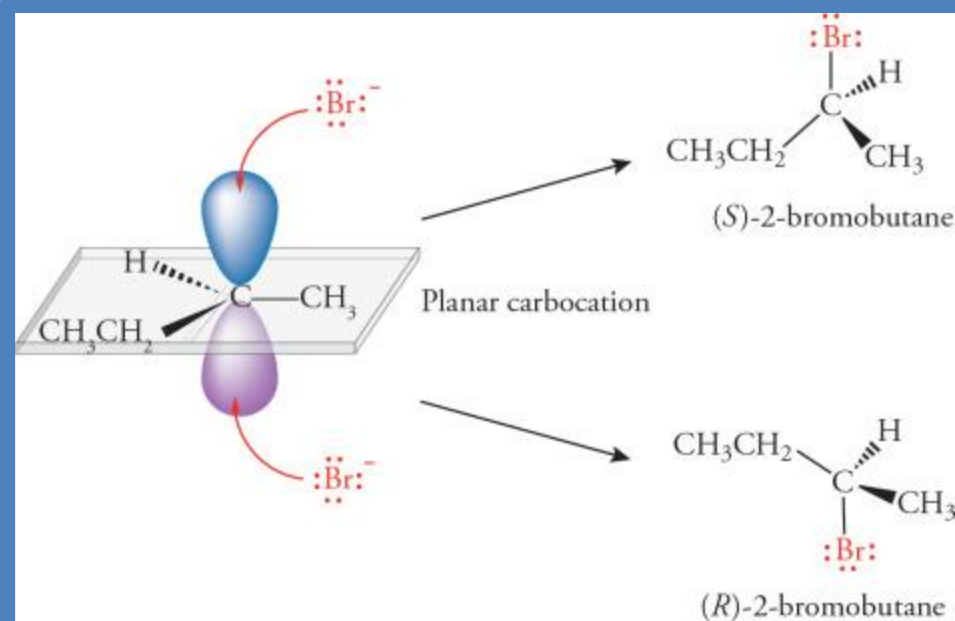
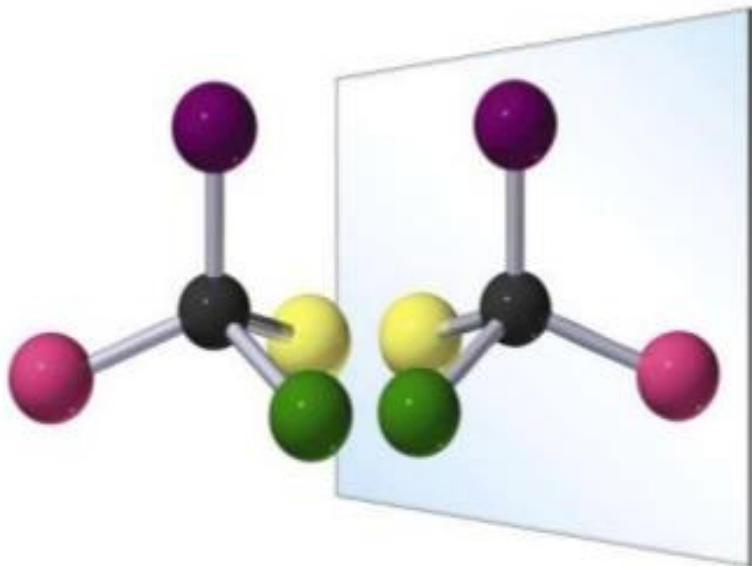


STEREOCHEMICAL ASPECTS OF ORGANIC SYNTHESIS

Dr Gohar Taqi Kazimi

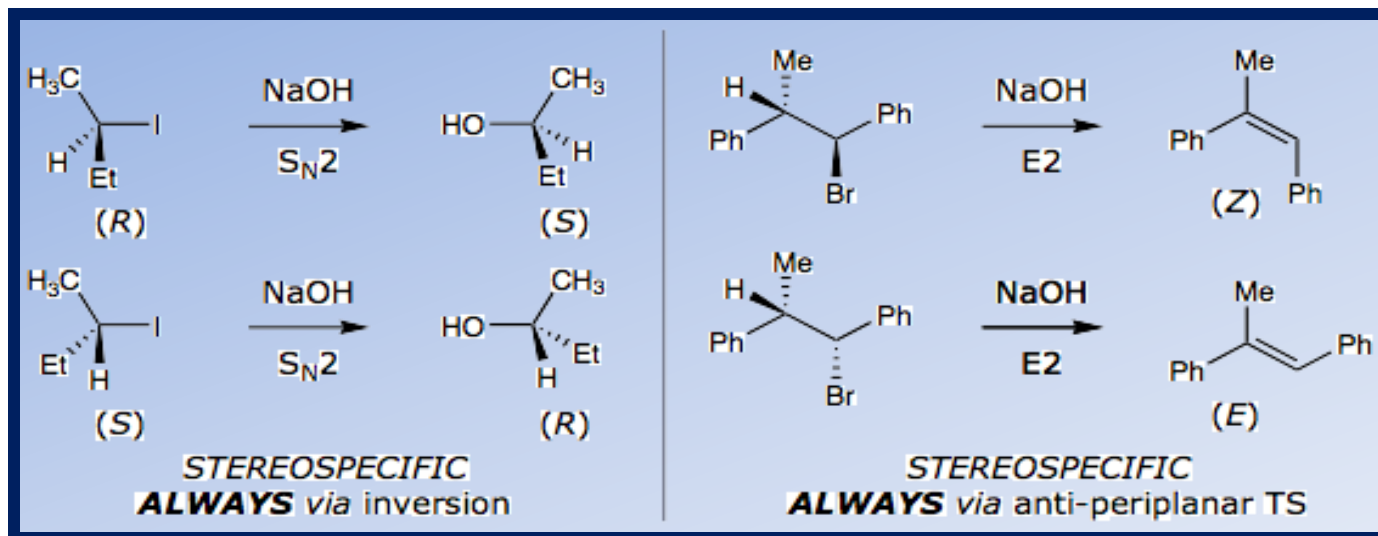
Assistant Professor
University of Sargodha



