Introduction to Stereoselective Organic Synthesis

- 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

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Introduction to Stereochemistry – Quick Revision

- 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
**Stereoisomers**

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

- Stereoisomers are not the same — as they cannot be superimposed.

- Not stereoisomers — different connectivity related as constitutional isomers (structural isomers).

  - Superimposable.
Introduction to Stereoselective Organic Synthesis

Stereoisomers

These two stereoisomers are related as object and mirror image.

Stereoisomers which are related as non-superimposable object and mirror image are termed enantiomers – mirror-image stereo).

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.”

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.

![Chemical structures of phosphines, sulfoxide, phosphine oxide, and 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.

![Chemical structure of 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 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.

\[ (+-\text{thalidomide}, [\alpha]_{D}^{21} = +63 (c \ 2.03, \text{DMF}) \]

sedative, hypnotic, stops morning sickness

\[ (-\text{thalidomide}, [\alpha]_{D}^{21} = +63 (c \ 2.03, \text{DMF}) \]

teratogen, foetal damage, congenital malformation

\[ (+-\text{limonene} \] oranges

\[ (--\text{limonene} \] lemons

\[ (-\text{carvone} \] spearmint

\[ (+\text{-carvone} \] caraway and dill

\[ (\text{S}(-)\text{-nicotine} \] 

\[ \text{L-DOPA} \]
Optical rotation.

Schematic of a polarimeter.

Specific rotation: $[\alpha]_D^T = \alpha / c \times l$

- $\alpha$ = observed rotation
- $D$ = wavelength of sodium “D” line – 589 nm
- $c$ = concentration of solution in g cm$^{-1}$
- $l$ = length of cell in dm (usually 1 dm)
- $T$ = temperature in °C

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 starting 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 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 least 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

**Isomers**: compounds with the same molecular formula

**Constitutional isomers** (structural isomers): same molecular formula, different connectivity

**Stereoisomers**: Same molecular formula, same connectivity, different disposition of atoms in space

**Enantiomers**: Stereoisomers related as non-superimposable object and mirror image

**Diastereomers**: All stereoisomers not related as enantiomers
**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.

<table>
<thead>
<tr>
<th>substituent</th>
<th>1st atom</th>
<th>2nd atom</th>
<th>priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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*. 

[Diagram of molecules with substituents and stereochemistry notation]
- **Cahn-Ingold-Prelog Sequence Rules - continued**

Treat double and triple bonds as multiple single bonds:

<table>
<thead>
<tr>
<th>substituent</th>
<th>treat as</th>
<th>1st atom</th>
<th>2nd atom</th>
<th>priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>OH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>C-O</td>
<td>C-O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₂OH</td>
<td>CH₂OH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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 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.

Assign (E) or (Z) to the following alkenes:
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 $(R)$.

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.

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 sp³-hybridised carbon atoms look tetrahedral.

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

Fischer projection

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
- Newman projection
  - Staggered conformation
  - 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 possess 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.

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 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.

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 \( aS \)), \( M \) corresponds to \( R \) (or \( aR \)).

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

\[
\begin{align*}
&\text{HO}_2\text{C} & \text{CO}_2\text{H} \\
&\text{O}_2\text{N} & \text{CO}_2\text{H} \\
&\text{NO}_2 & \text{NO}_2
\end{align*}
\]

- Anticlockwise, therefore \( M \), or \( R \) (\( aR \)).

Assign stereochemical descriptors to the following molecules:

- Helical and planar chirality are also important.

Introduction to Stereoselective Organic Synthesis


- Slow rotation around single bonds in amides is a well-known phenomenon in organic chemistry.

- The temperature dependence of the $^1$H NMR of dimethyl formamide is a classic example.

- As can be seen in the above example, rotation around the amide C-N is restricted.

- This is a form of atropisomerism which can have implications in drug design and synthesis.
Atropisomerism in Drug Discovery

- Atropisomerism in Drug Discovery

\[ \text{Cl} \quad \text{fast rotation} \quad t_{1/2} = 1.6 \text{ min (37 °C)} \]

enantiomers


Stereogenic N-CO bond

Stereogenic Ar-CO axis

Actually exists as mixture of four separable diastereomeric atropisomers

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.

\[
\begin{align*}
\text{(E)-butene} & \quad \text{mp} = -105 \, ^\circ \text{C} \\
& \quad \text{bp} 1\, ^\circ \text{C} \\
& \quad ^{13}\text{C NMR 124.5, 17.0 ppm}
\end{align*}
\]

\[
\begin{align*}
\text{(Z)-butene} & \quad \text{mp} = -139 \, ^\circ \text{C} \\
& \quad \text{bp 3.7} \, ^\circ \text{C} \\
& \quad ^{13}\text{C NMR 124.2, 11.4 ppm}
\end{align*}
\]

\[
\begin{align*}
\text{(1S, 2R)-ephedrine} & \quad \text{mp 37-39} \, ^\circ \text{C} \\
& \quad [\alpha]_D^{24} = +8.1, \, c = 3 \, \text{in EtOH}
\end{align*}
\]

\[
\begin{align*}
\text{(1R, 2S)-ephedrine} & \quad \text{mp 37-39} \, ^\circ \text{C} \\
& \quad [\alpha]_D^{24} = -8.1, \, c = 3 \, \text{in EtOH}
\end{align*}
\]

\[
\begin{align*}
\text{(1S, 2S)-pseudoephedrine} & \quad \text{mp 118-120} \, ^\circ \text{C} \\
& \quad [\alpha]_D^{20} = +52, \, c = 0.6 \, \text{in EtOH}
\end{align*}
\]

\[
\begin{align*}
\text{(1R, 2R)-pseudoephedrine} & \quad \text{mp 118-120} \, ^\circ \text{C} \\
& \quad [\alpha]_D^{20} = -51, \, c = 0.6 \, \text{in EtOH}
\end{align*}
\]

NMR spectra taken from Sigma-Aldrich website
Prochirality – has 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.

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.

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

- 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

<table>
<thead>
<tr>
<th>Add mixture of</th>
<th>Add mixture of</th>
<th>Add mixture of</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S, S) and (R, S) diastereomers to column with an achiral stationary phase e.g. SiO$_2$</td>
<td>(R) and (S) enantiomers to column with an achiral stationary phase e.g. SiO$_2$</td>
<td>(R) and (S) enantiomers to chiral column – chiral stationary phase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Column contains SiO$_2$ for example (achiral stationary phase)</th>
<th>Column contains SiO$_2$ modified with a chiral, non-racemic compound – chiral stationary phase</th>
<th>Chiral modifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>R, S</td>
<td>S, S</td>
<td>R</td>
</tr>
<tr>
<td>S, S</td>
<td>R, S</td>
<td>S</td>
</tr>
</tbody>
</table>

- add mixture of (S, S) and (R, S) diastereomers to column with an achiral stationary phase e.g. SiO$_2$
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

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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

\[ \text{enantiomers} \rightarrow \text{diastereomers} \]

\[ \begin{align*}
(R) & : (S) = x:y \\
\text{unequal mixture of enantiomers} & \rightarrow \text{diastereomers} \\
\text{ratio is x:y if no kinetic} & \text{resolution} \\
\end{align*} \]

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 alcochol 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.

