

5.1 Why stereochemistry decides what a drug does

Enantiomers have identical melting points, spectra (in achiral environments) and reactivity towards achiral reagents, but a living body is built from chiral molecules, so to a receptor, an enzyme or a transporter the two enantiomers are different substances. One enantiomer of carvone smells of spearmint, the other of caraway, a harmless illustration of a serious rule. In medicines the rule decides efficacy and safety together: only one enantiomer of ethambutol carries the antitubercular activity while the other is associated with the ocular toxicity; levodopa is the drug and its enantiomer is not. The thalidomide disaster is the standard caution: the (R) enantiomer is the sedative and the (S) enantiomer is teratogenic, but because the two interconvert in the body, administering the pure enantiomer would not by itself have prevented the tragedy, the deeper lesson being that stereochemistry must be understood, not merely separated. Diastereomers, by contrast, differ in every physical property and behave as ordinary different compounds, which is precisely what makes resolution (section 5.9) possible.

5.2 Optical activity and specific rotation

Enantiomers rotate the plane of plane-polarised light by equal amounts in opposite directions. The measured rotation, α , depends on path length, concentration, solvent, temperature and wavelength, so the comparable quantity is the **specific rotation**, defined as the observed rotation divided by the product of path length in decimetres and concentration in grams per millilitre, conventionally measured at the sodium D line (589 nm) and quoted with its temperature: $[\alpha]_D$. A pure enantiomer has a characteristic value; the ratio of a sample's rotation to that of the pure enantiomer gives its **optical purity**, numerically equal to the **enantiomeric excess**, $ee = (\text{majority enantiomer} - \text{minority enantiomer}) / \text{total} \times 100$. A 50:50 mixture, a **racemate**, rotates nothing at all and has ee zero. Modern practice measures ee directly by chiral chromatography, but polarimetry remains the pharmacopoeial identity test for chiral drugs and the definition from which the whole language of this unit hangs.

5.3 The CIP sequence rules and R/S assignment

Assigning R and S: the CIP procedure

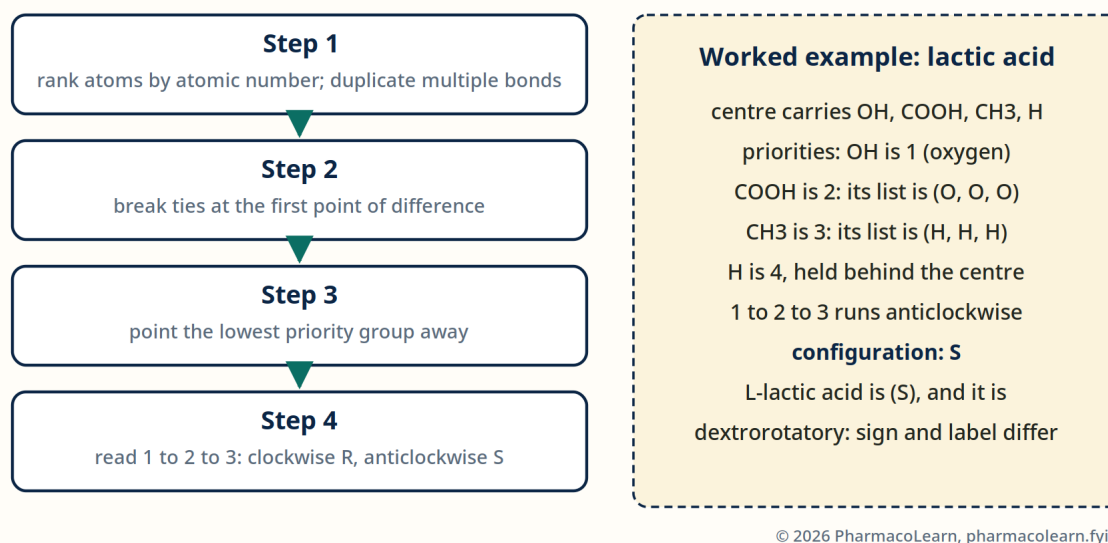


Figure: The CIP procedure in four steps, worked through for lactic acid: the natural L form is (S) yet dextrorotatory, a standing warning that sign and configuration are different things.

Absolute configuration is assigned by the **Cahn-Ingold-Prelog** rules. At a stereocentre, the four attached atoms are ranked by atomic number. Ties are broken by listing the atoms attached to each tied atom in decreasing order and comparing the lists at the first point of difference. Multiple bonds are expanded by the duplicate atom convention: a doubly bonded atom is treated as duplicated, so a carbonyl carbon counts as bonded to (O, O, and the third substituent), which is why a carboxyl group outranks a hydroxymethyl group. Isotopes rank by mass, deuterium above hydrogen. With priorities 1 to 4 assigned, the molecule is viewed with priority 4 pointing away; if the sequence 1 to 2 to 3 runs clockwise the centre is **R** (rectus), if anticlockwise, **S** (sinister).

