7

Synthesis of Medium and Large Ring Compounds

7.1 Synthesis by high dilution principle

7.1.1 What is high dilution principle?

Intramolecular cyclisation is an essential part to synthesize medium (8 to 11-membered) and large ring (12-membered and over) from an acyclic precursor. Several factors influence during the intramolecular ring closure.

(i) 'Distance factor'—For the formation of n-membered ring, the new bond must be formed between two atoms which are separated by (n–2) other atoms and it follows that, as 'n' increases, there is a decreasing probability of the molecule adopting a conformation in which the 'reactive' atoms are sufficiently close for bond formation to occur.

(ii) There are various kinds of 'Strain factors'. Angle strain and cis-double bonds nature in the cyclised compound may destabilise it relative to its acyclic precursor.

(iii) Unfavourable steric interactions in the cyclised product (e.g. 1, 3-syn-diaxial repulsion between the substituents and transannular interactions).

(iv) Angle strain and unfavourable steric interactions in the transition state for the ring-closure step—and if the ring-closure step is reversible, the equilibrium may lie in favour of the acyclic precursor.

Medium and large rings may be synthesised by high dilution principle.

According to this principle, by using sufficiently dilute solution of the acyclic precursor (diester, dicyanide, bromo acid and acyl chloride of benzene derivative), the intermolecular

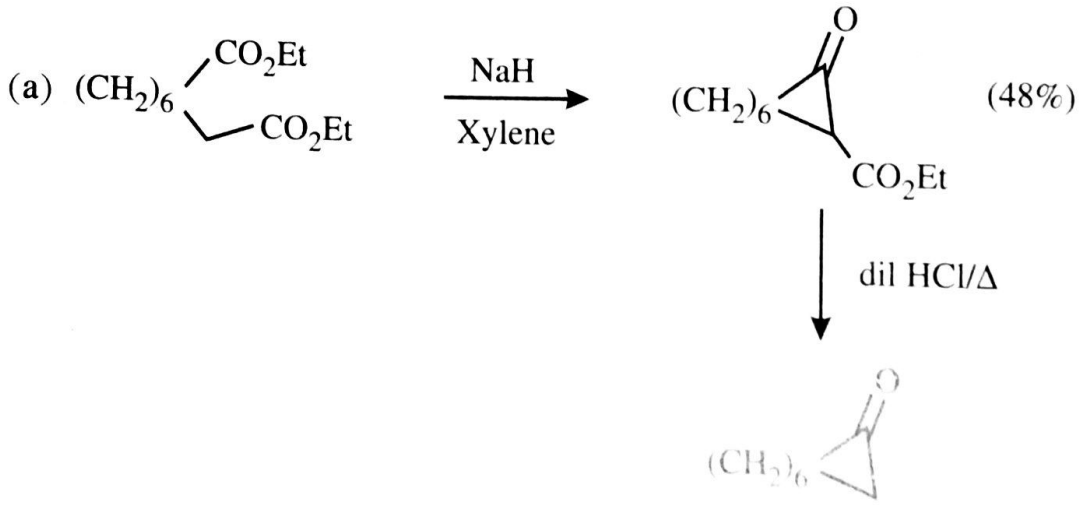
distance can be made greater than the intramolecular reactive centres. Thus, the cyclic compound is formed instead of linear condensation product. In order to apply high dilution principle it is necessary to have all the reactants in solution in a suitable solvent.

7.1.2 High dilution technique

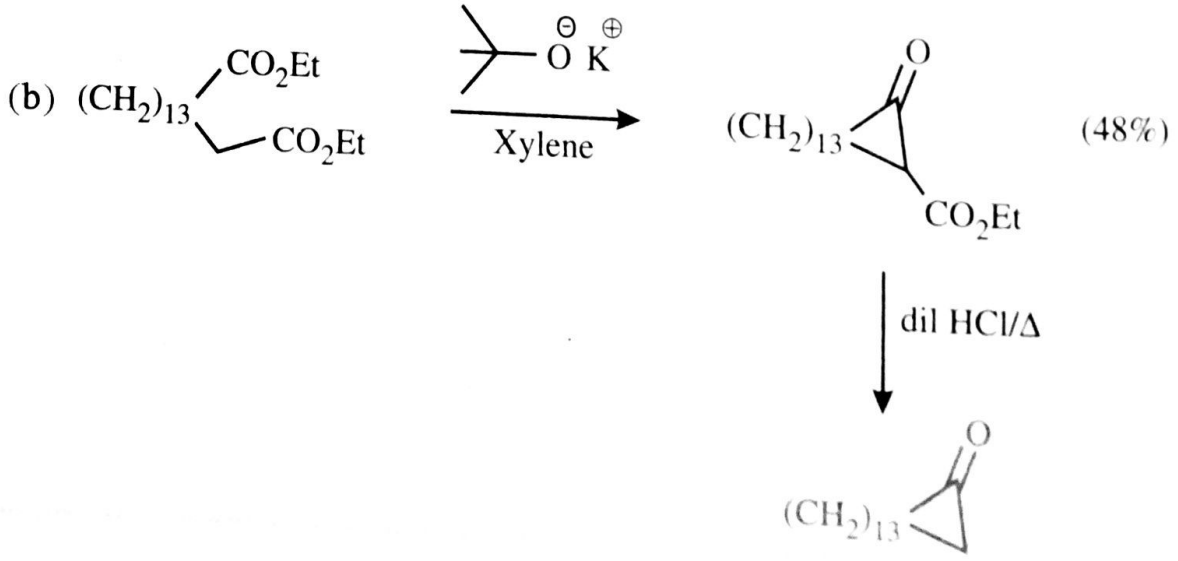
The acyclic precursor is introduced very slowly into the reaction medium so that its concentration is always very low 10^{-3} (M) or less—at this concentration the probability of intermolecular reaction is greatly reduced. Under such high dilution conditions, Dieckmann or related reactions lead to acceptable yields of medium and large rings.

7.1.3 Synthesis of medium and large ring compounds with high dilution principle

(i) Monoketone from diester

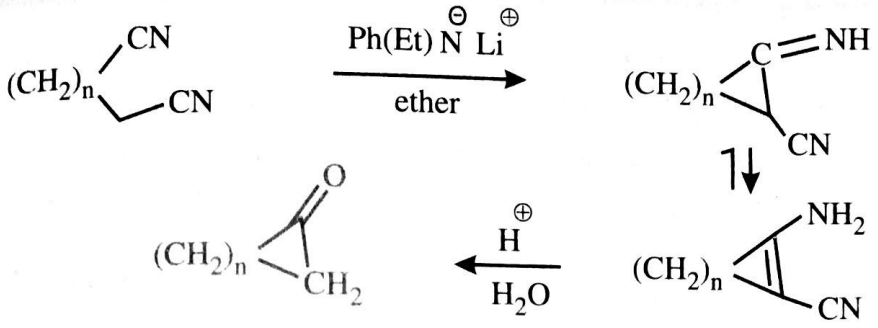


The diester (1M) solution is added dropwise over nine days to a stirred suspension of the hydride (2.5 fold excess ~ 1M).



The diester (4M solution) is added to base (4.8 fold excess ~ 4M) dropwise over 24 hours.

