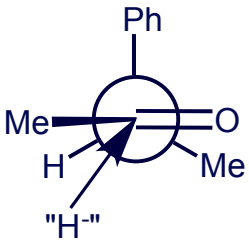
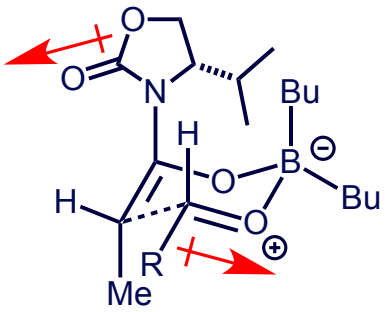
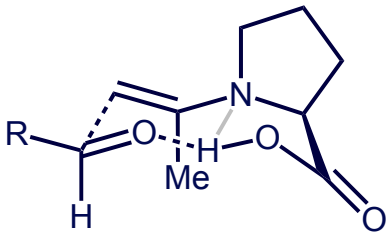
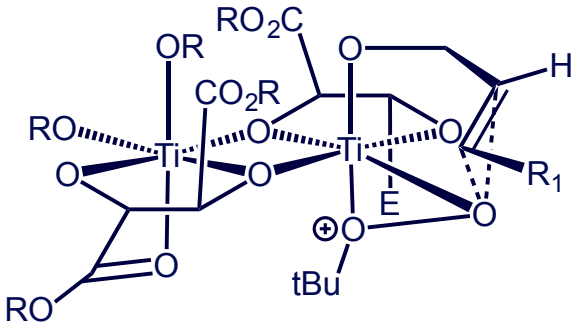
# Introduction to Stereoselective Organic Synthesis




- *Advanced Organic Chemistry: Parts A and B*, Francis A. Carey, Richard J. Sundberg
- *Organic Chemistry*, Jonathan Clayden, Nick Greeves, Stuart Warren, Peter Wothers
- *Stereochemistry of Organic Compounds*, Ernest L. Eliel, Samuel H. Wilen
- *Selectivity in Organic Synthesis*, Robert S. Ward
- *Asymmetric Synthesis*, Garry Procter

SBM

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## Table of Contents

**Stereoselective Synthesis**

- There are many different types of selectivity in organic synthesis:

  Chemoselectivity – functional group discrimination

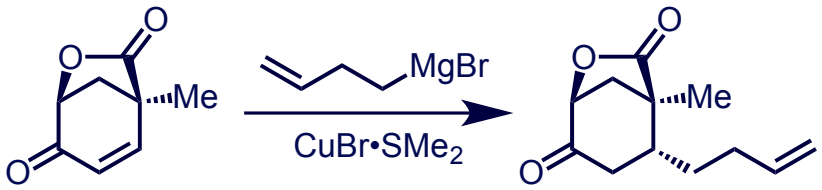
  Regioselectivity – product structural isomer discrimination

  Stereoselectivity – product stereoisomer discrimination

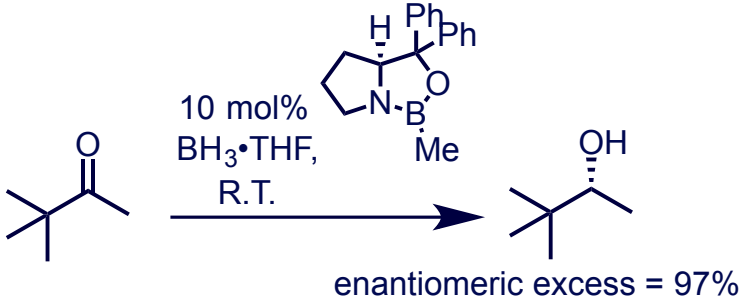
- We will be primarily concerned with *stereoselectivity* which covers:

  Diasteroeselectivity – product diastereomer discrimination

  Enantioselectivity – product enantiomer discrimination




chemoselective - enone reacts in preference to lactone (ester)
regioselective - 1,4- not 1,2-addition to enone
(dia)stereoselective - one major diastereomer formed




enantiomeric excess = 97%

enantioselective - one
major enantiomer formed

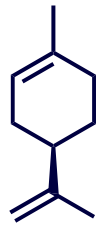
- To explain the above (and other) reactions we need to consider the following control elements: i) steric and electronic factors, ii) stereoelectronic effects, iii) associative substrate-reagent interactions (e.g. hydrogen bonding).

- In order to do this it is imperative to draw ***clear conformational diagrams***.

## The importance of controlling stereochemistry

*Why do we require reliable and predictable methods for stereocontrolled synthesis*?

- *n* Stereocentres in a molecule means there are up to $2^n$ stereoisomers.
- Poor stereocontrol in synthesis is inelegant and wasteful.
- Absolute and relative structure determination by synthesis.
- Each enantiomer of a chiral molecule (e.g. natural product) frequently has a different biological activity.
- Pharmaceutical companies required to develop chiral drugs as single enantiomers.
  - in 1988 the Food and Drug Administration (USA) required all new chiral drugs to be marketed as single enantiomers



(*R*)-(+)-limonene
smells of oranges

(*S*)-(-)-limonene
smells of lemons

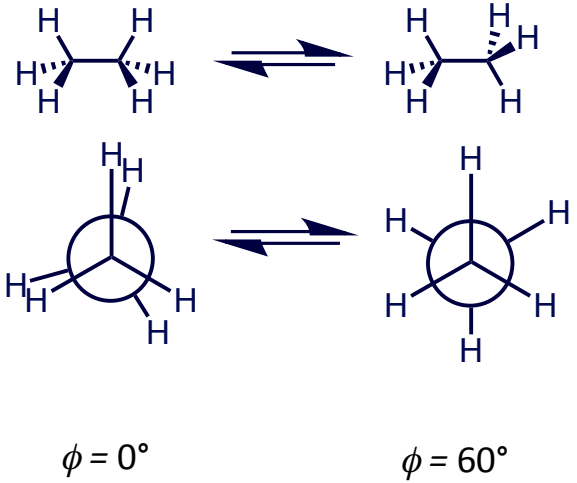
(*S*)-(-)-thalidomide
teratogen

(*R*)-(+)-thalidomide
sedative

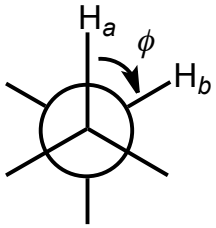
For a discussion of the FDA's ruling see: W. H. De Camp, *Chirality*, **1989**, *1*, 2-6.

## Conformational Analysis Recap

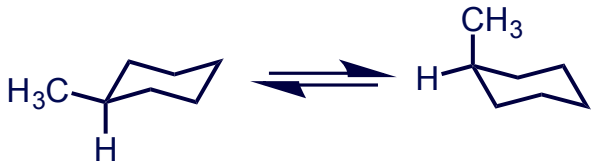
- Conformations – stereoisomers which can be interconverted by rotations about single bonds.
- Conformers, or conformational isomers – conformations corresponding to a distinct potential energy minimum.
- Conformational analysis: the assessment of the relative energies (or thermodynamic stabilities), reactivities, and physical properties of alternative conformations of a molecular entity, usually by the application of qualitative or semi-quantitative rules or by semi-empirical calculations.




$\phi$ = 0° $\phi$ = 60°

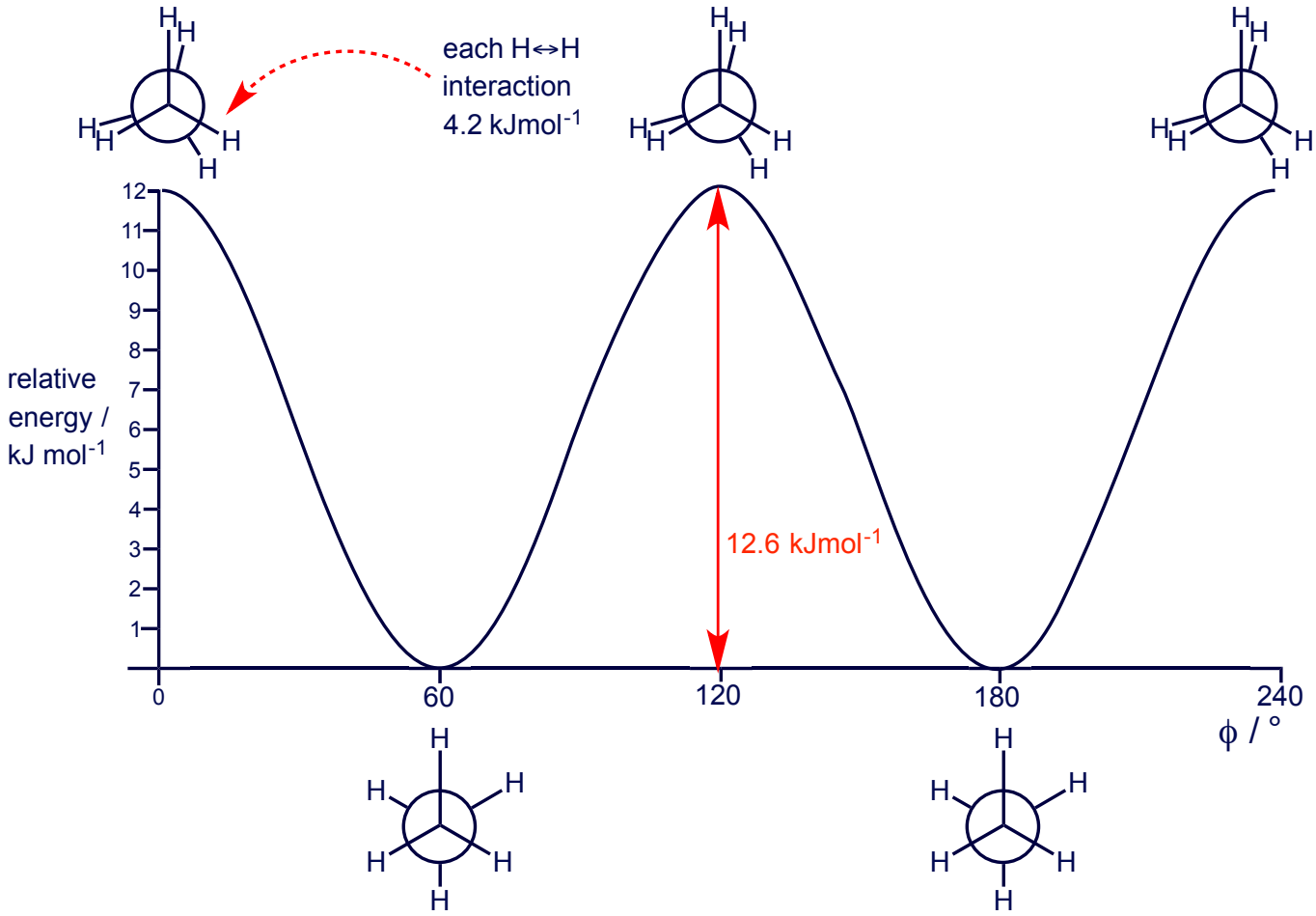



$\phi$ is the torsion angle




methylcyclohexane

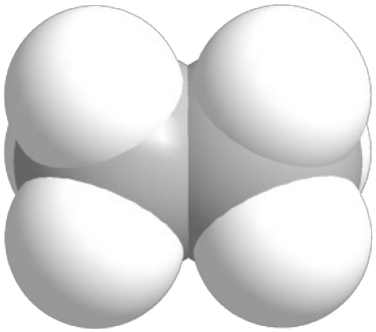
# Conformational Analysis of Ethane

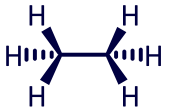



- Ethane has an infinite number of conformations due to free rotation around the C-C bond.
- There are three energy minima (staggered conformations) and three energy maxima (eclipsed conformations) in one 360 ° cycle.
- In the eclipsed conformation of ethane the hydrogen atoms do not touch.
- Why is the eclipsed conformation at the energy maxima?
- Each H↔H interaction corresponds to *ca*. 4.2 kJmol$^{-1}$

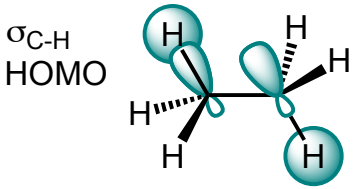
## Conformational Analysis of Ethane

- The electrons in the C-H bonds repel one another and this is greatest in the eclipsed conformation.
- In the staggered conformation there is better overlap between the $\sigma_{C-H}$ and $\sigma^*_{C-H}$ orbitals which is energy lowering.

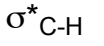


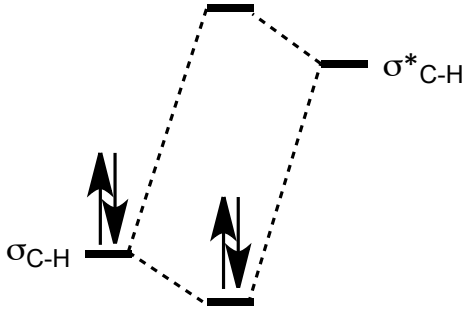



eclipsed



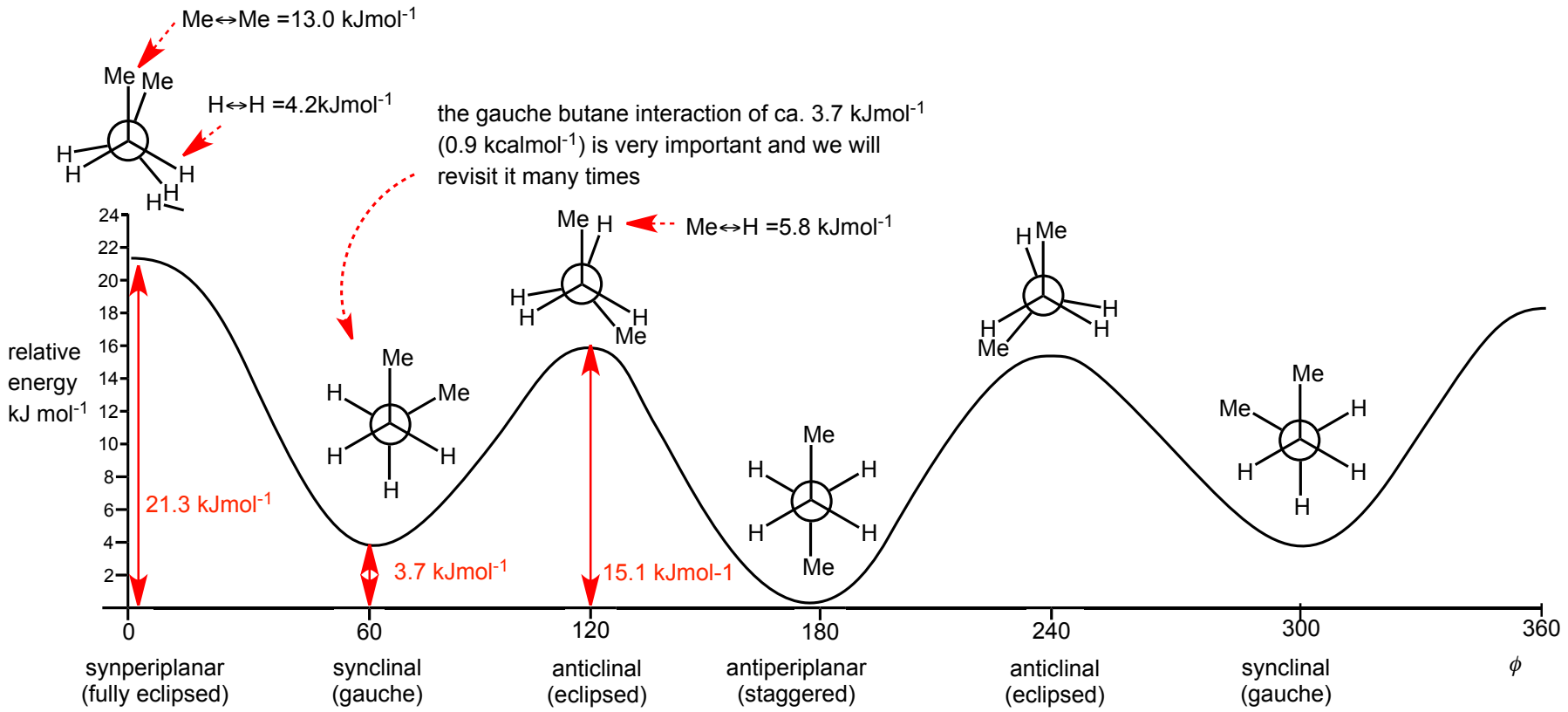

staggered




(HOMO = **H**ighest **O**ccupied **M**olecular **O**rbital; LUMO = **L**owest **U**noccupied **M**olecular **O**rbital)

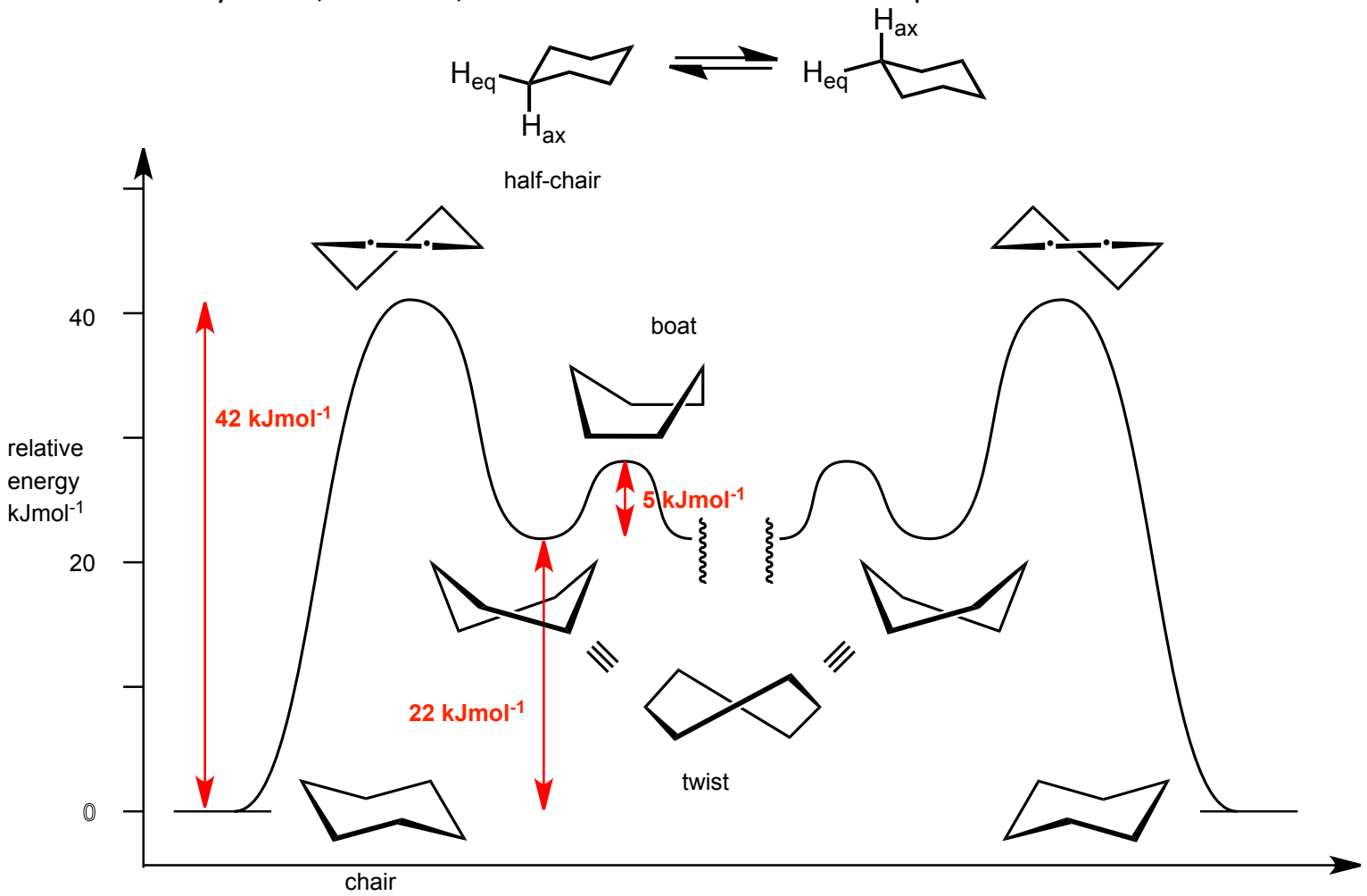
# Conformational Analysis of butane




- Conformational analysis of butane is similar to that of ethane.
- Each eclipsing Me↔Me interaction corresponds to *ca*. 13.0 kJmol$^{-1}$
- Each eclipsing Me↔H interaction corresponds to *ca*. 5.8 kJmol$^{-1}$
- Each eclipsing H↔H interaction corresponds to *ca*. 4.2 kJmol$^{-1}$
- The gauche butane interaction (Me↔Me) is worth 3.7 kJmol$^{-1}$

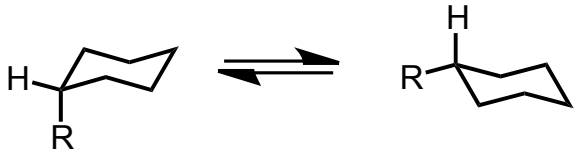
## Conformational analysis of cyclohexane

- The most stable conformations of cyclohexane are the two interconvertible chair forms.
- The chair forms interconvert by the twist form; the boat form is a transition state for the interconversion of various twist forms.
- The key thing to remember is that when one chair ring flips to give the other chair, all “up” substituents stay “up” and all “down” substituents stay down; however, all axial substituents become equatorial and *vice versa*.



## Substituted Cyclohexanes

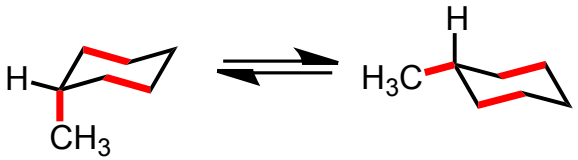
- Substituents larger than hydrogen prefer to be in the less sterically hindered equatorial position.
- The -ΔG value for the interconversion shown below in monosubstituted cyclohexanes is known as the 'A-value' and is used as a measure of the steric demand of the substituent – the greater the preference for the equatorial conformer the larger the 'A-value'.
- The 'A-value' therefore provides a quantitative measure of the how bulky various groups are.




| R | -ΔG (A) | R | -ΔG (A) | R | -ΔG (A) |
|---|---|---|---|---|---|
| H | 0 | F | 1.4 | CN | 0.84 |
| Me | 7.3 | Cl | 2.5 | CHO | 3.0 |
| Et | 7.5 | Br | 2.1 | COMe | 5.0 |
| iPr | 9.3 | I | 2.1 | $CO_2Me$ | 5.2 |
| tBu | 20 | OH | 2.5-4.4 | $CO_2H$ | 5.9 |
| Ph | 11.7 | $NH_2$ | 5.1-7.1 | $CO_2^-$ | 8.4 |

all values in $kJmol^{-1}$

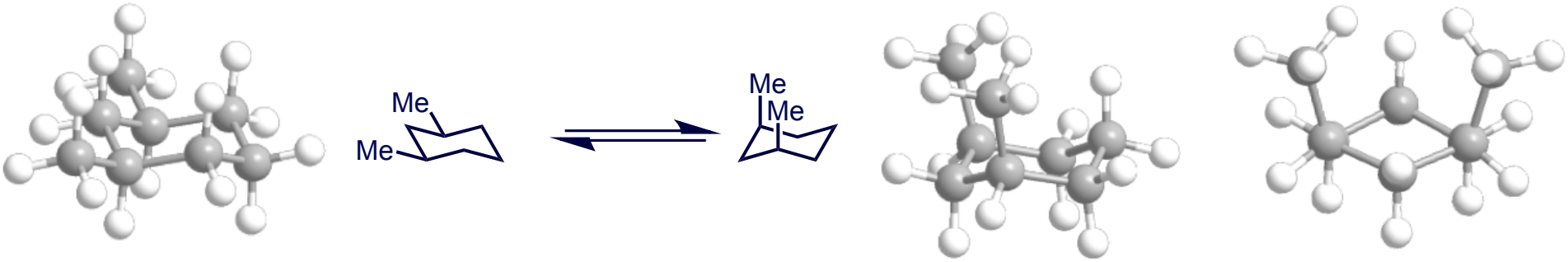
For R = $CH_3$




- With $CH_3$ in the axial conformer there are 2 x gauche butane interactions which are absent in the equatorial isomer.

- Based on this analysis we would expect methyl cyclohexane to have an A-value of 2 x 3.7 = 7.4 $kJmol^{-1}$ which is in good agreement with the experimental value.

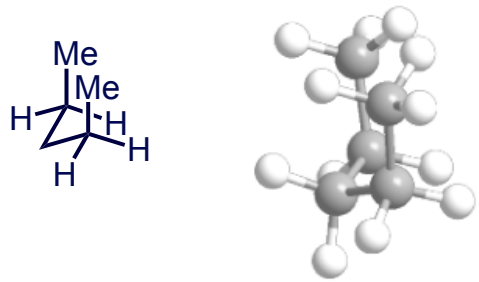
- With disubstituted cyclohexanes the "A-values" can be used additively provided the substituents do not interact in either chair conformation (e.g. in 1,4-disubstituted systems).
- With *cis*-1,3-dimethyl cyclohexane the diequatorial conformer is favoured to a very large degree.



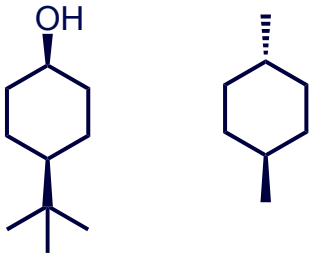

- $\Delta G° = +23\ kJmol^{-1}$ for the above equilibrium.

***Question:*** What is the value in $kJmol^{-1}$ for the Me↔Me interaction above?

- In acyclic systems this "1,3-dixaial" interaction is referred to as the "*syn*-pentane" interaction as shown below (this is the least stable conformer of pentane).




- ***Question:*** What is the most favourable conformation of each of the molecules below?



## Stereoselective organic synthesis

- To synthesise a single diastereomer of a molecule efficiently it is necessary to use stereoselective reactions either controlled by the substrate or controlled by the reagent / catalyst.

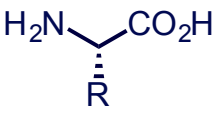
- To synthesise a single enantiomer of a molecule the above approach may be used with a resolution occurring at some stage.

- To synthesise a single enantiomer of a molecule without resorting to resolution, a chiral pool starting material may be used.

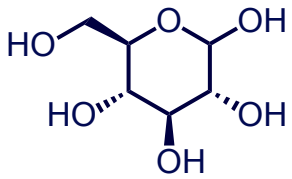
- Using an enantiomerically pure (chiral pool) starting material then allows the introduction of further stereocentres using substrate or reagent-controlled reactions.

- Using an enatiomerically pure reagent, auxiliary or catalyst to "install" the required stereochemical information into the product gives much greater flexibility to the synthetic approach.

**The Chiral Pool** Amino acids Sugars Terpenes Hydroxy acids etc.




α-amino acids



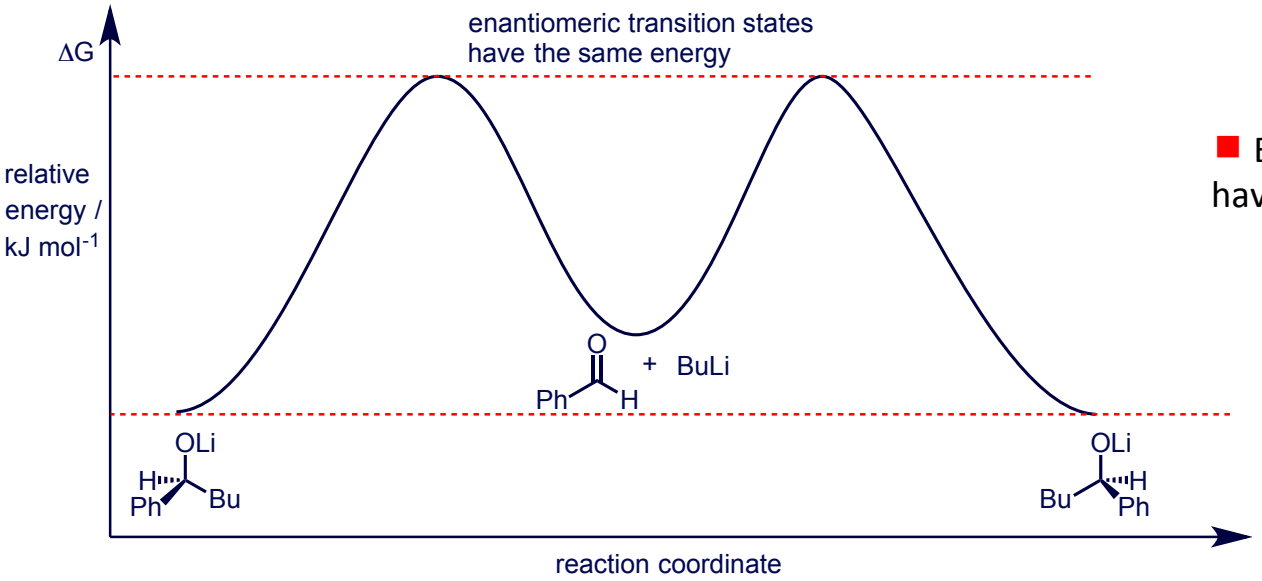

D-hexoses


α-pinene (terpene)


tartaric acid

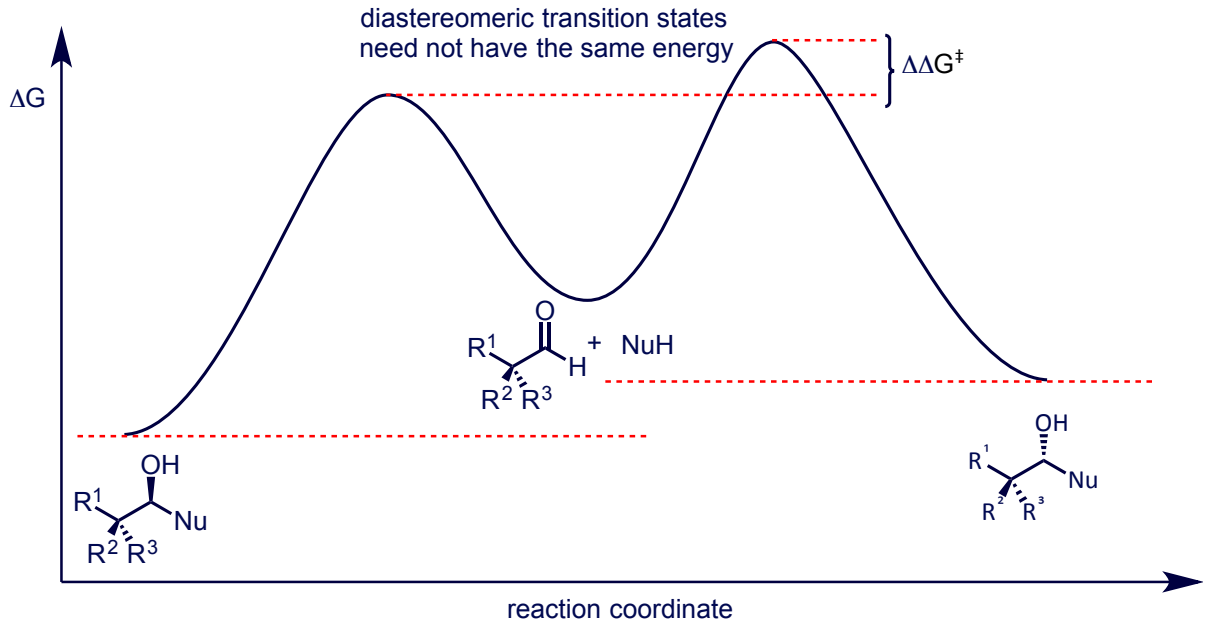
For a review of substrate controlled chemical reactions see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.*, **1993**, *93,* 1307.

# Diastereoselectivity



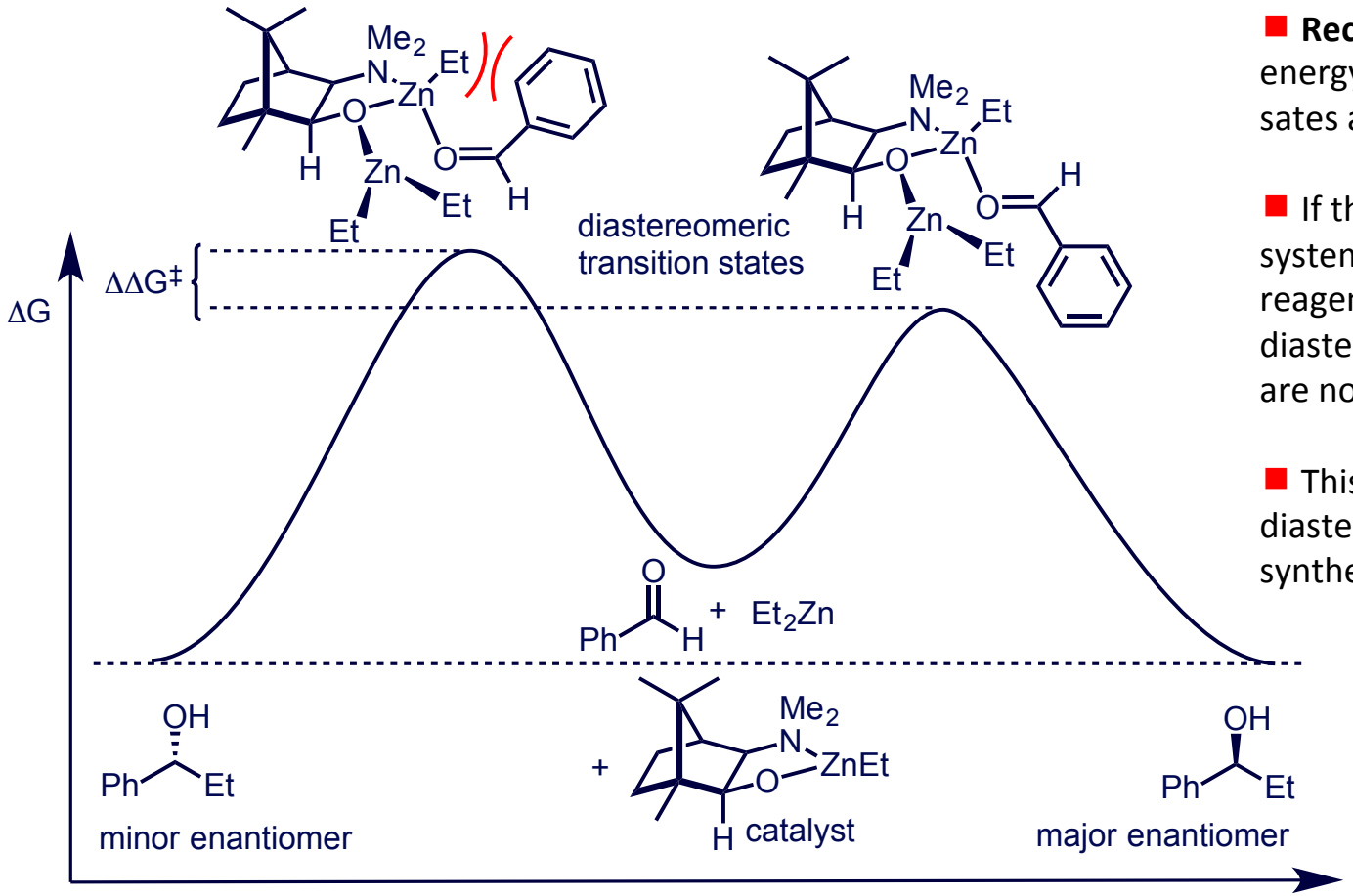

- Enantiomeric transition states have the same energy

- Diastereomeric transition states generally do not have the same energy



## Asymmetric induction: Enantioselective Synthesis

*Example*: Addition of diethylzinc to aldehydes in the presence of a chiral catalyst




- **Recap:** enantiomers are equal in energy and hence enantiomeric transition sates are equal in energy
- If there is a source of chirality in the system (e.g. chiral substrate, chiral reagent, chiral catalyst) then we can have diastereomeric transition states which are not necessarily equal in energy.
- This forms the basis for *all* diastereoselective and enantioselective synthesis.

*Note: all of these reactions are under kinetic control – i.e. the reaction outcome is determined by the relative energy of the competing transitions sates NOT by the relative energy of the products.*

## Asymmetric Induction

- Under kinetic control the selectivity depends on the difference in energy of the two transition states ($\Delta\Delta G^{\ddagger}$) and the ratio of products is determined by the Boltzmann distribution

$$\text{Product 1 / Product 2} = e^{-\Delta\Delta G^{\ddagger}/RT}$$

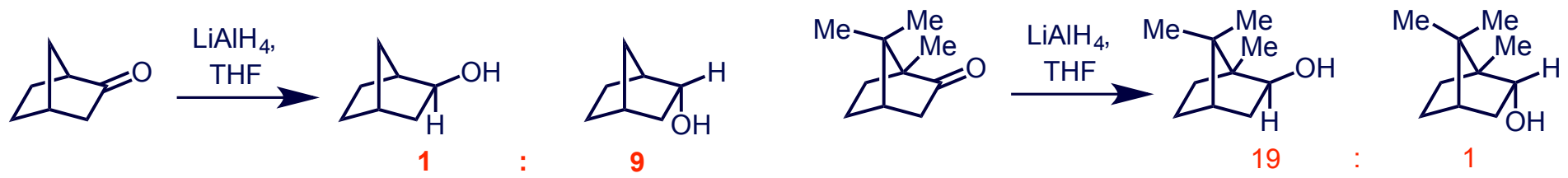
- This ratio depends on the temperature - lowering the temperature results in increased selectivity.

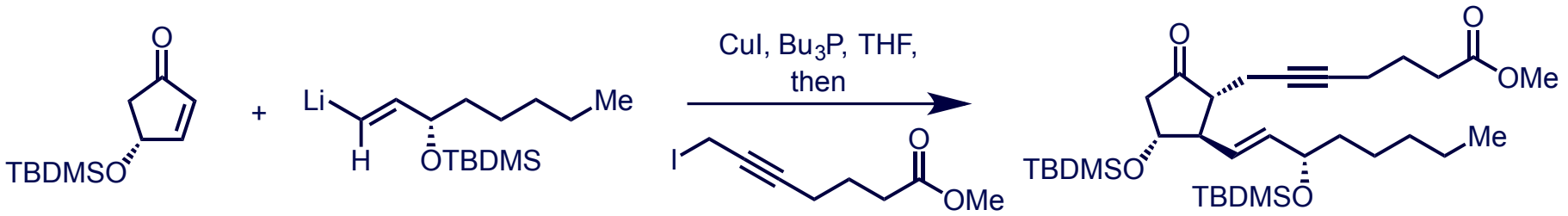
| $\Delta\Delta G^{\ddagger}$ / kJmol$^{-1}$ | T | product ratio |
|---|---|---|
| 8.0 | 25 °C (298 K) | 25:1 |
| 8.0 | -78 °C (195 K) | 139:1 |

| product ratio | d.e. (or e.e.) | $\Delta\Delta G^{\ddagger}$ / kJmol$^{-1}$ |
|---|---|---|
| 1 | 0 | 0.00 |
| 3 | 50 | 2.72 |
| 9 | 80 | 5.44 |
| 19 | 90 | 7.30 |
| 99 | 98 | 11.4 |
| 999 | 99.8 | 17.1 |
| 9999 | 99.98 | 22.8 |

all values calculated at 25 °C (298 K)

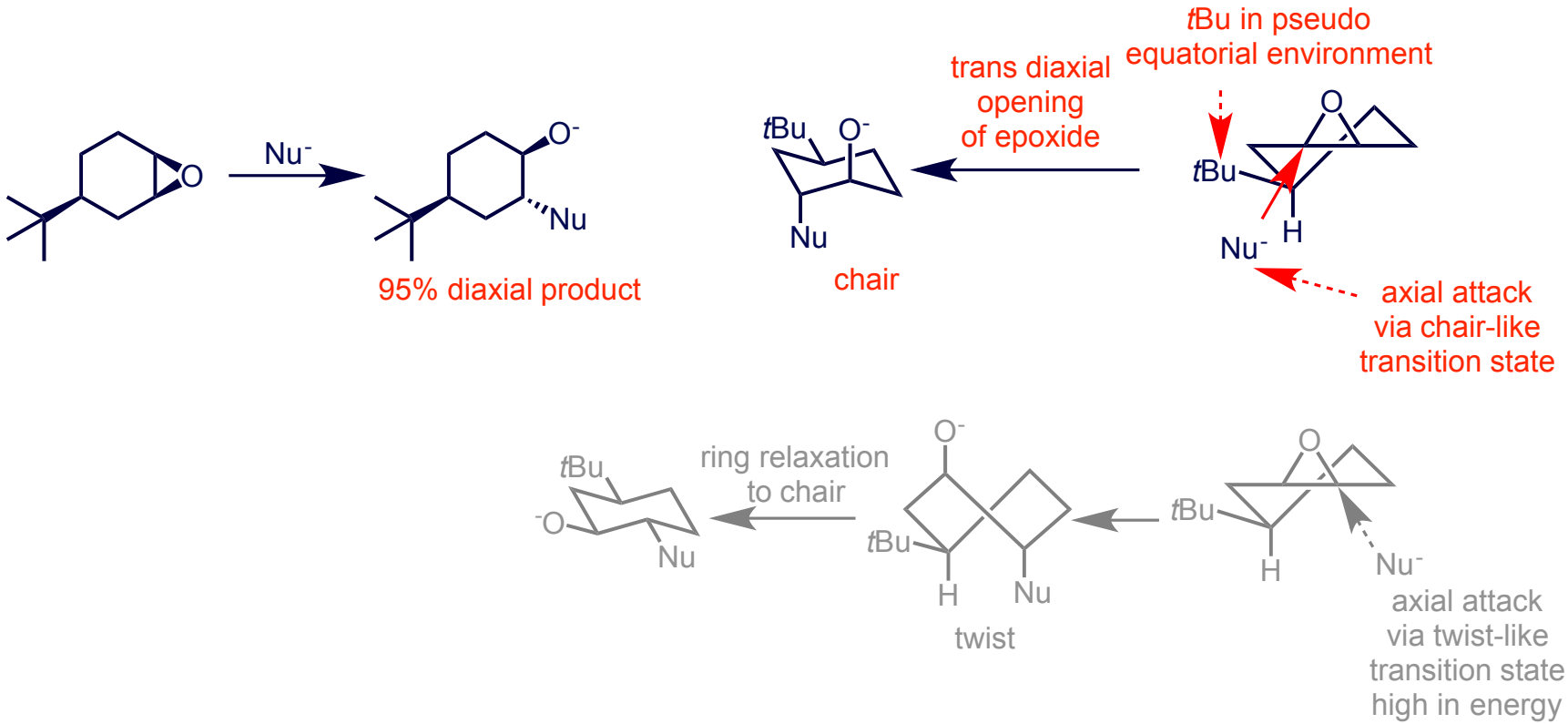
- With cyclic systems the diastereocontrol is frequently easy to rationalise.



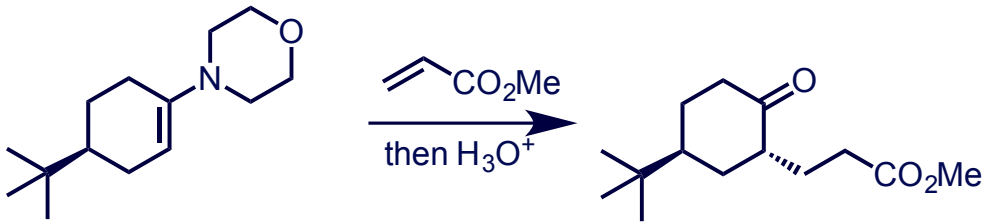




M. Suzuki, A. Yanagisawa, R. Noyori, *J. Am. Chem. Soc.*, **1985**, *107*, 3348.

■ Remember that in the cyclohexene, cyclohexanone and related systems, both electrophilic and nucleophilic attack are stereoelectronically controlled. *Axial* attack *via* chair-like transition states is preferred.



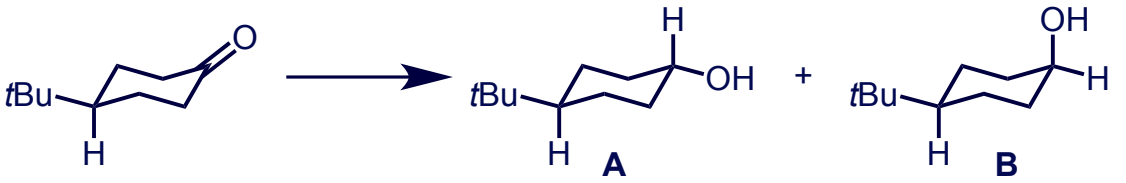

***Problem***: Explain the stereochemical outcome of the following reaction.



# Diastereoselective Addition to carbonyl compounds

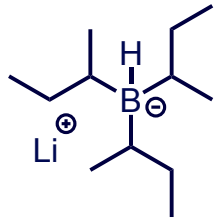
*Example: reduction of cyclohexanones*

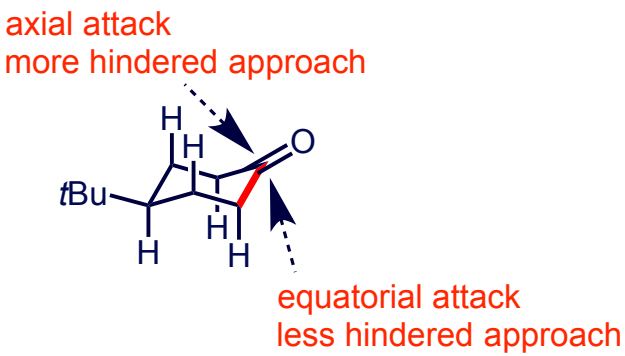
- In general with "small" hydride reagents e.g. $LiAlH_4$ and $NaBH_4$, the major diastereomer arises from "axial" attack of "$H^-$".
- For "large" hydride reagents e.g. $H\text{-}BR_3^-$, the major diastereomer arises from "equatorial" attack.

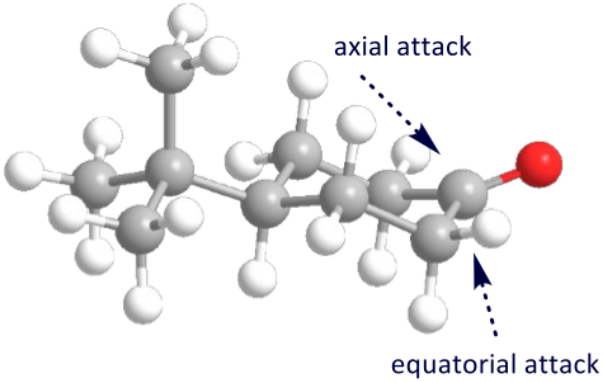



| Reagent | Ratio, **A**:**B** |
|---|---|
| $LiAlH_4$ | 93:7 |
| $NaBH_4$ | 79:21 |
| DIBAL-H | 72:28 |
| L-Selectride | 8:92 |
| K-Selectride | 3:97 |

L-Selectride =




- Equatorial attack is favoured sterically so why do "small" nucleophiles favour axial attack?

*(Remember, nucleophilic attack on carbonyl compounds takes place* via *the Burgi-Dunitz trajectory – more later)*

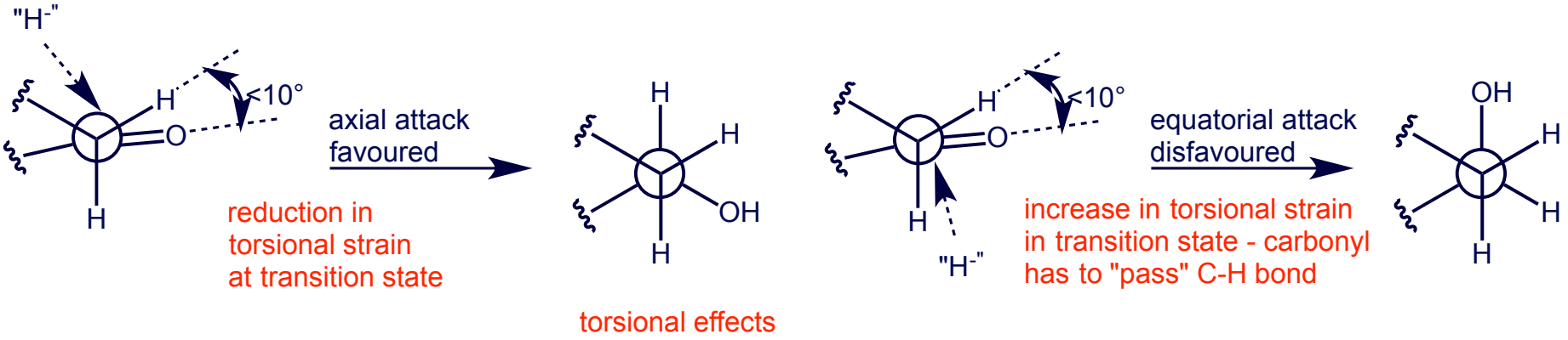
## Addition to cyclohexanone – torsional effects

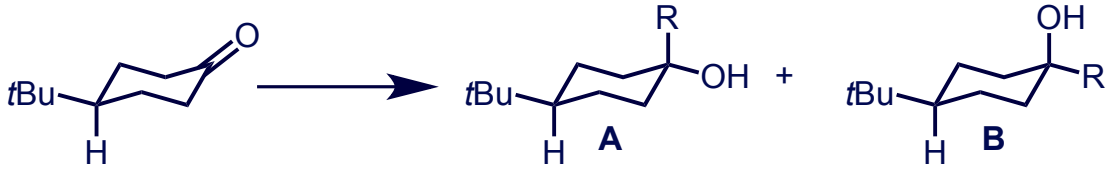
- For axial attack there is a *decrease* in torsional strain (eclipsing interactions) in proceeding from the starting material to the transition state.

- For equatorial attack there is an *increase* in torsional strain (eclipsing interactions) in proceeding from the starting material to the transition state.

- Therefore, large nucleophiles attack across the equatorial face of the C=O group – axial attack is precluded sterically.

- With small nucleophiles, torsional effects dominate and hence attack across the axial face of the C=O group dominates.

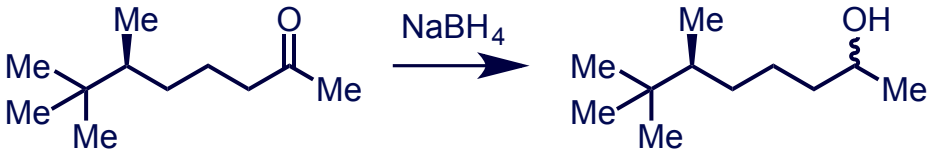


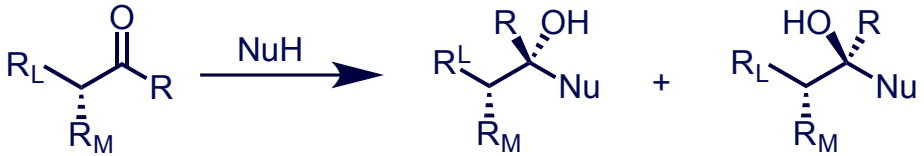

| Reagent | Ratio, **A**:**B** |
|---|---|
| EtMgBr | 53:47 |
| *i*PrMgBr | 18:82 |
| *t*BuMgBr | 0:100 |

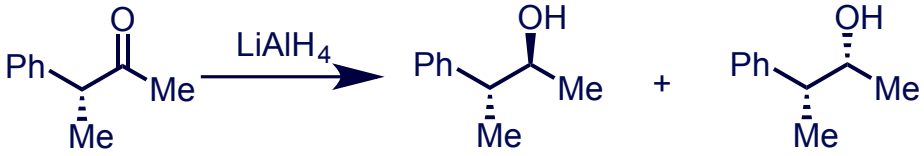
## Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

- Molecules with a high degree of flexibility tend to react unselectively.




- Aldehydes and ketones with α-stereocenters show some selectivity.

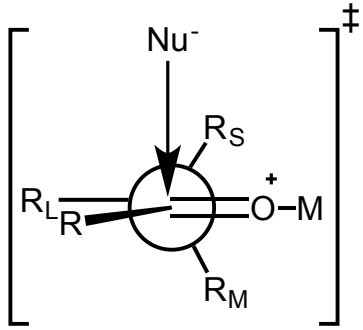



- The addition of nucleophiles to aldehydes and ketones bearing an α-stereocentre has been the subject of a good deal of research and numerous models to rationalise the selectivities have been put forward.

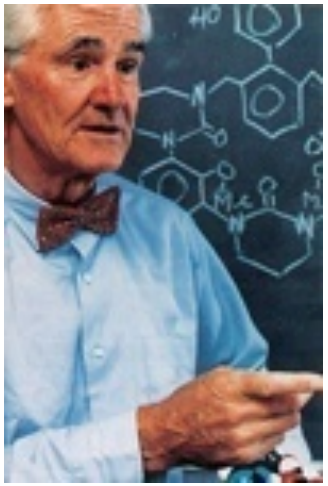
# Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

## Historical Perspective



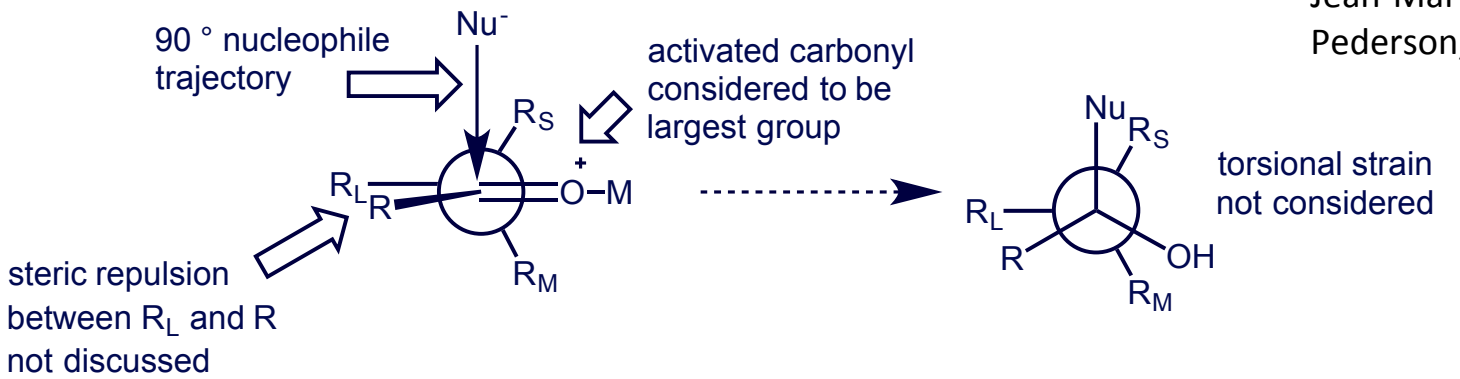

Cram acyclic model

- Cram's Rule: "In reactions of the following type, that diastereomer will predominate which would be formed by the approach of the entering group from the *least hindered side of the double bond when the rotational* conformation of the C–C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric centre."



Donald J. Cram, Nobel Prize with Jean-Marie Lehn and Charles J. Pederson, 1987

Features and problems

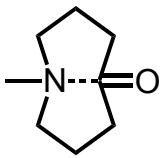


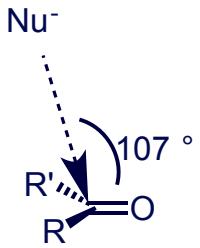

Cram, D. J.; Elhafez, F. A. A., *J. Am. Chem. Soc.*, **1952**, *74*, 5828
Different model put forward by Karabatos in 1967; Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89,* 1367

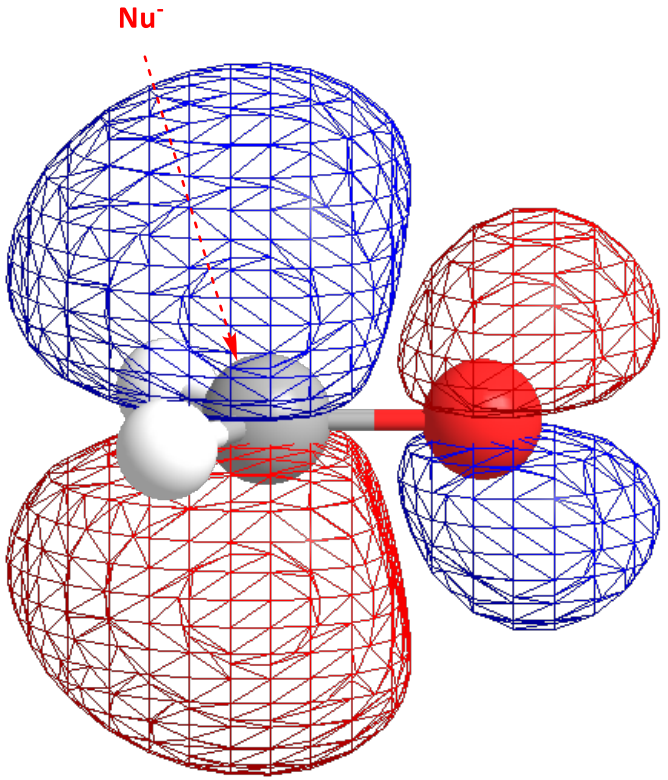
# Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

## The Bürgi-Dunitz trajectory

- Cram's rule assumes that the nucleophile approaches perpendicular to the plane of the carbonyl group.
- In the 1970s two crystallographers, Hans-Beat Bürgi and Jack D. Unitz, determined the trajectory of attack on a carbonyl group by analysis of the X-ray structures of a number of cyclic amino ketones.
- The Burgi-Dunitz angle is approximately 107 ° - close to the tetrahedral angle.
- Attack along the Burgi Dunitz trajectory maximises overlap of the nucleophile HOMO with the LUMO of the carbonyl group (π* orbital).



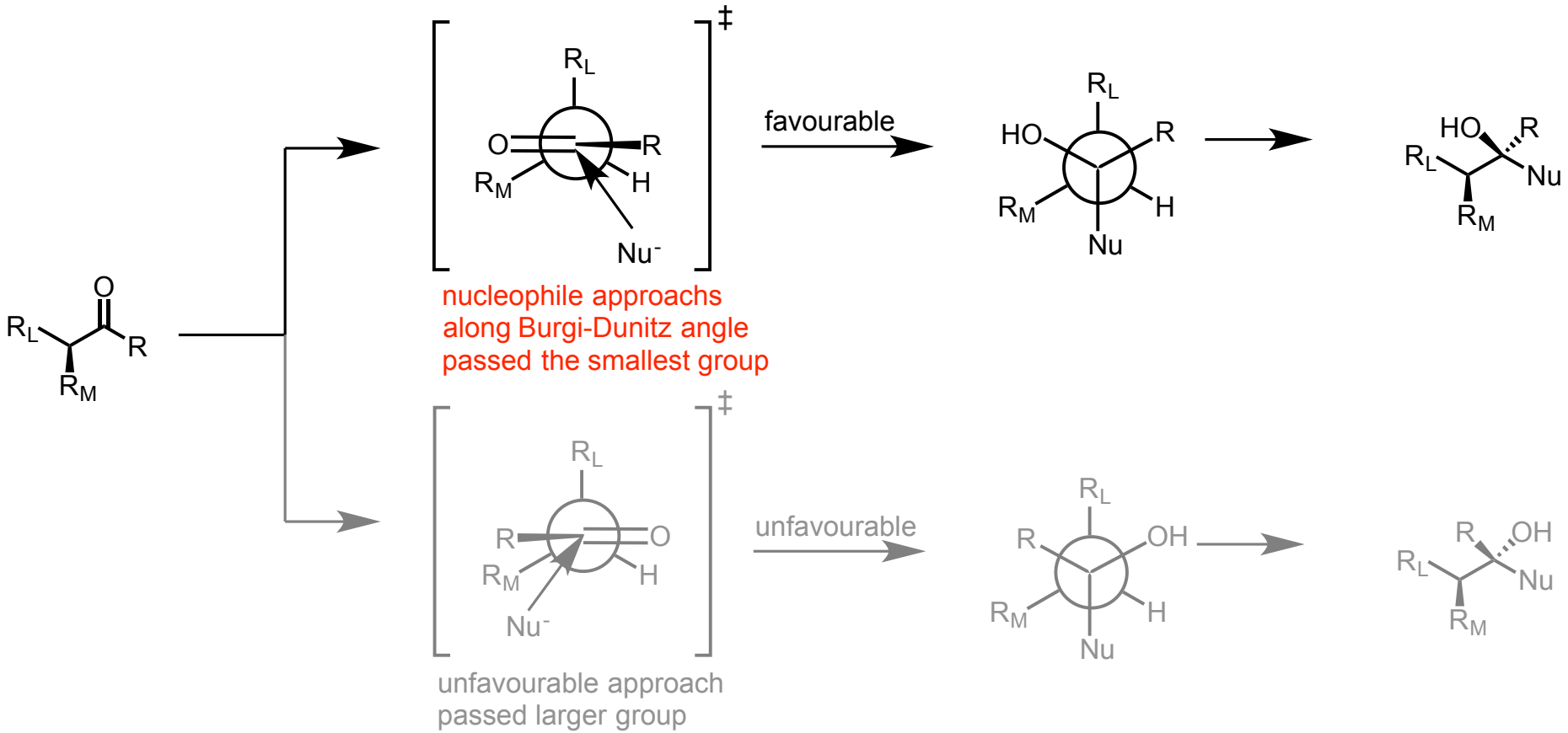

Bürgi, H.B.; Dunitz, J.D.; Lehn , J.M., G. Wipff, *Tetrahedron,* **1974**, *30*, 1563.

# Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

- **Felkin-Anh Model** – most widely used and accepted model for addition of nucleophiles to α-chiral aldehydes and ketones

**Assumptions**:

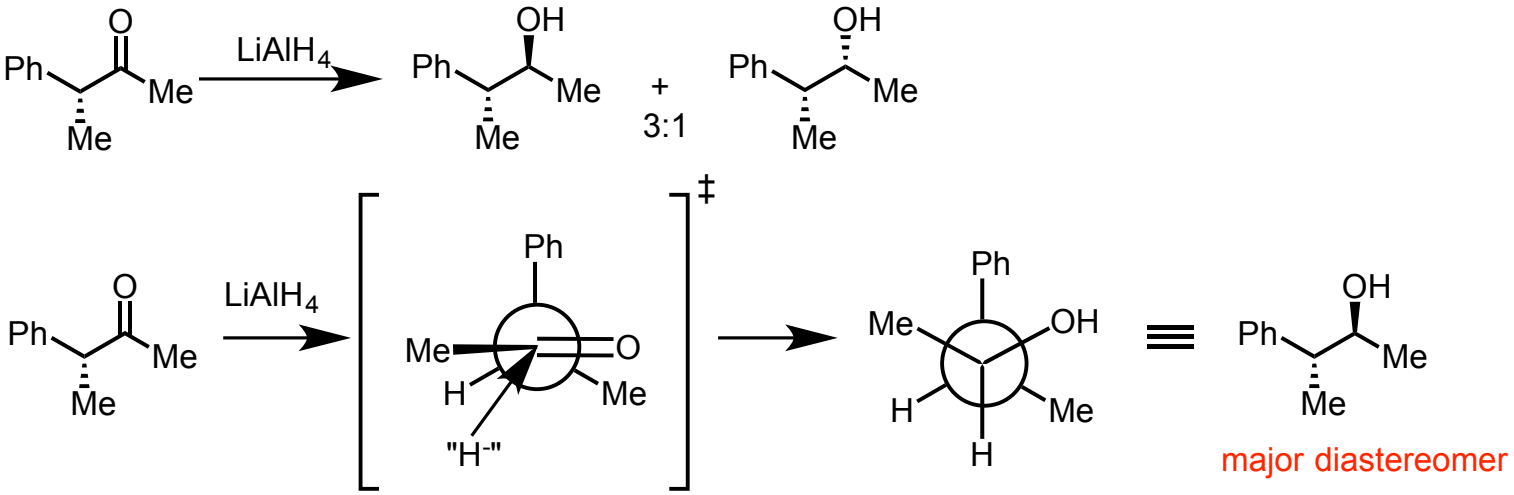
- Transition states are all reactant-like rather than product like.
- Torsional strain considerations are dominant hence staggered transition state conformations are dominant.
- Reactive conformation has the largest group perpendicular to the plane containing the carbonyl group RC=O.
- The nucleophile approaches along the Burgi-Dunitz trajectory ~107° for best overlap with the C=O π* orbital.

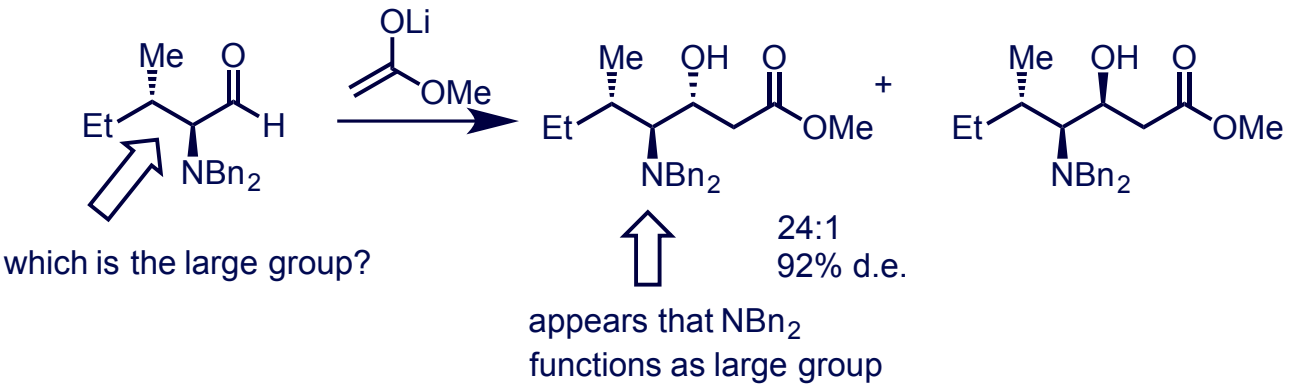



Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199; Anh, N. T.; Eisenstein, O. *Nouv. J. Chim*. **1977**, *1*, 61; Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065; Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563

# Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

*Examples*



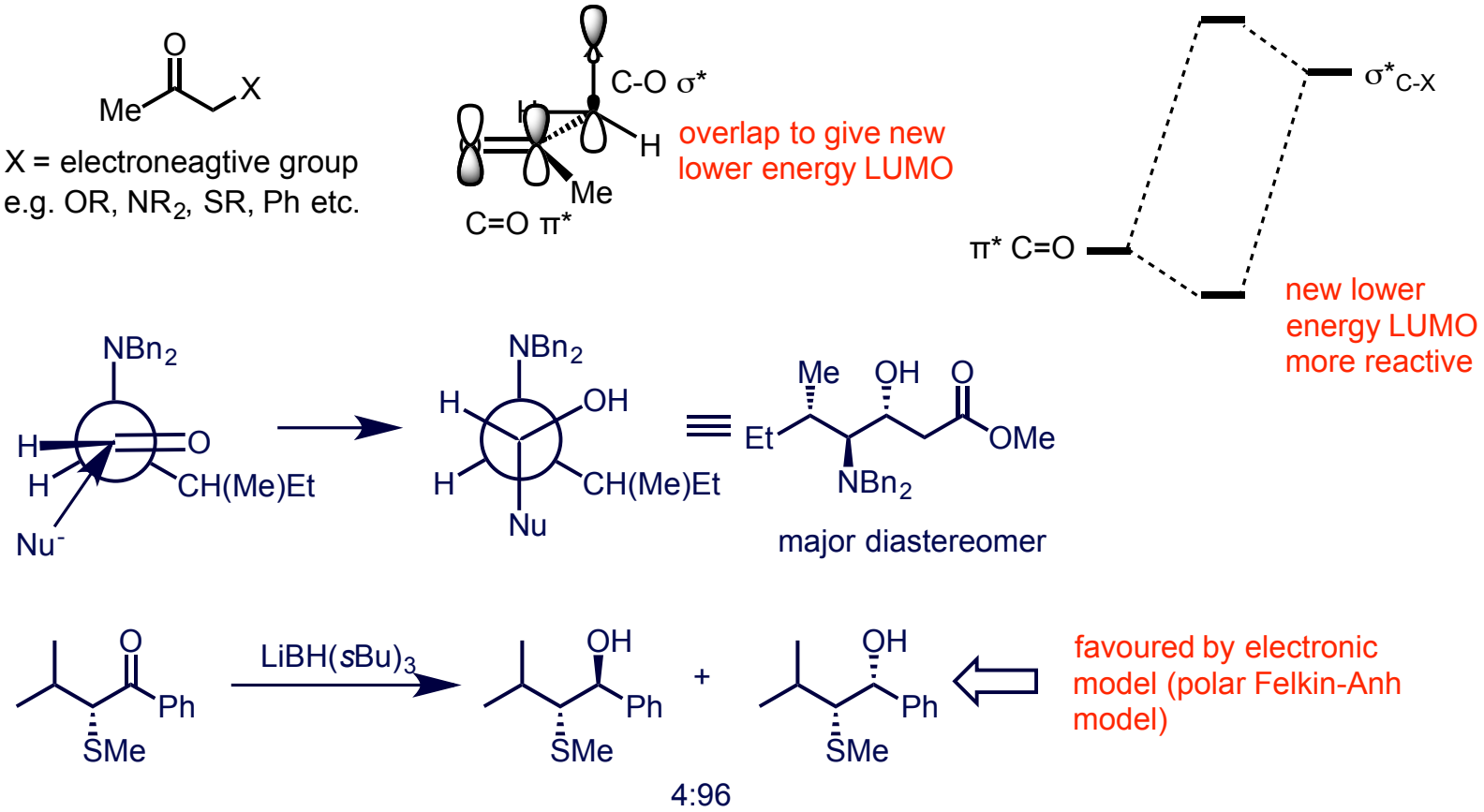




- Why is the stereocontrol so good when $NBn_2$ and CH(Me)Et are similar in size?

# Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

**Polar Felkin-Anh Model** – use for aldehydes/ketones with α-electronegative groups.

- Conformations where electronegative groups are perpendicular to the plane of the RC=O group are more reactive to nucleophilic attack.



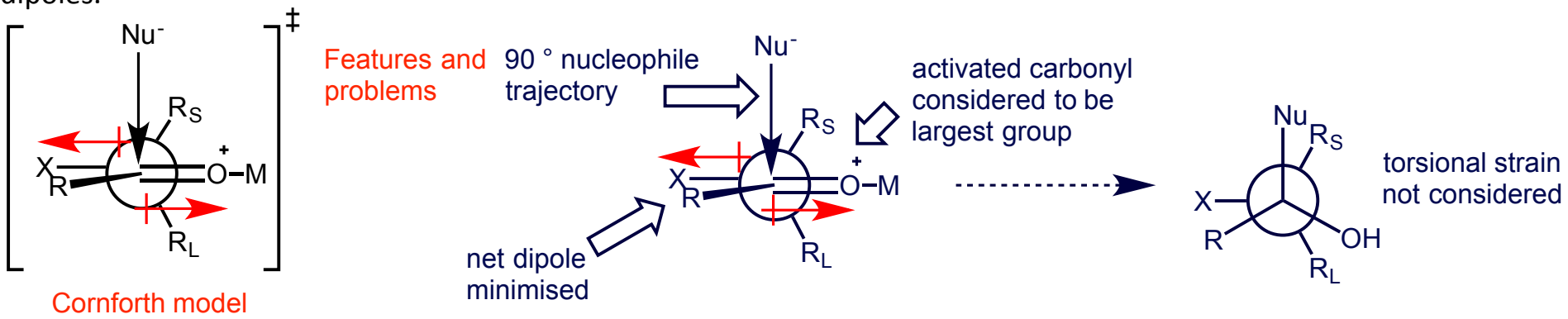

- Note: the reactive conformation of the substrate is not necessarily the ground state conformation. As all of the above reactions are kinetically controlled it is the energies of the competing transition states which are important.

Anh, N. T.; Eisenstein, O. *Nouv. J. Chim*. **1977**, *1*, 61

# Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

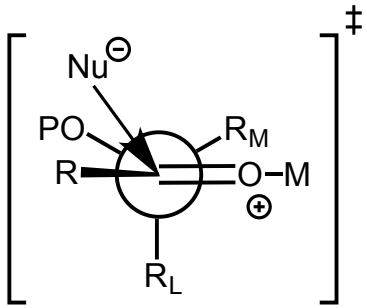
■ **Cornforth-Evans Model** - polar Felkin-Anh model does not support all of the available experimental data (nevertheless it is a useful predictive tool).

■ In the 1950s Cornforth proposed a model for addition to α-heteroatom substituted carbonyls based on the minimisation of dipoles.




■ In 2003 the Cornfoth model was modified by Evans to take into account the Burgi-Dunitz angle and minimisation of torsional strain.

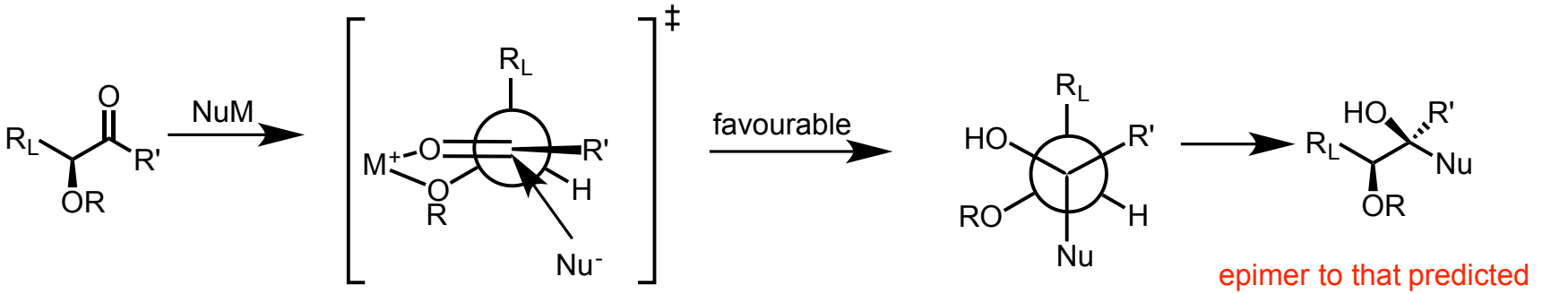
■ The model predicts the same major diastereomer as the polar-Felkin-Anh model but assumes a more ionic transition state with dipole minimisation.

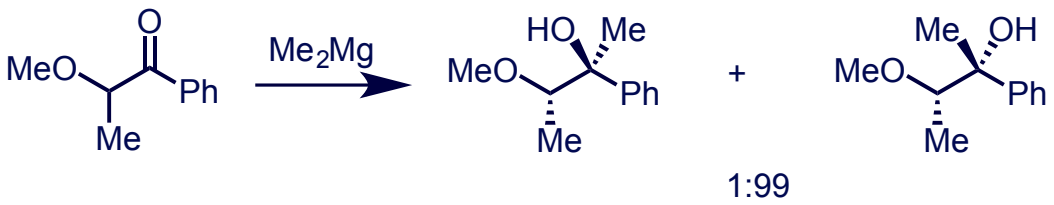



D. A. Evans, S. J. Siska, V. J. Cee, *Angew. Chem., Int. Ed.*, **2003**, *42*, 1761.

## Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

■ **Cram-Chelate model** – use for aldehydes/ketones with α-electronegative groups when chelation between the α-electronegative group and the carbonyl group is possible.




■ Two things are required for chelation control: i) a heteroatom available for coordination to a metal ion;
ii) a metal ion that favours coordination to both C=O and the heteroatom.

■ $Mg^{2+}$ , $Zn^{2+}$ , $Al^{3+}$ , $Ce^{3+}$ , $Ti^{4+}$ generally excellent at chelation (highly charged cations generally good).

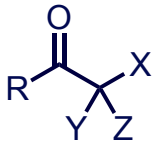
■ $Li^{+}$ sometimes can chelate.

■ $Na^{+}$ and $K^{+}$ generally poor at chelating.

Cram, D. J.; Elhafez, F. A. A., *J. Am. Chem. Soc.*, **1952**, *74*, 5828
Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748

# Acyclic Stereocontrol – attack on aldehydes and ketones with α-stereocentres

## Summary



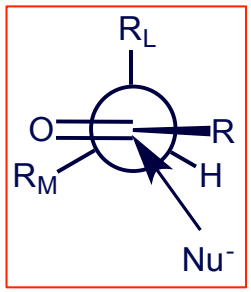

Is there a heteroatom at the α-stereogenic centre?

**YES**

Is there a metal ion capable of chelation with the heteroatom?

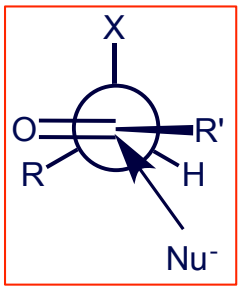
**NO**

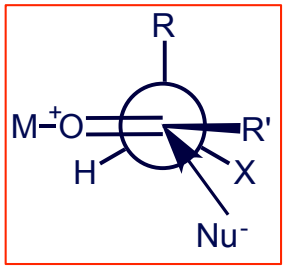
Use Felkin-Anh model:
consider reactions on conformations with largest group perpendicular to RC=O plane.




**NO**

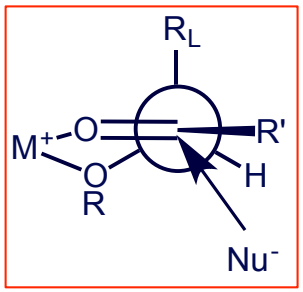
Use polar Felkin-Anh model:
consider reactions on conformations with the most electronegative atom perpendicular to RC=O plane.
Or use Evans-Cornforth model – minimise dipoles.



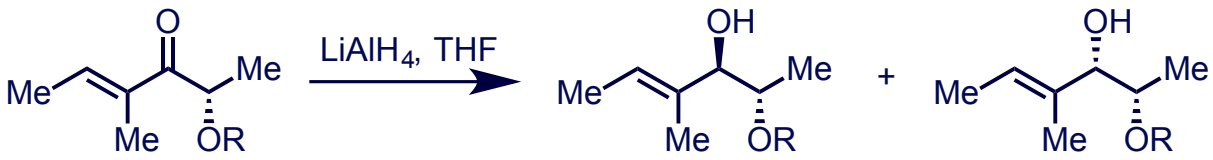

**YES**

Use Cram-chelate model:
consider reactions on conformations with C=O and heteroatom chelated by metal ion.



**Problem:** Rationalise the stereochemical course of the following reactions.

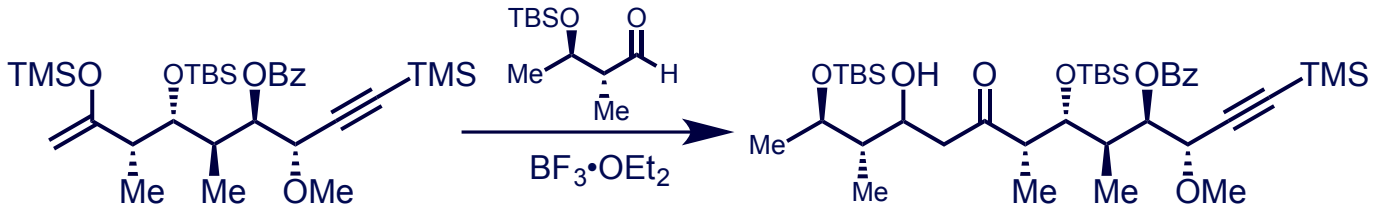
L. E. Overman, R. J. McCready, *Tetrahedron Lett.*, **1982**, *23*, 2355.




| | | |
|---|---|---|
| R = $CH_2OBn$ | 70 | 30 |
| R = $SiPh_2tBu$ | 5 | 95 |

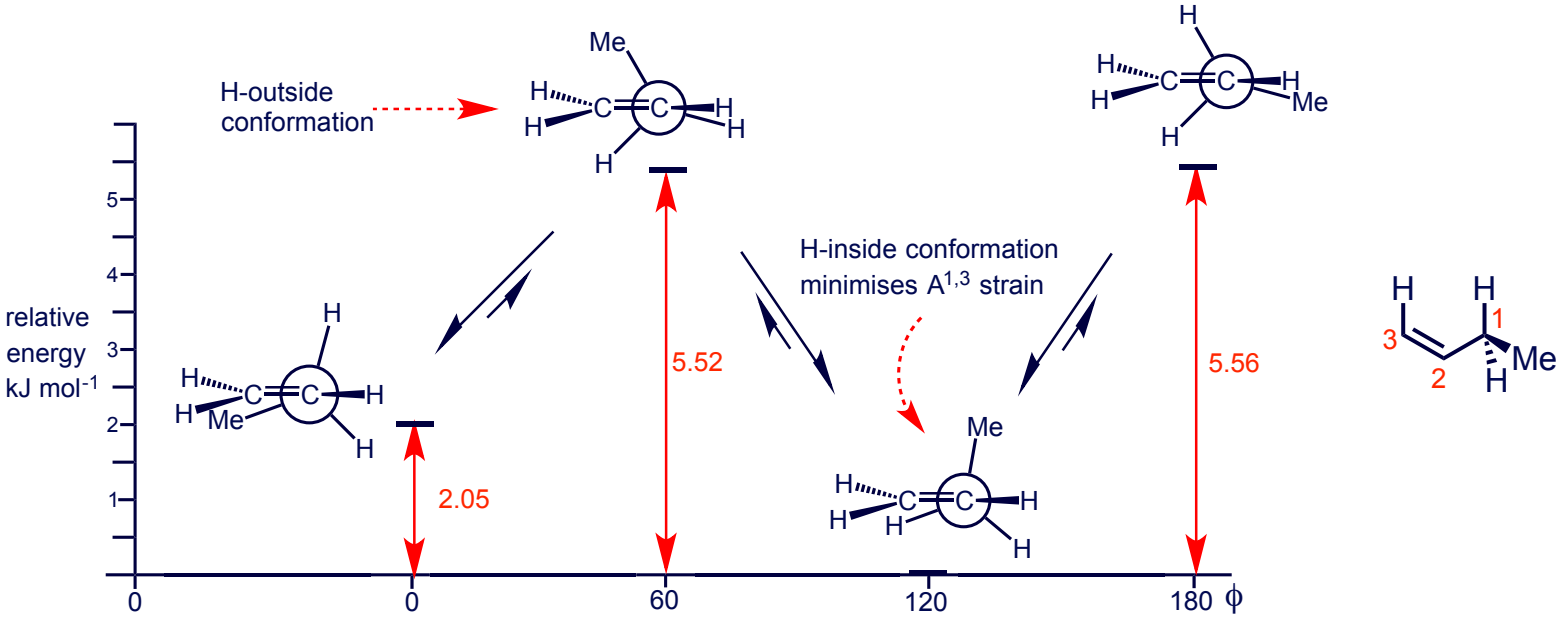
**Problem:** Predict the stereochemical outcome of the following reaction.

T. B. Durham, N. Blanchard, B. M. Savall, N. A. Powell, W. R. Roush, *J. Am .Chem. Soc.*, **2004**, *126*, 9307.

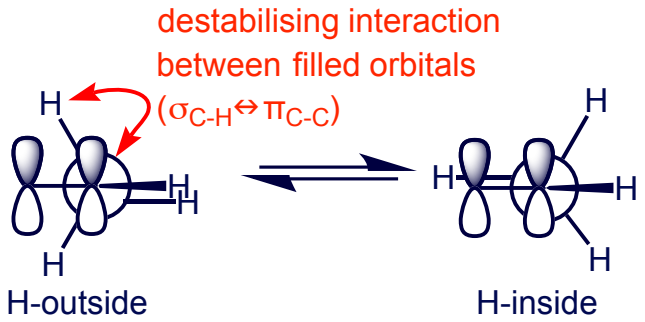


# Acyclic Stereocontrol – attack on alkenes with α-stereocentres

- The low energy conformations of alkenes carrying allylic substituents have one substituent eclipsing the alkene.
- The lowest energy conformation of but-1-ene has the hydrogen atom (smallest group) eclipsing the alkene.
- Another low energy conformation has the methyl group eclipsing the alkene.
- Eclipsing the smallest group with the alkene minimises allylic 1,3-strain ($A^{1,3}$ strain).




- The H-outside conformation suffers from destabilising overlap of filled orbitals which is absent in the H-inside conformation.
- With (Z)-alkenes the difference in energy between Me-inside and H-inside is greatly increased.

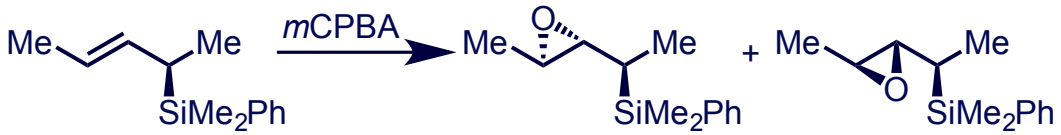



Wiberg, K. B.; Martin, E., *J. Am. Chem. Soc.* **1985**, *107*, 5035.
Dorigo, A. E., Pratt, D. W., Houk, K. N., *J. Am. Chem. Soc.* **1987**, *109*, 6591.
For a review see: R. W. Hoffmann, *Chem. Rev.*, **1989**, *89*, 1841.

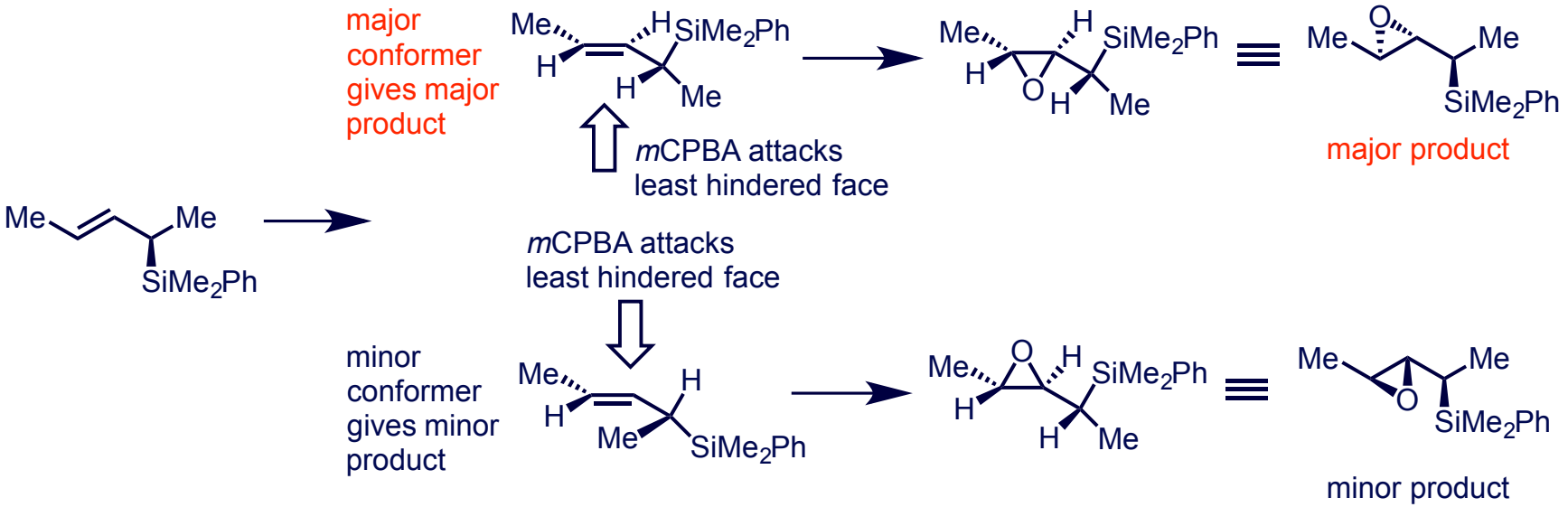
# Acyclic Stereocontrol – attack on alkenes with α-stereocentres

## Strategy

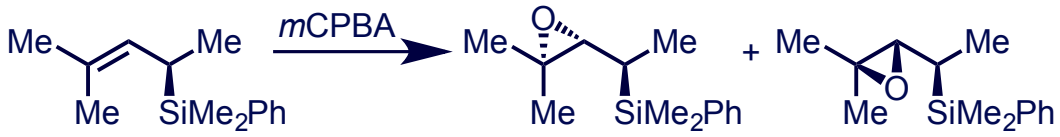
- Draw lowest energy conformation of alkene.
- Is the approach of the reagent to both sides of the alkene equally favourable?
- Watch out for groups capable of delivering the reagent to one face of the alkene.

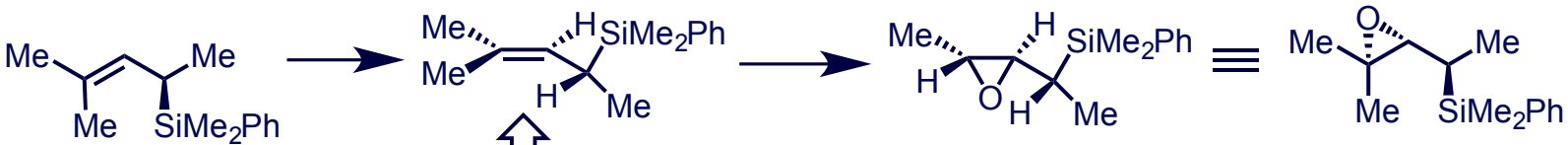



61:39



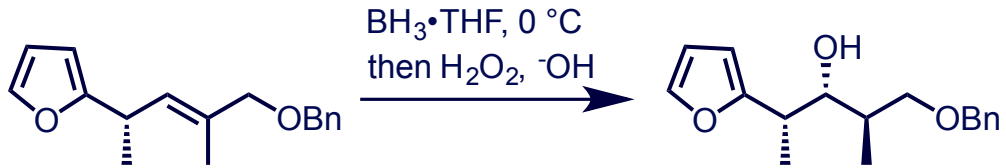
# Acyclic Stereocontrol – attack on alkenes with α-stereocentres




for *cis*-alkenes
only one heavily populated
conformer

***Problem***: Explain the stereochemical outcome of the following reaction from Kishi's synthesis of monensin.
G. Schmid, T. Fukuyama, K. Akasaka, Y. Kishi, *J. Am. Chem. Soc.*, **1979**, 101, 259.




***Problem***: Predict the stereochemistry of the major diastereomer formed in the following reaction.
W. Bernhard, I. Fleming, D. Waterson, *Chem. Commun*, **1984**, 28.

## Diastereoselective synthesis – Chiral Auxiliaries

- In order to achieve asymmetric synthesis, at least one component in the reaction must be chiral and non-racemic.
- A general approach is the use of chiral auxiliaries.
- A prochiral substrate is attached to a chiral, non-racemic group – the chiral auxiliary.
- The reaction is conducted which results in diastereomeric products which may be readily separated.
- Cleavage of the auxiliary from the purified reaction mixture yields the chiral, non-racemic, products.
- The requirements of a good chiral auxiliary are as follows:

    i) enantiomerically pure and available as both enantiomers

    ii) cheap and available in quantity

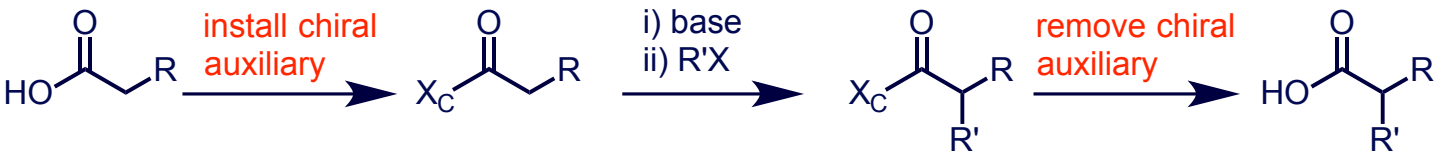
    iii) easy to introduce into the substrate

    iv) gives high and predictable diastereocontrol

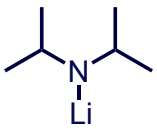
    v) easy to purify the major diastereomer

    vi) easy to remove from product without loss of diastereomeric and enantiomeric purity

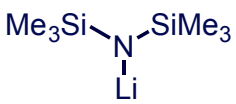
# Diastereoselective Enolate Alkylation



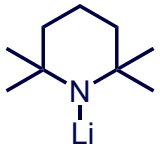

- Reaction proceeds by formation of the corresponding enolate which reacts with an electrophile to give the product.
- Reaction requires a strong non-nucleophilic base to deprotonate the carbonyl compound.
- $pK_{a\ (water)}$ ketone ~ 20, ester ~ 25, amide ~ 26
- Requires a base with a higher $pK_a$ (of the conjugate acid) for complete deprotonation.
- Typically use, LDA, LiHMDS (and NaHMDS, KHMDS), and LiTMP – other more esoteric bases can also be used.



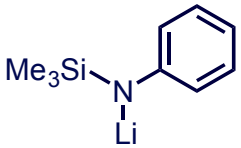

LDA
lithium diisoproylamide
36 (THF)



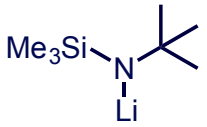

LiHMDS
lithium hexamethyldisilazide
26 (THF)
$pK_{a\ (conjugate\ acid)}$




LiTMP
lithium tetramethylpiperidide
37 (DMSO)

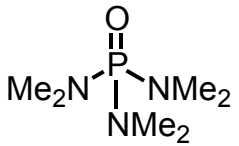



LiTMSA
lithium (trimethylsilyl)anilide

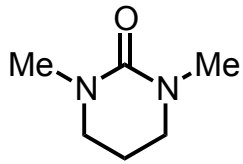



LiBTMSA
lithium *N*-*t*-butyl(trimethylsilyl)amide

## Control of Enolate Geometry

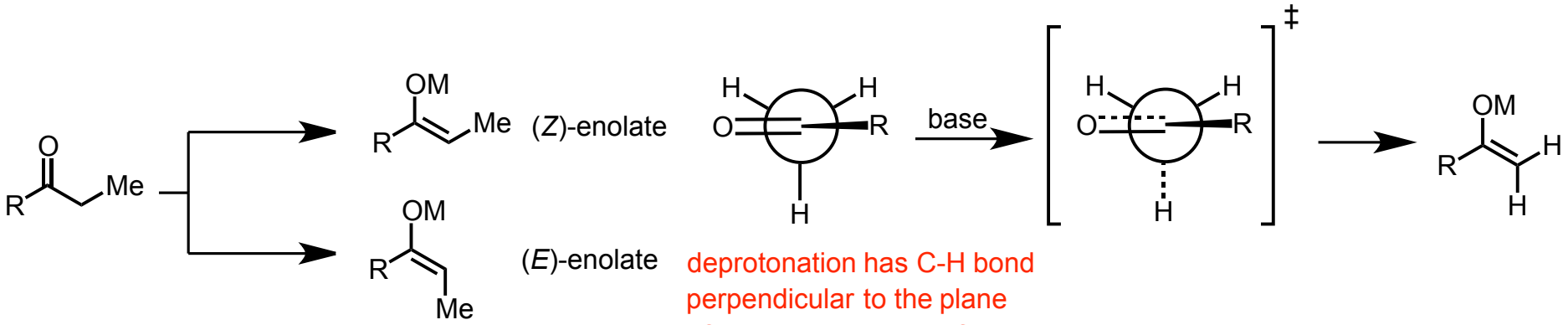



HMPA




DMPU

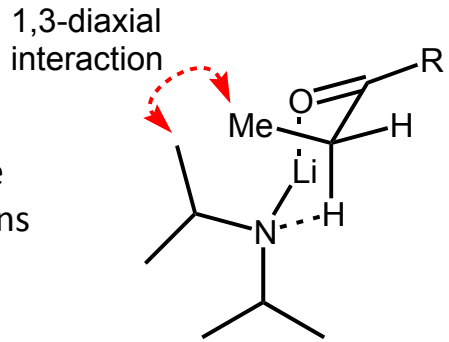
- Control of enolate geometry is crucial in diastereoselective enolate alkylation reactions.
- (*Z*)-Enolates are thermodynamically more stable than (*E*)-enolates.
- As the size of R increases the ratio (*Z*):(*E*) increases.
- In the presence of additives such as HMPA and DMPU (*Z*)-enolates predominate for esters as well as amides and ketones.
- Take home message, **E**sters give ***E***-enolates, amides give *Z*-enolates.



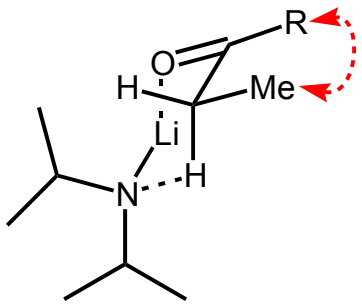

deprotonation has C-H bond perpendicular to the plane of the carbonyl group for maximum orbital overlap ($_{C\text{-}H}$ to $\neq^*_{C=O}$)

- **Ireland Model**

(*Z*):(*E*)-ratio depends on a balance between the 1,3-diaxial interactions and the developing $A^{1,3}$ strain.




(*Z*)-enolate transition state

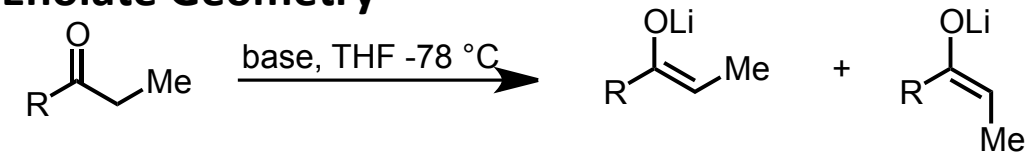


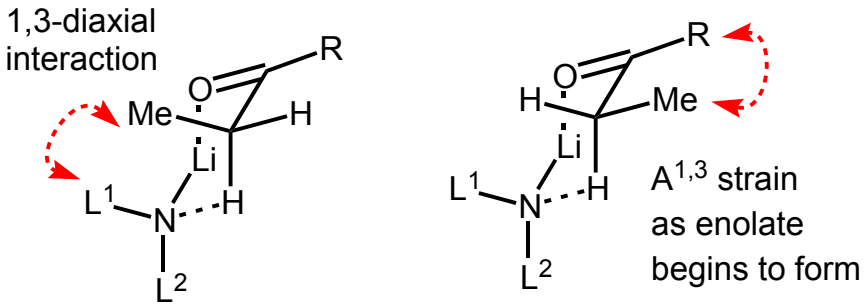

(*E*)-enolate transition state

$A^{1,3}$ strain as enolate begins to form

R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.*, **1976**, *98,* 2868.

# Enolate Geometry



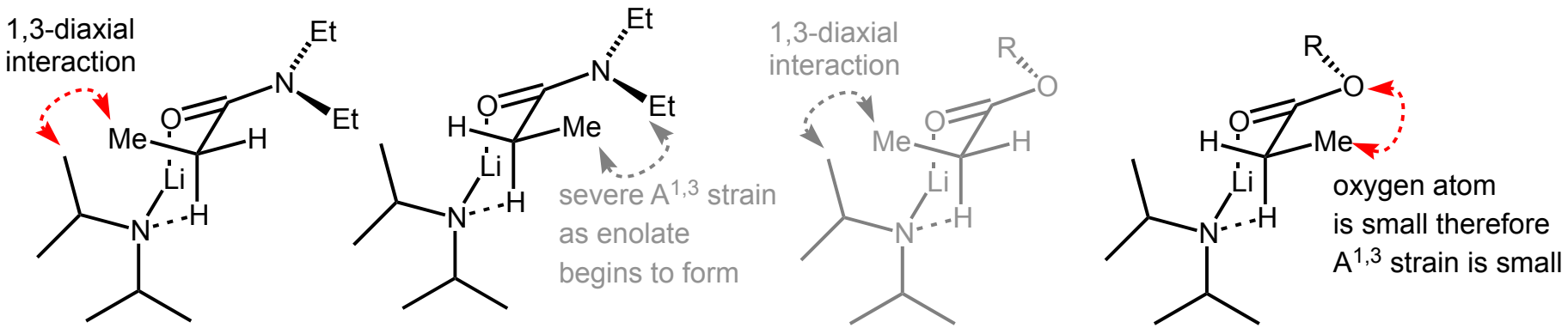




(*Z*)-enolate transition state (*E*)-enolate transition state

**ketones**

| R | base | (E):(Z) |
|---|---|---|
| Et | LDA | 70:30 |
| | LiTMP | 80:20 |
| | LiHMDS | 34:66 |
| | LiTMSA | 7:93 |
| | LiBTMSA | 94:6 (at RT) |

L. Xie, K. M. Isenberger, G. Held, L. M. Dahl, *J. Org. Chem.*, **1997**, *62*, 7516




(*Z*)-enolate transition state (*E*)-enolate transition state (*Z*)-enolate transition state (*E*)-enolate transition state
(lower in energy,
(*Z*)-enolate major diastereomer) (lower energy transition state,
(*E*)-enolate, major product)

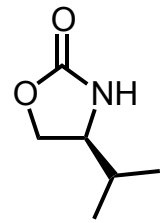
**amides** **esters**

- For amides, developing $A^{1,3}$ strain always bad, therefore give (*Z*)-enolates under all conditions.
- In the presence of HMPA, ketones and esters both give high preference for (*Z*)-enolates.

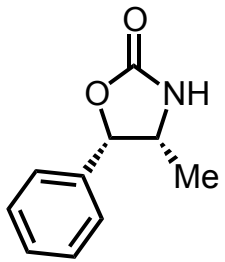
*Note: this is a useful model but enolate formation with lithium amides involves mixed aggregates see: D.* Collum, F. Romesberg, F. *J. Am. Chem. Soc.* **1995**, *117*, 2166.

## Diastereoselective Enolate alkylation

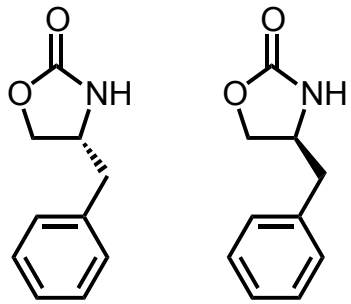
- Generally use amides as substrates - they give complete control over enolate geometry.
- Oxazolidinone auxiliaries of Evans are widely used for asymmetric alkylation.



valine-derived oxazolidinone

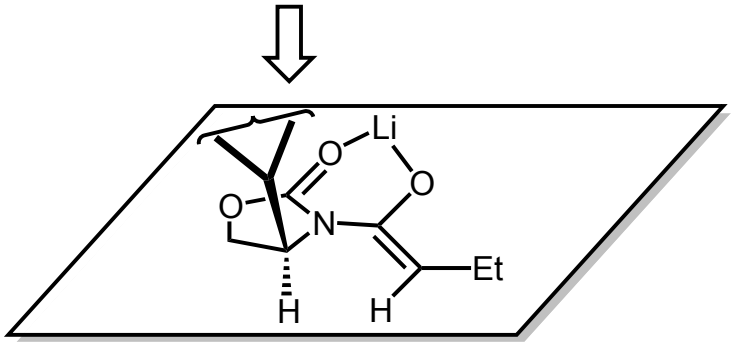


ephedrine-derived oxazolidinone

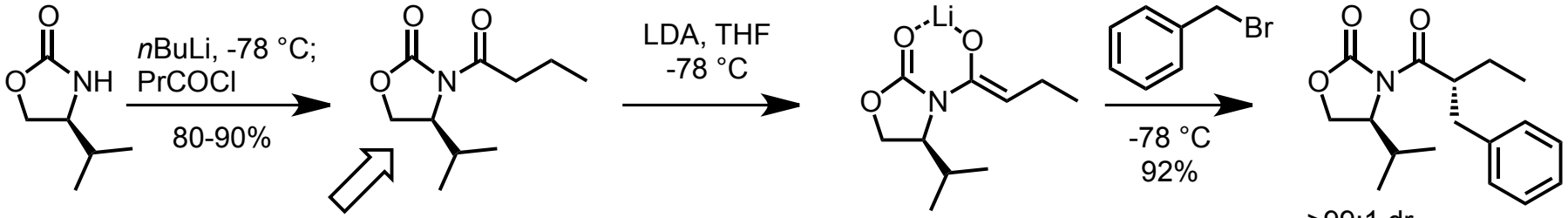


phenylalanine-derived oxazolidinone

*i*Pr group blocks one face of enolate



less hindered approach of electrophile to chelated enolate passed H-atom




imides are closer to esters than to amides in terms of acidity, enolate nucleophilicity and cleavage chemistry

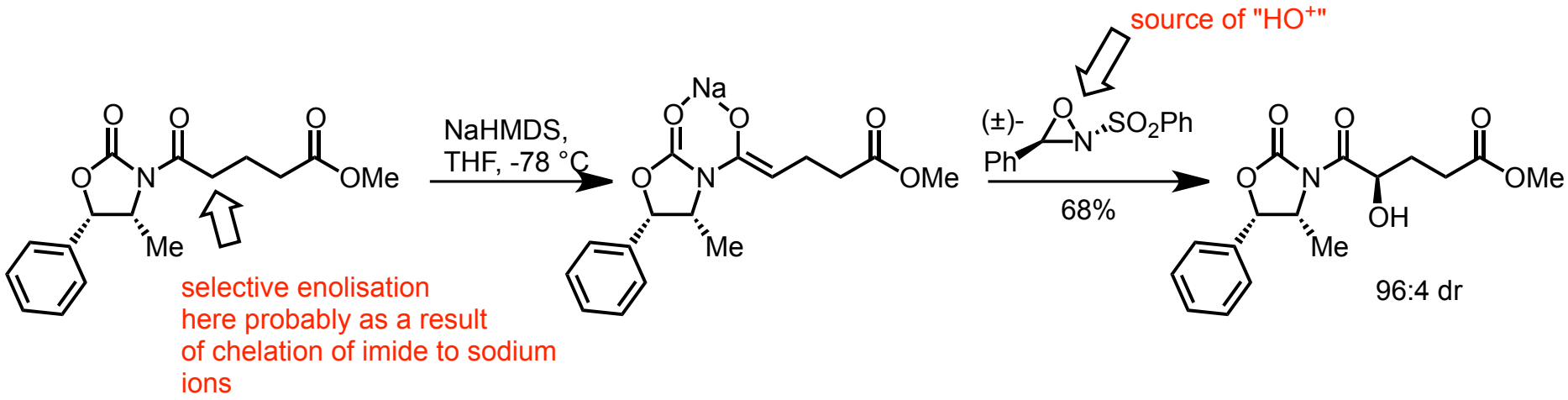
(*Z*)-enolate formed with very high selectivity chelated geometry presumed in ground and transition state

*i*Pr group blocks one face of chelated enolate

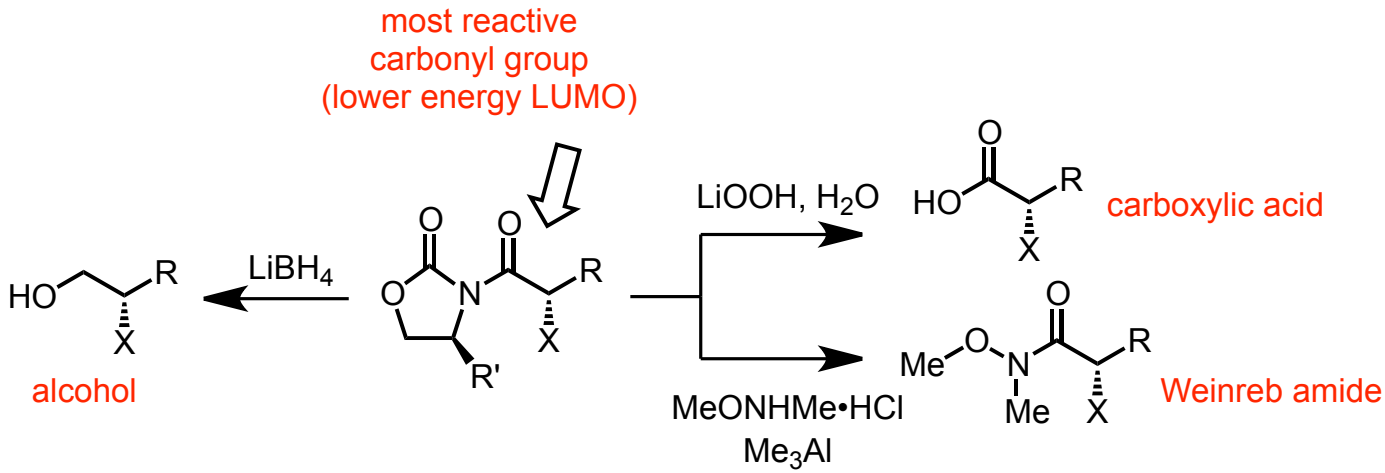
Evans, D.A: Britton. T.C; Dorow, R.L; Dellarfa, J.F., *J. Am. Chem. Soc.*, **1986**, *108*, 6395;
Evans, D.A; Britton, T.C; Dorow, R.L; Dellarfa, J.F., *Tetrahedron*, **1988**, *44*, 5525.

## Diastereoselective Enolate alkylation

- The oxazolidinone enolates react readily with a variety of reactive electrophiles, such as MeI, BnBr, allylBr, NBS, trisyl azide, oxaziridines, azodicarboxylates.
- Less reactive electrophiles e.g. β-branched alkyl halides do not react.
- Diastereocontrol in all of these reactions is predictable (from proposed chelated enolate) and high.



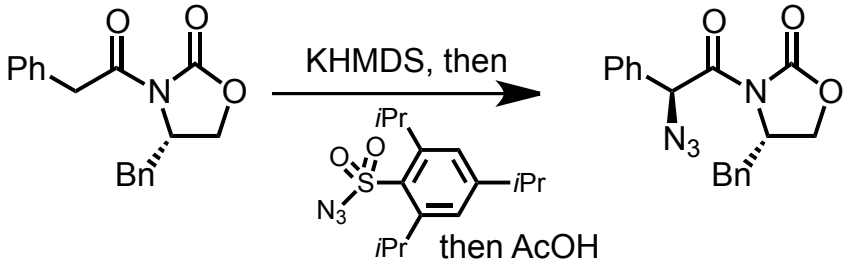

- **Auxiliary cleavage**

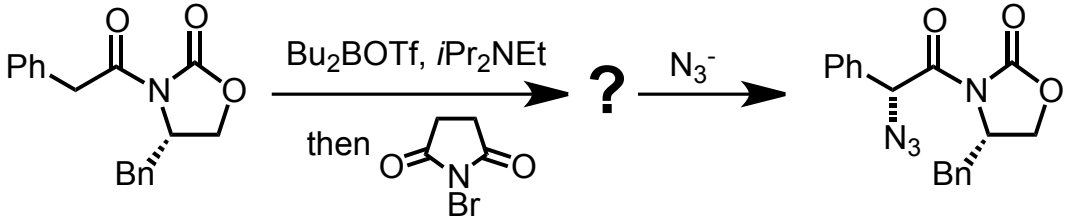


## Diastereoselective Enolate alkylation

***Problem***: Provide a mechanism for the following reactions explaining the stereochemical outcome

Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.



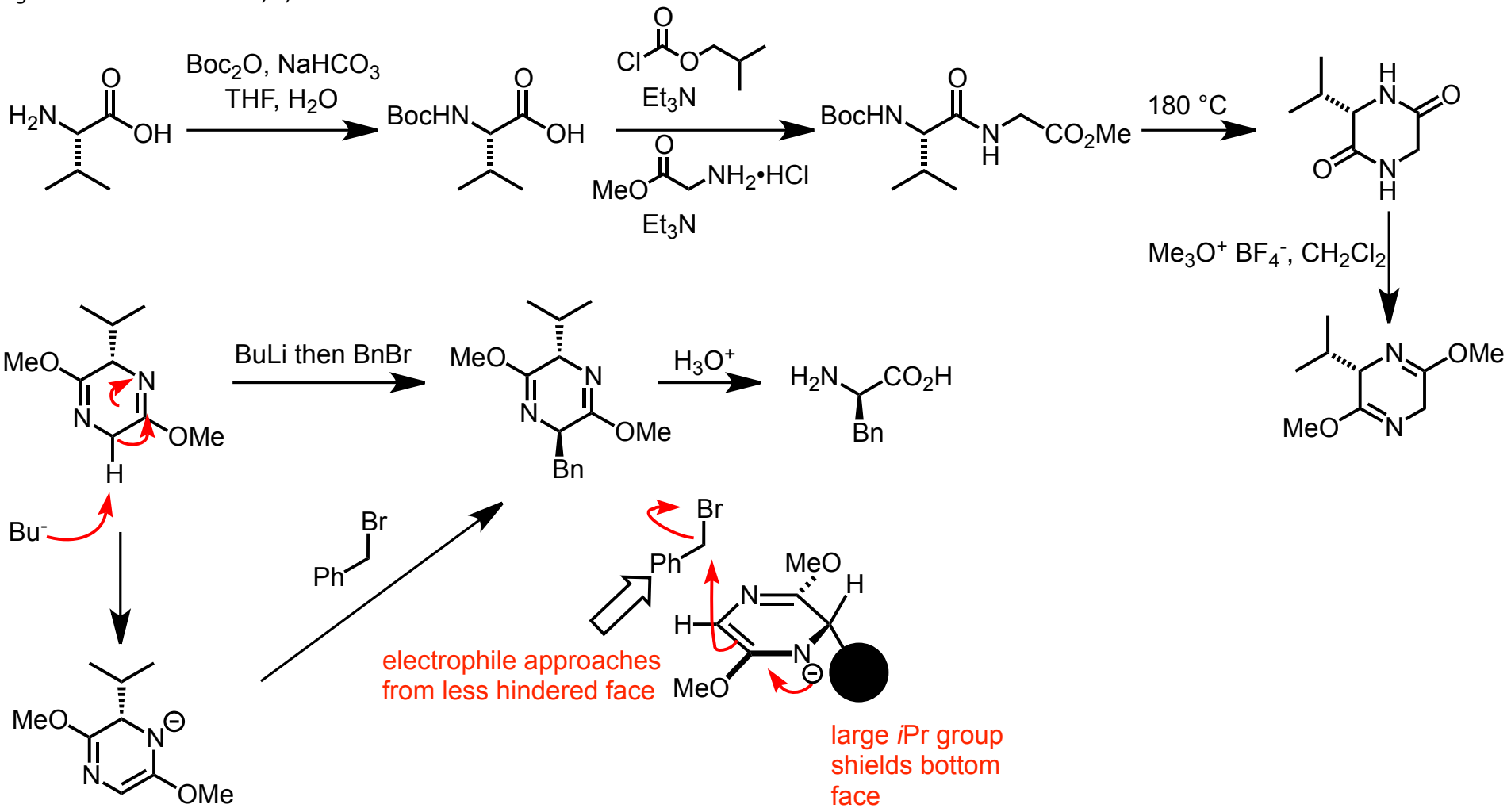



# Diastereoselective Enolate alkylation – the Schollkopf auxilliary

## Synthesis of α-substituted and α-disubstituted amino acids

U. Schollkopf, *Pure Appl. Chem.* **1983**, *55*, 1799-1806; U. Schollkopf, *Tetrahedron*, **1983**, *39*, 2085.

Synthesis of Scholkopf's auxilliary see: S. D. Bull, S. G. Davies, W. O. Moss, *Tetrahedron: Asymmetry* **1998**, *9*, 321-327; J. Chen, S. P. Corbin, N. J. Holman, *Org. Process Res. Dev.* **2005**, *9*, 185-187.



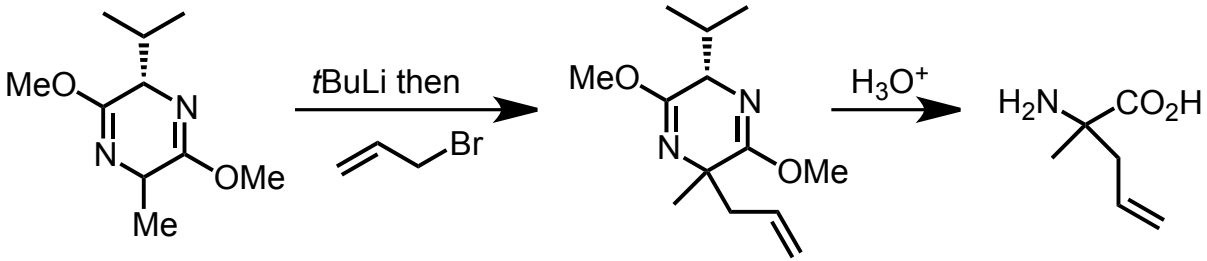
## Diastereoselective Enolate alkylation – the Schollkopf auxilliary

U. Schollkopf, *Pure Appl. Chem.* **1983**, *55*, 1799-1806; U. Schollkopf, *Tetrahedron*, **1983**, *39*, 2085.

- *t*BuLi has recently been recommended for deprotonation of substituted Shcollkopj auxiliaries; P. A. Magriotis, S. Vassiliou, C. Dimitropoulos, *Synlett* **2003**, 2398-2400.

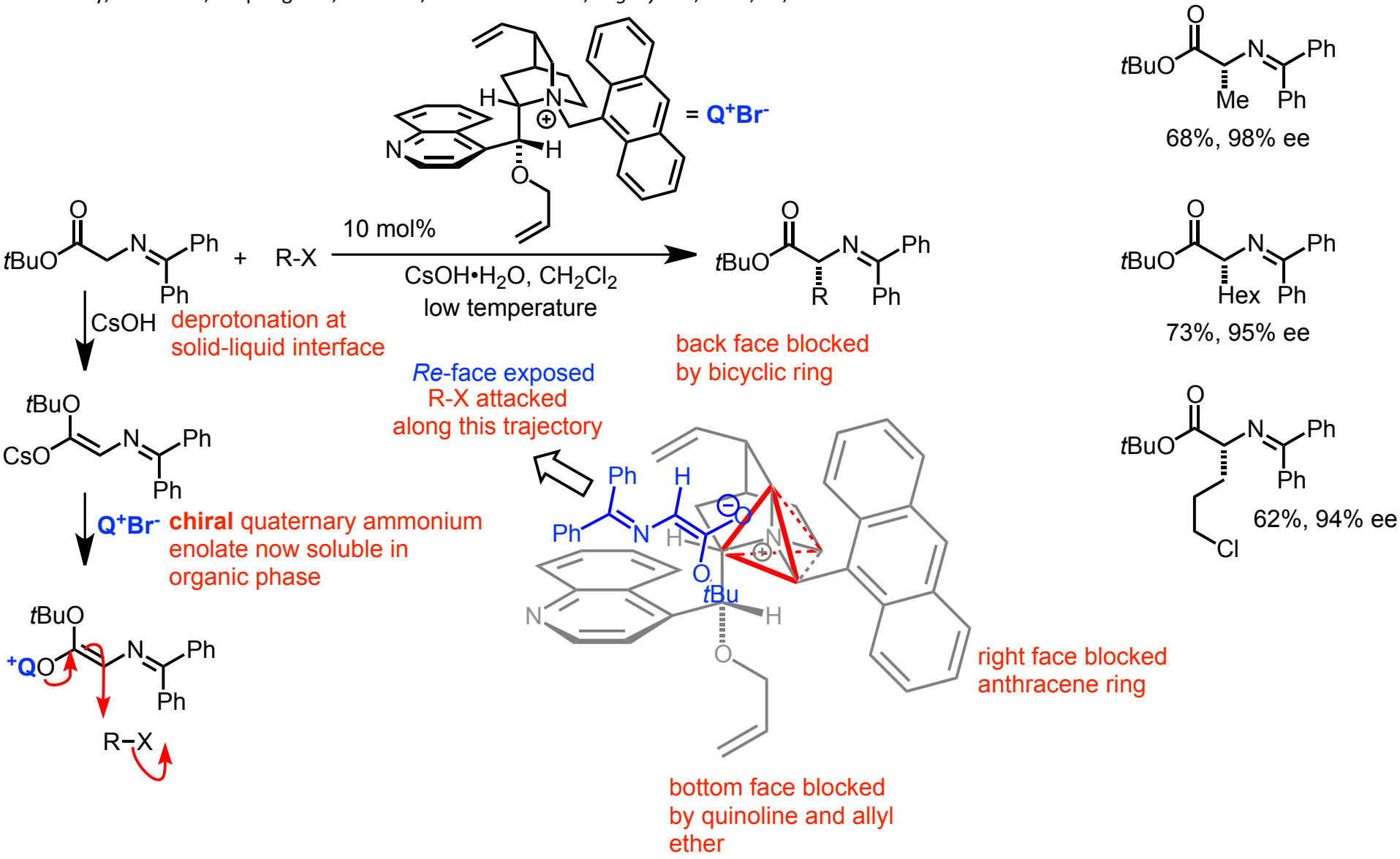
***Problem***: Predict the stereochemistry of the final product in the following reaction sequence.

U. Schollkopf, *Tetrahedron*, **1983**, *39*, 2985.



# Catalytic Asymmetric Phase Transfer Catalysis – Synthesis of Unnatural Amino Acids

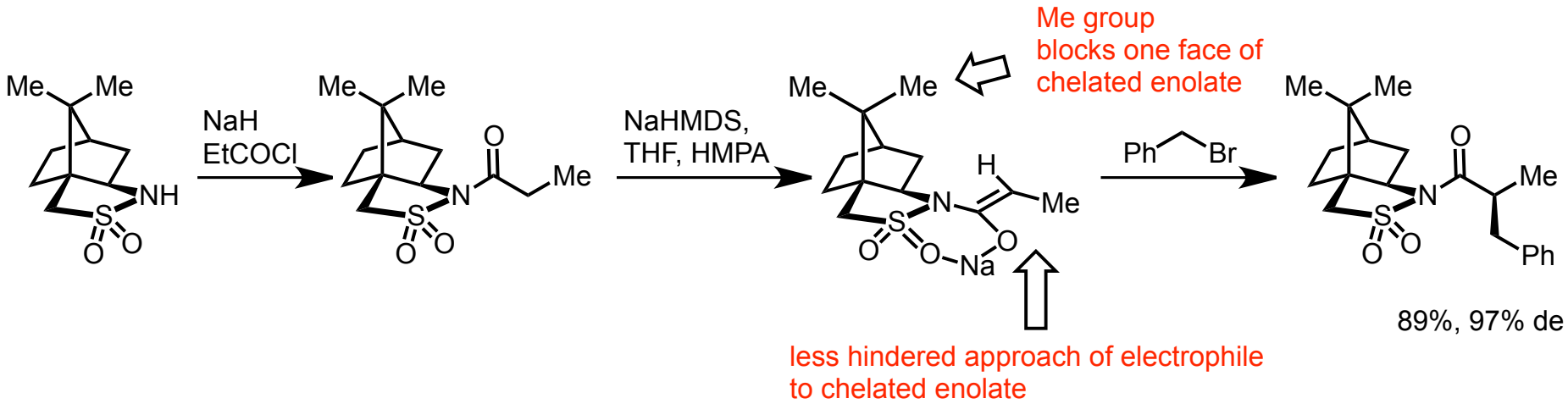
Seminal work: O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353-2355.
B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595-8598; E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.
Reviews: B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518-525; T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *46*, 4222-4266.
E. J. Corey, M. C. Noe, S. Springfield, J. Amato, E. J. J. Grabowski, *Org. Synth*., **2003**, *80*, 38.



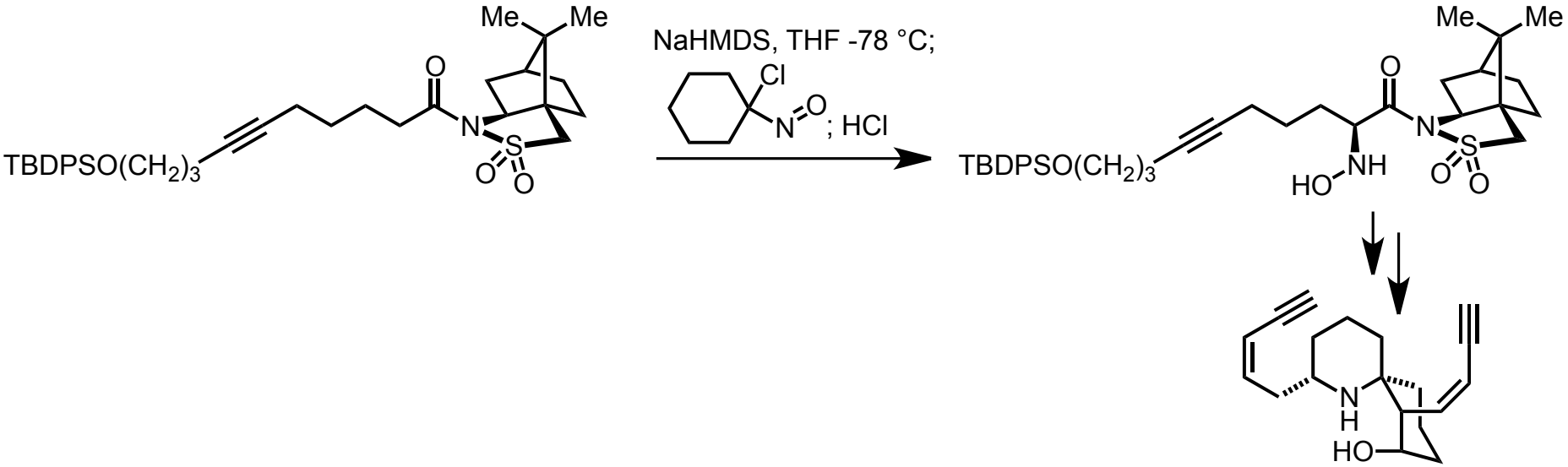
## Diastereoselective Enolate alkylation Oppolzer method

- Similar to the oxazolidinone methodology but uses a camphor derived sultam.

Oppolzer, W; Moretti, R.; Thomi, S. *Tetrahedron Lett.*, **1989**, *41*, 5603-5606




**Problem**: What is the mechanism of the following reaction?




(-)-histrionicotoxin

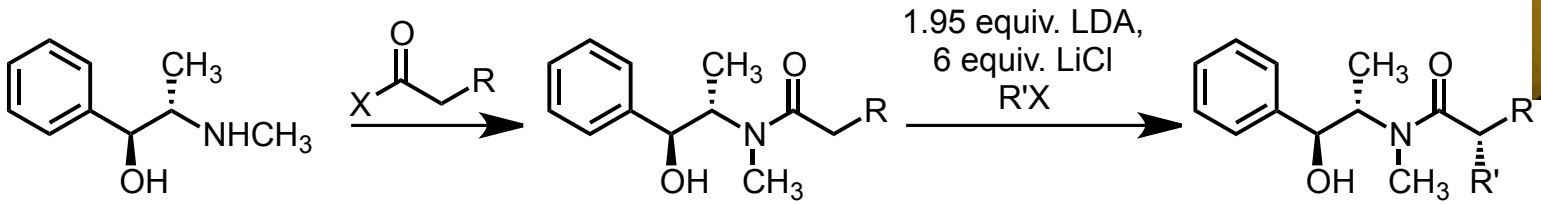
Williams, G. M; Roughley, S. D., Davies, J. E.; Holmes, A.B. *J. Am. Chem. Soc.*, **1999**, *121*, 4900-4901

# Diastereoselective Enolate Alkylation Myers method


- Based upon pseudoephedrine amides.
- Pseudoepherdrine is cheap and available in both enantiomeric forms.

Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.*, **1997**, *199*, 6496-6511.

- Amide enolates much more reactive than imide enolates (amides have a higher $pK_a$ than imides) and hence unactivated alkyl halides may be used.
- Pseudoephedrine is a restricted substance in many countries. Myers has introduced "pseudoephenamine" which is equally effective and unrestricted see: M. R. Morales, K. T. Mellem, A. G. Myers, *Angew. Chem. Int. Ed.*, **2012**, *51*, 4568; K. T. Mellem, A. G. Myers, *Org. Lett.*, **2013**, *15*, 5594; I. B. Seiple, J. A.M. Mercer, R. J. Sussman, Z.Zhang, A. G. Myers, *Angew. Chem. Int. Ed.*, **2014**, *53*, 4642



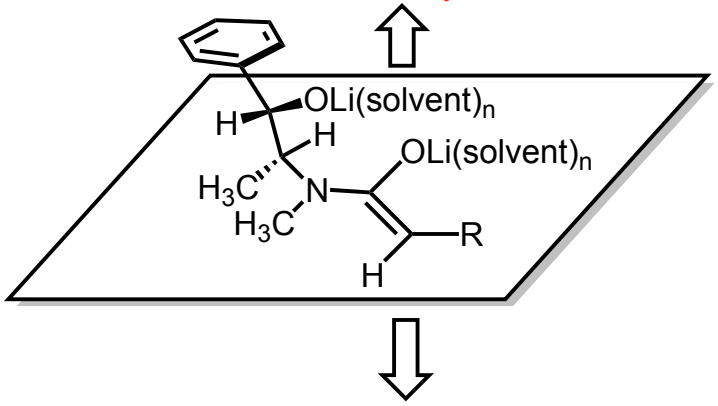

pseudoephedrine

pseudoephedrine amide
formed from, acid chloride, anhydride, mixed anhydride etc.

good yields
highly diastereoselective

| R | R'X | de % | yield % |
|---|---|---|---|
| $CH_3$ | BnBr | 94 | 90 |
| $CH_3$ | BuI | 98 | 80 |
| Bu | BnBr | 98 | 83 |
| iPr | BnBr | 98 | 83 |

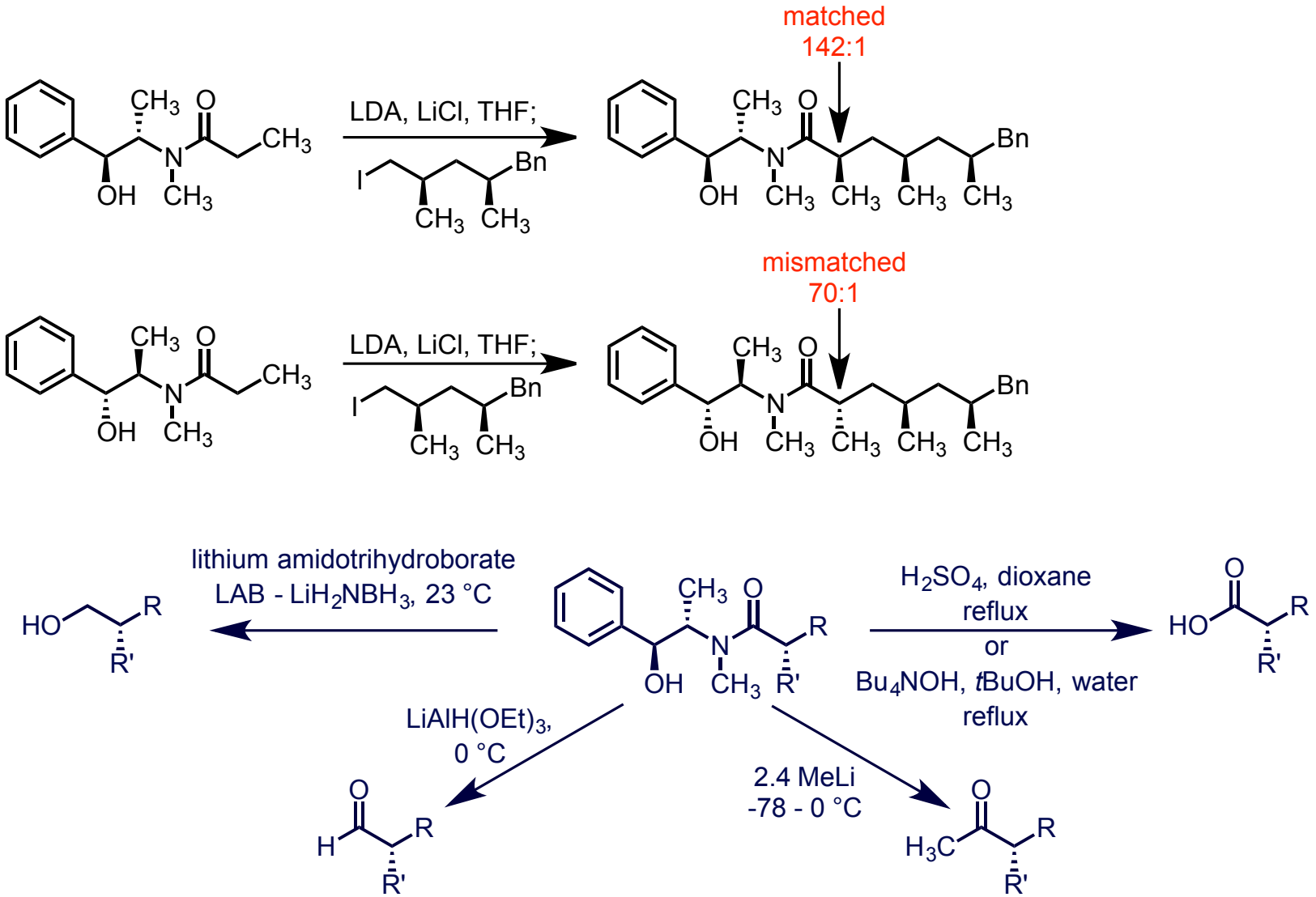
other enolate π-face
blocked by solvent




less hindered approach
of electrophile to (*Z*)-enolate

# Diastereoselective Enolate Alkylation Myers method

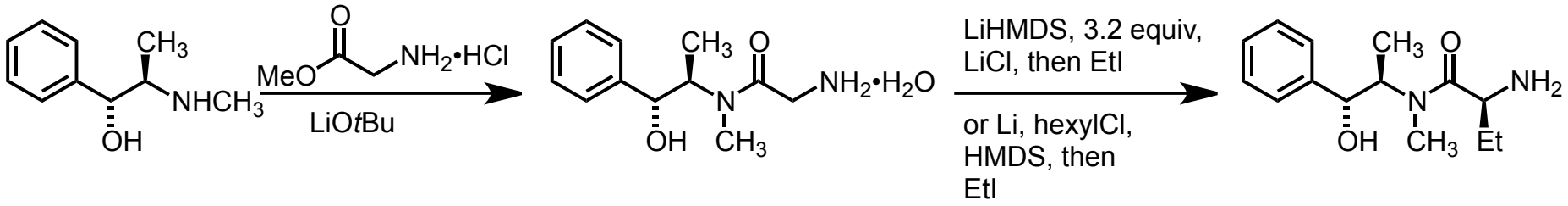
- Pseudoephedrine amides enolates are Reactive enough for β-branched electrophiles




Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, *5,* 457.

