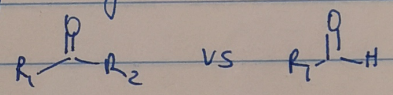
Lecture XXV: Dynamic Stereochemistry

04-01-2020

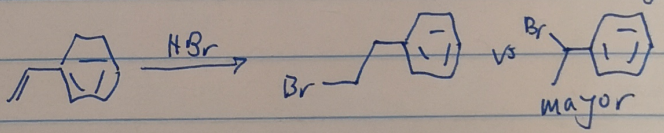
So far, we have talked about individual compounds: static stereochemistry and conformational analysis. Today, we will start talking about stereochemical outcomes of reactions: dynamic stereochemistry. This is of huge practical importance, as we need enantiopure drugs and other products of pharmaceutical industry.

Selectivity in a chemical reaction can be:

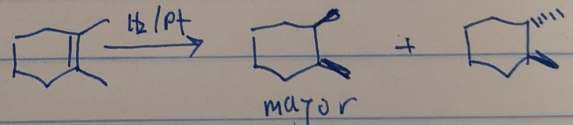
Chemoselectivity: distinguishing one functional group from another



Regioselectivity: preference for one direction of bond breaking



Stereoselectivity: preference for the formation of one stereoisomer over



Let's look at some key terminology.

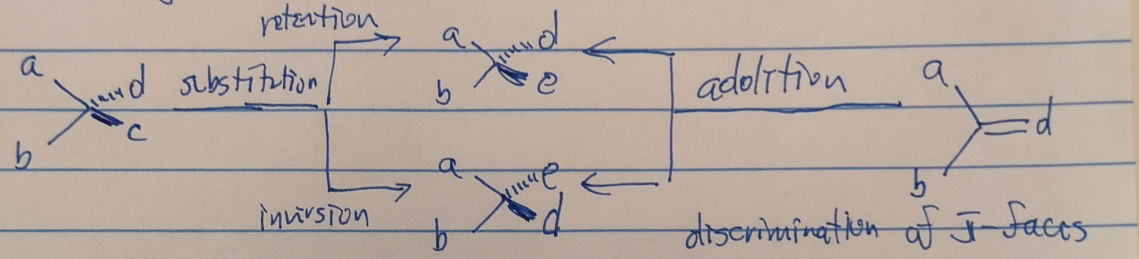
$A \longrightarrow$ (R)-B (50%) + (S)-B (50%) — stereorandom rxn (no stereoselectivity)

$A \longrightarrow$ (R)-B (excess) + (S)-B — stereoselective rxn, ee can be calculated

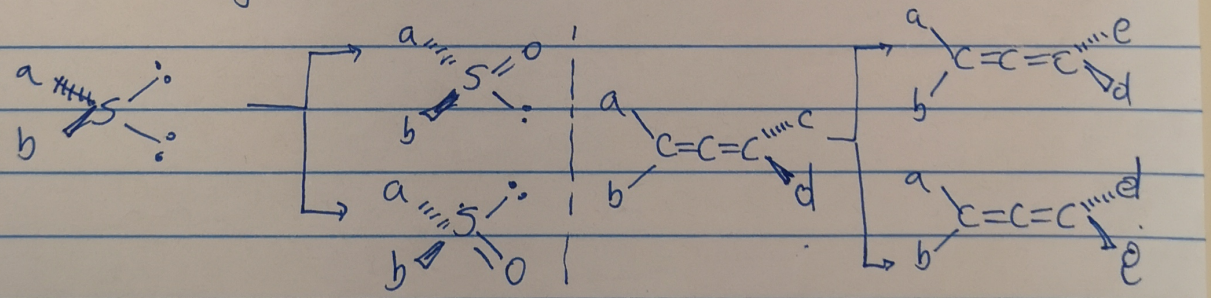
$A \longrightarrow$ (R)-B — stereospecific or highly stereoselective

What is the difference between stereospecific and stereoselective? Stereospecific should be used only when there is a mechanistic explanation of why one isomer cannot be formed: S_N2 reaction, Diels-Alder rxn, hydroboration of alkenes. If the reaction "just works" very well, it is stereoselective.

