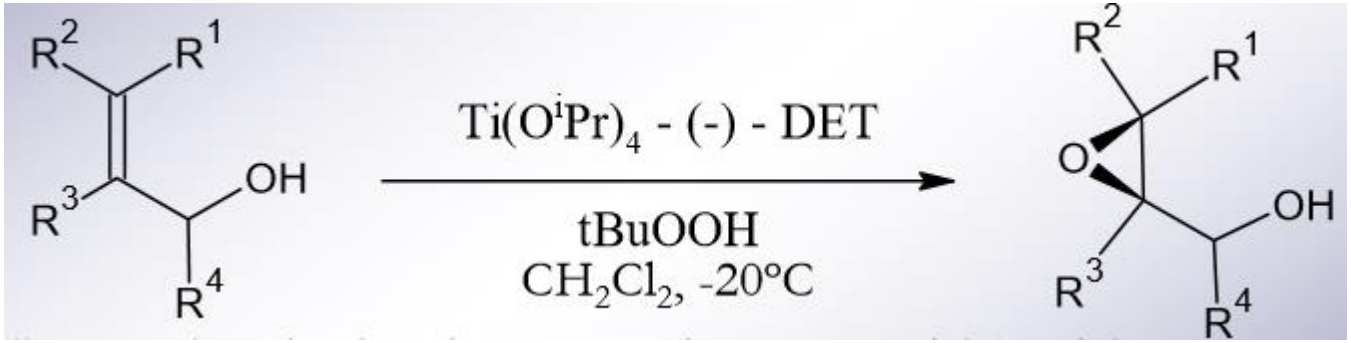
EPOSSIDAZIONE ASIMMETRICA (AE) DEGLI ALCHENI

Epossidazione Asimmetrica (AE) di Sharpless



1. Converte **alcol allilici** primari e secondari in 2,3-epossialcoli

2. La reazione è altamente enantioselettiva

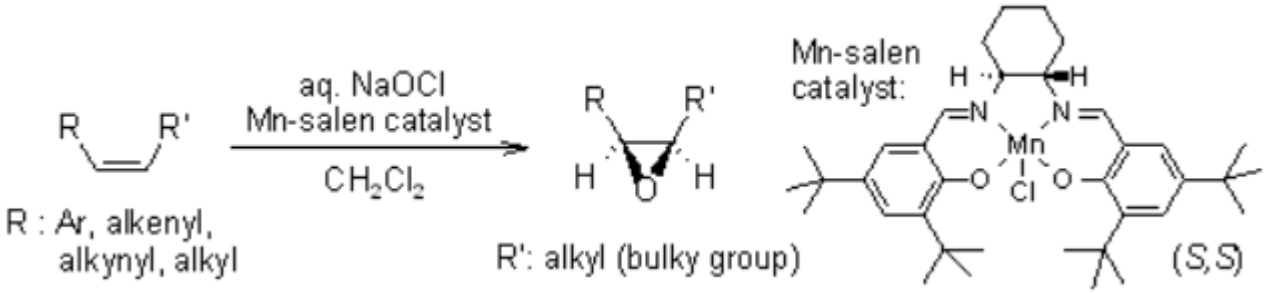
3. L'enantiomero prodotto dipende dalla stereochimica del catalizzatore usato, cioè (+) oppure (–) tartrato

4. Catalizzatore: titanio tetra-isopropossido con dietiltartrato

5. tBuOOH ossidante

6. DCM (CH_2Cl_2) e -80 °C

Epossidazione Asimmetrica (AE) di Jacobsen-Katsuki

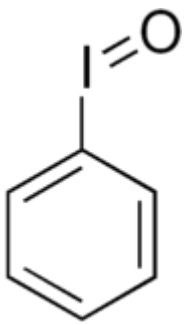


1. Complementare alla AE di Sharpless
2. Riportata indipendentemente da Jacobsen e Katsuki negli anni 90
3. Catalizzatori simili, più semplici quelli di Jacobsen
4. Catalizzatore: complesso chirale di Mn(III)-salen
5. Ossidante: NaOCl
6. Condizioni: 0°C, DCM

Table 2. Typical oxidants used in transition-metal catalyzed reactions

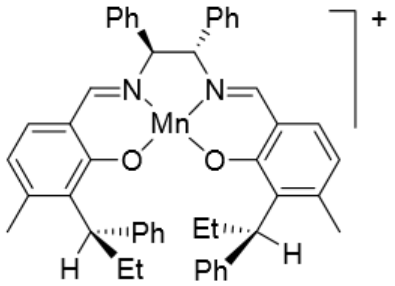
Oxidant	*Active oxygen (wt.%)*	*By-product*
O_2/reductant	50.0	H_2O
H_2O_2[a]	47.0	H_2O
NaOCl	21.6	NaCl
CH_3CO_3H	21.1	CH_3CO_2H
t-BuOOH	17.8	*t*-BuOH
$KHSO_5$	10.5	$KHSO_4$
MCPBA	9.3	*m*-Cl-$C_6H_4CO_2H$
$NaIO_4$	7.5	$NaIO_3$ (NaI)
PhIO	7.3	PhI

a) Based on 100% H_2O_2.

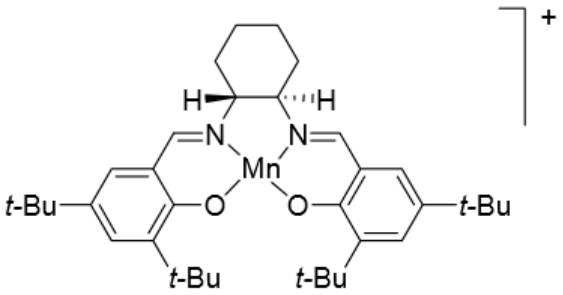


Iodosylbenzene

Iodosylbenzene and other iodosylarenes were the first oxidants reported to effect alkene epoxidation in the presence of achiral or chiral metalloporphyrins.[9,23,24] Although iodosylbenzene has certain disadvantages, such as costliness, low oxygen content, low solubility, and instability, which make it impractical in preparative use, it has been frequently used as terminal oxidant in mechanistic investigations.[21,22] Kochi



complesso di Mn(III) di Katsuki



complesso di Mn(III) di Jacobsen

salen = *N*,*N*-ethylenebis(salicyldeneaminato)

- Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. "Enantioselective Epoxidation of Unfunctionalized Olefins Catalyzed by (salen)Manganese Complexes," *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803.
- R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron Lett.* **1990**, *31*, 7345.