# Diastereoselective Enolate Alkylation Myers method

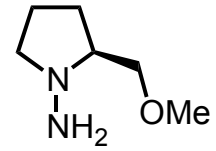
- Rationalise the chemistry in the following sequence



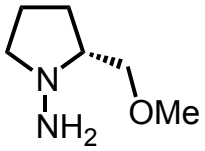

A. G. Myers, P. Schnider, S. Kwon, D. W. Kung, *J. Org. Chem.* **1999**, *64*, 3322-3327.

# Diastereoselective Enolate Alkylation of Ketones and Aldehydes– Enders' SAMP and RAMP

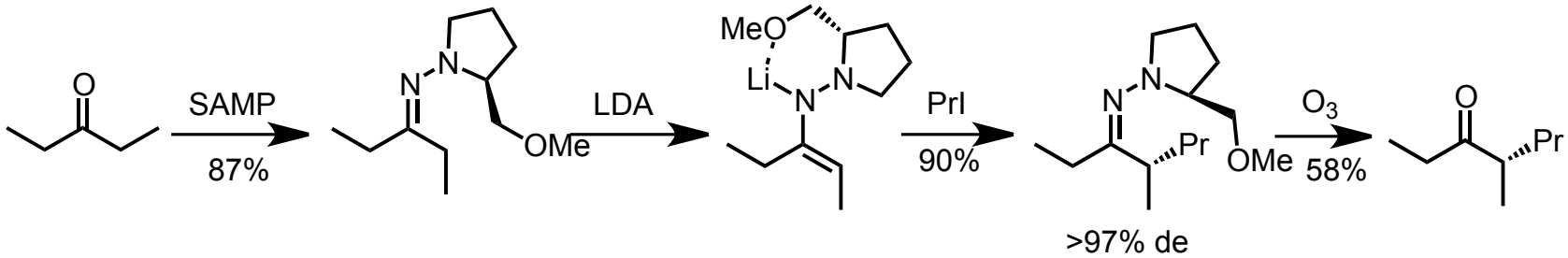
Job, A.; Janeck, C. F.; Battray, W.; Peters, R.; Enders, D. *Tetrahedron,* **2002**, *58*, 2253-2329

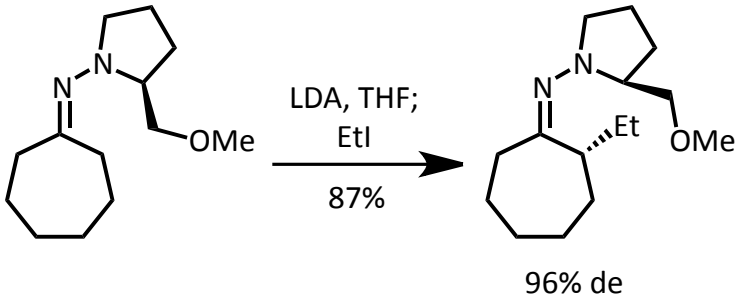


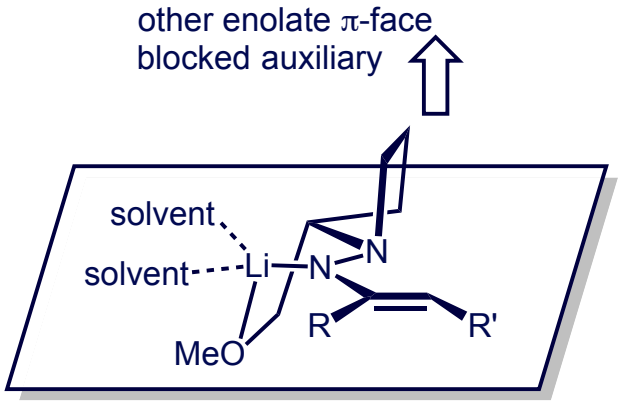

(*S*)-1-amino-2-methoxypyrrolidine
SAMP

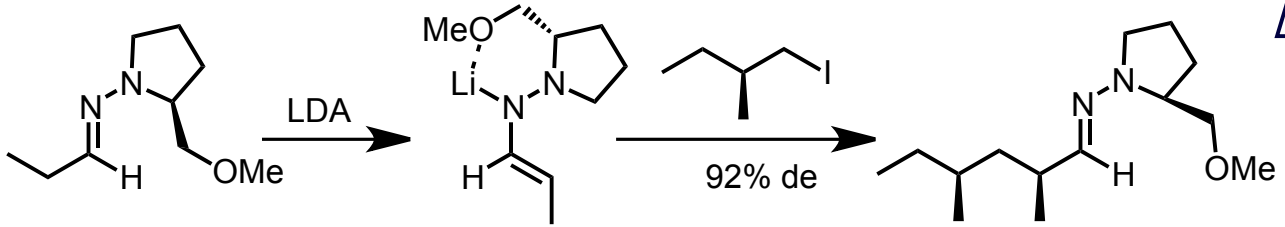



(*R*)-1-amino-2-methoxypyrrolidine
RAMP



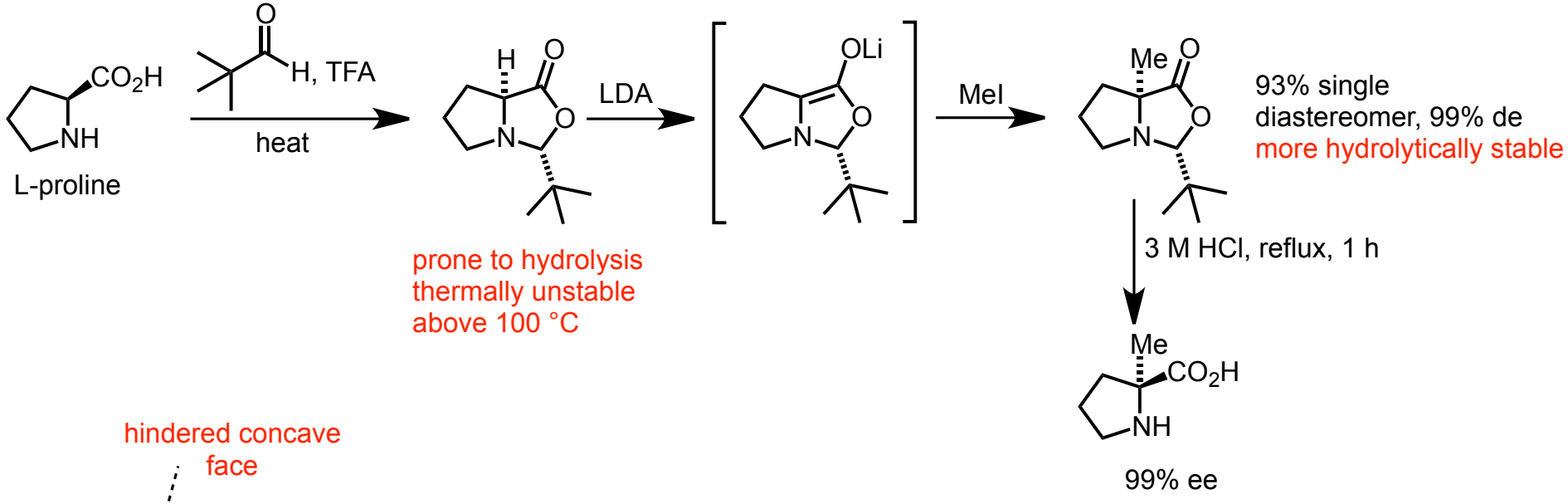

less hindered
approach for
electrophile to (*E*)-enolate

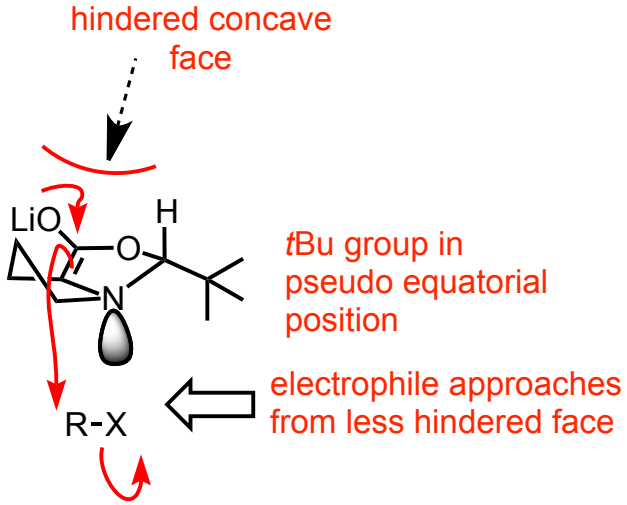
# Seebach – Self Reproduction of Chirality

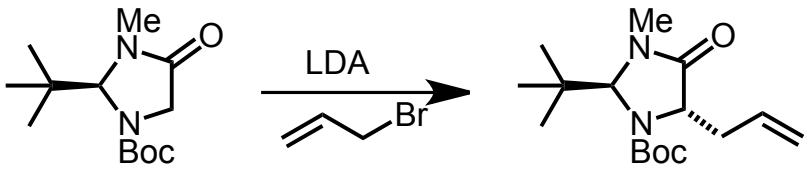
- Alkylation of proline-derivative without loss of enantiomeric purity or the need for a chiral auxilliary

D. Seebach, M. Boes, R. Naef, W. B. Schweizer, *J. Am. Chem. Soc.* **1983**, *105*, 5390-5398**;** A. K. Beck, S. Blank, K. Job, D. Seebach, Th. Sommerfeld, F. Narjes, L. E. Overman, *Org. Synth*. **1995**, *72*, 6

Review: D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem. Int. Ed.* **1996**, *35*, 2708-2748.

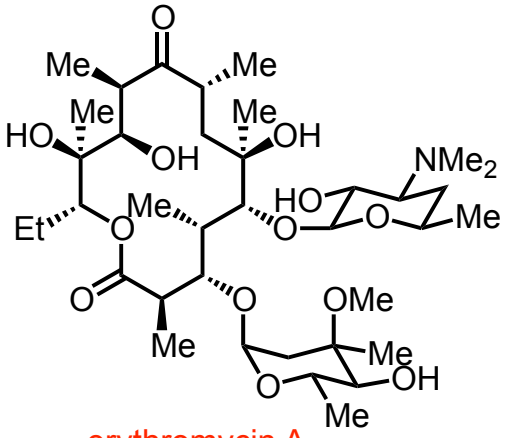


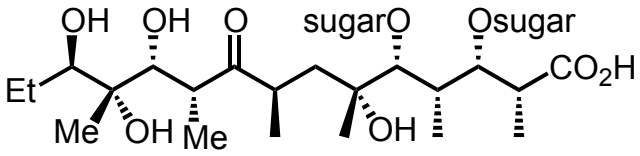

R. Fitzi, D. Seebach, *Tetrahedron* **1988**, *44*, 5277-5292.

# The Aldol Reaction - Importance

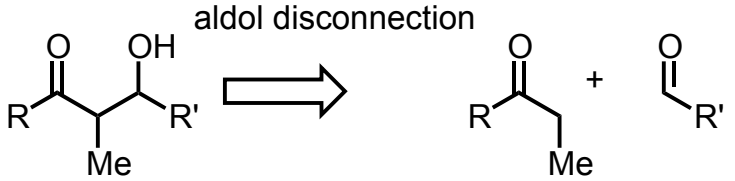



erythromycin A
macrolide antibiotic

*"Erythromycin…looks at present quite hopelessly complex, particularly in the view of its plethora of asymmetric centers"*
*- Woodward (1956)*
Nobel Laureate 1965 for achievements in the art of organic synthesis.
1st total synthesis of erythromycin A in 1981.



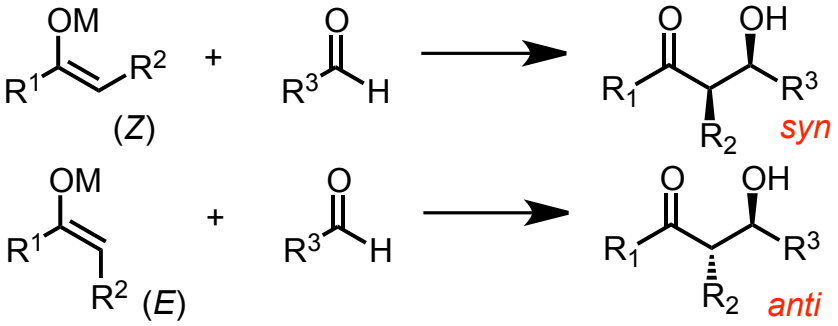

erythromycin A seco-acid




■ The aldol reaction is an exceptionally important reaction in organic synthesis, particularly for the synthesis of biologically active polypropionate natural products.

For an interesting article regarding the discovery of the aldol reaction see: Gordin, M. D. *J. Chem. Ed.*, **2006**, 561.
Zimmerman, *J. Am .Chem. Soc.*, **1956**, *19*, 1920.

# The Aldol Reaction

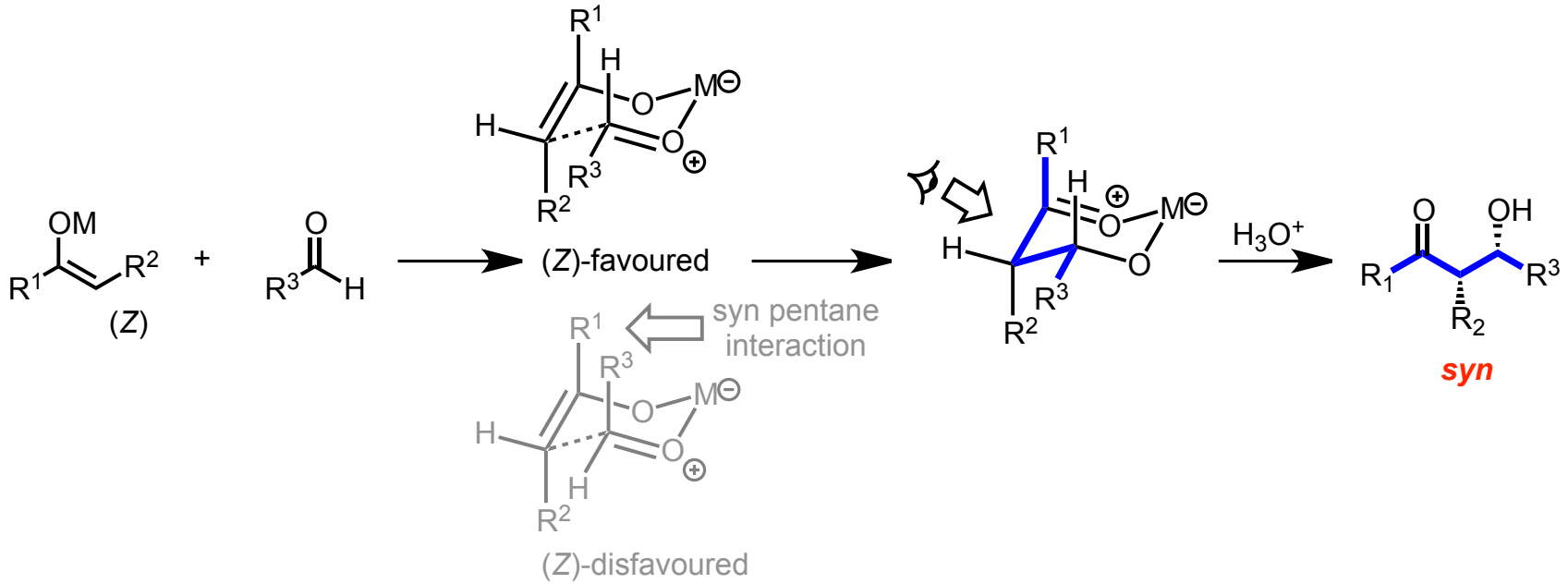



- General rule (with many exceptions):
(***Z***)-enolates give ***syn***-aldols
(*E*)-enolates give *anti*-aldols

- Enolate geometry is very important because many aldol reactions proceed *via* chair-like transition states – the Zimmerman and Traxler model.

**Zimmerman Traxler Transition states**

- Draw a chair transition state with the aldehyde substituent equatorial.

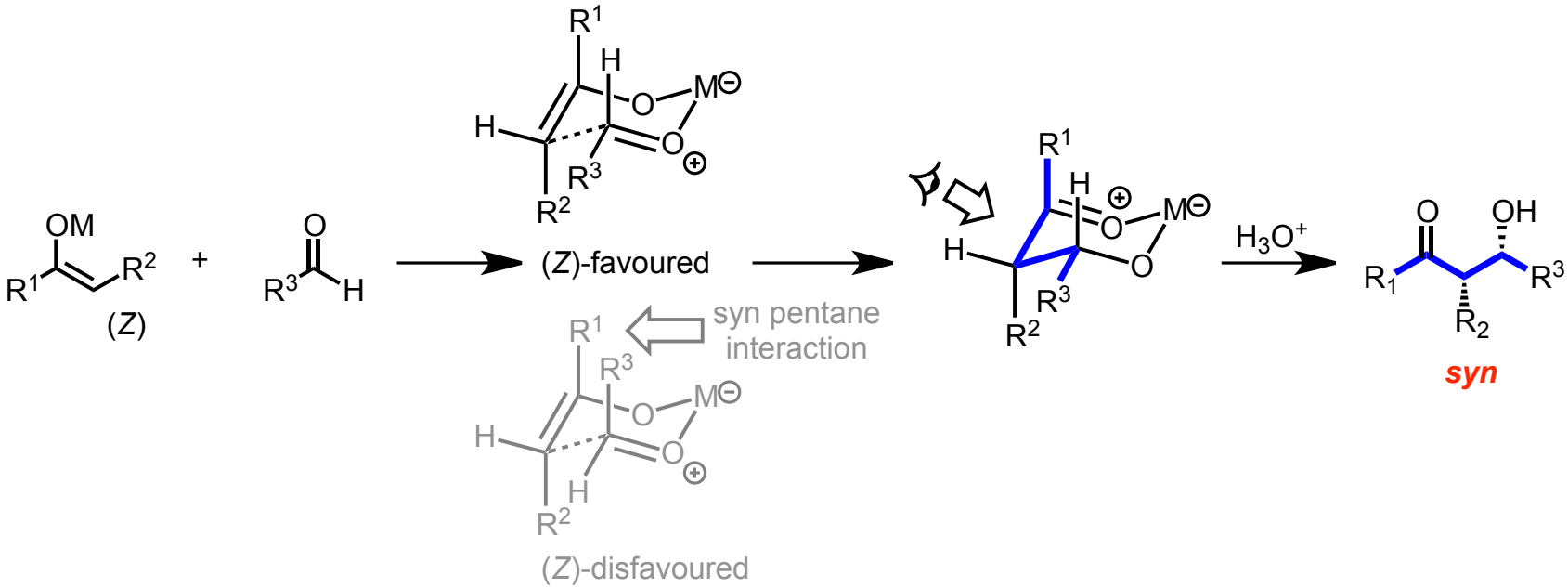



H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.*, **1957**, *79*,1920.

# The Aldol Reaction

## Zimmerman Traxler Transition states

- Draw a chair transition state with the aldehyde substituent equatorial.

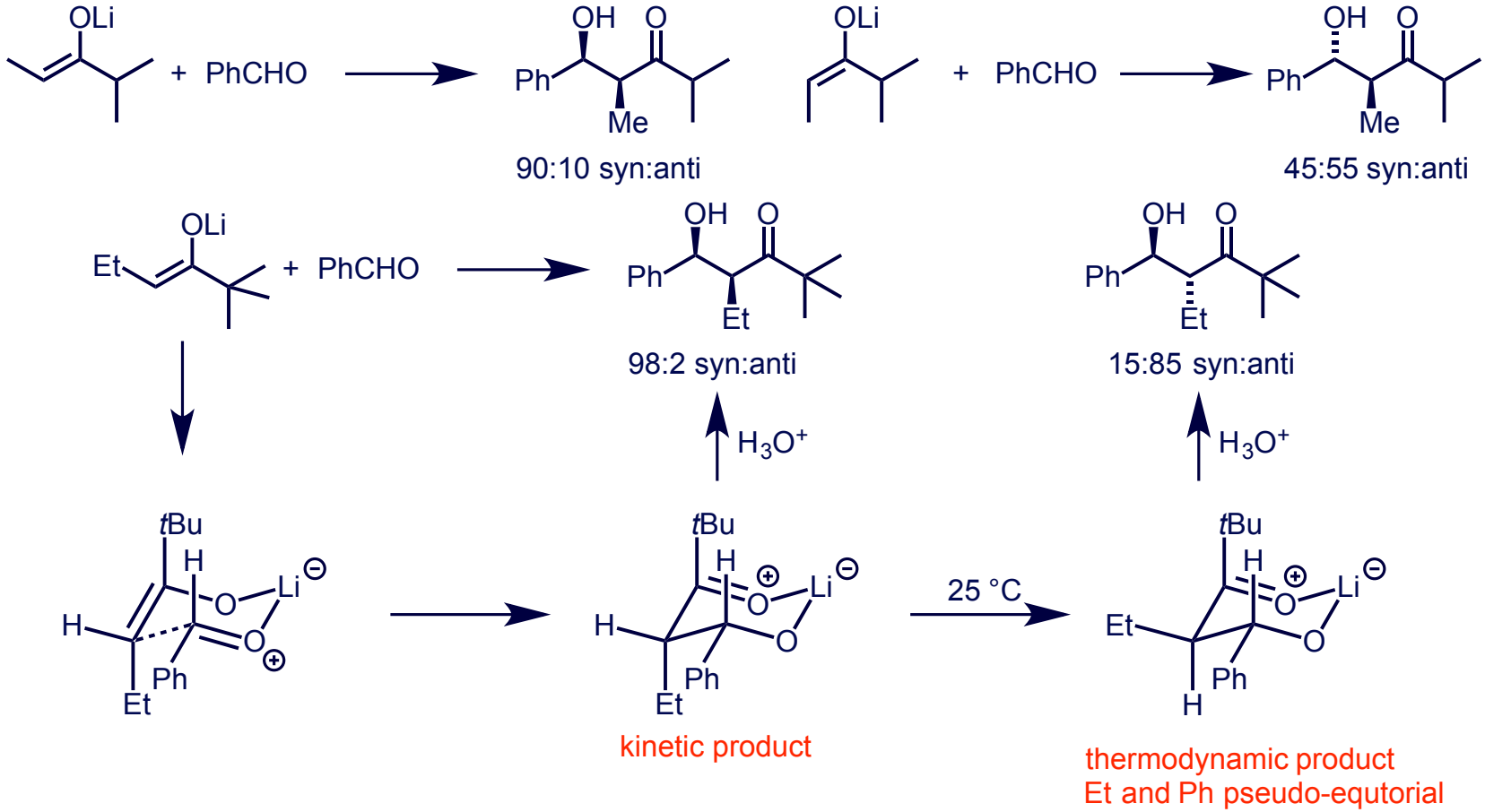



## General Observations

- (*Z*)-Enolates give *syn*-aldols; (*E*)-enolates give *anti*-aldols.
- For lithium enolates (*Z*)-enolates give higher diastereocontrol than (*E*)-enolates.
- For (*Z*)-lithium enolates the highest *syn* selectivity is achieved with large $R^1$ and $R^3$.
- For (Z)-lithium enolates increasing the size of $R^2$ results in reduced *syn*-selectivity.
- Boron enolates give higher diastereocontrol than lithium enolates due to the shorter B-O bond length and hence tighter transition state, as well as the defined ligands on boron (Li-O = 1.92-2.00 Å; B-O 1.36-1.47 Å).

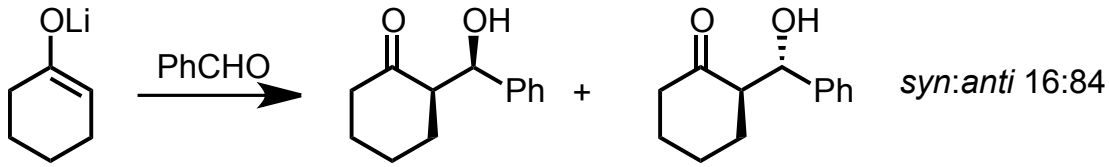
H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.*, **1957**, *79*,1920.

## The Aldol Reaction Examples




■ The aldol reaction is reversible, it is therefore possible for the kinetic aldol products to equilibrate. *Note that in the above example it is the lithium aldolates which undergo equilibration rather than the aldols themselves*

***Question***: Draw a transition state to rationalise the formation of the major diastereomer in the following reaction.

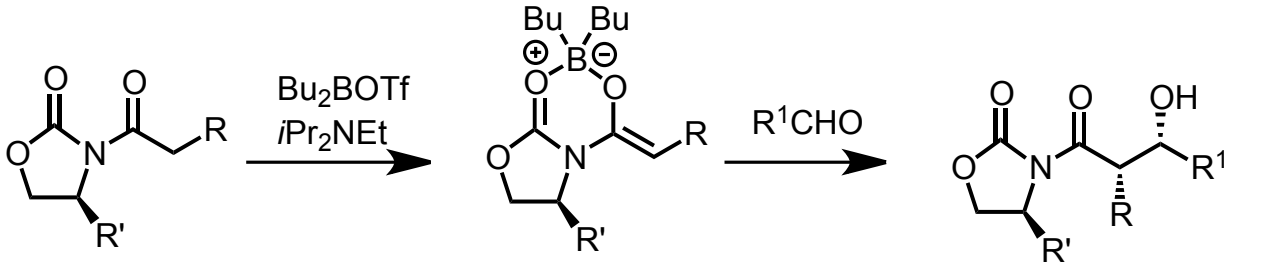


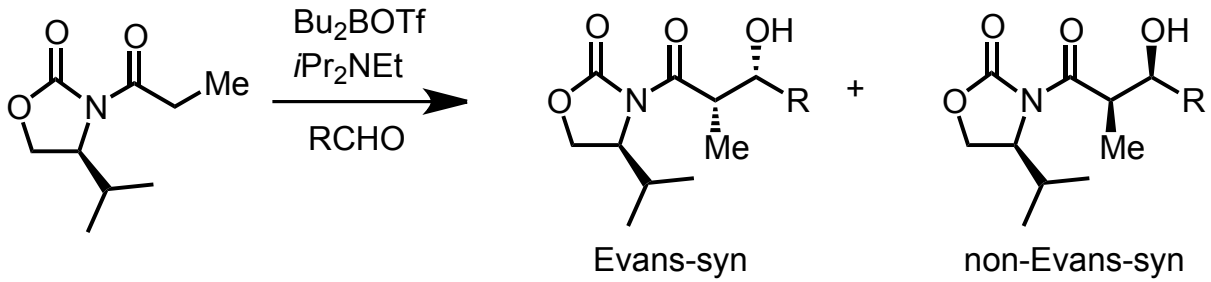

*syn*:*anti* 16:84

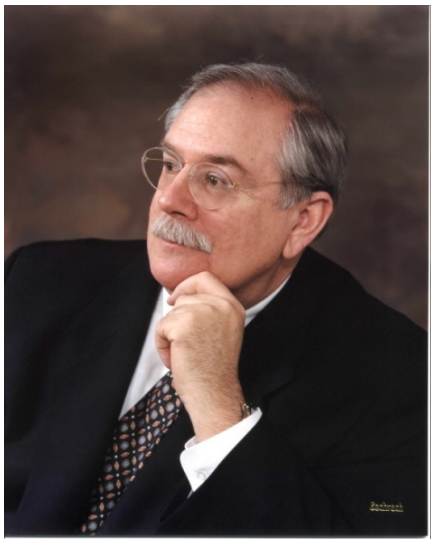
For equilibration of lithium aldolates see: Heathcock, C. H.; Lampe, J. *J. Org. Chem.*, **1983**, *48*, 4330.

## The Evans Aldol Reaction

- The most important asymmetric aldol methodology was developed by D. A. Evans (Harvard).
- The oxazolidinone chiral auxiliaries of Evans are very effective at absolute stereocontrol during the aldol reaction.
- The Evans method is one of the most reliable and widely used methods in organic synthesis.



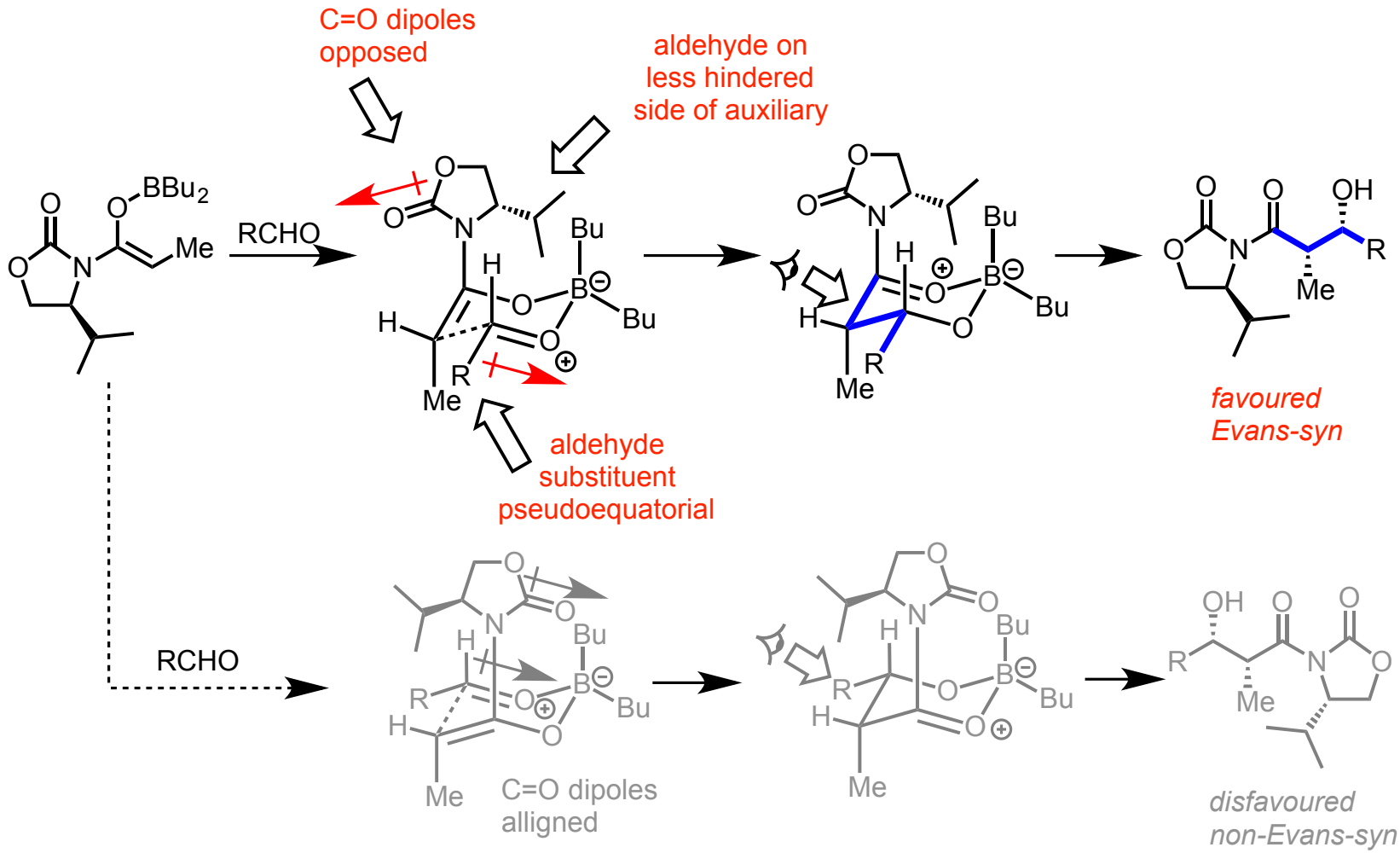
syn:anti selectivities all >99:1

Evans, D. A. *Aldrichimica Acta*, **1982**, *15*, 23; Gage, J. R.; Evans, D. A. *Org. Synth*, **1990**, *68*, 83.

# The Evans Aldol Reaction

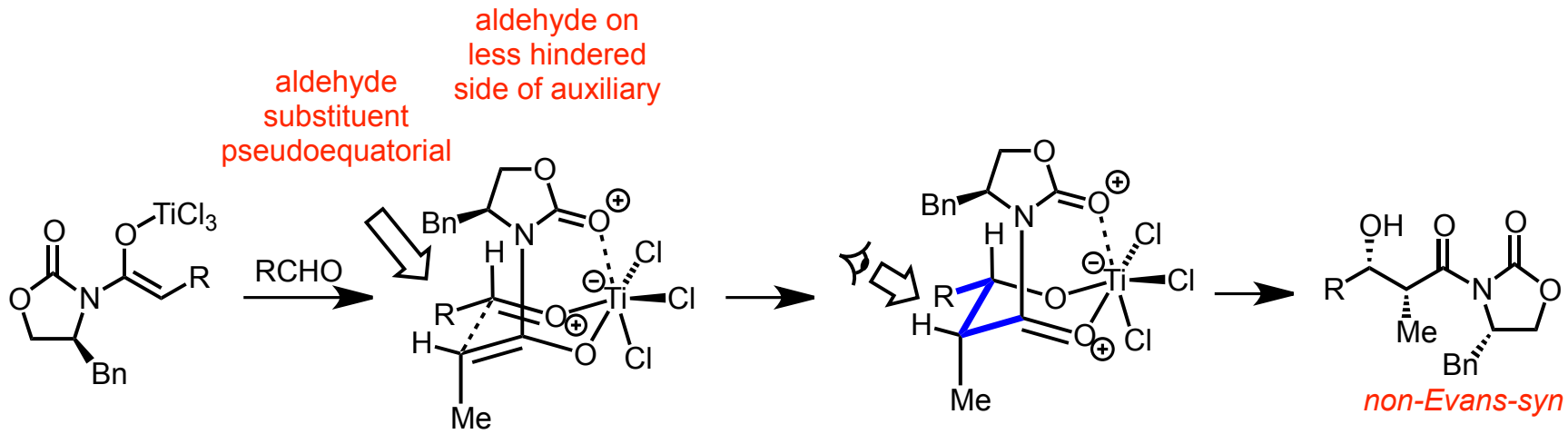
**Key points**

- 6-Membered Zimmerman-Traxler transition state.
- Aldehyde R group goes equatorial.
- Aldehyde approaches away from large alkyl group on auxiliary.
- The dipoles of the carbonyl of the auxiliary and the aldehyde are opposed.



## Crimmins Extension of the Evans Aldol Reaction

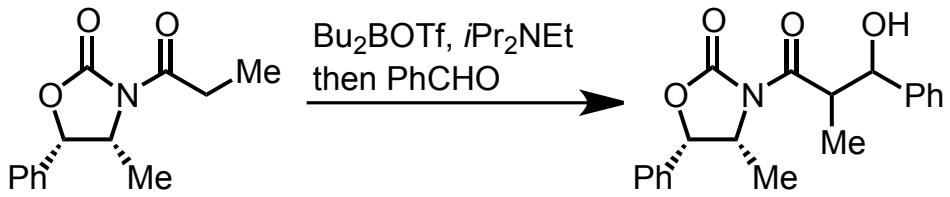
- it is possible to gain access to non-Evans syn aldols using $TiCl_4$ and a base with: oxazolidinones, or oxazolidinethiones or thiazolidinethiones




M. T. Crimmins, B. W. King, E. A. Tabet, K. Chaudhary, *J. Org. Chem.*, **2001**, *66*, 894; M. T. Crommins, J. She, *Synlett*, **2004**, 1371.

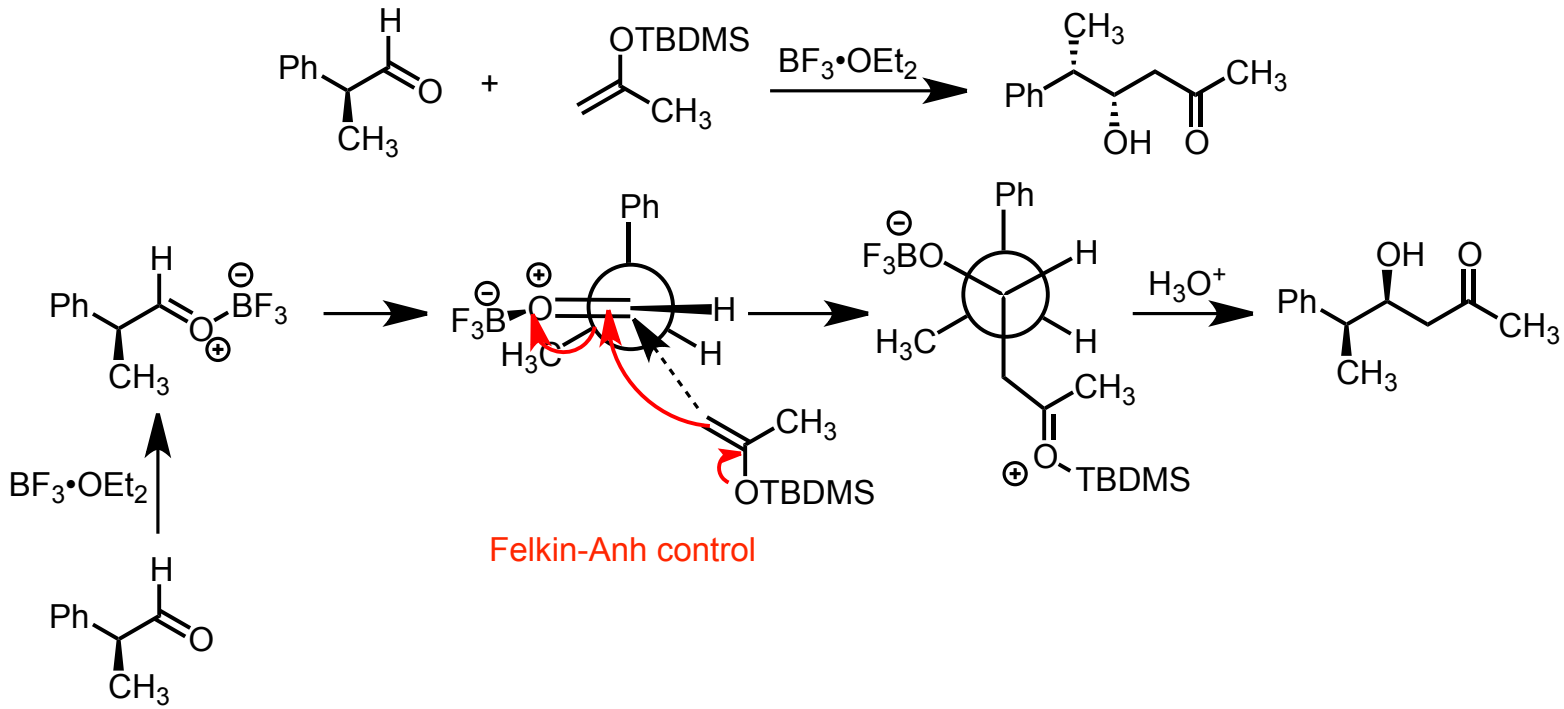
## The Evans Aldol Reaction

***Problem:*** Predict, with a clear transition state diagram, the stereochemistry of the aldol product in the following reaction.



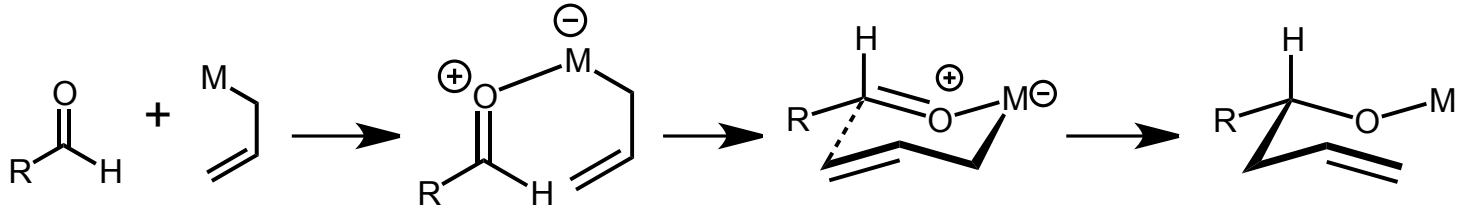
## Use of chiral aldehydes and achiral enolates

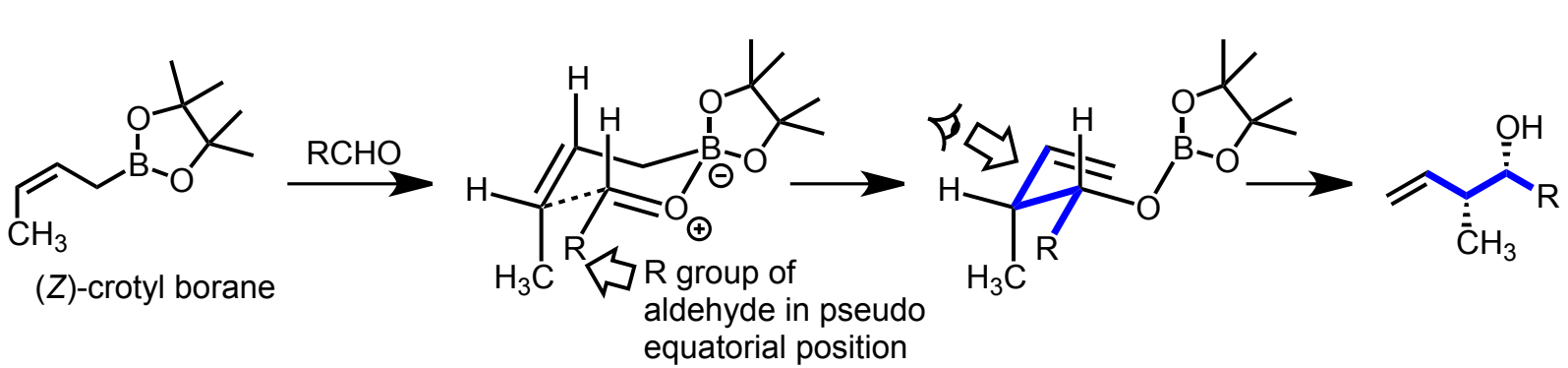
- When an enolate is added to an aldehyde which carries an α-sterocentre the two faces of the aldehyde are diastereotopic and the major product is generally that predicted by the Felkin-Anh model.
- The diastereocontrol for the Felkin product is particularly good in the case of the Mukaiyama aldol reaction.
- The Mukaiyama aldol reaction is the Lewis acid catalysed addition of a silyl enol ether or silyl ketene acetal to aldehydes and ketones.
- Silyl enol ethers are not nucleophilic enough to react directly with aldehydes or ketones.
- Addition of a Lewis acid increases the electrophilicity of the carbonyl compound.
- Silylenol ether are unable to coordinate the aldehyde or ketone and hence the reactions occur through "open" transition states.



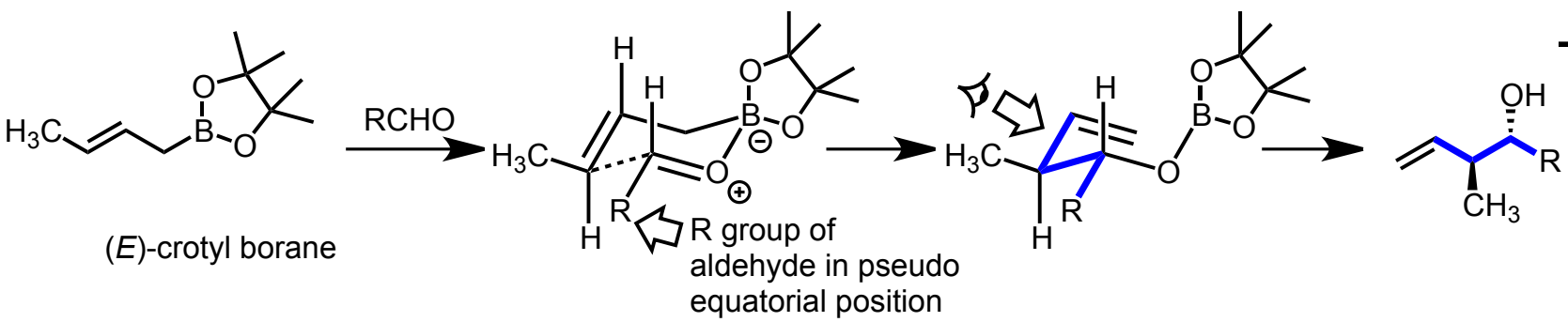
## Diastereoselective Allylation reactions

- A range of allyl and crotyl metals will add to aldehydes.
- If the metal is Lewis acidic the reactions occur by cyclic "closed" Zimmerman-Traxler transition states.
- If the metal is not Lewis acidic an open transition state may operate.
- Allyl and crotyl boron reagents are the most widely used for diastereo- and enantioselective allylation reactions.
- These reactions are analogous to the aldol reactions discussed above.
- As with the aldol reaction, (*Z*)-crotylboranes give *syn* products; (*E*)-crotyl boranes give *anti* products.






| R | *syn*:*anti* |
|---|---|
| Ph | 94:6 |
| $CH_3$ | 93:7 |
| *i*Pr | 96:4 |

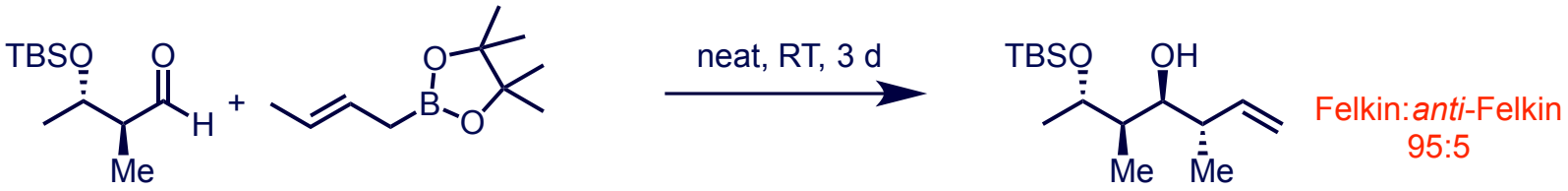


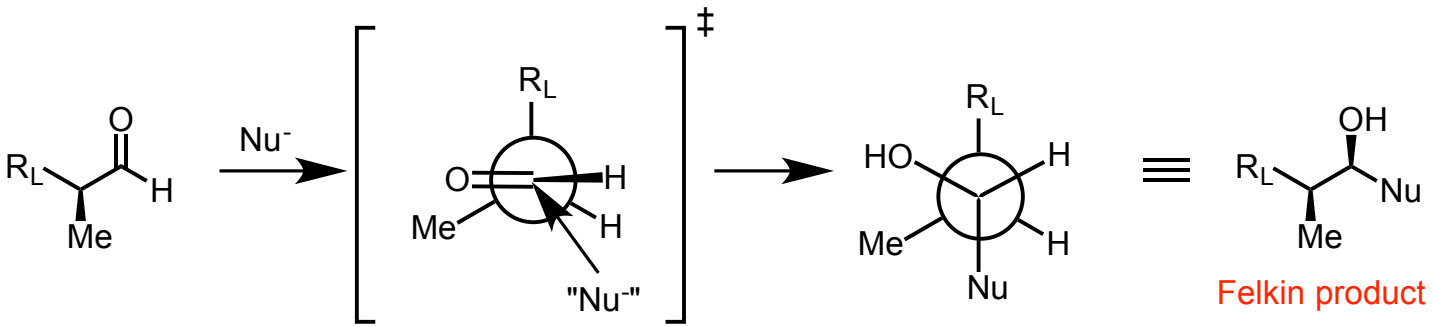

| R | *syn*:*anti* |
|---|---|
| Ph | 4:96 |
| $CH_3$ | 3:97 |
| *i*Pr | 6:94 |

Hoffmann, R.; Zeiβ, H. –J. *J. Org. Chem.*, **1981**, *46*, 1309

## Diastereoselective Allylation reactions

- α-Chiral aldehydes and (*E*)-crotyl boronates give predominantly **Felkin** products
- α-Chiral aldehydes and (*Z*)-crotyl boronates give predominantly **anti-Felkin** products




Hoffmann, R.; Zeiβ, H. –J. *J. Org. Chem.*, **1981**, *46*, 1309

# Diastereoselective Allylation reactions

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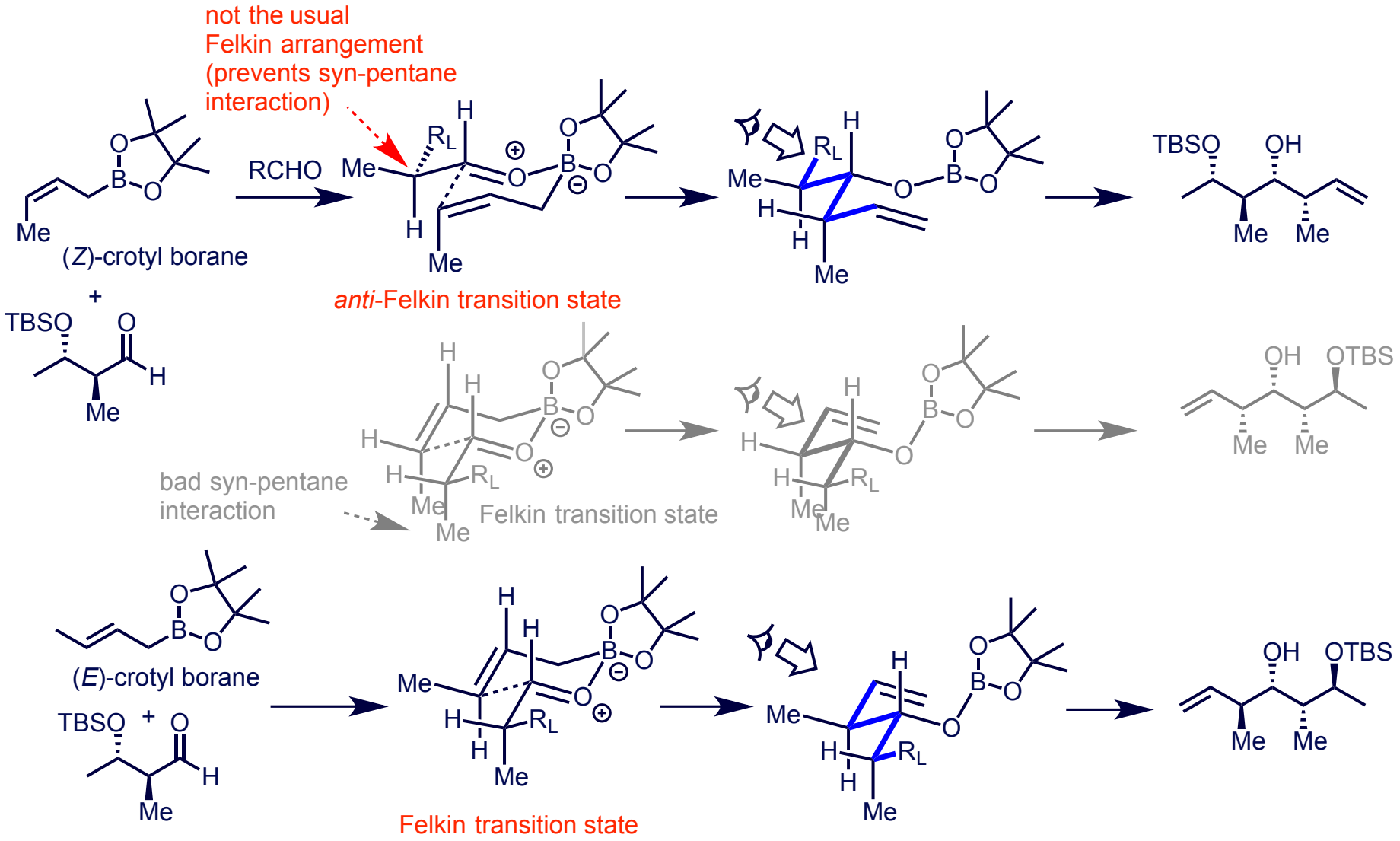


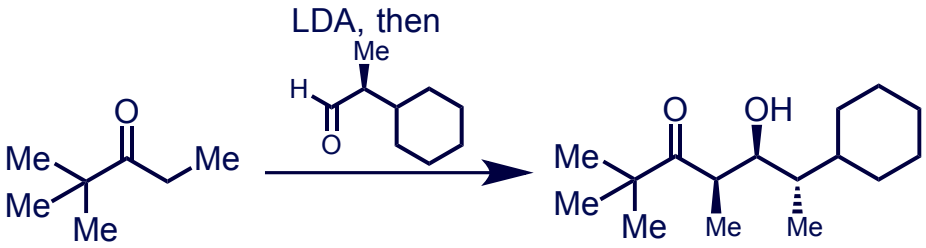

Hoffmann, R.; Zeiβ, H. –J. *J. Org. Chem.*, **1981**, *46*, 1309

This *anti*-Felkin preference is also seen with (*Z*)-enolates.

- α-chiral aldehydes and (*E*)-enolates give predominantly **Felkin** products.
- α-chiral aldehydes and (*Z*)-enolates give predominantly **anti-Felkin** products or products with low diasterocontrol.

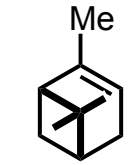
***Problem:*** Rationalise the stereochemical outcome of the following reaction.

S. Masamune, S. A. Ali, D.L. Snitman, D. S. Garvey, *Angew. Chem. Int. Ed.*, **1980**, 19, 557

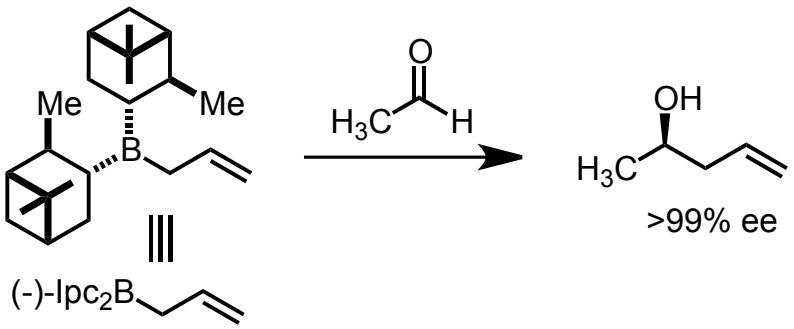


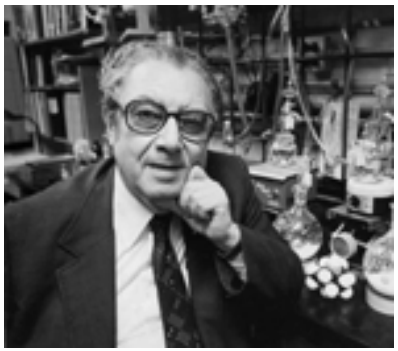
## Enantioselective Allylation and Crotylation reactions

- H. C. Brown has developed *B*-allyldiospinocampheyl borane and the corresponding (*E*) and (*Z*)-crotyl derivatives.
- All of the reagents are readily prepared from inexpensive α-pinene which is available in quantity in both enantiomers.
- These reagents react rapidly with aldehydes at low temperature to give the products in excellent yield and enantiomeric excess.
- As with the aldol reaction, the (***Z***)-crotyl borane gives the ***syn*** product and the (*E*)-crotyl borane gives the *anti*-product.

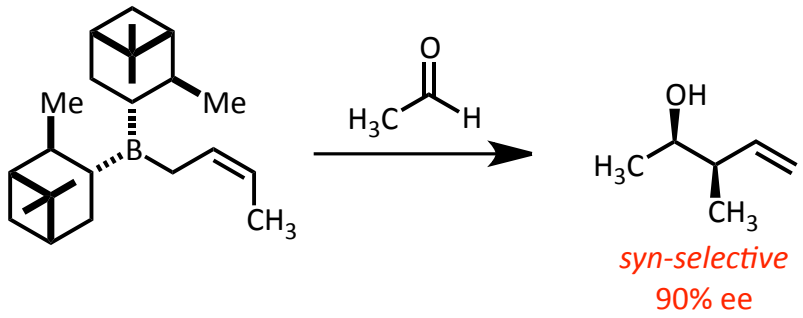


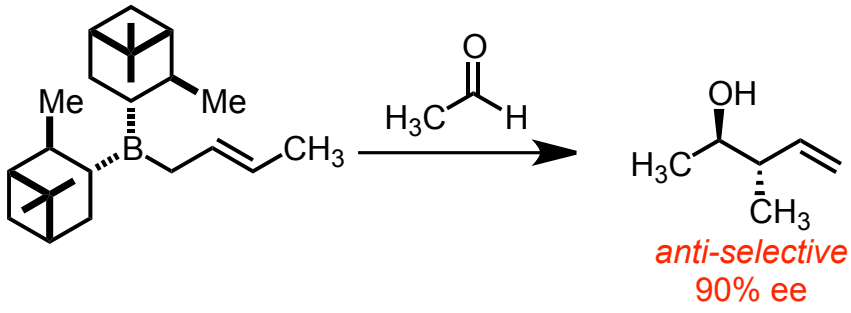

α-pinene



Nobel Prize with Georg Wittig, 1979

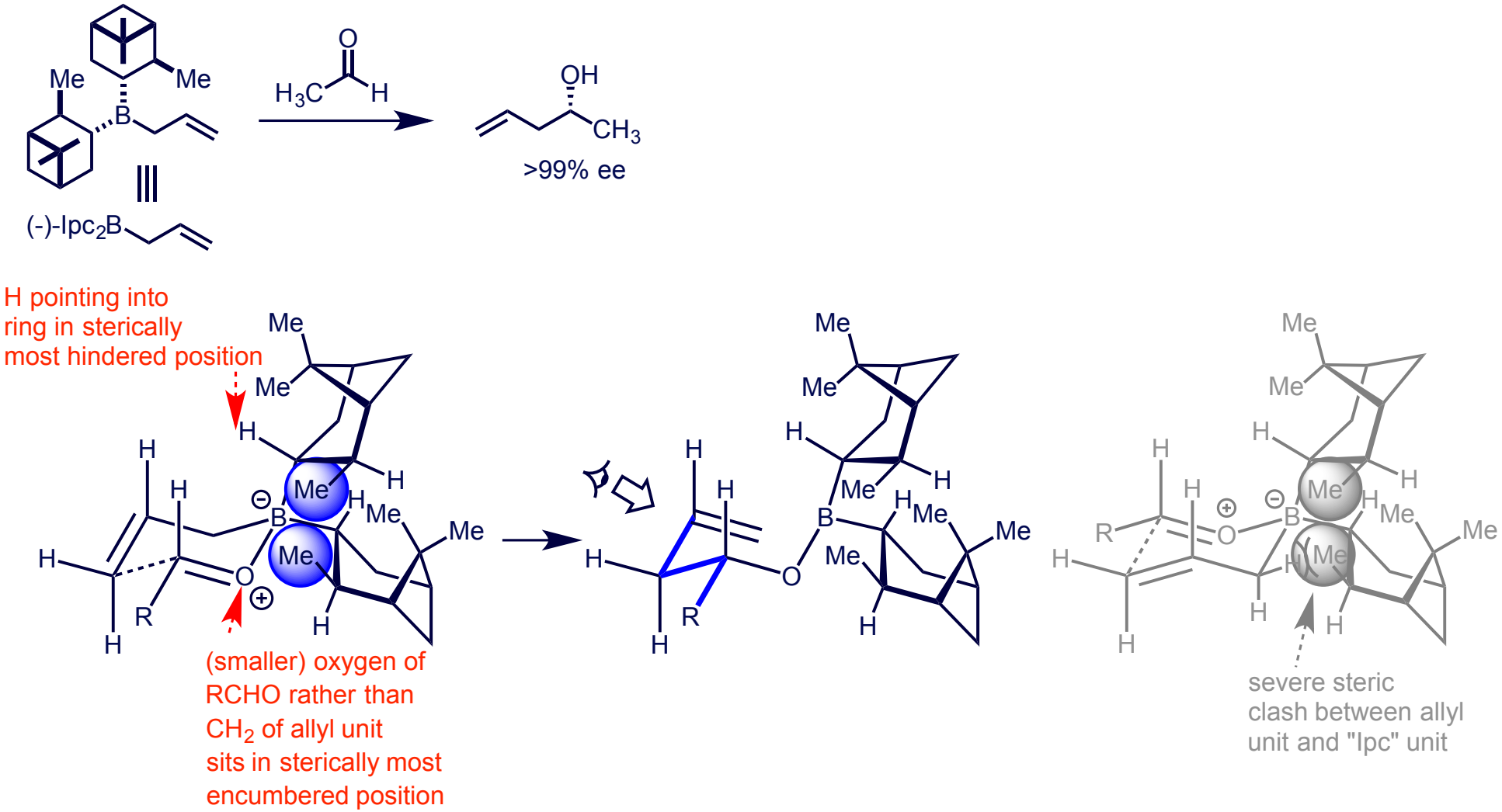



Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.*, **1983**, *105*, 2092.
Racherla, U. S.; Brown, H. C. *J. Org. Chem.*, **1991**, *56*, 401.

## Enantioselective Allylation and Crotylation reactions

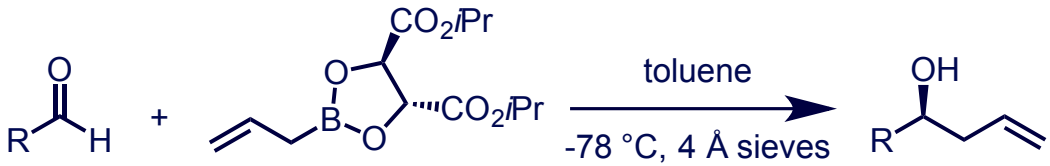
■ The model to rationalise the stereoselectivity involves minimising the interaction of the allyl/crotyl unit with the Ipc –ligands.



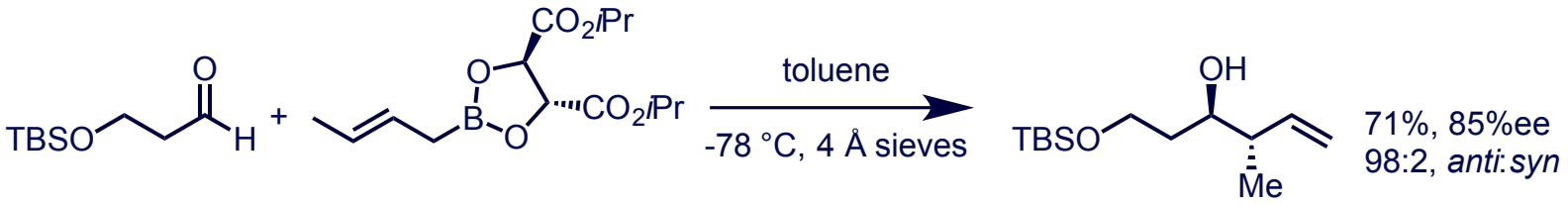

Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.*, **1983**, *105*, 2092.
Racherla, U. S.; Brown, H. C. *J. Org. Chem.*, **1991**, *56*, 401.

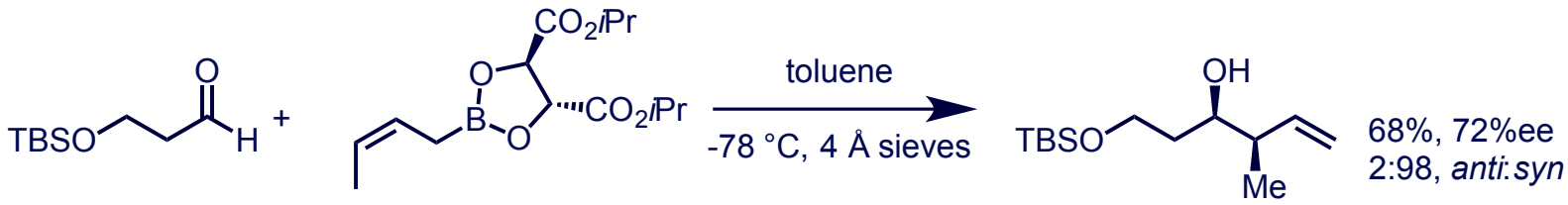
# Enantioselective Allylation and Crotylation reactions

- W. R. Roush has developed chiral allyl and crotyl boronate reagents based on tartrate esters and amides.

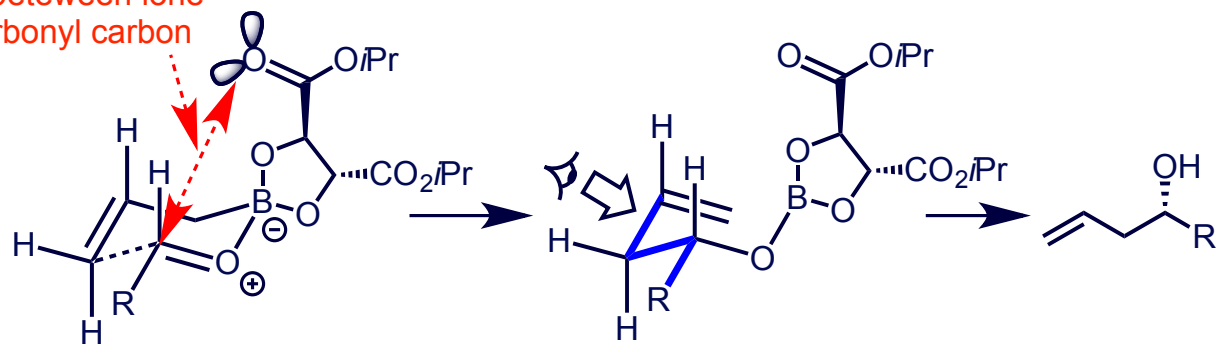


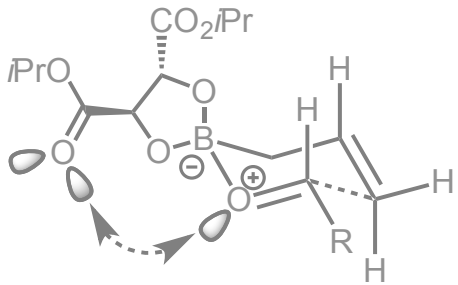

| RCHO | yield / % | ee / % |
|---|---|---|
| $nC_9H_{19}CHO$ | 86 | 79 |
| $cC_6H_{11}CHO$ | 77 | 78 |
| PhCHO | 78 | 71 |




attractive electrostatic interaction beteween lone pair and carbonyl carbon



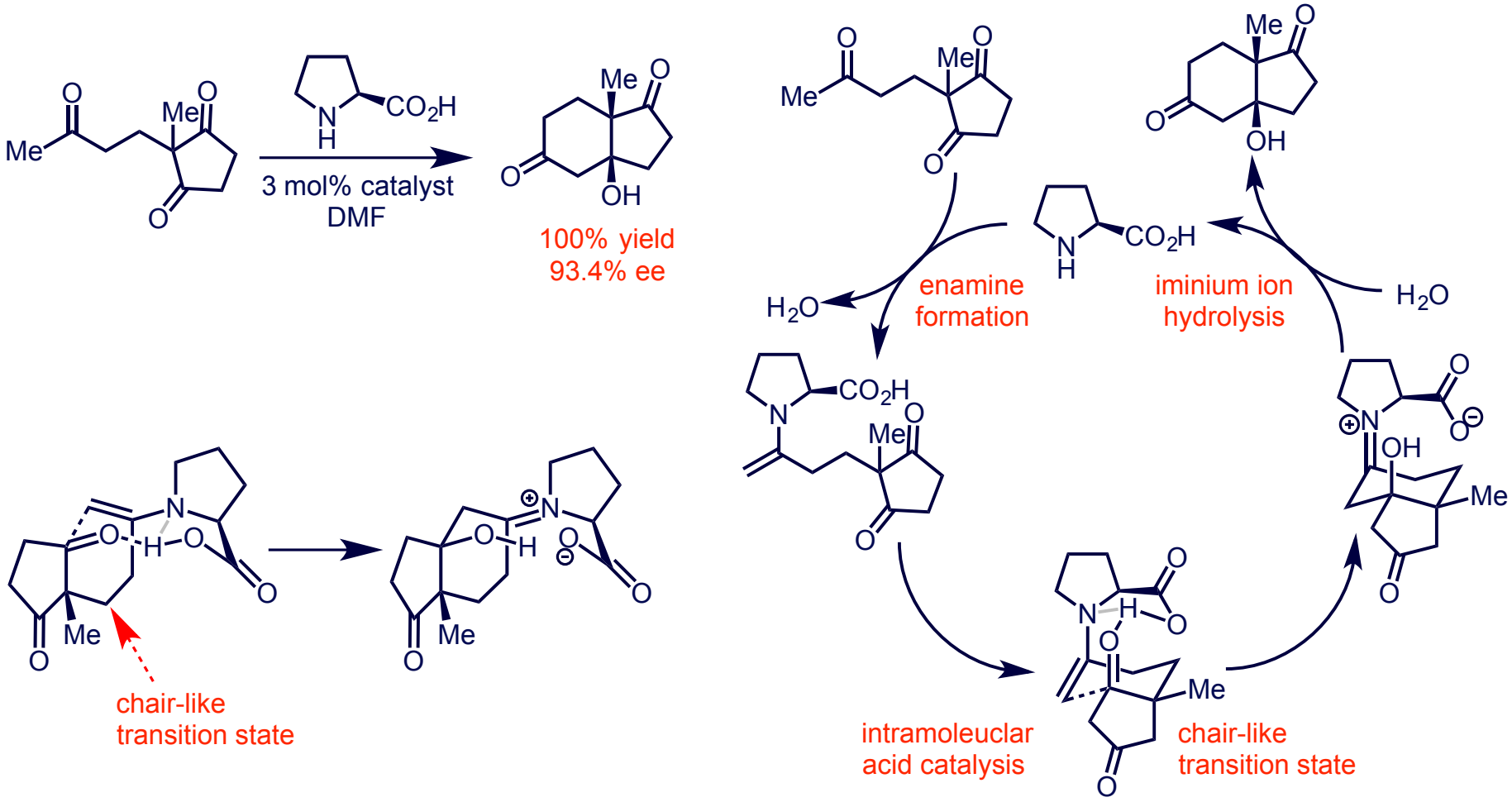




unfavourable lone-pair lone-pair repulsion

Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.*, **1990**, *112*, 6339.
Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.*, **2002**, *124*, 10692-10697.
For a discussion of the formyl hydrogen bond see: E. J. Corey, D. Barnes-Seeman, T. W. Lee, *Tetrahedron Lett.*, **1997**, *38*, 4351.

# Catalytic Asymmetric Aldol Reactions – Introduction to Organocatalysis

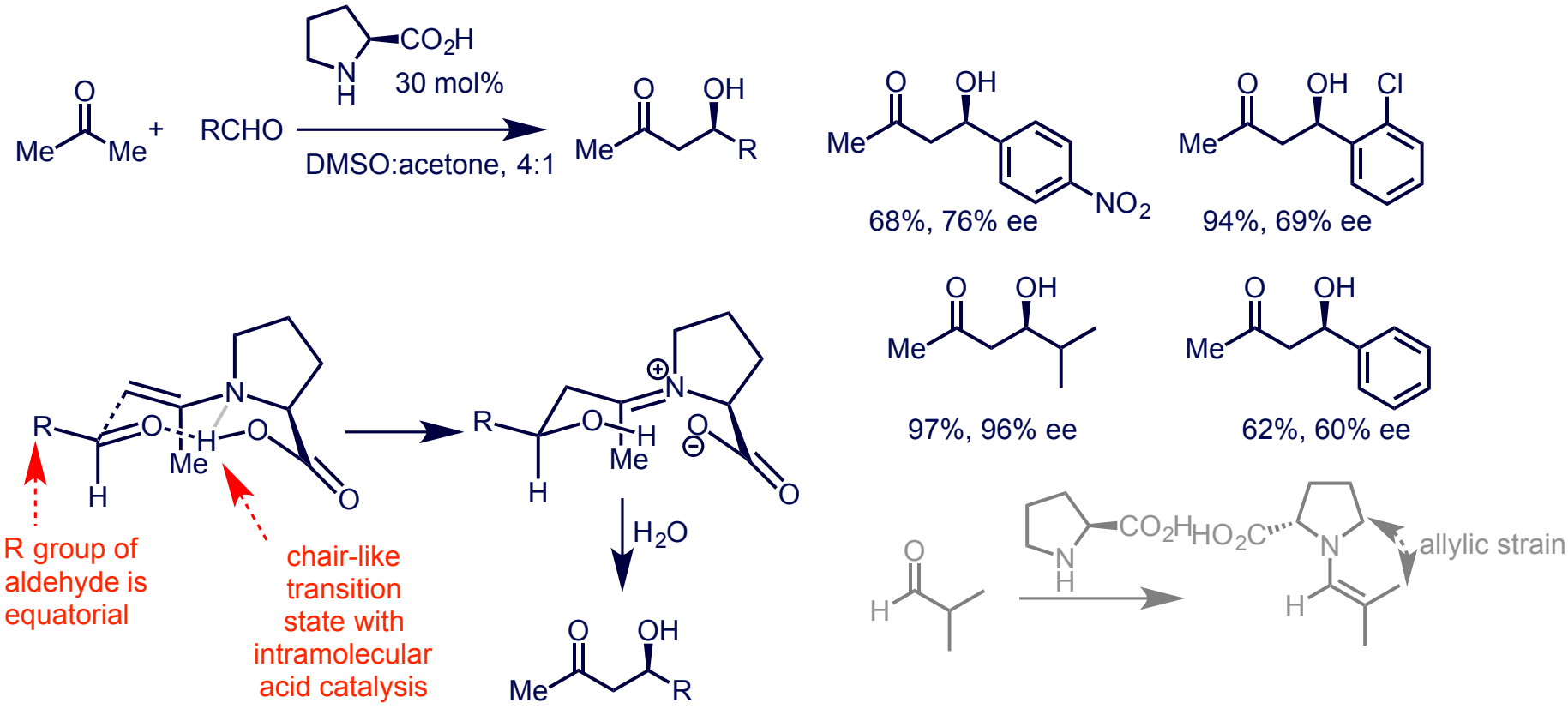
- The Hajos, Parrish, Wiechert reaction – intramolecular proline-catalysed aldol reaction.




Hajos, Z. G.; Parrish, D. R. ; *J. Org. Chem.*, **1974**, 39, 1615.
Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.*, **1971**, *10*, 496.
Overview of mechanistic studies: Alleman, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. M. *Acc. Chem. Res.*, **2004**, *37*, 558.

