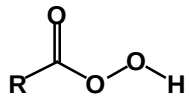
Alkene Epoxidations

- A huge topic which we will only skim the surface of
- References will be include for those who want more detail

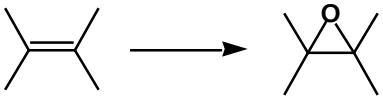
Peracids: The Prilezhaev (Prileschajew) Reaction

Reagent:

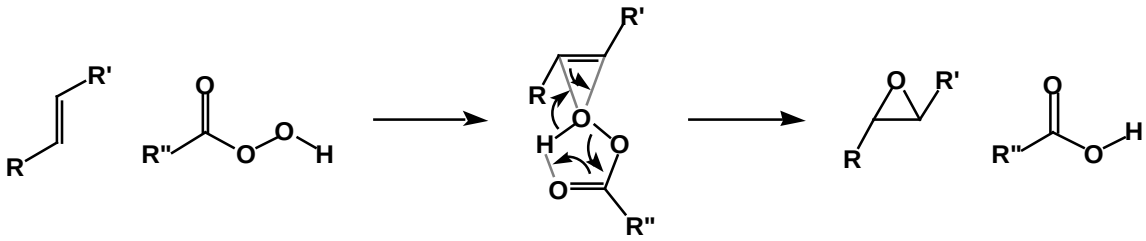


- for the Caddick group with their love of named reactions

Transformation:

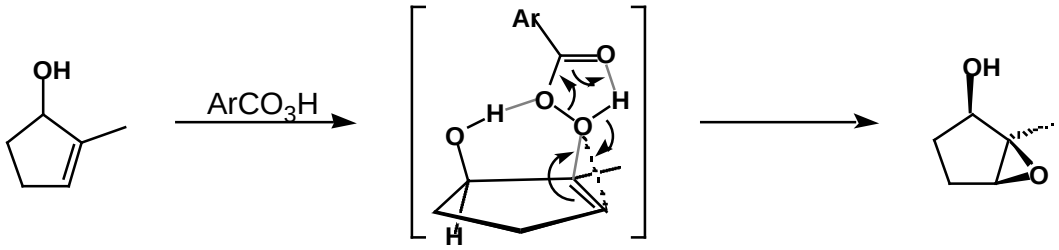


General Mechanism



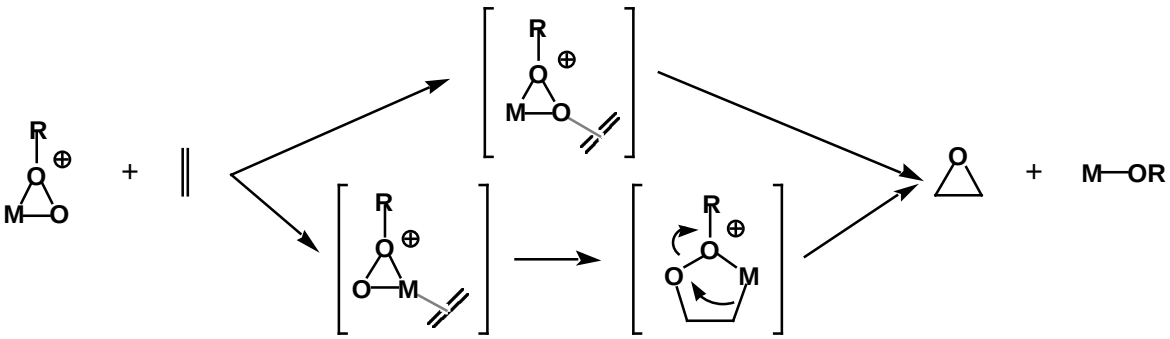
Use in Synthesis

- Peracids much weaker acids than carboxylic acids (pK_a 8.2 vs 4.8)
- But carboxylic acid is a by-product so *buffer* with $NaHCO_3$
- Peracids are ***electrophilic*** so electron withdrawing groups on R good (*m*CPBA)
- Electron-rich alkenes more reactive
- ***Hydrogen-bonding*** can direct epoxidations



Hydroperoxides

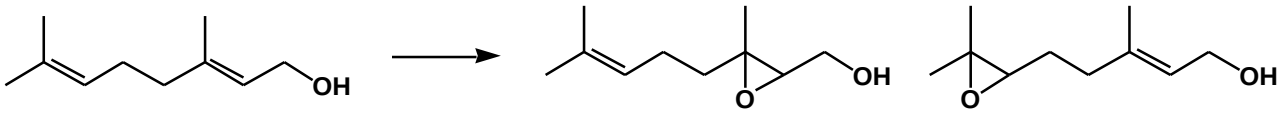
- H_2O_2 & alkyl hydroperoxides require the presence of a transition metal to initiate epoxidation
- *t*BuO_2H (**TBHP**) favoured as safe, soluble and stable in anhydrous solvents and cheap



Directed Epoxidations Utilising Hydroperoxides

93CR1307 (directed reactions)

