Asymmetric Synthesis

→ Most of the biologically important molecules are chiral and because of this, generating chiral centers with defined geometry from scratch or from achiral substrates is of utmost importance in synthetic organic chemistry.

→ Asymmetric synthesis is defined as a reaction in which an achiral unit in an ensemble of substrate molecules is converted into a chiral unit in such a manner that unequal amounts of the stereoisomers are produced.

OR

→ A chemical reaction in which one or more new elements of chirality are created in a substrate molecule and which produces the stereoisomeric products (enantiomeric or diastereomeric) in unequal amounts.

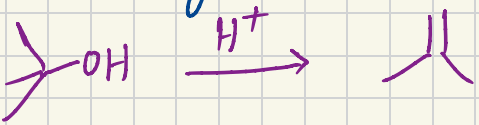
→ Traditionally also known as stereoselective synthesis, but only those stereoselective reactions that lead to the formation of a chiral product with an enantiomeric excess (ee) can be called asymmetric.

Stereoselective reaction

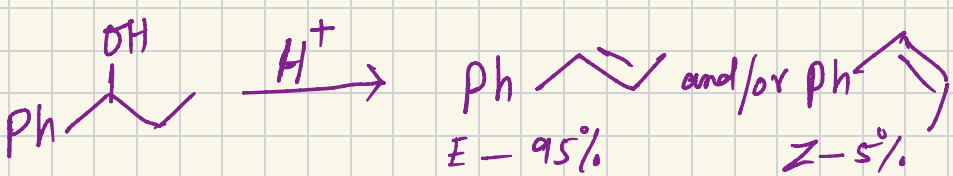
B and C are stereoisomers

If A undergoes a chemical reaction and produces only B or C (not both), the we can say that A has undergone a stereo-selective reaction.

In stereoselective reactions, there is a choice that more than one product (stereoisomer) may be formed, but only one is produced because it is favoured by kinetic or thermodynamic control.



only one product is possible



E – 95% Z – 5%

Since E-alkene is more stable than Z-alkene and is the major product. This is an example of the stereoselective reaction.

Stereospecific Reaction

A and C are stereoisomers

$A \longrightarrow B$

$C \longrightarrow D$

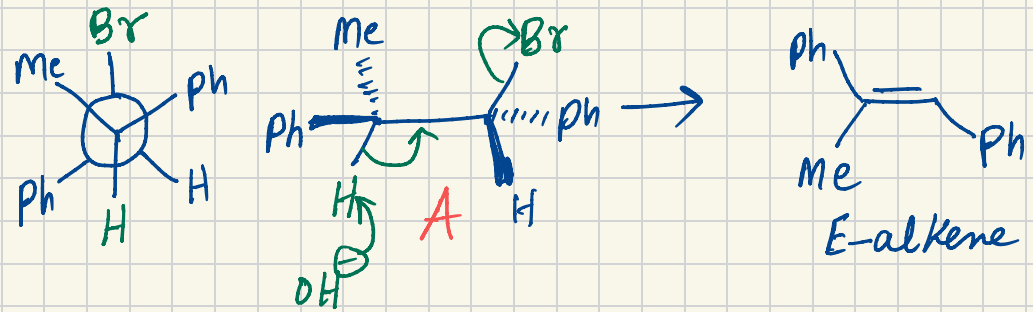
B and D are stereoisomers as well

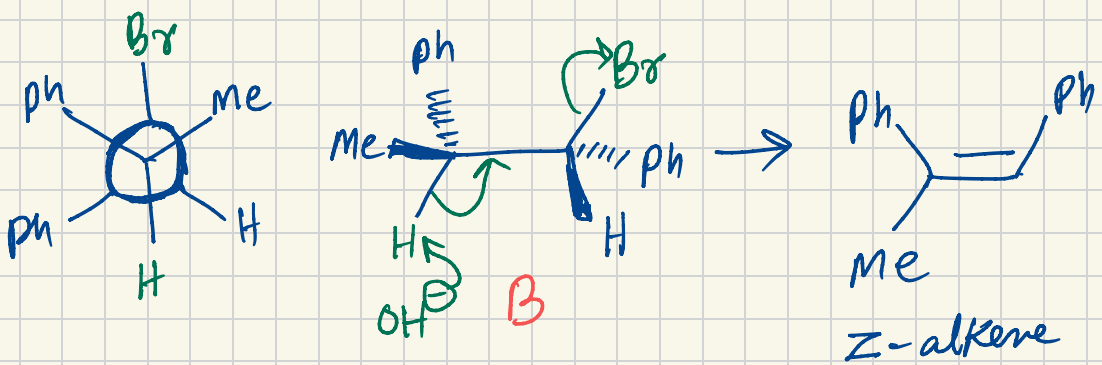
Reactions where a single enantiomer is obtained as the product and the stereochemistry of the product is decided by the stereochemistry of the reactant are known as stereospecific reactions. In stereospecific reactions, there is no choice and a single enantiomeric product is produced as decided by the mechanism of the reaction and the stereochemistry of the reactant used.

