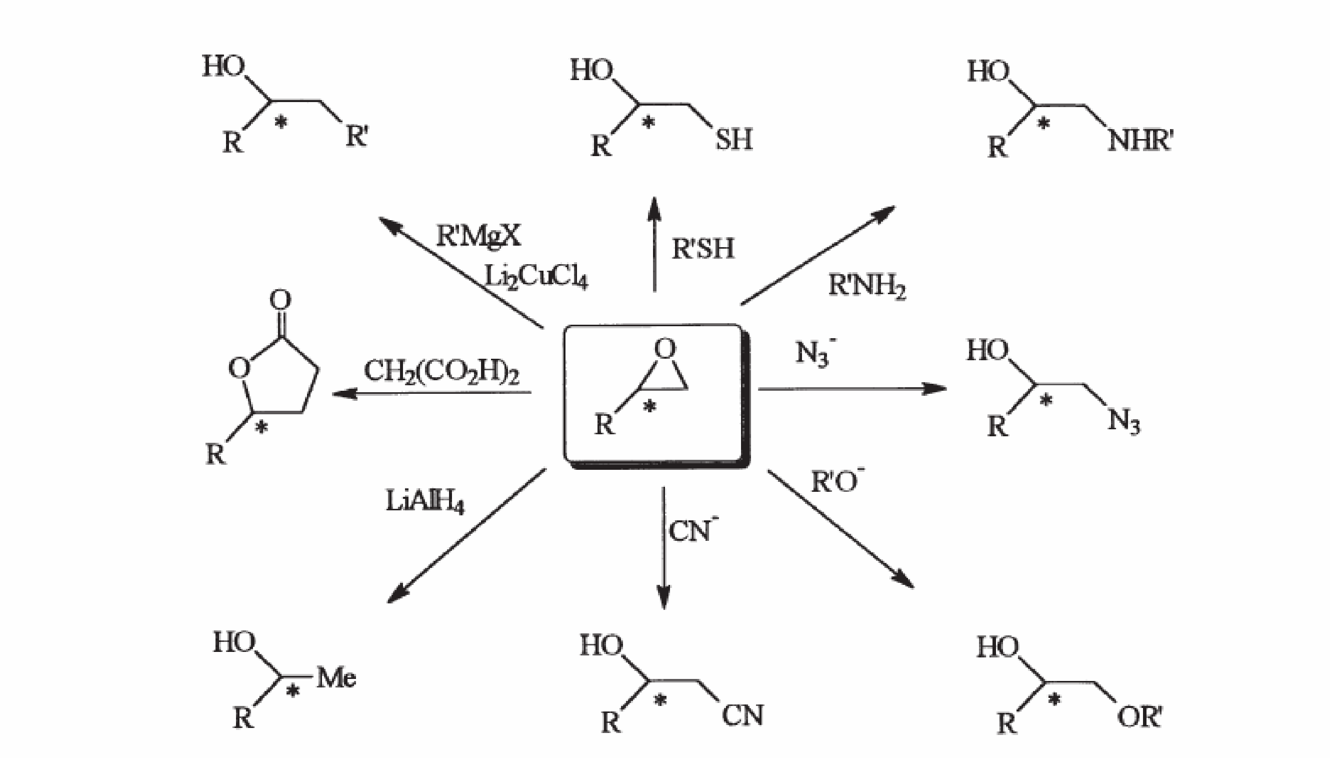
A Short Story about Epoxidations



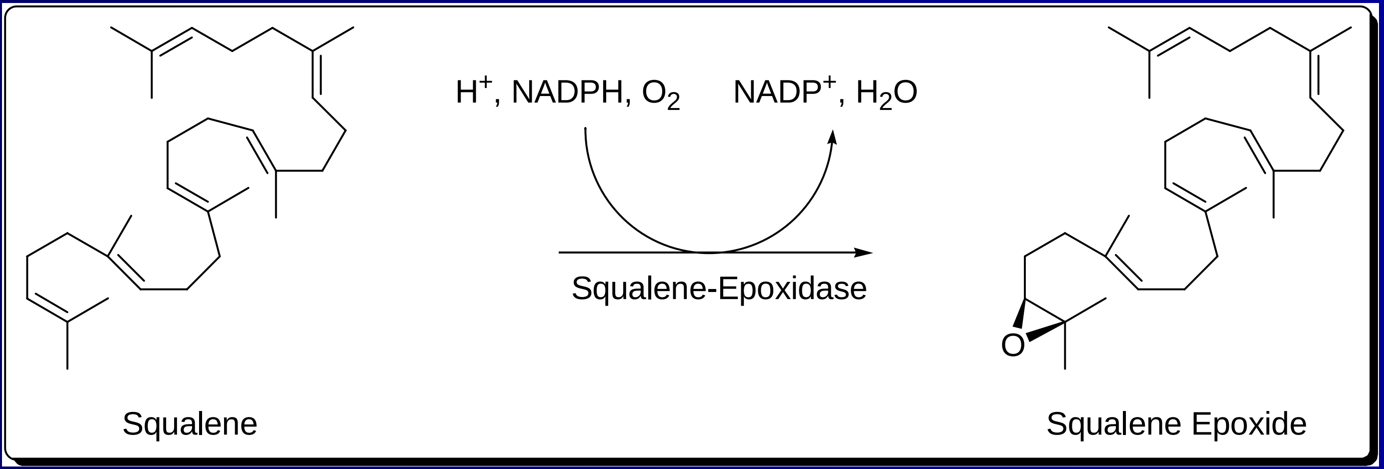
Content:

- Epoxidations mediated by Enzymes
- Developments in Chemical Epoxidations
  - Epoxidations with Peracids, Dioxiranes, Oxaziridines &
  - Jacobsen-Katsuki-Epoxidation
  - Shi-Epoxidation
  - Chlorohydrine-Procedure
  - Halcon-Procedure
  - Sharpless-Epoxidation

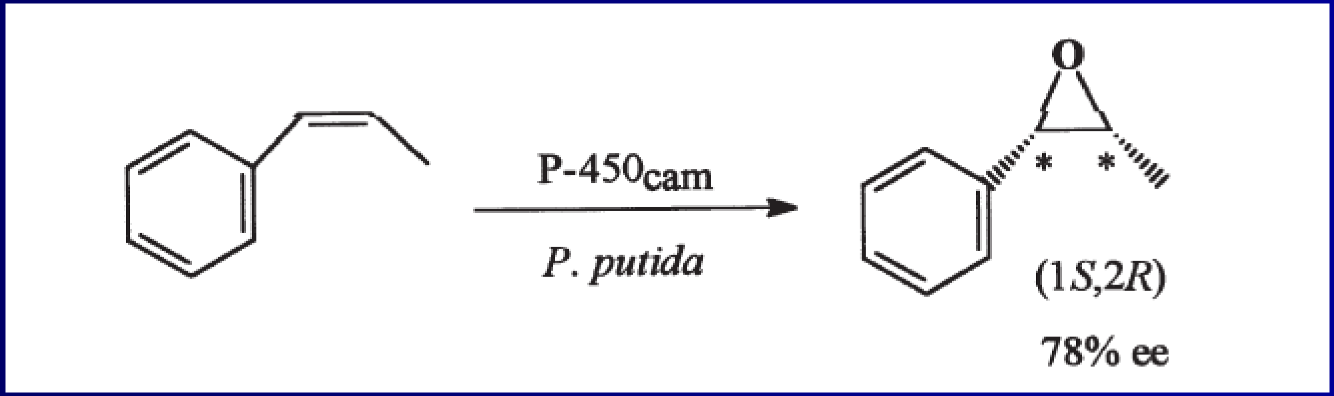
- Summary

Epoxidations in biological systems and natural occuring structures

Epoxidation of Squalene in the Steroid Biosynthesis

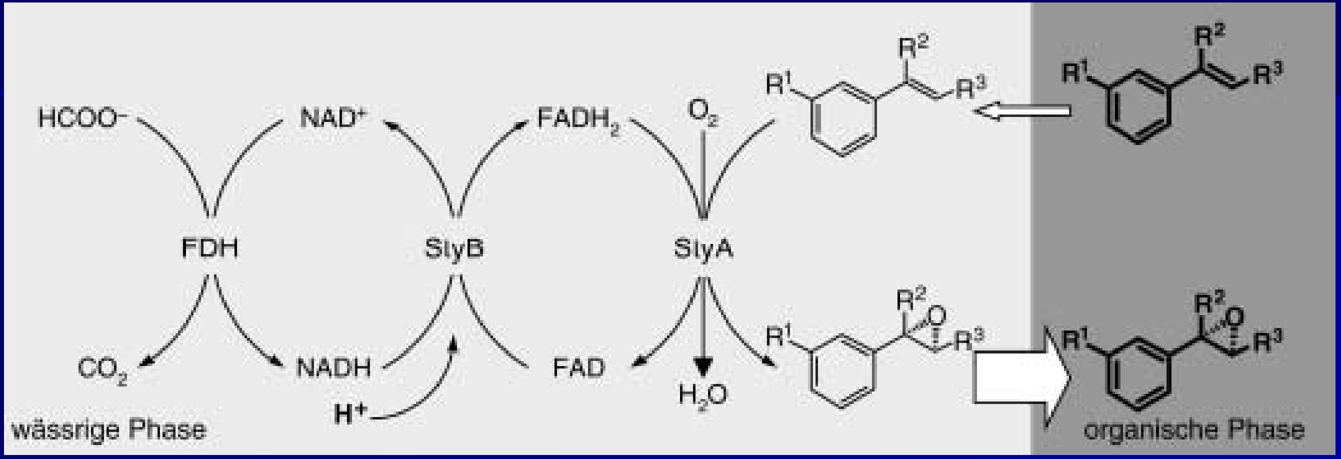


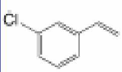
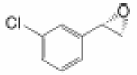
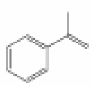
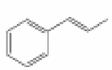
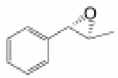
Stereoselective Epoxidation of *cis-β-*methylstyrene using Cytochrome P-450_{cam} from Pseudomonas putida



Ortiz de Montellano, P.R. et. *al J. Am. Chem. Soc.* **1991**, *113*, 3195 – 3198

Biocatalytic Epoxidation of Styrene in a two-phase System



Edukt	Produkt	Eduktkonz. [mM]	Umsatz [%]	P_0 [U g^{-1}][a]	P_D [U g^{-1}][b]	TN_{StyA}[c]	TN_{NAD+}[d]	*ee*	Ausbeute nach Produktreinigung [%]
 1	 1a	50 (+25)[e]	90.5	108	48	2171	66	> 99.9	73
 2	 2a	50	87.9	112	44	1844	56	98.1	75
 3	 3a	50 (+19)[e]	95.3	118	66	2867	87	99.7	87

[a] Anfangsproduktivität P_0: Aktivität in den ersten 30 Minuten der Reaktion. [b] Durchschnittliche Produktivität P_D: Durchschnittliche Aktivität, die über die gesamte Reaktionsdauer gemessen wurde. [c] TN_{StyA}: Wechselzahl für StyA = (Mol gebildetes Produkt) (Mol eingesetztes StyA)$^{-1}$ [d] TN_{NAD+}: Wechselzahl für NAD$^+$ = (Mol gebildetes Produkt) (Mol eingesetztes NAD$^+$)$^{-1}$ [e] In Klammern ist die Substratmenge angegeben, die während der Reaktion zugegeben wurde.