Worked example, lactic acid. The stereocentre carries OH, COOH, CH₃ and H. Oxygen (atomic number 8) is priority 1. Both remaining carbons are tied at the first atom; comparing their substituent lists, the carboxyl carbon counts as bonded to (O, O, O) once its double-bonded oxygen is duplicated, against the methyl carbon's (H, H, H), so COOH is priority 2 and CH₃ priority 3, H priority 4. Natural L-lactic acid, the acid of muscle and of fermented milk, has these priorities running anticlockwise with H behind, and is therefore (S)-lactic acid; it is also dextrorotatory, a permanent reminder that the sign of rotation cannot be predicted from the R/S label.

Assigning R or S at a stereocentre

1. Rank the four atoms attached by atomic number.
2. Break ties with the substituent lists, first point of difference; expand double and triple bonds into duplicated atoms.
3. Put the lowest priority group pointing away from you.
(If it points towards you, assign, then reverse the answer.)
4. Read 1 to 2 to 3: clockwise is R, anticlockwise is S.

5.4 Meso compounds and pseudoasymmetric centres

Tartaric acid has two identical stereocentres and three stereoisomers, not four: (2R,3R), which is dextrorotatory; its mirror image (2S,3S); and the (2R,3S) form, which is superposable on its own mirror image because it contains a **plane of symmetry** through its middle. This internally compensated, achiral form is a **meso compound**: it has stereocentres and yet is optically inactive, and its physical properties

differ from the chiral pair. A subtler case is the **pseudoasymmetric centre**: a tetrahedral atom attached to two constitutionally identical groups that differ only in their own configuration (one R, one S), plus two different groups. The centre of 2,3,4-trihydroxyglutaric acid, when the outer centres are (2R,4S), is such a case: swapping its H and OH produces a stereoisomer, so the centre is stereogenic, yet the molecule as a whole is achiral. CIP gives these centres the lowercase descriptors **r** and **s**. Meso and pseudoasymmetric cases are the standing proof that "has stereocentres" and "is chiral" are not the same statement.

5.5 Symmetry, axes and chirality without a stereocentre

A molecule is achiral if it possesses an **improper axis of symmetry** (S_n), of which the commonest examples are a mirror plane (a plane of symmetry, S_1) and a centre of inversion (S_2). Proper rotation axes (C_2 , C_3 and so on) are compatible with chirality and are common in chiral molecules; (R)-BINAP of Unit 4 is chiral and has a C_2 axis. Chirality also exists without any tetrahedral stereocentre: **axial chirality** appears in allenes with different substituents at each end (the two pi systems are perpendicular, so the molecule is a twisted, non-superposable mirror pair), in hindered biphenyls whose rings cannot rotate past each other (atropisomerism; the basis of BINAP and of vancomycin's rigid shape), and in spiranes. Helicenes and suitably substituted cyclophanes extend the list. The general definition survives all cases: a molecule is chiral when it is not superposable on its mirror image, and every assignment system in this unit is bookkeeping for that single fact.

5.6 Fischer projections and D and L notation

The **Fischer projection** compresses a stereocentre into a cross: horizontal bonds project towards the viewer, vertical bonds away. It follows strict rules: rotating a Fischer projection by 180 degrees in the plane leaves the configuration unchanged; rotating by 90 degrees, or lifting it out of the plane, inverts it; exchanging any two groups inverts the centre, so two exchanges restore it. Fischer assigned the hydroxyl of glyceraldehyde: on the right in a projection with the aldehyde at the top defined the **D** series, on the left the **L** series, an arbitrary choice later proved lucky, since D-(+)-glyceraldehyde is indeed (R). The notation survives where families are compared: sugars are D or L by the configuration at the highest numbered stereocentre (most natural sugars are D), and alpha amino acids are L when the amino group sits on the left with the carboxyl group at the top (nearly all natural amino acids are L, and, because of the priority of the CH_2SH group, cysteine is the famous case where an L amino acid is (R) rather than (S)).

5.7 cis-trans isomerism and E and Z notation

For alkenes, the older cis-trans language works only when each double bond carbon carries one substituent that can be matched with the other (the two hydrogens of 2-butene: cis-2-butene has both methyls on the same side, trans-2-butene opposite). When all four substituents differ, cis and trans become meaningless and the **E/Z system** takes over: apply CIP ranking at each end of the double bond independently; if the two higher priority groups are on the same side the alkene is **Z** (zusammen, together), if opposite, **E** (entgegen). Thus cis-2-butene is (Z)-2-butene and trans-2-butene is (E)-2-butene, but for many substituted alkenes the two languages disagree, and only E/Z is unambiguous. The physical consequences of geometry are large: maleic acid (cis-butenedioic acid, Z) melts near 130 degrees Celsius and readily forms a cyclic anhydride because its carboxyl groups are neighbours, while fumaric acid (the E isomer) melts near 287 degrees, is far less soluble, and cannot form the same anhydride; the body exploits the difference, since fumarate is a metabolic intermediate and maleate is not.

