Organic Chemistry I

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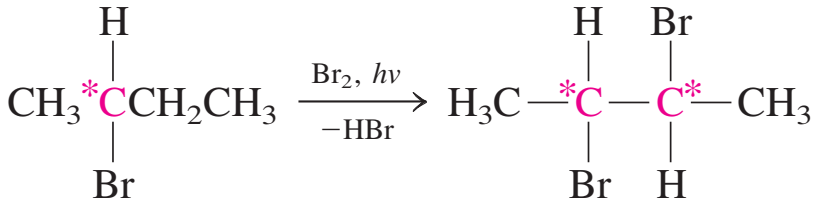
MESO COMPOUNDS

2,3-dibromobutane can be obtained by the radical bromination of 2-bromobutane.



2,3-Dibromobutane

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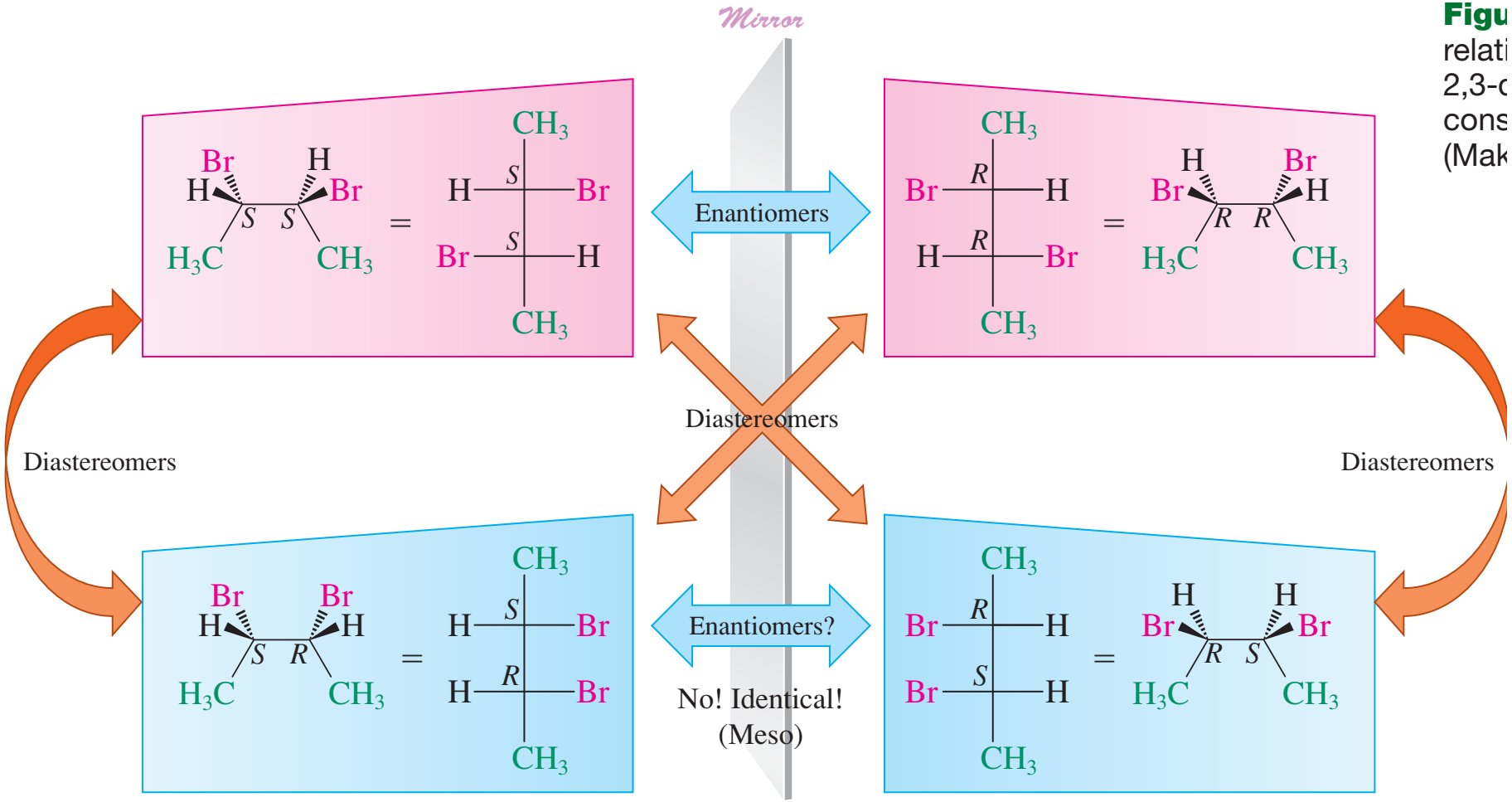
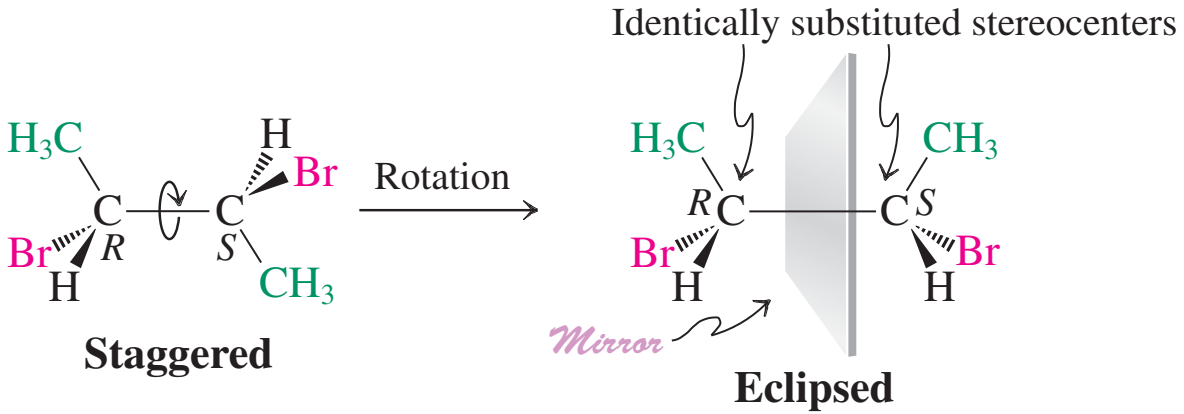
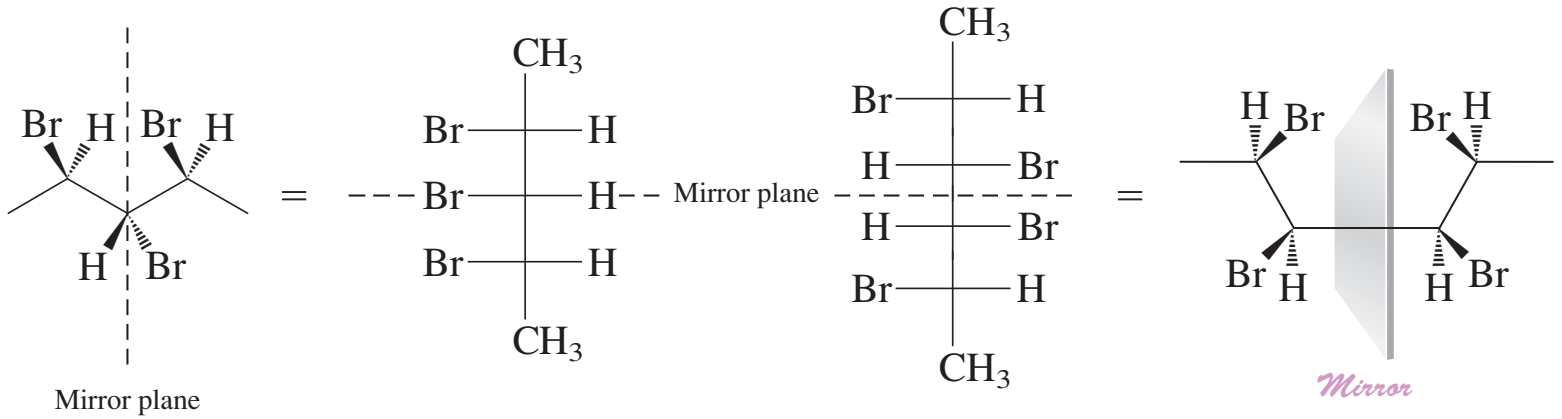