STEREOSPECIFIC REACTIONS;

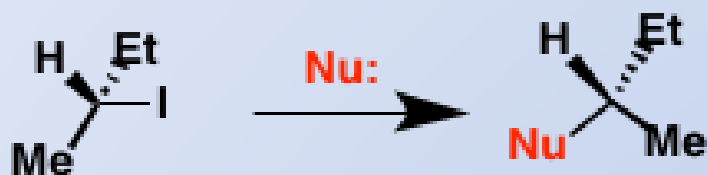
It is a reaction that only allows formation of one stereoisomer. The best-known example being the S_N2 reaction, which always proceeds with inversion of stereochemistry at the reacting centre.

The stereochemistry of the reactant completely determines the stereochemistry of the product without any other option.



The S_N2 is a *stereospecific* reaction: a given starting material produces *only one* product

The S_N2 proceeds with *inversion*.



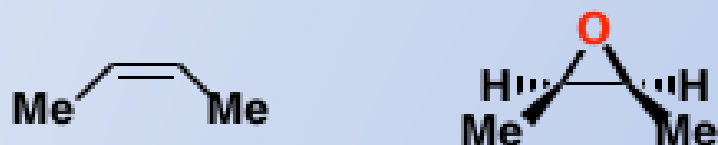
only product

(a 50:50 mixture of the two iodides will produce a 50:50 mixture of the two products)

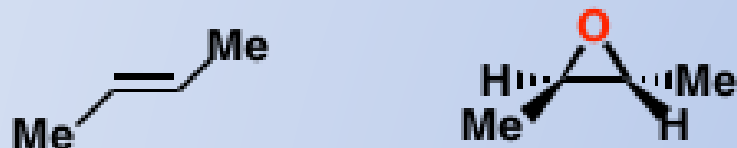


only product

Epoxidation is also stereospecific: cis alkenes give **only** cis products, and trans alkenes give **only** trans products.



only product



only product

Other stereospecific reactions:

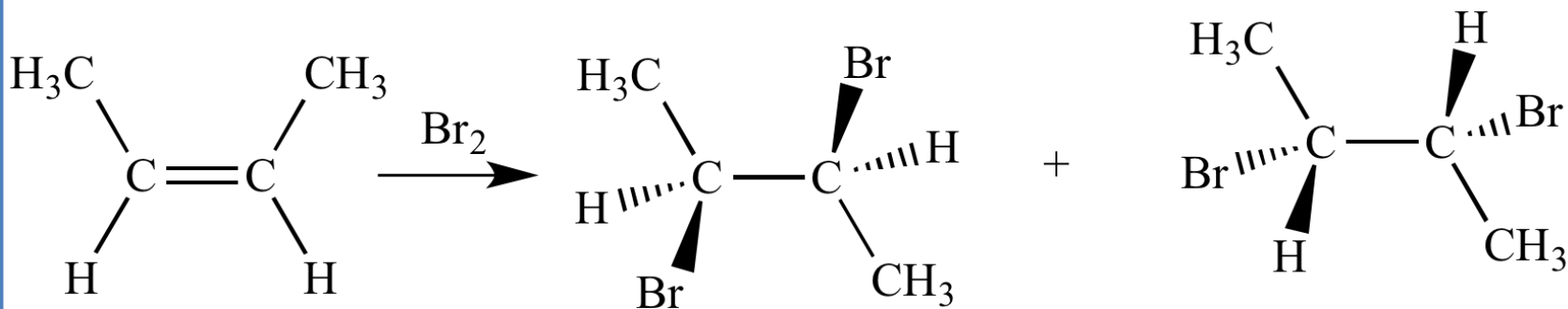
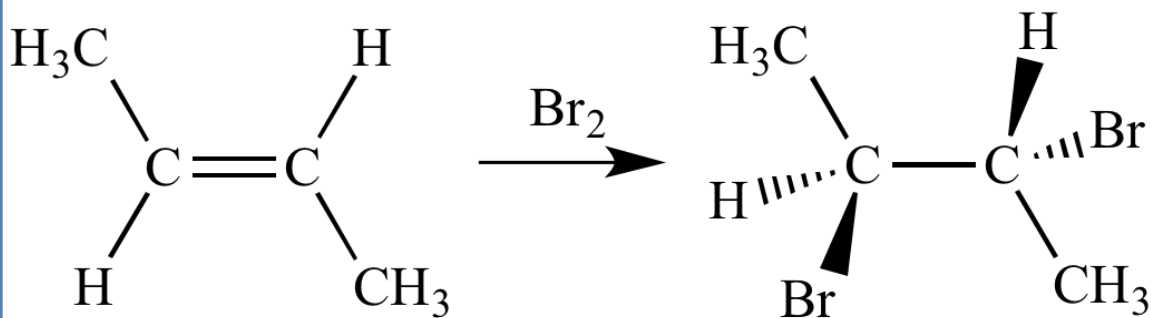
alkene bromination (gives trans dibromide)

Hydroboration (hydrogen and boron are delivered *cis*)