→ In stereospecific reactions different stereoisomeric products are obtained from different stereoisomeric reactants

Example of Stereospecific reaction

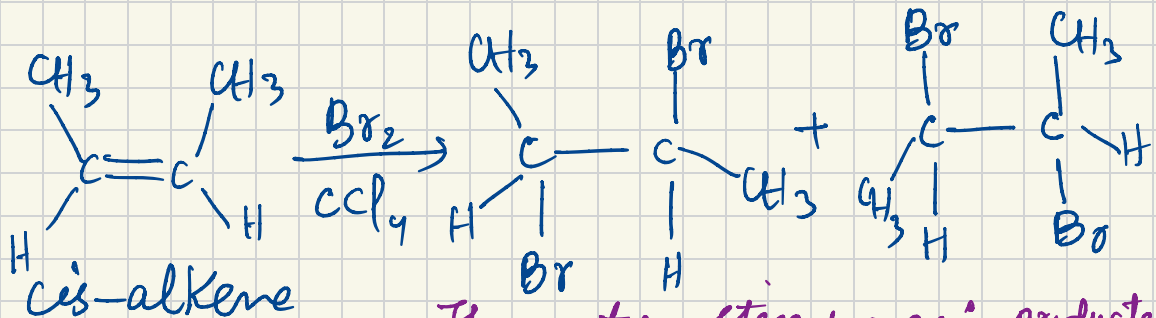
E2 elimination reaction from stereoisomeric reactants with two chiral centers can be stereospecific





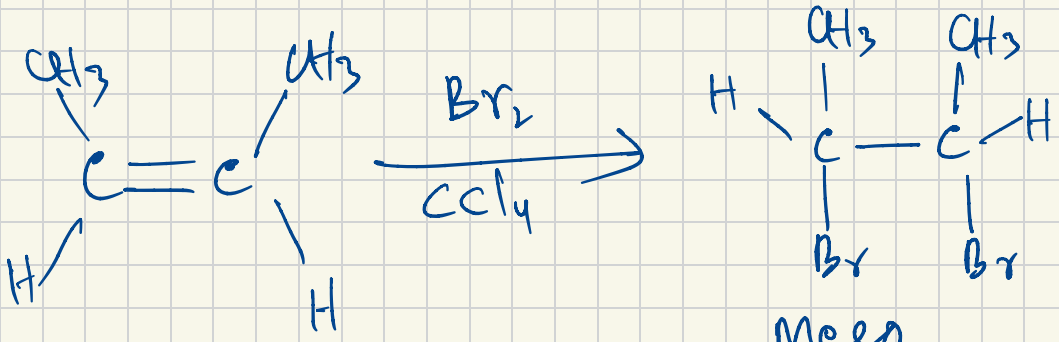
A and B are diastereomers and depending upon which diastereomer is used in the reaction, we can get either E or Z-alkene. Such reactions are called stereospecific reactions.

More examples of Stereoselective & Stereospecific Reactions



These two stereoisomeric products are produced as Br_2 always adds in anti fashion.

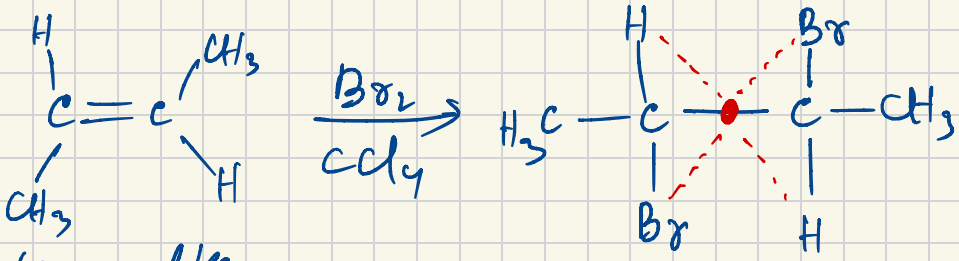
If Br_2 could add in Syn fashion, we will get another stereoisomer that would be meso due to a plane of Symmetry



Meso.

Not obtained

→ Starting from the same reactant, only one set of products (dl-pair) is obtained. The reaction is Stereoselective.



trans-alkene

This is meso as well as it has a Centre of Symmetry

Here only one product (meso compound) is produced and hence again Stereoselective.

→ The overall addition of Br_2 to this alkene is Stereospecific as well as the Stereochemistry of the product is decided by the Stereochemistry of the reactant.

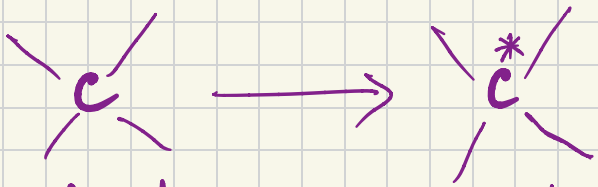
cis alkene ⟶ dl pair

trans alkene ⟶ Meso product

A unique example where the individual reactions are Stereoselective and the overall reaction is Stereospecific as well. True for But-2-ene.