A compound that contains two stereocenters but is superimposable with its mirror image is a **meso compound** (*mesos,* Greek, middle). A characteristic feature of a meso compound is the *presence of an internal mirror plane,* which divides the molecule such that one half is the mirror image of the other half.



Two identically substituted stereocenters give rise to only three stereoisomers

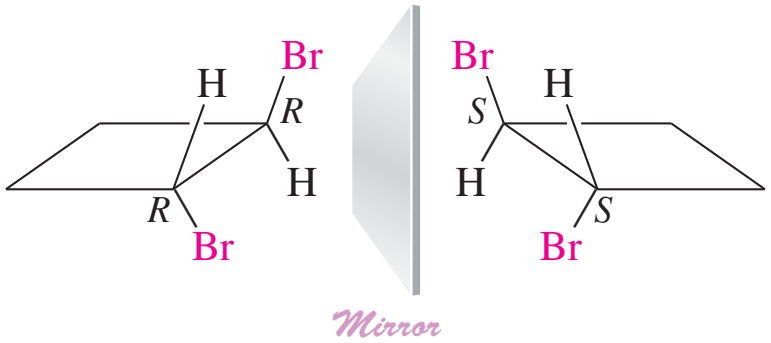
Meso Compounds with Multiple Stereocenters



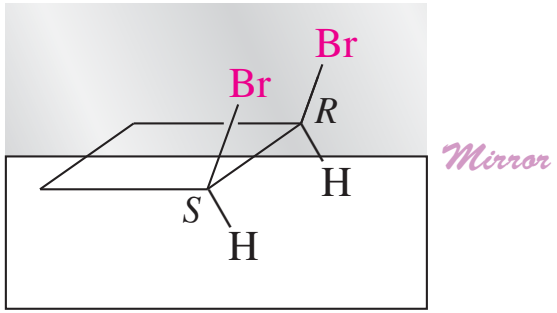
Cyclic compounds may also be meso

Trans-1,2- dibromocyclobutane exists as two enantiomers (*R*,*R* and *S*,*S*) and may therefore be optically active.

The cis isomer has an internal mirror plane and is meso, achiral, and optically inactive.



