PG CH S1- 02 (DSC)

TWO YEAR MASTER'S DEGREE COURSE

(CBCS in Accordance with NEP 2020)

SEMESTER - I

ORGANIC CHEMISTRY- I

CHEMISTRY

Hiranya Chandra Bhuyan School of Science and Technology

KRISHNA KANTA HANDIQUI STATE OPEN UNIVERSITY

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Organopalladium in C-C formation (Heck reaction, Stille, Suzuki, Sonogashira and Negishi Coupling).

COURSE INTRODUCTION

This course has been designed for postgraduate learners enrolled in the M.Sc. Chemistry programme. This course provides an advanced understanding of organic reaction mechanisms, selectivity, and modern synthetic methods. It covers energy profiles, reaction intermediates, and the role of rate-determining steps, along with concepts of kinetic and thermodynamic control.

The course begins with the energy profiles of organic reactions, helping learners distinguish between transition states and intermediates, and understand the significance of rate-determining steps in multistep reactions. It then explores the concepts of kinetic and thermodynamic control, along with important principles such as the Hammond postulate and Curtin-Hammett principle, which are essential for predicting reaction outcomes.

Students are introduced to various methods for studying organic reaction mechanisms, including kinetic and non-kinetic approaches, isotope labeling techniques, and cross-over experiments. The course also covers linear free energy relationships (LFER).

A major focus is placed on different types of selectivity in organic reactions-chemoselectivity, regioselectivity, stereoselectivity, and stereospecificity, along with their practical illustrations in substitution, elimination, and addition reactions. Important concepts such as neighbouring group participation and stereoelectronic effects are discussed to explain reactivity patterns.

The course further introduces important strategies in organic synthesis, including protection and deprotection of functional groups, formation of C=C through various named reactions, and polarity inversion (umpolung) using organosulphur compounds. It also emphasizes the role of enolates, enamines, and carbanions in forming new C-C bonds.

Advanced synthetic methods such as hydroboration, Mitsunobu reaction, allylic bromination, and the use of organometallic reagents (including Pd-catalyzed coupling reactions like Heck, Suzuki, and Sonogashira) are covered to highlight modern developments in organic chemistry.

Overall, this course provides students with essential knowledge for reaction design, mechanism analysis, and predicts advanced organic synthesis**.**

UNIT-WISE DESCRIPTION

Unit 1: Energy Profiles of Organic Reactions
This unit explains the concept of energy changes during reactions, distinguishing between transition states and intermediates. It covers multistep reaction energy profiles, the importance of the rate-determining step, and the effect of catalysts on reaction pathways.

Unit 2: Kinetic vs Thermodynamic Control
This unit focuses on the difference between kinetically and thermodynamically controlled reactions. It introduces key concepts such as the Hammond postulate and Curtin–Hammett principle to explain product distribution.

Unit 3: Methods of Studying Reaction Mechanism
Unit 3 discusses various techniques to study reaction mechanisms, including kinetic and non-kinetic methods. It emphasizes isotope labeling, kinetic isotope effects, and crossover experiments for mechanistic understanding.

Unit 4: Linear Free Energy Relationships (LFER)
This unit deals with the relationship between structure and reactivity using Hammett and Taft equations. It also explains the influence of conformation, stereoelectronic effects, and neighbouring group participation on reaction rates.

Unit 5: Chemoselectivity, regioselectivity, stereoselectivity and stereospecificity
This unit introduces and defines chemoselectivity, regioselectivity, stereoselectivity, and stereospecificity in organic reactions.

Unit 6: Examples of Selectivity in Organic Reaction
This unit provides practical examples of different types of selectivity in substitution, elimination, and addition reactions.

Unit 7: Neighbouring Group Effects
This unit explains the concept of neighbouring group participation and its role in stabilizing intermediates and influencing reaction pathways.

Unit 8: Protection and Deprotection in Organic Synthesis
Unit 8 focuses on strategies for protecting and deprotecting functional groups such as aldehydes, ketones, alcohols, and amines during multi-step synthesis.

Unit 9: Formation of C=C Bonds
This unit covers various methods for forming carbon–carbon double bonds, including elimination reactions and named reactions like Wittig, McMurry, Peterson, Julia, and Tebbe olefination.

Unit 10: Use of Organosulphur Compounds for reversal of polarity
This unit introduces the concept of polarity reversal using organosulphur compounds, particularly the Corey-Seebach umpolung strategy.

Unit 11: Application of Enolates and Enamines

This unit explains the formation and reactions of enolates and enamines, including their role in aldol, Michael, alkylation, and acylation reactions, along with important carbanion reactions.

Unit 12: Hydroboration and Trialkylsilyl Halides in Organic Synthesis.

This unit discusses hydroboration reactions and the use of trialkylsilyl halides in organic synthesis.

Unit 13: Mitsunobu reaction, Wohl-Ziegler Allylic Bromination.

This unit covers the mechanisms and synthetic applications of the Mitsunobu reaction and Wohl-Ziegler allylic bromination.

Unit 14: Use of Organometallic Reagents in formation of carbon-carbon bonds

This unit introduces organometallic chemistry, focusing on palladium-catalyzed cross-coupling reactions such as Heck, Stille, Suzuki, Sonogashira, and Negishi reactions.

UNIT 1: ENERGY PROFILES OF ORGANIC REACTIONS

UNIT STRUCTURE

1.1 Learning Objectives
1.2 Introduction
1.3 Transition state vs. reaction intermediate
1.4 Energy profile of multistep reactions
1.5 Rate limiting step
1.6 Catalysed and uncatalysed reactions
1.7 Let Us Sum Up
1.8 Answers to Check Your Progress
1.9 Further Reading
1.10 Model Questions

1.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- Learn the concept of reaction coordinate diagram/energy profile diagram and interpret such diagrams.
- Differentiate reaction intermediates (I) and transition states (TS).
- Understand the concept of rate determining step (rds) and choose rds of a multistep mechanism from energy profile diagram.
- Understand why rate of catalysed reactions are significantly higher compared to that of the uncatalysed one.

1.2 INTRODUCTION

Most chemical reactions occur as a result of collision among the reactant molecules that results in bond cleavage and new bond formation due to redistribution of electrons. The reactants possess two types of energies, viz. (i) Potential energy (PE) in the form of bond vibrations, non-covalent interactions among the reactant molecules as well as solvents (in case of solution phase reactions), strain energy, etc., and (ii) Kinteic Energy (KE) arising out of translational motion of the molecules.

At the time of collision during a reaction, the movement of the reactant molecules decreases. As a result, KE is decreased and PE is increased due to conformational strain and deformation of the bonds in the molecules. If the increase of PE is high enough, bond becomes so strained that it results in dissociation to form highly energetic species that release energy to form the product(s).

Thus, the reactants collide with each other, go to a high energy state and then make a downhill journey to form the product. There would be huge number of molecules in a reaction mixture even it is done at very low concentration (if a reaction is done at µmol concentration, the number molecules will be in the range of 10^{17} as there are 6.0323×10^{23} molecules in one mol). All the reactant molecules may not follow the exact pathway

regarding its energetic changes during transformation products. The weighted average of all such pathways or the minimum energy pathway taken by the reactants to transform into the products is termed as the reaction coordinate.

A two dimensional plot of energy (PE) vs. reaction coordinate is called the energy profile diagram or reaction coordinate diagram. For a single step reaction, the energy profile diagram is shown in Fig. 1.

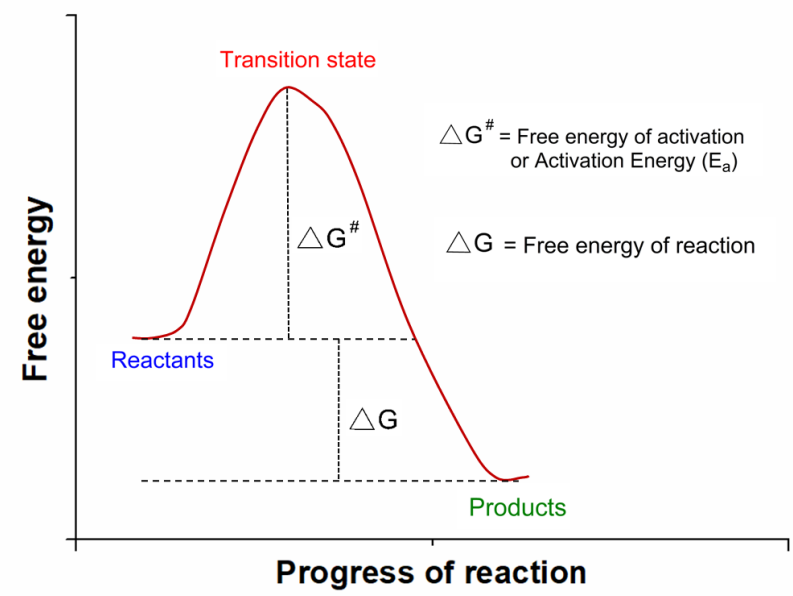


Figure 1: Energy profile diagram (or reaction coordinate diagram) for a one step exothermic reaction.

1.3 TRANSITION STATE VS. REACTION INTERMEDIATE

Imagine, you have to cross a mountain range of 10 km to visit one valley (plain area) from another. You will encounter many mountain peaks of unequal heights during the journey. You can choose many pathways to reach your destination. Some will involve crossing through high peaks and some through low peaks. The molecules energy and conformation also changes like this pathway - going from a low energy valley to a higher energy state, then to low energy valleys and then going uphill again and going down, ultimately reaching very low lying valley (or the product). The pathway of crossing the mountain in which you can pass through the lowest possible peak will be the minimum energy pathway, as you will spend least energy for this journey compared to the other possible pathways (Fig. 2). Likewise, the reactant molecules may go to the products through many pathways. The pathway where the molecules need to cross lowest energy peak is our minimum energy pathway.

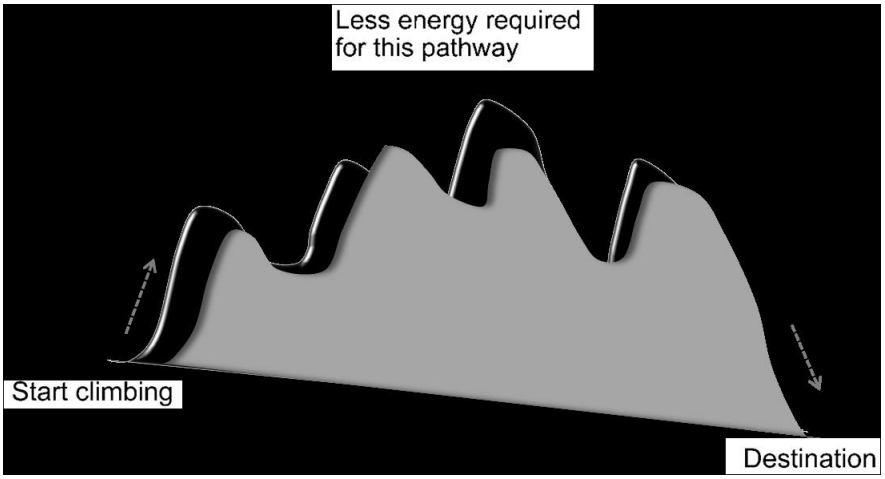


Figure 2: Comparison of hill crossing pathway showing the minimum energy pathway.

The structure of the chemical species at the highest peak (energy) (Fig. 1) on the lowest energy pathway during conversion of reactant to product is called transition state (TS). It is a hypothetical state. It can be visualized using theoretical calculations, but cannot be isolated or detected through experiment. As the molecules come close and collide, their PE increases reaching maximum at some point after collision. Bond starts to break and form as a result of collision. We can imagine infinite number of such species with partial bond formation or cleavage during this time period. Out of these species, the one possessing the highest energy PE is the transition state. The TS represents the most strained or unstable structure involved in the reaction that proceeds through the lowest energy pathway.

Typical bond vibration frequencies are in the range of 10^{13} to 10^{14} Hz. This means that a bond oscillates approximately about 10^{13} times in one second. Thus, one oscillation takes 10^{-13} to 10^{-14} s. If a species from after collision of reactants exists for longer than this time period, we can assume that bond vibration is taking place and a real species is formed. Any such chemical species can be considered as reaction intermediate. TS will have lifetime smaller than bond vibration time. Intermediates can be isolated, trapped inside a matrix, trapped by chemical reaction or may be identified through spectroscopic evidences without isolation. Thus, any species with lifetime larger 10^{-13} to 10^{-14} s can be termed as intermediates provided that there is some proof for its existence.

The amount of energy required to attain the TS is called the activation energy (E_a) [or free energy of activation ($\Delta G^{\#}$)]. The activation energy is the PE, which is the difference between Gibbs free energy of TS and Gibbs free energy of reactants. One must note that when we talk about free energy of reactants or products, it should be actually visualized as potential energy in the form of the Gibbs free energy at that particular position on the reaction coordinate diagram consisting of the entire solution. That means, we should consider all reactants, intermediates, products, and solvents at the particular point. When we consider free energy at reactant's position, there will be contributions from mostly reactants and solvents with small/negligible amount of products/intermediates.

A relatively stable structure is given by a low energy depression (well) in the curve, reactive intermediates are in high energy shallow wells (Fig. 3), and transition states are peaks.

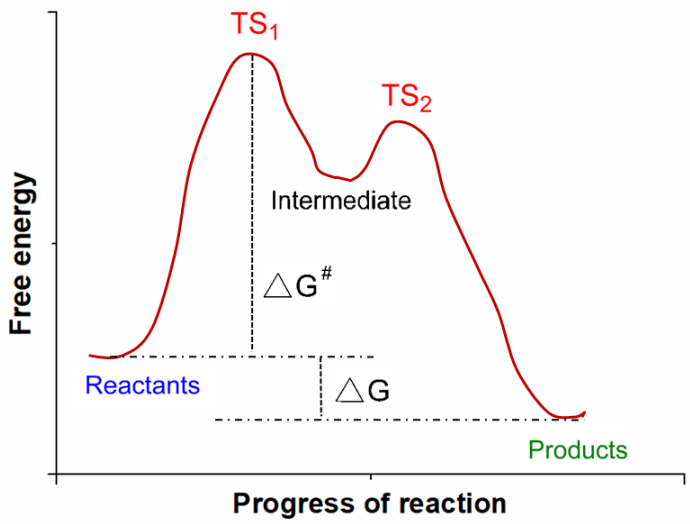


Figure 3: Energy profile diagram for a two-step reaction.

Transition state should be drawn by showing the bonds formed and cleaved as dotted bond (means a partial bond). In contrast, all bonds are shown as normal bond in an intermediate. The transition state of a reaction is also called activated complex. The activated complex is a molecular entity that has a lifetime no longer than a vibration, meaning that there is a particular movement of atoms that tilts the activated complex in the direction of product or reactant. Like all structures along the reaction coordinate, except for the end points, the activated complex is a species that exhibits some structural characteristics of both the reactant and the product. What makes the transition state unique is that it represents a point along the reaction coordinate that reflects the most strained or unstable structure involved in the reaction through the lowest energy pathway.

1.4 ENERGY PROFILE OF MULTISTEP REACTION

In a one-step reaction, the reactants are converted into products directly without forming any intermediate. We get one TS for such reaction. In a two-step reaction, the reactants first get converted to intermediate and then to products (Fig. 3). Here, we will encounter one reaction intermediate and two TS for the two steps. A three step reaction will have two intermediates and three TS and so on. Thus, in case of multistep reaction, the number TS will be equal to the number of steps, while intermediates will be one less than total number of steps.

Intermediates are highly unstable species compared to reactants. Thus, their free energy will be higher compared to reactant. Now, if we consider a two-step reaction, the first step yielding an unstable intermediate. This means this step will be an endergonic one with high E_a (Fig. 3). If you consider conversion of the intermediate to reactant, that is reverse of step one, this will be kinetically and thermodynamically more favourable as

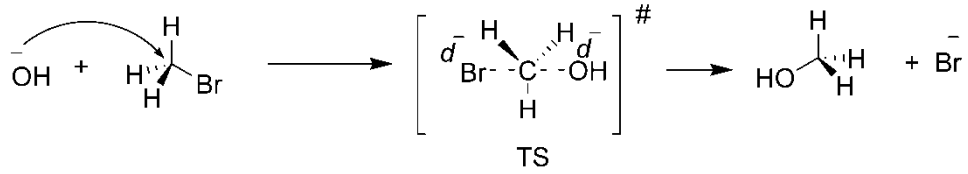
the activation energy is less and the products are more stable. Thus, in the mechanism, we may write this step as a reversible one favouring the starting compound rather than the intermediate. The second step is the conversion of the intermediate to the products. If the products are more stable compared to the reactants, this step will be an exothermic reaction with low E_a.

Let us consider a S_N2 reaction of methyl bromide (a 1° alkyl halide) with sodium hydroxide (a strong nucleophile). The reaction is a one step process with hydroxide ion attacks from the backside of the leaving group (bromide ion).

Overall reaction

$$CH_3Br + NaOH \longrightarrow CH_3OH + NaBr$$

Mechanism



TS

There will be only one TS and no intermediate. C-O bond is formed and C-Br bond is broken as the reactants are converted into products. So, these two bonds will be partial bonds in the TS. The energy profile diagram for this reaction can be drawn as shown in Fig 4.

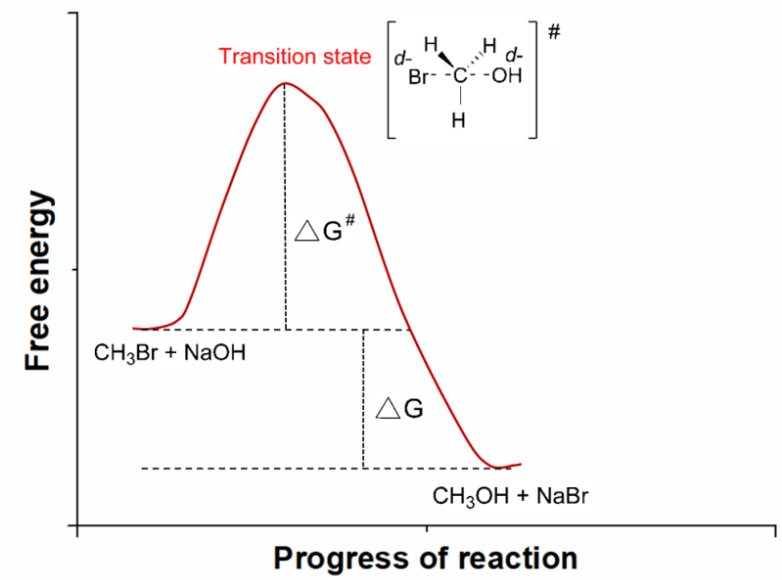
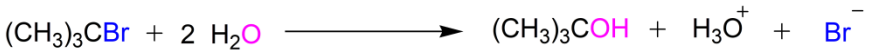


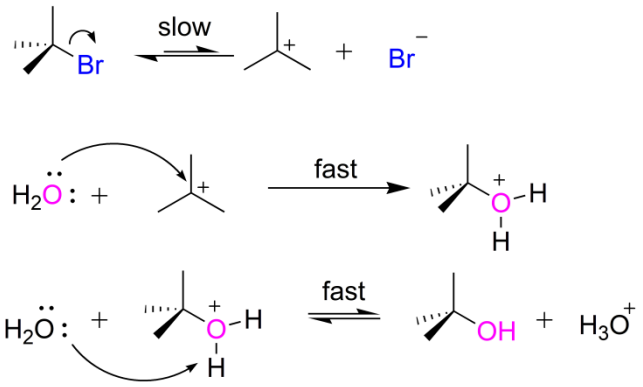
Figure 4: Energy profile diagram for a S_N2 (one step) reaction showing the transition state.

Let us now consider a S_N1 reaction between *tert*-butylbromide (a 3° alkyl halide) and H_2O (a weak nucleophile). The mechanism involves formation of a carbocation as the leaving group departs in the first step. Then the nucleophile attacks at the carbocation intermediate to give a protonated alcohol. The last step involves proton exchange between the protonated alcohol and the solvent molecules.

Overall reaction



Mechanism



The step one involves formation of highly reactive intermediate from a less reactive starting compound. In the next step, a stable protonated alcohol is formed from an unstable carbocation intermediate. The third step is proton exchange with comparable stability of reactants and products. Thus, step one is expected to have high activation energy compared to the other steps. We will have two intermediates, one highly unstable (carbocation) and the other is stable (protonated alcohol). There will be three TS for the mechanism drawn above. The energy profile diagram is shown in Fig. 5.

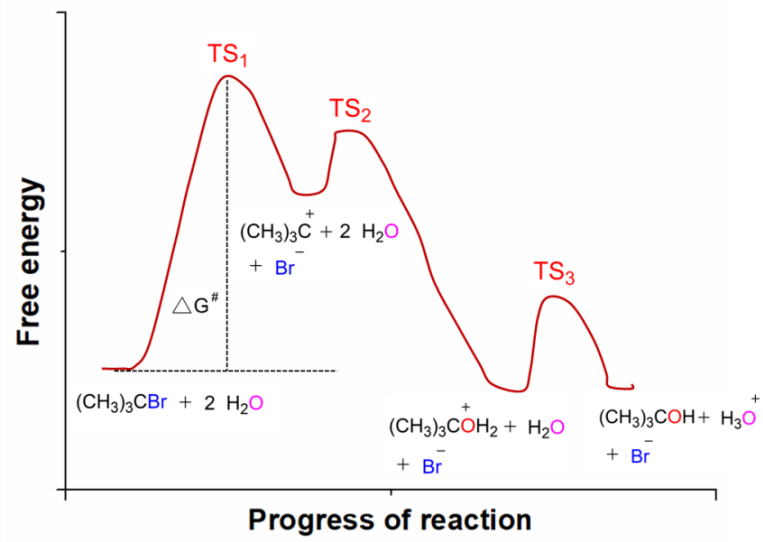


Figure 5: Energy profile diagram for a S_N1 (three step) reaction.

1.5 RATE LIMITING STEP

Rate limiting step is the slowest step in a multistep reaction. In case of one step reaction there is no ambiguity. When there is only one step to a reaction, it is obviously the rate determining step. In multistep reaction, generally one among the multiple steps tends to be significantly slow compared to the others. The slowest step of the reaction mechanism, whose rate determines the observed rate of product formation, is called the

rate determining step (rds) or rate limiting step (rls). Both the names carry the same meaning in most of the reaction mechanisms. This step is commonly the step that passes through the highest energy transition state.

Energy profiles of different two step reactions are given in the Fig. 6 to show the rate determining step. In 6a and 6d, the first steps are rate determining where as the second steps are rate determining in 6b and 6c.

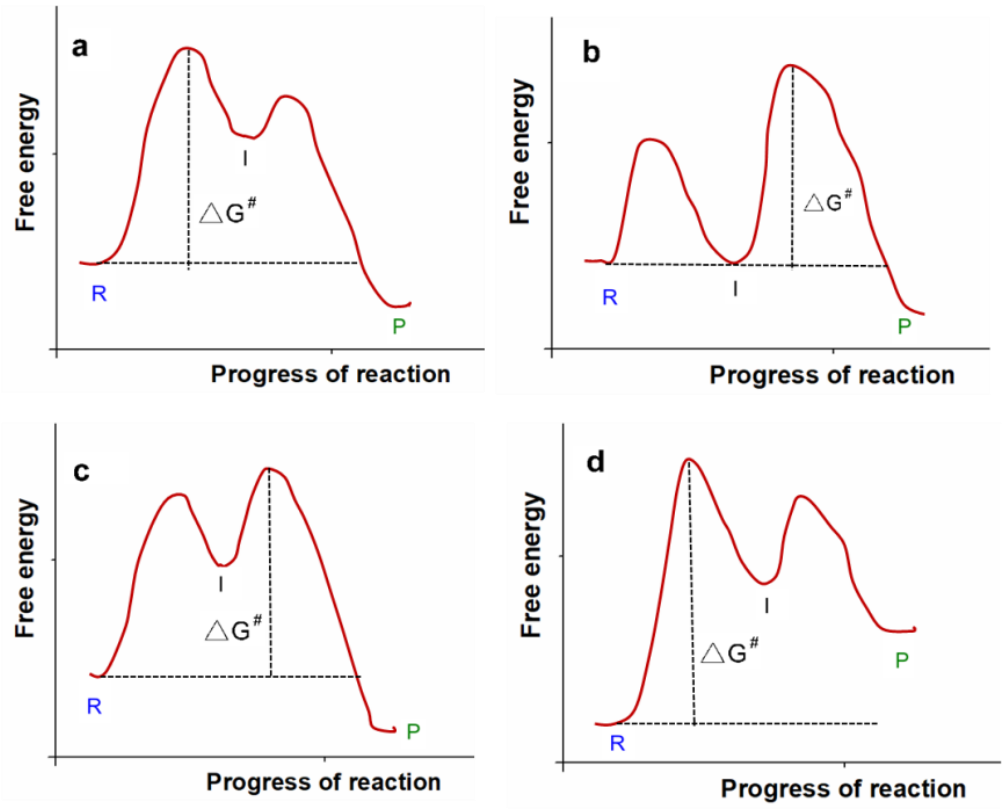


Figure 6: Energy profile diagrams for two step reactions showing the rate determining steps.

Arrhenius equation can be used to calculate the rate of a chemical reaction E_a (refer to unit 2). More the activation energy less will be the rate for the step. This means the step involved with highest activation energy will be the slowest step in the mechanism.

1.6 CATALYSED AND UNCATALYSED REACTIONS

A catalyst increases a rate of reaction. The catalyst offers a low energy pathway for the reactant to cross over to the product. The activation energy for a catalysed reaction is much lower compared to the uncatalysed one.

Let us understand the rate enhancement by taking enzyme catalysed reaction as a representative example. Enzymes are classical examples of catalyst that can increase rate to many fold compared to uncatalysed one. For example, carboxypeptidase A enhances peptide hydrolysis rate by a factor of 10^{11}. A common mechanism involved in enzyme catalysed reaction is given below. The enzyme (E) binds with the substrate (S) to form an enzyme substrate complex (ES), which is then converted to enzyme product

complex (EP) and in the final step the product (P) is released from EP regenerating the enzyme.

$$E + S \rightleftharpoons ES \rightleftharpoons EP \rightleftharpoons E + P$$

A common energy profile diagram encountered for this mechanism is shown in Fig.7. The $\Delta G^{\#}$ for the enzyme catalysed reaction is much lower compared to that of the uncatalysed one.

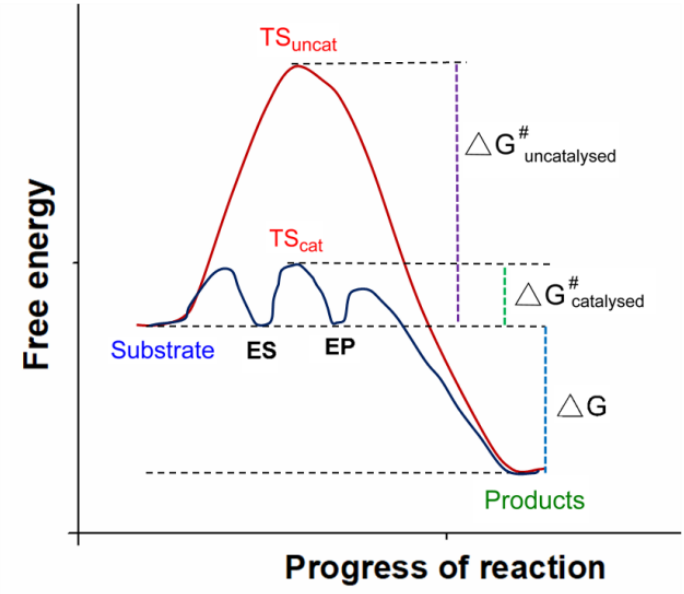


Figure 7: Comparison of energy profile diagrams among an uncatalysed reaction and an enzyme catalysed reaction.

Let us understand how an enzyme lowers the activation energy. The enzyme interacts and binds with the substrate through many non-covalent interactions (H-bonding, Van der Waals force, electrostatic interaction, etc.). The energy derived (released) from such interaction is called the binding energy, ΔG_B. These weak interactions are even stronger in the TS compared to that of the substrate, and results in lowering of energy of the TS compared to the uncatalysed one.

For a first-order reaction, a reaction accelerates by a factor 10, when activation energy is lowered by approximately 5.7 kJ/mol (under conditions commonly found in cells). One single weak interaction releases about 4 to 30 kJ/mol. When a substrate binds to enzyme, many weak interactions may occur between enzyme and substrate/TS. Such interactions can lower activation energies by the 60 to 100 kJ/mol. So, the enzyme is able to accelerate the reaction many fold.

However, there are some barriers for lowering the activation energy. These are:
(i) When enzyme binds with the substrate, motion of the two molecules (substrate and the enzyme) decreases. This results in decrease in entropy.
(ii) Enzyme and substrates are solvated through hydrogen-bonded water. This salvation layer should be broken for interaction of enzyme with water.
(iii) In many enzyme catalysed reactions, distortion of substrates must occur, which requires energy.
(iv) Holding of the catalytic functional groups of the active site in proper alignment.

All these barriers are overpowered by binding energy. In other catalysed reactions beside enzyme catalysis, similar lowering of the activation energy must occur, which increases the rate of the reaction significantly.

W CHECK YOUR PROGRESS

Q1. What is an energy profile diagram?
Q2. What is a transition state?
Q3. What is a reaction intermediate?
Q4. Define rate determining step.
Q5. What is activation energy?
Q6. How does an enzyme decrease rate of a reaction?
Q7. How many transition state and reaction intermediates will be encountered in a four step reaction?
Q8. How much energy is released in a noncovalent interaction?
Q9. Is it possible to determine the structure of TS and reaction intermediate?
Q10. In a reaction profile diagram, Y axis is free energy. Is this energy kinetic energy or potential energy?

2 1.7 LET US SUM UP

- The minimum energy pathway is that is taken by reactants to transform into the products is termed as the reaction coordinate. A two dimensional plot of energy (PE) vs. reaction coordinate is called the energy profile diagram or reaction coordinate diagram.
- The state or species with highest point (energy) on the lowest energy pathway during conversion of reactant to product is called as transition state. Any such chemical species can be considered as reaction intermediate if its life time exceeds that of typical bond vibration which is in the range of 10^{-13} to 10^{-14} s.
- The step of the reaction mechanism, whose rate determines the observed rate of product formation, is called the rate determining step (rds). This step is commonly the step that passes through the highest energy transition state.
- A catalyst offers a low energy pathway for the reactant to cross over to the product. The activation energy for a catalysed reaction is much lower compared to the uncatalysed one thereby increases the rate of the reaction manifold.

K 1.8 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: The minimum energy pathway is that is taken by reactants to transform into the products is termed as the reaction coordinate. A two dimensional plot of energy (potential energy) vs. reaction coordinate is called the energy profile diagram or reaction coordinate diagram.

Answer to Q2: Transition state is the highest energy state on the lowest energy pathway during conversion of reactant to product. It is a hypothetical state.

Answer to Q3: In a multistep reaction, chemical species formed in one step is consumed in another step. After completion of the reaction, such species are not found in the reaction mixture. Any such chemical species can be considered as reaction intermediate if its life time exceeds that of typical bond vibration, which is in the range of 10^{-13} to 10^{-14} s.

Answer to Q4: The slowest step of a reaction mechanism, whose rate determines the observed rate of product formation, is called the rate determining step (rds). This step is commonly the step that passes through the highest energy transition state.

Answer to Q5: Activation energy is the difference between the free energy of the transition state and the free energy of the reactants. Reactant molecules needed to pass through this energy barrier for going into products.

Answer to Q6: An enzyme interacts with reactants and transition state through many non-covalent interactions. This releases binding energy, which in turn provides a low energy pathway for the reaction.

Answer to Q7: The number of TS is equal to the number of steps. Number of intermediates will be one less than the number of steps. Thus, the answer is 4 and 3.

Answer to Q8: One single noncovalent interaction releases about 4 to 30 kJ/mol, depending on the type of interaction.

Answer to Q9: TS is a hypothetical species and hence it cannot be detected physically. We cannot determine its structure experimentally. However, we may do theoretical calculation to predict its structure. In contrast, the reaction intermediates can be isolated/detected/trapped to determine their structure experimentally.

Answer to Q10: Potential energy. When the reactant molecules collide with each other during a reaction, their kinetic energy decrease and potential energy increase.

O 1.9 FURTHER READING

- Eric V. Anslyn, and Dennis A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books.
- Michael B. Smith and Jerry March, *March's Advanced Organic Chemistry*, Wiley-Interscience, A John Wiley & Sons, Inc., Publication.
- Jonathan Clayden Nick Greeves and Stuart Warren, *Organic Chemistry*, Oxford University Press.
- Paula Yurkanis Bruice, Organic Chemistry, Pearson.
- Francis A. Carey and Richard J. Sundberg, *Advanced Organic Chemistry, Part-A,* Springer Science.

M 1.10 MODEL QUESTIONS

Q1. Draw the transition state for an S_N2 reaction between ethyl bromide and sodium cyanide.

Q2. Write the mechanism for nitration of benzene using concentrated nitric acid and concentrated sulphuric acid.
Q3. Draw the energy profile diagram showing the intermediate and transition states for the reaction mentioned in Q2.
Q4. Draw an approximate energy profile diagram for a three step reaction, where second step is the rate determining.
Q5. Write the mechanism for reaction of 1-fluoro-2,4-dinitrobenzene with sodium methoxide. Draw the transition states for this mechanism.
Q6. Draw the energy profile diagram showing the intermediate and transition states for the reaction mentioned in Q5.
Q7. Which among uncatalysed and catalysed reactions, will lower higher activation energy and why?
Q8. What is binding energy for an enzyme? How does it help to lower the rate of the reaction?
Q9. Draw the energy profile diagram for an enzyme catalysed reaction where the steps are – (i) Enzyme and substrate associate to form enzyme-substrate complex ES (ii) the ES directly converted to product and the free enzyme.
Q10. How a rate of a reaction is related to activation energy?

UNIT 2: KINETIC VS. THERMODYNAMIC CONTROL OF ORGANIC REACTIONS

UNIT STRUCTURE

2.1 Learning Objectives
2.2 Introduction
2.3 Kinetically and thermodynamically controlled Organic reactions
2.4 Hammond postulate
2.5 Curtin-Hammett Principle
2.6 Let Us Sum Up
2.7 Answers to Check Your Progress
2.8 Further Reading
2.9 Model Questions

2.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- Learn the concept of kinetic control and thermodynamic control of organic reactions.
- Learn the effect of rate of a reaction (k) and reaction equilibrium (K) on product formation
- Understand Hammonds postulate and apply it to predict the selectivity of reactions.
- Understand Curtin-Hammett principle and apply it to predict product composition and selectivity in organic reactions.

2.2 INTRODUCTION

Kinetic word is derived from the Greek word "*kinein"* which means 'to move'. In a chemical reaction this move is the speed at which reactants move into products. Thus, the kinetics of a reaction is associated with rate of the conversion of reactants to products. On the other hand, thermodynamics is related to stability of the products. When two or more products are formed in a reaction, their ratios are dependent on the rates of the reactions and stability of the products. If the reaction rate controls the formation of the major product, it is called a kinetically controlled reaction. If stability of the product controls the formation of the major product, the reaction is termed as thermodynamically controlled reaction.

Let us recall some of the fundamental equations which you have read in UG courses.

$$mA + nB \rightleftharpoons qC + sD$$

$$K_{eq} = \frac{[Products]}{[Reactants]} = \frac{[C]^q [D]^s}{[A]^m [B]^n}$$

K_{eq} = Equilibrium constant

The relative concentration of products and reactants at equilibrium depend on their relative stabilities. The product with more stability will be present at greater concentration at equilibrium.

Concentration of products > Concentration of reactants, if $K_{eq} > 1$

Concentration of reactants > Concentration of products, if $K_{eq} < 1$

We know another relation $\Delta G = -RT\ln K_{eq}$

ΔG = Free energy of products – Free energy of reactants = $\Delta H - T\Delta S$

ΔH = heat change during the reaction = energy of bond broken – energy of bond formed + any changes in resonance, strain or salvation energies.

ΔS = entropy change during the reaction = freedom of motion of products – freedom of motion of reactants

If $K_{eq} > 1$, ΔG = -ve, the reaction is spontaneous (favourable in forward direction)

If $K_{eq} < 1$, ΔG =+ve, the reaction is non-spontaneous (favourable in backward direction)

When, (i) ΔG = -ve, the reaction is termed as exergonic (releases energy)

(ii) ΔG = +ve, the reaction is termed as endergonic (absorbs energy)

(iii) ΔH = -ve, the reaction is termed as exothermic (releases heat)

(iv) ΔH = +ve, the reaction is termed as endothermic (absorbs heat)

The relation $\Delta G = \Delta H - T\Delta S$, when applied for transition state can be written as

$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$

$\Delta G^{\ddagger}$ = free energy of activation

= free energy of transition state – free energy of reactants

$\Delta H^{\ddagger}$ = enthalpy of activation = difference in bond energies including strain, resonance, solvation energies between TS and reactants

$\Delta S^{\ddagger}$ = entropy of activation = entropy of transition state – entropy of reactants

Large $\Delta G^{\ddagger}$ means high energy barrier for the reaction

Small $\Delta G^{\ddagger}$ means less energy barrier for the reaction

Large $\Delta G^{\ddagger}$ implies high energy barrier for the reaction, the rate of the reaction will be low.

However, you should keep in mind that $\Delta G^{\ddagger}$ is not directly related to rate of a reaction.

The E_a (activation energy) is related to the rate of a reaction given by the **Arrhenius equation** $k = Ae^{-(Ea/RT)}$

k = rate constant,

A = pre exponential factor that represents the frequency of collisions between reactant molecules with the proper orientation to react.

R = the universal gas constant = 8.314 $Jmol^{-1}K^{-1}$

T = temperature in Kelvin

Activation energy can be measured experimentally which related to enthalpy of activation
$E_a = \Delta H^{\ddagger} + RT$
E_a has only enthalpy component, but $\Delta G^{\ddagger}$ has entropy component also. However, their values are similar when T is low and $\Delta S^{\ddagger}$ is small. So, we can take E_a to be a close substitute for $\Delta G^{\ddagger}$. Therefore, sometimes both the terms activation energy and free energy of activation is used as synonym, but actually these are different. In our SLM also, we have used them interchangeably.

2.3 KINETICALLY AND THERMODYNAMICALLY CONTROLLED ORGANIC REACTIONS

The rate of a chemical reaction is governed by the activation energy. Activation energy is directly linked to the energy of the TS. Thus, in a kinetically controlled reaction, the ratio the products formed is dependent on the relative energies of the transition states leading to these products. The product, for which TS energy is less, will be the major product. The thermodynamic stabilities of the products do not matter here. In case of thermodynamically controlled reaction, the relative energies of the products govern the ratio of the products formed. In this case, the activation energies do not matter. The product which has more stability will be formed in more amounts. In many reactions, the product whose rate of formation is high is also the more stable product. In such cases, the product formation is kinetically controlled and as well as of thermodynamically controlled.

However, it should be noted that when two or more products are possible, there will be always possibility of both kinetic control and thermodynamic control. We can manipulate and optimize most reaction conditions either to make the products under kinetic control or under thermodynamic control.

Consider a situation where reactant A can be converted to B and C, respectively (Fig 1 and 2). B is thermodynamically less stable than C. However, the activation energy required for going to B is less than that required for formation of C. Now, the molecules of A will convert more rapidly into B as the rate for this conversion will be higher ($\Delta G^{\#}_C > \Delta G^{\#}_B$). In this situation, the reaction will be kinetically controlled and the product B will be kinetic product (major product also).

Now, we change the reaction condition by increasing the temperature. The molecules will now have high energy and so they will be able to achieve high activation energy. Think about the reverse reactions that is going from B to A and going from C to A. For the reaction B to A, less activation energy will be required compared to the reaction C to

A ($\Delta G^{\#}_{C\ rev} > \Delta G^{\#}_{B\ rev}$). If the B molecules possess enough energy to achieve activation $\Delta G^{\#}_{B\ rev}$, the reaction A to B will be now reversible. If, the C molecules cannot achieve $\Delta G^{\#}_{C\ rev}$ for reverse back to A, then C will be unreactive in such condition. What will happen now is that A will covert to both B and C (more rapidly to B), B will reverse back to A again, but not C. When this process continues, concentration of C will build up, we will get C as the main product, which is thermodynamically more stable. At this condition the reaction is thermodynamically controlled and C is the thermodynamic product.

The temperature and other reaction conditions for achieving kinetic or thermodynamic control will be different for different reactions.

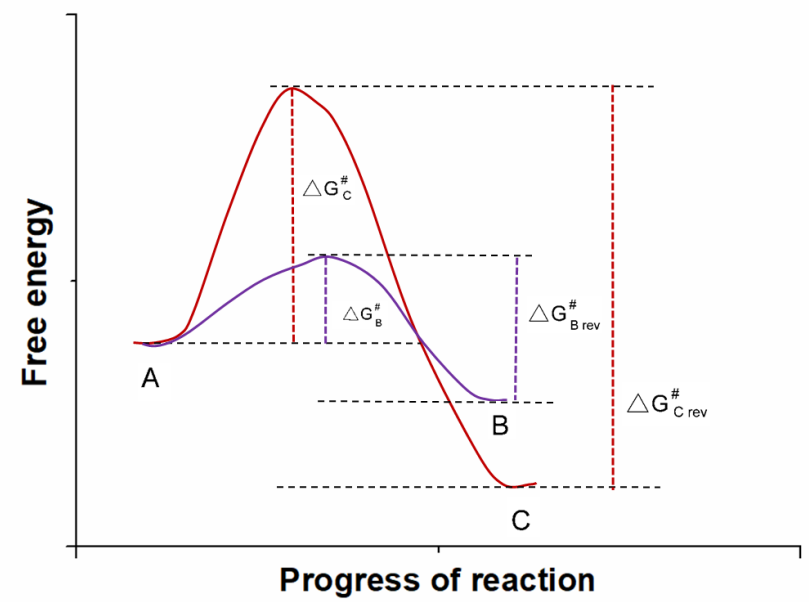


Figure1: Energy profile diagrams showing possibility of kinetic and thermodynamic control.

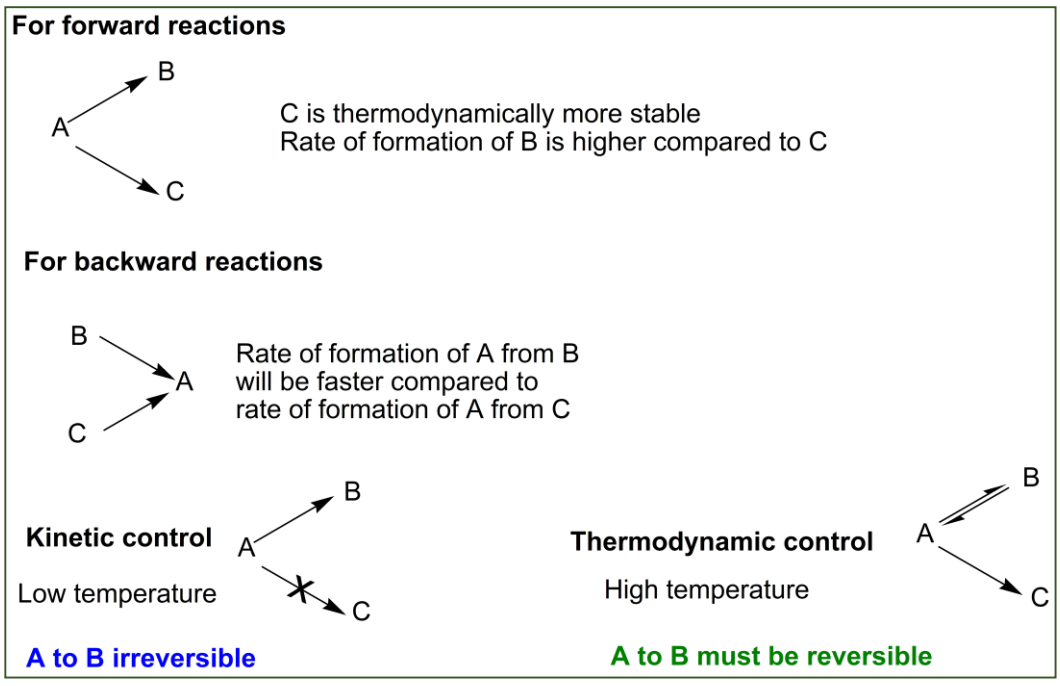


Figure 2: Schematic diagram showing of kinetic and thermodynamic control.

Reaction of α,β-unsaturated carbonyl compound with nucleophile can yield two types of nucleophilic addition reactions- (i) Direct addition through attack at the carbonyl carbon and (ii) Conjugate addition through attack at the C=C bond (Fig. 3). Conjugate addition gives thermodynamically more stable product as the weak C=C bond is broken and the strong C=O bond. However, the TS will be high in energy for conjugate addition as more number of partially broken bonds will be present compared to the TS of direct addition. Thus, the direct addition is faster and the reaction can be done at low temperature (kinetically controlled). By increasing the temperature, the direct addition can be made reversible and we can achieve thermodynamically controlled conjugate addition.

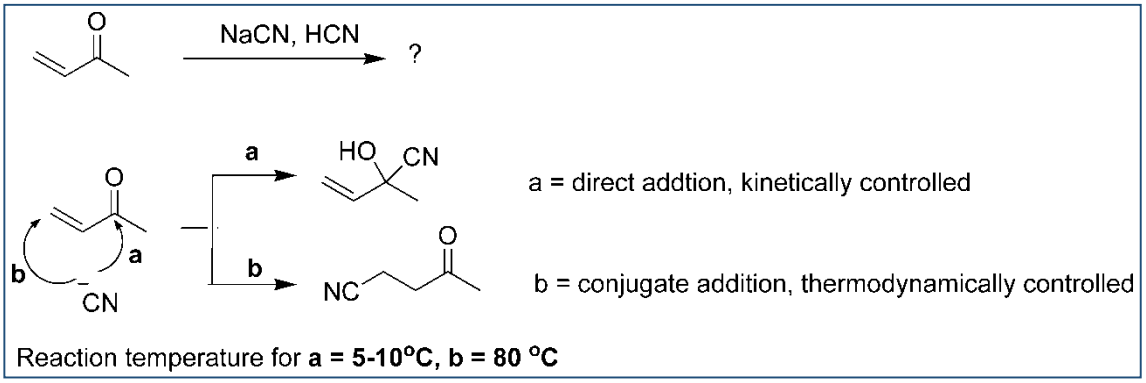


Figure 3: Direct and conjugate addition to α,β-unsaturated carbonyl compound

2.4 HAMMOND POSTULATE

In unit 1, we learned that TS have very little lifetime to be characterized. Thus, there is no experiment to show us how the TS of a reaction looks like. George S. Hammond, in 1955, stated a postulate for correlating the structure of a TS with the structures of reactant, intermediate or product. The postulate state "*If two states, as for example, a TS and a reactive intermediate, occur consecutively in a reaction process and have nearly the same energy content, their inter-conversion will involve only a small reorganization of the molecular structures."* Therefore, the geometric structure of a state can be predicted by comparing its energy to the species with the least energy gap along the reaction coordinate.

The postulate can be interpreted in simple words. If in a reaction coordinate diagram, the energy of the TS is very close to the energy of the intermediate, the structure of the TS state will be very close to that of the intermediate. If the intermediate is formed due to breaking of a bond, that bond will be highly stretched in the TS also, as their energies are very close. On the other hand, if the intermediate is formed due to a new bond formation, that bond will be also highly associated in the TS.

Besides intermediate, the postulate can be extended to reactant and products. In a highly exergonic reaction, the energy of the reactant will be closed to the energy of the TS. In such case, structure of the TS will be similar to that of reactant. In case of a highly endergonic reaction, the product's energy will be close to that of TS. Here, TS and the product will have similar structures.

Hammond's postulate work well in those reactions where the energy difference of the TS is not large compared to that of reactant, intermediate or product. We can understand the postulate by examining the reaction profile diagram shown in Fig. 4. Four one step reactions are represented here. It should be emphasized that the gradual or continuum decrease of activation energy shown in this figure is applicable to reaction of similar starting compounds only. In the curve a, the energy of TS1 is close to that of product rather than reactant. Thus, structure of TS1 will resemble to the structure of product. As we go from profile a to d, there will be a shift of structure of the transition states more towards the structure of reactant. TS4 is close to reactant, so its structure will be more like that of the reactant.

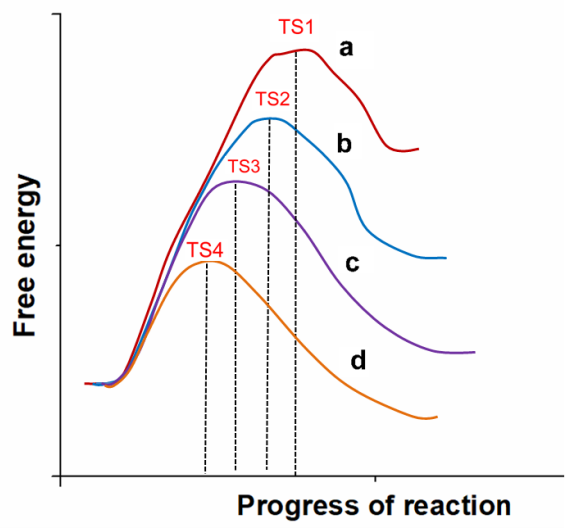


Figure 4: Energy profile diagrams that obey Hammond's postulate.

Let us apply Hammond's postulate to see why tertiary alkyl halide reacts more rapidly in S_N1 reaction. The mechanism of this reaction is discussed in unit 1. If we consider three alkyl halides, primary, secondary and tertiary; we will get 1°, 2° and 3° carbonations in the rate determining steps. We know that the stability orders of carbocations are 3°>2°>1°. Again, since the carbocations will be highly unstable compared to the alkyl halides, the rate determining step is endothermic (endergonic) as shown in Fig. 5. The TS of these reactions will therefore resemble the structure of the carbocations rather than alkyl halide according to Hammond's postulate. This means as the carbocation is positively charged, the TS will also have partially positive character. Now, electron donating group/hyperconjugation stabilizes a carbocation. The same stabilizing effect will be also applicable in case of the TS because of its structural similarity with the carbocation. Thus, as 3° carbocation is the most stable, the TS leading to the 3° carbocation will also be more stable (less in energy) compared to those for 2° and 1°. Thus, activation energy for the reaction involving tertiary alkyl halide will be least and consequently this reaction will be the fastest.

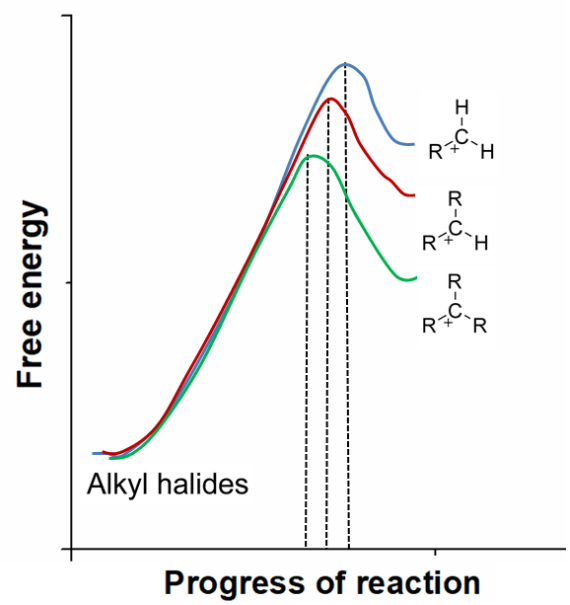


Figure 5: Energy profile diagrams showing resemblance of TS with carbocations. Energy profile for only the step one of S_N1 reaction is shown here.

While stating the Hammond postulate, energy contribution was taken only from PE. Entropy changes arising from restriction of movement of reactants or from solvent reorganisation were not taken into consideration. Nevertheless, the postulate is very useful and can be treated as the guiding principle for visualization of the structures of TS.

2.5 CURTIN–HAMMETT PRINCIPLE

In organic chemistry, the effect of conformation on reactivity is an important aspect. If the reactant is a mixture of two raplidly equilibrating conformers, what decides the structure of the major product – relative stability of the conformers or the free energy of the transition states? The answer lies in the Curtin-Hammett principle which states, "*The relative amounts of product formed from two critical conformations are completely independent of the relative populations of the conformations and depend only upon the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of conformational interconversion.*"

Let us consider a reaction where two conformers (C_1 and C_2) of a reactant can react to produce two different products D and E, respectively (Figs. 6 & 7). If the conformers C_1 and C_2 can rapidly interconvert with one another in the reaction conditions, the product formed will be governed by the activation energy of the corresponding reactions, but not by the stabilities of the conformers C_1 and C_2. Let us also consider, C_1 is less stable than C_2 and conversion of C_1 to the product needs less activation energy, then the product D formed from C_1 will be the major product. Thus, the energy of the TS is the deciding factor for product composition, not the energy of the conformer.

Reaction

A ⟶ D+ E

C_1 and C_2 are coformers of A

C_1 and C_2 are interconvertible at reaction condition $C_1 \rightleftharpoons C_2$

Rate of interconversion is higher compared to the rates of reactions

$C_1 \longrightarrow D$ activation enegy $\triangle G^{\#}_{C1}$

$C_2 \longrightarrow E$ activation enegy $\triangle G^{\#}_{C2}$

If $\triangle G^{\#}_{C1} > \triangle G^{\#}_{C2}$ then E will be the major product

If $\triangle G^{\#}_{C2} > \triangle G^{\#}_{C1}$ then D will be the major product

Stability of C_1 and C_2 has no impact onproduct composition

Figure 6: Schematic diagram representing Curtin-Hammett principle.

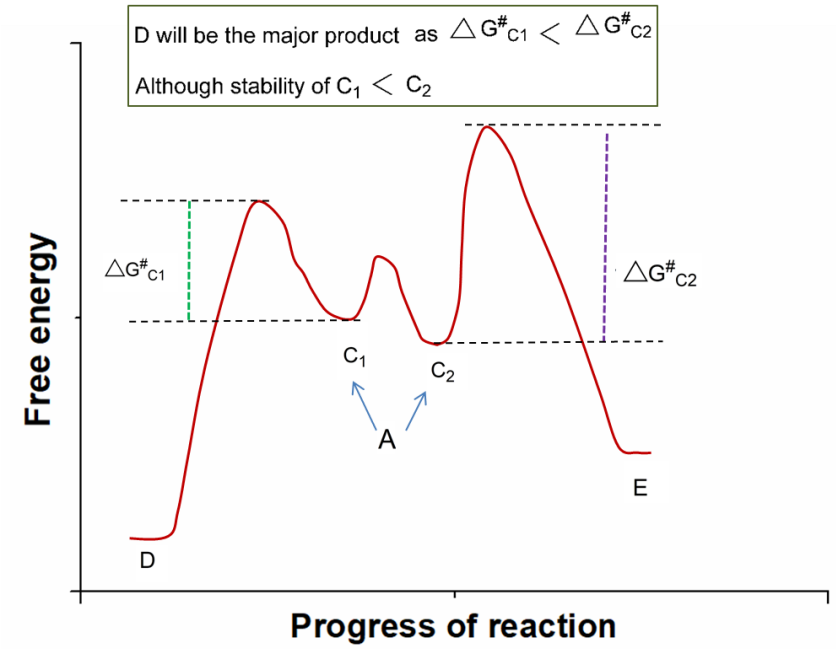


Figure 7: Energy profile diagram explaining the Curtin-Hammett principle.

The Curtin-Hammett principle can be applied to predict the product composition in E2 reaction of menthyl chloride (Fig.8). Menthyl chloride can exist in two chair conformations. In the stable conformer all the groups (isopropyl, chlorine, and methyl) are in equatorial positions. It can flip to another conformer where all the groups are in axial positions. But, this conformer is highly unstable compared to the other. However, if a strong base is applied to achieve an E2 reaction, the stable conformer does not react. This is because the antiperiplanar positions for H and Cl required is not achievable.

Without antiperiplanar requirement the activation energy of the reaction will be too high. On the other hand, the unstable intermediate can react as antiperiplanar positions for H and Cl is met here. The activation energy will be low for this case. Thus the product of the reaction is governed by the activation energies, but not by the stability of the conformers.
One should keep in mind that the reaction is quite slow because of the high energy barrier for conversion among the conformers.

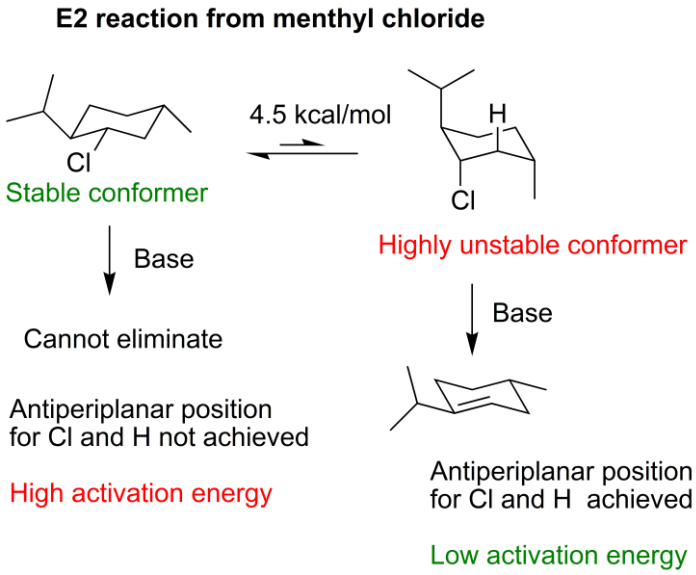


Figure 8: Possibilities of elimination (E2) reaction from menthyl chloride.

W CHECK YOUR PROGRESS

Q1. What are exothermic and endothermic reactions?
Q2. What are exergonic and energetic reactions?
Q3. Is it possible to make a Kinetic controlled reaction to thermodynamic controlled reaction?
Q4. State the Hammond's postulate.
Q5. Explain why 3° alkyl halide reacts faster in S_N1 reaction applying Hammond's postulate
Q6. Reversibility of reaction is required for Kinetic control or thermodynamic control?
Q7. Kinetic controlled reactions are governed by..... and thermodynamic controlled reactions are governed by .....
Q8. State the Curtin-Hammett principle.
Q9. Which determines the final product composition in reaction where more than one conformers are possible?
Q10. How do ΔG and $\Delta G^{\ddagger}$ related to spontaneity of chemical reaction?

2 2.6 LET US SUM UP

- In kinetically controlled reaction, the ratio the products formed is dependent on the relative energies of the transition states leading to these products.

- In case of thermodynamically controlled reaction, the relative energies of the products govern the ratio of the products formed. In this case, the activation energies do not matter.
- For kinetic control, the reactions should be irreversible, whereas for thermodynamic control the reaction with less activation energy should be reversible.
- If in a reaction coordinate diagram, the energy of the TS is very close to the energy of the intermediate, the structure of the TS state will be very close to that of the intermediate. If the intermediate is formed due to breaking of a bond, that bond will be highly stretched in the TS also, as their energies are very close.
- The relative amounts of product formed from two critical conformations of a reactant are completely independent of the relative populations of the conformations and depend only upon the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of conformational interconversion.

K 2.7 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: Exothermic reactions are reactions with negative ΔH and endothermic reactions are reactions with positive ΔH.

Answer to Q2: Exergonic reactions are reactions with negative ΔG and endergonic reactions are reactions with positive ΔG.

Answer to Q3: May be possible if activation energy required for the reverse of the kinetic controlled reaction is achievable by optimizing reaction conditions.

Answer to Q4: *If two states, as for example, a TS and a reactive intermediate, occur consecutively in a reaction process and have nearly the same energy content, their inter-conversion will involve only a small reorganization of the molecular structures.*

Answer to Q5: In S_N1 reaction carbocation intermediate is formed. 3º carbocation is more stable compared to 2º and 1º. The TS leading to formation of carbocation will be closer in energy to the carbocation rather than the alkyl halide. As 3º carbocation is more stable, the corresponding TS will be also more stable. Thus, this reaction will have less activation energy and consequently 3º alkyl halide will react rapidly in S_N1 reaction.

Answer to Q6: For thermodynamic control.

Answer to Q7: Kinetic controlled reactions are governed by activation energy and thermodynamic controlled reactions are governed by stability of products.

Answer to Q8: The relative amounts of product formed from two critical conformations are completely independent of the relative populations of the conformations and depend only upon the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of conformational interconversion.

Answer to Q9: Activation energy determines the product composition, not the stabilities of the conformers.

Answer to Q10: If ΔG is negative the reaction is spontaneous. $\Delta G^{\ddagger}$ is not related to spontaneity.

O 2.8 FURTHER READING

- Eric V. Anslyn, and Dennis A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books.
- Michael B. Smith and Jerry March, *March's Advanced Organic Chemistry*, Wiley-Interscience, A John Wiley & Sons, Inc., Publication.
- Jonathan Clayden Nick Greeves and Stuart Warren, *Organic Chemistry*, Oxford University Press.
- Paula Yurkanis Bruice, Organic Chemistry, Pearson.
- Francis A. Carey and Richard J. Sundberg, *Advanced Organic Chemistry, Part-A,* Springer Science.

M 2.9 MODEL QUESTIONS

Q1. What is the relation between activation energy and rate of a reaction?
Q2. What is the relation between equilibrium constant and free energy of reaction?
Q3. Which among conjugate addition and direct addition to α,β-carbonyl compound is kinetically controlled? Explain with the help of energy profile diagram.
Q4. Drawing suitable energy profile diagrams explain the Hammond's postulate.
Q5. To achieve thermodynamic controlled, do you need heating for all types of reaction? Explain.
Q6. Use Curtin-Hammett principle to predict the major product in E2 reaction of neomenthyl chloride.
Q7. Draw suitable energy profile diagram to elucidate Curtin-Hammett principle.
Q8. Draw the mechanisms and structures of transition states for the reactions shown in fig 3.
Q9. Explain the thermodynamic control and kinetic control in addition of hydrogen bromide with 1,3-butadiene.

UNIT 3: METHODS OF STUDYING ORGANIC REACTION MECHANISM

UNIT STRUCTURE

3.1 Learning Objectives
3.2 Introduction
3.3 Kinetic and non-kinetic methods of studying organic reaction mechanism
3.4 Isotope labelling studies
3.5 Kinetic isotope effects
3.6 Cross-over experiment
3.7 Let Us Sum Up
3.8 Answers to Check Your Progress
3.9 Further Reading
3.10 Model Questions

3.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- Learn the concept of determination of organic reaction mechanism.
- Understand isotope labelling studies for studying reaction mechanism.
- Learn kinetic isotope effects for understanding the rate determining step of reaction mechanism.
- Understand kinetic and non-kinetic methods for determination of organic reaction mechanism.

3.2 INTRODUCTION

Reaction mechanism is a sequential account of the step/s involved during a reaction. This account encompasses details of electron movement, changes in energies during bond cleavage and formation, and also the rates of formation of products in each of the steps.

A reaction mechanism is the most essential component for understanding the reaction, executing new reaction of similar kind, predicting products of unknown reactions. A mechanism is proposed based on different types of experimental evidences as well as theoretical calculations. A proposed mechanism will be regarded as the valid one which can be correlated with all the experimental results available. A proposed mechanism can become invalid in future, if new experimental findings cannot be interpreted with its help. Several experimental studies are conducted to prove a proposed mechanism, which you will learn in this unit.

3.3 KINETIC AND NON-KINETIC METHODS OF STUDYING ORGANIC REACTION MECHANISM

Kinetic methods of studying organic reaction mechanism rely on the rates at which the reaction proceeds. In a multistep reaction, the rates of all elementary steps also need to be monitored, if possible. Here we change different parameters of the reactions and then compare the rates of those reaction for deciding the rate law, rate determining step, etc. Common kinetic methods are - (i) studying the effect of concentration of reactants on the rate of the reaction, (ii) kinetic isotope effect.

Non-kinetic methods are not related to rates. Here we mostly do analysis of the compounds formed after the overall reaction and also for the elementary steps. That means, structures of all possible the intermediates and the products are tried to be characterized. These methods include (i) identification of all products, (ii) isolation/detection of intermediates, (iii) isotope labelling studies, and (iv) crossover experiment.

For a proposed mechanism to be accepted as valid one, the mechanism must be able to predict formation of each and every product in approximately the observed proportions. If intermediate is proposed, there should evidence for formation of the intermediate.

3.4 ISOTOPE LABELLING STUDIES

Isotope labelling study is a non-kinetic method used for determination of organic reaction mechanism. In isotopic labelling studies, isotope of a suitable element is replaced with another isotope which can later be tracked and detected in the intermediate or product. Common radioactive isotope labelling uses ^{14}C for ^{12}C, ^{18}F for ^{19}F, and ^{131}I for ^{127}I. Non-radioactive isotopes such as D in place of H, ^{18}O for ^{16}O, etc., can also be used. The presence of the radioactive isotopes can be detected from the radioactivity of the intermediate or product. Non-radioactive isotopes like D and ^{18}O can be detected by mass spectrometry or by IR, NMR spectroscopy, etc. Generally, it is not necessary to use completely labelled compounds. Partially labelled material is usually sufficient in isotope labelling studies.

For example, in acidic catalysed hydrolysis of methyl acetate (an ester) by labelled H_2O^{18}, the following two situations may arise. (a) If H_2O^{18} attacks the carbonyl carbon and substitutes the $-OCH_3$ group, ^{18}O will be incorporated in the acid molecule (acetic acid in this case). (b) If H_2O^{18} attacks C atom of methoxy group, ^{18}O will be incorporated in the methanol molecule (Fig. 1).

Let us separate the two products, viz. acetic acid and methanol, and subject them to mass spectrometric analysis. In acetic acid, if we get a peak at m/z of 60 only (exact mass of acetic acid considering ^{16}O), then it means that ^{18}O is not incorporated in the acetic acid molecule. Thus, the reaction should follow the pathway **b**. If we get another peak at m/z 62, then it shows incorporation of ^{18}O in acetic acid to imply that the pathway **a** is favourable. Similar interpretation can also be done by analysing the methanol molecule formed.

