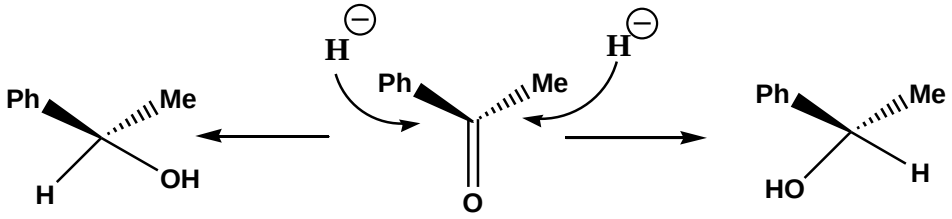
Module 3
Stereoselective reactions: Classification, Terminology and Principles

Classification and terminology of Stereoselective reactions

There are following two broad types of stereoselectivity: Stereoselective and Stereospecific reactions:

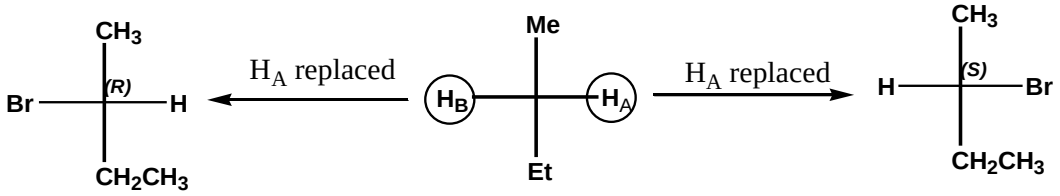
a. Stereoselective reactions: A single starting material gives one or more stereoisomers and one stereoisomer is obtained in greater amount than the other isomers. Such reactions are called **stereoselective** reactions. The starting material has a prostereogenic element present in it.

Now let us understand, what is **prostereogenic molecule** with the following examples.



In the above example, addition of hydride to two different faces gives rise to two different stereoisomers. Such faces, which on reaction give rise to different stereoisomers are called **stereoheterotopic faces**.

Let us study the following example:



In the above example, replacement of H_A and H_B give rise to two enantiomers. Hence, the carbon atom attached to these two protons are called **stereoheterotopic ligands**.

Molecules which have stereoheterotopic ligands and faces are called **prostereogenic**. These molecules can be converted to stereoisomers by appropriate chemical or biochemical reactions.

A reaction will be stereoselective if and only if the substrate contains prostereogeic elements, i.e. prostereogenic ligands and/or faces in it. Molecules which have stereoheterotopic ligands and faces are called prostereogenic. So, presence of enantiotopic and diastereotopic groups/faces are necessary, which are modified to give rise to stereoisomers.

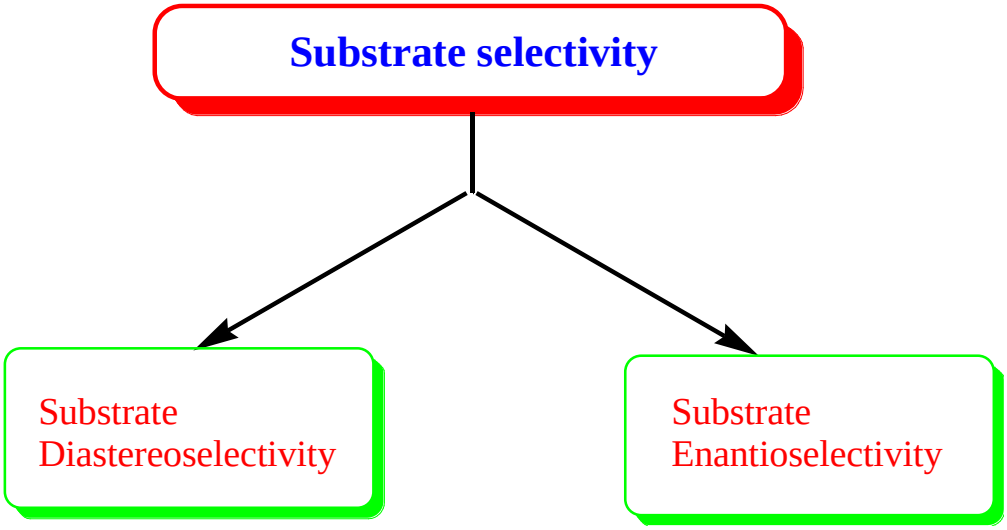
b. Stereospecific reactions: In these reactions, two different stereoisomers, which may be diastereoisomers or enantiomers react under similar conditions at different rates and give rise to different products. These products can be stereoisomers or in some cases constitutional isomers.