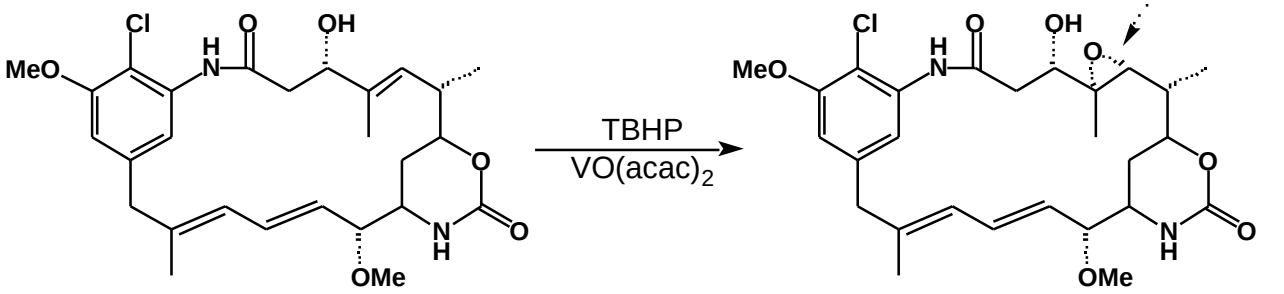
• The use of transition metals can allow *directed epoxidations*
• Use to control ***chemoselectivity***



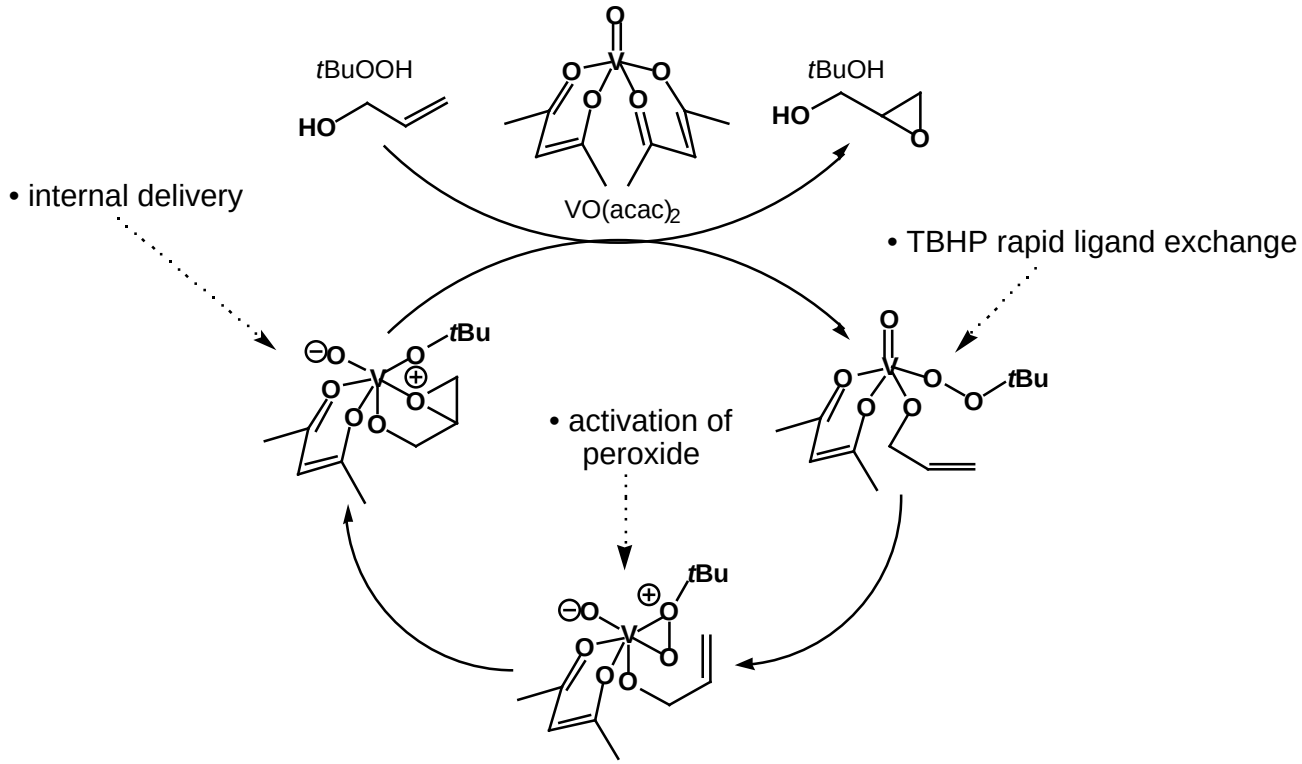
*m*CPBA:	1	:	2
TBHP / $VO(acac)_2$	49	:	1

• Used to control ***stereoselectivity***

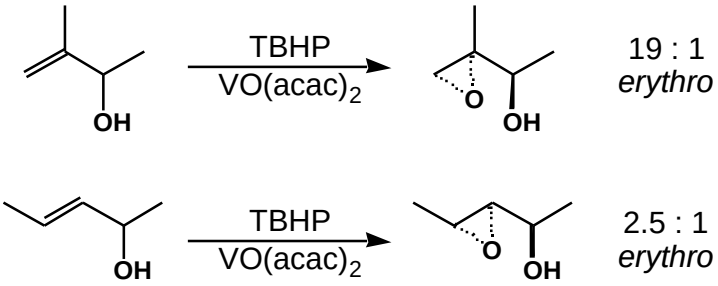
• chemo- and stereoselective



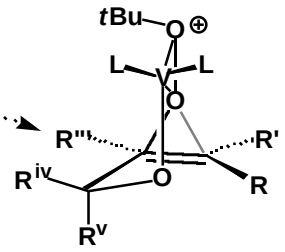
Mechanism



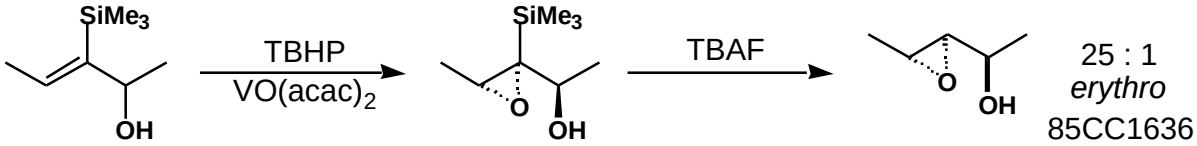
Acyclic systems also show good selectivity



• biggest effect is R'''.