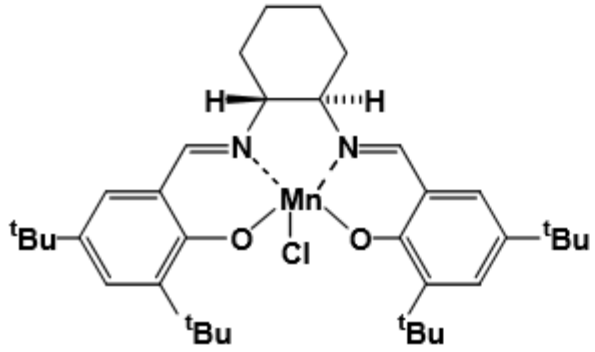
Reviews:

E. N. Jacobsen *Asymmetric Catalytic Epoxidation of Unfunctional;ized Olefins*; 1st ed; Ojima, I., Ed.; VCH: New York, 1993, p 159

T. Katsuki *J. Mol. Cat. A: Chem.* **1996**, *113*, 87.

Chiral Mn(salen) Catalysts: Overview

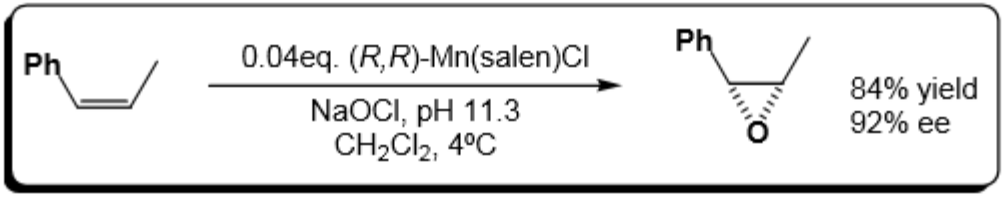
Review: Katsuki *Coord. Chem. Rev.* **1995**, *140*, 189.



Stoichiometric co-oxidants:
Usually aq. NaOCl, CH_2Cl_2
mCPBA / NMO (low temperature) or iodosylbenene ($PhIO/CH_3CN$)

Preparation of catalyst: *Organic Syntheses*, **1998**, *75*, 1.
Polymer supported catalyst:
e.g. Janda, *J. Am. Chem. Soc.*, **2000**, *122*, 6929.

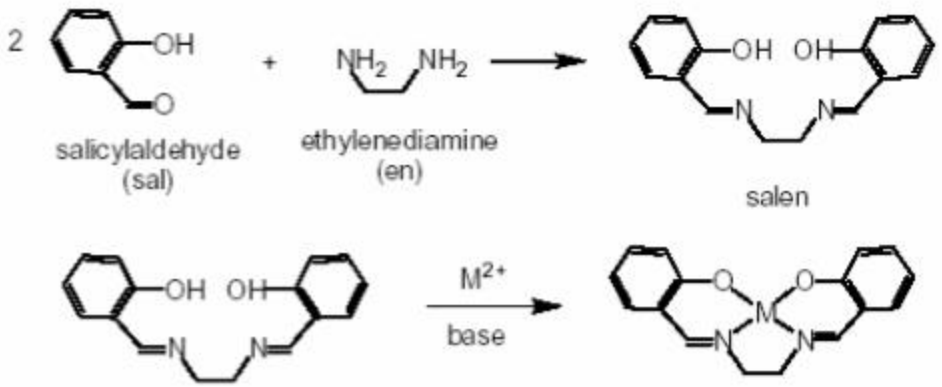
***Cis*-Disubstituted alkenes**: *J. Am. Chem. Soc.* **1991**, *113*, 7063.
Trisubstituted alkenes: *J. Org. Chem.* **1994**, *59*, 4378.
Tetrasubstituted alkenes: *Tetrahedron Lett.* **1995**, *36,* 5123.
Cinnamate esters: *Tetrahedron* **1994**, *50,* 4323.



TON 50

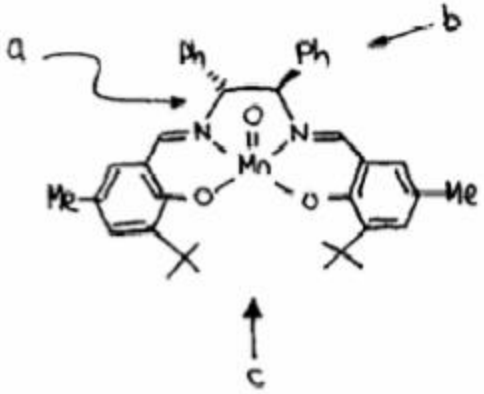
- Poor enantioselectivities for *trans*-disubstituted and terminal alkenes (but see Katsuki, *Synlett*, **2000**, 1557)
- Via radical intermediate, so stereospecificity with respect to alkene geometry sometimes eroded. Can use to make trans-epoxides from cis-alkenes: Jacobsen, *J. Am. Chem. Soc.* **1994**, *116,* 6937.
- Asymmetric epoxidation of *E*-alkenes using Cr(salens): Gilheany, *Org. Lett.* **2001**, *3*, 663, and refs. therein

- design of the ligand



Ligand design: the metal complex possesses key structural features which contribute to the enantioselectivity [J. Am. Chem. Soc. (1991) 113, 7063]

metalloporphyrin complex



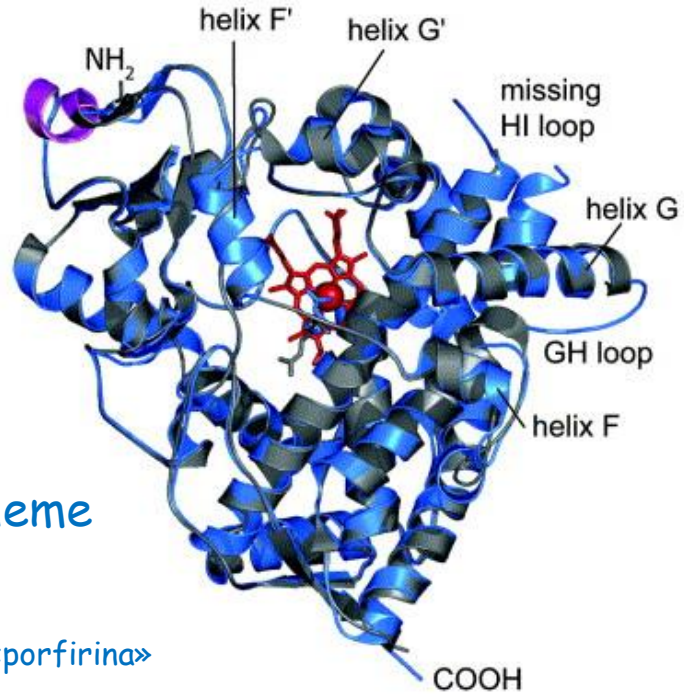
- the salen is essentially planar
- oxo ligand is in apical position of a square pyramid
- t-butyl groups prevent substrate from approaching the front face (path c)
- phenyl group points up slightly, preventing approach from path b