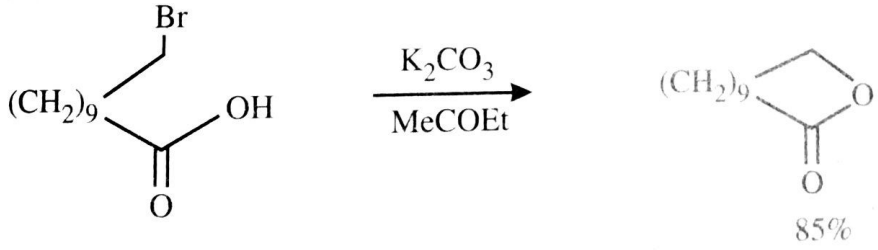
(ii) Monoketone from dicyanide



7-membered ring	95% yield
8-membered ring	88% yield
9-13-membered ring	< 15% yield
14 or more membered ring	60-80% yield

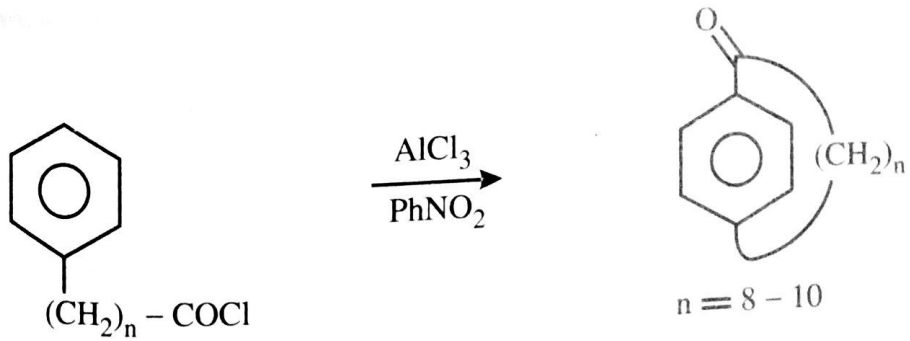
Ph (Et) N Li —soluble in ether and it is highly hindered base so as to minimise its reaction as a nucleophile with nitrile group.

(iii) Lactone from bromoacid



Bromoacid (0.15M solution) is added over 2-days to the base (~ 0.25M).

(iv) Aromatic ketone from acylchloride

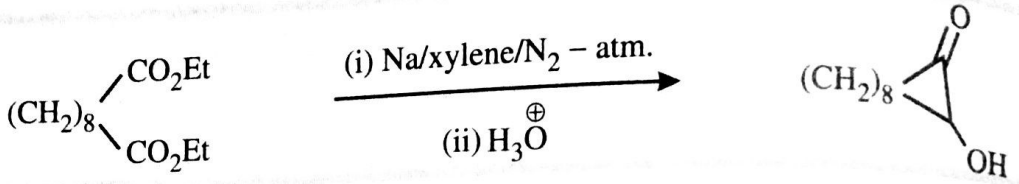


Substrate acylchloride is added dropwise in a mixture of lewis acid $AlCl_3$ and nitro benzene solvent.

7.2 Synthesis by acyloin condensation method

7.2.1 Synthesis of medium and large ring compounds

Long chain diester gives cyclic acyloin, since the reaction is heterogeneous, taking place on the surface of the metal, no need to employ high dilution method.



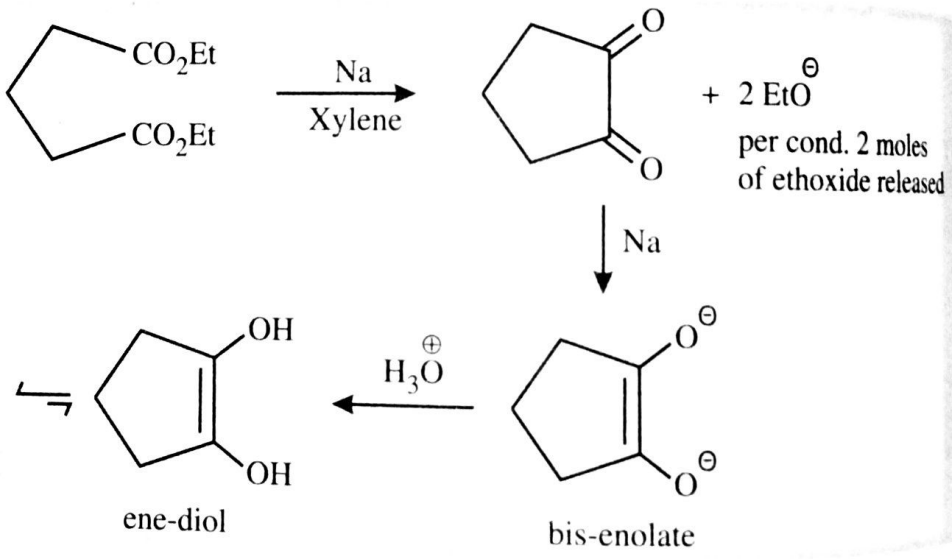
Diester (undiluted) added over 3 hours to a suspension of sodium (4-fold excess) in xylene.

7.2.2 What are the usual complications in acyloin condensation in the preparation of four to seven membered rings? How are these difficulties overcome?

Complications:

(a) In the four to seven membered rings there is a steric strain (angle strain, conformational strain) compare to medium and large rings.

(b)

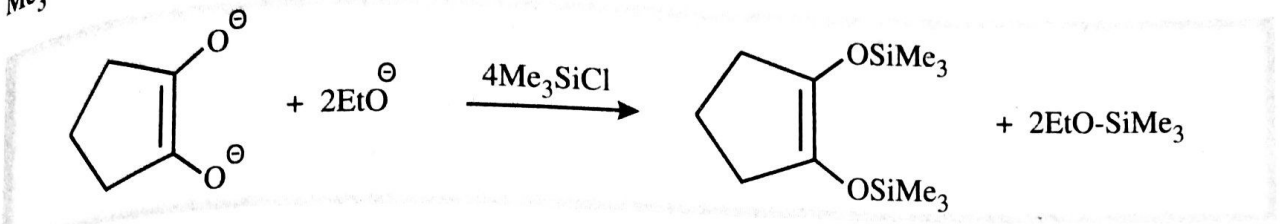


The ethoxide ion produced during the acyloin condensation gives competitive reactions or wasteful base catalysed side reactions as for example β-eliminations, Dieckmann condensation to give cyclic β-keto ester or Claisen ester condensation (linear condensation) to give acyclic β-keto ester.

(c) The bis-enolate or ene-diol produced in the acyloin condensation is oxygen sensitive and hence impurity in the products.

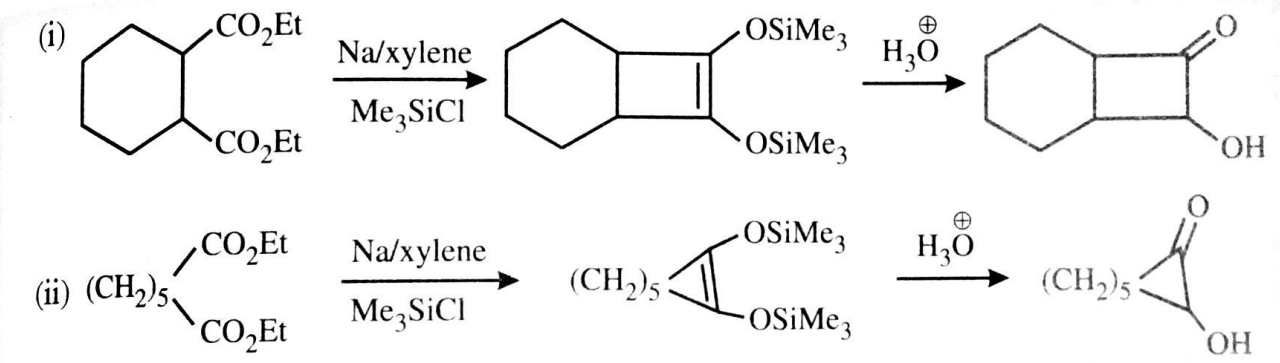
(d) Throughout the acyloin condensation reaction, the medium should be neutral but here basic in nature (due to $EtO^{\ominus}$).