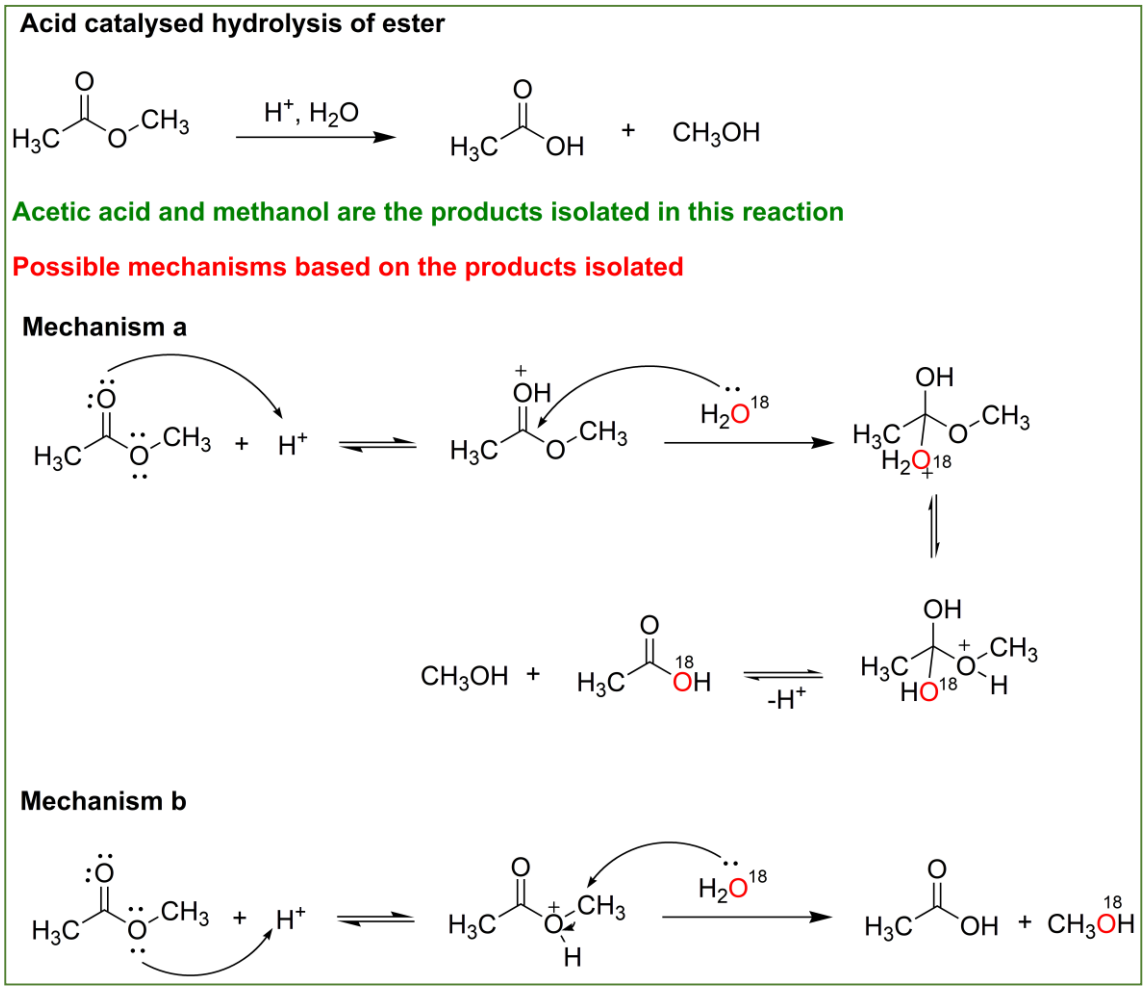
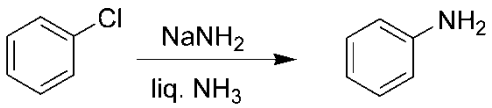


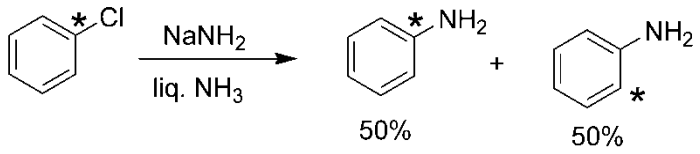
Figure 1: Possible mechanism of acid catalysed ester hydrolysis and isotope labelling study.

D_2O can also be used in place of H_2O^{18} in this labelling experiment. In such case, deuterium will be incorporated in the products. Now, incorporation of D can be verified not only by mass spectrometry, but also by IR (O-H and O-D bonds have distinct stretching frequencies) and NMR spectroscopy (D is NMR active but ^{18}O is inactive in NMR).

Let us consider the following nucleophilic aromatic substitution reaction.



At first sight, this reaction looks like to follow S_N1 or S_N2 type of mechanism. However, on labelling the C atom attached to Cl of chlorobenzene with ^{14}C, two products are obtained as shown below.



Finding of product with labelled C at the adjacent position of the leaving immediately disqualifies a S_N1 or S_N2 mechanism. Thus the reaction must follow a different mechanism. A mechanism through the formation of benzyne intermediate was proposed which can justify attachment of the nucleophile at *ipso* (meaning same) and *ortho* positions with respect to the leaving group (Fig. 2). In this mechanism, a symmetrical benzyne intermediate is formed from chlorobenzene. The nucleophile now has two equally accessible electrophilic C atoms to attack. This leads to formation of two products in equal amounts. You should keep in mind that the isotope labelling experiment alone cannot justify the formation of the benzyne intermediate. Other experiments were also conducted for trapping and identification of the benzyne to prove the mechanism. In most the mechanistic studies, there are number of experiments performed and the following mechanism (Fig. 2) is proposed by analysing and interpreting all the experimental data. In the following reaction (benzyne mechanism), two products are obtained where labelling ^{14}C are different. This observation immediately disqualifies a S_N1 or S_N2 mechanism.

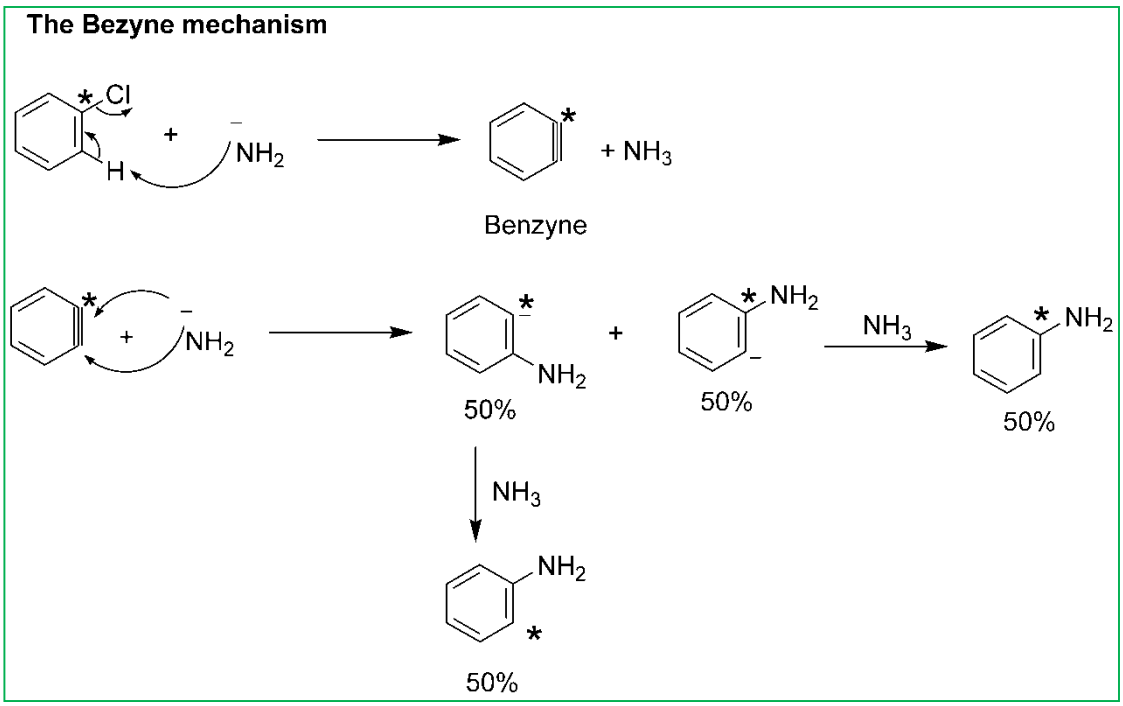


Figure 2: Benzyne mechanism

3.5 KINETIC ISOTOPE EFFECTS

Kinetic isotope effect (KIE) is a kinetic method for determining a reaction mechanism. In this method, an atom (most commonly H atom) is substituted with an isotope (most commonly D). Now, the rate of the reaction is measured for the compound with H and for the compound with D. The isotope effect can be defined as the ratio of rate constants, where the numerator is the rate constant for the reaction with the natural abundance

isotope (H), and the denominator is the rate constant for the reaction with the substituted isotope (D). Let us consider two hypothetical reactions where a compound X-H and X-D undergo heterolysis of the X-H/X-D bond. Then the isotope effect will be defined as k_H/k_D. When D is used, it can also be specifically called as deuterium kinetic effect.

$$X{-}H \xrightarrow{k_H} X^- + H^+$$

$$X{-}D \xrightarrow{k_D} X^- + D^+$$

$$\text{Kinetic isotope effect} = \frac{k_H}{k_D}$$

What is the origin of kinetic isotope effect? Why is H chosen for most kinetic isotope effect studies? Two bonds with two isotopes will have different bond dissociation energies. All bonds in a molecule are dynamic and keep on vibrating at all times. The minimum vibrational energy of a bond is called the zero point energy (ZPE).

The ZPE of a bond depends on the mass of the atoms attached to the bond. The bonds with heavier atoms will have a lower ZPE compared to the lighter ones due to higher reduced mass. Thus C-D bond have lower ZPE and consequently high bond dissociation energy than C-H bond which can be understood from the Morse curve shown in Fig. 3. Thus, a reaction, where C-D bond breaks, will have higher activation energy. Consequently, the rate of reaction involving C-H dissociation will be high compared that involving C-D dissociation. This is the origin of kinetic isotope effect.

Vibrational energy for harmonic oscillator

$$E_v = \left(n + \frac{1}{2}\right) h\nu \qquad n = 0,1,2.....$$

Zero point enery $E_v = \frac{1}{2} h\nu \qquad (n = 0)$

$$\nu = \frac{1}{2}\sqrt{\frac{k}{m}} \qquad m = \frac{m_1 m_2}{m_1 + m_2}$$

ν = vibrational frequency

m_1 and m_2 = masses of the atoms attached to the bond

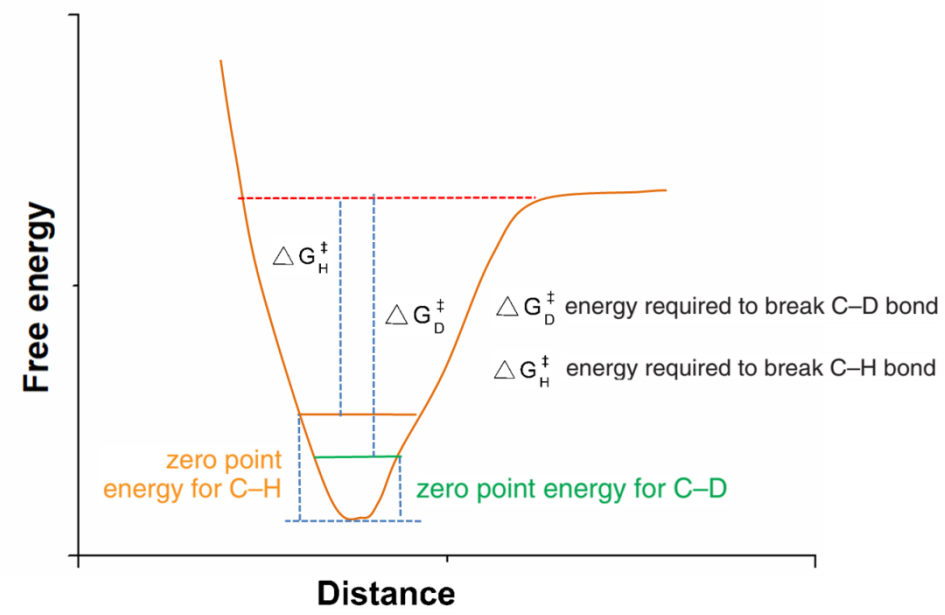


Figure 3: Morse curve showing ZPE and bond dissociation energy for C-H and C-D bonds.

Answer to the second question can also be drawn from the reduced mass. When H is replaced by D, reduced mass increases approximately by a factor of 2 for C-D bond compared with C-H bond. Isotopes of no other elements have such profound effect on the reduced mass (e.g. reduced mass for C-D= 1.71, C-H =0.92, C-O^{18} =7.2, C-O^{16} = 6.85). The effect of deuterium isotopic labelling on bond dissociation energy is greatest and so it is used very commonly.

Typical deuterium isotope effects for reactions in which C-H bond breaks is in the range of 1-8. When the C-H bond is broken in the rate determining step, the effect is called as primary kinetic isotope effect and the range is about 3-8. If the C-H bond does not break in the rate determining step, the effect is called as secondary kinetic isotope effect and the range is about 1-2. A value of 1 means no kinetic isotope effect, that the dissociation of C-H, if any, does not influence the rate of the reaction.

Let us take an example of elimination reaction of an alkyl halide [1-(2-bromoethyl)benzene] with a strong base (Fig. 4). The kinetic isotope effect for this alkylhalide is found to be 7.1. A high value indicates a primary kinetic isotope effect and implies that C-H bond breaks in the rate determining step. The alkyl halide has option to undergo the reaction either through E1 or E2 mechanism. Since C-H bond does not break in the rate determining step of E1 mechanism, this reaction must occur through E2 mechanism.

[Note: An alkyl halides like [1-(2-bromoethyl)benzene] reacts with a strong base via an E2 mechanism (concerted bimolecular elimination) rather than an E1 mechanism. Because the E1 mechanism requires forming a carbocation intermediate in a slow first step. Primary carbocations have very high energy and are extremely unstable, so they do not form. A strong base actively forces a one-step bimolecular pathway rather than waiting for ionization.]

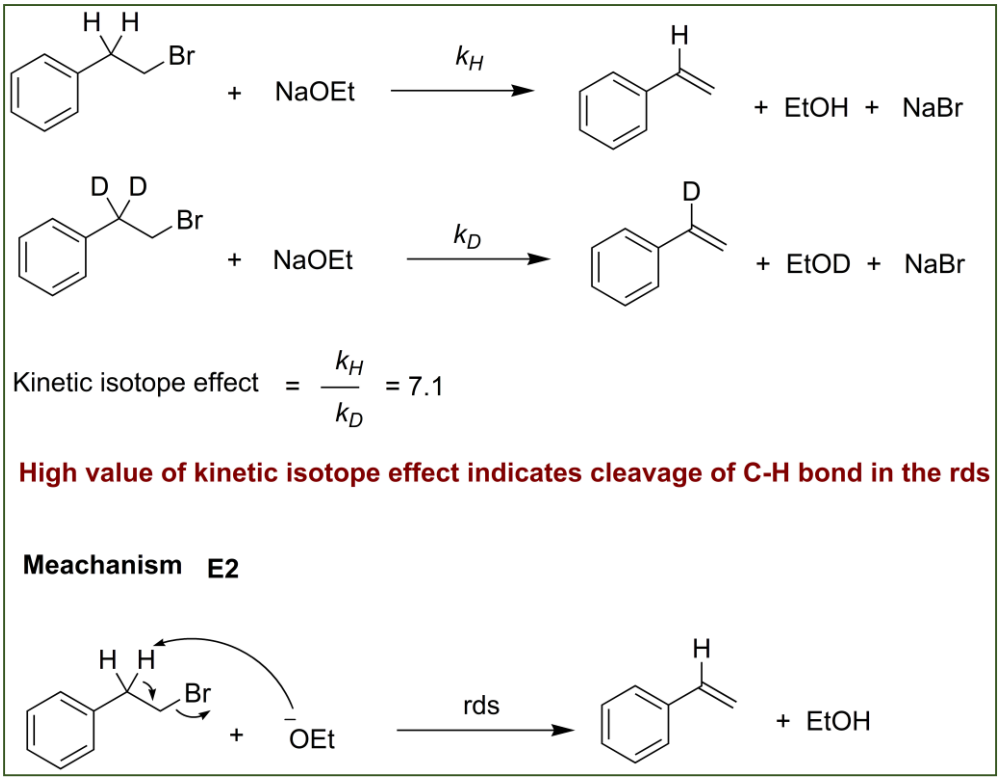


Figure 4: Primary kinetic isotope effect in E2 reaction.

We know that benzene can be converted to nitrobenzene by reacting with a mixture of conc. nitric acid and conc. sulphuric acid. For this reaction, the kinetic isotope effect is equal to 1 (Fig. 5). This means that there is no influence of C-H bond breaking in the overall rate of the reaction. This indicates that C-H bond breaks in a step other than the rate determining step. Thus, the electrophile ($^+NO_2$ here) must react with the aromatic compound in the rate determining step and also the C-H bond should no cleave at this step. So, a two step mechanism was proposed - first slow rate determining step involves the attack of the electrophile and second step is the removal of proton. The observed kinetic isotope effect can be justified this mechanism.

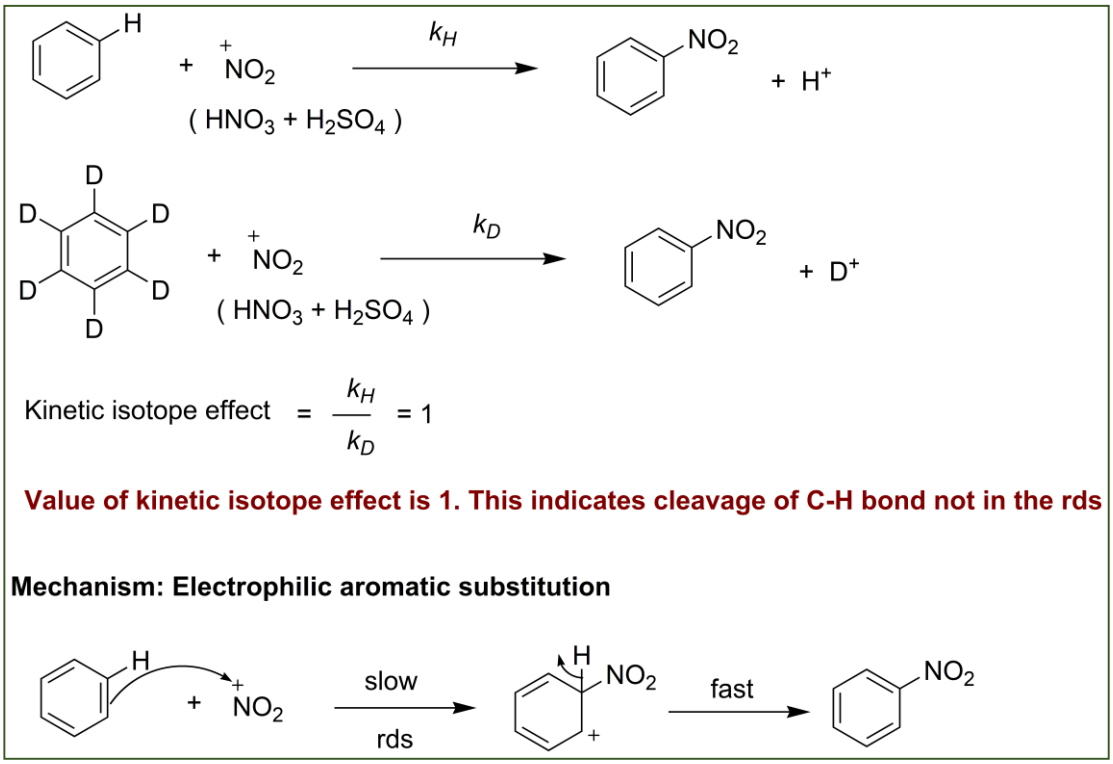


Figure 5: Electrophilic aromatic substitution reaction with no kinetic isotope effect.

We may also observe opposite of the above mentioned KIE. That means a reaction with deuterated compound may react faster than non-deuterated one. Here value of k_H/k_D will be less than 1. Such isotope effect is called as inverse kinetic isotope effect. In other cases, the rate of a reaction may also be influenced by deuterated solvents. For example, if a reaction is done in H_2O and D_2O, the rates may not be same in both solvents. Such isotope effect is called solvent kinetic isotope effect. This happens when there is exchange of H between reactant and solvent molecules during the reaction. This is represented as k_{H2O}/k_{D2O}.

Let us see an example where both solvent and inverse kinetic isotope effects are observed. The elimination reaction of a tertiary amine by base in aqueous solution is shown in Fig. 6. Normal KIE for this reaction is low and indicates that H is not removed in the rds. This rules out an E2 mechanism. Since the C attached to the leaving group is primary alkyl, an E1 mechanism is also not favourable. Thus, the mechanism here is E1cB.

If we do the reaction in D_2O as solvent instead of H_2O, the rate of the reaction increases and a k_{H2O}/k_{D2O} (solvent KIE) value of 0.13 is observed. The KIE value is significantly less than 1, so it is an inverse KIE also.

Why do we observe an inverse KIE? The answer lies in the mechanism. The first step of the reaction (E1cB mechanism) is deprotonation of the reactant to yield the conjugate base. The amine group then leaves to yield the alkene product. The amine is not a very good leaving group and the conjugate base is relatively strong base. Thus, the conjugate base has enough time to abstract H^+/D^+ from the solvent and reverse back to the

reactant. Abstraction of proton from H_2O is faster than abstraction of deuterium from D_2O (as O-H bond will break easily compared to O-D bond). This means the conjugate base can reverse to the starting compound at faster rate when the reaction is done in H_2O compared to D_2O. The forward reaction to produce the conjugate base is thus slow in H_2O and consequently the overall reaction is also slow and we observe an inverse KIE. Whether we observe KIE or inverse KIE or solvent KIE, the concept is same everywhere, C-D/O-D bond breaks slowly compared to C-H/C-D bonds. The inverse KIE was observed in the above example because the KIE is taking place in the backward reaction.

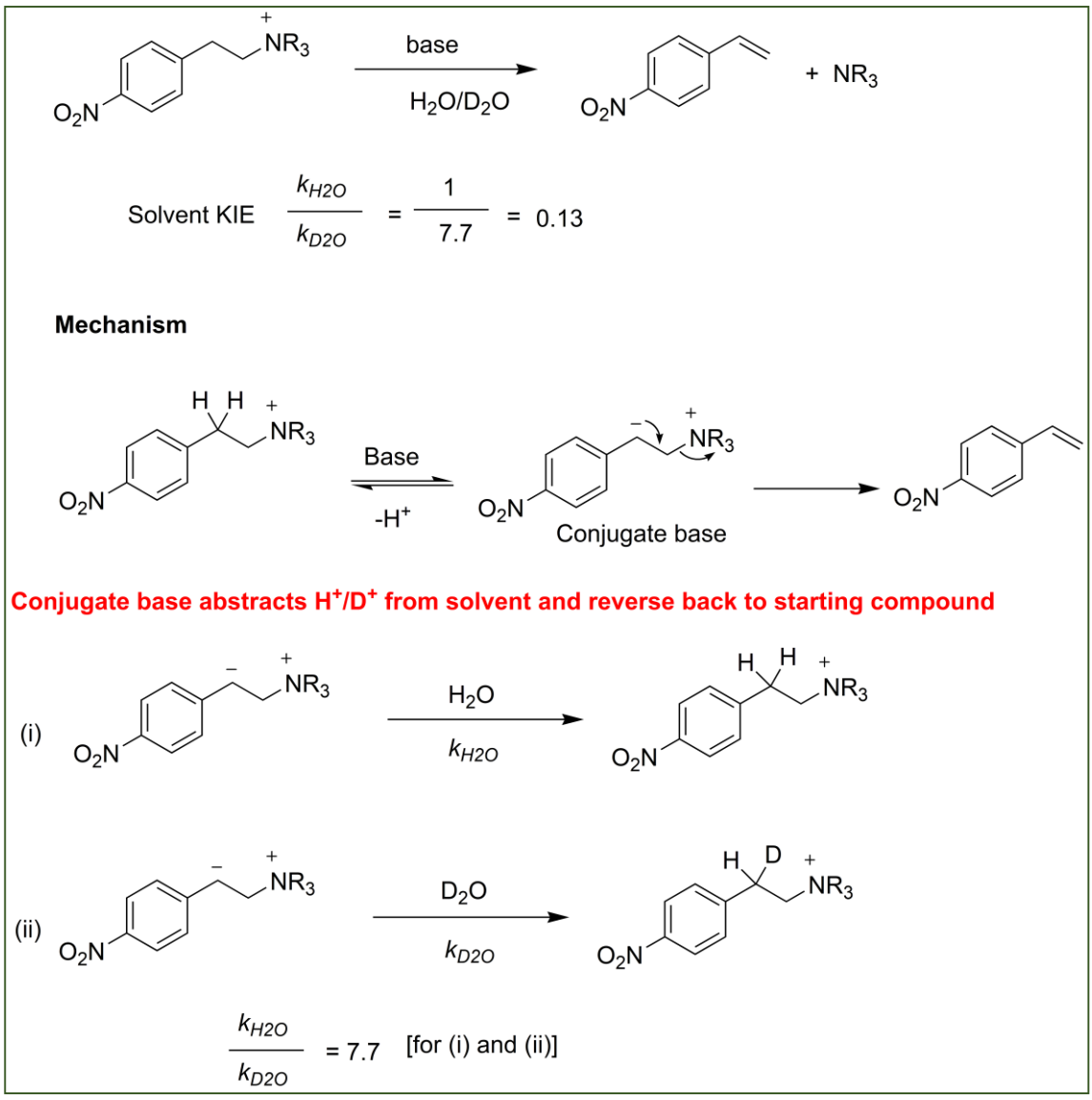


Figure 6: Solvent and inverse KIE in E1cB reaction.

Secondary kinetic isotope effects arise from isotopic substitution at a bond which is not being broken during the reaction and generally involve a change in bond hybridization or involvement of the bond in hyperconjugation.

3.6 Cross-over experiment

A cross-over experiment is used to determine whether intermediates are formed or not in a reaction mechanism. A cross-over experiment can indicate whether the reaction is intramolecular or intermolecular. For cross-over experiment, we need to do at least two reactions starting with two similar reactants. The reactants can be labelled with isotope or we can take two reactants with a light variation in the substituents. The formation of crossover product indicates formation of intermediate and an intermolecular mechanism. Let us consider a hypothetical reaction where A-B yields a product C-D (Fig. 7). Now, we take mixture of two starting compound A-B and the labelled one A*-B*. If the reaction proceeds with formation of no intermediate, then we will obtain C-D and C*-D*. However, if intermediates are formed, we should obtain the crossover products C-D* or C*-D which can only be formed by combination of intermediates one from A-B and the other from A*-B*. It should be emphasized that in some reaction, if the intermediates formed do not move apart due to close association, we may not get crossover products.

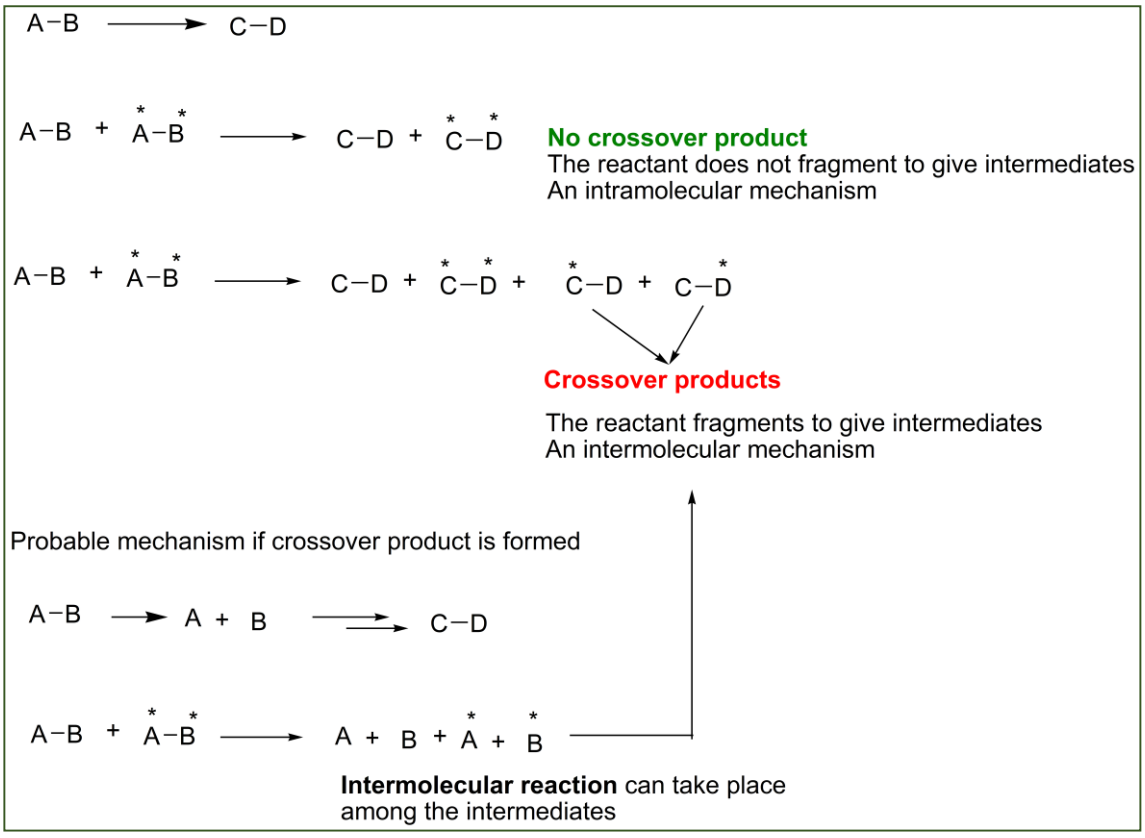


Figure 7: Schematic diagram showing crossover experiment.

For example, crossover products can be observed in the Fries rearrangement where an intermolecular rearrangement of phenolic ester takes place in the presence of $AlCl_3$ or light (Fig. 8). Here instead of isotopic labelling, substitution patterns of the reactants are changed.

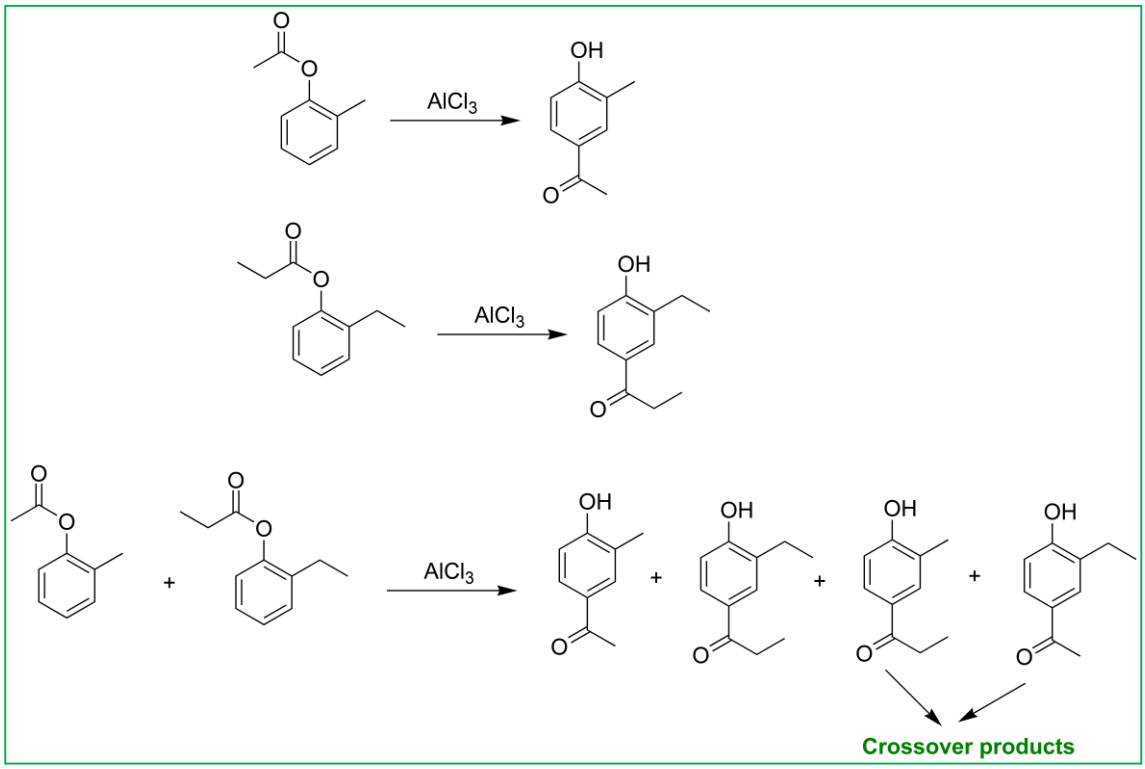


Figure 8: Crossover experiment for Fries rearrangement.

W CHECK YOUR PROGRESS

Q1. What are kinetic and non-kinetic methods for studying reaction mechanism?
Q2. Mention any two kinetic and two kinetic non-kinetic methods for studying reaction mechanism.
Q3. What do you mean by isotope labelling study?
Q4. What is kinetic isotope effect?
Q5. What is crossover experiment?
Q6. Define zero-point energy.
Q7. How can a labelled isotope be tracked in a product?
Q8. For kinetic isotope effect study H/D is chosen most of the times. Why?
Q9. If crossover products are obtained, then the mechanism will be intramolecular or intramolecular?
Q10. What is inverse kinetic isotope effect?

2 3.7 LET US SUM UP

- A reaction mechanism is the most essential component for understanding the reaction, executing new reaction of similar kind, predicting products of unknown reactions. A mechanism is proposed based on different types of experimental evidences as well as theoretical calculations. A proposed mechanism will be regarded as the valid one which can be correlated with all the experimental results available.

- The methods for studying reaction mechanism may be divided into two broad classes- kinetic and non-kinetic. Kinetic methods of studying organic reaction mechanism rely on the rates at which the reaction proceeds. Non-kinetic methods are not dependent on the reaction rates. Here we mostly do analysis of the compounds formed after the overall reaction and also for the elementary steps. That means structures of all possible the intermediates and the products are tried to be characterized.
- Isotope labelling study is non-kinetic method used for determination of organic reaction mechanism. In isotopic labelling studies, isotope of a suitable element is replaced with another isotope which can later be tracked and detected in the intermediate or product. Common isotopes are labelling with radioactive isotope such as ^{14}C for ^{12}C, ^{18}F for ^{19}F, ^{131}I for ^{127}I, etc. Non-radioactive isotopes such as D in place of H, ^{18}O for ^{16}O etc. can also be used.
- Kinetic isotope effect is on type of kinetic methods of determining the mechanism. In this method, an atom is substituted with one of its isotopes. The isotope effect can be defined as the ratio of rate constants, where the numerator is the rate constant for the reaction with the natural abundance isotope and the denominator is the rate constant for the reaction with the substituted isotope.
- A cross-over experiment is used to determine whether intermediates are formed or not in a reaction mechanism. A cross-over experiment can indicate whether the reaction is intramolecular or intermolecular.

K 3.8 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: Kinetic methods of studying organic reaction mechanism rely on the rates at which the reaction proceeds. Non-kinetic methods are not related to rates. Here we mostly do analysis of the compounds formed after the overall reaction and also for the elementary steps. That means structures of all possible the intermediates and the products are tried to be characterized.

Answer to Q2: Kinetic methods- (i) studying the effect of concentration of reactants on the rate of the reaction, (ii) kinetic isotope effect. Non-kinetic methods- (i) isotope labelling studies (ii) crossover experiment.

Answer to Q3: Isotope labelling study is non-kinetic method used for determination of organic reaction mechanism. In isotopic labelling studies, isotope of a suitable element is replaced with another isotope which can later be tracked and detected in the intermediate or product.

Answer to Q4: A comparison of the rate of reaction of a compound with the rate of reaction of an identical compound in which one of the atoms has been replaced by an isotope.

Answer to Q5: A cross-over experiment is used to determine if a reactant breaks apart to form intermediates that are released to solution before they recombine to give product. To accomplish this kind of experiment, we use two similar reactants, one that is labelled in some manner to distinguish it from the other. The label can be a different substituent or an isotope.

Answer to Q6: All bonds in a molecule are dynamic and keep on vibrating at all times. The minimum vibrational energy of a bond is called the zero-point energy.

Answer to Q7: Using techniques such as IR, NMR spectroscopy, mass spectrometry, measuring the radioactivity etc.

Answer to Q8: Since from going to D from H, the mass is increased 2 times. Such profound increase in mass is not possible for isotopes of other elements.

Answer to Q9: Intermolecular

Answer to Q10: A reaction with D labelled compound reacts faster than the non-labelled one. Here value of k_H/k_D will be less than 1.

O 3.9 FURTHER READING

- Eric V. Anslyn, and Dennis A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books.
- Michael B. Smith and Jerry March, *March's Advanced Organic Chemistry*, Wiley-Interscience, A John Wiley & Sons, Inc., Publication.
- Jonathan Clayden Nick Greeves and Stuart Warren, *Organic Chemistry*, Oxford University Press.
- Paula Yurkanis Bruice, Organic Chemistry, Pearson.
- Francis A. Carey and Richard J. Sundberg, *Advanced Organic Chemistry, Part-A,* Springer Science.

M 3.10 MODEL QUESTIONS

Q1. Discuss how a reaction mechanism can be determined?
Q2. Take a suitable example not mentioned in this SLM, to show the utility of isotope labelling studies.
Q3. How will you prove incorporation of ^{18}O in the product?
Q4. Discuss why C-D bond dissociation energy is more compared to C-H bond dissociation energy.
Q5. What are primary KIE and secondary KIE? Explain with appropriate examples.
Q6. Explain inverse KIE with the help of suitable example.
Q7. How can crossover experiment justify a mechanism to be intramolecular or intermolecular? Explain.
Q8. What is solvent KIE?
Q9. How does isotope labelling study helps to ascertain oxirene intermediate formation in Wolff rearrangement reaction?

UNIT 4: LINEAR FREE ENERGY RELATIONSHIPS (LFER)

UNIT STRUCTURE

4.1 Learning Objectives
4.2 Introduction
4.3 Thermodynamic and Kinetic Foundation of LFER
  4.3.1 Free Energy and Chemical Equilibrium
  4.3.2. Free Energy of Activation and Reaction Rates
4.4 The First Hammett Plot
  4.4.1 Non-Conformity of o- Substituted and Aliphatic Compounds
4.5 The Hammett Equation
  4.5.1 Derivation of the Hammett Equation
  4.5.2 Substituent constant, σ_x
  4.5.3 Reaction Constant, ρ
4.6 Steric Effects
  4.6.1 Taft Equation
4.7 Effects of conformation on reactivity
  4.7.1 Anomeric effect
  4.7.2 Neighbouring group participation (NGP)
4.8 Let Us Sum Up
4.9 Answers to Check Your Progress
4.10 Further Reading
4.11 Model Questions

4.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- learn the concept of Hammett equation, effect of substitution on reaction rates.
- learn to relate structure and reactivity on a quantitative basis.
- learn how the steric and polar factors affect the Hammet equation
- familiarize yourself with effect of conformation on reactivity of a reaction.

4.2 INTRODUCTION

In organic chemistry, the reactivity of molecules is strongly influenced by their structure. Changes in substituents attached to a reactive centre often lead to systematic variations in reaction rates and equilibrium constants. These variations arise because substituents alter the electronic environment of molecules, thereby affecting the stability of reactants, intermediates, transition states, and products.

Linear energy free relationship (LFER) provides a quantitative basis to connect molecular structure with chemical reactivity. The fundamental assumption of LFER is that the reaction mechanism remains constant across the series under investigation. Under this condition, substituent effects influence the free energy of reactants, transition states, and products in a proportional manner, leading to linear correlations. Therefore, the term

"linear free energy relationship" refers to the observation that changes in free energy associated with a series of related reactions often show a linear correlation with substituent or structural parameters. When a set of structurally similar compounds undergoes the same type of reaction without a change in mechanism, the effect of substituent on reaction rates or equilibria can often be represented by simple linear equations. These relationships not only provide quantitative insight into substituent effects but also serve as powerful tools for mechanistic analysis. Prominent examples of LFER include the Hammett equation, Taft equation, Brønsted relationship, and Swain–Lupton model, which together form the basis of modern structure–reactivity studies in organic chemistry.

4.3 THERMODYNAMIC AND KINETIC FOUNDATION OF LFER

Linear Free Energy Relationships are fundamentally rooted in thermodynamics and kinetics. The free energy changes associated with chemical reactions determine both their feasibility and their rates. Substituents influence these free energy changes by altering electronic distribution, stability of intermediates, and transition state energies. Therefore, understanding the thermodynamic and kinetic basis of substituent effects is essential for interpreting and applying LFER in organic chemistry.

4.3.1 Free Energy and Chemical Equilibrium

Gibbs free energy (ΔG): The Gibbs free energy change (ΔG) is a thermodynamic quantity that determines whether a chemical reaction is spontaneous and to what extent it proceeds toward equilibrium. For a chemical reaction:

$$\text{Reactants} \rightleftharpoons \text{Products}$$

The free energy change is given by:

$$\Delta G = \Delta H - T\Delta S$$

Where, ΔH = enthalpy change, T = temperature, and ΔS = change in entropy. The standard free energy change (ΔG°) determines whether a reaction is thermodynamically favourable.

- If $\Delta G^\circ < 0 \rightarrow$ reaction is spontaneous.
- If $\Delta G^\circ > 0 \rightarrow$ reaction is non-spontaneous.

Relationship between ΔG and Equilibrium Constant (K): The standard free energy change of a reaction is directly related to its equilibrium constant (K) by the equation:

$$\Delta G^\circ = -RT \ln K$$

Or

$$\Delta G^\circ = -2.303\, RT \log K$$

Where, R is the gas constant and T is the absolute temperature.

This relationship shows that changes in free energy correspond to changes in equilibrium constants. Therefore, any structural modification that alters ΔG will also influence the position of equilibrium.

4.3.2 Free Energy of Activation and Reaction Rates

According to transition state theory, chemical reactions proceed through a high-energy intermediate state known as the transition state. The free energy difference between the reactants and the transition state is called the free energy of activation ($\Delta G^{\ddagger}$).

For a reaction:

[Reactants] → [Transition State] → [Products]

The free energy of activation, $\Delta G^{\ddagger}$ determines the rate at which the reaction occurs.

Relationship between free energy of activation ($\Delta G^{\ddagger}$) and Rate Constant (k): The quantitative basis of linear free energy relationships arises from transition state theory, which relates the rate constant of a reaction to the Gibbs free energy of activation. According to the Eyring equation,

$$k = (k_B T / h) \exp^{(-\Delta G^{\ddagger} / RT)}$$

The rate constant depends exponentially on the free energy of activation. Taking the logarithm of this expression shows that the logarithm of the rate constant is linearly related to the free energy of activation.

$$\log k = -2.303RT\ \Delta G^{\ddagger} + \log (k_B T / h)$$

Where k_B is the Boltzmann constant, h is Planck's constant, R is the gas constant, and T stands for temperature.

This section 4.1 shall help in better understanding of the Hammett plot elaborated in the later part.

4.4 THE FIRST HAMMETT PLOT

The first clear example of a linear free-energy relationship was reported by Hammett in 1933. He examined the reaction of a series of methyl esters (1) with NMe_3,

$$RCO_2Me + NMe_3 \xrightarrow{k} RCO_2^- + {}^+NMe_4 \qquad \textbf{(1)}$$

Hammett observed that the rates of these reactions were directly related to the ionization constants of the corresponding substituted carboxylic acids (2) in water,

$$RCO_2H + H_2O \overset{K}{\rightleftharpoons} RCO_2^- + H_3O^+ \qquad \textbf{(2)}$$

Thus, when log k for the reaction of the esters (1) was plotted against log K for the ionization of the corresponding acids (2), a reasonably straight line was obtained. In practice, Hammett plotted the more convenient quantities −log k versus −log K, since these gave easily handled positive numbers. This linear relationship is illustrated schematically in Fig.1

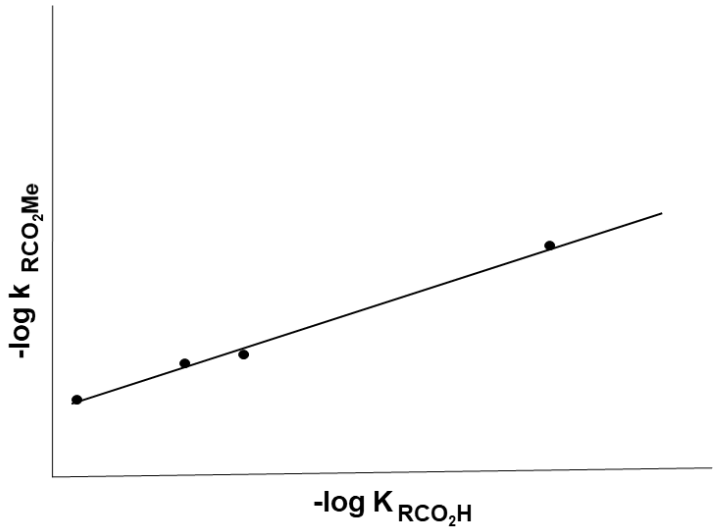


Fig. 1: Plot of log k for the reaction of the esters (RCO_2Me) against log K for the ionization of the corresponding acids (RCO_2H).

Both equilibrium constants (K) and rate constants (k) are related to free energy changes in the following way:

$$\log K = -\Delta G^{\circ}/2.303\,RT \qquad [\textit{from sec 4.3.1}]$$

$$\log k = (-\Delta G^{\ddagger}/2.303\,RT) + \log (k_B T/h) \qquad [(\textit{from sec 4.3.1}]$$

Since both log K and log k are directly proportional to free energy terms, a linear relationship between them implies that substituent effects influence both the equilibrium free energy and the activation free energy in a proportional manner. The existence of a straight-line relationship in Fig. 1, implies that there is also a linear relationship between the free energy of activation, $\Delta G^{\ddagger}$ for the reaction of ester and the standard free energy change, ΔG° for ionization of the corresponding acids in water. Because of this proportional relationship between the free energy terms of two different reaction series, such straight-line plots are referred to as **linear free energy relationships (LFERs).**

Another early example studied by Hammett is illustrated in Fig. 2. In this case, the reaction examined was the base-catalysed hydrolysis of a series of ethyl esters (3):

$$RCO_2Et + OH^- \xrightarrow{k} RCO_2^- + EtOH \qquad \textbf{(3)}$$

The rate constants (log k) for this reaction were plotted against the ionization constants (log K) for the corresponding substituted carboxylic acids in water (2).

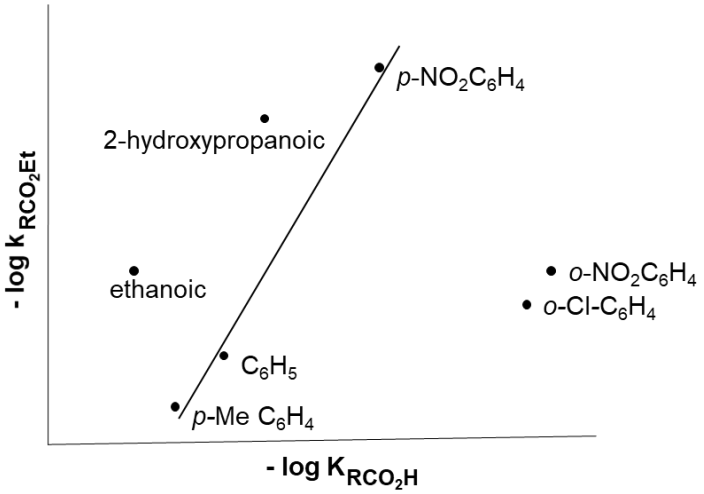


Fig. 2: Plot of log k for the reaction of the ethyl esters (RCO_2Et) against log K for the ionization of the corresponding acids (RCO_2H).

Judged by the standards of Fig. 1, the plot in Fig. 2, appears somewhat disappointing. A reasonably good straight-line relationship is observed only for benzoic acid and its *para*-methyl (*p*-Me) and *para*-nitro (*p*-NO_2) derivatives.

However,

The *ortho*-nitro (*o*-NO_2) and *ortho*-chloro (*o*-Cl) benzoic acid derivatives deviate significantly from the straight line on one side.

- The aliphatic acids, such as ethanoic acid and 2-hydroxypropanoic acid, lie far from the line on the opposite side.

Hammett found that straight-line relationships were generally not obtained when data for *ortho*- substituted benzene derivatives or aliphatic compounds were included in the same correlation. However, when the analysis was restricted to reactions of *meta*- and *para*-substituted benzene derivatives, excellent linearity was obtained. This observation, later illustrated clearly for ester hydrolysis reactions, proved to be valid for a wide range of different reactions involving substituted aromatic systems.

Furthermore, when only *meta*- and *para*- substituted benzoic acid derivatives are considered, an excellent straight-line relationship is obtained between log k for ester hydrolysis and log K for acid ionization (Fig 3).

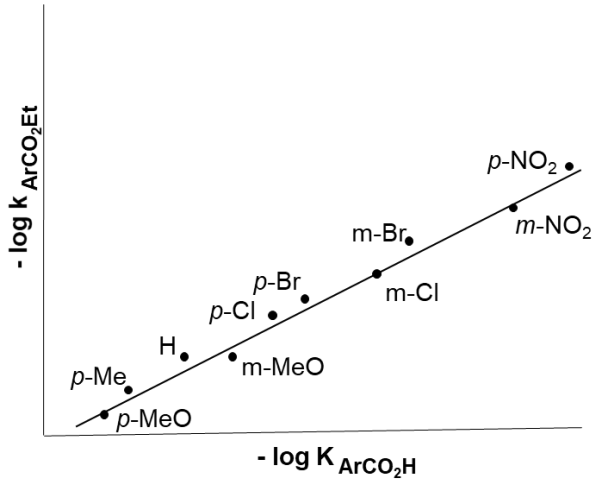
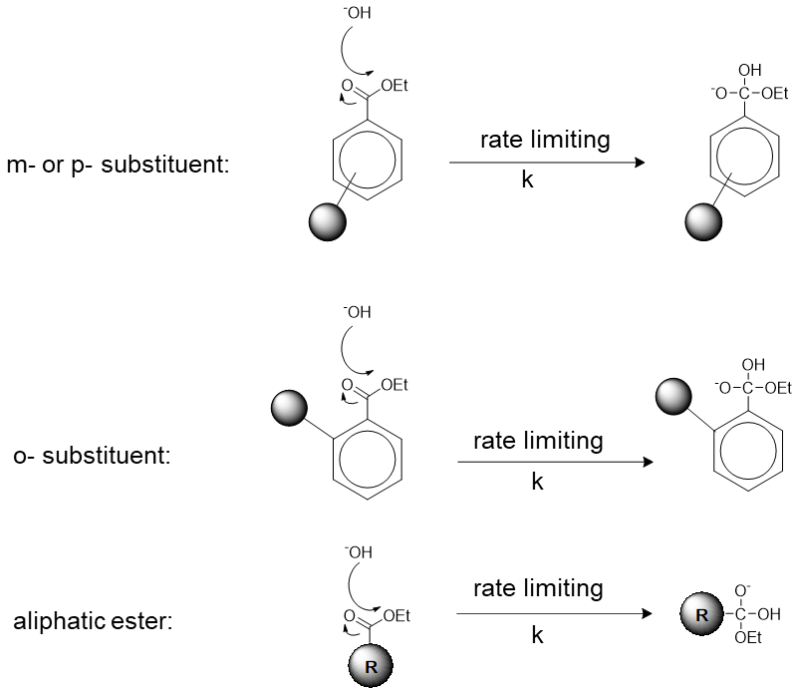


Fig. 3: Plot of log k for the reaction of the substituted benzoic esters ($ArCO_2Me$) against log K for the ionization of the corresponding benzoic acids ($ArCO_2H$).

In this case, substituents such as *p*-Me, *p*-OMe, *p*-Cl, *p*-Br, *m*-Cl, *m*-Br, *m*-NO_2 and *p*-NO_2 all lie close to a single straight line. The unsubstituted compound (H) also fits the correlation. This confirms that when substituent effects are transmitted mainly through electronic influences (inductive and resonance effects), a reliable linear free-energy relationship is obtained.

4.4.1 Non-conformity of *o*-substituted and Aliphatic Compounds

The reason for the failure of *ortho*-substituted benzene derivatives and aliphatic compounds to obey the same correlation is not difficult to understand. In the base-catalysed hydrolysis of esters, the rate-determining step involves nucleophilic attack of hydroxide ion on the carbonyl carbon to form a tetrahedral intermediate.



For *m*- or *p*-substituted esters:

- The substituent is positioned away from the reaction centre.
- In the relatively rigid aromatic system, it exerts essentially no steric effect on the approach of the nucleophile.
- The reaction rate is therefore governed predominantly by electronic effects.

For *o*-substituted esters:

- The substituent is located adjacent to the reaction centre.
- During nucleophilic attack by OH^-, steric crowding increases in the transition state.
- This additional steric interaction destabilizes the transition state and affects the rate independently of electronic effects.

Thus, *ortho* substitution introduces steric effects that are not accounted for in a simple electronic correlation, causing deviation from the Hammett line.

For aliphatic esters:

- The structural environment differs significantly from the rigid aromatic system.
- Electronic transmission through an aliphatic chain is not directly comparable to that through a benzene ring.
- As a result, these compounds also deviate from the aromatic correlation.

4.5 THE HAMMETT EQUATION

Although linear correlations were observed for many reactions of meta- and para-substituted benzene derivatives, a simple mathematical expression was still required to make these relationships practically useful for predicting or analysing new reactions. It was Hammett who provided such a quantitative expression.

4.5.1 Derivation of the Hammett Equation

A straight-line relationship can generally be represented by the equation,

$$y = mx + c$$

where, m is the slope of the line and c is the intercept.

If we apply this general linear form to the straight-line correlation obtained for substituted aromatic systems (as shown in Fig. 3), the equation can be written as:

$$\log k_X = \rho \log K_X + c \quad \textbf{(4)}$$

Here,

- k_X represents the rate constant for the reaction of a benzene derivative containing substituent X

- K_X represents the equilibrium constant (usually for ionization of the corresponding substituted benzoic acid)
- ρ is the slope of the straight line (reaction constant)
- c is the intercept of the line.

A similar equation may be written for the unsubstituted compound, when X = H

$$\log k_H = \rho \log K_H + c \quad \textbf{(5)}$$

If equation (5) is subtracted from equation (4), the intercept c is eliminated, giving:

$$\log k_X - \log k_H = \rho(\log K_X - \log K_H) \quad \textbf{(6)}$$

which can also be written as

$$\log (k_X / k_H) = \rho \log (K_X / K_H) \quad \textbf{(7)}$$

This step is important because it removes the constant term and expresses the relationship entirely in terms of differences relative to the unsubstituted compound. Thus, the change in rate caused by substituent X is directly proportional to the corresponding change in equilibrium constant.

4.5.2 Substituent Constant, σ_x

Hammett selected the ionisation of meta- and para-substituted benzoic acids in water at 25°C as the standard reference reaction for defining substituent effects. This reaction was chosen because reliable and accurate aqueous ionisation constant (K_X) data were already available in the literature for a wide range of m- and p-substituted benzoic acids.

If K_X represents the ionisation constant of a substituted benzoic acid and K_H of unsubstituted benzoic acid, Hammett defined the substituent constant, σ_X as:

$$\sigma_X = \log (K_X/K_H) \quad \textbf{(8)}$$

The substituent constant σ_X represents the electronic effect of a substituent relative to hydrogen. For a given substituent in a specific position (meta or para), the value of σ_X remains constant, regardless of the reaction in which the substituted benzene derivative participates. In other words, σ_X is a property of the substituent and its position on the aromatic ring, not of the reaction.

Using known values of K_X (or pK_a) for the aqueous ionisation of m- and p-substituted benzoic acids, the corresponding σ values can be calculated. A representative set of values is given below:

Substituent (X)	**$\sigma_{m\text{-}x}$**	**$\sigma_{p\text{-}x}$**
Me	–0.07	–0.17
H	0	0

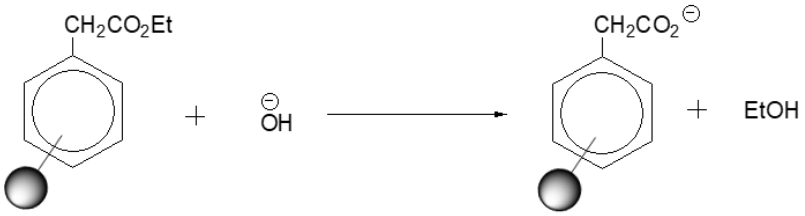
Substituent (X)	$\sigma_{m\text{-}x}$	$\sigma_{p\text{-}x}$
MeO	+0.12	–0.27
HO	+0.12	–0.37
F	+0.34	+0.06
Cl	+0.37	+0.23
Br	+0.39	+0.23
$COCH_3$	+0.38	+0.50
CN	+0.56	+0.66
NO_2	+0.71	+0.78

As expected, the value of σ for a given substituent depends on its position on the aromatic ring. The substituent effect in the *meta* position differs from that in the *para* position because resonance interactions operate more effectively at the para position, while the meta position mainly reflects inductive effects.

4.5.3 Reaction Constant, *ρ*

Having obtained a range of substituent constants, σ_X , it becomes possible to determine the value of the reaction constant, ρ for any reaction of interest. This is usually done graphically.

For example, consider the base-catalysed hydrolysis of *meta*- and *para*-substituted ethyl benzoates:



From kinetic measurements, we determine:

- k_H , the rate constant for the unsubstituted ester
- k_X , the rate constants for at least three differently substituted esters

Since the values of σ_X for these substituents are already known, we can plot log (k_X / k_H) against σ_X. According to the Hammett equation,

$$\log\ (k_X / k_H) = \rho\sigma_X$$

the slope of the resulting straight line gives the value of ρ for the reaction. For this hydrolysis carried out in aqueous ethanol at 30°C, the value of ρ is found to be **+0.82**. The values of ρ for a wide range of reactions for *m*- and *p*-substituted benzene derivatives are listed below:

	Reaction	Type	ρ
1.	Reaction of substituted anilines ($ArNH_2$) with 2,4-dinitrochlorobenzene in EtOH (25°C)	**k**	**–3.19**
2.	Reaction of substituted anilines ($ArNH_2$) with benzoyl chloride in C_6H_6 (25°C)	**k**	**–2.69**
3.	Solvolysis of substituted benzyl chlorides ($ArCH_2Cl$) in aqueous acetone (69.8°C)	**k**	**–1.88**
4.	Reaction of substituted phenoxides (ArO^-) with ethyl iodide in EtOH (25°C)	**k**	**–0.99**
5.	Esterification of substituted benzoic acids ($ArCO_2H$) with MeOH (acid-catalysed, 25°C)	**k**	**–0.09**
6.	Acid-catalysed hydrolysis of substituted methyl benzoates in aqueous MeOH (25°C)	**k**	**+0.03**
7.	Ionisation of substituted phenylacetic acids ($ArCH_2CO_2H$) in H_2O (25°C)	**K**	**+0.47**
8.	Reaction of substituted benzyl chlorides with iodide ion in acetone (20°C)	**k**	**+0.79**
9.	Base-catalysed hydrolysis of substituted ethyl benzoates in aqueous ethanol (30°C)	**k**	**+0.82**
10.	Ionisation of substituted benzoic acids in water (25°C) — *standard reaction*	**K**	**+1.00**
11.	Ionisation of substituted phenols (ArOH) in water (25°C)	**K**	**+2.01**
12.	Reaction of substituted benzonitriles (ArCN) with H_2S (base) in EtOH (60.6°C)	**k**	**+2.14**
13.	Base-catalysed hydrolysis of substituted ethyl benzoates in aqueous EtOH (25°C)	**k**	**+2.51**
14.	Ionisation of substituted anilinium ions in water (25°C)	**K**	**+2.73**

The standard reaction, aqueous ionisation of m- and p-substituted benzoic acids at 25°C has, ρ = 1, by definition. For any particular reaction under specified conditions, the value of ρ remains constant regardless of which m- or p-substituent is present.

4.6 STERIC EFFECTS

In the earlier treatment of linear free energy relationships, application of the Hammett equation was restricted to meta- and para- substituted benzene derivatives. The reactions of ortho- substituted derivatives and aliphatic compounds were excluded because steric and other effects led to deviations from linearity. In such cases, plots of log (k/k_0) against σ were frequently curved or irregular. The divergence from linearity arises because the Hammett equation primarily accounts for polar (electronic) effects of substituents. In ortho-substituted aromatic compounds and in aliphatic systems, steric hindrance and solvation effects significantly influence the reaction rate, thereby disturbing simple linear correlations.

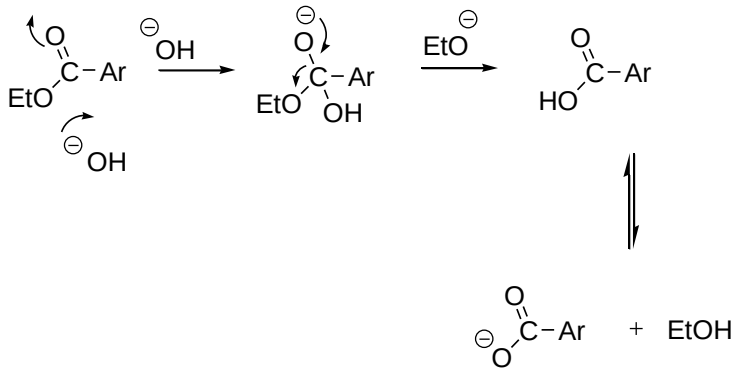
The diagnostic value of deviations from Hammett linearity stimulated attempts to extend the equation to a broader range of compounds. The most general and successful extension was proposed by Robert W. Taft, leading to the formulation of the Taft equation.

4.6.1 Taft Equation

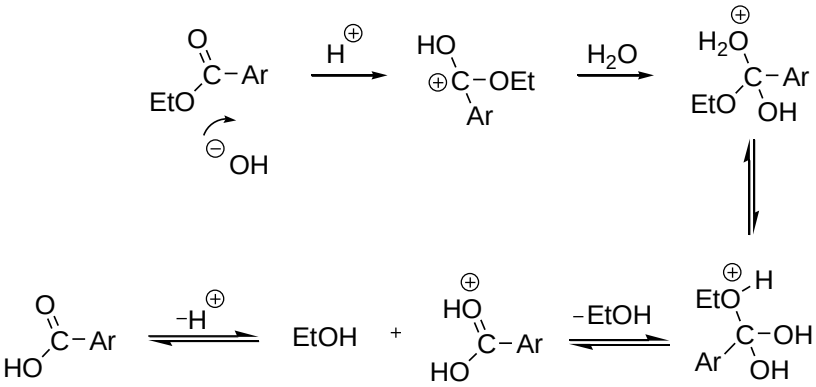
Taft began by examining the hydrolysis of substituted benzoate esters under base-catalysed conditions and acid-catalysed conditions. For base-catalysed hydrolysis, the reaction constant was found to be ρ = + 2.51. This large positive value indicates considerable sensitivity of the reaction to substituent electronic effects. In the rate-determining step, nucleophilic attack by OH^- on the carbonyl carbon leads to development of negative charge in the transition state, which is stabilized by electron-withdrawing substituents.

For acid-catalysed hydrolysis, the reaction constant was, ρ = + 0.03. This value is nearly zero, indicating that the reaction rate is almost independent of substituent effects. Although redistribution of positive charge occurs in the slow step, the observed rate constant (k_{obs}) depends on both the equilibrium constant of the preceding protonation step (K_1) and the rate constant of the slow step (k_2). The substituent effects in these two steps largely compensate each other, resulting in an overall ρ value close to zero.

Base-catalysed hydrolysis:

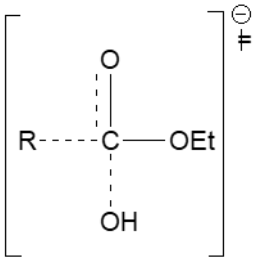


Acid-catalysed hydrolysis:

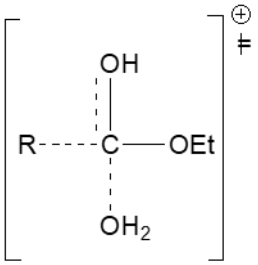


Extension to Aliphatic Esters

Taft extended this comparison to aliphatic esters of the type RCO_2Et. The transition states for the rate-determining step in both acid- and base-catalysed hydrolysis are tetrahedral in structure and closely similar in geometry. The only difference is that the transition state in acid hydrolysis contains two additional protons. Since protons are very small, their steric influence is negligible. Consequently, the steric effect exerted by the substituent R is substantially the same in both reactions. Because the steric contributions are essentially identical in acid- and base-catalysed hydrolysis, they cancel when the two reactions are compared. This permits isolation of the polar effect of substituent R.



T.S. for base catalyzed hydrolysis



T.S. for acid catalyzed hydrolysis

On this basis, Taft proposed a Hammett-type relationship:

$$\log [k_R/k_0]_{base} - \log [k_R/k_0]_{acid} = \rho^* \sigma_{R^*} \quad \textbf{(9)}$$

The value of ρ^* was obtained by subtracting the ρ value for acid-catalysed hydrolysis (0.03) from that for base-catalysed hydrolysis (2.51).

$$\rho^* = 2.51 - 0.03 = 2.48$$

Methyl (Me) was chosen as the reference substituent, and by definition, $\sigma^*(Me) = 0$. By measuring rate constants for a series of aliphatic esters and applying the above equation, values of σ* for various substituents were determined. These σ* constants represent the pure polar effect of aliphatic substituents, largely free from steric contributions.

The more general Taft relationship is expressed as:

$$\log k_R/k_{Me} = \rho * \sigma_{R} * \quad \textbf{(10)}$$

This equation has been successfully applied to a variety of reactions of aliphatic compounds, yielding linear correlations and extending the scope of linear free energy relationships beyond aromatic systems. Taft's treatment thus provided a systematic method for separating polar and steric effects and enabled quantitative correlation of reaction rates in aliphatic compounds.

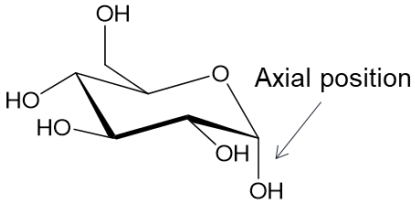
4.7 EFFECTS OF CONFORMATION ON REACTIVITY

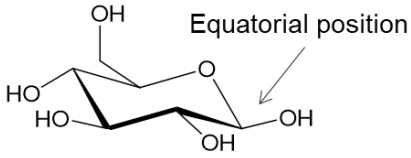
There is a profound effect of conformation on chemical reactivity due to the stereo-electronic component and steric factors associated with the molecules.

4.7.1 Anomeric Effect

The anomeric effect is a stereo-electronic phenomenon observed in heterocyclic systems, most notably in carbohydrates like glucose. It describes unexpected stability of certain conformations that would normally be considered less stable based solely on steric factors. Generally, anomeric effect renders extra stability to the axial orientation of an electronegative group (carrying a lone pair of electrons) at the anomeric carbon (C-

1) over the equatorial orientation. While steric rules for cyclohexanes generally favor equatorial positions to avoid 1,3-diaxial interactions, certain pyranose systems deviate from this rule.

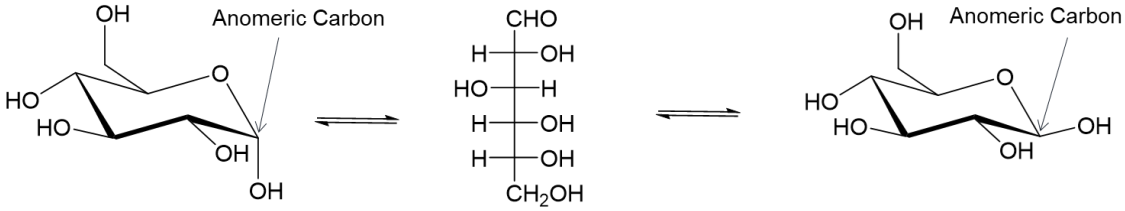




The Classic Example of D-Glucose

The term was first coined by, Lemieux to explain why the alpha-anomer of methyl D-glucose (with an axial -OCH_3 group) is more stable than the beta-anomer (with an equatorial -OCH_3 group), despite the beta-anomer being predicted as more stable by standard conformational analysis.

* Anomeric Carbon: C-1 in the cyclic hemiacetal form of glucose is called the anomeric carbon.



α -anomer

Structure of D- glucose
in Fischer projection

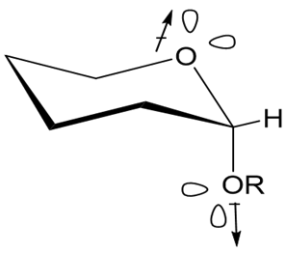
β -anomer

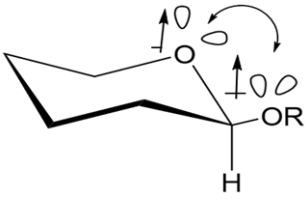
Causes of the Anomeric Effect

There are two primary scientific schools of thought regarding its cause:

A. Destabilizing Electronic Effect (Electrostatic Repulsion)

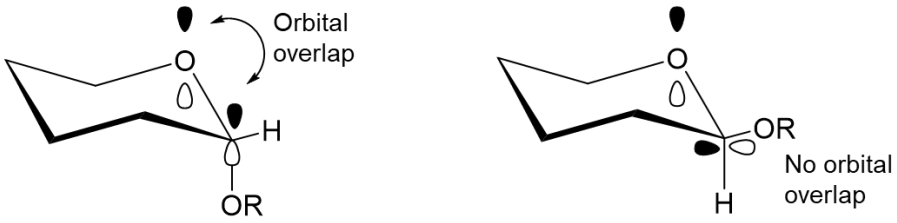
Some chemists argue that the effect is due to dipole-dipole repulsion or electron pair-electron pair repulsion (also known as the rabbit ear effect). In the equatorial conformer, the dipoles of the ring oxygen and the substituent oxygen are somewhat parallel, leading to unfavourable repulsion. In the axial conformer, these dipoles are directed away from each other, reducing repulsion.