# Catalytic Asymmetric Aldol Reactions – Introduction to Organocatalysis

- The Hajos, Parrish, Wiechert reaction was developed into an intermolecular reaction by Barbas and List

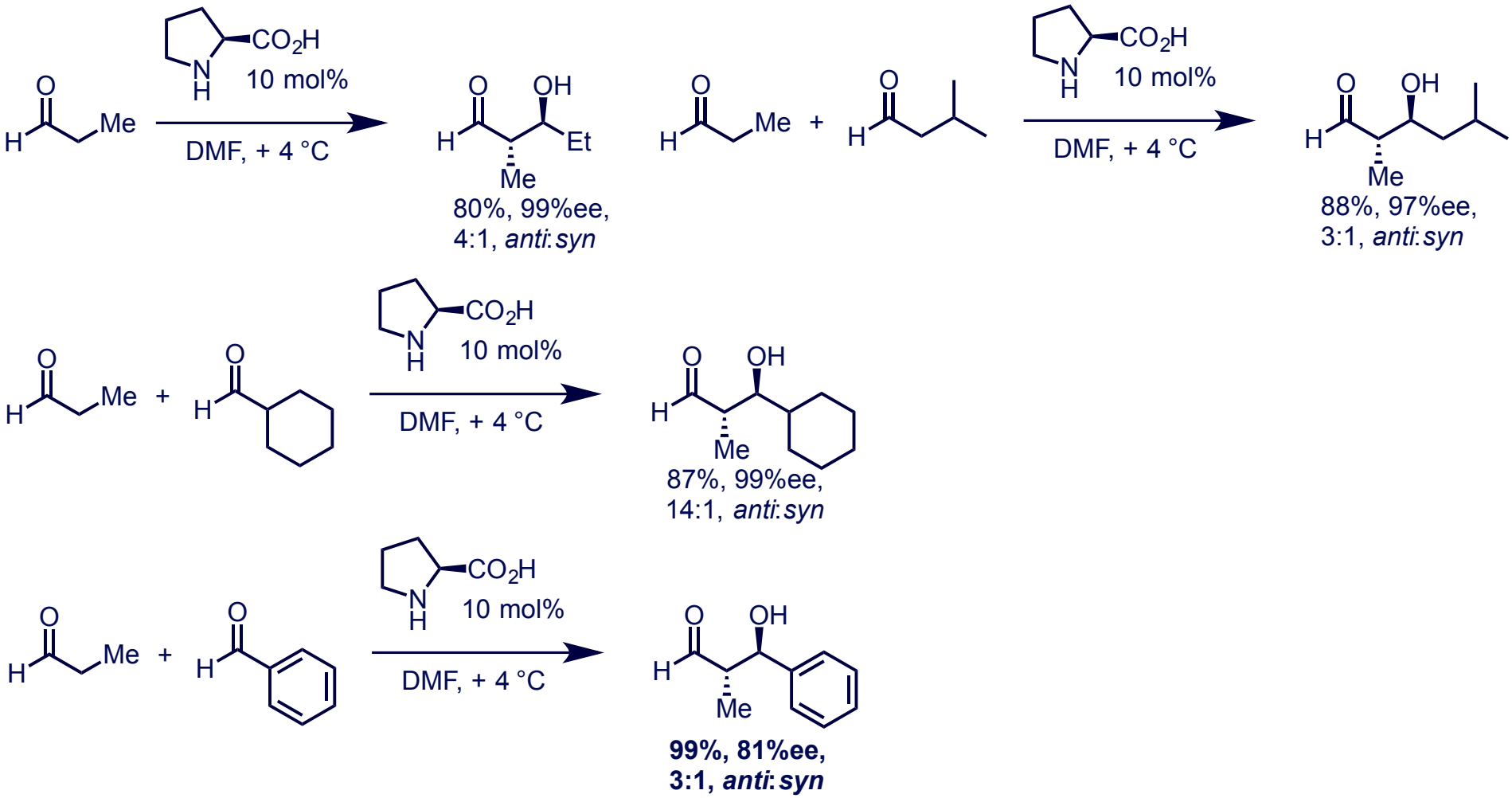



- Aldol reaction uses non-enolisable aldehydes or α-branched aldehydes which do not readily form enamines (due to $A^{1,3}$ strain).
- Mechanism involves enamine formation from acetone followed by reaction with RCHO *via* Zimmerman-Traxler type transition state.

List, B.; Lerner, R. A.; Barbas III, C. F.; *J. Am. Chem. Soc.*., **2000**, *122*, 2395.

# Catalytic Asymmetric Aldol Reactions – Introduction to Organocatalysis

- MacMillan developed an efficient cross aldol reaction of aldehydes.




- Aldol reaction uses non-enolisable aldehydes or α-branched aldehydes which do not readily form enamines.
- Mechanism involves stereoselective enamine formation from $CH_3CH_2CHO$ followed by reaction with acceptor aldehyde.
- Donor aldehyde ($CH_3CH_2CHO$) added slowly over course of reaction to prevent homo-aldol reaction.

Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.,* **2002**, *124*, 6798.

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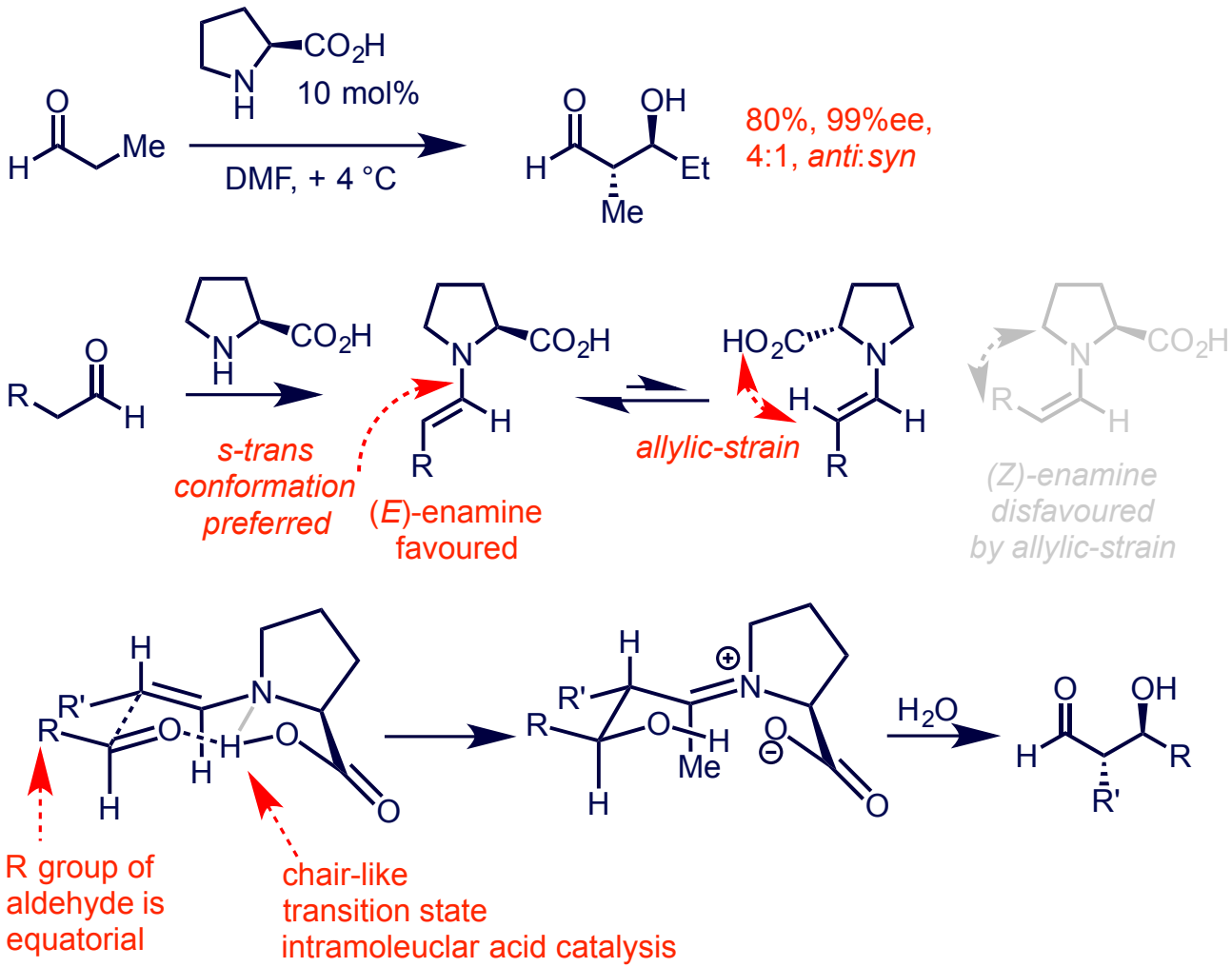


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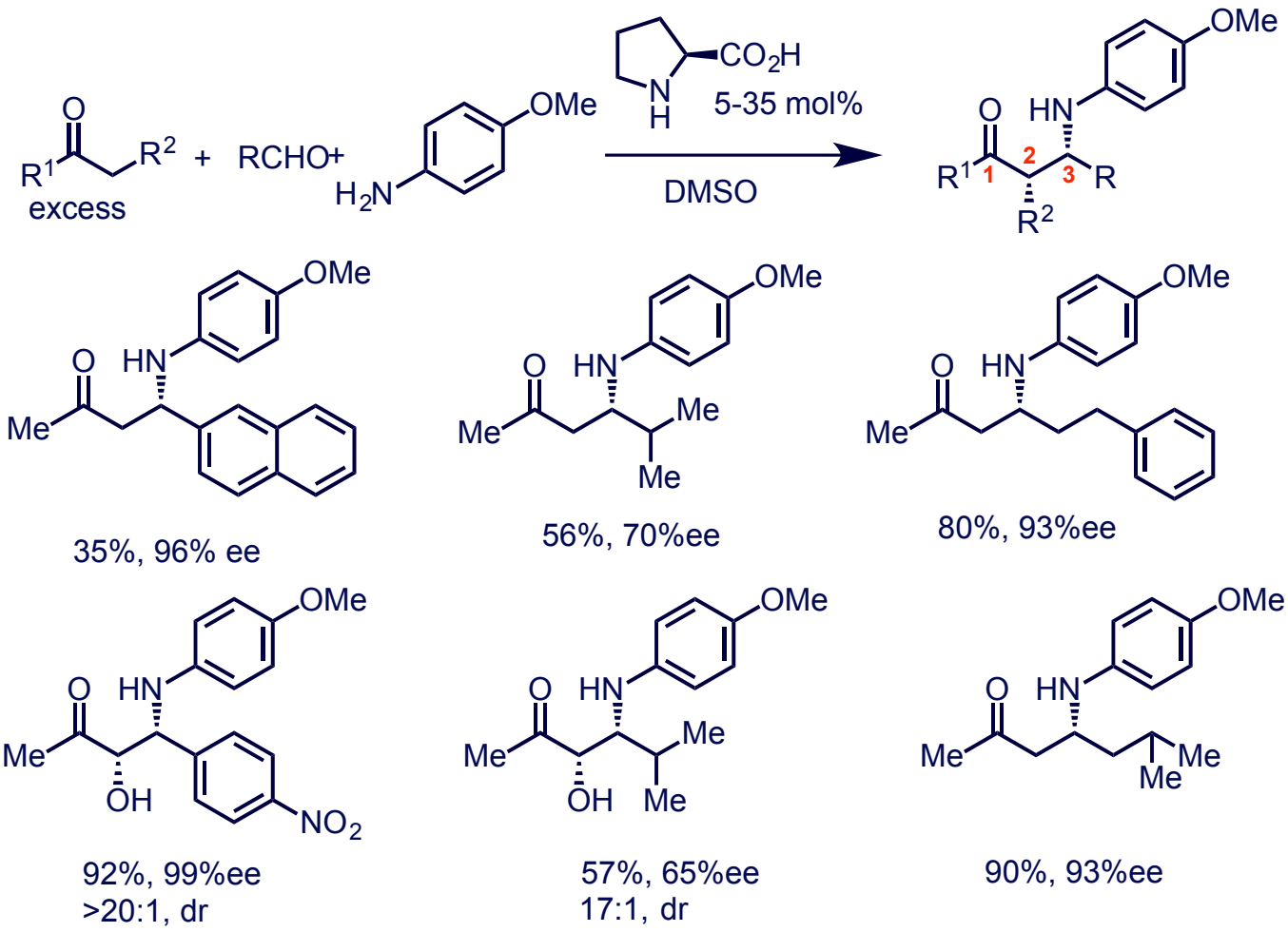
Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.,* **2002**, *124*, 6798.

# Catalytic Asymmetric Mannich Reactions

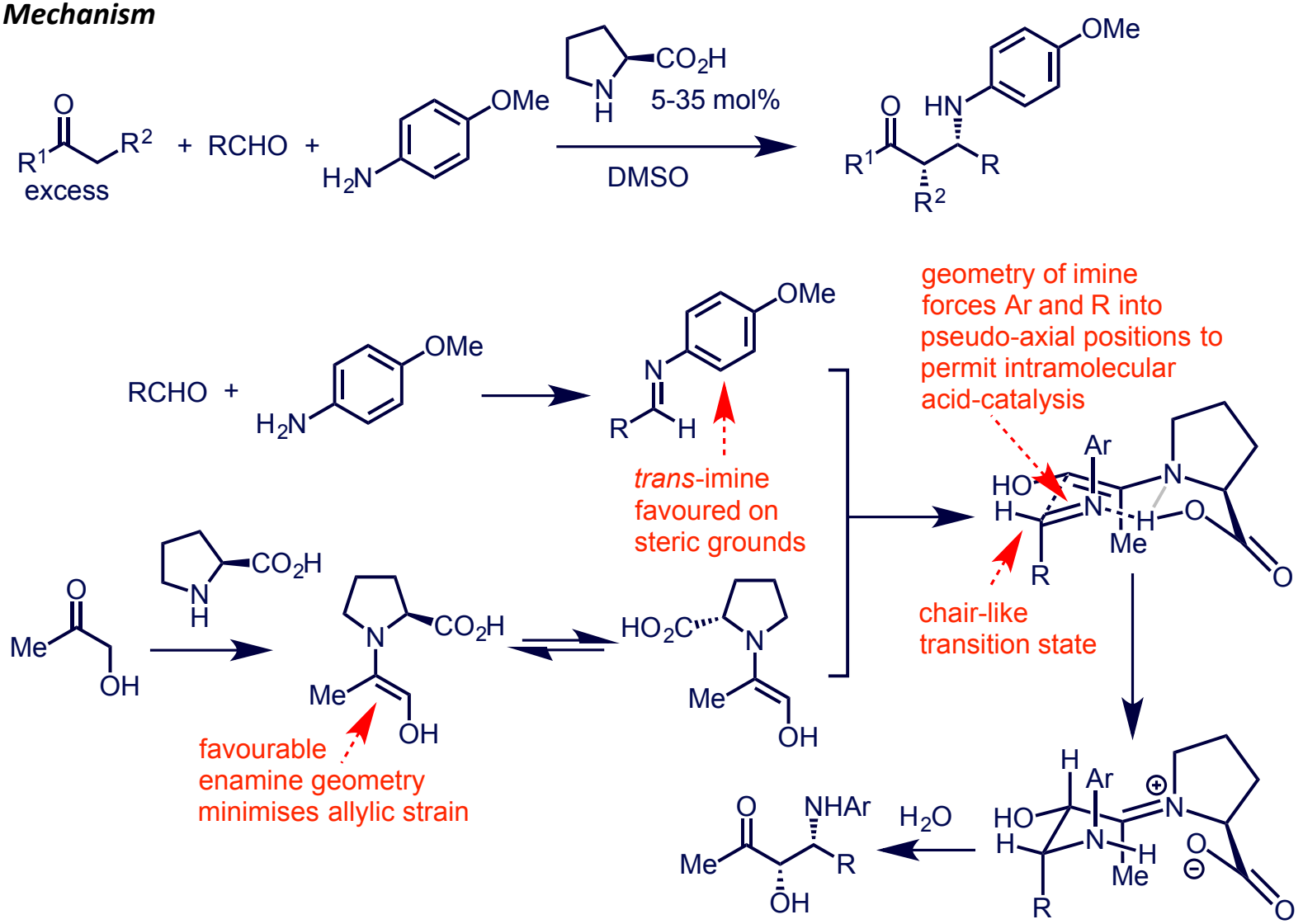



- Imine formed *in situ* between aldehyde and amine.
- Opposite absolute configuration at C-3 compared with aldol reaction.
- *syn*-Diastereomer predominates (*anti* predominates in aldol reaction).

List, B.; *J. Am. Chem. Soc.*, **2000**, *122*, 9336.

# Catalytic Asymmetric Mannich Reaction

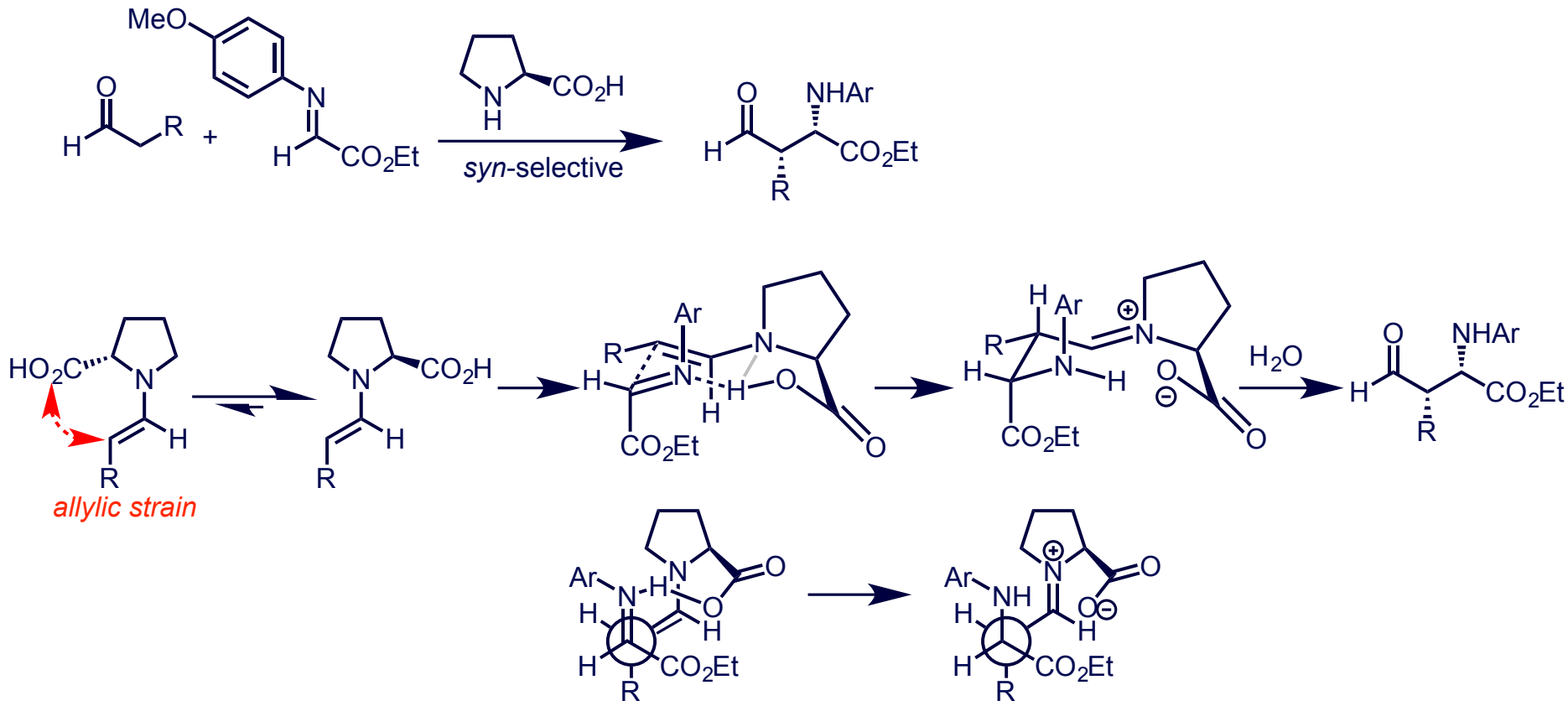
***Mechanism***




List, B.; *J. Am. Chem. Soc.*, **2000**, *122*, 9336.
W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, and C. F.Barbas III, *J. Org. Chem.* **2003**, *68*, 9624.

## Catalytic Asymmetric Mannich Reaction – anti selective – catalyst design

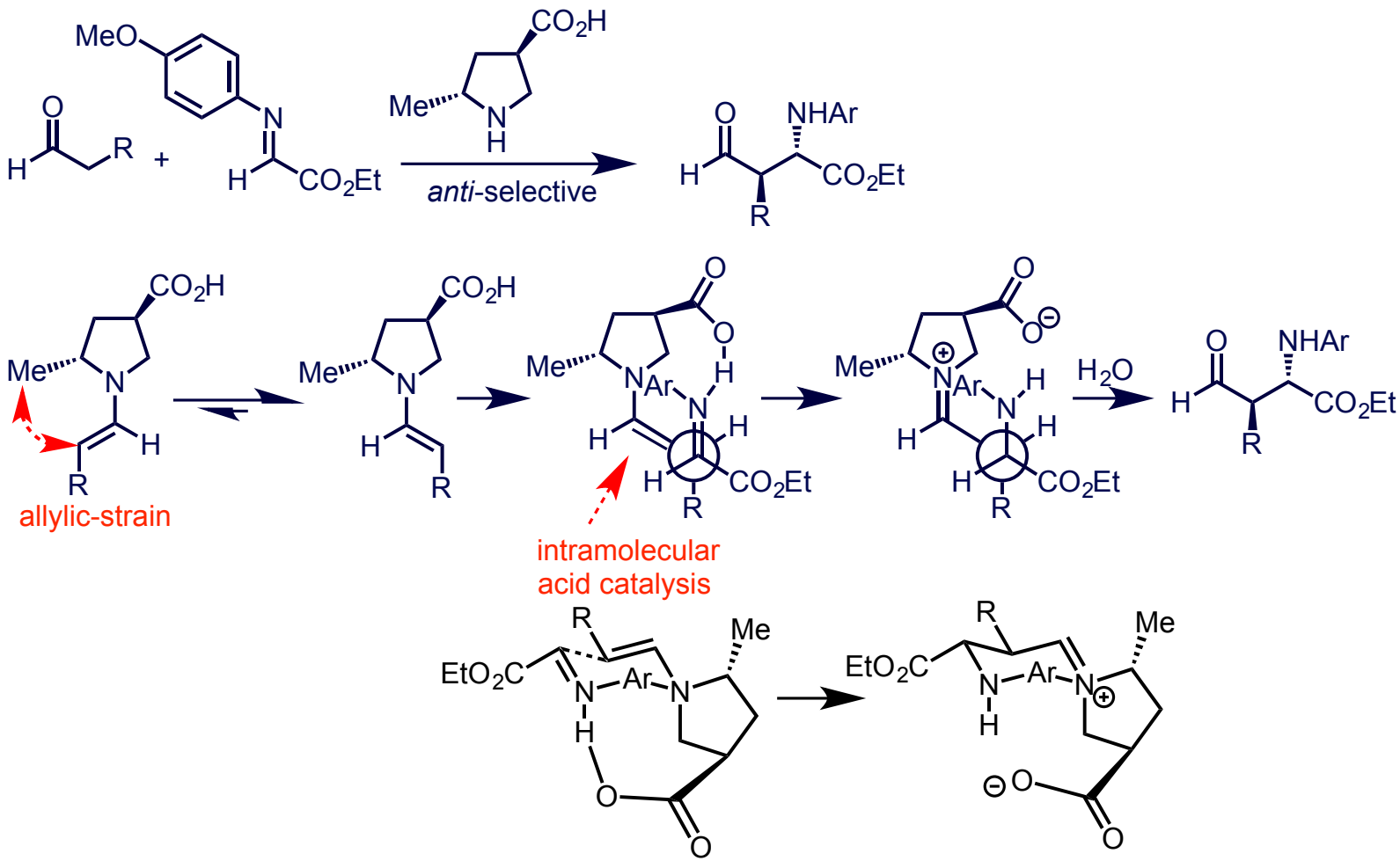
- As noted above, the *syn*-selective Mannich reaction proceeds *via* a chair like transition state from the thermodynamically most favourable enamine conformation.
- In order to have an *anti*-selective Mannich reaction it is necessary either to have the imine attacked from the opposite face, or have the enamine attack from the opposite face.




W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, and C. F.Barbas III, *J. Org. Chem.* **2003**, *68*, 9624.

## Catalytic Asymmetric Mannich Reaction – anti selective – catalyst design

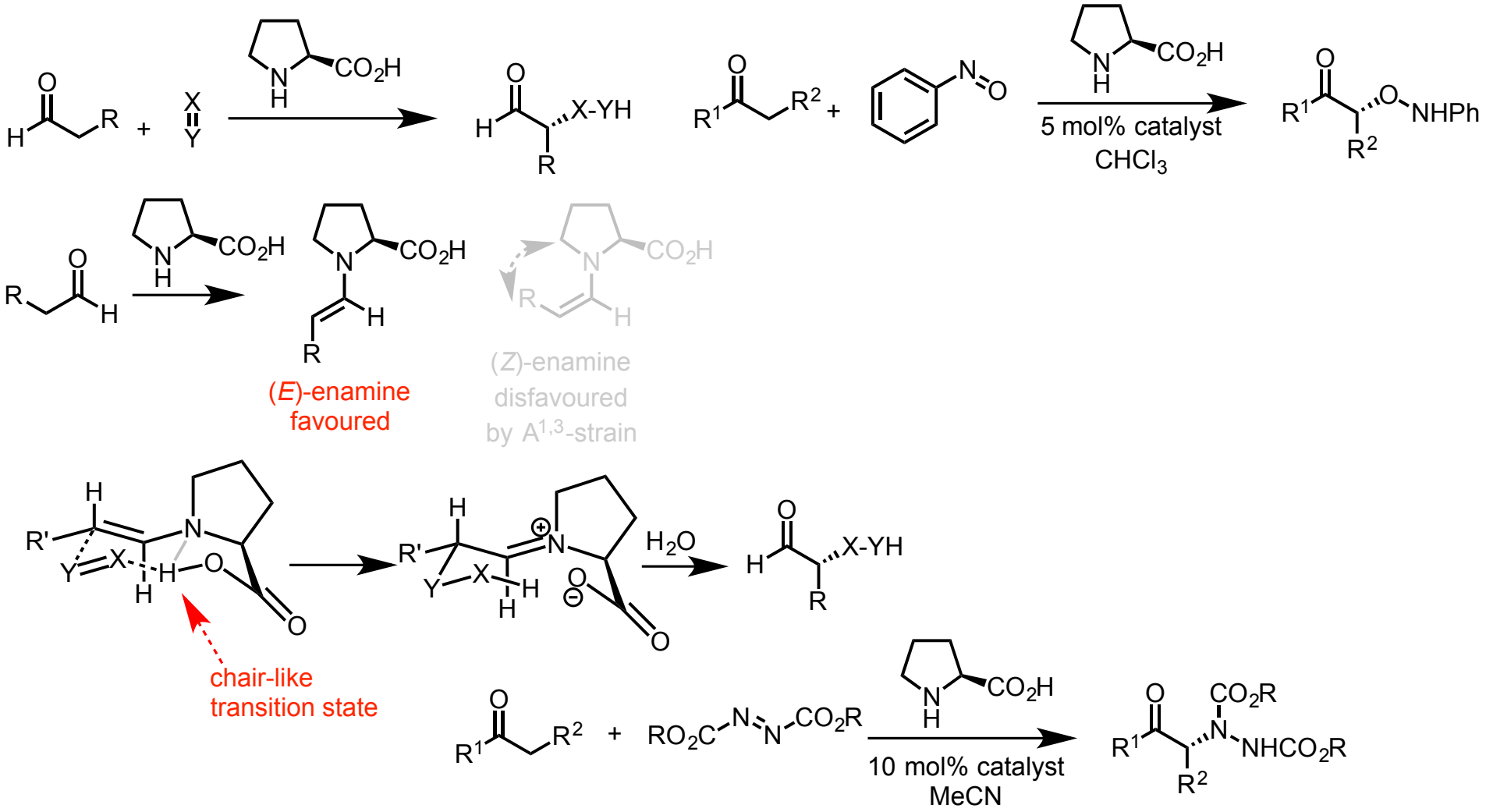
■ Use of a β-amino acid derivative of proline containing an α'-substituent biases the enamine conformation resulting in an *anti*-selective Mannich reaction.




S. Mitsumori, H. Zhang, P. H. –Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas, III, *J. Am. Chem. Soc.*, **2006**, *128,* 1040.

## Catalytic Asymmetric α-functionalisation

■ Treatment of aldehydes with a range of X=Y electrophiles gives α-functionalised aldehydes with high enantiomeric excess.

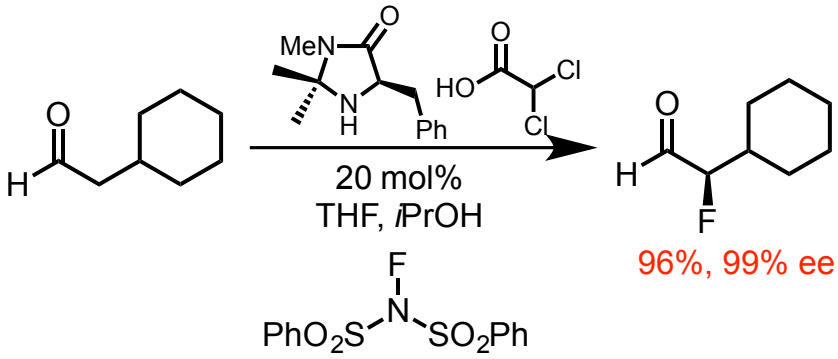


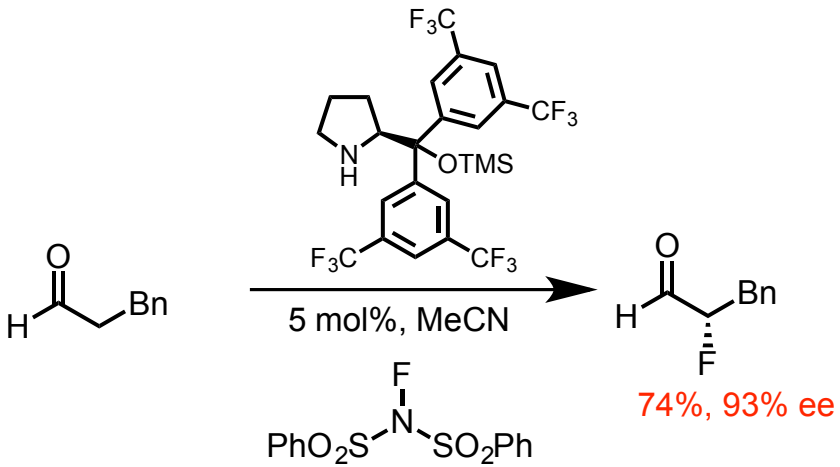

For a review of asymmetric enamine catalysis see: S. Mukherjee, J. W. Yang, S. Hoffmann, B. List. *Chem. Rev.*, **2007**, *107*, 5471.

# Organocatalytic Aldol-Type Reactions - Problems

Propose mechanisms to account for the following enantioselective transformations.

Teresa D. Beeson and David W. C. MacMillan, *J. Am. Chem. Soc*, **2002**, *124*, 6798.



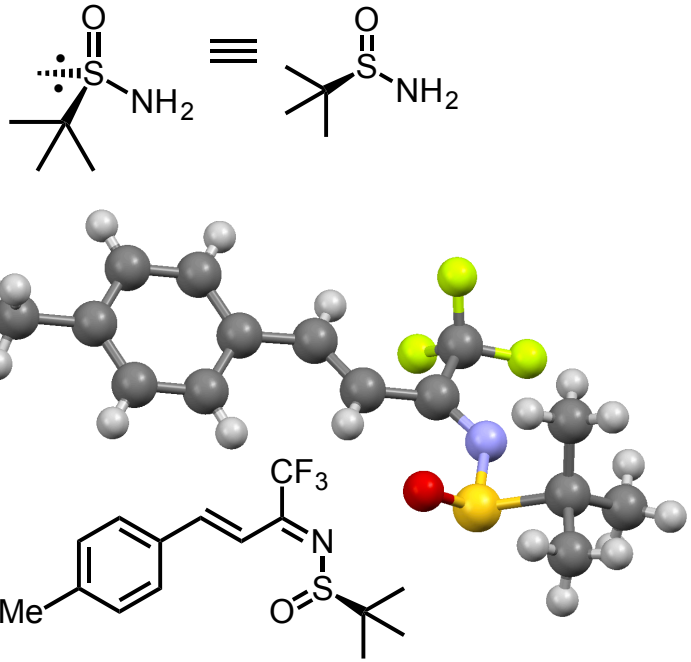



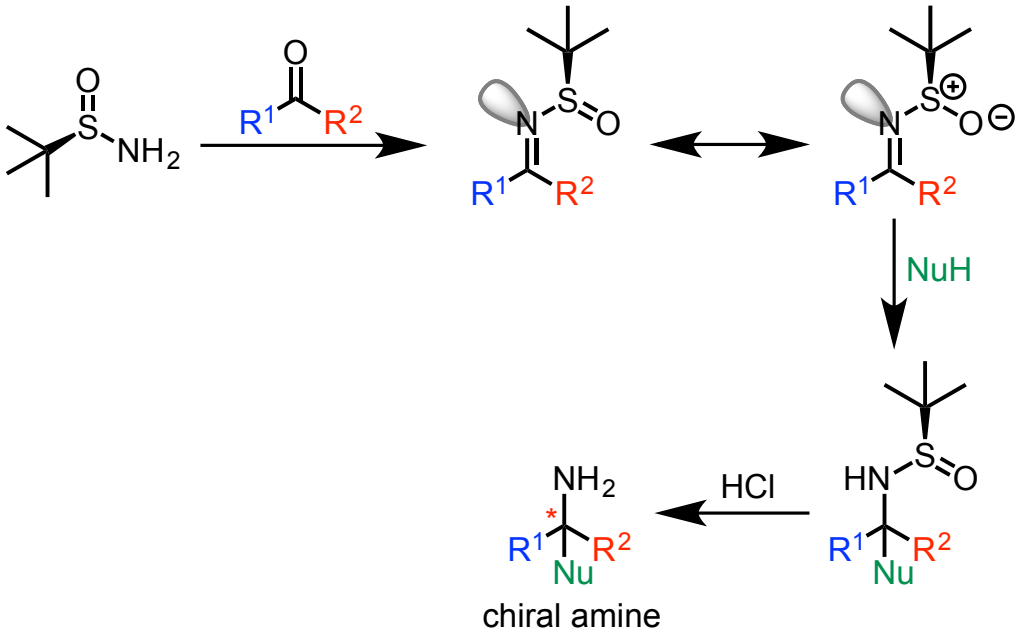

Mauro Marigo, Doris Fielenbach, Alan Braunton, Anne Kjærsgaard, and Karl Anker Jørgensen, *Angew. Chem., Int. Ed.*, **2005**, *44*, 3703

## Chiral Ammonia Equivalents

There are numerous chiral ammonia equivalents, two of the most widely used are Ellman's sulfinamide and Davies' lithium amides.

- Ellman's sulfinamide; J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984-995; M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600-3740.
- The sulfinamide is tetrahedral at sulfur due to the presence of a lone pair of electrons and hence is chiral
- The sulfinamide reacts readily with a wide variety of aldehydes and ketones to give the corresponding aldimines and ketimines.
- *t*-Butylsulfinimyl aldimines are much more hydrolytically stable and tautomerise less readily than alkyl, aryl or carbamoyl imines
- *t*-Butylsulfinimyl aldimines are more electrophilic than aryl or alkyl imines
- In the addition products the *t*-butylsulfinyl group reduces the nucleophilicity of the amine – useful protecting group
- *t*-Butysulfinyl amines are stable to strong bases, nucleophiles, Pd-catalysed cross-coupling reactions, metathesis etc.
- Removal of *t*-butylsulfinyl group readily occurs in high yield on treatment with methanolic HCl

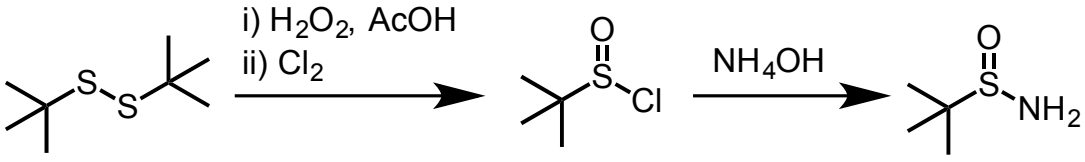


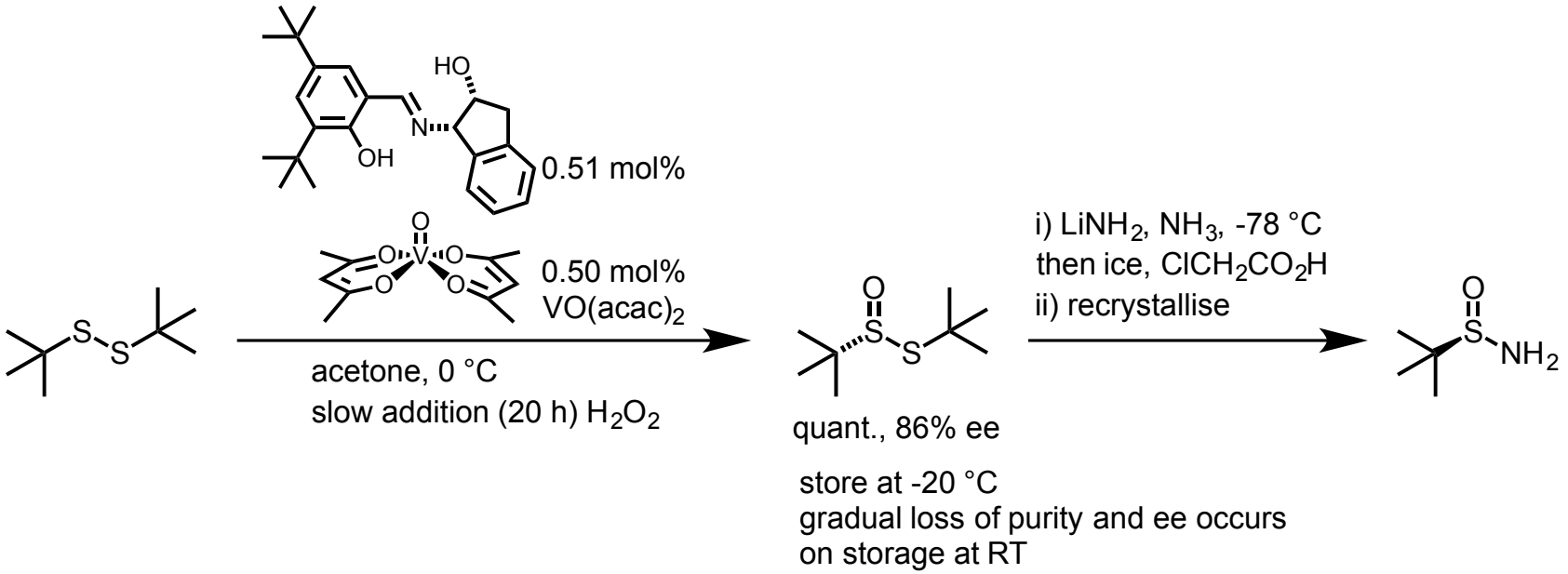

X-ray structure: Z. J. Liu, J. T. Liu, *Chem. Commun.* **2008**, 5233-5235.

# *t*-Butylsulfinamides

■ Synthesis of racemic *t*-butylsulfinamide; Netscher, T.; Prinzbach, H. *Synthesis* **1987**, 683; Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am.Chem. Soc.* **1998**, *120*, 8011.




■ Enantiomerically pure *t*-butylsulfinamide can be synthesised in a number of ways – the catalytic asymmetric synthesis below is used on the ton-scale for commercial production of the sulfinamide; D. J. Weix, J. A. Ellman, X. Wang, D. P. Curran *Org. Synth*. **2005**, *82*, 157.

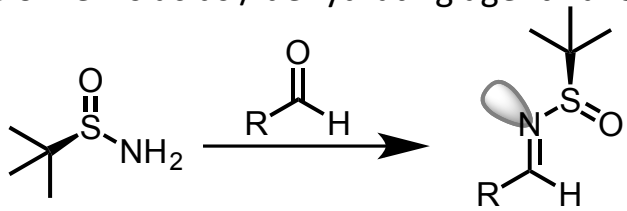



J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984-995; M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600-3740.

## *t*-Butylsulfinamides

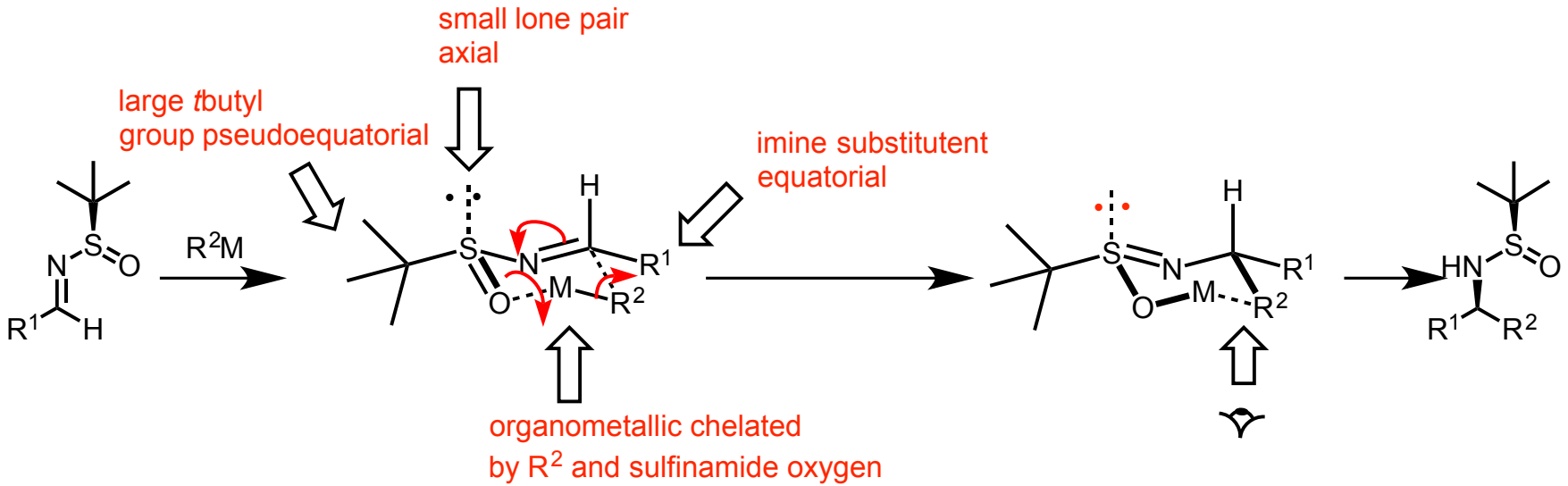
- Reaction of *t*-butylsulfinamide with aldehydes gives (*E*)-aldimines which can be purified by silica gel chromatography with no loss of optical purity – ketimines are significantly less stable to silica gel and have to be purified rapidly

- A range of Lewis acids / dehydrating agent have been used – $CuSO_4$ and $Ti(OEt)_4$ are particularly effective.



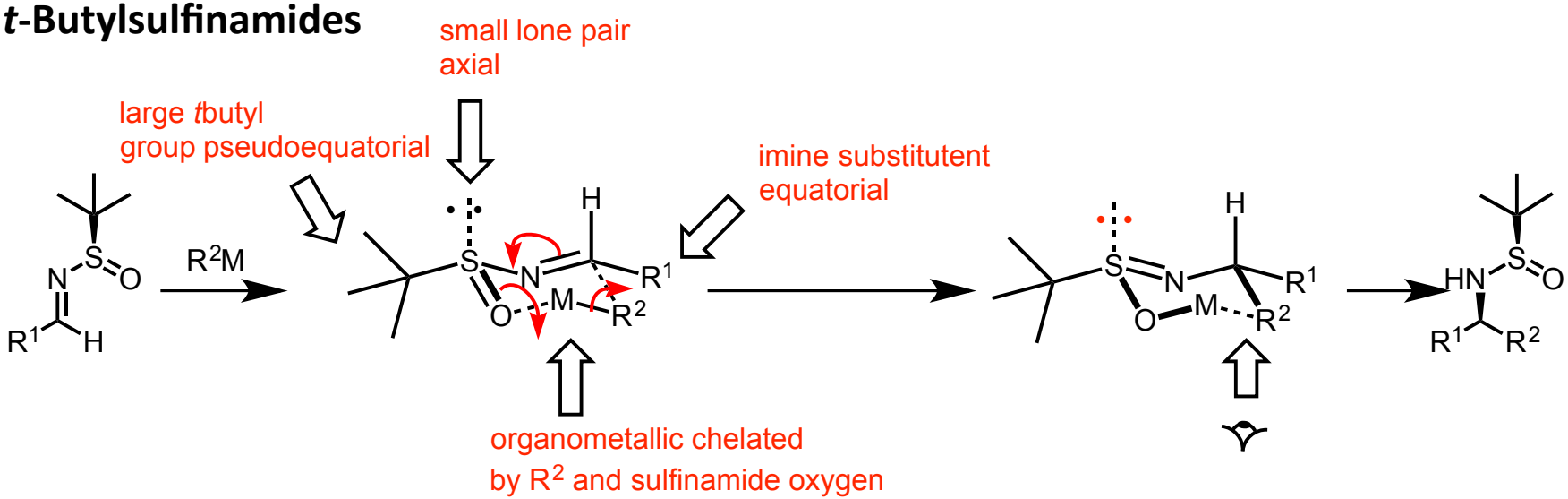
- Addition of organometallic reagents to aldimines – synthesis of amines

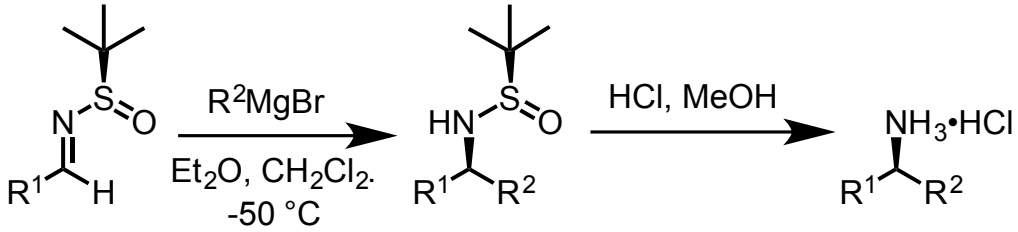
- The model below is appropriate for chelating metals in non-polar solvents

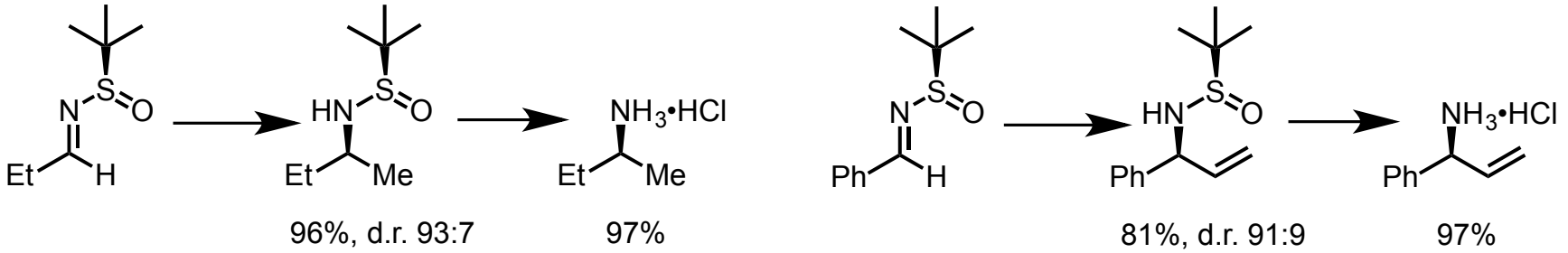



J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984-995; M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600-3740.

## *t*-Butylsulfinamides



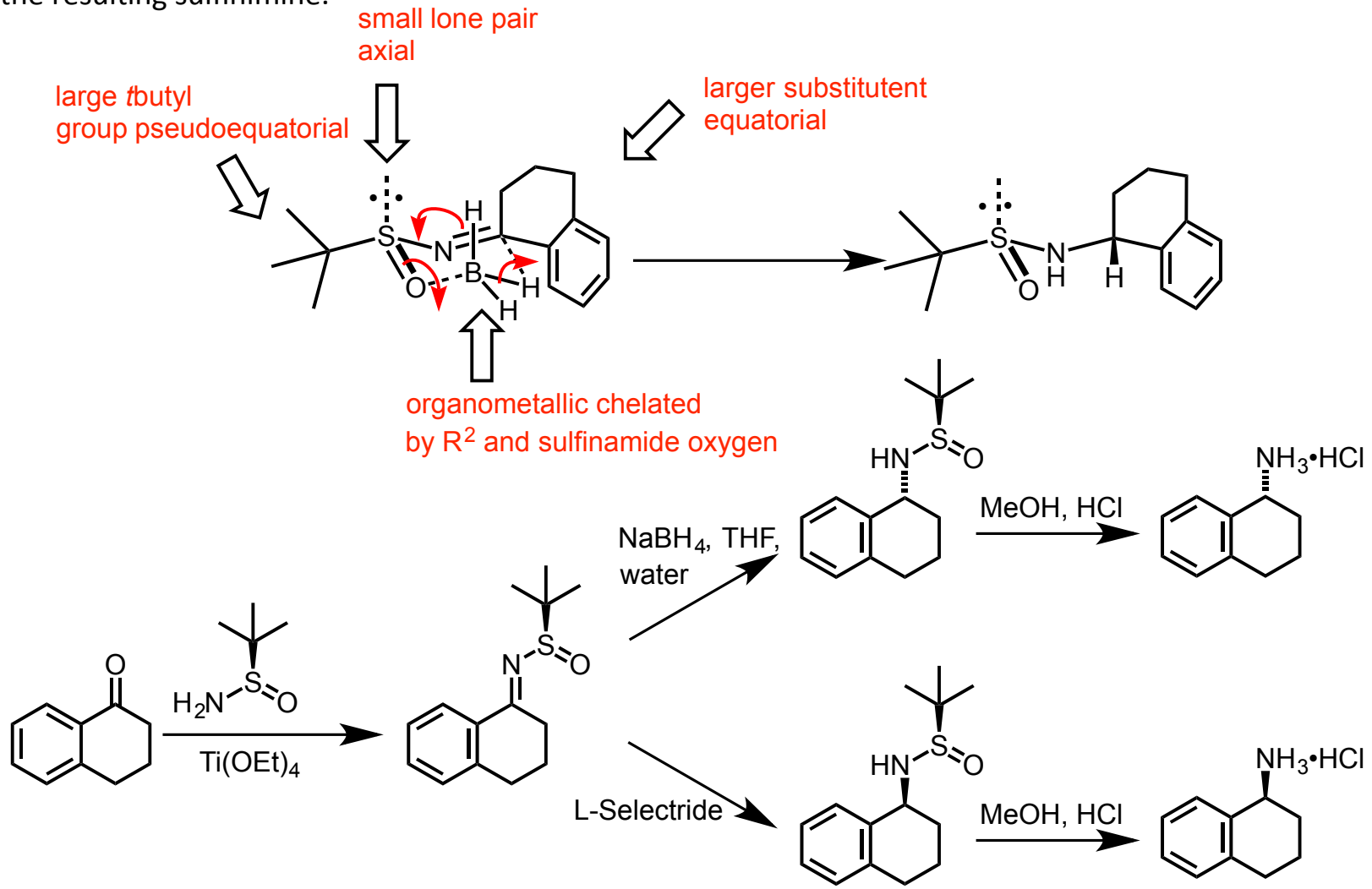




J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984-995; M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600-3740.

## *t*-Butylsulfinamides

■ Reduction of ketimines with $NaBH_4$ or L-Selectride (Li tri-*sec*-butylborohydride) gives different major diastereomers of the resulting sulfinimine.




J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984-995; M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600-3740.

# *t*-Butylsulfinamides

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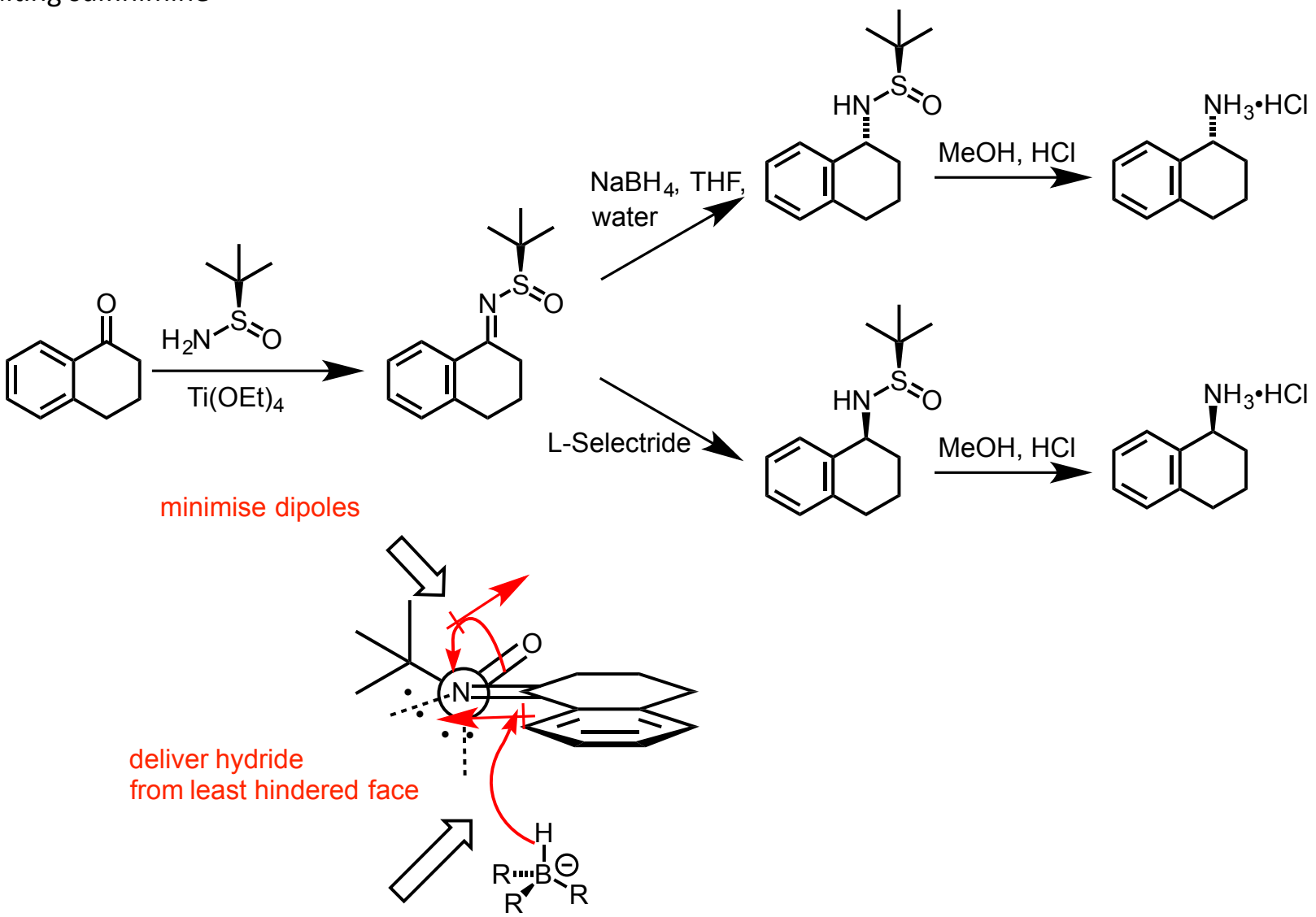
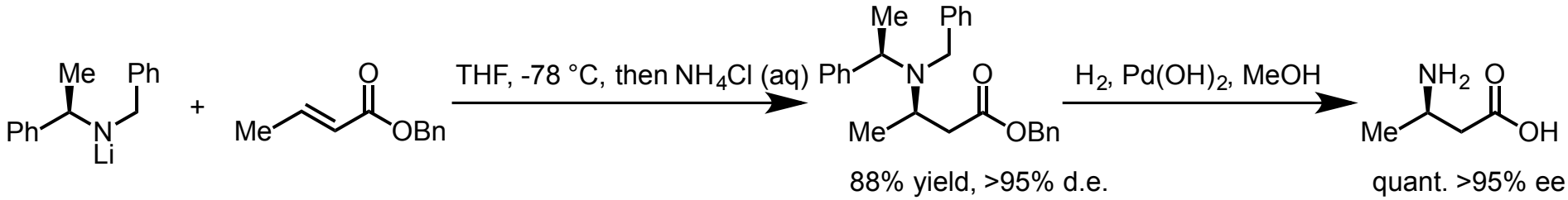



J. T. Colyer, N. G. Andersen, J. S. Tedrow, T. S. Soukup, M. M. Faul, *J. Org. Chem.* **2006**, *71*, 6859-6862;
J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984-995;.

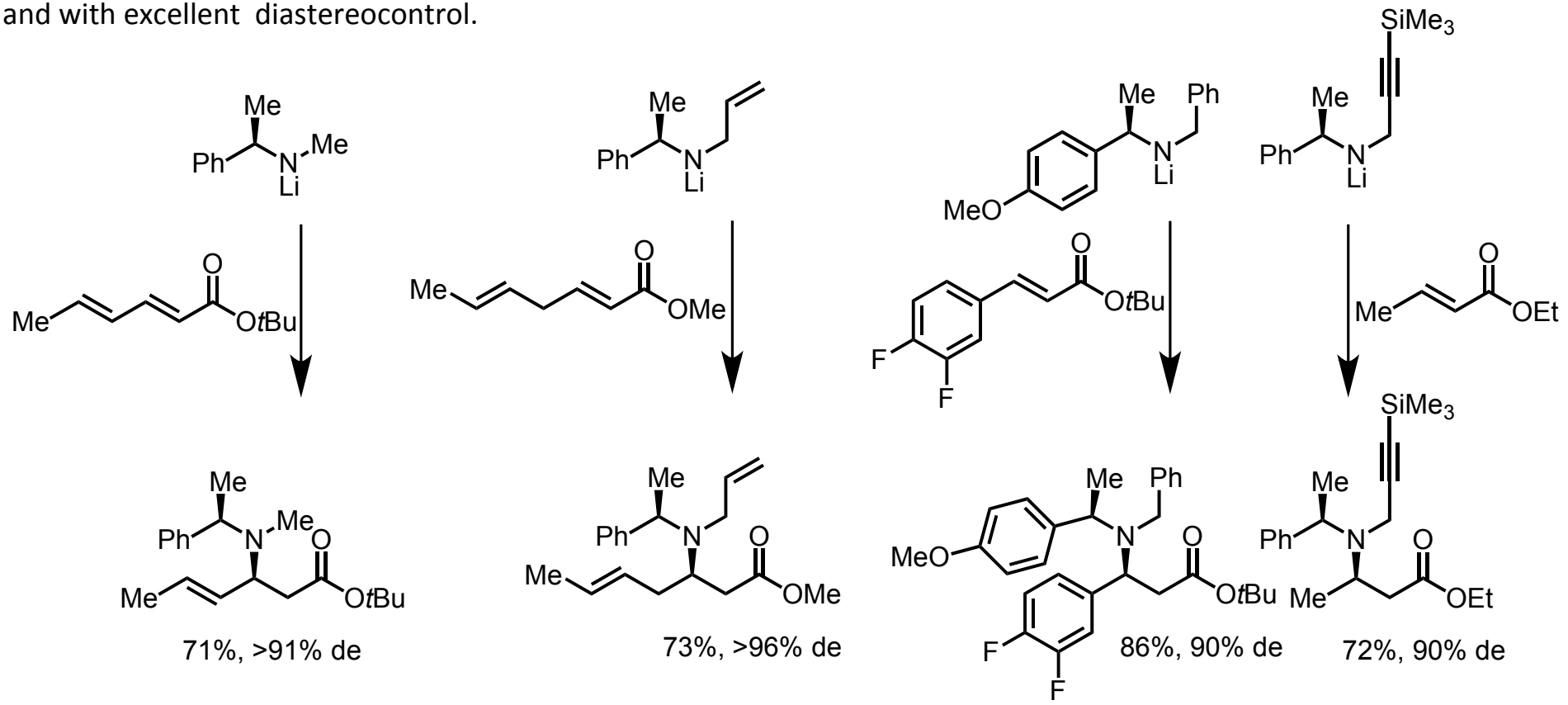
## Davies Lithium Amides

- An excellent reagent for the synthesis of β-amino acids and derivatives thereof;

S. G. Davies, A. D. Smith, P. D. Price, *Tetrahedron: Asymmetry* **2005**, *16*, 2833-2891; S. G. Davies, A. M. Fletcher, P. M. Roberts, D. Hughes, *Org. Synth.*, **2010**, *87*, 143.

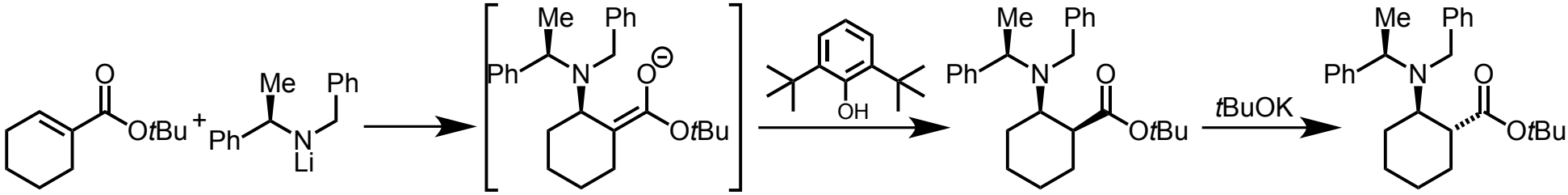



- All of the following lithium amides (and others) undergo conjugate addition to α,β-unsaturated esters in high yields and with excellent diastereocontrol.

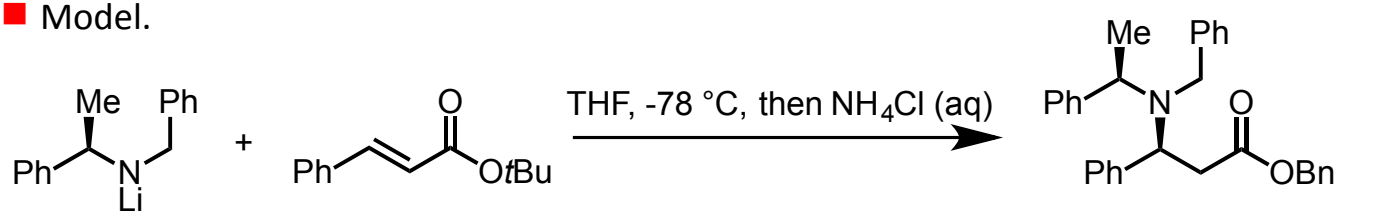


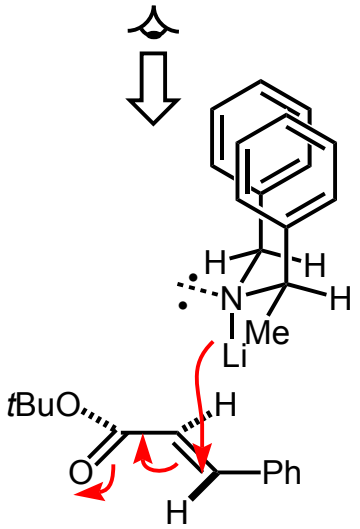
# Davies Lithium Amides

- Also applicable to cyclic α,β-unsaturated esters: S. G. Davies, O. Ichihara, I. Lenoir, I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411-1415.

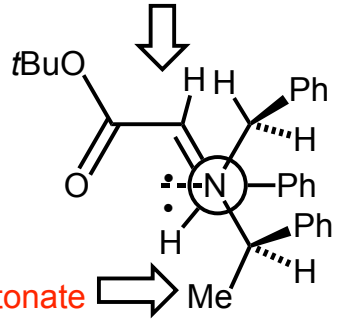



- Model.



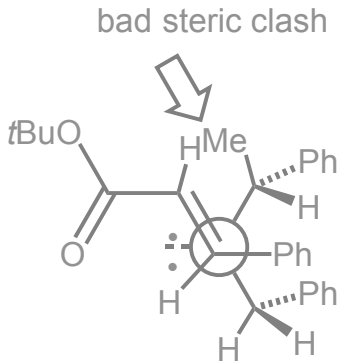

amide attacks crotonate opposite to large phenyl groups




Me group sits away from crotonate

favoured

bad steric clash

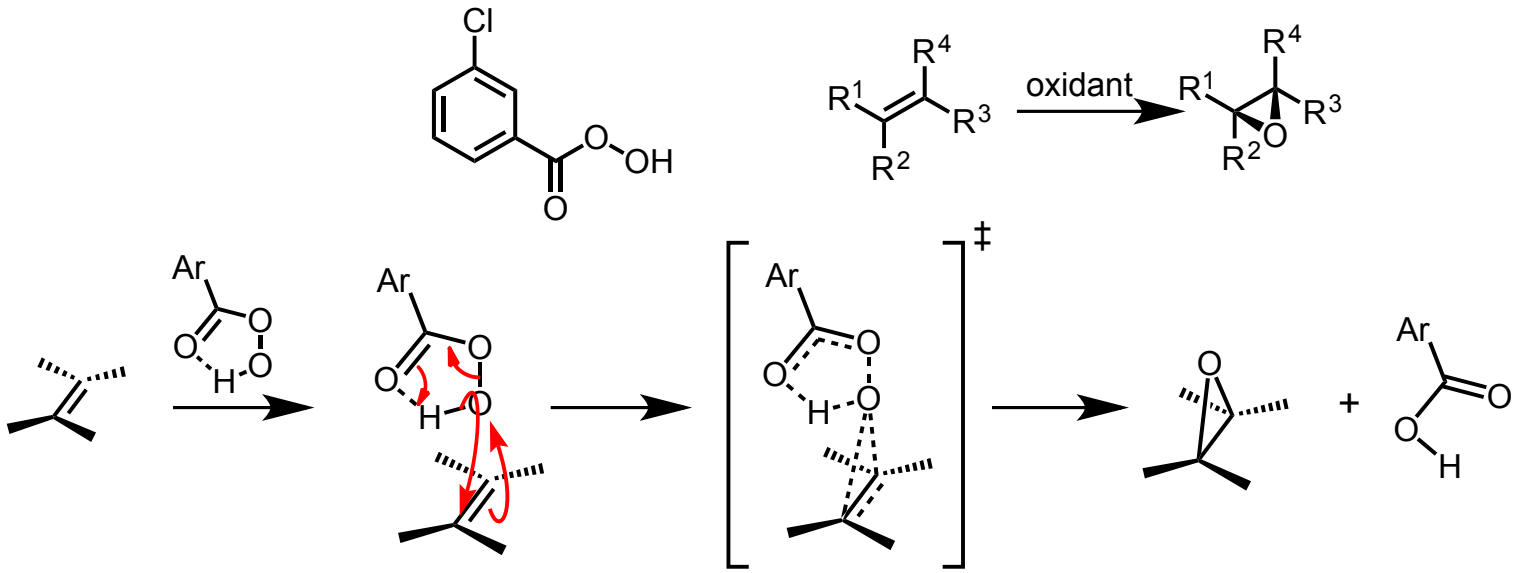


# Asymmetric Oxidation (Epoxidation and Dihydroxylation)

## Epoxidation

- Epoxides are exceedingly versatile intermediates in organic chemistry as there are numerous methods for their synthesis.
- They are readily converted into a wide range of products due to their spring-loaded nature.
- The epoxidation of alkenes is generally stereospecific – i.e. *cis*-alkenes give *cis*-epoxides and *trans*-alkenes give *trans*-epoxides.
- The classic oxidant is *meta*-chloroperbenzoic acid – *m*CPBA.