All these complications may be avoided by the treatment of trimethyl silyl chloride Me_3SiCl.



1. Me_3SiCl acts as a scavanger (remover) for the ethoxide ion.
2. Bis-enolate is protected as bis-trimethyl silyl enol ether which may be isolated and purified before hydrolysis to get acyloin.
3. No competitive or side reactions since ethoxide ion is removed.
4. Medium is kept neutral.

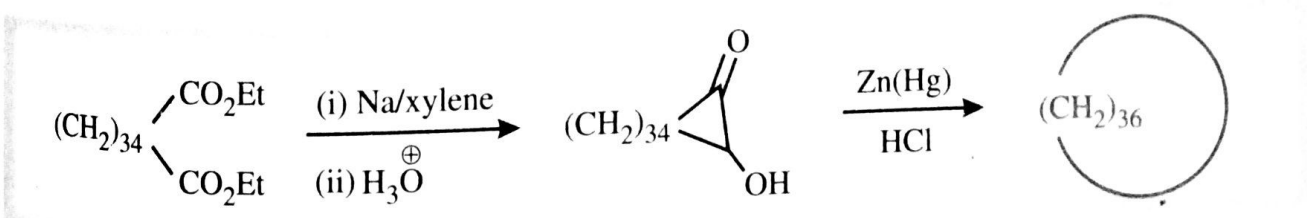
Thus for example,



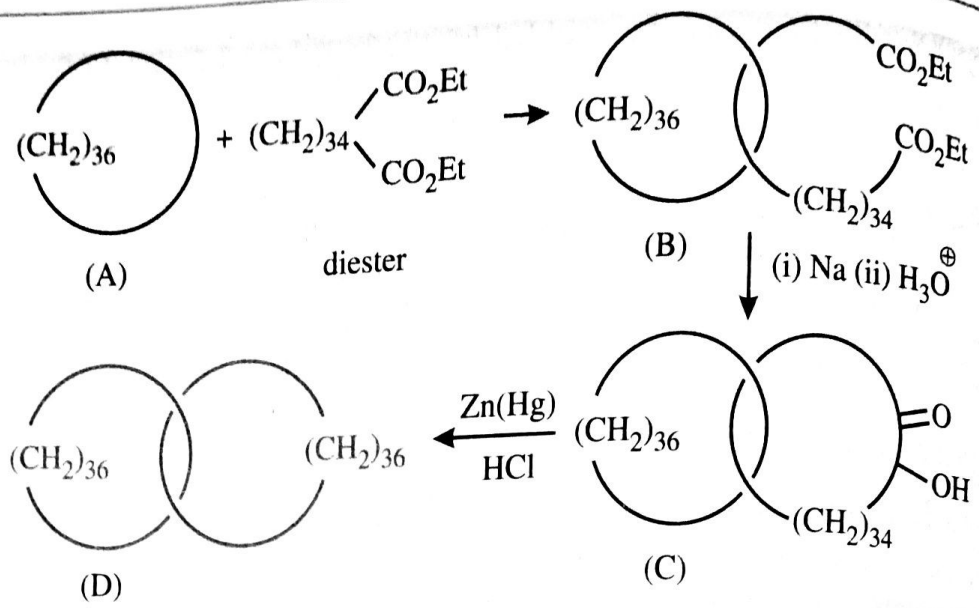
7.2.3 Synthesis of catenane with acyloin condensation method

Catenane which contain large ring may be synthesized by the following steps using acyloin condensation.

(a) An acyloin condensation on the diester of the C_{36}-dicarboxylic acid give the cyclic acyloin. This is reduced under clemmensen reduction condition and the C_{36}-cycloalkane is formed.



(b) A repetition of the reaction in the presence of C_{36}-cycloalkane (A) is anticipated to give (C) since there is a chance that some molecules of diester will get threaded through (A) before cyclisation of (B) and indeed the catenane (D) was isolated.



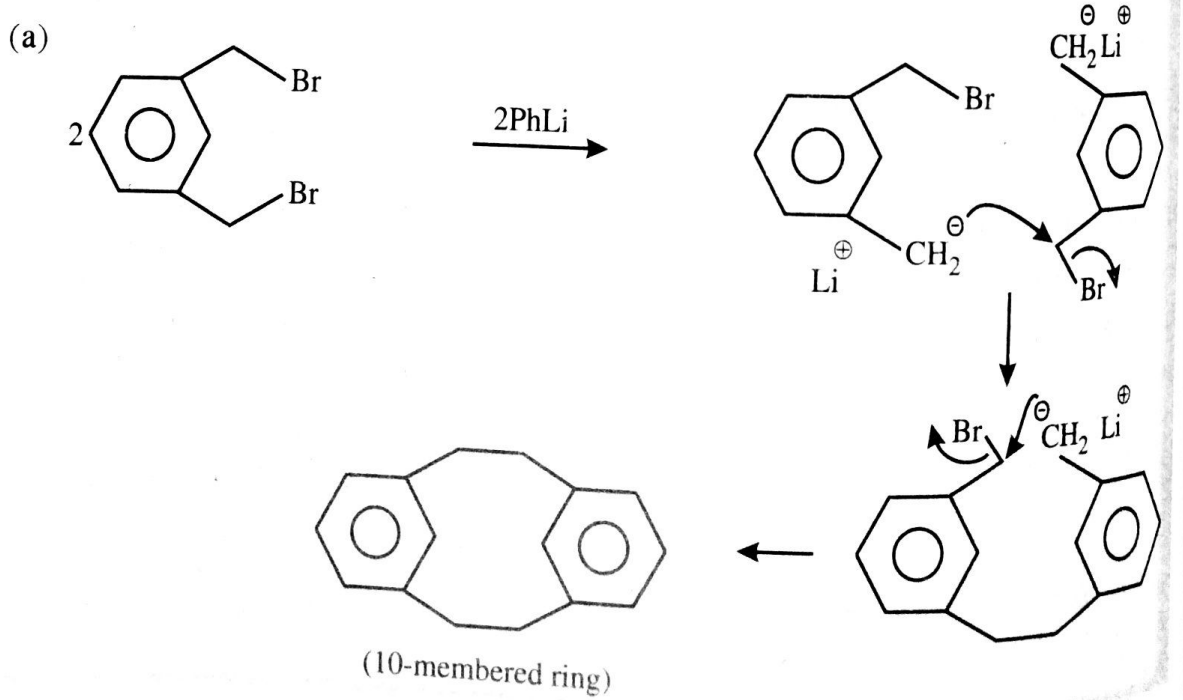
This type of synthesis is known as statistical synthesis.

The ready formation of large rings where the two ends of the chain must approach each other is thought due to the two ends becoming attached to the nearby sites on the surface of the sodium.

7.3 Construction of medium and large rings taking advantage of restricted rotation

If a long chain of atoms contains one or more rigid sections, in which free rotation about bonds is not possible, there may be an increased chance of cyclisation to form a medium or large rings.