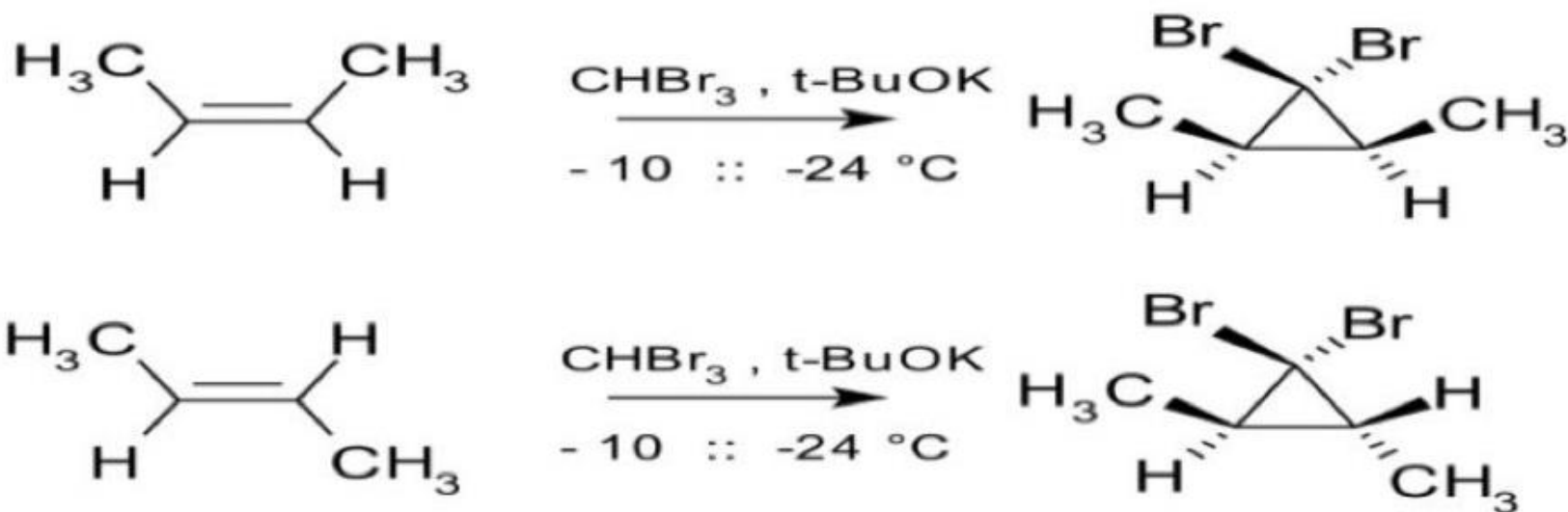
Hydrogenation (hydrogens are delivered *cis* to double bonds)

E2 (proceeds through *anti* transition state)

The addition of molecular bromine to 2-butene is stereospecific. The addition of molecular bromine to (*E*)-2-butene gives meso-2,3-dibromobutane, whereas addition of molecular bromine to (*Z*)-2-butene gives a racemic mixture of (*2S,3S*)-2,3-dibromobutane and (*2R,3R*)-2,3-dibromobutane.

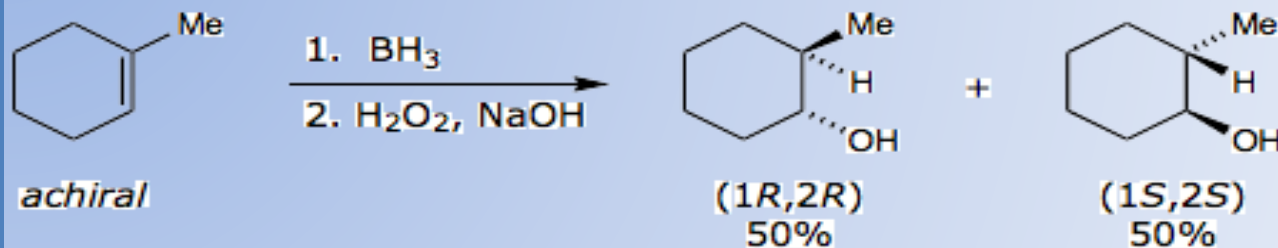


The addition of singlet carbene to alkene is stereospecific in that the geometry of alkene is retained in the final product. e.g., dibromocarbene upon reaction with cis-2-butene give 2,3-dimethyl-1,1-dibromo cyclopropane, while trans isomer give trans cyclopropane.



HYDROBORATION IS STEREOSPECIFIC

only *syn*-addition is observed

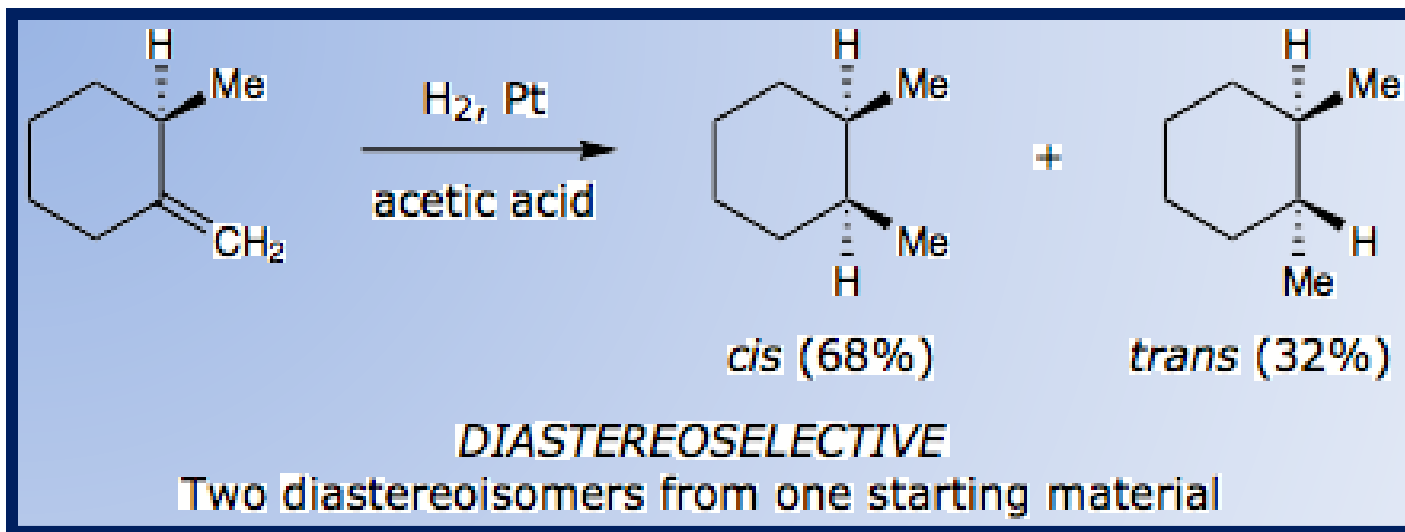


Re and *Si* addition give enantiomeric transition states with the same energy (e.e. 0%)

STEREOSELECTIVE REACTIONS:

It is a process in which one stereoisomer predominates over another when two or more may be formed.