• therefore use temporary blocking group



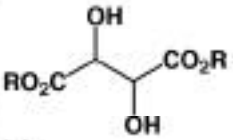
• this all leads on to probably the most famous epoxidation system…

Sharpless Asymmetric Epoxidation (S.A.E.)

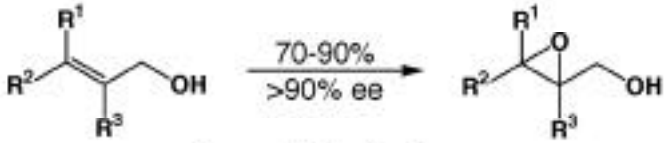
- ***It is often forgotten that this was the FIRST GENERAL ASYMMETRIC CATALYST***
- Still used extensively, many syntheses have SAE as the keystep or at least introduce chirality *via* the SAE

Reagent:

TBHP, $Ti(OiPr)_4$, DCM,
(catalytic when 4Åms used)

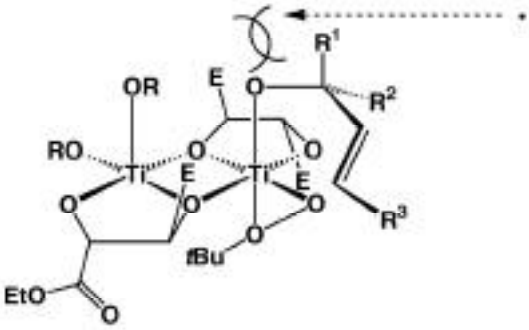


Transformation:

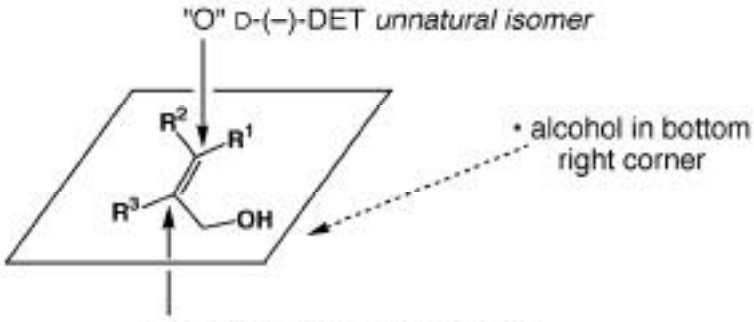


General Mechanism:

- same as outlined before.
- intermediate believed to look like:

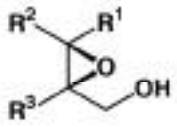


- Should be noted that there are **8** different binding modes for Ti and tartrate
- Which isomer of DET do you use

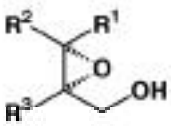


- with left-hand point thumb in direction of alcohol (not Falmer bar)

- if you want "O" on top its on your k**N**uckles so use **N**egative (–)-DET



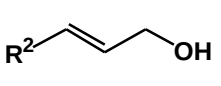
- if you want "O" on bottom its on your **P**alm so use **P**ositive (+)-DET

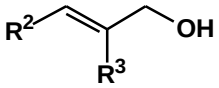


Use in Synthesis

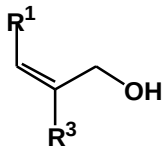
- DCM is an uniquely efficient solvent
- Complex can not be stored
- Catalyst must be aged