Stereospecific reactions are highly stereoselective. It is because, one diastereoisomer gives a single stereoisomeric product exclusively.

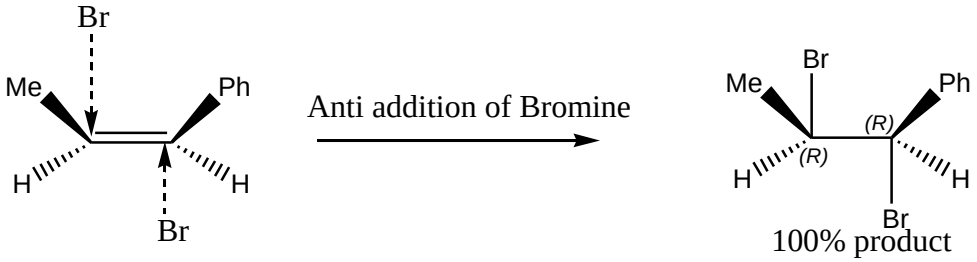
Remember, stereoselectivity is product selectivity and stereospecificity is substrate selectivity.

Substrate selectivity

Substrate stereoselectivity can be divided into two types:
Substrate diastereoselectivity and substrate enantioselectivity.

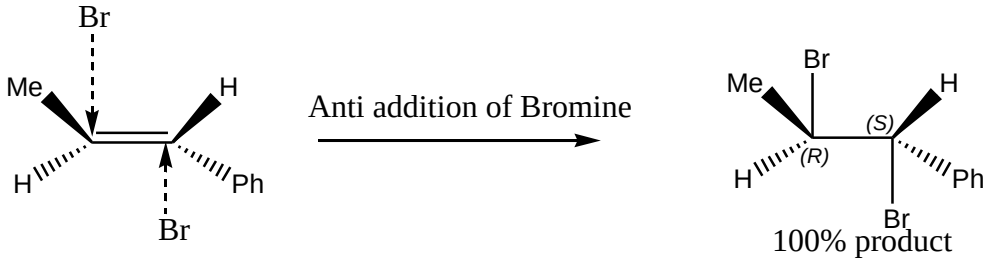


Let us study the bromination of alkenes to understand the stereospecificity. Bromination is an anti addition which proceeds through the formation of bromonium ion. In the example shown below, *Z* isomer gives (*R,R*) product and *E*-isomer gives (*R,S* product). So, the two stereochemically different isomers *Z* and *E* give rise to two different stereoisomers under identical reaction conditions. In this stereospecific reaction, there is substrate diastereoselectivity as the two diastereoisomers are reacting under identical conditions.