Comparison of \(^1\)H NMR spectra of the diastereomeric Mosher’s esters can allow assignment of absolute configuration.
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.

$\alpha$D$^20$ = -12 (c = 20 in water) 
(-)-tartaric acid - unnatural

$\alpha$D$^20$ = +12.4 (c = 20 in water) 
(+) -tartaric acid - natural
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.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\xrightarrow{\text{LiAlH}_4} 
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
+ 
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\xrightarrow{3:1}
\]

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 on 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

<table>
<thead>
<tr>
<th>Amino acids</th>
<th>Sugars</th>
<th>Terpenes</th>
<th>Hydroxy acids etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-amino acids</td>
<td>D-hexoses</td>
<td>α-pinene (terpene)</td>
<td>tartaric acid</td>
</tr>
</tbody>
</table>

\[
\text{H}_2\text{N}-\text{CO}_2\text{H} \quad \text{HO}-\text{O}-\text{OH} \quad \text{Me} \quad \text{HO}-\text{O}-\text{OH} \quad \text{HO}-\text{O}-\text{OH} \quad \text{Me} \quad \text{HO}-\text{O}-\text{OH} \quad \text{HO}-\text{O}-\text{OH} \quad \text{Me} \quad \text{HO}-\text{O}-\text{OH}
\]

\[\alpha\text{-amino acids} \quad \text{D-hexoses} \quad \alpha\text{-pinene (terpene)} \quad \text{tartaric acid}\]
- Synthesis of chiral auxiliaries using chiral pool starting materials


![Chemical structures and reactions](image-url)
Synthesis of chiral auxiliaries using chiral pool starting materials


From chiral pool

\[
\text{(S)-proline} \xrightarrow{\text{LiAlH}_4} \text{OH} \xrightarrow{\text{HOCOMe}} \text{CONH} \xrightarrow{\text{KOH}} \text{SAMP} \xrightarrow{\text{KOCI, KOH}} \text{OCONH}_2 \xrightarrow{\text{K N≡C=O}} \text{NOMe}
\]

\[
\text{MeO} \xrightarrow{\text{LDA}} \text{MeO} \xrightarrow{\text{PrI}} >97\% \text{ de} \xrightarrow{\text{O}_3} \text{Pr}
\]

\[
\text{87%} \xrightarrow{\text{SAMP}} \text{87%} \xrightarrow{\text{PrI}} >97\% \text{ de}
\]
Synthesis of chiral catalysts using the chiral pool – e.g. TADDOL - $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolan-4,5-dimethanol

TADDOLs are useful reagents and catalysts for a large number of asymmetric transformations.


\[
\text{NH}_2\text{CO}_2\text{H} \xrightarrow{\text{Cl} \cdot \text{O} \cdot \text{Bn}} \xrightarrow{\text{NaOH, water}} \text{NH}_2\text{CO}_2\text{H} \xrightarrow{\text{MeOH, BF}_3 \cdot \text{OEt}_2} \xrightarrow{\text{excess PhMgBr}} \text{NH}_2\text{CO}_2\text{Me} \xrightarrow{\text{MeB(OH)}_2} \text{MeB(OH)}_2
\]

(R)-BINAP tartrate complex crystallises from solution; (S)-BINAP remains in mother liquors

(S)-BINAP recovered from mother liquors can be crystallised with (-)-2,3-dibenzoyl-L-tartaric acids to very high ee

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:
  
  Diastereoselectivity – product diastereomer discrimination
  
  Enantioselectivity – product enantiomer discrimination

\[
\text{O} \quad \text{O} \\
\text{Me} \\
\text{MgBr} \\
\text{CuBr•SMe}_2 \\
\rightarrow \\
\text{Me} \\
\text{O} \quad \text{O} \\
\text{Me} \\
\text{CuBr•SMe}_2
\]

- 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?

- $n$ Sterocentres 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

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.

\[ \phi = 0^\circ \quad \phi = 60^\circ \]
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.

(HOMO = Highest Occupied Molecular Orbital; LUMO = Lowest Unoccupied Molecular Orbital)
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 $-\Delta G$ 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.

![Substituted Cyclohexanes Diagram](image)

<table>
<thead>
<tr>
<th>R</th>
<th>$-\Delta G$ (A)</th>
<th>R</th>
<th>$-\Delta G$ (A)</th>
<th>R</th>
<th>$-\Delta G$ (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0</td>
<td>F</td>
<td>1.4</td>
<td>CN</td>
<td>0.84</td>
</tr>
<tr>
<td>Me</td>
<td>7.3</td>
<td>Cl</td>
<td>2.5</td>
<td>CHO</td>
<td>3.0</td>
</tr>
<tr>
<td>Et</td>
<td>7.5</td>
<td>Br</td>
<td>2.1</td>
<td>COMe</td>
<td>5.0</td>
</tr>
<tr>
<td>iPr</td>
<td>9.3</td>
<td>I</td>
<td>2.1</td>
<td>CO$_2$Me</td>
<td>5.2</td>
</tr>
<tr>
<td>tBu</td>
<td>20</td>
<td>OH</td>
<td>2.5-4.4</td>
<td>CO$_2$H</td>
<td>5.9</td>
</tr>
<tr>
<td>Ph</td>
<td>11.7</td>
<td>NH$_2$</td>
<td>5.1-7.1</td>
<td>CO$_2^-$</td>
<td>8.4</td>
</tr>
</tbody>
</table>

- 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.

all values in kJmol$^{-1}$
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. 

\[ \Delta G^\circ = +23 \text{ kJmol}^{-1} \] for the above equilibrium.

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

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

**Problem:** 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 enantiomerically 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

<table>
<thead>
<tr>
<th>Amino acids</th>
<th>Sugars</th>
<th>Terpenes</th>
<th>Hydroxy acids etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-amino acids</td>
<td>D-hexoses</td>
<td>α-pinene (terpene)</td>
<td>tartaric acid</td>
</tr>
</tbody>
</table>

**Diastereoselectivity**

- Enantiomeric transition states have the same energy.
- Diastereomeric transition states generally do not have the same energy.