Cyt P450

Catalizza varie
Reazioni tipicamente
di ossidazione
di un substrato

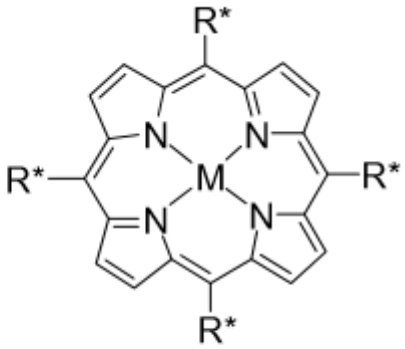
Contiene un gruppo heme
Fe-porfirina

NB: differenza tra «heme» e «porfirina»

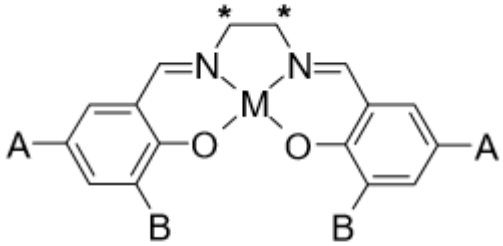


Il cyt P450 svolge un ruolo chiave nella **ossidazione di composti xenobiotici (farmaci)** e quindi influenza anche l'azione ed eventuali effetti collaterali dei farmaci. E' da tempo anche un **target nelle terapie antitumorali.** Vedete ad es, questo articolo:

https://la.repubblica.it/saluteseno/news/un-passo-in-avanti-per-capire-i-meccanismi-del-tumore-al-seno/6138/



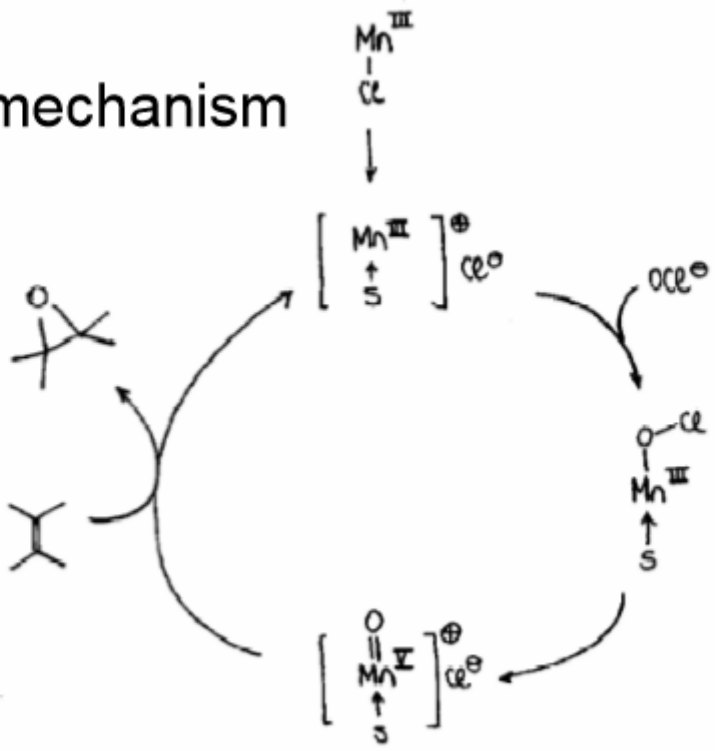
1



2

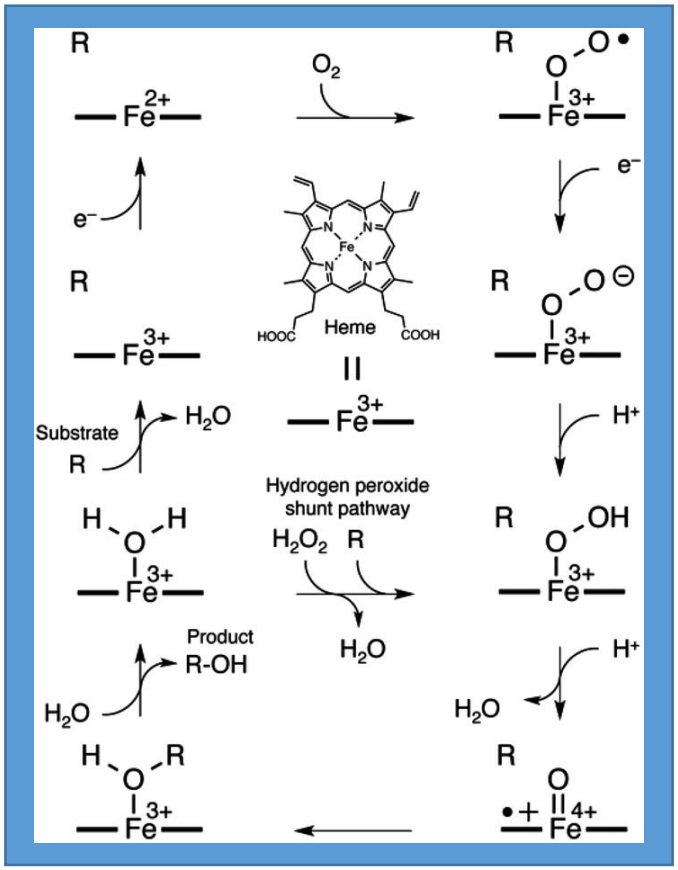
Figure 1. General structures for (**1**) chiral porphyrin and (**2**) chiral salen complexes.