Z-isomer

100% product

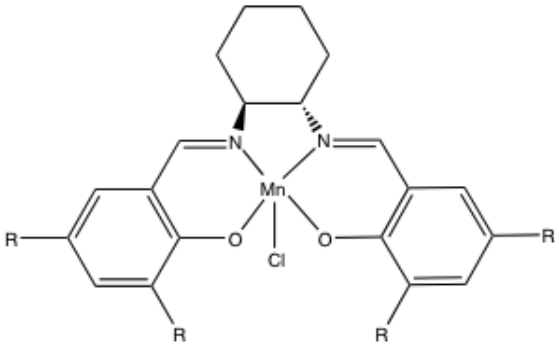


E-isomer

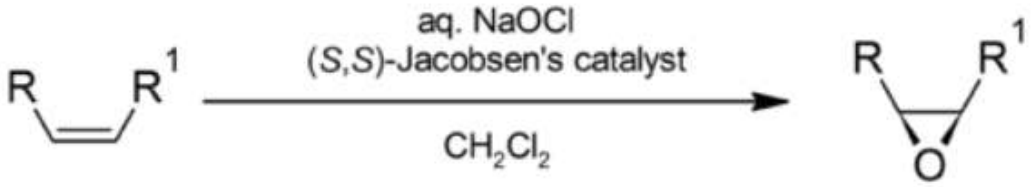
100% product

Generally, we observe substrate diastereoselectivity in the reactions.

Substrate enantioselectivity is observed when ordinary reactions are carried out in presence of chiral reagents. For example, Jacobsen epoxidation is an example of substrate enantioselectivity.



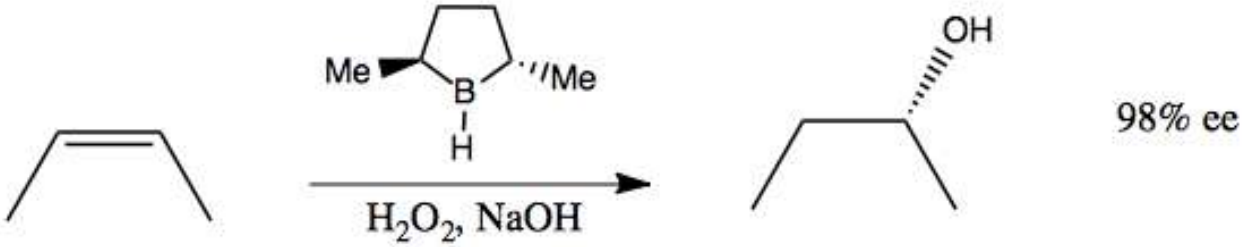
Jacobsen catalyst

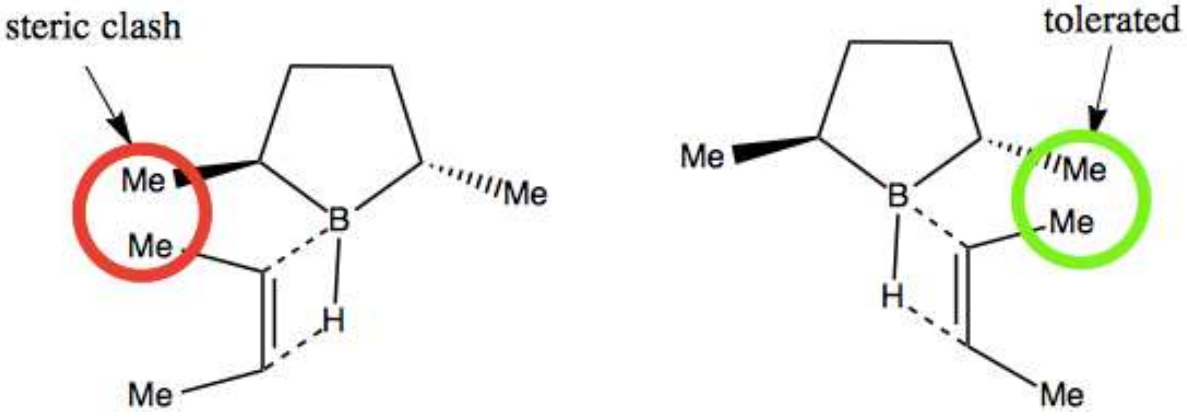


R = aryl, alkenyl, alkynyl, alkyl group

R^1 = bulky alkyl group

Instead of chiral reagent, we can also use chiral substrate to give rise to enantioselectivity as in case of Masasmune hydroboration.