The diagrams illustrate the energy profiles of enantiomeric and diastereomeric transition states. The reaction coordinates and energy changes ($\Delta G$) are shown, highlighting the differences in energy levels.
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 states 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 transition states 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

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

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

<table>
<thead>
<tr>
<th>(\Delta\Delta G^\ddagger) / kJmol(^{-1})</th>
<th>T</th>
<th>product ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0</td>
<td>25 °C (298 K)</td>
<td>25:1</td>
</tr>
<tr>
<td>8.0</td>
<td>-78 °C (195 K)</td>
<td>139:1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>product ratio</th>
<th>d.e. (or e.e.)</th>
<th>(\Delta\Delta G^\ddagger) / kJmol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>2.72</td>
</tr>
<tr>
<td>9</td>
<td>80</td>
<td>5.44</td>
</tr>
<tr>
<td>19</td>
<td>90</td>
<td>7.30</td>
</tr>
<tr>
<td>99</td>
<td>98</td>
<td>11.4</td>
</tr>
<tr>
<td>999</td>
<td>99.8</td>
<td>17.1</td>
</tr>
<tr>
<td>9999</td>
<td>99.98</td>
<td>22.8</td>
</tr>
</tbody>
</table>

all values calculated at 25 °C (298 K)
With cyclic systems the diastereocontrol is frequently easy to rationalise.

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.

\[ \text{Nu}^- + \text{Nu} \rightarrow \text{Chair} \text{ product} \]

95% *diaxial* product

*trans* *diaxial* equatorial environment

*axial* attack *via* chair-like transition state
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 $\alpha$-stereocentres

Historical Perspective

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."

Features and problems

- 90° nucleophile trajectory
- Activated carbonyl considered to be largest group
- Torsional strain not considered
- Steric repulsion between $R_L$ and $R$ not discussed

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

Cram, D. J.; Elhafez, F. A. A., J. Am. Chem. Soc., 1952, 74, 5828
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. Dunitz, determined the trajectory of attack on a carbonyl group by analysis of the X-ray structures of a number of cyclic amino ketones.
- The Bürgi-Dunitz angle is approximately 107 ° - close to the tetrahedral angle.
- Attack along the Bürgi Dunitz trajectory maximises overlap of the nucleophile HOMO with the LUMO of the carbonyl group (π* orbital).

**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.

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

Examples

Why is the stereocontrol so good when NBn₂ 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.

\[
\begin{align*}
X &= \text{electronegative group} \\
&= \text{e.g. OR, NR}_2, \text{SR, Ph etc.}
\end{align*}
\]

\[
\begin{align*}
\text{C}=\text{O} \quad \pi^* \\
&\text{C}-\text{X} \quad \sigma^* \\
\end{align*}
\]

\[
\begin{align*}
\text{overlap to give new lower energy LUMO} \\
\text{new lower energy LUMO more reactive}
\end{align*}
\]

\[
\begin{align*}
\text{major diastereomer} \\
\end{align*}
\]

\[
\begin{align*}
4:96
\end{align*}
\]

- 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.

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 Cornforth 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.

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.; 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?

- NO
  - Use Felkin-Anh model: consider reactions on conformations with largest group perpendicular to RC=O plane.

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

- 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.

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{OR} & \quad \text{LiAlH}_4, \text{THF} & \quad \text{Me} & \quad \text{Me} & \quad \text{OH} & \quad \text{OR} & \quad \text{Me} & \quad \text{Me} & \quad \text{OH} & \quad \text{OR} \\
\text{R} &= \text{CH}_2\text{OBn} & & 70 & & 30 \\
\text{R} &= \text{SiPh}_2\text{tBu} & & 5 & & 95
\end{align*}
\]

**Problem:** Predict the stereochemical outcome of the following reaction.
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 (A1,3 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.**
**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.

\[ \text{Me} = \text{H} \]

\[ \begin{array}{c}
\text{Me} \equiv \text{SiMe}_2\text{Ph} \\
\text{Me} \equiv \text{SiMe}_2\text{Ph} \\
\text{Me} \equiv \text{SiMe}_2\text{Ph} \\
\end{array} \]

\[ \text{mCPBA, adds} \]

\[ \text{least, hindered, face} \]

\[ \text{major & product} \]

\[ \text{minor & product} \]

\[ \begin{array}{c}
\text{Me} \equiv \text{SiMe}_2\text{Ph} \\
\text{Me} \equiv \text{SiMe}_2\text{Ph} \\
\text{Me} \equiv \text{SiMe}_2\text{Ph} \\
\end{array} \]

\[ \text{61:39} \]
Acyclic Stereocontrol – attack on alkenes with α-stereocentres

Problem: Explain the stereochemical outcome of the following reaction from Kishi’s synthesis of monensin.

Problem: Predict the stereochemistry of the major diastereomer formed in the following reaction.
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 $\sim 20$, ester $\sim 25$, amide $\sim 26$
- Requires a base with a higher $pK_a$ (of the conjugate acid) for complete deprotonation.
- Typically use, LDA, LiHMDS (and NaHMDS, KHMDS), and LiTMP

![Diagram of Diastereoselective Enolate Alkylation]

- LDA, lithium disopropylamide, $pK_a$ (conjugate acid) 36 (THF)
- LiHMDS, lithium hexamethyldisilazide, $pK_a$ 26 (THF)
- LiTMP, lithium tetramethylpiperidide, $pK_a$ 37 (DMSO)
Control of Enolate Geometry

- 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 absence of additives such as HMPA or DMPU, esters give predominantly (E)-enolates whereas ketones and amides give predominantly (Z)-enolates.
- In the presence of additives such as HMPA and DMPU (Z)-enolates predominate for esters as well as amides and ketones.
- Take home message, Esters give E-enolates, other carbonyls (ketones and amides) give Z-enolates.

- Ireland Model
  (Z):(E)-ratio depends on a balance between the 1,3-diaxial interactions and the developing $A^{1,3}$ strain.
For amides, developing \( \text{A}^{1,3} \) strain always bad, therefore give (Z)-enolates under all conditions.
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.

**Diastereoselective Enolate alkylation**

- 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.
- iPr group blocks one face of chelated enolate.

Valine-derived oxazolidinone

Ephedrine-derived oxazolidinone

Phenylalanine-derived oxazolidinone

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-branch alkyl halides do not react.
- Diastereocontrol in all of these reactions is predictable (from proposed chelated enolate) and high.

- Auxiliary cleavage
  - most reactive carbonyl group (lower energy LUMO)
  - source of “HO⁺”
  - selective enolisation here probably as a result of chelation of imide to sodium ions
  - Alcohol
  - Weinreb amide
Diastereoselective Enolate alkylation

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


![Mechanism Diagram](image-url)
Diastereoselective Enolate alkylation – the Schollkopf auxilliary

Synthesis of α-substituted and α-disubstituted amino acids


**Chemical Equations and Diagrams:**

- **Equation 1:**
  \[
  \text{Boc}_2\text{O, NaHCO}_3 \rightarrow \text{BocHNCO}_2\text{Me}
  \]

- **Equation 2:**
  \[
  \text{BuLi then BnB} \rightarrow \text{BnNHCO}_2\text{Me}
  \]

- **Equation 3:**
  \[
  \text{H}_2\text{NCO}_2\text{Me} \rightarrow \text{H}_2\text{NCO}_2\text{Bn}
  \]

- **Equation 4:**
  \[
  \text{Bu}^+ \rightarrow \text{MeO}
  \]

- **Equation 5:**
  \[
  \text{Ph} \rightarrow \text{Br}
  \]

**Notes:**
- Electrophile approaches from less hindered face
- Large iPr group shields bottom face
Diastereoselective Enolate alkylation – the Schollkopf auxiliary


- $t$BuLi has recently been recommended for deprotonation of substituted Schollkopf 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.