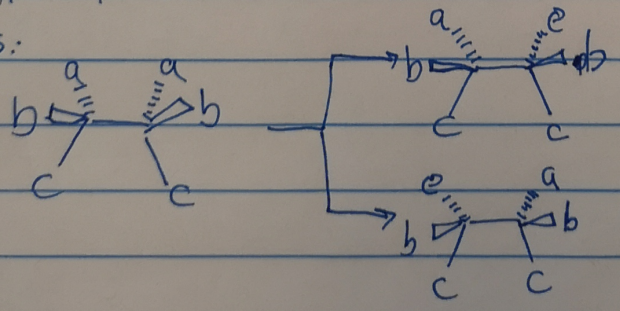
How can we get into stereoselectivity issues?



Those rxns will lead to enantiomers if starting from achiral substrates, and diastereomers if starting from chiral substrates. More exotic versions of ligand substitution are:



Finally, desymmetrization of meso compounds can be viewed as analogous:



In general, the biggest challenge is the creation of the first stereocenter: in other words, ensuring enantioselectivity. If starting

with a chiral enantiopure compound, diastereoselectivity is generally easier to achieve. In other words:

$$A \longrightarrow \underset{50\%}{(R)\text{-}B} + \underset{50\%}{(S)\text{-}B}$$

affecting this ratio is hard

$$(R)\text{-}E \longrightarrow \underbrace{(R)/(R)\text{-}D + (R)/(S)\text{-}D}$$

these are diastereomers, so their stabilities and rates of formation are different

Spontaneous breaking of mirror symmetry is impossible (although we will see an exception at the very end of class):

$$\underset{\substack{\text{achiral}\\ \text{or}\\ \text{racemic}}}{A} + \underset{\text{achiral}}{B} \xrightarrow[\text{catalyst}]{\text{achiral}} \underbrace{C + D}_{\text{must be achiral or racemic}}$$

Symmetry breaking needs to be facilitated, either stoichiometrically or catalytically:

this is enantiopure now — diastereomers, different amounts

$$A + B^* \longrightarrow A\text{-}B^* \xrightarrow{\text{rxn}} C^R\text{-}B^* + C^S\text{-}B^*$$

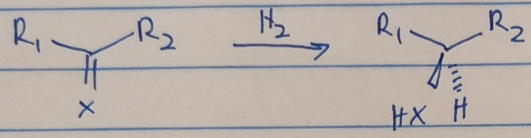
chiral auxiliary → easily appended and removed

available as a single ~~diastereomer~~ enantiomer

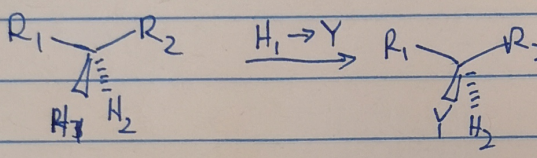
More modern, asymmetric catalysis, uses a catalytic amount of a chiral species:

$$A \xrightarrow[B]{cat^*} [A\text{-}cat^*\text{-}B]^{\ddagger} \longrightarrow AB^* \text{ enantioenriched}$$

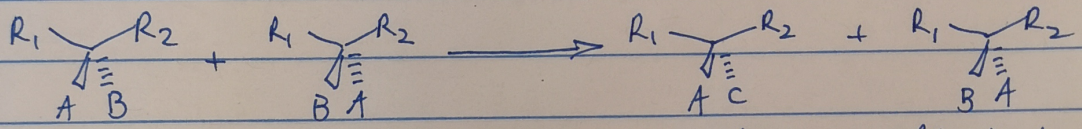
Enantioselectivity-inducing processes:



face differentiation

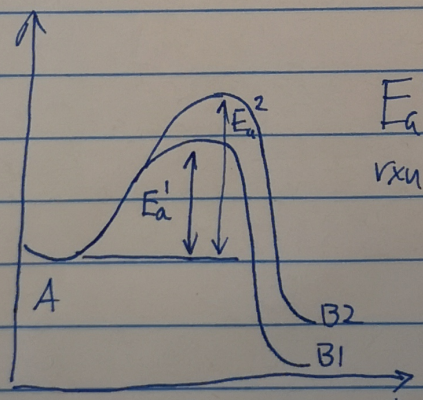


topos differentiation



enantiomer differentiation
(kinetic resolution)