Principle of Asymmetric Synthesis

Asymmetric Induction

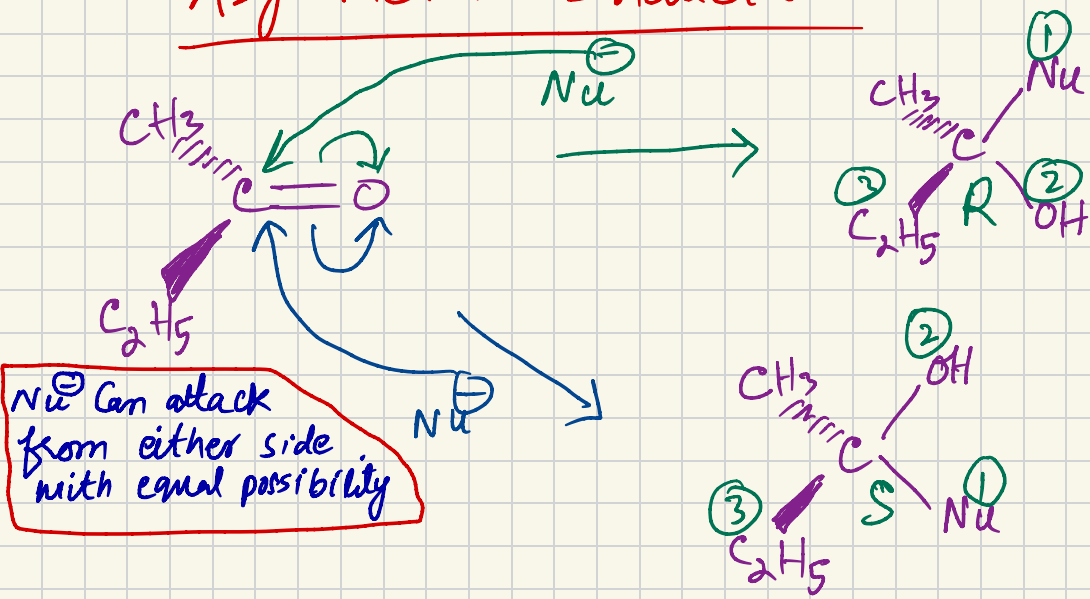


achiral Center Chiral Center

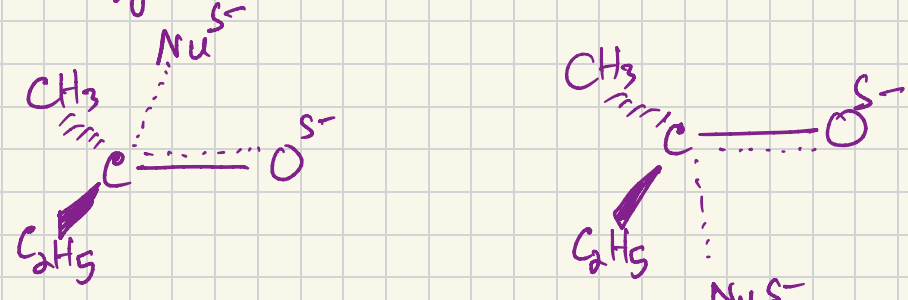
→ Conversion of an achiral molecule into a chiral molecule in such a manner that one of the enantiomer is formed as the major (or the only) product. Such a reaction is known as asymmetric synthesis.

→ In order to understand how to achieve asymmetric induction (introduction of asymmetric center) in a reaction, we will consider the nucleophilic addition to the carbonyl group.

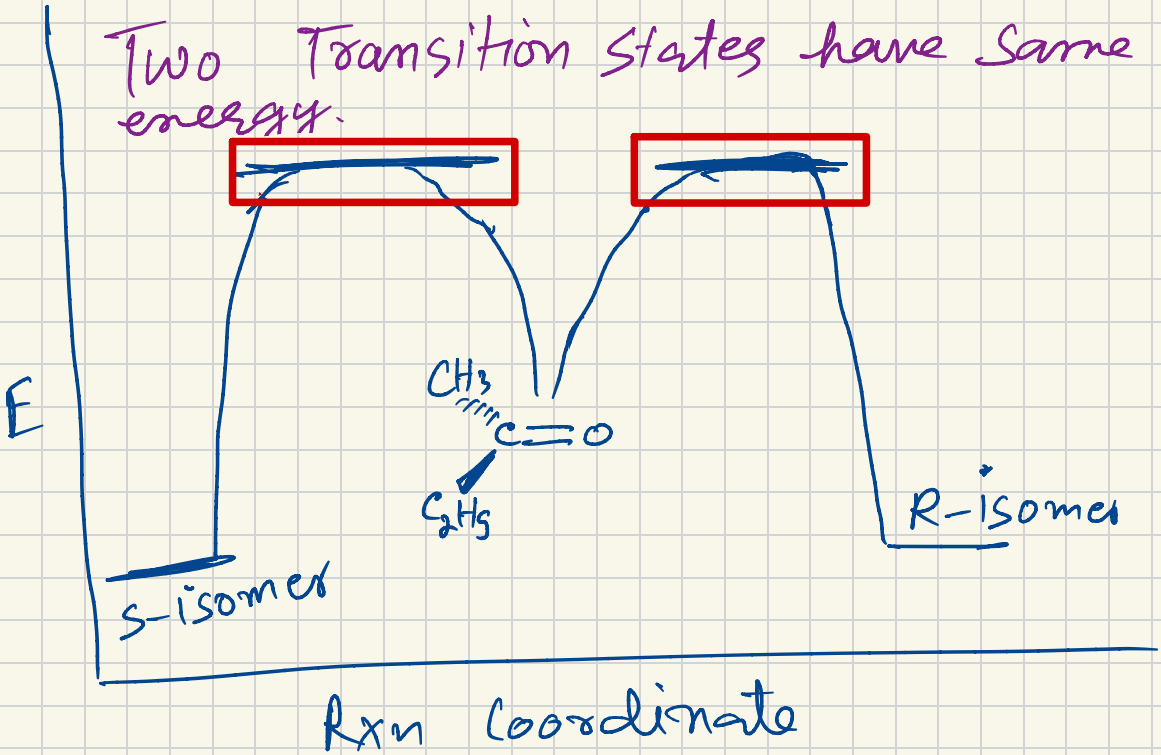
Asymmetric Induction



The two enantiomeric products are produced in equal amounts and hence a racemic mixture is obtained. This happens because the transition states leading to these products are also enantiomeric and have same energy.



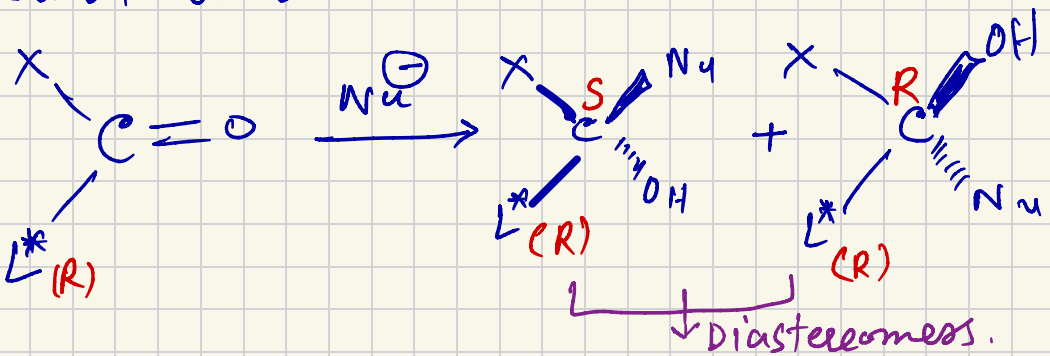
Transition states leading to the formation of two enantiomers are also mirror images and hence have exactly equal energy.