Schmidt, A. et *al* *Angew. Chem.* **2004**, *116,* 2215 – 2218

Asymmetric epoxidation reactions catalyzed by Chloroperoxidase (CPO)

Substrates	ee epoxides (%)	Absolute configuration (epoxide)	Epoxide yield (%)
cis-2-heptene	96	2*R*,3*S*	78
cis-2-octene	92	2*R*,3*S*	82
cis-2-methylstyrene	96	1*S*,2*R*	67
1,2-dihydronaphtalene	97	1*R*,2*R*	85
styrene	49	*R*	23
p-chlorostyrene	66	*R*	35
p-bromostyrene	68	*R*	30
p-nitrostyrene	28	*R*	5
α-methylstyrene	89	*R*	55
$PhOCH_2C(CH_3)= CH_2$	89	*R*	22
2-methyl-heptene	95	*R*	23
$EtCO_2CH_2C(CH_3)=CH_2$	94	*R*	34
3-bromo-2methyl-1-propene	62	S	61
4-bromo-2-methyl-1-butene	88	*R*	93
5-bromo-2-methyl-1-pentene	95	*R*	89
6-bromo-2-methyl-1-hexene	87	*R*	33
7-bromo-2-methyl-1-heptene	50	*R*	42

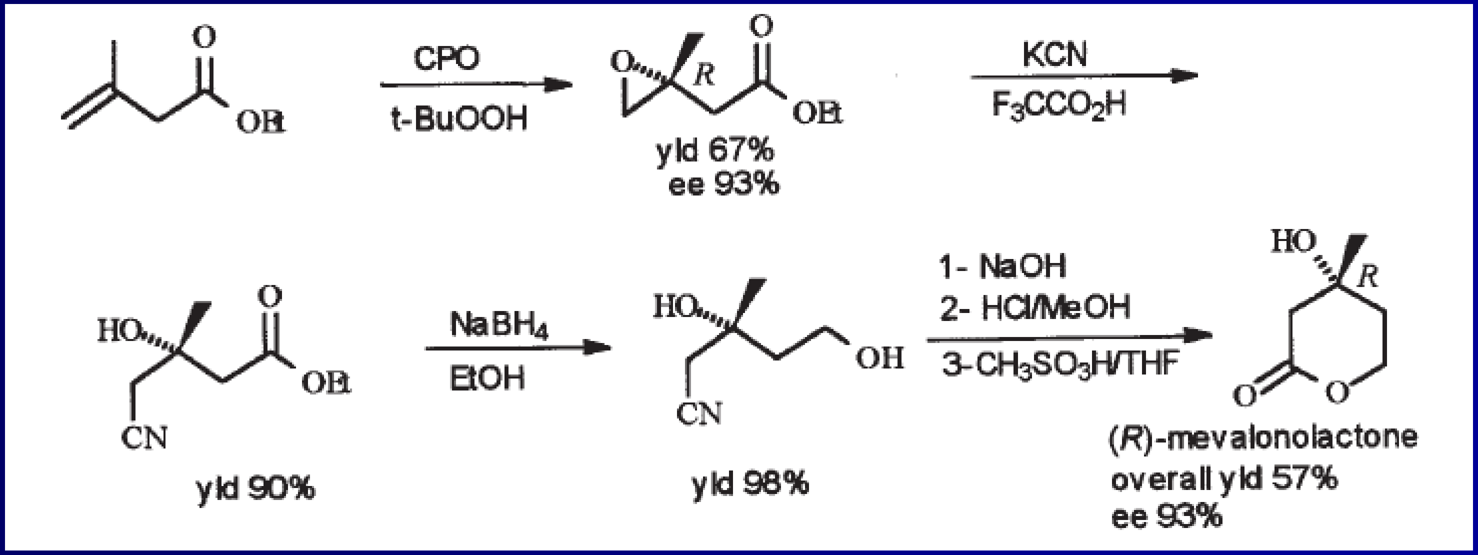
Entry 1-4: Jacobsen, E.N. et *al. J. Am. Chem. Soc.* **1993**, *115*, 4415 – 4416

Entry 5-8: Colonna, S. et *al. Tetrahedron: Asymmetry* **1993**, *4*, 1325 – 1330

Entry 9-12: Dexter, A.F. et *al. J. Am. Chem. Soc.* **1995**, *117*, 6412 – 6413

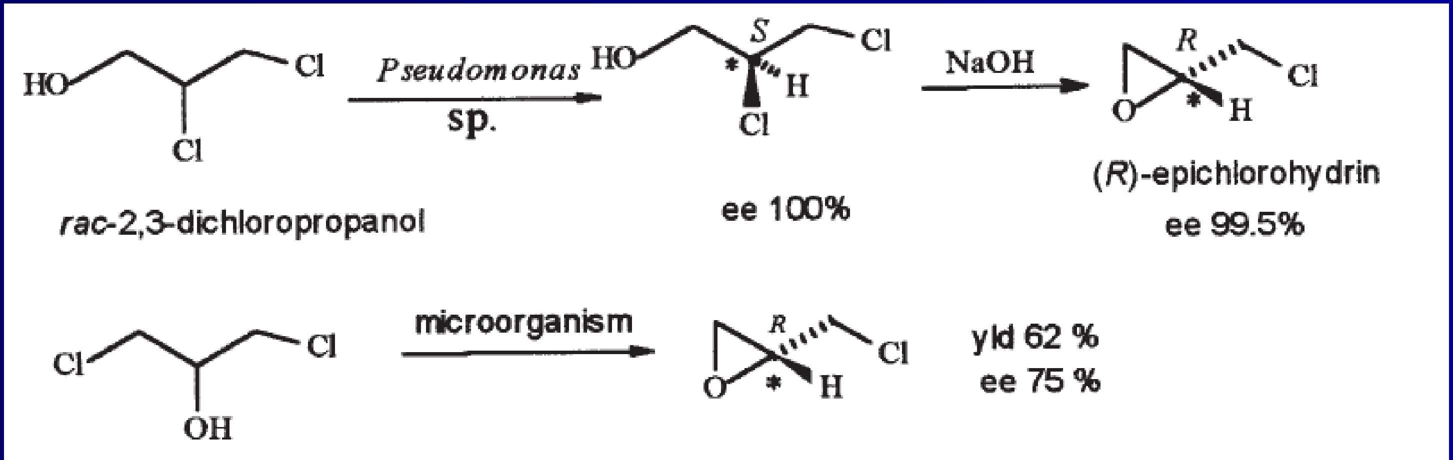
Entry 13-17: Lakner, F.J. et *al. J. Am. Chem. Soc.* **1997**, *119*, 443 – 444

Synthesis of (*R*)-mevalonolactone through stereoselective bioepoxidation of methallylproprionate using CPO



Lakner, F.J. et *al. J. Org. Chem.* **1996**, *61*, 3923 – 3935

Enantioselective degradation of halohydrines: Synthesis of (*R*)-epichlorohydrine

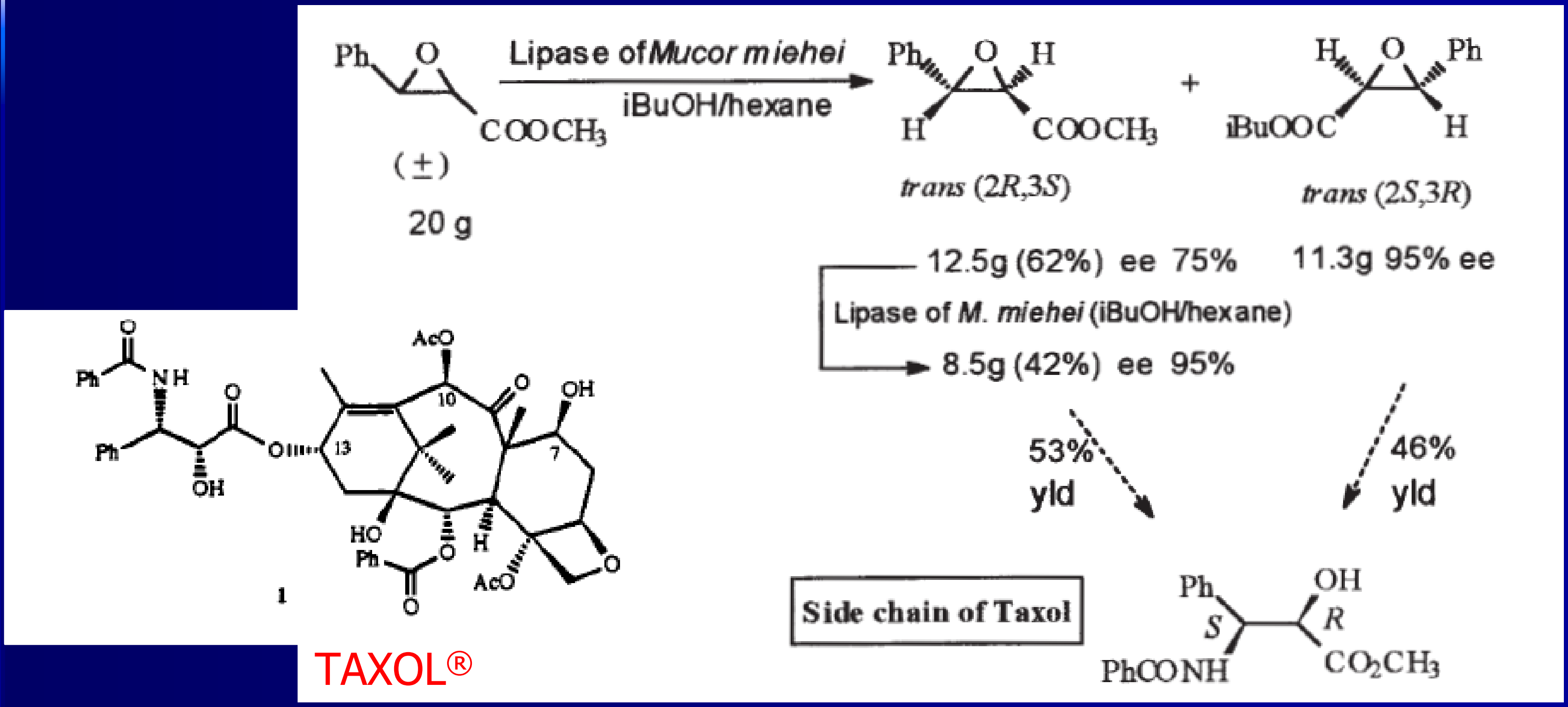


Kasai, N. et *al. J. Indust. Microbiol. Biotech.* **1992**, *9*, 97 – 101;

Nagasawa, T. et *al. Appl. Microbiol. Biotechnol.* **1992**, *36*, 478;

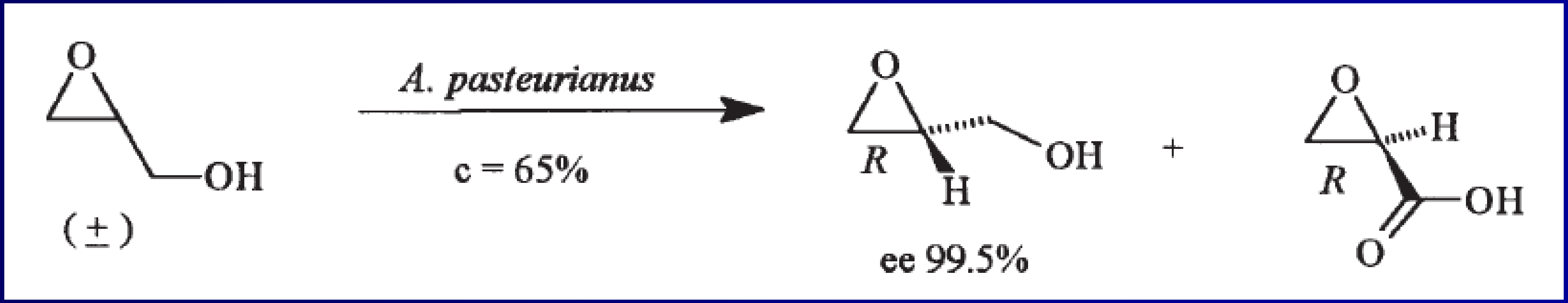
Nakamura, T. et *al. Agric. Biol. Chem.* **1991**, *55*, 1931.