Enantiomers of chiral diastereomer
***trans*-1,2-Dibromocyclobutane**



1*R*,2*S* same as 1*S*,2*R*

Meso diastereomer

***cis*-1,2-Dibromocyclobutane**

STEREOCHEMISTRY IN CHEMICAL REACTIONS

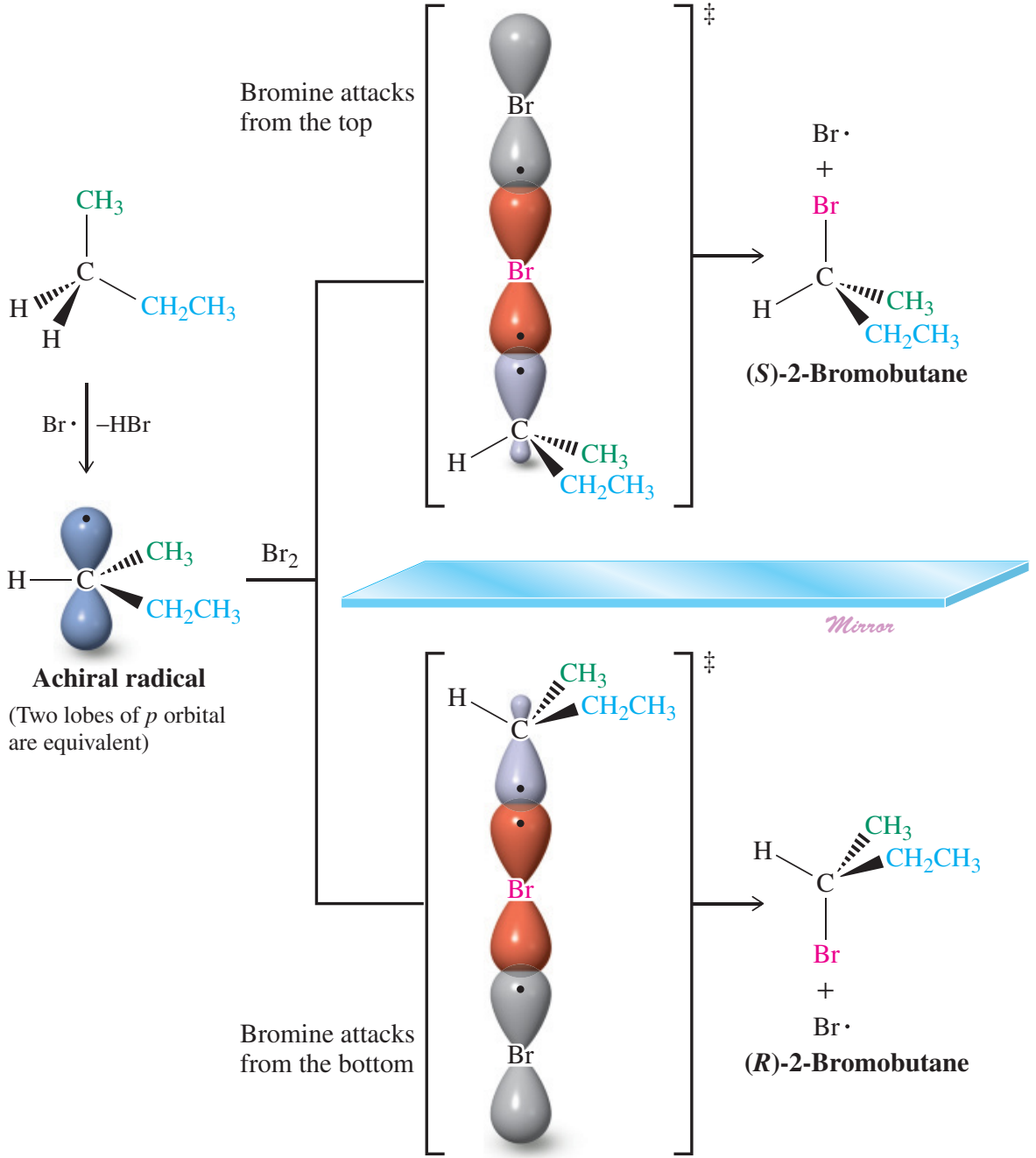
As a model, the conversion of achiral butane into chiral 2-bromobutane will be considered.

The radical mechanism explains why the bromination of butane results in a racemate

The radical center has two equivalent reaction sites (a planar, sp^2-hybridized)—the two lobes of the *p* orbital—that are equally susceptible to attack by bromine in the second step.

The two transition states resulting in the respective enantiomers of 2-bromobutane are mirror images of each other. They are enantiomeric and therefore energetically equivalent. The rates of formation of *R* and *S* products are hence equal, and a racemate is formed.

In general, *the formation of chiral compounds* (e.g., 2-bromobutane) *from achiral reactants* (e.g., butane and bromine) *yields racemates.* Or*, optically inactive starting materials furnish optically inactive products.*


Bromine attacks from the top
CH3
C
H
H
CH2CH3
Br·
–HBr
H
C
CH3
CH2CH3
Achiral radical
(Two lobes of p orbital are equivalent)
Br2
Br
Br
C
H
CH3
CH2CH3
‡
Br·
+
Br
C
H
CH3
CH2CH3
(S)-2-Bromobutane
Mirror
H
C
CH3
CH2CH3
‡
Br
Br
Bromine attacks from the bottom
H
C
CH3
CH2CH3
Br
+
Br·
(R)-2-Bromobutane
Enantiomeric transition states
(Equal in energy)