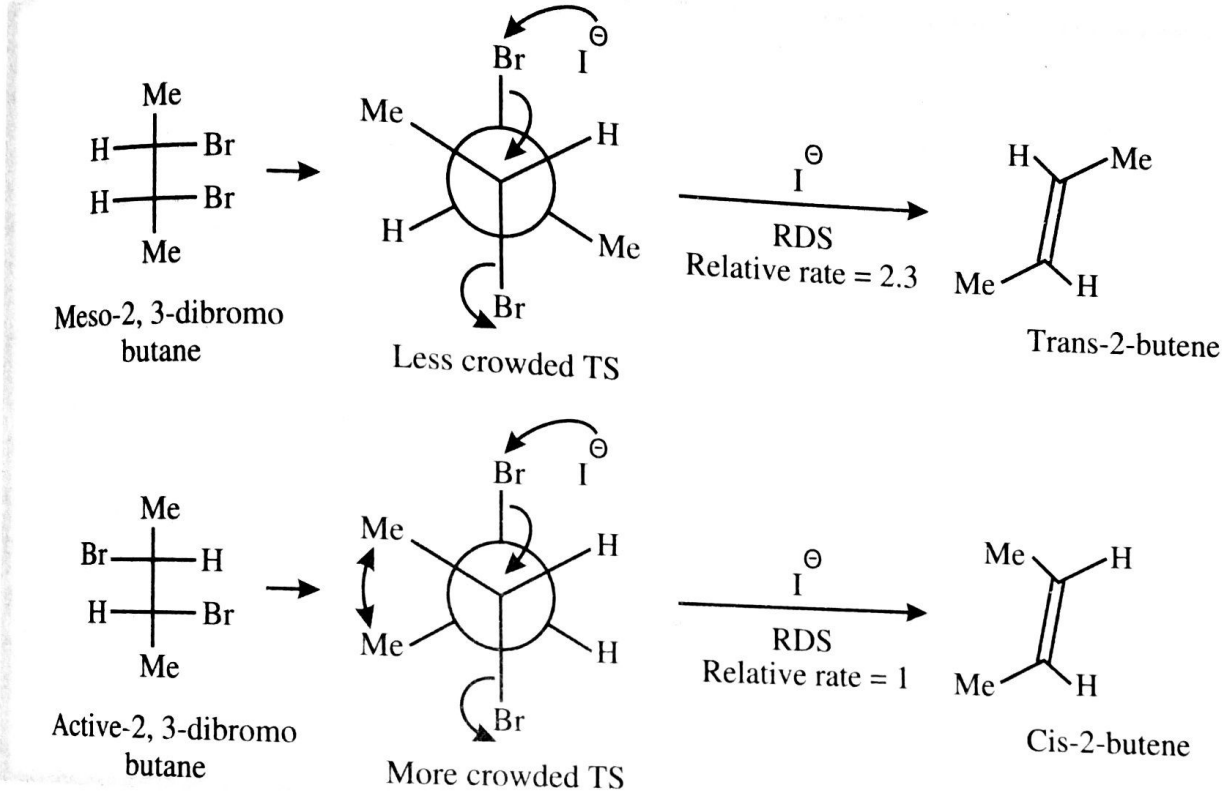
Thus for example,



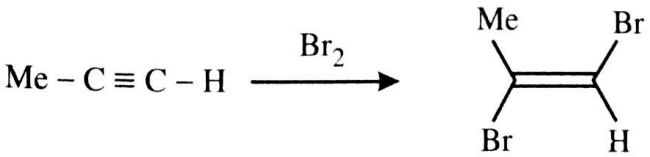
8.1.1 What is stereospecific reaction?

1. **Stereospecific reaction is a reaction in which a reactant can exist as different stereoisomers (diastereomer or enantiomer) and each stereoisomeric reactant leads to a different stereoisomeric product (diastereomer or enantiomer) under identical conditions.**

As for example, Iodide-induced debromination of meso and active 2, 3-dibromo butane (E2 reaction) which are diastereomeric gives *trans*-2-butene and *cis*-2-butene respectively which are diastereomeric.



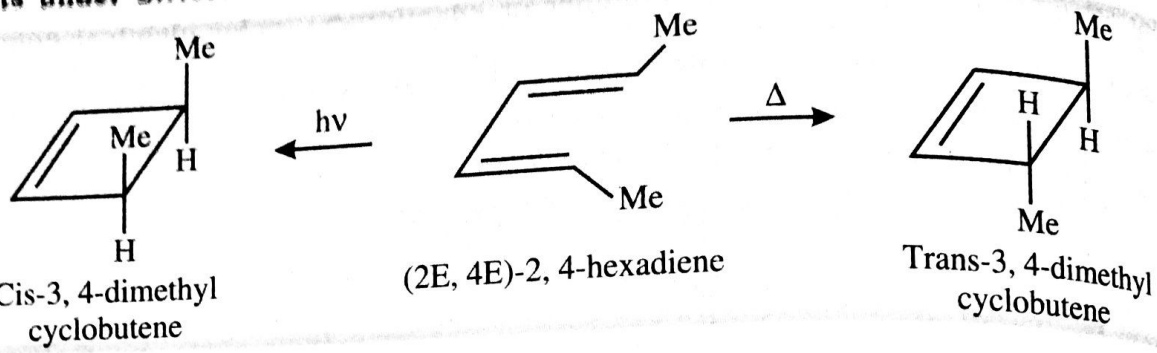
If a reaction is carried out on a reactant that has no stereoisomers, it cannot be stereospecific. As for example, addition of bromine to methyl acetylene produces trans 1, 2-dibromo propene predominantly and this is not a stereospecific reaction (but stereoselective since some amount of *cis* product formed) although product is a stereoisomer.



Stereospecificity is not related with the chirality or optical activity.

2. **In a stereospecific reaction different stereoisomers (diastereomer or enantiomer) produces different products stereochemically at different rates under identical conditions.** As for example, during the debromination of the meso and active 2, 3-dibromo butane, the meso isomer reacts 2.3 times faster than the active isomer since TS correspond to active is more crowded and one gauche-butane interaction is greater than the TS correspond to the meso isomer.

3. Stereospecific reaction may also be defined as a reaction in which a reactant can exist as different stereoisomers and one single stereoisomeric reactant leads to different products under different conditions.



Cis-3, 4-dimethyl cyclobutene

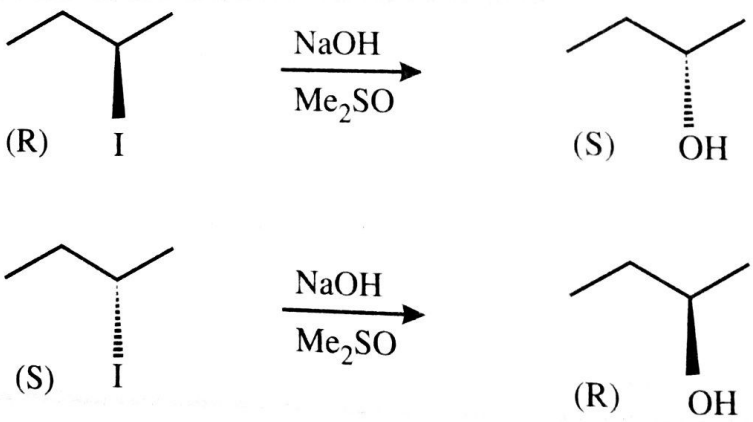
(2E, 4E)-2, 4-hexadiene

Trans-3, 4-dimethyl cyclobutene

2, 4-hexadiene may exist in different stereoisomeric forms (2E, 4E or 2Z, 4Z or 2E, 4Z) and on giving thermal and photoenergy to the (2E, 4E) –2, 4-hexadiene produces *trans* and *cis*-isomer respectively and stereospecifically.