*"If carbonyl compounds have been said to be virtually the backbone of organic synthesis, the epoxides correspond to at least one of the main muscles" - Professor D. Seebach*

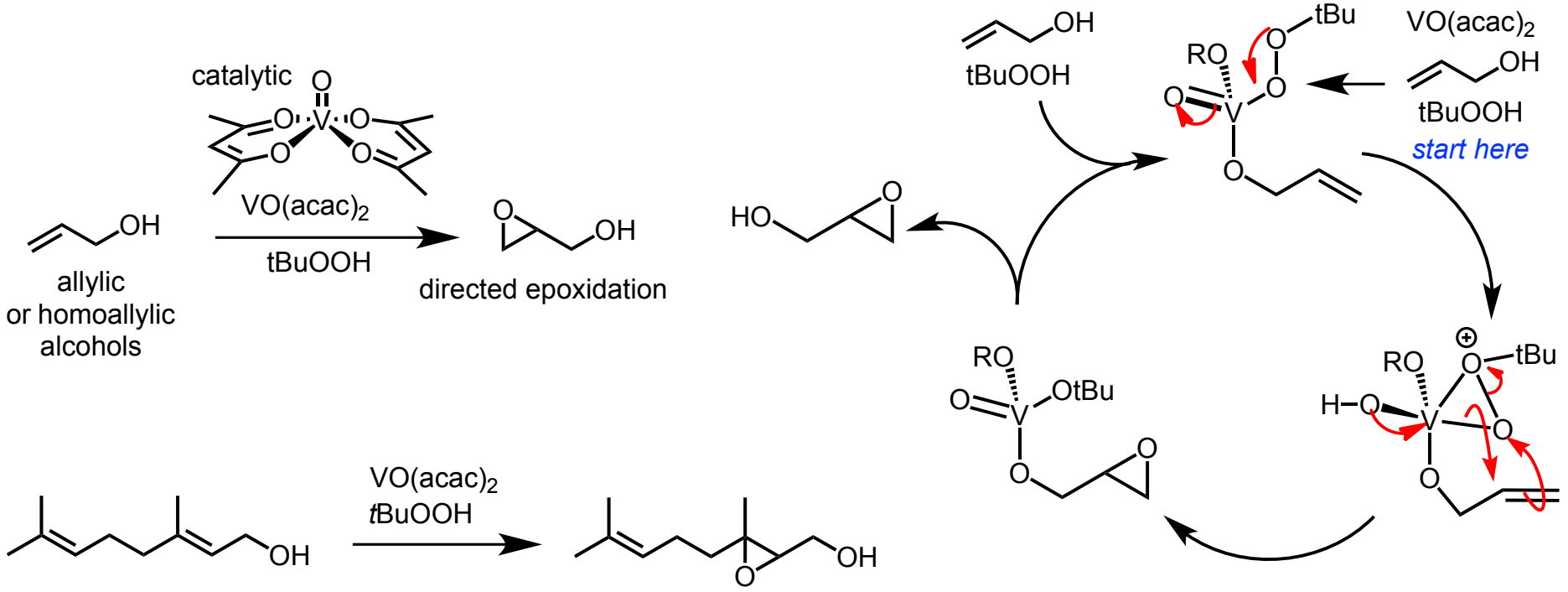



primary stereoelectronic interaction - $\pi_{C=C} \rightarrow \sigma^*_{O-O}$

# Asymmetric Oxidation (Epoxidation and Dihydroxylation)

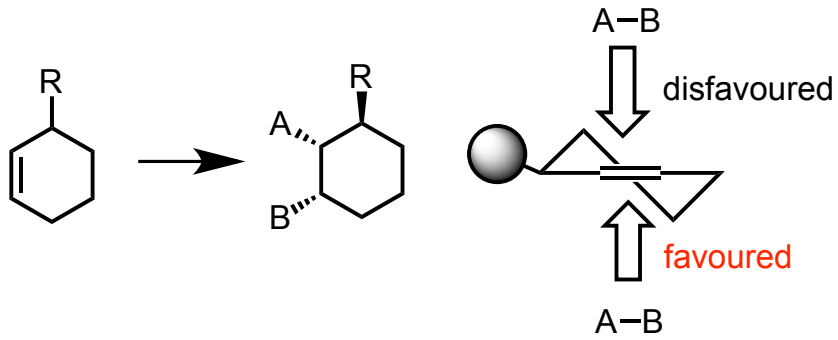
## Epoxidation

- Transition metal catalysts in the presence of a suitable oxidant will epoxidise alkenes.
- The use of vanadyl(acac)$_2$ and *t*butylhydroperoxide (*t*BuOOH) allows the epoxidation of allylic and homoallylic alcohols.
- The use of Ti(O*i*Pr)$_4$ and a tartrate ester in place of VO(acac)$_2$ allows the highly enantioselective epoxidation of allylic alcohols (see later).

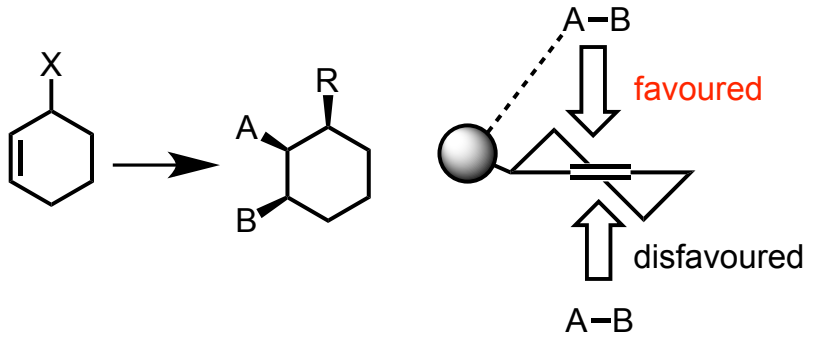



For a review see: Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta,* **1979**, *12,* 63.

# Diastereoselective Epoxidation

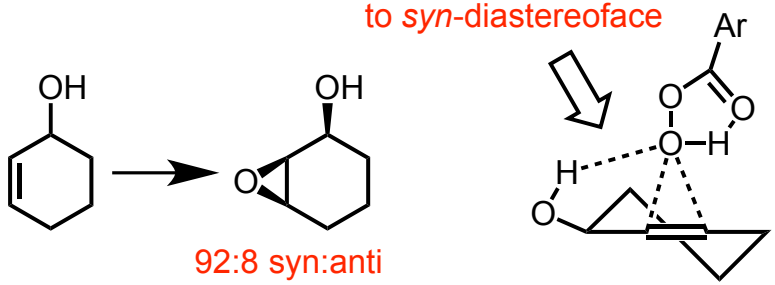



non-bonding interactions disfavour *syn* diastereoface



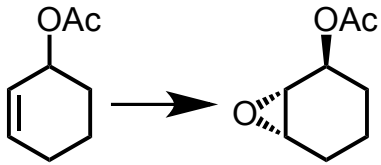

bonding between X and reagent favours syn diastereoface

substrate is H-bond donor - directs peracid to *syn*-diastereoface



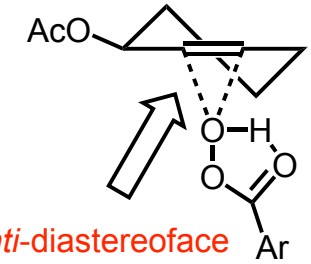

92:8 syn:anti

$k_{rel}$ = 0.55 (relative to cyclohexene)

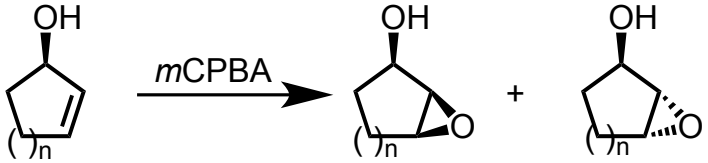



37:63 syn:anti

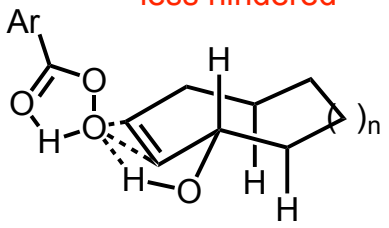
$k_{rel}$ = 0.046 (relative to cyclohexene)




*anti*-diastereoface less hindered

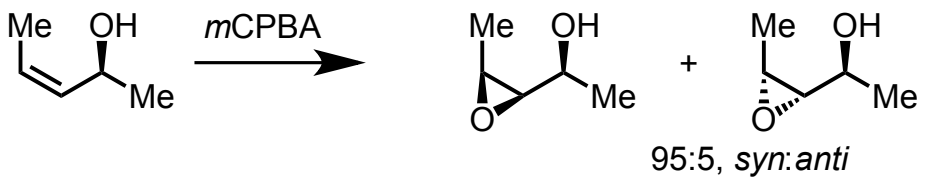


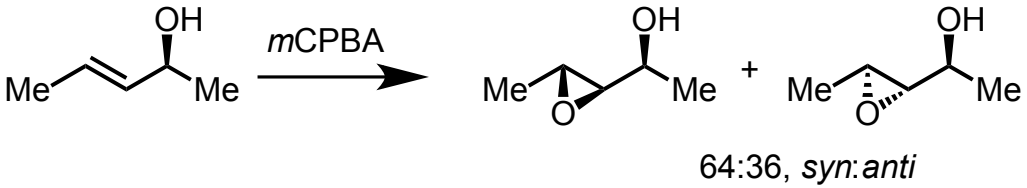

| Ring Size | syn:anti |
|---|---|
| 5 | 84:16 |
| 6 | 95:5 |
| 7 | 61:39 |
| 8 | 2:98 |
| 9 | 2:98 |

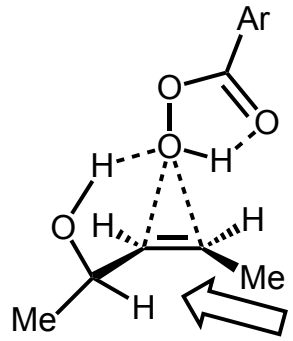



- $VO(acac)_2$, *t*BuOOH gives high syn selectivity for ring sizes 5-8.

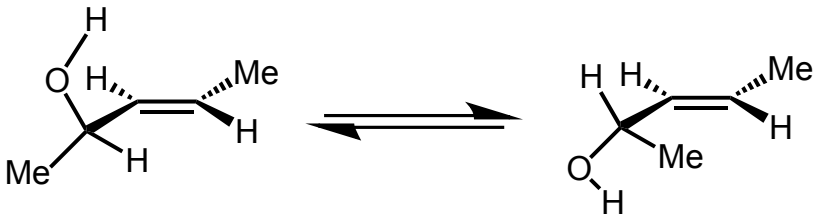
# Diastereoselective Epoxidation Acyclic Systems



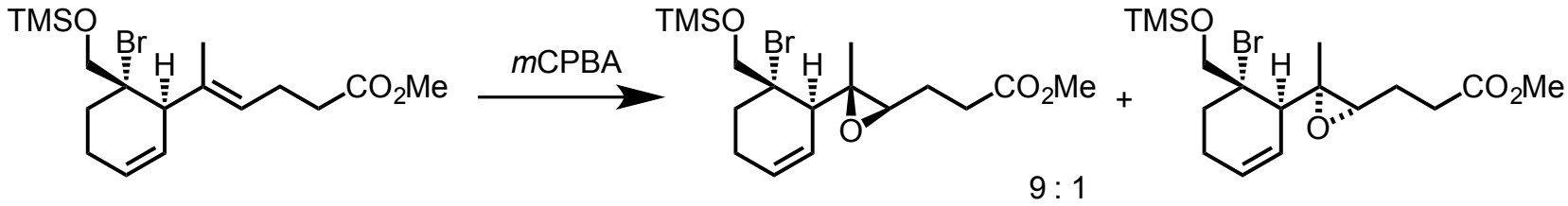

minimise $A^{1,3}$-strain
*m*CPBA directed to
same face as OH




for the *trans*-alkene the two low energy conformers are similar in energy hence the poor selectivity

***Problem:*** Explain the outcome of the following reaction.

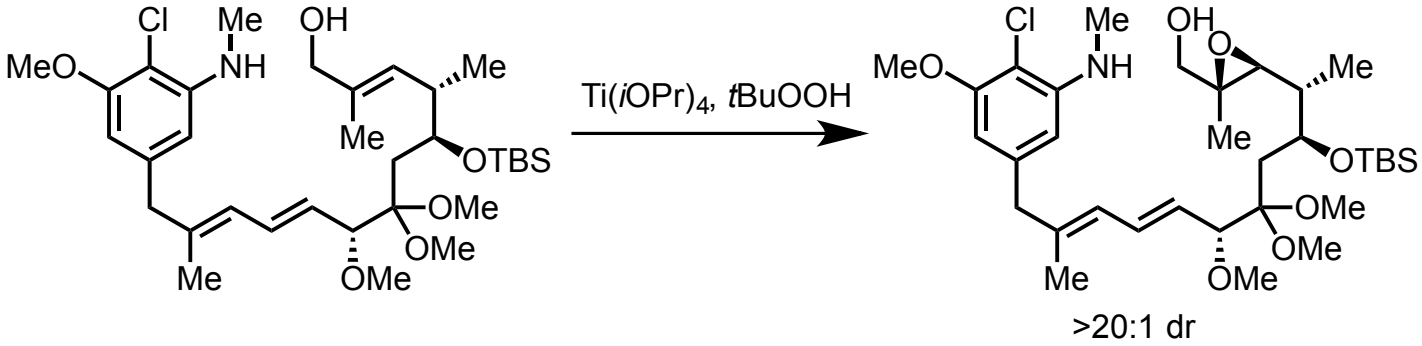
E. J. Corey, B. B. Snider, *J. Am. Chem. Soc.*, **1972**, *94*, 2549.



## Diastereoselective Epoxidation Acyclic Systems

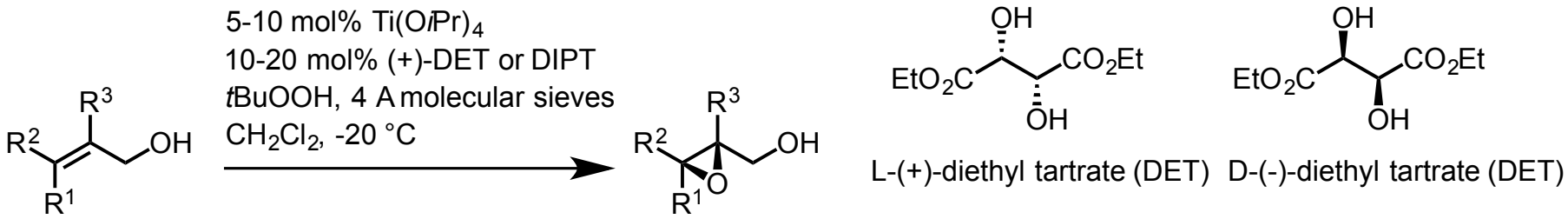
***Problem:*** Explain the outcome of the following reaction.

M. Kitamura, M. Isobe, Y. Ichikawa, T. Goto, *J. Am. Chem. Soc.*, **1984**, *106*, 3252.



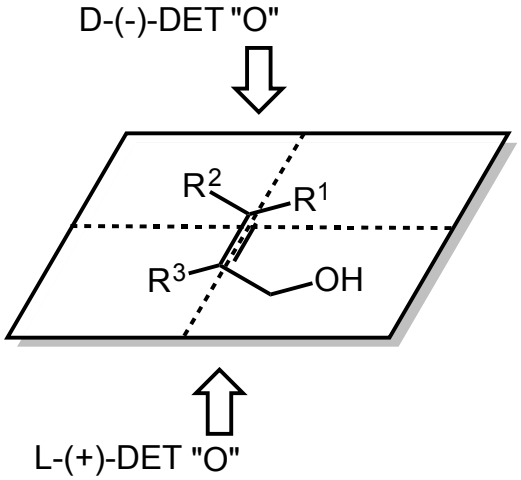

>20:1 dr

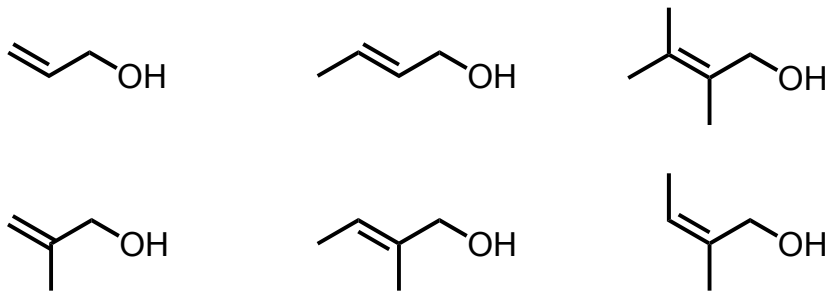
# Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)



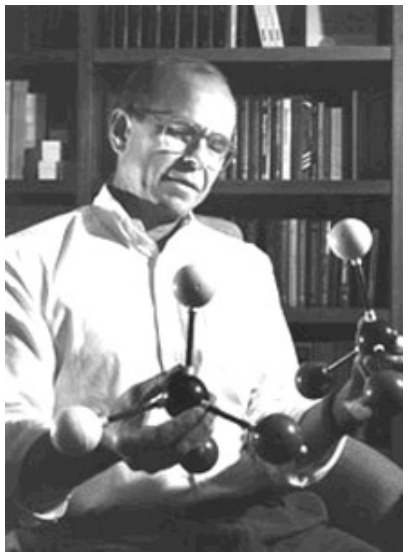

L-(+)-diethyl tartrate (DET) D-(-)-diethyl tartrate (DET)

- Sharpless mnemonic.
- Draw allylic alcohol as though it resembles the letter "L".
- D-(-)-DET delivers "O" **down** onto the alkene – conversely L-(+)-DET delivers "O" from below.
- Applicable to most alkene types - (*Z*)-alkenes are less reactive than (*E*)-alkenes.




(Z)-disubstituted olefins are less reactive but still give products with reasonable selectivity

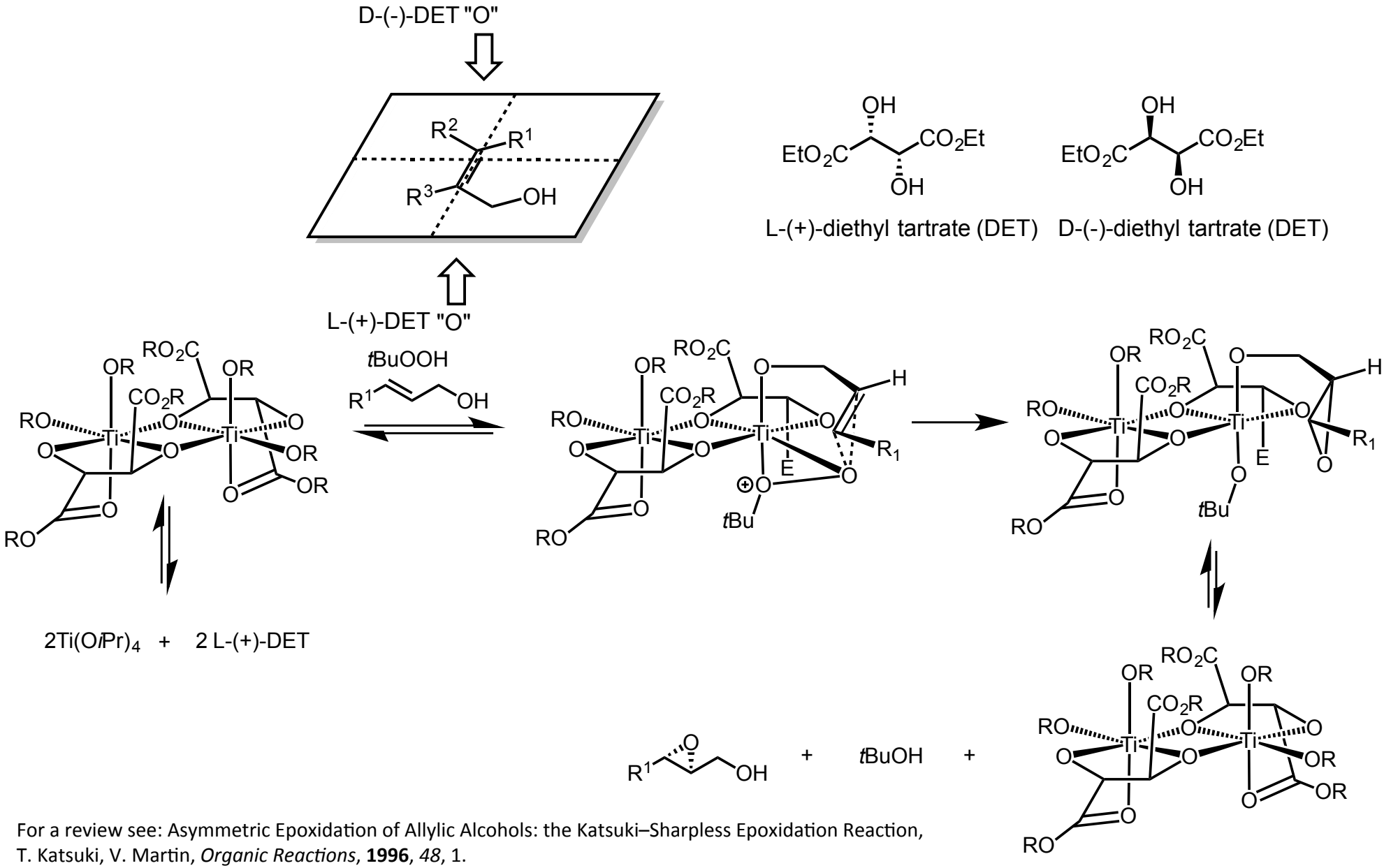


K. Barry Sharpless Nobel Prize 2001 with W. S. Knowles and R. Noyori for asymmetric catalysis

For a review see: Asymmetric Epoxidation of Allylic Alcohols: the Katsuki–Sharpless Epoxidation Reaction, T. Katsuki, V. Martin, *Organic Reactions*, **1996**, *48*, 1.

# Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

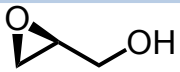
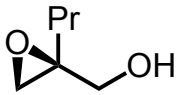
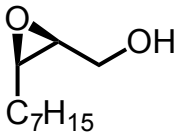
- Mechanism.




For a review see: Asymmetric Epoxidation of Allylic Alcohols: the Katsuki–Sharpless Epoxidation Reaction, T. Katsuki, V. Martin, *Organic Reactions*, **1996**, *48*, 1.

# Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

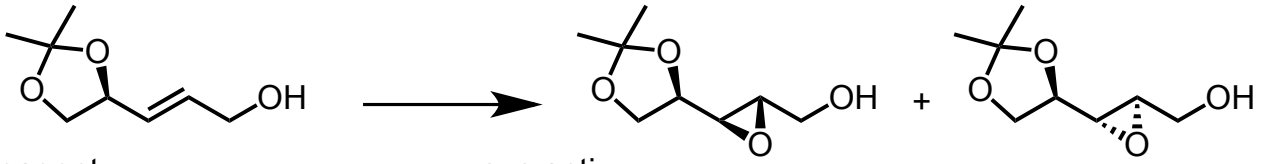
- Examples of Sharpless Epoxidation

| Product | Tartrate | Yield / % | ee / % |
|---|---|---|---|
|  | L-(+)-DIPT | 65 | 90 |
|  | L-(+)-DIPT | 89 | 98 |
|  | L-(+)-DET | 88 | 95 |
|  | L-(+)-DET | 74 | 86 |
|  | L-(+)-DET | 95 | 91 |

For a review see: Asymmetric Epoxidation of Allylic Alcohols: the Katsuki–Sharpless Epoxidation Reaction, T. Katsuki, V. Martin, *Organic Reactions*, **1996**, *48*, 1.

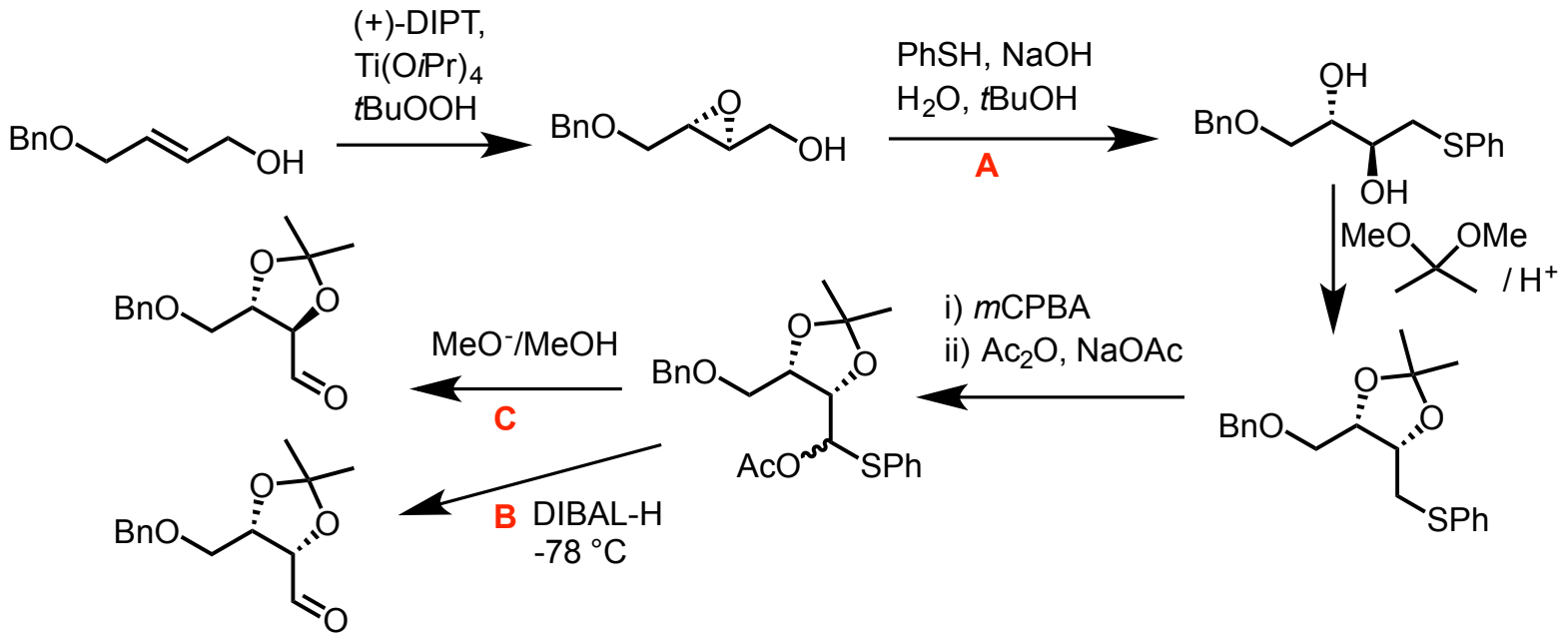
# Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

- Reagent control in the Sharpless Asymmetric Epoxidation




| Reagent | syn:anti | |
|---|---|---|
| *m*CPBA | 1:1.4 | |
| $VO(acac)_2$ | 1:1.8 | |
| $Ti(OiPr)_4$/*t*BuOOH | 1:2.3 | |
| $Ti(OiPr)_4$/D-(-)-DIPT/*t*BuOOH | 1:90 | matched |
| $Ti(OiPr)_4$/L-(+)-DIPT/*t*BuOOH | 22:1 | mismatched |

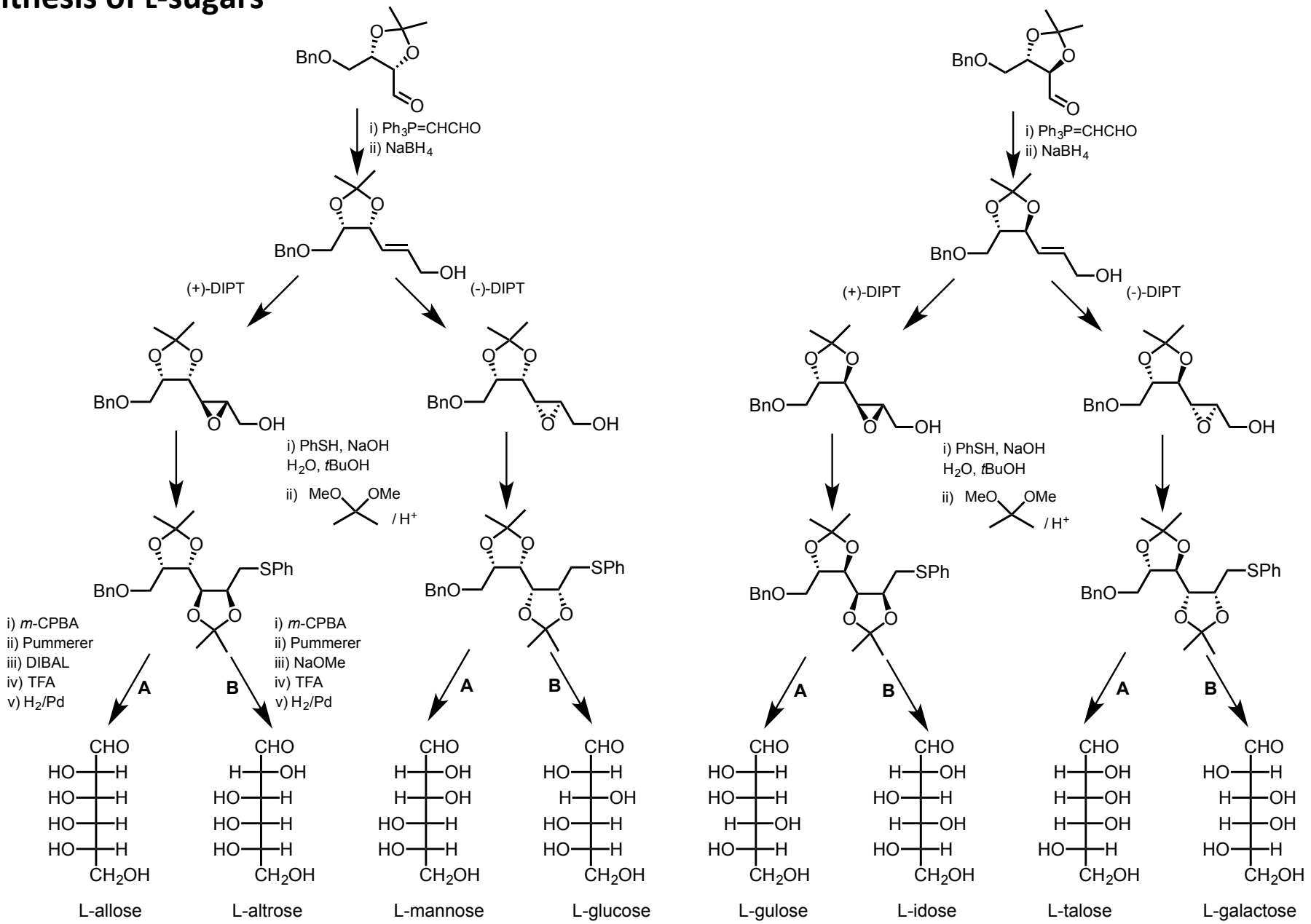
- Products are diastereomeric.
- Sense of induction dominated by catalyst (reagent/catalyst control).
- The stereocentre of the substrate either reinforces (**matched)** or erodes (**mismatched)** the influence of the catalyst.




***Question:*** Explain steps **A**, **B** and **C**.

S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed, III, K. B. Sharpless, F. J. Walker, *Science,* **1983**, *220,* 949.

# Synthesis of L-sugars

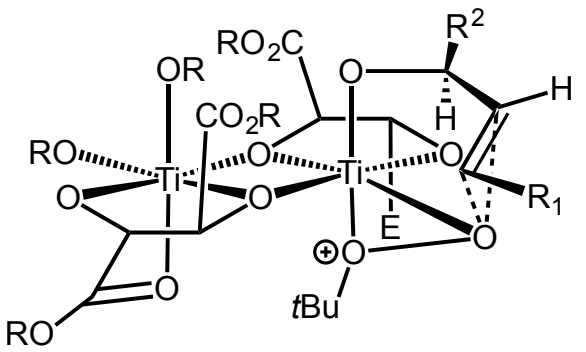



S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed, III, K. B. Sharpless, F. J. Walker, *Science,* **1983**, *220,* 949.

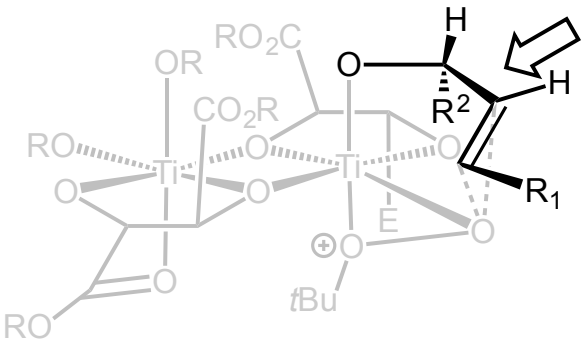
# Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

## Kinetic Resolution of Secondary Alcohols

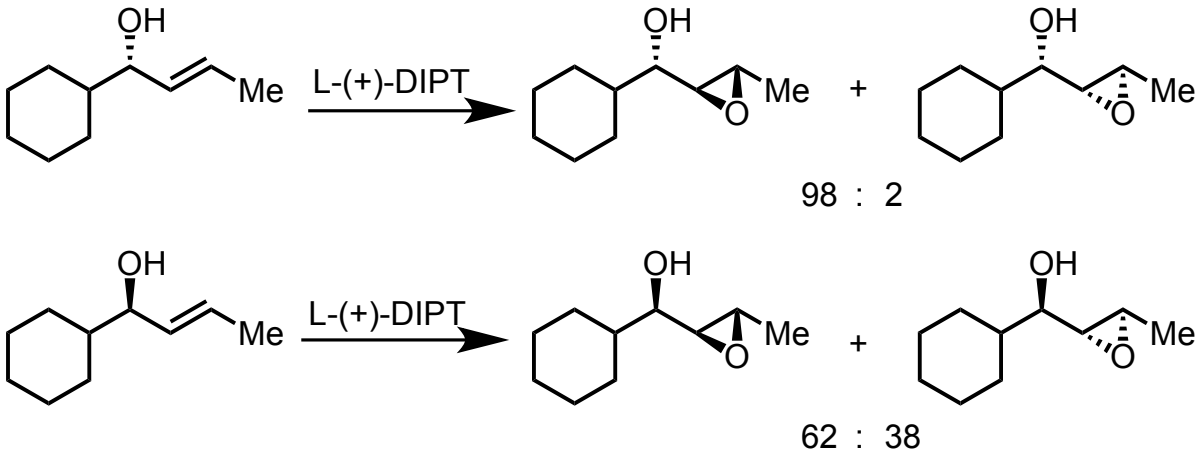
- What happens if we submit a racemic secondary allylic alcohol to the SAE reaction with the L-(+)-tartrate ligand?
- Analysis of the proposed transition state would lead us to expect that one enantiomer would be epoxidised significantly faster than the other enantiomer.




favoured
fast reacting




clash between $R^2$ and catalyst
disfavoured
slow reacting

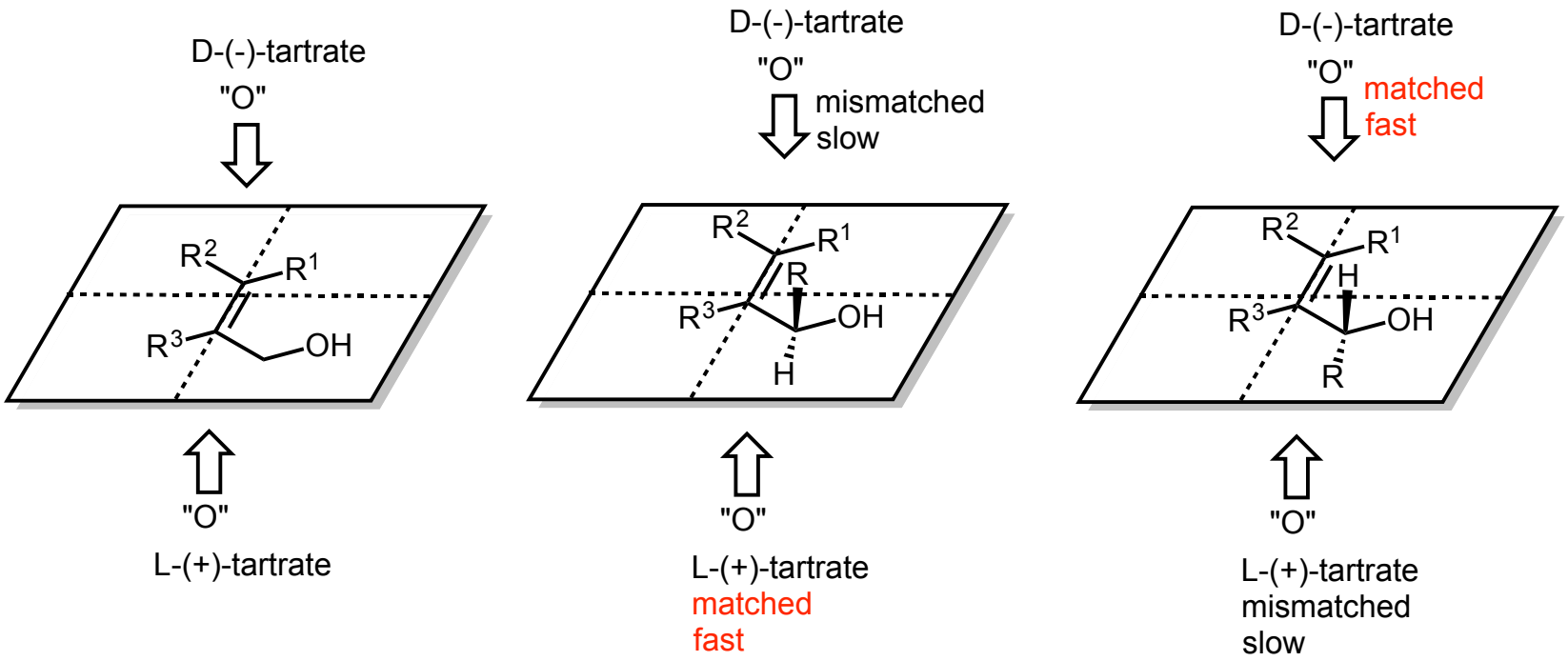



$$\text{Selectiviry factor, } S = \frac{k_{fast}}{k_{slow}} = 104$$

- Using racemic substrate means that the enantiomeric excess of the substrate increases as the reaction progresses – this is a ***kinetic resolution***.

# Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

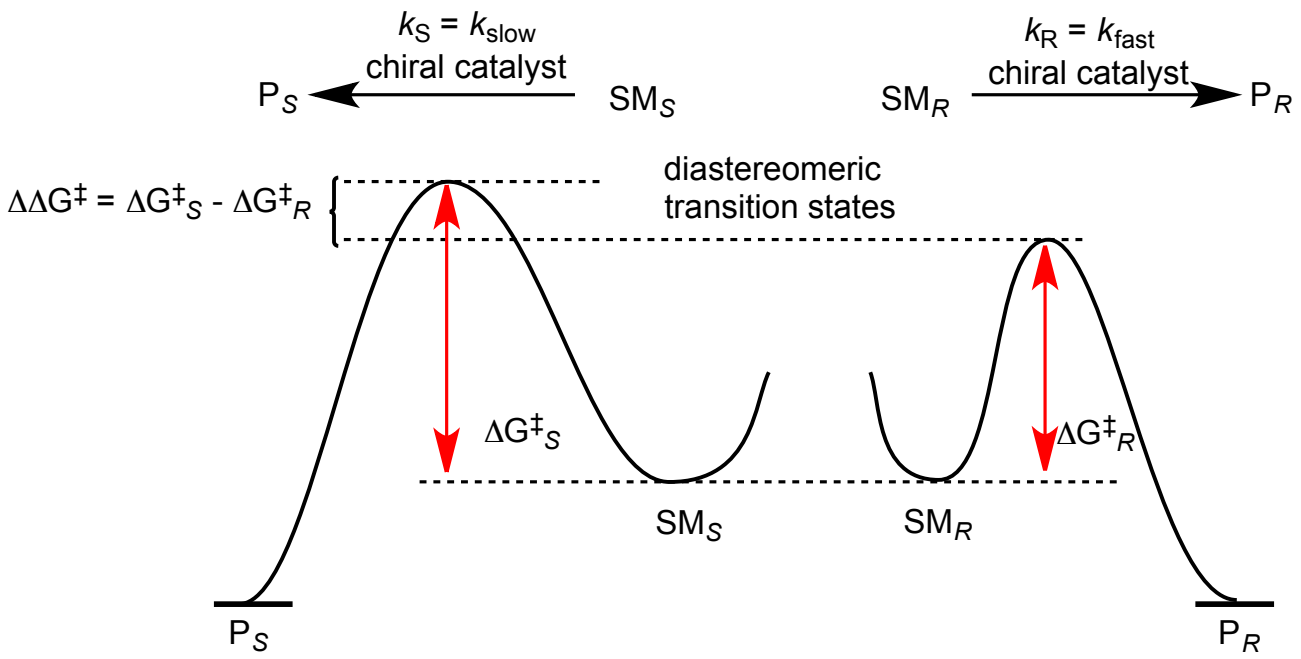
- Kinetic Resolution of Secondary Alcohols – extended Sharpless mnemonic.




- The products of a kinetic resolution are diastereomers (therefore readily separable).
- For the SAE reaction *S* varies between 15 and 140.

## Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

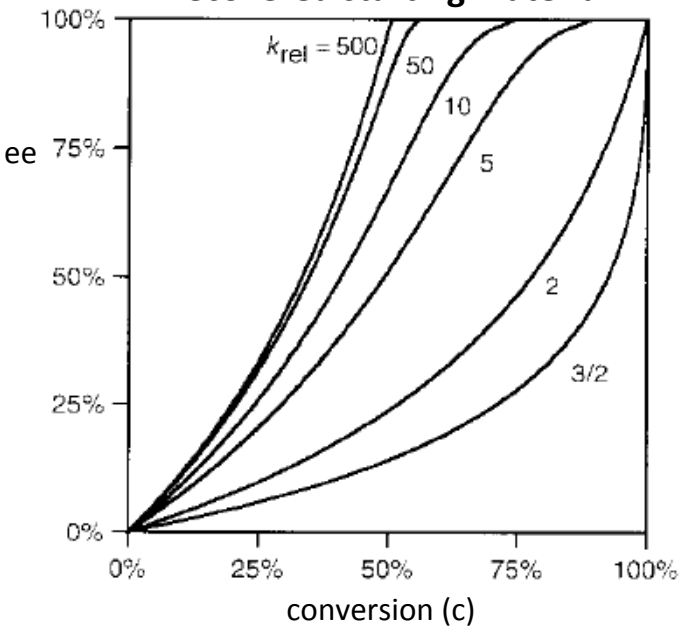
- In kinetic resolutions, enantiomers of a racemic starting material (SM) react at different rates to form a product (P) that may or may not be chiral.
- In a catalytic kinetic resolution, the relative rates of reaction for the substrate enantiomers (S) are dictated by the magnitude of $\Delta\Delta G^{\ddagger}$.
- This corresponds to the difference in energies between the diastereomeric transition states.
- Therefore $k_{rel} = e^{-\Delta\Delta G/RT} = S$.



# Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

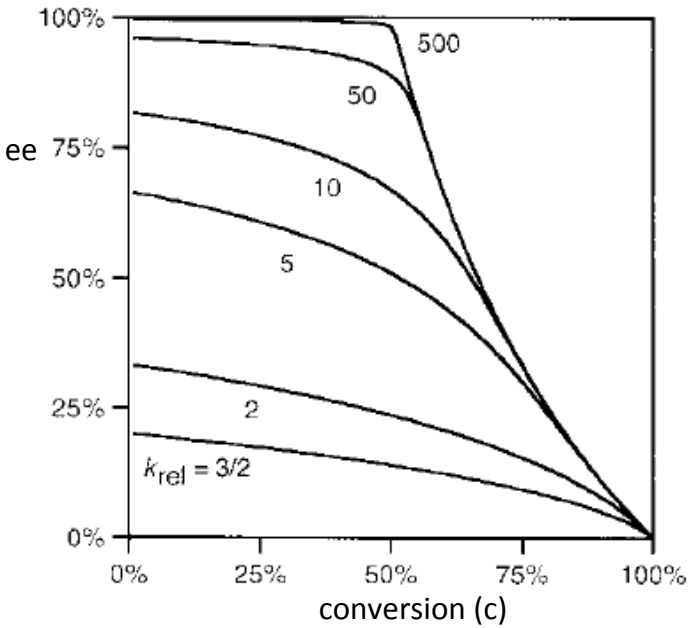
- Usually, enantioselective reactions of prochiral substrates yield products with constant ee during the reaction.
- In a kinetic resolution the enantiomeric excess varies as a function of conversion.
- As the reaction progress the enantiomeric excess of the recovered starting material ***increases*** and the enantiomeric excess of the product ***decreases***.
- The maximum enantiomeric ratio of the product (i.e. R/S) is at the start of the reaction and is equal to $k_{rel}$ e.g. if $k_{rel}$ = 5 then $er_{initial}$ = 5 hence $ee_{initial}$ = $ee_{max}$ = 67%
- Below are graphs which plot ee *vs* conversion for various $k_{rel}$ for product and recovered starting material. These equations were originally proposed by Kagan: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

**Recovered starting material**




$$k_{rel} = \frac{\ln[(1 - c)(1 - ee)]}{\ln[(1 - c)(1 + ee)]}$$

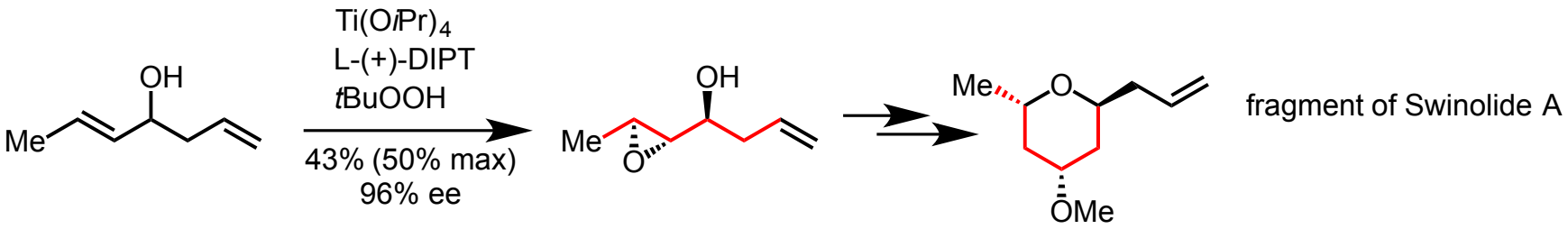
**Product**




$$k_{rel} = \frac{\ln[(1 - c)(1 + ee)]}{\ln[(1 - c)(1 - ee)]}$$

taken from: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

# Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)



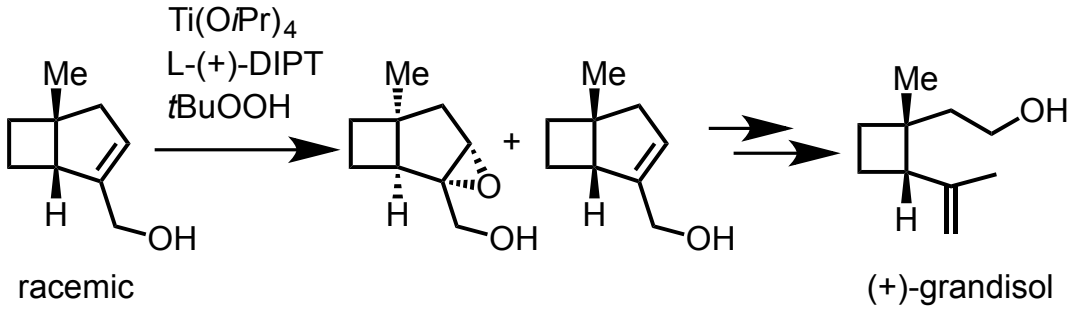

Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron*, **1995**, *51*, 9393.


52% conversion
44% yield
94%ee

54% conversion
44% yield
94%ee

63% conversion
34% yield
98%ee

51% conversion
45% yield
86%ee

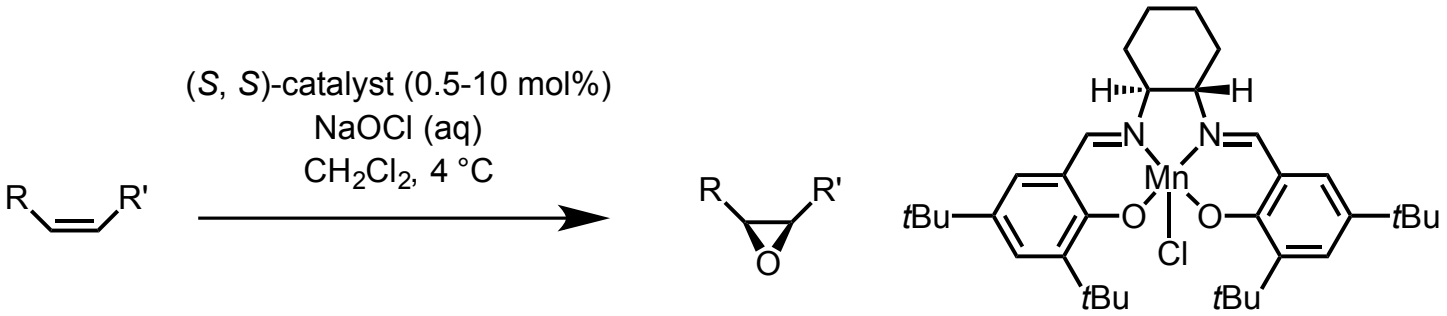



| T / °C | conversion % | % recovered substrate | ee recovered substrate % |
|---|---|---|---|
| -20 | 80 | 18 | >98 |
| -40 | 60 | 39 | 95 |
| -60 | 55 | 34 | 90 |

***Problem:*** Explain, using the Sharpless mnemonic, the outcome of the above kinetic resolution.

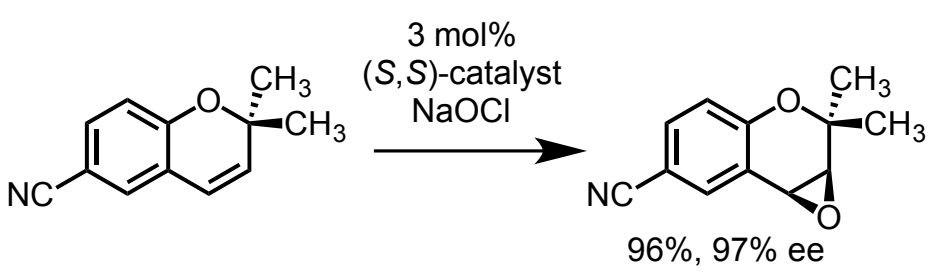
D. P. G. Hamon, K. L. Tuck, *J. Org. Chem.* **2000**, *65*, 7839.

# Enantioselective Epoxidation of Unfunctionalised Olefins - Jacobsen Epoxidation

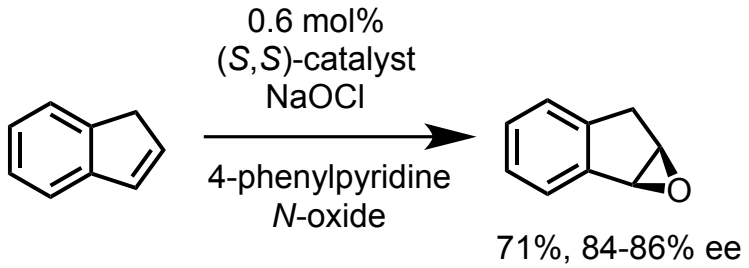



(*S*, *S*)-catalyst

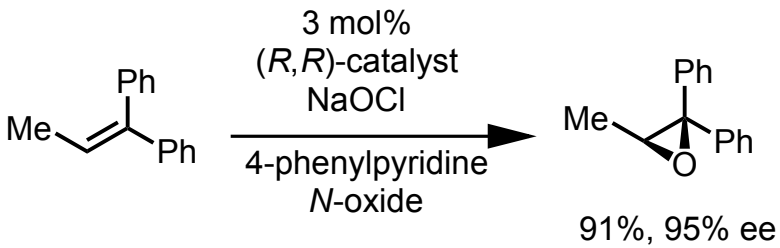
- Selectivity is determined through nonbonded interactions.
- Generally R is a group conjugated to the alkene (aryl, alkenyl, alkynyl), R can be bulky.
- *cis*-Disubstituted olefins are epoxidised with high enanatiomeric excess – *trans*-disubstituted olefins are poor substrates.
- Trisubstituted olefins with conjugated groups are good substrates; terminal olefins are poor substrates.
- Addition of *N*-oxides (ligands for Mn) can be beneficial for yield and ee.



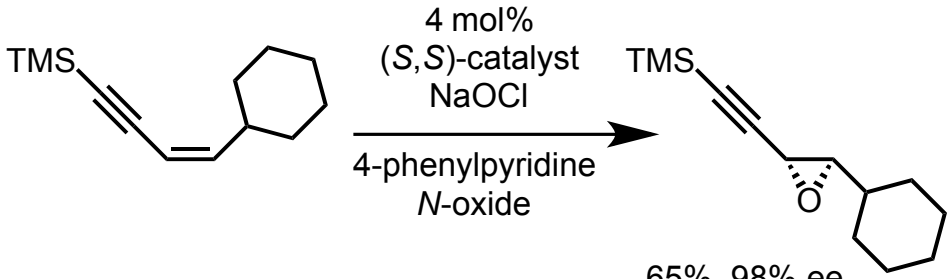

96%, 97% ee




71%, 84-86% ee




91%, 95% ee



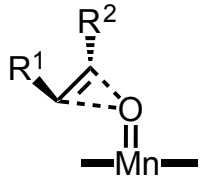

65%, 98% ee
*trans*:*cis*, 5.2:1

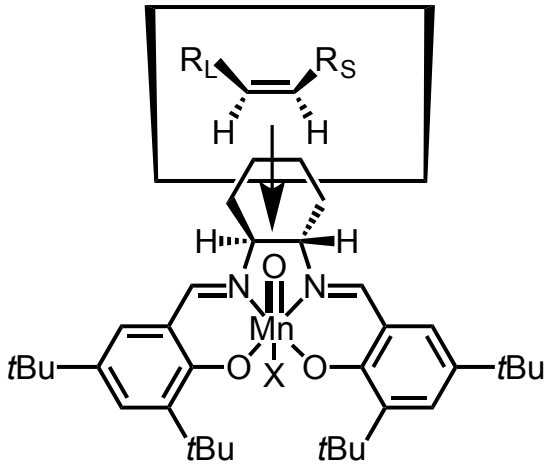
For reviews and mechanistic discussion see: T. Linker, *Angew. Chem. Int. Ed.*, **1997**, *36*, 2060; T Katsuki, *Synlett*, **2003**, 281.

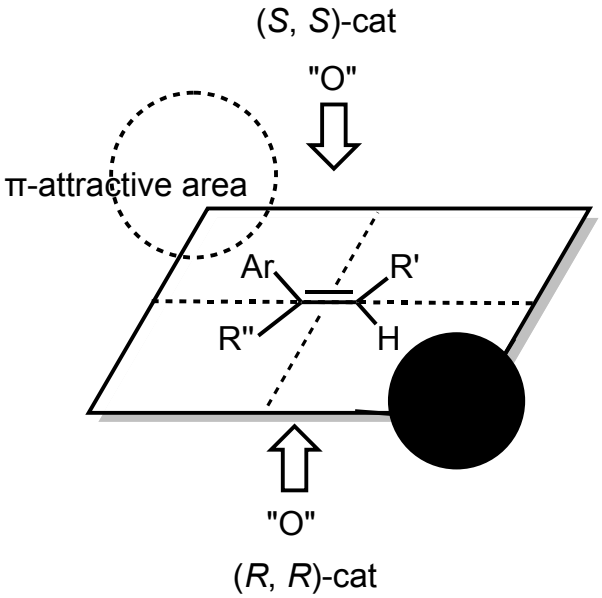
# Enantioselective Epoxidation of Unfunctionalised Olefins - Jacobsen Epoxidation

## Model for Selectivity

- The exact mechanism of the reaction is still being debated.
- Jacobsen has proposed approach of alkene side on to manganese(V) oxo complex.
- The alkene is proposed to approach over the diamino cyclohexane moiety with the Ar group approaching away from the axial C-H bond to avoid nonbonded interactions.
- Many other models have also been proposed including a recent one by E. J. Corey (Kurti, L. Blewett, M. M., Corey, E. J. *Org. Lett.*, **2009**, *11*, 4592).




R" = H disubstituted olefins
R" = alky/aryl - trisubstituted olefins

## Mnemonic for Jacobsen Epoxidation

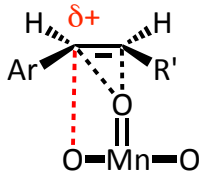
- *cis*-Olefins – place aryl, alkenyl, alkynyl (Ar) = $R_L$ substituents in upper left quadrant and H atom in lower-right quadrant.
- Trisubstituted olefins – place hydrogen in lower-right quadrant.

For reviews and mechanistic discussion see: T. Linker, *Angew. Chem. Int. Ed.*, **1997**, *36*, 2060; T Katsuki, *Synlett*, **2003**, 281.

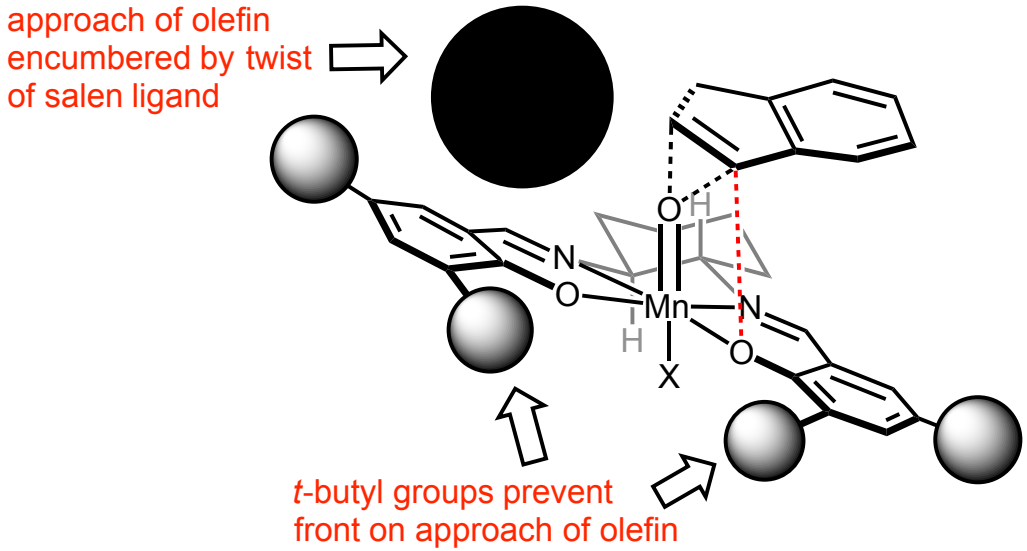
# Enantioselective Epoxidation of Unfunctionalised Olefins - Jacobsen Epoxidation

**Corey Model for Selectivity** - Kurti, L.; Blewett, M. M.; Corey, E. J. *Org. Lett.*, **2009**, *11*, 4592.

- Corey proposes that there is face on approach of the olefin to the Mn(V) oxo moiety.
- Oxygen transfer occurs with an asynchronous transition state leading to a build up of positive charge at the "benzylic" end of the alkene which is stabilised by donation of electron density from the phenolic oxygens of the salen ligand.

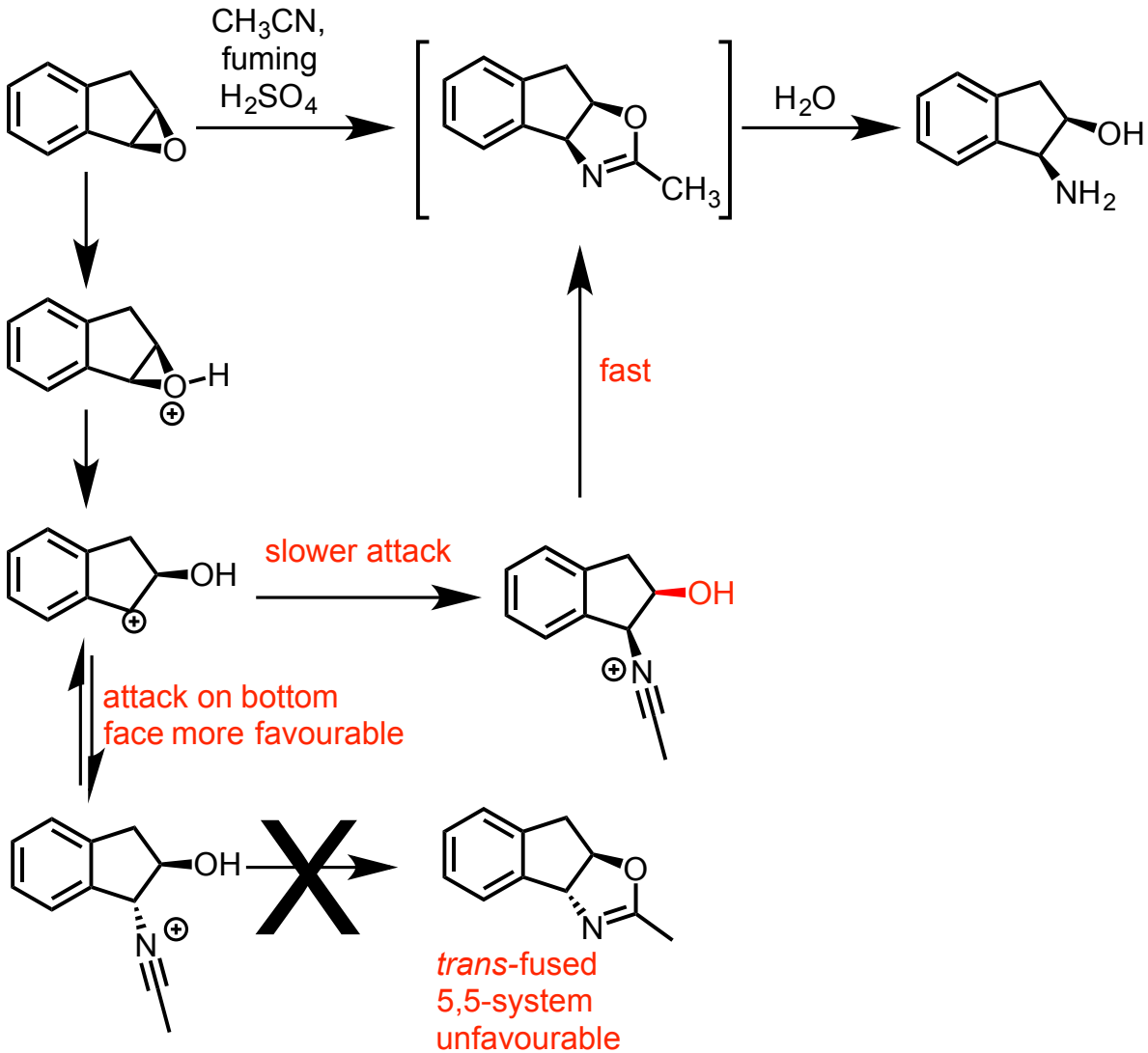


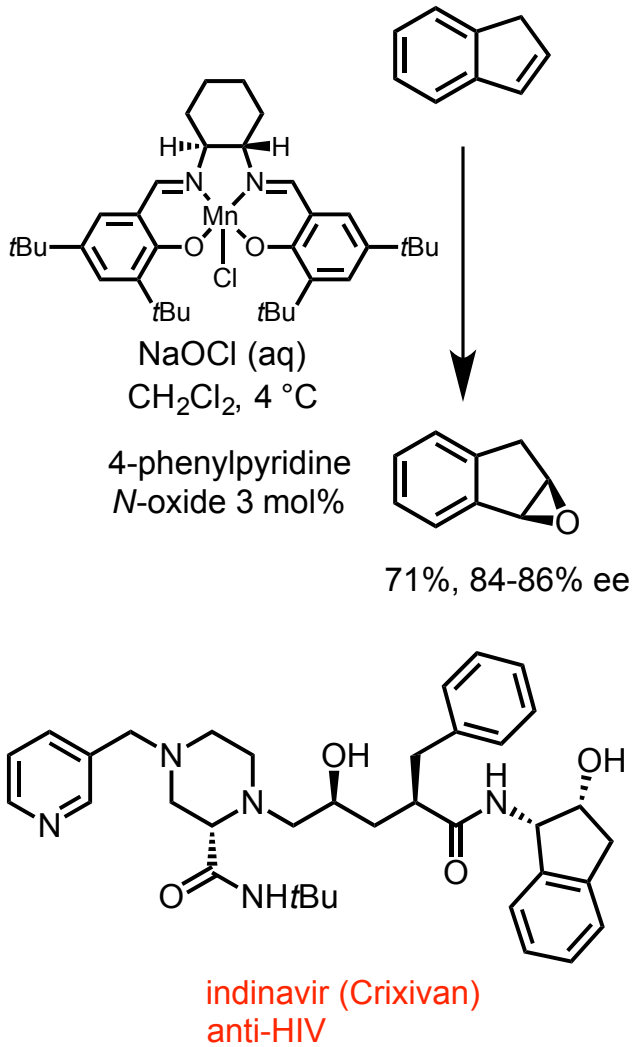

- The diaminocyclohexane moiety induces a twist in the salen ligand such that approach of the alkene from one quadrant is completely blocked.
- *t*Butyl groups prevent front on approach.
- Alkene approaches from only open quadrant and undergoes epoxidation with stabilisation of the developing benzylic positive charge by donation from one of the phenolic oxygen atoms of the salen ligand.



# Enantioselective Epoxidation of Unfunctionalised Olefins - Jacobsen Epoxidation

## Synthesis of aminoindanol

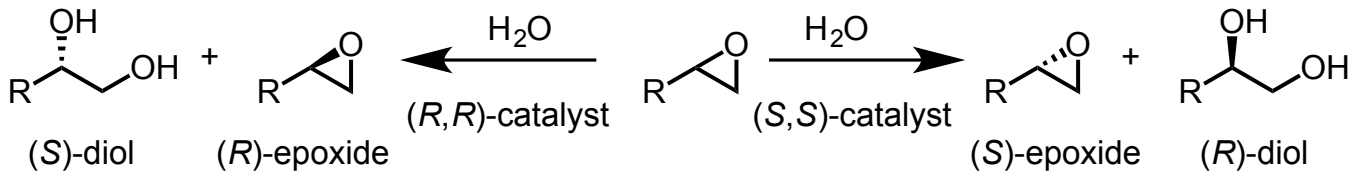


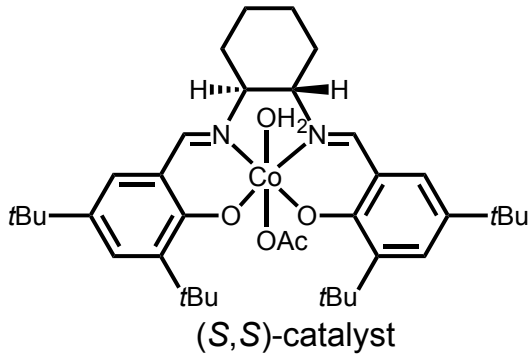




J. F. Larrow, E. Roberts, T. R. Verhoeven, K. M. Ryan, C. H. Senanayake,, P. J. Reider, E. N. Jacobsen, *Org. Syn.*, *76*, 46.

# Terminal Epoxides – Jacobsen Hydrolytic Kinetic Resolution

- Terminal epoxides are poor substrates for most enantioselective epoxidation reactions.
- Jacobsen has developed an excellent method for the kinetic resolution of terminal epoxides.
- Treatment of a terminal epoxide with the cobalt salen catalyst and water gives both the diol and recovered epoxide in excellent enantiomeric excess and yield.



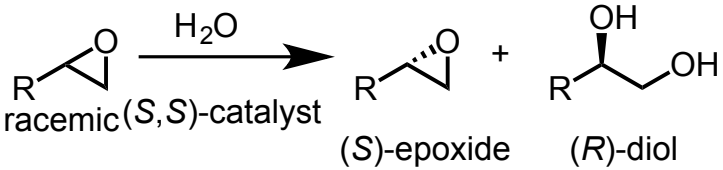
(*S*,*S*)-catalyst

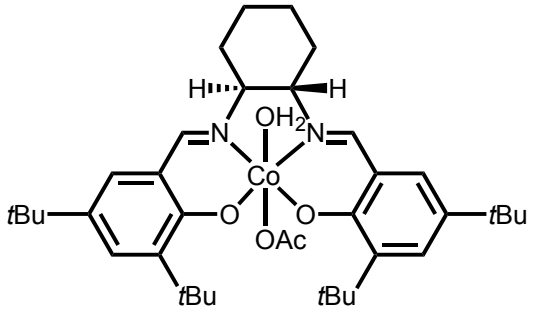
| | | | | **epoxide** | | **diol** | | |
|---|---|---|---|---|---|---|---|---|
| R | cat (mol %) | $H_2O$ (equiv.) | time (hours) | ee (%) | yield (%) | ee (%) | yield (%) | $k_{rel}$ |
| $CH_3$ | 0.2 | 0.55 | 12 | >98 | 44 | 98 | 50 | >400 |
| $CH_2Cl$ | 0.3 | 0.55 | 8 | 98 | 44 | 86 | 38 | 50 |
| nButyl | 0.42 | 0.55 | 5 | 98 | 46 | 98 | 48 | 290 |
| Ph | 0.8 | 0.70 | 44 | 98 | 38 | 98 | 39 | 20 |
| $CH{=}CH_2$ | 0.64 | 0.50 | 20 | 84 | 44 | 94 | 49 | 30 |

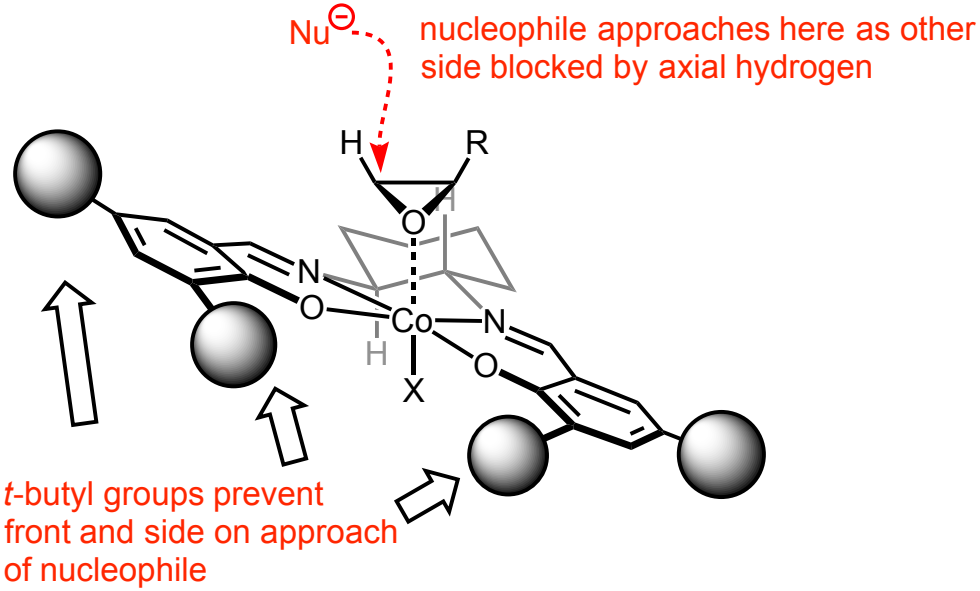
- The kinetic resolution of terminal epoxides and the asymmetric ring opening of *meso*-epoxides has wide scope using various metal salen catalysts and nucleophiles including: azide, carboxylate, phenoxide etc.