Transesterification of Epoxide-bearing Substrates using Lipases in the Synthesis of the side chain of TAXOL®



Gou, D.M. et *al. J. Org. Chem.* **1993**, *58*, 1287 – 1289

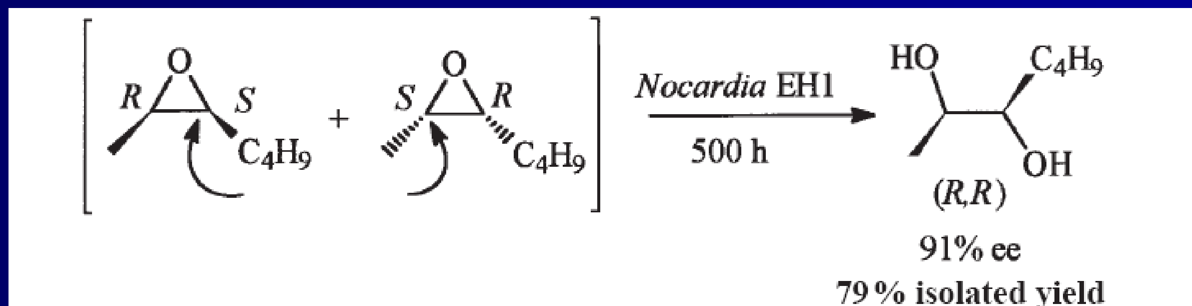
Kinetic resolution via biotransformation



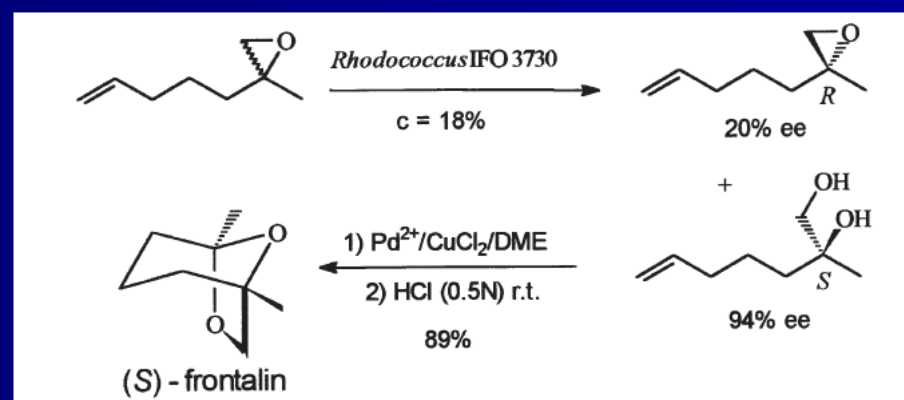
Machado, S.S. et *al.* **1999**, *International Conference on Biotechnology for Industrial Production of Fine Chemicals. Zermatt, Switzerland*

Use of Bacterial Enzymes

- Deracemisation of (±)-*cis*-2,3-epoxyheptane via enantioselective biohydrolysis



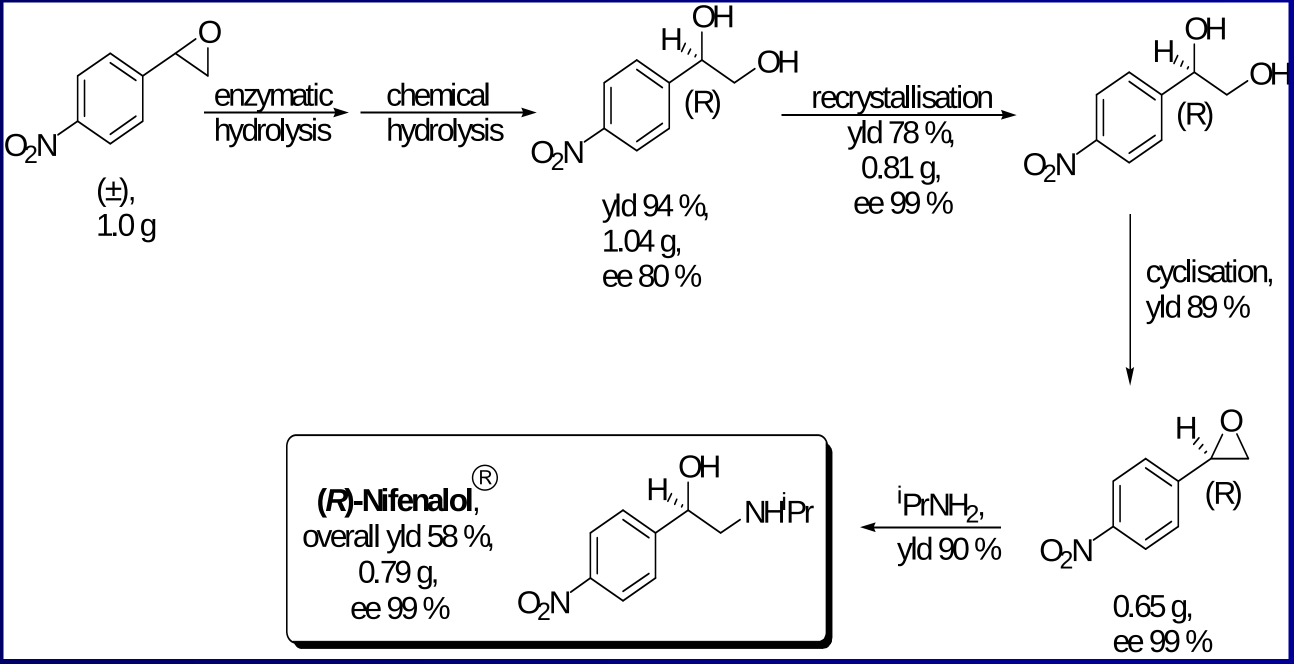
- Chemoenzymatic Synthesis of (*S*)-Frontalin



Faber, K. et *al. Tetrahedron Lett.* **1996**, *37*, 8379 – 8382; *Synthesis* **1997**, *156.*

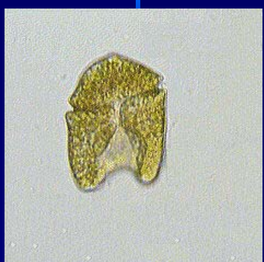
Chemoenzymatic Deracemisation of *p*-Nitrostyreneoxide in the Synthesis of (*R*)-Nifenalol®

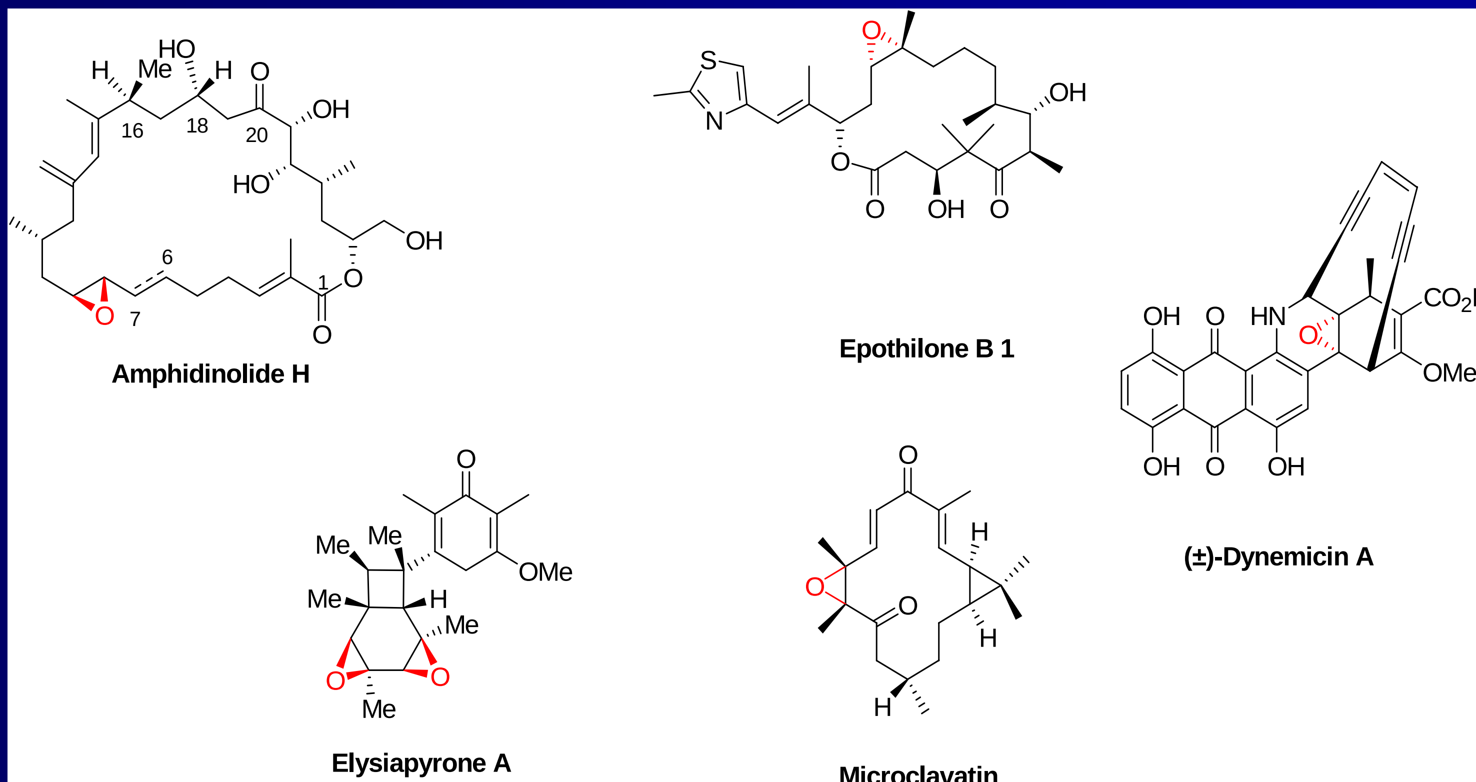
β-Recptor blocker



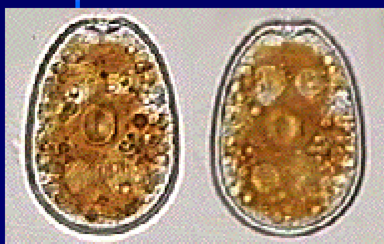
Furstoss, R. et *al.* *Tetrahedron* **1997**, *53*, 9707 – 9714.