B. Stabilizing Electronic Effect (Hyperconjugation)

Others consider it a stabilizing effect that occurs when a lone pair of the ring oxygen is anti-periplanar to the polar C-X bond (where X = OR, halogen, etc.). The p-orbital of the ring oxygen overlaps with the σ^* (antibonding) orbital of the C-X bond. This is equivalent to double-bond no-bond resonance, providing extra stability to the axial conformer.



4.7.2 Neighbouring Group Participation (NGP)

Neighbouring Group Participation (NGP) refers to the direct involvement of a group adjacent to a reaction center in the course of a chemical reaction. Instead of behaving as a passive substituent, the neighbouring group actively participates by temporarily forming a bond to the reaction center. This participation usually leads to the formation of a cyclic or bridged intermediate and results in unusual stereochemistry and/or remarkable rate acceleration. NGP is one of the clearest examples of symphoria Greek: *sympherein*, to bring together usefully (*sym*, together + *pher/phor*, *to bring*), where reacting groups are already positioned within the same molecule in a favorable spatial arrangement.

In most ordinary nucleophilic substitution reactions, an external nucleophile attacks a carbon bearing a leaving group. In NGP, however, a neighbouring atom or group within the same molecule acts as an internal nucleophile. Because it is already present and properly oriented, it enjoys a high effective concentration and avoids the entropic and solvent-related disadvantages faced by external nucleophiles. The result is often a faster reaction and distinctive stereochemical outcomes.

In Unit 7, you will learn in detail about neighbouring group participation with various examples.

W CHECK YOUR PROGRESS

Q1. How does the Eyring equation relate the rate constant to the free energy of activation?

Q2. Why did Hammett exclude ortho-substituted benzene derivatives from his linear correlations?

Q3. In the Hammett equation, what does the substituent constant (σ_x) represent?

Q4. What reaction did Hammett select as the standard reference for defining substituent effects?

Q5. How did Taft separate polar and steric effects in aliphatic compounds?

Q6. What is the anomeric effect?
Q7. What are the two primary scientific theories explaining the causes of the anomeric effect?
Q8. What is Neighbouring Group Participation (NGP)?
Q9. What does the value of the reaction constant (ρ) indicate in a Hammett plot?
Q10. What is "anchimeric assistance" in the context of neighbouring group?

2 4.8 LET US SUM UP

- Linear energy free relationship (LFER) provides a quantitative basis to connect molecular structure with chemical reactivity.
- An LFER is based on the observation that changes in free energy associated with related reactions or equilibria often show a linear correlation with substituent or structural parameters.
- LFER not only provide quantitative insight into substituent effects but also serve as powerful tools for mechanistic analysis.
  - The first clear example of a linear free-energy relationship was reported by Hammett.
  - Application of the Hammett equation was restricted to meta- and para-substituted benzene derivatives. The reactions of ortho- substituted derivatives and aliphatic compounds were excluded because steric and other effects led to deviations from linearity.
  - Taft equation provided a systematic method for separating polar and steric effects and enabled quantitative correlation of reaction rates in aliphatic compounds.
  - Anomeric effect is the extra stability of an axial orientation of an electronegative group (carrying a lone pair of electrons) at the anomeric carbon (C-1) over the equatorial orientation.
  - Neighbouring group actively participates by temporarily forming a bond to the reaction center. This participation usually leads to the formation of a cyclic or bridged intermediate and results in unusual stereochemistry and/or remarkable rate acceleration.

K 4.9 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: According to the Eyring equation, the rate constant depends exponentially on the free energy of activation. This is expressed in a linear logarithmic form as $\log k = -2.303RT\,\Delta G^{\ddagger} + \log (k_B T / h)$.

Answer to Q2: Ortho-substituted derivatives were excluded because the substituent is located adjacent to the reaction centre. During nucleophilic attack, this introduces steric crowding that destabilizes the transition state, affecting the rate independently of electronic effects.

Answer to Q3: The substituent constant represents the electronic effect of a substituent relative to hydrogen. It is a property of the specific substituent and its position (meta or para) on the aromatic ring, rather than the reaction itself.

Answer to Q4: Hammett selected the aqueous ionisation of meta- and para-substituted benzoic acids at 25°C as the standard reference reaction.

Answer to Q5: Taft compared base-catalysed and acid-catalysed hydrolysis of aliphatic esters. He noted that their transition states are closely similar in geometry, meaning the steric contributions are essentially identical and cancel each other out when the two reactions are compared, isolating the pure polar effect.

Answer to Q6: The anomeric effect is a stereo-electronic phenomenon, commonly observed in carbohydrates like glucose, where an axial orientation of an electronegative group at the anomeric carbon (C-1) is unusually more stable than the equatorial orientation.

Answer to Q7: The two primary theories are a destabilizing electronic effect caused by electrostatic repulsion (also known as the rabbit ear effect) and a stabilizing electronic effect known as hyperconjugation.

Answer to Q8: NGP refers to the direct involvement of an adjacent group in a chemical reaction. Instead of acting passively, this neighbouring group acts as an internal nucleophile and temporarily forms a bond to the reaction center.

Answer to Q9: The reaction constant (ρ) represents the slope of the straight line in a Hammett plot. A large positive value indicates considerable sensitivity of the reaction to substituent electronic effects

Answer to Q10: Anchimeric assistance occurs during an S_N2-like migration when the neighbouring group assists in expelling the leaving group in a single concerted step.

O 4.10 FURTHER READING

- Sykes, P., A guidebook to Mechanism in Organic Chemistry, Pearson.
- Carroll, F. A., Perspectives on Structure and Mechanism in Organic Chemistry, Brooks/Cole.
- Carey, F. A. and Sundberg, R. J., Advanced Organic Chemistry Part A: Structure and Mechanisms, Springer.
- Isaacs, N. S., Physical Organic Chemistry, Longman.
- Bruckner, R., Advanced Organic Chemistry: Reaction Mechanisms, Academic Press.

M 4.11 MODEL QUESTIONS

Q1. What is the fundamental assumption of Linear Free Energy Relationships (LFER)?

Q2. What two quantities did Hammett plot against each other to create the first linear free energy relationship graph?

Q3. Why do aliphatic esters fail to correlate properly on a standard Hammett plot?

Q4. What is the mathematical expression for the Hammett equation derived by eliminating the intercept?

Q5. In the acid-catalysed hydrolysis of benzoate esters, why is the reaction constant (ρ) nearly zero?

Q6. What reference is used in Taft equation?

Q7. What is the primary advantage of the Taft equation over the standard Hammett equation?

Q8. What is the definition of the substituent constant (σ_x) in terms of equilibrium constants?

Q9. In a cyclic carbohydrate like D-glucose, which carbon is identified as the anomeric carbon? C-1 in the cyclic hemiacetal form of glucose is called the anomeric carbon.

UNIT 5: CHEMOSELECTIVITY, REGIOSELECTIVITY, STEREOSELECTIVITY AND STEREOSPECIFICITY

UNIT STRUCTURE

5.1 Learning Objectives
5.2 Introduction
5.3 Reactivity-selectivity principle
5.4 Chemoselectivity
5.5 Regioselectivity
5.6 Stereoselectivity
5.7 Stereospecificity
5.8 Let Us Sum Up
5.9 Further Reading
5.10 Answers to check your progress
5.11 Model Questions

5.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- learn the concept of chemoselectivity, regioselectivity, stereoselectivity and stereospecificity.
- define chemoselectivity with relevant examples.
- define regioselectivity with relevant examples.
- define stereoselectivity and stereospecificity and differentiate between them.

5.2 INTRODUCTION

In this unit, we will discuss different types of selectivity in chemical reactions. Before discussing these in details, at first we have to know the basic concept of reactivity. Reactivity of a chemical compound refers to its tendency to undergo a chemical reaction. This characteristic is crucial for understanding how different compounds interact with one another, influencing their behaviour and transformation in various chemical processes. The reactivity of organic compounds mainly depends on their functional groups and the rest of the molecule generally do not take part.

Alkanes, the simplest class of organic molecules are extremely unreactive because they contain no functional group. However, their un-reactivity has been considered as an advantage to use them as solvents. For example, pentane and hexane are often used as solvents in chemical laboratory. It is interesting to note that the reactivity-selectivity principle was primarily discussed on the classic example of Free-Radical Halogenation, which involves alkane as substrate.

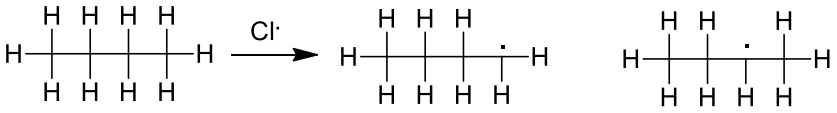
Although C=C double bond and C≡C triple bonds are not purely functional groups, consisting of, say, oxygen or nitrogen atoms, C=C double bond and C≡C triple bonds impart reactivity to an organic molecule. So it is pertinent to consider C=C double bond and C≡C triple bond as functional groups. While we will discuss reactivity and selectivity, we will take these into account.

5.3 REACTIVITY-SELECTIVITY PRINCIPLE

In a reaction, there are at least two components, in which we can talk about selectivity - Substrate and Reagent.

A relationship between reactivity and selectivity was once considered as general principle in organic chemistry. That stated – '**in a set of similar reactions, the more reactive a reagent is, the less selective it is** or vice versa, *i.e*, **the less reactive is the reagent, the more selective it is'**.

The classic example of reaction, in which the reactivity-selectivity principle was illustrated, is the **halogenation of alkane**. When a chlorine radical reacts with butane, it can abstract a hydrogen atom from a terminal carbon, thereby forming a primary alkyl radical or it can abstract a hydrogen atom from an internal carbon, thereby forming a secondary alkyl radical.



1^0–radical 2^0–radical

From experimental observation, it was already established that at room temperature, it is 5 times easier for a chlorine radical to abstract a hydrogen atom from a tertiary carbon than from a primary carbon and it is 3.8 times easier to abstract a hydrogen atom from a secondary carbon atom than from a primary carbon.

Relative rates of formation of alkyl radical by a chlorine radical at room temperature

tertiary > *secondary* > *primary*

5 > 3.8 > 1

For example, in the chlorination of alkanes, the rate of hydrogen substitution is

tertiary > *secondary* > *primary*

If the temperature is raised above 300 °C, chlorine becomes more reactive and the substitution becomes less selective, the rate of substitution being the same for 1°-, 2°- and 3°-hydrogen. A possible basis for this reactivity-selectivity principle is that more reactive the reagent is, the more likely it will react at every collision, i.e., there would be less discrimination between the various positions of attack by the reagent. The less reactive the reagent is, the more will be the electronic distribution in the substrate play a part, thereby resulting in more discrimination at the various positions.

In its attack on alkanes, the bromine atom is much more selective than the chlorine atom (with relative rate factors of 1600 **:** 82 **:** 1 as compared with 5.0 **:** 3.8 **:** 1). It is also much less reactive than the chlorine atom (only 1/375000 as reactive toward methane). This is

just one example of a general relationship: in a set of similar reactions, the less reactive the reagent, the more selective it is in its attack. In the attack by the comparatively unreactive bromine atom, the transition state is reached late in the reaction process, after the alkyl group has developed considerable radical character. In the attack by the highly reactive chlorine atom, the transition state is reached early, when the alkyl group has gained very little radical character.

However, this is a qualitative principle only and cannot be applied as a rule of thumb, Limitations of this principle are:

i) it only applies to processes which obey a rate- equilibrium relationship;
ii) it only operates for relatively simple processes;
iii) reactions in which solvation factors contribute substantially to the overall energy change, the principle may break down.

Though the Reactivity-Selectivity Principle was put forward as a general principle, later, after extensive studies on various reactions it was found that the principle cannot be generalised to all types of reactions. The theoretical basis of the Reactivity-Selectivity Principle may be useful in cases where it is supported by experiment. More useful frameworks for understanding selectivity may be derived from specialized analysis of reaction classes. A conclusive general theory to explain any relationship between reactivity and selectivity is still not available.

So, the **Reactivity-Selectivity Principle (RSP)**, once a tenet of organic chemistry, was more or less abandoned by 1980.

But selectivity in organic chemistry is a fundamental aspect, as selectivity plays a crucial role in determining the outcome of reactions. Understanding of selectivity is essential for synthesis of complex molecules with desired properties. Selectivity is the preference of a reaction to occur in a particular manner, yielding a specific product. So to synthesize a product with desired structure and stereochemistry and to minimize by-products, understanding of selectivity is important.

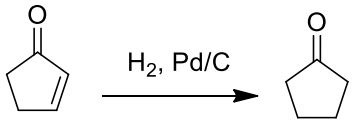
There are three different types of selectivity in organic reaction, viz., **Chemoselectivity, Regioselectivity and Stereoselectivity**. Diastereoselectivity, enantioselectivity and Stereospecificity are different types of selectivities under stereoselectivity.

5.4 CHEMOSELECTIVITY

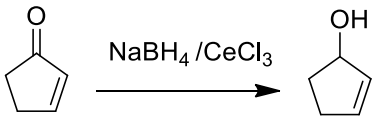
In a bifunctional/multifunctional compound, if a reagent reacts with one of the functional groups preferentially, even though the other group(s) is/are apparently susceptible to the reaction condition, the reaction is called a **Chemoselective reaction** and the reaction is said to display **Chemoselectivity**.

Examples:

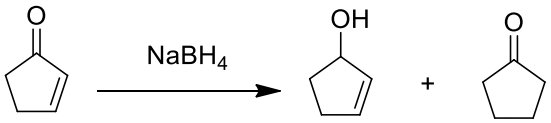
1) Chemoselective reduction of C=C over C=O



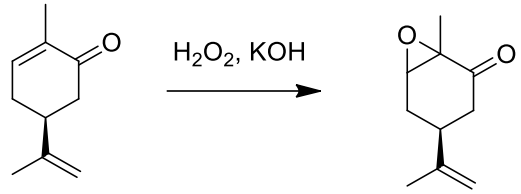
2) Chemoselective reduction of C=O over C=C



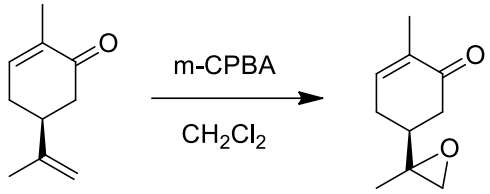
When $NaBH_4$ is used without $CeCl_3$, then both the functional groups are reduced without selectivity.



3) Chemoselective epoxidation of α, β-unsaturated ketones over alkenes



4) Chemoselective epoxidation of alkenes over α, β-unsaturated ketones



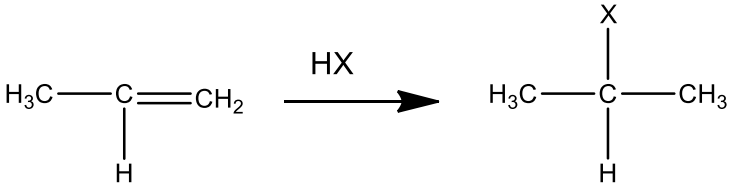
5.5 REGIOSELECTIVITY

Regioselectivity is the preferential formation of one structural or positional isomer over others in a chemical reaction, where bond-making or bond-breaking occurs at a specific location. It is commonly observed in addition reactions to unsymmetrical alkenes (e.g., addition reactions following Markovnikov's and Anti-Markovnikov's rule) and substitutions. Elimination reactions also exhibit regioselectivity following Saytzef's Rule. Regioselectivity is often controlled by steric or electronic factors.

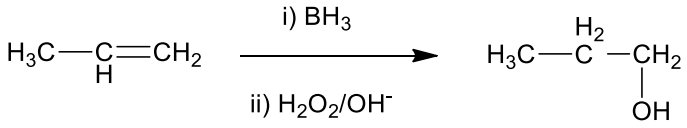
Hence, a **regioselective reaction** is a reaction which predominantly produces one of several possible structural isomers.

Examples of regioselective reactions:

Addition of hydrogen halide to alkene: When hydrogen halides add to alkenes, hydrogen adds to the carbon with **more** hydrogen atoms. This is called Markovnikov's addition.

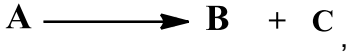


Hydration of alkenes via Hydroboration-Oxidation: When hydration of alkenes is carried out via Hydroboration-Oxidation, hydrogen adds to the carbon with **less** hydrogen atoms. This is called Anti-Markovnikov's addition.



5.6 STEREOSELECTIVITY

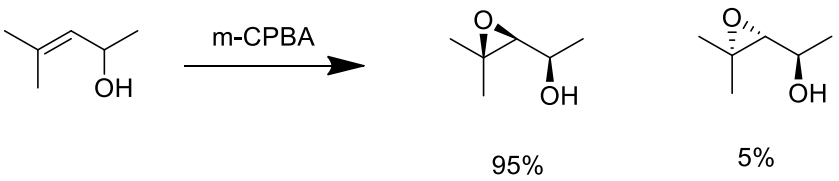
Stereoselective Reactions are those, where one stereoisomer of a mixture is produced (or destroyed) more rapidly than another.
In other words, a reaction where one stereoisomer of a mixture of product is formed preferentially over another is called stereoselective reaction. For example, in the following reaction, if B is formed preferentially than C, where B and C are stereoisomers, then the reaction is stereoselective.



where B is formed preferentially over C.

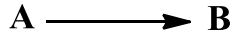
A stereoselective reaction is one in which the reactant is not **necessarily** chiral.

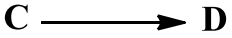
One example of stereoselective reaction is the epoxidation of an allylic alcohol by *m*-CPBA. The orientation of *m*-CPBA toward the double bond can be directed by the hydroxyl group and the allylic alcohol epoxidizes to give a 95:5 ratio of diastereoisomers.



5.7 STEREOSPECIFICITY

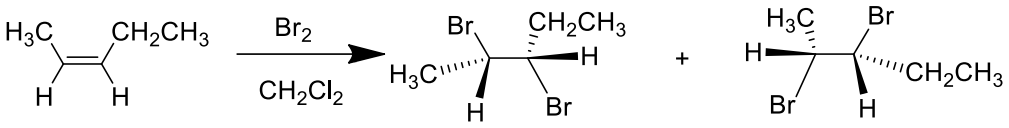
In a **Stereospecific reaction**, the reactants can exist as stereoisomers and each stereoisomeric reactant forms different stereoisomeric product or a different set of stereoisomeric products.
For example, in the following reactions, where A and C are stereoisomers and B and D are stereoisomers. If A forms only the stereoisomer B and C forms only the stereoisomer D, then the reactions shall be called as stereospecific reactions.





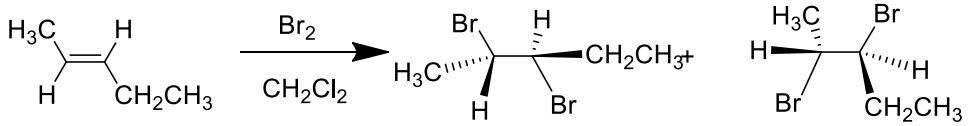
A stereospecific reaction is also stereoselective.
But a stereoselective reaction is *not necessarily* stereospecific.

For example, the addition of Br_2 to *cis*-2-pentene forms only the threo enantiomers.



cis-2-pentene Threo enantiomers

Similarly, the addition of Br_2 to *trans*-2-pentene forms only the erythro enantiomers. Because the *cis* and *trans* isomers form different products, the reaction is stereospecific.



trans-2-pentene Erythro enantiomers

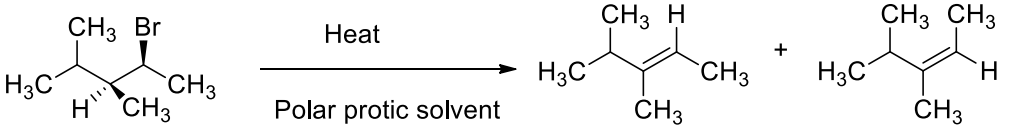
The reaction is also stereoselective, because only two of the four stereoisomers are formed in either case.

W CHECK YOUR PROGRESS

Q1. If a molecule containing both a keto and an ester group is reduced by sodium borohydride ($NaBH_4$) only the keto group is reduced leaving the ester group unreacted. What type of selectivity is this?

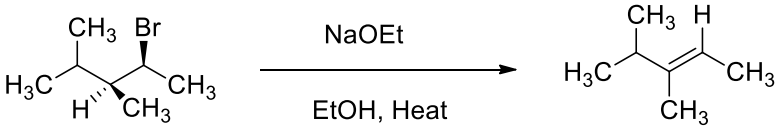
Q2. Addition of HBr to propene gives 2-bromopropane as the main product instead of 1-bromopropane. What type of selectivity is this?

Q3. In the following example of elimination via E1 pathway, the reaction yields the alkene stereoisomer, where the two bulkiest groups are *trans* (*E*) to each other. However, the (*Z*) isomer is also formed as minor product. What type of selectivity is this?



E-alkene (Major) Z-alkene, Minor

Q4. If the substrate alkane of the above example is treated with strong base like NaOEt, then the elimination follows E2 pathway and results in formation of the E-alkene only. What type of selectivity is this?



E-alkene (only product)

2 5.8 LET US SUM UP

- The reactivity of organic compounds mainly depends on their functional groups and the rest of the molecule generally do not take part.
- A classical relationship stated that – 'in a set of similar reactions, the more reactive a reagent is, the less selective it is or vice versa, i.e, the less reactive is the reagent, the more selective it is', which was known as Reactivity-Selectivity Principle (RSP).
- RSP is qualitative principle only and cannot be applied as a rule of thumb.
- There are three different types of selectivity in organic reactions, viz., Chemoselectivity, Regioselectivity and Stereoselectivity.
- Diastereoselectivity and Enantioselectivity are two types of Stereoselectivity.
- Chemoselectivity is defined as the selective reactivity of a functional group in the presence of other functional groups, allowing for specific chemical reactions to occur without affecting other parts of the molecule
- Regioselectivity is defined as the selective formation of one regioisomer as the major product.
- Stereoselectivity is defined as the selective formation of one stereoisomer over another.
- Stereospecificity is defined as the formation of a specific stereoisomer as the exclusive product. In other words, a stereospecific reaction proceeds in such a way that it leads to the formation of a particular stereoisomer, and no other stereoisomers are generated as byproducts.
- A stereospecific reaction is also stereoselective. But a stereoselective reaction is *not necessarily* stereospecific

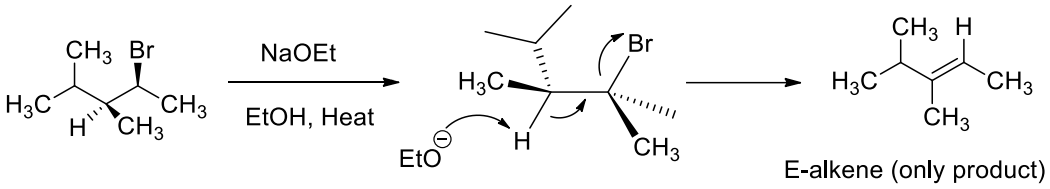
K 5.9 ANSWERS TO CHECK YOUR PROGRESS

Answer to the Q1: The reaction is chemoselective. Because only one functional group is reduced selectively in presence of the other.

Answer to the Q2: The reaction is regioselective. Because one positional isomer is formed as main product.

Answer to the Q3: The reaction is stereoselective. Because only one isomer is produced preferentially over the other.

Answer to the Q4: This reaction is also stereoselective. But it is stereospecific too. Because the stereochemistry of the product is determined by the stereochemistry of the starting material. Here, for the E2 pathway anti-arrangement between C-H and C-Br (the leaving group) is required which results only in the formation of the E-alkene.



E-alkene (only product)

O 5.10 FURTHER READING

- Robert Thornton Morrison, Robert Neilson Boyd, S. K. Bhattacharjee Organic Chemistry, 7th Edition, 2011, Pearson
- Paula Yurkanis Bruice, Organic Chemistry, 7th Edition, Pearson
- Herbert Mayr, Armin R Ofial, The reactivity-selectivity principle: an imperishable myth in organic chemistry, Angew Chem Int Ed Engl, 2006, 45(12):1844-54, DOI: 10.1002/anie.200503273

M 5.11 MODEL QUESTIONS

Q1. Write the statement of Reactivity-Selectivity Principle. Comment on its validity.
Q2. Define chemoselectivity. Give one example of chemoselective reduction.
Q3. Explain- “A stereospecific reaction is also stereoselective. But a stereoselective reaction is not necessarily stereospecific”.

UNIT 6: EXAMPLES OF SELECTIVITY IN ORGANIC REACTION

UNIT STRUCTURE

6.1 Learning Objectives
6.2 Introduction
6.3 Examples of Chemoselective Reactions
6.4 Examples of Regioselective Reactions
6.5 Examples of Stereoselective Reactions
6.6 Examples of Stereospecific Reactions
6.7 Let Us Sum Up
6.8 Answers to Check Your Progress
6.9 Further Reading
6.10 Model Questions

6.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- illustrate chemoselectivity, regioselectivity, stereoselectivity and stereospecificity with various examples of reactions.
- predict the most possible products in reactions where there is possibility of formation of a set of different products
- suggest suitable reagents for obtaining a desired product in a reaction, where there is a range of similar reagents with varying degree of reactivity.
- Streamline a reaction sequence by choosing proper reagents and reagent conditions with the knowledge of selectivity

6.2 INTRODUCTION

Selectivity: Most organic molecules contain more than one functional group, and most functional groups can react in more than one way. So organic chemists often have to predict which functional group will react, where it will react, and how it will react. These questions are what we call selectivity.
As you have already learnt in the previous Unit, that there are three main types of selectivity: chemoselectivity, regioselectivity, and stereoselectivity.

Chemoselectivity is which functional group reacts;

Regioselectivity is where it reacts.

Stereoselectivity is how the group reacts with regard to the stereochemistry of the product.

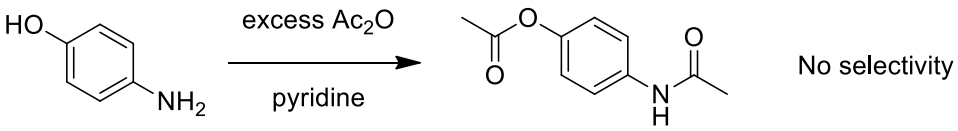
In this Unit, you will learn about these selectivities in various kind of organic reactions with suitable examples.

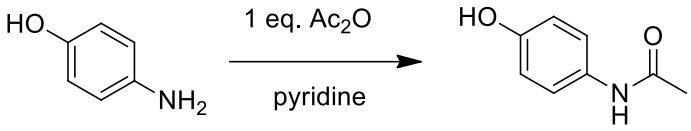
6.3 CHEMOSELECTIVE REACTION

Chemoselectivity is the selectivity of a reagent or a reaction condition for one functional group over another. Chemoselectivity is exhibited by different types of organic reactions and reagents. We will discuss some examples, which will suitably represent the chemoselectivity of the reactions.

1) Chemoselectivity in nucleophilic substitution: Acylation of an aromatic amino group in presence of a phenolic –OH group:

Let us take the synthesis of the painkiller (antipyretic analgesic), paracetamol. 4-Aminophenol could react with acetic anhydride at both nitrogen and oxygen to give a compound containing an amide and an ester functional group. This is what happens on heating with **excess** acetic anhydride (Ac_2O) in toluene.



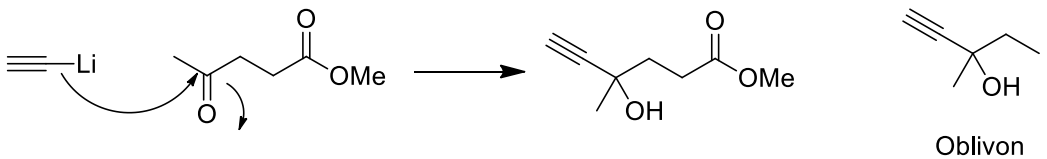


Chemoselective acylation of -NH_2 group

But with just one equivalent of acetic anhydride in the presence of a base (pyridine), only the NH_2 group is acylated to generate paracetamol as the product. This is an excellent example of **chemoselectivity**arising out of higher nucleophilicity of the -NH_2 group than the OH group.

3) Chemoselectivity in addition of organometallic reagents to carbonyl groups

We know that ketones are more reactive than esters, amides and carboxylates, because the ketone lacks the additional heteroatom present in the other groups that can stabilize the carbonyl group by conjugation with the lone pair of heteroatom. Therefore, ketones are more reactive towards Grignard reagents and organolithiums than esters. This selectivity has been utilized in developing anticonvulsants related to a tranquillizer, oblivon. To accomplish this synthesis, lithium acetylide is reacted to ketones, and a tertiary alcohol is prepared by chemoselective reaction of the keto group in the presence of the ester.



Oblivon

4) Chemoselectivity in reductions

Chemoselective reductions can be carried out by using chemoselective reducing agents. Here is an account of such reducing reagents, from which suitable reagent may be

selected for various compounds having functional groups of unequal reactivity toward reducing reagents. Lithium aluminium hydride ($LiAlH_4$) reduces almost any carbonyl group without selectivity. Sodium borohydride ($NaBH_4$) reduces aldehyde or a ketone in the presence of an ester group.

These chemoselectivities are typical of these two most commonly used reducing agents:

Diisobutyl aluminium hydride [DIBAH, *i*-butyl)$_2$AlH] is a specific reducing agent for ester, which reduces esters to aldehydes.

Carbonyl groups can be reduced chemoselectively in the presence of a cyano, nitro, alkoxy carbonyl group by various reducing agents. We will discuss these reactions in Reduction part in Semester II.

6.4 REGIOSELECTIVE REACTIONS

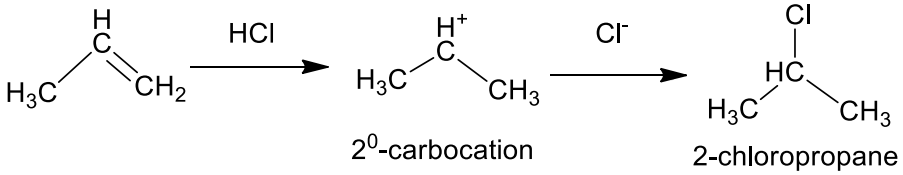
Regioselectivity is the preference for bond making at a particular position of a substrate when there is possibility of bond formations at other possible positions also. In other words, there is a preference of one reactive site over the others in a molecule.

1) Regioselectivity of Electrophilic Addition Reactions in alkenes:

These are the reactions, in which the regioselectivity of reactions was elaborately studied. Even, originally the term 'regioselectivity' was restricted to addition reactions of unsymmetrical reagents to unsymmetrical alkenes. However, regioselectivity is not only restricted to these reactions, but these are important reactions are always illustrated in the study of regioselectivity.

When an unsymmetrical alkene undergoes an electrophilic addition reaction, there is choice for the electrophile to add to two different sp^2 carbons. In such cases, the major product of the reaction is the one obtained by adding the electrophile to the sp^2 carbon that results in the formation of the more stable carbocation.

For example, when propene reacts with HCl, the proton can add to the C-1 to form a secondary carbocation, or it can add to the C-2 to form a primary carbocation. The secondary carbocation is formed more rapidly because it is more stable than the primary carbocation. The product of the reaction, therefore, is 2-chloropropane. This is stated as **Markovnikov addition reactions**, where the **Markovnikov's rule** states that when an asymmetrical reagent is added to an asymmetrical alkene, then the negative half of the reagent will attach to the carbon atom containing fewer hydrogen atoms.

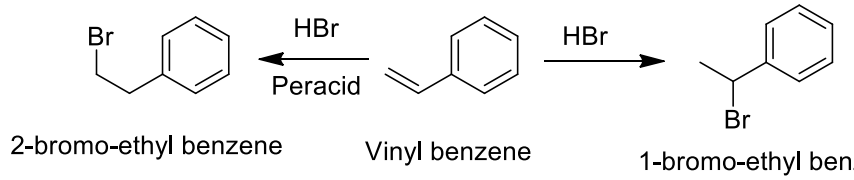


2^0-carbocation

2-chloropropane

There are additions which do not follow Markovnikov's rule. These ae called Anti-Markovnikov's addition. The best example to explain the **Markovnikov and anti-**

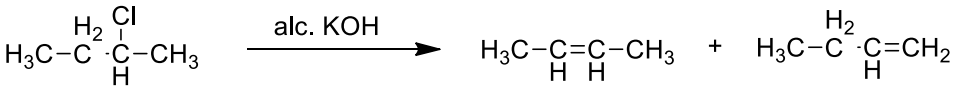
Markovnikov addition reactions is the reaction of hydrobromic acid (HBr) with styrene (vinylbenzene). The reaction gives 1- bromoethylbenzene through Markovnikov addition. The same reaction, if performed in the presence of peracids undergoes Anti-Markovnikov addition to give 2- bromoethylbenzene.



2) Regioselectivity in elimination reaction

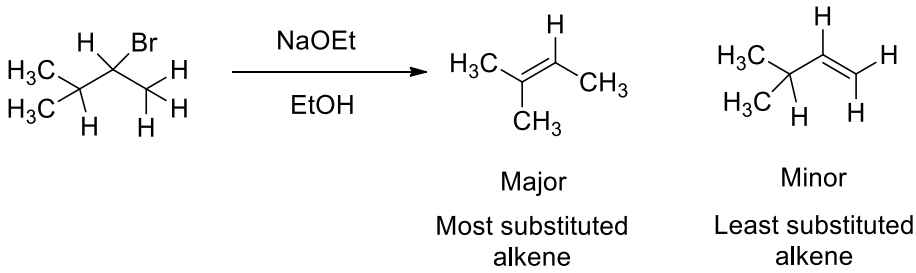
In an alkene formation reaction by a 1,2-elimination reaction (e.g. dehydration and dehydrohalogenation), more than one alkene may form. Which constitutional isomer will form is determined by two opposite rules., *viz.*, **Saytzef's Rule** and **Hoffman's Rule**.

Saytzef's Rule states that in a 1,2-elimination reaction, the most substituted alkene will be the predominant product. For example, when 2-chlorobutane is heated with alcoholic KOH, an elimination reaction (dehydrohalogenation) takes place and a mixture of 1-butene and 2-butene is formed.



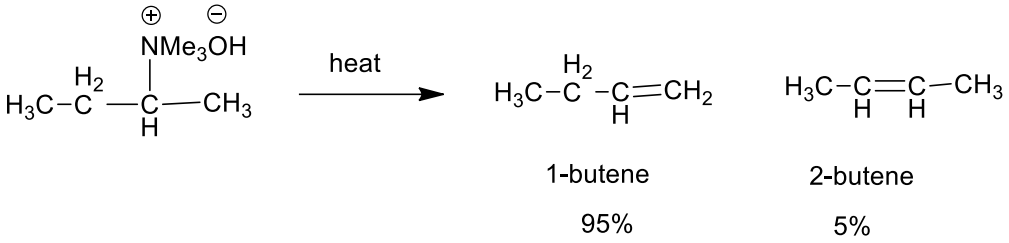
According to Sayzef's Rule, 2-butene should be formed predominantly, since 2-butene has the most substituted double bond (two carbons bearing the double bond should have the least number of hydrogens). And, experimentally, 2-butene is formed predominantly.

Similar example is the dehydrobromination of 2-bromo-3-methyl butane, which yields the most substituted 2-methyl but-2-ene as the major product. And 3-methyl but-1-ene forms as minor product.



Hoffman's Rule also deals with regioselectivity in alkene formation by 1,2-elimination. Contrary to Saytzef's Rule, Hoffman's Rule states that the least substituted alkene should be predominantly formed. For example, when sec-butyltrimethylammonium

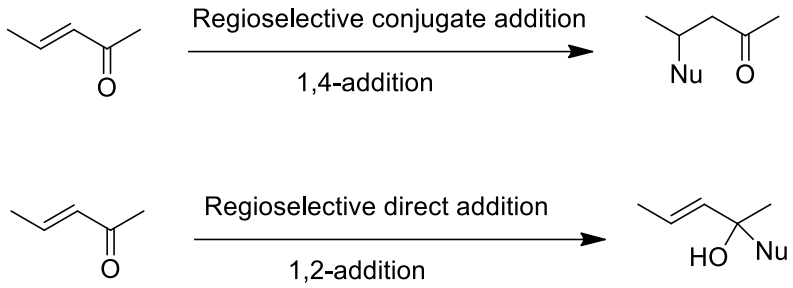
hydroxide is heated, 1-butene will be formed predominantly. And this according to Hofmann's Rule.



Now, why does 1-butene forms preferentially? There are two explanations for this.

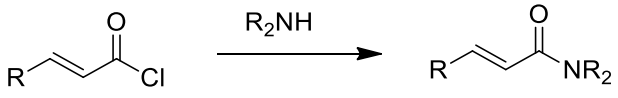
I. There are two kinds of β-H in the substrate. The β-H of the CH_3 group is more acidic than the β-H of the -CH_2- group So, the β-H of the –CH_3 group will be abstracted by the OH^- group. And the least substituted 1-butene is formed predominantly.
II. The steric crowding on β-C of the -CH_2- group is more than the β-C of the CH_3-group. So β-H is abstracted by OH^- group from the less crowded β-C.

3) Regioselectivity in nucleophilic addition to an unsaturated ketone takes place in a 1,2- or 1,4-fashion. This is another simple example of regioselectivity.

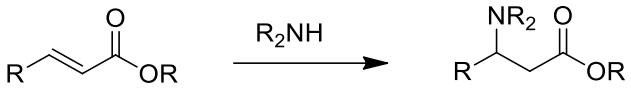


The first difference between the two routes is that the product from direct addition keeps the alkene but loses the carbonyl group while conjugate addition keeps the carbonyl group but loses the alkene. As a C=O π bond is stronger than a C=C π bond, conjugate addition gives the thermodynamic product. But as the carbonyl group is more electrophilic than the far end of the alkene, especially to charged, hard nucleophiles, direct 1,2-addition gives the kinetic product. So direct 1,2-addition is favoured by low temperature and short reaction time, while conjugate addition is favoured by higher temperature and longer reaction time.

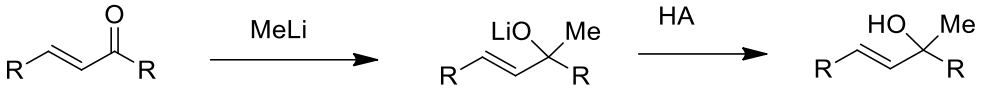
The second difference depends on how electrophilic is the α,β-unsaturated carbonyl compound. The more electrophilic groups, such as aldehydes and acid chlorides tend to prefer direct 1,2-addition.



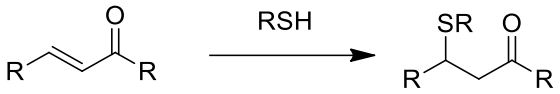
The less electrophilic carbony groups, such as ketones or esters, tend to prefer conjugate addition.



It is similar with the choice of nucleophile: hard nucleophilic species, such as MeLi or Grignard reagents, prefer direct addition, particularly as they react irreversibly,



while soft nucleophilic species, like amines and thiols, prefer conjugate addition.



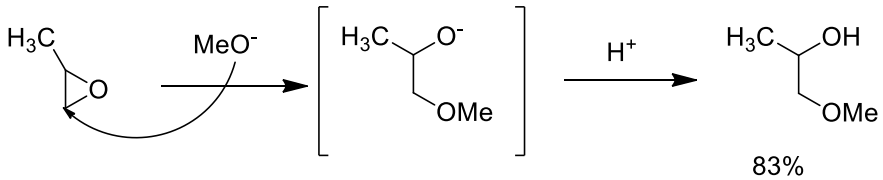
These nucleophiles add reversibly to the C=O group, giving an opportunity for any direct addition product to revert to starting materials and react again.

So, in this case, the regioselectivity depends on the following reaction conditions.

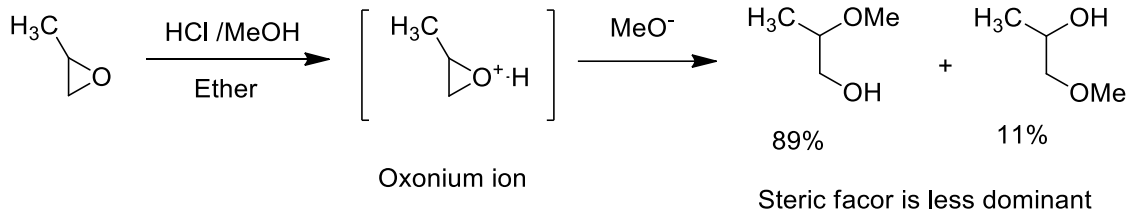
a) Reactivity of the carbonyl group
   I. Since the aldehyde group is much more reactive than ketones toward nucleophile, so majority of the addition in α,β-unsaturated aldehydes takes place as 1.,2-addition.
   II. Conversely, since ketones are less reactive than aldehydes toward nucleophile, so majority of the addition in α,β-unsaturated ketones take place as 1,4-addition.
b) Reactivity of the reagent
   I. Organolithium versus Grignard reagent
   II. Dialkyl cuprate versus Grignard reagent
c) Steric hindrance
   I. Steric hindrance at carbonyl group favours 1,4 addition whereas
   II. steric hindrance at 3-position favours 1,2 addition

5) Regioselectivity in cleavage of epoxide

Although epoxides contain strained three-membered rings, they require either acid catalysis or a powerful nucleophile to cleave. In an epoxide, there are two electron-deficient carbon atoms due to the presence of the electronegative O-atom. So epoxide rings are cleaved by nucleophiles by attacking at either of these two carbons.
Generally, regioselective addition of nucleophile to an unsymmetrical epoxide is governed by the steric factor and the nucleophile attacks the less hindered carbon atom.



But the steric hindrance is less predominant in the attack by CH_3OH in acidic medium and the regioselectivity is opposite in this case.

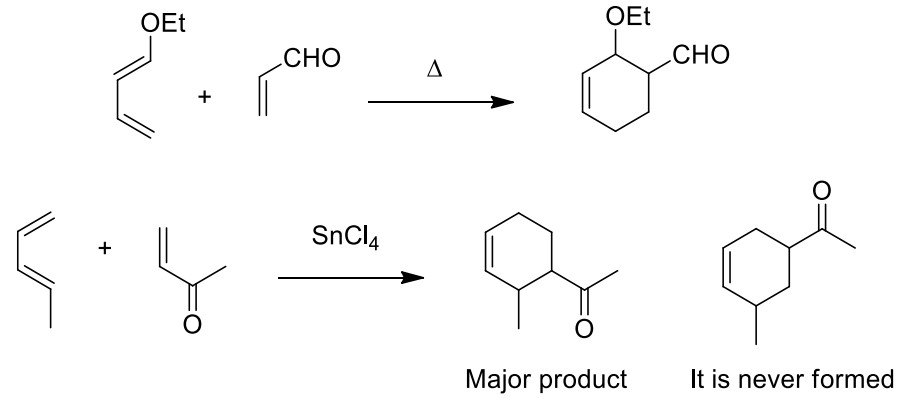


In the above reaction, on protonation of the epoxide oxygen, oxonium ion is formed where, there is a substantially polarised C-O bond. The partial positive charge is more stabilized on the 2°-C atom (an ensuing 2°-Carbocation). So attack by MeO^- is more directed to this carbon. As a result, steric factor has become less predominant.

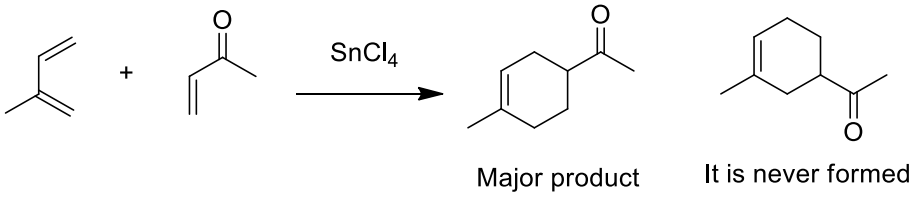
So, we can say that, regioselectivity of epoxide opening depends on the conditions.

6) Regioselectivity in Diels-Alder Reaction

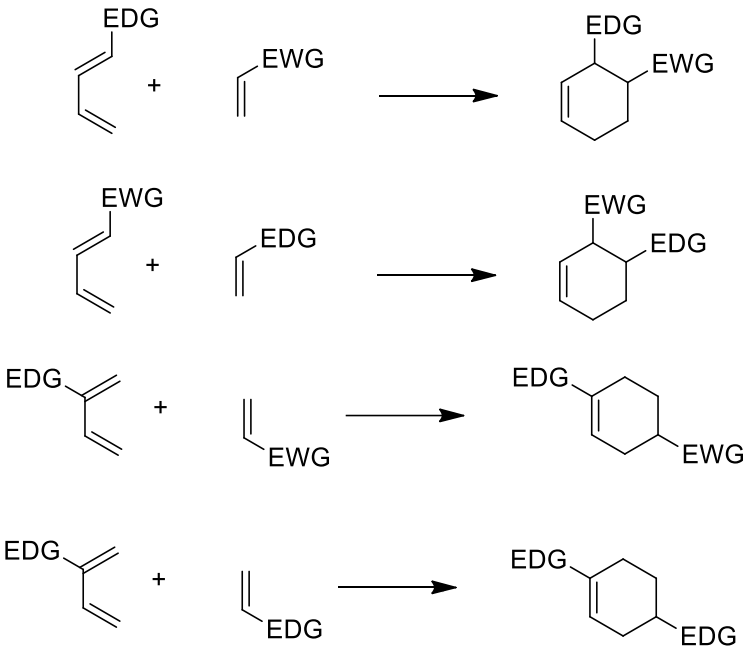
Diels Alder reaction between an unsymmetrical diene and an unsymmetrical dienophile are regioselective.
For example,
For most dienes, substituted on the first carbon atom of the diene system, when react with most dienophile, the major product has the two substitutions '*ortho*' to each other. In other words, product is substituted '*ortho*-like' and never '*meta*-like'.



And, if the substituent is on the second carbon of the diene system, the major product is substituted '*para*-like', and never '*meta*-like'.



The regioselectivity of Diels Alder reaction can be summarised as follows.

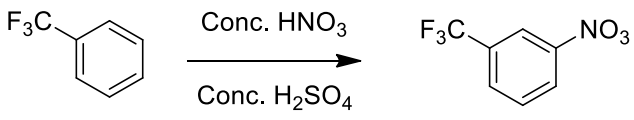


EDG = Electron Donating Group and **EWG** = Electron Withdrawing Group

7) Regioselectivity in electrophilic aromatic substitution reactions.

In electrophilic substitution of an aromatic ring, the functional group present in the aromatic ring directs where the electrophile will attack, i.e., at *ortho-, meta-* or *para-* positon. This is the reaction's regioselectivity. You have already learnt various aromatic substitution reaction on aromatic systems having *o-* and *p*-directing groups and *m*-directing groups.

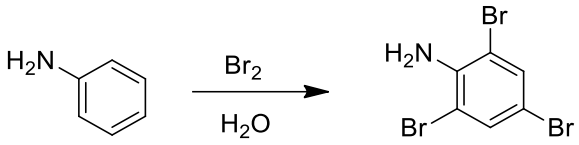
An electron-donating substituent favours ortho/para and an electron-withdrawing substituent favours meta substitution. Although meta substitution is usually slower than ortho/para substitution (because electron-withdrawing groups deactivate the ring), it usually gives the meta product alone.



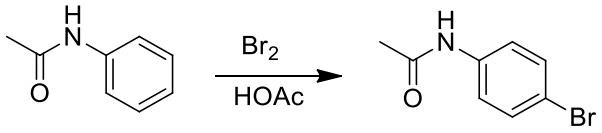
CF_3- group is meta directing

96% meta product only

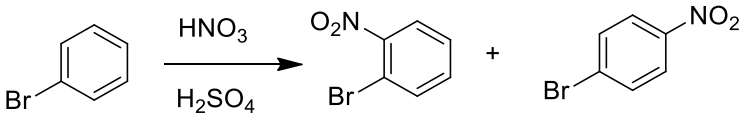
Most reactions of benzene rings with electron-donating substituents give ortho/para mixtures and, if the substituent is very electron-donating, both ortho and para substitution takes place in the same molecule.



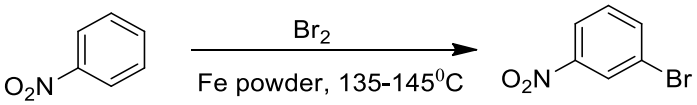
By reducing the reactivity of the substituent and increasing its size, control in favour of the para product can usually be achieved. In this reaction by acylation of the amino group, the electron donating effect of amino group is reduced. And also the size of it increased. So, only para directing effect of the substituent is favoured and para-bromo product is formed.



Altering the sequence of reactions, the regioselectivity may be controlled in aromatic electrophilic substitution. Choosing the right route to an aromatic product is essential if you want to get one particular isomer. We can illustrate this with the synthesis of the isomers of bromonitrobenzene. Because the bromo substituent is ortho, para-directing and the nitro group meta-directing, it is possible to make all three isomers by exploiting the regioselectivity of electrophilic substitution. Nitration of bromobenzene would give the ortho and para isomers while bromination of nitrobenzene would give the meta isomer. The selectivity of the first reaction is not good. Because bromine is small and not very electronegative, so steric hindrance is weak and the ortho positions are not deactivated. Furthermore, there are two ortho positions but only one para: a typical result is about 37% ortho, 1% meta, and 62% para.

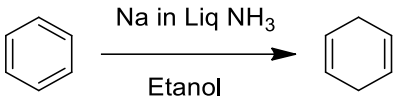


Bromination of nitrobenzene is remarkably good, considering the unreactivity of nitro benzene in electrophilic aromatic substitution. One recipe uses iron powder and bromine at 140 °C and gives 74% of the meta product. We shall need these reactions in the next section.



8) Regioselectivity in Birch reduction

It is another important example of regioselectivity. In this reduction method, aromatic rings undergo a 1,4-reduction to provide unconjugated cyclohexadienes. This reaction is performed by sodium or lithium metal in liquid ammonia and in the presence of an alcohol. Here, the site of reduction is dependent upon the type of substitution present in the aromatic ring. Without any substitution in the aromatic ring, the reduction of simple benzene gives cyclohexadiene.



We will discuss the regioselectivity in Birch reduction when electron donating (e.g., -OCH_3) and electron withdrawing (e.g., -COOH) groups are attached, in the section 'reduction by dissolving metal' in Semester 2.

6.5 STEREOSELECTIVE REACTIONS

Stereoselectivity is the preferential formation of one stereoisomer in a chemical reaction. This can be further classified into:

- Enantioselective reactions
- Diastereoselective reactions
- Stereospecific reactions
- Stereoselective reactions

Enantioselective reactions: The stereoselective reactions where a reactant gives enantiomeric products or enantiomers in unequal amounts are called enantioselective reactions.

Diastereoselective reactions: The stereoselective reactions where a reactant gives diastereomeric products or diastereomers in unequal amounts are called diastereoselective reactions.

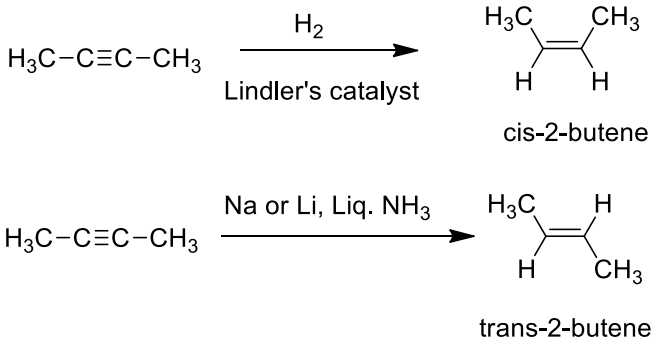
Stereospecific reactions: Those stereospecific reactions where the stereochemistry of the starting material determines the stereochemistry of the product are called stereospecific reactions. For example, S_N2 reactions.

Stereoselective reactions: The stereospecific reaction where one stereoisomer of a product is formed preferentially over another is known as stereoselective reaction.

In the previous Unit, we have already discussed about addition of Br_2 to *cis*-2-pentene and *trans*-2-pentene is stereospecific as the *cis* and *trans* isomers form different products. You have also learnt that since *cis*-2-pentene forms two out of four stereoisomers, and, *trans*-2-pentene forms two out of four stereoisomers, both the reactions are stereoselective.

1) Stereoselectivity in partial reduction of alkyne to alkene

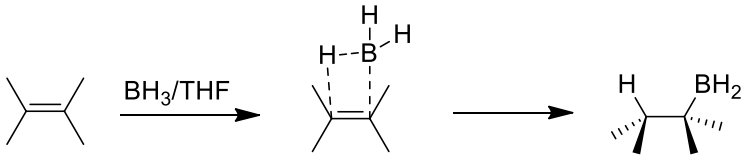
Hydrogenation of 2-butyne with H_2-Lindler's catalyst, i.e. Pd/$CaCO_3$-$Pb(OAc)_2$-quinoline, gives *cis*-but-2-ene, but with Na-Liquid NH_3 gives *trans*-but-2-ene.



We will discuss these in detail in Semester 2.

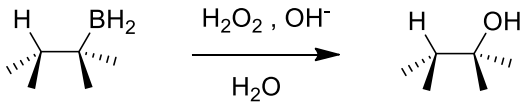
2) Hydroboration–Oxidation of an alkene is a stereoselective Reaction

The addition of borane (or R_2BH) to an alkene is a concerted reaction. The boron and the hydride ion add to the two sp^2 carbons of the double bond at the same time. Because the two species add simultaneously, they must add to the same side of the double bond—that is, it is a syn addition.

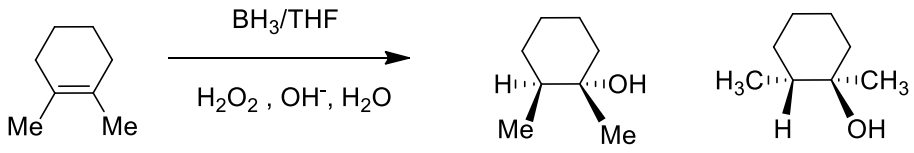


Addition of borane is a syn addition

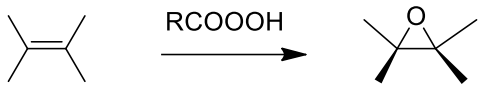
When the resulting alkylborane is oxidized by reaction with hydrogen peroxide and hydroxide ion, the OH group ends up in the same position as the boron group it replaces. Consequently, the overall reaction, called hydroboration–oxidation, amounts to a syn addition of water to a carbon–carbon double bond.



Because only *syn* addition occurs, hydroboration–oxidation is **stereoselective**— only two of the four possible stereoisomers are formed.
If the reactant is cyclic, *syn* addition forms only the enantiomers that have the added groups on the same side of the ring.



Addition of peracid to alkene is a stereoselective reaction.
The addition of a peroxyacid to an alkene to form an epoxide is a concerted reaction; the oxygen atom adds to the two sp^2 carbons at the same time. Therefore, it must be a syn addition.

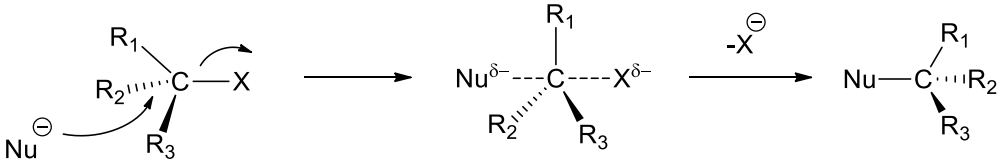


alkene epoxide

The oxygen can add from above or from below the plane containing the double bond. Therefore, addition of a peroxyacid to an alkene forms two stereoisomers. *Syn* addition to a *cis*-alkene forms the *cis*-enantiomers. Because only *syn* addition occurs, the reaction is stereoselective. (If you turn the stereoisomer on the right upside down, you can see that it is the mirror image of the stereoisomer on the left.)

6.6 STEREOSPECIFIC REACTIONS

Stereospecific reactions are those, in which different stereoisomeric reactants form different stereoisomeric product or a different set of stereoisomeric products. A classic example of a stereospecific reaction is the S_N2 mechanism which refers to a bimolecular nucleophilic substitution. In the case of a S_N2 reaction, there will always be an inversion of stereochemistry at the chiral centre.

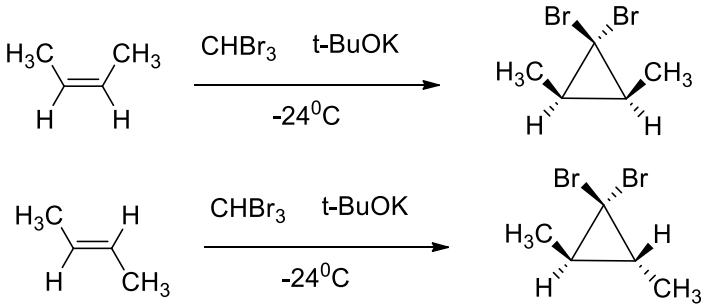


The nucleophile approaches from the opposite to the C-X bond

So, if you carry out an S_N2 reaction on starting materials that are enantiomers of each other, then the reactions will result in products that are themselves enantiomers of each other.

U LET US KNOW MORE

The addition of singlet carbenes to alkenes is **stereospecific**. For example, in the following addition of the dibromocarbene, *cis*-2-butene yield *cis*-2,3-dimethyl-1,1-dibromocyclopropane, whereas the *trans* isomer exclusively yields the *trans*-cyclopropane.



$CHBr_3$ generates the singlet carbene :CBr_2 which adds stereospecifically to the alkene.

This addition remains stereospecific even if the starting alkene is not isomerically pure, as the products' stereochemistry will match with that of the reactants.

W CHECK YOUR PROGRESS

Q1. Is the reaction of 2-butene with HBr (a) regioselective, (b) stereoselective, and (c) stereospecific?

Q2. Is the reaction of 1-butene with (a) HBr regioselective, (b) stereoselective, and (c) stereospecific

2 6.7 LET US SUM UP

- Chemoselectivity is the selectivity of a reagent or a reaction condition for one functional group over another.
- Regioselectivity is the preference for bond making at a particular position of a substrate when there is possibility of bond formations at other possible positions also.
- **Markovnikov's rule** states that when an asymmetrical reagent is added to an asymmetrical alkene, then the negative half of the reagent will attach to the carbon atom containing fewer hydrogen atoms.
- Saytzef;s Rule states that in in alkene formation 1,2-elimination reaction, the most substituted alkene will be the predominant product.
- Hoffman's Rule states that in alkene formation by 1,2-elimination reaction, the least substituted alkene will be the predominant product.
- In addition of a nucleophile to a α,β-unsaturated carbonyl compound, as a C=O π bond is stronger than a C=C π bond, conjugate addition gives the thermodynamic product.
- As the carbonyl group is more electrophilic than the alkene, especially to charged, hard nucleophiles, direct addition gives the kinetic product.
- Direct addition is favoured by low temperatures and short reaction times while conjugate addition is favoured by higher temperatures and longer reaction times, provided the 1,2 addition is reversible.
- In α,β-unsaturated carbonyl compound, the more electrophilic groups, such as aldehydes and acid chlorides tend to prefer direct addition.
- The less electrophilic such as ketones or esters tend to prefer conjugate addition.
- Hydroboration–oxidation of alkene is **stereoselective,** because only *syn* addition occurs. Epoxidation of alkene is stereoselective, because only *syn* addition occurs,

K 6.8 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1:

a) The reaction of 2-butene with HBr is **not regioselective**. Because 2-butene is a symmetric molecule, i.e., both carbons of the double bond are equally substituted. So, HBr adds the same way regardless of which carbon receives the proton, resulting in only 2-bromobutane.

b) The reaction is not stereoselective because it forms a racemic mixture.

c) The reaction is not stereospecific because both *cis*- and *trans*-2-butene yield the same racemic product.

Answer to Q2:

a) The reaction of 1-butene with HBr is **regioselective**. Because 1-butene is a symmetric molecule, i.e., both carbons of the double bond are **not** equally substituted. So, the addition of HBr to 1-butene takes place following Markovnikov's rule. Under normal conditions, it preferentially forms **2-bromobutane** (a secondary bromide) as the major product, rather than 1-bromobutane, due to the formation of a more stable secondary carbocation intermediate. In the presence of peroxides, the other isomer, **1-bromobutane** is formed (Anti-Markovnikov's rule), via a radical mechanism.

b) The reaction of 1-butene with HBr is **not stereoselective** and **not stereospecific**, as it produces a racemic mixture of 2-bromobutane. Because the intermediate carbocation is trigonal planar and achiral, allowing for equal attack on either face by the bromide ion. That means, neither *syn* nor *anti* addition is favored, resulting in no preference for one stereoisomer over the other.

c) Since the reaction of 1-butene with HBr is **not stereoselective,** so, it is **not stereospecific** too. Since all stereospecific reactions are stereoselective.

O 6.9 FURTHER READING

- Jagadamba Singh and L. D. S. Yadav, Organic Synthesis, Pragati Prakashan
- Ratan Kumar Kar, Applications of Redox and Reagents in Organic Synthesis, Vol.1, NCBA
- Paula Yurkanis Bruice, Organic Chemistry, 7th Edition, Pearson
- Jonathon Clayden, Nick Greeves and Stuart Warren, Organic Chemistry, 2nd Ed. OUP, 2023

M 6.10 MODEL QUESTIONS

Q1. Define regioselectivity and give one example of regioselectivity in each of i) aromatic electrophilic substitution reaction and ii) reduction of alkyne.

Q2. Illustrate regioselectivity in elimination reaction applying Saytzef's Rule and Hoffman's Rule.

Q3. Give one example of regioselective ring opening of epoxide.

UNIT 7: NEIGHBOURING GROUP EFFECTS

UNIT STRUCTURE

7.1 Learning Objectives
7.2 Introduction
7.3 Definition of Neighbouring Group Effects
7.4 The discovery of Neighbouring Group Effects
7.5 Effect of Neighbouring Group in Reaction Rate
7.6 Neighbouring Group Participation by Oxygen, Nitrogen and Halogen
  7.6.1 Neighbouring Group Participation by Oxygen Atom
  7.6.2 Neighbouring Group Participation by Nitrogen Atom
  7.6.3 Neighbouring Group Participation by Halogen Atom
7.7 Neighbouring Group Participation by Double bond, Aryl group and σ-bond
  7.7.1 Neighbouring Group Participation by π–electrons of alkene
  7.7.2 Neighbouring Group Participation by Aryl Group
  7.7.3 Neighbouring group participation by cyclopropyl group
7.8 Let Us Sum Up
7.9 Answers to Check Your Progress
7.10 Further Reading
7.11 Model Questions

7.1 LEARNING OBJECTIVES

In this unit, you will learn about:

- neighbouring group participation (NGP) or anchimeric assistance in chemical reaction and its unexpected reaction outcomes
- atoms and functional groups taking part in anchimeric assistance
- mechanism of NGP
- effects of NGP in product formation in a reaction
- effects of NGP on reaction rate
- outcomes of anchimeric assistance for various reactions
- how to know if anchimeric assistance is operational

7.2 INTRODUCTION

When a reaction takes place, we know that various factors come into effect, viz., polar factor, steric factor and solvent effect. But there is another important factor which can also contribute to the reactivity of a substrate in a reaction. This is related to the structural feature of the substrate that may determine how fast a reaction will take place and the product. Such a structural feature present in the neighbourhood of the reaction site is called a neighbouring group. Therefore, a neighbouring group can be defined as:
An atom or a group of atoms or a functional group close to the site of a chemical reaction in a substrate molecule.

Neighbouring groups can direct a reaction to take place in an **unexpected high rate** and/or to yield product with **unexpected stereochemistry**. Such unexpected or unusual behaviour of reactants in a reaction is the result of the reaction site and the neighbouring group being brought closer together and held in exactly the right position for the reaction to take place. The phenomenon involves the bringing together of reactants into proper spatial relationship, which may be termed as **symphoria**. [Greek: *sympherein*, to bring together usefully (*sym*, together + *pher/phor*, *to bring*).
Effect of neighbouring group is observed in different kinds of reactions. There are examples of such effect in nucleophilic substitution in ordinary substrates, catalysis by transition metal complexes, and the action of enzymes in living cells.

7.3 NEIGHBOURING GROUP PARTICIPATION AND EFFECT

When a neighbouring group participates in a reaction without necessarily leading to an intramolecular rearrangement, the participation is known as **Neighbouring Group Participation (NGP)**. Usually the neighbouring group remains on the β-C, but it may remain farther away and in such case, the group comes near to the reaction site due to facile spatial arrangement of the reaction site of the substrate molecule.
Although NGP encompasses various kind of participation of a neighbouring group in a reaction, **it is defined by IUPAC as the direct interaction of the reaction site with a lone pair of electrons of an atom or with σ- or π- electrons which are already present in the substrate molecule, but not conjugated with the reaction site**.
During neighbouring group participation, generally cyclic T.S.s are developed. 3 to 6-membered cyclic T.S.s are commonly generated and 6-membered cyclic T.S.s are the most stable T.S.
The participation takes place because the reacting atoms are ***near to each other*** and ***in exactly the right position***, which is termed as **symphoria**: **the bringing together of reactants into the proper spatial relationship**.

Salient features of Neighbouring Group Participation

Cyclic intermediate: In nucleophilic substitution, the neighboring group acts as an internal nucleophile to displace the leaving group, forming a cyclic intermediate (often 3, 5, or 6-membered), which is then opened by an external nucleophile.

Retention of configuration in nucleophilic substitution: Unlike normal nucleophilic substitution, where inversion of configuration takes place, NGP often results in **retention of configuration** due to two successive inversions (one by the neighboring group, one by the external nucleophile).

Acceleration of reaction rate: Reactions with NGP are often thousands of times faster than standard intermolecular reactions.

Participating Groups: Since a neighbouring group is to form a bridged intermediate, it must have electrons to form the extra bond. These may be lone pairs of electrons on atoms like S, N, O or bromine; π-electrons of a double bond (alkenes) or aromatic ring (phenyl) or even, in some cases, σ-electrons.

As already stated, neighbouring group participation may have effect in

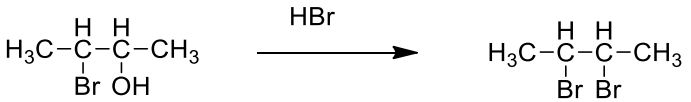
i) nature of product formation and
ii) rate of the reaction

In other words, if you notice unexpected increase in reaction rate and unexpected change in the stereochemistry of product, you may predict neighbouring group participation in the reaction mechanism.

7.4 DISCOVERY OF NEIGHBOURING GROUP EFFECTS

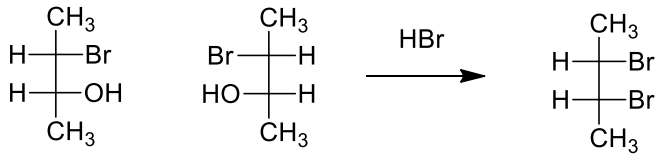
Neighbouring group effect was first discovered by Winstein and Lucas in 1939. When they described the stereochemistry of the reaction of 3-bromo-2-butanol with conc. hydrobromic acid, the concept of neighbouring group effect was first put forward.

The reaction of 3-bromo-2-butanol with conc. hydrobromic acid appears to be a normal nucleophilic substitution. In the reaction nucleophilic attack (S_N1 or S_N2) by bromide ion on the protonated alcohol takes place and 2,3-dibromo-butane is formed.