4. Stereospecific reaction may be thought in terms of transition state (TS) geometry.

A. If any stereoisomer gives reaction which goes via one and only one single TS to give another stereoisomer exclusively then it is obviously stereospecific reaction provided basic condition is fulfilled i.e. other stereoisomer should give opposite stereo product via single TS. As for example, any pure S_N2 reaction where nucleophile and leaving groups are different (if nucleophile and leaving groups are same then both the stereoisomers will give dl product which is also stereospecific because of common single TS) goes via one single TS (involving pentavalent SP^2 carbon).

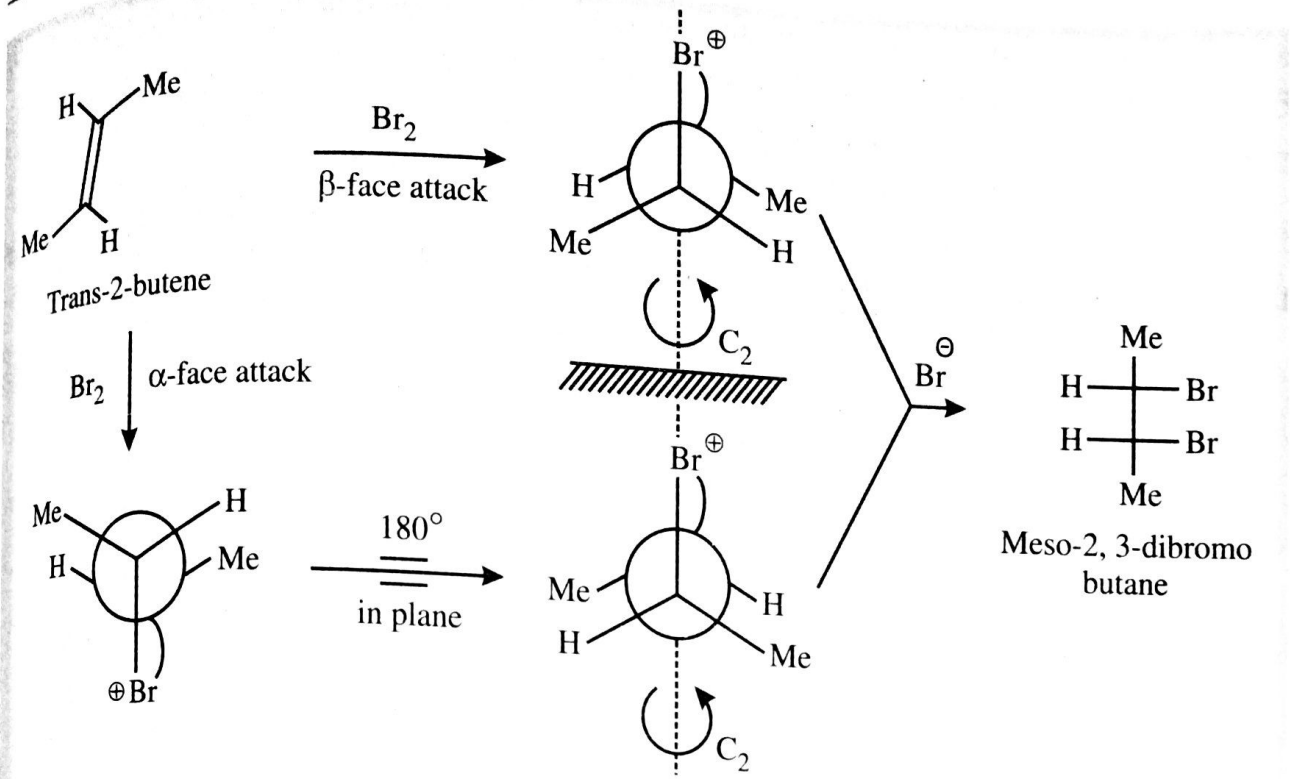


B. If any stereoisomer gives reaction which may go via two TS and which are homomeric then the reaction will be stereospecific.

Example (i)

Bromination of *trans*-2-butene gives meso-2, 3-dibromo butane.

Trans-2-butene has got two enantiotopic faces and on reaction with bromine to both the faces of it gives two chiral cyclic bromonium ion intermediates which are homomeric.



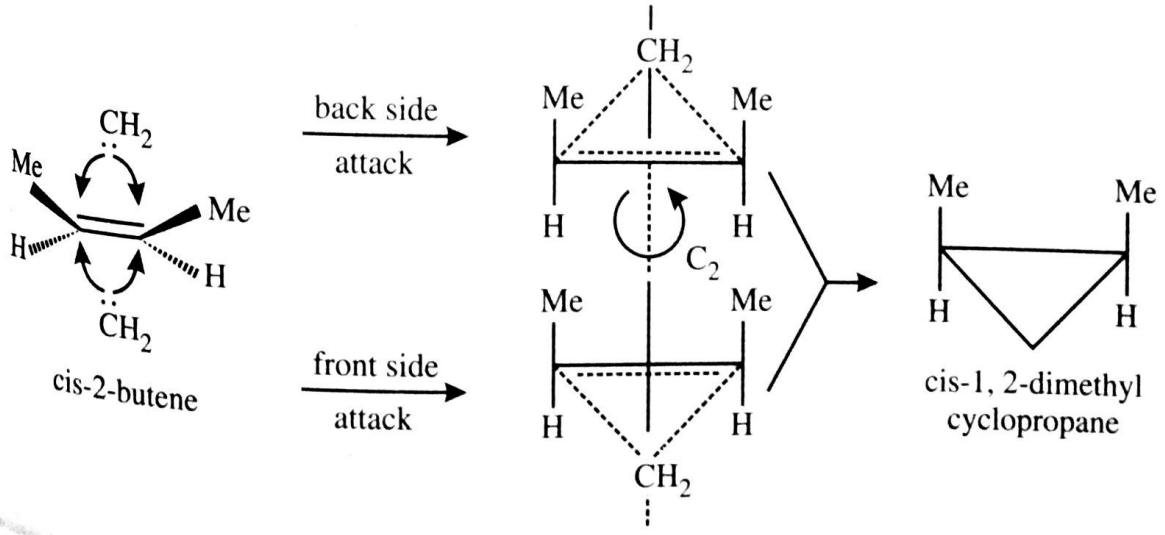
Chiral homomeric intermediates.

The two intermediates arise due to α-and β-face attack of trans-2-butene with bromine are chiral (since the two intermediates are non-superposable mirror images) and homomeric (since each intermediate has got C_2-symmetry). Attack with bromide ion either to the front or back carbon of any intermediate (produces homomeric TS) giving homomers (single product).

Example (ii)

Reaction of singlet methylene to the *cis*-2-butene gives *cis*-1, 2-dimethyl cyclopropane (Meso).