→ For one enantiomer to be formed in major quantity, its transition state has to have lesser energy than the transition state leading to another enantiomer. This happens when the transition states share a diastereomeric relation rather than an enantiomeric one.

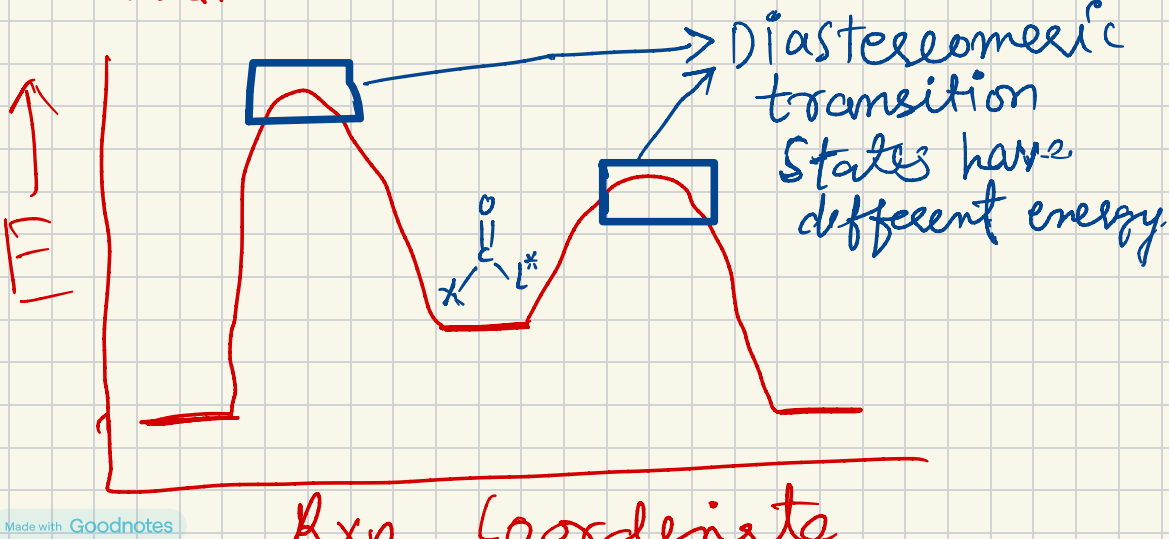
Asymmetric Induction

Lets now consider the nucleophilic addition to the Carbonyl group that is already attached to a chiral Center



→ Since the reaction produces a pair of diastereomers, the transition states must also be diastereomeric.

Diastereomeric transition states have different energies making one of the products kinetically more accessible.



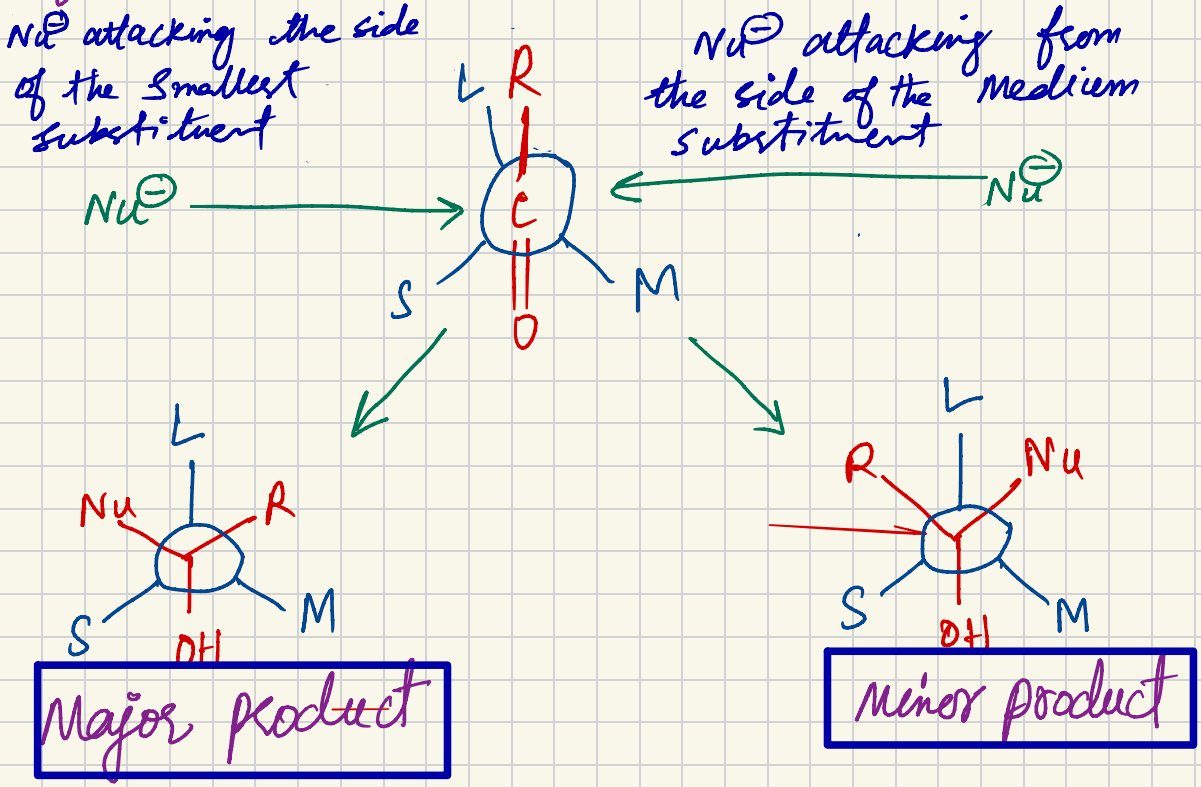
Asymmetric Induction

With diastereomeric transition states having different energy, the pathway involving the low energy transition state will be favoured and hence a particular diastereomer will be formed in major quantity as compared to the the other diastereomer.