- proposed mechanism

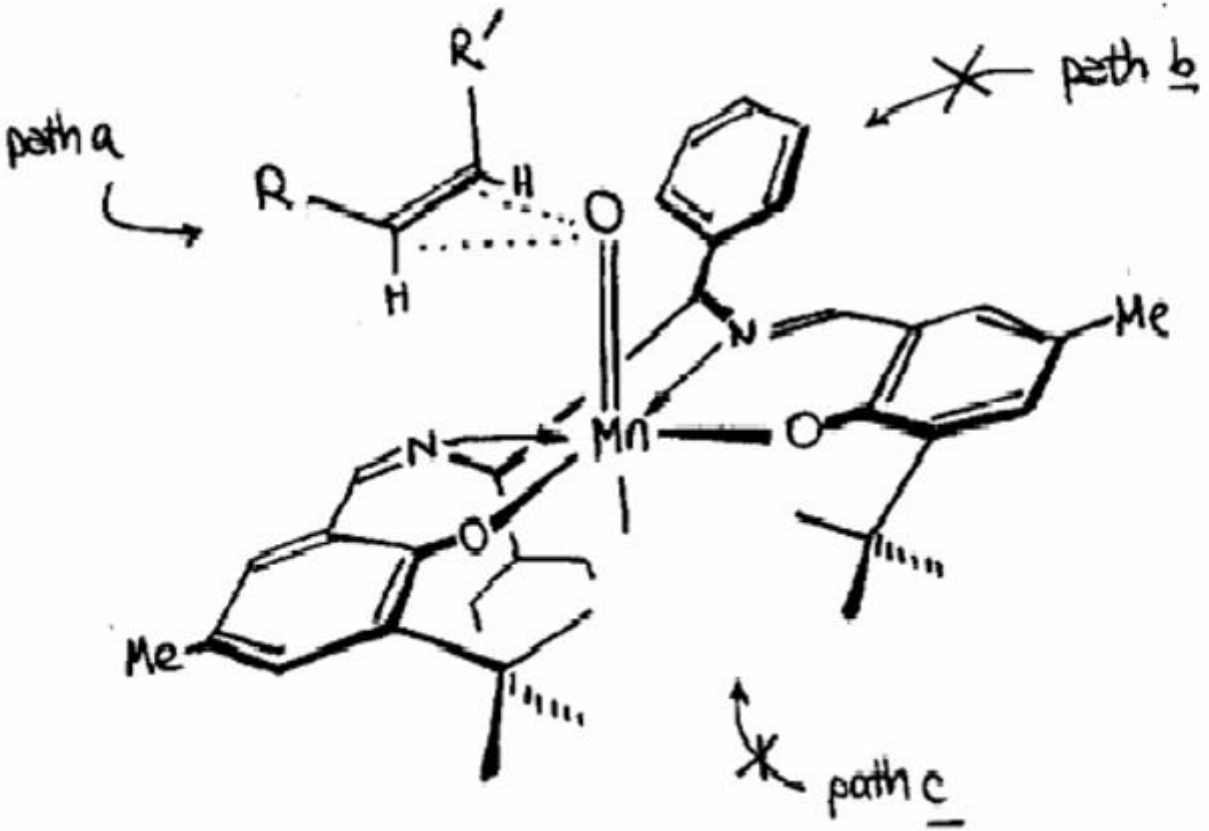


S = solvent

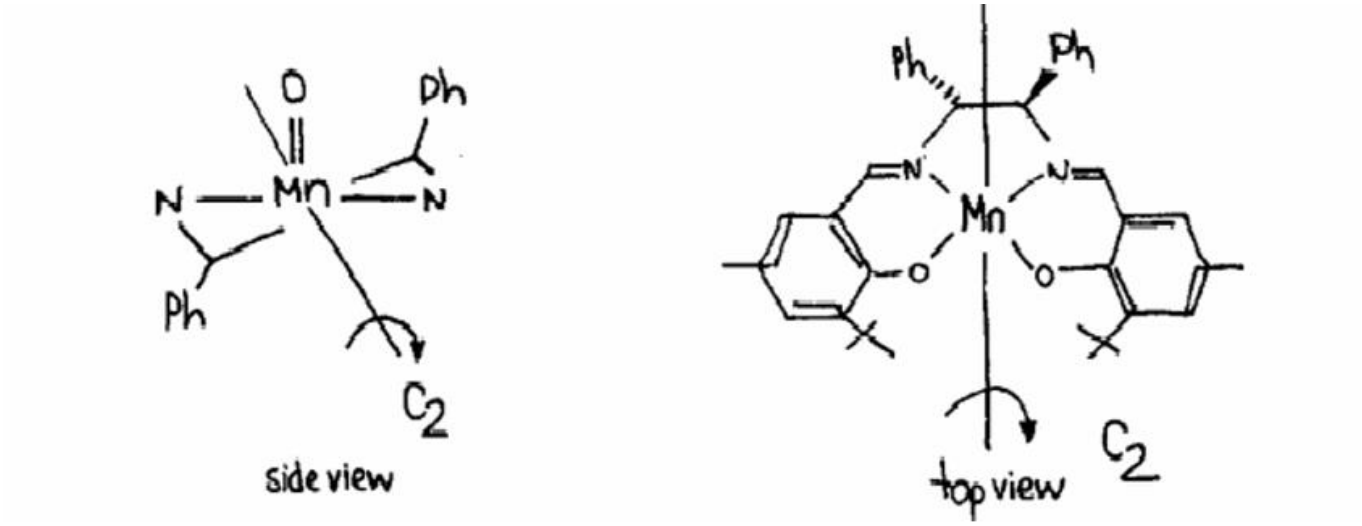
Cyt P450



Therefore, the epoxide approaches the catalyst via path a. Here is a 3-D view of the "side-on perpendicular" approach.

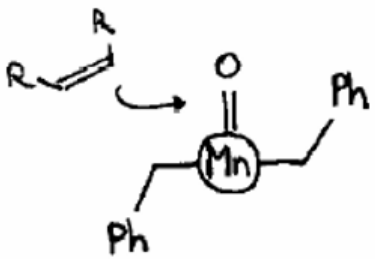


The ethylene diamine bridge is constricted. Here is a view of the bridge as if you were looking down path c (oxygens omitted)



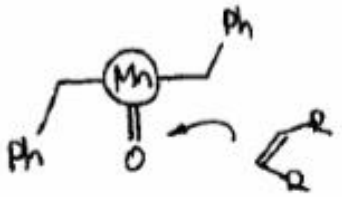
The essential symmetry element of the catalyst is the C_2-rotation axis.