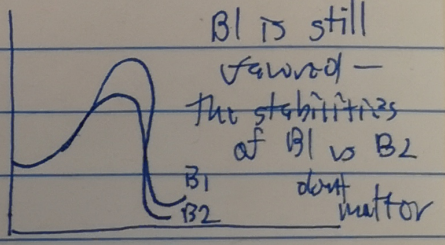
What are the energetic origins of selectivity? That depends on whether a rxn is under kinetic or thermodynamic control. Kinetically controlled rxns proceed irreversibly to give stable products. Most rxns used in synthesis are kinetically controlled.



$E_a^1 < E_a^2$, B1 forms faster than B2

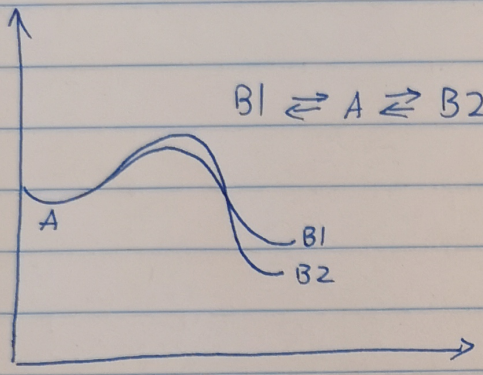
rxn is selective for B1

or



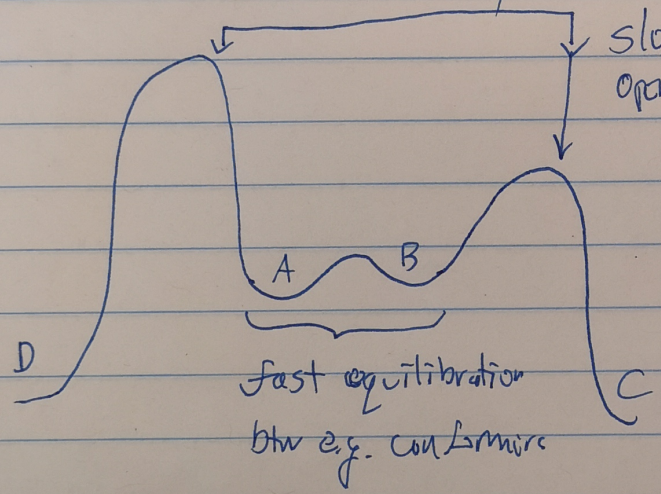
Rates of formation determine relative amounts of products

In a thermodynamically controlled reaction, energy barriers are lower and the products can go back to A and each other;



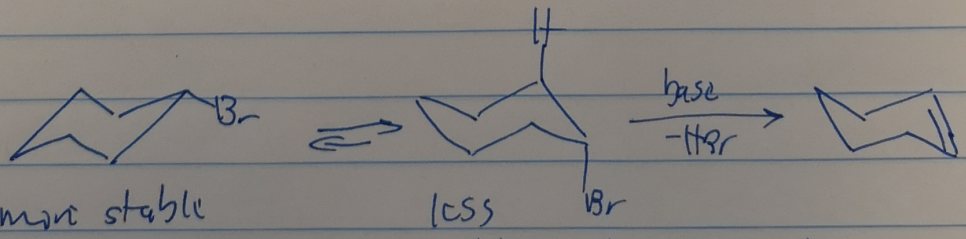
Ea's are all low, so they don't matter anymore: Instead it is the relative stabilities of B1 and B2 that determine their final ratio $\Delta G_{B1}/\Delta G_{B2}$

The two are in fact commonly seen together:



This is the Curtin-Hammett principle, which states that in this case, the dominant final product will come from the faster reacting conformer (B), not the more stable one (A):

$$A \rightleftharpoons B \rightarrow C$$



more stable — less stable but more reactive