Olefin oxidation

K. Barry Sharpless (The Scripps Research Institute, La Jolla, California) - 2001 Nobel Prize "for his work on chirally catalyzed oxidation reactions".
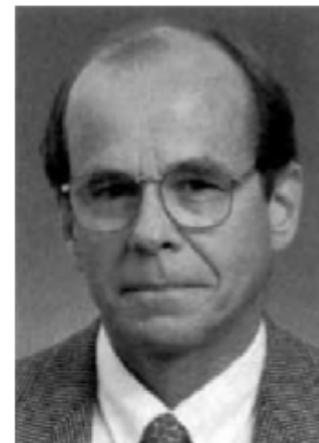
1980	**Asymmetric epoxidation (AE)**
1987	**Asymmetric dihydroxylation (AD)**

The process for the selective oxidation of olefins have long been among the most useful tools for day-to-day organic synthesis because of these appealing characteristics of olefins:
- they are among the *cheapest* functionalized organic starting materials,
- most simple olefins are *prochiral*, providing a prominent portal to the chiral world.
(K. B. Sharpless, Nobel Lecture, 2001)

K. Barry Sharpless and his co-workers have discovered and developed widely used catalytic oxidation processes, including the first general methods for stereoselective oxidation– the Sharpless reactions for asymmetric epoxidation, dihydroxylation, and aminohydroxylation of olefins. His mentors at Dartmouth College (BA in 1963), Stanford College (PhD in 1968 and postdoctoral research), and Harvard University (further postdoctoral research) were Prof. T. A. Spencer, Prof. E. E. van Tamelen, Prof. J. P. Collman, and Prof. K. Bloch, respectively. Before 1990, when he became W. M. Keck Professor of Chemistry at the Scripps Research Institute, Prof. Sharpless was a member of Faculty at the MIT (1970 - 77, 1980 - 90) and Stanford (1977 - 80). Prof. Sharpless' s honors include the Chemical Sciences Award of the National Academy of Sciences, the Roger Adams and Arthur C. Cope Awards from the American Chemical Society, the Tetrahedron Award, the King Faisal Prize, the Prelog Medal, the Wolf Prize, the Nobel Prize.

EPOSSIDAZIONE ASIMMETRICA (AE)
DEGLI ALCHENI
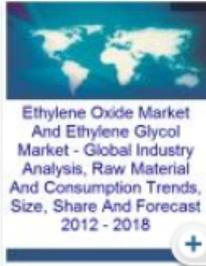
Ethylene Oxide Market And Ethylene Glycol Market - Global Industry Analysis, Raw Material And Consumption Trends, Size, Share And Forecast 2012 - 2018

DESCRIPTION | **TABLE OF CONTENTS** | **SUMMARY** | **COMPANIES MENTIONED** | **FORMATS / FAQ**

Ethylene oxide is an epoxide by direct oxidation of ethylene at room temperature. It is a key raw material for the production of ethylene glycol which is used in various applications like PET bottles, detergents, paints and solvents.

The global demand for ethylene oxide was estimated to be worth over $28,000 million in the year 2011 and is expected to cross $40,000 million in 2018, growing at a CAGR of over 6% from 2013 to 2018. Asia pacific and North America dominate the ethylene oxide market, accounting for over 60% of the total demand in 2011. However, strong growth is expected from Asia-Pacific, Eastern and Central Europe, Middle East and South America in the coming few years.

Ethylene glycol market was estimated to be worth over $24,000 million in 2011 and is expected to cross $38,000 million by 2018, growing at a CAGR of over 7% from 2013 to 2018. Monoethylene glycol (MEG) is the most important ethylene glycol which accounting over 90% of the overall ethylene glycol production.

Strong demand for polyester fibers and PET resins coupled with growing demand for automotive antifreeze is expected to drive market demand in the next five years. Crude oil price-volatility together with unfavorable regulatory scenario is the key concern for market participants today.

FEATURED COMPANIES

Akzonobel

Basf Ag

Clariant Ag

Dow Chemicals

Exxon Mobil Corporation

Formosa Plastic Group

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Propylene Oxide

Applications

Propylene oxide is a highly reactive chemical used as an intermediate for the production of numerous commercial materials. It reacts readily with compounds containing active hydrogen atoms, such as alcohols, amines, and acids. Therefore, propylene oxide is used worldwide to produce such versatile products as:

- Polyether polyols (polyglycol ethers)
- Propylene glycols
- Propylene glycol ethers

Polyether polyols are one of the main components in polyurethane systems and are used in many consumer applications, such as rigid foam insulation and flexible foam seat cushions. Polyether polyols make up the largest share of propylene oxide usage, between 60% and 70% of the total volume. Propylene glycol consumes another 20% of the total volume while propylene-based glycol ethers comprise about 5%. The remaining share goes into other propoxylated or specialty organic compounds.

Other products made using propylene oxide are:

- Flame retardants
- Modified carbohydrates (starches)
- Synthetic lubricants
- Oil field drilling chemicals
- Textile surfactants

Use the links on the left to learn more about propylene oxide applications.

For Propylene Oxide Safety Data Sheets, Technical Data Sheets and other technical documents, please go to Technical Information.

www.dow.com

Come si preparano gli EPOSSIDI?

Scheme 1

cis-2-Butene → RCO₃H → Meso

trans-2-Butene → RCO₃H → (±)
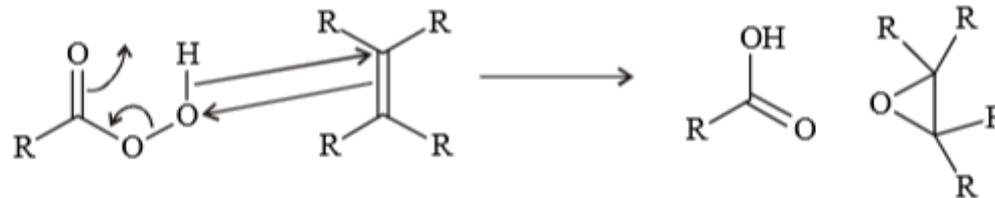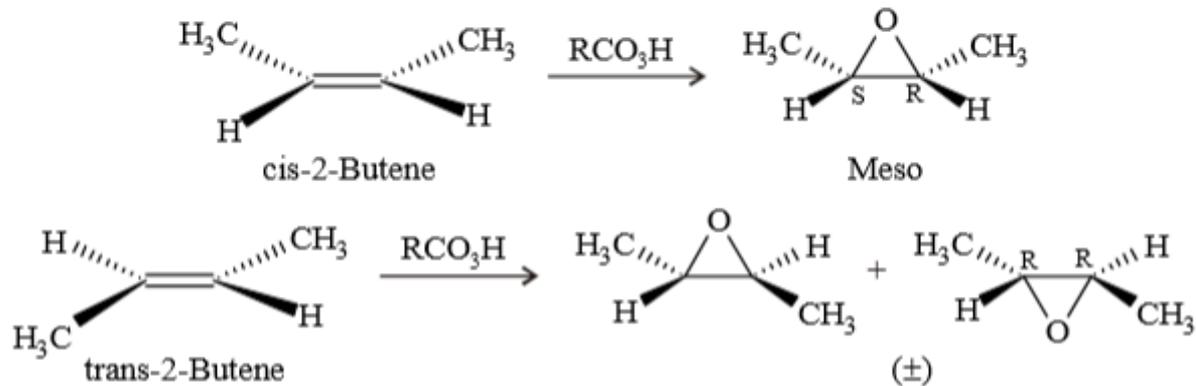
1- ALCHENI + PEROSSIACIDI

Come si preparano gli EPOSSIDI?

Scheme 1

H₃C⁄⁄⁄ ̿̿̿ CH₃ $\xrightarrow{RCO_3H}$ H₃C⁄⁄⁄ ̿̿̿ CH₃

cis-2-Butene   Meso

H⁄⁄⁄ ̿̿̿ CH₃ $\xrightarrow{RCO_3H}$ H₃C⁄⁄⁄ ̿̿̿ H   +   H₃C⁄⁄⁄R R ⁄⁄⁄H

trans-2-Butene   (±)
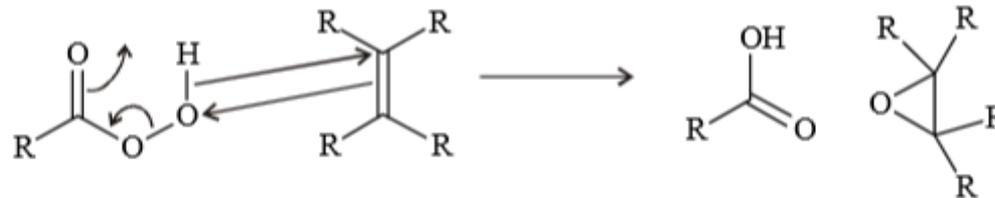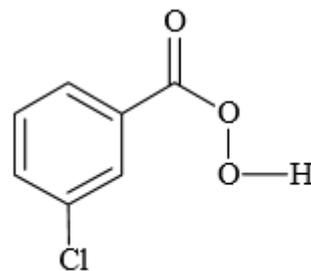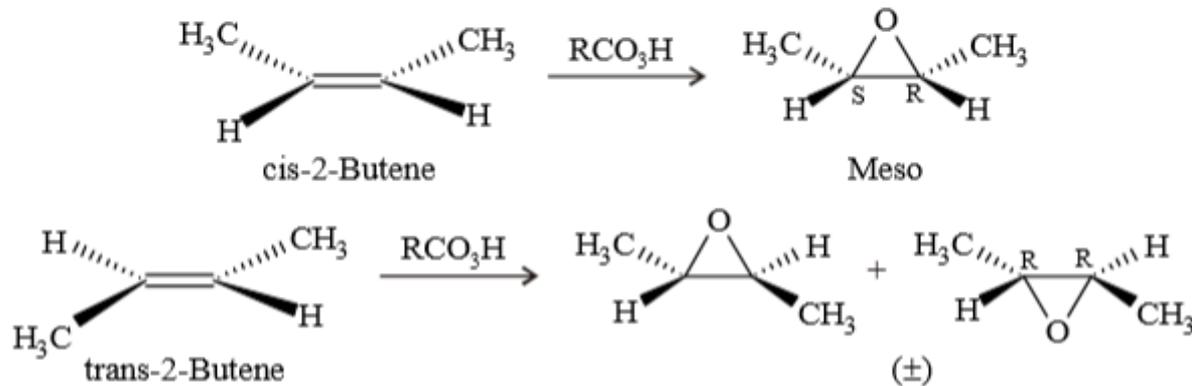
m-Chloroperoxybenxoic acid
(MCPBA)
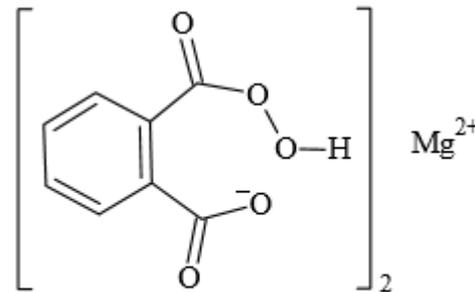
Magnesium monoperoxyphthalate
(MMPPP)