The presence of a stereocenter affects the outcome of the reaction

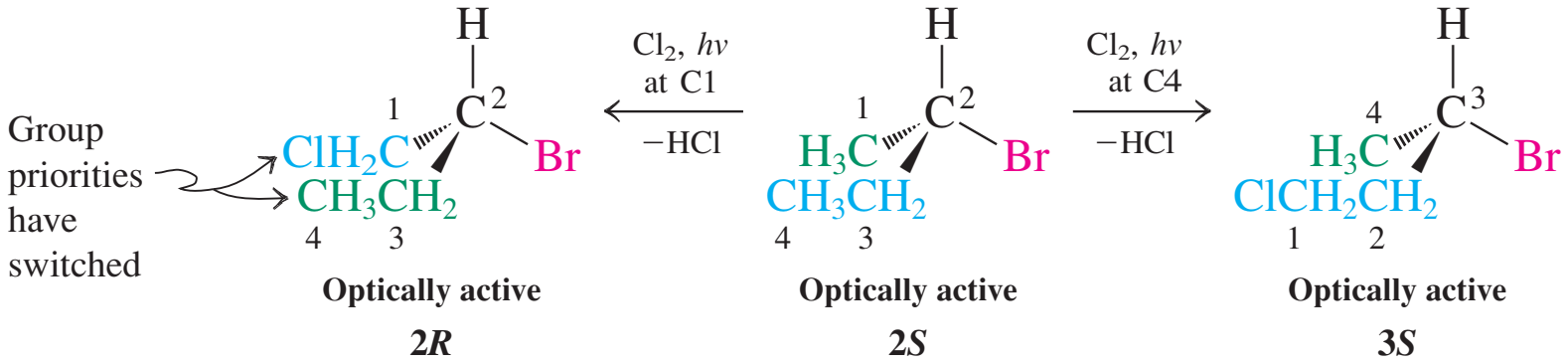
Halogenation of a chiral and enantiomerically pure molecule.

In the radical chlorination of the *S* enantiomer of 2-bromobutane, the chlorine atom has several options for attack: the two terminal methyl groups, the single hydrogen at C2, and the two hydrogens on C3.

Chlorination of either terminal methyl group is straightforward. *Both of these chlorination products are optically active because the original stereocenter is left intact.*

The conversion of the C1 methyl into a chloromethyl unit changes the sequence of priorities around C2, its designated configuration changes from *S* to *R.*

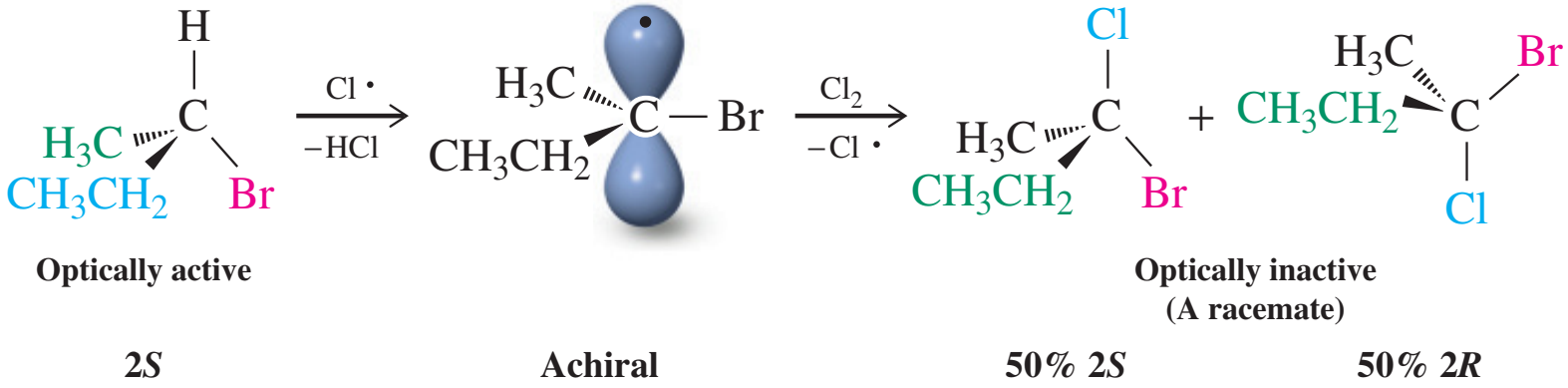
Chlorination of (*S*)-2-Bromobutane at Either C1 or C4



Chlorination can occur at C2 of (*S*)-2-bromobutane from either side through enantiomeric transition states of equal energy, producing (*S*)- and (*R*)-2-bromo-2-chlorobutane at equal rates and in equal amounts.

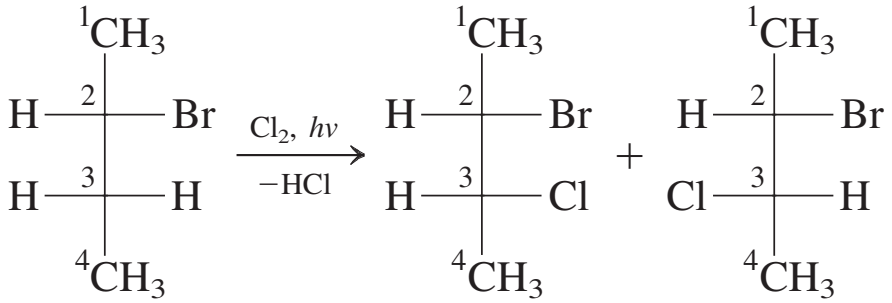
Halogenation at the stereocenter leads to a racemic mixture (no optical activity). A racemate forms in this case because hydrogen abstraction from C2 furnishes a planar, sp^2-hybridized, achiral radical.