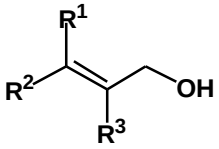
Substrates



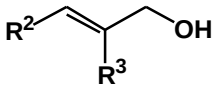


Yield = good
e.e. = 90 %

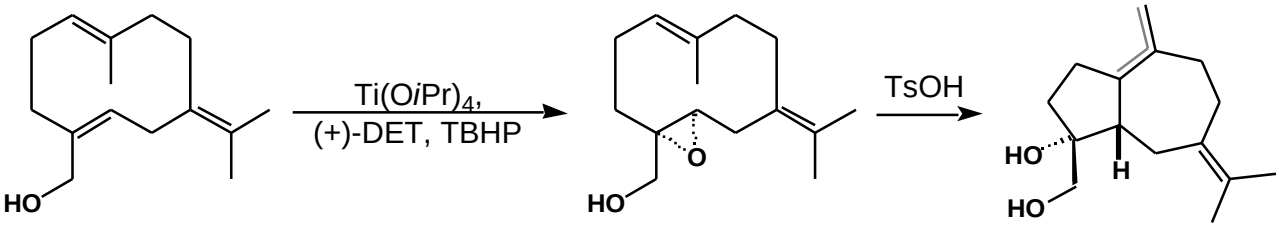




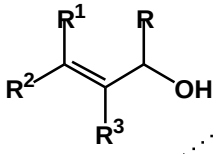
few examples
but generally good



Poor
substrate

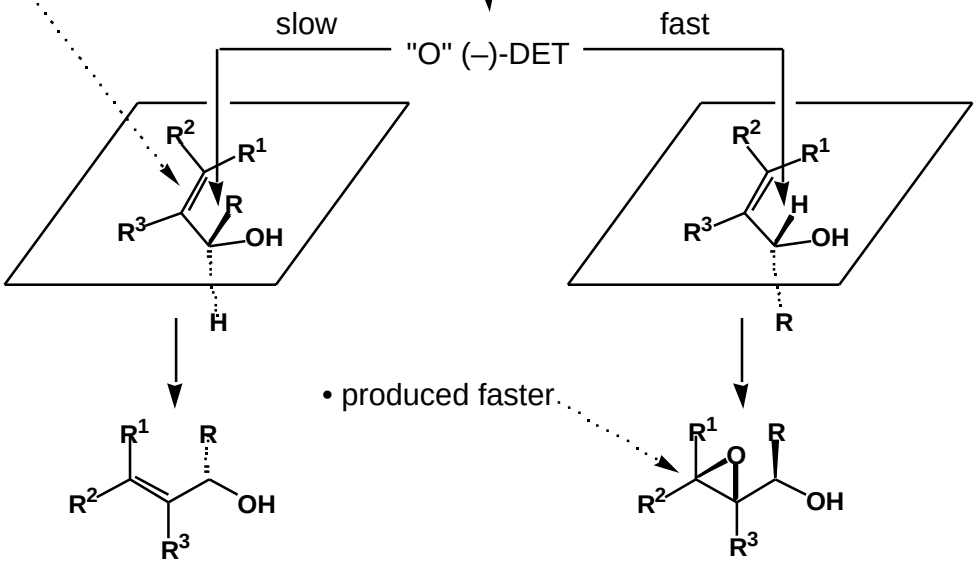


Kinetic resolution



- must stop reaction before 100% completion or you will just recover a different racemate
- both enantiomers react ***just*** at different rates

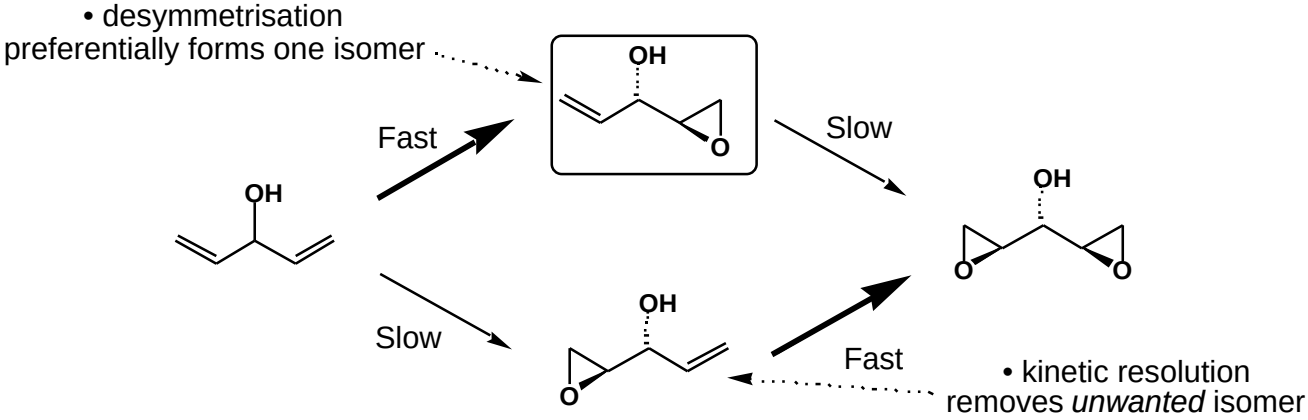
- R group hinders attack and slows epoxidation down



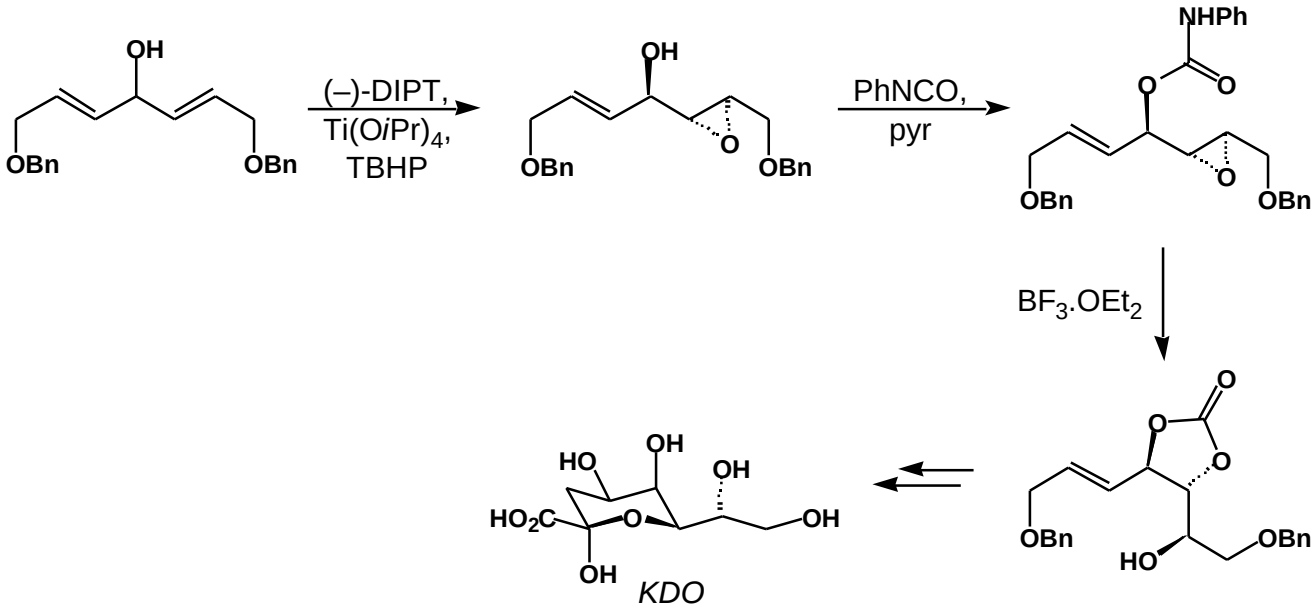
- produced faster

- If allylic alcohol is the desired product use **0.6 equiv. TBHP**
- If epoxy alcohol is the desired product use **0.45 equiv. TBHP**