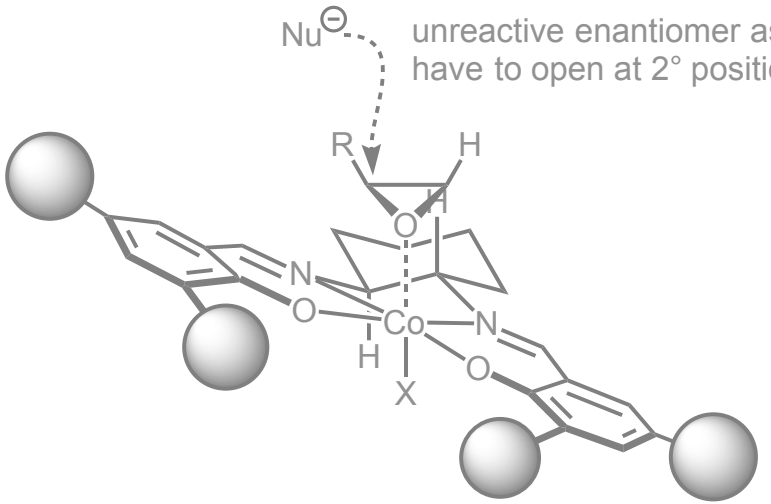
E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421.

# Terminal Epoxides – Jacobsen Hydrolytic Kinetic Resolution

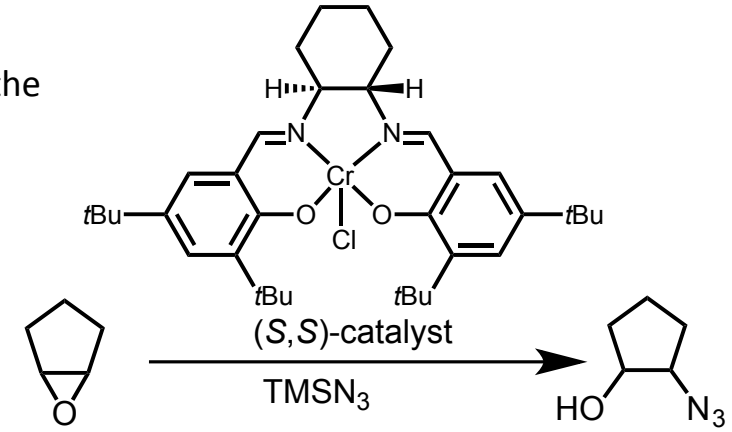


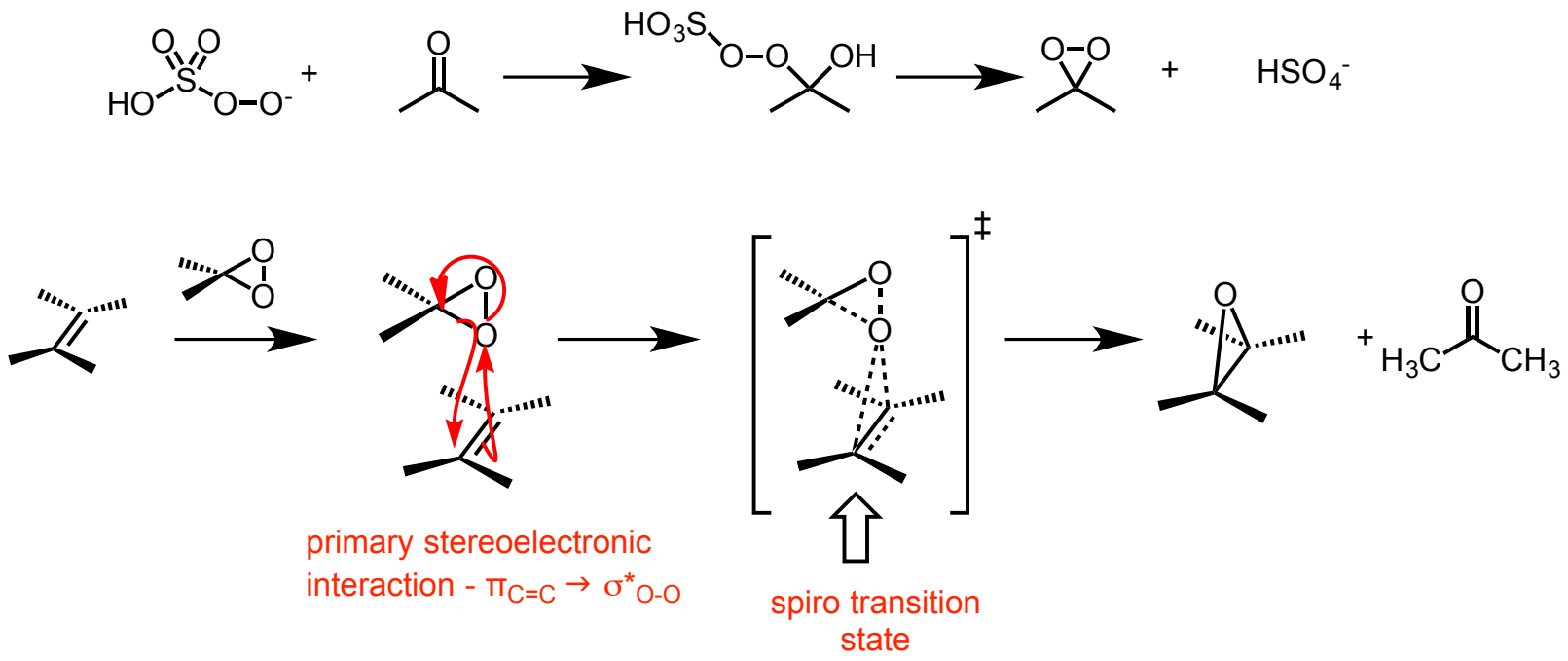

***Problem:*** Predict the stereochemical outcome of the following reaction.




E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421.

## Epoxidation with Dioxiranes

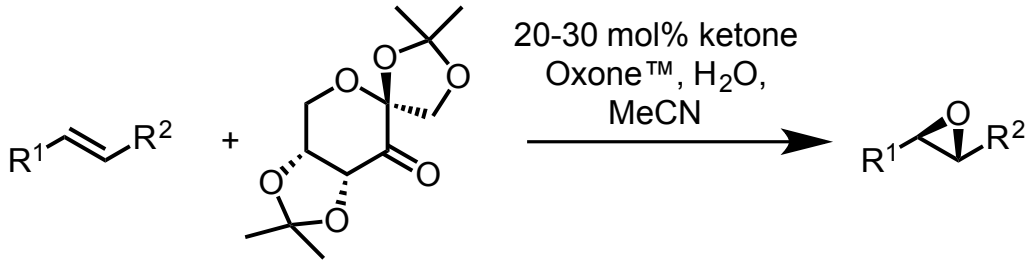
- Dioxiranes have recently been established as exceedingly active epoxidising agents.
- Dimethyl dioxirane and methyltrifluoromethyl dioxirane are readily prepared from the corresponding ketone and Oxone™
- Epoxidation is rapid, and high yielding - the only by-product is the ketone.
- The mechanism is similar to the mechanism using a peracid.



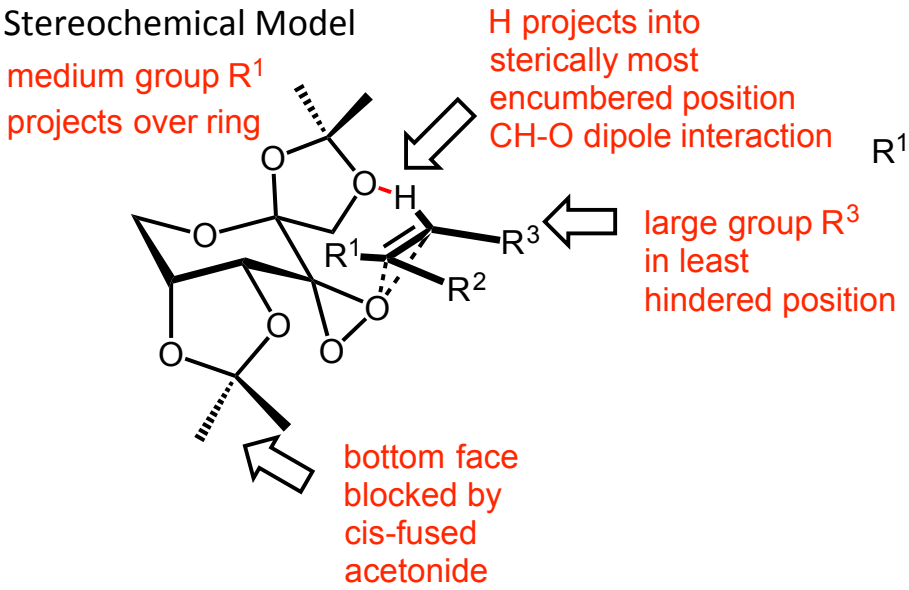

For the synthesis of dimethyldioxirane see: R, W. Murray, M. Singh, *Org. Synth.*, **1997**, *74*, 91.

# Enantioselecitve synthesis of *trans*-epoxides – Shi Epoxidation

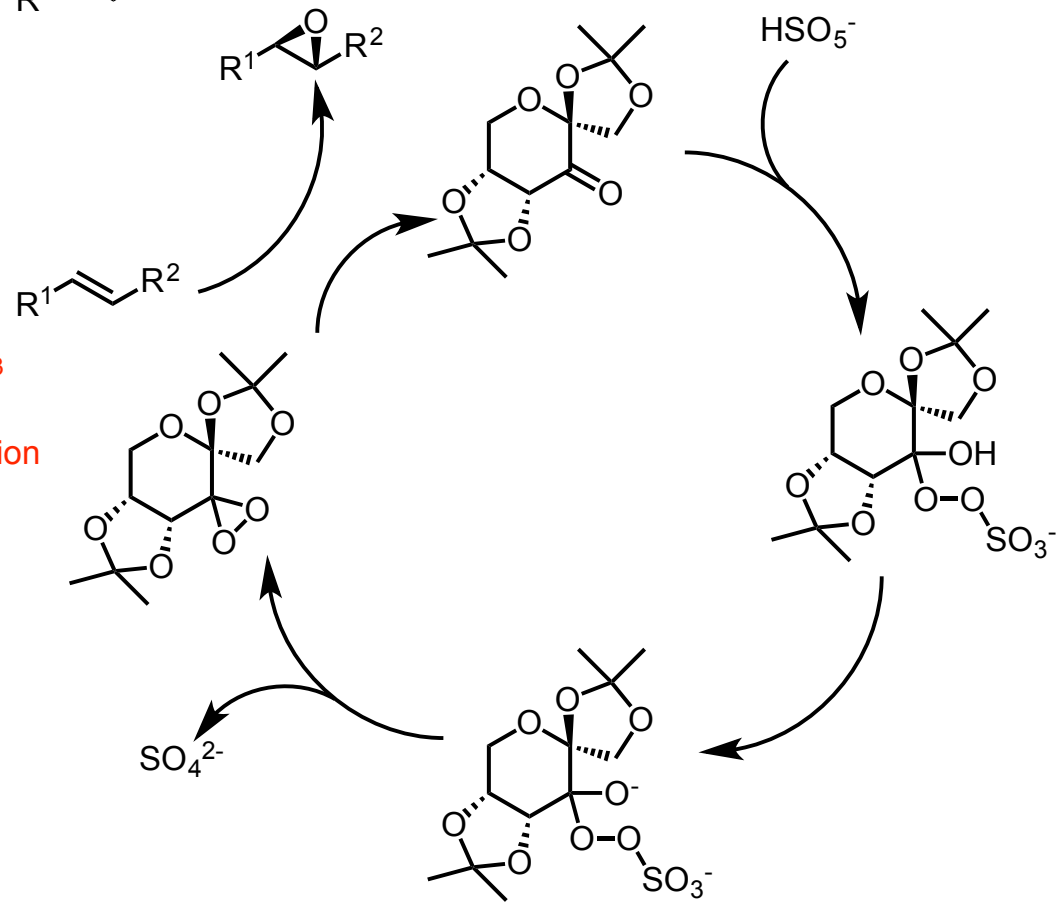
- Yian Shi has developed a highly efficient enantioselective epoxidation of *trans*-alkenes using *in situ* generated chiral dioxiranes.




- Stereochemical Model




- Catalytic Cycle

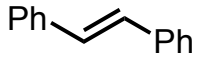
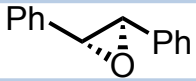
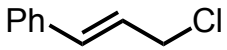
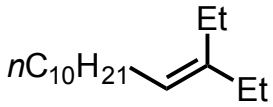
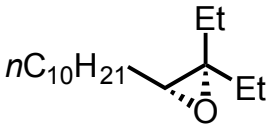
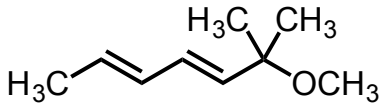
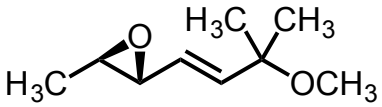
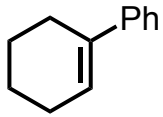
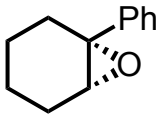



- Higher ee's with smaller $R^1$ and larger $R^3$.
- Good for *trans*-alkenes and trisubstituted alkenes .
- Conjugated dienes react at more electron rich alkene.

Wang, Z.-X.; Tu, W; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119,* 11224.
Frohn, M.; Shi, Y. *Synthesis* **2000**, *14,* 1979.

## *trans*-Epoxides – Shi Epoxidation

- Shi's ketone is readily prepared from D-fructose on large scale.
- L-fructose may be readily prepared from cheap L-sorbose.

| Substrate | Product | Yield (%) | ee (%) |
|---|---|---|---|
|  |  | 73 | 95 |
|  |  | 61 | 93 |
|  |  | 94 | 89 |
|  |  | 65 | 89 |
|  |  | 94 | 98 |

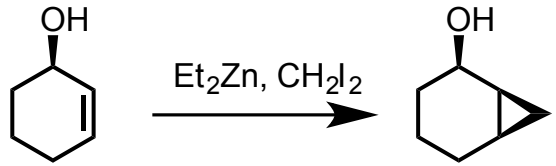
- With a related catalyst *cis*-alkenes may be epoxidised with high ee.

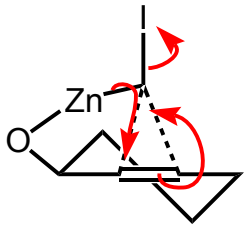
Wang, Z.-X.; Tu, W; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119,* 11224.
Frohn, M.; Shi, Y. *Synthesis* **2000**, *14,* 1979.

## Cyclopropanation: the Simmonds-Smith Reaction – an aside

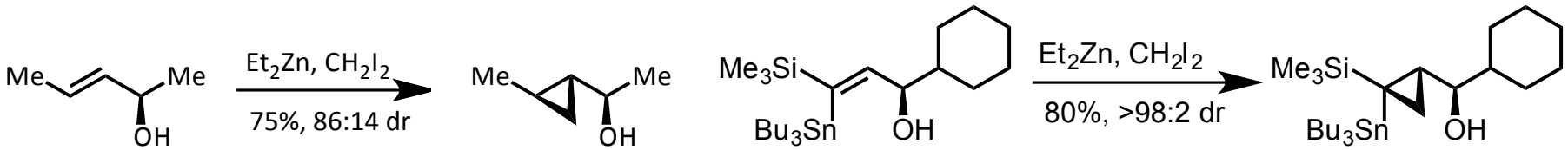
■ Review of stereoselective cyclopropanation: H. Lebel, J. F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977-1050; review of recent developments in asymmetric cyclopropanation see: H. Pellissier, *Tetrahedron* **2008**, *64*, 7041-7095.

■ Generally cyclopropanation on least hindered face of the alkene but directed cyclopropanation, *via* a zinc alkoxide, occurs with allylic alcohols.



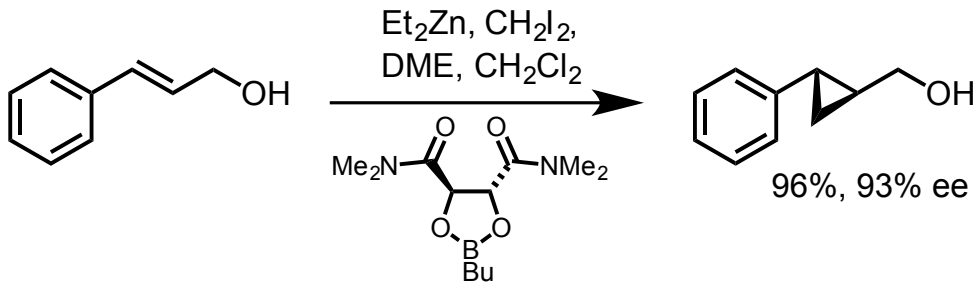








■ Asymmetric cyclopropanation of allylic alcohols is readily achieved using a chiral boronic acid additive

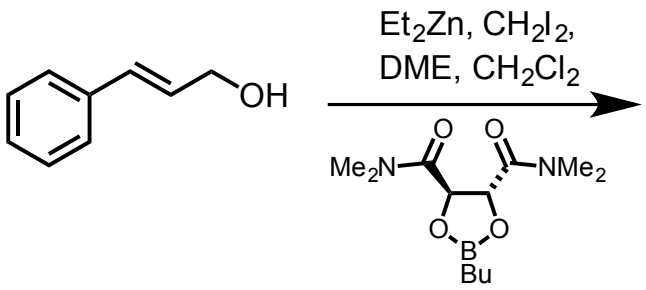
A. B. Charette, H. Lebel, *Org. Synth*. **1999**, *76*, 86.

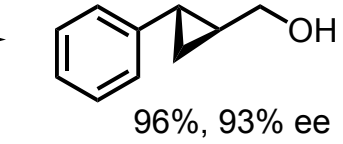


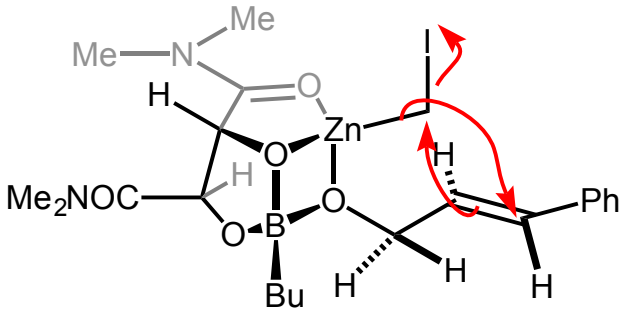

■ "***CAUTION!*** The previously reported preparation of $Zn(CH_2I)_2$ without a complexing additive is highly exothermic and a violent decomposition sometimes occurred. For safety reasons the use of $Zn(CH_2I_2)$•DME as reported here is mandatory if this reaction is carried out on an 8 mmol scale. If the internal temperature during formation of the reagent is carefully monitored, the procedure reported here is extremely safe even on larger scales." A. B. Charette, H. Lebel, *Org. Synth*. **1999**, *76*, 86; A. B. Charette, S. Prescott, C. Brochu, *J. Org. Chem.* **1995**, *60*, 1081-1083.

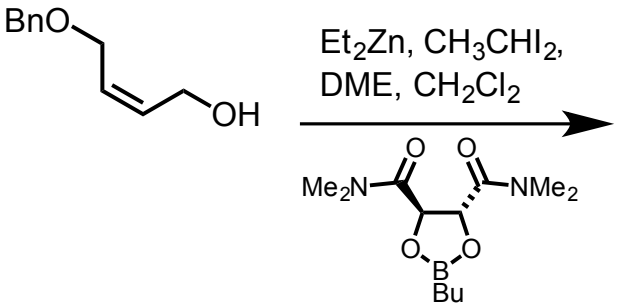
# Cyclopropanation: the Simmonds-Smith Reaction – an aside

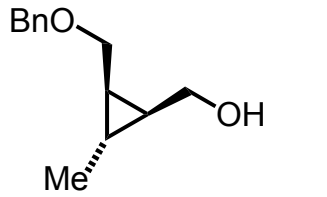
- Review of stereoselective cyclopropanation: H. Lebel, J. F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977-1050.
- Model for Charette cyclopropanation: T. Wang, Y. Liang, Z. X. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 9343-9353.
  - zinc bonded to $CH_2I$ group and coordinated by three oxygen atoms to give a rigid, bowl-shaped tricyclic structure
  - the allylic alcohol (now a zinc alkoxide) is positioned away from the tricyclic structure so as to minimise $A^{1,3}$-strain
  - the carbene is delivered selectively to one face of the alkene

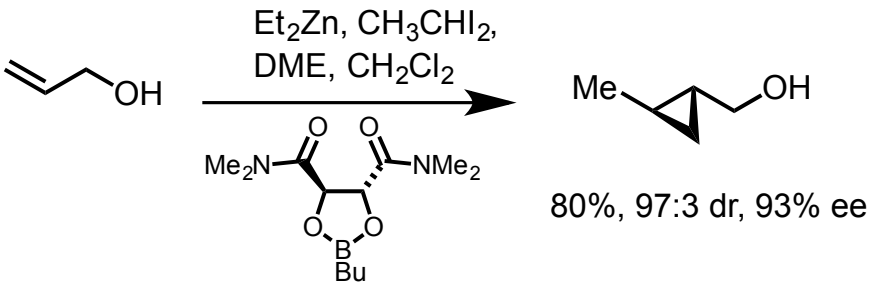


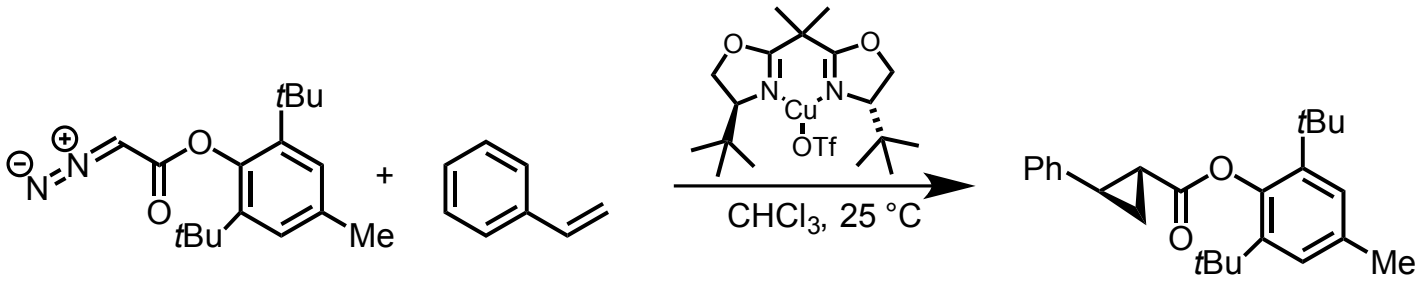



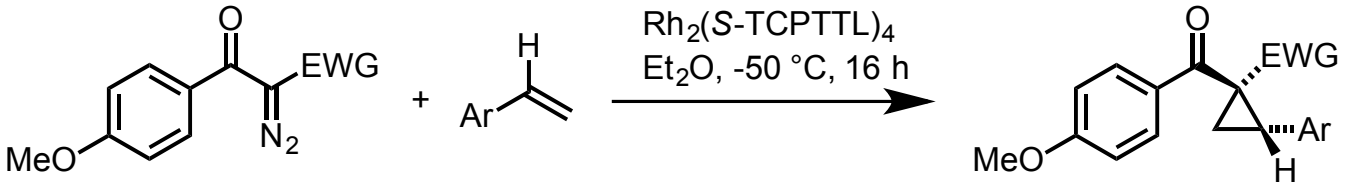
## Cyclopropanation: metal catalysts and diazo compounds

- Seminal publication: D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726-728.
- Model for Evans cyclopropanation: J. M. Fraile, J. I. Garcia, V. c. Martinez-Merino, J. A. Mayoral, L. Salvatella, *J. Am. Chem. Soc.* **2001**, *123*, 7616-7625.




85%, 94:6 dr, 99% ee

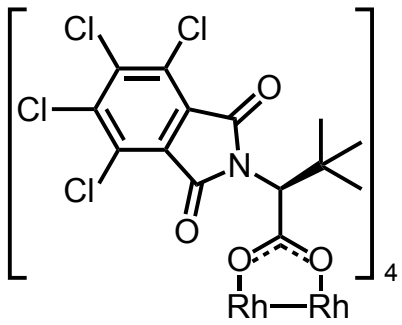
- For recent work with a chiral rhodium catalyst see: V. N. Lindsay, C. Nicolas, A. B. Charette, *J. Am. Chem. Soc.* **2011**, *133*, 8972-8981.




EWG = $NO_2$, CN, $CO_2Me$,

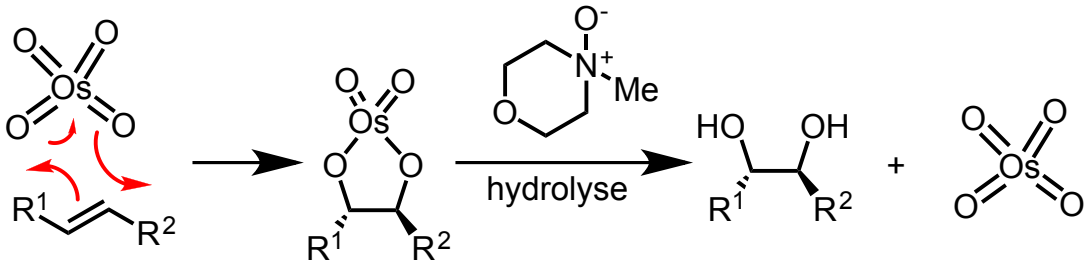
up to 91% yield
up to 98% de
up to 98% ee

$Rh_2$(*S*-TCPTTL)$_4$ =



## Dihydroxylation

- Dihydroxylation of alkenes with $OsO_4$ is stereospecific (*cis*-addition) and occurs *via* [3 + 2] mechanism.
- $OsO_4$ is both toxic and volatile.
- The most common procedure is the Upjohn procedure which uses catalytic amounts of $OsO_4$ with NMO as the stoichiometric oxidant.

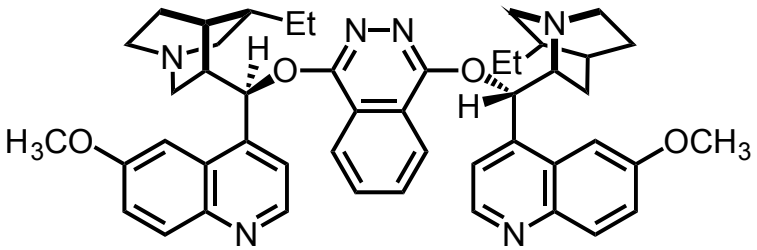



## Sharpless Asymmetric Dihydroxylation

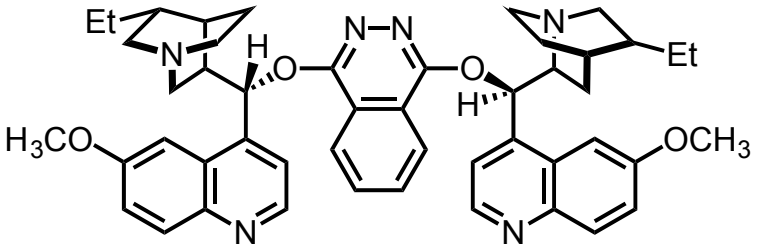

high and predictable enantiomeric excess

AD-mix for 1 mmol olefin contins
3 mmol $K_3Fe(CN)_6$ - [oxidises Os(VI) to Os(VIII)]
3 mmol $K_2CO_3$
0.01 mmol $(DHQD)_2$-PHAL or $(DHQ)_2$PHAL
0.002 mmol $K_2OsO_2(OH)_4$ - [Os(VI)]

$C_2$-symmetric, pseudo-enantiomeric ligands



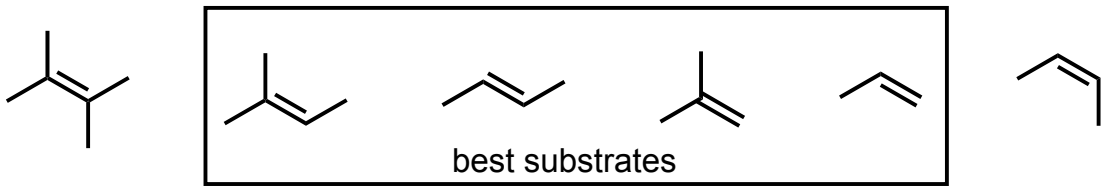
$(DHQD)_2$-PHAL
Ligand for AD-mix-β

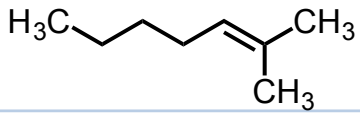
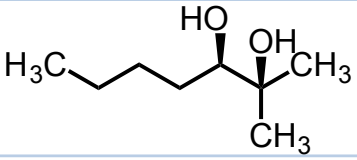
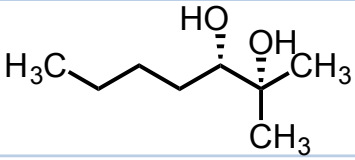
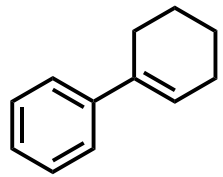
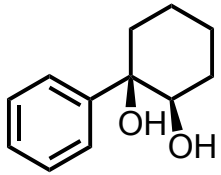
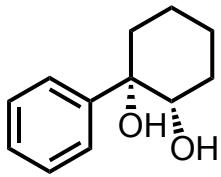
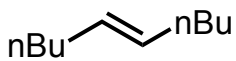
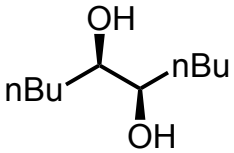
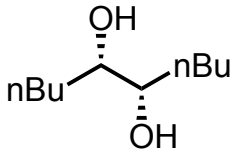
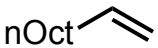
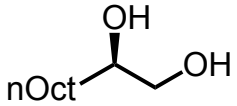
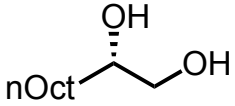


$(DHQ)_2$-PHAL
Ligand for AD-mix-α

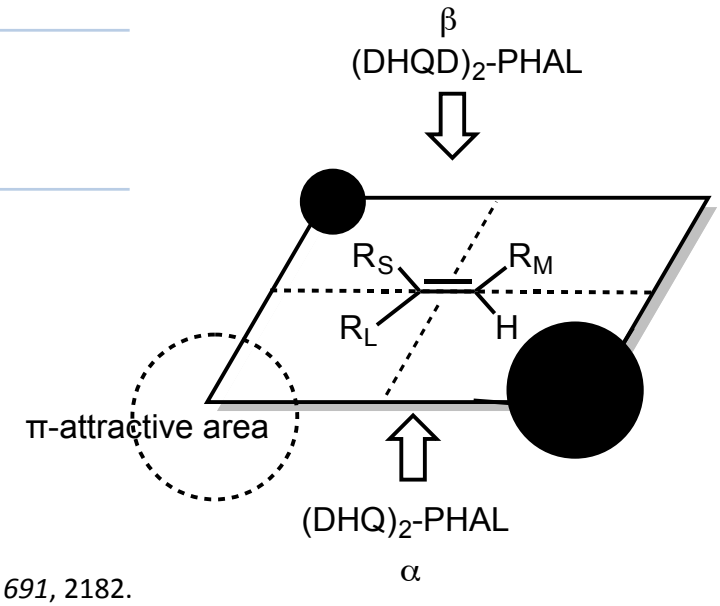
For a review see: Sharpless, K. B.; et. al. *Chem. Rev.*, **1994**, *94,* 2483.

# Sharpless Asymmetric Dihydroxylation



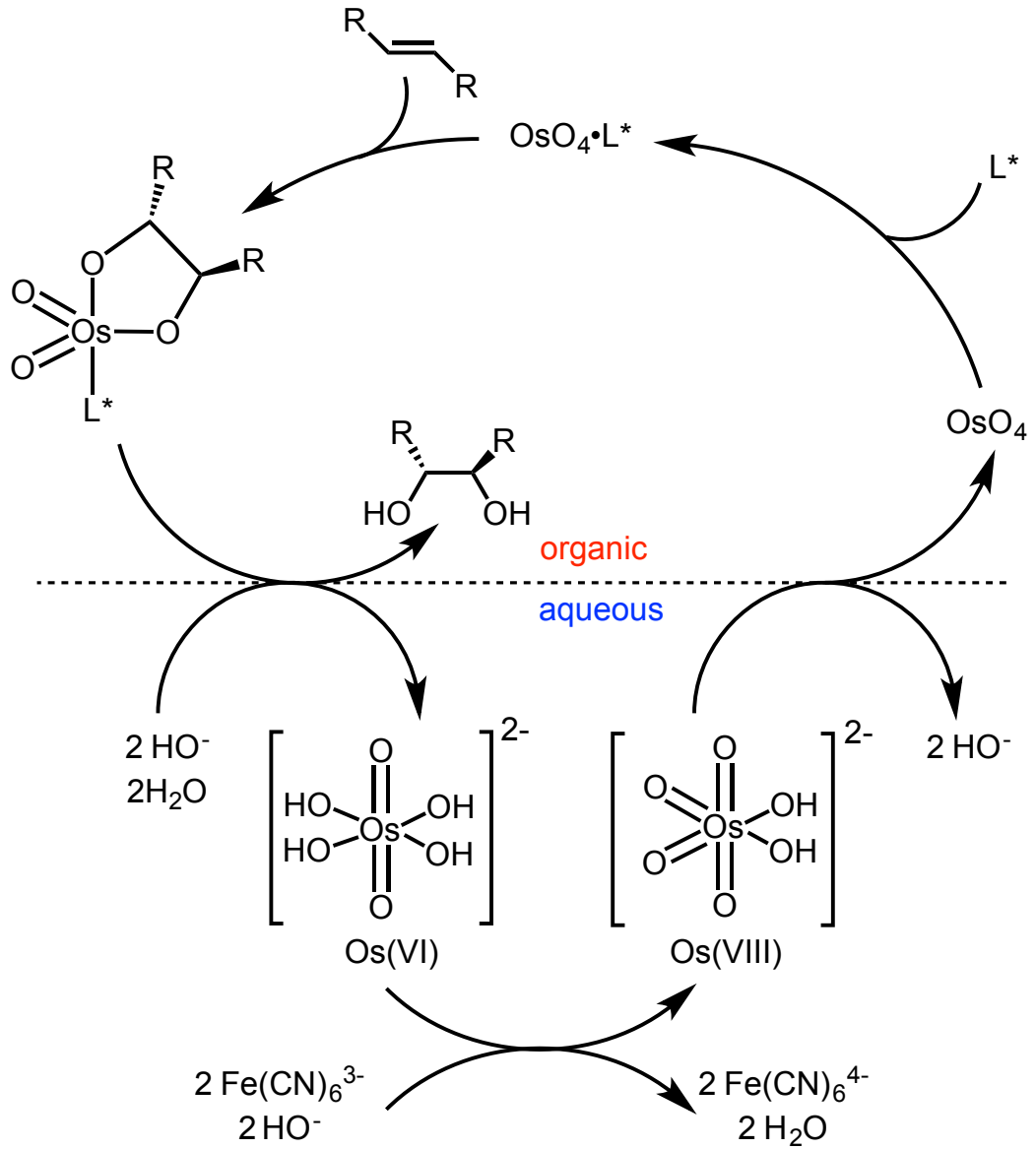

| Substrate | AD-mix-β $(DHQD)_2$-PHAL | AD-mix-α $(DHQ)_2$-PHAL |
|---|---|---|
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

**Mnemonic**

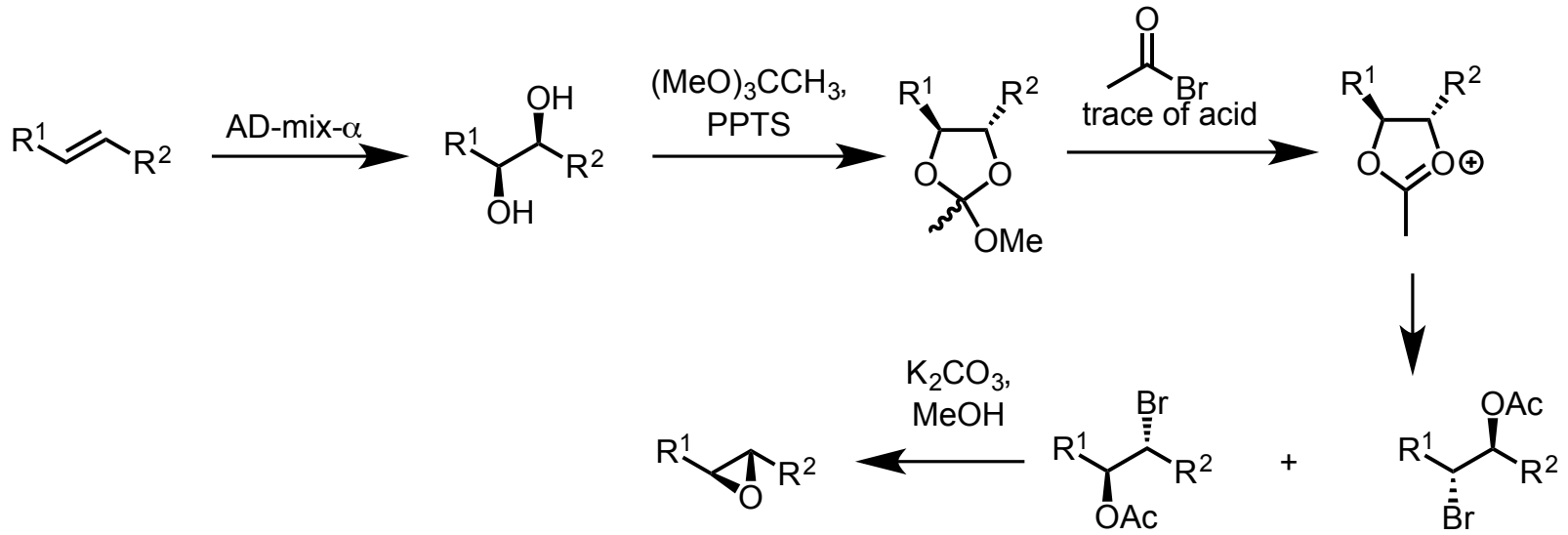



For an updated mnemonic and recent mechanistic discussions see:
Fristrup, P.; Jensen, G. H.; Andersen, M. L. N.; Tanner, D.; Norby, P-. O. *J. Organomet. Chem.,* **2006**, *691*, 2182.

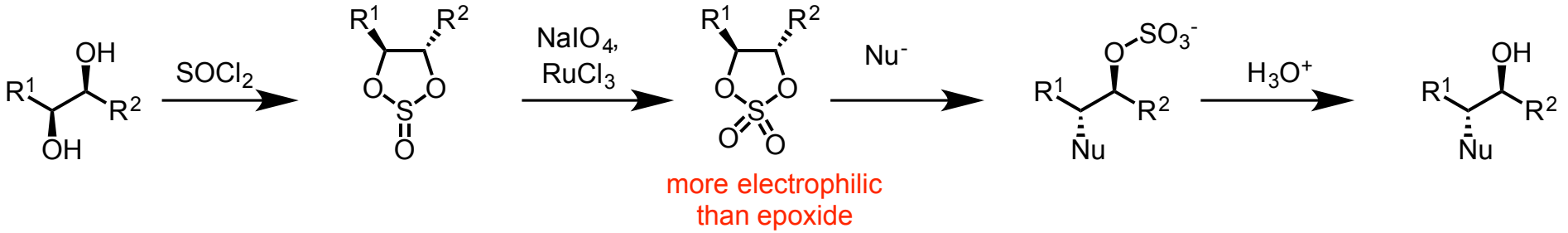
# Sharpless Asymmetric Dihydroxylation - mechanism



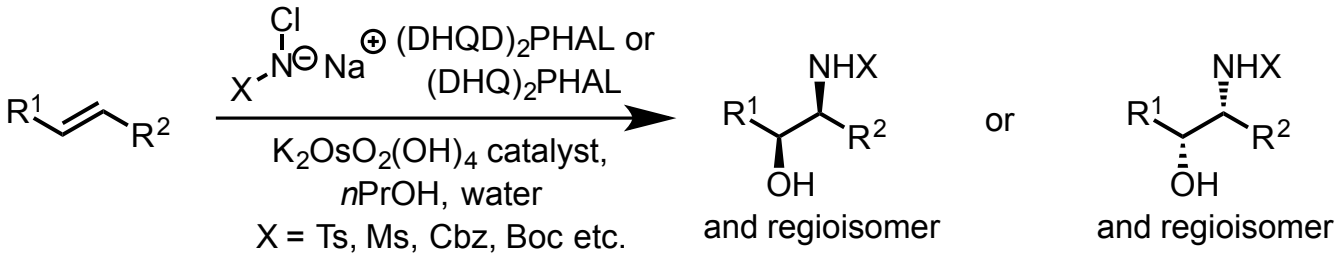
## Useful Reactions of Chiral Diols



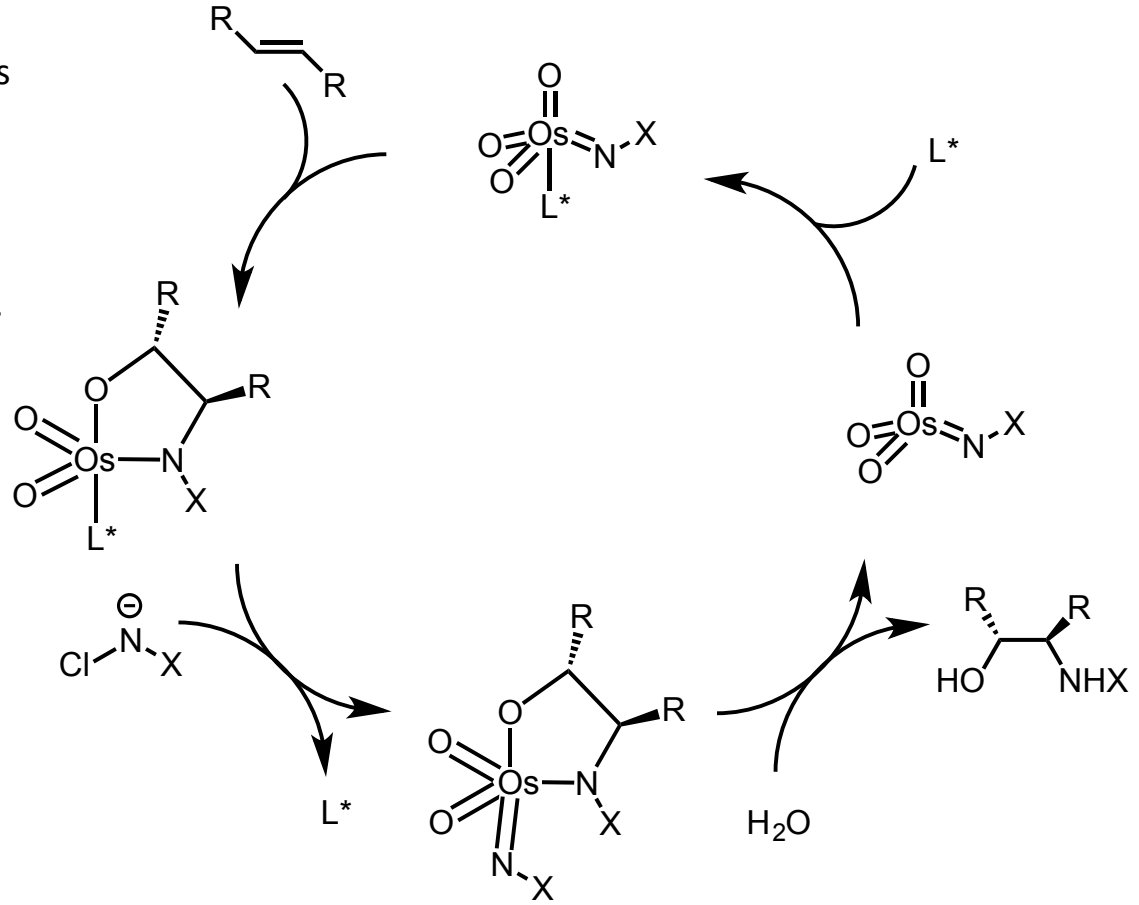

H. C. Kolb, K. B. Sharpless *Tetrahedron,* **1992**, *48*, 10515.



# Sharpless Asymmetric Aminohydroxylation

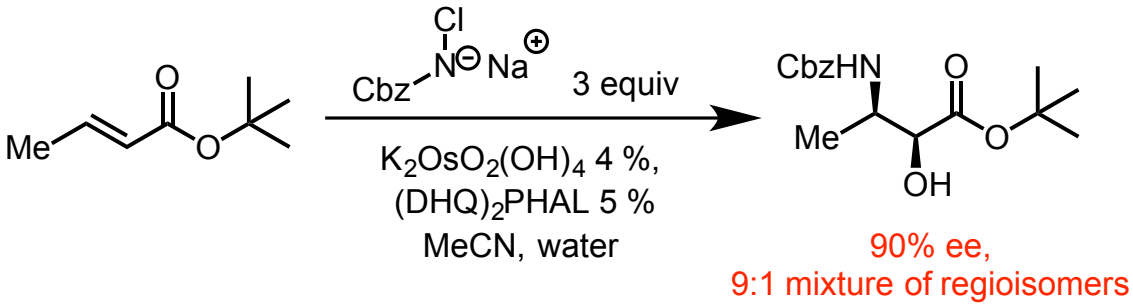



- Sharpless Asymmetric Aminohydroxylation gives amino alcohol derivatives with high enantiomeric excess.
- Similar mechanism to Sharpless Asymmetric dihydroxylation.
- Similar enantioselectivities and substrate scope.
- Regioisomeric products are frequently formed.
- In general, nitrogen adds to the less substituted carbon.
- With cinnamates major regioisomer is β-amino ester.
- With styrenes the benzyl amine is the major regioisomer.

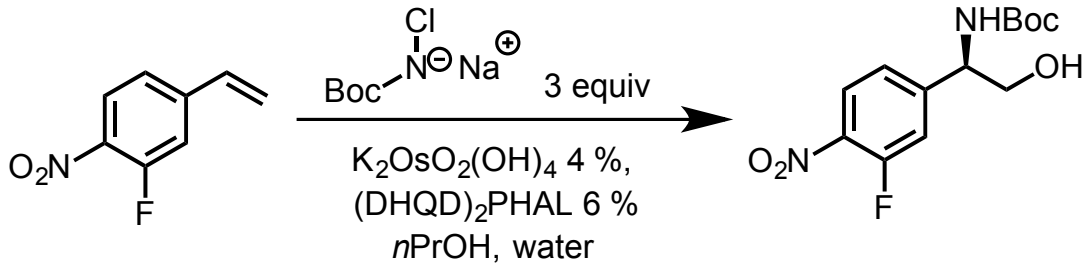



For a review see: Bodkin, J. A.; McLeod, M. D.; *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733.

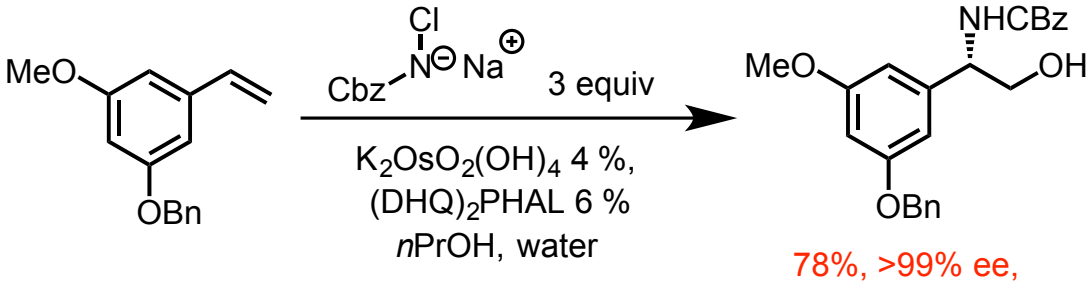
# Sharpless Asymmetric Aminohydroxylation




90% ee,
9:1 mixture of regioisomers




75%, 97% ee,



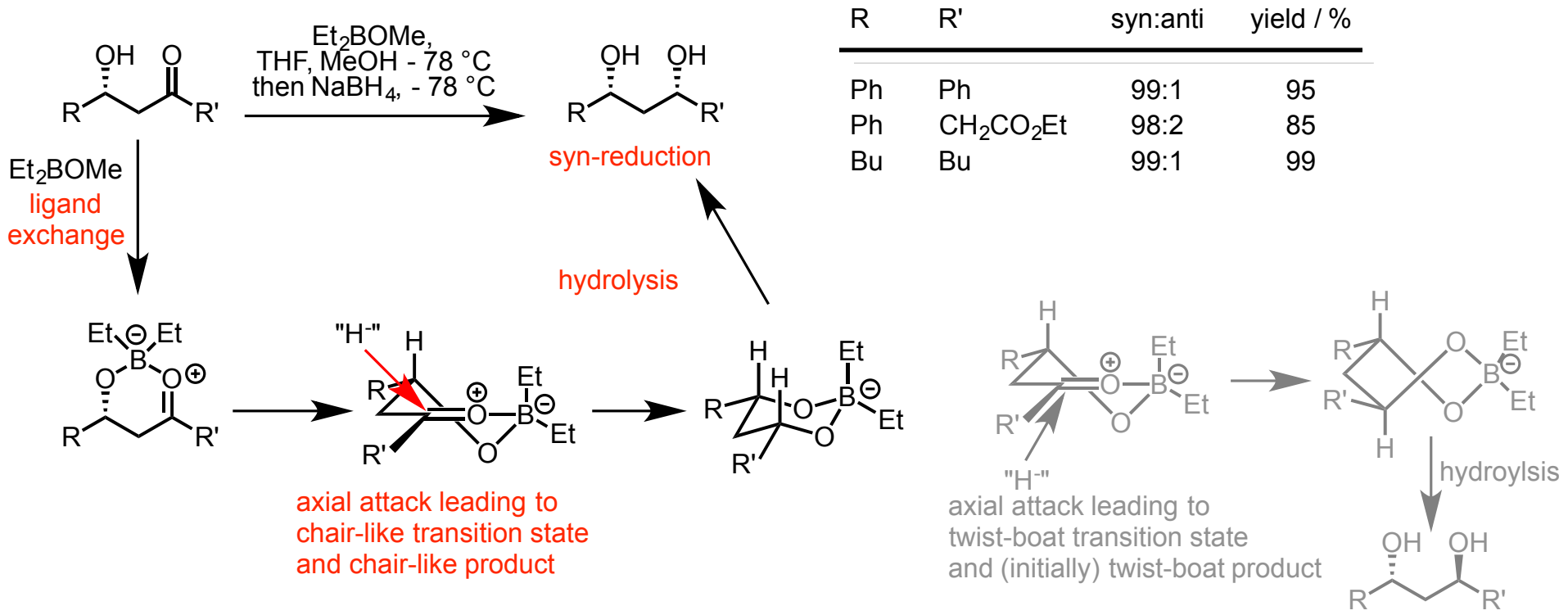

78%, >99% ee,

Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J. –H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.*, **2001**, *23*, 1862.

## Diastereoselective Reduction

- The stereochemical outcome of the addition of hydride (and nucleophiles in general) to α-chiral aldehydes and ketones may be rationalised using the Felkin-Anh and related models (see above).
- A number of methods for the highly diastereoselective addition of hydride to β-chiral ketones have been developed.
- As noted previously the addition of nucleophiles to carbonyl compounds bearing remote stereocentres generally gives products with low diastereoselectivity due the flexible nature of the substrates.
- One solution to the flexibility problem is to form a temporary ring – this tactic is used in a number of procedures for the reduction of β-chiral ketones.

## Naraska / Prasad Reduction – syn-selective reduction of β-hydroxyketones

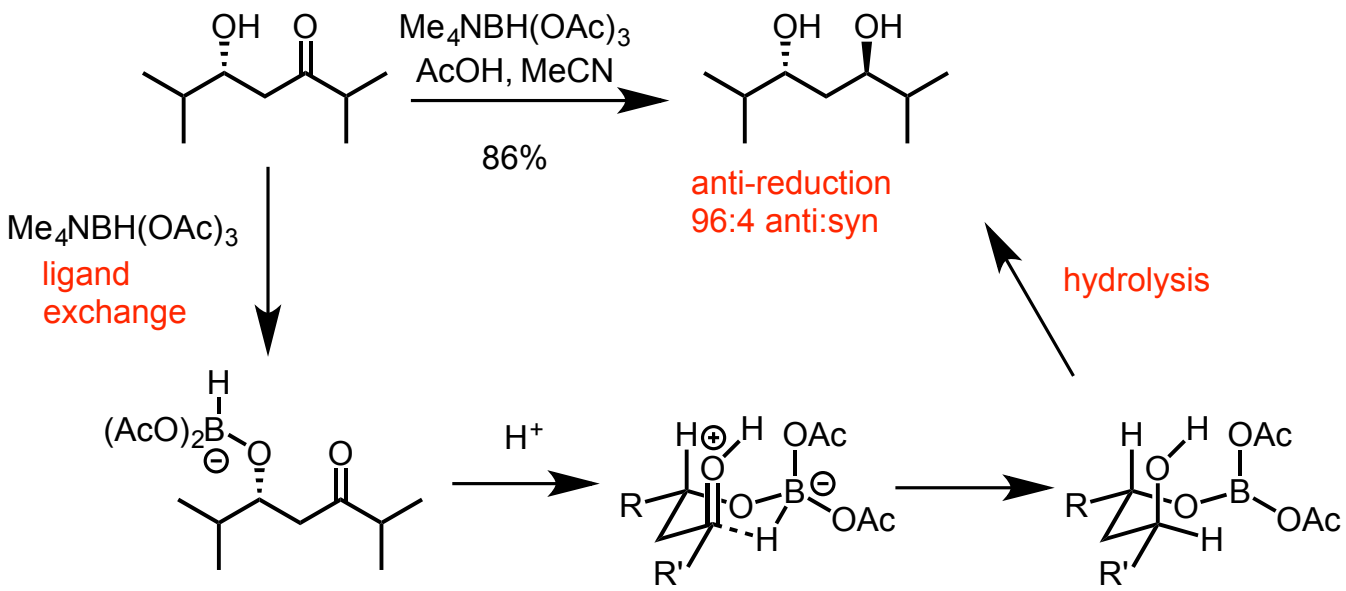


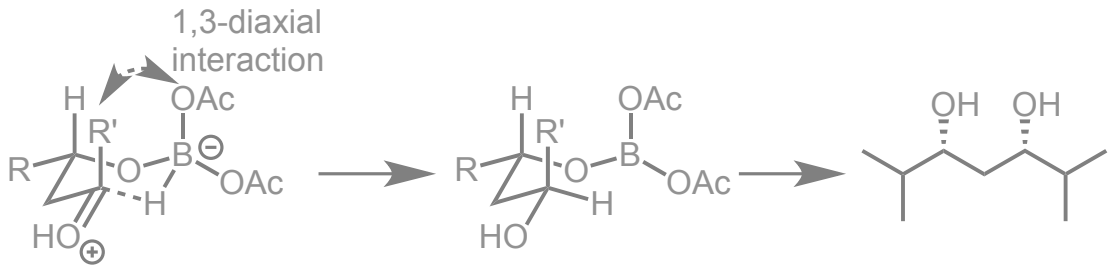

| R | R' | syn:anti | yield / % |
|---|---|---|---|
| Ph | Ph | 99:1 | 95 |
| Ph | $CH_2CO_2Et$ | 98:2 | 85 |
| Bu | Bu | 99:1 | 99 |

K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Tetrahedron Lett.*, **1987**, *28,* 155-158.
K. Narasaka, F.-C. Pai, *Tetrahedron,* **1984**, *40,* 2233-2238.

# Diastereoselective Reduction

## Evans-Saksena *anti*-selective reduction of β-hydroxy ketones



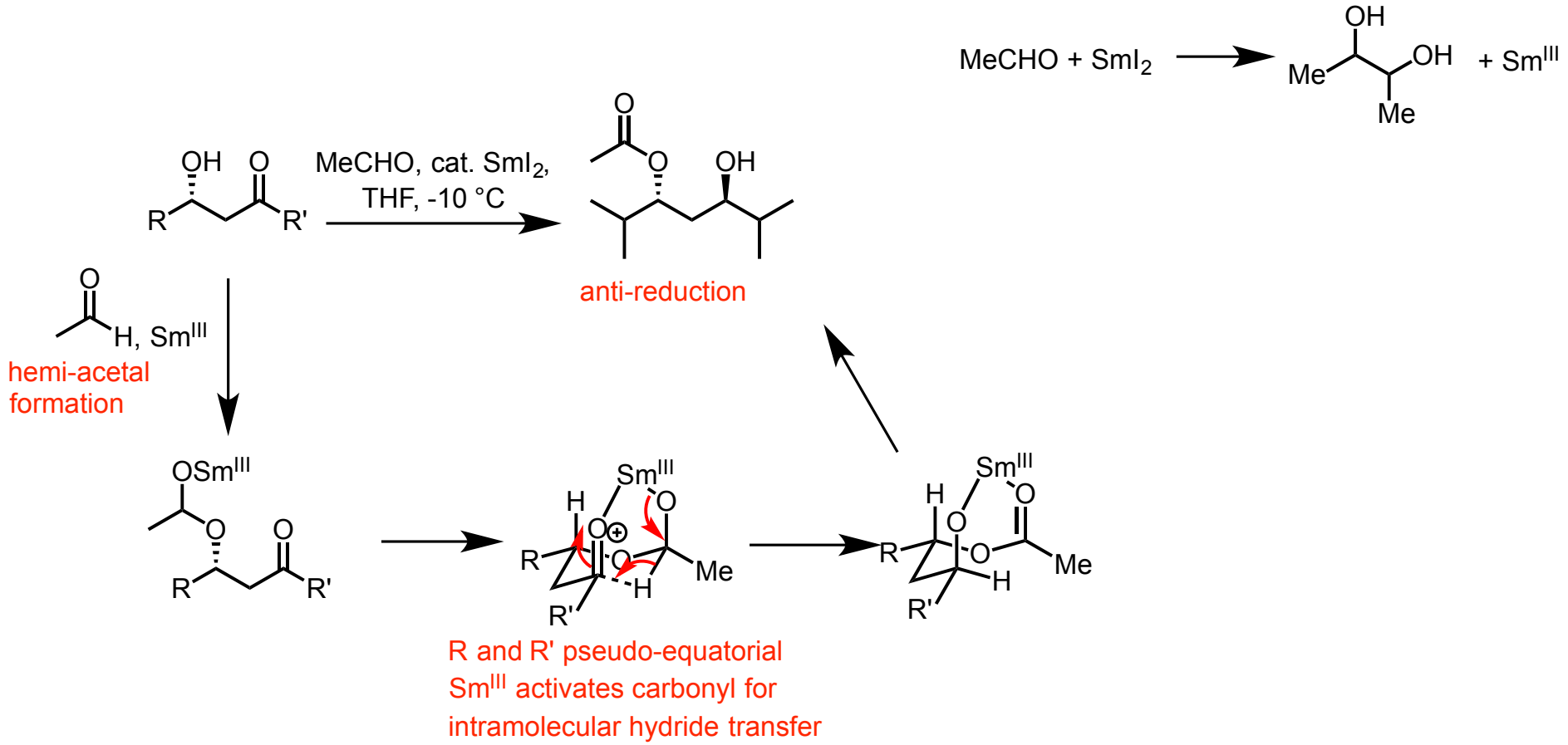




D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.,* **1988,** *110,* 3560-3578.

# Diastereoselective Reduction

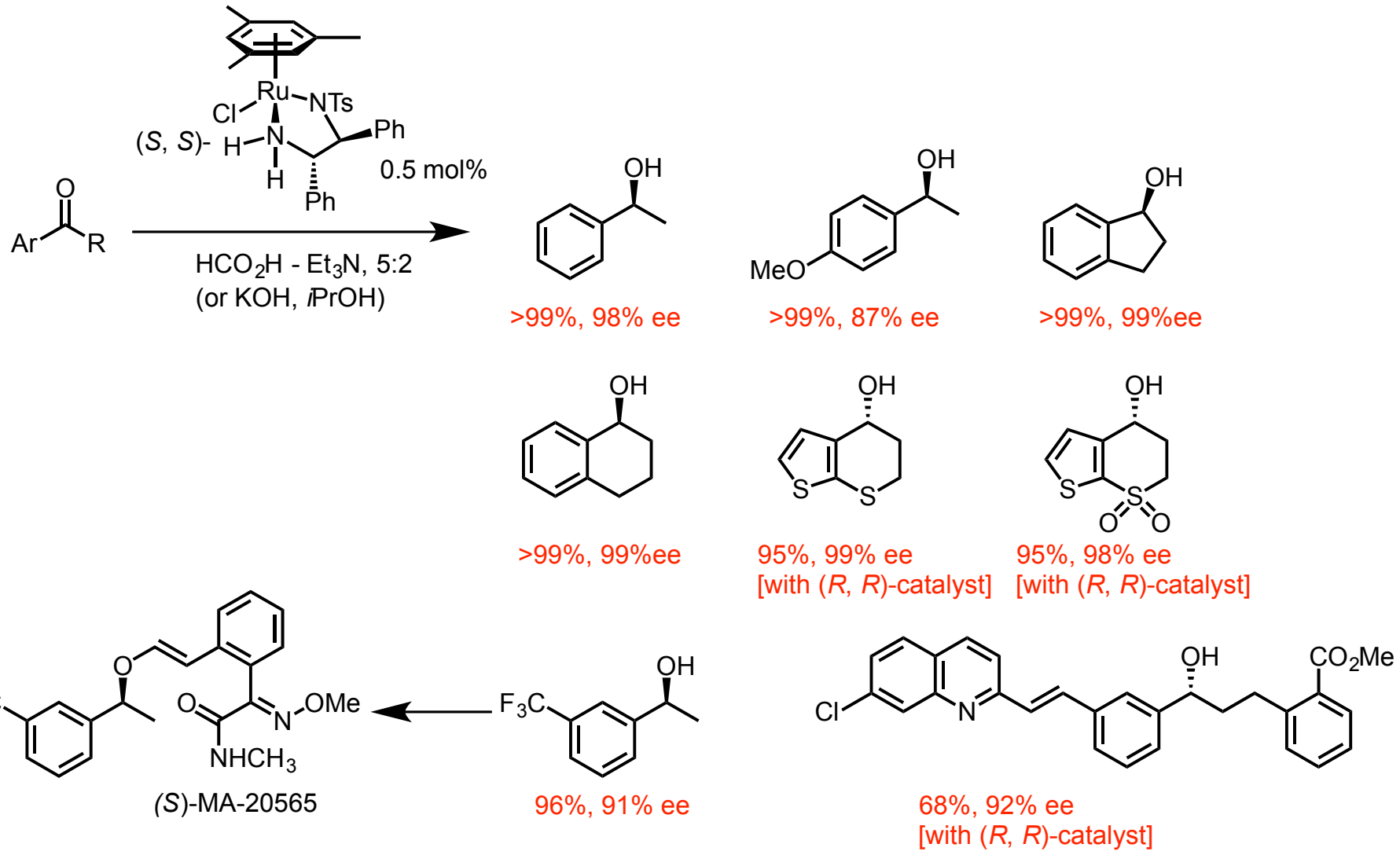
**Evans-Tishenko *anti*-selective reduction of β-hydroxy ketones with *in situ* protection**

- Samarium catalysed intramolecular Meerewein-Pondorf-Verley reduction.
- Samarium(II) iodide initially induces pinacol coupling of some of the aldehyde which gives $Sm^{III}$ which is the active catalyst.
- A hemiacetal forms between the substrate and remaining aldehyde followed by intramolecular hydride transfer to give the product with high yield and high 1,3-*anti* diastereocontrol.



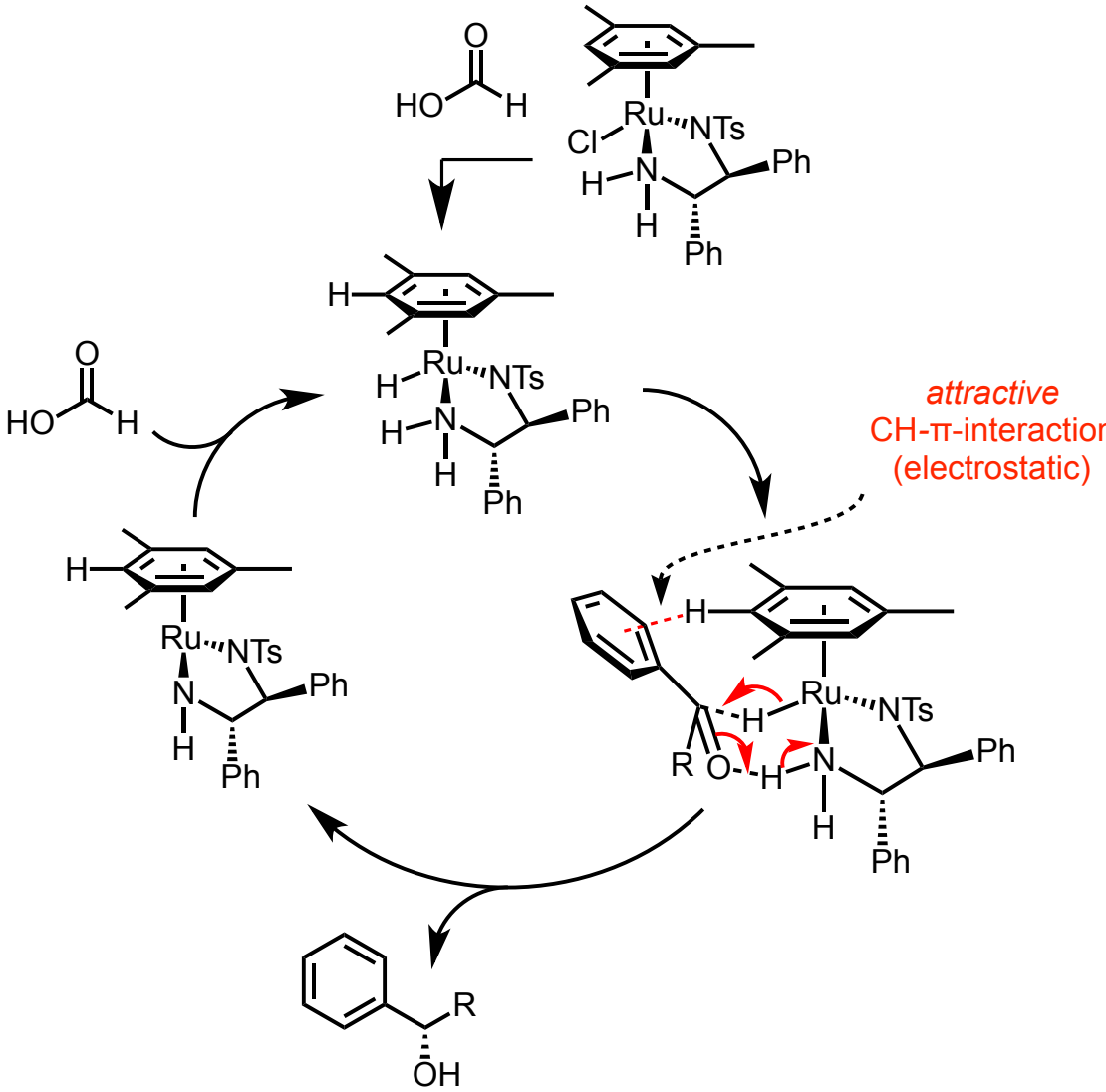

D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.*, **1990**, *112,* 6447-6449.

# Catalytic Asymmetric Reduction of Ketones




For perspective and leading references see: Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.*, **2001**, *66*, 7932.

# Catalytic Asymmetric Reduction of Ketones – transfer hydrogenation

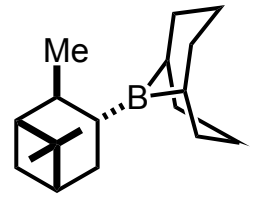



- Aryl ketones and propargylic ketones are the best substrates.
- Low catalyst loading.
- Can be conducted in an open reaction vessel at high substrate (up to 10 M) concentration.
- Mechanism related to classical Meerewein-Pondorf-Verley reduction.

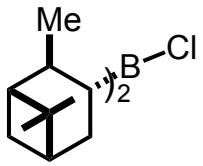
For perspective and leading references see: Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.*, **2001**, *66*, 7932.

