Key Concepts in Stereoselective Synthesis

1 Strategies in synthesis

The type of complex molecule synthesis determines the need for control of absolute configuration.

1.1 Linear

In many linear syntheses, all stereochemistry is set relative to an initial stereocenter. Some of these syntheses give final products that are racemic, even though the targets contain multiple stereocenters. Today, most of the natural product synthesis are enantioselective.

![Erythronolid B](image)

1.2 Convergent

In a convergent synthesis, two complex building blocks are brought together at a later stage in the synthesis. Each of the building blocks must be enantiomerically pure and in the correct absolute configuration.

![6-deoxy-Erythronolid B](image)

Corey *JACS* 1978, 100, 4618 & 4620

Evans *JACS* 1998, 120, 5921
1.3 Iterative

In an iterative synthesis (see chapter 13), similar building blocks and reactions are used in a repetitive fashion to build complex molecules with relatively few reagents and conditions. Each of the building blocks must be enantiomerically pure and in the correct configuration. Peptide synthesis is another important example of this synthetic strategy.

1.4 Late stage functionalization and semi-synthesis

The selective reactions of complex molecules by chemical reagents have long been used for the preparation of derivatives and semi-synthesis. New reagents that effect chemoselective and regioselective functionalization of complex molecules are an important area of contemporary research and often involves the use of chiral reagents or catalysts.

1.5 Asymmetric vs. racemic synthesis

In a racemic synthesis, a target molecule is produced as a 50-50 mixture of enantiomers. If the target has multiple chiral centers, the correct diastereomer (with the correct relative configuration) is produced.

Asymmetric synthesis is the preparation of only one of the two possible enantiomers of the final product. This can be accomplished by a number of techniques, including:

1) **chiral pool** (chiral starting materials) – at least one of the stereocenters derives from an enantioenriched starting material such as a sugar or an amino acid.

2) **resolution** – a mixture of enantiomers is separated by chemical, chromatographic, or catalytic (often enzymatic) resolution. This can be done at any stage of the synthesis.

3) **chiral auxiliaries** – an enantiopure appendage is used to introduce new stereocenters in a defined relative configuration (substrate control). This appendage is later removed and often recycled.

4) **enantioselective synthesis** – new stereocenters are introduced by reagent control from a chiral reagent that does not itself become part of the product. When substoichiometric quantities of the chiral reagent are used, it is known as **catalytic, enantioselective synthesis**.
2 Key stereochemical terminology

Stereochemical terminology in organic chemistry can refer to the structure of a molecule or to properties of a physical sample of the molecule. It is very important to recognize the distinction and to use the correct terminology.

2.1 Properties of a molecule

A molecule (or any object) is **chiral** if it is non-superimposable on its mirror image (its *enantiomer*). In organic chemistry, it is usually the case that a molecule that has at least one carbon with four different substituents is **chiral**. Such carbons or other stereogenic elements are known as **chiral centers**.

2.1.1 Stereochemical terminology for molecules

- **achiral** – a molecule or object that is superimposable on its mirror image
- **chiral** – a chiral molecule is non-superimposable on its mirror image. Often, chiral organic molecules contain at least one stereocenter (or stereogenic center) which is usually a tetrahedral carbon with 4 different substituent groups.
- **meso** – a molecule that is superimposable on its mirror image due to an internal plane of symmetry.

![Chemical structures](image)

2.1.2 Absolute configuration, Cahn-Ingold–Prelog

The absolute configuration of a chiral center is its specific 3-D structure, usually assigned as \((R)\) or \((S)\) by the Cahn-Ingold-Prelog rules. It cannot be determined from optical rotation.