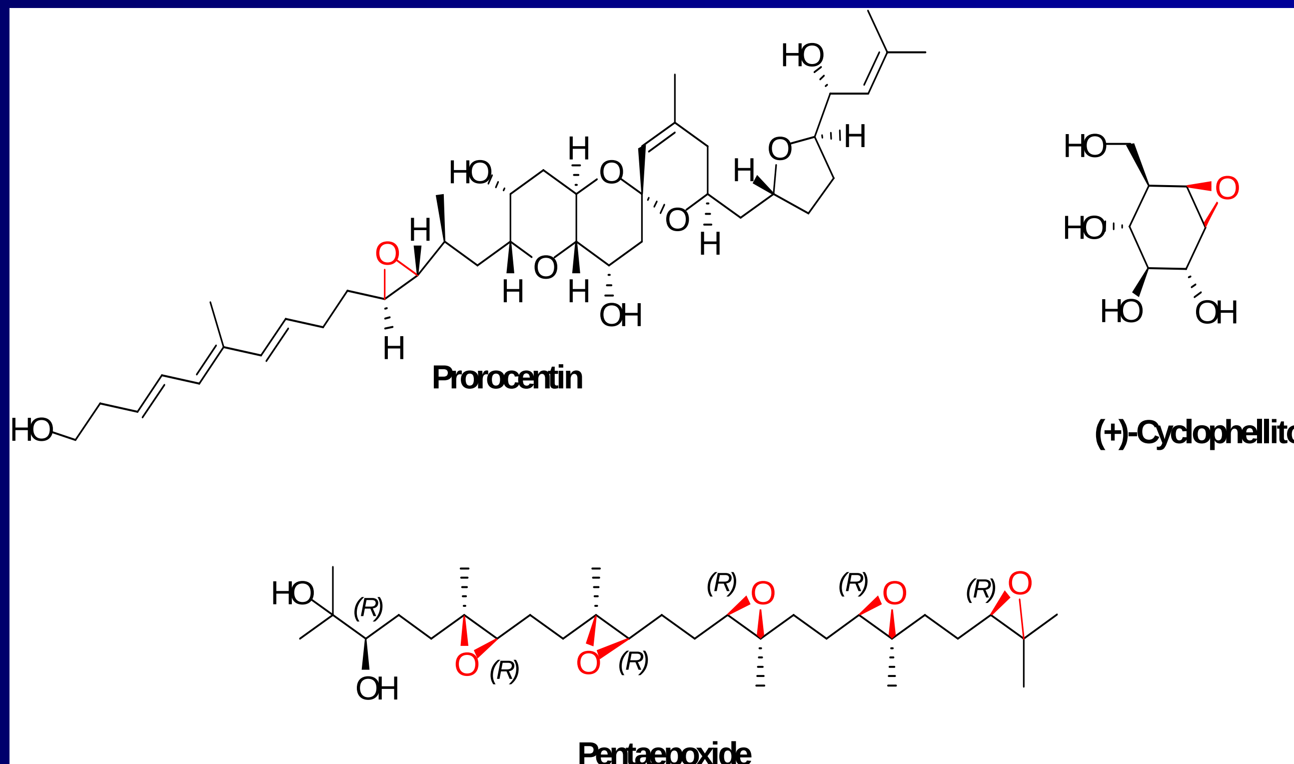
Selected Natural Products containing one or more Epoxide-Subunit(s)





Selected Natural Products containing one or more Epoxide-Subunit





Developments in Chemical Epoxidations

Methods for Chemical Epoxidations:

- Epoxidations with Dioxiranes, Oxaziridines & Air
- Jacobsen-Katsuki-Epoxidation
- Shi-Epoxidation
- Epoxidations with Peracids
- Chlorohydrine-Procedure
- Halcon-Procedure
- Sharpless-Epoxidation

Epoxidations with chiral Peracids or chiral Dioxiranes & Oxaziridines

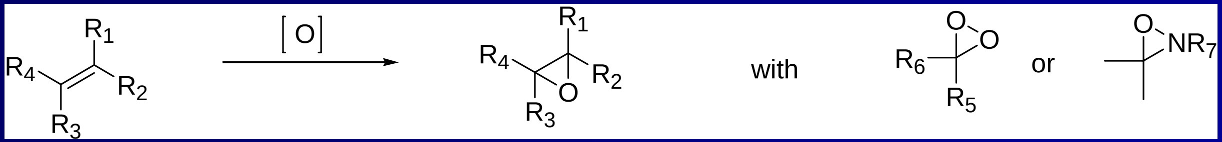
Asymmetric Epoxidations using chirale Peracids:

Disadvantages:

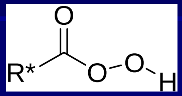
low ee-values (≤ 20%) with Peracids

→ stereogenic center seems to be to far away from the reaction center → no significant energy discrimination concerning the diastereomorphic transitionstate

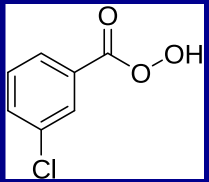
With Dioxiranes or Oxaziridines ee-values up to 73% are possible



Prileshaev-Epoxidation

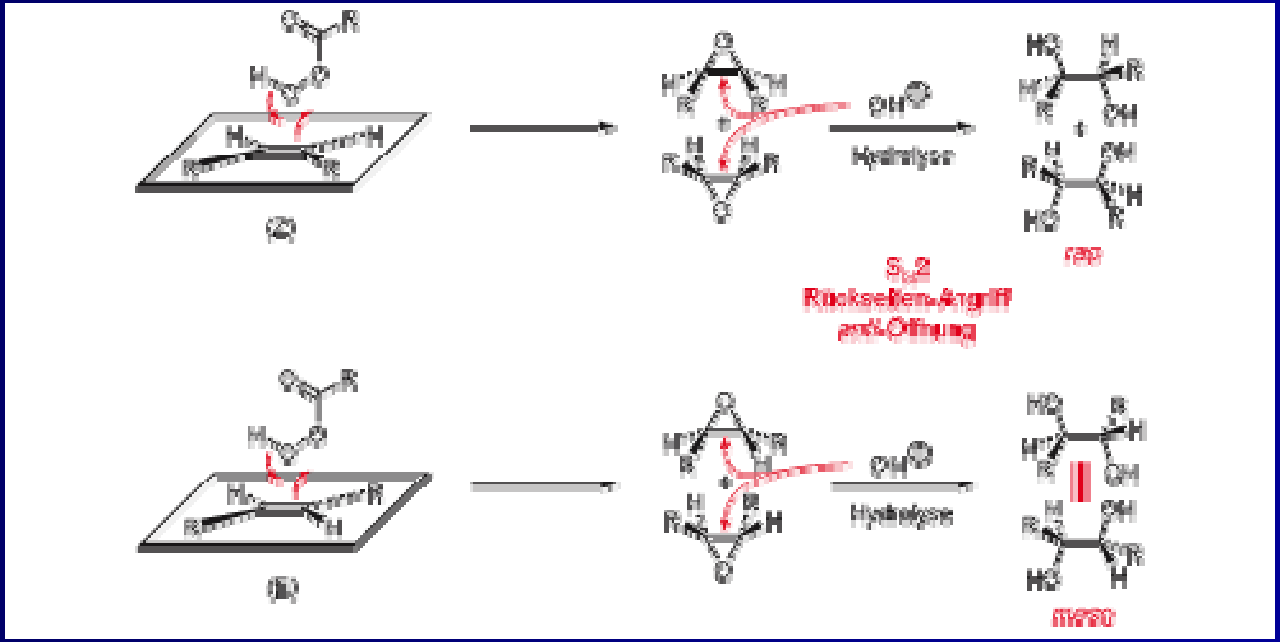
R^*CO_3H = 

R* = Chiral Substituent



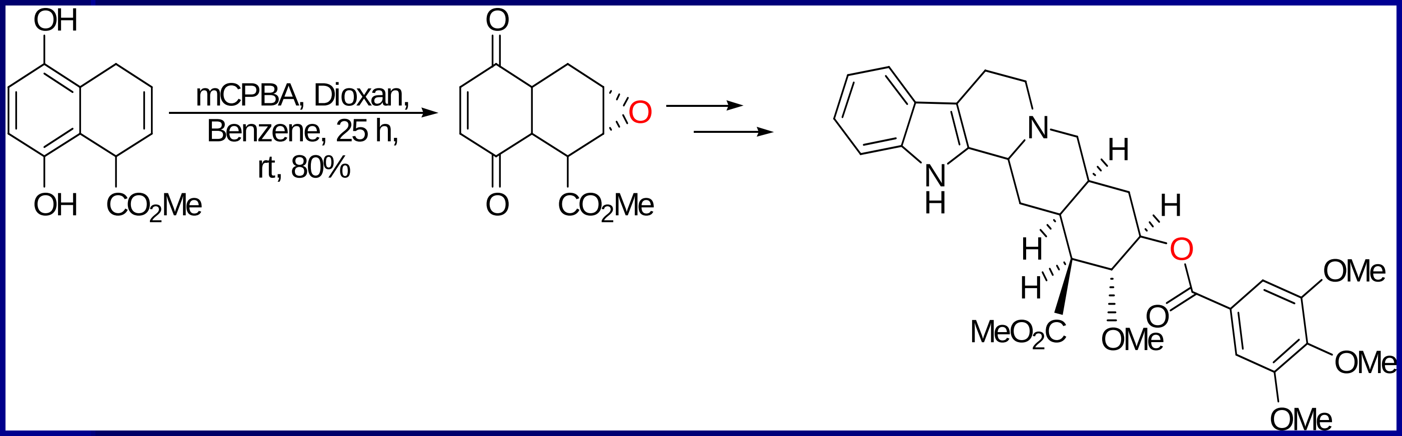
- Mostly used Peracid: mCPBA
- Peracids are elecrophilic Oxidizing Agents, because of a positively polarised Oxygen
- Stereospecific syn-Addition of an Oxygen from the Peroxy-moiety to the C-C-Doublebond $\longrightarrow$ $sp^3 \rightarrow sp^2$
- concerted Mechanism
- in the TS, the positively charged Oxygen attacks the electronrich Doublebond, while the Hydrogen forms a H-Bond with the Carbonylgroup

Mechanism of the Epoxidation with Peracids



Peracid Epoxidation in the Synthesis of the Natural Product Reserpine

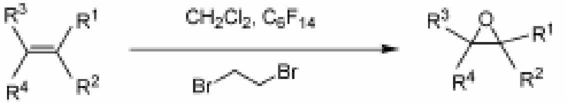
Totalsynthesis of Reserpine by Woodward:



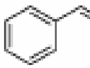
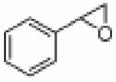
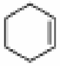
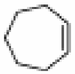
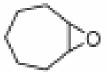
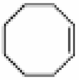
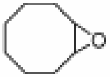
Woodward, R.B. et *al. Tetrahedron* **1958**, *2*, 1 – 57

Examples for the Use of Peracids in Synthesis

Epoxides using the Phase-Vanishing Technique

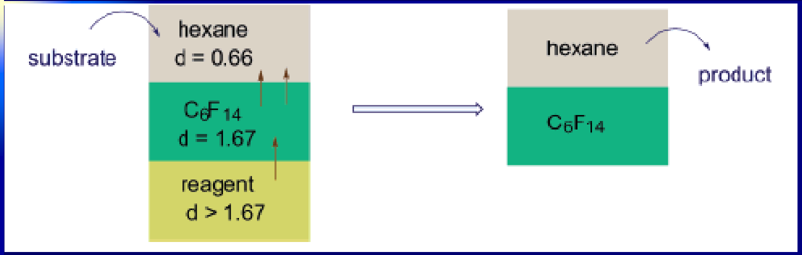


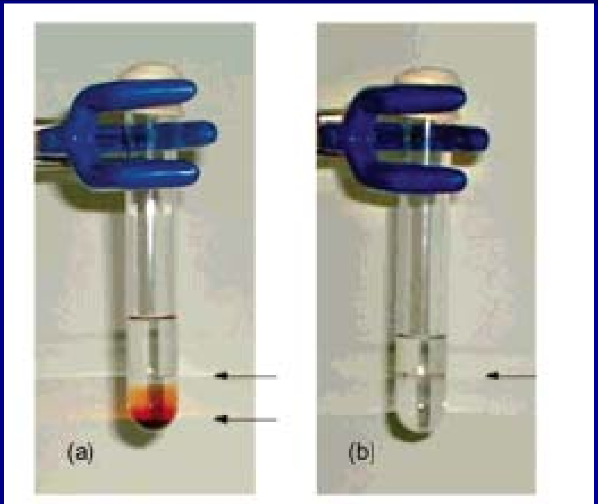
6 → 7

entry	alkene	epoxide	yield(%)[b]	literature yield (%)
1		 7a	96	5-89[7f,g,k]
2		 7b	78	46-91[7f,g,k-n]
3		 7c	92	46-91[7f,k-m]
4		 7d	95	78-96[7e,g,i,k-m,o]
5		 7e	86	59-67[7m,o]