Addition of singlet methylene to the *cis*-2-butene goes via cyclic concerted and one step process. Attack of singlet methylene from the front or backside of *cis*-2-butene gives two TS which are superposable to each other (since on C_2-operation in any one TS mutual conversion occurs) and gives single product.



two homomeric TS (presence of C_2-vertical)

9. Rules for stereospecific addition to alkene

(i) $R-CH=CH-R$

Reagents	Stereochemistry of the alkene	Addition mode	Stereochemistry of the products
Br_2 (Bromination)	*cis*	trans addition	threo dl pair
	trans	trans addition	meso
$KMnO_4$ (Hydroxylation)	*cis*	cis addition	meso
	trans	cis addition	threo dl pair
(ii) $R_1-CH=CH-R_2$			
Br_2 (Bromination)	*cis*	trans addition	threo dl pair
	trans	trans addition	erythro dl pair
$KMnO_4$ (Hydroxylation)	*cis*	cis addition	erythro dl pair
	trans	cis addition	threo dl pair

8.1.2 What is stereoselective reaction?

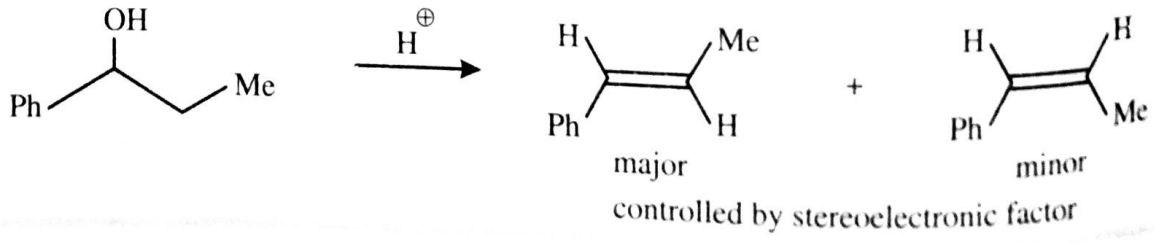
1. **Stereoselective reactions are those reactions in which a given structure (may or may not be stereoisomeric) produce diastereomeric products in unequal amounts.**

Stereoselectivity is not related with chirality or optical activity.

In all stereoselective reactions since products are diastereomeric and unequal amount and therefore the two transition states are diastereomeric and have got different free energy and consequently energy of activation (Ea) are different and therefore reaction pathway has a choice. The pathway of lower energy of activation is preferred and kinetically controlled and forms predominantly.

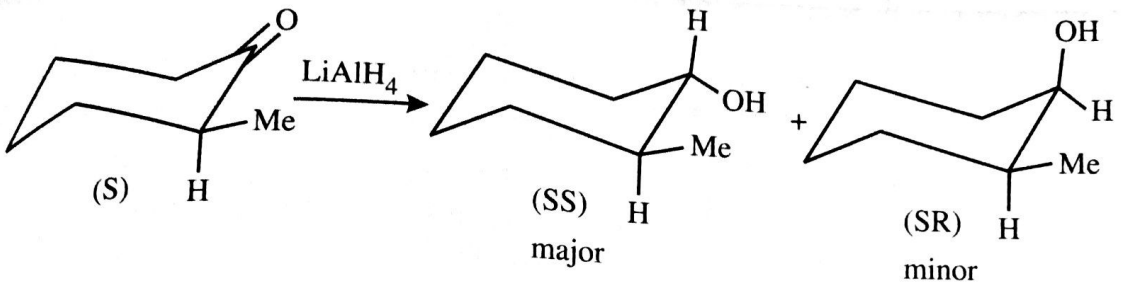
In the stereoselective reactions stereoselectivity is controlled by several factors stereoelectronic factor, steric factor, electronic effects (including participation of chelate and hydrogen bonds), bond rotation and spin inversion etc.

Example (i)



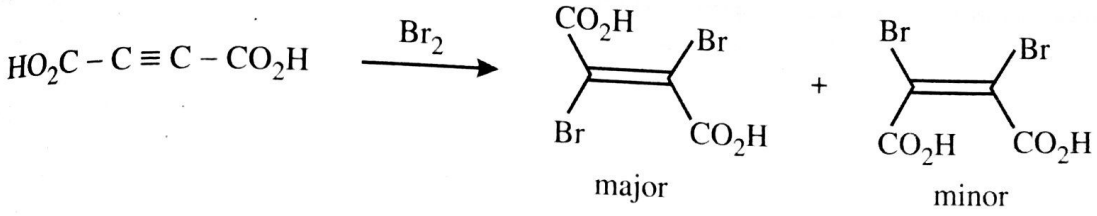
controlled by stereoelectronic factor

Example (ii)



controlled by stereoelectronic factor and thermodynamic stability of the product

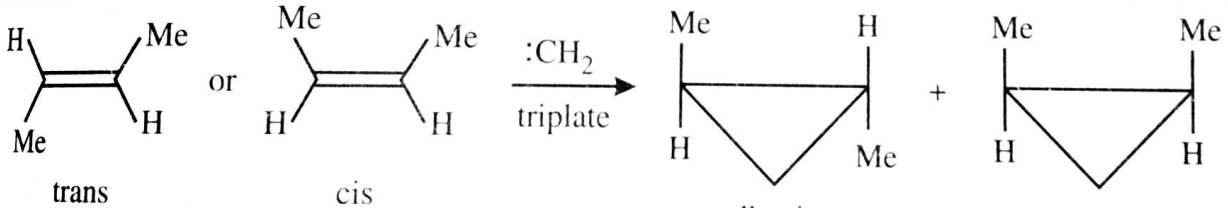
Example (iii)



controlled by stereoelectronic factor

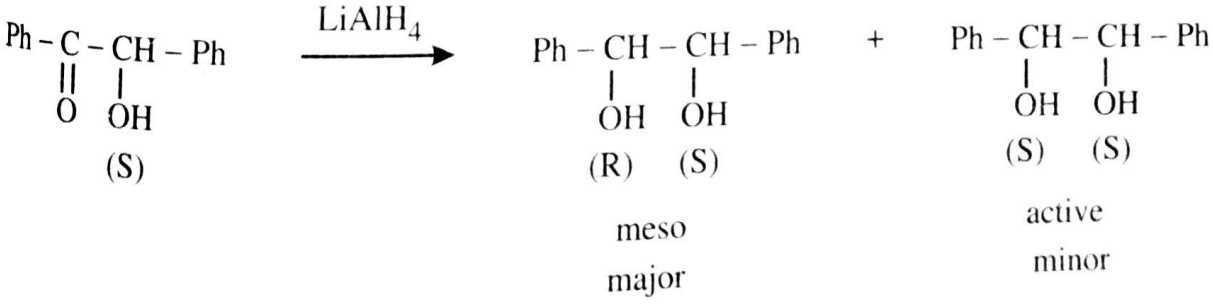
2. Stereoselective reactions are those reactions in which a given structure or structures (stereoisomeric) produces dl pair (or active) and meso in unequal amount.

Example (i)



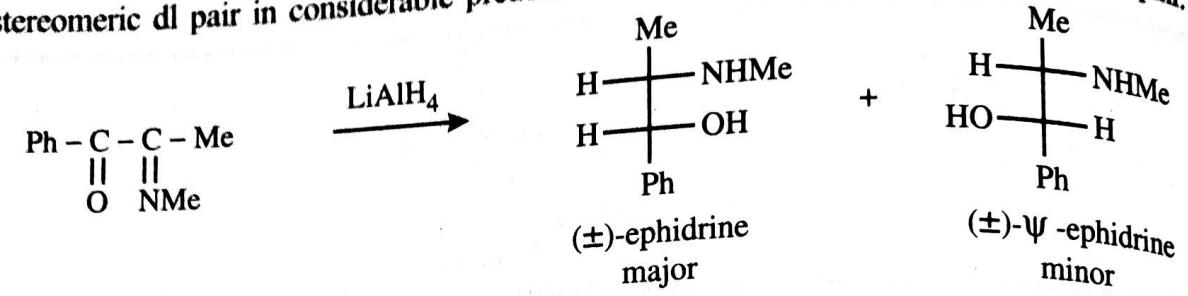
controlled by steric and bond rotation versus spin inversion