• Although very useful, kinetic resolution only allows a maximum of 50 % yield
• ***Desymmetrisations*** allow a theoretical 100 % yield



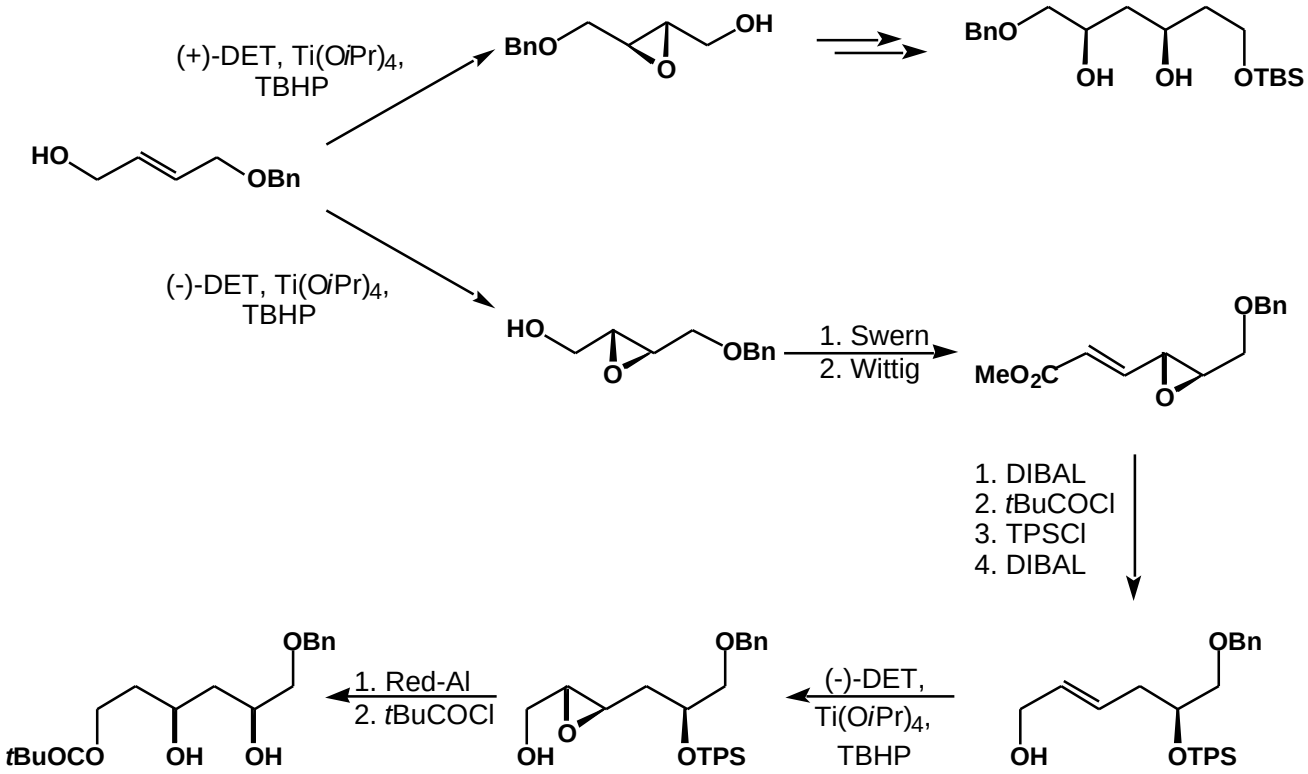
• Attractive strategy due to combining initial desymmetrisation with a subsequent kinetic resolution to result in very impressive enantiomeric excesses
• e.e. of desired product increases with time (84 % 3hrs → >97 % 140 hrs)



What have we learnt?
• Peracids and hydroperoxides are good epoxidising reagents
• Use of transition metals allows directed epoxidations
• SAE is the cornerstone of many total synthesis
• It works well for the majority of *trans* allylic alcohols
• It can be used in kinetic resolution or desymmetrisation reactions

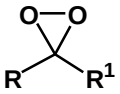
References:
directed: 93CR1307
Sharpless: 87JACS5765(good), Comp.Org.Syn. Vol.7, Ch.3.2, 91CR437
Resolution: 81JACS464
Desymmetrisation: 87JACS1525, 94ACR9
KDO: 90T4793

• Two building blocks from KC Nicolaou's synthesis of amphotericin B show the power of SAE