→ Now which diastereomeric transition state will have less energy, is decided by looking at the conformations of the Carbonyl Compd. with nucleophile attacking the low energy Conformation.

→ The low energy conformation of the Carbonyl group is decided by the Cram's rule or by the Felkin-Anh model

CRAM'S RULE: According to the Cram's rule the most favored (low energy) conformation of the Carbonyl compound is the one where the L-group is anti to the carbonyl group and then Nucleophile preferentially attacks from the side of the smaller substituent.



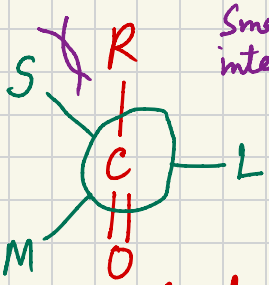
Major product

Minor product

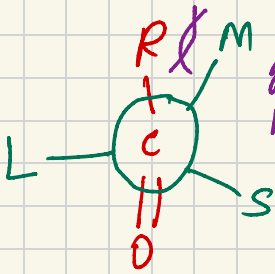
→ The nucleophile attacks at an angle of 107° to the carbonyl group – also known as the Burgi-Dunitz angle or Burgi-Dunitz trajectory.

Felkin-Anh model

Even though Cram's rule correctly predicted the major enantiomer formed, but it turns out that the low energy conformer of the Carbonyl compound as predicted by the Cram is not correct. The low energy Conformation of the Carbonyl compound was correctly predicted by Felkin and Anh to be the one that has the largest group perpendicular to the Carbonyl group.



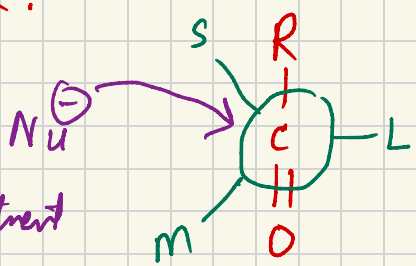
Small group interacting with R

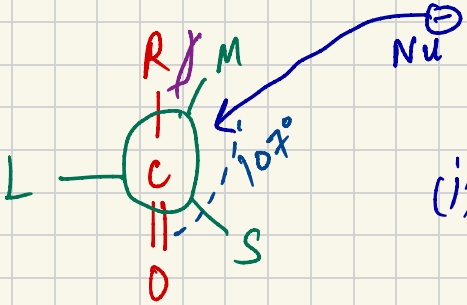


Medium group interacting with R.

Favoured Conformation for the attack.

The $Nu^{\ominus}$ then attacks from the side that is opposite to L-group from the smaller Substituent side at 107° angle.

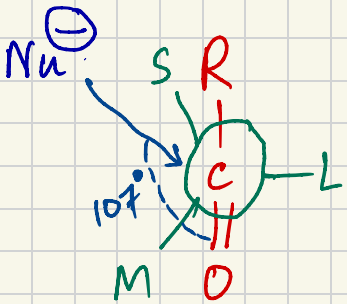




There are two issues with this conformation

(i) Destabilizing interaction between R and M groups

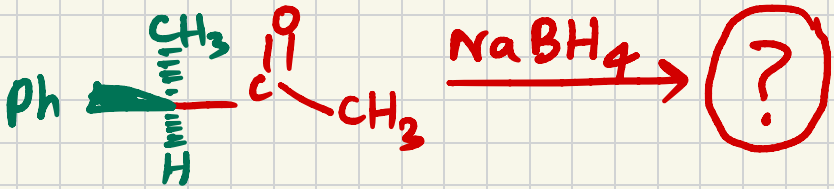
(ii) When $Nu^{\ominus}$ attacks at Burgi-Dunitz trajectory (107°), it has come closer to Medium sized group.



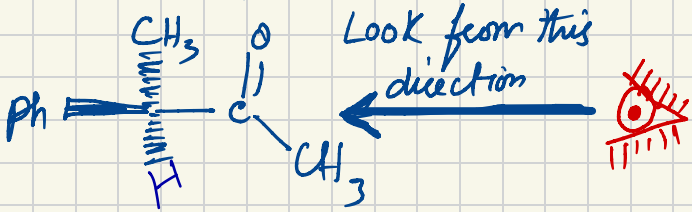
Attack on this conformation solves both these issues.

→ The product obtained from Felkin-Anh Model is the same as that predicted by the Cram's model. It is just that the low energy conformation of the carbonyl compound was correctly predicted by Felkin and Anh and not by Cram.

Problem: Cram's Model



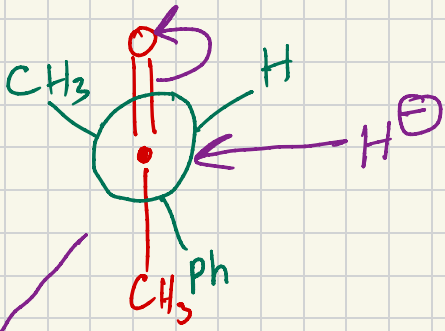
Step-I: Draw the newman projection of the Carbonyl. Since we have to keep the Carbonyl Carbon on the front, we have to look from that side to make newmann projection.