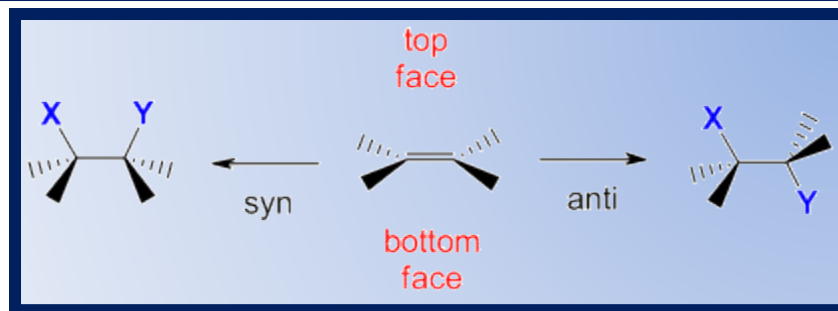
- If the products are enantiomers, the reaction is *enantioselective*.
- if they are diastereoisomers, the reaction is *diastereoselective*.
- Stereoselectivity is dominated by the *structural features* of the reactants.



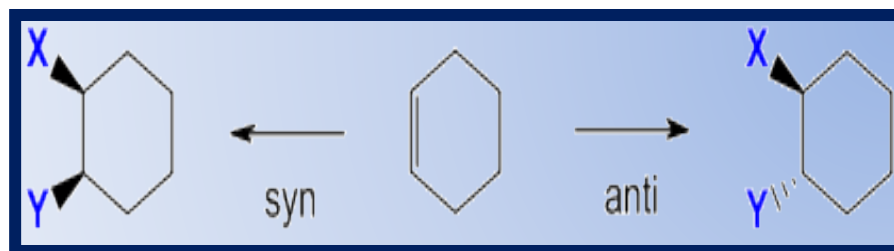
The reaction above is *stereospecific* (only *syn* addition) but the *stereoselectivity* is low. Optically active products cannot be created using achiral (or racemic) starting materials in an achiral solvent. The product in such a case must also be achiral (or racemic).



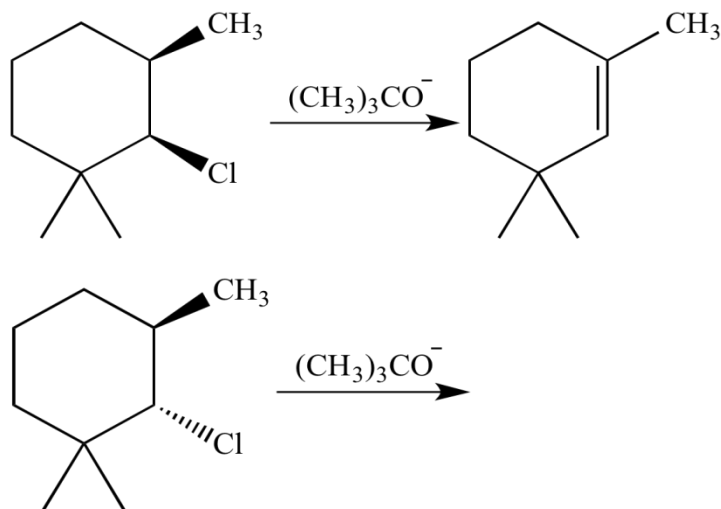
When an alkene undergoes addition, two new sigma bonds are formed. **Syn addition** results when the two new bonds are both formed to the same face of the alkene, in this case they are shown to have formed on the top face. **Anti addition** results when the two new bonds have formed to opposite faces.



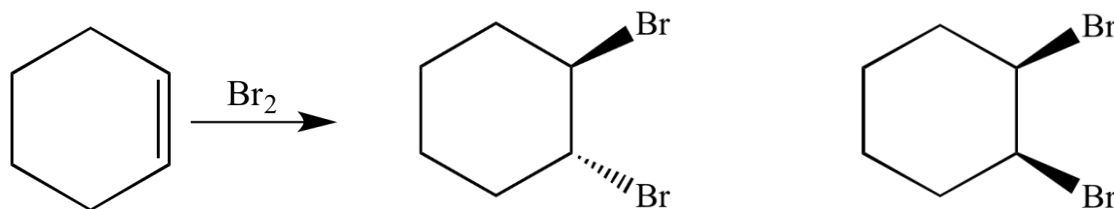
In the case of a simple alkene like ethene, the free rotation of the C-C bond means that the two product structures are *conformational isomers* and rapidly interconvert. However with cyclic alkenes, where the ring structure prevents the free rotation, the two products are *stereoisomers* and are more obvious.



E_2 reaction is stereoselective reaction because only the cis diastereomer react.



The addition of molecular bromine to cyclohexene is stereoselective because Trans-1,2-dibromocyclohexane is formed. Cis-1,2-dibromocyclohexane is not formed



Relationship

Each reactant (stereoisomer) produces a different product (stereoisomer) or a different set of products (stereoisomer).

A single reactant gives two or more products (stereoisomer), and one product is more than the other product/s.