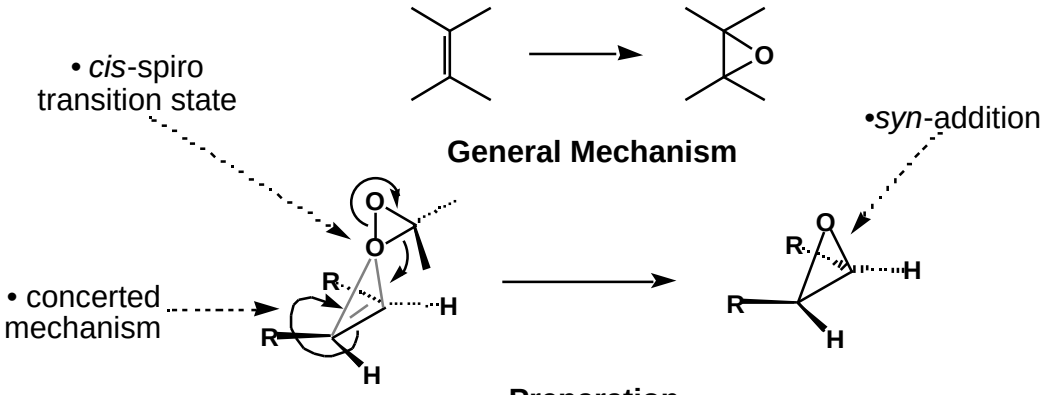


Dioxirane Epoxidations

Reagent:

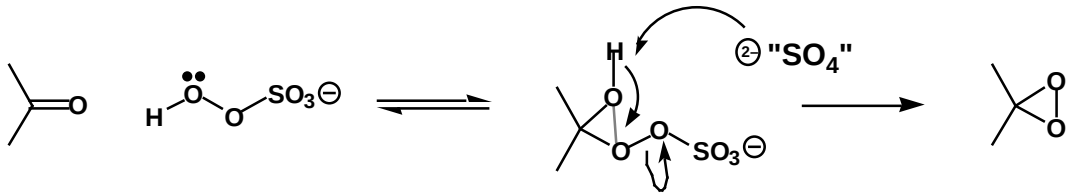


Transformation:



Preparation

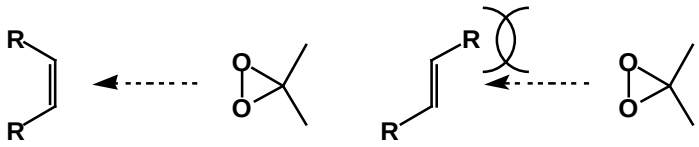
- Most common dioxirane is **dimethyldioxirane (DMDO)**
- Prepared as a pale yellow solution in acetone by the action of **oxone** or **caroate $KHSO_5$**



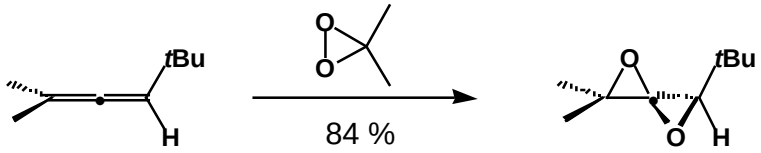
- ~0.08–0.10 M acetone solution "distilled" off with carrier gas to prevent further reaction of oxone and DMDO

Use in Synthesis

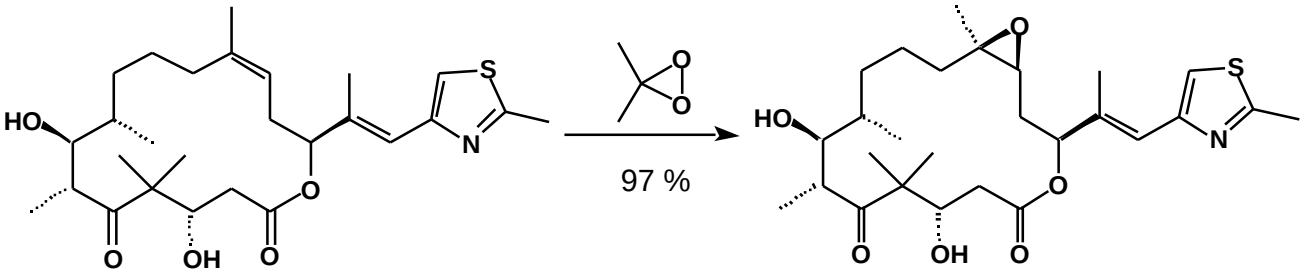
- *cis*-alkenes react more efficiently for steric reasons (~7-9 times more reactive)



- Stereocentrol is a result of ***steric interactions***
- Addition of DCM or H_2O decreases stability therefore increases reactivity
- Used at low temperature and neutral conditions (as generates acetone as a by-product)
- Mild so can generate very sensitive epoxides

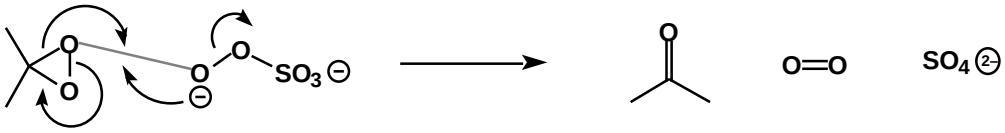


- **Disadvantages:** VERY reactive, heteroatoms and hydroxyl groups can be oxidised
- **Disadvantages:** Even *unactivated* C–H can be oxidised