Example (ii)

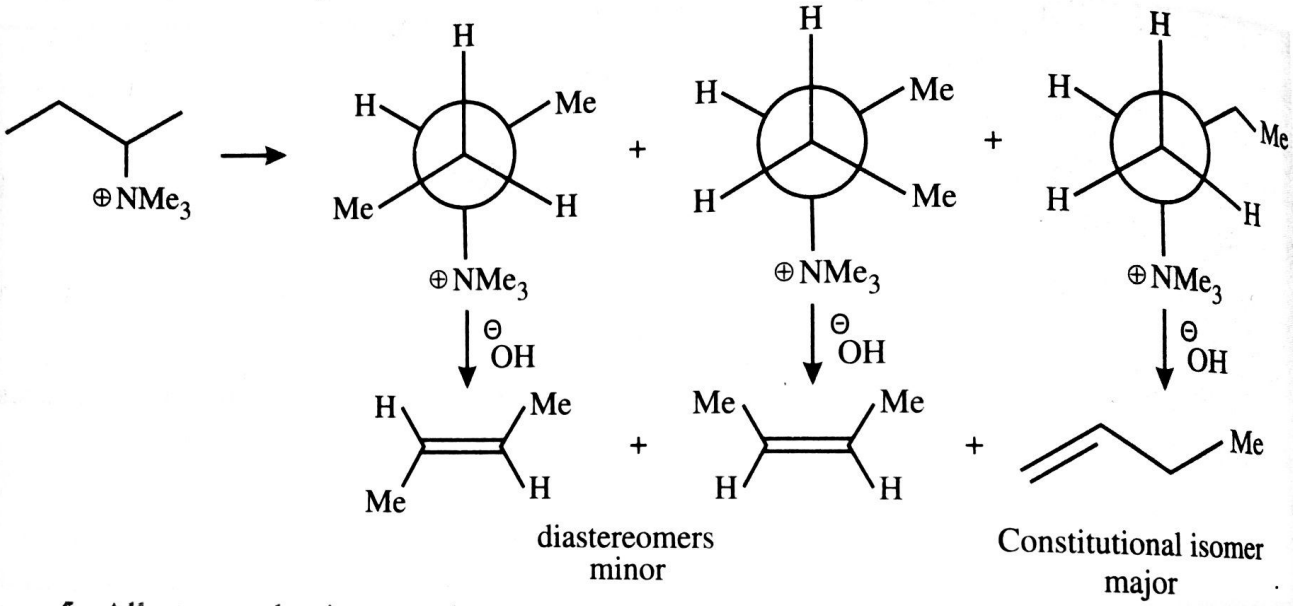


controlled by steric factor in the TS

3. Stereoselective reactions are those reactions in which a given structure produces one diastereomeric dl pair in considerable predominance over the other diastereomeric dl pair.



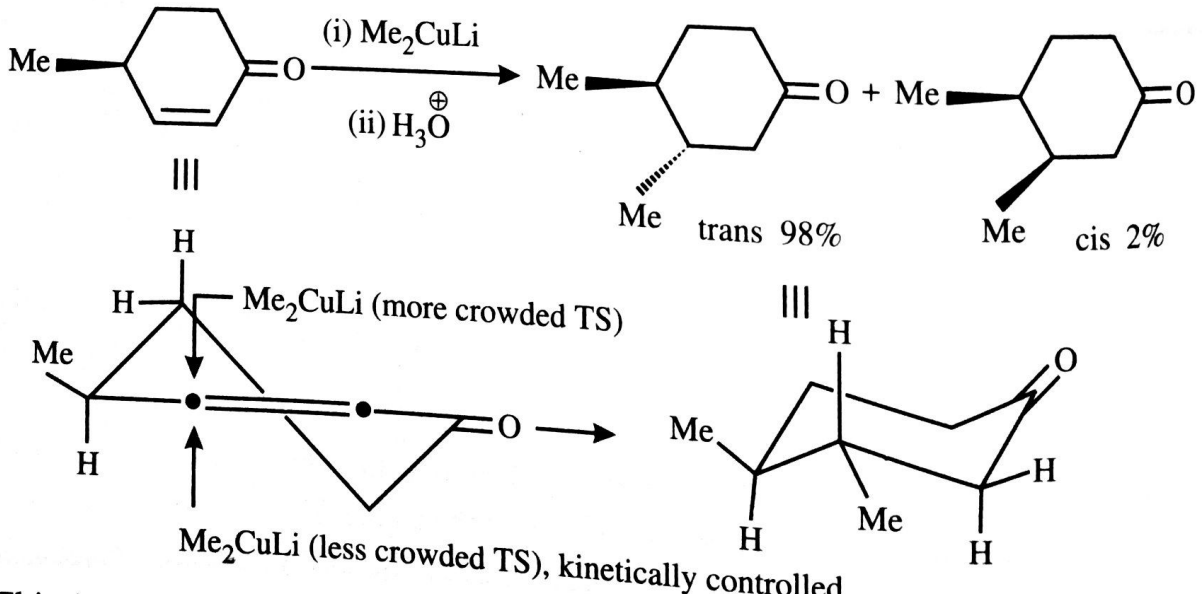
4. Diastereomeric conformers react through diastereomeric transition states to give either diastereomeric products or constitutional products.



5. All stereoselective reactions are product selectivity. Product selectivity are of two types.

(a) Product diastereoselectivity which is again are of two types.

(i) Diastereoselectivity with kinetic control in which case the stereoselectivity depends on the free energies of the respective transition states.



This is a diastereomeric excess (de) synthesis.

8.1.4 What is regioselective reaction?

For substrates which are capable of reacting at more than one centres but react at one centre with a higher rate than at the others to give constitutional or positional isomers is the regioselective reaction.

Reaction of a particular functional group or position in the substrate molecule, in a desired way (control of the reactivity of functional groups or position) may be done either by selective reagent or by protection of comparable undesired functional group/position or by activating a desired reacting centre—these are all control of regioselectivity.

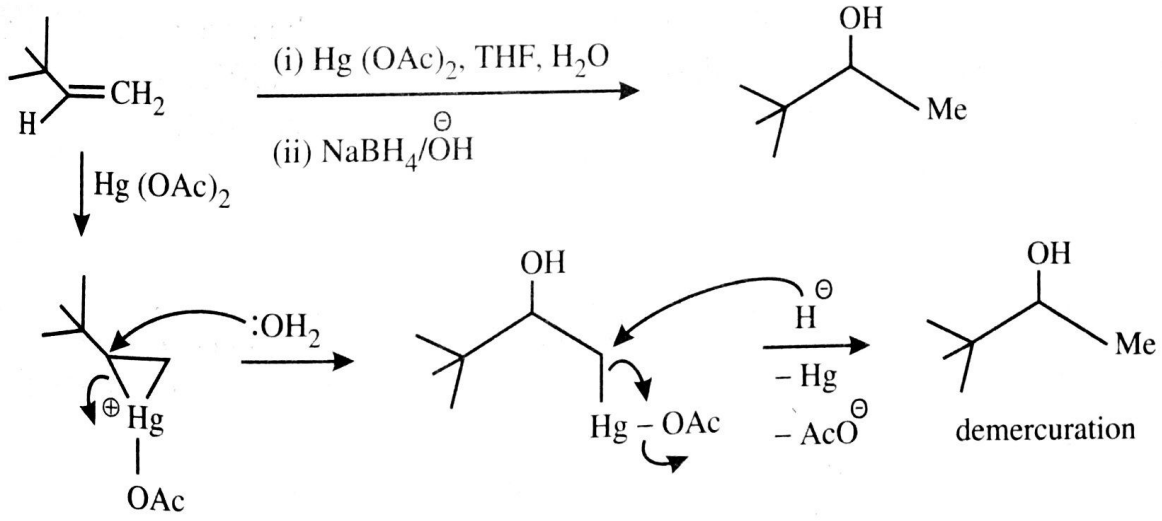
During the addition of unsymmetrical reagent (as for example H_2O) to the unsymmetrical alkene there is a regioselective problems, this may be controlled by selective reagents (e.g. Markownikov hydration by oxymercuration-demercuration process and anti Markownikov hydration by hydroboration process).