Stereoselettività
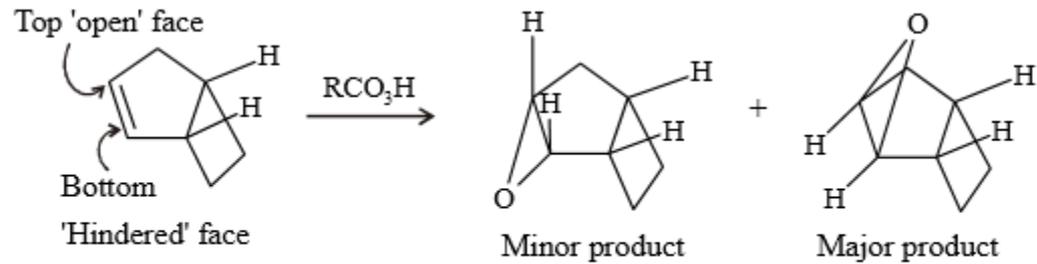
Scheme 5
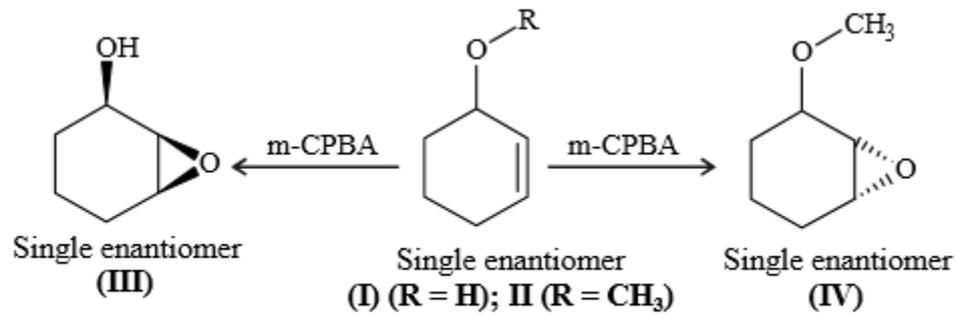
Scheme 6

La reazione con il peracido avviene dal lato meno ingombrato

Come si preparano gli EPOSSIDI?
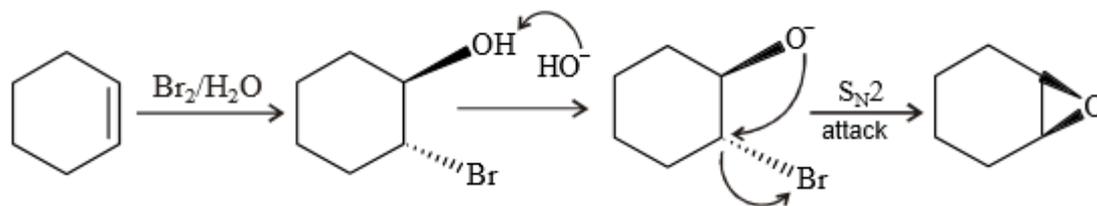
2- ALCHENI → aloidrine → epossidi

Gli epossidi sono intermedi utili in quanto l'apertura dell'anello avviene per attacco di vari nucleofili.

La selettività dipende dalle caratteristiche steriche ed elettroniche dell'epossido e del nucleofilo, nonché dalle condizioni di reazione (ad es. catalisi acida).

Quando il Nu è H_2O si ottiene un DIOLO VICINALE con stereochimica opposta rispetto alla diidrossilazione degli alcheni con tetraossido di Osmio (quindi sono 2 reazioni complementari)
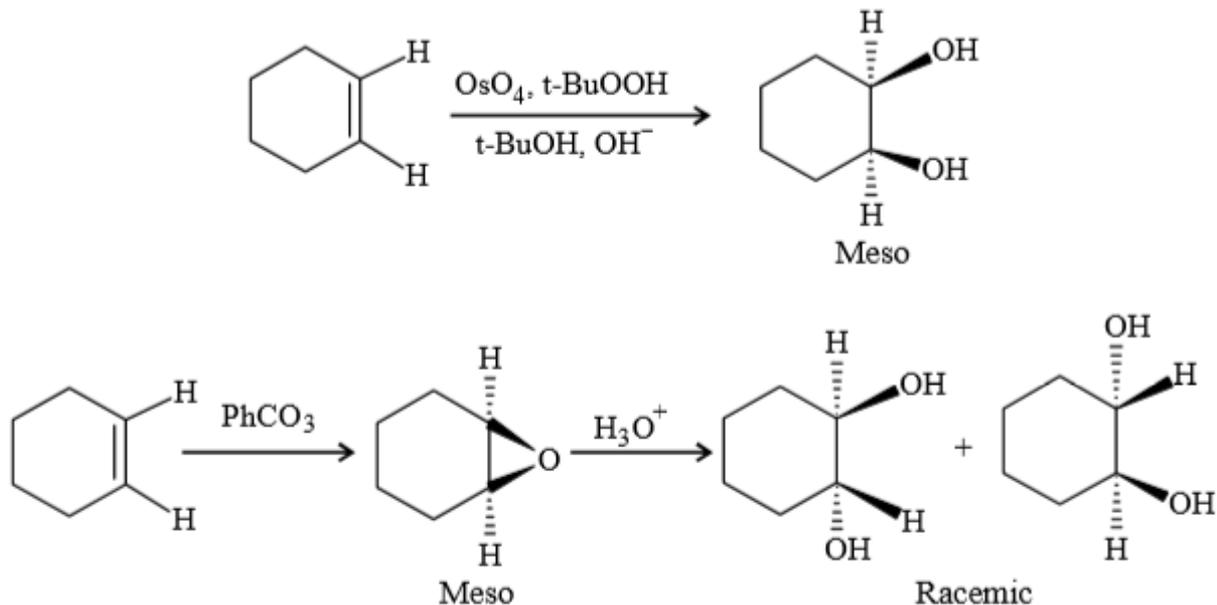
Alkyl hydroperoxides (ROOH) also convert alkenes into epoxides under catalysis by a transition metal and allylic alcohols give epoxy alcohols with the OH group on the same side as the epoxy group **(Scheme 13)** as the almost exclusive product. The mechanism of the reaction involves the initial coordination of the metal with both; the allylic alcohol as well as hydroperoxide and by the subsequent displacement at the peroxy group by the alkene moiety. Thus, as shown **(Scheme 13)**, vanadium (V) species yield a reactive complex (I) by the displacement of two alkoxy ligands.
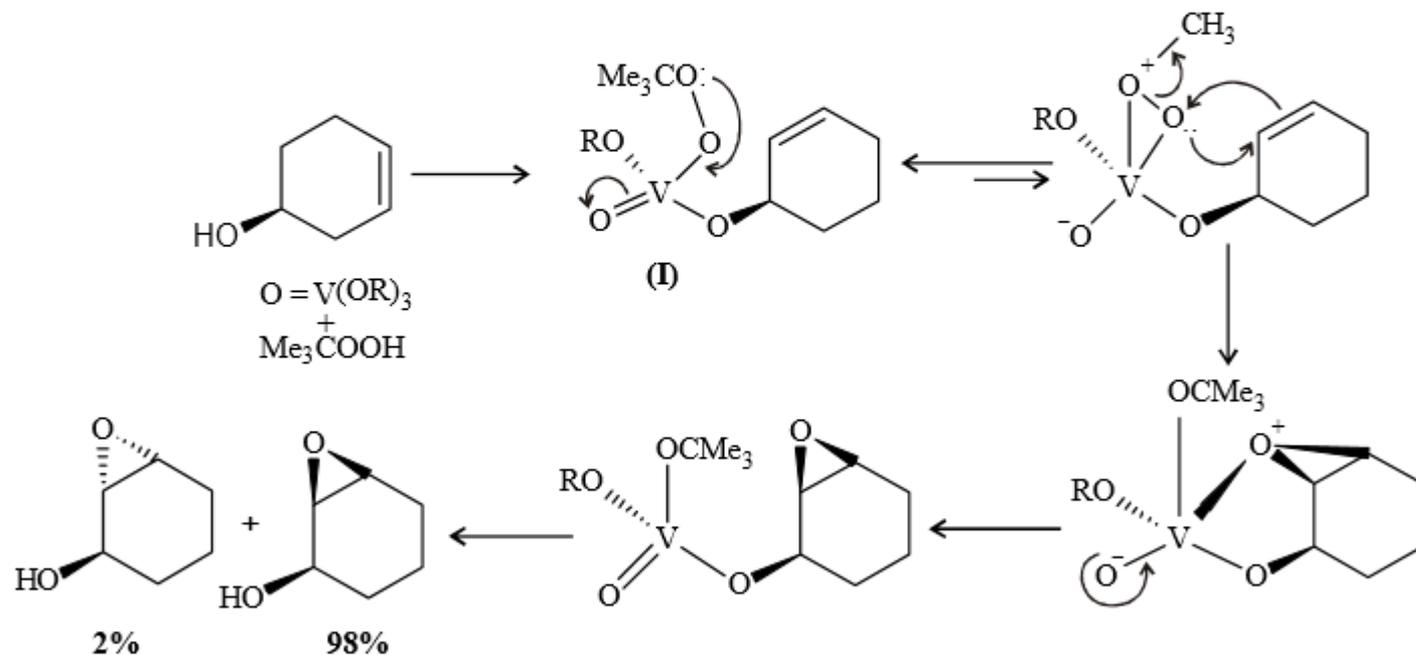
Scheme 13

It is here that the students should be impressed that this diastereoselective epoxidation of **(Scheme 13)** was made enantioselective by the incorporation of a chiral ligand on the transition metal. This field was developed by Professor Sharpless. The

Epossidazione Asimmetrica (AE) di Sharpless

$$\text{Ti(O}^i\text{Pr)}_4 \text{ - (-) - DET}$$

$$\text{tBuOOH}$$
$$\text{CH}_2\text{Cl}_2, \ -20°\text{C}$$
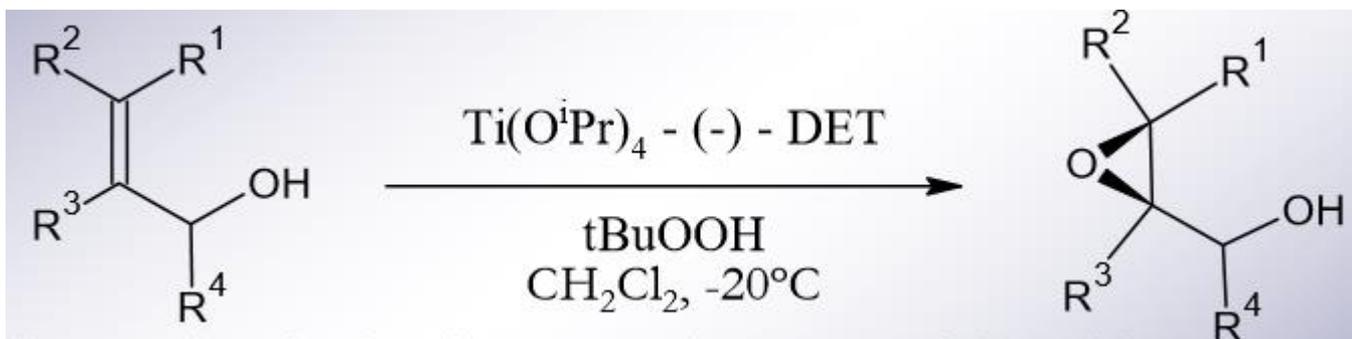
1. Converte alcol allilici primari e secondari in 2,3-epossialcoli

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$_2$Cl$_2$) e -80 °C

Sharpless asymmetric epoxidation (AE)

Allows the enantioselective epoxidation of prochiral allylic alcohols. The oxidant is *tert*-butyl hydroperoxide (TBHP). The reaction is catalyzed by Ti(OPr^i)$_4$. The asymmetric induction is achieved by adding an enantiomerically pure tartrate derivative, which also makes the reaction *faster*.