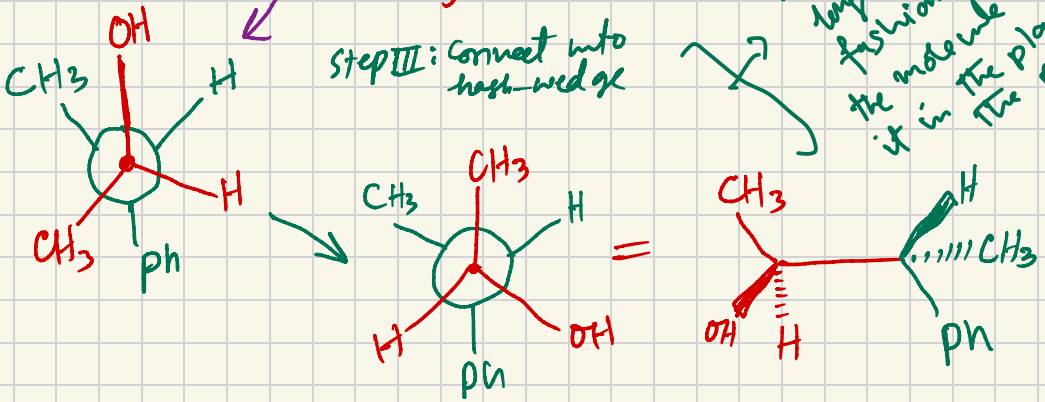
The Ph, $-CH_3$ & -H are in clock-wise order when looked at from Carbonyl side

Ph = L, $-CH_3$ = M, H = S

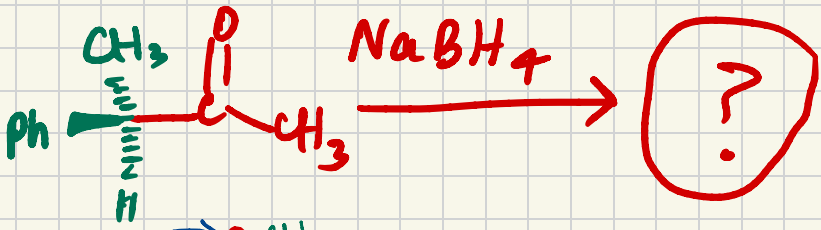
Step-II: $Nu^{\ominus}$ attacks from the side of the Smaller group.

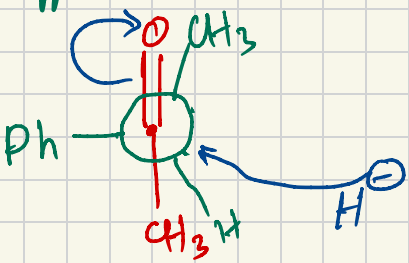


While converting Newman to wedge, keep the longest chain in anti fashion & then rotate the molecule to bring it in the plane of the paper

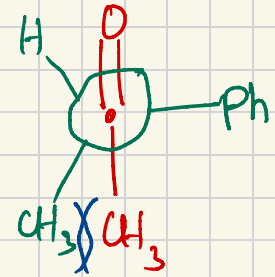


Solving the Same problem using Felkin-Anh Model

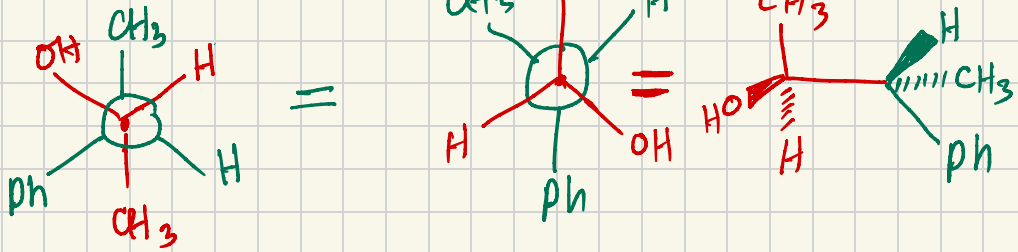




Favoured Conformation
(most stable conformation)



Destabilizing Interaction
(Less stable as compared to the other one)



→ We can clearly see that Cram's model and Felkin Anh model gave the same product, even though they start from different conformations of the carbonyl compound.

Catagories of Asymmetric Synthesis

Different methods to carry out asymmetric synthesis

- Chiral pool
- Chiral Auxillaries
- Chiral reagents
- Asymmetric Catalysis

Synthesis of a chiral compound in laboratory from achiral or racemic reactants always produces products as a racemic mixture of the two enantiomers. Inorder to make enantiomerically pure products, we have to start with

What came first!

Enantiomerically pure reactant?

OR

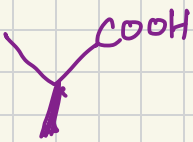
Enantiomerically pure product?

Catagories of Asymmetric Synthesis

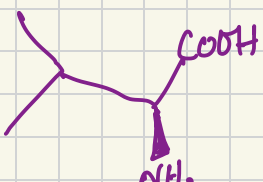
1. Chiral pool:

Nature provides a wide variety of enantiomerically pure compounds that can be easily extracted and then used in a number of ways to make more of the enantiomerically pure compounds. This collection of of naturally available pure enantiomeric compounds is known as the chiral pool. Various classes of compounds that make up the chiral pool are;

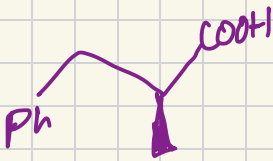
1. Amino acids and their derivatives



S (+) alanine

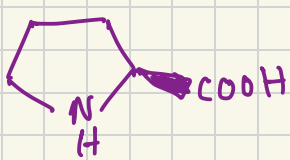


S(+)valine

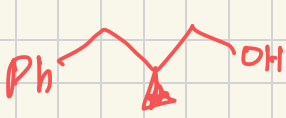


S(−)phenylalanine

Amino alcohols and hydroxy acids are chiral amino acid derivatives.