Verkade, J.G. et *al. Org. Lett.* **2003**, *5*, 3787 - 3790

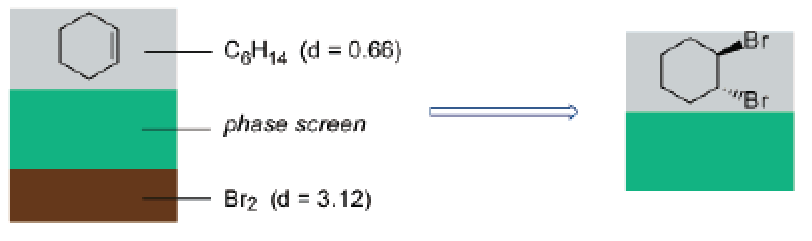
Excurse: The Concept of Phase-Vanishing-Technique (PV)





- The fluorinated solvent regulates the rate of reagent transport and acts as a phase screen medium ⟶ important for controlling heat in exothermic reactions, especially on large scale
- the concept is based upon the density of the resulting 3 layers

Example for PV in the bromination reaction of cyclohexen

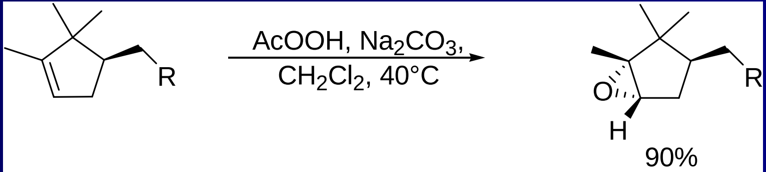


Curran, D.P. et *al. J. Am. Chem. Soc.* **2002**, *124*, 12946 – 12947

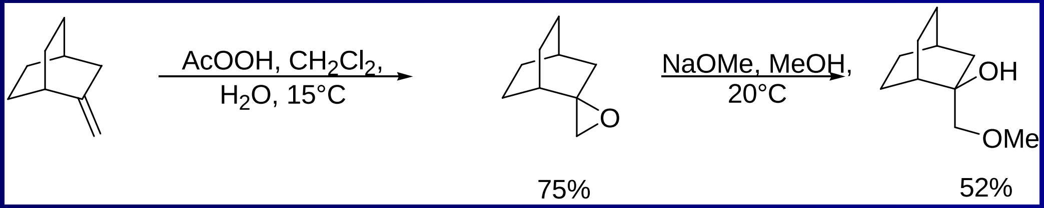
Curran, D.P. et *al. J. Am. Chem. Soc.* **2003**, *5*, 1167 – 1169

Two more Examples of Epoxidations using Peracids

Synthesis of α-Camphol-Epoxide:



Synthesis of Epoxyderivative of 2-Methylene-bicyclo[2.2.2]octane:

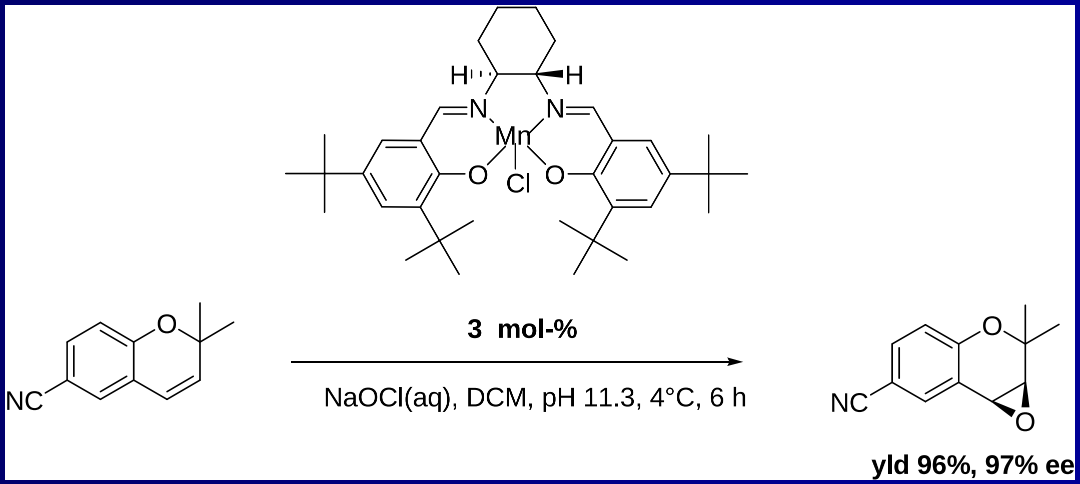


α-Camphol-Epoxide: Schulz, K. et *al. Liebigs Ann. Chem.* **1993**, *9*, 987 – 991

Epoxy-Methylene-bicyclo[2.2.2]octane: Kaysan, L.I. et *al. Zh. Org. Khim.* **1992**, *28*, 502 – 512

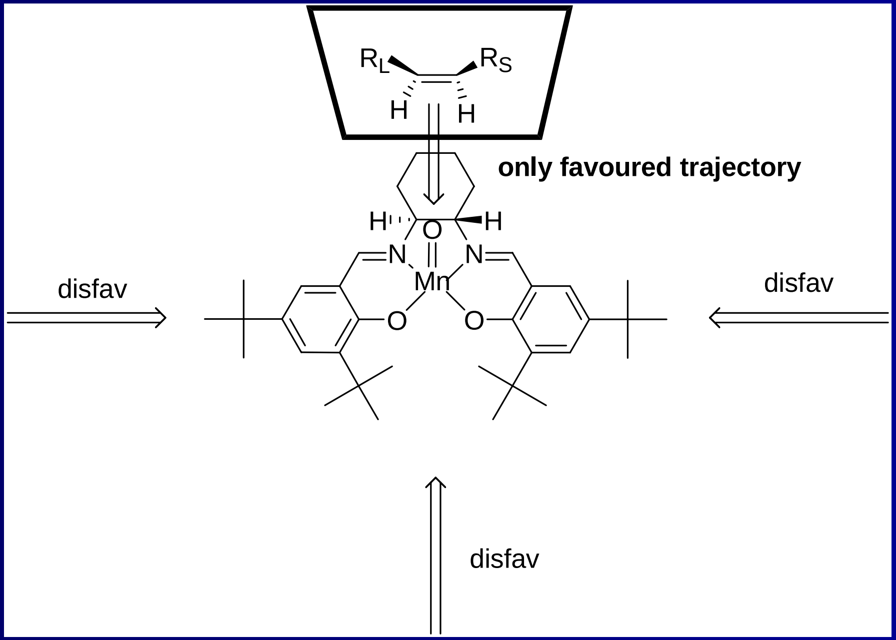
Jacobsen-Katsuki-Epoxidation

- Very efficient Catalyst-systems using Salen-Complexes with Mn-, Fe- or Co as metall
- low Catalyst loadings (0.5 – 8 %)
- yields up to 97 %, ee-values up to 98+ %
- Cat is exellent for cis-di- & trisubstituted Olefins



Jacobsen, E.N. et *al. J. Am. Chem. Soc.* **1991**, *113*, 7063 - 7064

Highly ordered TS !!



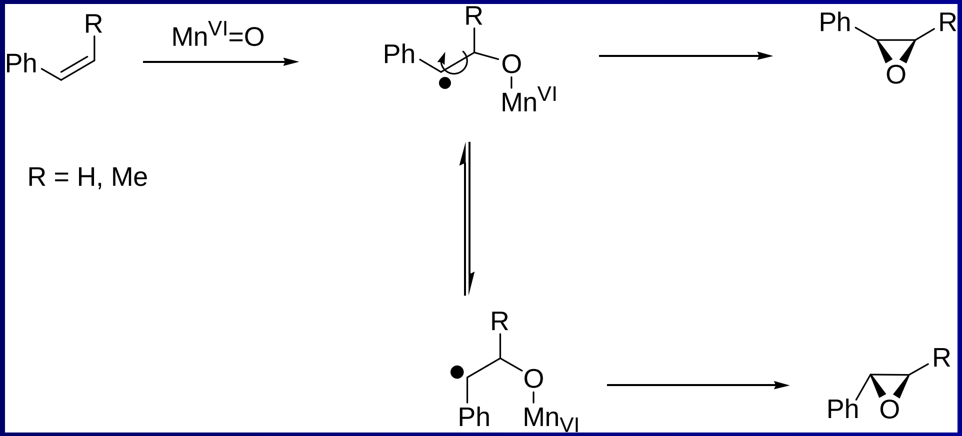
For conjugated & stabilised Olefins a radical mechanism is possible

→ Isomerisation of the Intermidiate because of rotation

→ rcts at low T → no rotation occurs

→ addition of Ammoniasalts accelerates the rotation &

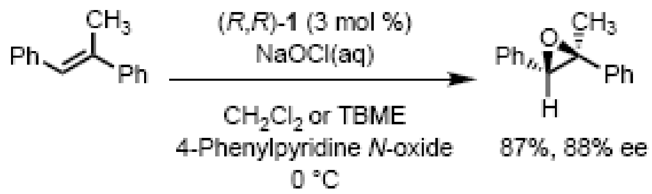
only products from the expected *E* -Olefins may be isolated !

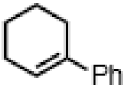
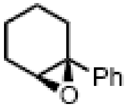
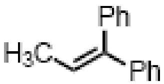
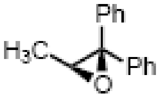
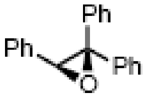


Access to enantiomerically pure *trans* - Styreneoxides

Examples for the Asymmetric Jacobsen Epoxidation

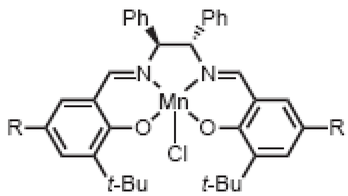
Trisubstituted Olefins:



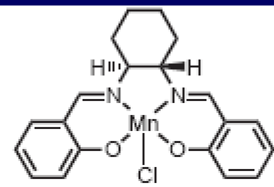
olefin	epoxide[a]	yield, %	ee, %
		69	93
		91	95
		97	92

Jacobsen, E.N. et *al. J. Org. Chem.* **1994**, *59*, 4378 – 4380

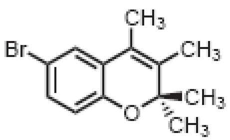
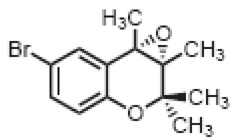
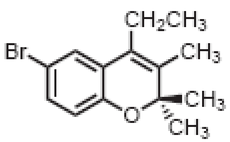
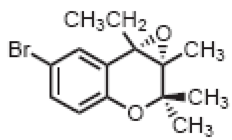
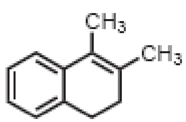
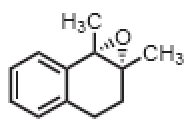
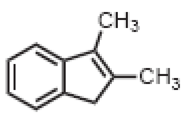
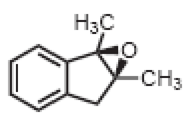
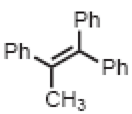
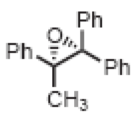
Tetrasubstituted Olefins:



R = CH_3, (*S*,*S*)-**2**
R = OCH_3, (*S*,*S*)-**3**



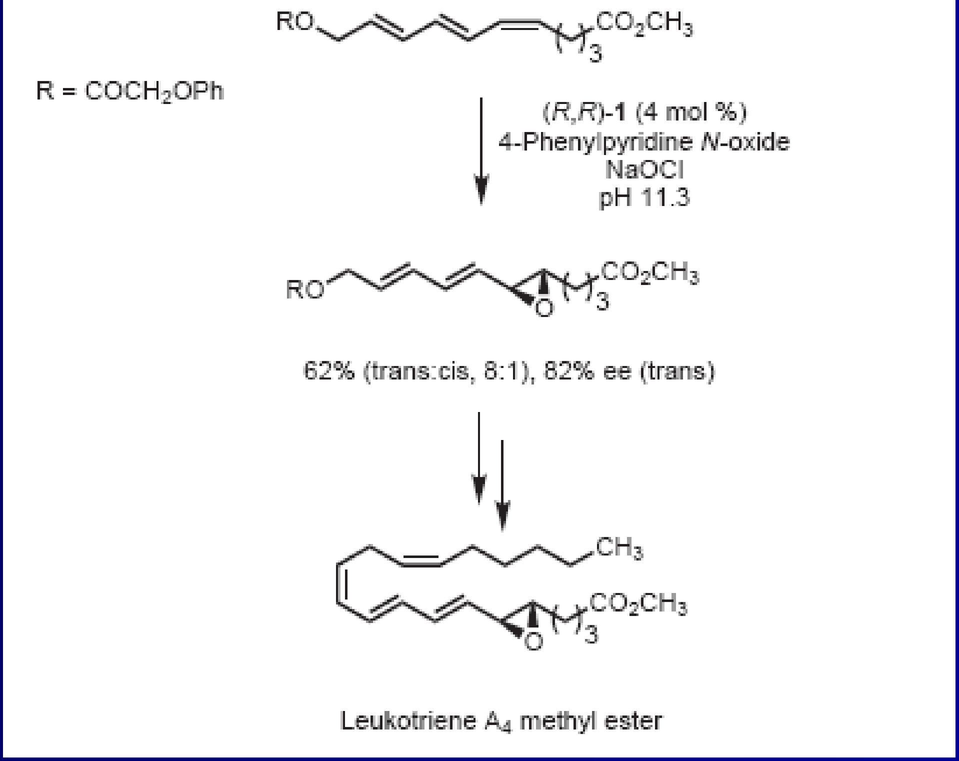
(*S*,*S*)-**4**

olefin	catalyst	epoxide	epoxide yield, %	ee, %
	(*S*,*S*)-**2**		84	96
	(*S*,*S*)-**2**		81	97
	(*S*,*S*)-**3**		45	65
	(*R*,*R*)-**3**		37	35
	(*S*,*S*)-**4**		12	46

- High ee-values are not general occurring
- Chromene derivatives undergo epoxidation with higher enantioselectivity, when compared to Indene derivatives

Jacobsen, E.N. et *al. Tetrahedron Lett.* **1995**, *36*, 5123 – 5126

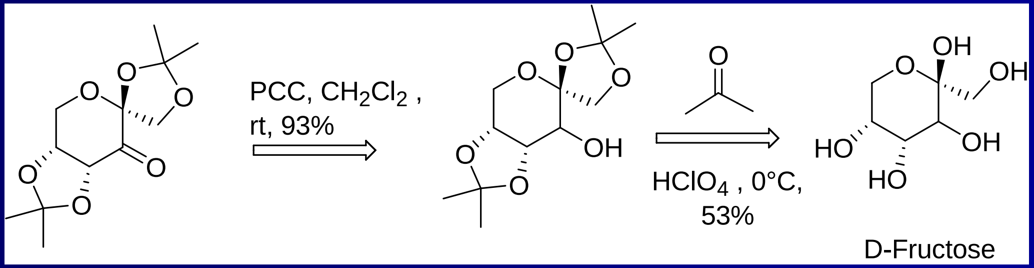
Synthesis of the Key Intermediate for Leukotrienemethylester A_4 through Asymmetric Jacobsen Epoxidation:



Jacobsen, E.N. et *al. J. Org. Chem.* **1993**, *58*, 6939 – 6941

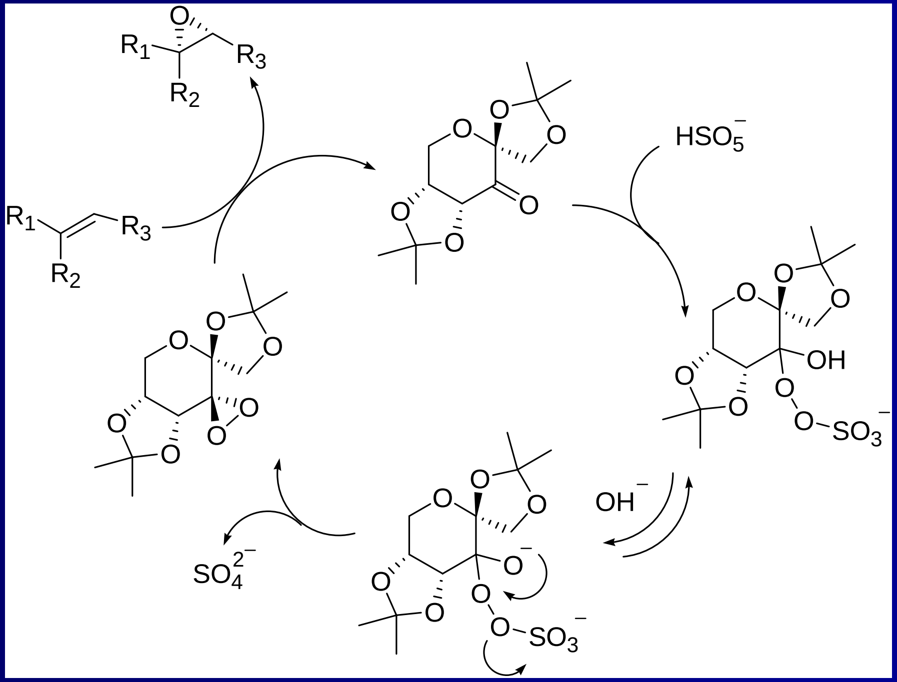
Shi - Epoxidation

- Example for the organocatalytic conversion of Olefins to Epoxides
- easily prepared Ketone-Catalyst, derived from inexpensive D-Fructose by Ketalisation & PCC-Oxidation
- if pH-value is below 8, the Catalyst decomposes faster then it reacts with the Substrate via the Baeyer-Villiger-Pathway



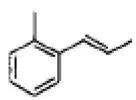
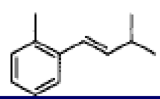
Mechanism of Shi-Epoxidation

- Oxidation of the Ketone to Dioxiran by HSO_5^- (Oxone ®)
- Deprotonation of the resulting Hydroxy moiety & formation of the catalytically active species
- Epoxidation of the Olefin & Regeneration of Ketone



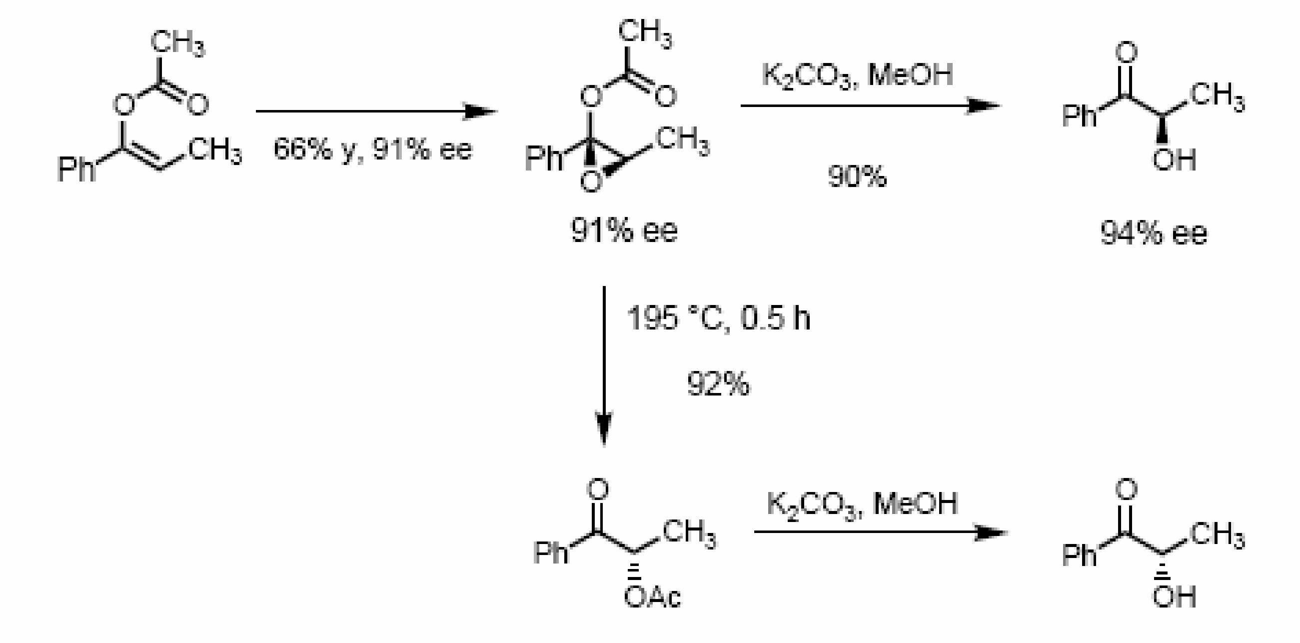
Shi, Y. et *al. J. Am. Chem. Soc.* **1997**, *119*, 11224 – 11235

Selected Examples for Asymmetric Shi-Epoxidations

Substrate	Method[a]	T (°C)	Yield[c] (%)	ee (%)	Config.[j]
	A	0	74	93[g]	(+)-(R,R)[23c]
	B	0	87	94[g]	
	C	0	71	**95.2**[e]	
	C	0	55	94.0[e]	(+)-(R,R)[k]
	A	0	61	93[g]	(+)-(2S,3R)[23c]
	C	0	49	**96.2**[f]	
	A	0	41	93[g]	(+)-(2S,3R)[k]
	C	-10	91[d]	93.3[f]	(+)-(R,R)[k]
	C	-10	78[d]	95.7[f]	(-)-(R,R)[k]