(*R*,*R*)-diethyl tartrate
(+)-DET

(*S*,*S*)-diethyl tartrate
(-)-DET

^{t}Bu
O-OH + Ti(OPr^i)$_4$

Y = -COOR
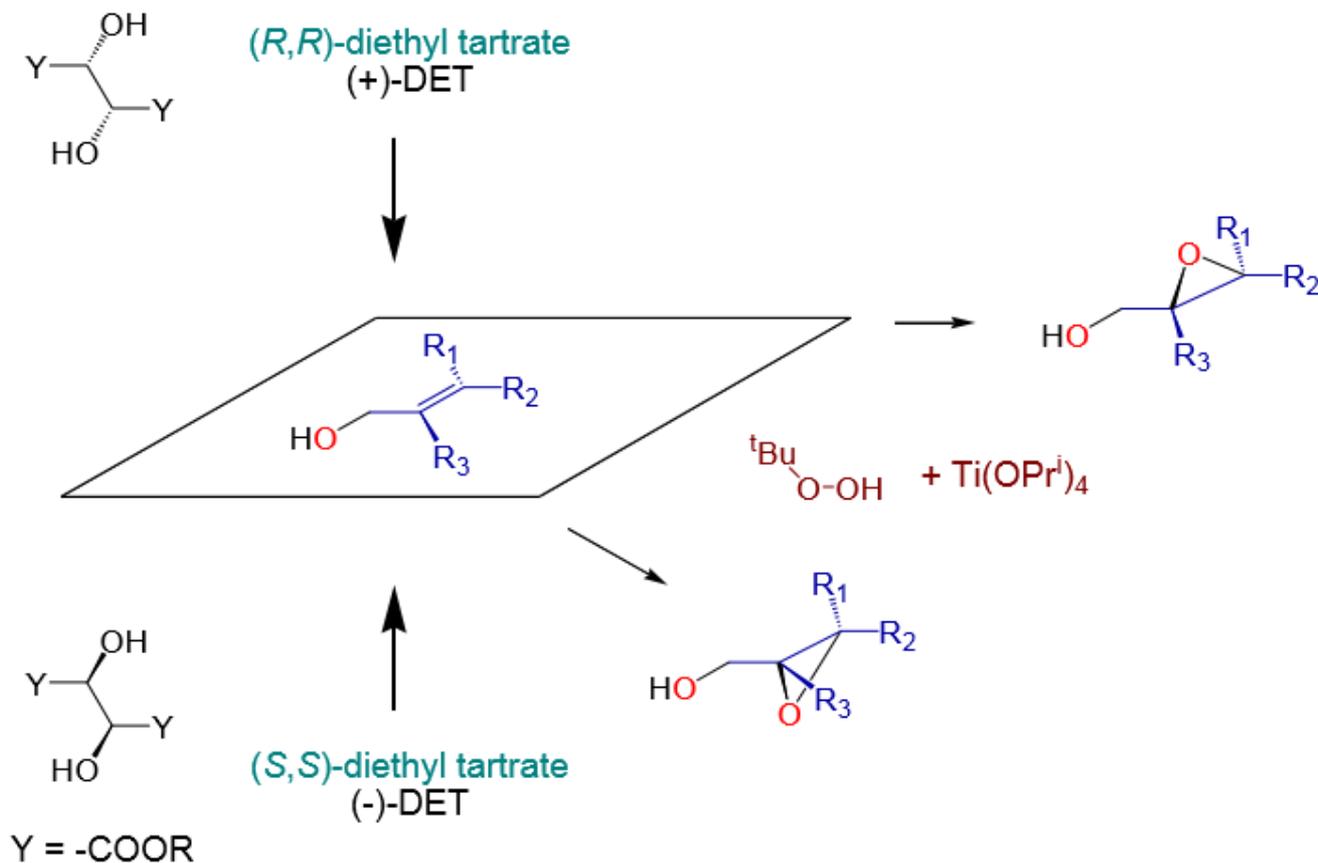
The Catalyst

$Ti(O^iPr)_4$ catalyst
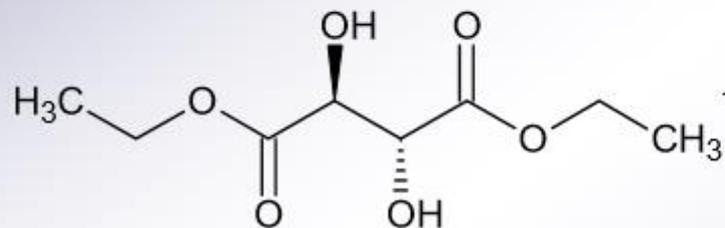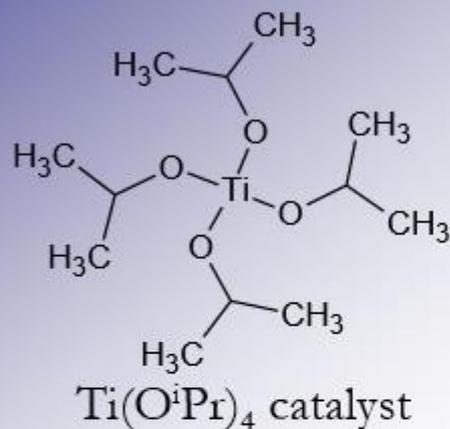
Diethyl Tartrate (DET)
Chirally controls reaction
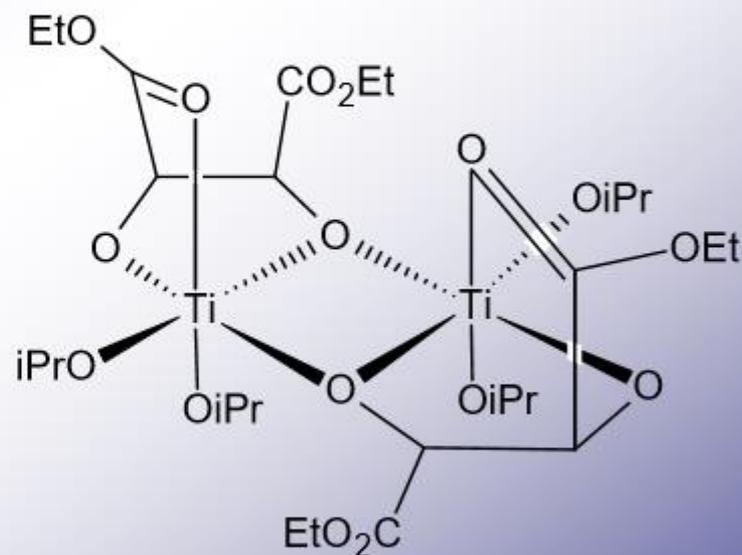
- Via rapid ligand exchange of O^iPr and diethyl tartrate

The tartrate-induced acceleration of the titanium-catalyzed epoxidation reaction came as a surprise. We ultimately found 24 metals other than Ti that catalyze the epoxidation of allylic alcohols by TBHP, but all these systems were strongly inhibited or killed by adding tartrate! Ligand-decelerated catalysis was clearly the rule, while ligand acceleration was the extraordinarily valuable exception. Sharpless, in Nobel lecture.


geraniol

$M(OR)_n$

TBHP
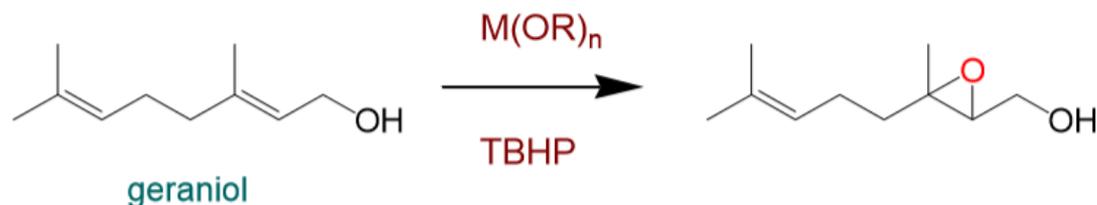
Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn							
Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd							
La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg							

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lw

The tartrate-induced acceleration of the titanium-catalyzed epoxidation reaction came as a surprise. We ultimately found 24 metals other than Ti that catalyze the epoxidation of allylic alcohols by TBHP, but all these systems were strongly inhibited or killed by adding tartrate! Ligand-decelerated catalysis was clearly the rule, while ligand acceleration was the extraordinarily valuable exception. Sharpless, in Nobel lecture.
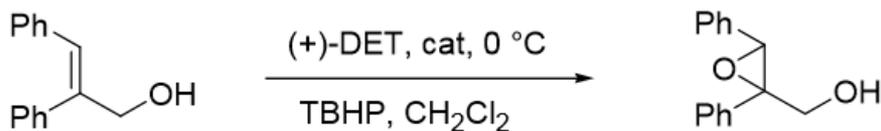
M(OR)$_n$	ee %	configurazione al C-2
Al(OtBu)$_3$ (25 giorni)	5	R
MoO$_2$(acac)$_2$ + (+)-DIPT (40 °C)	15	R
VO(OnPr)$_3$	17	R
Zr(OiPr)$_4$	10	R
Hf(OiPr)$_4$	3	R
Nb(OEt)$_5$	0	-
Ta(OiPr) + (+)-DIPT (23 °C)	39	R
Ta(OEt)$_5$	47	S
Sn(OiPr)$_4$	no reaction	
Ti(OiPr)$_4$ (2h, a -20 °C)	95	S

Mechanism of epoxidation

Unraveling the mechanism of the AE was largely the PhD work of M. G. Finn. His exploration during the early to mid-1980s of the AE's titanium-tartrate catalyst system exposed a *complex mixture of species in dynamic equilibrium*. M. G. discovered the main species [Ti(dipt)(OPr^i)$_2$]$_2$ (DIPT, diisopropyl tartrate) is substantially more active than the other species present - significantly, it is *five to ten times more active* than Ti(OR)$_4$.