**Catalytic Asymmetric Phase Trasnfer Catalysis – Synthesis of Unnatural Amino Acids**


\[
\begin{align*}
\text{tBuO} & \quad \text{N} \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \quad \text{Ph} \\
\text{CsOH} & \quad \uparrow \quad 10 \text{ mol\%} \\
\text{tBuO} & \quad \text{N} \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \quad \text{Ph} \\
\text{CsOH} & \quad \uparrow \quad \text{Q}^+\text{Br}^- \\
\text{tBuO} & \quad \text{N} \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \quad \text{Ph} \\
\text{tBuO} & \quad \uparrow \quad \text{R}-\text{X} \\
\text{R} & \quad \text{X} \\
\text{Q}^+ & \quad \text{Br}^-
\end{align*}
\]

- deprotonation at solid-liquid interface
- \textit{Re}-face exposed
- \textit{R}-\text{X} attacked along this trajectory
- \textit{Chiral} quaternary ammonium enolate now soluble in organic phase
- \textit{Back} face blocked by bicyclic ring
- \textit{Bottom} face blocked by quinoline and allyl ether
- \textit{Right} face blocked anthracene ring
Diastereoselective Enolate alkylation Oppolzer method

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


\[
\text{Me group blocks one face of chelated enolate}
\]

\[
\text{less hindered approach of electrophile to chelated enolate}
\]

\[
89\%, 97\% \text{ de}
\]

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


\[
\text{(-)-histrionicotoxin}
\]
Diastereoselective Enolate Alkylation Myers method

- Based upon pseudoephedrine amides.
- Pseudoephedrine is cheap and available in both enantiomeric forms.
- Amide enolates much more reactive than imide enolates (amides have a higher pK_a than imides) and hence unactivated alkyl halides may be used.

**Experimental Details**

<table>
<thead>
<tr>
<th>R</th>
<th>R’X</th>
<th>de %</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH_3</td>
<td>BnBr</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>CH_3</td>
<td>Bu</td>
<td>98</td>
<td>80</td>
</tr>
<tr>
<td>Bu</td>
<td>BnBr</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>iPr</td>
<td>BnBr</td>
<td>98</td>
<td>83</td>
</tr>
</tbody>
</table>
Diastereoselective Enolate Alkylation Myers method

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

Diastereoselective Enolate Alkylation Myers method

Rationalise the chemistry in the following sequence

Diastereoselective Enolate Alkylation of Ketones and Aldehydes—Enders’ SAMP and RAMP


(S)-1-amino-2-methoxypyrrolidine

(R)-1-amino-2-methoxypyrrolidine

\[
\begin{align*}
\text{SAMP} & \quad \text{RAMP} \\
\text{LDA, THF; EtI} & \quad \text{LDA} \\
\text{MeO} & \quad \text{Li} \\
\text{MeO} & \quad \text{Pr} \\
\text{OMe} & \quad \text{OMe} \\
\text{Pr} & \quad \text{Pr}
\end{align*}
\]

Diastereoselective Enolate Alkylation of Ketones and Aldehydes—Enders’ SAMP and RAMP


(S)-1-amino-2-methoxypyrrolidine

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\text{LDA, THF; EtI} & \quad \text{LDA} \\
\text{MeO} & \quad \text{Li} \\
\text{MeO} & \quad \text{Pr} \\
\text{OMe} & \quad \text{OMe} \\
\text{Pr} & \quad \text{Pr}
\end{align*}
\]
Seebach – Self Reproduction of Chirality

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


The Aldol Reaction - Importance

"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.

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.
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.

**The Aldol Reaction**

**Zimmerman Traxler Transition states**

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

\[
\text{OM} \quad \text{R}^1 \quad \text{H} \quad \text{R}^2 \quad \text{R}^3 + \quad \text{OH} \quad \rightarrow \quad (Z)-\text{favoured}
\]

\[
\begin{align*}
\text{OM} & \quad \text{R}^1 \quad \text{H} \quad \text{R}^2 \quad \text{R}^3 \\
\text{H} & \quad \text{OM} \quad \text{R}^1 \quad \text{H} \quad \text{R}^2 \quad \text{R}^3
\end{align*}
\]

\[
\text{syn pentane interaction}
\]

**General Observations**

- (Z)-Enolates give *syn*-aldols; (E)-enolates give *anti*-aldols.
- For lithium enolates (Z)-enolates give higher diastereoselectivity 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 diastereoselectivity 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).

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

\[
\text{OLi} \quad \text{PhCHO} \quad \rightarrow \quad \text{Ph} \quad \text{OH} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{OH}
\]

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.

The Evans Aldol Reaction

\[ \text{Aldol Reaction} \]

\[ \begin{align*}
\text{O} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{R} \\
\text{R'} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{R'} \\
\end{align*} \]

\[ \text{Bu}_2\text{BOTf} \quad \text{iPrNET}_2 \]

\[ \begin{align*}
\text{Bu} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{R} \\
\text{R'} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{R'} \\
\end{align*} \]

\[ \text{exclusive (Z)-enolate formation} \]

\[ \begin{align*}
\text{R}^1\text{CHO} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{OH} & \quad \text{R}^1 \\
\text{R'} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{OH} & \quad \text{R} \\
\end{align*} \]

\[ \text{very high syn-selectivity} \]

\[ \begin{align*}
\text{O} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{R} \\
\text{Me} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{R} \\
\end{align*} \]

\[ \text{Bu}_2\text{BOTf} \quad \text{iPrNET}_2 \]

\[ \begin{align*}
\text{O} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{R} \quad \text{Me} \\
\text{Me} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{R} \\
\end{align*} \]

\[ \text{RCHO} \]

\[ \begin{align*}
\text{O} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{OH} & \quad \text{Me} \\
\text{R} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{OH} & \quad \text{Me} \\
\end{align*} \]

Evans-syn

\[ \begin{align*}
\text{O} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{OH} \\
\text{Me} & \quad \text{O} & \quad \text{N} & \quad \text{C} & \quad \text{O} & \quad \text{OH} \\
\end{align*} \]

non-Evans-syn

\[ \text{syn:anti selectivities all >99:1} \]

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.
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-stereocentre the two faces of the aldehyde are diastereotopic and the major product is generally that predicted by the Felkin-Anh model.
- The diastereoccontrol 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.

\[
\text{RCHO} + \text{M} \rightarrow \text{RCHO} + \text{M} \rightarrow \text{RCHO} + \text{M} \rightarrow \text{RCHO} + \text{M}
\]

**Enantioselective Allylation and Crotylation reactions**

- H. C. Brown has developed $B$-allyldiospinocampheryl borane and the corresponding ($E$) and ($Z$)-crotyl derivatives.
- All of the reagents are readily prepared from inexpensive $\alpha$-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.