Control of stereochemistry is the control of geometry and the control of regiochemistry is the control, as for example, where the double bond is formed if more than one choices of eliminations are possible for a given structure in an elimination reaction i.e. of fixing the double bond predominantly in our desired choice. Oppositely when unsymmetrical reagent is added to the unsymmetrical double bond then more than one choices are possible to give constitutional products. Therefore, any preferential reaction product over the other to give constitutional or positional isomers is the regioselectivity.

The following examples are some illustrations of regioselective reactions.

1. Regioselective hydration of unsymmetrical alkene*

(a) Markownikov hydration via oxymercuration-demercuration process

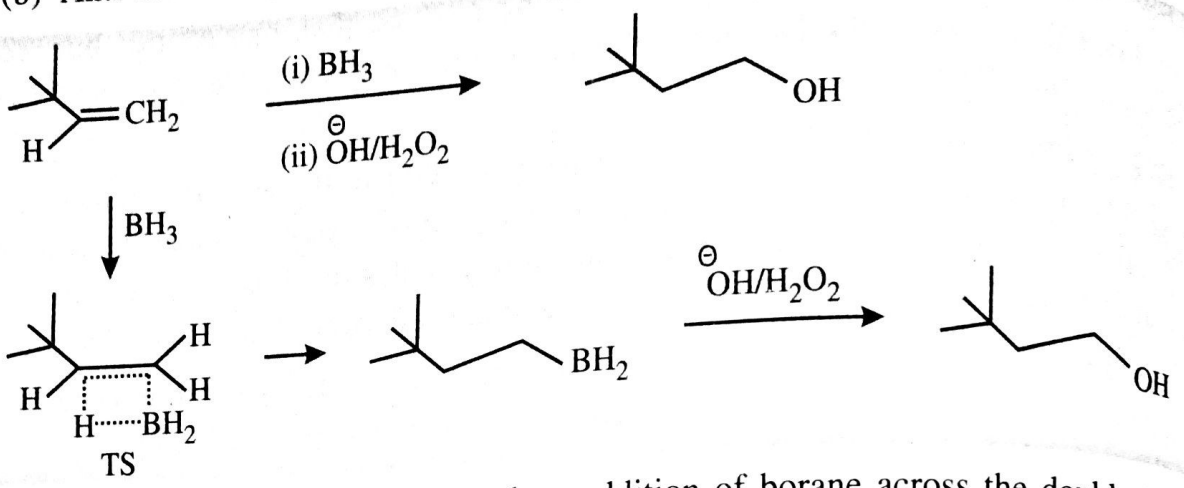


acet (oxymercuration)

This reaction is creditful in the sense it does not give descrete carbonium ion (as in the case of dil H_2SO_4 treatment) and hence no rearrangement occurs. Solvent nucleophile H_2O attacks preferentially to the more electrophilic carbon adjacent to the tertiary butyl group.

*For details see author's "Organic Synthesis" vol. 1

(b) Anti Markownikov hydration via hydroboration

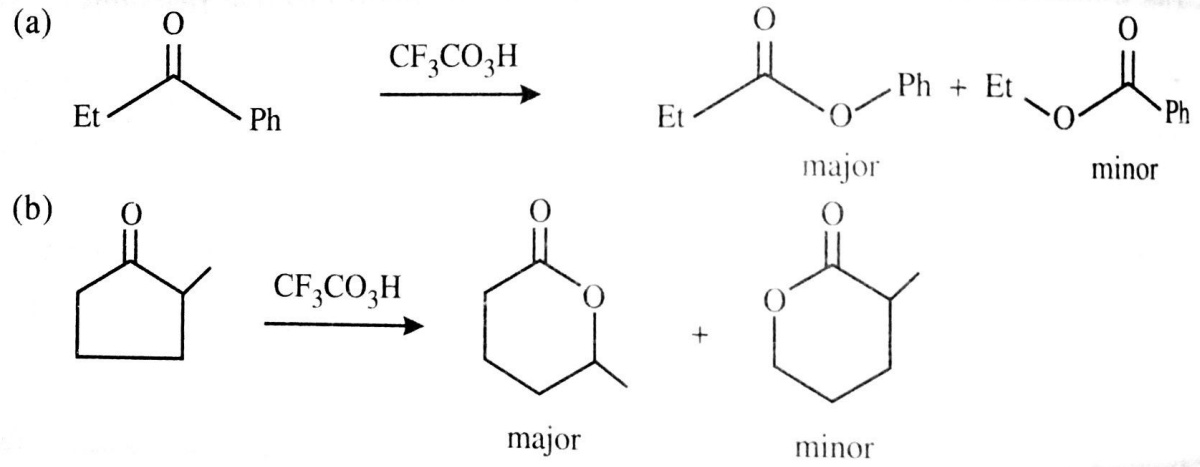


The first step of hydroboration involves addition of borane across the double bond of the substrate, with the formation of carbon-boron bond at the less sterically hindered end. This is then converted to the alcohol with hydrogen peroxide in base medium. The net result of hydroboration and oxidation is the anti Markownikov hydration of the double bond.

In this case regioselectivity is controlled by steric factor (cyclic cis addition of BH_3).

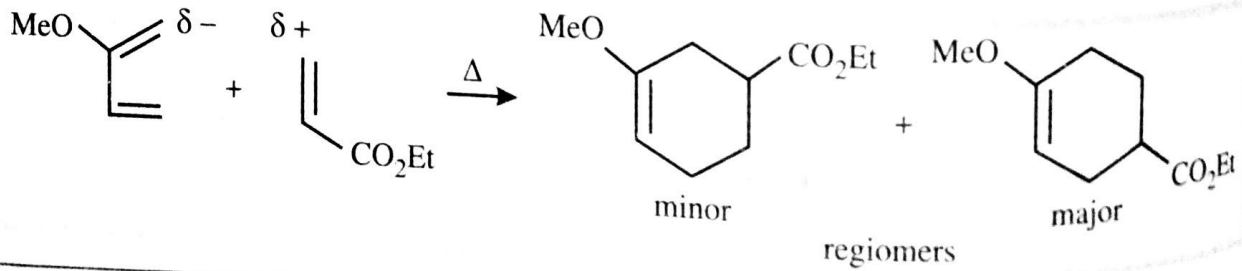
2. Regioselective oxidation of ketones to ester—the Baeyer-Villiger reaction.*

Baeyer-Villiger oxidation which transforms acyclic ketones to ester and cyclic ketones to lactones. The reaction proceeds involving a 1, 2-migration of an alkyl group to the electron deficient oxygen atom.



In this case regioselectivity is controlled by preferential migration of the alkyl groups Migratory aptitude: tertiary alkyl > secondary alkyl > phenyl > primary alkyl.

3. Regioselective Diels-Alder reaction



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