***** ALL STEREOSPECIFIC REACTIONS ARE ESSENTIALLY STEREOSELECTIVE.**

***** ALL STEREOSELECTIVE REACTIONS ARE NOT ESSENTIALLY STEREOSPECIFIC.**

Regioselective Reaction

A reaction that selectively generates one possible product over another is called regioselective. That is, a choice of final product exists.

Addition of non-symmetrical reagent (i.e. A-B where A is not equal to B) to a non-symmetrical alkene (i.e. where the groups at each end of the double bond are different), then two isomeric products that are constitutional isomers can be obtained. For example, the reaction of HCl with propene gives 1-chloropropane and 2-chloropropane.

Reaction of propene and HCl.



Normally, 2-chloropropane is the major product. Since one product is favoured over the other, the reaction is said to be regioselective. If 2-chloropropane were the only product then the reaction is said to be regiospecific.

Regioselectivity in organic chemistry refers to the favoring of a reagent to bond to one atom over another (think 'region' when you see the prefix 'regio-'). It turns out that chemists can predict with a high degree of accuracy how a reagent will react simply by looking at the nature of the reagent itself and the substrate it is going to ultimately react with.

Regiospecific Reactions

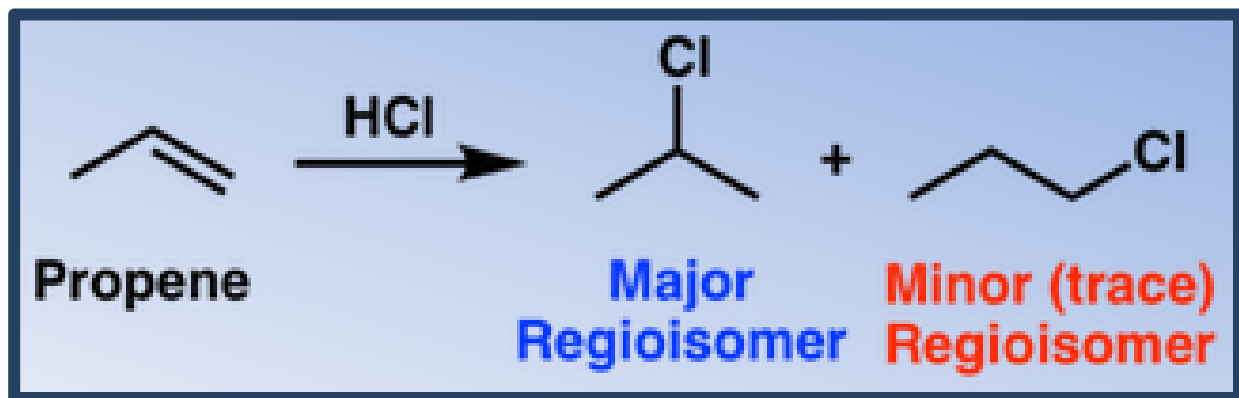
Regiospecific reactions are those reactions where the same choice isn't there. A regiospecific reaction exclusively gives only one, specific product.

A regioselective reaction can be made regiospecific by controlling the factors affecting the reaction, like temperature, pressure, presence of a catalyst, etc.

Reaction of propene with HCl makes one specific isomer, **isopropyl chloride** and not any of the **n-propyl isomers**.

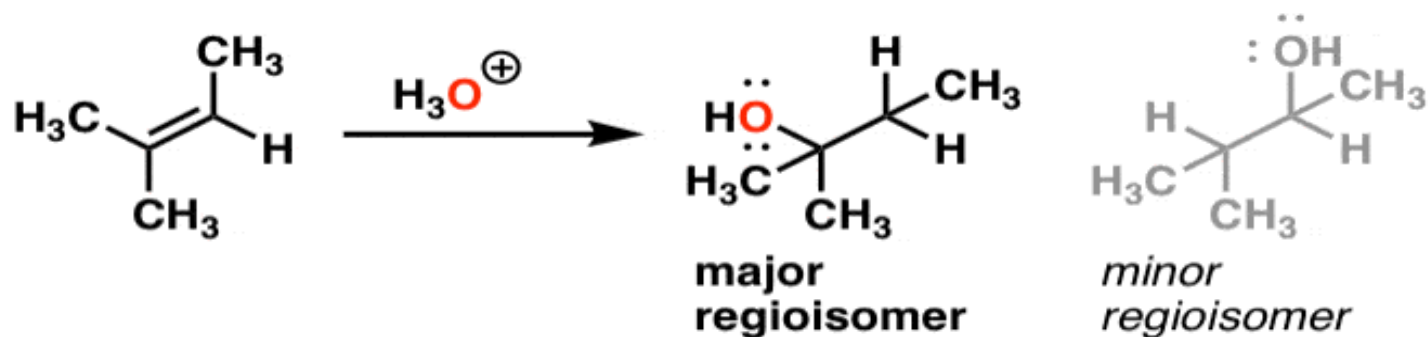
In the reaction of propene with hydrochloric acid (HCl), two possible products are possible, both of which are called **regioisomers** (isomers of a compound with the same atom-makeup but different connectivity of the atoms). It turns out, however, that only one of the products is formed as the major product and only trace amounts of the minor is observed.

We can say that the reaction is thus regioselective in the sense that even though two products are possible, only one of them is actually formed.