**Cahn-Ingold-Prelog**

1. **Rank substituents:**
   1. Higher molecular weight
   2. If identical move to next atom away from chiral center
   3. Multiple bonds count as two identical substituent atoms
2. Position lowest substituent in back
3. If a line from \(R_1\) to \(R_2\) is clockwise \(\rightarrow (R)\) configuration
   
   counterclockwise \(\rightarrow (S)\) configuration


The absolute configuration of a chiral center can be assigned by:

a) correlation to a compound of known absolute configuration

![Chemical reaction](image)

b) The formation a derivative with a known chiral center and determination of the relative configuration. A very common approach is to use Mosher’s ester.

Bode *JACS* 2010, 132, 8810
c) In some cases, by X-ray crystallography. In this case a heavy atom (sulfur or higher) must be in the structure to be determined and relatively close to a stereocenter.

2.1.3 Planar, axial, topological chirality and chirality at atoms other than carbon

Restricted rotations about sigma bonds and other structural features also give rise to chiral molecules. There are many such examples.

Important stereochemical terms that refer to the properties of a sample, NOT the structure of a molecule:

- **racemic** – a 50/50 mixture of two enantiomers
- **scalemic** – a sample with a non-racemic mixture of enantiomers, which can be:
  - **enantioenriched (optically active)** – a sample that contains both enantiomers, one in excess
  - **enantiotomerically pure (optically pure)** – a sample that contains only one enantiomer (>99.5% ee)

From the structure of a molecule in a paper or book, it is not possible to determine if the sample concern is enantiomerically pure or not. In this course, we will try to use the following nomenclature:
Enantiomers cannot be differentiated by most analytical methods (NMR, UV, IR, MS, melting point) as enantiomers have identical physical properties. The ratio of enantiomers can be determined by:

1) Optical rotation (less accurate and requires an enantiopure reference sample)
2) NMR with chiral shift reagents (formation of transient diastereomeric complexes)
3) Separation of enantiomers by chromatography on chiral solid supports [High Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), Super Critical Fluid Chromatography (SFC)]

The ratio of enantiomers (er) is most often expressed as % enantiomeric excess:

\[
\% \text{ ee} = \frac{\text{(enantiomer A} - \text{ enantiomer B)}}{\text{(enantiomer A} + \text{ enantiomer B)}} \times 100
\]

example: for a sample that has an enantiomeric ratio (er) = 66:22

\[
\% \text{ ee} = \frac{100 \times (66 - 22)}{(66 + 22)} = \frac{44}{68} \times 100 = 50% \text{ ee}
\]

2.3 Diastereomers (stereoisomers that are not enantiomers)

Diastereomers are stereoisomers that are not enantiomers. They have the same connectivity but differ in their spatial arrangements. Molecules with multiple stereocenters have diastereomers. Geometrical isomers (i.e. substituted olefins) are also considered diastereomers.

2.3.1 Relative stereochemistry

The relationship between the configuration of stereocenters within a molecule is known as relative stereochemistry. There is no formal naming system, but several colloquial nomenclatures are used, including: syn/anti, threo/erythro, chiral/meso, cis/trans (for cyclic structures)
Relative configuration can be determined by a number of methods, the most important of which are NMR (often accurate) and X-ray crystallography (always accurate). Often, the relative configuration of a complex natural product is determined years before the absolute configuration is established.

2.3.2 Olefin geometry

Olefin isomers are identified by cis/trans or (E)/(Z) designations. Under normal circumstances, olefins do not interconvert between geometric isomers.

2.3.3 Exo/endo & syn/anti geometry

Exo/endo and syn/anti are used in many different ways. A common usage is in defining the stereochemical course of reactions such as Diels-Alder cycloadditions. In this case, endo/exo refer to the orientation of a substituent group in the transition state of the cycloaddition, leading to a product of defined geometry.

2.4 alpha/beta

Alpha and beta are used to define the faces of molecules, particularly carbohydrates.

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Dunitz *ACIE* 2010, 49, 4503
2.5 Prochirality

A prochiral proton or group is one that leads to a chiral center when substituted or modified.

![Diagram of prochirality]

sp² hybridized compounds have prochiral faces, often referred to as the re and si faces.