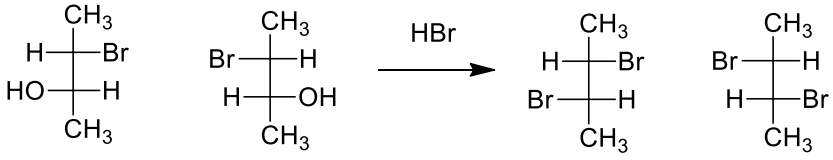
3-bromo-2-butanol 2,3-dibromo-butanol

However, stereochemical studies revealed unexpected result. Winstein and Lucas found that (racemic) *erythro* 3-bromo-2-butanol yields only the *meso* dibromide and (racemic) *threo* 3-bromo-2-butanol yields only the *racemic* dibromide



Erythro
Racemic

Meso

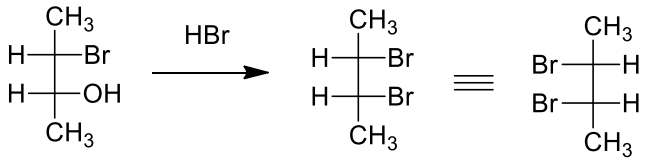


Threo
Racemic

Racemic

The results suggested that the reaction proceeded with complete retention of configuration. But it is known that nucleophilic substitution takes place with inversion of configuration or with racemisation.

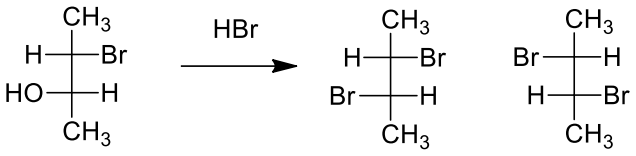
To further study the unusual observation, they carried out the reaction with optically active 3-bromo-2-butanol. From optically active *erythro* 3-bromo-2-butanol, they obtained the expected optically inactive product, the *meso* dibromide.



Erythro
Optically active (d or l)

Meso

But either of the optically active *threo* 3-bromo-2-butanol also yielded optically inactive product, the racemic dibromide.



Threo
Optically active (d or l)

I II

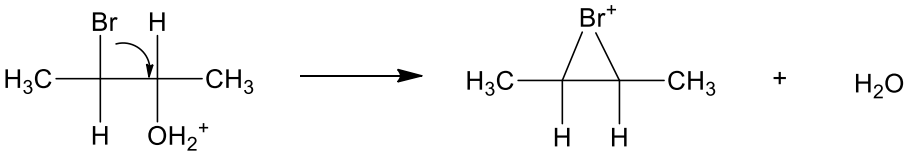
Racemic

In one of the products, the product **I**, there is retention of configuration. But in the other product, **II**, there is inversion not only at the carbon bearing the hydroxyl group, but also at the carbon bearing the bromine. It meant that exactly half the molecules reacted with complete retention, and the other half with this strange double inversion (resulting in retention).

These results cannot be explained by a simple S_N1 or S_N2 mechanism. Winstein and Lucas proposed that instead of forming an open carbocation, the reaction proceeds through a bridged bromonium ion. The reaction was explained as a two-step mechanism where two consecutive nucleophilic substitution led to retention of configuration.

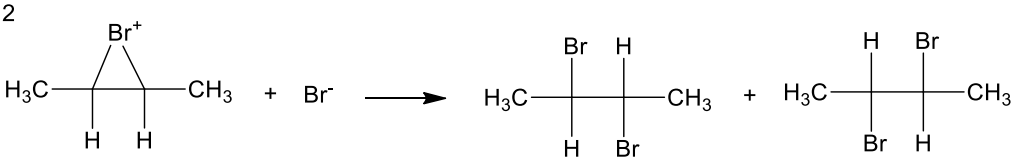
In the first step, the neighbouring group (Br) acts as a nucleophile, attacking intramolecularly the substitution centre (the carbon bearing the protonated –OH group) and displaces H_2O. As a result, a three-membered cyclic bromonium ion is formed.

Step I



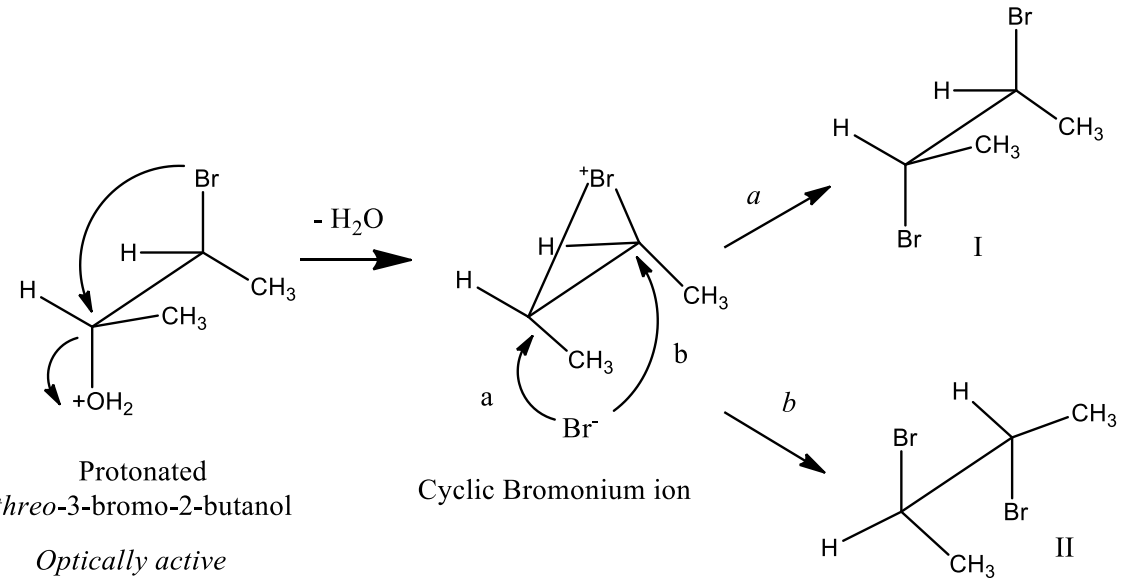
In the next step, the external nucleophile (Br^-) attacks the bromonium ion from either side from backside displacing the neighbouring group.

Step 2



Attack on one side gives the product with retention of configuration at both the carbons while attach at the other side gives the product with inversion of configuration at both the carbons and retaining the overall configuration. Because attack can occur at either carbon of the bromonium ion, two stereochemical pathways are possible and since both the pathways occur equally, the final product becomes racemic.

This was the first clear demonstration of neighboring group participation leading to unusual stereochemistry.



Protonated
threo-3-bromo-2-butanol

Optically active

Cyclic Bromonium ion

I and II are enantiomers
Racemic 2,3-dibromobutane

Since the first step is slow and is rate determining, the reaction follows first order kinetics and there is no effect of concentration of Br^- on rate of reaction.

Neighboring group effects are closely related to carbocation rearrangements. Carbocations can rearrange when a hydrogen or an alkyl group migrates, along with its bonding pair of electrons, to an electron-deficient carbon. Such rearrangements were among the earliest evidence for carbocation intermediates and remain one of their strongest indicators.

When a leaving group departs, it generates an electron-deficient carbon. A nearby group may help relieve this deficiency. It may stabilize the carbocation indirectly by inductive or resonance effects while remaining in place. More importantly for this discussion, it may directly participate by forming a bond to the electron-deficient carbon. When this occurs, the process is an example of intramolecular nucleophilic substitution.

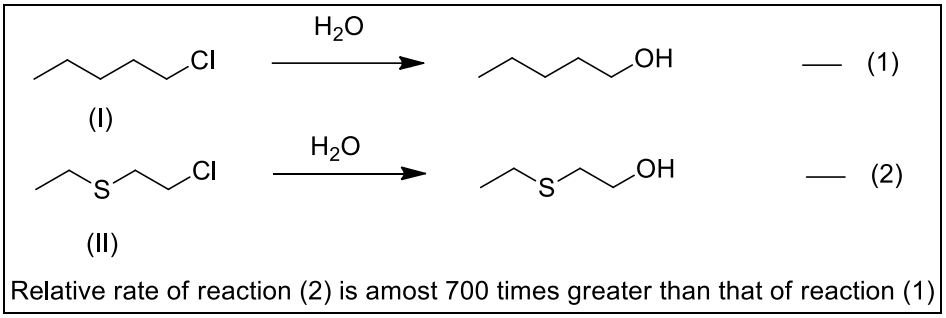
Like ordinary nucleophilic substitution, migration can occur in two ways. In an S_N1-like migration, the leaving group first departs to form a carbocation, and then the neighbouring group migrates. While, in an S_N2-like migration, the neighbouring group

assists in expelling the leaving group in a single concerted step, which is called *anchimeric assistance*.

7.5 EFFECT OF NEIGHBOURING GROUP IN REACTION RATE

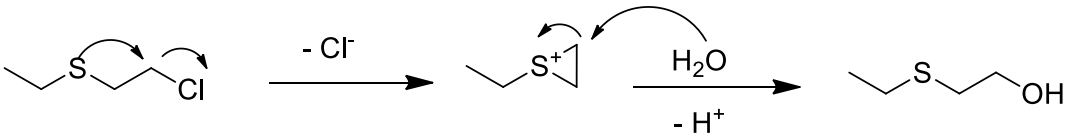
When the neighbouring group participation operates during the rate determining step of a reaction, usually the reaction rate is significantly increased. This effect is then termed as **Anchimeric Assistance**.

For illustration, let us take the example of anchimeric assistance of sulphur atom. Sulphur atoms act as powerful nucleophiles and the participation of sulphur as a neighbouring group is common.
Both n-pentyl chloride (I) (or any ordinary primary alkyl halide) and 2-chloroethyl-ethyl sulphide (II) give their corresponding alcohols on reaction with water.



Relative rate of reaction (2) is amost 700 times greater than that of reaction (1)

But the rate of reaction of the sulphur containing substrate, viz., 2-chloroethyl-ethyl-sulphide (II) is 700 times greater than that of *n*-pentyl chloride (I). The reaction in case of (I) is simple S_N2 displacement of chloride with water. But in case of the substrate (II), sulphur atom takes part as a neighbouring group and displaces the leaving group (chloride).
The faster rate of the reaction may be interpreted in terms of the **ready availability of the neighbouring group as internal nucleophile** for the attack in the first step, i.e. the rate determining step.



The configuration of the carbon containing the leaving group in the product is retained. In normal S_N2 reaction, it would have been inverted. So this is a reaction where NGP resulted in rate enhancement as well as in change in the stereochemistry of the normal product of nucleophilic substitution.

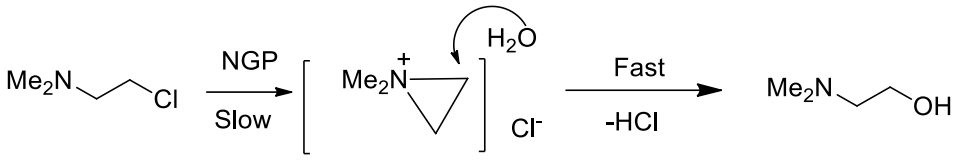
7.6 NEIGHBOURING GROUP PARTICIPATION BY O, N AND X

In the previous section, while you have learnt about effect of NGP on reaction rate, you have learnt that sulphur acts as neighbouring group. Like sulphur, oxygen, nitrogen and

halogens can also act as neighbouring group to participate in reactions resulting in unexpected product or in rate enhancement or in both.

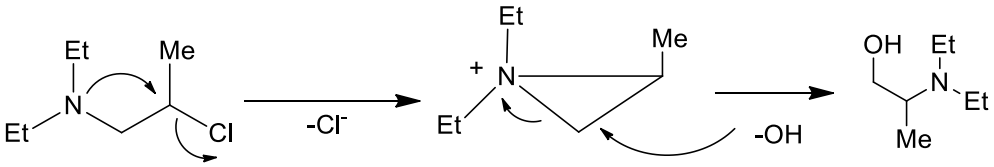
7.6.1 Neighbouring group participation by nitrogen atom

One example of Nitrogen acting as a neighbouring group is the hydrolysis of $Me_2NCH_2CH_2Cl$ (2-chloro-*N,N*-dimethyl-ethanamine) to $Me_2NCH_2CH_2OH$, i.e. 2-(dimethylamino)-ethanol. Participation of nitrogen atom as neighbouring group is due to the greater stability of the cyclic iminium ion intermediate, corresponding to sulphonium ion intermediate.



However, the rate is significantly slower, unlike the hydrolysis of 2-chloroethyl-ethyl-sulphide, discussed earlier. The rate is slower because of greater electronegativity of nitrogen atom compared to that of sulphur atom.

Another example of reactions involving nitrogen as neighbouring group is the reaction of 2-chloro-*N,N*-diethylpropan-1-amine with a dilute solution of NaOH.

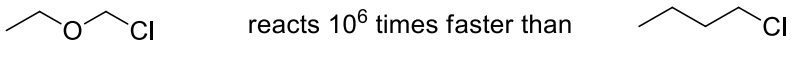


In the above reaction, the substrate is a secondary alkyl chloride. But note that the product alcohol is a primary alcohol and a rearranged product. This happened because of NGP by nitrogen.

7.6.2 Neighbouring group participation by oxygen atom

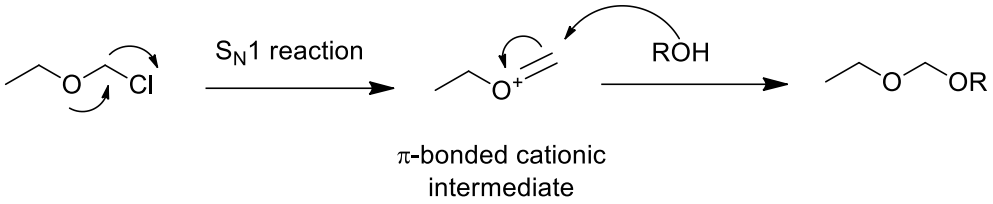
In section 7.5, you have learnt that participation of sulphur atom as a neighbouring group is common. Similar participation of O-atom is also observed.

Let us take the example of reactions of ethoxymethyl chloride and 1-chlorobutane with nucleophiles, say water. Both of these compounds give their corresponding alcohols on reaction with water. But the presence of oxygen results in huge change in reaction rate.



Ethoxymethyl chloride 1-chlorobutane

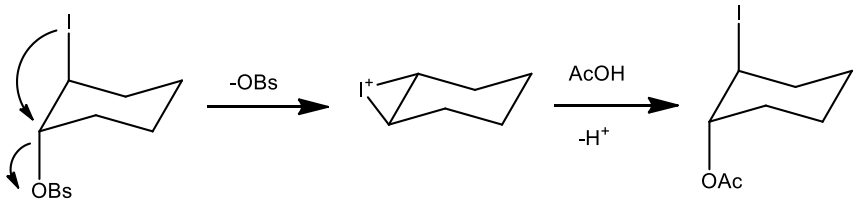
The mechanism is neighbouring group participation of oxygen atom.



Like in the case of sulphur assisted nucleophilic substitution in 2-chloroethyl-ethyl-sulphide, ionization of the starting material is assisted by the lone pair of electron on oxygen by forming a π-bond. In case of the previous example of sulphur assisted reaction, the sulphide assisted by forming a σ-bond in a three-membered ring.

7.6.1 Neighbouring group participation by halogen atoms

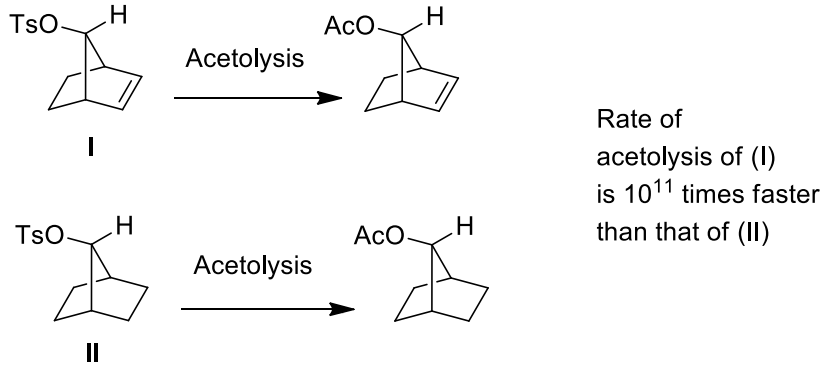
In acetolysis of *trans*-2-iodocyclohexylbrosylate, it is observed that the configuration remains the same at the asymmetric carbon. This unexpected stereochemical outcome in this nucleophilic substitution is due to neighbouring group participation of a halogen atom, viz., iodine atom. [Brosylate: *p*-bromobenzenesulfonyl, *p*-Br-C_6H_4-SO_3- group].



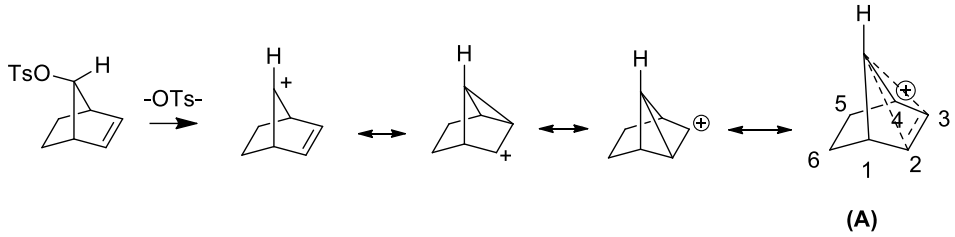
7.7 NEIGHBOURING GROUP PARTICIPATION BY DOUBLE BOND AND ARYL GROUP

7.7.1 Neighbouring group participation by π-electrons of alkene

The π-electrons of an alkene can stabilise a transition state by helping to delocalise the positive charge of a carbocation. For example, acetolysis of norbornenyl tosylate (I) is 10^{11} times faster than that of norbornyl tosylate (II).

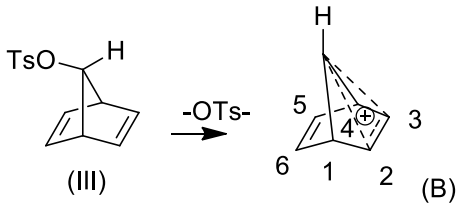


The carbocation intermediate will be stabilised by resonance where the positive charge is delocalised over several atoms.



(A)

[**Let us know more**: The rate showed that the C=C must have assisted. But the formation of the carbocation (A) (this is called non-classical carbocation, since the positive charge is not localized in one atom, but delocalised over several atoms) can be proved indirectly with the help of an NMR study of the acetolysis with relatively stable norbornadienyl tosylate (III).

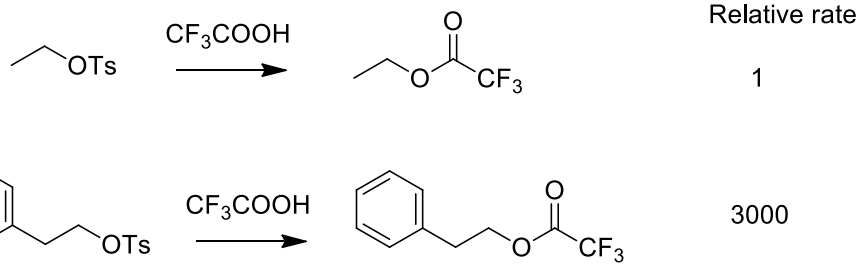


(III) (B)

As we know that NMR study reveals the number of protons as well as nature of protons present in a compound. *In situ* NMR data of the reaction showed that in (B), 2, 3 and 5, 6 protons are not equivalent. Thus, there must be interaction between one double bond and the positively charged carbon atom. As it happens in norbonadienyl tosylate, hence similar kind of interaction is true in case of (A) also].

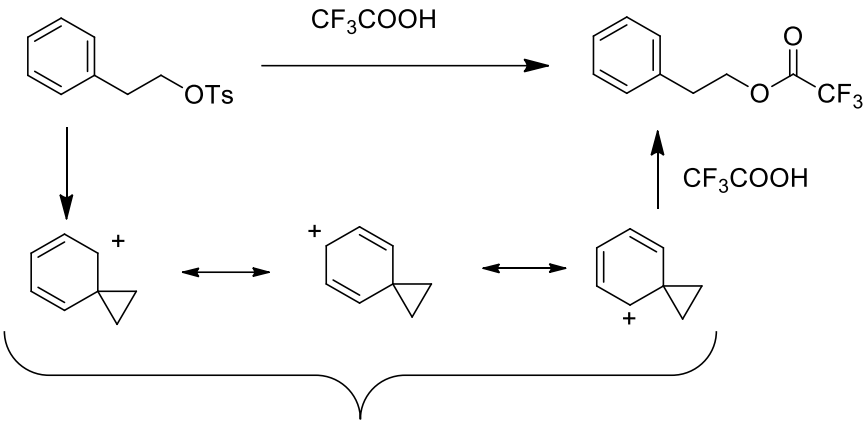
7.7.2 Neighbouring group participation by π-electrons of aromatic ring

Aromatic **π-electrons** are very effective neighboring groups. In the following two reactions, the rate of the second reaction is 3,000 times faster than the first reaction. As there is no heteroatom present with lone pair of electron, it must be the presence of the benzene ring containing a **π-electron** system.



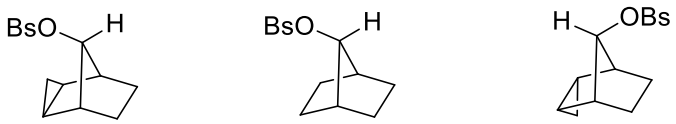
The first reaction is a normal S_N2 reaction. But the second reaction is two successive S_N2 reactions. Here, in the first step, the phenyl ring acts as a nucleophile to displace the tosylate group. This generates a phenonium ion intermediate with a three membered

ring. In the second step, trifluoroacetate nucleophile opens up the three membered ring and restoring the aromaticity of the phenyl ring.



7.7.3 Neighbouring group participation by cyclopropyl group

Solvolysis of the compound (1) is 5 times faster than compound (2). So, there must be neighbouring group participation of the cyclopyl ring.



(1) **(2)** **(3)**

But orientation of the cyclopropyl ring also has some effect. Solvolysis of compound (3) is 3 times slower than (1).

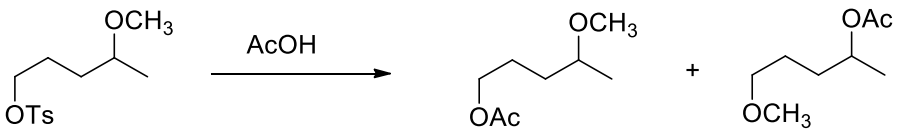
LET US KNOW MORE

In the formation of non-classical or bridged carbo-cations **in some cases**, neighbouring groups like C=C bonds and C-H σ-bonds assist. But it should be kept in mind that there is **no necessary relation between neighbouring group participation and formation of non-classical carbo-cations**.

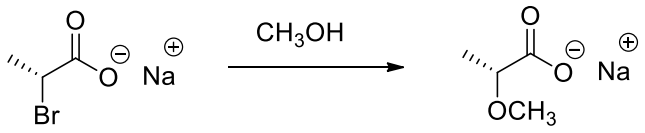
W CHECK YOUR PROGRESS

Q1) *Trans*-2-chlorocyclohexanol gives epoxycyclohexane in high yield on reaction with base. However, the *cis*- isomer does not react this way. Why?

Q2) With the help of neighbouring group participation principle, propose a mechanism to explain how both products are formed in the reaction.



Q3) Propose a mechanism to explain the outcome of the following reaction. (Take help of neighbouring group participation principle).

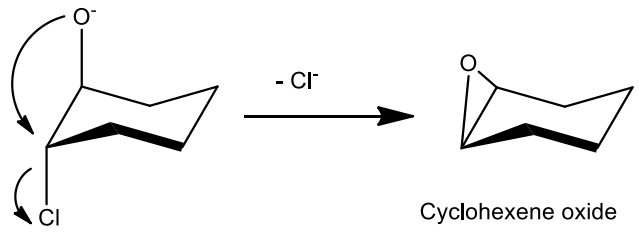


7.8 LET US SUM UP

- An atom or a group of atoms or a functional group close to the site of a chemical reaction in a substrate molecule is called a neighbouring group.
- Neighbouring groups can direct a reaction to take place in an **unexpected high rate** and/or to yield product with **unexpected stereochemistry**.
- Such unexpected or unusual behaviour of reactants in a reaction is the result of NGP that takes place due to proper orientation of functional groups with the NG, which is often termed as **symphoria**.
- Anchimeric assistance is a case of intra molecular catalysis where NGP leads to enhancement of rate of reaction.
- Anchimeric assistance involves two steps where first step is rate determining step, leading to overall first order kinetics.
- For reactions that may go by S_N2 mechanism, if anchimeric assistance is involved, the reactions proceed with retention of configuration.
- Various functional groups containing nitrogen, oxygen, sulphur, bromine, iodine and chlorine may participate in NGP
- Double bond and phenyl ring can also function as NGs in SN reactions.
- Neighbouring groups with electron releasing property are more efficient.
- In NGP the intermediate has a cyclic structure which may lead to normal, rearranged or cyclic product.

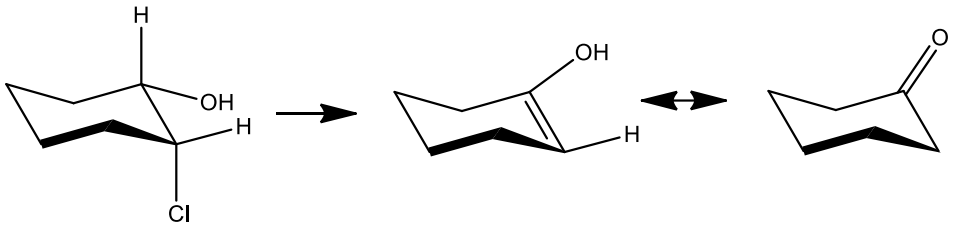
7.9 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: In the conformation of a 1,2-*trans*- cyclohexane either the groups can be diaxial or diequatorial. In the diaxial conformation (anti-coplanar conformation) nucleophilic oxygen (O^-) displaces Cl^- via a backside attack (Neighbouring group participation)



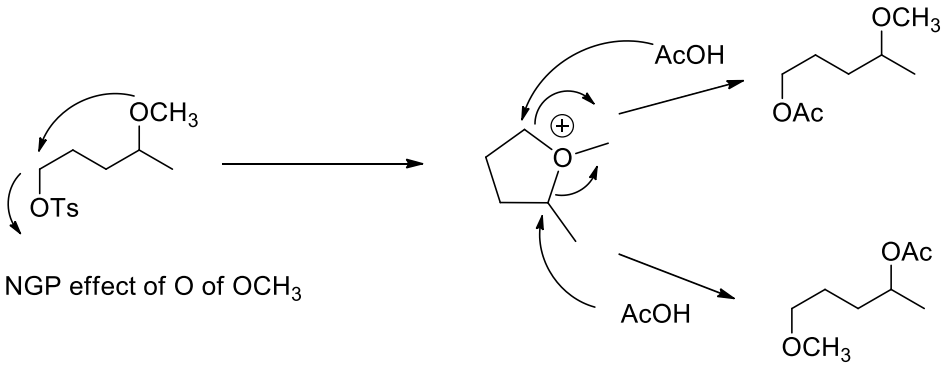
In a 1,2-*cis*- cyclohexane, one group must be axial and the other group equatorial. In one conformation, Cl and H are diaxial, and this situation can lead to elimination, i.e.,

dehydrochlorination to give a vinyl alcohol which finally gives a ketone. (In this conformation, both the departing groups are trans- and coplanar).

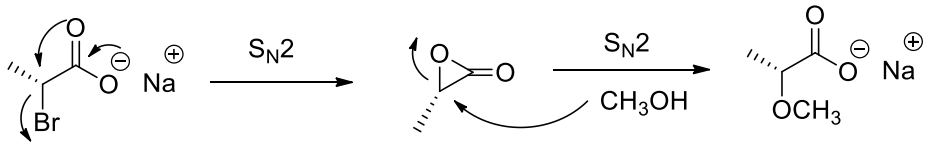


Answer to the Q2: If the reaction was a simple substitution reaction, only the first product would have formed. As it is seen that the two given products were formed, it can be explained by applying neighbouring group participation.

The ether O is a very good internal nucleophile. It can form a cationic five-membered cyclic intermediate. This common intermediate can lead to the formation of both the products, depending on which carbon in the intermediate, AcOH would attack.



Answer to the Q3: This is an example of a substitution reaction, that proceeds with retention of configuration. In this case, the internal nucleophile is a carboxylate that formed an epoxide-type intermediate which reacts quickly with the methanol solvent. Those two consecutive S_N2 reactions results in overall retention of configuration.

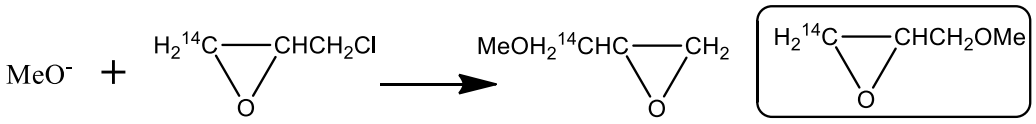


7.10 FURTHER READING

- Robert Thornton Morrison, Robert Neilson Boyd, S. K. Bhattacharjee Organic Chemistry, 7th Edition, 2011, Pearson
- P. S. Kalsi, Organic Reactions and their Mechanisms, New Age International Publishers, New Delhi
- Jerry March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 4th Edition, Wiley-Interscience Publication, 1992

7.11 MODEL QUESTIONS

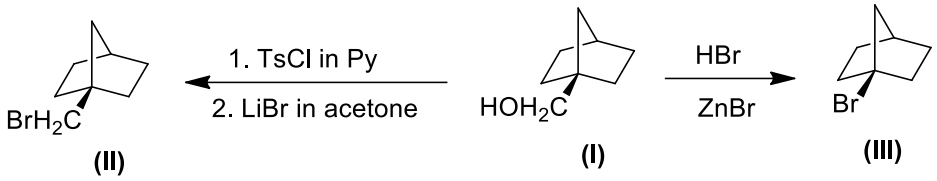
Q1. Explain the outcome of the following reaction



Not formed

.

Q2. Explain the formation of the products, shown in the following reactions.



(II) (I) (III)

Q3. What are the three essential steps in the general mechanism of Neighbouring Group Participation?

UNIT 8: PROTECTION AND DEPROTECTION IN ORGANIC SYNTHESIS

UNIT STRUCTURE

8.1 Learning Objectives
8.2 Introduction
8.3 Protecting groups, Protection and Deprotection
8.4 Characteristics of an Ideal Protecting Group
8.5 Protection and deprotection of alcohols
  8.5.1 Principles of Protection of alcohols
  8.5.2 Acetals and Ketals as Protecting Group of Alcohols
  8.5.3 Ethers as Protecting Group of Alcohols
  8.5.4 Esters as Protecting Group of Alcohols
  8.5.5 Protecting Groups for 1,2 and 1,3 alcohols
8.6 Protection and deprotection of carbonyl group
  8.6.1 Principles of Protection of carbonyl groups
  8.6.2 Acetals and Ketals as Protecting Group of Carbonyl groups
8.7 Protection and deprotection of - NH_2
  8.7.1 Principles of Protection of Amino Group
  8.7.2 Carbamates as Protecting Group of Amino Group
  8.7.3 Amides as Protecting Group of Amino Group
8.8 Let Us Sum Up
8.9 Answers to Check Your Progress
8.10 Further Reading
8.11 Model Questions

8.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- learn the art of reacting one functional group with a reagent, while keeping another functional group present in the substrate inert, although both the functional groups are susceptible toward the reagent.
- know about various protecting groups, used to prevent various functional groups from reacting under various conditions
- know how to remove (deprotect) the protecting groups after the desired reaction is carried out

8.2 INTRODUCTION

When we have to carry out organic synthesis, we come across various types of substrates. Some may contain only one functional group and some may contain different types of functional groups with different types of reactivity. In case of compounds with one kind of functional group, it is easier to carry out reactions. Because during the

reaction with a particular reagent, the other part of the molecule or substrate remains inert or unreactive toward the reagent.
In case of molecules having two functional groups of unequal reactivity, the more reactive group will definitely react first while the less reactive group will probably remain unreacted. But both the groups may also react under the given reaction conditions leading to formation of a mixture of products leading to low yield of the desired product. To avoid such a situation, you must selectively make one functional group inactive, while leaving the other reactive.
You will now learn how to make a reactive functional group chemically inert under a reaction condition by converting it to a chemically inert derivative. This process is called **Protection of functional group**.
In brief, protection of a particular functional group, say, G, is done, when a reaction is desired to be carried out at one site of the molecule, while the group G is expected to remain unaffected.

8.3 PROTECTING GROUPS, PROTECTION AND DEPROTECTION

To protect a group, it is converted into a suitable derivative by some simple chemical conversion. The derivative, which is inert toward the reaction to be carried out, is generally called '**Protecting group**'.

A Protecting Group is a derivative of a functional group, which can be introduced and then subsequently removed, in order to prevent an undesired reaction, or other adverse influence in a programme of synthesis.

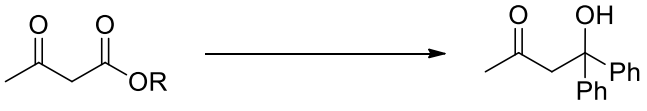
A Protecting Group is introduced into a molecule by chemical modification of a functional group in order to attain chemoselectivity in a subsequent reaction and remove it whenever necessary.

In other words, **a protecting group is a group, use of which makes it possible for a functional group to react selectively in the presence of another reactive group.**

After the reaction is carried out at the desired site of the molecule, the protecting group can be removed by some simple reaction. This process is called **Deprotection**.

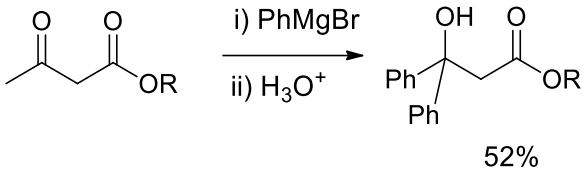
So, in common practice, use of a protecting group adds two steps to a synthetic route.

For example, to convert the keto ester (**1**) to the tertiary alcohol (**2**), you have to treat the keto ester with a Grignard reagent, i.e. PhMgBr, followed by hydrolysis.

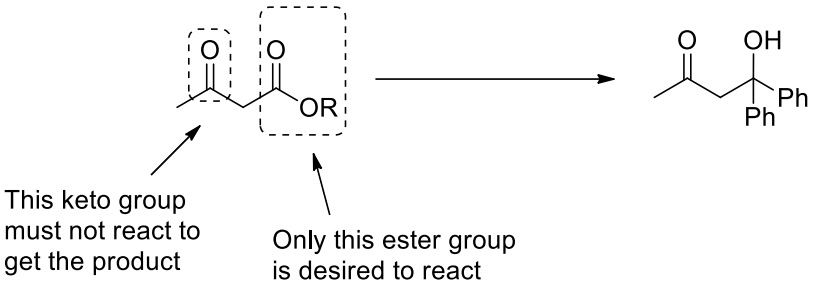


1 **2**

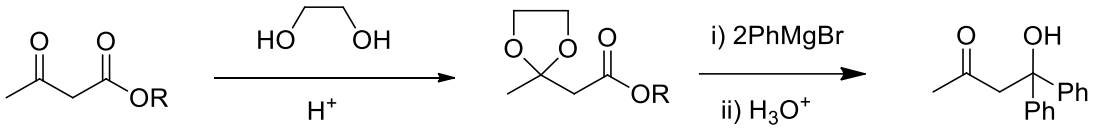
But we know that a keto group is more reactive toward Grignard reagent than an ester group. If you do not protect the keto group, you will mainly get the following product.



So, to convert the less reactive ester group to a tertiary alcohol, you have to make the keto group unreactive in the reactions to be carried out. In other words, you have to protect the keto group, by using a protecting group, say, **G**.



One simple way to protect the keto group, is to convert it to a ketal. That means, you can use ketal group as a protecting group for keto group. The ketal group will not react with Grignard reagent, while the ester group reacts.



In the first step, the more electrophilic ketone carbonyl group is converted to ketal group, which is no longer reactive toward the Grignard reagent, i.e. PhMgBr.

Then PhMgBr is added, two equivalents of which add to the ester group.

On subsequent acid hydrolysis, you will get the tertiary alcohol. On the same hydrolysis condition, the ketal is also converted to its original keto group.

A ketal is an ideal choice here, because ketals are stable to base, (the condition of the reaction here), but are readily converted to ketone under acidic hydrolysis.

8.4 CHARACTERISTICS OF AN IDEAL PROTECTING GROUP

Protecting groups are like **"Painter's Tape".**

Selection of protecting group is a balancing act of ease of preparation and deprotection. In choosing a protecting group, three important considerations are to be taken into account.

i) The nature of the functional group requiring protection
ii) The reaction condition under which the protecting group should be stable

iii) The conditions that can be tolerated for removal of the protecting group

With these considerations keeping in mind, protecting groups are chosen. An ideal protecting group should have the following characteristics.

i) The reagent for a protecting group should be easily available and stable.
ii) The protecting group should be simple to introduce, in quantitative yield.
ii) It should be stable in the reaction condition, that is to be followed.
iv) The protecting group should be stable either in acid or in base media and also stable with redox reagent
v) It should be easy to remove, in quantitative yield, after the desired reaction is over.
vi) A protecting group should not possess or introduce a chiral centre in the substrate. In other words, it should not change the stereochemistry of the substrate, unless it is desired. (However, while protecting –OH group by THP group, a stereogenic centre is generated. We will discuss it later)

In the given example, ketal satisfies all the characteristics of an ideal protecting group for keto group.

It is to be noted that no universal protecting group exists.

Common functional groups, that need protection in a variety of reactions in organic synthesic processes. These are

i) alcohols
ii) carbonyl groups (aldehydes and ketones)
iii) amines
iv) carboxylic groups
v) alkenes

For these functional groups, various protecting groups have been suggested and designed. These are widely used in organic synthesis, particularly complex and multistep syntheses. Alongwith the protecting groups, respective deprotection conditions have also been designed.

Here, we will discuss only about the protection and deprotection of alcohols, carbonyl compounds and amines.

8.5 PROTECTION AND DEPROTECTION OF ALCOHOLS

Before discussing about protection and deprotection of alcohols, you must know why alcohols need protection.

8.5.1 Principles of Protection of alcohols

The –OH group to alcohol has nucleophilic character due to the lone pair of electrons on the oxygen atom. As a result, alcohols react with oxidising agents to give carbonyl compounds and on reactions with other electrophiles viz., alkyl halides and acyl halides, they give ethers and esters, respectively.

So, protection of alcohol may be required because:

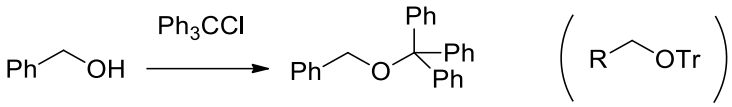
- the hydroxyl group is nucleophilic.

- it may react with electrophiles.
- it may undergo oxidation.
- it may interfere with coupling reactions.
- it may participate in acid-base reactions.

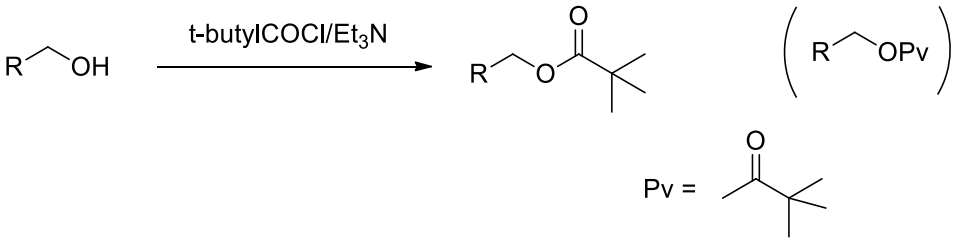
So, when electrophilic reagents are to be used on –OH containing substrates in certain synthetic step, and, reactions at selected hydroxyl sites are to be avoided, the nucleophilic behaviour of alcohols must be deactivated.

This can be done by two ways:

i) **By putting a bulky protecting group on the hydroxyl oxygen** which can sterically prevent it from competing effectively for electrophiles.
For example, the triphenyl methyl (trityl, Tr) ether protecting group where rotation about the O-CPh_3 bond is very fast and the phenyl rings occupy a large volume around the oxygen atom to prevent the approach of anything except the smallest electrophiles, e.g. H^+.



ii) **By delocalising the lone pairs of electrons by conjugation** with e.g., a carbonyl π–system.
For example, pivaloate (Pv) esters can be introduced selectively on to 1°-OH groups. As a result, the lone pair of electrons on oxygen will be delocalized with the carbonyl group making it unavailable for electrophilic attack. On the other hand, the carbonyl group will also be sterically hindered by the bulky *t*-butyl group toward attack by any nucleophilic agent.



Another reason for protection of alcohol is that hydroxyl group possesses a readily removable proton which interferes with the action of strong basic reagents including Grignard reagents and other organometallic reagents that are destroyed by protonation.

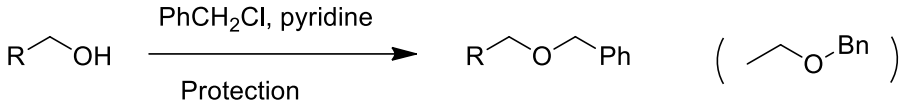


This problem can be solved by replacement of the hydroxyl proton with relatively inert group. For example, alcohol can be converted to ether to make the –OH group masked to survive a wide range of reactions conditions. But remember that converting to a simple n-alkyl ether is not helpful. Because it is not easy to revert it to alcohol after the necessity is over. Thus, some ether with some special features are to be used to protect the –OH

group. Those feature make these groups susceptible to attack by some specific reagents or under specific conditions. This property is used to remove the group in deprotection. Examples of such groups are: Tetrahydropyran (THP) group, Methoxy ethoxy methyl (MEM, $CH_3O\text{-}CH_2CH_2\text{-}O\text{-}CH_2$), benzyl, t-butyl and trialkylsilyl ethers. Besides ethers, there are other types of protecting groups for alcohols. The choice of these PG depends on the other functionality present in the molecule and the nature of the reaction conditions that have to be performed.

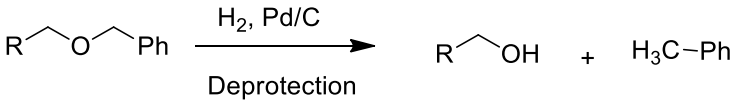
8.5.2 Ethers as Protecting Group of alcohols

Alcohol can be converted to ether by nucleophilic attack on a suitable alkyl halide, e.g. benzyl chloride.

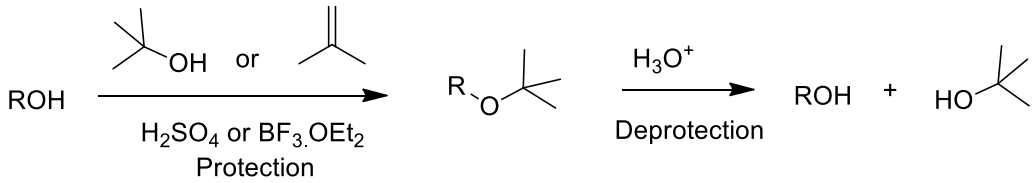


Benzyl ether, stable to base, mild acid and
a wide range of oxidizing and reducing agent

Then after performing necessary reactions on the other part, R, without affecting –OH, the protecting group may be removed by **catalytic hydrogenolysis** under neutral condition.

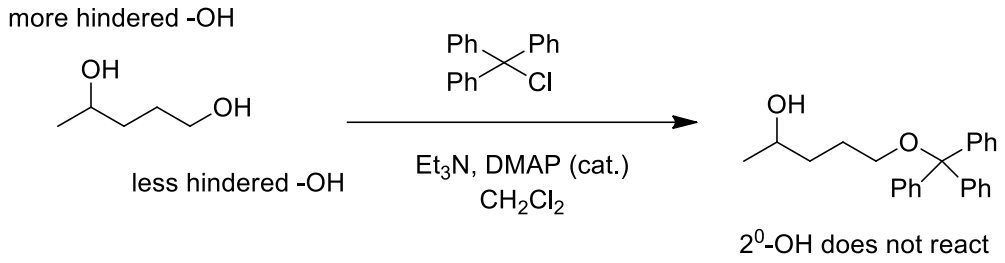


Another example of protecting group of alcohols is *t*-butyl group, which is introduced as follows.



Installation and removing a *t*-butyl group requires stronger (acidic) conditions. However, while in place, it is stable and inert to nearly all conditions other than strong acid.
Deprotection: Owing to the stability of the t-butyl cation, *t*-butyl ethers can be cleaved under moderately acidic condition. Trifluoroacetic acid in an inert solvent is frequently used. Aqueous Phosphoric acid and 4N HCl is also used.

Triphenylmethyl (Trityl, Tr) group is the most important for protection of 1°-alcoholic group, since only 1°-alcohols react at a useful rate with trityl chloride in pyridine or Et_3N. Hence, trityl group is used for selective protection of 1°-alcohols, where 2°- and 3°- OH groups are also present in the substrate. In addition to selective protection of 1°-alcoholic group, the trityl group offers good resistance to bases.

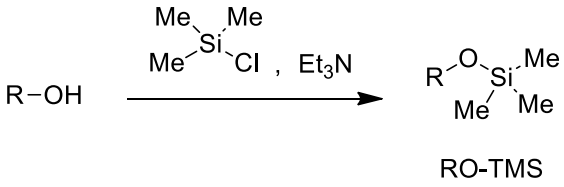


Deprotection: Trityl ethers are readily cleaved by hot aqueous acid treatment or by hydrogenolysis.

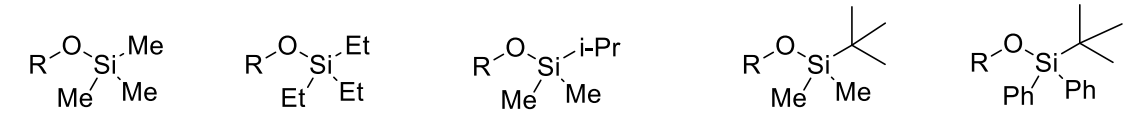
Silyl ethers as protecting groups

Trialkylsilyl ether derivatives such as Trimethylsilyl (TMS) ethers have been widely used for protection of alcohols, due to the fact that they can be readily introduced and removed under mild condition. Moreover, a wide range of silylating agent are available for use. These silicon-based protecting groups reduce the nucleophilicity of the oxygen atom both electronically and sterically.

These are prepared by reaction of an alcohol with trialkylsilyl chloride, in presence of a base.

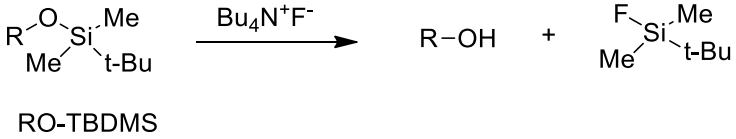


There is a wide range of silyl PG. Commonly used are as given below.



Trimethylsilyl	Triethysilyl	Isopropyldimethylsilyl	Tertiary-butyl-di-methyl silyl	Tertiary-butyl-di-phenyl-silyl

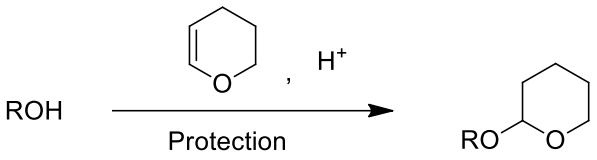
Deprotection: Deprotection can be done by water, aqueous acids and fluoride salt. Choice of reagent depends on the structure of the substrate. Fluoride salt is used because silicon has a strong affinity for fluoride, and hence the O-SiR_3 bond is prone to cleavage by fluoride salts, such as tetra-*n*-butyl ammonium fluoride (*n*-$Bu_4N^+F^-$, TBAF), which is soluble in organic solvents such as THF and CH_2Cl_2. Pyridine.HF and ammonium fluoride can also be used.



RO-TBDMS

8.5.3 Acetals and Ketals as Protecting Group of alcohols

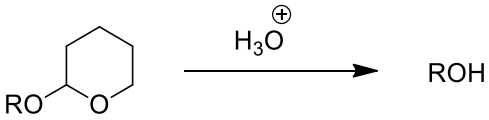
Tetrahydropyranyl ether (RO-THP) is a widely used acetal protecting group for alcohol. Note that the name is ether, but looking at the structure you will understand that it is overall an acetal group.



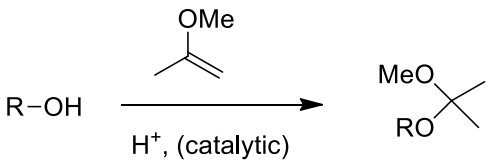
Tetrahydropyranyl (THP) ether
stable to oxidation, reduction and base

The THP group is readily introduced by reaction of the alcohol with dihydropyran in presence of acid catalyst, e.g., TsOH, $BF_3.OEt_2$ or $POCl_3$.

Deprotection: THP group is readily hydrolysed under aqueous acidic conditions with AcOH-THF, TsOH etc.

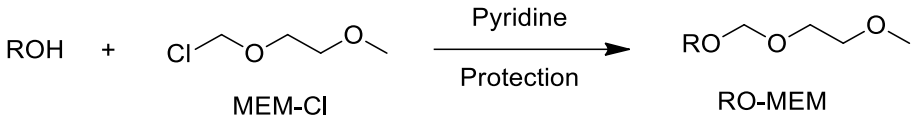


Disadvantage: THP group does not fulfil an important requirement to be an ideal protecting group. It is already mentioned in Section 8.4 that a protecting group should not possess or introduce a chiral centre in the substrate. But THP group produces a new stereogenic centre at C-2 of the tetrahydropyran ring. But in case of an achiral alcohol, it does not create difficulties, since a racemic mixture is produced. But in case of chiral alcohol, a mixture of diastereomers is produced which may complicate purification and characterisation.
To avoid this problem, **methyl-2-propenyl ether** may be used for protection.



Deprotection can be done under milder condition than those required for THP ethers.

∝-halo ethers are also used for protection of alcohols. MOM-Cl (Methoxymethyl chloride, $MeOCH_2CH_2OCH_2Cl$) is reacted with an alcohol in presence of a base (Pyridine or *i*-Pr_2N) produces the corresponding formaldehyde acetal.



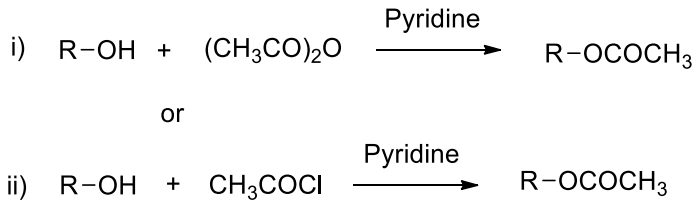
Deprotection is done by treatment with aqueous acid.

8.5.4 Esters as Protecting Group of alcohols

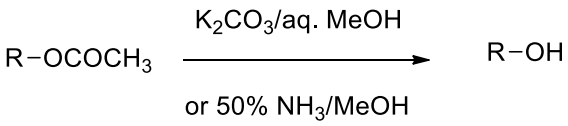
Esters are very much useful for protection of alcohols. Esters are generally prepared from an alcohol and an acid chloride or anhydride. Steric hindrance plays a significant role in determining the selectivity of alcohol towards acylation. The ease of acylation in various alcohols can be generalised as – i) 1°-alcohols can be acylated more readily than a 2°-alcohol. ii) Among the 2°-alcohols, those in less hindered positions can be acylated more readily than those in more hindered position. Iii) 3°-alcohols are acylated only slowly and to acylate them, very reactive acylating reagents are required. Iv) The above trends are very prominent with bulky acylating agents.

Some examples of most commonly used esters for alcohols are illustrated here.

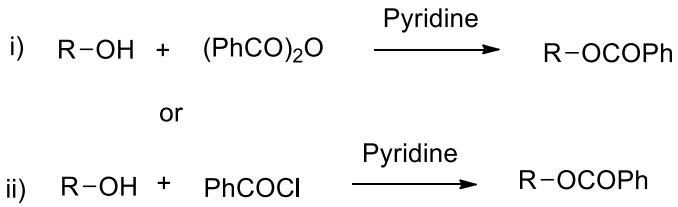
Acetate ester:



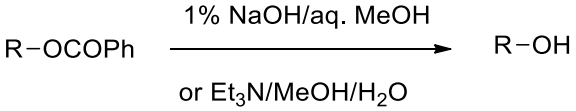
Deprotection can be done by hydrolysis under basic condition.



Benzoate ester:



Deprotection can be done by hydrolysis under basic condition. However more basic condition than that for acetate ester is required. Because benzoate esters are more stable to hydrolysis than acetate ester.



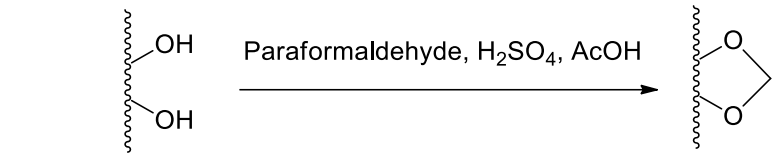
8.5.5 Protecting Groups for 1,2 and 1,3 alcohols

Cis-1,2-diols and *cis*- and *trans*- 1,3-diols can be protected as cyclic acetals and ketals (viz., dioxolanes and dioxanes) or as cyclic ortho esters. These protecting groups are often used in protection of *cis*-1,2-diols in nucleosides.

8.5.5a Cyclic acetals and ketals

Cyclic acetals and ketals are formed by reaction of a diol and a carbonyl group in the presence of an acid catalyst. The resultant dioxolanes and dioxanes are stable to alkaline conditions (generally applied for alkylation or acylation), to reducing agents like $LiAlH_4$ and Na-Hg and to catalytic hydrogenation. However, benzylidene and acetals/ketals are prone to catalytic hydrogenation. Dioxolanes and dioxanes are also stable to some oxidizing agents.
Examples of cyclic acetal as protecting group for diols:

Methylene Acetal:

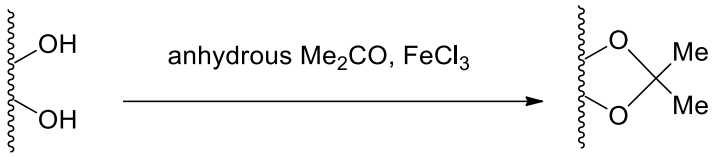


cis-1,2 diol or *cis*- and *trans*- 1,3 diol group of a sugar or any compound

Methylene acetal

Deprotection can be achieved by hydrolysis under acidic condition.

Acetonide: Acetonides may be prepared by reaction of a diol with acetone and an acid.



Deprotection can be achieved under a variety of acid catalysed hydrolysis.

8.5.5b Cyclic ortho esters

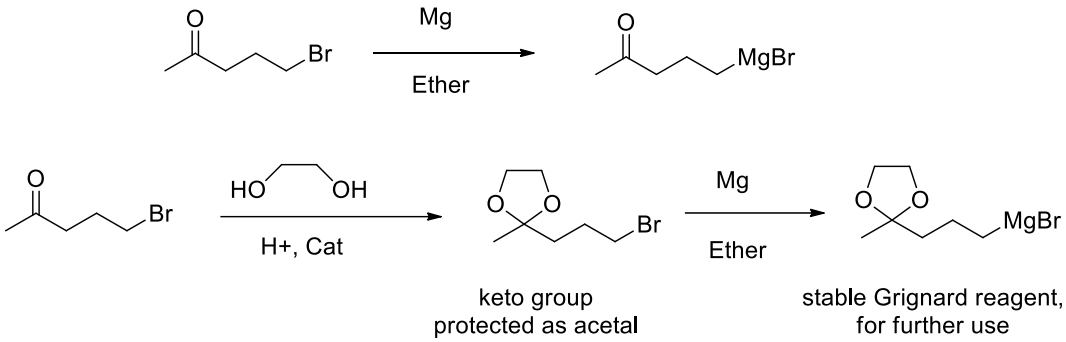
Orthoformates, methoxymethylene acetals, dimethoxymethylene ortho esters and cyclic carbonates are examples of cyclic orthoesters, often used for protection of diols.

8.6 PROTECTION AND DEPROTECTION OF CARBONYL GROUP

Both aldehydes and ketones require protection during synthetic sequences. The methods of protection and deprotection for both these classes of compounds are almost same with certain differences due to their difference in electrophilicity. These are discussed together.

8.6.1 Principles of Protection of carbonyl groups

A carbonyl group requires protection during synthetic sequences, because carbonyl group is susceptible to attack by a wide variety of reagents, such as, strong or moderately strong nucleophiles including organometallic reagents, acidic/basic/catalytic hydride reducing agent and some oxidant. To achieve desired chemoselectivity, carbonyl group needs to be protected against attack by these reagents.
Let us illustrate it with an example of preparation of the Grignard reagent (A), which is to be prepared with the following bromoketone. But it is impossible to prepare, because the Grignard reagent, formed will attack the keto group, i.e. it would react with itself. By protecting the keto group, by acetal formation, the protected Grignard reagent is prepared, from the same bromoketone.



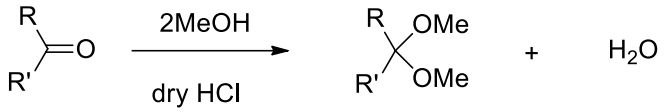
Acetals, are stable to base and to basic nucleophiles, so the keto group, now protected, will no longer be reactivity problem. Now the Grignard reagent may be reacted with an electrophile as required, and after that the ketone can be recovered by hydrolysing the acetal in dilute acid. **The acetal is functioning here as a protecting group because it protects the ketone from attack by the Grignard reagent**.

8.6.2 Acetals and Ketals as Protecting Group of Carbonyl groups

In the section 8.3, and in the above example, you have seen that acetal worked as a useful protecting group for carbonyl groups. For protection of carbonyl group, cyclic or acyclic acetal or ketal and cyclic and acyclic thioacetal or thioketal may be used. The protecting group is introduced by treating the carbonyl compounds in presence of acid with an alcohol, diol, thiol, dithiol.
Cyclic and acyclic acetals and ketals are stable to aqueous and non-aqueous bases, nucleophiles including organometallic reagent and to hydride reduction.
The oxygen containing acetals and ketals are readily cleaved by acid hydrolysis. Thioacetal and thioketals are cleaved under neutral conditions by Hg (II) or Ag(I) or Cu(II) salts.

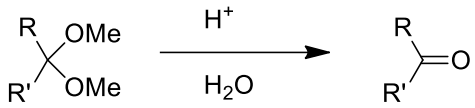
8.6.2.a Acyclic acetals or ketals

Commonly used acetals are dimethyl acetals or ketals. But acyclic acetals prepared from ketones are usually unstable. So, these are mostly used for protection of aldehydes.

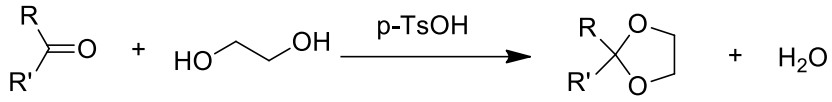


R = H, Alkyl, Ph R' = H, Alkyl, Ph, $PhCH_2$ etc

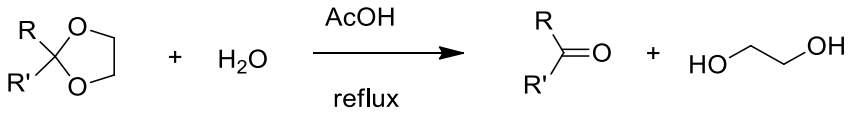
Deprotection is done by treatment with acid.



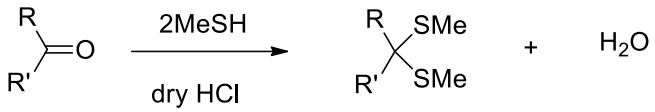
8.6.2.b Cyclic acetal or ketal



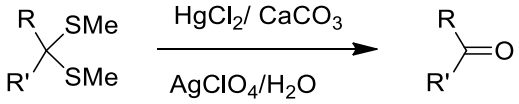
The deprotection may be done by acid catalysed hydrolysis (dil. HCl or aq. AcOH or TFA/H_2O or pTsOH in acetone is used).



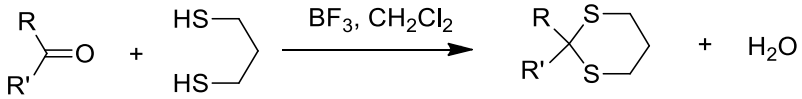
8.6.2.c Acyclic thioacetal or thioketal



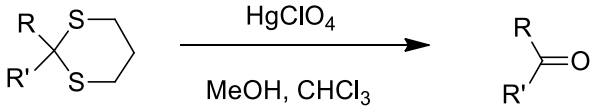
Deprotection:



8.6.2.d Cyclic thioacetals and thioketals



Deprotection:



Remember: Five membered and six membered cyclic acetals and thioacetals are derivatives of 1,3-dioxolane, 1,3-dioxane, 1,3-dithiolane and 1,3-dithiane respectively.

8.7 PROTECTION AND DEPROTECTION OF AMINO GROUP

Amino group is present in a wide range of compounds. One very important class of biologically important compounds containing amino group is amino acids and these are involved in the synthesis of one of the most important classes of biological molecules: peptides. Biological system synthesizes peptides and proteins by selectively coupling amino acids. But when you have to perform it in the laboratory, you will encounter with a number of challenges. One of the most important challenges is the protection of the amino group.

8.7.1 Principles of Protection of Amino Group

Amines are highly nucleophilic and hence, possess greater affinity for electrophiles. Unlike alcohols, it is difficult to protect amines through alkylation. Because of the presence of the lone pair of electrons, nitrogen could be protonated/alkylated. Again, primary and secondary amines are prone to oxidation and NH bonds undergo metallation on treatment with organometallic reagents.

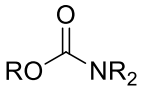
So, it is difficult to carry out reactions of compounds containing amino group with electrophiles without reacting with the amino group. Amino groups thus need to be protected by protecting lone pair of electrons on nitrogen, such that other desired reaction on the compound with electrophiles can be performed keeping the amino group inert. The protection of the amino group can be done by

i) The nitrogen lone pair can be brought into conjugation with π-system.
ii) The nucleophilicity of the amino group can be reduced by steric hindrance.
iii) Using protecting groups that involve the lone pair of electrons in another bond

Numerous protecting groups have been developed for amino groups like carbamates and amides.

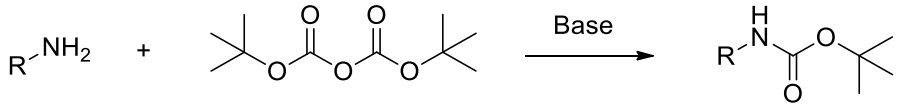
8.7.2 Carbamates as Protecting Group of Amino Group

Carbamates are a sort of hybrid of an ester and an amide, but their chemistry resembles most closely that of an amide.



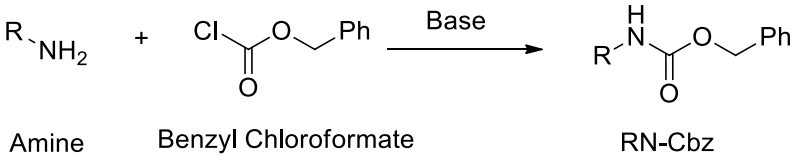
A carbamate

Carbamates (>NCOOR) are formed by reaction of an amine with an azido or chloroformate or with an appropriate anhydride. Many carbamates have been used as protecting groups of amines. But the most useful are *t*-butyl carbamate (*t*-BOC, = *t*-**b**utyl**o**xy**c**arbamate), benzyl (Cbz, = Carboxybenzyl, sometimes written as just Z-)) etc. The Boc group, t-BuOCO, is introduced with $(t\text{-BuOCO})_2O$, known as Boc anhydride.



amine Boc-anhydride

t-BOC group can be readily cleaved (deprotected) by acidic hydrolysis.
Cbz group is introduced by using Benzyl Chloroformate

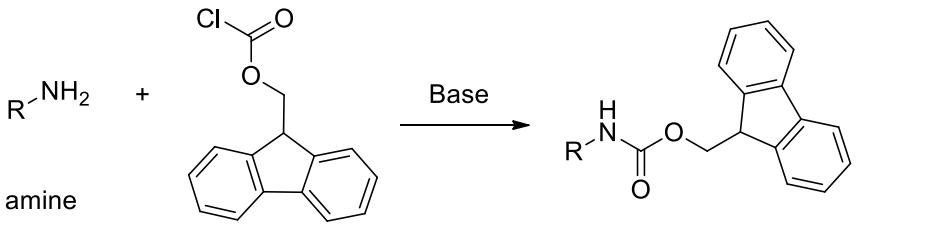


Amine Benzyl Chloroformate RN-Cbz

Protection by Cbzgroup

Cbz group can be cleaved (deprotected) by hydrogenolysis by H_2 with Pd-C catalyst.

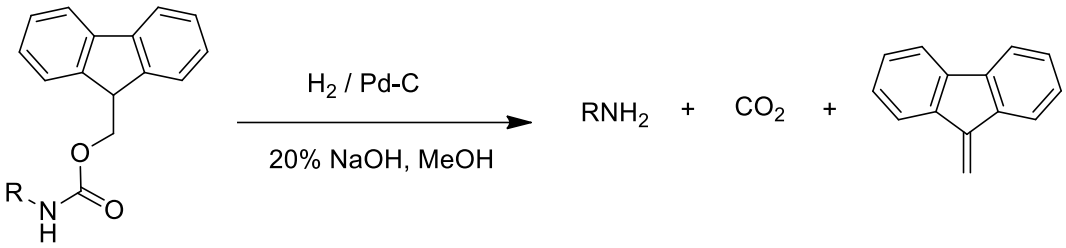
9-Fluorenylmethyl carbamate (Fmoc) protection of amines can be carried out with 9-Fluorenylmethyloxy carbonyl chloride in the presence of pyridine or $NaHCO_3$.



9- Fluorenylmethyl-chloroformate or 9- Fluorenylmethyloxy carbonyl chloride

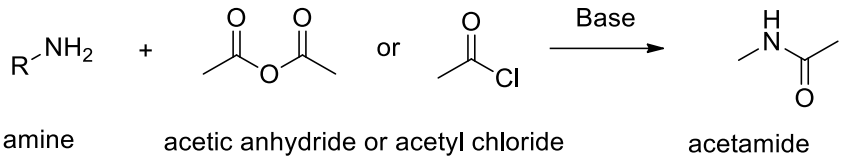
9- Fluorenylmethyl-carbamate or RN-Fmoc

It can be cleaved by catalytic hydrogenolysis.

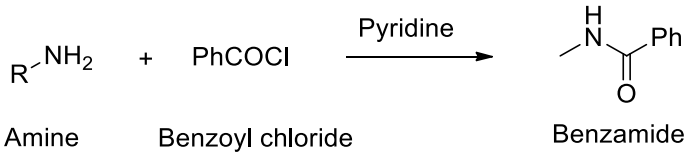


8.7.3 Amides as Protecting Group of Amino Group

Amides serve as a good protecting group for amines as these can be easily prepared by reaction of an amine with acid chloride and anhydride. Amides are relatively stable compounds, and are cleaved by heating in strongly acidic or basic conditions. So these protecting groups can be used only where other functional groups can tolerate such harsh conditions.
Many N-acyl derivatives are prepared for protection of amino group. Formamide, acetamide, Chloroacetamide, acetoactamide, benzamide are some examples of amide protecting groups.
Phthalimide is an example of cyclic imide, used for protection of amino group.



Deprotection can be done by strong acid hydrolysis



Benzoyl group can also be cleaved by strong acid hydrolysis.

W CHECK YOUR PROGRESS

Q1) What is the logic of protection of a functional group?
Q2) Define 'protecting group' in chemical transformations?
Q3) Enumerate the characteristics of an ideal protecting group.
Q4) Name two widely used protecting groups for alcohol.
Q5) Name a suitable protecting group for a 1°–OH group in the presence of 2°-OH and 3°-OH.
Q6) What is the principle of using Tetra-n-butyl ammonium fluoride (TBAF) for deprotection of silyl ether protecting group of alcohols?