S(−) proline

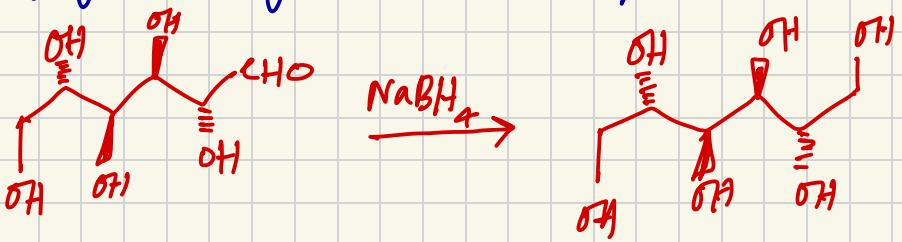


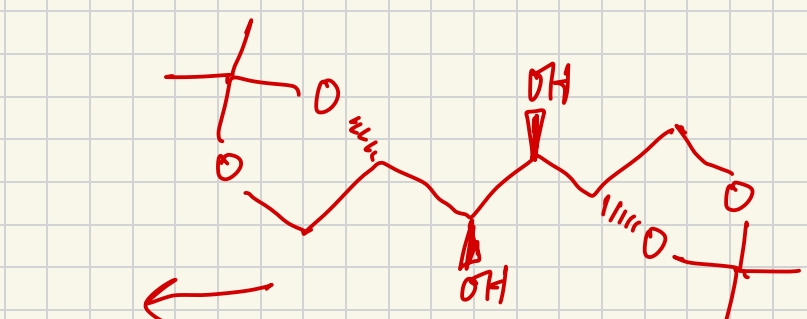
amino alcohol

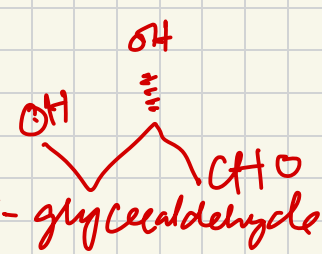
S-hydroxy acid

2. Carbohydrates and their derivatives

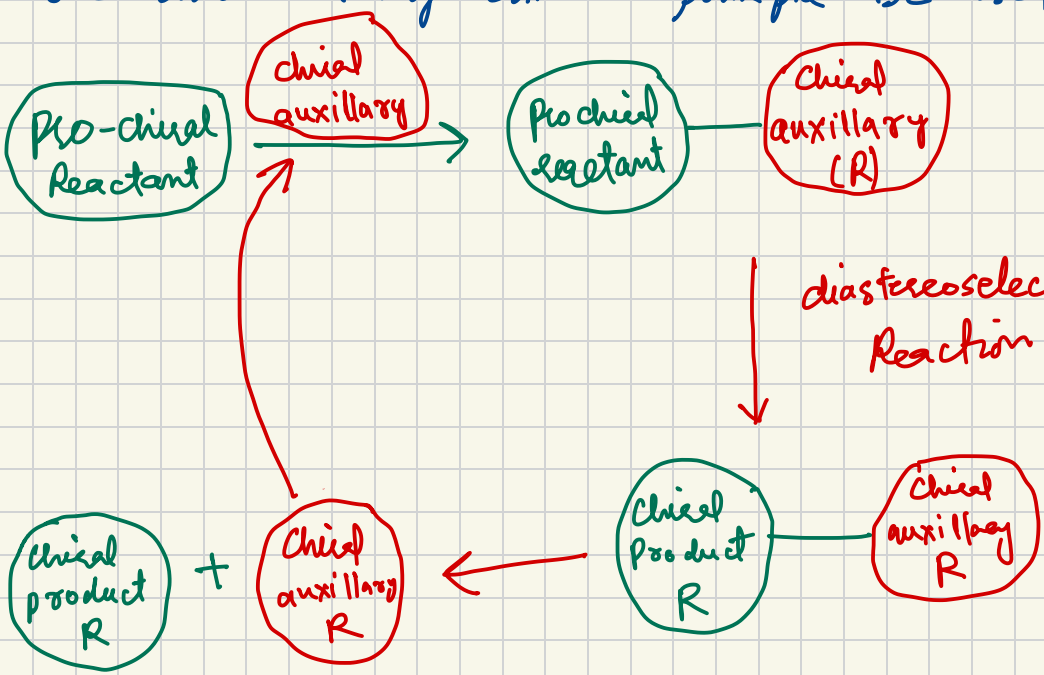
A number of chiral and enantiomerically pure carbohydrates exist naturally and can be used to prepare a wide variety of enantiomerically pure and useful compounds. One such compound is D-mannose from which enantiomerically pure glyceraldehyde can be prepared.







Chiral Auxillary: A chiral auxillary is an enantiomerically pure compound (usually from chiral pool) that is attached to a prochiral molecule and assists it to react in a diastereoselective manner such that only one diastereomer is allowed to form. The chiral auxillary is then removed from the diastereomeric product, giving us the product molecule as a single pure enantiomer. The chiral auxillary can in principle be used again.