Crystal structure of a
closely related complex,
[Ti(DBTA)(OPr^i)$_2$]$_2$, where DBTA =
(*R,R*)-N,N-dibenzyl-tartramide
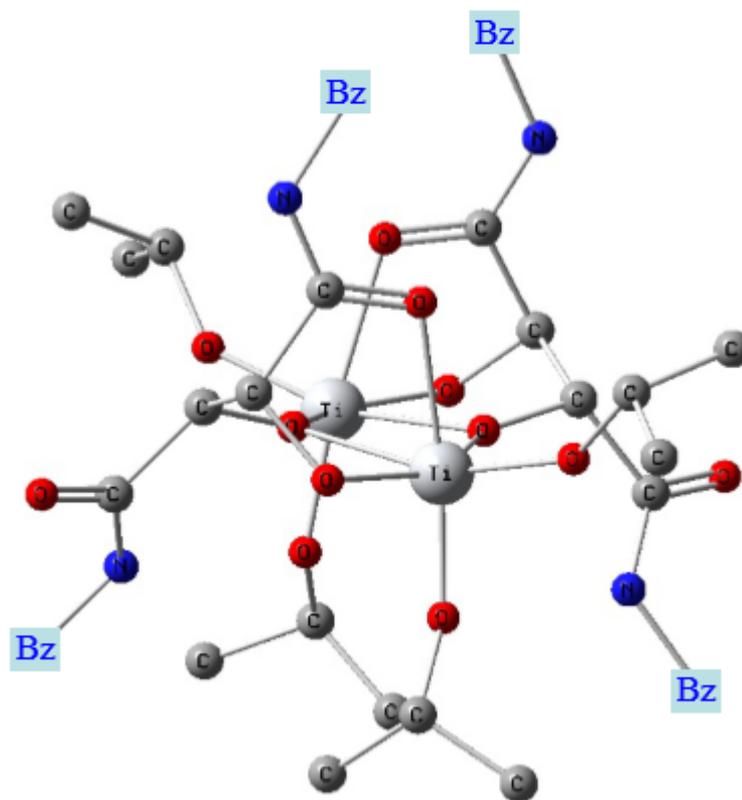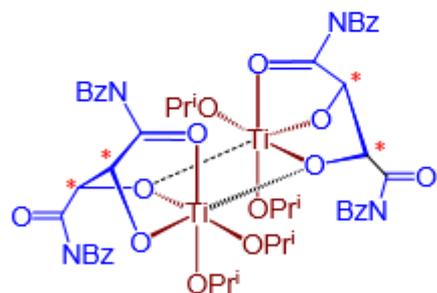
M. G. Finn's thesis work has appeared in
a) *JACS* **1991**, *113*, 106; b) *JACS* **1991**, *113*, 113.

Sharpless, *Angew. Chem.* **2002**, *41*, 2024

● considerazioni meccanicistiche

$$Ti(OR)_4 \ + \ tartrate \ \rightleftharpoons \ [Ti(tartrate)(OR)_2] \ + \ 2\ ROH$$
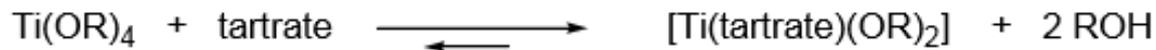
il tartrato ha una cost. di binding e una acidita' maggiore dell'alcossido

$$velocita' = k \ \frac{[Ti(tartrate)(OR)_2][TBHP][\text{alcool allilico}]}{[\text{alcool inibitore}]^2}$$

$[Ti(OR)_2(\text{tartrato})]$ $\xrightleftharpoons[\substack{ROH \\ K_1}]{TBHP}$ $[Ti(OR)(TBHP)(\text{tartrato})]$

$ROH \updownarrow \substack{\text{alcool} \\ \text{allilico}} \quad K'_2$ $\qquad\qquad ROH \updownarrow \substack{\text{alcool} \\ \text{allilico}} \quad K_2$

$[Ti(OR)(\text{alcool allilico})(\text{tartrato})]$ $\xrightleftharpoons[\substack{ROH \\ K'_1}]{TBHP}$ $[Ti(TBHP)(\text{alcool allilico})(\text{tartrato})]$

$k_e \downarrow$ epossidazione

$K_1 K_2 = K'_1 K'_2$

$[Ti(\text{Ot-Bu})(\text{epossi alcool})(\text{tartrato})]$
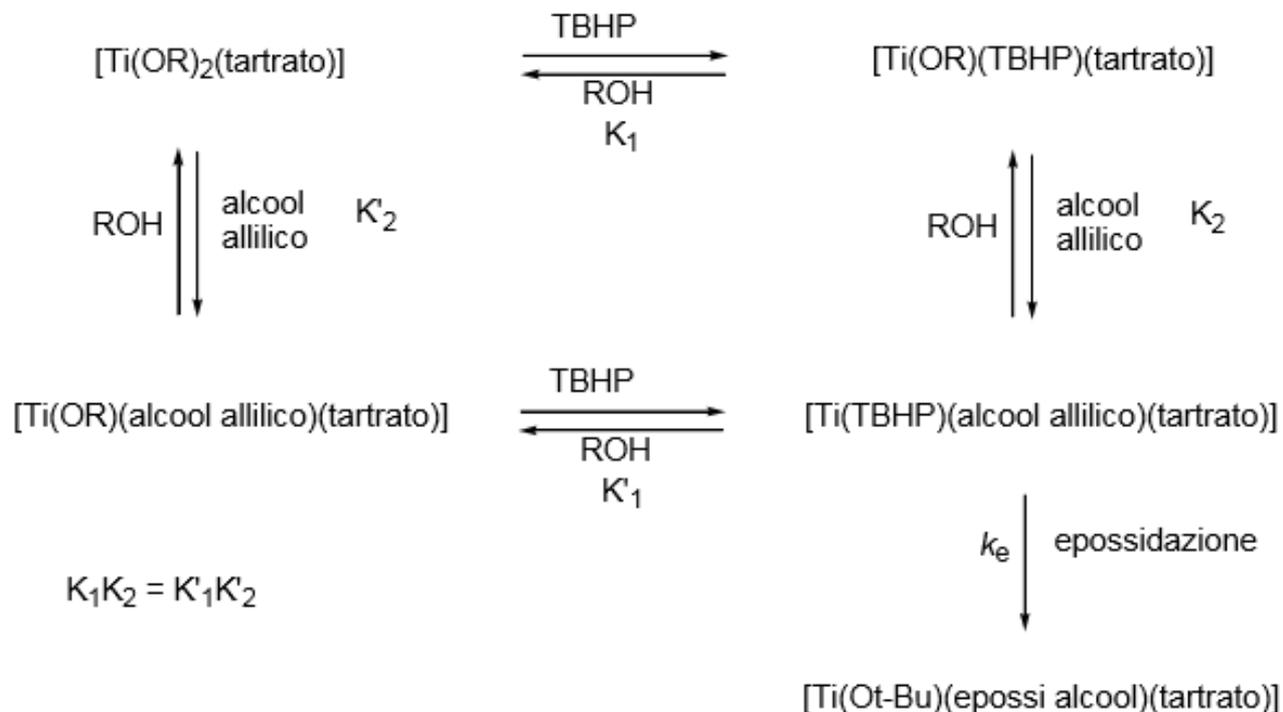
● considerazioni meccanicistiche
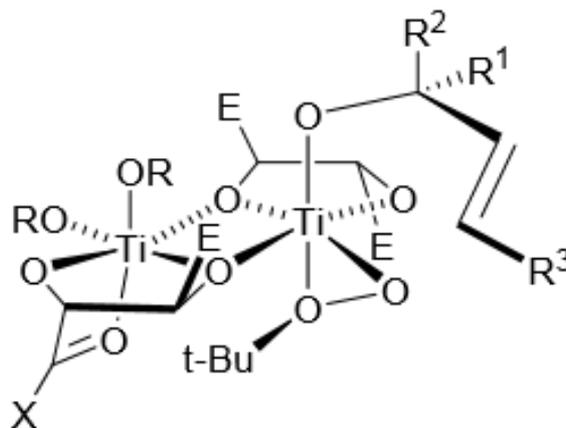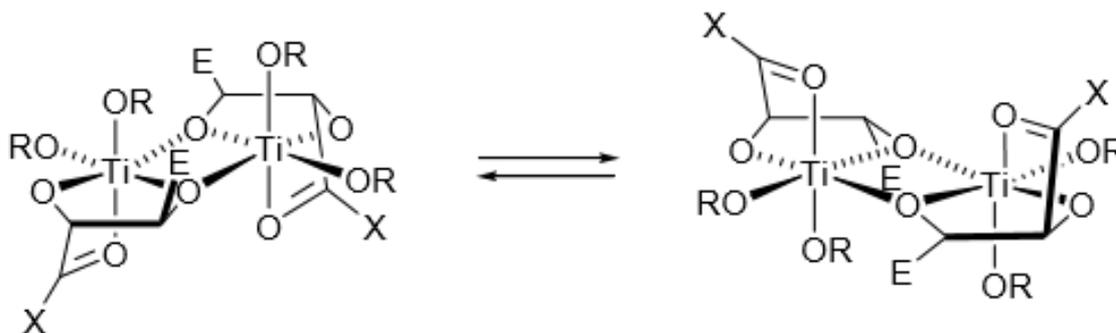
E = CO₂Et
X = OEt

struttura proposta per il catalizzatore "attivo"