2 8.8 LET US SUM UP

- Protection is actually deactivation (completely inert) of a functional group, position or ring in a given sequence of reaction.
- A Protecting Group is introduced into a molecule by chemical modification of a functional group in order to attain chemoselectivity in a subsequent rreaction and then the protecting group is removed by a reaction which is called deprotection.
- In the process of protection,
    - A protecting group is introduced in a molecule by derivatization of a functional group (Protection)
        - to attain chemoselectivity in a subsequent reaction
- After the desired reaction is carried out, the protecting group is removed by deprotection.
- Ethers, silyl ethers, acetals, esters are commonly used protecting groups of alcohols.
- Acetals, thioacetal, ketals and thioketals are commonly used protecting groups of carbonyl groups.
- Carbamates and amides are commonly used protecting groups for amines.

K 8.10 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: Protection of a functional group is required when the functional group is not desired to react while some transformation is to be carried out on other functional group of similar reactivity in the substrate.

Answer to Q2: A Protecting Group is a derivative of a functional group, which can be introduced and then subsequently removed, in order to prevent an undesired reaction, or other adverse influence in a programme of synthesis.

Answer to Q3: The characteristics of an ideal protecting group (PG) are:

i) The PG should be simple to introduce, in quantitative yield

ii) The reagent for a PG should be easily available and stable

ii) It should be stable in the reaction condition, that is to be followed.

iv) The PG should be stable in acid, base and redox reagent

v) It should be easy to remove, in quantitative yield, after the desired reaction is over.

vi) A PG should not possess or introduce a chiral centre in the substrate.

Answer to Q4: Silyl ether group, e.g. trimethyl silyl (TMS) and Acetal group (Tetrahydropyran (THP)

Answer to Q5: Triphenylmethyl (Trityl, Tr) group

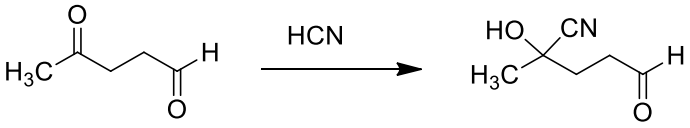
Answer to Q6: Because silicon has a strong affinity for fluoride, and hence the O-SiR_3 bond in silyl ether protected alcohol, is prone to cleavage by fluoride salts, such as tetra-*n*-butyl ammonium fluoride (*n*-$Bu_4N^+F^-$, TBAF),

O 8.11 FURTHER READING

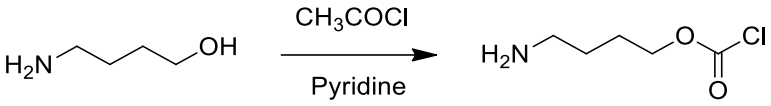
- Protecting Group Chemistry, Oxford Primer, Oxford University Press, 2000.
- P. J. Kocienski, Protecting Groups, 3rd edn, Thieme, 2003.
- P. G. M. Wuts and T. Greene, Greene's Protecting Groups in Organic Synthesis, Wiley, 2007
- J. Clayden, N. Greeves and S. Warren, Organic Chemistry, 2nd Ed. OUP, 2023
- J. Singh and L. D. S Yadav, Organic Synthesis, Volume 2, Pragati Prakashan

M 8.12 MODEL QUESTIONS

Q1. Using a suitable protecting group, how would you carry out the following conversion?



Q2. Using a suitable protecting group, how would you carry out the following conversion?

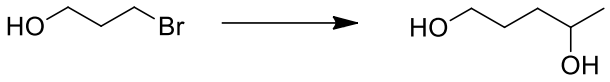


Q3. Describe the use of the following as protecting groups in organic synthesis.

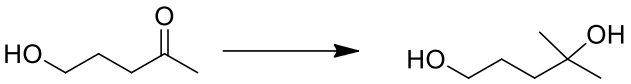
a) TBDMS (*t*-butyldimethylsilyl) group
b) F-moc group
c) 1,3-dioxolane
d) THP

Q4. Using a suitable protecting groups, how would you carry out the following conversions?

i)



ii)



UNIT 9: FORMATION OF C=C BONDS

UNIT STRUCTURE

9.1 Learning objectives
9.2 Introduction
9.3 Elimination reactions
  9.3.1 E1 Reaction
  9.3.2 E2 reaction
  9.3.3 Saytzeff and Hofmann's rule
  9.3.4 E1cB reaction
9.4 Syn elimination
  9.4.1 Pyrolysis of esters
  9.4.2 Chugaev reaction
9.5 Witting reaction
9.6 McMurry reaction
9.7 Peterson olefination
9.8 Julia Reaction
9.9 Tebbe olefination
9.10 Let us sum up
9.11 Answers to check your progress
9.12 Further Reading
9.13 Model Questions

9.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- learn about the concept of formation of C=C in organic chemistry
- learn about the various elimination reactions.
- learn about the mechanisms of important *syn* elimination reactions
- learn about the synthesis of alkenes via some name reactions

9.2 INTRODUCTION

The formation of carbon - carbon double bonds (C=C) is one of the most fundamental transformations in organic chemistry, since C=C is the key feature of structure of the important class of organic compounds, alkenes. Alkenes are important structural units found in many natural products, pharmaceuticals, and industrial chemicals. Important processes for synthesis of alkenes includes i) Condensation and coupling methods, ii) Elimination methods and iii) Carbonyl oleifination methods, iv) Alkyne reduction methods and v) Metal catalysed and Coupling reactions.

i) Condensation and coupling methods include Aldol Condensation, Knoevenagel Condensation etc,
ii) Elimination methods usually refer to β-elimination

iii) Carbonyl olefination methods include Witting reaction, McMurry reaction, Peterson olefination, Julia Reaction, Tebbe olefination etc.
iv) Alkyne reduction methods include partial reduction of C-C triple bond and
v) Metal catalysed and coupling reactions refer to reactions like Heck reaction and alkene metathesis reactions.

Among the various methods available for the synthesis of alkenes, elimination reactions play a crucial role because they provide a straightforward and efficient pathway for converting saturated compounds (containing carbon-carbon single bond) into unsaturated ones (containing carbon-carbon double bond). In addition to these classical mechanisms, many named reactions have been developed that efficiently generate carbon–carbon double bonds through elimination processes.
Therefore, understanding the mechanisms, factors affecting the reactions, and the applications of named elimination reactions is essential for designing efficient synthetic strategies. This chapter focuses on the formation of C=C bonds via elimination reactions**,** and carbonyl olefination reactions discussing both the fundamental mechanistic aspects and important named reactions used in organic synthesis.

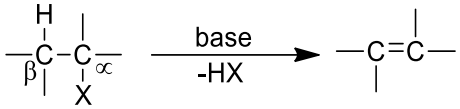
9.3 ELIMINATION REACTIONS

A carbon–carbon π bond (C=C) is most commonly formed by elimination reactions, where a small molecule is removed from a saturated compound to give an alkene. There are three types of elimination reactions:

1. E1: Unimolecular elimination reaction
2. E2: Bimolecular elimination reaction
3. E1cB: Conjugate base elimination reaction

9.3.1 E1 Reaction or Unimolecular Elimination Reaction

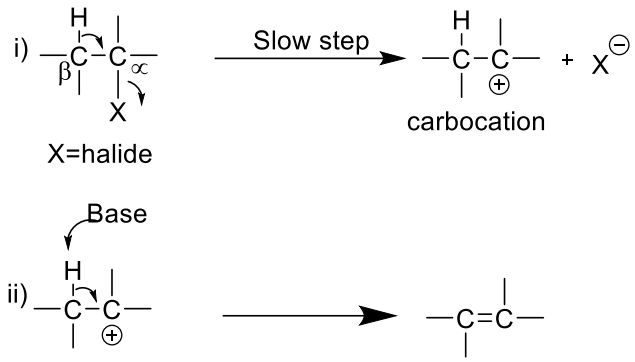
To study elimination reactions, alkyl halides are a good family of compounds, because they have relatively good leaving groups. That is, the halide ions are easily displaced.
There are two types of important elimination reactions, E1 and E2 reactions. Let us discuss E1 reaction taking the following example.



In E1 (E for Elimination, 1 for Unimolecular) reaction, there are two steps.

- In the first step, the leaving group leaves and the carbocation intermediate is formed. This is the rate determining (slow) step and does not involve the base. So this step is unimolecular.
- In the second step a weak base takes the proton from the substrate to form the alkene compound.

Mechanism:

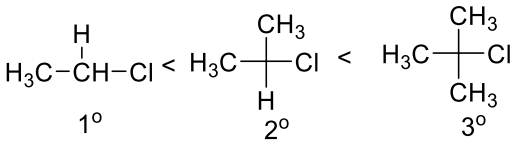


Since, the first step is the rate determining step, so rate of the reaction will be

$$\text{Rate} \quad \alpha \quad [\text{R-X}]^1$$

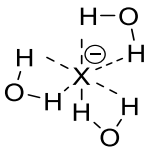
Factors that affect the reaction:

1. Stability of the carbocation: Since the increasing order of stability of carbocation is 1° < 2° < 3°, so the rate of the reaction will be in the increasing order in different alkyl halide as 1° < 2° < 3°. For example:



2. Weak base: Since already carbocation is formed in the first step, so weak base can eliminate the proton. Example: methanol, ethanol, water etc.

3. Solvent: In this case, the solvent should be polar protic. Polar which can decrease the electrostatic force between C-X and protic solvent will solvate the anion (X^-) so that it cannot attack back this carbocation.



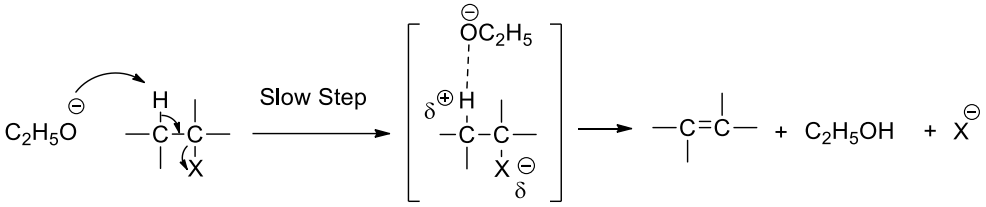
4. Leaving group: Rate is proportional to ability of the leaving group which can more easily detach from the substrate. Example:

$$I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$$

9.3.2 E2 Reaction or Bimolecular Elimination Reaction

Here is an example of E2 reaction, where, E stands for elimination and 2 stands for 'bimolecular'.

This is a single step reaction. This needs a strong base. In this case a transition state is formed where H and leaving group are anti-periplanar to each other.



Since, only one step is there so the rate of an E2 reaction depends linearly on the concentrations of both the alkyl halide and the base (in this case, methoxide ion).

$$\text{Rate} \propto [\text{Alkyl halide}]^1\,[\text{Base}]^1$$

The rate law tells us that both the alkyl halide and the base are involved in the transition state of the rate-determining step, indicating a one-step reaction. The given mechanism which portrays an E2 reaction as a concerted one-step reaction agrees with the observed second-order kinetics:

Factors that affect the reaction:

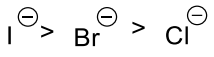
1. **Substrate**: Substrates that can form stable alkene will increase the rate of the reaction. Tertiary alkyl halides undergo E2 easily because they form more stable alkenes. Reactivity order is same with that of E1 elimination:

   Tertiary (3°) > Secondary (2°) > Primary (1°)

2. **Strong Base**: Stronger base favours E2 elimination. Example: alcoholic NaOH/ KOH, $NaNH_2/NH_3$.

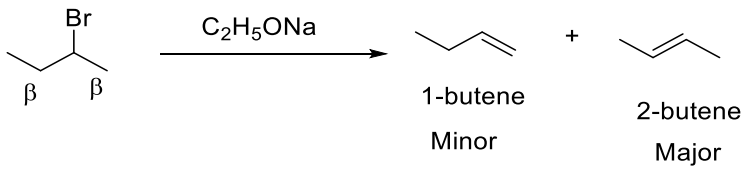
3. **Solvent**: In this case, the solvent should be polar aprotic. Polar which can decrease the electrostatic force between C-X and aprotic solvent which cannot solvate the anion (base). Example: DMSO, DMF, acetone etc.

4. **Leaving group**: Rate is proportional to ability of the leaving group which can more easily detach from the substrate. Example:



9.3.3 Determination of the major product in elimination reaction

Saytzeff's rule: With Unsymmetrical alkyl halide, if the base is smaller more substituted alkene is formed as a major product. This is known as Saytzeff rule.



Hoffmann rule: Less substituted alkene will form as a major product. This happens when

i) the base is bulky

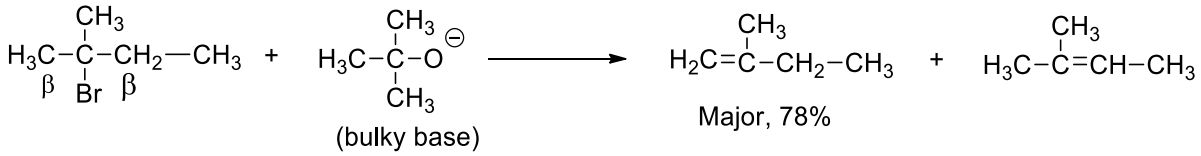
ii) the leaving group is poor leaving group such as NR_3^+, F^-, etc.

iii) steric hindrance at beta carbon atom and

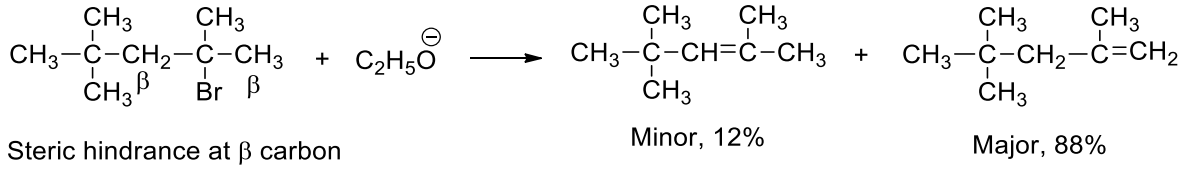
iv) when alkyl halide contains one or more double bonds

Examples:

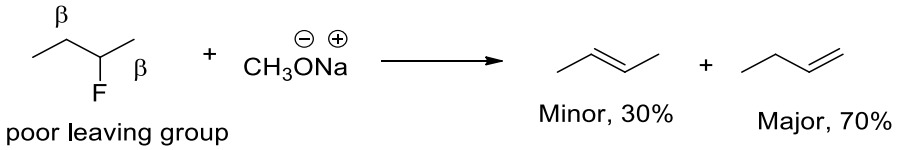
Case 1: When the base is bulky



Case 2: When there is steric hindrance at beta carbon atom



Case 3: When the leaving group is poor



9.3.4 E1cB Reaction or Conjugate-base unimolecular elimination reaction

In this reaction first proton will loss to form carbanion then removal of leaving group form the alkene. Conversion of carbanion to an alkene is the rate determining step. This elimination, since proceeds through the formation of conjugate base of the starting material, is known as E1cB.

The reaction is unimolecular reaction because reaction velocity depends only on the concentration of conjugate base of the substrate.

Main characteristics of the reaction are:

i) Substrate which can stabilize the carbanion intermediate i.e β-carbon should contain electron withdrawing group e.g. carbonyl, nitro, cyano, sulphonyl etc.

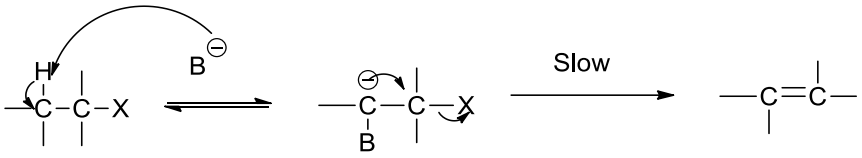
ii) Product formation generally take place by Hoffmann rule (less substrate alkene is formed).

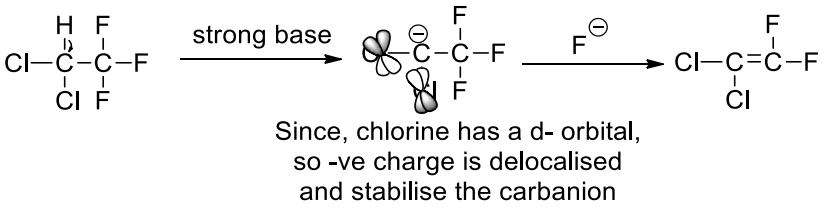
iii) Leaving group is generally poor leaving group (e.g. F^-)

iv) β-hydrogen should be highly acidic so that the carbanion formation may take place easily.

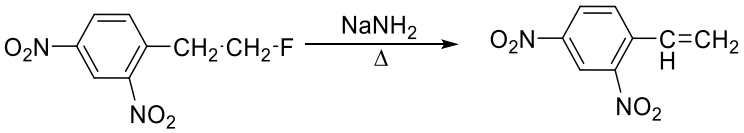
v) Strong base needed.

Examples:
i) Treatment of 2,2-dichloro-1,1,1-trifluoroethane with a strong base form a carbanion which can stabilise by the vacant d-orbitals.





ii) Reaction of 1-(2-fluoroethyl)-2,4-dinitrobenzene with sodamide form the alkene.



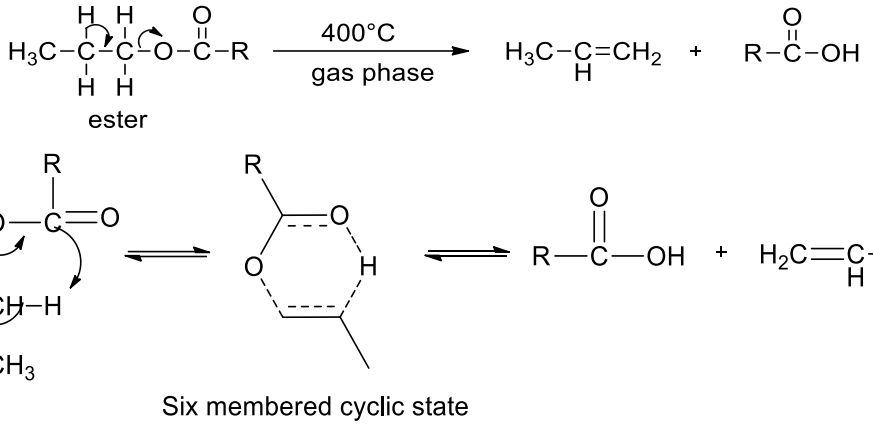
9.4 SYN ELIMINATION: (E1 ELIMINATION)

Syn elimination is an elimination reaction in which the β-hydrogen and the leaving group are removed from the same side (*syn*-coplanar) of the molecule.
This is opposite to anti-elimination (like in E2), where they must be *anti*-periplanar.

Examples:

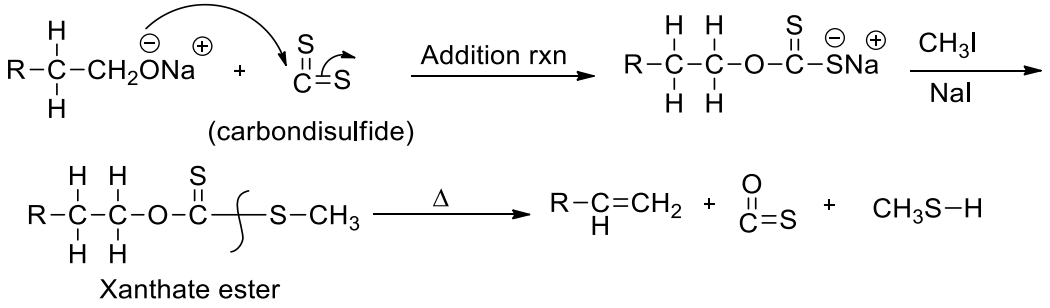
9.4.1 Pyrolysis of esters

- Pericyclic elimination reaction; concerted step (one stop)
- Five or six membered cyclic transition state formed
- Do not involve acidic or basic catalyst
- Depends on temperature
- β -hydrogen needed
- Ester decomposes at very high temperature and pressure into alkenes and acid. Here, carbonyl group of ester acts as a base, attacking β-hydrogen intramolecularly *via* a six membered transition state.

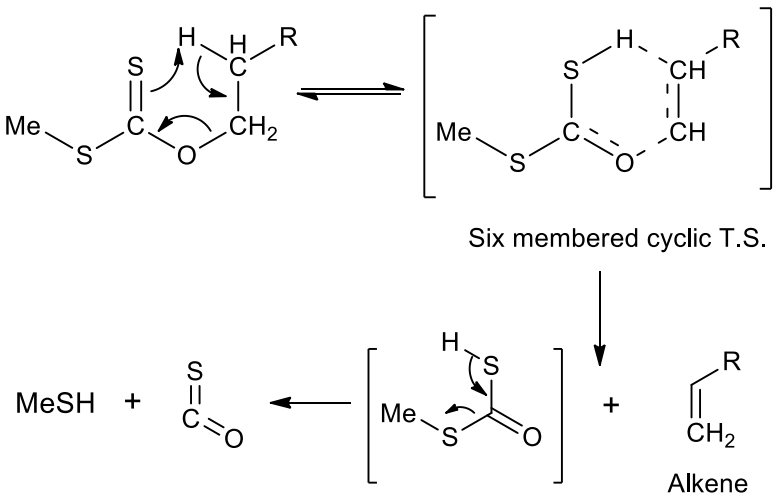


9.4.2 Chugaev Reaction

Pyrolysis of Xanthate esters into alkene is known as Chugaev reaction. Xanthate is prepared by the reaction of alkoxide with carbon disulphide followed by treatment with methyl iodide. When heated to about 200 °C, this ester is decomposed by an intramolecular elimination. In a 6-membered cyclic transition state the hydrogen atom is removed from the carbon atom β- to the xanthate oxygen in a syn-elimination. The side product decomposes to carbonyl sulfide (OCS) and methanethiol.

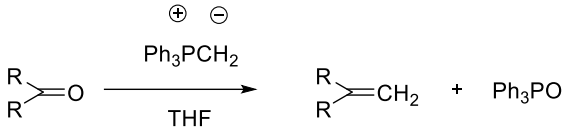


Mechanism:



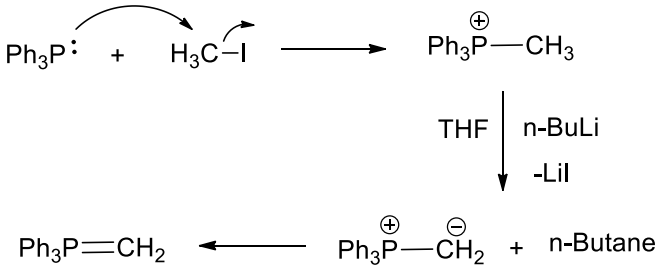
9.5 WITTIG REACTION

The reaction of aldehydes or ketones with phosphonium ylide to produce alkene is known as Wittig reaction. The mechanism involves nucleophilic attack by the ylide on the carbonyl carbon, producing an intermediate (betaine or oxaphosphetane), which collapses to form an alkene and triphenylphosphine oxide.

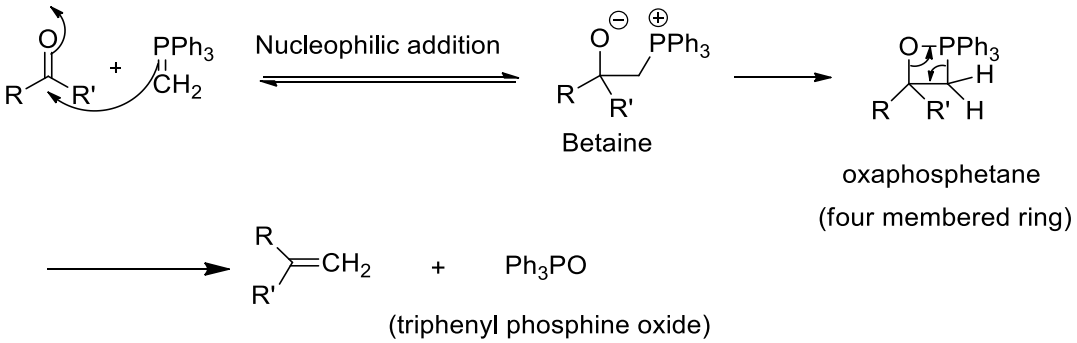


Formation of ylide:

The ylide is prepared by the reaction of triphenylphosphine and methyliodide in presence of base



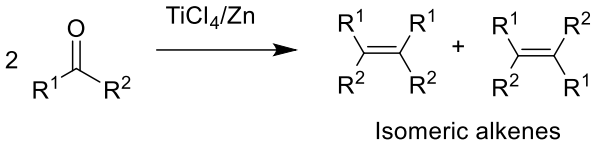
Mechanism of the reaction:



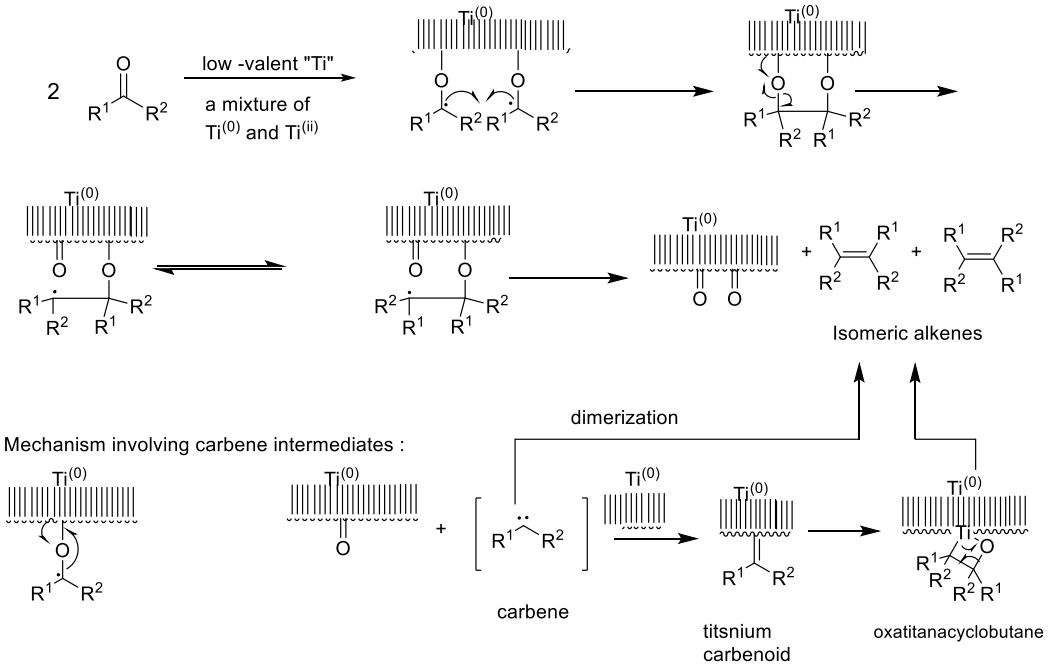
9.6 McMURRY REACTION

The McMurry reaction is a reductive coupling reaction in which two carbonyl compounds (aldehydes or ketones) are coupled using low-valent titanium to form an alkene (C=C bond). Low-valent titanium species generated from the following reaction:

$TiCl_4$ + Zn or $TiCl_3$ + $LiAlH_4$, sometimes $TiCl_4$ + Mg. $TiCl_4$ or $TiCl_3$ is reduced to Ti(0) or Ti(II). Usually dry THF or ether is used as solvent in this reaction.

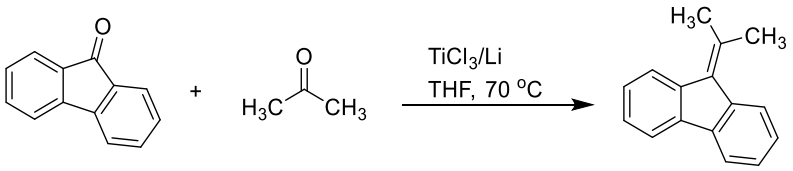


Mechanism:

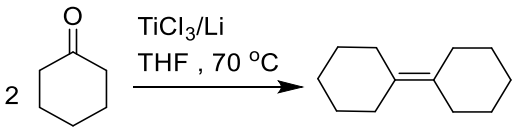


Examples:

i) Reaction of 9*H*-fluoren-9-one with acetone undergoes coupling reaction in presence of titanium chloride to produce the coupled alkene product.

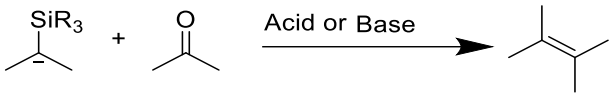


ii) Two molecules of cyclohexanone undergo coupling reaction in presence of titanium chloride and Li to form the corresponding alkene.



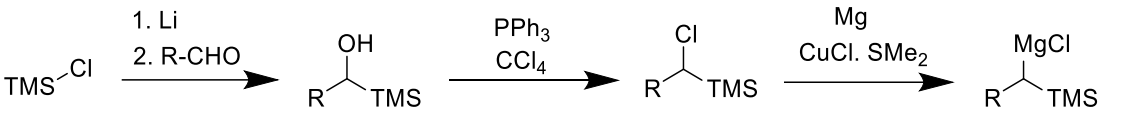
9.7 PETERSON OLEFINATION

The Peterson olefination (or Peterson reaction) is an organic reaction that converts carbonyl compounds (aldehydes or ketones) into alkenes using silyl carbanions, forming hydroxysilane intermediates. It is a versatile alternative to the Wittig reaction, with the advantage of producing easily removed silyl by-products. Stereocontrol is achieved by choosing acidic or basic elimination conditions. In acidic condition, *cis*-alkene is formed via anti-elimination and in basic condition, trans-alkene is formed via concerted *syn* elimination.



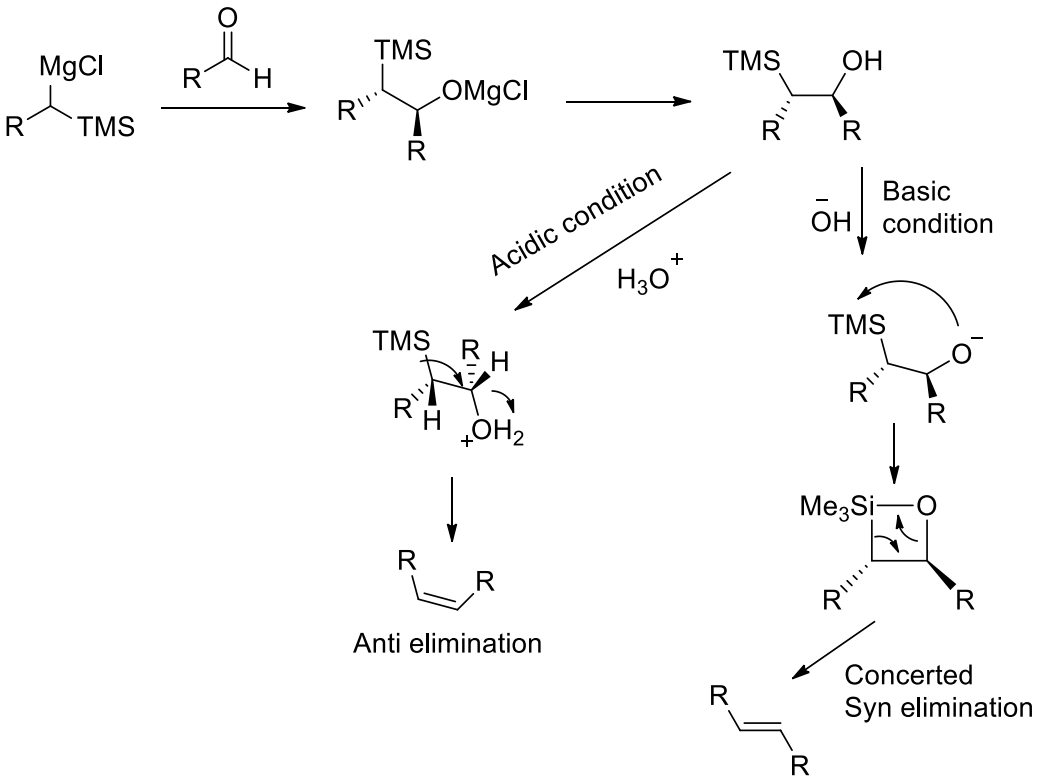
Mechanism:

Formation of silyl carbanion:



Silyl carbanion

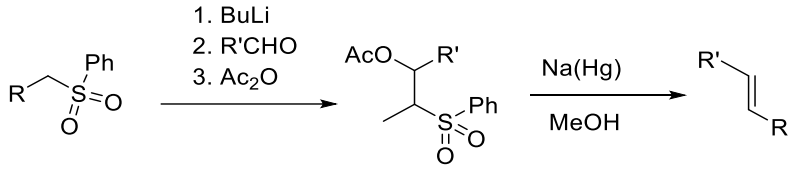
Reaction:



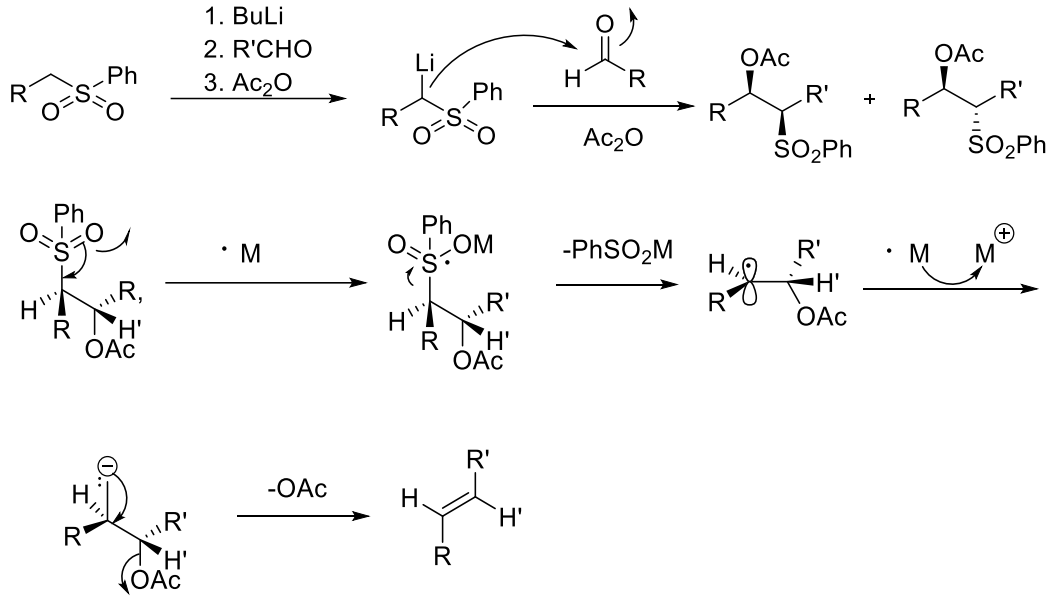
9.8 JULIA REACTION

The Julia reaction (or Julia olefination) is a powerful organic method developed in 1973 that couples an aldehyde or ketone with an alkyl phenyl sulfone to form an alkene, usually with high selectivity. It proceeds through an acyloxysulfone intermediate, which is reduced by sodium amalgam or samarium iodide to form the double bond.

First carbanion is formed by the treatment of sulfone with strong base followed by attack on aldehyde and reaction with acetic anhydride to from sulfonylalkyl acetate which on free radical reaction with sodium amalgam produces alkene. Both diastereomers of sulfonylalkyl acetate passes through same radical intermediate to explain the (*E*)-selectivity.

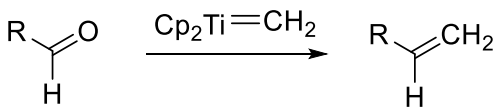


Mechanism:



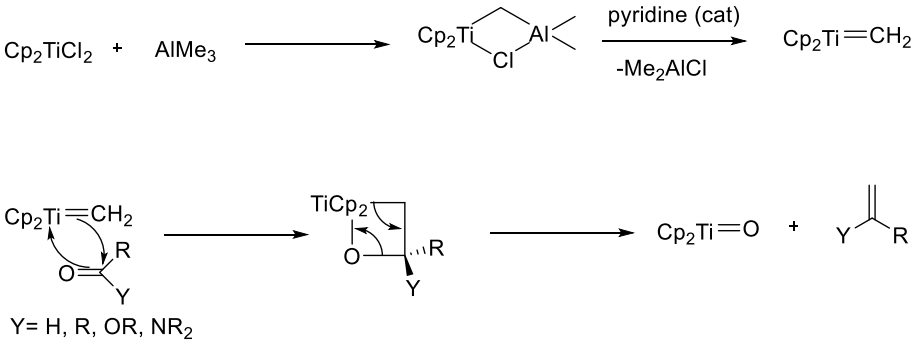
9.9 TEBBE OLEFINATION

The Tebbe olefination is a chemical reaction that converts carbonyl compounds (aldehydes, ketones, esters, and lactones) into terminal alkenes (methylenation) using the Tebbe reagent $Cp_2TiCH_2ClAlMe_2$. The Tebbe reagent, acts as a nucleophilic methylene source (CH_2) to convert carbonyls into terminal alkenes.



Mechanism:

Tebbe reagent activated by a Lewis base (e.g., pyridine), it generates a highly reactive titanocene methylene (Schrock carbene), which forms an intermediate oxatitanacyclobutane with the carbonyl, breaking down to the alkene and titanium-oxo species.



W CHECK YOUR PROGRESS

Q1. What is an E1 reaction? What type of substrates favour E1 reactions?
Q2. What is an E2 reaction? What type of substrates favour E2 reactions?
Q3. Predict the major product when 2-bromobutane undergoes elimination reaction with sodium methoxide?
Q4. What is Witting reaction? Explain with an example?
Q5. Explain the mechanism of *syn* elimination in the pyrolysis of esters.
Q6. Explain Chugaev reaction with reaction mechanism.
Q7. What is Hofmann elimination? How does it differ from Saytzeff's rule?
Q8. How is the alkene formed in the Peterson olefination?
Q9. Which reagents are commonly used in the McMurry reaction?
Q10. What are the main reactants in the Julia reaction?

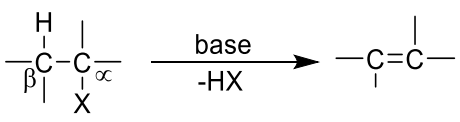
2 9.10 LET US SUM UP

- The formation of carbon - carbon double bonds (C=C) is the key feature of structure of the important class of organic compounds, alkenes.
- Important processes for synthesis of alkenes includes
  - i) Condensation and coupling methods,
  - ii) Elimination methods and
  - iii) Carbonyl oleifination methods,
  - iv) Alkyne reduction methods and
  - v) Metal catalysed and Coupling reactions
- elimination provide a straightforward and efficient pathway for converting saturated compounds into unsaturated ones
- There are three types of elimination reactions:
  - i) E1: Unimolecular elimination reaction
  - ii) E2: Bimolecular elimination reaction
  - iii) E1cB: Conjugate base elimination reaction

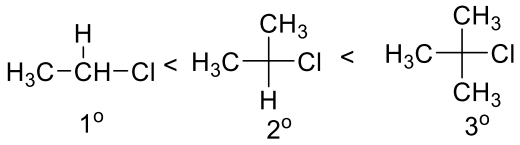
- E1 elimination (unimolecular elimination) is a two-step reaction where an alkyl halide or alcohol loses a leaving group to form a carbocation intermediate. **A weak base** then removes a neighboring proton to create a double bond (alkene). The reaction follows first-order kinetics.
- E2 elimination is a single step reaction. It requires a **strong base**.
- Both E1 and E2 elimination are favoured by tertiary and secondary alkyl halide substrates, because they form stable carbocations.
- With Unsymmetrical alkyl halide, if the base is smaller **more substituted alkene** is formed as a major product. This is known as Saytzeff rule.
- With a bulky base, a poor leaving group and steric hindrance at β-carbon, **less substituted alkene** forms as a major product. This is known as Hoffmann rule
- Substrates that contain electron withdrawing group (EWG) at β-carbon to the leaving group, undergo E1CB elimination. In this reaction proton is lost at first to form a carbanion, that is stabilized by the EWG at β-carbon. Then the alkene is formed by loss of the leaving group. A strong base is required for the reaction.
- *Syn* elimination is an elimination reaction in which the β-hydrogen and the leaving group are removed from the same side (*syn*-coplanar) of the molecule.
- Pyrolysis of esters (for example Chugaev pyrolysis of Xanthate ester is an example of syn-elimination.
- Wittig reaction is the reaction between an aldehyde or ketone with phosphonium ylide to produce alkene.
- McMurry reaction is a reductive coupling reaction between two carbonyl compounds in presence of low-valent titanium to form an alkene.
- Peterson olefination is the conversion of carbonyl compounds to alkenes using silyl carbanions via hydroxysilane intermediate.
- Julia reaction is the coupling of an aldehyde or ketone with an alkyl phenyl sulfone to form an alkene.
- Tebbe olefination is the convertion of carbonyl compounds (aldehydes, ketones, esters, and lactones) into terminal alkenes (methylenation) using the Tebbe reagent $Cp_2TiCH_2ClAlMe_2$.

K 9.11 ANSWERS TO CHECK YOUR PROGRESS

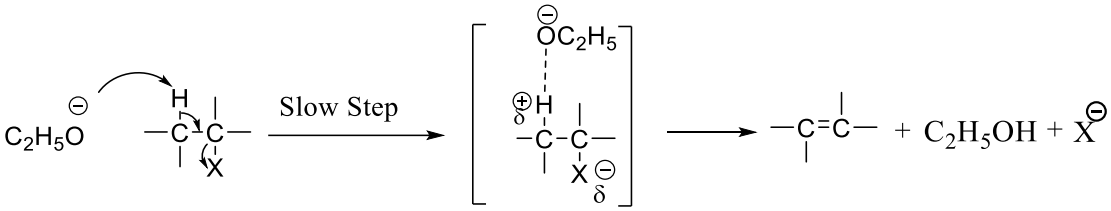
Answer to Q1: An E1 reaction is a two-step elimination reaction in which the leaving group first departs to form a carbocation intermediate, followed by removal of a proton to produce an alkene.



Tertiary alkyl halides favor E1 reactions because they can form stable carbocation intermediates than secondary substrates and primary alkyl halides.



Answer to Q2: An E2 reaction is a one-step elimination reaction where the base removes a proton while the leaving group leaves simultaneously, leading to the formation of a double bond.

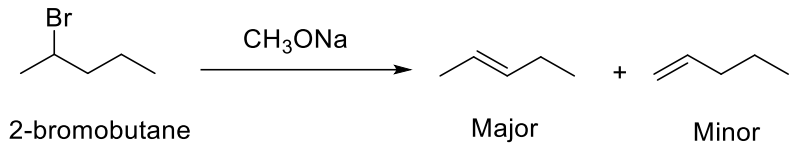


Transition State

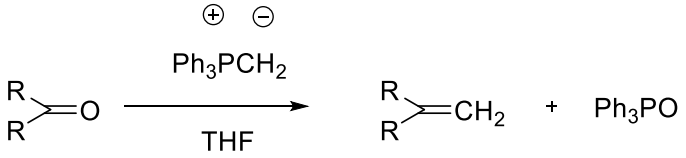
Substates that can form stable alkene will increase the rate of the reaction. Tertiary alkyl halides undergo E2 easily because they form more stable alkenes. Reactivity order:

Tertiary (3°) > Secondary (2°) > Primary (1°)

Answer to Q3: With small base like sodium methoxide, 2-bromobutane follow Satyzeff rule and more substituted alkene will form as a major product.

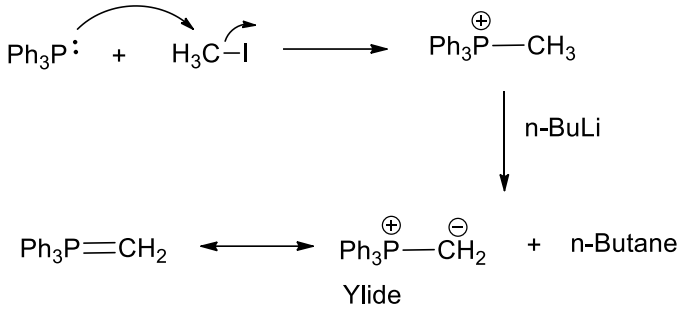


Answer to Q4: The reaction of aldehydes or ketones with phosphonium ylide to produce alkene is known as Wittig reaction. The mechanism involves nucleophilic attack by the ylide on the carbonyl carbon, producing an intermediate (betaine or oxaphosphetane), which collapses to form an alkene and triphenylphosphine oxide.

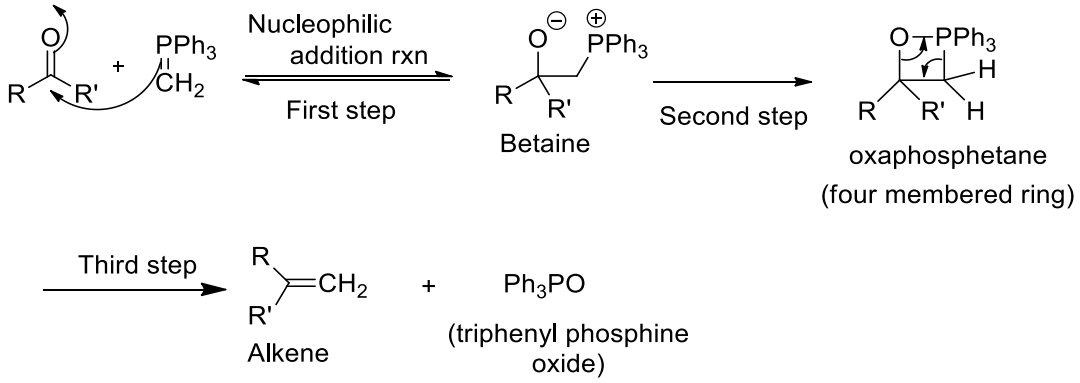


Formation of ylide:

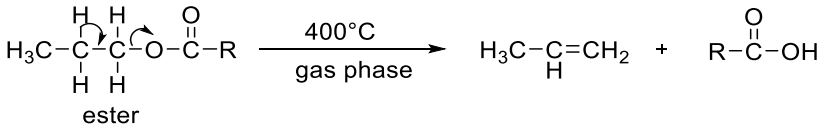
The ylide is prepared by the reaction of triphenylphosphine and methyliodide in presence of base



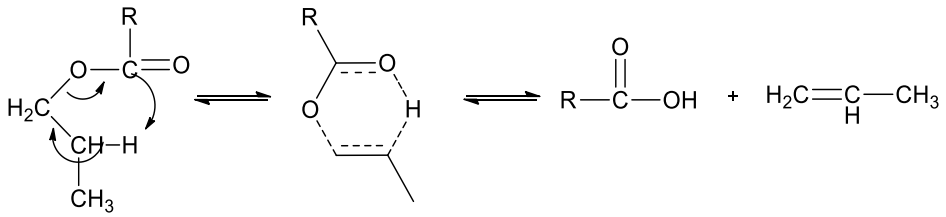
Mechanism of the reaction:



Answer to Q5: Ester decomposes at very high temperature and pressure into alkenes and acid. Here, carbonyl group of ester acts as a base, attacking β-hydrogen intramolecularly *via* a six membered transition state.

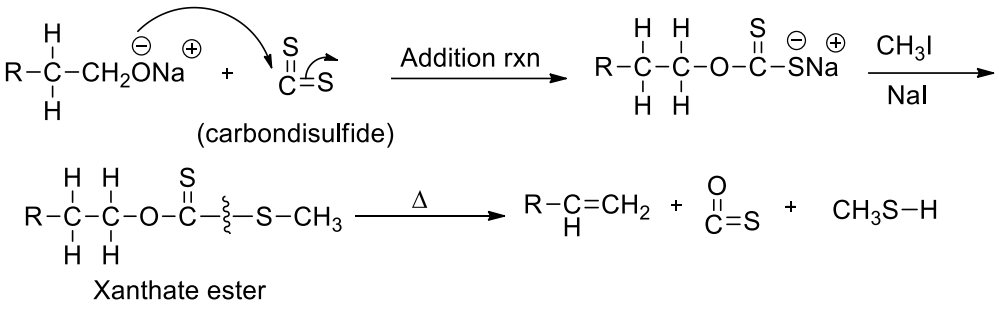


Mechanism

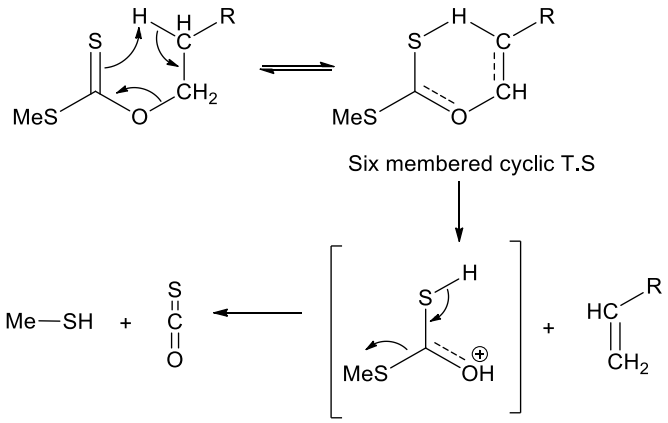


Six membered cyclic T.S.

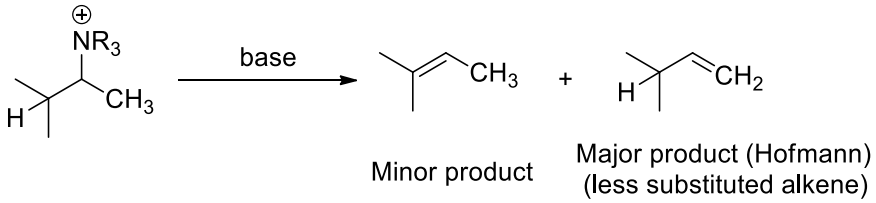
Answer to Q6: Pyrolysis of Xanthate esters into alkene is known as Chugaev reaction. Xanthate is prepared by the reaction alkoxide with carbon disulphide followed by treatment with methyl iodide. When heated to about 200 °C, this ester decomposed by an intramolecular elimination. In a 6-membered cyclic transition state the hydrogen atom is removed from the carbon atom β to the xanthate oxygen in a syn-elimination. The side product decomposes to carbonyl sulfide (OCS) and methanethiol.



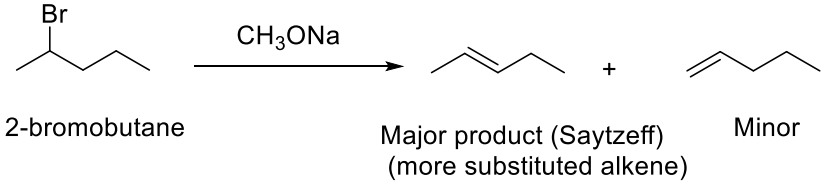
Mechanism:



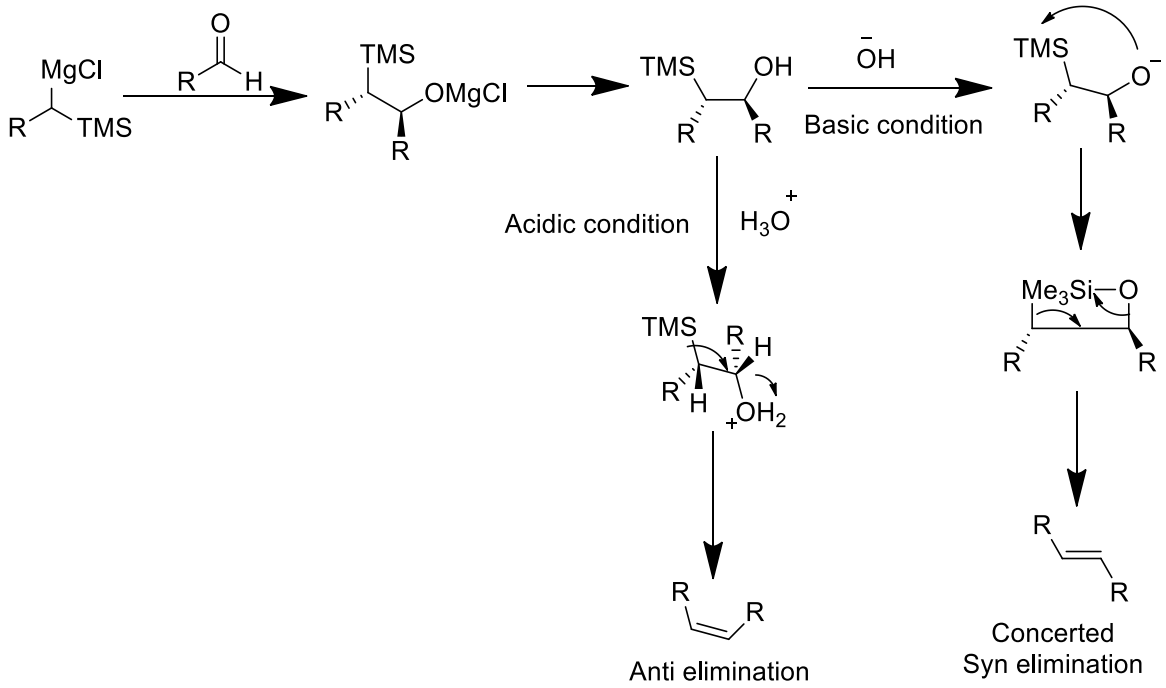
Answer to Q7: Hofmann elimination is an elimination reaction in which a quaternary ammonium hydroxide undergoes elimination upon heating to produce an alkene and a tertiary amine. In this reaction, the least substituted alkene is usually formed as the major product. This preference occurs because the bulky ammonium leaving group and strong base favor removal of the most accessible β-hydrogen, leading to the less substituted double bond.



In contrast, Zaitsev's rule (also called Saytzeff's rule) states that during elimination reactions, the more substituted alkene is generally formed as the major product because it is thermodynamically more stable due to greater alkyl substitution.



Answer to Q8: The Peterson olefination (or Peterson reaction) is an organic reaction that converts carbonyl compounds (aldehydes or ketones) into alkenes using silyl carbanions, forming hydroxysilane intermediates.



Answer to Q9: Low-valent titanium reagents generated from: $TiCl_4$ / Zn–Cu couple, $TiCl_3$ / $LiAlH_4$ or $TiCl_4$ / Zn

Answer to Q10: The reaction involves: phenyl sulfone derivatives, aldehydes or ketones and a strong base such as sodium amide or butyllithium.

O 9.12 FURTHER READING

- Morrison, Boyd, Bhattacharjee. Organic Chemisty, Seventh edition.
- Wade, Simek, Singh. Organic Chemistry, ninth edition.
- Bruice, Bhattacharya. Organic Chemistry, eighth edition.

M 9.13 MODEL QUESTIONS

Q1. Explain Tebbe reaction with mechanism.
Q2. Explain Julia reaction with mechanism.
Q3. Explain Peterson olefination with mechanism.
Q4. Explain McMurry with mechanism.

UNIT 10: USE OF ORGANOSULPHUR COMPOUNDS FOR REVERSAL OF POLARITY

UNIT STRUCTURE

10.1 Learning Objectives
10.2 Introduction
10.3 Umpolung
10.4 Corey-Seebach Reaction (Dithiane Chemistry)
10.5 Why Sulphur Is Ideal for Umpolung
10.6 Synthetic Importance
10.7 Let Us Sum Up
10.8 Answers to Check Your Progress
10.9 Further Reading
10.10 Model Questions

10.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- understand the concept of reversal of the natural polarity of functional groups in organic reactions.
- describe the formation of 1,3-dithiane from carbonyl compounds.
- explain how aldehydes or ketones react with 1,3-propanedithiol under acidic conditions to form a 1,3-dithiane protecting group.
- predict nucleophilic reactions of the dithiane anion

10.2 INTRODUCTION

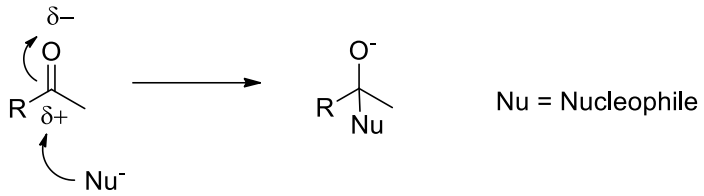
Organosulfur compounds are mostly utilized in organic chemistry for umpolung (polarity inversion), a technique that reverses the natural reactivity of a functional group to enable new chemical bonds. Organosulfur compounds play a major role in umpolung chemistry because sulphur can stabilize adjacent carbanions and form structures that temporarily invert the normal polarity of carbonyl groups. The most classic example is dithiane chemistry (Corey-Seebach reaction), where a carbonyl group (normally an electrophile) is converted into a masked nucleophilic acyl anion.

10.3 UMPOLUNG

Umpolung is a German word means inversion of polarity that refers to reversal of the normal reactivity (polarity) of a functional group.

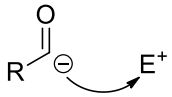
Polarity inversion in organic chemistry is the chemical modification of a functional group with the aim of the reversal of polarity of that group. The concept was introduced by Elias James Corey and Dieter Seebach. Polarity analysis during retrosynthetic analysis shows a chemist when umpolung strategy is required to synthesize a target molecule. When

required, temporary modification of that functional group is done by reversal of polarity to achieve the required polarity for the particular synthesis.
For example, the carbonyl group is electrophilic at the carbon atom and hence is susceptible to attack by nucleophilic reagents. Thus, the carbonyl group reacts as a **formyl cation or as an acyl cation**.



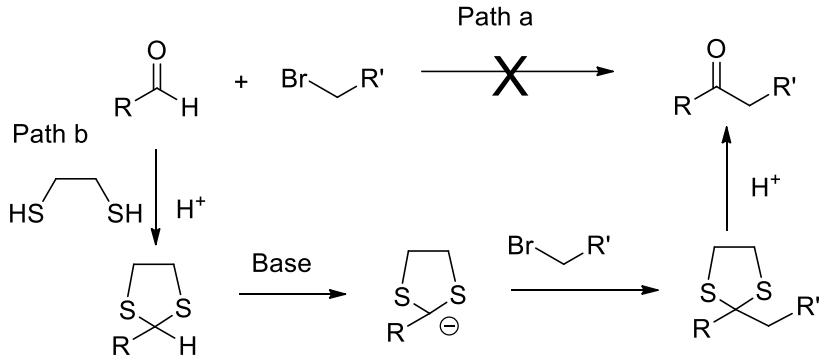
Normal reactivity of carbonyl carbon

A reversal of the positive polarity of the carbonyl group will make it to act as **a formyl or acyl anion.**



Reaction of carbonyl carbon after
Reversal of polarity of the carbon

To achieve this, the carbonyl group is converted to a derivative whose carbon atom has the negative polarity. After its reaction with an electrophilic reagent, the carbonyl is regenerated by using appropriate reagent/reaction.
The temporary modification of a carbonyl group so that the carbon atom behaves as a nucleophile in displacement and addition reactions is of great utility in organic synthesis.



As the carbonyl carbon (C=O) behaves as an electrophile and cannot act as nucleophile. But using organosulphur chemistry, we can reverse this carbonyl carbon to nucleophilic (acyl anion equivalent) carbon. Umpolung allows the carbonyl carbon itself to behave like a nucleophile, enabling bond formations that are otherwise difficult. This strategy is known as Corey-Seebach reaction.

10.4 COREY-SEEBACH REACTION (DITHIANE CHEMISTRY)

The most famous umpolung method uses 1,3-dithiane. (In the previous example, 1,2-dithiane was used).

Step 1: Formation of dithiane

A carbonyl compound reacts with 1,3-propanedithiol in acid.
Carbonyl compound is converted to 1,3-dithiane (thioacetal)
Polarity of the carbonyl carbon is reversed.

Step 2: Generation of acyl anion equivalent

The hydrogen attached to the carbon atom, which is connected to the two sulphur atoms is acidic. Because sulphur has large orbitals and polarizability, so the two sulphur atoms stabilize the negative charge, formed by removal of the hydrogen atom by a strong base such as *n*-BuLi or LDA removes this proton.
As a result, Dithiane carbanion is formed, which behaves like an acyl anion equivalent.

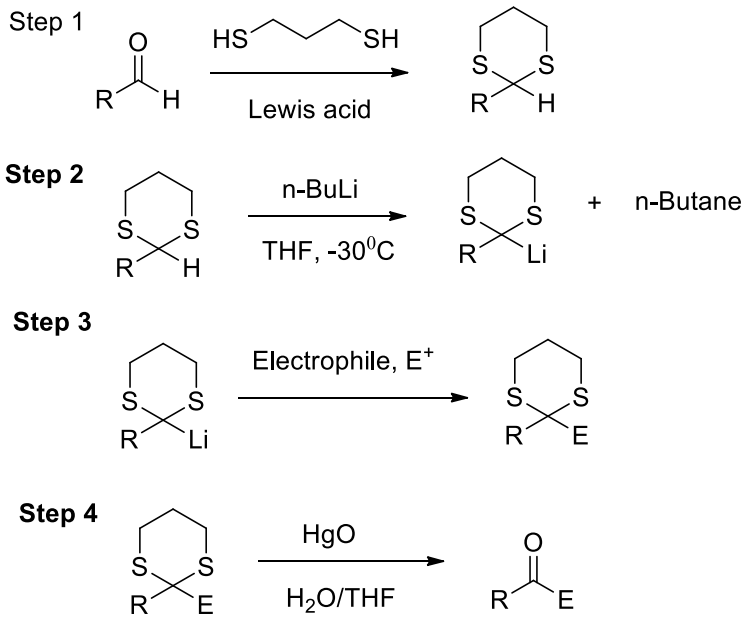
Step 3: Carbon–Carbon bond formation

The nucleophilic carbon attacks electrophiles such as alkyl halides, epoxides and carbonyl compounds.
For example, dithiane carbanion + R–X → substituted dithiane
This forms new C–C bonds at the carbonyl carbon position.

Step 4: Regeneration of carbonyl compound

Finally, the dithiane is hydrolyzed using reagents like $HgCl_2$/HgO, NBS or Raney Nickel. This restores the carbonyl group.

By using this strategy, new ketone or aldehyde with extended carbon chain is prepared.



Scheme 10.1: Corey-Seebach reaction

10.5 WHY SULPHUR IS IDEAL FOR UMPOLUNG

Sulphur is chosen because of the following properties of sulphur.

- High polarizability
- Stabilizes adjacent carbanions
- Forms stable thioacetals
- Easily removed later

This makes organosulphur groups powerful temporary polarity modifiers.

10.6 SYNTHETIC IMPORTANCE

The Corey-Seebach strategy is used for:

- Chain extension of aldehydes/ketones
- Complex molecule synthesis
- Natural product synthesis
- Controlled C–C bond formation

It is considered one of the classic umpolung strategies in organic chemistry.

U LET US KNOW MORE

The Corey-Seebach Reaction is a fundamental transformation in Organic Chemistry that allows chemists to reverse the natural polarity of a carbonyl compound. This is achieved using dithiane chemistry, where a carbonyl compound is temporarily converted into a 1,3-Dithiane.

W CHECK YOUR PROGRESS

Q1) What is the main concept demonstrated by the Corey-Seebach reaction?
Q2) Why is the hydrogen between the two sulphur atoms in a dithiane acidic?
Q3) Which reagents are commonly used to generate the dithiane carbanion?
Q4) What type of species does the deprotonated dithiane represent?
Q5) What is the main synthetic advantage of the Corey-Seebach reaction?

2 10.7 LET US SUM UP

- The Corey–Seebach Reaction is an important reaction in Organic Chemistry that allows reversal of the normal polarity (umpolung) of a carbonyl group using 1,3-dithiane chemistry.
- The Corey–Seebach reaction uses 1,3-dithiane as an acyl anion equivalent, allowing chemists to form C–C bonds at the carbonyl carbon via polarity inversion (umpolung).

K 10.8 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: The main concept demonstrated by the Corey–Seebach Reaction is umpolung (polarity inversion) of a carbonyl compound.

Answer to Q2: The hydrogen between the two sulphur atoms in a 1,3-dithiane is acidic because the conjugate base formed after its removal is stabilized by the two adjacent sulphur atoms.

Answer to Q3: Commonly Used Reagents

i) *n*-Butyllithium (*n*-BuLi) is the most commonly used base. It strongly deprotonates the carbon between the two sulphur atoms to form the lithium dithiane carbanion.

ii) Lithium diisopropylamide (LDA), a strong, non-nucleophilic base.

iii) Sodium hydride (NaH), which is also capable of removing the acidic proton from dithiane.

Answer to Q4: It is acyl anion equivalent.

Answer to Q5: The advantage of Corey-Seebach reaction is that, it achieves umpolung (polarity inversion) of a carbonyl carbon atom. By converting an electrophilic aldehyde into a nucleophilic 1,3-dithiane anion equivalent, it allows for nucleophilic acylation, enabling carbon-carbon bond connections that are impossible under normal reactivity patterns.

O 10.9 FURTHER READING

- Michael B. Smith: Organic Synthesis (4th Ed.), Academic Press.
- Clayden, Greeves and Warren: Organic Chemistry (2nd Edition), Oxford University Press.
- P. S. Kalsi: Organic Reaction and Their Mechanisms, New Age Publication.

M 10.10 MODEL QUESTIONS

Q1. What are the key points of Corey-Seebach reaction?
Q2. What is Umpolung? Why Umpolung is important?
Q3. Explain the use of organosulphur compounds for reversal of polarity (umpolung) with the help of the Corey–Seebach reaction?
Q4. Why is the hydrogen in dithiane acidic?
Q5. How is the original carbonyl group regenerated after C–C bond formation?
Q6. Corey–Seebach reaction? Explain with suitable example.

UNIT 11: APPLICATION OF ENOLATES AND ENAMINES

UNIT STRUCTURE

11.1 Learning Objectives
11.2 Introduction
11.3 Kinetic and Thermodynamic Enolate
11.4 Lithium and Boron Enolates in the Aldol Reaction
11.5 Lithium and Boron Enolates in the Michael Reaction
11.6 Alkylation of Enolates
11.7 Acylation of Enolates
11.8 Alkylation and Acylation of Enamines
11.9 Reactions Involving Carbanions
    11.9.1 Henry Reaction
    11.9.2 Nef Reaction
    11.9.3 Baylis-Hillman Reaction
11.10 Let Us Sum Up
11.11 Answers to Check Your Progress
11.12 Further Reading
11.13 Model Questions

11.1 LEARNING OBJECTIVES

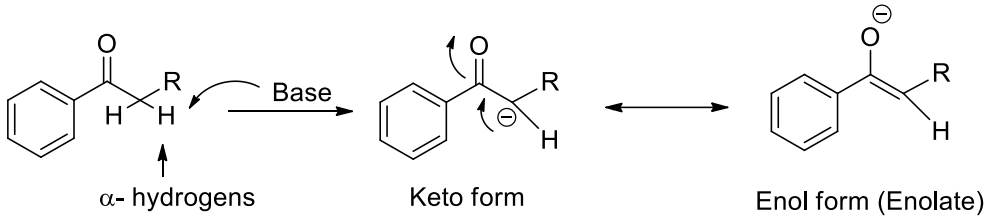
After going through this unit, you will be able to:

- explain the formation, structure and reactivity of enolates and enamines;
- distinguish between kinetic and thermodynamic enolates;
- describe the role of lithium and boron enolates in stereoselective aldol and Michael reactions;
- explain the alkylation and acylation reactions of enolates;
- discuss the synthetic applications of enamines;
- describe the mechanisms of the Henry, Nef and Baylis–Hillman reactions; and
- apply the concepts of enolate and enamine chemistry in carbon–carbon bond-forming reactions.