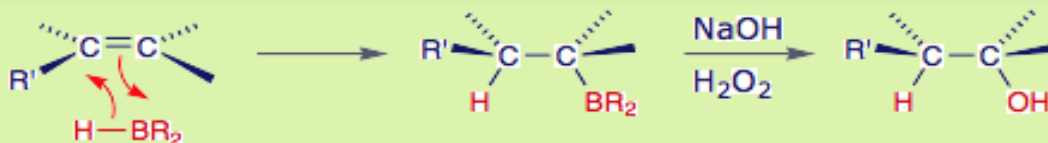
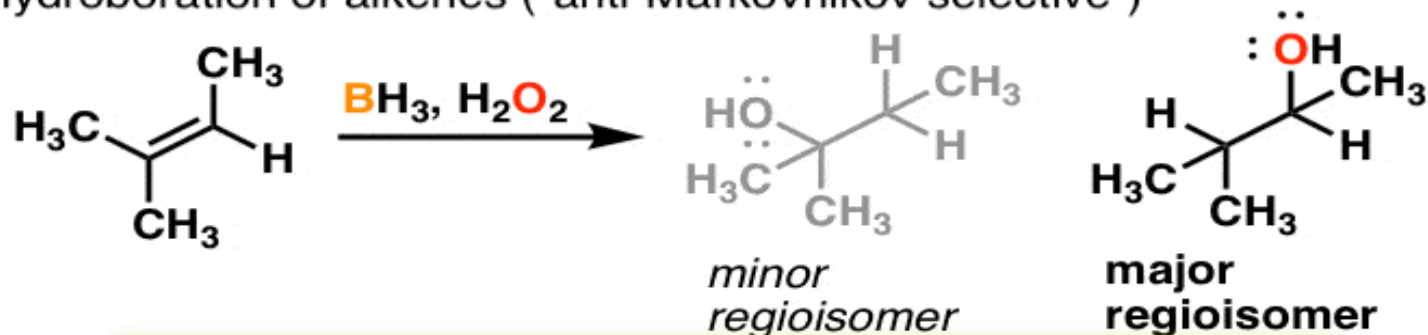


Regioselective reactions

Hydration of alkenes with acid (“Markovnikov-selective”)



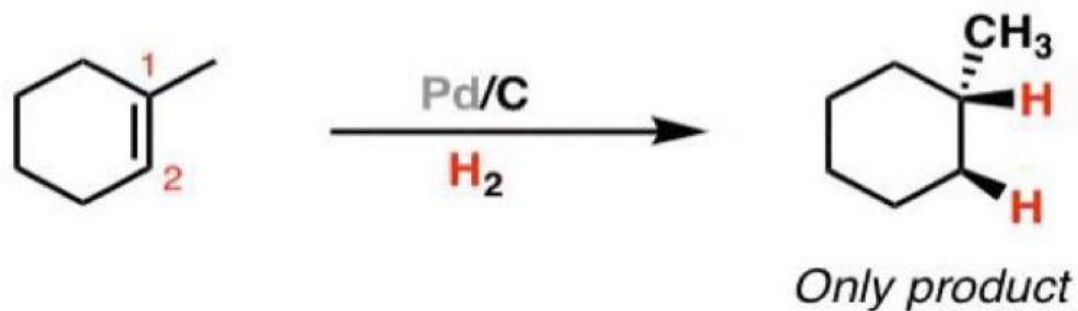
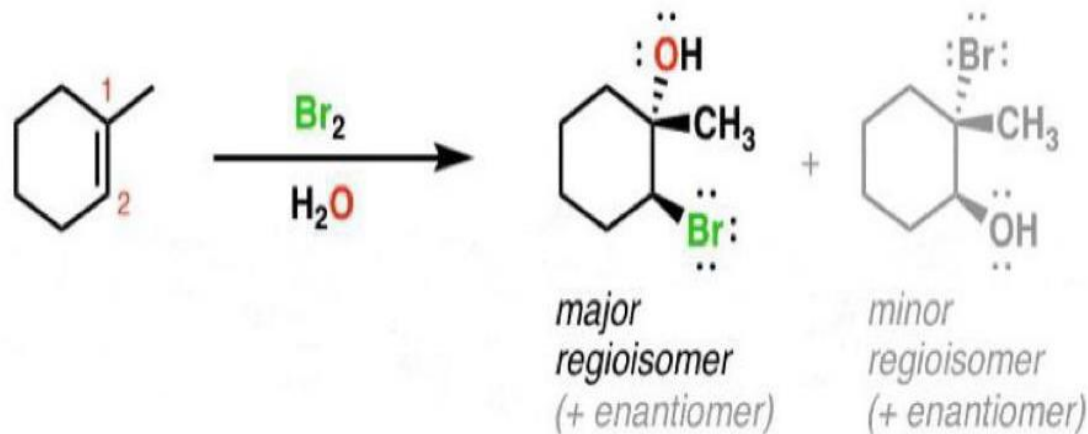
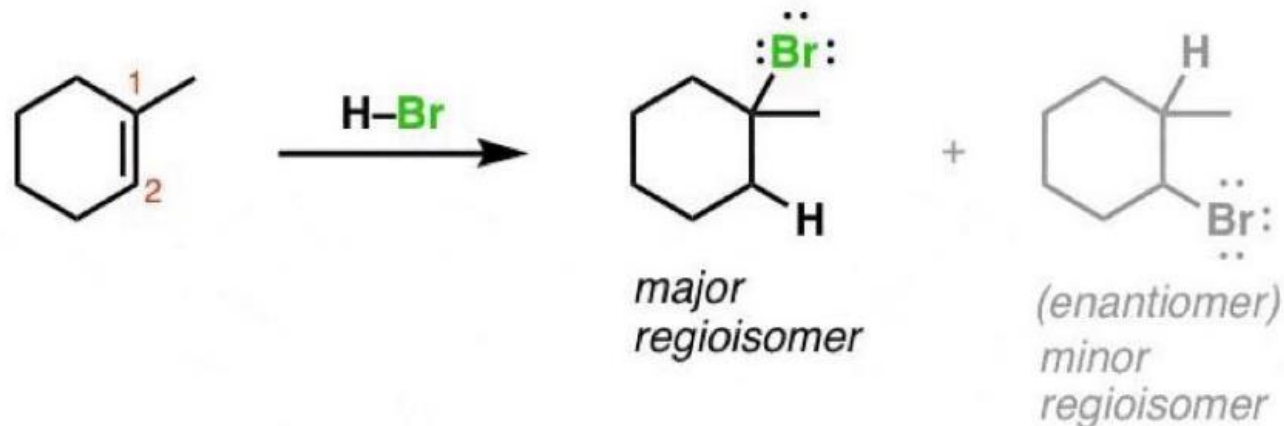
Hydroboration of alkenes (“anti-Markovnikov selective”)