http://www.chemtube3d.com/AsymCat-tartrate.html

https://www.youtube.com/watch?v=PhMWrrFv_6I

**Sharpless Asymmetric Epoxidation Catalytic Cycle**
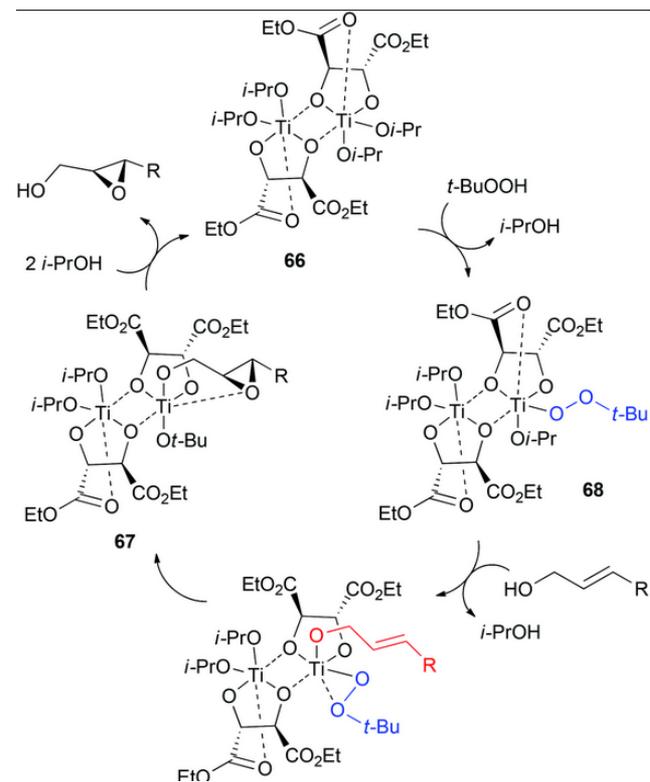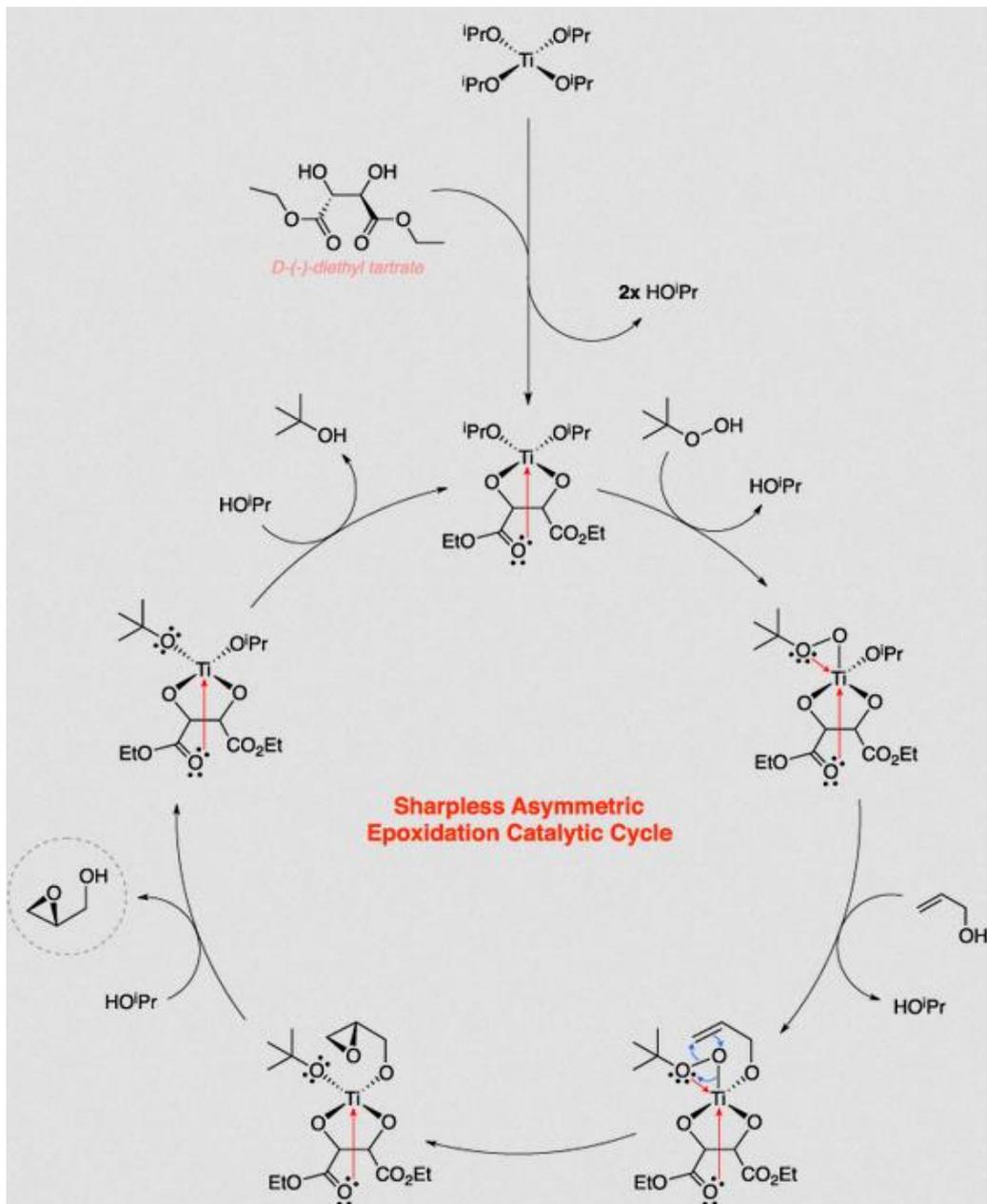
Mechanism of AE
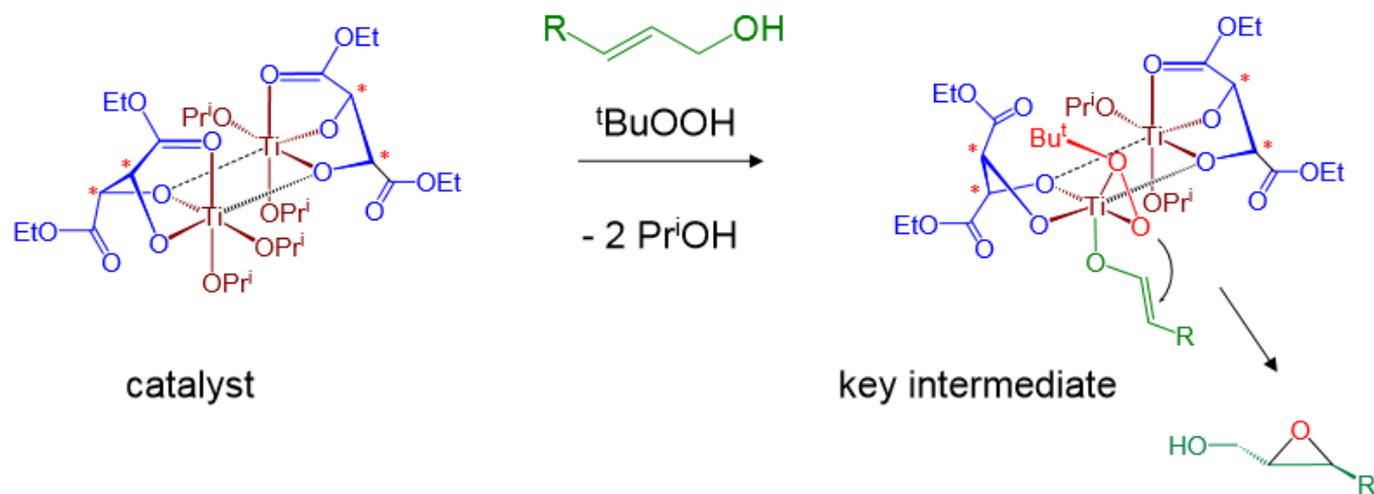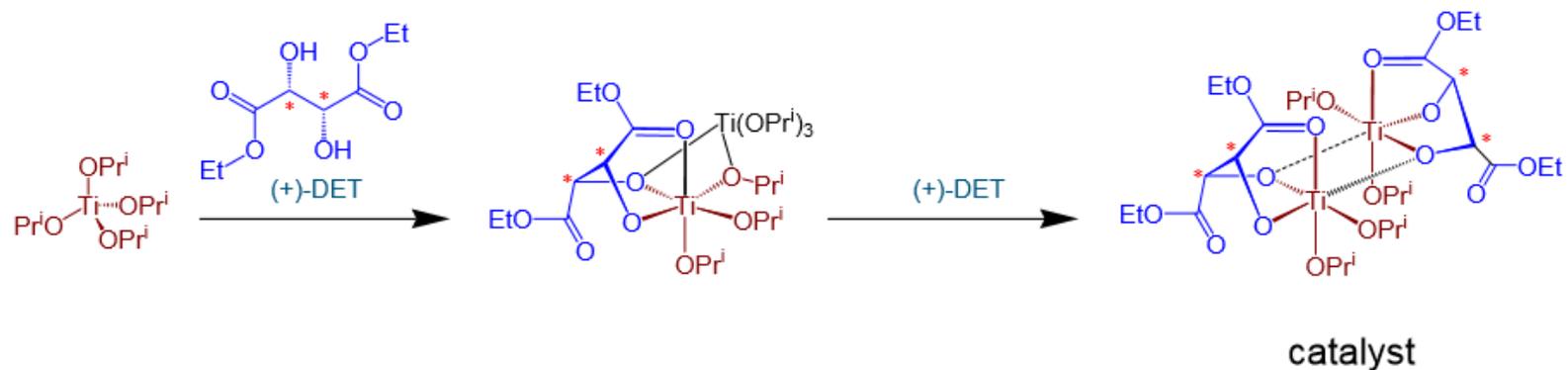
reattività del substrato

#	substrato	velocità relativa
1		0.048
2		0.060
3		0.220
4		0.420
5		1.00
6		1.20
7		4.38
8		1.48
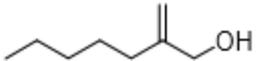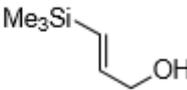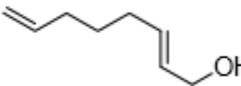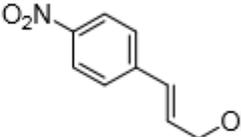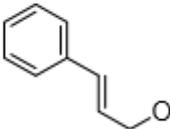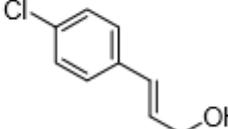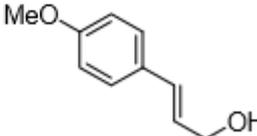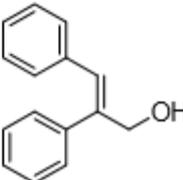
*L'alchene agisce da NUCLEOFILO*

REATTIVITA' del SUBSTRATO
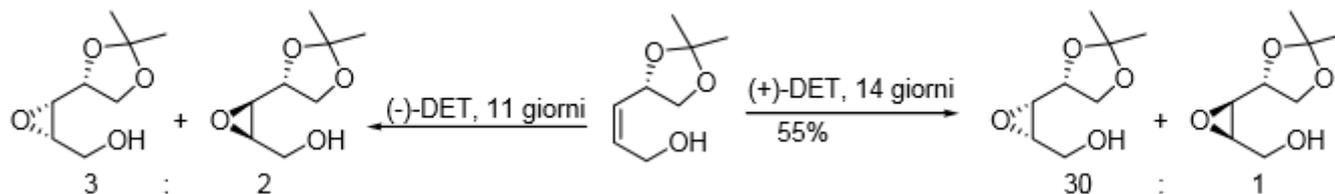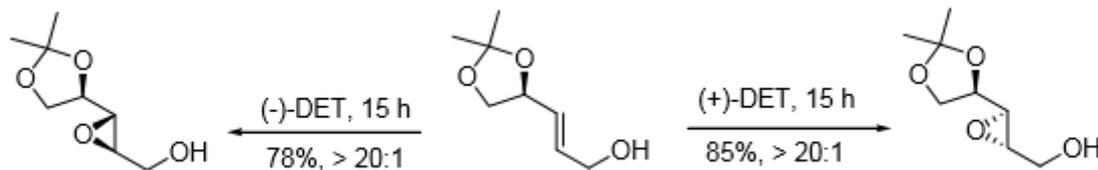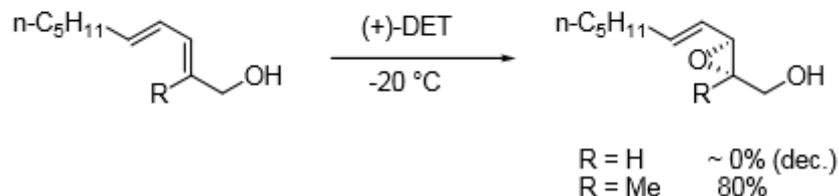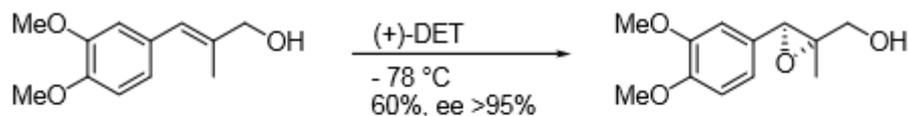
NB: cis-trans ≠ E-Z (Cahn-Ingold-Prelog) le lettere E e Z sono iniziali di *entgegen* (opposti) e *zusammen* (insieme), ruspettivamente. Indicano la posizione dei gruppi a maggior priorità (regole Cahn-Ingold-Prelog), rispetto al doppio legame. *Se i gruppi a più alta priorità si trovano dalla stessa parte rispetto al doppio legame, il nome del composto è preceduto dalla lettera Z*; in caso contrario si antepone la lettera E.