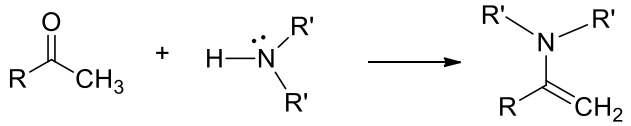
11.2 INTRODUCTION

In organic synthesis, the construction of new carbon–carbon bonds is one of the most important tasks. Among the various reactive intermediates used for this purpose, **enolates** and **enamines** occupy a special place because they provide efficient and versatile methods for introducing substituents at the *α*-position of carbonyl compounds. You may recall from your earlier studies that hydrogen atoms attached to the carbon adjacent to a carbonyl group (*α*-hydrogens) are relatively acidic. When a suitable base removes an *α*-hydrogen, an enolate ion is formed. The negative charge in an enolate is delocalized between carbon and oxygen through resonance, making it a highly useful

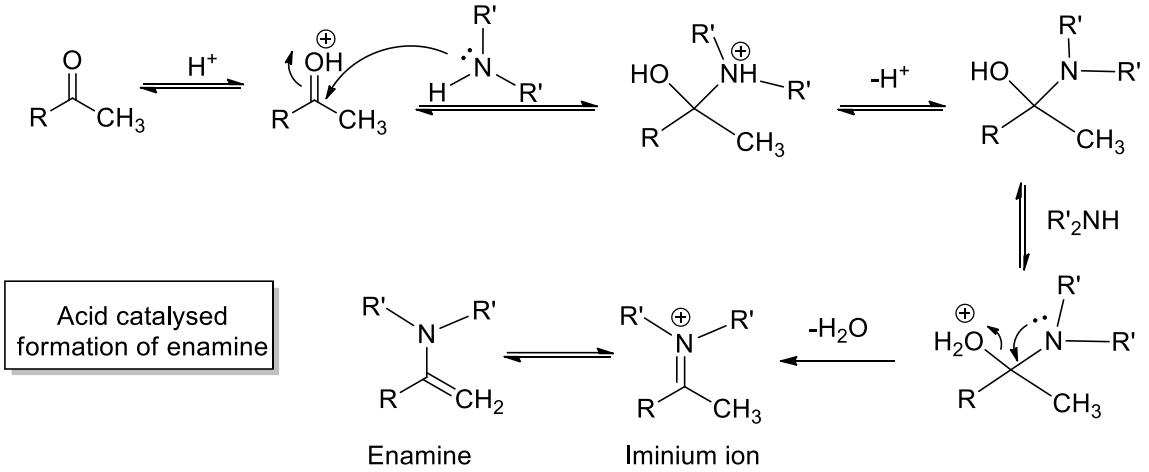
nucleophilic intermediate. Because of this dual character, enolates can react with a variety of electrophiles to form new carbon–carbon and carbon–heteroatom bonds.



Another important class of intermediates derived from carbonyl compounds is the **enamines**. An enamine is an unsaturated organic compound containing an amino group adjacent to a carbon-carbon double bond. Enamines are formed by the reaction of a secondary amines with an enolisable aldehyde or ketone.



The mechanism of acid catalysed formation of an enamine is illustrated here. The mechanism involves alternate protonation and deprotonation on oxygen and nitrogen.



Enamines are neutral molecules, yet they behave as nucleophiles at the *α*-carbon because of the stabilizing effect of resonance (imine-enamine).

Enamines often participate in reactions similar to those of enolates. Since enamines can be generated and used under relatively mild conditions, they are particularly valuable when sensitive functional groups are present in the substrate.

The synthetic utility of enolates and enamines extends far beyond simple laboratory reactions. These intermediates are extensively employed in the synthesis of pharmaceuticals, agrochemicals, natural products and advanced functional materials. In addition, the development of metal enolates, particularly lithium and boron enolates, has enabled highly stereoselective carbon–carbon bond-forming reactions, which are crucial in the preparation of biologically active molecules.

In this unit, you will learn how enolates and enamines are generated, how their structures influence their reactivity, and how they are employed in important synthetic transformations such as Aldol, Michael, alkylation, acylation, Henry, Nef and Baylis–

Hillman reactions. The concepts discussed in this unit form the foundation of many advanced synthetic methodologies used in contemporary organic chemistry.

11.3 KINETIC AND THERMODYNAMIC ENOLATE

In many carbonyl compounds, more than one *α*-hydrogen is available for abstraction. As a result, deprotonation can occur at different *α*-carbon atoms, leading to the formation of different enolate ions. The particular enolate formed depends largely on the reaction conditions employed. In such cases, two types of enolates are commonly encountered: kinetic enolates and thermodynamic enolates. Understanding the difference between these two enolates is extremely important because it allows chemists to control the outcome of many synthetic reactions, including alkylation, Aldol and Michael reactions etc.

Consider an unsymmetrical ketone containing two different *α*-carbon atoms. Removal of a proton from either *α*-position can generate two different enolates. One enolate may form more rapidly, whereas the other may be more stable. Under appropriate conditions, either of these enolates can become the major product.

The enolate that forms more rapidly is known as the kinetic enolate, whereas the more stable enolate formed under equilibrium conditions is known as the thermodynamic enolate.

Thus, a kinetic enolate is the enolate that is formed fastest during deprotonation. It generally results from the removal of the most accessible or least hindered *α*-hydrogen atom. Since the reaction is controlled by the rate of proton removal, the product formed most rapidly predominates.

Kinetic enolates are usually generated under conditions that prevent equilibration of the products. Therefore, the initially formed enolate remains unchanged and becomes the major species in the reaction mixture.

The formation of kinetic enolates is favoured by:

- strong, bulky bases such as lithium diisopropylamide (LDA);
- low temperatures (typically around –78 °C);
- short reaction times; and
- irreversible reaction conditions.

In many cases, the kinetic enolate possesses the less substituted carbon–carbon double bond and is therefore less stable than the thermodynamic enolate.

A **thermodynamic enolate** is the more stable enolate that forms when the reaction is allowed to reach equilibrium. Under such conditions, initially formed enolates can interconvert, and the most stable enolate eventually predominates. Thermodynamic enolates are often more substituted. Because the reaction is controlled by the relative stability of the products rather than the rate of formation, the most stable enolate becomes the major product.

The formation of thermodynamic enolates is favoured by:

- smaller or less hindered bases;
- higher reaction temperatures;

- longer reaction times; and
- reversible or equilibrium conditions.

Thus, while kinetic enolates are formed more rapidly, thermodynamic enolates are formed in greater amounts when equilibrium is established.

Factors Affecting Enolate Formation

Several factors determine whether a kinetic or thermodynamic enolate will be formed. These are:

1. **Nature of the Base:** Bulky bases such as LDA preferentially remove the least hindered proton and therefore favour kinetic enolate formation. Smaller bases can allow equilibration and often favour the thermodynamic product.
2. **Temperature:** Low temperatures reduce equilibration and favour kinetic control. Higher temperatures provide sufficient energy for reversible proton transfer and favour thermodynamic control.
3. **Reaction Time:** Short reaction times generally favour kinetic products, whereas longer reaction times permit equilibration and lead to thermodynamic products.
4. **Solvent and Metal Counter-Ion:** The solvent and the nature of the metal ion associated with the enolate can influence both the rate of formation and the stability of the enolate. Consequently, these factors also affect product distribution.

11.4 LITHIUM AND BORON ENOLATES IN THE ALDOL REACTION

Aldol reaction is one of the most important C–C bond-forming reactions in organic chemistry. In this reaction, an enolate ion reacts with an aldehyde or ketone to produce a *β*-hydroxy carbonyl compound, commonly known as an aldol product. The reaction is widely employed in the synthesis of pharmaceuticals, natural products and complex organic molecules. Although simple enolates can readily participate in Aldol reactions, the use of metal enolates provides better control over reactivity and stereochemistry. Among the various metal enolates, lithium enolates and boron enolates are particularly important because of selective carbon–carbon bond formation under controlled conditions.

The nature of the metal associated with the enolate significantly influences the structure, reactivity and stereochemical outcome of the Aldol reaction. Therefore, understanding the behaviour of lithium and boron enolates is essential for designing stereoselective synthetic routes.

Lithium enolates are commonly generated by treating aldehydes, ketones or esters with strong lithium bases such as lithium diisopropylamide (LDA). When a carbonyl compound containing *α*-hydrogen atoms is treated with LDA at low temperature (typically at around -78°C, to minimize side reactions and to favour the formation of kinetic enolates), deprotonation occurs to produce the corresponding lithium enolate. Lithium enolates are highly reactive nucleophiles and react readily with aldehydes and ketones to form aldol products. Because of their high reactivity, they are widely used in synthetic organic chemistry. However, their tendency to aggregate in solution can sometimes reduce stereochemical control during the reaction.

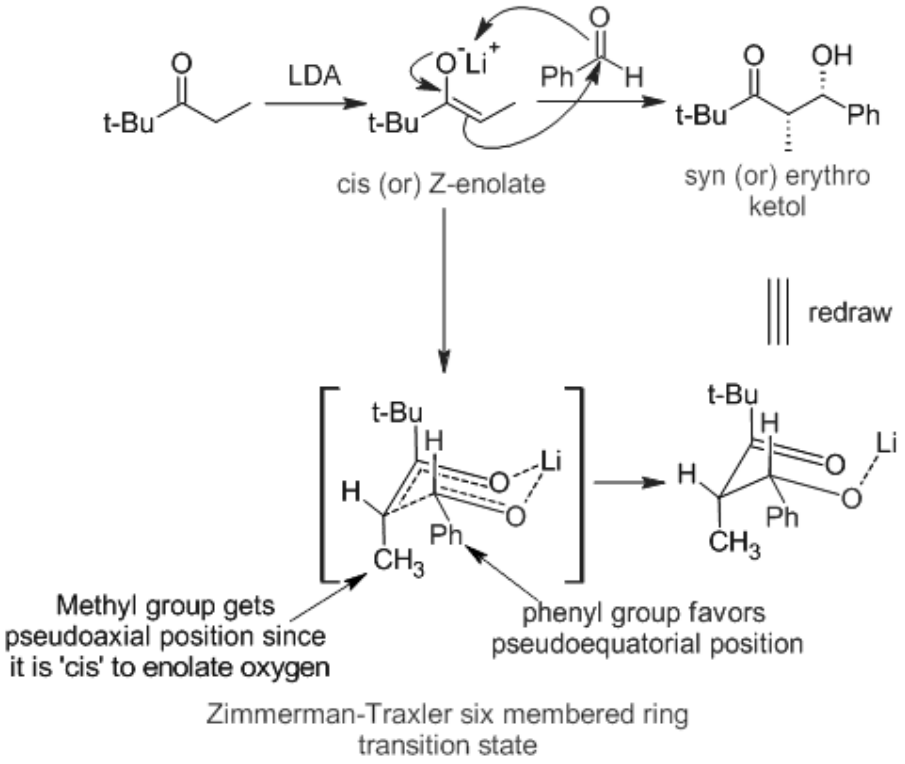


Figure 11.1: Lithium enolates in Aldol Reaction.

In an Aldol reaction, the carbon atom of the lithium enolate attacks the carbonyl carbon of an aldehyde or ketone. This nucleophilic addition generates a new C–C bond and produces an alkoxide intermediate. Subsequent protonation of the alkoxide yields the *β*-hydroxy carbonyl compound. Example of Aldol reaction involving lithium enolate is shown in **Figure 11.1**. First, the lithium enolate is treated with a carbonyl compound to form the lithium enolate. The lithium enolate can exist in either *Z* or *E* configuration. In many commonly studied systems, *Z*-enolates tend to favour the formation of *syn* aldol products, whereas *E*-enolates tend to favour anti aldol products. Here, *cis*- or *Z*- enolate is formed (see Fig 11.1). This enolate then reacts with benzaldehyde to form the desired product. This diastereoselectivity of the reaction is due to the formation of a cyclic six membered transition state (**Zimmerman-Traxler transition state**) in which the bulky group of carbonyl compound favourably takes pseudo-equatorial position, whereas the bulky group on the enolate has to take pseudo-axial position. This leads to the formation of *syn* product.

Boron enolates are generated using organoboron reagents and are widely recognized for their excellent stereoselectivity in Aldol reactions. They are typically prepared by treating a carbonyl compound with a boron reagent in the presence of a suitable base. Commonly used boron reagents include dialkylboron triflates and related organoboron compounds. Unlike lithium enolates, boron enolates generally provide high stereo control in aldol reactions and widely used in asymmetric aldol synthesis. Also, they form less aggregation than lithium enolates.

Boron enolates are commonly generated by treating a carbonyl compound with a dialkylboron triflate in the presence of a suitable base such as diisopropylethylamine (**Figure 11.2**).

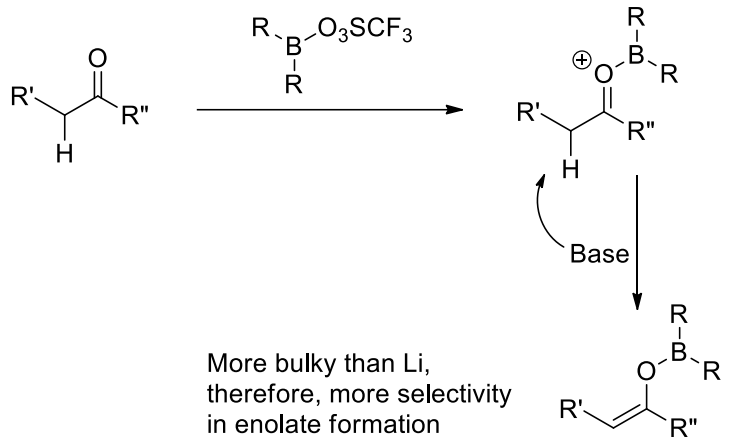


Figure 11.2: Formation of boron enolates

Like lithium enolates, boron enolates now react with aldehydes through a highly organized cyclic transition state known as the **Zimmerman-Traxler transition state**. In this six-membered cyclic arrangement, both the enolate and the aldehyde participate in a concerted process that determines the stereochemistry of the product. The formation of the enolate is more selective in the case of boron enolates as compared to lithium salts due to two reasons:

1. The boron-oxygen bonds are shorter, therefore the cyclic transition state formed is more compact and rigid thus allowing the substituents to play a greater part in the stereocontrol.
2. The substituents on the boron atom (R) can be made very bulky in order to control selectivity for the enolate formed.

A good example of stereoselectivity imparted in aldol synthesis using boron enolates involves the aldol condensation of cyclohexanone. When cyclohexanone is reacted with alkylated boron triflate, it forms selectively the *E*-enolate yielding the *anti*-product in greater yields.

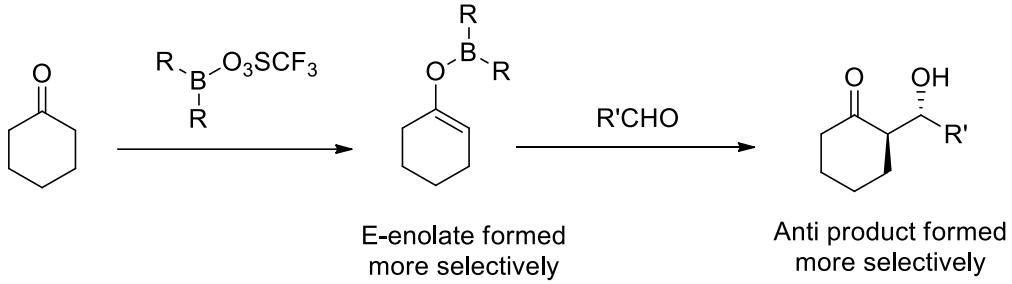


Figure 11.3: Stereoselectivity using boron enolate in aldol condensation

The development of lithium and boron enolate chemistry has greatly expanded the synthetic utility of the Aldol reaction. The proper choice of metal enolate influences not only the formation of new carbon–carbon bonds but also the stereochemical outcome of the reaction. Thus, lithium and boron enolates have become indispensable tools in

modern organic synthesis and continue to play a vital role in the preparation of structurally complex molecules.

11.5 LITHIUM AND BORON ENOLATES IN THE MICHAEL REACTION

Michael reaction is another important carbon–carbon bond-forming reaction in organic chemistry. It involves the nucleophilic addition of an enolate or enolate equivalent to an *α,β*-unsaturated carbonyl compound, commonly referred to as a Michael acceptor. Since the nucleophile attacks the *β*-carbon atom of the unsaturated system, the reaction is classified as a 1,4-conjugate addition reaction.

The Michael reaction provides an efficient method for constructing complex carbon skeletons and is widely employed in the synthesis of pharmaceuticals, natural products and fine chemicals. Among the various nucleophiles used in Michael additions, lithium enolates and boron enolates are particularly important because they allow selective formation of carbon–carbon bonds. The nature of the metal associated with the enolate significantly influences the reactivity, selectivity and stereochemical outcome of the reaction.

Lithium enolates are commonly generated by treating carbonyl compounds with strong lithium bases such as lithium diisopropylamide (LDA). When a carbonyl compound containing *α*-hydrogen atoms is treated with LDA, deprotonation occurs to produce the corresponding lithium enolate. These enolates are highly reactive nucleophiles and readily participate in Michael addition reactions.

In a typical Michael reaction, the carbon atom of the lithium enolate attacks the *β*-carbon atom of the Michael acceptor. The *π*-electrons of the double bond now shift towards the carbonyl group, generating an enolate intermediate that is subsequently protonated to form the final product.

Because of their high nucleophilicity, rapid reaction rates, and moderate stereoselectivity, lithium enolates are widely used in: synthesis of diketones and keto esters, construction of cyclic compounds, preparation of pharmaceutical intermediates, formation of C–C bond in multistep synthesis *etc*.

Although lithium enolates are highly reactive, greater stereochemical control is often required in complex organic synthesis. In such situations, **boron enolates** are frequently employed. A carbonyl compound (ketone/ester) is converted to a boron enolate using dicyclohexylboron chloride and a base such as triethylamine. The boron enolates then react with an *α,β*-unsaturated carbonyl compound to produce the Michael addition product with high stereoselectivity.

The reaction often proceeds with excellent stereochemical control and generates products with predictable stereochemistry. The products obtained are commonly 1,5-dicarbonyl compounds that serve as useful intermediates in synthetic chemistry.

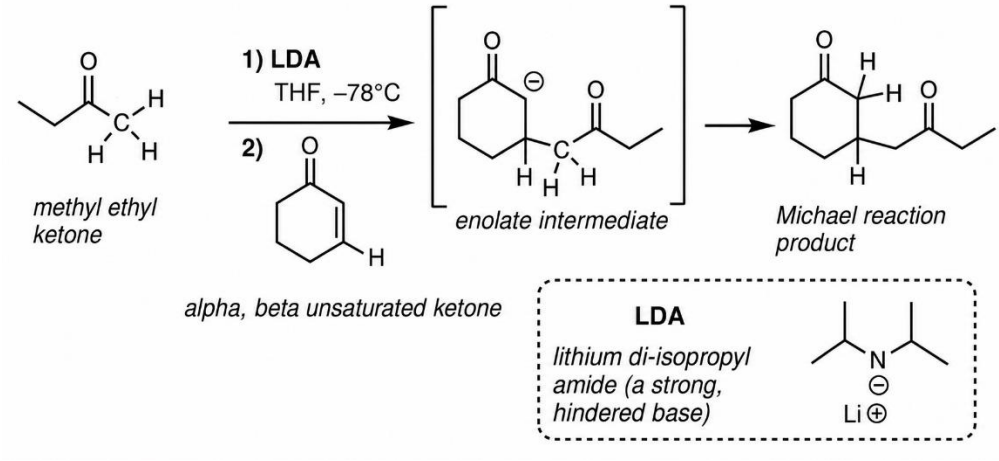


Figure 11.4: Michael addition of a lithium enolate to an *α*,*β*-unsaturated carbonyl compound.

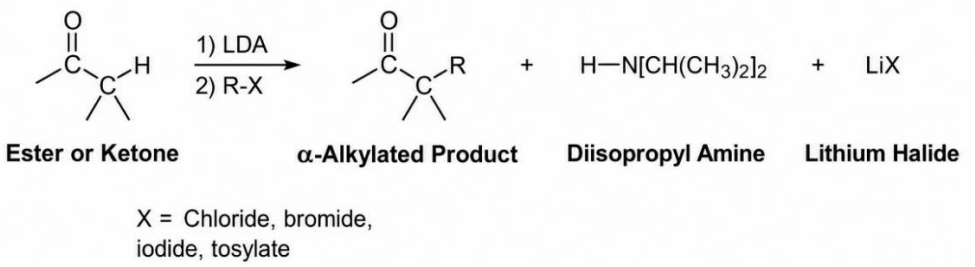
The development of lithium and boron enolate chemistry has greatly expanded the synthetic utility of the Michael reaction. These enolates provide versatile methods for the formation of carbon–carbon bonds and enable the synthesis of structurally complex molecules.

The choice of metal enolate influences not only the efficiency of the Michael addition but also the stereochemical outcome of the reaction. Consequently, lithium and boron enolates continue to play an important role in modern synthetic organic chemistry, particularly in the synthesis of biologically active compounds and natural products.

11.6 ALKYLATION OF ENOLATES

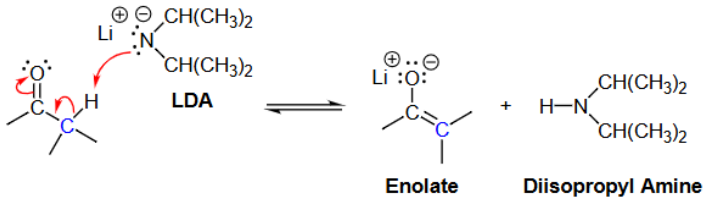
In alkylation of enolates, an enolate ion acts as a nucleophile and reacts with an alkyl halide to introduce an alkyl group at the *α*-carbon of a carbonyl compound. As a result, a new carbon-carbon bond is formed, leading to the synthesis of substituted carbonyl compounds. In most cases, primary alkyl halides and methyl halides are preferred because they readily undergo nucleophilic substitution reactions. Secondary alkyl halides may react more slowly and often give competing elimination products. Tertiary alkyl halides usually undergo elimination rather than substitution and are therefore unsuitable for enolate alkylation.

The mechanism of the reaction generally proceeds through an S_N2 mechanism. The nucleophilic carbon atom of the enolate attacks the electrophilic carbon atom of the alkyl halide, resulting in the displacement of the halide ion and formation of a new carbon–carbon bond. This reaction is widely used for the synthesis of *α*-substituted aldehydes, ketones and esters. The general reaction for alkylation of enolates can be written as:

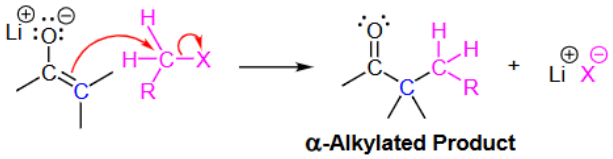


The possible mechanism of the reaction involves the following steps:

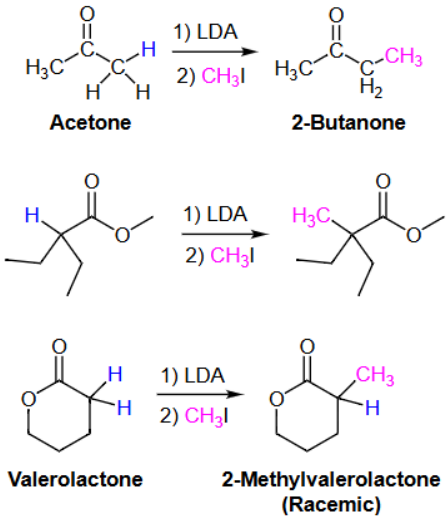
1) **Enolate formation**:



2) **S_N2 attack**:



Examples:



11.7 ACYLATION OF ENOLATES

Acylation of enolates is an important carbon–carbon bond-forming reaction in which an enolate ion reacts with an acylating agent to form a new carbon–carbon bond adjacent to a carbonyl group. In this reaction, an acyl group (RCO–) is introduced at the *α*-carbon of a carbonyl compound, leading to the formation of compounds containing two carbonyl

groups separated by a single carbon atom. Such compounds are known as 1,3-dicarbonyl compounds and constitute valuable intermediates in organic synthesis.

The reaction begins with the generation of an enolate ion from a ketone, ester, or other carbonyl compound using a strong base. The enolate ion is a resonance-stabilized nucleophile in which the negative charge is delocalized between the oxygen atom and the *α*-carbon atom. Although both atoms possess nucleophilic character, carbon–carbon bond formation occurs through attack of the *α*-carbon on the electrophilic carbonyl carbon of an acylating agent.

Several reagents can serve as acylating agents, including acid chlorides, acid anhydrides, and esters. Among these, acid chlorides are particularly reactive because the chloride ion is an excellent leaving group. When the enolate attacks the carbonyl carbon of the acylating agent, a tetrahedral intermediate is formed. Subsequent elimination of the leaving group restores the carbonyl functionality and produces the acylated product.

One of the most important examples of enolate acylation is the **Claisen condensation**.

For example,

$$CH_3COCH_3 + LDA \longrightarrow \bar{C}H_2COCH_3$$

$$\bar{C}H_2COCH_3 + CH_3COCl \longrightarrow CH_3COCH_2COCH_3$$

In this reaction, the enolate ion attacks the carbonyl group of the ester molecule, resulting in the formation of a *β*-keto ester. Because the product contains a highly acidic *α*-hydrogen atom located between two carbonyl groups, it is often deprotonated under the reaction conditions. Consequently, an additional equivalent of base is required, and the neutral *β*-keto ester is obtained only after acidification of the reaction mixture.

Successful acylation requires careful choice of reaction conditions. Strong, non-nucleophilic bases such as lithium diisopropylamide (LDA) are frequently employed to generate the enolate quantitatively and suppress competing side reactions. Low temperatures are often used to control enolate formation and improve selectivity. In addition, the choice of acylating agent significantly influences the reaction rate and yield.

Thus, acylation of enolates represents a fundamental method for carbon–carbon bond formation in organic chemistry. By introducing an acyl group at the α-position of a carbonyl compound, the reaction provides efficient access to 1,3-dicarbonyl systems, which are among the most versatile building blocks in synthetic chemistry.

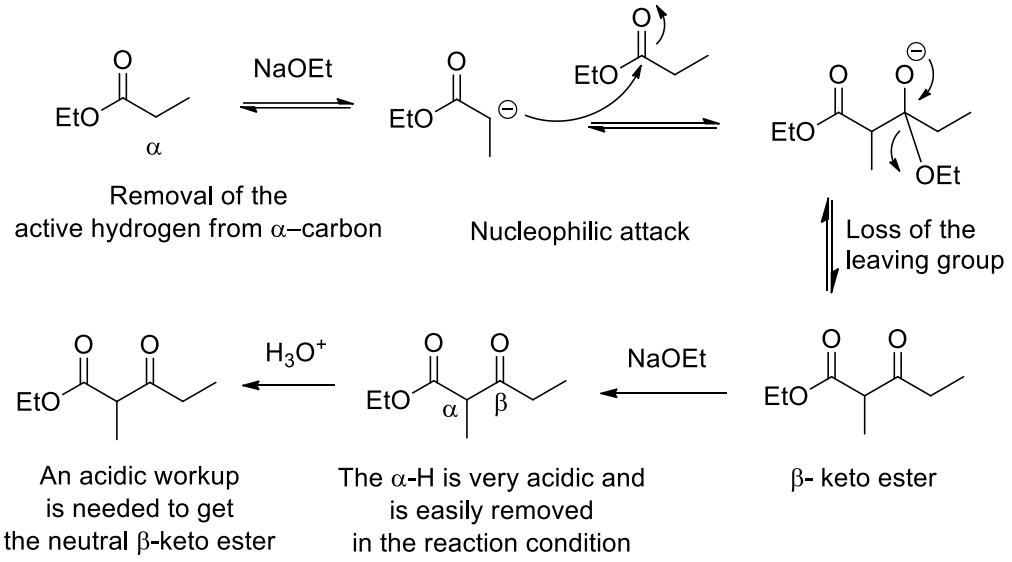
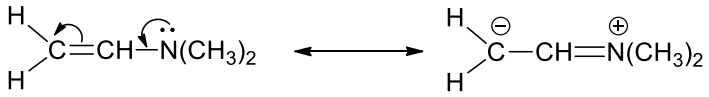


Figure 11.5: Mechanism of Claisen Condensation.

11.8 ALKYLATION AND ACYLATION OF ENAMINES

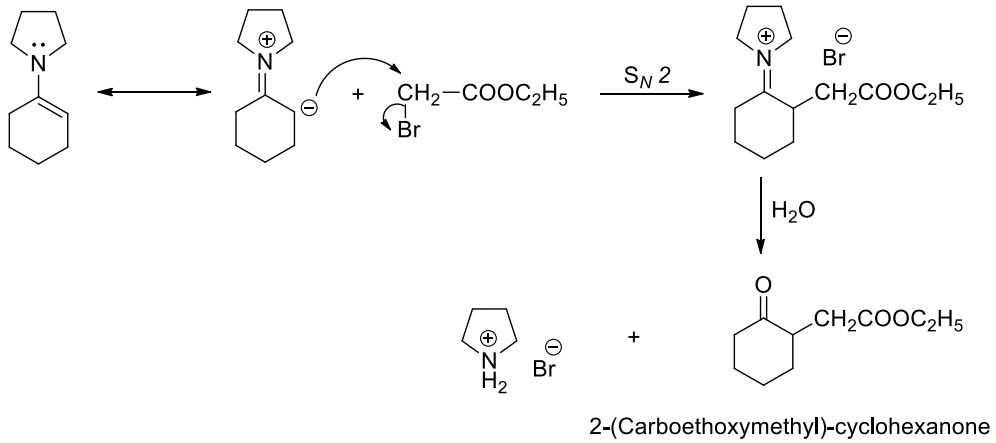
Enamines are useful intermediates for the formation of carbon–carbon bonds. They may be regarded as nitrogen analogues of enolates. Their reactivity as carbon nucleophiles is a result of the dipolar character of one of the resonance structures which shows that the carbon atom β to the nitrogen has a partial negative charge. As this carbon has considerable carbanion character, enamines behave as nucleophiles.



Unlike the basic conditions required for the generation of enolate anions, a base is not required for the activation of enamines as nucleophiles. Hence, they provide a useful mechanism to functionalize the carbon adjacent to a carbonyl group while avoiding the common side reactions associated with strong bases.

Alkylation of Enamines

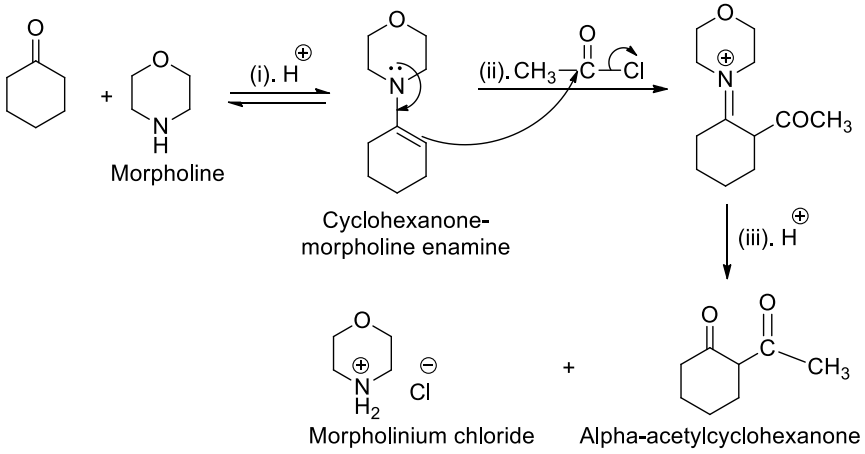
Enamines undergo alkylation with suitable alkylating agents, such as alkyl halides. The *α*-carbon atom of the enamine acts as a nucleophilic centre and attacks the electrophilic carbon atom of the alkyl halide. An iminium salt is formed, which on hydrolysis gives the corresponding α-alkylated carbonyl compound. **Avoids Over-alkylation:** Direct alkylation of enolates often leads to multiple alkylations because the product can be more reactive than the starting material. Enamines are less nucleophilic than fully charged enolates, ensuring **mono-alkylation**.



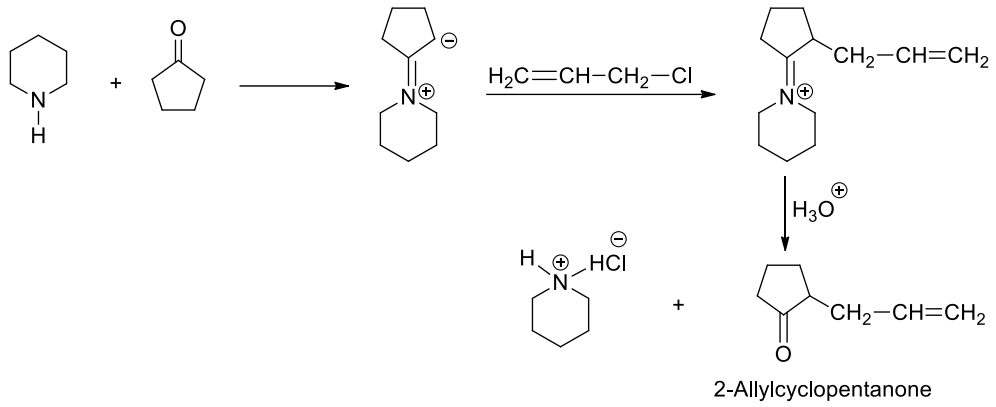
This sequence of enamine formation, alkylation and subsequent hydrolysis is known as the Stork enamine reaction. It provides a useful method for the α-alkylation of aldehydes and ketones and for the formation of carbon–carbon bonds.

Acylation of Enamines

Enamines can also undergo acylation with suitable acylating agents, such as acid chlorides or acid anhydrides. The α-carbon atom of the enamine attacks the electrophilic carbonyl carbon of the acylating agent, followed by hydrolysis to give an α-acylated carbonyl compound.



Enamines are important intermediates in the synthesis of variety of ketones which find application in a large number of chemical transformations. 2-Allyl cyclopentanone, for instance, can be synthesised through the following reaction sequence:



2-Allylcyclopentanone

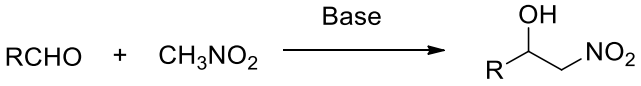
11.9 REACTIONS INVOLVING CARBANIONS

A large number of organic reactions proceed through the formation of carbanions or carbanion-like intermediates, which play a crucial role in carbon–carbon and carbon–heteroatom bond formation. A carbanion is a chemical species in which a carbon atom bears a negative charge and possesses a lone pair of electrons. Due to the presence of this negative charge, carbanions are electron-rich species and therefore act as strong nucleophiles. In many cases, they also exhibit strong basic character. The ability of carbanions to donate an electron pair to electrophilic centres makes them highly useful intermediates in organic synthesis.

Carbanions participate in a wide variety of reactions that are fundamental to modern organic synthesis. These reactions provide efficient methods for constructing complex molecular frameworks through the formation of new carbon–carbon bonds. Among the numerous reactions involving carbanion or carbanion-like intermediates, the **Henry reaction, Nef reaction** and **Baylis–Hillman reaction** are particularly important because of their synthetic versatility and broad applications in the preparation of biologically active compounds, pharmaceuticals and natural products.

11.9.1 Henry Reaction

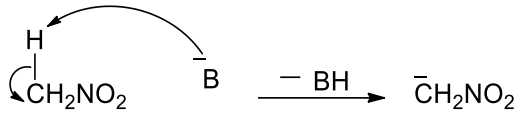
The Henry Reaction (also called the Nitroaldol Reaction) is an important reaction in organic chemistry where a nitroalkane reacts with an aldehyde or ketone in the presence of a base to form *β*-nitro alcohols. These *β*-nitro alcohols can be converted into *β*-amino alcohols or nitroalkenes, which are important intermediates in pharmaceutical and natural product synthesis.
For example,



Mechanism

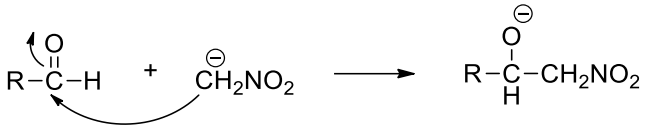
Step 1: Formation of nitroalkane carbanion

Base removes *α*-hydrogen from the nitroalkane.



Step 2: Nucleophilic attack

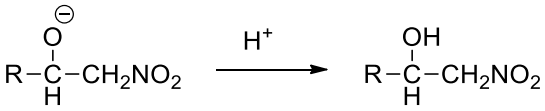
The nitronate ion attacks the carbonyl carbon of aldehyde/ketone.



Alkoxide intermediate

Step 3: Protonation

The alkoxide gets protonated, forming *β*-nitro alcohol.



Important features of Henry reaction

- Forms C–C bond
- Produces *β*-nitro alcohols
- Similar to aldol reaction
- Nitro group can later be converted into amines

11.9.2 Nef Reaction

Conversion of primary or secondary nitroalkanes into aldehydes or ketones by treatment with strong acid after forming the nitronate salt is called Nef reaction. During this conversion nitronate salt is formed in basic medium. The mechanism of the reaction involves the following steps:

Step 1: *Deprotonation*: The *α*-hydrogen next to the nitro group is acidic and so, a base removes this hydrogen to form a nitronate ion.

Step 2: *Nitronate formation*: The anion is stabilized by resonance between oxygen atoms.

Step 3: *Protonation and hydrolysis*: When treated with strong acid, the nitronate ion undergoes hydrolysis.

Step 4: *Carbonyl formation*: The nitro group is converted into a carbonyl group, producing the desired aldehyde or ketone.

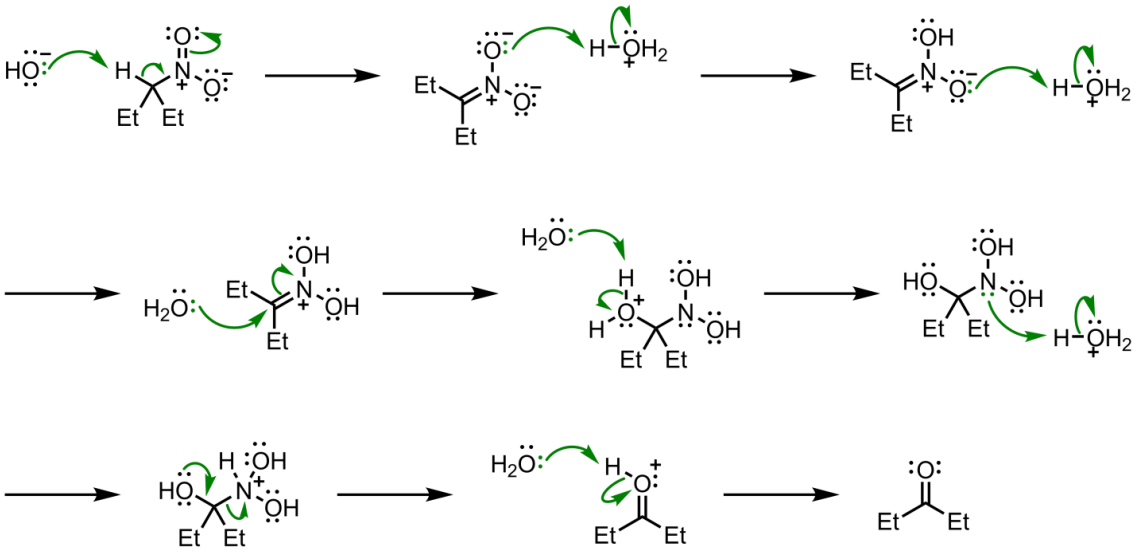
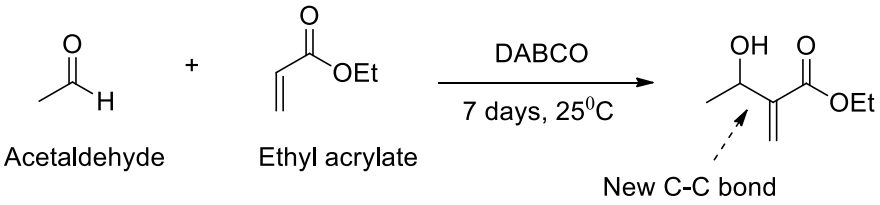


Figure 11.6: Mechanism of Nef Reaction.

However, there are certain limitations of Nef reaction such as tertiary nitroalkanes do not undergo Nef reaction as there is no *α*-hydrogen; and strong acidic conditions sometimes may cause side reactions leading to unwanted products.

11.9.3 Baylis-Hillman Reaction

Another C–C bond formation reaction is Baylis-Hillman reaction which involves the coupling of an aldehyde (or ketone) with an activated alkene (usually with an electron-withdrawing group like –COOR, –CN) in the presence of a nucleophilic catalyst (like DABCO or tertiary amines) to form an allylic alcohol.



This is a modification of aldol reaction. The difference is that the enolate is not formed by deprotonation, but by conjugate addition.
The reaction mechanism involves the following steps:

Step 1: Activation of the alkene by the nucleophilic catalyst (DABCO or DMAP) forming a zwitterionic intermediate. (DABCO = **D**i**A**za**B**i**C**yclo-[2.2.2]-**O**ctane).

Step 2: Nucleophilic attack on the aldehyde.

Step 3: Proton transfer to form the alcohol.

Step 4: Elimination of the catalyst to regenerate it.

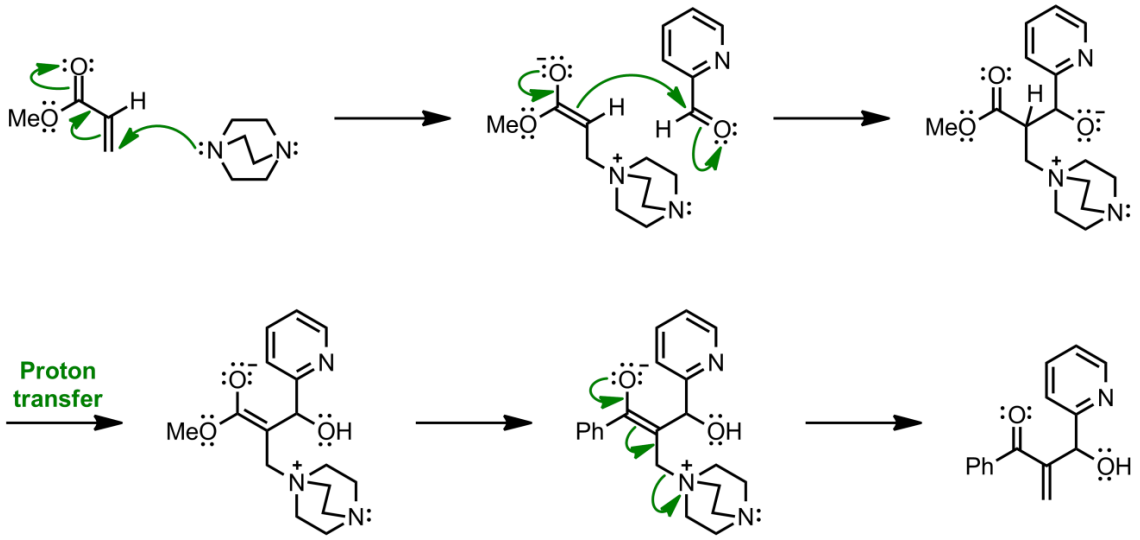


Figure 11.7: Mechanism of Baylis-Hillman reaction.

[Note: DABCO is nucleophilic because of its 'tied back' alkyl groups on nitrogen. But more importantly, it is a good leaving group because it has a low pK_a value, for which it easily leaves in the last step.]

W CHECK YOUR PROGRESS

Q1) Explain why the most substituted enolate is usually the thermodynamic product.

Q2) Why are boron enolates more stereoselective than lithium enolates in aldol reaction?

Q3) Why do lithium enolates sometimes give 1,2-addition instead of the desired 1,4-conjugate addition in Michael reaction?

Q4) Compare the electrophiles used in alkylation vs acylation reactions.

Q5) What types of products are formed from primary vs secondary nitroalkanes during Nef reaction?

Q6) What is the key intermediate in the Nef reaction?

Q7) Explain why the Baylis-Hillman reaction is considered atom-economical?

Q8) What will be the product when acetaldehyde reacts with nitromethane in NaOH?

2 11.10 LET US SUM UP

- Enolates are extremely important intermediates formed when a hydrogen atom next to a carbonyl group is removed by a base. Two different types of enolates can form depending on reaction conditions: kinetic enolates and thermodynamic enolates.
- In the Aldol reaction, the type of metal enolate used strongly affects reactivity, stereochemistry, and selectivity. Two of the most commonly studied are lithium enolates and boron enolates.

- The Michael reaction is another important reaction where lithium and boron enolates can act as nucleophiles. Their behavior influences reactivity, selectivity, and product formation.
- The alkylation of enolates is a very important reaction in organic chemistry used to form new carbon–carbon (C–C) bonds. In this reaction, an enolate ion reacts with an alkyl halide to introduce an alkyl group at the α-carbon of a carbonyl compound. The acylation of enolates is a reaction in which an enolate ion reacts with an acylating reagent to introduce an acyl group (–CO–R) at the α-carbon of a carbonyl compound. This reaction is widely used to form *β*-dicarbonyl compounds.
- Reactions involving carbanions are very important in organic synthesis because they allow the formation of new carbon–carbon (C–C) bonds. In these reactions, a carbanion or carbanion-like intermediate acts as a nucleophile and attacks an electrophilic carbon.
- Some important examples are the Henry reaction, Nef reaction and Baylis–Hillman reaction.

K 11.11 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: The most substituted enolate is often the thermodynamic product because, under reversible conditions, different enolates can interconvert. The enolate with the greater overall stability predominates at equilibrium. Greater alkene substitution generally contributes to greater enolate stability.

Answer to Q2: Boron enolates are monomeric, less aggregated and reacts through a rigid Zimmerman–Traxler transition state, which controls the approach of the aldehyde. Lithium enolates are aggregated and less organized, leading to lower stereoselectivity.

Answer to Q3: Lithium enolates sometimes give 1,2-addition because they are hard, highly reactive nucleophiles that preferentially attack the carbonyl carbon rather than the softer *β*-carbon of the *α,β*-unsaturated system.

Answer to Q4: In alkylation, enolates react with alkyl halides as electrophiles, whereas in acylation, they react with acid chlorides or anhydrides to form *β*-dicarbonyl compounds.

Answer to Q5: In the Nef reaction, primary nitroalkanes give aldehydes, while secondary nitroalkanes give ketones.

Answer to Q6: The key intermediate in the Nef reaction is the nitronate anion formed by deprotonation of the nitro compound.

Answer to Q7: The Baylis–Hillman reaction is considered atom-economical because all atoms of the aldehyde and the activated alkene are incorporated into the final allylic alcohol product without forming significant byproducts.

Answer to Q8: When acetaldehyde reacts with nitromethane in NaOH, the product is a *β*-nitro alcohol via the Henry (nitroaldol) reaction.

O 11.12 FURTHER READING

- Michael B. Smith: Organic Synthesis (4th Ed.), Academic Press.
- W. Carruthers and I. Coldham; Modern Methods of Organic Synthesis (4th Ed.), Cambridge.
- Clayden, Greeves and Warren: Organic Chemistry (2nd Edition), Oxform University Press.
- P. S. Kalsi: Organic Reaction and Their Mechanisms, New Age Publication.

M 11.13 MODEL QUESTIONS

Q1. Define kinetic enolate and thermodynamic enolate.
Q2. Explain why a bulky base favors the formation of the kinetic enolate.
Q3. Explain the difference between lithium enolates and boron enolates in the context of the Aldol reaction.
Q4. Why do lithium enolates sometimes undergo 1,2-addition instead of the desired 1,4-conjugate addition?
Q5. Define alkylation of enolates and acylation of enolates.
Q6. Explain the mechanism of the Henry reaction.
Q7. Show the stepwise mechanism for the reaction of nitromethane with benzaldehyde.
Q8. Define the role of nitronate ion in the Nef reaction.
Q9. Explain the mechanism of the Nef reaction with stepwise electron movement.
Q10. Compare the mechanism of Nef reaction with Henry reaction.
Q11. Which reagents and catalysts are used in Henry reaction?
Q12. How does a nitroalkane form a carbanion in base medium?
Q13. Why do tertiary nitroalkanes not undergo Nef reaction?
Q14. Explain the mechanism of Baylis-Hillman reaction.
Q15. What are the required substrates for a classic Baylis-Hillman reaction?
Q16. What are the key features of Baylis-Hillman reaction?

UNIT 12: HYDROBORATION AND TRIALKYLSILYL HALIDES IN ORGANIC SYNTHESIS

UNIT STRUCTURE

12.1 Learning Objectives
12.2 Introduction
12.3 Hydroboration in Organic Synthesis
- 12.3.1 Overview of Hydroboration
- 12.3.2 Borane and Borane Complexes
- 12.3.3 Hydroboration of Alkenes
- 12.3.4 Mechanism of Hydroboration
- 12.3.5 Regioselectivity of Hydroboration
- 12.3.6 Stereochemistry of Hydroboration
- 12.3.7 Hydroboration-Oxidation of Alkenes
- 12.3.8 Bulky Boranes
- 12.3.9 Hydroboration of Alkynes
- 12.3.10 Synthetic Applications of Organoboranes
- 12.3.11 Advantages and Limitations of Hydroboration

12.4 Trialkylsilyl Halides in Organic Synthesis
- 12.4.1 Introduction to Trialkylsilyl Halides
- 12.4.2 Structure and Nature of Trialkylsilyl Halides
- 12.4.3 Common Trialkylsilyl Halides
- 12.4.4 Preparation and General Reactions
- 12.4.5 Silylation of Alcohols
- 12.4.6 Formation of Silyl Ethers
- 12.4.7 Protection of Alcohols and Phenols
- 12.4.8 Deprotection of Silyl Ethers
- 12.4.9 Selective Protection and Deprotection
- 12.4.10 Synthetic Applications of Trialkylsilyl Halides

12.5 Let Us Sum Up
12.6 Answers to Check Your Progress
12.7 Further Reading
12.8 Model Questions

12.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- define hydroboration and describe borane and its complexes.
- explain the mechanism, regioselectivity, and stereochemistry of hydroboration.
- describe hydroboration-oxidation of alkenes to alcohols.
- explain hydroboration of alkynes and the role of bulky boranes such as 9-BBN.

- describe the structure and reactivity of trialkylsilyl halides.
- explain silylation, protection, and deprotection of alcohols and phenols.
- discuss the importance of protecting groups in multistep organic synthesis.

12.2 INTRODUCTION

In this unit, two important aspects of modern synthetic chemistry namely hydroboration and trialkylsilyl chemistry are discussed. Both reactions provide useful methods for controlling the reactivity and selectivity of functional groups during multistep transformations. **Hydroboration** involves the addition of a B–H bond of borane (BH_3) or a borane complex across a carbon–carbon multiple bond. It is particularly useful for the conversion of alkenes into alcohols with anti-Markovnikov regioselectivity and syn addition. Hydroboration also provides organoboron compounds, which are valuable intermediates in synthetic chemistry. **Trialkylsilyl halides** are widely used for the temporary protection of reactive functional groups, especially alcohols and phenols. Reaction with these reagents forms silyl ethers, which protect the functional groups from unwanted reactions during subsequent synthetic steps. The protecting groups can later be removed under suitable conditions to regenerate the original functional groups.

Thus, this chapter focuses on the principles, mechanisms, selectivity, and synthetic applications of hydroboration and trialkylsilyl chemistry, including the protection and deprotection of functional groups.

12.3 HYDROBORATION IN ORGANIC SYNTHESIS

Hydroboration is a valuable reaction in organic chemistry where borane (BH_3) or a borane complex reacts with alkenes and alkynes, adding hydrogen and boron across the double bond. The reaction is particularly notable for its regioselectivity (anti-Markovnikov addition) and stereochemistry (syn addition). It is often followed by an oxidation step to convert the boron intermediate into a hydroxyl group, thus producing alcohols.

12.3.1 Overview of Hydroboration

Hydroboration involves the addition of borane (BH_3) or borane complexes (such as diborane, B_2H_6) to alkenes or alkynes. The outcome of the reaction is the formation of a trialkylborane intermediate.

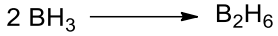
Hydroboration-oxidation is a common two-step reaction that converts alkenes into alcohols. The first step involves the hydroboration, where borane adds to the alkene and the second step is an oxidation, where the boron group is replaced by a hydroxyl group.

$$CH_2{=}CH_2 + BH_3 \longrightarrow (CH_3CH_2)_3B$$

$$(CH_3CH_2)_3B \xrightarrow{H_2O_2/\bar{O}H} 3\ CH_3CH_2OH$$

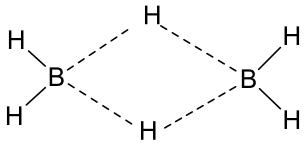
12.3.2 Borane and Borane Complexes

Borane (BH_3) is an electron-deficient compound in which boron has only six electrons around it. Therefore, BH_3 is highly reactive and readily reacts with compounds that can donate an electron pair. In the free state, borane is unstable and tends to associate or form complexes with suitable donor molecules. It is commonly represented as a monomeric species, but it readily undergoes dimerisation:



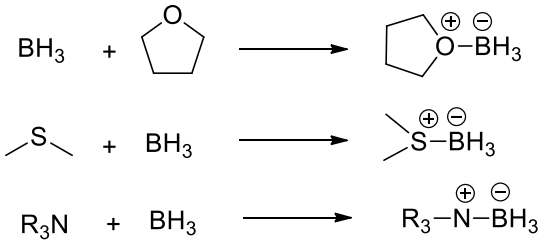
$$2\ BH_3 \longrightarrow B_2H_6$$

The dimer, **diborane (B_2H_6)**, contains two bridging hydrogen atoms and is an important source of borane for hydroboration reactions.



Borane Complexes:

Because free BH_3 is highly reactive, it is commonly used in the form of stable borane complexes with Lewis bases such as tetrahydrofuran (THF), dimethyl sulfide (Me_2S), and ammonia.



$$BH_3 + \text{(THF)} \longrightarrow \text{(THF)}\text{–}BH_3$$

$$Me_2S + BH_3 \longrightarrow Me_2S\text{–}BH_3$$

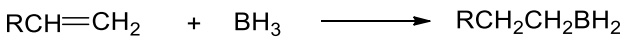
$$R_3N + BH_3 \longrightarrow R_3N\text{–}BH_3$$

These complexes act as convenient and controlled sources of BH_3. They readily add to C=C bonds during hydroboration.

12.3.3 Hydroboration of Alkenes

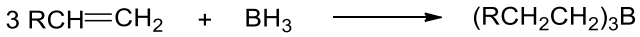
Hydroboration is the addition of a B–H bond across the C=C bond of an alkene. The reaction occurs in a single step, with boron and hydrogen adding from the same side (**syn addition**). Boron preferentially attaches to the less substituted carbon, giving an **anti-Markovnikov** product.

General Reaction:



$$RCH{=}CH_2 + BH_3 \longrightarrow RCH_2CH_2BH_2$$

Since one molecule of BH_3 can react with three molecules of an alkene.



$$3\ RCH{=}CH_2 + BH_3 \longrightarrow (RCH_2CH_2)_3B$$

The reaction is commonly carried out using BH_3.THF or BH_3.SMe_2.

Example:
Hydroboration of propene:

$$CH_3CH{=}CH_2 \quad + \quad BH_3 \xrightarrow{BH_3.THF} (CH_3CH_2CH_2)_3B$$

On oxidation with hydrogen peroxide in alkaline medium, it gives propan-1-ol, demonstrating the anti-Markovnikov nature of hydroboration-oxidation.

$$(CH_3CH_2CH_2)_3B \xrightarrow[OH^-]{H_2O_2} 3CH_3CH_2CH_2OH$$

12.3.4 Mechanism of Hydroboration

Hydroboration is a concerted mechanism, meaning the addition of boron and hydrogen occurs simultaneously in a single step. The process is syn addition, so both boron and hydrogen are added to the same side of the double bond.

Step 1: Nucleophilic attack

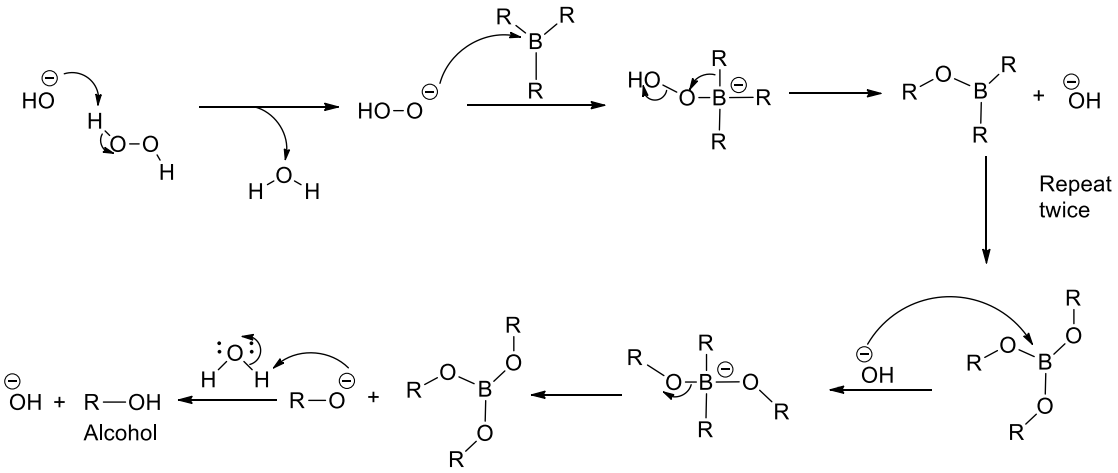
The borane (BH_3), an electron-deficient species approaches the alkene. Since boron is less electronegative than carbon, it forms a bond with the carbon of the double bond that is less substituted (more electron-rich). This results in the hydrogen (H) adding to the more substituted carbon (anti-Markovnikov addition), and boron adds to the less substituted carbon.

Step 2: Formation of Trialkylborane

This addition creates a trialkylborane intermediate. The addition is syn, meaning both the boron and hydrogen add to the same side of the alkene.

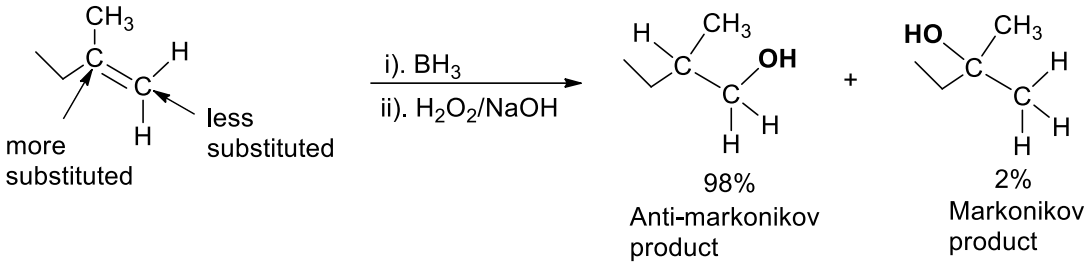
Step 3: Oxidation

The trialkylborane intermediate is treated with hydrogen peroxide (H_2O_2) and a base (often NaOH), which oxidizes the boron group to a hydroxyl group (OH^-). The outcome is an alcohol, with the hydroxyl group added to the less substituted carbon (anti-Markovnikov orientation).



12.3.5 Regioselectivity of Hydroboration

One of the most important features of the hydroboration reaction is its regioselectivity. Hydroboration of an unsymmetrical alkene generally occurs with **anti-Markovnikov addition**. In hydroboration, boron (B) adds to the less substituted carbon of the alkene (terminal carbon in a terminal alkene), while hydrogen (H) adds to the more substituted carbon (the internal carbon). This is the opposite of Markovnikov's Rule, which dictates that the more substituted carbon receives the positive part (such as hydrogen) during electrophilic addition reactions.



For example:

Hydroboration reaction of propene ($CH_3CH{=}CH_2$):

In hydroboration, boron adds to the terminal carbon and hydrogen adds to the internal carbon. After oxidation, this gives 1-propanol.

$$CH_3CH{=}CH_2 \xrightarrow[THF]{BH_3} CH_3CH_2CH_2BH_2 \xrightarrow[OH^-]{H_2O_2} CH_3CH_2CH_2OH$$

This regioselectivity is governed by both steric and electronic factors. Because boron is larger than hydrogen, its attachment to the less hindered carbon is sterically favoured. At the same time, in the concerted transition state, the more substituted carbon develops greater partial positive character, which is better stabilized by alkyl groups.

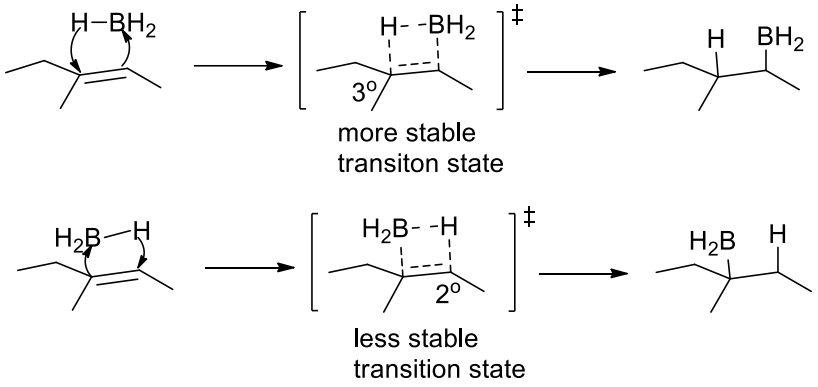
12.3.6 Stereochemistry of Hydroboration

Hydroboration is a **stereospecific syn addition reaction**, in which the boron atom and hydrogen atom add to the same face of the alkene. The reaction occurs through a concerted four-centre transition state, so no carbocation intermediate is formed.

For example, hydroboration of an alkene can be represented as:

$$R^1R^2C{=}CR^3R^4 \xrightarrow{BH_3} R^1R^2(CH){-}C(BH_2)R^3R^4$$

Here, H and BH_2 are added from the same side of the double bond.

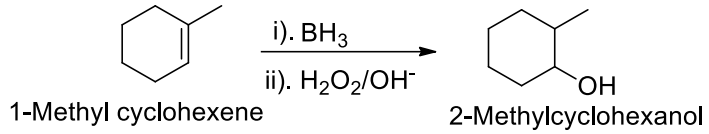


Hydroboration of Cyclic Alkenes:

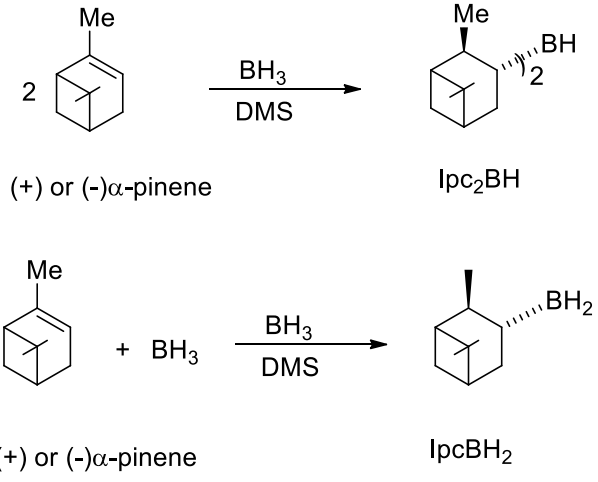
The hydroboration of cyclic alkenes is a two-step stereospecific reaction that converts a cycloalkene into a cycloalkanol via *syn*-addition and *anti-Markovnikov* regiochemistry, meaning the hydrogen atom and the hydroxyl (–OH) group add to the same face of the ring at adjacent carbons without any carbocation rearrangements.

Example: Hydroboration of 1-methylcyclohexene

In 1-methylcyclohexene, hydroboration occurs preferentially at the **less substituted carbon** of the double bond. The boron atom attaches to the less substituted carbon, while hydrogen is added to the carbon bearing the methyl group. Oxidation then converts the C–B bond into C–OH.



(+)- α-pinene form diisopinocamphenyl borane ((+)-Ipc_2BH) and (+)-monoisopinocamphenyl borane (+)-$IpcBH_2$).



The stereochemical outcome is therefore determined by the:

- geometry of the alkene

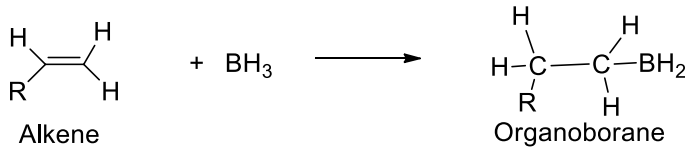
- steric hindrance
- nature of substituents
- structure of the borane reagent

12.3.7 Hydroboration-Oxidation of Alkenes

Hydroboration-oxidation is a two-step organic reaction that converts an alkene into an alcohol. The hydroxyl group (-OH) adds to the less-substituted carbon (anti-Markovnikov selectivity) via a *syn* addition mechanism (hydrogen and boron add to the same face of the double bond) without carbocation rearrangements. It is usually followed by oxidation to convert the carbon-boron bond into a C-O bond.

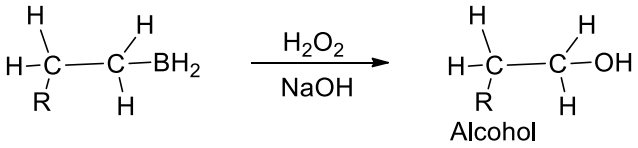
Step 1: Hydroboration

In the first step, an alkene is treated with borane (BH_3) which breaks the C-C π bond and forms a C-H and C-B bond.



Step 2: Oxidation

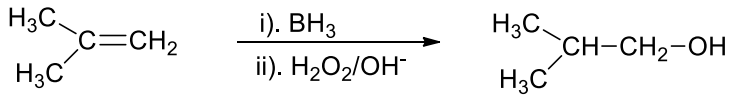
In the second step an oxidant such as H_2O_2 is added, usually in the presence of base such as NaOH or KOH. A rearrangement then occurs where the C-B bond is broken and a new C-O bond is formed.

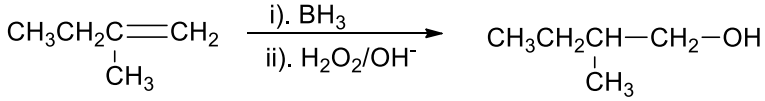


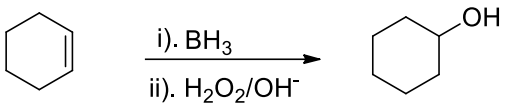
Examples:

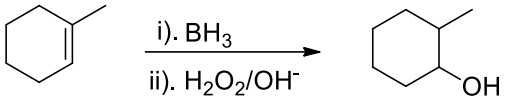
1. $CH_3CH{=}CH_2 \xrightarrow[\text{ii). } H_2O_2/OH^-]{\text{i). } BH_3} CH_3CH_2CH_2OH$

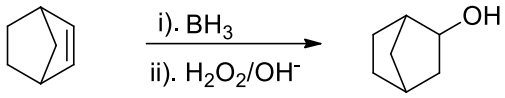
2. $CH_3CH_2CH{=}CH_2 \xrightarrow[\text{ii). } H_2O_2/OH^-]{\text{i). } BH_3} CH_3CH_2CH_2CH_2OH$

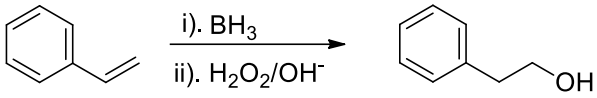
3. 

4. 

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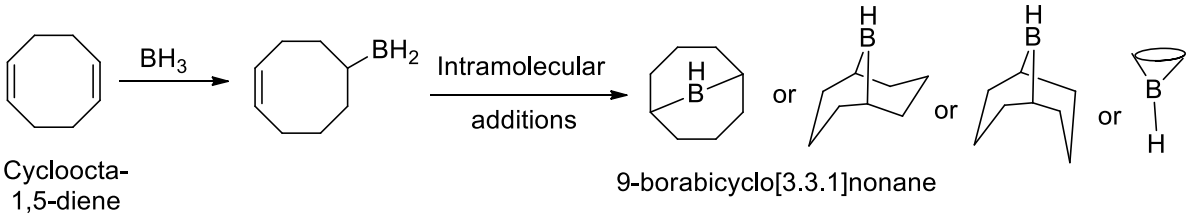
Important features:

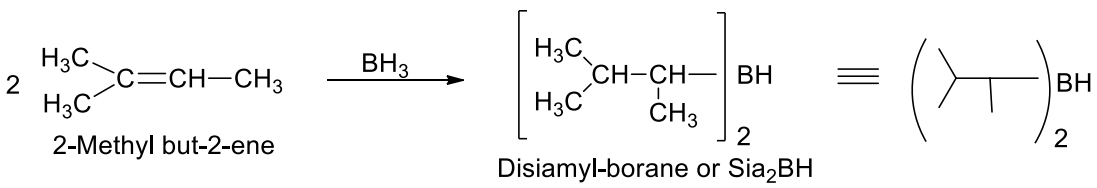
i. Anti-Markovnikov addition: The –OH group ultimately appears on the less substituted carbon of the double bond.
ii. Syn addition: H and B are added from the same face of the alkene.
iii. No carbocation intermediate: Therefore, carbocation rearrangements do not occur.
iv. Stereospecific reaction: The stereochemistry of cyclic alkenes can be predicted from the syn addition.
v. Boron is replaced by –OH during oxidation.