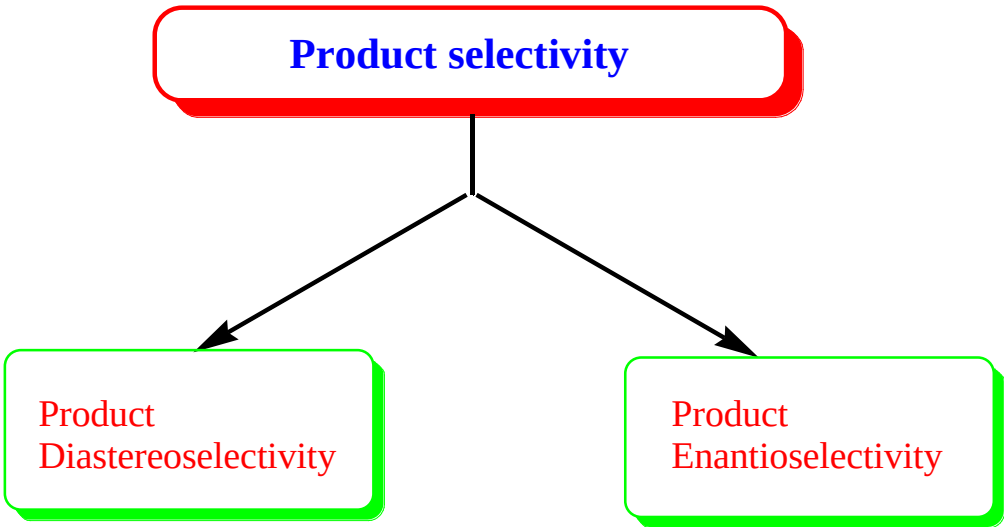




Regioselectivity is also a form of substrate selectivity. We have discussed examples of regioselective reactions in Module 1.

Product selectivity

If one reactant can give two or more products and one of the product is formed as the major product with greater percentage than other products, then it is called product selectivity. When the products are stereoisomers, then the product selectivity is called product stereoselectivity, which can be of following two types:



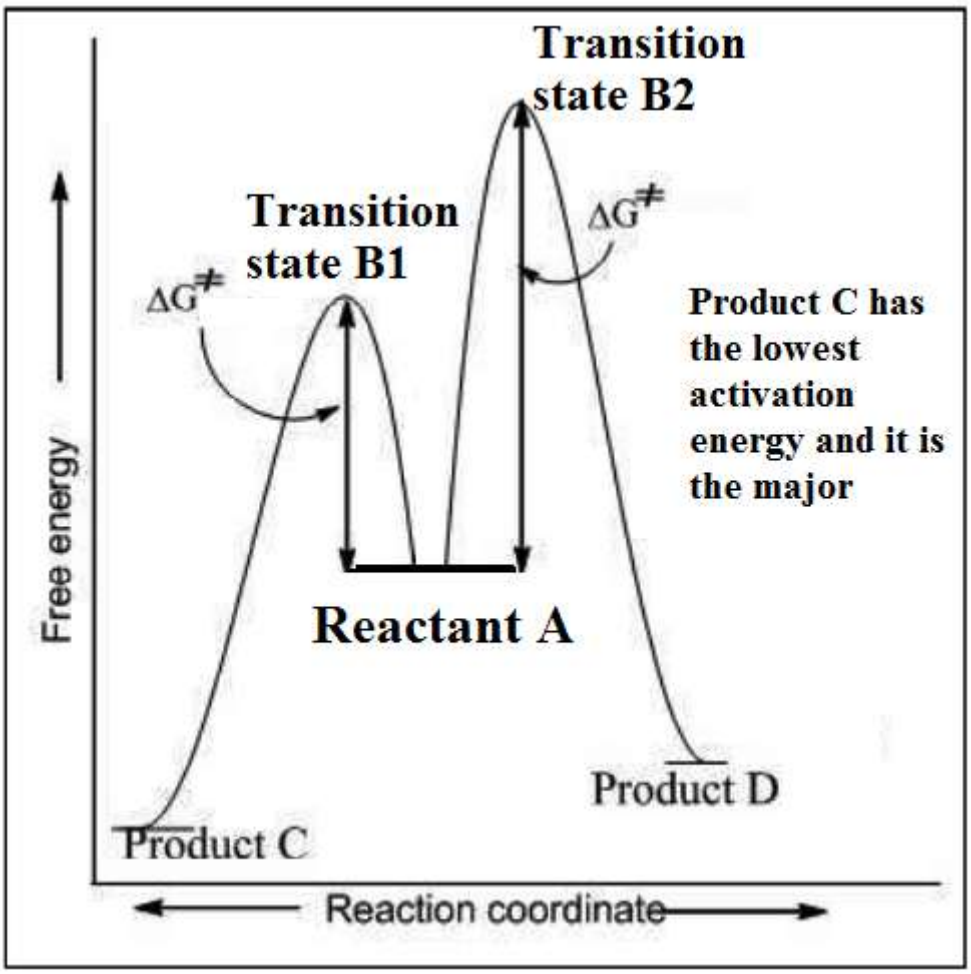
When a reactant gives rise to two diastereoisomeric products, and one of the diastereoisomer is formed in excess compared to the other, then it is product diastereoselectivity. We often use the word "***diastereoselectivity***" instead of product diastereoselectivity. The excess of one diastereoisomer over the other is called ***diastereomeric excess (de)***.