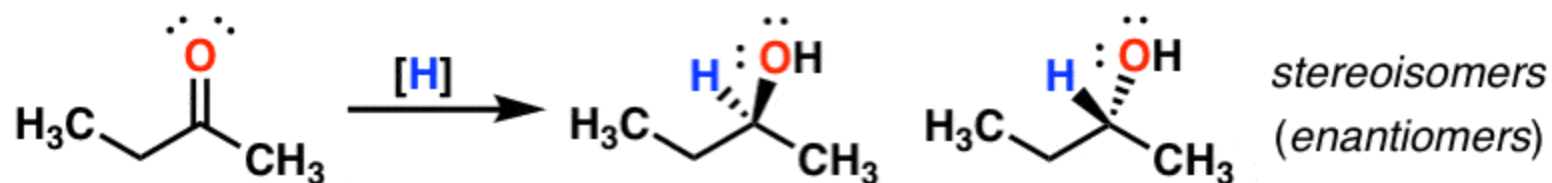
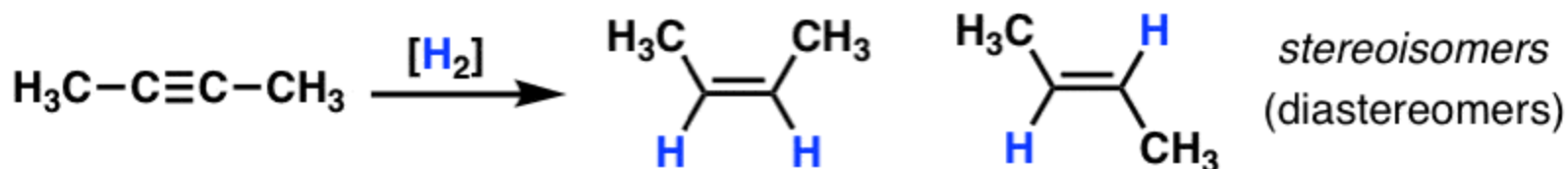
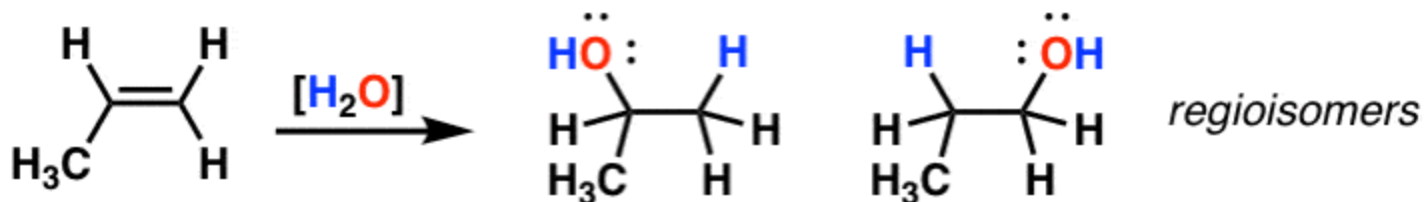
ADDITION OF H₂O TO C=C via HYDROBORATION

- **Stereospecific:** **syn-addition** via concerted mechanism
- **Reagent is any borane** R₂BH
- **Regioselective:** B adds to least substituted end of alkene
- **Mild conditions, fast and efficient**

The reaction of HBr and HOX with alkenes are the examples of regioselective reaction. On the other hand halogenation or hydrogenation of alkenes do not produce regio-isomers.