Chlorination of (*S*)-2-Bromobutane at C2



The chlorination of (*S*)-2-bromobutane at C3 does not affect the existing chiral center. However, *the formation of a second stereocenter gives rise to diastereomers.*

Chlorination of (*S*)-2-Bromobutane at C3



2*S* **Optically active**

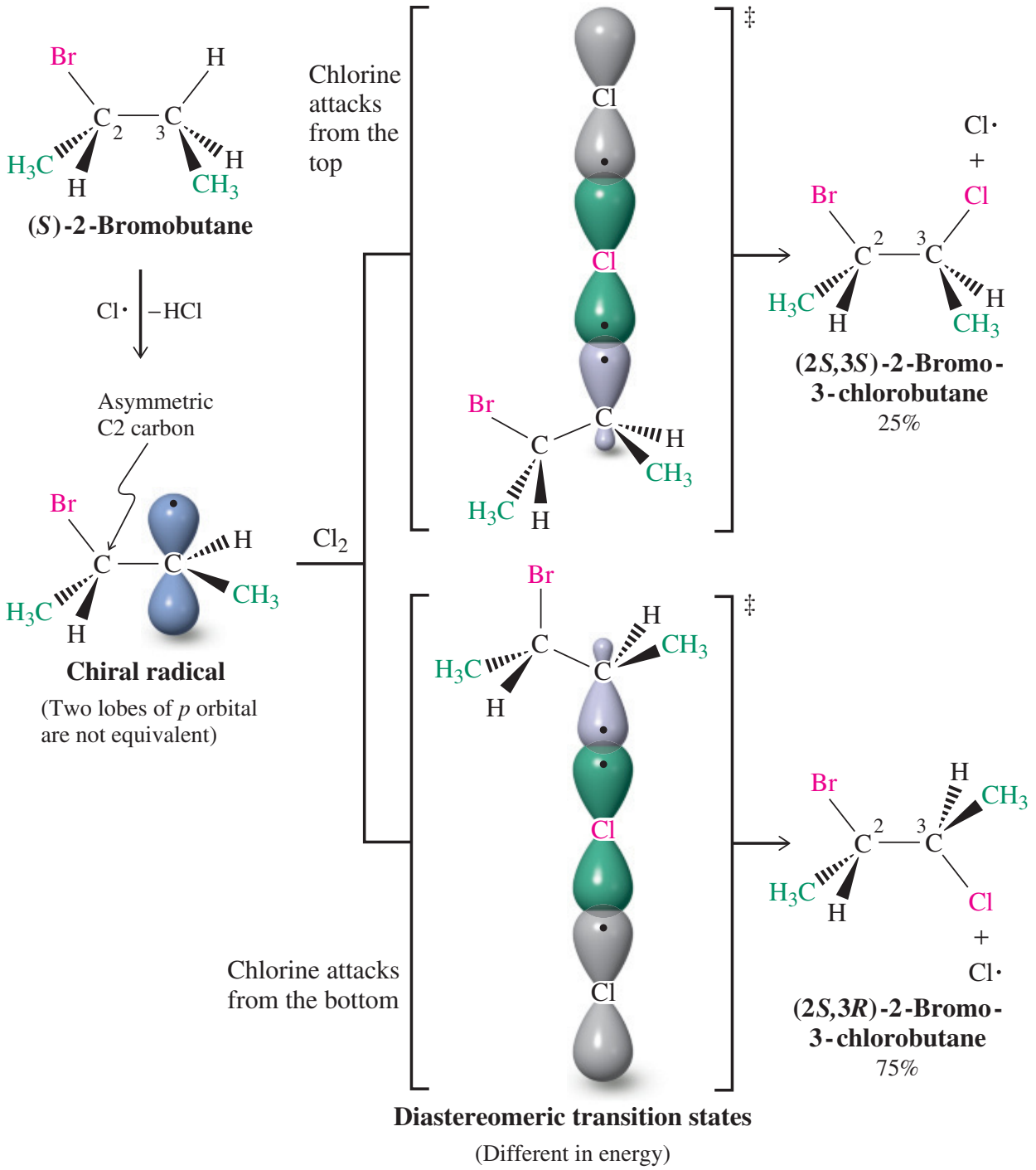
2*S*,3*R* **Optically active**

2*S*,3*S* **Optically active**

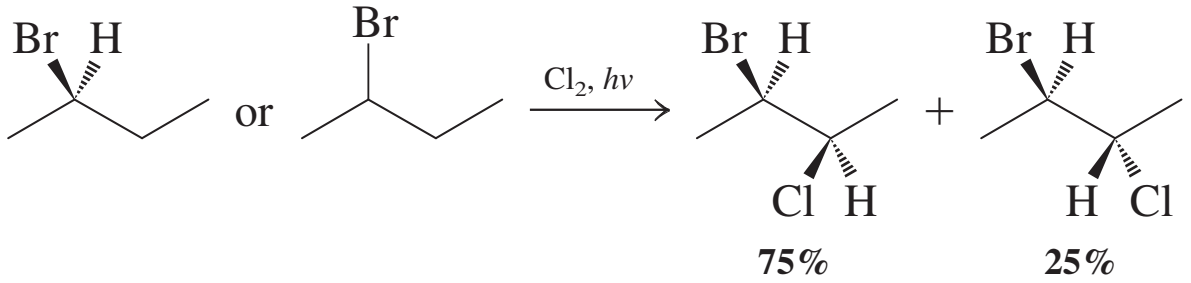
(Unequal amounts)

By abstraction of either one of the hydrogens results in a radical center at C3, two faces of this radical are *not* mirror images of each other, because the radical retains the asymmetry of the original molecule as a result of the presence of the stereocenter at C2. Thus, the two sides of the *p* orbital are not equivalent.