This ensures that the substrate sees only one environment, and hence, enantioselectivity is established.

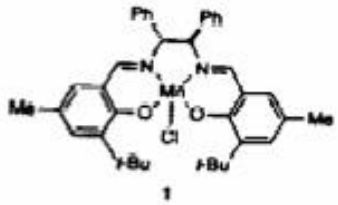


Here is a cartoon of the complex. The olefin can approach the complex only through the open cleft.

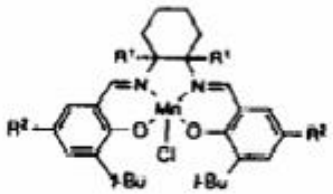
Now suppose the oxo ligand is located at the bottom instead.



Convince yourself that this is the same picture as the one above!

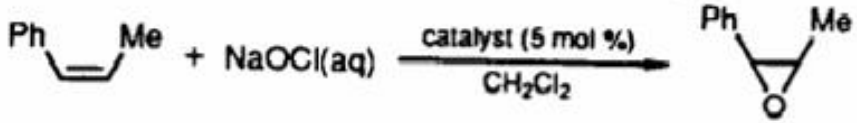


1



2: R^1 = Me, R^2 = Me
3: R^1 = H, R^2 = Me
4: R^1 = Me, R^2 = t-Bu
5: R^1 = H, R^2 = t-Bu

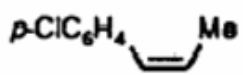
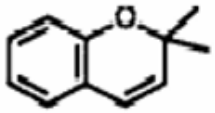
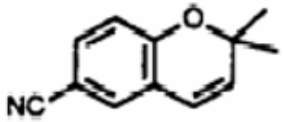
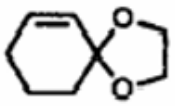
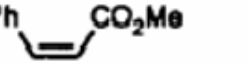
Table I. Asymmetric Epoxidation of *cis*-β-Methylstyrene with Catalysts 1–5



entry	catalyst	yield,[a] %	ee, %	epoxide confign
1	(*R*,*R*)-**1**	88	84	1*R*,2*S*-(+)
2	(*S*,*S*)-**2**	54	49	1*S*,2*R*-(−)
3	(*S*,*S*)-**3**	87	80	1*S*,2*R*-(−)
4	(*S*,*S*)-**4**	56	55	1*S*,2*R*-(−)
5	(*S*,*S*)-**5**	81	92	1*S*,2*R*-(−)

[a] Determined by GC by integration against an internal quantitative standard.

Table II. Asymmetric Epoxidation of Representative Olefins by Catalyst **5**[a]

entry	olefin	epoxide yield,[b] %	ee,[c] %	equiv of **5** required for complete reactn
1		84	92	0.04
2		67	92	0.04
3		72	98	0.02
4		96	97	0.03
5		63	94	0.15
6[d]		65[e]	89	0.10

[a] Reactions were run at 4 °C according to the general procedure outlined in ref 4. [b] Isolated yields based on olefin unless otherwise indicated. [c] Determined by analysis of the isolated epoxides by ^{1}H NMR in the presence of Eu(hfc)$_3$ and by capillary GC using a commercial chiral column (J & W Scientific Cyclodex-B column, 30 m × 0.25 mm i.d., 0.25-μm film). All reactions were run in duplicate with both enantiomers of **5**, and ee values were reproducible to ±2%. [d] Reaction carried out in the presence of 0.4 equiv of 4-phenylpyridine *N*-oxide. [e] Yield determined by GC.

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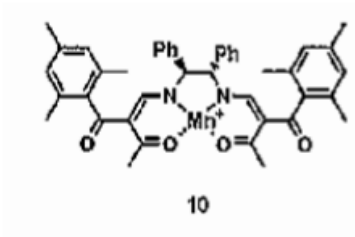

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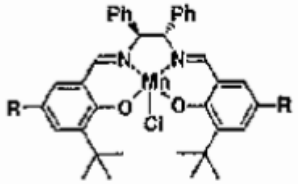
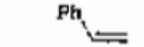
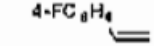
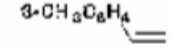
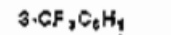
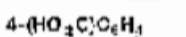
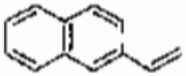


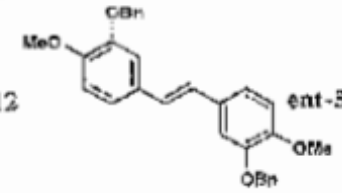
11, a: R= OSi(Pr-*i*)3, b: R= Me, c: R= OMe

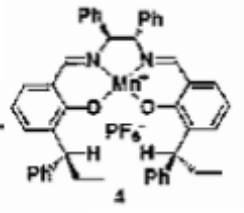
asymmetric epoxidation of monosubstituted olefins using (salen)manganese(III) complexes as catalysts

Entry	Substrate	Catalyst	Solvent	Oxidant	Temp.	Yield (%)	% ee	Confign	Ref.
1		9	CH_2Cl_2	NaOCl[a]	-18 °C	5	70	-	[33]
2		11a	CH_2Cl_2	*m*-CPBA[b]	-78 °C	88	86	-	[24]
3	"	9	CH_3CN	PhIO	-24 °C		26	-	[32]
4		11a	CH_2Cl_2	*m*-CPBA[b]	-78 °C	83	85	-	[25]
5		11c	CH_2Cl_2	*m*-CPBA[b]	-78 °C	83	80	-	[25]
6		11a	CH_2Cl_2	*m*-CPBA[b]	-78 °C	85	82	-	[25]
7		11a	CH_2Cl_2	*m*-CPBA[b]	-78 °C	85	82	-	[25]
8		10	C_6H_6	O_2[c]	rt	49	48	-	[27]

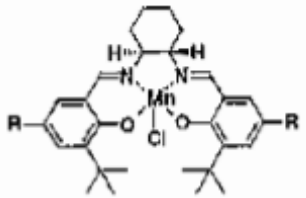
a) Aqueous NaOCl saturated with sodium chloride was used.
b) Reaction was carried out in the presence of excess *N*-methylmorpholine *N*-oxide.
c) Reaction was carried out in the presence of pivalaldehyde.