Walsh and Kozlowski, *Fundamentals of Asymmetric Catalysis*, Appendix A

3 Stereochemistry of reactions

3.1 Loss of stereochemistry

3.1.1 Racemization

Racemization is the loss of enantiopurity by a stereomutation.

![Diagram of racemization]

Chibata, *JOC 1983, 48, 843*

3.1.2 Epimerization

Epimerization is a stereomutation at a single stereocenter. If a molecule has more than one stereocenter, it results in a mixture of diastereomers.

![Diagram of epimerization]

3.1.3 Loss of chirality

Some reactions destroy a chiral center, sometimes leading to an achiral product.

![Diagram of loss of chirality]

3.2 Stereoretention (stereocenters not involved in the reactions)

Stereocenters close to a site of chemical reaction, but not involved in the reaction, are often epimerized. When they are “retained” without loss of enantiopurity, the process is known as stereoretention or stereo preservation. Note that this is not the same as retention of stereochemistry.
3.3 Stereospecific reactions

In **stereospecific reactions**, the stereochemistry of the starting material determines the stereochemistry of the product. For a reaction to be stereospecific, the stereochemical transfer must be perfect. If it is not, it is a **stereoselective reaction**.

3.3.1 Inversion

Example: Mitsunobu Reaction (S$_{N}$2)


3.3.2 Retention

Double inversion

Anchimeric participation of chloride leads to retention of the configuration via an intermediate cyclic chloronium ion

Carreira *Nature 2009, 457, 573*

3.3.3 Stereospecific alkene functionalizations

Many reactions of alkenes are stereospecific and give the products as a single diastereomer

Shi *JOC 2004, 69, 327*

3.4 Diastereoselective reactions

Yamamoto *JACS 1988, 110, 4475*
3.5 Substrate controlled diastereoselective reactions (of molecules with preexisting stereocenters)

3.5.1 Cyclic stereocontrol

3.5.2 Acyclic stereocontrol (i.e. Felkin addition, chelation control, etc)

3.5.3 Directed reactions

3.5.4 Substrate control

3.5.5 Reagent control

Overman *Tet. Lett.* 1982, 23, 2355

Hoveyda and Evans *Chem. Rev.* 1993, 93, 1307

Masamune *ACIE* 1985, 24, 1

Masamune *ACIE* 1985, 24, 1
3.6 Enantioselective reactions

3.6.1 Stoichiometric reagents


3.6.2 Catalytic asymmetric synthesis

Shi *JACS* 1997, 119, 11224

4 Other important selectivity terms

4.1 Regioselectivity

"A regioselective reaction is one in which one direction of bond making or breaking occurs preferentially over all other possible directions."

(http://www.iupac.org/goldbook/R05243.pdf)

There are many ways in which the term regioselective is used. Occasionally specialized terms are used to describe regioselectivity such as *linear/branched* (i.e. in hydroformylations) and *internal/terminal* (olefin functionalization), *endocyclic/exocyclic*, *equatorial/axial*, and many more.

Reusch *JOC* 1980, 45, 5012
4.2 Chemoselectivity

“Chemoselectivity is the preferential reaction of a chemical reagent with one of two or more different functional groups.” ([http://www.iupac.org/goldbook/C01051.pdf](http://www.iupac.org/goldbook/C01051.pdf))

Bode ACIE 2006, 45, 1248

4.3 Group selectivity


5 Importance of asymmetric catalysis

5.1 All enantioenriched molecules derived from natural sources

Enantiomerically enriched chiral substance can only be generated from other chiral starting materials or by enantioselective reactions using chiral, enantiomerically enriched reagents or catalysts. The natural world is enantiomerically enriched: all genetically encoded amino acids are L-configured (usually (S)) and most natural sugars D-configured. Until the advent of asymmetric catalysis, very few methods to prepare chiral compounds were available. The chiral pool is now greatly expanded due to advances in asymmetric catalysis and biocatalysis. Some readily available, naturally derived chiral compounds include:

- ephedrine
- proline
- cinchona alkaloid
- tartaric acid
- glucose
- pinene

Enzymes often make excellent enantioselective catalysts and are commonly used by the pharmaceutical industry. A limitation is that only one enantiomer of enzymes is available and only one enantiomer of the product may be produced.