5.8 Resolution of racemates and enantiopure separation

A racemate from an achiral synthesis must be **resolved** when only one enantiomer is wanted. Racemates come in three physical types, and the type decides the method: **conglomerates** (mechanical mixtures of

enantiomer crystals, a small minority) can in principle be separated directly; **racemic compounds** (both enantiomers in one crystal lattice, the great majority) cannot; solid solutions are worst of all. The methods:

- **Direct crystallisation:** Pasteur's 1848 manual separation of the hemihedral crystals of sodium ammonium tartrate, a conglomerate below about 27 degrees Celsius, founded stereochemistry; preferential crystallisation with seeding scales the same idea for conglomerates.
- **Diastereomeric salt formation, the industrial workhorse:** the racemic acid is treated with a single-enantiomer base (or the racemic base with a chiral acid such as tartaric or mandelic acid, or resolving bases such as 1-phenylethylamine and the cinchona alkaloids). The two products are diastereomers, differ in solubility, and separate by crystallisation; acid-base work-up then liberates the resolved enantiomer and the resolving agent is recycled. Classical resolution of racemic naproxen by this method supplied the (S) drug for years.
- **Kinetic resolution:** a chiral reagent, catalyst or enzyme reacts with one enantiomer faster, ideally leaving the other untouched at 50 percent conversion; the Sharpless epoxidation of a racemic secondary allylic alcohol and lipase-catalysed acylations are the standard examples, and dynamic kinetic resolution, racemising the slow enantiomer in situ, lifts the 50 percent ceiling.
- **Chromatographic separation:** chiral stationary phases (polysaccharide derivatives above all) separate enantiomers analytically for ee measurement and preparatively; simulated moving bed chromatography runs the separation continuously at production scale. This is the modern meaning of **enantiopure separation** when resolution by crystallisation fails.

5.9 Asymmetric synthesis, strategy one: the chiral pool

The **chiral pool** strategy buys chirality from nature: begin with an enantiopure natural product (a sugar, amino acid, hydroxy acid or terpene) whose stereocentres are already correct, and build the target around them, never creating the key stereocentres from scratch. The pool's most used building blocks include the protein amino acids, tartaric and lactic acids, D-mannitol (converted to a protected glyceraldehyde, a three-carbon chiral unit) and L-serine (converted to Garner's aldehyde, a protected alpha-amino aldehyde that feeds countless heterocycle and sphingolipid syntheses). The strategy is unbeatable when the target maps onto a pool member (many beta-lactam, statin side chain and nucleoside syntheses are pool-based) and useless when it does not; the stereocentres you are given are the ones you must use.

5.10 Asymmetric synthesis, strategy two: chiral auxiliaries

A **chiral auxiliary** is an enantiopure controller attached to the substrate for one stereochemistry-setting step and removed afterwards. It works by making the two faces of a planar reactive centre diastereotopic: the auxiliary blocks one face, the reaction happens on the other, and cleavage releases the product with the new stereocentre set. The canonical example is the **Evans aldol reaction**: an N-propionyl oxazolidinone (the auxiliary derived from a chiral amino alcohol) is converted with dibutylboron triflate to its (Z)-boron enolate, which adds to an aldehyde through a chair-like Zimmerman-Traxler transition state to give the syn aldol product with very high diastereoselectivity; hydrolysis then removes the auxiliary, which is recovered and reused, and leaves an enantiopure beta-hydroxy carbonyl fragment of the kind polyketide drugs are made from. Oppolzer's camphorsultam and Myers' pseudoephedrine amides run the same logic for alkylations. Auxiliaries cost two extra steps (attach, remove) and are stoichiometric, but they are predictable, general and deliver diastereomers, which can be purified by ordinary crystallisation before the auxiliary comes off: reliability is their virtue.

5.11 Asymmetric synthesis, strategy three: chiral catalysts, and stereoselective synthesis with examples

Catalytic asymmetric synthesis (Unit 4, sections 4.7 and 4.9) replaces the stoichiometric controller with a substoichiometric chiral catalyst: Sharpless asymmetric epoxidation sets two stereocentres of an allylic alcohol with titanium tartrate; Knowles and Noyori hydrogenations make amino acid and alcohol products at industrial scale; the Corey-Bakshi-Shibata oxazaborolidine reduces ketones predictably with borane. This is the most atom-economical strategy (principle 9 again) and the first choice when a catalyst exists for the transformation.

