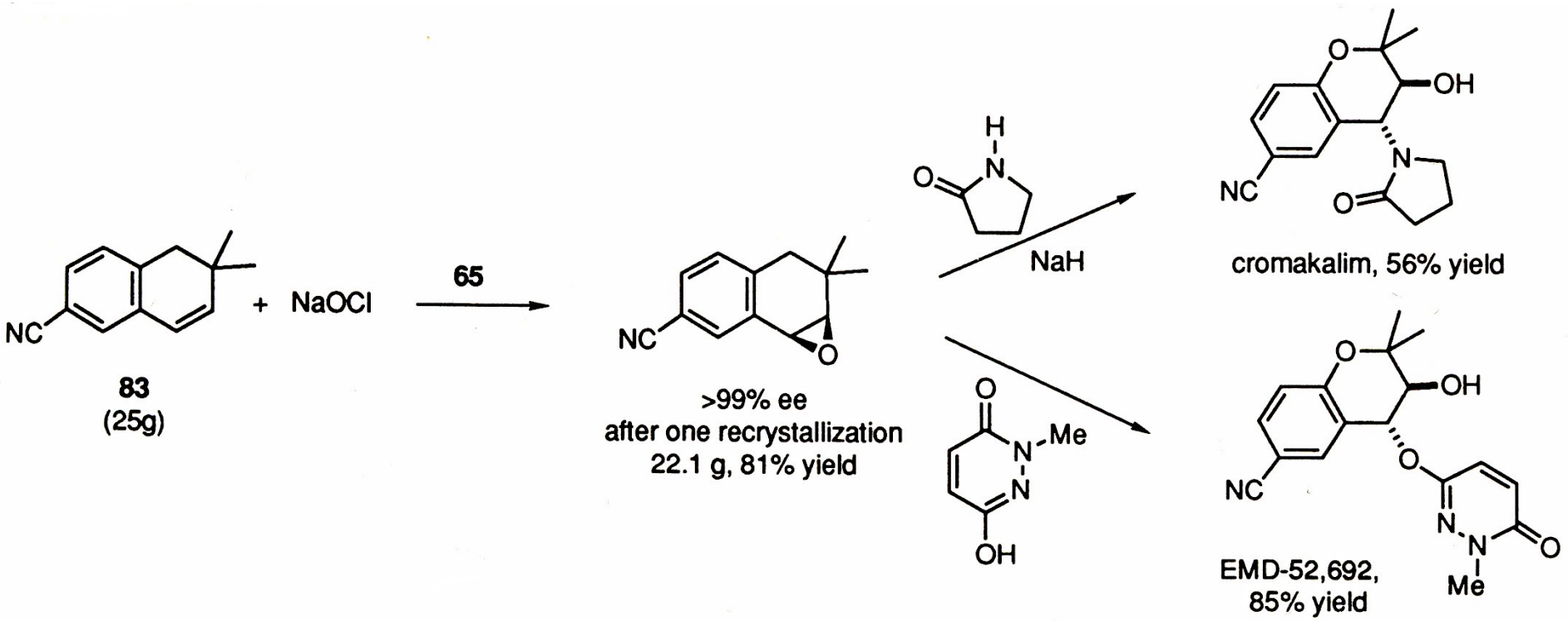



**Figure 9** Energy diagrams for oxo transfer to alkenes: (a) concerted mechanism and (b) stepwise nonpolar mechanism.

# CATALYTIC OXIDATION

Oxidation is one of the major chemical transformations.



# CATALYTIC OXIDATION