When a reactant gives rise to two enantiomeric products, and one of the enantiomer is formed in excess compared to the other, then it is product enantioselectivity. We often use the word "***enantioselectivity***" instead of product enantioselectivity. The excess of one diastereoisomer over the other is called ***diastereomeric excess (de)***.

Principles of stereoselective reactions

The principle of diastereoselective reactions for kinetically controlled reactions:

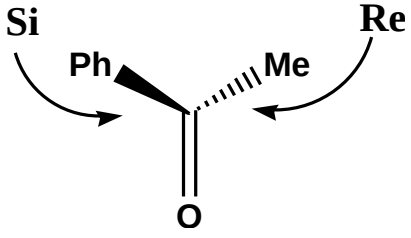
Suppose we have a reactant with a stereoheterotopic face. It is being attacked by a reagent and two diastereomeric transition states are formed. Since, the transition states are diastereomeric, they will have different free energies and hence they will give rise to two diastereomeric products. The greater is the difference between free energies of the reactants, greater will be the diastereoselectivity or de.



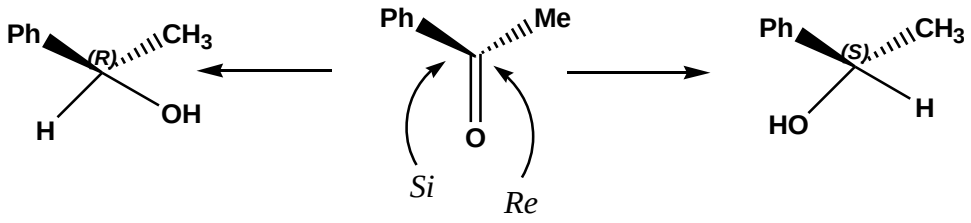
In the above example, C shows the lowest activation energy and hence it is the major diastereoisomer. A difference of 10 kJ/mol at ambient temperature leads to the formation of the preferred isomer in about 98% yield.