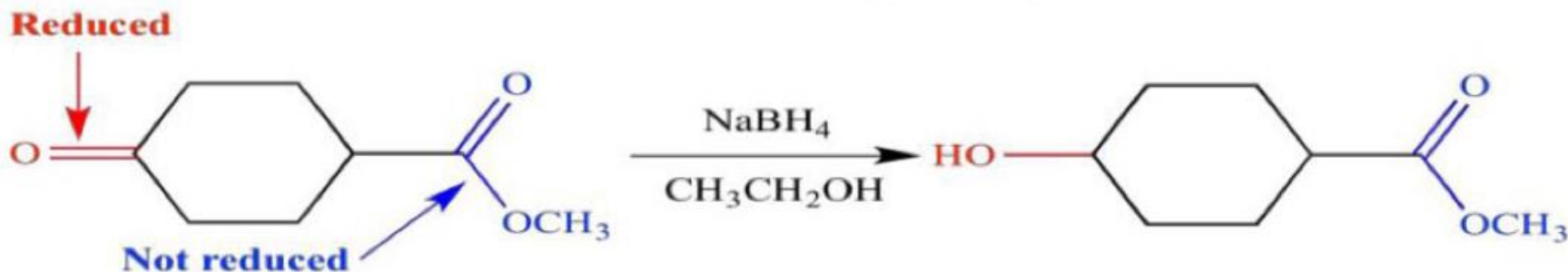


Different types of isomers

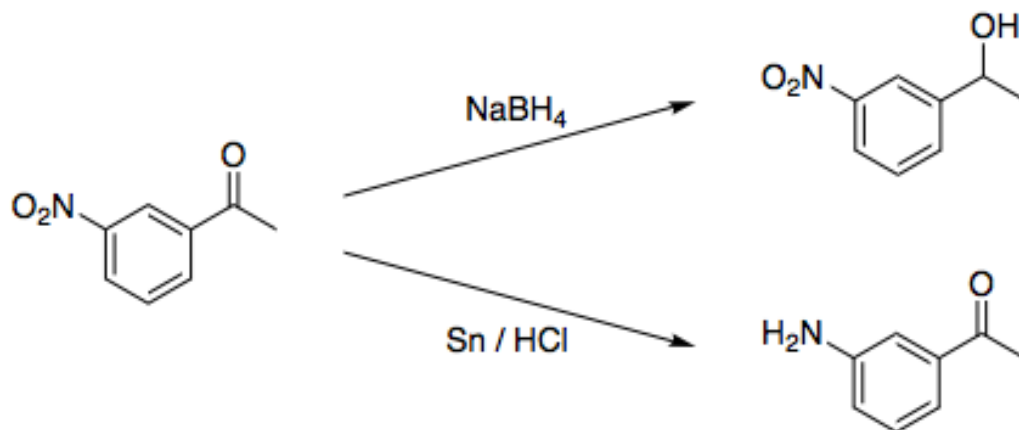
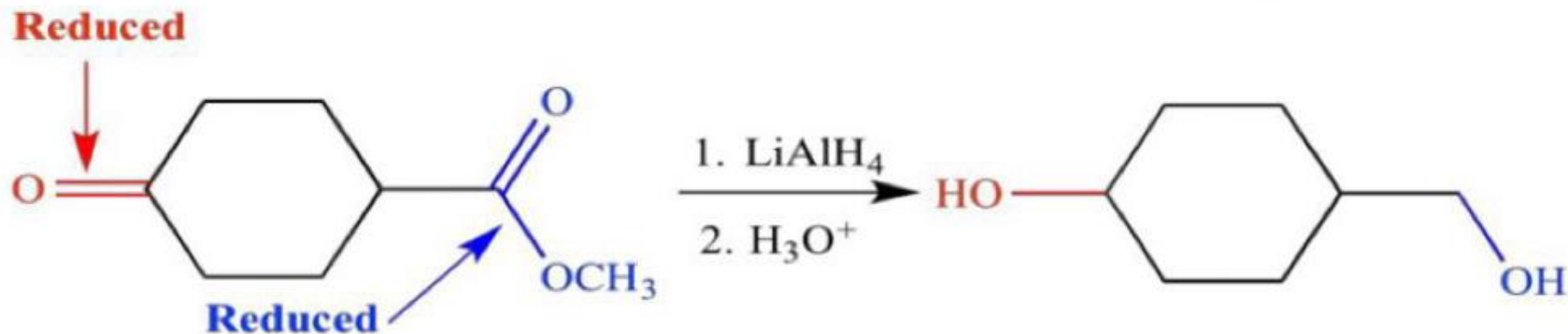


Chemoselectivity

It is the selective reactivity of one functional group in the presence of other groups. A reaction that operates on one functional group exclusively in the presence of other functional groups. Protecting groups can be used instead of chemoselectivity but with the disadvantage of having to perform two additional synthesis steps (protection and deprotection). In the following example the ketone is reduced but the ester is unchanged so the NaBH_4 reduction is chemoselective.

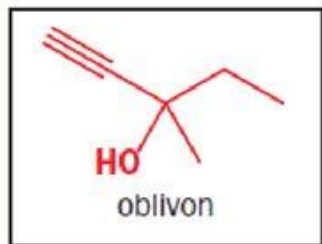


This LiAlH_4 reduction is not chemoselective because the ketone and ester are both reduced by LiAlH_4

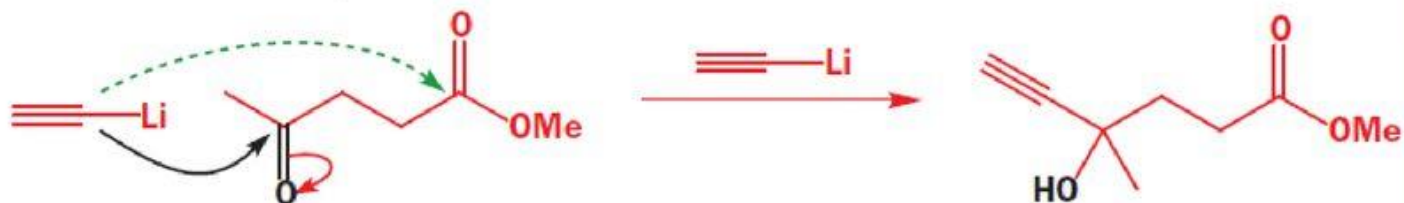


When 3'-nitroacetophenone is treated with NaBH_4 , only the carbonyl group is reduced (top); When reacted with tin and hydrochloric acid only the nitro group is reduced (bottom)

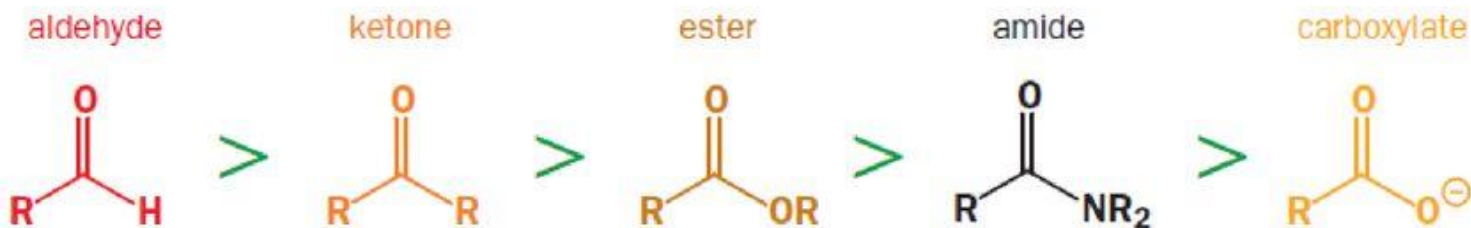
CHEMOSELECTIVITY



ketone is more electrophilic than ester



reactivity towards nucleophiles



reduced by NaBH₄

not reduced by NaBH₄