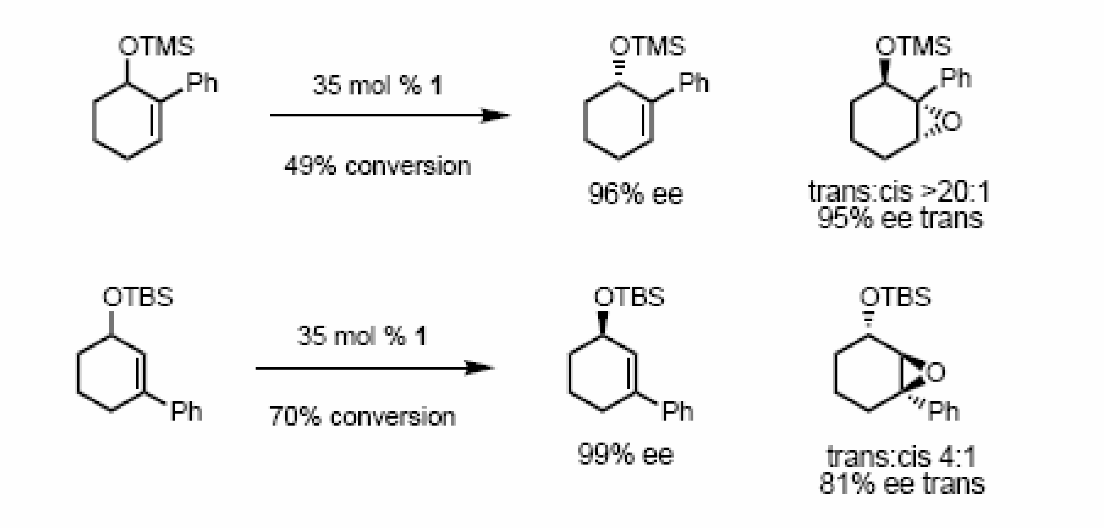
Shi, Y. et *al. J. Am. Chem. Soc.* **1997**, *119*, 11224 – 11235

Preparation of α-Hydroxyketones in either enantiomeric form from Enol Esters



Shi. Y. et *al. J. Am. Chem. Soc.* **1999**, *121*, 7718 – 7719

Examples for the kinetic resolution of rac-1,3- and 1,6-Cyclohexens via Shi-Epoxidation

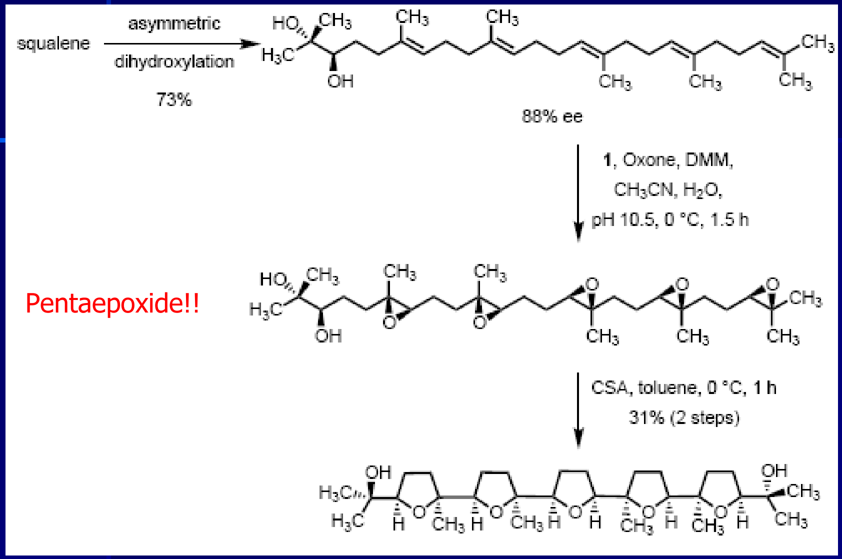


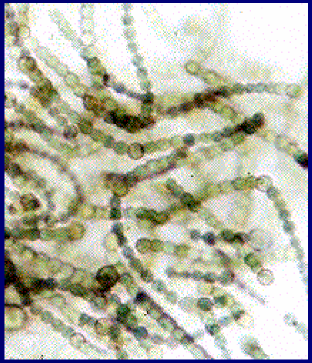
Possibility to provide enantiomerically enriched allyl sily ethers

Shi, Y. et *al. J. Am. Chem. Soc.* **1999**, *121*, 7718 – 7719

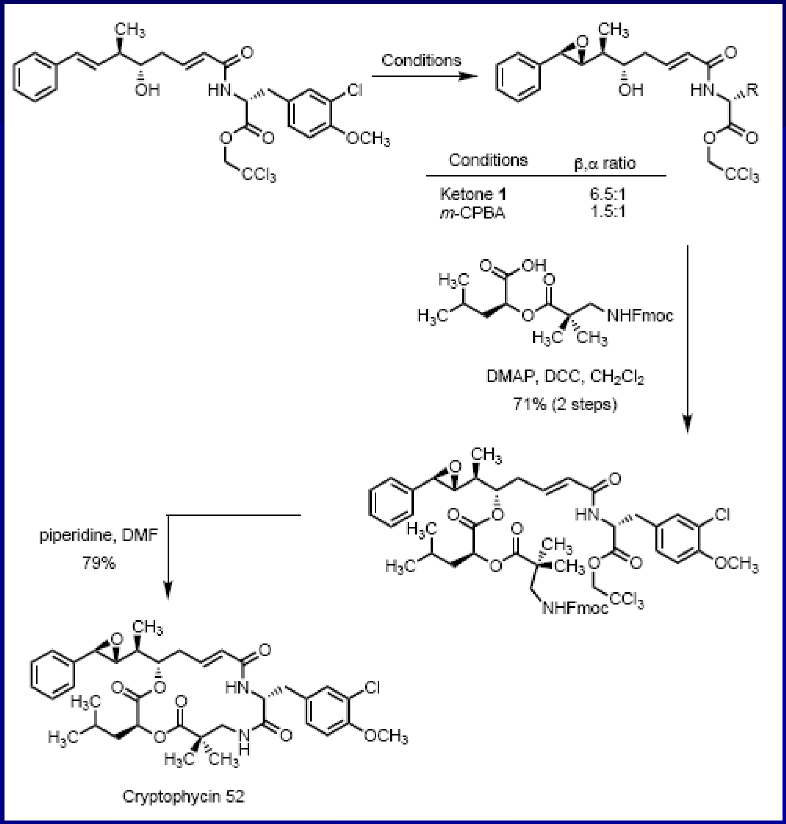
The Shi-Epoxidation in the Synthesis of Glabrescol & Cryptophycin 52:

Glabrescol:





Cryptophycin 52:



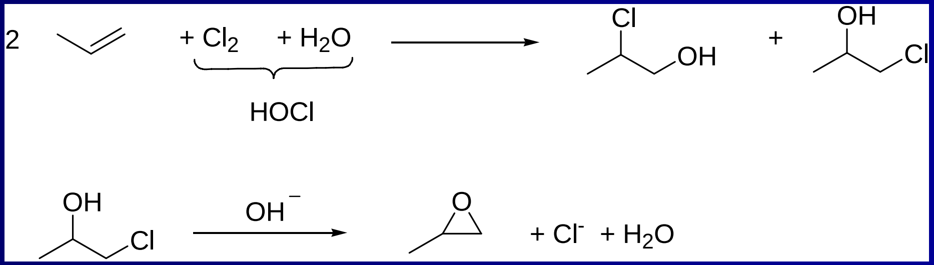
In the case of Cryptophycin 52 only the Shi-Epoxidation gave the desired Epoxide in a 6.5:1 ratio, while other procedures never exceeded a 2:1 ratio !

Glabrescol: Corey, E.J. et *al. J. Am. Chem. Soc.* **2000**, *122*, 4831 – 4832

Cryptophycin 52: Moher, E.D. et *al. Org. Lett.* **2002**, *4*, 1813 – 1815

Chlorohydrine-Procedure for Epoxidations

- was to play an important role in large scale production of propenoxide (561kt/1992)[1]
- 55 % of propenoxide was produced like that (1985)
- 1st: rct of propen with HOCl to form the corresponding chlorhydrine
- 2nd: alkaline dehydrohalogenation to form propenoxide



1: Forschungsstelle für Umweltpolitik – FU Berlin – Report 99-2

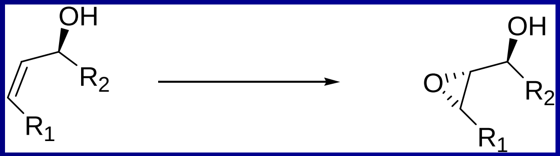
Halcon-Procedure for Epoxidations

Good Method for the Epoxidation of Allylic alcohols:

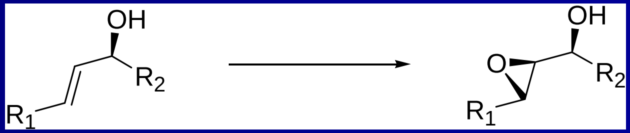
→ Hydroxygroup activates the Doublebond & has a directing effect on the Epoxidation – Hydroxy Group coordinates with the Metalcenter

Substrate rcts with Hydroperoxide in the Presence of a Transitionmetal-Catalyst (V, Ti, Mo – e.g.: $VO(acac)_2$) in nonaqueous media

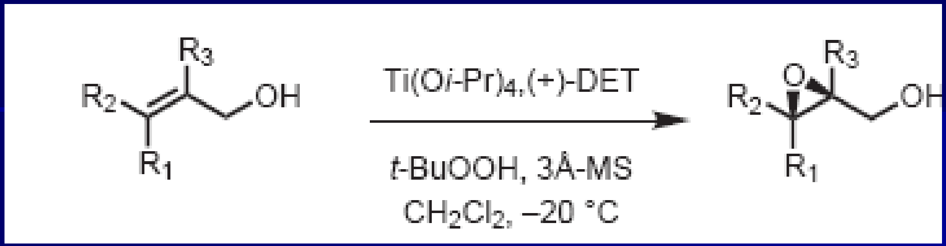
Z-Isomer: Oxygen mostly *anti* to Hydroxy group



E-Isomer: Oxygen mostly *syn* to Hydroxy group



The Sharpless-Asymmetric-Epoxidation



Nobel Price in 2001

Applicable for Allylic Alcohols

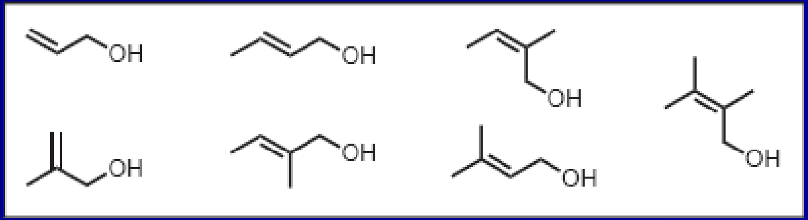
5 – 10 mol-% Catalyst are nessecary in the Presence of 3 or 4 Å-MS

10 – 20 mol-% ecess of Tartrate vs . $Ti(O^iPr)_4$

(+)- & (-)-DET are readily available and inexpensive

(+)- & (-)-DIPT sometimes lead to higher selectivity

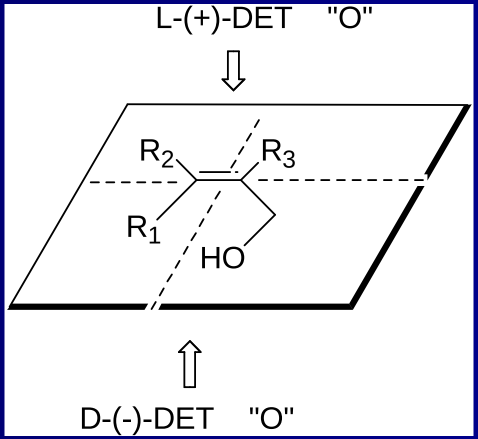
Substitution Patterns:

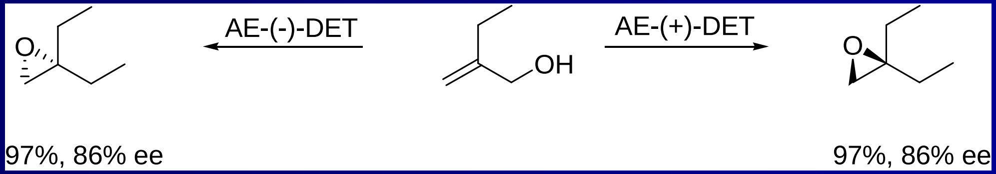


Z-disubstituted olefins are least reactive & selective !!