# Asymmetric Reduction of Ketones – chiral boranes / borohydrides

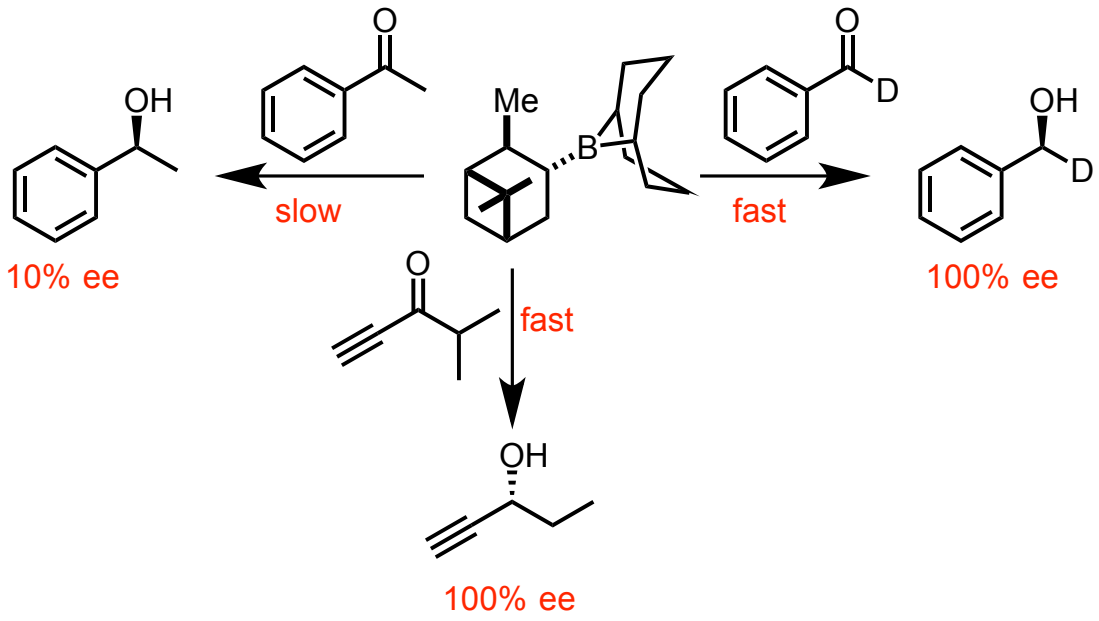
- Treatment of ketones with chiral boranes can result in highly enantioselective asymmetric reduction.
- The most efficient reagents for this reduction are Alpine-borane™ and DIP-chloride

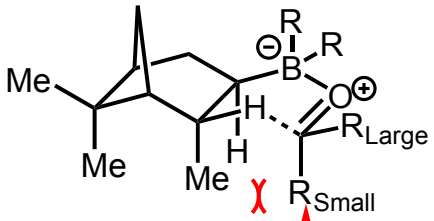



Alpine-borane™




DIP-Cl
(diisopinocampheylboron chloride)



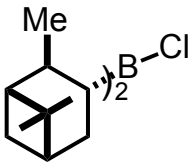




small group
buttresses against
axial Me group

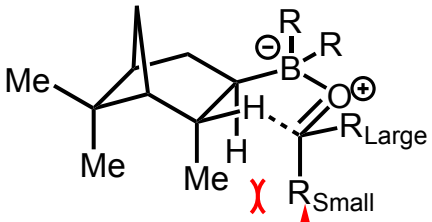
For a review see: Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.*, **1995**, *500*, 1.

# Asymmetric Reduction of Ketones – chiral boranes / borohydrides

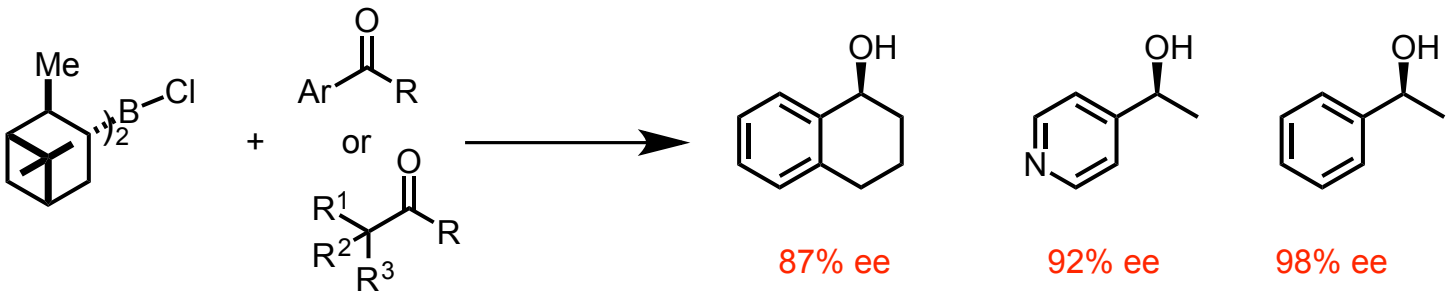
- More Lewis acidic than Alpine-borane™ due to electronegative chlorine atom.
- reduces wide variety of ketones with high enantioselectivity.
- Ar group is the "large" group.




DIP-Cl
(diisopinocampheylboron chloride)




small group
buttresses against
axial Me group



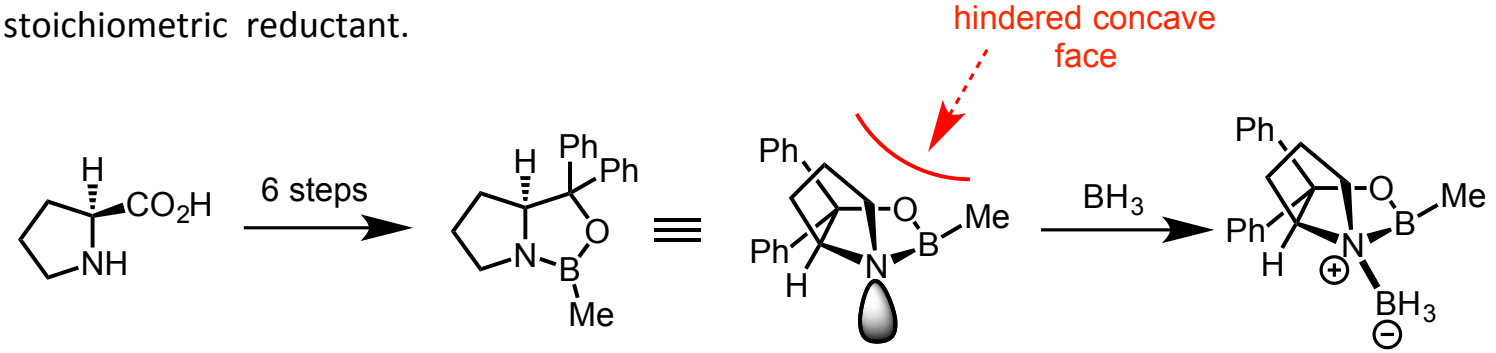

87% ee 92% ee 98% ee

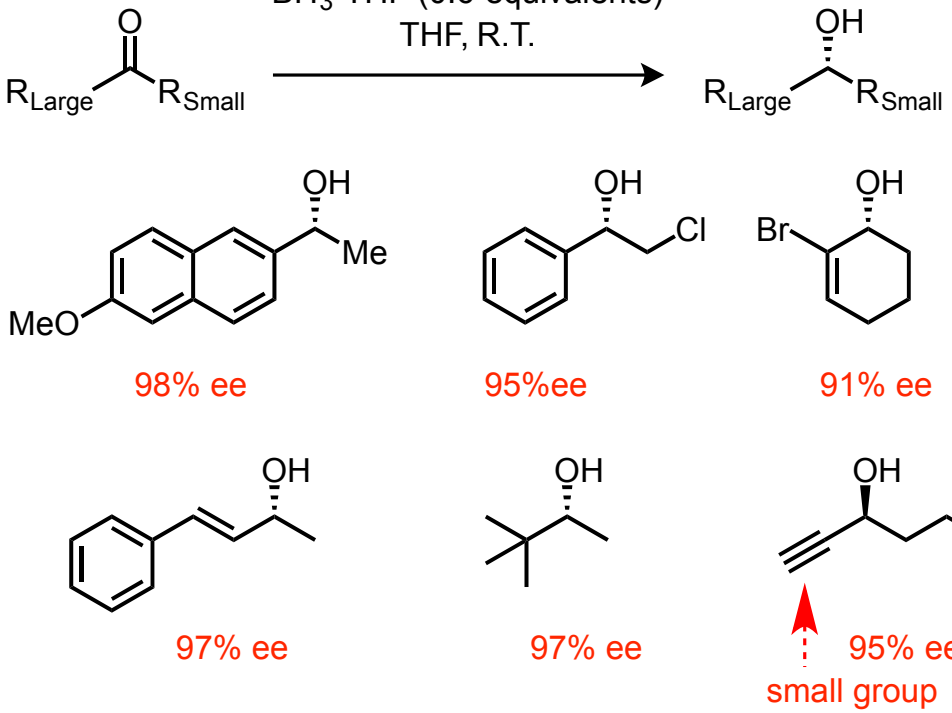
95% ee 91% ee

For a review see: H. C.; Ramachandran, P. V. *J. Organomet. Chem.*, **1995**, *500*, 1.

# Catalytic Asymmetric Reduction of Ketones Corey, Bakshi, Shibata (CBS)-reduction

■ E. J. Corey has developed a highly effective catalytic asymmetric reduction of prochiral ketones using $BH_3$ as the stoichiometric reductant.



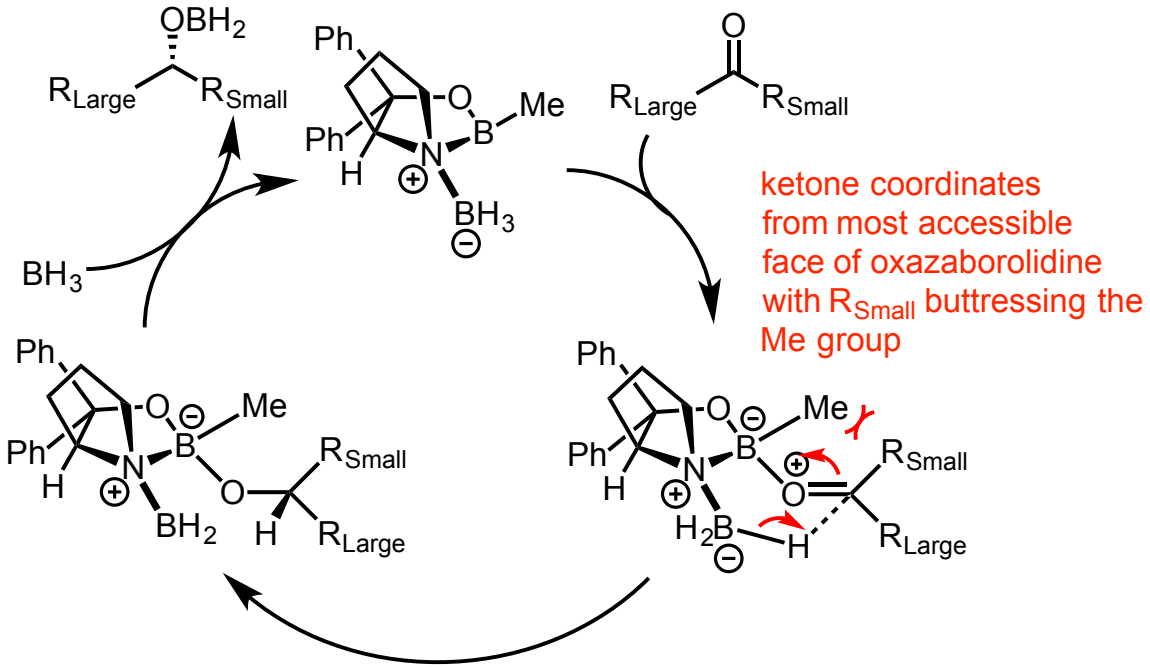



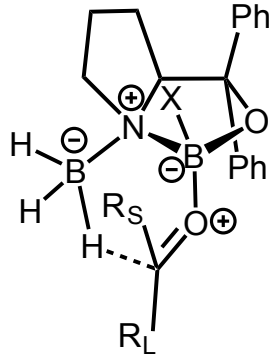

E. J. Corey, Nobel Prize, 1990 for or his development of the theory and methodology of organic synthesis

For a review see: Corey, E. J.; Helal, C. J.; *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

# Catalytic Asymmetric Reduction of Ketones - Corey, Bakshi, Shibata (CBS)-reduction

## Mechanism

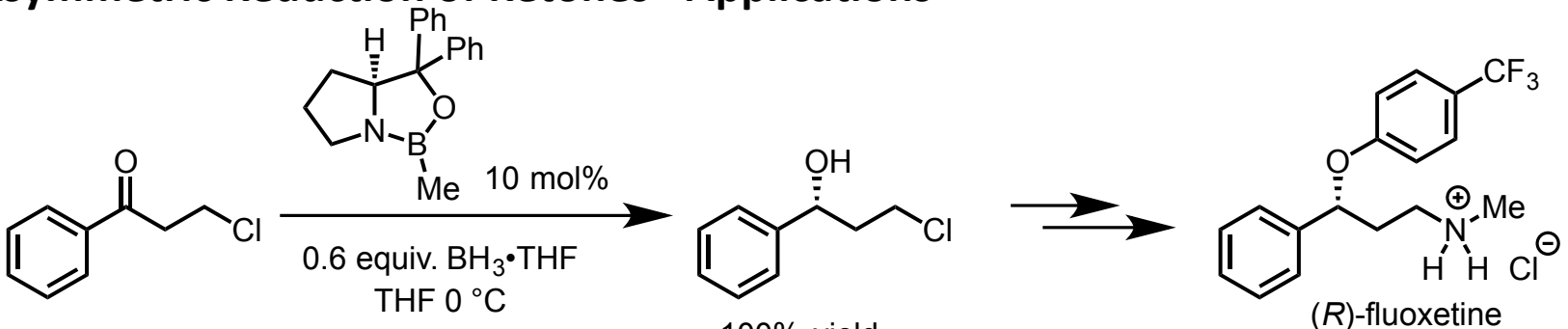


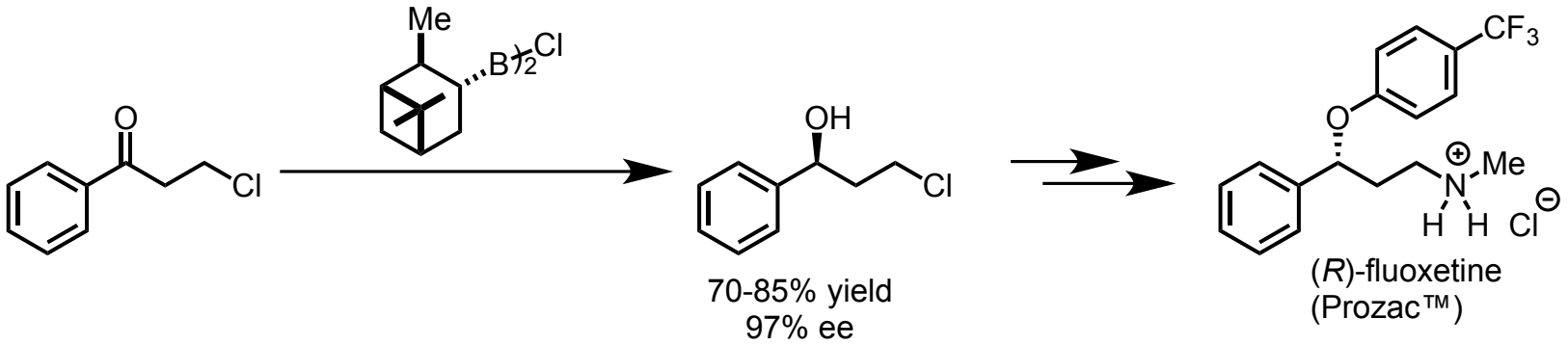

alternative perspective

For a review see: Corey, E. J.; Helal, C. J.; *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
For a large scale CBS-reduction (>1.5 kg) see: Duquette, J.; Zhang, M.; Zhu, L.; Reeves, R. S. *Org. Process Res. Dev.* **2003**, *7*, 285

## Asymmetric Reduction of Ketones - Applications

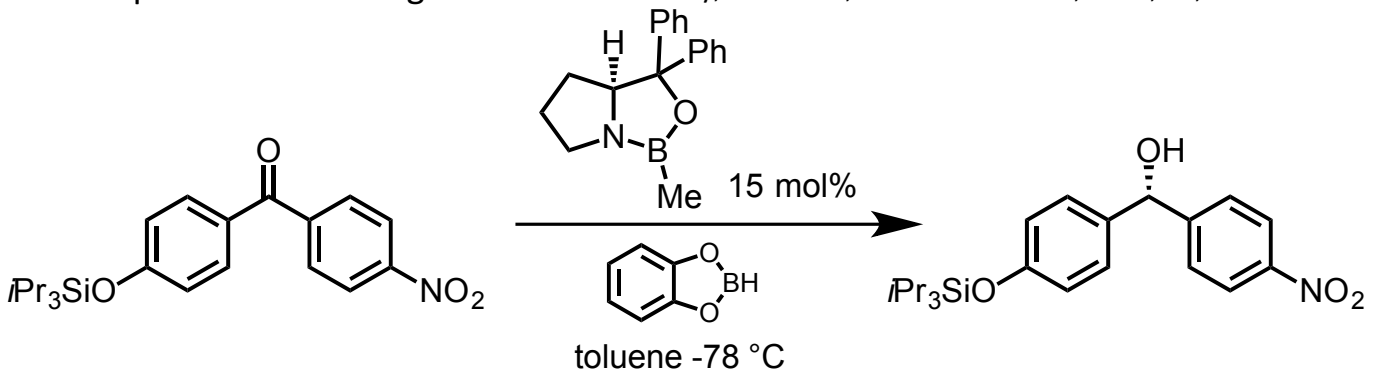



Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.*, **1989**, *30*, 5207.

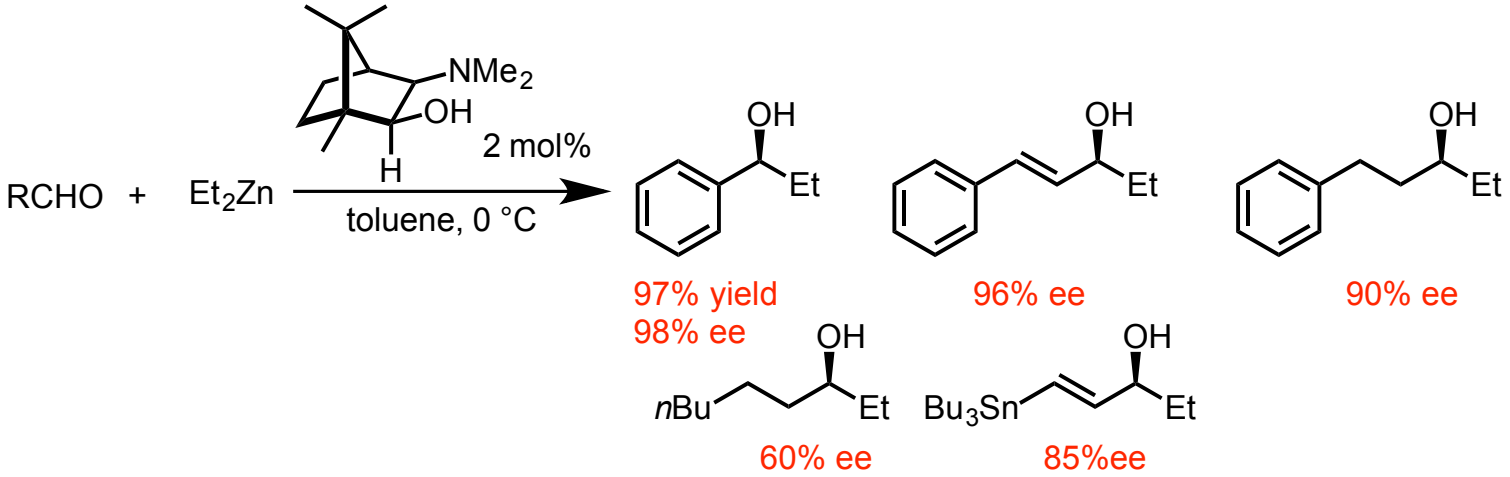



Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.*, **1988**, *53*, 2916.

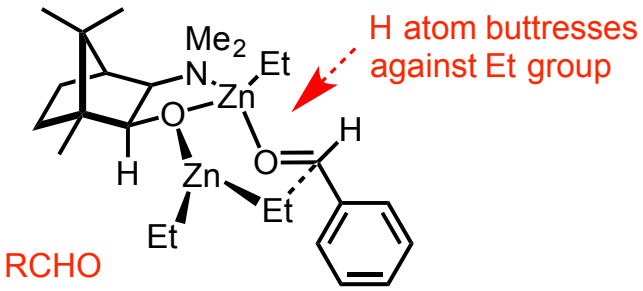
***Problem:*** Explain the following reaction. E. J. Corey, C. J. Helal, *Tetrahedron Lett.*, **1995**, *36*, 9153.

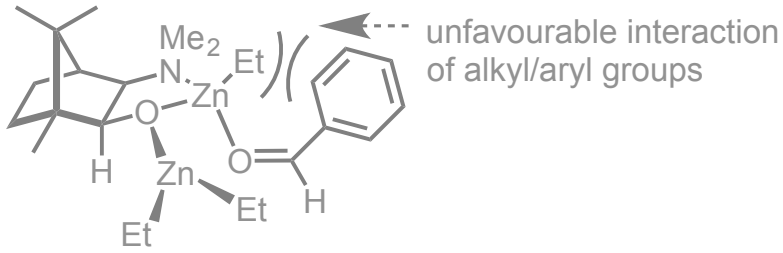


# Asymmetric Addition of Diethylzinc to aldehydes




- Active catalyst formed from reaction of $Et_2Zn$ with amino alcohol.
- Coordination of a second molecule of $Et_2Zn$ and of RCHO gives pre-transition state assembly.
- Et group delivered selectively to one the two prochiral faces of the aldehyde.
- Aliphatic aldehydes generally give products with moderate enantiomeric excess.

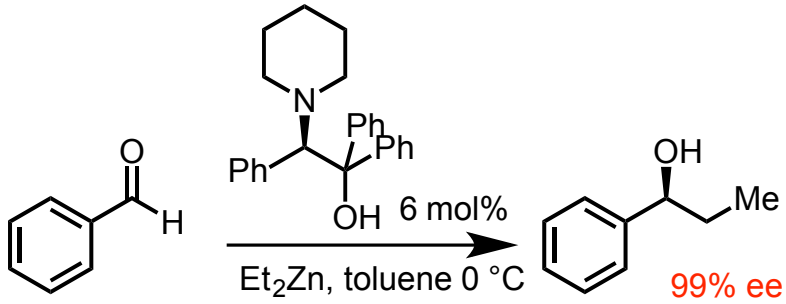


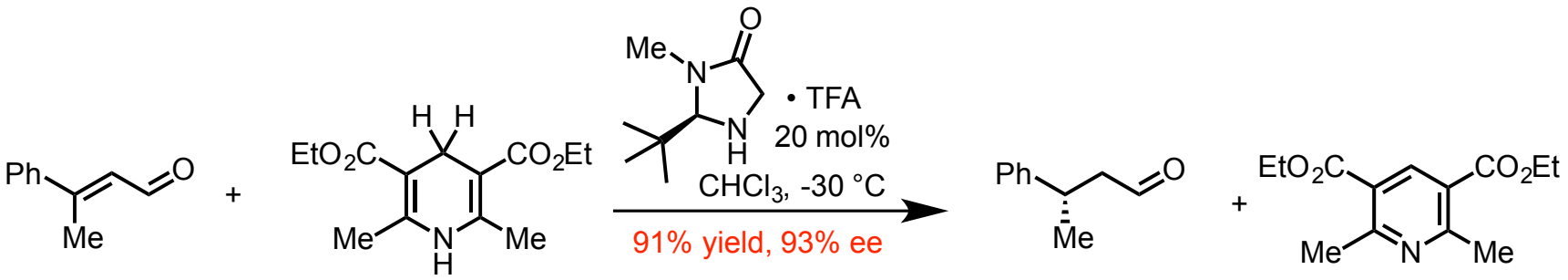

For a review see: Noyori, R; Kitamura, M. *Angew. Chem. Int. Ed.*, **1991**, *30*, 49.

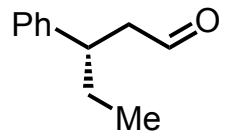
***Problem:*** Rationalise the stereochemical outcome of the following reaction.

J. Va´zquez, M. A. Pericas, F. Maseras, A. Lledos, *J. Org. Chem.*, **2000**, *65*, 7303.

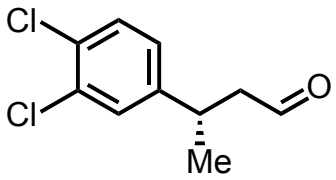


# Catalytic Asymmetric Reduction with Organocatalysts

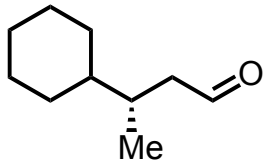


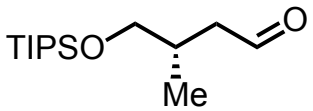

74%, 94% ee



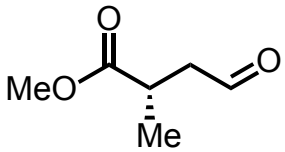

92%, 97% ee



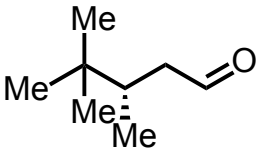

95%, 91% ee




74%, 90% ee



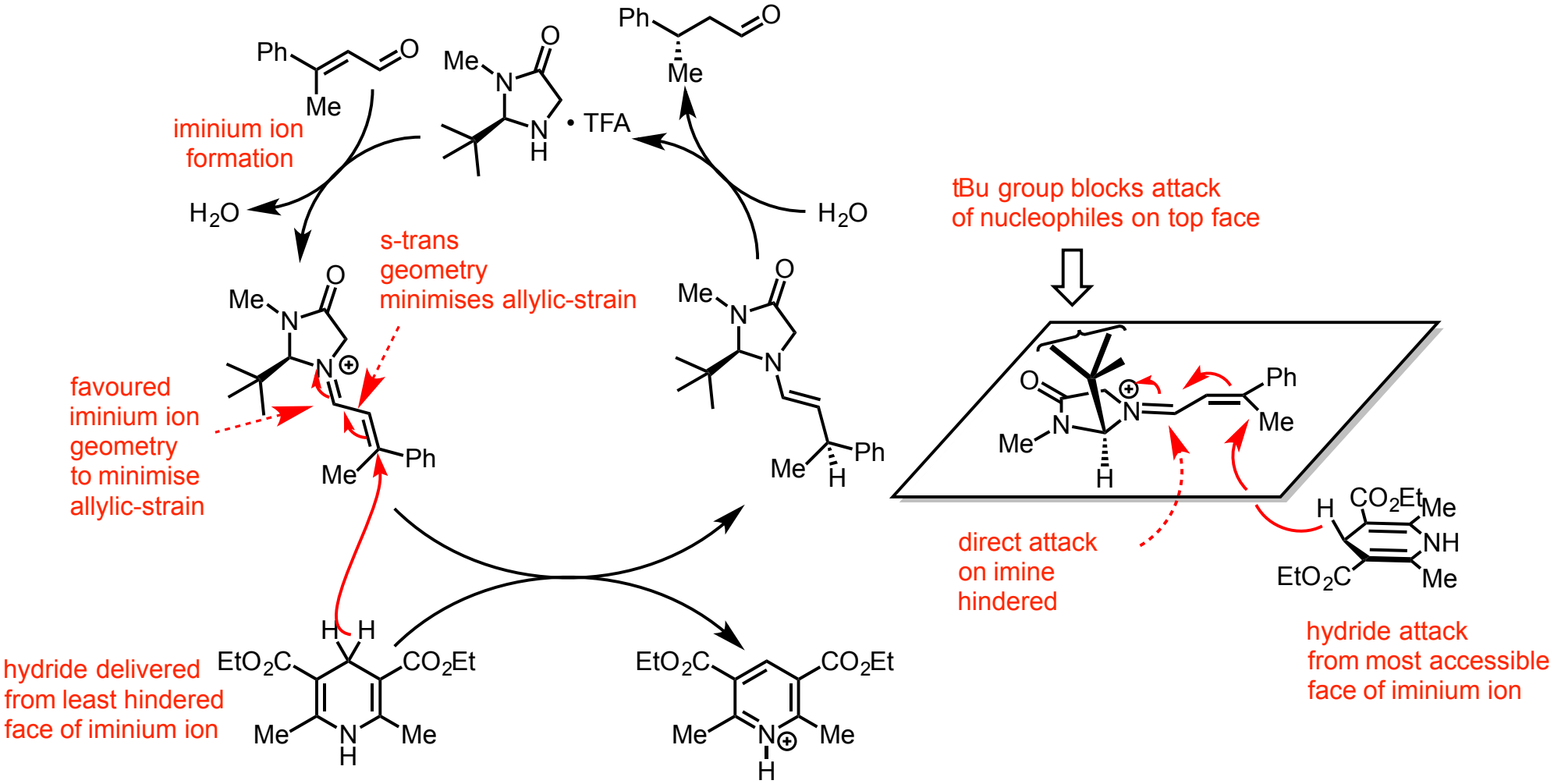

83%, 91% ee




95%, 97% ee

S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2005**, *127*, 32.

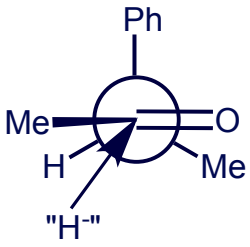
# Catalytic Asymmetric Reduction with Organocatalysts

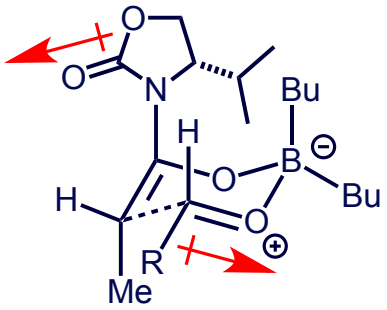


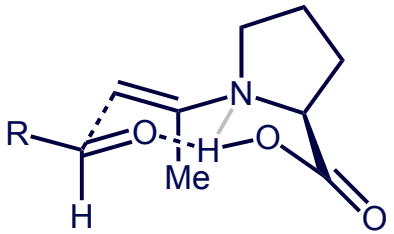

- α,β-Unsaturated iminium ion more electrophilic than α,β-unsaturated aldehyde (lower energy LUMO).
- Asymmetric iminium ion catalyst complementary to asymmetric enamine catalysis.
- LUMO lowering *via* asymmetric α,β-unsaturated iminium ion formation is a general and useful concept for asymmetric catalysis.

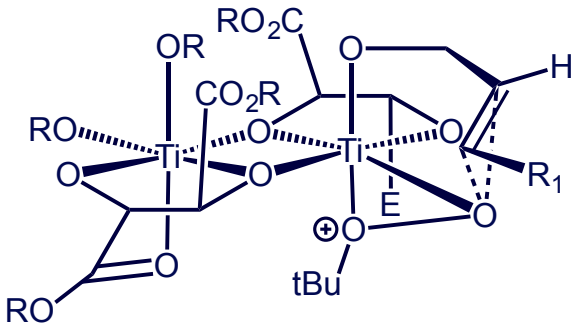
S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2005**, *127*, 32.

## Summary




- In order to rationalise the stereochemcial outcome of many of the reactions you have seen you need to consider:

i) steric and electronic factors
ii) steroelectronic effects
iii) associative substrate-reagent interactions

- In order to do this it is imperative to draw ***clear conformational diagrams***.

Appendix Overview

- Definitions and terminology
- Chirality and identifying chiral compounds
- Biological importance
- Optical activity
- Diastereomers
- CIP sequence rules
- Absolute and relative configuration
- Methods for representing stereochemistry
- All types of chirality
- Atropisomerism
- Diastereomers and enantiomers
- Separating enantiomers
- Assigning absolute configuration
- The chiral pool
- Synthesis of some chiral auxiliaries and catalysts

## Glossary of terms

*achiral* – not chiral *i.e.* molecule/object has a superimposable mirror image. If a molecule can gain access to a conformation which has a plane of symmetry (or centre of inversion) it will be *achiral,*

*chiral* – Molecules (and objects) which have a non-superimposable mirror image,

*chiral centre* – see stereogenic centre,

*diastereomers* – *stereoisomers* which are not related as *enantiomers*.

*enantioenriched* – consisting of an excess of one *enantiomer*.

*enantiopure* – consisting of a single *enantiomer*.

*enantiomers* - *stereoisomers* which are related as non-superimposable object and mirror image,

*meso* compound - a *stereoisomer* with two or more *stereocentres* but which is itself *achiral*.

*optically active* – rotates the plane of plane polarised light – can only occur with non-racemic samples

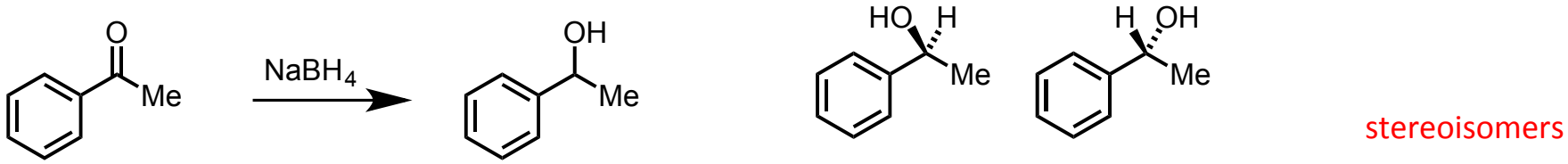
*racemate* or *racemic mixture* – 50:50 mixture of *enantiomers*; a *racemate* is *optically inactive*.

*racemisation* – the conversion of one *enantiomer* (or an excess of one *enantiomer*) into a 50:50 mixture of *enantiomers*.

*stereogenic centre (stereocentre)* – an atom (generally carbon) with four *non-identical* substituents – also called a *chiral centre.*

*stereoisomers* – isomers with the same connectivity – i.e. A linked to B linked to linked to C etc, but different disposition of atoms in space.

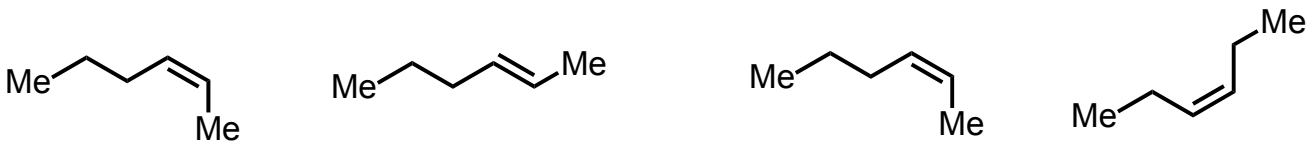
- Stereoisomers




stereoisomers

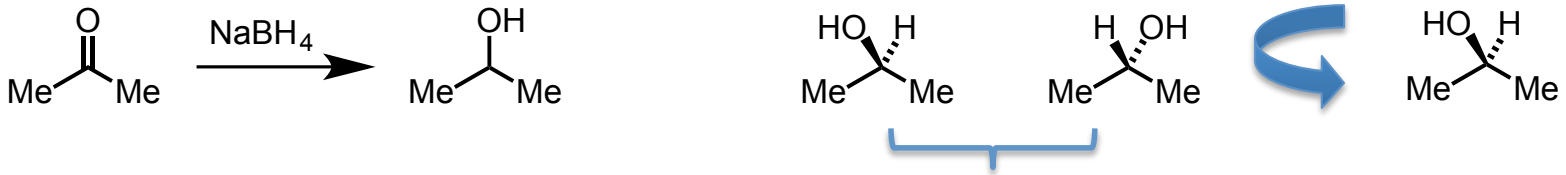
not the same – as cannot be superimposed

- Stereoisomers – isomers with the same connectivity – i.e. A linked to B linked to linked to C etc., but different disposition of atoms in space.



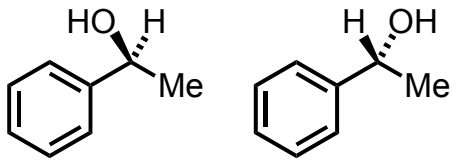

stereosisomers

**not** stereoisomers – different connectivity
related as *constitutional* isomers (structural isomers)

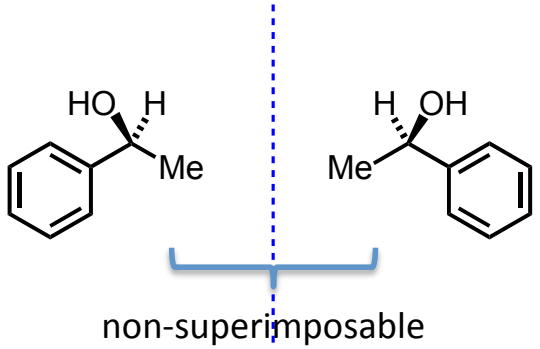



superimposable

- Stereoisomers




these two stereoisomers are related as object and mirror image



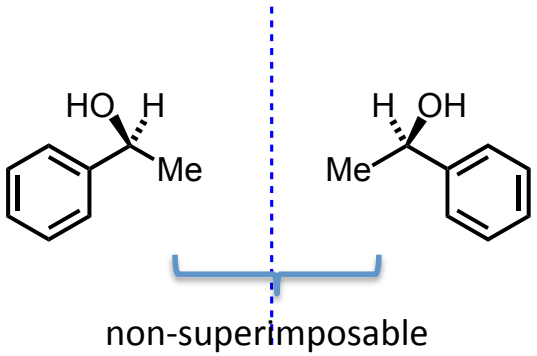

stereoisomers

not the same – as cannot be superimposed

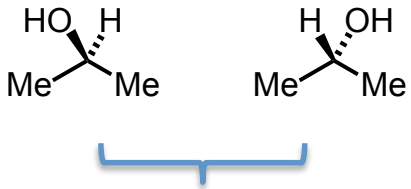
non-superimposable

- Stereoisomers which are related as non-superimposable object and mirror image are termed enantiomers – mirror-image stereoisomers.
- Molecules (and objects) which have a non-superimposable mirror image are called *chiral.*
- The term 'chiral' was introduced by Lord Kelvin:

> *" I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."*



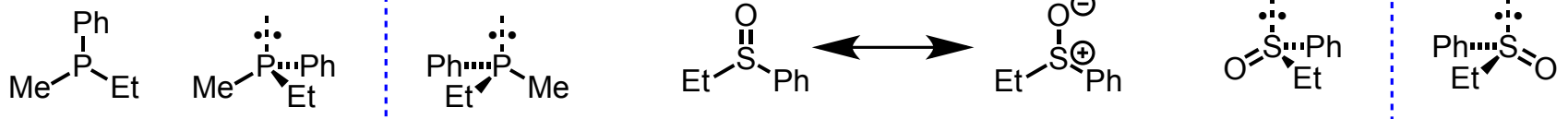

non-superimposable




superimposable

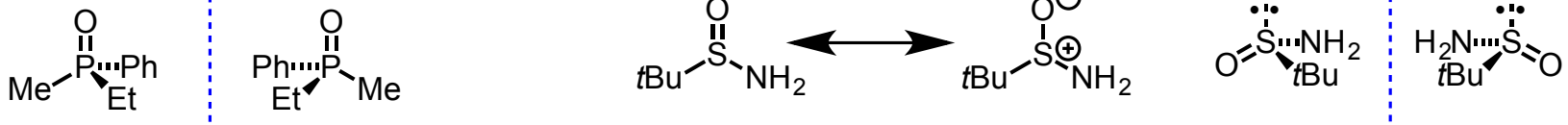
- A carbon atom (or other atom bearing for different substituents) is termed a ***stereogenic centre*** or ***stereocentre*** – frequently termed a chiral centre.
- Compounds in which one or more carbon atoms have four non-identical substituents are the largest class of chiral molecules.
- Conversely a molecule (or object) is termed 'achiral' if it is superimposable on its mirror image.

- Chiral molecules are not restricted to those having a carbon atom carrying four different substituents.
- Sulfoxides, sulfinamides, phosphines and phosphine oxides can all be chiral and are frequently configurationally stable at room temperature.
- The central atom (P or S) can carry four different substituents one of which can be a lone pair of electrons.




phosphines

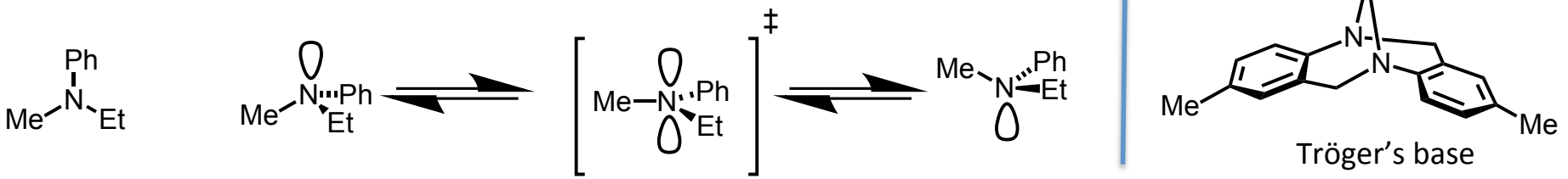
sulfoxide




phosphine oxide

sulfinamide

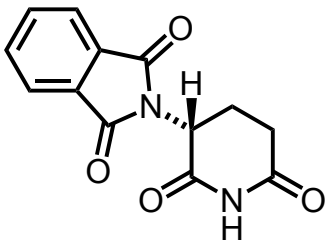
- Generally amines that have three different groups on nitrogen cannot be resolved into separate enantiomers as very rapid pyramidal inversion occurs at room temperature.



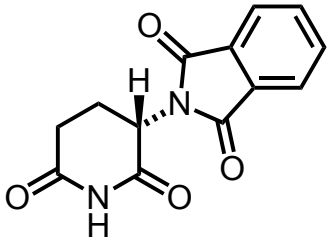

Tröger's base

- If the nitrogen substituents can be 'tied-back' to prevent pyramidal inversion then the amine may be resolved.

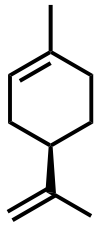
- Enantiomers have exactly the same property in a non-chiral (*achiral*) environment – i.e they are the identical (in an achiral environment).
- Enantiomers have *different* properties in a *chiral* environment e.g. an enzyme.
- Separated enantiomers rotate the plane of *plane polarised light* in equal but opposite directions – this is optical activity and the sample is said to be optically active.
- Optical activity was first demonstrated by Pasteur in 1848 and led to the idea of tetrahedral carbon.
- Jean Baptiste Biot (1774-1862) first showed that some natural substances can rotate the plane of plane polarised light.



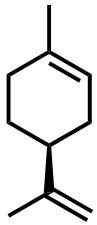
(+)-thalidomide, $[\alpha]_D^{21}$ = +63 (*c* 2.03, DMF)
sedative, hypnotic, stops morning sickness



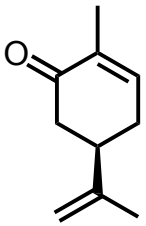
(-)-thalidomide, $[\alpha]_D^{21}$ = +63 (*c* 2.03, DMF)
teratogen, foetal damage, congenital malformation



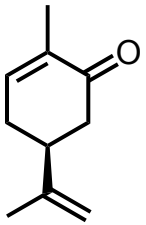
(+)-limonene
oranges



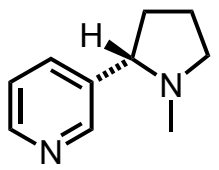
(-)-limonene
lemons



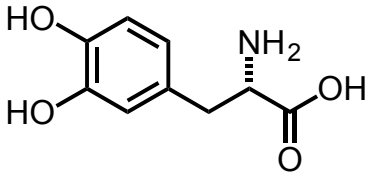
(-)-carvone
spearmint



(+)-carvone
caroway and dill

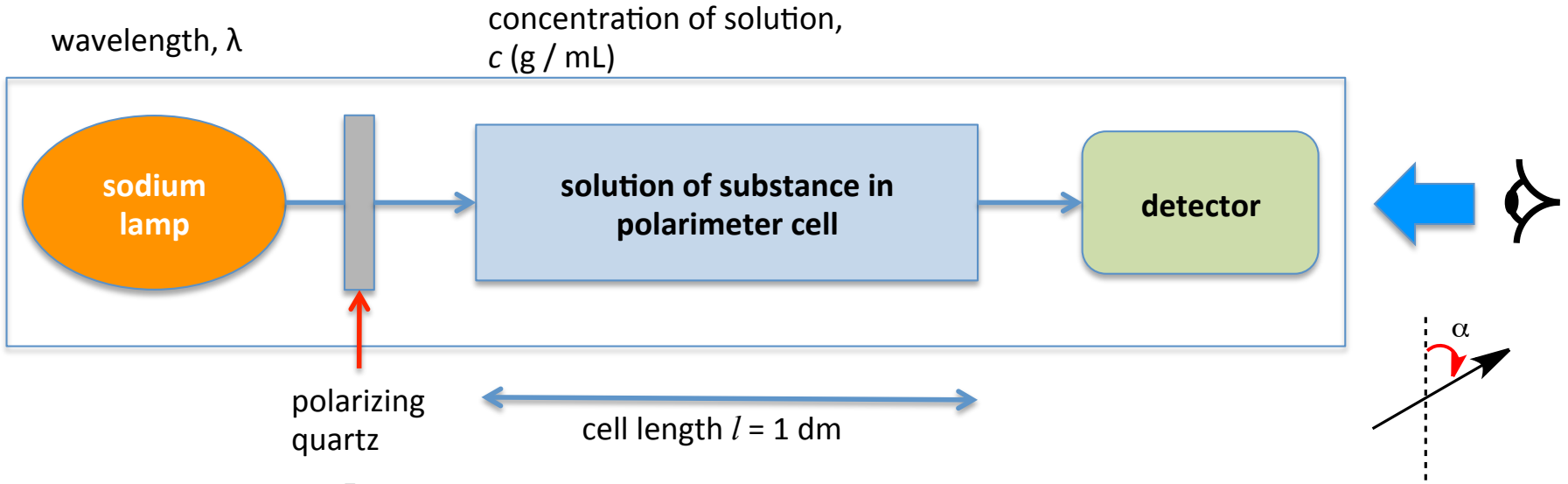


(*S*)-(-)-nicotine



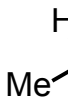
L-DOPA

- Optical rotation.
- Schematic of a polarimeter.

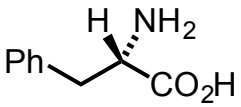



Specific rotation: $[\alpha]_D^T = \alpha / c \times l$
α = observed rotation
D = wavelength of sodium "D" line – 589 nm
$c$ = concentration of solution in g / mL
$l$ = length of cell in dm (usually 1 dm)
T = temperature in °C

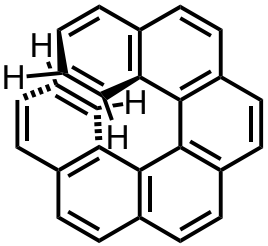
rotation to the right
dextrorotatory (+)
rotation to the left
levorotatory (-)



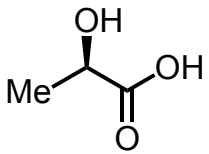
(S)-L-(+)-alanine
$[\alpha]_D$ = +14.7



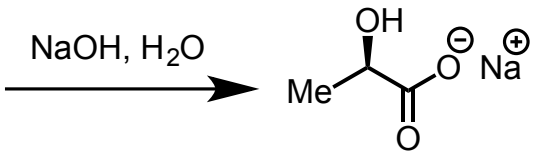
(S)-L-(–)-phenylalanine
$[\alpha]_D$ = –35.2



hexahelicene
$[\alpha]_D$ = +3640!



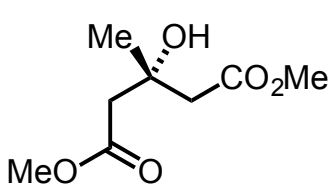
(*R*)-D-(-)-lactic acid
$[\alpha]_D$ = -3.8

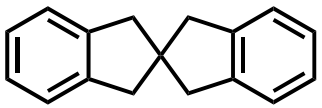


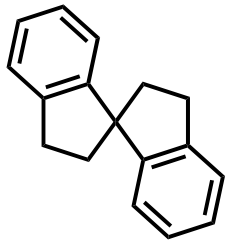

(*R*)-sodium lactate
$[\alpha]_D$ = +13.5

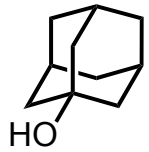
- There is no simple connection between structure and specific rotation; however, single enantiomers always show equal and opposite rotation if the specific rotation is measured under identical conditions.

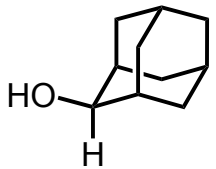
- The magnitude of the specific rotation depends on the wavelength, the temperature, the concentration and the solvent, among other things.
- A 1:1 mixture of *enantiomers* is termed a *racemic mixture* (or *racemate*), a *racemic mixture* is optically inactive.
- *Achiral* (non-chiral) molecules do *not* rotate the plane of plane polarised light and are optically inactive.
- If a reaction is to produce an excess of one enantiomer over the other then the reaction must be conducted in a chiral, non-racemic environment e.g. in the presence of an enzyme or enantiomerically enriched reagent or catalyst.
- *No* optically active material can be generated if all the staring material, reagents and conditions are either *achiral* or *racemic* i.e. optically inactive.
*i.e. we cannot have a reaction which makes an excess of one enantiomer, unless there is a chiral – non-racemic component to the reaction.*
- *Note:* a sample of a chiral molecule may contain a single enantiomer or it may be a mixture of enantiomers - depending on how it was made.
- Which of the following molecules are chiral?

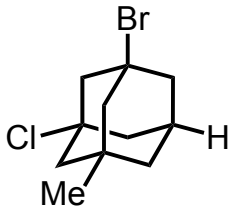


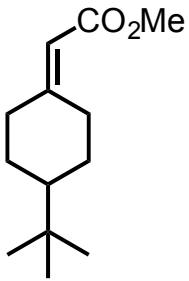





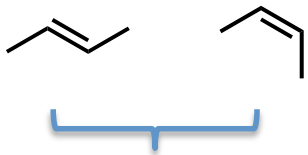


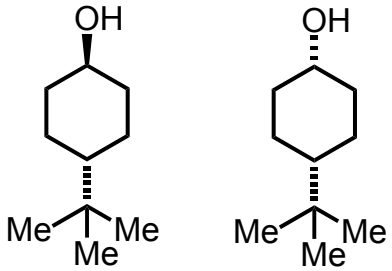



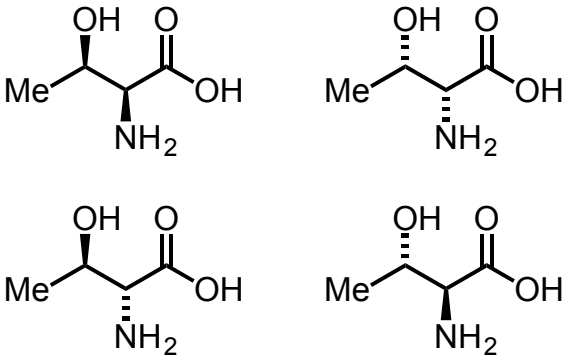
- Stereoisomers which are not enantiomers are termed **diastereomers**.



diastereomers



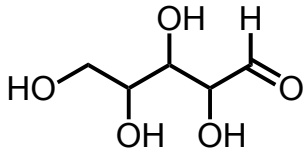
diastereomers



- Diastereomers have different physical and chemical properties – different NMR spectra, IR spectra, melting point, boiling point etc. – they are ***different*** compounds.

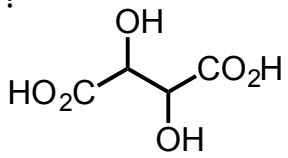
- Remember enantiomers are related as non-superimposable object and mirror image and hence only have different properties in a chiral environment – they are identical in an achiral environment – more on this later.

- Draw all the stereoisomers of the following compound. What are the stereochemical relationships between the various pairs of stereoisomers?



- As you may know, if a compound has *n* stereogenic centres (or more generally stereogenic elements) the maximum number of stereoisomers will be $2^n$.

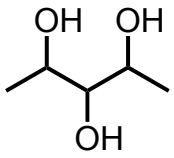
■ Meso compounds – how many stereoisomers of tartaric acid are there? How many of them are chiral?

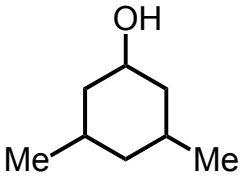


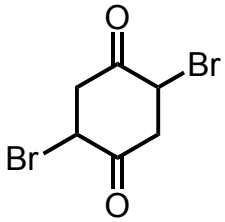

■ A simple definition of a *meso* compound is a stereoisomer with two or more stereocentres but which is itself achiral.

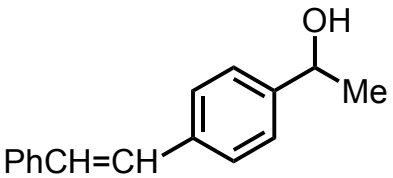
A fuller definition is that a 'meso compound is an achiral member of a set of diastereomers that includes at lest one chiral member'. *Elliel*

■ Draw all the stereoisomers of the following compounds. What are the stereochemical relationships between the various pairs of stereoisomers? Which of the stereoisomers are chiral? Identify any *meso* compounds.



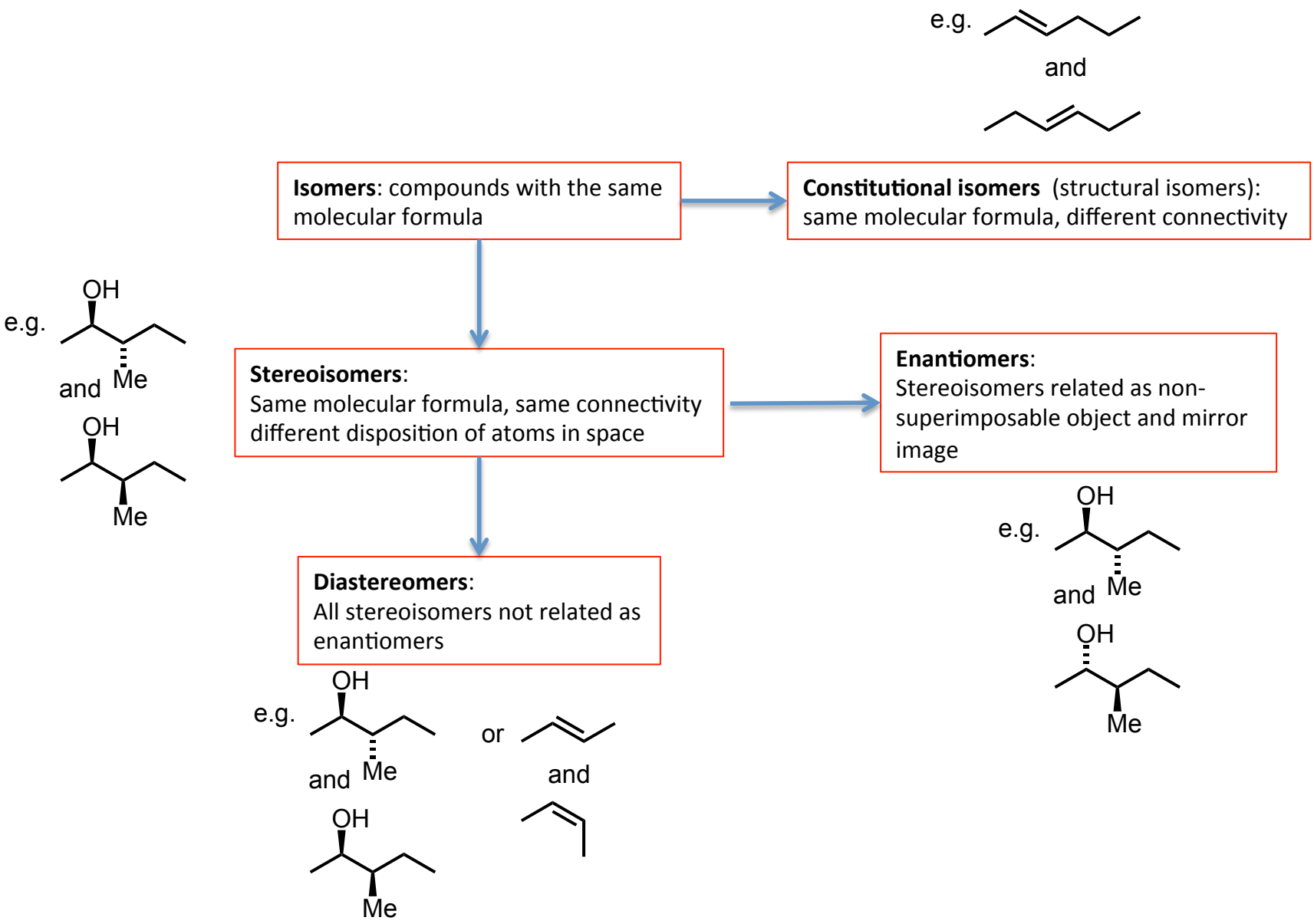




■ To investigate how many stereoisomers a compound has the following method may be useful:

i) If the compound is acyclic draw it in zig-zag fashion
ii) Identify the stereocentres
iii) Decide how many diastereomers there are by putting substituents, with defined stereochemistry on the stereocentres
iv) Look for possible planes of symmetry (or centres of inversion) and hence decide which diastereomers are chiral – identify *meso* compounds
v) Draw the enantiomers of any chiral diastereomers by inverting *all* of the stereogenic centres

*from Clayden, Greeves, Warren & Wothers*

## Flow chart of isomers



## *Cahn-Ingold-Prelog Sequence Rules*

It is important to be able to label the *configuration* of a *stereocentre* centre in much the same way as geometrical isomers of double bonds are termed *cis* and *trans.*

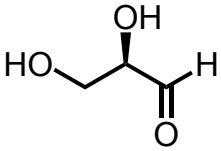
*R* = Rectus (Latin for 'right') and *S* = sinister (Latin for 'left') are used to label the configurations of *stereogenic* centres.

- Assign the priority of each atom directly attached to the stereocentre on the basis of atomic number – higher atomic number = higher priority. If atoms directly attached to the stereocentre have the same atomic number move down each substituent one atom at a time until the *first* difference is reached, with higher atomic number always being the first point of difference.

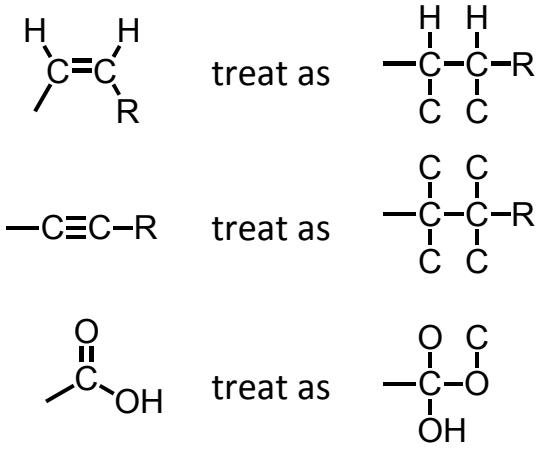
| substituent | 1st atom | 2nd atom | priority |
|---|---|---|---|
| OH | O | | 1 |
| $CO_2H$ | C | O | 2 |
| $CH_3$ | C | H | 3 |
| H | H | | 4 |

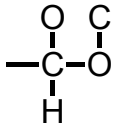

- Draw molecule with the lowest priority substituent (priority 4) at the rear.
- 1→2→3 is clockwise the stereochemical descriptor is *R.*
- 1→2→3 is anticlockwise the stereochemical descriptor is *S.*

## *Cahn-Ingold-Prelog Sequence Rules - continued*

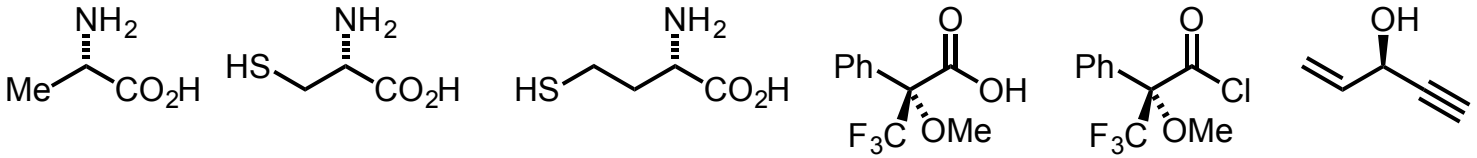

D-(+)-glyceraldehyde

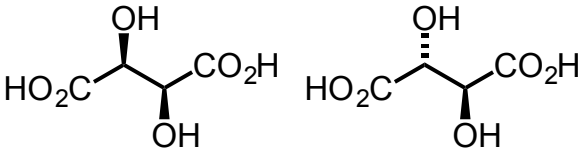
Treat double and triple bonds as multiple single bonds:




| substituent | treat as | 1st atom | 2nd atom | priority |
|---|---|---|---|---|
| OH | OH | O | H | 1 |
| CHO |  | C | O, O | 2 |
| $CH_2OH$ | $CH_2OH$ | C | O, H, H | 3 |
| H | H | H | | 4 |

## Assign *R* and *S* stereochemical descriptors to the following molecules.





see Vollhardt and Shore, *Organic Chemistry*

■ *Cahn-Ingold-Prelog Sequence Rules - continued*

The CIP rules can be extended to the assignment of double bond geometry.

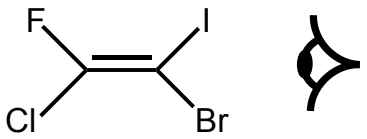
*Example*

Look at one end of the double bond and decide which substituent has higher priority.

Look at the other end of the double bond and decide which substituent has higher priority.

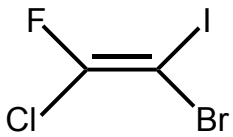
Double bond is (*Z*) if the the higher order substituents are on the same side of the double bond.

Double bond is (*E*) if the higher order substituents are on the opposite side of the double bond.

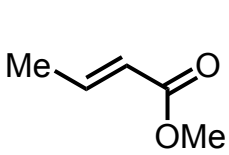


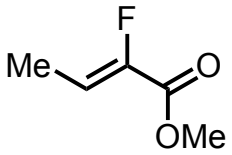

I > Br,
I has higher priority

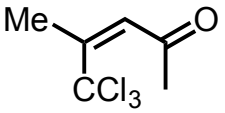
Cl > F,
Cl has higher priority



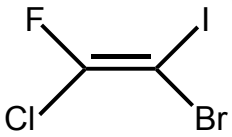

■ Assign (*E*) or (*Z*) to the following alkenes




higher priority

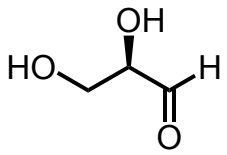



higher priority

double bond is (*E*)
(highest priority substituents are
on opposite side of the double bond)

- Absolute and relative configuration.

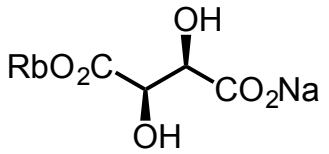
- Before 1951 we did not know the absolute configuration of any molecule i.e. we did not know what the actual 3-D arrangement of atoms was. For example we could not tell if (+)- tartaric acid was (*R, R*) or (*S*, *S*).
- Rosenhoff had arbitrarily assigned the absolute configuration of D-(+)-glyceraldehyde as (*R*).



D-(+)-glyceraldehyde

- Many compounds were assigned absolute configuration by tedious chemical degradation, if they were related to the assigned configuration of D-glyceraldehyde they were called D-compounds, regardless of the direction of optical rotation (if they were related to the enantiomer of D-glyceraldehyde they were called L-compounds).

- Now D and L only used for amino acids and sugars.



(+)-tartaric acid
sodium rubidium salt
(*R, R*)

- Most natural sugars are D.
- Natural amino acids are L.

- In 1951 **Johannes Martin Bijvoet** (1892-1980) used X-ray crystallography to assign the absolute configuration to sodium rubidium (+)-tartrate tetrahydrate – Rosenhoff had guessed correctly.

- Absolute and relative configuration can therefore be defined as follows:

If we know which enantiomeric series a molecule is in we know its absolute configuration.
If we only know its relative configuration we only know how the stereogenic centres within a molecule are related to one another.

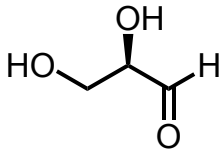
- To put it another way:

"When the stereochemistry drawn on a molecule means 'this diastereomer' we say we are representing **relative stereochemistry**; when it means 'this enantiomer of this diastereomer' we say we are representing its **absolute configuration**" *from Clayden, Greeves, Warren and Wothers.*

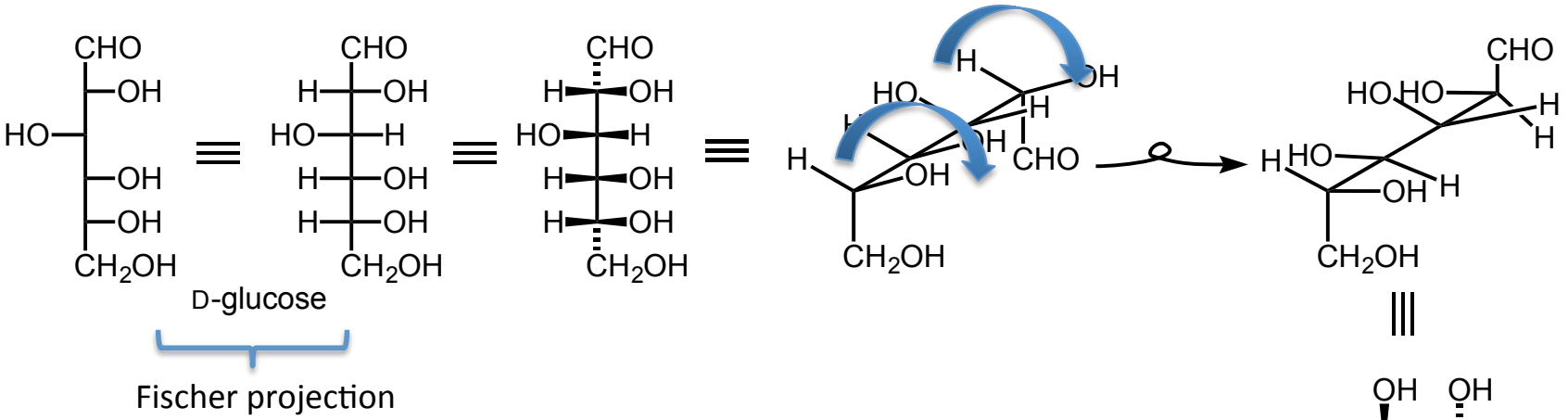
- Drawing molecules in 3D – various representations.

- There are numerous methods of drawing molecules to show the 3D arrangements of atoms and groups.

- The zig-zag method is convenient and has the major advantage that all $sp^3$-hybridised carbon atoms look tetrahedral.



- Fisher projections are an historic method of representing sugars and, occasionally, amino acids.

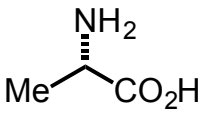



- To assign whether a sugar is D or L, draw in a Fischer projection with the most oxidised carbon at the top.

- If the OH is pointing to the right on the highest numbered stereogenic carbon then the sugar is D.

- If the OH is pointing to the left on the highest numbered stereogenic carbon then the sugar is L.

- Is (*S*)-alanine D or L?




- Is (*R, R*)-tartaric acid D or L?

- Historical aside and confusing nomenclature

D-glyceraldehyde is called D as it was dextrorotatory – that is it rotated the plane of plane polarised light in a clockwise direction.

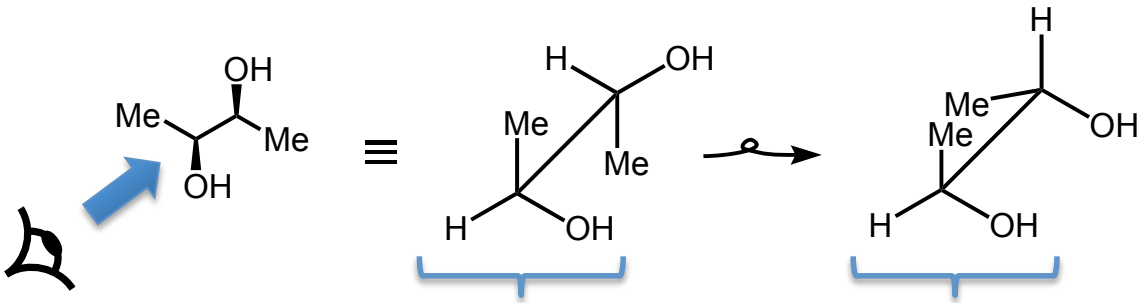
- Many compounds were then related to glyceraldehyde and classified as D or L.

- This 'D or L' had no relation to the sign of the optical rotation of the compounds just how its absolute configuration related to D-glyceraldehyde.

- Confusingly the letters '*d*' and '*l*' (lower case) were used to denote dextro and levorotatory and '*dl*' to denote a racemic mixture.