substrati *Z sostituiti reagiscono meno* (o per nulla!)
e con minor selettività, rispetto a quelli *(E) sostituiti*

Sharpless AE

Substitution patterns:
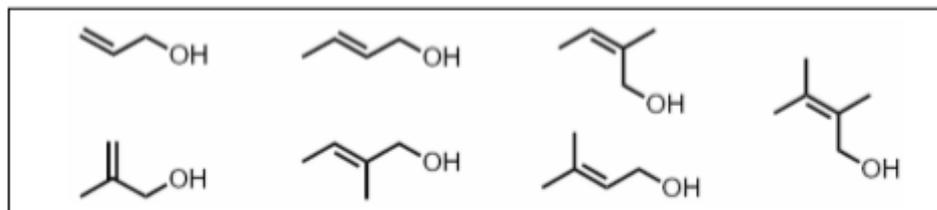
Z-disubstituted olefins are less reactive and selective:
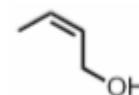
"I was inspired by enzymes. They take one olefin or two olefins and do their asymmetric magic. I thought, we can do that. If we find a good system, we'll need six catalysts – one for each class of olefins. But what really blew us away was that the titanium catalyst worked for every one – for all six classes!" Sharpless in interview to *Science Watch* **1995.**

Disubstituted:

(+)-DET, TBHP
CH_2Cl_2, -20 °C

> 90 % ee
60 - 70 % yield

Trisubstituted:

(+)-DET, TBHP

> 98 % ee
79 % yield

Disubstituted:

(+)-DET, TBHP

95 % ee
88 % yield

Tetrasubstituted:

(+)-DET, TBHP

> 94 % ee
90 % yield **7**
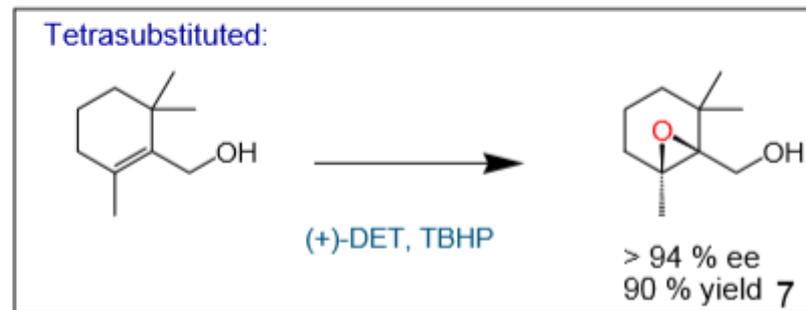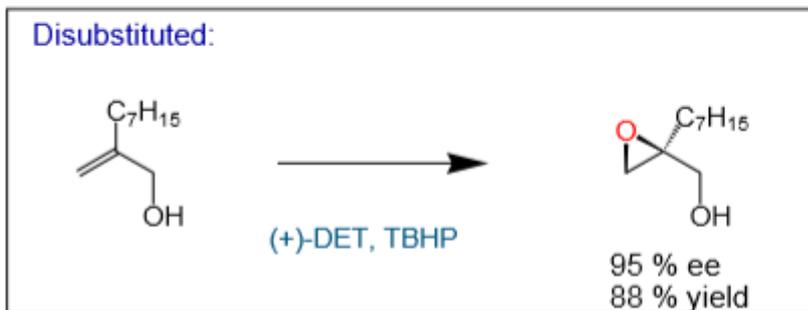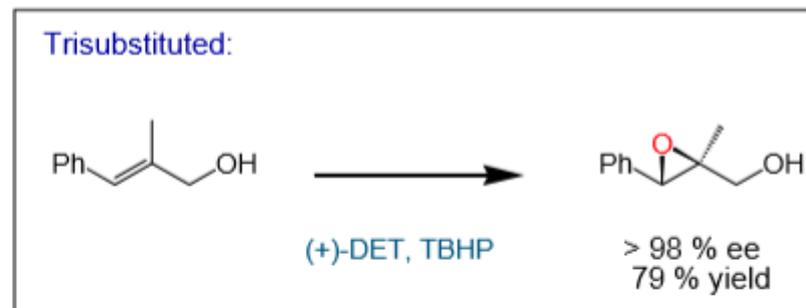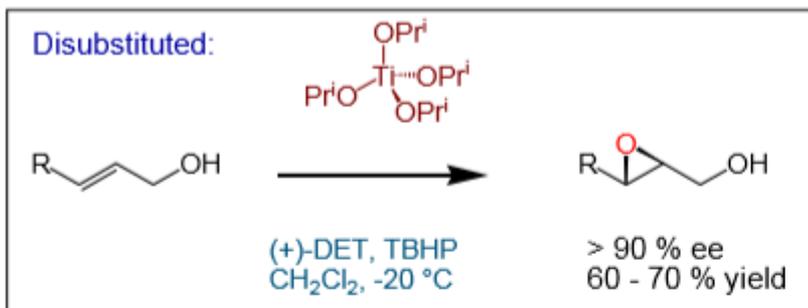
Sharpless AE - examples

product	Ti(%)	tartarate (%)	°C	h	yield (%)	ee (%)
(epoxy-CH₂OH)	5	(+)-DIPT (6.0)	0	2	65	90
Ph–(epoxy-CH₂OH)	5	(+)-DIPT (7.5)	−20	3	89	>98
Pr–(epoxy-CH₂OH)	4.7	(+)-DET (5.9)	−12	11	88	95
C₇H₁₅–(epoxy-CH₂OH)	10	(+)-DET (14)	−10	29	74	86
Ph–CH₃(epoxy-CH₂OH)	5	(+)-DIPT (7.5)	−35	2	79	>98
BnO–CH₃(epoxy-CH₂OH)	100	(+)-DET (142)	−20	14	80	80
H₃C–CH₃ / CH₃ epoxy-CH₂OH	5	(+)-DET (7.4)	−20	0.75	95	91
Ph–CH₃ / Ph epoxy-CH₂OH	120	(−)-DET (150)	−20	5	90	94
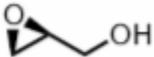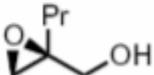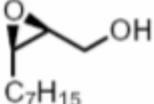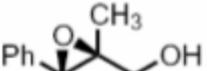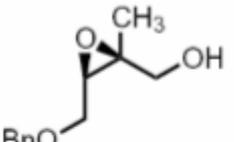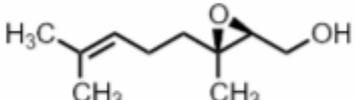
JACS **1987**, *109*, 5765; *Catalytic Asymmetric Synthesis* **1993**, 103-158.

● compatibilita' di gruppi funzionali

| gruppi funzionali compatibili	gruppi funzionali **non** compatibili
acetali, chetali, aldeidi e chetoni alcoli (se in posizione remota) alcheni, alchini ammidi, azidi, idrazidi esteri carbossilici epossidi, eteri nitrili, nitro, piridine silil eteri solfoni e solfossidi tetrazoli uree e uretani	ammine acidi carbossilici tioli fenoli (la maggior parte) fosfine

● uso per la risoluzione di alcoli allilici

● ossidazione di alcoli omoallilici

● condizioni di reazione

● rapporto titanio: legante 1: ≥1.2

un eccesso di DET rallenta la reazione perchè va ad occupare il sito catalitico sul titanio

$$Ti(OR)_4(tartrato)_2 \rightleftarrows Ti(tartrato)_4$$

"attivo"   "inattivo"
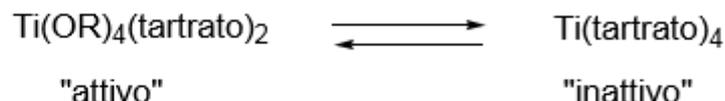
● la presenza di acqua (presente nel TBHP) rallenta la reazione e fa diminuire l'enantioselettività

di solito si allontana dopo mescolamento del TBHP con il solvente organico CH_2Cl_2, DCE, benzene, toluene o eptano e distillazione dell'azeotropo

oppure si usa cumene idroperossido commerciale senza ulteriori trattamenti

● di solito si usano 1.5 – 2 eqivalenti di ossidante per avere reazioni più veloci

● la presenza di setacci molecolari 3- o 4Å aumentano incredibilmente l'attività e quindi consentono l'uso di quantità catalitiche 5% di calizzatore

MIGLIORAMENTI della REAZIONE

Ci sono molte aree da poter migliorare, soprattutto osservando la prima reazione riportata.

Ad esempio potenziali problemi sono:

1. Necessità di quantità quasi stoichiometriche di catalizzatore

2. Substrati solubili in acqua sono difficilmente isolabili dopo la reazione

3. Necessità di usare basse temperature (con alti costi su larga scala)

4. Alcuni substrati reagiscono con bassissime velocità

MIGLIORAMENTI della REAZIONE

Uso dei SETACCI MOLECOLARI.

Inizialmente la reazione richiedeva quantità quasi Stechiometriche del catalizzatore. L'**ACQUA:**

- **Distrugge il catalizzaatore**
- **Apre l'epossido (agendo da nucleofilo)**

I setacci molecolari assorbono l'acqua e permettono di usare quantità catalitiche del catalizzatore (ca. 10%), riducendo i costi e rendendo la reazione più efficiente.
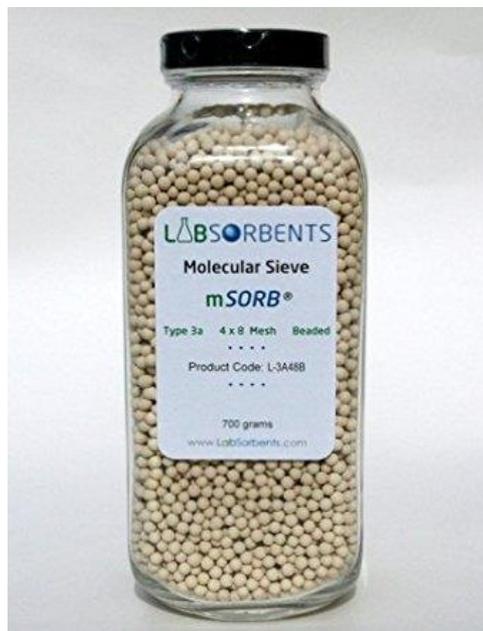
- Utilizzando le condizioni del primo lavoro di Sharples su AE per produrre 100 kg di (R)-glicidolo
  sarebbero stati necessari 380 kg di Ti (OiPr)$_4$ e 275 kg di D-(-)-dietiltartrato
  considerando poi il costo dei reagenti, la difficoltà per isolare i prodotti e gli scarti risulta che il
  processo non può essere utilizzato a livello industriale

  - In presenza di setacci molecolari: per 100 kg di (R)-glicidolo servirebbero 20 kg di Ti (OiPr)$_4$
    e 15 kg di D-(-)-dietiltartrato con l'aggiunta di 40 kg di setacci molecolari che costano poco
    e sono facilmente riciclabili.