12.3.8 Bulky Boranes

Several bulky boranes have been developed to improve the selectivity of hydroboration reactions.

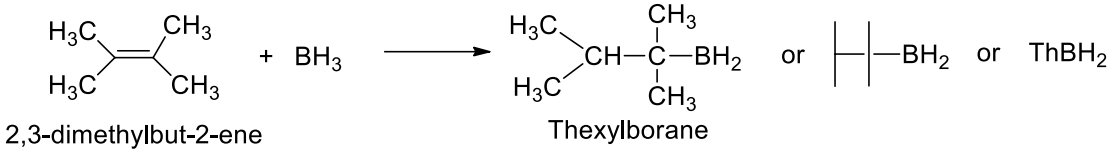
Two commonly used dialkylboranes are 9-BBN (9-borabicyclo[3.3.1]nonane) and Sia_2BH (disiamylborane) are exceptionally **regioselective** because of its much hindered structure.





These two reagents are used in those cases where one hydroboration is required.

When two hydroborations are required, thexylborane is used which is prepared from 2,3-dimethyl-2-butene.



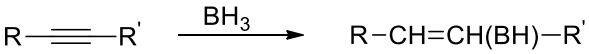
2,3-dimethylbut-2-ene Thexylborane

Bulky boranes are useful when:

- high regioselectivity is required;
- multiple hydroboration must be minimised;
- a terminal alkene must be selectively transformed;
- an alkyne must be converted selectively into a useful intermediate.

12.3.9 Hydroboration of Alkynes

Hydroboration is not restricted to alkenes; alkynes also undergo hydroboration. The reaction involves the addition of a B–H bond across the carbon-carbon triple bond. It is particularly useful for the preparation of aldehydes and ketones through subsequent oxidation.



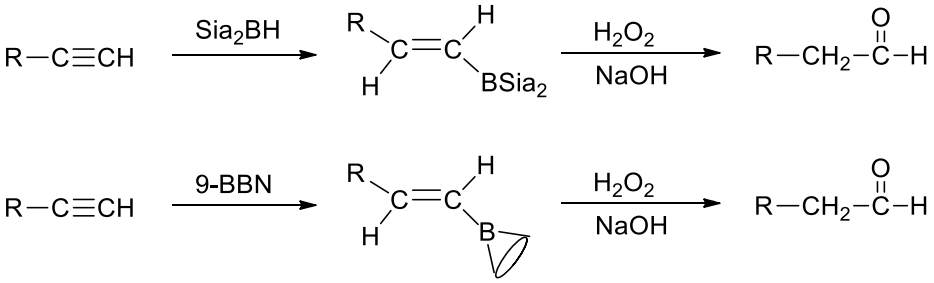
The resulting vinylborane can undergo further reactions or oxidation.

For terminal alkynes, the reaction is commonly carried out using a **bulky borane** reagent, such as 9-BBN and Sia_2BH. Bulky boranes are preferred because they reduce unwanted side reactions and provide better **regioselectivity**.

1. Hydroboration-Oxidation of Terminal Alkynes:

Terminal alkynes undergo hydroboration followed by oxidation to give aldehydes. In hydroboration of an unsymmetrical terminal alkyne, boron attaches preferentially to the terminal carbon, while hydrogen is added to the more substituted carbon. After oxidation and tautomerisation gives anti-Markonikov product (aldehyde).

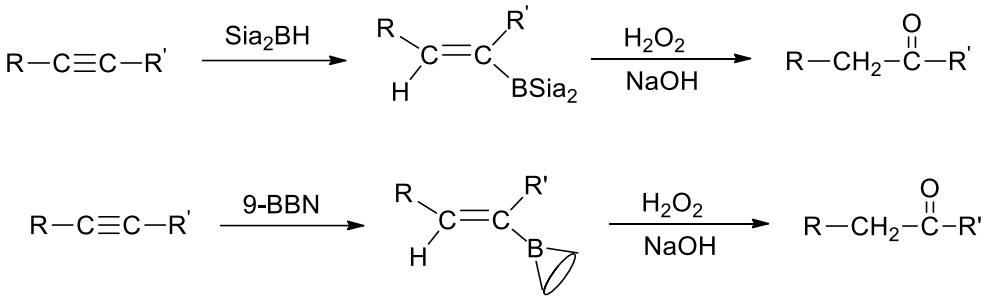
A sterically hindered dialkylborane Sia_2BH reacts with alkyne to give vinylborane.



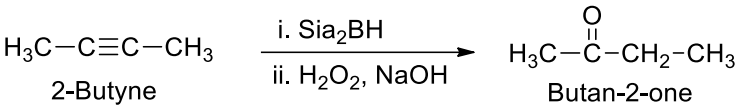
Thus, these reactions provide an important method for converting a terminal alkyne into an aldehyde.

2. Hydroboration-Oxidation of Internal Alkynes:

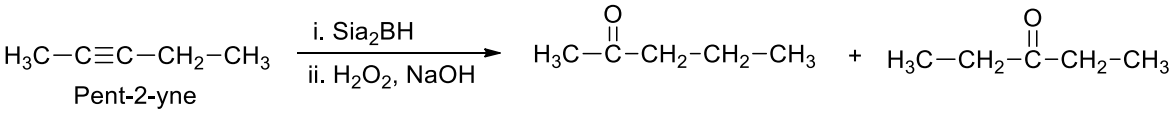
Internal alkynes generally give **ketones** after oxidation.



Example:



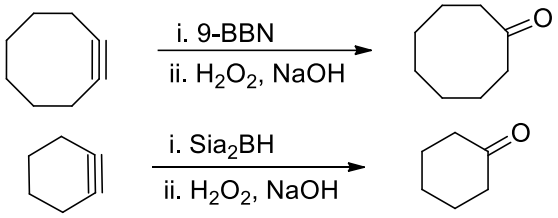
For an **unsymmetrical** internal alkyne, hydroboration-oxidation can give a mixture of ketones because boron can add to either of the two alkyne carbons.



3. Hydroboration of cyclic alkynes:

Cyclic alkynes also undergo hydroboration-oxidation.

For example; cyclooctyne gives cyclooctanone and cyclohexyne gives cyclohexanone



Important features:

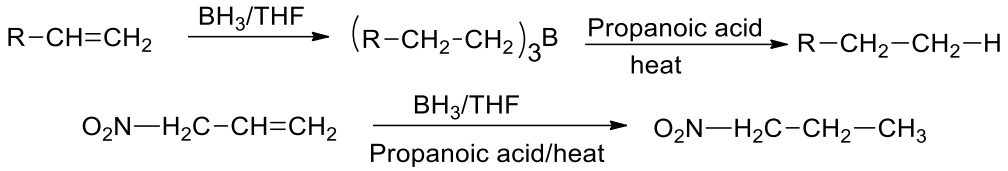
1. Hydroboration of alkynes is syn addition.
2. It proceeds through a concerted mechanism.
3. Bulky boranes such as 9-BBN and Sia_2BH are preferred.
4. The reaction generally shows anti-Markovnikov regioselectivity.
5. Terminal alkynes give aldehydes after oxidation.
6. Internal alkynes give ketones after oxidation.
7. The initially formed enol undergoes keto-enol tautomerisation.

12.3.10 Synthetic Applications of Organoboranes

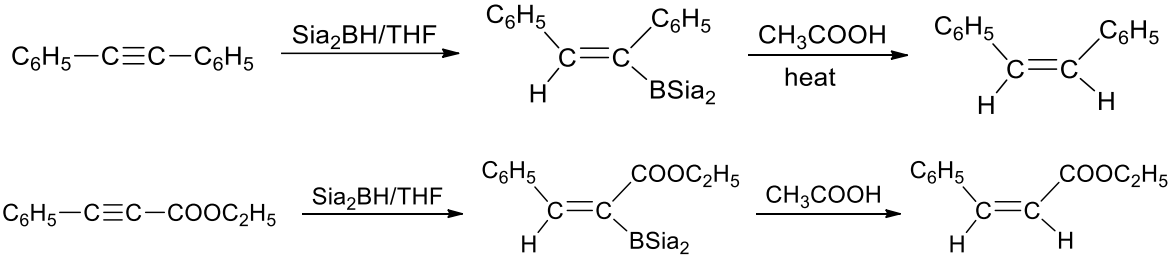
Organoboranes are valuable intermediates in organic synthesis because the carbon-boron (C–B) bond can be transformed into several useful functional groups. They are particularly important in hydroboration-oxidation, C-C bond formation, and functional-group transformations.

(1) Preparation of alkanes and alkenes

Organoboranes on protonolysis give the corresponding alkanes. In this reaction boron atom is replaced by hydrogen. Protonolysis is best affected with an organic carboxylic acid. Boiling of propanonic acid is often used with alkyl boranes.

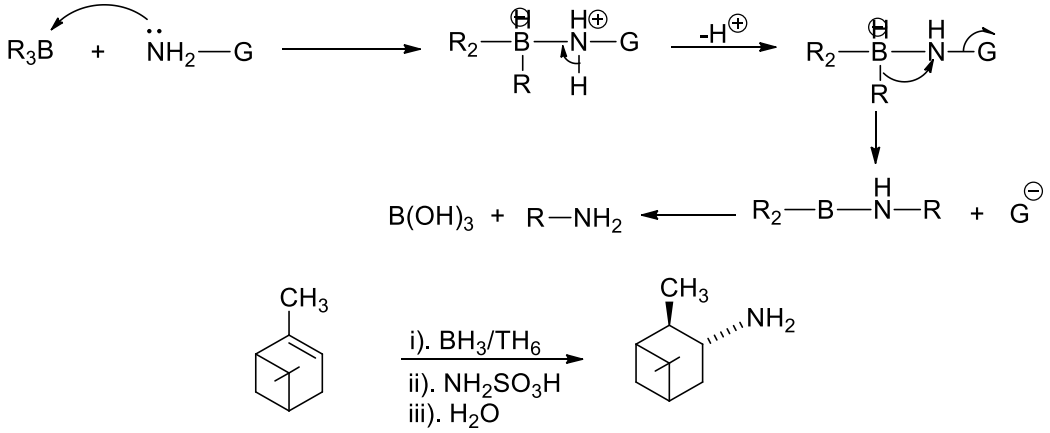


As discussed earlier, alkynes react with diborane to give trialkylborane but sterically hindered dialkylborane Sia_2BH reacts with alkynes to give vinyl derivatives which on protonolysis gives *cis* alkenes.



(2) Preparation of amines

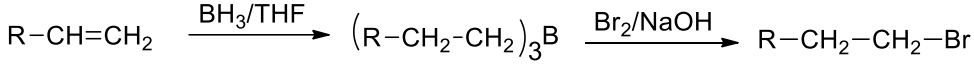
Organoboranes can be converted to amines. The boron atom can be replaced by amino group. The reagent (chloroamine or hydroxylamine-o-sulphonic acid) initially reacts as a nucleophile by adding at boron and then rearrangement with expulsion of leaving group 'Cl' or sulphate ion follows:



α-pinene

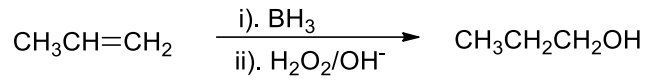
(3) Preparation of alkyl halides

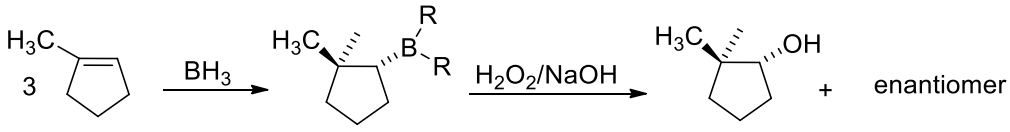
Organoboranes reacts with halogen in presence of basic medium to give alkyl halides in which boron is replaced by halo group.



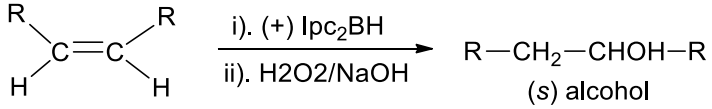
(4) Synthesis of alcohols:

The most familiar application is the conversion of alkenes into alcohols. Hydroboration followed by oxidation provides an important method for converting alkenes into anti-Markovnikov alcohols.

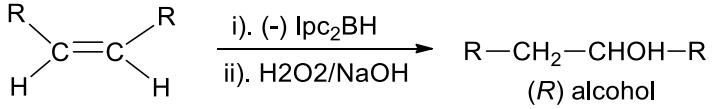




(+) Ipc_2BH gives (*S*)-alcohol with 1,2-disubstituted (Z) alkenes



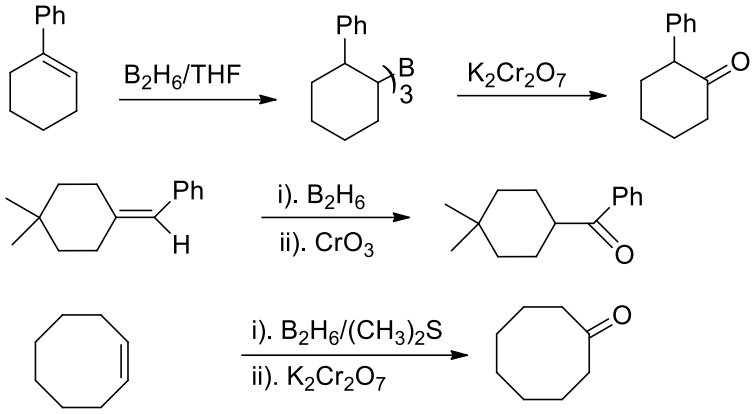
Similarly, (-) Ipc_2BH gives (*R)*-alcohol with (Z) alkenes



Ipc_2BH reacts very slowly with (*E*)-alkenes but the less hindered (+) or (-)$IpcBH_2$ can be used effectively.

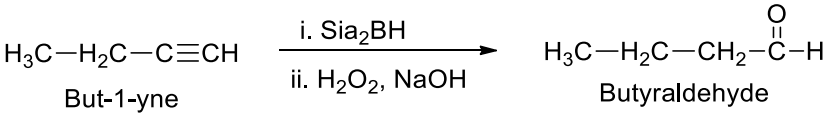
(5) Preparation of aldehydes and ketones:

Ketones can be readily obtained by oxidation of trialylborane with strong oxidizing agents such as chromic acid, pyridinium chlorochromate and $K_2Cr_2O_7$. In this reaction boron atom is replaced by oxygen.

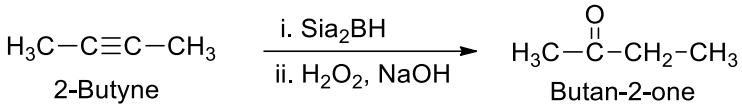


Organoboranes formed from terminal alkynes can be oxidised to give aldehydes, whereas internal alkynes generally give ketones.

Terminal alkyne-

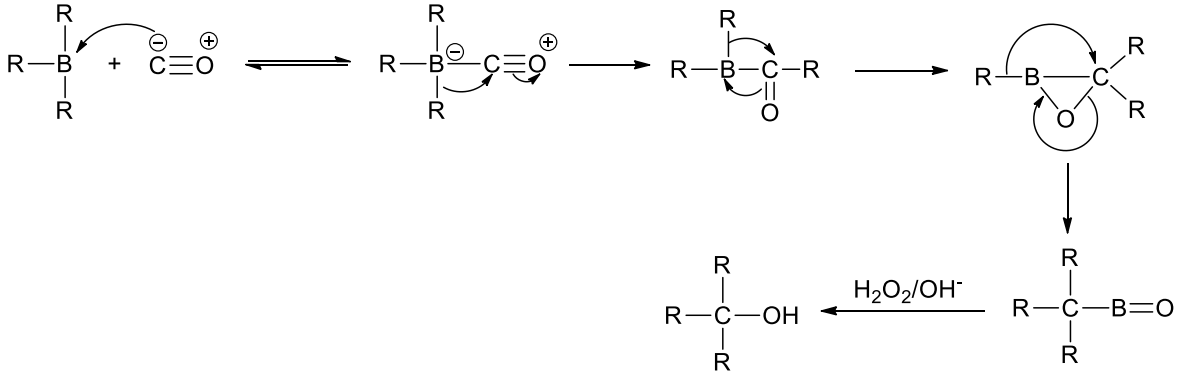


Internal alkyne-

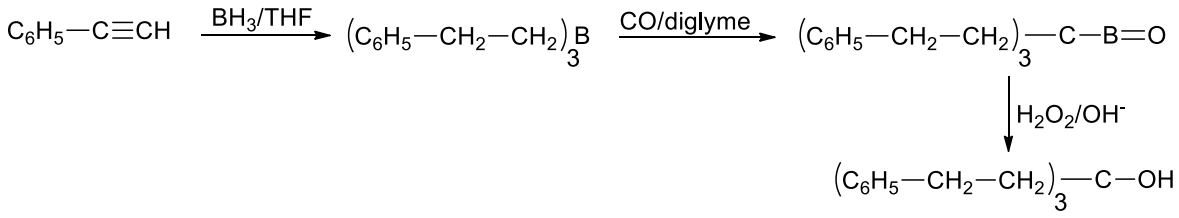


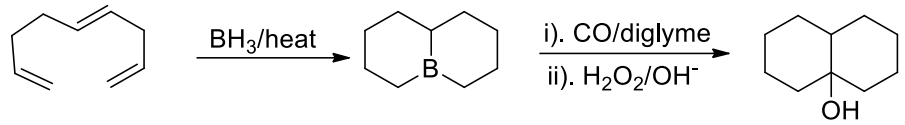
(6). Carbonylation of organoboranes:

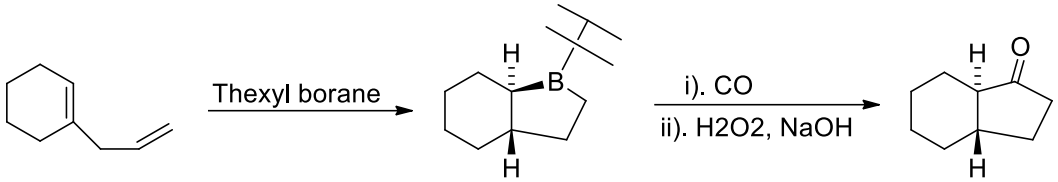
Trialkylboranes react with carbon monoxide in the presence of diglyme to give R_3CBO which upon oxidation with H_2O_2 in alkaline medium gives alcohol. The reaction takes place as follows:



This reaction is very useful for preparation of 3° alcohol.



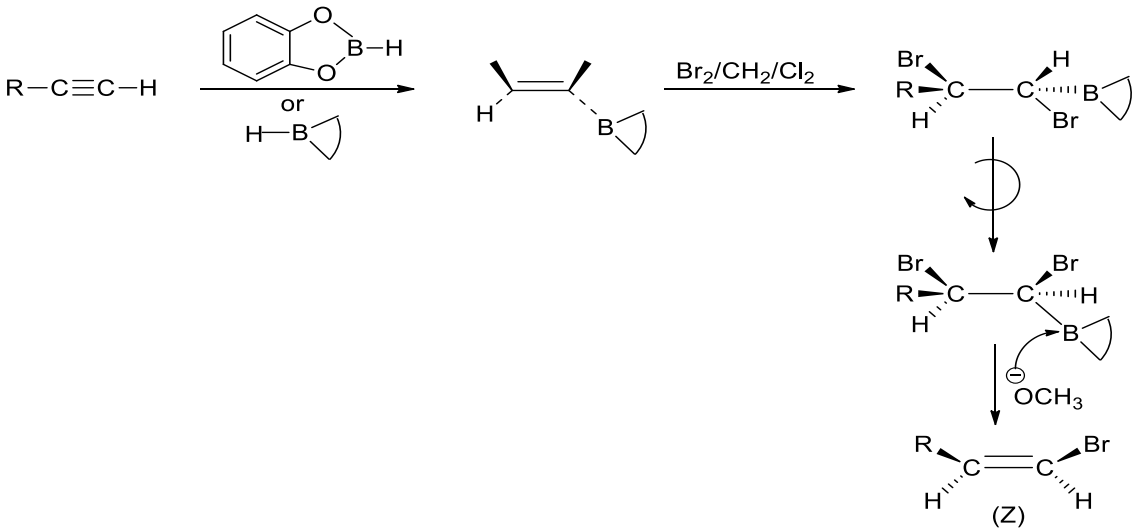




If carbonylation reaction is carried out in presence of small amount of water, then it inhibits the migration of third alkyl group from boron to carbon. This leads the formation of ketone after oxidation.

(7). Preparation of vinyl halides:

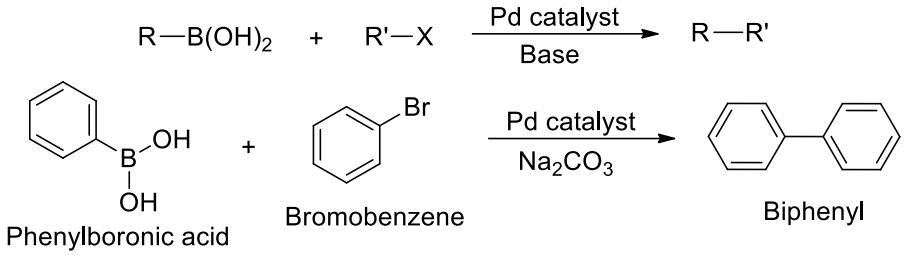
Alkynes can beconverted into vinyl halide by the use of catechoborane followed by the addition of bromine. The adduct gives anti elimination of boron and bromine in presence of base (RO^-). This reaction is highly **stereoselective** and the product has (Z)-configuration.



On the other hand, terminal alkyne gives (E) product with catechoborane followed by hydrolysis.

(8). Carbon-Carbon bond formation (Suzuki coupling):

One of the most important applications of organoboranes is the **Suzuki-Miyaura cross-coupling** reaction. In this reaction, an organoboron compound reacts with an aryl or vinyl halide in the presence of a palladium catalyst and base to form a new C–C bond.



(9). Synthesis of complex organic molecules:

Organoboron compounds can be incorporated into multistep synthetic sequences. Their predictable reactivity and compatibility with many functional groups make them valuable in the synthesis of pharmaceuticals, natural products and other complex molecules.

12.3.11 Advantages and Limitations of Hydroboration

Advantages

- Gives anti-Markovnikov alcohols.
- Shows high regioselectivity.
- Hydroboration occurs by syn addition.
- Does not normally involve carbocation rearrangement.
- Provides useful organoboron intermediates.
- Can be applied to both alkenes and alkynes.
- Bulky boranes provide improved selectivity.

Limitations

- Some borane reagents are sensitive to air and moisture.
- Borane reagents require careful handling.
- Appropriate borane reagents must be selected for highly selective transformations.
- Subsequent oxidation is generally required when alcohols are the desired products.

12.4 TRIALKYLSILYL HALIDES IN ORGANIC SYNTHESIS

Trialkylsilyl halides are important reagents in organic chemistry used mainly as protecting groups for alcohols and other functional groups during multi-step synthesis. They help chemists temporarily block reactive groups so that other reactions can occur without interference.

12.4.1 Introduction to Trialkylsilyl Halides

Trialkylsilyl halides are organosilicon compounds containing a silicon atom bonded to three alkyl groups and one halogen atom. They are represented by the general formula:

$$R_3SiX$$

Where, R is an alkyl group and X is usually Cl, Br or I.

These reagents react easily with alcohols, phenols, and carboxylic acids to form silyl ethers, which act as protecting groups. The most commonly used trialkylsilyl halides are trimethylsilyl chloride (**TMSCl**) and tert-butyldimethylsilyl chloride (**TBDMSCl**).

Commonly encountered halides include chlorosilanes, bromosilanes and iodiosilanes.

Trialkylsilyl halides are particularly important because they readily react with oxygen-containing functional groups such as alcohols and phenols.

Their most important application in this context is the formation of **silyl ethers**, which are widely used as protecting groups.

12.4.2 Structure and Nature of Trialkylsilyl Halides

Trialkylsilyl halides are organosilicon compounds containing a silicon–halogen (Si–X) bond, where the silicon atom is attached to three alkyl groups.

$$R_3Si^{\delta+}\text{-}X^{\delta-}$$

The silicon atom is therefore electrophilic, making trialkylsilyl halides readily susceptible to attack by nucleophiles.

For example:

$$R_3Si\text{—}Cl + Nu^- \longrightarrow R_3Si\text{—}Nu + Cl^-$$

12.4.3 Common Trialkylsilyl Halides

Common trialkylsilyl halides are given below:

Reagent	**Name**	**Abbreviation**
$(CH_3)_3SiCl$	Trimethylsilyl chloride	TMSCl
$(C_2H_5)_3SiCl$	Triethylsilyl chloride	TESCl
$(CH_3)_3SiCl$	Triethylsilyl bromide	TMSBr
(*t*-Bu)$(CH_3)_2SiCl$	*tert*-Butyldimethylsilyl chloride	TBDMSCl or TBSCl

Among these, TMSCl and TBSCl/TBDMSCl are especially important in synthetic organic chemistry. The choice of reagent depends on the desired stability of the protecting group and the conditions required for its subsequent removal.

12.4.4 Preparation and General Reactions

Trialkylsilyl halides, **$R_3Si–X$** (R = alkyl group; X = Cl, Br or I), are important organosilicon compounds which can be prepared by reactions involving organosilicon compounds and suitable halogenating or substitution processes

Preparation:

Trialkylsilyl halides can be prepared by several methods.

1. Reaction of silicon tetrachloride with a Grignard reagent

Alkyl groups can be introduced onto silicon by reacting silicon tetrachloride with an appropriate Grignard reagent:

$$SiCl_4 + 3RMgCl \longrightarrow R_3SiCl + 3MgCl_2$$

Example:

$$SiCl_4 + 3CH_3MgCl \longrightarrow (CH_3)_3SiCl + 3MgCl_2$$

Thus, trimethylsilyl chloride (Me_3SiCl) is obtained from silicon tetrachloride and methylmagnesium chloride.

2. Reaction of chlorosilanes with organolithium reagents

Trialkylsilyl halides can also be prepared through controlled substitution of Si-Cl bonds using organolithium reagents.

$$R_2SiCl_2 + R'Li \longrightarrow R_2R'SiCl + LiCl$$

Further substitution can give other substituted chlorosilanes depending on the stoichiometry.

3. Halogen exchange

A trialkylsilyl chloride can undergo halogen exchange with a metal halide.

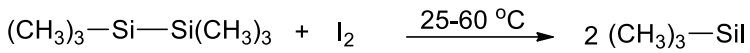
$$R_3SiCl + NaBr \longrightarrow R_3SiBr + NaCl$$

This provides access to other trialkylsilyl halides such as R_3SiBr.

Chlorotrimethylsilane undergoes halogen exchange with either lithium iodide in chloroform or NaI in methyl cyanide

$$(CH_3)_3—SiCl \xrightarrow[\text{or } NaI/CH_3CN]{Li/CHCl_3} (CH_3)_3—SiI + LiCl \text{ or } NaCl$$

It can also be prepared from hexamethyldisilane, when heated with I_2 at 25-60 ^oC to afford trimethylsilyl iodide (TMSI).

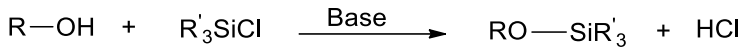


General Reactions:

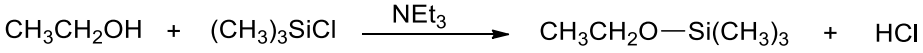
The high affinity of silicon for oxygen, nitrogen, sulfur and halogens makes trialkylsilyl halides useful as silylating reagents.

1. Reaction with alcohols

Alcohols react with trialkylsilyl halides in the presence of a base to form **silyl ethers**:



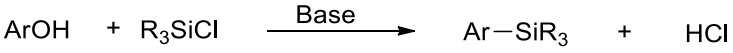
For example:



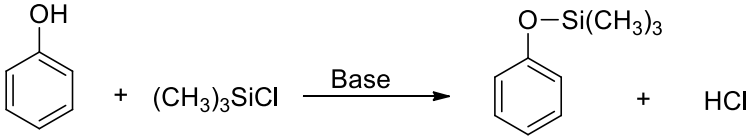
The resulting silyl ether protects the hydroxyl group from further reaction.

2. Reaction with phenols

Phenols are similarly converted into silyl ethers:

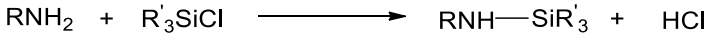


For example:



3. Reaction with amines

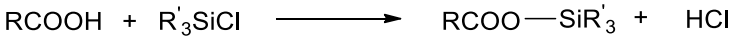
Primary and secondary amines can undergo silylation.



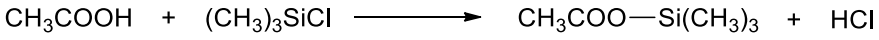
This reaction is useful for modifying the reactivity and volatility of amines.

4. Reaction with carboxylic acids

Carboxylic acids react with trialkylsilyl halides to produce **silyl esters**.

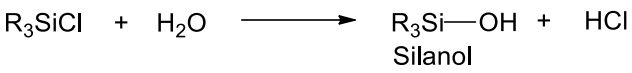


For example:

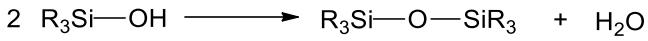


5. Reaction with water

Trialkylsilyl halides are readily hydrolysed by water.



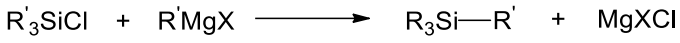
The initially formed silanol may undergo condensation.



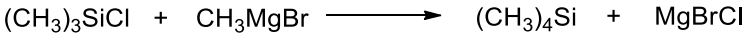
Thus, trialkylsilyl halides are generally handled under anhydrous conditions.

6. Reaction with organometallic compounds

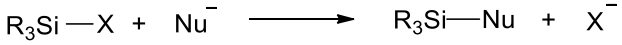
Trialkylsilyl halides undergo substitution with organolithium or Grignard reagents to form new Si–C bonds:



For example:



- The general reactivity of trialkylsilyl halides can be represented as:



Where, Nu^- = RO^-, $C_6H_5O^-$, $RCOO^-$, $RCOONH_2$ etc.

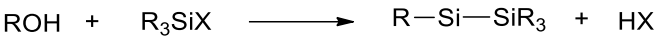
The reaction occurs readily because the **Si–X** bond is susceptible to nucleophilic substitution and silicon has a strong affinity for electronegative atoms.

Among the various trialkylsilyl halides, trimethylsilyl chloride (TMSCl) is particularly important because it is inexpensive, readily available and widely used for the protection and derivatization of functional groups.

12.4.5 Silylation of Alcohols

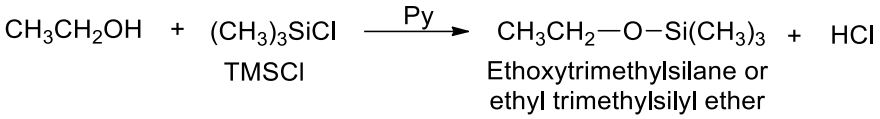
Silylation of alcohols is the conversion of an alcohol group −OH into a **silyl ether** $-O-SiR_3$. The reaction is widely used for protection of alcohols, because the resulting silyl ethers are generally stable toward many bases and nucleophiles and can later be removed under suitable conditions.

The general reaction is:

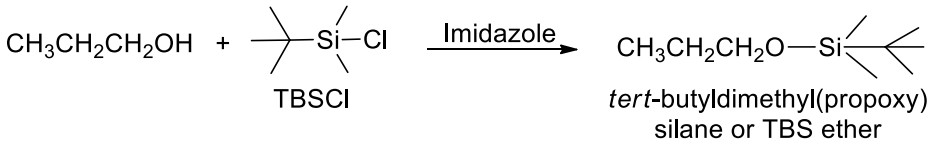


Where, X is usually Cl, and R = alkyl or aryl.
The most common silylating reagents are trimethylsilyl chloride (TMSCl)**,** tert-butyldimethylsilyl chloride (TBDMSCl or TBSCl)**,** triisopropylsilyl chloride (TIPSCl) and tert-butyldiphenylsilyl chloride (TBDPSCl)**.**
A base such as pyridine, triethylamine or imidazole is generally used to neutralize the HCl formed.

- **Trimethylsilylation**:

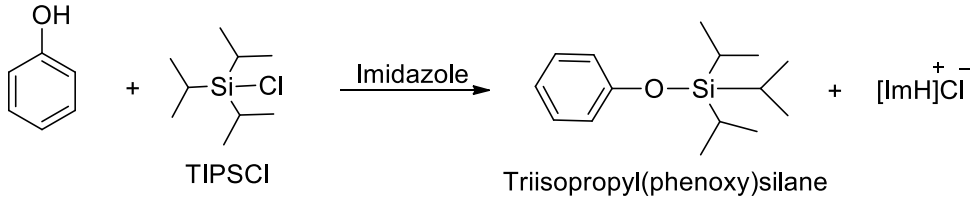


- **Tert-Butyldimethylsilyl chloride** (TBSCl) is one of the most important reagents for protecting alcohols.



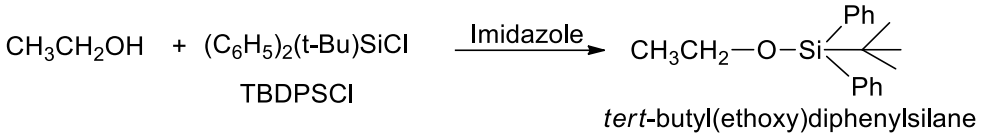
The product is a TBS ether, which is particularly useful because they are relatively stable during many subsequent synthetic reactions but can be removed selectively with fluoride ions.

- **Triisopropylsilyl chloride** (TIPSCl) gives a more sterically hindered silyl ether.



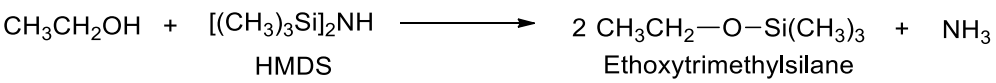
TIPS ethers are more resistant to cleavage than many smaller silyl ethers because of the steric bulk around silicon.

- **Tert-butyldiphenylsilyl chloride** (TBDPSCl**)** is another important reagent for alcohol protection.



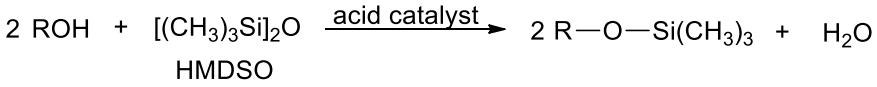
The bulky TBDPS group provides high stability and is useful when selective protection of one alcohol in a polyol is required.

- Alcohols can also be silylated using **hexamethyldisilazane** (HMDS).



HMDS is particularly useful for introducing the trimethylsilyl group.

- Alcohols can also undergo silylation with **hexamethyldisiloxane** (HMDSO) under acidic catalytic conditions.



12.4.6 Formation of Silyl Ethers

Silyl ethers are compounds in which the hydrogen atom of an alcohol is replaced by a silyl group. They have the general structure:

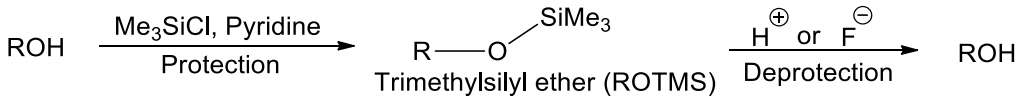
$$R\text{-}O\text{-}SiR'_3$$

Where, R and R′ may be alkyl or aryl groups.
Silyl ethers are commonly prepared by reacting alcohols with suitable silylating reagents in the presence of a base or catalyst which is discussed in section 12.4.5. They are important as protecting groups for alcohols in organic synthesis.

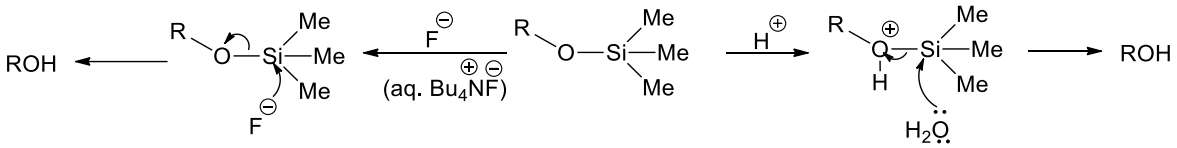
12.4.7 Protection of Alcohols and Phenols

Alcohols and phenols contain reactive hydroxyl groups that may interfere with other reactions during multistep organic synthesis. Therefore, the −OH group is often converted into a less reactive derivative called a **protecting group**. After the desired reaction has been completed, the protecting group is removed under suitable conditions to regenerate the alcohol or phenol. (You have already studied in **Unit 8**).

Trialkylsilyl ether derivatives such as trimethylsilyl (TMS) ethers have been found to have widespread use for the protection of alcohols in organic synthesis. These are prepared by the reaction of an alcohol with trimethylsilyl chloride (TMSCl) in presence of a base. However, trimethylsilyl ethers are not particularly stable and are cleaved under acidic or basic conditions and are attacked by certain nucleophiles as shown below in Scheme **12.1**.

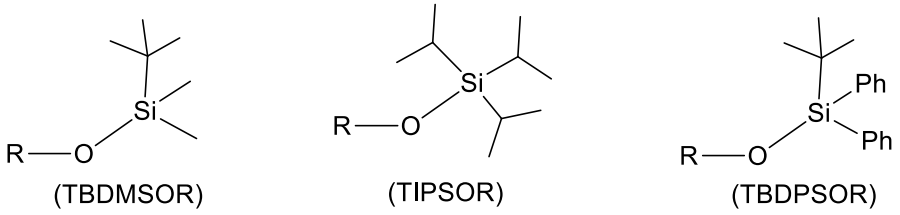


The mechanism of deprotection as:



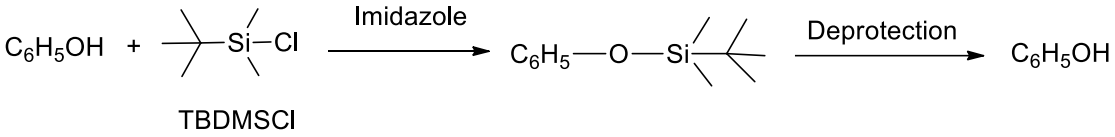
Scheme 12.1: Trimethylsilyl ether as protecting group for alcohols

To overcome the problem of easy cleavage of trimethylsilyl ethers under basic or acidic conditions a number of more bulky trialkylsily protecting groups have been developed such as *t*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), and *t*-butyldiphenylylsilyl (TBDPS) ethers.



Protection of a phenol

Phenol can be protected as its tert-butyldimethylsilyl (TBDMS) ether

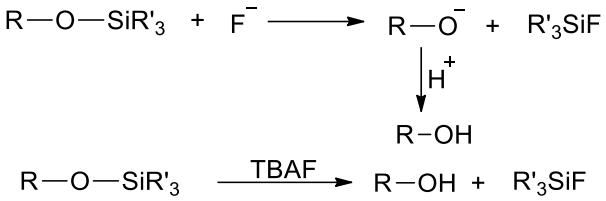


12.4.8 Deprotection of Silyl Ethers

Silyl ethers are commonly deprotected by **cleavage** of the Si–O bond to regenerate the original alcohol or phenol. The most widely used method involves fluoride ions, because silicon has a strong affinity for fluorine.

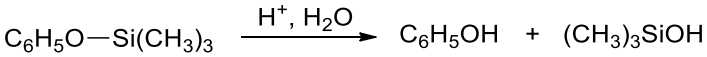
1. Deprotection with Fluoride Ions

Tetrabutylammonium fluoride (**TBAF**) is one of the most commonly used reagents for the removal of silyl protecting groups.



2. Acidic Deprotection

Silyl ethers can also be cleaved under acidic conditions, particularly when relatively labile groups such as TMS are present.



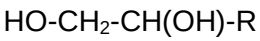
12.4.9 Selective Protection and Deprotection

Selective protection and deprotection are important strategies in multistep organic synthesis, particularly when a molecule contains two or more hydroxyl groups with different reactivities. A suitable silyl protecting group can be introduced at one hydroxyl group and later removed without affecting other protecting groups or functional groups.

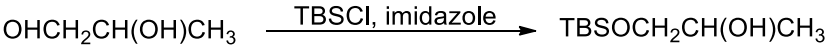
Selective Protection:

When a molecule contains primary and secondary alcohol groups, the **less sterically hindered** primary alcohol generally reacts preferentially with a bulky silyl chloride under suitable conditions.

For example, in a molecule containing both primary and secondary hydroxyl groups:



Selective protection of the primary alcohol can be achieved using TBDMSCl:

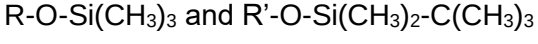


The secondary hydroxyl group remains unprotected and can therefore undergo further reactions.

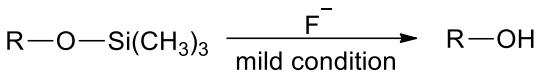
Selective Deprotection:

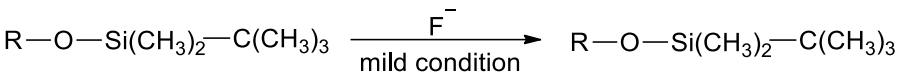
Different silyl protecting groups have different stabilities. This allows one protecting group to be removed while another remains intact.

For example, consider a molecule containing TMS and TBDMS ethers.



Treatment under mild conditions can preferentially remove the more labile TMS group while the more stable TBS ether can remain protected.





However, stronger fluoride conditions like TBAF can subsequently remove the TBS group:

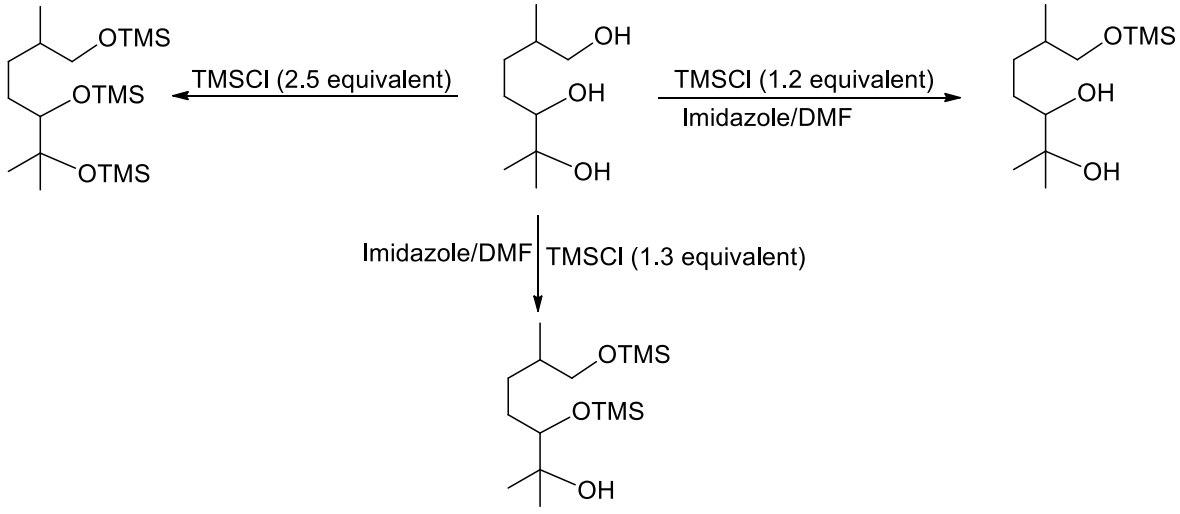
12.4.10 Synthetic Applications of Trialkylsilyl Halides

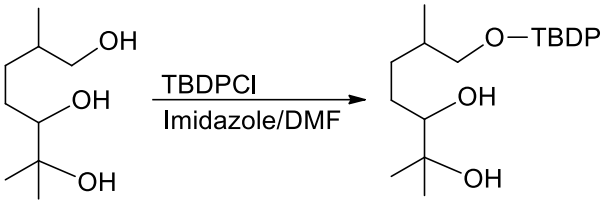
Trialkylsilyl halides such as trimethylsilyl chloride (TMSCl) and tert-butyldimethylsilyl chloride (TBSCl) are important reagents in organic synthesis. Their major applications arise from their ability to convert alcohols, phenols, carboxylic acids, and other functional groups into silyl derivatives, which can be used as protecting groups or as reactive synthetic intermediates.

1. Protection of Alcohols

Trialkylsilyl halides are widely used for the protection of hydroxyl groups and you have already learnt about is in **Unit 8**. Here you will learn in details about protection of alcohols by using trialkyl silyl halide.

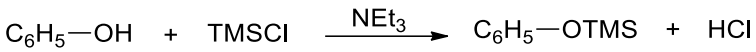
Alcohols react with silyl chlorides in the presence of a base such as imidazole or triethylamine to form silyl ethers.Replacement of one of the methyl groups with a much more sterically tert-butyl group gives *t*-butyldimethylsilyl halide (TBDMS-X). This reagent is used with imidazole in DMF. This reagent protects primary alcoholic group in presence of 2^0-alcohols. Tertiarybutyl diphenylsilyl halide (TBDPS-X) is also used and it protects only unhindered 1^o-alcohols in presence of 2^0-alcohols.





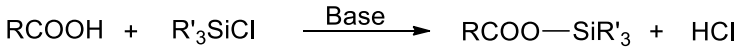
2. Protection of Phenols

Phenols can also be converted into silyl ethers using trialkylsilyl halides.



3. Protection of Carboxylic Acids

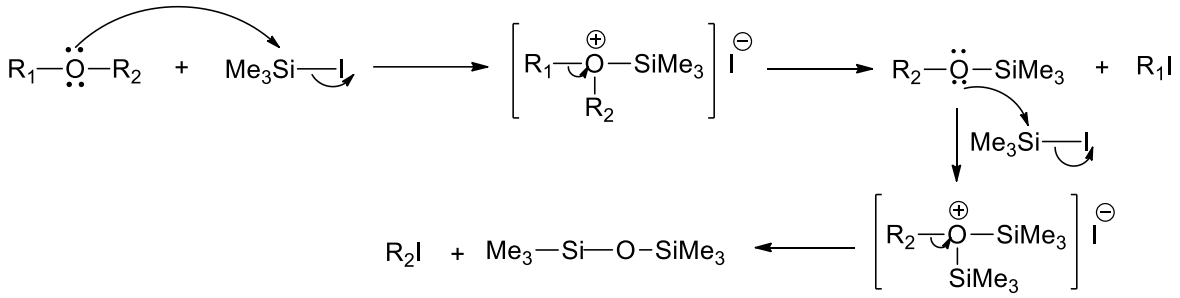
Trialkylsilyl halides can convert carboxylic acids into **silyl esters**.



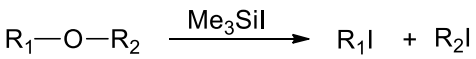
4. Used as Nucleophilic reagent in oxygen-carbon bond cleavage reaction

Trimethylsilyl iodide ($(CH_3)_3SiI$) is used for dealkylation reactions of wide variety of compounds containing C-O bond.

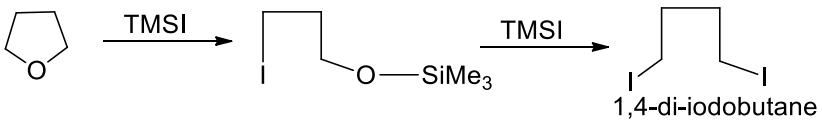
(a). Ether: Ether reacts with the reagent to afford the alkyl iodide and trimethylsilyl ether, which further reacts with the reagent to give another alkyl iodide.



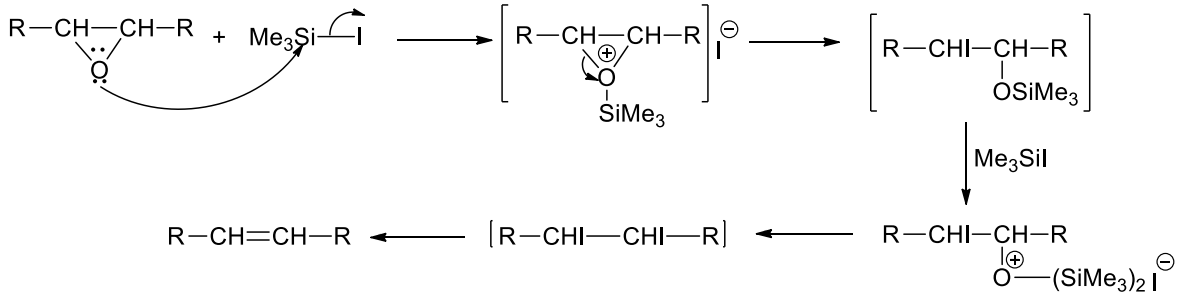
Overall reaction:



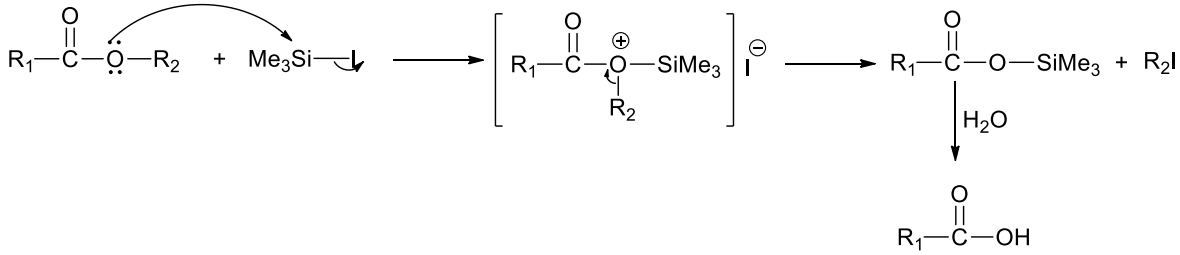
Cyclic ethers afford the iodosilyl ethers and then diiodide.



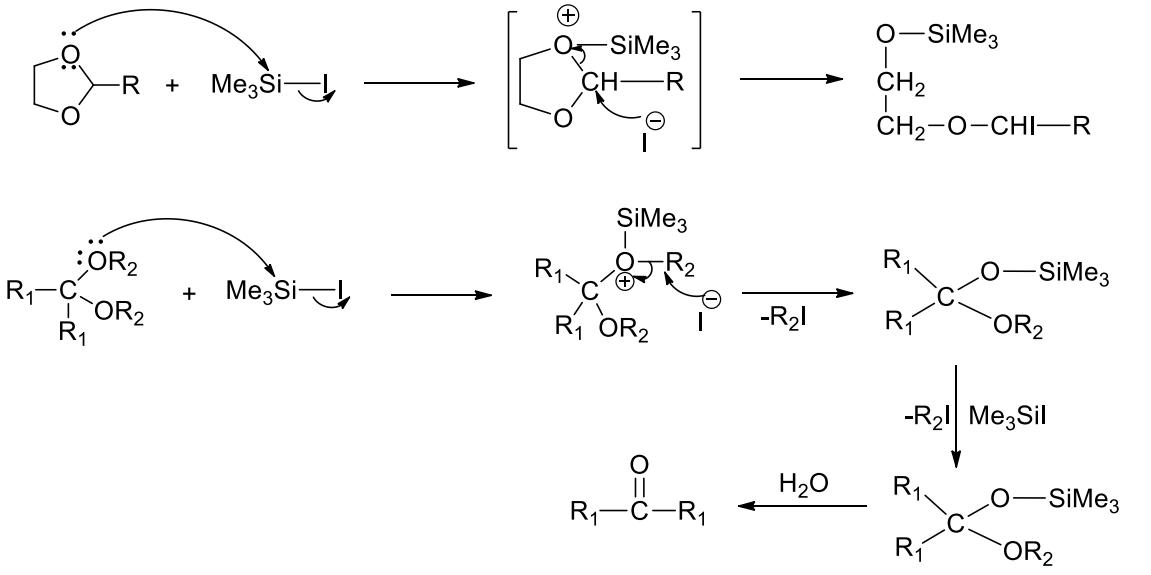
(b). Epoxides: Reaction of epoxides with one equivalent of reagent gives the *vicinal* siloxyl iodide. This compound further reacts with reagent to afford corresponding **alkenes**.



(c). Esters: The ester is treated with the reagent to form an initial oxonium intermediate which suffers attack by iodide. The trimethylsilyl ester is cleaved with H_2O during work up. Aryl esters are not cleaved by the reagent.

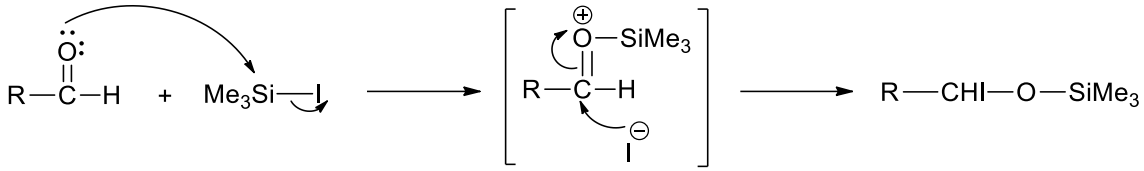


(d). Acetals: Acetals can be cleaved in analogy to ethers providing a new functionalized product or simply the parent ketone.

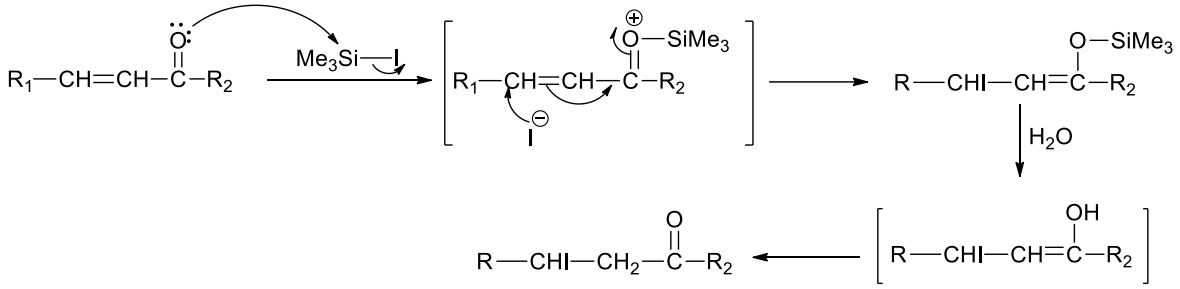


5. Use of trimethylsilyl iodide in nucleophilic addition reaction

Trimethylsilyl iodide gives addition reaction with aldehydes and ketones. Product of addition reaction is α–iodotrimethylsilyl ether



α,β-unsaturated ketones undergo conjugate addition with trimethylsilyl iodide to afford β-iodo adduct in high yield.



U LET US KNOW MORE

Hydroboration is a powerful and versatile reaction in organic chemistry, mainly used for converting alkenes into alcohols with high regio- and stereoselectivity. Boron attaches to the less substituted carbon (*anti*-Markovnikov addition). Hydrogen attaches to the more substituted carbon.

Trialkylsilyl halides are widely used reagents in organic chemistry for protection and functionalization of reactive groups. Trialkylsilyl halides (R_3SiX) are primarily used in organic synthesis as protecting groups for alcohols and phenols, forming silyl ethers that are stable under many conditions and can be selectively removed when needed.

W CHECK YOUR PROGRESS

Q1. What is Hydroboration-Oxidation?
Q2. What type of stereochemistry occurs in hydroboration?
Q3. Predict the product of hydroboration-oxidation of propene.
Q4. Why is BH_3 able to react with three molecules of alkene?
Q5. Why are bulky boranes preferred for alkynes?
Q6. Write the general formula of trialkylsilyl halides?
Q7. Give two examples of trialkylsilyl halides.
Q8. What is the main role of trialkylsilyl halides in organic synthesis?

2 12.5 LET US SUM UP

- Hydroboration is the addition of a B–H bond across C=C or C≡C bonds. Hydroboration of alkenes generally gives anti-Markovnikov products with syn addition. The reaction proceeds through a concerted four-centre transition state without carbocation rearrangement.
- Hydroboration-oxidation converts alkenes into alcohols, with –OH appearing at the less substituted carbon. Bulky boranes such as 9-BBN and Sia_2BH improve regioselectivity and minimise multiple hydroboration. Hydroboration of terminal alkynes followed by oxidation generally gives aldehydes, whereas internal alkynes give ketones.
- Organoboranes are useful intermediates for alcohols, alkanes, alkenes, halides and C–C bond formation, particularly in Suzuki-Miyaura coupling.
- Trialkylsilyl halides (R_3SiX) are important silylating reagents used mainly for the protection and functionalisation of alcohols and phenols.
- Reaction of alcohols or phenols with silyl halides forms silyl ethers, which protect the –OH group during multistep synthesis.
- Common protecting groups include TMS, TBS/TBDMS, TIPS and TBDPS groups, which differ in stability and ease of removal. Fluoride ions, particularly TBAF, are widely used for the deprotection of silyl ethers.
- Selective protection and deprotection of silyl ethers enable the controlled manipulation of different functional groups in multistep organic synthesis.

K 12.6 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: Hydroboration-Oxidation Reaction is an important reaction in Organic Chemistry used to convert alkenes into alcohols. It is a two-step reaction in which an alkene reacts with borane followed by oxidation to produce an alcohol.

Answer to Q2: In the Hydroboration-Oxidation Reaction, the hydroboration step shows *syn* stereochemistry.

Answer to Q3: The final product is 1-propanol.

Answer to Q4: BH_3 can react with three molecules of alkene because it has three B–H bonds and an electron-deficient boron that can sequentially form three B–C bonds, producing a trialkylborane.

Answer to Q5: Simple borane (BH_3) can undergo repeated addition to an alkyne. Bulky boranes reduce the possibility of undesired multiple hydroboration and provide improved selectivity.

Answer to Q6: The general formula of trialkylsilyl halides is R_3SiX.

Answer to Q7: Trimethylsilyl chloride (TMSCl) and Triethylsilyl bromide (TESBr).

Answer to Q8: The main role of trialkylsilyl halides in organic synthesis is to act as protecting groups for reactive functional groups, especially alcohols, phenols, and amines.

O 12.7 FURTHER READING

- Michael B. Smith: Organic Synthesis (4th Ed.), Academic Press.
- P. S. Kalsi: Organic Reaction and Their Mechanisms, New Age Publication.
- J .Singh & L.D.S. Yadav-Organic Synthesis
- Clayden, Greeves and Warren: Organic Chemistry (2nd Edition), Oxford University Press.

M 12.8 MODEL QUESTIONS

Q1. Define hydroboration. State two advantages of hydroboration in organic synthesis.
Q2. Why does boron attach to the less substituted carbon in hydroboration reaction?
Q3. Explain the mechanism, regioselectivity and stereochemistry of hydroboration of alkenes with suitable examples.
Q4. Describe the hydroboration–oxidation reaction of alkenes
Q5. What are bulky boranes? Give two examples.
Q6. What are trialkylsilyl halides? Discuss their structure, preparation, chemical properties and importance in organic synthesis.
Q7. What are silyl ethers? Why are they useful in organic synthesis?
Q8. Name two commonly used silyl protecting groups.
Q9. What type of compound is formed when alcohol reacts with trialkylsilyl chloride?
Q10. Which reagent is commonly used to remove the silyl protecting group?

UNIT 13: MITSUNOBU REACTION, WOHL-ZIEGLER ALLYLIC BROMINATION

UNIT STRUCTURE

13.1 Learning Objectives
13.2 Introduction
13.3 Mitsunobu Reaction
13.4 Mechanism of Mitsunobu Reaction
13.5 Application of Mitsunobu Reaction
13.6 Wohl-Ziegler Allylic Bromination
13.7 Mechanism of Wohl-Ziegler Allylic Bromination
13.8 Application of Wohl-Ziegler Allylic Bromination
13.9 Let Us Sum Up
13.10 Answers to Check Your Progress
13.11 Further Reading
13.12 Model Questions

13.1 LEARNING OBJECTIVES

After going through this unit, you will be able to:

- Learn the principles and general features of the Mitsunobu reaction and Wohl-Ziegler allylic bromination.
- Learn about the mechanism involved in both the reactions.
- Understand the stereo-chemical outcome and reaction conditions required for these transformations.
- Acquire an overview of synthetic applications of these reactions in organic synthesis.

13.2 INTRODUCTION

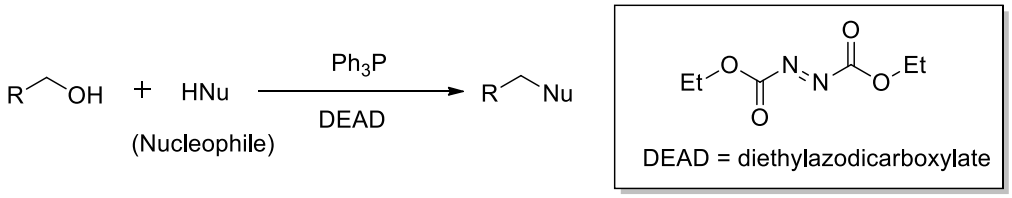
In this unit, we will discuss two important Name reactions, the Mitsunobu reaction and the Wohl-Ziegler allylic bromination, which are usually used in organic synthesis. The Mitsunobu reaction converts alcohols into various functional groups through a nucleophilic substitution reaction with inversion of configuration, while the Wohl-Ziegler allylic bromination introduces bromine at the allylic/benzylic position of alkenes using *N*-bromosuccinimide under radical conditions.

In this unit we will study the mechanisms and synthetic applications of these reactions, highlighting their importance in the synthesis of biologically active molecules, pharmaceuticals and other complex organic compounds.

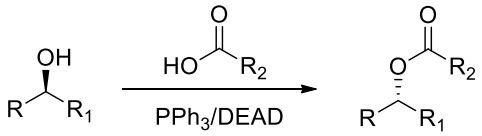
13.3 MITSUNOBU REACTION

This reaction was developed by Oyo Mitsunobu in 1967. It is an organic reaction that converts an alcohol into a variety of functional groups, such as esters, ethers, thioethers

and amine using trialkyl/triaryl phosphine and dialkylazodicarboxylate reagents A general scheme of the Mitsunobu reaction is presented below.



When the nucleophile is a carboxylic acid, the product is an ester.



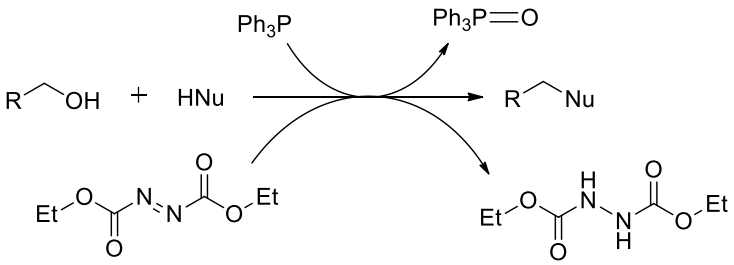
In this reaction, alcohol reacts with the phosphine to generate a good leaving group. Then it undergoes an inversion of configuration in S_N2 fashion as the nucleophile displaces it.

The reaction is useful because rather than the use of two steps to convert the OH group first to a good leaving group (for example, a sulfonate ester) and then to displace it, this reaction allows us to convert an alcohol directly to an S_N2 product in one operation. In this reaction, the alcohol becomes the electrophile, the nucleophile is usually relatively weak (e.g., the conjugate base of a carboxylic acid). A common side product is produced when the azodicarboxylate displaces the leaving group instead of the desired nucleophile.

13.4 MECHANISM OF MITSUNOBU REACTION

One of the commonly used arylphosphine reagents for the reaction is triphenylphosphine (PPh_3). Phosphines are nucleophilic, but not basic like amines. The other reagent is diethyl azodicarboxylate (DEAD).

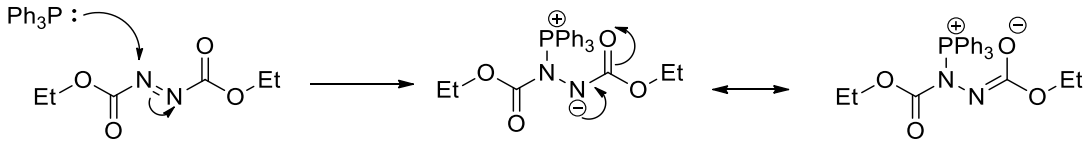
The reaction may be considered as a dehydrative redox reaction also. Because due to the affinity of phosphorus for oxygen and the affinity of the N=N moiety toward hydrogen, there is an overall loss of a H_2O unit (OH must be removed from the alcohol and H from the nucleophile) as shown below. In the process, Ph_3P is converted to $Ph_3P{=}O$ and DEAD is converted to its reduced form.



This process ends up in very stable molecules, viz., the P=O and N-H bonds are strong where the N=N bond was weak, compensating for the sacrifice of the strong C-O bond in the starting alcohol.

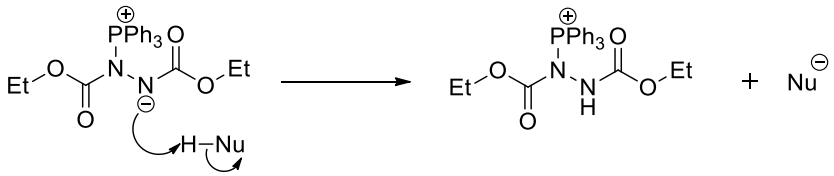
Here is a step-by-step mechanism of the reaction.

Step I: This step involves neither the alcohol nor the added nucleophile. Here, the phosphine adds to the weak N=N π bond to give an anion stabilized by one of the ester groups.

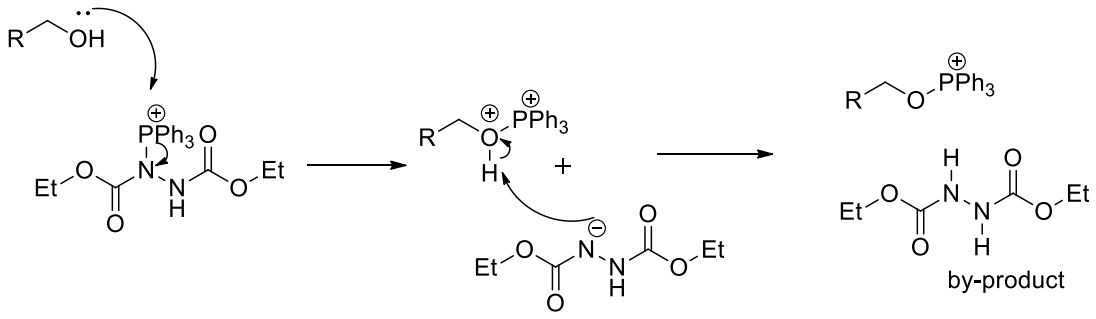


Stabilization of the nitrogen anion by the ester group

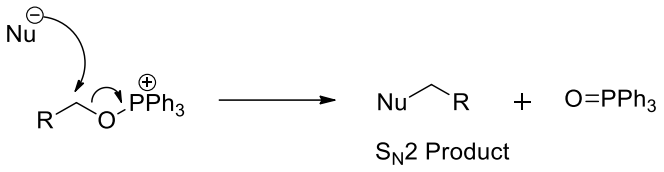
Step II: The nucleophile has been added as its conjugate acid 'HNu' (this might be a carboxylic acid). The anion produced by this first step is basic enough to remove a proton from this acid, generating Nu^- ready for reaction.