Asymmetric epoxidation of *trans*-disubstituted olefins using (salen)manganese(III) or (salen)-chromium(III) complexes as catalysts

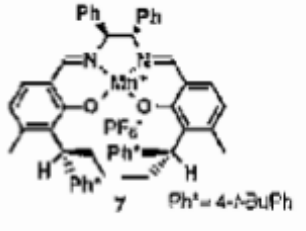
Entry	Substrate	Catalyst	Solvent	Oxidant	Temp.	Yield (%)	% ee	Confign	Ref.
1		**5a**	CH_2Cl_2	NaOCl		23 (2:1)[a]	46[b]	-	[34]
2		**7**	CH_3CN	PhIO		61	9	1*R*,2*R*	[19]
3	"	ent-**5a**	CH_2Cl_2-MeOH	H_2O_2		34	47	1*R*,2*R*	[15c]
4	"	**4**	CH_2Cl_2[c]	PhIO	rt	32	56	1*R*,2*R*	[19]
5	"	**12**	CH_2Cl_2[d]	PhIO	rt	-	83	1*R*,2*R*	[35]
6		**5a**	CH_2Cl_2	NaOCl	-	-	25	1*S*,2*S*	[36]
7	"	**8b**	CH_3CN	PhIO	rt	37	67	1*R*,2*R*	[37]
8	"	**8b**	"	"	0 °C	30	73	1*R*,2*R*	[37]
9	"	**8b**	"	"	-20 °C	37	77	1*R*,2*R*	[37]
10	"	**8b**	"	"	-40 °C	17	81	1*R*,2*R*	[37]
11	"	**7**	"	"	rt	65	62	1*R*,2*R*	[19]
12		ent-**5b**	CH_2Cl_2, 2,4,6-$Me_3C_6H_2IO$		5 °C	-	30	1*R*,2*R*	38



4



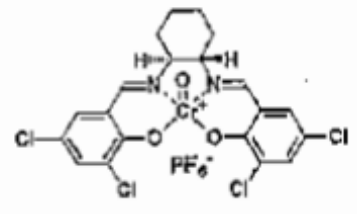
5, a: R= *t*-Bu, b: R= Me



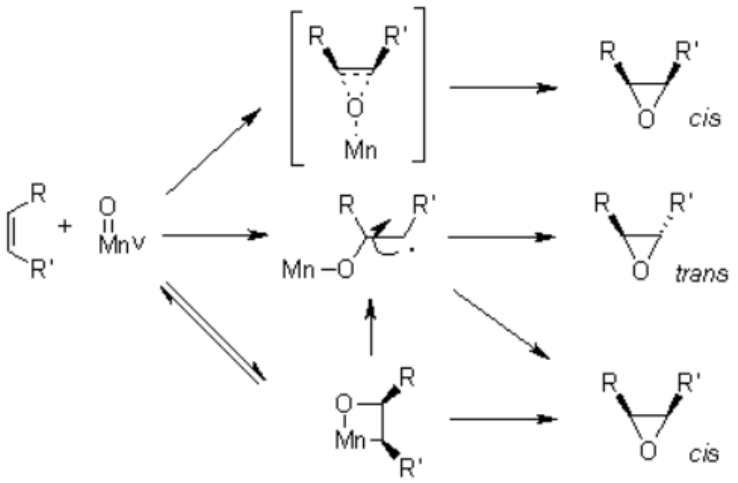
7 Ph* = 4-*t*-BuPh

8, a: X=AcO⁻, b: X= PF_6^-

a) Product is a mixture of *trans*- and *cis*-epoxides. Numbers in parentheses are a ratio of *trans*- and *cis*-epoxides.
b) The number stands for the e.e. of *trans*-epoxide.
c) Reaction was carried out in the presence of 2-methylimidazole.
d) Reaction was carried out in the presence of triphenylphosphine oxide.
e) Data taken from Refs. [34] (entry 1) and [38] (entry 12).



Discussions of the mechanism of the oxygen transfer to the double bond have led to controversy. Depending on the substrate and additives, the formation of side products with *trans* stereochemistry points to a radical mechanism, whereas alkyl-substituted olefins stereoselectively give only *cis* products via a concerted mechanism. The suggested formation of manganaoxetanes receives support from calculations on a theoretical level, and from experiments reported by Katsuki using derivatives of the Jacobsen catalyst.

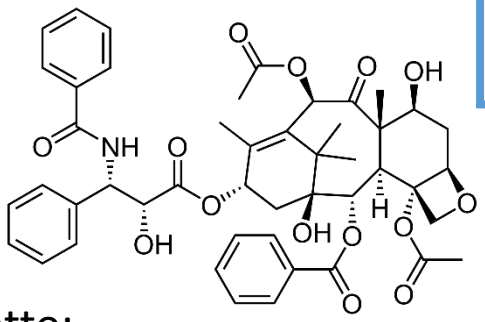


Il Tassolo è stato isolato alla fine degli anni '60 dalla corteccia dell'albero di Tasso (Taxus brevifolia), e commercializzato come Taxol per la chemioterapia.

http://nativeplantspnw.com/pacific-yew-taxus-brevifolia/

Applicazioni

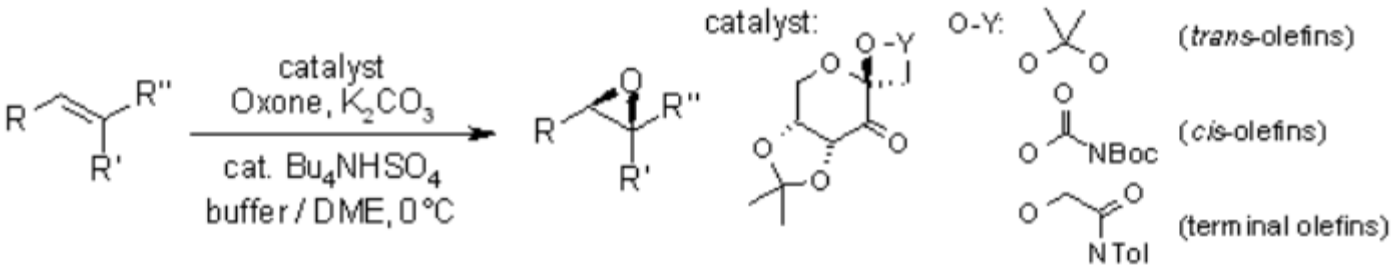
Sintesi del Taxolo



Vedete il link qui sotto:

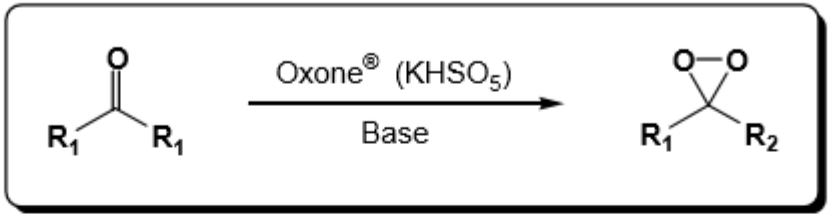
https://en.wikipedia.org/wiki/Paclitaxel_total_synthesis

Epossidazione Asimmetrica (AE) di Shi



1. Complementare alla AE di Sharpless e Jacobsen
2. OK per alcheni trans
3. ORGANOCATALIZZATORE derivato dal fruttosio
4. Ossidante: Oxone forma diossirani (instabili) *in situ*
5. Condizioni: 0°C, sistemi bifasici con tampone e phase-transfer catalyst
6. Aggiunta di K_2CO_3 accelera la reazione ma rende l'oxone instabile

Dioxiranes



oxone: prodotto commerciale, (potassio perossomonosolfato), $2KHSO_5\ KHSO_4\ K_2SO_4$

- Electrophilic oxidants, but successful for epoxidation of electron poor alkenes:
  e.g. Baumstark, *J. Org. Chem.*, **1993**, *58*, 7615.

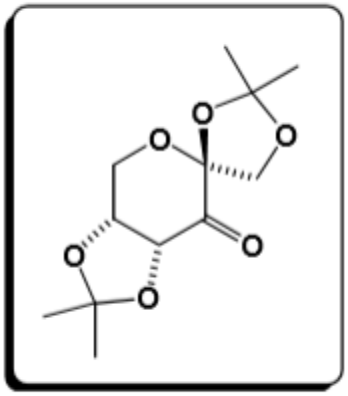
- **Isolation of dioxiranes: neutral, anhydrous oxidants**

Preparation of dimethyldioxirane (DMDO) solutions: Adam, *Chem. Ber.*, **1991**, *124*, 2377.
More concentrated, "acetone free" solutions: Messeguer, *Tetrahedron Lett.*, **1996**, *37*, 3585.

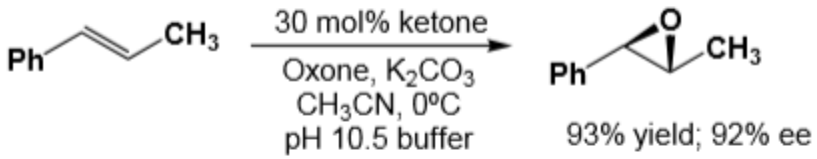
- ***In situ* dioxirane formation**

Biphasic, CH_2Cl_2 / H_2O: Denmark, *J. Org. Chem.*, **1995**, *60*, 1391.
Monophasic, CH_3CN / H_2O: Yang, *J. Org. Chem.*, **1995**, *60*, 3887.
In situ DMDO prep.: Shi, *J. Org. Chem.*, **1998**, *63*, 6425.
Trifluoroacetone + H_2O_2: Shi, *J. Org. Chem.*, **2000**, *65*, 8808.

Chiral Dioxiranes: Asymmetric Epoxidation of trans-Alkenes



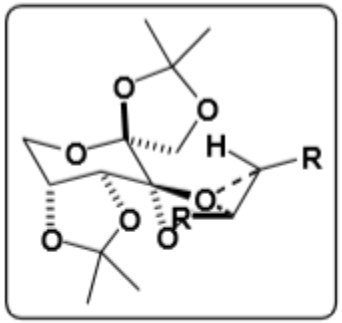
Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224.
Review: Shi, *Synthesis*, **2000**, 1979.



(Use of H_2O_2 as primary oxidant: *Tetrahedron Lett.*, **1999**, *40*, 8721; *Tetrahedron*, **2001**, *57*, 5213.)

- Preparation: 2 steps from D-fructose (enantiomer available in 5 steps from L-sorbose)
- Excellent enantioselectivities for epoxidation of trisubstituted and *trans*-disubstituted alkenes
- Poor ee for *cis*- and terminal alkenes

- Ketone decomposes by Baeyer-Villiger reaction - cannot be recycled. High pH conditions required.



- **Other substrate types**:

Conjugated dienes: *J. Org. Chem.* **1998**, *63*, 2948
Enynes: *Tetrahedron Lett.* **1998**, *39*, 4425.

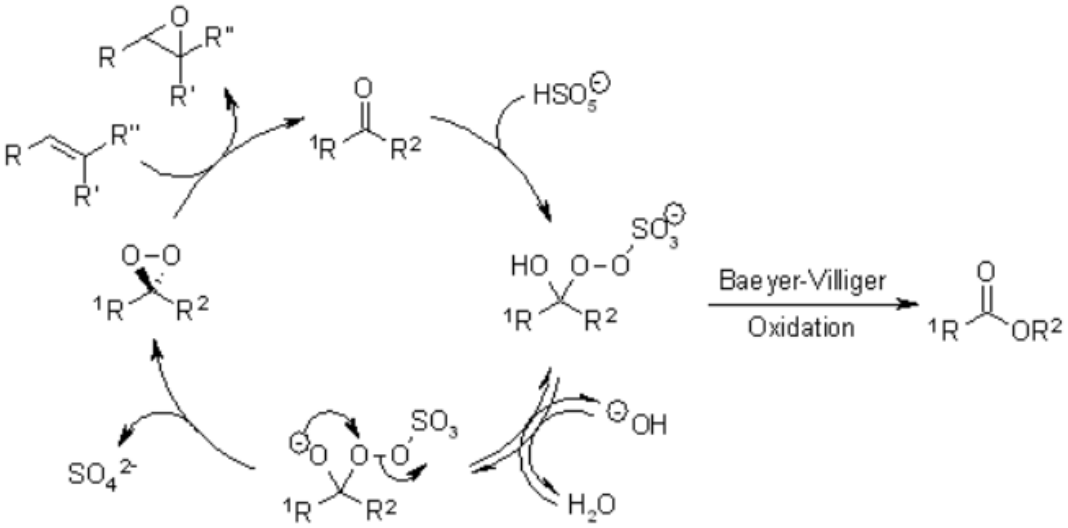
Modified catalyst for *cis*-alkenes: *J. Am. Chem. Soc.* **2000**, *122*, 11551.
Terminal alkenes: *Org. Lett.*, **2001**, *3*, 1929.