Two distinctions close the unit. A **stereospecific** reaction converts each stereoisomer of reactant into a defined stereoisomer of product by mechanistic necessity: anti bromination turns (E)-2-butene into meso-2,3-dibromobutane and (Z)-2-butene into the racemic pair, with no crossover. A **stereoselective** reaction merely prefers one stereoisomeric product from a single reactant: the Zimmerman-Traxler control of enolate geometry in aldol reactions ((Z)-enolates give syn products, (E)-enolates anti) makes aldol chemistry **diastereoselective**, and every method of this unit, pool, auxiliary or catalyst, is a device for making some bond-forming step stereoselective. In practice routes are judged by the combination of diastereomeric ratio, enantiomeric excess, and whether the unwanted isomer can be recycled.

Strategy	Source of stereocontrol	Controller amount	Extra steps	Best suited to
Chiral pool	A natural enantiopure starting material	It is the starting material	None for the borrowed centres	Targets whose skeleton maps onto a sugar, amino acid or terpene
Chiral auxiliary	A recoverable group attached to the substrate	Stoichiometric, but recycled	Attach and remove	Predictable, crystalline intermediates; aldol and alkylation chemistry
Chiral catalyst	A chiral ligand, enzyme or organocatalyst	Substoichiometric, sometimes ppm levels	None	Scale manufacture; hydrogenation, epoxidation, reduction

Frequently Asked Questions

Q: Why is a microwave reaction finished in ten minutes when the same mixture needs six hours in an oil bath? Because the microwave heats the mixture itself, not the vessel wall, and sealed vessels let the solvent run far above its boiling point. The rate increase is thermal: rapid heating plus superheating, each 10 degrees roughly doubling the rate by the Arrhenius equation.

Q: What is the difference between atom economy and the E factor? Atom economy is a paper calculation: the fraction of the reactants' mass that can appear in the product, ignoring yield and solvents. The E factor is measured on the real process: kilograms of everything wasted per kilogram of product, solvents and work-up included. A route can have perfect atom economy and a dreadful E factor.

Q: Boc or Fmoc: why has Fmoc become the default solid phase strategy? Fmoc deprotection uses piperidine instead of repeated strong acid, and the final cleavage uses trifluoroacetic acid instead of liquid HF, so the method is safer, easier to automate and continuously monitored by the ultraviolet absorbance of the fulvene by-product. Boc chemistry survives for long, aggregation-prone sequences where its acidic cycles keep the chain dissolved.

Q: Why is racemisation such a central problem in peptide synthesis? Because the activated carboxyl component can cyclise to an oxazolone whose alpha proton is easily lost, erasing the stereocentre before the amine attacks. Urethane protecting groups, racemisation-suppressing additives such as HOBt and Oxyma, and planning fragment couplings at glycine or proline junctions are the standard defences.

Q: How do I predict whether an electrocyclic reaction is conrotatory or disrotatory? Count the pi electrons. A 4n system closes thermally in the conrotatory sense and photochemically in the disrotatory

sense; a 4n plus 2 system does the exact opposite, thermal disrotatory and photochemical conrotatory.

Q: Why does the Diels-Alder reaction usually give the endo product when the exo product is more stable? The endo transition state is stabilised by secondary orbital interactions between the dienophile's substituents and the diene's pi system, so the endo product forms faster. It is a kinetic product: give the reaction time and heat to become reversible, as in furan cycloadditions, and the exo product accumulates.

Q: If homogeneous catalysts are more selective, why does industry prefer heterogeneous catalysts so often? Because separation and lifetime dominate plant economics. A heterogeneous catalyst is filtered off or stays in its reactor, is recycled for months and cannot contaminate the product with dissolved precious metal, an especially strict requirement in drug manufacture. Homogeneous catalysis wins where its selectivity or mild conditions are decisive and recovery is engineered in.

Q: What does Wilkinson's catalyst not reduce, and why does that matter? Under its usual mild conditions it hydrogenates carbon-carbon double bonds, the least hindered fastest, while leaving carbonyls, nitro groups, nitriles and benzyl ethers intact. That chemoselectivity lets a chemist reduce one double bond in a polyfunctional drug intermediate without protecting everything else.

Q: How does a phase transfer catalyst move hydroxide into an organic phase? It does not move hydroxide alone: a lipophilic quaternary ammonium cation pairs with the anion in the aqueous phase and carries the pair into the organic solvent, where the anion is weakly solvated and therefore highly reactive. The cation returns with the leaving group anion and repeats the shuttle thousands of times.

Q: A compound has two stereocentres but is optically inactive. How? It is a meso compound: the two centres have opposite configurations and the molecule contains a symmetry element (a plane through its middle in meso tartaric acid), so it is superposable on its mirror image and its two halves cancel each other's rotation internally. Chirality is a property of the whole molecule, not a count of stereocentres.

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