- ARCO Chemical ha iniziato nel 1986 a comercializzare prodotti ottenuti con il metodo di Sharpless.

(S,S)-(-)-DET
non naturale

HO,,,, CO₂Et
HO CO_2Et

[O]

R²=R¹

R² —— R¹

R³

R³ —— OH (epoxide, top right)

Ti(Oi-Pr)₄
TBHP, CH₂Cl₂

R²
R³

R¹
OH

[O]

(R,R)-(+)-DET
naturale

HO, CO₂Et
HO CO_2Et

R²
R³

R¹
OH
O
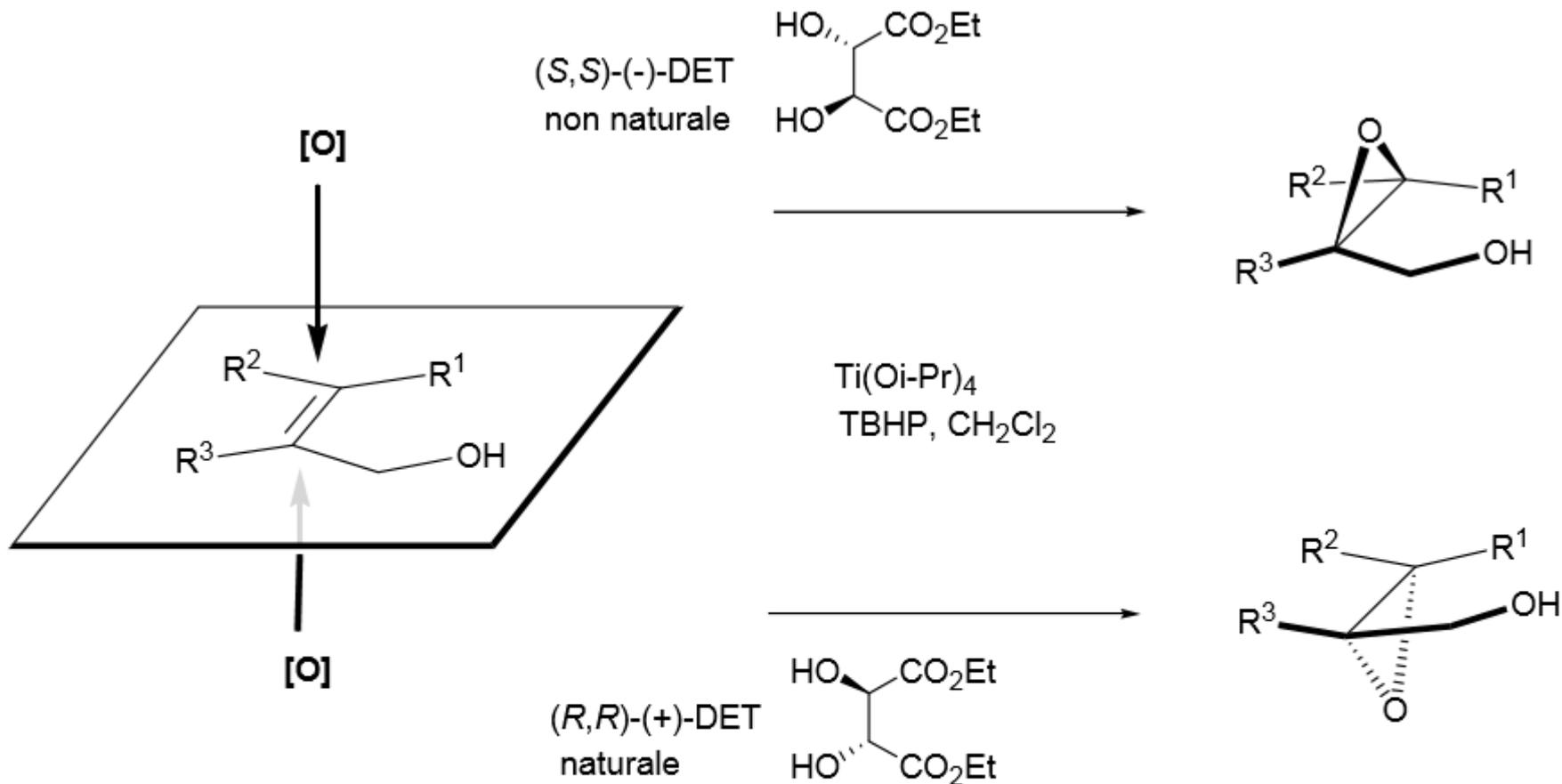
• altri leganti sono usati come il DMT e il DIPT
• altri ossidanti come il cumilidroperossido danno ottimi risultati

• meccanismo: *J. Am. Chem. Soc.* **1991**, *113*, 106 and 113.

# Diagramma di flusso per la produzione del glicidolo

riducente

| sistema di raffreddamento | sistema di rilascio in sicurezza | riduzione del perossido | → recupero del solvente |

perossido

filtro

reattore

H₂O

glicidolo

recupero del prodotto (estrazione) — glicidolo in acqua → distillazione — glicidolo crudo → purificazione

solvente

reagenti

catalizzatore

setacci molecolari

impurezze
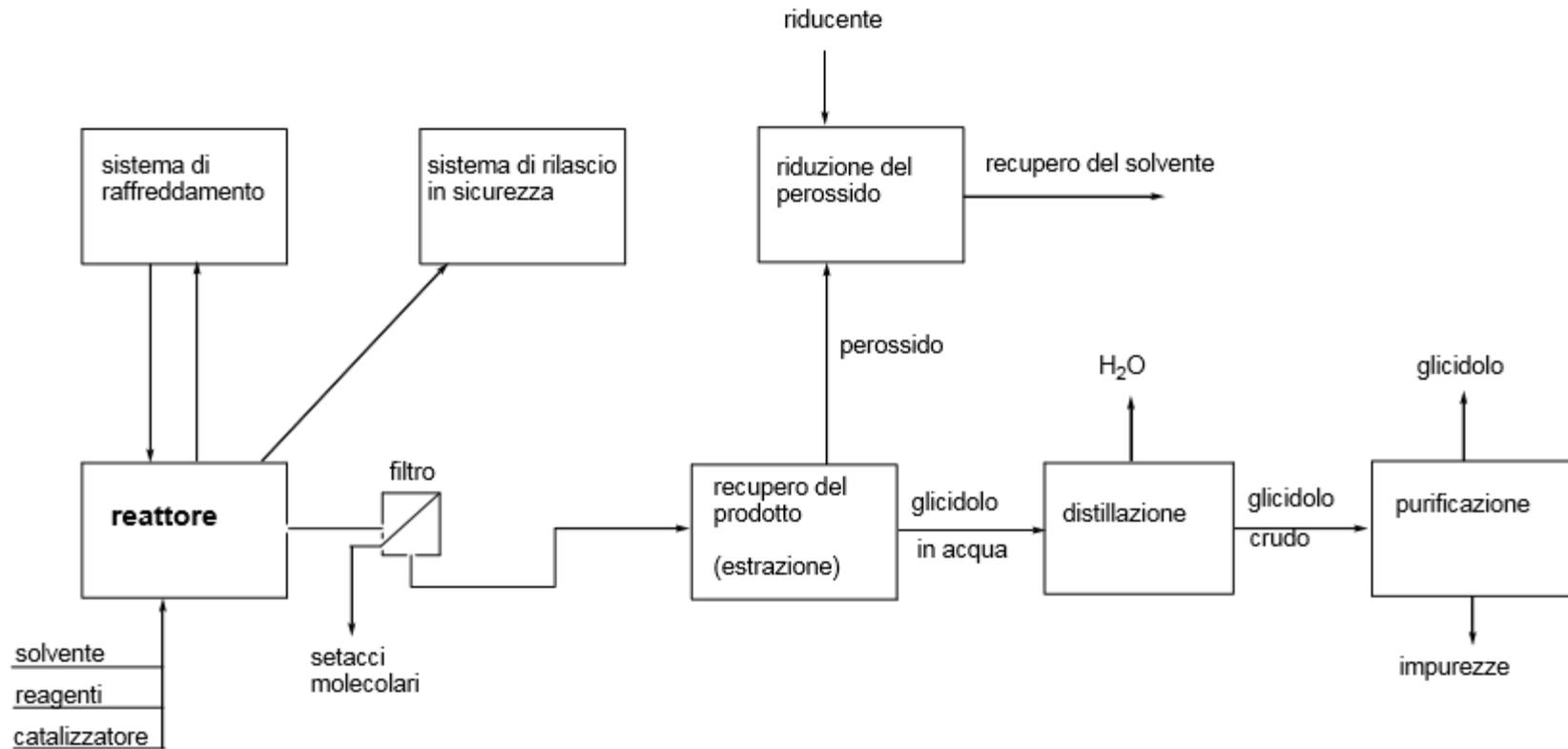
Cumilidroperossido come ossidante

MIGLIORAMENTI della REAZIONE

Ancoraggio del catalizzatore su supporto solido.

L'ncoraggio su un supporto solido (polimero come polistirene, oppure gel di silice) rende la reazione **eterogenea** e permette:

- un agile recupero del catalizzatore

- di lavorare in flusso (processo continuo) su scala industriale

- combinare i vantaggi del supporto solido con l'informazione chirale inserendo il tartrato nel polimero:
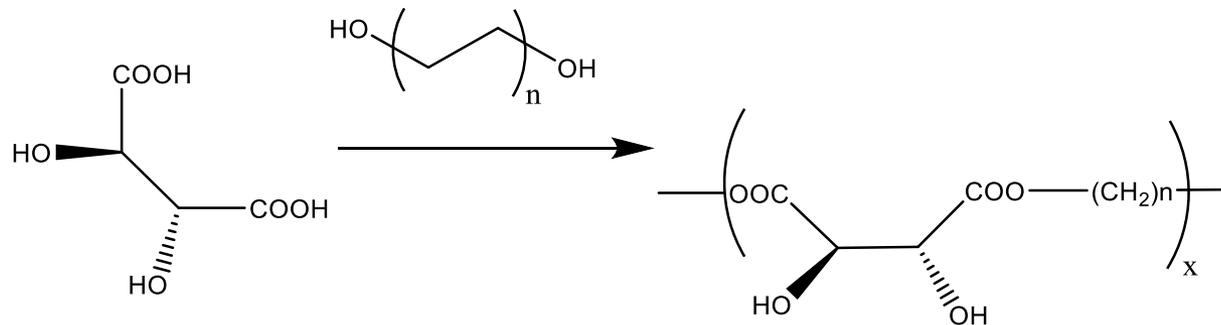
APPLICAZIONI