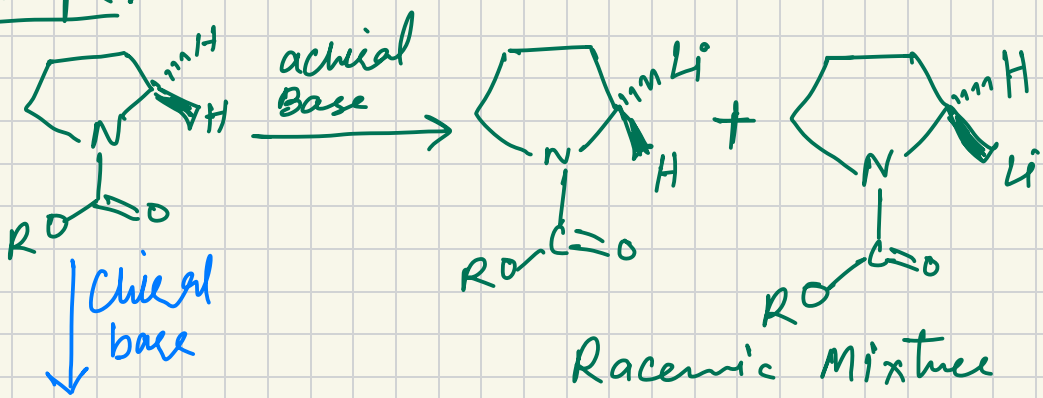
→ Chiral auxillary is recycled & used again and again, but the reaction is not catalytic as stoichiometric amounts of the chiral auxillary are used.

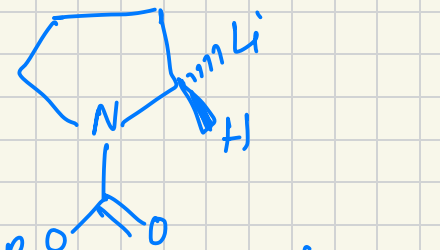
→ The chiral auxillary used is generally selected from the chiral pool of the enantiomerically pure amino acids, Carbohydrates or their derivatives.

Chiral Reagents: Chiral reagents are enantiomerically pure reagents that can be treated with prochiral reactants to produce unequal amounts of the enantiomeric products.

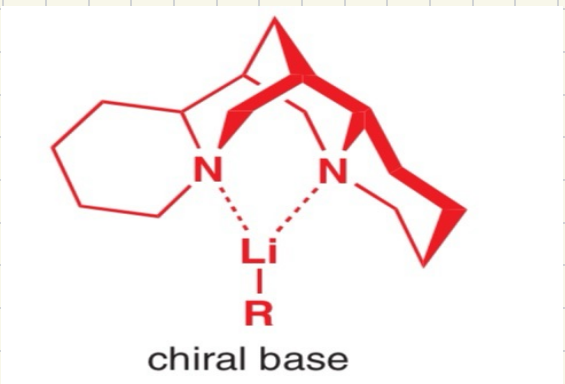
→ Reactions involving use of the chiral pool or chiral auxillary have stereochemistry controlled at the reactant/substrate side. Using the chiral reagents gives us the choice to choose one reagent as per the requirements of the enantiomeric product that needs to be prepared.

Example:

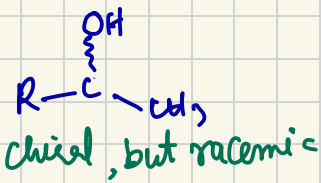




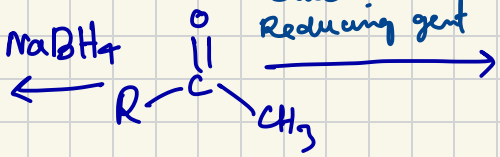
enantiomerically pure organolithium

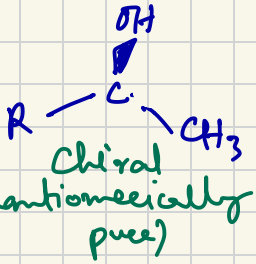


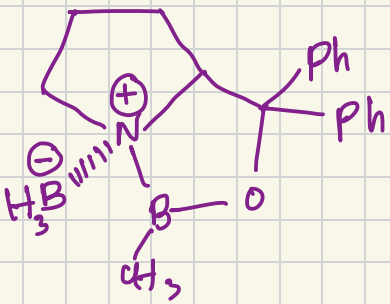
Chiral Reagent :



Chiral, but racemic







Active Reducing Agent

→ when used in pure enantiomeric form carries out asymmetric reduction of a number of functional groups.

↓

Known as the CBS reagent after the names of Corey, Bakshi and Shibata, the chemists who invented it.

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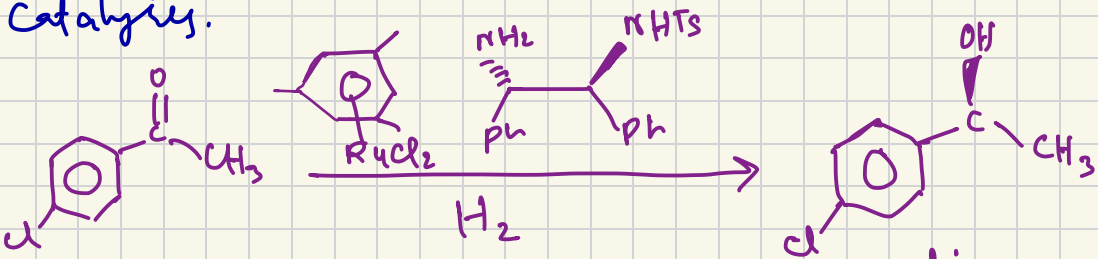
Asymmetric Catalysis:

Apart from chiral reagents, it is also possible to use catalysts that are chiral to carry out asymmetric synthesis. The example of CBS reagent for the asymmetric reduction was the only method used until recently when a Ruthenium based catalyst containing a chiral ligand was used to do the asymmetric reduction. An example of asymmetric catalysis.



S-enantiomer formed with upto 95% ee.

→ Asymmetric catalysis can be defined as the method for asymmetric synthesis where where a chiral catalyst inplace of a chiral reagent is used.

→ If the chiral catalyst is a transition metal complex, almost every single time, the chirality in the catalyst is due to a chiral ligand and different enantiomers of the ligand can be used to produce the different enantiomers of the product.

→ Chiral pool & Chiral auxillary
↓
Substrate control of the chirality

→ Chiral Reagent & Asymmetric Catalysis
↓
Reagent Control