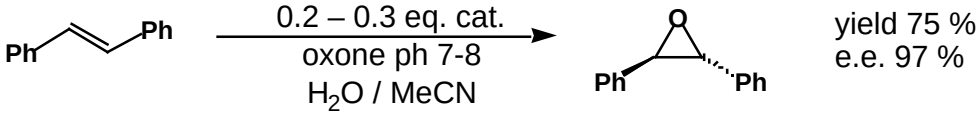
Catalytic Variant

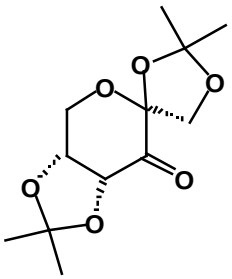
• As the dioxirane precursor, the ketone, is regenerated during the reaction only a catalytic quantity is required ***if*** dioxirane generated ***in situ***
• Possible if pH is kept between 7.0 – 7.5 with phosphate or bicarbonate buffer
• if pH too ***low*** then dioxirane formation can not proceed (deprotonation impossible *viva supra*)
• if pH too ***high*** dioxirane destroyed by oxone



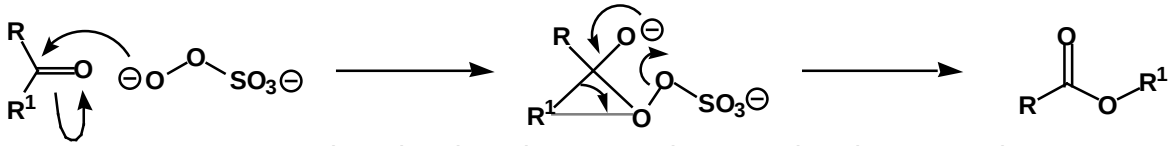
Catalytic Asymmetric Variant

• Shi has developed an asymmetric variant using a chiral sugar derivative
97JOC2328

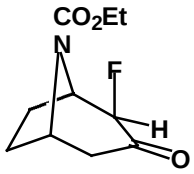




• High catalyst loadings are required as the ketone decomposes *via* Baeyer-Villiger reaction



• Armstrong has developed a more robust catalyst (00TA2057)
• Operates < 10 mol% and up to 76 % e.e.

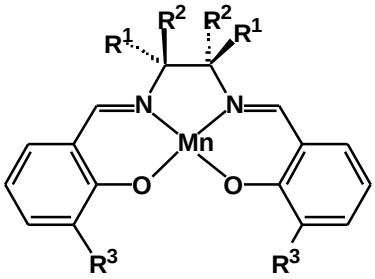


What have we learnt?
• Dioxiranes are extremely powerful oxidants that function under very mild conditions
• Readily generated from ketones
• Ketones can be used catalytically
• Asymmetric variant now possible

Jacobsen–Katsuki Epoxidation

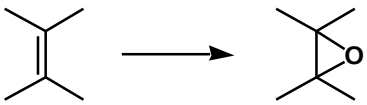
• Aim to develop an asymmetric epoxidation catalyst which would operate on substrates ***with no functionality for preco-ordination***
• A number of reasonably efficient porphyrin based oxo–transfer reagents were developed but the real success story has been the us of ***SALEN–based*** reagents

Reagent:



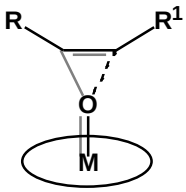
NaOCl
(bleach)

Transformation:

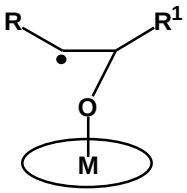


General Mechanism

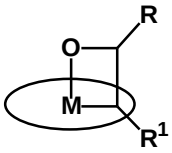
• Still contraversial
97Ang2060
•Possibilities



concerted

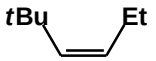


stepwise
(radical or polar)

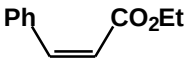


oxametallocycle

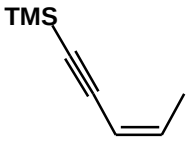
• oxidations proceed with a degree of scrambling of geometry



> 99 : 1 *cis* : *trans* epoxide



78 : 22 *cis* : *trans* epoxide

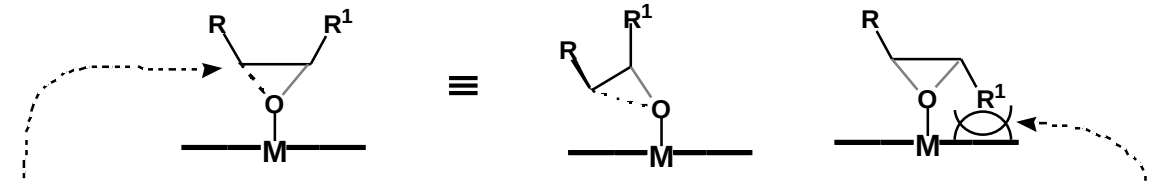


29 : 71 *cis* : *trans* epoxide

• Suggests that concerted mechanism is not occurring
• Present believe is probably ***radical - stepwise*** mechanism (00Ang589)