If the rate of attack at the two faces of the radical differ, the two diastereomers should be different. The two transition states leading to products are not mirror images of each other and are not superimposable: They have different energies and represent different pathways.


(S)-2-Bromobutane
Cl· –HCl
Asymmetric C2 carbon
Chiral radical
(Two lobes of p orbital are not equivalent)
Cl2
Chlorine attacks from the top
Chlorine attacks from the bottom
‡
(2S,3S)-2-Bromo-3-chlorobutane
25%
(2S,3R)-2-Bromo-3-chlorobutane
75%
Diastereomeric transition states
(Different in energy)

Attack at C1, C2, or C4 will result in racemic 2-bromo-1-chlorobutane, 2-bromo-2-chlorobutane, and 3-bromo-1-chlorobutane, respectively. Importantly, attack at C3 will still give two compounds, namely, the 2*S*,3*S*/2*R*,3*R* (25%) and 2*S*,3*R*/2*R*,3*S* diastereomers (75%) of 2-bromo-3-chlorobutane.



Stereoselectivity is the preference for one stereoisomer

A reaction that leads to the predominant (or exclusive) formation of one of several possible stereoisomeric products is **stereoselective.**

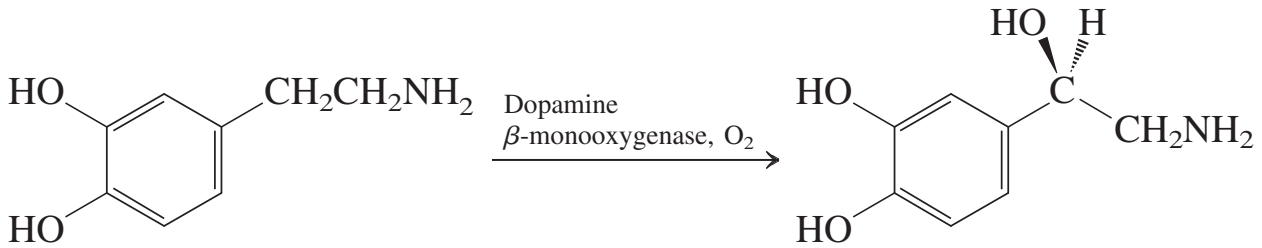
The chlorination of (*S*)-2-bromobutane at C3 is stereoselective, as a result of the chirality of the radical intermediate. The corresponding chlorination at C2 is not stereoselective: The intermediate is achiral and a racemate is formed.

Asymmetric synthesis

In the laboratory, chemists use enantiomerically pure reagents or catalysts to convert achiral compounds into one enantiomer of product (enantioselectivity). In nature, enzymes perform this job.

In all cases, reagent, catalyst, or enzyme that is responsible for introducing the stereocenter compatible with their own chirality.

An example from nature is the enzyme-catalyzed oxidation of dopamine to (-)-norepinephrine. The chiral reaction environment created by the enzyme gives rise to 100% stereoselectivity in favor of the enantiomer shown.



Dopamine **(−)-Norepinephrine**

RESOLUTION: SEPARATION OF ENANTIOMERS

The generation of a chiral structure from an achiral starting material furnishes a racemic mixture. How can pure enantiomers of a chiral compound be obtained?

One possible approach is to start with the racemate and separate one enantiomer from the other. This process is called the **resolution** of enantiomers.

Some enantiomers, such as those of tartaric acid, crystallize into mirror-image shapes, which can be manually separated. However, this process is time consuming, not economical for anything but minute-scale separations, and applicable only in rare cases.

A better strategy for resolution is based on the different physical properties of diastereomers. Find a reaction that converts a racemate into a mixture of diastereomers.

The *R* forms of the original enantiomer mixture can be separable from the corresponding *S* forms by fractional crystallization, distillation, or chromatography of the diastereomers.