Savile and Janey Science 2010, 329, 305

The study of the origin of the enantiomerically pure amino acids is an active field, with numerous theories. There is no apparent reason, other than chance, for the configuration of the molecules found in nature.

Breslow PNAS 2009, 106, 9144 & PNAS 2010, 107, 5723
5.2 All new pharmaceuticals must be single enantiomer

In 1992, the US Federal Drug Administration (FDA) decreed that all new molecular entities (drugs) be approved as single enantiomers. Previously, mixtures of enantiomers were sold even though the two enantiomers often had completely different biological activities.

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm

5.3 Enantiomers have different biological properties

5.3.1 Example of fragrances

5.3.2 Industrial catalytic enantioselective processes

Examples

Barham Chem. Rev. 2010, 110, 2313

Noyori JACS 1987, 109, 5856

5.4 Nobel prizes related to stereochemistry and asymmetric catalysis

“Since their launch in 1901, the Nobel Prizes have rewarded more achievements in the study of carbon-based substances, otherwise known as organic chemistry, than in any other traditional chemistry discipline.”
- Derek Barton and Odd Hassel (1969)
- John Cornforth and Vladimir Prelog (1975)
- Donald Cram, Jean-Marie Lehn and Charles Pedersen (1987)
- William Knowles, Ryoji Noyori and Barry Sharpless (2001)

5.5 Historical and contemporary names in catalytic, enantioselective synthesis (selected names)

Enantioselective Lewis acid catalysis: Mukaiyama, Yamamoto, Corey, Evans, Mikami, Carreira, Shibasaki, many others
Transition metal catalysis: Trost, Overman, Backvall, Pfaltz, Togni, Hayashi, Sigman, Stoltz, Doyle, Davies, Hoveyda, Feringa, Kundig, many others
Oxidation: Sharpless, Jacobsen, Katsuki, Shi
Reduction: Knowles, Noyori, Backvall, Corey, Pfaltz, Zhang

Organocatalysis: Vedejs, Fu, List, Barbas, Jacobsen, Miller, Macmillan, Jorgensen, Enders, Akiyama, Terada, Bode, Reuping, Maruoka, Hayashi

6 Problems with enantioselective catalysis

6.1 Catalyst generality

A major problem with catalytic enantioselective synthesis is the fact that in many cases, small changes in the substrates dramatically change the results. The search for “general” catalysts is an important topic but is probably unobtainable.

[Chemical structures shown]

Schrock and Hoveyda JACS 2006, 128, 5153

6.2 Catalyst identification

It is often very difficult to identify the best ligand or metal ligand-combination for a given transformation. Most major pharmaceutical and related companies now have entire units dedicated to screening catalysts for enantioselective reactions. Each substrate often requires extensive optimization. Strategies that allow rapid generation and optimization of enantioselective catalysts are in great demand.

Example: this peptide catalyst for Morita-Baylis-Hillman reactions was selected first from a random library of 105 peptides and then subjected to further optimization.
6.3 Preparation of chiral catalysts and ligands

Many good chiral catalysts require multiple synthetic steps and are very expensive to produce. The cost of the catalyst is often prohibitive.

6.4 Substrate scope

Many catalytic enantioselective reactions are severely limited in substrate scope. Often only substrates with aryl groups are tolerated, and the process is not suitable for other substrates.

While this reaction shows high selectivities with aromatic substrates, aliphatic and functionalities are not tolerated or give low selectivities.

6.5 Sub-optimal enantioselectivities

Although it is sometimes possible to crystallize products with modest enantiomeric excess to enantiopurity, this is often difficult and requires extensive optimization. Many powerful enantioselective reactions are not used because they deliver sub-optimal enantioselectivities.