- **Stable catalysts:**

Armstrong, *Chem. Commun.* **1998**, 625; *Tetrahedron: Asymmetry*, **2000**, *11*, 2057.
Shi, *Org. Lett.* **2001**, *3*, 715.

Mechanism of the Shi Epoxidation

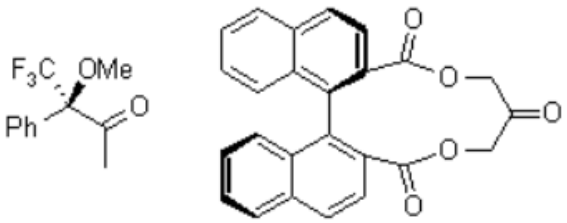
The epoxidizing species is believed to be a dioxirane, which is a powerful epoxidation reagent. These are not indefinitely stable, but can be generated *in situ* by oxidation of a ketone with potassium peroxymonosulfate (Oxone). The sulfate - as a good leaving group - facilitates the ring closure to the dioxiranes. As the ketone is regenerated, only catalytic amounts of it are needed. In addition, chiral ketones can be used for a catalyzed, enantioselective epoxidation, since the ketone substituents are close to the reacting center.



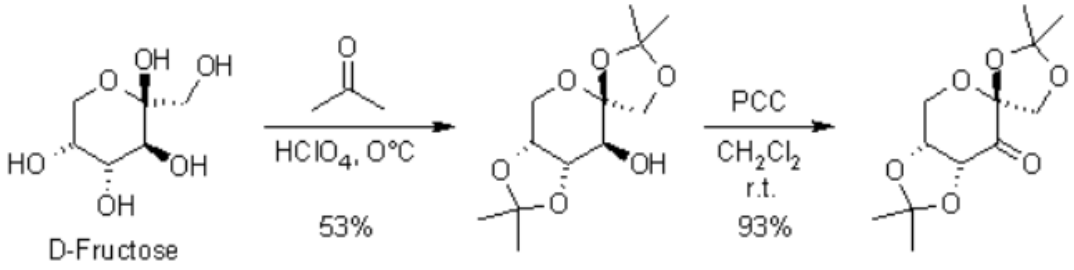
Reactions are conducted in buffered, often biphasic mixtures with phase transfers catalysts. Addition of K_2CO_3 to the reaction mixture increases the rate of formation of the dioxirane but also lowers the stability of Oxone. However, a higher pH also disfavors the Bayer-Villiger Oxidation as a side reaction, so the catalysts remain more active. Therefore the autodecomposition of Oxone at high pH can be overridden if the ketone is sufficiently reactive. The enhancements in reaction rate can also be explained by a higher nucleophility of Oxone under more basic conditions. In any case, a careful use of buffered media is often needed.

http://www.organic-chemistry.org/namedreactions/shi-epoxidation.shtm

The reactivity of the ketones can be increased by electron-withdrawing groups in the α-position. From early attempts at building active catalysts, it was learned that trifluoromethyl ketones improved the activity, but other electron-withdrawing groups can also be used. These factors also lower the rate of the Bayer-Villiger Oxidation. As ketones with a hydrogen in the α-position are prone to racemization, chiral elements have often been placed in other positions. Some early catalysts are shown here:



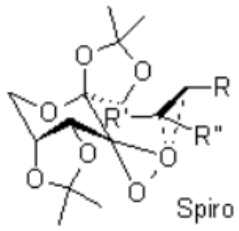
In 1996, a fructose-derived ketone was developed as a highly effective epoxidation catalyst. This ketone can be synthesized in two steps from the very cheap chiral starting material D-fructose by ketalization and oxidation. As L-fructose can be synthesized from L-sorbose, the enantiomer of this catalyst is also conveniently available.



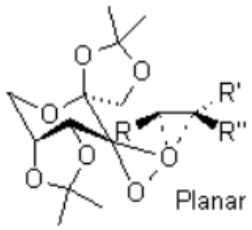
In this catalyst, the stereocenters are close to the reacting center, so the stereochemical communication between substrate and catalyst is efficient. The presence of fused rings or quaternary centers α to the carbonyl group minimizes epimerization of the stereogenic centers. Electron-withdrawing substituents activate the carbonyl.

http://www.organic-chemistry.org/namedreactions/shi-epoxidation.shtm

A spiro transition state seems to be favored due to a stabilizing oxygen lone pair interaction with the π* orbital of the alkene, which cannot be achieved in the planar transition state.



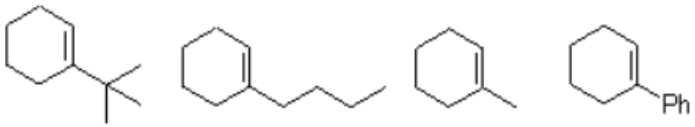
Spiro



Planar

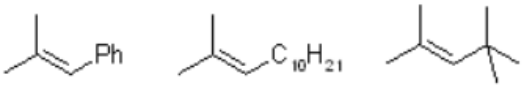
The main competing mode is the planar transition state shown; this is somewhat more favored with trisubstituted olefins if R' is bulky (a), whereas bulkier R substituents disfavor the planar transition state (b).

a)



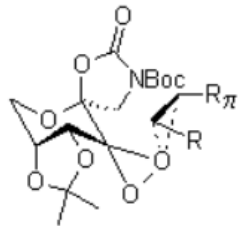
ee: 26% 79% 81% 98%

b)



ee: 76.4% 86.5% 91%

Later developments enabled the conversion of *cis*-substituted alkenes and terminal olefins by varying the substitution pattern of the catalyst. For example a Boc-protected lactam allows the conversion of *cis*-olefins.
Here, an interaction between groups with a π-system and the spiro oxazolidinone can be assumed, so conjugated styrenes and enynes give products in high enantiomeric excess:



A recent publication also shows selective conversions of terminal olefins. Here, the planar transition state is favored due to steric reasons. With an *N*-tolyl lactam ketone, the attractive interaction between aryl substituents of the olefin and the catalyst could be improved even further.