![Nobel Prize with Georg Wittig, 1979](image)

Enantioselective Allylation and Crotylation reactions

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

Enantioselective Allylation and Crotylation reactions

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

\[
\text{RCO}_2\text{Pr} + \text{B(OH)}_2\text{CO}_2\text{Pr} \xrightarrow{\text{toluene}} \text{COR} + \text{OH}
\]

\[
\begin{array}{c|c|c}
\text{RCHO} & \text{yield/\%} & \text{ee/\%} \\
\hline
nC_9H_19\text{CHO} & 86 & 79 \\
cC_6H_{11}\text{CHO} & 77 & 78 \\
\text{PhCHO} & 78 & 71 \\
\end{array}
\]

Catalytic Asymmetric Aldol Reactions – Introduction to Organocatalysis

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

Catalytic Asymmetric Aldol Reactions – Introduction to Organocatalysis

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

\[
\text{Me} - \text{Me} + R\text{CHO} \xrightarrow{\text{DMSO:acetone, 4:1}} \text{Me} - \text{OH} \\
\text{Me} - \text{OH} \xrightarrow{\text{H}_2\text{O}} \text{Me} - \text{OH}
\]

- Aldol reaction uses non-enolisable aldehydes or α-branched aldehydes which do not readily form enamines (due to A¹,³ strain).
- Mechanism involves enamine formation from acetone followed by reaction with RCHO via Zimmerman-Traxler type transition state.

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 CH₃CH₂CHO followed by reaction with acceptor aldehyde.
- Donor aldehyde (CH₃CH₂CHO) added slowly over course of reaction to prevent homo-aldol reaction.

Catalytic Asymmetric Aldol Reactions – Introduction to Organocatalysis

- MacMillan developed an efficient cross aldol reaction of aldehydes.

\[
\begin{align*}
\text{HCHO} & \xrightarrow{\text{Pybox}} \text{CH}_{3}\text{CH}_{2}\text{CHO} \\
\text{Me} & \quad 10 \text{ mol\% DMF, } + 4 \text{ °C} \\
\end{align*}
\]

\[
\begin{align*}
80\%, 99\% \text{ ee, } 4:1, \text{ anti:} \text{syn} \\
\end{align*}
\]

- Aldol reaction uses non-enolisable aldehydes or \(\alpha\)-branched aldehydes which do not readily form enamines
- Mechanism involves stereoselective enamine formation from \(\text{CH}_3\text{CH}_2\text{CHO}\) followed by reaction with acceptor aldehyde
- Donor aldehyde \((\text{CH}_3\text{CH}_2\text{CHO})\) added slowly over course of reaction to prevent homo-aldol reaction

Catalytic Asymmetric Mannich Reactions

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

Catalytic Asymmetric Mannich Reaction

Mechanism

\[ \text{RCHO} + \text{H}_2\text{N}\text{Me} \rightarrow \text{RCHMe}\text{H} \]

\[ \text{RCHMeOH} \rightarrow \text{RCHMeCONHMe} \]

\[ \text{RCHMeCONHMe} + \text{ArCHO} \rightarrow \text{RCHMeCONHAr} \]

\[ \text{RCHMeCONHAr} + \text{H}_2\text{O} \rightarrow \text{RCHMeCOOAr} \]


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.

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.

Catalytic Asymmetric α-functionalisation

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

Chiral Ammonia Equivalents

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


- 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*-Butylsulfinyl 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.

**t-Butylsulfinamides**


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.

**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

---

**t-Butylsulfinamides**

large $\text{t}$-butyl group pseudo-equatorial

small lone pair axial

imine substituent equatorial

organometallic chelated by $R^2$ and sulfinamide oxygen

---

**t-ButylSulfinamides**

- Reduction of ketimines with NaBH₄ or L-Selectride (Li tri-sec-butylborohydride) gives different major diastereomers of the resulting sulfinimine.

![Chemical Reaction Diagram]

**t-Butylsulfinamides**

Reduction of ketimines with NaBH₄ or L-Selectride (Li tri-sec-butylborohydride) gives different major diastereomers of the resulting sulfinimine.

![Chemical diagram showing the reduction of ketimines with NaBH₄ or L-Selectride resulting in different major diastereomers of the resulting sulfinimine.](image-url)

Predict the major diastereomer formed in the following reaction.
Davies Lithium Amides

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

\[
\begin{align*}
\text{Me} & \text{O} \text{Bn} \\
\text{Ph} & \text{N} \text{Li} \\
\text{Me} & \text{Ph} \\
\text{H}_2, \text{Pd(OH)}_2, \text{MeOH} & \to \text{Me} \text{NH}_2 \text{COOH} \\
\text{THF, -78 °C, then NH}_4\text{Cl (aq)} & \to \text{Me} \text{OBn} \text{CO} \text{Me} \text{Ph} \\
\text{88% yield, >95% d.e.} & \to \text{Me} \text{OEt} \text{CO} \text{Me} \text{Ph} \\
\text{quant. >95% ee} & \to \text{Me} \text{MeO} \text{CO} \text{Me} \text{Ph} \\
\end{align*}
\]

- 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


\[
\text{Ph} \text{O} \text{tBu} + \text{Me} \text{N} \text{Li} \rightarrow \text{Ph} \text{N} \text{O} \text{tBu} + \text{Me} \text{N} \text{Li}
\]

- Model.

\[
\text{Ph} \text{N} \text{Li} + \text{Ph} \text{O} \text{tBu} \text{C} \rightarrow \text{Ph} \text{N} \text{O} \text{tBu}
\]
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 – mCPBA.

"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
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 tbutylhydroperoxide (tBuOOH) allows the epoxidation of allylic and homoallylic alcohols.
- The use of Ti(OiPr)$_4$ and a tartrate ester in place of VO(acac)$_2$ allows the highly enantioselective epoxidation of allylic alcohols (see later).

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)$_2$, tBuOOH gives high syn selectivity for ring sizes 5-8.
Diastereoselective Epoxidation Acyclic Systems

Problem: Explain the outcome of the following reaction.
Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

- 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.

Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

Mechanism.

Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

Examples of Sharpless Epoxidation

<table>
<thead>
<tr>
<th>Product</th>
<th>Tartrate</th>
<th>Yield / %</th>
<th>ee / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-(+)-DIPT</td>
<td>65</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>L-(+)-DIPT</td>
<td>89</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>L-(+)-DET</td>
<td>88</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>L-(+)-DET</td>
<td>74</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>L-(+)-DET</td>
<td>95</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

- Reagent control in the Sharpless Asymmetric Epoxidation

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Reagent</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCPBA</td>
<td>1:1.4</td>
</tr>
<tr>
<td>VO(acac)$_2$</td>
<td>1:1.8</td>
</tr>
<tr>
<td>Ti(OiPr)$_4$/tBuOOH</td>
<td>1:2.3</td>
</tr>
<tr>
<td>Ti(OiPr)$_4$/D-(-)-DIPT/tBuOOH</td>
<td>1:90</td>
</tr>
<tr>
<td>Ti(OiPr)$_4$/L-(+)-DIPT/tBuOOH</td>
<td>22:1</td>
</tr>
</tbody>
</table>

- 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.

Synthesis of L-sugars

**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.

![Diagram showing reaction and selectivity](image)

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 $k_{rel} = e^{\Delta \Delta G/RT} = S$. 

\[
\Delta \Delta G^\ddagger = \Delta G^\ddagger_S - \Delta G^\ddagger_R
\]

\[
k_S = k_{slow}
\]

\[
k_R = k_{fast}
\]
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 graph](image1)

![Product graph](image2)

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

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

Enantioselective Epoxidation of Allylic Alcohols (Sharpless Asymmetric Epoxidation)

\[
\begin{align*}
\text{Me} & \text{OH} \\
\text{Me-CH} & \text{CH} \quad \text{OH} \\
\text{Ti(OPr)}_4 & \text{L-(+)-DIPT} \\
\text{tBuOOH} & \\
\end{align*}
\]

43% (50% max) 96% ee

fragment of Swinolide A


<table>
<thead>
<tr>
<th>T / °C</th>
<th>conversion %</th>
<th>% recovered substrate</th>
<th>ee recovered substrate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>80</td>
<td>18</td>
<td>&gt;98</td>
</tr>
<tr>
<td>-40</td>
<td>60</td>
<td>39</td>
<td>95</td>
</tr>
<tr>
<td>-60</td>
<td>55</td>
<td>34</td>
<td>90</td>
</tr>
</tbody>
</table>

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

Enantioselective Epoxidation of Unfunctionalised Olefins - Jacobsen Epoxidation

- 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 enantiomeric 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.

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).

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.

\[ R'' = \text{H disubstituted olefins} \]
\[ R'' = \text{alky/aryl - trisubstituted olefins} \]

Enantioselective Epoxidation of Unfunctionalised Olefins - Jacobsen Epoxidation


- 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.
- tButyl 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 aminoisindanol

\[
\begin{align*}
\text{CH}_3\text{CN,} & \quad \text{fuming} \\
\text{H}_2\text{SO}_4 & \\
\rightarrow & \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{tBu} & \quad \text{tBu} \\
\text{H} & \quad \text{Cl} \\
\rightarrow & \\
\text{NaOCl (aq)} & \\
\text{CH}_2\text{Cl}_2, 4^\circ\text{C} & \\
4\text{-phenylpyridine} & \\
\text{N-oxide 3 mol\%} & \\
\rightarrow & \\
\text{71\%, 84-86\% ee} & \\
\end{align*}
\]

\[
\begin{align*}
\text{attack on bottom} & \quad \text{face more favourable} \\
\rightarrow & \\
\text{trans-fused} & \\
\text{5,5-system} & \\
\text{unfavourable} & \\
\end{align*}
\]

\[
\begin{align*}
\text{indinavir (Crixivan)} & \\
\text{anti-HIV} & \\
\end{align*}
\]

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.

\[
\begin{align*}
\text{OH} & \quad \text{OH} \quad + \quad \text{H}_2\text{O} \\
\text{(S)-dil} & \quad \text{(R)-epoxide} \quad \xy
to
\text{(S)-epoxide} \quad \xy
to
\text{(S)-epoxide} \quad \xy
to
\text{(R)-dil}
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>cat (mol %)</th>
<th>H\textsubscript{2}O (equiv.)</th>
<th>time (hours)</th>
<th>ee (%)</th>
<th>yield (%)</th>
<th>ee (%)</th>
<th>yield (%)</th>
<th>(k_{rel})</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH\textsubscript{3}</td>
<td>0.2</td>
<td>0.55</td>
<td>12</td>
<td>&gt;98</td>
<td>44</td>
<td>98</td>
<td>50</td>
<td>&gt;400</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl</td>
<td>0.3</td>
<td>0.55</td>
<td>8</td>
<td>98</td>
<td>44</td>
<td>86</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>nButyl</td>
<td>0.42</td>
<td>0.55</td>
<td>5</td>
<td>98</td>
<td>46</td>
<td>98</td>
<td>48</td>
<td>290</td>
</tr>
<tr>
<td>Ph</td>
<td>0.8</td>
<td>0.70</td>
<td>44</td>
<td>98</td>
<td>38</td>
<td>98</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>CH=CH\textsubscript{2}</td>
<td>0.64</td>
<td>0.50</td>
<td>20</td>
<td>84</td>
<td>44</td>
<td>94</td>
<td>49</td>
<td>30</td>
</tr>
</tbody>
</table>

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

Terminal Epoxides – Jacobsen Hydrolytic Kinetic Resolution

Problem: Predict the stereochemical outcome of the following reaction.

Epoxidation with Dioxiranes

Epoxidation

- 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.

Enantioselective synthesis of trans-epoxides – Shi Epoxidation

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

\[
\text{R}_1^1 \text{R}_2^2 + \text{Oxone}^{\text{TM}}, \text{H}_2\text{O}, \text{MeCN} \rightarrow \text{R}_1^1 \text{R}_2^2
\]

20-30 mol% ketone

**Catalytic Cycle**

- **Stereochemical Model**
  - Medium group R\textsuperscript{1}\ projects over ring
  - Large group R\textsuperscript{3}\ in least hindered position
  - Bottom face blocked by *cis*-fused acetonide

- Higher ee’s with smaller R\textsuperscript{1}\ and larger R\textsuperscript{3}.
- Good for trans-alkenes and trisubstituted alkenes.
- Conjugated dienes react at more electron rich alkene.