Allylic tertiary Alcohols are not sucessfully epoxidized under Sharpless Conditions

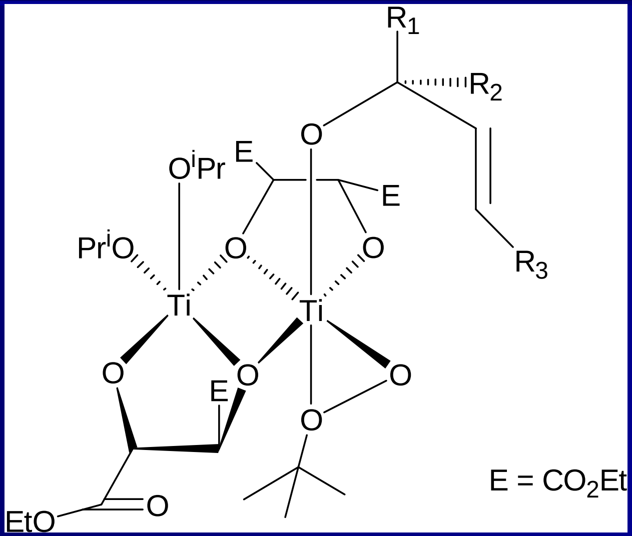
Mnenomic for Selectivity & Application





Sharpless, K.B. et *al. J. Am. Chem. Soc.* **1980**, *102*, 5974 – 5976

TS of the Sharpless-Epoxidation



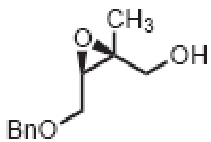
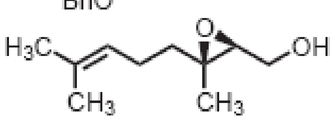
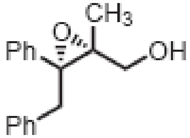
In the Complex the O^{i}Pr Group is Substituted by Tartrate & Hydroperoxide

The chiral Cat may be regenerated by Oxidation

Presence of Water heavily disturbs the Enantioselectivity

e.g. 1 eq of H_2O: 90% ee $\longrightarrow$ 50% ee !!

Examples of Sharpless-Epoxidation

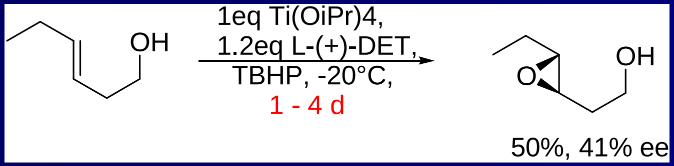
product	Ti(%)	tartarate (%)	°C	h	yield (%)	ee (%)
	5	(+)-DIPT (6.0)	0	2	65	90
	5	(+)-DIPT (7.5)	–20	3	89	>98
	4.7	(+)-DET (5.9)	–12	11	88	95
	10	(+)-DET (14)	–10	29	74	86
	5	(+)-DIPT (7.5)	–35	2	79	>98
	100	(+)-DET (142)	–20	14	80	80
	5	(+)-DET (7.4)	–20	0.75	95	91
	120	(–)-DET (150)	–20	5	90	94

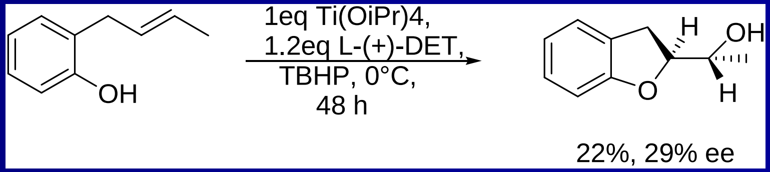
Sharpless, K.B. et *al. J. Am. Chem. Soc.* **1987**, *109*, 5765 – 5780

Sharpless, K.B. in *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH, New York, **1993**; pp. 103 – 158

Sharpless-Epoxidation with Homoallyic & Bishomoallylic Alcohols

- Rates of Epoxidation are usually slower
- Enantiofacial selectivity of the Catalyst is reversed for all 3 & also generally lower





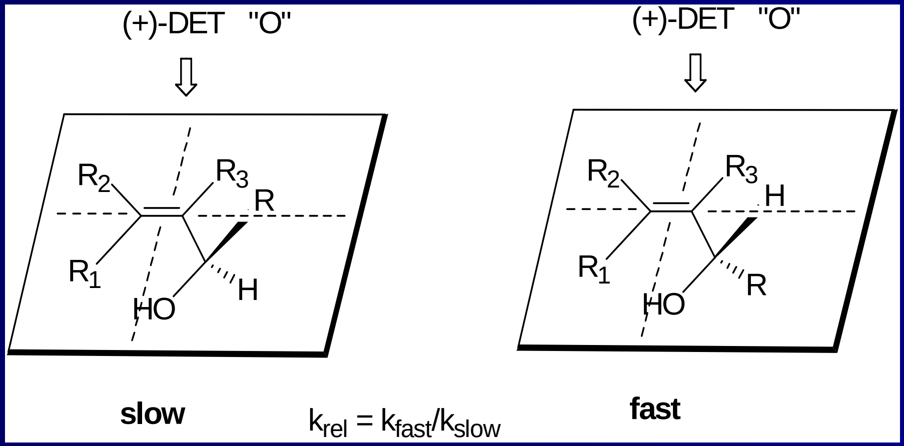
Sharpless, K.B. et *al. J. Org. Chem.* **1984**, *49*, 3707 – 3711

Hosokawa, T. et *al. J. Organometal. Chem.* **1989**, *370*, C13 – C16

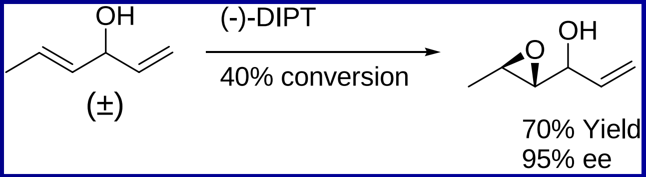
Other Examples see: Sharpless, K.B. in *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**, pp. 103 – 158

Kinetic Resolution through Sharpless Chemistry

Contact between the C1 Substituent (R) & the Catalyst predicts a slow reacting Isomer



Disubstituted Doublebond is more reactive then Monosubstituted (k_{rel} ~ 100)



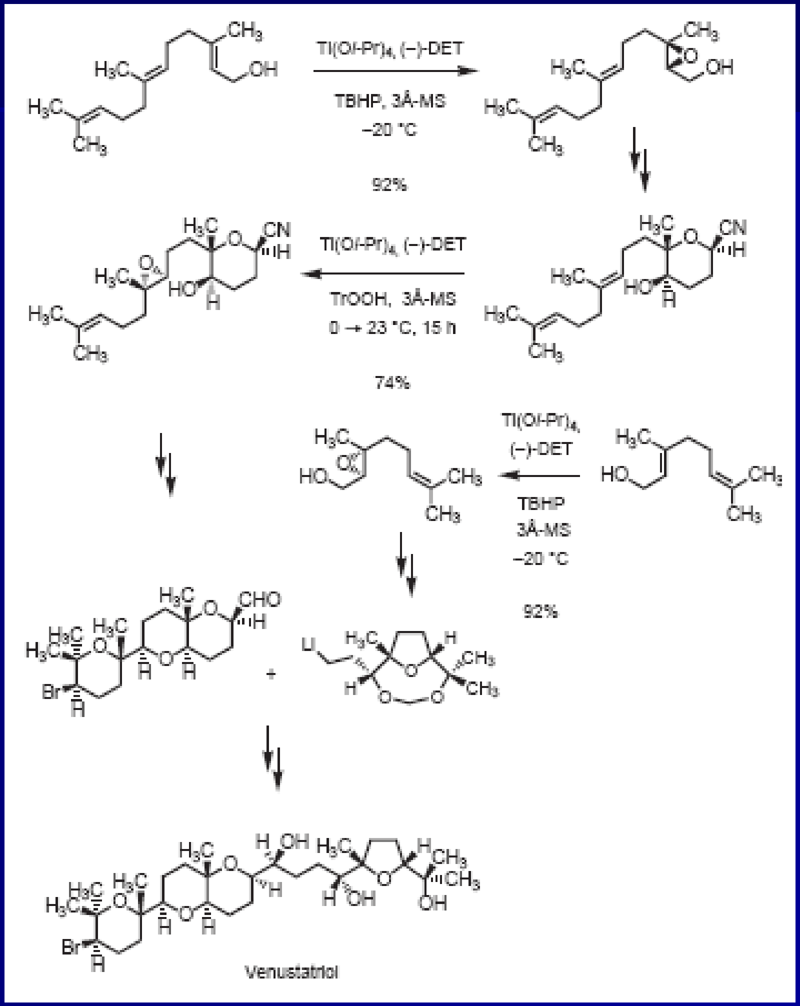
$k_{rel} \geq 25$, except for *Z*-disubstituted Allylic alcohols

Application of the Sharpless-Epoxidation in Synthesis

Synthesis of Venustradiol:

Tetraoxacyclic squalenoid with antiviral activity

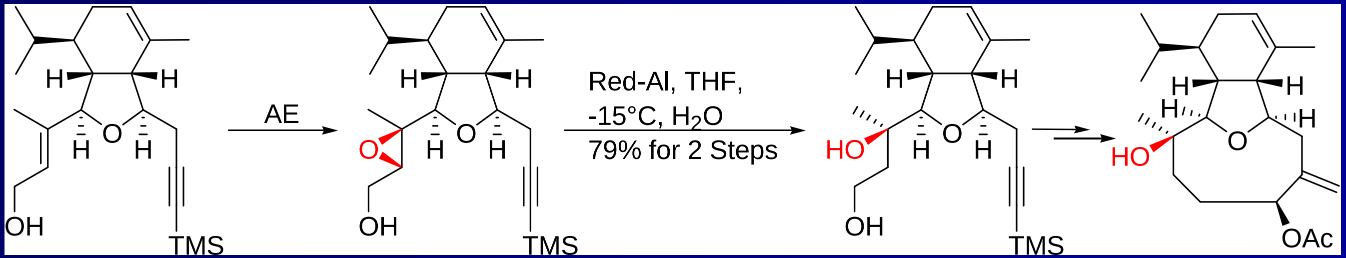
3 Epoxidations applied



Corey, E.J. et *al. Tetrahedron Lett.* **1988**, *29*, 3171 – 3174

Synthesis of (-)-7-Deacetoxyalcyonin Acetat

- Eunicellin diterpenes: marine metabolites from gorgonian & soft corals
- Unique tricyclic ring system, containing hydroisobenzofuran- & oxonane subunits, as well as an exocyclic Doublebond
- Evidence for biological activity to deter mollusk predation



Overman, L.E. et *al. J. Am. Chem. Soc.* **1995**, *117*, 10391 – 10392

Summary

- Epoxidations, Kinetic Resolution of Epoxides with Enzymes are highly Selective, although the Mechanisms are not fully understood for a lot of reactions, because their complex, 3-dim Structure is not known in detail.
- Using Enzymes in the Lab means biologically occuring Selectivities are not reproducible, due the special environmental conditions in vivo, which are hardly reachable in the flask.
- Many Organisms like Germs, Fungi, Plants or marine creatures are producing Epoxide bearing Substances, which are highly active.
- Modern Chemical Epoxidation Methods mimic enzyme-like ones concerning selectivity & also have a comparable broad Substrate scope.
- To days Catalysts are highly tuneable & specific for some kind of Substrates, although selectivity problems may arise in the Total Synthesis of Natural Products due to their complexity .
- Often they are not longer air- or moisture sensitive.

Thank You !!