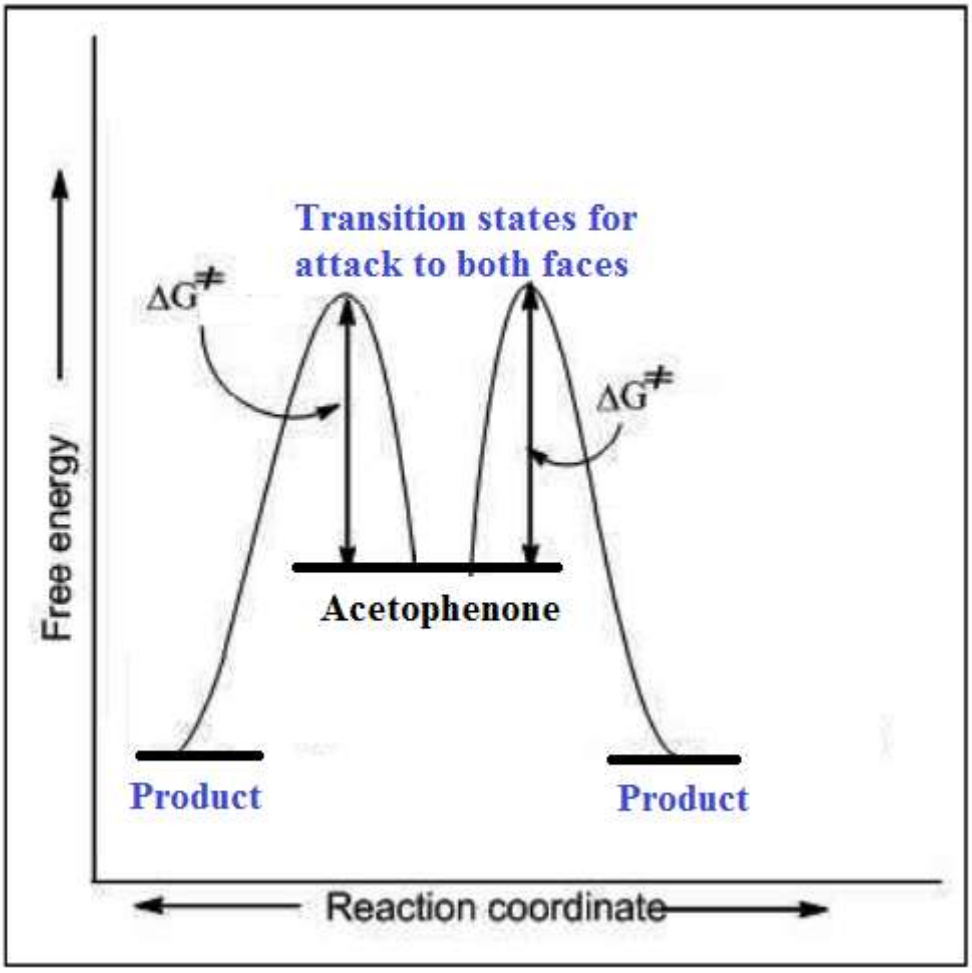
The principle of enantioselective reactions for kinetically controlled reactions:

Let us understand the example of enantioselective reactions with an example. Acetophenone has two stereoheterotopic faces as shown below, these are *Re* and *Si* faces.