**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.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph–Ph</td>
<td>Ph–O–Ph</td>
<td>73</td>
<td>95</td>
</tr>
<tr>
<td>Ph–Cl</td>
<td>Ph–O–Cl</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td>nC_{10}H_{21}Et</td>
<td>nC_{10}H_{21}O–Et</td>
<td>94</td>
<td>89</td>
</tr>
<tr>
<td>H_3C_CH_3OCH_3</td>
<td>H_3C_CH_3OCH_3</td>
<td>65</td>
<td>89</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph–NO</td>
<td>94</td>
<td>98</td>
</tr>
</tbody>
</table>

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

Cyclopropanation: the Simmonds-Smith Reaction – an aside


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

\[
\begin{align*}
\text{Et}_2\text{Zn} & \quad + \quad \text{CH}_2\text{I}_2 \\
\text{Me}\text{CH}==\text{CMe} & \quad \text{Et}_2\text{Zn}, \text{CH}_2\text{I}_2 \\
\text{Me}\text{CH}==\text{CMe} & \quad \text{Et}_2\text{Zn}, \text{CH}_2\text{I}_2
\end{align*}
\]

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


- “CAUTION! The previously reported preparation of Zn(CH₂I₂) without a complexing additive is highly exothermic and a violent decomposition sometimes occurred. For safety reasons the use of Zn(CH₂I₂)•DME as reported here is mandatory if this reaction is carried out on a >8 mmole 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

  - zinc bonded to CH₂I 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 A₁,₃-strain
  - the carbene is delivered selectively to one face of the alkene

\[
\text{Et}_2\text{Zn}, \text{CH}_2\text{I}_2, \text{DME, CH}_2\text{Cl}_2 \rightarrow \text{Ph} \end{equation}\]

96%, 93% ee

\[
\text{BnO} \rightarrow \text{Et}_2\text{Zn}, \text{CH}_3\text{CHI}_2, \text{DME, CH}_2\text{Cl}_2 \rightarrow \text{Me} \end{equation}\]

80%, 98:2 dr, 94% ee

80%, 97:3 dr, 93% ee
Cyclopropanation: metal catalysts and diazo compounds


![Chemical reaction diagram and product structure](image)

- For very 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 = NO₂, CN, CO₂Me,
**Dihydroxylation**

- Dihydroxylation of alkenes with OsO₄ is stereospecific (cis-addition) and occurs via [3 + 2] mechanism.
- OsO₄ is both toxic and volatile.
- The most common procedure is the Upjohn procedure which uses catalytic amounts of OsO₄ with NMO as the stoichiometric oxidant.

![Dihydroxylation reaction scheme]

**Sharpless Asymmetric Dihydroxylation**

AD-mix for 1 mmol olefin contains
- 3 mmol K₂Fe(CN)₆ - [oxidises Os(VI) to Os(VII)]
- 3 mmol K₂CO₃
- 0.01 mmol (DHQD)₂-PHAL or (DHQ)₂-PHAL
- 0.002 mmol K₂OsO₂(OH)₄ - [Os(VI)]

**C₂-symmetric, pseudo-enantiomeric ligands**

![Sharpless ligands]

**Sharpless Asymmetric Dihydroxylation**

![Chemical structures](image)

**best substrates**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>AD-mix-(\beta) (DHQD)(_2)-PHAL</th>
<th>AD-mix-(\alpha) (DHQ)(_2)-PHAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3)C=CHCH=CH(\text{CH}_3)</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
</tr>
<tr>
<td>Benzene</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
</tr>
<tr>
<td>nBu=nBu</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
</tr>
<tr>
<td>nOct=nOct</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
</tr>
</tbody>
</table>

**Mnemonic**

Sharpless Asymmetric Dihydroxylation - mechanism

$$\text{organic}$$

$$\text{aqueous}$$

$$\text{OsO}_4 \cdot \text{L}^*$$

$$\text{OsO}_4$$

$$\text{Os(VI)}$$

$$\text{Os(VIII)}$$

$$\text{2 Fe(CN)}_6^{3-}$$

$$\text{2 Fe(CN)}_6^{4-}$$

$$\text{2 H}_2\text{O}$$

$$\text{2 HO}^-$$

$$\text{2 HO}^-$$
Useful Reactions of Chiral Diols


*more electrophilic than epoxide*
**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.

Sharpless Asymmetric Aminohydroxylation

\[
\text{MeO} \quad \text{Cbz} \quad \text{Cl} \quad \text{Na} \quad 3 \text{ equiv} \quad K_2\text{OsO}_2(\text{OH})_4 \ 4\% , \\
\text{O}_2\text{N} \quad \text{Fr} \quad (\text{DHQ})_2\text{PHAL} \ 6\% \\
\text{MeCN, water} \\
90\% \text{ ee}, \ 9:1 \text{ mixture of regioisomers}
\]

\[
\text{O}_2\text{N} \quad \text{Fr} \quad \text{Boc} \quad \text{Cl} \quad \text{Na} \quad 3 \text{ equiv} \quad K_2\text{OsO}_2(\text{OH})_4 \ 4\% , \\
\text{Fr} \quad \text{Boc} \quad \text{Cl} \quad \text{Na} \quad 3 \text{ equiv} \quad K_2\text{OsO}_2(\text{OH})_4 \ 4\% , \\
\text{nPrOH, water} \\
75\% , 97\% \text{ ee},
\]

\[
\text{MeO} \quad \text{Cbz} \quad \text{Cl} \quad \text{Na} \quad 3 \text{ equiv} \quad K_2\text{OsO}_2(\text{OH})_4 \ 4\% , \\
\text{Fr} \quad \text{Boc} \quad \text{Cl} \quad \text{Na} \quad 3 \text{ equiv} \quad K_2\text{OsO}_2(\text{OH})_4 \ 4\% , \\
\text{nPrOH, water} \\
78\% , >99\% \text{ ee},
\]

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 to 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

\[
\text{Et}_2\text{BOMe, THF, MeOH - 78 °C then NaBH}_4, - 78 °C}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>syn:anti</th>
<th>yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>99:1</td>
<td>95</td>
</tr>
<tr>
<td>Ph</td>
<td>CH\textsubscript{2}CO\textsubscript{2}Et</td>
<td>98:2</td>
<td>85</td>
</tr>
<tr>
<td>Bu</td>
<td>Bu</td>
<td>99:1</td>
<td>99</td>
</tr>
</tbody>
</table>

Diastereoselective Reduction
Evans-Saksena *anti*-selective reduction of β-hydroxy ketones

\[
\text{Me}_4\text{NBH(OAc)}_3 \rightarrow \text{anti-reduction 96:4 anti:syn}
\]

\[
\text{R and R'} \text{ pseudo-equatorial}
\]

\[
\text{acid catalysis activates carbonyl intramolecular hydride transfer}
\]

Diastereoselective Reduction

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

- Samarium catalysed intramolecular Meerwein-Pondorf-Verley reduction.
- Samarium(II) iodide initially induces pinacol coupling of some of the aldehyde which gives SmIII 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.

\[
\text{MeCHO + SmI}_2 \rightarrow \begin{array}{c}
\text{OH} \\
\text{OH} \\
\text{Me} \\
\text{Me} \\
+ \text{Sm}^{\text{III}}
\end{array}
\]

Asymmetric Reduction - Hydrogenation of Alkenes

- In general asymmetric hydrogenation of alkenes requires homogeneous catalysis.
- Chelating chiral diphosphine ligands along with Rh(I) or Ru(II) catalysts and alkenes or ketones which may chelate to the metal give rise to products with high enantiomeric excess.
- Hydrogen is cheap and atom economic.