Stereoselectivity

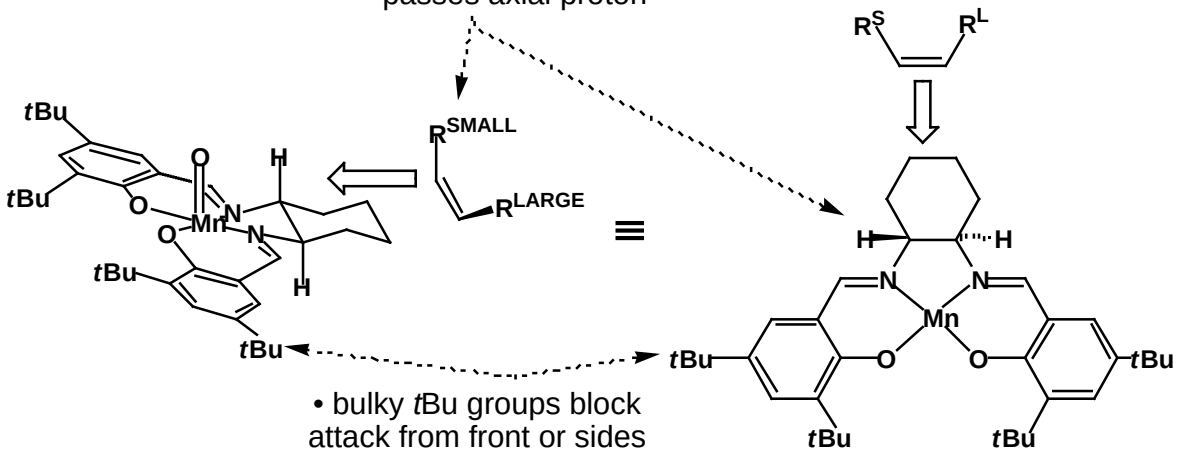
- My interpretation would again suggest that Katsuki and Jacobsen disagree on this
- Both agree that alkene approaches metal oxo complexes ***side-on***



- approach so that π-HOMO of alkene overlaps with π*-LUMO of oxo

- *cis* alkenes work well
- *trans* alkenes generally bad

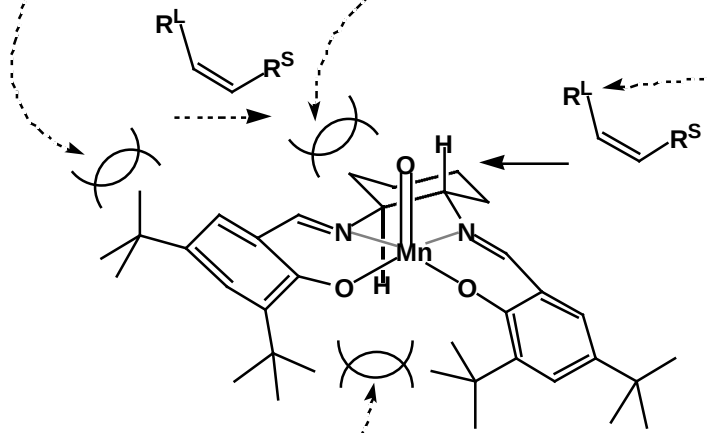
- small substituent passes axial proton



- bulky *t*Bu groups block attack from front or sides

- Jacobsen implies attack on oxo-species occurs from the back face over the diamine bidge
- Katsuki implies that skewed shape of salen complex results in attack from the side

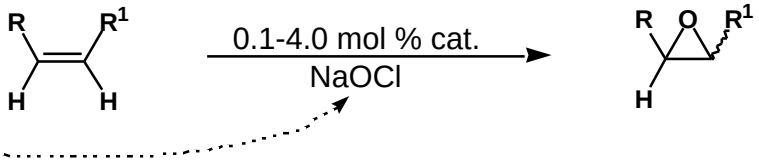
- skewed shape of salen complex shields one side of nucleophile
- back face blocked by H of cyclohexane group



- large substituent far from bulky front face

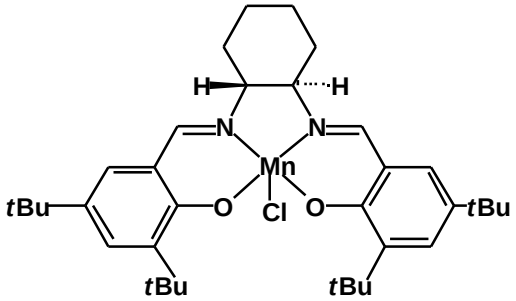
- bulky *t*Bu groups block approach from front

Use in Synthesis

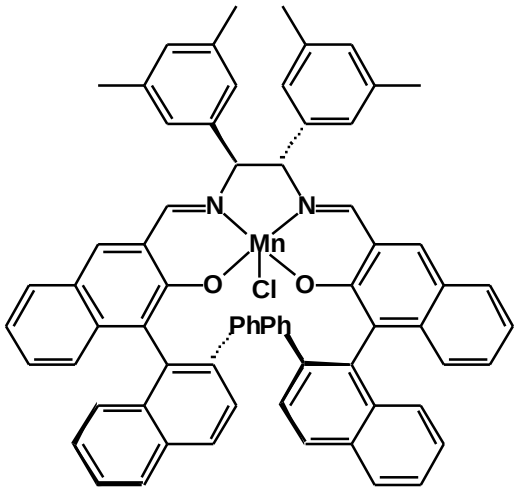


• other oxidants can be used

• Wide range of substrates tolerated
• *Cis* better than *trans*

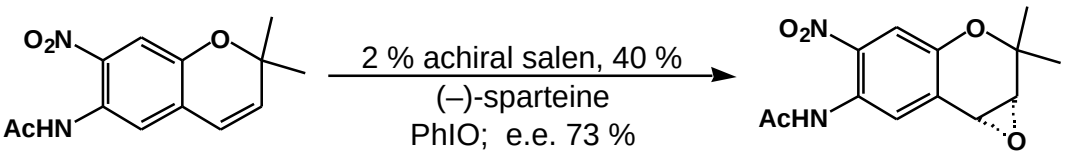


Yields = 63-87 %
e.e. = 86-98 %
cis-alkenes



Yields = 41-91 %
e.e. = 83-99 %
cis-alkenes
limited success with
trans-alkenes (e.e. 50%)

Recent Development



• use of an ***achiral salen complex*** in conjunction with a second ligand gives good (and cheaper, control

What have we learnt?
• Unfunctionalised alkenes can be catalytically epoxidised with good selectivity