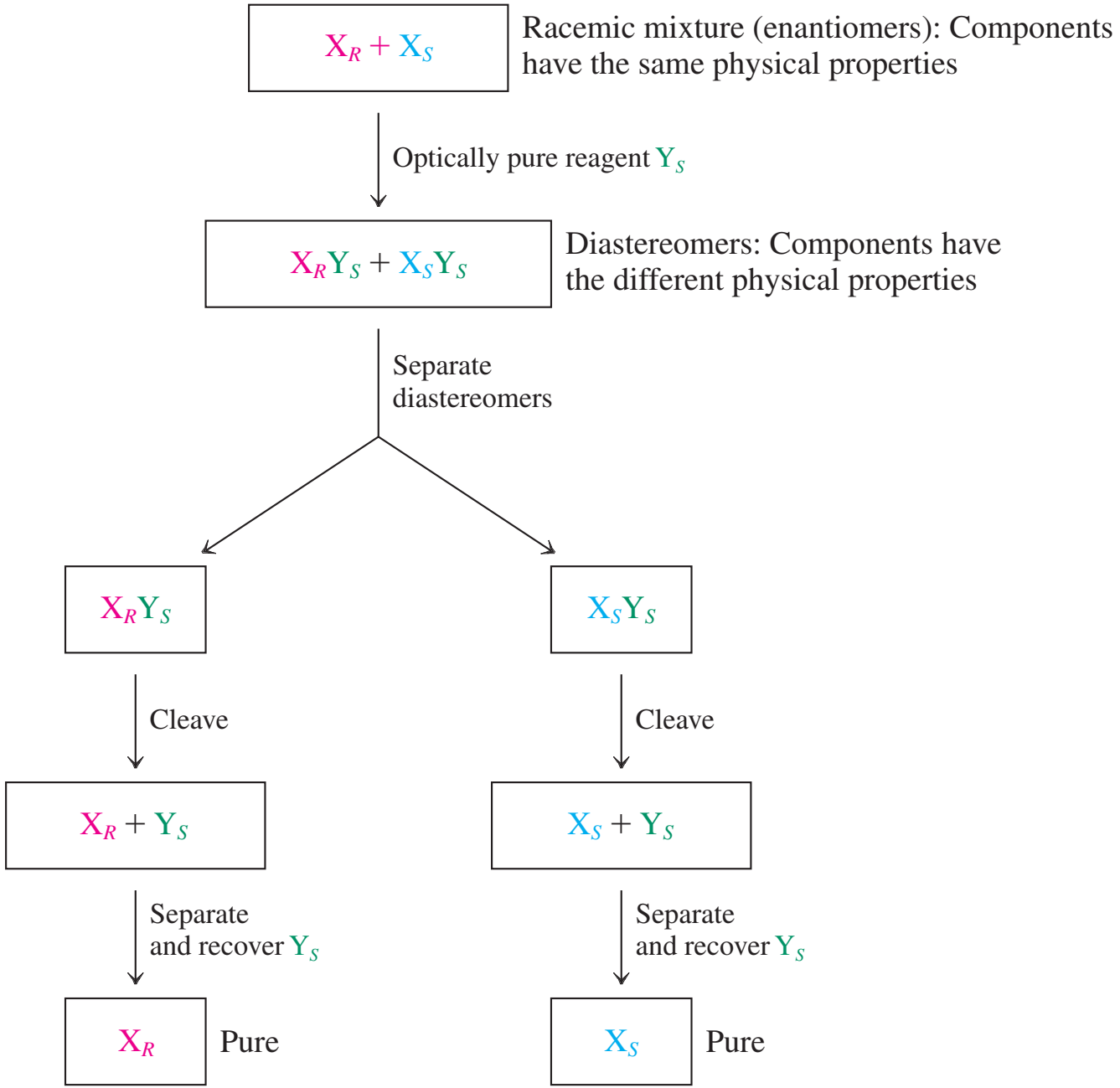
How can such a process be developed?

The trick is to add an enantiomerically pure reagent that will attach itself to the components of the racemic mixture.

For example, we can imagine reaction of a racemate, $X_{R,S}$ (in which X_R and X_S are the two enantiomers), with an optically pure compound Y_S. The reaction produces two optically active diastereomers, X_RY_S and X_SY_S, separable by standard techniques.

Now the bond between X and Y in each of the separated and purified diastereomers is broken, liberating X_R and X_S in their enantiomerically pure states.

In addition, the optically active agent Y_S may be recovered and reused in further resolutions.


$X_R + X_S$
Racemic mixture (enantiomers): Components have the same physical properties
Optically pure reagent Y_S
$X_RY_S + X_SY_S$
Diastereomers: Components have the different physical properties
Separate diastereomers
X_RY_S
X_SY_S
Cleave
Cleave
$X_R + Y_S$
$X_S + Y_S$
Separate and recover Y_S
Separate and recover Y_S
X_R
Pure
X_S
Pure

An example is (+)-2,3-dihydroxybutanedioic acid [(1)-(*R,R*)-tartaric acid].

A popular reaction employed in the resolution of enantiomers is salt formation between acids and bases. For example, (+)-tartaric acid functions as an effective resolving agent of racemic amines.

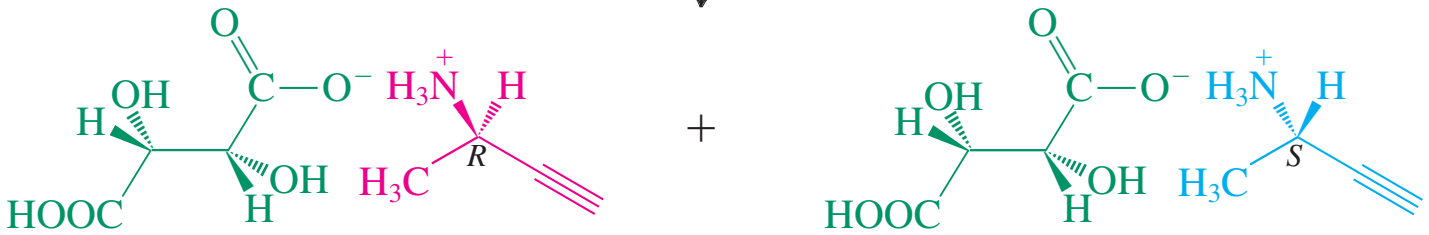
The racemate is first treated with (+)-tartaric acid to form two diastereomeric tartrate salts.

The salt incorporating the *R*-amine crystallizes on standing and can be filtered away from the solution, which contains the more soluble salt of the *S*-amine.

Treatment of the (+) salt with aqueous base liberates the free amine, (+)-(*R*)-3-butyn-2-amine.