Step III: Since oxygen and phosphorus have a strong affinity toward each other, so the positively charged phosphorus is now attacked by the alcohol, displacing a second nitrogen anion in an S_N2 reaction at phosphorus. The nitrogen anion generated in this step is stabilized by conjugation with the ester, but rapidly removes the proton from the alcohol to give an electrophilic R-O-PPh_3^+ species and the reduced form of DEAD as a by-product.



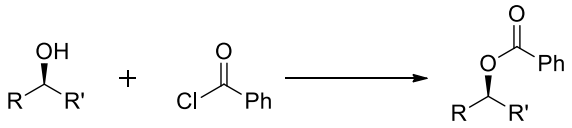
Step IV: Finally, the anion of the nucleophile can attack the phosphorus derivative of the alcohol in a normal S_N2 reaction at carbon with the phosphine oxide as the leaving group. And the final products are obtained.



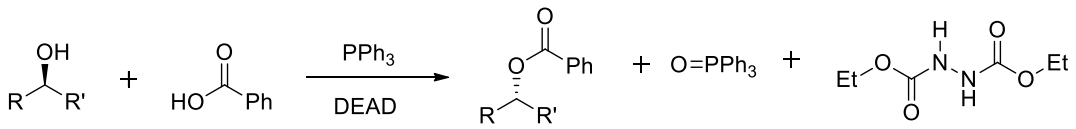
The whole process takes place in one operation. The four reagents are all added to one flask and the products are the phosphine oxide, the reduced azo diester and the product of an S_N2 reaction on the alcohol.

This vital S_N2 step leads to inversion of configuration as it always does in S_N2 reactions. This is one of the important strength of the Mitsunobu reaction. It is a reliable way to replace OH by a nucleophile with inversion of configuration. One important example is the formation of esters from secondary alcohols with inversion. Normal ester formation leads to retention as the C-O bond of the alcohol is not broken. Comparison of these two reactions are presented below.

Ester formation from a secondary alcohol
with retention of configuration



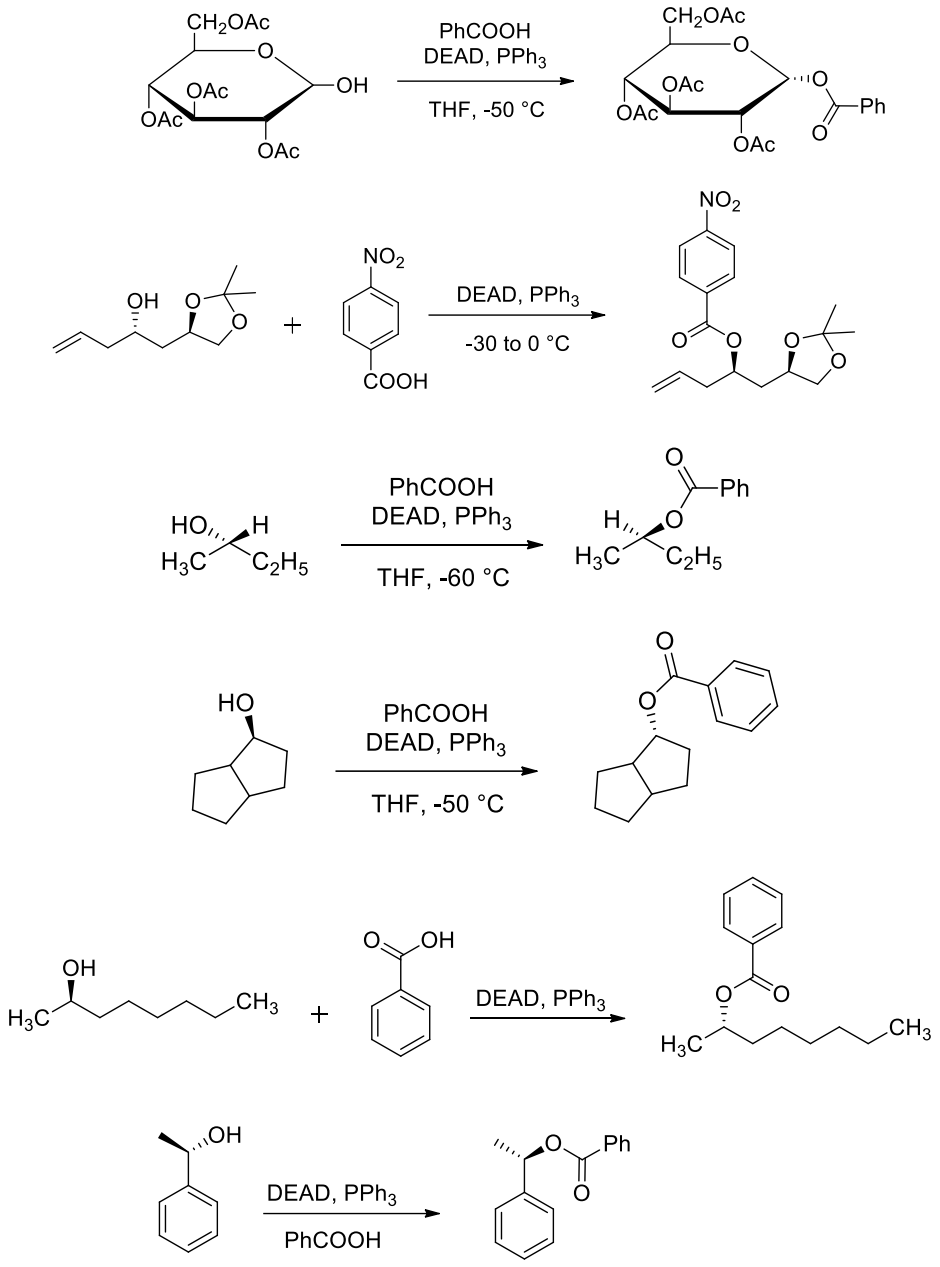
Ester formation from a secondary alcohol with inversion of configuration by Mitsunobu reaction



13.5 APPLICATION OF MITSUNOBU REACTION

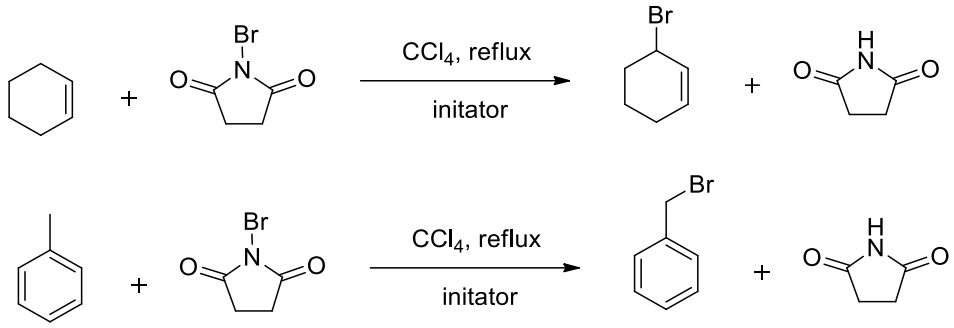
The Mistunobu reaction has found widespread use in many fields because of high reliability and extensive versatility. It is mostly used in the total synthesis of biologically active natural products such as (+)-Catechin (an antioxidant) and (+)-Vinblastine (an antineoplastic agent used in the treatment of various types of cancers such as bladder cancer, melanoma and testicular cancer). This reaction has been used to synthesize Quinine, Colchicines (used in the treatment of Gout), Morphine, Strychnine (a toxic, crystalline alkaloid used as a pesticide, particularly for killing small vertebrates such as birds and rodents).

Here are some examples of Mistunobu reaction for the synthesis of various organic molecules.



13.6 WOHL-ZIEGLER ALLYLIC BROMINATION

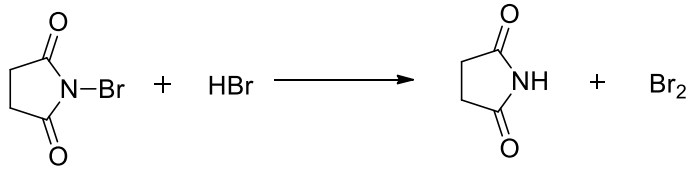
It is the bromination at an allylic or benzylic position of a hydrocarbon substrate with *N*-bromosuccinimide (NBS) under radical initiating conditions to provide the corresponding allylic or benzylic bromide. Conditions used to promote the radical reaction are typically radical initiators, light and/or heat. Carbon tetrachloride (CCl_4) is typically used as the solvent in this reaction. The general scheme of the reaction is given below.



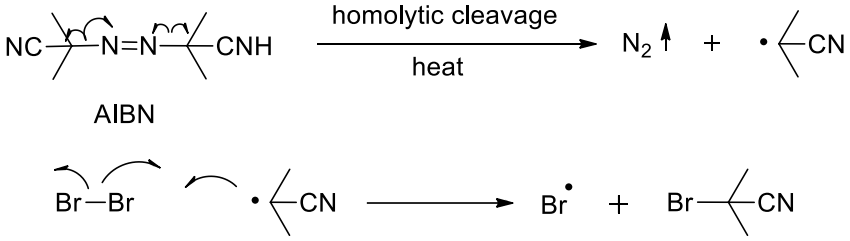
13.7 MECHANISM OF WOHL-ZIEGLER ALLYLIC BROMINATION

NBS is the most commonly used reagent to produce low concentrations of bromine. Commercial NBS usually contains trace amounts of Br_2 and HBr impurities, which help kick-start the radical chain process under light or heat. The reaction proceeds through the following steps as discussed below.

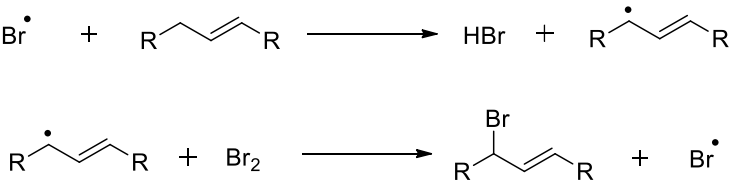
Pre-initiation step: When suspended in CCl_4, NBS reacts with trace amounts of HBr to produce a low concentration of Br_2 to facilitate the allylic bromination reaction.



Initiation step: Once the NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light or radical initiator such as AIBN (Azobisisobutyronitrile) to produce bromine radicals.



Propagation step: One bromine radical produced by homolytic cleavage in the initiation step removes allylic hydrogen of the alkene molecule. A radical alkene intermediate is generated which is stabilised by resonance. The stability provided by delocalisation of the radical in the alkene intermediate is the reason that substitution at the allylic position is favoured over competing reactions such as addition at the double bond.

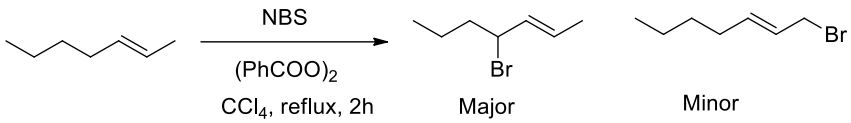


The intermediate radical then reacts with a Br_2 molecule to generate the allylic bromide product and regenerate the bromine radical, which continues the radical chain mechanism.

Important Note:

1) Since the Br_2 that is used in the reaction is generated during the course of the reaction, so it is always present in low concentration. Therefore, the vicinal dibromide which formed when a high concentration of Br_2 is employed is not formed.

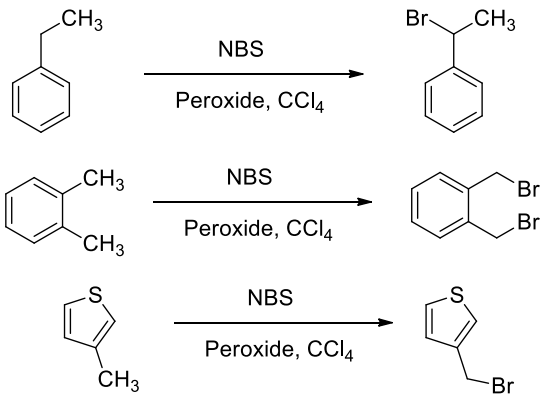
2) If the alkene reactant is asymmetric, that means if there are two allylic positions, then two monobromo derivatives may be formed. However, bromine is attached to allylic methylene groups much more rapidly than allylic methyl groups. For example, in 2-heptene; a secondary position is substituted more rapidly than primary.



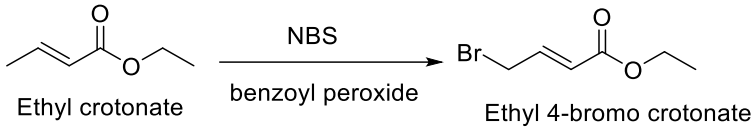
3) In a typical reaction, a stoichiometric amount of NBS solution and a small quantity of initiator are added to a solution of the substrate in CCl_4, and the reaction mixtrure is stirred and heated to the boiling point. Initiation of the reaction is indicated by more vigorous boiling. The heat source may need to be removed. When all NBS (it is denser than the solvent) has been converted to succinimide (which floats on top), the reaction indicates its completion. Due to the high toxicity and ozone-depleting nature of CCl_4, trifluorotoluene has been proposed as an alternatiove solvent suitable for the reaction.

13.8 APPLICATION OF WOHL-ZIEGLER ALLYLIC BROMINATION

Here are some examples of Wohl-Ziegler allylic bromination, in which bromination takes place in the benzylic position.

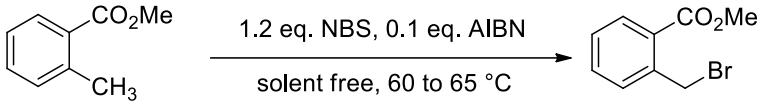


Unsaturated acids, esters, aldehyde and ketone also undergo allylic bromination. In the example given below, you can see, ethyl crotonate reacts with NBS in the presence of benzoyl peroxide as initiator. It gives ethyl 4-bromo crotonate as the product.

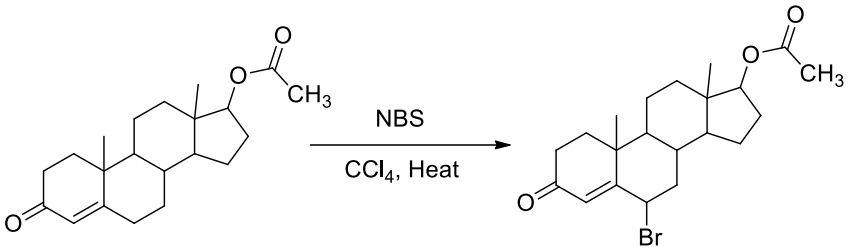


Ethyl crotonate Ethyl 4-bromo crotonate

Another similar example is given below.



Under similar conditions, testosterone acetate is converted into 6-bromotestosterone acetate by NBS.



Testosterone acetate 6-Bromo Testosterone acetate

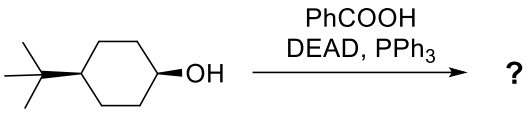
W CHECK YOUR PROGRESS

Q1: In the Mitsunobu reaction, the stereochemistry at the chiral centre shows
- (a) Retention
- (b) Racemization
- (c) Inversion
- (d) No change

Q2: The Mitsunobu reaction generally occurs with
- (a) Strong nucleophiles only
- (b) Weak acidic nucleophiles
- (c) Only halide ions
- (d) Only amines

Q3: Which of the following is a common by-product of the Mitsunobu reaction?
- (a) Triphenylphosphine oxide
- (b) Water
- (c) Methane
- (d) Carbon dioxide

Q4: Draw the product obtained from the given reaction



Q5: The reagent commonly used in the Wohl-Ziegler reaction is

(a) Br_2
(b) NBS
(c) HBr
(d) NaBr

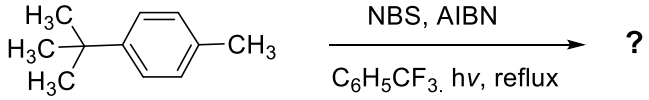
Q6: The main function of NBS in allylic bromination is to

(a) Provide high concentration of bromine
(b) Maintain a low concentration of bromine
(c) Act as a solvent
(d) Act as a catalyst

Q7: Fill in the Blanks

The solvent often used in the Wohl Ziegler reaction is _____.

Q8: Draw the product obtained from the given reaction.



2 13.9 LET US SUM UP

- The Mitsunobu reaction converts alcohols into other functional groups such as esters, ethers and amines using PPh_3 and DEAD as reagents.
- The reaction proceeds through an S_N2 mechanism leading to inversion of configuration at the chiral center.
- The major by-products of the reaction are triphenylphosphine oxide and the reduced azo compound.
- The reaction is useful because it converts an alcohol into a substitution product in a single step.
- The Wohl-Ziegler allylic bromination involves bromination at the allylic/benzylic position of alkenes using NBS under radical conditions such as light, heat or radical initiators.
- NBS helps to maintain a low concentration of Br_2 preventing addition across the double bond and favouring allylic substitution.
- Allylic bromination products are useful intermediates in the synthesis of various organic compounds and pharmaceuticals

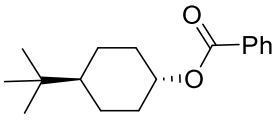
K 13.10 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: (c) Inversion

Answer to Q2: (b) Weak acidic nucleophiles

Answer to Q3: (a) Triphenylphosphine oxide

Answer to Q4:

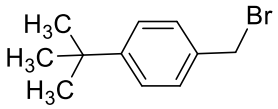


Answer to Q5: (b) NBS

Answer to Q6: (b) Maintain a low concentration of bromine

Answer to Q7: Carbon tetrachloride

Answer to Q8:



O 13.11 FURTHER READING

- Organic Chemistry (2nd ed. 2012)- J. Clayden, N. Greeves and S. Warren, Oxford University Press.
- Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications (4th Expanded Ed., 2009), Jie Jack Li, Springer.
- Principles of Organic Synthesis, R. O. C. Norman and J. M. Coxon, ELBS.

M 13.12 MODEL QUESTIONS

Q1. Explain the mechanism of the Mitsunobu reaction in detail.
Q2. Discuss the role of triphenylphosphine and azodicarboxylate in the reaction.
Q3. Which reagent is commonly used in the Wohl-Ziegler Reaction?
Q4. What would happen if the concentration of Br_2 becomes high during allylic bromination?
Q5. Discuss the mechanism and synthetic utility of the Wohl-Ziegler Reaction.
Q6. Why is NBS preferred for allylic bromination?
Q7. What stereochemical change occurs during the Mitsunobu reaction?
Q8. Explain the role of light or radical initiators in the Wohl-Ziegler reaction.

UNIT 14: USE OF ORGANOMETALLIC REAGENTS IN FORMATION OF CARBON-CARBON BONDS

UNIT STRUCTURE

14.1 Learning Objectives
14.2 Introduction
14.3 The Heck Reaction
14.4 Mechanism of Heck Reaction
14.5 Suzuki Coupling
14.6 Mechanism of Suzuki Coupling
14.7 Sonogashira Coupling
14.7.1 Ene-diynes and the Bergmann cyclization
14.8 Mechanism of Sonogashira Coupling
14.9 Stille Coupling
14.10 Mechanism of Stille Coupling
14.11 Negishi Coupling
14.12 Mechanism of Negishi Coupling
14.13 Let Us Sum Up
14.14 Answers to Check Your Progress
14.15 Further Reading
14.16 Model Questions

14.1 LEARNING OBJECTIVES

After going through this unit, you will be able to learn:

- Importance of organometallic reagents in the formation of C-C bonds in modern organic synthesis.
- Principles and synthetic applications of the Heck reaction in organopalladium chemistry.
- Reactions and mechanisms of important palladium catalyzed cross coupling reactions such as Suzuki coupling and Stille coupling.
- The role of alkynes and copper co-catalyst in the Sonogashira coupling.
- The use of organozinc reagents and the mechanism involved in the Negishi coupling.

14.2 INTRODUCTION

During the latter half of the 20th century, transition metals played a central role in the development of synthetic organic chemistry. Their incorporation into catalytic methodologies revolutionized the synthesis of complex organic molecules. A wide range of transition metal catalyzed reactions were developed, significantly expanding the synthetic toolbox available to chemists. The reactivity of transition metals arises from their ability to adopt multiple oxidation states and to coordinate with organic substrates. Through such coordination, they can activate otherwise unreactive molecules and facilitate the formation of new chemical bonds under relatively mild conditions. This

capacity for substrate activation has rendered transition metals indispensable in modern synthetic strategies.

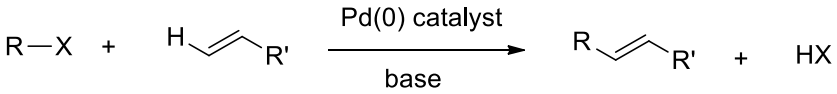
Among these metals, palladium (Pd) emerged as one of the most versatile and extensively utilized catalysts. An early and influential development was the Pd catalyzed oxidation of ethylene to acetaldehyde in the presence of O_2, a transformation that became industrially significant as the 'Wacker' processes. This discovery inspired extensive research into Pd catalyzed transformations. Subsequent investigations into Pd catalyzed carbonylation and cross coupling reactions led to highly efficient methodologies for C-C bond formation. Indeed, transition metals, particularly Pd have been instrumental in the development of reactions for constructing both carbon-carbon double and single bonds, processes that are fundamental to the synthesis of pharmaceuticals, agrochemicals and advanced materials. Organopalladium species tolerate many different functional groups and promote a variety of C-C bond forming reactions with extremely high chemo- and regioselectivity. The Pd is typically derived from $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ or by in situ reduction of a Pd(II) species such as $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$.

The profound impact of metal catalyzed C-C bond forming reactions was formally recognized when the Nobel Prize in Chemistry was awarded in 2005 for advances in metal catalyzed formation of C=C bonds and again in 2010 for the development of Pd catalyzed cross coupling for C-C bond formation reactions. These achievements highlight the transformative role of transition metals in modern organic synthesis.

In this unit, we will study the use of organopalladium reagents in the formation of C-C bonds. We will also study the mechanism and synthetic application of Heck reaction, Stille, Suzuki, Sonogashira and Negishi coupling reactions.

14.3 THE HECK REACTION

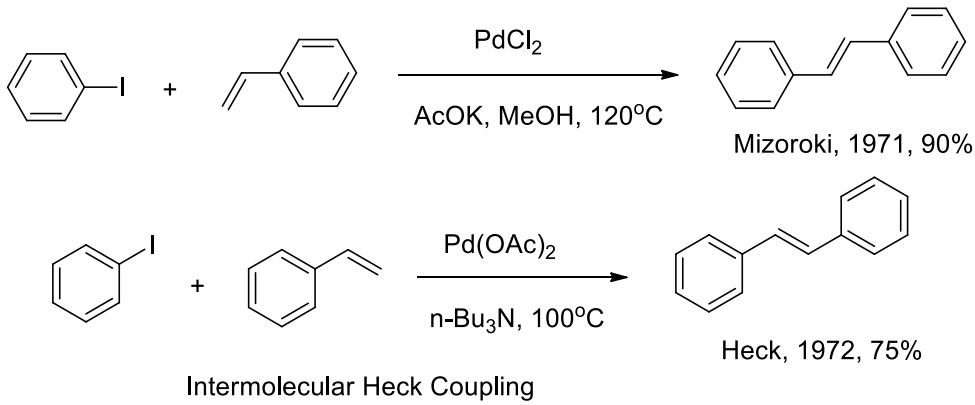
Heck reaction was independently discovered by T. Mizoroki in 1971 and R. F. Heck in 1972. The classical reaction involves the Pd catalyzed coupling between an alkene with an organic halide or triflate (R-X) to form a new alkene molecule.



The R group can be aryl, vinyl or any alkyl group without ß-hydrogens on sp^3 carbon atom. The group X can be a halogen or triflate (OSO_2CF_3). The most widely used catalyst for this reaction is Pd as Pd(II) in the form of a salt or complex, or as Pd(0). A base such as an amine is necessary to remove the liberated acid, HX. The reaction is stereoselective with a tendency for *trans* coupling as the Pd halide group and the bulky organic residue move away from each other in the reaction sequence by bond rotation. Typical catalysts are Pd(0)-phosphine complexes, $Pd(PPh_3)_4$, or in situ catalysts such as $Pd(OAc)_2/PPh_3$.

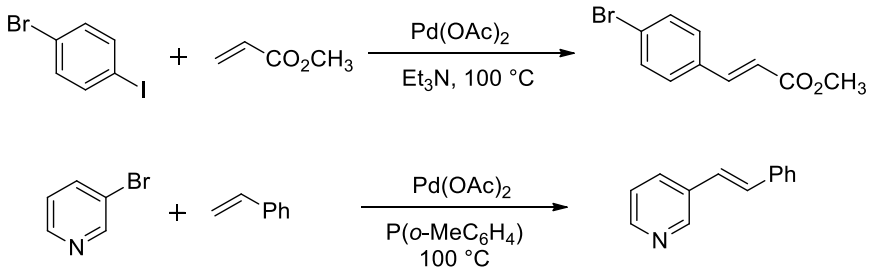
Chelated phosphines with larger bite angles such as dppf and $Ph_2P(CH_2)_nPPh_2$ (where n=2 to 4) have also been used in several cases along with $Pd(OAc)_2$, $Pd_2(dba)_3$ and (π-allyl)Pd complexes. Here, you can see the general scheme of the Heck reaction.

Examples of intermolecular Heck reaction:

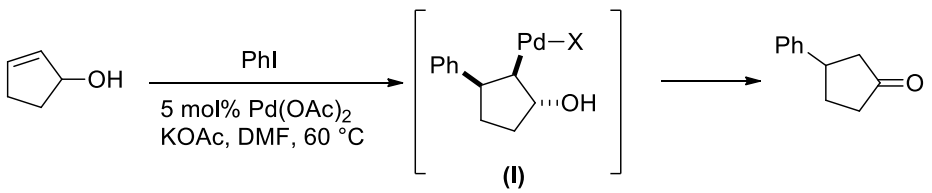


Intermolecular Heck Coupling

Generally, these reactions are carried out in polar aprotic solvents such as CH_3CN, DMSO or dimethylacetamide (DMAc). The reaction time and temperature depend on the type of organic halide used. If the halide is more reactive, the reaction proceeds faster and under milder conditions. For example, iodo compounds are more reactive than bromo or chloro compounds. Because of this high reactivity, auxiliary ligands like phosphines are often not required. In such cases, polar solvents like DMF, DMAc or NMP work very well, especially when used together with NaOAc as a base. These conditions help the reaction proceed smoothly and efficiently. With an aryl bromide, the ligand tri-*o*-tolylphosphine is effective. The addition of a metal halide or tetra-alkylammonium halide can promote the Heck reaction. The reactions illustrating the above cases are presented below:

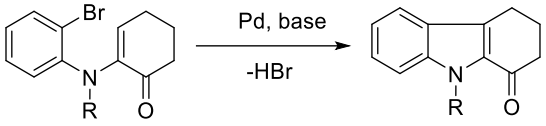


A mixture of alkenes can result when there is a choice of ß-hydrogen atoms for the β-hydride elimination step (see the mechanism). There is a preference for the formation of the more stable alkene. For example, reaction between iodobenzene and the allylic alcohol gave the intermediate organopalladium(II) species (**I**). ß-Hydride elimination leads to the formation of a more stable enol, which upon keto-enol tautomerism gives the corresponding ketone.

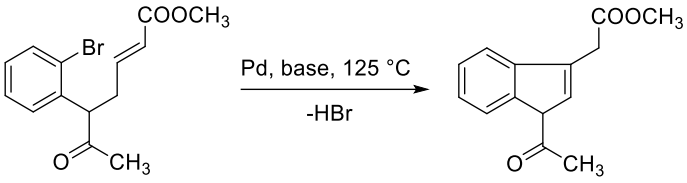


The reactions usually occur both on intermolecular and intra-molecular level, although intermolecular reactions are common. Organic halides that contain β-hydrogens are

generally not suitable because they tend to form unwanted olefins at the Pd(II) center instead of giving the desired product. The reactivity of olefins also depends on their structure. Electron-rich, di-substituted or cyclic olefins are usually less reactive than electron-deficient, mono-substituted olefins. One major advantage of the Heck reaction is that it tolerates many different functional groups. Because of this, it is widely used to prepare carbocyclic and heterocyclic compounds as well as C-C bonded isomerized products, including many natural products.



Intramolecular Heck coupling



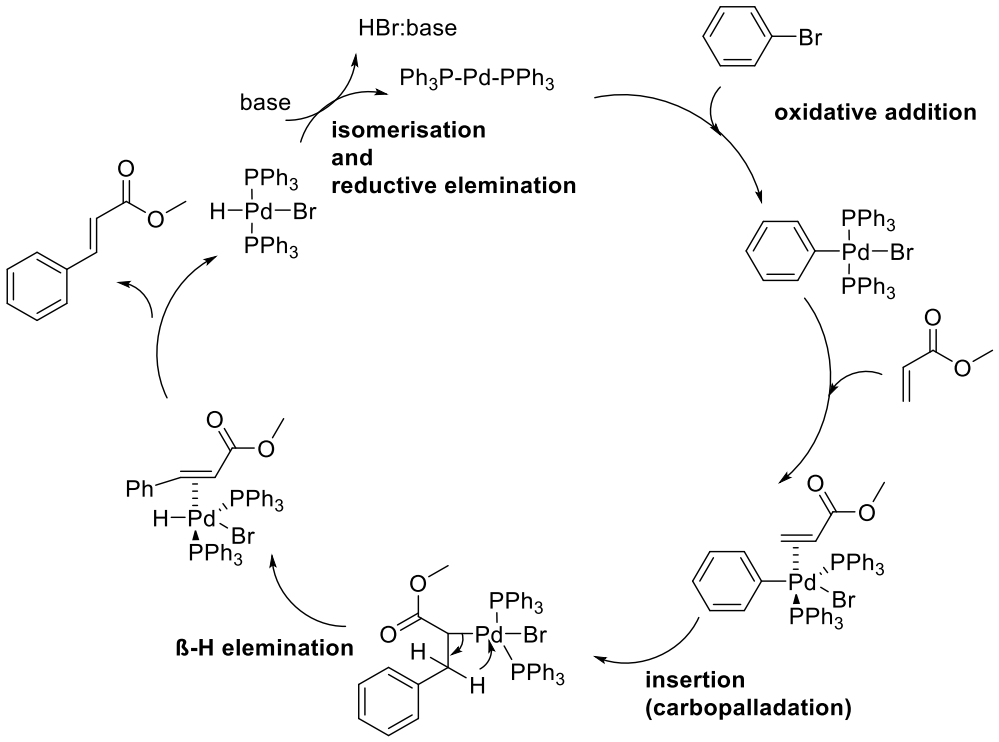
Coupling with isomerisation

14.4 MECHANISM OF HECK REACTION

Here, you can observe the stepwise mechanism of the Heck reaction.

- The active catalyst in the reaction is a Pd(0) complex that contains two PPh_3 ligands. This 14-electron Pd(0) species is the reactive form that starts the catalytic cycle (**Scheme 1**).
- At first, Pd(0) undergoes oxidative addition with an organic halide to form a Pd(II) complex.
- After that, the alkene coordinates to Pd(II) species.
- After coordination, a key step called 1,2-migratory insertion (**carbopalladation**) takes place in which the carbon group attached to Pd adds across the double bond of the alkene, forming a new C-C bond.
- Then, **β-hydride elimination** step occurs in which β-hydrogen is removed and a new substituted alkene is formed with the release of Pd(II).
- In the final step, a base helps to convert Pd(II) back into Pd(0).

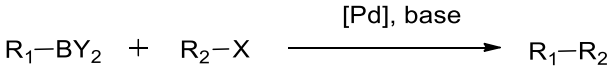
- The regeneration of Pd(0) is important because it allows the catalytic cycle to continue and the reaction to proceed further.
- Both the carbopalladation and β-hydride elimination steps occur in a *syn*-selective manner i.e., they happen from the same side of the molecule.



Scheme 1: Catalytic cycle for Heck reaction

14.5 SUZUKI COUPLING

Suzuki coupling, also called Suzuki-Miyaura coupling, is a Pd catalyzed cross coupling reaction between organoboron compounds (usually a boronic acid or ester) and organic halides. It is an important method for forming C-C bonds. The general scheme of the Suzuki coupling is shown below.

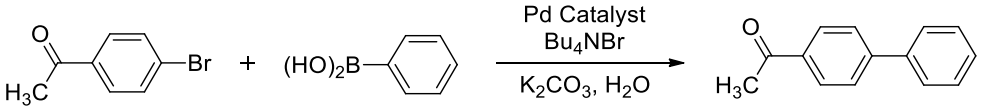


$$R_1{-}BY_2 + R_2{-}X \xrightarrow{[Pd],\ base} R_1{-}R_2$$

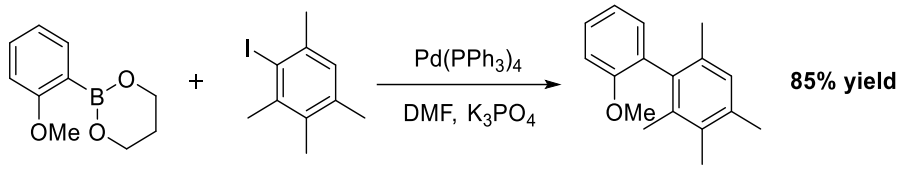
Where,

BY_2= $B(OH)_2$, $B(OR^-)_2$, 9-BBN, $BR_3^-K^+$, $B(CHCH_3CH(CH_3)_2$
X= I, Br, $OSO_2(C_nF_{2n+1})$ and Cl (with bulky electron-rich phosphines)
R_1= aryl, alkenyl and alkyl (under special conditions)
R_2= aryl, alkenyl, alkynyl, benzyl, allyl
[Pd]= $Pd(PPh_3)_4$, $PdCl_2(R_3P)_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $PdCl_2(dppf)$
base= Na_2CO_3, NaOEt, Net_3, K_3PO_4 or CsF

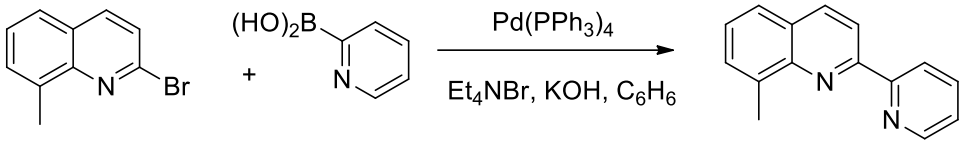
Here is a simple example of Suzuki coupling reaction between 4-bromo acetophenone and phenylboronic acid to give the corresponding coupling product.



Suzuki coupling is often used for aryl-aryl cross couplings. Sterically hindered substrates also undergo Suzuki coupling. In the following example, the reactants have three *ortho* substituents around the incipient newly formed bond and still undergoes coupling with excellent yield.



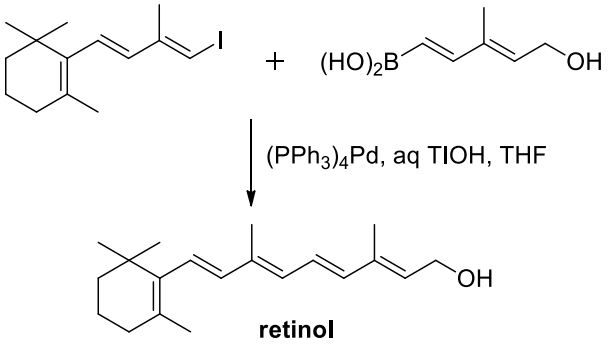
Aromatic heterocycles also undergo Suzuki reaction. The 2-position of a pyridine is very electrophilic and not at all nucleophilic. Yet, when either the halide or the boronic acid is present in this position, coupling reactions can still occur.
Here, neither of these substituents (the halide and the boronic acid) worked as a 'nucleophilic carbon'. Rather it is a coupling of the two substituents to ensure cross coupling and prevent dimerization.



Conventional methods for coupling of aryl groups typically require reagents and catalysts that are incompatible with molecules bearing polar functional groups. But, Suzuki coupling can tolerate the presence of functional groups in the coupling partners. So it has become one of the most powerful reactions in synthetic organic chemistry for C-C bond formation.

This reaction requires conditions milder than that for the Heck reaction. The boronic acids are stable in air and water. Moreover, as the boron species that is formed as a by-product is relatively nontoxic, so, this reaction is preferred in pharmaceutical industries.

The substrates are not restricted to aryls only, but include alkyls, alkenyls and alkynyls. Trifluoroborates, organoboranes or cyclic boronate esters can also be used in place of boronic acids. However, the base is a necessary component of the reaction to activate the boronic acid. The activation of the boron atom enhances the polarisation of the organic ligand and thus facilitates transmetallation. Here is an example of Suzuki coupling utilized in the synthesis of retinol.



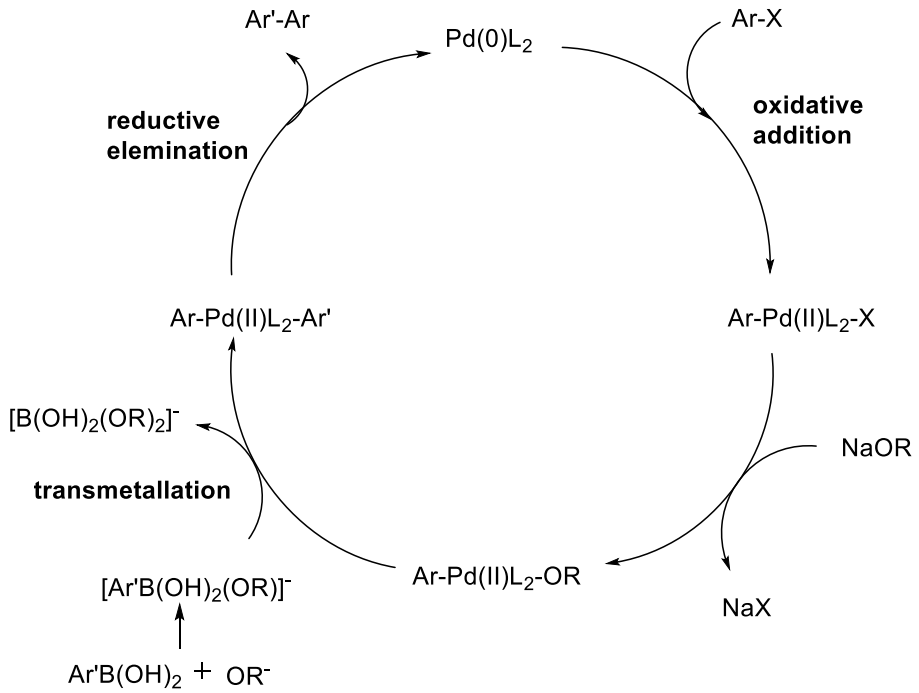
retinol

The scope and utility of Suzuki coupling have been widely improved in terms of substrates (including highly hindered substrates), low amount of catalyst, room temp. reaction and asymmetric synthesis.

The reaction conditions have also undergone a variety of changes. These include carrying out the reaction in ionic liquids such as [bmim]BF_4 or in water with microwave irradiation and conducting the reaction with extremely small amounts of Pd.

14.6 MECHANISM OF SUZUKI COUPLING

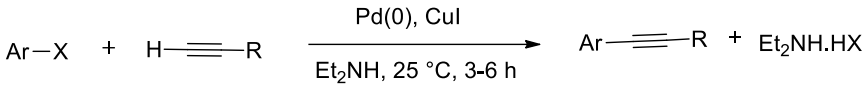
Here, you can observe the stepwise mechanism of the Suzuki coupling. The reaction proceeds through a catalytic cycle involving three main steps (**Scheme 2**). The first step is oxidative addition in which a Pd(0)L_2 catalyst reacts with the aryl halide, Ar-X to form an Ar-Pd(II)-X complex, during which Pd is oxidized from Pd(0) to Pd(II). In the next step the base activates the boronic acid and transmetallation takes place. In this step, a base such as NaOR or NaOH reacts with the boronic acid, Ar'B$(OH)_2$ to generate a more reactive borate species. This activated borate transfers the aryl group, Ar' to Pd, forming a Pd(II) complex containing both aryl groups, Ar-Pd(II)-Ar'; this process is known as transmetalation. Finally, the two aryl groups attached to Pd combine to produce the coupled product Ar-Ar', while Pd(II) is reduced back to Pd(0), thereby regenerating the catalyst and allowing the catalytic cycle to continue. This step is known as reductive elimination.



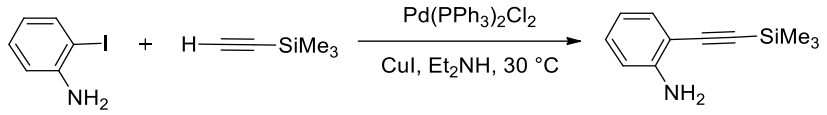
Scheme 2: Catalytic cycle for Suzuki coupling

14.7 SONOGASHIRA COUPLING

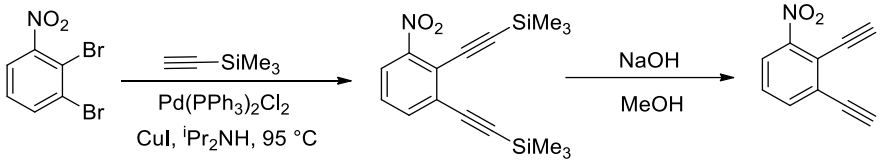
The coupling reaction between terminal alkynes and aryl or vinyl halides under catalytic amounts of Pd(0) complex with copper iodide as a co-catalyst is known as the Sonogashira reaction. The reaction is performed in the presence of a base. As in the Suzuki coupling, one reactant is aryl or vinyl halide, but the alkyne needs no metal to activate it. The reaction works with the alkyne itself. The reaction is like the Heck reaction.



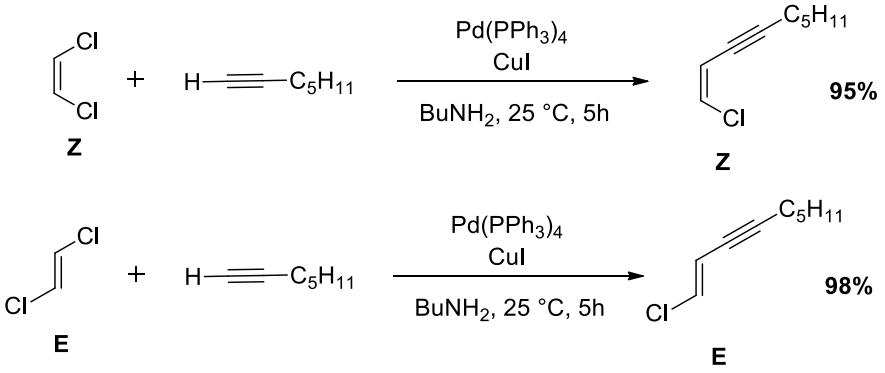
Example:



The reaction takes place in mild conditions, often at room temperature and therefore a large number of functional groups are not affected. Sonogashira coupling of trimethylsilyl alkyne followed by treatment with a strong base or a fluoride source is a common strategy used for introducing terminal alkyne groups.



It is usually more convenient, as in the Heck reaction, to use a stable and soluble Pd(II) derivative such as $Pd(PPh_3)_2Cl_2$ instead of Pd(0). This is rapidly reduced *in situ* to give a coordinatively unsaturated, catalytically active, Pd(0) species. The geometry of the alkene is generally preserved so that *cis* (*Z*) and *trans* (*E*) dichloroethylene give the two different geometrical isomers of the enyne in >99% stereochemical purity as well as excellent yield.

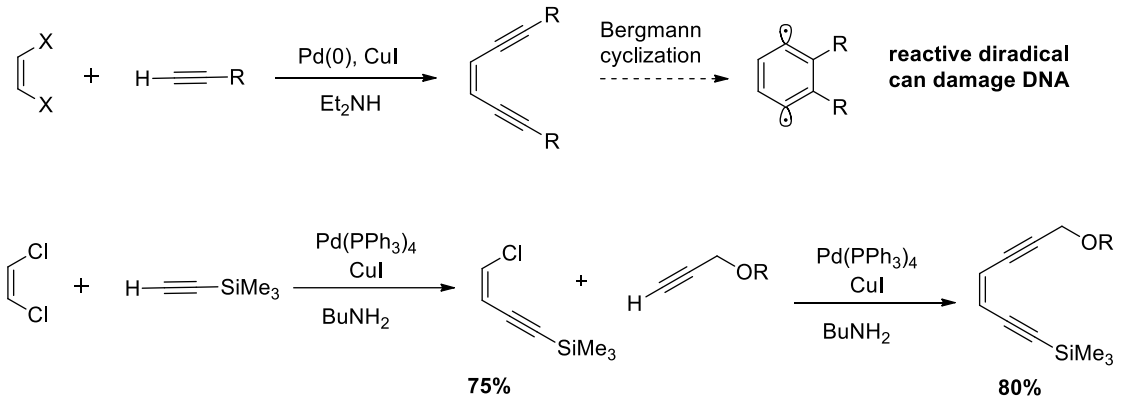


The reaction provides a method for making even conjugated acetylenic compounds, an important class of molecules that have found application in diverse areas ranging from natural products and pharmaceuticals to molecular organic materials (example, molecular wires) in nanoscience.

14.7.1 ENE-DIYNES AND THE BERGMANN CYCLIZATION

The Sonogashira reaction provides an important way to make the ene-diyne antibiotics. Symmetrical ene-diynes may be synthesized in one step from two molecules of a

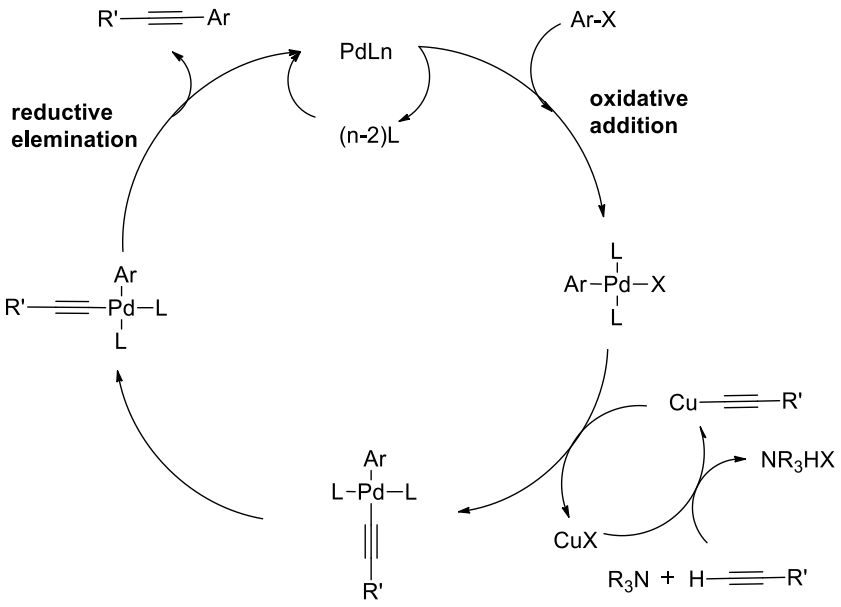
terminal alkyne and Z-dihaloethylene. The ene-diyne part of the molecule can undergo the remarkable Bergmann cyclization to give a benzene diradical. The ene-diyne is able to penetrate DNA and the diradical is able to react with DNA for which these compounds show anticancer activity. To make the most biologically active compounds, however, the reaction is performed sequentially, allowing different functionality on each of the alkyne units.



14.8 MECHANISM OF SONOGASHIRA COUPLING

The reaction occurs under mild conditions and at room temperature.

- First, the aryl halide or triflate undergoes oxidative addition to the Pd(0) catalyst forming a Pd(II) intermediate.
- At the same time, the terminal alkyne reacts with a base and a copper (I) salt (usually CuI) to form an alkynyl copper species.
- This copper acetylide then undergoes transmetallation with the organopalladium(II) complex, transferring the alkynyl group to Pd.
- Finally, reductive elimination occurs, coupling the aryl and alkynyl groups to give the arylalkyne product and regenerating the Pd(0) catalyst (**Scheme 3**).



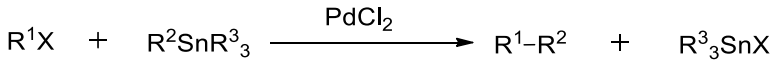
Scheme 3: Catalytic cycle for Sonogashira coupling

The amine serves both as a base to assist in forming the alkynyl copper species and to reduce the Pd(II) pre-catalyst to Pd(0).

14.9 STILLE COUPLING

Stille coupling reactions was introduced by J. K. Stille in 1971. This is a cross coupling reaction involving organotin based reagents and organohalides catalyzed by Pd. The organometallic reagent may in some cases be completely aliphatic, but coupling can still occur as shown below.

The main drawbacks of this reaction compared to Suzuki coupling is the toxicity of the tin compounds and their poor solubility in water due to their low polarity. This has limited its use in pharmaceuticals.



Where,

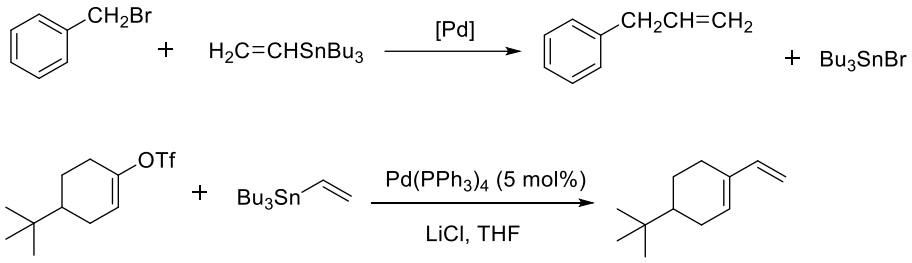
X = Br, I, OSO_2CF_3, OAc, Cl (when L = PBu_3)

R^1 = acyl, alkenyl, aryl, allyl, benzyl

R^2 = alkynyl, alkenyl, aryl, allyl, benzyl, acetyl

R^3 = Me, n-Bu

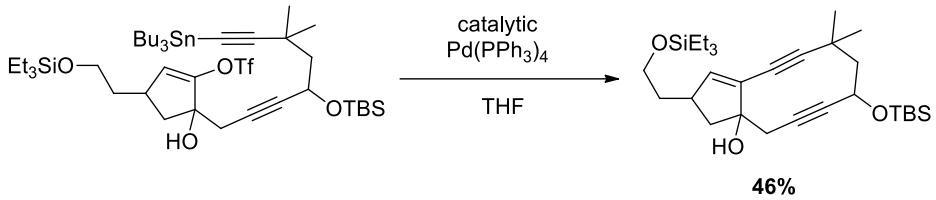
Examples of the Stille coupling are-



Salient features are

- The organostannyl reagent does not require any activation like Suzuki coupling.
- The R^1 group of the halide preferably should not have β-hydrogens as this will initiate β-hydrogen elimination instead of reductive elimination.
- The organostannane, however, can have β-hydrogens (see step 3 in the catalytic cycle, Scheme 4).
- Unlike in Suzuki coupling, no base is required for this reaction.
- A wide range of functional group are unaffected and the halide substrate with NO_2, CN, OMe, COOR, COOH and even CHO groups are tolerated.
- The presence of air also does not affect the reaction.

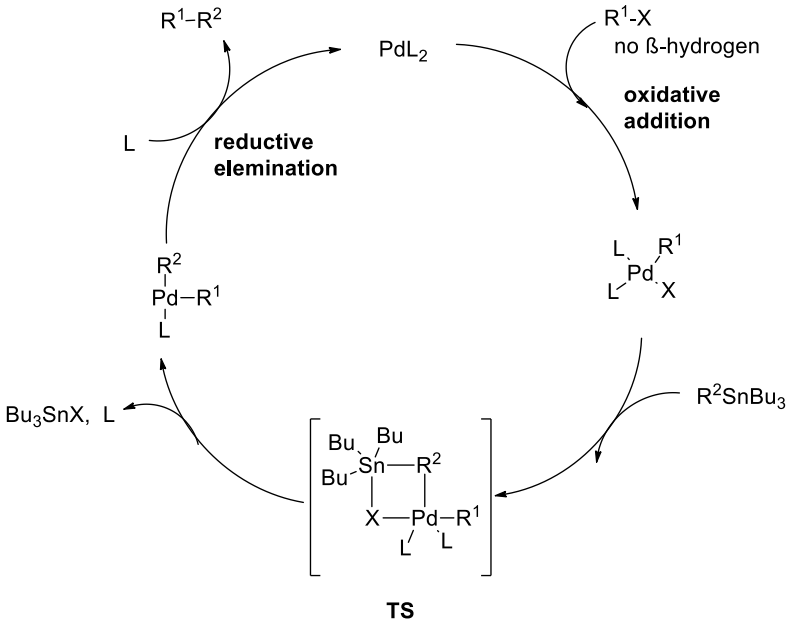
The Stille reaction is widely used to make bonds between sp^2 carbon atoms, but it also works with sp carbons. Here is an example, in which a challenging formation of a 10-membered ring containing two alkynes takes place.



14.10 MECHANISM OF STILLE COUPLING

The mechanism involves the following steps.

- Oxidative addition of the vinyl or aromatic triflate or halide to give an organopalladium intermediate.
- Transmetallation with the organostannane forms another organopalladium intermediate with two Pd-C σ-bonds.
- A reductive elimination step releases the product and thereby regenerates the Pd(0) catalyst.

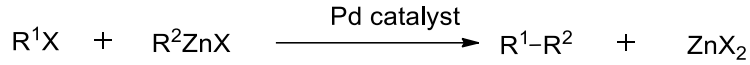


Scheme 4: Catalytic cycle for Stille coupling

14.11 NEGISHI COUPLING

Negishi coupling is the Ni or Pd catalyzed cross coupling reaction for the formation of a new C-C bond. It involves an organozinc compounds and various unsaturated organic halides or sulfonates (aryl, vinyl, benzyl or allyl etc.). The use of orgnozinc reagents

allows greater functional group tolerance in both coupling partners. The most widely used ligand for this reaction is PPh_3. Unlike many coupling reactions, this reaction does not require a base. The general scheme for the reaction is presented below.



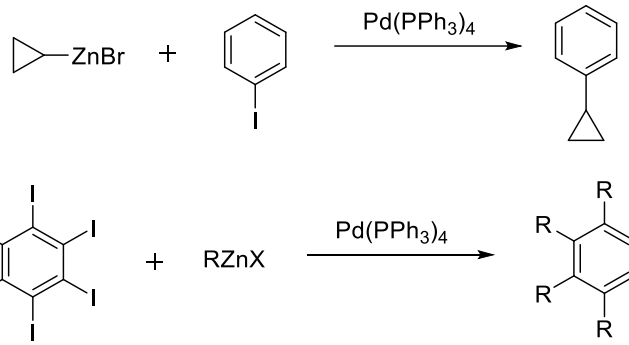
Where,

X= Br, I, OSO_2CF_3, Cl

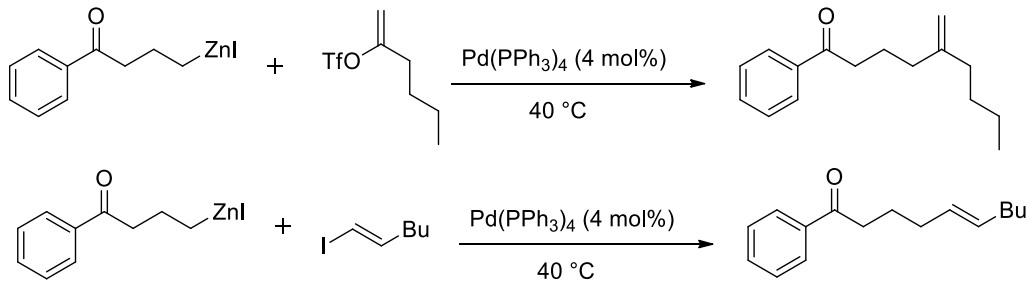
R^1= alkenyl, aryl, allyl, benzyl, alkynyl, vinyl

R^2= alkyl, alkenyl, aryl, allyl

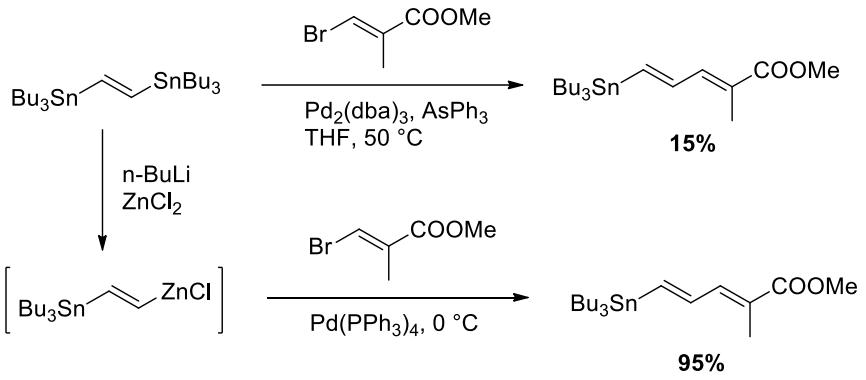
Examples:



This method is often used for coupling of heterocyclic rings. Negishi coupling was reported in 1977 that allowed the preparation of unsymmetrical biaryls in good yields. Later it was not restricted to the formation of biaryls. Both organic halides and diorganozinc compounds can be used as starting materials. Various Pd salts can be used, the simplest of which is $Pd(PPh_3)_4$. For example, you can see the coupling of the organozinc iodide reacts with the trifluoromethanesulfonate or the iodide to give the corresponding couple products as shown below.



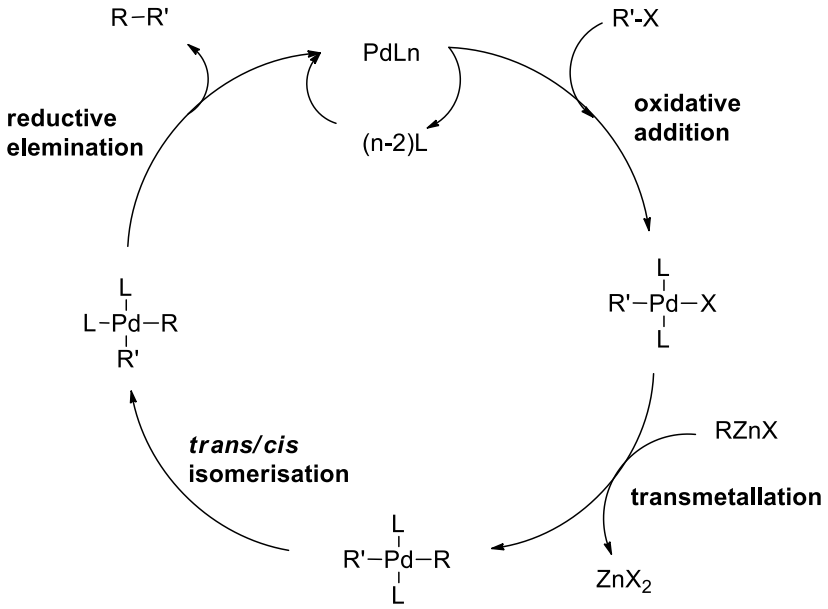
Along with Suzuki coupling, Negishi coupling is also an important method of Pd catalyzed alkenylation coupling. Negishi coupling is often preferred over Stille coupling for alkenylation as shown in the following example.



14.12 MECHANISM OF NEGISHI COUPLING

The active catalyst in Negishi Coupling is Pd(0) and the mechanism is as follows.

- Oxidative addition of R'X to Pd(0) to give an organopalladium compound.
- Transmetallation, in which the organic group, R on zinc is transferred to Pd.
- Thus, the two organic groups are assembled on the same Pd atom via Pd-C bonds.
- Next, isomerization from *trans* to *cis* takes place, bringing the two organic groups into a suitable position for bond formation.
- Finally, the R' and R groups couple with each other to give a new C-C bond and R-R' is released from Pd.
- In this process Pd(II) is reduced to Pd(0) and therefore the final step is called a reductive elimination.

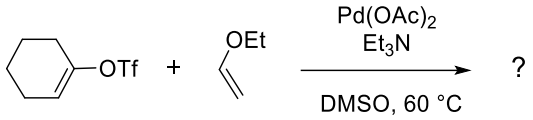


Scheme 5: Catalytic cycle for Negishi coupling

CHECK YOUR PROGRESS

Q 1: The step responsible for formation of the C-C bond is
(a) Oxidative addition
(b) Migratory insertion
(c) Reductive elimination
(d) Ligand dissociation

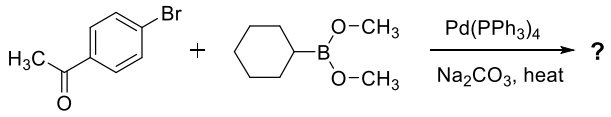
Q 2: Complete the reaction:



Q 3: The role of the base in the Suzuki reaction is to
(a) Reduce palladium
(b) Oxidize palladium
(c) Activate the boronic acid
(d) Remove halide

Q 4: The Suzuki reaction is especially useful in pharmaceutical synthesis because
(a) It requires high temperature
(b) It forms toxic by-products
(c) Boron by-products are relatively non-toxic
(d) It uses strong acids

Q 5: Draw the product obtained from the given reaction.

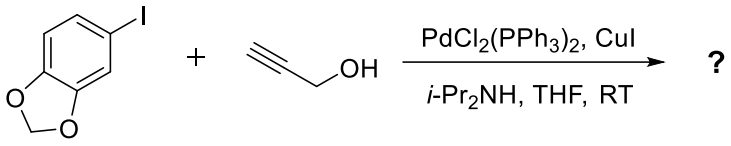


Q 6: Which of the following substrates is required in Sonogashira coupling?
(a) Internal alkyne only
(b) Terminal alkyne
(c) Alcohol
(d) Ester

Q 7: The oxidation state change of Pd during the catalytic cycle is
(a) Pd(II) → Pd(IV) → Pd(II)
(b) Pd(0) → Pd(II) → Pd(0)
(c) Pd(I) → Pd(III) → Pd(I)
(d) Pd(II) → Pd(0) → Pd(II)

Q 8: What is the role of CuI in the reaction?

Q 9: Draw the product obtained from the given reaction.



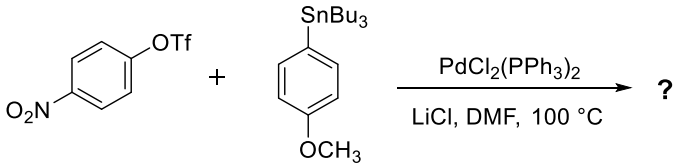
Q 10: The step in which the organic group from tin is transferred to palladium is called
(a) Oxidative addition
(b) Reductive elimination
(c) Transmetallation
(d) Hydrolysis

Q 11: The organometallic reagent used in the Stille coupling reaction contains
(a) Boron (b) Tin (c) Zinc (d) Magnesium

Q 12: Fill in the Blanks:

During the reaction, the oxidation state of palladium changes from _____ to _____ in the oxidative addition step.

Q 13: Draw the product obtained from the given reaction.

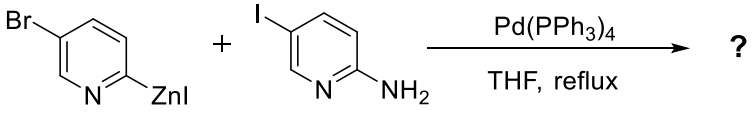


Q 14: The organometallic reagent used in Negishi coupling contains
(a) Boron
(b) Zinc
(c) Tin
(d) Magnesium

Q 15: Which halide reacts fastest in Negishi coupling?
(a) Aryl chloride
(b) Aryl bromide
(c) Aryl iodide
(d) Alkyl fluoride

Q 16: Fill in the Blanks:
The organozinc compound acts as the _____ partner in the reaction.

Q 17: Draw the product obtained from the given reaction.



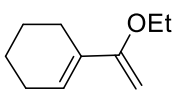
2 14.13 LET US SUM UP

- Organometallic reagents are widely used in organic synthesis for the formation of C-C bonds which are fundamental for building complex organic molecules.
- Pd catalyzed cross coupling reactions are among the most important methods for C-C bond formation in modern synthetic chemistry.
- The importance of Pd catalyzed cross coupling reactions was recognized by the 2010 Nobel Prize in Chemistry awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their pioneering work.
- These reactions generally involve the coupling of an organic halide or pseudo halide with an organometallic reagent in the presence of a Pd catalyst.
- The catalytic cycle usually proceeds through three key steps: oxidative addition, transmetallation and reductive elimination.
- The Heck reaction involves the coupling of aryl or vinyl halides with alkenes to form substituted alkenes.
- The Suzuki coupling uses organoboron compounds and is widely applied because of their stability and low toxicity.
- The Stille coupling involves organotin reagents and is useful for forming complex carbon frameworks.
- The Sonogashira coupling enables the coupling of terminal alkynes with aryl or vinyl halides to produce substituted alkynes.
- The Negishi Coupling uses organozinc reagents which show high reactivity and good functional group tolerance.

K 14.14 ANSWERS TO CHECK YOUR PROGRESS

Answer to Q1: (b) Migratory insertion

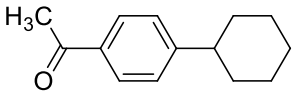
Answer to Q2:



Answer to Q3: (c) Activate the boronic acid

Answer to Q4: (c) Boron by-products are relatively non-toxic

Answer to Q5:

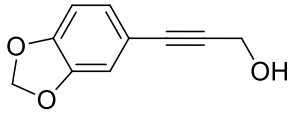


Answer to Q6: (b) Terminal alkyne

Answer to Q6: (b) Pd(0) → Pd(II) → Pd(0)

Answer to Q8: CuI acts as a co-catalyst and helps in the formation of the alkynyl copper (copper acetylide) intermediate, which facilitates transmetallation.

Answer to Q9:

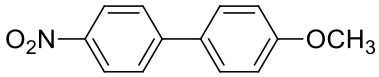


Answer to Q10: (c) Transmetallation

Answer to Q11: (b) Tin

Answer to Q12: 0 to +2

Answer to Q13:

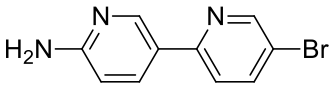


Answer to Q14: (b) Zinc

Answer to Q15: (c) Aryl iodide

Answer to Q16: nucleophilic

Answer to Q17:



O 14.15 FURTHER READING

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- Basic Organometallic Chemistry: Concepts, Syntheses and Applications- B. D. Gupta, A. J. Elias.
- Organic Chemistry (2nd ed. 2012)- J. Clayden, N. Greeves & S. Warren, Oxford University Press.
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M 14.16 MODEL QUESTIONS

Q1. What is the role of Pd catalyst in cross coupling reactions?
Q2. Name the organometallic reagent used in Suzuki coupling.
Q3. Which reaction couples alkynes with aryl halides?
Q4. What type of bond is mainly formed in Pd catalyzed coupling reactions?
Q5. Name the reaction that uses organotin reagents.
Q6. Which reaction involves organozinc reagents?
Q7. What is the first step in most Pd catalyzed coupling reactions?
Q8. Discuss the role of oxidative addition in organopalladium reactions.
Q9. What is transmetallation? Explain its importance in cross coupling reactions.
Q10. Explain why Pd is widely used as a catalyst in cross coupling reactions.
Q11. Write the general reaction scheme and mechanism of the Heck reaction.
Q12. Explain the role of boronic acids in Suzuki coupling.
Q13. Write the general mechanism of Suzuki coupling.
Q14. Discuss the advantages of Suzuki coupling over other cross coupling reactions.
Q15. Explain the mechanism of the Stille coupling reaction.
Q16. Write the general reaction and catalytic cycle of the Sonogashira reaction.
Q17. Explain the role of copper co-catalyst in Sonogashira coupling.
Q18. What are the applications of Sonogashira coupling in organic synthesis?
Q19. Explain the role of organozinc reagents in Negishi coupling.
Q20. Write the general mechanism of the Negishi reaction.
Q21. Compare Suzuki and Stille coupling reactions with respect to reagents and advantages.
Q22. Differentiate between Negishi and Suzuki coupling reactions.
Q23. Compare Sonogashira and Heck reactions in terms of substrates and products.
Q24. Discuss the advantages of cross coupling reactions in modern organic synthesis.