Although this chemistry was perfect for preparing monomers for beta3-peptide synthesis, the sub-optimal enantioselectivity forced researchers to adopt a longer, less efficient route using a chiral auxiliary. The chiral auxiliary approach, however, allowed the preparation of a number of monomers in high enantiomeric excess.
6.6 Non-standard protecting groups

In many cases, protecting groups are selected for compatibility with the catalytic enantioselective reactions rather than their utility in the resulting products. This leads to catalytic enantioselective reactions that give products that cannot be further elaborated due to the lack of methods to remove the “protecting groups”. For example, despite the importance of enantiopure beta-amino acids, few catalytic enantioselective routes are actually used to make the monomers.

![Chemical structure]

Terada ACIE 2006, 45, 2254

6.7 Complicated and sensitive reaction conditions

Many catalytic enantioselective reactions suffer from very sensitive and delicate reaction conditions. This makes repeating the reactions very difficult, often leading to frustration. For example, the following reaction is very useful and simple to set up, but often difficult to execute.

![Chemical structure]

Macmillian JACS 2002, 124, 6798
Pihko Tet. Lett. 2003, 44, 7607

6.8 Good ee vs. useful transformations

In recent years, academic scientists have focused more on enantioselectivity than on the usefulness of a given transformation. This has led to a large body of highly enantioselective reactions of limited utility and with poor substrate scope that are published only due to high ee. Often, more interesting reactions reported for the first time in racemic form are overlooked. In contrast, the early days of the field were focused on developing enantioselective reactions of the most useful processes such as hydrogenation, epoxidation, and ketone reduction.

![Chemical structure]

Lu ACIE 2010, 49, 7753
6.9 Cost vis-à-vis traditional methods

Very often, traditional methods such as resolution by salt formation are simple and cheaper than even a good catalytic enantioselective process. This is particularly true of transition metal-catalyzed reactions employing palladium, rhodium, iridium or other expensive metals. The few catalytic enantioselective processes used in industry with these metals are extremely effective and use very low catalyst loadings.

Brown’s stoichiometric chiral allylation reagent:

\[
\begin{array}{c}
\text{Me} \\
\text{B} \\
\text{2} \\
\end{array}
\begin{array}{c}
\text{H} \\
\text{Ph} \\
\text{1.0 equiv} \\
\text{1.0-1.5 equiv} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{OH} \\
\text{Ph} \\
\text{94% ee} \\
\end{array}
\text{Et}_2\text{O}, -78 \degree \text{C}
\]

Brown \textit{JOC} \textbf{1991}, \textit{56}, 401

Krische’s catalytic asymmetric allylation

\[
\begin{array}{c}
\text{OAc} \\
\text{Reagents:} \\
\text{Cs}_2\text{CO}_3 (20 \text{ mol\%}) \\
\text{P} - \text{Cl-MeO-BIPHEP} (5 \text{ mol\%}) \\
\text{PhOH} \text{ (50 \text{ mol\%})} \\
0.2 \text{ M THF, 100 \degree C, 20 h} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{OH} \\
\text{Ph} \\
73\% \text{ yield} \\
94\% \text{ ee} \\
\end{array}
\]

Krische \textit{JACS} \textbf{2008}, \textit{130}, 14891

6.10 Patents and licensing

There have been numerous cases where demands for royalties to use a catalytic enantioselective reaction in the preparation of an important molecule prevented its eventual adoption. An excellent case is the preparation of chiral amino indanol, which was needed for the synthesis of an anti-HIV drug. A method using Jacobsen’s epoxidation was owned by Sepracor. Merck instead contracted a company to produce it by a biotechnological approach. Olefin metathesis using Grubbs’ catalysts suffers from similar problems, as the company that owns the license demands large royalties for its use. This has led to new variants from companies and other groups that get around the intellectual property.

\[
\begin{array}{c}
\text{NH}_2 \\
\text{15, 2f} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{Indinavir} \\
\end{array}
\]