Racemic (*R*,*S*)-3-butyn-2-amine **(+)-Tartaric acid**

H_2O, several days



Dextrorotatory (+)-tartrate salt of *R*-amine

$[\alpha]_D^{22°C} = +24.4$

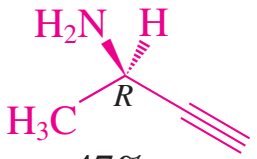
Crystallizes from solution

Levorotatory (+)-tartrate salt of *S*-amine

$[\alpha]_D^{22°C} = -24.1$

Stays in solution

K_2CO_3, H_2O



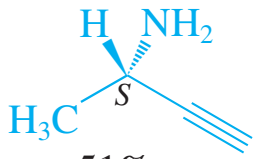
47%

(*R*)-(+)-3-Butyn-2-amine

$[\alpha]_D^{22°C} = +53.2(\pm 1)$

b.p. 82°–84°C

K_2CO_3, H_2O



51%

(*S*)-(−)-3-Butyn-2-amine

$[\alpha]_D^{20°C} = -52.7(\pm 1)$

b.p. 82°–84°C

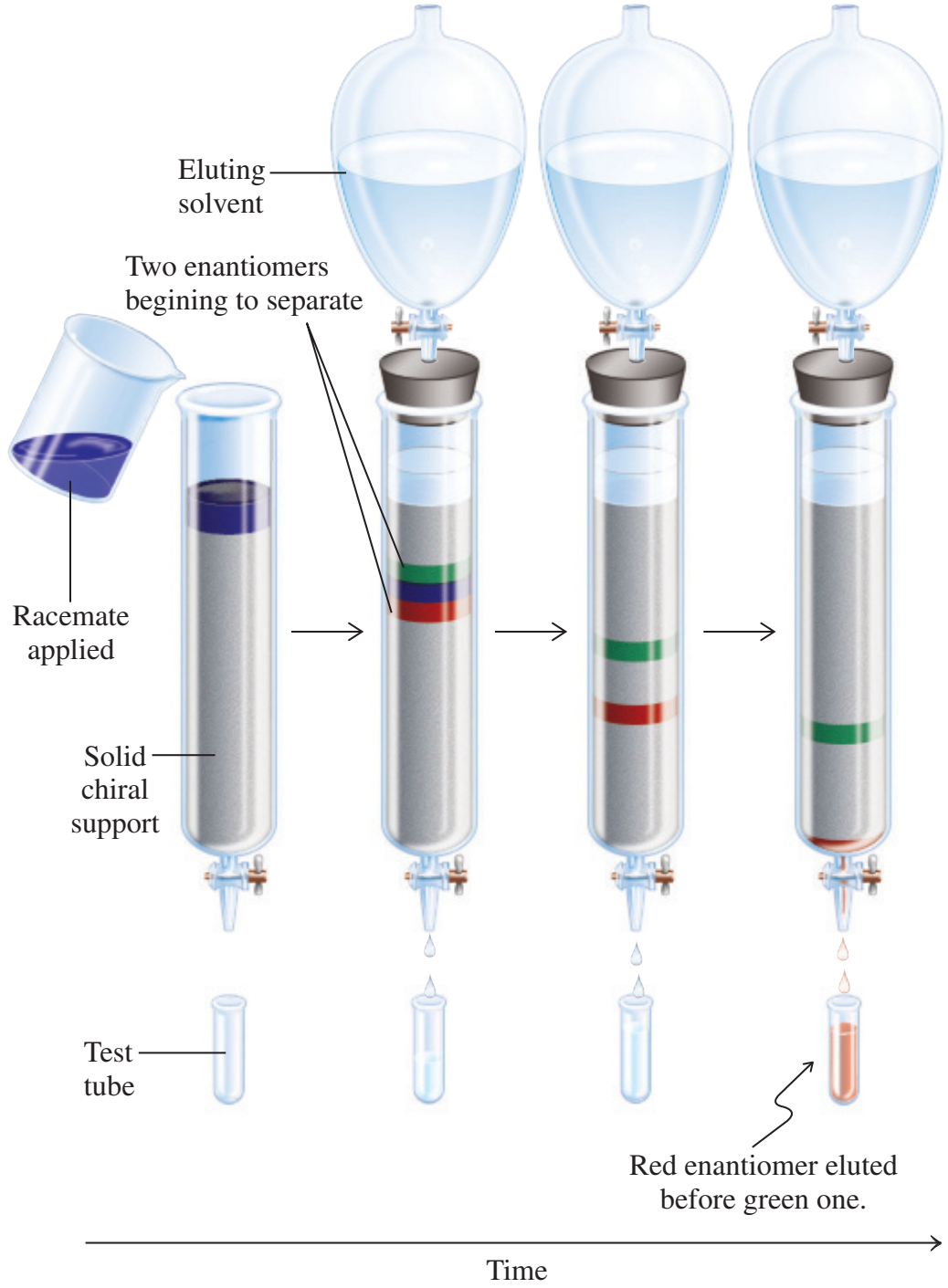
A very convenient way of separating enantiomers without the necessity of isolating diastereomers is by so-called **chiral chromatography**.

The optically active auxiliary [such as (+)-tartaric acid or any other suitable cheap optically active compound] is immobilized on a solid support (such as silica gel, SiO_2, or aluminum oxide, Al_2O_3).

This material is then used to fill a column, and a solution of the racemate is allowed to pass through it.

The individual enantiomers will reversibly bind to the chiral support to different extents (because this interaction is diastereomeric) and therefore be held on the column for different lengths of time (retention time).

Therefore, one enantiomer will elute from the column before the other, enabling separation.


Eluting solvent
Two enantiomers begining to separate
Racemate applied
Solid chiral support
Test tube
Red enantiomer eluted before green one.
Time