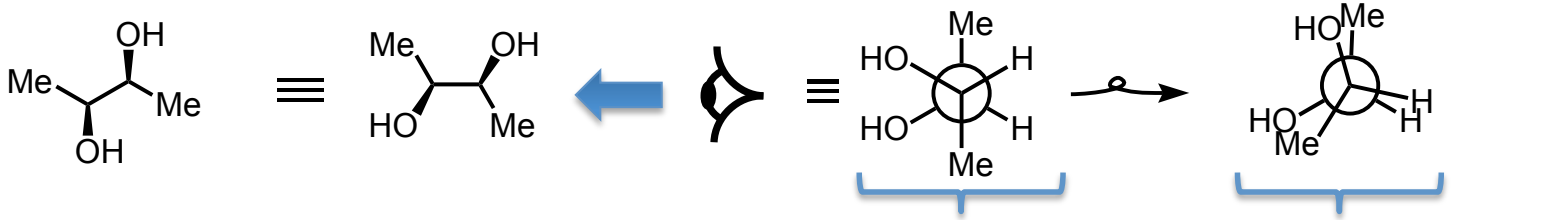
- The modern way of indicating dextro and levorotatory is to use (+) and (-) respectively and to use (±) to denote a racemic mixture.

- Sawhorse and Newman projections – frequently useful depictions when drawing curly arrow mechanisms.




sawhorse representation staggered conformation

sawhorse representation eclipsed conformation




Newman projection staggered conformation

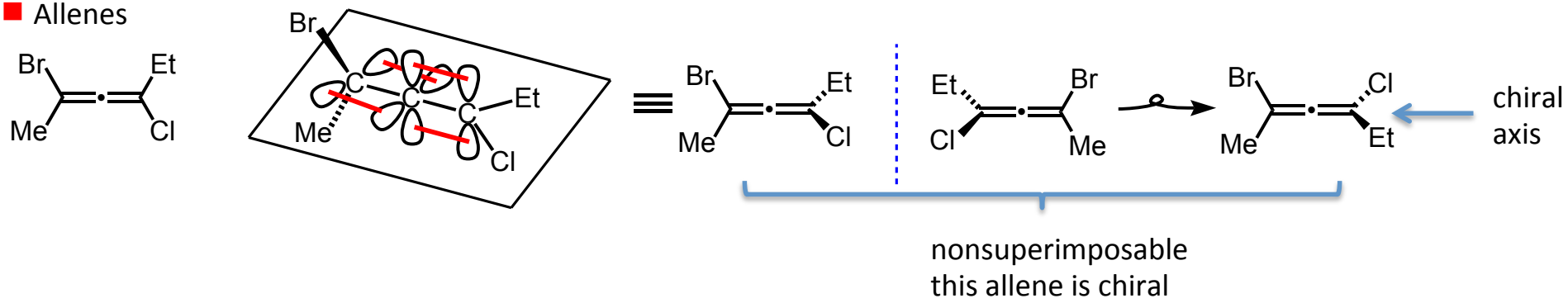
Newman projection eclipsed conformation

- So far we have mainly looked at 'central' chirality – we will now look at planar, axial and helical chirality.

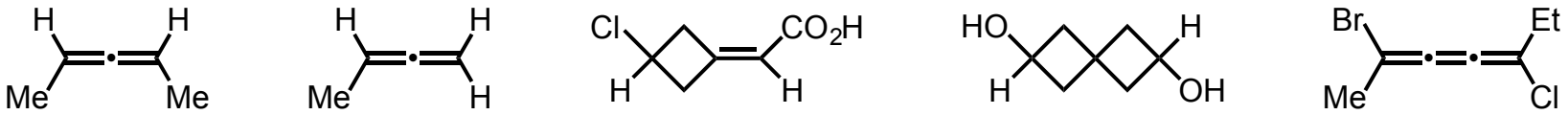
- Chirality is a molecular property (in fact a property of an object) so it is not necessary for a molecule to posses a stereocentre (chiral centre) in order to be chiral.

- The necessary and sufficient condition for a molecule to be chiral is that it is non-superimposable on its mirror image (i.e that it lacks an improper axis of rotation ($S_n$).

- Allenes



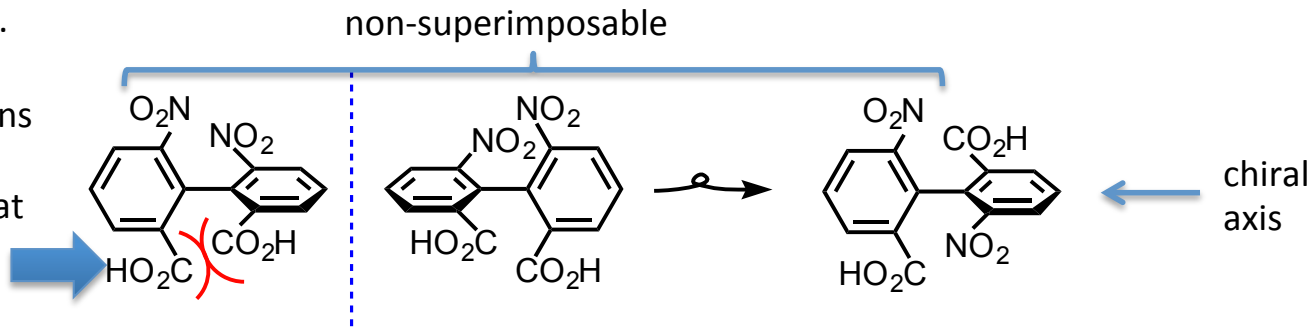

- Which of the following molecules are chiral?



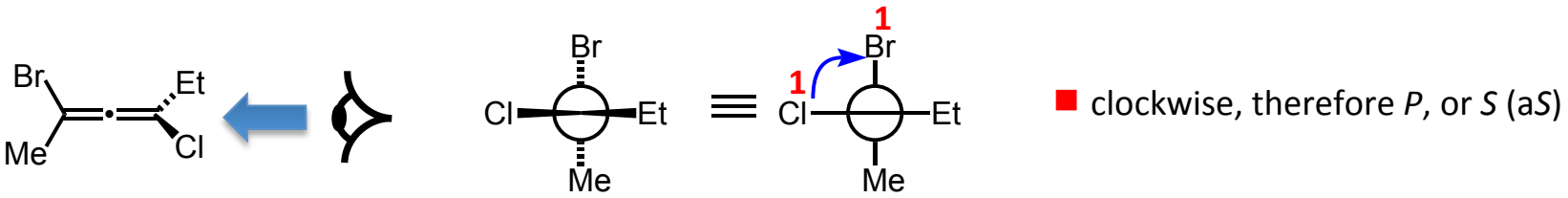
- Atropisomers and axial chirality – biphenyls
- Atropisomers may be defined as stereoisomers resulting from restricted rotation about single bonds.

The (arbitrary) definition of atropisomers is that they have a half of at least 1000s at a given temperature (>20 kcal•mol$^{-1}$) – the rotational barrier needs to be high enough that the separate isomeric species can be isolated.

severe steric hindrance means rotation around the central C-C single bond only occurs at high temperature and this compound can be resolved




- We can assign stereochemical descriptors to chiral allenes and biaryls.

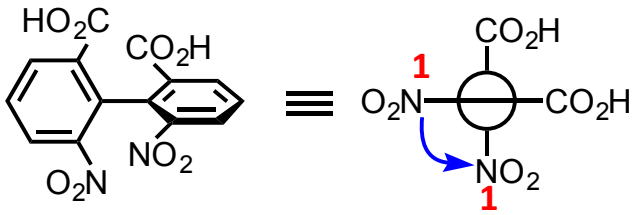



- clockwise, therefore *P*, or *S* (a*S*)

- Draw allene in Newman projection, assign CIP priority to the groups at the front and then the groups at the back.
- Consider only the highest ranked group at the front and at the back.
- When moving from the highest ranked group at the front to the highest ranked group at the back, if the motion is clockwise then the allene is *P* (plus), if anticlockwise the allene is *M* (minus).
- *P* corresponds to *S* (or a*S*), *M* corresponds to *R* (or a*R*).

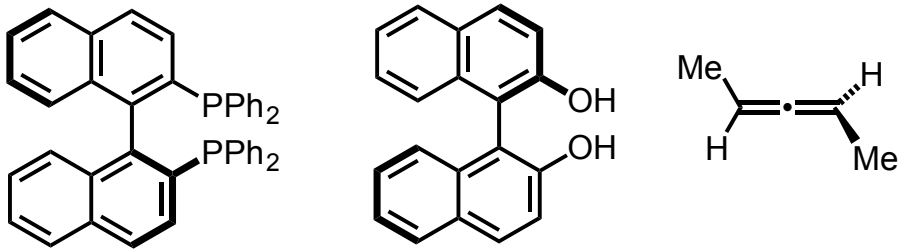
For a full desicussion of CIP rules see: V. Prelog, G. Helmchen, *Angew. Chem. Int. Ed.* **1982**, *21*, 567-583.

- The same assignment can be made with biaryls – we consider the substituents nearest the single bond first.

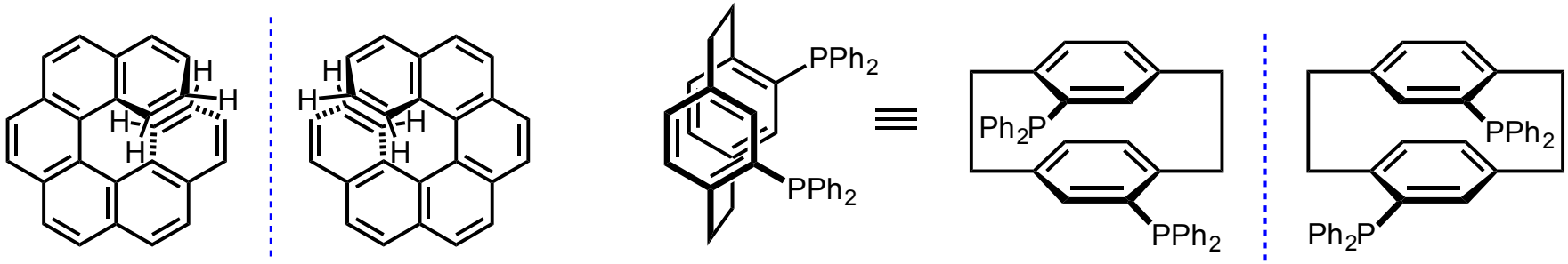



- Anticlockwise, therefore *M*, or *R* (a*R*).

- Assign stereochemical descriptors to the following molecules




- Helical and planar chirality are also important

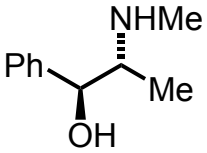



For a full desicussion of CIP rules see: V. Prelog, G. Helmchen, *Angew. Chem. Int. Ed.* **1982**, *21*, 567-583.

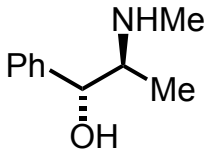
- Properties of enantiomers and diastereomers.
- NMR – single enantiomers have exactly the same properties in an *achiral* environment – i.e. an NMR tube.
- Enantiomers are basically the same compound in an *achiral* environment, same rate of reaction with achiral reagents, same retention time on silica etc. – makes then very difficult to separate from a racemic mixture.
- Diastereomers are different compounds, we should expect them to have different physical properties.

(*E*)-butene
mp = -105 °C
bp 1°C
$^{13}$C NMR 124.5, 17.0 ppm

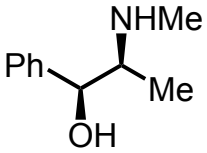
(*Z*)-butene
mp = -139 °C
bp 3.7 °C
$^{13}$C NMR 124.2, 11.4 ppm



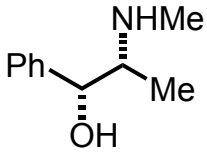

(1*S*, 2*R*)-ephedrine
mp 37-39 °C
$[\alpha]_D^{24}$ = +8.1, c = 3 in EtOH



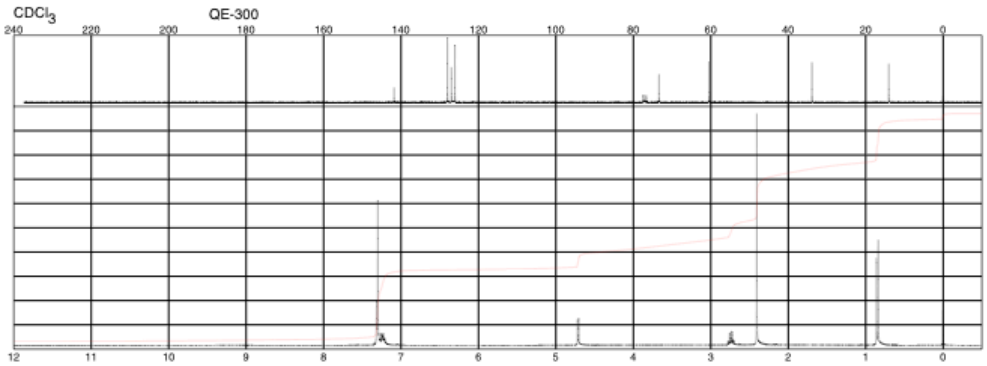

(1*R*, 2*S*)-ephedrine
mp 37-39 °C
$[\alpha]_D^{24}$ = -8.1, c = 3 in EtOH

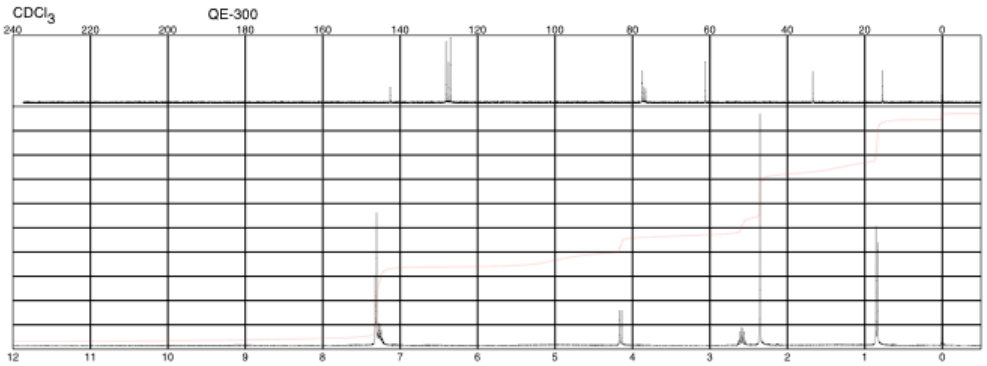



(1*S*, 2*S*)-pseudoephedrine
mp 118-120 °C
$[\alpha]_D^{20}$ = +52, c = 0.6 in EtOH




(1*R*, 2*R*)-pseudoephedrine
mp 118-120 °C
$[\alpha]_D^{20}$ = -51, c = 0.6 in EtOH

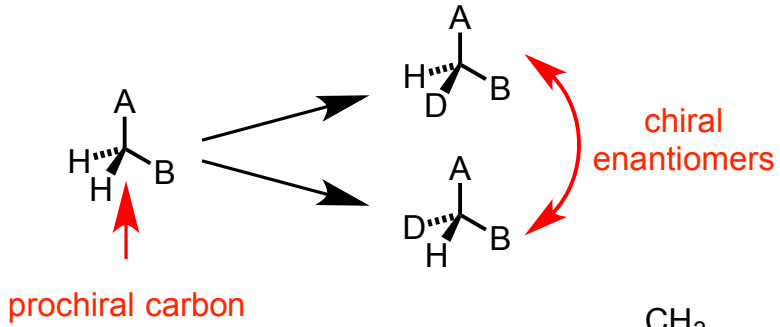


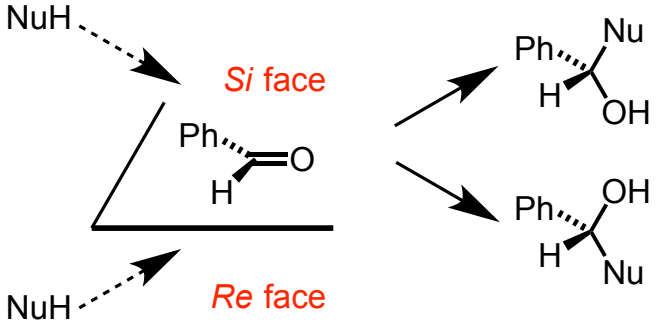

NMR spectra taken from Sigma-Aldrich website

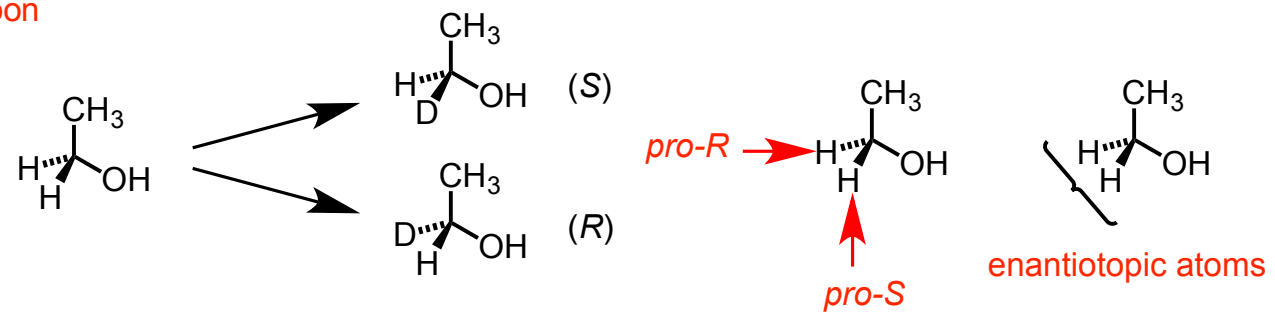
- **Prochirality** – has a several meanings – we will look at two of them.

- Prochiral groups

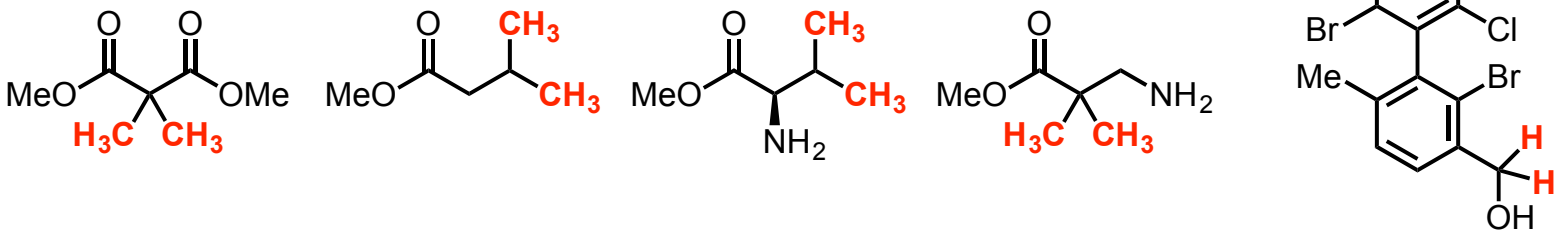



- Prochiral faces



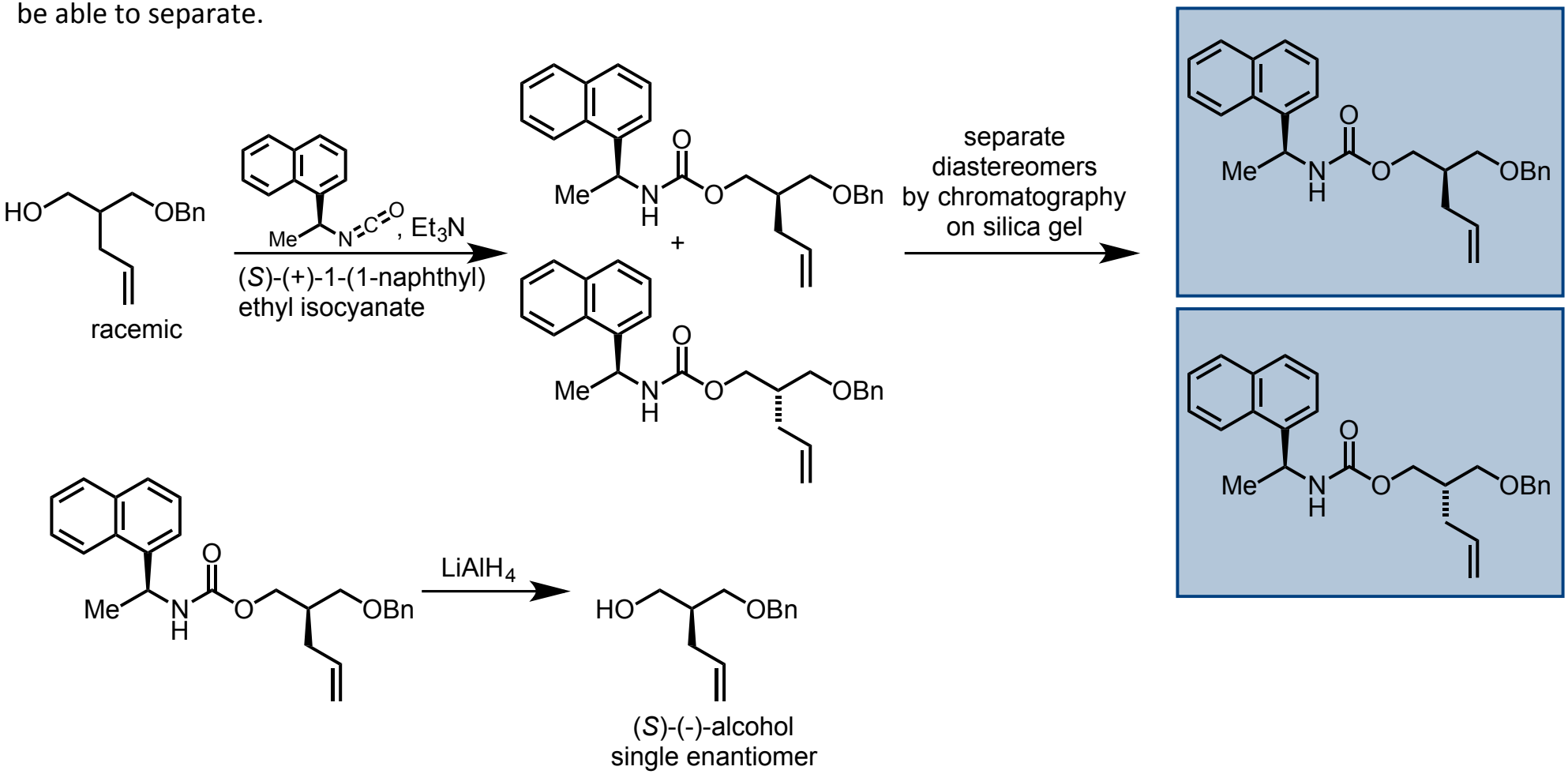




***Problem***: What is the relationship between the indicated groups in the following molecules (homotopic, enantiotopic etc.)?



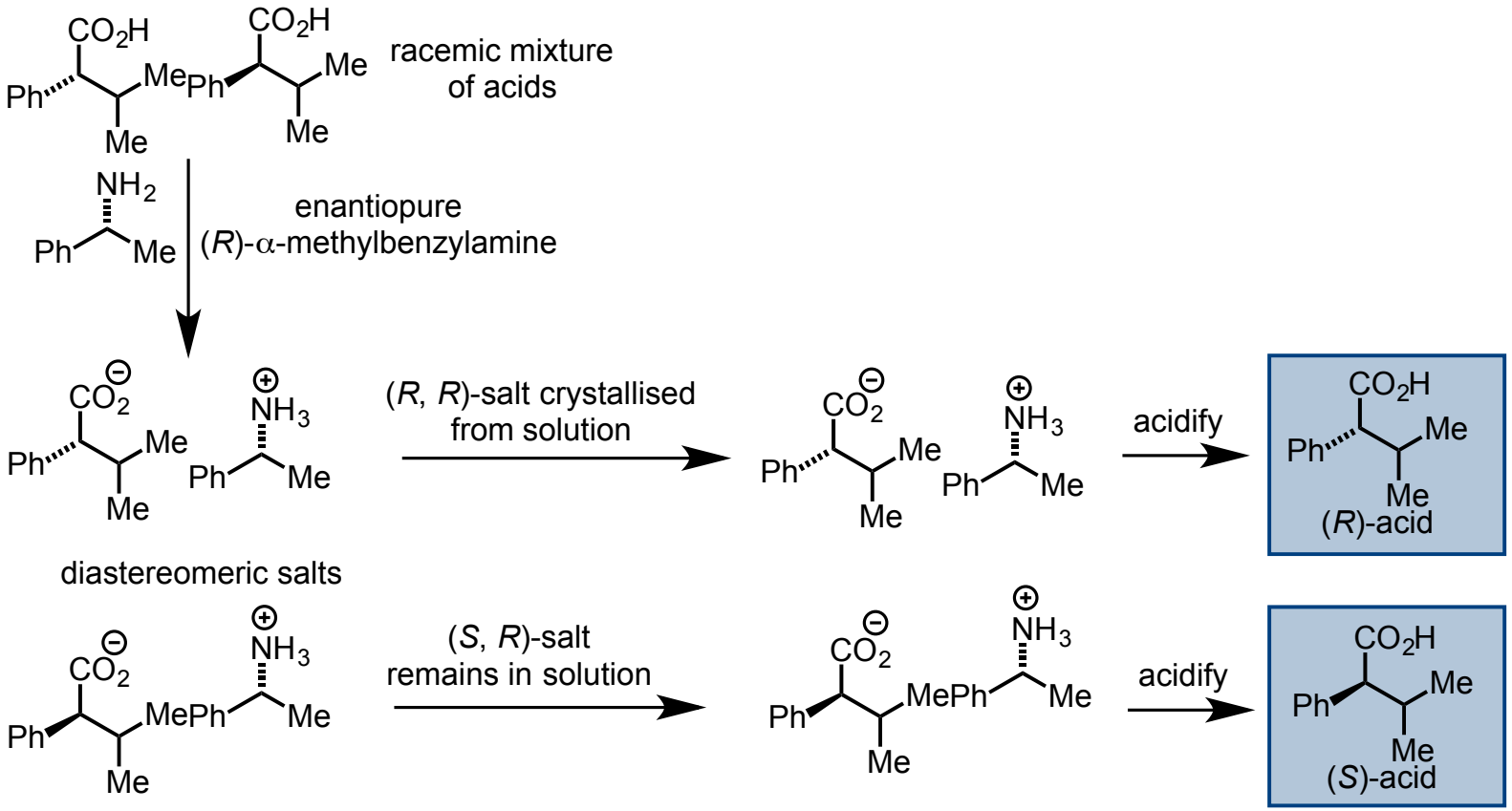

- We should always expect diastereotopic groups (frequently protons or methyl groups) to be at different chemical shift in the NMR spectrum – diastereotopic groups are fundamentally different.

- Separating diastereomers – diastereomers are different molecules, and have different physical properties, as seen with ephedrine and pseudoephedrine. We should therefore expect to be able to separate diastereomers by standard methods including: chromatography on silica, crystallisation, distillation etc.
- We can use this property of diastereomers indirectly in order to separate mixtures of enantiomers.
- A racemic mixture is a 1:1 mixture of enantiomers.
- If we react the racemic mixture with a single enantiomer of a reagent we will produce diastereomers which we should be able to separate.

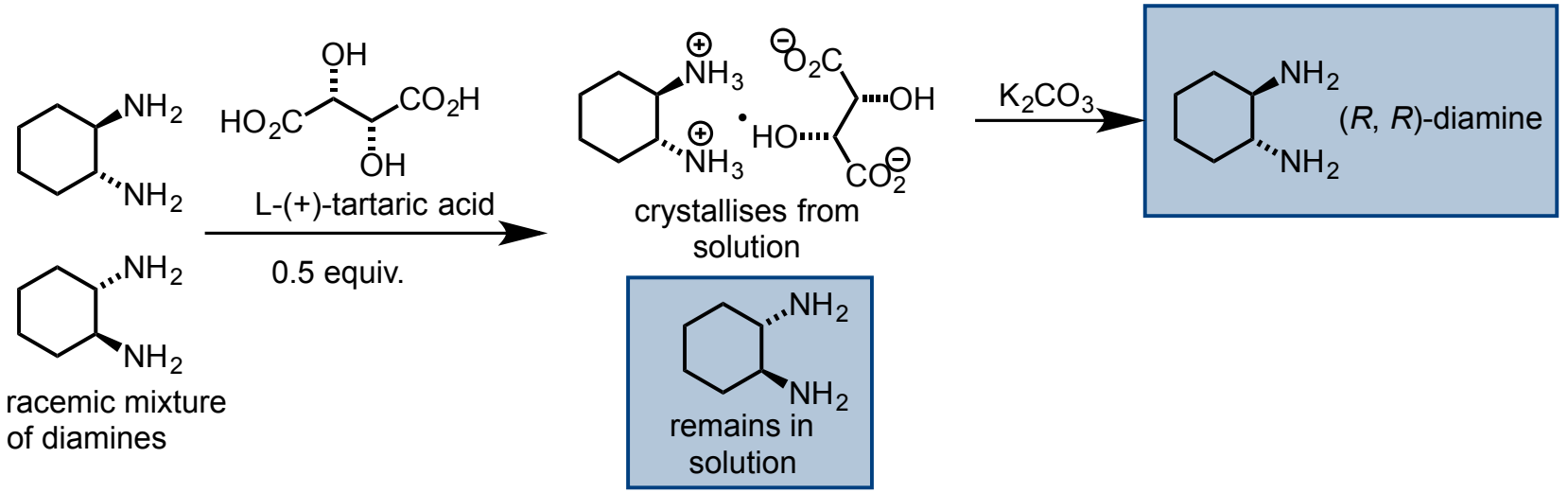



Fukuyama, C. L. J. Wang, Y. Kishi, *J. Am. Chem. Soc.* **1979**, *101*, 260-262.

- It can be much more efficient to do a resolution by selective crystallisation of diastereomeric salts.
- Diastereomeric salts, much like diastereomers, have different physical properties including melting points and solubility and hence selective crystallisation is frequently possible.



- It can be much more efficient to do a resolution by selective crystallisation of diastereomeric salts.




J. F. Farrow, E. N. Jacobsen, C. H. Senanayake, J. Liu, I. Shinikai, *Org. Synth.*, **1998**, *75*, 1.

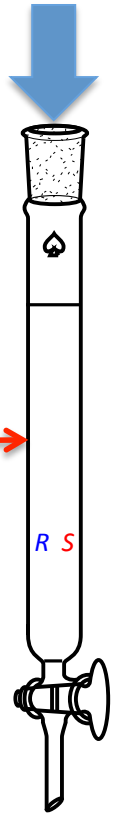
■ We can also separate a mixture of enantiomers by chromatography on a chiral (non-racemic) column – v. good method.

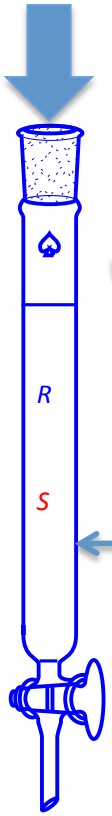
add mixture of (*S*, *S*) and (*R*, *S*) diastereomers to column with an achiral stationary phase e.g. $SiO_2$

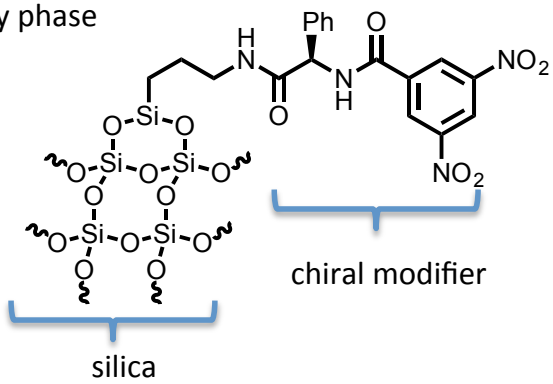
add mixture of (*R*) and (*S*) enantiomers to column with an achiral stationary phase e.g. $SiO_2$

add mixture of (*R*) and (*S*) enantiomers to chiral column – chiral stationary phase


column contains $SiO_2$ for example (achiral stationary phase)



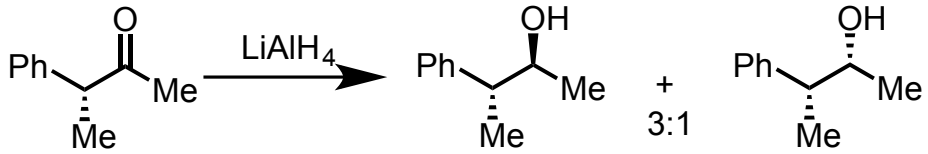

column contains $SiO_2$ modified with a chiral, non-racemic compound – chiral stationary phase

■ separation of diastereomers on silica gel (achiral stationary phase)
■ diastereomers have different affinity for stationary phase ($SiO_2$) and flow through column at different rates resulting in separation - (*S*, *S*) and (*R*, *S*) elute separately

■ separation of enantiomers not possible on silica gel (achiral stationary phase)
■ enantiomers have the same affinity for stationary phase ($SiO_2$) and flow through column at same rates, no separation results - (*R*) and (*S*) elute together

■ separation of enantiomers using a chiral stationary phase
■ the enantiomers flowing down the chiral column have diastereomeric interactions with the chiral stationary phase and hence flow through the column at different rates - (*R*) and (*S*) elute separately

- Given that diastereomers are different, NMR methods will probably tell us if we have a pure compound.
- Imagine you did the following reaction beginning with enantiopure starting material.
- You wish to accurately measure the ratio of diastereomers produced (the diastereomeric ratio d.r.) what do you do?
- What do you do if the crude reaction mixture is crystalline or partly crystalline?

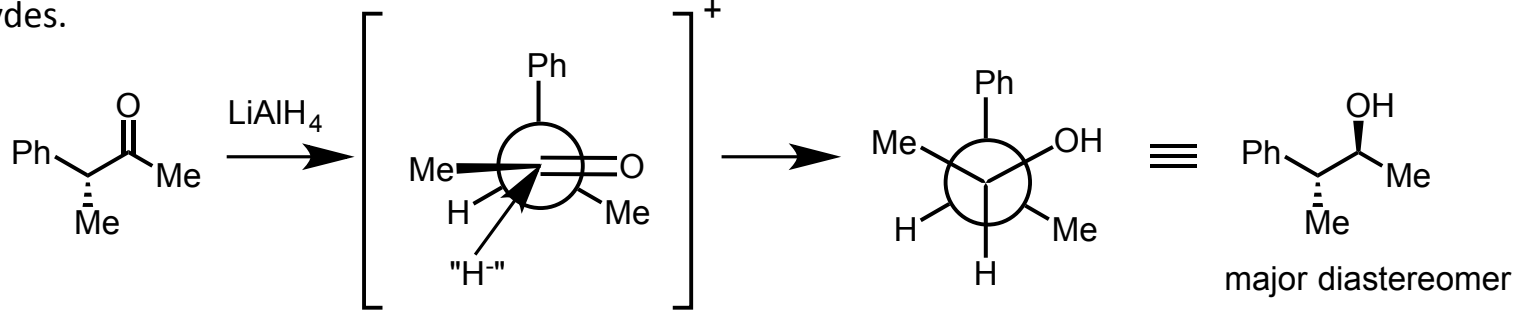



- The way you sample your reaction / product is incredibly important – it is very important to take a representative sample if you are trying to measure ratios of diastereomers (or enantiomers).

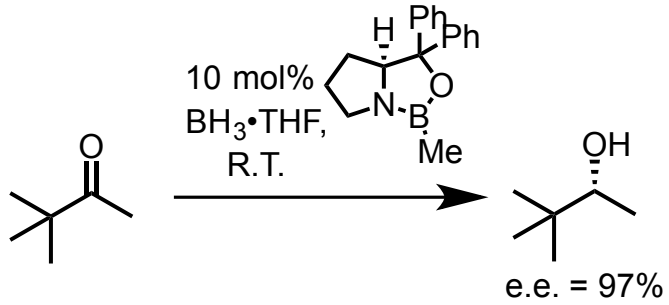
- Let's say you have done the above reaction, measured the d.r. and then separated the diastereomers by chromatography – how would you find out which diastereomer is which?

- If the samples were crystalline, X-ray crystallography would give a definitive result.
It might be possible to assign the configuration of the above diastereomers by NMR methods – in the above case this would likely be difficult and also might be ambiguous.

- It might be possible to predict which is the major diastereomer based on models for addition of nucleophiles to α-chiral aldehydes.



- Even more challenging – you do a catalytic asymmetric reaction which gives the product in high yield and high enantiomeric excess (e.e.).




$$\text{e.e.} = \frac{[R] - [S]}{[R] + [S]} \times 100$$

- You can measure the enantiomeric excess by chiral HPLC but you must run the HPLC of the racemic material so you know the retention times of both enantiomers and that they are indeed separable on the chiral column.

- You cannot measure the enantiomeric excess by NMR as the enantiomers have the same NMR.

- How do you know which is the major enantiomer you have?

- If you turn your enantiomers into diastereomers then you should be able to determine the diastereomeric ratio, and hence the enantiomeric excess by NMR – you may also be able to assign the absolute configuration of the product.

- A useful method for determining the enantiomeric excess of a secondary alcohol by NMR is to use Mosher's esters.

- Mosher's esters can also be used to assign the absolute configuration of a chiral secondary alcohol.

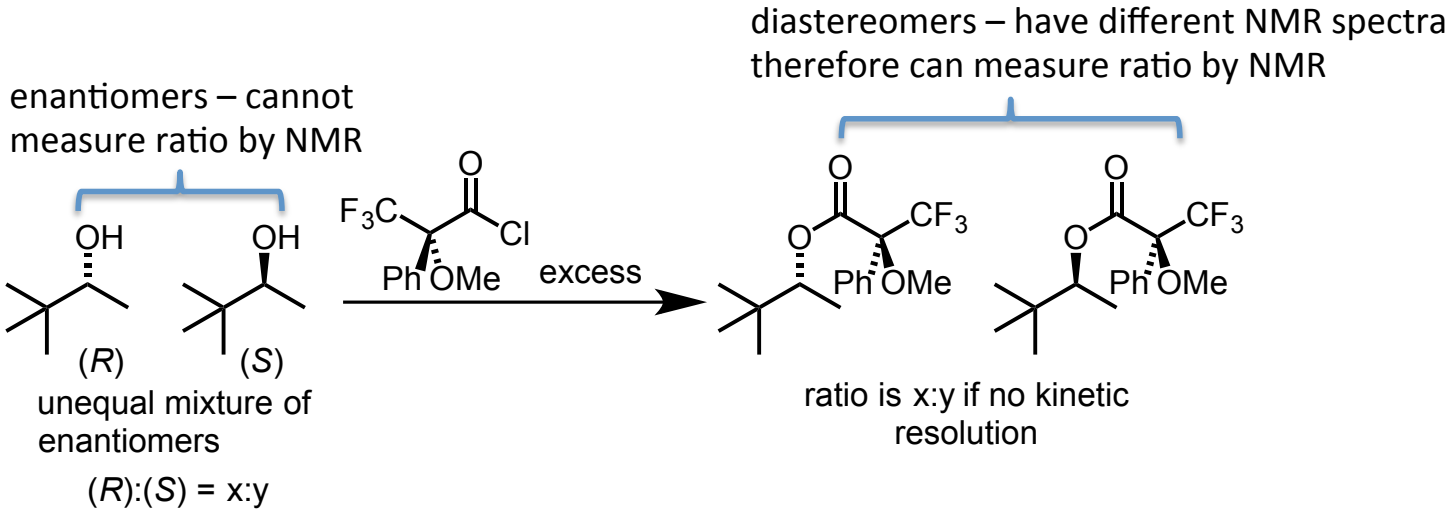
- The Mosher's acids and acid chlorides are commercially available


J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543-2549.

- Important properties of a chiral derivatising reagent are as follows:

i) The chemistry involved does not cause racemisation of the chiral centres in the substrate/product or in the reagent

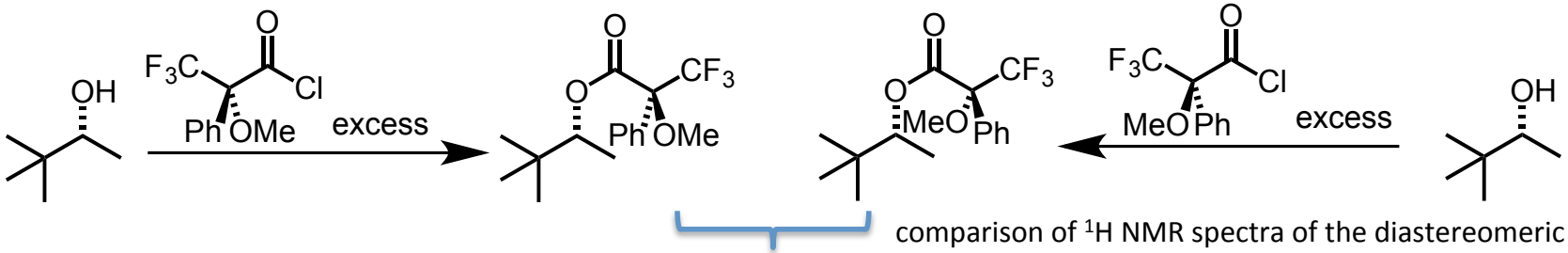
ii) Reaction of the derivatising reagent is quantitative with both enantiomers of the substrate – if this is not the case kinetic resolution can occur leading to incorrect reporting of dr and ee




- If there has been no kinetic resolution, the ratio of diastereomers measured by NMR corresponds to the ratio of enantiomers of the chiral secondary alcohol.

- Additionally, the absolute configuration of a chiral secondary alcohol can be determined by derivatising the secondary alcohol separately with both enantiomers of the Mosher's acid or acid chloride followed by careful NMR analysis see:

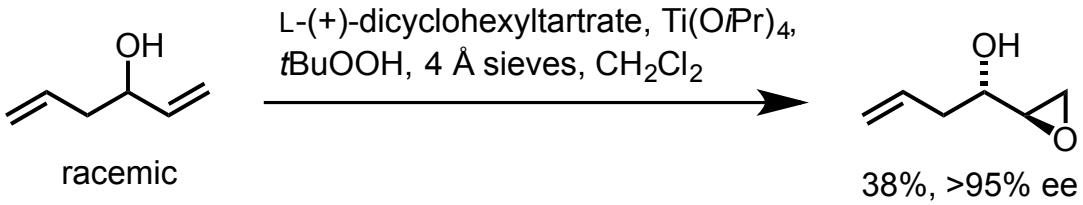
I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.




J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543-2549.

- Example of assignment of the absolute configuration of a secondary alcohol:

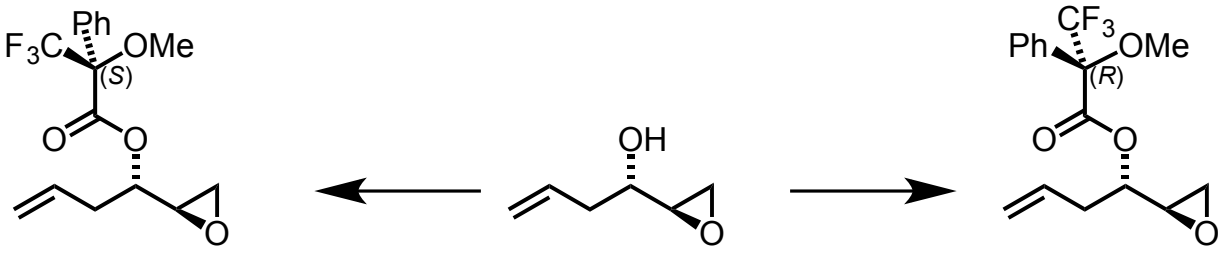
I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.

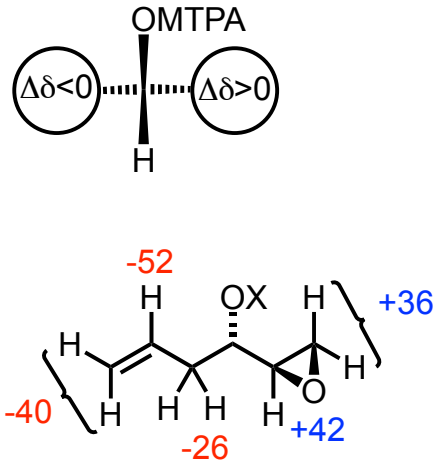



- Sharpless oxidative kinetic resolution of the racemic allylic alcohol above gives the epoxide in high enantiomeric excess. The absolute configuration of the epoxy alcohol can be assigned as follows:
- Derivatise alcohol separately with both enantiomers of the Mosher acids / acid chlorides
- The differences in $^1$H NMR chemical shifts of the protons either side of the ester group are determined with

$\Delta\delta = \delta_{S\ ester} - \delta_{R\ ester}$

- The MTPA ester is drawn as shown with positive values of Δδ on the RHS and the negative values are on the LHS which gives the absolute configuration shown



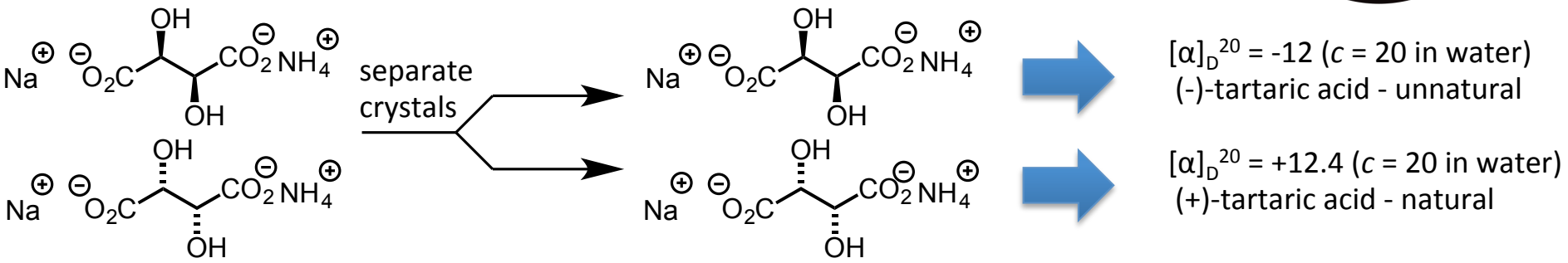

Δδ values in Hz

- Recap – the main methods for determining the absolute configuration of a compound are as follows:

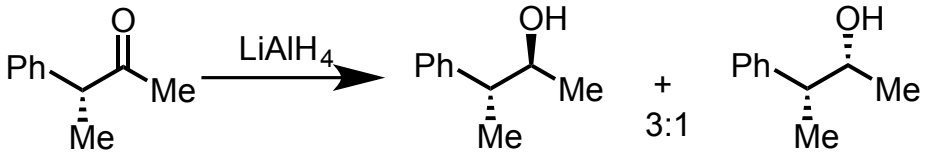
i) X-ray crystallography of the compound – generally requires presence of an atom heavier than silicon
ii) Compare optical rotation with literature data – requires optical rotation to be measured under near identical conditions to that reported in the literature
iii) Derivatise compound with a reagent containing a heavy atom and use X-ray crystallography
iv) Derivatise compound with a reagent of known absolute configuration – may now be possible now to assign absolute configuration by NMR or X-ray crystallography

- Racemates and single enantiomers.
- A racemate is a 1:1 mixture of enantiomers.
- If a racemate crystallises it can either crystallise so that each crystal contains both enantiomers (a racemic crystal) or such that each crystal is either (*R*) or (*S*) – this is termed a conglomerate and approximately 5-10% of chiral crystalline materials crystallise in this manner.

- Sodium ammonium tartrate crystallises as a conglomerate, which allowed Pasteur to separate the enantiomeric crystals by hand.

- If you do a reaction which gives you an excess of one diastereomer then it is possible to do a crystallisation which either increases the proportion of the major diastereomer, and leaves the minor diastereomer in solution or *vice versa* due to the different solubilities of the diastereomers – hence the importance of correct sampling noted previously.




- If you do a reaction which gives you an excess of one enantiomer then it is possible to do a crystallisation which either: increases the proportion of the major enantiomer in the solid, or increases the proportion of the major enantiomer in the mother liquors – the same is true for the minor enantiomer.

- Again this highlights importance of proper sampling.

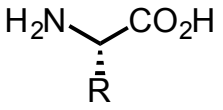
- Take home message – crystallisation can help to purify compounds and may well change the enantiomer composition – but not necessarily in your favour!

■ Generation of chirality – the chiral pool

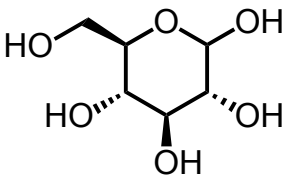
As stated previously *no* optically active material can be generated if all the staring material, reagents and conditions are either *achiral* or *racemic* i.e. optically inactive. Stated another way, if a *chiral* compound is synthesised from *achiral* or *racemic* reactants, reagents, and catalysts, then it will be formed as a *racemate.*

Ultimately to generate *non-racemic* material (material which is optically active) it is necessary to utilise molecules from the *chiral pool* i.e. from the vast array of *enantiopure* and *enantioenriched* molecules which occur in Nature. This may mean that one directly uses a substance from the *chiral pool* as a reagent, or maybe the substance is used as a catalyst to make a *non-racemic* reagent which is subsequently used for a different transformation. However, somewhere along the way a molecule from the *chiral pool* will have been utilised.

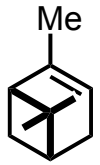
**The Chiral Pool** Amino acids Sugars Terpenes Hydroxy acids etc.



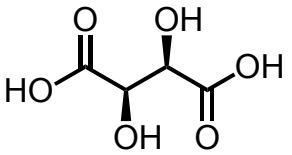

α-amino acids




D-hexoses



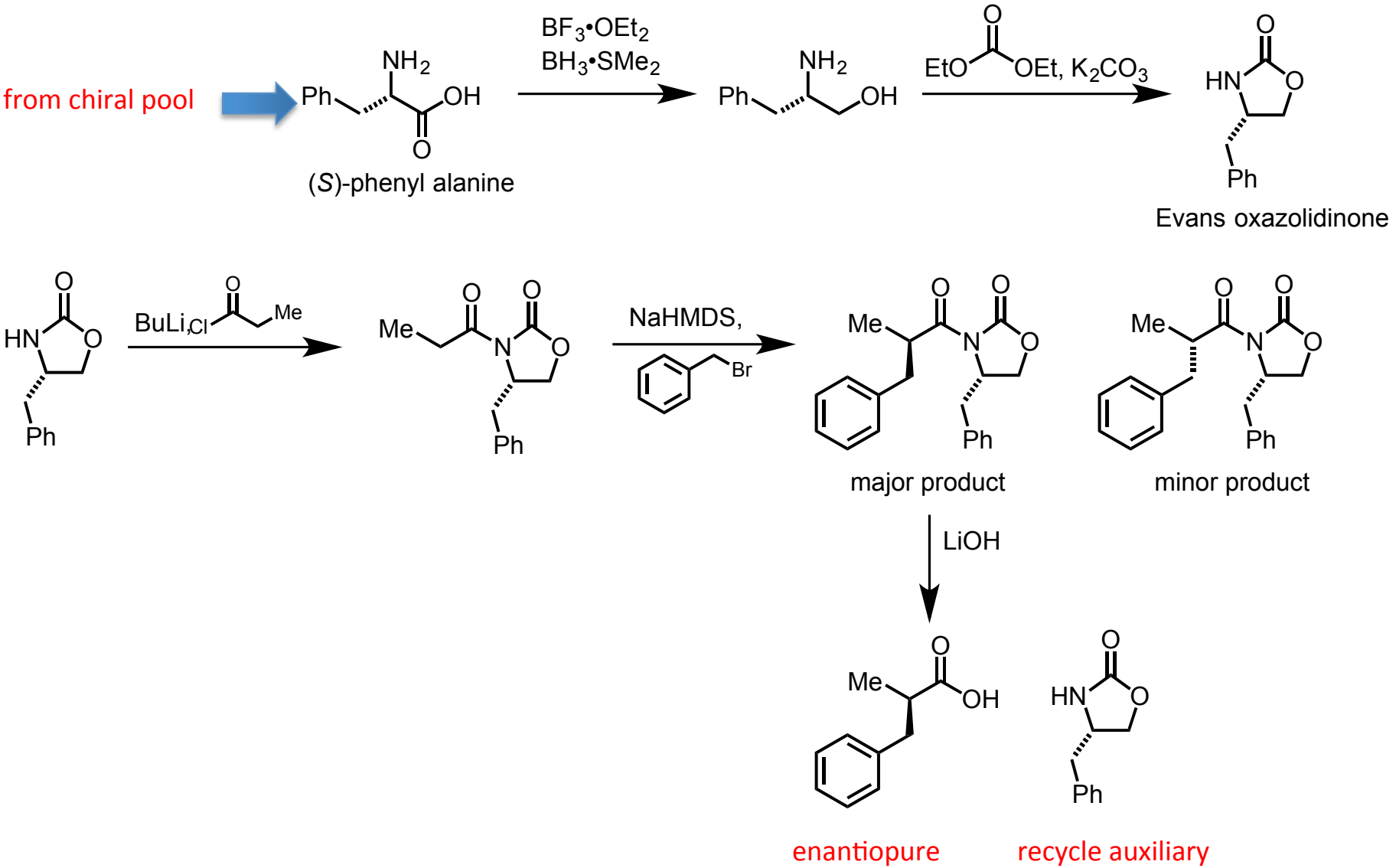

α-pinene (terpene)




tartaric acid

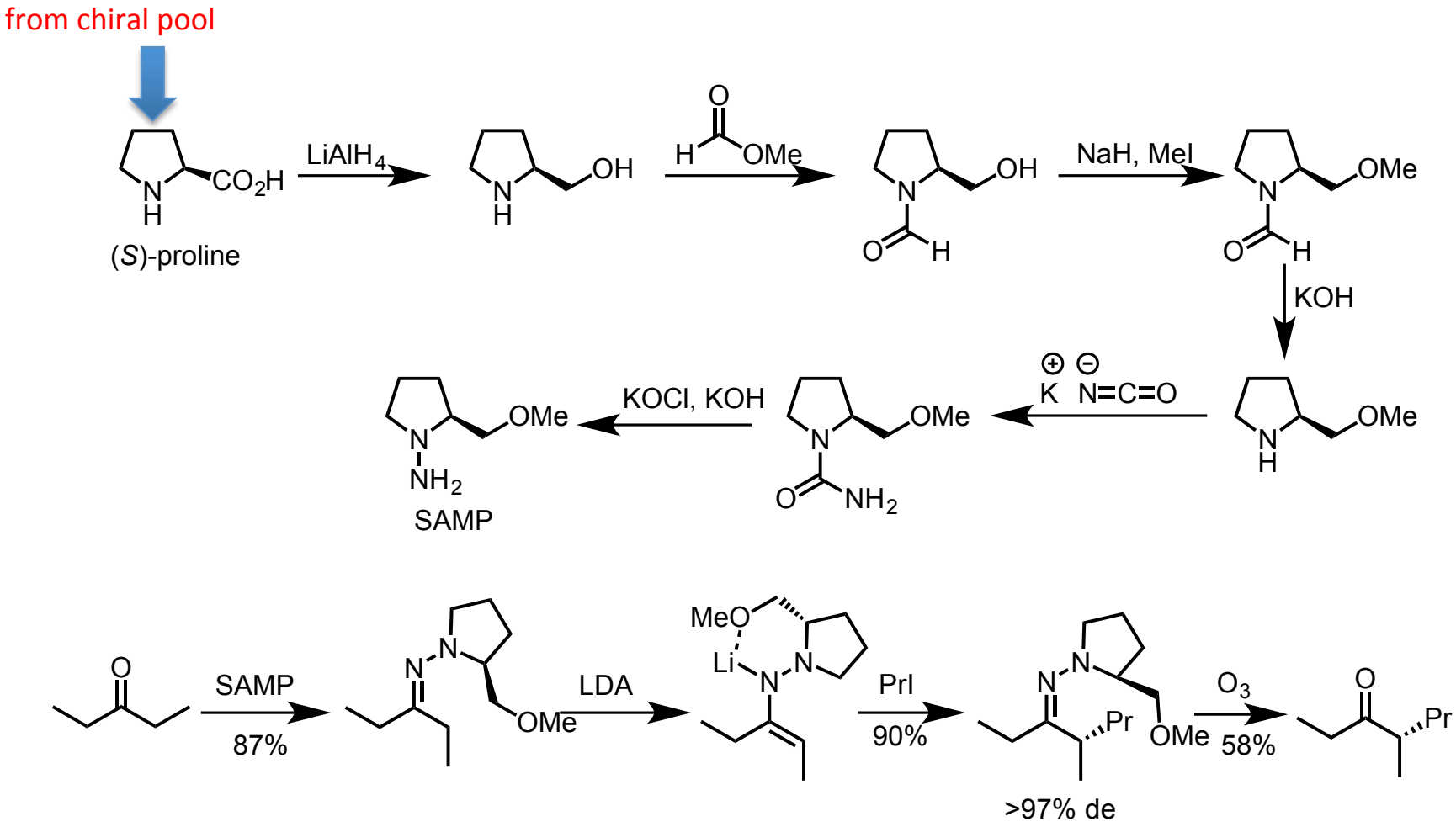
- Synthesis of chiral auxiliaries using chiral pool starting materials

- Evans oxazolidinone – very useful for asymmetric enolate alkylation and aldol reactions: J. R. Gage, D. A. Evans, P. G. Meister, L. A. Paquette, *Org. Synth.*, **1990**, *68*, 77.



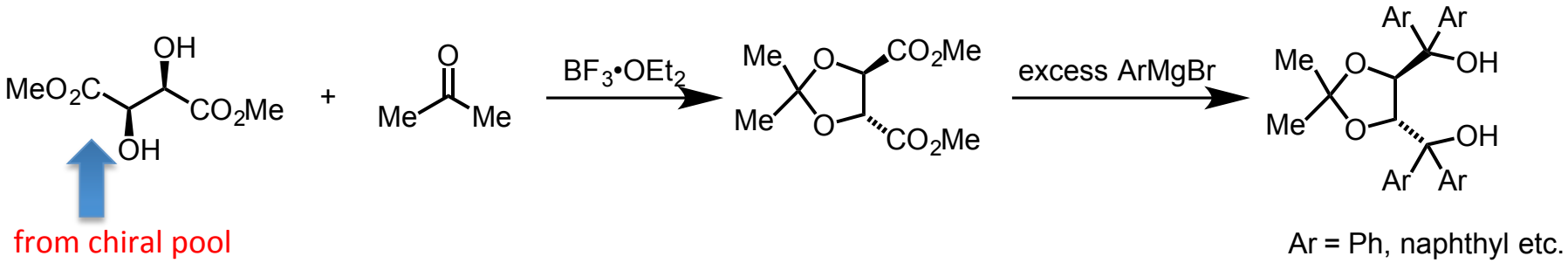
- Synthesis of chiral auxiliaries using chiral pool starting materials

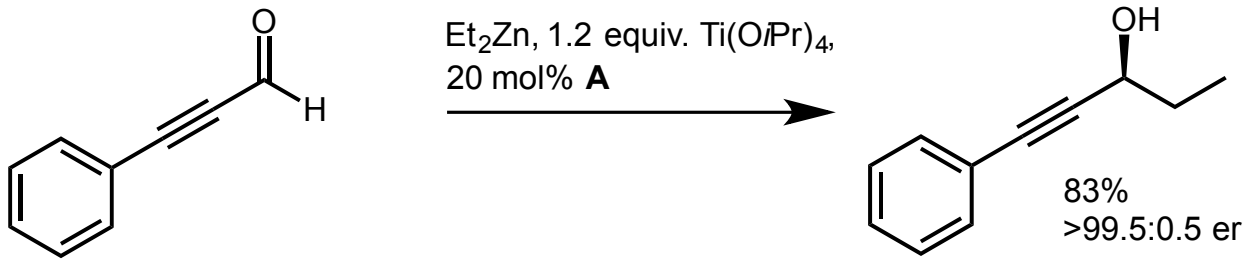
- SAMP and RAMP – chiral auxiliaries for the enolate alkylation of aldehydes and ketones: D. Enders, P. Fey, H. Kipphardt, A. Yanagisawa, R. Noyori, *Org. Synth*, **1987**, *65*, 173.

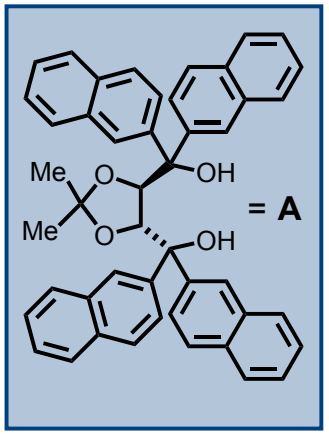


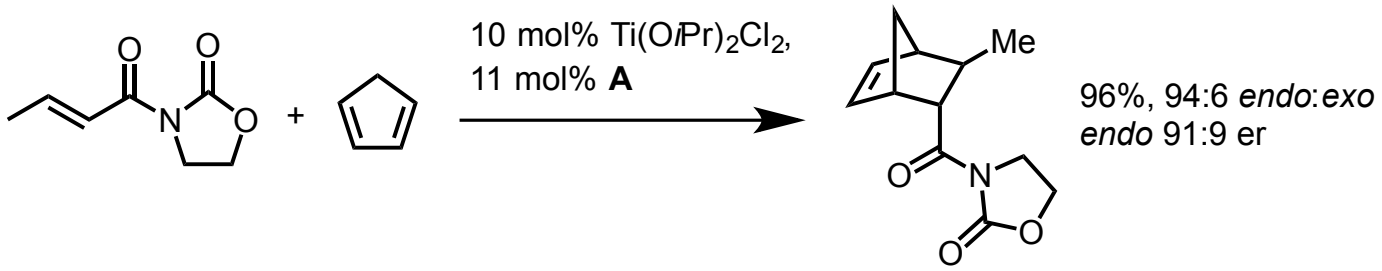
- Synthesis of chiral catalysts using the chiral pool – e.g. TADDOL - α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol
- TADDOLs are useful reagents and catalysts for a large number of asymmetric transformations.

For a review see: D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem. Int. Ed.* **2001**, *40*, 92-138.
A. K. Beck, P. Gysi, L. La Vecchia, D. Seebach, C. E. Bennett, W. R. Roush, *Org. Synth*. **1999**, *76*, 12.

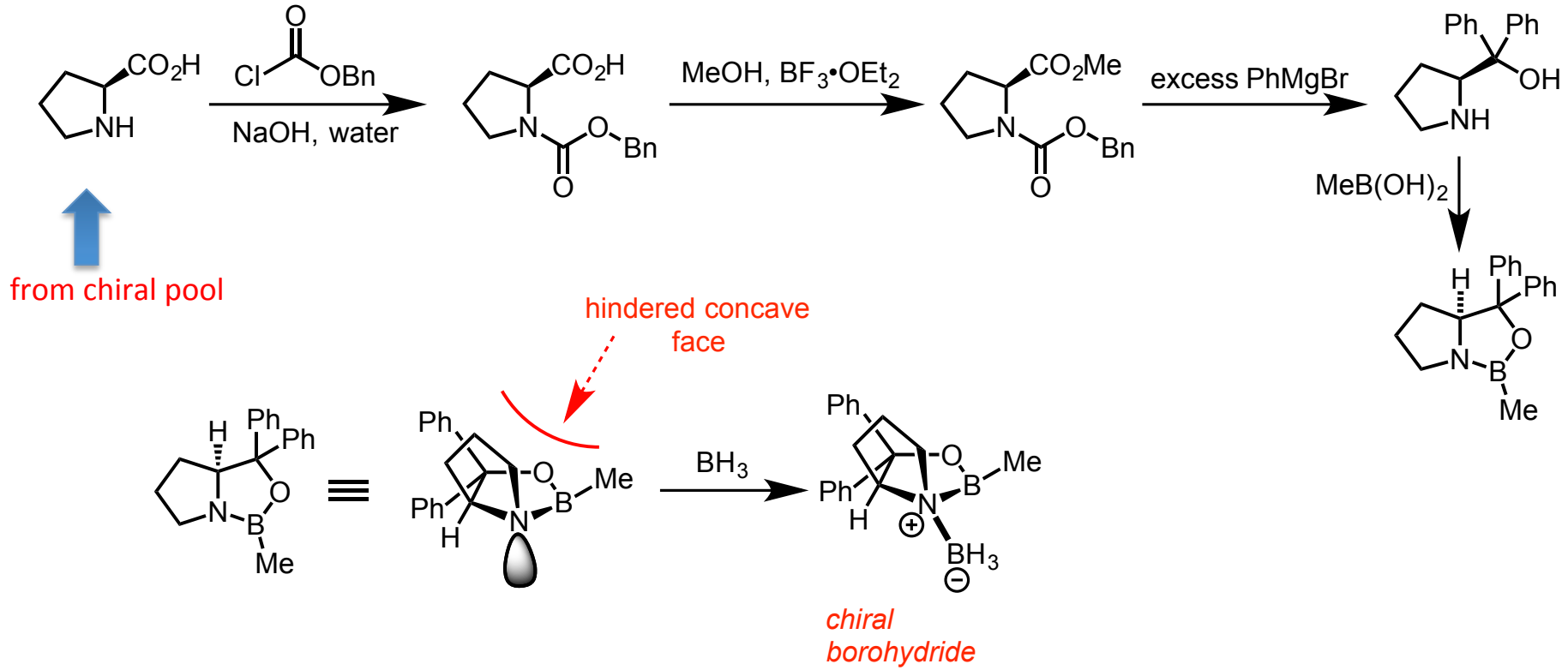


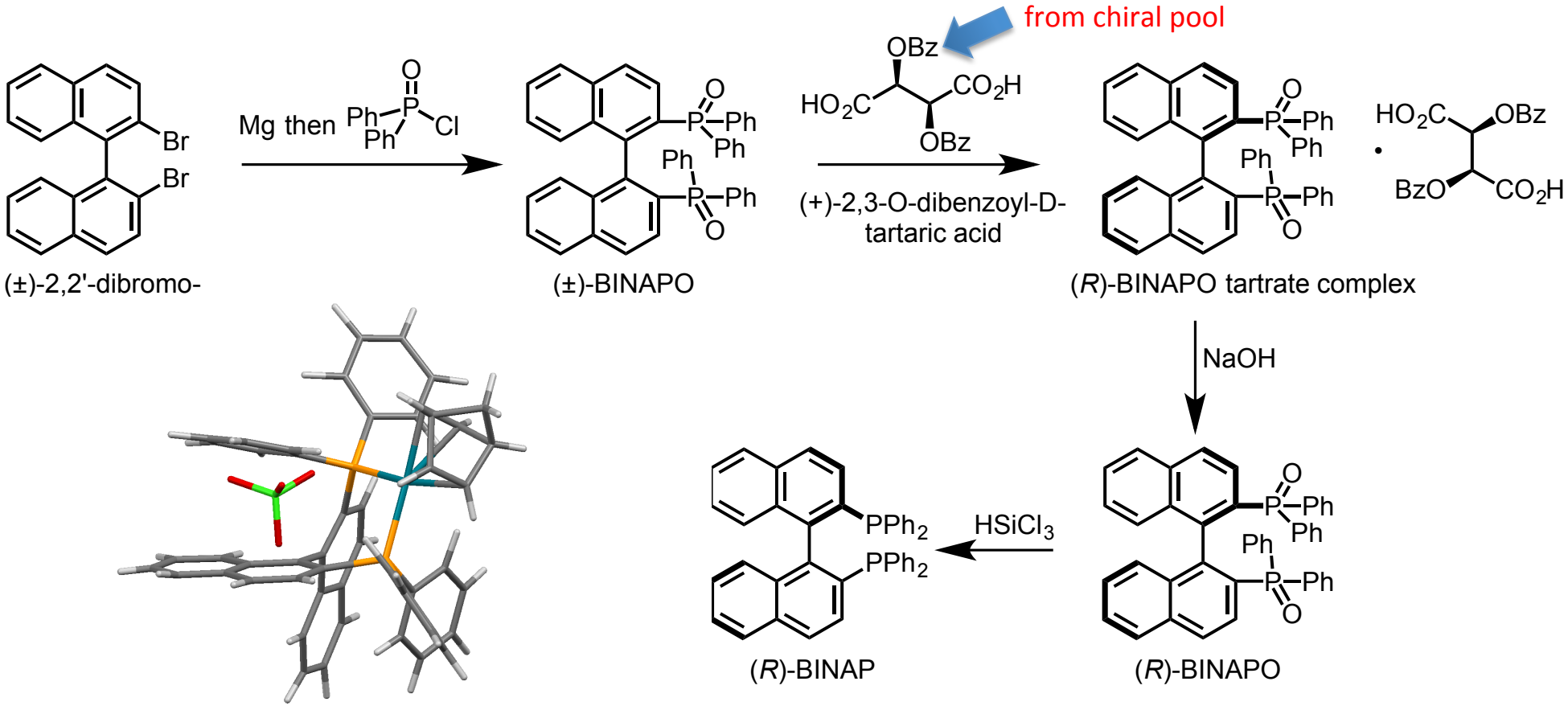



■ Synthesis of chiral catalysts using the chiral pool – the CBS reduction - E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861-2863.; E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926.



- Synthesis of enantiopure (*R*) and (*S*)-BINAP – H. Takaya, S. Akutagawa, R. Noyori, M, Cereghetti, A. Rageot, M. Vecchi, G. Saucy, *Org. Synth*, **1989**, *67*, 20. BINAP is an excellent chiral ligand for numerous catalytic asymmetric reactions.




- (*R*)-BINAPO tartrate complex crystallises from solution; (*S*)-BINAPO remains in mother liquors
- (*S*)-BINAPO recovered from mother liquors can be crystallised with (-)-2,3-dibenzoyl-L-tartaric acids to very high ee
- Absolute configuration (*R*)-BINAP determined by X-ray cystallography of the Rh(I) norbornadiene perchlorate salt:
Toriumi, K.; Ito, T.; Takaya, H.; Souchi, T.; Noyori, R. *Acta Crystallogr., Sect. B* **1982**, *B38*, 807–812.