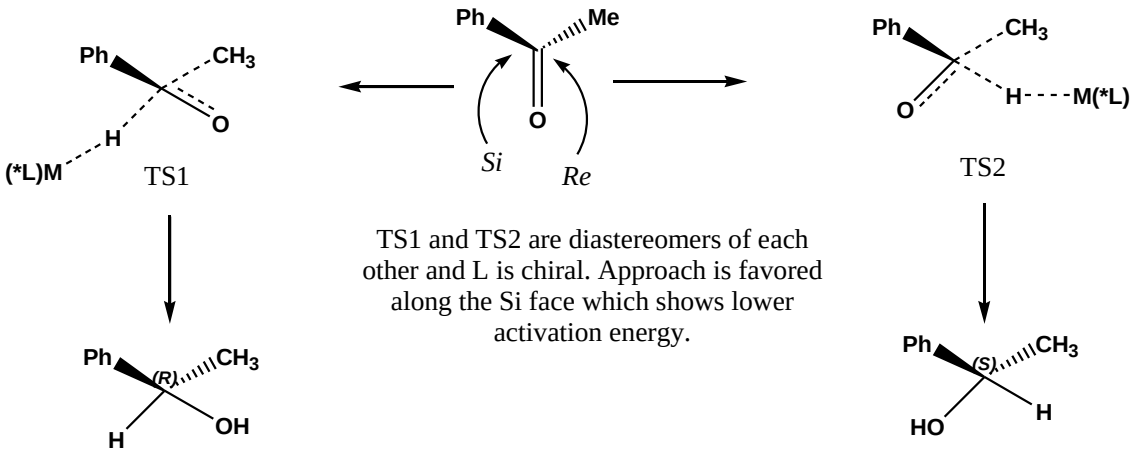
Now, we have a an organometallic hydride, H-M(L) as the reagent. Here, M is the metal and **L is the organic ligand, which is achiral.** This hydride can approach either face of acetophenone. When H-M(L) approaches the Re face of acetophenone, it gives rise to the "S" product and when H-M(L) approaches the Si face of acetophenone, it gives rise to the "R" product. These two products are enantiomers of each other. Enantiomers have the same free energy of the transition states and hence they will be formed in equal amounts giving a racemic mixture. Energy profile of this reaction is shown below:



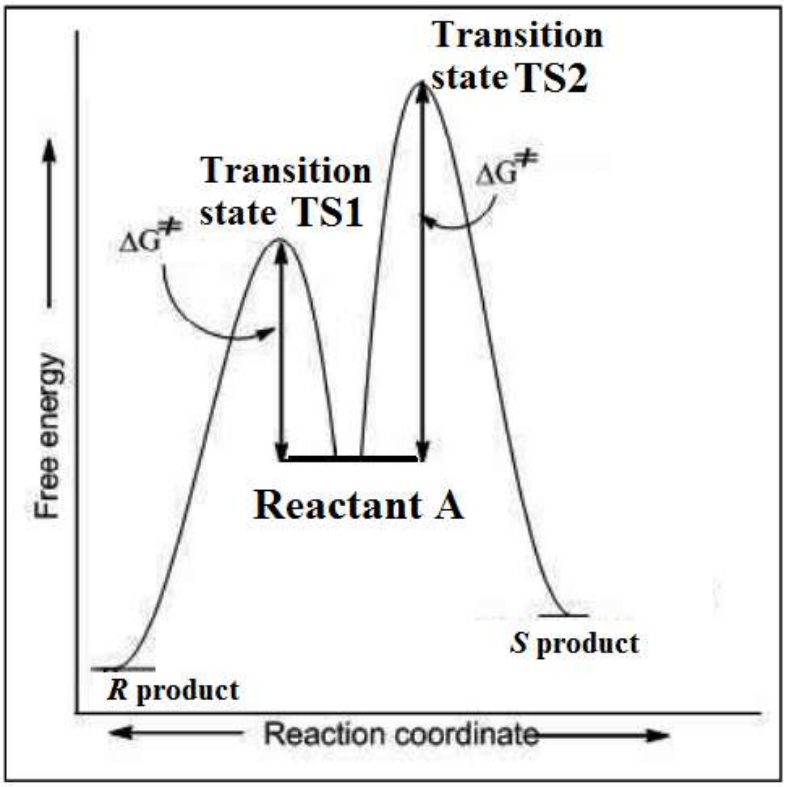


Now, suppose **L is the organic ligand, which is chiral.** This hydride can approach either face of acetophenone. When H-M(L) approaches the Re face of acetophenone, it gives rise to the "S" product and when H-M(L) approaches the Si face of acetophenone, it gives rise to the "R" product. These two transition states are diastereomers of each other. Since, the transition states are diastereomeric, they will have different free energies and hence they will give rise to two diastereomeric products. After removal of the chiral ligand, the products become enantiomeric to each other. So, the stereoselectivity is achieved through the formation of two diastereoselective transition states.

