Two chiral centres (diastereoisomers)

- A molecule with 1 stereogenic centre exists as 2 stereoisomers or enantiomers.
- Enantiomers have identical physical properties in an achiral environment.
- A molecule with 2 stereogenic centres can exist as 4 stereoisomers.
- Enantiomers (mirror images) still have identical physical properties.
- Diastereoisomers (non-mirror images) have different properties.

[Diagram showing two enantiomers of an epoxide with different melting points.]
Diastereoisomers

- **Enantiomers** differ only by their absolute stereochemistry (R or S etc)
- **Diastereoisomers** differ by their relative stereochemistry
- **Relative stereochemistry** - defines configuration with respect to any other stereogenic element within the molecule but does NOT differentiate enantiomers

In simple systems the two different relative stereochemistries are defined as below:

- A molecule can only have one enantiomer but any number of diastereoisomers
- The different physical properties of diastereoisomers allow us to purify them
- The differences between diastereoisomers will be the basis for everything we do...
Diastereoisomers II

- If a molecule has 3 stereogenic centres then it has potentially 8 stereoisomers (4 diastereoisomers & 4 enantiomers)
- If a molecule has \( n \) stereogenic centres then it has potentially \( 2^n \) stereoisomers
- Problem is, the molecule will never have more than \( 2^n \) stereoisomers but it might have less...
Meso compounds

- Tartaric acid has 2 stereogenic centres. But does it have 4 diastereoisomers?
- 2 diastereoisomers with different relative stereochemistry
- 2 mirror images with different relative stereochemistry
- 1 is an enantiomer
- The other is identical / same compound
- Simple rotation shows that the two mirror images are superimposable
Meso compounds II

- **Meso compounds** - an achiral member of a set of diastereoisomers that also includes at least one chiral member
- Simplistically - a molecule that contains at least one stereogenic centre **but** has a **plane of symmetry** and is thus **achiral**
- Meso compounds have a plane of symmetry with \((R)\) configuration on one side and \((S)\) on the other

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{OH} \\
\text{HO} & \quad \text{CO}_2\text{H} \\
\text{rotate LHS} & \\
\text{HO}_2\text{C} & \quad \text{OH} \\
\text{HO} & \quad \text{CO}_2\text{H}
\end{align*}
\]

- Another example...

\[
\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

achiral
non-superimposable on mirror image
(but it is symmetric!)

\[
\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

achiral
plane of symmetry
superimposable on mirror image (meso)
Chiral derivatising agents

- Difference in diastereomers allows **chiral derivatising agents** to **resolve** enantiomers

![Diagram of chiral derivatisation process]

- **Remember a good chiral derivatising agent should:**
  - Be enantiomerically pure (or it is pointless)
  - Coupling reaction of both enantiomers must reach **100%** (if you are measuring ee)
  - Coupling conditions should not **racemise** stereogenic centre
  - Enantiomers must contain point of **attachment**
  - Above list probably influenced depending whether you are measuring %ee or preparatively separating enantiomers
Chiral derivatising agents: Mosher’s acid

- Popular derivatising agent for alcohols and amines is α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) or Mosher’s acid
- Difference in nmr signals between diastereoisomers (above): $^1H$ nmr $\Delta \delta = 0.08 \text{ (Me)}$  
  $^{19}F$ nmr $\Delta \delta = 0.17 \text{ (CF}_3\text{)}$
- Typical difference in chemical shifts in $^1H$ nmr 0.15 ppm  
  $^{19}F$ nmr gives one signal for each diastereoisomer
- No $\alpha$-hydrogen so configurationally stable
- Diastereoisomers can frequently be separated

- In many cases use of both enantiomers of MTPA can be used to determine the absolute configuration of a stereocentre (73JACS512, 73JOC2143 & 91JACS4092)
Chiral derivatising agents: salts

- No need to covalently attach chiral derivatising group can use **diastereoisomeric ionic salts**
- **Benefit** - normally easier to recover and reuse reagent
- Use of non-covalent interactions allows other methods of resolving enantiomers...
Resolution of enantiomers: chiral chromatography

- **Resolution** - the separation of enantiomers from either a racemic mixture or enantiomerically enriched mixture
- **Chiral chromatography** - Normally HPLC or GC
- A racemic solution is passed over a chiral stationary phase
- Compound has rapid and reversible diastereotopic interaction with stationary phase
- Hopefully, each complex has a different stability allowing separation

![Diagram of resolution of enantiomers](image)
Chiral chromatography

- Measurements of ee by HPLC or GC are quick and accurate (±0.05%)  
- Chiral stationary phase may only work for limited types of compounds  
- Columns are expensive (>£1000)  
- Need both enantiomers to set-up an accurate method
NMR spectroscopy: chiral shift reagents

- Chiral **paramagnetic lanthanide** complexes can bind reversibly to certain chiral molecules via the metal centre
- Process faster than nmr timescale and normally observe a **downfield shift** (higher ppm)
- Two diastereomeric complexes are formed on coordination; these may have different nmr signals

![Chemical structure]

- **Problems** - as complexes are paramagnetic, line broadening is observed (especially on high field machines)
- Compound must contain **Lewis basic lone pair** (OH, NH$_2$, C=O, CO$_2$H etc)
- Accuracy is only ±2%
Chiral shift reagents II

New reagents are being developed all that time that can overcome many of these problems

1H NMR spectra (400 MHz) of valine (0.06 M, [D]/[L] = 1/2.85) in D₂O at pH 9.4
Enzymatic resolution

- **Enzymes** are very useful for the resolution of certain compounds
- Frequently they display very high selectivity
- There can be limitations due to solubility, normally only one enantiomer exists and can be too substrate specific
- Below is the rationale for the selectivity observed above...

Enzyme interaction with enantiomers:
- Diastereomeric interaction of enzyme lone pair with $\sigma^*$ orbital of C–F of (S)-enantiomer favoured over interaction with (R)-enantiomer.