# composti di interesse farmaceutico accessibili dal glicidolo otticamente attivo
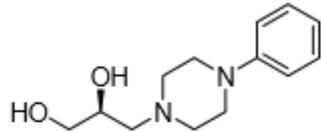
Levo-Dropropizine
Anti-tosse
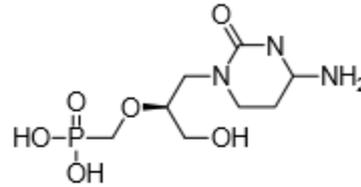
Cidofovir
AIDS
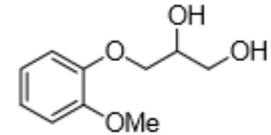
**Guaifenesin**
Anti-tosse
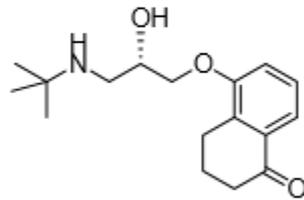
Levobunolol
oftalmico
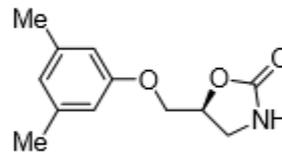
Metaxalone
Rilassante muscolare
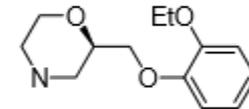
Viloxazine
Anti-depressivo
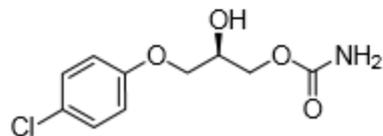
Chlorophenesin carbamate
Rilassante muscolare

10
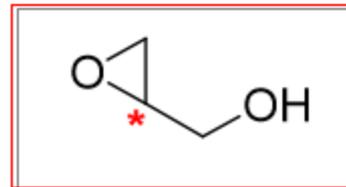
Applications in Synthesis:

RO⌐⌐⌐OH (R = CHPh₂) → Ti(O*i*-Pr)₄, (+)-DIPT / TBHP, –20 °C → epoxide, 92%, >95% ee

PhSH, NaOH, H₂O/*t*-BuOH, Δ → 71%

RO⌐⌐(OH)(OH)SPh

1. 2,2-dimethoxypropane, cat. POCl₃
2. *m*-CPBA, –78 °C
3. Ac₂O, NaOAc, Δ

93%, 3-steps → acetonide OAc SPh intermediate

K₂CO₃, CH₃OH, 25 °C → 100% → **syn** aldehyde

DIBAL-H, CH₂Cl₂, –78 °C → 91% → **anti** aldehyde

• HWE-olefination, reduction, and AE provides an iterative route to the synthesis of polyols.
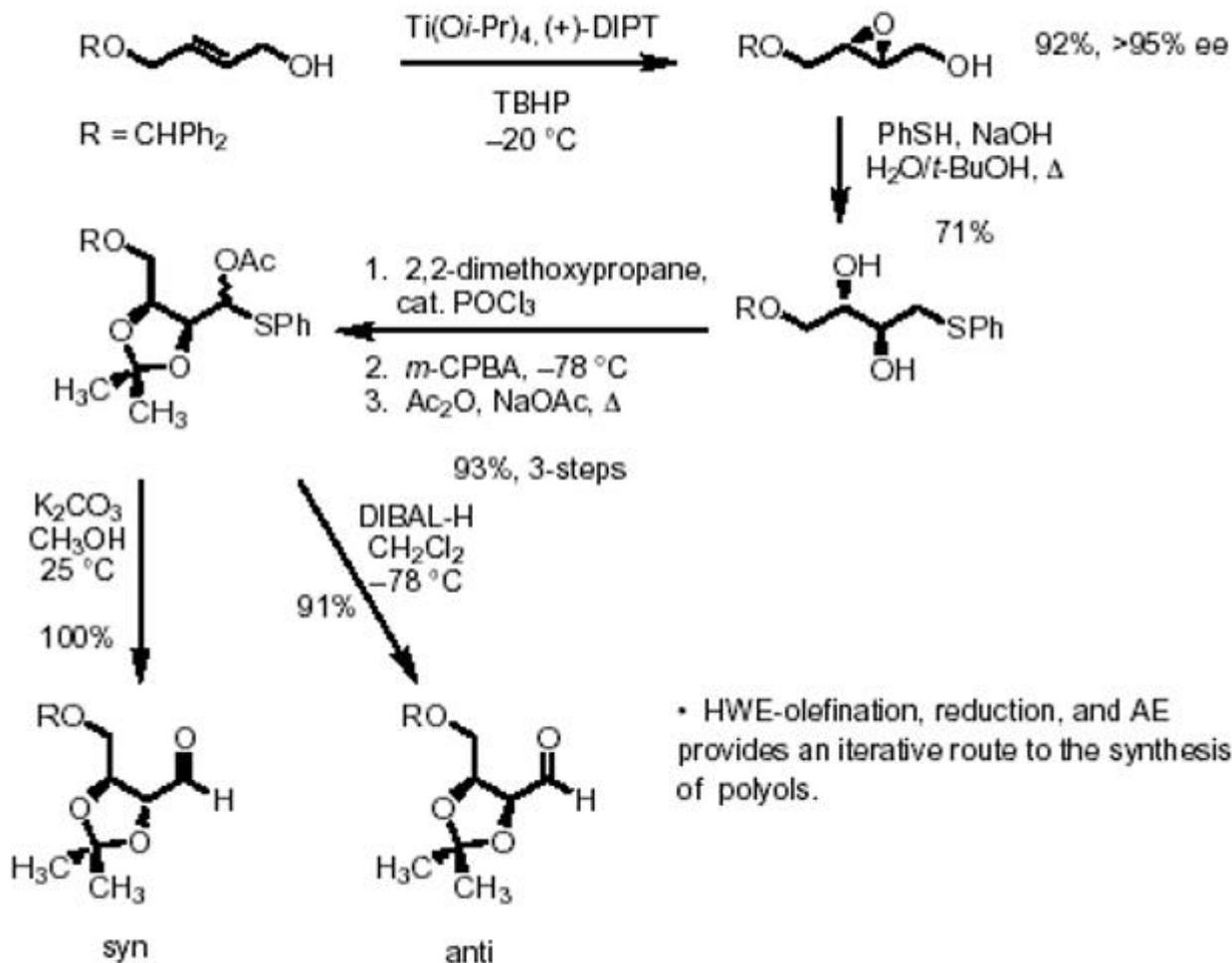
Ko, S. Y.; Lee, A. W. M.; Masamune, S; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* 1990, *46*, 245-264.
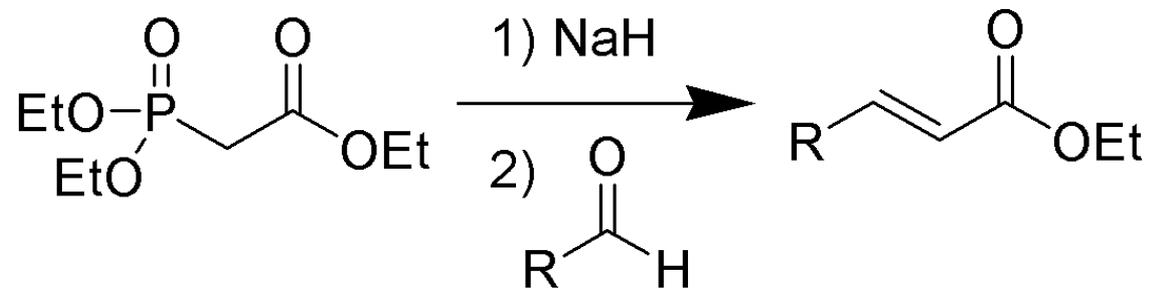
Horner-Wadsworth-Emmons

(ii) Synthesis of other sensitive biologically active compounds

In an industrial process, the American Company, J. T. Baker, employs this process to make synthetic disparlure, which is the pheromone of the gypsy moth (**Scheme 17**).
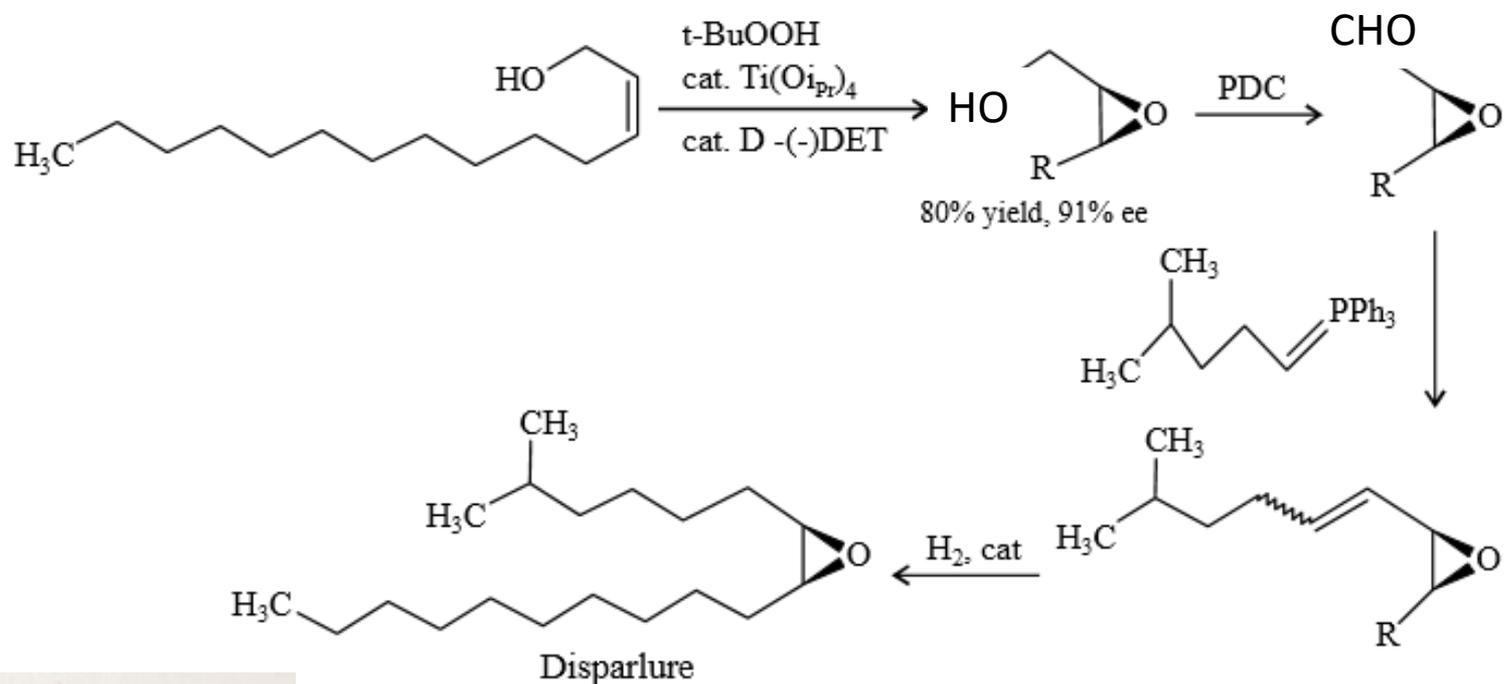
Scheme 17

Falena infestante alberi della frutta

Sintesi totale del Disparlure in 4 steps:
B.E. Kossier *et al. JACS* **1981**, *103*, 464