Energy profile of this reaction is shown below:



TS1 and TS2 are diastereomers of each other and L is chiral. Approach is favored along the Si face which shows lower activation energy.


Transition state TS2
Transition state TS1
ΔG≠
ΔG≠
Free energy
Reactant A
S product
R product
Reaction coordinate

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Assignments

1. What is substrate selectivity?
2. What is product selectivity?
3. Draw and explain the energy profile of an enantioselective reaction.
4. Draw and explain the energy profile of a diastereoselective reaction.
5. Regioselectivity is which type of selectivity?
    a) Substrate
    b) Product
    c) Both (a) and (b)
    d) None of the above
6. Differentiate between stereoselective and stereospecific reactions.
7. What do you mean by a stereoheterotopic ligand?
8. Describe hydride addition of acetophenone as a diastereoselective process with energy diagram.
9. What is a prostereogenic centre?
10. What is the principle of stereoselectivity?

References used for preparing E-content and for further reading

1. E.L. Eliel, S.H. Wilen and L.N. Mander, Stereochemistry of Organic Compounds, John Wiley & Sons, New York, 1994.
2. S. Sengupta, Basic Stereochemistry of Organic Molecules, 2009.
3. D. Nasipuri, Stereochemistry of Organic Compounds, 2nd Edn., Wiley Eastern, New Delhi, 1993.
4. S. Sengupta, Basic Stereochemistry of Organic Molecules, 2009.
5. D. Nasipuri, Stereochemistry of Organic Compounds, 2nd Edn., Wiley Eastern, New Delhi, 1993.
6. J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 5th Edn., John Wiley, New York, 1999.
7. S. P. McManus, Organic Reactive Intermediates, Academic Press, New York, 1973.
8. F.A. Carey and R.J. Sundberg, Advanced Organic Chemistry Part A and Part B, 4th Edn., Plenum Press, New York, 2001.
9. T. L. Gilchrist and C. W. Rees, Carbenes, Nitrenes and Arynes, Nelson, New York, 1973.
10. T. H. Lowry and K.C. Richardson, Mechanism and Theory in Organic Chemistry, 3rd Edn., Harper and Row, New York, 1998.
11. D. L. Nelson and M.M. Cox, Lehninger: Principles of Biochemistry, W.H. Freeman Co, London, 2005.
12. T. W. G. Solomons, Organic Chemistry,
13. G. M. Loudon, Organic Chemistry
14. J. Clayden, N. Greeves, S. Warren, Organic Chemistry, 2nd Ed., (2012), Oxford University Press.
15. I. Fleming, Frontier Orbitals and Organic Chemical Reactions, John Wiley, 1980.
16. W. Caruthers, Modern Methods of Organic Synthesis, 3rd Edn., Low Price Edition, Cambridge University Press, 1996.
17. H. O. House, Modern Synthetic Reactions, 2nd Edn., Benjamin, 1971.
18. P. Sykes: A Guide to Mechanism in Organic Chemistry.
19. J. A. Joule and K. Mills: Heterocyclic Chemistry (4^{th} Edn).
20. T. L. Gilchirst, Heterocyclic Chemistry, 3^{rd} Edn, Pearson, 2005.
21. R. N. Morrison, R. N. Boyd, Organic Chemistry, 6th Edn., Dorling Kindersley (India) Pvt. Ltd. (Pearson Education).
22. R. O. C. Norman and J. M. Coxon: Principle of organic synthesis
23. I. L. Finar, Organic Chemistry, Vol I, 6th Edn., Addison Wesley Longmann, London, 1998.
24. I. L. Finar, Organic Chemistry, Vol II, 5th Edn., ELBS, London, 1995.