Asymmetric Reduction Hydrogenation of Alkenes

**Mechanism**

- In general, with rhodium(I) diphosphine complexes the mechanism of the reaction involves coordination of the substrate, oxidative addition of dihydrogen, and reductive elimination to give the product.
- Coordination of the substrate to the catalyst results in diastereomeric complexes which are in equilibrium.
- The minor diastereomeric complex undergoes (irreversible) oxidative addition of dihydrogen faster than the major diastereomer.
- Therefore the major enantiomer of the product is derived from the minor diastereomeric catalyst/substrate complex – this is an example of Curtin-Hammett kinetics.

---

**Diagram:**

- **Major Diastereomer**
  - Coordination of the substrate to the catalyst results in diastereomeric complexes which are in equilibrium.
  - The minor diastereomeric complex undergoes (irreversible) oxidative addition of dihydrogen faster than the major diastereomer.
  - Therefore the major enantiomer of the product is derived from the minor diastereomeric catalyst/substrate complex – this is an example of Curtin-Hammett kinetics.

- **Minor Diastereomer**
  - Coordination of the substrate to the catalyst results in diastereomeric complexes which are in equilibrium.
  - The minor diastereomeric complex undergoes (irreversible) oxidative addition of dihydrogen faster than the major diastereomer.
  - Therefore the major enantiomer of the product is derived from the minor diastereomeric catalyst/substrate complex – this is an example of Curtin-Hammett kinetics.
Asymmetric Hydrogenation

- BINAP Ruthenium(II) complexes have much wider substrate scope than for rhodium.
- They operate by a different mechanism to the Rh(I) catalysed hydrogenations.
Asymmetric Hydrogenation - Applications

\[
\text{\textbf{naproxen}, 92\% \text{ yield}, 97\% \text{ ee}}
\]

\[
\text{\textbf{96\% ee}}
\]

\[
\text{\textbf{98\% ee}}
\]
General Rh-Catalyzed Hydrogenation System – DUPHOS and BPE Ligands

- Based on very nucleophilic trialkyl or trialkylaryl phosphines which bind very tightly to metal centre.
- Rigid – well ordered transition states.
- In general the major diastereomeric substrate metal complex gives the major enantiomer.

\[ \text{PhNHAc} \rightarrow 0.2\%[\text{Rh}(R,R)-\text{Me-DuPHOS})(\text{COD})]^{\text{+}}\text{TFO}^{-} \rightarrow \text{PhNHAc} \]

\[ 4 \text{ atm H}_2, \text{ MeOH} \rightarrow 96\% \text{ ee} \]

Catalytic Asymmetric Reduction of Ketones

\[
\text{(S)-BINAP RuX}_2 \xrightarrow{\text{EtOH, H}_2 (50-100 \text{ atm})} \text{RH}_2\text{Y} \]

<table>
<thead>
<tr>
<th>R</th>
<th>Y</th>
<th>Yield / ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>NMe_2</td>
<td>72/96</td>
</tr>
<tr>
<td>Ph</td>
<td>NMe_2</td>
<td>85/95</td>
</tr>
<tr>
<td>Me</td>
<td>CH_2OH</td>
<td>100/98</td>
</tr>
<tr>
<td>Me</td>
<td>CO_2Et</td>
<td>100/95</td>
</tr>
</tbody>
</table>

Catalytic Asymmetric Reduction of Ketones

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 Meerwein-Pondorf-Verley reduction.

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.

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.

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.

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

Mechanism

Asymmetric Reduction of Ketones - Applications

\[
\text{Ph-CH-CH-CH-Cl} + \text{BH}_3 \cdot \text{THF} \rightarrow \text{Ph-CH-CH-CH-Cl} \rightarrow \text{Ph-CH-CH-CH-Cl}
\]


\[
\text{Ph-CH-CH-CH-Cl} \rightarrow \text{Ph-CH-CH-CH-Cl} \rightarrow \text{Ph-CH-CH-CH-Cl}
\]


Asymmetric Addition of Diethylzinc to aldehydes

Active catalyst formed from reaction of Et₂Zn with amino alcohol.
- Coordination of a second molecule of Et₂Zn 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.

Problem: Rationalise the stereochemical outcome of the following reaction.

Catalytic Asymmetric Reduction with Organocatalysts

\[ \text{PhCH} = \text{CHCO} + \text{EtO}_2\text{CCH} = \text{CMeCO}_2\text{Et} \rightarrow \text{PhCH} = \text{CHCO} + \text{EtO}_2\text{CCH} = \text{CMeCO}_2\text{Et} \]

- 91% yield, 93% ee

\[
\begin{align*}
\text{PhCH} = \text{CHCO} & \quad 74\%, 94\% \text{ ee} \\
\text{Cl}_2\text{CHCH} = \text{CHCO} & \quad 92\%, 97\% \text{ ee} \\
\text{Cyclohexanone} & \quad 95\%, 91\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
\text{TIPSOCH} = \text{CHCO} & \quad 74\%, 90\% \text{ ee} \\
\text{MeOCCH} = \text{CHCO} & \quad 83\%, 91\% \text{ ee} \\
\text{Me}_2\text{CCH} = \text{CHCO} & \quad 95\%, 97\% \text{ ee}
\end{align*}
\]
Catalytic Asymmetric Reduction with Organocatalysts

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

In order to rationalise the stereochemical 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**.
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.

enantiocenriched – 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.
**Racemisation**

*Racemisation* is the conversion of one enantiomer (or an excess of one enantiomer) into a 50:50 mixture of enantiomers. To draw a mechanism for *racemisation* you need to be able to draw the conversion of one enantiomer into the other enantiomer. Alternatively if you can draw a mechanism which involves an intermediate that contains a *plane of symmetry* then the product will be *racemic*.

**Problems** - the following compounds racemise under the conditions shown provide a mechanism (the starting materials are all enantiopure)

\[
\text{PhOH} \quad \text{N-OH} \quad \text{PhH} \quad \text{OMe} \quad \text{PhMeOMe} \quad \text{PhO} \quad \text{MeOH}
\]

racemises in acid  racemises in acid  racemises in acid  racemises in acid  racemises in base  racemises in acid  racemises in base

The following reactions all yield racemic products provide explanations (the starting materials are all enantiopure)

\[
\text{PhOH} \quad \text{PBr}_3 \quad \text{PhBr} \quad \text{CO}_2\text{Me} \quad \text{NaOMe, then MeI} \quad \text{MeO}_2\text{CMe} \quad \text{acidi}
\]

The reaction products and mechanisms are illustrated in the diagrams above.
Chirality is the property of the object and a number of every day objects are chiral.

Dice can clearly exist as enantiomers but they can also exist as diastereomers.

The question is how many stereoisomers of a standard dice (die) are there? And what are their relationship to one another?

We will define a standard dice as one where the numbers on opposite faces must add to seven.

The ‘two’ and ‘three’ must be drawn along a diagonal as above, the six can be drawn as above or rotated through 90°.
